The Effects of Comvita Manuka Honey on Oral Mucositis in Patients treated with Radiation Therapy to the Head and Neck

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Principal Investigator
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Abstract

Mucositis is a common side effect of radiation therapy to the head and neck region and one that causes considerable discomfort for patients. Mucositis compromises patients’ ability to eat, drink and talk thus affecting patient health and quality of life. Currently there is no worldwide standard for the prevention or treatment of oral mucositis; care is limited to symptom control. Honey has anti-bacterial and potential anti-inflammatory properties and three trials overseas investigated its effect on radiation-induced oral mucositis. The three trials conducted in Malaysia, Iran and Egypt found that honey did reduce the incidence of severe mucositis in head and neck patients. This New Zealand mucositis trial aimed to verify the results from the three overseas trials by comparing the effects of manuka honey with current best practice on oral mucositis in head and neck patients.

This report analyses a sub-set of the patients recruited to the trial; those from the Wellington and Dunedin departments. A total of 14 patients were recruited to the trial from these departments, nine recruited to the honey arm and five to the control arm. Four honey patients withdrew from the trial due to issues with the honey application and one patient withdrew from the control arm. Honey arm patients were given manuka honey and instructed to swirl 20mL (amended to 10mL) around their oral cavity and then swallow three times a day, these patients also had access to the standard of care. The control arm patients were treated with the standard of care alone.

Patient assessment involved three times weekly mucositis scoring using the TROG multi-site mucositis scoring system, weekly weight and fortnightly quality of life assessment using a 65 question form adapted from the European organisation for Research and Treatment of Cancer questionnaires (EORTC QLQ-C30 and EORTC QLQ HN35). Patients were also asked to fill in food and drug diaries to assess changes in food intake and pain medication. Results showed that manuka honey was not well tolerated by our patient cohort. Patients complained of extreme nausea and stinging sensations in the oral cavity. The honey had to be diluted to be better tolerated (1:3 with another liquid). Contradictory to previous studies, preliminary analysis showed that manuka honey did not affect the extent of oral mucositis in the small cohort of New Zealand head and neck patients when taken in addition to current best practice.
Acknowledgements

The health and wellbeing of our patients is our number one priority, and to ensure we give them the best standard of care we need to practice evidence-based medicine and participate in clinical trials. I would like to acknowledge all the patients who participated in the New Zealand manuka honey trial. These patients were all undergoing intense cancer treatment but put time and energy into adhering to the trial requirements.

A big thank you to the staff at the Wellington Blood and Cancer Centre for supporting the trial and allowing me to combine the roles of research assistant and radiation therapist. Thank you to those who helped with the mucositis scoring and collection of the quality of life forms and food diaries. I would also like to acknowledge the Christchurch Oncology Department for allowing me time to complete this report.

The University of Otago Research Fund allowed the trial to go ahead financially and the Comvita Company supplied the manuka honey free of charge. Thank you.

My supportive family and friends deserve acknowledgement, thank you for the support, encouragement and for your proofreading!

Dr Patries Herst is the most enthusiastic scientist I have met and her passion for research is infectious. A huge thank you for being the driving force behind this trial and giving me the opportunity to get involved in research. I truly appreciate all your encouragement and advice.
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Chapter 1 INTRODUCTION

This research project describes a case series conducted at the Wellington Blood and Cancer Centre which investigated the effect of manuka honey on mouth ulcers in patients treated with radiation therapy for head and neck cancer.

1.1 Head and neck cancer

Cancer is a malignant disease which is characterised by a series of cellular and genetic changes that lead to abnormal cell proliferation with the potential to invade surrounding tissues and metastasize to distant locations. Cancer cells can originate from many areas of the body and cause symptoms specific to the region where the tumour manifests. The head and neck is an important region of the body because it is essential for many physiological functions and is critical for a person's appearance, expression and social interactions. Cancer within the head and neck region can cause structural deformities and disrupt the functions of this region which can lead to a significant decrease in patients’ quality of life (Bomford & Kunkler, 2003).

Figure 1. Diagram illustrating structures of the head and neck region
Due to the large number of structures present in the head and neck region there are many potential cancer sites including the lip, base of tongue, gum, floor of mouth, palate, parotid, tonsil, nasal cavity, para-nasal sinuses, oropharynx, nasopharynx, hypopharynx, larynx and thyroid gland.

Head and neck tumours vary not only by site but also by pathophysiology, biological behaviour and their sensitivity to treatment modalities. Squamous cell carcinoma (SCC) is the most common type of cancer in the head and neck region. It accounts for more than 90% of all malignant lesions in the mouth. The most common sites for oral SCC are the tongue and floor of mouth then at a lower frequency the soft palate, gingiva and buccal mucosa (Cabral et al., 2010).

Head and neck tumours can invade local structures, spread to lymph nodes and metastasise to other organs of the body. The lymph drainage of the head and neck region is complex and is categorised by levels (Appendix A). Due to the ability of tumours to readily metastasise via lymph, the assessment and treatment of the neck lymph nodes is of utmost importance in disease management (Rosenthal, 2009). The most common site of distant metastasis is the lungs but other sites include the mediastinal lymph nodes, liver, brain and bones (Washington & Leaver, 2006).

1.1.1 Incidence

The incidence of head and neck cancer varies around the world, however most authors report that head and neck cancers account for between three and five percent of all cancers (Yarbro et al., 2004). Head and neck cancer has been described as the sixth most common cancer worldwide and its incidence is increasing in most parts of the world (Evans et al., 2003).

Each year the New Zealand Ministry of Health (MOH) publishes a detailed report on the incidence of cancer; Cancer: New Registrations and Deaths. In 2007 the report showed there were 711 head and neck cancer registrations in New Zealand with 191 people dying of the disease. Head and neck cancer made up 3.6% of all cancers registered that year (NZ Health and Information Service, 2009).
Head and neck tumours are reported as being more common in males than females and are historically more common in older people although they are becoming increasingly common in younger people (Toner & O’Regan, 2009).

1.1.2 Predisposing factors
A number of predisposing factors for cancers of the head and neck region have been identified with alcohol and tobacco being the most common.

_Alcohol and tobacco_
Tobacco smoke contains more than 300 carcinogens that can damage DNA. Alcohol is an independent risk factor but also increases tobacco related carcinogenesis. The synergistic effect of alcohol and tobacco was described by Evans et al. (2003) as resulting from increased mucosal absorption of carcinogens (from both tobacco and alcohol), from the chronic inflammation and the increased solubility of carcinogens in alcohol compared to saliva. Alcohol independent of tobacco shows an increased risk of cancer especially in the oral cavity. Alcoholism may also lead to impaired metabolism resulting from liver dysfunction and nutritional deficiencies that may promote carcinogenesis (Evans et al., 2003).

_Environmental and occupational exposure_
Ultraviolet light exposure has been described as a common risk factor for head and neck cancer. Other environmental risk factors can relate to an individual’s occupation. Evans et al. (2003) highlighted that people involved in nickel refining, woodworking, metal work and work with textile fibres have an increased risk of head and neck cancer, as do car mechanics.

_Diet_
Dietary factors may also have an influence on the incidence of head and neck cancer as iron and vitamin A, C and E deficiencies have been linked to cancer. Nasopharyngeal cancer is also associated with the consumption of salted fish (Vokes et al., 1993).

_Viral infection_
Increasing evidence suggests that viruses contribute to the cause of head and neck cancer. The Human Papilloma Virus and Epstein-Barr Virus are associated with a specific type of head and neck cancer; nasopharyngeal cancer (Myers et al., 2003).
1.1.3 Symptoms
The symptoms of head and neck cancer vary with the location of the primary tumour and the stage of the cancer. Patients with early stage cancer frequently have only vague symptoms and minimal physical abnormalities. The vague symptoms include pain, ulcers that do not heal and hoarseness. Often early stage cancers of the oropharynx and hypopharynx do not produce any symptoms so are commonly diagnosed in later stages. Cancers in later stages have easily detectable signs and symptoms which include pain, airway obstruction, cranial neuropathies, trismus, dysphasia and decreased mobility of the tongue (Vokes et al., 1993).

1.1.4 Diagnosis
Disease diagnosis follows a number of procedures including a complete physical examination involving inspection of the oral mucosa, palpation of floor of mouth and all aspects of the tongue as well as thorough palpation of the neck. Further investigations may include examination with a flexible fibre-optic nasopharygoscope, radiologic evaluation to assess the extent of local and regional spread of the tumour and its depth of invasion. Biopsies are taken to define the primary tumour and identify possible sites of secondary tumours. Fine needle aspiration (FNA) biopsies are often done first and then excisional biopsies are used for further investigation (Vokes et al., 1993).

1.1.5 Staging
The TNM (tumour, node and metastasis) staging system is a commonly used system to stage head and neck cancers. The system integrates all the clinically available information to stage the tumour, nodes and distant metastases.

Table 1. Stage grouping of oral cancer (Evans et al., 2003)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1<em>N0<strong>M0</strong></em></td>
</tr>
<tr>
<td>II</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>III</td>
<td>T3N0M0</td>
</tr>
<tr>
<td></td>
<td>T3N1M0</td>
</tr>
<tr>
<td>IV</td>
<td>T1-3N2M0</td>
</tr>
<tr>
<td></td>
<td>Any T, N3, M0</td>
</tr>
<tr>
<td></td>
<td>Ant T, any N, M1</td>
</tr>
</tbody>
</table>

* *T1-T3 indicates the increasing size of the primary lesion; T1 – 2cm or less, T2 – 2-4cm, T3 – >4cm in greatest dimension. T4 indicates the tumour has infiltrated an adjacent structure. Tx indicates primary tumour cannot be assessed.

** The nodal staging is uniform for all sites. Nx indicates regional lymph nodes cannot be assessed, N0-3 describes progressive involvement of lymph nodes.

*** Mx indicates the presence of distant metastases cannot be assessed. M0 indicates no distant metastases, M1 indicates distant metastases are present.
The risk of distant metastasis correlates with nodal stage, the risk is less than 10 percent with N0 or N1. In patients with T4 lesions the presence of distant metastases in lungs, liver or bones should be ruled out before aggressive local or regional therapy is commenced.

1.1.6 Head and neck cancer sites

As outlined above there are many potential sites of head and neck cancer, this report later describes a trial in which patients had cancers of seven different sites (maxillary gingiva, tongue, tonsil, palate, nasal cavity, floor of mouth and Waldeyer's ring). Each of these sites has their own symptoms and preferred method of disease management:

*Maxillary gingiva* lesions often mimic common inflammatory lesions but are normally painless. Primary treatment is surgery with a radical neck dissection to treat metastatic lymph nodes. Radiotherapy is used as adjuvant post-operative treatment and chemotherapy is sometimes used for adjuvant or palliative treatment (Cabral et al., 2010).

*The tongue* is a large muscular organ (made of six paired muscles both intrinsic and extrinsic) which has a mobile anterior portion and a non-mobile portion (base of tongue) (Evans et al., 2003). Tongue tumours are often asymptomatic and can enlarge considerably before producing symptoms. They often present with a painless mass or ulcer that does not heal and often appear on the lateral borders of the tongue. Treatment can involve surgery (glossectomy) and/or radiation therapy. Post-operative radiation therapy can be used to target the primary site and nodal involvement. Lymph from the tongue drains to the sub-mental and sub-mandibular glands (Appendix A) on both sides so tumours of the tongue require bilateral neck treatment (Myers et al., 2003).

*Tonsils* are small structures that are part of the immune system. Tonsillar tumours commonly present in advanced stages as an ulcer or lump or with symptoms of pain, bleeding or difficulty swallowing. Primary treatment is commonly surgery depending on the stage of the tumour and the patient’s state of health. Radiation therapy and chemotherapy are also commonly used.

The palate or roof of mouth separates the mouth from the nasal cavity and consists of a bony hard palate and a muscular soft palate at the rear. Tumours of the hard palate are rare and
usually present with a painless mass which can spread into the nasal cavity or skull base (Myers et al., 2003). The lymph from the roof of mouth drains to the retropharyngeal and then deep cervical nodes (Evans et al., 2003).

The nasal cavity is divided in the midline by the nasal septum (cartilage and bone) and opens anteriorly through the nares and posteriorly into the nasopharynx. Tumours in this area are rare and have similar presenting symptoms to those of more common benign conditions. They have the propensity for early spread and involvement of surrounding critical structures which means that most patients present with advanced-stage disease. Lymph drainage from the nasal cavity is to the sub-mandibular nodes, upper jugular and retropharyngeal lymph nodes.

The floor of mouth (FOM) is a horseshoe-shaped space from the lower alveolar ridge to the under surface (ventral) of the tongue. The FOM contains openings for sub-mandibular and sub-lingual salivary gland ducts (Evans et al., 2003). Cancers arise on the anterior surface and can spread to the bone and ventral aspect of the tongue and also the sub-mandibular duct (Myers et al., 2003). Tumours are often asymptomatic and can arise in regions of leukoplakia or erythroplakia. Surgical resection and radiation therapy are often used in conjunction. Bite blocks are commonly used when treating with radiation therapy to spare the roof of mouth. The lymph drainage for the floor of mouth is to the sub-mental and sub-mandibular lymph nodes.

Waldeyer's ring or pharyngeal lymphoid ring is a ring of lymphoid tissue located in the pharynx at the back of the oral cavity. The ring consists of the pharyngeal tonsil, the tubal tonsil, the palatine tonsils and the lingual tonsils. The Waldeyer's ring is a potential site of lymphoma which is a lymphoproliferative disorder. Lymphoma often presents with painless lymphadenopathy but the masses can become more painful with rapid growth. Lymphomas are sensitive to chemotherapy and radiation therapy (Myers et al., 2003).
1.2 Head and neck cancer treatment

The control of the primary tumour and the regional nodal metastases is of upmost importance for treatment of head and neck cancers regardless of the type, site or stage of the disease. While achieving disease control to reduce mortality treatment also needs to reduce deformity and maintain tissue and organ function and minimise side effects.

A multidisciplinary approach is the best way of achieving cure and structure, function and aesthetic preservation. The multidisciplinary team consists of a large number of medical professionals including radiation oncologists, medical oncologists, dentists, maxillofacial prosthodontists, nutritionists, head and neck surgeons, neurosurgeons, plastic surgeons, oral surgeons, pathologists, oncology nurses, radiologists, social workers, radiation therapists, speech therapists and pain intervention teams. The specific team that is involved in each individual case depends on the treatment modality choice.

The main treatment options are surgery, chemotherapy, radiation therapy or a combination of these. The choice is based on factors relating to the disease such as the tumour type, site and stage and also patient related factors such as previous treatment, co-morbidities and the impact on quality of life (Figure 2.). The availability of treatment modalities and expertise of the medical team may also impact on the decision but with all these factors taken into account the decision is ultimately the patient’s.
Using a combination of the above treatment options allows the best preservation of cosmesis and function compared with a single treatment modality, for example the use of post-operative radiation therapy compared to radical surgery alone (Washington and Leaver, 1996). Early stage tumours can often be managed with a single modality but advanced tumours require multidisciplinary treatment.

1.2.1 Surgery

Surgical procedures are used in the diagnosis of the disease (excisional biopsies) as well as being part of the disease management plan. Evans et al. (2003) states that despite the advances in head and neck cancer management surgery remains the most dependable and effective method of eliminating gross malignant disease. Surgery is used as a curative modality where en-block resections are performed to remove the primary tumour and
involved neck lymph nodes. Elective neck dissections are also effective for disease control in patients with no neck nodes involved but there is potential for spread (Hosal et al., 2000). Depending on the amount of involved and normal surrounding tissue that needs to be removed reconstructive procedures can be carried out which may involve grafts. Surgical procedures are also used for palliative salvage therapy.

Surgery is beneficial for early stage cancers as it reduces the risk of salivary deficiencies often resulting from radiation therapy. A recent review by Gil & Fliss (2009) describes that surgical advances now allow minimally invasive treatment using reliable microscopic and endoscopic procedures. The advances in these surgical procedures have improved patients’ quality of life and prolonged survival.

1.2.2 Chemotherapy
Chemotherapy is a systemic cytotoxic treatment which causes a range of side effects throughout the body depending on the combination of drugs administered. Toxicities include renal impairment, hearing impairment, peripheral neuropathy and neutropenia. Due to these side effects and the fact that head and neck cancer patients often have a poor health (co-morbidities) and nutritional status the use of chemotherapy as a front-line modality has not been favourable (Washington & Leaver, 1996). In the past chemotherapy was used for patients with metastatic disease, patients who had locally recurrent disease and as a form of salvage therapy when surgery and radiation therapy were no longer options. Now chemotherapy is commonly used in conjunction with surgery and/or radiation therapy. The timing of chemotherapy delivery can be neo-adjuvant, adjuvant, concomitant or rapidly alternating (Evans et al., 2003). Chemotherapy is commonly used concomitantly with radiation therapy in patients with advanced disease. The chemotherapy agent (often Cisplatin) is used to increase the sensitivity of cancer cells to radiation. Cisplatin inhibits DNA synthesis by forming DNA cross-links and Cisplatin combinations have been shown to produce the highest overall survival and complete remission rates (Evans et al., 2003).

R-CHOP is a chemotherapy regime used in lymphoma patients. The combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone followed by involved field radiation therapy is effective with regard to progression free survival and overall survival (Pfreundschuh et al., 2006).
1.2.3 Radiation therapy

Radiation therapy (RT) uses ionising beams to eradicate tumour cells by damaging the cells’ deoxyribonucleic acid (DNA). The ionising radiation which is measured in absorbed dose (amount of ionising radiation energy absorbed per unit mass of tissue, Gray Gy) initiates a chain of events when it enters tissue. First the radiation ionises water molecules to produce ions and high energy electrons which cause a cascade of further ionisation events. As the electrons lose their energy they are captured by molecules in the cell (mainly water molecules) to produce free radicals (reactive oxygen species ROS) such as superoxide, hydrogen peroxide and free hydroxyl radicals. These metabolites damage chemical bonds in the cell’s macromolecules, the most important in terms of cell death is DNA damage. DNA damage includes single stranded breaks (SSBs), double stranded breaks (DSBs), base damage (BD) and strand cross-linking (CL). SSBs, BD and CL are relatively easy and quick to repair successfully but DSB repair is more difficult due to the lack of a complimentary undamaged template to direct the repair process. The irreparable breaks lead to chromosome damage and damage to the cells mitotic apparatus resulting in mitotic catastrophe when the cell attempts to divide (Joiner & van der Kogel, 2009). Damaged cells can also die by apoptosis but this is less frequent than the mitotic death (Myers et al., 2003).

RT can be delivered in the form of external beam or brachytherapy, external beam being more common for head and neck cancers. RT has been used in combination with surgery since the 1920s (Evans et al., 2003). RT is used post-operatively when there have been adverse pathologic features such as inadequate margins, microscopic nodal disease or perineural invasion. The majority of head and neck patients will receive radiation therapy as part of their treatment.

Radiation therapy is customised for each individual patient and there is a variety of tools and techniques used in designing a treatment plan. Proton beams of 6 or 10 megavolt (MV) energy are delivered by a linear accelerator (LINAC) and are commonly used to treat head and neck patients. The beam energy determines the depth of penetration of the beams; the higher the energy the more penetrating the beam. Beam design depends on the isodose distribution that is required to encompass the target volume (the depth of the tumour and the areas of potential spread).
Recent developments

Advances in technology in both imaging and treatment in the past decade have seen a significant improvement in loco-regional control and disease-free survival. The significant improvements in imaging (CT, PET and MRI) and the increased accuracy of three-dimensional conformal treatment and on-treatment imaging allow higher prescribed doses to be delivered to the tumour or tumour bed and lower doses to the surrounding healthy tissue minimising side effects. Intensity modulated radiation therapy (IMRT) uses computer-assisted multi-leaf collimators with real-time portal imaging to deliver multiple beams of differential intensity with minimal human intervention. Increased accuracy of imaged guided radiation therapy (IGRT) allows for tighter margins, limiting dose to adjacent healthy tissue.

Radiation therapy delivery

A radical course of radiation therapy is normally given as a prescribed number of fractions delivered daily Monday to Friday over a period of three to seven weeks. The fractionation increases the differential effect of radiation on tumour compared with normal tissues. Conventional fractionation regimes use 1.8-2Gy per fraction but hypo- and hyper-fractionation regimes exist. A recently published paper (Rusthoven et al., 2008) reports that altered fractionation regimes, namely hyper-fractionation and accelerated radiation therapy have been associated with improved loco-regional control and disease-free survival.

The accuracy of radiation treatment delivery depends on the reproducibility of patient set-ups. This is an important factor when considering the number of critical structures in close proximity to the treatment area. Most oncology departments use masks to stabilise patients during the CT planning scan and treatment delivery. Generally patients are positioned supine with their neck extended and shoulders displaced inferiorly to allow better access to the lymph nodes of the neck without treating through the shoulders. Mouth-bites or tongue depressors may also be used to displace the tongue or palate from the treatment volume. Often curative plans use a ‘shrinking field’ technique in which the primary site receives the highest dose and the peripheral areas at risk for microscopic tumour spread receive a lower dose.

Radiation therapy is often used with concurrent systemic therapy to improve loco-regional control and overall survival in patients with more advanced disease (Rusthoven et al., 2008).
Combining radiation with chemotherapy allows improved tumour control, organ preservation and increased survival rates but it has been recently reported that with longer patient follow-up there is evidence emerging that the survival improvements may be at the expense of increased late toxicity (fibrosis and dysphagia leading to feeding tube dependency) (Myers et al., 2003).

1.3 Radiation-induced side effects

Radiation is unable to distinguish between tumour cells and normal cells. Although normal cells are better able to minimise free radical damage and are able to repair their DSBs more efficiently RT leads to acute and chronic side effects (Joiner & van der Kogel, 2009).

The cells that are in the process of dividing are particularly sensitive to radiation so cell populations with high division rates are more quickly affected by radiation. Tissues with high division rates in the head and neck region include mucosa which lines the oral cavity and throat, the salivary glands and the taste buds. Damage to these structures results in the more common side effects experienced by patients.

RT to the head and neck region puts a number of organs at risk (Figure 1.). Some sensitive head and neck structures have relatively low tolerance doses and excess dose to these structures may result in chronic side effects for the patient. These structures are dose-limiting and include the oral cavity (mucositis), spinal cord (myelopathy), lens of eyes (cataracts), brain (necrosis), retina (blindness), ear (deafness) and thyroid and pituitary glands (hormonal imbalance). Side effects such as severe mucositis and oral fungal infection (candidiasis) disrupt the function and integrity of the mouth.

