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FULL PAPER

Improving target dose coverage and organ-at-risk sparing in intensity-modulated radiotherapy of advanced laryngeal cancer by a simple optimization technique

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Objective: To evaluate a simple optimization technique intended to improve planning target volume (PTV) dose coverage and organ-at-risk (OAR) sparing in intensity-modulated radiotherapy (IMRT) of advanced laryngeal cancer.

Methods: Generally acceptable initial IMRT plans were generated for 12 patients and were improved individually by the following two techniques: (1) base dose function-based (BDF) technique, in which the treatment plans were reoptimized based on the initial IMRT plans; (2) dose-controlling structure-based (DCS) technique, in which the initial IMRT plans were reoptimized by adding constraints for hot and cold spots. The initial, BDF and DCS IMRT plans and additionally generated volumetric modulated arc therapy (VMAT) plans were compared concerning homogeneity index (HI) and conformity index (CI) of PTVs prescribed at 70 Gy/60 Gy (PTV70/PTV60),

OAR sparing, monitor units (MUs) per fraction and total planning time.

Results: Compared with the initial IMRT and DCS IMRT plans, the BDF technique provided superior HI/CI, by approximately 19–37%/4–11%, and lower doses to most OARs, by approximately 1–7%, except for the comparable HI of PTV60 to DCS IMRT plans. Compared with VMAT plans, the BDF technique provided comparable HI, CI and most-OAR sparing, except for the superior HI of PTV70, by approximately 13%. The BDF technique produced more MUs and reduced the planning time.

Conclusion: The BDF optimization technique for IMRT of advanced laryngeal cancer can improve target dose homogeneity and conformity, spare most OARs and is efficient.

Advances in knowledge: A novel optimization technique for improving IMRT was assessed and found to be effective and efficient.

In recent decades, the treatment paradigm for advanced laryngeal cancer has shifted from one of primary surgery, such as total laryngectomy, as the gold standard, towards non-surgical organ-preserving treatment using radiotherapy or chemoradiotherapy. The major advantages of radiotherapy or chemoradiotherapy are the avoidance of an operation and anatomic preservation of the larynx, with no definite compromise in overall survival.^{1,2} An advanced form of radiotherapy is intensity-modulated radiotherapy (IMRT), which uses intensity-modulated, non-uniform radiation beams to increase the delivery of radiation to the planned treatment volume, while minimizing the irradiation of normal tissue outside the target. Marta et al³ performed a systematic review and meta-analysis, and indicated that IMRT could reduce the

incidence of grades 2–4 xerostomia in patients with head and neck cancers without compromising locoregional control and overall survival, compared with conventional radiotherapy technique. Monaghan et al⁴ reported the comparison of clinical outcomes of IMRT and conventional fields in the treatment of laryngeal cancer, excluding T1 tumours, and suggested that the therapeutic ratio may be improved by further refinements in the IMRT technique and normal tissue sparing. Therefore, it is important to improve the IMRT technique for advanced laryngeal cancer by improving the target dose coverage for tumour local control and reducing the dose to normal adjacent tissues for less subsequent morbidity following larynx irradiation.

However, IMRT planning for advanced laryngeal cancer is challenging owing to target volumes with concave shapes and organs at risk (OARs), such as the spinal cord, oral cavity, parotid glands and carotid. Additionally, the target volumes are often given different prescription dose levels.⁵ There are a limited number of studies that have focused on the IMRT planning technique for advanced laryngeal cancer, but others have assessed its use for other head and neck cancers. Chau *et al*⁶ proposed a split-organ delineation approach to reduce the dose to parotid in nasopharyngeal cancer IMRT planning, and a similar technique was investigated by Zhang *et al*.⁷ Their studies demonstrated that the dose to parotid could be reduced significantly, but the doses to other OARs were increased, although not significantly. In fact, this planning technique only considered the tradeoffs between the parotids and other organs. Some other studies have investigated the optimal beam arrangement and number, which are important steps for generating high-quality IMRT plans.^{8,9} However, it was still difficult to achieve optimal plans because of the differences between optimizer plans and deliverable treatment plans,¹⁰ which can be caused by an optimization-convergence error (OCE).^{11,12} The OCE must be introduced into IMRT planning in current treatment planning systems, because at present, the treatment planning computer is not fast enough for the optimizer to use a full volume dose calculation algorithm as the engine of the optimizer and requires the use of a simplified algorithm instead. Owing to the OCE, the final dose distribution may not meet the objectives of optimization, although the dose distribution in the optimizer has met them.

Therefore, we proposed an optimization technique to improve the IMRT plans of advanced laryngeal cancer by means of compensating for the OCE. To evaluate its application and to demonstrate the dosimetric superiority of this technique, the initial IMRT plans were used for longitudinal comparison to assess the efficacy of this new technique and another optimization technique for lateral comparison. Volumetric modulated arc therapy (VMAT)

technique, an advanced IMRT technique with continually rotational gantry, which was previously reported to be dosimetrically superior^{13,14} or comparable¹⁵ over conventional IMRT technique in head and neck cancer, was utilized for further comparison in this study.

