Proton beam therapy for oropharyngeal cancer (TORPEdO): a phase 3, randomised controlled trial

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Summary

Background The clinical benefits of intensity-modulated proton therapy (IMPT) compared with intensity-modulated radiation therapy (IMRT) for patients with oropharyngeal squamous cell carcinoma remain uncertain with respect to treatment-related effects on physical function and quality of life. We aimed to compare late functional, patient-reported, disease control, and survival outcomes between IMPT and IMRT.

Methods We did a phase 3 trial (TORPEdO) in 20 UK National Health Service hospitals. We randomly assigned (2:1) patients with locally advanced oropharyngeal squamous cell carcinoma to IMPT or IMRT (70 Gy in 33 fractions, for 6·5 weeks) with two cycles of high-dose cisplatin (100 mg/m², every 3 weeks). Co-primary endpoints at 12 months were gastrostomy-tube dependence (use of feeding tube for nutrition) or severe weight loss (≥20% from baseline) and University of Washington quality of life (UW-QoL) mean physical composite score for saliva, taste, chewing, swallowing, speech and appearance. The study was registered with the ISRCTN registry, ISRCTN16424014; recruitment is complete and follow-up is ongoing.

Findings Between Feb 25, 2020, and June 13, 2023, we randomly assigned 205 patients (99 [48%] with T3 or T4 disease and 44 [22%] with bilateral neck lymph node involvement (N2[c]); 136 [66%] to IMPT and 69 [34%] to IMRT). 163 (80%) patients were male and 42 (20%) were female. Ethnicity data were self-reported by 177 (86%) patients; most were White British (167 [94%]). At 12 months, gastrostomy-tube dependence occurred in two (2%) of 119 patients in the IMPT group and in one (2%) of 59 patients in the IMRT group and severe weight loss occurred in 20 (18% [97·5% CI 11 to 28]) of 110 patients in the IMPT group and in three (6% [1 to 17]) of 53 patients in the IMRT group (combined odds ratio 2·80 [97·5% CI 0·75 to 10·4]; p=0·079). Mean UW-QoL physical composite scores at 12 months were 78·3 in the IMPT group versus 77·1 in the IMRT group (difference 1·3 [97·5% CI −3·7 to 6·2]; p=0·56). There were 14 serious adverse events in 12 patients (nine assessed as unrelated to the study treatment [four in the IMPT group and five in the IMRT group] and five study treatment-related [one IMPT *vs* four IMRT]); the most common events were acute kidney injury (five [36%]) and thromboembolism (four [29%]). There were no treatment-related deaths. At a median follow-up of 28·3 months (IQR 26·5 to 39·3), 24-month freedom from loco-regional recurrence rates were 94% (99% CI 86–98) in the IMPT group versus 97% (82–100) in the IMRT group (hazard ratio [HR] 2·6 [99% CI 0·3 to 20·3; 95% CI 0·5–12·4]; p=0·24), and overall survival rates were 95% (86 to 98) in the IMPT group versus 95% (81–99) in the IMRT group (HR 1·6 [99% CI 0·3 to 8·8; 95% CI 0·4 to 5·9; p=0·47).

Interpretation IMPT and IMRT had similar late physical quality of life scores, gastrostomy-tube dependence, local control, and overall survival. In health-care settings where IMPT is not used routinely for oropharyngeal squamous cell carcinoma, IMRT remains the standard of care.

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Introduction

Intensity-modulated radiation therapy (IMRT) with concurrent chemotherapy is the standard of care for locally advanced oropharyngeal squamous cell carcinoma.[1] Most patients are cured, but severe late effects impair quality of life (QoL).[2] Poor swallowing outcomes (MD Anderson Dysphagia Inventory [MDADI] composite scores <60) can affect a third of patients 2 years after treatment,[3] with a decline in University of Washington QoL (UW-QoL) physical functioning score at 12 months.[4] A meta-analysis (1366 patients in 25 studies) showed persistent QoL deterioration in physical, emotional, and global domains at 12 months.[5] A multi-institutional analysis of 1238 patients treated with IMRT and concurrent chemotherapy reported a 12-month gastrostomy dependence of 8·6%.[6]

Intensity-modulated proton therapy (IMPT) for oropharyngeal squamous cell carcinoma can reduce

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Research in context

Evidence before this study

We searched PubMed for studies comparing proton with photon radiation therapy for oropharyngeal cancer from database inception to June 30, 2025, using combinations of the search terms "oropharyngeal cancer", "oropharyngeal squamous cell carcinoma", "OPSCC", "proton therapy", "proton beam therapy", "intensity-modulated proton therapy", "IMPT", "intensity-modulated radiation therapy", and "IMRT". Intensity-modulated radiation therapy (IMRT) for oropharyngeal cancer achieves high cure rates but can be associated with late toxicities that adversely affect long-term physical function and quality of life. Intensity-modulated proton therapy (IMPT) might reduce radiation doses to surrounding normal tissues involved in swallowing, chewing, taste, salivation, and speech. Before this study, comparative evidence consisted mainly of small retrospective or observational studies. More recently, a multicentre randomised phase 3 trial done in the USA showed non-inferiority of proton therapy for disease control. Uncertainty remained regarding comparative patient-reported and functional measures, post-treatment trajectories, and the extent to which findings can be generalised across health-care systems using contemporary IMRT planning.

Added value of this study

This randomised trial extends the evidence base by prospectively assessing patient-reported physical function and quality of life over 2 years within a publicly funded health-care system, where barriers to accessing proton beam therapy were minimised. By focusing on patient-reported outcomes and functional effects, the trial provides a robust basis for comparisons between IMRT and IMPT. This design provides confidence in the interpretation of findings and helps clarify the clinical relevance of dosimetric advantages attributed to IMPT, in the context of modern radiotherapy practice.

Implications of all the available evidence

Taken together, the available randomised evidence indicates that both IMPT and IMRT are effective treatment options for oropharyngeal cancer, with similar disease control and late functional effects. The findings highlight the importance of patient-reported measures, modern radiotherapy techniques, and rigorous trial design in evaluating new, complex, and resource-intensive technologies. These findings underscore the need for randomised evidence to inform treatment modality selection and health-system decision making across diverse clinical and funding contexts. In health-care settings where IMPT is not used routinely for oropharyngeal squamous cell carcinoma, IMRT remains the standard of care.

radiation doses to organs at risk (OARs) including the contralateral parotid gland, oral cavity, and swallowing structures,[7,8] which is potentially associated with fewer adverse physical effects compared with IMRT. Observational data support the theoretical clinical benefits of IMPT.[9–11] A matched cohort study of 50 patients treated with IMPT and 100 treated with IMRT found IMPT reduced gastrostomy-tube dependence or severe weight loss (≥20% from baseline) at 12 months (odds ratio [OR] 0·23 [95% CI 0·07–0·73]; p=0·01).[11]

Given the importance of developing evidence to support complex costly new treatments, we designed a prospective randomised trial to assess the clinical benefits of IMPT over IMRT for oropharyngeal squamous cell carcinoma.

Methods

Study design and participants

TORPEdO was a phase 3, multicentre, open-label, randomised controlled trial done at 20 UK National Health Service hospitals. The trial design was published[12] and the protocol is in the appendix (p 37). Eligible participants had newly diagnosed oropharyngeal squamous cell carcinoma and were suitable for concurrent chemoradiotherapy, including bilateral neck treatment. Key exclusion criteria were feeding tube insertion required for nutrition before treatment, N3 disease, upfront neck dissection, use of induction chemotherapy, contraindication to the use of cisplatin for cycle 1 concurrent chemotherapy, and previous head and neck radiotherapy. Sex was self-reported and collected by participating site; ethnicity was self-declared directly by participants via a self-administered form.

The trial was investigator-initiated and sponsored by the Institute of Cancer Research (ICR) and approved by the North West - Greater Manchester West Research Ethics Committee (19/NW/0700). There was patient and public involvement in the trial design,[13] participant information sheets, oversight (Trial Management Group and Trial Steering Committee), and dissemination. All participants provided written informed consent. The ICR Clinical Trials and Statistics Unit (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 an Independent Data Monitoring Committee and Trial Steering Committee.

See Online for appendix

Minimisation and masking

Participants were centrally randomised (2:1) to IMPT (The Christie, Manchester, UK, and University College London Hospital, London, UK) or IMRT (local referring centre) via minimisation with a random element. A 2:1 allocation ratio was selected and endorsed by patient

representatives to support recruitment and to maximise data on IMPT. Treatment was not masked. Balancing factors were randomising centre, site of disease (tonsil: yes *vs* no), T stage (T1 or T2 *vs* T3 or T4), bilateral neck nodes (no: N0, N1 [p16-positive], or N2b [p16-negative] *vs* yes: N2 [p16-positive] or N2c [p16-negative]), p16 status (positive: yes *vs* no), smoking status (current smoker within 1 year or >10 packs per year history: yes *vs* no).

