Proton versus photon radiotherapy for patients with oropharyngeal cancer in the USA: a multicentre, randomised, open-label, non-inferiority phase 3 trial

*Steven J Frank, Paul M Busse, J Jack Lee, David I Rosenthal, Mike Hernandez, David M Swanson, Adam S Garden, G Brandon Gunn, Samir H Patel, James W Snider, Daniel J Ma, Jason K Molitoris, Nancy Y Lee, Upendra Parvathaneni, Mark W McDonald, Noah S Kalman, Alexander Lin, Nasiruddin Mohammed, Christina Henson, Christian Hyde, Gopal K Bajaj, Sanford R Katz, Roi Dagan, William H Morrison, Jay P Reddy, C David Fuller, Shalin J Shah, Jack Phan, Gregory M Chronowski, Lauren Mayo, Erich M Sturgis, Renata Ferrarotto, Xiaorong R Zhu, Xiaodong Zhang, Li Wang, Katherine A Hutcheson, Adel K El-Naggar, Amy C Moreno, Anna Lee, Michael T Spiotto, Neil D Gross, Stephen Y Lai, Jay J Liao, Jonathan Paly, Zhongxing Liao, Robert L Foote, on behalf of The University of Texas MD Anderson Cancer Center Clinical Trial Consortium**

Lancet 2026; 407: 174–84

Published **Online** December 11, 2025 https://doi.org/10.1016/S0140-6736(25)01962-2

See **Comment** page 112

*Members listed in the appendix (pp 13–14)

Department of Radiation Oncology (Prof S J Frank MD, Prof D I Rosenthal MD, Prof A S Garden MD, Prof G B Gunn MD, Prof W H Morrison MD, J P Reddy MD PhD, Prof C D Fuller MD PhD, Prof S J Shah MD, Prof J Phan MD PhD, Prof G M Chronowski MD, L Mayo MD, L Wang PhD, A C Moreno MD, A Lee MD, M T Spiotto MD PhD, Prof Z Liao MD), **Department of Biostatistics** (Prof J J Lee PhD, M Hernandez MS, D M Swanson PhD), **Department of Head and Neck Surgery** (Prof E M Sturgis MD, Prof K A Hutcheson PhD, Prof N D Gross MD, Prof S Y Lai MD PhD), **Department of Thoracic-Head & Neck Medical Oncology** (Prof R Ferrarotto MD), **Department of Radiation Physics** (Prof X R Zhu PhD, Prof X Zhang PhD), **and Department of Anatomical Pathology** (Prof A K El-Naggar MD), **The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Otolaryngology-Head and Neck Surgery, Baylor College of Medicine, Houston, TX, USA** (Prof E M Sturgis MD); **Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA** (Prof P M Busse MD PhD,

Summary

Background Radiotherapy is an integral component of treatment for oropharyngeal cancer. Toxicity from the current state-of-the-art photon radiotherapy, intensity-modulated radiation therapy (IMRT), has prompted the search for alternative, less toxic therapies. One such alternative that might de-intensify treatment is proton therapy. In this trial, we aimed to directly compare IMRT with intensity-modulated proton therapy (IMPT), both concurrent with systemic therapy, hypothesising comparable disease control and survival and lower toxicity.

Methods This randomised, multicentre, open-label, non-inferiority, phase 3 trial was conducted in 21 sites (cancer centres or universities) in the USA. Patients (aged ≥18 years) with stage III or stage IV oropharyngeal cancer and an Eastern Cooperative Oncology Group performance status of 0–2 were recruited and randomly assigned 1:1 to receive IMPT or IMRT. All patients were treated with radiotherapy to 70 Gy in 33 fractions to the primary tumour site and cervical lymphadenopathy. The type, schedule, and dose of induction or concurrent systemic therapy were chosen locally by each institution's multidisciplinary tumour board and were consistent with international guidelines. The primary endpoint was progression-free survival and was assessed in the intention-to-treat population; safety outcomes were assessed in the per-protocol population (ie, patients who received the assigned therapy). A non-inferiority margin of 9 percentage points for progression-free survival at 3 years was used. This trial is registered with ClinicalTrials.gov (NCT01893307) and is closed to further accrual after prespecified interim analysis.

Findings From Oct 10, 2013, to May 1, 2022, 440 patients consented (median age 61 years [IQR 55–68], 399 [91%] male, 409 [93%] White); 221 were allocated to the IMPT group (with 160 [72%] receiving IMPT) and 219 to the IMRT group (136 [62%] receiving IMRT). At a median follow-up time of 3·2 years, progression-free survival rates for the IMPT group were 82·5% (95% CI 76·1–87·3) at 3 years and 81·3% (74·5–86·5) at 5 years; corresponding rates for the IMRT group were 83·0% (76·7–87·7) and 76·2% (68·0–82·6; hazard ratio [HR] 0·88 [95% CI 0·57–1·35]; p=0·005 for non-inferiority of IMPT). Overall survival rates after IMPT were 90·9% at 5 years versus 81·0% after IMRT (HR 0·58 [95% CI 0·34–0·99]; p=0·045). Treatment-related deaths occurred in nine patients; six in the IMRT group and three in the IMPT group. Deaths from disease progression occurred in 27 patients; 18 in the IMRT group and nine in the IMPT group. 5-year disease control rates for IMPT versus IMRT were similar between treatment groups (local recurrences 2·9% *vs* 5·6%, p=0·474; regional recurrences 3·4% *vs* 3·2%, p=0·860; and distant metastases 9·1% *vs* 8·9%, p=0·897). Severe lymphopenia was more common in the IMRT group (89% *vs* 76%), as were dysphagia (49% *vs* 31%), xerostomia (45% *vs* 33%), and gastrostomy tube dependence (40·2% *vs* 26·8%; p=0·018).

Interpretation IMPT showed non-inferiority to IMRT for progression-free survival, improvement in overall survival, similar disease control, and reduced high-grade toxicity relative to IMRT. Treatment-related and post-progression deaths occurred more frequently with IMRT. IMPT is a new standard-of-care treatment option for patients with oropharyngeal cancer.

Funding MD Anderson Cancer Center, Massachusetts General Hospital, National Institutes of Health, Hitachi America.

Research in context

Evidence before this study

We identified relevant studies through searches of PubMed, ClinicalTrials.gov, and the WHO International Clinical Trial Registry Platform for open or closed randomised controlled trials from database inception to Dec 31, 2024. Search terms were "oropharyngeal carcinoma OR cancer OR neoplasm", "IMPT versus IMRT", "protons versus photons", "randomized trials", and "phase III trials". We found no published randomised controlled trials that directly compared intensity-modulated proton therapy (IMPT) with intensity-modulated radiation (photon) therapy (IMRT) for patients with oropharyngeal cancer. We found one case-controlled observational study that concluded that IMPT was associated with reduced rates of feeding tube dependency and severe weight loss compared with IMRT with similar disease outcomes. However, these data alone are insufficient to recommend IMPT over IMRT concurrent with systemic therapy for patients with advanced stage oropharyngeal cancer. There are two ongoing phase 3 head and neck trials comparing IMPT with IMRT: the TORPEdO trial in the UK (ISRCTN16424014) and the Danish Head and Neck Cancer Group 35 trial in Denmark (NCT04607694). Additionally, the ARTSCAN V phase 2 randomised controlled trial in Sweden is ongoing and comparing IMRT with IMPT for head and neck patients with tonsillar cancer (NCT03829033).

Added value of this study

To the best of our knowledge, this is the first phase 3 randomised controlled trial that compares proton versus photon radiotherapy for patients with advanced stage oropharyngeal cancer. This study shows that IMPT is non-inferior to IMRT for progression-free survival, IMPT reduces the hazard of death by 42%, and IMPT reduces high-grade toxicity relative to IMRT.

Implications of all the available evidence

This study shows that IMPT is a safe and effective treatment that de-intensifies concurrent chemoradiation strategies with IMRT. We recommend proton therapy as a new standard-of-care option for patients with head and neck oropharyngeal cancer. Although early outcomes suggest an improvement in overall survival with IMPT compared with IMRT, long-term follow-up analysis and additional phase 3 trial data will provide a robust assessment of survival outcomes in patients with oropharyngeal cancer.