METHODS AND MATERIALS

Patient characteristics

A total of 12 patients with previously untreated, histologically confirmed squamous cell cancer of the larynx with Stages T3–T4, N0–N2, M0 were retrospectively identified. The sample size calculation was based on our pilot study. The staging of cancer of the larynx was performed according to the American Joint Committee on Cancer 6th edition TNM staging system, with stage grouping based upon the extent of primary tumour and metastatic disease. Table 1 shows the patient characteristics.

CT simulation

All the patients were scanned in the supine position under thermoplastic mask immobilization of the head, neck and shoulders. The contrast-enhanced CT images were taken at 3 mm per slice by Philip Big Bore Brilliance CT (Philips Medical Systems Inc., Cleveland, OH). The CT images were then transferred to the Eclipse™ v. 10.0 treatment planning system (Varian® Medical System, Palo Alto, CA) for the delineation of target volumes and OARs and treatment planning.

Target delineation and definition of organs at risk

All target volumes were delineated slice by slice on the treatment planning CT images by radiation oncologists, according to the International Commission on Radiation Units and Measurements (ICRU) report 83 guidelines.¹⁶ Gross tumour volume (GTV) was defined as the gross disease determined using the planning CT, MR and clinical information. The GTV included the primary laryngeal tumour, as well as all the positive involved regional lymph nodes. The clinical target volume prescribed at 60 Gy (CTV60) was defined as the GTV plus a 5 to 10-mm margin for potential microscopic spread and the regional lymphatic

Table 1. Patient characteristics

Patient	Gender	Age (years)	Weight (kg)	Height (cm)	Diagnosis	Stage
1	Male	60	59.9	166	Glottic SCC	T3N0M0
2	Male	74	51	164	Glottic SCC	T4N0M0
3	Male	76	48	165	Supraglottic SCC	T3N1M0
4	Male	65	59	167	Glottic SCC	T4N0M0
5	Male	59	63	163	Supraglottic SCC	T4N2M0
6	Male	64	61	159	Glottic SCC	T3N0M0
7	Male	75	48.5	158	Supraglottic SCC	T3N2M0
8	Male	62	66	163	Glottic SCC	T3N2M0
9	Male	52	65	162	Supraglottic SCC	T4N2M0
10	Male	70	48	168	Supraglottic SCC	T3N0M0
11	Male	44	82	168	Supraglottic SCC	T3N0M0
12	Male	75	59.5	165	Glottic SCC	T4N0M0

SCC, squamous cell carcinoma.

drainage area of harbouring metastatic disease. The planning target volumes (PTVs), PTV70 and PTV60, were generated by a 5-mm outer margin of the GTV and CTV60, respectively. The PTV70 and PTV60 were also generated 3 mm away from the surface of the body to avoid the parts extended outside of the body and the build-up effect. The mean volumes of PTV70 and PTV60 were 75 ± 34 and $542 \pm 198 \text{ cm}^3$, respectively. To evaluate the dose homogeneity of PTV60 without being affected by the higher doses of PTV70, PTV60_only was defined as the PTV60 from which 1-cm expansion volume of PTV70 was subtracted.

The OARs, including the spinal cord, brainstem, thyroid, carotid, oral cavity and parotid glands, were outlined on each image following anatomic definitions. Planning OAR volumes (PRVs) were created for the spinal cord and brainstem by adding a 5-mm margin around them and were denoted as PRV spinal cord and PRV brainstem, respectively. Normal tissue was defined as the body minus both of the PTVs.

Intensity-modulated radiotherapy and volumetric modulated arc therapy planning

Seven coplanar fields of 6-MV photon beams from TrueBeam® (Varian Medical System) linear accelerator were created for each simultaneously integrated boost plan in Eclipse v. 10.0. For each IMRT plan, seven fields were placed at approximately evenly distributed gantry angles, 210°, 260°, 310°, 0°, 50°, 100° and 150°. All the collimator angles were set to 90°, this was intended to better protect the spinal cord, except for the gantry angle 260° and 50° with collimator 0°. For each VMAT plan, two arcs were generated with the collimators rotated to 10–30°, which aimed at minimizing the tongue and groove effect. Dose–Volume Optimizer (DVO v. 10.0.28; Varian® Medical System, Palo Alto, CA) and Progressive Resolution Optimizer (PRO v. 10.0.28, Varian Medical System) algorithms were used for IMRT and VMAT optimizations, respectively. Anisotropic analytical algorithm (AAA v. 10.0.28, Varian Medical System) was applied for final dose calculations, with a grid size of 2.5 mm. The prescription doses to the PTV70 and PTV60 were 70 Gy (2.19 Gy per fraction) and 60 Gy (1.88 Gy per fraction), respectively, both given in 32 fractions. The dose scheme followed the protocol, of Cancer Hospital of Shantou University Medical College. Each treatment plan was normalized, such that 95% of PTV70 was covered by 100% of the physician's prescribed dose of 70 Gy. Some ring-like structures were contoured with the aim of making an isodose conformal to the target volume.

In the optimization objective settings, PTV coverage was given the highest priority, followed by the avoidance of overdosing the OARs. The goals of the PTV and OAR constraints are shown in Table 2.

