Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial

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Summary

Background Patients with human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma have high survival when treated with radiotherapy plus cisplatin. Whether replacement of cisplatin with cetuximab—an antibody against the epidermal growth factor receptor—can preserve high survival and reduce treatment toxicity is unknown. We investigated whether cetuximab would maintain a high proportion of patient survival and reduce acute and late toxicity.

Methods RTOG 1016 was a randomised, multicentre, non-inferiority trial at 182 health-care centres in the USA and Canada. Eligibility criteria included histologically confirmed HPV-positive oropharyngeal carcinoma; American Joint Committee on Cancer 7th edition clinical categories T1–T2, N2a–N3 M0 or T3–T4, N0–N3 M0; Zubrod performance status 0 or 1; age at least 18 years; and adequate bone marrow, hepatic, and renal function. We randomly assigned patients (1:1) to receive either radiotherapy plus cetuximab or radiotherapy plus cisplatin. Randomisation was balanced by using randomly permuted blocks, and patients were stratified by T category (T1–T2 *vs* T3–T4), N category (N0–N2a *vs* N2b–N3), Zubrod performance status (0 *vs* 1), and tobacco smoking history (≤10 pack-years *vs* >10 pack-years). Patients were assigned to receive either intravenous cetuximab at a loading dose of 400 mg/m² 5–7 days before radiotherapy initiation, followed by cetuximab 250 mg/m² weekly for seven doses (total 2150 mg/m²), or cisplatin 100 mg/m² on days 1 and 22 of radiotherapy (total 200 mg/m²). All patients received accelerated intensity-modulated radiotherapy delivered at 70 Gy in 35 fractions over 6 weeks at six fractions per week (with two fractions given on one day, at least 6 h apart). The primary endpoint was overall survival, defined as time from randomisation to death from any cause, with non-inferiority margin 1·45. Primary analysis was based on the modified intention-to-treat approach, whereby all patients meeting eligibility criteria are included. This study is registered with ClinicalTrials.gov, number NCT01302834.

Findings Between June 9, 2011, and July 31, 2014, 987 patients were enrolled, of whom 849 were randomly assigned to receive radiotherapy plus cetuximab (n=425) or radiotherapy plus cisplatin (n=424). 399 patients assigned to receive cetuximab and 406 patients assigned to receive cisplatin were subsequently eligible. After median follow-up duration of 4·5 years, radiotherapy plus cetuximab did not meet the non-inferiority criteria for overall survival (hazard ratio [HR] 1·45, one-sided 95% upper CI 1·94; p=0·5056 for non-inferiority; one-sided log-rank p=0·0163). Estimated 5-year overall survival was 77·9% (95% CI 73·4–82·5) in the cetuximab group versus 84·6% (80·6–88·6) in the cisplatin group. Progression-free survival was significantly lower in the cetuximab group compared with the cisplatin group (HR 1·72, 95% CI 1·29–2·29; p=0·0002; 5-year progression-free survival 67·3%, 95% CI 62·4–72·2 *vs* 78·4%, 73·8–83·0), and locoregional failure was significantly higher in the cetuximab group compared with the cisplatin group (HR 2·05, 95% CI 1·35–3·10; 5-year proportions 17·3%, 95% CI 13·7–21·4 *vs* 9·9%, 6·9–13·6). Proportions of acute moderate to severe toxicity (77·4%, 95% CI 73·0–81·5 *vs* 81·7%, 77·5–85·3; p=0·1586) and late moderate to severe toxicity (16·5%, 95% CI 12·9–20·7 *vs* 20·4%, 16·4–24·8; p=0·1904) were similar between the cetuximab and cisplatin groups.

Interpretation For patients with HPV-positive oropharyngeal carcinoma, radiotherapy plus cetuximab showed inferior overall survival and progression-free survival compared with radiotherapy plus cisplatin. Radiotherapy plus cisplatin is the standard of care for eligible patients with HPV-positive oropharyngeal carcinoma.

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Introduction

Human papillomavirus (HPV) is the cause of a subgroup of oropharyngeal squamous cell carcinoma that is increasing in incidence in many countries, including the USA. Prognosis is better for patients with HPV-positive oropharyngeal carcinoma compared with HPV-negative oropharyngeal carcinoma when treated with radiotherapy plus high-dose cisplatin (3-year survival 82·4% *vs* 57·1%).[1]

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Research in context

Evidence before this study

Over the past decade, systematic reviews have estimated that patients diagnosed with human papillomavirus (HPV)-positive oropharyngeal carcinoma have less than half the risk of death compared with that of patients diagnosed with HPV-negative oropharyngeal carcinoma. The high survival for patients with HPV-positive oropharyngeal carcinoma has prompted increased concern regarding late toxicity of therapy. On Sept 28, 2018, we searched PubMed with no language restrictions using the terms "survival" AND "head and neck cancer" AND "meta-analysis" and identified several meta-analyses on the effect of adding chemotherapy to radiotherapy for the treatment of locoregionally advanced head and neck cancer. Addition of platinum-based chemotherapy to radiotherapy is estimated to reduce the mortality of patients with head and neck squamous cell carcinoma by 26%, leading to an absolute 5-year benefit of 8%. This benefit was similar when restricted to the subgroup of patients with oropharyngeal carcinomas. Addition of cisplatin to radiotherapy was shown to significantly increase both acute and late toxicity of therapy. Only a single randomised trial evaluated addition of cetuximab—an antibody against epidermal growth factor receptor—to radiotherapy in locoregionally advanced head and neck squamous cell carcinoma, with the primary endpoint of locoregional control and a secondary endpoint of overall survival. Cetuximab was estimated to reduce mortality by 27%, leading to an absolute 5-year survival benefit of 9·2%. Overall acute toxicity, late toxicity, and patient-reported quality of life did not worsen with the addition of cetuximab to radiotherapy. After regulatory approval of cetuximab by the US Food and Drug Administration in 2006, use of this drug increased substantially, and it has become a common clinical practice to substitute cetuximab for cisplatin. However, to our knowledge no randomised prospective clinical trials have directly compared overall survival for radiotherapy plus cetuximab with radiotherapy plus cisplatin.

Added value of this study

This study is one of the first randomised, prospective clinical trials exclusive to all patients diagnosed with locoregionally advanced HPV-positive oropharyngeal carcinoma. This study was designed as a classical non-inferiority trial to investigate the hypothesis that substitution of cetuximab for cisplatin would maintain a high proportion of cures while reducing acute and late therapy toxicity. Radiotherapy plus cetuximab did not meet the criteria for non-inferiority for overall survival when compared with radiotherapy plus cisplatin. Cetuximab was estimated to increase the risk of death by 45% (hazard ratio 1·45, 95% CI 1·03–2·05), the risk of cancer progression or death by 72% (1·72, 1·29–2·29), and locoregional failure by 105% (2·05, 1·35–3·10). Proportions of overall moderate to severe acute and late toxicity were similar between the treatment groups, although numbers of specific toxicities differed significantly. In this study designed to compare overall survival in patients treated with radiotherapy plus cetuximab with radiotherapy plus cisplatin, cetuximab was found to be inferior. As our study was restricted to patients with HPV-positive oropharyngeal cancer, a similar trial in HPV-negative head and neck squamous cell carcinoma is warranted.

Implications of all the available evidence

This clinical trial of patients with HPV-positive oropharyngeal cancer establishes radiotherapy plus cisplatin as the standard of care. Cetuximab should not be substituted for cisplatin for patients with HPV-positive oropharyngeal cancer who are platinum eligible.