Introduction

The incidence and mortality of oropharyngeal cancer have increased over the past three decades, owing to the increasing prevalence of human papillomavirus (HPV)-mediated disease, although HPV-negative tumours, commonly associated with a history of smoking, are still prevalent.[1,2] Treatment approaches have evolved in parallel and now largely consist of multimodality therapy—ie, radiation therapy, systemic therapy, and surgery. One component of multimodality treatment is photon-based intensity-modulated radiation therapy (IMRT), in which photon radiation beam intensities are modulated to increase precision while simultaneously reducing exposure to surrounding non-cancer tissues.[3] IMRT was established as a standard of care for head-and-neck cancer after a phase 3 trial showed that it reduced xerostomia by sparing the parotid glands, as compared with the earlier technique of conventional 3D conformal radiation therapy.[4] However, despite the parotid sparing, IMRT resulted in unexpected oral cavity toxicities from exposure of tissues in the radiation beam path.[5] Phase 3 cooperative group trials of IMRT, given with concurrent chemotherapy, have consistently shown severe toxicity, including severe end-of-treatment malnutrition and gastrostomy-tube dependence, in more than 60% of patients.[6,7] Toxicity de-intensification approaches tested to date in phase 3 trials have been unsuccessful and include replacing cisplatin with cetuximab,[7,8] substituting trans oral robotic surgery for radiation therapy,[9] and reducing the radiation dose given as IMRT.[10]

Proton therapy is an alternative form of radiotherapy that has unique physical and biological properties through the use of charged particles rather than the high-energy x-rays of photon therapy.[11] Intensity-modulated proton therapy (IMPT) has enabled reductions in toxicity relative to IMRT by reducing the radiation dose to non-target non-cancer tissues.[12–14] IMPT represents a novel radiation-based de-intensification strategy for both HPV-positive and HPV-negative oropharyngeal tumours, as it reduces radiation exposure to the oral cavity, larynx, brain, and brainstem, including the integral radiation dose to the entire head and neck and skull base region.[15] Early reports suggest that IMPT can achieve similar disease control rates with less toxicity than IMRT.[16] In this trial, we aimed to directly test the hypothesis that IMPT for patients with oropharyngeal cancer can achieve disease control and survival rates comparable to those of IMRT while reducing toxicity.[17]

Methods

Study design

This randomised, multicentre, open-label non-inferiority phase 3 trial was conducted in 21 sites (cancer centres or universities) in the USA (appendix p 8).[17,18] The quality assurance process required each participating site to be credentialed in IMRT and IMPT in the same manner as the National Cancer Institute (NCI)-funded clinical trial cooperative group NRG Oncology (formerly named the Radiation Therapy Oncology Group [RTOG]). The Imaging and Radiation Oncology Core (IROC) was established for the NCI Clinical Trials Network for trials

J Paly DO); **Department of Radiation Oncology, Mayo Clinic–Arizona, Phoenix, AZ, USA** (Prof S H Patel MD); **Department of Radiation Oncology, University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA** (J W Snider MD); **Department of Radiation Oncology, School of Medicine, University of Maryland, Baltimore, MD, USA** (J W Snider MD, J K Molitoris MD PhD); **Mayo Clinic–Rochester, Rochester, MN, USA** (Prof D J Ma MD, Prof R L Foote MD); **New York Proton Center–Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York City, NY, USA** (N Y Lee MD); **Department of Radiation Oncology, University of Washington, Seattle, WA, USA** (Prof U Parvathaneni MD, J J Liao MD); **Winship Cancer Institute of Emory University, Atlanta, GA, USA** (Prof M W McDonald MD); **Department of Radiation Oncology, Miami Cancer Institute, Miami, FL, USA** (N S Kalman MD); **Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA** (Prof A Lin MD); **Northwestern Medicine, Feinberg School of Medicine, Chicago, IL, USA** (N Mohammed MD); **Department of Radiation Oncology, University of Oklahoma Health Sciences, Oklahoma City, OK, USA** (C Henson MD); **McLaren Proton Therapy Center, Karmanos Cancer Center, Detroit, MI, USA** (C Hyde MD); **Inova Radiation Oncology and Mather Proton Therapy Center, Schar Cancer Institute. Fairfax, VA, USA** (G K Bajaj MD); **Willis-Knighton Cancer Center, Shreveport, LA, USA** (S R Katz MD); **University of Florida Health Proton Institute, Jacksonville, FL, USA** (R Dagan MD)

Correspondence to:
Prof Steven J Frank, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
sjfrank@mdanderson.org

See **Online** for appendix

that contain imaging or radiation therapy. Both IROC Houston and IROC St Louis were incorporated in this trial as part of the National Institutes of Health–NCI U19 grant. IROC Houston ensured quality assurance for treatment delivery through a head and neck phantom credentialing process for each of the participating sites for both IMPT and IMRT. After each study site was activated (ie, when all necessary administrative, regulatory, and logistical preparations are completed, and the site is authorised to begin enrolling participants), the clinical trial Principal Investigator (SJF) reviewed the first five patients' treatment plan contours to ensure that each institution complied with the institutional review board (IRB)-approved protocol; IROC St Louis and the MD Anderson Cancer Center performed quality assurance by reviewing and storing each treatment plan for all patients treated on the trial. Adaptive planning was permitted per institutions and physician discretion. From the beginning of the trial, regulatory control of the trial and database has been managed by the MD Anderson Cancer Center with annual site visits for the participating institutions (appendix p 8). Patient enrolment was permitted to continue at each site during the COVID-19 pandemic, and since that time, annual site visits have been performed virtually with each institution.

The protocol was approved by The University of Texas MD Anderson Cancer Center IRB (ethics approval number 2012-0825) and subsequently by the IRBs at each participating institution. The study protocol is available in the appendix (pp 15–61). This trial is registered with ClinicalTrials.gov (NCT01893307) and its status is closed to patient accrual, with estimated study completion in 2031.

