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Xerostomia Health-related Quality of Life: NRG Oncology RTOG 0537

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Conflict of Interest: Dr. Singh reports that his institution has received per-case reimbursement from RTOG. Dr. Yom reports a research grant from Genentech, Inc. and royalties from UpToDate, Inc.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Author Contributions

Conception and design: Drs. Wyatt, Pugh, Wong, Sagar, Yom, Berk

Data acquisition: Drs. Wong, Sagar, Singh, Koyfman, Nguyen-Tân, Yom, Cardinale, Sultanem Hodson, Krempl, Yeh, Berk, Ms. Lukaszczyk

Data analysis and interpretation: Drs. Wyatt, Pugh, Wong, Sagar, Yom, Berk

Drafting and revision of manuscript: Drs. Wyatt, Pugh, Wong, Sagar, Singh, Koyfman, Nguyen-Tân, Yom, Cardinale, Sultanem, Hodson, Krempl, Yeh, Berk, Ms. Lukaszczyk

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Abstract

Purpose—The purpose of this secondary analysis was to determine change in overall Health-related Quality of Life (HRQOL) based on patient data obtained from NRG Oncology RTOG 0537 as measured by the RTOG-modified University of Washington Head and Neck Symptom Score (RM-UWHNSS).

Methods—A multi-site prospective randomized clinical trial design stratified 137 patients with post-radiation therapy xerostomia according to prior pilocarpine (PC) treatment and time after radiation therapy and/or chemotherapy and randomized patients into two groups. Patients were assigned to acupuncture or PC. Twenty-four sessions of acupuncture-like transcutaneous nerve stimulation (ALTENS) were administered over 12 weeks, or oral PC (5 mg) three times daily over the same 12 weeks. The RM-UWHNSS was administered at baseline and at 4, 6, 9 and 15 months after the date of randomization.

Results—There were no between-arm differences in change scores on the RM-UWHNSS in the individual items, total score, or factor scores. For statistical modeling, race and time were significant for all outcomes (total and factor scores), while treatment arm was not significant. The ALTENS arm showed greater yet non-significant improvement on outcomes compared to the PC arm.

Conclusion—Although no significant treatment differences were seen in this trial, patients receiving ALTENS consistently had lower scores, indicating better function, as compared to those receiving PC. Radiation-induced xerostomia improved over time for all patients.

Keywords

Radiation-induced xerostomia (RIX); symptom management; head & neck cancer; acupressure-like transcutaneous nerve stimulation (ALTENS)

Introduction

Xerostomia is a common symptom among head and neck cancer patients undergoing external beam radiation. Xerostomia occurs in about 65% [1] of head and neck cancer patients who receive external beam radiation. This symptom can be distressing and cannot be reversed. Cholinergic agonists such as pilocarpine (PC) have minimal benefit and significant side effects [2]. Post-radiation xerostomia has been shown to reduce health related quality of life (HRQOL) [1].

One non-invasive therapy that has potential to improve post-radiation xerostomia is acupuncture-like transcutaneous nerve stimulation (ALTENS) [3]. ALTENS is a non-invasive alternative to needle acupuncture that provides low-intensity stimulation to acupuncture points. Eliminating the requirement for invasive needling allows ALTENS treatments to be administered with minimal training, requiring primarily the knowledge of the location of the active acupuncture points.

The Radiation Therapy Oncology Group (RTOG) conducted a Phase II study of ALTENS for radiation-induced xerostomia wherein patients reported improved saliva production and a reduction in xerostomia symptoms, there was no significant change in HRQOL when

compared with baseline data [3].The RTOG then completed a randomized trial of ALTENS for radiation-induced xerostomia, NRG Oncology RTOG 0537, which showed that ALTENS did not increase whole salivary production over that seen with PC [4].

However, the sensation of xerostomia is a complex phenomenon, and patients may benefit from ALTENS beyond just whole salivary production. Therefore, this is a secondary analysis of the change in overall HRQOL, as measured by the RTOG-modified University of Washington Head and Neck Symptom Score (RM-UWHNSS) for the NRG Oncology RTOG 0527 patients. Specifically assessed was the effect of treatment on the total and subscale score across time while adjusting for patient and clinical factors.

Materials and Methods

Eligibility criteria

Inclusion criteria were:

1. age ≥18 years;
2. completion of radiation (intensity modulated, IMRT or standard conformal) with or without chemotherapy 3 months to 2 years before study entry;
3. no evidence of head/neck disease recurrence and patients who were disease free from other invasive malignancies for at least 3 years prior to study entry;
4. reported grade 1 or higher xerostomia (CTCAE v3.0) with a residual basal WSP ≥ 0.1 ml per minute;
5. 0 to 2 Zubrod performance status;
6. if receiving PC or cevimeline, were required to discontinue these medications at least 2 weeks prior to randomization.

