

Original Research Article

Optimizing laryngeal sparing with intensity modulated radiotherapy or volumetric modulated arc therapy for unilateral tonsil cancer



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ABSTRACT

Background and purpose: Minimizing radiation dose exposure to nearby organs is key to limiting clinical toxicities associated with radiotherapy. Several treatment modalities such as split- or whole-field intensity-modulated radiotherapy (SF-IMRT, WF-IMRT) and volumetric modulated arc therapy (VMAT) are being used to treat tonsillar cancer patients with unilateral neck radiotherapy. Herein, we provide a modern dosimetric comparison of all three techniques.

Materials and methods: Forty patients with tonsillar cancer treated with definitive, ipsilateral neck SF-IMRT were evaluated. Each patient was re-planned with WF-IMRT and VMAT techniques, and doses to selected organs-at-risk (OARs) including the larynx, esophagus, and brainstem were compared.

Results: No significant differences in target coverage existed between plans; however, the heterogeneity index improved using WF-IMRT and VMAT relative to SF-IMRT. Compared to SF-IMRT, WF-IMRT and VMAT plans had significantly lower mean doses to the supraglottic larynx (31 Gy, 18.5 Gy, 17 Gy; $p < 0.01$), the MDACC-defined larynx (13.4 Gy, 10.5 Gy, 9.8 Gy; $p < 0.01$), and RTOG-defined larynx (15.8 Gy, 12.1 Gy, 11.1 Gy; $p < 0.01$), respectively. Mean esophageal dose was lowest with SF-IMRT over WF-IMRT and VMAT (5.9 Gy, 12.2 Gy, 11.1 Gy; $p < 0.01$) but only in the absence of lower neck disease. On average, VMAT plans had shorter treatment times and required less monitor units than both SF-IMRT and WF-IMRT.

Conclusion: In the setting of unilateral neck radiotherapy, WF-IMRT and VMAT plans can be optimized to significantly improve dose sparing of critical structures compared to SF-IMRT. VMAT offers additional advantages of shorter treatment times and fewer required monitor units.

1. Introduction

Head and neck cancer (HNC) is a prevalent oncologic diagnosis worldwide with over 650,000 cases and 330,000 deaths annually [1,2]. For patients presenting with early stage oropharyngeal cancer, the National Comprehensive Cancer Network recommends management through either upfront surgery or definitive radiotherapy (RT) [3]. While the latter treatment option allows for potential organ preservation, it can often be associated with debilitating acute and long-term toxicities such as dysphagia and xerostomia [4,5].

Continued advancements in the treatment planning and delivery aspects of radiation therapy have led to improvements in dose sparing

of normal head and neck structures such as the parotids, spinal cord, and larynx, otherwise referred to as organs at risk (OAR). The traditional three-field approach consisting of two opposed lateral beams to treat the primary tumor matched to an anteroposterior (AP) beam to target the lower neck has largely been replaced by more modern techniques such as intensity modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT). IMRT, which uses non-uniform fluence over multiple beam angle arrangements, has been shown to optimize target conformity, OAR sparing, and dose distribution when treating several types of cancers [6–9]. IMRT can be delivered as whole field (WF-IMRT) to the head and neck or as a split field (SF-IMRT) plan using a mono-isocentric beam-split matching technique

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[10–12]. VMAT, a variation of IMRT that delivers radiation via intensity modulated beam arcs, can provide equivalent or better dose conformity with shorter treatment times than static field IMRT alone [13,14]. However, concerns regarding unnecessary higher doses to the larynx with WF-IMRT or VMAT continue to make SF-IMRT a preferred treatment modality.

Most of the current literature comparing contemporary radiotherapy techniques used for treating HNCs is restricted to the evaluation of only two methods [15,16]. Moreover, the majority of these studies involve full neck radiotherapy, leaving it unclear if conclusions drawn therein are applicable in the setting of unilateral neck radiotherapy. Patients with well-lateralized tonsillar cancer can achieve excellent locoregional control after ipsilateral radiotherapy or chemoradiotherapy. To our knowledge, limited data exists regarding the optimal RT technique for this subgroup of HNC patients. The objective of this dosimetric study was to compare SF-IMRT, WF-IMRT, and VMAT planning for tonsillar cancer patients requiring unilateral neck radiotherapy.

