Dysphagia-optimised intensity-modulated radiotherapy versus standard intensity-modulated radiotherapy in patients with head and neck cancer (DARS): a phase 3, multicentre, randomised, controlled trial

Christopher Nutting, Laura Finneran, Justin Roe, Mark A Sydenham, Matthew Beasley, Shree Bhide, Cheng Boon, Audrey Cook, Emma De Winton, Marie Emson, Bernadette Foran, Robert Frogley, Imran Petkar, Laura Pettit, Keith Rooney, Tom Roques, Devraj Srinivasan, Justine Tyler, Emma Hall, on behalf of the DARS Trialist Group

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Head and Neck Unit (Prof C Nutting FRCR, S Bhide FRCR), Department of Speech, Voice and Swallowing (J Roe PhD), Patient and Carer's Advisory Group (R Frogley), and Department of Physics (J Tyler MSc), The Royal Marsden Hospital, London, UK; Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, UK (Prof C Nutting, L Finneran MSc, M A Sydenham BSc Hons, M Emson BSc, Prof E Hall PhD); The Institute of Cancer Research, London, UK (S Bhide); Department of Surgery and Cancer, Imperial College, London, UK (J Roe); Bristol Cancer Institute, United Hospitals Bristol, Bristol, UK (M Beasley FRCR); Oncology Department, The Royal Wolverhampton NHS Trust, Wolverhampton, UK (C Boon FRCR); Gloucestershire Oncology Centre, Cheltenham General Hospital, Cheltenham, UK (A Cook FRCR); Department of Oncology, Royal United Hospital Bath, Bath, UK (E De Winton FRCR); Department of Oncology, Weston Park Hospital, Sheffield, UK (B Foran FRCR); Guys Cancer Centre, Guys and St Thomas' Hospital, London, UK (I Petkar FRCR); Lingen Davies Cancer Centre, Royal Shrewsbury Hospital, Shrewsbury, UK (L Pettit FRCR);

Summary

Background Most newly diagnosed oropharyngeal and hypopharyngeal cancers are treated with chemoradiotherapy with curative intent but at the consequence of adverse effects on quality of life. We aimed to investigate if dysphagia-optimised intensity-modulated radiotherapy (DO-IMRT) reduced radiation dose to the dysphagia and aspiration related structures and improved swallowing function compared with standard IMRT.

Methods DARS was a parallel-group, phase 3, multicentre, randomised, controlled trial done in 22 radiotherapy centres in Ireland and the UK. Participants were aged 18 years and older, had T1–4, N0–3, M0 oropharyngeal or hypopharyngeal cancer, a WHO performance status of 0 or 1, and no pre-existing swallowing dysfunction. Participants were centrally randomly assigned (1:1) using a minimisation algorithm (balancing factors: centre, chemotherapy use, tumour type, American Joint Committee on Cancer tumour stage) to receive DO-IMRT or standard IMRT. Participants and speech language therapists were masked to treatment allocation. Radiotherapy was given in 30 fractions over 6 weeks. Dose was 65 Gy to primary and nodal tumour and 54 Gy to remaining pharyngeal subsite and nodal areas at risk of microscopic disease. For DO-IMRT, the volume of the superior and middle pharyngeal constrictor muscle or inferior pharyngeal constrictor muscle lying outside the high-dose target volume had a mandatory 50 Gy mean dose constraint. The primary endpoint was MD Anderson Dysphagia Inventory (MDADI) composite score 12 months after radiotherapy, analysed in the modified intention-to-treat population that included only patients who completed a 12-month assessment; safety was assessed in all randomly assigned patients who received at least one fraction of radiotherapy. The study is registered with the ISRCTN registry, ISRCTN25458988, and is complete.

Findings From June 24, 2016, to April 27, 2018, 118 patients were registered, 112 of whom were randomly assigned (56 to each treatment group). 22 (20%) participants were female and 90 (80%) were male; median age was 57 years (IQR 52–62). Median follow-up was 39·5 months (IQR 37·8–50·0). Patients in the DO-IMRT group had significantly higher MDADI composite scores at 12 months than patients in the standard IMRT group (mean score 77·7 [SD 16·1] *vs* 70·6 [17·3]; mean difference 7·2 [95% CI 0·4–13·9]; p=0·037). 25 serious adverse events (16 serious adverse events assessed as unrelated to study treatment [nine in the DO-IMRT group and seven in the standard IMRT group] and nine serious adverse reactions [two *vs* seven]) were reported in 23 patients. The most common grade 3–4 late adverse events were hearing impairment (nine [16%] of 55 in the DO-IMRT group *vs* seven [13%] of 55 in the standard IMRT group), dry mouth (three [5%] *vs* eight [15%]), and dysphagia (three [5%] *vs* eight [15%]). There were no treatment-related deaths.

Interpretation Our findings suggest that DO-IMRT improves patient-reported swallowing function compared with standard IMRT. DO-IMRT should be considered a new standard of care for patients receiving radiotherapy for pharyngeal cancers.

Funding Cancer Research UK.

Introduction

Cancers of the pharynx are common, affecting around 3000 patients in the UK each year.[1] For most newly diagnosed patients, radiotherapy or chemoradiotherapy is the treatment of choice. These treatments are curative for the majority of patients but have adverse effects on quality of life.[2] The most common long-term side-effects of radiotherapy to the pharynx are dry mouth, dysphagia, and soft tissue fibrosis.[3]

The causes of swallowing dysfunction after radiotherapy are multifactorial but are largely related to radiation of the pharyngeal musculature responsible for the initiation and completion of swallowing. The wall of the pharynx is composed of an interior longitudinal layer of muscles and

Research in context

Evidence before this study

We searched PubMed using the terms "head and neck cancer" AND ("radiotherapy" OR "radiation" OR "IMRT") AND ("dysphagia" OR "DARS" OR "MDADI" OR "swallowing outcomes") AND "randomised trial" to find research published in any langauge between Aug 1, 2000, and Aug 1, 2022. No randomised studies were identified. Two small series of patients treated with dysphagia-optimised radiotherapy were found. The literature showed that poor swallowing outcomes affect most patients with head and neck cancer in the long-term after radiotherapy. Observational data suggest that the radiation dose delivered to the muscles of the pharynx during radiotherapy for head and neck cancer was related to swallowing function after treatment, with lower doses being associated with better swallowing outcomes. Phase 2 data from small, single centre, non-randomised trials suggested that swallowing function was improved if the radiation dose to parts of the muscles of the pharynx can be reduced to 50 Gy or less using intensity-modulated radiotherapy (IMRT).

Added value of this study

To our knowledge, this is the first phase 3 trial to compare dysphagia-optimised IMRT (DO-IMRT) with standard IMRT in patients with head and neck cancer. DO-IMRT reduces the radiation dose to the pharyngeal constrictor muscles. Our results show patient-reported superior swallowing function after 12 months in participants treated with DO-IMRT compared with those treated with standard IMRT. We also showed improvements in clinician-reported outcomes with DO-IMRT.

Implications of all the available evidence

This level 1 evidence supports a new gold standard for radiotherapy of patients with head and neck cancer. Future research should aim to further reduce the radiation dose to the dysphagia and aspiration risk structures to refine the DO-IMRT technique.