Exclusion criteria included unstable cardiac disease, pacemaker in-situ, chronic obstructive pulmonary disease, respiratory illness requiring hospitalization, acute bacterial or fungal infection requiring intravenous treatments and pregnancy.

The study was reviewed and approved by the Institutional Review Board at the participating institutions. Written informed consent was obtained from all patients prior to randomization.

Study design

This phase II–III randomized clinical trial (RCT) was conducted comparing ALTENS with oral PC [5,6]. The phase II portion was designed to determine feasibility of delivery of ALTENS at multiple sites and measured preliminary efficacy. The phase III portion stratified patients according to prior PC treatment and time after radiation therapy and/or chemotherapy (Figure 1). Zelen's treatment allocation scheme was used to balance patient factors other than institutions [7]. Within each stratum, patients were randomized in a 1:1 ratio to either ALTENS or PC treatment.

Instrument

Patient-reported HRQOL assessment was prospectively measured using the RM-UWHNSS (Appendix 1). It contains components of the original UWHNSS and additional questions assessing pain and mucous resulting in 15 total items. The UWHNSS is a self-administered, validated instrument designed for head and neck cancer patients with varying tumor sites and stages that has demonstrated responsiveness to clinical change [8]. The four major discriminant factors have been determined to be mucous amount and consistency, eating, pain, and activities. The RM-UWHNSS contains the employment question from UWHNSS version 1, all questions in the UWHNSS version 3 except for shoulder disability [9], and additional questions assessing mouth pain, throat pain, mucous amount, and mucous consistency. It has been used in previous RTOG clinical trials including RTOG 9901 and RTOG 0244. The item format for new items is modeled after the question stems for the original UWHNSS. Each question has five levels of functioning (Likert-type scale), ranging from no dysfunction to total dysfunction. For each question, patients are instructed to circle the statement that best describes their level of function during the past week. The RM-UWHNSS was administered at baseline and at 4, 6, 9 and 15 months after the date of randomization.

Intervention Arms

ALTENS Arm—ALTENS treatments were administered with a Codetron™ (model 902-C, EHM Rehabilitation Technologies Ltd., Ontario, Canada) trans-epidermal neural stimulator (TENS) unit and Karaya electrode pads. Bilateral acupuncture points: SP6, ST36, LI4 using negative electrodes and CV24 using the positive electrode were stimulated [3,5]. Sequences of 250 millisecond square pulses with a 4 Hz repetition rate were delivered. Each acupuncture point, except CV24, was stimulated for 10 seconds at a time. CV24, the site for the common electrode, was stimulated throughout the treatment session. Stimulation intensity (between level 3 to 6 on the machine) was adjusted to produce a deep strong aching sensation at each acupuncture point. Random switching among electrodes enabled by the Codetron™ embedded random circuit was employed to prevent brain habituation to stimulation [10].

ALTENS treatment was started within 14 days after study enrollment. All patients were scheduled for 24 ALTENS sessions (20 minutes each, two sessions per week), over 12 weeks. Two weeks without treatment was allowed and all outstanding sessions were administered in the remainder of the 12 week period, not to exceed three sessions per week. All treatments were delivered at RTOG participating academic and community-based institutions.

Staff administering the ALTENS received training at RTOG meetings. Slides of training materials and a training video were posted on the RTOG website. For each patient, photographs of electrode pad positions on the acupuncture points were sent electronically to the principal investigator for rapid approval before the third treatment session.

Pilocarpine (PC) Arm—PC is the most commonly used sialogogic agent approved by the FDA for RIX. Pilocarpine is a naturally occurring alkaloid that is a muscarinic-cholinergic

agonist, and it causes stimulation of cholinergic receptors on the surface of the salivary exocrine glands, resulting in salivation [11].

For this study, the PC treatment started within 14 days of enrollment. Patients received 5 mg PC orally three times daily for 12 weeks and then stopped. There was no make-up for missed doses. Dose modification was permitted due to PC intolerance. Patients completed drug diaries and returned all medications for counting to determine treatment compliance.

Statistical considerations

Descriptive statistics were generated to characterize the study cohort. Patients who completed the 15-item RTOG-modified UWHNSS were compared to those who did not complete it. Respondents in the two arms were compared at each time point. Fisher's exact test was used to compare categorical variables. Wilcoxon–Mann–Whitney test using the normal approximation and t-test were used to compare continuous variables depending on the normality of the data. RTOG-modified UWHNSS factor domain and total symptom scores were averaged using all items answered by the patient, similar to that of the validated tool. Specifically, for the total score, at most two missing items were permitted (B. Yueh, personal communication, 2012) while subscale scores required all items to be completed.