2. Materials and methods

2.1. Patient population

A total of 40 patients with pathologically confirmed squamous cell carcinoma of the tonsil were included in this study. All patients were treated with definitive ipsilateral neck radiotherapy or chemoradiotherapy using a SF-IMRT technique at MD Anderson Cancer Center (MDACC) from 2008 to 2014. Reasons for exclusion included tumor extension into laryngeal structures, a diagnosis other than tonsillar cancer and receipt of bilateral neck radiotherapy or surgery. Detailed patient and tumor characteristics are summarized in [Supplemental Table 1](#). The median patient age was 53 years (range, 34–83 years) and the majority were males ($n = 30$, 75%). Clinical stage distribution based on the American Joint Committee on Cancer 7th edition [3] ranged from I to IVA with 65% of patients presenting with stage IVA disease. Treatment laterality was evenly split among patients and 54% exhibited level III neck disease ($n = 14$). The median prescribed dose to the high-risk PTV was 66 Gy (range 63–70 Gy).

2.2. Radiation treatment planning specifications

For all treatments, patients were placed in the supine position and immobilized using a thermoplastic mask that included the head, neck and shoulders. A treatment planning CT scan with 0.3 cm slice thickness was acquired for each patient in the treating position. Target volumes were contoured on all planning CT slices and included the clinical target volumes (CTV), which encompassed the gross primary tumor and involved lymphatic drainage with margin, and the planning target volumes (PTV), which was the CTV with a uniform 5 mm expansion to account for motion and setup uncertainties. The spinal cord, brainstem, esophagus, and laryngeal substructures including the supraglottic and subglottic larynx, and the arytenoids were all contoured as OARs. Two larynx definitions were contoured and compared in this study: the MDACC larynx, as bounded by the superior and inferior aspects of the thyroid cartilage, and the RTOG larynx, as defined by RTOG protocol 1016 guidelines [17]. The RTOG larynx volume extends from the inferior aspect of the hyoid bone inferiorly to the cricoid cartilage with inclusion of the infrahyoid but not suprahoid epiglottis. We defined the supraglottic and subglottic larynx as the volumes of the RTOG larynx extending superiorly and inferiorly, respectively, beyond the borders of the MDACC larynx. Since dysphagia after radiotherapy can be, in part, attributable to dose exposure to the surrounding constrictor muscles and cricopharyngeal muscle [18], the cricopharyngeal muscle was also delineated in each patient plan as an OAR to compare doses by treatment modality.

Radiation treatment plans were generated using the Pinnacle Treatment Planning System (Philips Healthcare, Andover, MA) for 6-

MV beam energy Varian linear accelerator (Varian Medical Systems, Palo Alto, CA). For conventional SF-IMRT planning, the isocenter was placed approximately 1–1.5 cm superior to the level of the arytenoids. Superior step and shoot IMRT fields were half-beam blocked and matched to an anterior beam set to a dose of 50 Gy in 25 fractions with a larynx and/or full midline block. Nodes that were involved below the level of the match line were boosted with either photon and/or electron beams. For WF-IMRT and VMAT techniques, coplanar beam or arc arrangements were selected. The addition of anterior fields with sagittal MLCs or a sagittal anterior arc to simulate the anteroposterior low-neck field used in SF-IMRT was investigated. However, these additions resulted in minimal optimization of RT plans in the unilateral neck setting and were therefore not used. The planning goals for WF-IMRT and VMAT were the same as SF-IMRT, which were to achieve > 98% coverage for clinical target volumes (PTVs) while meeting or exceeding OAR dose constraints of SF-IMRT plans. Additional constraints added to WF-IMRT and VMAT during plan optimization included the larynx, esophagus, arytenoids and cricopharyngeus. The goal was to limit the dose to these structures to as low as possible without compromising tumor coverage as dictated by initial SF-IMRT planning directives.

