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ORIGINAL REPORT

Quality of Life in Head and Neck Cancer Patients After Treatment With High-Dose Radiotherapy Alone or in Combination With Cetuximab

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ABSTRACT

Purpose
In this randomized, phase III study, quality of life (QoL) was assessed in patients with locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN) after high-dose radiotherapy alone or in combination with cetuximab.

Patients and Methods
Patients with stage III or IV nonmetastatic and measurable squamous cell carcinoma of the oropharynx, hypopharynx, or larynx were eligible. QoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and EORTC QLQ Head and Neck Cancer–Specific Module at baseline, week 4, and at months 4, 8, and 12 postbaseline.

Results
In this study, one of the largest conducted in a population of patients with locoregionally advanced SCCHN, 424 patients received radiotherapy alone (213 patients) or radiotherapy plus cetuximab (211 patients). Radiotherapy/cetuximab significantly improved locoregional control ($P = .005$) and overall survival ($P = .03$) compared with radiotherapy alone, without significantly increasing radiotherapy-associated adverse events. The current analysis focused on the impact of cetuximab on the QoL. Compliance with completion of QoL questionnaires was high in both arms. QoL worsened during treatment and improved after cessation of treatment, reaching baseline levels at 12 months. There were no significant differences in QoL scores between the treatment arms. This was particularly notable for global health status/QoL, social functioning, social eating, and social contact. Pretreatment global health status/QoL was identified as a significant prognostic variable in these patients.

Conclusion
The addition of cetuximab to radiotherapy significantly improved locoregional control and increased overall survival without adversely affecting QoL.

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INTRODUCTION

Cancer of the head and neck can have profound effects on quality of life (QoL).[1] The proximity of head and neck cancers to many anatomic structures involved in important aspects of physiological and social functions and the collateral damage often associated with the treatment of the disease can have profound deleterious effects on QoL. These may not be readily appreciated or quantified in the routine care of head and neck cancer patients or taken into account when evaluating therapeutic options.[2,3]

Most patients with squamous cell carcinoma of the head and neck (SCCHN) present with stage III or IV disease.[4] Conventional therapy for these patients commonly involves radiotherapy alone or in combination with chemotherapy (chemoradiotherapy [CRT]); surgery is reserved for salvage treatment.[5] Radiotherapy-associated toxicities, such as xerostomia,[6] are well documented and can have a significant impact on QoL.[7] The use of CRT has improved both locoregional control and survival beyond that achieved with radiotherapy alone, but is also associated with significant increases in toxicity.[8-10] The main factors affecting the QoL of patients with locoregionally advanced SCCHN who undergo CRT are xerostomia, taste disturbances, dietary restrictions, dysphagia, and pain.[11] Problems with social interactions and depression have also been reported.[12,13]

Cetuximab (Erbitux; ImClone Systems Inc, Branchburg, NJ, licensed to Merck KGaA, Darmstadt, Germany) is an immunoglobulin G1 monoclonal antibody that specifically targets the epidermal growth factor receptor and competitively inhibits endogenous ligand binding.[14] Tumor epidermal growth factor receptor expression is commonly associated with more aggressive disease and decreased survival.[15,16] Strong synergistic antitumor effects of cetuximab and radiation observed in preclinical studies prompted the investigation of cetuximab in combination with radiotherapy in the clinical setting.[17,18]

Cetuximab has a favorable safety profile; the most common adverse effects are skin reactions, typically an acne-like rash.[19,20] Nail disorders, commonly occurring on the great toes and thumbs, are observed less frequently.[18] Infusion-related reactions, which occur most frequently during the first administration of cetuximab, are also reported, and are severe in some patients.[21]

Recently reported results from a randomized phase III study described the combination of cetuximab and radiotherapy to be significantly more effective than radiotherapy alone in the treatment of locoregionally advanced SCCHN.[18] Importantly, cetuximab did not significantly increase radiotherapy-associated adverse effects. The impact of cetuximab on QoL is largely unknown, and this article reports the findings of a QoL assessment carried out as a secondary end point in this study.

