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OPTIMISING NUTRITION SUPPORT IN PATIENTS WITH HEAD AND NECK CANCER

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Abstract

Background: Nutrition support is essential for patients with head and neck cancer. Poor nutritional status and weight loss are associated with reduced quality of life, treatment interruptions and an increased risk of unplanned hospital admissions which also contribute to increased healthcare costs. There are a number of patient, clinical and treatment characteristics which have been found to increase the risk of swallowing and nutrition difficulties during treatment. This information has been used to identify which groups of patients may therefore benefit from placement of a proactive gastrostomy prior to commencement of treatment. A local protocol for this purpose is in place at the Royal Brisbane and Women's Hospital. Historically this approach of nutrition support was shown to be effective in improving nutrition outcomes and reducing admissions for patients receiving radiotherapy, however more recently in studies of patients receiving concurrent chemoradiotherapy this no longer appears to be an adequate intervention to achieve maintenance of weight or nutritional status. In addition, with the advent of advancing radiotherapy techniques and emerging human papillomavirus-related tumours, there are questions as to whether proactive gastrostomy placement is still warranted.

Objectives: The objectives of the research in this thesis were firstly to determine the impact of new radiotherapy techniques on nutrition outcomes; how this may influence the protocol for predicting proactive gastrostomy placement; and the impact of human papillomavirus status on nutrition outcomes. As adherence to the protocol had been declining in light of the advancing radiotherapy techniques, the second objective was to compare the nutrition outcomes of patients treated according to the local protocol to those that weren't. Finally the third main objective was to investigate a novel pre-treatment nutrition intervention strategy to determine if this would improve nutrition outcomes compared to standard care with proactive gastrostomy placement.

Methods: The first objectives were addressed through retrospective cohort studies and included patients treated for head and neck cancer over a one year period following commencement of helical intensity-modulated radiotherapy. The second objective was addressed through a prospective comparative cohort study. Patients were recruited over a two year period and observed throughout standard care during treatment and for one month post-treatment. Nutrition outcomes (weight loss and incidence of tube feeding) and clinical outcomes (unplanned admissions) were collected and compared between the protocol adherent group (proactive gastrostomy placement) and non-adherent group (no proactive gastrostomy placement; managed with oral diet and tube feeding as required).

The final objective was addressed through a prospective randomised controlled trial. Patients were recruited over three years if they were planned for proactive gastrostomy insertion prior to treatment. They were randomised to either standard care or to the early nutrition intervention whereby prophylactic enteral nutrition was prescribed before treatment. Primary outcome of weight loss was collected at three months post-treatment, as well as nutritional status, body composition, quality of life and treatment outcomes.

Results: In summary the results from this research have found that patients still have significant weight loss and a high requirement for tube feeding despite the advancing radiotherapy techniques. The protocol for proactive gastrostomy insertion remains valid for use and there is a potential that human papillomavirus status may be an additional parameter that could help to further select appropriate patients for tube feeding. Adherence to the protocol did show improved nutritional outcomes and less unplanned admissions. The early nutrition intervention however was not found to be effective at improving patient outcomes, but this finding was limited following poor adherence to the intervention.

Discussion: Overall this research has contributed significantly to the field with five published manuscripts (Chapters 4-7) and three under review (Chapter 8). This research provides the first study to report on the nutrition outcomes following helical intensity-modulated radiotherapy. Whilst the protocol for proactive gastrostomy insertion remains valid with this type of treatment, the research has shown that additional adjustments could be made to improve the predictive ability even further. The method of tube feeding remains controversial in the literature. Randomised controlled trials are particularly challenging due to strong patient preferences for the mode of tube feeding thus limiting consent for randomisation. The comparative cohort study within this thesis is in favour of the proactive approach and provides a contribution to the body of literature on this topic to assist clinicians in making an informed decision. Finally although the early nutrition intervention was not found to be effective at improving outcomes as hypothesised, the findings from the study did highlight the number of barriers that patients face in achieving nutrition prescriptions throughout the course of treatment including; clinical symptoms, environmental factors and various psychosocial issues. These will be important to investigate in future research to enable the design of effective multidisciplinary models of care to overcome and address these barriers to allow patients to achieve nutrition goals and optimal outcomes.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

Manuscripts in peer-reviewed journals (*included in thesis)

*Brown, T., Banks, M., Hughes, B., Kenny, L., Lin, C., Bauer, J. (2017). Tube feeding during treatment for head and neck cancer - adherence and patient reported barriers. *Oral Oncology*, *72*, 140-149. doi:10.1016/j.oraloncology.2017.07.017

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*Brown, T., Banks, M., Hughes, B., Lin, C., Kenny, L., Bauer, J. (2016, October). *Early feeding via a prophylactic gastrostomy – preliminary findings from a randomised controlled trial in high risk head and neck mucosal SCC (HNSCC) patients undergoing chemoradiotherapy.* Paper presented at the 18th Australia and New Zealand Head and Neck Cancer Society ASM and the International Federation of Head and Neck Oncological Societies 2016 World Tour, Auckland, New Zealand.

