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ORIGINAL ARTICLE

Optimising Radiation Therapy Dose to the Swallowing Organs at Risk: An In Silico Study of feasibility for Patients with Oropharyngeal Tumours

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Abstract

Recent evidence suggests that reducing radiotherapy dose delivered to specific anatomical swallowing structures [Swallowing Organs at Risk (SWOARs)] may improve swallowing outcomes post-treatment for patients with head and neck cancer. However, for those patients with tumours of the oropharynx, which typically directly overlap the SWOARs, reducing dose to these structures may be unachievable without compromising on the treatment of the disease. To assess the feasibility of dose reduction in this cohort, standard IMRT plans (ST-IMRT) and plans with reduced dose to the SWOARs (SW-IMRT) were generated for 25 oropharyngeal cancer patients (Brouwer et al. in Radiother Oncol 117(1):83–90, https://doi.org/10.1016/j.radonc.2015.07.041, 2015; Christianen et al. in Radiother Oncol 101(3):394–402, https://doi.org/10.1016/j.radonc.2011.05.015, 2011). ST-IMRT and SW-IMRT plans were compared for: mean dose to the SWOARs, volume of pharynx and larynx receiving 50 Gy and 60 Gy (V50 and V60 respectively) and overlap between the tumour volume and the SWOARs. Additionally, two different SWOARs delineation guidelines (Brouwer et al. in Radiother Oncol 117(1):83–90, https://doi.org/10.1016/j.radonc.2015.07.041, 2015; Christianen et al. in Radiother Oncol 101(3):394–402, https://doi.org/10.1016/j.radonc.2011.05.015, 2011) were used to highlight differences in calculated volumes between existing contouring guidelines. Agreement in SWOARs volumes between the two guidelines was calculated using a concordance index (CI). Despite a large overlap between the tumour and SWOARs, significant ($p < 0.05$) reductions in mean dose to 4 of the 5 SWOARs, and V50/V60 for the pharynx and larynx were achieved with SW-IMRT plans. Low CIs per structure (0.15–0.45) were found between the two guidelines highlighting issues comparing data between studies when different guidelines have been used (Hawkins et al. in Semin Radiat Oncol 28(1):46–52, https://doi.org/10.1016/j.semradonc.2017.08.002, 2018; Brodin et al. in Int J Radiat Oncol Biol Phys 100(2):391–407, https://doi.org/10.1016/j.ijrobp.2017.09.041, 2018). This study found reducing dose to the SWOARs is a feasible practice for patients with oropharyngeal cancer. However, future prospective research is needed to determine if the extent of dose reduction achieved equates to clinical benefits.

Keywords Head and neck cancer · Radiation therapy planning · Swallowing organs at risk · Dose optimisation · Dysphagia

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Introduction

Advancements in radiation therapy (RT) techniques and the incorporation of chemotherapy for head and neck cancer over the past three decades has led to improved survival rates while preserving anatomical structures [1–3]. However, it is widely recognised that RT, with or without chemotherapy [(C)RT], results in significant symptom burden post-treatment, including short- and long-term swallowing dysfunction [4–7]. To improve swallowing outcomes, it is recommended for patients to have a pre-treatment swallowing assessment and regular contact with a speech pathologist during and after treatment, in order to provide preventative swallowing exercises and support with oral intake [8]. However despite these practices, patients continue to experience dysphagia, along with a multitude of negative functional and psychosocial outcomes following (C)RT [9]. These significant toxicities have driven investigations into enhancing treatment regimens by reducing morbidity without impacting on patient survival [10, 11]. Advancements in existing treatment methods with intensity-modulated radiation therapy (IMRT) has provided the ability to minimise the dose received by surrounding healthy head and neck structures whilst delivering the prescribed dose to the tumour, thereby reducing the severity of dysphagia and other toxicities. Implementation of parotid-sparing IMRT, in which RT dose to the parotid glands is limited, has demonstrated an improvement in rates of xerostomia [12–15]. Although the reduced toxicity from this practice has also been associated with improvements in dysphagia and quality of life, patients continue to experience swallowing dysfunction after parotid-sparing IMRT [11].

