Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-231-2825.

1. **Grantee Institution:** American College of Radiology

2. **Reporting Period (start and end date of grant award period):** 1/1/2011-12/31/2014

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Stephen M. Marcus, M.S.

4. **Grant Contact Person's Telephone Number:** 267-940-9403

5. **Grant SAP Number:** 4100054841

6. **Project Number and Title of Research Project:** #4: The Evaluation of Quality of Life (QOL) Endpoints in RTOG Studies

7. **Start and End Date of Research Project:** 1/1/2011 – 12/31/2014

8. **Name of Principal Investigator for the Research Project:** Stephanie Shook Pugh, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ $249,178.16

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Pugh	Principal Investigator	1% Yrs 1-2; 10% Yr 3; 17% Yr 4	$39,345.20
George	Statistician	25% Yr 1; 58% Yr 2; 7% Yr 3; 3% Yr 4	$96,220.78
Paulus	Statistician	7% Yr 4	$7,288.09
Seiferheld	Statistician	4% Yr 2; 21% Yr 4	$21,078.92

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Christopher Jones, MD	Investigator	2%
Lisa Kachnic, MD	Investigator	2%
Margaret C Wilmoth, PhD, MSS, RN, FAAN	Investigator	2%
Naresh Jha, MBBS	Investigator	2%
Minh Tam Truong, MD	Investigator	2%
Canhua Xiao, PhD	Investigator	2%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No_____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you

able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds awarded:
None	☐NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes_____ No____X_____

If yes, please describe your plans:

12. Future of Research Project. What are the future plans for this research project?

The combined analysis for PSS-HN in RTOG 0129 and 0522 will be conducted in the future (aims 4 and 5). There are no future plans for the other aims.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes_____ No____X_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
Other				
Unknown				
Total				

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No____X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes_____X____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

Within our organization, these results, although recently published, will provide prior data for designing subsequent protocols.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of

your institution (e.g., entire university, entire hospital system)?

Yes___X_____ No_____

If yes, please describe the collaborations:

Collaboration with the first author of the manuscript took place during the analysis as well as during manuscript development.

16(B) Did the research project result in commercial development of any research products?

Yes_____ No_____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No____X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project

work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

***Aim 1: RTOG 9408: Patient's perception of quality of sexual function*:** The original intent was to have a stand-alone QOL manuscript but as the primary endpoint manuscript was being prepared for NEJM, it was decided that the QOL analysis better served the GU community by being published in the context of the primary efficacy analysis (Jones 2011). Due to the sudden nature of this decision, we failed to inform the first author of the primary endpoint manuscript to include the grant acknowledgment.

Statistical Methods for *Aim 1*

RTOG 9408 is a randomized Phase III trial investigating the effect of the combination of Zoladex and flutamide used prior to and during definitive radiation therapy on the patient's perception of quality of sexual function. A secondary objective is to determine the effect of the treatment on sexual function for patients in good prognosis with locally confined adenocarcinoma of the prostate.

Patients were randomly assigned to radiotherapy plus short-term androgen-deprivation therapy (ADT, the combined-therapy group) or radiotherapy alone. The chi-square test was used to test differences in patients' responses to the Sexual Adjustment Questionnaire between treatment arms.

Statistical Results for *Aim 1*

A total of 2028 patients were randomized to RTOG 9408. Forty-nine patients were ineligible, withdrew consent, or were lacking pretreatment data, leaving 1979 eligible patients who were available for evaluation (992 in the radiotherapy-alone group and 987 in the combined-therapy group). The treatment groups were balanced, with no significant differences in demographic or tumor-related characteristics.

At the pretreatment, 1-year, and 2-year evaluations, the Sexual Adjustment Questionnaire completion rates were 88%, 70%, and 27%, respectively. Before treatment, 48% of the respondents in the combined-therapy group and 54% of those in the radiotherapy-alone group reported that they were "always or almost always able to have an erection" ($P = 0.15$); the respective rates at 1 year were 21% and 31% ($P = 0.004$) (Table 1.1). Scores at 1 year, as compared with the pretreatment scores, were improved in 9% of the patients, the same in 33%, and worse in 58%, with no significant differences between the groups.

Table 1.1
Effect of Short-Term ADT on Erectile Function, According to Responses to the Sexual Adjustment Questionnaire*

Response	Short-Term ADT plus RT	RT Alone	P-value (chi-square test)
	number/total number (percent)		
Baseline			
Always or almost always	169/349 (48)	186/344 (54)	0.15
Sometimes	87/349 (25)	87/344 (25)	0.93
Almost never or never	54/349 (15)	44/344 (13)	0.33
Did not try	30/349 (9)	22/344 (6)	0.32
Not applicable/Not answered	11/349 (3)	7/344 (2)	0.48
One year			
Always or almost always	59/284 (21)	85/274 (31)	0.004
Sometimes	66/284 (23)	62/274 (23)	0.95
Almost never or never	94/284 (33)	69/274 (25)	0.054
Did not try	58/284 (20)	55/274 ()20	1.00
Not applicable/Not answered	13/284 (5)	4/374 (1)	0.04

* Responses were to the question, "When sexually excited, are you able to get an erection?"
ADT denotes androgen-deprivation therapy.

Conclusions for *Aim 1*

The primary endpoint of this study was to determine the efficacy of the combined-therapy vs. radiation alone. The efficacy gains experienced by the combined-therapy group were achieved with minimal temporary acute hepatic toxic effects and some decreased erectile function at 1 year, but with no increased risk of death from intercurrent disease, serious cardiovascular toxic effects, or acute or long-term gastrointestinal or genitourinary complications of radiotherapy.

Aim 2: RTOG 0247: Assessment of QOL changes from combined modality therapy: This study was presented at ASTRO 2011 and the manuscript is currently being developed.

Statistical Methods for *Aim 2*

RTOG 0247 is a randomized phase II trial for patients with locally advanced rectal cancer receiving neoadjuvant chemoradiation. Patients with cT3-4NxM0 rectal cancer were randomly assigned to 50.4Gy and capecitabine with irinotecan (CapeIrRT) or oxaliplatin (CapeOxRT) followed by surgery and 4 months FOLFOX. QOL & bowel function were assessed using the EORTC QLQ-C30 and QLQ-CR38 instruments at pretreatment, completion of chemoradiation, completion of post-operative chemotherapy [approximately one year], and at two years. The

mean of the change in scores from pretreatment to the follow-up time points was analyzed by arm & gender. Declines & improvements were classified into 7 categories based on changes in the scale score:

- Large decline was calculated as a decrease of ≥ 20 points
- Moderate decline was calculated as a decrease between 10 and <20 points
- Little decline was calculated as a decrease between 5 and <10 points
- No change was calculated as a decrease in <5 points to an increase in <5 points
- Little improvement was calculated as an increase between 5 and <10 points
- Moderate improvement was calculated as an increase between 10 and <20 points
- Large improvement was calculated as an increase in 20 points or more

Subset analyses by gender were also conducted.

Statistical Results for *Aim 2*

There 146 patient accrued and of 104 evaluable patients (52 each arm), QLQ-C30 and QLQ-CR38 bowel symptom pretreatment participation was 89% and 87%, respectively, in the CapeIrRT arm and 92% and 85%, respectively, in the CapeOxRT arm, with attrition for each assessment of 42% and 27%, respectively, for the CapeIrRT arm and 42% and 33%, respectively, for the CapeOxRT at 2 years. Pretreatment characteristics included: median age 57 years; 71% male; 87%T3; 47%N+. For paired assessments, the QLQ-C30 global QOL mean change moderately declined post-CRT (CapeIrRT: -10.3, SD 23.7; CapeOxRT: -12.2, SD 23.5), and at 2 years, remained slightly below baseline with CapeIrRT (-6.8, SD 28.3), and returned to baseline with CapeOxRT (-1.3, SD 14.4). The post-CRT global QOL decline was greater in females as seen in Table 2.1.

The QLQ-CR38 gastrointestinal (GI) symptom mean change improved post-CRT, notably with CapeOxRT (CapeIrRT: 5.9, SD 22.3; CapeOxRT: 20.3, SD 22.1). At 2 years, remained slightly improved with CapeOxRT (6.7, SD 12.7), and returned to baseline with CapeIrRT (0.4, SD 20.3). The pretreatment to 2 year mean GI change improved only in females on the CapeIrRT arm, as seen in Table 2.1, while both genders reported improvements with CapeOxRT. The QLQ-CR38 defecation symptom mean change improved post-CRT (CapeIrRT: 4.8, SD 21.6; CapeOxRT: 8.8, SD 21.8), and at 2 years, declined to baseline. The baseline to 1 year mean defecation score change largely improved in females on the CapeOxRT arm, as seen in Table 2.1. Both genders returned to baseline at 2 years. No gender differences were observed on the CapeIrRT arm.

Conclusions for *Aim 2*

Global QOL declined and patient-reported bowel function improved after CRT with both regimens. At 2 years, patient-reported QOL and GI symptom scores suggest a more favorable profile on the CapeOxRT arm. In analysis of gender differences, patient-reported GI symptoms demonstrated a decline in males only on the CapeIrRT arm.

Table 2.1
Mean Change Scores

	CapeIrRT: Males	CapeIrRT: Females	CapeOxRT: Males	CapeOxRT: Females
	Mean Change (SD)			
QLQ-C30				
Post-CRT: Global QoL	-6.1 (23.2)	-18.1 (23.5)	-7.3 (18.7)	-29.8 (31.5)
QLQ-CR38				
2 Year: GI	-4.5 (21.8)	8.3 (15.4)	5.8 (14.3)	9.3 (6.0)
1 Year: Defecation	1.0 (18.6)	-3.4 (15.5)	9.9 (15.6)	26.2 (14.3)

Aim 3: RTOG 0630: Exploring QOL in soft tissue sarcomas (STS): This manuscript is currently being developed.