2.3. Studied parameters and statistical analysis

Target coverage (defined as the percentage of PTV covered by the prescription dose), dose sparing of OARs, and treatment specifications including total delivery time and number of monitor units delivered between SF-IMRT, WF-IMRT, and VMAT plans were compared. Quality metrics such as conformity index (CI) and heterogeneity index (HI) were also evaluated. The CI, which can be used as part of the planning optimization procedure, was defined as the quotient of the prescription isodose volume divided by the PTV (i.e. $CI = \text{treated volume}/\text{PTV}$) while the HI, which evaluates dose gradients within a PTV, was defined as the ratio of the highest dose received by 5% of the PTV to the lowest dose received by 95% of the PTV. All patient plans were optimized. Comparison of the metrics between treatment planning techniques was performed using the Tukey-Kramer method, a post-hoc test which allows for comparison of all possible pairs of means. Additional

Table 1

Dosimetric comparison of SF-IMRT, WF-IMRT, and VMAT planning techniques.

Parameter	SF-IMRT	WF-IMRT	VMAT
Supraglottic larynx (Dmean)	31 ± 8.7 Gy	18.5 ± 5.9 Gy**	17 ± 5.7 Gy**
Subglottic larynx (Dmean)	10.2 ± 5.2 Gy	13.3 ± 4 Gy*	12.1 ± 3.5 Gy
MDACC larynx (Dmean)	13.4 ± 5.4 Gy	10.5 ± 2.5 Gy**	9.8 ± 2.2 Gy**
RTOG larynx (Dmean)	15.8 ± 4.8 Gy	12.1 ± 2.9 Gy**	11.1 ± 2.7 Gy**
Cricopharyngeus (Dmean)	8.7 ± 4.1 Gy	11.3 ± 4.4 Gy*	10.5 ± 4.1 Gy
Arytenoids (Dmean)	8 ± 4.4 Gy	7.9 ± 1.7 Gy	7.5 ± 1.6 Gy
Esophagus (Dmean)	5.9 ± 5.2 Gy	12.2 ± 4.1 Gy**	11.1 ± 4.1 Gy**
Cord (Dmean)	12.7 ± 3.6 Gy	15 ± 3.6 Gy*	13.5 ± 4 Gy
Cord (Dmax)	39.2 ± 4.1 Gy	34.8 ± 6.2 Gy**	32.8 ± 7.2 Gy**
Brainstem (Dmean)	14.7 ± 4.6 Gy	10.7 ± 3.9 Gy**	9.5 ± 4 Gy**
Brainstem (Dmax)	41.6 ± 4.7 Gy	33.3 ± 8.5 Gy**	29.5 ± 8.4 Gy**
PTV coverage, %	97.5%	98.8%	98.7%
V105	6.9%	4.2%	4.1%
Conformity Index	0.59 ± 0.1	0.64 ± 0.1	0.65 ± 0.1
Heterogeneity Index	1.37 ± 0.7	1.10 ± 0.3*	1.07 ± 0.3*
Total monitor units (MU)	831 ± 92	614 ± 45*	502 ± 39** ^a
Delivery time (minutes)	8 ± 1.2	7.1 ± 0.9**	1.5 ± 0.3** ^a

Abbreviations: Dmax, maximum dose; Dmean, mean dose; Gy, Gray; SF-IMRT, Split field intensity modulated radiation therapy; PTV, planning target volume; WF-IMRT, whole field intensity modulated radiation therapy; V105, volume receiving 105% of the prescribed dose; VMAT, volumetric modulated arc therapy. Mean and max doses are reported as dose ± standard deviation (Gy).

* $p < 0.05$ compared to SF-IMRT.

** $p < 0.01$ compared to SF-IMRT.

^a $p < 0.01$ compared to WF-IMRT.