Side effects can be acute or chronic depending on the total dose a specific tissue receives over the course of treatment (Table 2.). The severity of radiation induced side effects depends upon treatment factors (total dose, the size of the fields and the specific site of treatment) and patient related factors (alcohol and tobacco use and increasing age). The use of concomitant chemotherapy (described above) increases the risk of serious side effects (Trotti, 2000).
Table 2. Acute and chronic radiation-induced side effects in head and neck cancer patients (adapted from Chambers et al., 2004)

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral mucositis</td>
<td>Mucosal fibrosis and atrophy</td>
</tr>
<tr>
<td>Infection (fungal, bacterial)</td>
<td>Xerostomia</td>
</tr>
<tr>
<td>Salivary gland dysfunction</td>
<td>Dental caries</td>
</tr>
<tr>
<td>(Sialadenitis, Xerostomia)</td>
<td>Infections (fungal, bacterial, viral)</td>
</tr>
<tr>
<td>Taste dysfunction</td>
<td>Soft tissue necrosis</td>
</tr>
<tr>
<td></td>
<td>Osteoradionecrosis</td>
</tr>
<tr>
<td></td>
<td>Taste dysfunction (dysgeusia, ageusia)</td>
</tr>
<tr>
<td></td>
<td>Muscular/cutaneous fibrosis</td>
</tr>
<tr>
<td></td>
<td>Maturational disturbances</td>
</tr>
</tbody>
</table>

1.3.1 Mucositis

Mucosa or mucous membrane lines all the body cavities that have direct or indirect contact with the external environment (Yarbro et al., 2004) and it serves as an important protective mechanism for deeper organs and tissues against microorganisms (Shih et al., 2003).

The oral mucosa consists of a smooth layer of epithelial cells (stratified squamous) overlying lamina propria which consists of fibroblasts and connective tissue, small blood vessels (capillaries), inflammatory cells (macrophages) and extracellular matrix (ECM) (Shih et al., 2003).

There are slight differences in the oral cavity mucosa. The lining mucosa is the most abundant type and is located on the inner aspects of the cheeks and lips, the ventral tongue and soft palate. This mucosa type is distributed over loose connective tissue and consists of non-keratinizing squamous epithelium and is particularly susceptible to trauma. The other type of mucosa is known as specialized mucosa and is keratinised. This type is found on the dorsal aspect of the tongue and consists of numerous papillae that contain sensory nerve endings for taste. These two different types of mucosa may react differently to radiation trauma.

Mucositis is the inflammation and ulceration of the mucosal membranes. Oral mucositis is the most common side effect of radiation therapy to the head and neck region and it has been used to guide therapy since the founding of radiation therapy. Despite increased awareness in recent times, there is a higher frequency of mucositis due to the use of more intensive altered
radiation fractionation and concurrent chemotherapy regimens. Mucositis represents a significant clinical and economic burden in oncology (Gibson et al., 2008).

The epithelial cells of the mucosa are particularly sensitive to radiation and due to their high turnover rate (life span of three to five days) will show radiation damage within a few weeks of treatment. When exposed to radiation the epithelial cells become inflamed and die and then they are sloughed off. There are large numbers of stem cells in the mucosa that are able to differentiate and replace the lost cells. Confluent mucositis develops when the cell death exceeds the cell renewing process i.e. there is inadequate replacement of the lost cells (Joiner & van der Kogel, 2009).

Mucositis research over the last decade has lead to the development of a five phase model of mucositis caused by chemotherapy and/or radiation therapy (Gibson et al., 2008). These stages describe the sequential interaction of cells, cytokines and oral microflora and demonstrate that mucositis is a complex process and not just a result of direct clonogenic cell death of epithelial stem cells (see Figure 3.).

![Diagram of mucositis pathophysiology](image)

**Figure 3.** Diagram of mucositis pathophysiology (Gibson et al., 2008) (see text for an explanation of the different stages)

**Initiation** involves the simultaneous effects of DNA and non-DNA damage within epithelial and sub-mucosal cells and the generation of reactive oxygen species (ROS).
**Up-regulation and message generation.** In the next stage the DNA strands break and the ROS activate multiple transcription factors. A series of events leads to cell cycle arrest, DNA repair or apoptosis. 

**Signalling and amplification** follows where pro-inflammatory cytokines (interleukin (IL)-1 and IL-6) and tumour necrosis factor (TNF-α) accumulate and target the tissues of the sub-mucosa causing a positive feedback signal to amplify the reaction. 

**Ulceration** (most clinically significant stage) occurs when mucosal integrity is lost and lesions develop which are vulnerable to superficial bacterial colonisation. Bacterial cell wall products induce immune cells to produce cytokines leading to further inflammation and apoptosis. 

**Healing** generally only occurs once treatment has ceased. This stage involves epithelial cell migration, proliferation and differentiation of healing tissue. Integrity of the mucosa is restored.

Other authors have described a similar process of mucositis with slight variations in the descriptions of events at each particular phase (Biron et al., 2000). Sonis (1998) and Shih et al. (2003) described the process as a four phase process; inflammatory, epithelial, ulcerative/bacterial and healing phases.

The duration of mucositis is proportional to the degree of mucosal stem cell depletion; it can take weeks or months to heal depending on stem cell recovery. Excessive stem cell depletion may result in chronic open wounds known as soft tissue necrosis. Other late effects include mucosal scarring and loss of mucosal compliance contributing to chronic dysphagia (Rosenthal & Trotti, 2009).

**Risk of developing mucositis**

Not all patients are at equal risk of developing mucositis. The incidence and severity of mucositis varies depending on the type of cancer, its management and patient related factors (Barasch & Peterson, 2003). Some of these individual and treatment related factors are listed in Table 3.
Table 3. Risk factors associated with developing severe oral mucositis

<table>
<thead>
<tr>
<th>Individual factors</th>
<th>Treatment related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Dose</td>
</tr>
<tr>
<td>Gender</td>
<td>Specific location</td>
</tr>
<tr>
<td>Smoking</td>
<td>Volume mucosa (head and neck) irradiated</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>Fractionation</td>
</tr>
<tr>
<td>Nutritional status</td>
<td>Energy</td>
</tr>
<tr>
<td>Co-existing disease, infection</td>
<td>Beam arrangement</td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>Previous irradiation</td>
</tr>
<tr>
<td>Tumour site</td>
<td>Surgery</td>
</tr>
<tr>
<td>Oral health</td>
<td>Concurrent chemotherapy</td>
</tr>
<tr>
<td>Normalcy of saliva</td>
<td></td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td></td>
</tr>
</tbody>
</table>

The tissue of younger patients may heal faster than that of older patients. Gender affects the rate of wound healing (Robson et al., 2009) so may affect rate of wound development (mucositis). Alcohol and tobacco use increase the susceptibility of mucositis by contributing to the inflammatory process. Individuals with better nutrition are likely to ingest more protein, vitamins and anti-oxidants which aid the healing process. Co-morbidities or infection can increase the risk of mucositis by delaying the healing process (vascular changes). The tumour site influences the risk of mucositis as different tissues have slightly different sensitivities as well as different levels of exposure to mechanical and chemical trauma. Mucosa that is adjacent to metallic fillings is at greater risk because of increased radiation scatter from the filling (Shih et al., 2003). Poor oral health increases the risk of developing severe mucositis and associated infection. The normalcy of saliva affects the development of mucositis and may be linked to increased infection or dental problems. In addition some individuals may be more genetically predisposed to developing mucositis.

Treatment related factors include the total dose delivered and the fractionation regime (higher dose fractionation regimes lead to more severe acute side effects). The specific location of the tumour, the beam arrangement and the volume of mucosa that is irradiated affects patients’ risk of mucositis. Areas that have had previous irradiation have already suffered damage, the sub-lethal damage to the DNA decreases the ability of tissues to heal. Prior surgery means the tissue has already undergone a huge healing process and grafted areas may contain tissue that is more or less resistant to radiation compared to normal mucosal tissue (e.g. ulnar graft).
Chemotherapy agents have differing mucosal toxicity and as described above some act synergistically with radiation (Gibson et al., 2008). Chemotherapy and RT affect the oral mucosa differently and cause mucositis via different processes. All oral mucosa is susceptible to radiation-induced mucositis but only the movable mucosa develops chemotherapy-induced injury. Chemoradiation patients often develop mucositis earlier and to a more severe degree.

Understanding the different factors that affect the incidence of mucositis can help determine high risk patients and enable healthcare providers to initiate prophylactic measures to minimize the incidence and severity of oral mucositis.
Figure 4. Diagram showing the synergistic effect of chemotherapy and radiation therapy in the oral cavity
Grading of oral mucositis

A number of systems are used to grade the severity of mucositis. The World Health Organisation (WHO), Radiation Therapy Oncology Group (RTOG) and the National Cancer Institute Common Toxicity Criteria (NCI-CTC) all use scoring systems from grade one to four (increasing grade with increasing mucositis severity). The NCI system has separate scores for appearance and function whereas the WHO score combines both elements into a single score. The Trans-Tasman Radiation Oncology Group (TROG) also designed a system with five grades (0-4) based on the appearance of the mucosa (Table 4.). It is this system that is used in the New Zealand mucositis trial.

Table 4. The TROG mucositis scoring system

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Within normal limits or healed</td>
</tr>
<tr>
<td>1</td>
<td>Erythema (may experience mild pain not requiring analgesics)</td>
</tr>
<tr>
<td>2</td>
<td>Patchy mucositis/pseudomembranes which may produce an inflammatory discharge (may experience moderate pain requiring analgesia)</td>
</tr>
<tr>
<td>3</td>
<td>Confluent mucositis/pseudomembranes (may include severe pain requiring opioid analgesics)</td>
</tr>
<tr>
<td>4</td>
<td>Ulceration, haemorrhage or necrosis</td>
</tr>
</tbody>
</table>

The oral mucositis assessment scale (OMAS) is another scoring system that was developed in 1999 and was used in one of the overseas mucositis trials described below. This system only has grades from 0 to 3 based on the appearance and extent of redness and ulceration in the mouth.

1.3.2 Impact of mucositis

Mucositis causes a number of effects which contribute to a reduction in patients’ quality of life during radiation treatment.

Oral pain

Mucositis-associated oral pain results from the loss of the epithelial lining, ulceration and the associated oedema. Also during the inflammatory response neurotransmitters are released which stimulate pain receptors (Yarbro et al., 2004). The pain is often poorly controlled with standard analgesics or topical anaesthetics. When the pharyngeal mucosa is affected the pain and burning sensations are more intense when the patient is swallowing or speaking.
Weight loss/malnutrition

Head and neck cancer patients commonly have poor nutritional statues prior to treatment which diminishes further through a number of mucositis related side effects such as dysphagia and the loss of taste and saliva. Low mood also decreases appetite (Mueller et al., 1995). Inadequate nutrition leads to weight loss and the possible requirement of feeding tube insertion. Some patients’ ability to talk can be affected by mucositis and many report sleep and mood disturbances. Decreased energy levels result directly from the radiation therapy but also from the lack of nutrition and from the negative mood.

Xerostomia

The three pairs of major salivary glands in the head and neck region; the parotid, sub-mandibular and sub-lingual glands are responsible for 90% of all salivary secretions which are normally in excess of one litre per day (Chambers et al., 2004). Irradiation of these salivary glands during treatment of head and neck cancer leads to a decrease in the amount and quality of saliva produced causing patients to suffer dryness of the mouth. Dryness of the mouth is known as xerostomia and causes oral discomfort, altered taste, nutritional impairment (difficulty with mastication and swallowing) and dental decay. Xerostomia can be temporary or permanent depending on the total dose the salivary glands receive, it has been reported at as little as 6Gy and can be permanent at greater than 30Gy. Xerostomia ranges from slight dryness, moderate dryness (poor response on stimulation) to complete dryness of the mouth (no response on stimulation) depending on the volume and dose of the glands irradiated. Xerostomia may also be caused or exacerbated by the concomitant or sequential use of chemotherapy agents (Chambers et al., 2004). Different RT fractionation regimes may also impact on the degree of xerostomia; patients treated with continuous hyperfractionated accelerated radiotherapy (CHART) experienced less dryness of the mouth compared to conventional fractionation regimes (Leslie & Dische, 1991).

Rosenthal et al. (2008) reported that the problem of excessive, viscid mucus in the mouth and throat is a burdensome symptom for many patients although it is rarely reported. This mucous may be caused by changes in saliva composition (pH level, electrolyte and immunoglobulin (Ig) content) or be a product of mucositis or could result from a combination of these two factors (Chambers et al., 2004).
Infection

Damaged mucosal tissues can easily develop infections caused by microorganisms including fungi, viruses (herpes) and a wide variety of bacteria due to the loss of normal tissue responses. The loss of the normal immune responses is due to decreased saliva volume, alterations in saliva quality and decreased levels of immunity. The reduction in IgA, IgM and IgG causes a change in the oral microbial flora which leads to a decrease in oral hygiene and increased susceptibility to opportunistic infections when pathogens colonize the inflamed mucosal surfaces (Yarbro et al., 2004). Some patients are at risk of developing life threatening infection (septicaemia) (Worthington et al., 2009).

An infection in a region of mucositis will exacerbate the existing mucositis making the patient’s condition more severe and prolonging the duration of mucositis. An example of this is a bacterial infection where the bacteria release endotoxins which are mediators of the inflammatory process in the oral mucosa (Yarbro et al., 2004).

Candidiasis infection (Candida albicans) is a common yeast infection in head and neck patients. It is commonly known as oral thrush, is painful and presents with erythema or discrete white plaques so can often be confused with mucositis. Treatment involves the use of antifungal drugs such as the topical application of nystatin (Silverman, 1999).

Taste changes

Taste buds line the tongue and oral cavity mainly in the circumvallate and fungiform papillae and are sensitive to radiation (Silverman, 1999). They are radiosensitive due to their high cell turnover and are in the radiation fields for most treatments. It is the microvilli and outer surfaces of the taste buds that suffer radiation damage causing changes in taste sensations (Yarbro et al., 2004). The incidence of these changes is dose dependant and commonly noticed above 10Gy (one week of treatment). Partial loss of taste is known as hypogeusia and complete loss ageusia. Distorted taste sensation is known as dysgeusia and it has been reported that the sweet taste is affected more than the salty taste. Taste changes are probably linked with saliva changes as Silverman (1991) described that saliva probably has a modulating effect on the acuity of some tastes (sour, bitter, salt, sweet) through biochemical interactions and saliva probably provides an ionic environment in signal transduction.
The duration of taste changes varies between patients; recovery may occur within two to four months after treatment but some patients may experience a permanent decrease in taste perception (Yarbro et al., 2004). Taste is closely linked to appetite so reduction or alteration in taste perception affects nutritional status and quality of life. The olfactory senses are not often affected so patients should smell food to partially counteract the loss of taste.

_**Nausea and vomiting**_

In head and neck patients nausea and vomiting generally only occur in those receiving chemotherapy. These are two of the most feared toxicities and usually happen rapidly after chemotherapy delivery. Anticipatory nausea and vomiting is a conditioned response that occurs before chemotherapy administration due to inadequately controlled emesis from a previous treatment. Nausea and the taste changes impact on patients’ ability to tolerate certain foods (honey).

_**Hospitalisation and treatment delays**_

Patients with severe mucositis have increased resource requirements and are often admitted to hospital causing a substantial burden on the health care system (Gibson et al., 2008). In severe cases of mucositis treatment (chemotherapy and radiation therapy) may have to be delayed to allow for healing. Treatment delays have the potential to compromise local tumour control through tumour cell repopulation and therefore they risk patient survival. The planned radiation dose may have to be decreased which also leads to reduced survival. Duncan and colleagues (1996) found an increase in risk of relapse and cancer-related mortality in laryngeal cancer patients following a gap in radiation treatment. They suggest that if treatment is prolonged (there is a gap longer than four days) additional radiation dose should be prescribed to compensate for increased cell proliferation (Duncan et al., 1996). The increase in prescribed total dose is likely to lead to more severe acute side effects and a greater probability of late tissue complications for the patient.
1.4 Management of head and neck patients

Oral mucositis is the most prevalent side effect of radiation treatment to the head and neck area which severely affects patient quality of life. Management of oral mucositis is critical to maintain the patients food pathway, avoid interruption in the delivery of radiation treatment and to avoid hospitalisation and the need for parenteral or tube feeding.

Currently there is no standard treatment for oral mucositis in head and neck patients worldwide and there is a lack of clinical data to direct patient care. The Food and Drug Administration (FDA) have no approved intervention for prevention of radiation induced mucositis (Rosenthal & Trotti, 2009). Current management of oral mucositis is limited to symptom control including pain relief and maintenance of good oral hygiene.

1.4.1 Oral hygiene

Patients require education about the use of mouthwashes to keep the oral cavity clean and about avoiding irritants including spicy and course foods, smoking and alcohol (including mouthwashes that contain alcohol). Teeth and gums should be cleaned frequently with soft toothbrushes and fluoride toothpaste (Biron et al., 2000). Oral mouthwashes currently advocated are salt and baking soda, hydrogen peroxide or benzydamine hydrochloride (difflam). Dodd et al. (2003) reported that baking soda is effective in reducing the pain of radiation induced mucositis and can help slough off cellular debris in the oral cavity. Regular review of the oral cavity should be conducted to highlight any areas of concern. A study investigating an antimicrobial intervention suggested that emphasis of strict oral hygiene may significantly reduce the incidence of mucositis (Trotti et al., 2004).

1.4.2 Dental management

Head and neck patients are referred for dental assessments prior to radiation treatment for prophylactic elimination of teeth at risk of decay with the aim of decreasing oral complications (Ang & Garden, 2002).

1.4.3 Pain relief

Topical anaesthetics and mixtures containing anaesthetics allow a temporary reduction in oral cavity pain, however the pain relief action of these agents also causes a reduction in patients’
taste and thermal perception. After applying topical anaesthetic patients are at risk of burning or biting parts of their oral cavity which can lead to further ulceration and pain. Bongela and xylocaine viscous are two commonly used topical anaesthetics. Yarbro et al. (2004) described the use of oral bandages and gels that congeal in the oral cavity to form a layer on the ulcerated surfaces providing pain relief.

Many patients experience mucositis that is severe enough to require systemic analgesia. There are a number of medications (opioid or non-opioid) available but carry side effects (nausea, dizziness and constipation). Most of these medications are taken orally but can be given intravenously (IV). Common pain relief includes paracetamol (non-opioid drug), ibuprofen (non-steroidal anti-inflammatory drug), codeine, oxycodone, morphine (opioid drugs) and amitriptyline (a tricyclic antidepressant).

### 1.4.4 Nutritional management

The risk of weight loss is high for head and neck patients so nutritional support is imperative. A dietician makes regular assessments and gives advice about diet modification including texture changes, high calorie, high protein intake and nutritional supplements (Fortisip/Ensure plus).

**Enteral feeding**

Used to enable patients to meet nutritional requirements when they are no longer able to ingest via their oral cavity.

- Nasogastric (NG) feeding is generally a short term solution (less than four weeks) in which fine bore tubes are placed through the patient’s nasal cavity, down their throat and into their stomach (Evans et al., 2003).

- Gastrostomy feeding is a longer term approach (used for periods longer than four weeks) which is more cosmetically acceptable to patients as they can be covered when not being used and they avoid some of the complications that may arise with the long-term use of NG tubes. The tubes for gastrostomy feeding are inserted via endoscopy so are called percutaneous endoscopic gastrostomies (PEG). PEGs are retained in the stomach through the use of a flange or balloon and occasionally have complications (infection, leakage or bleeding) (Evans et al., 2003).
1.4.5 Infection

Infections are managed with antibiotic and antifungal ointments or lozenges, regular cleaning and salt water rinses. Some radiation therapy departments use antifungal medication prophylactically; patients are prescribed antifungal medication when treatment commences. Antibiotic lozenges may be used to try and prevent bacterial colonisation and reduce inflammation of damaged mucosa (Sutherland & Browman, 2001).

1.4.6 Specific treatment of oral mucositis

Identifying agents which can be used to prevent or treat radiation induced mucositis is a primary concern for researchers and clinicians. Recent research has focussed on therapies that interfere with the causative factors of mucositis with the aim of diminishing its incidence and severity. These therapies protect normal mucosa through direct radioprotection or manipulation of growth factors and cytokines that are involved in mucosal repopulation (Garden, 2003). Recent studies have shown that amifostine is effective in reducing mucositis by protecting healthy tissue from radiation (Antonadou et al., 2002). Other therapies attempt to inhibit inflammation or infection and promote healing (Garden, 2003). One report describes the use of lasers to decrease mucositis through increased cell division and synthesis of myofibroblasts (Biron et al., 2000).

Humidification

Humidifiers can reduce the incidence and severity of mucositis by keeping the mucosa moist (37°, 100% humidity), an extension of the general principal of moist wound care in wound management (Morton et al., 2008). A randomised phase II clinical trial is currently being conducted in New Zealand and Australia through the trans-Tasman Radiation Oncology Group (TROG) investigating the effectiveness of humidification compared to the standard of care.

Benzydamide hydrochloride

Difflam is a non-steroidal drug commonly used to treat the symptoms of mucositis through anti-inflammatory mechanisms (Epstein et al., 2001). It has been described as the most successful mouthwash to date and is recommended by the American Cancer Society.

Research has more recently focussed on plants as sources of biologically active compounds to combat treatment reactions. Extracts such as chamomile and aloe vera have been trialled
in the past with mixed outcomes. An ideal oral care solution or product for head and neck cancer patients needs to reduce oral flora, have an acceptable taste, reduce oral pH, assist in re-epithelialisation of the mucosa and be non-toxic and non-irritating to the oral tissue.
1.5 Honey

1.5.1 Composition
Honey is a saturated solution of sugar that is made from nectar collected from flowers by bees of the genera *Apis* and *Meliponinae* (Namias, 2003). The nectar is mixed with enzymes in the beehives and is placed in wax cells (honeycombs). A ripening process follows where the enzymes (invertase) convert the sucrose into glucose and fructose and the overall water content is reduced. As well as sugars honey contains small quantities of enzymes, amino acids, vitamins, minerals (calcium, iron, zinc, potassium, phosphorous, magnesium, selenium, chromium, manganese) and organic acids. The exact composition of a specific honey is variable and depends on the geographical and floral source of the nectar (Robson et al., 2009).

1.5.2 Medical purposes
Honey had been used for medical purposes since ancient Egyptian civilisation and has been referenced in ancient medical writings from Greece and India. It is considered the oldest wound dressing. The use of honey in medicine declined in the 20th Century with the discovery of antibiotics but as some bacteria became antibiotic resistant honey has been reconsidered as an attractive alternative (Robson et al., 2009). In recent times honey has been used to treat burns, surgical wounds, gastric and diabetic ulcers as well as many skin conditions including eczema, psoriasis, ringworm, athletes foot and acne (Molan, 2006).

1.5.3 Antibacterial properties
There is a large body of evidence demonstrating the antibiotic nature of honey. Robson et al. (2009) assessed 105 patients with open wounds in a randomised clinical trial to compare conventional dressings with a honey dressing. The trial found that the healing times for those patients with the honey dressing were reduced compared to those with conventional treatment. The reduction in the healing times was thought to be due to the anti-bacterial and anti-inflammatory action of the honey.

The antibacterial property of honey is due to its acidic nature (pH ranging from 3.2 to 4.5 (Bardy et al., 2007)), its high sugar content and thus low water activity (honey is able to draw water out of bacteria) and the production of hydrogen peroxide. Manuka honey is a specific
type of honey derived from the manuka tree (*Leptospermum scoparium*), a New Zealand indigenous plant (Maddocks-Jennings et al., 2009). This type of honey has an additional antibacterial component previously referred to as the unique manuka factor (UMF), now known to be methylglyoxal (MGO) (Stephens, 2009). Several studies have reported that manuka honey has a significantly higher level of antibacterial activity compared to other honeys. Mavric et al. (2008) found this activity originates from MGO.

