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Title

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ORIGINAL REPORT

Randomized Phase III Trial of Concurrent Accelerated Radiation Plus Cisplatin With or Without Cetuximab for Stage III to IV Head and Neck Carcinoma: RTOG 0522

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A B S T R A C T

Purpose
Combining cisplatin or cetuximab with radiation improves overall survival (OS) of patients with stage III or IV head and neck carcinoma (HNC). Cetuximab plus platinum regimens also increase OS in metastatic HNC. The Radiation Therapy Oncology Group launched a phase III trial to test the hypothesis that adding cetuximab to the radiation-cisplatin platform improves progression-free survival (PFS).

Patients and Methods
Eligible patients with stage III or IV HNC were randomly assigned to receive radiation and cisplatin without (arm A) or with (arm B) cetuximab. Acute and late reactions were scored using Common Terminology Criteria for Adverse Events (version 3). Outcomes were correlated with patient and tumor features and markers.

Results
Of 891 analyzed patients, 630 were alive at analysis (median follow-up, 3.8 years). Cetuximab plus cisplatin-radiation, versus cisplatin-radiation alone, resulted in more frequent interruptions in radiation therapy (26.9% v 15.1%, respectively); similar cisplatin delivery (mean, 185.7 mg/m² v 191.1 mg/m², respectively); and more grade 3 to 4 radiation mucositis (43.2% v 33.3%, respectively), rash, fatigue, anorexia, and hypokalemia, but not more late toxicity. No differences were found between arms A and B in 30-day mortality (1.8% v 2.0%, respectively; P = .81), 3-year PFS (61.2% v 58.9%, respectively; P = .76), 3-year OS (72.9% v 75.8%, respectively; P = .32), locoregional failure (19.9% v 25.9%, respectively; P = .97), or distant metastasis (13.0% v 9.7%, respectively; P = .08). Patients with p16-positive oropharyngeal carcinoma (OPC), compared with patients with p16-negative OPC, had better 3-year probability of PFS (72.8% v 49.2%, respectively; P < .001) and OS (85.6% v 60.1%, respectively; P < .001), but tumor epidermal growth factor receptor (EGFR) expression did not distinguish outcome.

Conclusion
Adding cetuximab to radiation-cisplatin did not improve outcome and hence should not be prescribed routinely. PFS and OS were higher in patients with p16-positive OPC, but outcomes did not differ by EGFR expression.

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INTRODUCTION

Treatment of patients with locally advanced head and neck carcinomas (HNCs) remains a challenge. A thorough meta-analysis of randomized trials[1] showed that adding cisplatin concurrently to radiotherapy improved progression-free survival (PFS), overall survival (OS), and organ preservation, but only approximately 50% of patients survived more than 5 years. Moreover, radiation-cisplatin regimens induce severe acute and late morbidity.[2] These observations inspired the search for alternative therapy approaches.

Available data showed that most HNCs express high levels of epidermal growth factor receptor (EGFR),[3-5] that high EGFR expression was associated with poor response to radiation[4] or chemoradiotherapy,[5] and that EGFR inhibitors sensitized

tumors to cisplatin[6] or radiation.[7-9] A pivotal trial of the anti-EGFR antibody cetuximab and radiation therapy demonstrated that administering eight weekly doses of cetuximab concurrently with radiotherapy to patients with previously untreated locally advanced HNC significantly improved the median survival time and rates of locoregional control (LRC) and OS without increasing radiation-associated acute toxicity.[10] Furthermore, in patients with metastatic disease, adding cetuximab to cisplatin increased the response rate.[11] Another ongoing trial addressed the combination of cetuximab and platinum-based therapy, ultimately with positive results.[12] Because cetuximab enhances HNC response to both radiation and cisplatin, it was hypothesized that adding cetuximab to the radiation-cisplatin platform would improve PFS of patients with locally advanced HNC. Although a phase II trial of a radiation-cisplatin-cetuximab triplet was closed early because of two deaths, one myocardial infarction, one case of bacteremia, and one case of atrial fibrillation,[13] longer follow-up data revealed encouraging rates of 3-year OS and LRC. Therefore, Radiation Therapy Oncology Group (RTOG) investigators launched a

phase III trial (RTOG 0522), with close monitoring, to examine the efficacy of this triplet. This article presents the overall outcome and results of planned correlative studies.

PATIENTS AND METHODS

Protocol and Treatment

Eligible patients had untreated, histologically confirmed, stage III or IV (T2N2-3M0 or T3-4, any N, M0) squamous cell carcinoma of the oropharynx, hypopharynx, or larynx; Zubrod performance status 0 to 1; age ≥ 18 years; any tobacco status; and adequate bone marrow, hepatic, and renal functions. Lifetime tobacco exposure was determined at enrollment using a standardized questionnaire.

Patients were stratified by tumor site (larynx v other), nodal stage (N0 v N1-N2b v N2c-N3), Zubrod performance status (0 v 1), use of intensity-modulated radiotherapy (IMRT; yes v no), and receipt of pretreatment fused positron emission tomography/computed tomography scan (yes v no), and were randomly assigned to radiotherapy with concurrent cisplatin without (arm A) or with cetuximab (arm B) in a 1:1 ratio using permuted block
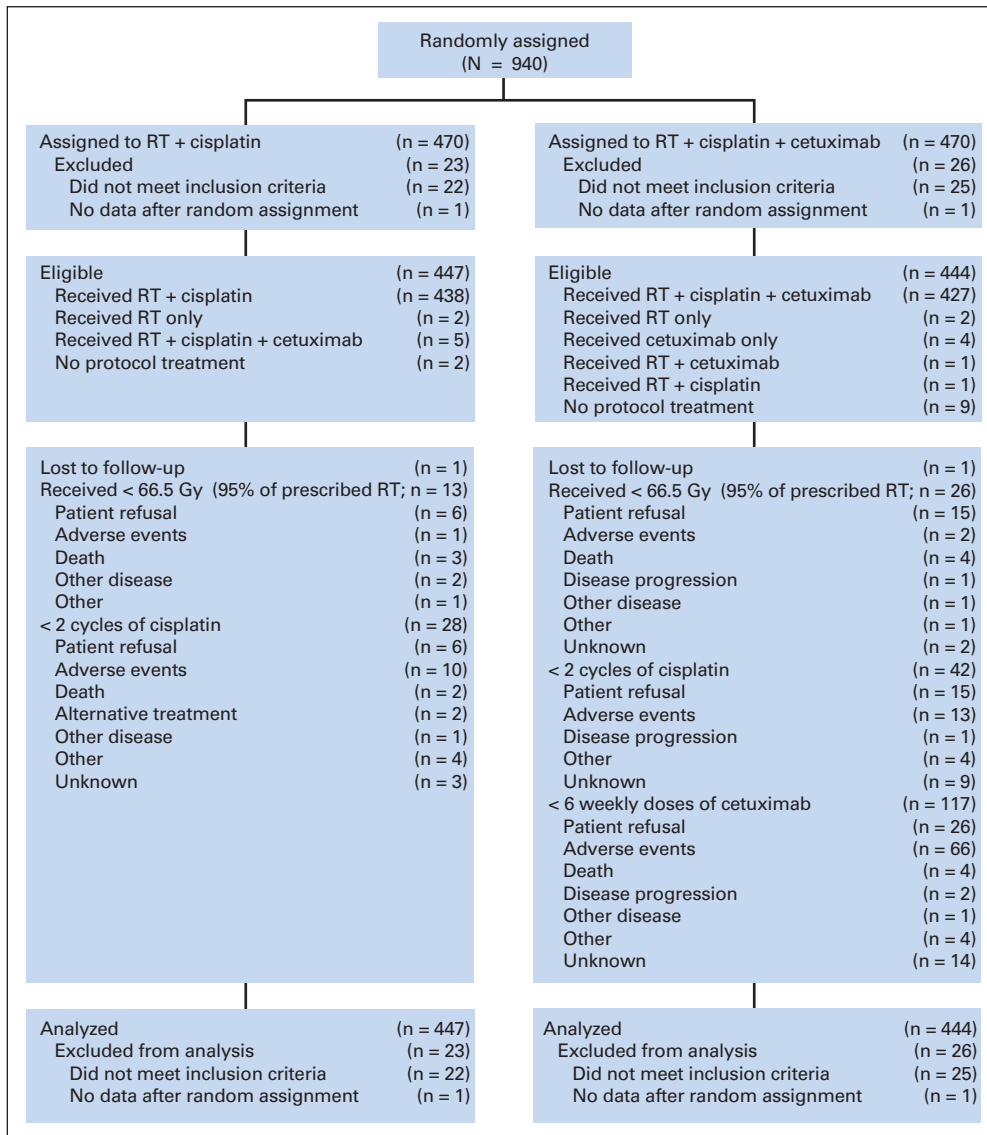
Fig 1. CONSORT diagram. RT, radiotherapy.