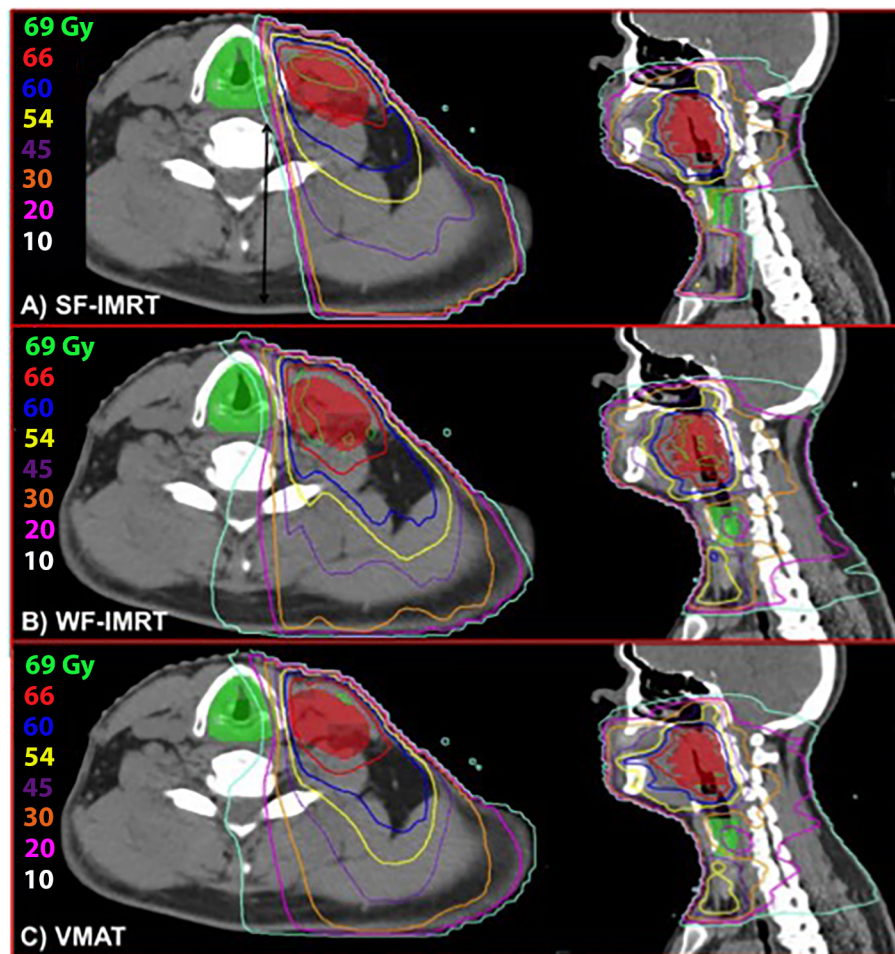


Fig. 1. Axial and sagittal planning CT images depicting isodose distributions for SF-IMRT, WF-IMRT, and VMAT plans created for one patient with left-sided disease. The black arrow in A references the sectioning position for the sagittal plane images. Abbreviations: SF-IMRT, split field intensity modulated radiation therapy; WF-IMRT, whole field IMRT; VMAT, volumetric modulated arc therapy. Dose scale is in Gray (Gy).

comparisons of relevant dosimetric parameters were performed after stratifying the cohort according to neck laterality or the presence of level III (lower neck) disease. Results were reported as mean \pm standard deviations, and a $p < 0.05$ was considered statistically significant. All analyses were performed using the JMP Pro 12 software package (SAS, Cary, NC).

3. Results

3.1. Target dose coverage, conformity, heterogeneity

The target coverage was $\geq 97.5\%$ for all three planning techniques and slightly higher for WF-IMRT ($p < 0.05$) and VMAT (Table 1). The calculated mean \pm standard deviation PTV volume receiving $> 105\%$ of the prescribed dose was $6.9\% \pm 11.3\%$ with SF-IMRT, $4.2\% \pm 5.5\%$ with WF-IMRT, and $4.1\% \pm 5.7\%$ with VMAT ($p > 0.05$). WF-IMRT and VMAT produced plans with comparable conformity index measures as SF-IMRT; however, the heterogeneity index was significantly improved at 1.1 ± 0.3 with WF-IMRT and 1.1 ± 0.3 with VMAT compared to 1.4 ± 0.7 with SF-IMRT. Fig. 1 shows representative isodose distributions for the SF-IMRT, WF-IMRT, and VMAT plans.