Statistical Methods for *Aim 3*

Cohort A (patients receiving neoadjuvant or adjuvant chemotherapy or both or patients receiving concurrent or interdigitated chemotherapy) closed with 12 patients entered. Cohort B (patients not receiving chemotherapy) closed with 86 patients entered. Due to the early accrual closure in Cohort A, only Cohort B results were reported. Four tools, the Musculoskeletal Tumor Rating Scale (MSTS), the Toronto Extremity Salvage Score (TESS), the Functional Assessment of Cancer Therapy-General (FACT-G), and the Sexual Adjustment Questionnaire (SAQ), were collected at 4 time points: pretreatment, and 1, 1.5, and 2 years from start of treatment. For the MSTS and TESS, mean scores were compared against the NCIC trial preoperative arm using a two-sample t-test. For all 4 tools, the QOL means in patients with Grade 0-1 and Grade 2+ late toxicity (lymphedema and/or subcutaneous fibrosis and/or joint stiffness) at 2 years were calculated with and without adjustment for one additional covariate using an Analysis of Covariance (ANCOVA) framework. Trends over time were evaluated using the generalized linear mixed model adjusting for baseline covariates (age, gender, race, performance status, tumor location, T stage, and histology). Pearson correlation coefficients were calculated between each pair of tools at each time point. A significance level of 0.05 was used for all models.

Statistical Analysis for *Aim 3*

Six patients in Cohort B were ineligible per protocol criteria and 1 patient did not start protocol therapy leaving 79 analyzable patients. Sixty-two of 79 patients (78.5%) consented to participate in the QOL study.

Results of the comparison with the NCIC Trial Preoperative Arm are located in Table 3.1. Of the 20 patients with MSTS scores at 2 years, only 2 (10.0%) had Grade 2+ late toxicity at 2 years. With and without adjustment for a single covariate, the mean MSTS scores are roughly 31 for patients with Grade 0-1 late toxicity and 25 for patients with Grade 2+ toxicity. None of the covariates approach significance at the 0.05 level. The 4 patients with Grade 2+ late toxicity had mean 2-year TESS scores 10-15 points lower than the 22 patients with Grade 0-1

late toxicity. Wound complication approaches significance (p=0.10) but no other covariates approached significance.

The pretreatment FACT-G total score mean is 81.0 and the 2-year mean is 89.3, with the increase due to emotional and functional well-being. The 4 patients with Grade 2+ late toxicity had mean 2-year FACT-G scores 0-5 points lower than the 22 patients with Grade 0-1 late toxicity. RT type approaches significance (p=0.07) but no other covariates approach significance.

The pretreatment SAQ mean is 41.5 and the 2-year mean is 45.3, with increases in all 3 subscales indicating worse sexual adjustment. The 3 patients with Grade 2+ late toxicity had mean 2-year SAQ scores 0-6 points lower than the 14 patients with Grade 0-1 late toxicity. Age is significantly associated with SAQ scores at 2 years, both as a continuous variable (p=0.002) or dichotomized as > 60 vs. ≤ 60 (p=0.02). No other covariates approach significance at the 0.05 level.

Results of the adjusted least squares means from the mixed effects models are located in Table 3.2. The least squares means are very stable from pretreatment to 2 years (31.34, 30.56, 30.76, and 30.89) for MSTS and (87.28, 87.16, 87.11, 85.25) TESS. For both tools, none of the changes from pretreatment are statistically significant and none of the covariates approached significance. The least squares means for the FACT-G increase over time with the change from pretreatment to 2 years nearly statistically significant (5.13 point increase, p=0.07), and none of the changes from pretreatment are statistically significant. The least squares means for the SAQ are higher at all 3 post-treatment time points relative to pretreatment (36.25 to 41.49 to 42.34 to 40.60) with the 1-year and 1.5-year changes from pretreatment statistically significant (1-year: 5.24 point increase, p=0.02; 1.5-year: 6.09 point increase, p=0.005) and a nearly significant change from pretreatment to 2 years (4.35 point increase, p=0.08, Table 6.5). Age (p=0.008), gender (p=0.05), and histology (p=0.03) are significantly associated with SAQ score.

Strong positive correlations between measures occurred between MSTS and TESS at 1.5 years (r=0.74, p<0.001) and 2 years (r=0.43, p=0.07), between MSTS and FACT-G at 1.5 years (r=0.50, p=0.03). TESS and FACT-G are highly correlated at all 4 time points: baseline r=0.62, p<0.001; 1 year: r=0.58, p<0.001; 1.5 years: r=0.51, p=0.005; 2 years: r=0.63, p<0.001. TESS and SAQ have a strong negative association at baseline (r=-0.34, p=0.03).

Table 3.1

Comparison of MSTS & TESS with NCIC Trial Preoperative Arm at 2 Years

Tool	Cohort	n	Mean	Standard deviation	Standard error of the mean	p-value (t-test)
MSTS Total score	RTOG 0630 cohort B	20	30.7	4.66	1.04	0.6810
	NCIC preoperative arm	35	30.0	7.90	1.34	
TESS Total Score	RTOG 0630 cohort B	27	81.6	18.64	3.59	0.4076
	NCIC preoperative arm	34	85.4	17.10	2.93	

Table 3.2
Least Squares Means from Generalized Linear Mixed Models

Tool	Time point	Mean	Change from pretreatment	p-value
MSTS	Pretreatment	31.34	--	--
	1 year	30.56	-0.78	0.4760
	1.5 years	30.76	-0.58	0.6059
	2 years	30.89	-0.45	0.6956
TESS	Pretreatment	87.28	--	--
	1 year	87.16	-0.11	0.9664
	1.5 years	87.11	-0.17	0.9538
	2 years	85.25	-2.03	0.4947
FACT-G	Pretreatment	83.72	--	--
	1 year	87.72	4.00	0.1289
	1.5 years	88.01	4.29	0.1126
	2 years	88.85	5.13	0.0666
SAQ	Pretreatment	36.25	--	--
	1 year	41.49	5.24	0.0181
	1.5 years	42.34	6.09	0.0053
	2 years	40.60	4.35	0.0798

Adjusted for age (> 60 vs. ≤ 60), gender (male vs. female), race (non-white vs. white), Zubrod performance status (1 vs. 0), tumor location (lower/hips/buttocks vs. upper extremity), T stage (T2 vs. T1), and histology (liposarcoma vs. other).

Conclusions for *Aim 3*

At 2 years, neither MSTS nor TESS showed improvement over the NCIC preoperative arm. Grade 2+ toxicity at 2 years may be associated with poorer MSTS, TESS, and FACT-G relative to Grade 0-1 toxicity. FACT-G may improve over time and SAQ may get worse over time while MSTS and TESS are stable. TESS and FACT-G are highly correlated. Compliance at the post-treatment time points was poor which compromises our ability to draw meaningful conclusions. All results should be considered hypothesis-generating.

Aim 4: RTOG 0129: Evaluation of radiation specific QOL: This manuscript was submitted to the Journal of Clinical Oncology.

Statistical Methods for *Aim 4*

Patients were randomized to receive standard radiation therapy fractionation (SFX) for 7 weeks plus cisplatin or accelerated radiation therapy fractionation (AFX) by concomitant boost for 6 weeks plus cisplatin. Three tools, the Performance Status Scale for Head and Neck cancer patients (PSS-HN), the Head and Neck Radiotherapy Questionnaire (HNRQ), and the Spitzer Quality of Life Index (SQLI), were collected at 8 time points: pretreatment, 1 of the last 2 weeks of treatment, 3 months from start of treatment, and 1, 2, 3, 4, and 5 years from start of treatment.

Time-weighted average QOL between pre-treatment and 12 months was calculated using area under the curve (AUC); only patients with all 4 assessments (pre-treatment, last 2 weeks of treatment, 3 months, and 12 months) were included in analysis. Cross-sectional exploratory analysis of raw scores was conducted at each time point. The change from pretreatment scores were calculated and compared for each follow-up time point.

Cross-sectional and change scores were compared by: (1) p16 status in patients with oropharyngeal cancer (OPC); and (2) OPC risk-of-death groups (low, intermediate, and high, according to four factors: HPV status, pack-years of tobacco smoking, tumor stage, and nodal stage, Ang 2010). For 2 groups, group means were compared by a two-sample t-test. For 3 or more groups, group means were compared by a one-way analysis of variance (ANOVA) F-test. Pre-treatment characteristics were compared by Fisher's exact test or Chi-square test (categorical variables) or Wilcoxon rank-sum test (continuous/ordinal variables). A multivariate Cox proportional hazards model was used to determine the prognostic effect of pre-treatment QOL scores on survival outcomes, including overall survival (OS), progression-free survival (PFS), local-regional failure (LRF), and distant metastasis (DM).

Statistical Analysis for *Aim 4*

RTOG 0129 enrolled 743 patients and 4 withdrew consent, 17 were retrospectively declared ineligible, and one had no follow-up, leaving 721 analyzable patients. Only patients who completed the QOL questionnaires were included in this analysis. No significant differences in pre-treatment characteristics, including p16 status, were found between the two treatment arms.

