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Quality of life and performance status from a sub-study conducted within a prospective phase III randomized trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for locally advanced head and neck carcinoma: NRG Oncology RTOG 0522

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Other Trial information:

Registration: NRG Oncology RTOG 0522 was registered with the National Cancer Institute (NCT00265941) and approved by the central and institutional review boards of all the participating centers. All patients provided written informed consent to participate in the study. Patients included in the QOL study provided additional consent to participate in the QOL component of the study.

Protocol: access online http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0522

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Abstract

Purpose—To analyze the quality of life (QOL) and performance status (PS) (secondary outcome) of stage III-IV head and neck cancer (HNC) patients enrolled on a prospective randomized phase III trial, comparing radiation-cisplatin without (CIS) or with cetuximab (CET/CIS). The QOL hypothesis proposed a between-arm difference in FACT-H&N-Total score of ≥ 10% of the instrument range from baseline to 1-year.

Methods and Materials—Patients with QOL/PS study consent completed the Functional Assessment of Cancer Therapy-Head and Neck (FACT-HN), Performance Status Scale for HNC (PSS-HN), and EuroQol (EQ-5D) at baseline through to 5-years. Pretreatment QOL/PS scores were correlated with outcome and p16-status in oropharyngeal cancer (OPC) patients.

Results—Of 818 analyzable patients, the 1-year change from baseline score for FACT-HN-Total was −0.41(CIS arm) and −5.11 (CET/CIS arm) (p=0.016), representing a 3.2% between-arm change of FACT-HN-Total score. Mean EQ-5D-index and PSS-HN scores were not significantly different between arms. P16-positive OPC patients had significantly higher baseline and 1-year scores for PSS-HN, FACT-HN-Total, physical, functional subscales, and 2-years for EQ-5D-index compared to p16-negative OPC patients. Higher pretreatment PSS-HN-diet, PSS-HN-eating, FACT-HN and EQ-5D-index scores were associated with better overall (OS), and progression-free (PFS) survival on multivariate analysis. Higher baseline FACT-HN-Total, functional, physical subscale, and EQ-5D-index scores were associated with improved OS, PFS in p16-positive OPC, but not for p16-negative and non-OPC patients.

Conclusion—There was no clinically meaningful difference in QOL/PS between arms. P16-positive OPC patients have significantly higher QOL/PS than p16-negative patients. Pretreatment QOL/PS is a significant independent predictor of outcome in locally advanced HNC.

SUMMARY

In this prospective randomized study, no differences in quality of life (QOL) and performance status (PS) were found between concurrent accelerated concomitant cisplatin with or without cetuximab. Distinct QOL/PS profiles were found between p16-positive and negative OPC patients. P16-positive OPC patients demonstrated higher baseline and 1-year QOL/PS scores using FACT-HN and PSS-HN, and greater acute PS decline at the end of treatment, compared to p16-negative patients. Pretreatment QOL/PS was independently correlated with survival.

INTRODUCTION

Treatment intensification by adding chemotherapy to radiation have demonstrated gains in overall survival (OS) for locally advanced head and neck cancer (HNC) (1). Associated with these gains in survival are potential increased toxicities, which may impair performance status (PS) and function, including the ability to eat, speak and socialize, which can impact quality of life (QOL)(2–4). QOL is an important endpoint, as it is a multidimensional measure of the patient's perception of effect of the disease or treatment.

The recognition of the increasing incidence of human papilloma virus (HPV) associated oropharyngeal carcinoma (OPC), and superior survival outcomes in HPV positive OPC patients (5), gives increasing importance to understanding the differences in QOL between HPV positive and negative OPC patients. Current prospective trials evaluating treatment de-intensification for p16-positive OPC and treatment intensification for p16-negative patients necessitates a better understanding of the QOL differences by p16-status and its potential impact on clinical endpoints, which may help inform clinical decisions and assist in the design of future prospective HNC trials.

In a large randomized study, combining cetuximab and radiotherapy improved progression-free survival (PFS) and overall survival (OS) without compromising QOL (6); therefore, it was hypothesized that adding cetuximab to cisplatin-radiation would further enhance survival over cisplatin-radiation without worsening the patient's function and QOL. The results of the randomized trial NRG Oncology RTOG 0522 of concurrent accelerated radiation with cisplatin with or without cetuximab for locally advanced HNC, demonstrated more treatment interruptions and acute grade 3 and 4 toxicities in the CET/CIS arm without gains in PFS or OS (7). The impact of adding cetuximab to cisplatin-based radiotherapy on longitudinal QOL/PS has not been previously described. Therefore, the purpose of this study is to prospectively assess longitudinal QOL/PS in patients enrolled on NRG Oncology RTOG 0522, using the Performance Status Scale for Head and Neck Cancer (PSS-HN), the Functional Assessment of Cancer Therapy-Head & Neck (FACT-HN), and the EuroQol (EQ-5D) and to evaluate differences in QOL/PS between arms. The QOL hypothesis proposed that adding cetuximab to cisplatin-radiotherapy would result in a between-arm difference in FACT-H&N total score from baseline to 1-year of ≥ 10% of the instrument range. An exploratory objective was to compare longitudinal QOL/PS in OPC patients by p16-status in a prospective multicenter clinical trial.

METHODS AND MATERIALS

Eligible patients with untreated histologically confirmed squamous cell carcinoma of the oropharynx, hypopharynx, or larynx with stage III-IV disease (T2N2-3M0, T3-4 any N M0) and with consent for the QOL/PS study were analyzed according to the treatment arm; radiation-cisplatin without (CIS) or with cetuximab (CET/CIS). Protocol eligibility, stratification, tumor tissue evaluation for p16 expression, treatment details and survival outcomes has been previously published (7).

