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ORIGINAL REPORT

Postoperative Chemoradiotherapy and Cetuximab for High-Risk Squamous Cell Carcinoma of the Head and Neck: Radiation Therapy Oncology Group RTOG-0234

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ABSTRACT

Purpose
To report results of a randomized phase II trial (Radiation Therapy Oncology Group RTOG-0234) examining concurrent chemoradiotherapy and cetuximab in the postoperative treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) with high-risk pathologic features.

Patients and Methods
Eligibility required pathologic stage III to IV SCCHN with gross total resection showing positive margins and/or extracapsular nodal extension and/or two or more nodal metastases. Patients were randomly assigned to 60 Gy radiation with cetuximab once per week plus either cisplatin 30 mg/m^2 or docetaxel 15 mg/m^2 once per week.

Results
Between April 2004 and December 2006, 238 patients were enrolled. With a median follow-up of 4.4 years, 2-year overall survival (OS) was 69% for the cisplatin arm and 79% for the docetaxel arm; 2-year disease-free survival (DFS) was 57% and 66%, respectively. Patients with p16-positive oropharynx tumors showed markedly improved survival outcome relative to patients with p16-negative oropharynx tumors. Grade 3 to 4 myelosuppression was observed in 28% of patients in the cisplatin arm and 14% in the docetaxel arm; mucositis was observed in 56% and 54%, respectively. DFS in this study was compared with that in the chemoradiotherapy arm of the RTOG-9501 trial (Phase III Intergroup Trial of Surgery Followed by Radiotherapy Versus Radiochemotherapy for Resectable High Risk Squamous Cell Carcinoma of the Head and Neck), which had a hazard ratio of 0.76 for the cisplatin arm versus control (P = .05) and 0.69 for the docetaxel arm versus control (P = .01), reflecting absolute improvement in 2-year DFS of 2.5% and 11.1%, respectively.

Conclusion
The delivery of postoperative chemoradiotherapy and cetuximab to patients with SCCHN is feasible and tolerated with predictable toxicity. The docetaxel regimen shows favorable outcome with improved DFS and OS relative to historical controls and has commenced formal testing in a phase II/III trial.

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INTRODUCTION

A substantial proportion of patients with squamous cell carcinoma of the head and neck (SCCHN) undergo primary surgery. For patients with high-risk pathologic features, recurrence rates following surgery alone are high. Traditionally, postoperative radiation for high-risk patients has been the standard adjuvant approach.[1,2] Two major phase III clinical trials—Radiation Therapy Oncology Group RTOG-9501 (Radiation Therapy With or Without Chemotherapy in Treating Patients With Head and Neck Cancer That Has Been Removed During Surgery) and European Organisation for Research and Treatment of Cancer EORTC-22931 (High-Dose Radiation Therapy With or Without Chemotherapy in Treating Patients With Head and Neck Cancer)—randomly assigned high-risk postoperative patients to adjuvant radiation alone or radiation with concurrent cisplatin.[3,4] These trials corroborated broader meta-analysis results demonstrating a small but defined survival benefit for selected patients receiving concurrent radiation and chemotherapy[5] but with greater acute and overall toxicity with the

addition of cisplatin. A combined analysis of these trials identified patients most likely to benefit from the addition of cisplatin, specifically those with positive resection margins and/or extracapsular tumor extension in cervical lymph nodes.[6]

Since publication of these phase III trials, the use of cisplatin (100 mg/m^2 once every 3 weeks) during postoperative radiation has become an accepted standard therapy for high-risk patients with SCCHN. However, many high-risk patients with SCCHN are not considered good candidates for high-dose cisplatin because of advanced age, renal insufficiency, auditory dysfunction, and/or poor performance status. One promising alternative strategy involves the incorporation of molecular targeting agents such as cetuximab, inhibitor of the epidermal growth factor receptor. With phase III trial data confirming improved survival when radiation and cetuximab are combined in the definitive treatment setting,[7-9] the rationale for examining radiation combined with cetuximab in the postoperative setting was pursued. Phase III data identified a survival benefit when cetuximab was combined with cytotoxic chemotherapy in the metastatic and/or recurrent SCCHN setting.[10] In addition, docetaxel is recognized as a potent radiation sensitizer in the primary treatment of SCCHN.[11-13] These results provided background for this phase II RTOG randomized trial, which enrolled 238 high-risk patients with SCCHN.

PATIENTS AND METHODS

Patient Characteristics

Eligible patients had American Joint Committee on Cancer pathologic stage III or IV squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, and they had completed gross total resection (Table 1). Patients had one or more pathologic high-risk factors (extracapsular nodal extension, involvement of two or more regional lymph nodes, microscopically involved resection margins).

p16 Immunohistochemistry

Automated p16 immunohistochemistry staining using the monoclonal anti-p16^{INK4a} (clone E6H4; MTM Laboratories, Heidelberg, Germany) was performed. Tumor was considered positive if strong and diffuse nuclear and cytoplasmic staining in 70% of the tumor was present.

Human Papillomavirus In Situ Hybridization

Formalin-fixed paraffin-embedded tumor specimens were evaluated for human papillomavirus 16 (HPV16) DNA by using an in situ hybridization–catalyzed signal amplification method (Dako GenPoint, Carpinteria, CA). All tumors were further evaluated for 12 additional oncogenic HPV types by using a biotinylated probe cocktail (HPV Probe Cocktail; Dako GenPoint). Single, multiple, or confluent dots in the nuclei in either analysis were defined as an HPV-positive tumor.

Randomization and Treatment

Patients were stratified according to Zubrod performance status (0 *v* 1), high-risk category (involved margins *v* high-risk [two or more positive nodes or extracapsular nodal extension]), and the planned use of intensity-modulated radiation therapy (IMRT) and were randomly assigned according to the method of Zelen[14] to receive cisplatin and cetuximab once per week or docetaxel and cetuximab once per week concurrently with radiation.

Radiation was given once per day at 2 Gy to a minimum dose of 58 Gy and a maximum dose of 66 Gy over 5.5 to 6.5 weeks. Initially, treatment planning could be two-dimensional or three-dimensional conformal; a study amendment allowing IMRT was approved midway through the study (November 2005). Radiation treatment interruptions were permitted for grade 4 mucous or skin reactions. Intravenous (IV) cetuximab was started 5 to 9 days before radiation with a loading dose of 400 mg/m^2 and was followed by six once-per-week infusions of 250 mg/m^2 during radiation. For patients randomly assigned to cisplatin, six once-per-week infusions were delivered at 30 mg/m^2 during radiation. For patients randomly assigned to docetaxel, six once-per-week infusions were delivered at 15 mg/m^2 during radiation.

Table 1. Pretreatment Characteristics by Assigned Treatment

Characteristic	RT + Cisplatin-Cetuximab (n = 97) No.	%	RT + Docetaxel-Cetuximab (n = 106) No.	%
Age, years				
Median	57		55	
Range	27-80		21-79	
Sex				
Male	77	79.4	74	69.8
Female	20	20.6	32	30.2
Zubrod performance status*				
0	48	49.5	54	50.9
1	49	50.5	52	49.1
Primary site				
Oral cavity	45	46.4	50	47.2
Oropharynx	38	39.2	36	34.0
Hypopharynx	5	5.2	7	6.6
Larynx	9	9.3	13	12.3
Surgical pathologic T stage				
T1	19	19.6	25	23.6
T2	33	34.0	32	30.2
T3	14	14.4	22	20.8
T4	31	32.0	27	25.5
Surgical pathologic N stage				
N0	3	3.1	4	3.8
N1	7	7.2	7	6.6
N2a	8	8.2	7	6.6
N2b	56	57.7	68	64.2
N2c	22	22.7	18	17.0
N3	1	1.0	2	1.9
Surgical pathologic AJCC stage				
III	6	6.2	7	6.6
IV	91	93.8	99	93.4
High-risk factor (per institution, as randomized)*				
Positive margin(s)†	14	14.4	16	15.1
High risk	83	85.6	90	84.9
Positive margin(s)‡				
No	53	54.6	62	58.5
Yes	41	42.3	42	39.6
Unknown	3	3.1	2	1.9
Extracapsular nodal extension‡				
No	16	16.5	29	27.4
Yes	58	59.8	62	58.5
Unknown	23	23.7	15	14.2
Two or more pathologically positive nodes‡				
No	15	15.5	17	16.0
Yes	82	84.5	89	84.0
IMRT planned*				
No	61	62.9	64	60.4
Yes	36	37.1	42	39.6

Abbreviations: AJCC, American Joint Committee on Cancer; IMRT, intensity-modulated radiation therapy; RT, radiation therapy.
*Stratification factor. IMRT stratification began in November 2005.
†Patients with both positive margins and another risk factor were to be stratified as positive margins.
‡Per central review.

Premedication, allowing physician discretion, included diphenhydramine 50 mg IV 30 to 60 minutes before the first dose of cetuximab, dolasetron 100 mg IV 30 minutes before cisplatin delivery, or dexamethasone 20 mg IV before docetaxel delivery. Doses were reduced for hematologic toxicity, serum creatinine levels, fatigue, nausea/vomiting, neuropathy, mucositis, and rash. Cetuximab was discontinued for grade 3 to 4 hypersensitivity, and docetaxel was discontinued for grade 4 hypersensitivity. Quality assurance reviews were performed for radiation therapy, chemotherapy, and cetuximab.

Follow-Up Evaluations

Adverse events were scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Patients were assessed once per week during radiation for performance status, weight, blood counts, serum levels, and adverse events. Follow-up evaluations were performed every 3 months for the first 2 years, every 6 months in years 3 to 6, then annually. Computed tomography or magnetic resonance imaging scans to assess recurrence were performed at 6 months and as clinically indicated. Patient's vital status, disease status, nutritional status (feeding tube use), smoking status (cigarettes), nonprotocol therapy, and adverse events were recorded at each follow-up session.

Study End Points and Statistical Considerations

The primary end point was disease-free survival (DFS). Failure was defined as local, regional, or distant progression, second primary tumor, or death. The trial was designed to determine whether either regimen showed sufficient promise to be pursued in a subsequent phase III study, primarily on the basis of improvement in DFS relative to a similar cohort treated with chemoradiotherapy in RTOG-9501. By using the method of Dixon and Simon,[15] 104 patients per arm were required to detect a $\geq$ 33% reduction in the failure rate (improving 2-year DFS from 53.9% to 66.1%) relative to control with 80% power (one-sided $\alpha = .05$). Allowing for 10% ineligibility, the total sample size was 230 patients. Patients that met all eligibility criteria and started protocol therapy were included in the analysis and were grouped according to their random treatment assignment.