Northern Ireland Cancer Centre, Belfast City Hospital, Belfast, UK (K Rooney FRCR); **Clinical Oncology, Norfolk and Norwich University Hospital, Norwich, UK** (T Roques FRCR); **Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK** (D Srinivasan FRCR)

Correspondence to: Prof Christopher Nutting, Head and Neck Unit, The Royal Marsden Hospital, London SW3 6JJ, UK
chris.nutting@rmh.nhs.uk

an external circular layer of muscles comprising the three pharyngeal constrictors. The organs at risk in the swallowing mechanism have been identified as the superior, middle, and inferior constrictor muscles, the glottis and supraglottic larynx, and the anterior oral cavity.[4]

The clinical consequences of swallowing dysfunction after radiotherapy can be mild, with restriction of diet or modification of swallowing function, or might be severe, particularly if swallowing is so badly affected that aspiration of food into the lungs is a risk, resulting in the requirement for a permanent gastrostomy tube and long-term supportive care.[5–7] A clinically relevant and statistically significant deterioration in swallowing function has been observed using patient-reported outcome measures following radiotherapy for head and neck cancer, with little improvement at 1 year and almost half of patients highlighting swallowing as a priority concern.[8–9] In a review, aspiration rates of 30–62% were reported in studies using objective instrumental measures of swallowing, in addition to patient-reported outcome measures, in patients with symptomatic and asymptomatic head and neck cancer who had received chemoradiotherapy.[10] These negative functional and social impacts are accompanied by a negative effect on mortality, with aspiration contributing to 19% of non-cancer deaths.[11]

Intensity-modulated radiotherapy (IMRT) is the most widely used radiotherapy technique for head and neck cancer in the UK. Previous studies have confirmed that IMRT can be used to treat head and neck cancer effectively while reducing toxicity by sparing organs at risk, such as the salivary glands.[3] Dysphagia-optimised IMRT (DO-IMRT) is a novel radiotherapy technique that reduces radiation dose to the pharyngeal muscles known as the dysphagia and aspiration risk structures.[12] We aimed to test the hypothesis that DO-IMRT would reduce long-term swallowing problems compared with standard IMRT.

Methods

Study design and participants

DARS was a parallel-group, phase 3, multicentre, randomised controlled trial of DO-IMRT versus standard IMRT undertaken at 22 radiotherapy centres in Ireland and the UK (appendix p 9). The full protocol has been published previously and is provided in the appendix.[13]

See Online for appendix

Eligible patients were aged 18 years or older with biopsy-confirmed squamous cell carcinoma of the oropharynx or hypopharynx with no clinical evidence of metastatic disease (stage I–IVB; T1–4, N0–3, M0) and without previous malignancy (except non-melanoma skin cancer and cervical carcinoma in situ), who were suitable for radical chemoradiotherapy and had a WHO performance status of 0 or 1 and creatinine clearance more than 50 mL/min. Only patients requiring bilateral neck radiotherapy were included. Previous radiotherapy or major surgery to the head and neck region and current or previous tracheostomy placement was not permitted. Patients with tumours involving the posterior pharyngeal wall, post cricoid, or those with retropharyngeal nodes or pre-existing swallowing problems unrelated to cancer diagnosis were not eligible. Patients were recruited by their clinical care teams and provided written informed consent before enrolment. Participants could discontinue study treatment at any time, at their own request or at discretion of their treating clinician and would be treated as per standard practice and followed up for recurrence and survival. Participant sex was self-reported.

The trial was approved by Queens Square Research Ethics Committee (London, UK; 15/LO/1464), sponsored

by The Royal Marsden NHS Foundation Trust, and conducted in accordance with the principles of Good Clinical Practice. The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU; London, UK) coordinated the study and carried out central data management, statistical data monitoring, and all analyses. The trial management group was overseen by independent data monitoring and trial steering committees (appendix p 10).

Randomisation and masking

A two-stage registration and randomisation enrolment process was used to avoid bias, with clinician outlining of target volumes completed after registration and before randomisation. Participants were centrally randomly assigned (1:1) by ICR-CTSU to receive either standard IMRT or DO-IMRT. Treatment allocation used a minimisation algorithm incorporating an 80% random element; balancing factors were centre, use of induction and concomitant chemotherapy (none *vs* concomitant chemotherapy alone *vs* induction and concomitant chemotherapy), tumour type (hypopharynx *vs* human papillomavirus [HPV]-positive oropharynx *vs* HPV-negative or HPV-unknown oropharynx) and American Joint Committee on Cancer (AJCC) tumour stage (1–2 *vs* 3–4). Participants and speech and language therapists were masked to treatment allocation.

Procedures

All participants in both groups underwent radiotherapy planning in accordance with the DARS radiotherapy protocol.[13] In brief, a five-point immobilisation shell was used and a contrast-enhanced radiotherapy CT planning scan of the neck was done in the treatment position. Gross tumour volumes of the primary tumour and any lymph node metastases were localised and 10 mm margins added to construct a high-dose clinical target volume (CTV 65 Gy). A second clinical target volume (CTV 54 Gy) covered elective lymph nodal regions at risk of harbouring occult microscopic disease and the remaining primary tumour subsite. Margins of 3–5 mm were added to form planning target volumes (PTV 65 Gy and PTV 54 Gy) as per treating institutions' planning protocols.

The pharyngeal constrictor muscles were defined anatomically using MRI scans.[14] Two organs at risk were delineated: the superior and middle pharyngeal constrictor muscles as a single structure and the inferior pharyngeal constrictor muscle. For the DO-IMRT group only, mandatory and optimal dose constraints were applied to these organs at risk where not overlapping with CTV 65 Gy to achieve mean doses less than 50 Gy or lower if possible. Radiotherapy was given over 6 weeks. The dose was 65 Gy given in 30 fractions over 6 weeks to PTV 65 Gy and 54 Gy in 30 fractions over 6 weeks to PTV 54 Gy (appendix pp 61–62). Treatment interruptions were managed in accordance with Royal College of Radiologists guidelines. Before activation, each participating site completed a radiotherapy quality assurance programme run by the National Institute for Health Research funded Radiotherapy Trials Quality Assurance.[15]

Baseline investigations included a diagnostic CT or MRI scan of the head and neck region, chest x-ray or CT of the thorax, a full blood count, renal function test, electrolyte measurement, liver function tests, histology report, dental assessment, and baseline toxicity assessment.

All participants in both groups with adequate haematological and renal function (creatinine clearance ≥60 mL/min before starting treatment [amended from ≥50 mL/min via protocol amendment May 5, 2017]) received concomitant intravenous cisplatin 100 mg/m^2 on day 1 and day 29 of radiotherapy. Where cisplatin chemotherapy was contraindicated, participants had concurrent intravenous carboplatin (area under the curve 5, day 1 and day 29), or radiotherapy alone.

Participants were assessed for acute toxicity using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0[16] weekly during radiotherapy and for weeks 1–4 and at 8 weeks after radiotherapy. Specific acute toxicities of interest included dermatitis, mucositis, dysphagia, hoarse voice, weight loss, fatigue, and dry mouth Late toxicity was assessed at 3, 6, 12, 18, and 24 months after radiotherapy using NCI CTCAE version 4.0 and radiotherapy side-effects were graded with the Late Effects on Normal Tissues–Subjective Objective Management Analytic (LENT–SOMA) scoring systems.[17–18] Specific late toxicities of interest were dysphagia (oesophageal stricture and aspiration), voice changes, and fatigue. Centres were encouraged to use a reactive approach to feeding tubes, placing them only if there was a clinical requirement during treatment. All centres were encouraged to use prophylactic swallowing exercises. Clinical follow-up was according to standard practice. Swallowing function was evaluated by a speech and language therapist or a trained delegate at baseline and at 3, 6, 12, 18, and 24 months after treatment using a water swallowing test[19] and the Performance Status Scale for Head and Neck cancer (PSS-HN).[20] PSS-HN scores are scaled 0–100, with good performance defined as scores greater than 50 (appendix p 8). Given the multicentre nature of this study, clear standard operating procedures were developed and refined in partnership with speech and language therapists working in participating centres to ensure that swallowing evaluations were undertaken consistently.[13] In a subset of centres, optional video-fluoroscopic examination of swallowing function was assessed using the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) at baseline and at 12 months and 24 months after radiotherapy.

Patient-reported outcomes were measured using the MD Anderson Dysphagia Inventory (MDADI), which has 20 questions, each with a 5-point Likert scale.[21] The composite total score ranges from 20, indicating very low functioning, to 100, indicating extremely high functioning and is the sum of the emotional, functional,

and physical problems subscales. A global subscale addressing the impact of swallowing problems on quality of life is scored separately (appendix pp 3–4). The University of Washington Quality of Life Questionnaire (UW-QOL) version 04 was used to assess patient-reported outcomes.[22] The UW-QOL examines 12 domains (scaled from 0 [worst] to 100 [best]), including swallowing and swallowing-related functions. The questionnaire asks patients to select up to three domains of most importance to them over the past seven days; and has three global questions on health-related and overall quality of life (appendix pp 5–7). Both questionnaires were administered on paper, in the clinic at baseline and by mail to the participant at 3, 6, 12, 18, and 24 months after treatment.

