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ORIGINAL REPORT

E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx— ECOG-ACRIN Cancer Research Group

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ABSTRACT

Purpose

Human papillomavirus (HPV)–associated oropharyngeal squamous cell carcinoma (OPSCC) is treatment-responsive. Definitive chemoradiation results in high cure rates but causes long-term toxicity and may represent overtreatment of some patients. This phase II trial evaluated whether complete clinical response (cCR) to induction chemotherapy (IC) could select patients with HPV-associated OPSCC for reduced radiation dose as a means of sparing late sequelae.

Methods

Patients with HPV16 and/or p16-positive, stage III-IV OPSCC received three cycles of IC with cisplatin, paclitaxel, and cetuximab. Patients with primary-site cCR to IC received intensity-modulated radiation therapy (IMRT) 54 Gy with weekly cetuximab; those with less than cCR to IC at the primary site or nodes received 69.3 Gy and cetuximab to those regions. The primary end point was 2-year progression-free survival.

Results

Of the 90 patients enrolled, 80 were evaluable. Their median age was 57 years (range, 35 to 73 years), with the majority having stage T1-3N0-N2b OPSCC and a history of ≤ 10 pack-years of cigarette smoking. Three cycles of IC were delivered to 77 of the 80 patients. Fifty-six patients (70%) achieved a primary-site cCR to IC and 51 patients continued to cetuximab with IMRT 54 Gy. After median follow-up of 35.4 months, 2-year progression-free survival and overall survival rates were 80% and 94%, respectively, for patients with primary-site cCR treated with 54 Gy of radiation (n = 51); 96% and 96%, respectively, for patients with < T4, < N2c, and ≤ 10 pack-year smoking history who were treated with ≤ 54 Gy of radiation (n = 27). At 12 months, significantly fewer patients treated with a radiation dose ≤ 54 Gy had difficulty swallowing solids (40% *v* 89%; $P = .011$) or had impaired nutrition (10% *v* 44%; $P = .025$).

Conclusion

For IC responders, reduced-dose IMRT with concurrent cetuximab is worthy of further study in favorable-risk patients with HPV-associated OPSCC. Radiation dose reduction resulted in significantly improved swallowing and nutritional status.

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INTRODUCTION

Human papillomavirus (HPV)–associated oropharyngeal squamous cell carcinoma (OPSCC) incidence is rising in developed countries.[1] In the United States, the proportion of HPV-associated OPSCC is now 71%.[2] HPV-associated OPSCCs are clinically and molecularly distinct and have better overall survival (OS) than HPV-negative OPSCC.[3,4] The first prospective trial to correlate tumor HPV status with survival was E2399, which investigated induction chemotherapy (IC) followed by paclitaxel concomitant with 70 Gy of radiotherapy.[4,5] Patients with HPV-positive OPSCC, compared with those with HPV-negative OPSCC, had significantly improved response to IC (82% *v* 55%; $P = .01$), 2-year progression-free survival (PFS; 85% *v* 50%; $P = .05$) and OS (94% *v* 58%; $P = .004$).[4] This excellent survival for

ASSOCIATED CONTENT

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Appendix

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patients with HPV-associated OPSCC, often defined by overexpression of the surrogate biomarker p16, has been corroborated.[6,7] Large series have identified high tumor stage and significant tobacco exposure as poor prognostic features.[6-8] Concurrent high-dose cisplatin and 70-Gy radiation achieve high cure rates in HPV-associated OPSCC.[6,7] However, significant acute and late toxicities result from chemoradiation.[9-11] A mean radiation dose of > 47 Gy to pharyngeal constrictors, 25-30 Gy to parotid, and > 30 Gy to thyroid glands may cause moderate to severe swallowing impairment, aspiration, feeding-tube dependence, stricture, xerostomia, and hypothyroidism.[12-14] Concurrent cisplatin significantly increases acute toxicity[9] and may increase late noncancer mortality.[11] Patients with HPV-associated OPSCC have a younger median age and lower comorbidity index compared with those with HPV-negative disease, and may carry radiation sequelae for decades.

In head and neck squamous cell cancer, alternate radiosensitizers may reduce toxicity and IC may identify radiosensitive tumors. Cetuximab, an epidermal growth factor receptor-directed antibody, is active in head and neck carcinoma as monotherapy,[15] with chemotherapy,[16,17] or when added to radiation.[18] No increase in noncancer mortality has been detected.[19] An analysis in p16-positive OPSCC revealed a hazard ratio of 0.38 (range, 0.15 to 0.94) for OS, with the addition of cetuximab to radiation.[20]

Trials using cetuximab-containing IC[21-23] demonstrated a 69% clinical complete response (cCR) at the primary site, reducing tumor burden to subclinical disease. We hypothesized that in treatment-responsive patients, doses analogous to adjuvant radiation doses would be adequate for subclinical disease. A 22% reduction of radiation dose to treat the subclinical disease could reduce late sequelae of xerostomia and dysphagia, correlated with radiation doses exceeding 55 Gy.[12,24] Furthermore, an association between chemoresponsiveness and locoregional control with definitive radiation has been demonstrated in a series of trials from the University of Michigan, with responsiveness correlated with HPV copy number.[25,26] Thus, patients with HPV-associated cancer and a primary-site cCR to IC were hypothesized to constitute a subgroup suitable for radiation dose reduction.