To further extend the capabilities of IMRT, a growing body of literature is exploring the potential benefits of reducing the RT dose delivered to swallowing organs at risk (SWOARs) (also referred to in some literature as the Dysphagia Organs at Risk "DARS") [16], with the aim to further improve swallowing function post-treatment without compromising dose to the planning target volume (PTV) [16–18]. Although the true clinical benefit of dose reduction to these key swallowing structures (i.e. 'optimising' dose to these structures) is yet to be definitively determined with a randomised control trial [19], superior outcomes including lower dysphagia, stricture and aspiration rates have been identified in single-arm studies with patients receiving SWOARs-optimised IMRT in comparison to the historical literature with standard IMRT outcomes [20–22]. Additionally, a clinically validated 'normal tissue complication probability' (NTCP) model has been used to identify theoretical benefits in swallowing which could be gained with SWOARs dose optimisation [23–26]. Although specific dose constraints to the SWOARs have yet to be established from the literature, recommendations developed by the Quantitative Analyses of Normal Tissue Effects in Clinic (QUANTEC) suggest that limiting the volume of the pharynx and larynx receiving 60 Gy (V60), and when possible 50 Gy (V50), can result in a clinical benefit to swallowing function [27].

These positive outcomes demonstrated with SWOARs-optimised planning methods may be especially beneficial for patients with oropharyngeal tumours, as they comprise a large proportion of head and neck cancer patients who experience significant and long-term dysphagia after (C)RT [7, 28]. However, SWOARs-optimised planning is not routinely implemented for this group in clinical practice [19]. This is in part due to the questions surrounding the feasibility of this planning technique, where the PTV often encompasses a large proportion of the SWOARs structures, especially the pharyngeal constrictor muscles [26, 29]. Although some studies have identified a reduction in the volume of the SWOARs receiving 50 Gy (V50) or 60 Gy (V60) could be achieved with SWOARs-optimised planning in heterogeneous cohorts [16, 24–26, 29], the benefit of this practice with oropharyngeal patients has not yet been established.

Another factor which should be considered when translating SWOARs-optimised plans in clinical practice is the variety of methods used for selecting and contouring these structures [30]. Significant variations in SWOARs delineations were previously established between 5 contouring guidelines, which may raise issues when comparing studies that have used different guidelines and determining clinical recommendations [30]. Hence to standardise clinical and research methods, a panel of radiation oncologists from Europe, North America, Asia and Australia recently developed a set of international consensus guidelines for computed tomography (CT)-based delineation of head and neck organs at risk [18]. Determining any differences that may occur with the SWOARs structures in these recent consensus guidelines and those used previously is yet to be established, and would help guide the extent of comparisons that can be made from studies using these different guidelines.

The potential to reduce negative swallowing outcomes for patients with oropharyngeal cancers through dose optimisation to the SWOARs is clinically motivating; however, systematic research is needed to determine what is feasible. Therefore, the current study employed an in silico comparative planning design to explore the extent of dose optimisation which can be achieved in this cohort. The primary aim of the study was to determine if a difference in mean dose delivered to the SWOARs between a standard IMRT plan (ST-IMRT) versus a SWOARs-optimised IMRT (SW-IMRT) plan can be achieved for patients with oropharyngeal tumours. The secondary aim was to examine the degree of overlap/consistency between contours of the SWOARs

structures using the Christianen et al. guidelines [17] used in many of the studies in the literature to date, versus the new international consensus guidelines [18]. The results of this research will help to inform if dose reductions to the SWOARs can be achieved through optimisation, and determine the extent to which previous data collected using the Christianen et al. guidelines can be compared to future studies which adopt the new international guidelines.