All participants had a clinical assessment to determine response to treatment at 6–8 weeks after completing radiotherapy. Radiological evaluation was performed with CT or MRI at 3 months;[23] there was no central review. Examination under anaesthesia with or without biopsy and fine needle aspiration of the lymph node was undertaken where there was suspicion of residual disease.

Outcomes

The primary outcome measure was MDADI composite score at 12 months after treatment completion.

Secondary patient-report outcomes were MDADI subscale scores, evaluation of the longitudinal pattern of swallowing function up to 24 months after treatment using the MDADI composite and subscale scores, and the UW-QOL swallowing, saliva, taste and chewing domains, importance ratings, composite scores, and global health-related and overall quality-of-life questions.

Secondary outcomes of clinician-rated speech and swallowing were reported using the PSS-HN normalcy of diet, place of eating, and understandability of speech scores.[20] Other secondary endpoints were acute and late toxicity rates, feeding tube status (presence of tube at 3 months, 12 months [primary timepoint of interest], and 24 months), time to first use of feeding tube (from randomisation), time feeding tube was in place, time feeding tube was in use, local and regional tumour control, resection rates (defined as the proportion of participants proceeding to surgical treatment [including neck dissection] after completion of radiotherapy), location of and time to tumour recurrence (from randomisation to date of local, regional, or distant disease recurrence, or death from head and neck cancer), and overall survival (defined as time from randomisation to date of death from any cause). The secondary outcome of the water swallowing test will be reported separately; the secondary outcome of videofluoroscopy will also be reported separately following central review.

Statistical analysis

In a previous cohort of patients treated with standard IMRT,[10] mean MDADI composite score 12 months after treatment completion was 72 (SD 13·8). Assuming this mean score and standard deviation, 84 participants were required to give 90% power to detect a clinically relevant 10-point improvement in MDADI composite score[24] at the two-sided 5% significance level. To allow for drop-out due to disease recurrence or death before 12 months and non-compliance with the 12-month questionnaire, it was assumed that 80% of randomly assigned participants would be evaluable for the primary endpoint. The target sample size was therefore 102 participants. The trial was not powered to detect differences in oncological outcomes. Sequential review of locoregional recurrences was undertaken by the independent data monitoring committee to protect against increased risk in the DO-IMRT group; there was no other formal interim analysis.

A statistical analysis plan was written before the analysis. All patient-reported outcome scores were calculated using standard algorithms. Unless specific

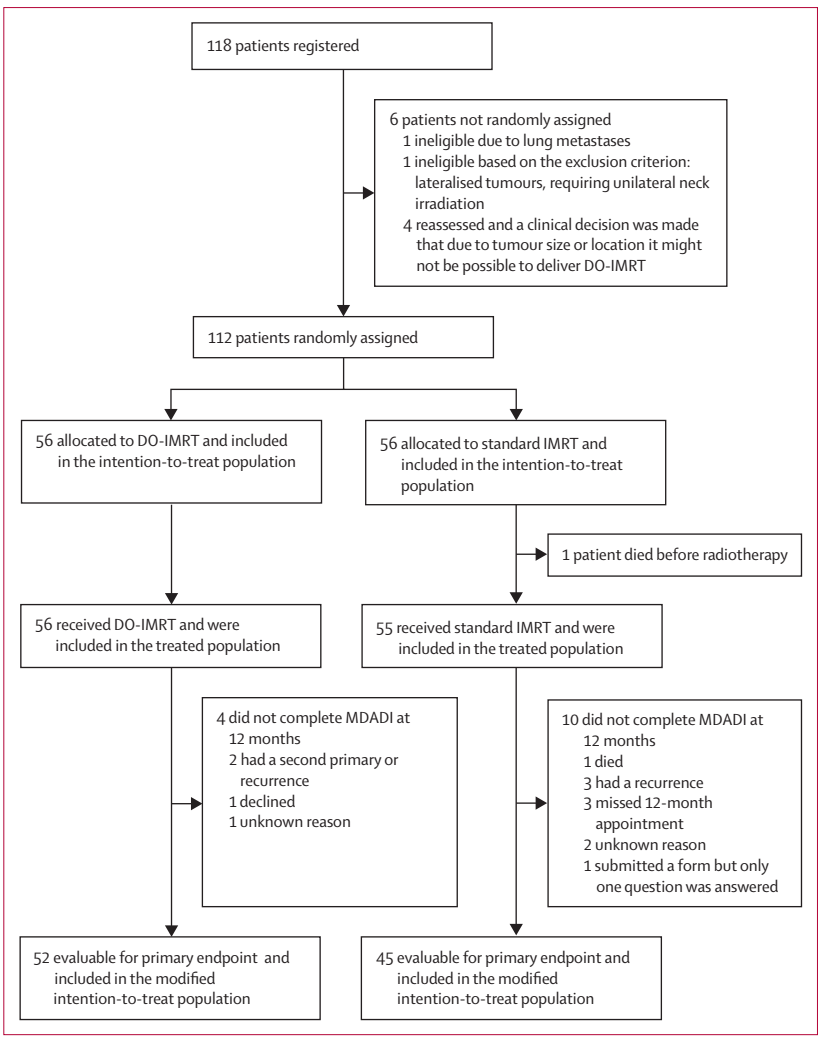

Figure 1: **Trial profile**
DO-IMRT=dysphagia-optimised intensity-modulated radiotherapy. IMRT=intensity-modulated radiotherapy. MDADI=MD Anderson Dysphagia Inventory.

	DO-IMRT group (n=56)	Standard IMRT group (n=56)
Sex		
Female	15 (27%)	7 (13%)
Male	41 (73%)	49 (88%)
Age at randomisation, years		
<40	3 (5%)	0
40–49	9 (16%)	12 (21%)
50–59	19 (34%)	26 (46%)
60–69	21 (38%)	14 (25%)
70–79	4 (7%)	4 (7%)
Site of tumour*		
Hypopharynx	2 (4%)	1 (2%)
Oropharynx, HPV positive	47 (84%)	46 (82%)
Oropharynx, HPV negative or unknown	7 (13%)	9 (16%)
Side of tumour		
Left	23 (41%)	20 (36%)
Midline	3 (5%)	5 (9%)
Right	30 (54%)	31 (55%)
AJCC stage*†		
1	3 (5%)	1 (2%)
2	2 (4%)	5 (9%)
3	16 (29%)	18 (32%)
4	35 (63%)	32 (57%)
T stage†		
T1	10 (18%)	10 (18%)
T2	30 (54%)	32 (57%)
T3	10 (18%)	8 (14%)
T4a	6 (11%)	6 (11%)
N stage†		
N0	6 (11%)	6 (11%)
N1	11 (20%)	8 (14%)
N2a	11 (20%)	6 (11%)
N2b	23 (41%)	31 (55%)
N2c	5 (9%)	4 (7%)
N3	0	1 (2%)
(Table 1 continues in next column)		
(Continued from previous column)		
Smoking history		
Current smoker	5 (9%)	6 (11%)
Ex smoker	25 (45%)	29 (52%)
Never smoked	25 (45%)	20 (36%)
Unobtainable	1 (2%)	1 (2%)
Intended use of chemotherapy*		
Concomitant only	49 (88%)	47 (84%)
Induction and concomitant	1 (2%)	4 (7%)
None	6 (11%)	5 (9%)
Feeding tube at randomisation		
No	46 (82%)	46 (82%)
Yes	10 (18%)	10 (18%)
Baseline MDADI composite score	87·2 (15·6; 40·0–100·0)	87·6 (12·8; 57·5–100·0)

Data are n (%) or mean (SD; range). AJCC=American Joint Committee on Cancer. DO-IMRT=dysphagia-optimised intensity-modulated radiotherapy. HPV=human papillomavirus. IMRT=intensity-modulated radiotherapy. MDADI=MD Anderson Dysphagia Inventory. TNM=tumour, node, metastasis. *Used as balancing factors in minimisation. †TNM version 7 and AJCC version 7 editions were used.