The universally accepted definition of QoL is that it is multidimensional (ie, comprises elements of emotional, social, and physical well-being), a process (ie, subject to change over a patient's lifetime), and subjective (relies primarily on the patient's own judgement). These three points will be taken into account in this report. First, two validated, multidimensional QoL instruments, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and the EORTC QLQ Head and Neck Cancer–Specific Module (H&N35), were used to assess QoL.[22,23] The QLQ-H&N35 assesses symptoms specifically associated with head and neck cancer and its treatments, whereas the QLQ-C30 assesses functioning and symptoms common to most cancer patients. In this study, particular attention was paid to the impact of cetuximab on social functioning and global health status/QoL assessed using the QLQ-C30, and to the effects of local treatment on QoL parameters related to swallowing and speech assessed using the QLQ-H&N35. Second, longitudinal data analyses techniques were used, to allow change over time to be explored and to allow for individual patient variability. To our knowledge, this is the first report of the effects of cetuximab in combination with radiotherapy on the QoL of patients with SCCHN.

PATIENTS AND METHODS

Study Design

This was a multicenter, open-label, stratified, randomized, phase III study in patients with stage III or IV nonmetastatic and measurable squamous cell carcinoma of the oropharynx, hypopharynx, or larynx. The primary end point was the duration of locoregional control, and secondary end points included overall survival and QoL. The study was conducted in accordance with the Declaration of Helsinki and was approved by national or local ethics committees, as appropriate. All patients provided written informed consent. Full details of the study and its results have been reported previously.[18]

Study Treatments

Patients were randomly assigned to treatment with radiotherapy (administered according to one of three fractionation regimens—once daily, twice daily, or concomitant boost for 6 to 7 weeks—selected by investigators before random assignment) either alone or in combination with cetuximab (initial dose 400 mg/m^2 during 120 minutes followed by weekly 60-minute infusions of 250 mg/m^2, which generally consisted of a total of seven to eight infusions for the duration of radiotherapy) initiated 1 week before radiotherapy. Patients were stratified according to Karnofsky performance status (KPS), nodal involvement, tumor stage, and radiotherapy regimen.

QoL Assessments

The EORTC QLQ-C30 (version 3.0) and the QLQ-H&N35 instruments were used to assess QoL.[22,23] For the QLQ-C30, 15 scales were derived from the initial 30 items: five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea and vomiting, pain), six single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and one global health status/QoL scale. For the QLQ-H&N35, 18 scales were derived from the initial 35 items: seven multi-item symptom scales (pain, swallowing, sensation, speech, eating from a social perspective, social interactions, and sexuality) and 11 single-item symptom scales (teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain medication use, nutritional supplementation, feeding tube requirement, weight loss, and weight gain). The scores for all scales were calculated according to the procedures defined in the EORTC Scoring Manual, and ranged from 0 to 100 after linear transformation.[21] Higher scores in functioning and global health status/QoL scales indicate a higher level of functioning and a better QoL, respectively, whereas higher scores in symptom scales represent a higher level of symptom.

QoL was evaluated in a longitudinal design in all randomly assigned patients who had at least one assessable questionnaire. Questionnaires were considered assessable if they were self-administered and had a date of assessment (within the visit window).

Statistical Methods

All statistical tests were two sided at the 5% level, without adjustments for multiple comparisons. The null hypothesis to be tested with regard to treatment effect was that there is no difference between the treatment arms.

QoL compliance was calculated as the ratio of the total number of patients with at least one assessable questionnaire to the total number of expected questionnaires (all patients alive at that time point) per time window.[24] The patterns of completion of questionnaires were explored to investigate the magnitude of missing data and the extent of intermittent missing data and monotone (ie, provision of a complete series of questionnaires before dropout) missing data.

Summary measures of QoL scores were generated.[25] Patients' actual scores and the changes relative to baseline were calculated for each functioning and global health status/QoL scale (best and worst scores) and each symptom scale (worst scores), and were compared between the treatment arms using the Wilcoxon nonparametric test.