High survival together with young age at diagnosis has promoted increased concern regarding late treatment-related toxicity for patients with HPV-positive oropharyngeal carcinoma.

Addition of platinum-based chemotherapy to radiotherapy has an estimated 8% absolute 5-year survival benefit (hazard ratio [HR] 0·74, 95% CI 0·67–0·82) for head and neck squamous cell carcinoma.[2] This benefit is similar for oropharyngeal carcinoma (HR 0·70, 95% CI 0·59–0·84).[3] However, moderate to severe acute toxicity is greater with addition of cisplatin.[4] Moreover, the combination of severe dysphagia, feeding tube dependence, or death without cancer progression after radiotherapy plus cisplatin is as high as 43% at 3 years.[5] In a landmark trial (IMC9815), addition of cetuximab—an antibody against the epidermal growth factor receptor (EGFR)—to radiotherapy improved survival for patients with head and neck squamous cell carcinoma, without increased toxicity.[6,7] The absolute 5-year survival benefit was 9·2%, and subgroup analysis suggested similar benefit for oropharyngeal carcinoma.[8] The relative risks and benefits of cetuximab versus cisplatin when added to radiotherapy for patients with locoregionally advanced head and neck squamous cell carcinoma are unknown.

We did a randomised clinical trial with a non-inferiority design to compare overall survival for patients with HPV-positive oropharyngeal carcinoma when treated with radiotherapy plus cetuximab versus radiotherapy plus cisplatin. We investigated the hypothesis that cetuximab would maintain a high proportion of patient survival and reduce acute and late toxicity.

Methods

Study design and patients

RTOG 1016 was a randomised, multicentre, non-inferiority trial at 182 health-care centres in the USA and Canada. Eligibility criteria included histologically confirmed HPV-positive oropharyngeal carcinoma; American Joint Committee on Cancer 7th edition[9] clinical categories T1–T2, N2a–N3 M0 or T3–T4, N0–N3 M0; Zubrod

performance status 0 or 1; age at least 18 years; and adequate bone marrow, hepatic, and renal function. For complete inclusion and exclusion criteria see the appendix. Patients were recruited into this study by their treating physicians.

Ethics approval was obtained from institutional review boards of participating institutions. Patients provided written informed consent.

Randomisation and masking

We randomly assigned patients (1:1) to receive either radiotherapy plus cetuximab or radiotherapy plus cisplatin. Randomisation was balanced by using randomly permuted blocks, and patients were stratified by T category (T1–T2 *vs* T3–T4), N category (N0–N2a *vs* N2b–N3), Zubrod performance status (0 *vs* 1), and tobacco smoking history (≤10 pack-years *vs* >10 pack-years). Treatment assignment was centrally generated at the NRG Oncology Statistics and Data Management Center (Philadelphia, PA, USA) and provided to the institution when the patient was entered. Treatment assignment was not masked to the participating site, the enrolling physician, or the responsible statistician.

Procedures

Patients were assigned to receive either intravenous cetuximab (Eli Lilly; Indianapolis, IN, USA) at a loading dose of 400 mg/m² 5–7 days before radiotherapy initiation, followed by cetuximab 250 mg/m² weekly for seven doses (total 2150 mg/m²), or cisplatin (commercially available and obtained by each individual institution) 100 mg/m² on days 1 and 22 of radiotherapy (total 200 mg/m²). All patients received accelerated intensity-modulated radiotherapy delivered at 70 Gy in 35 fractions over 6 weeks at six fractions per week (with two fractions given on one day, at least 6 h apart).

HPV status was determined by the established and validated surrogate of immunohistochemistry for p16 expression in a central laboratory (Polaris Innovation Laboratory at The Ohio State University; Columbus, OH, USA),[10] and tumours were classified as p16 positive if strong and diffuse nuclear and cytoplasmic staining was present in at least 70% of tumour cells.[10]

Patients provided their lifetime cigarette exposure history at enrolment via a standardised computer-assisted self-interview.

Quality of life outcomes (appendix) were assessed at baseline, end of treatment, and at 3 months, 6 months, and 12 months after treatment completion. Quality assurance review of chemotherapy and radiotherapy was done as per standard NRG Oncology protocol (appendix).

Outcomes

The primary endpoint was overall survival, defined as time from randomisation to death from any cause. Secondary endpoints included progression-free survival (time from randomisation to cancer progression or death); locoregional failure and distant metastasis (appendix); second primary tumours; overall and type-specific treatment-related (definitely, probably, or possibly related) adverse events that were acute (≤180 days) or late (>180 days) relative to treatment completion; early death (death due to adverse event or within 30 days of treatment completion); feeding tube placement; dental health; and quality of life. For a complete list of secondary study endpoints see appendix. Clinical or radiographic evidence of progression was investigator-assessed by clinical examination, imaging, or biopsy. Quality of life assessments were optional and limited to the first 400 patients who consented. Only the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire head and neck module (EORTC