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Brown, T., Findlay, M., Bauer, J. (2012, July). Evidence-based guidelines for the nutritional management of patients with head and neck cancer: Developing and maintaining guidelines on a wiki platform. Paper presented at the 8th International Conference on Head and Neck Cancer, Toronto, Canada. (Honourable Mention Award - Management of Long-Term Issues).

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Brown, T. (2016, November). *A patient-led nutrition assessment tool: the PGSGA.* Presented at the Research Forum, 10th International Head and Neck Cancer Quality of Life Conference, Liverpool, UK.

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Contributions by others to the thesis

Student dietitians assisted with data collection and completed preliminary data analysis for the studies in Chapter 5 (Vanessa Getliffe 2013 and Kym Wittholz 2014) as part of course DIET7302 in the Master of Dietetic Studies program, University of Queensland. The PhD candidate supervised these students and subsequently completed the studies for this thesis. Their contributions to the final studies are outlined above.

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Keywords

head and neck cancer, gastrostomy, nasogastric tube, enteral feeding, nutrition support, prophylactic, weight loss, malnutrition, quality of life, chemoradiotherapy

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List of Abbreviations

BMI	Body mass index
CRP	C-reactive protein
CRT	Chemoradiotherapy
HPV	Human papillomavirus
HNC	Head and neck cancer
IMRT	Intensity-modulated radiotherapy
MDT	Multidisciplinary team
MST	Malnutrition screening tool
NGT	Nasogastric tube
PEG	Percutaneous endoscopic gastrostomy
PG-SGA	Patient-generated subjective global assessment
ProPEG*	Prophylactic/Proactive gastrostomy**
QOL	Quality of life
RBWH	Royal Brisbane and Women's Hospital
RCT	Randomised controlled trial
RIG	Radiologically inserted gastrostomy
TNM	Tumour nodal metastasis staging

Note: Additional or alternative abbreviations have been used in chapters incorporating manuscript publications and therefore these are described accordingly within each chapter as part of the manuscript

*Please note this abbreviation has a more specific definition in Chapter 6 as part of a manuscript

**Prophylactic/Proactive gastrostomy refers to tubes placed pre-treatment using any method or technique

Chapter 1 **Introduction**

1.1 Background

1.1.1 Head and neck cancer

Head and neck cancer (HNC) is the seventh most common cancer worldwide (Bossola, 2015). The incidence is higher in males and in the African American population (Marur & Forastiere, 2008). The term HNC encompasses a range of tumour sites including the upper aero digestive tract (oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx), as well as the paranasal sinuses and the salivary glands (Mehanna, Paleri, West, & Nutting, 2010a). Presenting clinical symptoms can include hoarseness, stridor, dysphagia, otalgia, neck lump, mouth ulcers, and cranial nerve palsy (Mehanna, et al., 2010a).

Diagnosis is confirmed from physical examinations, including endoscopy and biopsy, with the extent of local and regional disease determined through various imaging techniques, such as MRI, CT and PET (Marur & Forastiere, 2008). The TNM staging system is used to classify cancer staging; with T stage accounting for tumour size, N stage accounting for degree of nodal spread, and M stage accounting for metastatic spread (Deschler & Day, 2008).

Treatment options are usually multimodality and can include surgery, radiotherapy, chemotherapy and/or biological therapy. It is important to consider optimal survival outcomes as well as the impact on functional outcomes and patient quality of life, and thus the role of the multidisciplinary team is essential for treatment planning (Mehanna, West, Nutting, & Paleri, 2010b)

Most HNCs are of squamous cell histology arising in the upper aero digestive mucosa (Argiris, Karamouzis, Raben, & Ferris, 2008). Established causative or risk factors include extensive use of tobacco and high consumption of alcohol, accounting for up to 80% of all cases (Stenson, 2010). However a sub group of HNC, particularly in the oropharynx, are caused by the human papillomavirus (Leemans, Braakhuis, & Brakenhoff, 2011).

Some dietary factors have also been associated with an increased risk of HNC, including low intakes of carotenoids and other protective micronutrients from fruits and vegetables (Stenson, 2010). As studies have shown that smokers eat less fruit and vegetables and micronutrients than non-smokers (Birkett, 1999; Dyer et al., 2003), these patients are often nutritionally compromised from the onset.