The PSS-HN and EQ-5D were collected at 8 time points: pretreatment, within the last 2 weeks of treatment, 3 months from start of treatment, and 1, 2, 3, 4, and 5-years from the start of treatment. FACT-HN was collected pretreatment and at 1 and 5-years from start of treatment. The PSS-HN (8) is a clinician rated instrument administered in an unstructured interview format consisting of 3 questions (scored from 0–100) separately analyzed to evaluate normalcy of diet, eating in public, and understandability of speech. Higher scores indicate better PS. A ≥20 point change was considered clinically significant for PSS-HN-diet and ≥25 points for eating and speech (8, 9).

FACT-HN version 4 (total score range 0–148) is a multidimensional patient reported outcome (PRO) instrument which includes the FACT-G core scale (range 0–108) containing 27 items encompassing four domains of well-being: physical, social/family, functional (each with 7 questions, range 0–28), emotional (6 questions, range 0–24) (10) and a fifth subscale of 12 additional HNC questions of which 10 are scored (range 0–40) (8). Handling of missing data was in accordance with the FACIT Administration and Scoring Guidelines at www.facit.org. Higher scores indicate better QOL.

The EQ-5D-3L, is a 3-level, five item PRO health utility instrument measuring five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A score of 1, 2 and 3 indicates no, some, and extreme problems, respectively. A unique health state is defined by combining 1 level from each of the 5 dimensions and converting to a single overall health index score (maximum score of 1 represents the best state of health) using the scoring algorithm described by Shaw et al (11). There are a total of 243 (3^5) possible health states. The second part of the EQ-5D, the Visual Analogue Scale was not included in this analysis.

The minimal important difference (MID), being the smallest difference reflecting a clinically important change in score was defined as at least a 10% change in the total instrument range for FACT-HN and EQ-5D (12).

Statistical Analysis

Change from baseline in total FACT-HN scores at 1-year between arms was compared using two-sample independent t-test. For PSS-HN, the frequency of patients with subscale scores of ≤ 50 representing moderate to severe impairment (8, 9) was estimated with its 95% confidence interval for each treatment arm at 3 and 12 months and compared between arms, based on Z statistic for testing binomial proportions. Change from baseline scores were categorized as improved, no change, or worsened. Change categories for each subscale were compared between arms using the Chi-square test. Comparisons of PSS-HN scores between patients with or without grade >3 physician graded dysphagia toxicity scored using the Common Terminology Criteria for Adverse Events (version 3) and feeding-tube status were performed using a two-sample independent t-test. The distributions of the EQ-5D index score were compared between arms at 3 and 12 months using the non-parametric Kolmogorov-Smirnov test. Spearman correlation coefficients between EQ-5D dimensions and global FACT-G score were computed at baseline, 1 and 5-years.

An exploratory cross-sectional comparison of QOL/PS scores between arms at each time point and change from baseline scores were compared for each time point after baseline.

In addition to the analysis by assigned treatment, an exploratory analysis of OPC patients stratified by p16-status was performed. For all comparisons for OPC by p16-status, group means were compared by a two-sample independent t-test. Equal variances were assumed unless the test for equality of variances was significant at $p<0.05$. For 3 or more groups, group means were compared by one-way analysis of variance (ANOVA), F test. Equal variances were assumed unless the test for equality of variances was significant at $p<0.05$. Mean values over time were also analyzed with the general linear mixed model and linear mixed models with non-linear time effects were also considered.

For the analysis of raw scores, all useable questionnaires were included even if the pre-treatment assessment was not completed. Per protocol, the cause of missing data was assumed to be random; however we imputed missing values for FACT-HN with the Markov chain Monte Carlo algorithm with a non-informative prior. Forty datasets were created and the results were combined per Rubin's formula (13). The distribution of pre-treatment characteristics and treatment assignment, were compared between patients with and without QOL/PS data using the Fisher's exact test or Chi-square test (categorical variables) or two-sample independent t-test and Wilcoxon rank-sum test (ordinal variables). Differences of > 20% were reported.

A multivariate Cox proportional hazards model was used to determine if the pretreatment QOL/PS scores had a prognostic impact on clinical outcomes, independent of other known prognostic factors. No adjustments of multiple comparisons were made for exploratory analyses. All tests are two-sided at 0.05 level.

RESULTS

Patient and Treatment Characteristics

Of the 940 patients enrolled, 49 were excluded (47 were ineligible; 2 patients had no follow-up), 73 patients did not provide QOL/PS study consent, leaving a total of 818 analyzable patients for the QOL/PS study as shown in the CONSORT diagram (Figure 1). Instrument completion rates were 87–89% at baseline, 73–77% in the last 2 weeks of treatment, 74–76% at 3 months, 60–63% at 1-year, 48–52% at 2-years, 43–45% at 3-years, 37% at 4-years and 20–21% at 5-years after treatment completion. Rates of QOL completion were similar between arms. Reasons for incomplete questionnaires are described in Supplemental Table 1 for FACT-HN. Compliance rates (excluding deceased patients or withdrawn consent) for FACT-HN questionnaires was 95%, (773/815), 75%, (538/720), 39%, (207/531) at baseline, 12 and 60 months respectively. When additionally excluding non-usable questionnaires or those completed outside the time window, the corresponding compliance rates were 88.7%, (723/815), 69.7%, (502/720), 29.4%, (156/531).

Patients without QOL/PS consent were more likely to have N2c–N3 tumors (43.8% versus 37.6%, $p=0.04$). No other differences in pretreatment characteristics were noted between

treatment arms. Table 1 shows pretreatment characteristics for patients with QOL/PS consent by treatment arms.