Table 1. Baseline Patient Demographic and Clinical Characteristics

| | All Eligible Patients | | | | Patients With Oropharyngeal Cancer and Tumor Specimens for p16 Assay | | | | | Patients With Tumor Specimens for EGFR Assay | | | | |
| | Arm A: RT + Cisplatin (n = 447) | | Arm B: RT + Cisplatin + Cetuximab (n = 444) | | p16 Positive (n = 235) | | p16 Negative (n = 86) | | | EGFR < 80%* (n = 235) | | EGFR ≥ 80%* (n = 145) | | |
Characteristic	No.	%	No.	%	No.	%	No.	%	P	No.	%	No.	%	P
Treatment assigned									.46†					.98†
RT + cisplatin	447	100.0	0	0	112	47.7	45	52.3		117	49.8	72	49.7	
RT + cisplatin + cetuximab	0	0	444	100.0	123	52.3	41	47.7		118	50.2	73	50.3	
Age, years									.14‡					.69‡
Median	57		58		56		58			57		58		
Range	31-79		34-76		36-76		40-75			36-79		31-79		
Sex									.009†					.92†
Male	387	86.6	399	89.9	221	94.0	73	84.9		205	87.2	127	87.6	
Female	60	13.4	45	10.1	14	6.0	13	15.1		30	12.8	18	12.4	
Race									.001§					.33§
White	411	91.9	399	89.9	223	94.9	74	86.0		211	89.8	129	89.0	
Nonwhite	33	7.4	39	8.8	9	3.8	12	14.0		22	9.4	12	8.3	
Unknown	3	0.7	6	1.4	3	1.3	0	0		2	0.9	4	2.8	
Zubrod performance status									.02†					.01†
0	292	65.3	295	66.4	174	74.0	52	60.5		162	68.9	81	55.9	
1	155	34.7	149	33.6	61	26.0	34	39.5		73	31.1	64	44.1	
Weight loss in last 6 months									.01§					.37§
< 5% of body weight	290	64.9	290	65.3	173	73.6	51	59.3		166	70.6	93	64.1	
≥ 5% of body weight	130	29.1	128	28.8	50	21.3	30	34.9		59	25.1	41	28.3	
Unknown	27	6.0	26	5.9	12	5.1	5	5.8		10	4.3	11	7.6	
Feeding tube use									.13§					.80§
No	380	85.0	388	87.4	209	88.9	71	82.6		202	86.0	126	86.9	
Yes	66	14.8	55	12.4	26	11.1	15	17.4		33	14.0	19	13.1	
Unknown	1	0.2	1	0.2	0	0	0	0		0	0	0	0	
Anemia‖									.009†					.46†
No	317	70.9	308	69.4	177	75.3	52	60.5		161	68.5	94	64.8	
Yes	130	29.1	136	30.6	58	24.7	34	39.5		74	31.5	51	35.2	
Primary tumor site														< .001†
Oropharynx	313	70.0	312	70.3	235	100.0	86	100.0		180	76.6	81	55.9	
Hypopharynx	33	7.4	29	6.5	0	0	0	0		12	5.1	14	9.7	
Larynx	101	22.6	103	23.2	0	0	0	0		43	18.3	50	34.5	
T category									.004‡					.13‡
T2	174	38.9	177	39.9	117	49.8	29	33.7		100	42.6	47	32.4	
T3	169	37.8	160	36.0	64	27.2	25	29.1		79	33.6	61	42.1	
T4	104	23.3	107	24.1	54	23.0	32	37.2		56	23.8	37	25.5	
N category									.76‡					.71‡
N0	45	10.1	54	12.2	12	5.1	6	7.0		24	10.2	23	15.9	
N1	41	9.2	40	9.0	15	6.4	9	10.5		18	7.7	17	11.7	
N2a	36	8.1	42	9.5	30	12.8	5	5.8		30	12.8	11	7.6	
N2b	139	31.1	154	34.7	94	40.0	32	37.2		78	33.2	39	26.9	
N2c	159	35.6	137	30.9	65	27.7	26	30.2		72	30.6	40	27.6	
N3	27	6.0	17	3.8	19	8.1	8	9.3		13	5.5	15	10.3	
AJCC stage¶									.92‡					.13‡
III	59	13.2	65	14.6	13	5.5	5	5.8		29	12.3	26	17.9	
IV	388	86.8	379	85.4	222	94.5	81	94.2		206	87.7	119	82.1	
Pretreatment PET/CT									.22†					.08†
No	159	35.6	156	35.1	73	31.1	33	38.4		85	36.2	40	27.6	
Yes	288	64.4	288	64.9	162	68.9	53	61.6		150	63.8	105	72.4	
Tobacco-smoking history, pack-years#									< .001‡					.74‡
Sample size	390		380		215		72			214		124		
Median	22.5		20.7		5.25		29			18		20		
Range	0-150		0-162		0-150		0-104			0-150		0-162		

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| | All Eligible Patients | | | | Patients With Oropharyngeal Cancer and Tumor Specimens for p16 Assay | | | | | Patients With Tumor Specimens for EGFR Assay | | | | |
| | Arm A: RT + Cisplatin (n = 447) | | Arm B: RT + Cisplatin + Cetuximab (n = 444) | | p16 Positive (n = 235) | | p16 Negative (n = 86) | | | EGFR < 80%* (n = 235) | | EGFR ≥ 80%* (n = 145) | | |
Characteristic	No.	%	No.	%	No.	%	No.	%	P	No.	%	No.	%	P
p16 expression in oropharyngeal primary tumor														.06†
Positive	112	35.8	123	39.4	235	100.0	0	0		138	76.7	52	64.2	
Negative	45	14.4	41	13.1	0	0	86	100.0		34	18.9	26	32.1	
Unknown	156	49.8	148	47.4	0	0	0	0		8	4.4	3	3.7	
EGFR immunostaining									.009†					
< 80% of tumor cells positive	117	26.2	118	26.6	138	58.7	34	39.5		235	100.0	0	0	
≥ 80% of tumor cells positive	72	16.1	73	16.4	52	22.1	26	30.2		0	0	145	100.0	
Unknown	258	57.7	253	57.0	45	19.1	26	30.2		0	0	0	0	

Abbreviations: AJCC, American Joint Committee on Cancer; CT, computed tomography; EGFR, epidermal growth factor receptor; PET, positron emission tomography; RT, radiotherapy.
*Percentage of cells staining positive for EGFR.
†Pearson χ^2 test.
‡Wilcoxon rank sum test.
§Pearson χ^2 test excluding unknowns.
‖Anemia is defined as a hemoglobin level of ≤ 13.5 g/dL for men and ≤ 12.5 g/dL for women.
¶AJCC sixth edition staging system.
#A pack-year is defined as the equivalent of smoking one pack of cigarettes a day for 1 year.

random assignment.[14] Accelerated radiotherapy regimens included 72 Gy in 42 fractions given over 6 weeks, using twice-a-day irradiation for 12 treatment days as previously reported.[15] When IMRT was used, a different accelerated schedule of twice-a-day dosing once a week for 5 weeks delivered 70 Gy in 35 fractions (2 Gy per fraction) over 6 weeks per the Danish Head and Neck Cancer Group (DAHANCA) 6 and 7 studies, which showed improved LRC and disease-specific survival compared with conventional fractionation.[16]

Cisplatin dose was 100 mg/m^2 on days 1 and 22 of radiotherapy based on projected findings from RTOG 0129, which showed no significant difference between accelerated fractionation plus two cycles of cisplatin and standard fractionation plus three cycles of cisplatin.[17] As in a previous trial, the cetuximab dose was 400 mg/m^2 the week before radiotherapy and then 250 mg/m^2 per week during radiotherapy.[10] Toxicity was evaluated weekly during therapy using the Common Terminology Criteria for Adverse Events (version 3). Adverse events reported as definitely, probably, or possibly related were considered treatment-related events. Imaging was performed 8 to 9 weeks after treatment, at 6 months, and then annually, with physical examination every 3 months for 2 years, every 6 months through year 5, and then annually to assess tumor status and toxicity.