Secondary efficacy end points were overall survival (OS), locoregional failure, and distant metastasis (DM). Rates for DFS and OS were estimated by the Kaplan-Meier method[16] and were compared with control with a one-sided log-rank test. Locoregional failure and DM rates were estimated by the cumulative incidence method[17] and were compared with control with a one-sided Gray's test.[18] The Cox model[19] was used to estimate hazard ratios (HRs). All failure times were measured from the date of random assignment to the date of failure, competing risk, or last follow-up.

Other secondary end points were treatment tolerance and toxicity. Tolerability was defined as having received $\geq$ 90% of the radiation dose, $\geq$ 95% of the cetuximab loading dose, and at least 4 weeks of cetuximab and cisplatin or docetaxel at doses $\geq$ 95% of the protocol prescription. Each regimen was monitored for excessive acute toxicity (defined as nonhematologic grade 4 toxicity within 90 days of the start of radiation or any grade 5 toxicity) in the initial 25 and 50 patients, and in the full cohort. By using the method of Fleming[20] with a target rate of 15% (the observed rate in RTOG-9501) and an unacceptable rate of more than 30%, if eight or more (of 25), 14 or more (of 50), or 23 or more (of total) patients experienced nonhematologic grade 4 toxicity within 90 days of the start of radiation or any grade 5 toxicity, the toxicity profile for that regimen would be considered unacceptable.

RESULTS

Study Population

Between April 2004 and December 2006, 238 patients were enrolled. Thirty-five patients (14.7%) were excluded from analysis (see Fig 1, CONSORT diagram) leaving 203 analyzable patients. Ninety-four percent of patients had stage IV disease, with oral cavity disease being the most common at 47%. High-risk features included extracapsular nodal extension (59% of patients), positive surgical margins (41% of patients), and two or more metastatic lymph nodes (84% of patients).

Treatment Compliance

Of patients in the study, 97% and 99% received at least 90% of the prescribed radiation dose on the cisplatin and docetaxel arms, respectively, and 99% and 97% received at least 95% of the cetuximab loading dose. At least four once-per-week doses of cetuximab with at least 95% of the prescribed dose were delivered in 89.7% and 88.7% of patients. At least four once-per-week doses of cytotoxic chemotherapy (cisplatin or docetaxel) with at least 95% of the prescribed dose were delivered in 86.6% and 88.7% of patients. Overall, the protocol treatment regimen was scored as tolerable in 80.4% of patients on the cisplatin arm and 84.9% of patients on the docetaxel arm.

IMRT was used in 78 patients (38.4%) and non-IMRT in 125 patients (61.6%). Nineteen percent of the IMRT patients on each arm had unacceptable variation in contouring of the tumor volume (seven of 36 for the cisplatin arm and eight of 42 for the docetaxel arm). More than 90% of the non-IMRT patients were scored per protocol or with acceptable variation for both arms. In the cisplatin arm, 86.6% received chemotherapy (cytotoxic plus cetuximab) per protocol and 55.8% received chemotherapy without modifications or delays per protocol. On the docetaxel arm, 92.5% received chemotherapy per protocol and 59.6% received chemotherapy without modifications or delays per protocol.

Treatment Outcome

After median follow-up of 4.4 years (range, 0.2 to 6.0 years) for surviving patients, 48 patients on the cisplatin arm experienced a DFS event (33 progressed and then died, eight progressed only, and seven died without progression) compared with 51 patients on the docetaxel arm (30 progressed and then died, 14 progressed only, and seven died without progression). There was a 24% reduction (HR, 0.76; 95% CI, 0.54 to 1.06) in the DFS failure rate for the cisplatin arm compared with control ($P = .05$; Fig 2A) and a 31% reduction (HR, 0.69; 95% CI, 0.50 to 0.96) for the docetaxel arm ($P = .01$; Fig 2B). These corresponded to 2.5% and 11.1% improvements in 2-year DFS relative to control. Forty patients on the cisplatin arm and 37 on the docetaxel arm have died. There was a 28% reduction (HR, 0.72; 95% CI, 0.50 to 1.03) in the death rate for the cisplatin arm relative to control ($P = .04$; Fig 2C) and a 44% reduction (HR, 0.56; 95% CI, 0.39 to 0.82) for the docetaxel arm ($P = .001$; Fig 2D).

The patterns of failure differed for the two study arms. With respect to DFS on the cisplatin arm, the first site of treatment failure was locoregional in 39.6%, distant in 37.5%, second primary in 8.3%, and death in 14.6%. For the docetaxel arm, these values were 43.1%, 19.6%, 23.5%, and 13.7%, respectively. Roughly two thirds of deaths were a result of the index cancer and, as with many SCCHN trials, a large percentage of deaths (24.7%) were unrelated to cancer or treatment, or were a result of unknown causes. Of interest, the primary benefit for the docetaxel arm appears related to improved distant control, with a 2-year DM rate of 13% in the docetaxel arm versus 25% in the cisplatin arm. These data reflect a 45% reduction in DM (Fig 3B) compared with control ($P = .03$). There was no change in locoregional failure rate compared with control for either arm (Fig 3C-D).

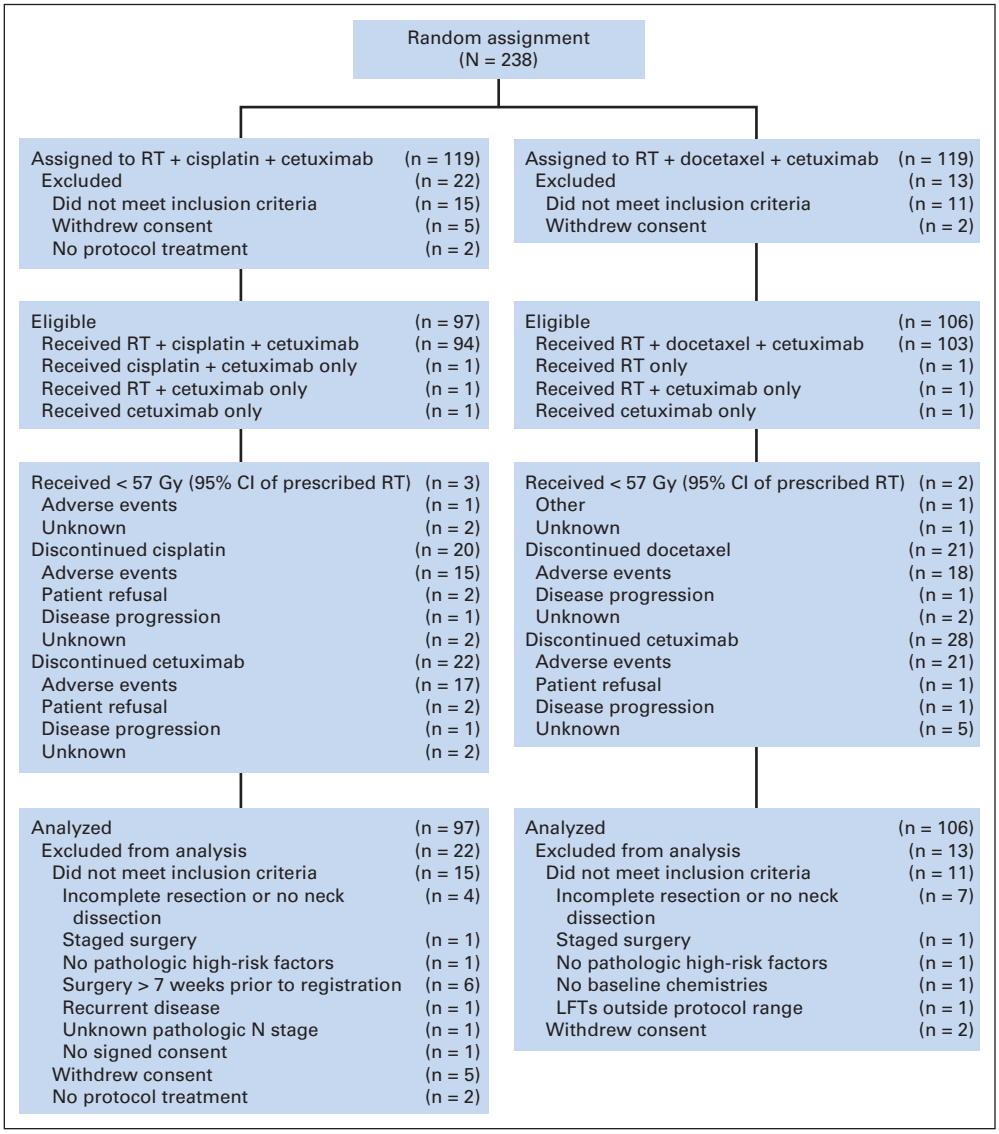

Fig 1. CONSORT diagram. LFT, liver function test; RT, radiation therapy.

Impact of p16 and HPV Status

Of 74 patients with oropharynx cancer, p16 status was determined for 54 patients (73.0%) and HPV status for 59 patients (79.7%). Forty-three (79.6%) of 54 patients had p16-positive tumors, and 43 (72.9%) of 59 had HPV-positive tumors (Appendix Table A1, online only). Three (5.6%) of the 54 patients with known status for both p16 and HPV had p16-positive but HPV-negative tumors. None had p16-negative and HPV-positive tumors. Patients with p16-positive oropharynx tumors had significantly improved outcome for both DFS and OS and within both treatment assignments compared with patients with p16-negative tumors (Fig 4). The results for HPV are not as strong for the docetaxel arm, but the HRs are still in approximately the same range as those of other published reports (Appendix Fig A1, online only).

Adverse Effects

The most common grade 3 to 4 acute nonhematologic adverse events observed in this study included mucositis (55.7% *v* 53.8%), dysphagia (38.1% *v* 36.8%), and skin rash (36.1% *v* 38.7%; Table 2). There was a greater hematologic toxicity for grade 3 to 4 effects of 27.8% observed on the cisplatin arm versus 14.2% on the docetaxel arm. There was a higher incidence of oral cavity mucositis observed when subset analysis was performed for patients treated with IMRT versus non-IMRT techniques, but there was no overall difference in mucositis when comparing patients treated with cisplatin versus docetaxel.