1.1.2 Overview of malnutrition in head and neck cancer

Accepted definitions of malnutrition from the International Statistical Classification of Diseases and Related Health Problems Tenth Revision, Australian Modification (ICD-10-AM) are; severe malnutrition if body mass index (BMI) <18.5 kg/m^2 or unintentional loss of weight (≥10%) with evidence of suboptimal intake resulting in severe loss of subcutaneous fat and/or severe muscle wasting, and mild-moderate malnutrition if BMI <18.5 kg/m^2 or unintentional loss of weight (5-9%) with evidence of suboptimal intake resulting in mild/moderate loss of subcutaneous fat and/or mild/moderate muscle wasting (National Centre for Classification in Health, 2010). Similarly the Academy of Nutrition and Dietetics and the American Society for Parental and Enteral Nutrition recently published their consensus statement for the diagnosis of malnutrition which requires at least two of the following six markers to be present: unintended weight loss; loss of muscle or subcutaneous fat; fluid accumulation; insufficient energy intake; and diminished functional status using handgrip strength (White, Guenter, Jensen, Malone, & Schofield, 2012). This definition has been compared to the assessment of nutritional status using the established Patient-Generated Subjective Global Assessment tool (Ottery, 2005) and was found to be in good agreement with 94% sensitivity (Mulasi et al., 2016).

Malnutrition rates at diagnosis have been reported at 30-50% (van Bokhorst-de van der Schueren et al., 1999). The prevalence of malnutrition may be changing with an increasing incidence of oropharyngeal HNC caused by the human papillomavirus (HPV) (Ramqvist & Dalianis, 2010). These patients typically are well-nourished, non-smokers, with low levels of alcohol intake, and overall have a better prognosis (Mallen-St Clair, Alani, Wang, & Srivatsan, 2016). Despite this, a recent cross-sectional study in cancer patients (n=366 with HNC) reported pre-treatment malnutrition prevalence at 49% (Hebuterne et al., 2014), and a smaller prospective longitudinal study (n=19) reported prevalence rates of 68% (Mulasi et al., 2016). Both of these rates are still high but neither of these studies provided details of HPV status.

1.1.3 Causes of malnutrition in head and neck cancer

The causes of malnutrition in patients with HNC are multifactorial (Figure 1-1). As well as the pre-treatment lifestyle factors described above, other psychosocial factors can play a role with pre-treatment depression associated with pre-treatment malnutrition (Britton et al., 2012; Kim et al., 2016), and also predictive of malnutrition during and post-treatment (Britton et al., 2012).

Tumour burden has physical effects from the tumour location itself, resulting in dysphagia or odynophagia, which can lead to a reduced or altered food intake prior to diagnosis, contributing to weight loss (Alshadwi et al., 2013). Tumour burden can also have consequences on loss of appetite and body composition through the complex metabolic effects and mediators of cancer cachexia (Couch et al., 2015).

Once treatment commences, side effects from surgery, radiotherapy and/or chemotherapy, such as worsening dysphagia/odynophagia, xerostomia, dysgeusia, mucositis, oral thrush, nausea/vomiting, fibrosis, trismus and poor appetite (Alshadwi et al., 2013), can increase the risk of worsening or developing malnutrition during the treatment trajectory (Mulasi et al., 2016). Physical symptoms can also persist into the post-treatment/rehabilitation phase and impact on the patients' psychological well-being (Turner et al., 2014), which has been shown to affect the patients' nutritional self-care behaviours (Britton et al., 2012).

1.1.4 Consequences of malnutrition

Malnutrition is well known to be associated with adverse clinical outcomes and costs across a range of clinical settings (Watterson et al., 2009). Nutritional status has long been recognised as the second most important factor in predicting long-term prognosis in HNC (Brookes, 1985).

