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FULL PAPER

Volumetric modulated arc therapy (VMAT) and simultaneous integrated boost in head-and-neck cancer: is there a place for critical swallowing structures dose sparing?

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Objective: To explore the potential of volumetric-modulated arc therapy (VMAT) to reduce the risk of swallowing problems after curative chemoradiotherapy.

Methods: 20 patients with head and neck cancer who previously underwent radiotherapy were selected. Radiotherapy was prescribed according to simultaneous integrated boost technique with all targets irradiated simultaneously over 30 daily fractions. Doses of 70.5 (67.5), 60.0 and 55.5 Gy were prescribed to primary tumour, high-risk nodal regions and low-risk nodal regions, respectively. Pharyngeal constrictor muscles (PCM) and glottic and supraglottic larynx (SGL) were considered organs at risk related to swallowing dysfunction (SW-OARs). Upper pharyngeal constrictor muscles (uPCM), middle pharyngeal constrictor muscles (mPCM) and lower pharyngeal constrictor muscles (lPCM) part of PCM were also outlined separately. Clinical standard plans (standard-VMAT) and plans aiming to spare SW-OARs (swallowing dysfunction-VMAT) were also created. Normal tissue complication probabilities (NTCP) for physician-rated swallowing dysfunction were calculated

using a recently predictive model developed by Christensen et al.

Results: Planning with two strategies demonstrated comparable planning target volume coverage and no differences in sparing of parotid glands and other non-swallowing organs at risk. SW-VMAT plans provided mean dose reduction for uPCM and SGL by 3.9 and 4.5 Gy, respectively. NTCP values for Radiation Therapy Oncology Group grade 2–4 swallowing dysfunction was decreased by 9.2%. Dose reductions with SW-VMAT depended on tumour location and overlap with SW-OARs.

Conclusion: VMAT plans aiming at sparing swallowing structures are feasible, providing a significant reduction in NTCP swallowing dysfunction with respect to conventional VMAT.

Advances in knowledge: Dysphagia is today considered one of the dose-limiting toxicities of chemoradiotherapy. The dose sparing of swallowing structures represents a major challenge in radiotherapy. VMAT is a complex new technology having the potential to significantly reduce the risk of dysphagia after curative chemoradiotherapy.

INTRODUCTION

Intensification of radiotherapy for locally advanced head and neck cancer (HNC) using altered fractionation and/or concomitant chemotherapy translated into an improvement of locoregional tumour control and survival rates,^{1,2} but at the cost of higher rates of treatment-related toxicities.^{3,4} In the last decade, an increasing attention has been paid to the problem of dysphagia in patients undergoing radiotherapy for HNC. Emphasis on dysphagia as a side effect of radiation therapy of squamous head-neck

tumours⁵ has grown over time for both the negative impact on quality of life⁶ and the associated risk of complications due to aspiration.⁷

Following the introduction of aggressive high-dose chemoradiotherapy, the incidence of radiation-induced dysphagia has considerably increased, reporting rates of 12–50% significant late dysphagia.^{8–11} It is now recognized that late dysphagia should be considered one of the dose-limiting toxicities of chemoradiotherapy, as important as

late xerostomia.^{12,13} Moreover, xerostomia can represent in itself a cause of dysphagia worsening. Also, the prevalence of this disorder has been underreported for a long time.¹³

Several clinical trials have analysed the relationship between the irradiated tissues and dysphagia assessing consistent data for the crucial structures related to swallowing dysfunction.^{14–20} In particular, pharyngeal constrictors muscles (PCM) and the glottic/supraglottic larynx (SGL) have been identified as principal organs in which dysfunction after chemoradiation causes dysphagia and aspiration.²¹ The common findings of these studies were that increased radiation dose to these structures resulted in higher level of dysphagia, all demonstrating a significant correlation between dysphagia/aspiration and the mean doses to PCM and SGL.^{14,15}