Based on these considerations, we tested whether reduction of radiation to 54 Gy, together with substitution of cetuximab for concurrent cisplatin, would minimize acute and late toxicity among patients with HPV-associated OPSCC whose response to IC provided a dynamic biomarker of radioresponsiveness. This paradigm would be deemed worthy of further study should it achieve comparable 2-year PFS to that of the patients positive for HPV treated in the E2399 trial.

METHODS

Study Design and Participants

This phase II single-arm study enrolled patients at 16 Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) sites between March 2010 and October 2011. Eligible patients had newly diagnosed resectable, stage III/IV OPSCC positive for p16 immunohistochemistry (IHC) and/or HPV16 in situ hybridization determined by a central laboratory.[27] Patients with unresectable disease, as previously defined,[28] were ineligible. ECOG performance status of 0-1 and adequate organ function (granulocyte count ≥ 1,000/mm^3; platelet count, ≥ 100,000/mm^3; total serum bilirubin level, ≤ 1.5 mg/dL; and creatinine clearance, ≥ 60 mL/min) were also required. Computed tomography (CT) or magnetic resonance imaging was mandatory. At baseline, the primary and cervical nodes were characterized as measurable (≥ 2.0 cm in at least one dimension with clinical and conventional radiographic methods or ≥ 1.0 cm with spiral CT scan) or nonmeasurable (< 2.0 cm or < 1.0 cm, respectively); at least one measurable lesion was required.

An institutional review board approved the protocol at the respective sites, and all patients provided written informed consent. This study was registered with ClinicalTrials.gov (NCT01084083).

IC and Response Assessment

Eligible patients received IC with cisplatin 75 mg/m^2 on day 1; paclitaxel 90 mg/m^2 on days 1, 8, and 15; and cetuximab 400 mg/m^2 on day 1 of cycle 1, followed by cetuximab 250 mg/m^2 weekly. Cycles were repeated every 21 days for three cycles. If cisplatin was not tolerated, substitution with carboplatin area under the curve (AUC) 5 was allowed after the first cycle.

Within 14 days of completing IC, clinical response at the primary and involved nodal sites was determined by a complete head and neck clinical examination, with mandatory fiberoptic nasopharyngolaryngoscopy by the initial head-and-neck surgeon, as well as CT or magnetic resonance imaging. Primary-site cCR was defined as complete disappearance of the primary lesion on manual and endoscopic inspection. Nodal cCR was defined as complete resolution of palpable adenopathy. Clinical and radiographic responses at primary and nodal areas were determined separately. A clinical partial response (PR) was defined as ≥ 30% decrease in the sum of the longest diameters of measurable lesions. Stable disease (SD) was defined as neither PR nor disease progression (PD). PD was defined as ≥ 20% increase in the sum of longest diameters of measurable disease or appearance of new lesions. The primary site clinical response determined the radiation dose to the oropharynx and the nodal clinical response determined the radiation dose to involved nodes.

Concomitant Cetuximab/Radiotherapy and Response Assessment

Patients with primary-site cCR to IC received 54 Gy in 27 fractions (intensity-modulated radiation therapy [IMRT]) to the primary site, whereas those with less than cCR were to receive 69.3 Gy in 33 fractions. Involved nodes with cCR to IC received 54 Gy in 27 fractions to nodes and those with less than cCR received 69.3 Gy in 33 fractions. A 1-cm margin was mandated around involved nodes to minimize the dose to the oropharynx. Uninvolved cervical nodes received 51.3 Gy in 27 fractions (1.9 Gy per fraction) to the clavicles bilaterally. Both cohorts continued weekly cetuximab to the end of radiotherapy. The Quality Assurance and Review Center and ECOG-ACRIN dosimetrist reviewed radiation treatment plans in real time. Treatment response was evaluated 8 weeks after completion of chemoradiation by the radiographic method used at baseline. Patients were evaluated every 6 months for 2 years. Adverse events were assessed after each cycle of IC and weekly during concomitant cetuximab/radiation, and graded according to Common Terminology Criteria for Adverse Events (version 4.0).

Toxicity Assessment Based on Radiation Dose

Late effects of treatment of lower versus standard-dose IMRT on patient-reported outcomes were measured at baseline, 12, and 24 months posttreatment using the Vanderbilt Head and Neck Symptom Survey version 2 (VHNSSv2), a 50-item survey that comprehensively assesses acute and late effects on patients with head and neck cancer treated with radiation-based therapy.[29] This manuscript reports only those results from the domains respecting difficulty swallowing solids and impaired nutrition. The questions in these domains are listed in Appendix Table A1 (online only).

Statistical Analysis

The study was designed to estimate the 2-year PFS rate for patients with HPV-associated OPSCC who achieved a primary-site cCR after IC and received reduced-dose radiation. Based on prior trials, at least a 69% cCR was expected.[21-23] A sample size of 75 eligible patients was required for at least 52 to be assigned reduced-dose radiation. To allow for 10% ineligibility, 83 patients were to be accrued. We hypothesized that 2-year PFS in patients who achieved primary-site cCR after IC and received 54 Gy of radiation would be similar to that observed in E2399 (85%). Widths of 95% CIs for the 2-year PFS rate were provided under various assumptions in the design.

Secondary end points included 2-year OS, clinical and radiologic responses at the primary and nodal sites after IC and after overall treatment, and safety and toxicity of treatment. OS was defined as the time from registration to death, censoring at last date of contact. PFS was defined as the time from registration to PD or death due to any cause, censoring patients without PD or death at the time of last disease evaluation. OS and PFS were estimated by the Kaplan-Meier method, along with 95% CI. A post hoc analysis was performed to estimate 2-year PFS and OS among patients without T4 or N2C disease and a smoking history of < 10 pack-years treated with 54 Gy of radiation, based on hypothesis-generating analyses in other series.[7,8] A log-rank test was used to compare OS or PFS between groups. Date of registration is time zero in estimating the curves. Because radiation-dose cohorts are defined 9 weeks later, postinduction outcome can be approximated by right-shifting curves by 9 weeks.

