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Quality of Life and Performance Status From a Substudy Conducted Within a Prospective Phase 3 Randomized Trial of Concurrent Standard Radiation Versus Accelerated Radiation Plus Cisplatin for Locally Advanced Head and Neck Carcinoma: NRG Oncology RTOG 0129

Canhua Xiao, PhD[*], **Qiang Zhang, PhD**[†], **Phuc Felix Nguyen-Tân, MD**[‡], **Marcie List, PhD**[§], **Randal S. Weber, MD**[||], **K. Kian Ang, MD**[||,1], **David Rosenthal, MD**[||], **Edith J. Filion, MD**[‡], **Harold Kim, MD**[¶], **Craig Silverman, MD**[#], **Adam Raben, MD**[**], **Thomas Galloway, MD**[††], **Andre Fortin, MD**[‡‡], **Elizabeth Gore, MD**[§§], **Eric Winquist, MD, MSc**[||||], **Christopher U. Jones, MD**[¶¶], **William Robinson, MD**[##], **David Raben, MD**[***], **Quynh-Thu Le, MD**[†††], and **Deborah Bruner, RN, PhD**[*]

[*]Emory University, Atlanta, Georgia

[†]NRG Oncology Statistics and Data Management Center, Philadelphia, Pennsylvania

[‡]Centre Hospitalier de l'Université de Montréal-Notre Dame, Montréal, Quebec, Canada

[§]The University of Chicago, Chicago, Illinois

[||]University of Texas-MD Anderson Cancer Center, Houston, Texas

[¶]Wayne State University, Karmanos Cancer Center, Detroit, Michigan

[#]James Graham Brown Cancer Center—University of Louisville, Louisville, Kentucky

[**]Christiana Care Health Services, Inc, CCOP, Newark, Delaware

[††]Fox Chase Cancer Center, Philadelphia, Pennsylvania

[‡‡]L Hotel-Dieu de Quebec, Québec City, Quebec, Canada

[§§]Medical College of Wisconsin, Milwaukee, Wisconsin

[||||]London Regional Cancer Program, London, Ontario, Canada

[¶¶]Sutter General Hospital, Formerly Radiological Associates of Sacramento, Sacramento, California

[##]Tulane University Medical Center, New Orleans, Louisiana

[***]University of Colorado, Denver, Colorado

Reprint requests to: Canhua Xiao, PhD, Emory University School of Nursing, 1520 Clifton Rd NE, Room 234, Atlanta, GA 30322-4207. Tel: (404) 712-9823; canhua.xiao@emory.edu.

[1]Deceased.

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†††Stanford University Medical Center, Stanford, California

Abstract

Purpose/Objective(s)—To analyze quality of life (QOL) and performance status (PS) for head and neck cancer (HNC) patients treated on NRG Oncology RTOG 0129 by treatment (secondary outcome) and p16 status, and to examine the association between QOL/PS and survival.

Methods and Materials—Eligible patients were randomized into either an accelerated-fractionation arm or a standard-fractionation arm, and completed the Performance Status Scale for the Head and Neck (PSS-HN), the Head and Neck Radiotherapy Questionnaire (HNRQ), and the Spitzer Quality of Life Index (SQLI) at 8 time points from before treatment to 5 years after treatment.

Results—The results from the analysis of area under the curve showed that QOL/PS was not significantly different between the 2 arms from baseline to year after treatment (*P* ranged from .39 to .98). The results from general linear mixed models further supported the nonsignificant treatment effects until 5 years after treatment (*P*=.95, .90, and .84 for PSS-HN Diet, Eating, and Speech, respectively). Before treatment and after 1 year after treatment, p16-positive oropharyngeal cancer (OPC) patients had better QOL than did p16-negative patients (*P* ranged from .0283 to <.0001 for all questionnaires). However, QOL/PS decreased more significantly from pretreatment to the last 2 weeks of treatment in the p16-positive group than in the p16-negative group (*P* ranged from .0002 to <.0001). Pretreatment QOL/PS was a significant independent predictor of overall survival, progression-free survival, and local-regional failure but not of distant metastasis (*P* ranged from .0063 to <.0001).

Conclusions—The results indicated that patients in both arms may have experienced similar QOL/PS. p16-positive patients had better QOL/PS at baseline and after 1 year of follow-up. Patients presenting with better baseline QOL/PS scores had better survival.

Introduction

Head and neck cancer (HNC) constitutes a group of mucosal cancers located in the upper aerodigestive tract, including oral cavity, oropharynx, hypopharynx, and larynx. In the United States, the incidence of HNC has increased; there were 40,250 new estimated cases in 2012 (1) and 55,070 in 2014 (2). The rise in HNC incidence is attributed to the increasing diagnosis of human papillomavirus (HPV)-associated oropharyngeal cancer (OPC) (3, 4). HPV-positive OPC has a favorable survival when compared with HPV-negative OPC (5–7). Because of the increased incidence and better survival in HPV-positive OPC patients who also present in earlier decades of life, understanding patients' health-related quality of life (QOL) has become important to guide future treatment regimens.