Procedures and treatment

Both groups received 70 Gy to the therapeutic target volume and 56 Gy to areas at lower risk of microscopic disease in 33 once-daily fractions over 6·5 weeks. A relative biological effectiveness (RBE; the increased biological effect of protons relative to photons) of 1·1 was used for IMPT. Targets and OAR outlining and planning were standardised, using the same planning priorities and challenging OAR dose targets to ensure full optimisation (appendix p 110). For IMPT planning, beam angles were selected on a per-patient basis. Five beams were typically used with a split-target approach that aimed to avoid regions of anatomical instability and dental amalgam, to reduce the dose to normal tissues and to maintain two beams treating all target volumes. The proton plans were analysed for robustness against 3-mm setup errors and 3·5% range uncertainty, with doses recalculated across several error scenarios and the worst-case dose reported for each structure, including targets and OARs. Verification imaging followed local practices. For IMRT, verification imaging was typically done using cone beam CT (CBCT) scans for the initial three fractions, with weekly images thereafter. If an out-of-tolerance error was detected and corrected, CBCT verification was done for the next two treatment fractions. For IMPT this was daily CBCT scans, with dosimetric review as necessary; plus, a week-3 repeat planning CT scan in both groups. Dose recalculation and radiation therapy replanning followed standardised criteria, which were the same for both modalities and designed to ensure that the planned and delivered doses matched. Radiotherapy replanning was performed when (1) the target coverage of the tumour or electively treated volumes did not meet the D99% and D95% protocol criteria and on visual review target coverage was deemed not to be clinically acceptable, (2) the cumulative dose to critical structures was more than 2% over tolerance or less as per local centre protocol, or (3) the mean dose to the parotid glands or oral cavity or submandibular glands increased by more than 3 Gy (RBE) assuming the entire treatment was delivered as per the verification scan. The UK Radiotherapy Trials Quality Assurance (RTTQA) group did independent pre-trial credentialing of outlining and planning, on-trial prospective review of outlines for all cases, and the first IMRT and IMPT plans per centre and retrospective on-trial review of all plans. The group was supported by professionals from a separate European proton centre (Skandion Clinic, Uppsala, Sweden). Chemotherapy was cisplatin 100 mg/m² on days 1 and 22 of radiotherapy, with carboplatin (area under the concentration–time curve 5) substitution for cycle 2 if required because of side-effects. Prophylactic or reactive feeding-tube placement followed the prespecified policy of the referring centre, independent of treatment allocation. Weight and feeding-tube dependence was assessed weekly during chemoradiotherapy, then at 6 weeks, and at 3, 6, 12, 18, 24 months after completion of treatment. Acute adverse events (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0 criteria) were assessed weekly during chemoradiotherapy then at 6 weeks and 3 months after treatment. Late adverse events (CTCAE version 5.0 and Late Effects Normal Tissue and Subjective, Objective, Management, and Analytic criteria [LENT-SOMA]) were assessed at 6, 12, 18, and 24 months after chemoradiotherapy. Functional assessments (100 mL water swallowing test and performance status scale for head and neck cancer patients [PSS-HN score]) were assessed at baseline and 3, 12, and 24 months after chemoradiotherapy. Patient-reported outcomes (PROs; UW-QoL score, EORTC Quality of Life Questionnaire [QLQ-C30] Quality of Life Head and Neck Module [QLQ-HN43] score, MDADI score, resource use, EQ-5D-5L score, and Work Productivity and Activity Impairment: Specific Health Problem Questionnaire score) were collected at baseline, end of treatment, 6 weeks and 3, 6, 12, 18, and 24 months after chemoradiotherapy, and annually up to 5 years. Follow-up continues until 5 years after chemoradiotherapy.

Outcomes

Co-primary endpoints (12 months after chemo-radiotherapy) were UW-QoL physical composite score (mean of swallowing, chewing, speech, taste, saliva, and appearance scores, where ≥4 items must be completed) and gastrostomy-tube dependence (use in past 3 weeks) or CTCAE grade 3 weight loss (≥20% from baseline; included to mitigate tube non-use or early removal bias). As a prespecified secondary objective, we analysed the same UW-QoL score endpoint at 12 months in an enriched cohort defined by a normal tissue complication probability (NTCP)-model,[14] with a predicted greater difference between the treatment groups than in the primary analysis of the full modified intention-to-treat (mITT) population. All secondary endpoints were prespecified; those reported here up to 2 years after chemotherapy were weight loss (≥10%) measured from 6 months post-treatment, tube status, acute and late side-effects, functional outcomes, resection rate, loco-regional control, and overall survival; those not yet reported included hearing loss (audiometry), trismus, secondary longitudinal health-related QoL (HR-QoL), LENT-SOMA score, and cost-effectiveness, which will be reported separately.

Statistical analysis

For gastrostomy-tube dependence or grade 3 weight loss (assuming a 25% IMRT event rate), 165 participants (110 IMPT and 55 IMRT) provided 80% power to detect an OR of 0·23 (ie, 7% IMPT event rate) at a two-sided 2·5% alpha. For UW-QoL physical composite score, 156 participants (104 IMPT and 52 IMRT) provided 86% power to detect an 8-point improvement (representing a moderate and clinically important increase) in the mean score (SD 14·05 each group) at a two-sided 2·5% alpha. This estimate was inflated by 18% to account for non-evaluability in the clinician-reported co-primary endpoint; the resulting sample size corresponded to an effective inflation of 22% for the patient-reported co-primary endpoint, giving a required total of 201 participants. Prespecified analysis within the NTCP subgroup estimated that for 150 evaluable patients the estimate of difference in mean change of HR-QoL score between subgroups would have a precision of ± 4·5 points (two-sided 95% CI).

In the co-primary analyses, we used an mITT population (excluding pre-12-month recurrence, death, withdrawal, or missing data rendering participants unevaluable; any missing data were assumed to be missing at random), a 10–15-month condonable window, and comparisons by randomisation. For co-primary endpoints, associations between treatment group and outcomes were assessed using multivariable linear or logistic regression with the endpoint as the dependent variable and treatment group as the independent variable. Regression models were adjusted for primary

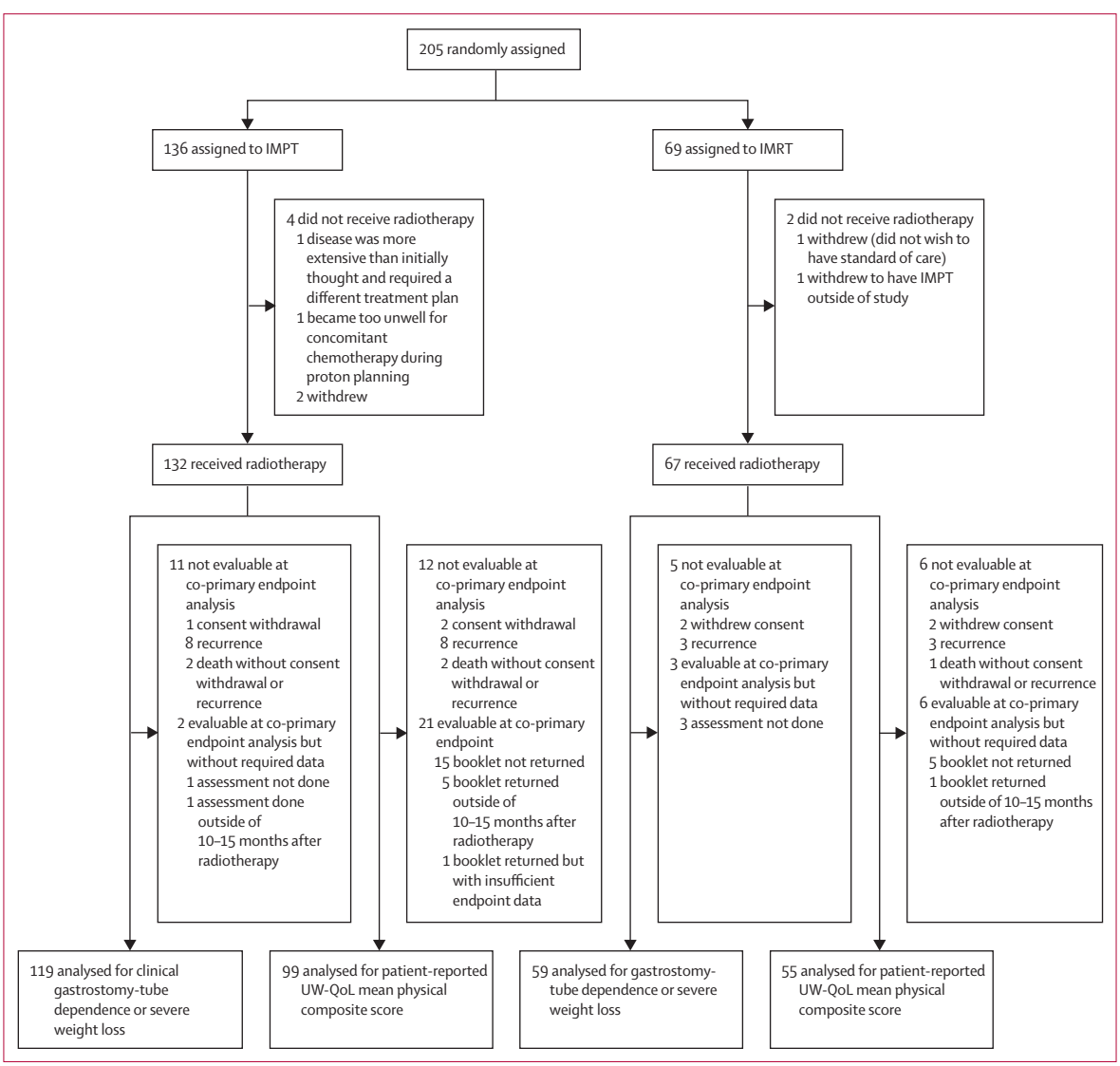


Figure 1: **Trial profile**
All patients who received their allocated radiotherapy received chemotherapy. Booklet refers to patient-reported outcome questionnaires. IMPT=intensity-modulated proton beam therapy. IMRT=intensity-modulated radiation therapy. UW-QoL=University of Washington quality of life.

disease site (tonsil *vs* other), smoking status (current smoker within 1 year or >10 pack-year history *vs* stopped smoking more than 1 year ago with ≤10 pack-year history or never smoked), concomitant chemotherapy (cisplatin administered on day 1 and day 22 of chemotherapy *vs* other cisplatin or carboplatin regimen), T stage at treatment (T1 or T2 *vs* T3 or T4), bilateral neck nodes at treatment (no: N0, N1 [p16-positive] or N2b [p16-negative] *vs* yes: N2 [p16-positive] or N2c [p16-negative]) and baseline BMI (continuous); p16 status was not included in the models as most tumours [96%] were p16-positive. The analysis of UW-QoL physical composite score was additionally adjusted for the baseline score (continuous raw score). We did multiple sensitivity analyses for the co-primary endpoints to assess the robustness of the missing at random assumption: (1) per protocol—all patients within the mITT population who received all doses of randomly allocated radiotherapy delivered in accordance with the protocol and at least the first dose of concomitant cisplatin; (2) second primary-free before the primary endpoint assessment; (3) salvage surgery-free before the primary endpoint assessment; (4) complete clinical composite primary endpoint—both gastrostomy-tube dependence and weight loss data available; (5) best clinical outcome assumed for evaluable patients without required endpoint data; (6) worst clinical outcome assumed for evaluable patients without required data and non-evaluable patients still alive at 12 months after chemoradiotherapy; (7) last observation carried forward for evaluable patients without required data and non-evaluable patients still alive at 12 months after chemoradiotherapy; (8) baseline BMI <30 kg/m² (patients who were up to and including overweight at randomisation); (9) and inclusion of co-primary endpoint data collected outside of the 10–15-month condonable window. Sensitivity analyses 1, 2, 3, 8, and 9 were applied to both the clinical-reported and patient-reported co-primary endpoints separately. Analyses 4–6 were only applicable to the clinician-reported co-primary endpoint and analysis 7 only to the patient-reported co-primary endpoint. Analyses 1–4 were prespecified under the statistical analysis plan; analyses 5–9 were included post hoc to further assess the robustness of the co-primary analyses. Sensitivity analyses are detailed in full in the appendix (pp 8–11).