The Fisher exact test was used to compare the patient-reported outcome event rate at 12 and 24 months' posttreatment using the 50-item VHNSSv2. Only patients who were progression free at the specified time who completed at least 50% of the items for a given symptom domain were considered evaluable for analysis; for each domain, an average score of ≥ 2 was considered as a clinically significant event. The *P* values reported in this analysis are nominal, without adjustment for multiple comparisons, given the exploratory nature of the analysis, and all are two-sided.

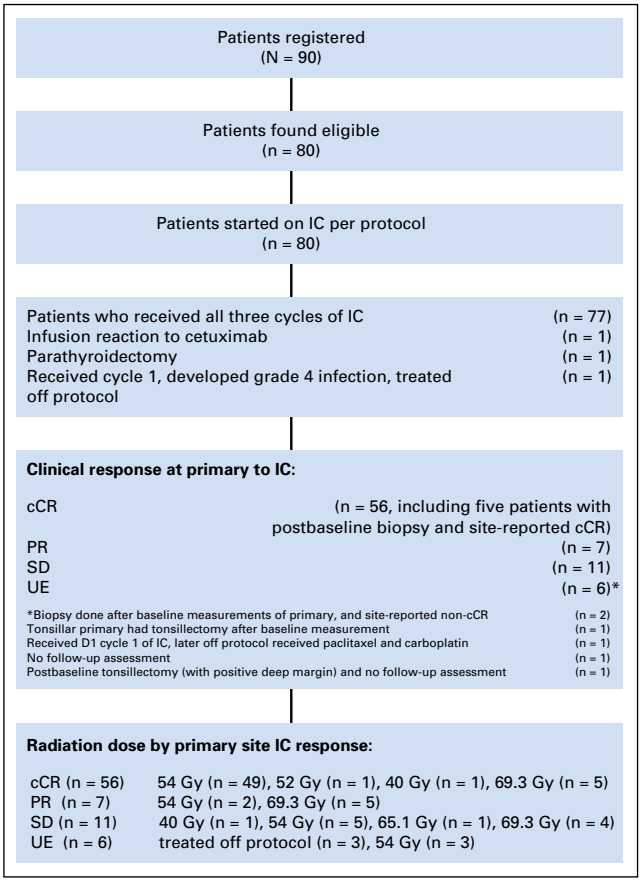

Fig 1. Patient flow diagram. cCR, clinical complete response; IC, induction chemotherapy; PR, partial response; SD, stable disease; UE, unevaluable.

RESULTS

Patient Characteristics

Ninety patients were enrolled at 16 ECOG-ACRIN centers between March 2010 and October 2011. Nine patients were ineligible (baseline scans out of window in three, no measurable disease in five, cardiac history in one, and one withdrew before treatment). The CONSORT diagram showing the treatment disposition of the 80 eligible patients is shown in Figure 1 and patient characteristics are listed in Table 1. The median age was 57 years (range, 35 to 73 years) and the majority had stage T1-3 (89% of 80 eligible patients), N0-N2b (69% of eligible patients) OPSCC and were not current smokers (84%). Ninety-six percent were p16 positive. HPV ISH and p16 status are listed in Appendix Table A2 (online only).

Treatment Delivery and Response

All three cycles of IC were administered to 77 of 80 eligible patients (96.2%). Three eligible patients received only one cycle of IC due to a grade 4 cetuximab infusion reaction, grade 3 infection, and an unrelated surgical procedure, respectively. Cisplatin dose was reduced for 14 patients who experienced grade 3 or 4 hematologic toxicity, neuropathy, or tinnitus. Carboplatin was substituted in two patients who had grade 3 neuropathy. Cetuximab dose was modified for 18 patients during IC, because of grade 3 or 4 acneiform rash, mucositis, or hypomagnesemia.

Clinical responses assessed within 14 days of completion of IC are listed in Table 2. Among the 77 patients who completed IC, a primary-site cCR was observed in 56 (70%; 95% CI, 59% to 80%), PR in seven, and SD in 11. Three patients were deemed unevaluable at the primary site: One underwent extensive primary-site tumor biopsy and two underwent tonsillectomy after baseline tumor measurements. Nodal cCR was observed in 46 of the 77 patients (58%; 95% CI, 46% to 68%), and four patients had no follow-up assessment of the cervical lymph nodes.

All 77 patients who completed IC proceeded to IMRT with cetuximab. Of the 56 patients with a primary-site cCR, 51 proceeded to 54 Gy of radiation per protocol and five received 69.3 Gy (considered a protocol deviation). Of the 51 who proceeded with 54 Gy per protocol, 49 received 54 Gy of radiation, one discontinued at 52 Gy because of grade 3 fatigue, and one at 40 Gy because of grade 3 mucositis and acneiform rash. These 51 patients who achieved cCR to IC and were treated with reduced-dose radiation constitute the per-protocol analysis set for low-dose radiation. Comparisons of outcome by low- and high-dose therapy as delivered are listed in Appendix Table A2.