Quality of life has become a standard endpoint in randomized clinical trials, and it provides essential information that can contribute to clinical decision making. In patients with HNC, QOL, especially the important domains related to eating, tasting, and speaking, is often severely reduced by concurrent chemoradiation therapy (8–10). Although most HPV-positive OPC patients are treated with concurrent chemoradiation therapy, QOL effects in this population are not well understood. Recent recognition of the different survival outcomes for

HPV-positive and HPV-negative patients has necessitated HPV-specific trials to identify the optimal treatment approach for minimizing morbidity while maintaining excellent survival for HPV-positive patients. Understanding the association between QOL, tumor p16 status (a surrogate for HPV-associated tumor), and survival may help inform the therapeutic ratio.

The NRG Oncology Radiation Therapy Oncology Group (RTOG) 0129 was a randomized phase 3 clinical trial powered to determine whether accelerated-fractionation—(AFX) relative to standard-fractionation—radiation therapy (SFX) could improve survival of 720 patients with advanced HNC. We have previously reported the survival endpoints (the primary objective), which did not show improved efficacy with accelerated fractionation but confirmed the prognostic significance of HPV (5, 7). Here, we report the results of QOL/PS endpoints, including the impact of treatment (1 of the secondary objectives) and p16 status on QOL/PS until 5 years' follow-up and the association between QOL/PS and survival (exploratory objectives).

Methods and Materials

Protocol and treatment

The RTOG 0129 trial was registered with the National Cancer Institute; all patients provided written informed consent to participate, including the current study.

Eligible patients were those who had untreated squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx with selected stage III or IV disease, and those age 18 years or older with Zubrod status 0 to 1, adequate major organ function, and no evidence of metastases. Patients were stratified by tumor site, nodal stage, and Zubrod performance status and were randomly assigned to either AFX or SFX. Patients in the AFX arm received a total radiation dose of 72 Gy in 42 fractions within 6 weeks plus 2 cycles of cisplatin (100 mg/m^2 on days 1 and 22). Patients in the AFX arm had a total dose of 70 Gy in 35 fractions within 7 weeks plus 3 cycles of cisplatin (100 mg/m^2 on days 1, 22, and 43). No intensity modulated radiation therapy (IMRT) was involved in this trial.

The patients' demographic and clinical characteristics were collected at enrollment or follow-up through chart review. Tumor tissue was evaluated for p16 expression as previously described (5, 11).

Quality of life and performance status measures

The QOL/PS data were obtained by use of the Performance Status Scale for Head and Neck (PSS-HN), Head and Neck Radiotherapy Questionnaire (HNRQ), and Spitzer Quality of Life Index (SQLI) and were collected using English at 8 time points: before treatment; within the last 2 weeks of treatment; 3 months from the start of treatment; and 1, 2, 3, 4, and 5 years from the start of treatment.

The PSS-HN is a clinician-rated evaluation conducted as an unstructured interview format that assesses 3 functions: Normalcy of Diet, Public Eating, and Understandability of Speech (12, 13). Each function is scored from 0 to 100 and analyzed separately. Higher scores

indicate better performance status. It has been demonstrated to be reliable and valid in HNC patients (12, 13).

The HNRQ is a patient-reported questionnaire administrated through a paper format; it measures radiation-related side effects and the overall well-being of HNC patients in the past week. The overall score is the mean of the 22 questions, with a range of 1 to 7. Higher scores indicate better QOL. This questionnaire has proved sensitive to treatment effects and is correlated highly with existing measures of toxicity and performance ratings in the HNC population (14).

The SQLI is a patient-reported QOL index asking questions about the past week and is administrated in a paper format. The overall score is the sum of the 5 questions, with a range of 0 to 10. Higher scores indicate better QOL. SQLI was selected to provide an overall QOL assessment for the purpose of deriving quality-adjusted life-years. Its validity and reliability have been established in cancer patients (15).

Statistical analysis

Questionnaires were included in the analysis if they were collected before treatment (on or before the start of treatment), in the last 2 weeks of treatment (4 weeks before or 2 weeks after the end of treatment), at 3 months (±6 weeks), and annually at 1 to 5 years (±3 months). Pretreatment characteristics were compared by Fisher exact test, χ^2 test (categoric variables), 2-sample *t* test, and Wilcoxon rank-sum test (ordinal variables).

Treatment effect on QOL/PS was analyzed in the following ways. Time-weighted average QOL/PS between pretreatment and 12 months was calculated by use of area under the curve (AUC) (16); this was the primary endpoint for QOL per protocol, with arms compared by *t* test with adjustment of multiple comparison using the Hommel procedure. Patients with all 4 assessments (pretreatment, last 2 weeks of treatment, 3 months, and 12 months, required for AUC calculations) for each questionnaire were included in the relevant analyses. Given the potential impact of missing data on the results, we also imputed missing values for the AUC analysis of PSS-HN, HNRQ, and SQLI using the Markov chain Monte Carlo algorithm with a noninformative prior. Forty datasets were created, and the results were combined per Rubin's formula (17). Additionally, mean values over time were analyzed with the general linear mixed model to include all potential patients with data at each time point to reduce the potential impact of missing data on the results (linear mixed models with nonlinear time effects were also considered). Furthermore, we conducted 2 other exploratory analyses in which no multiple comparisons or missing imputation adjustments were made: (*1*) a cross-sectional analysis of raw scores was conducted at each time point (pretreatment through 5 years); and (*2*) individual changes from pretreatment were calculated and compared for each follow-up time point.