Comparison between treatment arms for PSS-HN, FACT-HN and EQ-5D

No differences were seen between treatment arms in PSS-HN scores. The CET/CIS arm had a non-statistically significant higher percentage of patients with worsened PSS-HN scores at 3 and 12 months (Table 2).

The mean change from baseline to 1-year for the CIS arm and CET/CIS arm for FACT-G was +2.88 and −0.93 respectively, $p<0.001$ (3.5% between-arm change); FACT-functional subscale score was +1.73 (SD=6.6) and −0.09 (SD=6.96), p=0.004 (6.5% between-arm change in subscale score) and FACT-HN-Total scores was −0.41(SD=18.9) and −5.11 (SD=22.5), p=0.016 (3.2% between-arm change in total score), respectively. These were below the MID level defined in this study and did not reach the primary endpoint of the study. In an analysis of the FACT-HN subscales, all HN cancer specific problems recovered except for dry mouth without significant differences between arms (Supplemental Table 2).

The mean EQ-5D index scores (SD) at 3 months and 1-year for CIS arm were 0.78 (0.18) and 0.84 (0.17); CET/CIS arm were 0.77 (0.15) and 0.84 (0.16), (p=0.74 and 0.99) respectively. Differences in EQ-5D dimension for usual activities was worse in the cetuximab arm at 3 (p=0.008) and 12 (p=0.016) months. Protocol specified analysis of correlations between FACT-G Total and EQ-5D dimensions showed correlation greater than 0.5 between FACT-G scores and the EQ-5D anxiety dimension at all-time points, pain at baseline and 1-year, and activity at 1-year (Supplemental Table 3).

Analysis of Missing Data

Characteristics of patients who were included in the 1-year change from baseline analysis of FACT-HN were compared with those who were excluded. Patients included versus those who were excluded from the FACT-HN analysis demonstrated better Zubrod PS of 71.4% versus 58.7% ($p<0.001$), lower median pack-years of 20 versus 27.4 (p=0.04), and higher T3–4 category 56.9% versus 65.5% (p=0.005). We imputed data as described above for patients with missing FACT values and compared the score again for the primary endpoint, and the findings from the imputed data were similar to the non-imputed data. Table 3 shows cross-sectional comparisons for FACT-G, FACT-HN, and all subscales using observed and imputed data. A difference in social well-being at baseline between arms was not clinically meaningfully different.

Results from the general linear mixed model for FACT-G, FACT-HN, and all subscales are shown Supplemental Table 4. The main effect assigned treatment was not significant in any models. The main effect time point was significant for FACT-G, social well-being, emotional well-being, functional well-being, and additional head and neck concerns. The interaction effect between the assigned treatment and time point was significant for FACT-G and FACT-HN. Comparing to models with higher order time effects, the model with linear time effect had the lowest AIC, and the estimates from these models were more plausible and closer to the observed values for all tools.

Correlation of dysphagia, feeding tube rates and PSS-HN scores

Patients with feeding tubes or grade ≥3 dysphagia had significantly worse PSS-HN-diet and eating scores and to a lesser extent, PSS-HN-speech from baseline through to 5-years. Supplemental Figures 1 a – c shows the mean PSS-HN subscale scores with or without grade ≥3 dysphagia. PSS-HN subscale scores with or without a feeding tube are shown in Supplemental Figures 1d–f.

Pretreatment QOL/PS and Outcome

Multivariate analysis (adjusted for assigned treatment, age, Zubrod PS, smoking pack years, primary site, T-stage, and N-stage) demonstrated that for an increase in pretreatment scores for PSS-HN diet and eating, there was a reduction in hazard of death, PFS, locoregional failure (LRF) and distant metastases (DM). PSS-HN speech was not significant for any endpoint. FACT-G, FACT-HN-Total, and EQ-5D index scores were associated with reduced hazard of death, their effects on other outcomes can be found in Table 4.

Exploratory Analysis of QOL/PS in Oropharyngeal Cancer patients

Among OPC patients with QOL/PS consent, 74.7% (221/296) were p16-positive, while OPC patients without QOL/PS consent, 56% (14/25) were p16-positive. Mean raw QOL/PS scores in OPC patients by p16 status at baseline through to 5 years are shown in Supplemental Table 5. OPC p16-positive compared to p16-negative patients had significantly higher 1-year FACT-HN physical and functional well-being and additional concerns scores, had a greater deterioration in mean scores for PSS-HN-diet, (−75.4 (27.4) versus −63.6 (36), p =0.032); PSS-HN-speech, (−14.2 (21.7) versus −5.1 (18.4), p=0.006); comparing the last 2 week assessment to baseline. PSS-HN subscale scores by p16-status are shown in Supplemental Figures 2a–c. Mean raw scores for FACT-G, FACT HNC additional items and FACT-HN-Total scores stratified by p16-status are shown in Supplemental Figures 3a–c.

In OPC patients, higher scores for FACT-G, FACT-HN-Total score, FACT-physical, functional and additional items, EQ5D index scores were associated with better OS and PFS in p16-positive OPC in multivariate analysis. Higher FACT-HN total scores were associated with reduced risk of LRF for p16-positive OPC, while FACT-HN-total, FACT-physical, additional items, and EQ5D scores were also associated with reduced risk of LRF in p16-negative OPC. Higher QOL scores for FACT-G, FACT-HN-Total score, physical, functional and EQ-5D index score were associated with reduced risk of DM in p16-positive OPC patients (Supplemental Table 6).