Among the 18 patients with less than cCR at the primary site after IC, 10 proceeded to 69.3 Gy of radiation per protocol, and eight (two with PR, six with SD) proceeded to 54 Gy of radiation (considered a protocol deviation). The three unevaluable patients who had no residual primary tumor on clinical examination after

Table 1. Patient Characteristics

Characteristic	All (N = 80), No. (%)	cCR to IC Treated With ≤ 54 Gy (n = 51),* No. (%)	Other (n = 29),† No. (%)
Median age, years	57	58	56
Range	35-73	43-71	35-73
Sex			
Male	76 (95)	49 (96)	27 (93)
Female	4 (5)	2 (4)	2 (7)
ECOG performance status			
0	73 (91)	45 (88)	28 (97)
1	7 (9)	6 (12)	1 (3)
Race			
White, Hispanic	6 (8)	6 (12)	0 (0)
White, Non-Hispanic	66 (83)	40 (78)	26 (90)
White, unknown ethnicity	2 (3)	1 (2)	1 (3)
Black	4 (5)	2 (4)	2 (7)
Asian	1 (1)	1 (2)	0 (0)
NA	1 (1)	1 (2)	0 (0)
TNM stage			
III	12 (15)	7 (14)	6 (21)
IVA/B	68 (85)	44 (86)	23 (79)
T1	18 (23)	11 (22)	7 (24)
T2	41 (51)	26 (51)	15 (52)
T3	12 (15)	8 (16)	4 (14)
T4	8 (10)	6 (10)	2 (7)
N0-N1	13 (15)	7 (14)	6 (21)
N2 A, B	42 (54)	29 (57)	13 (45)
N2C	25 (31)	15 (29)	10 (34)
M0	80 (100)	51 (100)	29 (100)
HPV status			
HPV ISH+/P16 IHC−	3 (4)	1 (2)	2 (7)
HPV ISH−/P16 IHC +	15 (19)	14 (27)	1 (3)
HPV ISH+/P16+	62 (77)	36 (71)	26 (90)
Smoking status			
Never smoked	37 (46)	23 (45)	14 (48)
Pipe or cigar smoker only	4 (5)	2 (4)	2 (7)
Cigarette, ≤ 10 pk-yr	8 (10)	5 (10)	3 (10)
Cigarette, > 10-20 pk-yr	9 (11)	7 (14)	2 (7)
Cigarette, > 20 pk-yr	22 (28)	14 (27)	8 (28)
Current smoker			
No	67 (84)	42 (82)	25 (86)
Yes	13 (16)	9 (18)	4 (14)
Alcohol history			
< 1 drink per month	8 (10)	8 (16)	0 (0)
1-10 drinks per week	30 (37)	20 (40)	10 (34)
11-30 drinks per week	13 (16)	5 (10)	8 (28)
Unknown	29 (36)	18 (35)	11 (38)
Currently consuming alcohol			
Yes	50 (63)	32 (63)	18 (62)
No	30 (37)	19 (37)	11 (38)

Abbreviations: cCR, clinical complete response; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; IC, induction chemotherapy; IHC, immunohistochemistry; IMRT, intensity-modulated radiation therapy; ISH, in situ hybridization; NA, not applicable; pk-yr, pack-year.
*Includes patients with cCR to IC treated with ≤ 54 Gy (n = 51; Fig 1).
†Includes all other patients treated on this protocol outlined in CONSORT diagram (n = 29; Fig 1).

IC proceeded to 54 Gy of radiation. Therefore, a total of 62 of 80 eligible patients (77.5%) proceeded to 54 Gy of radiation and weekly cetuximab (51 with cCR at the primary site, eight with less than cCR at the primary site, and three unevaluable patients). The results of the PFS and OS analyses for all 62 patients treated with 54 Gy of radiation are listed in Appendix Table A3 (online only).

Among the nine patients assigned to 69.3 Gy of radiation per protocol, one discontinued after 65 Gy, because of grade 3 mucositis and acneiform rash. The median IMRT duration was 6 weeks for the 54-Gy and 7 weeks for the 69.3-Gy subgroups, respectively. Cetuximab dose modifications were required during IMRT for 22 of 77 patients (28%) for grade 3 rash, thromboembolism, mucositis, radiation dermatitis, and sepsis.

Toxicity

A summary of acute toxicity among all 89 eligible and ineligible patients who received any treatment is listed in Appendix Table A4 (online only). During IC, the most common grade 3 or 4 adverse events were acneiform rash (28%), lymphopenia (6%), and neutropenia (12%). With 54 Gy of radiation and concurrent cetuximab, the most frequent grade 3 adverse events were

Table 2. Post–Induction Chemotherapy Response and Overall Response to IMRT/Cetuximab

Chemotherapy	Primary, No. (%)		Nodal, No. (%)	
	Clinical	Radiographic	Clinical	Radiographic
Response to IC (N = 80)				
CR	56 (70)	39 (49)	46 (58)	4 (5)
PR	7 (9)	22 (28)	21 (26)	56 (70)
SD	11 (14)	9 (11)	8 (10)	17 (22)
UE	6 (8)*	10 (13)	5 (6)	3 (4)
Overall response to IC and IMRT/cetuximab (N = 80)				
CR	68 (85)	59 (74)	67 (84)	39 (49)
PR	0	6 (8)	6 (8)	37 (46)
SD	6 (8)	5 (6)	4 (5)	1 (1)
UE	6 (8)*	10 (13)	3 (4)	3 (4)

Abbreviations: CR, complete response; IC, induction chemotherapy; IMRT, intensity-modulated radiation therapy; PR, partial response; SD, stable disease; UE, unevaluable.
*Three patients received less than one cycle of ICT, and three patients had extensive primary tumor biopsy/tonsillectomy of primary after baseline tumor measurements were submitted.

mucositis (30%), dysphagia (15%), acneiform rash (12%), radiation dermatitis (7%), and lymphopenia (12%). The patients treated with 69.3 Gy of radiation and cetuximab had more frequent grade 3 mucositis (47%), dysphagia (29%), acneiform rash (24%), radiation dermatitis (12%), thromboembolism (6%), and lymphopenia (29%). The incidence of grade 4 toxicity was less than 5% in both cohorts.

