

RADIATION THERAPY ONCOLOGY GROUP

RTOG 1012

PHASE II RANDOMIZED TRIAL OF PROPHYLACTIC MANUKA HONEY FOR THE REDUCTION OF CHEMORADIATION THERAPY INDUCED ESOPHAGITIS- RELATED PAIN DURING THE TREATMENT OF LUNG CANCER

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 1012

Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer

SCHEMA

			For patients receiving once daily concurrent chemotherapy and radiation therapy (to at least 60 Gy)
S		R	Arm 1: Standard supportive care during concurrent
T	Percentage of Esophagus	A	chemotherapy and radiation
R	in Radiation Field	N	
A		D	Arm 2: 10 cc liquid Manuka honey 4 x/day* during
T	1. V60 < 30%	O	concurrent chemotherapy and radiation
I	2. V60 ≥ 30%	M	
F		I	Arm 3: 10 cc equivalent Manuka honey in lozenge form
Y		Z	4x/day* during concurrent chemotherapy and radiation
		E	

*Equally distributed throughout the waking hours, approximately at 8 AM, 12 PM, 4 PM, and 8 PM, 7 days/week

Patient Population: (See Section 3.0 for Eligibility)

Patients being treated with combination chemotherapy (definitive or adjuvant) and radiation therapy once daily for small cell or non-small cell lung cancer; at least 5 cm of the esophagus must be in the 60 Gy isodose volume.

Required Sample Size: 150

RTOG Institution # _____
RTOG 1012
Case # _____

ELIGIBILITY CHECKLIST (2/28/12)
(page 1 of 2)

- _____ (Y) 1. Is the patient being treated with combination chemotherapy (definitive or adjuvant) and radiation therapy once day for small cell or non-small cell lung cancer?
- _____ (Y) 2. Is at least 5 cm of the esophagus in the 60 Gy isodose volume?
- _____ (Y) 3. Is the patient \geq 18 years of age?
- _____ (Y) 4. Did the patient provide study specific informed consent?
- _____ (N) 5. Does the patient have metastatic disease?
- _____ (N) 6. Does the patient have the inability to swallow thick liquids prior to treatment?
- _____ (N) 7. Does the patient have a known hypersensitivity to honey?
- _____ (N) 8. Is patient not receiving chemotherapy?
- _____ (N) 9. Is the patient receiving more than one daily treatment?
- _____ (N) 10. Has the patient received prior chemotherapy or radiation therapy?
- _____ (N) 11. Is the patient unable to complete the required forms?
- _____ (N) 12. Does the patient have poorly controlled diabetes?

The following questions will be asked at Study Registration:

- _____ 1. Institutional person randomizing case
- _____ (Y) 2. Has the Eligibility Checklist been completed?
- _____ (Y) 3. In the opinion of the investigator, is the patient eligible?
- _____ 4. Date informed consent signed
- _____ 5. Patient's Initials (First Middle Last)
- _____ 6. Verifying Physician
- _____ 7. Patient ID
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnicity
- _____ 11. Gender
- _____ 12. Country of Residence

Continued on next page

RTOG Institution # _____
RTOG 1012
Case # _____

ELIGIBILITY CHECKLIST (2/28/12)
(page 2 of 2)

- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Method of Payment
- _____ 15. Any care at a VA or Military Hospital?
- _____ 16. Calendar Base Date
- _____ 17. Randomization date
- _____ 18. Specify the percentage of the esophagus in the radiation field (V60 < 30% vs. V60 ≥ 30%)
- _____(Y/N) 19. Is the patient simultaneously enrolled on an RTOG Lung treatment trial?
- _____ If yes:
Specify the RTOG study number
- _____ Specify the patient's case number
(to allow RTOG HQ to access the patient's RT data submitted to the ITC)
- _____(Y/N) 20. Will IMRT be used? (Credentialing is required for IMRT; see Section 5.0)

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Radiation Esophagitis

1.1.1 Mechanisms of Mucositis

Mucositis is the inflammatory disruption of an area of the normal surface epithelium of an organ. Terms for mucositis in individual organs include dermatitis, head and neck mucositis, esophagitis, enteritis, proctitis, and cystitis. Mucositis in all of these sites has a common pathway, allowing information from one area of study, such as mucositis of the head and neck, to be translatable to another area, such as esophagitis.

Mucositis can be modeled on a tissue scale and on a sub-cellular scale. The commonly accepted model of mucositis on the tissue scale is that of Sonis (1998). This model functions best to highlight the temporal effects, rather than the mechanistic effects, involved in tissue damage and healing. The model, shown in Appendix V, Figure 1, has 5 phases: Initiation, Damage, Inflammation, Ulceration, and Healing. Although Sonis labels Phase IV as mucositis in this figure, stage III represents inflammatory mucositis (erythema) and Phase IV represents ulcerative mucositis. Mucositis modifiers can be classified by where they intervene in the model. Radioprotectors, such as amifostine, work within Stage I, by decreasing the damage from the ionizing radiation. Anti-inflammatory agents such as non-steroidal anti-inflammatory drugs would inhibit inflammation in Phases II/III. Antifungal agents would intervene in Phase IV, by preventing superinfection. A growth factor such as KGF-alpha (palifermin) would stimulate epithelial regrowth during Phase V.

This model, although enlightening on a macroscopic level, gives no insight into the complexities of the cellular/subcellular mechanisms involved in the induction and resolution of mucositis. Figures 2 and 3 (Appendix V) model some of the mechanisms involved in Phase II-III (Figure 2) and Phase V (Figure 3) of the Sonis Model for dermatitis.

The most extensive data on epithelial healing in response to a trauma are available from the wound healing literature (Singer 1999). The phases of healing (Ethridge 2007) shown in Figure 4 (Appendix V) are similar to Phases III-V of the Sonis model. The initial insult causes damage to the surface epithelium, the submucosa, and the blood vessels. This allows infiltration by neutrophils, and represents the first phase of the reaction, inflammation. The denuded surface is then sealed with fibrin and platelets (Figures 2 and 3), and the platelets and neutrophils release cytokines and chemotactic compounds which attract mononuclear cells, including macrophages. The macrophages are the key cell in the repair process (see Figure 5, Appendix V). The macrophages debride the surface of the wound, induce repair of the extracellular matrix, and generate growth and motility factors to stimulate epithelial cell (keratinocyte) migration. Unlike dermal repair, scar formation during the repair process in mucositis is the exception rather than the rule.

Many of the cytokines and growth factors involved in the normal mucosal healing response are the same compounds that induce growth and spread of tumors. Table 1 (Appendix VI) lists a few of the cytokines involved in mucosal repair. Important compounds for mucosal healing include epidermal growth factor (EGF) and vascular epidermal growth factor (VEGF) [Ethridge 2007]. However, common treatments for tumors include anti-VEGF compounds and anti-EGF receptor compounds (Pourgholami 2008; Caraglia 2006). Further, compounds such as platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and transforming growth factor (TGF) also are implicated in cancer progression, and their inhibitors are being explored as therapies (Wang 2009; Gennigens 2006; Zhang 2009). RTOG has studied and is exploring the use of combined RT and epidermal growth factor receptor (EGFR) inhibition in several cancers, including head and neck cancer (RTOG 0522) and esophageal cancer (RTOG 0436). These compounds can be expected to increase the rate of radiation mucositis, necessitating better treatment options to ameliorate the mucositis. Care also must be taken if growth factors are used for mucositis to choose agents that potentially would not stimulate the cancer. A practical result of this concern is shown by the FDA's recent insertion of a "Box Warning" for a PDGF wound healing product, Regranex®, suggesting that there may be an increased risk of cancer among patients taking the product (Regranex® package insert). The warning states that:

- The incidence rate for all cancers was 10.2 per 1,000 person years for patients treated with Regranex® Gel and 9.1 per 1,000 person years for the comparators. Adjusted for several possible confounders, the rate ratio was 1.2, (95% confidence interval 0.7-1.9). Types of cancers varied and were remote from the site of treatment.
- The incidence rate for mortality from all cancers was 1.6 per 1,000 person years for those who received Regranex® Gel and 0.9 per 1,000 person years for the comparators. The adjusted rate ratio was 1.8 (95% confidence interval 0.7-4.9).
- The incidence rate for mortality from all cancers among patients who received 3 or more tubes of Regranex® Gel was 3.9 per 1,000 person years and 0.9 per 1,000 person years in the comparators. The adjusted rate ratio for cancer mortality among those who received three or more tubes relative to those who received none was 5.2, (95% confidence interval 1.6-17.6).

1.1.2 Incidence of Radiation Esophagitis

Esophagitis often is a limiting toxicity in designing combined chemotherapy and radiation therapy (RT) for lung cancer. Although the incidence of severe acute esophagitis in patients treated for lung cancer with standard RT alone is low, less than 2%, it is markedly higher when radiation and chemotherapy are combined. The addition of induction chemotherapy increases the risk of severe acute esophagitis slightly (Werner-Wasik 2000; Byhardt 1998), and chemotherapy given concurrently with radiation increases the incidence of severe esophagitis to 6-14% (Werner-Wasik 2000; Byhardt 1998; Werner-Wasik 1999). Although the combination is more toxic, RTOG 94-10 (Curran 2000) and the Furuse phase III randomized trial (1999) both demonstrated superior survival with concurrent chemotherapy over a sequential approach. Particular agents, such as adriamycin, cause severe primary or recall esophagitis at RT doses as low as 20.0 Gy (Boal 1979). Vokes, et al. (2002) reported 49% rate of grade 3 or higher esophagitis with concurrent gemcitabine and thoracic RT). In a multivariate analysis of patients with lung cancer treated with non-operative therapy, Werner-Wasik, et al. (2000) found predictors of severe esophagitis included concurrent chemotherapy and hyperfractionated RT.

Additional reports of aggressive RT fractionation demonstrating a higher incidence of esophagitis include a phase III study conducted by Ball, et al. (1995), which examined 100 patients with non-small cell lung cancer (NSCLC). The duration of symptomatic esophagitis was 1.4 months (mos.) in the conventional RT arm, 1.6 mos. in the conventional RT arm with concurrent carboplatin, 3.2 mos. in the accelerated arm, and 2.4 mos. in the accelerated RT plus carboplatin arm. Accelerated RT (defined as fractions of 2.0 Gy delivered twice daily) was the only significant factor in multivariate analysis of factors influencing the duration of esophagitis. Byhardt, et al. (1998) looked at toxicity in 5 RTOG trials using sequential and or concurrent chemotherapy with RT for advanced NSCLC. They found that hyperfractionated RT to a total dose of 69.6 Gy was associated with a 24-34% incidence of severe esophagitis. The CHART regimen (Continuous Hyperfractionated Accelerated Radiation Therapy), given without chemotherapy for locally advanced NSCLC, resulted in a 19% rate of severe esophagitis (Emami 1996). Concomitant boost technique with concurrent chemotherapy also has resulted in a dose-limiting incidence of esophagitis of 33% (Xiao 2004). The ECOG trial of once-a-day versus twice-a-day RT with concurrent cisplatin and etoposide for small cell lung cancer (SCLC) showed a survival advantage for twice-a-day radiation but at the expense of increased esophagitis. Specifically, 56% of patients in the once-daily arm did not experience esophagitis vs. only 37% of patients in the twice-daily arm. Moreover, the rates of Grade 3 esophagitis (defined as an inability to swallow solids, requiring narcotic analgesics, or the use of a feeding tube) were 11% in the once-daily arm versus 27% in the twice-daily arm (Turrisi 1999).

1.1.3 Prevention of Radiation Esophagitis

The classical, two-dimensional fields used in RT for lung cancer include the primary lesion, ipsilateral hilum, bilateral mediastinum, and often ipsilateral supraclavicular region, establishing elective nodal irradiation as a standard approach. The current trend is for smaller, tighter fields frequently encompassing only the grossly visible tumor or PET-positive tumor with a small margin (such an approach is used in a current trial for stage IIIA/IIIB NSCLC, RTOG 0617). The benefits include less irradiated lung volume and a shorter length of irradiated esophagus, which is assumed to decrease the probability of esophageal toxicity. This concept stems from reports that doubling the length of irradiated portion of the esophagus leads to a decrease of the LD50 dose, or dose causing the death of 50% of irradiated animals (Michalowski 1986).

However, the evidence that esophageal toxicity is minimized with shorter esophageal length irradiated is contradictory (Werner-Wasik 2000; Ball 1995; Choy 1999; Langer 1999).

In animal models, amifostine had been demonstrated to increase the amount of radiation that can be delivered before reaching mean lethal doses (LD50) from approximately 38.0 Gy to 60.0 Gy, achieving an overall Protection Factor (PF) of 1.5-1.6 for both acute and chronic esophageal damage (Ito 1986). Improved esophagitis with amifostine in phase II and III trials have been noted in patients with NSCLC receiving thoracic RT, with or without concurrent chemotherapy (Werner-Wasik 2001; Werner-Wasik 2002; Koukourakis 1996; Antonadou 2001; Antonadou 2002). In a randomized phase III trial, Antonadou, et al. (2001) examined 146 patients with lung cancer treated with thoracic RT who received daily infusion of amifostine (340 mg/m²) or no amifostine. They noted grade 2 or higher acute esophagitis in 32/72 RT patients vs. 6/72 in amifostine/RT patients (p<0.001) [Antonadou 2002]. In the subsequent study of chemoradiotherapy for lung cancer, a similarly significant decrease in esophagitis was observed (88% vs. 47%).