Intensity-modulated radiotherapy (IMRT) allowed the delivery of highly conformal dose distributions with steep dose fall out also for large and complex target shapes as for patients with HNC. Owing to the high level of dose conformity, tumour-dose escalation can be planned, maintaining the irradiation of critical structures within tolerance. Furthermore, IMRT allowed the simultaneous delivery of different doses to different target volumes within a single fraction, an approach called simultaneous integrated boost (SIB). IMRT has been successfully applied to spare salivary glands from high-dose radiation and reduce xerostomia toxicity,²² but, its role in swallowing organ sparing is nowadays less established. A few studies focused on the feasibility of IMRT to reduce the doses delivered to the critical structures responsible for dysphagia demonstrating that IMRT aiming at sparing the swallowing structures is feasible if such sparing was explicitly included in the dosimetric objectives of IMRT optimization process.¹⁶

Volumetric-modulated arc therapy (VMAT) is a complex rotational therapy technique in which highly conformal doses can be realized by varying the speed of gantry rotation, multileaf collimator shape and dose rate.²³ This technology is having a widespread implementation in patients with HNC, showing to provide similar plan quality with respect to fixed-field IMRT but with large reduction in treatment time and monitor units number.^{24–26} Anyway, to date, no studies explicitly assessed the feasibility of VMAT technique in reducing the dose to relevant anatomical structures involved with swallowing dysfunction. Owing to the complexity of all anatomical structures involved in head–neck cancer treatment, the introduction of PCM and SGL structures in VMAT optimization represents a major challenge in order to get a significant dose sparing without sacrificing tumour coverage or overdosing healthy tissues and other critical structures. In other words, it is unclear how the dose to the OARs (organs at risk) involved with the swallowing function is affected in VMAT optimization process.

In this study, we explored the swallowing organ-sparing potential of VMAT technique. In addition, we investigated if the amount of dose sparing in swallowing related structures (PCM and SGL) translated into significant reduction of NTCP (normal tissue complication probabilities) values for swallowing dysfunction.

METHODS AND MATERIALS

Patients

20 patients who had previously undergone primary radiotherapy for advanced head-and-neck cancer were randomly selected from our database for replanning. All patients required elective or therapeutic treatment of both sides of the neck. A moderately accelerated SIB treatment using VMAT and concurrent weekly cisplatin after neo-adjuvant chemotherapy was our standard treatment strategy.²⁷ Patient and tumour characteristics are shown in Table 1.

Table 1. Patient and tumour characteristics

Number of patients	20
Tumour location	
Larynx	7
Oropharynx	9
Nasopharynx	4
T stage	
T1	0
T2	6
T3	1
T4	12
Tx	1
N stage	
N0	6
N1	2
N2	11
N3	1
Clinical stage	
I	0
II	3
III	3
IV	14
Planning target volumes (cm ³)	
PTV1	239.8 ± 155.3
PTV2	561.7 ± 276.1
PTV3	766.4 ± 221.9
% PCM–PTV overlap, median (range)	
with PTV1	41.7% (13.4–73.0%)
with PTV2	74.7% (32.4–100.0%)
with PTV3	96.2% (78.8–100.0%)
% SGL–PTV overlap, median (range)	
with PTV1	19.1% (0.0–95.5%)
with PTV2	42.4% (7.4–100%)
with PTV3	56.0% (22.0–100.0%)

PCM, mpharyngeal constrictor muscle; PTV, planning target volume; PTV1, planning target volume 1; PTV 2, planning target volume 2; PTV 3, planning target volume 3; SGL, supraglottic larynx.

Simulation and volumes definition

Planning CT slices for each patient were obtained in the treatment position, at 4-mm intervals from the vertex to the level of the aortic arc. Clinical target volume 1 (CTV1) was considered as primary tumour plus 5–15 mm margin depending on anatomical boundaries. Clinical target volume 2 (CTV2) was defined as lymph nodes with high risk of occult metastases. Clinical target volume 3 (CTV3) included low-risk nodal regions. Lymph nodes were considered to bear metastasis in any case in which they were enlarged ≥ 1 cm on CT scan or showed increased metabolic activity at fluorine-18 fludeoxyglucose positron emission tomography-CT scan. High-risk lymph nodal regions were defined as those clinically negative but with high risk of occult metastases. Low-risk nodal regions were considered as those contiguous to high-risk ones. Anatomical boundaries of lymph nodal regions were outlined according to the classification proposed by Grégoire et al.²⁸ Corresponding planning target volumes (PTVs) were obtained by adding a 4-mm margin to CTVs.