The VHNSSv2 was completed at 12 months by 42 eligible patients treated with $<$ 54 Gy of radiation and nine with 69.3 Gy of radiation. At 12 months, significantly fewer patients treated with $\leq$ 54 Gy of radiation had difficulty swallowing solids (40% *v* 89%; P = .011) or had impaired nutrition (10% *v* 44%; P = .025).

PFS and OS

Data analyses of PFS and OS occurred after a median follow-up of 35.4 months (range, 3.9 to 41.6 months) among 69 surviving eligible patients (Table 3). At the time of this analysis, 11 of 80 evaluable patients had died, including eight of disease progression, one on-treatment sudden death without apparent cause after 56 Gy of IMRT and cetuximab, one death 4 months after termination from study while on nonprotocol treatment, and one death 2 months posttreatment as a result of accidental drowning. Two patients withdrew consent to follow-up at 3.9 and 7.7 months. Minimum follow-up for the remaining patients is 16 months. The 2-year PFS estimate for patients with a primary-site cCR treated to 54 Gy of radiation (n = 51) was 80% (95% CI, 65% to 89%; Fig 2). The 2-year OS for these 51 patients was 94% (95% CI, 82% to 98%; Fig 2). For all 80 evaluable patients, 2-year PFS was 78% (95% CI, 67% to 86%) and OS was 91% (95% CI, 82% to 96%).

In a post hoc analysis, the effect of patients' smoking history was evaluated. Among all patients treated with $\leq$ 54 Gy of radiation, 2-year PFS was significantly higher among patients with $\leq$ 10 pack-years compared with those with $>$ 10 pack-years of smoking (92% *v* 57%; P = .0014). A statistically significant difference in 2-year OS was also observed (93% *v* 86%; P = .040). Subset analysis combining tumor and nodal status with smoking history revealed a statistically significant difference in the 2-year PFS estimate for the subset of patients with a $\leq$ 10 pack-year smoking history, $<$ T4, $<$ N2c (n = 27) compared with those with T4 or N2c or $>$ 10 pack-year smoking history (n = 35) of 96% versus 71% (P = .010); the corresponding 2-year OS was 96% versus 91% (P = .13; Fig 3). The only death in the favorable-risk group was due to accidental drowning.

Table 3. Two-Year PFS and OS in Subsets Treated in the E1308 Trial

Cohort	2-Year PFS (95% CI)	2-Year OS (95% CI)
All patients (N = 80)	0.78 (0.67 to 0.86)	0.91(0.82 to 0.96)
cCR to IC, RRD 54 Gy (n = 51)	0.80 (0.65 to 0.89)	0.94 (0.84 to 0.99)
All cCR/PR/SD to IC, RRD $\leq$ 54 Gy (n = 62)	0.81 (0.69 to 0.89)	0.93 (0.83 to 0.97)
SRD (n = 15)	0.67 (0.38 to 0.85)	0.87 (0.56 to 0.96)
Subsets cCR to IC, treated on RRD (n = 51)		
Smoker $\leq$ 10 pk-yr (n = 30)	0.90 (0.71 to 0.97)	0.97 (0.79 to 0.995)
Smoker $>$ 10 pk-yr (n = 21)	0.65 (0.41 to 0.82)	0.90 (0.66 to 0.97)
Smoker $\leq$ 10 pk-yr, and $<$ T4N2c (n = 21)	0.95 (0.71 to 0.99)	0.95 (0.71 to 0.99)
Smoker $>$ 10 pk-yr or T4 or N2c (n = 30)	0.69 (0.49 to 0.83)	0.93 (0.75 to 0.98)
Non-T4a (n = 45)	0.84 (0.69 to 0.92)	0.95 (0.83 to 0.99)
T4a (n = 6)	0.50 (0.11 to 0.80)	0.83 (0.27 to 0.97)
N2c (n = 15)	0.73 (0.44 to 0.89)	0.93 (0.61 to 0.99)
Non-N2c (n = 36)	0.82 (0.65 to 0.92)	0.94 (0.79 to 0.99)

Abbreviations: cCR, complete clinical response; IC, induction chemotherapy; pk-yr, pack-year; OS, overall survival; PFS, progression-free survival; PR, partial response; RRD, reduced radiation dose; SD, stable disease; SRD, standard radiation dose.