### 1.5.4 Physical barrier

Honey can prevent infection by forming a physical protective barrier. The barrier stops tissue oxygenation by sealing damaged tissue from air and it allows a moist healing environment for new cells to grow. Honey also controls odour by destroying the bacteria that cause it. There have been reports of reductions in scar formation in areas applied with honey (Al-Waili & Saloom, 1999).

### 1.5.5 Immunomodulatory function

Molan (2001) reported that honey has an anti-inflammatory effect which has been demonstrated in histological studies of wounds in animals where there was no infection involved. Honey contains phenolic compounds which have anti-oxidant and free radical scavenging ability. Free radicals cause damage and prevent healing in areas of prolonged inflammation. Molan described the way honey has visibly reduced inflammation and oedema surrounding wounds and that pain (a feature of inflammation) is reduced with the application of honey.

Recent research supported an anti-inflammatory activity of certain honeys in acute inflammation (Van der Berg et al., 2008: Leong et al., manuscript in preparation). Tonks et al. (2003) reported that honey (three different varieties; manuka, pasture and jelly bush) modulates the action of monocytic cells. Honey affects the release of anti-inflammatory agents and growth factors from these cells (Tonks et al., 2003).

The anti-inflammatory properties of manuka honey may be relevant to the management of radiation-induced oral mucositis (decrease the incidence and/or severity). With respect to this three small clinical trials have shown that different types of honey were able to decrease the extent of radiation induced oral mucositis by at least 50%. These trials had very similar
methodology and were conducted in Malaysia (Biswal et al., 2003), Iran (Motallebnejed et al., 2008) and Egypt (Rashad et al., 2008).

All three trials used 20mL of undiluted honey three times a day as a topical application in 20 patients with an additional 20 patients receiving the standard care. Biswal et al. (2003) and Rashad et al. (2008) excluded chemoradiation patients and used a single site scoring system to measure the extent of mucositis. In the trial by Motallebnejad et al. (2008) a multiple site scoring system (OMAS) was used where the oral cavity was divided into nine areas and each area was scored separately. Standard care differed between the trials with control patients in the trial by Biswal et al. (2003) taking water, those in the trial by Motallebnejad et al. (2008) rinsing with saline solutions and control patients in the trial by Rashad et al. (2008) having access to analgesics, benzydamide hydrochloride, antibiotics and antifungal medication if necessary. The three trials are described in Appendix B.
1.6 **Aim and objectives of the study**

The three previous honey studies showed that different types of honey significantly reduced the extent of severe oral mucositis in their patient cohorts. The trials did however recommend that further multi-centre randomised trials were conducted to validate their findings.

New Zealand manuka honey produced by Comvita LTD is well known for its strong antibacterial activity based on its high MGO content. We hypothesized that Comvita manuka honey would be superior to best practice of care in decreasing radiation induced oral mucositis in head and neck patients in the New Zealand setting. The New Zealand manuka honey trial was designed to investigate the effects of manuka honey on radiation induced mucositis to validate the findings of the three overseas trials.

**1.6.1 Aim**

To determine whether medical grade manuka honey from Comvita LTD is superior to standard best practice in decreasing the extent of radiation-induced oral mucositis in a small cohort of New Zealand head and neck cancer patients.

The trial aimed to address the hypothesis by following head and neck cancer patients through their radiation treatment and comparing the effects of those receiving the department standard of care or manuka honey intervention.

**1.6.2 Objectives**

The primary objective of the trial was to determine the difference in the total mean mucositis scores for the treatment and control groups.

The secondary objectives were to determine the differences between the treatment and control groups with regard to:

- Percent of patients developing oral mucositis
- Time of onset and dose necessary for developing mucositis
- Weight loss/nutritional intake
- Quality of life (QoL)
• Changes in the oral microflora composition.

1.6.3 Study design
The trial was originally designed to be a stage II randomised single blinded study in which the research assistant responsible for patient assessment would not know which arm the patients were randomized to (control or treatment arm). Early on a number of protocol amendments were made (described in the methodology) including the removal of blinding and a change in the volume and application of the honey. It was originally calculated the trial would require a total of 120 patients in order to obtain statistical power. Preliminary analysis proved that it was not possible to obtain the required patient numbers and the required level of compliance. The most important amendment was a down-staging of the trial to a stage I clinical trial due to the adverse effects experienced by the patients on the honey arm.
Chapter 2 METHODOLOGY

2.1 Survey of New Zealand Oncology Departments

Currently there is no standard protocol for the care of head and neck cancer patients treated with radiation therapy in New Zealand. All eight radiotherapy departments (two private and six public departments) have slightly different recommendations and instructions that are given to patients to manage side effects including oral mucositis. Review of the current practice in the public departments was conducted to highlight the common recommendations between these centres. A staff member (the clinical tutor or head of department) from each of the six public departments was contacted via email and questioned about their department’s current practice for the care of head and neck patients. Each centre responded with a brief description of their current care which is reported in the results section.

2.2 Oral Mucositis Trial

This research study was set up as a single blinded multi-centre stage II clinical trial to determine the effect of Comvita manuka honey on the extent of oral mucositis in head and neck cancer patients. Only data from 13 patients from Wellington Regional Hospital and one patient from Dunedin Regional Hospital has been analysed in this thesis.

2.2.1 Participants

Participant numbers. This thesis analyses the results of 14 patients entered into the larger multi-centre clinical trial. From March 2009 to December 2009 13 patients who received radiation treatment at the Wellington Blood and Cancer Centre and one patient who received treatment at the Dunedin Oncology Centre were entered into the trial.

Inclusion/exclusion. Patients with head and neck cancer were eligible for enrolment if radiation or chemoradiation treatment was part of their disease management plan. It was a trial requirement that patients’ radiation plans delivered a minimum of 40Gy to at least two oral anatomical sites (as illustrated below in the mucositis assessment section). Patients were
excluded if they had received previous radiotherapy to the head and neck area, there was evidence of systemic disease or they had a history of diabetes or an allergy to honey. Each patient considered for the trial was given adequate information about the trial; its purpose and patient requirements all of which were included in the patient information sheet (Appendix C). Patients also had to understand the concept of the randomisation process to enable the oncologist or research assistant (RA) to obtain informed consent.

Randomisation. Originally patients were to be informed about the trial at their first specialist appointment (FSA) with the oncologist however this was amended and most patients were informed about the trial and referred for enrolment at their pre-treatment planning CT appointment. Patients who fitted the inclusion criteria and gave written informed consent had their details (initials, age, radiotherapy dose, chemotherapy) faxed to the University of Otago Wellington campus (Appendix D). The patient details were received by either the trial’s principal investigator (PI) Dr Patries Herst or the department physicist Ivan Luketina who randomised the patient using computer generated random numbers supplied by the University of Otago Statistician Gordon Purdie. The patients were randomized to either the control or honey arm. Randomisation was important to the trial protocol to avoid potential confounding from the various factors that influence mucositis. The two individuals involved in the randomisation process were not directly involved in patient care.

Patient protocol
All patients were educated on good oral hygiene, use of soft tooth brushes, fluoride toothpaste, avoiding spicy food, alcohol and tobacco. Patients were encouraged to rinse with water after each meal and sip small quantities of water when necessary.

Honey arm
From day one of radiation treatment patients in the honey arm were required to swirl 20mL (later amended to 10mL) of Comvita Active UM F30+ manuka honey around their mouth for one minute then swallow slowly to coat the oral cavity and pharynx. On treatment days patients were required to take the honey immediately before and after RT and six hours after RT. On non-treatment days patients were instructed to take the honey morning, afternoon and evening.
Control arm

Patients received the current standard of care as per their department protocol (see NZ departments current standard of care). The protocols differed slightly but most departments instructed their patients to use regular mouthwashes of bicarbonate soda and salt daily.

Adverse reactions

As stipulated in the ethics application if a patient developed an adverse reaction to the honey they had to stop using it immediately and this was to be recorded. All patients were seen on a daily basis (Monday to Friday) by radiation therapists and three times a week by the research assistant. Each patient enrolled was also seen by other allied health professionals who form the multi-disciplinary team; the clinical oncologist, oncology nurse, dietician and speech language therapist. Any adverse reactions were picked up and dealt with efficiently. Any breaks in patients’ treatment schedules due to reactions were recorded. A patient’s radiation oncologist could remove them from the trial if their treatment side effects were such that the use of the honey was causing harm.

Ethics Approval

The trial obtained ethics approval from the Multi-Region Ethics Committee in March 2009 (MEC/08/11/142). It was registered in the Australian New Zealand Clinical Trial Registry (ACTRN12608000180314).

Funding

The salary of Dr Patries Herst was covered by the University of Otago. The salaries of Dr David Hamilton and the other radiation oncologists were covered by the Capital and Coast District Health Board. The manuka honey was supplied by Comvita NZ LTD free of cost. There was no known conflict of interest on behalf of the study researchers or the Oncology department of Wellington or Dunedin hospital.
2.2.2 Measurements

*Mucositis*

The extent of oral mucositis was determined before the commencement of treatment and three times a week for the duration of treatment.

The method of mucositis scoring for this trial involved the assessment of fourteen oral mucosal areas (see Figure 5.).

![Diagram of oral mucosal areas](image)

**Figure 5. Diagram illustrating the fourteen oral sites that were assessed for mucositis**

Each area was assessed for the degree of radiation reaction and was assigned a value between zero and four depending on the reaction severity. The scoring system was adapted from that described by the Trans Tasman Radiation Oncology Group (TROG) in Table 4.
Number of sites at risk

The number of oral anatomical sites at risk was determined for each trial patient based on their individual treatment plan. A site was considered at risk of mucositis if it was receiving a dose of 40Gy or greater. A function on the Eclipse planning system allowed areas receiving more than a stipulated dose (40Gy) to be identified by creating a ‘dose cloud’ of dose above 40Gy. The transverse slices of a patient’s radiation plan and the 3D model of the patient and dose cloud were assessed to give the number of oral cavity sites at risk of mucositis. All patients were positioned head first (to gantry) supine and the transverse slices are viewed from the patient’s feet so orientated accordingly.

Mean mucositis scores

The 14 mucositis scores for each assessment were recorded on each patient’s individual mucositis scoring sheet (Appendix E). The sum of these scores at each dose was then divided by the number of sites at risk giving a mean mucositis score for a patient’s oral mucosa at given points in their treatment. Because the dose to the mucosa is the strongest indicator of mucositis, dividing total dose by the number of areas at risk minimizes dose-related confounding factors. This multiple site scoring system gives a more precise evaluation of the effect of the manuka honey on oral mucositis compared to a less complicated single scoring system which is often used in oral mucositis trials.

Consistency in scoring of oral mucositis

The research assistants from departments involved in the trial attended a training programme to learn how to accurately score mucositis. The training programme was led by radiation oncologist Dr David Hamilton from the Wellington Blood and Cancer Centre and included a Mucositis Scoring Competency Initial Credentialing Exam obtained from the TROG website. The training programme also included an open forum to discuss specific cases to ensure all assessors felt confident to accurately score mucositis. It was important that there was scoring consistency between departments to minimize the effect of inter-scorer variability. The assessor wore gloves and used a torch and tongue depressor (wooden spatula) to assess areas that were difficult to see. Any patients who had dentures were asked to remove them for treatment and assessment.
Weight Assessment

All head and neck patients receiving radiation therapy were weighed weekly. Regular recording of weight ensures there is not excessive variation which can impact on the accuracy of the radiation therapy plan (weight changes can alter the dose distribution). It is also important that patients maintain a relatively stable weight to cope with the energy sapping side effects of treatment. A radiation therapist or oncology dietician weighed each patient weekly.

Assessment of food intake and use of systemic analgesics

Patients were given a food/drug diary and were asked to record their food/fluid/medication intake on a daily basis. Recording later became weekly or when there was a significant change to the patient’s diet or medications, for example the move to NG or PEG feeding. Patients were asked to record the quantity and type of food and fluid they were consuming.

All head and neck patients had regular consultations with the oncologist and the oncology dietician throughout their treatment. The documentation from these appointments was also reviewed with regard to changes in the patient’s diet or medications. Discussion with the patient and review of their oncology notes revealed if they had a PEG inserted prior to treatment, during treatment or not at all.

Assessment of Quality of Life

The European Organisation for Research and Treatment of Cancer (EORTC) established a quality of life department which deals with the design, implementation and analysis of quality of life study within clinical trials. The department has input from a multidisciplinary team (oncologists, radiation therapists, surgeons, psychiatrists, palliative care specialists, psychologists, social workers and research methodologists) and has designed questionnaires to assess health-related quality of life (QoL) of cancer patients participating in international clinical trials. Two of these questionnaires were adapted for use in this oral mucositis trial; the EORTC QLC-C30 and the EORTC QLQ HN35. A four page QoL questionnaire was constructed and patients were asked to complete one every two weeks over their course of treatment. The 65 questions had slightly different scoring; questions 1 to 28 and 31 to 60 had a Likert scale of one to four (one indicating ‘not at all’, two ‘a little’, three ‘quite a bit’, four ‘very much’). Questions 29 and 30 had a Likert scale of 1 to 7 (1 being very poor and 7 being excellent). Questions 61 to 65 were yes/no questions.
Assessment of oral microflora

The research assistant took four tongue swabs during each patient’s treatment using a microswab. The first swab was taken at the start of radiation treatment and subsequent swabs were taken halfway through, at completion and at follow up of treatment. These swabs were taken for future analysis of changes in the composition of oral microflora over the patient’s course of treatment.

2.2.3 Trial timeline

The mucositis trial timeline (Figure 6.) began with the head and neck cancer patient being referred to a radiation oncologist to discuss their disease management plan, possible side effects and details of the trial at their first specialist appointment (FSA). Patients were given a participant information sheet (Appendix C) and were assessed for trial eligibility.

The patient then made the decision to pursue radiation therapy and was booked for a planning CT scan where the research assistant was able to discuss the trial in detail with the patient (or introduce the trial if the oncologist had been unable to do so prior), give them the trial arm protocol (Appendix F) and answer any questions. Written informed consent (Appendix G) was obtained before commencement of RT treatment.

The CT scan was performed with the patient immobilised in a thermoplastic mask. After the CT scan the patient’s information was sent to the planning department where an optimal radiation treatment plan was generated by planning radiation therapists in consultation with the radiation oncologist and the medical physics department. During the planning of the patient’s treatment their trial information was faxed to the University of Otago (Wellington campus) where randomisation was carried out as described earlier. Randomisation results were then faxed back to the oncology department and the patient was informed which trial arm they were in.

Patients in the honey arm were given their first jar of honey and instructed how to apply it once the radiation treatment started. All trial patients proceeded to treatment where they were given advice on the standard of care by the treatment radiation therapists. All patients were given the QoL questionnaires and food diaries and instructed when to fill them in and return them to the research assistant.
The data from the mucositis scores, weight measurements, food/fluid/drug diaries, QoL forms and tongue swabs was collected by the research assistant throughout treatment.

**Figure 6. Trial timeline**
2.2.4 Amendments

Several amendments were made to the original trial design and were approved by the Multi-region Ethics Committee.

1) The first amendment pertained to the blinding of the research assistant (person who recorded the mucositis scores) to the randomisation arm of each patient. The research assistant was the main point of contact for patients regarding trial information so the assistant had to be able to answer questions about the application of honey and to address patient concerns. There was no feasible way to maintain the blinded nature of the relationship.

2) An amendment was made to the timing of the trial introduction. Originally the trial was to be introduced by the oncologist at the patient’s initial consultation (informed consent could then be gained at the same appointment or by the oncologist at the CT scan). Oncologists reported that patients were often faced with ‘information overload’ at their first consultation (it was often at this consultation that the patients were finding out the severity of their disease) and so the trial was not mentioned. This resulted in head and neck patients arriving for their planning CT scan with no prior knowledge of the trial. The amendment allowed the oncologist to introduce the trial at the planning CT scan appointment and informed consent to be obtained by the research assistant in some cases.

3) Application of the honey was an area of concern for the patients randomised to the honey arm so changes were made to find a more tolerable method. Three treatment arm patients reported that 20mL of honey was too much to hold in the mouth so the amount to be taken three times daily was reduced to 10mL. It was then reported that due to the thick nature of manuka honey it was not easy to spread and swirl around the oral cavity. The honey was then diluted with water by a ratio of 1:3. The increased volume of liquid was applied over two mouthfuls and patients were instructed to hold the liquid in their mouth for as long as possible (ideally a minute). To combat the intense sweetness of the honey three patients diluted it with liquids other than water; organic apple juice, lemon and barley cordial and flat lemonade.
2.2.5 Head and neck RT setups
All head and neck patients are scanned and treated with an immobilisation mask which is made at the time of the CT appointment. These masks are made with spacers underneath the head rests to allow for the slight shrinkage that occurs between CT and treatment. The masks are reasonably tight for patients and can contribute to a feeling of restriction in the throat. Patients are able to swallow with these masks on although it can be more difficult than normal. Mouth-bites (also made at the time of the CT scan) are used in some instances with the aim of sparing certain peri-oral tissues and they allow the reproducible positioning of the intraoral tissues. These pieces of equipment allow reproducible setups to help minimise dose to normal tissues.

2.2.6 Data collection, entry and analysis
For each participant data from the oral mucositis scoring sheets (Appendix E) and weight measurements were entered into a Windows Excel '03 worksheet. From here common information and trends in the initial assessment form were analysed as described in the results section. Statistical analysis included determining averages and standard errors. All data was recorded and stored carefully to ensure patient confidentiality.

Descriptive analysis
The experiences of the nine patients who completed the trial were documented and reviewed to give a qualitative analysis of their experiences. The descriptions were based on verbal exchanges between patients and the research assistant at the three times weekly assessments and documentation in the clinical notes by other health professionals involved in the patients care (dietician, speech language therapist, clinical nurse specialist and the oncologist). The descriptive analyses allowed the identification of common experiences between the head and neck patients.

Mucositis analysis
Each patient’s mucositis scores were recorded manually (three times weekly as per the trial protocol) then entered into an Excel spreadsheet corresponding to the dose at each assessment. The sum of the mucositis grades for the 14 oral cavity sites was divided by the number of sites at risk giving the mean mucositis score for each assessment (TS/NSR). The mean mucositis score was graphed against dose. The individual patient results were
combined to give an overall picture of the mucosal changes for the honey and control groups and to illustrate the difference between the two groups. The mucositis scores were later assessed with regard to the percentage of patients who developed certain levels of mucositis, the dose at which mucositis first became apparent and the number of treatment delays related to mucositis.

**Weight analysis**
Graphs were produced for each patient to illustrate the changes in weight throughout treatment. The overall weight loss was recorded as was the percentage weight loss compared to their original weight. Graphs were produced to illustrate weight change of the honey patients compared to the control patients.

**Diet/medication analysis**
The food/fluid/drug diaries filled in by patients were reviewed and each patient’s diet at the beginning of treatment was compared to that at the end. There were four main descriptions of a patient’s diet; normal (regular food including solids), soft (only soft foods eaten, for example mashed potato, eggs, fish and well-cooked vegetables), fluids (oral or intravenous) and PEG/NG tube feeding (no oral foods). A diagram was used to illustrate the main changes in the patient’s diet from the beginning of treatment through to completion.

**Interpretation and analysis of the QoL questionnaires**
The QoL questionnaires contained 65 questions addressing various aspects of the patient’s health and wellbeing. For analysis seven categories (fatigue, pain, swallowing, oral cavity changes, nutrition, mood, psychosocial wellbeing and perception of QoL) were created with relevant questions being pooled under each category. The sum of the scores in each category gave the overall score for that category at that point in the patient’s treatment. All pooled questions had a scoring system of one to four (one indicating ‘not at all’ and four indicating ‘very much’).

A description of each category follows with the questions that were pooled to give the overall category score. Each category has a range and a description of what a greater score means.
Fatigue
Three questions were pooled under the fatigue category to indicate the impact of fatigue in the patient’s life at that point in time:
- Question 4 – *Do you need to stay in bed or a chair during the day*?
- Question 10 – *Did you need to rest*?
- Question 18 – *Were you tired*?

The patient reported score for fatigue ranges from three to 12, the greater the score the greater the experience of fatigue.

Pain
Six questions were pooled under the pain category to indicate the degree of pain the patient was experiencing at that point in time:
- Question 9 – *Have you had pain*?
- Question 19 – *Did pain interfere with your daily activities*?
- Question 31 – *Have you had pain in your mouth*?
- Question 32 – *Have you had pain in your jaw*?
- Question 33 – *Have you had soreness in your mouth*?
- Question 34 – *Have you had a painful throat*?

The patient reported score for pain ranges from six to 24, the greater the score the greater the experience of pain.

A yes/no question relating to the use of pain medication was also included in the pain section.
- Question 61 – *Have you used pain-killers*?

Swallowing
Three questions were pooled under the swallowing category to indicate the degree of swallowing difficulty the patient was experiencing at that point in time:
- Question 35 – *Have you had problems swallowing liquids*?
- Question 36 – *Have you had problems swallowing pureed food*?
- Question 37 – *Have you had problems swallowing solid food*?

The patient reported score for swallowing ranges from three to 12, the greater the score the more difficulty the patient had swallowing.
Oral cavity changes
Three questions were pooled under the oral cavity changes category to indicate the extent of negative changes experienced by the patient at that point in time.

- Question 41 – Have you had dry mouth?
- Question 42 – Have you had sticky saliva?
- Question 44 – Have you had problems with your sense of taste?

The patient reported score for oral cavity changes ranges from three to 12, the greater the score the more negative oral cavity changes.

Nutrition - nausea/vomiting/appetite
Five questions were pooled under the nutrition category to indicate the negative changes in nutrition that the patient experienced at that point in time:

- Question 13 – Have you lacked appetite?
- Question 14 – Have you felt nauseated?
- Question 15 – Have you vomited?
- Question 52 – Have you had trouble enjoying your meals?
- Question 49 – Have you had trouble eating?

The patient reported score for nutrition ranges from five to 20, the greater the score the more negative changes in nutrition.

Mood
Four questions were pooled under the mood category to indicate the patient’s perceived mood at that point in time:

- Question 21 – Did you feel tense?
- Question 22 – Did you worry?
- Question 23 – Did you feel irritable?
- Question 24 – Did you feel depressed?

The patient reported score for mood ranges from four to 16, the greater the score the more negative the mood.
Psychosocial

Three questions were pooled for the psychosocial category to indicate the negative impact on the patient’s psychosocial situation at that point in time:

- Question 26 – *Has your physical condition or medical treatment interfered with your family life?*
- Question 27 – *Has your physical condition or medical treatment interfered with your social activities?*
- Question 28 – *Has your physical condition or medical treatment caused you financial difficulties?*

The patient reported score for their psychosocial situation ranges from three to 12, the greater the score the more negative the patient’s psychosocial situation.

Perception of quality of life

Question 30 had a scoring system of one to seven (one indicated ‘very poor’ and seven indicated ‘excellent’), the higher the score the better the QoL. This question was included to give an indication of the patient’s perceived quality of life.

