### Title

Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study




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# Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study

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## Summary

**Background** Head and neck cancers positive for human papillomavirus (HPV) are exquisitely radiosensitive. We investigated whether chemoradiotherapy with reduced-dose radiation would maintain survival outcomes while improving tolerability for patients with HPV-positive oropharyngeal carcinoma.

**Methods** We did a single-arm, phase 2 trial at two academic hospitals in the USA, enrolling patients with newly diagnosed, biopsy-proven stage III or IV squamous-cell carcinoma of the oropharynx, positive for HPV by p16 testing, and with Zubrod performance status scores of 0 or 1. Patients received two cycles of induction chemotherapy with 175 mg/m² paclitaxel and carboplatin (target area under the curve of 6) given 21 days apart, followed by intensity-modulated radiotherapy with daily image guidance plus 30 mg/m² paclitaxel per week concomitantly. Complete or partial responders to induction chemotherapy received 54 Gy in 27 fractions, and those with less than partial or no responses received 60 Gy in 30 fractions. The primary endpoint was progression-free survival at 2 years, assessed in all eligible patients who completed protocol treatment. This study is registered with ClinicalTrials.gov, numbers NCT02048020 and NCT01716195.

**Findings** Between Oct 4, 2012, and March 3, 2015, 45 patients were enrolled with a median age of 60 years (IQR 54–67). One patient did not receive treatment and 44 were included in the analysis. 24 (55%) patients with complete or partial responses to induction chemotherapy received 54 Gy radiation, and 20 (45%) with less than partial responses received 60 Gy. Median follow-up was 30 months (IQR 26–37). Three (7%) patients had locoregional recurrence and one (2%) had distant metastasis; 2-year progression-free survival was 92% (95% CI 77–97). 26 (39%) of 44 patients had grade 3 adverse events, but no grade 4 events were reported. The most common grade 3 events during induction chemotherapy were leucopenia (17 [39%]) and neutropenia (five [11%]), and during chemoradiotherapy were dysphagia (four [9%]) and mucositis (four [9%]). One (2%) of 44 patients was dependent on a gastrostomy tube at 3 months and none was dependent 6 months after treatment.

**Interpretation** Chemoradiotherapy with radiation doses reduced by 15–20% was associated with high progression-free survival and an improved toxicity profile compared with historical regimens using standard doses. Radiotherapy de-escalation has the potential to improve the therapeutic ratio and long-term function for these patients.

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## Introduction

The identification of human papillomavirus (HPV) as a causative agent for oropharyngeal carcinoma has suggested that some head and neck squamous-cell carcinomas behave differently from others. HPV-positive head and neck cancers have distinct clinical and molecular characteristics[1–3] that notably affect prognosis and treatment response compared with HPV-negative cancers, with the risk of death being at least halved.[4–6] Many theories have been proposed to explain this difference, including differential sensitivity to therapeutic radiation.[7–9]

The recognition that HPV-positive head and neck squamous cell carcinoma responds particularly favourably to radiotherapy has prompted the suggestion that use of standard doses might expose patients to overtreatment and unnecessary toxic effects. For example, late dysphagia and xerostomia have been reported in a substantial proportion of survivors of head and neck cancer treated by radiotherapy.[10] We investigated whether a chemoradiotherapy regimen with reduced radiation dose would maintain survival outcomes while improving tolerability in patients with HPV-positive oropharyngeal carcinoma.

## Methods

### Study design and patients

We did a single-arm, phase 2 trial at the University of California, Davis, Sacramento, CA, USA, and the University of California, Los Angeles, Los Angeles, CA, USA (appendix p 1). Eligible participants were aged 18 years or older, had histologically confirmed newly diagnosed stage III or IV HPV-positive squamous-cell oropharyngeal carcinoma arising from the oropharynx, and had a Zubrod performance status score of 0 or 1. HPV positivity was defined as tumours that were positive

See Online for appendix

## Research in context

### Evidence before this study

We searched PubMed and MEDLINE for peer-reviewed, original studies published in English between Jan 1, 2000, and Jan 1, 2009, with the search terms "HPV", "oropharynx", and "radiation". When this trial was designed in 2009, we found no ongoing clinical investigations that focused on chemoradiotherapy with reduced radiation doses for oropharyngeal cancer positive for human papillomavirus (HPV). Many retrospective studies and subset analyses of prospective trials showed that HPV status had prognostic relevance for patients with newly diagnosed oropharyngeal cancer. Despite standard chemoradiotherapy regimens being associated with substantial side-effects, especially mucosal and oesophageal toxic effects, we identified no investigations of the potential usefulness of reducing the radiation dose. Some preclinical data suggested that HPV-positive squamous-cell cancers were more sensitive to therapeutic irradiation than HPV-negative cancers, which supported the potential for chemoradiotherapy regimens with reduced radiation to be efficacious. Given the rapid increase in the incidence of oropharyngeal cancers worldwide, we designed a phase 2 trial to investigate whether reduced-dose radiation would maintain progression-free survival while improving tolerability in patients with HPV-positive squamous-cell oropharyngeal cancer.