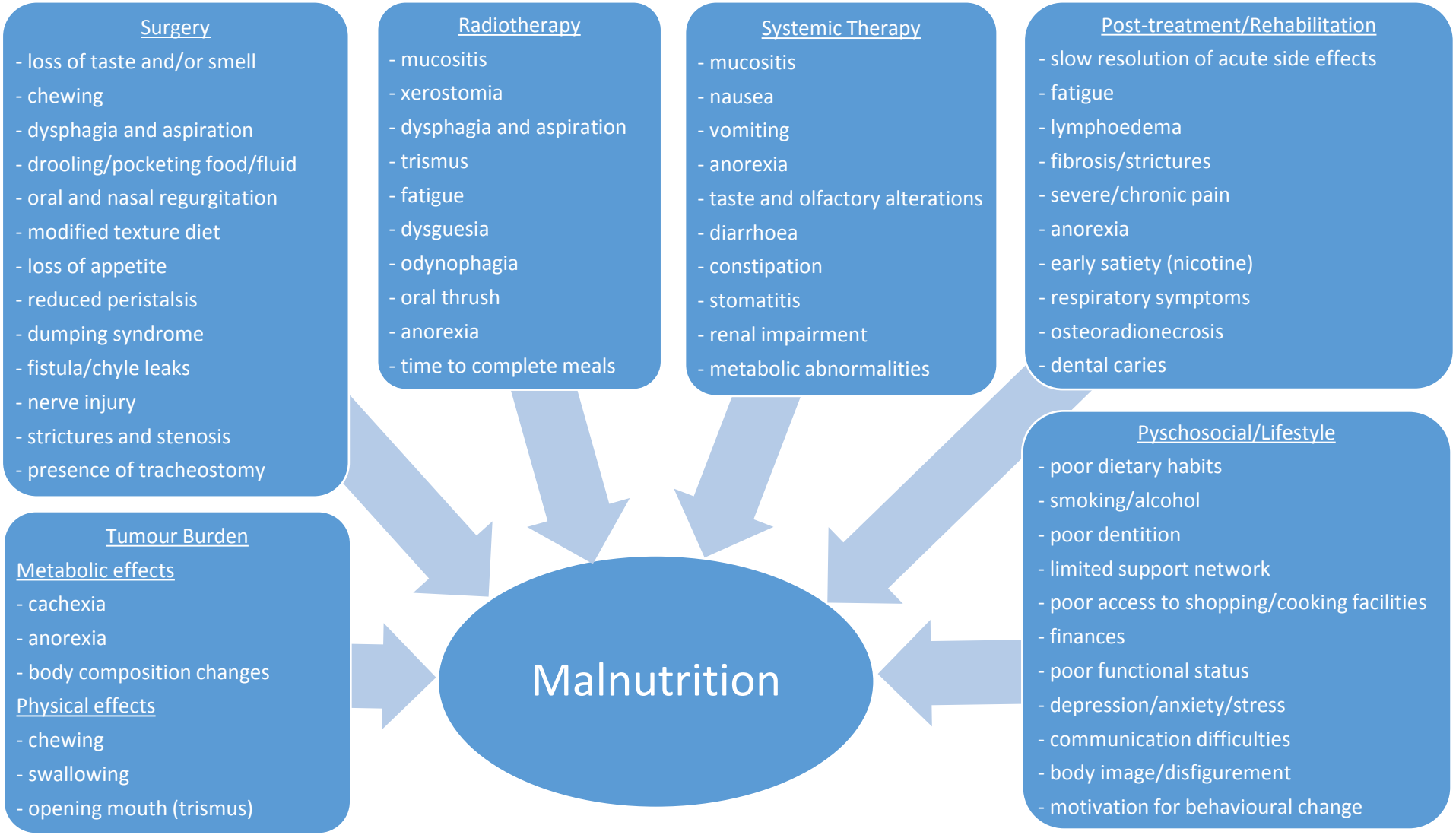


Figure 1-1: Causes of malnutrition in head and neck cancer

Source: Developed by author with adaptations from Talwar & Findlay, 2012

The consequences of malnutrition in HNC patients have been widely studied and include:

- **reduced immune function, increased risk of infection, and impaired wound healing** (Linn, Robinson, & Klimas, 1988a; Matthews, Lampe, & Dragosz, 1995; van Bokhorst-de van der Schueren et al., 1998)
- **increased admissions, complications, treatment interruptions and length of stay** (Capuano et al., 2008; Goodwin & Torres, 1984; Guo, Ma, & Zhang, 1994; Guo, Ma, Zhang, & Hu, 2007; Guo, Zhang, Ma, Zhang, & Huang, 1996; Linn & Robinson, 1988b; Linn et al., 1988a; Matthews et al., 1995; Ravasco, Monteiro-Grillo, Vidal, & Camilo, 2004; Shirodkar & Mohandas, 2005; van Bokhorst-de van der Schueren et al., 1997)
- **reduced quality of life (QOL), functioning and increased fatigue** (Capuano et al., 2010; Jager-Wittenaar et al., 2011a; Langius et al., 2013a; Ravasco et al., 2004; van den Berg, Rasmussen-Conrad, van Nispen, van Binsbergen, & Merkx, 2008)
- **increased risk of recurrence and reduced survival** (Brookes, 1985; Capuano et al., 2008; Goodwin & Torres, 1984; Kubrak et al., 2010; Mick, Vokes, Weichselbaum, & Panje, 1991; Platek et al., 2010; van Bokhorst-de van der Schueren et al., 2000)

Only two studies found that malnutrition at baseline had no impact on survival outcomes (Matthews et al., 1995; van Bokhorst-de van der Schueren, 1999). More recent studies have demonstrated the detrimental impact of weight loss on survival outcomes. In a large study with mixed cancer diagnoses (n=8160), it was reported that decreasing BMI and increasing percentage weight loss were both independent predictors of survival (Martin et al., 2015). Two randomised controlled trials (RCT) in HNC and colorectal cancer patients demonstrated individualised dietary counselling improved nutritional status/intake and QOL (Ravasco, Monteiro-Grillo, Marques Vidal, & Camilo, 2005a; Ravasco, Monteiro-Grillo, Vidal, & Camilo, 2005b). In a long-term follow-up study of their colorectal cohort – the patients with dietary counselling had better QOL and survival; with depleted nutritional intake/status predictive of shorter survival and late toxicity (Ravasco, Monteiro-Grillo, & Camilo, 2012). Meanwhile a study of HNC patients (n=1340), found weight loss was also a major prognostic indicator for survival (Langius et al., 2013b). The study reported >10% weight loss pre-treatment was associated with worse overall survival and disease-specific survival. In addition critical weight loss during radiotherapy (defined as >5% during or >7.5% by three months post-treatment) was significantly associated with worse disease-specific survival. Overall the body of evidence supports that malnutrition and weight loss have adverse consequences in this patient population and thus nutrition care plays a crucial role in optimising patient outcomes.

