

MANUKA HONEY:

An Investigation into the Effect of Manuka Honey on Oral
Mucositis in Patients Receiving Radiation Therapy to the
Head and Neck

Emma Parsons

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University of Otago, Dunedin, New Zealand

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Abstract

Head and neck cancer is the sixth most common type of cancer, with an estimated 650,000 registrations and 350,000 deaths worldwide annually (Parkin et al., 2005). The treatment for these types of cancers is becoming increasingly aggressive with the majority of patients receiving a combination of surgery, radiation therapy and chemotherapy to cure their cancer. Severe oral mucositis is a common side effect of these cytotoxic treatments with 60% of patients receiving radiation therapy and 92% of patients receiving chemoradiation developing it during the course of their treatment (Parulekar et al., 1998; Sonis, 1998; Dodd et al., 2000; Elting et al., 2003). Oral mucositis leads to many secondary complications including severe oral pain, difficulty in eating and swallowing, taste changes, infection, malnutrition and weight loss. Currently, there is no standard form of treatment for oral mucositis with the majority of treatments aimed at palliation of symptoms rather than preventing or treatment oral mucositis itself.

The research presented in this thesis investigates the effect of manuka honey on the prevention and treatment of radiation induced oral mucositis in patients receiving radiation therapy and chemoradiation for head and neck cancers at the Palmerston North Oncology Department. The original study was designed as a stage II randomised single blinded trial where patients were randomised into one of two arms. Patients in the control arm were given the standard treatments for oral mucositis in New Zealand including Benzydamine Hydrochloride (HCL), bicarbonate rinses, pain killers and anti-fungals. Patients in the experimental arm were given all standard treatments and were asked to gargle 20mls of undiluted manuka honey three times per day. Patients oral mucositis was scored three times per week, they were weighed once per week and asked to fill out a food and drug diary everyday and a quality of life questionnaire once every fortnight during treatment.

Due to poor patient compliance with the undiluted honey this trial was downgraded to a phase I pilot trial investigating the best way to administer manuka honey to treat oral mucositis. This thesis specifically reports the results for twelve patients recruited to this trial between March 2009 and December 2009.

Due to the early downgrading of this trial from a randomised phase II trial to a pilot trial the effects of pure undiluted manuka honey on radiation induced oral mucositis could not be assessed. There was no statistically significant difference in the severity of oral mucositis reported between those

taking diluted manuka honey and those using standard forms of treatment only. Patients taking diluted manuka honey appeared to have slightly less weight loss than those receiving standard treatments alone however this did not reach statistical significance. All patients, irrespective of whether they were taking honey or not, reported a severe decrease in quality of life throughout the course of their radiation therapy.

There were large issues with patient compliance in this trial. Even when the honey had been diluted significantly patients complained the honey tasted too sweet, made them feel nauseous and stung their oral mucosa. Due to these issues with compliance, it was not deemed ethical to continue with the current trial unless the honey is given to patients in a way which is tolerated better.

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CHAPTER 1 INTRODUCTION

Head and neck cancers are classified as malignancies of the upper aero-digestive tract including the mouth, pharynx, larynx, nasal cavity and sinuses. They are the sixth most common type of cancer, representing approximately 4% of all cancers worldwide with an estimated 650,000 registrations and 350,000 deaths worldwide annually (Parkin et al., 2005). In New Zealand alone, there were 641 head and neck cancer registrations on average annually from 2003-2005 (Ministry of Health, 2009).

Most patients diagnosed with a head and neck cancer will receive radiation therapy at some stage during their treatment. Radiation therapy plays a significant role as a primary treatment in early stage cancers and in the adjuvant treatment of later stage head and neck cancers. However, due to the radiation-induced DNA damage of surrounding critical structures, radiation therapy can cause debilitating side effects in patients such as skin reactions (erythema, dry desquamation, moist desquamation), xerostomia (dry mouth) and oral mucositis (mouth ulceration).

Oral mucositis is caused by a multi-step biological process, which will occur in 30 to 40% of patients receiving chemotherapy, 60% of patients receiving radiation therapy and 92% of patients receiving both chemotherapy and radiation therapy (Parulekar et al., 1998; Sonis, 1998; Dodd et al., 2000; Elting et al., 2003). It can cause serious secondary complications such as pain, difficulty in eating and swallowing, taste changes, infection, malnutrition and weight loss. It can also lead to a reduction in total dose delivered to the tumour bed and unscheduled treatment breaks. This can have a detrimental effect on local tumour control and thus patient survival (Rosenthal, 2007).

Historically, oral mucositis has been accepted as an inevitable part of cytotoxic head and neck treatments, with interventions aimed at palliation of symptoms. Although palliative treatments improve patient comfort, they do not address problems of tissue breakdown, secondary infection (primarily *Candida*) or impaired healing (Epstein et al., 2001). One of the latest interventions for the management of radiation-induced oral mucositis is natural honey (Biswal et al., 2003; Motallebnejad et al., 2008; Rashad et al., 2008). Honey has antimicrobial properties (Cooper et al., 1999) and promotes wound healing (Molan, 2001). This thesis reports on the effect of Comvita manuka medical grade honey on radiation-induced oral mucositis in 12 patients in Palmerston North Radiation Oncology Department.

1.1 CURRENT TREATMENT OF HEAD AND NECK CANCER

There is no universally accepted standard of “best practice” for the treatment of head and neck cancers. The goals of treatment are to eradicate the cancer, both demonstrable and microscopic disease, maintain physiological function and achieve acceptable cosmetic results (Rubin, 2001). Treatment is based on a multidisciplinary approach involving the input of surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, dieticians and social workers.

Patients with a head and neck malignancy may receive one or a combination of the following treatments: surgery, radiation therapy and/or chemotherapy. The treatments chosen are usually based on the site, stage and resectability of disease, as well as the age, general condition, co-morbidities, lifestyle and preference of the patient (Rubin, 2001). Each treatment option has inherent side effects; it is therefore necessary to find a balance between curing the cancer and not leaving the patient with severe late toxicities such as permanent disfiguration and loss of function.

Treatment of Early Stage Head and Neck Malignancies

Small primary lesions (T1-T2) with no lymph node metastases are generally best treated with one modality – either surgery or radiation therapy. The decision of which modality to use is mainly dictated by the site of the primary tumour. Small lesions with positive resection margins or lymph node involvement may need a combination of both radiation therapy and surgery (Rubin, 2001).

Surgery often involves resection of the primary tumour, dissection and staging of the cervical lymph nodes and reconstructive procedures. Surgery is frequently limited by the anatomical location of the tumour, patient co-morbidities and the desire to achieve organ preservation (Agris et al., 2008). For these reasons surgery is only appropriate for patients with low stage disease where the physiological function of the organ is maintained and acceptable cosmetic outcomes can be obtained.

Radiation therapy is the primary treatment of choice in early stage glottis, base of tongue and tonsillar cancer and results in high tumour control and cure rates for these cancers (Agris et al., 2008). Radiation therapy for head and neck cancers is typically given in daily fractions of 180cGy to 220cGy, five days a week to a total dose of 5500cGy to 7000cGy. In Palmerston North Radiation Oncology Department patients with head and neck cancers are treated to a total dose of 6000cGy to

6600cGy. Unfortunately, radiation therapy also causes DNA damage to cells of surrounding critical structures, resulting in acute side effects such as skin reactions, oral mucositis and xerostomia. These side effects can severely affect a patient's nutritional status and quality of life (Plevová, 2009).

Treatment of Late Stage Head and Neck Malignancies

Almost 66% of head and neck patients present with advanced-stage disease (Cognetti et al., 2008). Often all three treatment modalities are needed in order to obtain a cure for these patients. A major advancement in treatment for these patients in the past three decades has been the introduction of concurrent radiation therapy and chemotherapy (chemoradiation). Two large meta-analyses conducted by Pignon et al. (2000) and Budach et al. (2006) reported a large statistically significant survival benefit in favour of chemoradiation versus radiation alone for late stage head and neck malignancies. Buddach et al. (2006) analysed 20 trials with a total of 4000 participants and reported a survival benefit of 12.0 months (absolute survival benefit at two years of 13% to 15%) in the chemoradiation group. Pignon et al. (2000) analysed 63 trials with a total of 10,741 patients and reported an absolute survival benefit of 4% at two and five years. The difference in reported survival benefits between the two meta-analyses was thought to be due to the inclusion of studies using Bleomycin or Methotrexate in the meta-analysis of Pignon's review. These agents are no longer used in combination with radiation therapy as they have been shown to considerably enhance oral mucositis often resulting in increased late toxicities (Budach et al., 2006).

Due to the increasing evidence that concurrent chemoradiation positively influences survival, Cisplatin-based chemotherapy regimens are commonly used concurrently with radiation therapy in the cure of advanced stage malignancies. Whilst chemoradiation has been shown to improve survival, the two modalities given concurrently increase the severity of oral mucositis (Parulekar et al., 1998).

1.2 STRUCTURE OF THE ORAL MUCOSA

The oral mucosa consists of two layers: stratified squamous epithelium and the underlying lamina propria. The epithelium, like skin, consists of tightly packed epithelial cells with varying degrees of differentiation. The basal layer of the epithelium has undifferentiated stem cells that divide continuously whilst the outer layers undergo various morphological and biochemical changes (Winning & Townsend, 2000). The underlying lamina propria provides support to the epithelium and contains elastic and collagen fibres, blood vessels, nerves, lymphatic vessels and the secretory cells of the salivary glands (Martini and Nath, 2009).

The structure and biology of the oral mucosa depends on the location and function and can be divided into three different histological types: masticatory mucosa, lining mucosa and specialized mucosa. Masticatory mucosa lines the gingival and hard palate. These areas are subjected to compressive and frictional forces due to mastication therefore need to be strong and resilient to damage. The epithelial layer is a keratinized stratified squamous epithelium which provides protection against chemical, microbial and mechanical damage. The collagen fibres in the lamina propria of the masticatory mucosa are arranged in bundles to give extra strength (Winning & Townsend, 2000).

The lamina propria of the lining mucosa covers the lips, cheeks, vestibule, ventral surface of the tongue, alveola, soft palate and floor of mouth, contains fewer collagen fibres which are more loosely arranged and more elastic fibres (Winning & Townsend, 2000). This makes the lining mucosa more flexible and capable of distension. The epithelial layer is a non-keratinized stratified squamous epithelium. The dorsum of the tongue is covered by a specialized mucosa which is coated in epithelial projections called lingual papillae. These provide friction to help the tongue move and contain taste buds.

The stem cell population in the oral mucosa has a very high cell turnover rate resulting in the replacement of the entire mucosal lining every seven to 14 days (Shih et al., 2003). This rapid course of cell proliferation and constant epithelial replacement renders the mucosa susceptible to the effects of radiation and cytotoxic drugs that affect rapidly proliferating cells.

1.3 ORAL MUCOSITIS

Oral mucositis is the general term referring to inflammatory reactions and erosive, ulcerative lesions in the mouth and oropharynx that arise secondary to RT and certain chemotherapeutic agents (Dodd, 2004). The reported prevalence of oral mucositis from anti-cancer treatments varies considerably. The incidence of chemotherapy-induced oral mucositis is predicted to be between 30-40% (Sonis, 1998; Dodd et al., 2000; Elting et al., 2003). The combination of chemotherapy and radiation therapy substantially increases the risk of oral mucositis. In a survey of randomised studies comparing radiation therapy alone versus chemoradiation severe (Grade three or more) oral mucositis was reported in 60% of patients receiving only radiation therapy and 92% of patients receiving chemoradiation (Parulekar et al., 1998).

The consequences of severe oral mucositis are extensive. It is painful and can lead to bleeding, ageusia (lack of taste), dysphagia (difficulty eating) and dysphonia (difficulty speaking). This negatively impacts the patient's quality of life and often results in nutritional insufficiency and weight loss (Shih et al., 2003). Severe cases of oral mucositis can lead to unscheduled treatment breaks and/or dose reduction of both chemotherapy and radiation therapy. This has the potential to negatively impact on local tumour control and ultimately patient survival (Sonis, 1998; Parulekar et al., 1998; Dodd, 2004).

Many patients who are receiving chemotherapy become immunocompromised. In these neutropenic patients oral mucositis poses a significant risk for local and systemic infections (Sonis, 1998; Shih et al., 2003; Dodd, 2004). Local infections such as those of the oral yeast species, *Candida*, aggravate and prolong the duration of oral mucositis (Shih et al., 2003).

Furthermore, in a retrospective study of 599 patients suffering from chemotherapy induced myelosuppression, Elting and colleagues (2003) reported that oral mucositis was found to significantly increase costs due to the increased need for hospitalization, fluid replacements, antifungal treatments and broad spectrum antibiotics. The average days spent in hospital increased from 3.9 days in patients with no oral mucositis to 6.3 days in patients suffering from oral mucositis of any grade and 8.2 days in patients suffering from severe oral mucositis (Grade three to four). Murphy et al. (2007) estimated the increase in medical costs as a direct consequence of oral mucositis to average \$3,000 +/- \$1,000 United States Dollars (USD) per treatment episode.

Therefore, oral mucositis also has significant economic implications in addition to the impact on quality of life and treatment efficacy.

Biological Process of Oral Mucositis

Originally oral mucositis was thought to develop solely from the direct toxic effects of radiation therapy or chemotherapy on the epithelial stem cells. In 1998 Sonis proposed that oral mucositis was a biological process consisting of four phases: inflammatory-vascular phase, epithelial phase, ulcerative phase and healing phase. The model describes oral mucositis as a complicated multi-step process and provided a foundation for developing novel interventions targeted at specific phases in the process (Sonis, 2007). Since its implementation in 1998 this model has constantly evolved and presently is suggested to have five stages (Sonis, 2007) outlined in Figure 1.1.

PHASE 1: INITIATION

Initiation begins immediately after the administration of chemotherapy or radiation therapy. For those patients receiving fractionated radiation therapy the initiation process is triggered after each subsequent treatment (Sonis, 2007). Direct damage to DNA from cytotoxic treatment may lead to immediate cell death in basal epithelia. However, direct damage only accounts for a small number of cell deaths and does not result in the extensive injury seen with oral mucositis (Sonis, 2007). Most radiation damage is done by the subsequent generation of reactive oxygen species which trigger a cascade of biological events, leading to cell death.

PHASE 2: PRIMARY DAMAGE RESPONSE

The ability to repair DNA damage (innate radio tolerance) differs between cell types in both healthy tissues and tumour tissues. DNA damage results in the expression of transcription factors (such as nuclear factor-kappa B), resulting in the production of radio-protective cytokines (chemical intercellular messengers) that protect the cells from cell death (Neta, 1997). Interleukins 1, 3 and 12, interferon gamma, tumour necrosis factor alpha increase the production of growth factors which enhance tissue repair. Similarly, an increase in the expression of radical scavenging enzymes (such as superoxide dismutase), protects cells from further damage from reactive oxygen species.

However, chemotherapy and radiation therapy can also lead to an increase in the production of radiosensitizing cytokines and enzymes that increase the rate of apoptosis in the mucosa. The overall effect of cytokine release, protection or injury, depends, amongst other factors, on dose,

timing and tissue type. With respect to chemoradiation of the head and neck, this phase results in thinning of the mucosa and the advent of erythema and pain (Sonis, 2004).

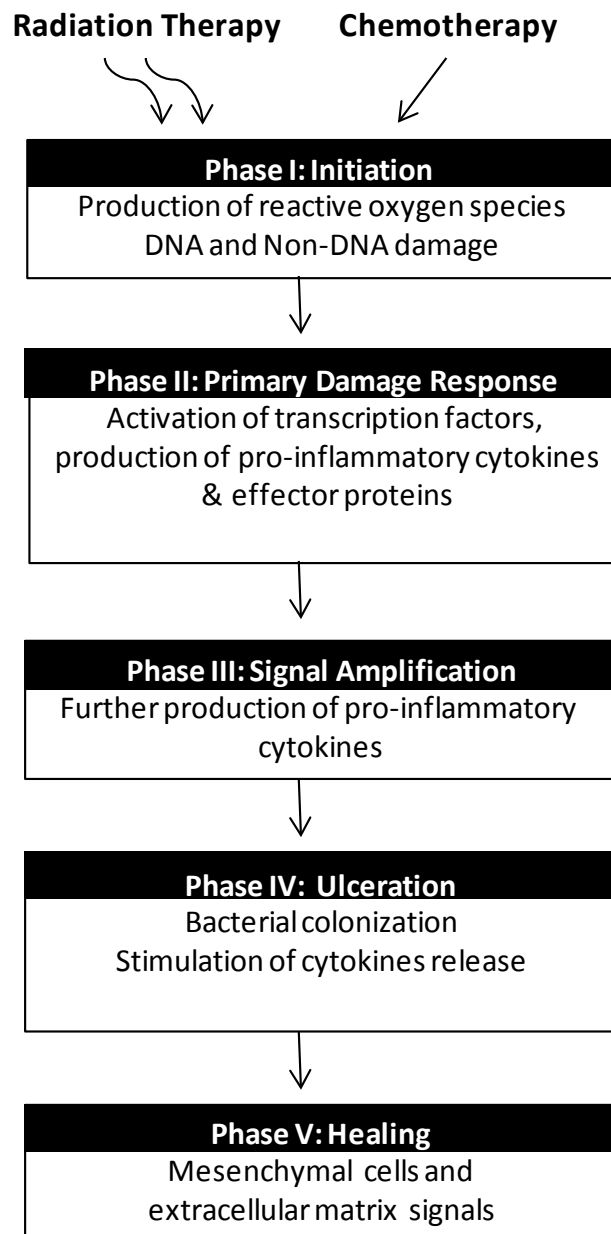


Figure 1.1: Biological phases of mucositis (Adapted from Sonis, 2004).

PHASE 3: SIGNAL AMPLIFICATION

In the first two phases, DNA damage activates normal damage response pathways on a cellular level (Sonis, 2007). In the case of the oral mucosa, some of the cytokines and proteins produced during this response magnify the initial injury through positive feedback loops. These positive feedback loops not only amplify the original biological signals resulting in increased tissue injury but they also

prolong damage by continuing to provide signals for days after the radiation therapy or chemotherapy is given (Sonis, 2007).

PHASE 4: ULCERATION

The ulcerative phase is responsible for the adverse health outcomes associated with oral mucositis. This phase is the most symptomatic for patients as the tissue becomes atrophic and functional trauma leads to ulceration. Sometimes these tissue erosions become covered in a white fibrous pseudo membrane. At this stage the mucosa and underlying tissues are most susceptible to infections and haemorrhaging.

PHASE 5: HEALING

Healing commences when the chemoradiation treatment is completed. The healing phase involves a replenishment of the epithelial stem cells from adjacent unaffected areas, followed by epithelial proliferation and differentiation, normalization of white blood cell counts and control of the microbial flora of the oral cavity (Shih et al., 2003). In most cases the ulcers of mucositis resolve spontaneously within two to three weeks following the completion of treatment (Sonis, 2007).

1.4 FACTORS AFFECTING ORAL MUCOSITIS SEVERITY

Not all patients who receive radiation therapy or chemotherapy to the head and neck are at the same risk of suffering from oral mucositis. There are many treatment-related and patient-related factors that affect the severity, onset and duration of oral mucositis. Identifying high risk individuals may be useful so they can start early on prophylactic measures and have adequate nursing support. Treatment-related and patient-related risk factors are discussed below.

Treatment-Related Factors

Both radiation therapy and chemotherapy can cause oral mucositis. The way in which treatment is given can affect the patient's risk of developing severe oral mucositis. Treatment related risk factors are outlined in Table 1.1.

Table 1.1 Treatment- Related Risk Factors for Developing Oral Mucositis.

RADIATION THERAPY RISK FACTORS	CHEMOTHERAPY RISK FACTORS
Total dose	Chemotherapy agent
Fractionation regimen	Delivery method
Anatomical area irradiated	Dose
Volume of tissue irradiated	Duration
Concurrent use of radiation therapy and chemotherapy	

Radiation Therapy Related Risk Factors

- As the total dose increases the patient's risk of oral mucositis increases, with symptoms usually beginning at approximately 2000cGy and peaking at 5000 to 6000cGy (Shih et al., 2003; Washington and Leaver, 2004).
- Hyper-fractionated regimens (two or more fractions per day) have been shown to substantially increase the severity of oral mucositis. Trotti et al. (2003) conducted a large meta-analysis of 33 studies with a total of 6,181 patients receiving radiation therapy to the head and neck. This study reported that 56% of patients receiving altered fractionation radiation therapy had grade three to four oral mucositis compared with 34% of patients receiving conventional radiation therapy regimens.

- The lateral borders and ventral surface of the tongue, soft palate and floor of mouth respond more intensely to radiation therapy than other areas of the mouth due to their high cell turnover and large blood supply (Shih et al., 2003).
- Irradiation of the salivary glands can increase the risk of developing oral mucositis. Irradiation of the salivary glands can reduce the production of saliva (xerostomia) and levels of immunoglobulin A, increasing the viscosity and acidity of the saliva (Köstler et al., 2009).
- The larger the field of irradiation the higher the risk of a patient developing severe oral mucositis as more of the surface of the oral cavity will be within the radiation field.

Chemotherapy Related Risk Factors

- The type of chemotherapy agent used heavily impacts on the risk of chemotherapy induced oral mucositis. Agents commonly associated with oral mucositis include anti-tumour antibiotics such as Daunorubicin, alkylating agents such as Cisplatin and anti-metabolites such as 5-FU and Methotrexate (Parulekar et al., 1998; Barasch & Peterson, 2003). More research is needed to establish the effects of multiple agent regimes on oral mucositis, (Dodd, 2004).
- The effect of the mode of delivery of chemotherapy agents on oral mucositis remains unclear. Compared to bolus infusions, prolonged or repetitive administration of low doses of cytotoxic agents are thought to be associated with an increased risk of developing oral mucositis (Köstler et al., 2009). High dose chemotherapy-regimens are associated with a greater risk of developing oral mucositis (Avritscher et al., 2004).
- The risk of developing oral mucositis also increases with the number of chemotherapy cycles and previous experiences of chemotherapy-induced mucositis (Köstler et al., 2009).

Patient-Related Factors

The frequency and severity of oral mucositis in patients receiving cytotoxic treatments is also affected by patient-related factors. Whilst the data on patient related factors are conflicting, some factors have been identified as likely to contribute to and exacerbate the extent of oral mucositis.

Table 1.2 Patient Related Risk Factors for Developing Oral Mucositis (Adapted from McGuire, 2002; Avritscher et al., 2004).

Factors	Effect on Mucosal Tissue Injury
Poor oral hygiene	↑
Poor oral health	↑
Poor renal function	↑
Smoking	Unclear
Age	↑ for paediatrics and elderly
Female Gender	↑
Poor salivary secretory function	↑
Low neutrophil levels	↑
Low body mass	↑

- Poor oral health has been highlighted in the literature as one of the most important risk factors for developing oral mucositis (Brown & Wingard, 2004). Pre-existing conditions such as gingivitis, periodontal disease, plaques and dental carries are likely to result in a higher incidence of oral mucositis (Shih et al., 2003).
- Intensive oral hygiene care may be associated with a reduction in the frequency of oral mucositis among patients receiving chemotherapy. It is thought that the extent and composition of the local microflora present in patients with poor oral hygiene may make them susceptible to oral mucositis (Shih et al., 2003; Avritscher et al., 2004). However Dodd et al. (1999) did not see a statistically significant difference in the severity and onset of oral mucositis between the frequency of brushing and flossing in 332 patients receiving stomatotoxic chemotherapy agents (doxorubicin, bleomycin, etoposide, 5-FU, methotrexate, paclitaxel or fludarabin). These results were supported by McCarthy et al (1998) in a study involving 63 patients receiving 5-FU.

- Wearing dental appliances such as false teeth or having sharp teeth has been reported as a possible risk factor due to possible concomitant trauma. Dodd et al. (1999) reported that the onset of mucositis in patients wearing dental appliances was on average five days sooner than those who did not. This however did not reach statistical significance ($p=0.21$).
- Patients report that food irritants (alcohol, spicy hot foods) cause irritation to an already damaged mucosa, increasing mucosal damage and pain levels.
- The effect of smoking on oral mucositis remains unclear. It is hypothesised that patients who have a history of smoking may be at a higher risk for developing mucositis because smoking can affect the healing capacity of the oral mucosa (Avritscher et al., 2004). However Dodd et al. (1999) did not find a statistically significant difference between smokers and non-smokers with respect to the severity of mucositis ($p=0.58$). Interestingly, the time to onset of mucositis did differ between the two groups from 33 days (smokers) to 21.85 days (non-smokers), but this was not statistically significant ($p=0.17$).
- Younger age is thought to be a risk factor due to a higher mucosal turnover rate; with an earlier onset observed in paediatric patients (Shih et al., 2003; Brown & Wingard, 2004; Avritscher et al., 2004). Elderly patients are also thought to be at increased risk of developing oral mucositis due to decreased renal function and compromised tissue recovery caused by the decline in stem cell reserves in elderly patients (Balducci & Extermann, 2000 cited by Avritscher et al., 2004).
- Women appear to be at a higher risk of developing oral mucositis than men (Avritscher et al., 2004). In a meta-analysis conducted by Sloan et al. (2000), involving six trials with a total of 731 patients, women were found to experience oral mucositis more frequently (63% vs. 52% $p=0.002$) than their male counterparts, and were twice as likely to develop severe oral mucositis.
- Low neutrophil levels are thought to negatively affect oral mucositis. McCarthy et al., 1998 found that low baseline levels of neutrophils significantly impacted on oral mucositis in patients receiving 5-FU. Seventy two percent of patients with a baseline neutrophil lower than $<4000\text{cells/mm}^3$ had at least one episode of mucositis compared to only 34.9% of patients with a baseline neutrophil $>4000\text{cells/mm}^3$.

Many patient-related risk factors for oral mucositis remain controversial. These include the effects of stress, inflammation, timing of treatments, previous cancer treatments, genetic factors and body mass on oral mucositis. Further research is needed to clarify which of these factors negatively impact oral mucositis, so their effect can be minimized, where possible.

1.5 EFFECTS OF ORAL MUCOSITIS ON INDIVIDUALS

The negative effects of oral mucositis on an individual are extensive and include oral pain, infection, weight loss and malnutrition, taste changes and poorer quality of life. It can also result in unscheduled treatment breaks which may negatively impact on tumour control and overall survival (Rosenthal, 2007).

Oral Pain and Analgesics Use

The experience of oral pain is unique to each individual and can be distressing to patients making it difficult to chew, swallow, eat and talk. Oral pain levels are closely related to the extent of oral mucositis and dysphagia. Most patients report peak mouth pain within one to two days of recording their peak oral mucositis score (Cella et al., 2003). The percentage of patients experiencing severe oral pain from mucositis varies in the literature. In a study undertaken by Murphy et al. (2009) of 75 patients receiving radiation therapy with or without chemotherapy for head and neck malignancies, 76% of individuals reported severe mouth and throat pain at anytime during the study. Trotti and colleagues (2003) compared the results of three trials (405 patients) which examined oral pain as an outcome and reported that 69.5% of patients suffered from oral pain.

Analgesics and topical anaesthetics are used by the majority of patients suffering from oral mucositis with 85% of patients using opioids at some stage during their treatment. However, pain caused by oral mucositis is usually poorly controlled with 51% of patients still reporting severe pain even after taking opioids (Murphy et al., 2009). Whilst it is widely accepted that severe oral mucositis leads to moderate to severe pain levels further understanding is needed on how this pain is manifested in order to affectively treat oral pain (McGuire, 2002).

Infection

Infection is potentially one of the most severe and life-threatening consequences of oral mucositis (Brown & Wingard, 2004). Normally, the healthy oral mucosa provides a barrier to many microorganisms preventing them filtering into the epithelium. Oral mucositis results in a loss of integrity of the mucosal lining leaving it susceptible to infection by microorganisms such as *Candida albicans*, herpes viruses and a wide range of bacteria.

The oral cavity contains a resident microflora which forms an ecosystem consisting of many bacterial and yeast species that protect the mouth from invasion by pathogens. Chemoradiation changes the oral microenvironment by decreasing salivary flow, pH and immunoglobulin A levels. This changes the composition of the oral microflora to a more pathogenic one, resulting in an increase in caries and periodontal disease as well as invasion of the mucosa (Shih et al., 2003). Elting et al. (2007) found that 72% of patients receiving chemoradiation and 18% of patients having radiation alone developed local infections ($p=0.001$).

Ulcerative oral mucositis can also provides portals for microorganisms to pass through the mucosa into underlying tissues and the bloodstream, which can be lead to life-threatening septicaemia when coupled with chemotherapy-induced neutropenia (Brown & Wingard 2004; Shih et al., 2003; Murphy et al., 2007). There is a lack of recent research on the impact of ulceration on the rate of sepsis in patients receiving cytotoxic treatments. Ruescher and colleagues (1998) assessed the incidence of alpha-haemolytic streptococcal bacteraemia in 24 patients undergoing myelosuppressive chemotherapy prior to stem cell transplantation. Patients who developed ulcerative oral mucositis as a consequence of the chemotherapy were three times more likely to suffer from bacteraemia. More research is needed to access the risk of sepsis in patients suffering from chemotherapy-induced oral mucositis and neutropenia as an estimated 40 to 60% of patients with sepsis die of these complications (Brown and Wingard, 2004).

Weight Loss and Malnutrition

Patients suffering from oral mucositis often find eating, drinking, chewing and swallowing painful. This combined with a reduced or distorted sense of taste can make eating very unpleasant resulting in malnutrition, weight loss and dehydration. This diminishing nutritional intake can exacerbate the extent of oral mucositis because there is an overall decrease in cell renewal and migration after a reduction of calories or protein deprivation (Shih et al., 2003).

Trotti and colleagues (2003), reported in a meta-analysis of eight trials investigating weight loss in 880 patients having treatment for head and neck cancers, mean weight loss ranged from 3.0-6.7kg. As expected, the extent of weight loss was directly related to the degree of oral mucositis. Elting et al. (2007) conducted a retrospective study of 599 patients receiving radiation therapy with or without chemotherapy and reported that 22% of patients with grade zero to two oral mucositis

experienced a loss of 5.0kg or more compared with 47% of patients with grade three to four oral mucositis. Furthermore, weight loss was more common in patients receiving chemoradiation compared to those receiving only radiation therapy (37% vs.56%; $p=0.006$).

For patients suffering from mild symptoms of pain and oral mucositis a soft food diet supplemented with meal replacements may be sufficient to prevent weight loss (Murphy et al., 2007). In cases where weight loss and dehydration are more severe patients may require intravenous fluids, placement of a percutaneous endoscopic gastrostomy (PEG) feeding tube or total parenteral nutrition (TPN). Some physicians will place PEG feeding tubes prophylactically prior to chemotherapy and/or radiation therapy. This remains controversial as other physicians believe prophylactic PEGs can result in lasting swallowing abnormalities (Murphy et al., 2007). The frequency with which PEG tubes are inserted varies drastically between cancer centres. Trotti et al. (2003) reported in a meta-analysis of five studies ($n=189$) that feeding tubes were inserted on average 19% of the time. He did not distinguish between feeding tubes inserted prophylactically and those inserted as a result of oral mucositis. In another trial undertaken by Murphy et al. (2009) comparing oral mucositis in patients treated with radiation therapy with and without chemotherapy, PEG tubes were placed in 51% of patients. Fifty six percent of these feeding tubes were placed prophylactically and the remaining 44% were placed during treatment due to severe oral mucositis resulting in malnutrition.

Taste Changes

Taste changes often occur with oral mucositis. Loss of taste is hypothesized to occur because of radiation therapy or chemotherapy induced injury to the microvilli and the outer surface of the taste cells (Shih et al., 2003). Patients whose oropharyngeal cavity is in the irradiation field rapidly lose their taste, with a loss of taste usually occurring between 1000 to 2000cGy (Shih et al., 2003). Cheng (2007) reported in a study of 55 patients with oral mucositis, that an increase in the intensity of oral mucositis resulted in an increase in the intensity of taste distortions ($p= 0.01$). Patients usually find it difficult to distinguish between sweet and salty foods and can complain of a constant bitter taste. Also patients receiving chemotherapy can complain of a metallic taste in their mouth (Brown & Wingard, 2004). The loss of taste is usually temporary with taste sensation improving 20-60 days after radiation treatment and fully recovered six to 12 months after the completion of treatment (Shih et al., 2003).

Quality of Life

It will be obvious from the discussions above on the effects of oral mucositis on pain, ability to eat, drink and speak, that severe oral mucositis compromises a patient's quality of life (QOL). The World Health Organisation defines QOL as an individual's perception of their position in life in the context of their culture and values systems in relation to their goals, expectations standards and concerns. Therefore QOL must be measured from the patient's perspective (Murphy et al., 2007). There are many tools that have been utilized to determine the QOL in patients receiving treatment for head and neck cancers such as the Medical Outcomes Study-Short Form-36 (MOS SF-36), the Sickness Impact Profile (SIP) and the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 30 (QLQ-30).

Cheng (2007) studied the effects of oral mucositis on QOL in 88 Hong Kong Chinese patients undergoing cancer therapy, using the Chinese version of the functional assessment of cancer therapy (FACT) questionnaire. This study found that QOL was significantly related to the perceived severity of the oral mucositis. Patients with severe mucositis reported lower physical, emotional, functional QOL scores than those with mild or no oral mucositis. The authors also reported that patients treated with combined chemo-radiotherapy perceived more intense oral mucositis and higher distress levels than patients treated with radiotherapy or chemotherapy alone (Cheng, 2007).

Dose Reductions and Unscheduled Treatment Breaks

Severe oral mucositis can result in dose reductions and unscheduled treatment breaks in chemotherapy and radiation therapy which can have long terms consequences for the patient. In a study of 599 patients receiving chemotherapy, Elting et al. (2003) reported that dose reductions were more than twice as common in patients with mucositis that those without (23% vs. 11%) . Reduced chemotherapy dose has been associated with poorer outcomes for patients including lower response rates, shorter disease-free intervals and decreased survival (Rosenthal, 2007).

Similarly, unscheduled breaks in radiation therapy in order to allow for healing of the mucosa affect patient outcomes negatively. For head and neck tumours there is little lag time in tumour repopulation during radiation therapy. Therefore breaks in treatment often result in tumour repopulation and reduced local control rates (10 to 12% per one week break in radiation therapy (Rosenthal, 2007)).

Patients receiving combined chemoradiation have an increased risk of dose modifications and treatment breaks. Rosenthal (2007) reported in a survey of five studies with a total of 1,267 patients, that treatment modifications due to oral mucositis were found in nine percent of patients receiving radiation therapy alone compared to 19% of patients treated with chemoradiation.

