

Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial



Hisham Mehanna, Max Robinson, Andrew Hartley, Anthony Kong, Bernadette Foran, Tessa Fulton-Lieuw, Matthew Dalby, Pankaj Mistry, Mehmet Sen, Lorcan O'Toole, Hoda Al Booz, Karen Dyker, Rafael Moleron, Stephen Whitaker, Sinead Brennan, Audrey Cook, Matthew Griffin, Eleanor Aynsley, Martin Rolles, Emma De Winton, Andrew Chan, Devraj Srinivasan, Ioanna Nixon, Joanne Grumett, C René Leemans, Jan Buter, Julia Henderson, Kevin Harrington, Christopher McConkey, Alastair Gray, Janet Dunn, on behalf of the De-ESCALaTE HPV Trial Group*



Summary

Background The incidence of human papillomavirus (HPV)-positive oropharyngeal cancer, a disease affecting younger patients, is rapidly increasing. Cetuximab, an epidermal growth factor receptor inhibitor, has been proposed for treatment de-escalation in this setting to reduce the toxicity of standard cisplatin treatment, but no randomised evidence exists for the efficacy of this strategy.

Methods We did an open-label randomised controlled phase 3 trial at 32 head and neck treatment centres in Ireland, the Netherlands, and the UK, in patients aged 18 years or older with HPV-positive low-risk oropharyngeal cancer (non-smokers or lifetime smokers with a smoking history of <10 pack-years). Eligible patients were randomly assigned (1:1) to receive, in addition to radiotherapy (70 Gy in 35 fractions), either intravenous cisplatin (100 mg/m² on days 1, 22, and 43 of radiotherapy) or intravenous cetuximab (400 mg/m² loading dose followed by seven weekly infusions of 250 mg/m²). The primary outcome was overall severe (grade 3–5) toxicity events at 24 months from the end of treatment. The primary outcome was assessed by intention-to-treat and per-protocol analyses. This trial is registered with the ISRCTN registry, number ISRCTN33522080.

Findings Between Nov 12, 2012, and Oct 1, 2016, 334 patients were recruited (166 in the cisplatin group and 168 in the cetuximab group). Overall (acute and late) severe (grade 3–5) toxicity did not differ significantly between treatment groups at 24 months (mean number of events per patient 4·8 [95% CI 4·2–5·4] with cisplatin vs 4·8 [4·2–5·4] with cetuximab; $p=0\cdot98$). At 24 months, overall all-grade toxicity did not differ significantly either (mean number of events per patient 29·2 [95% CI 27·3–31·0] with cisplatin vs 30·1 [28·3–31·9] with cetuximab; $p=0\cdot49$). However, there was a significant difference between cisplatin and cetuximab in 2-year overall survival (97·5% vs 89·4%, hazard ratio 5·0 [95% CI 1·7–14·7]; $p=0\cdot001$) and 2-year recurrence (6·0% vs 16·1%, 3·4 [1·6–7·2]; $p=0\cdot0007$).

Interpretation Compared with the standard cisplatin regimen, cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in terms of tumour control. Cisplatin and radiotherapy should be used as the standard of care for HPV-positive low-risk patients who are able to tolerate cisplatin.

Funding Cancer Research UK.

Copyright © 2018 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

The incidence of oropharyngeal squamous cell carcinoma is increasing rapidly in high-income countries,^{1,2} reaching epidemic proportions in some estimates.³ This increase has been attributed to a rise in human papillomavirus (HPV) infection. HPV-positive oropharyngeal squamous cell carcinoma is considered to be a distinct disease entity from HPV-negative head and neck cancer. The disease affects younger adults and treatment can be successful.⁴ HPV status, tumour nodal stage, and smoking history define three groups with distinct survival outcomes: low risk (HPV-positive, <10 pack-years; 3-year overall survival 93%), intermediate risk (HPV-positive,

>10 pack-years; 3-year overall survival 71%) and high risk (HPV-negative; 3-year overall survival 48%).⁴

Cisplatin-based chemoradiotherapy and cetuximab bioradiotherapy are both approved by the US Food and Drug Administration for treatment of head and neck cancer, with cisplatin being standard of care for advanced oropharyngeal squamous cell carcinoma in most countries. However, concurrent cisplatin therapy is associated with substantial increases in acute, sometimes life-threatening, toxicity,^{5–7} compared with radiotherapy alone. The treatment also increases long-term sequelae,^{5,7,8} including xerostomia and dysphagia. Consequently, young patients with HPV-positive

Lancet 2019; 393: 51–60

Published Online
November 15, 2018
[http://dx.doi.org/10.1016/S0140-6736\(18\)32752-1](http://dx.doi.org/10.1016/S0140-6736(18)32752-1)

See [Comment](#) page 5

*Members of the De-ESCALaTE HPV Trial Group are listed in the appendix

Institute for Head and Neck Studies and Education (InHANSE), University of Birmingham, Birmingham, UK (Prof H Mehanna PhD, A Kong PhD, T Fulton-Lieuw MSc); Newcastle University, Newcastle, UK (M Robinson PhD); University Hospitals Birmingham, Birmingham, UK (A Hartley FRCR); Weston Park Hospital, Sheffield, UK (B Foran FRCR); University of Warwick, Coventry, UK (M Dalby MA, P Mistry MSc, J Grumett BSc, C McConkey MSc, Prof J Dunn PhD); St James's Institute of Oncology, Leeds, UK (Prof M Sen FRCR); Queen's Centre for Oncology, Castle Hill Hospital, Cottingham, UK (L O'Toole FRCR); Bristol Haematology and Oncology Centre, Bristol, UK (H Al Booz FRCR); St James' University Hospital, Leeds, UK (K Dyker FRCR); Aberdeen Royal Infirmary, Aberdeen, UK (R Moleron MBBS); Royal Surrey County Hospital, Surrey, UK (S Whitaker FRCR); St Luke's Hospital, Cancer Trials Ireland, and St Luke's Institute of Cancer Research, Dublin, Ireland (S Brennan FFR RCSI); Cheltenham General Hospital, Cheltenham, UK (A Cook FRCR); Nottingham University Hospitals NHS Trust, Nottingham, UK (M Griffin FRCR); James Cook University Hospital, Middlesbrough, UK (E Aynsley FRCR); Abertawe Bro Morgannwg University Health

Board, Port Talbot, UK (M Rolles FRCR); Royal United Hospitals Bath NHS Foundation Trust, Bath, UK (E De Winton FRCR); University Hospital Coventry and Warwickshire NHS Trust, Coventry, UK (A Chan FRCR); Western General Hospital, Edinburgh, UK (D Srinivasan FRCR); Beatson West of Scotland Cancer Centre, Glasgow, UK (I Nixon FRCR); VU University Medical Centre, Amsterdam, Netherlands (Prof C R Leemans PhD, Prof Jan Buter PhD); National RTTQA Group, Royal Marsden Hospital, London, UK (J Henderson MSc); Institute of Cancer Research and Royal Marsden Hospital, London UK (Prof K Harrington PhD); and University of Oxford, Oxford, UK (Prof A Gray PhD)

Correspondence to: Prof Hisham Mehanna, Institute of Head and Neck Studies and Education (InHANSE), University of Birmingham, Birmingham B15 2TT, UK h.mehanna@bham.ac.uk
See Online for appendix

For the study protocol see <https://www.inhanse.org/patient-research/de-escalate/>

Research in context

Evidence before this study

Standard treatment for human papillomavirus (HPV)-positive oropharyngeal cancer (cisplatin-based chemoradiotherapy) results in considerable acute and long-term toxicity. Wide consensus exists about the need for de-escalation treatments with decreased toxicity and similar survival. Cetuximab, an epidermal growth factor receptor inhibitor approved by the US Food and Drug Administration, is thought to result in reduced toxicity and thus might represent an ideal form of de-escalation in this setting. Meta-analyses of existing small, mainly retrospective studies reported poorer outcomes with cetuximab than with cisplatin for head and neck cancers overall, but a possible benefit in HPV-positive oropharyngeal cancer.

oropharyngeal squamous cell carcinoma might endure substantial, life-changing side-effects of treatment, that could affect their quality of life, for several decades.