To generate an initial IMRT plan, the optimization objectives of each plan were adjusted until the plan was generally acceptable. Keeping the original optimization objectives unchanged, the two following techniques were applied individually to improve the quality of the initial IMRT plan: (1) reoptimization using base dose function (BDF IMRT plan) and (2) reoptimization with dose-controlling structures generated from hot and cold spots (DCS IMRT plan).^{17,18}

Table 2. Treatment planning constraints for advanced laryngeal cancer

Structures	Planning constraints
PTV70	$D_{95\%} = 70 \text{ Gy}$
PTV60	$D_{95\%} \geq 60 \text{ Gy}$
Spinal cord	$D_{\text{max}} < 45 \text{ Gy}$
PRV spinal cord	$D_{\text{max}} < 50 \text{ Gy}$
Brainstem	$D_{\text{max}} < 45 \text{ Gy}$
PRV brainstem	$D_{\text{max}} < 50 \text{ Gy}$
Thyroid	As low as possible
Carotid	As low as possible
Oral cavity	$D_{\text{mean}} < 35 \text{ Gy}$
Parotid glands	$D_{\text{mean}} < 40 \text{ Gy}$
Normal tissue	As low as possible

$D_{95\%}$, the dose that is reached or exceeded in 95% of the volume; D_{max} , maximum dose; D_{mean} , mean dose; PRV, planning organ-at-risk volume; PTV, planning target volume; PTV60, PTV prescribed at 60 Gy; PTV70, PTV prescribed at 70 Gy.

To generate a BDF IMRT plan, the number of fractions of the initial IMRT plan was reduced to 50% of prescribed number of fractions to generate a base dose plan, that is, from 32 to 16 in these cases. Then, a “top dose” plan was generated in the same way. After associating the base dose plan with the top dose plan by the base dose function, the top dose plan was reoptimized in 20 maximum iterations. When the final dose calculation was completed, the number of fractions of the optimized top dose plan was restored from 50% (16 fractions) to 100% (32 fractions) of the prescribed number of fractions. The resultant optimized top dose plan was the BDF IMRT plan.

To generate a DCS IMRT plan, the 105% of prescription doses of both of the PTVs were converted into dose-controlling structures, which were added as upper objectives, and the upper objectives were set to 0–2% lower than were prescription doses. By subtracting the prescription isodose volumes (PIVs) from PTVs, cold-spot structures were generated and were set to 0–3% higher than were prescription doses. After additional optimization objectives were added, the plan was reoptimized in 20 maximum iterations. After final dose calculation, the DCS IMRT plan was accomplished.

To generate a VMAT plan, the optimization objectives based on the objectives used in the initial IMRT plan were adjusted slightly, and the plan was reoptimized 1–3 times to achieve a clinically acceptable plan, as the optimization algorithm PRO was different from DVO.

All of the plans were conducted by a medical physicist. Distributed calculation framework (DCF) was employed for final volume dose calculation. The total planning time, taking into account the initial plans, was recorded to compare the planning efficiencies of the BDF, and DCS IMRT plans and VMAT plans. The monitor units (MUs) per fraction for each plan were also recorded.

Plan evaluation

To compare the four plans, dose–volume statistics, isodose distributions and cumulative dose–volume histograms (DVHs) were calculated. The DVHs were displayed in terms of absolute dose and normalized volume. The DVH indicates what fraction of the volume of a region of interest (OAR or target volume) received radiation doses above the specified values.¹⁹

According to the recommendations of ICRU report 83, $D_{x\%}$ represented the dose that is reached or exceeded in $x\%$ of the volume and V_{xGy} represented the % volume receiving at least x Gy dose. For the PTV, $D_{2\%}$ and $D_{98\%}$ were chosen as near-maximal and near-minimal doses for evaluating hot and cold spots, respectively. $D_{50\%}$ represented the median dose. The target dose homogeneity was measured with homogeneity index (HI) and was defined by the following formula:¹⁶

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}}$$

The target dose conformity was measured with the conformity index (CI). A CI proposed by Paddick²⁰ considers the location of the prescription isodose volume with respect to the target volume (TV), and was defined as follows:

$$CI = \frac{(TV \text{ within PIV})^2}{TV \times PIV}$$

The HI value was between 0 and 1, with 0 representing the ideal homogeneity, while the CI value was between 0 and 1, with 1 representing the ideal conformity. The D_{max} (maximum dose), D_{mean} (mean dose) and V_{xGy} were used for evaluating the doses delivered to the OARs. All the evaluation indicators used for PTVs and OARs are summarized in Table 3.

Statistical analysis

The differences between the BDF and initial IMRT plans, the differences between the BDF and DCS IMRT plans and the differences between the BDF IMRT plans and VMAT plans were evaluated using two-sided Wilcoxon signed rank test, in which p -value < 0.05 was considered to be significant. The data analysis was performed using SPSS v. 19 software (SPSS Inc., Chicago, IL).

RESULTS

All of the plans met the requirements of the specified planning constraints. For each plan, the $D_{95\%}$ of PTV70 was equal to 70 Gy and the $D_{95\%}$ of PTV60 was ≥ 60 Gy, and the maximum dose of PTV70 was much less than 77 Gy. The doses of all the OARs were limited to the tolerable levels.

