ORIGINAL ARTICLE

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

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ABSTRACT

BACKGROUND

We conducted a multinational, randomized study to compare radiotherapy alone with radiotherapy plus cetuximab, a monoclonal antibody against the epidermal growth factor receptor, in the treatment of locoregionally advanced squamous-cell carcinoma of the head and neck.

METHODS

Patients with locoregionally advanced head and neck cancer were randomly assigned to treatment with high-dose radiotherapy alone (213 patients) or high-dose radiotherapy plus weekly cetuximab (211 patients) at an initial dose of 400 mg per square meter of body-surface area, followed by 250 mg per square meter weekly for the duration of radiotherapy. The primary end point was the duration of control of locoregional disease; secondary end points were overall survival, progression-free survival, the response rate, and safety.

RESULTS

The median duration of locoregional control was 24.4 months among patients treated with cetuximab plus radiotherapy and 14.9 months among those given radiotherapy alone (hazard ratio for locoregional progression or death, 0.68; P=0.005). With a median follow-up of 54.0 months, the median duration of overall survival was 49.0 months among patients treated with combined therapy and 29.3 months among those treated with radiotherapy alone (hazard ratio for death, 0.74; P=0.03). Radiotherapy plus cetuximab significantly prolonged progression-free survival (hazard ratio for disease progression or death, 0.70; P=0.006). With the exception of acneiform rash and infusion reactions, the incidence of grade 3 or greater toxic effects, including mucositis, did not differ significantly between the two groups.

CONCLUSIONS

Treatment of locoregionally advanced head and neck cancer with concomitant high-dose radiotherapy plus cetuximab improves locoregional control and reduces mortality without increasing the common toxic effects associated with radiotherapy to the head and neck. (ClinicalTrials.gov number, NCT00004227.)

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*The investigators and centers participating in this study are listed in the Appendix.

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The treatment of locoregionally advanced squamous-cell carcinoma of the head and neck (hereafter called head and neck cancer) has evolved gradually from surgery as the mainstay of treatment to radiotherapy as the principal treatment.[1-6] More recently, additional benefit has been obtained with altered-fractionation radiotherapy (i.e., accelerated fractionation or hyperfractionated radiotherapy) and with radiotherapy combined with chemotherapy (chemoradiotherapy).[5-11] The value of chemoradiotherapy is, however, counterbalanced by increased and often prohibitive toxicity, particularly among patients with coexisting medical conditions and decreased performance status.[6,12]

The epidermal growth factor receptor (EGFR), a member of the ErbB family of receptor tyrosine kinases, is abnormally activated in epithelial cancers, including head and neck cancer.[13,14] The cells of almost all such neoplasms express high levels of EGFR, a feature associated with a poor clinical outcome.[13,15-20] Radiation increases the expression of EGFR in cancer cells, and blockade of EGFR signaling sensitizes cells to the effects of radiation.[21,22]

Cetuximab (Erbitux, ImClone Systems), an IgG1 monoclonal antibody against the ligand-binding domain of EGFR, enhances the cytotoxic effects of radiation in squamous-cell carcinoma.[23-27] In a preliminary study of radiotherapy plus cetuximab in patients with locoregionally advanced head and neck cancer, the regimen was well tolerated, and all the patients who could be assessed had a complete or partial regression.[28] Cetuximab as a single agent or combined with cisplatin was also associated with clinically significant rates of tumor regression in patients with platinum-refractory head and neck cancer.[29,30] For these reasons, we conducted a randomized, phase 3 study to determine the effect of adding cetuximab to radiotherapy in the treatment of patients with locoregionally advanced head and neck cancer.

METHODS

PATIENTS

Patients with stage III or IV,[31] nonmetastatic, measurable squamous-cell carcinoma of the oropharynx, hypopharynx, or larynx were eligible for this international phase 3 study. Criteria for eligibility also included medical suitability for definitive radiotherapy, a Karnofsky performance score of at least 60, and normal hematopoietic, hepatic, and renal function. Patients were ineligible if they had previously had cancer or had received chemotherapy within the preceding three years, or if they had undergone surgery or had previously received radiotherapy for head and neck cancer. Immunostaining of the tumor for EGFR was not required for eligibility, but tumor specimens were obtained for this purpose. The protocol was approved by the ethics review boards at the participating institutions, and all the patients provided written informed consent.