Radiotherapy was prescribed according to SIB technique with all PTVs irradiated simultaneously over 30 daily fractions. Doses of 70.5 Gy (2.35 Gy/fraction) for nasopharyngeal and oropharyngeal tumours or 67.5 Gy (2.25 Gy/fraction) for laryngeal tumours were prescribed to PTV1. Doses of 60.0 Gy (2.0 Gy/fraction) and doses of 55.5 Gy (1.85 Gy/fraction) were prescribed to the PTV2 and PTV3, respectively.

The following non-swallowing organs at risk (NSW-OARs) were delineated: spinal cord, brainstem, eyes, lens, optic chiasm, optic nerves, mandible and parotid glands. Planning organ-at-risk volumes (PRV) were defined for serial NSW-OARs using a 5-mm isotropic expansion.

PCM and SGL were considered as organs at risk related to swallowing dysfunction (SW-OARs) and delineated according to the guidelines described by Christianen et al.²⁹ The upper pharyngeal constrictor muscles (uPCM), middle pharyngeal constrictor muscles (mPCM) and lower pharyngeal constrictor muscles (lPCM) of PCM were also outlined separately. In addition, for each patient, the relative volume overlap of PCM, uPCM and SGL with PTVs was calculated (Table 1).

Treatment planning

All plans were created using the Oncentra MasterPlan® TPS v. 4.1 (Nucletron BV, Veenendaal, Netherlands) for 6-MV beams from an Elekta Precise linear accelerator (Elekta Ltd., Crawley, UK). All plans were generated with “dual-arc” feature, using the optimization process described previously in more detail.²⁴ For each patient, two SIB-VMAT treatment plans were created. The original standard plan (ST-VMAT) was created based on our dose–volume objectives without the inclusion of SW-OARs in the optimization process. According to International Commission on Radiation Units and Measurements 83,³⁰ the planning goals for PTVs were: $D_{98\%}$ no $< 90\%$ of prescribed dose for all PTVs, $V_{95\%}$ no $< 95\%$ for all PTVs and $D_{2\%}$ $< 107\%$ of prescribed dose for PTV1. $D_{98\%}$ and $D_{2\%}$ represent the minimum dose received by 98% (near-minimum dose) and 2% (near-maximum dose) target volume,

respectively. $V_{95\%}$ represents the target volume covered by 95% of prescribed dose. The maximum doses to the spinal cord, brain stem, lens, eyes and optic chiasm and nerve PRVs were set as 45, 54, 5, 40 and 55 Gy, respectively. Efforts aimed to reduce the mean dose to parotid glands as much as possible were attempted but without compromising the target coverage. In this process, by a trial-and-error adaptive adjustment of values and weights of objective function, the best clinical acceptable plan was obtained. Secondly, a new treatment plan based on the approved ST-VMAT final dose plan was created (SW-VMAT). All the dose–volume objectives for PTV coverage and NSW-OAR sparing remained unchanged. Then, objective values were added for the SW-OARs with priority to minimize the mean doses to PCM (in particular for uPCM) and SGL structures. In Masterplan optimization module, this task can be effectively performed using the so-called “max average dose” objective, which acts on the generalized equivalent uniform dose, in such a way as to penalize too high average dose values, therefore suitable for parallel OARs. No direct attempt to reduce the dose in the low–intermediate dose range was performed owing to the major overlap of PCM and SGL structures with the PTV3. Anyway, the use of the “max average dose” objective provides the optimization engine many more degrees of freedom “for lowering” the dose–volume histograms in the most appropriate dose ranges but without compromising PTV coverage, and in the few patients showing smaller overlaps of PCM or SGL with PTV3, the optimization engine is able to decrease the dose also in the low–intermediate dose range.

Evaluation tools

PTV coverage was compared in terms of $V_{95\%}$, D_{mean} , $D_{98\%}$ and $D_{2\%}$, these last two representing near minimum and near maximum, respectively. Conformity indexes (CIs), defined as the volume encompassed by the 95% isodose of each dose prescription divided by the PTV volumes, were used for plan comparison. For all OARs, plans were compared in terms of mean and maximal dose and percentage volume sparing achieved at various levels of dose prescription.