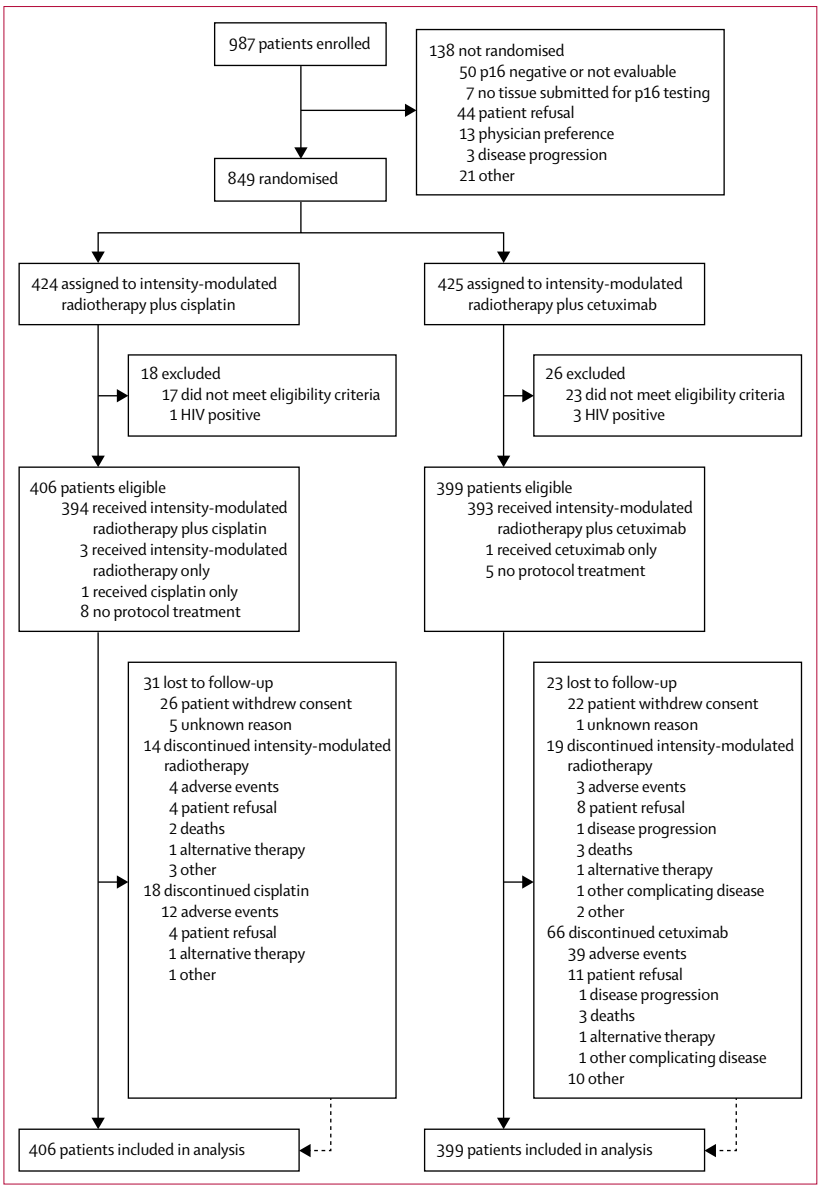


Figure 1: **Trial profile**

See **Online** for appendix

	Intensity-modulated radiotherapy plus cisplatin (n=406)	Intensity-modulated radiotherapy plus cetuximab (n=399)	Total (n=805)
Age (years)			
≤65	344 (85%)	345 (86%)	689 (86%)
>65	62 (15%)	54 (14%)	116 (14%)
Mean (SD)	57·7 (8·1)	57·4 (7·8)	57·6 (8·0)
Median (IQR)	58 (52–63)	58 (52–63)	58 (52–63)
Range	33–83	33–80	33–83
Sex			
Men	373 (92%)	355 (89%)	728 (90%)
Women	33 (8%)	44 (11%)	77 (10%)
Race			
White	380 (94%)	367 (92%)	747 (93%)
Black	17 (4%)	19 (5%)	36 (4%)
Other	2 (<1%)	8 (2%)	10 (1%)
Unknown	7 (2%)	5 (1%)	12 (1%)
Ethnicity			
Hispanic or Latino	11 (3%)	15 (4%)	26 (3%)
Not Hispanic or Latino	383 (94%)	369 (92%)	752 (93%)
Unknown	12 (3%)	15 (4%)	27 (3%)
Zubrod performance status			
0	295 (73%)	300 (75%)	595 (74%)
1	111 (27%)	99 (25%)	210 (26%)
Smoking history			
0 pack-years	194 (48%)	181 (45%)	375 (47%)
>0 to ≤10 pack-years	59 (15%)	68 (17%)	127 (16%)
>10 pack-years	153 (38%)	150 (38%)	303 (38%)
Mean (SD)	15·0 (23·5)	14·8 (23·9)	14·9 (23·7)
Median (IQR)	2 (0–22)	3 (0–24)	2 (0–23)
Range	0–147	0–202	0–202
Primary site			
Tonsillar fossa, tonsil	202 (50%)	199 (50%)	401 (50%)
Base of tongue	174 (43%)	179 (45%)	353 (44%)
Oropharynx, not otherwise specified	16 (4%)	15 (4%)	31 (4%)
Pharyngeal oropharynx	8 (2%)	5 (1%)	13 (2%)
Soft palate	4 (1%)	0	4 (<1%)
Vallecula	2 (<1%)	1 (<1%)	3 (<1%)
(Table 1 continues in next column)			

	Intensity-modulated radiotherapy plus cisplatin (n=406)	Intensity-modulated radiotherapy plus cetuximab (n=399)	Total (n=805)
(Continued from previous column)			
Tumour stage*			
T1	89 (22%)	86 (22%)	175 (22%)
T2	162 (40%)	163 (41%)	325 (40%)
T3	108 (27%)	100 (25%)	208 (26%)
T4	47 (12%)	50 (13%)	97 (12%)
Node category*			
N0	20 (5%)	14 (4%)	34 (4%)
N1	20 (5%)	25 (6%)	45 (6%)
N2a	59 (15%)	56 (14%)	115 (14%)
N2b	209 (51%)	208 (52%)	417 (52%)
N2c	82 (20%)	83 (21%)	165 (20%)
N3	16 (4%)	13 (3%)	29 (4%)
Overall stage*			
III	29 (7%)	31 (8%)	60 (7%)
IV	377 (93%)	368 (92%)	745 (93%)
Risk group per RTOG 0129[1]			
Low risk	289 (71%)	284 (71%)	573 (71%)
Intermediate risk	117 (29%)	115 (29%)	232 (29%)
Consented to patient-reported outcome or quality of life collection			
No	17 (8%)†	21 (10%)‡	38 (9%)§
Yes	196 (92%)†	185 (90%)‡	381 (91%)§

Data are n (%) unless otherwise indicated. *According to American Joint Committee on Cancer 7th edition. †n=213. ‡n=206. §n=419.

Table 1: **Patient and tumour baseline characteristics**

QLQ-H&N35) swallowing domain is reported here.[11] Additional quality of life endpoints will be reported elsewhere.

Adverse events were evaluated with National Cancer Institute Common Terminology Criteria for Adverse Events, version 4, and were assessed at baseline, once per week during radiotherapy, end of treatment, and 1 month and 3 months after treatment completion. Criteria for dose reduction or delay were prespecified. Per-protocol disease assessment (physical examination, including laryngopharyngoscopy, and if indicated, CT or MRI of the head and neck) and late adverse event data were required every 3 months for 2 years, every 6 months through year 5, and then annually. Chest X-ray or chest CT were done annually. Dental health was assessed according to a five-point scale developed for this trial as normal, mild changes or good dental health, moderate or fair dental health, severe changes in dental health, and life-threatening dental condition.

Statistical analysis

RTOG 1016 was initially designed to investigate whether radiotherapy plus cetuximab resulted in 5-year overall survival non-inferior to radiotherapy plus cisplatin by more than 9% (HR <1·4) on the basis of survival estimates generated from patients with p16-positive oropharyngeal cancer in RTOG 0129.[1] Using a group sequential design based on the Haybittle-Peto boundary with three interim analyses, one-sided α=0·05, and 80% power, 600 randomised eligible patients were required. The expected study duration was 8·5 years. On Dec 10, 2013, the study was amended to reflect higher survival noted for patients with p16-positive oropharyngeal cancer in RTOG 0522.[12] On the basis of the original study sample size and RTOG 0522 survival estimates, the expected study duration would have been increased by 5 years. The redesign (undertaken before any interim analyses had been done) called for a non-inferiority margin of 1·45 for the HR, larger than the initial margin, but with a smaller

absolute difference (7·6%) at 5 years. Using a group sequential design based on the Haybittle-Peto boundary with three interim analyses (after 45 of 180 deaths, 90 of 180 deaths, and 135 of 180 deaths), one-sided α=0·05, and 80% power, 800 randomised eligible patients were required. To allow for 20% non-randomisation and ineligibility, planned enrolment was up to 1000 patients. The revised expected study duration was 8·15 years.