3.2. OAR sparing

With respect to the larynx, WF-IMRT and VMAT achieved significantly more dose sparing to both the MDACC and RTOG larynx

definitions relative to SF-IMRT. The mean dose to the RTOG larynx was 12.1 Gy and 11.1 Gy versus 15.8 Gy for WF-IMRT, VMAT, and SF-IMRT plans, respectively, while the mean dose to the MDACC larynx was 10.5 Gy and 9.8 Gy versus 13.4 Gy, respectively ($p < 0.01$). Compared to SF-IMRT, doses to the supraglottic larynx were reduced by 40% and 45% using WF-IMRT and VMAT ($p < 0.01$). There was no difference in dose sparing of the subglottic larynx or cricopharyngeal muscle between SF-IMRT and VMAT plans. However, dose to these laryngeal substructures was higher with WF-IMRT plans compared to SF-IMRT ($p < 0.05$). Fig. 2 shows comparative dose-volume histograms for the RTOG larynx, MDACC larynx, and supraglottic larynx contoured for one patient with left-sided disease. On average, the maximum dose to the spinal cord with SF-IMRT plans was 5.4 Gy higher than with WF-IMRT and 6.4 Gy higher than VMAT plans ($p < 0.01$). Similar dosimetric trends among planning techniques were found when evaluating the mean and max dose to the brainstem. Only the esophagus was more consistently spared using SF-IMRT planning with a mean dose of $5.9 \text{ Gy} \pm 5.2 \text{ Gy}$ compared to WF-IMRT ($12.2 \text{ Gy} \pm 4.1 \text{ Gy}$) and VMAT ($11.1 \text{ Gy} \pm 4.1 \text{ Gy}$; $p < 0.01$). The overall cohort comparisons of several dosimetric and treatment parameters among the three planning techniques are shown in Fig. 3.

3.3. Subgroup analysis

When stratifying the cohort based on level III neck disease, lower laryngeal doses largely persisted in the absence or presence of ipsilateral level III nodal burden among WF-IMRT and VMAT compared to

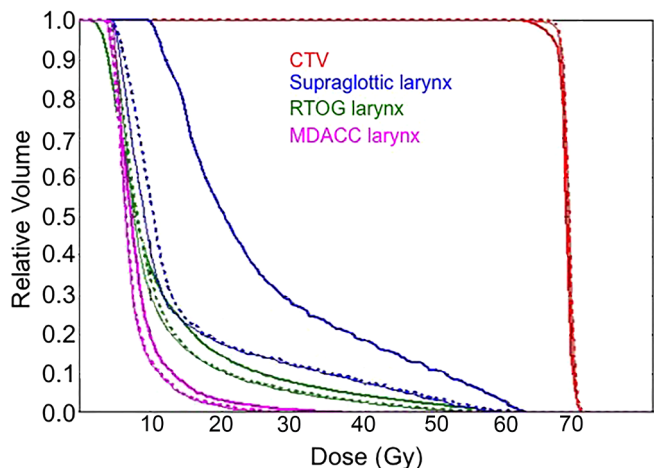


Fig. 2. Dose volume histogram comparison of RTOG larynx (green), MDACC larynx (magenta), supraglottic larynx (blue) and CTV (red) for one patient planned using SF-IMRT (thick solid lines), WF-IMRT (dashed lines), and VMAT (thin solid lines) techniques. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

SF-IMRT (Supplemental Table 2). Esophageal mean doses also remained higher in the absence of lower neck disease for WF-IMRT and VMAT plans but were comparable across all plans when level III nodal disease was present.