All the patients underwent screening within two weeks before the start of treatment. Primary disease was assessed by a comprehensive head and neck examination, including panendoscopy. Primary tumors and involved lymph nodes were staged according to the 1998 staging classification of the American Joint Committee on Cancer.[31] A computed tomographic (CT) or magnetic resonance imaging (MRI) scan of the head and neck and a chest radiograph were obtained. Percutaneous endoscopic gastrostomy was recommended.

TREATMENT

Head and neck radiotherapy with curative intent (a seven-to-eight-week course of treatment) was administered to patients in both groups of the trial. Investigators were required to select one of three radiotherapy-fractionation regimens, as detailed in Table 1, before patient registration. Uninvolved nodal areas of the neck were treated with 50 to 54 Gy, depending on the fractionation regimen used. Gross nodal disease received the same dose as the primary tumor. If, at registration, an investigator stipulated the need for neck dissection in patients with N2 or N3 disease of the neck (with such dissection formally recommended to take place four to eight weeks after the completion of radiotherapy), the dose administered to the involved lymph nodes was 60 Gy. In the case of uncontrollable pain, a maximum of two five-day treatment breaks were allowed after the study chairman (Dr. Bonner) had been contacted.

In the group assigned to receive radiotherapy plus cetuximab, administration of intravenous cetuximab was initiated one week before radiotherapy at a loading dose of 400 mg per square meter of body-surface area over a period of 120 minutes, followed by weekly 60-minute infusions

Table 1. Radiotherapy Regimens.

Regimen	Total Radiation Dose	Once-Daily Fractions	Twice-Daily Fractions
Once daily	70.0 Gy in 35 fractions	2.0 Gy/fraction; 5 fractions/wk for 7 wk	Not applicable
Twice daily	72.0–76.8 Gy in 60–64 fractions	Not applicable	1.2 Gy/fraction; 10 fractions/wk for 6.0–6.5 wk
Concomitant boost	72.0 Gy in 42 fractions	32.4 Gy; 1.8 Gy/fraction; 5 fractions/wk for 3.6 wk	Morning dose: 21.6 Gy; 1.8 Gy/fraction; 5 fractions/wk for 2.4 wk Afternoon dose: 18.0 Gy; 1.5 Gy/fraction; 5 fractions/wk for 2.4 wk

of 250 mg per square meter for the duration of radiotherapy. Premedication consisted of intravenous diphenhydramine (50 mg) or an equivalent histamine H_1–receptor antagonist. Before the initial dose was given, a test dose of 20 mg was infused over a 10-minute period, which was followed by a 30-minute observation period. Cetuximab was discontinued in the case of grade 3 or 4 hypersensitivity reactions but not delayed because of radiation-related toxic effects, nor was radiotherapy delayed because of cetuximab-related toxic effects.

Radiotherapy quality assurance included a rapid central review at the initiation of therapy and a final review after the completion of therapy. The rapid review required the investigator to submit the initial radiation-treatment plans (consisting of disease diagrams, a plan for the entire treatment, dosimetric calculations, simulation radiographs of all planned fields, beam-verification radiographs of the initial fields, and reports of CT or MRI scans) within five days after the initiation of treatment. After the rapid review, investigators were alerted to possible deviations from protocol treatment, and recommendations were made to address them. The completed treatment records, final dosimetric calculations, all beam-verification radiographs, and composite isodose distributions in three planes were submitted for the final review to permit determination of whether the investigators had complied with the initial treatment plan. The study chairman (J.A.B.) reviewed all the cases, except for those at his own institution, which were reviewed by the cochairs. Cases were classified as "compliant" or as involving a "minor deviation," an "acceptable major deviation," or an "unacceptable major deviation," in accordance with Radiation Therapy Oncology Group (RTOG) criteria,[32] with revisions consistent with modern radiotherapy practices.[33]

ASSESSMENTS

History taking, physical examination, and monitoring of adverse events and routine hematologic and chemical variables were performed weekly during radiotherapy. Disease assessments, which included history taking, physical examination, CT or MRI scanning of the head and neck, and if indicated, fiberoptic examinations, biopsies, and other relevant imaging studies, were performed at week 4 (except CT or MRI) and week 8 after radiotherapy, every four months thereafter for two years, and then semiannually during years 3, 4, and 5. Acute toxic effects were assessed through the eighth week after treatment, and late radiation effects were assessed thereafter with use of the RTOG toxicity scales.