We based our primary analysis on the modified intention-to-treat approach, whereby all patients meeting eligibility criteria are included. We did sensitivity analyses for the primary endpoint in the per-protocol subset, defined as randomly assigned patients who received 70 Gy of radiation and 200 mg/m² of cisplatin or eight doses of cetuximab. We assessed the primary endpoint with the Cox proportional hazards model. If the upper limit of the one-sided 95% CI for the HR was <1·45, we concluded non-inferiority was met. Additionally, we compared the treatment groups with the log-rank test, with reference to the one-sided alternative hypothesis of cetuximab failure greater than cisplatin failure (non-prespecified). All other statistical tests and 95% CIs mentioned here were two-sided. We estimated overall survival and progression-free survival with the Kaplan-Meier method, and compared the treatment groups with the log-rank test. We estimated locoregional failure, distant metastasis, and second primary tumours with cumulative incidence functions, and compared treatment groups by cause-specific log-rank tests and HRs.[13] We verified the proportional hazards assumption for the Cox model by supremum test with 1000 simulations. The safety analysis was limited to eligible patients who started treatment. We calculated mean raw T-scores (acute toxicity) and A-scores (late toxicity) according to the TAME method.[14] We compared numbers of adverse events and feeding tubes with Fisher's exact test. We compared mean T-scores, A-scores, and EORTC QLQ-H&N35 subscale scores on the swallowing domain from pretreatment to 1 year[11] by *t* test with unequal variances. We used the Benjamini-Hochberg procedure with 5% false discovery rate to adjust for multiple comparisons of numbers of adverse events and for unplanned analysis of overall survival and progression-free survival treatment effects in subgroups, including stratification factors, age, American Joint Committee on Cancer 8th edition staging,[15] and risk groups as defined in RTOG 0129.[1]

At the third interim analysis, although neither efficacy nor futility boundaries were crossed, the point estimate for the HR exceeded the non-inferiority margin. A recent

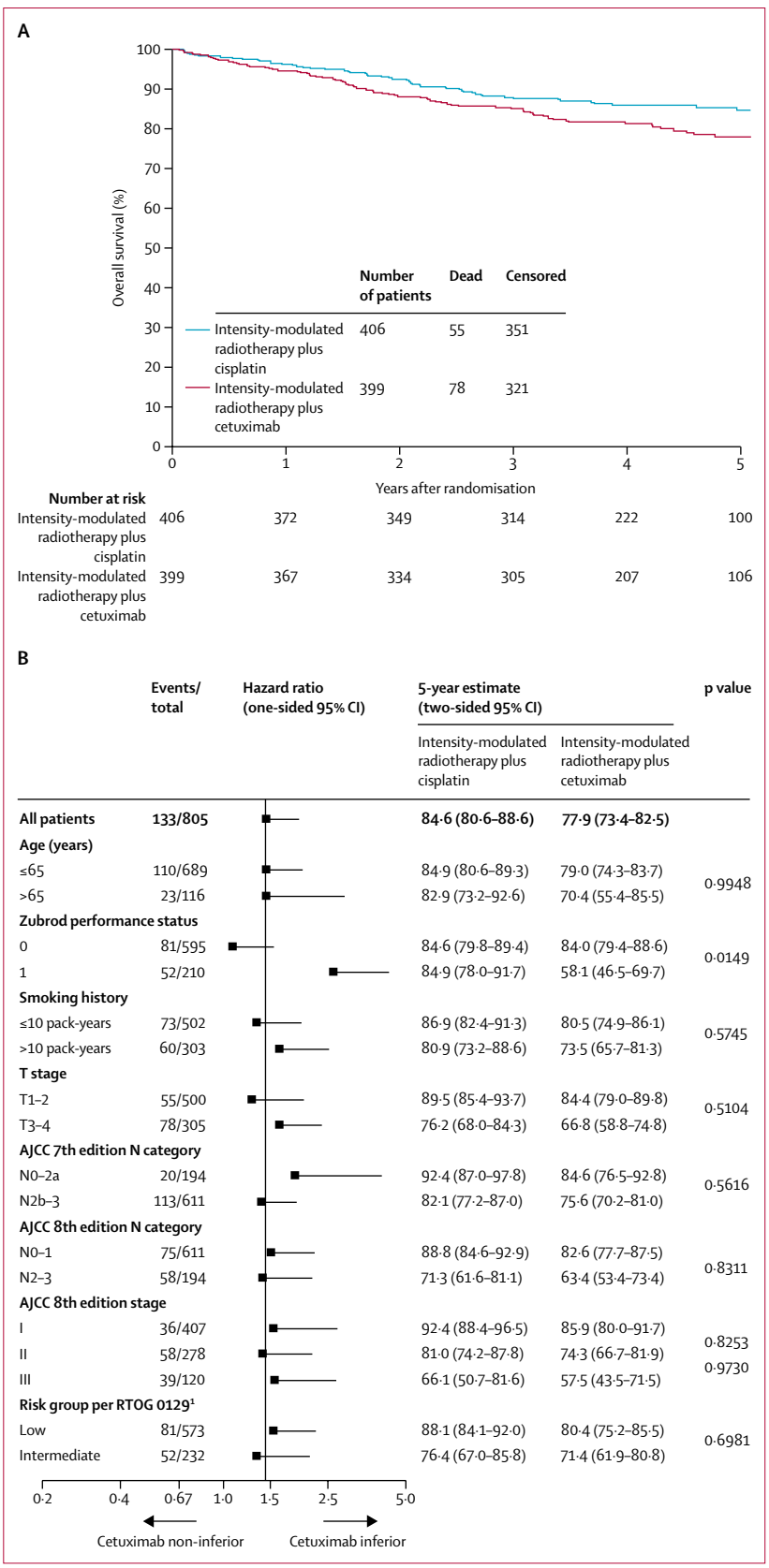


Figure 2: **Overall survival**

(A) Kaplan-Meier estimates of overall survival are shown according to assigned treatment. (B) Hazard ratios and 5-year overall survival estimates are shown for subgroups. Risk groups were as defined in RTOG 0129.[1] The reference line is at 1·45, the upper bound required for non-inferiority. p values are for the test for interaction between treatment and subgroup. AJCC=American Joint Committee on Cancer.