3.4. Treatment efficiency

The average treatment delivery time for unilateral neck irradiation was significantly shorter with WF-IMRT (7.1 ± 0.9 min) and VMAT (1.5 ± 0.3 min) plans in comparison to SF-IMRT plans (8 ± 1.2 min, $p < 0.01$). Similarly, total MUs required per plan were significantly fewer using WF-IMRT and VMAT than SF-IMRT. WF-IMRT and VMAT plans, on average, delivered 217 and 329 MUs less than SF-IMRT plans ($p < 0.01$) (Table 1).

4. Discussion

With the constant development and sophistication of radiation therapy modalities available in the modern era, it is clinically pertinent to investigate the most optimal applications for each in cancer care. For patients with oropharyngeal cancers, SF-IMRT has largely replaced opposed lateral beams given its higher conformity profile while

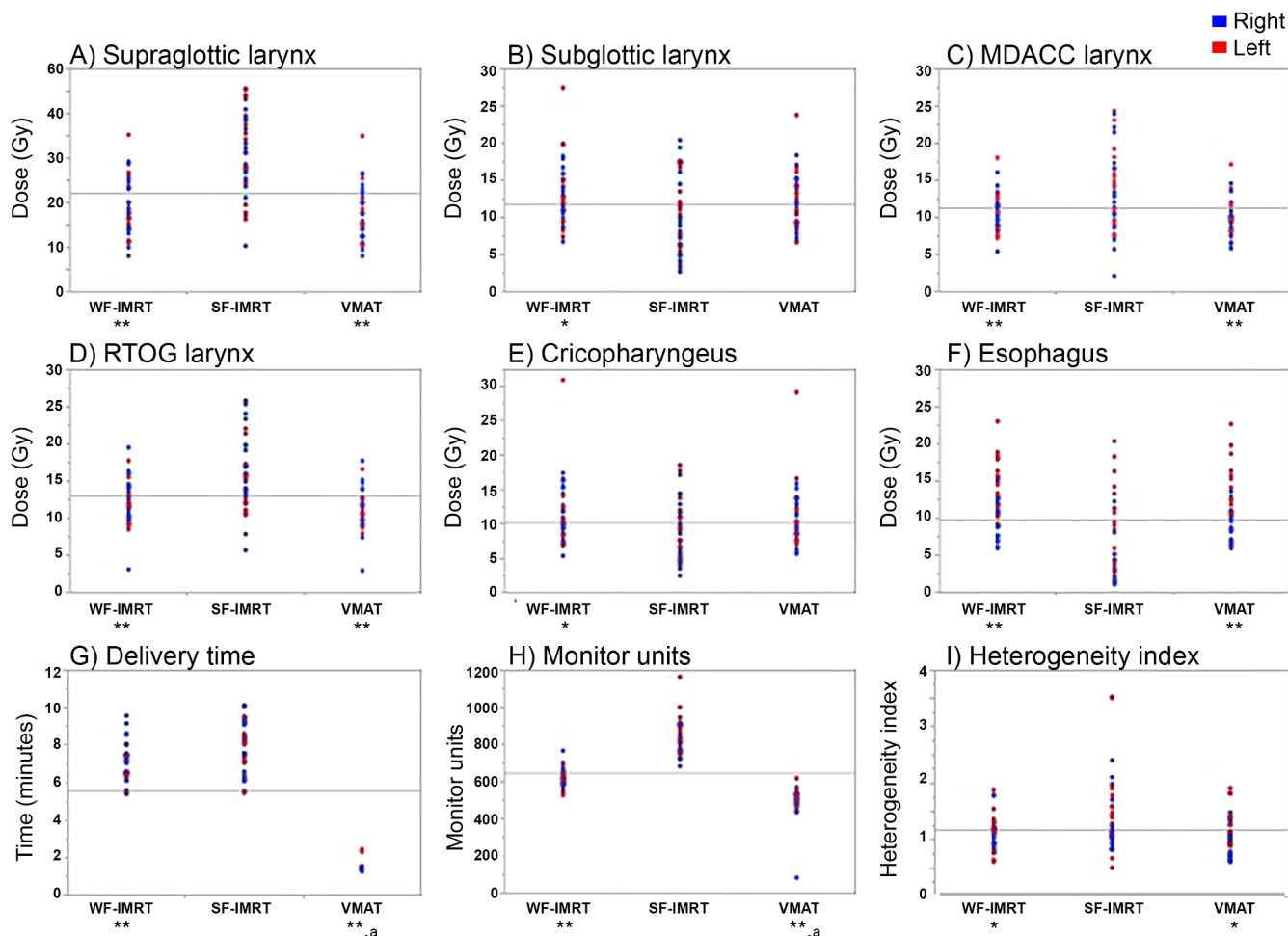


Fig. 3. Dosimetric comparisons between the three treatment techniques for A) mean supraglottic dose, B) mean subglottic dose, C) mean dose to MDACC larynx, D) mean dose to RTOG 1016 larynx, E) mean dose to cricopharyngeus, F) mean esophageal dose, G) total delivery time in minutes, H) total MU required, and I) the heterogeneity index. Patients treated to the left neck are depicted with red markers while those treated to the right neck are labeled with blue markers. (*), $p < 0.05$ compared to split field; (**), $p < 0.01$ compared to split field; (a), $p < 0.01$ compared to WF-IMRT field. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

significantly sparing the larynx from radiation through the use of a laryngeal block. In select patients with well-lateralized tonsil cancers, unilateral neck radiotherapy offers a de-intensification strategy to considerably reduce the volume of normal tissue exposed to radiation [19]. The present study demonstrates the ability of physicians to optimize current WF-IMRT and VMAT planning techniques relative to SF-IMRT for ipsilateral neck treatment in order to achieve equivalent target coverage and superior dose sparing of the larynx and its substructures.