Table 1: **Baseline characteristics**

scoring instructions stated otherwise, if more than 50% of questions in a quality-of-life subscale were completed, the scores were pro-rated. The sum of subscales was multiplied by the number of items in the subscale and then divided by the number of items actually answered. If 50% or more of the questions in a subscale had not been answered, the subscale was considered as missing.

Unless otherwise specified, analyses were conducted in the intention-to-treat population with fixed time-point analyses using all data available. No imputation was used for missing questionnaires. Primary endpoint analysis was done in the modified intention-to-treat population, including all randomly assigned participants with 12-month MDADI data available, with mean scores compared using two-sample *t*-test. Analysis of covariance was used to adjust for other patient and clinical factors (including baseline MDADI score, site of tumour, AJCC score, and use of chemotherapy) that might be associated with MDADI composite score at 12–24 months after treatment. A sensitivity analysis was conducted to only include participants with a 12-month MDADI assessment occurring within a 2-month timeframe of when the 12 month assessment was due.

Median radiation dose received by anatomical structures of interest were compared between treatment groups by Mann-Whitney test. Patient reported outcome scores were compared using two-sample *t*-tests with boxplots used to illustrate score distribution at each timepoint. Post-hoc analysis was done to illustrate the change from baseline scores over time. The proportion of participants who had a clinically relevant 10-point change in MDADI subscale scores was compared using a χ^2 test. UW-QOL importance ratings are presented as proportion of participants selecting each domain. Proportions of participants with PSS-HN scores greater than 75 or greater than 90 were compared between treatment groups using a χ^2 test.

Feeding tube status (tube in use at 12 months) and resection rate were compared between treatment groups using a two-sided Fisher's exact test or χ^2 test if there were a sufficient number of events. A quantitative description of time to first feeding tube use, time the tube was in place, time the tube was in use, and local and regional tumour control rates was also recorded.

Comparisons of clinician reported toxicity were performed in the population of randomly assigned

participants who received at least one fraction of radiotherapy (treated population). The proportions of participants with severe toxicities (grade 3 or higher) and any grade toxicity at any timepoint over the acute and late timeframes were compared between treatment groups using a two-sided Fisher's exact test or χ^2 test if there were a sufficient number of events.

Time-to-event endpoints are presented using Kaplan-Meier plots with treatment groups compared using the log-rank test in the intention-to-treat population. For time to recurrence, patients were censored at second primary cancer diagnosis, death from another cause, or date last seen; overall survival was censored at date last seen. Estimates of treatment effect (with 95% CIs) were made using unadjusted and adjusted (for balancing factors other than centre) Cox regression models, with a hazard ratio (HR) less than 1 favouring DO-IMRT. The proportional hazards assumption of the Cox model held when tested with Schoenfeld residuals.

To make some adjustment for multiple testing, a significance level of 1% was used for all secondary endpoints. Analyses were conducted using Stata version 16. The study is registered with the ISRCTN registry, ISRCTN25458988.

Role of the funding source

The funder of the study reviewed and approved the trial design but had no role in data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 24, 2016, and April 27, 2018, 118 patients were registered, 112 of whom were randomly assigned to DO-IMRT (n=56) or standard IMRT (n=56; figure 1). Participants' characteristics were balanced between treatment groups (table 1). Median age was 57 years (IQR 52–62), 22 (20%) participants were female, and 90 (80%) were male. No ethnicity data were collected.

Median follow-up was 39·5 months (IQR 37·8–50·0). 100 (89%) of 112 participants received concomitant chemoradiotherapy. Six (12%) of 50 participants in the DO-IMRT group and nine (18%) of 50 in the standard IMRT group had a chemotherapy dose reduction; nine (18%) participants in the DO-IMRT groups and seven (14%) in the standard IMRT group had a dose delay. 110 (98%) of 112 participants completed radiotherapy with doses as prescribed (one patient died before radiotherapy and one patient discontinued treatment after 20 fractions due to hyperosmolar non-ketotic syndrome). Median of the mean dose to the superior and middle pharyngeal constrictor muscle not overlapping with CTV 65 Gy was 57·2 Gy (IQR 56·3–58·3) in the standard IMRT group versus 49·7 Gy (49·4–49·9; p<0·0001) in the DO-IMRT group. Median of the mean dose to the inferior pharyngeal constrictor muscle not overlapping with CTV 65 Gy was 49·8 Gy (47·1–52·4) in the standard IMRT group versus 28·4 Gy (21·3–37·4; p<0·0001) in the DO-IMRT group. 67 (60%) of the 112 patients included in the trial had tonsil cancer for which sparing of a vertical strip of the contralateral pharyngeal constrictor muscle was achieved (appendix p 61).

	DO-IMRT group, mean (SD)	Standard IMRT group, mean (SD)	Mean difference (95% CI)*	p value (two sample *t*-test)	Adjusted mean difference (95% CI)†	p value (ANCOVA)
Baseline	87·2 (15·6)	87·6 (12·8)	−0·4 (−5·8 to 5·0)	0·89	..	..
3 months	70·3 (15·3)	67·5 (15·4)	2·8 (−3·1 to 8·7)	0·35	3·0 (−2·6 to 8·8)	0·29
6 months	73·4 (14·9)	68·3 (16·9)	5·2 (−1·1 to 11·4)	0·10	6·4 (0·3 to 12·5)	0·041
12 months	77·7 (16·1)	70·6 (17·3)	7·2 (0·4 to 13·9)	0·037	9·8 (3·5 to 16·0)	0·0030
18 months	78·7 (15·7)	73·7 (17·1)	5·0 (−1·8 to 11·8)	0·15	8·0 (1·5 to 14·5)	0·017
24 months	79·6 (16·5)	73·0 (17·4)	6·6 (−0·5 to 13·8)	0·070	11·1 (4·5 to 17·6)	0·0010

ANCOVA=analysis of covariance. DO-IMRT=dysphagia-optimised intensity-modulated radiotherapy. IMRT=intensity-modulated radiotherapy. MDADI=MD Anderson Dysphagia Inventory. *Mean difference is score for the DO-IMRT group minus score for the standard IMRT group. †ANCOVA adjusted for baseline MDADI composite score and clinical stratification factors (site of tumour, American Joint Committee on Cancer stage, and intended use of chemotherapy). The MDADI composite score is the average of 19 questions related to the emotional, functional, and physical aspects of swallowing. Patient responses were categorised on a five-point scale (strongly agree, agree, no opinion, disagree, or strongly disagree) and converted numerically from 1 (strongly agree) to 5 (strongly disagree). Scores were then summarised by multiplying the average score by 20 to yield score on a scale from 0 (worst) to 100 (best).

Table 2: **MDADI composite scores**

21 (88%) of 24 centres declared the use of prophylactic swallowing exercises. 52 (93%) patients in the DO-IMRT group and 45 (80%) patients in the standard IMRT group completed the 12-month MDADI questionnaire. At 12 months, patients in the DO-IMRT group had significantly higher MDADI composite scores than patients in the standard IMRT group (mean score 77·7 [SD 16·1] *vs* 70·6 [17·3]; mean difference 7·2 [95% CI 0·4–13·9]; p=0·037). After adjusting for baseline score and clinical balancing factors, the mean difference was 9·8 (95% CI 3·5–16·0; p=0·0030). The difference in MDADI composite score persisted at 24 months (table 2). Seven participants (four in the DO-IMRT group and three in the standard IMRT group) had 12-month MDADI scores reported less than 10 months or more than 14 months from the end of radiotherapy and were excluded from the sensitivity analysis. In this analysis, the mean difference was 7·0 (95% CI −0·2 to 14·1; p=0·056 [unadjusted]) and 9·9 (3·5 to 16·4; p=0·0030 [adjusted]; appendix p 12).

At 12 months, the MDADI global, emotional, functional, and physical subscales scores in the DO-IMRT group were not significantly different from those in the standard IMRT group (appendix p 10). Inspection of the longitudinal pattern of MDADI scores, change from baseline scores over time, and proportion of participants who had a clinically relevant change showed a similar pattern, with regard to differences between the groups, that persisted to 24 months (figure 2; appendix pp 13–16).