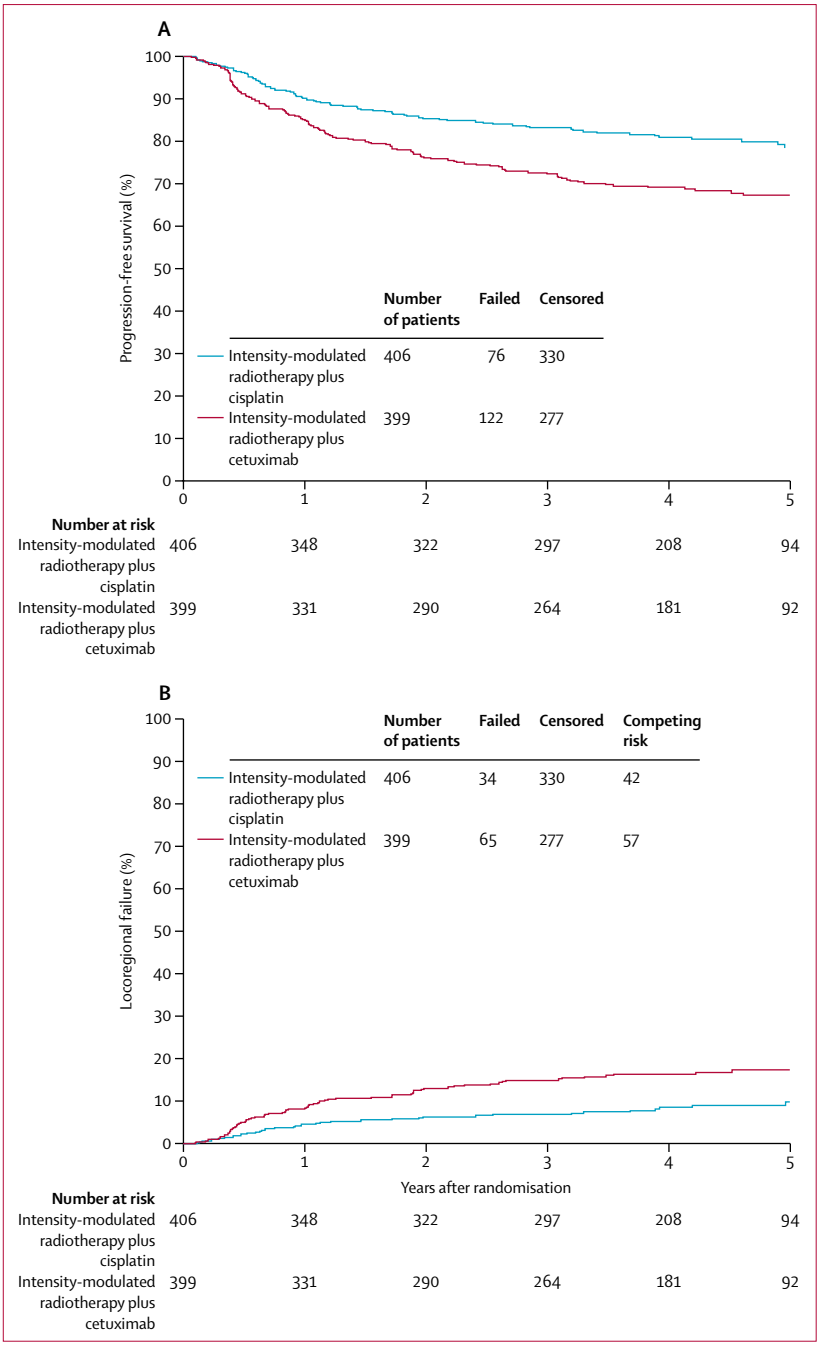


Figure 3: **Progression-free survival and locoregional failure**
(A) Kaplan-Meier estimates of progression-free survival are shown according to assigned treatment. (B) Cumulative incidence estimates of locoregional failure are shown according to assigned treatment.

methodology article[16] established that non-inferiority trials can be reliably stopped for futility if the observed HR equals or exceeds the prespecified non-inferiority margin after at least 50% of events. Additionally, our protocol futility boundary was relatively conservative (unlikely to lead to stopping except for a large deviation from non-inferiority). The observed HR would need to exceed 1·56 to satisfy the futility boundary. Although such a boundary protects against erroneous early stopping for futility, requiring an estimate above the upper boundary late in follow-up could be permitting undue risk. On the basis of these considerations, the NRG Oncology Data Monitoring Committee, which oversaw this study, recommended results could be disclosed.

All analyses were performed in SAS version 9.4. Data cutoff was May 14, 2018. This study is registered with ClinicalTrials.gov, number NCT01302834.

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. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 9, 2011, and July 31, 2014, 987 patients were enrolled in the trial, of whom 849 were randomly assigned to receive radiotherapy plus cetuximab or radiotherapy plus cisplatin (figure 1). 399 patients assigned to receive cetuximab and 406 patients assigned to receive cisplatin were subsequently eligible. Baseline characteristics of the eligible study population are shown in table 1. Patients were predominantly men and white, and had a median age of 58 years (IQR 52–63).

Cetuximab was administered per protocol in 344 (86%) of 399 patients (appendix). 339 (85%) patients in the cetuximab group received at least seven doses. The mean dose of cetuximab received was 1940·9 mg/m² (SD 520·1). In the cisplatin group, chemotherapy was given per protocol in 356 (88%) of 406 patients. Both cycles of cisplatin were given to 377 (93%) patients. The mean dose of cisplatin received was 184·7 mg/m² (SD 40·0).

Among patients for whom radiotherapy delivery was reviewed, 294 (86%) of 343 patients in the cetuximab group and 291 (83%) of 350 patients in the cisplatin group received radiotherapy per protocol or with acceptable variation. Distributions of radiotherapy dose, fraction number, and total duration in days were equivalent in both groups (appendix). At least 95% of the planned 70 Gy dose was delivered to 95% of patients in both the cetuximab and cisplatin groups.

After a median follow-up duration of 4·5 years, 133 patients died: 78 (59%) in the cetuximab group and 55 (41%) in the cisplatin group. Radiotherapy plus cetuximab did not meet the criterion for non-inferiority to radiotherapy plus cisplatin (HR 1·45, one-sided 95% upper CI 1·94; p=0·5056 for non-inferiority). Overall survival was significantly worse with cetuximab (two-sided 95% CI 1·03–2·05; log-rank p=0·0163) than with cisplatin. Estimated 5-year overall survival was 77·9% (95% CI 73·4–82·5%) in the cetuximab group and 84·6% (80·6–88·6) in the cisplatin group (figure 2). In the per-protocol subset the HR and one-sided

95% upper CI were 1·40 (2·05), and in all randomised patients the HR and one-sided 95% upper CI were 1·45 (1·91).

In a post-hoc analysis of the treatment effect, the one-sided 95% upper CI for the HR was greater than 1·45 for all demographic and clinical subgroups (figure 2). Relative to treatment with cisplatin, patients with a Zubrod performance score of 1 did significantly worse when treated with cetuximab (HR 2·66, one-sided 95% upper CI 4·32), and patients with a Zubrod performance score of 0 (HR 1·08, one-sided 95% upper CI 1·55) did not. However, after adjustment for multiple comparisons (unadjusted p=0·0149, but with nine tests this was not significant after adjusting for multiple comparisons using the Benjamini-Hochberg procedure), the test for interaction was not significant. Radiotherapy delivery indices were similar across patients stratified by treatment and Zubrod performance score (data not shown). Patients with a Zubrod performance score of 1 received a lower mean dose of cetuximab (1879 mg/m² *vs* 1961 mg/m²) than did patients with a Zubrod performance score of 0, but a slightly higher mean dose of cisplatin (192 mg/m² *vs* 182 mg/m²).

198 cancer progression events or deaths were reported—122 (62%) in the cetuximab group and 76 (38%) in the cisplatin group. Progression-free survival was significantly lower in the cetuximab group compared with the cisplatin group (HR 1·72, 95% CI 1·29–2·29; p=0·0002; 5-year progression free-survival 67·3%, 95% CI 62·4–72·2 *vs* 78·4%, 73·8–83·0; figure 3). A post-hoc analysis of the treatment effect of cetuximab versus cisplatin on progression-free survival in subgroups identified a larger difference for a Zubrod performance score of 1 (HR 2·68, 95% CI 1·62–4·42) than for a Zubrod performance score of 0 (1·43, 1·01–2·04), but after adjustment for multiple comparisons the difference was not significant (p=0·0454, but with nine tests this was not significant).

The risk of locoregional failure in the cetuximab group was more than twice that in the cisplatin group (HR 2·05, 95% CI 1·35–3·10; p=0·0005; 5-year proportions 17·3%, 95% CI 13·7–21·4 *vs* 9·9%, 6·9–13·6; figure 3). Salvage surgery was done at the primary site in 16 (4%) of 399 patients and at the regional lymph nodes in 31 (8%) of 399 patients in the cetuximab group. In the cisplatin group, salvage surgery was done at the primary site in 14 (3%) of 406 patients and at the regional lymph nodes in 26 (6%) of 406 patients.