### Added value of this study

Our results support the notion of unique radiosensitivity of HPV-positive oropharyngeal carcinoma. 2-year progression-free survival after treatment with chemoradiotherapy with reduced-dose radiation compared favourably with that achieved in historical controls treated with standard chemoradiotherapy regimens. Additionally, the toxicity profile was acceptable, with a lower frequency of mucosal and oesophageal adverse events compared with historical controls.

### Implications of all the available evidence

The radiation dose for head and neck squamous-cell cancer has remained similar for at least 50 years. Efforts are being made to find optimum reduced-dose treatment regimens for patients with HPV-positive head and neck cancers. Our findings show that patients with HPV-positive oropharyngeal squamous-cell carcinoma can be treated successfully with radiation doses of 15–20% less than those used historically while decreasing the risk of toxic effects. This approach has the potential to usher in a new standard of care for HPV-positive oropharyngeal carcinoma. A phase 3 trial of treatment with reduced-dose radiation is being planned.

for p16 on immunohistochemistry. Central testing to confirm p16 status was not required for this study, but the most commonly used test was the Ventana CINtec p16 histology kit with IgG mouse monoclonal antibody (Ventana Medical Systems, Tucson, AZ, USA). Smoking history was recorded but was not an eligibility criterion.

Participants were excluded if they were immunosuppressed, pregnant or breastfeeding, or had active lupus erythematosus or scleroderma, impaired liver or kidney function, uncontrolled cardiac disease, chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring admission to hospital, or an acute or fungal infection requiring treatment. Participants were also excluded if they had distant metastasis, malignant disease (except non-melanomatous skin cancer) in the previous 3 years, or had previously received treatment for their oropharyngeal carcinoma, including surgery; diagnostic biopsy of the primary site or nodal sampling of neck disease was allowed.

Laboratory studies were done within 4 weeks of enrolment with the following thresholds: adequate bone marrow function defined as absolute neutrophil count greater than $1{\cdot}5\times10^9$ cells per L, platelet count greater than $100\times10^9$ cells per L, and haemoglobin concentration greater than 80 g/L; adequate hepatic function defined as aspartate aminotransferase or alanine aminotransferase concentrations up to 2×the upper limit of normal (ULN); and adequate renal function defined as serum creatinine concentrations of at least 132 µmol/L or the institutional ULN and creatinine clearance at least 50 mL/min determined by 24 h collection or estimated by the Cockcroft-Gault formula. Women of childbearing potential had to have a negative serum pregnancy test within 7 days before the start of study treatment. The study protocol was approved by the human ethics committees of both universities, and all patients gave written informed consent. The study protocol is available in the appendix.

### Procedures

All patients were assessed by head and neck CT, MRI, or both, before enrolment and by whole-body PET at baseline. Tumours were staged with the 2009 American Joint Committee on Cancer staging classification.[11] On the basis of encouraging single-institutional data[12] and the results of a multi-institutional phase 2 study of 111 patients with stage III and IV squamous-cell carcinoma of the head and neck done by the Eastern Cooperative Oncology Group (ECOG),[13] we selected an initial regimen of two cycles of induction chemotherapy with 175 mg/m² paclitaxel infused over 3 h plus carboplatin (target area under the curve [AUC] of 6) as a 30 min infusion, given 21 days apart. This induction regimen was followed by chemoradiotherapy comprising 30 mg/m² paclitaxel infused over 1 h per week with definitive radiation given concurrently for 5–6 weeks. Chemoradiotherapy was initiated at least 2 weeks after completion of induction chemotherapy.

Dose modifications for induction chemotherapy were permitted if patients developed neutropenia or thrombocytopenia in cycle one, with reductions of paclitaxel to 150 mg/m² and carboplatin to a target AUC of 5. Dose reductions were also allowed if patients developed any high-grade hepatic or neuropathic adverse events or myalgia. During the chemoradiotherapy phase, paclitaxel could be withheld if patients developed grade 2 or worse neutropenia, thrombocytopenia, or neuropathy, and resumed if these events resolved to at least grade 1. Missed doses of paclitaxel were documented but not made up. Granulocyte-colony-stimulating factors could be used at the discretion of the treating physician.