Target coverage, homogeneity, conformity

As summarized in Table 4, the BDF IMRT plans provided significantly lower $D_{2\%}$ (by $2.2 \pm 1.2\%$ and $1.5 \pm 0.7\%$, respectively) and higher $D_{98\%}$ (by $0.3 \pm 0.2\%$ and $0.1 \pm 0.2\%$, respectively) of PTV70 than did the initial IMRT and DCS IMRT plans. The BDF IMRT plans also provided lower $D_{2\%}$ of PTV60_only (by $2.6 \pm 1.4\%$) and comparable $D_{98\%}$ of PTV60

Table 3. Evaluation indicators for the treatment plans of advanced laryngeal cancer

Structure	Evaluation indicator (s)
PTV70	$D_{2\%}$, $D_{98\%}$, $D_{50\%}$, $D_{95\%}$, HI, CI
PTV60	$D_{98\%}$, $D_{50\%}$, $D_{95\%}$, CI
PTV60_only	$D_{2\%}$, HI
Spinal cord	D_{max} , D_{mean}
PRV spinal cord	D_{max} , D_{mean}
Brainstem	D_{max} , D_{mean}
PRV brainstem	D_{max} , D_{mean}
Thyroid	D_{mean} , V_{30Gy} , V_{50Gy}
Carotid	D_{mean} , V_{35Gy} , V_{50Gy} , V_{63Gy}
Oral cavity	D_{mean}
Parotid glands	D_{mean} , V_{30Gy}
Normal tissue	D_{mean}

CI, conformity index; D_{max} , maximum dose; D_{mean} , mean dose; $D_{x\%}$, the dose that is reached or exceeded in $x\%$ of the volume; HI, homogeneity index; PRV, planning organ-at-risk volume; PTV, planning target volume; PTV60, planning target volume prescribed at 60 Gy; PTV70, PTV prescribed at 70 Gy; V_{xGy} , the % volume receiving at least x Gy dose.

than did the initial IMRT plans and provided comparable $D_{2\%}$ of PTV60_only and $D_{98\%}$ of PTV60 than did the DCS IMRT plans. When compared with VMAT plans, the BDF IMRT plans provided lower $D_{2\%}$ (by $0.7 \pm 0.8\%$) and comparable $D_{98\%}$ of PTV70, as well as comparable $D_{2\%}$ of PTV60_only and higher $D_{98\%}$ of PTV60 (by $0.3 \pm 0.5\%$). With regards to the HI, the BDF IMRT plans were significantly better than the initial IMRT, DCS IMRT and VMAT plans in PTV70 by $37.3 \pm 11.3\%$, $29.2 \pm 11.7\%$ and $13.2 \pm 15.9\%$, respectively, whereas the BDF IMRT plans were significantly better than the initial IMRT plans in PTV60_only by $18.6 \pm 8.4\%$. With regards to the CI, BDF IMRT plans were significantly better than the initial IMRT and DCS IMRT plans in both PTV70 (by $11.2 \pm 11.3\%$ and $9.7 \pm 6.6\%$, respectively) and PTV60 (by $4.2 \pm 1.9\%$ and $4.1 \pm 2.2\%$, respectively) but were comparable to the VMAT plans. Figures 1 and 2 show the dose distributions and the PTV DVHs of the four plans in one case. In the DVHs, the PTV70 curve of BDF IMRT plan was the steepest, indicating the most homogeneous dose distribution in PTV70, while the PTV60 curve of BDF IMRT plan was similar to those of DCS IMRT plan and VMAT plan, but slightly steeper than that of the initial IMRT plan. Figure 3 shows the mean HI and CI of PTVs in the four plans.

Organ-at-risk sparing

As shown in Table 5, the BDF technique tended to reduce most of the dose–volume values of the OARs compared with the initial IMRT and DCS IMRT plans. All the comparisons with the initial IMRT and DCS IMRT plans were statistically significant, except for the D_{mean} ($p = 0.158$), V_{30Gy} ($p = 0.059$) of the right parotid between BDF and the initial IMRT plans, and the V_{63Gy} of the IMRT carotid ($p = 0.060$) between BDF and DCS IMRT plans.

Table 4. Dosimetric parameters of the targets in the initial-, base dose function (BDF)-, dose-controlling structure (DCS)-based intensity-modulated radiotherapy (IMRT) plans and volumetric modulated arc therapy (VMAT) plans