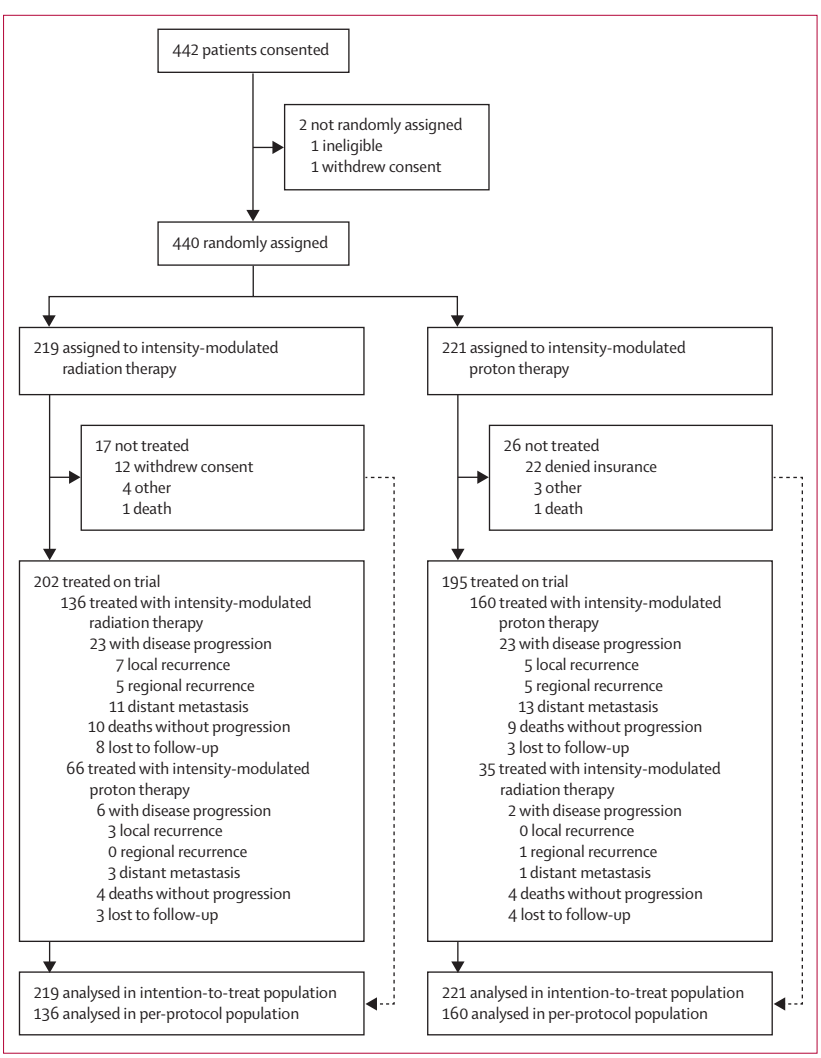

Figure 1: **Trial profile**

Patients

Patients aged 18 years and older with a diagnosis of stage III or stage IV oropharyngeal cancer (per the American Joint Commission on Cancer's 7th 2010 edition[19]) and Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 were eligible for the trial. Trial inclusion criteria were concurrent chemotherapy, radiation to the primary tumour site and bilateral neck lymph node regions, and tumour tissue available for HPV or p16 testing. Exclusion criteria were previous radiation treatment for head-and-neck mucosal primary tumours within the past 5 years, pregnancy or breastfeeding for female individuals, clinically significant cardiological, respiratory, renal, hepatic, gastrointestinal, or haematological disease, distant metastases, and previous neck dissection with therapeutic intent (appendix p 25). All patients had insurance (Medicare or commercial insurance), but this was not a requirement for participation. All systemic drugs were covered by patient insurance; the funders of the trial did not cover the cost of drugs or the study treatment.

Information on sex (female or male), race (White, Black, Asian, or other), and ethnicity (Hispanic or Latino, not Hispanic or Latino, or unknown) were self-reported. All patients provided written informed consent to be enrolled in the trial.

Randomisation and masking

The clinical trial research coordinators at each participating institution enrolled participants and the MD Anderson Cancer Center clinical trial management system utilised a built-in randomisation process to assign participants to different treatment groups. All patients were randomly assigned in a 1:1 ratio to receive IMPT or IMRT, both with concurrent systemic therapy. Randomisation was carried out electronically using permuted blocks with variable block sizes of four, six, and eight. Patients were stratified by HPV and p16 status, smoking status, and use of induction chemotherapy. Radiation target volumes were delineated by the treating radiation oncologist before randomisation.

	Intensity-modulated (photon) radiation therapy	Intensity-modulated proton therapy
Age, years		
<65	134/219 (61%)	138/221 (62%)
≥65	85/219 (39%)	83/221 (38%)
Mean age, years (SD)	61·5 (9·2)	61·5 (8·6)
Median age, years (IQR)	61 (55–68)	61 (56–67)
Age range, years	34–83	33–84
Sex		
Female	18/219 (8%)	23/221 (10%)
Male	201/219 (92%)	198/221 (90%)
Race		
White	204/219 (93%)	205/221 (93%)
Black	6/219 (3%)	9/221 (4%)
Asian	1/219 (<1%)	0/221
Other	8/219 (4%)	7/221 (3%)
Ethnicity		
Hispanic or Latino	11/219 (5%)	9/221 (4%)
Not Hispanic or Latino	197/219 (90%)	194/221 (88%)
Unknown	11/219 (5%)	18/221 (8%)
Smoking status		
Never smoker	111/219 (51%)	118/221 (53%)
Current smoker	16/219 (7%)	8/221 (4%)
Quit	92/219 (42%)	95/221 (43%)
Human papillomavirus p16 status		
Positive	207/219 (95%)	211/221 (95%)
Negative	12/219 (5%)	10/221 (5%)
Induction chemotherapy		
Yes	32/219 (15%)	29/221 (13%)
No	187/219 (85%)	192/221 (87%)
Eastern Cooperative Oncology Group performance status score		
0	174/219 (79%)	161/221 (73%)
1	45/219 (21%)	58/221 (26%)
2	0/219	2/221 (1%)
Charlson Comorbidity Index		
0	75/219 (34%)	80/221 (36%)
1	59/219 (27%)	56/221 (25%)
2	41/219 (19%)	47/221 (21%)
3+	44/219 (20%)	38/221 (17%)
Oropharynx sub-site		
Tonsil	83/219 (38%)	78/221 (35%)
Base of tongue	135/219 (62%)	142/221 (64%)
Pharyngeal wall	1/219 (<1%)	1/221 (<1%)
Tumour stage*		
T1	32/219 (15%)	30/221 (14%)
T2	78/219 (36%)	85/221 (38%)
T3	51/219 (23%)	59/221 (27%)
T4a	56/219 (26%)	44/221 (20%)
T4b	2/219 (1%)	3/221 (1%)
Nodal stage*		
N0	13/219 (6%)	10/221 (5%)
N1	13/219 (6%)	14/221 (6%)
N2a	15/219 (7%)	8/221 (4%)
N2b	110/219 (50%)	120/221 (54%)
N2c	67/219 (31%)	62/221 (28%)
N3	1/219 (<1%)	7/221 (3%)
Clinical stage*		
Stage III	18/219 (8%)	19/221 (9%)
Stage IVA	196/219 (89%)	191/221 (86%)
Stage IVB	5/219 (2%)	11/221 (5%)
Induction chemotherapy†		
Yes	24/202 (12%)	22/195 (11%)
No	178/202 (88%)	173/195 (89%)
Concurrent therapy†		
Yes	202/202 (100%)	195/195 (100%)
No	0/202	0/202
Radiation therapy†		
Intensity-modulated radiation therapy	136/202 (67%)	35/195 (18%)
Intensity-modulated proton therapy	66/202 (33%)	160/195 (82%)
Surgery†		
Yes	19/202 (9%)	13/195 (7%)
No	183/202 (91%)	182/195 (93%)
Treatment sequence†		
Induction chemotherapy, then concurrent therapy, then surgery	3/202 (1%)	1/195 (<1%)
Induction chemotherapy, then concurrent therapy	21/202 (10%)	20/195 (10%)
Concurrent therapy, then surgery	16/202 (8%)	12/195 (6%)
Concurrent therapy	162/202 (80%)	162/195 (83%)

Data are n/N (%), unless indicated otherwise. Percentages might not total 100% due to rounding.*Per the seventh edition of the American Joint Committee on Cancer staging manual. †Data provided for all patients who were randomly allocated to treatment groups and who did not withdraw from the trial before treatment.

Table 1: **Baseline characteristics**

Patients, people giving the interventions, those assessing outcomes, and those analysing the data were not masked to group assignment.

Procedures

Patients were treated in their assigned group except in two scenarios: patients assigned to receive IMPT were

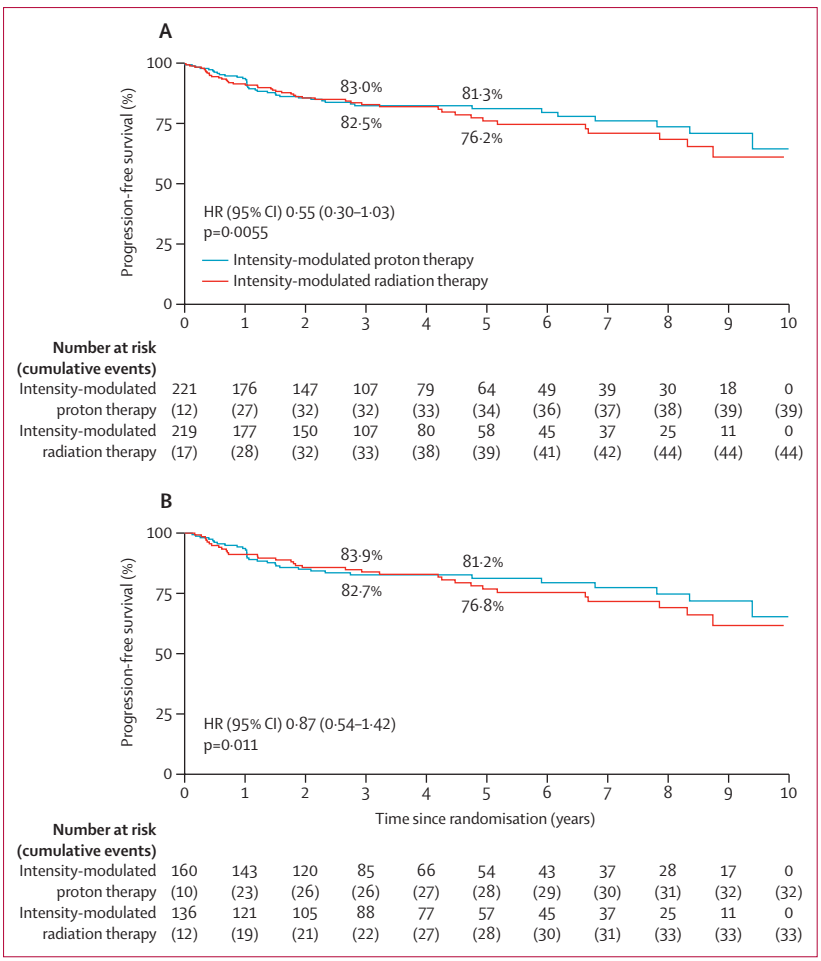

Figure 2: **Progression-free survival in the intention-to-treat population (A) and the per-protocol population (B)**
HR=hazard ratio.

