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Robustness Quantification Methods Comparison in Volumetric-Modulated Arc Therapy to treat Head and Neck Cancer

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Abstract

Background—To compare plan robustness of volumetric-modulated arc therapy (VMAT) with intensity-modulated radiation therapy (IMRT) and to compare the effectiveness of 3 plan robustness quantification methods.

Methods—VMAT and IMRT plans were created for 9 head and neck cancer patients. For each plan, 6 new perturbed dose distributions were computed using ± 3 mm setup deviations along each of the 3 orientations. Worst-case analysis (WCA), dose-volume histogram (DVH) band (DVHB), and root-mean-square-dose (RMSD) volume histogram (RVH) were used to quantify plan robustness. In WCA a shaded area in the DVH plot bounded by the DVHs from the lowest and highest dose per voxel was displayed. In DVHB we displayed the envelope of all DVHs in band graphs of all the 7 dose distributions. RVH represents the relative volume on the vertical axis and the RMSD on the horizontal axis. The width from the first two methods at different target DVH indices (such as $D_{95\%}$ and $D_{5\%}$) and the area under the RVH curves (AUC) for the target were used to indicate plan robustness. Results were compared using Wilcoxon signed-rank test.

Results—DVHB showed that the width at $D_{95\%}$ of IMRT was larger than that of VMAT (unit Gy) [1.59 vs 1.18] and the width at $D_{5\%}$ of IMRT was comparable to that of VMAT [0.59 vs 0.54]. WCA showed similar results between IMRT and VMAT plans [$D_{95\%}$: 3.28 vs 3.00; $D_{5\%}$: 1.68 vs 1.95]. RVH showed the AUC of IMRT was comparable to that of VMAT [1.13 vs 1.15]. No statistical significance was found in plan robustness between IMRT and VMAT.

Conclusions—VMAT is comparable to IMRT in terms of plan robustness. For the 3 quantification methods, WCA and DVHB are DVH-parameter dependent whereas RVH captures the overall effect of uncertainties.

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Conflicts of Interest Notification

None.

Keywords

VMAT; Plan Robustness; root-mean-square dose volume histogram; head and neck

INTRODUCTION

Volumetric-modulated arc therapy (VMAT) is an advanced form of intensity-modulated radiation therapy (IMRT) that delivers a precisely sculpted 3-dimensional dose distribution using a single or multi-arc treatment. VMAT has rapidly gained popularity in treating head and neck (H&N) cancer patients due to its lower integral dose and faster delivery compared to conventional static-field IMRT (hereinafter referred to as IMRT).(1–5) Despite technological advances in radiation treatment of H&N cancer, local relapse still remains a significant problem due to various factors.(6–11) Among them treatment delivery uncertainties such as patient setup uncertainties and organ motion might lead to target underdose and therefore are considered to be important factors contributing to local relapse. (12, 13) To ensure sufficient dose coverage to the treatment target and meet the clinical requirement for normal tissues, it is critically important to evaluate sensitivity of treatment plans to uncertainties.

Plan robustness quantification is a quantitative way to evaluate treatment plan sensitivity to uncertainties. Representative plan robustness quantification methods previously discussed in the literatures include worst-case analysis (WCA),(14, 15) dose-volume histogram band (DVHB),(16, 17) and root-mean-square-dose volume histogram (RVH).(18–21) The need for plan robustness quantification has been articulated for almost 3 decades;(22) but not implemented in routine clinical practice due to high computational cost. In external beam therapy planning, the influence of setup uncertainties and organ motion is addressed by adding predefined fixed margins to the clinical target volume (CTV) to form the planning target volume (PTV) in treatment planning and evaluated by the PTV dose distribution after planning.(23) The PTV concept relies on the assumption that dose cloud is static relative to the room coordinate system.(24) The validity of this assumption in photon therapy remains an active research topic. Recently some groups have proposed to use robust probabilistic planning to replace the concept of PTV in photon therapy.(25–31) For H&N cancer treatment, sensitivity of IMRT plans generated using PTV margins to patient setup uncertainties and organ motion has been extensively studied (32–42). However, there are few studies investigating sensitivity of VMAT plans to uncertainties (34). It is important to make sure that the superior dose distribution of VMAT can be delivered in the presence of uncertainties.