Indeed, excess laryngeal radiation exposure when planning radiation therapy treatments can result in debilitating toxicities including increased aspiration risk, long-term vocal dysfunction and dysphagia [20–22]. One study related incidences of laryngeal edema up to 45% at one year in patients receiving mean laryngeal doses of 44–57 Gy [23]. In 2005, Dabaja et al. reported mean doses to the larynx of 18.7 Gy with SF-IMRT compared to 47 Gy with WF-IMRT in the setting of bilateral neck radiotherapy ($P = 0.001$) [16]. Despite significantly higher doses with WF-IMRT, they were in accordance with acceptable dose constraint parameters set in the Radiation Therapy Oncology Group protocol 0022, a phase I/II study of conformal and IMRT for oropharyngeal cancer [24]. Several explanations potentially exist for the discrepancies observed in doses to the larynx in the Dabaja study, which include their manual selection of gantry, couch, and collimator angles or the use of outdated robust optimization features of the treatment planning software system.

We have recently submitted a similar dosimetric study for publication using bilateral neck SF-IMRT, WF-IMRT, and VMAT planning techniques in patients with locally advanced oropharyngeal cancers. With a cohort of 30 patients, the mean doses to the RTOG larynx were 25.8, 22.1, and 23 Gy, respectively, while mean doses to the MDACC larynx were 17.8 Gy, 16.9 Gy and 18.1 Gy. Doses to the RTOG larynx were significantly reduced with WF-IMRT relative to SF-IMRT, whereas all other comparisons were not significantly different. In the present study, the lower mean laryngeal doses associated with all three plans was expected due to only one side of the neck being irradiated. Although we found a statistically significant improvement in laryngeal and supraglottic sparing with WF-IMRT and VMAT over SF-IMRT, it has yet to be proven that this dosimetric advantage will lead to improved clinical toxicity profiles and quality of life for patients. However, efforts should be made to adopt stricter dose constraints to the larynx given our findings. Two methods we employed to optimize WF-IMRT and VMAT plans included drawing larger laryngeal avoidance structures that encompassed the cricopharyngeal muscle and abutted the cervical vertebral body to minimize dose in this region as well as using anterior partial fields with sagittal MLCs (for WF-IMRT) or sagittal anterior arcs (for VMAT) to simulate a laryngeal block [25].