Response was assessed by CT after induction chemotherapy. The timing of this assessment was decided by the treating physician, but was recommended to be done approximately 2 weeks after induction chemotherapy had finished. The patient's clinical response, classified with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, determined the radiation dose. Complete and partial responses were defined, respectively, as 100% or at least 30% decrease in the sum of the longest diameters of target lesions compared with baseline. Patients with complete or partial responses were prescribed 54 Gy in 27 fractions to the primary tumour and involved nodes and 43 Gy to uninvolved nodal areas of the neck. Patients with less than partial or no responses were prescribed 60 Gy in 30 fractions and 48 Gy to uninvolved areas. Intensity-modulated techniques were used to provide simultaneous integrated boost, and daily image guidance was required. Radiation target volumes were defined by the extent of disease before chemotherapy, as assessed by imaging and physical examination, including endoscopy, and adjusted to conform to anatomy after chemotherapy and acknowledged anatomical boundaries to tumour spread. The planning goal was to encompass at least 95% of the planning target volume with the isodose corresponding to the prescription dose.

Laboratory studies were complete blood counts with differential, metabolic panel with electrolytes, and liver function tests, obtained within 2 days before the start of each induction chemotherapy cycle and weekly during chemoradiotherapy. Patients were first followed up 2–4 weeks after completion of chemoradiotherapy. Disease assessments, which included history taking and physical and fibre-optic examinations, were also done every 3 months from the end of chemoradiotherapy for 1 year and then every 6 months thereafter. PET-CT was done around 3 months after completion of chemoradiotherapy and responses were assessed with RECIST version 1.1. Treatment-emergent adverse events were assessed with the Common Terminology Criteria for Adverse Events version 4.03. Early and late adverse events were defined as those occurring, respectively, within and after 90 days from the completion of chemoradiotherapy. Serious adverse events were reviewed throughout the study by the principle investigator.

Surgical salvage at the primary site was required for all patients with disease progression at any time. Patients with N1 or N2 disease who did not have a complete response 2–3 months after the end of chemoradiotherapy received surgical consultations to discuss neck dissection.

### Outcomes

The primary endpoint was 2-year progression-free survival (defined as time from enrolment until disease progression or death, with censoring of patients lost to follow-up). Patients who died within 2 years were classified as having disease progression unless no progression was specifically documented. If patients died without disease progression, survival data were censored at the last visit alive. Secondary endpoints were overall survival (defined as the time from treatment initiation to death from any cause), locoregional control (absence of tumour progression at irradiated sites), treatment-emergent adverse events, completion of planned therapy, and death during treatment or within 30 days of ending chemoradiotherapy. Quality of life was also a secondary endpoint, but will be presented elsewhere. Freedom from grade 3 or worse mucosal and oesophageal adverse events (defined as time from treatment initiation to grade a 3 adverse event) was analysed as a post-hoc endpoint.

### Statistical analysis

The target accrual goal was 50 patients. We used a two-stage Simon design[14] to enable early stopping of the trial if the study regimen was inactive or was efficacious enough to warrant further investigation in a phase 3 trial. We took 2-year progression-free survival of 72% or lower (null hypothesis) to indicate non-efficacy, which would lead to the trial being stopped, and of 86% or higher to indicate that the study could continue to phase 3. We did an interim analysis in April, 2014, after 25 patients had been enrolled. At this stage the study could be stopped if 19 or fewer patients were without disease progression within 2 years. A second interim analysis was done in June, 2016, at which stage, if 40 or fewer patients were progression free at 2 years, the reduced radiation dose would be deemed non-efficacious, whereas, if 41 or more patients were progression free at 2 years, the study regimen would be deemed suitable for assessment in a phase 3 trial. The trial was closed after the second interim analysis after meeting the criteria for proceeding to a phase 3 trial, and results are reported from the final analysis in December, 2016. We assumed the type I error would be 10%. Therefore, if 2-year progression-free survival was 78%, 81%, 85%, or 87%, the statistical power would be 32%, 52%, 78%, or 89%, respectively. Overall significance was set at 9% and the study power was calculated to be 81%.

We calculated 95% CIs for all actuarial endpoints with the Duffy-Santner approach.[15] Time-to-event distributions