Following the approach of Christianen et al.¹⁷ study to predict radiation-induced swallowing dysfunction, the normal tissue complication probabilities (NTCP) for physician-rated swallowing dysfunction 6 months after chemoradiation treatment were calculated using the formula:

$$\text{NTCP} = \frac{1}{e^{-S} + 1}$$

where $S = -6.09 + (0.057x \text{ mean dose to uPCM}) + (0.037x \text{ mean dose to SGL})$.

The Wilcoxon signed-ranks test was used for comparison with statistical significance assumed for $p < 0.05$.

RESULTS

Target coverage and conformity

Dosimetric data for PTVs and NSW-OARs are reported in Table 2. PTVs receiving at least 95% of prescribed dose were $> 95\%$

Table 2. Dosimetric results for target volumes and NSW-OARs

PTV coverage				NSW-OARs dose			
	ST-VMAT	SW-VMAT	<i>p</i> -value		ST-VMAT	SW-VMAT	<i>p</i> -value
PTV1				PRV spinal cord			
D_{mean} (%)	102.2 ± 0.8	101.7 ± 0.9	0.09	D_{max} (Gy)	45.5 ± 1.6	45.8 ± 1.6	0.55
V_{95} (%)	98.7 ± 1.5	98.4 ± 1.4	0.17	PRV brainstem			
D_{98} (%)	96.1 ± 2.2	95.1 ± 1.5	<0.01	D_{max} (Gy)	44.1 ± 7.3	43.7 ± 6.1	0.26
D_2 (%)	106.3 ± 1.1	106.9 ± 1.5	0.17	PRV optic chiasm			
CI1	1.57 ± 0.25	1.52 ± 0.28	<0.01	D_{max} (Gy)	15.6 ± 17.2	15.5 ± 8.2	0.92
PTV2				Eyes			
D_{mean} (%)	111.3 ± 3.4	111.7 ± 5.5	0.26	Right: D_{max}	6.2 ± 4.2	6.2 ± 5.2	0.17
V_{95} (%)	99.5 ± 0.6	99.4 ± 0.9	0.26	Left: D_{max}	6.8 ± 6.5	6.8 ± 7.2	0.64
D_{98} (%)	99.0 ± 2.5	97.9 ± 2.0	<0.01	Lens			
CI2	2.05 ± 0.66	2.03 ± 0.63	0.17	Right: D_{max}	2.4 ± 0.9	2.4 ± 1.0	0.94
PTV3				Left: D_{max}	2.5 ± 1.0	2.5 ± 1.1	0.26
D_{mean} (%)	115.3 ± 3.9	115.1 ± 3.9	0.26	Optic nerves			
V_{95} (%)	99.5 ± 0.6	99.1 ± 0.9	0.06	Right: D_{max}	5.5 ± 5.4	5.9 ± 6.0	0.40
D_{98} (%)	98.6 ± 1.8	97.6 ± 2.2	0.04	Left: D_{max}	6.9 ± 9.9	7.6 ± 11.0	0.69
CI3	1.66 ± 0.11	1.70 ± 0.20	0.02	Parotid (contralateral)			
				D_{mean} (Gy)	35.9 ± 6.2	35.2 ± 5.8	0.07

CI, conformity index; $D_{2\%}$, dose to 2% of PTV; $D_{98\%}$, dose to 98% of PTVs; D_{mean} , mean dose; NSW-OARS, non-swallowing organs at risk; PRV, planning organ-at-risk volume; PTV, planning target volume; $V_{95\%}$, volume receiving at least 95% of prescribed dose; VMAT, volumetric modulated arc therapy. Results are expressed as mean value ± standard deviation.

with both SW-VMAT and ST-VMAT plans. No significant difference was found in the mean dose for all PTVs. $D_{98\%}$ was found >90% for all patients and both techniques. SW-VMAT plans significantly improved target dose conformity for PTV1 (CI1: 1.52 vs 1.57, $p < 0.01$) but decreased the conformity for PTV3 (CI3: 1.70 vs 1.66, $p = 0.02$). Figure 1 shows the isodose distribution comparison for a representative patient.