- Question 30 – *How would you rate your overall quality of life during the past week?*

Each patient’s QoL forms were analysed after the patient had completed treatment. Questions relating to each of the seven categories were combined as described above and a visual interpretation of the changes in each patient’s quality of life was made in the form of two graphs; the perception of quality of life versus dose (increasing slope indicated improving QoL) and the negative change in the seven QoL categories versus dose (increasing slope indicates more negative change).
Chapter 3 RESULTS

3.1 Review of current New Zealand oncology department head and neck care

Review of the nationwide management of head and neck patients showed the lack of a standard protocol and highlights the importance of continued research to ensure the current standard of care is the gold standard for this vulnerable cohort of patients. The inter-department differences depend on department resources and staff (oncologist preference) as well as trial participation, for example the humidification trial. All six public departments recommend patients use a baking soda and salt based mouthwash to be used several times a day (the timing differed between departments).

Table 5. Standard of care for New Zealand departments

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<th>PN #</th>
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</tbody>
</table>

* Baking soda and salt mouthwash
# PN – Palmerston North
^ Chch – Christchurch

3.1.1 Auckland DHB

The Auckland Regional Oncology Unit gives each head and neck patient their own care diary (patient personal record). These are designed to help patients through their experience of cancer treatment and give patients a sense of control. The diary has different sections; contact information, side-effects information, swallowing and nutrition management, exercise instructions to maximise the neck and shoulder movement and information about the use of home humidifiers. Patients’ nutrition is carefully monitored by Auckland staff and dieticians are involved with head and neck patients to try and maintain patients’ weight over the course of treatment. Weight and diet details are recorded. Oral care advice is given and baking soda mouthwashes recommended. Systemic and topical pain relief is prescribed as required.
3.1.2 Waikato DHB
The Waikato DHB encourages head and neck patients to maintain good oral hygiene from start of treatment, including regular tooth brushing. Advice on social habits and foods to avoid is given at the beginning of patients’ treatment. The advice includes the cessation of smoking and alcohol consumption and avoidance of spicy foods. Mouthwashes such as difflam and sodium bicarbonate (1/2 teaspoon of salt and baking soda and water) are commonly used, as are analgesics and nystatin drops for prevention of candidiasis.

3.1.3 Palmerston North DHB (MidCentral DHB)
The oncology staff at the Palmerston North DHB ensure head and neck patients have a dental assessment prior to their radiation therapy. Patients are advised to use soft toothbrushes and fluoride toothpaste. They have regular assessment by a dietician and PEG tubes are inserted for patients who have significant weight loss. Patients are also advised to avoid smoking and drinking alcohol. Mouthwash instructions are given at the beginning of treatment; either baking soda (one teaspoon in a cup of lukewarm water four times a day) or difflam (10-20mL four times a day). The consultant oncologist may start patients on prophylactic anti-fungal medication (nystatin 1mL drop on the tongue four times a day) at start of treatment or when there is evidence of candida infection. Lip and gum care involves water-based moisturiser applied to lips and gums (mouth moisturiser or oral balance gel). The Palmerston North protocol details actions to be taken at each grade of mucositis;
Grade 1-2 mucositis: mouthwashes are to be continued as above every 2 hours. Baking soda swabs to be used to clean around teeth and staff are to check for the presence of infections and treat accordingly. Xylocaine viscous analgesia can be applied (5-10mLs swirled round mouth then swallowed) four times per day before eating to provide local anaesthetic effect. Analgesia is to be commenced as required, starting with paracetamol (tablets or liquid) and/or ibuprofen (tablets or liquid) before adding in opiate medication.
Grade 3 mucositis: the oncologist may decide the patient is to be admitted to the ward as they are likely to need IV fluids in addition to PEG feeding. Assessment of the oral cavity to identify any infections that are high risk at this grade of mucositis. Hourly mouthwashes are to be continued.
3.1.4 Wellington (Capital and Coast DHB)
Nursing care is focused on promoting oral hygiene, assessment, patient education and supportive care. Mouth care regimens are individualised according to patient needs with evidence based principals used to govern patient management. Patients have dental assessments prior to treatment. They have education on the likelihood of ulcers and fungal infections during treatment and how to reduce the risk of these developing: check the mouth twice daily for any sores, areas of pain, bleeding or white film. Salt and baking soda mouthwashes are encouraged four times a day. To combat a dry mouth patients are instructed to drink fluids often, chew sugar-free gum and to avoid hot, spicy or acidic foods and alcohol. The dietician is involved early in treatment and patients are advised on a high calorie soft food plan. Anti-nausea advice is also given including small frequent meals, regular water, avoiding fatty/spicy foods, sucking ice, peppermints or barley sugars. Avoiding food smells is beneficial if these trigger nausea. Good personal and oral hygiene, electric shaving (not blades) and the use of aqueous cream or aloe vera gel is encouraged. PEGs are inserted prophylactically in high risk patients while others may have them inserted part way through treatment if required.

3.1.5 Christchurch (Canterbury DHB)
Skin care advice (aqueous cream or pure aloe vera gel, salt water bathing, and dressings if required) is given as are instructions regarding oral care; salt water and baking soda washes after early meal. Soft toothbrushes or cotton buds are used to brush sensitive teeth/gums. Topical (xylocaine viscous) or oral analgesia is prescribed as required. The patient’s nutritional status is monitored regularly; soft food diet, supplements and weekly review by the dietician and/or speech language therapist. Most head and neck patients will have prophylactic PEGs inserted. Oral thrush is treated as required with antifungal medication and patients are encouraged to sip water regularly for dry mouth. The Christchurch department is involved in the TROG humidification trial so eligible patients may receive humidification as part of their treatment.

3.1.6 Dunedin (Southern DHB)
The Dunedin department has registered nurses assigned to assess head and neck patients (twice weekly). Patients are encouraged to commence strict oral hygiene at the earliest opportunity. This advice about mouthwashes and teeth cleaning is often given to patients
when they come for their planning CT scan and gives patients a good foundation for treatment. The baking soda and salt mouthwashes (made fresh each day) are to be used four times a day at the beginning of treatment and then hourly once significant side effects start to manifest. Patients are referred to the dental school for dental review if required. Increased water intake is encouraged, preferably two litres per day. Pain control consists of systemic pain relief and topical analgesics (xylocaine viscous). Oralife peppermint lip balm is recommended to combat erythema of the lips.
3.2 Mucositis trial: Patient results

The New Zealand mucositis trial was conducted through the University of Otago and was a multi-centre trial with three oncology centres participating; Palmerston North, Wellington and Dunedin. This analysis includes the data of patients from the Wellington oncology department and one patient from the Dunedin oncology department.

3.2.1 Patient recruitment

Trial recruitment began in March 2009 with the aim of recruiting as many eligible head and neck patients as possible. Recruitment continued until December 2009 when it was decided after preliminary analysis that undiluted honey was not well tolerated and that diluted honey in the form of a mouthwash did not affect the extent of oral mucositis.

Recruitment was slow in all three centres. The Wellington department saw 27 patients referred for radiation treatment for their head and neck cancer. When combined with the one Dunedin patient there was a total of 28 trial potential patients seen between March and December 2009. Of these patients only 50% (n=14) were recruited to the trial (see Figure 7.). The other 50% of head and neck patients (n=14) were unable to participate in the trial; three were not willing, five patients were excluded because they did not meet the selection criteria and six potential trial head and neck patients were missed due to time and resource constraints and a lack of communication. Of the five patients who did not meet the selection criteria three patients had received previous radiation treatment, one had a history of diabetes and the other had a mental health problem and did not understand the concept of randomisation meaning informed consent could not be obtained.

The 14 patients that were recruited to the trial were randomised; nine to the treatment arm and five to the control arm. The patients in the manuka honey arm commenced the honey application on day one of their radiation treatment adhering to the trial instructions.

36% of patients (n=5) recruited to the trial pulled out within one week of commencing the radiation treatment. Four of these patients were from the treatment (manuka honey) arm and
pulled out because they could not tolerate the manuka honey. One control patient pulled out after being admitted to hospital with pneumonia.

The four patients on the honey arm who pulled out all experienced problems with the application of the honey. One patient received concurrent chemotherapy and did not have sufficient antiemetics. He therefore suffered severe nausea and vomiting after the first day of chemotherapy. Because he also took the honey as instructed on day one he built a strong association between nausea and vomiting and honey so he could no longer tolerate the honey. This patient attempted to apply the honey several times after the initial incident but the association meant he suffered a gag reflex with each attempt. Another one of the four patients who pulled out had a strong dislike for honey and also suffered a gag reflex when trying to apply the honey.

An amendment was made to the treatment arm protocol and was approved by the Multi-region Ethics Committee. The change allowed the patients in the treatment arm to use less honey (10mL instead of 20mL) and dilute the honey (1:3) in water or other liquids.

Patient accrual was slow due in part to time and resource constraints. The oncologists were responsible for identifying potential trial patients when they met them at their FSA (first specialist appointment). Two oncologists reported that they found it difficult to deliver the information about the trial at the patient’s first appointment due to all the other information they were required to deliver. The oncologists advised that it would be better to mention the trial at a later date once the initial information regarding the patient’s disease management had time to sink in. It then became the research assistant’s responsibility to identify the potential patients before their CT planning scan but due to time constraints and a lack of communication six potential patients were missed. Another change to the original study design was made so the research assistant could gain trial patient consent at the patient’s planning CT scan (i.e. the oncologist did not have to).
Figure 7. Consort diagram illustrating patient flow through the oral mucositis trial
3.2.2 Personal construct

These results apply to the nine patients who completed to the trial.

Age
The average age of all patients recruited to the trial was 57.3 years (range 41 to 78). Overall patients in the honey group were younger than those in the control group. The average age of the control patients was 61 years (range 52 to 78) whilst for the honey patients the average was 54.4 years (range 41 to 69). The difference in the average age between the two groups was 6.6 years.

Gender
The trial recruited four (44.4%) female (three control, one honey) and five (55.6%) male (four honey, one control) patients. There were more males in the honey arm (80%) than the control arm, only 25% of controls were males.

Ethnicity
Seven trial patients (77.8%) were of European descent, one was a Pacific Islander and the other of Cook Island and Maori descent. The non-European patients were both in the control group.

General health
One of the trial inclusion criteria was that patients needed to be in good health therefore none of the patients had significant co-morbidities that impacted directly on their cancer treatment or participation in the trial. The trial patients were not questioned with regard to their smoking status or alcohol intake at the time of trial inclusion. The patient clinical oncology notes were reviewed to ascertain information relating to this. No patients had a reported history of alcohol or drug dependency and only one was documented as being a smoker (control patient).

3.2.3 Therapy construct

Radiation therapy
All patients included in the trial were receiving radical radiation treatment with the aim of local control. Each radiation plan was individualised to treat a specific volume of tissue.
critical for each patient’s management. The dose and number and orientation of beams, the shielding and patient set-up varied significantly to account for the variability in each patient’s disease and contour. Plans ranged from simple conformal parallel opposed fields delivering dose over one phase to the more complex conformal eleven field three phase plans. Four patients received a total dose of 70Gy, one received 66Gy, two received 60Gy, one a total of 40.8Gy (despite being prescribed 48Gy) and the other a total of 40Gy.

The volume of tissue included in the treatment field impacts on the amount of mucosa that is at risk of radiation induced inflammation. The mean mucositis scores account for this variation by dividing the total mucositis score by the number of oral cavity sites at risk of mucositis. All radiation plans were prescribed with the standard fractionation of 1.8-2Gy per fraction aside from one control patient who received 2.4Gy per fraction and one honey patient who in phase two received 1.3Gy per fraction. The dose per fraction affects the acute radiation reactions; the higher the dose per fraction the greater the risk of an acute reaction occurring.

Table 6. Treatment management of trial patients

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<td>√</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>WHC2</td>
<td>Control</td>
<td>70</td>
<td>Two</td>
<td>X</td>
<td>√ (Cisplatin)</td>
<td>X</td>
</tr>
<tr>
<td>WHC4</td>
<td>Honey</td>
<td>70</td>
<td>Two</td>
<td>√</td>
<td>√ (Cisplatin)</td>
<td>X</td>
</tr>
<tr>
<td>WHC6</td>
<td>Honey</td>
<td>40</td>
<td>Two</td>
<td>√</td>
<td>√ (R-CHOP)</td>
<td>X</td>
</tr>
<tr>
<td>WHC7</td>
<td>Control</td>
<td>70</td>
<td>Three</td>
<td>X</td>
<td>√ (Cisplatin)</td>
<td>√</td>
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<tr>
<td>DHC1</td>
<td>Honey</td>
<td>69.5</td>
<td>Two</td>
<td>√</td>
<td>√ (Cisplatin)</td>
<td>X</td>
</tr>
</tbody>
</table>

Surgery

Previous surgery may result in scar tissue which has been reported as being more susceptible to acute radiation-induced side effects. Seven (77.8%) patients had surgery prior to radiation treatment. The two who had not were control patients.

Chemotherapy

55.6% (n=5) of trial patients had chemotherapy as part of their treatment regime. Four had concurrent Cisplatin chemotherapy, the other patient had received R-CHOP chemotherapy prior to radiation treatment. Of the five patients who received chemotherapy three were
honey arm patients, the other two control patients. The other 44.4% (n=4) of trial patients received radiation therapy alone (two honey patients and two control patients).

Humidification
The use of humidifiers was a recent introduction into the protocol for the management of head and neck cancer patients at the Wellington department with two humidifiers being available for use. Humidification may be beneficial in treating mucositis in head and neck radiotherapy patients and because it had become part of the standard of care it would have been unethical to prevent honey trial patients from using humidifiers despite the potential for the use to confound the trial results. Three trial patients used humidifiers at some stage in their radiation treatment, two were control patients and one a honey arm patient.

Type and location of disease
All patients recruited to the trial were being treated for cancer of the head and neck region but the disease site varied between patients. There were seven different disease sites; the maxillary gingiva, the palate, the nasal cavity, the floor of mouth, Waldeyer's ring, tonsil (two) and the tongue (two). 88.9% of trial patients had been diagnosed with SCC, the other patient had non-Hodgkins lymphoma.

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxillary gingival</td>
<td>1</td>
</tr>
<tr>
<td>Palate</td>
<td>1</td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>1</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>1</td>
</tr>
<tr>
<td>Waldeyer’s Ring</td>
<td>1</td>
</tr>
<tr>
<td>Tonsil</td>
<td>2</td>
</tr>
<tr>
<td>Tongue</td>
<td>2</td>
</tr>
</tbody>
</table>

Stage of disease
As well as site tumour size and stage differed between patients (Table 7. and Figures 8. and 9.). Two patients had tumours whose size could not be assessed (Tx). One patient presented with a T1 tumour and one with a T2 tumour. Two patients had T3 staged disease and two had stage T4 disease. The other patient’s disease was staged 2A using a different staging system. Review of nodal involvement showed two patients had no known nodal spread, two
had N1 staged involvement, one had N2 and three had N3 staged involvement. The remaining patient was not staged using the TNM system.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Arm</th>
<th>Tumour stage</th>
<th>Nodal stage</th>
</tr>
</thead>
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<td>Control</td>
<td>Tx</td>
<td>N0</td>
</tr>
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<td>WHN3</td>
<td>Honey</td>
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<td>N1</td>
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<td>Control</td>
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<td>WHN5</td>
<td>Honey</td>
<td>T4</td>
<td>N0</td>
</tr>
<tr>
<td>WHC2</td>
<td>Control</td>
<td>T3</td>
<td>N2</td>
</tr>
<tr>
<td>WHC4</td>
<td>Honey</td>
<td>T3</td>
<td>N3</td>
</tr>
<tr>
<td>WHC6</td>
<td>Honey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHC7</td>
<td>Control</td>
<td>T2</td>
<td>N3</td>
</tr>
<tr>
<td>DHC1</td>
<td>Honey</td>
<td>T4</td>
<td>N3</td>
</tr>
</tbody>
</table>

Figure 8. Number of patients with each tumour stage as described by the TNM staging system

Figure 9. Number of patients with each nodal stage as described by the TNM staging system
**Honey tolerance**

Only 40% of the honey patients (n=2) finished treatment still applying the manuka honey and only one continued taking it three times a day, the other had reduced to two times due to the pain and fatigue. The other three honey patients applied the manuka honey for over two thirds of their radiation treatment but stopped the application prior to treatment completion. One stopped the honey at 28.8Gy (six fractions before treatment completion) due to severe pain and nausea (chemo patient), another stopped the honey application at 64Gy (one fraction before treatment completion) but had reduced the honey to once a day at 62Gy (two fractions before treatment completion), she was a non-chemo patient. The fifth patient who received concurrent chemotherapy stopped using the honey seven fractions prior to treatment completion (after 60.4Gy) due to severe pain. 60% of honey patients found they had to mix the honey with a liquid other than water to reduce the sweetness. These liquids included lemonade, organic apple juice and lemon and barley cordial.
3.3 Mucositis trial: Individual patient experiences

3.3.1 Honey patient WHN3

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<td>41</td>
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<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>Site of disease</td>
<td>Tongue (right anterolateral region)</td>
</tr>
<tr>
<td>Disease</td>
<td>SCC</td>
</tr>
<tr>
<td>Stage</td>
<td>T1N1M0</td>
</tr>
<tr>
<td>Treatment plan</td>
<td>Conformal radiation therapy</td>
</tr>
<tr>
<td>Radiation dose</td>
<td>66Gy/33#s</td>
</tr>
<tr>
<td>Treatment intent</td>
<td>Radical</td>
</tr>
<tr>
<td>Trial arm</td>
<td>Honey arm</td>
</tr>
<tr>
<td>PEG prior</td>
<td>No</td>
</tr>
<tr>
<td>Sites at risk</td>
<td>14</td>
</tr>
</tbody>
</table>

WHN3 was a 41 year old female who presented with a six month history of an ulcer on the right side of her tongue that had become painful in the two months prior to diagnosis. Diagnosis indicated a SCC of the right anterolateral aspect of the tongue. The disease was staged T1N1M0 and had poorly defined margins although was clear of the floor of mouth and the base of tongue. WHN3 was a non-smoker and light social drinker with good general health. She worked as an IT manager for a government department.

Proposed disease management was of radical intent and consisted of surgery and post-operative radiotherapy. The patient proceeded to surgery and underwent a tracheostomy, right partial glossectomy, right selective neck dissection (levels I-IV) and a right buccal flap. The radiation therapy plan was prescribed to deliver 66Gy in 33 fractions over three phases. Phase I delivered 50Gy in 25 fractions to the oral cavity and right upper and lower neck using a five field technique. Phase II treated this same area with slightly smaller field sizes to an additional 10Gy in 5 fractions. Then the right oral cavity alone received a further 6Gy in 3
fractions in phase III using two fields. The highly conformal plan used 6MV beams on all fields. The planned organ at risk was the spinal cord.

The patient was open to the trial concept and was randomised to the honey arm. She was a very compliant patient who was curious about every aspect of her treatment and had a firm belief that the honey was going to be beneficial. She had close involvement with the dietician, social worker, district nurse and speech language therapist as well as the weekly review with the consultant. The doctor had described that the side effects of the treatment included effects on speech and swallowing, possible nerve function changes including the mandibular nerve and hypoglossal function. There was also a risk of flap failure and problems related to poor nutrition.

Sites at risk
The three phase plan put all 14 oral cavity sites at risk. These sites were the upper and lower vermillion lip, the upper and lower labial mucosa, the upper and lower gingiva and the right and left buccal mucosa, the ventral and dorsal aspects of the tongue, the hard and soft palate, the floor of mouth and the oropharynx.

Figure 10. WHN3 oral cavity sites at risk

The following Figures illustrate the distribution of dose above 40Gy delivered by the conformal radiation plan.
Figure 11. WHN3 anterior view of the treatment area

Figure 12. WHN3 lateral view of the treatment area
Mucositis

The first reactions were reported in week three of treatment (28Gy) and included erythema of the floor of mouth, oropharynx and lower lip. There was also erythema of the lower labial mucosa which became patchy mucositis in week four of treatment and remained until completion of treatment. The upper labial mucosa developed patchy mucositis at 44Gy (week five), erythema at 50Gy and then patchy again at 52Gy until the end of treatment. The upper gingiva was clear of radiation reaction but the lower gingiva developed patchy mucositis in week three (28Gy) which became confluent briefly during week four (32Gy) and then healed to patchy mucositis and then erythema further through treatment. Also during week three (28Gy) the right buccal mucosa had visible erythema which became patchy mucositis the following week (32Gy). The left buccal mucosa and the ventral and dorsal aspects of the tongue showed patchy mucositis at 28Gy (week three) which remained until week seven when the mucositis became confluent. The hard and soft aspects were free of mucositis reaction until 60Gy when patchy mucositis developed and remained.
WHN3 experienced a weight gain over the course of her treatment which is unusual in a head and neck patient. The overall gain was 1.3kg which was a 2% gain compared to her initial weight.

Diet

The patient had been on a soft food diet since her surgical resection and remained on this throughout treatment with the addition of Fortisip supplements. Midway through treatment
she pureed her food and towards the end had a NG tube inserted and was commenced on IV fluids to treat her dehydration.

**QoL**

WHN3 was a very compliant patient who completed five forms.

---

**Figure 16. WHN3 change in perception of QoL score vs dose**
Figure 17. WHN3 negative change in QoL category scores vs dose

Changes in categories of QoL:

- Fatigue fluctuated throughout treatment; it reduced until halfway then increased and then reduced again towards treatment completion
- Pain increased over the course of the treatment
- Pain medication was used throughout treatment
- Swallowing got worse from the beginning to end with slight fluctuation in the middle of treatment
- Oral cavity changes and nutrition got worse over the course of treatment (there was a slight improvement in nutrition at completion of treatment)
- Mood fluctuated a lot which supports the discussions the research assistant had with patient
- Perception of QoL decreased over the course of the treatment but improved slightly at treatment completion

Patient’s descriptive experience

Toward the end of the first week (8Gy) WHN3 reported disliking taking the manuka honey but wanted to continue as she believed it would be beneficial. She mixed the honey with warm water prior to application but was unable to use it in the morning due to nausea (worse immediately after waking) so used it at lunchtime, late afternoon and in the evening.
During the first week the patient found the treatment had heightened her sense of smell which triggered her nausea. The patient reported finding the biotene mouthwash “much easier” to use than the honey because the honey was difficult to fully dissolve and “dregs” would be left in the bottom of the glass. At the beginning of week two WHN3 began mixing the honey with organic apple juice to make it more palatable. Later in week two (14Gy) there were no pain issues and the patient’s nausea was controlled with ondansetron. The QoL form filled out at this stage (16Gy) showed that the perceived QoL score remained the same compared to the beginning of treatment and the seven QoL categories had not changed dramatically.

The mouth had become more sensitive (she felt like she had “scrubbed too hard” on her gums) and dry especially on the right side. Regular paracetomol (especially before meals) was taken for the pain and the patient tried to eat bigger meals less often to prevent aggravation of the mucosa. She was also using a smaller, softer toothbrush. All these changes caused the patient a lot of stress and anxiety.

At the beginning of week three (22Gy) the patient used liquid panadol and codeine for pain relief. She was reluctant to talk because of the pain and had noticed a change in her voice. She avoided acidic foods and found that the source of pain was the area of previous surgery (the flap taken from the right upper gingiva).