A logistic regression model was used to test if the dropout process was missing completely at random.[26] The model included terms for clinical variables (T stage, T1-3 *v* T4; N stage, N0-1 *v* N2-3; tumor site, larynx *v* hypopharynx/oropharynx; KPS, ≤ 80 *v* > 80; age, continuous; and sex), assessment visit, treatment, visit by treatment interaction, and global health status/QoL. The Wald χ^2 test was used to evaluate the effect of QoL scores on dropout.

A repeated-measures multivariate analysis of variance model, which is valid under missing completely at random and missing at random dropout mechanisms, was used to generate the least squares mean estimates for the visit by treatment interaction, and the difference in least squares means and their associated SEs, included terms for clinical variables (see previous paragraph) and a treatment by visit interaction.[27,28] The variance-covariance structure was assumed to be autoregressive order 1. A pattern-mixture model, including the terms treatment, visit, and dropout pattern; an interaction between treatment and dropout pattern; and baseline clinical variables, was fitted for both the social functioning and global health status\QoL scales.[29] If insufficient numbers of patients existed in a dropout pattern, consecutive patterns were to

be combined to ensure convergence of the model. If the treatment effect in the final model was pattern dependent, the delta method was used to obtain the marginal treatment effect.[30] The null hypothesis of no treatment effect was tested using a Wald statistic.

The prognostic values of the baseline global health status/QoL, fatigue, and physical functioning scale scores were investigated. The three QoL variables were dichotomized at the median to yield good and poor scores, respectively. Survival curves and probabilities were estimated using the Kaplan-Meier technique.[31] The Cox proportional hazards regression model with stratification for treatment arm was used for both univariate and multivariate analyses. The multivariate model was used without a model selection procedure and included the baseline clinical variables and sex as covariates along with the three QoL scales of interest. The importance of a prognostic variable was assessed using the Wald χ^2 statistical test, as well as the hazard ratio (HR) and its 95% CI.

RESULTS

Summary of Clinical Results

Between April 1999 and March 2002, 424 patients were randomly assigned to treatment with radiotherapy alone (213 patients) or radiotherapy plus cetuximab (211 patients). The median duration of locoregional control was 24.4 months for the combined-therapy arm and 14.9 months for radiotherapy alone ($P = .005$). The corresponding median survival times were 49.0 and 29.3 months ($P = .03$). Five and eight patients discontinued treatment with cetuximab due to hypersensitivity reactions and skin toxicity, respectively. Less than 5% of patients required dose reduction and 15% of patients required treatment delays of at least 4 days. With the exception of acne-like rash and infusion-related events, the incidence of adverse events was comparable between the treatment arms. Importantly, the addition of cetuximab to radiotherapy did not seem to increase the incidence of common radiotherapy-associated toxicities significantly, including mucositis, xerostomia, dysphagia, pain, weight loss, and performance status deterioration.

QoL Compliance

Of the 424 patients randomly assigned, QoL questionnaires were not completed in two patients (both receiving radiotherapy/cetuximab) and were not assessable in three additional patients (two receiving radiotherapy/cetuximab and one receiving radiotherapy). Thus, 419 patients were assessable for QoL assessments. An analysis of compliance for QLQ-C30 questionnaires revealed that there was a reduction in both the number of patients (due to attrition of patients) and the proportion of assessable questionnaires received at successive visits (Table 1). The compliance rate was consistently higher in the combination-treatment arm across all time points.

Summary Measures

There were no statistically significant between-arm differences in the best and worst postbaseline QoL scores for the functioning and global health status/QoL scales, except for the best postbaseline physical functioning scale, which demonstrated a better score in the radiotherapy plus cetuximab arm (Table 2). However, the significance of this result was not supported by the repeated-measures multivariate analysis of variance, suggesting that it occurred by chance due to multiple testing. Large differences between baseline and worst postbaseline scores for the QLQ-C30 and QLQ-H&N35 multi-item symptom scales were noted for all scales, particularly for the swallowing, sensory problems, and social eating scales (Table 3). However, statistically significant differences between treatment groups were not apparent.