There is global consensus about the need for treatment de-escalation (reduction of toxicity while preserving anti-tumour efficacy) for these patients.⁹ One such strategy seeks to substitute cetuximab for cisplatin as the radiosensitiser. Radiotherapy can induce epidermal growth factor receptor (EGFR) expression in head and neck cancers, resulting in acquired resistance.¹⁰ Cetuximab, a targeted EGFR inhibitor, might help overcome this resistance and might also induce antibody-dependent cell-mediated cytotoxicity. In a randomised trial,¹¹ bioradiotherapy with cetuximab was shown to significantly improve overall survival compared with radiotherapy alone (median 49.0 months vs 29.3 months; hazard ratio [HR] 0.74; $p=0.03$) in patients with head and neck cancer, and, in an updated analysis,¹² in patients with HPV-positive oropharyngeal squamous cell carcinoma (HR 0.16 [95% CI 0.07–0.36]). Since toxicity rates (except for rash) were broadly similar between the two groups, cetuximab could potentially represent a less toxic alternative to cisplatin in this setting.

Conversely, an inverse association between HPV positivity and EGFR status has been reported.¹³ Therefore, EGFR inhibition might not be as effective as chemotherapy in HPV-positive oropharyngeal squamous cell carcinoma. Studies have reported conflicting results in this regard^{14,15} and, as yet, no randomised comparisons have been done in HPV-positive patients. The De-ESCALaTE trial aimed to compare the toxicity, survival, and time-to-recurrence outcomes of cetuximab versus cisplatin in patients with low-risk, HPV-positive oropharyngeal squamous cell carcinoma receiving radiotherapy in the curative setting. As these treatments might have different effects on quality of life, especially swallowing, relevant patient-reported outcomes were also measured between the two groups.

Added value of this study

Results of our open-label randomised controlled phase 3 trial show that, in patients with low-risk HPV-positive oropharyngeal cancer, not only did cetuximab result in similar rates of severe and all-grade toxicity to cisplatin but it importantly resulted in poorer overall survival and higher rates of locoregional recurrence and distant metastases than did standard cisplatin therapy.

Implications of all the available evidence

Concomitant cisplatin and radiotherapy should remain the standard of care for patients with low-risk HPV-positive oropharyngeal cancer. Our findings also suggest caution with de-escalation strategies and highlight the importance of phase 3 trial data before changing clinical practice.

Methods

Study design

This open-label randomised controlled phase 3 trial was done at 32 head and neck treatment centres in Ireland (n=1), the Netherlands (n=1), and the UK (n=30).

The first and last authors and the Trial Management Group designed the study, which was coordinated by Warwick Clinical Trials Unit. Sample collection and coordination was done by the University of Birmingham, UK, and p16 immunohistochemistry was done at Newcastle University, UK. The authors vouch for the accuracy and completeness of the data and analysis, and for adherence to the study protocol. All authors contributed to the writing of the manuscript. The study protocol is available online.

All treating hospitals were approved as head and neck treatment centres by their country's health authorities. All centres and oncologists completed the trial's central radiotherapy quality assurance accreditation (see appendix for more information).

Patients

Eligible patients were recruited by their treating clinicians. Patients had to be aged at least 18 years with a histologically confirmed diagnosis of advanced oropharyngeal squamous cell carcinoma (American Joint Committee on Cancer/International Union for Cancer Control [AJCC/UICC] tumour, node, and metastasis [TNM] 7th Edition manual: T3N0–T4N0, and T1N1–T4N3) that was classified as low risk as per the Ang classification:⁴ that is, the tumour sample had to be positive on p16 immunohistochemistry, and the patient had to be a non-smoker or have a lifetime self-reported smoking history of less than 10 pack-years. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and adequate renal, haematological, and hepatic function for cisplatin-based curative chemoradiotherapy.

Formalin-fixed, paraffin-embedded tumour samples were histologically confirmed to be squamous cell

carcinoma and tested in two quality-assured, central laboratories for p16 by immunohistochemistry, by use of proprietary reagents (CINtec Histology kit; Roche mtm labsAG; Basel, Switzerland). p16 was scored positive if 70% or more of malignant cells showed strong and diffuse nuclear and cytoplasmic staining.¹⁶ High-risk HPV DNA in-situ hybridisation was done with proprietary reagents (INFORM-HPV-III Family 16 Probe-B, Ventana Medical Systems Inc, Tuscon, USA). The probe cocktail detects HPV genotypes 16, 18, 31, 33, 35, 45, 52, 56, 58, and 66, and is visualised as a blue reaction product in malignant cells.¹⁷ Patients reported smoking history and alcohol consumption by self-completed questionnaires, and their comorbidities were graded by the recruiting clinician. Patients were excluded if they had T1–T2N0 disease or were classified as HPV-negative, high-risk, or HPV-positive oropharyngeal squamous cell carcinoma intermediate-risk on the Ang classification. The study was approved by the Coventry and Warwickshire Research Ethics Committee. Patients were recruited by their treating clinicians and all patients provided written informed consent.

Randomisation and masking

Eligible patients underwent computer-generated central randomisation. Patients were randomly assigned in a 1:1 ratio to receive cisplatin-based chemoradiotherapy or cetuximab bioradiotherapy. Trial-group assignments were balanced by use of a bespoke minimisation algorithm according to centre, tumour stage (TNM7: T1–T2 vs T3–T4), nodal stage (N0–1 vs N2–3), radiotherapy site (unilateral; bilateral), and planned gastrostomy insertion before treatment.

Procedures

Eligible patients were randomly assigned to undergo intensity-modulated radiotherapy with either three doses of intravenous cisplatin 100 mg/m² on days 1, 22, and 43 of radiotherapy or intravenous cetuximab 400 mg/m² loading dose 1 week before followed by seven weekly infusions of 250 mg/m² during radiotherapy. Patients were assessed for treatment response 12 weeks after radiotherapy completion by clinical examination and by CT, MRI, or PET-CT scan. Follow-up consisted of clinical examination, monthly in the first year and every 2 months in the second year, for at least 24 months after treatment completion.

Outcomes

The primary outcome was overall (acute and late) severe toxicity (grades 3–5). Treatment toxicity was assessed with the Common Toxicity Criteria Adverse Events (CTCAE), version 4, for a period of 24 months from the end of treatment. Secondary outcomes were overall survival, time to recurrence, quality of life, swallowing, and acute and late severe toxicities reported separately; suspected recurrences were assessed by imaging and

biopsy. Patients completed the paper-based European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 general (EORTC QLQ-C30, version 3) questionnaire and the EORTC QLQ-H&N35 questionnaire specific to head and neck cancers,¹⁸ and the M.D. Anderson Dysphagia Inventory¹⁹ at baseline before treatment, at radiotherapy completion, and then at 3, 6, 12, and 24 months after treatment.