RTOG 0522 was registered with the National Cancer Institute (NCT00265941) and approved by the central and institutional review boards of the 151 participating centers. All patients provided written informed consent to participate.

Planned Laboratory Studies

As in the previous trial,[17] immunohistochemical assays were used to assess p16 expression in specimens from oropharyngeal carcinomas (OPCs) by using a mouse monoclonal antibody (MTM Laboratories, Heidelberg, Germany) visualized with the Ventana XT autostainer using Ventana's one-view secondary detection kit (Ventana, Tucson, AZ). Stains were scored as positive when strong, diffuse nuclear and cytoplasmic staining was present in 70% of tumor cells.[18]

Specimens from OPCs and other primary tumors were available for EGFR immunohistochemical assay. Individual sections were deparaffinized in xylene, rehydrated with a serial alcohol gradient, and incubated in 3% hydrogen peroxide to block endogenous peroxidase. Antigen was retrieved by placing sections in 0.1 M of citrate buffer, steaming for 25 minutes, and incubating with anti-EGFR antibody (clone 31G7; Invitrogen, Grand Island, NY) diluted to 1:50 and a secondary conjugate antibody (EnVision polymer; DAKO, Carpinteria, CA) in buffer. Slides were developed with a 3,3′-diaminobenzidine chromogen kit and counterstained with hematoxylin. On the basis of the cut point defined from prior validation,[19] EGFR expression was scored in the following two ways: as less than 80% or 80% of tumor cells staining positive for EGFR and by a semiquantitative method (0, +, ++, or +++).

Statistical Analysis

All time-to-event end points were measured from random assignment to date of event or censoring. Patients were grouped by intent-to-treat analysis. PFS failure, the primary end point, was defined as locoregional failure (LRF)/ progression, distant metastasis (DM), or death. We further analyzed LRF (including neck dissection > 15 weeks after radiotherapy or salvage surgery for the primary site unless pathology showed no disease, and death as a result of cancer or unknown causes without a documented failure site) and DM as site of first failure. Other end points for this report included OS, adverse effects, compliance with protocol-defined treatment delivery, and p16 and EGFR expression. Quality-of-life end points and correlation of positron emission tomography findings with outcomes are being reported separately.

RTOG 0522 was initially designed with a sample size of 720 patients to detect a 25% reduction in the hazard associated with disease-free survival with 80% power and a one-sided test at the $P = .025$ level. The primary end point was changed to PFS in 2008 to allow comparisons with the end point in the international meta-analysis of event-free survival, which has been shown to be a surrogate for OS.[20] In addition, because the control group had better-than-expected disease-free survival/PFS, the sample size was increased to 945 patients to allow detection of a 25% reduction in the risk of PFS failure with 84% statistical power and a one-sided final test at the $P = .0238$ significance level, after three interim analyses and a planned final analysis at 434 treatment failures. When the third planned interim analysis yielded a conditional power

Table 2. Treatment-Related Adverse Events by Assigned Treatment

| Adverse Event* | % of Patients | | | | | |
| | Arm A: RT + Cisplatin | | Arm B: RT + Cisplatin + Cetuximab | | P† | |
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
Acute period‡						
No. of patients	447		444			
Any event	97	87	97	89	.70	.61
Dysphagia	86	57	82	53	.08	.25
Radiation mucositis	72	33	82	43	< .001	.002
Skin reaction outside portal§	14	1	82	20	< .001	< .001
Skin reaction inside portal‖	79	15	78	25	.87	< .001
Fatigue	60	9	65	14	.17	.03
Nausea	57	14	59	18	.59	.08
Hemoglobin	53	4	51	6	.55	.30
Weight decreased	50	2	52	2	.74	.80
Leukopenia NOS	49	19	50	19	.79	.80
Mucositis/stomatitis (clinical exam): pharynx	49	24	43	28	.11	.29
Vomiting NOS	38	9	42	10	.17	.56
Hyponatremia	34	10	42	13	.01	.29
Dysgeusia	39	0	36	0	.33	—
Dehydration	36	15	37	18	.63	.24
Dry mouth	35	6	37	7	.53	.28
Hypomagnesemia	21	2	36	3	< .001	.26
Neutrophil count	33	16	33	17	.89	.65
Pharyngolaryngeal pain	32	8	26	7	.05	.70
Anorexia	32	11	32	16	.89	.04
Salivary gland disorder NOS	31	2	27	4	.24	.07
Hypoalbuminemia	25	1	30	2	.11	.09
Oral pain	24	7	28	10	.17	.19
Hypocalcemia	16	1	26	3	< .001	.09
Hyperglycemia NOS	23	3	25	3	.48	.84
Hypokalemia	18	5	25	10	.007	.005
Constipation	24	1	24	1	.94	.75
Blood creatinine increased	24	2	17	2	.02	1.00
Platelet count decreased	21	2	22	2	.74	1.00
Lymphopenia	18	13	18	14	1.00	.63
Pyrexia	11	0	18	< 1	.003	.50
Laryngitis NOS	17	2	16	2	.59	.64
ALT increased	14	1	16	2	.35	.30
Tinnitus	16	1	15	< 1	.85	.12
Diarrhea NOS	10	1	16	2	.02	.58
Mucositis/stomatitis (clinical exam): larynx	13	5	13	5	1.00	.76
Alopecia	13	0	11	0	.40	—
AST increased	11	< 1	12	< 1	.40	1.00
Cough	11	< 1	12	1	.67	.37
Headache	4	0	12	1	< .001	.12
Laryngeal edema	11	2	10	1	.83	.77
Late period‡						
No. of patients	432		415			
Any event	97	54	97	60	.85	.11
Dysphagia	83	36	86	37	.16	.78
Dry mouth	75	4	75	5	1.00	.40
Skin fibrosis	44	1	46	2	.68	.79
Fatigue	45	3	41	3	.27	.55
Laryngeal edema	42	3	40	4	.58	.85
Dysgeusia	41	0	42	0	.94	—
Radiation mucositis	40	6	41	7	.78	.58
Laryngitis NOS	31	2	29	1	.50	.55
Weight decreased	29	7	29	8	.94	.61
Dermatology/skin, other	27	1	28	2	.59	.25

(continued on following page)

Table 2. Treatment-Related Adverse Events by Assigned Treatment (continued)

	% of Patients					
	Arm A: RT + Cisplatin		Arm B: RT + Cisplatin + Cetuximab		P†	
Adverse Event*	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
Salivary gland disorder NOS	28	1	25	< 1	.24	.62
Hemoglobin	26	1	25	2	.69	.41
Edema: head and neck	25	1	26	1	.64	.73
Pharyngolaryngeal pain	26	2	22	2	.30	.63
Mucositis/stomatitis (clinical exam): pharynx	23	5	24	7	.87	.47
Hearing impaired	23	5	23	5	1.00	.75
Skin reaction inside portal‖	18	2	22	4	.14	.06
Peripheral sensory neuropathy	16	< 1	20	1	.15	.68
Trismus	17	2	20	2	.33	1.00
Skin hyperpigmentation	18	0	18	0	1.00	—
Oral pain	17	2	17	3	.93	.41
Skin reaction outside portal§	3	< 1	17	< 1	< .001	1.00
Neuralgia NOS	17	2	16	3	.71	.83
Alopecia	14	0	16	0	.44	—
Tinnitus	15	1	13	< 1	.55	.62
Hypothyroidism	14	< 1	13	0	.76	1.00
Neck pain	10	1	13	1	.13	1.00
Nausea	12	3	13	3	.60	1.00
Anorexia	13	2	12	3	.83	.67
Cough	10	< 1	10	0	.82	1.00
Leukopenia NOS	10	2	10	2	.82	1.00

Abbreviations: NOS, not otherwise specified; RT, radiotherapy.
*Definitely, probably, or possibly related to treatment and occurring in at least 10% of patients in either arm.
†P values calculated using Fisher's exact test.
‡The acute and late periods are defined as ≤ 90 and > 90 days from start of radiation therapy, respectively.
§Pruritus; dermatitis exfoliative NOS; acne NOS; nail disorder NOS.
‖Radiation dermatitis NOS; radiation recall syndrome.

of less than 10%, the data monitoring committee recommended early reporting of results with 371 failure events. A planned subset analysis focused on treatment effect by p16 subgroups.