UW-QoL domain scores were generally higher in the DO-IMRT group than in the standard IMRT group (table 3). At 12 months, the domains most frequently cited as important were saliva, swallowing, and taste

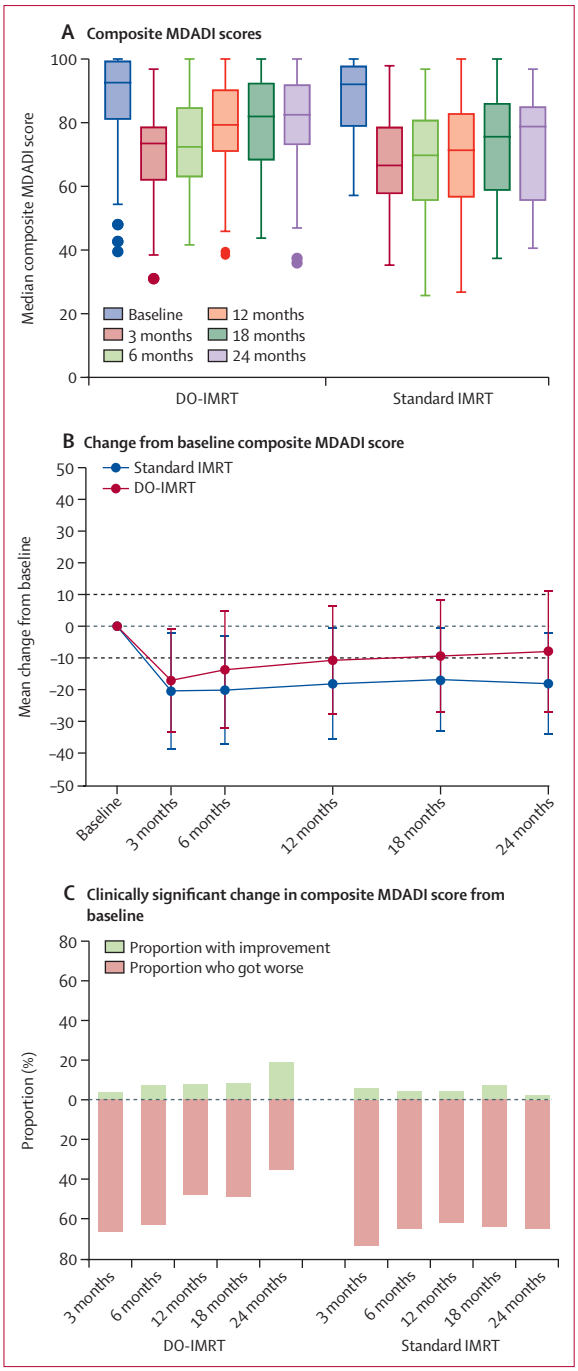

Figure 2: **Composite MDADI scores by treatment groups**
(A) Distribution of the composite MDADI score over time for both treatment groups: quartiles with median (box), 1·5 × IQR (whiskers), and any outliers beyond the whiskers. (B) Mean change from baseline for composite MDADI domain score (post-hoc analysis); error bars represent the SD, the central dotted line represents no change from baseline, and the top and bottom dotted lines represent a 10 point increase and a 10 point decrease, respectively. (C) Proportion of patients who had a 10 point (clinically significant) change for better or worse in composite MDADI score. DO-IMRT=dysphagia-optimised intensity-modulated radiotherapy. IMRT=intensity-modulated radiotherapy. MDADI=MD Anderson Dysphagia Inventory.

(appendix p 17). These domains were also the most highly ranked at 3 and 24 months (appendix p 17). Global questions of general health related quality of life, as well as the physical and socioemotional subscale scores were reported at 12 and 24 months (appendix pp 18–20).

At 12 months, scores of 90 or more were reported for PSS-HN normalcy of diet by 32 (62%) of 52 patients in the DO-IMRT group and 20 (45%) of 44 in the standard IMRT group. Scores of 75 or more were reported for PSS-HN eating in public scores by 44 (85%) patients in the DO-IMRT group and 33 (75%) in the standard IMRT group (appendix p 11). Understandability of speech scores were 75 or more for the duration of the study period for all participants (appendix p 11). Inspection of the longitudinal pattern of the PSS-HN score and the change from baseline scores showed a similar pattern that persisted to 24 months (appendix p 21).

At 12 months, there was no significant difference between the groups in the proportion of patients with a feeding tube inserted (appendix p 23). Details of feeding tube use, the time the tube was in place, and the time the tube was in use are shown in the appendix (p 24). Nine surgical treatments were reported by eight participants (all in the standard IMRT group) after the completion of radiotherapy treatment (p=0·0030; appendix p 24).

Maximum grade acute and late adverse events are shown in table 4. The most common grade 3–4 late adverse events were hearing impairment (nine [16%] of 55 in the DO-IMRT group *vs* seven [13%] of 55 in the standard IMRT group), dry mouth (three [5%] *vs* eight [15%]), and dysphagia (three [5%] *vs* eight [15%]). Further details by timepoint are shown in the appendix (pp 25–61). During radiotherapy, 42 (75%) of 56 participants in the DO-IMRT group and 48 (87%) of 55 in the standard IMRT group reported grade 3 or worse adverse events. The most common grade 3 or worse adverse events during radiotherapy (reported by >25% of all participants) were dysphagia (27 [48%] of 56 participants in the DO-IMRT group *vs* 32 [58%] of 55 in the standard IMRT group), oral mucositis (21 [38%] *vs* 31 [56%]), anorexia (16 [29%] *vs* 26 [47%]), pharyngeal mucositis (14 [25%] *vs* 21 [38%]), and dry mouth (11 [20%] *vs* 18 [33%]). In the acute post-treatment period, 40 (71%) of 56 participants in the DO-IMRT group and 47 (85%) of 55 in the standard IMRT group reported grade 3 or worse adverse events, with the most common being dysphagia (26 [46%] of 56 participants in the DO-IMRT group *vs* 39 [71%] of 55 in the standard IMRT group), oral mucositis (18 [32%] *vs* 26 [47%]), anorexia (12 [21%] *vs* 25 [45%]), pharyngeal mucositis (12 [21%] *vs* 22 [40%]) and dry mouth (ten [18%] *vs* 19 [35%]). Overall, grade 3 or worse acute adverse events were reported by 49 (88%) of 56 participants in the DO-IMRT group and 50 (91%) of 55 participants in the standard IMRT group, with no significant differences between groups.

At 3 months, four (7%) of 55 participants in the DO-IMRT group and 11 (20%) of 54 in the standard IMRT

group reported grade 3 adverse events (no patients had grade 4 adverse events; 32 [58%] *vs* 38 [70%] had grade 2 or worse adverse events); grade 3 adverse events reported by more than 5% of participants were dry mouth (one [2%] *vs* five [9%]; 26 [47%] *vs* 26 [48%] had grade 2 or worse) and dysphagia (two [4%] *vs* six [11%]; 17 [31%] *vs* 15 [28%] had grade 2 or worse). The only other adverse event reported by more than 10% of participants at grade 2 or worse was impaired hearing (six [11%] of 55 in the DO-IMRT group *vs* six [11%] of 54 in the standard IMRT group; appendix pp 37–39).

The number of participants with grade 3 or worse adverse events at 6 months was six (11%) of 55 participants in the DO-IMRT group versus six (11%) of 54 in the standard IMRT group (appendix pp 40–42), at 12 months was seven (13%) of 54 versus four (8%) of 50 (appendix pp 43–45), at 18 months was four (8%) of 53 versus four (8%) of 48 (appendix pp 46–48), and at 24 months was seven (13%) of 52 versus seven (15%) of 47 (appendix pp 49–51). Over all late toxicity follow-up timepoints, grade 3 or worse adverse events were reported in 15 (27%) of 55 participants in the DO-IMRT group and 20 (36%) of 55 participants in the standard IMRT group, with no significant differences between groups.