All item scores were transformed onto a scale from 20 to 100 with a score of 100 indicating poor HRQOL and a score of 20 indicating good HRQOL. Change scores were calculated by subtracting baseline scores from follow-up scores (follow-up – baseline). Thus a positive change score indicates a worsening HRQOL while a negative change score indicates an improvement. Change in individual question scores, factor domain scores, and total symptom score from baseline were evaluated at all follow-up time points (3, 6, 9, and 15 months). Graphs with 95% confidence intervals demonstrated the change in factor scores and total score over time for all patients. Following a previous analysis using the RTOG-modified UWHNSS, a 5 point difference in the mean change score was determined to be meaningful (Hoffman 2014) [12]. Potential floor and ceiling effects for deterioration status were evaluated using the 5 point difference.

A linear fixed-effect model, using maximum likelihood as the method of estimation with random intercepts and slopes, was constructed for the total symptom score and each factor score. Baseline score, time, and treatment arm were forced into the model as covariates. Time-by-treatment interaction, stratification factors and other baseline characteristics such as age (< 60 vs. ≥ 60 years old, Zubrod performance status (0 vs. 1, 2), gender (male vs. female), race (white vs. other), country (US vs. Canada), and prior chemotherapy (yes vs. no) were also considered for inclusion. Variables were retained in the model if $\rho < 0.10$.

To adjust for multiplicity while accounting for the correlated nature of the items and factors, alpha = 0.01 was used when testing the 15 items individually and the 4 factors. An alpha = 0.05 was used for all other tests, including the total score. All data were analyzed with SAS (v9.2 for Windows, SAS institute, Cary, NC) [13].

Results

To answer the Phase II portion of the study, the designed was feasible for delivery of ALTENS at multiple sites while measuring preliminary efficacy. Of these 146 eligible patients, 137 consented to participate in the HRQOL portion of the study and all of these patients completed the RM-UWHNSS at least once during the study (Figure 2). Pretreatment characteristics were similar between study arms (Table 1). Compliance for use of the tool was also relatively high with the lowest completion rate of 64.7% occurring at 15 months in the PC arm. Patients had similar baseline scores (Table 2).

In answer to the phase III (primary aim) of this secondary analysis, there were no differences in change scores in the individual items, total score, or factor scores (results not shown) of the RM-UWHNSS. Due to the strong correlations between baseline and follow-up scores as well as the lack of any differences in baseline scores between treatment arms, baseline was included as part of the outcome variable in the longitudinal models rather than as a covariate.

For the statistical modeling of the total and subscale scores, race and time were significant for all outcomes (total and factors scores) while treatment arm was not significant (Table 3). Specifically, time had a negative effect, meaning that scores improved over time, as seen in Figure 3. White patients tended to have better scores than non-white patients for total score and all four factor scores. Patients with prior chemotherapy tended to demonstrate more dysfunction in terms of the total score and eating factor score than patients with no prior chemotherapy (estimate of 4.10, $p=0.058$ for total score; estimate of 6.03, $p=0.034$ for eating factor score). Patients with prior PC use had a better mucus factor score meaning less dysfunction (estimate = −8.95, $p=0.023$). Patients with a Zubrod of 1 or 2 tended to have a poorer activity score, or more dysfunction, than patients of Zubrod 0. There were minimal ceiling effects, but due to the large number of floor effects, deterioration was measured as decline vs. no decline since many patients were unable to improve. There were no significant differences in deterioration status for each item at any of the follow-up time points between the treatment arms (results not shown).

Discussion

Although no significant treatment differences were seen in this prospective phase III trial evaluating ALTENS vs. PC in treating radiation-induced xerostomia, patients receiving ALTENS consistently had lower scores on the RM-UWHNSS, indicating better function, as compared to those receiving PC (Figure 2). A similar trend was noted in the primary analysis of this trial using a different xerostomia measure, The University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS) (Wong, 2015). Patients in both arms had similar baseline scores, and no significant differences were found with respect to change from baseline or deterioration status for the total score and each factor score. RIX did improve over time for all patients. Finally, the consistent positive trends noted in the ALTENS arm may suggest ALTENS can enhance recovery of salivary function. Future research is warranted to examine this hypothesize.

This study is distinct from other studies addressing RIX because it was a large randomized trial that incorporated both the standard of care with PC and introduced acupressure-like ALTENS, plus it included formal patient-reported assessments [14–16]. It is of utmost importance to include patient-reported end points on symptom intervention trials [17].