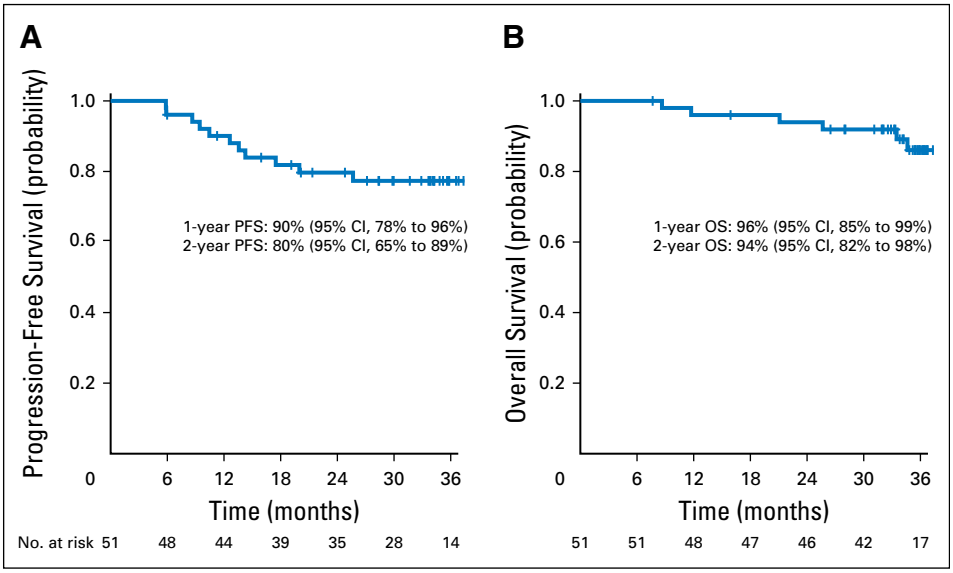

Fig 2. PFS (A) and OS (B) in cohort with clinical complete response to induction chemotherapy treated with low-dose radiation of 54 Gy (n = 51). OS, overall survival; PFS, progression-free survival.

Pattern of Failure

Pattern of failure, smoking status, TNM stage, PFS, and duration of follow-up are listed in Appendix Table A5 (online only). Among 51 patients with primary-site cCR to IC treated with ≤ 54 Gy of radiation, nine experienced treatment failure, including four with primary-site failure only, two with nodal failure only, two with nodal plus primary site failure, and one with distant failure only.

Second Malignancies

Four patients, three with > 10 pack-year smoking and one never-smoker, developed secondary primary cancers—specifically, adenosquamous carcinoma of the lung, gastroesophageal adenocarcinoma, larynx cancer, and nonmelanoma skin cancer.

DISCUSSION

This prospective study of radiation de-intensification in patients with HPV-associated OPSCC demonstrates that three cycles of IC with cisplatin, paclitaxel, and cetuximab result in an excellent cCR of 70%, reducing tumor burden to subclinical disease. We hypothesized that IC response would identify patients suitable for radiation dose reduction, and among the 51 patients with primary-site cCR treated with 54 Gy of radiation, the 2-year PFS estimate was 80%; the 95% CI of 65% to 89% encompasses our target 2-year PFS of 85% (Fig 2). Of interest, all treatment failures were among patients with a > 10 pack-year smoking history, and all occurred within the first 20 months of registration.

In this trial, baseline tumor and patient characteristics appeared more predictive of outcome than radiation dose or IC response. We conducted a post hoc analysis of outcome in putative

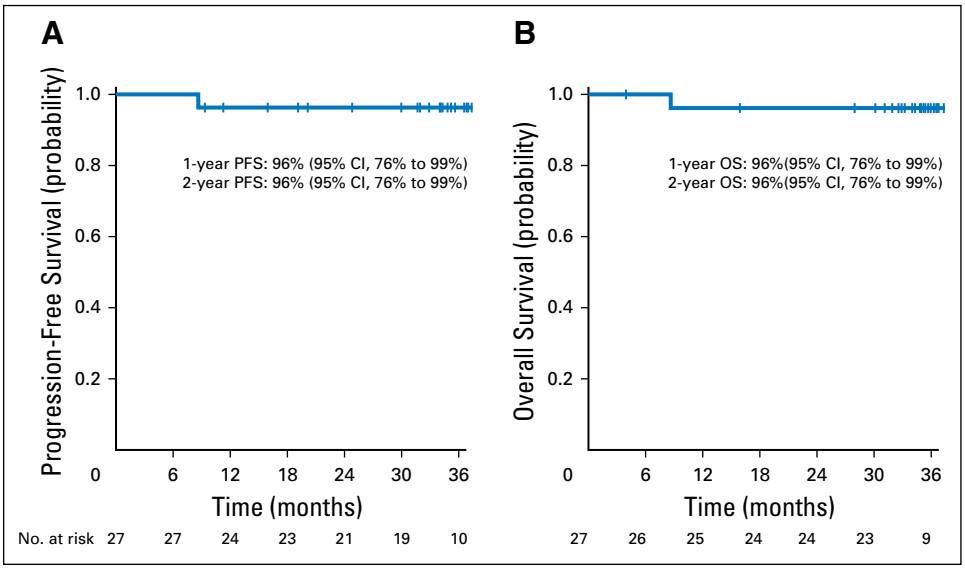

Fig 3. PFS (A) and OS (B) in favorable cohort (non-T4, non-N2c, ≤ 10 pack-year smokers) with clinical complete response to induction chemotherapy treated with low-dose radiation of 54 Gy (n = 27). OS, overall survival; PFS, progression-free survival.

favorable-risk patients, as previously reported.[7,8] Indeed, we observed patients treated with IC and reduced-dose radiation with low-volume disease (eg, T1-T3, N1-N2b) and < 10 pack-years of cigarette smoking to have high rate of disease control, with a 2-year PFS of 96% (95% CI, 76% to 99%) and OS of 96% (95% CI, 76% to 99%). The IC regimen of cisplatin, paclitaxel, and cetuximab was well tolerated among patients with HPV-associated OPSCC. Ninety-six percent of patients received all planned cycles, without major delays or increase in toxicity burden. Responders to IC treated with reduced-dose radiation had significantly improved swallowing and nutritional status. The design of the trial called for radiation dose reduction only for patients with primary-site cCR; however, a small number of patients with < cCR at the primary site (n = 11) also received 54 Gy of radiation in the context of this cooperative group trial. This sample is too small for formal analysis, but we note with interest that disease control was identical to that of the 51 patients with cCR to IC who were treated with ≤ 54 Gy of radiation.