Based on the AUC analysis, there were no significant differences from pre-treatment to one year post-treatment between the AFX and the SFX arm for all three QOL questionnaires: PSS-HN (Diet: mean 53.63 and 53.36, respectively, p=0.92; Eating: 67.10 and 65.81, respectively, p=0.67; Speech: 91.77 and 90.48, respectively, p=0.43), HNRQ (5.19 and 5.27, respectively, p=0.39), and SQLI (8.02 and 8.02, respectively, p=0.98). There were multiple time points on the cross-sectional raw score (Table 4.1) and change score analyses showing worse QOL endpoints among patients treated with AFX-C. During and immediately after treatment the AFX arm had larger decreases than those in the SFX arm: the mean changes in HNRQ were -2.20 and -1.82, respectively, p=0.002; and the mean changes in SQLI were -2.52 and -1.82, respectively, p=0.003. During the follow-up (from 3-months to 5-years post-treatment), the AFX arm demonstrated a slower recovery, compared to those in the SFX arm at 3 months for PSS-HN Diet (mean change -42.58 and -34.36, respectively, p=0.03), at 3 years for SQLI (mean change 0.16

and 0.62, respectively, p=0.04), and at 5 years for PSS-HN Speech (mean change -4.52 and 1.45, respectively, p=0.01) and SQLI (mean change 0.16 and 0.78, respectively, p=0.01). Most changes are clinically significant between the two arms, based on the minimal important difference defined as at least 5% of the instrument range (Ringash 2007).

For patients with OPC, p16 status was significantly associated with QOL (see Figure 4 A-E). Based on change score data analysis, all QOL scales, excluding PSS-HN Speech, decreased more significantly from pre-treatment to the last 2 weeks of treatment in the p16-positive group compared to the p16-negative group (PSS-HN Diet: mean -66.83 and -42.41, respectively, p<0.0001; PSS-HN Eating: mean -55.86 and -34.51, respectively, p=0.0002; HNRQ: mean -2.59 and -1.49, respectively, p<0.0001; SQLI: mean -3.00 and -1.46, respectively, p<0.0001.) This gap resolved gradually by 3-months or 1-year post-treatment.

Similar results to the QOL between p16 status for OPC were also observed in oropharynx risk-of-death groups: the low risk-of-death oropharynx group had the best QOL at pre-treatment, while the high risk group had the worst QOL (p values for all QOL scales ranged from 0.0124 to < 0.0001); this beneficial effect in the low risk-of-death group existed in long-term follow-up from 1- to 4-years post-treatment for PSS-HN Diet (p values ranged from 0.0017 to <0.0001) and from 2- to 5-years post-treatment for PSS-HN Eating (p values ranged from 0.0458 to <0.0001), but not for PSS-HN Speech, HNRQ, and SQLI. All QOL scales except Speech decreased more from pre-treatment to the last 2 weeks of treatment for the low and intermediate risks groups.

The findings from the multivariate Cox proportional hazards models showed that pre-treatment QOL, got all 3 QOL questionnaires, is a significant independent prognostic factor for OS, PFS, and LRF, but not DM. Survival based on p16 status and primary sites (OPC vs. non-OPC) was also examined separately. The only significant finding was for non-OPC patients: when HNRQ or SQLI increased 1 point, the HR estimate for OS was 0.75 (95% CI, 0.63-0.89) or 0.89 (95% CI, 0.81-0.97), reflecting a 25% or 11% reduction, respectively.

Table 4.1
Cross Sectional Comparison of PSS-HN, HNRQ, and SQLI Mean Scores Between Treatment Arms

Instrument	Treatment	Statistic	Time point: Pre-treatment	Last 2 weeks	3 months	1 year	2 years	3 years	4 years	5 years
PSS-HN Diet	SFX + cisplatin	n	328	298	259	199	155	129	112	92
		Mean	75.06	21.14	43.01	70.20	78.06	80.39	77.95	77.07
		SD	32.59	25.92	33.79	32.41	29.30	29.59	31.20	31.61
	AFX-C + cisplatin	n	315	274	260	209	163	128	127	114
		Mean	78.41	25.18	39.12	71.67	75.03	78.91	79.45	79.04
		SD	30.06	26.92	33.73	32.80	32.61	31.93	31.73	29.18
		p-value	0.1762	0.0680	0.1893	0.6484	0.3843	0.7000	0.7131	0.6431
PSS-HN Eating	SFX + cisplatin	n	328	271	247	194	155	128	113	95
		Mean	85.29	42.71	57.49	80.67	87.58	87.11	86.95	85.53
		SD	27.77	34.16	36.13	28.45	26.17	25.87	24.80	26.19
	AFX-C + cisplatin	n	317	257	250	212	160	125	129	114
		Mean	87.62	41.73	59.00	80.66	83.44	87.00	84.11	88.38
		SD	26.80	33.47	35.83	28.65	30.18	25.52	28.29	22.36
		p-value	0.2792	0.7393	0.6401	0.9973	0.1946	0.9730	0.4104	0.3969
PSS-HN Speech	SFX + cisplatin	n	330	298	266	196	154	129	112	92
		Mean	92.12	84.31	88.44	92.98	95.45	93.60	92.86	97.55
		SD	19.94	22.83	21.51	15.77	10.87	16.02	17.25	7.47
	AFX-C + cisplatin	n	314	276	262	212	161	128	130	115

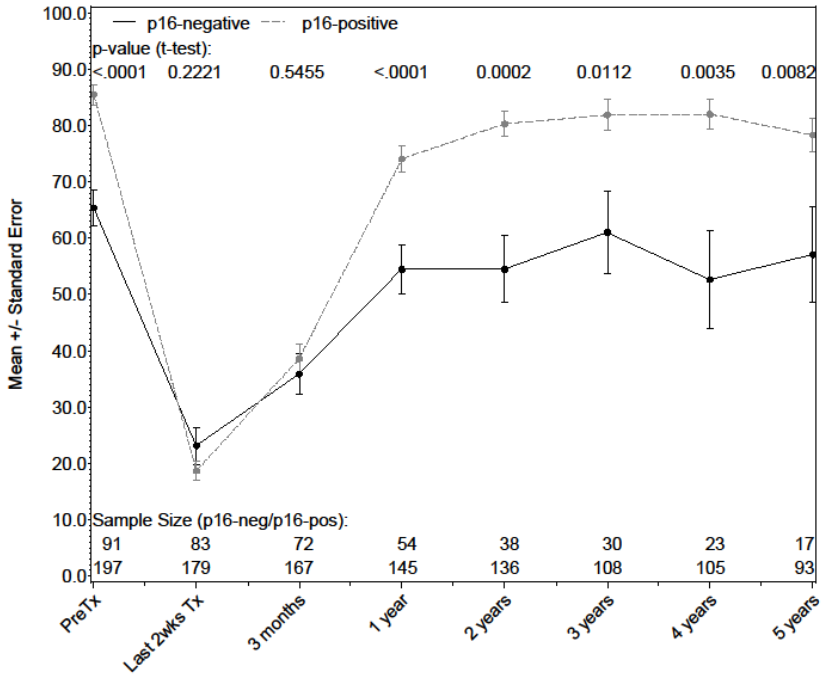
Table 4.1
Cross Sectional Comparison of PSS-HN, HNRQ, and SQLI Mean Scores Between Treatment Arms

Instrument	Treatment	Statistic	Time point							
			Pre-treatment	Last 2 weeks	3 months	1 year	2 years	3 years	4 years	5 years
		Mean	93.47	84.51	90.36	92.81	95.19	96.29	94.04	91.30
		SD	16.99	23.89	19.58	17.67	13.84	13.71	17.55	21.21
		p-value	0.3546	0.9188	0.2834	0.9148	0.8481	0.1503	0.5993	0.0038
HNRQ Score	SFX + cisplatin	n	327	283	248	199	159	128	113	99
		Mean	5.78	3.94	5.02	5.73	5.98	6.01	6.01	6.07
		SD	1.05	1.14	1.05	0.97	0.79	0.74	0.94	0.97
	AFX-C + cisplatin	n	319	258	249	206	162	135	134	118
		Mean	5.83	3.71	4.92	5.66	5.93	5.96	5.98	5.95
		SD	0.96	1.22	1.11	1.07	0.89	0.89	1.01	1.04
		p-value	0.4961	0.0226	0.3054	0.5234	0.6130	0.6015	0.7787	0.3927
SQLI Score	SFX + cisplatin	n	318	272	238	190	155	127	111	95
		Mean	8.17	6.27	7.55	8.86	9.05	9.13	9.17	9.35
		SD	2.09	2.16	2.18	1.71	1.57	1.42	1.66	1.38
	AFX-C + cisplatin	n	306	257	247	199	160	132	128	112
		Mean	8.63	6.25	7.65	8.81	9.13	9.21	9.24	9.21
		SD	1.70	2.18	2.01	1.80	1.49	1.39	1.40	1.66
		p-value	0.0026	0.9020	0.6091	0.7610	0.6712	0.6543	0.7194	0.5091

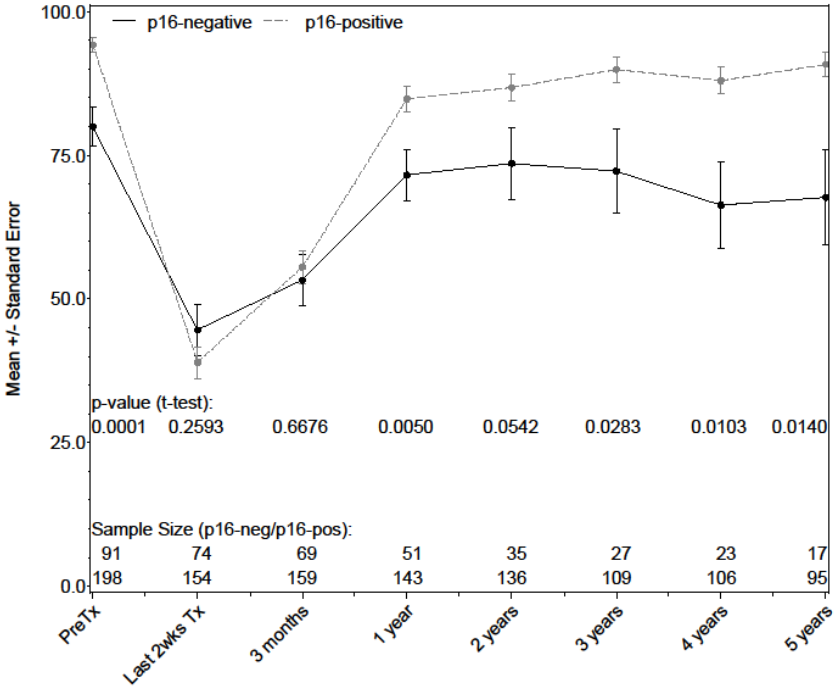
Abbreviations: AFX-C, accelerated-fractionation radiotherapy by concomitant boost; HNRQ, Head and Neck Radiotherapy Questionnaire; PSS-HN, Performance Status Scale for head and neck cancer; SD, standard deviation; SFX, standard-fractionation radiotherapy; SQLI, Spitzer Quality of Life Index.