Materials and Methods

Participants

A cohort of 25 consecutive patients were recruited who had an oropharyngeal squamous cell carcinoma, received (C)RT treatment with curative intent at the Prince of Wales Hospital, Australia and had all RT treatment plans available for analysis. Previous research has identified a reduction in mean dose to the SWOARs of 66.9 Gy and 62.7 Gy in ST-IMRT and SW-IMRT plans respectively [29]. Power calculations from this prior research indicated that in order to identify a difference of approximately 4 Gy to the SWOARs, a minimum sample size of 23 patients was needed to provide 95% power at a 5% (2-tailed) significance level. Demographics of the 25 participants are detailed in Table 1. The clinically used treatment plans for these 25 patients were not implemented in the current study. Rather the original CT scans, with delineations for the PTV1, PTV2 and relevant organs at risk (OARs; brainstem, spinal cord, spinal cord planning organ risk volume [PRV] and left and right parotid glands), were used to generate in silico ST-IMRT and SW-IMRT treatment plans in this study.

Table 1 Demographics of patient data used for the in silico planning

Demographic	*n* (%)
Gender	
Male	20 (80)
Female	5 (20)
Age	
< 65 years	18 (72)
> 65 years	7 (28)
T stage[a]	
T1	13 (52)
T2	6 (24)
T3	6 (24)
T4	0
N stage[a]	
N0	1 (4)
N1	8 (32)
N2	16 (64)
N3	0
Neck treatment	
No neck	1 (4)
Unilateral	7 (28)
Bilateral	17 (68)
HPV status	
HPV positive	20 (80)
HPV negative	0
No data	5 (20)[b]
Treatment modality	
Definitive radiation therapy	3 (12)
Concurrent chemoradiotherapy	22 (88)

[a]American Joint Committee on Cancer 7th edition

[b]No data due to collection of HPV status only recently introduced

Planners, Equipment and Prescription Dose

Prior research has indicated maximal optimisation can be achieved by experienced radiation therapy researchers with adequate planning time [25]. Three senior radiation therapists were involved in contouring, and one senior radiation therapist completed planning for all ST-IMRT and SW-IMRT plans. All were allowed as much time as needed to complete their tasks. An additional radiation therapist not involved in the planning evaluated the plans to confirm the PTV and OARs criteria were met.

The Elekta Monaco treatment planning system (Stockholm, Sweden; version 5.0) was used to generate all plans with the Monte Carlo algorithm. CT scans for all patients were acquired in the treatment position with a slice thickness of 3 mm. Patients were planned using an IMRT technique with a simultaneous integrated boost. Delineation of tumour volumes respected the clinical and imaging findings, and adjacent normal tissue. Patients were planned to receive unilateral neck treatment for lateralised tonsillar primaries and bilateral neck treatment for base of tongue and tonsillar primaries with N2 or ipsilateral N3 disease. Margins around the respective planning target volumes reflected the extent of disease and distortion of adjacent normal tissue. Thus up to 5 mm margins were utilised as per current guidelines [31]. The presence of lymph node metastases were demonstrated by clinical and imaging means, and the nodal groups subsequently defined and treated as per Robins et al. [32]. Total prescription dose was 68 Gy in 34 fractions to the primary tumour and 56 Gy in 34 fractions to the elective tumour volume. The primary objective was that at least 98% of the PTVs were to be covered with 95% of the prescribed dose (PTV1 D98/PTV2 D98). OAR constraints were as follows: a maximum dose of 54 Gy for the brainstem, 45 Gy for the spinal cord, 50 Gy for the spinal cord PRV and mean dose to at least one parotid gland of < 26 Gy, based on Deasy et al. [33].

Contouring the SWOARs Structures

In addition to the original delineation of the PTV1, PTV2 and OARs, the SWOARs structures were contoured independently on each CT dataset using both (a) the international consensus guidelines [18] and (b) the Christianen et al. guidelines [17]. The Christianen et al. guidelines define the anatomical boarders of 7 SWOARs: the *superior, middle* and *inferior pharyngeal constrictor muscles, base of tongue, supraglottic larynx, glottic larynx* and *cricopharyngeal inlet*. For the purposes of this research, an eighth structure representing the set of *whole pharyngeal constrictors* was also contoured. In comparison, the international guidelines [18] include descriptions for contouring 5 'clinical' structures: the *whole pharyngeal constrictor, supraglottic larynx, glottic larynx, extended oral cavity,* and *cricopharyngeal inlet*. However for research purposes the guideline allows the *whole pharyngeal constrictor* to be subdivided into the *superior, middle* and *inferior pharyngeal constrictor muscles*. This was done to allow direct comparisons of these guidelines with the Christianen et al. data. In addition the *extended oral cavity* in the international consensus guideline can further be subdivided into the *oral tongue* and *anterior oropharynx*. The *anterior oropharynx* structure was used in this study to compare with the *base of tongue* structure reported by Christianen et al. [17].