One patient on the docetaxel arm experienced a grade 5 adverse event likely related to protocol therapy (pneumonia and myocardial ischemia), and one patient on the cisplatin arm experienced a grade 5 adverse event unrelated to protocol treatment. Per protocol design, both arms were considered to have an acceptable toxicity profile (as measured by grade 5 or acute nonhematologic grade 4 toxicity). The boundaries were not crossed for either arm at the first or second interim analysis or at the final analysis. The rates of unacceptable toxicity, 9.3% for the cisplatin arm (nine of 97) and 12.3% for the docetaxel arm (13 of 106) compared favorably to the rate of 15% observed in RTOG-9501. The most common grade 3 late toxicity was dysphagia (6.0% *v* 3.2%; Table 3). A comprehensive summary

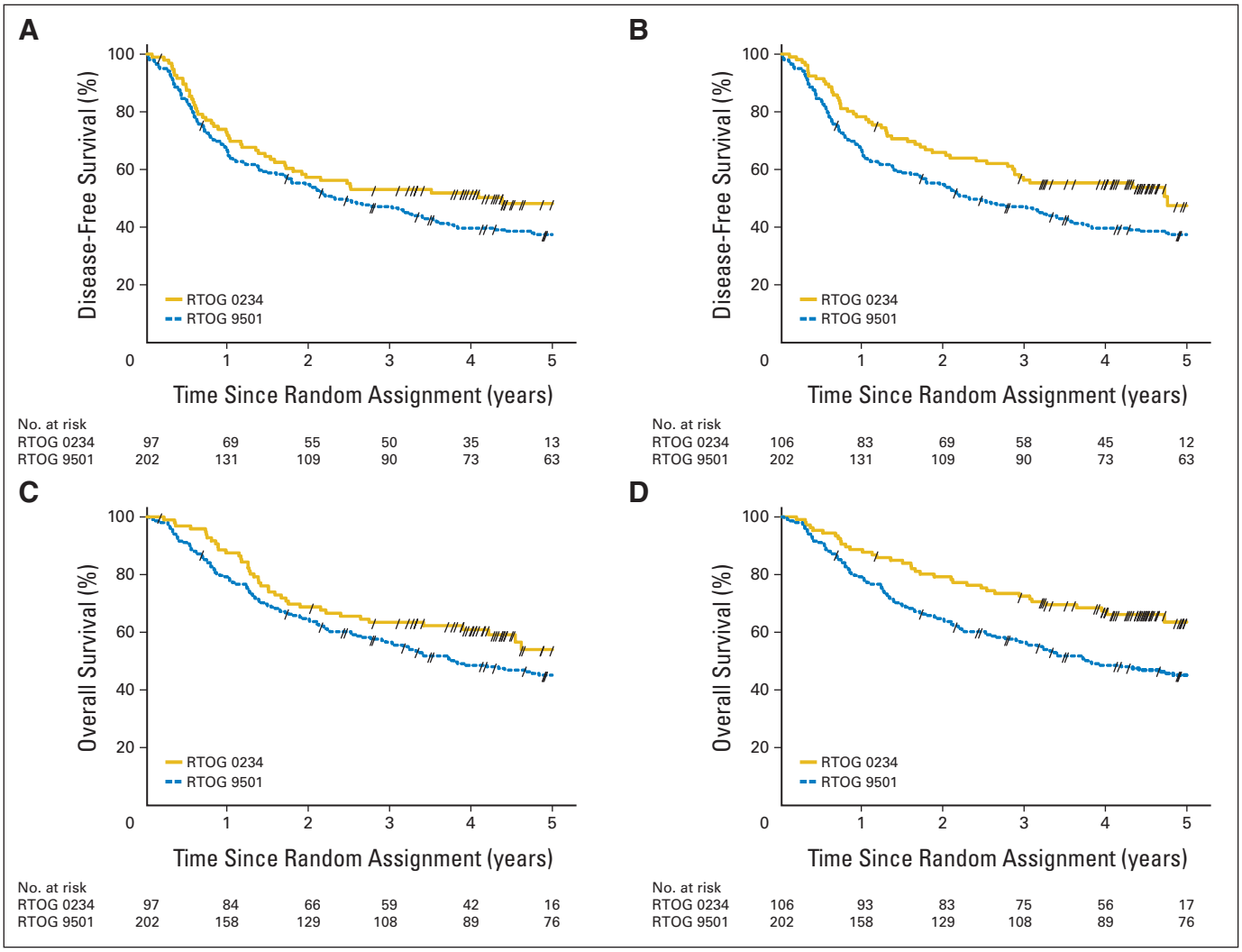

Fig 2. (A-B) Disease-free survival (DFS) and (C-D) overall survival (OS) estimates for patients in Radiation Therapy Oncology Group RTOG-0234 (Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 [Cetuximab] for Advanced Squamous Cell Carcinoma of the Head and Neck) compared with patients in the radiation-cisplatin arm of RTOG-9501 (Phase III Intergroup Trial of Surgery Followed by Radiotherapy Versus Radiochemotherapy for Resectable High Risk Squamous Cell Carcinoma of the Head and Neck). Two-year DFS estimate was 54.8% (95% CI, 47.9% to 61.7%) for RTOG-9501 and 57.3% (95% CI, 47.4% to 67.2%) for the RTOG-0234 cisplatin arm. (A) Hazard ratio [HR], 0.76; 95% CI, 0.54 to 1.06; $P = .05$; 2-year DFS estimate was 65.9% (95% CI, 56.9% to 75.0%) for the docetaxel arm. (B) HR, 0.69; 95% CI, 0.50 to 0.96; $P = .01$. Two-year OS estimate was 64.7% (95% CI, 58.1% to 71.3%) for RTOG-9501 and 68.8% (95% CI, 59.5% to 78.0%) for the RTOG-0234 cisplatin arm. (C) HR, 0.72; 95% CI, 0.50 to 1.03; $P = .04$; 2-year OS estimate was 79.2% (95% CI, 71.4% to 86.9%) for the docetaxel arm. (D) HR, 0.56; 95% CI, 0.39 to 0.82; $P = .001$. Tick marks indicate censored observations.

of adverse events is provided in Appendix Tables A2 and A3 (online only).

DISCUSSION

For patients with SCCHN with high-risk features (extracapsular nodal extension, tumor involving resection margins), locoregional failure rates remain high.[6,20,21] Approaches to reducing recurrence rates include the use of postoperative radiation alone and, more recently, postoperative chemoradiotherapy.[3,4] The OS benefit of adding cisplatin to radiation in this setting is modest and is accompanied by incremental toxicity. A substantial cohort of patients with SCCHN do not tolerate 100 mg/m^2 cisplatin once every 3 weeks during radiation. In an effort to exploit the known favorable interaction between radiation and cetuximab, this trial examined the addition of cetuximab and either cisplatin or docetaxel once per week to radiation in the postoperative setting. The cetuximab-docetaxel arm compared favorably with the cetuximab-cisplatin arm with regard to DFS and OS outcome, mainly because of a reduction in the incidence of DMs.

The role of cetuximab in the treatment of SCCHN continues to evolve. The randomized trial by Bonner et al[7,8] identified a survival benefit for cetuximab combined with radiation over radiation alone in patients with locoregionally advanced SCCHN. The randomized trial by Vermorken et al[10] identified a survival benefit for cetuximab combined with cisplatin-fluorouracil over cisplatin-fluorouracil alone in patients with SCCHN with recurrent or metastatic disease. These major clinical trial results confirm a favorable interaction of cetuximab with radiation and of cetuximab with cytotoxic chemotherapy, respectively. Conversely, RTOG-0522 (Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent

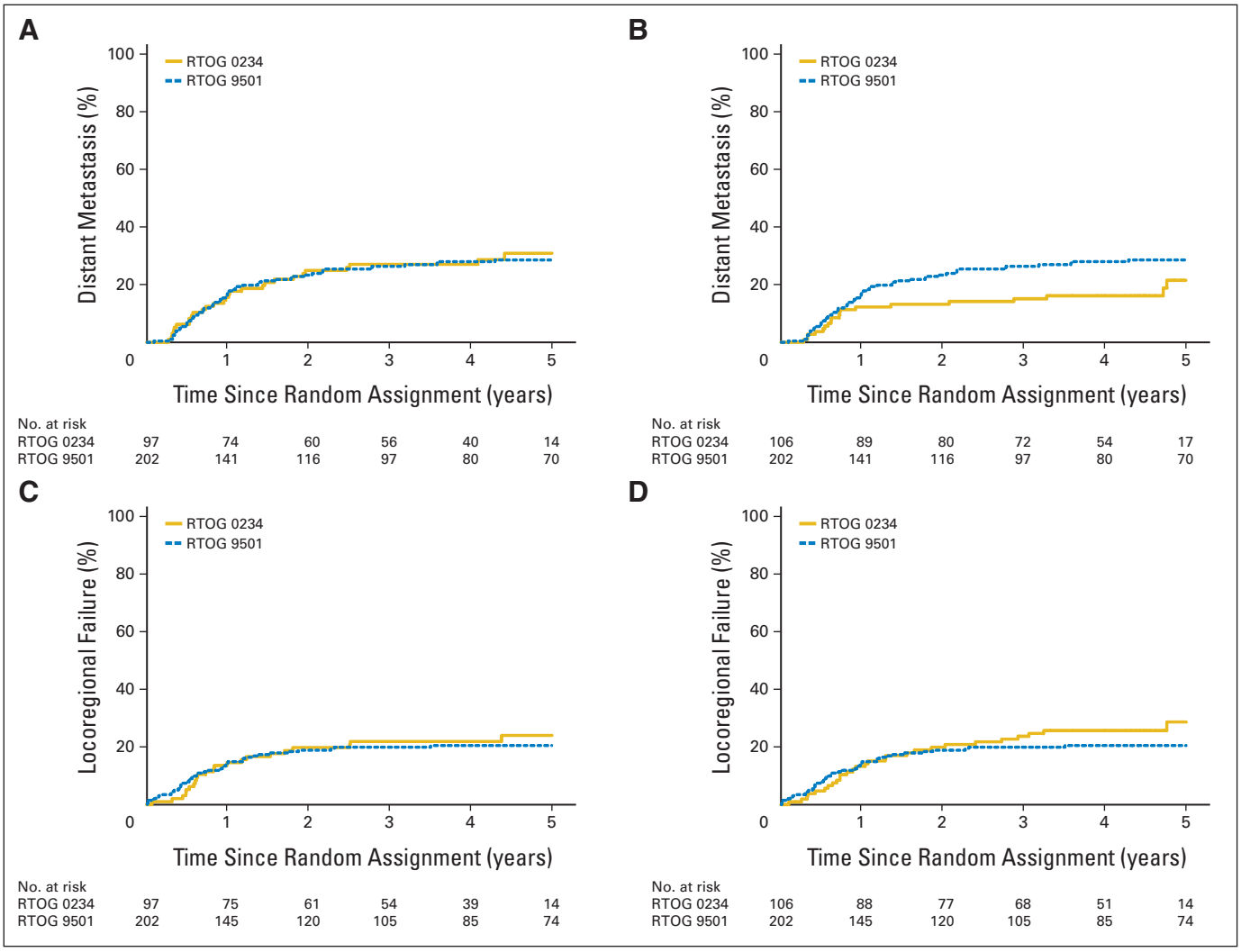

Fig 3. Time to (A-B) distant failure and (C-D) locoregional failure estimates for patients in Radiation Therapy Oncology Group RTOG-0234 (Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 [Cetuximab] for Advanced Squamous Cell Carcinoma of the Head and Neck) compared with patients in the radiation-cisplatin arm of RTOG-9501 (Phase III Intergroup Trial of Surgery Followed by Radiotherapy Versus Radiochemotherapy for Resectable High Risk Squamous Cell Carcinoma of the Head and Neck). Two-year distant failure estimate was 23.4% (95% CI, 17.5% to 29.2%) for RTOG-9501 and 25.0% (95% CI, 16.3% to 33.7%) for the RTOG-0234 cisplatin arm. (A) Hazard ratio [HR], 0.96; 95% CI, 0.61 to 1.51; $P = .43$; 2-year distant failure estimate was 13.2% (95% CI, 6.7% to 19.7%) for the docetaxel arm. (B) HR, 0.55; 95% CI, 0.33 to 0.93; $P = .03$. Two-year locoregional failure estimate was 18.9% (95% CI, 13.4% to 24.3%) for RTOG-9501 and 19.8% (95% CI, 11.8% to 27.8%) for the RTOG-0234 cisplatin arm. (C) HR, 1.05; 95% CI, 0.63 to 1.76; $P = .66$; 2-year locoregional failure estimate was 19.9% (95% CI, 12.2% to 27.5%) for the docetaxel arm. (D) HR, 1.16; 95% CI, 0.72 to 1.87; $P = .86$.

Accelerated Radiation, Cisplatin, and Cetuximab [C225] [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas) did not demonstrate a survival benefit with the addition of cetuximab to radiation and cisplatin in the primary SCCHN treatment setting.[21a] The findings from that study identified improved DFS and OS for both study arms compared with historical controls (RTOG-9501) in the same high-risk SCCHN population. Of note, the docetaxel arm showed a more favorable outcome with an 11.1% improvement in 2-year DFS compared with the radiation-cisplatin arm of RTOG-9501. Patterns of failure analysis identified a reduction in DMs as the dominant driver of improved outcome in the docetaxel arm. However, we are cautious with the interpretation and comparison of results from the current randomized phase II study initiated 4 years after the completion of RTOG-9501.

The observation of improved DFS and OS for the docetaxel arm, related to improved systemic disease control, is an intriguing finding. A total prescribed dose of only 90 mg/m^2 docetaxel was administered, and this alone would not have been predicted to exert a major effect on DMs. Epidermal growth factor receptor inhibition can induce senescence in cells sustaining DNA double-strand breaks,[22] and docetaxel may induce DNA double-strand breaks that lead to a cell death response.[23] It may be that microscopic foci of metastatic disease could be induced to senesce following systemic treatment with docetaxel and cetuximab. although cisplatin can also induce cell senescence, it appears to do this preferentially in p53 wild-type cells (Osman and Myers, unpublished observations, January 2012). With the majority of non-HPV tumors having p53 mutations, this lack of cisplatin-induced cell senescence in mutant p53 tumor cells might account for differences in the development of DMs.

Both treatment arms of this study were found to be reasonably safe, tolerable, and effective compared with the historical control population from the RTOG-9501 trial. The high DFS and OS observed in

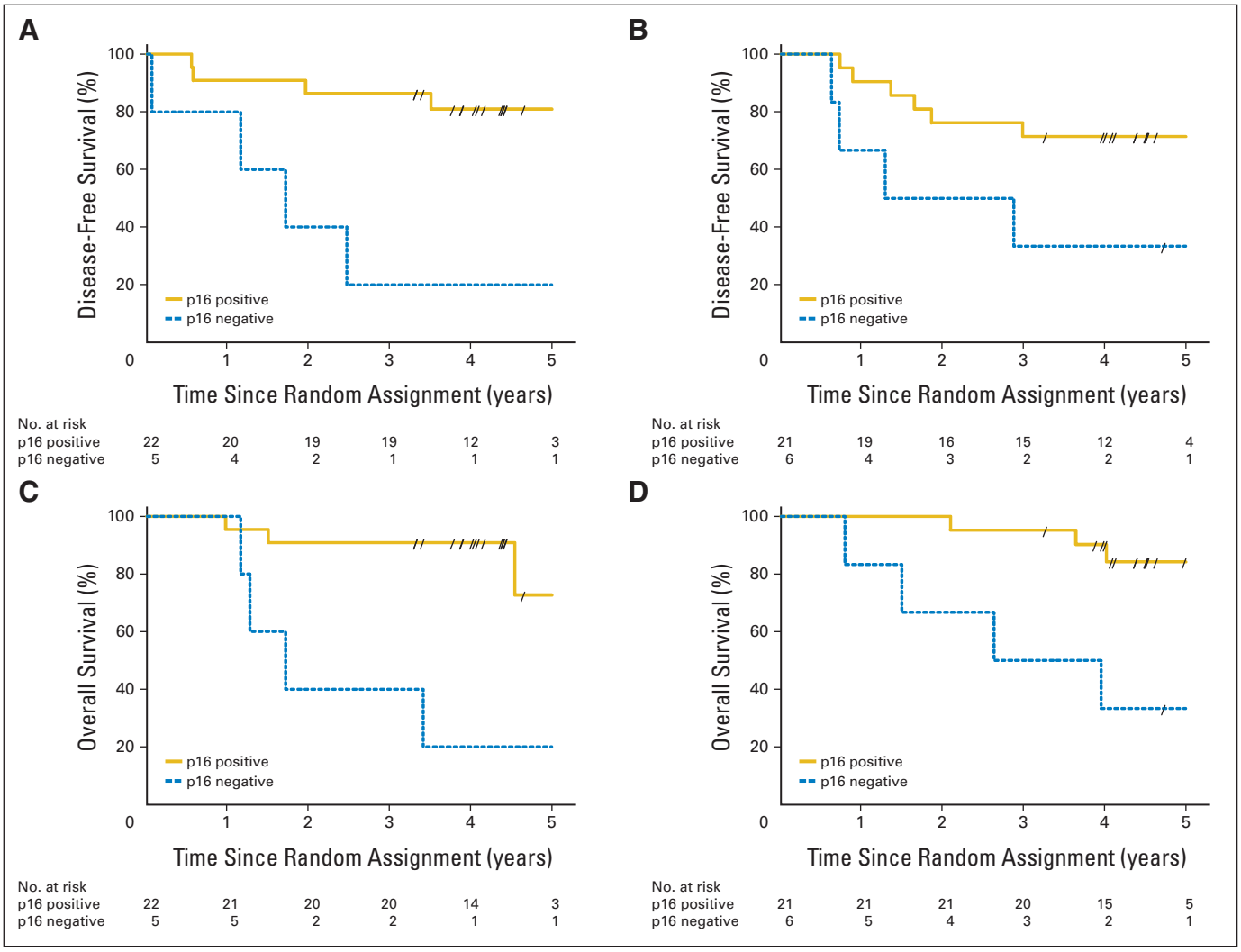

Fig 4. (A-B) Disease-free survival (DFS) and (C-D) overall survival (OS) estimates for patients with oropharynx cancer in Radiation Therapy Oncology Group RTOG-0234 (Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 [Cetuximab] for Advanced Squamous Cell Carcinoma of the Head and Neck) by p16 status. On the cisplatin arm, 2-year DFS estimate was 86.4% (95% CI, 72.0% to 100.0%) for patients with p16-positive tumors and 40.0% (95% CI, 0.0% to 82.9%) for patients with p16-negative tumors. (A) Hazard ratio [HR], 0.14; 95% CI, 0.03 to 0.58; $P = .002$. On the docetaxel arm, 2-year DFS estimate was 76.2% (95% CI, 58.0% to 94.4%) for patients with p16-positive tumors and 50.0% (95% CI, 10.0% to 90.0%) for patients with p16-negative tumors. (B) HR, 0.29; 95% CI, 0.08 to 1.02; $P = .04$. On the cisplatin arm, 2-year OS estimate was 90.9% (95% CI, 78.9% to 100.0%) for patients with p16-positive tumors and 40.0% (95% CI, 0.0% to 82.9%) for patients with p16-negative tumors. (C) HR, 0.13; 95% CI, 0.03 to 0.59; $P = .002$. On the docetaxel arm, 2-year OS estimate was 100.0% for patients with p16-positive tumors and 66.7% (95% CI, 28.9% to 100.0%) for patients with pl6-negative tumors. (D) HR, 0.14; 95% CI, 0.03 to 0.65; $P = .003$. Tick marks indicate censored observations

the docetaxel arm suggest direct comparison against the standard-of-care regimen (cisplatin-radiation) for high-risk postoperative patients with SCCHN as a potential future step. Indeed, this comparison is being performed in the RTOG 1216 phase II/III trial (Randomized Phase II/III Trial of Surgery and Postoperative Radiation Delivered With Concurrent Cisplatin Versus Docetaxel Versus Docetaxel and Cetuximab for High-Risk Squamous Cell Cancer of the Head and Neck) that commenced enrollment in March 2013. To date, it remains unknown whether once-per-week docetaxel or cisplatin with cetuximab (or the combination) provides the most critical addition to radiation. It appears that the weekly drug administration schedule in this study may be associated with improved compliance and reduced toxicity versus the every-3-week delivery schedule in RTOG-9501. Although the high-risk pathologic features are valuable in identifying risk categories for recurrence, it would be ideal to further individualize the selection of patients most likely to benefit from cetuximab, cytotoxic chemotherapy, or even higher doses of radiation. This would require the identification of reliable biomarkers that better predict rates and patterns of recurrence for individual patients. One such biomarker is of course HPV status, and the post hoc analysis of p16 status from this trial confirms a powerful positive impact of p16 on DFS and OS similar to that observed in recent SCCHN reports.