1.6 SCORING ORAL MUCOSITIS

In an environment where cancer treatments are constantly changing it is important that new treatments are evaluated in terms of their side effects and complications such as oral mucositis are documented using a reliable and reproducible scoring system. There is no universally accepted tool for scoring oral mucositis which makes it difficult to compare studies that have assessed various interventions. Commonly used scoring systems can be divided into two categories: those that document the general appearance of the oral cavity and anatomical distribution of the mucosal lesions and those that also assess oral health, function and patient morbidity factors (Parulekar et al., 1998). Common scoring systems are summarised in Table 1.3.

Table 1.3 Summary of Commonly used Mucositis Scoring Systems. (Adapted from Parulekar et al., 1998; Hsaio & Sonis, n.d.).

System	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO	No changes	Soreness with erythema	Erythema, ulcers, can eat solids	Ulcers, liquid diet only	Alimentation not possible
RTOG	No change over baseline	May experience mild pain not requiring analgesic	Patchy mucositis may experience pain requiring analgesics	Confluent fibrinous mucositis may include severe pain requiring narcotics	Ulceration, haemorrhage or necrosis
OMI- 20 item – mouth separated into nine anatomical areas					
OMI Erythema	Normal	Mild erythema	Moderate erythema	Severe erythema	
OMI Ulceration	No ulceration	>0cm ² - <1cm ²	1cm ² - <2cm ²	>2cm ²	
NCI CTC v.2 (For Radiation Treatment)	No changes	Erythema	Patchy pseudo membranous reaction (patches generally < or = to 1.5cm in diameter)	Confluent pseudo membranous reaction (> or = to 1.5cm in diameter)	Necrosis or deep ulceration
NCI CTC (For Chemotherapy)	No changes	Painless ulcers, erythema, or mild soreness in the absence of lesions	Painful erythema, edema, or ulcers, but can eat or swallow	Painful erythema, edema, or ulcers requiring IV hydration	Severe ulcerations or requires nutritional support
OMAS – mouth separated into nine anatomical areas					
OMAS Ulceration	Normal	Less than 1 cm sq.	Between 1-3 cm sq.	Greater than 3 cm sq.	N/A
OMAS Erythema	Normal	Not severe	Severe	N/A	N/A

Key = WHO: World Health Organisation, RTOG: Radiation Therapy and Oncology Group, OMI: oral mucositis index, NCI: National Cancer Institute, CTC: common toxicity criteria, OMAS= oral mucositis assessment scale, N/A: not applicable, IV: intravenous.

Anatomical Scoring Tools

The oral mucositis index (OMI) was first developed in 1992 by Schubert and colleagues. They suggested a 34-item version analysing erythema, ulceration, atrophy and edema. This scoring system was limited to trained dental professionals because of the amount of specialized experience and knowledge needed to rate each parameter (McGuire, 2002). In 2002, McGuire working closely with Schubert simplified the OMI scale to a 20-item scoring system which could be used by non-dental professionals. This scoring system scored erythema, ulceration, atrophy of the dorsal tongue and oedema of the lateral tongue giving a total score from zero to 60. This system details the location and extent of oral mucositis and measures changes associated with mucositis as it develops and resolves (McGuire, 2002). A disadvantage of this scoring system is that it measures the degree of tissue injury but does not give information about the subjective and functional components of oral mucositis (McGuire, 2002).

Functional Scoring Tools

Many oral mucositis scoring systems utilize a combination of objective, functional and symptomatic variables (Sonis et al., 2004). These scoring systems include the World Health Organisation (WHO) scoring system, National Cancer Institute common toxicity criteria (NCI CTC), Radiation Therapy Oncology Group (RTOG) scoring system, and the Oral Mucositis Assessment Scale (OMAS). In a recent review of 400 trials, 43% of studies used the NCI CTC, 38% used WHO scoring system, 5% used scales based co-operative groups such as RTOG and the remaining studies used study-specific scales (Sonis et al., 2004). The WHO scoring system was developed in 1979, and combines the appearance of mucositis and eating ability into a single score from zero to four. The NCI CTC and RTOG scoring systems built on the original WHO scoring system combining symptoms (pain), signs (erythema, ulceration) and function (eating and swallowing) to get a more holistic idea of the oral mucositis (Sonis et al., 2004).

The OMAS scale was designed by Sonis et al. (1999). It includes both objective (erythema, ulceration) and subjective (mouth pain, ability to swallow and function) parameters, and can be used by people with minimal training in large scale multi-site clinical trials (McGuire, 2002). This scoring system separates the objective measurements from the functional measurements. The objective measurement divides the mouth into 9 different anatomical areas and gives each a score from zero

to three for ulceration and zero to two for erythema. Patients are then asked to fill out a questionnaire indicating their pain levels, swallowing capabilities and what they are able to eat. This system has undergone extensive testing demonstrating its reliability, validity and ease of use (McGuire, 2002).

Study-Specific Scoring Tools

Some studies use a panel of specialists and clinicians to develop their own oral mucositis scoring system that meets the specific needs of the study. Epstein et al. (2001) developed a multi-site scoring system in their study of Benzydamine HCL (difflam) in the prophylaxis of radiation-induced oral mucositis in 172 patients in 16 different centres. Epstein and colleagues divided the mouth into fourteen anatomical areas and then distinguished which of these areas were at risk of ulceration. They defined an area at risk as an anatomical region receiving at least 4000cGy. Each of the 14 areas was then given a grade zero to four (Table 1.4). The mean mucositis score was found by adding each score for the 14 sites and then dividing by the number of areas at risk. By dividing the sum of the fourteen sites by the areas at risk the researcher gained a meaningful score which was not diluted by the areas outside the radiation field which were not expected to develop oral mucositis. This scoring system reflects the assessor's perception of the oral mucositis and not the patient's perception as there is no functional part to this scoring system. However, it is simple to use and can be used by non-dental professionals as it requires very little training and expertise.

Table 1.4 Scoring System used by Epstein et al. (2001).

Scoring System	Grade 0	Grade 1	Grade 2	Grade 3
<i>Epstein et al., 2001 multi-site scoring system</i>	Within normal limits/ healed	Erythema	Single ulcer less than 1cm	Single ulcer greater than 1cm or multiple ulcers

1.7 CURRENT TREATMENT OF ORAL MUCOSITIS

Oral mucositis is an inevitable side effect of some chemotherapy agents and radiation therapy to the head and neck region. Treatments have historically been aimed at the palliation of symptoms associated with oral mucositis such as pain and dysphagia, and treatment of secondary complications such as weight loss and malnutrition. These palliative treatments, whilst improving patient comfort, do not address problems of tissue breakdown, secondary infection (primarily *Candida*) or impaired healing (Epstein et al., 2001). Thus, there is a real need for novel treatments that can prevent oral mucositis or reduce its severity and duration (Posner and Haddad, 2007).

In 1998, Sonis proposed a four-stage model (later developed into a five stage model) that described oral mucositis as a complex multifactorial process. An increased understanding of the pathobiology of mucositis has led to the development of novel agents that aim to target or block the disease process at a single or multiple points along this continuum (Figure 1.2) thus preventing the development of oral mucositis (Posner and Haddad, 2007).

Currently, there is a lack of large randomised clinical trials to validate the use of different treatments. Most studies are limited by their small sample size and inconsistent use of valid and reliable measuring tools (Eilers & Million, 2007). This means that the treatment of oral mucositis remains largely based on historical and anecdotal evidence rather than clinical research-based evidence. Some of the novel agents that have been developed or are in clinical trials for the treatment and prevention of oral mucositis are discussed below. This is not an exhaustive list of agents available but rather an overview of the interventions that have been thoroughly tested, show promising results or are already in clinical use.

1.7.1 Oral Care Protocol

Oral care is considered the foundation of mucosal health, integrity and function (Harris et al., 2008). It is important because it reduces the impact of treatment on the oral flora and restricts opportunistic infections (Worthington et al., 2007). Most cancer departments have an oral care protocol for head and neck patients however the specific components, methods and frequency of oral care differs between centres as no particular protocol has been proven to be more effective. The core components of most oral care protocols are discussed in Table 1.5.

Table 1.5 Core elements of Oral Protocols. (Adapted from Harris et al., 2008; Cawley & Benson, 2005).

RECOMMENDED PRACTICES	THINGS TO AVOID
• Attend pre-treatment dental check-up • Clean teeth • Treat dental caries • Remove problematic teeth • Brush all teeth surfaces, twice daily with a soft toothbrush • Floss teeth once daily • Maintain adequate hydration • Keep lips and mouth moist • Use sipper bottle • Use water-based moisturisers to keep lips moist • Maintain adequate consumption of vitamins and proteins • Rinse with mild mouthwash e.g. saline or bicarbonate soda	• Avoid tobacco and alcohol • Avoid spicy, acidic and coarse foods • Avoid very hot or cold foods • Avoid the use of commercial mouthwashes that contain alcohol as they have drying effect

Due to the ethical considerations of withholding proper oral care, it is difficult to conduct randomised controlled studies on this subject. In 1997, Shih and colleagues evaluated the effect of oral care protocols on reducing oral mucositis in 30 patients undergoing radiation therapy. Patients were separated into three groups, the control group received no oral care instructions, experimental group one (E1) was advised to begin the oral care protocol one day prior to radiation therapy and experimental group two (E2) was advised to begin with the oral care protocol one week prior to treatment. This study reported that patients in E2 had later onset of mucositis than those in the control and E1 groups with a median onset time of 12.0 days for the control group, 15 days for the E1 group and 21 days for the E2 group. In addition, only 45% of patients developed oral mucositis in the E2 group compared with 75% in the E1 group and 100% in the control group.

A decrease in oral mucositis incidence in patients using an oral care protocol was also reported by Cheng and colleagues (Cheng et al., 2001). This study of 42 children suffering from chemo- induced oral mucositis showed a 38% reduction in the incidence of oral mucositis in children using the oral

care protocol compared to the control group. Severity of oral mucositis and related pain were also reduced by using the oral care protocol. Despite the lack of blinding, unclear descriptions about the oral hygiene used by the control group and small sample sizes, these studies suggest that the use of an oral care protocol improves patient outcomes. In support of these results, a large Cochrane review by Worthington et al. (2007), reported that oral care protocols prevented or lessened oral mucositis. Further research is needed to determine the optimal oral care regime for different patient cohorts.

Some oral care protocols include rinsing with bicarbonate mouthwash, saline solution or sterile water. Although these bland rinses have been a primary part of the palliative care of oral mucositis there is very little literature supporting their use. Most current studies use washes such as saline solution or bicarbonate mouthwash as the control group when testing new products.

1.7.2 Chlorhexidine Mouthwashes

Chlorhexidine is a bisbiguanide which has broad spectrum antibiotic properties and is used to control plaque-dependent oral disease such as caries and gingivitis (Shih et al., 2002). Chlorhexidine was thought to affect oral mucositis by suppressing the oral micro flora (Shih et al., 2002). Early trials showed some benefit in the use of chlorhexidine for chemo-induced oral mucositis (Harris et al., 2008). However large systematic reviews by Worthington et al. (2007), Potting et al. (2006), Shih et al. (2002), and Rubenstein et al. (2004) all report that chlorhexidine is not effective in reducing the incidence or severity of oral mucositis. The Multinational Association of Supportive Care in Cancer (MASCC) therefore does not support the use of chlorhexidine in the treatment of oral mucositis (Rubenstein et al., 2004).

1.7.3 Magic™ Mouthwash

Magic mouthwash is a combination of lidocaine, diphenhydramine, and magnesium or aluminium hydroxide, commonly used in clinical practice (Dodd et al., 2000; Cawley & Benson, 2005). The Diphenhydramine and lidocaine have local analgesic properties and lessen oral pain whilst the magnesium and aluminium hydroxide enhance coating of the mouth (Chan & Ignoffo, 2005). Some cancer centres choose to add nystatin to their Magic mouth wash, an antifungal agent which prevents oral *Candida* infections.

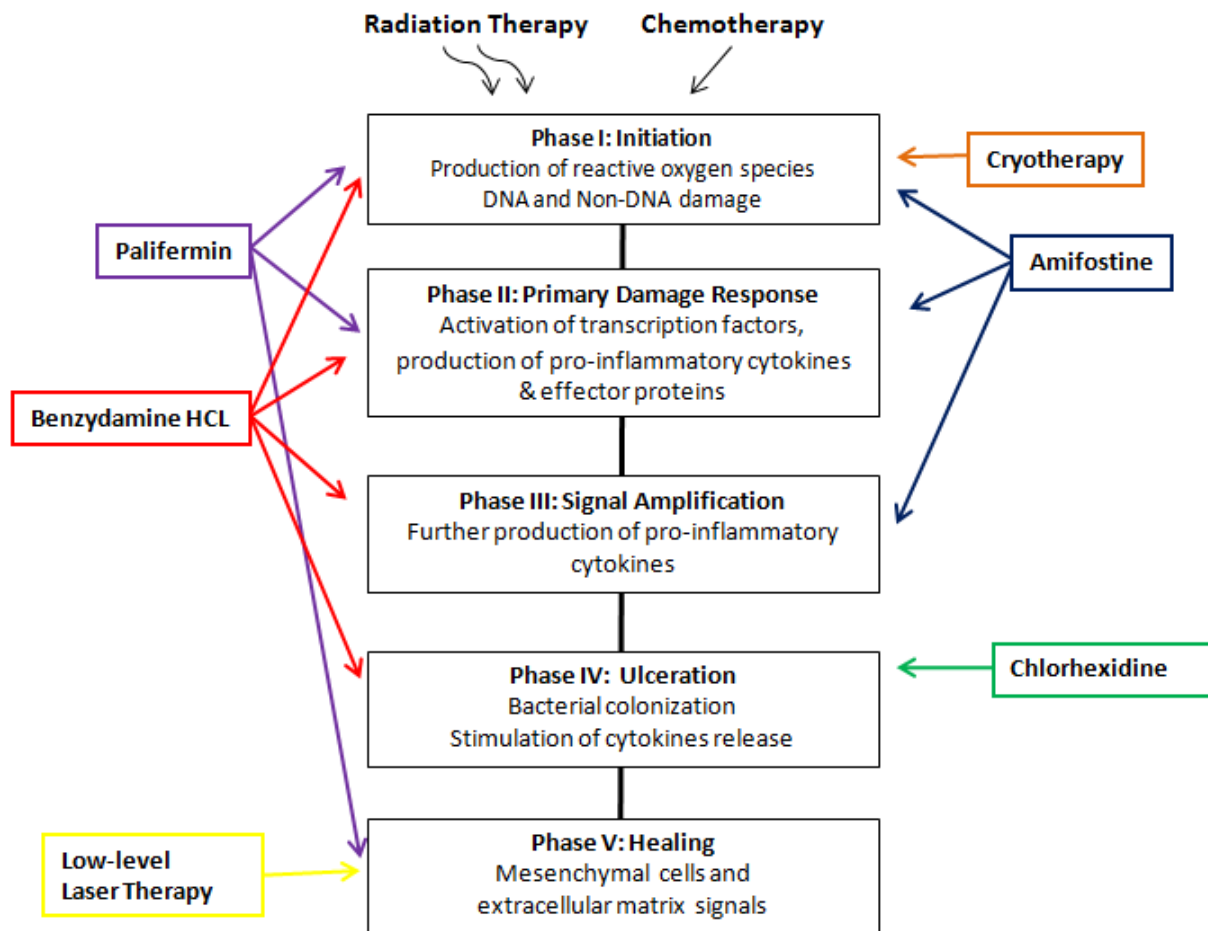


Figure 1.2 Development of oral mucositis five stage model by Sonis, 2007 and possible pathways of intervention for the treatment and prevention of oral mucositis. Adapted from Stockman et al.(2006).

Dodd et al., (2000) completed a large (n=200) double-blinded randomised study investigating the effects of three mouthwashes on chemotherapy-induced oral mucositis. The three mouthwashes included a salt and baking soda (SBS) mouthwash, chlorhexidine (CL) rinse and magic mouthwash (MM). This study measured the time to resolution of oral mucositis in the three different arms. The authors found there was no difference in the time to resolution between the three different mouthwash arms (SBS=7.0 days, CL=6.59, MM=7.17 $p=0.23$) and thus recommended using the salt and baking soda mouthwash because it is more economical. Interestingly, a quarter of the patients in this study withdrew from the trial (n=47) citing reasons of hospitalization, severe pain, nausea, bad tasting mouth wash and didn't like the numbing effect. Unfortunately, Dodd and colleagues did not report which arm of the trial these patients belonged to. This would have provided invaluable evidence as patient compliance with using any intervention is vital in assessing its effectiveness.

Despite the lack of literature supporting the use of magic mouthwash it is still commonly used in practice (Chan & Ignoffo, 2005). There are concerns about the use of magic mouthwash as the

numbing effect creates a potential for injury or difficulty swallowing. In addition, some of the formulations contain alcohol which can have a drying effect on the oral mucosa.

1.7.4 Palifermin

Palifermin is a recombinant human keratinocyte growth factor that stimulates the growth and maturation of epithelial cells (Harris et al., 2008). A large phase III trial compared palifermin to a placebo in 202 patients receiving intensive chemotherapy and radiation therapy prior to bone marrow transplantation (Spielberger et al., 2004). The incidence of severe oral mucositis was 63% in the palifermin group compared with 98% in the placebo group ($p<0.001$). The median duration of oral mucositis was six days in the palifermin group and nine days in the placebo group. Palifermin significantly decreased the incidence of grade four mucositis. The findings of this study are supported by those of trials conducted by Rosen et al. (2006), Nasilowska-Adamska et al. (2007) and Lagner et al. (2008).

Palifermin has now been approved in the United States for the use of oral mucositis in patients with haematological malignancies receiving chemoradiation prior to stem cell transplantation (Cawley & Benson, 2005). Due to the high cost of Palifermin, it has only been approved for use in patients with a high risk of developing oral mucositis (Harris et al., 2008). Currently, this agent is in phase III clinical trials, both in United States and Europe for patients receiving chemoradiation for head and neck cancers (Posner et al., 2007).

1.7.5 Amifostine

Amifostine is a free radical scavenger designed to selectively protect normal tissues from radical-induced DNA damage and prevent upregulation of inflammatory pathways caused by radiation and cytotoxic drugs (Posner et al., 2007). This agent has been shown to be effective in preventing acute and late xerostomia in patients receiving radiation therapy for head and neck malignancies (Rubenstein et al., 2004; Posner et al., 2007; Harris et al., 2008). Amifostine is also used to reduce the risk of neutropenia and nephrotoxicity for patients receiving cisplatin and combination cyclophosphamide and cisplatin regimens (Posner et al., 2007).

Data available on the effects of amifostine on oral mucositis are contradictory. Worthington et al. (2007) concluded from a meta-analysis of eleven trials involving a total of 845 patients, that amifostine had a small benefit in preventing (Risk Ratio (RR) = 0.95) and reducing the severity (RR=0.88) of oral mucositis in patients receiving radiation therapy to the head and neck. These findings were supported by a meta-analysis by Stockman et al. (2006) of seven randomised clinical studies conducted between 1998 and 2003. Five of the seven studies showed a significant reduction in severe oral mucositis (grade three or four) in patients receiving amifostine. The remaining two studies showed either a non statistical reduction in mucositis in patients getting amifostine or no change at all.

Since the publication of these two reviews in 2007 one more clinical trial has investigated the effect of amifostine on oral mucositis. This was a randomised phase two trial of 58 patients receiving radiation therapy and weekly Carboplatin/Paclitaxel for the treatment of head and neck cancers (Haddad et al., 2009). Haddad and colleagues reported no change in the severity of oral mucositis with 75% of patients in the amifostine group and 70% of patients in the control group developing grade three or four oral mucositis. The authors hypothesized that the increased toxicity of a combination of Carboplatin/Paclitaxel and concomitant boost radiation was so great that a small benefit from amifostine was not demonstrated in their study. If this is true then amifostine may have limited use in preventing oral mucositis in the future as treatment regimens for head and neck cancers are becoming increasingly aggressive with the discovery of new chemotherapy drugs and better radiation therapy techniques. Side effects associated with amifostine include nausea, vomiting, and transient hypotension (Cawley and Benson, 2005).

1.7.6 Low Level Laser Therapy (LLLT)

Low energy helium-neon laser uses pure light to produce photochemical reactions in cells (Cawley and Benson, 2005). This has been reported to promote healing of ulceration and reduce pain and inflammation, with no toxicities. Reviews done by Stockman et al. (2006) and Rubenstein et al. (2004) as well as several randomised trials have supported the use of LLLT in the treatment of oral mucositis. LLLT delayed the time to onset of oral mucositis to 14 days from eight days in the control group in a study of 34 bone marrow transplant patients (Chor et al., 2010). LLLT also reduced the severity of lesions in a study by Khouri et al. (2009) involving 22 patients. This study reported a mean oral mucositis grade of 1.74 in the LLLT group compared with 2.45 in the control group ($p=0.02$).

Many studies have used LLLT once severe oral mucositis is present. These studies reported increased healing in patients receiving LLLT and reduced pain scores (Antunes et al., 2008; Simões et al., 2009).

There is an accumulating body of evidence to support the use of LLLT in the treatment of oral mucositis. However, LLLT requires expensive equipment, specialist operators and training and treatment can often be time consuming (Rubenstein et al., 2004).

1.7.7 Cryotherapy

Cryotherapy uses ice chips or ice cold water for the prevention of oral mucositis in patients receiving short-acting chemotherapy such as 5-FU (Harris et al., 2008). Patients suck on ice prior to, during and after rapid infusions of chemotherapy. This is thought to result in vasoconstriction reducing the exposure of the oral cavity mucous membranes to the cytotoxic agent (Harris et al., 2008). In a Cochrane review, Worthington et al. (2007) reported that cryotherapy may be beneficial in preventing or reducing the severity of oral mucositis. The use of cryotherapy to prevent oral mucositis in patients receiving bolus 5-FU is supported in the Multinational Association of Supportive Care in Cancer (MASCC) 2005 guidelines (Keefe et al., 2007). Studies have been inconsistent in their reporting on compliance. Patients who do not cope well with the cold will not comply therefore affecting its efficacy (Harris et al., 2008). Further research is needed into the compliance, duration and intensity of cryotherapy required to reduce oral mucositis.

1.7.8 Benzylamine Hydrogen Chloride

Benzylamine Hydrogen chloride is a non-steroidal drug with analgesic, anaesthetic, anti-inflammatory and antimicrobial properties (Harris et al., 2008). The majority of the studies on the effectiveness of Benzylamine were undertaken in the 1980s. Most of these early studies had small sample sizes but were of fairly good quality as they were double blinded, placebo controlled randomised studies. The majority of studies showed a delay in the onset and reduction in the severity of oral mucositis as well as pain in patients treated with Benzylamine (Shih et al., 2002).

A pivotal large multicentre, randomised, double-blinded, placebo controlled clinical trial was published by Epstein and colleagues in 2001. This trial investigated the use of Benzylamine for prophylaxis of radiation-induced oral mucositis. It was conducted in 16 centres in North America and

recruited a total of 172 patients, 84 of whom were treated with Benzydamine prior to, during and after radiation therapy. The remaining 88 participants were given a placebo treatment. This study found that in patients receiving a conventional fractionation radiation therapy, Benzydamine significantly reduced erythema and ulceration by approximately 30% compared to the placebo ($p=0.006$). This relationship was not reflected in patients receiving an accelerated RT regimen ($>220\text{cGy}$ per day). The accelerated therapy group had more severe oral mucositis than those receiving standard fractionations (with and without chemotherapy). Epstein et al. (2001), hypothesized that there may be a threshold beyond which the oral rinse did not control the cascade of inflammatory events connected with high daily doses of radiation therapy. This study also reported a significant delay in the use of systemic analgesics in those receiving Benzydamine ($p<0.05$).

Epstein et al. (2001) further reported that 26% of patients receiving Benzydamine and 25% of patients treated with a placebo did not complete the study. Of those who did not complete the Benzydamine, five had adverse reactions, five reported a lack of efficacy, one did not complete radiation therapy, 10 withdrew consent and one was lost to follow up. There was no information given about the compliance with the mouthwash. Cheng, (2004) analysed the efficacy, acceptance and tolerance of mouthwashes such as Chlorhexidine and Benzydamine in 34 children suffering from chemotherapy-induced oral mucositis. He reported that there was a mean compliance of 94% in those taking Benzydamine. However in the presence of ulceration 33% of patients diluted the mouthwash to relieve the stinging.

The results of these trials support the use of Benzydamine in the prophylaxis of radiation-induced oral mucositis. Based on this evidence the MASCC guidelines (2005) have also recommended the use of Benzydamine for the prevention of radiation-induced mucositis due to conventional radiation therapy (Keefe et al., 2007). It is used widely throughout Europe and Canada, however not in America as it has not been approved by the U.S Food and Drug Administration (Harris et al., 2008).

1.7.9 Honey

Honey has been used medically throughout history since Egyptian civilisations. Honey is a by product of flower nectar which becomes concentrated by dehydration inside a beehive (Biswal et al., 2003). It has an acidic pH (around 3.9), high viscosity and osmolarity which inhibits microbial growth and enhances epithelisation, thus promoting tissue healing (Motallebnejad et al., 2008).

Honey has been shown to be effective for the treatment of acute and chronic wounds such as ulcers and burns. A large Cochrane review of 16 trials (n=2554) by Jull et al. (2009) showed that honey improved healing times in mild to moderate, superficial and partial thickness burns compared with conventional dressings. This suggested that honey might be useful in the healing of ulceration in the oral cavity. If successful, honey would provide a simple, safe and inexpensive treatment of oral mucositis.

To date three clinical trials have investigated the effect of honey on oral mucositis. Biswal et al. (2003), were the first to report that honey decreased the extent of oral mucositis in a randomised study of forty patients undergoing radiation therapy. Patients receiving chemoradiation were excluded from the trial. Patients in the honey arm rolled 20mls of pure tea plant honey in their mouth three times daily. Patients in the control arm received no additional treatment for mucositis. This trial found that 20% of patients in the honey arm developed grade three or four oral mucositis compared with 75% in the control arm ($p<0.00058$). The median mucositis score was grade one in the honey arm compared to grade two in the control arm. Furthermore, honey showed to be beneficial in maintaining patient's weight with 55% of the honey-treated patients showed either static weight or a weight gain during radiation therapy compared with 25% in the control arm ($p<0.05$).

Two similar clinical studies have been published since (Motallebnejad et al., 2008; Rashad et al., 2008). Both studies recruited 40 participants and randomised them evenly to a control arm or honey arm. Rashad et al., (2008) investigated the effect of clover honey on oral mucositis in patients receiving chemoradiation for head and neck tumours. All patients in the trial used Benzylamine HCL mouthwash, antibiotics and anti-fungals were given as required and gastric feeding tubes were placed when necessary. Patients in the honey arm were also advised to swirl with 20mls of honey three times daily using the same protocol as Biswal et al. (2003). Rashad et al. (2008) reported that three (15%) patients in the honey arm experienced grade three or four mucositis compared with 12 patients (60%) in the control arm. Five patients in the control arm were forced to take a treatment break as a consequence of oral mucositis compared with no patients in the honey arm. Furthermore, Rashad reported a significant decrease in Candida colonisation with 15% of patients in the honey group suffering from infection compared with 60% in the control group ($p=0.003$).

Motallebnejad et al., (2008) investigated the effect of honey on oral mucositis in patients receiving radiation therapy for head and neck cancer only. Patients randomised to the honey arm swirled with 20mls of honey from the thymus plant, three times daily like the previous trials. Those in the control arm rinsed with saline solution before and after each radiation therapy session. Mean oral mucositis scores were significantly better in the honey group throughout the entirety of treatment ($p=0.000$). The mean OMAS score (Section 1.6) for patients in the honey arm was 8.0 in week six compared to 20.0 in the control group. Also those in the honey arm had significantly less weight loss with the average weight loss for the honey arm of 1kg compared with 6.3kg in the control arm ($p<0.001$).

All three studies supported the use of honey in the prevention and treatment of oral mucositis. However, none of the three studies discussed the issue of patient compliance or patient withdrawals. Only Rashad et al. (2008), investigated patients receiving combined chemoradiation, which is becoming increasingly popular as the treatment of choice for later stage head and neck malignancies. This was also the only study that used an acceptable control treatment (Benzylamine HCl), the other two studies compared honey to no treatment or saline solution. Most centres use a variety of treatments such as bicarbonate mouthwashes, Benzylamine HCl, topical anaesthetics such as xylocaine viscous and systemic analgesics such as codeine and morphine. More clinical trials need to be conducted that specifically test the effect of honey in chemoradiation settings, using an acceptable standard of best practice of care.

1.8 AIM AND OBJECTIVES OF THE CURRENT STUDY

Aim

To investigate the effect of Comvita manuka medical grade honey on oral mucositis in patients receiving radiation therapy to the head and neck in Palmerston North Hospital.

Specific Objectives

- To compare the time to onset of oral mucositis in patients receiving Comvita manuka medical grade honey with patients receiving standard care for oral mucositis.
- To determine if Comvita manuka medical grade honey decreases total mean mucositis scores using the multi-site mucositis scoring system compared to patients receiving standard care.
- To determine whether Comvita manuka medical grade honey reduces weight loss and malnutrition compared to patients receiving standard care.
- To compare the quality of life of patients receiving Comvita manuka medical grade honey with that of patients receiving standard care, using the EORTC QLQ-30 and EORTC H&N-35 questionnaires.

CHAPTER 2 METHODOLOGY

2.1 ORIGINAL PHASE II STUDY

Phase II study design

The original study was designed as a stage II randomised single blinded trial where the research assistants who assess the level of oral mucositis are not aware of which arm the patient is randomised to. At the beginning of the trial it became apparent that blinding the research assistants would be very difficult due to the large amount of interaction that they had with the participants. They are the first person the patient goes to with questions about the honey therefore it was decided not to attempt to blind the research assistant.

Participant numbers

The original trial intended to recruit 120 patients over two years in three radiation oncology departments in New Zealand (NZ). The number of patients required for the trial was based on results of a trial by Biswal et al. (2003), taking into account the probability of a smaller difference in the effect of honey on oral mucositis. Control patients in Biswal's trial did not use any medication to alleviate their oral mucositis symptoms. In NZ, all patients are treated for oral mucositis-related symptoms with difflam, NSAIDs and opioids when necessary (standard practice for control patients). Patients in the honey arm of the trial would receive honey in addition to standard practice. This thesis analyses the results of twelve participants that were recruited between March 2009 and November 2009 in Palmerston North Hospital.

Inclusion and exclusion criteria

In order to be eligible for the trial patients had to receive radiation therapy to the head and neck region and receive 4000cGy to at least two of 14 anatomical regions in the mouth (Figure 2.1). Patients were excluded if they had diabetes mellitus, an allergy to honey, previous radiation therapy, evidence of distant metastases or had a Karnofsky performance status score of less than 70% (Table 2.1).

Table 2.1 Karnofsky Score (Adapted from World Health Organisation, 2011)

<i>Karnofsky Score</i>	<i>Description</i>
100%	normal, no complaints, no signs of disease
90%	capable of normal activity, few symptoms or signs of disease
80%	normal activity with some difficulty, some symptoms or signs
70%	caring for self, not capable of normal activity or work
60%	requiring some help, can take care of most personal requirements
50%	requires help often, requires frequent medical care
40%	disabled, requires special care and help
30%	severely disabled, hospital admission indicated but no risk of death
20%	very ill, urgently requiring admission, requires supportive measures or treatment
10%	moribund, rapidly progressive fatal disease processes
0%	Death

Treatment versus control

The severity of oral mucositis depends mainly on the radiation dose received by areas of the mouth, in addition to whether or not the patient is receiving adjuvant chemotherapy (Kostler et al., 2009). Patients were grouped according to the treatment prescribed by the Radiation Oncologist and then randomised to receive either Honey or Standard treatment alone. This resulted in four arms:

- A – Patients receiving less than 6000cGy, without chemotherapy
- B – Patients receiving less than 6000cGy, with chemotherapy
- C – Patients receiving 6000cGy or more, without chemotherapy
- D – Patients receiving 6000cGy or more, with chemotherapy

Randomisation

For each patient, information on the total dose of radiation received, as well as the presence or absence of chemotherapy was sent to the principal investigator. The principal investigator then randomised (using computer-generated random numbers) the patient to either the treatment arm or control care arm in the appropriate stream. Patients randomised to the control arm received the standard of care. Those randomised to the treatment arm received honey in addition to the standard care.

Standard Care

Standard care in Palmerston North Radiation Oncology Department involves a series of mouth washes, pain relief and prophylactic percutaneous endoscopic gastrostomy (PEG) instalment. Patients are started on mouth washes either at the beginning of treatment or when they first begin to experience symptoms of oral mucositis depending on their radiation oncologist's preferences. They are advised to first gargle with a mixture of one teaspoon of baking soda with one glass of water. Patients are then recommended to gargle with Difflam (Benzydamine HCl), and then Nystatin (anti-fungal agent). They are recommended to do this routine four times daily.

In addition, patients are given pain medication if the oral mucositis becomes uncomfortable. Analgesics include Panadol, non-steroidal anti-inflammatory drugs and opioids such as a morphine elixir. They can also be prescribed xylocaine viscous which is a local anaesthetic numbing the mouth and throat. Patients are advised to have a PEG inserted prior to radiation therapy treatment in order to maintain their nutritional status during treatment if they are receiving bilateral head and neck irradiation or they are receiving neoadjuvant chemotherapy. In addition, they have weekly sessions with the dietician in order to monitor their weight and dietary advice.

Standard Care + Honey

Participants that were randomised to the treatment arm were recommended to use both the standard care and honey for the duration of their treatment. The honey was given to the participant on their first day of radiation therapy treatment. The research assistant showed them how to take the honey, and discussed the "honey regimen". They were also given a participant protocol sheet (Appendix A) to take home which outlines the instructions for honey use. The honey regimen consisted originally of swirling 20mls of undiluted honey around the mouth, three times daily: 15 to 30 minutes prior to radiation therapy, 15 to 30 minutes after radiation therapy and six hours later. On weekends patients were told to continue taking the honey three times daily: morning, afternoon and evening. After three days of treatment the research assistant would check that the patient understood how to take the honey and the honey regimen.

Ethics

The phase II clinical trial was approved by the Multi-Region Ethics Committee. (Protocol number: MEC/08/11/142).

Registration

The phase II trial was registered by the Australia New Zealand Clinical Trials Registry (Protocol number: ACTRN12608000180314).

Funding

The salary of the principal investigator Dr Patries Herst was paid by the University of Otago. The salaries of Dr Nik Nedev, Dr Claire Hardie and Hannah Thompson were paid by Midcentral District Health Board. The salary of the research assistant was paid by a University of Otago Research Grant. Also a level I (\$3000) scholarship was awarded by the Radiotherapy and Oncology trust in Palmerston North to the research assistant to contribute towards study fees

2.2 PHASE I STUDY

The phase II trial commenced in March 2009. By June 2009 four patients were recruited in Palmerston North with two participants allocated to the control arm and two randomised to the treatment arm. The first control patient completed the trial without any problems. The second control patient withdrew on day two citing too much paper work as his reason. The first participant randomised to the treatment arm withdrew on his ninth day of treatment (1800cGy). He complained that the honey made him nauseous due to the amount and frequency of taking the honey, its taste and its texture. The second patient to be randomised to the honey also withdrew from the trial at the end of his second week of treatment. He found the honey to be nauseating and painful. Both Wellington and Dunedin radiation oncology centres were also struggling with patient withdrawal from the trial for similar reasons.