The patient was referred to an immunologist after experiencing ongoing nausea and diarrhoea, she was advised to limit her fruit and vegetable intake (due to a possible fructose intolerance). However she continued mixing the honey with apple juice as she thought the honey was more important. The honey application continued to cause pain especially over the back molar area and her lips felt like they had “been in the sun”. She also complained of a mild sore throat.

Despite using morphine three times a day at the end of week three (28Gy) WHN3 still noticed pain when chewing and swallowing and found that eating took a long time. As a result of the pain and the development of thick saliva the patient’s food intake had decreased and she was taking one Fortisip supplement per day.
Grade two mucositis was evident after three weeks and was more prominent on the left side. There was significant pain and loss of taste. It was interesting to note that the mucositis on left side of the tongue was a definite line one day and only patchy the next indicating a degree of healing overnight.

Towards the end of week four (36Gy) the pain was better managed however there was an increase in nausea. The patient’s morphine prescription was decreased because of the nausea and she was instructed to increase her Fortisip use to three per day. The level of mucositis had decreased and the patient reported that the honey stung less but tasted like salt.

After four weeks of treatment (40Gy) the patient was emotionally fragile. She was introduced to humidification use and was instructed to use the humidifier at night to help moisturise her dry mouth. Later in the week (44Gy) the patient reported significant fatigue and new areas of mucositis were developing.

Five weeks of treatment resulted in high levels of pain especially where the back molars touched the tongue. The patient also experienced pain that radiated up to her left ear and she found that all meals required puree consistency. There was a decrease in the perceived QoL score and a negative change in six of the seven QoL categories at this point in the treatment. Interestingly, the pain category did not increase.

In the following fractions the patient’s pain and mucositis increased, she could no longer eat solid food and had moved on to a completely pureed diet. She had further loss of saliva and a croaky voice. The humidifier was used every night from 10:30pm to 6:30am. The patient also used biotene dry mouth toothpaste and was started on nystatin for possible oral thrush infection.

After six weeks of treatment (60Gy) the patient was still using the honey despite it causing a bad stinging sensation. The pain had increased again despite being on severodol (morphine) and panadol for pain, diazepam for insomnia and anxiety, difflam for pain and inflammation and pilocarpine for dry mouth. During the final week of treatment (62Gy) the patient suffered from pain, reflux, fatigue, constipation and nausea. There were areas of grade three mucositis and as a result of these significant reactions she was admitted to hospital for NG
tube insertion. She was in extreme pain at this time so only took honey once a day. The visible mucositis on the tip of the patient’s tongue had increased.

Antiemetic medication and fluids continued to be administered via IV line over the following fractions. The patient was also given subcutaneous pain medication. WHN3 was unable to adhere to the honey regime in hospital and she felt like she had “lost control”. Treatment was completed after delivery of 70Gy and the patient was soon discharged from hospital.
3.3.2 Honey patient WHC4

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<td>Age at trial inclusion</td>
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<td>Gender</td>
<td>Male</td>
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<td>Site of disease</td>
<td>Palate</td>
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<tr>
<td>Disease</td>
<td>SCC</td>
</tr>
<tr>
<td>Stage</td>
<td>T3N3M0</td>
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<tr>
<td>Treatment plan</td>
<td>Chemoradiation</td>
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<td>Radiation dose</td>
<td>70Gy</td>
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<td>Treatment intent</td>
<td>Radical</td>
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<tr>
<td>Trial arm</td>
<td>Honey</td>
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<tr>
<td>PEG prior</td>
<td>No (inserted at 20Gy)</td>
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<tr>
<td>Sites at risk</td>
<td>10</td>
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</table>

WHC4 was 56 years of age when he was diagnosed with SCC of the soft palate and was referred for radical post operative chemoradiation. The disease was staged T3N3M0 and the recommended chemoradiation involved three weekly Cisplatin and a radiation dose of 70Gy with the aim of local control.

The delivery of the radiation was split over two phases. Phase I used an 11 field conformal beam arrangement to treat the bilateral upper and lower neck to 50Gy. A simpler three field plan was used in phase II to treat the upper neck alone (primary site and involved nodes) to an additional 20Gy. The oncologist required the spinal cord dose to be kept below 45Gy and the brain stem below 54Gy to avoid late complications. A combination of 6 and 18 MV beams were used.

This patient was very open to the trial concept and despite disliking the taste of standard honey was willing to participate. He was randomised to the honey arm. Conversation with the patient indicated he believed the manuka honey was going to be beneficial.
The patient’s setup was that of a standard head and neck with a customised mask. His dentures were removed for treatment and for mucositis assessments. As well as the three weekly assessments with the research assistant the patient had close contact with the clinical nurse specialist, dietician, PEG nurse and had a weekly review with the oncologist.

_Sites at risk_

The two phase 70Gy conformal plan put ten oral cavity sites at risk including the upper and lower gingiva, the right and left buccal mucosa, the ventral and dorsal aspects of the tongue, the hard and soft palate, the floor of mouth and the oropharynx.

![Diagram of oral cavity sites at risk](image)

**Figure 18. WHC4 oral cavity sites at risk**

The following Figures illustrate the distribution of dose above 40Gy delivered by the conformal radiation plan.
Figure 19. WHC4 anterior view of the treatment area

Figure 20. WHC4 lateral view of the treatment area
Figure 21. WHC4 transverse slices at the isocentre, 1.2cm superior and 4.5cm superior to the isocentre

*Mucositis*

The first reactions were visible on the soft and hard palate after 16Gy (week two). Patchy mucositis was evident on these areas and remained until 40Gy when it became confluent until the end of treatment. The upper lip became erythematous at 16Gy and remained so until healing in week three (32Gy). Both the ventral and dorsal aspects of the tongue developed patchy mucositis at 22Gy which remained until the completion of treatment. The left and right buccal mucosa also began reacting at 22Gy. The right side had erythema until 42Gy when it became patchy mucositis that remained until the completion of treatment. The left side had patchy mucositis at 22Gy which remained until 42Gy where it became confluent until the end of treatment.

Figure 22. WHC4 mean mucositis scores (TS/NSR) vs dose
**Weight**

WHC4’s weight fluctuated throughout treatment with a total weight loss of 3.8kg equivalent to a percentage weight loss of 6.2.

![Figure 23. WHC4 change in weight vs dose](image)

**Diet**

At the beginning of treatment the patient had a normal dietary intake but soon experienced difficulties maintaining adequate nutrition due to the radiation effects. A PEG was inserted and the patient was PEG dependent until the last week of treatment when it was removed and the patient went back to a soft diet supplemented with four Fortisips per day.

**QoL**

Despite WHC4 being a very compliant man he only completed three QoL questionnaires over the course of treatment.
Figure 24. WHC4 change in perception of QoL score vs dose

Figure 25. WHC4 negative change in QoL category scores vs dose

Changes in categories of QoL:

- Fatigue decreased
- Pain increased from beginning to halfway and then decreased towards the end of treatment back to the initial level
- Pain medication was used the whole way through the treatment
- Swallowing difficulties increased
- Oral cavity changes got worse up to halfway and then improved slightly
- Nutrition changes gradually got worse
- The patient’s mood remained the same the whole way through treatment
- Psychosocial affects of the treatment got better
- Perception of QoL remained the same until a slight decrease towards the end of treatment

Patient’s descriptive experience

The first reactions the patient noticed were changes to his taste sensations which occurred after the first week of treatment (10Gy). Despite these changes he was able to maintain a good diet and did not suffer much weight loss. At 10Gy the patient reported that he was eating well but was becoming aware of a metallic taste at the back of his mouth. His pain medication at this stage included soluble panadol and codeine. Toward the end of his second week of treatment (16Gy) grade one mucositis became evident and from the patient’s descriptions xerostomia had developed. The patient was encouraged to supplement his diet with one Fortisip per day as there had been a 2Kg weight loss at this point.

At the end of week two (20Gy) the honey caused a lot of stinging when swirled around the patient’s mouth. Until this point WHC4 had been using the honey (10mLs) three times a day. The patient was keen to continue with the honey and was advised by the oncologist to use anaesthetic (difflam) prior to administering honey, he was also advised to add warm water (30mLs) to make honey less thick. Otherwise the patient was eating well with softer foods and was keen to delay the use of his recently inserted PEG for as long as possible.

After delivery of 22Gy WHC4 had a very sore throat with patchy ulcerations (grade two mucositis). The patient’s diet incorporated pureed foods at this stage and he reported an increase in the length of time required to eat a meal. The dietician advised him to have two Fortisips per day but these were not easily tolerated. WHC4 required an analgesia review due to an increase in mucositis related pain after the weekend. With the addition of xylocaine viscous and morphine the pain was much improved at delivery of 24Gy.

WHC4’s food intake decreased one fraction later due to another increase in the level of pain and reduction in taste. Another increase in Fortisip nutrition (four per day) was advised along with the introduction of overnight PEG feeding. The patient was persisting with the honey
application despite the associated pain which had not decreased with the introduction of difflam prior to application.

At the end of week three of treatment (30Gy) the patient had lost 3Kg. His pain medication had to be increased to include morphine elixir two to three times per day. The QoL form filled in after delivery of 32Gy illustrates the negative effect treatment had on six of the seven QoL categories when compared to the beginning of treatment. At this stage the patients perceived QoL score remained the same.

At 36Gy WHC4 was in a lot of pain especially on the left upper gingiva area and found the pain more intense when using the honey. By mixing the honey with warm water he was able to soften it enough to be able to swirl it around his mouth and coat the mucosa. The patient was very persistent with the honey, he was reassured he could stop if the pain became too intense and to report any changes to the research assistant.

The level of mucositis had increased throughout the mouth after 40Gy. At 42Gy there was severe confluent mucositis and suspected candida infection. The patient’s mouth was very sore and his morphine use had increased. Nutritional intake had decreased and the weight loss since the start of treatment was now 4.5Kg. Soft meals, Fortisip supplements and overnight PEG feeding advice was reiterated.

At the end of week five (50Gy) the patient reported vomiting and a severe headache. Grade two mucositis was obvious in the oral cavity. The main issue for the patient at this stage was swallowing and trying to maintain his weight with the use of Fortisips after experiencing problems with his PEG (placement and infection).

After week six (60Gy) the mucositis appeared to have stabilised. Patchy mucositis was noted on the soft and hard palate and on the left buccal mucosa. The patient found that all food, fluids and medications stung but he reported that things were not getting worse. After the initial problems were addressed WHC4 was able to use his PEG frequently with additional oral intake occasionally. His weight had also stabilised at this point and the patient looked better and sounded more cheerful. The QoL questionnaire filled in after six weeks of treatment reported that all the QoL categories had improved aside from the nutrition category.
The overall perceived QoL score had, however, got worse compared to the score after three weeks of treatment.

Fatigue had increased after 62Gy (early in week seven) and the patient had begun to mix the honey with flat lemonade to reduce the sweetness and thickness of the honey. The patient’s PEG was taken out after 68Gy due to difficulties feeding through it and severe nausea. WHC4 continued with Fortisip nutritional supplements and soft foods through to treatment completion.
3.3.3 Honey patient WHN5

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<td>PEG prior</td>
<td>No</td>
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<tr>
<td>Sites at risk</td>
<td>9</td>
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</table>

WHN5 was a 60 year old male who was diagnosed with moderately differentiated SCC of the floor of mouth. The disease was staged T4N0M0 and classified as grade 2. The tumour was primarily on the left side with extension across the anterior midline.

Surgery was recommended as the primary treatment option so shortly after diagnosis the patient proceeded to surgical resection of the floor of mouth tumour and bilateral selective (levels I-III) neck dissection. An ulnar forearm free flap reconstruction was also performed to try and preserve function and cosmesis of the patient’s mouth as much as possible. One of the surgical margins was very small (0.15mm) so the patient was referred for adjuvant radiotherapy. A conformal radiotherapy plan was designed to deliver 60Gy in 30 fractions to the tumour bed. Treatment intent was radical with aim to improve local control. Two direct lateral radiation beams of 6MV energy were targeted to the PTV.

The patient’s management involved a multidisciplinary team including the oncology dietician, district nurse, speech language therapist and clinical nurse specialist. Prior to surgical intervention the patient had a full dental clearance.
This patient was randomised to the honey arm of the study and adhered to the guidelines very well (he maintained use of the honey throughout his treatment). He filled in his food diaries regularly and his QoL forms twice.

_Sites at risk_

The conformal radiation therapy plan consisted of two directly opposed beams shaped with MLC to conform the 60Gy dose to the target area. Nine areas at risk were identified on the Eclipse plan including the upper and lower gingiva, the left and right buccal mucosa, the ventral and dorsal aspects of the tongue, the hard and soft palate and the floor of mouth.

![Figure 26. WHN5 oral cavity sites at risk](image)

The following Figures illustrate the distribution of dose above 40Gy delivered by the conformal radiation plan.
Figure 27. WHN5 anterior view of the treatment area

Figure 28. WHN5 lateral view of the treatment area
Figure 29. WHN5 transverse slices at the isocentre, 1.8cm superior and 2.1cm inferior to the isocentre

**Mucositis**

Patchy mucositis became evident at 40Gy with no prior evidence of mucosal erythema. The areas affected included the right buccal mucosa and the ventral and dorsal aspects of the tongue. The patchy mucositis remained in these three areas until completion of the patient’s treatment.

Figure 30. WHN5 mean mucositis score (TS/NSR) vs dose

**Weight**

WHN5 did not suffer a large weight loss over the course of treatment; total weight loss was 0.9kg which was 1.7% of his initial weight.
Figure 31. WHN5 change in weight vs dose

*Diet*

Due to the effects of surgery the patient was on a pureed diet and ‘thin’ fluids before radiation therapy commenced. His diet remained the same over the course of radiation therapy.

*QoL*

WHN5 only filled in two QoL forms but these were able to give an indication of QoL towards the end of treatment compared to that at the beginning.
Changes in categories of QoL:

- Fatigue reduced over the course of treatment
- Pain level increased slightly
- There was no requirement for pain medication over the course of the treatment
- Swallowing ability remained the same
- Oral cavity changes improved
• Nutrition improved slightly
• Mood improved over the course of treatment
• Psychosocial effects and perceived QoL also improved

A lot of these results were unusual, usually a head and neck patient experiences more negative changes the further through treatment they progress. It may be that this patient experienced a reduction in anxiety, got used to the treatment and the side effects or it is possible that the effects of the previous surgery diminished the more time that passed causing a perceived improvement in QoL.

Patient’s descriptive experience
The patient found the mouth-bite and mask very uncomfortable and early in treatment the mask had to be loosened and assessed by the oncologist. Treatment proceeded and the patient started using the soda and salt mouthwash every two hours as well as the honey three times daily. The honey was diluted with warm water to make the honey easier to apply to the oral mucosa.

During the first week of treatment the patient handled the honey and mouthwashes well and there was no evidence of mucositis and no descriptions of pain. Since his surgery WHN5 had maintained a good diet, he knew the importance of maintaining a high calorie and high protein diet throughout treatment and was well-equipped with a blender to puree his food. The first reaction the patient noticed toward the end of the first week was a slightly dry mouth, mainly at night.

Towards the end of week two (18Gy) no further radiation effects were evident; the mouth was clear of mucositis and infection and the patient had made no changes to his eating or drinking. The dryness of mouth became more evident after 38Gy (week four) but this did not cause any alterations in oral intake. The patient had been prescribed bongela and was using it sparingly.

During week five (44Gy) the patient noticed pain in the right buccal area although it was not severe enough to warrant pain medication. He found that the honey stung more on the right side of the mouth and more so than the other mouthwash he was using. The oral pain did not
extend to the throat. At the end of week five (48Gy) an area of ulceration developed on the right side of the patient’s mouth but it still did not require oral analgesia. At this stage the patient reported a good appetite with no nausea; he was drinking without pain and was trying to supplement his diet with one Fortisip per day.

After 50Gy patchy mucositis was evident and the right ulcer was clearly visible but “not too painful”. WHN5’s QoL form reported his pain level was worse than the beginning of treatment, his swallowing had got slightly worse but the other five categories had marginally improved which was interesting given the cumulative effect of the radiation dose.

At this stage in his treatment the patient was continuing with the honey three times a day. He was instructed to continue coating all the oral mucosa by moving his tongue although his tongue movement was limited by his graft. It was interesting to note that despite an increase in pain his perceived QoL score had improved.

For the rest of the treatment the patient maintained the same pureed diet with no other changes in the oral cavity; the level of mucositis remained the same. Over the whole course of treatment delivery of 60Gy the patient only suffered 0.9kg weight loss which results from his good oral intake throughout treatment.
### 3.3.4 Honey patient WHC6

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<td>PEG prior</td>
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<tr>
<td>Sites at risk</td>
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WHC6 was a 46 year old male who presented to his GP with a two to three month history of a lump in the right side of his neck. Investigations indicated an enlarged right jugulo-diagastric lymph node and an unusual looking right tonsil. WHC6 was diagnosed with diffuse large B cell lymphoma (Non-Hodgkin’s lymphoma) of the Waldeyer's Ring staged 2A.

The patient proceeded to a tonsillectomy and once it was confirmed that his disease was confined to his neck alone chemoradiation was recommended for disease management. R-CHOP chemotherapy was commenced and tolerated well. Adjuvant radiation therapy ensued with a total of 40Gy advised for local control. The radiation treatment was of radical intent and the therapy course was divided over two phases; phase I delivered 36Gy in 20 fractions (1.8Gy per fraction) then phase II delivered 4Gy in 2 fractions to the ICRU reference point.

The treatment plan involved a six field conformal technique for phase I (four fields for the upper neck and two for the lower) then a simpler two field conformal plan for phase II. The plan used a combination of 6 and 18MV beams. The overall plan aimed to treat both sides of Waldeyer’s ring and the right neck nodes and supraclavicular fossa.
WHC6 met the trial criteria and was randomised to the honey arm. He was a compliant man who gave good descriptions of his experience. Despite persisting through initial discomfort when taking the honey he found it too difficult to continue after 28.8Gy (six fractions prior to treatment completion) when he had a bad case of mucositis associated pain that was not well controlled with analgesia.

Sites at risk

The two phase conformal plan for WHC6 put five sites of his oral cavity at risk of mucositis including the right buccal mucosa, the ventral and dorsal aspect of the tongue, the floor of mouth and the oropharynx.

![Diagram of oral cavity sites at risk](image)

**Figure 34. WHC6 oral cavity sites at risk**

The following Figures illustrate the distribution of dose above 40Gy delivered by the conformal radiation plan.
Figure 35. WHC6 anterior view of treatment area

Figure 36. WHC6 lateral view of treatment area
Mucositis

At 18Gy the first reactions became evident, six areas of mucositis and two of erythema. The right and left buccal mucosa had patchy mucositis from 18Gy to 25.1Gy which then fluctuated throughout treatment. Reactions of the ventral aspect of the tongue also fluctuated as did the buccal mucosa. The dorsal aspect of the tongue and the hard and soft palate had patchy mucositis at 18Gy until 25.2Gy then these areas healed slightly and erythema was evident until the end of treatment. The floor of mouth and oropharynx were erythematous from 18Gy until treatment completion.
Weight
Three weeks prior to radiation treatment commencing the patient weighed 100.8kg, he then gained two kilos as his eating improved as the effects of his prior surgery reduced. At the beginning of radiation treatment WHC6 weighed 103kg and over the course of treatment lost 5.4kg, this corresponded to a percentage weight loss of 5.2% compared to his day one (of radiation treatment) weight.

Figure 39. WHC6 change in weight vs dose

Diet
WHC6 had suffered earlier diet changes due to the effects of surgery but these had improved so he was back to ‘normal’ food at the beginning of radiation treatment. Radiation effects caused him to reduce his intake to soft food towards the end of treatment.

QoL
WHC6 completed two QoL forms over the course of his treatment which illustrate the negative changes in his QoL. In his final week of treatment it was obvious (through verbal communication) WHC6 had a significantly lower mood and although he did not fill in a QoL form at this time his QoL had reduced.
Changes in categories of QoL:

- Fatigue and pain increased
- The patient used pain medication the whole way through treatment
- Swallowing became more difficult
- The oral cavity changes became more negative
- The patient reported nutrition level remained the same
- Mood became more negative
- Psychosocial aspects of treatment remained the same
- There was a decrease in perception of QoL

*Patient’s subjective experience*

The patient had lost a small amount of weight after his tonsillectomy then gained eight kilograms during his course of chemotherapy. Upon commencement of radiotherapy he had a good appetite and was eating a normal diet with three meals a day. After 7.2Gy had been delivered (week one) the patient had noticed mild tiredness and nausea but no skin reaction. He was using the manuka honey three times a day with no problems. After 9Gy the patient began to find the sweetness of the honey difficult to tolerate, it was contributing to his nausea. To avoid ceasing the honey completely he was advised to mix it 1:3 with lemon and barley juice. There were no reports of mucositis or erythema. The patient’s first QoL questionnaire showed a low perceived QoL score of three.

Oral changes continued as the dose delivered increased. After 10.8Gy (week two) the patient reported no taste; “everything tastes like cardboard”. He reported a cotton wool ball or flour feeling in his mouth but no pain. WHC6 was continuing with the honey but only managing it twice a day and had to spit it out after swirling it around his mouth because it made him nauseous if he swallowed it.

At 16.2Gy (end of week two) WHC6 reported his mouth was uncomfortable and very dry. He was attempting to eat normal food but found it “very very” difficult to swallow. The patient reported drinking water constantly and feeling very tired. At 18Gy the pain in his mouth increased and there was visible mucositis causing difficulty with eating, he was only managing jelly and ice-cream. WHC6 persisted with the honey and followed a stringent mouth wash regime with baking soda, difflam, nystatin and the honey mixture between two and four times a day. The patient also monitored his codeine intake to maintain a good level of pain control. The doctor described “quite a marked radiation reaction and thickened saliva”. The patient’s perceived QoL score at this point had decreased and six of the seven QoL categories were reported as worse compared to earlier in his treatment.

At 28.8Gy the patient stopped taking honey after finding it too much to tolerate. The initial mucositis had subsided but the inflammation caused the buccal mucosa to puff out and press
against teeth causing a painful ridge of mucosal tissue. The patient began taking biotene mouthwash to combat the constant dry mouth. After another fraction a metallic taste had developed.

At completion of the course of treatment there was grade two mucositis, a dry mouth and pain that was managed with codeine. The patient’s nutrition had been maintained through oral intake.
### 3.3.5 Honey patient DHC1

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<td>Treatment plan</td>
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<td>PEG prior</td>
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<td>Sites at risk</td>
<td>8</td>
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DHC1 was a 69 year old male of European descent who was diagnosed with SCC of the base of tongue. The patient had a two year history of a lump on the left side of his neck. He had been seen in October 2007 with a small lump which was thought to be a dental problem. There was little change in the size of the lump until early 2009 when it began rapidly increasing in size. As well as the visible lump other symptoms of the disease included a slight husky voice and discomfort below the left ear. There were no symptoms of dysphagia, aspiration or throat pain.

DHC1 was a non-smoker but had worked around smokers for 30 years. He had a moderate alcohol intake. His only reported co-morbidities were hypertension and florid disseminated superficial actinic porokeratosis (DSAP). The patient’s disease was staged T4N3cM0 and his recommended disease management plan included Cisplatin and 5FU chemotherapy used in conjunction with IMRT treatment delivering a total prescribed dose of 69.5Gy. The radiation plan was delivered over two phases with 6MV beams used in both. Phase I used a nine field plan to target the oropharynx and the right and left supraclavicular fossa with 50Gy delivered in 25 fractions. Phase II involved a three field boost of 19.5Gy in 15 fractions (1.3Gy per
fraction) to the oropharynx alone. The patient met the trial criteria and was consented and randomised to the manuka honey arm.