NSW-OAR sparing analyses

No significant differences were found in the maximum dose for lens, eyes, optic nerves, chiasm ($p = 0.92$), spinal cord ($p = 0.55$) and brainstem ($p = 0.26$). In addition, SW-VMAT plans did not result in increased parotid dose ($p = 0.07$).

SW-OAR sparing analyses

Mean dose, $V_{60\text{Gy}}$ and $V_{65\text{Gy}}$ were lowest with SW-VMAT plans for all patient groups (Table 3). Considering all patients, mean doses for PCM, uPCM and SGL were reduced by 4.0 Gy (range: 0.7–6.6), 3.9 Gy (range: 0.1–6.1 Gy) and 4.5 Gy (range: 0.4–10.5 Gy), respectively. This results in a mean reduction of NTCP values for Radiation Therapy Oncology Group (RTOG) grade 2–4 swallowing dysfunction of 9.2% (range: 4.4–16.9%). Significant sparing of SW-OARs structures was obtained also for V_{60} and V_{65} metrics; SW-VMAT plans decreased the V_{60} for uPCM and SGL from 81.3% to 63.3% and from 62.2% to 47.1%, respectively.

Mean doses and NTCP value reduction widely varied among patients as shown in Figure 2. Patients with oropharyngeal or nasopharyngeal tumours have PTVs that significantly overlapped with uPCM, allowing only for a 5.1% of mean dose reduction for this structure. On the other hand, patients with laryngeal tumours show a higher reduction of uPCM mean dose (8.2%) but an obvious smaller SGL mean dose reduction (2.4%) than patients with upper tumour location (10.1%). Because of this balance, the absolute NTCP gain with SW-VMAT resulted similar between the two patient groups (9.5% for oronasopharynx tumours vs 8.6% for laryngeal tumours).

Figure 3 shows the relationship between the mean dose reduction in uPCM and SGL structures and the percent volume of these structures overlapping the high-dose target volume (PTV1). Focusing on the uPCM–PTV1 overlap (Figure 3a), the analysis highlights a fairly linear relationship for patients with nasopharynx or oropharynx tumour location, indicating that greater overlaps result in a smaller reduction of the average dose to uPCM structure. On the other hand, no specific trend was found for patients with larynx tumours, which have a minimal if not absent uPCM–PTV1 overlap, allowing for a greater dose sparing. A similar behaviour was found considering the dependence of dose reduction in SGL structure according to the SGL–PTV1 overlap (Figure 3b).

Figure 1. Axial, sagittal and coronal dose distributions with ST-VMAT and SW-VMAT for a representative patient.

DISCUSSION

Based on the pioneering study of Eisbruch et al²¹ that identified the PCM and the SGL as dysphagia- and aspiration-related structures, a large number of subsequent studies demonstrated significant relationships between the absorbed dose to these structures and swallowing outcomes after radiotherapy. The most predictive dosimetric indices for the PCMs were found to be the mean dose^{14–19} and the volume receiving more than 60 Gy^{14,18} and 65 Gy^{14,31} in the uPCM. Similarly, the most predictive dosimetric indices for the SGL were the mean dose^{17,20} and the volume receiving >50 Gy.^{14,16,20} Almost all of these studies were retrospective, including different types of treatment techniques, and lacked adjustments to pre-therapy swallowing abnormalities. Among them, one prospective study was led by Christianen et al¹⁷ with the aim to identify which dose–volume histogram parameters and pre-treatment factors were the most important to predict physician- and patient-rated radiation-induced swallowing dysfunction in order to develop predictive models for swallowing dysfunction. Their analysis revealed that a model based on the mean dose to the uPCM and the mean dose to the SGL was most predictive for grade 2 or more swallowing dysfunction according to the RTOG/European Organisation for Research and Treatment of Cancer late-radiation morbidity-scoring criteria at 6 months after chemoradiotherapy.

Recently, van der Laan et al³² applied the aforementioned Christianen's predictive model to assess the potential benefit of swallowing-sparing IMRT in an *in silico* planning comparative study. They demonstrated that whole-field IMRT had the potential to reduce the mean dose to uPCM and SGL by 4.7 Gy and 5.7 Gy, respectively, translating in a mean NTCP reduction for physician-rated RTOG grade 2–4 swallowing dysfunction of 8.9%.