The goal of this study is to evaluate sensitivity of VMAT to patient setup uncertainties and to compare plan robustness of VMAT with IMRT for H&N cancer patients. A secondary goal of this work is to compare the performance between plan robustness quantification methods for photon therapy.

MATERIALS AND METHODS

Patient Data and Treatment Planning

We retrospectively evaluated treatment plans for 9 H&N cancer patients who were treated at our institution using VMAT. Patient and treatment characteristics for these patients are shown in Table I. Institutional review board approval was obtained for the use of this data (IRB No. XXXX). Patients were treated with radiation alone, or as part of multimodal therapy in combination with surgery with or without chemotherapy (Table I).

As for the radiation therapy, VMAT with 2 or 3 arcs was used (Table I). All 9 patients had been prescribed at 2 dose levels administered using simultaneous integrated boost technique. The target region receiving a high prescribed dose was referred to as CTV_{high} and the region receiving a low prescribed dose as CTV_{low}. CTVs were delineated by a physician, with CTV_{high} defined as the high risk microscopic disease volume (gross tumor volume or post-operative tumor bed with non-uniform 5–10 mm margin) including the high-risk nodal volume adjacent to gross disease considered to be at risk of harboring subclinical disease. CTV_{low} typically encompassed a 10 to 15 mm margin beyond CTV_{high} and low-risk nodal volumes. PTV_{high} and PTV_{low} were formed by uniform expansion of the corresponding CTV by 3 mm. Doses to targets and critical normal structures (eg, brainstem, optic chiasm, optic nerves) were constrained to meet acceptable tolerance dose values whenever possible as defined in the departmental H&N cancer treatment protocol (Supplemental Table I). The dose covering a percentage of the structure's volume (D%) and the volume of the structure receiving a certain dose (V_{Gy}) were used for dosimetric evaluation and planning purposes.

All patients were re-planned using IMRT with 7 or 9 non-opposed, equally spaced, co-planar fields. Both VMAT and IMRT plans used the same structure sets, prescription doses, and numbers of fractions as shown in Table I. IMRT plans were normalized to have the same D_{95%} of the PTV_{high} as in the VMAT plans. All VMAT and IMRT plans were generated using the Eclipse version 11 (Varian Medical Systems) by experienced dosimetrists or physicists and were approved by physicians.

Robustness Quantification Methods

Inter-fractional patient set-up uncertainties were modeled by applying both positive and negative shifts of the iso-center of the patient in the antero-posterior, superior-inferior, and lateral directions by the same margin as was used for defining the PTV (i.e., 3 mm). The original VMAT and IMRT plans were used for all the recalculations, yielding 7 (nominal plus 6 perturbed) dose distributions per plan per patient. In total 126 dose distributions were calculated. We used 3 in-house developed robustness quantification methods:

1. WCA (14, 15): In the WCA method, the highest and the lowest dose values in each voxel from the original and the perturbed dose distributions formed a hot dose distribution with the highest values and a cold dose distribution with the lowest values. Each structure was displayed by a shaded area that was bound by the dose-volume histograms (DVHs) from the cold and hot dose distributions. The width of the DVH bands corresponded to the plan robustness for the structure indicated (Figure 1a).