Parameter	Initial IMRT	BDF IMRT	DCS IMRT	VMAT	<i>p</i> -value		
					BDF IMRT vs initial IMRT	BDF IMRT vs DCS IMRT	BDF IMRT vs VMAT
PTV70							
$D_{2\%}$ (cGy)	7397 ± 104	7231 ± 48	7342 ± 41	7281 ± 79	0.002	0.002	0.012
$D_{98\%}$ (cGy)	6927 ± 28	6945 ± 15	6935 ± 25	6941 ± 21	0.004	0.041	0.239
$D_{50\%}$ (cGy)	7201 ± 32	7135 ± 29	7185 ± 28	7161 ± 45	0.002	0.003	0.015
$D_{95\%}$ (cGy)	7000 ± 0	7000 ± 0	7000 ± 0	7000 ± 0	1.000	1.000	1.000
HI	0.065 ± 0.015	0.040 ± 0.008	0.057 ± 0.007	0.047 ± 0.013	0.002	0.002	0.019
CI	0.763 ± 0.088	0.841 ± 0.065	0.768 ± 0.055	0.836 ± 0.039	0.008	0.002	0.530
PTV60							
$D_{98\%}$ (cGy)	5954 ± 99	5943 ± 22	5939 ± 72	5923 ± 27	1.000	0.695	0.028
$D_{50\%}$ (cGy)	6467 ± 79	6353 ± 51	6327 ± 54	6377 ± 46	0.002	0.136	0.071
$D_{95\%}$ (cGy)	6088 ± 74	6031 ± 17	6049 ± 54	6023 ± 14	0.023	0.638	0.347
CI	0.855 ± 0.028	0.890 ± 0.026	0.856 ± 0.027	0.887 ± 0.029	0.002	0.002	0.388
PTV60_only							
$D_{2\%}$ (cGy)	6745 ± 138	6570 ± 84	6532 ± 121	6534 ± 58	0.002	0.071	0.136
HI	0.131 ± 0.030	0.105 ± 0.016	0.101 ± 0.027	0.102 ± 0.012	0.002	0.099	0.480

CI, conformity index; $D_{x\%}$, the dose that is reached or exceeded in $x\%$ of the volume; HI, homogeneity index; PTV, planning target volume; PTV60, PTV prescribed at 60 Gy; PTV70, PTV prescribed at 70 Gy.

The $D_{\max}$ and D_{mean} delivered to the spinal cord in BDF IMRT plans were $3.0 \pm 1.7\%/3.8 \pm 1.4\%$ lower than those of the initial IMRT plans, respectively, and $3.6 \pm 2.3\%/4.0 \pm 1.9\%$ lower than those of DCS IMRT plans, respectively. The $D_{\max}$ and D_{mean} to the PRV spinal cord were $3.0 \pm 1.9\%/4.1 \pm 1.5\%$ lower than those of the initial IMRT plans, respectively, and $4.1 \pm 1.7\%/4.2 \pm 1.9\%$ lower than those of DCS IMRT plans, respectively. The $D_{\max}$ and D_{mean} to the brainstem were $5.4 \pm 4.9\%/4.7 \pm 3.5\%$ lower than those of the initial IMRT plans, respectively, and $5.9 \pm 5.2\%/4.0 \pm 3.6\%$ lower than those of DCS IMRT plans, respectively. The $D_{\max}$ and D_{mean} to the PRV brainstem were $5.7 \pm 5.7\%/5.2 \pm 4.1\%$ lower than those of the initial IMRT plans, respectively, and $6.6 \pm 6.1\%/4.8 \pm 4.3\%$ lower than those of DCS IMRT plans, respectively. For the thyroid, the D_{mean} , $V_{30\text{Gy}}$ and $V_{50\text{Gy}}$ were reduced by $2.9 \pm 2.0\%/1.0 \pm 1.4\%/2.5 \pm 2.5\%$, respectively, compared with the initial IMRT plans and by $2.2 \pm 1.9\%/0.9 \pm 1.3\%/2.5 \pm 2.1\%$, respectively, compared with DCS IMRT plans. For the carotid, the D_{mean} , $V_{35\text{Gy}}$, $V_{50\text{Gy}}$ and $V_{63\text{Gy}}$ were reduced by $2.6 \pm 1.2\%/0.2 \pm 0.3\%/0.4 \pm 0.4\%/22.9 \pm 12.0\%$, respectively, compared with the initial IMRT plans and by $1.5 \pm 1.0\%/0.2 \pm 0.3\%/0.4 \pm 0.5\%/9.2 \pm 11.0\%$, respectively, compared with DCS IMRT plans.

With regard to the oral cavity, the D_{mean} was $4.6 \pm 2.8\%/4.5 \pm 2.3\%$ lower than those of the initial IMRT and DCS IMRT plans, respectively. Moreover, the D_{mean} and $V_{30\text{Gy}}$ of the left parotid were $3.4 \pm 3.3\%/0.9 \pm 1.2\%$ lower than those of the initial IMRT plans, respectively, and $3.5 \pm 2.9\%/1.4 \pm 1.4\%$ lower than those of DCS IMRT plans, respectively, while the D_{mean} and $V_{30\text{Gy}}$ of the right parotid were $2.7 \pm 4.6\%/1.0 \pm 1.6\%$ lower than those of the initial IMRT plans, respectively, and $3.8 \pm 3.5\%/1.8 \pm 1.6\%$ lower than those of DCS IMRT plans, respectively. With respect to the normal tissue, the D_{mean} was reduced by $4.0 \pm 1.8\%/3.6 \pm 2.1\%$ compared with the initial IMRT and DCS IMRT plans, respectively.

When compared with the VMAT plans, BDF IMRT plans demonstrated no significant differences in most of the OARs. However, the BDF IMRT plans showed a significantly higher $D_{\max}$ of the brainstem by $16.2 \pm 24.5\%$, less $V_{63\text{Gy}}$ of the carotid by $15.0 \pm 19.4\%$ and less $V_{30\text{Gy}}$ of the left parotid by $1.2 \pm 1.5\%$.