DISCUSSION

In this sub-study from a phase III multicenter randomized trial, longitudinal QOL/PS scores were not significantly different between treatment arms. There was a strong correlation between grade >3 dysphagia, feeding tube rates and lower PSS-HN scores, at all-time points measured in this study, which highlights the utility of PSS-HN as a quick provider obtained measure and remains relevant for patients treated in the 3D and IMRT era. The 1-year change from baseline FACT-HN-Total score was statistically different between arms with a

trend for worse QOL in the CET/CIS arm, but that on most measures the differences were too small to be clinically significant and were not sustained over time. Our primary analysis assessed the change in QOL relative to the baseline values to minimize the effects of differences in baseline scores between arms. The between-arm difference of 3.2% of the FACT-HN total instrument range was below the defined MID of 10% for this analysis and did not reach the primary endpoint of the study. Statistical methods to determine the MID include anchor-based methods (based on patient reported change over time or experience at a given time or where groups may be anchored to PS or another QOL instrument) or distribution-based (using 33% to 50% of the standard deviation, or 1 standard error of measurement) (14). Ringash et al, found that for FACT-HN, a minimum 4.3% (range, 4–6%) increase in score for a positive MID and a 8.6% (range, 6–14%) decrease in score for a negative MID was clinically important, resulting in a general rule of thumb that a 5% positive or a 10% negative change is considered clinically meaningful in QOL(12). The MID for the EQ-5D index scores calculated by Pickard et al (15), was 0.06 (6% of total score) based on FACT-G quintiles, also falls within the range of MID defined by Ringash et al.

Short-term evaluation of QOL using FACT-HN during and acutely after RT was not included in the original study design and in hindsight, increased acute toxicity findings could have impacted QOL and omission of FACT-HN at the end of RT in the study design was a significant limitation of the study. To further understand the impact of acute toxicities during treatment, symptom burden instruments such as the MD Anderson Symptom Inventory for Head and Neck (MDASI-HN), have been shown to document severity of patient reported symptoms relating to acute mucositis with greater sensitivity than FACT-HN(16). Instruments specific to EGFR inhibitors such as FACT-EGFR-18(17) may be able to further characterize the symptom burden and changes in QOL relating to specific acute dermatologic and oral toxicities of cetuximab.

Since patients without QOL/PS consent were more likely to have N2c–N3 tumors, these patients with more advanced nodal disease were not included in the QOL/PS sub-study which potentially introduces bias and may have reduced the ability to detect potential differences in QOL/PS between treatment arms, which was a limitation of the study.

Our missing data analysis for FACT found that the results were similar with or without missing data imputations. The high rate of missing data and the plateau of QOL scores beyond 2-years suggests decreased utility in collecting longitudinal QOL beyond this time point in large prospective trials.

An important study finding was the distinct QOL/PS profile for OPC patients by p16-status and pretreatment QOL/PS scores were independently correlated with better OS, PFS, LRC and DM outcomes. In p16-positive OPC, most superior QOL/PS scores were associated with OS, PFS and DM. OPC p16-negative patients, only FACT-HNC additional items, were associated with OS, PFS, but none was significant for DM. QOL/PS parameters were nonsignificant in the p16-negative OPC and non-OPC population likely due to the small sample size comprising only 9% and 30% of the RTOG 0522 QOL cohort respectively. This is in contrast to RTOG-9003 and RTOG-9111 trials which demonstrated baseline FACT-HN-Total score and functional scores were independently predictive of LRC but not OS, however

in this pooled cohort, 37.8% were OPC and 62.2% were non-OPC patients. (18). P16-positive OPC patients demonstrated higher baseline and 1-year FACT-physical, functional, total and HNC-additional scores compared to p16-negative patients. Acute deterioration in scores for PSS-HN-diet and eating in both treatment arms in the last 2 weeks of treatment to 3 months, with p16-positive OPC patients experiencing a greater decline in PSS-HN-diet and eating. However, they demonstrated faster recovery compared to p16-negative patients, which suggests different longitudinal PS trajectories by p16-status for OPC patients. These findings are also consistent with recent findings in a Trans-Tasman Radiation Oncology Group, TROG-02.02 (HeadSTART) randomized trial which also demonstrated similar acute decline using FACT-HN after treatment, despite superior baseline QOL profile in p16-positive OPC patients(19). Similarly, RTOG 0129, found similar QOL decline during chemoradiation compared to p-16 negative OPC patients(20). Since p16-positive OPC patients are usually younger, often non-smokers, have less co-morbidity and have higher expected survival, QOL/PS profile after chemoradiotherapy, it may no longer be acceptable for patients to accept significant QOL/PS decline during treatment and in the acute post-treatment setting.