The effect of laterality was also assessed with all treatment modalities. For the entire cohort, the mean esophageal dose was significantly higher with WF-IMRT (12.2 Gy) and VMAT (11.1 Gy) compared to SF-IMRT (5.9 Gy; $P < 0.01$). This difference was most pronounced in the absence of lower neck nodal disease, an observation that is reasonable considering that by not targeting the lower neck with higher doses, the dose fall off with a laryngeal block would likely be sharper than what can be achieved with WF-IMRT and VMAT plans. When the lower neck is involved, WF-IMRT and VMAT plans yielded comparable doses to the esophagus, regardless of laterality, while still maintaining superior dose sparing of the MDACC, RTOG and supraglottic larynx OARs. Therefore, we submit that WF-IMRT and VMAT for unilateral neck radiotherapy should take precedence as they offer effective conformity, particularly for lower neck nodal targets, and they do not exhibit an uncertainty at a match line which is a relevant issue with SF-IMRT, particularly when gross disease is present at or near the junction. However, the use of SF-IMRT may be preferred in instances when dose to midline structures such as esophagus and spinal cord below the larynx need to be minimized beyond their tolerated constraints.

In our study, treatment delivery times were significantly faster with VMAT (1.5 min) compared to both WF-IMRT (7.1 min) and SF-IMRT (8 min). Moreover, there was a 26% and 40% reduction of required total monitor units when using WF-IMRT or VMAT techniques, respectively, over SF-IMRT. Reduction in MUs can theoretically result in less dose scatter to surrounding normal tissues. The latter finding has been reproduced in multiple other studies such as Pursely et al. who reported an average reduction of 35% in required MUs using VMAT over standard IMRT technique for unilateral neck irradiation [26]. They also found that VMAT plans could be optimized using two, 360° arcs with avoidance sectors around the contralateral parotid instead of using two, 260° or 270° arcs. In our study, we used 2 arcs for our VMAT plans with each arc spanning 200–220°. For IMRT, planning quality and delivery efficiency can be optimized by examining doses associated with the use of fewer beams and/or number of intensity levels [27].

There are several limitations to this study. Firstly, our non-randomized cohort of 40 patients can be considered small, but compared to other dosimetric comparison studies [26,28], it is a relatively large sample size that was well distributed with 50% of patients receiving treatment to either the right or left neck. Furthermore, we did not investigate treatment-related outcomes including associated toxicities and patient quality of life. Other studies previously mentioned have demonstrated the correlations between dose and expected toxicity profiles [20,21]. Small dose-fractionation differences between SF (2 Gy per fraction) versus WF (1.8–2 Gy per fraction via simultaneous integrated boost) techniques for volumes below the match line and their potential clinical implications were not evaluated in this study. Herein we examine and compare various dosimetric parameters between SF-IMRT, WF-IMRT, and VMAT plans for HNC treatment as potential surrogates to acute and long-term toxicities based on historical data. However, additional investigations are required to determine whether the dosimetric advantages seen with WF-IMRT and VMAT techniques translate into an appreciable clinical benefit without affecting survival outcomes. Studies optimizing VMAT plans (i.e. through the use of non-coplanar arcs to reduce dose to the esophagus) are also warranted to determine if further dosimetric and/or clinical benefits can be observed with VMAT over SF-IMRT and WF-IMRT. Lastly, the potential clinical benefit of these treatments should also be further stratified by HPV status which was not evaluated in our study.

In conclusion, ipsilateral neck radiotherapy delivered via WF-IMRT or VMAT techniques for the management of early, well-lateralized tonsillar cancers was superior to conventional SF-IMRT. Both WF-IMRT and VMAT plans can be optimized to result in equivalent target coverage as SF-IMRT plans while offering improved laryngeal dose sparing, shorter treatment times, and delivery of fewer required monitor units. Compared to WF-IMRT, VMAT plans were associated with even greater benefits with regards to treatment delivery times and required MUs, warranting further studies and a shift in clinical practice to consider VMAT planning as an optimal standard of care for well-lateralized tonsil cancers.

Acknowledgement

None.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.phro.2019.04.002>.

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