STUDY DESIGN

Patients were stratified according to Karnofsky performance status (60 to 80 vs. 90 to 100; higher numbers indicate better performance), nodal involvement (N0 vs. N+), tumor stage (T1 through T3 vs. T4), and radiation-fractionation regimen (concomitant boost vs. once daily vs. twice daily). A minimization method was used in the random assignment of patients to receive radiotherapy alone or radiotherapy plus cetuximab.[34]

The primary end point was the duration of locoregional control, defined as the absence of progression of locoregional disease at the scheduled follow-up visits. To ensure the consistency and objectivity of the results, the investigator-generated data were submitted for blinded review by an independent committee of experts, according to prospectively developed uniform guidelines. The committee determined the dates of a first documented locoregional progression or recurrence, a first documented distant metastasis, or a second primary tumor. Secondary end points included overall survival, progression-free survival,

the overall response rate, and safety. Investigators' assessments of response during the first year were used to derive the best overall response. The response was considered complete if no disease could be detected and was considered partial if there was a reduction of at least 50 percent in the sum of the bidimensional products of the measurements of all lesions. Complete and partial responses required confirmation after a minimum of four weeks.

STATISTICAL ANALYSIS

Patients treated with radiotherapy alone were expected to have a locoregional-control rate of 44 percent at one year, according to historical data.[10,32,35] The combined treatment with cetuximab was hypothesized to yield a one-year rate of locoregional control of 57 percent or greater.[32,36] Assuming a constant hazard rate with a uniform accrual rate for a period of 18 months and an additional follow-up time of 12 months, we calculated that 208 patients per treatment group would provide the study with 90 percent power to detect a difference in the duration of locoregional control at the 5 percent significance level with use of a two-sided log-rank test.

Evaluations of efficacy were performed on an intention-to-treat basis. The duration of locoregional control was defined as the time from randomization until the first documented progression or recurrence of locoregional disease or until death from any cause. Progression-free survival time was calculated from the day of randomization until the first documented progression (locoregional or distant) or until death from any cause. Overall survival was calculated from the time of randomization until death from any cause.

The distribution of time-to-event variables was estimated by the Kaplan–Meier method, treatment effects were compared with use of a stratified log-rank test, and the three-year rates were compared between treatment groups with the use of a Z-test. The Cox regression method was used to estimate the hazard ratio. Response rates were compared between treatment groups with use of the Cochran–Mantel–Haenszel test.

The study was designed by ImClone Systems and the study chairman (J.A.B.) in collaboration with the lead investigators and was managed by ImClone Systems and Merck. ImClone Systems collected and analyzed the data. The article was written by Dr. Bonner with assistance from the other authors, who vouch for the accuracy and completeness of the data presentation and analysis.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between April 1999 and March 2002, 424 patients from 73 centers in the United States and 14 other countries were randomly assigned to receive high-dose radiotherapy alone (213) or high-dose radiotherapy plus cetuximab (211). The treatment groups were balanced with regard to demographic and tumor-related characteristics (Table 2). EGFR expression was tested in tumor specimens from 81 percent and 79 percent of the patients in the radiotherapy-only and combined-treatment groups, respectively. EGFR immunostaining was detected in all the tumor samples from patients in the radiotherapy-plus-cetuximab group and in all but three of the samples from patients treated with radiotherapy alone (Table 2). The distribution of tumors based on the proportions of tumor cells with EGFR immunostaining was nearly identical in the treatment groups.

Regarding the radiation-fractionation schemes, concomitant boost radiotherapy was selected most frequently (56 percent), followed by once-daily fractionation (26 percent) and twice-daily fractionation (18 percent).

COMPLIANCE

Four patients were randomly assigned to a study group but received no treatment. They were included in the analyses of efficacy but excluded from the safety analyses. Three others discontinued treatment after one dose of cetuximab without any radiotherapy.