Cross-sectional and change scores were compared by p16 status in patients with OPC using a 2-sample *t* test; this comparison included all potential patients having data at each time point. Multivariate Cox proportional hazards models were used to determine the prognostic effect of pretreatment QOL/PS scores as continuous variables on survival outcomes, including overall survival (OS), progression-free survival (PFS), local-regional failure

(LRF), and distant metastasis (DM). The definition of survival outcomes was published previously (18).

With 126 analyzable patients per arm, the study had at least 86% power to detect a difference of 7 (standard deviation=18) for PSS-HN between the arms as indicated by RTOG 9003 (19). All analyses were done using SAS 9.4 with a 2-sided significance level of .05. The clinical significance was determined using a ≥20 point change for PSS-HN Diet and ≥25 points for Eating and Speech (13), and using minimal important difference of at least 10% of the instrument range for HNRQ and SQLI (13, 20).

Results

Patient characteristics

The NRG RTOG 0129 opened to patient accrual on July 30, 2002, and closed on June 23, 2005, with 743 patients entered. Four patients withdrew consent to participate, 17 were retrospectively declared ineligible, and 1 patient had no follow-up, leaving 721 analyzable patients. Patients who completed the QOL/PS questionnaires formed the cohort for this analysis, which included all follow-up data submitted through January 3, 2013 (Fig. 1).

Table 1 shows the percentage of patients who completed each questionnaire at all 4 time points for AUC analysis. Because the demographic and clinical characteristics for patients who completed each questionnaire were similar, we selected the first questionnaire, PSS-HN Diet (n=281), to report the pretreatment characteristics by treatment arms and p16 status (for OPC patients) in Table 2. Most patients were white (84.7%) men (82.6%) with OPC (64.8%). Among OPC patients, 74.1% were positive for p16. No significant differences in pretreatment characteristics, including p16 status, were found between the 2 treatment arms. Additionally, the patients' characteristics were compared between those who were included in the AUC analysis and those who were not, and patients in the AUC analysis had better Zubrod performance scores (Zubrod 0: 63.7% vs 54.1%; P=.01), lower rates of feeding tubes (18.9% vs 26.1%; P=.02), and more p16-positive cases (63.4% vs 51.3%; P=.02) than those who were not.

Similar to the larger trial population, p16-positive OPC patients with PSS-HN data had a lower cumulative cigarette pack-years (P<.001), were younger (P=.05), and had a relatively lower rate of feeding tube or gastrostomy (P=.06) compared with p16-negative OPC patients.

Quality of life and performance status between treatment arms

The AUC analysis for data from before treatment to 1 year after treatment showed no significant differences between the AFX and SFX arms for all 3 questionnaires: PSS-HN (Diet: mean 53.63 and 53.36, respectively, P=.92; Eating: 67.10 and 65.81, respectively, P=.67; Speech: 91.77 and 90.48, respectively, P=.43), HNRQ (5.19 and 5.27, respectively, P=.39), and SQLI (8.02 and 8.02, respectively, P=.98). The imputed data showed similar nonsignificant results: PSS-HN (Diet: 51.98 vs 51.58, P=.84; Eating: 65.55 vs 63.48, P=.28; Speech: 90.01 vs 88.89, P=.32), HNRQ (5.08 and 5.16, P=.25), and SQLI (7.83 and 7.78, P=.67). The results from general linear mixed models further supported the nonsignificant

treatment effects until 5 years after treatment (*P*=.95, .90, .84, .20, and .26 for PSS-HN Diet, Eating, and Speech, HNRQ, and SQLI, respectively) (Table 3). The model with linear time effect had the lowest AIC, and the estimates from linear models were more plausible and closer to the observed values for all tools.

Multiple time points on the cross-sectional raw score (Table E1; available at www.redjournal.org) and change score analyses (Fig. E1; available at www.redjournal.org) showed nonsignificant results similar to the AUC analysis, even though a few worse QOL/PS scores (raw scores or change scores) were shown in the AFX arm compared with the SFX arm (all of them were not clinically significant).