In contrast to these previous findings, RTOG 98-01 (Movsas 2005), a phase III randomized study of amifostine for esophagitis prevention examined 243 patients with locally advanced NSCLC who received 2 courses of induction chemotherapy (carboplatin and paclitaxel) followed by concurrent twice-daily thoracic RT and weekly low-dose carboplatin and paclitaxel (Movsas 2002). Patients were randomized to receive amifostine or no amifostine. Amifostine did not demonstrate a reduction in severe esophagitis (30% rate with amifostine vs. 34% without); however, based on patient diaries, the swallowing dysfunction measured over time was significantly lower with amifostine (p=0.03). In this trial, only 40% of all RT fractions were “protected” by amifostine infusion in that study and only 29% of patients received amifostine according to protocol requirements. It is unwise to conclude that poor patient compliance was necessarily why the amifostine failed to show efficacy; it is equally likely that the poor compliance was because the amifostine was not sufficiently beneficial.

The use of non-steroidal compounds to prevent radiation esophagitis also has been studied. Neither indomethacin nor naproxen showed significant efficacy in small randomized trials (Milas 1992; Nicolopoulos 1985). Non-randomized trials have shown an apparent efficacy of GM-CSF and glutamine, and preclinical studies suggest that administration of manganese superoxide dismutase-plasmid/liposome prior to radiation inhibits esophagitis (Koukourakis 1999; Algara 2007; Epperly 2004).

1.2 Honey

1.2.1 Honey As a Mucosal Healing Stimulant

Honey was recommended for wound healing in the ancient Egyptian Ebers Papyrus of 1500 B.C. (Sipos 2004). It has been in continuous use in Western medicine since that time. Recently, its use as an effective wound dressing has been shown in clinical trials (Ingle 2006; Shukrimi 2008; Yapucu 2007; Okeniyi 2005).

Honey has several activities that may contribute to its ability to induce wound healing. Honey is known to be strongly bacteriostatic (Al-Waili 2004; Lusby 2005). For example, in a randomized trial of honey versus hydrogel dressings for venous leg ulcers, methicillin resistant staph aureus infection was eliminated in 70% of the honey patients versus 16% of the hydrogel patients. Honey also is active against *candida albicans*, a common superinfection of mucositis patients (Gethin 2008; Koc 2008; Irish 2006). It also has been shown to have anti-viral activity (Al-Waili 2004b).

Honey directly interacts with the humoral processes of wound healing. In-vitro studies show that honey decreases the release of inflammatory reactive oxygen species and increases TNF-alpha release from macrophages (Tonks 2001). Honey also stimulates TNF-alpha, IL-1beta, and IL-6 from immortalized monocyte culture (Tonks 2003). As shown in Figure 4 (Appendix V), these 3 cytokines are stimulating epithelial cell growth factors. The mechanism of this stimulation is not known. One study showed that the stimulation is most probably due to endotoxin (and thus lipopolysaccharide) within the honey, whereas another study demonstrated the effect to be independent of lipopolysaccharide (Timm 2008; Tonks 2007). The latter study also found that blocking toll like receptor 4 (TRL4) inhibits the effectiveness of honey for TNF

alpha release, again independent of lipopolysaccharide presence. Another possible mechanism of action is the ability of honey to increase nitric oxide levels. Nitric oxide may be beneficial to normal wound healing, and systemic administration of honey increases tissue nitric oxide levels (Efron 2000; Al-Waili 2003; Erguder 2008).

1.2.2 Clinical Trials of Honey for Treatment of Mucositis

While no trials of honey in the treatment or prevention of radiation-induced esophagitis have yet to be reported, 3 randomized trials of honey for the prevention of radiation mucositis have been published and provide the rationale for the proposed study. All 3 mucositis trials used an identical honey dosing schedule. The first report was from Biswal, et al. (2003). In this study, 40 patients receiving at least 60 Gy of head and neck irradiation were randomized to receive either 20 ml of pure Malaysian tea plant (*Camellia sinensis*) honey 15 minutes before, 15 minutes after, and 6 hours after RT or normal care. The primary endpoint was oropharyngeal mucositis as measured by the RTOG grading system. The rates of combined grade 3 and 4 mucositis in the honey group was 20%, whereas it was 75% in the control group ($p = 0.00058$). Biswal and colleagues reported no complications from the honey.

In Montallebnejad, et al. (2008), 40 patients were randomized to either 20 ml of honey (from *Thymus* and *Astragale* in the Alborz mountains in northern Iran) 15 minutes before, 15 minutes after, and 6 hours after RT, or 20 ml of saline before and after RT. The primary endpoint was oropharyngeal mucositis as measured by the Oral Mucositis Assessment Scale (OMAS), for which a lower score represents less mucositis. The treatment group had a statistically significant lower OMAS score than the control group at 6 weeks, median OMAS 2.0 versus 14.0 respectively. Further, the mean weight loss in the treatment group was 1.0 kg versus 6.3 kg in the control group ($p=0.000$).

In the third trial from Rashad, et al. (2009), 40 patients receiving concurrent chemotherapy and RT for head and neck cancer were randomized to either honey (clover honey, *Trifolium alexandrenum*) or standard of care. As in the other trials, the honey was administered 15 minutes before, 15 minutes after, and 6 hours after RT. Mucositis was scored by the WHO/RTOG scale. In the honey group, no patient developed grade 4 mucositis, and 3 developed grade 3. In the control group, 3 patients developed grade 4 mucositis and 9 patients developed grade 3 mucositis ($p < 0.05$). *Candida* colonization was found in 15% of the treatment group, and 65% of the control group ($p=0.007$). Rashad, et al. do not report on toxicity but stated that all patients took the honey throughout the RT.

In all 3 studies, the authors indicate that there was excellent compliance, minimal toxicity, and good efficacy with the use of honey. However, the conclusiveness of these trials is limited due to small patient numbers, the use of only objective measures, and the lack of a placebo control. An ongoing trial in British Columbia (Manuka Honey for Radiation-induced Oral Mucositis: a Randomized Placebo-controlled Trial, H07-02297) is addressing these problems. One hundred eighty patients will be randomized to either 5 ml of honey or a synthetic equivalent 4 times a day during RT. The primary measure is RTOG grade 3 and 4 objective mucositis, and secondary endpoints include weight loss, "quality of life" (QOL) measured weekly on a 0-10 scale, and mouth/throat pain measured weekly on a 0-10 scale. However, there are limitations in this trial, including the lower dose of honey that was given in the other trials and the use of non-validated subjective scales.

1.2.3 Manuka Honey

Honey is a bio-organic compound and as such has no fixed composition. It is strongly influenced by the source of pollen for the bees. A source of well studied, quantified honey reduces the inhomogeneity inherent in honey. Manuka (*Leptospermum scoparium*) honey is a standardized honey harvested in New Zealand that has been the subject of extensive testing and is considered the standard medicinal honey. The initial research was done by the lab of Peter C. Molan of The University of Waikato in New Zealand (Allen 1991; al Somal 1994; Willix 1992). They showed that unlike most honeys, Manuka honey maintained its antibacterial activity after removal of hydrogen peroxide with catalase (Allen 1991). They standardized the non-peroxide antibacterial activity as the "Unique Manuka Factor" (UMF), which is the antibacterial effect of the Manuka honey as related to the antibacterial effect of phenol. For example, a UMF of 10 will kill staph aureus as effectively as a 10% phenol solution. Recently, methylglyoxal was identified as being directly correlated with the UMF factor (Adams 2008).

Methylglyoxal is a growth inhibiting factor, and therefore, it is unlikely that it is related to the epidermal healing effects of honey (Portero-Otin 2002). However, it represents a simpler way to standardize the UMF of Manuka honey.

Honey can contain pathogens, such as botulism from clostridial spores (Midura 1979). Molan (1996) showed that the UMF factor in Manuka honey was stable after 50 kGy of gamma irradiation and that the honey was sterilized after 25 kGy.

1.3 Measurement of Esophagitis-Related Pain

There is no validated, standard measurement for esophagitis. The most commonly used measurement scales are CTCAE, v. 4 and the RTOG scale (Appendix VII), both of which are objective observer-scored scales, rather than patient-reported scales. These scales have not been validated and are intended to be used to score toxicity rather than as primary endpoints for trials.

RTOG 98-01 was a randomized phase II trial testing amifostine as a protector against radiation esophagitis. Although the primary endpoint, grade 3 CTC, v. 2.0 acute esophagitis, did not show an improvement with amifostine, the patient-reported dysphagia was improved with amifostine (Movsas 2005). Further, an analysis of the quality of life (QOL) data from RTOG 98-01 showed that although the EORTC QLQ-30 global QOL score showed no overall difference between the 2 arms, the pain symptom subscale showed a statistical improvement with amifostine ($p=0.015$) [Sarna 2008]. The EORTC QLQ-30 pain symptom subscale consists of 2 items of the 30-item QLQ-30: question 9, "Have you had pain?" and question 19, "Did pain interfere with your daily activities?", rated on a 1-4 Likert scale: "Not at All", "A Little", "Quite a Bit", and "Very Much". Within the EORTC QLQ LC-13 symptom scale, no factor, including dysphagia or pain in the chest, showed a significant difference. Physician-reported dysphagia was the same between the 2 arms, but both the patient-reported dysphagia and weight loss were significantly improved with amifostine ($p = 0.04$ and 0.045 , respectively).

Based upon the data from RTOG 98-01, a reasonable primary endpoint for the proposed trial is patient-reported pain on swallowing at 4 weeks using the Numerical Rating Pain Scale (NRPS; see Section 1.3.1). In secondary endpoints, additional measures include the following:

- The NRPS weekly during treatment;
- Patient-reported dysphagia log (the patient completes a swallowing diary daily during treatment and then at 12 weeks from the start of treatment);
- The EORTC QLQ-30 global score and pain symptom subscale (at baseline and at 4 and 12 weeks);
- The percent weight change from baseline to 4 weeks;
- Adverse events as measured by the CTCAE, v. 4, utilized for consistency across RTOG esophagitis trials (weekly during treatment and at 12 weeks).

1.3.1 The Numerical Rating Pain Scale (NRPS)

The NRPS is a simple measure of pain on an 11-point scale (0-10). In a study comparing the reliability and validity of several measures of pain intensity, the composites of 0-10 ratings have been shown to be useful when maximal reliability was necessary in studies with relatively small sample sizes or in clinical settings in which monitoring of changes in pain intensity in individuals is needed [Jensen, 1999]. This measure also is recommended in an IMMPACT article (Dworkin 2005). The index pain will be limited to pain from esophagitis by asking the patient specifically about pain with swallowing.

1.3.2 The EORTC Quality of Life Questionnaire (QLQ-30)

The EORTC QLQ-30 is a 30-item self-reporting questionnaire developed to assess the quality of life of cancer patients. Version 3.0 is the most recent version. The QLQ-30 is grouped into 5 functional subscales (role [2 items], physical [5 items], cognitive [2 items], emotional [4 items], and social functioning [2 items]). In addition, there are 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting). All of the scales range in score from 0-100. A high score represents a high/healthy level of functioning. In this study, the 30-item questionnaire providing a global QOL score and the pain subscale (2 items of the 30 items, as described above) will be used. The QLQ-30 is a copyrighted instrument that has been translated into 81 languages, validated (Aaronson 1993), and has been used in more than 3,000 studies worldwide.

1.3.3 The NCI's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (2/28/12)

The PRO-CTCAE is an item bank consisting of individual items to assess adverse symptom events from the patient perspective. The PRO-CTCAE was developed to complement the CTCAE, under an ongoing contract with the NCI. To date, 78 symptoms in the CTCAE have been developed for patient self-reporting via the PRO-CTCAE (Basch, 2010). A multi-site cognitive interviewing study has been completed to refine these items (Hay, 2010), and a validation study is ongoing (Dueck, 2010). In addition, a web interface was built to administer items to patients via computers at clinic visits (Chilukuri, 2009).

The purpose of including the PRO-CTCAE in a clinical trial is to improve our understanding of the patient experience of adverse events (AEs). Evidence suggests that clinician-reporting of AEs may substantially underestimate the incidence and severity of symptoms occurring as a consequence of treatment (Basch, 2010). Moreover, the potential to misjudge the incidence and severity of adverse events is particularly likely with symptoms such as fatigue, pain, and depression, which only can be gauged accurately by the person experiencing the symptom, and with side effects such as mouth dryness, voice hoarseness, and difficulty swallowing, which are often subtle and may be difficult for clinicians to grade using standard CTCAE grading methods.

Inclusion of the PRO-CTCAE in the current trial is part of an ongoing NCI contract to assess the feasibility of incorporating the PRO-CTCAE into cooperative group clinical trials. The assessment of feasibility will include evaluation of the requirements, viability, and cost of providing computer hardware and training to clinical sites; patient willingness and capacity to complete PRO-CTCAE forms via web interface at clinic visits; administrative burden associated with implementing this system; site-level acceptance of this approach to toxicity assessment; and the capacity of PRO-CTCAE items to distinguish between study arms.

Notably, the inclusion of PRO-CTCAE is an investigational component of this trial. PRO-CTCAE has not been validated as a tool either to guide AE reporting or to supplement clinical practice. Therefore, the inclusion of the PRO-CTCAE in this trial should not alter the standard approach to AE reporting described elsewhere in this protocol.

1.4 Manuka Honey for Radiation Esophagitis

Honey has been shown to stimulate skin wound re-epithelialization well as prevent head and neck radiation mucositis. The mechanism of action may be a combination of its antibacterial and antifungal activity and its macrophage stimulatory ability. The epithelium of the esophagus is similar to that of both the skin and the oropharynx, a relatively thick squamous epidermis, and the mechanisms of mucositis are similar for all 3 surfaces. Therefore, the hypothesis of this trial is that honey will reduce radiation esophagitis equally as well as it reduces oropharyngeal mucositis.

The 10 cc dose (approximately 2 level teaspoons) four times a day was chosen for the proposed study after discussions with the principal investigator, Phillipa Hawley, MD, of an ongoing trial of Manuka honey for oropharyngeal mucositis (British Columbia Cancer Agency, NCT00615420), in which 10 cc was better tolerated than 20 cc. Specifically, in preliminary testing for the trial, it found that the maximum tolerable dose of Manuka honey among healthy volunteers was 10 ml (Hawley 2011). Above this dose, there was excessive gagging and discomfort with swallowing. Because Manuka honey is the only standardized, medical honey commercially available, it is necessary for reproducibility within and between trials to use Manuka honey. Therefore, the 10 ml dose was chosen to allow the highest rate of reproducibility and tolerance. With each dose, patients will refrain from eating 1 hour prior to and 1 hour after swallowing the honey.

The suppliers of the Manuka honey, the honey growers of New Zealand, also will provide a lozenge form of the honey. The lozenge is made by evaporating the majority of the water from the honey. The lozenge is then sealed in an airtight package to prevent reaccumulation of the water. The use of the lozenge form allows testing of whether there is an innate factor in the honey that affects mucositis or whether the complete liquid is needed.

1.5 Rationale for a Randomized Phase II Trial

The overarching goal of this phase II trial is to explore the efficacy of Manuka honey and provide the information needed to determine the appropriate endpoints for a subsequent definitive phase III trial. This phase II trial will provide important data on the prevalence and degree of esophagitis during modern chemoradiation for lung cancer, using a combination of patient-reported measurement tools to enhance the data previously obtained in cooperative group trials that primarily utilized the CTCAE, v. 3.0 criteria.

Two forms of honey are being tested, the standard liquid form and a lozenge form. All previous studies have used liquid honey. If the lozenge form is as active as the liquid, then there is likely an innate anti-mucositis activity of the honey independent of its physical form. The lozenge form has many advantages, including more regulated dosing, easier storage, easier distribution, and easier monitoring of patient compliance.

Further, the use of a patient-reported outcome, pain, as the primary endpoint for radiation esophagitis or head and neck mucositis never has been performed at the RTOG or other cooperative group. The use of pain as the endpoint introduces complexities that need to be evaluated in the phase II setting, as follows:

- Confirming the data of RTOG 98-01 that pain is the most sensitive patient-reported outcome for esophagitis. Pain will be compared to the other secondary outcomes, and within the arms, to confirm its sensitivity.
- There is no standard method of accounting for analgesic use when pain is the primary endpoint. RTOG 97-14, a randomized trial of 1 versus 10 fractions for bone metastases, used relief of pain as the primary endpoint but did not account for analgesic use. The subsequent trial, RTOG 0631(SBRT for spine metastases), opened to accrual in August 2009, evaluates pain relief “with no increase in narcotic pain medication”. Therefore, analgesic use will be monitored in the proposed study, and a secondary endpoint will show if analgesic use influences the reported pain measure. It is hypothesized that increasing summed pain will require increased analgesic use.

A randomized phase II trial is necessary for the following reasons: 1) The tolerability of this regimen and the compliance of patients taking it during chemoradiation therapy is unknown; 2) The activity of a lozenge form of honey is unknown; and 3) Historical controls prove unreliable in establishing efficacy of interventions for symptom management.

2.0 OBJECTIVES

2.1 Primary Objective

Evaluate the relative efficacy of 4 times a day consumption of liquid or lozenge Manuka honey to delay or prevent radiation esophagitis-related pain (during combined chemotherapy and radiation therapy for lung cancer) as compared to standard supportive treatment, as measured at week 4 by Numerical Rating Pain Scale (NRPS) for pain upon swallowing

2.2 Secondary Objectives

- 2.2.1 Evaluate the trend of severity of radiation esophagitis-related pain during combined chemotherapy and radiation therapy for lung cancer using weekly measurements of the NRPS;
- 2.2.2 Evaluate the adverse events associated with Manuka honey, as measured by CTCAE, v. 4;
- 2.2.3 Evaluate the severity of radiation esophagitis (grade 3-4, CTCAE, v. 4);
- 2.2.4 Assess weight loss (percent weight change from baseline to 4 weeks);
- 2.2.5 Assess quality of life (QOL) and pain, as measured by the EORTC QLQ-30 global QOL score and pain symptom subscale;
- 2.2.6 Assess patient-reported dysphagia via a daily patient log;
- 2.2.7 Assess nutritional status, as measured by the mean change in serum prealbumin levels from baseline to 4 weeks;
- 2.2.8 Assess opioid use by collecting the patient’s narcotic use in the previous 24 hour period at each weekly evaluation;
- 2.2.9 Evaluate patient-reported adverse events associated with Manuka honey using the PRO-CTCAE.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility

- 3.1.1** Patients being treated with combination chemotherapy (definitive or adjuvant) and radiation therapy once daily for small cell or non-small cell lung cancer [primary population for the trial];

Note: Patients can receive chemoradiotherapy while enrolled on an RTOG lung trial or while not enrolled on an RTOG lung trial. Patients cannot receive chemoradiotherapy while enrolled on a single institution trial or trials coordinated by other cooperative groups [to increase the homogeneity of the population].

- 3.1.2** At least 5 cm of the esophagus must be in the 60 Gy isodose volume in 1.6 to 2.0 Gy fractions [to insure that there is a significant risk for esophagitis among the patients];

- 3.1.3** Age \geq 18 [RTOG standard];

- 3.1.4** Patients must provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

- 3.2.1** Patients with metastatic disease [to increase the homogeneity of the population];

- 3.2.2** Patients with an inability to swallow thick liquids prior to treatment [to insure that the patient will be able to swallow the honey];

- 3.2.3** Patients with a known hypersensitivity to honey [to avoid unnecessary toxicity];

- 3.2.4** Patients not receiving chemotherapy [to increase the homogeneity of the population];

- 3.2.5** Patients receiving more than once-daily treatments [to increase the homogeneity of the population];

- 3.2.6** Patients who have received prior chemotherapy or radiation therapy [to increase the homogeneity of the population];

- 3.2.7** Patients unable to complete the required forms; however, verbal completion is adequate if recorded on the form daily [patient-reported pain is the primary endpoint];

- 3.2.8** Diabetes is not a contraindication to study enrollment, but patients with poorly controlled diabetes should not be enrolled.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

- 4.1.1** Physical exam, including weight within 2 weeks prior to treatment;

- 4.1.2** Baseline serum prealbumin levels, within 2 weeks prior to treatment;

- 4.1.3** Baseline EORTC QLQ-30 and pain subscale, NRPS, and patient's swallowing diary within 1 week prior to treatment;

- 4.1.4** Baseline PRO-CTCAE within 2 weeks prior to treatment.

4.2 Highly Recommended Evaluations/Management

Not applicable to this study.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements

5.1.1 *Pre-Registration Requirements for IMRT Treatment Approach*

In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit <http://rpc.mdanderson.org/rpc> and select "Credentialing" and "Credentialing Status Inquiry".

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the RPC web site at <http://rpc.mdanderson.org/rpc/>; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the

institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

The institution or investigator must complete a new IMRT Facility Questionnaire and send it to RTOG for review prior to entering any cases, and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at <http://atc.wustl.edu>. Upon review and successful completion of the “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.1.2 Pre-Registration for 3D-CRT Treatment Approach

Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients onto this study.

The new Facility Questionnaire (one per institution, available on the ATC website at <http://atc.wustl.edu>) is to be sent to RTOG for review prior to entering any cases. Upon review and successful completion of a “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing.

5.2 Regulatory Pre-Registration Requirements (2/28/12)

5.2.1 **U.S. institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, https://www.ctsu.org/public/CTSUIRBcertif_Final.pdf. The study-related regulatory documentation also may be e-mailed to the CTSU at CTSURegulatory@ctsu.cocccg.org. This must be done prior to registration of the institution’s first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)
*Note: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number

5.2.4 Pre-Registration Requirements for the Initial Shipment of Manuka Honey (2/28/12)

5.2.4.1 **U.S. Institutions:**

All pre-registration requirements must be met before registering the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org under protocol-specific materials/regulatory resources. U.S. institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

5.2.5 Pre-Registration Requirements for PRO-CTCAE (2/28/12)

5.2.5.1 Identifying/Obtaining a Computer for Patient Use

Sites must have a web-enabled computer accessible in participating clinics for patients to use to complete the PRO-CTCAE online at selected visits. Sites may either use existing computer hardware if these are reliable and available for this purpose, or a computer (i.e., a wireless tablet or laptop computer) can be sent to the site.

Sites should contact proctcae@mskcc.org to arrange for testing the adequacy of computer hardware and connectivity, and/or to arrange for computer hardware to be shipped for this purpose. **Note:** Priority will be given to CCOP sites for provision of computers. If an institution that is provided with a computer does not accrue patients in a timely manner, RTOG reserves the right to transfer the computer to another institution.

5.5.5.2 Site Personnel Training for PRO-CTCAE

Sites must identify personnel who will train patients to self-enter PRO-CTCAE data upon enrollment and who will follow-up with patients at scheduled visits (see schedule in Appendix II) for subsequent logins to the PRO-CTCAE system. These personnel will need to undergo training and receive passwords to use the system. Sites should contact Dr. Ethan Basch (ebasch@mskcc.org) and the PRO-CTCAE coordinators (proctcae@mskcc.org) with the

name(s) of personnel identified for this role, and to arrange for such personnel to complete online training.

5.3 Registration

5.3.1 Online Registration (2/28/12)

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via <http://phrp.nihtraining.com/users/login.php>).
- A representative from the institution must complete the Password Authorization Form at <http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpBu5AQ%3d&tabid=219> (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (<http://www.rtog.org>), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@acr-arrrs.org.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

- ### **6.1**
- Radiation therapy, delivered concurrently with chemotherapy, will be determined by the treating radiation oncologist. At least 5 cm of esophagus must be in the 60 Gy isodose volume to ensure that there is significant risk of esophagitis. Institutions will document the treatment given on the appropriate case report form (see Section 12.1).

7.0 DRUG THERAPY

Institutional participation in chemotherapy/drug studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Protocol treatment must begin on the day the patient begins radiation therapy.

7.1 Chemotherapy

7.1.1 Chemotherapy, delivered concurrently with radiation therapy, will be determined by the treating medical oncologist. Institutions will document the chemotherapy drug given, the doses planned, and the doses that the patient actually received on the appropriate case form (see Section 12.1).

7.2 Protocol Treatment

7.2.1 Arm 1

Patients will receive standard supporting care for esophagitis-related pain as needed during concurrent chemotherapy and radiation treatment. The following regimen is recommended, but the local standard of care is permitted.

- A compound containing viscous lidocaine and magnesium aluminum oxide (Maalox®);
- Liquid or solid oxycodone, 5-10 mg, every 3 hours as needed.

The use of sucralfate is discouraged because it is ineffective.

7.2.2 Arm 2

Patients will swallow 10 cc (approximately 2 level teaspoons) of liquid Manuka honey 4 times per day while awake over an approximately 12 hour period (e.g. 8 a.m., Noon, 4 p.m., and 8 p.m.) 7 days/week during concurrent chemotherapy and radiation treatment..

Patients will swallow the honey slowly over 3-5 minutes to allow coating of the esophagus. Patients do not need to swish the honey throughout the mouth. With each dose, patients will refrain from eating and drinking for 1 hour after swallowing the honey to avoid disruption of the honey-mucosal surface interface.

Patient compliance will be evaluated weekly in clinic visits. Patients are expected to receive 4 doses per day (28 doses per week), 7 days a week, during chemoradiation. Patients who take at least 15 doses of honey per week will be considered compliant. Patients that do not begin honey or require a feeding tube will be considered inevaluable.

See Section 9.1 for details of permitted supportive care for Arm 2 patients.

7.2.3 Arm 3

Patients will place 2 lozenges (the equivalent of 10 cc of liquid Manuka honey), one at a time, in the mouth, allow each lozenge to dissolve on the tongue/in the mouth, swallowing the honey as it dissolves. Patients will do this 4 times per day while awake over an approximately 12 hour period (e.g. 8 a.m., Noon, 4 p.m., and 8 p.m.) 7 days/week during concurrent chemotherapy and radiation treatment..

The patient should refrain from chewing the lozenge or swallowing it whole. Patients do not need to swish the honey throughout the mouth. Patients will refrain from eating and drinking for 1 hour after swallowing the honey to avoid disruption of the honey-mucosal surface interface.

Patient compliance will be evaluated weekly in clinic visits. Patients are expected to receive 4 doses per day (28 doses per week), 7 days a week, during chemoradiation. Patients who take at least 15 doses of honey per week will be considered compliant. Patients that do not begin honey or require a feeding tube will be considered unevaluable.

See Section 9.1 for details of permitted supportive care for Arm 3 patients.

7.3 Manuka Honey

7.3.1 Description

Honey is a bio-organic compound and as such has no fixed composition. Manuka (*Leptospermum scoparium*) honey is a standardized honey harvested in New Zealand that has been the subject of extensive testing and is considered the standard medicinal honey. Manuka

16 will be utilized for this study because this strength is readily available. The strength refers to the honey's antimicrobial activity.

Manuka honey is a more viscous honey than standard, commercially available, food-grade honeys (Madden 2011), Preliminary testing for a trial of Manuka honey for radiotherapy-induced oral mucositis (British Columbia Cancer Agency, NCT00615420) found the maximum tolerable dose among healthy volunteers was 10 ml (Hawley 2011). Above this dose there was excessive gagging and discomfort with swallowing.

Manuka honey for this study will be from a single lot. The documentation for the certification of the UMF rating will be provided by the honey growers. The honey will be irradiated in a Cobalt generator to 30 kGy to sterilize it. One percent of the lot (i.e. 1% of the jars of liquid honey and 1% of the lozenge packs; 1 lozenge per randomly selected pack will be tested) will be randomly selected by EMSL Analytical, Inc. for bacterial contamination testing and will conduct standard testing for clostridium, osmolality, and sugar content. This testing will be done for the Manuka honey provided for this trial throughout the course of the study.

7.3.2 Supply (2/28/12)

New Zealand honey growers will provide Manuka honey to patients on study free of charge, and it will be distributed by Aptuit, Inc. Honey is Generally Recognized As Safe (GRAS). The use of Manuka honey in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption.

The Study Agent Shipment Form (SASF); available on the RTOG web site, www.rtog.org under protocol-specific materials/regulatory resources for U.S. sites must be submitted to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. The completed SASF document may also be e-mailed to the CTSU at CTSURegulatory@ctsu.cocccg.org.

The drug supply will not be shipped by Aptuit, Inc. until the patient has been registered. RTOG will notify Aptuit, Inc. to initiate each of these shipments after registration of the patient. Aptuit, Inc. will ship drug according to the following schedule:

RTOG 1012 Shipment Schedule				
Patient Randomized	Initial e-order sent by RTOG	Initial e-order received by Aptuit (before 1 p.m. EST)	Initial order shipped by Aptuit	Initial order received at site
Monday	Monday	Monday	Tuesday	Wednesday
Tuesday	Tuesday	Tuesday	Wednesday	Thursday
Wednesday	Wednesday	Wednesday	Thursday	Friday
Thursday	Thursday	Thursday	Monday	Tuesday
Friday	Friday	Friday	Monday	Tuesday

Please contact the drug distributor listed in the protocol directly for shipment tracking information and anticipated delivery dates or if a shipment has not been received by the expected date.

At the completion of the study, unused supplies will be destroyed at the site according to the institution's policy for drug destruction.

Questions about supply and delivery should be directed to:

Aptuit (KCM)
10245 Hickman Mills Drive
Kansas City, MO 64137

Logistics Department
E-mail: logistics-kcm@aptuit.com
Fax: 866-600-0029

Phone: 816-767-6000 ext. 6775 / Toll Free 800-887-8429 ext. 6775

7.3.3 Accountability

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

7.3.4 Storage and Stability

Manuka honey is stable but should be kept between 10 and 90 degrees Fahrenheit. It can be stored in a refrigerator but does not need to be. It should be stored with the lid on.

7.3.5 Adverse Events

Patients may experience a burning of the mouth or esophagus when swallowing the honey.

7.4 Dose Modifications for Manuka Honey

If a patient cannot tolerate the full dose (10 cc or approximately 2 level teaspoons), the patient should take a reduced dose of 5 cc (approximately 1 level teaspoon). If the patient tolerates the 5 cc dose for 2 days, then the patient should again attempt the full dose (10 cc) again. If the patient cannot tolerate the full dose, then the patient will continue to take the reduced 5 cc dose. If the patient cannot tolerate a 5 cc dose, the patient should discontinue the honey, and the patient will be followed as specified in Section 12.1.

7.5 Modality Review

The Principal Investigator, Lawrence Berk, MD, PhD, will perform a Treatment Assurance Review of all patients who receive or are to receive treatment in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Principal Investigator, Lawrence Berk, MD, PhD, will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Berk will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

7.6 Adverse Events (2/28/12)

The NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4 will be utilized for adverse event (AE) reporting. CTCAE v. 4 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of CTCAE, v. 4.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site ([https://webapps.ctep.nci.nih.gov/openapps/plsql/qadeers_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/qadeers_main$.startup)).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (<http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx>) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

7.6.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. January 2005; <http://ctep.cancer.gov/reporting/adeers.html>]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.7 also must be reported via AdEERS.**

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.6.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons and to fulfill

the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. **Note:** Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.6.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system **within 30 days of AML/MDS diagnosis**. If reporting in CTCAE, v. 4, the event(s) may be reported as 1) Leukemia secondary to oncology chemotherapy; 2) Myelodysplastic syndrome; or 3) Treatment-related secondary malignancy.

7.7 AdEERS Expedited Reporting Requirements (2/28/12)

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies within 30 Days of the Last Administration of the Agent/Intervention
1,2

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)				
NOTE: Investigators MUST immediately report to the sponsor (NCI) ANY Serious Adverse Events, whether or not they are considered related to the agent/intervention (21 CFR 312.64)				
An adverse event is considered serious if it results in ANY of the following outcomes:				
<ol style="list-style-type: none"> 1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) A congenital anomaly/birth defect. 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). 				
ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.				
Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

NOTE: Deaths clearly due to progressive disease should **NOT** be reported via AdEERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a non-CTEP-IND:

Not applicable to this study.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy for Arm 2 or Arm 3 Patients

9.1.1 If Arm 2 or Arm 3 patients require supporting care for esophagitis-related pain during concurrent chemotherapy and radiation treatment, the following regimen is recommended, but the local standard of care is permitted.

- A compound containing viscous lidocaine and magnesium aluminum oxide (Maalox®);
- Liquid or solid oxycodone, 5-10 mg, every 3 hours as needed.

The use of sucralfate is discouraged because it is ineffective and may interfere with the honey.

9.1.2 Supplemental treatments, such as biologics, must be documented on the appropriate case report forms (see Section 12.1).

9.2 Permitted Supportive Therapy for All Patients

- Nutritional supplements;
- Appetite stimulants.

9.3 Feeding Tubes

Feeding tubes are discouraged unless needed for severe or rapid malnutrition or for dysphagia preventing adequate nutrition. If a feeding tube is placed, honey must be discontinued, and the patient will be followed as specified in the protocol.

9.4 Prohibited Therapy

9.4.1 Therapeutic use of honey other than the Manuka honey provided for this trial is not allowed while patients are on study. Patients also must avoid honey-flavored medical products and/or sugary, viscous substances.

9.4.2 Amifostine is not permitted.

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II.

11.2 Quality of Life Assessments

NOTE: For this study, patients must consent to complete a daily swallowing diary and the quality of life and pain assessments. See Appendix II for assessment timeframes.

11.2.1 Patient's Swallowing Diary (see Appendix X)

The patient is asked to rate his/her swallowing ability each day during treatment and at 12 weeks from the start of treatment. The rating scale is as follows: 1=No problem; 2=Mild soreness only; 3=Can swallow solids with some difficulty; 4=Cannot swallow solids; 5=Cannot swallow liquids. Institutions will keep the diaries as source documentation and will report the patients' scores via the Cover Sheet for Swallowing Diary (DP), as specified in Section 12.1.

11.2.2 Numerical Rating Pain Scale (NRPS) [see Appendix IX]

The NRPS is an 11-point scale (0-10). Patients are instructed that 0 indicates no pain and that 10 indicates the worst pain imaginable. In general, scores of 1-4 indicate mild pain, scores of 5-6 indicate moderate pain, and scores of 7-10 indicate severe pain. The NRPS is only available in English. Patients can complete the NRPS in approximately 1 minute. Institutions will keep the pain scale as source documentation and will report the patients' scores via the Cover Sheet for the NRPS (QP) as specified in Section 12.1.

11.2.3 EORTC QLQ-30 and Pain Subscale

The QLQ-30 is a 30-item, self-reporting questionnaire that is grouped into 5 functional subscales and 3 multi-item symptom scales. The EORTC QLQ-30 pain symptom subscale consists of 2 items of the 30-item QLQ-30: question 9, "Have you had pain?" and question 19, "Did pain interfere with your daily activities?". The QLQ-30 has been translated into 81 languages, specified at http://groups.eortc.be/qol/questionnaires_qlqc30.htm. Patients can complete the 30-item questionnaire in approximately 15 minutes.

11.2.4 PRO-CTCAE (2/28/12)

In this trial, PRO-CTCAE responses will be collected at clinic visits via computers using an online questionnaire at scheduled time points (see schedule in Appendix II). To complete this electronic questionnaire, site research personnel who have been trained to use the PRO-CTCAE system (see Section 5.5.5.2) will register participating patients into the PRO-CTCAE software system for this trial, assign a user name and password for that patient, teach that patient how to self-report symptoms via the PRO-CTCAE system, and remain available to patients to assist them with self-reporting via computer at each required login time point. If a visit is rescheduled/delayed, the PRO-CTCAE self-report can be rescheduled using the scheduling feature of the PRO-CTCAE software. If a patient attends a scheduled visit but misses a scheduled PRO-CTCAE self-report, a grace period of up to 3 business days is allowed for the patient to complete the self-report at a subsequent visit. If the patient does not have a scheduled visit during this timeframe, site research personnel will call the patient to administer the questionnaire via telephone, enter the responses into the PRO-CTCAE software, and assess the reason for missing the login via the Missed Login Form (Appendix XIII).

If a patient is unable to complete the PRO-CTCAE form via computer or if there is technical difficulty with the computer, the form can be printed and completed either by the patient or by site research personnel via a verbatim interview (i.e. reading the PRO-CTCAE items to the patient and recording responses unaltered). Site research personnel will then enter these responses into the PRO-CTCAE online interface. Site research personnel will be taught how to print the paper backup forms and enter the results into the PRO-CTCAE system during the PRO-CTCAE training

11.2.4.1 Clinical Research Associate (CRA) Survey (2/28/12)

In order to assess the feasibility of implementing the PRO-CTCAE at sites, CRAs at participating sites will complete the "Brief CRA PRO-CTCAE Survey" available on the RTOG web site, www.rtog.org on the 1012 protocol page under "Miscellaneous". The purpose of this survey is to explore the barriers and challenges to widespread adoption of the PRO-

CTCAE system for use in cooperative group clinical trials. The survey and discussion will focus on the amount of time required to learn how to use the system, to teach patients to use the system, to follow-up information in the system, and to address any technical issues. Other effort or costs associated with implementing the system will be explored. This survey also will ask if personnel are willing to participate in a brief discussion about the feasibility of the PRO-CTCAE at their site

CRAs will complete the survey at 14 weeks after the first after the first patient is enrolled at each site. Each CRA at participating sites will complete the survey **once** and will send the completed survey to:

Lauren Rogak
 PRO-CTCAE Project Manager
 Memorial Sloan-Kettering Cancer Center
 307 East 63rd Street
 New York, NY 10065
 FAX: 646-735-0011
 E-mail: rogakl@mskcc.org

11.4 Criteria for Discontinuation of Protocol Treatment

- Placement of a feeding tube;
- Inability to tolerate Manuka honey.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (2/28/12)

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
EORTC QLQ-30 (QL)	
Cover Sheet for Numerical Rating Pain Scale (NRPS) [QP]	
Cover Sheet for Swallowing Diary (DP)	
PRO-CTCAE (See Section 11.2.4)	
NRPS (QP)	Weekly during treatment (weeks 1-6); Note: Only patient reporting during treatment
PRO-CTCAE (See Section 11.2.4)	
Swallowing Diary (DP)	
EORTC QLQ-30 (QL)	4 weeks from the start of treatment; Note: Sites submit the QP form.

Cover Sheet for Numerical Rating Pain Scale (NRPS) [QP]
PRO-CTCAE (See Section 11.2.4)

Treatment Form (TF) At end of treatment
Cover Sheet for Swallowing Diary (DP)
Cover Sheet for Numerical Rating Pain Scale (NRPS) [QP]

Daily treatment chart (T5) Within 1 week of RT end
Color copy of DVH (DV) **V60 must be included**
Radiotherapy Form (T1)

EORTC QLQ-30 (QL) 12 weeks from the start of treatment; **Note:** if there are no adverse events to report, submit a Communication Memo (CM) for suppression.
Cover Sheet for Numerical Rating Pain Scale (NRPS) [QP]
Cover Sheet for Swallowing Diary (DP)
PRO-CTCAE (See Section 11.2.4)
Adverse Event Form (AE)

NOTE: For cases not registered to an RTOG lung trial, RTOG HQ may need to request additional RT data.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

Radiation esophagitis-related pain, 4 weeks from the start of treatment as measured by the Numerical Rating Pain Scale for pain on swallowing (NRPS)

13.1.2 Secondary Endpoints

- 13.1.2.1** Radiation esophagitis during treatment as measured weekly during treatment and 12 weeks from the start of treatment by the NRPS;
- 13.1.2.2** Dysphagia via daily patient log;
- 13.1.2.3** Quality of life and pain, as measured by the EORTC QLQ-30 global QOL score and pain symptom subscale at 4 and 12 weeks;
- 13.1.2.4** Radiation esophagitis grade 3-4 (CTCAE, v. 4);
- 13.1.2.5** Weight loss (percent change from baseline to 4 weeks);
- 13.1.2.6** Nutritional status (change in serum prealbumin levels from baseline to 4 weeks);
- 13.1.2.7** Opioid use;
- 13.1.2.8** Adverse events associated with Manuka honey using CTCAE, v. 4;
- 13.1.2.9** Patient reported adverse events associated with Manuka honey using the PRO-CTCAE.

13.2 Sample Size

13.2.1 Stratification and Randomization

Patients will be stratified by the percentage of the esophagus in the radiation field (V60 ≤ 30% vs. V60 > 30%). Previous analysis has shown that the rate of esophagitis is dependent on the volume receiving higher dose, and there is a higher rate of esophagus if greater than 30% of the esophagus receives more than 60 Gy (Rose 2009). The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution. Within each stratum, patients will be randomized in a 1:1 ratio to treatment arms until the accrual of this study is met in order to avoid any imbalance in radiation volume.

13.2.2 Sample Size Justification

Given that a standard Manuka honey regimen has not been well established for reducing severity of esophagitis-related pain and that the use of historical controls proves unreliable in establishing the efficacy of interventions for symptom management, a randomized phase II design including a standard arm will be used to determine if a phase III trial is warranted (Rubinstein 2005). The experimental arms (Arms 2 and 3) will be compared with a standard arm (Arm 1). There will not be a comparison between the 2 experimental arms (i.e. only Arm 1 vs. Arm 2 and Arm 1 vs. Arm 3).

The sample size is specified to provide adequate power to address the specific primary hypotheses that the use of Manuka honey in the liquid or lozenge form (Arm 2 or Arm 3) will result in a clinically significant reduction in the severity of patient-reported chemoradiation-induced esophagitis as compared to standard supportive care (Arm 1). We do not expect the Manuka honey to prevent esophagitis but anticipate reduced severity. The changes of esophagitis-related pain due to chemoradiation at 4 weeks from baseline will be the primary endpoint. Esophagitis-related pain will be measured using patient-reported pain on swallowing as assessed by the Numerical Rating Pain Scale (NRPS). Minimal variation is expected between this local pain assessment and the global pain assessment used in RTOG 98-01 (EORTC QLQ-30 pain symptom scale), for which historical data is available. The sample size is therefore calculated using the EORTC QLQ-30 pain symptom subscale from RTOG 98-01.

RTOG 98-01 was a randomized phase III trial evaluating the use of amifostine (AM) for mucosal protection in patients receiving both induction and concurrent chemotherapy with hyperfractionated radiation for the treatment of inoperable stage II-III/A-B NSCLC. Although the primary objective evaluated esophagitis according to the CTCAE v. 3.0 criteria, the EORTC QLQ-30 was assessed as a secondary objective. Published results focus on changes prior to induction chemotherapy and 6 weeks post-concurrent chemoradiation. Non-published data will be used to focus on changes prior to and immediately after concurrent chemoradiation. RTOG 98-01 accrued 223 patients, of which 123 were randomized to no AM. Thirty-nine patients completed the EORTC QLQ-30 pain symptom subscale both prior to and immediately after chemoradiation. The pain subscale ranges from 0-100 with higher scores indicating increased pain severity. The mean increase in pain severity for these patients was 20.9 (standard deviation [SD]=5.9).

Despite restricting the use of hyperfraction and allowing non-NSCLC patients in the proposed trial, we expect patients receiving standard supportive care (Arm 1) to have a similar increase in esophagitis-related pain from pre-to-post chemoradiation as evidenced in RTOG 98-01. We expect patients receiving Manuka honey to experience statistically significant less esophagitis-related pain.

The null hypothesis (H₀) is that the use of Manuka honey in either liquid or lozenge form is not effective in reducing esophagitis-related pain versus the alternative hypothesis (H_A) that the use of Manuka honey is effective in reducing esophagitis-related pain. The hypotheses are:

$$H_{01}: \mu_1 \leq \mu_2 \text{ vs. } H_{A1}: \mu_1 > \mu_2 \text{ and } H_{02}: \mu_1 \leq \mu_3 \text{ vs. } H_{A2A}: \mu_1 > \mu_3$$

where, μ_1 , μ_2 , and μ_3 denote the mean change score from the baseline of Arm 1, Arm 2, and Arm 3 at 4 weeks, respectively. 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 significant level of 0.1 before the Bonferroni adjustment) and 80% statistical power for each hypothesis testing, 45 patients per arm would be required to detect at least 15% relative reduction (absolute difference of mean change score of 3.1 and effect size=0.53) in the NRPS score change at 4 weeks from baseline. As this is a phase II trial, patients that do not receive any Manuka honey treatment or require a feeding tube will be considered inevaluable (Section 7.2). Adjusting for 5% clinically ineligible and 5% inevaluable cases by a total of 10%, **a target sample size of 150 patients is required for this study.**

13.3 Patient Accrual

RTOG phase III treatment trials for this lung population will be open simultaneously with RTOG 1012. The RTOG Lung Cancer Committee has reviewed the eligibility criteria and honey regimen for RTOG 1012 and determined that symptom management will not interfere with the administration or evaluation of the disease treatment. Patients will be allowed to simultaneously enroll in RTOG 1012 and a treatment trial and receive their chemoradiation as specified in the treatment trial protocol.

RTOG 98-01 accrued 243 patients averaging 5.7 patients per month. We anticipate accruing 5 patients per month. No accrual is expected during the first 3 months after trial activation as institutions obtain IRB approval. A total accrual of 5 patients is expected during the next 3 months. Monthly accrual is then expected to reach 5 patients per month for total accrual duration

of 29 months. The RTOG Data Monitoring Committee (DMC) will evaluate patient accrual semiannually.

13.4 Analysis Plan

Promising results would provide evidence to support a future phase III trial to definitively evaluate Manuka honey for the reduction of esophagitis-related pain.

13.4.1 Primary Endpoint

The primary endpoint is change in esophagitis-related pain (NRPS pain on swallowing) from baseline to 4 weeks where a low score represents less pain and a high score represents more pain. Patients who do not receive any Manuka honey treatment or require a feeding tube will be considered inevaluable. All evaluable patients assessed at 4 weeks will be included in the analysis. Although missing assessments should be minimized due to current improved data collection methods, some patients alive at 4 weeks may not be assessed. Sensitivity analyses will be conducted to determine the impact of the exclusion.

The primary endpoint will be evaluated using the two-sample t-test with a significance level of 0.05 (one-sided) for the following 2 hypotheses separately. We hypothesize a relative decrease of 15% in the NRPS score change at 4 weeks from baseline (absolute difference of mean change score of 3.1 and effect size=0.53) due to honey.

$$H_{01}: \mu_1 \leq \mu_2 \text{ vs. } H_{A1}: \mu_1 > \mu_2 \text{ and } H_{02}: \mu_1 \leq \mu_3 \text{ vs. } H_{A2A}: \mu_1 > \mu_3$$

The following action will be taken based on the testing results:

If neither Arm 2 or Arm 3 is better than Arm 1 (fail to reject both H_{01} and H_{02}), then there is not enough evidence to conclude that honey is effective in reducing esophagitis-related pain, and there is no support for a subsequent Phase III study.

If either Arm 2 or Arm 3 (not both) is better than Arm 1 (reject H_{01} or reject H_{02}), then it can be concluded that there is strong support for a subsequent phase III trial with the experimental arm (Arm 2 or Arm 3) that rejected the null hypothesis.

If both Arm 2 and Arm 3 are better than Arm 1 (reject H_{01} and reject H_{02}), then it can be concluded that there is strong support for a subsequent phase III trial with the experimental arm (Arm 2 or 3) that has a lower mean pain score. If Arm 2 and Arm 3 have the same mean pain score, then Arm 3 would be chosen because of the convenience of the lozenge form.

In addition to the evaluation of esophagitis-related pain at 4 weeks, overall severity of esophagitis during treatment will be evaluated using the general linear model, allowing for adjustments due to covariates of interest such as the percentage of esophagus irradiated, type of chemotherapy, surgery status, treatment arm, and compliance.

13.4.2 Secondary Endpoints

13.4.2.1 Patient-Reported Outcomes

The EORTC QLQ-30 will be completed at baseline and at 4 and 12 weeks from start of treatment. The pain symptom subscale (2 items) will evaluate pain and the global score (30 items) will evaluate quality of life at week 6 post-treatment. Each ranges from 0-100 with lower scores indicating lesser burden and improved symptoms or quality of life. The patient will complete a swallowing diary daily during treatment and at 12 weeks from the start of treatment. The scores at baseline and during treatment per patient will be used to evaluate the symptom trends using the general linear model with (at minimum) stratification variable (percentage of esophagus irradiated), chemotherapy, surgery, treatment arm, and compliance. The coefficient of treatment arm will be tested at the significance level of 0.05.

13.4.2.2 Weight Loss and Nutritional Status

Patient weight loss will be evaluated by comparing the percent weight change per patient from baseline to 4 weeks between treatment arms using the Wilcoxon-rank sum test at the significance level of 0.05. Patient nutritional status will be evaluated using the Wilcoxon-rank sum test to compare the change in serum prealbumin levels per patient from baseline to 4 weeks between treatment arms at the significance level of 0.05.

13.4.2.3 Opioid Use

Patients with at least 1 reported administration of opioid analgesic will be considered to have received opioid analgesics. The total dose of opioid analgesics will be the sum of all opioid analgesic administrations that have been converted to morphine equivalents. Use of opioid analgesics will be assessed for a 24-hour period before completing the assessment weekly during chemoradiation. The relationship between analgesic use and esophagitis-related pain will be evaluated using the general linear model with (at minimum) stratification variable (percentage of esophagus irradiated), chemotherapy, surgery, treatment arm, and compliance.

13.4.3.4 Adverse Events (CTCAE, v. 4)

Adverse events related to Manuka honey will be reported. Additionally, the incidence of grade 3-4 radiation induced esophagitis during treatment will be compared between treatment arms using Fisher's exact test at the significance level of 0.05.

13.4.2.5 Patient-Reported Adverse Events (PRO-CTCAE)

Patient-reported adverse events related to Manuka honey will be reported using the PRO-CTCAE which looks to detect a difference in a symptom of interest between each experimental arm (Arms 2 and 3) and the control arm (Arm 1). For each PRO-CTCAE item, the change in the patient-reported score from baseline to 4 weeks will be computed and compared between each experimental arm and the control arm (i.e. 2 comparisons) using two-sample t-tests. Supplemental investigation will use analysis of covariance to compare the measurement at 4 weeks while adjusting for the baseline value as well as t-tests comparing maximum post-baseline score and maximum change from baseline between the arms. Due to the lack of prior data on the PRO-CTCAE, moderate effect sizes of 0.6 and 0.69 (in standard deviation units) were chosen for use in this study (Cohen 1988). For the 45 patients with data in each arm, we will have 80% power to detect an effect size of 0.60 and 90% power to detect an effect size of 0.69 with a Bonferonni adjusted two-sided significance level of 0.05 (overall alpha per symptom of 0.10). The primary item of interest assesses difficulty swallowing, with all other items considered secondary.

13.5 Interim Reports to Monitor Study Progress

Interim reports will be prepared semiannually until the primary efficacy analysis has been accepted for presentation or publication. These reports will contain the following, at a minimum: patient accrual rate and projected completion date for accrual phase; total institution accrual; patient exclusions and reasons for exclusion; pretreatment characteristics for eligible patients; patient compliance with baseline quality of life assessments; frequency and severity of adverse events. The interim reports will not contain treatment results with respect to the primary or secondary endpoints.

The RTOG Data Monitoring Committee (DMC) will monitor the study for safety and feasibility.

In addition, adverse events for this study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means.

13.6 Reporting the Initial Treatment Results

The primary hypothesis of this study is to evaluate the efficacy of Manuka honey for preventing radiation induced esophagitis-related pain and determine the appropriate parameters for a future definitive phase III trial. The analysis will be reported when 135 eligible patients have been followed for at least 1 month. It will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; and observed results with respect to the primary and secondary endpoints. The primary hypothesis will be evaluated using the two-sample t-test as specified in the analysis plan. Also, where feasible, treatment evaluation with respect to all endpoints will be compared within each racial and ethnic category.

13.7 Gender and Minorities

In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of women and minorities will be examined during the interim reports. Based on accrual statistics from RTOG 9801, the projected accrual by gender, race, and ethnicity is shown below:

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	2	4	6
Not Hispanic or Latino	56	88	144
Ethnic Category: Total of all subjects	58	92	150
	Gender		
Racial Category	Females	Males	Total
American Indian or Alaskan Native	0	0	0
Asian	2	4	6
Black or African American	5	10	15
Native Hawaiian or other Pacific Islander	0	0	0
White	51	78	129
Racial Category: Total of all subjects	58	92	150

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APPENDIX I

RTOG 1012

Informed Consent Template for Cancer Treatment Trials (NCI Template Date: August 2009) **(English Language)**

Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have lung cancer for which you are going to receive a combination of radiation treatment and chemotherapy, and this treatment may irritate your esophagus (esophagitis).

Why is this study being done?

Irritation of your esophagus (tube between your mouth and stomach for food) may feel like pain or burning when swallowing or may feel like difficulty in swallowing [esophagitis]. As a result of the combination of radiation treatment and chemotherapy they receive for their lung cancer, most patients experience irritation of their esophagus.

The standard supportive care for esophagitis-related pain is the use of medications to mask pain. Standard care does not prevent pain.

In clinical trials, honey has been shown to be an effective wound dressing and has been shown to prevent blistering in the mouth (mucositis) as a result of radiation treatment. In this study, the researchers hope that honey will delay or prevent the pain in your esophagus while you are receiving cancer treatment, allowing you to swallow more easily and eat more comfortably. The honey given to patients in this study is Manuka honey, a standardized honey that has been thoroughly tested and is considered the standard medicinal honey.

The purpose of this study is to compare the effects, good and/or bad, of standard supportive care with honey on you and your esophagitis-related pain to find out which is better. In this study, you will get either the standard supportive care or the honey. However, if you receive the honey and it does not prevent esophagitis-related pain, your doctor will give you medicine to help with your pain.

How many people will take part in the study?

About 150 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study, you will need to have the following exams, tests or procedures:

- A physical examination, including documentation of your weight
- A blood test (about 2 teaspoons of blood will be taken from your vein) to evaluate your nutrition

- You will complete a quality of life questionnaire asking how your life has been affected by cancer and its treatment and about pain you may be experiencing. This questionnaire will take about 15 minutes to complete.
- You will rate your pain by circling one number on a scale of 0-10.
- You will record your swallowing ability by choosing one number on a scale of 1 to 5.

In addition, before beginning treatment, you will be asked to answer questions about your symptoms using a computer. This information is part of a research project for the National Cancer Institute (NCI) to understand if patient reporting of symptoms will better inform clinical staff about the side effects of cancer treatment.

It is important that you understand that the symptom information you provide will not be seen by your doctor or nurse and is for research purposes only. Therefore, if you are experiencing symptoms that worry you, you cannot rely on this system to communicate this information to your doctor. You should tell your doctor about these problems.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have a one in three chance of being placed in one of the groups.

If you are in group 1 (often called "Arm A"), you will receive standard supportive care for esophagitis-related pain (medications to mask pain) while you are receiving radiation and chemotherapy.

If you are in group 2 (often called "Arm B"), you will receive liquid honey that may delay or prevent esophagitis-related pain. You will slowly swallow 2 level teaspoons of honey to allow coating of the esophagus. You do not need to swish the honey in your mouth. You will swallow the honey 4 times a day (for example at 8 a.m., noon, 4 p.m. and 8 p.m.), 7 days a week while you are receiving radiation and chemotherapy. You should not eat or drink for 1 hour after swallowing the honey.

If you are in group 3 (often called "Arm C"), you will receive honey in tablet form (a lozenge) that may delay or prevent esophagitis-related pain. You will let 2 tablets melt in your mouth (one at a time) to allow coating of the esophagus. You should not chew the honey tablet or swallow it whole. You will take the 2 tablets 4 times a day (for example at 8 a.m., noon, 4 p.m. and 8 p.m.), 7 days a week while you are receiving radiation and chemotherapy. You should not eat or drink for 1 hour after letting the lozenges melt in your mouth.

Patients in any group must not eat or drink any honey while on study, other than that provided for group 2 and group 3 patients. In addition, all patients must not eat or drink sugary, thick substances or honey-flavored medicinal products while on study.

During the study, you will need these tests and procedures:

Each day during treatment: You will record your swallowing ability by choosing one number on a scale of 1-5.

Weekly during treatment:

- You will rate your pain by circling one number on a scale of 0-10.
- You will be asked to answer questions about your symptoms using a computer.
- Evaluation of any side effects from treatment you may be having

At 4 weeks from the start of treatment:

- A physical examination, including documentation of your weight
- A blood test (about 2 teaspoons of blood will be taken from your vein) to evaluate your nutrition
- You will be asked to answer questions about your symptoms using a computer.
- You will complete a quality of life questionnaire asking how your life has been affected by cancer and its treatment and about pain you may be experiencing. This questionnaire will take about 15 minutes to complete.
- You will rate your pain by circling one number on a scale of 0-10.

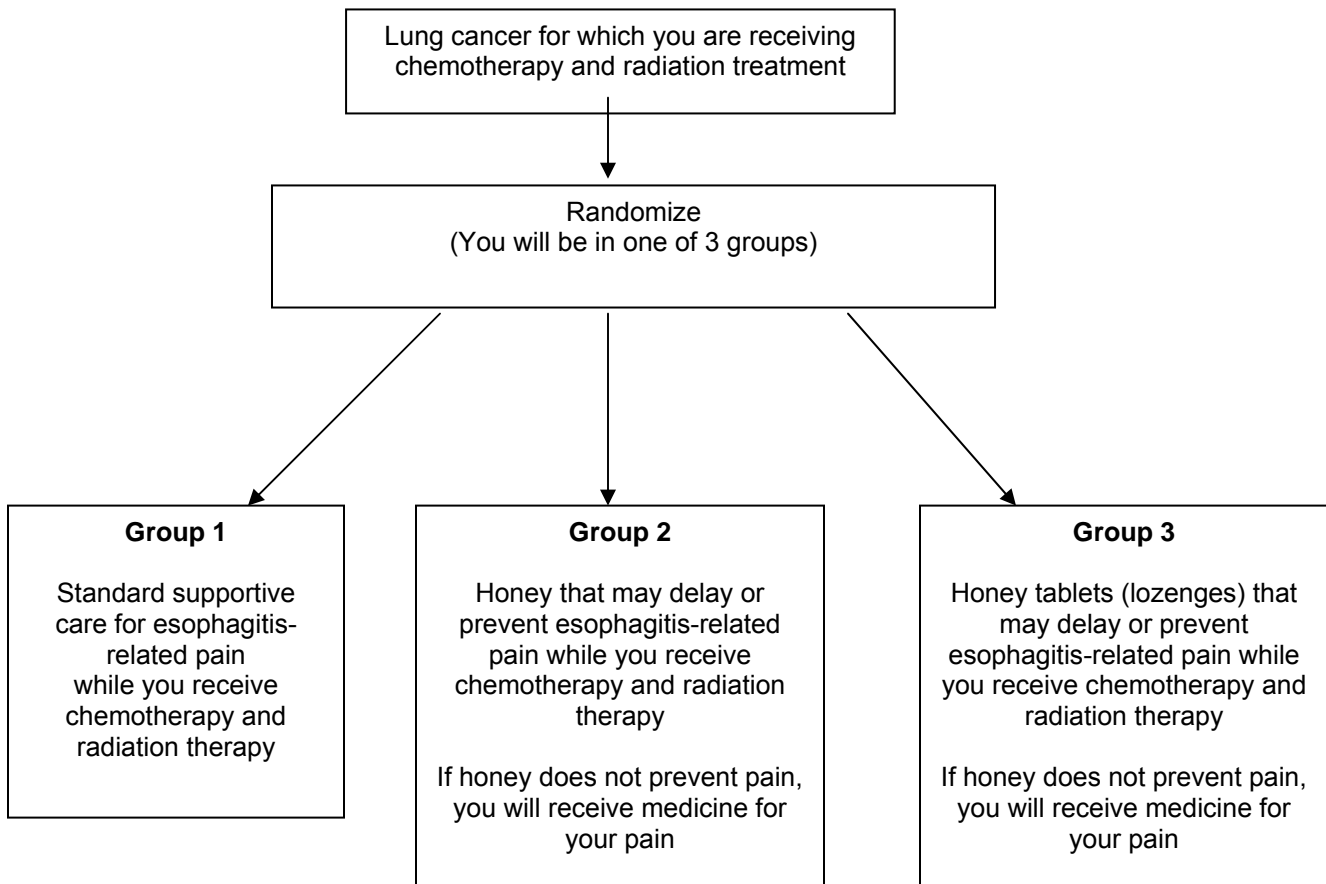
When you are finished with treatment:

At 12 weeks from the start of treatment:

- Evaluation of any side effects from treatment you may be having
- You will be asked to answer questions about your symptoms using a computer.
- You will complete a quality of life questionnaire asking how your life has been affected by cancer and its treatment and about pain you may be experiencing. This questionnaire will take about 15 minutes to complete.
- You will record your swallowing ability by choosing one number on a scale of 1- 5.
- You will rate your pain by circling one number on a scale of 0-10.

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study?

You will receive standard supportive care or honey while you receive chemotherapy and radiation therapy for your lung cancer (usually 6 weeks). At 12 weeks from the start of supportive care or honey, you'll be seen in a follow-up visit.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the honey.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to Manuka honey include those which are:

Less Likely: Burning of the mouth or esophagus when swallowing the honey

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make it easier for you to swallow more easily or eat more comfortably while receiving chemotherapy and radiation therapy for your cancer. While researchers hope that honey delay or prevent esophagitis-related pain resulting from cancer treatment, there is no proof of this yet. We do know that the information from this study will help researchers learn more about honey as a treatment for esophagitis-related pain. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private? (2/28/12)

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Pharmaceutical Collaborator (supplier of Manuka honey, the Active Manuka Honey Association)

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov> as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of study results. You can search this web site at any time.

[Note to Local Investigators: The above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The New Zealand honey growers will supply honey at no charge while you take part in this study. Even though it probably won't happen, it is possible that the supplier may not continue to provide the honey for some reason. If this would occur, the study would close.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Monitoring Committee (DMC) will be regularly meeting to monitor safety and other data related to this study. The Committee members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://www.cancer.gov/cancertopics/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II

STUDY PARAMETER TABLE

Assessments	Pre-Treatment	Weekly During Treatment	At 4 weeks from Start of Treatment	At 12 weeks from Start of Treatment
Physical Exam, with weight	Within 2 weeks prior to treatment		X	
Serum prealbumin levels	Within 2 weeks prior to treatment		X	
EORTC QLQ-30 and pain subscale	Within 1 week prior to treatment		X	X
NRPS		X	X	X
Patient-reported swallowing diary		Daily		X
PRO-CTCAE	Within 2 weeks prior to treatment	X	X	X
Adverse event evaluation		X		X

APPENDIX III

ZUBROD PERFORMANCE SCALE

- 0 Fully active, able to carry on all predisease activities without restriction**
- 1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
- 3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
- 4 Completely disabled. Cannot carry on self-care. Totally confined to bed**
- 5 Death**

APPENDIX IV

AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

LUNG

Primary Tumor (T)

- TX** Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
- T0** No evidence of primary tumor.
- Tis** Carcinoma *in situ*
- T1** Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
- T1a** Tumor 2 cm or less in greatest dimension
- T1b** Tumor more than 2 cm but 3 cm or less in greatest dimension
- T2** Tumor more than 3 cm but 7 cm or less with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
- T2a** Tumor more than 3 cm but 5 cm or less in greatest dimension
- T2b** Tumor more than 5 but 7 cm or less in greatest dimension
- T3** Tumor more than 7 cm or one that directly invades any of the following: parietal (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
- T4** Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodules in a different ipsilateral lobe

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

Regional Lymph Nodes (N)

- NX** Regional lymph nodes cannot be assessed
- N0** No regional lymph nodes metastasis
- N1** Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension
- N2** Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
- N3** Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

- M0** No distant metastasis
- M1** Distant metastasis
- M1a** Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion*
- M1b** Distant metastasis

* Most pleural (and pericardial effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element, and the patient should be classified as M0.

STAGE GROUPING

Occult Carcinoma	TX, N0, M0
Stage 0	Tis, N0, M0
Stage IA	T1a-b, N0, M0
Stage IB	T2a, N0, M0
Stage IIA	T2b, N0, M0
	T1a-b, N1, M0
	T2a, N1, M0
Stage IIB	T2b, N1, M0
	T3, N0, M0
Stage IIIA	T1a-b, N2, M0
	T2a-b, N2, M0
	T3, N1-2, M0
	T4, N0-1, M0
Stage IIIB	T1a-b, N3, M0
	T2a-b, N3, M0
	T3, N3, M0
	T4, N2-3, M0
Stage IV	Any T, Any N, M1a-b

APPENDIX V

Mucositis Models

Figure 1. Pathobiology of Mucositis (Sonis 1998)

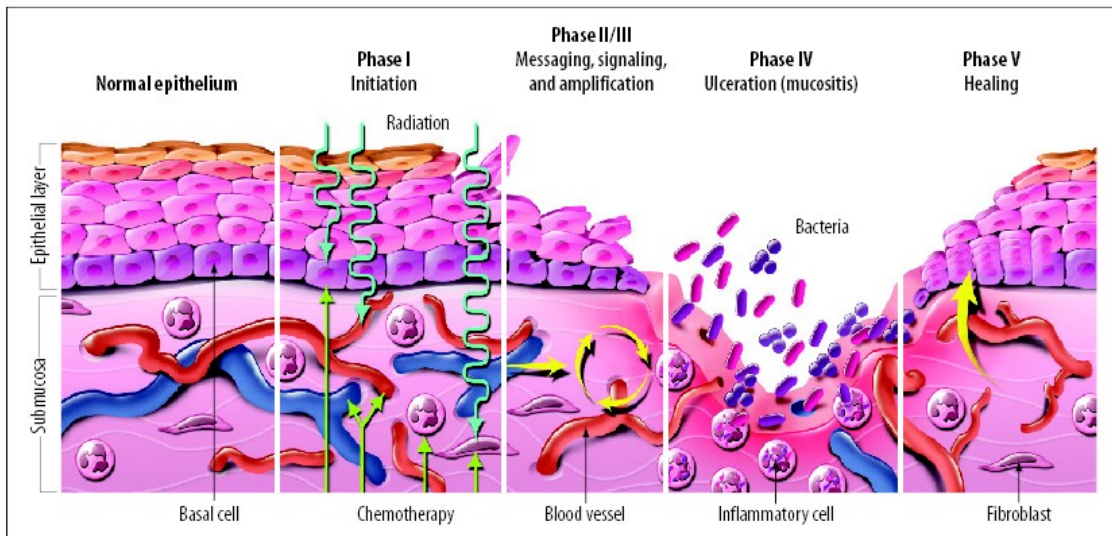
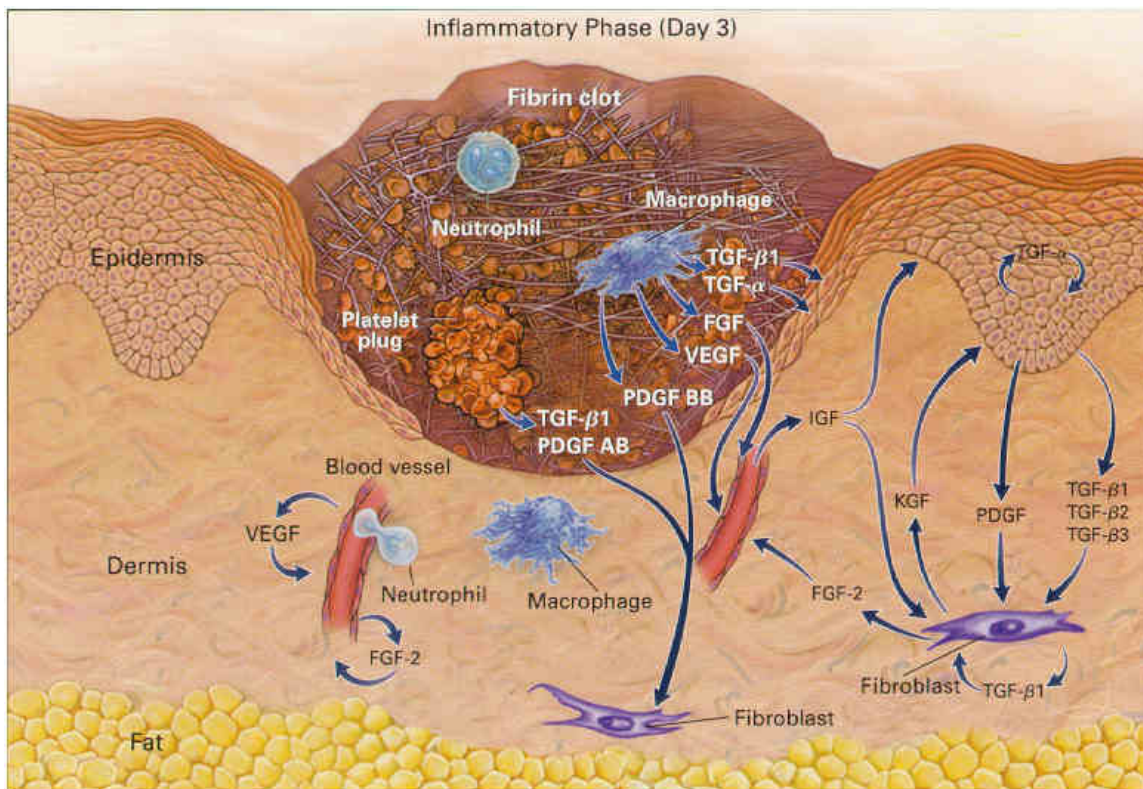
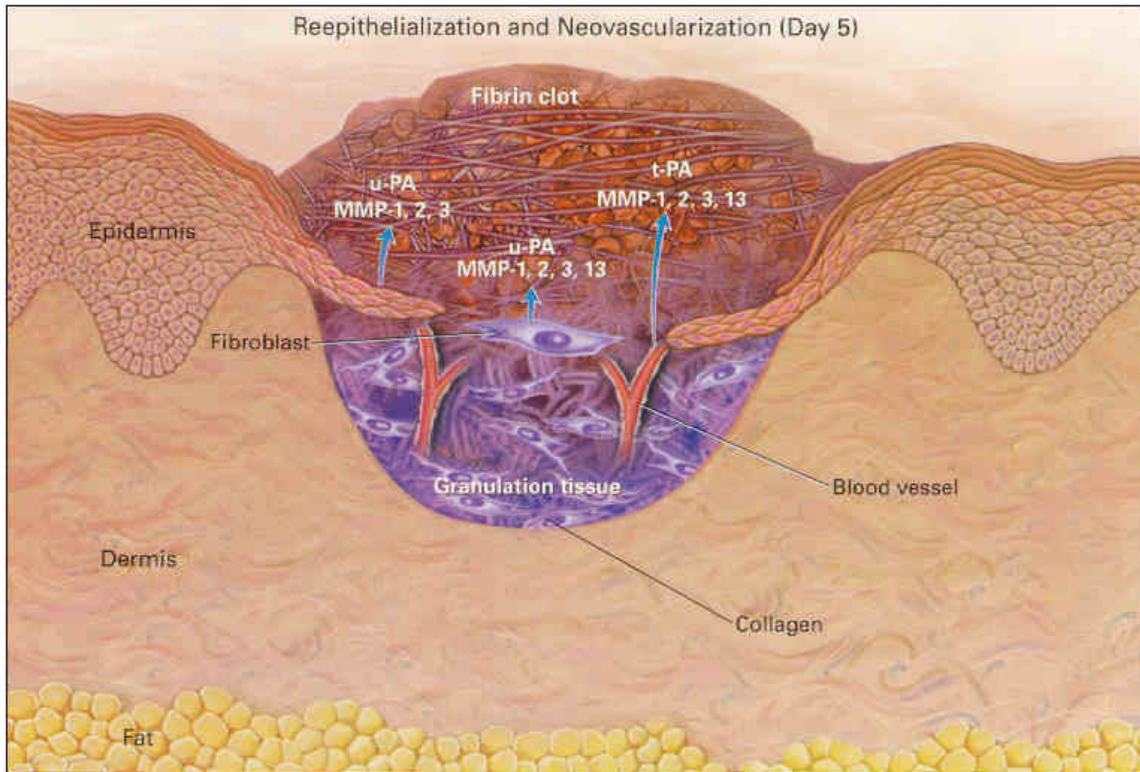


Figure 2: Microdynamics of Phase II/III of the Sonis Model in Dermatitis (Singer 1999)



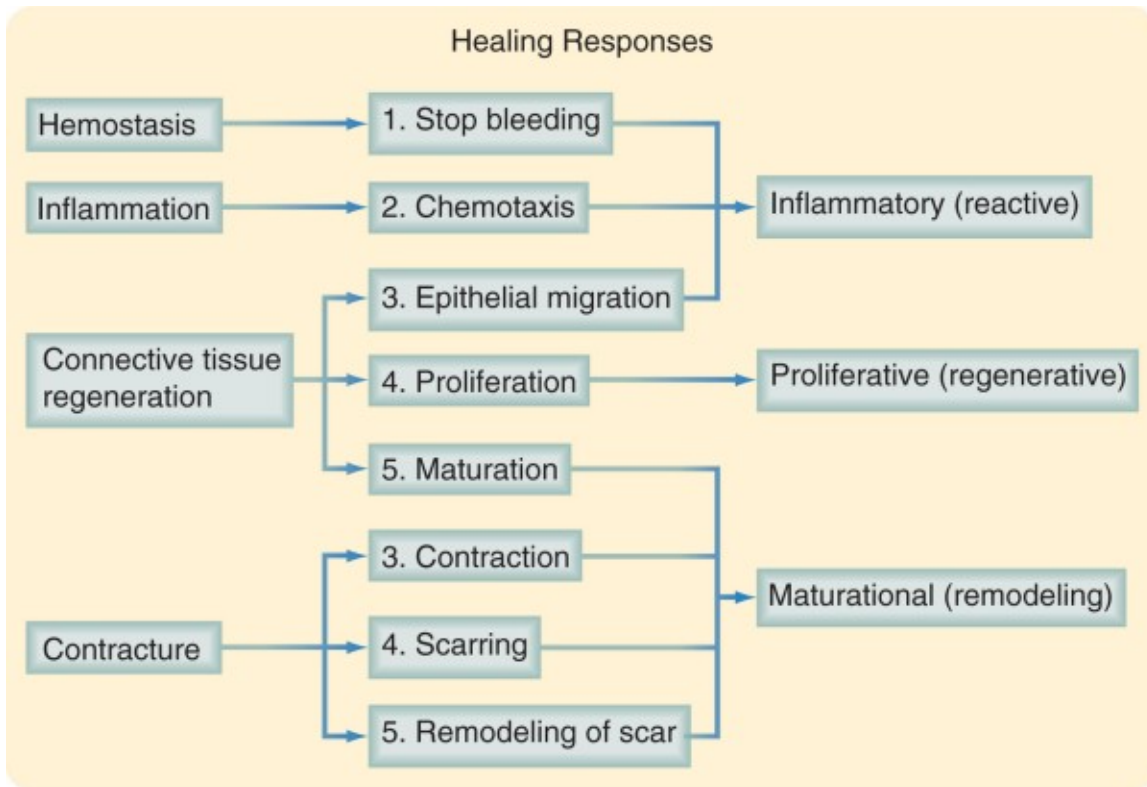
APPENDIX V (Continued)

Figure 3: Microdynamics of Phase V of the Sonis Model in Dermatitis (Singer 1999)



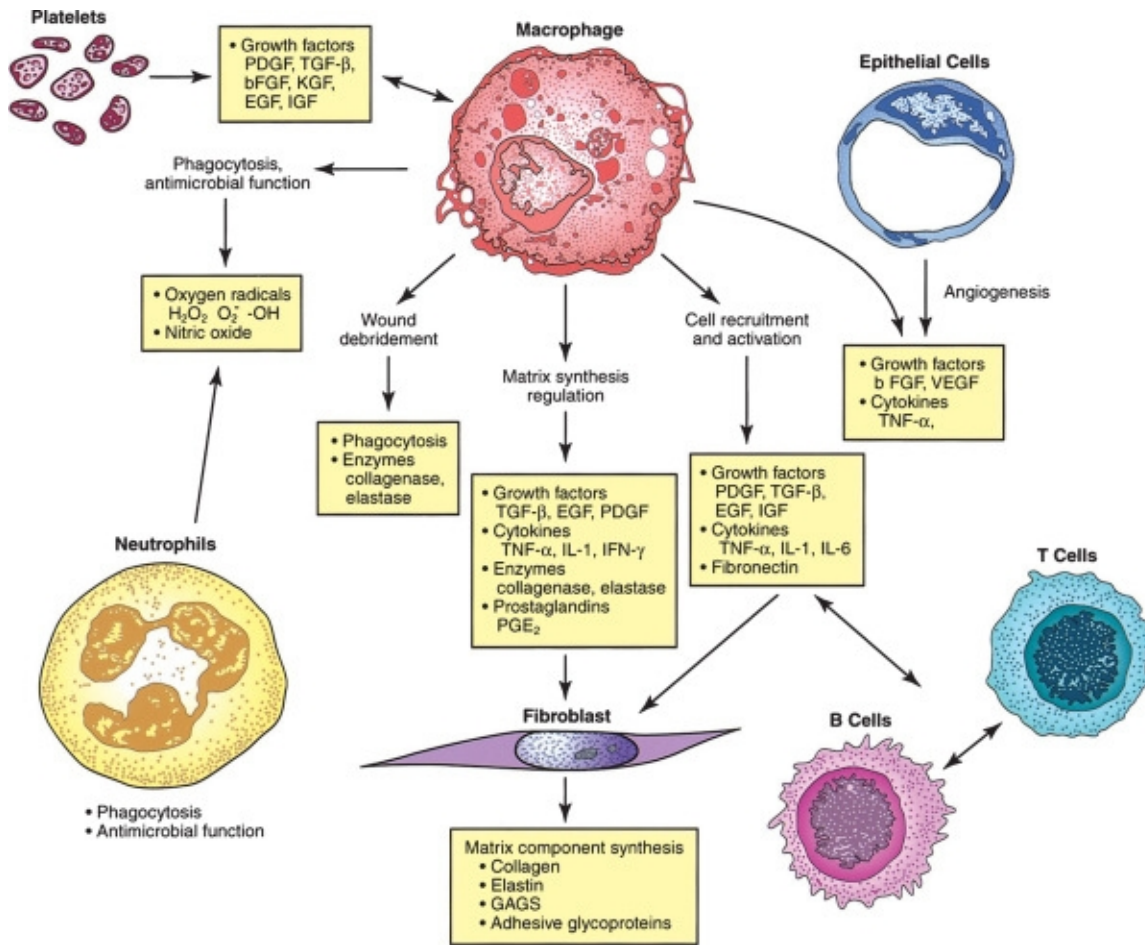
APPENDIX V (Continued)