Figure 1. Dose distributions of the initial-, base dose function (BDF)-, dose-controlling structure (DCS)-based intensity-modulated radiotherapy (IMRT) plans and volumetric modulated arc therapy (VMAT) plans in one case. PTV, planning target volume; PTV60, PTV prescribed at 60 Gy; PTV70, PTV prescribed at 70 Gy.

One example of the DVHs for the OARs of the four plans is shown in Figure 4. It appeared that most of the DVH curves of the OARs of BDF IMRT plans shifted slightly to the left, indicating lower doses received.

Planning time and monitor units

As shown in Table 6, the BDF IMRT plans required less planning time than did the DCS IMRT plans by $21.3 \pm 9.3\%$ and VMAT plans by $74.6 \pm 3.3\%$. However, the MUs per fraction of BDF IMRT plans were $6.6 \pm 4.2\%$ and $201.3 \pm 81.8\%$ more than those of the initial IMRT and VMAT plans, respectively, but were comparable to those of the DCS IMRT plans ($p = 0.308$).

DISCUSSION

The main advantage of radiotherapy for advanced laryngeal cancer lies in organ preservation,^{1,21–23} and IMRT plays an important role in this situation.^{24,25} To achieve a better therapeutic ratio, it is necessary to further develop the IMRT technique. This study demonstrated that the proposed BDF optimization technique has the ability to further improve the target coverage and further spare approximately 1–7% of the dose delivered to the OARs. Additionally, the BDF technique could achieve similar dosimetric superiority as the VMAT delivery technique.

The main advantage of the BDF technique lies in its ability to improve the dose homogeneity. The improved homogeneous dose distribution may have a potential clinical benefit, because the PTVs in advanced laryngeal cancer typically encompass tissues, such as the mucosa and submucosal tissue, carotid²⁶ and bone, all of which may undergo severe acute reactions or late complications if significant overdose occurs in these areas.²⁷ Furthermore, as a large proportion of carotid arteries were included in the PTVs, the high dose of hot spot may be delivered to carotid arteries, and this may result in radiation-induced vascular side effects, which are serious and may be life threatening, such as, stroke,²⁸ carotid intima medial thickness increasing,^{29,30} vessel wall abnormality²⁶ and other cerebrovascular events.^{31–33} This study showed that the BDF technique could largely reduce the V_{63Gy} by approximately 23%, 9% and 15% compared with the initial IMRT, DCS IMRT and VMAT plans. This efficacy may reduce the risk of carotid disease.

In terms of target conformity and neighbouring-OAR sparing, the BDF technique showed satisfactory superiority, except when compared with the VMAT plans. The BDF technique provided better conformity, which could better spare the surrounding healthy tissue, and it also significantly reduced the dose delivered to most of the surrounding OARs, including the (PRV) spinal

Figure 2. Dose-volume histograms for planning target volume prescribed at 70 Gy (PTV70) and PTV prescribed at 60 Gy (PTV60) of the initial-, base dose function (BDF)-, dose-controlling structure (DCS)-based intensity-modulated radiotherapy (IMRT) plans and volumetric modulated arc therapy (VMAT) plans in one case.

cord, (PRV) brainstem, thyroid, oral cavity, parotids and normal tissue.

The BDF technique could reduce the maximum dose and mean dose delivered to the (PRV) spinal cord and (PRV) brainstem by approximately 1–2 Gy in IMRT plans. The reductions of doses to the spinal cord and brainstem were intended to reduce the risks of radiation myelitis and brainstem necrosis.³⁴ Reductions of the doses to the spinal cord or brainstem could be beneficial to patients with laryngeal cancer with recurrent or locally persistent diseases, especially when a second course of treatment is necessary.³⁵

The thyroid is a concern in IMRT because hypothyroidism has been reported to occur in between 6% and 48% of cases.^{36–39} Akgun et al⁴⁰ and Cella et al⁴¹ recommended the thyroid volume receiving ≥ 30 Gy ($V_{30\text{Gy}}$) as a possible predictor of hypothyroidism. This study showed that the BDF technique could reduce the $V_{30\text{Gy}}$, $V_{50\text{Gy}}$ ⁴² and mean dose⁴⁰ delivered to the thyroid in IMRT plans. As such, it could have a meaningful impact in reducing the incidence of hypothyroidism after radiotherapy.