The final review of radiotherapy revealed that the mean and median doses for the once-daily, twice-daily, and concomitant-boost regimens were 67.5 and 70.0 Gy, 74.2 and 74.4 Gy, and 71.2 and 72.0 Gy, respectively, with no differences between the two treatment groups. Compliance was also balanced: overall, 44 percent of the patients were treated as stipulated, 31 percent received treatment with minor variations, and 12 percent received treatment with acceptable major variations. Unacceptable major variations occurred in 6 percent of the patients randomly assigned to radiotherapy alone and 4 percent of those assigned to combined therapy, and 6 percent and 9 percent

Table 2. Characteristics of the Patients.*

Characteristic	Radiotherapy Alone (N=213)	Radiotherapy plus Cetuximab (N=211)	P Value
Age — yr			0.24†
Median	58	56	
Range	35–83	34–81	
Sex — no. (%)			0.72
Male	169 (79)	171 (81)	
Female	44 (21)	40 (19)	
Karnofsky performance score — no. (%)‡			0.47§
60	6 (3)	6 (3)	
70	16 (8)	15 (7)	
80	49 (23)	42 (20)	
90	103 (49)	113 (54)	
100	38 (18)	34 (16)	
Site of primary tumor — no. (%)			0.25
Oropharynx	135 (63)	118 (56)	
Larynx	51 (24)	57 (27)	
Hypopharynx	27 (13)	36 (17)	
American Joint Committee on Cancer stage — no. (%)			0.74
III	52 (24)	55 (26)	
IV	161 (76)	156 (74)	
Tumor stage			0.83
T1	17 (8)	13 (6)	
T2	50 (23)	50 (24)	
T3	81 (38)	85 (40)	
T4	65 (31)	62 (29)	
TX	0	1 (<1)	
Node stage			0.62
N0	38 (18)	42 (20)	
N1	39 (18)	42 (20)	
N2a	21 (10)	12 (6)	
N2b	47 (22)	48 (23)	
N2c	44 (21)	52 (25)	
N3	24 (11)	15 (7)	
EGFR immunostaining — no. (%)			0.66¶
≤50% of cells positive	89 (42)	91 (43)	
>50% of cells positive	81 (38)	75 (36)	
Unknown	40 (19)	45 (21)	
Undetectable	3 (1)	0	

* Percentages may not total 100 because of rounding. P values were determined with the use of Fisher's exact test.
† The P value is for the comparison between patients less than 60 years of age and those 60 years of age or older.
‡ The score was unknown for one patient in each group.
§ The P value is for the comparison between scores of 60, 70, or 80 and scores of 90 or 100.
¶ The P value is for the comparison between positivity of 50 percent or less and positivity of more than 50 percent.

of patients in those groups, respectively, could not be evaluated for radiation. A total of 208 patients were treated with cetuximab, and 90 percent of them received all planned doses (median number of doses, eight).

Neck dissections were planned for 36 percent of the patients and performed in 25 percent, with identical rates in the two treatment groups. The use of salvage surgery and subsequent chemotherapy was also well balanced between the treatment groups.

EFFICACY

The duration of control of locoregional disease was significantly longer among the patients treated with radiotherapy plus cetuximab than among those treated with radiotherapy alone (hazard ratio for locoregional progression or death, 0.68; 95 percent confidence interval, 0.52 to 0.89; P=0.005) (Table 3 and Fig. 1). The median duration of locoregional control was 24.4 months with combined therapy and 14.9 months with radiotherapy alone. The one-, two-, and three-year rates of locoregional control achieved with radiotherapy plus cetuximab (63, 50, and 47 percent), were significantly higher than those achieved with radiotherapy alone (55, 41, and 34 percent, respectively; P<0.01 for the comparison at three years). Overall, the addition of cetuximab to high-dose radiotherapy resulted in a 32 percent reduction in the risk of locoregional progression.

As Table 3 and Figure 2 show, the difference in the Kaplan–Meier estimates of overall survival favored radiotherapy plus cetuximab. With a median follow-up of 54.0 months, the median survival time was 49.0 months among patients treated with combined therapy and 29.3 months among those given radiotherapy alone (P=0.03). Survival rates at two years (62 percent vs. 55 percent) and at three years (55 percent vs. 45 percent) also favored the combination regimen (P=0.05 for the comparison at three years).

There was a 26 percent reduction in the risk of death in the group that received radiotherapy plus cetuximab, as compared with the group that received radiotherapy alone (hazard ratio, 0.74; 95 percent confidence interval, 0.57 to 0.97). Median progression-free survival was 17.1 months among patients treated with radiotherapy plus cetuximab and 12.4 months among those treated with radiotherapy alone. The risk of disease progression was also significantly lower in the combined-treatment group (hazard ratio, 0.70; 95 percent confidence interval, 0.54 to 0.90; P=0.006). The two- and three-year rates of progression-free survival were 46 and 42 percent, respectively, with radiotherapy and cetuximab and 37 and 31 percent with radiotherapy alone (P=0.04 for the comparison at three years). There was also a significant difference in the best overall response rate (i.e., the rate of complete and partial responses), as assessed by the investigator, in favor of combined treatment (74 percent vs. 64 percent; odds ratio, 0.57; 95 percent confidence interval, 0.36 to 0.90; P=0.02).