Linear regression models as described for the co-primary QoL endpoint were repeated for the analysis of MDADI composite score and EORTC QLQ-C30 global health status at 12 months after chemoradiotherapy, adjusting for the appropriate baseline score. For these two models, testing was done at the 1% significance threshold, in line with prespecified multiplicity adjustments for the HR-QoL secondary endpoint.

PSS-HN subscales were dichotomised at binary cut-offs of 90 for diet normalcy, 75 for place of eating, and 100 for speech understandability (lower scores indicate greater restriction). For diet normalcy and place of eating, we used additional trinary cut-offs of 50, 60–80, 90 for diet normalcy and 50, 75, and 100 for place of eating. Proportions were compared at 3, 12, and 24 months after chemoradiotherapy using χ^2 test or Fisher's exact test (expected number <5). Swallow function (100 mL water test) results were compared at 3, 12, and 24 months using two-sample *t* tests or Mann–Whitney two-sample tests when distributions did not follow a normal distribution.

	IMPT	IMRT	Total
Centre-reported data			
Sex			
Male	107/136 (79%)	56/69 (81%)	163/205 (80%)
Female	29/136 (21%)	13/69 (19%)	42/205 (20%)
Age at randomisation	56·9 (52·8–61·8)	57·7 (52·6–62·7)	57·1 (52·7–62·3)
Primary disease site			
Tonsil	75/136 (55%)	41/69 (59%)	116/205 (57%)
Base of tongue	60/136 (44%)	25/69 (36%)	85/205 (42%)
Posterior pharyngeal	0	2/69 (3%)	2/205 (1%)
Soft palate	1/136 (1%)	1/69 (1%)	2/205 (1%)
Bilateral neck lymph node involvement			
No (N0, N1 [p16-positive] or N2b [p16-negative])	106/136 (78%)	55/69 (80%)	161/205 (79%)
Yes (N2 [p16-positive] or N2c [p16-negative])	30/136 (22%)	14/69 (20%)	44/205 (21%)
T stage			
T1 or T2	70/136 (52%)	36/69 (52%)	106/205 (52%)
T3 or T4 (p16-positive) or T4a (p16-negative)	66/136 (49%)	33/69 (48%)	99/205 (48%)
AJCC/UICC stage (8th edition)			
1	48/136 (35%)	27/69 (39%)	75/205 (37%)
2	47/136 (35%)	22/69 (32%)	69/205 (34%)
3	39/136 (29%)	19/69 (28%)	58/205 (28%)
4a	2/136 (1%)	1/69 (1%)	3/205 (1%)
p16 status*			
Positive	132/136 (97%)	65/69 (94%)	197/205 (96%)
Negative	4/136 (3%)	4/69 (6%)	8/205 (4%)
Current or ex-smoker, number of pack-years†	15·0 (6·0–30·0)	17·8 (8·0–33·0)	15·0 (6·0–30·0)
Patient's smoking history†‡			
Current smoker	6/135 (4%)	3/69 (4%)	9/204 (4%)
Ex-smoker, stopped within past year	14/135 (10%)	8/69 (12%)	22/204 (11%)
Ex-smoker, stopped >1 year ago	50/135 (37%)	30/69 (44%)	80/204 (39%)
Never smoked	65/135 (48%)	28/69 (41%)	93/204 (46%)
WHO performance status†			
0	125/135 (93%)	68/69 (99%)	193/204 (95%)
1	10/135 (7%)	1/69 (1%)	11/204 (5%)
BMI (kg/m²) at baseline (continuous)†	28·3 (26·1–32·5)	27·2 (24·9–30·4)	28·0 (25·6–31·7)
Feeding tube required for nutrition at baseline†			
No	135/135 (100%)	69/69 (100%)	204/204 (100%)
Prophylactic feeding tube fitted†			
Yes	35/135 (26%)	26/69 (38%)	61/204 (30%)
No	98/135 (73%)	42/69 (61%)	140/204 (69%)
NA	2/135 (1%)	1/69 (1%)	3/204 (1%)

(Table 1 continues on next page)

	IMPT	IMRT	Total
(Continued from previous page)			
Patient-reported data			
Ethnicity			
White British	112/117 (96%)	55/60 (92%)	167/177 (94%)
White Irish	2/117 (2%)	0	2/177 (1%)
Any other White background (specify)§	2/117 (2%)	3/60 (5%)	5/177 (3%)
Mixed: White and Black Caribbean	1/117 (1%)	0	1/177 (1%)
Asian or Asian British: Indian	0	1/60 (2%)	1/177 (1%)
NA	0	1/60 (2%)	1/177 (1%)
Highest education level			
GCSE or lower	43/117 (37%)	27/60 (45%)	70/177 (40%)
A level or equivalent	26/117 (22%)	13/60 (22%)	39/177 (22%)
Bachelor's degree or above	34/117 (29%)	14/60 (23%)	48/177 (27%)
Other (specify)¶	8/117 (7%)	2/60 (3%)	10/177 (6%)
NA	6/117 (5%)	4/60 (7%)	10/177 (6%)
Employment status			
Employed	64/117 (55%)	31/60 (52%)	95/177 (54%)
Unemployed	11/117 (9%)	6/60 (10%)	17/177 (10%)
Self-employed	24/117 (21%)	11/60 (18%)	35/177 (20%)
Retired	18/117 (15%)	12/60 (20%)	30/177 (17%)

Data are n/N (%) or median (IQR). Categorical data with 0 counts in both groups are not presented. Sex was self-reported and collected by site. Ethnicity was self-declared by the patient on the patient-reported outcomes demographics questionnaire sent to the patient by sites and received by the Institute of Cancer Research Clinical Trials and Statistics Unit. All patients were M0 as per the TORPEdO eligibility criteria. No patients were reported to be N2a (p16-negative). No patients were underweight at baseline (BMI <18·5 kg/m^2). IMPT=intensity-modulated proton beam therapy. IMRT=intensity-modulated radiation therapy. NA=not available. *One IMRT patient was incorrectly randomly assigned under the p16 status negative; status was corrected after treatment allocation. †One patient (IMPT) withdrew following randomisation with balancing factor data available but no baseline assessment information for extended smoking, tube use, or other symptom data were available. ‡Two patients (IMPT) were incorrectly randomly assigned as stopped smoking >1 year ago and ≤10 pack-year history, or never smoked; status was corrected after treatment allocation. §In the IMPT group, ethnicities were White Canadian and White Hungarian. In the IMRT group, other ethnicities were White North American, White South African, and NA. ¶In the IMPT group, other education levels were Higher National Certificate, Ordinary National Certificate; Higher National Diploma, Member of the Chartered Institute of Procurement and Supply, Level 3 Child and Social Care, National Vocational Qualification, never took any, Ordinary National Certificate, passed 11+ examination and did not take any other qualification, and professional engineering certifications. In the IMRT group, other levels of education were high school diploma and Higher National Diploma.

Table 1: **Baseline characteristics**

Time-to-event endpoints were measured from date of randomisation. Loco-regional control was defined as the time from randomisation to loco-regional recurrence—ie, recurrence at the primary site or in the neck. Patients were censored at time of distant recurrence or death before loco-regional recurrence or last clinical assessment of response for those alive and disease free. New cancer primaries were not considered censoring events. Where there was residual regional-only (neck) nodal disease salvaged by a neck dissection with removal of gross disease (R0 or R1 resection), this did not constitute a loco-regional recurrence. Overall survival was calculated as time from randomisation until the date of death from any cause or censored at the date last seen alive. Cause of death and relation to treatment were reported by investigators on the trial case report form. We used Kaplan–Meier methods to estimate 24-month event-free proportions. We calculated hazard ratios (HRs) using Cox regression models, adjusted for primary disease site (tonsil *vs* other), smoking status (current smoker within 1 year or >10 pack-year history *vs* stopped smoking >1 year ago with ≤10 pack-year history or never smoked), T stage at treatment (T1 or T2 *vs* T3 or T4) and bilateral neck nodes at treatment (no: N0, N1 [p16-positive] or N2b [p16-negative] *vs* yes: N2 [p16-positive] or N2c [p16-negative]); p16 status was not included in the models as most tumours [96%] were p16 positive.

Acute adverse events were treatment-emergent adverse events occurring up to and including 3 months after completion of radiotherapy; late treatment-emergent adverse events were assessed from more than 3 months to 2 years. Serious adverse events were defined as unanticipated events meeting standard seriousness criteria. The proportions of patients in the acute and late phases with any adverse events of at least grade 2 or grade 3, and adverse events due to radiotherapy were compared between groups using χ^2 test or Fisher's exact test (expected number <5). Prespecified adverse events of interest (dry mouth, dysgeusia [change in taste], dysphagia, fatigue, osteonecrosis of jaw [mandible], and superficial soft tissue fibrosis) were also compared at 3, 12, and 24 months after chemoradiotherapy.