1.2 Theoretical model

In 2011, an Australian Dietitian Steering Committee published online “Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer” (Head & Neck Guideline Steering Committee, 2011), which have been endorsed internationally by the Dietitians Association of Australia, Dietitians New Zealand, British Dietetic Association and are connected to another on-line resource “Practice-based Evidence through Nutrition” from the Dietitians of Canada. The use of wiki platform technology has meant the guidelines can continually be updated and revised as new evidence is published (Brown et al., 2013a). These guidelines used a framework adapted from recognised Nutrition Care Models (Hakel-Smith & Lewis, 2004; Lacey & Pritchett, 2003; Splett & Myers, 2001) which consist of three phases:

- Appropriate access to nutrition care (nutrition screening and assessment)
- Quality nutrition care (nutrition diagnosis and intervention - including goals, prescription and implementation)
- Nutrition monitoring and evaluation (measuring and evaluating outcomes)

Outcomes assessed during the monitoring and evaluation phase have been established as a cascade of events following quality nutrition care. Initially resulting in improved intermediate outcomes (i.e. nutritional outcome measures), which flow on to an improvement in clinical, cost and patient outcomes (Figure 1-2) (Splett, 1996). The research questions addressed in this thesis will therefore be applied in the context of this theoretical nutrition care model and the results will be used to provide any relevant updates to the online evidence-based guidelines (Head & Neck Guideline Steering Committee, 2011).