Figure 4: Phase of Wound Healing (Ethridge 2007)



APPENDIX V (Continued)

Figure 5: Monocyte Activity Within Surface Healing



APPENDIX VI

Cytokines that Affect Wound Healing (Ethridge 2007)

CYTOKINE	ABBREVIATION	SOURCE	FUNCTIONS
Platelet-derived growth factor	PDGF	Platelets, macrophages, endothelial cells, keratinocytes	Chemotactic for PMNs, macrophages, fibroblasts, and smooth muscle cells; activates PMNs, macrophages, and fibroblasts; mitogenic for fibroblasts, endothelial cells; stimulates production of MMPs, fibronectin, and HA; stimulates angiogenesis and wound contraction; remodeling
Transforming growth factor- β (including isoforms β 1, β 2, and β 3)	TGF- β	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, fibroblasts	Chemotactic for PMNs, macrophages, lymphocytes, and fibroblasts; stimulates TIMP synthesis, keratinocyte migration, angiogenesis, and fibroplasia; inhibits production of MMPs and keratinocyte proliferation; induces TGF- β production
Epidermal growth factor	EGF	Platelets, macrophages	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration
Transforming growth factor- α	TGF- α	Macrophages, T lymphocytes, keratinocytes	Similar to EGF
Fibroblast growth factor-1 and -2 family	FGF	Macrophages, mast cells, T lymphocytes, endothelial cells, fibroblasts	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration, angiogenesis, wound contraction, and matrix deposition
Keratinocyte growth factor (also called FGF-7)	KGF	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation
Insulin-like growth factor	IGF-I	Macrophages, fibroblasts	Stimulates synthesis of sulfated proteoglycans, collagen, keratinocyte migration, and fibroblast proliferation; endocrine effects similar to those of growth hormone
Vascular endothelial cell growth factor	VEGF	Keratinocytes	Increases vasopermeability; mitogenic for endothelial cells

APPENDIX VII

Severity Scales for Acute Radiation Esophagitis

Grade	RTOG Scale	CTCAE, v. 4
1	Mild dysphagia or odynophagia, requiring topical anesthetic, non-narcotic agents or soft diet	Asymptomatic: clinical or diagnostic observations only. Intervention not necessary
2	Moderate dysphagia or odynophagia, requiring narcotic agents or liquid diet	Symptomatic; altered eating/swallowing; oral supplements indicated.
3	Severe dysphagia or odynophagia with dehydration or weight loss (>15% of pre-treatment baseline), requiring nasogastric feeding	Symptomatic; severely altered eating/swallowing, tube feedings, TPN or hospitalization indicated.
4	Complete stricture, ulceration, perforation, or fistula	Life-threatening consequences; urgent operative intervention indicated.
5	Death	Death

APPENDIX VIII

Analgesic Conversion Tables

<u>EQUIANALGESIC POTENCY CONVERSION</u>		
<u>Name</u>	<u>Equianalgesic Dose (mg) po</u>	
Morphine	60	
Hydromorphone (<i>Dilaudid</i>)	7.5	
Methadone (<i>Dolophine</i>)	20	
Oxycodone	30	
Levorphanol (<i>Levo-Dromoran</i>)	4	
Codeine	200	
Vicodin	60	
<u>TRANSDERMAL FENTANYL (<i>DURAGESIC</i>) DOSE PRESCRIPTION BASED UPON DAILY MORPHINE EQUIVALENCE</u>		
<u>Oral 24-hour morphine (mg/day)</u>	<u>Duragesic Dose (ug/h)</u>	
45-134	25	
135-224	50	
225-314	75	
315-404	100	
405-494	125	
495-584	150	
585-674	175	
675-764	200	
765-854	225	
855-944	250	
945-1034	275	
1035-1124	300	
<u>NARCOTIC EQUIVALENCY INDEX</u>		
<u>NARCOTIC</u>	<u>ROUTE</u>	<u>CONVERSION FACTOR</u>
Morphine	IM/IV	1.00
	po	0.17 for single dose trial; 0.33 for chronic administration
Hydromorphone (<i>Dilaudid</i>)	IM	6.67
	po	1.33
Codeine	IM	0.08
	po	0.05
Oxycodone*	IM	0.67
	po	0.33
Levorphanol (<i>Levodromoran</i>)	IM	6.25
	po	3.13
Meperidine (<i>Demerol</i>)	IM	0.10
	po	0.03
Methadone (<i>Dolophine</i>)	IM	1.38
	po	0.69
* 1 tablet of Tylox, Percocet, or Percodan contains 5 mg of oxycodone.		

APPENDIX IX

Numerical Rating Pain Scale (NRPS)

Date:

My oral pain on swallowing today (on a scale of 0-10)

(please circle the appropriate number)

0 1 2 3 4 5 6 7 8 9 10

I have taken pain medication today. Yes No

The name of your pain medication: _____

What is the dose you are taking? _____

How do you take your pain medication? (for example, by mouth, by patch, by injection) _____

How often do you take your pain medication? (for example, once a day, twice a day) _____

APPENDIX X

Instructions for Institutions: Provide the swallowing diary (below) to patients, and keep the swallowing diaries as source documentation. Do **not** submit patients' swallowing diaries to RTOG Headquarters. Sites will complete the Cover Sheet for Swallowing Diary (DP) as specified on the DP form and submit the DP form at the time points specified in Section 12.1.

Patient Swallowing Diary

Instructions for the patient: This is a calendar on which you are to record your swallowing ability each day of the week.

Be sure to turn in the sheets at the end of each week during treatment, and at 12 weeks from the start of treatment to the contact person listed below.

You will **fill out a column** by **adding the date**, by **writing in one number** that reflects your swallowing, before treatment begins, each day during radiation treatment, at end of treatment, and at 12 weeks after radiation completion of radiation.

You will receive at least 9 pages, one for each week and some extras. It is very important that we know how you feel, especially concerning your swallowing. If you have comments, be sure to add them to the page.

Please sign your name and date at the bottom of each page turned in.

If you have any questions,
contact: _____ Telephone: _____

HAVE YOU HAD ANY PROBLEMS WITH SWALLOWING TODAY?

DATE								
DAY OF WEEK	Pre-treatment	Mon	Tues	Wed	Thur	Fri	Sat	Sun
1=None								
2=Mild soreness only								
3=Can swallow solids with some difficulty								
4=Cannot swallow solids								
5=Cannot swallow liquids								

COMMENTS:

Patient signature

Date:

APPENDIX XI

PRO-CTCAE MATERIALS

MedDRA, PRO-CTCAE, and CTCAE, v. 4 Terms

CTCAE v4 / MedDRA Term	PRO-CTCAE Term	CTCAE v4 System Organ Class (SOC)
1. Anorexia	Decreased appetite	Metabolism and nutrition disorders
2. Anxiety	Anxiety	Psychiatric disorders
3. Concentration impairment	Problems with concentration	Nervous system disorders
4. Constipation	Constipation	Gastrointestinal disorders
5. Cough	Cough	Respiratory, thoracic and mediastinal disorders
6. Depression	Feelings that nothing could cheer you up	Psychiatric disorders
	Sad or unhappy feelings	Psychiatric disorders
7. Dermatitis radiation	Skin burns from radiation	Injury, poisoning and procedural complications
8. Diarrhea	Loose or watery stools (diarrhea)	Gastrointestinal disorders
9. Dry mouth	Dry mouth	Gastrointestinal disorders
10. Dry skin	Dry skin	Skin and subcutaneous tissue disorders
11. Dysgeusia	Problems with tasting food or drink	Nervous system disorders
12. Dyspepsia	Heartburn	Gastrointestinal disorders
13. Dysphagia	Difficulty swallowing	Gastrointestinal disorders
14. Dyspnea	Shortness of breath	Respiratory, thoracic and mediastinal disorders
15. Fatigue	Fatigue, tiredness, or lack of energy	General disorders and administration site conditions
16. Headache	Headache	
17. Hiccups	Hiccups	Respiratory, thoracic and mediastinal disorders
18. Hoarseness	Hoarse voice	Respiratory, thoracic and mediastinal disorders
19. Insomnia	Insomnia (including difficulty falling asleep, staying asleep, or waking up early)	Psychiatric disorders
20. Memory impairment	Problems with memory	Nervous system disorders
21. Mucositis oral	Mouth or throat sores	Gastrointestinal disorders
22. Nausea	Nausea	Gastrointestinal disorders
23. Pain	Pain	General disorders and administration site conditions
24. Pruritus	Itchy skin	Skin and subcutaneous tissue disorders
25. Rash maculopapular	Rash	Skin and subcutaneous tissue disorders
26. Skin hyperpigmentation	Unusual darkening of the skin	Skin and subcutaneous tissue disorders

APPENDIX XI (Continued)

MedDRA, PRO-CTCAE, and CTCAE, v. 4 Terms (Continued)

27.	Urticaria	Hives (itchy red bumps on the skin)	Skin and subcutaneous tissue disorders
28.	Voice alteration	Voice changes	Respiratory, thoracic and mediastinal disorders
29.	Vomiting	Vomiting	Gastrointestinal disorders
30.	Wheezing	Wheezing (whistling noise in the chest with breathing)	Respiratory, thoracic and mediastinal disorders

APPENDIX XI (Continued) (2/28/12)

Example of PRO-CTCAE Screen Shot from Patient Web Interface

The screenshot shows a patient web interface with a blue header bar. On the left, it says "Welcome ryle.mane". On the right, there are "home" and "Log out" buttons. Below the header, there is a "Progress:" indicator with a progress bar. The main content area contains the instruction "Please think back over the past 7 days :". There are two question boxes. The first question is "What was the SEVERITY of your WATERY EYES (TEARING) at their WORST?" with radio button options: None, Mild (selected), Moderate, Severe, and Very severe. The second question is "How much did WATERY EYES (TEARING) INTERFERE with your usual or daily activities?" with radio button options: Not at all, A little bit, Somewhat, Quite a bit, and Very much. At the bottom left is a "Back" button with a left arrow, and at the bottom right is a "Continue" button with a right arrow.

APPENDIX XI (Continued) (2/28/12)

Missed PRO-CTCAE Login Form

If a patient misses a scheduled PRO-CTCAE self-report, the form below must be completed. The patient may complete the PRO-CTCAE form within 2 business days if there is a return visit to clinic during that timeframe. Otherwise, site personnel must call the patient at home and conduct the survey, then enter the patient's responses into the PRO-CTCAE software system (for technical assistance, contact Dr. Ethan Basch ebasch@mskcc.org).

1) Date of missed scheduled PRO-CTCAE Self-report: ____/____/____

2) Did the patient attend the visit, but not complete the PRO-CTCAE self-report?

Yes, attended the visit (go to Question #3)

No, the patient did not attend the visit (go to Question #4)

3) Why did the patient not self-report using the PRO-CTCAE at the visit?

Too sick

Refused

Technical problems with computer

Technical problems with internet connection

Technical problems with PRO-CTCAE website

Staff not available to assist patient

Other (specify): _____

4) Within 2 business days of the missed self-report, the patient may complete the self-report in clinic via computer, or if the patient does not have another visit scheduled, site personnel should call the patient at home to complete the questions, then these responses should be entered into the PRO-CTCAE software system. Please select one of the below:

Patient returned within 2 business days and DID complete the self-report

Patient returned within 2 business days and DID NOT completed the self-report

Patient was called at home and completed the questions via this interview

Unable to reach patient by telephone