A noteworthy advantage of IMRT in the treatment of head and neck cancer appears to be the ability to preserve the parotid function.^{43,44} Our findings demonstrated that the BDF technique could reduce the mean dose delivered to parotid glands by approximately 1–2 Gy, as well as the $V_{30\text{Gy}}$.^{45,46} This may have some clinical benefits because many studies have found that the mean dose to parotid gland is closely related to the function of the parotid gland. Hsiung et al⁴⁷ found that the correlation between the mean parotid dose and the percentage decrease of parotid maximal excretion ratio (MER) at 9 months post-IMRT (dMER) was statically significant. Moreover, xerostomia resulting from parotid gland dysfunction contributes to dental decay, oral infections, fissures and dysphagia and is one of the most prevalent factors affecting the quality of life after radiotherapy.²⁷ Accordingly, the incidence of xerostomia may be reduced by the BDF technique.³

Furthermore, the BDF technique could also reduce the mean dose to the oral cavity by approximately 1 Gy. This reduction may reduce the risk of radiation-induced oral mucositis, of which the main modifying factor is the radiation dose received by the oral cavity.⁴⁸ Oral mucositis often interferes with the patient's quality of life and nutrition, as a result of pain and dysphagia. Mucositis also increases the risk of systemic infections, owing to disrupted mucosal barriers, and as a result, the treatment may need to be suspended, thus negatively impacting tumour control.⁴⁹

Figure 3. Mean homogeneity index and mean conformity index for planning target volume prescribed at 70 Gy (PTV70) and PTV prescribed at 60 Gy (PTV60) (PTV60_only) in the initial, base dose function (BDF)- and dose-controlling structure (DCS)-based intensity-modulated radiotherapy (IMRT) plans, and volumetric modulated arc therapy (VMAT) plans.

Table 5. Dosimetric parameters of the organs at risk in the initial, base dose function (BDF)-, dose-controlling structure (DCS)-based intensity-modulated radiotherapy (IMRT) plans and volumetric modulated arc therapy (VMAT) plans

Parameter	Initial IMRT	BDF IMRT	DCS IMRT	VMAT	<i>p</i> -value		
					BDF IMRT <i>vs</i> initial IMRT	BDF IMRT <i>vs</i> DCS IMRT	BDF IMRT <i>vs</i> VMAT
Spinal cord							
$D_{\max}$ (cGy)	3992 ± 137	3873 ± 148	4019 ± 124	3876 ± 106	0.003	0.002	0.875
D_{mean} (cGy)	2792 ± 493	2683 ± 459	2797 ± 483	2728 ± 437	0.002	0.002	0.182
PRV spinal cord							
$D_{\max}$ (cGy)	4523 ± 194	4384 ± 182	4570 ± 176	4417 ± 166	0.002	0.002	0.374
D_{mean} (cGy)	2793 ± 459	2675 ± 419	2794 ± 440	2728 ± 407	0.002	0.002	0.084
Brainstem							
$D_{\max}$ (cGy)	2338 ± 1318	2238 ± 1302	2346 ± 1308	1965 ± 1245	0.028	0.008	0.010
D_{mean} (cGy)	560 ± 695	540 ± 675	550 ± 671	542 ± 602	0.004	0.012	0.308
PRV brainstem							
$D_{\max}$ (cGy)	3306 ± 1183	3145 ± 1214	3339 ± 1196	2959 ± 1140	0.012	0.012	0.071
D_{mean} (cGy)	656 ± 656	630 ± 642	647 ± 635	633 ± 598	0.004	0.006	0.480
Thyroid							
D_{mean} (cGy)	5322 ± 1195	5180 ± 1213	5287 ± 1190	5264 ± 1321	0.003	0.005	0.099
$V_{30\text{Gy}}$ (%)	85.8 ± 20.8	84.8 ± 21.5	85.7 ± 20.7	85.0 ± 23.2	0.018	0.018	1.000
$V_{50\text{Gy}}$ (%)	73.8 ± 24.5	71.3 ± 25.0	73.8 ± 24.5	74.1 ± 26.2	0.008	0.005	0.074
Carotid							
D_{mean} (cGy)	5993 ± 880	5842 ± 870	5930 ± 867	5891 ± 917	0.002	0.004	0.084
$V_{35\text{Gy}}$ (%)	92.1 ± 14.0	91.9 ± 14.2	92.1 ± 14.0	91.6 ± 14.9	0.028	0.028	0.917
$V_{50\text{Gy}}$ (%)	90.8 ± 14.9	90.3 ± 15.2	90.8 ± 14.9	90.3 ± 15.5	0.017	0.012	0.674
$V_{63\text{Gy}}$ (%)	60.6 ± 18.2	37.7 ± 24.3	46.9 ± 17.9	52.7 ± 20.8	0.002	0.060	0.019
Oral cavity							
D_{mean} (cGy)	2320 ± 862	2225 ± 860	2320 ± 875	2274 ± 931	0.002	0.002	0.530
Left parotid							
D_{mean} (cGy)	2518 ± 1366	2461 ± 1362	2528 ± 1381	2509 ± 1356	0.008	0.004	0.117
$V_{30\text{Gy}}$ (%)	36.3 ± 22.3	35.4 ± 22.1	36.8 ± 22.7	36.6 ± 22.3	0.009	0.005	0.008
Right parotid							
D_{mean} (cGy)	2620 ± 1246	2570 ± 1252	2656 ± 1271	2546 ± 1235	0.158	0.006	0.480
$V_{30\text{Gy}}$ (%)	37.7 ± 20.0	36.8 ± 20.1	38.6 ± 20.6	37.0 ± 20.3	0.059	0.003	0.875

(Continued)

Table 5. (Continued)

Parameter	Initial IMRT	BDF IMRT	DCS IMRT	VMAT	<i>p</i> -value		
					BDF IMRT <i>vs</i> initial IMRT	BDF IMRT <i>vs</i> DCS IMRT	BDF IMRT <i>vs</i> VMAT
Normal tissue							
D_{mean} (cGy)	1205 ± 270	1159 ± 268	1199 ± 264	1171 ± 287	0.002	0.003	0.308

D_{max} , maximum dose; D_{mean} , mean dose; PRV, planning organ-at-risk volume; $V_{x\text{Gy}}$, the % volume receiving at least x Gy dose.