Quality of life and performance status between p16 status for OPC only

For patients with OPC, p16 status was significantly associated with QOL/PS (Fig. 2). Before treatment, patients with p16-positive OPC displayed significantly better QOL/ PS than did p16-negative patients on all 3 questionnaires (PSS-HN Diet: mean 85.48 and 65.38, respectively, *P*<.0001; PSS-HN Eating: mean 94.19 and 79.95, respectively, *P*=.0001; PSS-HN Speech: mean 98.21 and 92.86, respectively, *P*=.0103; HNRQ: mean 6.04 and 5.53, respectively, *P*<.0001; SQLI: mean 8.83 and 8.10, respectively, *P*=.0056). After treatment, p16-positive patients showed significantly better scores on PSS-HN Diet and Eating from 1 year up to 5 years after treatment compared with p16-negative patients (*P* ranged from .0112 to <.0001 for Diet and from .0283 to .0050 for Eating). However, this significant beneficial effect of p16-positive status was not evident in PSS-HN Speech, HNRQ, and SQLI for most of the follow-up time points, even though p16-positive patients always had relatively higher scores on these scales than did p16-negative patients. Only PSS-HN Diet was clinically significant.

On the basis of change score data analysis, all QOL/PS scales, excluding PSS-HN Speech, decreased more significantly from before treatment to the last 2 weeks of treatment in the p16-positive group compared with the p16-negative group (PSS-HN Diet: mean change −66.83 and −42.41, respectively, *P*<.0001; PSS-HN Eating: mean change −55.86 and −34.51, respectively, *P*=.0002; HNRQ: mean change −2.59 and −1.49, respectively, *P*<.0001; SQLI: mean change −3.00 and −1.46, respectively, *P*<.0001). This gap resolved gradually by 3 months or 1 year after treatment (Fig. E2; available at www.redjournal.org). All these differences in the mean changes between p16-positive and p16-negative groups, excluding PSS-HN Eating, were clinically significant.

Quality of life, performance status, and survival outcomes

Our findings showed that pretreatment QOL/PS, including all 3 questionnaires, was a significant independent prognostic factor for OS, PFS, and LRF but not DM (Table 4) after treatment, age, Zubrod score, primary site, T stage, and N stage were controlled for. For instance, PSS-HN Speech score was significant for LRF with a hazard ratio (HR) per 25 points of 0.81 (95% CI, 0.70–0.94), reflecting a 19% reduction of risk. We also examined survival based on p16 status and primary sites (OPC vs non-OPC) separately. Table E2 (available at www.redjournal.org) showed the results for HNRQ and SQLI. HNRQ and SQLI were significant only for OS in non-OPC patients (HR per 1 point: 0.75 [95% CI,

0.63–0.89] and 0.89 [95% CI, 0.81–0.97], respectively), reflecting a 25% and 11% reduction of risk, respectively.

Discussion

This large, international, multi-institutional phase 3 trial provided 3 major findings related to QOL/PS. First, QOL/PS was similar in both arms. Second, p16 status was associated with QOL/PS in OPC patients. Finally, pre-treatment QOL/PS was a significant independent prognostic factor for survival in patients with locally advanced HNC.

We did not find any significant differences on QOL/PS between the 2 arms from AUC analyses. This is similar to our published survival and toxicities results, which showed no significant differences for survival and grade 3 or 4 toxicities in the 2 arms (5, 7). The majority of the results from the cross-sectional exploratory analyses echoed the main findings from the AUC analyses. The lack of difference between the 2 arms may suggest that the effect of the AFX with 1 more week of radiation is similar to that of the SFX with an extra third cycle of cisplatin (7).

Patients with p16-positive OPC have better QOL/PS before treatment and 1 to 5 years after treatment; the patients' normalcy of diet and public eating are clinically significantly better in p16-positive patients than in p16-negative patients. The beneficial effect of p16-positive status might be partially due to the younger age, better functional status at diagnosis, and less tobacco abuse, as shown in our data and in other studies (5, 18). The fact that p16-positive patients tend to have smaller T stage, which most likely allows for a smaller high dose volume in radiation therapy fields and therefore less toxicity, might also contribute to better QOL/PS. Our finding about better pretreatment QOL/PS in p16-positive patients is consistent with published studies (21–23). However, our study is the only study that reports prospectively QOL data related to p16 status from pre-treatment to 5 year after treatment.

Despite the beneficial effect of p16-positive status on QOL/PS before and up to 5 years after treatment, p16-positive patients had a significantly larger decrease in QOL/PS toward the end of the treatment than did p16-negative patients. The reason for this cannot be explained by the fact that p16-positive patients had better pretreatment scores. However, the larger decreases suggest that p16-positive patients are significantly affected by the intensity of treatment and may benefit from treatment de-escalation strategies as long as excellent survival outcomes are maintained. Currently, several randomized clinical trials are being conducted to test different treatment strategies by p16 status. It would be important to collect QOL data in these trials to validate our observations. Two published studies did find a larger drop in QOL in p16-positive patients than in p16-negative patients, but at different times: 1 study was similar to ours (23), and another was conducted 3 months to 1 year after treatment (22).

Two of our findings indicate that the association between p16 status and QOL/PS is independent of treatment. First, p16 status was significantly associated with QOL/PS before treatment for all scales. Second, there seemed to be no interaction effects between p16 status and treatment arms on QOL/PS (data not shown). In other words, whether p16-positive or

p16-negative patients were in the AFX arm or the SFX arm did not affect their association with QOL/PS. A published study also found that QOL in p16-positive patients did not differ among those who received primary surgery with or without adjuvant therapy, compared with those treated with primary chemoradiation (21).

