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A Randomized Phase II Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis During the Treatment of Lung Cancer: Results of NRG Oncology RTOG 1012

Shannon Fogh, MD[1], **Snehal Deshmukh, MS**[2], **Lawrence B. Berk, MD**[3], **Amylou C. Dueck, PhD**[4], **Kevin Roof, MD**[5], **Sherif Yacoub, MD, PhD**[6], **Thomas Gergel, MD**[7], **Kevin Stephans, MD**[8], **Andreas Rimner, MD**[9], **Albert DeNittis, MD, MS**[10], **John Pablo, MD**[11], **Justin Rineer, MD**[12], **Terence M. Williams, MD, PhD**[13], and **Deborah Bruner, PhD, RN, FAAN**[14]

[1]University of California San Francisco, San Francisco, CA

[2]NRG Oncology Statistics and Data Management Center, Philadelphia, PA

[3]University of South Florida, Tampa, FL

[4]Mayo Clinic in Arizona, Scottsdale, AZ

[5]Southeast Cancer Control Consortium, Inc., CCOP, Winston-Salem, NC

[6]York Cancer Center, York, PA

[7]Geisinger Medical Center CCOP, Danville, PA

[8]Cleveland Clinic Foundation, Cleveland, OH

[9]Memorial Sloan Kettering Cancer Center, New York, NY

[10]Main Line CCOP, Wynnewood, PA

[11]Lewis Cancer & Research Pavilion at St. Joseph's/Candler, Savannah, GA

[12]UF Health Cancer Center – Orlando Health, Orlando, FL

[13]Ohio State University Medical Center, Columbus, OH

[14]Emory University, Atlanta, GA

Abstract

Corresponding author: Shannon E. Fogh MD, Department of Radiation Oncology, University of California San Francisco, 505 Parnassus Ave, Room L-08, Box 0226, San Francisco, CA 94143, Office: 415-353-8950, Fax: 415-353-8679, Shannon.Fogh@ucsf.edu.

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Purpose—Randomized trials have shown that honey is effective for prevention of radiation-induced mucositis in head and neck cancer patients. Because there is no efficacious preventative for radiation esophagitis in lung cancer patients, this trial compared liquid honey, honey lozenges, and standard supportive care for radiation esophagitis.

Methods—Patients were stratified by percentage of esophagus receiving specific radiation dose (V60Gy esophagus < or ≥ 30%), then randomized between supportive care, 10 ml of liquid Manuka honey four times a day or 2 lozenges (10 ml of dehydrated Manuka honey) four times a day during concurrent chemotherapy and radiotherapy. The primary endpoint was patient-reported pain on swallowing utilizing an eleven point (0–10) scale at 4 weeks (Numerical Rating Pain Scale, NRPS). The study was designed to detect 15% relative reduction of change in NRPS score. Secondary endpoints were trend of pain over time, opioid use, clinically-graded and patient-reported adverse events, weight loss, dysphagia, nutritional status and quality of life.

Results—53 patients were randomized to supportive care, 54 randomized to liquid honey and 56 to lozenge honey. There was no significant difference in the primary endpoint of change in the NRPS at 4 weeks between arms. There were no differences in any of the secondary endpoints except for opioid use at 4 weeks during treatment between the supportive care and liquid honey arms which was found to be significant (p=0.03) with more patients on the supportive care arm taking opioids.

Conclusion—Honey as prescribed within this protocol was not superior to best supportive care in preventing radiation esophagitis. Further testing of other types of honey and research into the mechanisms of action are needed.

Keywords

Manuka honey; esophagitis; radiotherapy; radioprotective agents

Introduction

Esophagitis is a painful and often dose-limiting toxicity in combined therapy for advanced lung cancer. The risk of severe esophagitis increases with induction and concurrent chemotherapy, hyperfractionation, and concomitant boosts.[1–7]

Agents used to prevent esophagitis have demonstrated conflicting results. In pre-clinical and clinical trials, amifostine has demonstrated potential.[8–13] However, a phase III randomized trial (RTOG 9801),[14] found no significant impact on severe esophagitis in patients who received amifostine, although the study did demonstrate significant improvement in patient-reported swallowing function. Non-steroidal agents have also failed to demonstrate reduction in radiation esophagitis.[15,16]

Honey has been used for centuries for wound healing,[17] and several randomized trials have demonstrated its effectiveness in this setting.[18–21] Compelling attributes of honey include its bacteriostatic, antifungal and anti-viral properties.[22,23] Small, randomized trials using honey for prevention of radiation mucositis in patients receiving radiation for head and neck cancers found significant benefit and reduction in mucositis in the groups receiving honey.[24–27] In addition, honey was well tolerated with minimal toxicity.

Given the common mechanistic pathways of mucositis and esophagitis, NRG Oncology developed this randomized phase II trial, NRG Oncology RTOG 1012 (ClinicalTrials.gov Identifier: NCT01262560), to assess the effect of Manuka honey on radiation-induced esophagitis.

Materials and Methods

Patients

Eligible patients had diagnosis of small cell or non-small cell lung cancer being treated with once daily radiation therapy to ≥ 60 Gy and concurrent chemotherapy. At least 5 cm of the esophagus was required within the 60 Gy isodose volume. Patients with metastatic disease, uncontrolled diabetes, hypersensitivity to honey, inability to swallow thick liquids, prior chemotherapy or radiation therapy were ineligible. All patients signed a study specific informed consent prior to participation.