PFS and OS probabilities were estimated using the Kaplan-Meier method,[21] and LRF and DM probabilities were estimated using the cumulative incidence method.[22] PFS and OS were compared using log-rank tests,[23] and LRF and DM were compared using failure-specific log-rank tests.[24] Toxicity rates were compared using Fisher's exact tests, and hazard ratios (HRs) were estimated using Cox proportional hazards models.[25] Outcomes were compared for patients with p16-positive versus p16-negative OPCs and for patients whose tumors had 80% versus less than 80% tumor cells staining positive for EGFR. Missing p16, EGFR, and pack-year values were imputed 20 times using conditional model specification for multivariable imputation via Gibbs sampling,[26] the resulting data sets were combined using Rubin's formula, and sensitivity analyses were conducted to validate the robustness of the imputation procedure.

Study design, implementation, data collection, analysis, interpretation, and article preparation were performed by the authors as representatives of the RTOG Head and Neck Committee and the RTOG Statistical Center. The authors had complete access to all data. The first author (K.K.A., trial chair) and last author (R.S.A.) serve as guarantors of all analyses and article content.

RESULTS

Patient Characteristics and Treatment Parameters

Patients were accrued from November 2005 through May 2009. Of the 940 patients enrolled, 891 were analyzed (47 patients were excluded for not meeting inclusion criteria and two were excluded for

lack of post–random assignment data; Fig 1). Table 1 lists demographic and baseline features of the 891 patients assigned to receive radiation-cisplatin alone (arm A; n = 447) or radiation-cisplatin plus cetuximab (arm B; n = 444) along with p16 and EGFR assay results. Briefly, 786 patients (88.2%) were men, 767 patients (86.1%) had stage IV disease, 625 patients (70.1%) had OPC, 258 patients (29.0%) had ≥ 5% weight loss during the preceding 6 months, and 121 patients (13.6%) had a feeding tube placed before treatment. Of the 321 OPCs assayed, 235 (73.2%) were positive for p16. Of the 380 tumors (261 OPCs and 119 other primary tumors) analyzed for EGFR expression, 145 (38.2%) had positive staining in ≥ 80% of tumor cells. Baseline characteristics and outcomes were compared between patients with and without known p16 status, EGFR status, and pack-years of smoking. Significant differences were present in race, T category, and OS between patients with and without known pack-years. However, sensitivity analysis for data missing not at random,[27,28] in which the missing pack-years value was reimputed with mean pack-years varying from +20 pack-years to −20 pack-years for the nonresponders, showed consistent model estimates for treatment effects and other covariates.

Appendix Table A1 (online only) lists the details of treatment delivered. Overall, IMRT was used in 86.4% and 86.7% of patients in arms A and B, respectively. In arms A and B, 97.5% and 94.8% of patients received at least 60 Gy, and 93.7% and 90.5% of patients received two cisplatin cycles, respectively. In arm B, 432 patients

(97.3%) received the loading cetuximab, but only 327 patients (73.6%) received six or more weekly cetuximab doses as specified. The incidence of interruption of radiotherapy as a result of toxicity was significantly higher in arm B (26.9% *v* 15.1% in arm A; *P* = .001).

Toxicity End Points

More treatment-related grade 5 adverse events took place in the cetuximab arm (10 events in arm B *v* three events in arm A; *P* = .05). However, death rates within 30 days of treatment completion were similar between the two arms (2.0% with cetuximab *v* 1.8% without; *P* = .81). Table 2 lists the distribution of worst grade adverse effects. The cetuximab arm had significantly higher rates of grade 3 to 4 skin reactions (both inside and outside radiation volumes), radiation mucositis, fatigue, anorexia, and hypokalemia up to 90 days from the start of therapy. However, no significant differences were observed between the arms in rates of adverse effects after 90 days. In arms A and B, rates of feeding tube dependency were 21.2% (95% CI, 17.2% to 25.7%) and 18.8% (95% CI, 15.0% to 23.2%) at 1 year (*P* = .47), 13.5% (95% CI, 10.0% to 17.8%) and 11.9% (95% CI, 8.6% to 15.9%) at 2 years (*P* = .56), and 12.1% (95% CI, 8.4% to 16.8%) and 7.0% (95% CI, 4.2% to 10.8%) at 3 years (*P* = .05), respectively.

Outcome End Points

At the time of analysis (June 2012), 630 patients were alive with a median follow-up time of 3.8 years. No significant differences were found between arms in PFS (primary end point), OS, LRF, or DM (Fig 2). The 3-year PFS probabilities were 61.2% (95% CI, 56.7% to 65.8%) for arm A and 58.9% (95% CI, 54.2% to 63.6%) for arm B (*P* = .76). The 3-year probabilities for OS were 72.9% (95% CI, 68.7% to 77.1%) for arm A and 75.8% (95% CI, 71.7% to 79.9%) for arm B (*P* = .32); the 3-year LRF probabilities were 19.9% (95% CI, 16.2% to 23.7%) for arm A and 25.9% (95% CI, 21.7% to 30.1%) for arm B (*P* = .97); and the 3-year DM probabilities were 13.0% (95% CI, 9.9% to 16.2%) for arm A and 9.7% (95% CI, 6.9% to 12.6%) for arm B (*P* = .08).

Trends were noted toward differential cetuximab treatment effects in patients with OPCs with known p16 status. For PFS, the treatment effect HRs were 1.57 for p16-positive OPC and 0.86 for p16-negative OPC (*P* for interaction = .12); imputation and adjustment for known prognostic factors reduced these HRs (1.29 *v* 0.92, respectively; *P* for interaction = .31). For OS, the corresponding HRs were 1.42 for patients with p16-positive OPC and 0.69 for patients with p16-negative OPC (*P* for interaction = .13); after imputation and
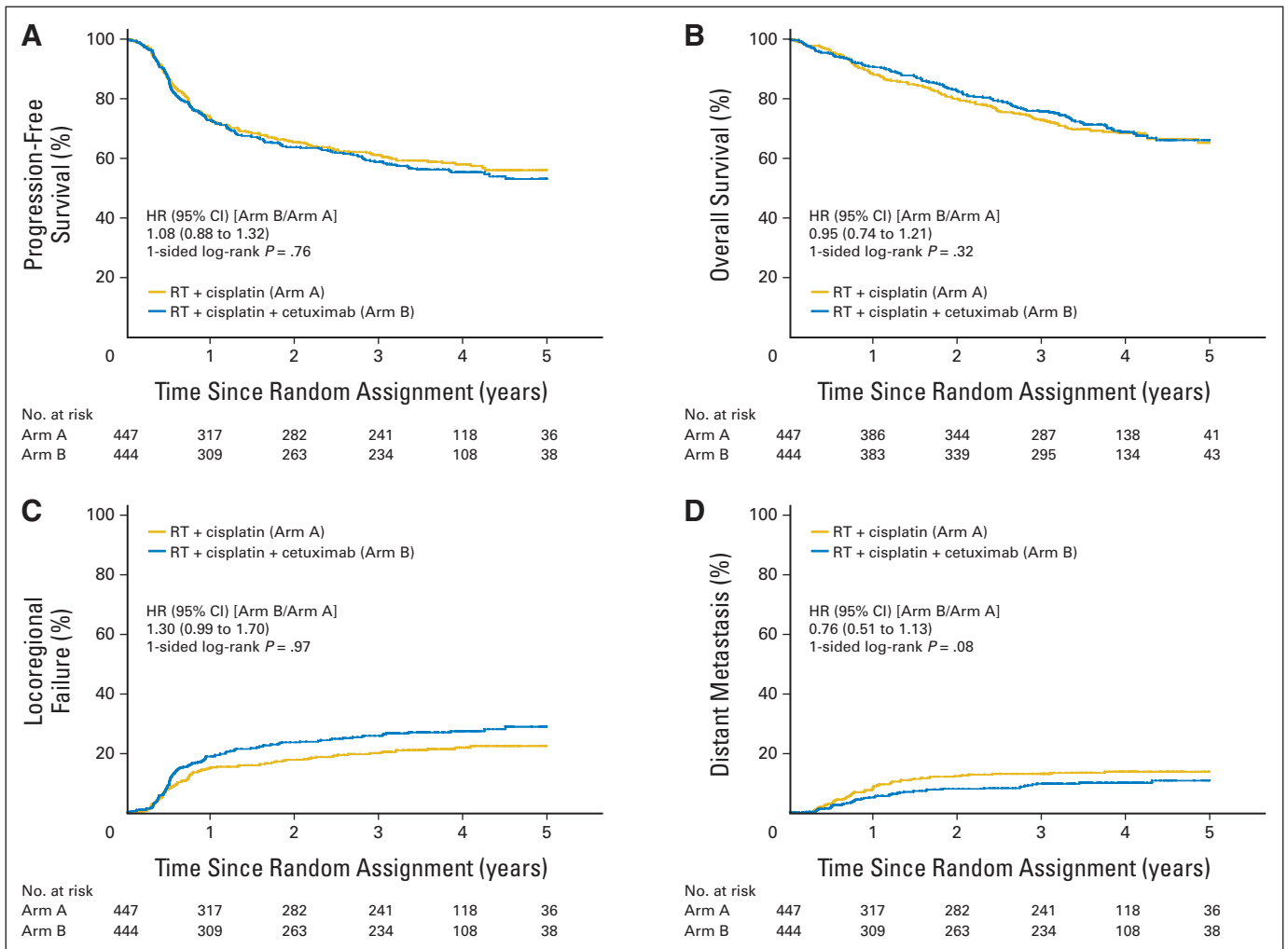