Figure 4. Raw Scores for Quality of Life by p16 status

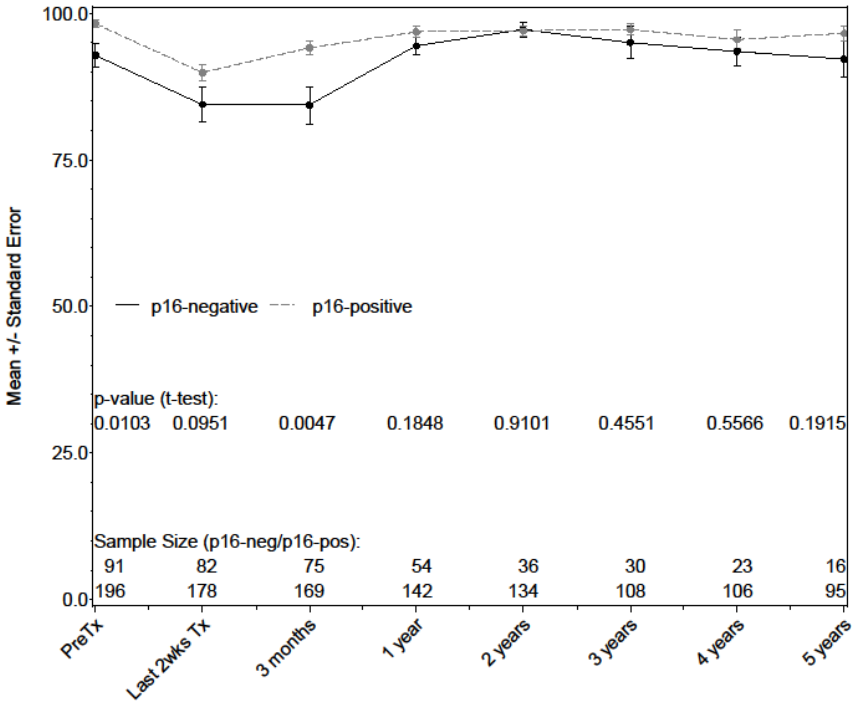
A. PSS-HN Normalcy of Diet



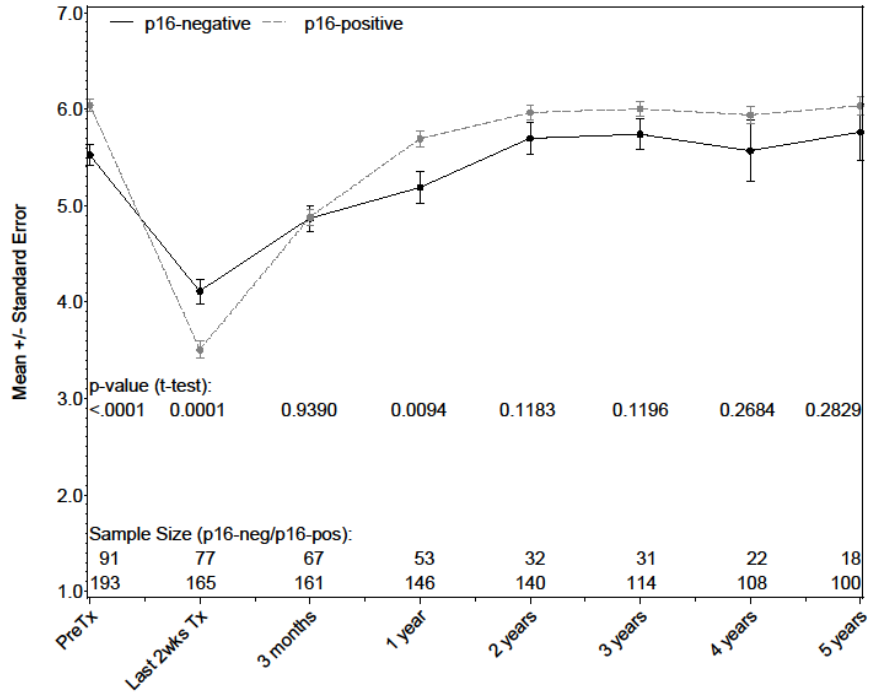
B. PSS-HN Public Eating



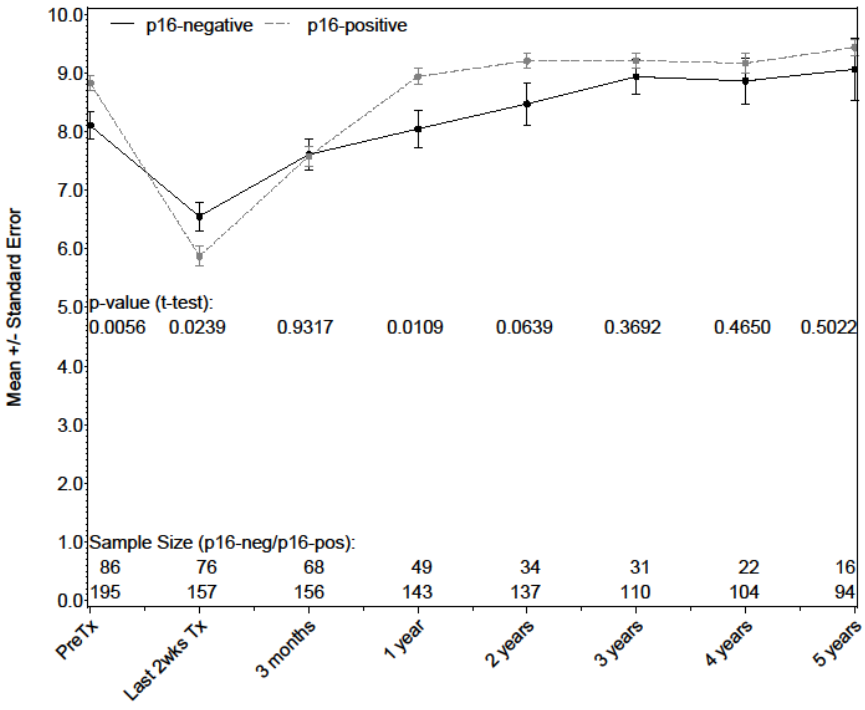
C. PSS-HN Understandability of Speech



D. HNRQ



E. SQLI



Conclusions for *Aim 4*
This analysis indicated worse QOL in the AFX group compared to the SFX group. p16-positive patients had better QOL prior to treatment and from 1-year up to 5-years after treatment compared to p16-negative patients. However, p16-positive patients had a larger drop in QOL 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 prior to treatment was an independent prognostic factor for survival supporting its potential use as a stratification factor in future trials.

Aim 5: RTOG 0522: Assessment of QOL, performance and health utilities: This manuscript was submitted to the Journal of Clinical Oncology.

Statistical Methods for *Aim 5*
RTOG 0522 randomized patients to receive radiation-cisplatin without (arm A) or with cetuximab (arm B) (Ang 2014). A separate QOL consent was required for this study. The Performance Status Scale for Head and Neck Cancer (PSS-HN) and EuroQol's 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. The Functional Assessment of Cancer Therapy-Head & Neck (FACT-HN) was collected pretreatment and at 1 and 5-years from start of treatment.

For PSS-HN, the frequency of patients with subscale scores of ≤ 50 representing moderate to severe impairment (List 1990, 1996) were 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. A ≥20 point change was considered clinically significant for PSS-HN-diet and ≥25 points for eating and speech. 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 treatment arms at 3 and 12 months using the non-parametric Kolmogorov-Smirnov test. The Spearman correlation coefficient between EQ-5D dimensions and global FACT-G score were computed at baseline, 1 and 5-years.

An exploratory cross-sectional comparison of QOL scores between treatment arms at each time point and change from baseline scores were compared for each time point after baseline. The minimal important difference (MID), being the smallest difference reflecting a clinically important change in score was defined as at least a 5% change in the total instrument score (Ringash 2007).

An exploratory analysis of OPC patients stratified by 1) p16 status, and 2) OPC risk-of-death groups, as defined in *Aim 4* was performed (Ang 2010). For all comparisons for OPC by p16 status and OPC risk-of-death groups, group means were compared by a two-sample independent t-test. For 3 or more groups, group means were compared by one-way analysis of variance (ANOVA) F-test. A multivariate Cox proportional hazards model was used to determine if the pretreatment QOL scores had a prognostic impact on outcome, independent of other known prognostic factors.

Statistical Analysis for *Aim 5*
Of the 940 patients enrolled, 49 were excluded (47 were ineligible; 2 patients had no follow-up), 73 patients did not provide QOL study consent, leaving a total of 818 analyzable patients for the QOL study.