The small sample size is a limitation to interpretation of these outcomes and the subset analyses. In addition, the sample size restricted assessment of whether observed differences in acute toxicities experienced with radiation doses of 54 Gy and 69.3 Gy were statistically significant. A correlative study using the VHNSSv2 to assess late toxicity will be reported separately. Deviations from the protocol-specified dose occurred in 13 of 80 patients, a higher rate than seen in other multicenter induction trials.[30] Given that deviations included doses both higher and lower than per protocol, we suspect deviations arose principally because of unfamiliarity with the novel treatment paradigm. We have attempted to limit the impact of these deviations on our conclusions by presenting the prespecified analysis of patients with cCR who received reduced-dose radiation.

In conclusion, differences in tumor biology and improved treatment responsiveness in HPV-associated OPSCC compared with smoking-related cancers led us to propose a shorter duration of radiation to decrease acute and chronic toxicity, particularly swallowing solids and nutritional alteration, while maintaining excellent cure rates. In this radiation-deintensification trial for HPV-associated oropharynx cancer, we used induction chemotherapy as a biomarker of responsiveness, and demonstrated radiation dose could be reduced in a subset of patients with HPV-positive OPSCC showing tumor sensitivity to chemotherapy, while maintaining previously described tumor control and survival rates. Responders to IC who received reduced-dose radiation appeared to have significantly less late swallowing dysfunction on specific domains of a patient-reported outcome instrument. This finding provides justification for further study of radiation deintensification but requires validation in a larger comparative trial. Patient selection will be critical to optimal implementation of this strategy in future trials, because we observed that patients with minimal smoking history and low-volume tumors achieved the best disease control with de-escalation of definitive treatment. This approach warrants phase III testing in favorable-risk patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients with HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx— ECOG-ACRIN Cancer Research Group

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Appendix

Table A1. Vanderbilt Head and Neck Symptom Survey, Version 2: Itemized Questions in Domains Included in This Report

Domain	Specific Questions
Difficulty swallowing solids	I have trouble eating certain solid foods. Food gets stuck in my mouth. Food gets stuck in my throat. I choke or strangle on solid foods. I cough after I swallow. Swallowing takes great effort. It takes me longer to eat because of my swallowing problem.
Impaired nutrition	Losing weight Lost appetite Liquid supplement use Trouble maintaining weight

Table A2. 2-Year PFS and OS, by HPV and p16 status

Cohort	2-Year PFS (95% CI)	2-Year OS (95% CI)
HPV ISH+/P16 IHC−[3]	0.67 (0.05 to 0.95)	0.67 (0.05 to 0.95)
HPV ISH−/P16 IHC+[15]	0.57 (0.28 to 0.78)	0.87 (0.56 to 0.96)
HPV ISH+/P16 IHC+ (n = 62)	0.83 (0.71 to 0.91)	0.93 (0.83 to 0.97)

Abbreviations: HPV, human papillomavirus; IHC, immunohistochemistry; ISH, in situ hybridization; OS, overall survival; PFS, progression-free survival.

Table A3. 2-Year PFS and OS: Intention-to-Treat Analysis and All Patients Treated With RRD (n=62)

Cohort	2-Year PFS (95% CI)	2-Year OS (95% CI)
All patients (N = 80)	0.78 (0.67 to 0.86)	0.91 (0.82 to 0.96)
cCR to ICT, RRD 54 Gy (n = 51)	0.80 (0.65 to 0.89)	0.94 (0.84 to 0.99)
cCR/PR/SD to ICT, RRD ≤ 54 Gy (n = 62)	0.81 (0.69 to 0.89)	0.93 (0.83 to 0.97)
SRD (n = 15)	0.67 (0.38 to 0.85)	0.87 (0.56 to 0.96)
Subsets cCR to ICT, treated on RRD (n = 62)		
Smoker ≤ 10 pk-yr (n = 40)	0.92 (0.78 to 0.97)	0.97 (0.83 to 0.97)
Smoker > 10 pk-yr (n = 22)	0.62 (0.38 to 0.79)	0.86 (0.62 to 0.95)
Smoker ≤ 10 pk-yr and < T4N2c (n = 27)	0.96 (0.76 to 0.99)	0.96 (0.76 to 0.99)
Smoker > 10 pk-yr or T4 or N2c (n = 35)	0.71 (0.52 to 0.83)	0.91 (0.75 to 0.97)
Non-T4a (n = 55)	0.85 (0.72 to 0.92)	0.94 (0.83 to 0.98)
T4a (n = 7)	0.57 (0.17 to 0.84)	0.86 (0.33 to 0.99)
N2c (n = 19)	0.79 (0.53 to 0.92)	0.95 (0.68 to 0.99)
Non-N2c (n = 43)	0.79 (0.53 to 0.92)	0.95 (0.68 to 0.99)

Abbreviations: cCR, complete clinical response; OS, overall survival; PFS, progression-free survival; pk-yr: pack-year; PR, partial response; RRD, reduced radiation dose; SD, stable disease; SRD, standard radiation dose.