Statistical analysis

A target sample size of 304 patients (152 in each group) was calculated to enable detection of reductions greater than 25% in the overall number of severe (grade 3–5) acute and late toxicities with a two-sided test at the 5% level of significance, allowing for 10% dropout with greater than 90% power, assuming an average of 2.5 overall severe events per patient.

Recruitment of 304 patients was also estimated to allow detection of a 50% reduction in late severe toxicities with at least 90% power and a 25% or greater reduction in acute severe toxicities with 85% power. An additional 30 patients were recruited to allow for withdrawals and any higher risk (T4,N3) patients recruited. The interim analysis was done after the first 200 patients were recruited. More details are provided in the appendix.

An intention-to-treat analysis was done for all outcomes, and a per-protocol analysis was done for primary outcomes and secondary outcomes of toxicity and survival. All patients allocated to treatment groups were included in the intention-to-treat analysis, even if they did not receive the treatment. Patients who withdrew or who had major protocol violations as assessed by the independent trial monitoring team were excluded from the per-protocol analyses. All analyses were unblinded.

Mean numbers per patient of toxicity events (short-term [acute] toxicity and adverse long-term [late] effects, based on the TAME method of reporting toxicities⁶) were compared by *t* tests. Proportions of patients affected by one or more toxicity event were compared by Pearson's χ^2 test. A severe toxic event was defined as a toxicity assessed as grade 3–5 by CTCAE, version 4. The type of event was characterised by the CTCAE, version 4, System Organ Class and Term. Toxicities were classified as acute if they first appeared during or up to 3 months after treatment, and were classified as late if they persisted, or first appeared, more than 3 months up to 24 months after treatment. Multiple occurrences of events of a single toxicity type within an analysis time period are counted as a single event. Events that were present both within 90 days after treatment and remained after that period were counted as acute events and also as late events but were not counted twice when analysing the overall number of acute and late events. Toxicities reported as part of a serious adverse event notification but that were not reported as a toxicity event were added to the counts of toxicity events.

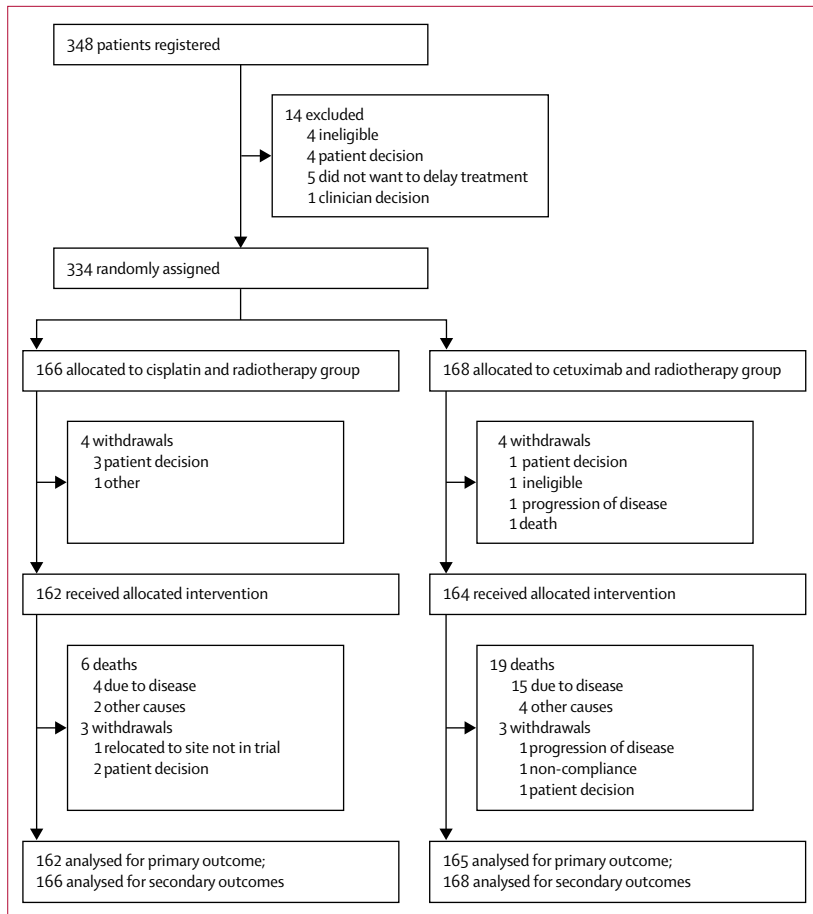


Figure 1: Trial profile

Overall survival and time to recurrence were measured from the date of randomisation and compared by the log-rank test with all-cause mortality in the intention-to-treat population.

Deaths were classified as being due to head and neck cancer or to other causes. Recurrences could be loco-regional or distant, or both. Patients who died from head and neck cancer causes as the first event were classed as recurrences. New primaries and persistent nodal disease (detected within 90 days from randomisation) were not included in the analysis of time to recurrence. Patients on follow-up and patients lost to follow-up were censored at the last date at which they were known to be alive. 95% CIs were generated with a univariate Cox proportional hazards model. The proportional assumption was tested by plotting the observed Kaplan-Meier values against the Cox predicted values. The effect of randomised treatment on outcome was also assessed after adjusting for known prognostic factors with a multivariate Cox proportional hazards model. Two post-hoc subgroup sensitivity analyses examined the association with overall survival of the very low-risk group with TNM-8 stage I and II disease, and those who were doubly positive for p16 and HPV-DNA in-situ hybridisation.

Standard scoring methods were applied to quality-of-life questionnaires.¹⁸ Missing quality-of-life scores were not imputed. All scores were normalised, ranging from 0 to 100, and transformed to unweighted summated scales in which higher scores indicated better health. Global quality of life was assessed with the EORTC QLQ C30 global measure. Separate comparisons were made at each timepoint. Unadjusted p values were used. On the EORTC questionnaires and the M.D. Anderson Dysphagia Inventory, a 10-point difference in scores was considered to be clinically relevant.^{19,20} Analyses were done with Stata, version 15.1.

This trial is registered with the ISRCTN registry, number ISRCTN33522080.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 12, 2012, and Oct 1, 2016, 334 patients were recruited (166 in the cisplatin group and 168 in the cetuximab group). There were seven withdrawals from the treatment protocol before treatment started and six after starting treatment (figure 1; appendix). All patients allocated to treatment groups were included in the intention-to-treat analyses, and 159 patients in the cisplatin group and 162 in the cetuximab group were included in the per-protocol analyses. There was no crossover between groups.

We observed no notable imbalances in baseline characteristics (age, tumour site, tumour stage, smoking history, performance status, and comorbidities) between the two groups (table 1; appendix). The mean age was 57 years. 80% of patients were men, 65% had T1–T2 disease (TNM 7), 76% had N2–N3 disease (TNM 7), and 46% were either current or past smokers, with a median lifetime smoking history of 8 pack-years (table 1). Of the 324 (97%) patients tested for HPV-DNA on in-situ hybridisation, 304 (94%) were positive, 20 were negative, and ten were unknown. At the 3-month post-treatment assessment, 165 (51%) patients were assessed with PET-CT and 162 (49%) by MRI, with equal distribution among the groups.