Median OAR doses (IMRT *vs* IMPT) were compared via Wilcoxon rank-sum ($p<0·01$ significance). To address concerns around the potential for a learning curve effect, we did a post-hoc analysis of OAR doses for IMPT in the first (cohort 1) and second (cohort 2) halves of the trial. NTCPs were calculated per patient from retrospective comparative plans for moderate-to-severe xerostomia (6 months; EORTC QLQ-HN43 Q12 "quite a bit or very much"), dysphagia (6 months; CTCAE version 5.0 grade ≥2), and feeding-tube dependence (6 months).[14] In a pre-planned analysis, the Dutch proton treatment thresholds (delta NTCP models photons–protons ≥10% xerostomia or dysphagia, ≥5% feeding-tube dependence, or ≥15% combined xerostomia plus dysphagia) defined enriched or unenriched cohorts in which we assessed the 12-month delta mean (95% CI) UW-QoL physical composite scores for IMPT versus IMRT.

A two-sided familywise type I error rate of 5% across the two co-primary endpoints was controlled using a Bonferroni procedure ($\alpha=0·025$ per co-primary endpoint), and statistical significance in either endpoint was considered sufficient for trial success. Co-primary endpoints were presented with two-sided 97·5% CIs and analyses by NTCP subgroups presented with two-sided 95% CIs. Secondary endpoints related to HR-QoL were considered confirmatory and analysed at a two-sided significance level of 1%. Adverse event secondary endpoints were also considered confirmatory and analysed at 0·5% to account for multiple comparisons. Time-to-event secondary endpoints, including loco-regional recurrence and overall survival, were considered exploratory and analysed at 1%.

Consistency between results—eg, of similar endpoints, symptoms, or QoL subscales—was considered when interpreting findings.

All analyses were based on data as of Sept 3, 2025, and done using Stata (version 19.0). The study was registered with the ISRCTN registry, ISRCTN16424014.

Role of the funding source

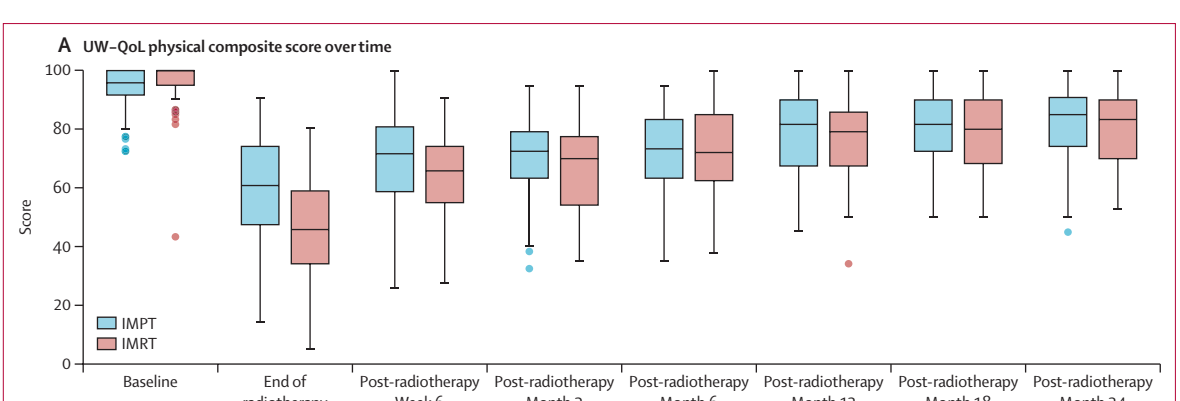
The funder of the study reviewed and approved the trial design but had no role in data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 25, 2020, and June 13, 2023, we randomly assigned 205 patients (136 [66%] to IMPT and 69 [34%] to IMRT; figure 1); 99 (48%) with T3 or T4 disease and 44 (22%) with bilateral neck lymph node involvement (N2[c]). Recruitment was paused from March, 2020, to May, 2020, because of the COVID-19 pandemic, as NHS England prioritised the proton beam therapy service for non-trial patients (appendix p 12). Of 205 patients, 163 (80%) were male and 42 (20%) were female. Ethnicity data were self-reported by 177 (86%) patients; most were White British (167 [94%]; table 1; appendix p 13).

199 (97%) of 205 participants received allocated treatment (132 [97%] of 136 in the IMPT group and 67 [97%] of 69 in the IMRT group). The total number of IMPT missed fractions was 130 (3%) of 4356 in 65 (49%) of 132 patients, compensated by weekend day (65 [50%] of 130) or twice daily (62 [48%] of 130) treatments, with no patient receiving more than six fractions per week. For three (2%) of 136 patients, a single fraction was added by an additional day at the end. For IMRT, the total number of missed fractions was three (<1%) of 2211 in three (4%) of 67 patients, compensated by weekend day (n=1) or twice daily (n=2) treatments. All compensation used the same modality, except for one patient receiving IMPT who had a single IMRT fraction. Most common reasons for IMPT interruptions were cyclotron breakdown (47 [72%] of 65), service (six [9%]), acute adverse events (five [8%]). Reasons for IMRT interruptions were acute adverse events (n=2) and bank holiday (n=1). Both groups had a median duration of radiotherapy of 44 days (IQR 44–44). Radiotherapy replanning during treatment was required in 81 (61%) of 132 patients in the IMPT group and 20 (30%) of 67 in the IMRT group. All patients who underwent radiotherapy also received concomitant chemotherapy. 138 (69%) of 199 patients had two cisplatin cycles (89 [67%] of 132 in the IMPT group and 49 [73%] of 67 in the IMRT group), 49 (25%) of 199 received cisplatin then carboplatin (35 [27%] of 132 in the IMPT group and 14 [21%] of 67 in the IMRT group), four (2%) of 199 received two carboplatin cycles (three [2%] of 132 in the IMPT group and one [1%] of 67 in the IMRT group), and eight (4%) of 199 received one cisplatin cycle only (five [4%] of 132 in the IMPT group and three [4%] of 67 in the IMRT group). Per-centre policy for feeding-tube placement was prophylactic for 12 (60%) of 20 patients and reactive for eight (40%).

Gastrostomy-tube dependence or grade 3 weight loss (≥20%) at 12 months was evaluable in 178 (87%) of 205 patients (119 [67%] in the IMPT group and 59 [33%] in the IMRT group). 163 patients (110 [67%] in the IMPT group and 53 [33%] in the IMRT group) had both feeding-tube and weight loss data; 15 patients (nine [60%] in the IMPT group and six [40%] in the IMRT group) had feeding-tube data only and no patients had weight loss data only. Event rates were 21 of 119 (18% [97·5% CI 11 to 27]) in the IMPT group versus four of 59 (7% [2 to 18]) in the IMRT group (difference 11% [<1 to 22]; adjusted OR 2·80 [0·75–10·41]; p=0·079; appendix p 14), driven by weight loss (20/110 [18%; 11–28] in the IMPT group and 3/53 [6%; 1–17] in the IMRT group). Gastrostomy-tube dependence was low (2/119 [2%; <1 to 7] in the IMPT group and 1/59 [2%; <1 to 10] in the IMRT group), reducing from earlier timepoints (appendix p 15). Feeding-tube use at any time was lower in the IMPT group (61 [45%] of 135) than in the IMRT group (40 [58%] of 69), but with fewer prophylactic placements in the IMPT group (35 [26%] of 135 *vs* 26 [38%] of 69). Median end-of-treatment weight loss was 6% (IQR 3–9) in the



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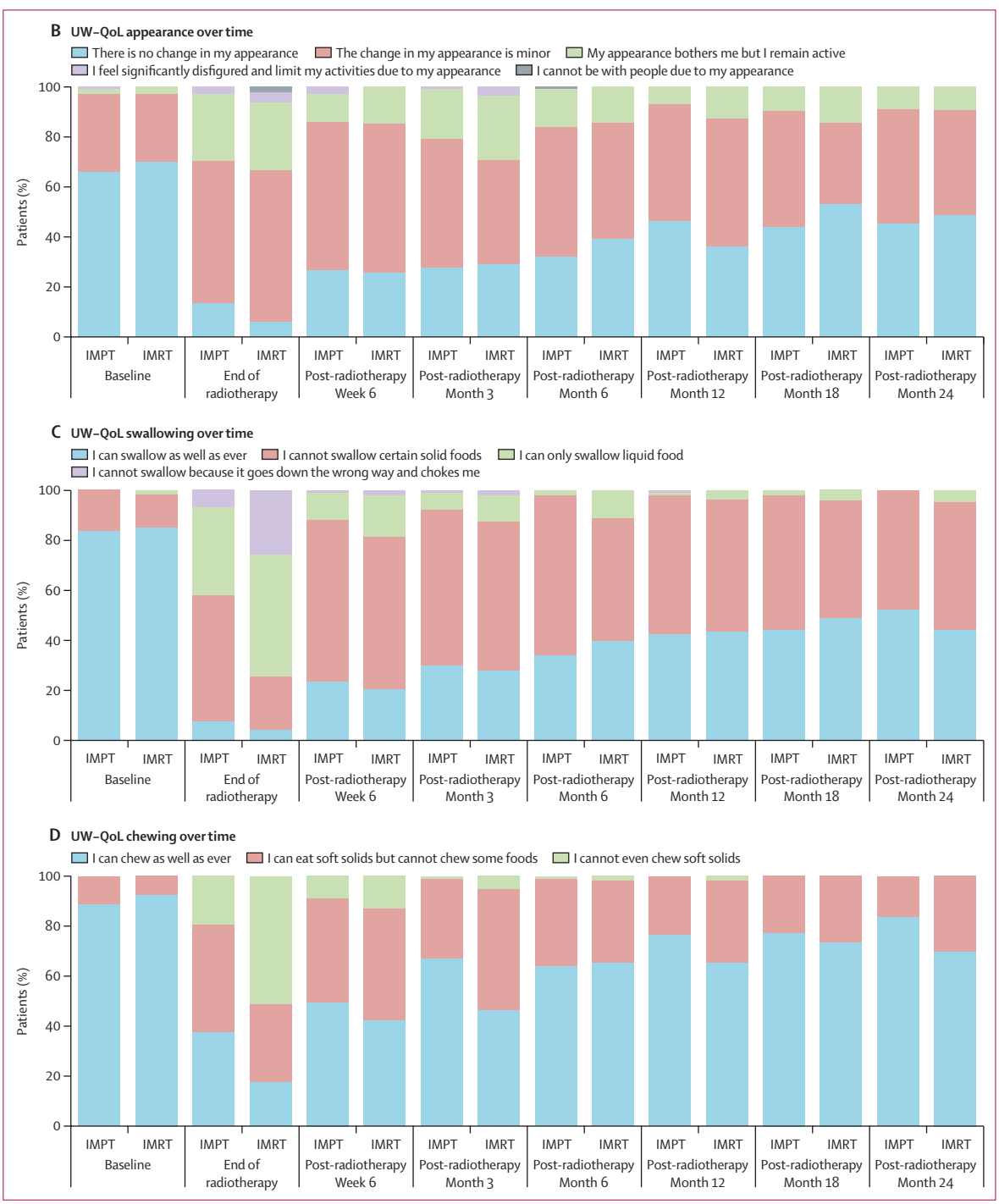
IMPT group and 7% (5–11) in the IMRT group. At the end of chemoradiotherapy, no patient in either group experienced grade 3 weight loss. By 6 months post-chemoradiotherapy, grade 3 weight loss occurred in 20 (17%) of 116 patients in the IMPT group, compared with three (5%) of 56 in the IMRT group. At 12 months, the rate of grade 3 weight loss for IMPT peaked (20 [18%] of 110). The rate of grade 3 weight loss remained low and stable from 6 weeks to 12 months in the IMRT group (range 5–8%). By 24 months, 12 (13%) of 95 patients had grade 3 weight loss in the IMPT group, with no cases in the IMRT group. Weight loss of grade 2 or higher (≥10%) was more common in the IMPT group, especially in those with a baseline high (BMI [≥25 kg/m²]), with a