denied insurance and therefore crossed over to the IMRT group; or patients assigned to receive IMRT were approved for IMPT insurance, refused randomisation to the IMRT group, and crossed over to the IMPT group. The treating physicians had no role in crossover consideration.

The unit of proton dose is gray (Gy) expressed as relative biological effectiveness (RBE)-weighted absorbed dose using a RBE weighting factor of 1·1 Gy. All patients were treated with radiotherapy to 70 Gy in 33 fractions to the primary tumour site and cervical lymphadenopathy. All patients received comprehensive irradiation of the bilateral neck with simultaneous integrated boost doses to areas considered to be at increased risk of microscopic nodal disease. The type, schedule, and dose of induction or concurrent systemic therapy were chosen locally by each institution's multidisciplinary tumour board and were consistent with National Comprehensive Cancer Network (NCCN) guidelines. Disease was restaged at 8–12 weeks after completion of concurrent therapy, and lymph node dissection was performed at that time at the discretion of the treating surgical oncologist for patients with suspected residual neck disease.

For more on **National Comprehensive Cancer Network guidelines** see https://www.nccn.org/guidelines/category_1

Outcomes

The primary endpoint of the trial was progression-free survival; progression was defined by the first event of local disease progression or recurrence, regional disease progression or recurrence, distant metastasis, or death. Prespecified secondary endpoints were overall survival and other disease-related outcomes, such as patterns of failure, distant metastasis-free survival, and second primary cancer, patient-reported quality-of-life outcomes, and cost-effectiveness (appendix pp 19–20, 50–54). Patients at The University of Texas MD Anderson Cancer Center provided separate written consent for collection of peripheral blood and tissues at specified timepoints per protocol to assess blood and tissue biomarker ability to predict outcomes. Patient-reported quality-of-life outcomes correlated with toxicities, institution treatment planning approaches, other disease-related outcomes, cost-effectiveness analysis, and exploratory objectives will be communicated in separate reports.

Safety outcomes were grade 3–5 adverse events, which were assessed, graded, and documented according to the NCI Common Terminology Criteria for Adverse Events, version 4.0 at each timepoint per protocol or at the time of a serious adverse event.

All prespecified primary and secondary endpoints were centrally assessed and reviewed annually by The University of Texas MD Anderson Cancer Center IRB, and all serious adverse events were centrally reviewed and presented annually to The University of Texas MD Anderson Cancer Center Data Safety Monitoring Board (DSMB).

Statistical analysis

We assumed a non-inferiority margin of 9 percentage points for progression-free survival at 3 years, which was estimated relative to historical data showing an 80% overall survival estimate at 3 years for patients given concurrent systemic therapy with IMRT.[20] Progression-free survival was considered to be a surrogate for overall survival, which would substantiate the projected 9 percentage point non-inferiority margin and provide alignment with RTOG 1016. The corresponding test was a hazard ratio (HR) of 1·535 or higher under the null hypothesis versus a HR less than 1·535 under the alternative hypothesis. The method of Lan and DeMets with O'Brien–Fleming stopping boundaries was used to establish an interim analysis with an early stopping p-value threshold of 0·006. The protocol gave allowance to increase sample size for potential dropouts due to insurance-related issues to a total of 518 patients. Assuming 440 randomised and evaluable patients with 72 progression-free survival

events at interim and 144 progression-free survival events at the conclusion of the trial, we had 80% power with type I errors of 0·006 at the interim analysis and 0·05 at the final analysis with the log-rank test.[17] Based on interim analysis, after enrolling and randomly allocating 440 patients (with 83 progression-free survival events), additional patient accrual was stopped by the DSMB as the data were sufficiently mature to conclude that the trial had met its primary endpoint of non-inferiority and to reject the null hypothesis. The final report of the trial will occur after 144 events or 10 years.

Comparisons for categorical variables were conducted using χ^2 tests or Fisher's exact tests. All time-to-event outcomes, such as progression-free survival and overall survival, were measured from the date of randomisation to the date of the event or the date of censoring according to the method of Kaplan–Meier. Kaplan–Meier plots were used to visualise the time-to-event information by treatment group, and log-rank tests were used to compare treatment groups. Cox proportional hazards regression was used to assess the time-to-event outcomes. Patients were censored at the time of their last contact.

The primary outcome and overall survival estimates were assessed in the intention-to-treat population. Sensitivity analyses on the primary endpoint and secondary survival estimates were also assessed in the per protocol population (ie, patients who received the assigned therapy). Post-hoc analyses were conducted for covariates of interest (ie, age, sex, smoking status, ECOG score, oropharynx subsite, induction chemotherapy status, concurrent treatment drug, HPV–p16 status, T status, and N status) to explore the direction and magnitude of the treatment effect. Safety outcomes were assessed in the per-protocol population and analysed with respect to superiority according to the method of Kaplan–Meier and not adjusted for multiplicity. All analyses were conducted with Stata (version 18) and R (version 4.5.1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Oct 10, 2013, to May 1, 2022, 442 patients consented to be enrolled, two were not randomly allocated to treatment groups, 221 were allocated to the IMPT group, and 219 to the IMRT group (figure 1). At randomisation, the median patient age was 61 years (IQR 55–68), the mean age was 61·5 years (SD 8·9), 399 (91%) of 440 patients were male, and 409 (93%) were White (table 1).

In the intention-to-treat population, for the IMPT group, the mean time from diagnosis to treatment start was 1·67 months (SD 2·2) and the median time was 1·31 months (range 0·39–29·47); for the IMRT group, the mean time was 1·59 months (SD 1·64) and the median time was 1·15 months (range 0·20–17·22; p=0·179; appendix p 2). In the per-protocol population, for the IMPT group, the mean time from diagnosis to treatment start was 1·65 months (SD 2·34) and the median time was 1·41 months (range 0·39–29·47); for the IMRT group, the mean time was 1·41 months (SD 1·31) and the median time was 1·08 months (range 0·20–12·65; p=0·0075; appendix p 3). Of the patients who were randomly allocated to treatment groups and who did not withdraw from the trial before treatment, 46 (12%) of 397 patients received induction chemotherapy and all 397 (100%) patients received concurrent systemic therapy (360 [91%] with weekly concurrent platinum-based chemotherapy and 37 [9%] with weekly concurrent cetuximab per NCCN). Of the 37 patients given concurrent cetuximab, 23 (11%) were randomised to IMRT, and 14 (7%) were randomised to IMPT (p=0·102). 19 (9%) of 202 patients in the IMRT group and 13 (7%) of 195 patients in the IMPT group had lymph node dissection on disease restaging at their first follow-up visit after concurrent therapy; at that time, four patients in the IMRT group and zero in the IMPT group were found to have positive lymph nodes. Crossovers between