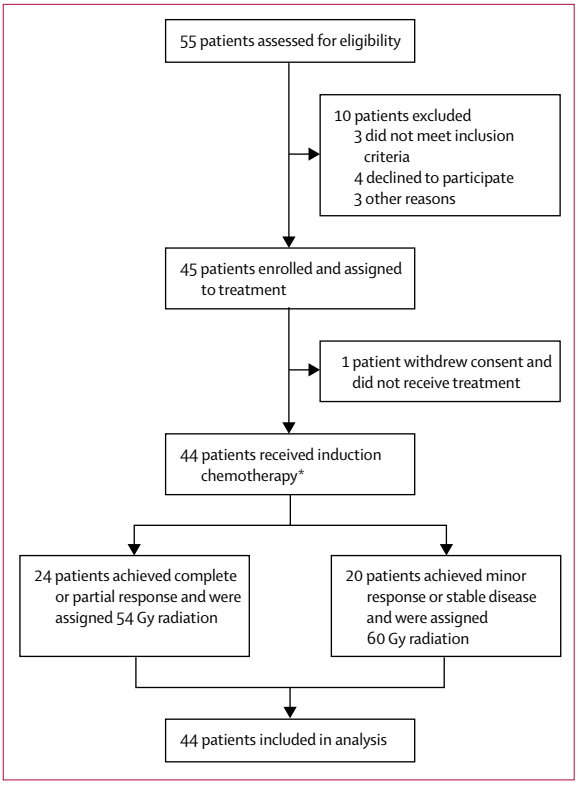


***Figure 1:*** **Trial profile**
*One patient had an allergic reaction to paclitaxel and was subsequently treated with carboplatin only, including during chemoradiotherapy.

were estimated with the Kaplan-Meier method. Data for adverse events, including 30-day mortality, were presented with descriptive statistics. Data for all endpoints were analysed in all eligible patients who completed protocol treatment. Post-hoc analysis of freedom from grade 3 or worse mucosal and oesophageal adverse events was compared between radiation dose groups with the log-rank test.

After this trial was started, several risk classification schemes for HPV-positive oropharyngeal cancer were proposed,[4,16,17] of which the International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S) has been internally and externally validated.[17–19] We did a post-hoc analysis to determine how many patients would be included in each ICON-S stage.

All data were centrally reviewed. Statistical analyses were done with SAS version 9.4. This trial is registered with ClinicalTrials.gov, numbers NCT02048020 and NCT01716195.

### 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 the final responsibility for the decision to submit for publication.

## Results

Between Oct 4, 2012, and March 3, 2015, we enrolled 45 patients, 26 with disease involving the tonsils and 19 with disease involving the base of tongue. All patients had evidence of p16-positive squamous-cell carcinoma of the oropharynx on biopsy and measurable disease at enrolment. One patient was removed from the study after withdrawal of consent (figure 1). The baseline characteristics of the remaining 44 patients included in the per protocol analysis are shown in table 1. The median age of patients was 60 years (IQR 54–67), and no patients were active smokers at enrolment.

After two cycles of induction chemotherapy, the median time to CT scan to assess response was 14 days (IQR 10–17). Five (11%) of 44 patients had complete response at all disease sites, and 19 (43%) patients had partial responses. These 24 patients were prescribed 54 Gy radiation. The remaining 20 (45%) patients had less than partial responses or stable disease and were prescribed 60 Gy radiation. No patient had locoregional or distant disease progression during induction chemotherapy. All patients completed induction chemotherapy and chemoradiotherapy, except one who had an allergic reaction to paclitaxel and was subsequently treated with carboplatin only, including weekly during chemoradiotherapy (target AUC 1·5) at the physician's discretion after achieving less than a partial response to induction chemotherapy. No patient discontinued treatment at any time. 37 (84%) of 44 patients received all planned cycles of weekly paclitaxel during chemoradiotherapy, and the remaining seven (16%) missed doses for various reasons, including toxic effects, social reasons, and patient's choice.

At the first assessment 3 months after completion of chemoradiotherapy, 37 (84%) of 44 patients had a complete response at all disease sites. Seven (16%) patients had partial responses and disease was found to be resolved fully on follow-up imaging. No patient underwent neck dissection for suspected residual disease.

Median follow-up was 30 months (IQR 26–37). One (2%) patient developed distant metastasis and three (7%) patients had locoregional disease recurrence; 2-year progression-free survival was 92% (95% CI 77–97) and 2-year locoregional control was 95% (80–99; figure 2). The distant metastasis occurred in a male patient aged 57 years who had had T2N2a squamous-cell carcinoma of the base of tongue at enrolment and had received 60 Gy radiation after a less than partial response to induction chemotherapy. Pulmonary metastasis was reported at 12 months after the completion of chemoradiotherapy and the patient was referred for systemic therapy, which led to resolution of disease. The three locoregional recurrences occurred in one man aged 51 years who had never smoked and had T1N2b poorly differentiated squamous-cell carcinoma disease involving the right tonsil at enrolment who

received 60 Gy radiation after a less than partial response to induction chemotherapy and had local recurrence 23 months after completion of chemoradiotherapy; one man aged 59 years who had a 20 pack-year smoking history and T4N2b poorly differentiated disease involving the base of tongue at enrolment who received 54 Gy radiation after a partial response to induction chemotherapy and developed regional recurrence in the left cervical neck 16 months after completion of chemoradiotherapy; and one man aged 63 years who had never smoked and had T2N2b moderately differentiated squamous-cell carcinoma involving the right tonsil at enrolment who received 60 Gy radiation after a less than partial response to induction chemotherapy and developed regional recurrence in the right cervical neck 15 months after the completion of chemoradiotherapy. None of these three patients had evidence of distant metastasis at the time of locoregional relapse, and all were without evidence of disease after surgical salvage.