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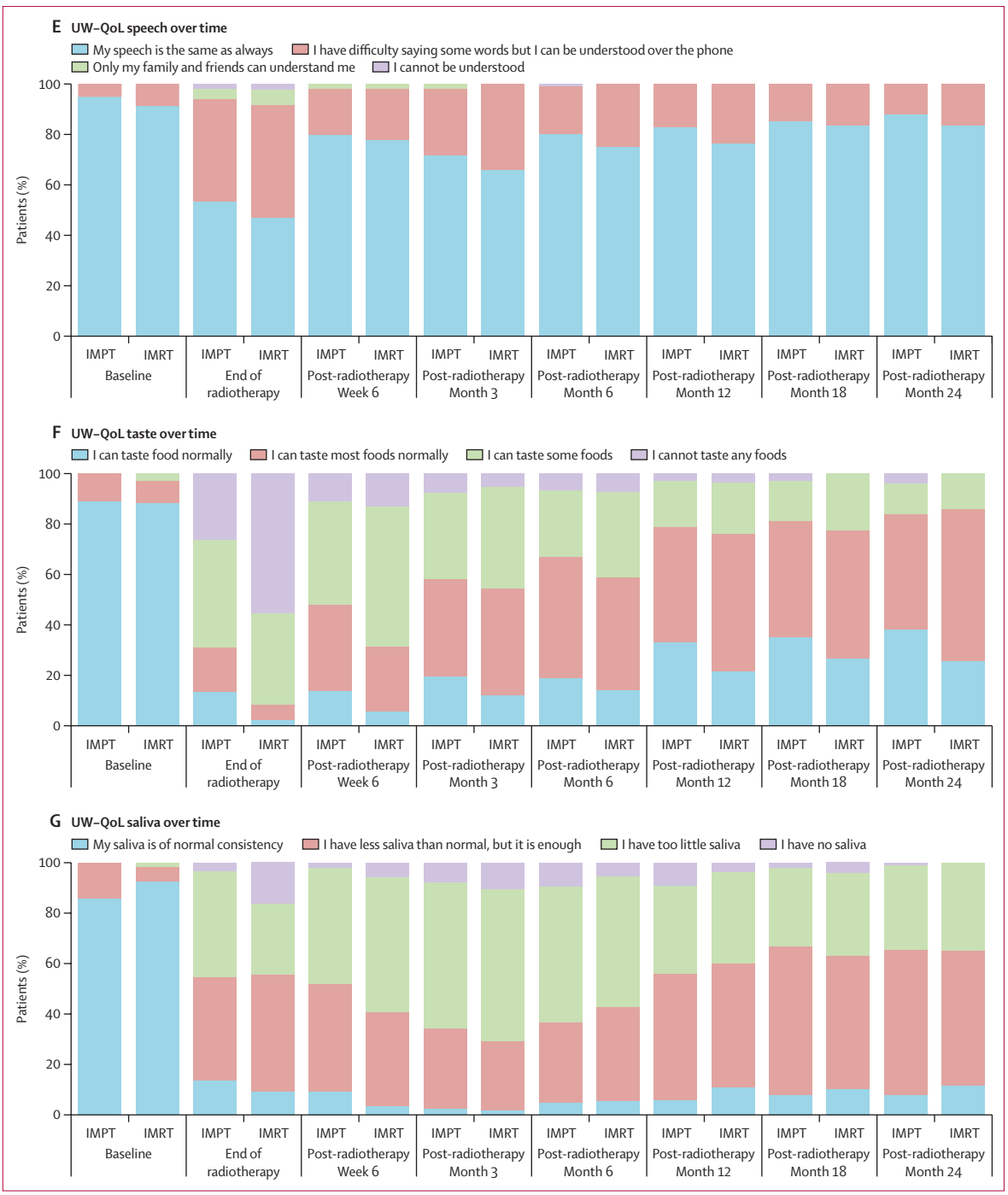

Figure 2: **UW-QoL score over time**

Proportion of patients in each category are presented for composite score (A), and subscales for appearance (B), swallowing (C), chewing (D), speech (E), taste (F), and saliva (G). IMPT=intensity-modulated proton beam therapy. IMRT=intensity-modulated radiation therapy. UW-QoL=University of Washington quality of life.

median maximum loss from week 6 to month 24 of 14% (IQR 10–20) in the IMPT group versus 11% (9–16) in the IMRT group (appendix pp 16–17). Few patients with grade 3 weight loss became underweight (BMI <18·5 kg/m²) by month 12 (two [2%] of 119 in the IMPT group and two [4%] of 59 in the IMRT group).

UW-QoL physical composite score was evaluable at 12 months for 154 (75%) of 205 patients (99 [73%] in the IMPT group and 55 [80%] in the IMRT group). Adjusted mean scores were 78·3 (97·5% CI 75·4 to 81·3) in the IMPT group versus 77·1 (73·1 to 81·0) in the IMRT group (difference 1·3 [97·5% CI −3·7 to 6·2]; p=0·56;

	IMPT			IMRT			Total		
	0–1	2	3	0–1	2	3	0–1	2	3
Acute events (during radiotherapy until 3 months post-radiotherapy)									
Preferred term									
Oral or pharyngeal mucositis or pain (mouth or throat)	10 (8%)	73 (55%)	49 (37%)	3 (4%)	28 (42%)	36 (54%)	13 (7%)	101 (51%)	85 (43%)
Dysphagia	67 (51%)	49 (37%)	16 (12%)	31 (46%)	20 (30%)	16 (24%)	98 (49%)	69 (35%)	32 (16%)
Weight loss	55 (42%)	63 (48%)	14 (11%)	26 (39%)	34 (51%)	7 (10%)	81 (41%)	97 (49%)	21 (11%)
Skin reaction or changes	33 (25%)	87 (66%)	12 (9%)	28 (42%)	36 (54%)	3 (5%)	61 (31%)	123 (62%)	15 (8%)
Oral or pharyngeal dryness	53 (40%)	73 (55%)	6 (5%)	23 (34%)	39 (58%)	5 (8%)	76 (38%)	112 (56%)	11 (6%)
Decreased appetite	123 (93%)	5 (4%)	4 (3%)	59 (88%)	4 (6%)	4 (6%)	182 (91%)	9 (5%)	8 (4%)
Fatigue	101 (77%)	27 (21%)	4 (3%)	35 (52%)	29 (43%)	3 (5%)	136 (68%)	56 (28%)	7 (4%)
Dehydration	129 (98%)	2 (2%)	1 (1%)	60 (90%)	4 (6%)	3 (5%)	189 (95%)	6 (3%)	4 (2%)
Salivary gland inflammation	126 (95%)	5 (4%)	1 (1%)	57 (85%)	9 (13%)	1 (2%)	183 (92%)	14 (7%)	2 (1%)
Dysphonia	124 (94%)	8 (6%)	0	61 (91%)	5 (8%)	1 (1%)	185 (93%)	13 (7%)	1 (1%)
Dysgeusia (change in taste)	76 (58%)	56 (42%)	0	23 (34%)	44 (66%)	0	99 (50%)	100 (50%)	0
Laryngeal oedema or inflammation	124 (94%)	8 (6%)	0	62 (93%)	5 (8%)	0	186 (93%)	13 (7%)	0
Alopecia	127 (96%)	5 (4%)	0	64 (96%)	3 (5%)	0	191 (96%)	8 (4%)	0
Pain (head and neck or other)	130 (98%)	2 (2%)	0	63 (94%)	4 (6%)	0	193 (97%)	6 (3%)	0
Lower respiratory tract infection including aspiration	129 (98%)	3 (2%)	0	66 (99%)	1 (2%)	0	195 (98%)	4 (2%)	0
Lower respiratory tract infection	129 (98%)	3 (2%)	0	66 (99%)	1 (2%)	0	195 (98%)	4 (2%)	0
Cough	129 (98%)	3 (2%)	0	67 (100%)	0	0	196 (98%)	3 (2%)	0
Trismus	129 (98%)	3 (2%)	0	67 (100%)	0	0	196 (98%)	3 (2%)	0
Lymphoedema	130 (98%)	2 (2%)	0	67 (100%)	0	0	197 (99%)	2 (1%)	0
Soft tissue fibrosis	132 (100%)	0	0	67 (100%)	0	0	199 (100%)	0	0
Skin or soft tissue reaction including fibrosis	132 (100%)	0	0	67 (100%)	0	0	199 (100%)	0	0
Recall phenomenon	132 (100%)	0	0	67 (100%)	0	0	199 (100%)	0	0
Worst radiotherapy-related CTCAE grade*	0	66 (50%)	66 (50%)	0	19 (28%)	48 (72%)	0	85 (43%)	114 (57%)
Late events (6 months to 24 months post-radiotherapy)									
Preferred term									
Weight loss	93 (74%)	15 (12%)	18 (14%)	51 (81%)	9 (14%)	3 (5%)	144 (76%)	24 (13%)	21 (11%)
Hearing impairment	107 (85%)	7 (6%)	12 (10%)	53 (84%)	5 (8%)	5 (8%)	160 (85%)	12 (6%)	17 (9%)
Dry mouth	94 (75%)	29 (23%)	3 (2%)	51 (81%)	12 (19%)	0	145 (77%)	41 (22%)	3 (2%)
Oral or pharyngeal mucositis or pain (mouth, throat)	121 (96%)	3 (2%)	2 (2%)	59 (94%)	3 (5%)	1 (2%)	180 (95%)	6 (3%)	3 (2%)
Dysphagia	113 (90%)	11 (9%)	2 (2%)	55 (87%)	8 (13%)	0	168 (89%)	19 (10%)	2 (1%)
Pain (head and neck, other)	124 (98%)	1 (1%)	1 (1%)	59 (94%)	3 (5%)	1 (2%)	183 (97%)	4 (2%)	2 (1%)
Fatigue	122 (97%)	3 (2%)	1 (1%)	55 (87%)	8 (13%)	0	177 (94%)	11 (6%)	1 (1%)
Soft tissue fibrosis	122 (97%)	3 (2%)	1 (1%)	63 (100%)	0	0	185 (98%)	3 (2%)	1 (1%)
Osteonecrosis (of jaw)	124 (98%)	1 (1%)	1 (1%)	63 (100%)	0	0	187 (99%)	1 (1%)	1 (1%)
Laryngeal oedema or inflammation	125 (99%)	0	1 (1%)	63 (100%)	0	0	188 (99%)	0	1 (1%)
Dysgeusia (change in taste)	114 (90%)	12 (10%)	0	60 (95%)	3 (5%)	0	174 (92%)	15 (8%)	0
Dysphonia	121 (96%)	5 (4%)	0	63 (100%)	0	0	184 (97%)	5 (3%)	0
Trismus or problems with jaw movement	124 (98%)	2 (2%)	0	60 (95%)	3 (5%)	0	184 (97%)	5 (3%)	0
Skin reaction or changes	123 (98%)	3 (2%)	0	63 (100%)	0	0	186 (98%)	3 (2%)	0
Dysaesthesia	124 (98%)	2 (2%)	0	62 (98%)	1 (2%)	0	186 (98%)	3 (2%)	0
Cough	124 (98%)	2 (2%)	0	63 (100%)	0	0	187 (99%)	2 (1%)	0