Following the van der Laan approach, we analysed the performance of more complex VMAT technique in this context.

The ability of VMAT to achieve a high level of fluence modulation in order to further reduce irradiation in swallowing-related structures has not been explicitly investigated, and some data are present only in a few comparative planning studies between different delivery techniques.^{33–35} This, despite the worldwide implementation of this technique, is gradually replacing fixed-field IMRT, thanks to its advantages in terms of treatment efficiency. VMAT planning optimization process is much more complex than fixed-field IMRT. While for IMRT, the fluence map optimization problem can be solved to near optimality (in mathematical words, it represents a convex optimization problem), the goal of VMAT optimization aiming to find the optimal trajectories of the leaves of a multileaf collimator represents a large-scale non-convex optimization problem.³⁶ This problem is mainly due to the coupling between adjacent angles; because the leaves cannot move faster than physically possible, field aperture at any one angle depends on the field apertures from adjacent angles. The need to consider all motion constraints of VMAT in terms of maximum leaf speed, valid dose rates and gantry speed dramatically increases the complexity of the optimization problem. These computational challenges may have a direct impact on VMAT clinical plan quality, posing the question whether VMAT is able to produce optimal treatment plans in situations with complex-shaped targets and several normal structures adjacent to or overlapping the target volumes.³⁷

Nonetheless, this planning comparative study demonstrated that the doses to the SW-OARs can be significantly reduced during VMAT planning, without compromising the overall plan quality. With respect to conventional ST-VMAT plans, the mean doses in PCM and SGL structures were reduced by an amount of 4–5 Gy. According to the Christianen predictive model,¹⁷ the NTCP of RTOG grade 2–4 swallowing dysfunction were consequently reduced by 9.2%, a result strongly in agreement with the van der Laan findings (8.9% of NTCP reduction). These results were obtained without increasing the dose to NSW-OARs and without compromising overall target coverage, with only a small decrease in the D_{98} near-minimum metric, equal to about 1%, that was considered not clinically significant.

However, an increased spill of low–intermediate dose in healthy tissues was observed in SW-VMAT plans. In particular, we found that the body volume receiving 52.7 Gy (*i.e.* 95% of prescribed dose to low-risk areas) was slightly increased with SW-VMAT plans, resulting in a poorer dose conformation to the nodal low-risk target (CI3: 1.70 vs 1.66). In contrast, the dose conformity to primary tumour was significantly better with SW-VMAT, showing

Table 3. Dosimetric results and normal tissue complication probabilities for SW-OARs