Table 3 shows the effect of treatment on the duration of locoregional control and survival according to tumor stage, primary site, and type of radiation treatment. Almost all hazard ratios favored combined treatment; however, the study was not powered to detect differences among the subgroups.

The cumulative rates of incidence of distant metastases at one and two years were similar in the two groups (Table 3). The most common sites of metastases were lung (70 percent) and bone (22 percent). Two years after treatment, second primary cancers, mostly in the lungs, had developed in 5 percent of the patients undergoing radiotherapy alone and 8 percent of those receiving combined therapy.

SAFETY

Four patients discontinued cetuximab because of hypersensitivity reactions after the test dose or first dose. Of nine other patients who discontinued cetuximab, eight did so because of a grade 3 acneiform rash. Fewer than 5 percent of the patients required a dose reduction; treatment was delayed by at least four days in 14 percent, most commonly because of cetuximab-induced rash.

Acute adverse events occurring in at least 10 percent of the patients in either treatment group, regardless of cause, are listed in Table 4. With the exception of acneiform rash and infusion-related events, the incidence rates of severe (grades 3, 4, and 5) reactions were similar in the two treatment groups. Notably, cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck, including mucositis, xerostomia, dysphagia, pain, weight loss, and performance-status deterioration.

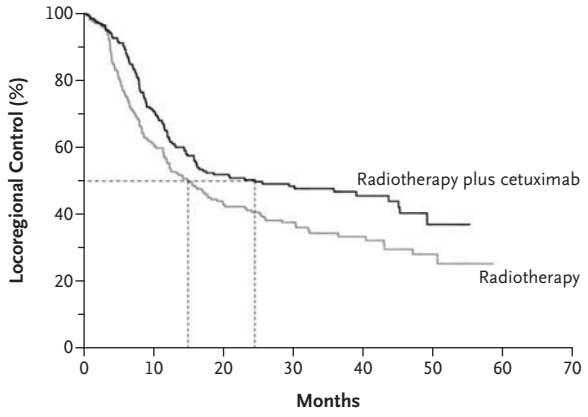
Severe late effects related to radiation were reported in about 20 percent of the patients in

Table 3. Antitumor Efficacy.

Variable	Radiotherapy Alone (N=213)	Radiotherapy plus Cetuximab (N=211)	Hazard Ratio (95% CI)*	P Value†
Locoregional control				
Median duration (mo)	14.9	24.4	0.68 (0.52–0.89)	0.005
Rate at 2 yr (%)	41	50		
Median duration according to site (mo)‡				
Oropharynx	23.0	49.0	0.61	
Larynx	11.9	12.9	0.69	
Hypopharynx	10.3	12.5	0.92	
Median duration according to stage (mo)‡				
Stage III	16.2	38.9	0.69	
Stage IV	13.5	20.9	0.73	
Progression-free survival				
Median duration (mo)	12.4	17.1	0.70 (0.54–0.90)	0.006
Rate at 2 yr (%)	37	46		
Overall survival§				
Median duration (mo)	29.3	49.0	0.74 (0.57–0.97)	0.03
Rate at 3 yr (%)	45	55		
Median duration according to site (mo)‡				
Oropharynx	30.3	>66.0	0.62	
Larynx	31.6	32.8	0.87	
Hypopharynx	13.5	13.7	0.94	
Median duration according to stage (mo)‡				
Stage III	42.9	55.2	0.77	
Stage IV	24.2	47.4	0.77	
Median duration according to radiotherapy regimen (mo)¶				
Once daily	15.3	18.9	1.01	
Twice daily	53.3	58.9	0.74	
Concomitant boost	31.0	>66.0	0.64	
Cumulative incidence of distant metastasis				
Rate at 1 yr (%)	10	8		
Rate at 2 yr (%)	17	16		