2. DVHB (16, 17): In the DVHB method, the envelope of all DVHs in band graphs of all dose distributions associated with the corresponding uncertainties was displayed. The width of the DVH bands was also used to indicate the plan robustness for the structure (Figure 1b). In the WCA and DVHB methods, the width varied if they were chosen at different DVH parameters. In this work, DVH parameters were chosen to be at $D_{95\%}$ (indication of cold spots induced by uncertainties) and $D_{5\%}$ (indication of hot spots induced by uncertainties).
3. RVH (18–20) (analogous to the error-bar volume histograms proposed by Albertini *et al.*(21)): In the RVH method, for the targets the root-mean-square dose deviation (RMSD) of voxels was calculated as the square root of the sum square of the differences between the dose calculated under the uncertainty scenarios and the nominal scenario and the mean dose of those 7 doses. This was then used to construct the RVH, which represented the relative volume (y) on the vertical axis and the RMSD (x) on the horizontal axis (Figure 1c). Similar to DVH, this meant that y% of the volume of the indicated structure had the RMSD at least $\times$ Gy. For example, the point in Fig. 1(c) as indicated by the *green star* showed that 55% of the volume of the indicated volume had the RMSD of at least 1.0 Gy.

For normal tissues, only the perturbed doses larger than the nominal dose per voxel were considered. The positive differences between the perturbed doses and nominal dose were used to calculate the RMSD and then RVH was constructed accordingly. We further simplified the RVH for both targets and normal tissues to compare the 2 plans' robustness by calculating the area under the curve (AUC) of the RVH, which gave a single numerical value for the plan's robustness for a given volume of interest: the smaller the AUC; the more robust the plan was for the structure between competing plans. For an ideally robust plan the RVH curve of a volume of interest should coincide with the vertical axis. Therefore the AUC of this structure would be zero.

Statistical Analysis

The width at $D_{95\%}$ and $D_{5\%}$, of CTV_{high} and CTV_{low} derived from WCA and DVHB and the AUC of the CTV_{high} and CTV_{low} RVH were used to assess plan robustness of targets. The AUC of the spinal cord, brainstem, left parotid, right parotid, and mandible RVH was used to assess plan robustness of normal tissues.

We performed statistical comparison analyses of the results from both plans. The means of all plan robustness indices i.e., the widths of DVHs from the WCA and DVHB methods and the AUC from the RVH method were calculated. The data were compared with the non-parameter Wilcoxon signed-rank test, using JMP Pro 10 software (SAS Institute Inc.). A *P* value less than 0.05 was considered statistically significant.

RESULTS

Figure 1 shows the plan robustness comparison between VMAT and IMRT for patient #1 using the 3 plan robustness quantification methods: (a) WCA, (b) DVHB, and (c) RVH. From Figure 1 the width at D_{95%} of the CTV_{high} from WCA was 4.2 vs. 3.6 (IMRT vs. VMAT; unit Gy) and the width at D_{95%} of the CTV_{high} from DVHB was 1.6 vs. 0.76, which suggested that VMAT was more robust than IMRT (Figure 1a). However, the width at D_{5%} of the CTV_{high} from WCA was 1.2 vs. 2.1, and the width at D_{5%} of the CTV_{high} from DVHB was 0.34 vs. 0.38, suggesting that IMRT was more robust than VMAT (Figure 1b). From Figure 1c, RVH shows that if RMSD was less than 1.6 Gy (*blue star*), IMRT had smaller volumes than VMAT given the same RMSD (i.e., IMRT was more robust than VMAT). However, if RMSD was larger than 1.6 Gy, IMRT had a very slightly larger volume than VMAT given the same RMSD (i.e., VMAT was more robust than IMRT).

Figure 2 shows the comparison of robustness results for CTV_{high} for 9 patients between IMRT (*blue*) and VMAT (*red*) plans: (a) the width at D_{95%} from WCA, (b) the width at D_{5%} from WCA, (c) the width at D_{95%} from DVHB, (d) the width at D_{5%} from DVHB, and (e) the AUC from the RVH curve.

Within the same plan robustness quantification method, different conclusions would be drawn if the widths from the WCA and DVHB method were chosen at different DVH parameters. For example, the WCA method derived different results for patient 1, 3, and 4 if the results were chosen at different DVH parameters. See Figure 2a with Figure 2b. Likewise the DVHB method derived different results for patient 1, 4, and 5. See Figure 2c with Figure 2d.