Pretreatment QOL/PS is a significant independent prognostic factor for OS, PFS, and LRF in our population. This finding is consistent with published studies not only in HNC patients (23–28) but also in other cancer patients (29). However, the findings are not consistent for different QOL domains, and the physical functioning domain has been shown to be more prognostic for survival than other QOL domains, such as social and emotional functions (25).

The prognostic effect of QOL/PS on survival is also independent of Zubrod performance scores. We further compared the effect of QOL/PS and Zubrod scores on survival (data not shown). Our findings showed that Zubrod scores were more strongly associated with survival than QOL/PS. This indicates that QOL might be secondary to Zubrod scores to be used as a stratification factor for clinical trials. Additionally, QOL might be considered in addition to randomization to ensure that treatment arms are balanced.

The study had limitations. First, the attrition rate for QOL was relatively high if we used the number of all patients initially accrued as the denominator (Table 1). Further data analysis showed that patients who could not complete the questionnaires were more likely to have lower performance status, higher rates of feeding tubes, and p16-negative status. This is consistent with missing data patterns in other QOL studies, and it also indicates current difficulties in collecting QOL data in RTOG trials with similar treatment regimens. However, the attrition rate appeared to be much lower (ranging from 30% to 37%) if we used the eligible patients at 1 year as the denominator, as many QOL studies have done. Our data collection window for the last 2 weeks of treatment was relatively large, so these data might not reflect the actual QOL toward the end of treatment. The participants were mainly white and men, which may not represent the demographic characteristics of all HNC patients. Data collected through chart review might produce missing or inaccurate information. Furthermore, our data for the beneficial effect of p16 status on QOL/PS should be applied only to OPC patients, not to other HNC patients. Also, only 20% of our OPC patients were p16-negative, whereas a recent meta-analysis reported 27.8% after 2005 (30). Additionally, the study included only patients receiving conventional radiation therapy, not IMRT. Admittedly, all limitations may affect the generalizability of current findings even though these are mostly consistent with other published results.

In conclusion, our primary endpoint for QOL/PS AUC analysis did not show any significant differences between the 2 treatment arms, which suggests the similar effect of AFX with 1 more week of radiation and the SFX with an extra cycle of cisplatin. The p16-positive patients had better QOL/PS before treatment and from 1 year up to 5 years after treatment compared with p16-negative patients. However, p16-positive patients had a larger drop in QOL/PS during treatment, supporting de-escalation of treatment intensity, provided cure rates are maintained. Until less intensive therapies are available, better supportive care will be needed, particularly near the end of treatment. Our data also demonstrated that QOL/PS

before treatment was an independent prognostic factor for survival, which might indicate its potential use as a stratification factor secondary to Zubrod and as a balancing factor in future trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

This large, international, multi-institutional phase 3 trial yielded 3 major findings related to quality of life (QOL)/performance status (PS). First, QOL/PS was similar in both accelerated and standard radiation therapy arms. Second, p16-positive oropharyngeal cancer patients experienced better QOL/PS than did p16-negative patients. Finally, pretreatment QOL/PS was a significant independent prognostic factor for survival in patients with locally advanced head and neck cancer.

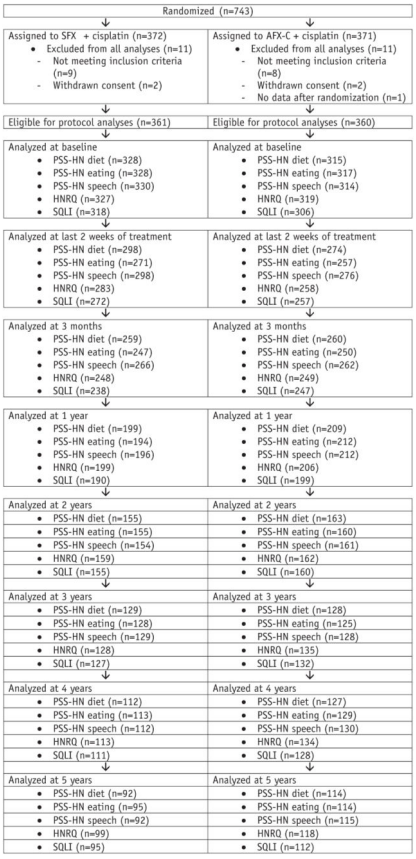

Fig. 1.

Consolidated **S**tandards **O**f **R**eporting **T**rials graph. *Abbreviations:* AFX-C = accelerated-fractionation radiation therapy by concomitant boost; HNRQ = Head and Neck Radiotherapy Questionnaire; PSS-HN = Performance Status Scale for head and neck cancer; SFX, standard-fractionation radiation therapy; SQLI = Spitzer Quality of Life Index.