One limitation was the lower than anticipated patient compliance. The total score of the RM-UWHNSS had only 61% statistical power to detect an effect size of 0.5 at 9 months. The number of patients who withdrew consent was 16 with 11 patients enrolled on the PC arm. A large contributing factor to missing data was the number of consent withdrawals, which were almost double in the PC arm. This was a substantial case of missing data, and contributed to the imbalance in evaluable patients between the arms. Patients appeared to be missing at random, but there may have been unaccounted differences between patients in the ALTENS and PC arms. Second, although the phase III portion of the protocol called for a sample size of 144 patients, only 103 were evaluated for the RTOG-modified UWHNSS end point; therefore, the lack of difference between ALTENS and PC may have been a result of insufficient sample size.

Despite the challenges of this study, ALTENS produced comparable HRQOL to PC. It is also important to note the non-invasive and non-medicating factors associated with ALTENS. Further, no side effects are noted with ALTENS. Anecdotally, study clinicians reported that more patients dropped out of the PC arm because they were looking for a non-medication intervention and preferred to not be inconvenienced by visits for standard of care medication and monitoring. When designing HRQOL studies, convenience and patient burden must be major considerations.

Given the considerable morbidity associated with RIX, efforts are still needed to more successfully intervene to prevent or diminish this incapacitating toxicity. While there are new initiatives on the horizon such as gland sparing RT, gene transfer and bone marrow cells, the discovery must go on for ways to improve salivary gland function [18,19]. Finally, symptom intervention trials must continue to include patient-reported outcomes since provider perceptions of RIX can differ from patient perception of symptom burden [20].

Acknowledgments

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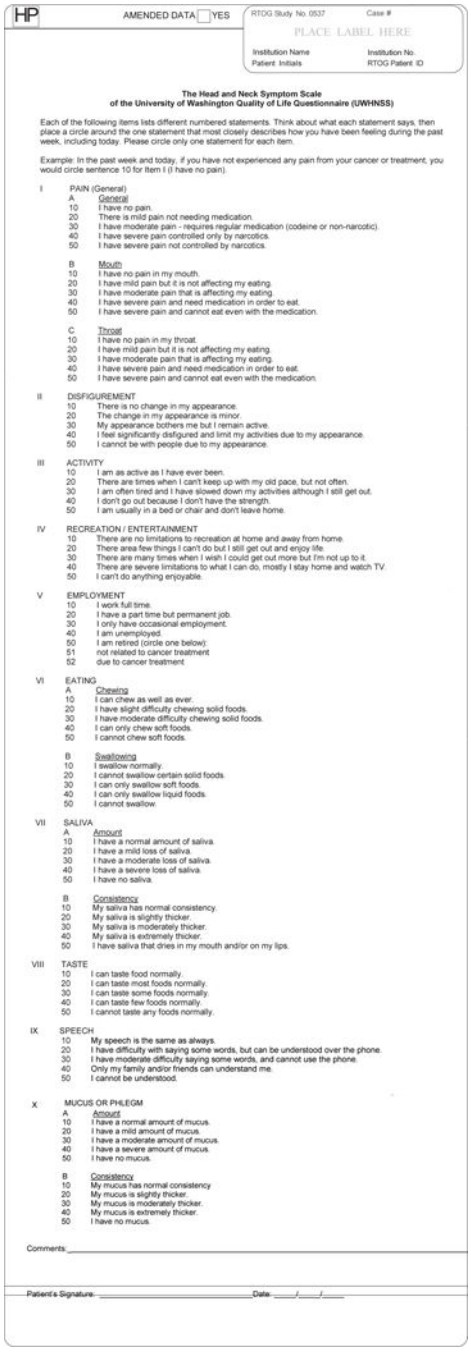
Appendix 1–The Head and Neck Symptom Scale of the University of Washington Quality of Life Questionnaire (UWHNSS)



HP AMENDED DATA ☐ YES

RTOG Study No. 0537 Case #

PLACE LABEL HERE

Institution Name Institution No.

Patient Initials RTOG Patient ID

The Head and Neck Symptom Scale
of the University of Washington Quality of Life Questionnaire (UWHNSS)

Each of the following items lists different numbered statements. Think about what each statement says, then place a circle around the one statement that most closely describes how you have been feeling during the past week, including today. Please circle only one statement for each item.

Example: In the past week and today, if you have not experienced any pain from your cancer or treatment, you would circle sentence 10 for Item I (I have no pain).

I PAIN (General)
A General
10 I have no pain.
20 There is mild pain not needing medication.
30 I have moderate pain - requires regular medication (codeine or non-narcotic).
40 I have severe pain controlled only by narcotics.
50 I have severe pain not controlled by narcotics.

B Mouth
10 I have no pain in my mouth.
20 I have mild pain but it is not affecting my eating.
30 I have moderate pain that is affecting my eating.
40 I have severe pain and need medication in order to eat.
50 I have severe pain and cannot eat even with the medication.

C Throat
10 I have no pain in my throat.
20 I have mild pain but it is not affecting my eating.
30 I have moderate pain that is affecting my eating.
40 I have severe pain and need medication in order to eat.
50 I have severe pain and cannot eat even with the medication.