Study design

All institutions obtained institutional review board approval prior to patient recruitment. Patients were stratified according to percentage of esophagus receiving 60 Gy (V60Gy < 30% vs. V60 ≥30%). Patients were randomized using permuted block randomization[28] to receive standard supportive care (Arm 1), 40 ml of liquid Manuka honey (Arm 2) or 8 Manuka honey lozenges (Arm 3) during concurrent chemoradiation.

Treatment

Manuka honey (*Leptospermum scoparium*) was chosen to reduce inhomogeneity; inherent in honey and minimize variability in the treatment regimen. It is a thoroughly tested standardized honey representing the medicinal standard.[29–31] It differs from other honeys as it maintains antibacterial effect after hydrogen peroxide removal. This antibacterial activity is numbered (based on similarity to phenol effectiveness) and referred to as the “Unique Manuka Factor” (UMF). A UMF of 10 would have bacteriostatic properties of 10% phenol solution. The suppliers also provided lozenges made by evaporating most water from the honey to allow testing of whether an innate factor in the honey influenced mucositis or if liquid form is required for benefit.

Manuka 16 was utilized based on availability and the UMF rating was documented by the growers. To sterilize the honey to ensure known pathogens were not present, the honey was irradiated to 30 kGy based on a study showing that at least 25 kGy is needed for sterilization.[32] Irradiation has been shown not to affect honey’s antibacterial qualities.[33] For quality assurance, 1% of the honey was randomly selected by EMSL Analytical, Inc. for testing for clostridium, osmolality, and sugar content.

Patients in either experimental arm were instructed to take 10 cc of liquid Manuka honey or 2 lozenges 4 times per day, over an approximately 12 hour period daily during concurrent chemoradiation. Patients were instructed to refrain from eating or drinking one hour after swallowing. Patients were considered compliant if they took ≥15 doses per week. Control group patients received standard supportive care. A compound containing viscous lidocaine

and magnesium aluminum oxide (Maalox®) was recommended with liquid or solid oxycodone, 5–10 mg, every 3 hours as needed.

Assessments

Patient-reported esophagitis-related pain associated with swallowing on the Numerical Rating Pain Scale, NRPS, was collected at baseline, weekly during treatment, and 12 weeks from start of treatment. The NRPS uses an 11-point scale (0–10). Composites of 0–10 ratings have demonstrated maximal reliability when measuring pain intensity with small sample sizes or in clinical scenarios requiring tracking of changes in pain.[34] Additionally, a patient-reported dysphagia log was collected during treatment and 12 weeks from start of treatment.

The EORTC Quality of Life Questionnaire (QLQ-C30) global health status and pain subscales were collected at baseline, 4 and 12 weeks. The global health status subscale includes two questions on the patient's rating of his/her health and quality of life (QOL). Response options are on a 1–7 Likert scale with 1 representing "very poor" and 7 "excellent". The pain subscale includes two questions to understand if the patient has pain or if pain interfered with daily activities. It is scored on a 1–4 Likert scale with 1 representing "not at all" and 4 representing "very much".[35]

Patients completed up to 53 items measuring 30 adverse events from the Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE) library at baseline, weekly during treatment, and at 12 weeks. The library contains items for patients to self-report adverse events including frequency, severity, and/or interference with usual or daily activities on 5-level verbal descriptor scales (e.g., for severity, 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe).[36,37] Adverse events were selected based on common adverse events across cancer patients[38] as well as additional adverse events related to the study patients, radiation and honey treatments.

Patients' weight, nutritional status, and opioid use were collected pre-treatment and at treatment week 4. Adverse events were measured by the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.

Endpoints

The primary endpoint was to evaluate the relative efficacy of Manuka honey to delay or prevent radiation esophagitis-related pain during chemoradiation for lung cancer compared to standard supportive treatment as measured by NRPS for pain upon swallowing at 4 weeks. Secondary endpoints included esophagitis related pain trends using weekly NRPS measurements, QOL and pain as measured by the EORTC QLQ-C30, and patient reported dysphagia with a patient log. Additional secondary endpoints included weight loss and nutritional status at 4 weeks, opioid use as demonstrated by patient's narcotic use in the 24 hours prior to weekly evaluation, adverse events as measured by CTCAE v. 4 and PRO-CTCAE.

Statistical Design

This study was designed based on the mean increase in pain severity on RTOG 9801, measured by the pain subscale of the EORTC QLQ-C30, which was 20.9 (standard deviation [SD] =5.9). Despite restricting use of hyperfractionation and allowing non-NSCLC patients in this trial, patients receiving standard supportive care (Arm 1) were expected to have a similar increase in esophagitis-related pain from pre-to-post chemoradiation; patients receiving Manuka honey were expected to experience less pain. Based on a two sample t-test for difference of means at a significance level of 0.05 after adjusting for multiple comparisons (one-sided with an overall significance level of 0.1 before the Bonferroni adjustment) and 80% statistical power for each hypothesis test, 45 patients per arm were required to detect at least 15% relative reduction (absolute difference of mean change score of 3.1) in the NRPS score change at 4 weeks from baseline. Patients randomized to receive honey but did not receive any or those that required a feeding tube were considered inevaluable for analysis. Adjusting by 10% for ineligibility and non-compliance, the target sample size was 150 patients.