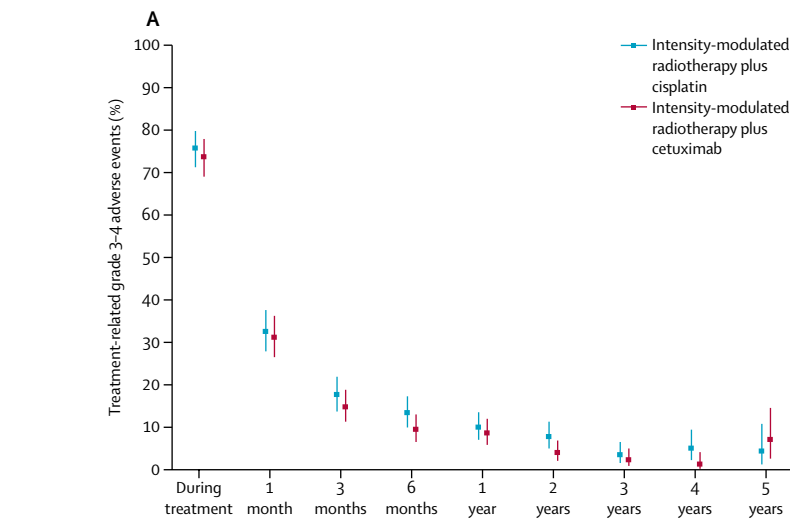
We found no significant difference in distant metastasis with cetuximab versus cisplatin (HR 1·49, 95% CI 0·94–2·36; p=0·09; 5-year proportions 11·7% *vs* 8·6%). Among those with progression-free survival failure, locoregional failure alone occurred in 47 (39%) of 122 patients in the cetuximab group and 23 (30%) of 76 patients in the cisplatin group. Corresponding numbers for distant metastases alone were 43 (35%) of 122 patients and 31 (41%) of 76 patients. Nearly all first sites of distant metastases were lung, liver, or bone (or a combination thereof) in both treatment groups. Second primary tumour occurrence was not significantly different between the treatment groups (HR 0·99, 95% CI 0·61–1·58; p=0·95).

The number of early deaths was the same in the cetuximab and cisplatin groups (6 of 394 patients in the cetuximab group; 6 of 398 in the cisplatin group; 1·5%, 95% CI 0·6–3·3; p=1·0; table 2). In the radiotherapy plus cetuximab group there were six early deaths: one grade 5 respiratory failure reported as probably related to treatment at 37 days after the end of treatment, one grade 5 cardiac arrest reported as possibly related to treatment at 1 day after the end of treatment, one grade 5 sudden death not otherwise specified reported as possibly related to treatment at 1 day after the end of

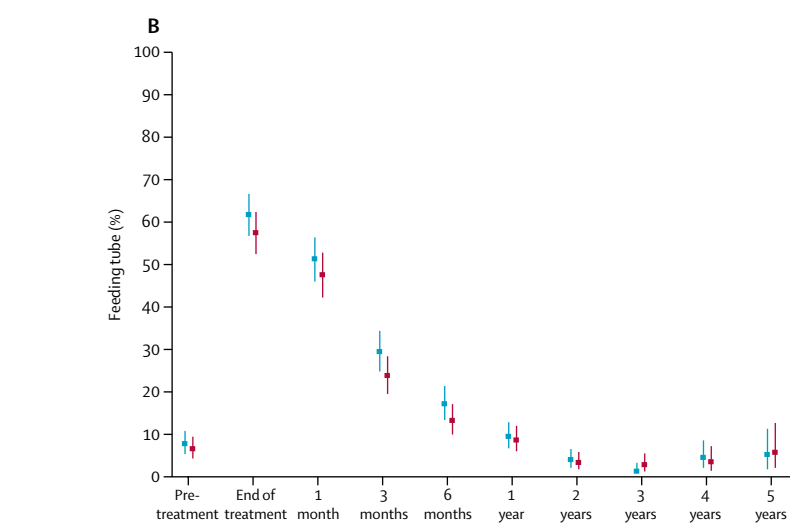
	Intensity-modulated radiotherapy plus cisplatin	Intensity-modulated radiotherapy plus cetuximab	p value
Acute period patient total	398	394	..
Early death	6 (1·5%)	6 (1·5%)	1·0000
Grade 3–4 overall	325 (81·7%)	305 (77·4%)	0·1586
Grade 3–4 anaemia	11 (2·8%)	0	0·0009*
Grade 3–4 hearing impaired	12 (3·0%)	1 (0·3%)	0·0032*
Grade 2–3 dry mouth	198 (49·7%)	211 (53·6%)	0·2872
Grade 3–4 dysphagia	149 (37·4%)	126 (32·0%)	0·1171
Grade 3–4 mucositis oral	165 (41·5%)	182 (46·2%)	0·1974
Grade 3 nausea	76 (19·1%)	32 (8·1%)	<0·0001*
Grade 3–4 vomiting	48 (12·1%)	16 (4·1%)	<0·0001*
Grade 3 fatigue	23 (5·8%)	17 (4·3%)	0·4178
Grade 3–4 dermatitis radiation	32 (8·0%)	49 (12·4%)	0·0462
Grade 3–4 lymphocyte count decreased	68 (17·1%)	69 (17·5%)	0·9252
Grade 3–4 neutrophil count decreased	61 (15·3%)	2 (0·5%)	<0·0001*
Grade 3 weight loss	31 (7·8%)	23 (5·8%)	0·3241
Grade 3–4 white blood cells decreased	48 (12·1%)	0	<0·0001*
Grade 3–4 anorexia	89 (22·4%)	61 (15·5%)	0·0144*
Grade 3–4 dehydration	61 (15·3%)	24 (6·1%)	<0·0001*
Grade 3-4 hyponatremia	21 (5·3%)	4 (1·0%)	0·0008*
Grade 3–4 acute kidney injury	13 (3·3%)	1 (0·3%)	0·0017*
Grade 3–4 pharyngeal mucositis	54 (13·6%)	40 (10·2%)	0·1535
Grade 3–4 rash acneiform	1 (0·3%)	37 (9·4%)	<0·0001*
Grade 3–4 pain (all terms)	58 (14·6%)	50 (12·7%)	0·4694
Mean raw T-score	3·19	2·35	<0·0001*
Late period patient total	383	375	..
Grade 3–4 overall	78 (20·4%)	62 (16·5%)	0·1904
Grade 3–4 hearing impaired	24 (6·3%)	8 (2·1%)	0·0060*
Grade 2–3 dry mouth	123 (32·1%)	126 (33·6%)	0·6991
Grade 3–4 dysphagia	17 (4·4%)	23 (6·1%)	0·3318
Grade 3 weight loss	17 (4·4%)	11 (2·9%)	0·3366
Grade 3–4 osteonecrosis of jaw	8 (2·1%)	3 (0·8%)	0·2234
Grade 3–4 pain (all terms)	5 (1·3%)	8 (2·1%)	0·4154
Mean raw A-score	0·38	0·27	0·1189

Data are n or n (%). *Significant after adjustment for multiple comparisons.