At this stage of the trial it was clear that changes needed to be made to the way in which the participants used the honey. Therefore the trial was changed down to a phase I trial that tested the best way to administer the honey.

For this trial the inclusion and exclusion criteria remained unchanged. The majority of patients were allocated to the treatment arm receiving honey. Ethics approval was gained for two amendments after the first application. The first amendment to the ethics application was for the honey to be reduced to 10mls and be diluted in water (1:1). Four patients were recruited to the trial under this amendment. The second amendment was for the honey to be diluted in other fluids such as tea or ginger ale (1:3). A further four patients were recruited after this amendment. Permission was granted on both occasions under the same protocol number.

2.3 MEASUREMENTS

2.3.1 Mean Oral Mucositis Scores

The scoring system used for this trial was similar to the multi-site scoring system used in many large multi-centre clinical trials (Epstein et al., 2001) (Section 1.6). The mouth was divided into 14 separate anatomical areas: The upper and lower gingival, upper and lower vermillion lip, upper and lower labial mucosa, ventral and dorsal tongue, left and right buccal mucosa, soft palate, hard palate, floor of mouth and the oropharynx. Figure 2.1 illustrates where these areas are located in the oral cavity. Each of the fourteen areas was given a mucositis score from zero to three.

0= within normal limits or healed

1= Erythema

2= Patchy ulceration/pseudomembranes

3= Confluent ulceration/pseudomembranes

The mean oral mucositis score was calculated by adding the scores for each of the sites and dividing this by the number of areas at risk (receiving at least 4000cGy, based on the radiation therapy treatment plan). Oral mucositis scores were determined three times per week from start to completion of radiation therapy treatment by the research assistant.

2.3.2 Weight Measurements

Participants were weighed on their first day of treatment and weekly after this. All participants were weighed on the same scales in the radiation oncology department to minimise the effect of random errors from using different scales. Small systematic errors in the weights due to scales inaccuracies were deemed not to be significant for the purpose of this study.

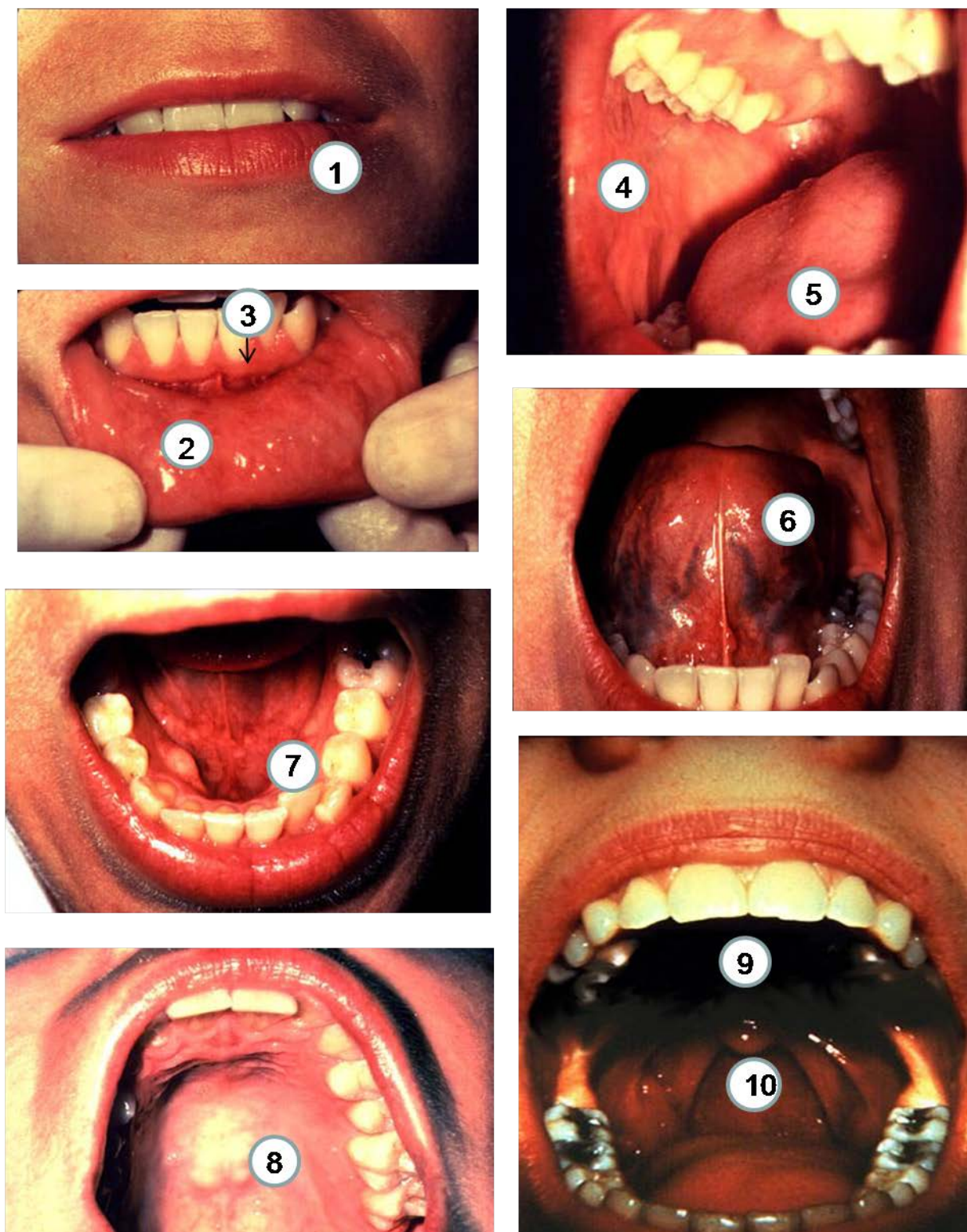


Figure 2.1 Photographs of different anatomical locations in the mouth. 1= Vermillion Lip, 2= Labial Mucosa, 3= Gingival, 4=Buccal Mucosa, 5= Dorsal Tongue, 6= Ventral Tongue, 7= Floor of Mouth, 8= Hard Palate, 9= Soft Palate, 10= Oropharynx. Adapted from National Institute of Dental and Craniofacial Research, 2009.

2.3.3 Food and Drug Diaries

All participants were given the standard information provided in Palmerston North Hospital regarding diet and nutrition. The information was given orally at their pre-treatment information session, and in written form. Patients were advised to drink plenty of fluids, avoid smoking, alcohol, hot and spicy foods as these may make reactions more severe. They also were booked in to see the dietician in clinic once per week to assess their nutritional intake. In addition, participants were asked to record their food and drug intake on a daily basis whilst on treatment. They were also asked to document their use of alcohol, tobacco, analgesics and other medications whilst on treatment. This information was collected from the patients by the research assistant at the end of each week.

2.3.4 Quality of Life Questionnaires

Participants were asked to fill out two Quality of Life questionnaires (QOL) on a fortnightly basis (Appendix B). The first of these questionnaires was the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-30. This was a tool generated to assess patients' general QOL and has been validated in several clinical trials in Europe and USA. While this questionnaire enables comparisons to be made across patient populations, it does not provide adequate data about disease-specific symptoms and treatment side-effects experienced by patients with head and neck cancers. Therefore, patients also filled in the more specific EORTC H&N 35. This questionnaire has been validated by a large trial of over 600 in 12 different countries and nine different languages making it one of the most widely tested disease-specific QOL questionnaires in cancer patients (Bjorndal, et al. 2000).

Patients were asked to assess their average QOL overall on a scale from one (very poor) to seven (excellent) with a higher scores indicating a better QOL. In addition, patients were asked to specifically assess areas of their life such as pain, problems with swallowing, their appearance, their family and social lives and interest in sex on a scale from one (not at all) to four (very much), with higher scores indicating a worse QOL.

2.4 TRIAL TIMELINE

The oral mucositis trial began with the potential participant meeting with their radiation oncologist to discuss radiation therapy treatment. The radiation oncologist mentioned the trial to the patient, gave them the Participant Information sheet (Appendix C) and told the patient that the research assistant would discuss the trial with them at their planning scan.

The research assistant then discussed the trial with the patient immediately after the planning computed tomography scan. The patient was given further written and verbal information about the mucositis trial. Patients were given several weeks between their planning scan and the first day of treatment to consider their participation.

On the patients' first day of treatment they consented or declined participating in the trial. The trial's informed consent form (Appendix D) was signed by the patient and filed in the patient notes. During the phase II trial patients were randomised to either the treatment arm or standard care arm. The majority of participants on the phase I trial were allocated to the treatment arm. Two patients in the phase I trial were allocated to the control arm in order to increase the number of controls. Baseline weight (Section 2.3.2) and mucositis score (Section 2.3.1) were noted. Participants were given their first QOL questionnaire (Section 2.3.4) and food and drug diary (Section 2.3.3) for week one. Participants on the treatment arm were given their first dose of honey after their first treatment and advised to repeat the honey six hours after treatment.

During treatment mucositis scores were determined three times weekly. Weight measurements and food and drug diaries were completed on a weekly basis. QOL questionnaires were completed four times whilst on treatment: the first day of treatment, week three, week five and on the last day of treatment. On the patients last day of treatment they were weighed, their last food and drug diary and QOL questionnaires were collected and a final oral mucositis score was done. The trial timeline is shown in Figure 2.2.

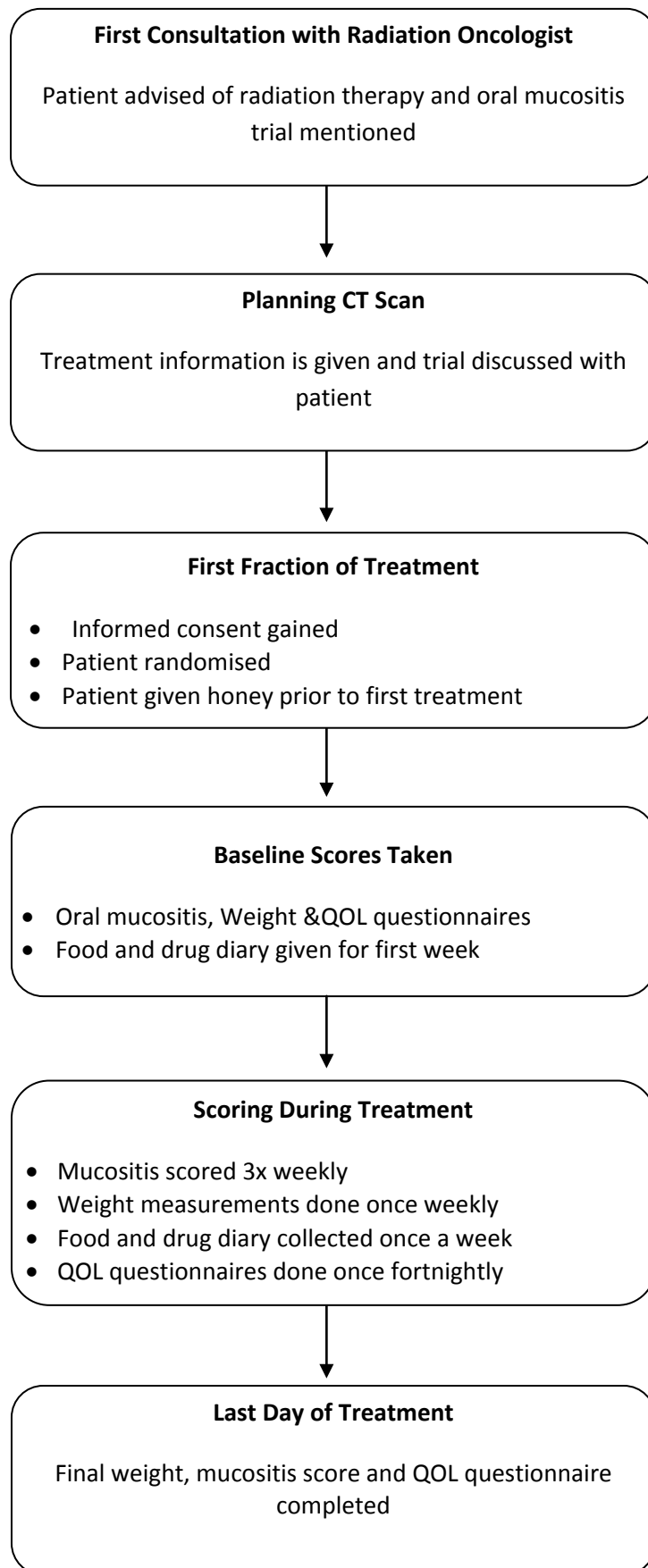


Figure 2.2*Trial Timeline*

2.5 DATA COLLECTION AND ANALYSIS

In order to ascertain the number of anatomical areas a patient had at risk of developing oral mucositis, the research assistant looked at the patient's radiation therapy treatment plan on the planning system. Transverse and sagittal images of the oral cavity were taken from the planning system as a record of the dose received by the oral cavity. The areas deemed at risk were then entered into a windows excel 2003 worksheet. The mucositis scores and weight measurements were entered into the same worksheet as were any extra notes made by the research assistant. Mean oral mucositis scores were then calculated. The information gained in these worksheets on each patient was then collated into a master sheet for further analysis (Appendix E).

2.6 PATIENT RECRUITMENT AND FLOW

The oral mucositis trial officially opened for patient recruitment on 1st of March 2009. Due to complications starting the trial in Palmerston North department the first patient was not recruited until March 20th 2009. The final patient was recruited to the trial on the 13th of October 2009. Participant flow through the trial is shown in the consort diagram in Figure 2.3.

Patients diagnosed with head and neck cancer in the Midcentral region are discussed at a fortnightly multidisciplinary meeting attended by radiation oncologists, medical oncologists, head and neck surgeons, pathologists and other health care professionals. The best treatment plan for each patient is decided at this meeting. If radiation therapy is recommended these patients are referred to the radiation oncologist for their first consultation.

From 20th of March 2009 until October 2009, 56 patients were referred to radiation oncology to receive radical radiation therapy to the head and neck. Of these patients 37 (66%) were predicted to receive a reasonable dose to their oral cavity. Patients receiving radiation therapy to the larynx, neck nodes only, upper face tumours and ethmoid tumours were expected to receive little or no dose to their oral cavity. The research assistant attended the planning scan of the eligible patients and assessed their performance status (Karnofsky score). Twelve of the 37 patients were excluded from the trial due to poor performance status (Karnofsky score less than 70%).

Twenty five patients were considered eligible for the trial. Due to unforeseen circumstances such as the research assistant's absences or the patient being sent away after their planning scan before the research assistant could meet with them, the trial was not discussed with nine eligible patients. The trial was discussed with sixteen patients. Of these patients, twelve were recruited and four declined to participate in the trial citing too much paper work (n=2) and just wanting to get through the treatment (n=2) as the reasons for not participating. No patients were excluded due to previous radiation therapy to the head and neck. Patients with distant metastasis were not counted in the initial 56 patients as they were not receiving radiation as a curative treatment.

Of the twelve patients recruited to the trial eight completed the trial (66%) and four (33%) withdrew during the trial. The first patient was a control and withdrew due to too much paperwork being involved, and the other three patients withdrew due to side effects of the honey.

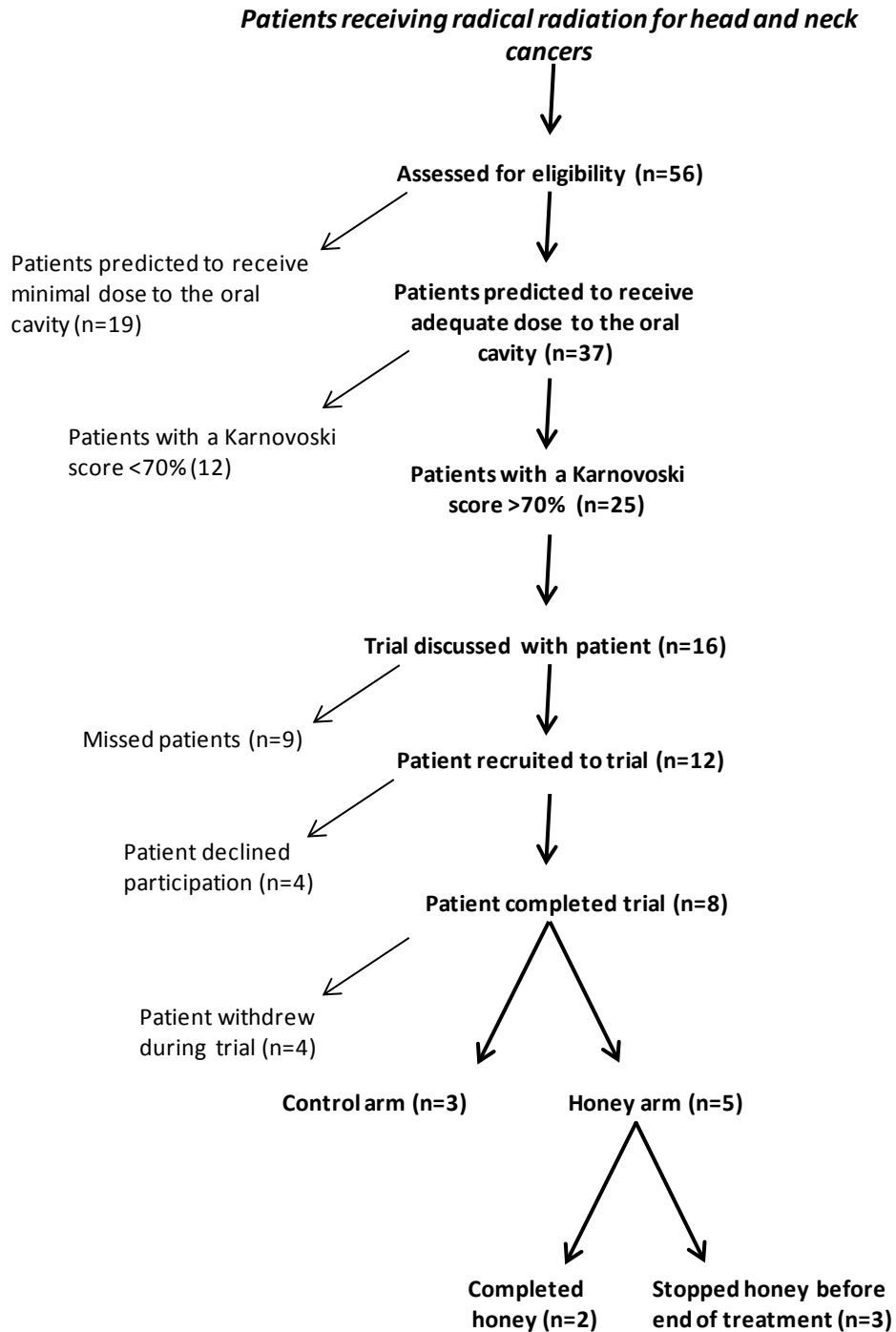


Figure 2.3 Consort Flow Diagram Showing Course of Patients Through Trial.

This diagram outlines the flow of patients through the trial. 12 patients were recruited to trial, four withdrew and eight completed the trial. Only two of five patients in the honey arm completed the six week period of honey with the remaining three patients ceasing taking the honey before their last day of treatment.

CHAPTER 3 RESULTS

3.1 INITIAL ASSESSMENT

Patient Construct

Twelve patients were recruited to the oral mucositis trial. Of these twelve patients four were allocated to the control arm and eight were allocated to the honey arm. Of the twelve patients originally enrolled three patients in the control arm and five in the honey arm completed the trial. However, only two of the five patients in the honey arm took the honey until the end of their treatment with the remaining three patients stopping the honey at some stage during their treatment. The details for the patients recruited to the trial are illustrated in Table 3.1.

Age: The average age of the participants in the trial was 59.1 years, ranging from 39 to 79 years of age. This is similar to the national average age with registrations for head and neck cancers in 2005 peaking in the 55 to 60 years category (Ministry of Health, 2009).

Sex: All patients recruited to the trial were male. Out of the 56 patients screened for the trial there were a few females however they did not meet the inclusion criteria due to their oral cavity not receiving enough dose or a poor performance status. National statistics from 2005 show that males are approximately two times more likely to be diagnosed with a head and neck cancer than females (Ministry of Health, 2009).

Smoking: Eighty-five percent of head and neck cancer are linked to tobacco use (National Cancer Institute, 2009). The risk of a smoker developing oral cancer depends on the number of cigarettes smoked per day and the duration of years of smoking (Petti and Scully, 2009). Of the twelve patients recruited to the trial eight (66.7%) were either currently smoking or ex-smokers. Three (25%) participants were non-smokers and for one patient (8.3%) their cigarette use was unknown.

Alcohol usage: The addition of alcohol to tobacco smoking further increases the risk for oral cancer. The combination of alcohol and tobacco transforms moderate drinking and smoking people, who normally have low or no head and neck cancer risk, into high-risk subjects (Petti, 2009). In this study, six (50%) patients drank alcohol, four were “moderate” and two (33.3%) were very heavy alcohol consumers. The level of alcohol consumption of the remaining six patients was unknown.

Table 3.1 Patient Characteristics

Parameter	Control Arm (%)	Study Arm (%)
Total Number of Patients	4	8
Female	0	0
Male	4 (100%)	8 (100%)
Average Age	54.5 years old	61.38 years old
Smoking (Past or Present)	4 (100%)	3 (37.5%)
Alcohol Intake known	2 (50%)	4 (50%)
Staging		
T1	3 (75%)	4 (50%)
T2	0	1 (12.5%)
T3	0	0
T4	1 (25%)	2 (25%)
Unknown T stage	0	1 (12.5%)
N0	1 (25%)	2 (25%)
N1	0	1 (12.5%)
N2	3 (75%)	5 (62.5%)
N3	0	0
Site		
Tongue	2 (50%)	5 (62.5%)
Hard Palate	1 (25%)	0
Tonsil	1 (25%)	2 (25%)
Parotid	0	1 (12.5%)
Withdrawals	1 (25%)	3 (37%)

Diagnosis: All twelve patients recruited to the oral mucositis trial were diagnosed with a squamous cell carcinoma. Seven participants (58.3%) had their tumour located on their tongue; three participants (25%) had their tumours in their tonsils, one participant had his tumour on his hard palate (8.3%) and the remaining one man (8.3%) had a parotid tumour.

Staging: Patients with Head and Neck cancers are staged using the World Health Organization's TNM staging. This system details the extent of the primary tumour (T stage), whether there are any lymph node metastases (N stage) and the presence or absence of distant metastases. Seven (58.3%) patients were diagnosed with a stage T1 tumour, one patient (8.3%) had a stage T2, three (25%) had a stage T4 cancer and for one patient (8.3%) staging information was not available. For the lymph node staging two patients (16.7%) had a N0 stage, one person (8.3%) had a N1 stage and eight (66.7%) had a N2 stage. None of the patients had distant metastases as this was an exclusion criterion for the trial.

Therapy Construct

Treatment options for patients diagnosed with a head and neck malignancy are surgery, radiation therapy and/or chemotherapy. Treatment depends on the type and location of their primary tumour, the stage of the cancer, the patient's performance status, and clinician and the patient preference amongst other things.

Surgery: Seven patients (58.3%) had radical surgery to remove the primary tumour. Of these seven patients, six (86%) patients also underwent a neck dissection. Four (57.1%) of these patients had the ipsilateral neck nodes or bilateral neck nodes removed and two had only one to two cervical lymph nodes removed. In Palmerston North Hospital, PEG feeding tubes are inserted for patients who receive high doses to one or both sides of their head and neck and have neo-adjuvant chemotherapy. PEG tubes were implanted for five (41.7%) patients.

Radiation therapy: All twelve patients were treated in Palmerston North Hospital over six weeks using Intensity Modulated Radiation Therapy (IMRT). This is a more precise way of delivering higher radiation doses to the tumour whilst minimizing the dose to the surrounding critical structures. Fifty percent (six) of the patients recruited to the trial received total dose of 6000cGy , 200cGy per fraction, one fraction per day, five fractions per week for six weeks to the 100% isodose curve with 6MV photons. The remaining 50% received a total dose of 6600cGy given in the same time period at an accelerated rate of 220cGy per fraction. Seven patients (58.3%) had ipsilateral neck nodes included in the radiation field and four (33.3%) received radiation therapy to both the ipsilateral and contralateral neck nodes. Only one (8.3%) of the twelve patients had no neck nodes included in the radiation therapy fields.

Chemotherapy: Eight of the twelve patients (66.7%) recruited to the trial received neo-adjuvant chemotherapy. The standard chemotherapy regimen given to patients with head and neck cancers in Palmerston North Hospital is three cycles of Cisplatin based chemotherapy. The first cycle is a combination of Cisplatin and Fluorouracil (5FU) given over three to five days, prior to radiation therapy. The final two cycles are given concurrently with weeks one and four of radiation treatment and consist of Cisplatin as a single agent. Five patients (62.5%) received the entire three courses of chemotherapy. The remaining three people (37.5%) were only given the two concurrent cycles of Cisplatin due to time constraints.

3.2 INDIVIDUAL PATIENT RESULTS

In this chapter individual patient results will be discussed separately. Each patient had oral mucositis scores taken three times per week. Once a week they completed food and drug diaries and were weighed to record their nutritional intake and weight loss. Also once fortnightly patients completed two questionnaires the EORTC QLQ-30 & EORTC QLQ H&N -35 in order to assess the impact of the treatment and the trial on their quality of life. The results for each patient who completed the trial are discussed separately as each patient's treatment, side effects and experience were unique.

3.2.1 Control Patient A: PHN-1

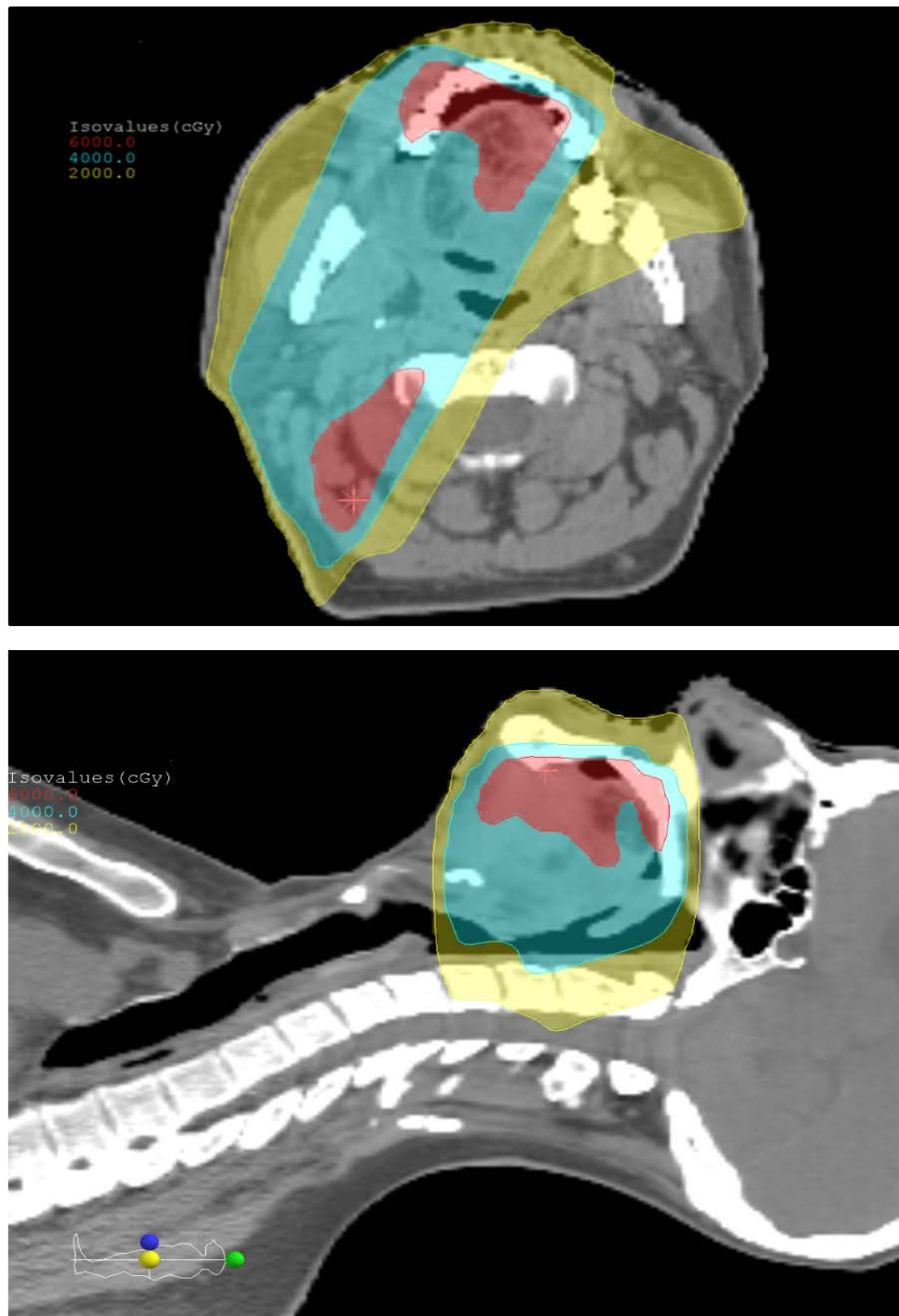
Patient details

Table 3.2 Patient Details for PHN-1

PATIENT DETAILS	
Randomisation number	PHN-1
Gender & Age	Male, 44
Karnofsky score	80%
Tumour details	Squamous cell carcinoma of the tongue
Stage	T1N0M0
Radiation therapy treatment regimen	IMRT 6000cGy in 30#, 200cGy per #, 1# per day, 5# per week, for 6 weeks to 100% with 6MV photons
Areas at risk (>4000cGy)	12/14
Chemotherapy treatment regimen	None
Randomisation Arm	Standard Treatment

PHN-1 was the first patient to complete the trial. His treatment regimen included a right hemiglossectomy with selective neck dissection followed by adjuvant IMRT to his right tongue only. Figure 3.1 shows the dose the oral cavity of this patient received. Xerostomia and erythema of the oral mucosa can begin to occur at approximately 2000cGy followed by oral mucositis at approximately 3000cGy (Washington and Leaver, 2009). For this patient, the 2000cGy isodose curve encompasses the whole oral cavity, lips, oropharynx, right parotid glands and a large amount of soft tissue. In order to be eligible for the trial, patients must have more than two of 14 areas of the mouth receiving at least 4000cGy. For this patient, the cyan 4000cGy isodose curve (Figure 3.1) encompasses most of the oral cavity with 12 of 14 possible areas of the oral cavity receiving at least 4000cGy. The left buccal mucosa is not an area at risk as the dose to the area does not reach

4000cgy. The floor of mouth is not an area at risk as due to his surgery this area was impossible to assess. The red 6000cGy isodose curve (Figure 3.1) shows that, in this patient, the anterior aspect of the oral cavity including the gums, anterior tongue, lips and right buccal mucosa receive very high doses of 6000cGy or more. PHN-1 was randomised to the standard care (control) arm of the phase II trial. PHN-1 did not receive PEG feeding as he was having no neck irradiation or chemotherapy.



3.1.2 Transverse and sagittal views of dose to oral cavity for PHN-1

Figure 3.1 Transverse and Saittal views of dose to the oral cavity for PHN-1.
6000cGy = red area, 4000cGy (areas at risk) = cyan area, 2000cGy = yellow area

Mean Oral Mucositis Scores

Figure 3.2 illustrates how the mean mucositis scores varied over time for patient PHN-1. For the first two weeks of treatment PHN-1 experienced no reactions in the oral mucosa. At a total dose of 2000cGy the patient's labial mucosa ulcerated. This was expected as this is the area receiving 100% of the prescribed dose. From 2000cGy to 3600cGy the extent of oral mucositis expanded to the labial mucosa, buccal mucosa, dorsal and ventral tongue, palate and floor of mouth. The patient's oral mucositis stabilized from 3600cGy to 4800cGy, and then worsened for the last 1200cGy with the vermillion lips, oropharynx and gingival ulcerating. The patient had a maximum mean mucositis score in the final weeks of his treatment of 2.1 which is high in comparison to most patients who took part in the trial.

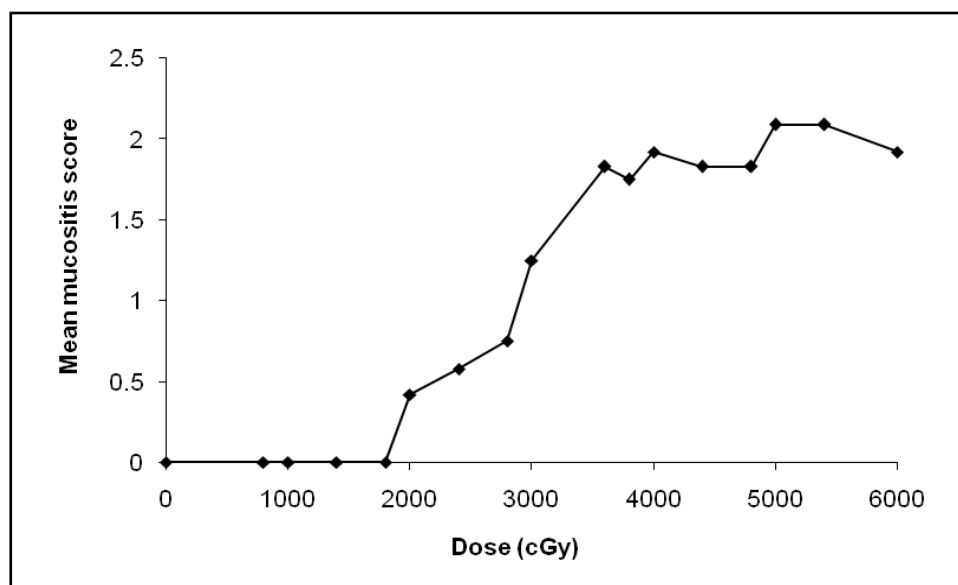


Figure 3.2 Mean mucositis scores for PHN-1 during treatment.

Quality of Life Questionnaires

Figure 3.4 depicts the results of the most relevant questions from the EORTC quality of life (QOL) questionnaires, completed by PHN-1 at two weekly intervals from the beginning of treatment until four weeks after the completion of treatment. The top graph demonstrates how PHN-1's pain increased during his time on treatment and decreased following the completion of treatment. His ability to taste and swallow food deteriorated peaking in severity at five weeks, however began to recover four weeks following treatment. The final graph depicts the answers to questions surrounding the patient's general QOL. PHN-1 found that communicating and eating with his friends and family became difficult around week five. He stated that his appearance bothered him a little at the start and end of treatment which is also the time that he found socializing with friends and family to also be a little more difficult than prior to his treatment. QOL is rated on a scale from one

to seven with one being very poor to seven being excellent. PHN-1 rated his quality of life as 5/7 (week one and three) 4/7 (weeks five and seven) demonstrating a slight reduction in his perception of the QOL as treatment progressed and side effects increased.