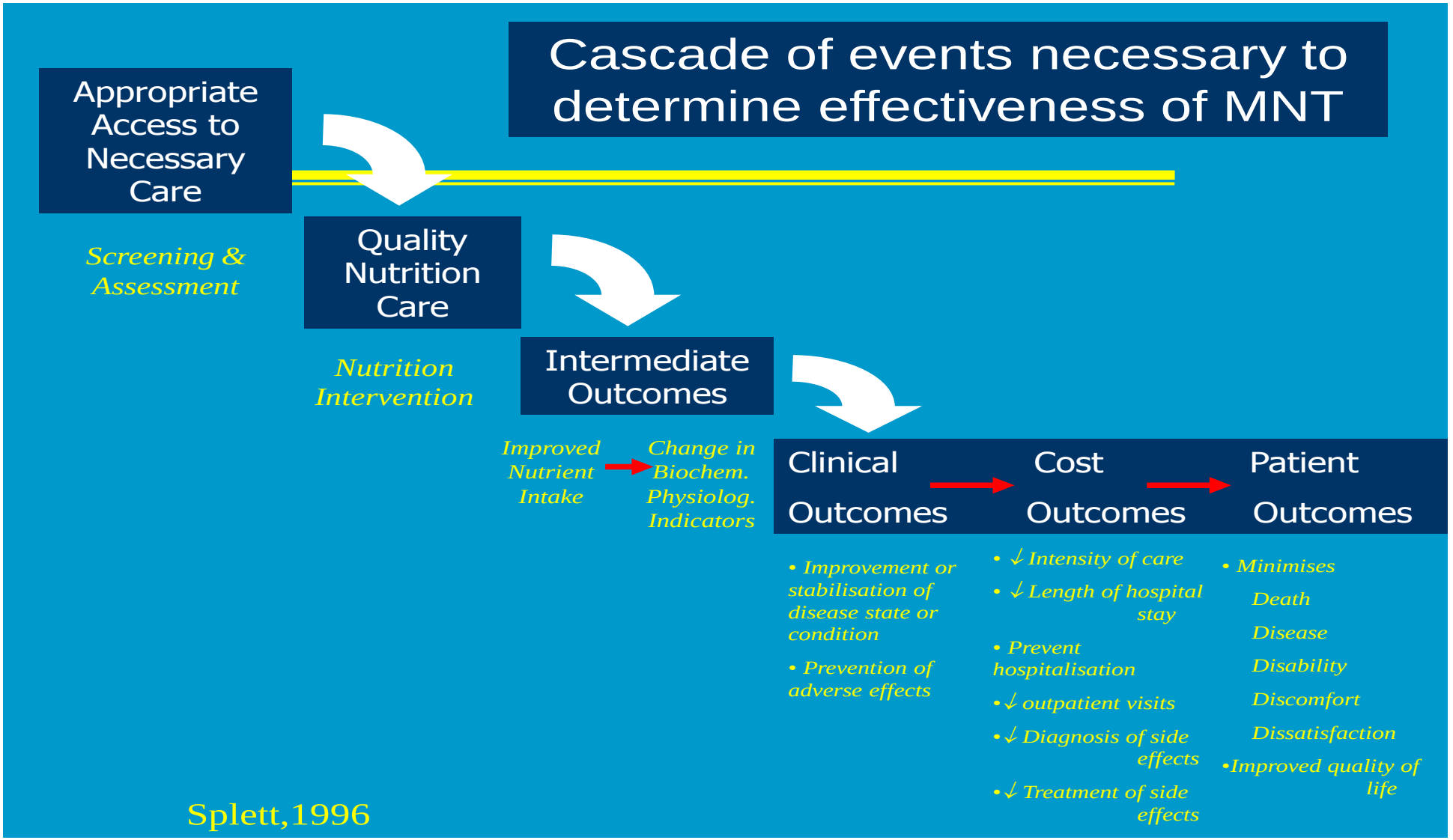


Figure 1-2: Theoretical Model – Nutrition Care Model

Source: Splett, 1996. Abbreviations: MNT = Medical Nutrition Therapy

Chapter 2 **Literature Review**

2.1 Literature review methodology

The Cochrane Database of Systematic Reviews, CENTRAL, PubMed, MEDLINE, EMBASE, CINAHL and AMED databases were searched in January 2012 and repeated in January 2017. Search terms included: “head and neck cancer” AND “radiotherapy OR radiation OR chemoradiotherapy OR chemoradiation” AND “enteral nutrition OR enteral feeding OR tube feeding OR gastrostomy OR PEG”. The outcomes were not specified in the search strategy thus allowing for a range of outcome measures to be considered including weight, nutritional status, quality of life and other clinical outcomes. Inclusion criteria for the review were a diagnosis of mucosal head and neck cancer, curative intent treatment, radiotherapy as part of the treatment plan, and the study of a nutrition intervention and associated outcome. Exclusions were applied for thyroid and oesophageal cancers, primary treatment with surgery and those where nutrition parameters were not the primary outcomes of the study. The search was limited to articles in English only and included all adult human studies from 1980 onwards. The strength of the evidence was assessed using the National Health and Medical Research Council “NHMRC Levels of Evidence and Grades for Developers of Guidelines” (NHMRC, 2009) and rated between levels I (highest) to level IV (lowest). The quality of the studies were assessed using the Academy of Nutrition and Dietetics “Evidence Analysis Manual: Steps in the Academy Evidence Analysis Process” whereby an overall rating of positive, neutral or negative quality was assigned (Academy of Nutrition and Dietetics, 2016). As part of this quality assessment tool the data from each individual study was reviewed to account for any author bias in their own conclusions.

2.2 Access to appropriate nutrition care : Identification of future nutritional risk

It is widely acknowledged that the dietitian should be part of the multidisciplinary team for treating patients with HNC (Head & Neck Guideline Steering Committee, 2011). Patients should be screened for malnutrition risk at diagnosis (Isenring et al., 2013; Watterson et al., 2009), as pre-treatment weight loss and malnutrition have been associated with reduced survival outcomes (Kubrak et al., 2010; Platek et al., 2010). Many studies frequently classify severity of weight loss outcomes using the accepted definition of clinically significant weight loss $\geq$10% (National Centre for Classification in Health, 2010), however poorer survival outcomes have been shown with weight loss <10% (Langius et al., 2013b; Martin et al., 2015). Therefore it is also important to recognise patients who may be well-nourished at diagnosis but are at future risk of nutritional deterioration, and provide appropriate timely intervention and education (Talwar, Donnelly, Skelly, & Donaldson, 2016).

The literature has identified a range of tumour, treatment and patient characteristics available to clinicians at diagnosis that are associated with future weight loss and/or need for tube feeding as discussed below.

2.2.1 Predictors of weight loss

There have been fourteen studies which have investigated predictors of weight loss following treatment for HNC. The type of treatment varies between studies, including single, double and triple modality, which means care needs to be taken in the interpretation. The results of all the studies are summarised in Table 2-1.There was only one level I positive quality study (Trotti et al., 2003) which was a systematic review on mucositis and impact on outcomes. Although this was a pooled cohort of 6181 patients from 33 RCT's, only 10 studies reported on the outcome of weight loss. A significant association between grade 3-4 mucositis and weight loss was reported (r=0.83, p=0.001), with a mean weight loss of 6-12%.

This likely explains why other treatment-related factors such as higher radiotherapy dose, larger radiotherapy fields and hyperfractionated/accelerated regimens are also associated with weight loss, (Larsson, Hedelin, Johansson, & Athlin, 2005; Mallick et al., 2013; Munshi et al., 2003) as higher rates of mucositis would also be expected. The most common treatment factor associated with weight loss, was the addition of chemotherapy, supported by two level III studies (Mallick et al., 2013; Walsh et al., 2011) and three level IV studies (Beaver, Matheny, Roberts, & Myers, 2001; Munshi et al., 2003; Nugent, Parker, & McIntyre, 2010a). A post-treatment neck dissection in a patient population predominantly treated with chemoradiotherapy (CRT) was also found to be associated with an increased risk of weight loss (O'Shea, Byrne, Tuckett, O'Leary, & Sheahan, 2015).