Sites at risk
DHC1’s two phase IMRT plan was highly conformal but put eight oral cavity sites at risk of developing mucositis. These sites included the hard and soft palate, the left and right buccal mucosa, the oropharynx and floor of mouth as well as the ventral and dorsal aspects of the tongue.

Figure 42. DHC1 oral cavity sites at risk

Mucositis
There were no visible reactions until the sixth week of treatment (53.9Gy) when erythema was noted on the soft palate and oropharynx. These areas went on to develop confluent mucositis at 63Gy. Also at 63Gy the hard palate became erythematous and then soon developed confluent mucositis which remained until the end of treatment. During week seven (60.4Gy) the floor of mouth developed erythema which increased to confluent mucositis later in the week. The upper lip did not react at all during treatment but the lower lip developed erythema during the last week. Also in the last week of treatment the lower labial mucosa and lower and upper gingiva became erythematous while the upper labial
mucosa developed patchy mucositis. The right and left buccal mucosa developed confluent mucositis (63 and 66.9 respectively), as did the ventral and dorsal aspects of the tongue.

![Figure 43. DHC1 mean mucositis score (TS/NSR) vs dose](image)

**Figure 43. DHC1 mean mucositis score (TS/NSR) vs dose**

**Weight**

DHC1 had a 12kg weight loss over the course of the radiation treatment which was a percentage weight loss of 12.8. Due to the effects of the radiation treatment the patient went on to lose another 6.5kgs after treatment was completed.

![Figure 44. DHC1 change in weight vs dose](image)

**Figure 44. DHC1 change in weight vs dose**
**Diet**

At the beginning of treatment the patient had a normal diet. As the treatment reactions began to manifest DHCl’s diet became predominantly soft and then towards the end of treatment the patient required NG tube insertion and significant Fortisip supplementation.

![Diagram showing diet progression]

**QoL**

DHCl was a motivated individual who was keen to comply with the trial requests and he filled in five QoL questionnaires over the course of his treatment. Review of these questionnaires gives a good illustration of his experience.

![Graph showing change in QoL score vs dose]

**Figure 45.** DHCl change in perception of QoL score vs dose
Figure 46. DHC1 negative change in QoL categories vs dose

Changes in categories of QoL:
- Fatigue fluctuated throughout treatment but there was an overall increase from beginning to end
- Pain increased throughout treatment although there was a slight decrease at treatment completion
- Swallowing became significantly more difficult
- There were negative oral cavity changes until midway through treatment when they stabilised
- Nutrition fluctuated throughout treatment but was worse at the end
- Mood became worse over the course of treatment then improved at the completion close to the level it was at the beginning
- The psychosocial effects became more negative
- The patient’s perceived QoL decreased over the course of treatment but there was a slight improvement at the end of treatment which may be due to better management of his symptoms in hospital

Patient’s descriptive experience

After one week of treatment (10Gy) the patient weighed 93.6kg but felt this was 1kg above his normal weight. He had a normal diet with a reduction in the amount of spice and chillies he was eating. The tumour had been causing a reduction in his ability to open his mouth and
move his tongue and there had also been reports of occasional haemoptysis. During week two (16Gy) the patient vomited despite taking antiemetic medication, his saliva was thick and he had lost his taste. The dietician advised him to increase his fluid intake at this point.

Completion of week three saw DHC1 eating a good range of foods despite food “tasting terrible”. The left lymph node was visibly smaller and the patient described the skin in the area feeling “less tight” and he was able to open his mouth wider than last week. The patient was a little more nauseous because he was not taking his medications routinely. Despite his dry mouth and thick saliva there was no visible mucositis.

A week later (40Gy) there was another noticeable reduction in the palpable neck node and there was still no mucositis visible in the patient’s oral cavity. The patient was experiencing bloody discharge from his nose which was thought to be related to his chemotherapy. At this point the patient reported that his taste had improved but he still had a reduced appetite and worked hard to eat a variety of foods (small amounts often).

The patient was continuing with the honey application but found it was irritating his lips. He was advised to dilute the honey, maintain regular teeth cleaning and was given advice on how to avoid irritation to the skin in the treatment area which had become red and itchy.

There were still no signs of mucositis halfway through week five (46Gy). At the end of this week the patient’s weight had decreased and food was no longer enjoyable, he found eating a “chore”. These nutritional changes were due to lack of taste, thick saliva and pain when swallowing. DHC1 was advised to take two Fortisips per day to help with nutritional maintenance and he was given advice on a high energy, high protein diet. Panadol was prescribed for pain. The patient’s oral mucosa was intact at this stage.

Over the following weekend (52.6Gy) the patient did not eat or drink due to pain so oxycontin was commenced. One fraction later the patient experienced a difficult evening in which he woke with difficulty breathing due to the thick mucous in his throat. His pain control had improved with the addition of xylocaine viscous.

At the end of week six (56.6Gy) morphine was required to enable eating. The patient maintained a soft diet and one Fortisip per day, he found slightly thicker fluids easier to
swallow. The patient tried pure aloe vera juice to soothe the inflammation in the throat and to aid swallowing because he was becoming dehydrated (had only had 1.5L over the previous three days). At this stage in the treatment hiccups were also a frequent problem and the application of the honey was very painful.

After 60.4Gy the patient was admitted to hospital and reported feeling miserable. There were areas of confluent mucositis but the oropharynx could not be assessed due to the level of pain when the patient opened his mouth. DHC1 stopped using the honey at this stage.

There was further increase in the level of pain during week seven, medicine was difficult to swallow and sweet foods and Fortisips led to a “burning feeling”. A NG tube was inserted to try and stabilise the patient’s nutritional status.

Treatment was completed after delivery of 69.5Gy and at this stage the patient was having three or four Fortisips per day via his NG tube including overnight pump feeding. He had no taste and was on regular morphine pain relief. The patient filled in a questionnaire about the honey application. He reported that he had tried to adhere to the guidelines for applying the honey but as the treatment progressed he found he could not always manage due to the burning feeling. He also reported the honey was not easy to use and was messy.
3.3.6 Control patient WHN1

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A 78 year old female, WHN1 was the eldest of the trial patients. She was referred for radiation therapy after presenting with a recurrent SCC of the maxillary gingiva. Initial disease management had involved surgical resection of the tumour and after the disease recurred WHN1 had another surgical procedure to remove the local recurrence. Two months after the local recurrence resection radical radiation therapy was commenced with the prescription of 48Gy in 20 fractions, 2.4Gy per fraction.

The treatment plan utilised 6MV parallel opposed (POP) conformal fields to target the mouth alone. A mouth bite and mask were used to improve accuracy and remove the tongue from the treatment area as much as possible. WHN1 was randomised to the control arm of the trial so received the current standard of care at the Wellington department. WHN1 had close dietician and district nurse involvement throughout her course of treatment. Although the initial plan prescription was 48Gy the treatment was completed prematurely after delivery of 40.8Gy (17 fractions) due to severe confluent mucositis across the labial gingiva with poorly controlled pain.
Sites at risk

The simple POP treatment plan put seven of the patient’s oral cavity sites at risk of mucositis. These include the upper vermilion lip, the upper labial mucosa, the upper gingiva, right and left buccal mucosa, the dorsal aspect of the tongue and the hard palate.

![Diagram of oral cavity sites at risk](image)

Figure 47. WHN1 oral cavity sites at risk

The following Figures illustrate the distribution of dose above 40Gy delivered by the conformal radiation plan.
Figure 48. WHN1 the anterior view of the treatment area

Figure 49. WHN1 lateral view of the treatment area
Mucositis

The first reactions were evident at the beginning of week three (28.8Gy); erythema on the upper gingiva and right buccal mucosa. These two sites progressed to patchy mucositis at 31.2Gy (later in week three) then confluent mucositis shortly after (36Gy and 40.8Gy respectively). The left buccal mucosa developed patchy mucositis at the end of week three (36Gy) which became confluent at the end of treatment (40.8Gy). The upper lip although painful over the whole course of treatment first developed erythema at 31.2Gy then patchy mucositis at treatment completion. Patchy mucositis was evident on the upper labial mucosa at 31.2Gy and went on to become confluent at 36Gy.

Figure 50. WHN1 transverse slices at the isocentre and 1.2cm superior to the isocentre

Figure 51. WHN1 mean mucositis score (TS/NSR) vs dose
Weight

WHN1 did not suffer an overall weight loss during her radiation treatment. Despite an initial increase her weight then dropped back to that at the beginning of treatment.

![Weight change graph](image)

*Figure 52. WHN1 change in weight vs dose*

Diet

WHN1 had been on a soft diet since her surgery so continued this throughout radiation treatment. As the pain in her gingiva increased she moved to pureed meals three times a day supplemented with Fortisip.

QoL

WHN1 only completed two QoL forms toward the end of her treatment which unfortunately does not give a base measure for comparison.
Figure 53. WHN1 change in perception of QoL score vs dose

Figure 54. WHN1 negative changes in QoL category scores vs dose

Changes in categories of QoL:

- Fatigue remained the same
- Pain increased
- Pain medication was used the whole way through treatment
- There was no change in the patient’s ability to swallow
- No changes were reported in the patient’s oral cavity
- The patient’s nutritional state became more negative throughout treatment
- Mood decreased
- The psychosocial effect remained the same as did the perceived QoL.
Patient’s descriptive experience

The first three fractions proceeded without the patient experiencing any symptoms but toward the end of the first week of treatment (9.6Gy) the patient developed a burning sensation in her right upper lip area despite there being no evidence of mucositis.

At the end of week two (24Gy) there were no visible mucositis reactions but the patient had marked discomfort at the previous surgical sites (anterior/superior gingiva and right/superior gingiva), this neuropathic pain had remained since surgery but became slightly worse so amitriptyline was prescribed. During week three (28.8Gy) WHN1 had a painful nasal canal with minor bleeding from the nose, she required an analgesia assessment and an increase in pain medication. After delivery of 31.2Gy the patient was very unwell with a painful mouth and ulcerations on the upper gingiva and upper labial mucosa. The area of pain was where the buccal mucosa was tight against one of her remaining teeth.

Although eating proved very difficult at this stage the patient persisted with soft foods and Fortisip supplementation. There was severe nasal congestion due to thick mucous in her nasal passages, she was advised to use steam inhalation to combat the congestion.

After four weeks of treatment (delivery of 40.8Gy) areas of confluent ulceration were evident on the whole of the upper labial mucosal surface and the lip was swollen and very painful. The patient was adamant she wanted the treatment stopped and felt “her body had had enough”. The oncologist reviewed the patient and advised staff to cease treatment. WHN1 was using bongela, xylocaine viscous, codeine, and panadol and after pain review at 40.8Gy morphine was added.

The patient’s perceived QoL score did not change between weeks three and four despite a negative change in the mood and nutrition categories. It was interesting that although the patient’s weight fluctuated during treatment there was no overall weight loss. The high dose per fraction and the pain associated with the treatment would have made weight loss more likely.

The patient used a humidifier at night during the last week of treatment and continued to use it after treatment completion. The aim was to try and break down the mucous in her mouth and throat. She found it beneficial as it improved her ability to breathe through her nose.
3.3.7 Control patient WHC2

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WHC2 was a 54 year old male who presented with advanced, poorly differentiated SCC of the left tonsil. The staging investigations this patient underwent indicated T3N2M0 disease. The tumour was described as a firm nodular mass at the base of the sternocleidomastoid muscle.

Chemoradiation was the recommended treatment for radical disease management. Cisplatin was the prescribed chemotherapy agent to act as a radio-sensitizer used in conjunction with a 70Gy total dose radiation plan to be delivered in 35fractions (2Gy per fraction) over seven weeks. WHC2 consented to chemoradiation and trial participation and was randomised to the control arm to receive the standard of care at the Wellington department. Pre-treatment procedures involved a dental review and PEG insertion.

The 70Gy radiation plan utilised an eleven field technique and split the dose delivery over two phases; phase I targeted the oropharynx and whole neck to deliver 50Gy in 25 fractions using a combination of 6 and 18MV beams. Phase II followed delivering 20Gy in 10 fractions to a smaller volume containing the left tonsil and neck node. The planned organ at risk for both phases was the spinal cord and shielding was used to avoid excess dose to this
structure. Due to the side effect risk of the chemoradiation treatment the patient had close
dietician and nursing involvement as well as the standard weekly doctor review and
d fortnightly blood tests.

Sites at risk
The eleven field conformal two phase plan put eight of WHC2’s oral cavity sites at risk
including the right and left buccal mucosa, the ventral and dorsal aspects of the tongue, the
hard and soft palate, the floor of mouth and the oropharynx.

Figure 55. WHC2 oral cavity sites at risk

The following Figures illustrate the distribution of dose above 40Gy delivered by the
conformal radiation plan.
Figure 56. WHC2 anterior view of treatment area

Figure 57. WHC2 lateral view of the treatment area
**Mucositis**

WHC2 did not experience any oral mucosal reactions until 50Gy had been delivered (five weeks). Patchy mucositis on the soft and hard palate became evident at the beginning of week six of treatment. All other oral cavity areas remained clear of erythema, patchy or confluent mucositis for the whole duration of the treatment.

**Weight**

The patient suffered a 14.2kg weight loss over the course of treatment which corresponded to a 12.3% decrease from the start of treatment.
Figure 60. WHC2 change in weight vs dose

Diet
The patient had regular contact with the oncology dietician and from communication with the patient and review of his clinical notes it was evident his diet changed significantly over the course of treatment as illustrated in the diagram below.

QoL
This patient did not complete any QoL forms throughout his treatment.

Patient’s descriptive experience
Over the delivery of the first two weeks of treatment (20Gy) WHC2 reported no pain or nausea and there was no evidence of mucositis at assessment. Despite the lack of reactions the patient lost over 5kgs in these first 10 fractions. Hiccups were a problem for him for a couple of days.

During his third week of treatment (22Gy) the patient was admitted to hospital with severe dysphagia and dehydration, he was suffering from a sore stomach and throat, nausea and a headache. There were no visible reactions in his mouth but it was likely that there was mucositis developing in his throat. He reported his sore throat had limited his eating and
described the sensation of “a lump in the throat”. Despite his reluctance to pump feed via his PEG he was instructed to increase his Fortisip PEG delivery to four per day.

At the end of his third week (30Gy) there was written report of a visible decrease in the size of the left neck mass. WHC2’s throat was still sore and he was started on morphine. At 36Gy there were still no visible oral cavity changes although the sore throat descriptions indicated significant oropharyngeal mucosal changes. The patient’s taste has decreased and he was maintaining nutritional intake primarily through PEG use with some additional oral intake. WHC2 reported feeling very nauseated from the chemotherapy, would often try to eat or use the PEG and then vomit soon after. He was unable to swallow tablets orally so they were administered through his PEG for the remainder of his treatment (any oral medications had to be crushed). He was also started on IV fluids at this point.

After delivery of 40Gy (4 weeks) the patient had to be admitted via ambulance to the short stay unit due to severe nausea and vomiting. Immediately prior to admission he had no oral intake and no Fortisips via his PEG. He had lost over 10kgs since the first week of his treatment. The throat pain was still severe but there was still no visible mucositis. The patient felt better after staying overnight in hospital.

Partway through week five of treatment (44Gy) WHC2 had better pain control and his nausea and vomiting had settled so he was able to be discharged from hospital two fractions later. Back at home after 48Gy the patient reported no nausea or vomiting and had recommenced PEG feeding. He felt a lot better when not on chemotherapy.

During the sixth week of treatment (50Gy) the patient had a very dry mouth and throat describing it like “lava” or “chillies” in his throat. He was using the salt and baking soda mouthwashes which he found eased the pain temporarily. At this stage his nutritional intake was maintained via PEG use and Fortisip supplements. Most of the oral cavity was clear although the roof of the mouth had patchy mucositis.

There was another increase in the level of dysphagia described by the patient at 52Gy, on examination there was evidence of thick saliva and patchy mucositis. Liquid pain medication was administered for the sore throat. At 54Gy the mucositis level had decreased and after 68Gy the patient felt “like things were picking up”. WHC2 was an admitted to hospital for
his chemotherapy delivery and for better antiemetic control. At the completion of treatment the patient had lost a total of 14kgs since the first week. At this point he was pump feeding over night and taking three Fortisips per day to prevent further weight loss.

The lack of visible mucositis on all oral cavity areas aside from the soft and hard palate was unusual. The soft and hard palate were two of eight oral cavity sites that were considered at risk of mucositis.
### 3.3.8 Control patient WHN4

<table>
<thead>
<tr>
<th>Patient</th>
<th>WHN4</th>
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<tbody>
<tr>
<td>Date of Birth</td>
<td>22/02/1949</td>
</tr>
<tr>
<td>Age at trial inclusion</td>
<td>60</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>Site of disease</td>
<td>Nasal cavity</td>
</tr>
<tr>
<td>Disease</td>
<td>SCC</td>
</tr>
<tr>
<td>Stage</td>
<td>TxN1M0</td>
</tr>
<tr>
<td>Treatment plan</td>
<td>Conformal radiation therapy</td>
</tr>
<tr>
<td>Radiation dose</td>
<td>60Gy/30#s</td>
</tr>
<tr>
<td>Treatment intent</td>
<td>Radical</td>
</tr>
<tr>
<td>Trial arm</td>
<td>Control arm</td>
</tr>
<tr>
<td>PEG prior</td>
<td>No</td>
</tr>
<tr>
<td>Sites at risk</td>
<td>8</td>
</tr>
</tbody>
</table>

WHN4 was a 60 year old female diagnosed with SCC recurrence of the left nasal cavity. Due to previous surgery for the initial tumour the new recurrence tumour size was unable to the staged but the nodal status was classified as N1 and there was no evidence of metastatic spread at the time of diagnosis; TxN1M0.

Disease management involved a course of post-operative radiotherapy to the left sub-mandibular area delivering a total of 60Gy in 30 fractions. Prior surgery had involved a sub-mandibular resection which had caused a left facial weakness and limited range of motion. The treatment intent was radical with no adjuvant chemotherapy. A conformal beam arrangement using three 6MV beams was able to treat the target area while minimising dose to normal tissues. A mouth-bite and mask were used to stabilise the patient’s treatment position. The patient was keen to participate in the trial and was randomised to the control arm.
Sites at risk

The three field conformal plan put eight oral cavity sites at risk including the lower labial mucosa and lower gingiva, the left buccal mucosa, and the ventral and dorsal aspects of the tongue, the soft palate, the floor of mouth and the oropharynx.

Figure 61. WHN4 oral cavity sites at risk

The following Figures illustrate the distribution of dose above 40Gy delivered by the conformal radiation plan.
Figure 62. WHN4 anterior view of the treatment area

Figure 63. WHN4 lateral view of the treatment area
Figure 64. WHN4 transverse slices at the isocentre and 1.5cm inferior to the isocentre

*Mucositis*

Patchy mucositis became evident at 36Gy on the left and right buccal mucosa and the ventral aspect of the tongue. The patchy mucositis remained on these three areas then healed after 44Gy and there were no reports of any other erythema or mucositis.

Figure 65. WHN4 mean mucositis score (TS/NSR) vs dose

*Weight*

WHN4 suffered an 11.4kg weight loss which was equivalent to a percentage weight loss of 12.6.
Diet

The patient had undergone two surgical procedures which had affected her ability to eat, her standard diet consisted of soft pureed foods and fruit juices. WHN4 continued with her soft diet throughout treatment and supplemented her diet with Ensure drinks.

QoL

WHN4 filled in three QoL questionnaires throughout her course of treatment.
Changes in categories of QoL:

- Fatigue increased gradually throughout treatment
- Pain increased midway through the treatment and then remained the same
- Pain medication was used the whole way through the treatment
- Swallowing became significantly more difficult as the treatment progressed but then got better toward the end of treatment
- Negative oral cavity changes became slightly worse during treatment
- Nutrition got significantly worse midway through treatment then improved towards the end of treatment which was probably a result of WHN4 learning to manage her nausea and food intake (soft food and ENSURE supplements)
- Mood became worse midway through treatment then improved a little
- Psychosocial aspects of treatment got gradually worse
- Perception of QoL reduced significantly midway through treatment then remained at this low level until the end of treatment

*Patient’s descriptive experience*

After three fractions (6Gy) the patient had noticed a throbbing feeling in her mouth close to the areas of previous surgery. She often woke up with a dry mouth and during the day experienced a tired “heavy” feeling. At the end of the first week (10Gy) there were no oral cavity changes evident on examination and there was no new pain in her mouth from the radiation treatment (only that which remained since the surgery). The patient had maintained a pureed diet since the surgery and had found pineapple juice useful to combat her dry mouth. At this stage in the radiation treatment the patient was using biotene mouthwash and the baking soda and salt mouthwash.

At the completion of week two (20Gy) WHN4 found it difficult to open her mouth and was given exercises to try and increase this range of motion. Difflam spray was recommended before using the mouthwashes to try and reduce the associated burning sensation. Paracetomol was the patient’s only source of pain relief at this stage as codeine caused her to become nauseated. Her diet now included high calorie smoothies and Ensure drinks.

During week three of treatment (24Gy) WHN4 found her dry throat caused her to get pills stuck which subsequently caused dry retching and vomiting. These reactions in turn increased the pain in her throat and so she increased her medication to codeine despite the associated nausea. At this stage there was no visible mucositis in the oral cavity. The dietician instructed the patient to increase her Ensure use due to her loss of interest in food.

Pain in WHN4’s neck and throat increased another level at the end of week three. She was reviewed by the oncologist and admitted for IV fluids and anti-nausea medication. The
patient’s QoL form illustrates her poor condition with a large reduction in her perceived QoL score. The patient reported all seven QoL categories had got worse.

Over the next couple of fractions the patient suffered vomiting even with water alone. She was discharged from hospital but then did not eat for two days and only managed to drink 400mL of water a day. WHN4 was then readmitted to hospital through ED for further IV management as she was severely dehydrated. The pain in her mouth was not well managed so was increased to morphine (capsule and liquid) and paracetamol. WHN4 described a strong metallic taste in her mouth.

The end of week four (38Gy) saw the patient experience a similar feeling like something being stuck in her throat. She maintained her morphine medication and amitriptyline was introduced for her left sided neuropathic pain. Ondansetron was also added at this stage to combat her nausea after ongoing weight loss. Minimal mucosal reactions were evident.

At 46Gy (week five) oral thrush medication was prescribed for the patient and better pain control allowed an increase in her appetite. WHN4 was able to gradually increase her oral intake of soft foods.