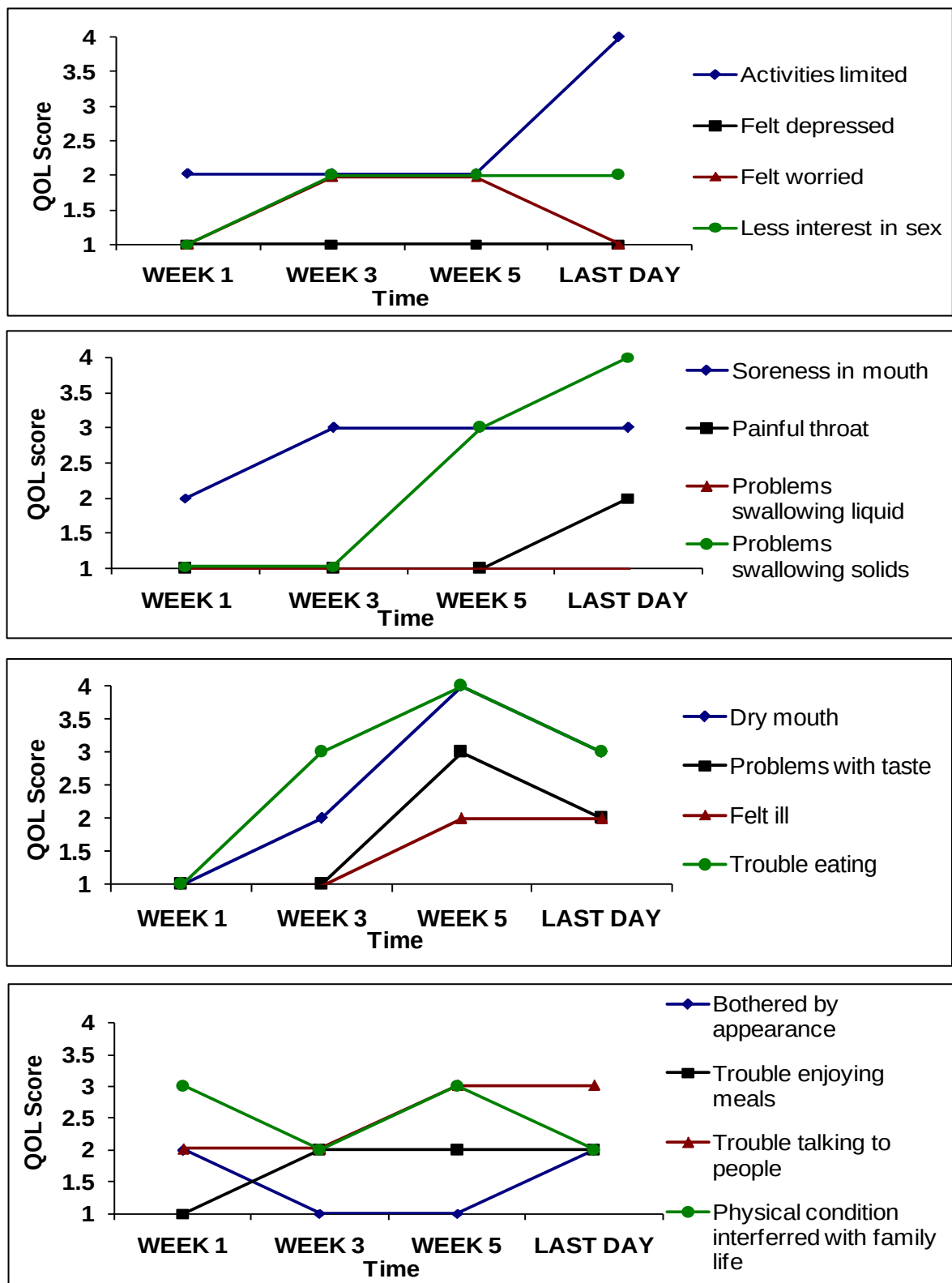


Figure 3.3 EORTC Quality of Life Questionnaire H&N35 Results for PHN-1.

QOL scores 1 = Not at all, 2 = A Little, 3 = Quite a bit, 4= Very much

Weight and Food Intake

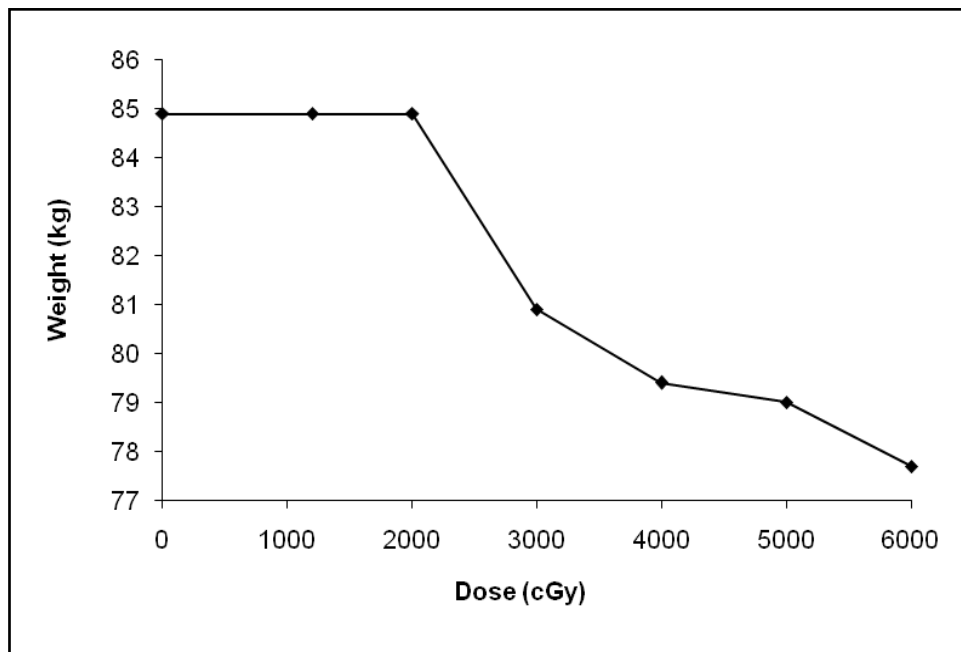


Figure 3.4 Weight measurements for PHN-1 during treatment.

PHN-1 lost 8.5% (7.2kg) of his baseline weight (84.9kg) during treatment (Figure 3.4). Weight loss started after 2000cGy, with 5.5kg lost between 2000cGy to 4000cGy followed by a further 1.7kg between 4000cGy to 6000cGy.

Between zero and 2000cGy, Patient PHN-1 experienced very minor side effects: his weight remained stable he had no oral mucositis and was able to eat a variety of soft and hard food with ease. He reported low pain scores in the QOL questionnaires which corresponded with his lack of analgesics use. Although he reported his general QOL to be good, he did experience problems with his self image and found talking difficult, which was attributed to his tongue surgery.

At 2200cGy eating was becoming painful and difficult and PHN-1 began using mouthwashes and gels such as Difflam and Bonjela to soothe the oral mucosa. His diet during this time changed from a normal pre-treatment intake to a high calorie soft food diet consisting of yoghurts, smoothies and porridge. He began to supplement his intake with the meal replacement product, Fortisip. By 3500cGy the patient's oral intake was reduced to a liquid diet heavily supplemented with Fortisip. His pain ratings increased and eating, tasting and swallowing became unpleasant. His general QOL remained fairly good during this time however, eating and socializing with his friends became more difficult. By 4000cGy, PN-1 had lost 5.5kg.

From 3600cGy to 6000cGy the patient's average oral mucositis scores increased slightly from 1.8 to 2.1. His average QOL decreased from 5/7 to 4/7 with eating and communicating with friends becoming difficult. PHN-1 reported he had "quite a bit" of trouble with swallowing and found eating to be very difficult. He lost a further 1.7kg resulting in a total weight loss of 8.5% of his baseline weight. During the last two weeks of PHN-1 radiation therapy his diet was heavily supplemented by Fortisip and the patient was taking oral morphine to help with the increasingly severe oral mucositis.

After PHN-1 completed treatment his oral mucositis began to heal slowly with only the dorsal tongue remaining ulcerated at two and four weeks post radiation. He continued to lose weight, weighing only 72.7kg four weeks after treatment. Bringing his total weight loss up to 14.4% of baseline weight). His average QOL remained a 4/7 at two weeks post treatment but increased to a 5/7 four weeks post treatment.

3.2.2 Control Patient B: PHC-4

Patient Details

Table 3.3 Patient Details for PHC-4

PATIENT DETAILS	
Randomisation number	PHC-4
Gender and Age	Male, 66
Karnofsky score	90%
Tumour details	Squamous cell carcinoma of the left hard palate
Stage	T1N2aMO
Radiation therapy treatment regimen	IMRT 6000cGy in 30#, 200 cGy per #, 1# per day, 5# per week, for 6 weeks to 100% with 6MV photons
Areas at risk (>4000cGy)	10/14
Chemotherapy treatment regimen	Cisplatin 2 courses: week 1 & 4 of RT treatment.
Randomisation Arm	Standard Treatment

PHC-4 was the second control patient to be recruited to the trial; a 66 year old man who presented with a squamous cell carcinoma of the left hard palate. This patient underwent primary radical surgery with free flap reconstruction and a modified left-sided neck dissection, followed by adjuvant chemo-radiation. A PEG feeding tube was suggested for this patient to maintain his oral intake however the patient chose not to have one. The patient's whole oral cavity and left side of his neck received 2000cGy (Figure 3.5). PHC-4 had 10/14 at risk areas His lower vermillion lip, right buccal mucosa and floor of mouth received less than 4000cGy therefore were not deemed as areas at risk. The patient was restricted in how far he could open his mouth therefore the oropharynx was not accessible for scoring and was also removed from the areas at risk. The anterior portion of the mouth including the tongue, gums and hard palate received very high doses of 6000cGy or more. PHC-4 was randomised to the standard care (control) arm of the initial phase II trial.

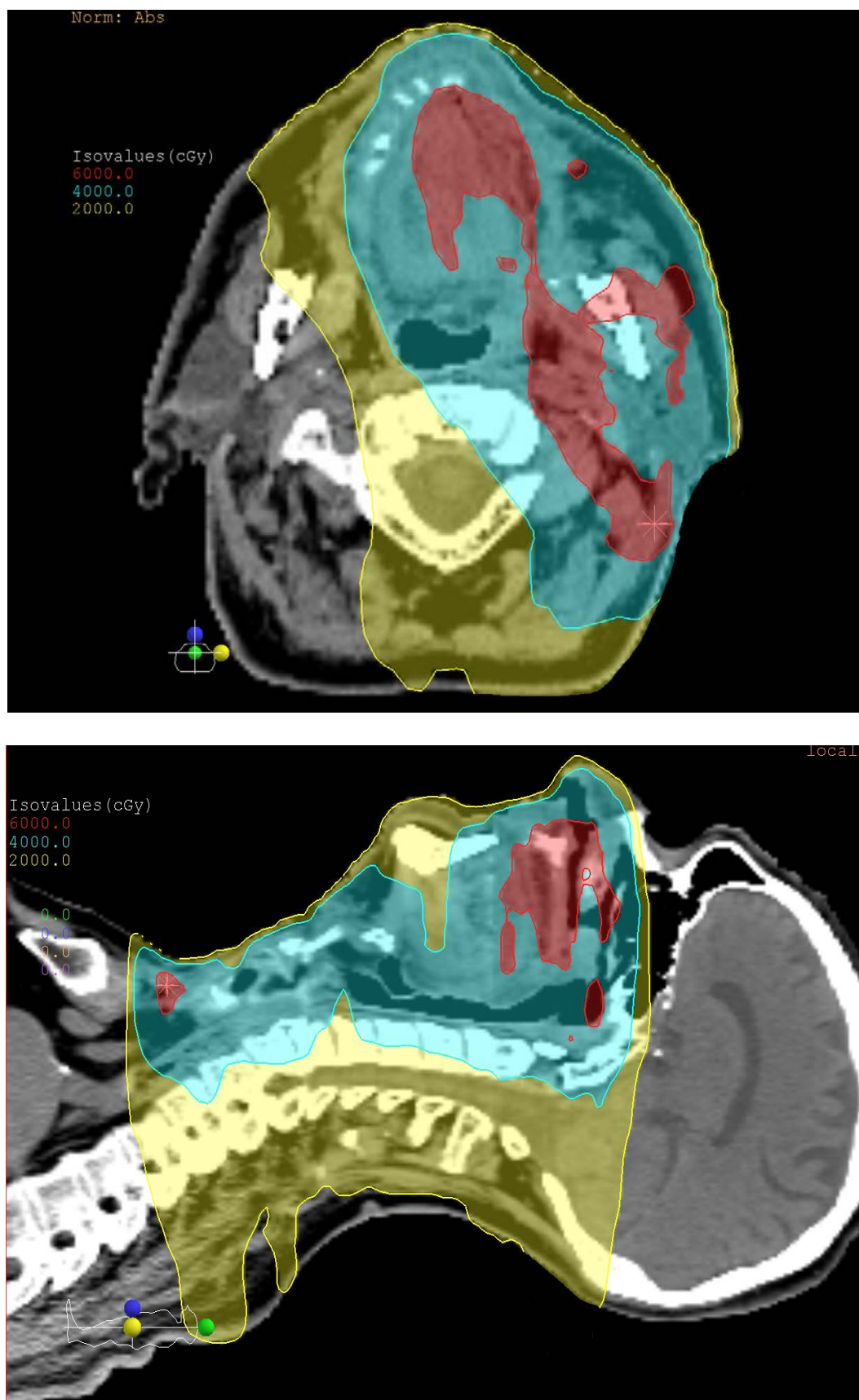


Figure 3.5 Transverse and Saittal views of dose to the oral cavity and neck for PHC-4.
 6000cGy = red area, 4000cGy (areas at risk) = cyan area, 2000cGy = yellow area

Mean Oral Mucositis Scores

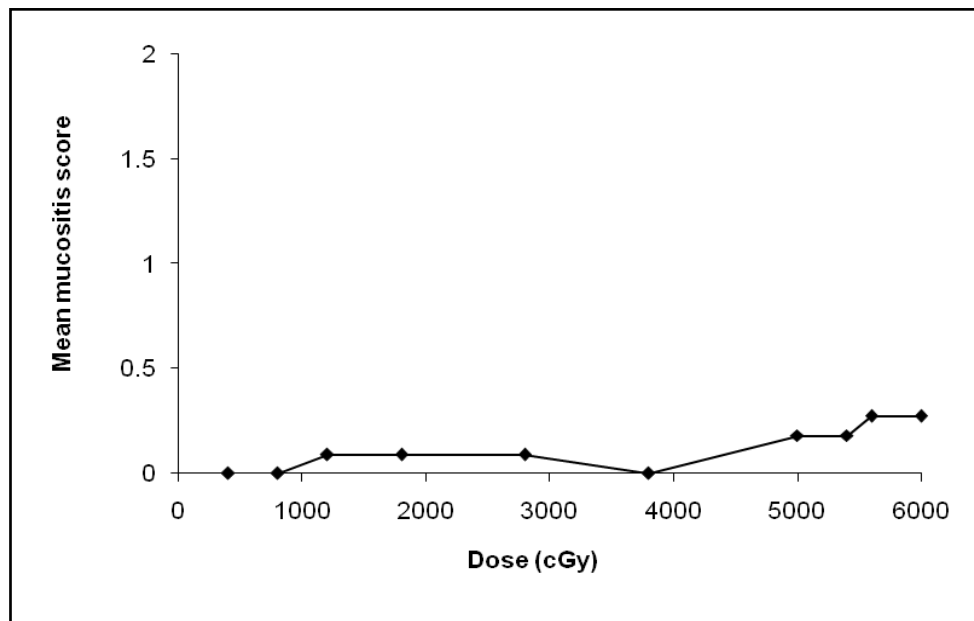


Figure 3.6 Mean Oral Mucositis Scores for PHC-4 During Treatment.

PHC-4 experienced very little oral mucositis during his entire treatment apart from a slight erythema and ulceration of the left buccal mucosa and soft palate at 5000cGy (Figure 3.6). His maximum mean mucositis score was very low (0.27) compared to the other seven patients who completed the trial. This lack of oral mucositis was unexpected as PHC-4 continued to drink substantial amounts of alcohol and smoke during treatment, against the advice of staff and radiation oncologists.

Quality of Life Questionnaire

PHC-4 average QOL decreased between the first and fourth week of treatment (Figure 3.7). At the start of treatment the patient reported have “A little”, pain in his mouth, jaw and throat. The pain in his throat and soreness in his mouth increased to “quite a bit” by the fourth week of treatment. By the fourth week of treatment PHC-4 reported “quite a bit” of problems swallowing solid foods and had “very much” difficulties with his sense of taste. As a result eating became increasingly difficult during his time on treatment. PHC-4 rated his average quality of life at the beginning of treatment as a 4/7 which decreased to 2/7 by week four of treatment.

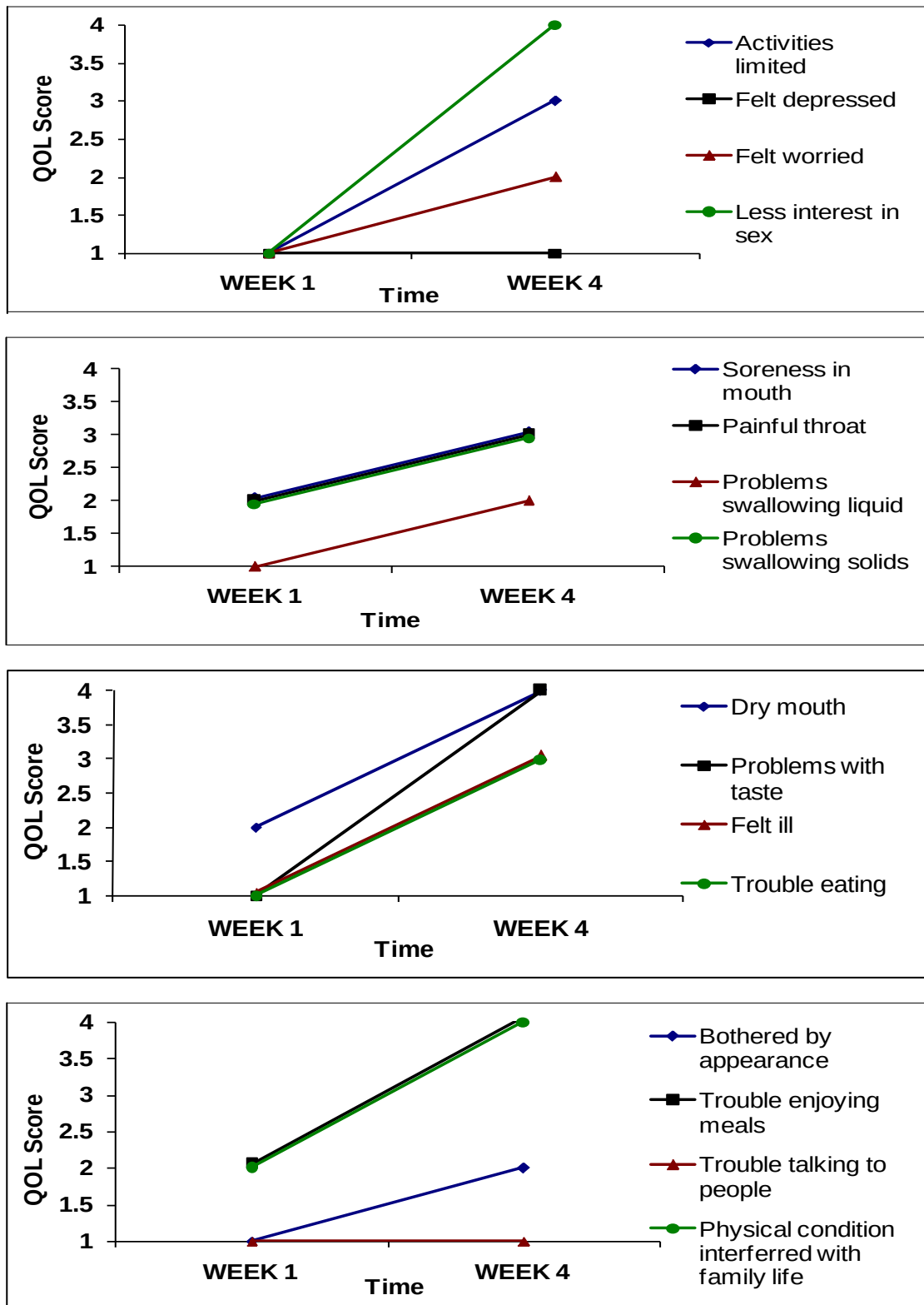


Figure 3.7 EORTC Quality of Life Questionnaire H&N35 Results for PHC-4.

QOL scores 1 = Not at all, 2 = A Little, 3 = Quite a bit, 4= Very much

Weight and Food Intake

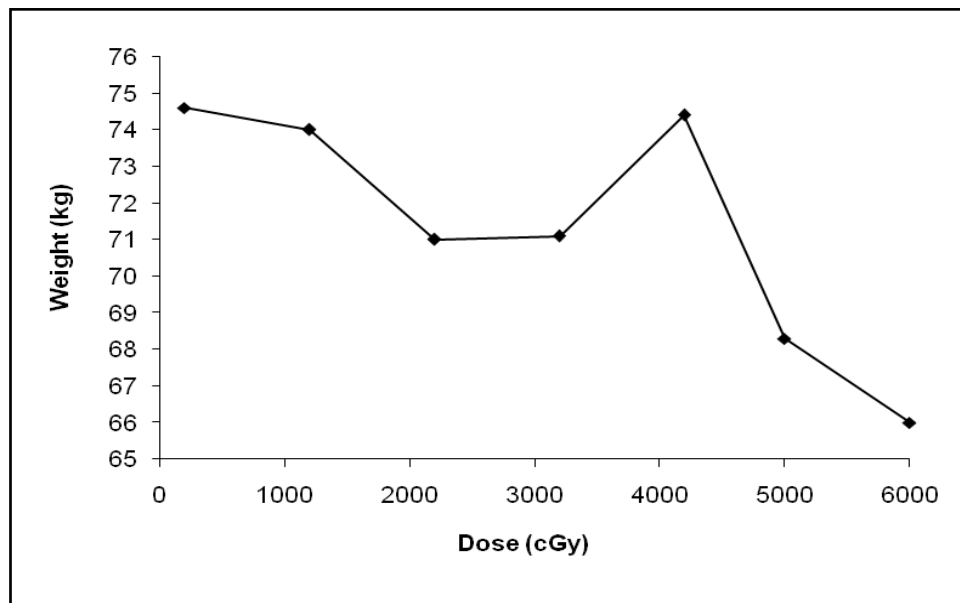


Figure 3.8 Weight measurements for PHC-4 during treatment.

This patient's compliance with filling in the food and drug diary was particularly poor. He completed only one of his food and drug diaries so the information gained on nutritional intake was done by observation and discussion with the patient. The patient's oral intake was sub-optimal at the beginning of treatment with food substituted heavily with alcohol and cigarettes. By 1800cGy the patient reported that he was not eating much due to nausea from the chemotherapy and lack of desire to do so. He reported feeling dizzy, shaky and weak and appeared unwell. This corresponded to a 3.6kg weight loss from 0cGy to 2000cGy. This was 4.8% of his baseline weight of 74.6kg. He was advised to increase oral intake and supplement his oral intake with the meal replacement Fortisip.

At 2800cGy the patient reported that he was not eating anything however was drinking approximately six Fortisip a day and maintained his weight from 2000cGy to 3000cGy. At 4000cGy the patient gained 3.4kg almost reaching his original weight, but this is likely to have been due to the fact that he was admitted to the ward for his second cycle of Cisplatin. Prior to his chemotherapy treatment he was given a large amount of fluids to rehydrate him. In the weeks following his chemotherapy (4000cGy to 6000cGy) he weight decreased down to 66kg on his last day, bringing his overall weight loss to 8.6kg (11.5% of his baseline weight). There were several issues with compliance with this patient. He was a heavy smoker and drank large amounts of alcohol regularly despite being advised not to do so whilst on treatment. He completed only one of the six food and drug diaries and two of the four quality of life questionnaires. No follow up information was gathered as he does not live locally.

3.2.3 Control Patients C: PHC-8

Patient Details

Table 3.4 Patient Details for PHC-8

PATIENT DETAILS	
Randomisation number	PHC-8
Gender and Age	Male, 67
Karnofsky score	90%
Tumour details	Squamous cell carcinoma of the right dorsum of the tongue
Stage	T4N2cM0
Radiation therapy treatment regimen	IMRT 6600cGy in 30#, 220 cGy per #, 1# per day, 5# per week, for 6 weeks to 100% with 6MV photons
Areas at risk (>4000cGy)	13/14
Chemotherapy treatment regimen	Cisplatin 3 courses: 3 weeks prior to treatment, week 1 & week 4 of RT treatment.
Randomisation Arm	Standard treatment

The third control patient to participate in the trial was patient PHC-8; a 67 year old man diagnosed with a squamous cell carcinoma of the right dorsum of the tongue (Table 3.3). He was referred for neoadjuvant chemo-radiation therapy. The patient had a PEG tube inserted to help him maintain his nutrition during treatment. Figure 3.9 illustrates the high doses that this patient's oral cavity received. All 14 areas of the mouth received at least 4000cGy with the tongue, oropharynx, floor of mouth and soft palate receiving very high doses of at least 6000cGy. The oropharynx was removed as an area at risk, as due to the patient's restricted jaw movement it was difficult to assess therefore could not be scored accurately. This left a total of 13 of 14 areas of the mouth at risk. PHC-8 was randomised to the standard care (control) arm of the initial phase II trial.

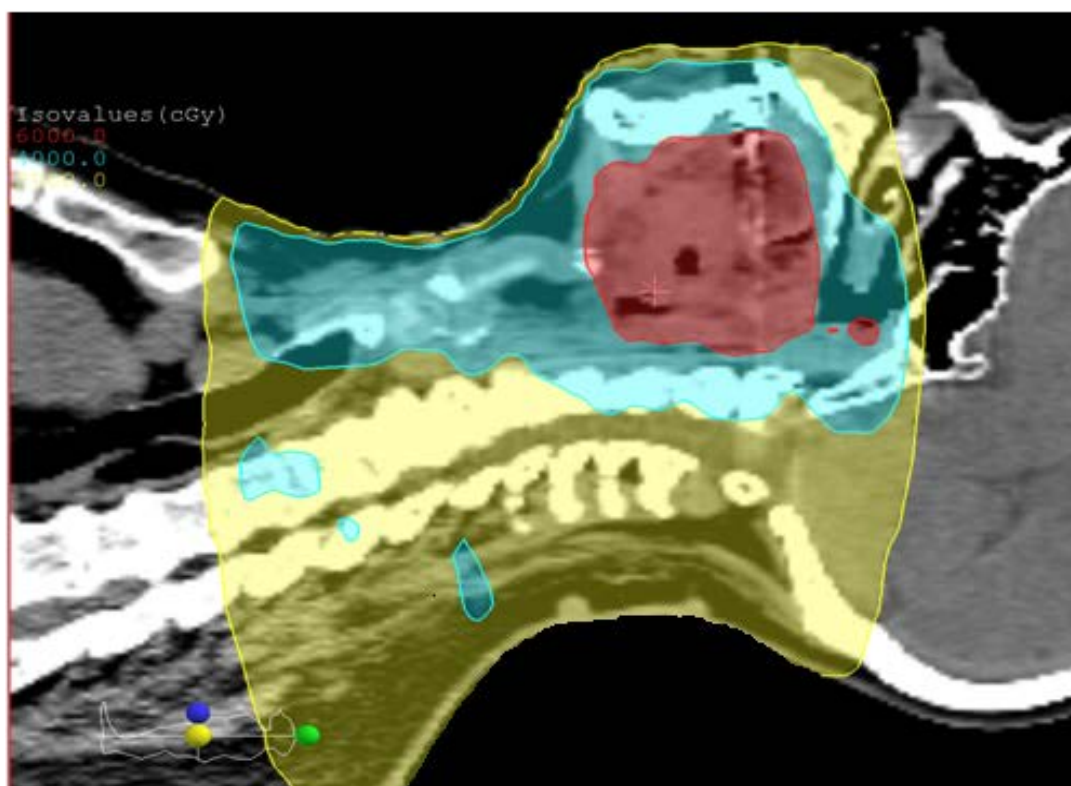
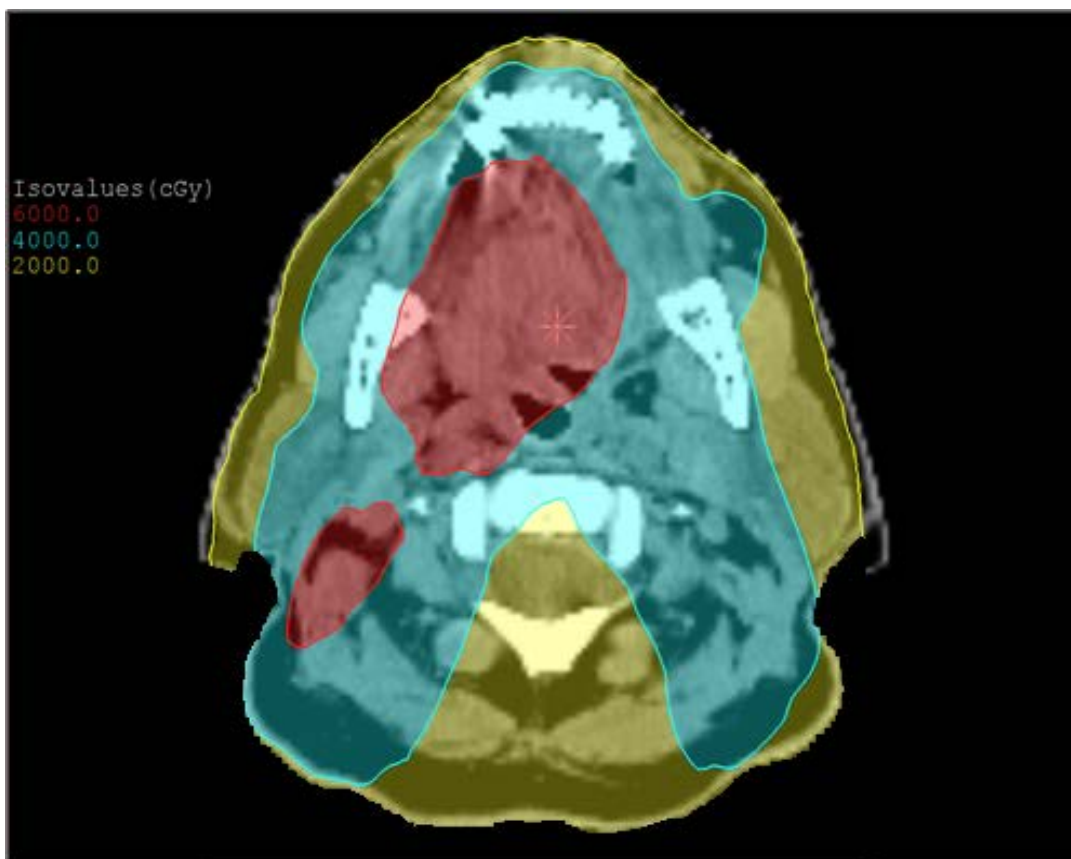


Figure 3.9 Transverse and Saittal views of dose to the oral cavity and neck for PHC-8.
 6000cGy = red area, 4000cGy (areas at risk) = cyan area, 2000cGy = yellow area

Mean Oral Mucositis Scores

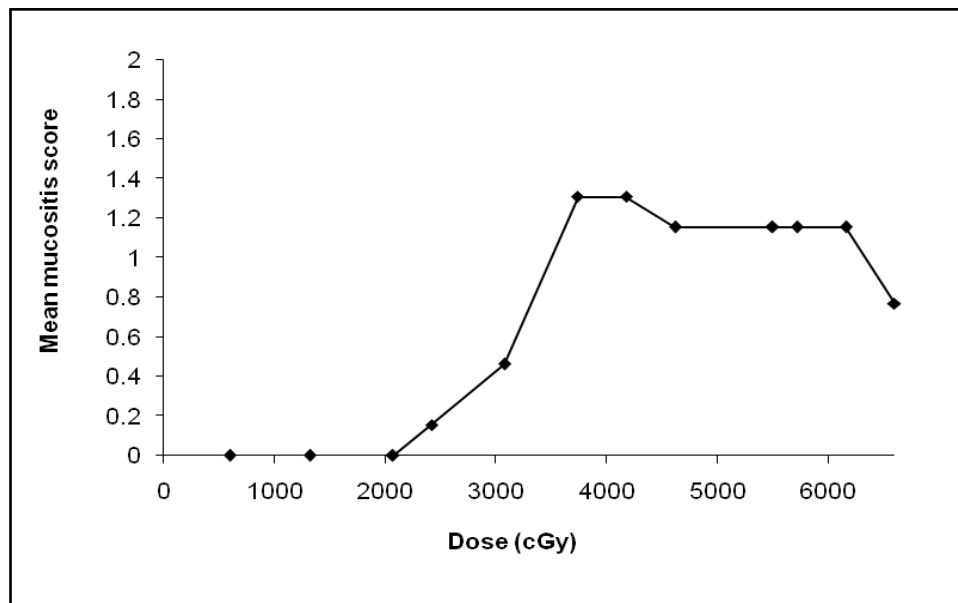


Figure 3.10 Mean Oral Mucositis Scores for PHC-8 During Treatment.

PHC-8 experienced a rapid worsening of his oral mucositis between 2000cGy and 4000cGy (Figure 3.10). The upper and lower gingival, lower labial mucosa and right buccal mucosa were the first to ulcerate at approximately 3000cGy. This was followed soon after by the ulceration of the hard and soft palate, upper labial mucosa and tongue by 3700cGy. Between 4500cGy and 6000cGy the patient's oral mucositis seemed to regress slightly with the ulceration on the upper labial mucosa healing. From 6000cGy to 6600cGy his oral mucositis regressed further with the ulceration on the gingival and labial mucosa healing completely. He did however have a two day break in treatment during his last week due to a machine breakdown and then a further two days off treatment for the weekend between 6000cGy and 6600cGy. This may have contributed to the healing of parts of his mouth in the last week. PHC-8 had a maximum mean oral mucositis score of 1.3 at approximately 4000cGy, which was moderate in comparison to the other participant's scores.