II DISFIGUREMENT
10 There is no change in my appearance.
20 The change in my appearance is minor.
30 My appearance bothers me but I remain active.
40 I feel significantly disfigured and limit my activities due to my appearance.
50 I cannot be with people due to my appearance.

III ACTIVITY
10 I am as active as I have ever been.
20 There are times when I can't keep up with my old pace, but not often.
30 I am often tired and I have slowed down my activities although I still get out.
40 I don't go out because I don't have the strength.
50 I am usually in a bed or chair and don't leave home.

IV RECREATION / ENTERTAINMENT
10 There are no limitations to recreation at home and away from home.
20 There area few things I can't do but I still get out and enjoy life.
30 There are many times when I wish I could get out more but I'm not up to it.
40 There are severe limitations to what I can do, mostly I stay home and watch TV.
50 I can't do anything enjoyable.

V EMPLOYMENT
10 I work full time.
20 I have a part time but permanent job.
30 I only have occasional employment.
40 I am unemployed.
50 I am retired (circle one below):
51 not related to cancer treatment
52 due to cancer treatment

VI EATING
A Chewing
10 I can chew as well as ever.
20 I have slight difficulty chewing solid foods.
30 I have moderate difficulty chewing solid foods.
40 I can only chew soft foods.
50 I cannot chew soft foods.

B Swallowing
10 I swallow normally.
20 I cannot swallow certain solid foods.
30 I can only swallow soft foods.
40 I can only swallow liquid foods.
50 I cannot swallow.

VII SALIVA
A Amount
10 I have a normal amount of saliva.
20 I have a mild loss of saliva.
30 I have a moderate loss of saliva.
40 I have a severe loss of saliva.
50 I have no saliva.

B Consistency
10 My saliva has normal consistency.
20 My saliva is slightly thicker.
30 My saliva is moderately thicker.
40 My saliva is extremely thicker.
50 I have saliva that dries in my mouth and/or on my lips.

VIII TASTE
10 I can taste food normally.
20 I can taste most foods normally.
30 I can taste some foods normally.
40 I can taste few foods normally.
50 I cannot taste any foods normally.

IX SPEECH
10 My speech is the same as always.
20 I have difficulty with saying some words, but can be understood over the phone.
30 I have moderate difficulty saying some words, and cannot use the phone.
40 Only my family and/or friends can understand me.
50 I cannot be understood.

X MUCUS OR PHLEGM
A Amount
10 I have a normal amount of mucus.
20 I have a mild amount of mucus.
30 I have a moderate amount of mucus.
40 I have a severe amount of mucus.
50 I have no mucus.

B Consistency
10 My mucus has normal consistency.
20 My mucus is slightly thicker.
30 My mucus is moderately thicker.
40 My mucus is extremely thicker.
50 I have no mucus.

Comments: _____

Patient's Signature: _____ Date: ____/____/____

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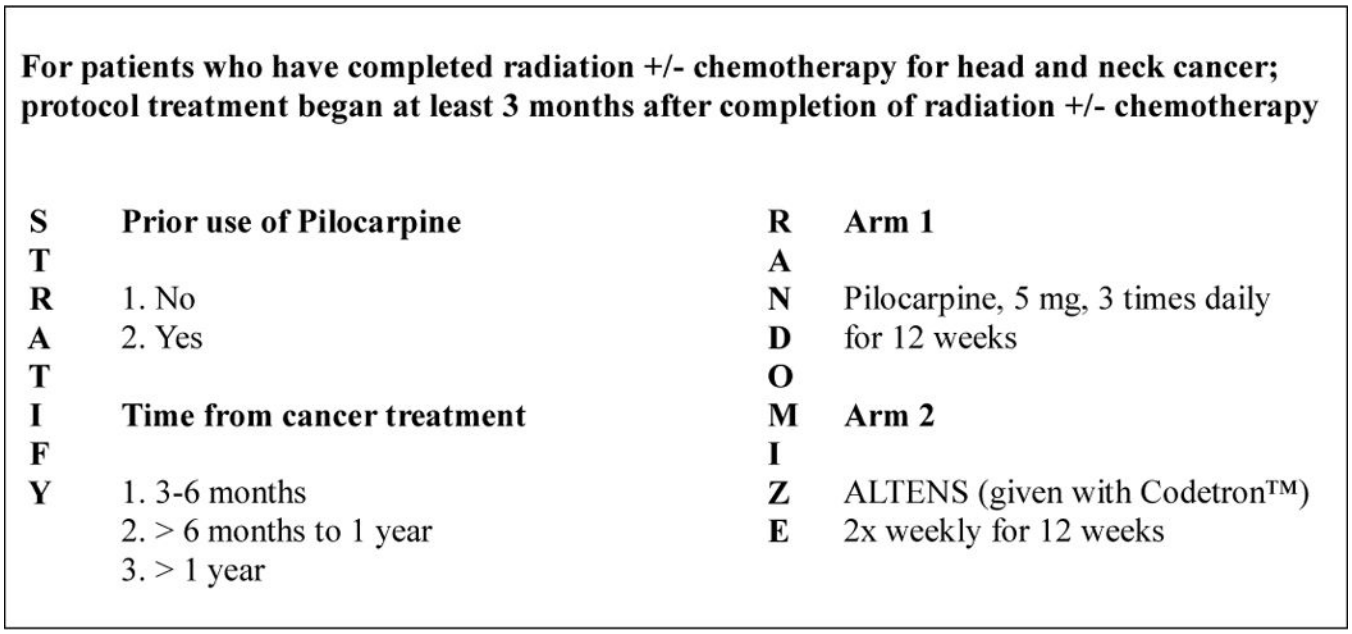