(Table 2 continues on next page)

	IMPT			IMRT			Total		
	0–1	2	3	0–1	2	3	0–1	2	3
(Continued from previous page)									
Decreased appetite	125 (99%)	1 (1%)	0	62 (98%)	1 (2%)	0	187 (99%)	2 (1%)	0
Lower respiratory tract infection	126 (100%)	0	0	62 (98%)	1 (2%)	0	188 (99%)	1 (1%)	0
Pharyngeal stenosis or stricture	125 (99%)	1 (1%)	0	63 (100%)	0	0	188 (99%)	1 (1%)	0
Salivary gland inflammation	125 (99%)	1 (1%)	0	63 (100%)	0	0	188 (99%)	1 (1%)	0
Alopecia	126 (100%)	0	0	63 (100%)	0	0	189 (100%)	0	0
Lymphoedema	126 (100%)	0	0	63 (100%)	0	0	189 (100%)	0	0
Dry skin	126 (100%)	0	0	63 (100%)	0	0	189 (100%)	0	0
Neurotoxicity	126 (100%)	0	0	63 (100%)	0	0	189 (100%)	0	0
Worst radiotherapy-related CTCAE grade†	48 (38%)	46 (37%)	32 (25%)	27 (43%)	27 (43%)	9 (14%)	75 (40%)	73 (39%)	41 (22%)
Worst radiotherapy-related CTCAE grade (excluding hearing impairment)‡	54 (43%)	49 (39%)	23 (18%)	31 (49%)	28 (44%)	4 (6%)	85 (45%)	77 (41%)	27 (14%)
Worst radiotherapy-related CTCAE grade (excluding hearing impairment and weight loss)§	66 (52%)	52 (41%)	8 (6%)	39 (62%)	22 (35%)	2 (3%)	105 (56%)	74 (39%)	10 (5%)

Comparisons between groups were tested at the p<0·005 significance threshold as specified in the statistical analysis plan. Comparisons were done using the χ^2 test or Fisher's exact test (expected n <5). Reported adverse events were considered radiotherapy-related following clinical review. For other adverse events see the appendix (p 24). No grade 4 events were reported. CTCAE=Common Terminology Criteria for Adverse Events. IMPT=intensity-modulated proton beam therapy. IMRT=intensity-modulated radiation therapy. *Proportions of patients with events grade 2 or worse were 100% (n=132) in the IMPT group and 100% (n=67) in the IMRT group. Proportions of patients with events grade 3 or worse were 50% (n=66) in the IMPT group and 72% (n=48) in the IMRT group (p=0·0035). †Proportions of patients with events grade 2 or worse were 62% (n=78) in the IMPT group and 57% (n=36) in the IMRT group (p=0·53). Proportions of patients with events grade 3 or worse were 25% (n=32) in the IMPT group and 14% (n=9) in the IMRT group (p=0·081). ‡Proportions of patients with events grade 2 or worse were 57% (n=72) in the IMPT group and 51% (n=32) in the IMRT group (p=0·41). Proportions of patients with events grade 3 or worse were 18% (n=23) in the IMPT group and 6% (n=4) in the IMRT group (p=0·029). §Proportions of patients with events grade 2 or worse were 48% (n=60) in the IMPT group and 38% (n=24) in the IMRT group (p=0·21). Proportions of patients with events grade 3 or worse were 6% (n=8) in the IMPT group and 3% (n=2) in the IMRT group (p=0·50).

Table 2: **Radiotherapy-related adverse events by worst CTCAE grade**

appendix p 18). Scores declined during chemoradiotherapy and then increased up to 12 months following treatment in both groups (figure 2A). Supporting analyses reported adjusted mean scores of 70·8 (99% CI 67·8 to 73·9) in the IMPT group versus 66·8 (62·4 to 71·3) in the IMRT group (difference 4·0 [99% CI –1·4 to 9·5]) at 3 months and 81·6 (78·8 to 84·5) in the IMPT group versus 79·9 (75·5 to 84·3) in the IMRT group (difference 1·7 [–3·6 to 7·0]) at 24 months (appendix pp 19–20). The longitudinal pattern of scores for the six component physical symptoms is shown in figure 2. From week 6 after chemoradiotherapy, differences between groups had resolved and remained similar until 24 months, with continued improvement in scores for both groups (figure 2). A subset of patients experienced severe symptoms during follow-up; at 3 months and 6 months approximately one in ten patients reported being able to swallow liquids only, a complete loss of taste, or no saliva (figure 2B–G). By 12 months, nearly all had achieved complete recovery or only mild problems with swallowing and chewing; however, about a fifth still reported being able to taste only some foods, and two-fifths had too little saliva (figure 2B–G).

Figure 1 outlines non-evaluability. Major protocol deviations occurred in six patients (five in the IMPT group and one in the IMRT group; appendix p 21): two patients did not start treatment (one clinical deterioration and one withdrawal after planned carboplatin substitution, both in the IMPT group), and four (three in the IMPT group and one in the IMRT group) were included in the mITT population but excluded from the per-protocol population for receiving carboplatin chemotherapy for cycle 1. Results of the prespecified sensitivity analyses were consistent with the primary analysis for both co-primary endpoints (appendix pp 8–11). The respective exclusions of patients within the mITT population with major protocol deviations, a second primary cancer recorded before the co-primary assessment, or salvage surgery before the co-primary assessment did not affect the findings for either co-primary endpoint (appendix pp 8–11). Repeating the clinical co-primary analysis only including patients with complete endpoint data also did not alter the findings (appendix pp 8–11). All post-hoc sensitivity analyses assessing the exclusion of patients from the mITT analysis because of non-evaluability or incomplete co-primary endpoint data further supported the primary

findings (appendix pp 8–11). The numbers of patients included in each sensitivity analysis are shown in the appendix (pp 8–11).

Radiation doses were lower in the IMPT group than in the IMRT group for most OARs including the highest priority structures (appendix p 22). OAR doses for IMPT were similar in the first and second halves of the trial (appendix p 23). Of the 153 (99%) of 154 patients evaluable for the UW-QoL primary endpoint with planning data, 78 (51%) were enriched (met Dutch IMPT thresholds; 61 [62%] of 99 in the IMPT group and 17 [31%] of 54 in the IMRT group). For the enriched cohort, UW-QoL physical composite mean scores were: 78·2 (95% CI 74·7 to 81·6) in the IMPT group versus 75·8 (69·3 to 82·3) in the IMRT group (difference 2·4 [–4·8 to 9·6]), and the unenriched cohort scores were 78·5 (74·2 to 82·9) versus 77·5 (73·1 to 82·0; difference 1·0 [–5·0 to 7·0]).