The oropharynx was the most common tumour characteristic associated with weight loss, and was supported by one level II study (positive quality) (Ottosson, Zackrisson, Kjellen, Nilsson, & Laurell, 2013), one level III-3 study (positive quality) (Lonbro, Petersen, Andersen, & Johansen, 2016), and three level IV studies (one positive and two neutral quality) (Beaver et al., 2001; Nourissat et al., 2010; Nugent et al., 2010a). There is also some evidence (level III-IV) that a more advanced stage is associated with increased risk of weight loss (Ehrsson, Langius-Eklof, & Laurell, 2012; Lonbro et al., 2016; Nourissat et al., 2010), however all of these studies were undertaken in patient populations receiving definitive or adjuvant radiotherapy alone.

The most common patient factor predictive of weight loss was a higher baseline weight or BMI, supported by three recent large positive quality studies (level II-IV) (Lonbro et al., 2016; Nourissat et al., 2010; Ottosson et al., 2013). Pre-treatment patient factors such as the presence of nutrition impact symptoms or dysphagia or poor performance status were all associated with weight loss (Kubrak et al., 2010; Munshi et al., 2003; Nourissat et al., 2010). The impact of age on weight loss is conflicting with two level III-3 positive quality studies reporting different outcomes. One study found that patients older than 60.9 years receiving definitive or adjuvant radiotherapy had less than half the odds (OR=0.46, p=0.005) of 10% or more weight loss compared to younger patients (Lonbro et al., 2016). Meanwhile another study found that patients over 65 years receiving CRT were more likely to experience weight loss (Chang et al., 2015).

In summary, the highest level of evidence and most consistent body of evidence supports that patients at greatest risk of weight loss are those with: oropharyngeal tumours; more advanced stage disease; higher weight/BMI at baseline; and treatment regimens which increases the risk of grade 3-4 mucositis, including the addition of chemotherapy.

Table 2-1: Summary of studies investigating predictors of weight loss in patients with head and neck cancer

Risk Factor	Total Studies	Level I	Level II	Level III	Level IV
Patient Factors					
Pre-treatment weight loss	1				Beaver 2001 (Ø)
Higher baseline weight or BMI	3		Ottosson 2013 (+)	Lonbro 2016 (+)	Nourissat 2010 (+)
Pre-treatment dysphagia	2				Nourissat 2010 (+) Kubrak 2010 (Ø)
Nutrition impact symptoms or opioid use pre-treatment	2				Nourissat 2010 (+) Kubrak 2010 (Ø)
Poor baseline performance status	2				Nourissat 2010 (+) Munshi 2003 (Ø)
Older age	1			Chang 2015 (+)	
Younger age	1			Lonbro 2016 (+)	
Tumour Factors					
Oral cavity	2			Lonbro 2016 (+)	Nourissat 2010 (+)
Oropharynx	5		Ottosson 2013 (+)	Lonbro 2016 (+)	Nourissat 2010 (+) Nugent 2010a (Ø) Beaver 2001 (Ø)
Nasopharynx	1				Beaver 2001 (Ø)
Hypopharynx	1				Nourissat 2010 (+)
Larynx	1			Lonbro 2016 (+)	
Higher N stage	1				O'Shea 2015 (+)
Higher TNM stage	3			Lonbro 2016 (+)	Nourissat 2010 (+) Ehrsson 2012 (Ø)
Treatment Factors					
Chemotherapy	5			Mallick 2013 (Ø) Walsh 2011 (Ø)	Nugent 2010a (Ø) Munshi 2003 (Ø) Beaver 2001 (Ø)
Multimodality treatments	1				O'Shea 2015 (+)
Nutrition impact symptoms or opioid use pre-treatment	1	Trotti 2003 (+)			
Higher RT doses	1				Munshi 2003 (Ø)
Larger RT fields/oral mucosa	1			Mallick 2013 (Ø)	
Accelerated or hyperfractionated RT	1				Larsson 2005 (Ø)

Abbreviations: BMI=Body Mass Index; TNM=Tumour, Nodal, Metastases Staging; RT=Radiotherapy. Quality rating: (+) = positive; (Ø) = neutral; (-) = negative.

2.2.2 Predictors of tube feeding

A number of prognosis studies have looked at which patient groups are more likely to require a gastrostomy or feeding tube. In this body of literature, as well as variations in inclusion criteria for tumour sites and treatment, there are also differences in tube type, placement timing, outcome measures and follow-up time points. The summary of factors associated with tube feeding requirement are in Table 2-2.