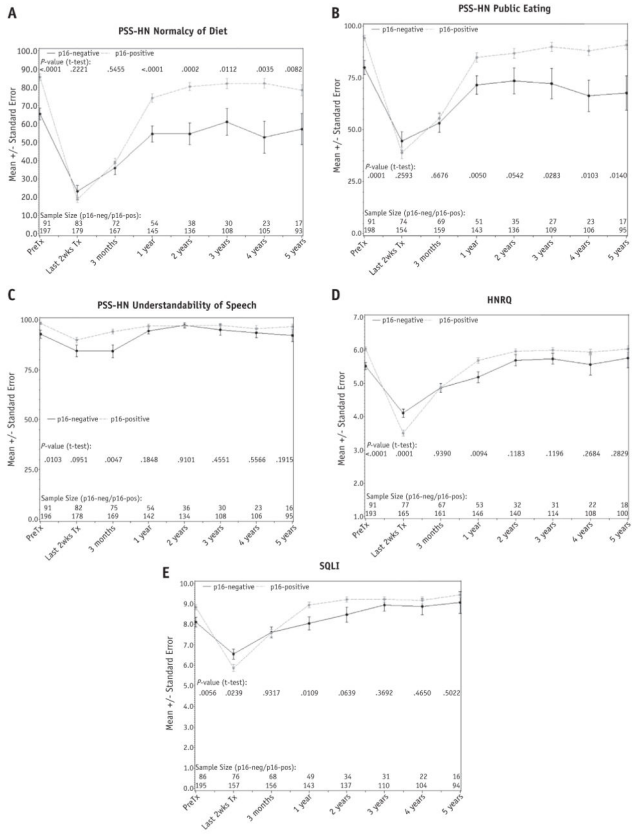

Fig. 2.

Raw scores for quality of life by p16 status. *Abbreviations:* HNRQ = Head and Neck Radiotherapy Questionnaire; PSS-HN = Performance Status Scale for Head and Neck cancer patients; SQLI = Spitzer Quality of Life Index; Tx = treatment. The significance level is $p < 0.05$.

Table 1

Completion status for area under the curve analysis

	Completed all 4 time points*		
Tool	**SFX + cisplatin (n=361)**	**AFX-C + cisplatin (n=360)**	**Total (N=721)**
PSS-HN normalcy of diet	141 (39.1%)	140 (38.9%)	281 (39.0%)
PSS-HN public eating	126 (34.9%)	131 (36.4%)	257 (35.6%)
PSS-HN speech	142 (39.3%)	145 (40.3%)	287 (39.8%)
HNRQ	139 (38.5%)	137 (38.1%)	276 (38.3%)
SQLI	116 (32.1%)	127 (35.3%)	243 (33.7%)

Abbreviations: AFX-C = accelerated-fractionation radiation therapy by concomitant boost; HNRQ = Head and Neck Radiotherapy Questionnaire; PSS-HN = Performance Status Scale for head and neck cancer; SFX, standard-fractionation radiation therapy; SQLI = Spitzer Quality of Life Index.

The denominator of the percentage for the SFX was 361, for the AFX was 360, and for the total was 721.

*Pretreatment, last 2 weeks of treatment, 3 months, and 12 months.

Table 2

Pretreatment characteristics for patients with PSS-HN diet data

Characteristic	SFX + cisplatin (n=141)	AFX-C + cisplatin (n=140)	p16-positive oropharynx (n=106)	p16-negative oropharynx (n=37)
Assigned treatment	N/A		*P*=.57	
SFX + cisplatin	141 (100.0%)	0 (0.0%)	57 (53.8%)	22 (59.5%)
AFX-C + cisplatin	0 (0.0%)	140 (100.0%)	49 (46.2%)	15 (40.5%)
Age, y	*P*=.13		*P*=.05	
Mean	56.4	54.8	54.1	57.4
Standard deviation	8.5	8.9	8.5	9.1
Median	56	55	53	57
Minimum-maximum	34–82	31–81	31–78	40–82
Q1–Q3	51–62	48–61	49–59	53–62
Gender	*P*=.88		*P*=.62	
Male	117 (83.0%)	115 (82.1%)	88 (83.0%)	29 (78.4%)
Female	24 (17.0%)	25 (17.9%)	18 (17.0%)	8 (21.6%)
Race	*P*=.18 (white vs nonwhite)		*P*=.41 (white vs nonwhite)	
American Indian or Alaskan native	4 (2.8%)	3 (2.1%)	2 (1.9%)	0 (0.0%)
Asian	1 (0.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Black or African American	20 (14.2%)	14 (10.0%)	9 (8.5%)	7 (18.9%)
White	115 (81.6%)	123 (87.9%)	93 (87.7%)	30 (81.1%)
Unknown	1 (0.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Ethnicity	*P*=1.00		*P*=1.00	
Hispanic or Latino	4 (2.8%)	4 (2.9%)	2 (1.9%)	1 (2.7%)
Not Hispanic or Latino	132 (93.6%)	134 (95.7%)	100 (94.3%)	36 (97.3%)
Unknown	5 (3.5%)	2 (1.4%)	4 (3.8%)	0 (0.0%)
Zubrod performance status	*P*=.46		*P*=.11	
0	93 (66.0%)	86 (61.4%)	74 (69.8%)	20 (54.1%)
1	48 (34.0%)	54 (38.6%)	32 (30.2%)	17 (45.9%)
Feeding tube or gastrostomy	*P*=.36		*P*=.06	
No	111 (78.7%)	117 (83.6%)	94 (88.7%)	28 (75.7%)
Yes	30 (21.3%)	23 (16.4%)	12 (11.3%)	9 (24.3%)
Cigarette pack-years *	*P*=.28		*P*<.001	
	(n=115)	(n=111)	(n=91)	(n=28)
Mean	32.0	27.8	18.7	42.3
Standard deviation	28.6	28.7	25.7	23.4
Median	31	21	10.8	42.75
Minimum-maximum	0–123	0–152	0–152	0–96
Q1–Q3	4–51	0–44	0–30	34.5–54.75
Primary site	*P*=.58		N/A	
Oral cavity	8 (5.7%)	6 (4.3%)	0 (0.0%)	0 (0.0%)