Different conclusions would be made from different plan robustness quantification methods. If D_{95%} was chosen, WCA showed consistent results with DVHB for every patient (Figure 2a vs. Figure 2c). However, the AUC of the CTV_{high} RVH curve suggested opposite results compared to WCA and DVHB for patient 1, 2, 5, and 7 (comparing Figure 2e with Figure 2a and Figure 2c). If D_{5%} was chosen, WCA indicated different results from DVHB for patient 2, 3, and 5 (Figure 2b vs. Figure 2d). The results from the AUC of the CTV_{high} RVH curve compared to the results either from WCA or from DVHB also varied from patient to patient (comparing Figure 2e with Figure 2b and Figure 2d).

Figure 3 shows the comparison of the mean values of the widths from the WCA and DVHB methods and the AUC from the RVH method of the CTV_{high} averaged over 9 patients between the IMRT (*blue*) and VMAT (*red*) plan: (a) widths from WCA and DVHB at D_{95%} and D_{5%} respectively, and (b) the AUC. *P* values from non-parametric Wilcoxon signed-rank tests were shown on top of columns. From all plan robustness evaluation metrics, the plan robustness of CTV_{high} from VMAT was not significantly different from IMRT, i.e., the plan robustness of VMAT was comparable to IMRT with respect to CTV_{high}. Similar results were also found for CTV_{low} (Supplemental Figure 1 and Supplemental Figure 2) except that the widths at D_{95%} of the DVHB method from IMRT were significantly smaller than those from VMAT (*P*=0.0039) (Supplemental Figure 2).

We also compared the plan robustness of normal tissues between the IMRT (*blue*) and VMAT (*red*) plan as shown in Figure 4. For simplicity only results from the AUC of RVH of the normal tissues like (a) spinal cord, (b) brainstem, (c) left parotid, (d) right parotid, and (e) mandible were included. Compared to IMRT, VMAT resulted in more robust dose distribution for spinal cord (8 out of 9), brainstem (4 out of 9), mandible (7 out of 9), left parotid (4 out of 9), and right parotid (3 out of 9) (Figure 4).

Patient averaged results of plan robustness comparison of the above normal tissues between the IMRT (*blue*) and VMAT (*red*) plan are shown in Figure 5. *P* values from non-parametric Wilcoxon signed-rank tests are shown on top of the columns. For all normal tissues, the plan robustness from VMAT was not significantly different from IMRT except mandible.

DISCUSSION

In this study, we have successfully implemented 3 robustness quantification methods to assess plan robustness in photon therapy. We found that VMAT plan robustness is statistically comparable to IMRT plan robustness for both target and normal tissues. The 3 robustness quantification methods presented here have their advantages and disadvantages.

We noticed that the comparison of WCA and DVHB depended on the selected DVH parameters, while the AUC of the RVH did not rely on DVH parameters. Therefore RVH provides a more comprehensive indicator of the plan robustness for the structure of interest with a simple numerical value (i.e., AUC). In clinical practice, it is preferable to have a single numerical value to indicate plan robustness because it can be easily incorporated into statistical analysis for comparison. In cases where the RVH curves from the competing plans intersect with each other and have similar AUCs, physicians and physicists need to examine the entire RVH curves closely and make a patient-specific judgment: either a larger volume with a small RMSD or a smaller volume with a large RMSD. This might also explain why plan robustness comparison results from WCA and DVHB depend on the DVH parameters. The RVH plot captures the overall effect of uncertainties on the dose to a volume of interest, which is analogous to the DVH for assessing the nominal dose.

More importantly, RVH opens a door to explicitly control plan robustness in optimization. The desired robustness may be specified in terms of a RMSD-volume constraint on the targets. Penalty parameters of RMSD-volume constraints may be adjusted to explicitly control the tradeoff between robustness and plan optimality.