In conclusion, QOL and PS were not significantly different between the treatment arms, along with the parent study, which did not demonstrate OS or PFS benefit of CET/CIS to CIS arms, although greater acute toxicity findings in the CET/CIS arm were not reflected in the QOL/PS results. OPC p16-positive patients demonstrated QOL/PS at baseline and 1-year after treatment compared to p16-negative patients, although p16-positive patients experienced greater decline of PS during treatment. Differences in baseline QOL/PS and OS and PFS by p16 status found in this study highlights the potential value of using pretreatment QOL/PS to stratify patient populations, while post-therapy QOL/PS may be incorporated into co-primary endpoints with survival in future clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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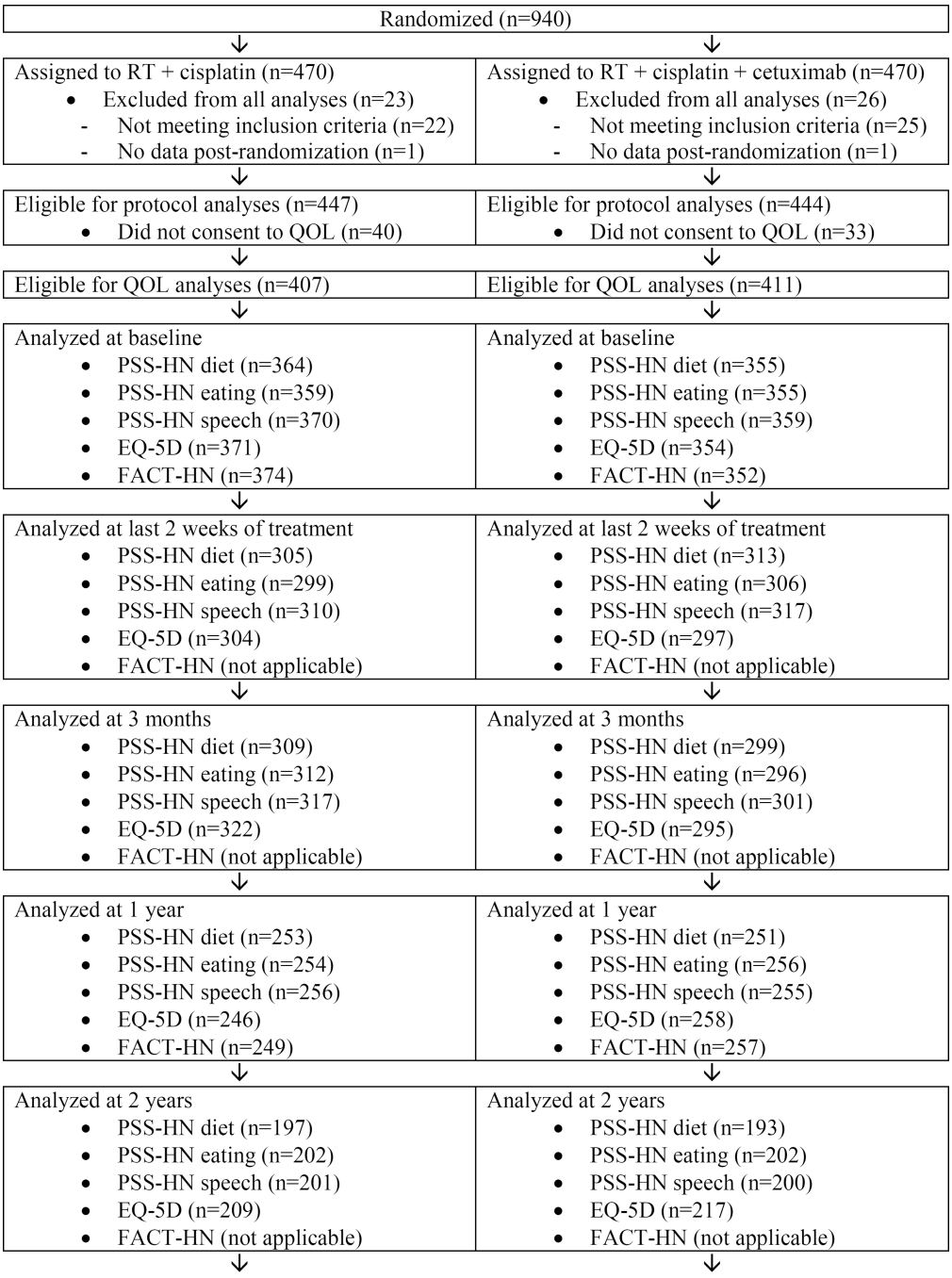