Table 2: **Prespecified treatment-related adverse events of interest or occurring in at least 5% of patients**



Number with adverse events/total	During treatment	1 month	3 months	6 months	1 year	2 years	3 years	4 years	5 years
Intensity-modulated radiotherapy plus cisplatin	301/398	120/369	63/359	48/361	36/360	24/311	9/261	9/179	4/92
Intensity-modulated radiotherapy plus cetuximab	290/394	113/363	54/367	33/352	30/351	12/303	6/258	2/173	6/86



Number with feeding tubes/total	Pre-treatment	End of treatment	1 month	3 months	6 months	1 year	2 years	3 years	4 years	5 years
Intensity-modulated radiotherapy plus cisplatin	30/398	243/395	185/363	106/363	62/366	34/368	12/324	3/279	8/184	5/101
Intensity-modulated radiotherapy plus cetuximab	25/394	225/393	172/364	86/365	46/354	30/356	10/317	7/269	6/181	5/90

Figure 4: **Treatment-related grade 3–4 adverse events and feeding tubes**
(A) Percentages of patients with treatment-related grade 3–4 adverse events according to assigned treatment. Error bars are 95% CIs. Timepoints 1 month and later are relative to the end of treatment. The following windows around each timepoint were used: 1 month, −2 to +4 weeks; 3 months, −4 to +6 weeks; 6 months, −6 to +8 weeks; and 1 year and later, ±3 months. (B) Percentages of patients with a feeding tube are shown according to assigned treatment. Error bars are 95% CIs. Timepoints 1 month and later are relative to the end of treatment. The following windows around each timepoint were used: 1 month, −2 to +4 weeks; 3 months, −4 to +6 weeks; 6 months, −6 to +8 weeks; and 1 year and later, ±3 months.

treatment, one grade 5 myocardial infarction reported as possibly related to treatment at 4 days after the end of treatment, one grade 5 death not otherwise specified reported as possibly related to treatment at 17 days after the end of treatment, and one grade 5 sudden death not otherwise specified reported as unrelated to treatment at 12 days after the end of treatment. In the radiotherapy plus cisplatin group there were six early deaths: one grade 5 cardiac arrest reported as possibly related to treatment 1 day after the end of treatment, one grade 5 sepsis reported as possibly related to treatment 4 days after the end of treatment, one grade 5 sudden death not otherwise specified reported as possibly related to treatment at 18 days after the end of treatment, two grade 5 sudden deaths not otherwise specified reported as unrelated to treatment at 2 days after the end of treatment, and one grade 5 sudden death not otherwise specified reported as unrelated to treatment at 7 days after the end of treatment. We recorded numbers of moderate to severe (Common Terminology Criteria for Adverse Events, version 4, grade 3–4) treatment-related acute and late adverse events (table 2, appendix). The proportion of one or more grade 3–4 acute adverse events was similar in the cetuximab and cisplatin groups (305 of 394 patients, 77·4%, 95% CI 73·0–81·5 *vs* 325 of 398 patients, 81·7%, 77·5–85·3; p=0·16). Acneiform rash was significantly more frequent in the cetuximab group, whereas myelosuppression, anaemia, nausea, vomiting, anorexia, dehydration, hyponatraemia, kidney injury, and hearing impairment were significantly more frequent in the cisplatin group.

An alternative measure of the overall acute toxicity burden for patients is provided by the T-score—the mean number of grade 3–4 acute adverse events per patient.[13] Patients in the cetuximab group had a significantly lower T-score than did those in the cisplatin group (raw T-score 2·35 *vs* 3·19; p<0·0001), corresponding to a 40% lower acute toxicity burden.

With regard to late toxicity in the cetuximab versus cisplatin groups, neither overall number of one or more grade 3–4 adverse events (62 of 375 patients, 16·5%, 95% CI 12·9–20·7 *vs* 78 of 383 patients, 20·4%, 16·4–24·8, p=0·1904; table 2) or mean number of grade 3–4 adverse events (raw A-score 0·27 *vs* 0·38; p=0·1189) were significantly different. Hearing impairment was significantly more common after treatment with cisplatin.

There were no notable differences between groups for treatment-related grade 3–4 adverse events over time (figure 4). At 1 year after treatment, 30 (8·5%, 95% CI 5·8–12·0) of 351 patients in the cetuximab group and 36 (10·0%, 7·1–13·6) of 360 patients in the cisplatin group had grade 3–4 adverse events.

At treatment completion, 225 (57·3%, 95% CI 52·2–62·2) of 393 patients in the cetuximab group and 243 (61·5%, 56·5–66·3) of 395 patients in the cisplatin group had a feeding tube (figure 4). These proportions dropped to 30 (8·4%, 5·8–11·8) of 356 patients in the

cetuximab group and 34 (9·2%, 6·5–12·7) of 368 patients in the cisplatin group at 1 year after treatment (p=0·79).

EORTC QLQ-H&N35 completion patterns, completion numbers, and reasons missing were similar between the groups. Patient-reported severity of swallowing problems increased in both the cetuximab and cisplatin groups from pretreatment to end of treatment, but no difference was observed between groups in change scores from baseline (mean 47·4 *vs* 48·0; p=0·86; appendix). At 1 year, the cetuximab group had a statistically significant increase in symptoms from pretreatment compared with the cisplatin group (7·6 *vs* 2·5; p=0·0382), but this difference was below the estimated clinically important difference.[17]

Before treatment, 294 (75%) of 394 patients in the cetuximab group had normal or mild changes or good dental health, and the mean number of native teeth in place was 21·4 compared with 283 (71%) of 398 patients with normal or mild changes or good dental health in the cisplatin group, with mean 20·9 native teeth in place (appendix). At 1 year after treatment, these rates were 223 (84%) of 267 patients in the cetuximab group, with mean 1·64 teeth lost, and 233 (87%) of 267 patients in the cisplatin group, with mean number of teeth lost 1·05.

Discussion

Radiotherapy plus cetuximab treatment led to inferior overall survival when compared with radiotherapy plus cisplatin treatment for patients with locoregionally advanced HPV-positive oropharyngeal carcinoma. The risks of cancer progression or death and locoregional failure were also greater with cetuximab. Profiles of moderate to severe acute and late toxicities were different for patients treated with cetuximab versus cisplatin, but proportions of one or more such events were similar. Nonetheless, the overall burden of acute toxicity was greater for patients treated with cisplatin than with cetuximab, as reflected by T-scores.

To our knowledge, RTOG 1016 is the first randomised trial to investigate toxicity amelioration or treatment de-intensification for patients with HPV-positive oropharyngeal carcinoma. We chose accelerated radiotherapy plus cisplatin as the control group to align with the investigational and control groups of RTOG 0129[1] and RTOG 0522,[12] as these trials provided comprehensive data on survival outcomes for HPV-positive oropharyngeal cancer. Additionally, RTOG 0129[1] showed that accelerated fractionated radiotherapy over 6 weeks with two cycles of cisplatin yielded similar outcomes to conventionally fractionated radiotherapy over 7 weeks with three cycles of cisplatin, with better chemotherapy compliance. The study design was based on data from the IMC9815 trial,[7,18] which reported that addition of cetuximab to radiotherapy improved survival without increased detriment to quality of life. Moreover, subgroup analysis suggested a greater survival benefit from cetuximab in subgroups with characteristics common to patients with HPV-positive tumours (eg, oropharyngeal subsite, age <65 years, and Zubrod performance status 0).[7] Subsequent retrospective biomarker analysis of the IMC9815 trial[8] suggested that survival benefit was greater from cetuximab for HPV-positive oropharyngeal carcinoma than for HPV-negative oropharyngeal carcinoma, although the interaction was not statistically significant. Despite these promising data, RTOG 1016 showed that cetuximab is less effective than cisplatin and should not be used alone as a de-intensification strategy for patients with HPV-positive oropharyngeal carcinoma.