Fig 2. Kaplan-Meier estimates of (A) progression-free and (B) overall survival and cumulative incidence estimates of (C) locoregional failure and (D) distant metastasis by assigned treatment. HR, hazard ratio; RT, radiotherapy.
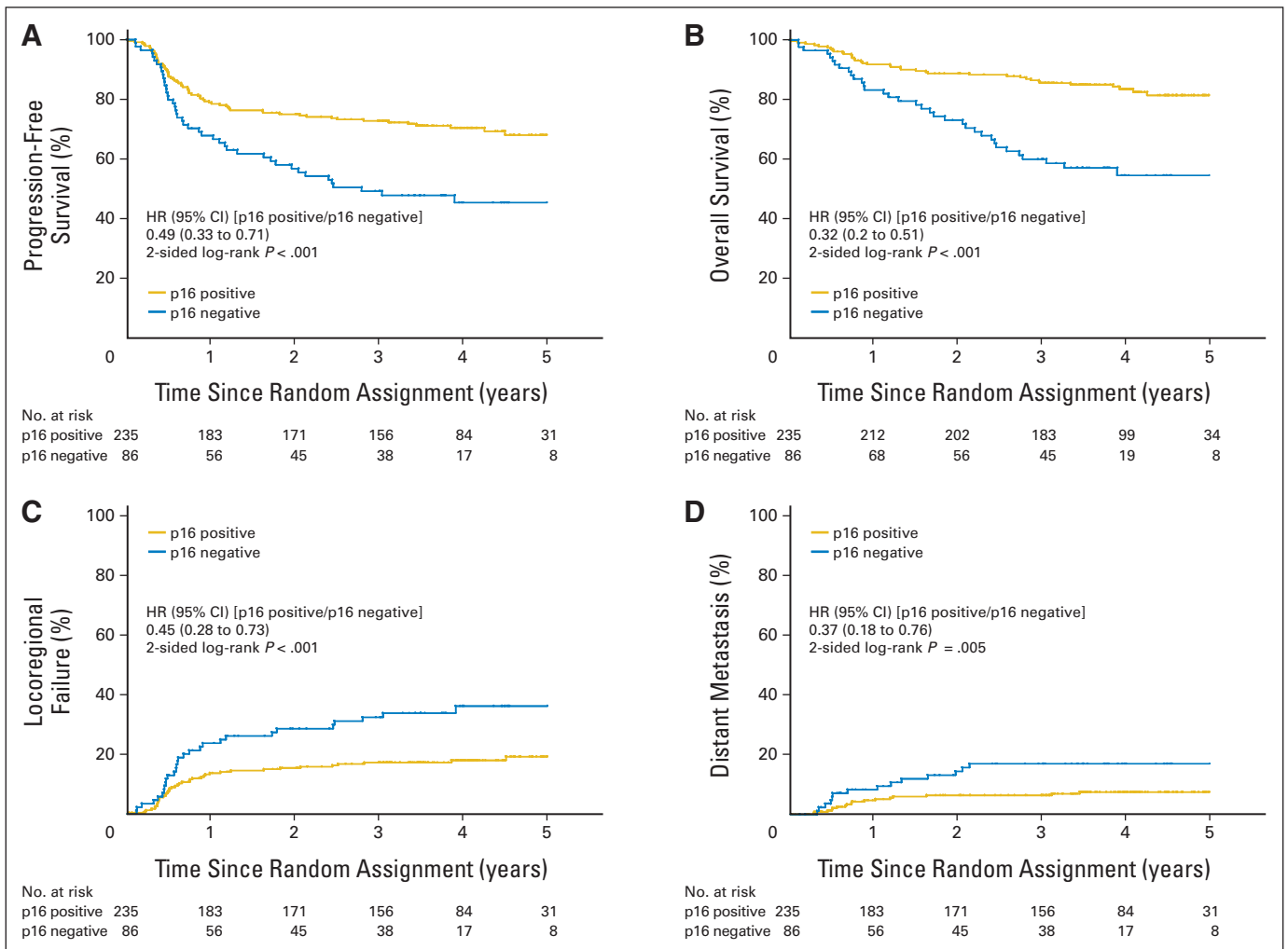
Fig 3. Kaplan-Meier estimates of (A) progression-free and (B) overall survival and (C) cumulative incidence estimates of locoregional failure and (D) distant metastasis by p16 expression in patients with oropharyngeal carcinoma. HR, hazard ratio.

adjustment for covariates, the HRs were 1.10 and 0.63, respectively (P for interaction $= .19$).

Because results were not significantly different between the two treatment arms, they were combined for the correlative analyses. Figure 3 shows that patients with p16-positive OPCs, compared with patients with p16-negative OPCs, had significantly better PFS (3-year probability, 72.8% v 49.2%, respectively; $P < .001$) and OS (3-year probability, 85.6% v 60.1%, respectively; $P < .001$) and a significantly lower probability of LRF (17.3% v 32.5%, respectively; $P < .001$) and DM (6.5% v 17.0%, respectively; $P = .005$). However, survival end points and pattern of relapse were not significantly different by tumor EGFR expression when scored with either our previous cut point of 80% tumor cells staining positive or using a four-level semiquantitative method (Appendix Figs A1 and A2, online only).

Figure 4 shows the forest plots of HRs of the effect of treatment by patient and tumor variables and by p16 and EGFR expression. With the exception of better OS for younger patients (age $\leq$ 50 years; HR, 0.45; 95% CI, 0.23 to 0.89; P for interaction $= .02$), the addition of cetuximab did not affect outcome. Primary laryngeal-hypopharyngeal carcinoma, p16-negative OPC, N2b-3 category, T4 tumor, more than

10 pack-years of cigarette smoking history, age greater than 50 years, and Zubrod performance status of 1 were associated with poorer PFS and OS in multivariable analysis (Table 3).