No patients died during treatment or within 30 days of completion of chemoradiotherapy. One patient died during follow-up, 2 months after completing treatment. This patient, who had a history of depression before the study, died by suicide. 2-year overall survival was, therefore, 98% (95% CI 85–100, figure 3).

Treatment-emergent adverse events during induction chemotherapy were generally infrequent and mild, with no reported events of grade 4 or worse and 26 (39%) of 44 patients having grade 3 adverse events (table 2). The most common grade 3 adverse events during induction chemotherapy were leucopenia in 17 (39%) of 44 patients and neutropenia in five (11%), and the most common during chemoradiotherapy were dysphagia in four (9%) and mucocytosis in four (9%; table 2). There were no cases of neutropenic fever. Three (7%) of 44 patients required dose reductions of paclitaxel and carboplatin in cycle two of induction chemotherapy because of neutropenia. Two patients required admission to hospital during chemoradiotherapy, one for aspiration pneumonia that resolved with intravenous antibiotics, and one for severe anxiety and panic attacks. Reduced-dose radiotherapy was associated with a much lower frequency of late adverse events than in historical controls (appendix p 1).

Three (7%) patients had gastrostomy tubes placed prophylactically before the first week of chemoradiotherapy because of investigator concerns about baseline alimentary status. A further three (7%) patients needed reactive gastrostomy tubes placed during chemoradiotherapy due to grade 3 dysphagia and weight loss. Severe late adverse events related to radiotherapy were seen in only two (5%) of 44 patients. These were grade 3 dysphagia seen at 3 months. No patients had oesophageal stricture, stenosis, or aspiration pneumonia after chemoradiotherapy had ended. One (2%) patient remained dependent on a gastrostomy tube 3 months after treatment. No patient was dependent on a gastronomy tube at 6 months. In a post-hoc analysis, 2-year freedom from grade 3 or worse mucosal-oesophageal adverse events was 85% (95% CI 80–90) for patients who received 54 Gy radiation and 86% (80–90) for those who received 60 Gy (p=0·47). Two patients had second malignancies (one had prostate adenocarcinoma 12 months after the completion of chemoradiotherapy and one had cutaneous squamous-cell carcinoma of the cheek 6 months after), but these were not judged to be related to protocol therapy.

| | Patients (n=44) |
|---|---|
| **Ethnic origin** | |
| White | 40 (91%) |
| Hispanic | 3 (7%) |
| Black | 1 (2%) |
| **Zubrod score** | |
| 0 | 34 (77%) |
| 1 | 10 (23%) |
| **Smoking history** | |
| Never smoked | 30 (68%) |
| ≤10 pack-years | 3 (7%) |
| 10–20 pack-years | 2 (5%) |
| 20–40 pack-years | 4 (9%) |
| >40 pack-years | 5 (11%) |
| **Primary tumour site** | |
| Tonsil | 26 (59%) |
| Base of tongue | 18 (41%) |
| **T stage** | |
| T1 | 16 (36%) |
| T2 | 18 (41%) |
| T3 | 3 (7%) |
| T4 | 7 (16%) |
| **N stage** | |
| N0 | 2 (5%) |
| N1 | 3 (7%) |
| N2a | 9 (20%) |
| N2b | 19 (43%) |
| N2c | 10 (23%) |
| N3 | 1 (2%) |
| **AJCC stage** | |
| III | 2 (5%) |
| IV | 42 (95%) |
| **ICON-S stage*** | |
| I | 27 (61%) |
| II | 9 (21%) |
| III | 8 (18%) |
| **NRG risk group†** | |
| Low | 23 (52%) |
| Other | 21 (48%) |

AJCC=American Joint Committee on Cancer. ICON-S=International Collaboration on Oropharyngeal Cancer Network for Staging. *Assessed in a post-hoc analysis. †Eligible for NRG HN002 trial.