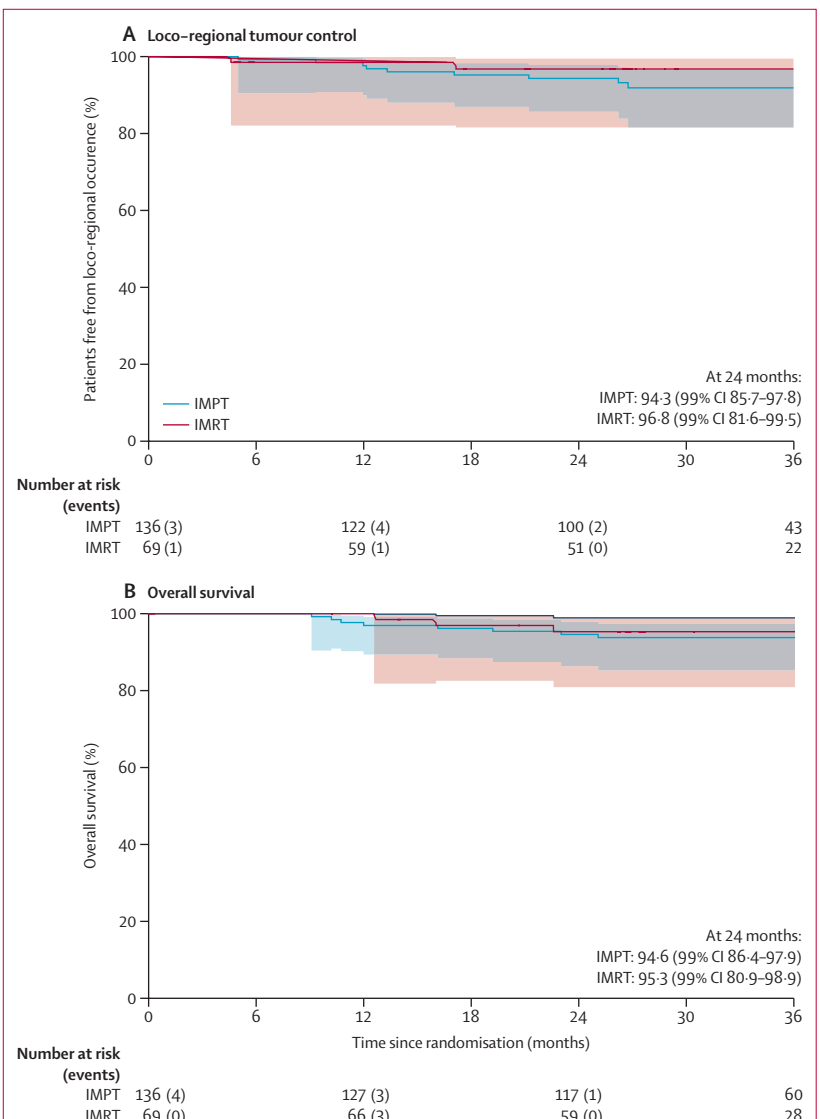

Figure 3: **Loco-regional recurrence and overall survival**
Kaplan–Meier curves for time to loco-regional recurrence (A) and overall survival (B). 24-month event-free survival presented with 99% CIs. IMPT=intensity-modulated proton beam therapy. IMRT=intensity-modulated radiation therapy.

Grade 3 radiotherapy-related acute adverse events occurred in 66 (50%) of 132 patients in the IMPT group and in 48 (72%) of 67 in the IMRT group (p=0·0035; table 2). Grade 3 late adverse events occurred in 32 (25%) of 126 patients in the IMPT group versus nine (14%) of 63 in the IMRT group (p=0·081; table 2), mainly hearing loss and weight loss from month 3. Excluding late hearing loss, grade 3 radiotherapy-related late adverse events occurred in 23 (18%) of 126 patients in the IMPT group versus four (6%) of 63 in the IMRT group (p=0·029; table 2) and, excluding hearing loss and weight loss, in eight (6%) in the IMPT group versus two (3%) in the IMRT group (p=0·50; table 2). No grade 4 radiotherapy-related events were reported. Regarding oral cavity and throat acute adverse events, grade 3 oral pharyngeal mucositis or pain (mouth and throat) occurred in 49 (37%) of 132 patients in the IMPT group versus 36 (54%) of 67 in the IMRT group, grade 3 dysphagia in 16 (12%) in the IMPT group versus 16 (24%) in the IMRT group, and grade 2 dysgeusia (change in taste) in 56 (42%) in the IMPT group *vs* 44 (66%) in the IMRT group. The appendix shows other adverse events (p 24) and results of additional analyses of adverse events (pp 30–32). There were no significant differences in CTCAE grades for prespecified adverse events of interest (including dry mouth, dysgeusia, or dysphagia) between the groups at 3, 12, or 24 months after chemoradiotherapy (appendix p 31). Two grade 4 events that were not related to radiotherapy occurred, both in the acute phase: constipation in one patient in the IMPT group and lymphopenia in one patient in the IMRT group. There were 14 serious adverse events in 12 patients (nine assessed as unrelated to the study treatment [four in the IMPT group and five in the IMRT group] and five as study treatment-related [one *vs* four]); the most common events were acute kidney injury (five [36%]) and thromboembolism (four [29%]). There were no treatment-related deaths.

MDADI mean composite scores at 12 months were 79·5 (99% CI 75·7 to 83·2) in the IMPT group versus 79·7 (74·5 to 84·8) in the IMRT group; difference –0·2 (–6·6 to 6·2; p=0·93; appendix p 33). There was no evidence of differences between binary and trinary PSS-HN subgroups for diet normalcy, speech, and public eating (appendix p 34). There was also no evidence of differences in swallow volume score at 3, 12, and 24 months (appendix p 35).

EORTC QLQ-C30 global health subscale scores at 12 months were 76·3 (99% CI 71·4 to 81·1) in the IMPT group versus 74·7 (68·1 to 81·3) in the IMRT group (difference 1·5 [–6·7 to 9·8]; p=0·62; appendix p 36).

Salvage neck dissection by 6 months occurred in one (1%) of 128 patients in the IMPT group and one (2%) of 66 in the IMRT group (p>0·99). At a median follow-up

of 28·3 months (IQR 26·5–39·3), loco-regional recurrences were nine (7%) in the IMPT group versus two (3%) in the IMRT group and 24-month freedom from loco-regional recurrence rates were 94% (99% CI 86–98) in the IMPT group versus 97% (82–100) in the IMRT group (hazard ratio [HR] 2·6 [99% CI 0·3–20·3; 95% CI 0·5–12·4]; p=0·24; figure 3A). Deaths were ten (7%) in the IMPT group versus three (4%) in the IMRT group and 24-month overall survival rates were 95% (99% CI 86–98) in the IMPT group versus 95% (81–99) in the IMRT group (HR 1·6 [99% CI 0·3–8·8; 95% CI 0·4–5·9; p=0·47; figure 3B).

A full health economic evaluation and cost-effectiveness analysis, based on hospital resource-use data, a patient-level resource-use questionnaire, and the EQ-5D-5L, is underway and will be reported in a separate publication.

Discussion

To our knowledge, this is the first randomised controlled trial with a primary objective to investigate late effects and QoL differences between IMPT and IMRT for head and neck cancer. For oropharyngeal squamous cell carcinoma, IMPT neither reduced late gastrostomy-tube dependence or severe weight loss nor improved long-term patient-reported physical HR-QoL or swallow function. These endpoints were selected as objective measures, identified by patients as meaningful,[13] and by stakeholders as sufficient to justify practice change.

Gastrostomy-tube dependence impairs QoL, reflecting severe swallow dysfunction and other functional problems including chewing difficulties, taste disturbance, or oral dryness. In a trial setting, severe weight loss as a combined endpoint with gastrostomy-tube dependence reduces bias from non-insertion or premature tube removal.[11] The assessment of gastrostomy-tube dependence at month 12 minimises the potential for bias and perceived lack of objectivity associated with the interpretation of tube use in the acute setting (ie, within 90 days after completion of radiotherapy). Such analysis also controls for policy variations between centres in the use of prophylactic or reactive tube placements, which might influence use during treatment. The validated UW-QoL physical composite score[15] assesses patient-relevant symptoms[13] and reduction in side-effects from the anticipated OAR sparing with IMPT versus IMRT. HR-QoL declines during therapy, improves from months 3 to 12, then stabilises, making the month-12 endpoint a reliable measure of lasting radiation effects.[16]

Gastrostomy-tube dependence at 12 months was low in both groups and severe (grade ≥3) weight loss at 12 months was more frequent with IMPT than IMRT. Few patients with severe weight loss became underweight by month 12, suggesting little clinically significant effect. We found no evidence that IMPT reduced weight loss. Weight loss was multifactorial, driven by treatment side-effects but also influenced by baseline BMI, intensity of nutritional support, patient and clinician perceptions towards feeding tubes,[17,18] and potentially higher patient expectations of avoiding tube placement with IMPT than with IMRT. Although mean UW-QoL scores for swallowing, chewing, taste, and saliva were similar between the groups from week 6 after chemoradiotherapy onwards, a subset of patients in both the IMPT and IMRT groups reported persistent moderate-to-severe symptoms throughout follow-up. The lower rate of feeding-tube placement with IMPT compared with IMRT at the end of treatment, combined with a possible reluctance by patients and clinicians to insert tubes after treatment completion, probably contributed to the greater subsequent weight loss observed in the IMPT group. Notably, prophylactic tube placement was more common with IMRT than IMPT. Although centres pre-declared their feeding-tube policy independent of treatment allocation and minimum criteria for tube use were protocol-defined, full standardisation was not feasible in a multicentre trial setting because of variation in hospital and community provision for the approaches.