DISCUSSION

This large phase III trial yielded several clinically important findings. The impetus for the study stemmed from strong previous phase III data showing that combining cisplatin or cetuximab concurrently with radiation improved PFS and OS of patients with locally advanced HNC[10,20] and that adding cetuximab to platinum-based chemotherapy improved OS of patients with recurrent or metastatic HNC.[12] Therefore, it is disappointing to discover that adding cetuximab to the radiation-cisplatin platform had no significant impact on PFS, OS, LRF, or DM. One plausible explanation for these negative results is that the toxicity burden of radiation-cisplatin is at the maximum-tolerated level, such that adding cetuximab caused radiotherapy interruption(s) in 26.9% of patients despite incomplete cetuximab administration in 26.4%. These compromises in therapy could explain the trend toward a higher LRF rate in the experimental arm.
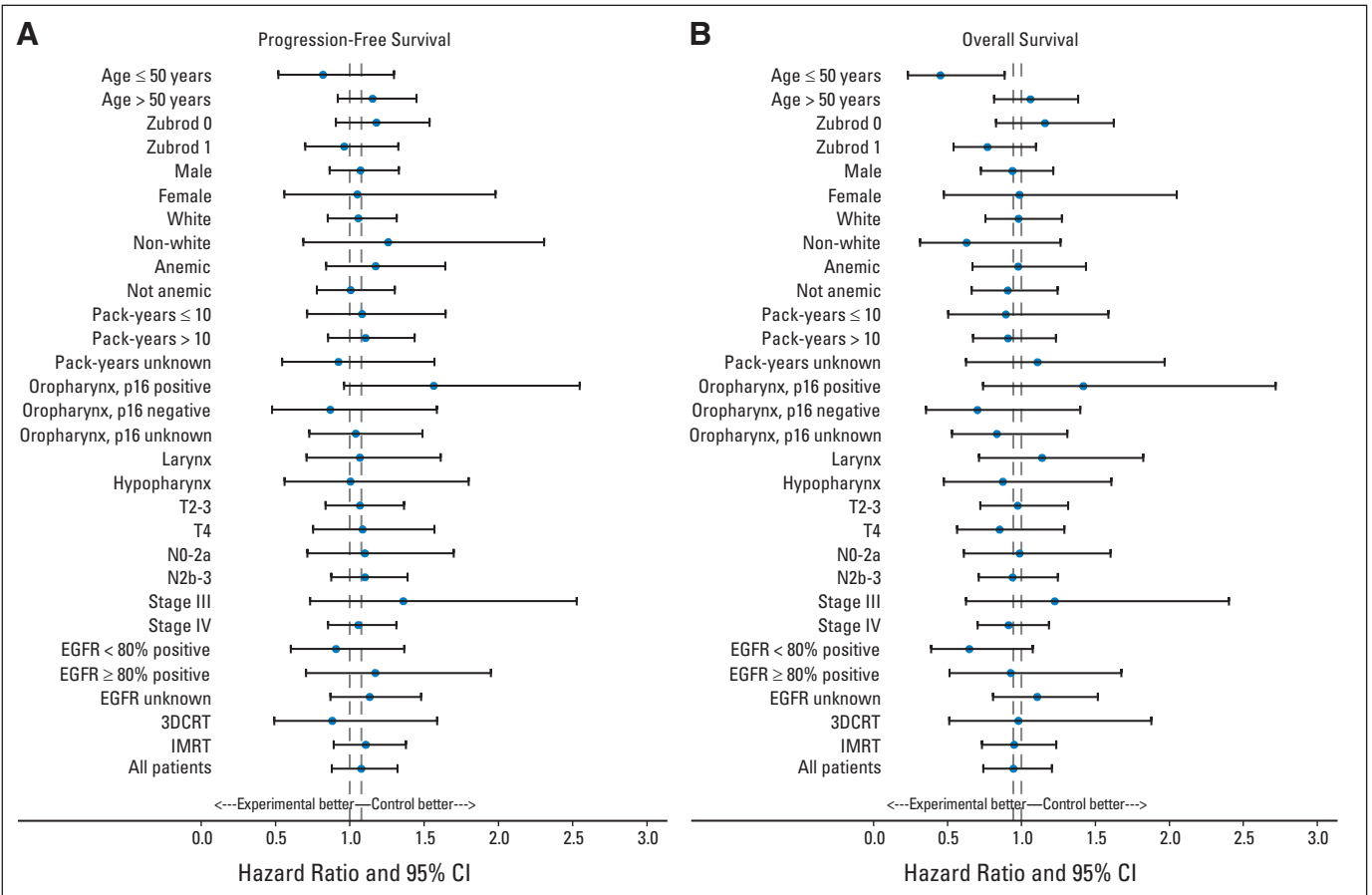
Fig 4. Forest plots of treatment effect for (A) progression-free and (B) overall survival. A hazard ratio of less than 1 indicates a benefit with the addition of cetuximab. Vertical lines are shown at a hazard ratio of 1.0 and the observed hazard ratio for the entire study population. There is a significant interaction ($P = .02$) between assigned treatment and age ($> v \leq 50$ years) for overall survival, indicating a treatment benefit for younger patients receiving cetuximab. EGFR, epidermal growth factor receptor; IMRT, intensity-modulated radiotherapy; 3DCRT, three-dimensional conformal radiotherapy.

Another potential explanation for lack of benefit is that platinum derivatives and cetuximab have similar mechanisms of radiation sensitization (i.e., inhibition of repair of radiation-induced DNA damage).[29,30] Consequently, tumors having proficient repair machinery would be resistant to both agents, and sensitive tumors would derive no additional benefit. If true, combining cetuximab with agents having different mechanisms of action is logical. For example, the antitubulin drug docetaxel produced promising results in combination with cetuximab and radiation in a preclinical study.[31] RTOG 1216 is currently comparing postoperative radiation plus docetaxel and cetuximab versus docetaxel versus cisplatin in high-risk patients.

In terms of toxicity, we did not observe severe cardiac or other events with the addition of cetuximab to radiation-cisplatin, as had been observed in a previous phase II trial.[12] Cetuximab exacerbated acute mucositis, in contrast to findings in the radiation-cetuximab trial,[10] and adding cetuximab was associated with more treatment-related deaths compared with radiation-cisplatin alone (10 v three deaths, respectively; $P = .05$). Cetuximab also increased the incidence of in-field skin reactions, without reaching the severity described in a previous case report.[32] In addition, cetuximab increased hypokalemia, fatigue, and anorexia, all contributing to incomplete cetuximab dosing in 26.4% of patients and interruption of radiotherapy in 26.9% of patients (Appendix Table A1). Because of the higher incidences of

these acute toxic effects without advantages in tumor control or survival, we advise against the routine use of cetuximab with cisplatin and radiation.

Although tissue collection and analysis were cumbersome before funding became available through formal mechanisms, we successfully collected biopsy specimens from 43% of patients. As summarized in a recent review,[33] several studies have established p16-positive OPC as a distinct entity with an excellent prognosis with current standard therapies. Our results confirmed that patients with p16-positive OPCs had significantly better PFS and OS and lower LRF rates than their p16-negative counterparts. In contrast to our previous finding,[17] however, we found in this study that patients with p16-positive OPCs also had a significantly lower DM rate. Lower tobacco exposure (5.25 pack-years, Table 1) is one possible explanation. Further analysis showed no significant interaction between treatment and p16 status, although trends were evident for worse PFS (HR, 1.57; P for interaction $= .12$) and OS (HR, 1.42; P for interaction $= .13$) for patients with p16-positive OPCs receiving cetuximab (Fig 3). The lack of such trends in the subset without tumor specimens for p16 assay is unexpected and may represent an imbalance in the arms for p16-positive status or a decrease in cisplatin/radiation delivery, which is perhaps more biologically relevant.

We previously validated that high tumor EGFR expression was associated with higher LRF and lower PFS and OS rates than low

Table 3. Hazard Ratios for Progression-Free and Overall Survival According to Patient Group