* The hazard ratio is for the outcome in the group assigned to radiotherapy plus cetuximab as compared with the group assigned to radiotherapy alone. Outcomes were as follows: progression of locoregional disease or death (in the analysis of locoregional control), progression of disease or death (in the analysis of progression-free survival), and death (in the analysis of overall survival). CI denotes confidence interval.
† P values were calculated by the log-rank test.
‡ The numbers of patients analyzed per group are listed in Table 2.
§ The median follow-up was 54.0 months in both groups.
¶ The analysis included the following numbers of patients: 55, 37, and 120 patients undergoing once-daily, twice-daily, and concomitant-boost therapy, respectively, in the group assigned to radiotherapy alone and 50, 38, and 117 patients, respectively, in the group assigned to radiotherapy plus cetuximab.

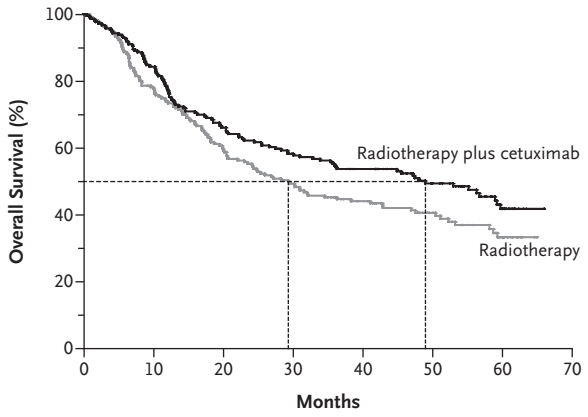
each group. The sites most commonly affected were the esophagus, salivary glands, larynx, mucous membranes, subcutaneous tissues, bone, and skin. Twelve patients in the radiotherapy group and 11 patients in the combined-therapy group died within 60 days after the last radiotherapy or cetuximab treatment. No death was known to be related to cetuximab.



No. at Risk						
Radiotherapy	213	122	80	51	30	10
Radiotherapy plus cetuximab	211	143	101	66	35	9

Figure 1. Kaplan–Meier Estimates of Locoregional Control among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

The hazard ratio for locoregional progression or death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.68 (95 percent confidence interval, 0.52 to 0.89; P=0.005 by the log-rank test). The dotted lines indicate the median durations of locoregional control.



No. at Risk							
Radiotherapy	213	162	122	97	73	47	22
Radiotherapy plus cetuximab	211	177	136	116	98	61	24

Figure 2. Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

The hazard ratio for death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.74 (95 percent confidence interval, 0.57 to 0.97; P=0.03 by the log-rank test). The dotted lines indicate the median survival times.

DISCUSSION

An exceptional feature of this randomized, phase 3 trial, which was carried out among patients with head and neck cancer who were treated with curative intent, was the finding of a survival advantage associated with the use of a molecular targeting agent, cetuximab, delivered in conjunction with radiation. We found that the addition of cetuximab to high-dose radiotherapy significantly increased both the duration of control of locoregional disease and survival among patients with locoregionally advanced head and neck cancer. These benefits were achieved without the prohibitive in-field toxic effects often associated with high-dose radiotherapy to the head and neck. Moreover, concomitant treatment with radiotherapy and cetuximab did not adversely affect the timely completion of definitive radiotherapy. The improvements in outcome achieved with radiotherapy plus cetuximab, as compared with radiotherapy alone (absolute survival benefit, 10 percentage points at three years), compare favorably with the greatest increases in efficacy that have been demonstrated for chemoradiotherapy as compared with radiotherapy alone.[11,37-39]

The superiority of the cetuximab-plus-radiotherapy regimen we used cannot be attributed to underperformance in the radiotherapy group; the efficacy results in this group were similar to results with radiotherapy alone in other, contemporaneous international trials.[10,40-43] Although some trials have found slightly higher rates of control with radiotherapy alone,[44] our results are similar or superior to the results of most other trials that used similar radiotherapy-fractionation schemes and total doses (70 to 75 Gy).[10,38-41,43,45] Furthermore, the Kaplan–Meier curves for both locoregional control and survival maintain a consistent separation, suggesting that the effects of the addition of a fixed course of cetuximab to radiotherapy persist for at least several years after the completion of treatment. However, because the number of patients who survived for five years after the completion of treatment is small, further follow-up is essential.