A non-significant slower recovery of PSS-HN scores from the last 2 weeks of treatment to 1-year was seen in arm B (Figure 5.1 a-c). Although arm B had a higher percentage of patients with worsened PSS-HN scores, the difference was non-significant. There was a trend for worsened PSS-HN speech in arm B at 12 months, 18.8% vs.10.9%, p=0.052 (Table 5.1).

The mean change from baseline to 1 year between arm A and arm B for FACT-G was +2.88 and -0.93, p<0.001 (3.5% difference in scores); FACT-functional score was +1.73 (SD=6.6) and -0.09 (SD=6.96), p=0.004 (6.5% difference in score) and FACT-HN-Total scores was -0.41(SD=18.9) and -5.11 (SD=22.5), p=0.016 (3.2% difference in score), respectively. These were below the MID level defined in this study.

The mean EQ-5D index scores (SD) at 3 months and 1-year for arm A were 0.78 (0.18) and 0.84 (0.17); arm B 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 arm B 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 each time point, pain at baseline and 1-year, and activity at 1-year.

Patients with feeding tubes or grade ≥3 dysphagia had significantly worse PSS-HN-diet and eating scores and to a lesser extent for PSS-HN-speech from baseline through to 5-years. Figure 5.1a-c shows mean the PSS-HN subscale scores with or without grade ≥3 dysphagia. PSS-HN subscale scores with or without a feeding tube are shown in figures 5.1d-f.

OPC p16-positive compared to p16-negative patients had a greater deterioration in mean scores for PSS-HN-diet, (-75.4 (27.4) vs. -63.6 (36), p =0.032); PSS-HN-speech, (-14.2 (21.7) vs. -5.1 (18.4), p=0.006); during the last 2 weeks compared to baseline. PSS-HN subscale scores by p16 status and OPC risk groups are shown in Figures 5.1a-f. Change from baseline for FACT-HN was significant for physical (p=0.02), emotional (p=0.04) and FACT-G (p=0.05) at 5-years, with low risk patients returning to higher or near baseline scores, while intermediate or high risk OPC patients had less recovery with lower or below baseline scores at 5-years.

For the whole patient cohort, multivariate analysis (adjusted for assigned treatment, age, Zubrod performance status, primary site, T-stage, and N-stage) demonstrated that for an incremental increase in pretreatment scores for PSS-HN diet (per 10 points) and eating (per 25 points), there was a reduction in hazard of death, PFS, locoregional failure (LRF) and distant metastases (DM). PSS-HN speech (per 25 point increase) was only significant for reduced hazard of DM. FACT-G, FACT-HN-Total, and EQ-5D index scores were associated with reduced hazard of death and PFS. Higher FACT-HN-Total score was associated with reduced hazard of LRF and higher EQ-5D-index score was associated with reduced hazard of DM (Table 5.2).

In OPC patients, higher scores for FACT-G and FACT-HN-Total score (per 10 points), FACT-physical, functional and additional items (per 1 point), EQ5D index scores (per 0.1 point) were associated with better OS and PFS in p16-positive OPC in multivariate analysis. FACT-HN-total scores were also associated with reduced risk of LRF in both p16-positive and 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 only.

Table 5.1
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 5.2
Association Between Baseline QOL Scores and Survival Outcome in all patients

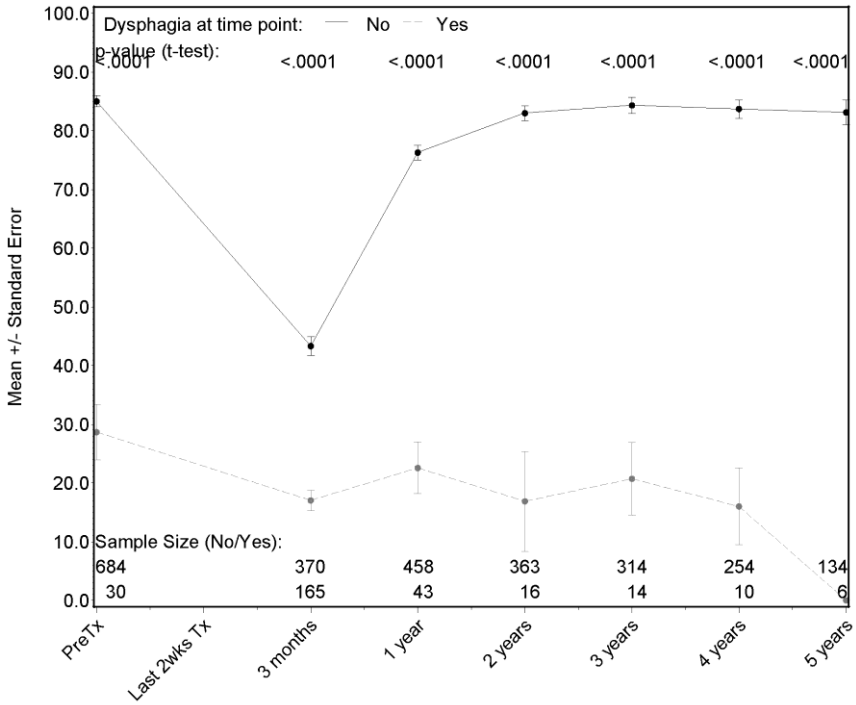
Model	QOL parameter	HR	95%CI	p-value
Overall survival:				
#1 (n=719; 234 events)	PSS-HN diet (per 10-pt increase)	0.869	0.830-0.909	<0.0001
#2 (n=714; 229 events)	PSS-HN eating (per 25-pt increase)	0.743	0.658-0.838	<0.0001
#3 (n=729; 235 events)	PSS-HN speech (per 25-pt increase)	0.877	0.735-1.047	0.1475
#4 (n=725; 234 events)	FACT-G total (per 10-pt increase)	0.876	0.805-0.952	0.0018
#5 (n=723; 233 events)	FACT-HN total (per 10-pt increase)	0.883	0.830-0.939	<0.0001
#6 (n=715; 229 events)	EQ5D index (per 0.1-pt increase)	0.855	0.798-0.917	<0.0001
Progression-free survival:				
#1 (n=719; 314 events)	PSS-HN diet (per 10-pt increase)	0.906	0.870-0.943	<0.0001
#2 (n=714; 311 events)	PSS-HN eating (per 25-pt increase)	0.765	0.685-0.855	<0.0001
#3 (n=729; 318 events)	PSS-HN speech (per 25-pt increase)	0.877	0.748-1.028	0.1058
#4 (n=725; 317 events)	FACT-G total (per 10-pt increase)	0.917	0.854-0.984	0.0166
#5 (n=723; 316 events)	FACT-HN total (per 10-pt increase)	0.923	0.875-0.973	0.0027
#6 (n=715; 310 events)	EQ5D index (per 0.1-pt increase)	0.897	0.844-0.954	0.0006
Local-regional failure:				
#1 (n=719; 170 events)	PSS-HN diet (per 10-pt increase)	0.897	0.850-0.946	<0.0001
#2 (n=714; 169 events)	PSS-HN eating (per 25-pt increase)	0.736	0.636-0.852	<0.0001
#3 (n=729; 170 events)	PSS-HN speech (per 25-pt increase)	0.844	0.686-1.038	0.1075
#4 (n=725; 173 events)	FACT-G total (per 10-pt increase)	0.917	0.833-1.010	0.0803
#5 (n=723; 172 events)	FACT-HN total (per 10-pt increase)	0.910	0.847-0.977	0.0092
#6 (n=715; 168 events)	EQ5D index (per 0.1-pt increase)	0.922	0.847-1.004	0.0623

Distant metastasis:				
#1 (n=719; 90 events)	PSS-HN diet (per 10-pt increase)	0.895	0.830-0.964	0.0036
#2 (n=714; 90 events)	PSS-HN eating (per 25-pt increase)	0.726	0.589-0.894	0.0026
#3 (n=729; 94 events)	PSS-HN speech (per 25-pt increase)	0.756	0.575-0.993	0.0445
#4 (n=725; 92 events)	FACT-G total (per 10-pt increase)	0.882	0.773-1.006	0.0618
#5 (n=723; 92 events)	FACT-HN total (per 10-pt increase)	0.920	0.833-1.015	0.0949
#6 (n=715; 91 events)	EQ5D index (per 0.1-pt increase)	0.852	0.761-0.953	0.0052

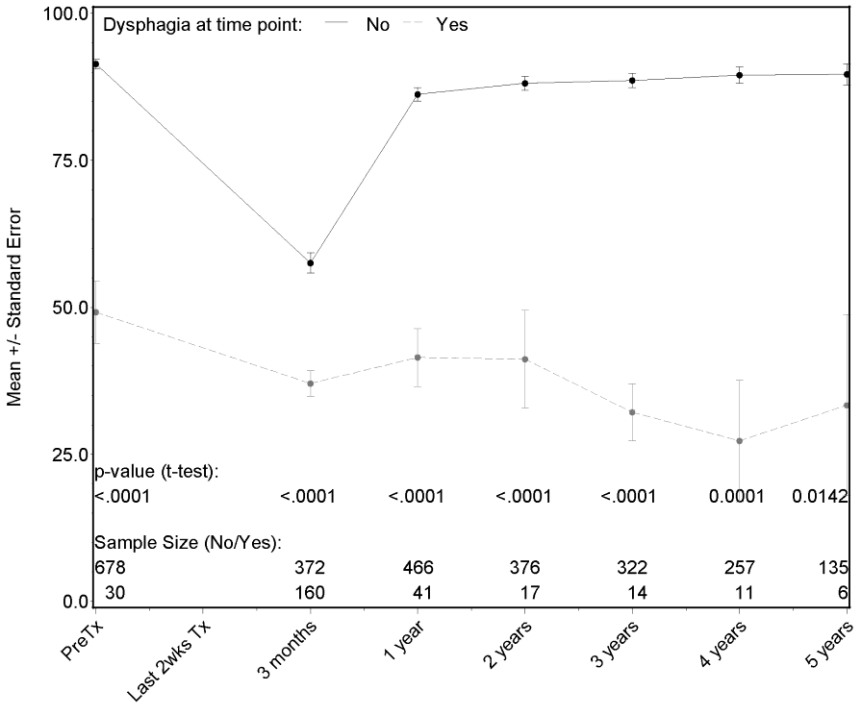
Abbreviations: CI, confidence interval; HR, hazard ratio
Adjusted for assigned treatment, age, Zubrod performance status, primary site, T stage, and N stage.