	Progression-Free Survival						Overall Survival					
	Patients With p16, EGFR, and Smoking Data			All Patients With Imputed Data			Patients With p16, EGFR, and Smoking Data			All Patients With Imputed Data		
Covariates	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
All primary tumor sites												
No. of patients		328			891			328			891	
Cetuximab (yes v no)	1.29	0.91 to 1.83	.16	1.13	0.92 to 1.38	.26	1.01	0.66 to 1.55	.96	0.98	0.77 to 1.25	.87
Age (> v ≤ 50 years)	1.22	0.78 to 1.92	.38	1.11	0.86 to 1.44	.43	2.22	1.10 to 4.47	.03	1.53	1.09 to 2.15	.01
Zubrod performance status (1 v 0)	1.25	0.87 to 1.81	.23	1.30	1.05 to 1.62	.02	1.46	0.94 to 2.26	.09	1.72	1.33 to 2.22	< .001
Pack-years of smoking (> v ≤ 10)	1.53	1.00 to 2.34	.05	1.35	1.03 to 1.75	.03	2.17	1.21 to 3.88	.009	1.55	1.11 to 2.17	.01
p16-negative v p16-positive OPC	1.61	0.97 to 2.69	.07	1.60	1.14 to 2.25	.007	2.17	1.16 to 4.04	.01	2.10	1.39 to 3.19	< .001
Non-OPC v p16-positive OPC	1.63	1.05 to 2.54	.03	1.79	1.34 to 2.38	< .001	1.93	1.12 to 3.34	.02	2.25	1.58 to 3.20	< .001
T category (T4 v T2-3)	1.33	0.89 to 1.98	.16	1.65	1.32 to 2.08	< .001	1.73	1.09 to 2.73	.02	1.86	1.43 to 2.43	< .001
N category (N2b-3 v N0-2a)	1.62	1.08 to 2.43	.02	1.75	1.36 to 2.26	< .001	1.51	0.92 to 2.47	.10	1.48	1.11 to 1.99	.008
EGFR (≥ v < 80% positive tumor cells)	0.93	0.64 to 1.35	.70	0.97	0.66 to 1.41	.86	0.99	0.63 to 1.56	.97	1.02	0.65 to 1.59	.94
OPC												
No. of patients		222			625			222			625	
Cetuximab (yes v no)	1.46	0.92 to 2.32	.11	1.14	0.88 to 1.48	.33	0.92	0.50 to 1.69	.79	0.87	0.63 to 1.21	.41
Age (> v ≤ 50 years)	1.16	0.67 to 2.01	.59	0.94	0.69 to 1.28	.70	3.19	1.13 to 9.02	.03	1.44	0.94 to 2.21	.10
Zubrod performance status (1 v 0)	1.34	0.83 to 2.17	.24	1.39	1.06 to 1.84	.02	1.77	0.97 to 3.24	.06	2.08	1.48 to 2.93	< .001
Pack-years of smoking (> v ≤ 10)	1.76	1.07 to 2.88	.03	1.45	1.07 to 1.96	.02	2.47	1.22 to 5.00	.01	1.73	1.17 to 2.57	.007
p16 negative v p16 positive	1.44	0.86 to 2.41	.17	1.51	1.06 to 2.15	.02	1.91	1.02 to 3.57	.04	1.94	1.26 to 2.98	.003
T category (T4 v T2-3)	1.70	1.03 to 2.82	.04	1.98	1.50 to 2.62	< .001	2.40	1.31 to 4.43	.005	2.55	1.81 to 3.58	< .001
N category (N2b-3 v N0-2a)	1.54	0.87 to 2.74	.14	1.72	1.21 to 2.44	.003	1.35	0.64 to 2.86	.43	1.32	0.87 to 2.00	.20
EGFR (≥ v < 80% positive tumor cells)	1.17	0.71 to 1.93	.53	1.07	0.67 to 1.72	.77	1.32	0.70 to 2.50	.39	1.14	0.67 to 1.93	.63

Abbreviations: EGFR, epidermal growth factor receptor; HR, hazard ratio from multivariable Cox model; OPC, oropharyngeal carcinoma.

tumor EGFR expression in two groups of patients treated with radiation alone in a prospective trial.[4,19] Assessments with the same method yielded no such association in the this study (Appendix Figs A1 and A2). It is plausible that cisplatin/cetuximab primarily sensitized tumors with high EGFR expression, thus annulling its prognostic significance. Unfortunately, this notion could not be addressed in this study because there was no radiation alone arm. However, a thorough analysis of the available residual tumor specimens, if made available, of patients enrolled onto the trial randomly assigning patients to receive radiation with or without cetuximab[10] could properly test this hypothesis. Another immunofluorescence-based assay method, the automated in situ quantitative assay (AQUA),[5] could be a better marker, but regrettably, no uncommitted residual tumor specimens are available for analysis.

Multivariable analysis again identified more than 10 pack-years of cigarette smoking as an independent predictor of poor prognosis; other predictors were p16-negative carcinoma, N2b-3 category, T4 tumor, and poor performance status. These consistent findings support the current strategy of designing trials for better biologically defined HNC entities. RTOG 1016, which is selectively enrolling patients with T1-2N2a-3 or T3-4 with any N category, p16-positive OPC, represents this new paradigm. It is anticipated that future trials will further refine study populations based on smoking status and other biologic tumor features. This means, however, that the number of patients eligible for a given trial will decrease progressively. Therefore, international collaborations are imperative to complete patient accrual in a timely fashion. Hence, it is desirable to commence discussions of funding for and logistics of establishing international cooperative group alliances.

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Appendix

	Arm A: RT + Cisplatin (n = 447)		Arm B: RT + Cisplatin + Cetuximab (n = 444)		
Table A1. Protocol Treatment Delivered by Assigned Treatment					
Treatment Component	No. of Patients	%	No. of Patients	%	P
Type of radiation administered					.008*
3DCRT	59	13.2	46	10.4	
IMRT	386	86.4	385	86.7	
None	2	0.4	13	2.9	
Radiation dose, Gy					.03†
Mean	69.1		67.2		
Standard deviation	8.0		13.2		
Median	70.0		70.0		
Range	0.0-72.6		0.0-72.0		
Q1-Q3	70.0-70.0		70.0-70.0		
< 60	11	2.5	23	5.2	
≥ 60	436	97.5	421	94.8	
No. of fractions					.03‡
Mean	35.3		34.2		
Standard deviation	4.7		7.0		
Median	35.0		35.0		
Range	0.0-42.0		0.0-42.0		
Q1-Q3	35.0-35.0		35.0-35.0		
< 30	11	2.5	23	5.2	
≥ 30	436	97.5	421	94.8	
Total duration of radiation, days					.42§
Mean	42.5		42.0		
Standard deviation	6.8		10.2		
Median	42.0		42.0		
Range	0.0-73.0		0.0-108.0		
Q1-Q3	40.0-44.0		40.0-45.0		
≤ 56	436	97.5	429	96.6	
> 56	11	2.5	15	3.4	
Radiation interruptions	445		431		< .001*
No	258	58.0	212	49.2	
Yes, as a result of toxicity	67	15.1	116	26.9	
Yes, as a result of other reason	120	27.0	103	23.9	
Tumor volume contouring score					
Per protocol	231	51.7	235	52.9	
Acceptable variation	169	37.8	152	34.2	
Unacceptable variation	27	6.0	23	5.2	
Not evaluable	20	4.5	34	7.7	
Organs at risk contouring score (IMRT only)	388		396		
Per protocol	208	53.6	220	55.6	
Acceptable variation	153	39.4	138	34.8	
Unacceptable variation	11	2.8	13	3.3	
Not evaluable	16	4.1	25	6.3	
Tumor-volume dose-volume analysis score (IMRT only)	388		396		
Per protocol	251	64.7	227	57.3	
Acceptable variation	87	22.4	117	29.5	
Unacceptable variation	37	9.5	26	6.6	
Not evaluable	13	3.4	26	6.6	

Treatment Component	Arm A: RT + Cisplatin (n = 447)		Arm B: RT + Cisplatin + Cetuximab (n = 444)		P
	No. of Patients	%	No. of Patients	%	
Cisplatin given					.06‖
None	4	0.9	16	3.6	
One cycle	24	5.4	26	5.9	
Two cycles	419	93.7	402	90.5	
Cumulative cisplatin dose, mg/m^2					.43¶
Mean	191.9		185.7		
Standard deviation	32.0		43.8		
Median	200.0		200.0		
Range	0.0-282.7		0.0-239.4		
Q1-Q3	198.4-200.3		197.1-200.0		
< 160	44	9.8	51	11.5	
≥ 160	403	90.2	393	88.5	
Cetuximab loading dose given					
No	443	99.1	12	2.7	
Yes	4	0.9	432	97.3	
Weekly cetuximab doses given					
None	442	98.9	35	7.9	
1-5 doses	1	0.2	82	18.5	
6-7 doses	4	0.9	323	72.7	
8 doses	0	0.0	4	0.9	

Table A1. Protocol Treatment Delivered by Assigned Treatment (continued)