It is valuable to acknowledge the importance of high-quality radiation planning and delivery on the outcome of patients with SCCHN. The study by Peters et al[24] that evaluated radiation quality assurance in the TROG HeadSTART (Phase III Randomized Trial of Concomitant Radiation, Cisplatin, and Tirapazamine Versus Concomitant Radiation and

Table 2. Selected Grade 1 to 4 Treatment-Related Acute Adverse Events by Assigned Treatment

	RT + Cisplatin-Cetuximab (n = 97) Grade								RT + Docetaxel-Cetuximab (n = 106) Grade							
	1		2		3		4		1		2		3		4	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Anorexia	7	7	22	23	16	16	0	0	9	8	20	19	9	8	0	0
Dehydration	1	1	18	19	10	10	0	0	1	1	9	8	4	4	1	1
Dry mouth	24	25	43	44	8	8	0	0	33	31	42	40	5	5	0	0
Dysphagia	9	9	22	23	37	38	0	0	8	8	32	30	39	37	0	0
Fatigue	24	25	41	42	10	10	0	0	28	26	45	42	6	6	1	1
Febrile neutropenia	0	0	0	0	3	3	1	1	0	0	0	0	0	0	0	0
Hemoglobin	43	44	11	11	4	4	0	0	44	42	6	6	0	0	0	0
Hypersensitivity NOS	2	2	1	1	3	3	0	0	3	3	3	3	2	2	1	1
Infection with grade 0 to 2 ANC	0	0	4	4	2	2	0	0	0	0	3	3	2	2	0	0
Infection with grade 3 to 4 ANC	0	0	3	3	2	2	0	0	0	0	3	3	2	2	0	0
Infection with unknown ANC	0	0	2	2	0	0	0	0	0	0	1	1	2	2	0	0
Leukopenia NOS	22	23	18	19	14	14	1	1	17	16	6	6	0	0	0	0
Lymphopenia	2	2	4	4	11	11	5	5	1	1	6	6	10	9	5	5
Metabolic/laboratory*	35	36	13	13	14	14	0	0	31	29	22	21	11	10	3	3
Mucositis/stomatitis†	7	7	25	26	50	52	4	4	9	8	30	28	49	46	8	8
Nausea/vomiting	19	20	21	22	14	14	0	0	21	20	19	18	7	7	0	0
Neutrophil count	11	11	6	6	7	7	0	0	3	3	1	1	0	0	0	0
Decreased platelet count	13	13	4	4	1	1	0	0	6	6	2	2	0	0	0	0
Rash‡	13	13	44	45	30	31	5	5	14	13	46	43	38	36	3	3
Decreased weight	21	22	21	22	7	7	0	0	17	16	19	18	6	6	1	1

NOTE. Treatment related: definitely, probably, or possibly related to protocol treatment (or with unknown relationship). Acute: within 1 year after start of treatment.
Abbreviations: ANC, absolute neutrophil count; NOS, not otherwise specified; RT, radiation therapy.
*Any event within the metabolic/laboratory category.
†Of the oral cavity, pharynx, larynx, or esophagus.
‡Acne, dermatitis, erythema multiforme, pruritis, or urticaria.

Cisplatin in Patients With Advanced Head and Neck Cancer) study identifies a 20% reduction in 2-year overall survival for patients with major deficiencies in radiation field design. In this study, 19% of the IMRT patients were identified as having major variations in target contouring. IMRT design expertise is highly experience-dependent in SCCHN, and the years 2004 to 2006 reflect a time frame during which many institutions were still gaining experience with head and neck IMRT techniques. Fortunately, the use of IMRT was a stratification factor and therefore was well balanced between the two arms.

In conclusion, the delivery of postoperative chemoradiotherapy (using cisplatin or docetaxel once per week plus 60 Gy radiation) with concurrent once-per-week cetuximab for patients with SCCHN who have high-risk pathologic features is feasible and tolerated with predictable toxicity. The radiation-docetaxel-cetuximab regimen

Table 3. Selected Grade 1 to 4 Treatment-Related Late Adverse Events by Assigned Treatment

	RT + Cisplatin-Cetuximab (n = 84) Grade								RT + Docetaxel-Cetuximab (n = 93) Grade							
	1		2		3		4		1		2		3		4	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Dry mouth	30	36	16	19	2	2	0	0	34	37	23	25	1	1	0	0
Dysphagia	13	15	8	10	5	6	0	0	15	16	19	20	3	3	0	0
Fatigue	6	7	3	4	1	1	0	0	10	11	3	3	0	0	0	0
Cosmesis fibrosis	2	2	2	2	1	1	0	0	3	3	3	3	0	0	0	0
Deep connective tissue fibrosis	3	4	4	5	1	1	0	0	1	1	14	15	0	0	0	0
Mucositis/stomatitis*	0	0	0	0	0	0	0	0	3	3	3	3	0	0	0	0
Skin fibrosis	9	11	10	12	1	1	0	0	16	17	8	9	0	0	0	0
Decreased weight	4	5	2	2	1	1	0	0	3	3	4	4	1	1	0	0

NOTE. Treatment related: definitely, probably, or possibly related to protocol treatment (or with unknown relationship). Late: more than 1 year after start of treatment.
Abbreviation: RT, radiation therapy.
*Of the oral cavity, pharynx, larynx, or esophagus.

shows particularly promising outcome with improvement in DFS and OS relative to RTOG historical controls and appears worthy of further investigation in high-risk patients with SCCHN. This evaluation is now moving forward in a phase II/III trial (RTOG 1216) that evaluates 60 Gy radiation plus cisplatin versus 60 Gy plus docetaxel versus 60 Gy plus the combination of docetaxel and cetuximab in the postoperative setting for high-risk patients with SCCHN.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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GLOSSARY TERMS

cetuximab: also called Erbitux or C225. Cetuximab is a monoclonal antibody that is designed to target the epidermal growth factor receptor and block its signaling activity by initiating receptor activation.

intensity-modulated radiation therapy: radiation treatment using beams with nonuniform fluence profiles that shape the dose distribution in the target volume and adjacent normal structures. Beam modulation is typically achieved via multileaf collimators or custom-milled compensators to achieve the appropriate fluence profiles calculated by inverse optimization algorithms. The radiation beam is divided into beamlets of varying intensity such that the sum from multiple beams via inverse planning results in improved tumor targeting and normal tissue sparing. A technique of radiation therapy delivery in which the intensity of each beamlet of radiation coming from a specific angle can be adjusted to provide a desired dose distribution when the doses delivered from all beamlets are added from a single angle and from all dose delivery angles. An advanced type of high-precision radiotherapy, which aims to improve the coverage of the radiotherapy target and/or minimize radiation dose to surrounding normal tissue.

p16: molecule that binds to cyclin-dependent kinase 4 and 6, thereby preventing their interaction with cyclin D. p16 (also known as $p16^{INK4}$) behaves as a negative regulator of proliferation and arrests cells in the G0/G1 phase of the cell cycle.

Appendix

Table A1. p16 and HPV Status by Assigned Treatment for Patients with Oropharynx Cancer

Status	RT + Cisplatin-Cetuximab		RT + Docetaxel-Cetuximab		Total	
	No.	%	No.	%	No.	%
	(n = 27)		(n = 27)		(n = 54)	
p16 status						
Negative	5	18.5	6	22.2	11	20.4
Positive	22	81.5	21	77.8	43	79.6
	(n = 31)		(n = 28)		(n = 59)	
HPV status						
Negative	7	22.6	9	32.1	16	27.1
Positive	24	77.4	19	67.9	43	72.9

Abbreviations: HPV, human papillomavirus; RT, radiation therapy.

Table A2. Grade 1 to 4 Treatment-Related Acute Adverse Events

Adverse Event	RT + Cisplatin-Cetuximab (n = 97) Grade				RT + Docetaxel-Cetuximab (n = 106) Grade			
	1	2	3	4	1	2	3	4
Maximum acute grade								
Overall	1	11	71	14	0	11	78	16
Nonhematologic	1	15	72	9	0	11	82	12
Allergy/immunology	3	1	3	0	4	4	2	1
Other	0	0	0	0	0	1	0	0
Hypersensitivity NOS	2	1	3	0	3	3	2	1
Allergic rhinitis NOS	1	0	0	0	1	0	0	0
Auditory/ear	3	6	0	0	1	7	1	0
Other	2	0	0	0	1	2	0	0
Hearing disability	1	0	0	0	0	0	0	0
Hearing impaired	0	1	0	0	0	3	1	0
Otitis externa NOS	0	1	0	0	0	0	0	0
Otitis media serous NOS	0	0	0	0	0	1	0	0
Tinnitus	0	4	0	0	0	2	0	0
Blood/bone marrow	25	19	21	6	34	16	10	5
Other	5	0	0	0	3	2	0	0
Haptoglobin	1	0	0	0	0	0	0	0
Hemoglobin	43	11	4	0	44	6	0	0
Hemolysis NOS	1	0	0	0	1	0	0	0
Leukopenia NOS	22	18	14	1	17	6	0	0
Lymphopenia	2	4	11	5	1	6	10	5
Neutrophil count	11	6	7	0	3	1	0	0
Decreased platelet count	13	4	1	0	6	2	0	0
Cardiac arrhythmia	0	1	0	0	3	3	0	1
Atrial fibrillation	0	0	0	0	0	1	0	1
Palpitations	0	0	0	0	1	0	0	0
Sinus tachycardia	0	0	0	0	0	2	0	0
Supraventricular tachycardia	0	0	0	0	1	0	0	0
Ventricular tachycardia	0	1	0	0	1	0	0	0
General cardiac	1	4	3	0	0	6	0	1
Other	0	0	0	0	0	3	0	0
Hypertension NOS	0	0	1	0	0	1	0	0
Hypotension NOS	1	4	2	0	0	4	0	0
Myocardial ischemia	0	0	0	0	0	0	0	1
Increased troponin I	0	0	0	0	0	0	0	1
Coagulation	1	0	0	0	1	0	2	0
Prolonged activated partial thromboplastin time	1	0	0	0	1	0	2	0
Prolonged prothrombin time	1	0	0	0	0	0	1	0
Constitutional symptoms	21	47	16	0	27	47	13	2
Other	0	0	0	0	2	1	0	0
Fatigue	24	41	10	0	28	45	6	1
Insomnia	2	6	0	0	5	7	0	0
Pyrexia	14	2	0	0	14	6	1	0
Rigors	5	2	0	0	9	3	0	0
Abnormal skin odor	1	0	0	0	0	0	0	0
Increased sweating	0	0	0	0	2	1	0	0
Decreased weight	21	21	7	0	17	19	6	1
Increased weight	0	0	0	0	0	2	0	0
Dermatology/skin	11	46	32	5	9	51	39	3
Acne NOS	21	28	11	0	9	38	15	0
Alopecia	13	4	0	0	16	4	0	0
Burn	1	2	0	0	1	1	0	0
Cheilitis	2	0	0	0	0	0	1	0
Negative culture wound	1	0	0	0	0	0	0	0
Decubitus ulcer	0	1	0	0	0	0	0	0
Exfoliative dermatitis NOS	7	10	6	1	12	16	6	1
Radiation dermatitis NOS	9	22	5	2	9	23	15	2