In Silico Computation of ST-IMRT and SW-IMRT

Two in silico treatment plans, a ST-IMRT and SW-IMRT plan, were generated for each patient. First, ST-IMRT plans were completed as per the original treatment prescription and OAR dose constraints, but did not restrict the dose to the SWOARs. A second SW-IMRT plan was then completed for the same patient, following the treatment prescription and OAR dose constraints, with further optimisation to reduce dose as much as possible to the SWOARs without compromising the PTV coverage. For this process, if the planner could further reduce dose to the SWOARs structures after the initial plan and constraints were completed, additional optimisation sequence(s) would occur. The 5 'clinical' structures from the international consensus guidelines were optimised within the plans, as opposed to the 8 'research' structures which are also described in the guidelines, in order to be consistent with recommended use of these guidelines within clinical practice.

The doses were reduced according to the following order of priority and protocol as per van der Laan et al. [24]: (1) whole pharyngeal constrictor mean dose < 66 Gy, (2) supraglottic larynx mean dose < 60 Gy, (3) glottic larynx V50 < 27%, (4) cricopharyngeal inlet to minimise the percent > 60 Gy, (5) extended oral cavity as low dose as possible without compromising PTV coverage. The average time (minutes) required to contour the SWOARs on the SW-IMRT plans, and the number of optimisation sequences required to generate the ST-IMRT plans and SW-IMRT plans, were recorded to provide a measure of time and computing resources for this practice. The total additional time needed to complete a SW-IMRT plan was calculated by summating the average time for contouring the SWOARs and the average time needed for the additional optimisation sequences in the SW-IMRT plan.

The quality and viability of the ST-IMRT and SW-IMRT plans were assessed by an independent senior radiation therapist to ensure the prescribed planning goals for PTV1, PTV2 and OARs were met. In addition, the PTV1 and PTV2 D98 values in the ST-IMRT and SW-IMRT plans were collected. Any plans which fell outside the maximum dose constraints were further reviewed by a radiation oncologist to ensure the plan was clinically acceptable. Care was taken during optimisation to ensure that the low-intermediate dose wash in healthy surrounding tissue was not considerably increased as a result of reducing dose to OARs and the SWOARs. Hence dose to the unspecified non-target tissue (NTT) and parotid glands were collected for all plans. The high and low dose NTT volumes were based on the prescription dose, with the high dose calculated as the volume of NTT that received 68 Gy or higher, and low dose calculated as the volume of NTT that received 56 Gy or higher.

The mean dose to each of the 5 'clinical' SWOARs structures was recorded for both the ST-IMRT and SW-IMRT plans. The V50 and V60 for the whole pharyngeal constrictor, glottis and supraglottis in both plans were also collected [27]. In addition, the mean percent dose spared (%DS) for each SWOARs structure in the optimised plan was calculated (ST-IMRT dose minus SW-IMRT dose, divided by the ST-IMRT dose for each patient), as was the percent overlap of each SWOARs structure with the PTV as per van der Laan et al. [25].

Analysis and Statistics

The quality and viability of the plans were investigated by comparing the tumour coverage, and ensuring the shift of dose to NTT and/or parotid glands were not excessively higher with SW-IMRT versus ST-IMRT plans. Wilcoxon matched pairs *t*-test (due to non-normal distribution) were calculated for the following variables: mean dose to the PTV1 and PTV2 D98, mean dose to the parotid glands and volume of NTT receiving > 68 Gy and > 56 Gy (high and low dose NTT, respectively).