Our findings are consistent with retrospective studies that reported reduced cancer control with cetuximab versus cisplatin in patients with HPV-positive and HPV-negative head and neck squamous cell carcinoma.[19–21] Although non-randomised studies are subject to selection bias and confounders (such as performance status and comorbidity), two randomised phase 2 trials also observed reduced locoregional control with radiotherapy plus anti-EGFR antibodies (either cetuximab or panitumumab) versus radiotherapy plus cisplatin.[22,23] However, these trials were not adequately powered to evaluate overall survival or non-inferiority in either HPV-positive or HPV-negative groups. The conclusions from our prospective, non-inferiority trial contradict those of a recent, retrospective meta-analysis of subgroups in clinical trials,[24] which concluded cetuximab was not inferior to cisplatin for HPV-positive oropharyngeal carcinoma, cautioning against use of such analyses for clinical decision making. A randomised trial[25] that showed similar progression-free survival, toxicity, and quality of life outcomes for addition of either panitumumab or cisplatin to radiation was not powered for non-inferiority.[25] Most of these studies reported reduced locoregional control with cetuximab, supporting our finding that cisplatin is a more potent radiation sensitiser.

HPV-negative head and neck squamous cell carcinoma is genetically distinct from HPV-positive oropharyngeal carcinoma. *EGFR* amplification, overexpression, and downstream signalling are more frequent in HPV-negative head and neck squamous cell carcinoma, whereas mutations downstream of *EGFR* (ie, activating in *PIK3CA*, inactivating in *PTEN*) that might mediate resistance to *EGFR*-targeted therapies are more frequent in HPV-positive oropharyngeal carcinoma.[26] Retrospective analyses of clinical trials investigating the addition of anti-*EGFR* antibodies to chemotherapy for recurrent metastatic head and neck squamous cell carcinoma have observed greater benefit in patients with HPV-negative cancer,[27] albeit inconsistently.[28] Given that the effect of cetuximab on these two cancers can differ, it might not be appropriate to extrapolate the results of RTOG 1016 to HPV-negative head and neck squamous cell carcinoma.

We considered p16 expression a sufficient surrogate marker for tumour E6/E7 mRNA expression in this trial because we were comparing two standard of

care regimens and neither represented true treatment de-intensification. We estimate that, at most, 7% of patients enrolled in the trial might have had HPV-negative cancer.[10] However, randomisation would be expected to balance the distribution in the two groups. A strong interaction between tumour HPV status and treatment assignment would be necessary to affect the inferences drawn from this trial.

In an analysis of RTOG 0129,[1] tumour HPV status, tobacco exposure, and tumour and nodal categories were used to assign patients with oropharyngeal carcinoma treated with radiotherapy plus cisplatin into subgroups at low, intermediate, and high risk of death (3-year overall survival 93% *vs* 71% *vs* 46%). HPV-positive patients are low risk unless tobacco pack-years exceed 10 and there are multiple nodes or a node larger than 6 cm in diameter, in which case they are intermediate risk. These data, together with results of the IMC9815 trial, have led to the common clinical practice of substitution of cetuximab for cisplatin in patients from the low-risk group, with worse performance status, or older age in the USA. Although not powered for subgroup analysis, our study suggests that this practice might compromise patient outcomes for those who can receive cisplatin. For platinum-ineligible cases, radiotherapy plus carboplatin and fluorouracil with[29] or without[30] cetuximab or cetuximab alone could be considered, on the basis of improvements in survival versus radiotherapy alone in clinical trials not exclusive to either HPV-positive oropharyngeal carcinoma or platinum-ineligible populations. Enrolment in current trials of radiotherapy plus immunotherapy in this patient population should be strongly encouraged where possible. We found that patients with a Zubrod performance score of 1 had the poorest outcomes with cetuximab, a finding that could not be explained by non-compliance with per-protocol therapy.

RTOG 1016 included all patients with locoregionally-advanced HPV-positive oropharyngeal carcinoma, whereas most de-intensification trials are generally limited to the low-risk group. Phase 2 de-intensification strategies show promising preliminary results for overall survival and progression-free survival with induction chemotherapy followed by reduced radiotherapy dose or volume in responders[31,32] or cisplatin and radiotherapy dose reduction.[33] Cetuximab led to worse outcomes in both low-risk and intermediate-risk groups in RTOG 1016, underscoring the importance of testing de-intensification strategies in non-inferiority trials with a control group of 70 Gy radiotherapy plus high-dose cisplatin. 5-year survival in RTOG 1016 was higher than in the radiotherapy plus cisplatin control groups of RTOG 0129[1] and 0522,[12] showing the importance of a contemporaneous control group.

Our analysis was on the modified intention-to-treat population. 5% of randomised patients were retrospectively declared ineligible and excluded from analysis. However, this is often noted in cooperative group trials and has been accounted for by over-enrolment to ensure achievement of the required sample size. Moreover, sensitivity analyses that were done for the primary endpoint in the per-protocol subset and all randomised patients showed similar HRs to the modified intention-to-treat population, confirming the robustness of the survival outcomes.

In summary, radiotherapy plus cetuximab did not meet the criterion for non-inferiority for overall survival relative to radiotherapy plus cisplatin. In this randomised trial exclusive to patients with HPV-positive oropharyngeal carcinoma with a primary endpoint of overall survival, we established radiotherapy plus cisplatin as the standard of care. Strategies to improve 5-year progression-free survival achieved with radiotherapy plus cisplatin, while reducing toxicity, are needed for HPV-positive oropharyngeal carcinoma. This might include the addition to or replacement of cetuximab or cisplatin with immunotherapy with checkpoint inhibitors.

Contributors

MLG and AMT did the literature search. MLG, AMT, JH, AE, PMH, DJA, EMS, BB, JAR, JR, JG, JJD, and QTL designed the study. MLG, AMT, JH, AE, PMH, DJA, EMS, BB, JAR, JR, JG, MY, SAK, DMB, MAR, ADC, JJB, CUJ, NED, SAS, SS, TJG, JP, and QTL collected and interpreted the data. MLG, AMT, JH, JJD, and QTL analysed the data and wrote the manuscript.

Declaration of interests

JJB reports grants from NRG during the conduct of the study. ADC reports consulting or advisory fees from Cota, Keyquest Health, Loxo Oncology, Atara Biotherapeutics, Aduro Biotech, and Pfizer, and clinical trial support from Threshold Pharmaceuticals, AstraZeneca, Innate Pharma, Bristol-Myers Squibb, CellSight Technologies, and Tessa Therapeutics. JJD reports compensated work on data monitoring committees from Merck & Co. MLG reports grants from The Oral Cancer Foundation and from the National Cancer Institute during the conduct of the study; personal consulting fees from Bristol-Myers Squibb, TRM Oncology, Genocea Biosciences, EMD Serono, Merck & Co, Eli Lilly, AstraZeneca, NewLink Genetics Corporation, Aspyrian, Celgene Corporation, Amgen, and Roche, all outside the submitted work; and received a Damon-Runyon Clinical Investigator Award from 2000–05, which was supported by a grant from Eli Lilly. SAK reports grants from Merck & Co. JP reports an advisory board honorarium from Accuray. All other authors declare no competing interests.

Data sharing

No additional data are available for this Article. Within 6 months of publication, the data from this article will be available for data sharing proposals at the National Cancer Institute NCTN/NCORP data archive: https://nctn-data-archive.nci.nih.gov/.

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