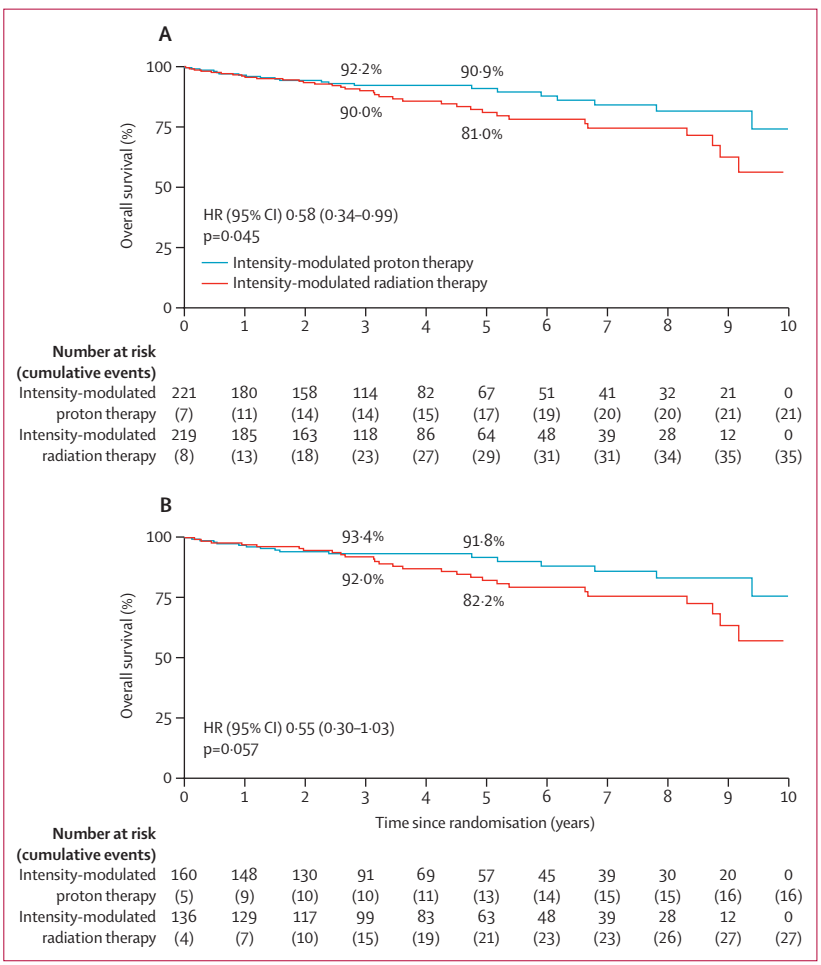

Figure 3: **Overall survival in the intention-to-treat population (A) and the per-protocol population (B)**
HR=hazard ratio.

IMPT and IMRT took place after randomisation and before treatment in 101 (23%) of 440 patients due to proton therapy insurance denial in the IMPT cohort or proton therapy insurance approval in the IMRT cohort and subsequent patient refusal of IMRT. Major trial deviations were uncommon (appendix p 9).

The intention-to-treat population consisted of 221 patients in the IMPT group and 219 patients in the IMRT group. Median follow-up time for both groups was 3·14 years (IQR 1·92–5·47). The progression-free survival rates in the IMPT group were 82·5% (95% CI 76·1–87·3) at 3 years and 81·3% (74·5–86·5) at 5 years; corresponding rates in the IMRT group were 83·0% (76·7–87·7) and 76·2% (68·0–82·6). The unadjusted HR for disease progression or death was 0·88 (0·57–1·35; p=0·0055), showing the non-inferiority of IMPT relative to IMRT (figure 2A). Also in the intention-to-treat population, overall survival rates in the IMPT group were 92·2% (87·1–95·3) at 3 years and 90·9% (85·0–94·6) at 5 years; corresponding rates in the IMRT group were 90·0% (84·5–93·6) and 81·0% (72·8–86·9); the HR was 0·58 (0·34–0·99; p=0·045), favouring IMPT over IMRT (figure 3A). The post-hoc subgroup analysis showed several covariates that had a protective effect with IMPT and reduction in risk of death. These covariates were age younger than 65 years, never smokers, ECOG score of 0, base of tongue tumour sub-site, no induction chemotherapy, and concurrent cisplatin (figure 4).

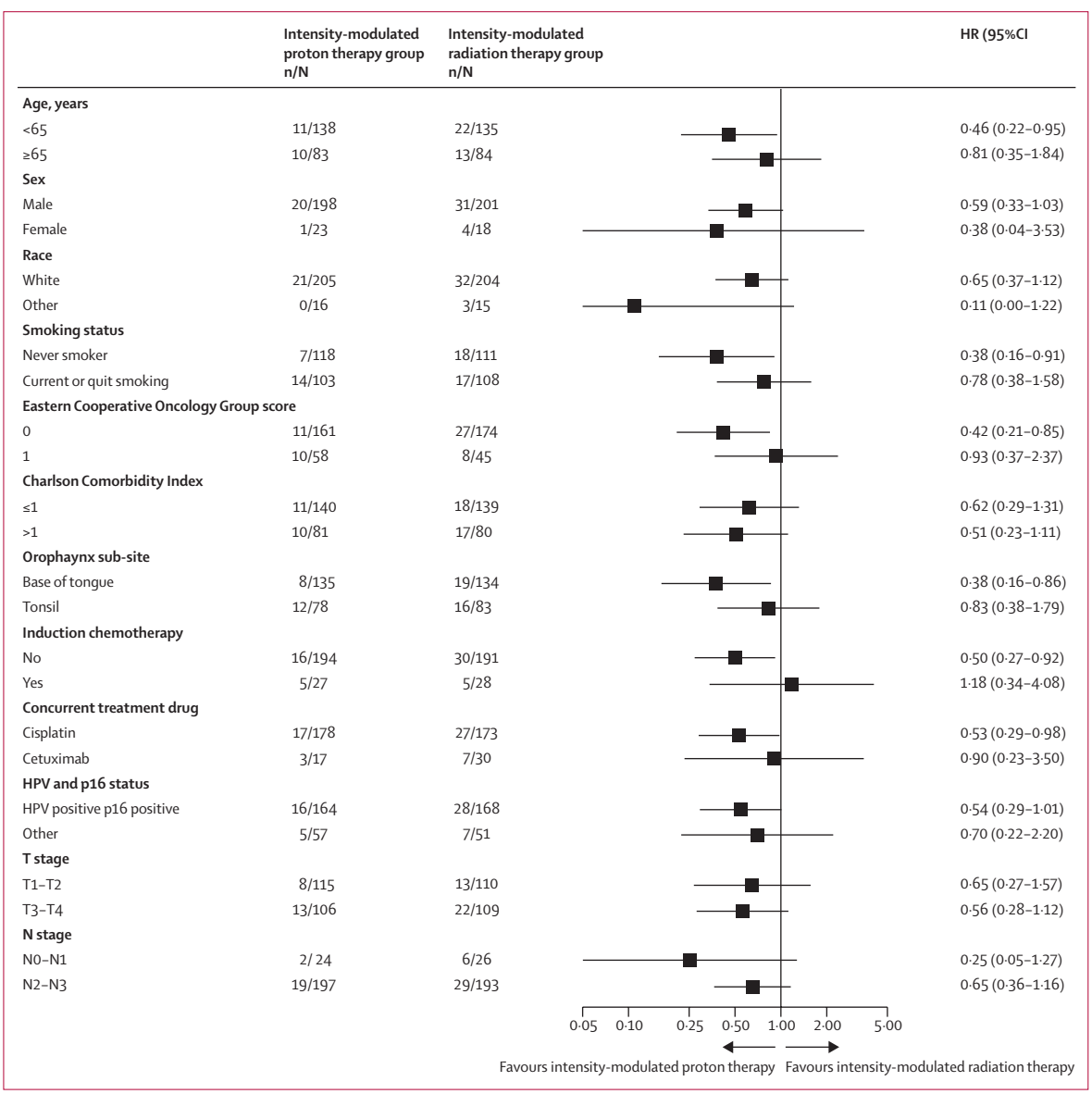

Figure 4: **Subgroup analysis of overall survival in the intention-to-treat population**
Data are number of events/number of patients at risk. HR=hazard ratio. HPV=human papillomavirus.