After six weeks (60Gy) WHN4 was able to eat a lot better, her diet consisted of Ensure supplements, yogurt, ice-cream and fluids. The oral thrush had cleared up and there was no pain or mucositis evident although the thick saliva remained. The patient was extremely relieved to finish treatment. She was advised to continue her Ensure supplemented diet and to increase her intake of water.
3.3.9 Control patient WHC7

<table>
<thead>
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<tbody>
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<td>Date of Birth</td>
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<tr>
<td>Age at trial inclusion</td>
<td>52</td>
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<tr>
<td>Gender</td>
<td>Female</td>
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<tr>
<td>Site of disease</td>
<td>Right tonsil</td>
</tr>
<tr>
<td>Disease</td>
<td>SCC</td>
</tr>
<tr>
<td>Stage</td>
<td>T2N3M0</td>
</tr>
<tr>
<td>Treatment plan</td>
<td>Chemoradiation (Cisplatin)</td>
</tr>
<tr>
<td>Radiation dose</td>
<td>70Gy</td>
</tr>
<tr>
<td>Trial arm</td>
<td>Control</td>
</tr>
<tr>
<td>PEG prior</td>
<td>Yes</td>
</tr>
<tr>
<td>Sites at risk</td>
<td>8</td>
</tr>
</tbody>
</table>

WHC7 was a 52 year old female of Cook Island and Maori descent. Her diagnosis followed a five month history of a lump in her right upper neck with no associated pain or problems swallowing or breathing. Investigations indicated a SCC of the right tonsil staged T2N3M0. The patient was referred for radical chemoradiation as her disease management plan.

WHC7 had a history of tobacco use and occasional alcohol intake. She worked as a fulltime caregiver at a rest home and continued to do so throughout her course of treatment. Prior to her treatment she underwent a total dental clearance and a PEG insertion.

The patient’s course of chemoradiation involved three weekly Cisplatin infusions and a total radiation dose of 70Gy. Three phases were used in the eleven field conformal radiation plan to target the sites of disease and possible microscopic spread without overdosing critical structures (the planned organ at risk was the spinal cord). Phase I targeted the oropharynx and bilateral upper and lower neck to 50Gy in 25 fractions. Phase II delivered an additional 10Gy in five fractions to the upper neck. Phase III followed with an additional 10Gy to the oropharynx and right upper neck. All three phases used a combination of 6 and 18MV beams.
During the delivery of phase I the patient lost a lot of weight and had to be re-scanned and re-planned with slight alterations in field sizes and beam weightings to account for the tissue deficit. Due to the intensive treatment the patient had close involvement with the dietician, social worker, district nurse, Pacific health centre and speech language therapist. She also had weekly blood tests to meet the chemotherapy criteria. WHC7 was consented for trial participation and was randomised to the control arm to receive the current standard of care at the Wellington department.

Sites at risk

The eleven field radiation plan which put eight oral cavity sites at risk including the right and left buccal mucosa, the ventral and dorsal aspect of the tongue, the hard and soft palate, the floor of mouth and oropharynx.

![Figure 69. WHC7 oral cavity sites at risk](image)

The following Figures illustrate the distribution of dose above 40Gy delivered by the conformal radiation plan.
Figure 70. WHC7 anterior view of treatment area

Figure 71. WHC7 lateral view of treatment area
Figure 72. WHC7 transverse slices at the isocentre, 3.6cm superior, 5.1cm superior and 7.2cm superior to the isocentre

*Mucositis*

WHC7 did not experience any mucositis, patchy or confluent, at any stage during her treatment. The only two areas that showed any sign of reaction were the left and right buccal mucosa in which erythema developed after 30Gy until the end of treatment.

Figure 73. WHC7 mean mucositis score (TS/NSR) vs dose
**Weight**

WHC7 had a significant weight loss of 12.5kg over the course of her treatment which was a percentage weight loss of 18.1.

![Figure 74. WHC7 change in weight vs dose](image)

**Diet**

Her diet had been affected by surgery prior to radiation treatment delivery and was then affected again by the radiation related reactions.

- Soft diet since her dental clearance
- PEG pump feeding, IV fluids

**QoL**

WHC7 filled in three QoL forms throughout her treatment which showed the negative change in QoL the further through treatment she progressed.
Figure 75. WHC7 change in the perception of QoL score vs dose

Figure 76. WHC7 negative change in QoL category scores vs dose

Changes in categories of QoL:
- Fatigue decreased slightly then increased more significantly toward the end of treatment
- Pain remained same during first half of treatment then increased more dramatically
- The patient used pain medication the whole way through treatment
• Swallowing problems reportedly decreased midway through treatment (which was unusual) then increased back to the initial level near the start of treatment
• Oral cavity changes stayed at a relatively low level the whole way through treatment
• Nutrition gradually got worse throughout treatment
• Mood became more negative towards the end of treatment
• Psychosocial effects remained fairly similar
• Perceived QoL gradually decreased over course of treatment

Patient’s subjective experience
The first reaction experienced by WHC7 was a dry mouth after three fractions (6Gy). At the end of week one her oral intake was normal and she was using baking soda and salt mouthwashes.

During week two (12G) there was no visible mucositis but the patient suffered from a loss of taste and nausea. The patient’s diet was significantly reduced by these reactions as she found it difficult to find foods she could tolerate without vomiting. Her diet consisted of ice cream, yogurt and one Fortisip per day administered via her PEG. WHC7 found ginger ale better tolerated than water alone. Later in week two of treatment the dietician advised WHC7 to increase her Fortisip intake to three per day.

The patient reported no areas of pain but white areas were visible on the tongue and buccal mucosa and were thought to be oral thrush. At the end of the week (20Gy) the tongue still had thrush which was being treated with nystatin four times a day. The rest of the mouth was clear with no pain. Midway through week three (24Gy) the patient had a further loss of interest in food and was advised to increase her Fortisip intake to four per day.

After three weeks (30Gy) there was pain in the throat (primarily when swallowing), thick saliva and slight erythema on the buccal mucosa. Three fractions later (36Gy) the patient was nauseated from chemotherapy and had been vomiting for three days. The nausea, vomiting, thick mucous and saliva in the mouth all contributed to a significant reduction in oral intake. The patient was trained to use the PEG for overnight feeding and advised to take anti-nausea medication prior to food.
Humidification was commenced after four weeks of treatment and difflam spray was prescribed to help relieve pain. Overnight PEG feeding continuation was encouraged. Despite increased pain medication (codeine) the throat pain increased after 44Gy. Humidification was ceased during week five (46Gy) because the patient did not find it helpful. At the end of five weeks of treatment the patient had a very low mood. Her pain medications were increased to include xylocaine viscous and morphine.

The patient had a challenging time through to the end of the seven weeks of treatment (70Gy) with dehydration being a major problem due to not being able to swallow water or other liquids without gagging. The patient was admitted to hospital in the middle of week seven (64Gy) when her blood levels indicated severe dehydration. IV fluids were administered on the ward. If this patient had been randomised to the honey arm it is unlikely she would have been able to adhere to the honey application protocol.
3.4 Mucositis trail: Comparison between the treatment and control arms

3.4.1 Oral mucositis

Mean average mucositis scores
Honey patients had higher mean average mucositis scores than control patients (Figure 77.) even though in this small cohort the differences were not statistically significant.

![Figure 77. A comparison of mean average oral mucositis scores of patients in control and honey arms](image)

Percentage of patients developing oral mucositis
88.9% of all patients developed mucositis. 100% of honey patients developed mucositis while only 75% of control patients did, the other 25% only developed erythema of the mucosa. With respect to the extent of mucositis 44.4% of patients developed a maximum of grade three mucositis, 44.4% of patients developed a maximum of grade two mucositis while 11.1% of patients only developed grade one mucositis (erythema). Of the four patients that developed grade three mucositis 75% (n=3) were honey patients. Of the four patients that
developed grade two mucositis 50% were honey patients. 60% of honey patients developed grade three mucositis compared with 25% of control patients (Table 8.).

**Dose to onset of mucositis**

The dose to onset of mucositis varied significantly in both groups but on average the patients in the honey arm developed mucositis at a slightly lower dose compared to the control patients. The average dose for the development of oral mucositis for the honey patients was 33Gy. The average dose to the first oral cavity change (erythema) was slightly lower 31.2Gy. The average dose for development of oral mucositis for the control patients was 39Gy while the average dose for the first oral cavity change (erythema) was 36.8Gy. The results indicate that the honey patients developed mucositis at a lower dose and experienced a more severe grade of mucositis compared to the control patients.

<table>
<thead>
<tr>
<th><strong>Table 9. Dose at onset of oral mucositis</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
</tr>
<tr>
<td>WHN1*</td>
</tr>
<tr>
<td>WHN3</td>
</tr>
<tr>
<td>WHN4</td>
</tr>
<tr>
<td>WHN5</td>
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<tr>
<td>WHC2</td>
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<tr>
<td>WHC4</td>
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<tr>
<td>WHC6</td>
</tr>
<tr>
<td>WHC7</td>
</tr>
<tr>
<td>DHC1</td>
</tr>
</tbody>
</table>

*N = no chemo, C = chemo

**Percent of patients having treatment delays resulting from oral mucositis**

No trial patients had treatment delays because of oral mucositis symptoms however one control patient had to complete treatment early due to mucositis toxicity. This patient’s radiation plan had a 2.4Gy fractionation regime instead of the standard 1.8-2Gy per fraction regime. It is known that the higher dose fractionation (compared to standard fractionation) causes more acute side effects. Five patients were hospitalised with mucositis related effects; three control patients (two of these patients received chemotherapy) and two honey patients (one of these received chemotherapy).
3.4.2 Weight loss and food intake

Eight out of nine trial patients (88.9%) lost weight over the course of radiation treatment. The honey patients had an average percentage weight loss of 4.8 compared with 10.7 for the control patients. Figure 78. shows the average weight loss of patients in the control arm compared to those in the honey arm over the course of treatment. Patients in the control arm lost significantly more weight than those in the honey arm (p<0.05).

![Comparison of weights between patients in control and honey arm](image)

Figure 78. Comparison of weights between patients in control and honey arm

![Percentage weight loss for control vs honey patients](image)

Figure 79. Percentage weight loss of all trial patients (blue = control patients, yellow = honey arm patients)
Supportive nutrition/feeding intervention

With respect to feeding intervention 55.6% of trial patients (n=5) required a PEG or NG tube; 33.3% of patients had a PEG inserted (two control patients and one honey patient) and 22.2% of patients required NG tube feeding towards the end of treatment to stabilise their weight. Slightly more honey patients (60%) had feeding intervention (PEG/NG) compared with control patients (50%).

All trial patients experienced a decline in their nutritional intake over the course of their treatment. As the side effects of mucositis (and its associated pain), taste and saliva changes and nausea manifested patients were forced to adjust their nutritional intake. Changes were made by the patients themselves following advice given to them by the various health professionals involved in their care and some changes were enforced by health professionals (IV fluids and NG tube).

Review of the patients’ dietary sheets and the dietician’s clinical notes showed several major changes that occurred throughout treatment. All patients experienced a reduction in appetite and loss of enjoyment associated with eating. Eating became a negative experience often associated with a lot of pain “it became a chore”.

Figure 80. Average percentage weight loss of control vs honey patients
Table 10. Percentage of patients in each trial arm requiring PEG/NG feeding, hospitalisation and analgesics

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>PEG/NG feeding</th>
<th>Hospitalisation</th>
<th>Analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honey</td>
<td>60%</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Control</td>
<td>50%</td>
<td>75%</td>
<td>100%</td>
</tr>
</tbody>
</table>

3.4.3. Use of systemic analgesics (frequency, type and quantity)

Eight (four honeys and four controls) of the nine trial patients (88.9%) were on pain medication from the beginning of their treatment to the end (Table 9.). All of these eight patients increased the quantity, frequency or type of pain medication the further through their treatment they were. The one patient who did not require any pain medication was WHN5 who was a honey arm patient who did not receive any concurrent chemotherapy. Patients who had had surgery prior to radiation often reported pain at the surgery site early on in the radiation treatment. This neuropathic pain differs from the pain associated with mucositis but it was not easy to distinguish between the two.

3.4.4 QoL

Compliance with the trial requirements of a QoL questionnaire every fortnight was an issue for a number of patients while others filled in the questionnaires more frequently. Some patients found the forms too time consuming and others forgot about them despite frequent reminders. The level of compliance was related to each patient’s personality and their inherent belief system (whether they considered the forms worthy of their time).

Table 11. Number of QoL forms filled in by each patient and the doses at which they were filled in

<table>
<thead>
<tr>
<th>Patient</th>
<th>Number of QoL forms (doses, Gy)</th>
<th>Trial arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHN1</td>
<td>3 (28.8, 36, 40.8)</td>
<td>Control</td>
</tr>
<tr>
<td>WHN3</td>
<td>6 (2,16,28,50,60,66)</td>
<td>Honey</td>
</tr>
<tr>
<td>WHN4</td>
<td>3 (8, 26, 54)</td>
<td>Control</td>
</tr>
<tr>
<td>WHN5</td>
<td>2 (10, 50)</td>
<td>Honey</td>
</tr>
<tr>
<td>WHC2</td>
<td>No QoL forms</td>
<td>Control</td>
</tr>
<tr>
<td>WHC4</td>
<td>3 (4, 32, 60)</td>
<td>Honey</td>
</tr>
<tr>
<td>WHC6</td>
<td>2 (9, 23.4)</td>
<td>Honey</td>
</tr>
<tr>
<td>WHC7</td>
<td>3 (10,32,60)</td>
<td>Control</td>
</tr>
<tr>
<td>DHC1</td>
<td>5 (22, 40, 50, 56.5, 69.5)</td>
<td>Honey</td>
</tr>
</tbody>
</table>

In general the patients in the honey arm were more compliant than the patients in the control arm at completing the QoL forms. The average change in perceived QoL score throughout
treatment for the honey patients was -1.2 while the score for the controls was -2.3. The control patients had a greater decrease in perceived QoL over the course of treatment compared to the honey patients although it is difficult to directly compare the two groups because of the differing levels of compliance and the small patient numbers.

Figure 81. Average change in QoL score for the control patients compared to the honey patients over the course of their treatment

Figure 82. Change in patients’ perceived QoL vs dose over the course of treatment
Chapter 4 DISCUSSION

4.1 Interpretation of results

4.1.1 Severity of oral mucositis

The results of the New Zealand mucositis trial suggest that honey does not decrease the severity of oral mucositis in the small cohort of patients. On the contrary, patients in the honey arm had a higher mean mucositis score compared to the patients in the control arm. All honey arm patients developed mucositis compared with only 75% of control patients. On average patients in the honey arm also first developed mucositis at a slightly lower dose compared to the control patients. These results suggest that the manuka honey is not superior to the current standard of care for head and neck patients.

The results do not correspond with the results of the three previous honey trials by Biswal et al. (2003), Rashad et al. (2008) and Motallebnejad et al. (2008) (described in Appendix B) which showed that honey decreased the severity of oral mucositis significantly.

There were differences between the three previous trials and the New Zealand trial with respect to the type of honey, the control group standard of care and the scoring system used. The main difference in methodology between the overseas trials and the New Zealand trial was the honey concentration. All three overseas trials used undiluted honey, whereas the New Zealand trial used diluted honey. This was a direct result of significant issues encountered with patient compliance. Biswal et al. (2003) and Rashad et al. (2008) did not mention issues with patient compliance although Motallebnejad et al. (2008) did mention that patients who experienced severe stinging of the mouth were removed from the trial.

Preliminary analysis of results from the three oncology departments involved in the New Zealand trial (Wellington, Palmerston North and Dunedin) showed that manuka honey was not well tolerated. Patients who experienced severe pain and nausea in response to the honey pulled out of the trial because it was unethical to coerce them into continuing with the honey application. Compliance with the honey application protocol also related to personality factors:
• Each individual has a different pain tolerance and patients with lower pain thresholds were more likely to stop taking honey when they found it caused a stinging sensation.

• The anticipatory nausea and vomiting phenomenon is a learned response that occurs in patients who have had a negative experience with chemotherapy. One trial patient who pulled had built a strong association between chemotherapy, manuka honey and nausea and vomiting so was unable to continue with the honey application.

• The patients who persisted with the honey application all shared an intrinsic belief that the honey was of benefit to them.

The intolerance of undiluted honey let to several amendments to the protocol, reducing the overall amount of honey from 20mL to 10mL and diluting the honey 1:3 with liquid. The lack of effect of the honey in the current study is most likely due to the diluting of the honey beyond its effective concentration.

All three overseas trials had control groups but two did not receive the same standard of care that is delivered in New Zealand. Most New Zealand head and neck patients are instructed on the use of salt and baking soda mouthwashes, have access to topical and systemic anesthetics and are cared for by a multidisciplinary team. The authors of the overseas trials did not report poor application compliance or significant patient drop-out.

4.1.2 Weight, nutrition and QoL
Interestingly the effect of honey on weight, nutritional status and patient QoL was very different to the effect on oral mucositis. The results of the weight loss comparison between the honey arm and the control arm patients correspond to the results from the Biswal et al. (2003) trial and the Motallebnejad et al. (2008) trial where on average the honey arm patients lost less weight than the control patients. A higher percentage of control patients required hospitalisation and analgesia over the course of treatment but a higher percentage of honey arm patients required PEG/NG feeding. The manuka honey appeared to have a positive effect on patients’ QoL with the average reduction in QoL score being less than the control patients. Despite this result the descriptive accounts of the experiences of the honey arm patients were often negative with regard to QoL.
4.2 Limitations of the current study

Bias is an inevitable aspect of research involving human participants which affects the validity and reliability of trial results. The strength of a clinical trial depends on how well its design and execution have reduced or taken into account the various types of bias to allow accurate conclusions to be drawn. Despite efforts to reduce sources of bias a number were identified in the New Zealand mucositis trial and are outlined below.

4.2.1 Selection bias
This bias occurs when the two groups to be compared have inherent differences which may influence the outcome.

Small participant numbers
The most significant limitation of the current study is the very small number of participants. Although it was originally planned that all head and neck patients referred for radiation therapy who met the inclusion criteria would be invited to participate in the trial, six potential patients were missed. In addition three patients declined participation in the trial. Informed consent was gained from all patients who participated, however, two potential patients were informed of the trial details but did not agree to the randomisation process so were unable to be recruited. The patients who did not participate in the trial may have had different reactions to the honey compared to those that did participate.

Age
The age of patients may affect the healing rate of oral mucositis with younger patients likely to have a faster rate of mucosal healing (Sonis, 1998). The average age of the patients in the honey arm was significantly younger than the patients in the control arm (54.4 vs 61 years) so age is a confounding factor. If the average age of the two trial arms were equal the mucositis scores of the honey arm patients may have been even higher compared to the control patients.

Smoking and alcohol intake
The oncology notes of the trial patients were reviewed with regard to smoking and alcohol use but because patients were not questioned directly and these factors were not taken into account in the randomisation process. Smoking and alcohol increase individuals risk for
developing cancer because they contain carcinogens and cause inflammation (Evans et al., 2003). For similar reasons these substances also increase the amount and severity of oral mucositis so they should be taken into account in mucositis trials to minimize confounding.

**Gender**
There were more males in the honey arm than the control arm (80% vs 25%) and this may have contributed to different mucositis scores between the two groups. The three overseas honey trials also had a greater percentage of males recruited to the trial and there were more males in the honey arm. Genetic differences may impact on rates of mucositis development and the mucosal response to manuka honey.

**Dose distribution**
The tumour site and stage differed between all the trial patients which meant the dose distribution in the oral cavity differed. The trial aimed to minimise the confounding effects of dose distribution by dividing the total mucositis score by the number of sites at risk. The two different types of mucosa in the oral cavity may have different sensitivities to radiation damage so tumour site may impact on the degree of mucositis.

**Planning software**
Eclipse planning software was used to plan the Wellington patients’ treatment and doses were modelled to achieve the best plan. The areas identified to be ‘at risk’ on the modelled plan were not always the areas where reactions became evident. There is a small degree of uncertainty in all modelling programmes. One specific factor that affects the accuracy of radiation modelling is the presence of metallic fillings. These alter the dose distribution within the oral cavity and may increase the severity of mucositis in the surrounding tissue. It is standard that patients have a dental review prior to starting radiation treatment but some patients proceed with fillings in place. The New Zealand trial patients’ teeth or fillings were not examined. The presence of fillings may have accounted for some of the variation between the number of sites identified to be at risk and those that did develop mucositis and if the honey or control arm patients had fillings the rates of mucositis could have been higher.

**Chemotherapy**
Concurrent chemotherapy has been shown to increase the severity of radiation induced reactions (Trotti, 2000). Two honey arm patients and two control arm patients received
concurrent Cisplatin chemotherapy but another honey patient had received neo-adjuvant R-CHOP chemotherapy. The greater average mean mucositis scores of the honey patients could have resulted from a higher percentage of the honey patients having received chemotherapy.

**Surgery**
Tissue that has undergone previous healing may have a different sensitivity to radiation and could have contributed to the varying rates of mucositis. The majority of trial patients (77.8%) had undergone surgery prior to radiation treatment referral. The two patients who had not were in the control arm of the trial.

**Humidifiers**
Three public oncology departments in New Zealand are participating in the TROG humidification trial to assess whether humidification can reduce oral mucositis in head and neck cancer patients receiving radiation therapy. The trial proposes that heated humidification of inspired air via a nasal interface may palliate symptoms of mucositis by reducing discomfort associated with dry, sticky secretions. The (Fisher and Paykel Healthcare) humidifiers used in the trial deliver gas which is heated and humidified to 37°C, 44 mgH₂O/L. Although the Wellington oncology department was not participating in the humidification trial two humidifiers became available for patient use early in 2009. The potential benefits (reduction in patient discomfort from oral dryness, reduction in pain severity and the decrease in sticky secretions) meant that the humidifiers became part of the standard of care for high risk head and neck patients. The use of humidification in three of the manuka honey trial patients (two controls and one honey patient) could have reduced the incidence or severity of mucositis independent of the manuka honey.

### 4.2.2 Randomisation bias
The purpose of randomisation is to avoid or reduce potentially confounding factors by making the honey and control arms comparable. Although the original trial was designed to randomize patients using computer-generated random numbers, after the protocol was changed to diluted honey, additional patients were put on the honey arm without further randomization. Due to the low patient numbers the two trial arms were unable to be matched and so patient variables such as age, gender and ethnicity and treatment variables such as PTV (planning target volume) location and size would have affected the rates and severity of mucositis between the two trial arms.
4.2.3 Participant bias
There were a number of instances where participant bias could have been introduced to the mucositis trial. Some patients may have agreed to be a part of the trial not because they wanted to but because they felt obliged to.

Reporting bias
Because some of the trial results are subjective they are affected by patients’ personalities, emotions and attitudes.

- It is possible that some patients do not act in their normal way when participating in a trial and they may have altered their reports (verbal and written) to appease the researcher.
- Pain is a subjective experience and is difficult to quantify; some people have lower pain thresholds than others (one patient in the honey arm who despite having visible mucositis did not notice any pain). The lack of an objective measure introduces a degree of variability in the comparison of pain levels.
- It is possible that the degree of oral mucositis (inflammation) was affected by patients’ psychology. (A lot of research has focussed on the effect of stress and negative personality traits on the immune system and the incidence of disease. It may be possible that personality traits also affect how much benefit patients derive from certain treatments.)
- The placebo effect may have influenced the trial results. Patients in the honey arm could have had a perceived increase in QoL when taking the honey (patients feel like they are taking control and doing something to alleviate treatment side effects).