It would be better to have more dose distributions included in all 3 robustness quantification methods. However, it may not be practical to do so in routine clinical practice using a commercial treatment planning system, which makes the computation time formidable. In order to show the influence of more uncertainty scenarios, we tried 14 uncertainty scenarios as defined in Casiraghi et al (43) in a couple of patients and found that the conclusions were still valid using those dose distributions. It is also important to evaluate the effect of rotational perturbation on plan robustness; this will be included in a future study.

Plan robustness represents our confidence level that the nominal plan can be delivered without significant quality degradation in the presence of uncertainties. It has been

extensively investigated in proton therapy because proton therapy, especially scanning beam proton therapy, is very sensitive to various uncertainties (2–9, 24). In photon therapy, integrating plan robustness into plan quality check is essential because it provides an indication of real-life plan quality, instead of computed plan quality. An important clinical application of plan robustness quantification is regarding selection of appropriate treatment modalities (photon vs. proton) for individual patients, which should be based on both plan quality and plan robustness. This remains an important research topic that requires further investigation and will be included in our future studies.

In summary, VMAT is comparable to IMRT in terms of plan robustness. Among the 3 robustness quantification methods, WCA and DVHB are DVH-parameter dependent whereas RVH captures the overall effect of uncertainties. Given lower integral dose and higher delivery efficiency, VMAT seems to be the preferred choice over IMRT at least for the H&N patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Comparison of plan robustness of the CTV_{high} for patient 1 using 3 robustness quantification methods: (a) WCA, (b) DVHB, and (c) RVH.

*Numbers on horizontal axis represent patients.

Figure 2.

Comparison of plan robustness of the CTV_{high} for 9 patients using 3 robustness quantification methods at different DVH parameters: (a) width at D_{95%} from WCA, (b) width at D_{5%} from WCA, (c) width at D_{95%} from DVHB, (d) width at D_{5%} from DVHB, (e) AUC of the CTV_{high} RVH curves.

Figure 3.

(a) Comparison of plan robustness of the CTV_{high} averaged over 9 patients using (a) width at D_{95%} from WCA and DVHB, width at D_{5%} from WCA and DVHB and (b) AUC from RVH curves. Numbers at the top of the columns are *P* values.

*Numbers on horizontal axis represent patients.

Figure 4.

Comparison of plan robustness of (a) spinal cord, (b) brainstem, (c) left parotid, (d) right parotid and (e) mandible for 9 patients using the corresponding AUCs.

Figure 5.

Comparison of plan robustness of spinal cord, brainstem, left parotid, right parotid, and mandible averaged over 9 patients using the corresponding AUCs. *P* values are shown on the top of the columns.

Patient Characteristics

Table 1

Patient	Age	Gender	Tumor Site	Treatment With Prescription Dose (in Gy) and Fractions	T Stage	N Stage
1	73	M	Nasopharynx (involving soft palate)	3-Arc VMAT (70/33)	T1	N0
2	63	F	Central skull base	Chemo-3-Arc VMAT (70/35)	T4b	N0
3	80	M	Supraglottis	2 Arc VMAT (66/33)	T2s	N2c
4	65	F	Oral tongue	surgery + combined modality chemoRT (3 Arc VMAT [70/35])	T2	N2b
5	62	M	Nasopharynx	Concurrent chemo-RT (Arc VMAT [70/33])	T4	N2
6	69	M	Base of tongue	Definitive chemo-RT (3 Arc VMAT [70/35])	T2/T3	N2b
7	69	M	Base of tongue	Surgery + chemo-RT (3 Arc VMAT [70/35])	T2	N2b
8	50	F	Base of tongue	Surgery + chemo-RT (3 Arc VMAT [70/35])	T1	N1
9	78	M	Oral Cavity	Surgery + adjuvant RT (2 Field VMAT [60/30])	T1	N1

Abbreviations: F, female; M, male; VMAT, volumetric-modulated arc therapy; RT, Radiotherapy; Chemo-RT, Chemo-radiotherapy