All (<i>n</i> = 20)				Tumour location			
				Oro-nasopharynx (<i>n</i> = 13)		Larynx (<i>n</i> = 7)	
	ST-VMAT	SW-VMAT	<i>p</i> -value	ST-VMAT	SW-VMAT	ST-VMAT	SW-VMAT
PCM							
<i>D</i> _{mean}	65.7 ± 4.1	61.7 ± 4.6	<0.01	66.9 ± 3.3	62.7 ± 3.9	63.4 ± 4.7	60.0 ± 5.2
<i>V</i> ₆₀	82.1 ± 19.8	62.3 ± 24.8	<0.01	84.9 ± 17.3	62.6 ± 25.9	76.8 ± 24.4	61.7 ± 24.3
<i>V</i> ₆₅	57.8 ± 23.4	41.9 ± 18.2	<0.01	61.4 ± 25.7	43.8 ± 21.2	51.1 ± 18.5	38.4 ± 11.3
uPCM							
<i>D</i> _{mean}	66.1 ± 5.8	62.2 ± 6.3	<0.01	68.8 ± 3.0	65.3 ± 3.5	60.9 ± 6.2	55.9 ± 6.9
<i>V</i> ₆₀	81.3 ± 26.4	63.3 ± 31.9	<0.01	93.4 ± 9.5	79.0 ± 24.1	55.3 ± 33.1	34.1 ± 30.2
<i>V</i> ₆₅	59.7 ± 37.2	42.9 ± 33.2	<0.01	78.8 ± 24.8	60.1 ± 24.4	18.3 ± 22.5	10.9 ± 16.0
mPCM							
<i>D</i> _{mean}	65.8 ± 4.4	62.0 ± 4.8	<0.01	65.8 ± 5.2	61.6 ± 5.7	65.9 ± 2.4	62.9 ± 3.1
<i>V</i> ₆₀	86.7 ± 23.3	63.1 ± 38.0	<0.01	84.9 ± 27.4	58.3 ± 39.3	90.5 ± 11.9	73.4 ± 30.1
<i>V</i> ₆₅	55.4 ± 40.7	39.7 ± 31.5	<0.01	51.6 ± 45.0	34.9 ± 33.1	63.6 ± 31.4	50.1 ± 27.4
lPCM							
<i>D</i> _{mean}	63.7 ± 4.4	59.7 ± 6.1	<0.01	61.7 ± 3.8	56.5 ± 4.2	67.9 ± 1.7	65.9 ± 3.2
<i>V</i> ₆₀	74.1 ± 36.0	46.6 ± 43.9	<0.01	62.1 ± 38.0	22.0 ± 35.2	100.1 ± 0.4	99.7 ± 0.4
<i>V</i> ₆₅	40.1 ± 41.8	27.5 ± 38.7	<0.01	20.2 ± 31.0	4.5 ± 12.9	83.1 ± 27.3	77.3 ± 25.1
SGL							
<i>D</i> _{mean}	62.9 ± 6.1	58.4 ± 7.2	<0.01	60.0 ± 5.7	53.9 ± 6.0	68.4 ± 1.3	66.6 ± 1.5
<i>V</i> ₆₀	62.2 ± 37.9	47.1 ± 42.0	<0.01	42.4 ± 32.5	22.2 ± 32.0	98.9 ± 1.8	93.2 ± 9.8
<i>V</i> ₆₅	45.1 ± 41.4	34.2 ± 37.6	<0.01	22.7 ± 32.9	11.6 ± 22.6	86.4 ± 14.0	76.1 ± 16.3
NTCP	0.50 ± 0.08	0.41 ± 0.08	<0.01	0.51 ± 0.08	0.41 ± 0.08	0.48 ± 0.08	0.40 ± 0.08

*D*_{mean}, mean dose; lPCM, lower pharyngeal constrictor muscles; mPCM, middle pharyngeal constrictor muscles; NTCP, normal tissue complication probabilities; PCM, pharyngeal constrictor muscles; SGL, glottis and supraglottic larynx; uPCM, upper pharyngeal constrictor muscles; *V*₆₀ and *V*₆₅, volume receiving at least 60 and 65 Gy, respectively. Results are expressed as mean value ± standard deviation, according to tumour location.

Figure 2. Average cumulative DVHs for (a) uPCM, (b) SGL and (c) NTCP Radiation Therapy Oncology Group grade 2–4 swallowing dysfunction sparing (patients were re-sorted according to the ST-VMAT NTCP values).

that during the optimization process, the dosimetric requests for SW-OARS dose sparing in terms of mean dose translate into a shift of the dose from different areas of PTVs and normal tissues, which tends to conform more to the primary tumours than to low-risk nodal areas. Again, this result is very similar to the finding of the study of van der Laan,³² who found an increased irradiation to the elective nodal areas using fixed-field IMRT technique when attempting to reduce SW-OAR dose. Because planning strategies for original ST-VMAT plans were considered optimal with respect to dose conformity, the increased

$V_{52.7}$ in normal tissue volumes in SW-VMAT plans was associated with a dose redistribution into non-specified volumes as a consequence of the dose pushed out from the swallowing organs. We accepted this behaviour as a reasonable price to be paid for the purpose of reducing the irradiation of swallowing-related structures, although the clinical consequences of this increased intermediate dose spill into normal tissues deserves a deeper investigation.