The mean dose to each of the 5 'clinical' SWOARs structures and the V50/V60 for the whole pharyngeal constrictor, glottis and supraglottis between the ST-IMRT and SW-IMRT plans were compared using the Wilcoxon matched pairs *t* test (due to non-normal distribution). The number

of optimising sequences to generate the ST-IMRT and SW-IMRT plans was compared using a repeated measures t-test. Significance for all statistical comparisons was set at $p < 0.05$. Descriptive statistics were used to report the %DS for each SWOARs structure in the optimised plan, and percent overlap of each SWOARs structure with the PTV.

To answer the secondary aim, the 8 SWOARs structures, as contoured using the Christianen et al. [17] guidelines and international consensus 'research' structure guidelines [18], were overlayed with the difference in contour volume and overlap expressed as a Concordance Index (CI) [34]. The CI provides information of position and volume of overlap, calculated by dividing the intersection of volumes and the union of volumes, with values of 1 representing perfect overlap and 0 representing no overlap [34].

Results

All plans were deemed to meet target volume coverage requirements for adequate treatment of the disease. Statistical analysis revealed no significant difference between the PTV1 D98 and PTV2 D98 of the ST-IMRT and SW-IMRT plans (Table 2). In addition, dose to the NTT and parotid glands were deemed acceptable, with both structures not significantly different between the two plans. Therefore all ST- and SW-IMRT plans were considered viable.

The mean dose to majority of the SWOARs was lower for the SW-IMRT plan compared to the ST-IMRT plan, with significant dose reductions observed for the whole pharyngeal constrictors ($p < 0.001$), supraglottis ($p < 0.001$), glottis ($p = 0.028$) and cricopharyngeal inlet ($p = 0.001$) (Table 3). The average percent volume spared was greatest for the whole pharyngeal constrictor of 4.81%, followed by the supraglottis. There was no significant change to dose to the extended oral cavity. The volume of the whole pharyngeal constrictor, supraglottic larynx and glottic larynx receiving 50 Gy (V50) was significantly reduced with the SW-IMRT plan, while the volumes receiving 60 Gy (V60) was reduced for the whole pharyngeal constrictor and supraglottic larynx (Table 4). The largest overlap between the PTV and SWOARs was found with the whole pharyngeal constrictor at 41% (Table 5).

The amount of time needed to contour the set of SWOARs reduced over time as the radiation therapist became familiar with the process, with an overall average of 30 min required for each patient. A mean of 2.2 versus 3.4 optimisation sequences were needed to obtain acceptable ST-IMRT and SW-IMRT plans, respectively. This difference was statistically significant (SD = 1.155; $t = -5.196$; $p < 0.001$). The average increase of 1.2 optimisation sequences would result in an estimated 40 min of extra clinical time to complete each SW-IMRT plan. Therefore the average total additional time for completing a SW-IMRT plan was 70 min

Table 2 Quality check of the ST-IMRT and SW-IMRT plans

	ST-IMRT		SW-IMRT		*Z*	*p*-value
	Mean	SD	Mean	SD		
PTV1 D98	54.72 Gy	± 1.25	54.72 Gy	± 1.498	−0.013	0.989
PTV2 D98	66.93 Gy	± 0.86	66.74 By	± 1.125	−1.461	0.144
Dose L parotid	21.87 Gy	± 12.26	21.94 Gy	± 12.50	−0.330	0.741
Dose R parotid	17.83 Gy	± 10.59	17.77 Gy	± 11.11	−1.112	0.266
Low dose non-target tissue	157.55 cc	± 49.66	158.97 cc	± 58.95	−0.283	0.778
High dose non-target tissue	5.881 cc	± 4.85	6.05 cc	± 5.06	−0.861	0.389