Late PROs and functional outcomes were similar between the groups. For UW-QoL score at 12 months, most patients reported mild swallowing difficulties, avoiding certain solid foods, had normal taste for most foods, and reduced but adequate saliva production, with no differences between IMPT and IMRT. The proportion of patients with late radiation-related grade 3 events showed less reduction from the acute (≤3 months) to late (>3 months to 2 years) phases in the IMPT group than in the IMRT group. Emergent events from the acute phase that were sustained to month 3 were only reported as late emergent when the grade increased from month 6 onwards. The numerically higher rates of late grade 3 events in the IMPT group than in the IMRT group therefore reflect more new events for IMPT than with IMRT. The apparent divergence in rates of acute and late events between IMRT (more acute) and IMPT (more late descriptively) suggests differential mechanisms predominate—eg, acute inflammation versus late vascular effects or fibrosis. The difference in late grade 3 event rates was primarily driven by weight loss observed from month 3 onwards. Hearing impairment was common in both groups, with cisplatin as a contributing factor.[19] Other radiotherapy-related late grade 3 events were observed in 6% of patients in the IMPT group and 3% in the IMRT group. Previous data comparing IMPT with IMRT are limited by small cohorts and retrospective studies;[20] the randomised phase 3 trial from the MD Anderson Cancer Center (MDACC) Clinical Trial Consortium reported that new-onset chronic (>90 days from end of treatment) grade 3 events were uncommon in both groups.[21] Long-term gastrostomy-tube dependence and late PROs for IMRT were better than in previous reports,[3–6] probably due to fully optimised function-sparing radiotherapy. The DARS trial[22] showed dysphagia-optimised IMRT enhanced swallowing

function versus standard IMRT. The TORPEdO trial optimised plans to spare 20 OARs and used contemporary outlining of target volumes.[23–25]

In the final week of chemoradiotherapy, the UW-QoL physical composite score was higher in the IMPT group than in the IMRT group. Radiation-related grade 3 acute events were less frequent in the IMPT group than in the IMRT group, including mucositis (37% *vs* 54%) and dysphagia (12% *vs* 24%). The lower rate of acute mucositis was correlated with the reduced planned median oral cavity dose with IMPT (36·5 Gy *vs* 47·2 Gy in the IMRT group). The higher replanning rate for IMPT was not thought to be contributory, as the process was standardised in the trial to ensure the planned and delivered doses matched, without amending the therapeutic target volume contours. Previous data on acute effects vary: a 2018–21 retrospective study[20] showed significantly lower acute dysphagia and mucositis with IMPT than with IMRT; pilot data from the DAHANCA 35 trial reported significantly higher acute skin reactions with IMPT than with IMRT (risk ratio 1·9 [95% CI 1·01–3·5]) and acute mucositis (1·5 [1·3–1·7]) with IMPT;[26] and in the MDACC-led trial there were lower reported rates of cumulative CTCAE grade 3 xerostomia (33% *vs* 45%) and dysphagia (34% *vs* 49%), but a higher proportion of skin reactions (24% *vs* 18%) with IMPT than with IMRT.[21] Treatment compliance was similar between groups. Only a small proportion of patients missed fractions because of acute adverse events (five [4%] of 132 patients and nine [<1%] of 4356 fractions in the IMPT group *vs* two [3%] of 67 patients and two [<1%] of 2211 fractions in the IMRT group). Both groups had the same duration of radiotherapy and adherence to two cycles of chemotherapy (96%). However, reduced acute adverse events might have implications beyond treatment compliance, including potential improvements in patient-experience metrics, hospitalisation rates, and unplanned care.

OAR dose reductions were seen with IMPT but did not translate to improved outcomes. Not all reductions lower NTCP, particularly away from the steep part of the sigmoid dose–effect curve, for which early and late effects have distinct dose–response patterns. PROs might not reflect these differences or small functional changes. For plan optimisation and reporting, mean doses to parallel OARs were used, reflecting routine clinical practice and providing input to existing NTCP models to ensure consistent methodology. However, radiation effects might not be adequately captured by mean dose alone, as proton and photon plans can have different intra-organ dose distributions despite similar mean values. For example, reducing dose in distal low-dose regions while increasing dose in proximal high-dose regions might increase the equivalent uniform dose and reduce anticipated differences between modalities. Further work to develop NTCP models that capture this aspect of dose heterogeneity is warranted but would need additional validation. Proton prescriptions assume an RBE of 1·1, but higher end-of-range values and tissue variations occur.[27] With no consensus on a variable RBE model, such a model is not used clinically. Using multiple proton beam fields (beam directions) to distribute the dose across different beam angles can help mitigate this effect, but biological differences remain. To address the effect of anatomical changes on the delivered dose, we did a week-3 rescan, daily CBCTs, dose recalculation, and replanning as indicated. Because of the steep fall off and range uncertainty, proton beams are more sensitive than photon beams to anatomical variation, such as tumour shrinkage or weight loss.[7] As anticipated, we observed higher replan rates in the IMPT group than in the IMRT group, which ensured the planned and delivered doses matched, as well as fair comparisons between the groups and to support NTCP analysis.

78 (51%) of 153 participants met the NTCP criteria for routine IMPT use in the Netherlands.[14] In this cohort with the greatest predicted benefit, we found no significant difference in UW-QoL physical composite mean scores between the IMPT and IMRT groups. Predictive models for radiation therapy toxicities are developed using specific patient populations, treatment techniques, and planning approaches that might limit generalisability. For proton therapy, uncertainties between planned and delivered dose,[28] together with variations in setup and range robustness,[29] might further reduce the accuracy of patient selection. These models might also not capture the full toxicity burden or its effect on QoL, and the association between delta NTCP and PROs might be limited. NTCP enrichment using a different model will be investigated within the ongoing DAHANCA 35 trial.[26]

In our study, most (98%) patients self-reported White ethnicity. Although there is a low incidence of Black (<1%), Asian (1%), and other (1%) minority ethnic groups compared with White ethnicity (92%; 4% unknown ethnicity) in the UK population of patients treated for oropharyngeal cancer,[30] these groups were under-represented in the trial, which might limit generalisability of the results. There might be broader structural inequities for patient access to proton beam therapy as a specialised and centralised service, although the treatment is publicly funded in the UK, accommodation near to the proton centres was provided by the NHS without charge, and travel costs were reimbursed in the trial to limit the effect of socioeconomic barriers to participation.

A limitation to the reproducibility of these results across institutions is that proton centres might use different planning techniques, robustness parameters, and quality-assurance frameworks. The assessment (and optimisation) of linear energy transfer (LET) and related biological models is an emerging approach in proton planning and was not used in this trial. Worldwide, LET-guided optimisation and variable RBE models remain areas of active research and early clinical

implementation rather than established standard practice.

A potential limitation to the analysis is the use of a modified rather than full intention-to-treat population; this analysis was pre-specified with the aim of assessing functional and QoL outcomes in patients with oropharyngeal squamous cell carcinoma who remained cancer free at 12 months following chemoradiotherapy. As no difference in planned tumour dose was anticipated between the modalities, differences in recurrence rates were not expected. Excluding patients who died or experienced recurrence might introduce bias, as the analysis population is conditioned on post-randomisation events. However, this analysis population was more appropriate for the estimand, and multiple sensitivity analyses showed that the conclusions were robust (appendix pp 8–11). The observed event rate for the clinical co-primary endpoint in the IMRT group was lower than the assumed rate used for the sample size calculation, which was based on the best available evidence at the time of study design. Although a larger sample size would have provided more precise estimates and allowed smaller differences to be detected, given that the event rates did not favour the experimental group, the conclusions of the study would not have changed.

Bias was minimised in the trial. Baseline characteristics and compliance were similar, with no crossover between groups. Radiotherapy outlining and planning followed a prospective quality-assured protocol. In addition to the independent quality assurance of plans for all cases, we were reassured that there was no evidence of a learning curve for IMPT planning, supported by the similar OAR doses in the first and second halves of the trial. Optimal OAR dose constraints were challenging, to ensure plans were fully optimised for each modality. As expected, there were more missed and compensated fractions in the IMPT group than in the IMRT group; however, with a maintained total dose, overall treatment time, maximum of six fractions per week, and the same dose per fraction, no differences in acute or late effects were expected. Neither proton centre experienced machine breakdown for more than 2 days. No major radiation guideline changes were needed. The trial accrued ahead of schedule over 3 years, maintaining consistent methodology and ensuring results are relevant to current practice. Median follow-up was 28·3 months with ongoing monitoring of late effects and physical QoL.

Loco-regional tumour control and overall survival were good in both groups for a cohort including adverse clinical factors. With patient and public support, the trial focused on late physical effects and QoL rather than non-inferiority of survival (no difference expected) to ensure efficiency and timely reporting. A further phase 3 trial of proton therapy compared with IMRT for oropharyngeal squamous cell carcinoma has been reported.[21] In this trial (n=440), IMPT met the prespecified criterion for non-inferiority with respect to progression-free survival, showed lower rates of certain high-grade physician-recorded cumulative toxicities, and showed an unexpected overall survival benefit at 5 years, without differences in cancer recurrence or progression rates. Direct comparisons between the trials are constrained by methodological and contextual differences, including variations in health-care delivery systems, socioeconomic barriers to proton therapy access, choice of primary endpoints, statistical designs, radiotherapy outlining, planning and quality-assurance processes, use of induction and concurrent systemic therapies, median follow-up duration (28·3 months *vs* 38·4 months), levels of toxicity, and patient-reported outcome reporting, as well as multiple factors within and between trials that influence the use of feeding tubes and the nutritional status of patients in the acute setting. Together, these landmark studies strengthen the evidence base for treatment decision making in oropharyngeal squamous cell carcinoma and underscore the value of randomised data in investigating advanced radiation technologies.

IMPT and IMRT showed similar late effects, physical QoL, gastrostomy dependence, swallow function, local control, and overall survival. The trial provides robust data on side-effect profiles and trajectories with modern treatments. Contemporary radiation contouring and advanced IMRT planning improved outcomes compared with previous series. Both modalities are effective and in health-care settings where IMPT is not used routinely for oropharyngeal squamous cell carcinoma, IMRT remains the standard of care.

Contributors

DJT is the chief investigator for the trial. EH is the trials methodology lead within the ICR-CTSU and provided oversight and guidance for trial management throughout the trial. DJT, CW, and EH were responsible for the study design. DJT, MT, HT, CW, and EH wrote the first draft of the manuscript. MT, HT, DJT, and EH had access to and verified the data. MT, HT, and EH were responsible for statistical analyses and contributed to data interpretation. DJT, JMP, MB, JL, CMN, NP, RP, SR, AT, GB, HB, FC, MC, ML, JR, JT, JW, and LW are members of the TORPEdO trial management group, which contributed to study design, was responsible for oversight throughout the trial, and contributed to data interpretation and manuscript preparation. DG and CC managed the study and data collection at ICR-CTSU and contributed to the manuscript preparation. HB is a patient advocate member of the trial management group and provided guidance for study documentation and reports. JMP, ML, 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

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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. 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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