How do our findings fit into current protocols for the treatment of head and neck cancer? For many years, radiotherapy has been an acceptable option for patients with locoregionally advanced head and neck cancer. More recently,

Table 4. Adverse Events.*

Adverse Event	Radiotherapy Alone (N=212)		Radiotherapy plus Cetuximab (N=208)		P Value†	
	All Grades	Grades 3–5	All Grades	Grades 3–5	All Grades	Grades 3–5
	percent of patients					
Mucositis	94	52	93	56	0.84	0.44
Acneiform rash	10	1	87	17	<0.001	<0.001
Radiation dermatitis	90	18	86	23	0.24	0.27
Weight loss	72	7	84	11	0.005	0.12
Xerostomia	71	3	72	5	0.83	0.32
Dysphagia	63	30	65	26	0.68	0.45
Asthenia	49	5	56	4	0.17	0.64
Nausea	37	2	49	2	0.02	1.00
Constipation	30	5	35	5	0.35	1.00
Taste perversion	28	0	29	0	0.83	—
Vomiting	23	4	29	2	0.18	0.42
Pain	28	7	28	6	1.00	0.84
Anorexia	23	2	27	2	0.26	1.00
Fever	13	1	26	1	0.001	1.00
Pharyngitis	19	4	26	3	0.10	0.80
Dehydration	19	8	25	6	0.16	0.57
Oral candidiasis	22	0	20	0	0.63	—
Coughing	19	0	20	<1	1.00	0.50
Voice alteration	22	0	19	2	0.47	0.06
Diarrhea	13	1	19	2	0.11	0.50
Headache	8	<1	19	<1	0.001	1.00
Pruritus	4	0	16	0	<0.001	—
Infusion reaction	2	0	15	3	<0.001	0.01
Insomnia	14	0	15	0	0.89	—
Dyspepsia	9	1	14	0	0.13	0.50
Increased sputum	15	1	13	<1	0.78	0.62
Infection	9	1	13	1	0.28	1.00
Anxiety	9	1	11	<1	0.75	1.00
Chills	5	0	11	0	0.03	—
Anemia	13	6	3	1	<0.001	0.006

* Adverse events that occurred in at least 10 percent of patients in either treatment group are shown, regardless of cause.
† P values were determined with the use of Fisher's exact test.

chemoradiotherapy has been found to improve locoregional control or survival over that with radiotherapy alone in selected groups of patients.[11,46] Such combination regimens, however, are associated with high rates of severe and protracted mucositis and an increased need for nutritional support and invasive procedures for that purpose.[10] Late toxic effects, particularly swallowing dysfunction, are also common.[12,43,47-49] A considerable proportion of patients with head and neck cancer have reduced performance status or coexisting conditions, and these patients may be particularly prone to such adverse events.[12,43,47-49] In our study, which included patients with Karnofsky performance scores ranging from 60 to 100, the use of radiotherapy plus cetuximab was not

associated with an excess of severe toxic effects, indicating that these results are applicable to most patients with locoregionally advanced disease.

A meta-analysis has suggested that regimens of aggressive altered-fractionation radiotherapy (i.e., accelerated fractionation or hyperfractionated radiotherapy) without chemotherapy improve overall survival,[50] and it remains controversial whether the addition of chemotherapy enhances the efficacy of altered-fractionation radiotherapy.[44,51] For example, in a randomized trial of twice-daily radiotherapy (total dose, 70 Gy) plus chemotherapy (cisplatin plus fluorouracil), as compared with twice-daily radiotherapy (total dose, 75 Gy) without chemotherapy, chemoradiotherapy improved both the duration of locoregional control and survival, with absolute benefits at three years of 26 percentage points ($P=0.01$) and 21 percentage points ($P=0.07$), respectively.[10] However, another phase 3 trial that evaluated chemotherapy combined with high-dose, fractionated radiotherapy, as compared with radiotherapy alone, found absolute increases in the duration of locoregional control and survival at two years of only 6 percentage points and 9 percentage points ($P>0.10$ for both comparisons), respectively.[39] The generally greater toxicity of regimens of altered-fractionation radiotherapy places limits on the incremental improvements in efficacy gained by the addition of chemotherapy. In contrast, cetuximab may make possible further gains in the efficacy of chemoradiotherapy regimens for head and neck cancer.