Discrete time point analyses, including that of the primary endpoint, were conducted using two-sided t-test if normally distributed or two-sided Wilcoxon rank sum test otherwise. Fisher's exact test was used to assess dichotomous variables. Changes over time were evaluated by linear fixed effects model using maximum likelihood estimation, allowing for adjustments due to treatment arm, percentage of esophagus irradiated, chemotherapy type, opioid use, and surgery status. Baseline scores were included in outcome variable if no significant differences between arms at baseline existed. The primary endpoint of change in esophagitis-related pain at 4 weeks was evaluated with a significance level of 0.05 (one-sided) for each treatment arm comparison to the control arm. All secondary endpoints were assessed using two-sided significance level of 0.05.

Change scores were calculated by subtracting baseline from follow-up. A low NRPS score represents less pain. For the EORTC QLQ-C30, a higher score represents a higher QOL for global health status while a higher pain subscale score represents higher pain. Therefore, a positive change score for the pain subscale score indicates increased pain while a positive score for global health status indicates improved QOL.

Nutritional status was measured using pre-albumin levels, and percent weight change was calculated for each patient. Opioid use was categorized as yes vs. no with unknown responses treated as missing. Dysphagia was reported with higher scores indicating more pain.

CTCAE grades were tabulated by arm as worst grade per adverse event per patient. PRO-CTCAE scores were similarly tabulated by arm as the worst score per item per patient across treatment and follow-up. Alternative presentations of PRO-CTCAE incorporating baseline will be reported separately.

Results

NRG Oncology RTOG 1012 enrolled 163 patients between February 2012 and October 2013 (Figure 1). Pretreatment characteristics were similar between arms. [Table 1] The median age was 65 years, 54% of patients were male, 52% of patients had treatment plans using IMRT and 61% of patients had less than 30% of esophagus in the radiation field. Treatment was per protocol or with an acceptable deviation in most patients (77.5%).

Compliance for NRPS completion at 4 weeks was similar in the supportive care and liquid honey arms; but lower in the lozenge honey arm. Consent withdrawal was the largest cause of missing data [Table 2]. Notably, compliance at 12 weeks for the lozenge honey arm was actually higher compared to week 4 or end of radiation therapy (72.2% at week 4, 70.4% at end of radiation and 74.1% at 12 weeks). Compliance for completion of the EORTC QLQ-C30 and dysphagia diary was slightly less than that of the NRPS. The largest cause of missing data for dysphagia was incomplete reporting by the patient, while the largest cause of missing data for the EORTC QLQ-C30 was consent withdrawal (10% at week 4 and 11.3% at 12 weeks). Compliance for completion of PRO-CTCAE was high for this population with PRO-CTCAE completion at 718/849 (85%) visits in which PRO-CTCAE was expected (reasons for noncompliance and other details about PRO-CTCAE administration will be reported separately).

The primary outcome of radiation esophagitis-related pain at 4 weeks was not significant in either comparison: supportive care vs. liquid honey ($p=0.92$) or supportive care vs. lozenge honey ($p=0.93$) [Table 3]. Since each arm has less than the required n=45, there is reduced power to detect the effect size of interest (76%).

There was significant improvement in change in NRPS from baseline to 12 weeks between the supportive care and lozenge arms ($p=0.02$) in favor of the lozenge arm. A linear fixed effects model found percentage of esophagus receiving 60 Gy or more (estimate= −0.47, $p=0.002$), opioid use (estimate= −0.52, $p=0.003$), and time (estimate=0.09, $p<0.0001$) as significant predictors of NRPS score but treatment arm was not. There were no significant differences between arms [Table 3] with respect to QOL and pain as measured by the EORTC QLQ-C30 or with respect to nutrition or weight loss [Table 4]. Only opioid use at 4 weeks during treatment between the supportive care and liquid honey arms was found to be significant ($p=0.03$) with more patients on the supportive care arm taking opioids. Percentage of esophagus receiving ≥60Gy (estimate= −0.19, $p=0.0002$), opioid use (estimate= −0.17, $p=0.005$), and time (estimate=0.06, $p<0.0001$) were significant predictors of dysphagia score. Treatment arm was not.

There were no grade 5 adverse events reported in the liquid honey arm (Supplemental Table 1). Two patients in the supportive care arm experienced grade 5 adverse events (sepsis, cardiac arrest) and one patient in lozenge honey arm (sepsis); none related to the study treatment. There was 1 grade 4 event (neutropenia) on the lozenge arm and 1 grade 4 event (thrombocytopenia) on the supportive care arm attributed to therapeutic treatment all thought to be unrelated to the study intervention. There were 140 patients who initiated treatment and had both CTCAE and PRO-CTCAE data for the 10 most commonly reported adverse

events from the patient. PRO-CTCAE scores across the 53 items (30 adverse events) were similar across arms, though PRO-CTCAE detected a higher proportion of nonzero and high (score 3 or 4) scores relative to the proportion of nonzero and high (grade 3 or higher) grades by CTCAE [Table 5]. No differences were noted between arms with respect to grade 3+radiation-induced esophagitis (2.0% vs. 12.5%, p=0.0.06 for liquid honey vs. supportive care; 6.0% vs. 12.5%, p=0.31 for lozenge honey vs. supportive care).

Discussion

Esophagitis is a common side effect of chemoradiation for lung cancer that can significantly impact quality of life and treatment efficacy. This trial compared the effectiveness of liquid honey, lozenges made by dehydrating honey, and standard supportive care in improving esophagitis related pain.

Recent trials have confirmed usefulness of honey. For example, in a randomized trial of honey compared to standard hydrogel dressings for venous leg ulcers, methicillin resistant staph aureus infection was eliminated in 70% of honey patients versus 16% of hydrogel patients.[17–21,39–42] More recently, honey has been investigated as a potential treatment for mucositis in patients receiving head and neck irradiation and several small-randomized trials demonstrated benefit with honey. [24–27]

Mucositis was scored in these trials by objective scales such as the RTOG scale and OMAS scale for mucositis. As there is no validated standard measurement for esophagitis, the CTCAE and RTOG scales are frequently used but are limited by dependency on the observer and do not take into account the patient perception. While RTOG 9801 did not demonstrate improvement in observed dysphagia in patients receiving amifostine, it did demonstrate improvement in patient reported dysphagia with the use of amifostine.[14] Furthermore, the pain subscale from the EORTC QLQ-C30 that evaluates the amount and the effect of pain showed significant benefit with amifostine.[43] Based upon data from RTOG 9801, a reasonable primary endpoint for the current trial was patient-reported pain. No significant changes in pain rating at 4 weeks were observed; however, the change score in the supportive care group (median of 1) was much lower than hypothesized. Additionally, at 12 weeks, the NRPS score change was significantly lower in the lozenge honey group vs. supportive care.

This measurement allows us to compare results to RTOG 9801, but not to the aforementioned trials. However, radiation-induced esophagitis was analyzed using CTCAE and found no difference between arms for grade 3 and 4 radiation-induced esophagitis.

Of note, these trials used different types of honey, highlighting challenges inherent to natural products. The exact composition of a particular batch of honey cannot be predicted and content can be affected by location of pollen.[27] Manuka honey was chosen to reduce this inhomogeneity. In this study, honey was irradiated to sterilize it from known pathogens.[44] It is possible that sterilization may have altered natural bacteria with therapeutic benefit in the honey. Interestingly, two recent trials also used Manuka honey and both studies did not

demonstrate the same benefit as the previously mentioned trials, but neither trial irradiated the honey suggesting this is not the cause of the negative outcome.

Even without a benefit compared to supportive care, the benefits of a bacteriostatic, more pleasant, less expensive alternative to pain medications or numbing agents, may be appealing. In this study, liquid Manuka honey was associated with decreased opioid use at 4 weeks. This could have a benefit if honey could decrease financial burden and side effects of prolonged opioid use. However, the endpoint of decreased opioid use at 4 weeks was significant only at .05 and uncorrected for the multiple endpoints evaluated. In addition, there was no effect by end of treatment or 12 weeks.

There are limitations to this study, particularly Manuka honey was chosen though it had not been used in previous trials at the time the trial was designed. It was assumed that all honeys would be equally active, however, because honey's properties vary, this may have been a poor assumption. Mucositis was presumed to be a generic process resulting from a common mechanism of inflammation and organ damage. It was assumed, perhaps incorrectly, that benefits seen in the head and neck would be generalizable to the esophagus. Manuka honey is available without prescription; so monitoring if control arm patients took honey off protocol was not possible. Additionally, with more than 50% of patients planned with IMRT in this study, it is possible that this lowered the percentage of esophagus receiving prescription dose. Overall, this population may have been at lower risk for severe esophagitis than RTOG 9801, which in turn might have affected power to detect a difference. Treating physicians in this study were not blinded to the study arm which may have impacted decisions to prescribe opioids. Finally, toxicity assessment using CTCAE was hampered by low and variable physician reporting; it was unclear whether all adverse events were reported. To address this prospectively, this study incorporated PRO-CTCAE to allow patients to self-report toxicities.

Conclusion

Manuka honey as prescribed within this protocol was not superior to best supportive care in preventing radiation esophagitis. Further studies are warranted to better understand if the link between honey microbiota, bacteriostatic properties and/or immune response to honey may demonstrate clinical benefit, and whether honey use can reduce opioid use for pain relief during treatment. This trial demonstrates the difficulty in using natural products in clinical trials because large variation of properties of different sources of the same agent is possible, and the active species in the agents are incompletely known.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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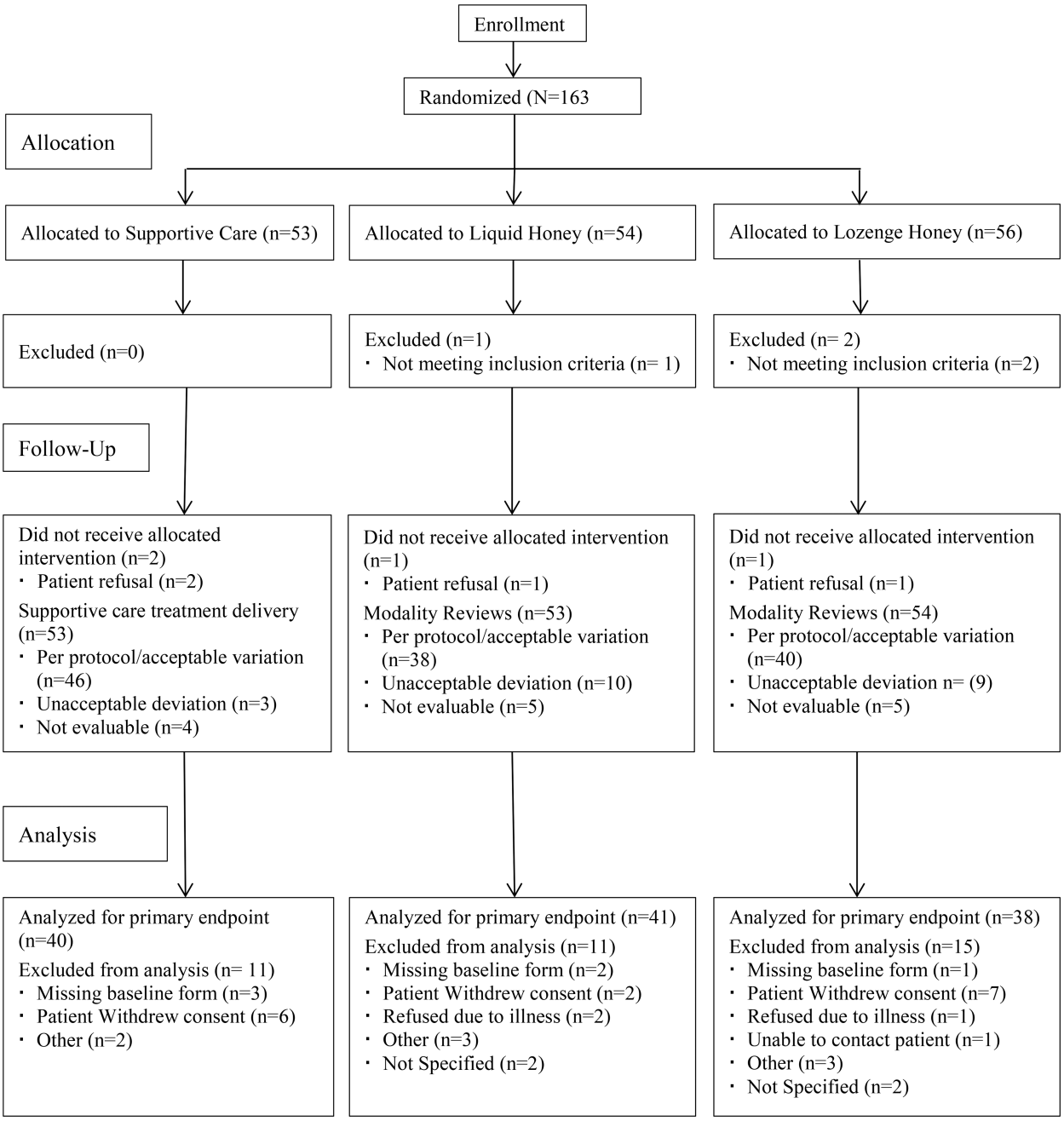

Figure 1.
CONSORT Diagram

Table 1

Pretreatment Characteristics

	Supportive Care (n=53)	Supportive Care (n=53)	Lozenge Honey (n=54)
Age (years)			
Median	65	66	65
Min - Max	45 – 85	37 – 83	47 – 83
Q1 - Q3	57 – 71	59 – 71	59 – 71
Gender			
Male	26 (49.1%)	29 (54.7%)	31 (57.4%)
Female	27 (50.9%)	24 (45.3%)	23 (42.6%)
Race			
American Indian or Alaskan Native	0 (0.0%)	1 (1.9%)	1 (1.9%)
Asian	2 (3.8%)	1 (1.9%)	1 (1.9%)
Black or African American	6 (11.3%)	5 (9.4%)	7 (13.0%)
White	44 (83.0%)	46 (86.8%)	45 (83.3%)
More than one race	1 (1.9%)	0 (0.0%)	0 (0.0%)
Ethnicity			
Hispanic or Latino	0 (0.0%)	1 (1.9%)	1 (1.9%)
Not Hispanic or Latino	51 (96.2%)	50 (94.3%)	52 (96.3%)
Unknown	2 (3.8%)	2 (3.8%)	1 (1.9%)
Use of IMRT			
No	24 (45.3%)	23 (43.4%)	30 (55.6%)
Yes	29 (54.7%)	30 (56.6%)	24 (44.4%)
Percentage of Esophagus in Radiation Field*			
V60 < 30%	33 (62.3%)	33 (62.3%)	32 (59.3%)
V60 > =30%	20 (37.7%)	20 (37.7%)	22 (40.7%)

Table 2

NRPS and EORTC QLQ-30 Patient Compliance

	Supportive Care (n=53)	Liquid Honey (n=53)	Lozenge Honey (n=54)
NRPS			
Baseline			
Completed, prior to start of treatment	46 (86.8%)	47 (88.7%)	51 (94.4%)
Completed, after start of treatment	2 (3.8%)	3 (5.7%)	1 (1.9%)
Not completed, patient unable to be contacted	1 (1.9%)	0 (0.0%)	0 (0.0%)
Not completed, institutional error	1 (1.9%)	1 (1.9%)	0 (0.0%)
Not completed, other reason	3 (5.7%)	2 (3.8%)	2 (3.7%)
Week 4 of RT			
Completed	43 (81.1%)	43 (81.1%)	39 (72.2%)
No Protocol Treatment	2 (3.8%)	1 (1.9%)	1 (1.9%)
CW withdrawal	6 (11.3%)	2 (3.8%)	7 (13.0%)
Not completed due to illness	0 (0.0%)	2 (3.8%)	1 (1.9%)
Unable to contact patient	0 (0.0%)	0 (0.0%)	1 (1.9%)
Other	2 (3.8%)	3 (5.7%)	3 (5.6%)
Not Reported	0 (0.0%)	2 (3.8%)	2 (3.7%)
End of RT			
Completed	37 (69.8%)	40 (75.5%)	38 (70.4%)
No Protocol Treatment	2 (3.8%)	1 (1.9%)	1 (1.9%)
CW withdrawal	6 (11.3%)	3 (5.7%)	7 (13.0%)
Not completed due to illness	1 (1.9%)	2 (3.8%)	2 (3.7%)
Institutional error	3 (5.7%)	0 (0.0%)	0 (0.0%)
Other	1 (1.9%)	3 (5.7%)	3 (5.6%)
Not Reported	3 (5.7%)	4 (7.5%)	3 (5.6%)
12 weeks from start of RT			
Completed	37 (69.8%)	36 (67.9%)	40 (74.1%)
No Protocol Treatment	2 (3.8%)	1 (1.9%)	1 (1.9%)
CW withdrawal	6 (11.3%)	3 (5.7%)	9 (16.7%)
Not completed due to illness	0 (0.0%)	2 (3.8%)	0 (0.0%)
Unable to contact patient	2 (3.8%)	2 (3.8%)	0 (0.0%)
Institutional error	1 (1.9%)	0 (0.0%)	0 (0.0%)
Other	2 (3.8%)	5 (9.4%)	3 (5.6%)
Not Reported	3 (5.7%)	4 (7.5%)	1 (1.9%)
EORTC QLQ-30			
Baseline			
Completed, prior to start of treatment	45 (84.9%)	45 (84.9%)	52 (96.3%)
Completed, after start of treatment	3 (5.7%)	4 (7.5%)	0 (0.0%)
Not completed, patient refused for other reason	2 (3.8%)	1 (1.9%)	0 (0.0%)
Not completed, patient unable to be contacted	1 (1.9%)	0 (0.0%)	0 (0.0%)

	Supportive Care (n=53)	Liquid Honey (n=53)	Lozenge Honey (n=54)
Not completed, institutional error	0 (0.0%)	1 (1.9%)	0 (0.0%)
Not completed, other reason	1 (1.9%)	1 (1.9%)	1 (1.9%)
Not received	1 (1.9%)	1 (1.9%)	1 (1.9%)
Week 4			
Completed, prior to start of treatment	38 (71.7%)	40 (75.5%)	43 (79.6%)
Not completed, patient refused due to illness	1 (1.9%)	0 (0.0%)	0 (0.0%)
No Protocol Treatment	2 (3.8%)	1 (1.9%)	0 (0.0%)
Not completed, patient refused for other reason	0 (0.0%)	2 (3.8%)	0 (0.0%)
Not completed, other reason	2 (3.8%)	1 (1.9%)	0 (0.0%)
CW withdrawal	6 (11.3%)	3 (5.7%)	7 (13.0%)
Not received	4 (7.5%)	6 (11.3%)	4 (7.4%)
12 weeks after RT			
Completed, prior to start of treatment	37 (69.8%)	38 (71.7%)	39 (72.2%)
Not completed, patient refused due to illness	0 (0.0%)	1 (1.9%)	0 (0.0%)
No Protocol Treatment	2 (3.8%)	1 (1.9%)	1 (1.9%)
Not completed, patient refused for other reason	1 (1.9%)	3 (5.7%)	2 (3.7%)
Not completed, institutional error	2 (3.8%)	0 (0.0%)	0 (0.0%)
Not completed, other reason	1 (1.9%)	1 (1.9%)	1 (1.9%)
CW withdrawal	6 (11.3%)	3 (5.7%)	9 (16.7%)
Not received	4 (7.5%)	6 (11.3%)	2 (3.7%)
Swallowing Diary			
Baseline			
Completed	45 (84.9%)	47 (88.7%)	48 (88.9%)
Completed after start of treatment	1 (1.9%)	3 (5.7%)	1 (1.9%)
CW withdrawal	4 (7.5%)	0 (0.0%)	3 (5.6%)
Unable to contact patient	0 (0.0%)	0 (0.0%)	1 (1.9%)
Institutional error	2 (3.8%)	0 (0.0%)	1 (1.9%)
Other	0 (0.0%)	2 (3.8%)	0 (0.0%)
Not Reported	1 (1.9%)	1 (1.9%)	0 (0.0%)
Week 4 of RT			
Completed	33 (62.3%)	37 (69.8%)	32 (59.3%)
No Protocol Treatment	2 (3.8%)	1 (1.9%)	1 (1.9%)
Consent withdrawal	6 (11.3%)	3 (5.7%)	8 (14.8%)
Not completed due to illness	0 (0.0%)	0 (0.0%)	1 (1.9%)
Other	1 (1.9%)	1 (1.9%)	2 (3.7%)
Unknown	1 (1.9%)	0 (0.0%)	1 (1.9%)
Not Reported	10 (18.9%)	11 (20.8%)	9 (16.7%)
End of RT			
Completed	30 (56.6%)	33 (62.3%)	26 (48.1%)
No Protocol Treatment	2 (3.8%)	1 (1.9%)	1 (1.9%)
Consent withdrawal	6 (11.3%)	3 (5.7%)	9 (16.7%)

	Supportive Care (n=53)	Liquid Honey (n=53)	Lozenge Honey (n=54)
Other	0 (0.0%)	0 (0.0%)	1 (1.9%)
Unknown	0 (0.0%)	0 (0.0%)	1 (1.9%)
Not Reported	15 (28.3%)	16 (30.2%)	16 (29.6%)
12 weeks after RT			
Completed	36 (67.9%)	38 (71.7%)	36 (66.7%)
No Protocol Treatment	2 (3.8%)	1 (1.9%)	1 (1.9%)
Consent withdrawal	6 (11.3%)	3 (5.7%)	9 (16.7%)
Institutional error	1 (1.9%)	0 (0.0%)	1 (1.9%)
Other	0 (0.0%)	4 (7.5%)	4 (7.4%)
Not Reported	8 (15.1%)	7 (13.2%)	3 (5.6%)

Table 3

Change Scores for NRPS and EORTC QLQ-C30

		Supportive Care	Liquid Honey	Lozenge Honey
NRPS	4 Weeks	(n=40)	(n=41)	(n=38)
	Median	1	1	1
	Min – Max	−1 – 10	−1 – 10	−5 – 9
			p=0.92	p=0.93
	End of RT	(n=36)	(n=38)	(n=37)
	Median	2	3	3
	Min – Max	0 – 10	−1 – 10	−3 – 10
			p=0.78	p=0.91
	12 Weeks	(n=36)	(n=34)	(n=39)
	Median	0	0	0
	Min – Max	−2 – 9	−4 – 9	−5 – 6
			p=0.68	p=0.02
EORTC QLQ-C30 Global Health Status	4 Weeks	(n=37)	(n=38)	(n=43)
	Median	0.0	0.0	0.0
	Min – Max	−91.7 – 50.0	−58.3 – 41.67	−58.3 – 66.67
			p=0.78	p=0.82
	12 Weeks	(n=36)	(n=35)	(n=39)
	Median	0.0	0.0	0.0
	Min – Max	−66.7 – 66.7	−58.3 – 41.7	−100 – 66.7
			p=0.67	p=0.88
EORTC QLQ-C30 Pain	4 Weeks	(n=37)	(n=38)	(n=43)
	Median	0.0	0.0	0.0
	Min – Max	−50.0 – 66.7	−100 – 66.7	−66.7 – 83.3
			p=0.94	p=0.37
	12 Weeks	(n=36)	(n=35)	(n=39)
	Median	0.0	0.0	0.0
	Min – Max	−83.3 – 83.3	−100 – 83.3	−100 – 83.3
			p=0.08	p=0.86

P-value calculated from two-sided Wilcoxon test with normal approximation

Table 4

Weight Loss, Nutritional Status, and Opioid Use

		Supportive Care	Liquid Honey	Lozenge Honey
Weight loss (%)	4 Weeks	(n=50)	(n=51)	(n=51)
	Median	−0.945	−0.4	−1
	Min – Max	−68.5 – 87	−10 – 10.4	−43.3 – 5.5
			p=0.53 *	p=0.88 *
Pre-albumin	4 Weeks	(n=50)	(n=51)	(n=51)
	Median	0	0	0
	Min – Max	−135.2 – 25.6	−22.3 – 290	−28 – 22
			p=0.20 *	p=0.28 *
Opioid Use	Baseline			
	No	45 (84.9%)	48 (90.6%)	45 (83.3%)
	Yes	6 (11.3%)	5 (9.4%)	7 (13.0%)
	Unknown	2 (3.8%)	0 (0.0%)	2 (3.7%)
			p=0.76 §	p=0.99 §
	Week 4			
	No	24 (52.2%)	33 (67.3%)	26 (54.2%)
	Yes	17 (37.0%)	7 (14.3%)	13 (27.1%)
	Unknown	5 (10.9%)	9 (18.4%)	9 (18.8%)
			p=0.03 §	p=0.50 §
	End of RT			
	No	19 (44.2%)	21 (44.7%)	19 (43.2%)
	Yes	19 (44.2%)	17 (36.2%)	18 (40.9%)
	Unknown	5 (11.6%)	9 (19.1%)	7 (15.9%)
			p=0.82 §	p=0.99 §
	Week 12			
	No	27 (62.8%)	34 (73.9%)	35 (79.5%)
	Yes	14 (32.6%)	8 (17.4%)	8 (18.2%)
	Unknown	2 (4.7%)	4 (8.7%)	1 (2.3%)
			p=0.14 §	p=0.14 §

* P-value calculated from two-sided Wilcoxon test with normal approximation

§ P-value from Fisher's exact test for Yes vs. No

Table 5

Clinically-Graded and Patient-Reported Adverse Events for the 10 Most Common Patient-Reported Adverse Events