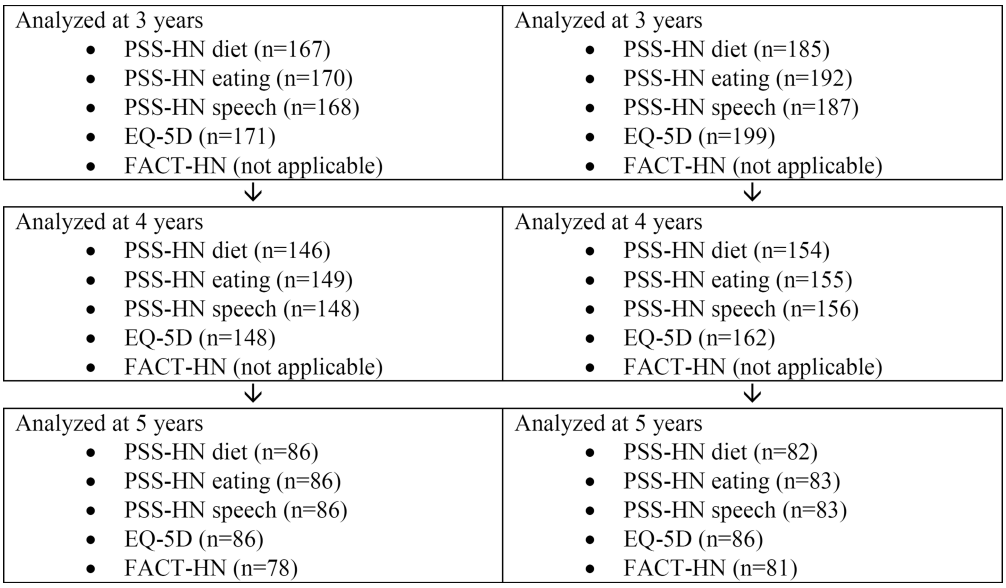

Figure 1.
CONSORT Diagram

Table 1

Pretreatment Characteristics for Patients with QOL Consent by Treatment Arm

	RT+cisplatin (n=407)	RT+cisplatin+ cetuximab (n=411)	p-value
Age (years)			0.047 (20)
Mean	56.1	57.3	
Std. Dev.	8.2	7.9	
Median	56	58	
Min – Max	31 – 79	36 – 76	
Q1 – Q3	50 – 61	51 – 63	
Gender			0.164 (20)
Male	351 (86.2%)	368 (89.5%)	
Female	56 (13.8%)	43 (10.5%)	
Race			0.294 (20)
American Indian or Alaskan native	3 (0.7%)	1 (0.2%)	
Asian	4 (1.0%)	2 (0.5%)	
Black or African-American	20 (4.9%)	33 (8.0%)	
White	377 (92.6%)	370 (90.0%)	
Unknown	3 (0.7%)	5 (1.2%)	
Ethnicity			0.175 (20)
Hispanic or Latino	17 (4.2%)	10 (2.4%)	
Not Hispanic or Latino	373 (91.6%)	386 (93.9%)	
Unknown	17 (4.2%)	15 (3.6%)	
Zubrod performance status			0.713 (20)
0	265 (65.1%)	273 (66.4%)	
1	142 (34.9%)	138 (33.6%)	
Feeding tube			0.416 (20)
No feeding tube	346 (85.0%)	358 (87.1%)	
Feeding tube, < 50% nutritional support	20 (4.9%)	24 (5.8%)	
Feeding tube, >/= 50% nutritional support	34 (8.4%)	24 (5.8%)	
Feeding tube, unknown nutritional support	6 (1.5%)	4 (1.0%)	
Unknown	1 (0.2%)	1 (0.2%)	
Cigarette pack-years (20)	(n=360)	(n=357)	0.911 (20)
Mean	27.4	27.6	
Std. Dev.	27.3	28.9	
Median	22.5	20.4	

	RT+cisplatin (n=407)	RT+cisplatin+ cetuximab (n=411)	p-value
Min – Max	0 – 150	0 – 162	
Q1 – Q3	0.5 – 43.25	0.2 – 42	
Primary site			0.967 (20)
Oropharynx	283 (69.5%)	289 (70.3%)	
Hypopharynx	29 (7.1%)	28 (6.8%)	
Larynx	95 (23.3%)	94 (22.9%)	
p16-status, limited to oropharynx	(n=142)	(n=154)	1.00 (20)
Negative	36 (25.4%)	39 (25.3%)	
Positive	106 (74.6%)	115 (74.7%)	
T stage			0.913 (20)
T2	157 (38.6%)	164 (39.9%)	
T3	158 (38.8%)	150 (36.5%)	
T4	92 (22.6%)	97 (23.6%)	
N stage			0.025 (20)
N0	40 (9.8%)	52 (12.7%)	
N1	36 (8.8%)	37 (9.0%)	
N2a	33 (8.1%)	40 (9.7%)	
N2b	130 (31.9%)	142 (34.5%)	
N2c	142 (34.9%)	124 (30.2%)	
N3	26 (6.4%)	16 (3.9%)	
AJCC stage (20)			0.484 (20)
III	54 (13.3%)	62 (15.1%)	
IV	353 (86.7%)	349 (84.9%)	
Type of radiation therapy			0.243 (20)
3D–CRT	56 (13.8%)	45 (10.9%)	
IMRT	351 (86.2%)	366 (89.1%)	
PSS-HN: normalcy of diet	(n=364)	(n=355)	0.055 (20)
Mean	80.5	84.5	
Std. Dev.	28.6	26.0	
Median	100	100	
Min – Max	0 – 100	0 – 100	
Q1 – Q3	50 – 100	60 – 100	
PSS-HN: eating in public	(n=359)	(n=355)	0.052 (20)

	RT+cisplatin (n=407)	RT+cisplatin+ cetuximab (n=411)	p-value
Mean	87.8	91.1	
Std. Dev.	24.8	20.5	
Median	100	100	
Min – Max	0 – 100	25 – 100	
Q1 – Q3	100 – 100	100 – 100	
PSS-HN: understandability of speech	(n=370)	(n=359)	0.033 (20)
Mean	93.4	95.8	
Std. Dev.	16.3	13.6	
Median	100	100	
Min – Max	0 – 100	0 – 100	
Q1 – Q3	100 – 100	100 – 100	
FACT-G Total Score	(n=374)	(n=351)	0.134 (20)
Mean	80.5	82.3	
Std. Dev.	16.2	16.1	
Median	82	85	
Min – Max	35 – 108	28 – 108	
Q1 – Q3	69.3 – 93.0	71.7 – 95.0	
FACT-HN-Total score	(n=372)	(n=351)	0.155 (20)
Mean	107.6	110.0	
Std. Dev.	22.7	22.4	
Median	109.3	114.0	
Min – Max	51.0 – 147.0	35.0 – 147.0	
Q1 – Q3	89.0 – 126.0	93.2 – 129.0	
EQ-5D: EQ Health Index Score	(n=366)	(n=349)	0.604 (20)
Mean	0.78	0.80	
Std. Dev.	0.18	0.17	
Median	0.82	0.83	
Min – Max	0.17 – 1.00	0.20 – 1.00	
Q1 – Q3	0.77 – 0.84	0.77 – 0.84	

Std. Dev. = standard deviation; Q1 = first quartile; Q3 = third quartile.

(20) A pack-year is defined as the equivalent of smoking one pack of cigarettes a day for 1-year.
(20) AJCC denotes American Joint Committee on Cancer, 6th edition.
(20) t test.
(20) Fisher’s exact test.
(20) Fisher’s exact test: white vs. non-white; unknown excluded.
(20) Fisher’s exact test: unknown excluded.
(20) Fisher’s exact test: feeding tube vs. no feeding tube; unknown excluded.
(20) Pearson chi-square test.
(20) Wilcoxon rank-sum test.