A few planning studies,^{33–35} aiming to compare fixed-field IMRT with rotational IMRT and/or tomotherapy, also considered critical swallowing structures in the evaluation of the various techniques' efficacy. Most of the results in these studies are not in agreement with our data as we do find higher average doses to swallowing-related structures. Possible causes of this discrepancy can be traced back mainly to a different definition of clinical volumes or in a major overlap between critical structures and target volumes. It should be noted that the oronasopharynx site considered in the present study differs considerably in PTV sizes

Figure 3. Relationships between the upper pharyngeal constrictor muscle (uPCM) (a) and the supraglottic larynx (SGL) and (b) the mean dose reduction and the relative overlap of uPCM and SGL with planning target volume 1 (PTV1) for the two patients groups [nasopharynx-oro-pharynx (○) and larynx group (●)].

from that of Clemente et al's³⁴ study (*i.e.*, average PTV1: 90 vs 240 cm³), owing to different expansion margins used to define the CTV. In addition, it is also expected that the relation of PTVs to swallowing critical organs can differ considerably among various studies. In the van Gestel study,³⁵ the authors explicitly excluded from the analysis some OARs as upper pharyngeal constrictor owing to a major overlap with the PTV, suggesting that the other swallowing OARs (as medium and lower pharyngeal constrictor and glottic and SGL) do not present major overlaps with PTVs. In our study, we have shown that the PCM and SGL present a median overlap of 96% and 56% with the low-risk nodal area, a situation that actually prevents a dose reduction in the low-intermediate range without compromising PTV coverage for most of the patients.

The potential of dose reduction in SW-OARs changed widely across patients, depending on the tumour site, tumour extension and the amount of overlap between SW-OARs and targets volumes. We observed that patients with oropharynx or nasopharynx tumours showed less dose reduction in the uPCM structure, since the overlap between the PTVs and uPCM hinders even more dose reduction in this structure. In contrast, patients with larynx tumours show significant larger dose reduction in uPCM structures than patients with oropharynx cancer. In other words, the primary tumour site strongly influenced the amount of dose sparing for SW-OARs structures, since it determines the degree of overlap between PTVs and SW-OARs. Moreover, since NTCP can be decreased by reducing the mean dose in both uPCM and/or SGL structures, selective efforts may be focused in the optimization process to further reduce the mean dose in the uPCM structure for patients with larynx tumours and to reduce the mean dose in the SGL structure for patients with oropharynx or nasopharynx tumours.

It must be underlined that the sparing of swallowing structures should be approached with extreme care. This is especially true if patients presented advanced T-stages and N-stages and received bilateral neck irradiation. This is a common circumstance that represents a challenging situation that further complicates SW-OARs sparing (as well as the sparing of parotid glands) because of larger PTVs and then larger overlap between target volumes and SW-OARs. Targets and critical structures

delineation and set-up reproducibility requires an even higher level of accuracy since additional sparing of swallowing structures requires steeper dose gradients near the targets in the proximity of these structures and the risk of missing subclinical tumour becomes critical. This way, our priority choice was to avoid any underdosage to the targets in the vicinity of the swallowing structures and only secondary to attempt to reduce the mean dose to PCM and SGL structures.

Finally, some observations need to be made with regard to the dose prescription. Prescribing a dose per fraction (at least in some patients) higher than the one normally used may represent a limitation of our analysis. However, it should be noted that the use of dose per fraction >2.2 Gy (up to 2.5 Gy/fraction) has been repeatedly proposed and tested in the treatment of nasopharyngeal^{38,39} and other head-neck carcinomas.^{40,41} In addition, the use of high doses per fraction on the GTV simultaneously with the reduction of the dose to the SW-OARs made it more challenging the possibility of achieving deep dose gradients. In our opinion, the demonstrated feasibility of this approach through VMAT-SIB automatically shows that this strategy is feasible even in the common case of lower doses per fraction. Furthermore, our analysis does not imply that we recommend the use of these treatments outside of clinical trials.

Another limitation of our analysis can be represented by the prescription of different doses in case of laryngeal cancer. However, the differences are very small and in any case are motivated by the need to respect the common dose-volume constraints of OARs.

CONCLUSION

In conclusion, in this study, we demonstrated that VMAT-SIB plans aiming at sparing swallowing structures are feasible, depending on tumour location and the overlap between SW-OARs and PTVs. The systematic use of dose objectives on anatomical structures involved in swallowing has the potential to reduce NTCP swallowing dysfunction with respect to conventional ST-VMAT. A key point remains to assess whether the absolute amount of dose sparing to these structures is sufficient to translate into detectable clinical outcomes.

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