Symptomatic Adverse Event[†]			Any Level (CTCAE Grade or PRO-CTCAE Score ≥1) [N (%)]			High Level (CTCAE Grade or PRO-CTCAE Score[*] ≥3) [N (%)]		
			Supportive Care (n=46)	Liquid Honey (n=47)	Lozenge Honey (n=47)	Supportive Care (n=46)	Liquid Honey (n=47)	Lozenge Honey (n=47)
Anorexia	CTCAE:		11 (23.9%)	15 (31.9%)	5 (10.6%)	1 (2.2%)	--	1 (2.1%)
	PRO-CTCAE:	Severity	35 (76.1%)	42 (89.4%)	42 (89.4%)	12 (26.1%)	11 (23.4%)	14 (29.8%)
		Interference	25 (54.3%)	36 (76.6%)	34 (72.3%)	9 (19.6%)	12 (25.5%)	13 (27.7%)
Anxiety	CTCAE:		4 (8.7%)	4 (8.5%)	2 (4.3%)	--	--	--
	PRO-CTCAE:	Frequency	34 (73.9%)	41 (87.2%)	44 (93.6%)	10 (21.7%)	12 (25.5%)	13 (27.7%)
		Severity	33 (71.7%)	40 (85.1%)	44 (93.6%)	9 (19.6%)	10 (21.3%)	9 (19.1%)
		Interference	23 (50%)	29 (61.7%)	26 (55.3%)	7 (15.2%)	8 (17%)	9 (19.1%)
Cough	CTCAE:		14 (30.4%)	21 (44.7%)	11 (23.4%)	--	1 (2.1%)	--
	PRO-CTCAE:	Severity	43 (93.5%)	44 (93.6%)	44 (93.6%)	12 (26.1%)	12 (25.5%)	5 (10.6%)
		Interference	28 (60.9%)	34 (72.3%)	33 (70.2%)	9 (19.6%)	11 (23.4%)	4 (8.5%)
Dysgeusia	CTCAE:		6 (13%)	8 (17%)	4 (8.5%)	--	--	--
	PRO-CTCAE:	Severity	37 (80.4%)	36 (76.6%)	43 (91.5%)	8 (17.4%)	5 (10.6%)	9 (19.1%)
Dyspepsia	CTCAE:		10 (21.7%)	6 (12.8%)	2 (4.3%)	--	--	--
	PRO-CTCAE:	Frequency	35 (76.1%)	37 (78.7%)	38 (80.9%)	15 (32.6%)	12 (25.5%)	13 (27.7%)
		Severity	35 (76.1%)	37 (78.7%)	38 (80.9%)	13 (28.3%)	8 (17%)	9 (19.1%)
Dysphagia	CTCAE:		17 (37%)	20 (42.6%)	16 (34%)	--	2 (4.3%)	--
	PRO-CTCAE:	Severity	35 (76.1%)	41 (87.2%)	40 (85.1%)	15 (32.6%)	9 (19.1%)	13 (27.7%)
Dyspnea	CTCAE:		9 (19.6%)	18 (38.3%)	14 (29.8%)	1 (2.2%)	3 (6.4%)	2 (4.3%)
	PRO-CTCAE:	Severity	38 (82.6%)	43 (91.5%)	42 (89.4%)	8 (17.4%)	9 (19.1%)	9 (19.1%)
		Interference	30 (65.2%)	37 (78.7%)	36 (76.6%)	7 (15.2%)	9 (19.1%)	8 (17%)
Fatigue	CTCAE:		28 (60.9%)	25 (53.2%)	22 (46.8%)	3 (6.5%)	--	1 (2.1%)
	PRO-CTCAE:	Severity	45 (97.8%)	46 (97.9%)	45 (95.7%)	17 (37%)	19 (40.4%)	18 (38.3%)
		Interference	43 (93.5%)	43 (91.5%)	44 (93.6%)	15 (32.6%)	21 (44.7%)	20 (42.6%)

Symptomatic Adverse Event†			Any Level (CTCAE Grade or PRO-CTCAE Score ≥1) [N (%)]			High Level (CTCAE Grade or PRO-CTCAE Score* ≥3) [N (%)]		
			Supportive Care (n=46)	Liquid Honey (n=47)	Lozenge Honey (n=47)	Supportive Care (n=46)	Liquid Honey (n=47)	Lozenge Honey (n=47)
Insomnia	CTCAE:		6 (13%)	5 (10.6%)	2 (4.3%)	--	1 (2.1%)	--
	PRO-CTCAE:	Severity	39 (84.8%)	40 (85.1%)	39 (83%)	11 (23.9%)	8 (17%)	13 (27.7%)
		Interference	31 (67.4%)	36 (76.6%)	34 (72.3%)	6 (13%)	8 (17%)	13 (27.7%)
Pain	CTCAE:		12 (26.1%)	16 (34%)	6 (12.8%)	1 (2.2%)	1 (2.1%)	1 (2.1%)
	PRO-CTCAE:	Frequency	36 (78.3%)	39 (83%)	43 (91.5%)	17 (37%)	16 (34%)	19 (40.4%)
		Severity	36 (78.3%)	39 (83%)	43 (91.5%)	14 (30.4%)	8 (17%)	14 (29.8%)
		Interference	30 (65.2%)	32 (68.1%)	35 (74.5%)	12 (26.1%)	10 (21.3%)	16 (34%)

*PRO-CTCAE score of 3 or 4 represents an adverse event frequency of “frequently” or “almost constantly”; severity of “severe” or “very severe”; or interference with usual or daily activities of “quite a bit” or “very much”.

†Maximum grades occurring during and post treatment are included.