Characteristic	SFX + cisplatin (n=141)	AFX-C + cisplatin (n=140)	p16-positive oropharynx (n=106)	p16-negative oropharynx (n=37)
Oropharynx	95 (67.4%)	87 (62.1%)	106 (100.0%)	37 (100.0%)
Hypopharynx	9 (6.4%)	14 (10.0%)	0 (0.0%)	0 (0.0%)
Larynx	29 (20.6%)	33 (23.6%)	0 (0.0%)	0 (0.0%)
p16 status, limited to oropharynx		*P*=.57	N/A	
	(n=79)	(n=64)	(n=106)	(n=37)
p16-negative	22 (27.8%)	15 (23.4%)	0 (0.0%)	37 (100.0%)
p16-positive	57 (72.2%)	49 (76.6%)	106 (100.0%)	0 (0.0%)
T stage		*P*=.33	*P*=.20	
T2	27 (19.1%)	37 (26.4%)	33 (31.1%)	6 (16.2%)
T3	74 (52.5%)	65 (46.4%)	45 (42.5%)	20 (54.1%)
T4	40 (28.4%)	38 (27.1%)	28 (26.4%)	11 (29.7%)
N stage		*P*=.70	*P*=.94	
N0	26 (18.4%)	30 (21.4%)	10 (9.4%)	2 (5.4%)
N1	24 (17.0%)	14 (10.0%)	13 (12.3%)	9 (24.3%)
N2a	9 (6.4%)	15 (10.7%)	13 (12.3%)	3 (8.1%)
N2b	45 (31.9%)	37 (26.4%)	38 (35.8%)	10 (27.0%)
N2c	27 (19.1%)	33 (23.6%)	21 (19.8%)	10 (27.0%)
N3	10 (7.1%)	11 (7.9%)	11 (10.4%)	3 (8.1%)
AJCC stage		*P*=.77	*P*= .29	
III	32 (22.7%)	29 (20.7%)	14 (13.2%)	8 (21.6%)
IV	109 (77.3%)	111 (79.3%)	92 (86.8%)	29 (78.4%)

Abbreviations: AJJC = American Joint Committee on Cancer, 6th edition; AFX-C = accelerated-fractionation radiation therapy by concomitant boost; N/A =not applicable; PSS-HN =Performance Status Scale for head and neck cancer; Q1 =first quartile; Q3 =third quartile; SFX =standard-fractionation radiation therapy.

*A pack-year is defined as the equivalent of smoking 1 pack of cigarettes a day for 1 year.

Table 3

Least squares means from general linear mixed models

Tool time point	Mean (standard error) SFX + cisplatin	AFX-C + cisplatin	*P* value
PSS-HN normalcy of diet			
Pretreatment	75.1 (1.7)	78.6 (1.8)	Treatment effect: *P*=.95
Last 2 weeks of treatment	20.8 (1.5)	24.9 (1.6)	Time point effect: *P*<.001
3 months	43.5 (2.0)	38.7 (2.0)	Treatment × time point interaction effect: *P*=.12
1 year	70.2 (2.2)	70.0 (2.1)	
2 years	75.2 (2.3)	73.7 (2.2)	
3 years	76.5 (2.3)	76.3 (2.3)	
4 years	75.2 (2.5)	74.1 (2.4)	
5 years	72.1 (2.8)	71.2 (2.6)	
PSS-HN public eating			
Pretreatment	85.4 (1.5)	87.5 (1.5)	Treatment effect: *P*=.90
Last 2 weeks of treatment	42.3 (2.0)	42.1 (2.1)	Time point effect: *P*<.001
3 months	56.6 (2.2)	58.7 (2.2)	Treatment × time point interaction effect: *P*=.67
1 year	80.6 (2.0)	79.1 (1.9)	
2 years	84.8 (2.2)	81.9 (2.1)	
3 years	82.6 (2.1)	83.7 (2.1)	
4 years	83.2 (2.3)	80.5 (2.2)	
5 years	81.4 (2.3)	81.7 (2.1)	
PSS-HN understandability of speech			
Pretreatment	92.2 (1.0)	93.5 (1.0)	Treatment effect: *P*=.84
Last 2 weeks of treatment	84.0 (1.3)	84.2 (1.4)	Time point effect: *P*<.001
3 months	88.1 (1.2)	90.4 (1.2)	Treatment × time point interaction effect: *P*=.03
1 year	92.3 (1.2)	91.9 (1.1)	
2 years	93.9 (1.0)	93.8 (1.0)	
3 years	91.3 (1.3)	93.5 (1.3)	
4 years	90.2 (1.5)	91.5 (1.5)	
5 years	93.6 (1.6)	88.5 (1.5)	
HNRQ			
Pretreatment	5.8 (0.1)	5.8 (0.1)	Treatment effect: *P*=.20
Last 2 weeks of treatment	3.9 (0.1)	3.7 (0.1)	Time point effect: *P*<.001
3 months	5.0 (0.1)	4.9 (0.1)	Treatment × time point interaction effect: *P*=.14
1 year	5.7 (0.1)	5.6 (0.1)	
2 years	5.9 (0.1)	5.8 (0.1)	
3 years	5.9 (0.1)	5.8 (0.1)	
4 years	5.9 (0.1)	5.9 (0.1)	
5 years	5.9 (0.1)	5.8 (0.1)	
SQLI			
Pretreatment	8.2 (0.1)	8.6 (0.1)	Treatment effect: *P*=.26