The median duration from randomisation to start of radiotherapy was 14 days (IQR 11–17) and did not differ between groups. Only eight (5%) patients in the cisplatin group and four (3%) in the cetuximab group received a dose of less than 70 Gy ($p=0.256$; appendix), all patients received a dose of 65 Gy or more, and 332 (99%) received intensity-modulated radiation therapy. Radiotherapy interruptions or modifications occurred in 12 (9%) patients receiving cisplatin and 14 (7%) receiving cetuximab.

In the cisplatin group, 62 (38%) patients received all three cycles of cisplatin, 83 (51%) received two cycles, and

16 (10%) received one cycle. Of those who received one or two cycles, nine received one or two doses of carboplatin instead (appendix). One patient did not receive any chemotherapy because of sepsis. The median total cisplatin dose received was 200 mg/m² (IQR 200–300) and 26 (16%) received less than 200 mg/m² in total. The main reasons for discontinuation or reduction in cisplatin dose were myelosuppression, oral or gastrointestinal toxicity, or nausea and vomiting.

In the cetuximab group, 130 (79%) patients received all eight cycles of cetuximab; 23 (14%) received seven cycles, mainly omitting the final dose (appendix). The median total cetuximab dose received was 2150 mg/m² (IQR 2133–2150). The main reasons for discontinuation were skin rash, patient decision, and oral or gastrointestinal toxicity.

Patients had a median follow up of 25.9 months (95% CI 25.5–26.0). The primary outcome of reported overall severe (grades 3–5) toxicity did not differ significantly between treatment groups; the mean number of events per patient was 4.8 (95% CI 4.2–5.4) for cisplatin and 4.8 (4.2–5.4) for cetuximab ($p=0.98$). Overall toxicity of all grades did not differ significantly either; the mean number of events per patient was 29.2 (95% CI 27.3–31.0) in the cisplatin group versus 30.1 (28.3–31.9) in the cetuximab group ($p=0.49$; table 2; appendix).

In the acute period, severe short-term toxicities did not differ significantly between groups; the mean number of events per patient was 4.4 (95% CI 3.9–4.97) for the cisplatin group versus 4.4 (3.8–4.9) for the cetuximab group ($p=0.84$). Rates of all-grade toxicity did not differ significantly either; the mean number of events per patient was 20.0 (95% CI 18.8–21.1) in the cisplatin group versus 20.4 (19.2–21.5) in the cetuximab group ($p=0.64$; table 2).

Severe late toxicity events (adverse long-term [late] events) did not differ significantly between the cisplatin and cetuximab groups (mean 0.4 vs 0.5 events per patient; $p=0.53$), and neither did all-grade late toxicity events (mean 9.4 vs 9.9 events per patient; $p=0.49$; table 2; appendix). The proportions of patients affected by either overall severe (grade 3–5) or all grade toxicities also did not differ significantly between the two groups (appendix).

Similar results were seen for all these outcomes in the per-protocol population (appendix). Furthermore, a post-hoc subgroup analysis of toxicity outcomes in patients who received the complete treatment regimens (three doses of cisplatin or eight doses of cetuximab) showed similar outcomes to the intention-to-treat analysis, with no significant differences between the two groups in any of the primary or secondary toxicity outcomes (appendix).

The range of toxicities differed between the two treatment groups (table 3). For cisplatin, the most common acute severe toxicities were gastrointestinal (mean 2.12 events per patient) and the most common

	Cisplatin group (n=166)	Cetuximab group (n=168)	All patients (n=334)
Age, years			
Mean	57.0 (7.8)	57.0 (8.3)	57.0 (8.0)
Median	56.5 (52.0–62.0)	57.0 (51.0–64.0)	57.0 (52.0–63.0)
Sex			
Men	132 (80%)	134 (80%)	266 (80%)
Women	34 (20%)	34 (20%)	68 (20%)
HPV testing results (n=324)			
p16-positive, HPV-ISH positive	151 (94%)	153 (94%)	304 (94%)
p16-positive, HPV-ISH negative	10 (6%)	10 (6%)	20 (6%)
Tumour stage (TNM 7)			
T1–T2	109 (66%)	107 (64%)	216 (65%)
T3–T4	57 (34%)	61 (36%)	118 (35%)
T4 only	32 (19%)	24 (14%)	56 (17%)
Nodal stage (TNM 7)			
N0–N1	40 (24%)	41 (24%)	81 (24%)
N2–N3	126 (76%)	127 (76%)	253 (76%)
N3 only	1 (1%)	1 (1%)	2 (1%)
Primary tumour laterality (n=328)			
Left only	80 (49%)	86 (52%)	166 (51%)
Right only	75 (46%)	67 (41%)	142 (43%)
Midline or any combination	8 (5%)	12 (7%)	20 (6%)
Primary subsite (n=329)			
Base of tongue	54 (33%)	58 (35%)	112 (34%)
Tonsil	107 (65%)	104 (63%)	211 (64%)
Other	3 (2%)	3 (2%)	6 (2%)
ECOG performance status (n=328)			
0	142 (87%)	149 (91%)	291 (89%)
1	22 (13%)	15 (9%)	37 (11%)
Current alcohol consumption (n=329)			
No	44 (27%)	37 (22%)	81 (25%)
Yes	120 (73%)	128 (78%)	248 (75%)
Median reported units per week	10.0 (4.0–20.0)	10.0 (4.0–20.0)	10.0 (4.0–20.0)
Ever smoked?			
No	94 (57%)	86 (51%)	180 (54%)
Yes	72 (43%)	82 (49%)	154 (46%)
Median pack years	6.5 (3.0–13.0)	8.0 (3.0–15.0)	8.0 (3.0–15.0)
Radiotherapy			
Unilateral	34 (20%)	34 (20%)	68 (20%)
Bilateral	132 (80%)	134 (80%)	266 (80%)
Planned PEG use before treatment			
No	57 (34%)	58 (34%)	115 (34%)
Yes	109 (66%)	110 (66%)	219 (66%)

Data are n (%), mean (SD), or median (IQR). There were no significant differences between the two treatment groups for any of the factors. Continuous variables were compared with t tests or Mann-Whitney U tests, and categorical variables compared with χ^2 test. HPV=human papillomavirus. ISH=in-situ hybridisation. TNM=tumour, node, and metastasis. ECOG=Eastern Cooperative Oncology Group. PEG=percutaneous endoscopic gastrostomy.

Table 1: Baseline characteristics of patients

late toxicities were gastrointestinal (mean 0.2 events per patient) and labyrinthine (otological symptoms including hearing loss, tinnitus, and vertigo; mean 0.1 events per patient). Cisplatin also caused more haematological, metabolic, and renal toxicity than did cetuximab. For

	Cisplatin plus radiotherapy (95% CI)	Cetuximab plus radiotherapy (95% CI)	p value
Primary outcome			
Overall			
Grade 3-5	4.81 (4.23-5.40)	4.82 (4.22-5.43)	0.98
All grades	29.15 (27.33-30.97)	30.05 (28.26-31.85)	0.49
Secondary outcomes			
Acute short-term toxicities			
Grade 3-5	4.43 (3.88-4.97)	4.35 (3.84-4.86)	0.84
All grades	19.96 (18.81-21.12)	20.35 (19.18-21.52)	0.64
Severe late toxicities			
Grade 3-5	0.41 (0.29-0.54)	0.48 (0.30-0.67)	0.53
All grades	9.44 (8.53-10.34)	9.87 (9.02-10.72)	0.49
t test used to compare treatment groups. No adjustments have been made for multiple testing. Toxicity assessed with Common Toxicity Criteria for Adverse Events, version 4.0.			
Table 2: Mean number of acute, late, and overall toxicity events per patient, by treatment group			

cetuximab, the most common severe toxicities were also gastrointestinal (mean 1.9 acute and 0.2 late events per patient). Cetuximab also caused more skin toxicity and infusion reactions in the acute phase than did cisplatin (table 3).

There were significantly more serious adverse events with cisplatin than with cetuximab. 162 adverse events (mean rate of one event per patient) occurred in patients receiving cisplatin and 95 events (mean rate of 0.6 events per patient) occurred in patients receiving cetuximab ($p < 0.0001$; appendix). The majority of serious adverse events (in 252 [98%] patients) resulted in admission to hospital. Serious adverse events in the cisplatin group were more likely (98 [61%] patients) to be assessed as related or possibly related to treatment than in the cetuximab group (18 [19%]; appendix). The most common serious adverse events for cisplatin were vomiting (in 48 [30%] patients) and nausea (in 46 [28%]), and those for cetuximab were vomiting (22 [13%]) and oral mucositis (21 [13%]; appendix). 114 (70%) serious adverse events with cisplatin resolved without sequelae compared with 59 (62%) with cetuximab.

A significant difference in 2-year overall survival was observed between cisplatin and cetuximab (97.5% vs 89.4%, HR 5.0 [95% CI 1.7-14.7], log-rank $p = 0.0012$; figure 2A) and in the 2-year recurrence rate (6.0% vs 16.1%, 3.4 [1.6-7.2]; log-rank $p = 0.0007$; figure 2B), in favour of cisplatin. After adjusting for known prognostic factors, the effect of treatment on overall survival (HR 5.9 [95% CI 2.0-17.8]; $p = 0.0015$) and recurrence (3.9 [1.8-8.2]; $p = 0.0004$) remained significant. Giving cetuximab instead of cisplatin was estimated to lead to one extra death at 2 years for every 12 patients treated (number needed to harm 12.3 [95% CI 7.0-50.8]). Similar results were seen for all above outcomes in the per-protocol population (appendix).

Overall, six patients died in the cisplatin group versus 20 in the cetuximab group. Cancer-related deaths occurred in four patients in the cisplatin group and in 15 in the cetuximab group. Four (2.5%) patients had persistent disease after cisplatin therapy, compared with five (3%) after cetuximab therapy. Significantly fewer recurrences were observed with cisplatin than with cetuximab (ten [6%] vs 29 [18%]; log-rank $p = 0.0007$; appendix). Significantly fewer locoregional recurrences (3% vs 12%, log-rank $p = 0.0026$) and fewer distant metastases (3% vs 9%, log-rank $p = 0.0092$) were observed with cisplatin than with cetuximab. Five (3%) patients in each group developed second primaries. 11 (7%) patients in the cisplatin group had neck dissection for possible persistent disease at the 3-month post-treatment assessment point, and none for recurrent disease after this timepoint. Ten (6%) patients in the cetuximab group had neck dissection for possible persistent disease at the 3-month post-treatment point, and two for recurrent disease after this timepoint.

We did two post-hoc subgroup sensitivity analyses. In the 276 patients with TNM8 stage I or II disease, a significant difference in 2-year overall survival was observed: 98.4% (95% CI 93.9-99.6) for the cisplatin group ($n = 133$) and 93.2% (87.4-96.4) for the cetuximab group ($n = 143$; HR 4.3 [95% CI 0.9-19.8], log rank $p = 0.0431$; appendix). In particular, the 58 patients with TNM8 stage III (T4 or N3) disease showed a larger 2-year overall survival detriment with cetuximab (67.1% [95% CI 42.5-83.1]) than with cisplatin (93.3% [75.9-98.3], HR 4.8 [95% CI 1.0-23.3], log rank $p = 0.0304$; appendix).

In the 304 (94%) patients who tested doubly positive for p16 and HPV-DNA, there was still a significant difference in 2-year overall survival between cisplatin (97.2% [95% CI 92.8-99]) and cetuximab (89.7% [83.2-93.8]; HR 4.4 [95% CI 1.5-13.1]; log rank $p = 0.0035$; appendix).

The mean global quality-of-life score on EORTC QLQ-C30 did not differ significantly between treatment groups at any of the timepoints (mean difference at 24 months of 1.51 points in favour of cisplatin, $p = 0.9976$; figure 2C). A significant difference in social functioning was observed in favour of cetuximab at the end of treatment (mean difference of 8.67 points, $p = 0.0374$), but this difference disappeared 6 months later. At 12 months and 24 months, a significant difference in role functioning was observed in favour of cisplatin (difference in mean scores of 8.32 points, $p = 0.0173$; appendix). None of the differences reached the minimal clinically important difference of 10 points.

In terms of swallowing, no significant differences were observed between the treatment groups as assessed by the global M.D. Anderson Dysphagia Inventory score (mean difference at 24 months of 6.90 points in favour of cisplatin, $p = 0.1279$; appendix). The only significant differences between the groups in the domains occurred at 12 months after treatment, and all were in favour of cisplatin (mean difference in emotional domain of

	Acute severe toxicity				Late severe toxicity				Overall severe toxicity			
	Cisplatin plus radiotherapy (n=162)		Cetuximab plus radiotherapy (n=165)		Cisplatin plus radiotherapy (n=162)		Cetuximab plus radiotherapy (n=165)		Cisplatin plus radiotherapy (n=162)		Cetuximab plus radiotherapy (n=165)	
	Mean events	Patients	Mean events	Patients	Mean events	Patients	Mean events	Patients	Mean events	Patients	Mean events	Patients
Blood and lymphatic system disorders	0.13	20 (12%)	0.01	2 (1%)	0.01	1 (1%)	0.01	2 (1%)	0.14	21 (13%)	0.02	4 (2%)
Cardiac disorders	0.01	2 (1%)	..	0	..	0	..	0	0.01	2 (1%)	..	0
Ear and labyrinth disorders	0.02	3 (2%)	0.04	4 (2%)	0.14	21 (13%)	0.05	8 (5%)	0.15	24 (15%)	0.08	12 (7%)
Gastrointestinal disorders	2.12	130 (80%)	1.88	129 (78%)	0.15	19 (12%)	0.21	23 (14%)	2.25	147 (91%)	2.09	151 (92%)
General disorders and administration site	0.20	31 (19%)	0.18	27 (16%)	0.01	2 (1%)	0.02	2 (1%)	0.22	33 (20%)	0.21	29 (18%)
Infections and infestations	0.16	19 (12%)	0.17	21 (13%)	0.01	1 (1%)	0.02	2 (1%)	0.16	19 (12%)	0.19	23 (14%)
Injury, poisoning, and procedural complications	0.16	26 (16%)	0.39	64 (39%)	..	0	0.01	1 (1%)	0.16	26 (16%)	0.39	65 (39%)
Investigations	0.08	11 (7%)	0.04	7 (4%)	0.01	2 (1%)	0.01	2 (1%)	0.09	13 (8%)	0.05	9 (6%)
Metabolism and nutrition disorders	0.61	77 (48%)	0.45	65 (39%)	0.02	4 (3%)	0.04	7 (4%)	0.64	81 (50%)	0.49	72 (44%)
Musculoskeletal and connective tissue disorders	0.07	10 (6%)	0.10	14 (9%)	0.02	4 (3%)	0.03	5 (3%)	0.09	13 (8%)	0.13	19 (12%)
Nervous system disorders	0.06	9 (6%)	0.10	16 (10%)	0.01	1 (1%)	0.02	3 (2%)	0.06	10 (6%)	0.12	19 (12%)
Psychiatric disorders	0.06	9 (6%)	0.04	7 (4%)	..	0	0.01	1 (1%)	0.06	9 (6%)	0.05	8 (5%)
Renal and urinary disorders	0.07	11 (7%)	..	0 (0%)	0.01	2 (1%)	0.01	1 (1%)	0.09	13 (8%)	0.01	1 (1%)
Respiratory, thoracic, and mediastinal disorders	0.60	78 (48%)	0.50	70 (42%)	0.02	3 (2%)	0.03	5 (3%)	0.62	81 (50%)	0.52	74 (45%)
Skin and subcutaneous tissue disorders	0.06	7 (4%)	0.42	50 (30%)	..	0	0.01	1 (1%)	0.06	7 (4%)	0.43	51 (31%)
Vascular disorders	0.02	4 (3%)	0.02	4 (2%)	0.01	1 (1%)	0.01	2 (1%)	0.03	5 (3%)	0.04	6 (4%)

Data are mean number of events per patient or number of patients with at least one severe toxicity (%). An event was defined as the incidence of a toxicity assessed with the Common Toxicity Criteria for Adverse Events (CTCAE), version 4. Severe toxicity classified as grade 3, 4, or 5 on CTCAE, version 4. A toxicity that reached grade 3–5 in the acute phase and continued as grade 3–5 into the late phase was counted as both acute and late toxicities, but only counted once in the overall toxicity category. If a patient had two or more severe toxicities, they were still counted once in the total count.

Table 3: Range of acute, late, and overall (combined) severe toxicities, by type, mean number of events per patient, and proportion of patients affected by one or more toxicity, by treatment group

5.13 points, $p=0.0151$; functional domain difference of 3.96 points, $p=0.0319$; physical difference of 6.40 points, $p=0.0113$; and overall function difference of 5.49 points, $p=0.0073$), but none reached the minimal clinically important difference of 10 points, and all differences became non-significant again by 24 months.

Discussion

HPV-positive oropharyngeal squamous cell carcinoma is projected to become the most common form of head and neck cancer in many developed countries.^{21,22} Results of our study show that, in the setting of low-risk oropharyngeal squamous cell carcinoma, the use of cetuximab bioradiotherapy instead of cisplatin-based chemoradiotherapy resulted in no overall benefit in terms of toxicity but showed significant detriment in tumour control. Our trial also highlights that the good survival outcomes of HPV-positive low-risk oropharyngeal squamous cell carcinoma are in part a function of the type of treatment received, and not merely a reflection of favourable intrinsic tumour biology. Therefore, cisplatin-based chemoradiotherapy should continue to be considered the standard of care in this setting.

Contrary to expectations from the findings of the initial cetuximab registration trial,¹¹ the rates of early, late, and overall serious toxicity resulting from cetuximab were not lower than those of cisplatin, although the toxicity profile was different. Global quality of life also appeared to be similar. Less than half of patients received the full dose of cisplatin because of toxicity. However, there was still a significant difference in survival compared with the cetuximab group in which most patients received the full regimen. Although cetuximab does result in fewer serious adverse events, this alone is not sufficient justification for its use in this setting. The findings of our study confirm those of other studies and meta-analyses comparing chemotherapy to bioradiotherapy with EGFR inhibitors in mixed head and neck cancer populations.^{23,24} Until now, to our knowledge, no randomised studies had been done in HPV-positive disease.

As HPV-positive oropharyngeal squamous cell carcinoma is a relatively new disease entity, there have been changes in risk classification schemes, its TNM staging system, and the use of p16 immunohistochemistry as the sole determinant of HPV positivity since the inception of this trial and during its conduct. We defined low-risk

patients according to the Ang classification,⁴ which is the most widely cited and used system. Since then, many other prognostic systems have been developed for this indication, each with different component factors. The new AJCC/UICC TNM 8th edition has included a new

classification for HPV-positive oropharyngeal squamous cell carcinoma. In this new classification, HPV-positive T4 and N3 cases, constituting stage III HPV-positive oropharyngeal squamous cell carcinoma, have been shown to have higher rates of distant metastases than stage I or II tumours.²⁵ Additionally, the use of p16 alone as a surrogate marker of HPV causation has been criticised, because in some studies the subsets comprising p16-positive, HPV-DNA-negative disease appear to have poorer outcomes, similar to patients with p16-negative and HPV-DNA-negative disease.²⁶ In other studies, this subset of patients showed similar survival to patients with p16-positive, HPV-positive disease.²⁷ To understand whether these factors affected our conclusions, we did post-hoc sensitivity analyses and found no difference in the results. Patients with T4 or N3 disease appeared to have even higher detriments in overall survival if they were treated with cetuximab than if they were treated with cisplatin. The numbers were small, however, leading to wide confidence intervals.

Our study was originally designed to test for differences in toxicity as a means of assessing whether cetuximab effectively reduces treatment-related toxicity for patients with HPV-positive oropharyngeal squamous cell carcinoma. We anticipated equivalent disease control and survival endpoints between study groups and did not formally power the study to show non-inferiority. Despite this limitation, the trial shows significant differences in both recurrence and survival endpoints in favour of cisplatin-based chemoradiotherapy. This outcome appears to be due to a relatively larger effect of cisplatin, compared with cetuximab, on locoregional control and distant metastases. We used p16 and HPV DNA in-situ hybridisation to assess HPV status, as this method is widely accepted¹⁶ and is recommended by the US National Comprehensive Care guidelines as one of the appropriate options for this purpose.²⁸ This could be viewed as a limitation, because HPV E6/E7 RNA evaluation by PCR is considered the gold standard for testing HPV status. However, this method is not easily feasible in the clinical setting; moreover, in our study, patients who were

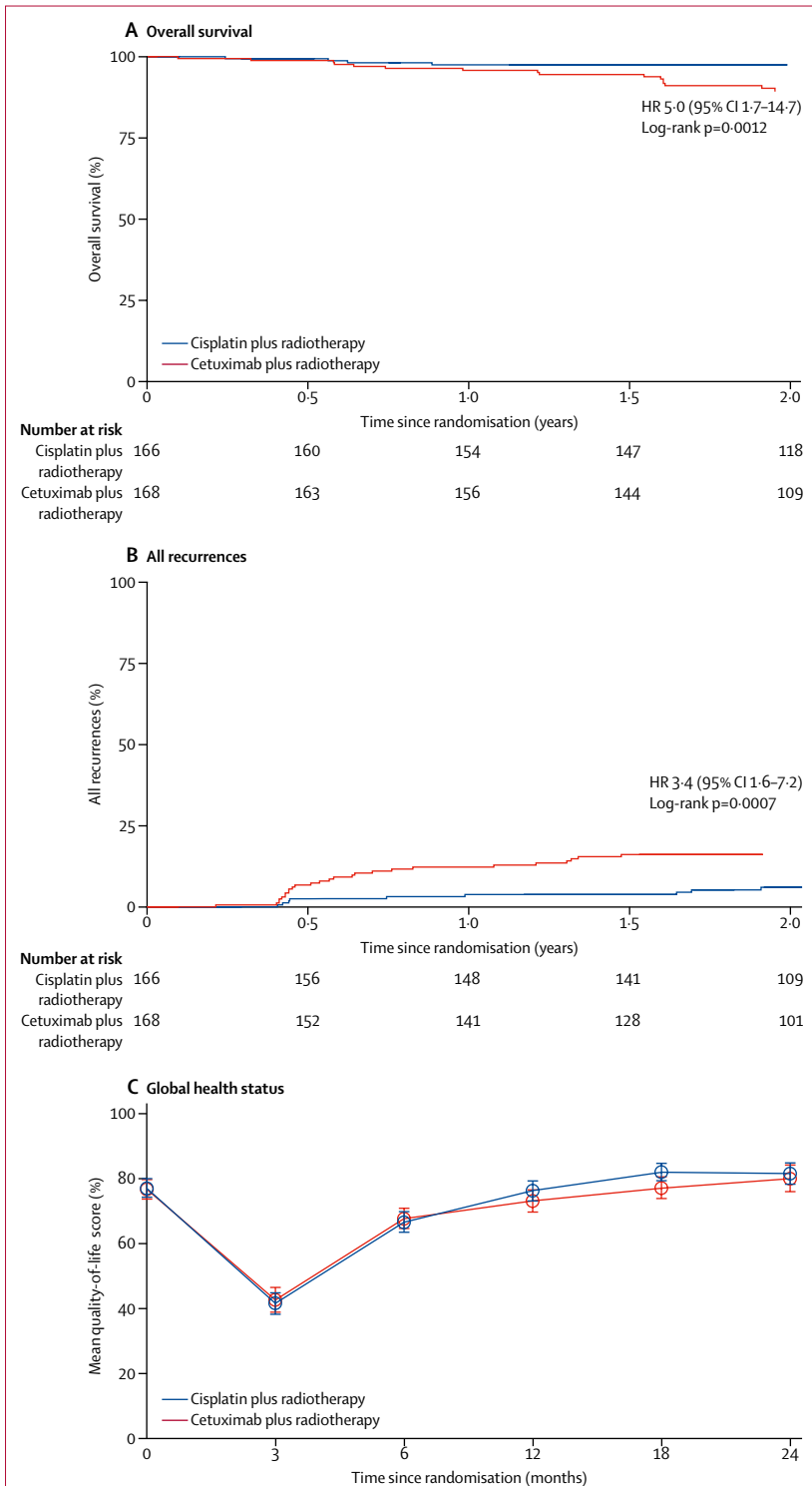


Figure 2: Overall survival, time to recurrence, and global quality of life scores, by treatment group

(A) Kaplan-Meier estimates of overall survival, by treatment group. 2-year survival was 97.5% (95% CI 93.5-99.1) in the cisplatin group and 89.4% (83.2-93.4) in the cetuximab group (hazard ratio [HR] 5.0 [95% CI 1.7-14.7]; log-rank p=0.0012). (B) Time to any recurrence or distant metastasis, by treatment group. Persistent disease (occurring within 90 days of treatment completion) and new primaries are not included. The 1-year recurrence rate was 3.8% (95% CI 1.7-8.2) in the cisplatin group and 12.9% (8.6-19.1) in the cetuximab group. The 2-year recurrence rate was 6.0% (95% CI 3.2-11.3) in the cisplatin group and 16.1% (11.3-22.8) in the cetuximab group (HR 3.4 [95% CI 1.6 to 7.2]; log-rank p=0.0007). (C) Mean global quality-of-life score over time, by treatment group, measured by European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 general (EORTC QLQ C30). Score 0 is worst quality of life and 100 is best quality of life; minimum clinically important difference 10 points (p=0.27).

p16-positive and HPV-positive showed similar survival rates to those who were p16-positive and HPV-negative.

Studies testing different de-escalation approaches for low-risk and intermediate-risk HPV-positive oropharyngeal squamous cell carcinoma are underway. Our data suggest that cisplatin-based chemoradiotherapy delivers substantially improved outcomes compared with bioradiotherapy with cetuximab, even in patients with good outcomes. Assuming that cetuximab does not reduce the efficacy of radiotherapy to control disease, these findings support the beneficial effects of adding cisplatin to radiotherapy in this group of patients. The reduced rate of distant metastasis also suggests that cisplatin might contribute to a systemic effect, even in low-risk patients. In light of our findings, we would advise caution with de-escalation strategies, especially those that remove systemic chemotherapy altogether, and strongly advocate that the results of phase 3 trials should be awaited before making any changes to routine clinical management.

This study is, to our knowledge, one of the first to compare cetuximab with cisplatin in combination with radiotherapy in the context of treatment de-escalation in HPV-positive disease. Not only did this trial show no reduction in toxicity with cetuximab but it also confirmed a statistically and clinically significant detriment in tumour control and survival endpoints with this therapy. These results have immediate implications for clinical practice and highlight the importance of doing comparative phase 3 trials in new indications, even for treatments that are already approved or have shown benefit in phase 2 trials.

Contributors

HM originated the idea and led on study design, conduct of the trial, data collection, analysis, and write up. MRob participated in conduct of the trial, data collection, analysis, and write up, and led on histopathology. AH, BF, TF-L, MD, MS, LO'T, HAB, KD, RM, SW, SB, ACo, MG, EA, MRol, EDW, ACh, DS, JG, CRL, JB, JH, KH, and CM were involved in conduct of the trial, data collection, analysis, and write up. IN was involved in the conduct of the trial and data collection. AK participated in conduct of the trial, data collection, analysis, and write up, and led on review of toxicities. PM led on data analysis and participated in write up. AG participated in conduct of the trial, data collection, data analysis, and write up, and led on health economics. JD led on study design and participated in conduct of trials, data collection, data analysis, and write up.

Declaration of interests

HM reports personal fees from Warwickshire Head Neck Clinic Ltd, AstraZeneca, MSD, Sanofi Pasteur, and Merck; grants from GlaxoSmithKline Biologicals, MSD, Sanofi Pasteur, Silence Therapeutics, GlaxoSmithKline, AstraZeneca, and several academic funders including the National Institute for Health Research (NIHR) Health Technology Assessment Unit, Cancer Research UK, and the Medical Research Council; and travel expenses from Sanofi Pasteur, MSD, and Merck, outside the submitted work. AK has received research grants from PUMA and AstraZeneca, and has received payments as a speaker, consultant, or in an advisory role from PUMA, Merck, BMS, MSD, and Avvinity Therapeutics Limited, outside the submitted work. BF has received speaker and lecturer fees from Merck Serono and Bristol-Myers Squibb. JD received a grant from Cancer Research UK to support the study. CM was supported by a grant from Cancer Research UK. PM was supported by a grant from Cancer Research UK. EA reports non-financial support and personal fees from Merck Serono outside the submitted work. JG was supported by a grant from Cancer Research UK.

LO'T reports non-financial support from Merck Serono outside the submitted work. MD was supported by a grant from Cancer Research UK. MRob reports grants from Cancer Research UK during the conduct of the study; and consultancy for Leica Biosystems. RM reports personal fees from Bristol-Myers Squibb and MSD outside the submitted work. CRL reports personal fees from the MSD Advisory Board, outside the submitted work. KH reports personal fees and non-financial support from Merck Serono during the conduct of the study; grants, personal fees, and non-financial support from AstraZeneca; personal fees, and non-financial support from Bristol-Myers Squibb; grants, personal fees, and non-financial support from MSD; and personal fees from Pfizer, outside the submitted work. All other authors declare no competing interests.

Data sharing

De-identified participant data and the data dictionary will be available along with the study protocol and statistical analysis plan from Jan 1, 2020, onwards. Please email M.L.Dalby@warwick.ac.uk. The final dataset will include basic demographics, tumour characteristics, treatment detail, survival, and quality of life and toxicity outcomes. Data will not include name, address, hospital number or date of birth, or any other identifying data. The data will be accompanied by metadata which gives a complete explanation of the data fields, the definition, the standards used such as TNM staging, and the units used. The data will be shared through custodianship by the principal investigator. A data access committee will be convened and will comprise the principal investigator and two other co-investigators. They will be responsible for assessing requests for data sharing about granting access. The data management committee will be responsible to the steering committee and requests for appeals will be made directly to the trial steering committee. The process for requesting data sharing will be as follows: the requestor will complete a two-page proforma requiring name and contact details of the requestor, the objectives of the study, the methodology, the expected outcome, the statistical analysis plan, whether the project will be a collaboration with the DeESCALaTE study organisers or will only acknowledge the study and its organisers, ethical committee approval, and funding and peer review details. The data sharing committee will meet at least twice a year to consider these requests. Urgent requests may be considered in between these meetings. In the event of a declined application, the requestors may lodge an appeal with the trial steering committee chairperson. The dataset will be stored with the principal investigator at the Institute of Head and Neck Studies and Education in the long term. The data will be available for public release from the time of publication of the main results of the study. Prior to that, access of the data may be considered in specific circumstances. After 5 years of publication of the result, the data may then be lodged with a data archiving facility. Requestors who are granted access to the data will be required to complete a data sharing agreement, which is based on the principles, content, and format published by the the National Cancer Research Institute (NCRI).

Acknowledgments

This study was supported by academic grant no C19677/A12834 provided by Cancer Research UK. We thank the patients and their families who participated in this study, clinicians and support staff who looked after these patients, members of the independent trial steering committee (Jonathan Ledermann, Vincent Gregoire, Louise Stanton, Martin Forster, Malcolm Babb, and Ralph Goodson), and members of the independent data and monitoring committee (Roger A'hern, Jan Vermorken, and Peter Hoskin). We also thank Gemma Jones for her administrative support throughout the trial and in preparation of the manuscript.

References

- 1 Castellsague X, Alemany L, Quer M, et al. HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients. *J Natl Cancer Inst* 2016; **108**: djv403.
- 2 Mehanna H, Beech T, Nicholson T, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer—systematic review and meta-analysis of trends by time and region. *Head Neck* 2013; **35**: 747–55.
- 3 Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol* 2010; **11**: 781–89.

For the NCRI template for access policy development see <http://www.ncri.org.uk/wp-content/uploads/2013/09/Initiatives-Biobanking-2-Access-template.pdf>

- 4 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.
- 5 Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol* 2008; **26**: 3582–89.
- 6 Trotti A, Pajak TF, Gwede CK, et al. TAME: development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group. *Lancet Oncol* 2007; **8**: 613–24.
- 7 Denis F, Garaud P, Bardet E, et al. Final results of the 94–01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol* 2004; **22**: 69–76.
- 8 Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol* 2013; **31**: 845–52.
- 9 Mehanna H. Update on de-intensification and intensification studies in HPV. *Recent Results Cancer Res* 2017; **206**: 251–56.
- 10 Dent P, Reardon DB, Park JS, et al. Radiation-induced release of transforming growth factor alpha activates the epidermal growth factor receptor and mitogen-activated protein kinase pathway in carcinoma cells, leading to increased proliferation and protection from radiation-induced cell death. *Mol Biol Cell* 1999; **10**: 2493–506.
- 11 Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006; **354**: 567–78.
- 12 Rosenthal DI, Harari PM, Giralt J, et al. Association of human papillomavirus and p16 status with outcomes in the IMCL-9815 phase III registration trial for patients with locoregionally advanced oropharyngeal squamous cell carcinoma of the head and neck treated with radiotherapy with or without cetuximab. *J Clin Oncol* 2016; **34**: 1300–08.
- 13 Reimers N, Kasper HU, Weissenborn SJ, et al. Combined analysis of HPV-DNA, p16 and EGFR expression to predict prognosis in oropharyngeal cancer. *Int J Cancer* 2007; **120**: 1731–38.
- 14 Pajares B, Trigo JM, Toledo MD, et al. Differential outcome of concurrent radiotherapy plus epidermal growth factor receptor inhibitors versus radiotherapy plus cisplatin in patients with human papillomavirus-related head and neck cancer. *BMC Cancer* 2013; **13**: 26.
- 15 Riaz N, Sherman E, Koutcher L, et al. Concurrent chemoradiotherapy with cisplatin versus cetuximab for squamous cell carcinoma of the head and neck. *Am J Clin Oncol* 2016; **39**: 27–31.
- 16 Singhi AD, Westra WH. Comparison of human papillomavirus in situ hybridization and p16 immunohistochemistry in the detection of human papillomavirus-associated head and neck cancer based on a prospective clinical experience. *Cancer* 2010; **116**: 2166–73.
- 17 Thavaraj S, Stokes A, Guerra E, et al. Evaluation of human papillomavirus testing for squamous cell carcinoma of the tonsil in clinical practice. *J Clin Pathol* 2011; **64**: 308–12.
- 18 Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *Eur J Cancer* 2000; **36**: 1796–807.
- 19 Chen AY, Frankowski R, Bishop-Leone J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M.D. Anderson dysphagia inventory. *Arch Otolaryngol Head Neck Surg* 2001; **127**: 870–76.
- 20 Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. *Eur J Cancer* 2001; **37**: 1331–34.
- 21 Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol* 2011; **29**: 4294–301.
- 22 Louie KS, Mehanna H, Sasieni P. Trends in head and neck cancers in England from 1995 to 2011 and projections up to 2025. *Oral Oncol* 2015; **51**: 341–48.
- 23 Beelen K, Opdam M, Severson TM, et al. PIK3CA mutations, phosphatase and tensin homolog, human epidermal growth factor receptor 2, and insulin-like growth factor 1 receptor and adjuvant tamoxifen resistance in postmenopausal breast cancer patients. *Breast Cancer Res* 2014; **16**: R13.
- 24 Bonner JA, Giralt J, Harari PM, et al. Association of human papillomavirus and p16 status with mucositis and dysphagia for head and neck cancer patients treated with radiotherapy with or without cetuximab: Assessment from a phase 3 registration trial. *Eur J Cancer* 2016; **64**: 1–11.
- 25 O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. *J Clin Oncol* 2013; **31**: 543–50.
- 26 Nauta IH, Rietbergen MM, van Bokhoven A, et al. Evaluation of the eighth TNM classification on p16-positive oropharyngeal squamous cell carcinomas in the Netherlands and the importance of additional HPV DNA testing. *Ann Oncol* 2018; **29**: 1273–79.
- 27 Saito Y, Yoshida M, Omura G, et al. Prognostic value of p16 expression irrespective of human papillomavirus status in patients with oropharyngeal carcinoma. *Jpn J Clin Oncol* 2015; **45**: 828–36.
- 28 NCCN Network. NCCN head and neck cancer guidelines 2018. https://www.nccn.org/professionals/physician_gls/default.aspx (accessed Oct 1, 2018).