Figure 5.1 Mean raw scores for PSS-HN Normalcy of Diet, Eating in public, and Understandability of Speech scores correlated with grade ≥3 dysphagia

5.1 a. Normalcy of Diet



5.1 b. Eating in Public



5.1 c. Understandability of Speech

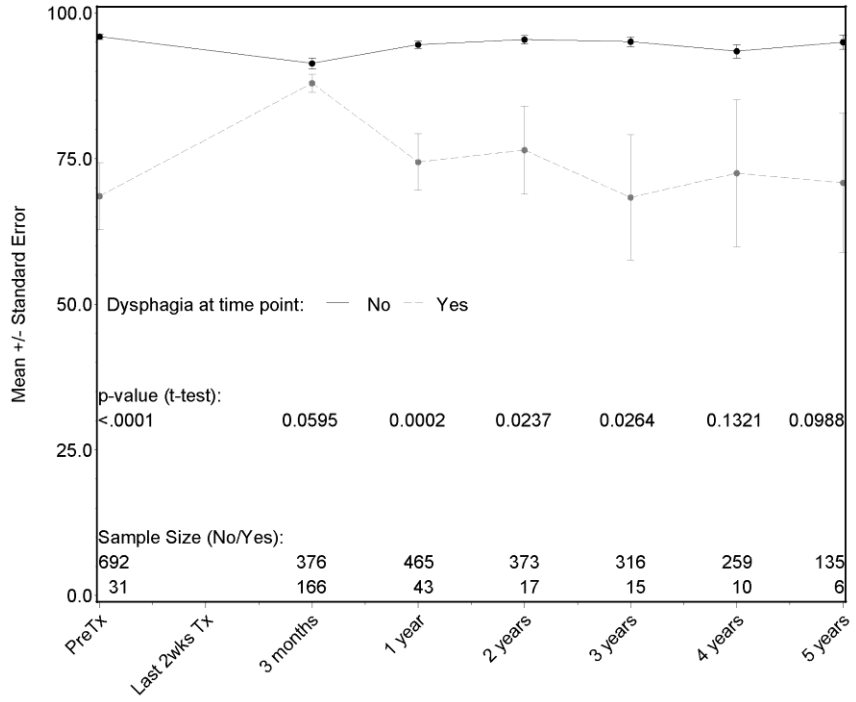
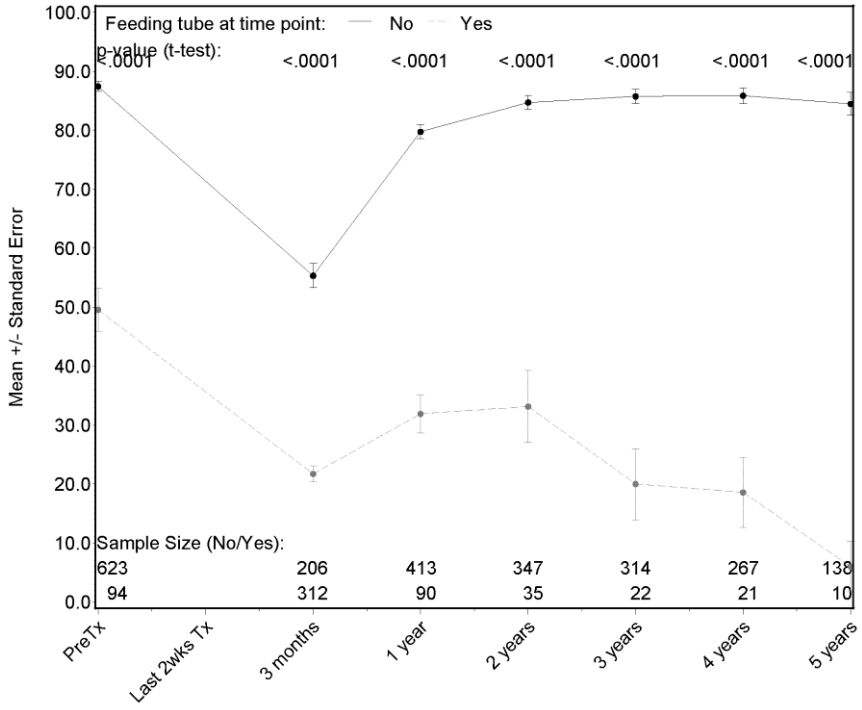
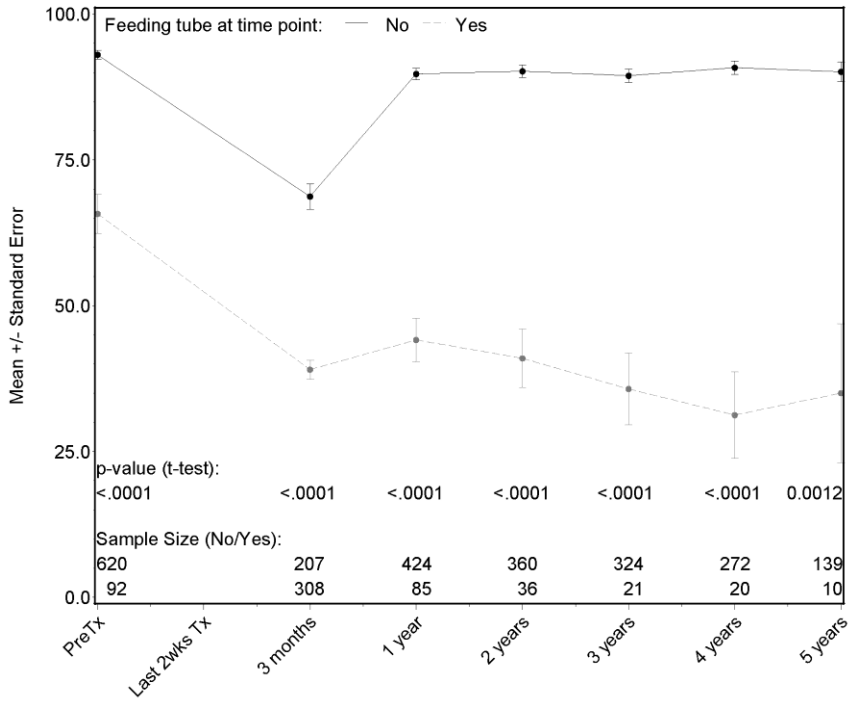


Figure 5.1 d-f Mean raw scores PSS-HN Normalcy of Diet, Eating in Public, and Understandability of Speech scores correlated with feeding tube status

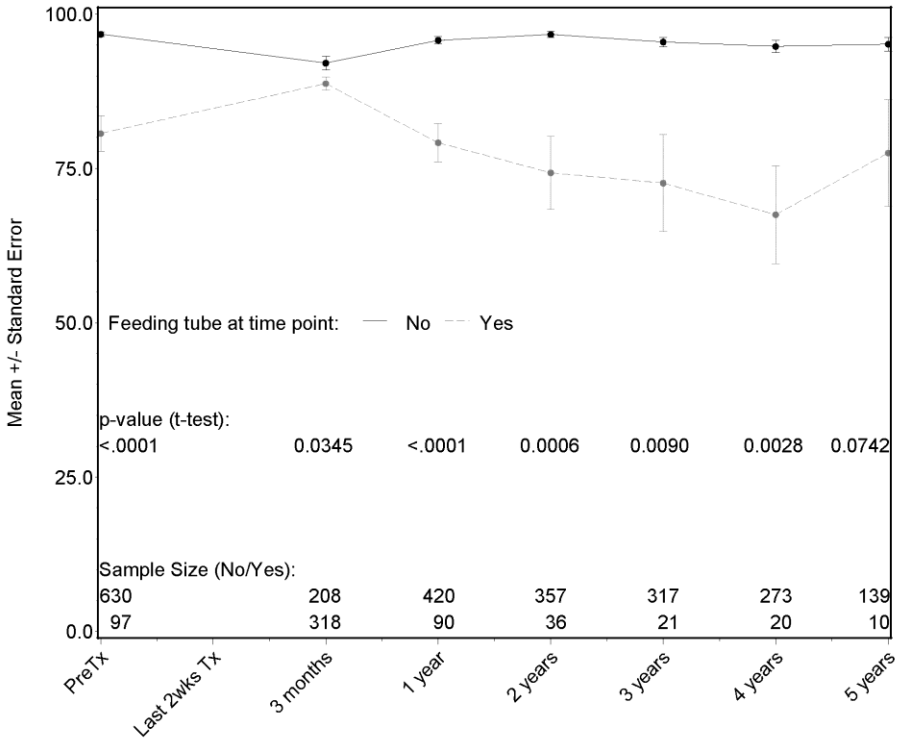
5.1 d. Normalcy of Diet



5.1 e. Eating in Public



5.1 f. Understandability of Speech



Conclusions for *Aim 5*
Differences in baseline QOL by p16 or OPC risk status found in this study and the potential prognostic value of pretreatment QOL scores using PSS-HN, FACT-HN and EQ-5D suggests that stratification in future clinical trials should incorporate pretreatment QOL, while post-therapy QOL may be incorporated into co-primary endpoints with survival to evaluate new treatment strategies to maximize survival while preserving good function and QOL in long-term survivors.

Aim 6*: *RTOG 0244: Preventing xerostomia and improving QOL: This manuscript was submitted to the International Journal of Radiation Oncology, Biology, and Physics.

Statistical Methods for *Aim 6*
RTOG 0244 was a single arm phase II trial assessing the reproducibility of the surgical technique of submandibular salivary gland transfer in a multi-institutional setting (Jha 2012). A modified version of the self-administered, validated instrument University of Washington Head and Neck Symptom Scale (UWHNSS) was used.

For the analysis, exploratory factor analysis results were used. Four items, disfigurement, employment, chewing and speech, were removed from the total score and each of these items is provided along with the mucus, pain, activities and eating factor scores as well as the total score. The four factors derived from the 11 remaining items are:

Factor 1: Mucus (amount of mucus or phlegm, consistency of mucus or phlegm)
Factor 2: Eating (swallowing, amount of saliva, consistency of saliva, taste)
Factor 3: Pain (general pain, mouth pain, throat pain)
Factor 4: Activities (activity, recreation/entertainment)

The total score uses the 11 items that were retained by the factor analysis. All items were scored from 0 to 100 and the mean was used to calculate the total and factor scores. In addition to missing data, a concern is missing items on a single assessment. The scoring procedure of the validated tool on how to handle missing items was then followed.

Fisher's exact test for categorical variables and two-sided Wilcoxon signed rank test with normal approximation for continuous variables were used for statistical testing. A subgroup analysis of patients who received both RT and surgery as per protocol or with acceptable variation was also performed.

Statistical Analysis for *Aim 6*
Forty-four patients were analyzable. There was not a separate QOL consent for this study, therefore all patients were considered for the analysis. At baseline, all 44 analyzable patients completed the UWHNSS as well as all 28 who completed treatment per protocol.

Due to the smaller number of patients reporting scores on UWHNSS questionnaire at 6 and 12 months, only scores at 3 months are presented. Distributions of each UWHNSS item as categorical variables are presented in Table 6.1. Change scores are provided in Table 6.2 for the 4 removed items, the overall score, and the factor scores. Change scores are calculated by subtracting the follow-up assessment from baseline. Since a low score indicates better function, a positive change score indicates improvement. The total score and factor scores showed improvement in function from baseline to 3 months while the remaining 4 items showed either improvement in function or no change in function.

The main focus of the utility of SGT procedure relates to the prevention of XRT induced xerostomia. The "amount of saliva" scores as reported by the participants on UWHNSS questionnaire are therefore of interest. At 3 months for all 44 patients on the study, 51.7% patients had mild or no loss of saliva. For the 28 patients treated as "per protocol", 66.6% patients had mild or no loss of saliva. In regards to consistency of saliva, at 3 months for all 44 patients, 46.7% patients had normal or slightly thicker saliva and for the 28 patients treated as "per protocol", 56.5% reported normal or slightly thicker saliva.

Conclusions for *Aim 6*
For further alleviation of xerostomia, future studies must focus on better sparing of the submandibular salivary gland in addition to parotids. The results of this study demonstrated that the technique of SGT procedure is reproducible in a multicenter setting and this particular analysis showed that it is a useful procedure for the prevention of XRT induced xerostomia.

Table 6.1
UWHNSS Baseline Distributions
(n=44)

General Pain	(n=44)
I have no pain	25 (56.8%)
There is mild pain not needing medication	10 (22.7%)
I have moderate pain - requires regular medication	6 (13.6%)
I have severe pain controlled only narcotics	3 (6.8%)
Mouth Pain	(n=43)
I have no pain	30 (69.8%)
I have mild pain but it is not affecting my eating	7 (16.3%)
I have moderate pain that is affecting my eating	5 (11.6%)
I have severe pain and cannot eat even with medication	1 (2.3%)
Throat Pain	(n=44)
I have no pain	26 (59.1%)
I have mild pain but it is not affecting my eating	11 (25.0%)
I have moderate pain that is affecting my eating	5 (11.4%)
I have severe pain and need medication in order to eat	2 (4.5%)
Disfigurement	(n=43)
There is no change in my appearance	32 (74.4%)
The change in my appearance is minor	10 (23.3%)
I feel significantly disfigured and limit my activities due to my appearance	1 (2.3%)
Activity	(n=44)
I am as active as I have ever been	24 (54.5%)
There are times when I can't keep up with my old pace but not often	7 (15.9%)
I am often tired and I have slowed down my activities although I still get out	12 (27.3%)
I don't go out because I don't have the strength	1 (2.3%)
Recreation/Entertainment	(n=43)
There are no limitations to recreation at home and away from home	25 (58.1%)
There are few things I can't do but I still get out and enjoy life	11 (25.6%)
There are many times when I wish I could get out more but I'm not up to it	4 (9.3%)
There are severe limitations to what I can do	3 (7.0%)

Table 6.1
UWHNSS Baseline Distributions
(n=44)

Employment	(n=43)
I work full time	19 (44.2%)
I have a part time but permanent job	4 (9.3%)
I only have occasional employment	1 (2.3%)
I am unemployed	10 (23.3%)
I am retired	9 (20.9%)
Chewing	(n=41)
I can chew as well as ever	31 (75.6%)
I have slight difficulty chewing solid foods	4 (9.8%)
I have moderate difficulty chewing solid foods	4 (9.8%)
I can only chew soft foods	2 (4.9%)
Swallowing	(n=41)
I swallow normally	31 (75.6%)
I cannot swallow certain solid foods	4 (9.8%)
I can only swallow soft foods	4 (9.8%)
I can only swallow liquid foods	2 (4.9%)
Amount of Saliva	(n=43)
I have a normal amount of saliva	42 (97.7%)
I have a moderate loss of saliva	1 (2.3%)
Consistency of Saliva	(n=44)
My saliva has normal consistency	39 (88.6%)
My saliva is slightly thicker	1 (2.3%)
My salvia is moderately thicker	4 (9.1%)
Taste	(n=43)
I can taste food normally	37 (86.0%)
I can taste most foods normally	2 (4.7%)
I can taste some foods normally	2 (4.7%)
I cannot taste any foods normally	2 (4.7%)
Speech	(n=44)
My speech is the same as always	39 (88.6%)
I have difficulty with saying some words but can be understood over the phone	5 (11.4%)

Table 6.1
UWHNSS Baseline Distributions
(n=44)

Amount of Mucus or Phlegm	(n=44)
I have a normal amount of mucus	30 (68.2%)
I have a mild amount of mucus	8 (18.2%)
I have a moderate amount of mucus	4 (9.1%)
I have a severe amount of mucus	2 (4.5%)
Consistency of Mucus or Phlegm	(n=42)
My mucus has normal consistency	30 (71.4%)
My mucus is slightly thicker	8 (19.0%)
My mucus is moderately thicker	4 (9.5%)

Table 6.2
UWHNSS 3 Month Change Scores

Total Score	(n=30)
Mean	23.3
Std. Dev.	11.4
Median	22. 7
Min - Max	-7. 3 - 41.8
Q1 - Q3	16. 4 - 31.1
Mucus	(n=29)
Mean	23.8
Std. Dev.	17.0
Median	20
Min - Max	-10 - 50
Q1 - Q3	10 - 40
Eating	(n=26)
Mean	31.0
Std. Dev.	12.8
Median	30
Min - Max	0 - 55
Q1 - Q3	25 - 40
Pain	(n=30)
Mean	11.8
Std. Dev.	15.8
Median	6. 7
Min - Max	-13.3 - 46.7
Q1 - Q3	0 - 26. 7
Activities	(n=31)
Mean	21.6
Std. Dev.	19.8
Median	30
Min - Max	-10 - 70
Q1 - Q3	0 - 30

References for all Aims:

Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *The New England Journal of Medicine.* Jul 1 2010;363(1):24-35.

Ang KK, Zhang Q, Rosenthal DI, et al: Randomized Phase III Trial of Concurrent Accelerated Radiation Plus Cisplatin With or Without Cetuximab for Stage III to IV Head and Neck Carcinoma: RTOG 0522. Journal of clinical Oncology: official journal of the American Society of Clinical Oncology, 2014.

Jha N, Harris J, Seikaly H, Jacobs JR, McEwan AJ, Robbins KT, Grecula J Sharma AK, Ang KK, A phase II study of submandibular gland transfer prior to radiation for prevention of radiation-induced xerostomia in head-and-neck cancer (RTOG 0244). *Int J Radiat Oncol Biol Phys*. 2012 Oct 1;84(2):437-42.

Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW, Leibenhaut MH, Husain SM, Rotman M, Souhami L, Sandler HM, Shipley WU. Radiotherapy and Short-Term Androgen Deprivation for Localized Prostate Cancer. *The New England Journal of Medicine.* Jul 14 2011;365(2):107-118.

Kachnic L, Winter K, Meropol NJ, Anne PR, Wong SJ, Watson JC, Mitchell EP, Pollock J, Lee RJ, Willett CG. Longitudinal Quality of Life (QOL) and Patient-Reported Bowel Function in RTOG 0247. *Int J Radiat Oncol Biol Phys*. 2011 Oct 1;81(2):S98.

List MA, Ritter-Sterr C, Lansky SB: A performance status scale for head and neck cancer patients. *Cancer*. 1990; 66:564-9.

List MA, D'Antonio LL, Cella DF, et al: The Performance Status Scale for Head and Neck Cancer Patients and the Functional Assessment of Cancer Therapy-Head and Neck Scale. A study of utility and validity. *Cancer*. 1996;77:2294-301.

Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer*. Jul 1 2007;110(1):196-202.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X___No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed

acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Quality of life in a prospective phase III randomized trial of concurrent accelerated radiation for locally advanced head and neck carcinoma: NRG Oncology RTOG 0522.	Minh Tam Truong, Qiang Zhang, David Rosenthal, Marcie List Rita Axelrod, Eric Sherman, Randal Weber, Phuc Felix Nguyen-Tan, Adel El-Naggar, Andre Konski, James Galvin, David Schwartz, Andy Trotti, Craig Silverman, Anurag Singh, Karen Godette, James a Bonner, Christopher U Jones, Adam Garden, George Shenouda, , Chance Matthiesen, Quynh-Thu Le, Deborah Bruner,	Journal of Clinical Oncology	January 2015	☒Submitted ☐Accepted ☐Published
2. Quality of life in a prospective phase III randomized trial of concurrent standard radiation vs. accelerated radiation plus cisplatin for locally advanced head and neck carcinoma: NRG Oncology RTOG 0129	Canhua Xiao, Qiang Zhang, Phuc Felix Nguyen-Tan, Marcie List, Randal S Weber, K. Kian Ang, David Rosenthal, Edith J Filion, Harold Kim, Craig Silverman, Adam Raben, Thomas Galloway, Andre Fortin, Elizabeth Gore, Eric Wingquist, Christopher U Jones, William Robinson, David Raben, Quynh-Thu Le, Deborah Bruner	Journal of Clinical Oncology	January 2015	☒Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes____X_____ No_____

If yes, please describe your plans:

There are 3 additional manuscripts that are currently in progress but have not yet been submitted:

1. Naresh Jha, Snehal Deshmukh, Hadi Seikaly, John R. Jacobs, A.J.B. McEwan, , Samuel Ryu, Cathy Clausen, Arnab Chakravarti, Susan Chafe, Anand K Sharma, Craig Pochini, Lorraine Portelance, Harold Kim, Schlomo Koyfman, , Quynh-Thu Le, *Results of Quality of Life for Phase II NRG RTOG 0244 Study Using Submandibular Salivary Gland Transfer Procedure for Prevention of Radiation-induced Xerostomia in Head and Neck Cancer Patients*

2. Lisa A. Kachnic, Kathryn Winter, Neal J. Meropol, Pramila Rani Anne, Stuart J. Wong, James C. Watson, Edith P. Mitchell, Jondavid Pollock, R. Jeffrey Lee, Christopher G. Willett, *Longitudinal Quality of Life (QoL) and Patient-Reported Bowel Function in NRG RTOG 0247*

3. Margaret Wilmoth, Jonathan Harris, Dian Wang, David G. Kirsch, Scott H. Okuno, Burton L. Eisenberg, John M. Kane III, X. Allen Li, David Lucas, William Kraybill, Carolyn R. Freeman, Steven Eric Finkelstein, Ying Hitchcock, Anurag K. Singh, Elizabeth Gore, Jonathan Beitler, Ivy A. Petersen, Benjamin Movsas, *Quality of Life Outcomes of a Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity*

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project.
Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

QOL endpoint in RTOG 9408, erectile dysfunction, supported the main conclusion of this landmark trial: that the efficacy gains experienced by the combined-therapy group were achieved with only some decreased erectile function at 1 year. Given that hormonal therapy can increase the risk of impotency of at least 80% compared to only 25-30% for RT alone (Banker 1988, Ray 1973, Rousseau 1988, Schover, 1993), the QOL endpoint strengthened the result of the primary endpoint of the study.

There are some cancers that lack sufficient QOL data or have inconsistent results. Rectal cancer and soft tissue sarcomas are two of these. In advanced stage head and neck squamous cell carcinomas, long-term QOL data is also limited. The results of the QOL endpoints in RTOG 0247, 0522, and 0630 are crucial to increasing our knowledge of the effects of treatment in these patient populations.

RTOG 0129 QOL results showed worse QOL in the accelerated fractionation arm as compared with the standard fractionation arm. This information is important for doctors to be aware of when treating patients. Another important conclusion of this study as well as

RTOG 0522, was the potential to use pre-treatment QOL as a stratification factor for future trials with survival as a primary endpoint.

RTOG 0622 showed that the treatment of interest, submandibular salivary gland transfer, is reproducible in a multi-institution setting and is a promising technique to prevent XRT induced xerostomia.

References:

Banker FL. The preservation of potency after external beam irradiation for prostate cancer. *Int. J. Rad. Onc. Biol. Phys.*. 15: 219-220, 1988.

Ray GR, Cassady JR, Bagshaw MA. Definitive radiation therapy of carcinoma of the prostate: a report on 15 years of experience. *Radiology* 106: 407-418, 1973.

Rousseau L, Dupont A, Labrie F, Couture M. Sexuality changes in prostate cancer patients receiving antihormonal therapy combining the antiandrogen flutamide with medical (LHRH Antagonist) or surgical castration. *Arch. Sex. Behav*. 17: 87-98, 1988.

Schover LR. Sexual rehabilitation after treatment for prostate cancer. *Cancer* 71 (3 Suppl): 1024-1030, 1993.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No___

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

PROFESSIONAL PROFILE/BIOSKETCH

NAME: PUGH, STEPHANIE SHOOK

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	DATE AWARDED *(if applicable)*	FIELD OF STUDY
University of Texas, Austin TX	B.S.	05/06	Mathematics
University of Pittsburgh, Pittsburgh PA	Ph.D.	08/10	Biostatistics

EMPLOYMENT AND POSITIONS HELD

INSTITUTION AND LOCATION	RESPONSIBILITIES	DATE
Neuro-Oncology Practice	Associate editor of biostatistics	10/2013 -
American College of Radiology, Philadelphia PA	Assistant director of statistics; design, monitoring, and analysis of clinical trials for CCOP/NCORP, brain, and genitourinary committees	9/2013 -
University of Pennsylvania, Philadelphia PA	Adjunct Scholar	6/2013 -
American College of Radiology, Philadelphia PA	Design, monitoring, and analysis of clinical trials for CCOP committee	9/2010 – 8/2013

HONORS

List any honors. Include present membership or leadership in relevant organizations or advisory groups.

2011 Outstanding Teamwork, American College of Radiology

SELECTED PEER-REVIEWED PUBLICATIONS

Ryu S, **Pugh SL**, Gerszten PC, Yin FF, Timmerman RD, Hitchcock YJ, Movsas B, Kanner AA, Berk LB, Followill DS, Kachnic LA. "RTOG 0631 Phase II/III Study of Image-Guided Stereotactic Radiosurgery for Localized (1-3) Spine Metastases: Phase II Results." *Practical Radiation Oncology*. 4(2):76-81, 2014.

Brown P, **Pugh SL**, Laack NN, Wefel JS, Khuntia D, Meyers C, Choucair A, Fox S, Suh JH, Roberge D, Kavadi V, Bentzen SM, Mehta MP, Watkings-Bruner D. "Memantine for the Prevention of Cognitive Dysfunction in Patients Receiving Whole-Brain Radiotherapy (WBRT): a Randomized, Double-Blind, Placebo-Controlled Trial Neuro-Oncology." *Neuro-Oncology*. 15(10):1429-1437, 2013.

Kachnic LA, **Pugh SL**, Tai P, Smith M, Gore E, Shah AB, Martin AG, Kim HE, Nabid A, and Lawton C. "RTOG 0518: Randomized Phase III Trial to Evaluate Zoledronic Acid for Prevention of Osteoporosis and Associated Fractures in Prostate Cancer Patients." *Prostate Cancer Prostatic Dis.* October 1, 2013; E-pub ahead of print

Hoffman KE, **Pugh SL**, James JL, Scarantino C, Movsas B, Valicenti RK, Fortin A, Pollack JD, Kim H, Brachman DG, Berk LB, Bruner DW, Kachnic LA. "The Impact of Concurrent Granulocyte Macrophage-Colony Stimulating Factor on Quality of Life in Head and Neck Cancer Patients: Results of the Randomized Placebo-Controlled Radiation Therapy Onocology Group 9901 Trial." *Quality of Life Research*. 2014 Feb 4. [Epub ahead of print]

Pisansky TM, **Pugh SL**, Greenberg RE, Pervez N, Reed DR, Rosenthal SA, Mowat RB, Raben A, Buyyounouski MA, Kachnic LA, Bruner DW. "Tadalafil to Prevent Erectile Dysfunction after Radiotherapy for Prostate Cancer – A Randomized, Double-Blind, Placebo-Controlled Trial (0831) of the Radiation Therapy Oncology Group." *JAMA*. 311(13):1300-1307, 2014.

Gondi V, **Pugh SL**, Tome WA, Caine C, Corn B, Kanner A, Rowley H, Kundapur V, DeNittis A, Greenspoon JN, Konski AA, Bauman GS, Shah S, Shi W, Wendland M, Kachnic L, Mehta M. "Preservation of Memory with Conformal Avoidance of the Hippocampal Neural Stem Cell Compartment during Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase 2 Multi-Institutional Trial." *JCO*. October 27, 2014. E-pub ahead of print.

PUBLIC SPEAKING OR PRESENTATIONS

Pugh SL, Ganz P, Deuck A, Troxel A, Dignam J. New Directions in Quality of Life Research. Invited session at the Society for Clinical Trials 34th Annual Meeting; May 19-22, 2013 in Boston, MA.

RESEARCH SUPPORT

INSTITUTION AND LOCATION	RESPONSIBILITIES	DATE
NIH/NCI/American College of Radiology	Senior biostatistician responsible for study design, monitoring, analysis, and reporting	06/01/94-05/31/15
State of Pennsylvania Department of Health	PI responsible for analysis of Quality of Life endpoints in RTOG protocols	1/1/11 – 12/31/14