Tool time point	Mean (standard error)		*P* value
	SFX + cisplatin	AFX-C + cisplatin	
Last 2 weeks of treatment	6.3 (0.1)	6.2 (0.1)	Time point effect: *P*<.001
3 months	7.5 (0.1)	7.6 (0.1)	Treatment × time point interaction effect: *P*=.12
1 year	8.6 (0.1)	8.7 (0.1)	
2 years	8.8 (0.1)	8.9 (0.1)	
3 years	8.9 (0.1)	9.1 (0.1)	
4 years	8.9 (0.1)	9.1 (0.1)	
5 years	9.1 (0.1)	9.0 (0.1)	

Abbreviations: AFX-C = accelerated-fractionation radiation therapy by concomitant boost; HNRQ = Head and Neck Radiotherapy Questionnaire; PSS-HN = Performance Status Scale for head and neck cancer; SFX, standard-fractionation radiation therapy; SQLI = Spitzer Quality of Life Index.

Table 4

Association between baseline QOL scores and survival outcome in all patients

Model	QOL parameter	HR	95% CI	*P* value
Overall survival				
#1 (n=643; 326 events)	PSS-HN diet (per 10-point increase)	.944	.910–.975	.0006
#2 (n=645; 326 events)	PSS-HN eating (per 25-point increase)	.871	.792–.957	.0041
#3 (n=644; 326 events)	PSS-HN speech (per 25-point increase)	.824	.724–.938	.0035
#4 (n=646; 328 events)	HNRQ (per 1-point increase)	.780	.704–.864	<.0001
#5 (n=624; 310 events)	SQLI (per 1-point increase)	.919	.867–.973	.004
Progression-free survival				
#1 (n=643; 364 events)	PSS-HN diet (per 10-point increase)	.953	.923–.984	.0033
#2 (n=645; 363 events)	PSS-HN eating (per 25-point increase)	.880	.805–.962	.0049
#3 (n=644; 364 events)	PSS-HN speech (per 25-point increase)	.823	.728–.931	.0019
#4 (n=646; 366 events)	HNRQ (per 1-point increase)	.789	.715–.871	<.0001
#5 (n=624; 350 events)	SQLI (per 1-point increase)	.912	.865–.963	.0008
Local-regional failure				
#1 (n=643; 222 events)	PSS-HN diet (per 10-point increase)	.931	.894–.969	.0005
#2 (n=645; 220 events)	PSS-HN eating (per 25-point increase)	.822	.738–.915	.0004
#3 (n=644; 220 events)	PSS-HN speech (per 25-point increase)	.809	.695–.942	.0063
#4 (n=646; 226 events)	HNRQ (per 1-point increase)	.759	.671–.857	<.0001
#5 (n=624; 218 events)	SQLI (per 1-point increase)	.880	.824–.939	.0001
Distant metastasis				
#1 (n=643; 89 events)	PSS-HN diet (per 10-point increase)	1.000	.933–1.072	.9994
#2 (n=645; 88 events)	PSS-HN eating (per 25-point increase)	.969	.794–1.182	.7539
#3 (n=644; 88 events)	PSS-HN speech (per 25-point increase)	.813	.634–1.043	.1031
#4 (n=646; 86 events)	HNRQ (per 1-point increase)	.898	.720–1.119	.3375
#5 (n=624; 82 events)	SQLI (per 1-point increase)	.948	.842–1.066	.3708

Abbreviations: CI = confidence interval; HNRQ = Head and Neck Radiotherapy Questionnaire; HR = hazard ratio; PSS-HN = Performance Status Scale for Head and Neck cancer patients; QOL = quality of life; SQLI = Spitzer Quality of Life Index.

Adjusted for assigned treatment, age, Zubrod performance status, primary site, T stage, and N stage.