All single items showed a worsening of symptoms from baseline (data not shown). The two items that showed the largest change from baseline in both arms were sticky saliva and dry mouth.

Change of QoL As a Function of Time

The least squares means estimate of the EORTC QLQ-C30 global health status/QoL scores as a function of treatment arm and the difference between treatment arms at each visit are shown in Figure 1. There was a small (albeit nonsignificant) difference in mean scores at baseline between the two treatment arms, which was maintained throughout the study period. This suggests that the addition of cetuximab did not adversely influence global health status/QoL scores. The general pattern for most of the QoL scales was that of a decrease in the postbaseline visits and thus a worsening of symptoms, followed by an increase in scores comparable to baseline levels by month 12. Only two tests for the 16 multi-item scales showed a significant difference between treatment arms, both in favor of radiotherapy/cetuximab at week 4: the swallowing scale (difference in least squares means scores, −8.12; $P = .004$,) and the speech problems scale (difference in least squares means scores, −5.92, $P = .028$). However, given that these differences were small and the results were not supported at other time points or by summary measure analysis, it is likely that these results occurred by chance due to multiple testing.

Table 1. Analysis of Compliance for QLQ-C30 Questionnaires by Protocol Planned Assessment (assessable for QLQ-C30 population)

	Radiotherapy Alone (n = 212)			Radiotherapy Plus Cetuximab (n = 207)		
Visit	No. of Patients in Time Window (N1)	No. of Patients With at Least One Questionnaire (N2)	Rate: N2/N1 (%)	No. of Patients in Time Window (N1)	No. of Patients With at Least One Questionnaire (N2)	Rate: N2/N1 (%)
Baseline	212	198	93.4	207	199	96.1
Week 4	210	189	90.0	204	189	92.3
Month 4	201	162	80.6	195	174	89.2
Month 8	168	123	73.2	186	145	78.0
Month 12	154	100	64.9	159	116	73.0

NOTE. N1 and N2 denote the numbers of patients used to calculate the proportion of patients with at least one questionnaire (N2/N1).
Abbreviation: QLQ-C30, Quality of Life Questionnaire C30.

Table 2. Best and Worst Postbaseline Scores for the QLQ-C30

Item	Radiotherapy Alone (n = 212) Mean	SD	Radiotherapy Plus Cetuximab (n = 207) Mean	SD	*P*
Global health status					
Best score	67.4	22.20	71.0	22.44	.1041
Worst score	42.2	22.41	44.3	22.98	.3372
Physical functioning					
Best score	83.0	21.51	87.5	17.53	.0281
Worst score	63.1	25.16	65.6	24.23	.3456
Role functioning					
Best score	80.2	27.44	83.2	25.55	.2384
Worst score	48.1	31.72	47.0	34.07	.7138
Emotional functioning					
Best score	79.1	23.37	81.9	19.43	.4650
Worst score	53.3	28.83	56.9	27.40	.3776
Cognitive functioning					
Best score	86.6	20.82	89.0	19.01	.2745
Worst score	66.5	27.29	67.1	27.67	.7952
Social functioning					
Best score	82.0	26.36	82.5	24.32	.8328
Worst score	54.1	33.05	51.7	32.17	.4132

NOTE. A higher score represents a higher level of functioning and a better QoL.
Abbreviations: QLQ-C30, Quality of Life Questionnaire C30; SD, standard deviation; QoL, quality of life.