Recall bias
Recall or memory bias could have been introduced to the trial when patients were asked to recall the events of the past few days (especially after weekends). Honey application and tolerability, food and fluid consumption and medication requirements may not have been accurately remembered. This bias probably applied to the QoL forms which were designed to reflect the patients QoL the week preceding the filling in of the questionnaire, it is possible the patient blocked out the true level of pain or fatigue they felt.
4.2.4 Compliance bias

Adherence to the honey protocol differed among patients and through discussion it was obvious that adherence was due to the patient’s perceived benefit from the honey. The patients who perceived a benefit were able to persevere through the pain and/or nausea. Compliance with filling in QoL questionnaires also differed significantly.

Inconsistency of adherence to honey protocol

The descriptive experiences of the patients in the honey arm show that undiluted honey was not well tolerated. Four patients randomised to the honey arm pulled out of the trial within the first ten days of treatment. The five honey patients that persisted with honey application frequently complained about the taste, texture and stinging nature of the honey. Only 40% of the honey patients (n=2) finished treatment still applying the manuka honey and 60% of honey patients found they had to mix the honey with a liquid other than water to reduce the sweetness. The 60% of honey patients who ceased honey application may have done so at the stage in treatment where the honey had the most benefit (patchy and confluent mucositis).

Sweetness

The sweetness of the honey was difficult to tolerate and associated with nausea. The sugar content was also of concern to one patient randomised to the honey arm who was worried about the increased risk of tooth decay. Tooth decay is a serious concern for head and neck patients who, due to saliva composition changes are at an increased risk of cavities. It is possible the high sugar content of honey makes it a cariogenic substance, however one report stated that honey is useful to treat gum disease (Bardy et al., 2007) and another study reported that honey is less cariogenic in dry mouth subjects (Sela et al., 1998).

Sticky saliva

Saliva changes are common in head and neck radiation therapy and the formation of thick ‘sticky’ saliva affects patients’ ability to swallow and causes patients considerable difficulty (Funegard et al., 1994). Patients with xerostomia may be less able to tolerate manuka honey due to thick saliva (one control patient developed ‘sticky’ saliva so severe she could not eat so it is unlikely she could have tolerated the honey if randomised to that arm).
**Exposure time**

The trial originally proposed that all patients in the honey arm swallowed the honey to coat the mucosal lining of the oropharynx after the oral cavity, this was however amended as patient honey tolerance became an issue. Patients were then asked to swallow the honey mixture if possible or to hold it in their mouth for as long as they could (ideally a minute) and then spit it out. These different exposure times could have influenced the results. The manuka honey may require a certain amount of time to have an effect (anti-inflammatory or otherwise) on the mucosa.

**Concentration**

Amendments were made to the honey application instructions to make it more tolerable. The honey was to be diluted by a ratio of 1:3 with water (or other liquids). Dilution decreases the concentration of all the compounds found in honey, including those responsible for its anti-inflammatory action. In addition it is possible that not all patients were equally precise in diluting the honey. The process of diluting the honey added hassle for patients.

As the trial proceeded it became apparent some honey jars had small amounts of ‘crystallised’ honey. The crystals were more difficult to dissolve in liquid and so more difficult to spread around the patient’s oral cavity. This would have affected the dilution factor (some honey arm patients found ‘dregs’ of honey were left in the bottom of the vessel used to mix the honey).

**Timing of honey application**

The timing of honey application differed between patients. It was originally proposed that patients would apply the manuka honey before and after treatment and then again six hours later. Some patients adhered to this protocol while others found this too difficult. Some had to travel in from the greater Wellington region so applied the honey a long time before and after treatment (travel times). Another patient experienced nausea in the morning so applied the honey three times later in the day.

**Honey Quality**

The proposed method of action of the manuka honey on oral mucositis relates to the anti-inflammatory properties of the honey constituents. Phenolic compounds may engage in
selective radical scavenging and methylglyoxal (MGO) has antibacterial activity (Stephens et al., 2009). The bioactivity of manuka honey and its potential benefit depends on the concentration of these compounds which may be affected by natural factors such as honey age, monoflorality and geographical source (localised environmental factors or genetic differences) (Stephens et al., 2009). In order to avoid these potentially confounding factors all the honey used for the trial was from the same supplier (collected from the same beehives, stored in the same conditions, tested for toxins and MGO content and gamma sterilized). The honey was distributed to the different oncology departments and trial patients. At the Wellington department the honey was stored in a refrigerator until given to patients who were instructed to store the honey in a cool place out of direct light. Despite intentions and instructions to keep the honey in stable conditions honey jars was likely exposed to different conditions which may have affected the composition of the honey.

Similarly high temperature effects may have altered the honey composition during microwaving of, or dilution of the honey with hot liquid prior to application (one patient warmed the honey in the microwave several times before being told this was not ideal).

Compliance with filling in food diaries and QoL questionnaires
The food diaries and QoL questionnaires were given to each patient with the same instructions but the compliance differed. It was originally proposed that the food/drug diaries would be filled out by the patients daily to gain insight into their diet and pain control and see how this changed over the course of treatment. Several patients reported daily recording too much of a hassle so moved to weekly recording or recording of significant changes in diet or medication administration (for example the reduction in food intake, move to NG or PEG feeding or the increase in amount or strength of pain relief). This change may not have allowed enough insight into the diet differences between the two trial arms. One patient did not complete any QoL forms.

4.2.5 Researcher bias
The attitudes and actions of the medical professionals (research assistant, nurse, dietician and radiation oncologist) who were involved in the trial patients’ care could have influenced the results and the level of compliance.
**Personal interaction**

The attitude of the oncologist who presented the trial to the patient would have influenced the patient’s decision to participate; some oncologists may have ‘pushed’ the trial more than others. It is important that patients are given all the necessary information without coercion but it is inevitable that some opinions are conveyed. Other health professionals involved may have encouraged patients to be more persistent with honey application. It became a bit of an ethical dilemma when patients were obviously suffering pain and/or nausea from the honey application; it was desirable patients continued with the application as long as possible for the purpose of the trial but patients should not be expected to tolerate more pain or discomfort than they would otherwise experience. All trials need to incorporate the values of medical ethics (beneficence and nonmaleficence) (Miller & Rosenstein, 2003).

**Mucositis scoring**

The blinded nature of the proposed trial design was quickly amended because the research assistant responsible for the mucositis scoring was the main point of contact for the patient. The honey application instructions were given to the patient by the assistant so to ensure that patients adhered to the protocol the researcher needed to know which arm the patients were randomised to. The lack of blinding may have subconsciously affected the research assistant’s mucositis scoring; the mucositis scores for the honey patients may have been lower than scores from an assistant who had been blinded.

**4.2.6 Measurement bias**

Measurement biases introduce systematic error when data is collected.

Consistency in mucositis scoring was addressed in the trial design by the mucositis scoring training session that the scorers attended prior to trial commencement. The scorer may have become more confident with the scoring process further into the trial. However it is possible that scoring inconsistencies were introduced the more time that passed since the training session. Although the same person did the majority of the scoring for all patients at the Wellington department there could have been inter-scorer variability between the participating departments.
Lighting conditions in the rooms where oral assessments took place could have affected the mucositis scores, especially the identification of oral erythema which is not as obvious as oral mucositis. Head lamps, torches and well-lit clinic rooms were used in most scoring cases but the light level could have varied.

Patient factors
Some patients found it difficult to open their mouths due to the effects of previous surgery or mucositis-related pain. This factor made oral cavity assessments more difficult and may have led to under scoring of some sites.

The mucosal lining of the oral cavity could have been affected by mechanical trauma not radiation damage (for example a head and neck patient eating some rough food which results in an area of perceived erythema). As outlined earlier the use of topical analgesics can increase a patient’s risk of biting or burning their oral mucosa due to reduced sensitivity, this could have affected mucositis scoring.

Infection
The presence of oral candidiasis may also have impacted on mucositis scoring. The layer of white film that is often associated with the yeast infection is similar to the appearance of oral mucositis. It is possible to confuse the two leading to potential under or over scoring of mucositis.

Timing of mucositis assessment
Assessments were done three times a week (Monday, Wednesday, Friday). Due to a public holiday falling on a Monday one patient had their oral cavity examined on a Tuesday and Wednesday. It was noted that there was a degree of healing of the oral mucosa overnight. One area of confluent mucositis was reported as patchy mucositis the next day. This example showed that mucositis is dynamic and that even during treatment mucosal healing is occurring. This highlights the issue of the timing of the mucositis assessments. Daily assessment may give a more accurate record of the progression of mucositis but would be more resource intensive and more difficult for patients to tolerate. The current study minimized the effect of timing by plotting the average mucositis score over the entire course of treatment.
4.3 Recommendations for future clinical trials

Patient accrual
Good lines of communication between all members of the patients’ multidisciplinary team will ensure maximum patient accrual to future trials. Department software systems can also help maximise patient accrual (for example the MOSAIQ software function that can identify patients by treatment site so that potential trial patients can be easily identified prior to their CT planning scan).

Dedicated research staff
Oncology departments involved in research should have dedicated research staff and adequate resources to enable valuable research to be carried out. Large scale clinical trials require time, money and commitment but they provide statistically significant data to improve current standards of care.

Mucositis scoring
Specific lighting conditions should be reproduced for each mucositis assessment. The mucositis scorers should have regular tests to ensure consistent correct mucositis scoring. More oncology department staff members should be trained to score mucositis to cover instances when the research assistant is unavailable. Continual monitoring of treatment machine schedules is required (by the research assistant) to ensure that all trial patients have their mucositis assessments conducted at the specified intervals.

Honey application
Further research is warranted to find the best way to apply manuka honey to the oral cavity so a higher level of compliance can be achieved. Dilutions that do not reduce the potential beneficial actions of honey should be investigated. The active constituents of manuka honey may also be present in manuka essential oil which may be better tolerated by patients. A study reported in the European Journal of Oncology Nursing investigated these oils and found that they were able to delay the onset of mucositis and reduce oral pain (Maddocks-Jennings et al., 2009). It may also be possible to remove the sugar content of manuka honey to reduce the intense sweetness (make the honey more tolerable) and reduce the potential risk of cavity formation.
Food diaries and QoL forms

Food diaries need to be presented in a more user-friendly format to encourage frequent recording. They should also include a section where the patient can report on their honey use and any problems they encounter. Patients should be clearly instructed on the QoL form requirements prior to trial inclusion to ensure they will comply to increase the future rate of return.

Patient information

More information about the patients recruited to trials would reduce the number of potential confounding factors. Patients should be questioned prior to treatment with regard to smoking (present or previous), alcohol intake, nutritional status, ethnicity and co-morbidities.
4.4 Conclusion

Oral mucositis causes considerable discomfort to patients and currently there is no definitive treatment (Maddocks-Jennings et al., 2009). Manuka honey may have an immunomodulatory effect and may be able to combat inflammatory processes such as mucositis. The New Zealand manuka honey trial was originally designed as a stage II randomized single blinded trial to determine whether Comvita manuka honey in addition to standard best practice is superior to standard best practice alone in decreasing the extent of radiation-induced oral mucositis.

In support of the hypothesis, three overseas trials showed that different honeys significantly reduced the extent of radiation-induced oral mucositis in patient cohorts in Malaysia, Iran and Egypt. The New Zealand trial, however, reported that undiluted manuka honey was not well tolerated by the patient cohort. Patients complained of extreme nausea and stinging sensations in the oral cavity and throat and the trial protocol had to be amended from 20mL of undiluted honey to 10mL of honey diluted in 30mL of water (or other liquid). Preliminary analysis showed that diluted manuka honey did not decrease the extent of oral mucositis in the small cohort of New Zealand head and neck cancer patients when taken in addition to current best practice.

Despite there being a lack of consistency in the care of head and neck patients in New Zealand patients are well looked after with respect to oral cavity reactions; most patients receive nutritional support, oral hygiene advice and pain relief as required along with frequent contact with their oncologist and other members of the multi-disciplinary team. The addition of manuka honey did not show any benefit and caused a large amount of discomfort with respect to taste and stinging.

The trial did not yield statistically significant results due to the small sample size and confounding factors but it did provide useful information about the tolerability of manuka honey in head and neck patients. The reports from trial patients can be used in future trials that involve honey application. Further research into ways to make manuka honey more tolerable to patients and improve patient compliance is warranted.
References


Glossary

**Adjuvant** refers to additional treatment; it describes the role of a therapy relative to other cancer treatments.

**Ageusia** is the loss of taste functions of the tongue, particularly the inability to detect sweetness, sourness, bitterness and saltiness.

**Amifostine** is used to reduce the incidence of neutropenia related fever and infection caused by DNA binding chemotherapeutic agents (chemo-protective drug).

**Amytriptyline** is the most widely used tricyclic antidepressant (TCA). It is used to treat depression and pain associated with nerves (neuropathic).

**Apoptosis** is the process of programmed cell death that occurs in multi-cellular organisms. Biochemical events lead to characteristic cell changes and death.

**Beneficence** describes a medical ethics value; taking actions that promote the wellbeing of others (those actions that serve the best interests of patients).

**Cisplatin** is a platinum based chemotheraphy drug used to treat various types of cancers. The platinum complex reacts by binding to and causing cross-linking of DNA which ultimately triggers apoptosis.

**Comvita** Company produces a number of healthcare products including manuka honey which is exported around the world as a food product as well as for medical use (Comvita supplied the honey for the New Zealand trial).

**Diazepam** is a benzodiazepine derivative drug used to reduce tension and anxiety.

**Disseminated superficial actinic porokeratosis (DSAP)** is an uncommon skin condition that causes red/brown scaly spots. It is due to an abnormal sun sensitivity leading to pre-cancerous skin cells.

**Dysgeusia** is the distortion of taste commonly caused by chemotherapy and or radiation therapy.

**Dysphagia** is the symptom of difficulty swallowing.

**Dysphasia** describes a speech disorder where an individual has difficulty producing or comprehending spoken or written language.

**Erythroplakia** is a flat red mucosal patch or lesion in the mouth (cannot be removed by scraping).

**Glossectomy** is the surgical excision of part or all of the tongue.

**Haemoptysis** is the coughing up (expectoration) of blood or blood-stained sputum from the bronchi, larynx or lungs.

**Immunoglobulin** (antibody) is a protein produced by plasma cells and lymphocytes and has an essential role in the immune system.

**Isocentre** is the point in space through which the central beam of radiation passes.

**Leukoplakia** a white mucosal patch on the mucous membrane of oral cavity (cannot be removed by scraping).

**Monoclonal antibody** is an antibody that binds to one cell type by recognising specific proteins on the surface of particular cancer cells. When used in cancer treatment they are designed to target a protein on the cancer cell surface and then trigger the body’s immune system to attack the cancer cell or cause the cancer cells to destroy themselves.

**Mono florality** describes honey that by international standards must come wholly or predominantly from the designated plant source.

**Morphine** is an alkaloid narcotic drug extracted from opium, used to relieve pain (M -Elson and sevredol are forms of morphine).

**Myofibroblast** is a type of fibroblast cell that have features similar to smooth muscle cells.
**Nasopharyngoscope** is an endoscope used to visually examine the nasal passages and nasopharynx.

**Neo-adjuvant** (chemotherapy) describes the administration of therapeutic agents prior to the main treatment. This treatment aims to reduce the size or extent of the cancer before the main intervention.

**Neuropathy** describes damage to the nerves of the peripheral nervous system.

**Neutropenia** is a haematological condition characterised by abnormally low numbers of neutrophils in the blood. Patients with this condition are more susceptible to bacterial infections and are at risk of developing life-threatening sepsis.

**Non-maleficence** describes a value of medical ethics; first do no harm to the patient.

**Ondansetron** is a serotonin receptor antagonist mainly used as an antiemetic to treat nausea and vomiting.

**Oxycontin** is a semi-synthetic opioid medication prescribed for relief of moderate to severe pain.

**Pilocarpine** is an alkaloid medicine used to stimulate saliva production to aid mastication, tasting and swallowing.

**R-CHOP** chemotherapy regimen consists of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone drugs.

**Rituximab** is a monoclonal antibody which binds to the CD20 protein found on the surface of B cell lymphocytes and the surface of abnormal B cell lymphocytes. Studies have shown an improved effect when rituximab is given in conjunction with CHOP.

**Sialadenitis** is inflammation of a salivary gland, most commonly the parotid gland.

**Trismus** is the inability to normally open the mouth and can result from many causes including inflammation in the oral cavity and medication use.

**UMF (unique manuka factor)** is a factor used to describe the antibacterial effect of honey. It is determined by comparing the antibacterial activity of the honey with a standard reference antiseptic (phenol). An UMF value of 20+ would be equivalent in antiseptic potency to a 20% solution of phenol.
Appendices

Appendix A

Lymph node drainage

The lymph nodes of the neck region are divided into four levels depending on their location as the Figure below shows. Level I includes the sub-mental and sub-mandibular nodes, levels II, III and IV (the upper, middle and lower thirds respectively) the internal jugular nodes and level V the nodes of the posterior triangle (Myers et al., 2003).
Appendix B

Manuka honey clinical trials

Topical application of honey in management of radiation mucositis. A Preliminary study
Support Care Cancer 2003
Biswal, B., Zakaria, A., Ahmad, N. M
The trial that was conducted in Malaysia in 2002 recruited 40 head and neck patients who received between 60 and 70Gy. The radiation treatment involved parallel opposed paired (POP) 6MV fields delivered by a linear accelerator. Patients receiving chemotherapy were excluded from the trial. Patients were randomised to the standard of care arm or the honey arm. Those patients in the honey arm were instructed to apply 20mL of honey three times a day. The application instructions were to rinse the whole of the oral mucosa and then swallow the honey to cover the pharyngeal mucosa. Mucositis was scored using the RTOG grading system. The results showed there were no changes in the grades one and two mucositis but there were fewer patients in the honey arm who developed severe mucositis (grade 3 or 4). Patients in both trial arms were advised on adequate fluid intake, supplementation of a high protein diet and oro-dental care.

Honey as topical prophylaxis against radiochemotherapy-induced mucositis in head and neck cancer
The Journal of Laryngology & Otology
In 2008 a trial reported from Egypt found there were more incidences of grade three mucositis in the control arm compared to the honey arm. 40 patients were also recruited to this trial and they received between 60 and 66Gy using POP fields and anterior beams to treat the lower neck region. The honey application was similar to the Biswal et al. study and assessment was conducted weekly. Patients were excluded from the trial if they had received previous chemoradiation treatment (to the upper airways), previous radical surgery of the primary tumour and/or regional lymph nodes. All patients were instructed to use benzydamine HCl and supportive oral care measures.

The Effect of Topical Application of Pure Honey on Radiation-induced Mucositis: A Randomised Clinical Trial
The Journal of Contemporary Dental Practice
Motallebnejad, M., Akram, S., Moghadamnia, A., Moulana, Z., Omidi, S.
The trial conducted in Iran also recruited 40 head and neck patients who received a total dose between 50 and 60Gy. This trial maintained a blinded nature. Patients were excluded from the trial if they had had previous chemoradiation treatment. All patients were advised to avoid alcohol, spicy or acidic foods and smoking. Good oral hygiene and nutritional intake was also encouraged during the course of radiotherapy. Patients on the honey arm were instructed to use 20mLs of honey three times a day and apply it to the oral mucosa and to swallow. The control arm used 20mLs saline three times daily. Patients who experienced severe burning were excluded from the trial. The mucositis scores were taken weekly with the assessor not being aware of which arm each patient belonged to. The Oral Mucositis Assessing Scale (OMAS) was used in this trial to grade nine oral cavity areas. The results of this trial supported Biswal’s study.
<table>
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<th>The effect of topical application of pure honey on radiation-induced mucositis randomized clinical trial</th>
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<td>Rashad et al.</td>
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<td>Less honey pts experienced grade 3 mucositis.</td>
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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 Patries Herst (027-3483945).
Appendix D

Patient randomisation fax sheet

Randomisation Fax Coversheet
Manuka Honey for Oral Mucositis Trial

Date: ________________________

To: Dr Patries Herst
Fax: 04 3855375
Tel: 04 3855475
Email: patries.herst@otago.ac.nz

From: _________________________________________________________
Tel: ___________________________________________________________

Hospital: ______________________________________________________

Fax: ___________________________________________________________

Patient Initials: _________________________________________________

Patient date of birth: ____________________________________________

Randomisation stream:

- □ ≥ 60 Gy plus concurrent chemotherapy
- □ ≥ 60 Gy
- □ < 60 Gy plus concurrent chemotherapy
- □ < 60 Gy

Randomisation Arm:
- □ Arm 1: Standard Care
- □ Arm 2: Standard Care + Honey

Patient Randomisation Number: _________________________________
Randomisation Date: ___________________________________________
Randomisation completed by: ____________________________________

Signature: ________________________________________________
Appendix E

Mucositis scoring sheet

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

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Mucositis score (0-4)</th>
</tr>
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<tbody>
<tr>
<td>Anatomical sites</td>
<td>areas at risk 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 Total score</td>
</tr>
<tr>
<td>Vermillion Lip (upper)</td>
<td></td>
</tr>
<tr>
<td>Vermillion Lip (lower)</td>
<td></td>
</tr>
<tr>
<td>Labial Mucosa (upper)</td>
<td></td>
</tr>
<tr>
<td>Labial Mucosa (lower)</td>
<td></td>
</tr>
<tr>
<td>Gingiva (upper)</td>
<td></td>
</tr>
<tr>
<td>Gingiva (lower)</td>
<td></td>
</tr>
<tr>
<td>Buccal mucosa (right)</td>
<td></td>
</tr>
<tr>
<td>Buccal Mucosa (left)</td>
<td></td>
</tr>
<tr>
<td>Tongue (ventral)</td>
<td></td>
</tr>
<tr>
<td>Tongue (dorsal)</td>
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</tr>
<tr>
<td>Palate (hard)</td>
<td></td>
</tr>
<tr>
<td>Palate (soft)</td>
<td></td>
</tr>
<tr>
<td>Floor</td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td></td>
</tr>
<tr>
<td><strong>Total Score (TS)</strong></td>
<td></td>
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<tr>
<td><strong>Number of sites at risk (NSR)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mean score (TS/NSR)</strong></td>
<td></td>
</tr>
</tbody>
</table>
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 advice by your oncologist.
Appendix G

Trial consent

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

<table>
<thead>
<tr>
<th>Language</th>
<th>Translation</th>
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<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>I wish to have an interpreter</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Maori</td>
<td>E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero</td>
<td>Ae</td>
<td>Kao</td>
</tr>
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<td>Cook Island</td>
<td>Ka inangaro au i tetai tangata uri reo</td>
<td>Ae</td>
<td>Kare</td>
</tr>
<tr>
<td>Fijian</td>
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<td>Io</td>
<td>Sega</td>
</tr>
<tr>
<td>Niuean</td>
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<td>E</td>
<td>Nakai</td>
</tr>
<tr>
<td>Samoan</td>
<td>Ou te manaomia i ai se fa'amatala upu</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tokelaun</td>
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<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tongan</td>
<td>Oku ou fiema ha fakatonulea</td>
<td>Io</td>
<td>Ikai</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature:</td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td></td>
</tr>
<tr>
<td>Researchers</td>
<td>Dr Patries Herst (ph 04-3855475 ext 4753; mobile 027-3483945) The Radiation Oncologist who is the local principal investigator</td>
</tr>
</tbody>
</table>