Table 3 Dose to the SWOARs in ST-IMRT versus SW-IMRT

SWOARs[a]	ST-IMRT mean dose (Gy)		SW-IMRT mean dose (Gy)		*Z*	*p*	Mean dose spared Gy (%)
	Mean	SD	Mean	SD			
Whole pharyngeal constrictor	56.26	5.75	53.35	6.61	−4.292	<0.001*	2.67 (4.81)
Supraglottic larynx	55.65	9.43	53.05	11.58	−3.996	<0.001*	1.7 (3.03)
Glottic larynx	48.82	11.23	47.23	10.57	−2.193	0.028*	1.4 (2.29)
Extended oral cavity	47.36	6.90	47.63	6.71	−0.821	0.412	−0.6 (−0.32)
Cricopharyngeal inlet	45.45	8.89	42.92	9.32	−3.215	0.001*	2.0 (4.06)

[a]International consensus guidelines [18] were used to delineate the SWOARs structures

*Significant value

Table 4 V50 and V60 to the pharynx (whole pharyngeal constrictor) and larynx (supraglottic larynx and glottic larynx)

	ST-IMRT Mean V50 (%)		SW-IMRT Mean V50 (%)		*Z*	*p*	ST-IMRT Mean V60 (%)		SW-IMRT Mean V60 (%)		*Z*	*p*
	Mean	SD	Mean	SD			Mean	SD	Mean	SD		
Whole pharyngeal constrictor	72.64	21.09	61.46	21.00	−4.286	<0.001*	43.36	18.01	39.78	17.20	−3.592	<0.001*
Supraglottic larynx	72.81	33.03	65.77	34.65	−3.945	<0.001*	40.60	28.14	34.60	25.82	−3.543	<0.001*
Glottic larynx	63.76	39.31	58.71	38.89	−2.059	0.039*	10.13	14.30	10.47	21.64	−1.590	0.112

*Significant value

Table 5 Overlap of SWOARs and PTV

SWOARs	Percent overlap of SWOARs and PTV	
	Mean	SD
Whole pharyngeal constrictor	41.02	± 19.45
Supraglottic larynx	28.95	± 27.49
Glottic larynx	8.32	± 21.85
Extended oral cavity	23.40	± 13.38
Cricopharyngeal inlet	4.58	± 15.12

(calculated by the summation of the contouring time and extra optimisation sequencing time).

The overlap volumes of the 8 SWOARs structures using Christianen et al. [17] and international consensus guidelines [18] are displayed in Table 6. The low CI values (all less than 0.5) indicate geometric comparisons of the SWOARs structures in these two guidelines are lacking in similarity.

Discussion

The current study used in silico planning for a group of patients with oropharyngeal tumours, to explore the feasibility of minimising radiotherapy dose to the SWOARs without impacting on dose to the PTV or NTT, or clinical workload. A significant improvement in mean dose to majority of the SWOARs (up to 5% dose reduction per SWOAR), as well as reductions in volume of the pharynx and larynx receiving 50 Gy (V50) and 60 Gy (V60), was found with a SW-IMRT versus ST-IMRT plan. When comparing the concordance between previously used contouring guidelines [17] and international consensus delineation guidelines [18], the current study found low-moderate levels of agreement in the CI calculations, suggesting a limited ability to compare outcomes across SWOARs optimisation studies. Nonetheless, the current study highlights significant dose reductions using the international consensus guidelines [18] are achievable, with no impact on tumour coverage, for patients with oropharyngeal cancer.

There are a limited number of studies that have investigated the amount of dose spared to the SWOARs with SW-IMRT versus ST-IMRT planning [24–26, 29]. From these heterogeneous studies, significant dose reductions were found, ranging from 3.9 to 5.6 Gy per structure with SWOARs-optimised planning [16, 24, 29], with a smaller mean dose to the SWOARs ultimately achieved for laryngeal/hypopharyngeal groups compared to the oropharyngeal/nasopharyngeal groups [24, 29]. The current oropharyngeal cohort also found a significant reduction in dose to the majority of the SWOARs with a SW-IMRT versus ST-IMRT plan. A lesser amount of dose reduction was achieved with a SW-IMRT plan in the current study (ranging from 1.4 to 2.7 Gy per SWOAR), however the final mean dose to the SWOARs were much lower when compared to previous oropharyngeal/nasopharyngeal groups (i.e. pharyngeal constrictor mean dose of 53.4 Gy in current study versus 62.7 Gy