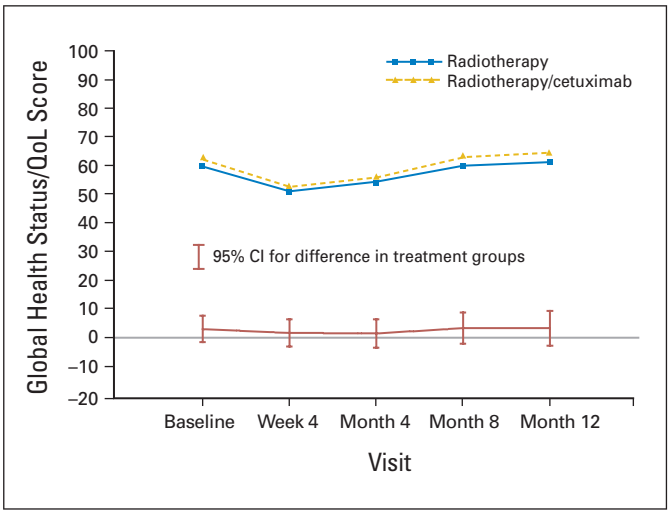

Fig 1. Least squares means estimate of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 global health status/quality of life (QoL) scores as functions of treatment group and difference between treatment groups (95% CIs) at each time point.

Analysis of Missing Data

Twenty-three patients completed the baseline questionnaire only and 33 completed both the baseline and week 4 questionnaires. One hundred sixty-four patients completed a questionnaire at all visits up to and including month 12. Monotone dropout patterns were observed in 343 patients. Intermittent missing questionnaires were also prominent. The dropout probability was higher in patients with a poor baseline KPS ($P = .014$), those receiving radiotherapy alone ($P = .021$), and those with a low global health status/QoL score ($P < .001$). Figure 2 presents the mean global health status/QoL scores by visit and dropout pattern for each treatment arm. Four dropout patterns, based on the visit at which the last questionnaire was completed, were defined as pattern 1, dropout at baseline or week 4 (60 patients); pattern 2, dropout at month 4 (72 patients); pattern 3, dropout at month 8 (71 patients); or pattern 4, dropout at or after month 12 (216 patients). Figure 2 illustrates that the mean global health status/QoL score decreased initially during radiotherapy in all dropout patterns. In both treatment arms there was a clear indication of differences between patterns with respect to mean global health status/QoL score. These findings were consistent with the logistic regression analysis. The plot indicates that the patterns are similar across treatment arms, in particular pattern 4, which represents the majority of patients. Analysis using pattern-mixture models for both the global health status/QoL and social functioning scales indicated no significant treatment differences between the two treatment arms ($P = .103$, and $P = .855$, respectively).

Prognostic Value of QoL Scales

Kaplan-Meier estimates of survival stratified by the baseline global health status/QoL scores are shown in Figure 3. Patients with a

Table 3. Change From Baseline to Worst Postbaseline Scores

Scale	Radiotherapy Alone (n = 212) Mean	SD	Radiotherapy Plus Cetuximab (n = 207) Mean	SD	*P*
Fatigue	27.9	28.86	29.7	28.52	.6408
Nausea and vomiting	19.7	27.41	20.9	28.06	.7814
Pain QLQ-C30	22.0	34.59	22.1	34.07	.8048
Pain QLQ-H&N35	27.4	30.52	25.8	31.84	.6551
Swallowing	35.1	32.28	34.2	31.23	.7878
Sensory problems	39.5	29.59	41.2	31.04	.5981
Speech problems	21.8	27.87	23.3	30.19	.6207
Trouble with social eating	33.3	33.94	34.4	32.59	.6301
Trouble with social contact	16.6	25.27	20.1	25.83	.4729
Less sexuality	28.6	39.38	26.3	35.07	.5669

NOTE. A higher score represents a higher level of symptom.
Abbreviations: SD, standard deviation; QLQ-C30, Quality of Life Questionnaire C30; H&N35, Head and Neck Cancer–Specific Module.