Fig. 1.
NRG Oncology/RTOG 0537 Study Schema

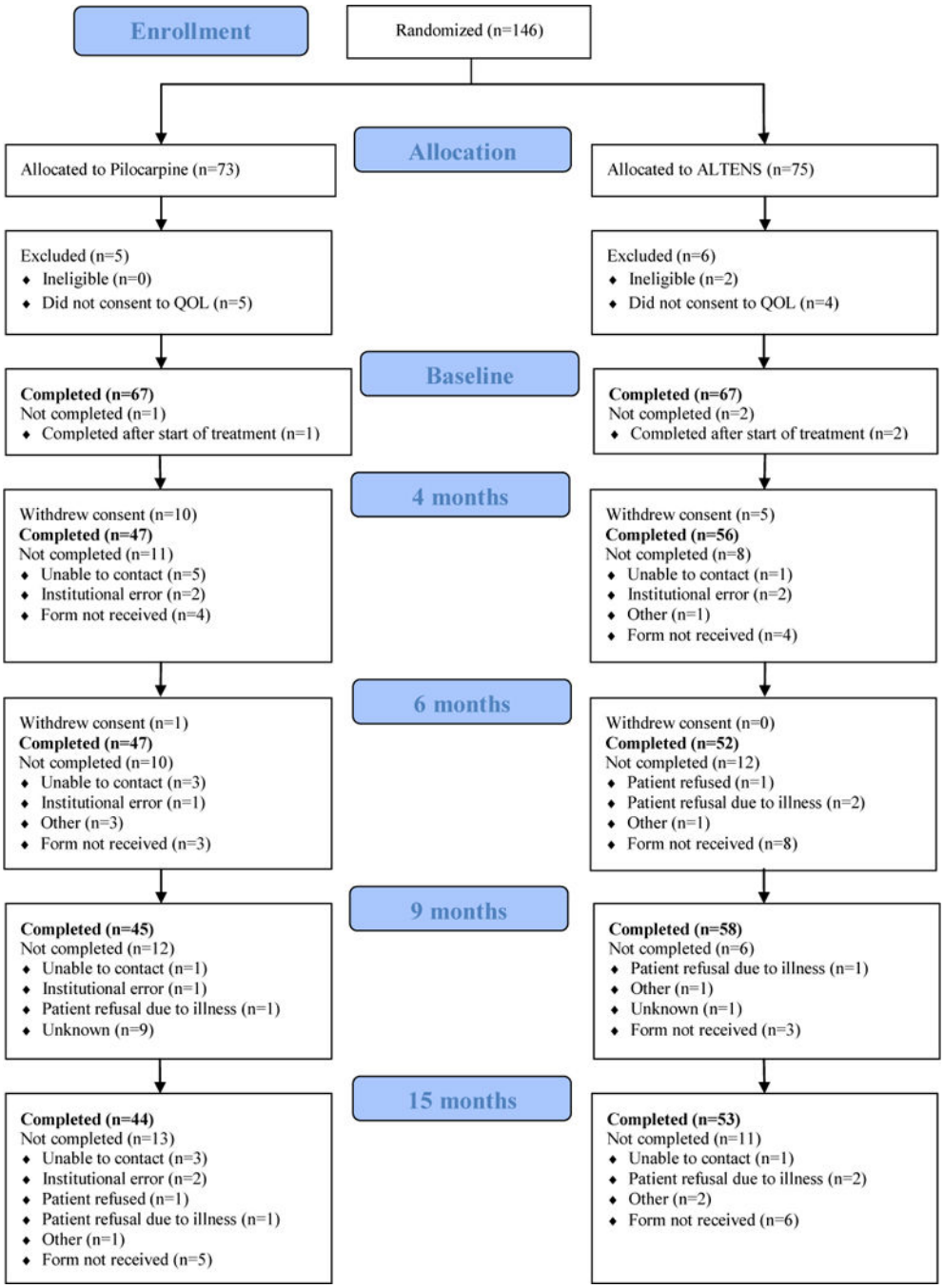