Table 6 Concordance Index (CI) between the Christianen et al. 2011 [17] and international consensus guideline delineations [18]

	Mean Christianen et al. volume (cm^3)	Mean international consensus volume (cm^3)	Mean CI (±SD)
Whole pharyngeal constrictor	18.47	14.67	0.45 (±0.07)
Superior pharyngeal constrictor	8.85	9.48	0.43 (±0.11)
Middle pharyngeal constrictor	3.36	3.31	0.42 (±0.11)
Inferior pharyngeal constrictor	5.11	2.94	0.33 (±0.08)
Anterior oropharynx/BOT	15.73	24.09	0.27 (±0.12)
Supraglottic larynx	6.62	13.11	0.32 (±0.11)
Glottic larynx	6.28	2.60	0.30 (±0.11)
Cricopharyngeal inlet	1.10	2.42	0.15 (±0.13)

[24] and 63.3 Gy [29] in previous studies). This may be related to there being a smaller initial dose to the SWOARs in the ST-IMRT plan prior to optimisation in the current study than those previously reported, and subsequently a lesser amount of dose reduction was achieved. In addition, the difference in patient demographics in regards to tumour site, T-stage and overlap of the PTV and SWOARs may also explain the differing outcomes between the current study and previous literature. Specifically, van der Laan et al. noted tumours with an intermediate overlap (versus small or large overlap) with the PTV and SWOARs benefited the most from optimisation, with a combined superior pharyngeal constrictor and supraglottic larynx overlap of > 75% with the PTV predicting less favourable dose reduction [25]. When comparing similar outcomes with the current study, the combined overlap of the pharyngeal constrictor and supraglottic larynx with the PTV was 70%, approaching the suggested 75% threshold for poor optimisation potential [25]. Despite our small dose reduction, the difference between SW- and ST-IMRT plans was statistically significant, thus requiring further examination to determine the functional benefit for patients with this dose improvement.

There is not currently a standardised dose limit recommended for the SWOARs structures which would translate to improved dysphagia post-treatment. The QUANTEC guidelines developed in 2010 are to date the most comprehensive clinical recommendations published for dose constraints to the head and neck structures [23]. These guidelines have recommended limiting the V50, and when possible V60, to the pharynx and larynx to improve swallowing outcomes post-treatment [27]. In a recent review of studies conducted since the QUANTEC publication, the recommendations were further upheld and 'well in line' with the more recent evidence, with a mean dose between 50 and 60 Gy to the pharynx and larynx continuing to demonstrate an increased risk of dysphagia [23]. Furthermore, other reviews have suggested that *any* dose reduction to these structures is clinically beneficial, independent of the degree of dose-minimisation [19, 35]. As the current study achieved a significant reduction in mean dose to 4 of the 5 SWOARs, as well as in all V50 and V60 values to the pharynx/larynx (with the exception of the V60 to the glottis), a degree of clinical benefit would be anticipated. These results suggest SW-IMRT planning may be a worthwhile practice to implement with oropharyngeal patients.

Although an improvement in the dose to the SWOARs has been identified in the current and previous studies, the anticipated clinical compromises of using SW-IMRT planning need to be taken into consideration. Due to the nature of RT treatment, dose that is reduced from the SWOARs during SW-IMRT planning must be shifted to other tissues in the area. It has been suggested that the degree of success with using SW-IMRT planning relies in part on the willingness of the treating oncologist to accept the shifted dose to be transposed to NTT (i.e. healthy surrounding tissue) [24]. However the true clinical implications of NTT dose are not yet well understood [23]. Early studies examining dose-distribution to surrounding structures have found dose shifts to submental musculature and oral cavity predict swallow dysmotility [36] and increased dysphagia burden in oropharyngeal patients post-treatment [25], thus posing potential barriers to translating SW-IMRT into clinical practice. In the current study, the extended oral cavity was the only SWOARs structure which did not improve with SW-IMRT planning, but at the same time did not significantly increase (mean 47.4 Gy and 47.6 Gy in ST-IMRT and SW-IMRT respectively). Additionally no significant difference in dose volumes for the NTT between ST- and SW-IMRT plans was found. The results of the current study suggest dose shifts to the NTT and oral cavity were not significant using SW-IMRT planning, and therefore additional related treatment toxicity would be unexpected.