Abbreviations: 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; Q1, first quartile; Q3, third quartile; RT, radiotherapy.
*Pearson χ^2 test.
†Pearson χ^2 test: $< v \geq 60$ Gy.
‡Pearson χ^2 test: $< v \geq 30$ fractions.
§Pearson χ^2 test: $\leq v > 56$ days.
‖Wilcoxon rank sum test.
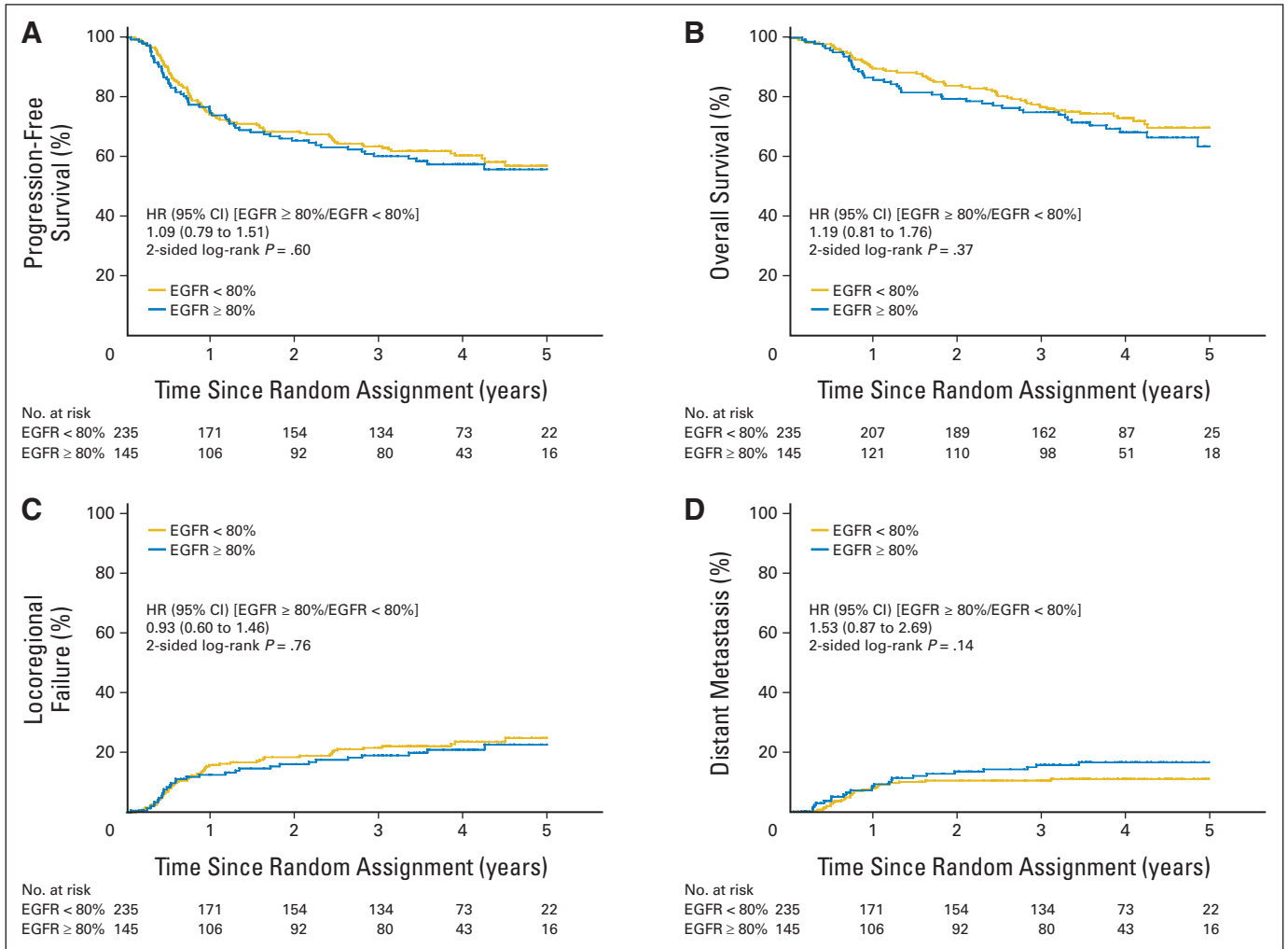¶Pearson χ^2 test: $< v \geq 160$ mg/m^2.

Fig A1. Kaplan-Meier estimates of (A) progression-free and (B) overall survival and (C) cumulative incidence estimates of locoregional failure and (D) distant metastasis by epidermal growth factor receptor (EGFR) expression using a cut point of 80% of tumor cells staining positive. HR, hazard ratio.
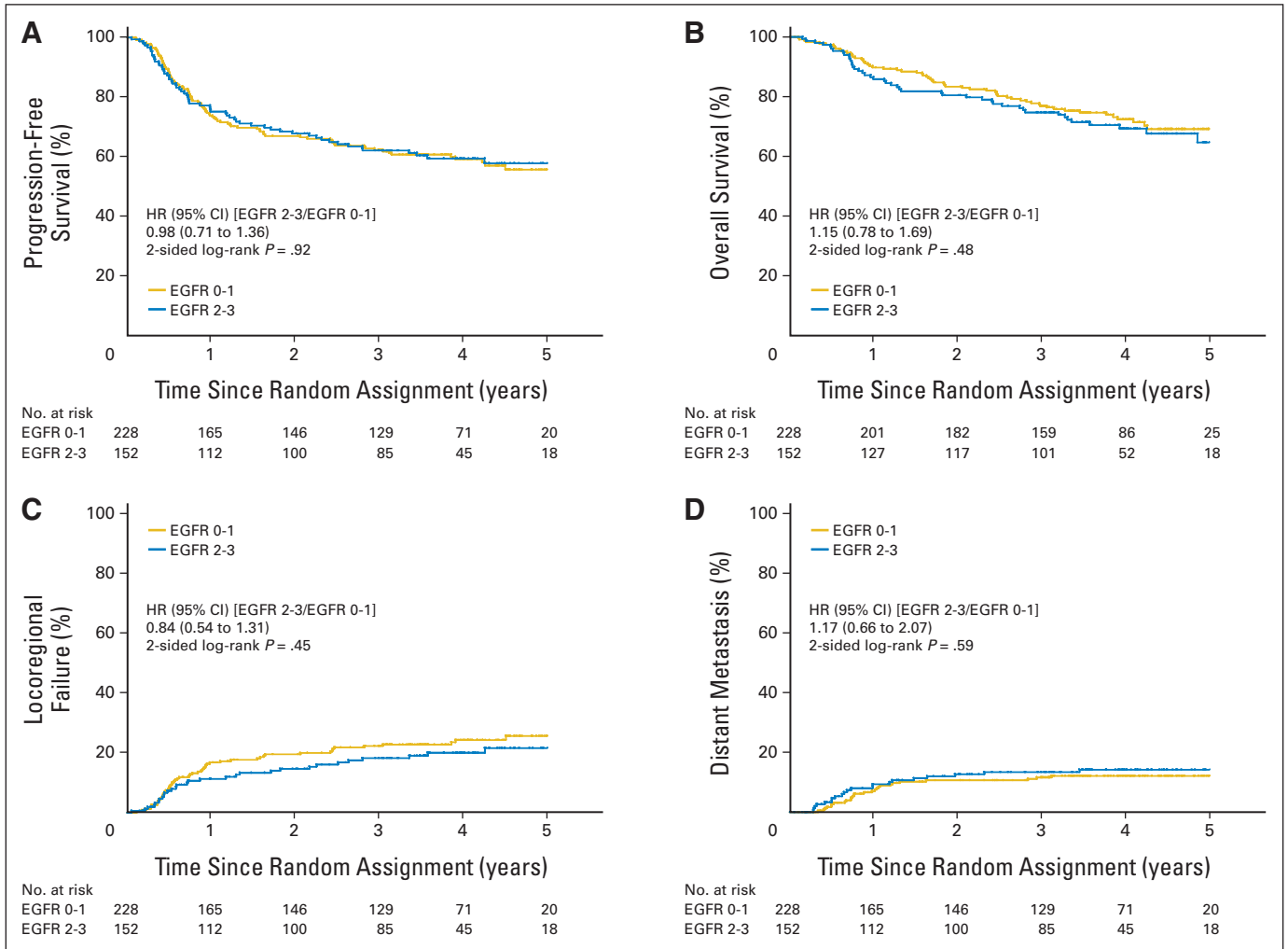
Fig A2. Kaplan-Meier estimates of (A) progression-free and (B) overall survival and cumulative incidence estimates of (C) locoregional failure and (D) distant metastasis by epidermal growth factor receptor (EGFR) expression using a four-level semiquantitative method. HR, hazard ratio.