Another advantage of BDF optimization technique lies in its planning efficiency. The planning time was reduced by approximately 21% by the BDF technique, compared with the DCS technique. The DCS technique is always time consuming owing to the contouring of dose-controlling structures and the requirement of multiple reoptimizations, while the BDF technique only requires modifying one parameter (the number of fractions) and one or two reoptimizations. BDF IMRT plans consume approximately 75% less time than do VMAT plans, in which the

optimization using PRO and the final dose calculation using AAA currently require a lot of time. The improvement of planning efficiency is thus beneficial, especially in daily busy workflows.

However, the BDF technique increases the MUs slightly. Increasing MUs of all the IMRT plans by approximately twice more than those of VMAT plans would increase the total body exposure owing to leakage radiation and would therefore increase the risk of secondary cancers.⁵⁰

Figure 4. Dose-volume histograms for [planning organ-at-risk volume (PRV)] spinal cord, (PRV) brainstem, thyroid, carotid, oral cavity, parotids and normal tissue of the initial, base dose function (BDF)-, dose-controlling structure (DCS)-based intensity-modulated radiotherapy (IMRT) plans and volumetric modulated arc therapy (VMAT) plans in one case.

Table 6. Planning time and monitor units (MUs) per fraction of the initial, base dose function (BDF)-, dose-controlling structure (DCS)-based intensity-modulated radiotherapy (IMRT) plans and volumetric modulated arc therapy (VMAT) plans

Parameter	Initial IMRT	BDF IMRT	DCS IMRT	VMAT	p-value		
					BDF IMRT vs initial IMRT	BDF IMRT vs DCS IMRT	BDF IMRT vs VMAT
Planning time (min)	NA	37 ± 4	48 ± 9	146 ± 18	NA	0.002	0.002
MUs per fraction	1556 ± 487	1656 ± 513	1599 ± 426	548 ± 58	0.006	0.308	0.002

NA, not applicable.

Conventionally, the base dose function in Eclipse is employed to optimize a top dose plan considering its base dose plan in order to obtain an optimal plan sum in the optimizer but not in the deliverable pattern with final dose distribution. However, in this technique, the base dose function was used in a different way, as it was used to achieve an optimal top dose plan in the deliverable pattern but not plan sum in the optimizer. After an optimal plan was achieved in the optimizer, the final dose calculation would result in a sub-optimal plan owing to the OCE. In the BDF technique, the base dose function was used to compensate for the OCE. If an OCE produced a hot spot in the final dose distribution, the top dose plan would produce a cold spot in the same location in the optimizer, and after calculating the final dose of the top dose plan, by the effect of OCE again, the dose of cold spot would achieve the desired level. The OCE is systematic, as it originates from three major sources, as described by Dogan et al.¹² The sources are tissue heterogeneity, multileaf collimator (MLC) modulator and optimization algorithm. Many investigators have studied possible solutions to OCE. Jones and Williams⁵¹ focused on the direct aperture optimization (DAO) technique, which can eliminate the error from MLC modulator, because the shapes and beam weighting of MLC apertures are considered in the optimizer. Unfortunately, this technique is not available in treatment planning systems with non-DAO optimization, such as Eclipse v. 10.0. Verbakel et al⁵² optimized IMRT plans of lung cancer by dividing PTV into regions containing lung tissue and regions excluding lung tissue, and the optimization objectives of the PTV regions containing lung tissue were set to a 2- to 4-Gy higher doses to compensate for the error from tissue heterogeneity. However, this approach only minimized one source of OCE, and it was complicated to divide

the two PTVs if applied to advanced laryngeal cancer. Zacarias and Mills⁵³ also employed the base dose function to solve the OCE, but this approach increased the planning time and planning steps because of the requirements of a recursive process and the combination of a base dose plan and some dose correction plans. Because this approach was complicated, it is not efficient enough, especially in busy daily routine workflows. On the contrary, the introduced optimization technique is much simpler and more efficient.

This study is the first to report the evaluation of the BDF optimization technique applied to advanced laryngeal cancer. However, there is a limitation in this study. We only investigated the dosimetric characteristics of the recommended technique and whether it can bring real benefits to patients is still unknown. Thus, further studies may need to be performed to evaluate its clinical outcomes by follow-up.

CONCLUSIONS

The BDF optimization technique not only improves the dose conformity and homogeneity in the target but also spares the OARs. Accordingly, it may improve the therapeutic ratio for the IMRT of advanced laryngeal cancer. Additionally, it can achieve similar dosimetric results to VMAT. Furthermore, it is very simple and can improve the IMRT planning efficiency. Consequently, the proposed BDF optimization technique should be introduced into the clinical daily routine practice for the radiotherapy of advanced laryngeal cancer.

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