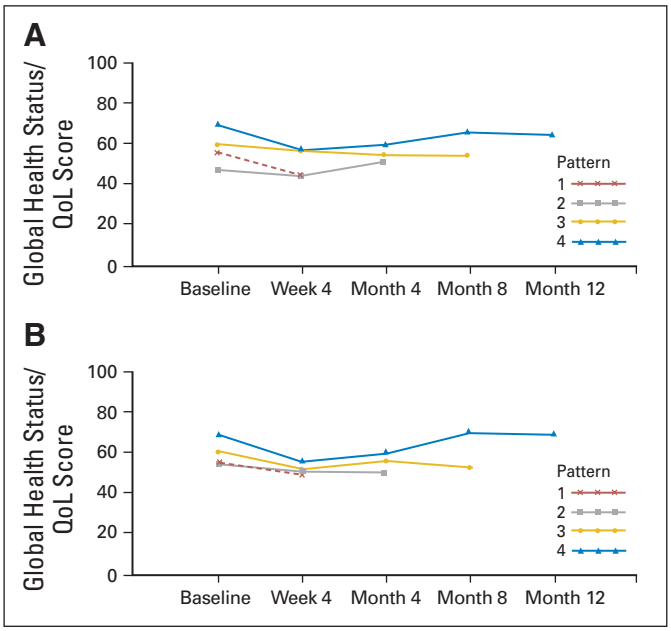

Fig 2. (A) Radiotherapy; (B) radiotherapy/cetuximab. Least squares means estimates of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 mean global health status as functions of treatment group and dropout pattern. QoL, quality of life.

higher global health status/QoL score at baseline survived significantly longer than patients with a lower global health status/QoL score at baseline (median survival, not reached *v* 18 months; $P < .001$). The univariate analysis results were similar for the physical functioning (median survival, 50.4 *v* 20.6 months, $P < .001$) and fatigue scales (median survival: 24.4 *v* 56.7 months; $P = .002$). Significant variables identified in the multivariate model were age (HR, 1.01; $P = .045$), T stage (HR, 1.64; $P = .001$), KPS (HR, 2.27; $P < .001$), and global health status/QoL (HR, 1.66; $P = .005$).

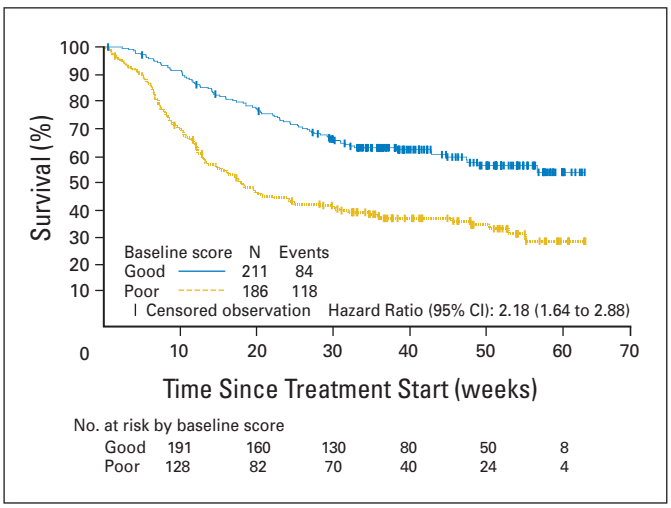

Fig 3. Kaplan-Meier survival curves stratified by baseline European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 global health status/quality of life scores.

DISCUSSION

In this randomized phase III study, QoL was assessed in patients with locoregionally advanced SCCHN after treatment with either high-dose radiotherapy alone or high-dose radiotherapy plus cetuximab. Compliance with completion of QoL questionnaires was high in both treatment arms, particularly in the combination-treatment arm. The results indicated an inverse relationship between QoL scores and the probability of dropout. These findings suggest that simplified analyses such as worst score summary measures are potentially biased in favor of the radiotherapy-alone arm, given that patients with a lower QoL tended to dropout early and the dropout rate was higher in the radiotherapy-alone treatment arm.

Although a few statistically significant differences in QoL between the treatment arms were demonstrated, these differences were small, inconsistent, and likely due to chance. Any negative impact of cetuximab-associated acne-like rash and infusion-related reactions should have been detected by the EORTC QLQ-C30 social functioning scale. However, no significant differences in this scale between the treatment arms were observed. The lack of significant differences between the treatment arms also was observed after application of the pattern-mixture model, which takes missing data and dropout pattern into account. This confirms the robustness of the results and also supports the findings of no treatment differences obtained using the best and worst score for both the global health status/QoL and social functioning scales.