Table A4. Acute Toxicity

	Treatment Phase								
	Induction			Concurrent RT			Concurrent RT		
	All Patients			RT > 54 Gy			RT ≤ 54 Gy		
	A (N = 89)			B (n = 17)			C (n = 67)		
	Grade, %			Grade, %			Grade, %		
Toxicity Type	3	4	5	3	4	5	3	4	5
Tinnitus	1	—	—	—	—	—	—	—	—
Anemia	1	—	—	6	—	—	—	—	—
Febrile neutropenia	—	1	—	—	—	—	—	—	—
Chest pain, cardiac	1	—	—	—	—	—	—	—	—
Myocardial infarction	1	—	—	—	0	—	—	—	—
Fatigue	4	—	—	6	—	—	6	—	—
Pain	—	—	—	6	—	—	—	—	—
Erythema multiforme	—	—	—	—	—	—	1	—	—
Palmar-plantar erythrodysesthesia	—	—	—	—	—	—	1	—	—
Rash, acneiform	23	5	—	24	—	—	12	—	—
Rash, maculopapular	2	—	—	—	—	—	3	—	—
Skin ulceration	—	—	—	—	—	—	3	—	—
Constipation	—	—	—	6	—	—	—	—	—
Diarrhea	5	—	—	—	—	—	—	—	—
Dry mouth	—	—	—	6	—	—	1	—	—
Dysphagia	1	—	—	29	—	—	15	—	—
Mucositis oral	1	—	—	47	—	—	30	—	—
Nausea	4	—	—	6	—	—	4	—	—
Oral pain	—	—	—	—	—	—	9	—	—
Vomiting	—	—	—	—	—	—	3	—	—
Gastrointestinal disorders, other	—	—	—	—	—	—	1	—	—
Anaphylaxis	—	1	—	—	—	—	—	—	—
Catheter-related infection	1	—	—	—	—	—	—	—	—
Device-related infection	1	—	—	—	—	—	—	—	—
Pharyngitis	—	—	—	—	—	—	1	—	—
Sepsis	—	1	—	—	—	—	—	1	—
Dermatitis radiation	—	—	—	12	—	—	7	—	—
Wound complication	1	—	—	—	—	—	—	—	—
ALT level increased	1	—	—	—	—	—	1	—	—
AST level increased	—	—	—	—	—	—	1	—	—
Cardiac troponin I level increased	1	—	—	—	—	—	—	—	—
CD4 lymphocyte count decreased	1	—	—	—	—	—	—	—	—
Lymphocyte count decreased	6	—	—	29	6	—	12	—	—
Neutrophil count decreased	10	2	—	—	—	—	—	—	—
WBC count decreased	5	1	—	—	—	—	—	—	—
Anorexia	4	—	—	12	—	—	6	—	—
Dehydration	6	—	—	6	—	—	3	—	—
Hyperkalemia	1	—	—	—	—	—	—	—	—
Hypokalemia	4	—	—	—	—	—	3	—	—
Hypomagnesemia	1	1	—	—	—	—	—	—	—
Hyponatremia	2	—	—	—	—	—	1	—	—
Hypophosphatemia	1	—	—	—	—	—	—	—	—
Arthralgia	1	—	—	—	—	—	—	—	—
Generalized muscle weakness	1	—	—	—	—	—	—	—	—
Myalgia	1	—	—	—	—	—	—	—	—
Pain in extremity	—	—	—	—	—	—	1	—	—
Headache	1	—	—	—	—	—	—	—	—
Neuralgia	—	—	—	—	—	—	1	—	—
Peripheral motor neuropathy	—	—	—	—	—	—	1	—	—
Peripheral sensory neuropathy	—	—	—	—	—	—	3	—	—
Tumor pain	—	—	—	6	—	—	—	—	—
Aspiration	—	1	—	—	—	—	—	—	—
Dyspnea	2	—	—	—	—	—	—	—	—
Hypoxia	1	—	—	—	—	—	—	—	—
Sore throat	—	—	—	—	—	—	3	—	—
Renal and urinary disorders, other	—	—	—	—	—	—	1	—	—
Hypotension	1	1	—	—	—	—	—	—	—
Thromboembolic event	4	—	—	6	—	—	—	—	—
Worst degree	45	12	—	76	6	—	55	1	—

NOTE. Dashes indicate no data.
Abbreviation: RT, radiation therapy.

Table A5. First Failure Pattern in Patients Treated With ≤ 54 Gy of Radiation

T Stage	N Stage	Smoking History (pack-years)	Primary Clinical Response to Induction	RT Dose to Primary (cGy)	RT Dose to Involved Nodes (cGy)	RT Dose to Uninvolved Nodes (cGy)	Time to First Failure (months)	Site of First Failure
3	2B	10-20	CR	5,400	7,000	5,130	14.3	Nodal
4	1	20-40	CR	5,400	5,400	5,130	13.6	Primary
2	2	20-40	CR	5,400	5,400	5,130	5.8	Distant
2	2C	10-20	CR	5,400	5,400	5,130	9.4	Nodal
2	2C	Pipe or cigar smoker only	CR	5,400	5,400	5,400	17.5	Primary
2A	2B	> 40	CR	5,400	5,400	5,130	10.4	Primary
4A	2C	> 40	CR	5,200	5,200	4,940	5.9	Primary
4A	2B	> 40	CR	5,400	5,400	5,130	19.9	Primary plus nodal
3	2C	Never smoked	CR	5,400	7,000	5,130	12.6	Primary plus nodal

Abbreviation: CR, complete response; RT, radiation therapy.