(continued on following page)

Table A2. Grade 1 to 4 Treatment-Related Acute Adverse Events (continued)

Adverse Event	RT + Cisplatin-Cetuximab (n = 97) Grade				RT + Docetaxel-Cetuximab (n = 106) Grade			
	1	2	3	4	1	2	3	4
Other	5	3	3	0	5	6	2	0
Dry skin	8	4	0	0	10	2	0	0
Erythema multiforme	1	2	0	0	0	6	2	0
Fat atrophy NOS	1	0	0	0	0	1	0	0
Flushing	0	0	0	0	3	0	0	0
Injection site reaction NOS	0	0	0	0	2	0	0	0
Localized exfoliation	1	2	0	0	1	1	0	0
Nail disorder NOS	0	1	0	0	0	0	0	0
Photosensitivity reaction NOS	1	0	0	0	1	0	0	0
Pruritus	5	2	1	0	10	2	0	0
Radiation recall syndrome	3	15	11	2	1	12	6	1
Skin atrophy	2	1	0	0	0	1	0	0
Skin fibrosis	8	10	0	0	11	6	1	0
Skin hyperpigmentation	15	7	0	0	14	3	0	0
Skin hypopigmentation	3	1	0	0	2	0	0	0
Telangiectasia	3	0	0	0	2	1	0	0
Ulceration	0	0	0	0	0	1	0	0
Urticaria NOS	0	0	1	0	1	0	0	0
Endocrine	1	5	0	0	1	4	0	0
Adrenal insufficiency NOS	0	1	0	0	0	1	0	0
Hypothyroidism	1	4	0	0	0	3	0	0
Thyrotoxicosis	0	0	0	0	1	0	0	0
GI	2	22	66	4	1	24	71	9
Abdominal distention	0	1	0	0	0	0	0	0
Acquired tracheoesophageal fistula	0	0	0	0	0	0	1	0
Anorexia	7	22	16	0	9	20	9	0
Constipation	11	5	0	0	14	6	0	0
Dehydration	1	18	10	0	1	9	4	1
Diarrhea NOS	15	7	0	0	12	4	4	0
Dry mouth	24	43	8	0	33	42	5	0
Dysgeusia	15	31	0	0	13	32	0	0
Dyspepsia	3	2	0	0	3	3	0	0
Dysphagia	9	22	37	0	8	32	39	0
Acquired esophageal stenosis	0	0	3	0	0	3	1	0
Esophagitis NOS	0	5	4	0	4	6	6	0
GI fistula, oral cavity	1	0	0	0	0	0	0	0
Flatulence	1	0	0	0	0	0	0	0
Other	2	2	0	0	2	6	1	0
Mucositis/stomatitis (clinical exam)								
Anus	0	0	0	0	0	2	1	0
Esophagus	0	1	1	0	0	0	1	0
Large bowel	1	0	0	0	0	0	0	0
Larynx	0	0	0	0	0	2	1	0
Pharynx	3	3	9	0	2	1	1	0
Trachea	0	1	0	0	0	0	0	0
Mucositis/stomatitis (functional/symptomatic)								
Esophagus	1	0	1	0	0	1	1	0
Larynx	0	0	1	0	0	0	0	0
Pharynx	1	1	5	0	1	4	5	0
Nausea	20	20	12	0	22	17	7	0
Necrotizing ulcerative gingivostomatitis	0	0	1	0	0	0	0	0
Pharyngeal stenosis	0	0	1	0	0	0	1	0
Radiation mucositis	6	18	33	3	11	22	30	7
Salivary gland disorder NOS	7	19	2	0	6	26	2	0
Stomatitis	2	8	9	1	3	12	18	2
Vomiting NOS	10	12	7	0	14	11	4	0

(continued on following page)

Table A2. Grade 1 to 4 Treatment-Related Acute Adverse Events (continued)

Adverse Event	RT + Cisplatin-Cetuximab (n = 97) Grade				RT + Docetaxel-Cetuximab (n = 106) Grade			
	1	2	3	4	1	2	3	4
Hemorrhage/bleeding	4	0	0	0	1	0	0	0
Epistaxis	1	0	0	0	0	0	0	0
Other	0	0	0	0	1	0	0	0
Intestinal stoma site bleeding	1	0	0	0	0	0	0	0
Respiratory tract hemorrhage NOS	2	0	0	0	0	0	0	0
Hepatobiliary/pancreas	0	0	0	0	0	1	0	0
Other	0	0	0	0	0	1	0	0
Infection	2	22	9	1	3	11	12	1
Bladder infection NOS	0	0	1	0	0	0	0	0
Bronchitis NOS	0	1	0	0	0	0	0	0
Febrile neutropenia	0	0	3	1	0	0	0	0
Gingival infection	0	5	1	0	0	1	1	0
Other	3	6	0	0	3	0	5	0
Infection with grade 3 or 4 neutrophils (ANC $< 1.0 \times 10^9$/L)								
Urinary bladder	0	0	1	0	0	0	0	0
Dental-tooth	0	0	0	0	0	1	0	0
External ear (otitis externa)	0	1	0	0	0	0	0	0
Middle ear (otitis media)	0	1	0	0	0	0	0	0
Mucosa	0	0	0	0	0	2	0	0
Muscle (infection myositis)	0	0	1	0	0	0	0	0
Pharynx	0	0	0	0	0	1	0	0
Skin (cellulitis)	0	0	0	0	0	0	2	0
Wound	0	1	0	0	0	0	0	0
Infection with normal ANC or grade 1 or 2 neutrophils								
Appendix	0	0	0	0	0	1	0	0
Blood	0	0	0	0	0	0	1	0
Catheter-related	0	0	0	0	0	1	0	0
Neck NOS	0	0	0	0	0	0	1	0
Upper aerodigestive tract NOS	0	3	1	0	0	0	0	0
Wound	0	1	1	0	0	1	0	0
Infection with unknown ANC								
Neck NOS	0	0	0	0	0	0	1	0
Oral cavity-gums (gingivitis)	0	0	0	0	0	1	0	0
Pharynx	0	1	0	0	0	0	0	0
Skin (cellulitis)	0	1	0	0	0	0	1	0
Nasopharyngitis	0	2	1	0	0	1	0	0
Opportunisitic infection	0	1	0	0	0	1	1	0
Pharyngitis	0	1	0	0	0	2	0	0
Pneumonia NOS	0	0	0	0	0	0	0	1
Sinusitis NOS	0	1	0	0	0	0	0	0
Skin infection	0	0	1	0	0	1	1	0
Lymphatics	16	7	2	0	14	11	1	0
Head and neck edema	12	7	2	0	12	10	1	0
Limb edema	2	0	0	0	1	0	0	0
Other	1	0	0	0	0	1	0	0
Lymphedema NOS	0	0	0	0	1	0	0	0
Lymphedema-related fibrosis	3	0	0	0	3	0	0	0
Metabolic/laboratory	35	13	14	0	31	22	11	3
Increased ALT	7	2	1	0	10	4	1	0
Increased AST	16	0	1	0	15	2	5	0
Increased blood alkaline phosphatase	5	0	0	0	11	0	0	0
Decreased blood bicarbonate	0	0	0	0	1	0	0	0
Increased blood bilirubin	4	0	0	0	3	3	1	0
Increased blood creatinine phosphokinase	0	0	0	0	0	1	0	1
Increased blood creatinine	3	3	0	0	3	1	0	1

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Table A2. Grade 1 to 4 Treatment-Related Acute Adverse Events (continued)

Adverse Event	RT + Cisplatin-Cetuximab (n = 97) Grade				RT + Docetaxel-Cetuximab (n = 106) Grade			
	1	2	3	4	1	2	3	4
Hypercalcemia	2	1	0	0	3	0	0	0
Hyperglycemia NOS	20	4	1	0	12	8	0	0
Hyperkalemia	12	1	1	0	3	4	0	0
Hypermagnesemia	4	0	0	0	6	0	0	0
Hypernatremia	1	0	0	0	1	1	0	0
Hypoalbuminemia	12	6	0	0	14	11	1	0
Hypocalcemia	12	3	2	0	8	7	2	0
Hypoglycemia NOS	0	0	0	0	2	0	0	0
Hypokalemia	14	0	4	0	9	1	5	1
Hypomagnesemia	20	6	1	0	11	0	0	0
Hyponatremia	24	0	5	0	22	0	3	0
Hypophosphatemia	0	1	0	0	1	0	0	0
Other	3	0	0	0	6	1	1	0
Musculoskeletal/soft tissue	12	8	4	0	9	19	4	0
Upper extremity (function)	0	0	0	0	1	0	0	0
Cosmesis fibrosis	2	0	0	0	1	2	0	0
Deep connective tissue fibrosis	2	5	1	0	2	8	1	0
Joint disorder NOS	1	0	0	0	1	0	0	0
Muscle weakness NOS	4	0	0	0	1	1	0	0
Facial muscle weakness, generalized or specific area (not due to neuropathy)	0	1	0	0	0	1	0	0
Other	2	1	0	0	3	2	0	0
Myositis	0	0	0	0	0	0	1	0
Osteonecrosis	0	1	1	0	0	1	0	0
Head soft tissue necrosis	0	1	0	0	0	0	1	0
Neck soft tissue necrosis	0	0	0	0	0	0	1	0
Trismus	4	2	2	0	4	6	1	0
Neurology	14	12	2	0	12	3	4	0
Agitation	0	0	0	0	0	1	0	0
Anxiety	1	3	0	0	1	2	1	0
Ataxia	0	0	0	0	0	1	0	0
Cognitive disorder	0	1	0	0	0	1	0	0
Confusional state	0	0	0	0	0	1	1	0
Depressed level of consciousness	0	1	2	0	0	0	1	0
Depression	1	5	0	0	2	2	2	0
Dizziness	9	2	0	0	4	0	0	0
Euphoric mood	0	0	0	0	0	1	0	0
Extrapyramidal disorder	0	0	0	0	1	1	0	0
Memory impairment	0	0	0	0	1	0	0	0
Mental status changes	0	0	0	0	0	1	0	0
Myelitis NOS	0	0	0	0	1	0	0	0
Other	1	1	0	0	0	0	0	0
Oculomotor nerve operation	0	1	0	0	0	0	0	0
Peripheral motor neuropathy	0	2	0	0	1	0	0	0
Peripheral sensory neuropathy	6	1	0	0	7	0	0	0
Aggravated psychosis	0	0	0	0	0	1	0	0
Speech disorder	0	0	0	0	0	1	1	0
Tremor	0	0	0	0	1	1	0	0
Trigeminal nerve disorder NOS	0	1	0	0	1	1	0	0
Ocular/visual	3	3	0	0	4	4	0	0
Conjunctivitis	0	2	0	0	1	3	0	0
Diplopia	0	1	0	0	0	0	0	0
Dry eye NOS	0	0	0	0	0	1	0	0
Other	2	0	0	0	0	0	0	0
Photophobia	1	0	0	0	0	0	0	0
Blurred vision	1	0	0	0	3	0	0	0