Quality of Life Questionnaires

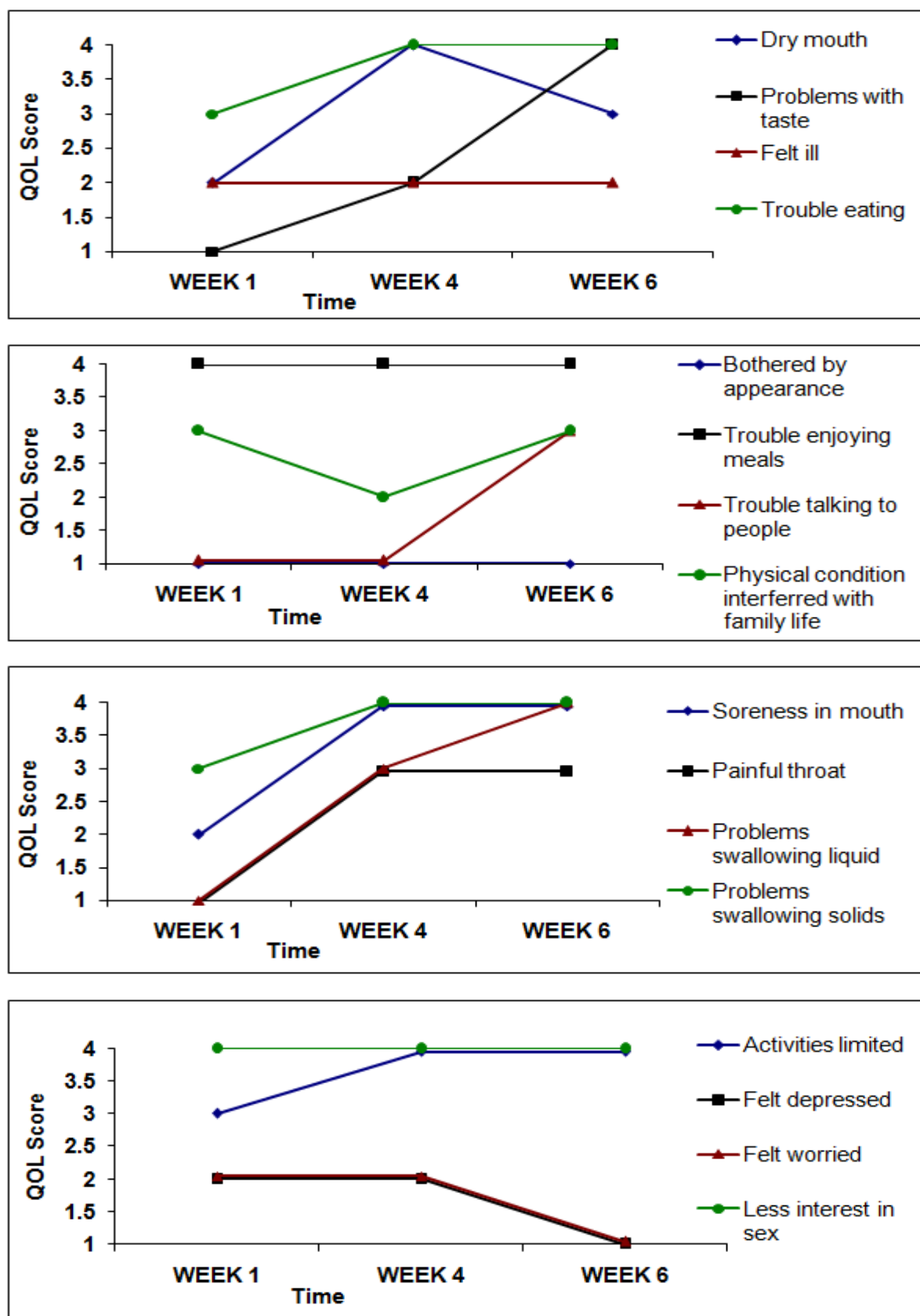


Figure 3.11 EORTC Quality of Life Questionnaire H&N35 Results for PHC-8.

QOL scores 1 = Not at all, 2 = A Little, 3 = Quite a bit, 4 = Very much

PHC-8's QOL questionnaires reflected a decrease in his quality of life during treatment from 5/7 (beginning of treatment) to 2/7 (week four), increasing slightly to 3/7 on his last day of treatment. PHC-8 also experienced a decrease in sense of taste and ability to swallow liquid and solid foods. His mouth became dry and the pain in his throat and mouth increased. He had trouble enjoying his meals from the beginning of treatment and this worsened as treatment continued. PHC-8 reported having less interest in sex during treatment. However his level of depression and worry decreased during his final weeks of treatment.

Weight and Food Intake

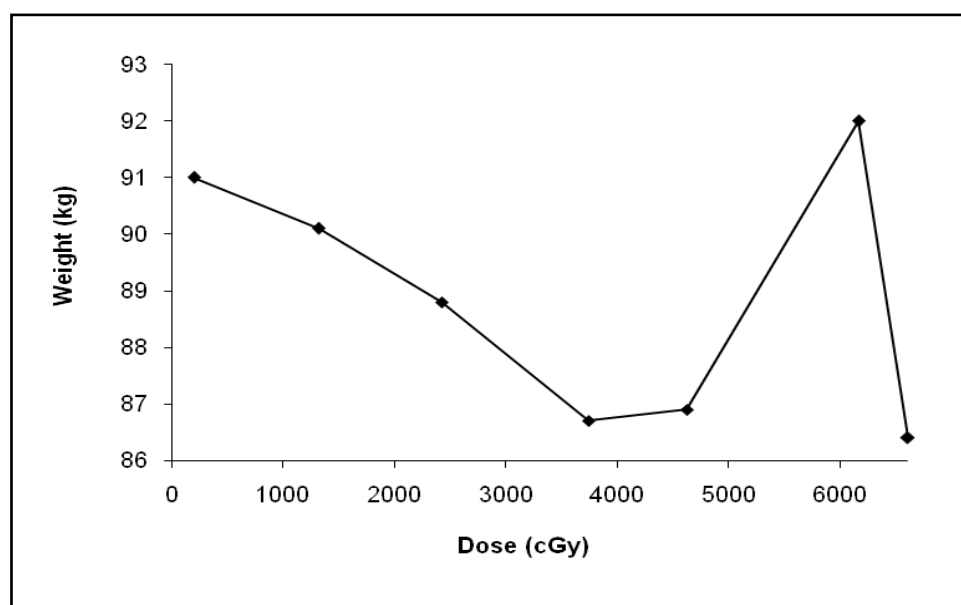


Figure 3.12 Weight measurements for PHC-8 during treatment.

PHC-8 experienced no oral mucositis up to 2000cGy and reported low pain scores although he did mention difficulty in eating and enjoying his meals from the beginning of treatment. Prior to radiation therapy he had already lost 18kg and in the first few weeks of his treatment he lost a further 2.2kg. This was due to his difficulties with eating, enjoying and swallowing solid foods as well as the nausea and vomiting he had experienced from his second course of chemotherapy. His food and drug diaries for the first week reflect a soft food diet which incorporated sufficient calories. His daily intake was supplemented by a single can of Fortisip a day. By week two he was having four cans of Fortisip daily which increased by the end of the week to five cans of Fortisip daily. His food intake was limited to very soft/pureed foods like porridge and soup. PHC-8 felt that his physical condition affected his family life “quite a bit” and limited his daily activities. It also severely impacted his interest in sex and he reported feeling “a little” worried and depressed. Although he rated his

overall QOL at 5/7, at this time he had had one course of chemo therapy and had yet to start radiation treatment.

From 2000cGy to 4000cGy the severity of the oral mucositis worsened, with a maximum mean mucositis score of 1.3 at 4000cGy. The patient's weight during this time dropped further by 1.9kg, and his diet in week three remained heavily supplemented with Fortisip drinking five cans daily in addition to milkshakes, ice cream or soup. By week four the patient's diet was totally dependent on six Fortisip a day via a PEG line. This was reflected in a drop in average QOL by week four to 2/7, with the level of pain in his mouth and throat increasing. Encouragingly, PHC-8 reported that the negative impact his treatment was having on his family life in the first week of treatment improved by week four.

From 4000cGy to 6600cGy the patient's oral mucositis appeared to be improving. His average QOL score increased from a 2/7 to a 3/7. His weight fluctuated most likely due to hydration after his admission to the hospital for his last course of chemotherapy. His diet however, remained entirely dependent on the PEG feeding of seven Fortisip daily. Overall, PHC-4 lost 4.6kg (5.0%) during treatment from his baseline weight of 91kg. After the completion of treatment no follow up was done on this man as he did not live locally.

3.2.4 Experimental Arm Patient A: PHC-5

Patient Details

Table 3.5 Patient Details for PHC-5

PATIENT DETAILS	
Randomisation number	PHC-5
Gender and Age	Male, 49
Karnofsky score	90%
Tumour details	Squamous cell carcinoma of the base of tongue
Stage	T2/T4,N2CM0
Radiation therapy treatment regimen	IMRT 6600cGy in 30#, 220cGy per #, 1 # per day, 5# per week, for 6 weeks to 100% with 6MV photons.
Areas at risk (>4000cGy)	10/14
Chemotherapy treatment regimen	Cisplatinum 3 courses: 3 weeks prior to treatment, week 1 & week 4 of RT treatment.
Randomisation Arm	Standard treatment + honey

PHC-5 was a 49 year old man recruited to the trial. He was diagnosed with a squamous cell carcinoma of base of tongue (Table 3.4) and received neo-adjuvant chemo-radiation therapy. The entire oral cavity, oropharynx and both sides of the neck were incorporated in the radiation field. The patient had a PEG feeding tube inserted prior to treatment to help maintain his nutrition. Figure 3.13 depicts the dose received by his oral cavity and neck. The 2000cGy includes most of the head and neck area. The 4000cGy isodose incorporates the majority of the oral cavity with only the vermillion lip and labial mucosa receiving a dose lower than 4000cGy, leaving the patient with 10 of 14 areas at risk. A large majority of the posterior oral cavity, including the oropharynx, posterior tongue and soft palate, received high doses of 6000cGy or more.

PHC-5 was allocated to the treatment arm of the phase II trial therefore he received the standard care as well as honey from the beginning of his treatment. The intention was for PHC-5 to use 10mls of undiluted honey, swirl it around his mouth to coat the oral mucosa and slowly swallow the honey, three times daily. There were many issues with compliance with this patient with respect to taking the honey. During the first week of the trial he only swirled one teaspoon of honey, three times daily. It was clarified that he was to take two teaspoons, three times daily. During week three the patient started to find it difficult to swirl and swallow the honey. He said it “felt acidic” on his mouth and throat. By the end of week four the patient had stopped taking the honey.

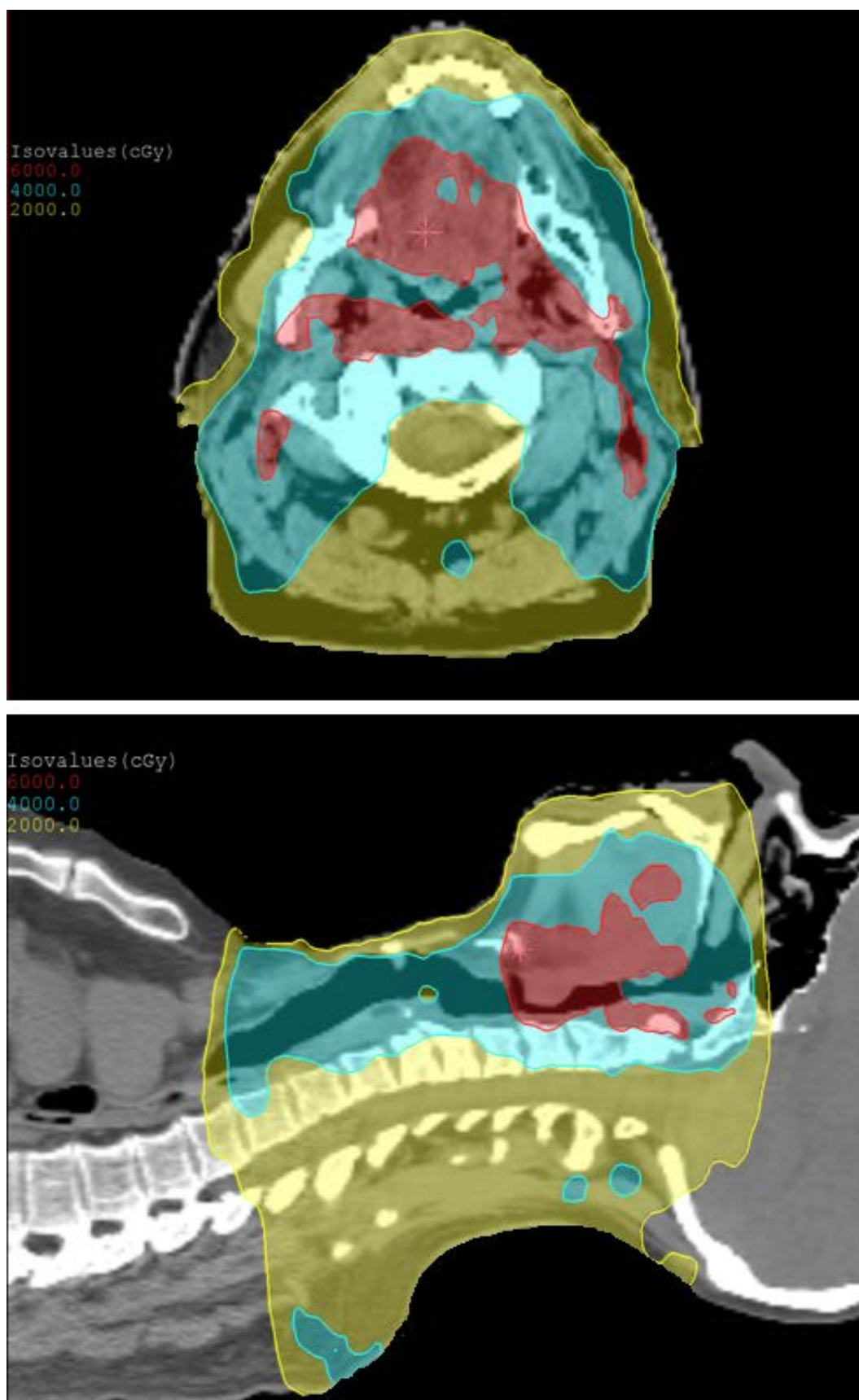


Figure 3.13 Transverse and Saittal views of dose to the oral cavity and neck for PHC-5.

6000cGy = red area, 4000cGy (areas at risk) = cyan area, 2000cGy = yellow area

Mean Oral Mucositis Scores

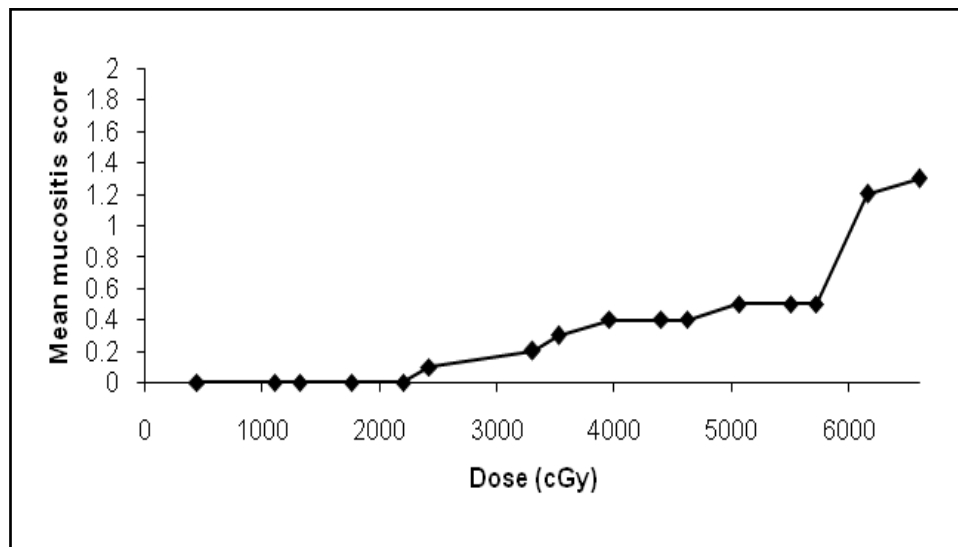


Figure 3.14 Mean Oral Mucositis Scores for PHC-5 During Treatment.

PHC-5 did not have any oral mucositis between 0cGy and 3300cGy. From 2200cGy to 3300cGy his soft palate and oropharynx became erythematic. From 3300cGy to 5720cGy his soft palate and oropharynx became ulcerated but the rest of the oral mucosa in the mouth remained unchanged. The patient's mean mucositis score increased rapidly from 5720cGy to 6600cGy. The upper and lower gingival became ulcerated, left and right buccal mucosa showed signs of erythema as did the hard palate. The soft palate and oropharynx scores increased from patchy mucositis to confluent mucositis. Overall this patient had fairly minimal oral mucositis until the final week of treatment. PHC-5 had also had his last course of chemotherapy in the 5th week of radiation treatment which may have contributed to the substantial increase in his oral mucositis scores in the final week. His maximum mean oral mucositis score was 1.3 on his last day which was moderate score compared to other patients recruited to the trial.

Quality of Life Questionnaires

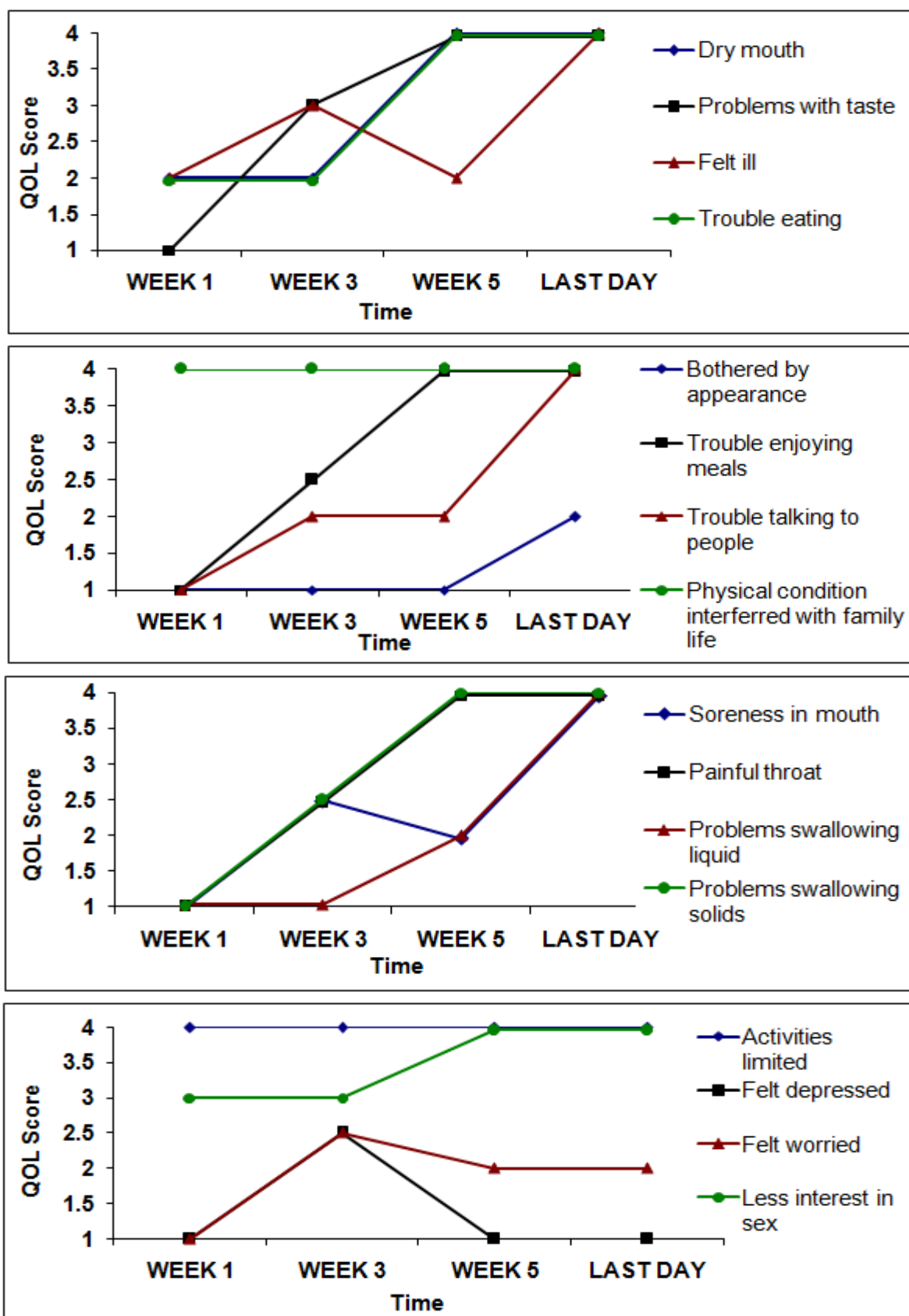


Figure 3.15 EORTC Quality of Life Questionnaire H&N35 Results for PHC-5.

QOL scores 1 = Not at all, 2 = A Little, 3 = Quite a bit, 4= Very much

PHC-5 completed four QOL questionnaires whilst on treatment. The answers for selected questions are depicted in Figure 3.15. His average QOL decreased from 4/7 at the start of treatment to 2/7 (weeks three and five) and 1/7 on the last day of treatment. He experienced a steady increase in pain in his mouth and throat during treatment and found eating, swallowing and enjoying meals increasingly difficult. Encouragingly, he did report that his worry and depression levels to decrease between week three and week five.

Weight and Food Intake

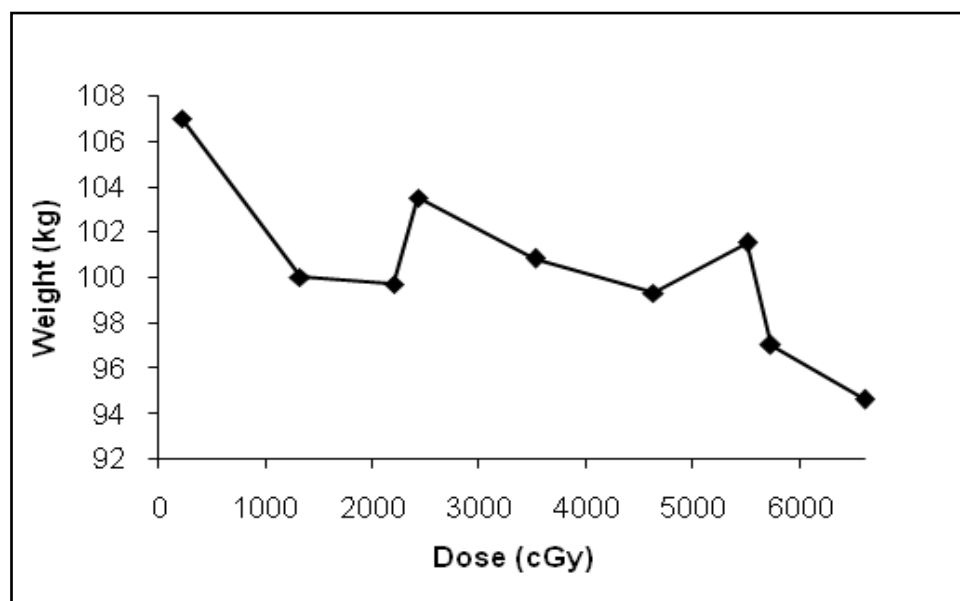


Figure 3.16 Weight measurements for PHC-5 during treatment.

PHC-5's weight fluctuated during treatment (Figure 3.16). In the first week of treatment his weight dropped from 107kg to 100kg (6.5% of his baseline weight). His food intake during week one was a mixture of solid food and soft foods with some meals replaced with ice blocks. He suffered from nausea and vomiting during his first week of treatment due to his second course of cisplatin based chemotherapy. From 1320cGy to 2200cGy his weight remained stable with a diet similar to week one. He had gained 3.8kg at 2420cGy but lost more weight between 2420cGy and 4620cGy (down to 99.3kg at 4620cGy). His diet during the third and fourth week of treatment was entirely based on pureed foods such as pureed apple and custard. In his fifth week of treatment PHC-5 gained 2.2kg. During this time the patient was admitted to the hospital for his final course of chemotherapy, receiving plenty of fluids for rehydration, which may explain the weight increase. His diet during the fifth and sixth week of his treatment was entirely dependent on PEG feeding with Fortisip. He was given morphine elixir to help with pain relief in his mouth. The number of Fortisip varied on a daily basis with PHC-5 only ingesting one Fortisip some days and seven on other days. By 6600cGy the

patient's weight had dropped to 94.6kg on his last day. PHC-5 lost a total of 12.4kg during his time on treatment which was a total of 11.6% of his baseline weight.

From 0cGy to 2200cGy there were no visual signs of oral mucositis in the patient's mouth. He did however lose 7.3kg due to inadequate oral intake and the nausea and vomiting associated with his second course of cisplatin based chemotherapy. He rated his average QOL at the beginning of his radiation therapy as a 4/7. He found his disease and treatment negatively impacted his family life, work, daily activities and interest in sex "quite a bit" to "very much". Although this was his first week of radiation therapy, PHC-5 had received two courses of cisplatin based chemotherapy which resulted in him spending time in hospital, feeling nauseous and severely fatigued. During this time he swirled with honey three times daily. Due to a misunderstanding about how much honey to take the patient only took 5mls of honey, three times daily for the first week. This was corrected during the second week with the patient swirling with 10mls of honey three times daily.

From 2200cGy to 5720cGy the patient's oral mucositis underwent some changes. His soft palate and oropharynx were beginning to appear inflamed and erythematous by 3300cGy and by 5720cGy these areas became ulcerated, however the rest of the oral mucosa in the mouth remained unchanged. From week three to week five the patient's weight fluctuated and his diet during this time was based on a mixture of pureed foods, liquid foods and Fortisip. He rated his average QOL as a 2/7 in the QOL questionnaires done at week three and week five. During week three and week four PHC-5 was taking the honey sporadically. By 4600cGy PHC-5 had completely stopped taking the honey saying it felt acidic and painful on his throat and mouth.

From 5720cGy – 6600cGy the patient's oral mucositis rapidly progressed. Seven of the ten areas at risk in PHC-5 mouth showed either ulceration or erythema. He completed his last round of chemotherapy. His weight continued to decrease and his diet was completely dependent on PEG feeding of the meal replacement Fortisip. He rated his average quality of life on his last day QOL questionnaire as the lowest possible score a 1/7. He could not talk with his pain scores in his mouth and throat both 4/4 (very much). PHC-5 had no follow up once his treatment had completed as he did not live locally.

3.2.5 Experimental Arm Patient B: PHN-2

Patient Details

Table 3.6 Patient Details for PHN-2

PATIENT DETAILS	
Randomisation number	PHN-2
Gender and Age	Male, 56
Karnofsky score	90%
Tumour details	Squamous cell carcinoma of the right tongue
Stage	T1N0M0
Radiation therapy treatment regimen	IMRT 6000cGy in 30#, 200cGy per #, 1# per day, 5# per week, for 6 weeks, to 100% with 6MV Photons
Areas at risk (>4000cGy)	14/14
Chemotherapy treatment regimen	None
Randomisation Arm	Standard treatment + honey

PHN-2 was a 56 year old man who has been diagnosed with a squamous cell carcinoma of the tongue in 2004. At this time he underwent a right hemiglossectomy and right supramohyoid neck dissection with no adjuvant treatment. In 2009 the patient was diagnosed with a squamous cell carcinoma of the right tongue (Table 3.4). It was unknown whether the lesion was a new primary or a recurrence. He underwent a further partial right glossectomy and was offered adjuvant radical radiation therapy to the tongue and right neck. As only one side of his neck was being irradiated and he was not receiving adjuvant chemotherapy a PEG tube was not advocated.

Figure 3.17 demonstrates the radiation dose received by the oral cavity and neck. For this patient, the 2000cGy isodose curve encompassed the whole oral cavity, lips, oropharynx, right parotid glands and a large amount of soft tissue. The 4000cGy isodose included the entire oral cavity resulting in 14 of 14 areas being deemed at risk of developing oral mucositis. A large portion of his oral cavity including the gingival, tongue, soft palate received high doses of 6000cGy or more.

PHN-2 was the second patient to complete the treatment arm of the trial. He was advised to swirl with 10mls of undiluted honey, three times daily. He was given the option of swallowing the honey or spitting it back out after 30 seconds. PHN-2 took the honey consistently for the first two weeks of treatment. At 2000cGy the patient reported that he found the honey difficult to cope with and it

was making him nauseous. He was advised at this stage to dilute the honey with water and spit out the honey rather than swallowing it. By 3000cGy the patient was no longer taking the honey.

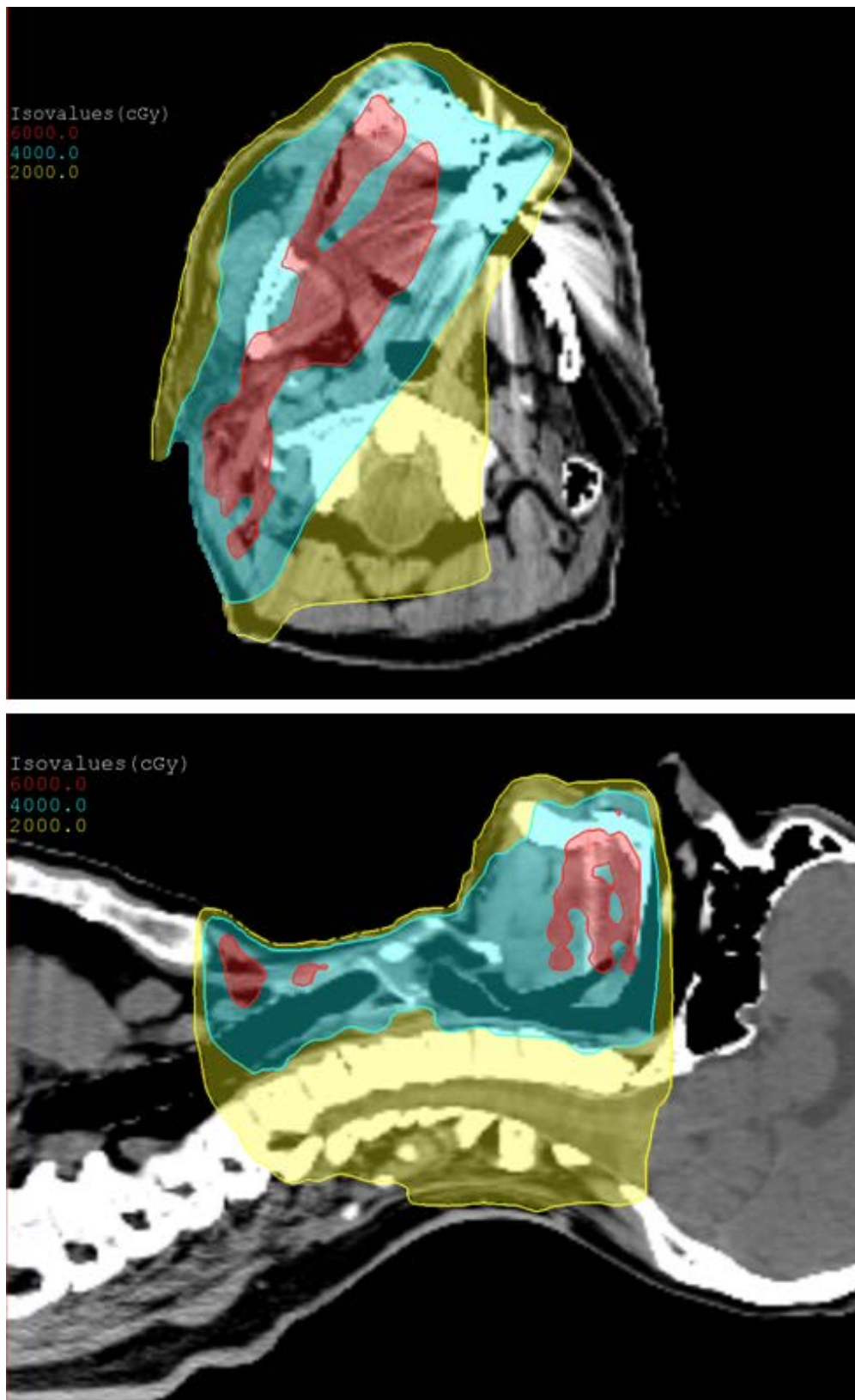


Figure 3.17 Transverse and Saittal views of dose to the oral cavity and neck for PHN-2. 6000cGy = red area, 4000cGy (areas at risk) = cyan area, 2000cGy = yellow area

Mean Oral Mucositis Scores

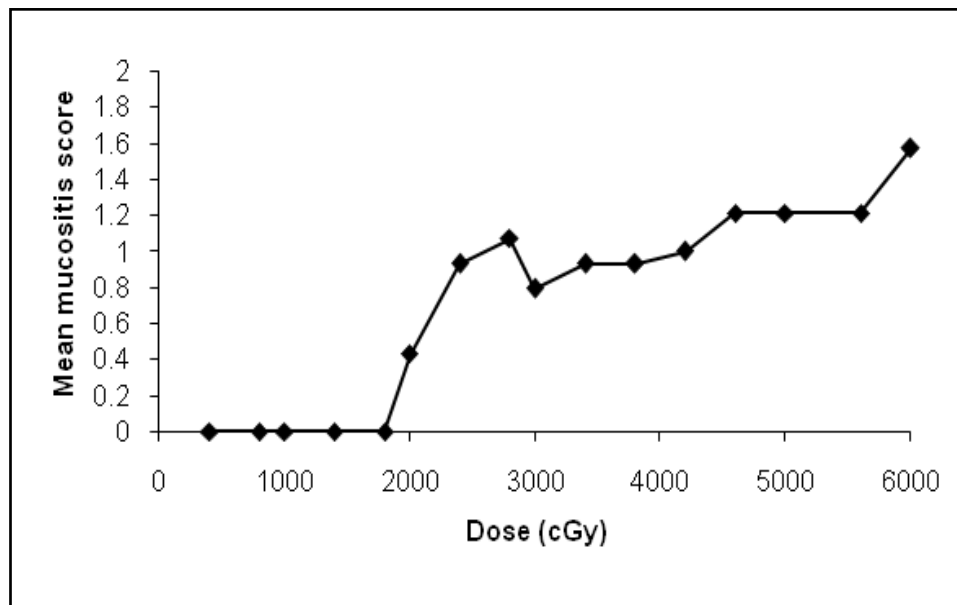


Figure 3.18 Mean Oral Mucositis Scores for PHN-2 During Treatment

PHN-2 started to experience oral mucositis at 2000cGy when his right buccal mucosa, ventral tongue, soft palate and floor of mouth appeared to be red and inflamed (Figure 3.18). His oropharynx also appeared slightly ulcerated. This progressed rapidly between 2000cGy and 2800cGy, with the lower labial mucosa, lower gingival, right buccal mucosa, floor of mouth, oropharynx, ventral and dorsal tongue ulcerating. After having two days off treatment for the weekend his oral mucositis appeared to have regressed slightly by 3000cGy with ulceration of the oropharynx and right buccal mucosa healing. From 3000cGy to 4200cGy the oral mucositis appeared to have stabilized getting only slightly worse with the vermillion lip ulcerating and the upper and lower gingival. By 6000cGy nine of fourteen areas at risk were ulcerated. The lower labial mucosa, right buccal mucosa, ventral and dorsal tongue were scored a 3/3 for confluent oral mucositis. Overall the patient's maximum mean oral mucositis score was 1.57 on his last day of treatment.