***Table 1*: Baseline characteristics**

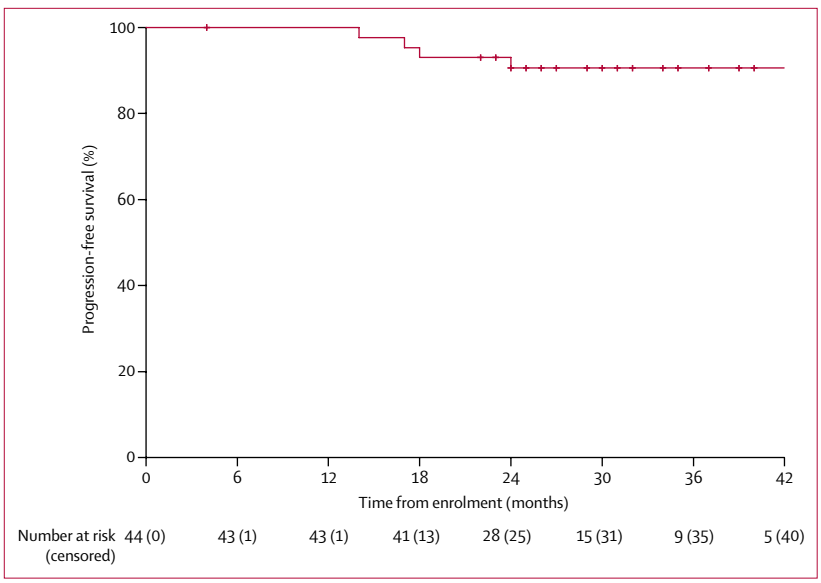


*Figure 2*: **Progression-free survival**

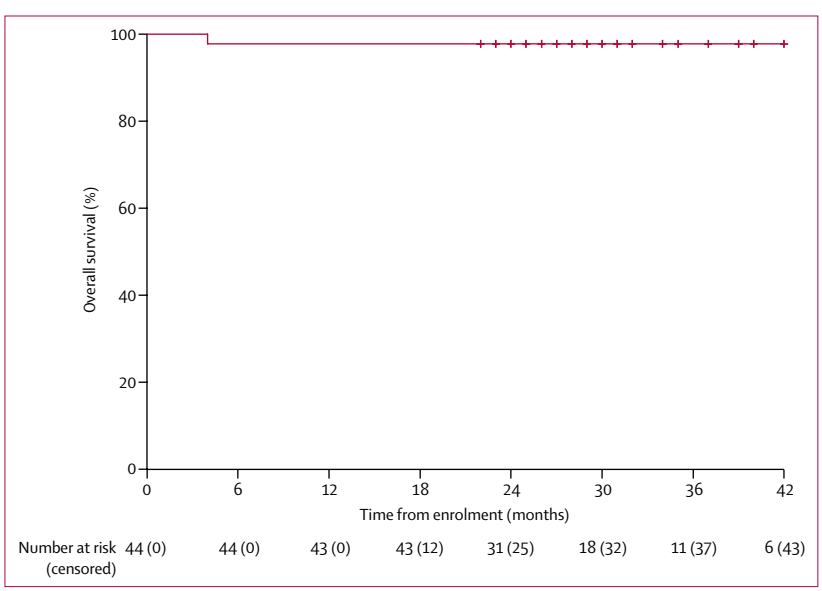


*Figure 3*: **Overall survival**

## Discussion

Our findings indicate that HPV-positive oropharyngeal squamous-cell carcinoma can be treated successfully with doses of radiation lower than the current standard of care. This regimen has the potential to alter standard practice for a disease in which treatment-emergent side-effects have historically been unacceptably high. It has been proposed that these cancers are more sensitive to therapeutic irradiation and cytotoxic chemotherapy than HPV-negative cancers, and that they could be treated effectively with reduced radiotherapy doses, but prospective data on suitable regimens have not been available.

Standard chemoradiotherapy regimens are associated with substantial toxic effects. Mucosal and oesophageal effects can be dose limiting. Reducing the radiation dose in selected patients with favourable biology (ie, HPV-positive tumours), therefore, has the potential to improve tolerability of treatment while preserving long-term function. Organs involved in salivary production, swallowing, and mucosal integrity, among others, have dose-related adverse effects. Probability models for complications in normal tissue show that for every 1 Gy increase in the mean dose to the parotid gland, the likelihood of xerostomia 1 year after the end of treatment increases by around 5%.[20] Likewise, increasing doses to the pharyngeal constrictor muscles, larynx, and cricopharyngeal inlet increases the probability of late dysphagia and gastrostomy-tube dependence, with a volume-dependent threshold for radiation-induced toxic effects at 55–60 Gy.[21,22] Studies using patient-reported outcomes have also shown associations between decreasing quality of life with increasing doses in survivors of head and neck cancer.[23]