Fig 2.
CONSORT Diagram

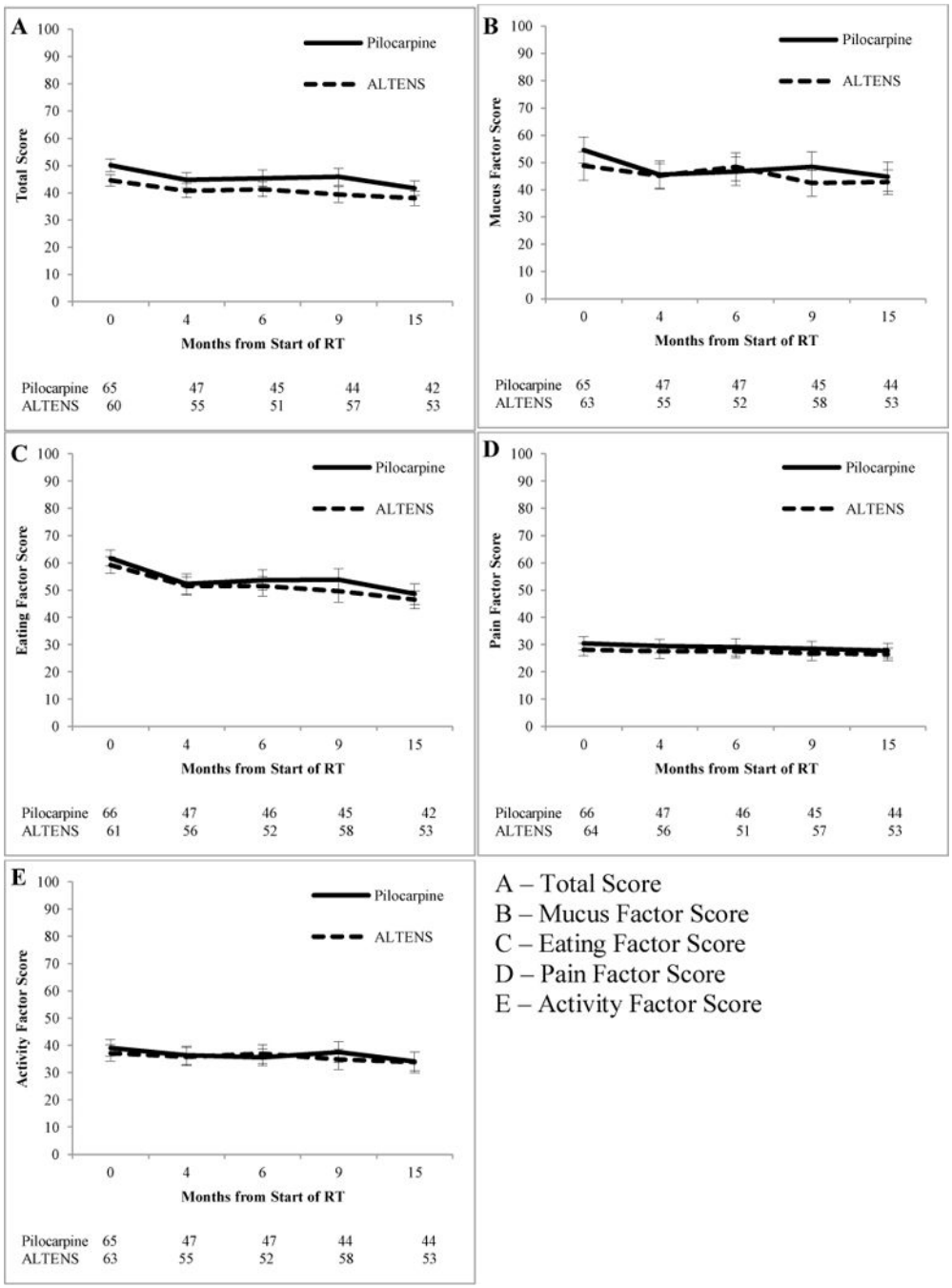

Fig. 3.