Quality of Life Questionnaires

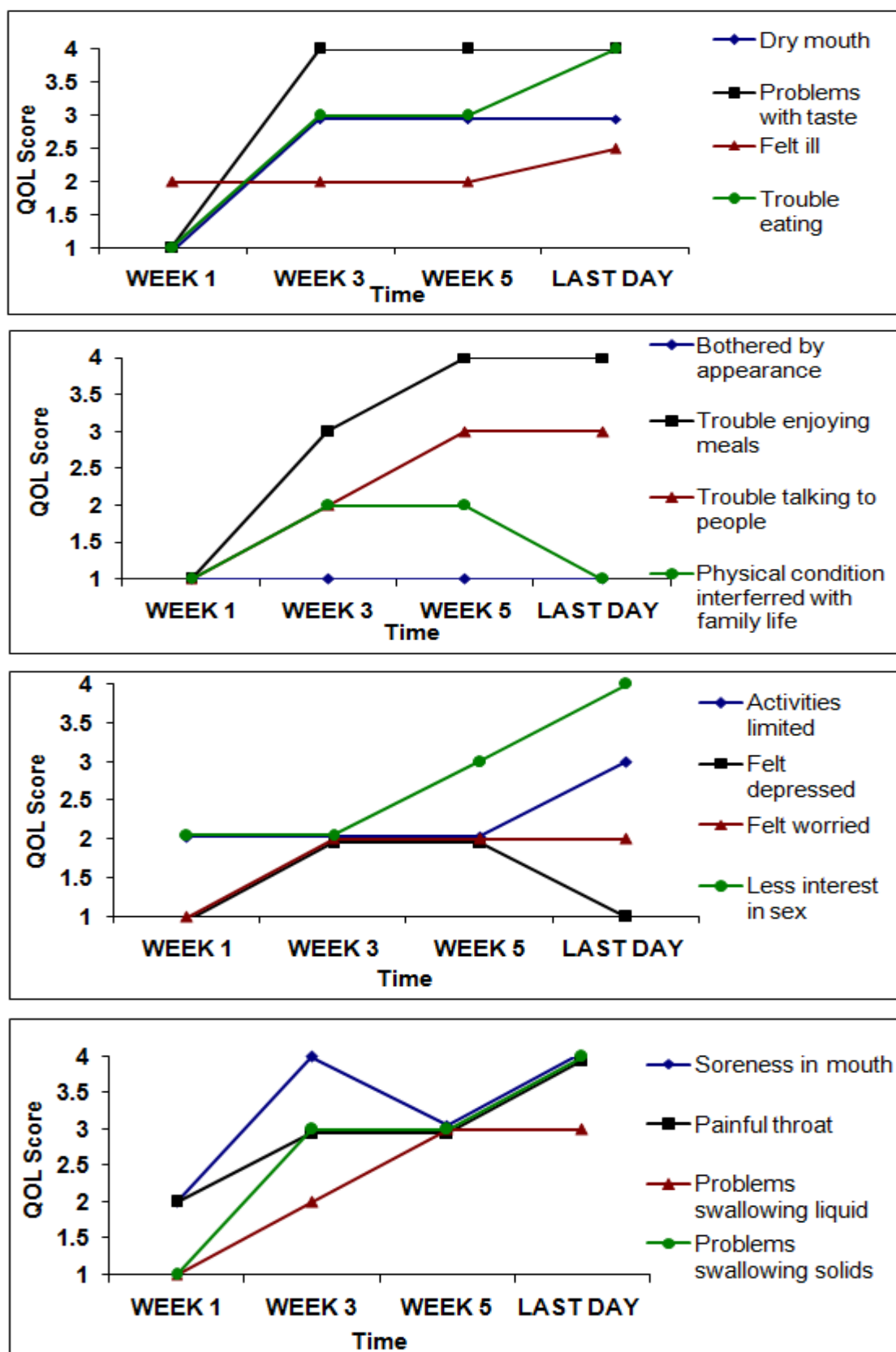


Figure 3.19 EORTC Quality of Life Questionnaire H&N35 Results for PHN-2.

QOL scores 1 = Not at all, 2 = A Little, 3 = Quite a bit, 4 = Very much

PHN-2 completed four QOL questionnaires during his treatment. He rated his average QOL on his first questionnaire as a 6/7. He reported “a little” pain in his throat and mouth however he had no problems swallowing liquid or solid foods. He had no problems with his sense of taste, enjoying meals, eating or a dry mouth but did report less interest in sex and felt “a little” ill. Although the patient had undergone prior surgery which may explain his early pain scores in his mouth and throat, he had not received adjuvant chemotherapy. By week three, average QOL scores decreased to 5/7 with higher pain scores in mouth and throat, increased difficulty with talking, swallowing, eating and enjoying meals. Almost all scores increased from a one (not at all) in the first QOL questionnaire to four by the third week.

By week five his average QOL had decreased to 4/7. Whilst his pain scores, problems with eating and dry mouth remained stable between week three and five, he reported less interest in sex and increased difficulty with enjoying his meals and talking to people. The pain scores for his mouth improved between week three and week five. Final QOL questionnaire PHN-2 rated his average QOL 4/7. His QOL worsened between week five and six with the majority of the questions scoring three (Quite a bit), or four (Very much). The two areas that improved in the final week of treatment were depression levels and the effect treatment had on family life.

Weight and Food Intake

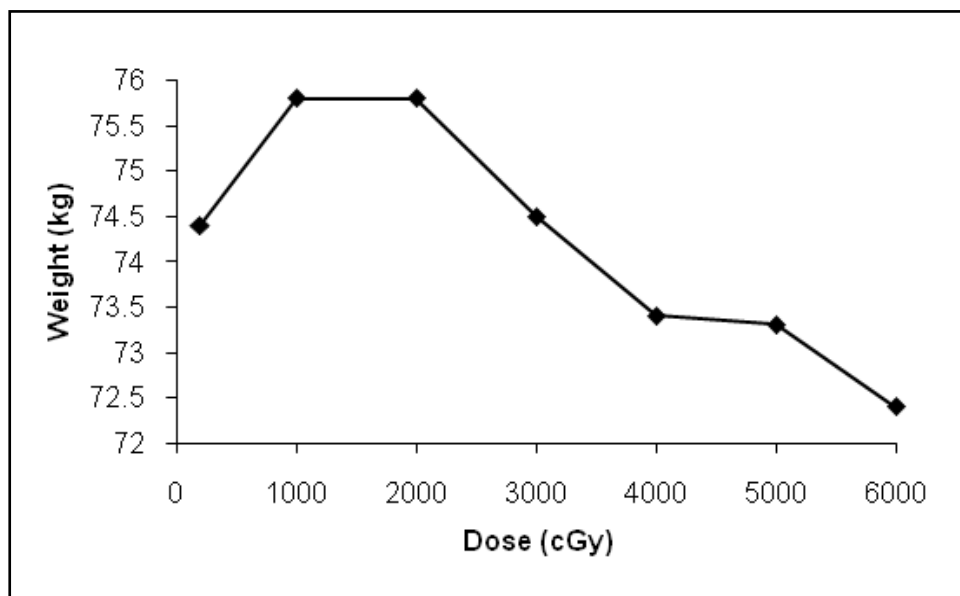


Figure 3.20 Weight measurements for PHN-2 during treatment.

Baseline weight for PHN-2 was 74.4kg, which increased to 75.8kg (1.9% increase from baseline weight) from 0cGy to 2000cGy (Figure 3.20). This may have been due to the dietician's input that all patients get during their first week of treatment. His diet during this time was normal with a variety of soft and hard foods and a good calorie intake. By 3000cGy PHN-2 was back to his original baseline weight. By the end of week three he was eating mainly soft foods and one to two Fortisip daily. His honey intake during this week decreased and by the fourth day of week three (approximately 2800cGy) the patient was no longer taking the honey. PHN-2 took regular mouth washes with bicarbonate soda, Difflam and Nilstat. His weight decreased further to 73.4kg (1.4% decrease from baseline weight) by 4000cGy. His diet during week four was similar to week three. By week five his diet consisted entirely of six Fortisip drinks a day. By 6000cGy PHN-2 weighed 72.4kg having lost 2kg (2.7% decrease of his baseline weight) during treatment.

This patient started showing signs of discomfort and oral mucositis in the first two weeks. In weeks three and four (2000cGy to 4000cGy) of his lower labial mucosa, gingival, ventral and dorsal tongue, and floor of mouth ulcerated. The soft palate and oropharynx showed signs of erythema. PHN-2 lost 2.4kg from 75.8kg at 2000cGy to 73.4kg at 4000cGy. His diet during week three and four was lighter than weeks one and two, with more soft foods included in his diet plus one to two Fortisip. His average QOL in week three decreased from 6/7 in week one to 5/7 by week three.

From 4000cGy to 6000cGy the oral mucositis worsened with ulceration of the right buccal mucosa and oropharynx. The lower labial mucosa, right buccal mucosa, ventral and dorsal tongue were upgraded to confluent mucositis, on the last day of treatment. In week five and six the patient's diet was replaced with six Fortisip daily. He lost further weight from 73.4kg at 4000cGy to 72.4kg on his last day. His average QOL dropped to 4/7 after week five. PHN-2 was followed up at six weeks post radiation therapy treatment as he lived locally. He rated his average QOL to be a 5/7, the majority of his oral mucositis had healed, however he had still not regained his sense of taste.

3.2.6 Experimental Arm Patient C: PHC-6

Patient Details

Table 3.7 Patient Details for PHC-6

PATIENT DETAILS	
Randomisation number	PHC-6
Gender and Age	Male, 39
Karnofsky score	80%
Tumour details	Squamous cell carcinoma of the anterior tongue
Stage	T4N2CM0
Radiation therapy treatment regimen	IMRT 6600cGy in 30#, 220cGy per #, 1# per day, 5# per week, for 6 week to 100%with 6 MV photons.
Areas at risk (>4000cGy)	12/14
Chemotherapy treatment regimen	Cisplatinum2 courses: week 1 &week 4 of RT treatment.
Randomisation Arm	Standard treatment + honey

PHC-6 was a 39 year old male diagnosed with a squamous cell carcinoma of the tongue. He underwent a partial glossectomy followed by a free flap reconstruction and a modified bilateral neck dissection removing 41 nodes (Table 3.7). He had a temporary tracheotomy in place and several post operative complications. He also had a PEG inserted to manage his nutritional intake.

Figure 3.21 demonstrates the high doses received by the oral cavity, with the 6000cGy isodose curve covering a large amount of the oral cavity. This patient had 9/14 high risk areas; His upper and lower vermillion lips were not considered to be an area at risk as they were receiving less than 4000cGy. Due to the patient's surgery PHC-6 had no floor of mouth or ventral tongue to assess therefore these were also not considered to be at risk. The patient's dorsal tongue was reconstructed out of normal skin rather than oral mucosa so this was also removed as an area at risk. PHC-6 was randomised to the treatment arm of the trial, receiving standard treatment from oral mucositis plus Manuka honey. He was instructed to take 10mls of honey three times daily. If this became difficult the patient was then advised to dilute the honey in water 1:1, and given the option to spit the honey out rather than swallowing it. PHC-6 had a radical surgery where most of his tongue was removed. He had fairly limited movement and functionality of the remaining part. This made it difficult for the patient to swirl the honey around his oral cavity and swallow the undiluted honey therefore he moved to diluting the honey and spitting it out early in his treatment. The patient reported that he had

stopped taking the honey at some stage during week four. The exact time at which he had stopped taking the honey and how well he complied with the honey prior to this is unknown.

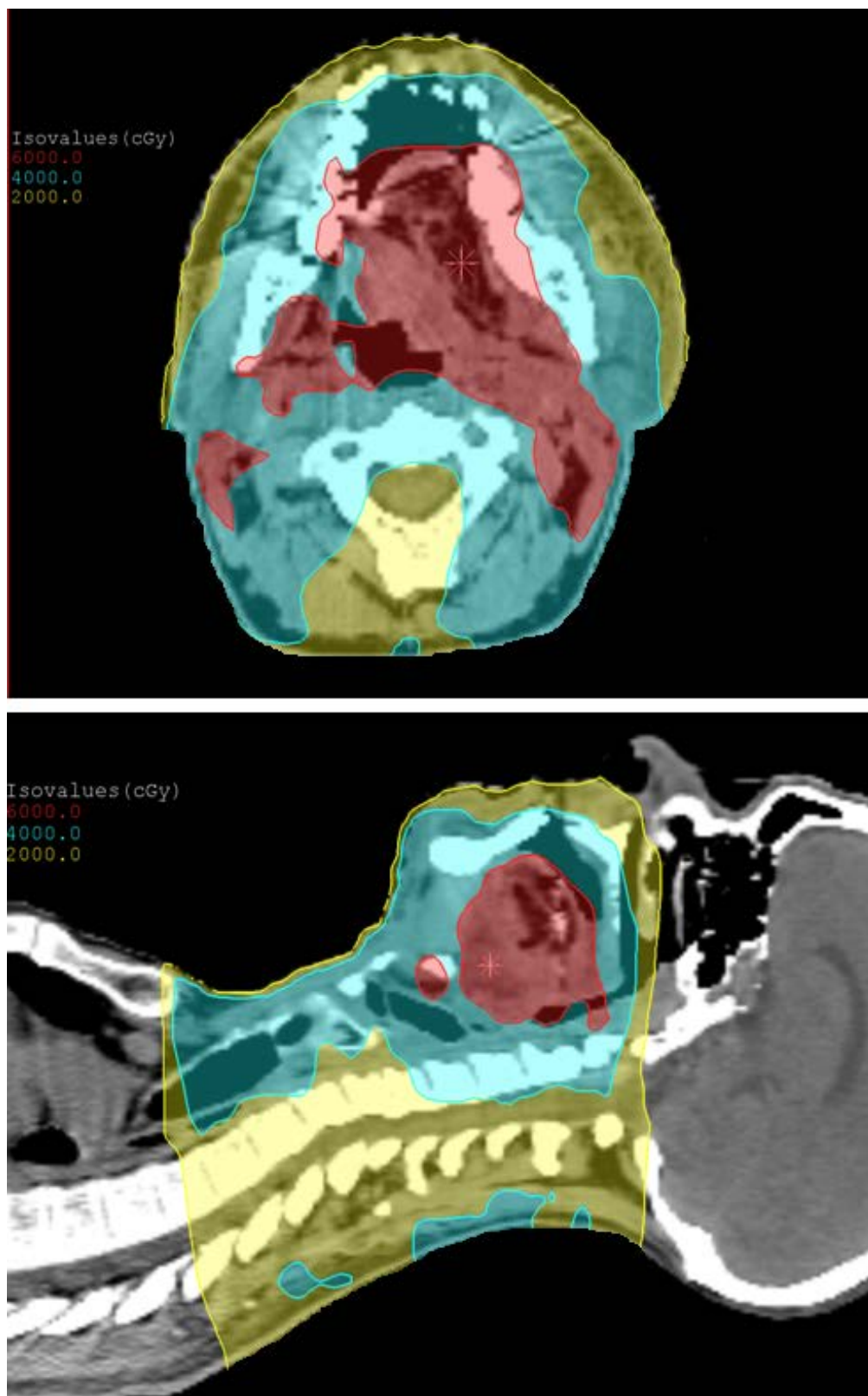


Figure 3.21 Transverse and Saittal views of dose to the oral cavity and neck for PHC-6.
6000cGy = red area, 4000cGy (areas at risk) = cyan area, 2000cGy = yellow area

Mean Oral Mucositis Scores

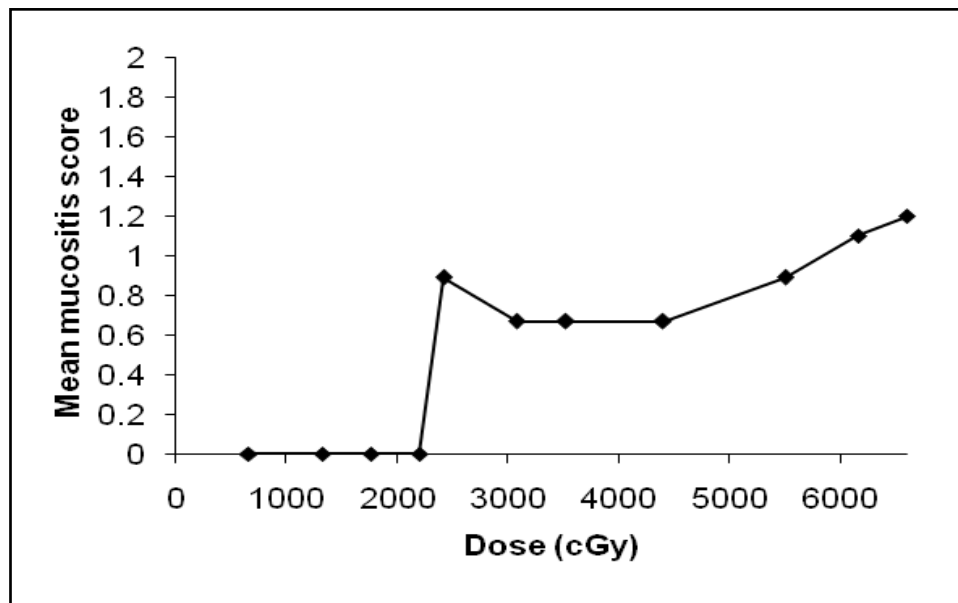


Figure 3.22 Mean Oral Mucositis Scores for PHC-6 During Treatment.

As can be seen in Figure 3.22, PHC-6 experienced no oral mucositis until 2420cGy when his upper and lower labial mucosa ulcerated. The left and right buccal mucosa, soft palate and oropharynx appeared inflamed and erythematic. By 3080cGy the lower labial mucosa had healed, and from 3080cGy to 5000cGy oral mucositis remained unchanged. At 5500cGy the patient's oral mucositis appeared to worsen with ulceration of the right and left buccal mucosa. By 6600cGy ulceration on the upper labial mucosa had healed. The oropharynx ulcerated in the final week. The maximum mean oral mucositis score for PHC-6 was 1.22.

PHC-6's oral mucositis was particularly difficult to assess due to the fact that most of the tongue was removed during the surgery. This made it very difficult for him to talk, eat and clear debris from his mouth and made assessment of the oral mucosa difficult. In addition, the patient suffered from severe oral thrush from early on in his treatment making it also difficult to assess the oral mucosa.

Quality of Life Questionnaires

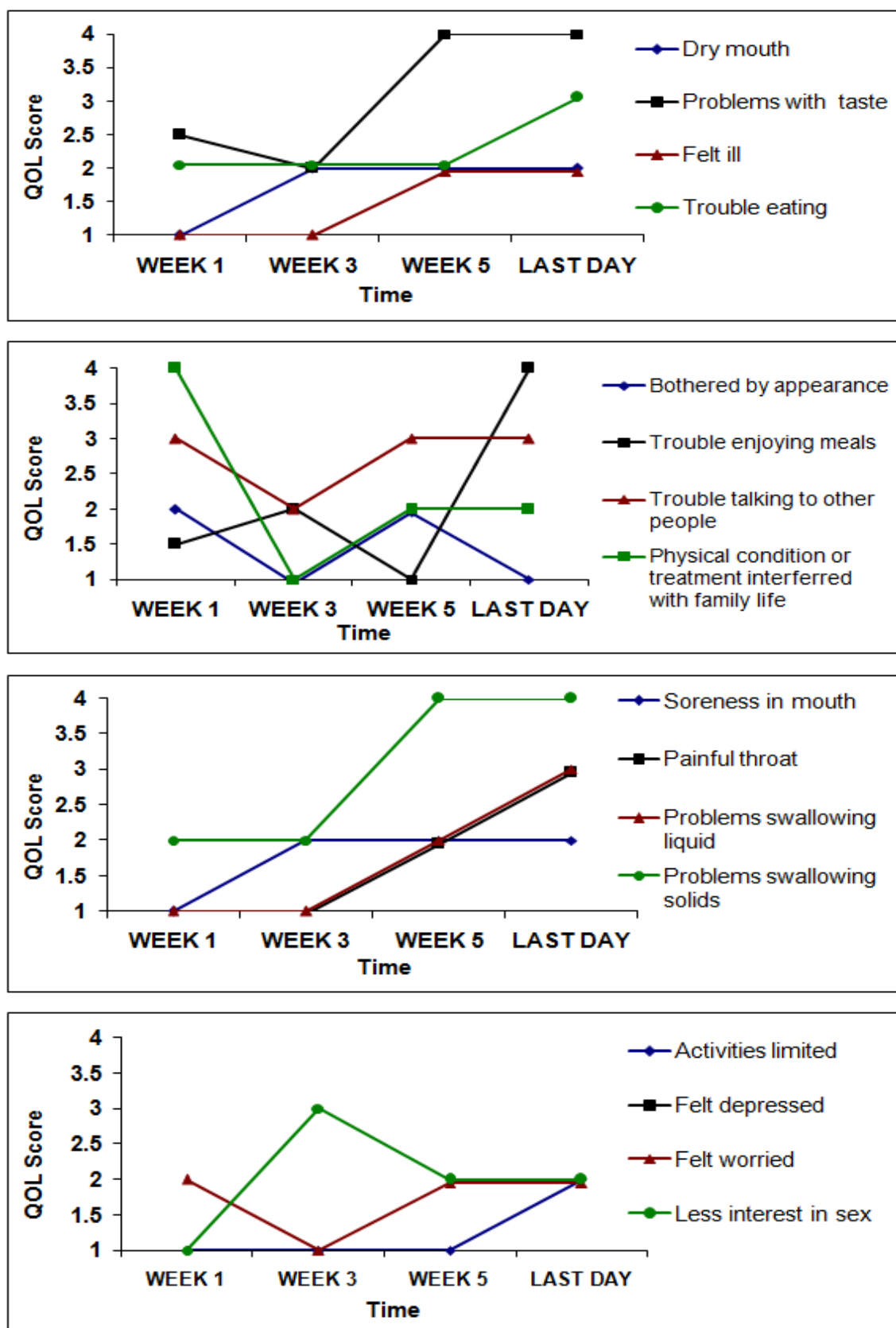


Figure 3.23 EORTC Quality of Life Questionnaire H&N35 Results for PHC-6.

QOL scores 1 = Not at all, 2 = A Little, 3 = Quite a bit, 4 = Very much

PHC-6 completed four QOL questionnaires whilst on treatment (Figure 3.23). In his week one questionnaire PHC-6 rated his average QOL 6/7, with the majority of questions scoring one (not at all), or two (a little). He reported low scores, no problems swallowing liquids and “a little” difficulty swallowing solids. His cancer and treatment affected his family life severely from the beginning of treatment and he had “quite a bit” of trouble talking to people due to his surgery. By week three his average QOL had decreased to 5/7. He had no pain in his throat or problems swallowing liquids, however swallowing solids remained “A little” difficult and his mouth became drier. The pain in his mouth increased from a one (Not at all) to a two (A little). PHC-6 also reported less interest in sex in his week three QOL questionnaire.

Average QOL scores remained unchanged at 5/7 for week five. PHN-6 did however report increasing pain in his throat and swallowing liquids and solid food became much more difficult. He rated his problems with sense of taste to be a four (Very much) however interestingly he rated his trouble enjoying eating to be a one (Not at all). He was however by this stage PEG feeding seven Fortisip daily so this may not reflect an increase in the enjoyment of food, but a lack of eating food altogether. His average QOL on the last day of treatment remained at 5/7. Between weeks five and six PHC-6 reported increasing difficulties with eating and increased pain in his throat leading to more difficulties with swallowing both liquids and solids. He felt that his treatment and physical condition limited his work and daily activities “A little”. The answers to most other questions between weeks five and six remained unchanged.

Weight and Food Intake

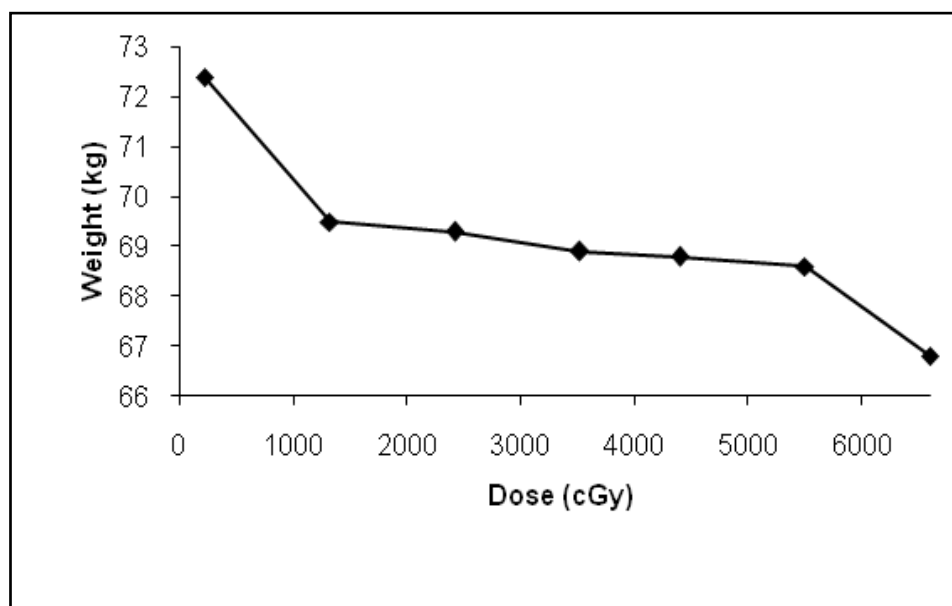


Figure 3.24 Weight measurements for PHC-6 during treatment.

From 0cGy to 2200cGy PHC-6 had no oral mucositis, a sub-optimal diet and lost 2.9kg. During the second week of his treatment his diet became completely dependent on Fortisip. His average QOL score in his first questionnaire was 6/7.

Between 2420cGy to 4400cGy the upper labial mucosa ulcerated and the left and right buccal mucosa, soft palate and oropharynx became inflamed. His mean mucositis score at 4400cGy was 0.67. His weight during this time remained fairly stable due to taking seven Fortisip drinks a day. His average QOL score during this time was 5/7. PHC-6 oral mucositis worsened from 4400cGy to 6600cGy with a mean mucositis score on the last day of treatment of 1.2. His weight dropped further in his final weeks of treatment with a total of 5.7kg weight loss during treatment. His average QOL score remained unchanged at 5/7. PHC-6 had no follow up once his treatment had completed as he did not live locally.

3.2.7 Experimental Arm Patient D: PHN-3

Patient Details

Table 3.8 Patient Details for PHN-3

PATIENT DETAILS	
Randomisation number	PHN-3
Gender and Age	Male, 74
Karnofsky score	90%
Tumour details	Squamous cell carcinoma of the left parotid
Stage	Staging information not available
Radiation therapy treatment regimen	IMRT 6000cGy in 30#, 200cGy per #, 1# per day, 5# per week, for 6 weeks to 100% with 6v photons.
Areas at risk (>4000cGy)	4/14
Chemotherapy treatment regimen	None
Randomisation Arm	Standard treatment + honey

PHN-3 was a 74 year old male diagnosed with a squamous cell carcinoma of the left parotid (Table 3.8). He had a left parotidectomy and excision of the left upper cervical lymph nodes. He received adjuvant radiation therapy to reduce the risk of local recurrence. This patient was allocated to the treatment arm of the trial and was advised to have 5ml of honey with 20mls of other fluids such as water, ginger ale or tea, three times daily in addition to standard oral care. PHN-3 did not have a PEG inserted because his mouth would be receiving a relatively low dose, he was not receiving chemotherapy and only one side of his neck was being irradiated.

PHN-3 did not receive a high dose to the oral cavity, with only 4/14 areas of the oral cavity deemed to be at risk (Figure 3.24): the upper and lower gingival in the posterior region of the oral cavity, the left buccal mucosa and the floor of mouth. PHN-3 was the first patient recruited to the trial who took the honey three times a day from the beginning to the completion of his treatment. He diluted the honey with water (10ml of honey in 30ml of water).

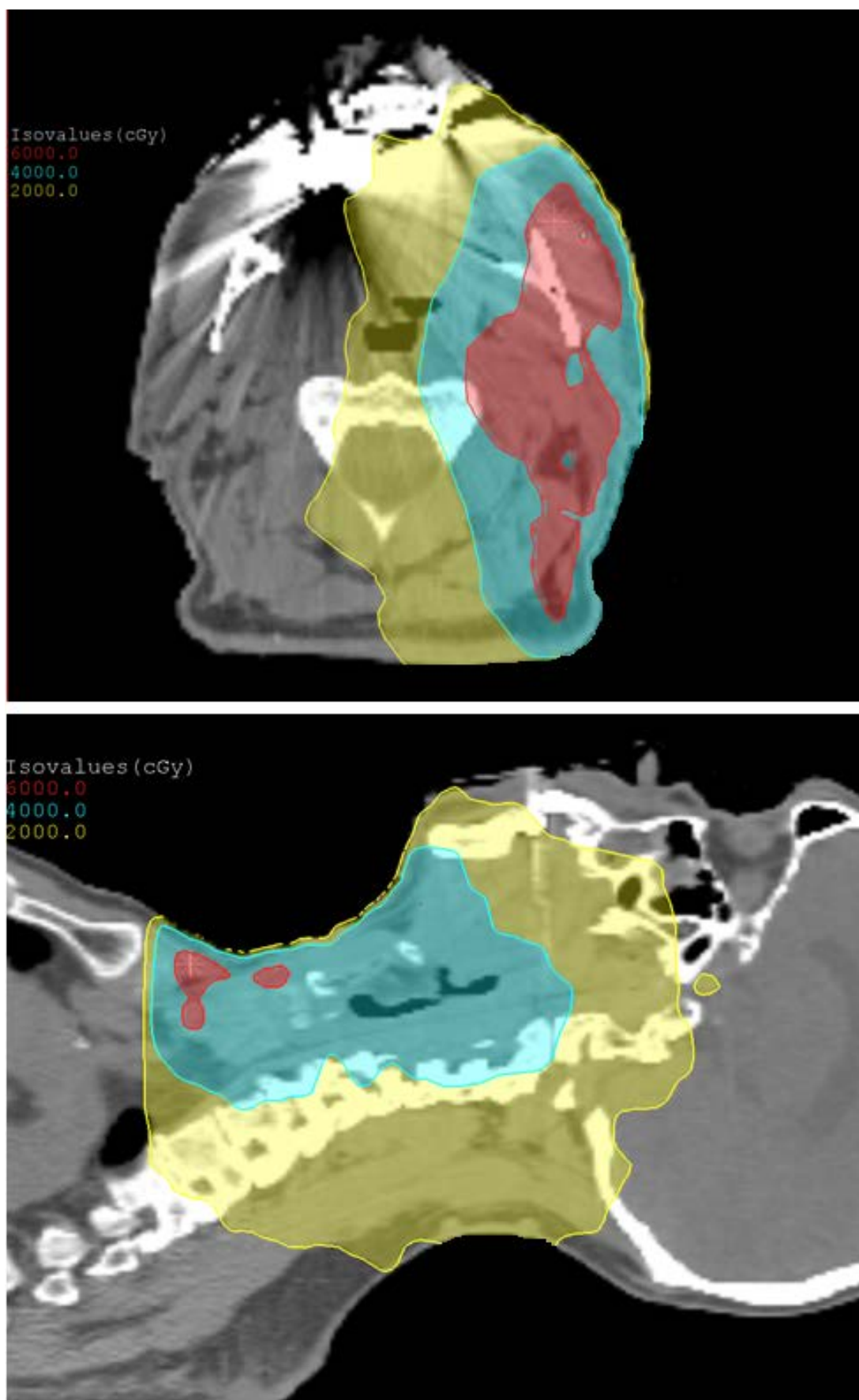


Figure 3.25 Transverse and Saittal views of dose to the oral cavity and neck for PHN-3
 6000cGy = red area, 4000cGy (areas at risk) = cyan area, 2000cGy = yellow area

Mean Oral Mucositis Scores

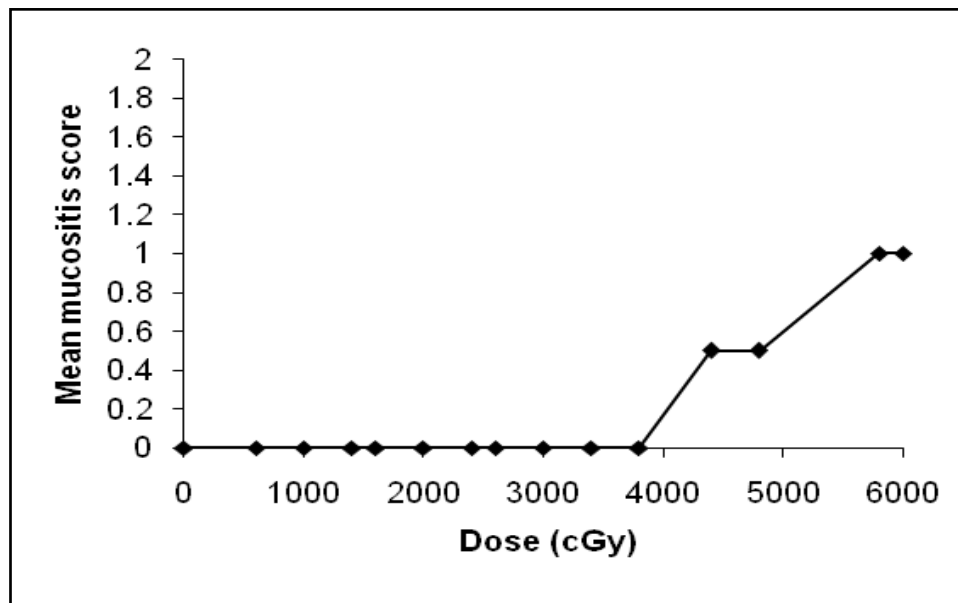


Figure 3.26 Mean Oral Mucositis Scores for PHN-3 During Treatment.

PHN-3 experienced very little oral mucositis during his time on treatment. At 4400cGy his upper gingival and posterior right buccal mucosa were inflamed. By 5800cGy these areas had ulcerated. PHN-3's highest mean mucositis score was 1 during his last week of treatment.

Quality of Life Questionnaires

PHN-3 completed QOL questionnaires at week one, three, five and six of treatment. The patient rated his average QOL score on his first day of treatment as 7/7. He answered one (Not at all) to all questions in both the EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires. His average QOL remained unchanged in week three. He reported "A little" problems swallowing solid food and enjoying his meals and also scored two (A little) from the questions concerning a dry mouth and sticky saliva. He had "Quite a bit" of problems with his sense of taste.