Correlative biomarker studies have convincingly established HPV status as the most important predictor of treatment outcomes in patients with oropharyngeal carcinoma; therefore HPV staining, typically assessed through the surrogate marker p16, is now done routinely. In an analysis of 433 patients with oropharyngeal carcinoma treated by chemoradiotherapy to the standard dose of 70 Gy, the Radiation Therapy Oncology Group[4] found striking differences between patients with HPV-positive and HPV-negative tumours in 3-year locoregional disease control (86% *vs* 65%) and overall survival (82% *vs* 57%). Of note, however, the risk of distant metastasis did not differ by HPV status (10% *vs* 13%). Other study findings support a shift towards recurrence being due mainly to distant metastasis in patients with HPV-positive disease.[16] These findings raise the question of whether a sequential treatment strategy of induction chemotherapy before chemoradiotherapy in an attempt to address micrometastasis would be optimum in patients with HPV-positive oropharyngeal carcinoma. In our study, only one patient had distant metastasis after treatment despite the inclusion of patients who were possibly at high risk of metastasis by T stage (23% had T3–T4 tumours at enrolment) and smoking history (25% >10 pack-years).

Although HPV staining has so far been used only for prognostic purposes, data, including ours, suggest that treatment could be individualised for patients with HPV-positive head and neck squamous-cell carcinoma. Survival with reduced doses of radiation in this study compared favourably with that seen in historical controls treated with the standard dose of 70 Gy for HPV-positive oropharyngeal carcinoma. Although differences between studies in patients and disease characteristics make direct comparisons impossible, it is apparent that

reduced-dose radiotherapy was associated with a much lower frequency of late adverse events than in historical controls. The closest comparison is with the ECOG 2399 study,[6] in which the same chemoradiotherapy regimen was used except that radiation was given to a dose of 70 Gy. 2-year overall survival and 2-year progression-free survival were 95% and 86%, respectively, which are similar to our findings of 98% and 92% with 15–20% less radiation. Moreover, in ECOG 2399, the incidence of grade 3 or worse dysphagia was 54% and of mucositis was 53%, compared with 9% for both in this study. Additionally, the proportion of patients needing gastrostomy-tube placement during treatment was much lower in our study (7% *vs* 26%). In a subset analysis of two prospective trials of chemoradiotherapy for locally advanced oropharyngeal cancer, with radiation doses of 70 Gy, the incidence of grade 3 or worse mucositis was 56%.[24] In that analysis, gastrostomy-tube dependence at 6 months was 17%, whereas in our study no patients had gastrostomy tubes at 6 months.

The mechanism of HPV-mediated response to radiotherapy is unclear. The most direct explanation is that HPV infection and the subsequent degradation of the p53 and retinoblastoma proteins by the viral products E6 and E7 somehow increase radiosensitivity of the host tumour, perhaps by interfering with mechanisms such as DNA repair, repopulation signalling, and cell-cycle redistribution.[25] Increasing evidence indicates the importance of the micro-environment in HPV-mediated radiation response. For example, radiotherapy increases the host immune response to viral antigens, which are expressed on tumours.[7,8] Elevated numbers of tumour-infiltrating lymphocytes and circulating white blood cells in patients with HPV-positive head and neck cancer are associated with improved prognosis, which suggests that the adaptive immune system contributes to the suppression of tumour progression.[26,27]

The optimum reduced-dose treatment regimens for patients with HPV-positive head and neck cancers are being investigated by various groups. The ECOG has completed a single-arm study of induction chemotherapy followed by chemoradiotherapy with reduced-dose radiation and cetuximab in patients with HPV-positive oropharyngeal cancer who achieved complete response.[28] We chose our seemingly aggressive dose-reduction approach on the basis of data that suggested exquisite radiosensitivity and robust and rapid responses to treatment in patients with HPV-positive oropharyngeal carcinoma.[28–30] Chera and colleagues[31] found in a phase 2 study of patients with HPV-positive oropharyngeal carcinoma that chemoradiotherapy with doses of 60 Gy radiation and weekly cisplatin was associated with pathological response in 86% of patients, based on biopsy and neck dissection after treatment. Data even suggest that radiotherapy without chemotherapy might be appropriate to treat HPV-positive oropharyngeal carcinoma.[32,33]