23 (63%) of 35 patients died with disease in the IMRT group; 11 (52%) of 21 patients died with disease in the IMPT group. Treatment-related deaths (ie, deaths during the acute phase of treatment occurring <90 days from the start of concurrent systemic therapy and radiotherapy) occurred in nine patients; six in the IMRT group and three in the IMPT group. Deaths from disease progression (ie, chronic phase deaths occurring >90 days from start of therapy in patients with recurrent disease) occurred in 27 patients; 18 in the IMRT group and nine in the IMPT group (appendix p 10). Two patients in the IMRT group died from suicide; one at the end of treatment and one at time of recurrence 52 months after randomisation. In exploratory overall survival analyses, the HR for progression as a time-varying covariate versus no progression was 23·9 (p<0·0001), while progression in the IMPT group was associated with a 51% hazard of death reduction (HR=0·49, p=0·11; appendix p 12). Of the patients who died, cetuximab had been given concurrently to five (14%) of 35 patients in the IMRT group and three (14%) of 21 patients in the IMPT group (p=0·977).

The per-protocol population consisted of 160 patients in the IMPT group and 136 patients in the IMRT group. The progression-free survival rates in the IMPT group were 82·7% (95% CI 75·6–87·9) at 3 years and 81·2% (73·5–86·9) at 5 years; in the IMRT group, these were 83·9% (75·8–88·7) at 3 years and 76·8% (67·2–83·2) at 5 years. The unadjusted HR for disease progression or death was 0·87 (0·54–1·42; p=0·011), showing the non-inferiority of IMPT relative to IMRT (figure 2B). In per-protocol analyses, overall survival rates in the IMPT group were 93·4% (88·0–96·4) at 3 years and 91·8% (85·1–95·6) at 5 years; in the IMRT group, these were 92·0% (85·0–95·2) at 3 years and 82·2% (72·8–87·9) at 5 years; the HR for overall survival was 0·55 (0·30–1·03; p=0·057; figure 3B). In the IMPT group, the cumulative incidences of local recurrence or progression were 2·9% (1·1–7·5) at 3 years and 2·9% (1·1–7·5) at 5 years; in the IMRT group these were 3·0% (1·1–7·8) at 3 years and 5·6% (2·5–12·4) at 5 years (p=0·474; appendix p 4). The cumulative incidences of regional recurrence or progression were 3·4% (1·4–7·9) at 3 years and 3·4% (1·4–7·9) at 5 years for the IMPT group and 3·2% (1·2–8·2) at 3 years and 3·2% (1·2–8·2) at 5 years for the IMRT group (p=0·860; appendix p 5). The cumulative incidences of distant progression were 9·1% (5·4–15·2) at 3 years and 9·1% (5·4–15·2) at 5 years for the IMPT group and 7·9% (4·3–14·2) at 3 years and 8·9% (5·0–15·6) at 5 years for the IMRT group (p=0·897; appendix p 6). Sites of distant metastasis included the lung (n=23), liver (n=2), bone (n=4), pancreas (n=1), and brain (n=1).

Table 2 presents the cumulative incidences of severe toxicities (grade 3 and worse) associated with IMPT or IMRT. Grade 3 or 4 lymphopenia was more common in the IMRT group (121 [89%] of 136 patients) than the IMPT group (121 [76%] of 160 patients), and neutropenia and thrombocytopenia were also more severe in the IMRT group. Grade 3 xerostomia (dry mouth) was more common with IMRT than IMPT (45% *vs* 33%), and grade 3 dysphagia was less common with IMPT than IMRT (34% *vs* 49%). The cumulative incidences of gastrostomy-tube dependence at 60 days after the start of treatment were 26·8% (95% CI 20·5–34·6) for IMPT and 40·2% (32·4–49·1) for IMRT (p=0·018; figure 5), and these differences remained significant when the crossover

	Intensity-modulated (photon) radiation therapy (n=136)			Intensity-modulated proton therapy (n=160)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Lymphopenia	75 (55%)	46 (34%)	0	103 (64%)	18 (11%)	0
Oral mucositis	60 (44%)	2 (2%)	0	65 (41%)	0	0
Dysphagia	67 (49%)	0	0	54 (34%)	0	0
Oral pain	32 (24%)	0	0	39 (24%)	0	0
Weight loss	75 (55%)	0	0	74 (46%)	0	0
Dermatitis radiation	25 (18%)	0	0	39 (24%)	0	0
Nausea	19 (14%)	0	0	17 (11%)	0	0
Xerostomia (dry mouth)	61 (45%)	0	0	52 (33%)	0	0
Neutropenia	9 (7%)	4 (3%)	0	3 (2%)	1 (1%)	0
Fatigue	9 (7%)	0	0	5 (3%)	0	0
Thrombocytopenia	2 (1%)	0	0	1 (1%)	0	0
Dehydration	3 (2%)	0	0	5 (3%)	0	0
Oesophagitis	3 (2%)	0	0	5 (3%)	0	0
Vomiting	3 (2%	0	0	6 (4%)	0	0
Anaemia	2 (1%)	0	0	1 (1%)	0	0
Aspiration	1 (1%)	1 (1%)	0	0	0	0
Osteoradionecrosis	2 (1%)	0	0	1 (1%)	0	0
Suicide	0	0	2 (1%)	0	0	0

Data are n (%). Severe adverse events are defined as grade 3 or worse adverse events per the Common Toxicity Criteria Adverse Events framework. Over 95% of severe adverse events occurred during treatment or within 90 days after treatment. All patients received concurrent systemic therapy.

Table 2: **Severe adverse events in the per-protocol population**

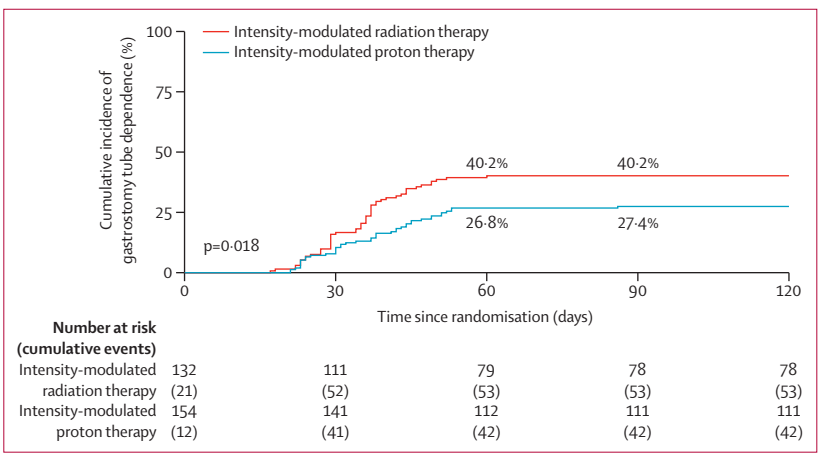

Figure 5: **Cumulative incidence of gastrostomy-tube dependence in the per-protocol population**
Patients with prophylactic gastrostomy tubes were excluded, four patients in the intensity-modulated radiation therapy group and six patients in the intensity-modulated proton therapy group.

patients were included (p=0·013). IMPT resulted in a 33% relative and 13% absolute reduction of gastrostomy-tube dependence compared with IMRT (figure 5). In the per-protocol cohort, four patients treated with IMRT were gastrostomy-tube dependent at 1 year, whereas no patients treated with IMPT were gastrostomy-tube dependent. New-onset chronic (greater than 90 days from end of treatment) grade 3 and higher toxicities were uncommon in both groups of the trial.

Discussion

The three main findings of this phase 3 clinical trial comparing proton versus photon radiation therapy for oropharyngeal cancer are as follows: IMPT was non-inferior to IMRT with respect to progression-free survival; IMPT led to an improvement in overall survival, with a 42% reduction of the hazard of death compared with IMRT; and IMPT reduced the rates of high-grade toxicities including lymphopenia, neutropenia, xerostomia, and dysphagia. The 5-year incidences of recurrence or progression were 2·9% locally, 3·4% regionally, and 9·1% distantly in the IMPT group. These data show the robust efficacy of IMPT in this prospective, controlled, multicentre setting, in which approximately 50% of patients presented with primary T3–T4 tumours and more than 80% had N2–N3 neck lymphadenopathy.