PHN-3 reported the same average QOL scores between week three and week five. He reported being "A little" tired and needing more rest during week five. PHN-3 rated his problems with sense of taste as four (Very much) and his trouble enjoying meals as three (Quite a bit). In his final week of treatment his QOL score decreased to 6/7. He reported "A little", pain in his throat and complained of a non-productive cough from treatment. Overall the patient appeared to have maintained a very good QOL during treatment.

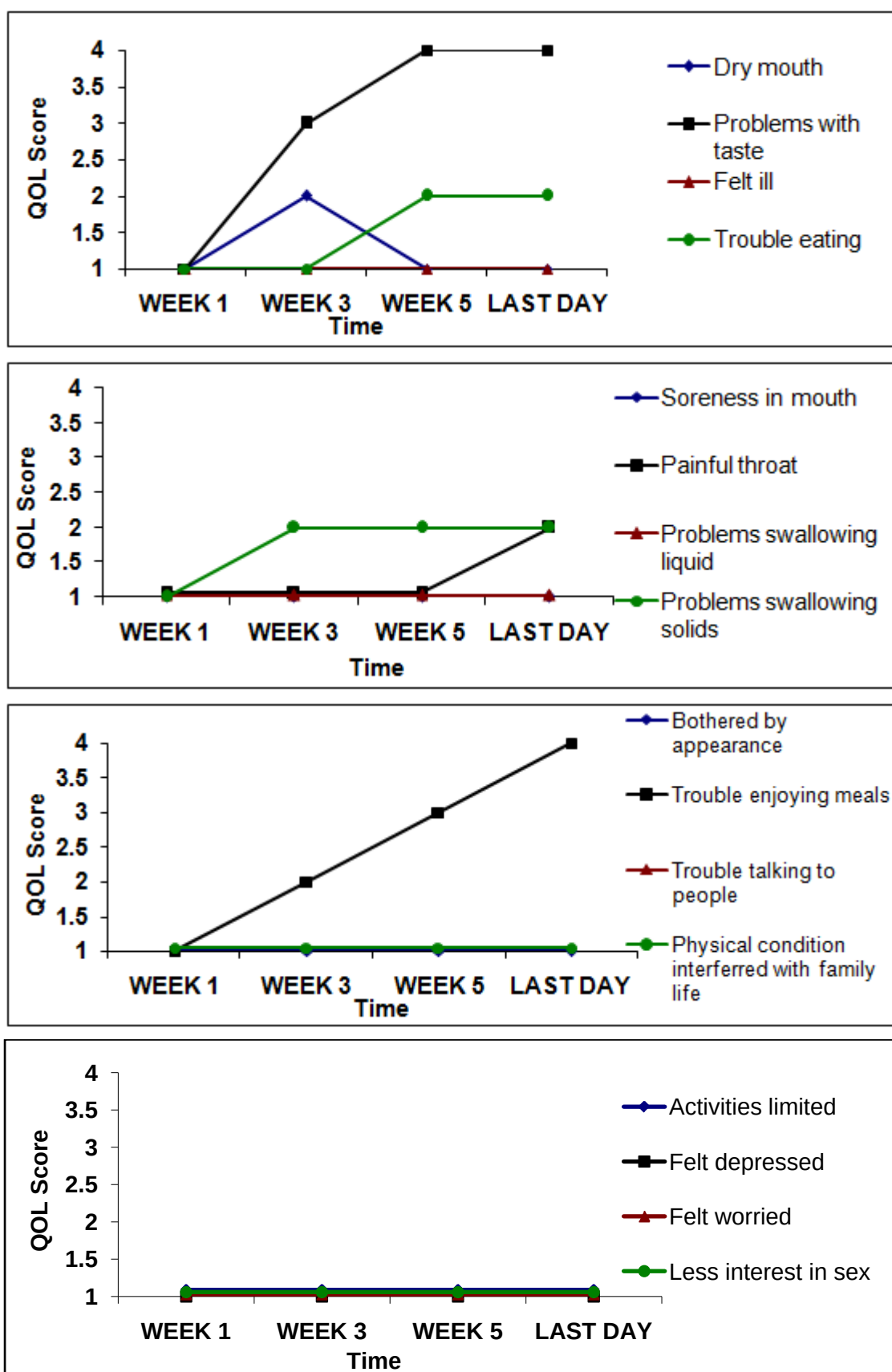


Figure 3.27 EORTC Quality of Life Questionnaire H&N35 Results for PHN-3.
 QOL scores 1 = Not at all, 2 = A Little, 3 = Quite a bit, 4= Very much

Weight and Food Intake

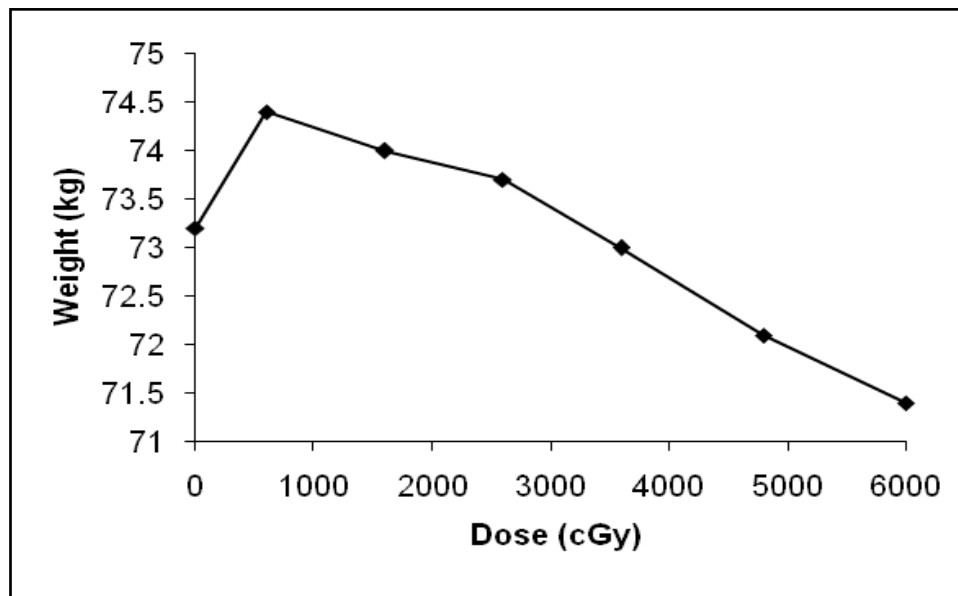


Figure 3.28 Weight measurements for PHN-3 during treatment.

PHN-3 gained weight from 73.2kg on his first day to 74.4kg at 1000cGy (Figure 3.27). This may be due to advice from the dietician seen in his first week of treatment to maintain good nutritional intake. From 1000cGy to 6000cGy he steadily lost weight, totaling 1.8kg (2.45% of baseline weight).

PHN-3's diet during his treatment remained excellent with a variety of soft and hard foods and an adequate calorie intake. It did not appear to be affected by the treatment with the same variety of soft and hard foods in the final weeks of treatment.

Up to 3800cGy PHN-3 had no oral mucositis, an adequate oral intake and lost only a small amount of weight overall. His average QOL score in his week one and week three was 7/7 showing a consistently high quality of life in the first four weeks of treatment. From 3800cGy to 6000cGy the patient developed a small amount of oral mucositis on his upper gingival and the posterior region of the right buccal mucosa. However this did not affect his diet and he lost only a small amount of weight in the final weeks of treatment weighing 71.4kg on his last day of treatment. His QOL score in week five remained excellent (7/7) but decreased to a 6/7 on his last day of treatment. There was no follow up done on PHN-3 as he did not live locally.

3.2.8 Experimental Arm Patient E: PHN-4

Patient Details

Table 3.9 Patient Details for PHN-4

PATIENT DETAILS	
Randomisation number	PHN-4
Gender and Age	Male, 79
Karnofsky score	80%
Tumour details	Squamous cell carcinoma of the left tongue
Stage	T1N2BM0
Radiation therapy treatment regimen	IMRT 6000cGy in 30#, 200cGy per #, 1 # per day, 5# per week for 6 weeks to 100% with 6MV photons
Areas at risk (>4000cGy)	12/14
Chemotherapy treatment regimen	None
Randomisation Arm	Standard treatment + honey

PHN-4 was a 79 year old male diagnosed with a squamous cell carcinoma of the left side of tongue (Table 3.8). He had a partial glossectomy and as the lesion was small the decision was made to monitor the neck nodes for metastases using frequent ultrasounds. However several months after his surgery he was found to have a lymph node metastasis in the left neck therefore he underwent a left-sided modified neck dissection. Due to the lymph node involvement of his cancer he was then referred for adjuvant radiation therapy to reduce the risk of local recurrence.

He had 12 of 14 anatomical areas deemed at risk of developing oral mucositis (Figure 3.28). His right buccal mucosa was not deemed to be at risk as it was not receiving 4000cGy. His oropharynx although was receiving high doses was not accessible to score due to limited jaw movement therefore was also removed as an area at risk. The remaining 12 areas were receiving at least 4000cGy with the left buccal mucosa, gingival and tongue receiving high doses of 6000cGy or more. PHN-4 did not have a PEG because he did not get neoadjuvant chemotherapy and was only having ipsilateral head and neck irradiation. This patient was randomised to the treatment arm of the trial. He took 5mls of honey mixed with 15mls of water, three times a day as recommended. PHN-4 was the second patient in the trial who took honey until the end of his treatment. However, he did have problems remembering to take the honey therefore only took it twice on some days.

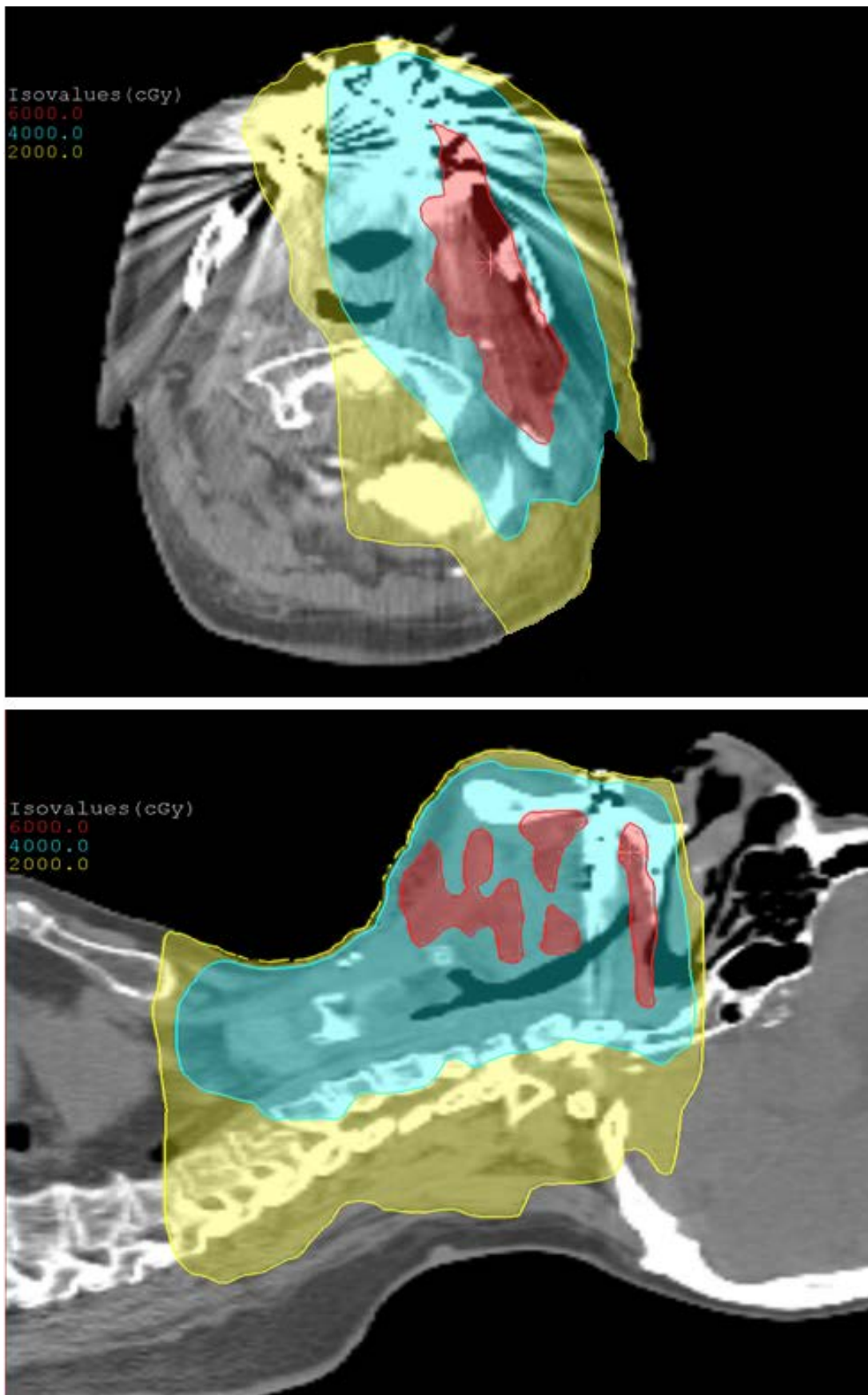


Figure 3.29 Transverse and Saittal views of dose to the oral cavity and neck for PHN-4.
6000cGy = red area, 4000cGy (areas at risk) = cyan area, 2000cGy = yellow area

Mean Oral Mucositis Scores

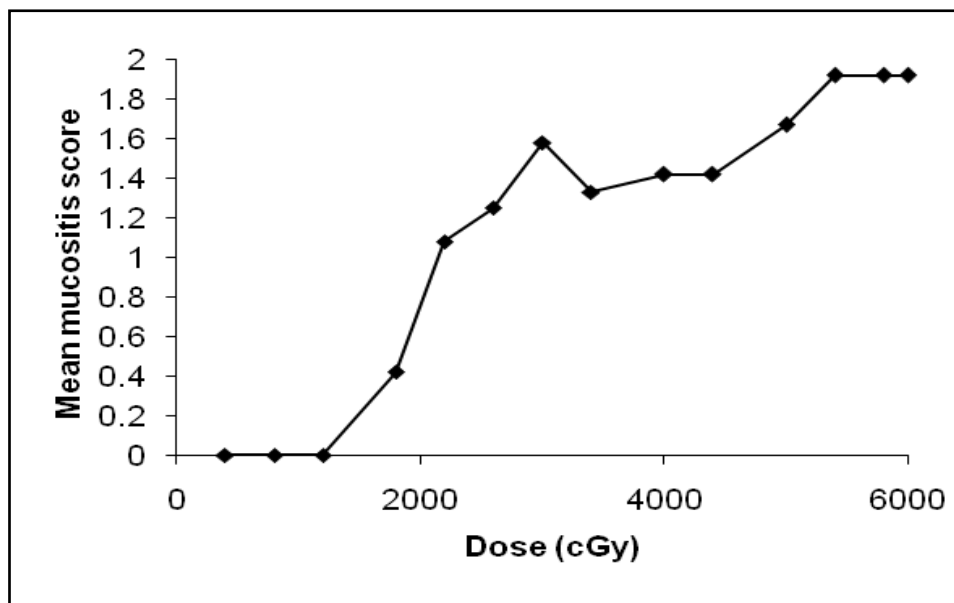


Figure 3.30 Mean Oral Mucositis Scores for PHN-4 During Treatment.

PHN-4 suffered from quite severe oral mucositis during his treatment (Figure 3.29). At 1800cGy his left buccal mucosa, soft palate and floor of mouth became inflamed and his ventral tongue ulcerated. Oral mucositis rapidly worsened between 1800cGy to 3000cGy with his mean mucositis score increasing from 0.42 at 1800cGy to 1.67 at 3000cGy. By 3000cGy PHN-4's upper and lower vermillion lips, upper and lower labial lips, left buccal mucosa, ventral tongue, soft palate and floor of mouth were ulcerated with four of these areas showing confluent mucositis. From 3000cGy to 4600cGy the oral mucositis appeared to regress slightly. From 4800cGy to 6000cGy the mean mucositis score increased. Whilst the ulceration on the upper and lower vermillion lip healed in the final weeks of treatment, the mucositis in the remaining ten areas of the mouth worsened. On the last day of treatment two areas of the mouth were scored as erythematic, and seven areas were scored for confluent mucositis. This gave a maximum mean mucositis score of 1.92.

Quality of Life Questionnaires

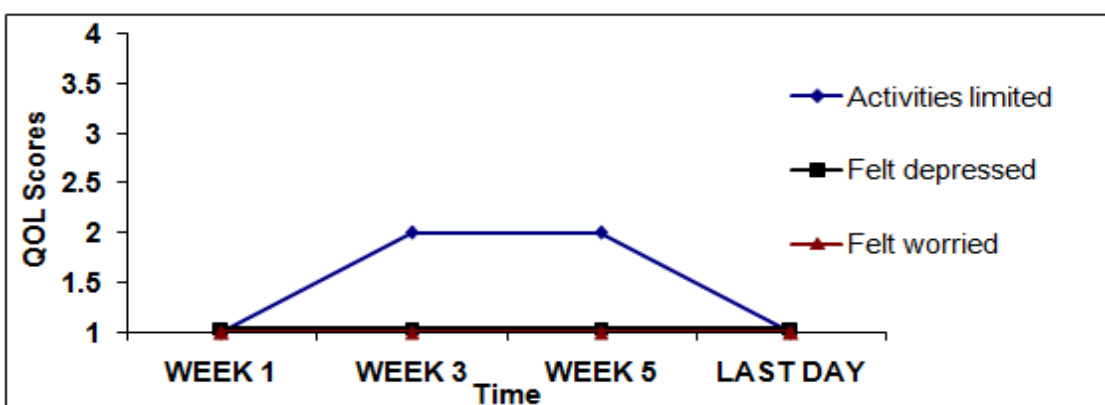
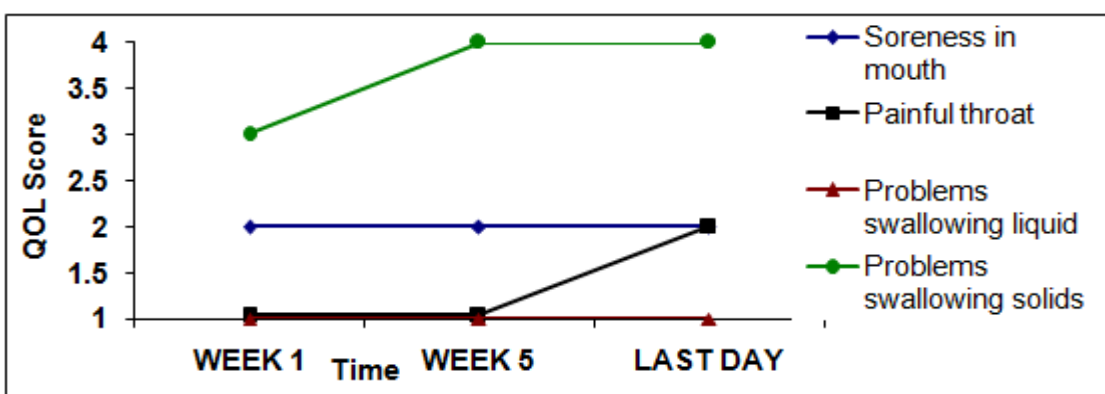
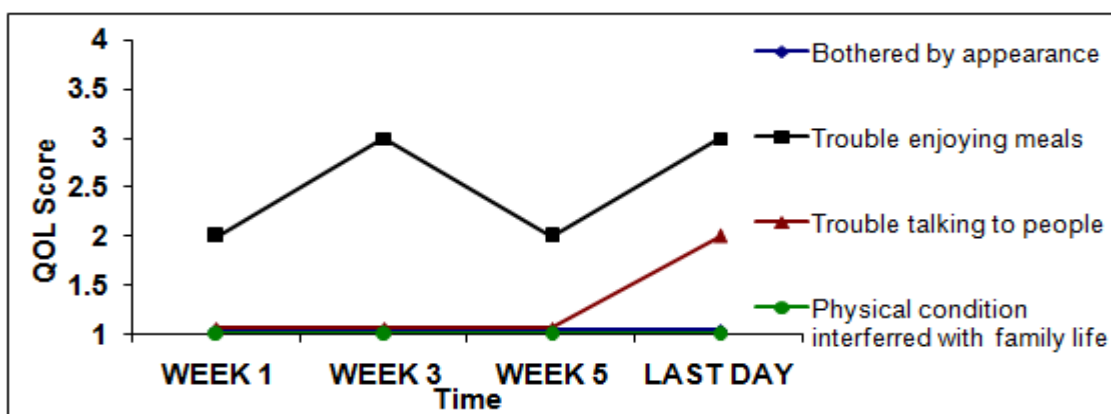
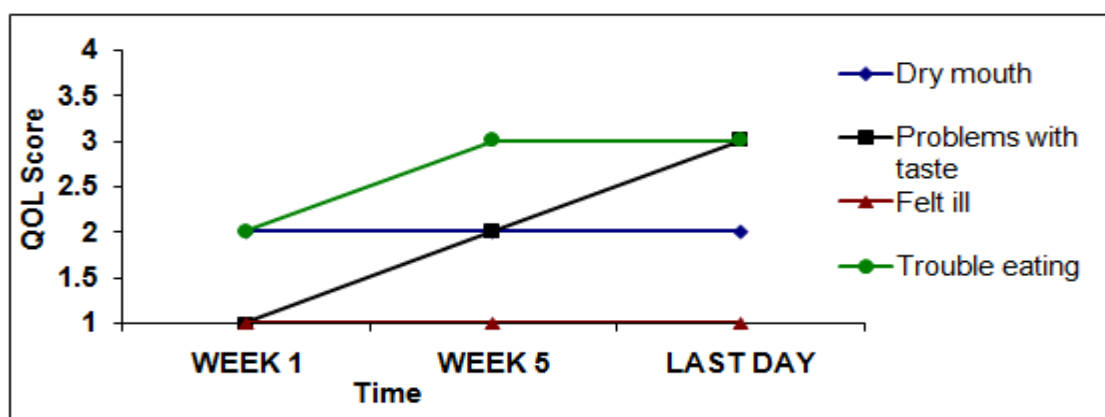


Figure 3.31 EORTC Quality of Life Questionnaire H&N35 Results for PHN-4.

QOL scores 1 = Not at all, 2 = A Little, 3 = Quite a bit, 4 = Very much

PHN-4 completed four QOL questionnaires during his treatment. On his first day of treatment PHN-4 rated his average QOL score as 5/7. The majority of his answers were a one (not at all), or two “A little”. He had “A little”, difficulties with eating and enjoying meals at the beginning of treatment. He had “A little”, pain in his mouth and “Quite a bit” of problems swallowing solid foods due to his tongue surgery. He ate softer foods from the beginning of treatment. By week three PHN-4 rated his average QOL score 4/7. For reasons unknown the patient only completed three of the four pages of the questionnaires therefore some information was missing. He did report increasing trouble enjoying meals and his treatment and physical condition was interfering “A little”, with his work and daily activities. His average quality of life remained stable at 4/7 in both his week five and six questionnaires. He reported having “A little”, pain in his mouth and throat. He had “Very much”, difficulties with swallowing solid food in week five and week six. He also had increasing difficulty talking to people, enjoying meals and problems with sense of taste in his final weeks of treatment.

Weight and Food Intake

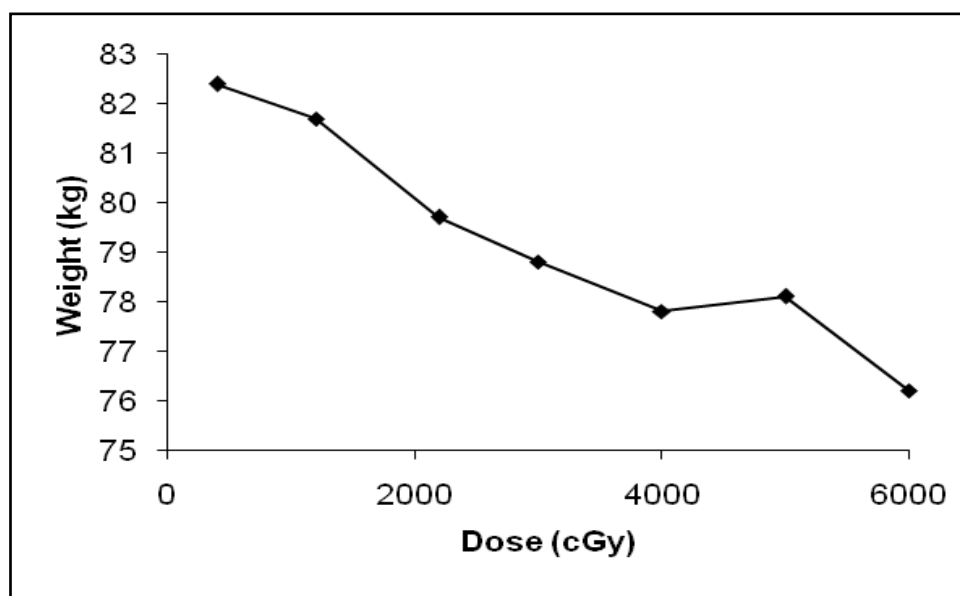


Figure 3.32 Weight measurements for PHN-4 during treatment.

PHN-4 consistently lost weight during treatment (Figure 3.32). PHN-4 weighed 82.4kg on his first day of treatment. By 2000cGy he had lost 2.7kg (3.3% of baseline weight). His diet during the first three weeks of treatment was normal with a good calorie intake, and a mixture of soft and hard foods. He continued to lose weight weighing only 76.2kg on his final day of treatment. This was a total weight loss of 6.2kg (7.5%) during treatment. His diet in the second part of his treatment was a mainly soft food diet with his meals pureed in a blender. His foods were fortified in order to increase his calorie intake.

From 0cGy to 1800cGy PHN-4 had no oral mucositis but lost 2.7kg. His average QOL score on the first day of treatment was 5/7. From 1800cGy to 3000cGy the patient's oral mucositis rapidly worsened with ulceration of the majority of the oral cavity.

From 3000cGy to 4600cGy PHN-4's oral mucositis regressed slightly. His weight during the third and fourth week continued to decrease losing a further 1.9kg between 2000cGy to 4000cGy. His diet in week three remained unchanged however by week four PHN-4 was pureeing his food in a blender as he was having difficulty swallowing solid foods. He rated his average QOL score at week three 4/7.

The patient's oral mucositis rapidly progressed from 4600cGy to 6000cGy. His weight continued to decrease losing a further 1.6 kg in the last two weeks of his treatment. His diet remained dominated by soft and pureed foods that had been fortified. His average QOL score remained unchanged between week three and his last day of treatment at 4/7. There was no follow up done on PHN-4 as he did not live locally.

3.3 COMPARISON BETWEEN HONEY AND CONTROL ARMS

3.3.1 Average Mean Oral Mucositis Scores

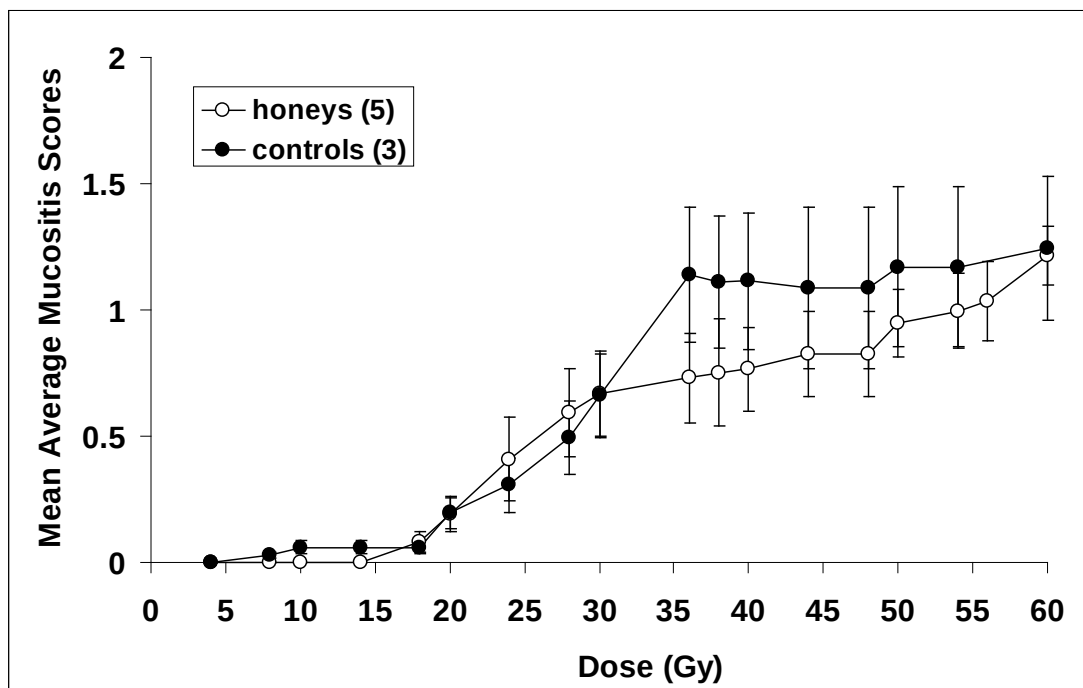


Figure 3.33 Average Mean Oral Mucositis scores for Patients on the Treatment Arm (Honeys) and the control arm (Controls).

Figure 3.32 compares the average mean oral mucositis scores for the patients in the control arm with those in the treatment arm. The mucositis scores of all honey patients were analyzed together, regardless of whether they had used honey till the end of treatment. Although the number of patients is very small (three control patients and five honey patients) it seems that from 3000cGy to 6000cGy the mean mucositis scores for the control patients were higher than for the honey patients. The error bars for the mean mucositis scores for the two arms overlap showing that the difference between the two arms is not statistically significant ($P>0.05$), which is entirely expected in such a small cohort.

3.3.2 Average Weight Loss

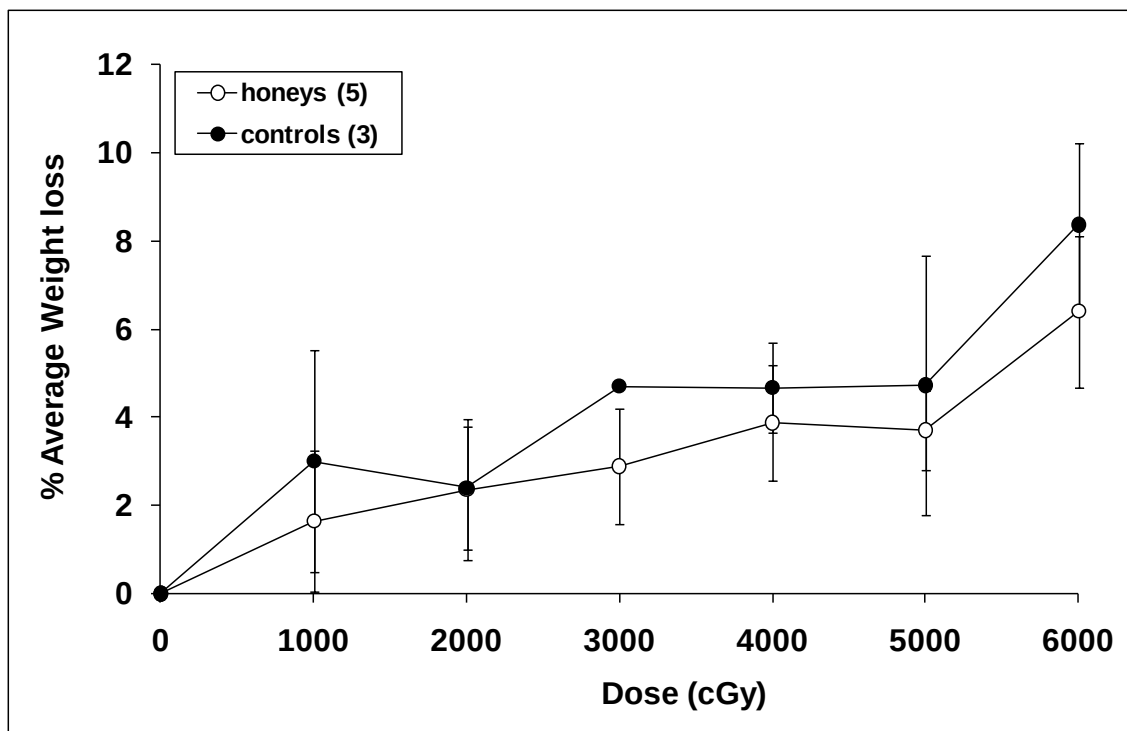


Figure 3.34 Average Weight loss for Patients on the Treatment Arm (Honeys) and the control arm (Controls).

The average percentage weight loss for patients on the control arm and those on the treatment arm are illustrated in Figure 3.33. Although the average percentage weight loss for the control arm was higher than that of the treatment arm, this was not statistically significant in this small cohort.

3.4 TRIAL EVALUATION FORMS

A post trial evaluation form (Appendix F) was introduced into the trial in September 2009 (after ethical approval was obtained as an amendment to the original protocol) when the issues regarding compliance with taking the honey were becoming apparent. This was intended to investigate how long participants took the honey for, whether they found it unpleasant and if so what aspects of the honey made it difficult to take. The evaluation form was distributed to the eight participants allocated to the treatment arm of the trial. Three of the participants filled out the evaluation on their last day of treatment and the other five participants were sent the form in the mail. Five (62.5%) participants returned the evaluation forms.

3.4.1 Timing of Honey

Patients were asked to report at what time of the day they took the manuka honey. The answers from this question showed that the majority of patients did not take the honey as recommended by the research assistant. Participants were advised to swirl with the honey 15 to 30 minutes prior to treatment, 15 to 30 minutes after treatment and 6 hours after radiation therapy. Only two of the five patients confirmed they followed these instructions. Two of the patients took the honey with meals and one patient reported that due to the other mouthwashes he was required to do four times daily (Bicarbonate soda mouthwash and Difflam), he was unsure when it was appropriate to take the manuka honey.

3.4.2 Thickness and Taste of the Honey

Participants were asked to discuss the texture and taste of the honey. Patients commented on the texture as being “syrupey”, and sometimes difficult to mix with the water. Two participants discussed how the undiluted honey was “Initially ok” but as treatment progressed and the mucositis got worse it became more difficult to take in undiluted form.

“Didn’t mind the thickness (of the honey) at all until the last chemotherapy treatment, then I watered it down...”, (PHC-5).

When asked to comment on the taste most patients agreed that the honey was “strong” tasting and “too sweet”. Two patients commented that whilst the taste was ok at the beginning, it became intolerable further on in their treatment.

“The taste was good at first but towards the end of my chemotherapy treatment I could not get anything in my mouth as anything would make me sick”, (PHC-5).