(20) Kolmogorov-Smirnov test.

Table 2

Comparison of patients with worsened, no change, and improved scores, and ≤ 50 scores for PSS-HN

		3 months		12 months	
		CRT	**CRT+ cetuximab**	**CRT**	**CRT+ Cetuximab**
Diet *	Worsened, n (%)	212 (75.2)	216 (79.4)	89 (38.0)	92 (41.2)
	No change, n (%)	60 (21.3)	48 (17.7)	118 (50.0)	105 (47.1)
	Improved, n (%)	10 (3.5)	8 (1.9)	27 (12.0)	26 (11.7)
	p-value	0.49		0.76	
	Proportion ≤ 50 (95%CI)	0.80 (0.75, 0.84)	0.85 (0.80, 0.89)	0.37 (0.31, 0.43)	0.37 (0.31, 0.44)
	p-value	0.13		0.87	
Eating *	Worsened, n (%)	189 (66.8)	198 (72.8)	62 (26.5)	77 (33.5)
	No change, n (%)	76 (26.9)	64 (23.5)	149 (63.7)	137 (59.6)
	Improved, n (%)	18 (6.3)	10 (3.7)	23 (9.8)	16 (6.9)
	p-value	0.19		0.19	
	Proportion ≤ 50 (95%CI)	0.62 (0.56, 0.67)	0.63 (0.59, 0.67)	0.18 (0.13, 0.23)	0.23 (0.18, 0.28)
	p-value	0.39		0.16	
Speech *	Worsened, n (%)	56 (19.1)	60 (21.7)	26 (10.9)	41 (18.8)
	No change, n (%)	215 (73.1)	205 (74.0)	193 (81.1)	179 (77.5)
	Improved, n (%)	23 (7.8)	12 (4.3)	19 (8.0)	11 (4.7)
	p-value	0.19		0.052	
	Proportion ≤ 50 (95%CI)	0.09 (0.06, 0.12)	0.08 (0.05, 0.12)	0.05 (0.02, 0.08)	0.04 (0.02, 0.07)
	p-value	0.81		0.67	

CRT-cisplatin-radiation control arm
CI-confidence interval

* Either 20+ points increase (improved) or decrease (worsened) from pretreatment was considered a clinically significant change for diet and 25 points for eating and speech.

Table 3

Cross-sectional comparison of FACT-HN mean scores between treatment arms

Instrument	Treatment	Statistic	Pre-treatment	1 year	5 years
FACT-G Total (observed data)	CRT	n	374	249	76
		Mean	80.55	85.51	89.66
		SD	16.18	17.25	15.87
	Cetuximab	n	351	256	81
		Mean	82.35	84.24	89.49
		SD	16.13	17.18	18.08
		p-value	0.1339	0.4070	0.9478
FACT-G Total (with imputed data)	CRT	n	407	362	262
		Mean	80.00	82.46	81.48
		SD	16.05	16.61	14.38
	Cetuximab	n	408	358	269
		Mean	81.25	81.91	81.67
		SD	15.94	16.41	14.86
		p-value	0.2745	0.6858	0.8950
FACT-HN Total (observed data)	CRT	n	372	247	76
		Mean	107.61	110.97	116.13
		SD	22.75	22.67	21.52
	Cetuximab	n	351	255	80
		Mean	109.99	108.85	116.32
		SD	22.40	23.24	24.52
		p-value	0.1554	0.3024	0.9585
FACT-HN Total (with imputed data)	CRT	n	407	362	262
		Mean	106.92	106.91	104.75
		SD	22.55	22.10	19.73
	Cetuximab	n	408	358	269
		Mean	108.49	105.96	104.88

Instrument	Treatment	Statistic	Pre-treatment	1 year	5 years
		SD	22.16	22.30	20.72
		p-value	0.3223	0.6063	0.9457
FACT PWB (observed data)	CRT	n	375	249	80
		Mean	22.30	22.68	23.38
		SD	5.08	4.75	4.86
	Cetuximab	n	353	257	81
		Mean	22.53	22.27	23.38
		SD	5.40	5.27	5.36
		p-value	0.5683	0.3556	0.9990
FACT PWB (with imputed data)	CRT	n	407	362	262
		Mean	22.17	21.98	21.59
		SD	5.05	4.70	4.41
	Cetuximab	n	408	358	269
		Mean	22.24	21.75	21.45
		SD	5.31	5.05	4.65
		p-value	0.8356	0.5639	0.7744
FACT SWB (observed data)	CRT	n	374	249	78
		Mean	23.30	23.27	22.92
		SD	5.09	5.02	6.11
	Cetuximab	n	352	257	81
		Mean	24.24	23.27	23.73
		SD	4.10	4.85	4.80
		p-value	0.0059	0.9974	0.3574
FACT SWB (with imputed data)	CRT	n	407	362	262
		Mean	23.17	22.60	21.38
		SD	5.02	4.82	4.84
	Cetuximab	n	408	358	269
		Mean	23.93	22.78	21.82

Instrument	Treatment	Statistic	Pre-treatment	1 year	5 years
		SD	4.12	4.64	4.40
		p-value	0.0211	0.6518	0.3694
FACT EWB (observed data)	CRT	n	374	249	78
		Mean	17.32	19.40	20.42
		SD	4.33	4.17	3.72
	Cetuximab	n	354	256	81
		Mean	17.34	19.17	20.23
		SD	4.61	4.12	4.44
		p-value	0.9547	0.5267	0.7696
FACT EWB (with imputed data)	CRT	n	407	362	262
		Mean	17.23	18.78	19.10
		SD	4.30	4.10	3.54
	Cetuximab	n	408	358	269
		Mean	17.17	18.65	18.97
		SD	4.52	4.05	3.75
		p-value	0.8444	0.7175	0.7439
FACT FWB (observed data)	CRT	n	374	250	78
		Mean	17.64	20.16	21.99
		SD	6.85	6.91	6.00
	Cetuximab	n	354	257	81
		Mean	18.27	19.55	22.14
		SD	6.70	6.82	6.94
		p-value	0.2104	0.3172	0.8825
FACT FWB (with imputed data)	CRT	n	407	362	262
		Mean	17.44	19.10	19.41
		SD	6.80	6.73	5.76
	Cetuximab	n	408	358	269
		Mean	17.91	18.74	19.44

Instrument	Treatment	Statistic	Pre-treatment	1 year	5 years
		SD	6.64	6.60	6.05
		p-value	0.3262	0.5177	0.9679
FACT Add. Conc. (observed data)	CRT	n	373	248	80
		Mean	27.14	25.24	26.02
		SD	8.74	7.43	7.70
	Cetuximab	n	354	256	81
		Mean	27.68	24.58	26.98
		SD	8.52	7.55	7.47
		p-value	0.4012	0.3245	0.4257
FACT Add. Conc. (with imputed data)	CRT	n	407	362	262
		Mean	26.92	24.45	23.27
		SD	8.67	7.49	7.36
	Cetuximab	n	408	358	269
		Mean	27.25	24.05	23.21
		SD	8.44	7.55	7.61
		p-value	0.6008	0.5329	0.9423

Abbreviations: SD, standard deviation; PWB, physical well-being; SWB, social well-being; EWB, emotional well-being; FWB, functional well-being; Add. Conc., head and neck cancer-specific additional concerns.

Higher scores indicate better QOL for all instruments.

Questionnaires inside the following time windows were included in analysis:

Pretreatment, on or before start of treatment;

Last 2 weeks of treatment, 4 weeks prior to 2 weeks after end of treatment;

3 months, ± 6 weeks;

1–5 years, ± 3 months.

Table 4

Association between Baseline QOL/PS Scores and Survival Outcome in All Patients

Model	QOL parameter	HR	95%CI	p-value
Overall survival:				
#1 (n=644; 202 events)	PSS-HN diet (per 10-pt increase)	0.875	0.832–0.919	<0.0001
#2 (n=638; 198 events)	PSS-HN eating (per 25-pt increase)	0.805	0.705–0.919	0.0013
#3 (n=653; 203 events)	PSS-HN speech (per 25-pt increase)	0.928	0.764–1.127	0.4506
#4 (n=654; 204 events)	FACT-G total (per 10-pt increase)	0.893	0.815–0.978	0.0152
#5 (n=652; 203 events)	FACT-HN total (per 10-pt increase)	0.892	0.834–0.955	0.0009
#6 (n=646; 200 events)	EQ5D index (per 0.1-pt increase)	0.875	0.812–0.942	0.0004
Progression-free survival:				
#1 (n=644; 278 events)	PSS-HN diet (per 10-pt increase)	0.916	0.877–0.957	<0.0001
#2 (n=638; 276 events)	PSS-HN eating (per 25-pt increase)	0.813	0.720–0.917	0.0008
#3 (n=653; 282 events)	PSS-HN speech (per 25-pt increase)	0.936	0.785–1.116	0.4618
#4 (n=654; 283 events)	FACT-G total (per 10-pt increase)	0.933	0.864–1.008	0.0788
#5 (n=652; 282 events)	FACT-HN total (per 10-pt increase)	0.934	0.882–0.989	0.0189
#6 (n=646; 277 events)	EQ5D index (per 0.1-pt increase)	0.916	0.858–0.979	0.0093
Locoregional failure:				
#1 (n=644; 153 events)	PSS-HN diet (per 10-pt increase)	0.907	0.856–0.961	0.0010
#2 (n=638; 152 events)	PSS-HN eating (per 25-pt increase)	0.779	0.664–0.915	0.0024
#3 (n=653; 153 events)	PSS-HN speech (per 25-pt increase)	0.873	0.697–1.094	0.2379
#4 (n=654; 157 events)	FACT-G total (per 10-pt increase)	0.938	0.846–1.041	0.2300
#5 (n=652; 156 events)	FACT-HN total (per 10-pt increase)	0.921	0.853–0.994	0.0347
#6 (n=646; 153 events)	EQ5D index (per 0.1-pt increase)	0.944	0.862–1.034	0.2119
Distant metastasis:				
#1 (n=644; 83 events)	PSS-HN diet (per 10-pt increase)	0.917	0.845–0.995	0.0368
#2 (n=638; 84 events)	PSS-HN eating (per 25-pt increase)	0.799	0.639–1.000	0.0498
#3 (n=653; 87 events)	PSS-HN speech (per 25-pt increase)	0.898	0.651–1.238	0.5105
#4 (n=654; 86 events)	FACT-G total (per 10-pt increase)	0.899	0.782–1.034	0.1367
#5 (n=652; 86 events)	FACT-HN total (per 10-pt increase)	0.943	0.849–1.046	0.2669
#6 (n=646; 85 events)	EQ5D index (per 0.1-pt increase)	0.866	0.771–0.974	0.0163

Abbreviations: HR, hazard ratio; CI, confidence interval; PSS-HN, Performance Status Scale for Head and Neck cancer patients; QOL, quality of life; PS, performance status.

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