To our knowledge, this is the first phase 3 trial in oropharyngeal cancer suggesting an improvement in overall survival from proton versus photon radiation therapy: at 5 years, the secondary outcome of absolute overall survival rate was 90·9% in the IMPT group and 81·0% in the IMRT group, with an HR of 0·58 (p=0·045). This trial's survival curve estimates for IMRT concurrent with systemic therapy are consistent with those of three consecutive cooperative group trials of concurrent therapy with IMRT for oropharyngeal tumours (RTOG 0129; RTOG 0522; RTOG 1016).[6,7,21] In the present trial, 235 (79%) of 296 patients were considered to have low-risk disease as defined in RTOG 0129, and the overall survival rate at 3 years for the IMRT group of 92·0% was consistent with overall survival in the low-risk population in RTOG 0129.[22] In RTOG 1016, overall survival estimates at 5 years were 84·5% for the patients given concurrent IMRT with cisplatin and 77·9% for those given IMRT plus cetuximab. In this trial, 91% of the patients were treated with concurrent platin-based chemotherapy and the 5-year overall survival estimate with IMRT was 82%. With equivalent rates of local, regional, and distant disease control between IMPT and IMRT in the current study, the unexpected improvement in survival outcomes with IMPT might reflect a reduction in death due to: less severe treatment-related toxicities; better survival after disease progression; unknown factors; or some combination of the above. The cause of death for patients in both the acute (ie, treatment-related deaths) and chronic (ie, deaths due to disease progression) settings suggests that patients given IMRT might be dying faster after progression than patients given IMPT. Models incorporating time-varying progression as a covariate and its interaction with IMPT suggested that one way in which proton therapy benefits patients is by reducing the hazard of death after progression. The interaction between time-varying covariate and the IMPT group did not reach statistical significance in the exploratory analysis. This result might be due to the estimation of this parameter being underpowered, because approximately half of the overall survival events included a progression before death, and the time between recurrence and overall survival events was typically short, making estimation more vulnerable to bias towards the null.

IMRT can result in chronic radiation fibrosis leading to late radiation-associated dysphagia, aspiration, pneumonia, and death.[23] Radiation-induced lymphopenia has been shown to have negative effects on long-term immunity in patients with head and neck cancer as long as 11 years after treatment.[24–26] Given the separation of the survival curves at 3 years in the current study, one might propose that IMRT-induced lymphopenia might result in overactivation of the immune system, with subsequent chronic inflammation resulting in T-cell exhaustion within the tumour microenvironment.[27] The observed improvement in survival with IMPT might also reflect alterations in the immune–oncology–microbiome axis.[28] Additionally, post-progression variation in salvage and palliative therapies could affect overall survival between the treatment groups. These potential mechanisms underlying the improvement in overall survival with IMPT are under active investigation.

The reduction of grade 3 and worse xerostomia with IMPT is noteworthy in this trial as this severe high-grade toxicity might be permanent and will likely persist and affect quality of life long after the patient is cured of their disease. The reduction of grade 2 and worse xerostomia resulted in IMRT becoming the standard of care over conventional radiation therapy, based on findings from a single phase 3 randomised head and neck trial with 94 patients.[4] Regarding gastrostomy-tube dependence, after approximately 3 weeks of concurrent therapy, the prevalence of malnutrition increases, which often necessitates gastrostomy-tube placement to sustain nutrition and hydration. All institutions on the trial had standard of care on-treatment support measures and research nurses monitoring patient care under protocol, and care was consistent with head and neck cooperative group trials. A multi-institutional study from three North American tertiary academic centres reported their findings from more than 2300 patients after IMRT for oropharyngeal cancer.[29] In that study, 82% of patients treated with IMRT and chemotherapy became gastrostomy-tube dependent. In the current trial, IMPT resulted in a 33% relative and 13% absolute reduction of gastrostomy-tube dependence compared with IMRT, making IMPT an innovative de-intensification approach for the management of oropharyngeal cancer.

This phase 3, multicentre, randomised trial investigated the clinical experience of patients with cancer treated with one of two US Food and Drug Administration-approved technologies, IMPT and IMRT. Treatment crossover occurred in 23% of patients (after randomisation and before treatment), largely due to issues with insurance authorisation of proton therapy, which in the current trial was obtained at the time of consultation and was not required before randomisation to avoid treatment delays from the insurance authorisation and appeal processes.[30] Crossover was anticipated and built into the design and protocol of this trial, which was approved by the principal IRB at The University of Texas MD Anderson Cancer Center and the IRBs of all participating institutions.[18] Although proton therapy has had regulatory approval for cancer treatment since 1988, regulatory clearance does not guarantee financial coverage for specific clinical indications (eg, oropharyngeal cancer) and patients are often denied access to proton therapy based on their individual insurance coverage policies. During the initial accrual phase of the trial, when a patient was denied proton therapy coverage after randomisation, withdrawal from the study resulted in loss of patient data with respect to toxicity, disease, and survival outcomes. The protocol for this phase 3 trial was amended to include patients on the trial in the event of crossover after randomisation but before treatment. With such crossover anticipated in both the IMPT and IMRT groups, we published simulations under a variety of scenarios to understand the influence of crossover on parameter estimation and power of the study when assessing the primary endpoint.[17] At the time of the interim analysis, the intention-to-treat and per-protocol statistical assessments by the DSMB concluded that non-inferiority with respect to progression-free survival had been established with rejection of the null hypothesis, and the trial was subsequently closed to further patient accrual.

This trial has several limitations. Delivery techniques for both IMPT and IMRT were being optimised over the course of the trial, and the radiation delivery systems differed among the participating institutions. Also, concurrent systemic therapy was prescribed at the discretion of the treating medical oncologist based on NCCN guidelines, which led to non-uniform induction and concurrent treatment regimens. However, only 14% of patients received induction chemotherapy, as the randomised trials have not shown improvement in clinical outcomes. Additionally, the post-progression salvage and palliative therapies were not controlled and were managed at the discretion of the treating oncologists which might affect overall survival between the treatment groups. Socioeconomic factors might reduce the generalisability of the findings to economically stable patients with insurance, although the intention-to-treat analysis yields a proton therapy parameter effect interpreted with respect to those to whom it was assigned, with balance assured by randomisation. However, the magnitude of the protective effect of IMPT could be even greater in those patients without the resources to manage severe toxicities of chemoradiation therapy. Additionally, geographical access to trial sites was limited to centres with proton therapy in predominantly academic centres. Regarding representativeness, 91% of trial patients were male, which is consistent with 90% male individuals enrolled in the phase 3 oropharyngeal RTOG 1016 trial,[7] however, 93% were White, which is not representative of the population of the USA. Despite these limitations, the intention-to-treat and per-protocol analyses consistently showed comparable progression-free survival outcomes between IMPT and IMRT, a protective effect of IMPT over IMRT for overall survival, and a reduction of high-grade toxicities with IMPT. To build trust from a social and community context, community outreach occurred during the design phase of the trial and designation of the primary endpoint. Furthermore, to break down linguistic and cultural barriers, multilingual materials and translators were available.

In this phase 3, multicentre, oropharyngeal cancer trial, IMPT showed non-inferior progression-free survival and reduced toxicity compared with IMRT. The trial's secondary outcome on overall survival also showed improvements with use of IMPT; however, long-term follow-up analysis and additional phase 3 trial data will provide a more robust assessment. This evidence shows that IMPT is a new standard-of-care treatment option for the management of oropharyngeal tumours.