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Table A2. Grade 1 to 4 Treatment-Related Acute Adverse Events (continued)

Adverse Event	RT + Cisplatin-Cetuximab (n = 97) Grade				RT + Docetaxel-Cetuximab (n = 106) Grade			
	1	2	3	4	1	2	3	4
Pain	10	42	14	0	19	42	13	0
Abdominal pain NOS	0	0	0	0	3	0	0	0
Arthralgia	1	0	1	0	1	0	0	0
Bone pain	0	1	0	0	1	0	0	0
Chest pain	0	2	0	0	1	0	0	0
Ear pain	2	0	0	0	2	0	0	0
Esophageal pain	2	2	0	0	1	3	0	0
Facial pain	1	0	0	0	0	2	2	0
GI pain NOS	1	0	0	0	0	0	0	0
Gingival pain	0	1	0	0	0	0	0	0
Headache	12	12	2	0	18	6	2	0
Laryngeal discomfort	1	0	0	0	0	1	0	0
Lip pain	1	1	0	0	0	1	1	0
Myalgia	1	0	1	0	2	1	0	0
Neck pain	7	7	1	0	4	4	1	0
Oral pain	3	16	7	0	4	27	8	0
Other	1	6	0	0	3	4	0	0
Pain NOS	0	1	0	0	0	3	0	0
Pain in extremity	0	0	0	0	1	0	0	0
Skin pain	0	2	2	0	0	3	2	0
External ear pain	0	1	0	0	1	0	0	0
Scalp pain	0	0	0	0	0	0	1	0
Pharyngolaryngeal pain	7	11	3	0	2	11	1	0
Sinus pain	0	0	0	0	0	1	0	0
Toothache	0	1	0	0	0	0	0	0
Pulmonary/upper respiratory	22	10	4	1	18	12	6	2
Acute respiratory distress syndrome	0	0	0	0	0	0	0	1
Aspiration	0	0	0	0	2	1	0	1
Atelectasis	0	0	0	0	1	1	0	0
Bronchospasm	0	0	0	0	1	0	0	0
Cough	10	2	0	0	16	1	0	0
Dyspnea	2	1	0	1	4	1	2	0
Hiccups	1	0	0	0	0	1	0	0
Hypoxia	0	0	1	0	0	0	3	0
Laryngeal edema	3	2	0	0	3	1	0	0
Laryngeal stenosis	1	0	0	0	0	0	0	0
Laryngitis NOS	14	7	2	0	10	7	1	1
Pleural effusion	0	0	0	0	0	1	0	0
Pneumonitis NOS	1	0	1	1	0	0	1	0
Pulmonary fibrosis	0	0	0	0	0	1	0	0
Other	0	0	0	0	0	3	1	0
Tracheal stenosis	0	0	0	0	1	1	0	0
Renal/genitourinary	1	1	1	0	0	0	1	0
Pollakiuria	1	1	0	0	0	0	0	0
Renal failure NOS	0	0	1	0	0	0	1	0
Other	0	0	1	0	0	0	0	0
Sexual/reproductive function	0	0	0	0	1	0	0	0
Erectile dysfunction NOS	0	0	0	0	1	0	0	0
Syndromes	0	0	0	0	0	1	0	0
Cytokine release syndrome	0	0	0	0	0	1	0	0
Vascular	0	0	1	0	0	0	0	0
Thrombosis	0	0	1	0	0	0	0	0
Unknown term	0	1	0	0	0	1	1	0

NOTE. Treatment related: definitely, probably, or possibly related to protocol treatment (or within unknown relationship). Acute: within 1 year after start of treatment.

Abbreviations: ANC, absolute neutrophil count; NOS, not otherwise specified; RT, radiation therapy.

Table A3. Grade 1 to 4 Treatment-Related Late Adverse Events

Adverse Event	RT + Cisplatin-cetuximab (n = 84) Grade				RT + Docetaxel-Cetuximab (n = 93) Grade			
	1	2	3	4	1	2	3	4
Maximum late grade								
Overall	17	28	14	0	20	42	13	1
Nonhematologic	18	28	13	0	20	42	13	1
Auditory/ear	1	1	0	0	1	7	0	0
Other	0	0	0	0	1	0	0	0
Hearing impaired	0	1	0	0	0	5	0	0
Tinnitus	1	1	0	0	0	4	0	0
Blood/bone marrow	3	5	1	0	4	4	0	0
Other	1	0	0	0	0	0	0	0
Hemoglobin	3	0	0	0	2	2	0	0
Leukopenia NOS	3	0	0	0	2	0	0	0
Lymphopenia	1	5	1	0	2	3	0	0
Decreased platelet count	1	0	0	0	1	0	0	0
Constitutional symptoms	10	5	2	0	10	7	1	0
Other	1	0	0	0	1	0	0	0
Fatigue	6	3	1	0	10	3	0	0
Insomnia	0	1	0	0	1	0	0	0
Decreased weight	4	2	1	0	3	4	1	0
Dermatology/skin	14	14	1	0	19	15	0	0
Alopecia	0	0	0	0	2	0	0	0
Negative culture wound	1	0	0	0	0	0	0	0
Decubitus ulcer	0	0	0	0	0	1	0	0
Radiation dermatitis NOS	3	0	0	0	1	0	0	0
Other	2	1	0	0	1	2	0	0
Dry skin	1	1	0	0	4	0	0	0
Fat atrophy NOS	0	0	0	0	1	0	0	0
Nail disorder NOS	0	1	0	0	0	0	0	0
Pruritus	1	0	0	0	0	0	0	0
Radiation recall syndrome	0	0	0	0	0	1	0	0
Skin atrophy	1	0	0	0	0	0	0	0
Skin fibrosis	9	10	1	0	16	8	0	0
Skin hyperpigmentation	7	2	0	0	6	3	0	0
Skin hypopigmentation	1	1	0	0	3	0	0	0
Telangiectasia	2	1	0	0	5	3	0	0
Ulceration	0	0	0	0	0	1	0	0
Endocrine	2	5	0	0	3	9	0	0
Adrenal insufficiency NOS	0	0	0	0	0	1	0	0
Other	1	0	0	0	0	0	0	0
Hypothyroidism	2	4	0	0	3	9	0	0
Thyrotoxicosis	0	1	0	0	0	0	0	0
GI	24	22	7	0	28	33	7	0
Acquired tracheoesophageal fistula	0	0	0	0	0	1	0	0
Anorexia	0	2	0	0	2	1	0	0
Dental prosthesis user	0	0	0	0	0	0	1	0
Diarrhea NOS	0	0	0	0	1	0	0	0
Dry mouth	30	16	2	0	34	23	1	0
Dysgeusia	15	2	0	0	16	5	0	0
Dyspepsia	0	0	0	0	0	1	0	0
Dysphagia	13	8	5	0	15	19	3	0
Acquired esophageal stenosis	1	0	3	0	0	4	2	0
Esophagitis NOS	0	1	0	0	1	1	0	0
Other	1	2	1	0	4	0	0	0
Mucositis/stomatitis								
Larynx (clinical exam)	0	0	0	0	1	0	0	0
Larynx (functional/symptomatic)	0	0	0	0	0	1	0	0

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Table A3. Grade 1 to 4 Treatment-Related Late Adverse Events (continued)

Adverse Event	RT + Cisplatin-cetuximab (n = 84) Grade				RT + Docetaxel-Cetuximab (n = 93) Grade			
	1	2	3	4	1	2	3	4
Nausea	0	0	0	0	2	0	0	0
Periodontal disorder NOS	0	1	0	0	2	0	1	0
Pharyngeal stenosis	0	1	0	0	0	2	1	0
Radiation mucositis	0	0	0	0	1	0	0	0
Salivary gland disorder NOS	5	5	0	0	3	5	0	0
Stomatitis	0	0	0	0	1	2	0	0
GI stoma stricture/stenosis (including anastomotic)	0	0	0	0	0	1	0	0
Tooth development disorder	0	1	0	0	0	0	0	0
Tooth disorder NOS	0	4	1	0	1	2	2	0
Vomiting NOS	0	1	0	0	1	0	0	0
Hemorrhage/bleeding	0	0	0	0	1	0	0	0
Epistaxis	0	0	0	0	1	0	0	0
Infection	0	0	0	0	1	5	0	0
Gingival infection	0	0	0	0	0	1	0	0
Other	0	0	0	0	1	0	0	0
Infection with normal ANC or grade 1 or 2 neutrophils								
Esophagus	0	0	0	0	0	1	0	0
Paranasal	0	0	0	0	0	1	0	0
Infection with unknown ANC								
Soft tissue NOS	0	0	0	0	0	1	0	0
Nasopharyngitis	0	0	0	0	0	1	0	0
Pneumonia NOS	0	0	0	0	0	1	0	0
Skin infection	0	0	0	0	0	1	0	0
Lymphatics	6	3	0	0	9	0	0	0
Head and neck edema	6	2	0	0	7	0	0	0
Lymphedema NOS	0	1	0	0	1	0	0	0
Lymphedema-related fibrosis	0	0	0	0	2	0	0	0
Metabolic/laboratory	2	2	0	0	1	1	1	0
Increased blood bilirubin	1	0	0	0	0	0	0	0
Increased blood creatinine	1	1	0	0	0	0	0	0
Hypercalcemia	1	0	0	0	1	0	0	0
Hyperglycemia NOS	1	0	0	0	1	1	0	0
Hyperkalemia	0	0	0	0	1	0	0	0
Hypernatremia	0	0	0	0	0	0	1	0
Hypoalbuminemia	0	1	0	0	0	0	0	0
Hypocalcemia	1	0	0	0	1	1	0	0
Hypokalemia	0	0	0	0	1	0	0	0
Hyponatremia	1	0	0	0	1	0	0	0
Other	1	0	0	0	0	0	0	0
Musculoskeletal/soft tissue	4	8	2	0	10	26	2	0
Cervical spine range of motion	1	0	0	0	0	0	0	0
Cosmesis fibrosis	2	2	1	0	3	3	0	0
Deep connective tissue fibrosis	3	4	1	0	1	14	0	0
Muscle weakness NOS	0	1	0	0	0	2	0	0
Muscle weakness, generalized or specific area (not due to neuropathy)								
Upper extremity	0	0	0	0	0	1	0	0
Facial	0	0	0	0	1	1	0	0
Left-sided	0	0	0	0	1	0	0	0
Muscular/skeletal hypoplasia	0	0	0	0	0	1	0	0
Other	1	0	0	0	6	1	0	0
Osteonecrosis	0	0	1	0	1	1	0	0
Osteoporosis NOS	0	0	0	0	0	0	1	0
Trismus	2	2	0	0	7	7	1	0