In conclusion, cetuximab plus radiotherapy is superior to radiotherapy alone in increasing both the duration of locoregional disease control and survival in locoregionally advanced head and neck cancer. This regimen represents a new therapeutic option for most patients with locoregionally advanced head and neck cancer and provides a foundation for additional studies directed toward further improvement in the outcome of this disease. Well-designed trials comparing this regimen with other forms of chemoradiotherapy are warranted. In the absence of these comparisons, physicians and patients should discuss the risks and benefits of each regimen on an individualized basis.

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APPENDIX

The following investigators and centers participated in this multicenter, multinational trial: D.M. Shin, M.S. Kies, and K.K. Ang (M.D. Anderson Cancer Center, Houston); J. Giralt, A. Eraso, and J. Baselga (Vall d'Hebron, Barcelona); J. Bonner, S. Spencer, and R. Ove (University of Alabama, Birmingham); P. Harari (University of Wisconsin, Madison); R. Cohen and P. Reid (University of Virginia, Charlottesville); C.U. Jones (Radiological Associates of Sacramento, Sacramento, Calif.); R. Sur (University of Witwatersrand, Johannesburg); D. Raben (University of Colorado, Aurora); M. Haigentz (Montefiore Medical Center, Bronx, N.Y.); J. Jassem (Medical University of Gdansk, Gdansk, Poland); L. Goedhals (University of the Free State, Bloemfontein, South Africa); V. Gregoire (St.-Luc University Hospital; Brussels); S. Korzeniowski (M. Sklodowska-Curie Institute, Krakow, Poland); M. de las Heras (Hospital Virgen de la Arrixaca, Murcia, Spain); G. Juillard (UCLA Medical Center, Los Angeles); L. Pandite (University of Miami, Miami); L. Gleich (University of Cincinnati, Cincinnati); G. Lowrey (West Florida Cancer Center, Pensacola); M. McLaughlin (Mayo Clinic Jacksonville, Jacksonville, Fla.); J. Tortochaux (Centre Jean Perrin, Clemont-Ferrand, France); K. Dicke (Arlington Cancer Center, Arlington, Tex.); A. Raben (Monmouth Medical Center, Long Branch, N.J.); G. Studer (Universitatsspital Zurich, Zurich, Switzerland); J.P. Jordaan (Addington Hospital, Durban, South Africa); P. Maingon (Centre Georges-François Leclerc, Dijon, France); R.-J. Bensadoun (Centre Antoine-Lacassagne, Nice, France); G. Calais (Hopital Bretonneau, Tours, France); M. Castine (Medical Oncology, Baton Rouge, La.); W. Court (Toledo Radiation Oncology, Garden City, N.Y.); M. Jackson (Royal Prince Alfred Hospital, Camperdown, Australia); L.P. Romasanta (Sergas Hospital do Meixoeiro, Vigo, Spain); C. Schultz (Medical College of Wisconsin, Milwaukee); S. Siena (Ospedale Niguarda Ca Granda, Milan); G. Almadori (Universita Cattolica del Sacro Cuore, Rome); D. Barton (University of Wisconsin, Wausau); L. Coia (Community Medical Center, Toms River, N.J.); D. Dalley (St. Vincent's Hospital, Darlinghurst, Australia); A. Kuten (Rambam Medical Center, Haifa, Israel); M. Langer (Indianapolis University, Indianapolis); J.-L. Lefebvre (Centre Oscar Lambret, Lille, France); R. Lynch (Andrew Love Cancer Centre, Geelong, Australia); J. McCann (Baystate Medical Center, Springfield, Mass.); D. Morgan (Nottingham City Hospital, Nottingham, United Kingdom); J. North (Dunedin Hospital, Dunedin, New Zealand); J. Orner (Roswell Park Cancer Institute, Buffalo, N.Y.); E. Mahmut Ozsahin (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland); R. Pfeffer (Chaim Sheba Medical Center, Tel Hashomer, Israel); B.J. Smit (Stellenbosch University, Cape Town, South Africa); G. Storme (Oncology Centrum, the Free University of Brussels, Brussels); R. Wall (Charleston Hematology Oncology, Charleston, S.C.); M. Birchall (University of Bristol, Bristol, United Kingdom); D. Brizel (Duke University, Durham, N.C.); S. Corso (Palmetto Hematology Oncology, Spartanburg, S.C.); S. Davis (Alfred Hospital, Prahran, Australia); L. Fayad (Nevada Cancer Center, Las Vegas); C. Fox (Wollongong Hospital, Wollongong,

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