It was also mentioned by patients in discussion with the research assistant that the honey became unpleasant and metallic tasting as treatment progressed.

3.4.3 Other Comments on Taking the Honey

Many patients reported verbally that taking manuka honey became difficult once their mouth ulcerated. The only patient who thought that reported taking the manuka honey was easy did not experience much oral mucositis during his treatment (PHN-3). Some participants reported a stinging sensation when using the honey whilst others reported that the honey felt “acidic and irritating”.

“After the first week of treatment the crystallization of the honey became irritating to my tongue surface. That was resolved somewhat by watering it down. At about week three I started losing my sense of taste and the use of the honey became intolerable.” (PHN-2).

3.4.4 Other Comments on the Trial

Four of the five patients did not identify any areas of the trial such as the QOL questionnaires, food and drug diaries, oral mucositis scores, to be challenging. One patient who withdrew from the trial in his second week identified that the food and drug diaries were difficult for him to complete at home and that the trial was “too much hassle”.

Overall, the evaluation forms reflected the reasons why many patients did not comply with the honey. Many did not understand how to take it correctly. It seems that most participants found the honey easy to take at the beginning of treatment but once their mouths starting to show signs of oral mucositis they found the honey unpleasant and stopped taking it.

CHAPTER 4 DISCUSSION

4.1 STUDY FINDINGS

4.1.1 Mean Oral Mucositis Scores

Oral mucositis is induced by cytotoxic cancer treatments such as radiation therapy and chemotherapy. The frequency and extent of oral mucositis depends on many factors including patient related factors such as age, oral health, hygiene, tobacco use and alcohol use and treatment related factors such as dose, fractionation and single versus multi-modality treatments. The factors thought to have the largest impact on the degree of mucosal damage are the total dose of radiation delivered to the oral mucosa and concomitant chemoradiation.

However, despite taking these factors into account mean oral mucositis scores varied considerably between patients in this study. For example, it was expected that patients with similar doses to their oral mucosa would experience similar degrees of oral mucositis. This was not the case with patients PHC-4 and PHC-5 who both received chemoradiation, had a total of 10/14 areas at risk and had a similar area of the mouth receiving 6000cGy or more. However the mean oral mucositis scores for these two patients varied considerably. PHC-4 had a maximum mean mucositis score of only 0.27 compared with PHC-5's maximum mean mucositis score of 1.3.

Furthermore, it was expected that those participants in the trial who received concomitant chemoradiation would experience more severe oral mucositis due to the increased mucosal injury from two cytotoxic treatments and also the increased total dose of radiation these patients received. Patients being treated with combined chemoradiation were treated to a total dose of 6600cGy compared with those patients receiving radiation only who were treated to a lower total dose of 6000cGy. This however was not reflected in the results of this study with an average mean mucositis scores for patients receiving chemoradiation of 1.02 compared with an average mean mucositis score of 1.65 for those patients receiving radiation only. These data show that there is a multitude of factors that affect the severity of a patient's oral mucositis.

This pilot study used a multi-site scoring system adapted from Epstein et al. (2001) to accurately score the severity of oral mucositis. This scoring system takes into account the effect of radiation dose on oral mucositis by averaging the combined scores from 14 anatomical areas by the number of areas receiving more than 4000cGy. Analysis of all mean mucositis scores demonstrated a slight decrease in mucositis score for honey patients compared with control patients, which was not statistically significant in this small cohort as evidenced by the large overlapping error bars.

The results of this study differ markedly from those from three small phase two randomised controlled clinical trials investigating the effect of honey on oral mucositis, using a similar study protocol. These three trials each recruited 40 patients, 20 of which were randomised to the control arm and 20 of which received 20mls of undiluted honey three times daily.

Biswal et al. (2003) conducted a clinical trial investigating the effect of tea plant honey on oral mucositis in patients receiving radiation therapy in Malaysia. The oral mucosa was assessed weekly using the RTOG grading system. This system gives the whole of the oral mucosa a single score from zero to four and contains information on both the appearance and function of the oral mucosa. Biswal et al. (2003) reported a significant reduction in the severity of oral mucositis in those patients treated with honey with only 25% of patients in the honey group developing grade three or four mucositis compared with 75% in the control arm.

Motallebnejad et al. (2008) and Rashad et al. (2008) conducted similar trials in Iran and Egypt respectively. Motallebnejad et al. (2008) used honey produced from the nectar of the *Thymus* and *Astragale* flowers whereas Rashad et al. (2008) used clover honey. Rashad et al. (2008) used the same scoring system as Biswal et al., (2003) and Motallebnejad et al. (2008) used the more complicated OMAS scoring system. This system is similar to one used in the current study and separates the oral mucosa into nine different anatomical areas with each area receiving a score for erythema (zero to three) and ulceration (zero to two) giving a total score between zero and 45. Both trials reported significant improvement in the severity of oral mucositis in patients receiving honey. Motallebnejad et al. (2008) showed that honey decreased cumulative mucositis scores by more than 50% and Rashad et al. (2008) reported a decrease in grade three or four mucositis of 50% in patients receiving honey.

The inclusion criteria differed between the trials; Biswal et al. (2003) and Motalebnejad et al. (2008) excluded patients receiving chemotherapy; whereas Rashad et al.(2008) and the current study included patients receiving chemotherapy.

The standard of care used for the control patients varied significantly between the trials. Control patients in the trial by Biswal et al. (2003) did not receive any treatment, Motalebnejad et al. (2008) used saline mouthwashes and Rashad et al. (2008) used Benzydamine HCl mouthwashes for all patients. The current trial treated the control patients with a combination of Benzydamine HCl mouthwashes, baking soda mouthwashes, nystatin and analgesics such as panadol, ibuprofen and morphine when appropriate.

However, despite using different types of honey, different scoring systems, different inclusion criteria and different control treatments, all three trials showed a 50% decrease in the severity of oral mucositis in the honey arm. This is in stark contrast to the minimal benefit seen in the current study.

The only way in which the current study differed significantly from all three previous trials is that the previous trials used undiluted honey and reported no problems with patient's compliance. Our cohort did not tolerate undiluted honey and all patients diluted the honey up to 1:3 and even then only two out of five patients used honey during their entire treatment. All patients reported that the honey was difficult to tolerate once their mouth began to ulcerate, and patients that had tongue surgery found it difficult to manipulate the honey to coat all the oral mucosa.

The results of this small cohort suggest that using diluted honey does not offer additional benefits to the high standard of care they receive in the New Zealand setting. However due to the poor tolerance of undiluted honey in our small patients cohort, we were unable to validate the positive effects of undiluted honey reported by the previous three trials.

4.1.2 Weight Changes and Food Intake

Patients suffering from oral mucositis often find eating, drinking, chewing and swallowing painful which leads to reduced food intake and weight loss. The average weight loss for patients having treatment for head and neck cancers is reported to be within 3.0-6.7kg (Trotti et al., 2003) and is directly related to the extent of oral mucositis (Elting et al., 2007). Patients receiving chemotherapy

and radiation therapy are more likely to lose weight than those receiving radiation therapy alone (Elting et al., 2007).

In the current trial, the average weight loss overall was 6.5kg which is at the higher end of the range reported by Trotti et al. (2003) in a meta analysis of eight trials with a total of 880 patients receiving treatment for head and neck cancers. In this small pilot trial, patients receiving combined chemoradiation lost more than patients receiving radiation therapy only (7.8kg versus 5.0kg). In the current study, control patients lost more weight than patients receiving manuka honey (average weight loss of 6.8kg and 6.1kg respectively), which was not statistically significant. Motalebnejad et al. (2008) support these results and reported that patients receiving honey experienced less weight loss (1.0kg) than the control patients (6.3kg) in his trial, which was statistically significant. Biswal et al. (2003) reported a similar trend in weight changes between the two arms, but did not quantify the amount of weight loss per patient.

The results of these three trials combined suggest that patients taking honey lose less weight. It also highlights weight loss as a significant issue in patients receiving radiation therapy for head and neck cancers especially those receiving combined chemoradiation.

4.1.3 Quality of Life Questionnaires

Head and neck cancers arise in areas which are necessary for vital activities such as speaking, eating and swallowing (Murphy et al., 2007). They also can result in cosmetic deformities which can have profound emotional and social effects (Murphy et al., 2007). The treatments used to cure these cancers add to this burden, therefore it is important when testing new treatments that we use an accurate tool to evaluate the impact on a patient's QOL. In the current study, the EORTC QLQ-30 and H&N-35 questionnaires were used to assess the effect of oral mucositis on a patient's general QOL. These two questionnaires used together obtained a comprehensive and multidimensional picture of the patient's general well being and oral health.

To date several studies have assessed the impact of oral mucositis on QOL, all of which have reported a decrease in patients QOL during cancer treatments (Dodd et al., 2001; Elting et al., 2003; Cheng, 2007). The current study also found a decrease in general QOL during treatment. Participants reported increases in pain in their mouths and throats, difficulty swallowing and altered sense of taste which resulting in eating and meal times becoming unpleasant. Furthermore, many patients

reported a difficulty with talking and communicating with people. A lack of enjoyment in meal times and a difficulty with communication impacted negatively on patient's social life with some patients avoiding social contact with friends and family.

The relationship between oral mucositis and QOL remains less clear (Murphy et al., 2007). Cheng (2007) investigated the effects oral mucositis on QOL in 88 Hong Kong Chinese patients undergoing cancer therapy. This study found that QOL was significantly related to the perceived severity of the oral mucositis. Patients with severe mucositis reported lower physical, emotional, functional QOL scores than those with mild or no oral mucositis. This was supported by the findings of Elting and colleagues (2008) in their study of 241 head and neck patients receiving radiation therapy with or without chemotherapy. This large trial reported the impact of mucositis on QOL was proportional to its severity, with even mild to moderate mucositis associated with a decrease in patient QOL.

Conversely, Dodd et al (2001) in a study of 77 patients receiving chemotherapy reported that the development of mucositis increased levels of depression and anger in patients but did not affect overall QOL. This trial focussed exclusively on patients receiving chemotherapy for head and neck cancers and excluded patients receiving concurrent radiation therapy to the head and neck. This group of patients are at high risk of severe treatment related symptoms therefore removing these patients may explain why this trial found no difference in the QOL with increasing oral mucositis.

A clear relationship between the severity of oral mucositis and QOL was not observed in the current study. Patients with the most severe oral mucositis did not necessarily report the lower quality of life scores. For example PHN-1 and PHN-4 had the highest mean oral mucositis scores recorded in the trial (2.1 and 1.92 respectively) and reported their general QOL on a scale from one (very poor) to seven (excellent), to be 5/7 in the first week to 4/7 in the final week of treatment when their oral mucositis was at its worst. Both patients, despite suffering from severe oral mucositis, reported only a small decrease in their QOL during treatment. Conversely, PHC-4 suffered from very mild oral mucositis (mean mucositis score of 0.27) however reported a very poor quality of life from 4/7 on his first day to 2/7 on his last day of treatment.

Cheng (2007) also reported that patients treated with combined chemo-radiotherapy perceived more intense oral mucositis and reduced QOL than patients treated with radiotherapy or chemotherapy alone. This trend was also seen in the current pilot trial. The average QOL score on the last day of treatment for patients not receiving chemotherapy was 4.5/7 (range 6/7 to 4/7). This

was considerably higher than the average QOL of 2.8/7 (range 5/7 to 1/7) on the last day of treatment for patients receiving chemotherapy. Also patients receiving concomitant chemoradiation also reported a lower average QOL on the first day of treatment than those receiving radiation only. This may have been due to the negative effects of the patient's health from the first cycle of chemotherapy which was given one week prior to their first QOL questionnaire.

Overall, it appears that oral mucositis adversely affects patients QOL especially those receiving concurrent chemoradiation however the current pilot trial was too small to show any clear proportional relationship between the severity of oral mucositis and patients QOL. What it does reflect is the multidimensional nature of patients perceived QOL.

4.2 LIMITATIONS OF THIS STUDY

4.2.1 Selection Bias

Sampling is the process by which a portion of the population is selected to represent an entire population; in this case patients treated with radiation therapy for head and neck cancers. This sample should reflect the key characteristics of a population. For example, a sample of patients receiving radiation therapy for head and neck cancer should include both men and women, patients receiving adjuvant surgery or chemotherapy and a variety of ethnical groups and age groups in order to truly represent this population. A systematic over-representation or under-representation of some segment of the population is referred to as selection bias (Polit and Beck, 2004). There are a number of selection biases in this small pilot trial.

Low patient numbers

The current study is a very small pilot trial and the aim was to determine the effect of manuka honey on the extent of oral mucositis in a small cohort of head and neck cancer patients. The small number of participants by itself indicates that the results of this study cannot be generalized to the entire population of head and neck cancer patients.

Inclusion criteria

In addition, we used inclusion criteria that excluded patients with previous radiation therapy to the head and neck area, those with diabetes and those that had low Karnofski scores (<70). This excluded patients with poor general health and often elderly patients. Due to the debilitating nature of head and neck cancers this excluded a large proportion of the general population from this study.

Gender representation

Only males elected to participate in this trial. Of the 620 people with head and neck cancers registered in New Zealand during 2005, 196 were female. In Palmerston North Hospital very few of the patients screened for eligibility in the trial were female. These women either did not meet the eligibility criteria or declined the trial.

Age representation

The average age of the participants in the trial was 59.1 years, ranging from 39 to 79 years of age. This is consistent with the national age registrations for head and neck cancers in 2005 peaking between 55 and 60 (Ministry of Health, 2009).

Smoking/alcohol consumption

Of the twelve patients recruited to the trial four were currently smoking and four were ex-smokers. As smoking is a known causative factor for head and neck cancers the high number of smokers in this trial is not surprising. The addition of alcohol to tobacco smoking further increases the risk for oral cancer. In this trial, 50% of patients had a moderate to heavy alcohol intake.

Tumour Location

Seven participants (58.3%) had their tumour located on their tongue; three participants (25%) had their tumours in their tonsils, one participant had his tumour on his hard palate (8.3%) and the remaining one man (8.3%) had a parotid tumour.

Randomisation

In order to minimize selection bias patients were randomised into the experimental and control arms in the initial phase two trial. Patients were first stratified according to the treatment which was prescribed (more or less than 6000cGy, with or without chemotherapy) and then randomised into either the honey arm or the standard treatment only arm. This stratified randomisation attempted to ensure that variables which strongly correspond with oral mucositis severity such as the high radiation doses or the presence of chemotherapy would be equally distributed between the two groups. Once the trial became a phase one trial, all patients received honey removing the need for randomisation.

4.2.2 Participant Bias

In the current trial the participants completed food and drug diaries weekly and QOL questionnaires fortnightly. These questionnaires and diaries may have been subjected to recall and response bias. For example, participants were asked to record their food and drink intake weekly. This may have been subject to recall bias if the patient did not fill the form out daily. Also the patient may have wanted to give answers that he or she may have thought were desirable such as exaggerating their actual oral intake.

Furthermore, Patients were not able to be blinded from which arm of the trial they were on. Patients that were allocated to the honey arm may believe that the honey reduced their oral mucositis therefore affected the evaluation of their symptoms. This participant bias was minimized as the majority of measurements such as the oral mucositis score and weight measurements were taken by the research assistant.

4.2.3 Researcher Bias

Researcher bias is the process by which the research assistant can influence the results in order to portray a desired outcome. In the current trial it was not deemed feasible to blind the research assistant therefore it is not possible to rule out a researcher bias. A second mucositis scorer could have been introduced who was completely blinded which would reduce the researcher bias and also the measurement bias.

4.2.4 Measurement Bias

Both the procedure involved in applying measurements and the objects being measured are susceptible to influences that can alter the results (Polit & Beck, 2004). Incorrect or inaccurate measurements can be a source of bias in a study therefore it is important to assess the quality of measurements.

Mean Oral Mucositis Scores

The scoring system used for this trial was adapted from the multi-site scoring system used by Epstein and colleagues (2001) in a large multi-centre trial investigating the effectiveness of Benzydamine HCL. Like all systems used to score oral mucositis there were a few limitations of this scoring method. First of all the number of areas at risk were defined as an area of the oral cavity receiving over 4000cGy. This was decided by the research assistant by viewing the patient's 3-D treatment plan on a computer. It was difficult to assess where each area of the oral cavity began and ended on a CT scan therefore errors in determining these areas at risk may be present. Also there is little evidence to suggest that 4000cGy is the dose at which oral mucositis begins. Literature suggests that oral mucositis can begin to occur at as little as 2000cGy to the oral cavity therefore this may have been a more appropriate dose for deeming areas "at risk" of developing oral mucositis.

Furthermore, whilst this scoring system took into consideration the number of areas at risk of developing oral mucositis for patients it did not distinguish between different doses. For example patients with seven areas receiving 4000cGy would be expected to get less severe oral mucositis than a patients with seven areas receiving 6500cGy.

The system used to measure oral mucositis was based solely on the research assistant observing and giving the oral mucosa a score between one and four. Therefore, it contains no information on the functional status of the oral mucosa in relation to eating, talking and swallowing which are arguably more important than the presence or absence of ulcers. As this measurement was done by the research assistant there is a possibility of researcher bias. Administration variation was minimized by the same researcher assistant scoring all patients oral mucositis.

Another difficulty in using this model for scoring oral mucositis was the presence of oral thrush. This made it very difficult to see the oral mucositis and may have lead to inaccurate measurements of some areas of the mouth.

Quality of Life Questionnaires

Patients were requested to complete the EORTC QLQ-30 and H&N 35 QOL questionnaires fortnightly. The validity of the results obtained from questionnaires such as these is governed by the participant's willingness or ability to provide accurate information (Polit & Beck, 2004). For example, the questions may be interpreted differently by different people, or subjects may give an answer that they believe to be more desired.

Food and Drug Diaries

Patients were asked to complete a food and drug diary each week. This proved to be time consuming and difficult for patients and many of the days of the week had the same diet recorded. In future trials, requesting a participant to record their food intake for one day per week would probably be sufficient enough to assess the patient's nutritional intake.

Weight

Participant's weight was measured on a weekly basis using the same scales located in radiation therapy. As the same set of scales were used for all measurements done for each patient, and as it is a purely objective measurement there should be minimal measurement bias involved.

4.2.5 Patients Compliance

As discussed in this thesis patients diagnosed with a head and neck malignancy often undergo one, or more commonly a combination of surgery, radiation therapy and chemotherapy to cure their cancer. These treatments are very aggressive, and result in patients suffering from a large range of debilitating side effects including severe skin reactions, xerostomia and severe oral mucositis. These side effects often lead to a loss of taste, infections, malnutrition, weight loss and trouble communicating. Therefore, patients receiving radiation therapy and/or chemotherapy are often of very poor general health and have a drastically reduced quality of life.

This trial aimed to alleviate severe oral mucositis and reduce the distress associated with it. Unfortunately, patients were unable to tolerate 20mls of undiluted honey which was the standard of treatment offered in previous clinical trials. Patients reported that the honey was too thick, tasted sickly and increased their nausea often already present from the chemotherapy. They also reported a stinging sensation due to the acidic pH of honey, which was unpleasant and intolerable when the patient's mucosa began to ulcerate. This led to large issues with patient's compliance. Many patients would forget to take the honey three times per day with the large majority of patients only remembering to take it twice per day (before and after radiation therapy). Other patients refused to take the honey as it became unpleasant resulting in a large number of the trial participants only taking the honey for the first three to four weeks of their treatment.

For these reasons, the investigators chose to dilute the honey into a form which it was more manageable for patients. This means that the full undiluted effects of Manuka honey on oral mucositis could not be assessed. However, even after diluting the honey 1:3 with water there was still large issues with compliance. Taking the Manuka honey seemed to cause a large amount of distress amongst the trial participants and from the findings of this study there is no evidence to suggest in its undiluted form it was beneficial to patients suffering from oral mucositis in New Zealand. For these reasons, it does not seem ethical to pursue this study further unless the honey can be changed into a form which is tolerable for patients and thus circumvent the issues with taste, texture and stinging of the honey.

4.3 CONCLUSIONS

This trial aimed to investigate the effects of manuka honey on oral mucositis. Oral mucositis is an inevitable side effect of current aggressive treatment modalities such as the use of concurrent chemoradiation. It was hoped that the honey would decrease the severity of oral mucositis thus reducing the distress it causes patients. Three recent trials undertaken by Biswall et al., 2003; Motallebnjad et al., 2008 and Rashad et al., 2008 showed undiluted honey to reduce the severity of oral mucositis, reduce infection rates and decrease weight loss in patients receiving radiation therapy to the head and neck.

This thesis reported the results for twelve patients, four of which were recruited to the original phase two trial and the remaining eight which were recruited to the pilot trial. There were large issues with patient compliance due to the taste, texture and burning sensation of undiluted honey which lead to the original phase two trial being downgraded to a pilot trial investigating the best way to administer the Manuka honey. In the pilot trial patients were advised to try diluting the honey 1:1 with water or to dilute the honey further (1:3) with any fluid of their choice ie tea, ginigerale etc.

Whilst this trial yielded some interesting insights into a patient's journey through radiation therapy and the side effects associated with this treatment, there was no statistically significant difference in the severity of oral mucositis reported between those taking Manuka honey and those using standard forms of treatment. Patients taking Manuka honey appeared to have slightly less weight loss than those receiving standard treatments alone however this did not reach statistical significance. All patients, irrespective of whether they were taking honey or not, reported a severe decrease in quality of life throughout the course of their radiation therapy.

The effects of pure undiluted Manuka honey on oral mucositis could not be adequately assessed due to poor compliance with the honey. Due to these issues with compliance, it was not deemed ethical to continue with the current trial unless the honey is given to patients in a way which is tolerated better.

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APPENDIX A

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Te Whare Wānanga o Ōtago

October, 2008

University of Otago, Wellington

Honey for Mouth Ulcers during Radiation Therapy

PROTOCOL FOR PARTICIPANTS

Please DO NOT tell the Research Assistant in which arm you are.

All patients

- Use good oral hygiene at all times, rinse with water after every meal.
- Brush two times a day using soft tooth brushes and fluoride toothpaste.
- Avoid very hot and/or spicy food, alcohol and tobacco.
- Take regular sips of water.
- Allowed: pain medication over the counter or prescription (note in diary). Other oral mouthwashes or medication prescribed by your oncologist (note in diary)

Honey Arm

Use the measuring spoon to measure out 20 ml of honey and swirl the honey around in your mouth slowly. Take your time (one to several minutes) to ensure that all parts on the inside of the mouth are covered with honey, especially the parts that hurt. Then slowly swallow the honey; this will coat the sides of the swallowing tube (oesophagus) as the honey slides down.

Mondays to Fridays

Do this 15-30 minutes before and 15-30 minutes after each radiation therapy treatment and again approximately 6 hours after treatment (3 times a day).

Saturday and Sundays (and other non-treatment days)

Take honey 3 times a day (morning, afternoon, evening)

Control Arm

Standard practice of care; follow the advise by your oncologist.



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31

--	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent



EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had pain in your mouth?	1	2	3	4
32. Have you had pain in your jaw?	1	2	3	4
33. Have you had soreness in your mouth?	1	2	3	4
34. Have you had a painful throat?	1	2	3	4
35. Have you had problems swallowing liquids?	1	2	3	4
36. Have you had problems swallowing pureed food?	1	2	3	4
37. Have you had problems swallowing solid food?	1	2	3	4
38. Have you choked when swallowing?	1	2	3	4
39. Have you had problems with your teeth?	1	2	3	4
40. Have you had problems opening your mouth wide?	1	2	3	4
41. Have you had a dry mouth?	1	2	3	4
42. Have you had sticky saliva?	1	2	3	4
43. Have you had problems with your sense of smell?	1	2	3	4
44. Have you had problems with your sense of taste?	1	2	3	4
45. Have you coughed?	1	2	3	4
46. Have you been hoarse?	1	2	3	4
47. Have you felt ill?	1	2	3	4
48. Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:

	Not at all	A little	Quite a bit	Very much
49. Have you had trouble eating?	1	2	3	4
50. Have you had trouble eating in front of your family?	1	2	3	4
51. Have you had trouble eating in front of other people?	1	2	3	4
52. Have you had trouble enjoying your meals?	1	2	3	4
53. Have you had trouble talking to other people?	1	2	3	4
54. Have you had trouble talking on the telephone?	1	2	3	4
55. Have you had trouble having social contact with your family?	1	2	3	4
56. Have you had trouble having social contact with friends?	1	2	3	4
57. Have you had trouble going out in public?	1	2	3	4
58. Have you had trouble having physical contact with family or friends?	1	2	3	4
59. Have you felt less interest in sex?	1	2	3	4
60. Have you felt less sexual enjoyment?	1	2	3	4

During the past week:

	No	Yes
61. Have you used pain-killers?	1	2
62. Have you taken any nutritional supplements (excluding vitamins)?	1	2
63. Have you used a feeding tube?	1	2
64. Have you lost weight?	1	2
65. Have you gained weight?	1	2

APPENDIX C
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Te Whare Wānanga o Ōtago

October, 2008

University of Otago, Wellington

Honey for Mouth Ulcers during Radiation Therapy

PARTICIPANT INFORMATION SHEET

You are invited to participate in a clinical trial which investigates the effect of honey on mouth ulcers experienced by patients who receive radiation therapy for head and neck cancers. All participation in this research is entirely voluntary and you are free to withdraw from the study or decline any particular question or test, at any time. Please discuss your participation in this trial with family and whanau and take the time to decide whether you wish to take part in this study.

1. Why should I participate in this study?

Radiation therapy to the head and neck is given with the aim of killing cancer cells in this area. However, irradiation may cause the lining of the mouth to become red and sore and ulcers may form. Ulceration can be painful and may interfere with eating, drinking, talking and, in extreme cases, it may be necessary to delay your treatment.

Currently, there is no “best treatment” for radiation-induced mouth ulcers. However, a few small studies have recently shown that pure honey may be effective in decreasing the extent of ulceration in the mouth. This trial aims to test the effect of pure New Zealand manuka honey on mouth ulcers in 120 people, receiving radiation therapy for certain head and neck cancers.

2. What does my participation in the study involve?

The trial starts as soon as your radiation therapy treatment begins and finishes 4 weeks after completion of treatment.

A. Randomization

Once you have been accepted into the trial you will be randomized to either the honey arm or the control arm. Randomization is done using a computer programme and cannot be influenced by the oncologist, the research

assistant or yourself. **It is important that you do not tell the research assistant whether you are in the honey or in the control arm.**

B. Protocol

All patients who enrol in this trial will be given a “***Protocol for Participants Sheet***”. This sheet contains detailed information on how to take care of your mouth during the trial and which types of food and drink to avoid, to minimize discomfort.

- If you are randomized to the honey arm you will need to swirl pure Comvita Manuka honey (provided by the research assistant) around in your mouth, coating the entire inside of your mouth, three times a day.
- If you are randomized to the control arm, you will not need to do anything extra. You will simply get the standard treatment prescribed by your doctor.

C. Assessments

1. Physical examination by the radiation oncologist at the start of the trial.

2. Blood tests

A blood test at the start and finish of the trial will determine your blood chemistry (sugar levels), blood cells and liver functions. The tests will be done in a certified medical laboratory.

3. Assessment of Mouth Ulceration

The extent of oral mucositis will be monitored three times a week during radiation therapy treatment by the research assistant, who will look inside your mouth to record the extent of redness and ulceration in different parts of your mouth. Two more assessments will be done 2 and 4 weeks after completion of radiation therapy treatment.

4. Weight Measurements

Having a sore mouth may affect what and how much you eat and drink, and this will be reflected in your weight. Your weight will be measured once a week during radiation therapy treatment and 2 and 4 weeks after completion of treatment.

5. Quality of Life Assessment

Radiation therapy to the head and neck will affect the way in which you experience life from day to day. We would like to carefully monitor how you are affected by your treatment by asking you to fill in the same questionnaire every 2 weeks from start to finish of the trial. This Quality of Life questionnaire is relatively short and is designed specifically for patients that have head and neck cancers.

6. Food/Drink/Drug Diary

Because we are interested in how your treatment affects your health and quality of life, we want you to write down what (and how much) you eat and drink every day. We would also like you to write down how

many pain killers you have used that day and what type(s) of pain killers these were. We also want you to write down whether you have had to use a feeding tube. Your protocol sheet will have an example of how to fill in such a diary.

7. Mini-tongue Swabs

Harmless bacteria and yeasts (“microflora”) are normally found in the mouth of healthy people where they do not cause any problems. In fact, the “good microflora” prevents “bad microflora” from causing dental caries and gum disease. Radiation therapy to the head and neck is likely to make changes to the microflora in your mouth, but at the moment we do not know much about those changes.



The research assistant will swab your tongue with a very small tongue swab (see photo) at the start of the trial, 3 weeks into radiation therapy treatment, at the completion of treatment and 4 weeks after completion of treatment.

The swabs remove a very small amount of saliva (containing the microflora) and some dead surface cells from your tongue. The swabs will be stored in a special buffer solution and frozen for further analysis at the end of the trial. We hope to be able to determine what happens to the microflora in your mouth, regardless of whether you are in the honey or control arm of the trial.

8. Returning to the hospital after completion of treatment

You will be asked to come back 2 and 4 weeks after the completion of your radiation therapy treatment for 2 further assessments of your mouth, 2 more questionnaires, weight measurements and a final tongue swab.

3. Are there any risks to me if I participate in this study?

Three overseas clinical trials have shown that honey helped to alleviate the symptoms associated with radiation-induced mouth ulcers.

- In the unlikely event of an adverse reaction to the honey you will be advised to stop using honey.
- In the unlikely event of a physical injury as a result of your participation in this study, you will be covered by the accident compensation legislation with its limitations. If you have any questions about ACC please feel free to ask your radiation oncologist, the research assistant or the principal investigator, Dr Patries Herst (027-3483945) for more information before you agree to take part in this trial.

4. Are there any costs involved if I participate in this study?

The only costs associated with this trial are those of attending the 2 week follow-up visit, for which we will reimburse you appropriately. The 4 week follow-up visit is part of standard care.

5. What will you do with the information?

The information from all participants will be kept completely confidential. During the trial, participant files will be kept at the local DHBs in a locked filing cabinet in the office of the research assistant. After the trial, patient information will be stored at the University of Otago, Wellington, in a locked filing cabinet in the office of the Principal Investigator, Dr Patries Herst, for at least 10 years; after which time the files will be destroyed. Only the official investigators and the research assistants will have access to this information.

After completion of the trial we will collate and analyse all the information from all participants of the study. This will tell us whether the manuka honey is better than bicarbonate soda mouth washes in treating radiation-induced mouth ulcers. If this is the case, we aim to conduct a larger multinational trial, and we would like to incorporate the data from this trial into this future study.

We anticipate that this will lead to a better and more standardized treatment for radiation-induced mouth ulcers in New Zealand.

Reporting:

- We will report on the results of this study in scientific reports and publications.
- You will be informed of the results of the study by a letter from the Principal Investigator, Dr Patries Herst

NO material will be published which can identify you personally.

6. Does the study have ethical approval?

Yes, the study has ethical approval from the Multi-Region Ethics Committee.

7. Do I have to participate in this study?

No, there is absolutely no requirement to participate in the study.

8. Can I withdraw from the study if I change my mind?

If you do agree to take part, you are free to withdraw from the study at anytime, without having to give a reason and this will in no way affect your future health care.

If you wish to withdraw please contact your doctor, the research assistant or the principal investigator, Dr Patries Herst (027-3483945) and advise them that you have decided to withdraw so that all information and data that have been collected about you will be entirely deleted from the database.

9. What if I have more questions or concerns about this study?

If you have any questions or concerns about your rights as a participant in this research study you can contact an independent health and disability advocate. This is a free NZ wide service provided under the Health and Disability Commissioner Act. Telephone 0800 555 050; Free Fax 0800 2787 7678 (0800 2 SUPPORT); Email: advocacy@hdc.org.nz. If there is a specific Māori issue/concern please contact Linda Grennell at 0800 37 77 661

If you have any questions or concerns about any aspects of this study, at any time, please call the principal investigator, Dr Ptries Herst (027-3483945).

APPENDIX D

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Te Whare Wānanga o Ōtāgo

October, 2008

University of Otago, Wellington

Honey for Mouth Ulcers during Radiation Therapy

INFORMED CONSENT

This form is to obtain your agreement to participate in our clinical trial which intends to find out whether New Zealand Manuka Honey decreases the extent of mouth ulcers during radiation therapy to the head and neck.

REQUEST FOR INTERPRETER

English	I wish to have an interpreter	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero	Ae	Kao
Cook Island	Ka inangaro au i tetahi tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai
Samoan	Ou te mana'o ia i ai se fa'amatala upu	Io	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania kin a gagana o na motu o te Pahefika	Io	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai

Informed Consent

- I have been given the opportunity to discuss my participation in this trial with family and whanau.
- I have had the opportunity to consider all the information presented and have had all my questions answered.
- I understand that my participation is completely voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care.

I would like to participate in this clinical trial and I give consent to participating in this study which includes:

1. Being randomized by computer to a honey arm and a control arm.
2. Following the guidelines of the honey arm and the control arm to the best of my abilities.
3. A physical examination by my doctor at the start of the trial.
4. Two blood tests at the start and after completion of the trial by a certified medical laboratory.
5. Weekly weight measurements.
6. Regular examinations of my mouth by the research assistant. These examinations will take place three times a week during radiation therapy treatment, 2 and 4 weeks after completion of treatment.
7. Filling in a quality of life questionnaire every two weeks until 4 weeks after completion of treatment.
8. Keeping a food/drink/drug diary in which I will record exactly what and how much food and fluids I have taken and how many and what type of pain killers or other drugs I have used.
9. Regular mini-tongue swabs, taken by the research assistant. These will be taken at the start of treatment, 3 weeks into treatment, at the end of treatment and 4 weeks after completion of treatment.
10. The use of my information as part of a future larger clinical trial.

Name:	
Signature:	
Date:	
Researchers	Dr Ptries Herst (ph 04-3855475 ext 4753; mobile 027-3483945) The Radiation Oncologist who is the local principal investigator

APPENDIX E

Mucositis scoring sheet

0= within normal limits or healed
 1= erythema
 2= patchy mucositis/ pseudomembranes
 3=confluent mucositis/ pseudomembranes
 4= necrosis

Anatomical Site	Areas at risk	Mucositis Scores 0-4						Total
		1	2	3	4	5	6	
Vermillion Lip (Upper)								
Vermillion Lip (Lower)								
Labial Mucosa (Upper)								
Labial Mucosa (Lower)								
Gingiva (Upper)								
Gingiva (Lower)								
Buccal Mucosa (Right)								
Buccal Mucosa (Left)								
Tongue (Ventral)								
Tongue (Dorsal)								
Palate (Soft)								
Palate (Hard)								
Floor								
Oropharynx								
Total Score								
Number of sites at risk								
Mean score								

Weight chart:

Dose (cGy)	Weight (Kg)
0	
1000	
2000	
3000	
4000	
5000	
6000	

Notes: