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Overview

Dysphagia-optimised Intensity-modulated Radiotherapy Techniques in Pharyngeal Cancers: Is Anyone Going to Swallow it?

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Abstract

Dysphagia after primary chemoradiotherapy or radiation alone in pharyngeal cancers can have a devastating impact on a patient's physical, social and emotional state. Establishing and validating efficient dysphagia-optimised radiotherapy techniques is, therefore, of paramount importance in an era where health-related quality of life measures are increasingly influential determinants of curative management strategies, particularly as the incidence of good prognosis, human papillomavirus-driven pharyngeal cancer in younger patients continues to rise. The preferential sparing achievable with intensity-modulated radiotherapy (IMRT) of key swallowing structures implicated in post-radiation dysfunction, such as the pharyngeal constrictor muscles (PCM), has generated significant research into toxicity-mitigating strategies. The lack of randomised evidence, however, means that there remains uncertainty about the true clinical benefits of the dosimetric gains offered by technological advances in radiotherapy. As a result, we feel that IMRT techniques that spare PCM cannot be incorporated into routine practice. In this review, we discuss the swallowing structures responsible for functional impairment, analyse the studies that have explored the dose–response relationship between these critical structures and late dysphagia, and consider the merits of reported dysphagia-optimised IMRT (Do-IMRT) approaches, thus far. Finally, we discuss the dysphagia/aspiration-related structures (DARS) study (ISRCTN 25458988), which is the first phase III randomised controlled trial designed to investigate the impact of swallow-sparing strategies on improving long-term function. To maximise patient benefits, improvements in radiation delivery will need to integrate with novel treatment paradigms and comprehensive rehabilitation strategies to eventually provide a patient-centric, personalised treatment plan.

Key words: DARS; dysphagia; dysphagia-optimised IMRT; pharyngeal cancers; superior pharyngeal constrictor

Statement of Search Strategies Used and Sources of Information

This overview is based on peer-reviewed articles identified via Pubmed using search terms including pharyngeal cancers, dysphagia-optimised IMRT, head and neck cancer, and dysphagia. Additional relevant papers were reviewed through searching reference lists for included studies.

Introduction

The recent emergence of predominantly good-prognosis, radiosensitive, human papillomavirus-driven pharyngeal tumours [1–3] has resulted in an enlarging cohort of cancer survivors living with devastating long-term functional impairments [4], paradoxically as a result of 'organ-preserving' primary chemoradiotherapy (CRT) or radiotherapy alone. Radiotherapy-induced dysphagia represents a substantial burden in this context, with nearly 50% of patients highlighting it as a distressing symptom a year after treatment completion [5]. Persistent swallowing dysfunction leads to increased aspiration risks, which is typically under-reported in most head and neck cancer (HNC) trials, where assessments are undertaken only at the onset of clinical symptoms, thereby failing to identify patients who aspirate silently, and detected only after incidental objective evaluation. Other consequences of swallowing dysfunction include prolonged feeding tube dependence, psychological disturbances and worsened health-related quality of life (HR-QoL) [6–13]. In comparison with radiotherapy, primary

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surgical options are limited to locally advanced hypopharyngeal cancers, where severe tumour-related symptoms compromise organ function; and in T1-2 N0 oropharyngeal cancers (OPC), where minimally invasive transoral surgery in conjunction with neck dissection might be an alternate function-preserving, less morbid therapeutic option [14]. However, a significant proportion of patients treated with transoral surgery require adjuvant radiotherapy-based treatment, thereby undermining the benefits of primary surgery [15]. There is, therefore, a real risk that current treatment approaches will lead to a generation of cured patients who are 'pharyngeal cripples' [16], and we feel that there is an urgent unmet need to devise efficient swallow-sparing radiotherapy strategies in pharyngeal cancer.

The introduction of fixed-field intensity-modulated radiotherapy (IMRT), with its ability to sculpt complex dose distributions, has revolutionised radiation delivery for pharyngeal cancer in the last decade. IMRT has been shown to improve HR-QoL by reducing long-term xerostomia, without compromising locoregional control [17]. Increasingly, there is a focus to establish dysphagia-optimised IMRT (Do-IMRT) strategies [18], which could translate into improved long-term symptom burden outcomes for pharyngeal cancer patients by reducing dose to critical swallowing structures. Refinements to existing technology, in the form of arc-based IMRT and adaptive radiotherapy, offer exciting potential to optimise current toxicity-sparing radiotherapy strategies and maximise patient benefits. Reducing dose to certain organs-at-risk does not always translate into meaningful preservation of long-term function, however, as highlighted by the mixed outcomes from other function-sparing radiotherapy trials in HNC [17,19] and, therefore, we feel it is essential to explore the clinical benefits of Do-IMRT within the context of a randomised study, before routine implementation. Here, we review the evidence base for Do-IMRT in pharyngeal tumours, and consider how the dysphagia/aspiration-related structures (DARS) study, our currently accruing multi-centre phase III randomised controlled trial, may facilitate further incremental benefits in swallowing outcomes.

Key Swallowing Structures and Dosimetric Correlation with Post-radiation Dysphagia

The swallowing process is complex, involving the intricate co-ordination of more than 25 pairs of muscles in the oropharynx and larynx, and cartilages [20]. Pioneering work by Eisbruch *et al.* [21] firmly established the strong influence of pharyngeal constrictor muscles (PCM) and glottis-supraglottic larynx (GSL) irradiation on persistent functional impairment after CRT in HNC [21]. Their study additionally showed that 50 Gy was the lowest maximal dose delivered to a stricture volume – a surrogate for late dysphagia, implying that it may be clinically advantageous to minimise the volumes receiving of $\geq$50 Gy (V_{50}) in such critical DARS. Compared with three-dimensional conformal radiotherapy, IMRT reduced DARS V_{50} by 7–10% on average, consequently motivating a number of centres to analyse the influence of the dose delivered to DARS on various measures of late dysphagia. In recent years, additional structures such as the oral cavity and the mylo/geniohyoid complex have also been implicated with persistent dysfunction [22,23].

Several statistically significant dose–response constraints for key swallowing structures have been proposed as a result (Table 1). Strong correlations exist between both partial volume doses and mean doses with persistent dysphagia outcomes, implying that the mean dose as a solitary dosimetric variable should suffice for planning optimisation [33].

Despite an abundance of published literature, it is challenging to make unequivocal conclusions regarding the optimal swallow-sparing parameters. The systematic review by Duprez *et al.* [34], which concurred that the mean dose to the PCM was a strong predictor of subsequent functional impairment, highlighted a number of crucial methodological and statistical variations among the analysed studies that hindered the validity of the review's outcomes. Significant heterogeneity in a number of confounding and prognostic variables, such as primary tumour location, tumour stage, use of concomitant chemotherapy, fractionation schedule and target volume definition, limit the conclusions that can be drawn. The robustness of the reported results is further diluted with the predominantly retrospective nature of most studies, together with small sample sizes and inconsistent recording of swallowing outcomes.

Nonetheless, what remains undisputed is that reducing the radiation dose to DARS, without compromising on survival outcomes, is an absolute prerequisite for improving long-term swallowing function [18,35]. Furthermore, the degree of sparing of individual DARS required to generate potential increments in function will vary, depending upon the site of the primary tumour. For instance, in primary NPC and OPC, the superior pharyngeal constrictors (SPC) will probably be irradiated to a radical dose compared with GSL and, consequently, more likely to account for swallowing difficulties after treatment completion. Focussed efforts to reduce the SPC dose in such scenarios will probably be advantageous, rather than sparing the GSL. Similarly, in hypopharyngeal cancers, the inferior constrictors and GSL radiation doses will probably play a more influential role on long-term swallowing function.

Having established a definitive correlation between DARS and dysphagia, the next step was to direct efforts prospectively to evaluate the long-term clinical and functional gains, if any, of reducing dose to DARS.

Approaches to Reduce Radiation Dose to Swallowing Structures

Reducing Mean Dose to the Superior Pharyngeal Constrictors and Supraglottic Larynx Using a Model-based Validation Approach

Designed and promoted successfully by a consortium of leading Dutch radiation oncologists primarily for the

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Table 1
Intensity-modulated radiotherapy (IMRT) studies investigating the correlation between radiation dose to swallowing structures and late dysphagia

Reference	Patient no.	Tumour site	Treatment modality	Dysphagia outcome measure	Dysphagia end point	Timing	DARS	Dosimetric parameters correlating with late dysphagia
[24]	36	OPC, NPC	CRT	VF UW-QOL HN-QOL RTOG/EORTC LRMS	Aspiration Stricture Grade 2 ORD PRD liquids PRD solids	3 months	PCM GSL – PCM Oesophagus, PCM PCM	Mean 60 Gy, V_{65}>50% V_{50}>50% Limited cases; statistical analysis not possible Mean dose – TNS Mean dose – TNS Mean dose – TNS
[22]	31	OPC	CRT	MBS MDADI	OPSE Composite MDADI score Aspiration	6–24 months	Anterior OC SPC – –	V30>65% V55>80% None predictive Limited cases, statistical analysis not possible
[25]	96	OC, OPC, NPC, HPC, larynx, unknown primary, maxillary sinus	IC+CRT CRT RT PORT	SPS Video swallow study	Aspiration Stricture	1–2 months	Larynx IC IC Larynx	Mean 48 Gy; V_{50}>21% Mean 54 Gy; V_{50} >51% Mean 54 Gy; V_{50}>51% V_{50} >21%
[26]	37	OPC, NPC, HPC, larynx	IC+CRT	MDADI RTOG/EORTC-scored dysphagia	MDADI score ORD	12 months	PCM Suprahyoid muscles	Nil significant
[27]	83	OC, OPC, NPC, HPC, larynx, unknown primary	CRT RT Cetuximab+RT	MBS	FT dependence Aspiration Stricture requiring dilatation	12 months	Larynx IPC Larynx IPC SPC MPC	Mean 51 Gy V_{60}>12% Mean 41 Gy, V_{60}>24% V_{60}>12% V_{65}>33% V_{65} > 75%
[28]	27	OC, OPC, HPC, larynx, unknown/other	CRT RT	HNCI	QoL score Weight loss FT rates Dietary modifications	12 months	– AEF False VC False VC Upper OS Lateral PW	Nil significant Mean 50 Gy, at the level of false VC
[29]	39	OC, OPC, HPC, larynx, unknown primary	CRT	CTCAE v2.0 UW-QOL	FT dependence	>192 days	IPC CPI	Mean 60 Gy; V_{65}>30%; V_{60}>60% Dmax 62 Gy
[23]	34	OPC	CRT	VF	Aspiration Stricture FT dependence Aspiration pneumonia	>12 months	SPC MHM	MHM V_{69} and SPC V_{70} associated with late dysphagia

(*continued on next page*)

Table 1 (*continued*)

Reference	Patient no.	Tumour site	Treatment modality	Dysphagia outcome measure	Dysphagia end point	Timing	DARS	Dosimetric parameters correlating with late dysphagia
[30]	354*	OC, OPC, NPC, HPC, larynx, unknown primary, other	RT CRT	RTOG/EORTC LRMS EORTC QLQ-H&N 35	>grade 2 dysphagia (primary end point) Patient-reported symptoms (secondary end point)	6 months	SPC SL	Mean dose to both most predictive of late toxicity Different predictive models were found for solid food, liquids, soft food and choking
[31]	259	OC, OPC, NPC, HPC, larynx	RT CRT Other	EORTC QLQ-H&N 35 MBS† DAHANCA dysphagia scale	PRD SPSS, aspiration >grade 2 dysphagia	3 years	GSL SPC, MPC	Mean dose 55 Gy Mean dose 60 Gy
[32]	56	OC, OPC, NPC, larynx, salivary glands	CRT IC+CRT RT, PORT	RTOG/EORTC LRMC	>grade 2 dysphagia	6 months	SPC	V60>70%

AEF, aryepiglottic fold; CPI, cricoid pharyngeal inlet; CRT, chemoradiation; DARS, dysphagia/aspiration-related structures; FT, feeding tube; GSL, glottis-supraglottic larynx; HNCI, Head and Neck Cancer Inventory; HN-QOL, head and neck quality of life; HPC, hypopharyngeal cancer; IC, induction chemotherapy; IPC, inferior pharyngeal constrictors; MBS, modified barium swallow; MHM, myelo-geniohyoid complex; MDADI, MD Anderson Dysphagia Inventory; MPC, middle pharyngeal constrictors; NPC, nasopharyngeal cancer; OC, oral cavity; OPC, oropharyngeal cancer; OPSE, oropharyngeal swallowing efficiency; ORD, observer-rated dysphagia; OS, oesophageal sphincter; PCM, pharyngeal constrictor muscles; PORT, postoperative radiotherapy; PRD, patient-reported dysphagia; PW, pharyngeal wall; RT, radiotherapy; RTOG/EORTC LRMS, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scale; SL, supraglottic larynx; SPC, superior pharyngeal constrictors; SPS, Swallowing Performance Scale; SPSS, Swallowing Performance Status Scale; TNS, threshold not specified; UW-QOL, University of Washington head and neck-related quality of life; VC, vocal cords; VF, videofluoroscopy.

* 38% of patients treated with intensity-modulated radiotherapy.

† 65 patients only.

selective implementation of proton therapy in their country, the normal tissue complication probability (NTCP) model-based concept is described as a practical alternative to randomised controlled trials, particularly where the principal aim of a novel radiation technique is toxicity reduction rather than survival gains. In this multi-step methodology, any potential benefit predicted during the early phases is subsequently confirmed by validating its model-based estimates in a cohort of patients who are prospectively followed-up [36,37].

Christianen *et al.* [30] initially determined that mean doses to the SPC and supraglottic larynx were most predictive of Radiation Therapy Oncology Group (RTOG) grade ≥ 2 dysphagia at 6 months after treatment completion in a heterogeneous group of HNC patients. Their subsequent *in silico* comparative planning study, in predominantly pharyngeal cancers, suggested a 8.9% reduction in mean NTCP (42% versus 33%) for the physician-rated toxicity scores with swallow-sparing IMRT (SW-IMRT) that was additionally optimised to reduce doses to SPC, supraglottic larynx, middle constrictors and oesophageal inlet, in that order of priority, compared with standard IMRT [38]. DARS-sparing was achieved by reducing planning target volume coverage in its vicinity until exactly 98% of the planning target volume received 95% of the prescribed dose, together with accepting a moderate shift of dose to non-specified tissues, such as the neck muscles and the oral cavity [39]. Absolute gains in NTCP values varied considerably, depending on the primary tumour site, nodal involvement and tumour stage. Finally, their model was clinically validated in a prospective cohort of 186 patients treated with SW-IMRT, where the mean predicted $NTCP_{SW\text{-}IMRT}$ for the entire group corresponded perfectly with the observed grade ≥ 2 dysphagia prevalence of 22.6%, and was significantly lower than the predicted $NTCP_{standard}$ of 27.5% [40]. The predicted differences were significantly larger (24.1% versus 32.2%) and, importantly, clinically relevant in about 50% of patients with a $\Delta NTCP$ ($NTCP_{standard} - NTCP_{SW\text{-}IMRT}$) $> 5\%$, with observed toxicity prevalence of 25.3%. Patients in this subset typically had higher T stages, primary OPC or NPC and were treated more often with conventional radiotherapy or CRT.

The group's novel SW-IMRT technique did not compromise target volume coverage, a detrimental limitation of some of the previous planning studies. Likewise, doses to the major salivary glands did not differ compared with standard IMRT, crucial as patients' perceptions of swallowing difficulties can often be influenced to varying degrees by co-existing xerostomia [41]. By excluding patients with grade > 1 dysphagia at baseline, the investigators ensured that any subsequently reported dysphagia was purely treatment-related.

Implementing such a model-based approach in routine clinical practice, however, will be resource- and time-intensive, with its success reliant on experienced physicists having iteratively to adjust the planning objectives for DARS until a suitable plan is achieved. Equally, treatment planning systems with a fully automated or class solution, where comparatively less effort is required to achieve a satisfactory plan, are less likely to spare DARS sufficiently to observe a clinical benefit. Crucially, as with any planning modelling exercise, the predictability of the reported benefits ultimately depends on the robustness of the primary end point selected to develop the particular model. In that context, the use of physician-scored, RTOG-graded dysphagia at 6 months to define post-radiotherapy long-term dysphagia is arguably the weakest link of the above model. The Dutch group justified the 6 month post-treatment timeline, as they felt it to be a reliable predictor of swallowing deterioration at subsequent timeframes. That is questionable, with numerous HNC studies showing substantial variation in swallowing outcomes beyond 6 months [5,42]. Furthermore, data recently published by the same group analysing patterns of RTOG-scored swallowing dysfunction after HNC treatment established that 23% of patients could have a clinically relevant change in the physician-reported dysphagia scores beyond 6 months, indicating that the 6 month timeline is inconsistent at predicting future toxicity [43]. The same study additionally showed the decreasing influence of radiation dose to supraglottic larynx over time, leaving the SPC as the sole significant variable.

It must also be emphasised that physician-reported swallowing scores often do not correlate well with patient-reported outcomes and, as a primary end point, may not necessarily provide the best measure of toxicity outcomes. For instance, in the Dutch group's model, NTCP-based reductions in patient-reported swallowing dysfunction with SW-IMRT were variable and lower than observer-rated NTCP reductions. Similar inconsistencies between observer- and subjective-reported dysphagia have also been reported in other studies, strengthening the argument for incorporating multidimensional complementary physician-scored, patient-reported and instrumental swallowing assessments [33,44,45].

Reduce the Radiation Dose to Parts of Dysphagia/Aspiration-related Structures Outside the Target Volume

Situated in close proximity to the PCM, both medial and lateral groups of retropharyngeal lymph nodes (RPN) have been historically included in radiation target volumes for pharyngeal cancer. As a result, the constrictors usually receive a substantial radiation dose, making it challenging to preserve long-term function. Feng *et al.* [24] observed that the practice of irradiating the entire uninvolved RPN compartment was inconsistent with the available evidence on patterns of nodal spread, as indicated by the paucity of metastasis to medial RPN in several surgical and radiological series. The group postulated that the medial group of RPN could be safely excluded from OPC target volumes in their novel Do-IMRT approach, thereby potentially improving function without affecting survival outcomes.

They prospectively evaluated their hypothesis in a selective group of stage III/IV OPC patients treated with primary CRT [42]. Parts of PCM, GSL and oesophagus in the region of the uninvolved medial RPN were spared by setting an optimal dose constraint <50 Gy in the IMRT planning

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objectives, which subsequently delivered mean doses of 48, 42 and 32 Gy, respectively, to the spared regions. Corresponding mean doses to the entire structures were 58, 48 and 34 Gy, respectively. With a median follow-up period of 3 years, the clinical outcomes of such dosimetric modulation in this single-arm study were no worse than standard approaches, with locoregional recurrence-free and disease-free survival rates of 96% and 88%, respectively. Crucially, there were no failures observed within or near the spared region, thereby establishing the safety of this swallow-sparing technique.

Patient-reported swallowing outcomes from two established questionnaires showed worsening soon after the completion of treatment, with gradual improvement through 12 months and subsequent stabilisation, whereas CTCAE v2.0-based observer-reported dysphagia scores at 12 months almost matched baseline levels. Unlike these two measures of swallowing toxicity, videofluoroscopy-related scores did not show longitudinal improvements, with no significant reductions observed beyond 3 months after treatment. The lack of late CTCAE-graded toxicities precluded any dosimetric analysis of observer-reported toxicities. Mean doses to PCM, GSL and oesophagus correlated significantly with worsening subjective and instrumental swallowing assessments, and different NTCPs with no particular threshold were observed with differing end points. The tolerance doses that estimated a 50% (TD_{50}) and 25% (TD_{25}) probability for videofluoroscopy-assessed dysphagia were 63 and 56 Gy, respectively, for PCM, and 56 Gy and 39 Gy, respectively, for supraglottic larynx [33]. The corresponding tolerance doses for patient-reported worsened outcomes were substantially higher, reflecting to some extent the increased sensitivity of videofluoroscopy to detect patients who aspirated silently.

The above study presents an innovative, practical and adaptable solution to generate a potentially beneficial toxicity-mitigating strategy in OPC; integrating existing knowledge of patterns of nodal disease spread into the IMRT planning objectives to further refine radiation delivery. Although the study only included patients with OPC, its methodology can be easily extended to other pharyngeal tumours too. A novel hypothesis at the time of study design, the concept of sparing the medial RPN from target volumes has been endorsed in the recently updated HNC nodal outlining consensus guidelines [46]. A relatively favourable patient-reported toxicity outcome, together with minimal physician-graded toxicity scores, supports the application of similar dysphagia-optimising strategies in randomised studies to better define its true benefits. Notably, the group has also reported that HR-QoL seems to remain stable with longer follow-up, with new late toxicity uncommon beyond 2 years [47].

It is clear that the above strategy cannot be extrapolated to all OPC; the study was selective by excluding any tumour with posterior pharyngeal wall or RPN involvement, explaining to a certain extent the excellent survival rates reported. The absence of a steep dose–response curve makes it difficult to establish definitive IMRT dose constraints for PCM and GSL, although the study authors have been using the videofluoroscopy-based TD_{25} information to guide their planning objectives at their centre. Sharp dose fall-offs would be expected in the regions of the spared structures, and currently available routine imaging techniques do not yet possess the required sensitivity to accurately define the mucosal extent of tumours; target contouring, therefore, would need to be more generous in such scenarios to reduce the risk of marginal recurrence, which eventually would prove to be counter-productive to the primary goal of toxicity reduction. Finally, attempting to spare the medial RPN with IMRT may result in a dose splash to adjacent structures linked to swallowing dysfunction, such as the salivary glands and oral cavity, which could potentially worsen long-term functional outcomes.

The Dysphagia/Aspiration-related Structures (DARS) Study

The above review elucidates key unambiguous points that should drive future Do-IMRT research strategies. First, a strong relationship exists between pharyngeal constrictor irradiation and long-term swallowing dysfunction in pharyngeal cancer, implying the need to spare this group of muscles as much as possible to preserve meaningful long-term function. Second, significant disparity exists between physician-reported outcomes and patients' perceptions of swallowing difficulties, making it imperative to include both subjective and objective measures of swallowing assessments to guide future toxicity-sparing strategies, particularly in the absence of a universally acceptable benchmark to measure swallowing function. Finally, in an era of evidence-based medicine, the lack of a gold-standard randomised study confirming the superiority of dysphagia-optimising radiation strategies affects the robustness of any perceived benefits reported so far and limits its incorporation into routine clinical practice.

The Cancer Research UK-funded DARS trial is currently open to recruitment and integrates the above core themes into its study design. Its results should provide a sound evidence base regarding the clinical and functional benefits of Do-IMRT in the future. The study is a UK multi-centre phase III randomised clinical trial with blinded assessments of key outcome measures, in patients undergoing radical primary CRT or radiation alone, for T1-4, N0-3, M0 primary pharyngeal cancer not involving the RPN or posterior pharyngeal wall and requiring bilateral neck irradiation [48]. Eligible patients will be randomised to either standard IMRT or Do-IMRT, where the mean dose to parts of pharyngeal constrictors lying outside the radical treatment volumes will be limited to <50 Gy. The primary objective of the study is to determine whether Do-IMRT improves swallowing outcomes, which will be evaluated as a patient-reported outcome using the MD Anderson Dysphagia Inventory (MDADI) composite score. The difference in the mean MDADI composite scores at 12 months after treatment completion between the two arms forms the primary end point of the trial. The MDADI composite score is a feasible, sensitive and validated patient-reported, swallow-

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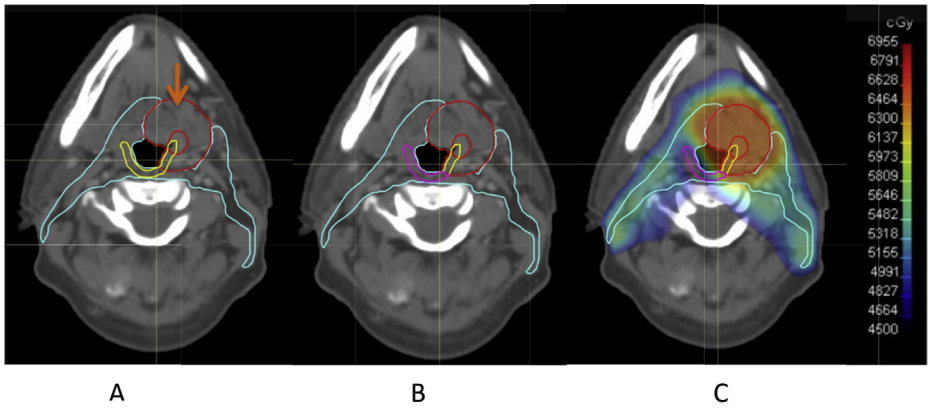

Fig 1. (A) Axial computed tomography scan showing gross tumour volume (red), clinical target volume (CTV1) for radical dose radiotherapy (red with arrow), CTV2 for prophylactic dose radiotherapy (cyan), superior/middle pharyngeal constrictor (SMPCM; yellow). (B) SMPCM lying outside CTV1 edited to create PlanSMPCM (pink). (C) PlanSMPCM is set a mean dose constraint of <50 Gy in the planning objectives.

specific questionnaire, designed for use specifically in the HNC population [49,50]. This 19-item quick to complete, written questionnaire integrates information from a patient's physical, emotional and functional level at various recovery points after treatment completion to generate an overall impairment score [5]. The MDADI is increasingly adopted in a number of head and neck studies as a functional outcome tool [51,52]. In addition to MDADI, swallowing outcomes will be comprehensively assessed using a multidimensional, longitudinal panel of objective and subjective functional outcome measures.

The planning technique is an adaptation of the methodology introduced by Feng *et al.* [42] and uses varying dose constraints for constrictor muscles depending upon the primary tumour site (Figure 1).

Conclusion

Evidence from the published literature on swallow-sparing radiotherapy strategies suggests that this approach is promising and requires further validation to confirm its clinical impact. As our quest for the optimal dysphagia-sparing radiotherapy strategy continues, encouraging dosimetric data are beginning to emerge for rotational IMRT [53] and, together with adaptive radiotherapy, this represents the next phase of investigative efforts to improve swallowing function. It is important to appreciate, however, that improvements in long-term swallow achievable through technological innovations in IMRT are finite, and by itself unlikely to eradicate deleterious post-radiation effects. Rather, it will serve as a useful adjunct to other modalities exploring similar end points. The role of protons is generating increasing interest, with retrospective toxicity-sparing outcomes emerging from single-centre institutions [54,55]. In the absence of randomised data though, it remains contentious whether any perceived benefits justify the high capital investment protons require, particularly in the current environment of stringent healthcare budgets. Strategies involving de-escalation of chemotherapy and radiotherapy [56], improving management of acute toxicities [57,58], using functional imaging to adapt radiotherapy [59], strengthening collaboration with speech and language therapists and dietetics to facilitate timely swallowing interventions and evaluating novel drug–radiotherapy combinations are some of the key measures that need to be incorporated to ultimately devise a successful personalised toxicity-mitigating approach in pharyngeal cancer.

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