Another factor impacting on the use of SW-IMRT planning in clinical practice is the extra workload required to contour and optimise these additional structures. Van der Laan et al. [25] was the only other study found which commented on the additional clinical time required for this practice, with an additional 7 optimisation sequences (for a total of 17) required to complete a SW-IMRT versus ST-IRMT plan. The current study had much lower average sequence numbers of 2.2 and 3.4 for ST-IMRT and SW-IMRT plans respectively. This is most likely due to the different treatment planning software used, with more automatic and longer optimisation time per sequence needed with the current facility's Elekta Monaco software (with Monte Carlo) versus the Pinnacle software used in van der Laan et al. [25]. Although the extra 1.2 optimisation sequences for a SW-IMRT plan was statistically significant in the current study, the estimated 70 extra minutes of clinical time per patient (when including extra contouring time) should be advocated for if this dose optimisation translated into meaningful change in post-treatment dysphagia.

Another factor impacting on the ability to compare outcomes across optimisation studies in head and neck cancer cohorts, has been the variation in delineation guidelines historically used for the SWOARs. The need for a clear selection, definition and boundaries for SWOARs structures has been previously highlighted [30]. In the current study, the new international consensus guidelines [18], which were developed to standardise SWOARs delineation, were found to have a low concordance with previously used Christianen et al. guidelines. This outcome was not unexpected, given notable differences exist between some of the structures chosen and anatomical boundaries defined for the SWOARs [18], as well as inter-observer variability which occurs during contouring. As it is anticipated that future studies and

clinical practice will use the international guidelines for contouring the SWOARs structures, any comparisons to previous literature using the Christianen et al. guidelines need to be interpreted with caution, given the notable structural differences which were found in the current study.

Limitations

Although this study confirmed a reduction in dose to the SWOARs was achievable, as this was only investigated using an in silico data analysis process, further study is required to identify the true clinical benefit for swallowing outcomes of implementing these guidelines into practice. Additionally the relatively small number of patients in the current study did not allow for further analysis to include other parameters (such as T-stage, bilateral neck treatment, PTV and SWOARS overlap) that may also impact on the feasibility of reducing dose to the SWOARS. The authors considered using the NTCP model, which has been implemented in previous studies, to predict dysphagia rates for this group. However, this was not completed as the international consensus guidelines do not include the same clinical SWOARs structures which were used in this model (i.e. the superior pharyngeal constrictor muscle included in the NTCP model is considered a 'research' structure only in the international consensus guidelines), and therefore impacted on the utilisation of this calculation. The authors are aware of a prospective randomised control trial examining clinical outcomes of ST-IMRT versus SW-IMRT which is currently underway [37], however this study has not incorporated the international consensus guidelines. Nonetheless, their data will provide further insight into potential benefits for swallowing outcomes using SW-IMRT.

Conclusions

A growing body of evidence has illustrated the potential benefit of SW-IMRT planning on dose to the SWOARs, however its translation into practice for patients with head and neck cancer is not yet routine. Inconclusive evidence on the feasibility of implementing this clinical practice has limited widespread uptake. Results from the current study add to this body of evidence, demonstrating the ability to spare dose to the SWOARs for oropharyngeal tumours (which have previously been assumed to have little/no potential benefit due to the overlapping tumour volume) without PTV and NTT compromise, and with potentially manageable impact on clinical resources. All efforts should be made to improve outcomes for this group, especially due to the large population of young patients with HPV-related disease who live for decades after treatment but are at risk of long-term dysphagia. Results for this study support that SW-IMRT should be considered as part of clinical practice for planning RT treatment for oropharyngeal tumours.

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Compliance with Ethical Standards

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