Contributors

SJF conceptualised the trial. SJF, PMB, RLF, DIR, ASG, JJL, and MH developed the trial design. JJL, MH, and DMS performed the statistical analysis. SJF wrote the first draft of the manuscript with input from JJL, MH, DMS, PMB, and RLF; all authors contributed to subsequent drafting of the manuscript and agreed to be accountable for all aspects of the manuscript. SJF, JJL, MH, and DMS analysed the data. All authors had full access to all of the data in the study. SJF, JJL, MH, and DMS directly accessed and verified the underlying data reported in the manuscript. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

SJF declares grant support for the trial from Hitachi paid to the University of Texas MD Anderson Cancer Center (UTMDACC); research grant support from National Association of Proton Therapy paid to UTMDACC; honoraria payments from Ion Beam Applications; consulting fees and honoraria from Boston Scientific; C4 Imaging (not related to manuscript) fees for Scientific Advisory Committee, as well as ownership interest and patents or royalties; and is a Board Member for National Association of Proton Therapy, a Board Member of the National Comprehensive Cancer Network, and Chair of the Proton Therapy Oncology Group Head and Neck Subcommittee. LW declares grant support from Hitachi paid to the UTMDACC. JWS declares research grant support from the South Florida Proton Research Foundation; consulting fees and travel support from Proton International; consulting fees, honoraria, and travel support from Siemens Healthineers–Varian Medical Systems; consulting fees and travel support from Partners in Healthcare Technology; and did not receive financial support for this Article. JP declares consulting fees from TAE Life Sciences; and did not receive financial support for this Article. CDF declares grants, honoraria, and travel support payments from Elekta; grants from Oncospace; royalties from Kallisio; honoraria and travel support payments from Siemens Healthineers–Varian Medical Systems; honoraria and travel

support payments from Philips Medical Systems; and honoraria payments from GE Healthcare. JKM declares grant support and consulting fees and honoraria from Siemens Healthineers–Varian Medical Systems. NYL declares consulting fees from Merck, Merck Serono, Nanobiotix, Galera, Leo SAB, and GlaxoSmithKline; and travel support from Shanghai JoAnn Medical Technology and Yingming consulting. NDG declares grant support and consulting fees from Regeneron; grant support from Ascendis; consulting fees from Merck and GeoVax; and honoraria from AiCME and OncLive. DIR declares honoraria from Merck. All other authors declare no competing interests.

Data sharing

Data collected for the study, including individual de-identified participant data, participant data with identifiers, and a data dictionary defining each field in the set, will be made available with publication. Additional, related documents will also be available (ie, study protocol, statistical analysis plan, informed consent form). Data access requests should be directed to the corresponding author of this publication via email (sjfrank@mdanderson.org) and will be shared with investigator support after approval of a proposal and with a signed data access agreement.

Acknowledgments

This clinical trial was supported by The University of Texas MD Anderson Cancer Center (P30CA016672); The Massachusetts General Hospital (U19CA021239); the National Institutes of Health (R03CA188162; P01CA285249); and Hitachi America (00054494). We thank the participants, their families, and the multicentre site personnel, whose dedication to contributing to science have made this trial possible; Menna Teferra for administrative support; Aileen Mapps for regulatory support; and Christine Wogan for scientific editorial support.

References

1 Zumsteg ZS, Luu M, Rosenberg PS, et al. Global epidemiologic patterns of oropharyngeal cancer incidence trends. *J Natl Cancer Inst* 2023; **115:** 1544–54.
2 You EL, Henry M, Zeitouni AG. Human papillomavirus-associated oropharyngeal cancer: review of current evidence and management. *Curr Oncol* 2019; **26:** 119–23.
3 Butler EB, Teh BS, Grant WH 3rd, et al. Smart (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 1999; **45:** 21–32.
4 Nutting CM, Morden JP, Harrington KJ, et al, and the PARSPORT trial management group. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011; **12:** 127–36.
5 Rosenthal DI, Chambers MS, Fuller CD, et al. Beam path toxicities to non-target structures during intensity-modulated radiation therapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2008; **72:** 747–55.
6 Nguyen-Tan PF, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. *J Clin Oncol* 2014; **32:** 3858–66.
7 Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin for human papillomavirus (HPV)-positive oropharyngeal cancer: a randomized, multicenter, non-inferiority clinical trial. *Lancet* 2019; **393:** 40–50.
8 Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet* 2019; **393:** 51–60.
9 Nichols AC, Theurer J, Prisman E, et al. Radiotherapy versus transoral robotic surgery for oropharyngeal squamous cell carcinoma: final results of the ORATOR randomized trial. *J Clin Oncol* 2024; **42:** 4023–28.
10 Yom SS, Torres-Saavedra P, Caudell JJ, et al. Reduced-dose radiation therapy for HPV-associated oropharyngeal carcinoma (NRG Oncology HN002). *J Clin Oncol* 2021; **39:** 956–65.
11 Blanchard P, Gunn GB, Lin A, Foote RL, Lee NY, Frank SJ. Proton therapy for head and neck cancers. *Semin Radiat Oncol* 2018; **28:** 53–63.
12 Gunn GB, Blanchard P, Garden AS, et al. Clinical outcomes and patterns of disease recurrence after intensity modulated proton therapy for oropharyngeal squamous carcinoma. *Int J Radiat Oncol Biol Phys* 2016; **95:** 360–67.
13 Frank SJ, Cox JD, Gillin M, et al. Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation to practice. *Int J Radiat Oncol Biol Phys* 2014; **89:** 846–53.
14 Blanchard P, Garden AS, Gunn GB, et al. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer—a case matched analysis. *Radiother Oncol* 2016; **120:** 48–55.
15 Taku N, Wang L, Garden AS, et al. Proton therapy for HPV-associated oropharyngeal cancers of the head and neck: a de-intensification strategy. *Curr Treat Options Oncol* 2021; **22:** 54.
16 Mendenhall WM, Beitler JJ, Saba NF, et al. Proton beam radiation therapy for oropharyngeal squamous cell carcinoma. *Int J Part Ther* 2023; **9:** 243–52.
17 Frank SJ, Blanchard P, Lee JJ, et al. Comparing intensity-modulated proton therapy with intensity-modulated photon therapy for oropharyngeal cancer: the journey from clinical trial concept to activation. *Semin Radiat Oncol* 2018; **28:** 108–13.
18 Hernandez M, Lee JJ, Yeap BY, et al. The reality of randomized controlled trials for assessing the benefit of proton therapy: critically examining the intent-to-treat principle in the presence of insurance denial. *Adv Radiat Oncol* 2020; **6:** 100635.
19 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC cancer staging manual, seventh edition. New York, NY: Springer, 2010.
20 Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol* 2014; **32:** 2940–50.
21 Caudell JJ, Torres-Saavedra PA, Rosenthal DI, et al. Long-term update of NRG/RTOG 0522: a randomized phase 3 trial of concurrent radiation and cisplatin with or without cetuximab in locoregionally advanced head and neck cancer. *Int J Radiat Oncol Biol Phys* 2023; **116:** 533–43.
22 Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010; **363:** 24–35.
23 Ramia P, Bodgi L, Mahmoud D, et al. Radiation-induced fibrosis in patients with head and neck cancer: a review of pathogenesis and clinical outcomes. *Clin Med Insights Oncol* 2022; **16:** 11795549211036898.
24 Dai D, Tian Q, Shui Y, Li J, Wei Q. The impact of radiation induced lymphopenia in the prognosis of head and neck cancer: a systematic review and meta-analysis. *Radiother Oncol* 2022; **168:** 28–36.
25 Tarpley JL, Potvin C, Chretien PB. Prolonged depression of cellular immunity in cured laryngopharyngeal cancer patients treated with radiation therapy. *Cancer* 1975; **35:** 638–44.
26 Gray WC, Chretien PB, Suter CM, et al. Effects of radiation therapy on T-lymphocyte subpopulations in patients with head and neck cancer. *Otolaryngol Head Neck Surg* 1985; **93:** 650–60.
27 Jiang Y, Li Y, Zhu B. T-cell exhaustion in the tumor microenvironment. *Cell Death Dis* 2015; **6:** e1792–1792.
28 Sepich-Poore GD, Zitvogel L, Straussman R, Hasty J, Wargo JA, Knight R. The microbiome and human cancer. *Science* 2021; **371:** eabc4552.
29 Setton J, Lee NY, Riaz N, et al. A multi-institution pooled analysis of gastrostomy tube dependence in patients with oropharyngeal cancer treated with definitive intensity-modulated radiotherapy. *Cancer* 2015; **121:** 294–301.
30 Ning MS, Gomez DR, Shah AK, et al. The insurance approval process for proton radiation therapy: a significant barrier to patient care. *Int J Radiat Oncol Biol Phys* 2019; **104:** 724–33.