Late LENT–SOMA grade 3 or worse adverse events were reported in 33 (60%) of 55 participants in the DO-IMRT group versus 28 (53%) of 53 participants in the standard IMRT group at 3 months, 22 (40%) of 55 versus 26 (48%) of 54 at 6 months, 22 (41%) of 54 versus 18 (36%) of 50 at 12 months, 18 (33%) of 54 versus 16 (33%) of 49 at 18 months, and 17 (33%) of 52 versus 14 (30%) of 47 at 24 months. Over all timepoints, 42 (76%) of 55 participants in the DO-IMRT group and 44 (80%) of 55 in the standard IMRT group had grade 3 or worse LENT–SOMA adverse events, with no significant differences between groups. 25 serious adverse events (16 serious adverse events assessed as unrelated to study treatment [nine in the DO-IMRT group and seven in the standard IMRT group] and nine serious adverse reactions [two in the DO-IMRT group and seven in the standard IMRT group]) were reported in 23 participants. The most frequently reported serious adverse events were fever (two [4%] of 55 in the standard IMRT group), vomiting (one [2%] of 56 in the DO-IMRT group and one [2%] in the standard IMRT group), viral illness (two [4%] in the DO-IMRT group), and acute kidney injury (two [4%] in the DO-IMRT group). The most frequent serious adverse reaction was acute kidney injury (five serious adverse reactions were reported in four of 111 patients (one participant in the DO-IMRT group, and three in the standard IMRT group).

Four local recurrences (two in the DO-IMRT group and two in the standard IMRT group), all located at the primary site, were reported. No regional recurrences were reported. Five patients reported a distant metastatic recurrence (three in the DO-IMRT group and two in the standard IMRT group; appendix p 22). One patient in the DO-IMRT group had both a local and distant recurrence. There was no evidence of a difference in the time to recurrence (HR 0·94 [95% CI 0·24–3·78]; p=0·94; appendix p 22). Using adjusted (for balancing factors other than centre) Cox regression models gave an HR of 0·91 (95% CI 0·22–3·70). Six second primary tumours were reported, in one (2%) of 56 participants in the DO-IMRT group and five (9%) of 56 participants in the standard IMRT group (p=0·099).

11 deaths were reported, five in the DO-IMRT group and six in the standard IMRT group. Cause of death for participants in the DO-IMRT group were head and neck cancer (n=3) and other cancer (n=2), and for participants in the standard IMRT group were head and neck cancer (n=2), other cancer (n=1), pneumonia (n=1), infection (n=1), and cardiovascular (n=1). No treatment-related deaths were reported. The overall survival rate was 91·1% (95% CI 80·4–97·0) in the DO-IMRT group and 89·3% (78·1–96·0) in the standard IMRT group (HR 0·79 [95% CI 0·24–2·59]; log-rank p=0·69). Using adjusted (for balancing factors other than centre) Cox regression models gave an HR of 0·73 (0·22–2·43; appendix p 22).

	DO-IMRT group		Standard IMRT group		p value comparing the means
	Mean score (SD)	Patients scoring 100	Mean score (SD)	Patients scoring 100	
3 months					
Swallowing	80·0 (16·1)	19/53 (36%)	70·0 (18·0)	8/53 (15%)	0·0042
Taste	51·3 (26·2)	5/53 (9%)	45·9 (28·1)	4/54 (7%)	0·32
Saliva	47·0 (28·3)	4/53 (8%)	36·0 (22·9)	0/54	0·040
Chewing	78·8 (26·8)	31/52 (36%)	68·3 (28·1)	21/52 (40%)	0·049
12 months					
Swallowing	81·3 (16·5)	21/52 (40%)	72·2 (16·7)	7/46 (15%)	0·0060
Taste	64·8 (26·8)	12/52 (23%)	52·9 (28·8)	5/45 (11%)	0·043
Saliva	53·7 (22·7)	3/52 (6%)	47·4 (27·8)	2/46 (4%)	0·24
Chewing	81·7 (28·1)	35/52 (67%)	73·9 (29·3)	24/46 (52%)	0·14
24 months					
Swallowing	81·3 (16·6)	19/47 (40%)	73·2 (18·2)	8/41 (20%)	0·031
Taste	70·0 (26·7)	16/48 (33%)	58·3 (31·1)	10/41 (24%)	0·079
Saliva	55·4 (25·4)	2/48 (4%)	54·4 (22·3)	1/41 (2%)	0·70
Chewing	87·5 (21·9)	36/48 (75%)	76·8 (24·0)	23/41 (56%)	0·054

The UW-QOL questionnaire domains of most interest are scaled evenly from 0 (worst) to 100 (best) according to the hierarchy of response. DO-IMRT=dysphagia-optimised intensity-modulated radiotherapy. IMRT=intensity-modulated radiotherapy. UW-QOL=University of Washington Quality of Life Questionnaire.

Table 3: **UW-QOL domain scores**

Discussion

To our knowledge, DARS is the first randomised trial to assess the effect of DO-IMRT on patient-reported swallowing outcomes. Sparing the constrictor muscles of the pharynx using DO-IMRT significantly improved the MDADI score at 1 year after treatment and beyond.

	DO-IMRT group					Standard IMRT group				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Acute toxicity*										
Acute kidney injury	52 (93%)	1 (2%)	0	3 (5%)	0	50 (91%)	2 (4%)	0	3 (5%)	0
Alopecia	11 (20%)	38 (68%)	7 (13%)	0	0	11 (20%)	41 (75%)	3 (5%)	0	0
Anaemia	22 (39%)	28 (50%)	5 (9%)	1 (2%)	0	24 (44%)	27 (49%)	4 (7%)	0	0
Anaphylactic reaction	55 (98%)	0	0	0	1 (2%)	55 (100%)	0	0	0	0
Anorexia	4 (7%)	10 (18%)	23 (41%)	19 (34%)	0	6 (11%)	8 (15%)	11 (20%)	30 (55%)	0
Blood alkaline phosphatase increased	56 (100%)	0	0	0	0	53 (96%)	1 (2%)	0	1 (2%)	0
Blood creatinine increased	54 (96%)	2 (4%)	0	0	0	51 (93%)	3 (5%)	0	1 (2%)	0
Blood uric acid increased	56 (100%)	0	0	0	0	54 (98%)	0	0	0	1 (2%)
Body temperature increased	55 (98%)	0	0	1 (2%)	0	55 (100%)	0	0	0	0
Candida infection	50 (89%)	2 (4%)	3 (5%)	1 (2%)	0	54 (98%)	1 (2%)	0	0	0
Colitis	56 (100%)	0	0	0	0	54 (98%)	0	0	1 (2%)	0
Constipation	9 (16%)	26 (46%)	21 (38%)	0	0	3 (6%)	32 (58%)	19 (35%)	1 (2%)	0
Cough	45 (80%)	10 (18%)	1 (2%)	0	0	48 (87%)	7 (13%)	0	0	0
Dehydration	21 (38%)	21 (38%)	7 (13%)	7 (13%)	0	19 (35%)	26 (47%)	3 (6%)	7 (14%)	0
Dermatitis radiation	0	11 (20%)	29 (52%)	16 (29%)	0	1 (2%)	12 (22%)	25 (46%)	17 (31%)	0
Diarrhoea	53 (95%)	2 (4%)	1 (2%)	0	0	46 (84%)	6 (11%)	2 (4%)	1 (2%)	0
Dry mouth	0	12 (21%)	30 (54%)	14 (25%)	0	0	20 (36%)	27 (49%)	27 (49%)	0
Dysgeusia	31 (55%)	15 (27%)	10 (18%)	0	0	42(76%)	6 (11%)	7 (13%)	0	0
Dyspepsia	49 (88%)	3 (5%)	4 (7%)	0	0	50 (91%)	2 (4%)	3 (5%)	0	0
Dysphagia	1 (2%)	3 (5%)	19 (34%)	33 (59%)	0	2 (4%)	2 (4%)	11 (20%)	40 (73%)	0
Fatigue	1 (2%)	16 (29%)	34 (61%)	5 (9%)	0	0	15 (27%)	28 (51%)	12(22%)	0
Gamma-glutamyltransferase increased	55 (98%)	1 (2%)	0	0	0	51 (93%)	1 (2%)	1 (2%)	2 (4%)	0
Haematoma NOS	55 (98%)	0	0	1 (2%)	0	55 (100%)	0	0	0	0
Hearing impaired	28 (50%)	23 (41%)	5 (9%)	0	0	25 (46%)	22 (40%)	6 (11%)	2 (4%)	0
Hiccups	52 (93%)	3 (5%)	1 (2%)	0	0	50 (91%)	4 (7%)	0	1 (2%)	0
Hoarseness	17 (30%)	27 (48%)	11 (20%)	1 (2%)	0	13 (24%)	25 (46%)	12 (22%)	5 (9%)	0
Hyperkalaemia	54 (96%)	1 (2%)	0	1 (2%)	0	55 (100%)	0	0	0	0
Hypernatraemia	55 (98%)	0	0	1 (2%)	0	55 (100%)	0	0	0	0
Hypokalaemia	53 (95%)	0	0	2 (4%)	1 (2%)	53 (96%)	0	1 (2%)	1 (2%)	0
Hyponatraemia	56 (100%)	0	0	0	0	52 (95%)	1 (2%)	0	2 (4%)	0
Hypophosphataemia	55 (98%)	0	0	1 (2%)	0	53 (96%)	1 (2%)	1 (2%)	0	0
Infection NOS	52 (93%)	1 (2%)	2 (4%)	1 (2%)	0	53 (96%)	0	1 (2%)	1 (2%)	0
International normalised ratio increased	55 (98%)	0	0	1 (2%)	0	55 (100%)	0	0	0	0
Laryngeal inflammation	34 (65%)	9 (17%)	8 (15%)	1 (2%)	0	27 (52%)	11 (21%)	10 (19%)	4 (8%)	0
Lower respiratory tract infection	54 (96%)	0	0	2 (4%)	0	52 (95%)	1 (2%)	2 (4%)	0	0
Lung infection NOS	55 (98%)	0	0	1 (2%)	0	55 (100%)	0	0	0	0
Lymphocyte count decreased	45 (80%)	2 (4%)	4 (7%)	3 (5%)	2 (4%)	48 (87%)	2 (4%)	3 (5%)	2 (4%)	0
Mouth ulceration	53 (95%)	2 (4%)	0	1 (2%)	0	53 (96%)	2 (4%)	0	0	0
Mucositis oral	0	5 (9%)	27 (48%)	24 (43%)	0	0	6 (11%)	14 (26%)	35 (64%)	0
Nausea	6 (11%)	15 (27%)	23 (41%)	12 (21%)	0	5 (9%)	14 (26%)	21 (38%)	15 (27%)	0
Neutropenia	53 (95%)	1 (2%)	0	2 (4%)	0	53 (96%)	0	0	2 (4%)	0
Neutropenic sepsis	55 (98%)	0	0	1 (2%)	0	55 (100%)	0	0	0	0
Non-ketotic hyperglycaemic-hyperosmolar coma	56 (100%)	0	0	0	0	54 (98%)	0	0	0	1 (2%)
Oral candidiasis	50 (89%)	2 (4%)	4 (7%)	0	0	51 (93%)	1 (2%)	3 (5%)	0	0
Pain	2 (4%)	5 (9%)	35 (63%)	14 (25%)	0	0	10 (18%)	28 (51%)	17 (31%)	0
Pharyngeal mucositis	9 (16%)	7 (13%)	23 (41%)	17 (30%)	0	7 (13%)	7 (13%)	15 (27%)	26 (47%)	0
Pharyngolaryngeal pain	39 (70%)	8 (14%)	7 (13%)	2 (4%)	0	45 (82%)	6 (11%)	3 (5%)	1 (2%)	0
Pneumoperitoneum	56 (100%)	0	0	0	0	54 (98%)	0	0	1 (2%)	0