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Table A3. Grade 1 to 4 Treatment-Related Late Adverse Events (continued)

Adverse Event	RT + Cisplatin-cetuximab (n = 84) Grade				RT + Docetaxel-Cetuximab (n = 93) Grade			
	1	2	3	4	1	2	3	4
Neurology	6	5	0	0	6	4	1	0
Agitation	0	1	0	0	0	0	0	0
Anxiety	0	0	0	0	1	1	0	0
Depression	1	2	0	0	0	1	0	0
Dizziness	0	1	0	0	0	0	0	0
Facial nerve disorder NOS	1	0	0	0	1	0	0	0
Hypoglossal nerve disorder NOS	1	0	0	0	0	1	0	0
Myelitis NOS	0	0	0	0	1	0	1	0
Other	1	0	0	0	1	1	0	0
Peripheral motor neuropathy	1	0	0	0	0	0	0	0
Peripheral sensory neuropathy	1	1	0	0	2	2	0	0
Speech disorder	0	0	0	0	0	1	0	0
Syncope	0	0	0	0	0	1	0	0
Trigeminal nerve disorder NOS	0	0	0	0	3	0	0	0
Ocular/visual	0	0	0	0	2	0	0	0
Photopsia	0	0	0	0	1	0	0	0
Blurred vision	0	0	0	0	1	0	0	0
Pain	11	7	1	0	4	10	1	0
Abdominal pain NOS	1	0	0	0	0	0	0	0
Arthralgia	2	1	0	0	0	0	0	0
Back pain	1	0	0	0	0	0	0	0
Bone pain	0	0	0	0	0	1	0	0
Ear pain	2	0	0	0	0	0	0	0
Esophageal pain	0	0	0	0	0	1	0	0
Facial pain	0	1	0	0	0	0	0	0
Headache	3	0	0	0	2	1	0	0
Myalgia	0	0	0	0	0	1	0	0
Neck pain	3	4	0	0	1	4	0	0
Oral pain	2	1	1	0	2	3	0	0
Other	0	0	0	0	0	1	0	0
Pain NOS	0	1	0	0	0	1	0	0
Pharyngolaryngeal pain	1	1	0	0	1	0	0	0
Sinus pain	0	0	0	0	1	0	0	0
Toothache	0	1	0	0	0	0	1	0
Pulmonary/upper respiratory	5	2	2	0	13	5	1	0
Aspiration	0	0	1	0	0	3	0	0
Cough	1	0	0	0	3	1	0	0
Dyspnea	2	0	0	0	3	1	0	0
Laryngeal edema	1	1	0	0	4	1	0	0
Laryngeal stenosis	0	0	0	0	0	1	0	0
Laryngitis NOS	0	1	1	0	6	2	1	0
Pneumonitis NOS	0	0	0	0	0	1	0	0
Pulmonary fibrosis	2	0	0	0	3	1	0	0
Other	1	0	0	0	1	0	0	0
Renal/genitourinary	0	0	1	0	0	0	0	0
Renal failure NOS	0	0	1	0	0	0	0	0
Surgery/intraoperative injury	1	0	0	0	0	0	1	0
Pharynx	0	0	0	0	0	0	1	0
Testis	1	0	0	0	0	0	0	0
Vascular	0	0	1	0	0	0	0	1
Other	0	0	0	0	0	0	0	1
Carotid artery injury	0	0	1	0	0	0	0	0

NOTE. Treatment related: definitely, probably, or possibly related to protocol treatment (or within unknown relationship). Late: more than 1 year after start of treatment.

Abbreviations: ANC, absolute neutrophil count; NOS, not otherwise specified; RT, radiation therapy.

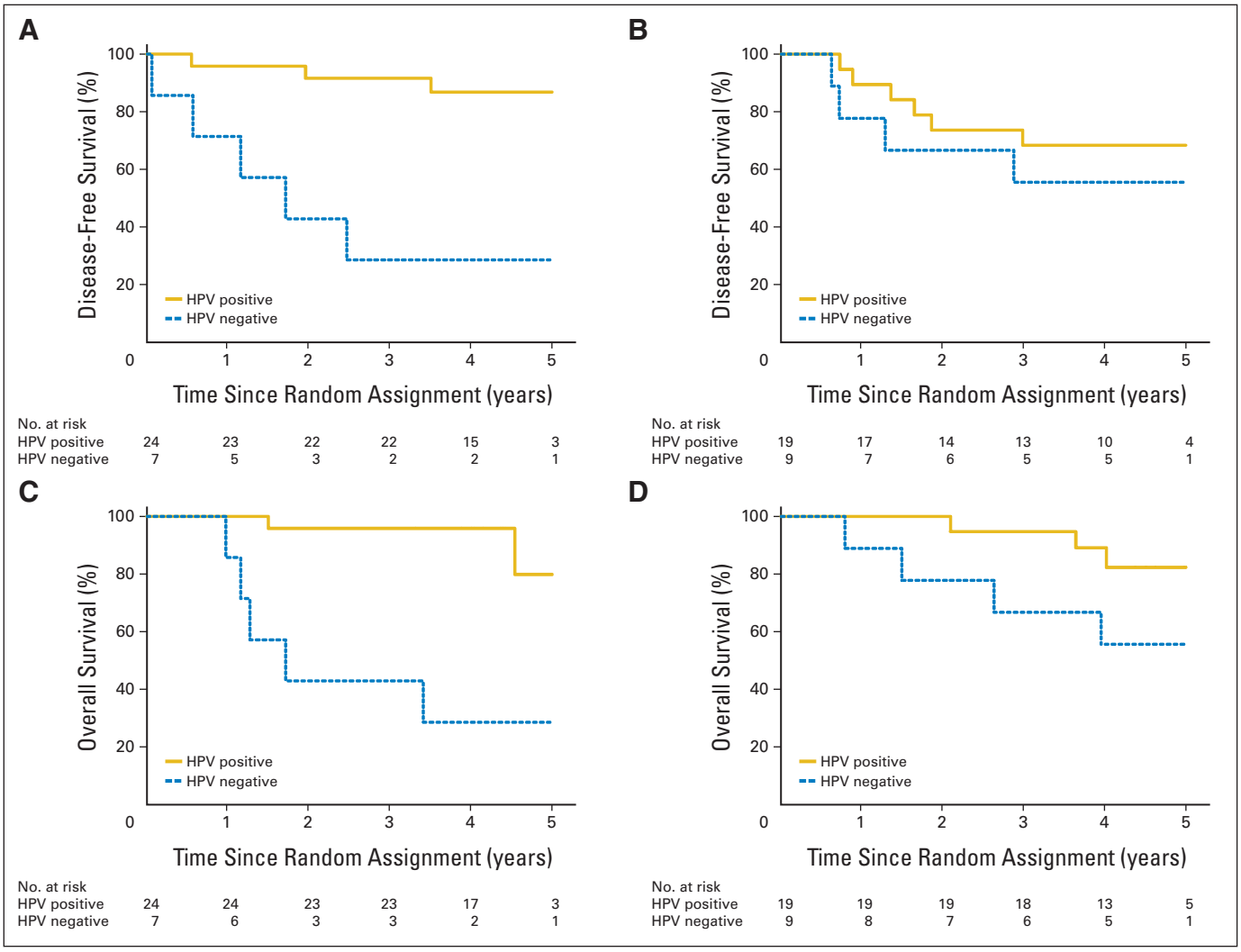

Fig A1. (A-B) Disease-free survival (DFS) and (C-D) overall survival (OS) estimates for patients with oropharynx cancer in Radiation Therapy Oncology Group RTOG-0234 (Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 [Cetuximab] for Advanced Squamous Cell Carcinoma of the Head and Neck) by human papillomavirus (HPV) status. On the cisplatin arm, 2-year DFS estimate was 91.7% (95% CI, 80.6% to 100.0%) for patients with HPV-positive tumors and 42.9% (95% CI, 6.2% to 79.5%) for patients with HPV-negative tumors. (A) Hazard ratio [HR], 0.11; 95% CI, 0.03 to 0.47; $P < .001$. On the docetaxel arm, 2-year DFS estimate was 73.7% (95% CI, 53.8% to 93.5%) for patients with HPV-positive tumors and 66.7% (95% CI, 35.9% to 97.5%) for patients with HPV-negative tumors. (B) HR, 0.60; 95% CI, 0.17 to 2.11; $P = .42$. On the cisplatin arm, 2-year OS estimate was 95.8% (95% CI, 87.8% to 100.0%) for patients with HPV-positive tumors and 42.9% (95% CI, 6.2% to 79.5%) for patients with HPV-negative tumors. (C) HR, 0.09; 95% CI, 0.02 to 0.44; $P < .001$. On the docetaxel arm, 2-year OS estimate was 100.0% for patients with HPV-positive tumors and 77.8% (95% CI, 50.6% to 100.0%) for patients with HPV-negative tumors. (D) HR, 0.30; 95% CI, 0.07 to 1.33; $P = .09$.