A Comparison of ALTENS vs. PC in Treating Radiation-Induced Xerostomia using the RM-UWHNSS

Table 1

Pretreatment Characteristics of Patients who Consented to QOL

	Pilocarpine (n=68)	ALTENS (n=69)	P-value[§]
Age (years)			
Median	58.5	58	0.61[†]
Min – Max	29 – 78	46 – 72	
Q1 – Q3	52.5 – 63	53 – 65	
Gender			
Male	59 (86.8%)	59 (85.5%)	0.99
Female	9 (13.2%)	10 (14.5%)	
Race			
American Indian or Alaska Native	1 (1.5%)	2 (2.9%)	0.51
Asian	4 (5.9%)	2 (2.9%)	
Black or African American	5 (7.4%)	2 (2.9%)	
White	58 (85.3%)	63 (91.3%)	
Ethnicity			
Hispanic or Latino	5 (7.4%)	1 (1.4%)	0.13
Not Hispanic or Latino	59 (86.8%)	66 (95.7%)	
Unknown	4 (5.9%)	2 (2.9%)	
Zubrod Performance Status			
0	55 (80.9%)	56 (81.2%)	0.99
1	13 (19.1%)	12 (17.4%)	
2	0 (0.0%)	1 (1.4%)	
Country of Residence			
United States	50 (73.5%)	50 (72.5%)	0.99
Canada	18 (26.5%)	19 (27.5%)	
Prior Chemotherapy			
No	13 (19.1%)	12 (17.4%)	0.83
Yes	55 (80.9%)	57 (82.6%)	
Time since RT +/− Chemotherapy[*]			
3–6 months ago	18 (26.5%)	18 (26.1%)	0.99
More than 6 months to 1 year ago	26 (38.2%)	27 (39.1%)	
1–2 years ago	24 (35.3%)	24 (34.8%)	
Prior Use of Pilocarpine[*]			
No	58 (85.3%)	58 (84.1%)	0.99
Yes	10 (14.7%)	11 (15.9%)	

[*] Stratification factor;

[§] P-value from fisher's exact test

[†] P-value from two-sided t-test assuming equal variances

Q1 = first quartile; Q3 = third quartile.

Table 2

RTOG-Modified UWHNSS Baseline Score

	Pilocarpine	ALTENS	P-value§
Total Score	(n=65)	(n=60)	
Mean (Std. Dev.)	47.9 (11.1)	44.5 (10.1)	0.23*
Median (Range)	49.1 (25.5–72.7)	43.6 (27.3–74.5)	
Mucus Factor Score	(n=65)	(n=63)	
Mean (Std. Dev.)	54.6 (23.1)	48.7 (24.7)	
Median (Range)	60.0 (20.0–100.0)	40.0 (20.0–100.0)	0.22
Eating Factor Score	(n=66)	(n=61)	
Mean (Std. Dev.)	61.7 (14.7)	59.3 (14.3)	
Median (Range)	60.0 (30.0–90.0)	55.0 (35.0–100.0)	0.44
Pain Factor Score	(n=66)	(n=64)	
Mean (Std. Dev.)	30.4 (11.9)	28.1 (10.9)	
Median (Range)	26.7 (20.0–60.0)	20.0 (20.0–60.0)	0.32
Activity Factor Score	(n=65)	(n=63)	
Mean (Std. Dev.)	39.1 (14.3)	37.1 (14.1)	
Median (Range)	40.0 (20.0–70.0)	40.0 (20.0–80.0)	0.73

Table 3

Fixed Effects Model

	Estimate (Std Error)	P-value*
Total Score		
Treatment (ALTENS vs. **Pilocarpine**)	−1.87 (1.66)	0.260
Time	−1.53 (0.23)	<0.001
Prior Chemotherapy (Yes vs. **No**)	4.10 (2.15)	0.058
Race (White vs. **Other**)	−10.04 (2.61)	<0.001
Mucus Factor		
Treatment (ALTENS vs. **Pilocarpine**)	−2.71 (2.89)	0.349
Time	−1.73 (0.64)	0.008
Race (White vs. **Other**)	−10.22 (4.59)	0.027
Prior Pilocarpine (Yes vs. **No**)	−8.95 (3.93)	0.023
Eating Factor		
Treatment (ALTENS vs. **Pilocarpine**)	−2.33 (2.18)	0.286
Time	−2.61 (0.32)	<0.001
Prior Chemotherapy (Yes vs. **No**)	6.03 (2.83)	0.034
Race (White vs. **Other**)	−12.27 (3.45)	<0.001
Pain Factor		
Treatment (ALTENS vs. **Pilocarpine**)	−1.23 (1.68)	0.464
Time	−0.43 (0.21)	0.049
Race (White vs. **Other**)	−6.35 (2.65)	0.017
Activity Factor		
Treatment (ALTENS vs. **Pilocarpine**)	−1.41 (2.09)	0.845
Time	−0.69 (0.28)	0.017
Race (White vs. **Other**)	−10.68 (3.39)	0.002
Zubrod (1,2 vs. **0**)	5.11 (2.73)	0.062

*P-value from t-test in comparison to the reference level

Bolded level is the Reference level.

Variables considered in model: age, Zubrod, gender, race, country, prior chemotherapy, time from end of prior therapy to registration, prior pilocarpine