| | Induction chemotherapy (n=44) | | Chemoradiotherapy (n=44) | |
|---|---|---|---|---|
| | Grades 1–2 | Grade 3 | Grades 1–2 | Grade 3 |
| Anaemia | 39 (87%) | 1 (2%) | 27 (61%) | 1 (2%) |
| Anorexia | 4 (9%) | 1 (2%) | 9 (20%) | 2 (4%) |
| Anxiety | 7 (16%) | 0 | 4 (9%) | 1 (2%) |
| Arthralgia | 9 (20%) | 1 (2%) | 4 (9%) | 0 |
| Bone pain | 6 (14%) | 0 | 2 (5%) | 0 |
| Constipation | 3 (7%) | 0 | 17 (39%) | 0 |
| Cough | 2 (5%) | 0 | 16 (36%) | 0 |
| Dehydration | 4 (9%) | 1 (2%) | 9 (20%) | 1 (2%) |
| Dysphagia | 20 (23%) | 0 | 19 (43%) | 4 (9%) |
| Hypokalaemia | 8 (18%) | 1 (2%) | 4 (9%) | 0 |
| Hypomagnesaemia | 5 (11%) | 0 | 5 (11%) | 0 |
| Hyponatraemia | 20 (23%) | 2 (5%) | 6 (14%) | 2 (5%) |
| Increased creatinine | 18 (41%) | 0 | 4 (9%) | 0 |
| Leucopenia | 23 (52%) | 17 (39%) | 37 (84%) | 3 (7%) |
| Mucositis | 16 (36%) | 1 (2%) | 34 (77%) | 4 (9%) |
| Nausea | 8 (18%) | 1 (2%) | 18 (41%) | 1 (2%) |
| Neuropathy | 9 (20%) | 0 | 3 (7%) | 0 |
| Neutropenia | 18 (41%) | 5 (11%) | 9 (20%) | 0 |
| Pneumonia | 0 | 0 | 1 (2%) | 1 (2%) |
| Dermatitis | 0 | 0 | 33 (75%) | 3 (7%) |
| Thrombocytopenia | 20 (23%) | 0 | 0 | 0 |
| Voice alteration | 0 | 0 | 6 (14%) | 0 |
| Vomiting | 5 (11%) | 0 | 0 | 0 |
| Xerostomia | 1 (2%) | 0 | 42 (95%) | 1 (2%) |

Grade 1–2 events that occurred in ≥10% of patients and all grade 3 events are shown. Some patients had more than one event. No grade 4 events were reported. No patients died from adverse events.

***Table 2*: Treatment-emergent adverse events**

Our trial had some limitations. First, we acknowledge that this single-arm trial was small, which leads to inherent challenges in drawing definitive conclusions and doing subset analyses. The heterogeneity of our study population in terms of eligibility criteria might also be a confounding factor. Variables such as smoking history, response to induction chemotherapy, and advanced T and N stages are proposed to be important for prognosis.[4,16,34] Finally, this study was not designed to assess the acceptability of induction chemotherapy for oropharyngeal cancer but to investigate the use of this approach as a means of selecting patients who might benefit from reduced-dose radiotherapy.

An additional limitation was that central review was not compulsory for assessment of p16 status. Pathologists generally score tumours as positive for HPV on the basis of strong and diffuse nuclear and cytoplasmic staining in more than 70% of the sample, but false-positive results have been reported in 2–7% of tests.[35,36] Although p16 expression is a reliable surrogate for tumour HPV status (concordance 96%),[37] it is not 100% accurate. Thus, it is possible that we included patients with HPV-negative

disease. Patients with false-positive p16 results do not have the favourable prognostic benefits associated with true HPV positivity.[38]

Lastly, the trial was started before the widespread adoption of risk classification schemes for HPV-positive oropharyngeal cancer proposed by Ang and colleagues[4] and O'Sullivan and colleagues.[17] The ICON-S classification system has also since been developed and internally and externally validated.[17–19] The heterogeneity in certain risk factors among the patients we included might cause difficulty in identifying the subset of patients for whom our reduced-dose regimen will be optimum.

In this prospective trial, we found that induction chemotherapy followed by chemoradiotherapy with the radiation dose reduced by 15–20% from the standard yielded similar 2-year progression-free and overall survival to standard radiotherapy regimens in patients with HPV-positive oropharyngeal carcinoma, with an acceptable toxicity profile. This treatment approach seems to hold considerable promise for a disease that is rapidly increasing in incidence. Our findings also provide reassurance to patients participating in ongoing trials of reduced-dose radiotherapy regimens. We believe that reduced-dose regimens have the potential to usher in a new standard of care for a disease in which the radiation dose has largely been the same for upwards of 50 years and might be exposing patients with HPV-positive head and neck cancers to overtreatment and an unacceptably high risk of toxic effects. A phase 3 study to investigate the efficacy of our regimen further is being planned.

#### Contributors

AMC, LQ, KK, and MED designed the study. AMC, KK, and MED did the literature search. All authors collected and interpreted the data. AMC, CF, P-CW, VB, HM, and EK did the data analysis and AMC, CF, P-CW, VB, and JG prepared the figures. All authors contributed to the writing of the report.

#### Declaration of interests

We declare no competing interests.

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