(Table 4 continues on next page)

	DO-IMRT group					Standard IMRT group				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
(Continued from previous page)										
Rhinorrhoea	53 (95%)	1 (2%)	1 (2%)	1 (2%)	0	54 (98%)	1 (2%)	0	0	0
Salivary duct inflammation	15 (27%)	11 (20%)	26 (46%)	4 (7%)	0	17 (31%)	7 (13%)	21 (38%)	10 (18%)	0
Sepsis	55 (98%)	0	0	0	1 (2%)	55 (100%)	0	0	0	0
Tinnitus	13 (23%)	34 (61%)	8 (14%)	1 (2%)	0	16 (29%)	32 (58%)	7 (13%)	0	0
Upper respiratory tract infection NOS	54 (96%)	0	1 (2%)	1 (2%)	0	53 (96%)	0	0	2 (4%)	0
Viral infection NOS	54 (96%)	0	1 (2%)	1 (2%)	0	55 (100%)	0	0	0	0
Vocal alterations	49 (88%)	5 (9%)	1 (2%)	1 (2%)	0	52 (95%)	2 (4%)	0	1 (2%)	0
Vomiting	17 (30%)	23 (41%)	10 (18%)	6 (11%)	0	16 (29%)	28 (51%)	8 (15%)	3 (6%)	0
Weight decreased	47 (84%)	5 (9%)	4 (7%)	0	0	51 (93%)	2 (4%)	2 (4%)	0	0
White blood cell count decreased	51 (91%)	1 (2%)	3 (5%)	1 (2%)	0	53 (96%)	2 (4%)	0	0	0
Late toxicity†										
Aspiration	52 (95%)	2 (4%)	1 (2%)	0	0	49 (89%)	4 (7%)	1 (2%)	1 (2%)	0
Cough	34 (62%)	20 (36%)	0	1 (2%)	0	33 (60%)	20 (36%)	2 (4%)	0	0
Dry mouth	0	19 (35%)	33 (60%)	3 (5%)	0	2 (4%)	9 (16%)	36 (65%)	8 (15%)	0
Dysgeusia	43 (78%)	6 (11%)	5 (9%)	1 (2%)	0	43 (78%)	8 (15%)	3 (6%)	1 (2%)	0
Dysphagia	11 (20%)	17 (31%)	24 (44%)	3 (5%)	0	12 (22%)	19 (35%)	16 (29%)	8 (15%)	0
Fatigue	46 (84%)	7 (13%)	2 (4%)	0	0	51 (93%)	3 (5%)	1 (2%)	0	0
Hearing impaired	25 (45%)	18 (33%)	3 (5%)	8 (15%)	1 (2%)	27 (49%)	18 (33%)	3 (5%)	7 (13%)	0
Hoarseness	32 (58%)	20 (36%)	3 (5%)	0	0	26 (47%)	27 (49%)	2 (4%)	0	0
Laryngeal oedema	47 (85%)	8 (15%)	0	0	0	40 (73%)	13 (24%)	2 (4%)	0	0
Mucosal inflammation	54 (98%)	0	1 (2%)	0	0	53 (96%)	1 (2%)	0	1 (2%)	0
Pharyngolaryngeal pain	36 (65%)	12 (22%)	6 (11%)	1 (2%)	0	40 (73%)	11 (20%)	4 (7%)	0	0
Superficial soft tissue fibrosis	44 (80%)	11 (20%)	0	0	0	47 (85%)	7 (13%)	1 (2%)	0	0
Telangiectasia	43 (78%)	11 (20%)	1 (2%)	0	0	41 (75%)	14 (25%)	0	0	0
Tinnitus	48 (87%)	5 (9%)	1 (2%)	1 (2%)	0	43 (78%)	9 (16%)	3 (5%)	0	0
Upper respiratory tract infection	55 (100%)	0	0	0	0	53 (96%)	1 (2%)	0	1 (2%)	0
Voice alterations	30 (55%)	24 (44%)	1 (2%)	0	0	24 (44%)	29 (53%)	1 (2%)	1 (2%)	0
Vomiting	54 (98%)	0	0	1 (2%)	0	54 (98%)	1 (2%)	0	0	0

The worst grade acute and late adverse events are shown. Adverse events reported by 10% or more of patients at grade 1–2 and all grade 3 and 4 events are listed. There were no grade 5 events. DO-IMRT=dysphagia-optimised intensity-modulated radiotherapy. IMRT=intensity-modulated radiotherapy. NOS=not otherwise specified. *DO-IMRT group N=56, standard IMRT group N=55. †DO-IMRT group N=55, standard IMRT group N=55.