Taken in conjunction with a significant improvement in locoregional control and overall survival compared with radiotherapy alone, the apparent lack of a negative impact on QoL of cetuximab combined with radiotherapy is noteworthy. Although CRT has also demonstrated improved locoregional control and survival compared with radiotherapy, the effects are achieved at the cost of increased toxicity, including dysphagia and mucosal and hematologic toxicities.[7,8,10,32] Moreover, CRT regimens can be difficult to implement in community practice.[32] In this study, radiotherapy plus cetuximab was well tolerated and cetuximab did not significantly increase common radiotherapy-associated toxicities, including mucositis, xerostomia, dysphagia, pain, weight loss, and performance status deterioration. More than 95% of all patients were able to receive the full dose of cetuximab in combination with radiotherapy.

Both the EORTC QLQ-C30 and QLQ-H&N35 modules were sufficiently sensitive to detect changes in QoL over time. The majority of scales demonstrated a worsening of QoL during treatment, with a corresponding increase in QoL post-treatment in both treatment arms. During treatment, the most significant impact of radiotherapy was seen on role functioning, fatigue, appetite loss (all assessed using the EORTC QLQ-C30), swallowing, sensory problems, and trouble with eating (all assessed using the QLQ-H&N35). This reduction in QoL was expected and can be attributed to the adverse effects of the radiotherapy. The subsequent relatively good scores at months 8 and 12 indicate that most symptoms are transient and resolve after treatment cessation. This phenomenon of a return to baseline QoL scores after treatment in patients still on study at 12 months has been observed elsewhere.[25,33]

Global health status/QoL was the only scale that was identified on multivariate analysis, after adjusting for other clinical variables, as a significant prognostic variable. Other studies have also suggested that baseline QoL is a prognostic variable for survival in patients with head and neck cancer.[34,35]

In summary, the addition of cetuximab to radiotherapy significantly improved locoregional control and survival compared with radiotherapy alone in patients with locoregionally advanced SCCHN, without apparently adversely affecting social functioning or global health status/QoL. These findings provide additional support that adding cetuximab to radiotherapy is an attractive therapeutic option for patients with locoregionally advanced SCCHN.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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ERRATA

The July 1, 2007, article by Maki et al entitled, "Randomized Phase II Study of Gemcitabine and Docetaxel Compared With Gemcitabine Alone in Patients With Metastatic Soft Tissue Sarcomas" (J Clin Oncol 25:2755-2763, 2007) contained an error. In the title, the "Results of Sarcoma Alliance for Research Through Collaboration Study 002" was inadvertently omitted, and should have been included as follows, "Randomized Phase II Study of Gemcitabine and Docetaxel Compared With Gemcitabine Alone in Patients With Metastatic Soft Tissue Sarcomas: Results of Sarcoma Alliance for Research Through Collaboration Study 002." The online version has been corrected in departure from the print.

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The June 1, 2007, article by Curran et al, entitled "Quality of Life in Head and Neck Cancer Patients After Treatment With High-Dose Radiotherapy Alone or in Combination With Cetuximab" (J Clin Oncol 25:2191–2197, 2007) contained errors.

In the Author Contributions section, James A. Bonner should have been acknowledged for:

Conception and design
Provision of study materials or patients
Collection and assembly of data
Data analysis and interpretation
Manuscript writing
Final approval of the manuscript

In the Authors' Disclosures of Potential Conflicts of Interest section, ImClone Systems Inc and Bristol-Myers Squibb Co should have been disclosed for James A. Bonner in the Honoraria category.

The online version has been corrected in departure from the print.

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The April 1, 2007, article by Loi et al, entitled "Definition of Clinically Distinct Molecular Subtypes in Estrogen Receptor–Positive Breast Carcinomas Through Genomic Grade" (J Clin Oncol 25:1239-1246, 2007), contained an error.

In the Materials and Methods section, under Tumor Samples, the last sentence of the second paragraph was given as:

"Each hospital's institutional ethics board approved the use of the tissue material, and written informed consent was obtained."

While it should have read:

"Each hospital's institutional ethics board approved the use of the tissue material for the purposes described in this paper, as many of the patients were deceased when the study was performed."

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