Table 4: **Acute and late toxicities graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events**

We chose the MDADI composite score as the primary outcome measure because it is the most widely used and validated patient-reported scoring system for assessment of swallowing following treatment for head and neck cancer.[21] Hutcheson and colleagues[24] found that a difference in MDADI composite score of 10 points is statistically associated with clinically meaningful between-group differences in swallowing, including gastrostomy tube use, aspiration, ability to take an oral diet, and normalcy of diet assessed using the PSS-HN. Our trial showed a between-group difference of 7·2 points on the MDADI composite score at 1 year, which was less than the predefined clinically meaningful score of 10 points at the time of study design. However, Carlsson and colleagues[25] suggested that smaller differences in MDADI were clinically significant. Our findings showed a 9·8 point difference in scores adjusted for tumour site, tumour stage, and chemotherapy use. This, together with supportive evidence provided by other patient-reported and clinician-reported secondary endpoints, is indicative of a meaningful benefit for patients. Inspection of individual patient changes of 10 points or more suggests that there are some patients who have good swallowing outcomes irrespective of allocated treatment and that average improvements are driven by a reduction in the proportion of patients with large negative changes—ie, by avoidance of large detriments in swallowing function. This is expected given the variability of volume of pharyngeal muscle sparing achieved between different patients.

Several secondary endpoints favoured DO-IMRT over standard IMRT. More participants who received DO-IMRT reported normalcy of diet and eating in public scores of more than 75 or more than 90 at 3, 12, and 24 months than did so after standard IMRT. However, these analyses included small patient numbers and were not statistically significant. Understandability of speech

is not affected by pharyngeal muscle function and, as expected, was not any different with DO-IMRT than with standard IMRT. The UW-QOL swallowing domain was statistically and clinically significantly improved with DO-IMRT compared with standard IMRT at 3 months and at 12 months and across all domains. More patients in the DO-IMRT group reported the best possible score. The improved swallow performance measured using the patient self-reported outcomes or speech and language therapist-reported outcomes support the primary end-point data and are particularly notable because the participants and speech and language therapists were masked to treatment allocation.

There are substantial changes to swallowing physiology following radiotherapy and chemoradiotherapy. Feng and colleagues[7] first showed that it was possible to reduce the radiation dose to the pharyngeal muscles using DO-IMRT, and that this approach led to good swallowing outcomes. No increase in local tumour recurrence was seen in the region of the spared pharyngeal muscles. Recovery of swallow function close to baseline measures was reported; however, this was a single group, non-randomised trial and therefore robust conclusions could not be made. Another small, phase 2 study in which sparing of the high pharyngeal constrictor muscles was performed concluded that preservation of swallow function was achieved in participants with oropharyngeal cancer with a mean superior pharyngeal constrictor muscle dose of 63 Gy.[5] In the present study, dose to the pharyngeal constrictor muscle was significantly reduced with DO-IMRT, and the magnitude of the improvements in swallow are consistent with the calculated normal tissue complication probability analysis.[7]

In a systematic review (including 16 papers and 1012 participants) relating to swallowing outcomes after IMRT for head and neck cancer,[10] only one prospective study consistently reported objectively measured outcomes as well as patient-reported outcomes and toxicity scores.[8] Five studies used a range of measures that could be attributed to all three domains of the WHO International Classification of Functioning, Disability, and Health Categories, thus representing a multidimensional assessment of swallowing.[8,12,26–28] Several studies have attempted to reduce the radiation dose delivered to anatomical sites that might have increased risk of dysphagia or aspiration as adverse events of radiotherapy. However, the studies differed in the anatomical structures assessed, and thus no conclusions could be drawn. A subsequent review has examined swallow-sparing radiotherapy regimens to reduce dysphagia severity, finding no compromise to planning target volumes and locoregional control rates.[29]

One limitation of our study is that it only reports swallowing outcomes measured up to 2 years after treatment. However, Vainshtein and colleagues[30] showed that swallow function after DO-IMRT was maintained up to 6 years and did not deteriorate over time. Additionally, our study participants had mostly HPV-positive oropharyngeal cancers, and the results might not necessarily be applicable to other patient groups. Despite encouragement to use prophylactic swallowing exercises, it is recognised that this was not applied universally and their use remains controversial. There are limitations as to how much organ sparing can be achieved with the current DO-IMRT technique described in this trial, as the use of narrower margins around the target volume is likely to risk geographical miss of tumour tissue and increased risk of tumour recurrence. One strength of our study is the multicentre nature of the trial supporting geographically dispersed representative recruitment from one of the most common clinical groups of head and neck cancer: more than 90% of participants had oropharynx cancer and 86% of participants received chemoradiotherapy. Other strengths include the concurrent use of prospectively collected patient, speech and language therapist, and clinician reported outcomes and mitigation for assessment bias through masking of patients and speech and language therapists. The trial benefited from collaboration between investigators concurrently evaluating swallowing outcomes in the context of clinical trials to refine processes of target volume and dysphagia and aspiration risk structure delineation and for the assessment of swallowing outcomes, with additional strengths being the national quality assurance programme for both radiotherapy and the interventional assessments by speech and language therapists.[13]

Our findings suggest that reducing dose to the pharyngeal constrictor muscle translates into patient benefit through improved swallowing function. It is not clear which parts of the pharyngeal constrictor muscle are most important in preservation of swallowing function. Additional knowledge in this area could enhance the DO-IMRT technique and additional benefits to patients might be possible using IMRT, proton beam, or adaptive radiotherapy techniques. Further research into the effect of different dose distributions on the dysphagia and aspiration risk structure should be undertaken to identify which patients are likely to benefit most from DO-IMRT. Modelling of the dose distributions against outcome might give some insights into which patients benefit the most from DO-IMRT, and what structures within the pharyngeal constrictor muscles are most important to maintain swallow function for patients in the future.

Contributors

CN is the chief investigator for the trial. EH is the trials methodology lead within the Institute of Cancer Research-Clinical Trials and Statistics Unit (ICR-CTSU) and provided oversight and guidance for trial management throughout the trial. CN, EH, and JR were responsible for the study design. CN, EH, JR, LF, and MAS wrote the first draft of the manuscript. CN, EH, and LF had access to and verified the data. EH and LF were responsible for statistical analyses and contributed to data interpretation. MB, SB, CB, AC, EDW, BF, RF, IP, LP, KR, TR, and DS are members of the DARS trial management group, which contributed to study design, was responsible for oversight throughout the trial, and contributed to data interpretation and manuscript preparation. MAS and ME managed

the study and data collection at ICR-CTSU and contributed to the manuscript preparation. RF is a patient advocate member of the trial management group and provided guidance for study documentation and reports. CN, KR, and JT developed the radiotherapy technique. IP, KR, and JT were responsible for radiotherapy quality assurance. All authors reviewed and approved the manuscript, had full access to all data in the study, and accept responsibility for the decision to submit for publication.

Declaration of interests

CN reports research funding paid to their institution from Cancer Research UK and stock options from Advanced Oncotherapy. LF, MAS, ME, and EH report research funding paid to their institution from Cancer Research UK. EH reports grants received by their institution as contribution to support central trial costs for non-commercial trials from Accuray, Varian Medical Systems, AstraZeneca, Janssen-Cilag, Bayer, Roche Products, and Merck Sharp and Dohm. CB reports leadership roles for OncoDNA and RCR Cyclotron Trust (unpaid). TR reports membership of the POPPY Trial independent data monitoring committee and being Vice President of Clinical Oncology at the Royal College of Radiologists. All other authors declare no competing interests.

Data sharing

De-identified individual participant data, together with a data dictionary defining each field in the set, will be made available to other researchers on request. Trial documentation including the protocol are available online.[13] The ICR-CTSU supports wider dissemination of information from the research it conducts and increased cooperation between investigators. Trial data are obtained, managed, stored, shared, and archived according to ICR-CTSU standard operating procedures to ensure the enduring quality, integrity, and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures, with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement, which describes the conditions for release and requirements for data transfer, storage, archiving, publication, and intellectual property. Requests are reviewed by the trial management group in terms of scientific merit and ethical considerations, including patients' consent. Data sharing is undertaken if proposed projects have a sound scientific or patients' benefit rationale, as agreed by the trial management group and approved by the independent data monitoring and steering committee, as required. Restrictions relating to patients' confidentiality and consent will be limited by aggregating and anonymising identifiable patients' data. Additionally, all indirect identifiers that could lead to deductive disclosures will be removed in line with ICR-CTSU data sharing guidelines.

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