Two level II positive quality studies (Lango et al., 2016; Ottosson et al., 2013) provide the highest level of evidence to support the following patient risk factors: low BMI, pre-treatment dysphagia, pre-treatment nutrition impact symptoms, heavy smoker, poor performance status, and older age. Although the study by Ottosson et al. (2013) has a large sample size (n=712), the findings are limited to patients receiving radiotherapy. The study by Lango et al. (2016) was completed in patients receiving (chemo) radiotherapy but had a small sample in comparison (n=84). Pre-treatment weight loss was the only other patient factor supported by a number of level III and IV studies (Beaver et al., 2001; Gardine et al., 1988; Mangar, Slevin, Mais, & Sykes, 2006; Mays, Moustafa, Worley, Waltonen & D'Agostino, 2014; Orphanidou et al., 2011).

In total there are four level II studies (three positive and one neutral quality) which also identify tumour sites, tumour staging and treatment to be important predictive factors. The highest level of evidence identifies: tumours of the oropharynx (Barnhart et al., 2017), followed by the hypopharynx and oral cavity (Ottosson et al., 2013); higher T stage (Brown et al., 2016a); higher overall TNM stage (Lango et al., 2016; Ottosson et al., 2013); and chemotherapy (Barnhart et al., 2017; Brown et al., 2016a; Lango et al., 2016). All of these factors were supported by a large number of level III-IV studies as well. Other key treatment factors were accelerated or hyperfractionated radiotherapy (Ottosson et al., 2013) and bilateral neck treatment (Barnhart et al., 2017). The level I systematic review also found grade 3-4 mucositis to be associated with feeding tube requirement (r=0.88, p=0.004) which was based on five RCT's, n=819 (Trotti et al., 2003).

In summary, the highest level of evidence and most consistent body of evidence supports that patients at greatest risk of requiring tube feeding are those with; oropharyngeal tumours, more advanced stage disease, receiving chemotherapy as part of treatment and of older age. This aligns quite closely to the risk factors identified for weight loss during treatment.

Table 2-2: Summary of studies investigating predictive factors of tube feeding requirement

Risk Factor	Total	Level I	Level II	Level III	Level IV
Patient Factors					
Pre-treatment weight loss	5			Mays 2014 (Ø) Orphanidou 2011 (Ø) Gardine 1988 (Ø)	Mangar 2006 (Ø) Beaver 2001 (Ø)
Low BMI	5		Ottosson 2013 (+)	Orphanidou 2011 (Ø) Strom 2013 (Ø) Wermker 2012 (Ø)	Mangar 2006 (Ø)
Low albumin	1				Mangar 2006 (Ø)
Pre-treatment dysphagia	6		Lango 2016 (+) Ottosson 2013 (+)	Mays 2014 (Ø) Orphanidou 2011 (Ø)	Larsson 2005 (Ø)
Nutrition symptoms or opioid use pre-treatment	5		Lango 2016 (+) Ottosson 2013 (+)	Orphanidou 2011 (Ø)	Larsson 2005 (Ø) Jeffery 2012 (-)
High alcohol	1				Schweinfurth 2001 (Ø)
High smoking	2		Lango 2016 (+)		Mangar 2006 (Ø)
Poor baseline performance status	6		Lango 2016 (+) Ottosson 2013 (+)		Yang 2016 (Ø) Poulsen 2008 (Ø) Mangar 2006 (Ø) Matuschek 2016 (-)
Older age	8		Ottosson 2013 (+)	Chang 2015 (+)	Beadle 2017 (Ø) Sachdev 2015 (Ø) Mangar 2006 (Ø) Al-Othman 2003 (Ø) Jeffery 2012 (-) Cheng 2006 (-)
Female gender	1				Mekhail 2001 (Ø)
Single	1			Locher 2013 (Ø)	
Tumour Factors					
Oral cavity	5		Ottosson 2013 (+)	Ahmed 2005 (Ø) Wermker 2012 (Ø)	Chen 2017 (+) Beaver 2001 (Ø)
Oropharynx	17		Barnhart 2017 (+)	Ahmed 2005 (Ø) Chepeha 2004 (Ø) Locher 2013 (Ø) Wermker 2012 (Ø) Gardine 1988 (Ø)	Chen 2017 (+) Beadle 2017 (Ø) Zauls 2013 (Ø) Ishiki 2012 (Ø) Nugent 2010a (Ø) Larsson 2005 (Ø) Beaver 2001 (Ø) Schweinfurth 2001 (Ø) Ringstrom 1999 (Ø) Matuschek 2016 (-) Cheng 2006 (-)

Risk Factor	Total	Level I	Level II	Level III	Level IV
Tumour Factors cont.					
Nasopharynx	1				Larsson 2005 (Ø)
Hypopharynx	7		Ottosson 2013 (+)	Ahmed 2005 (Ø)	Beadle 2017 (Ø) Ishiki 2012 (Ø) Larsson 2005 (Ø) Mekhail 2001 (Ø) Cheng 2006 (-)
Larynx	2			Locher 2013 (Ø)	Chen 2017 (+)
Higher T stage	10		Brown 2016a (Ø)	Ahmed 2005 (Ø) Mays 2014 (Ø) Strom 2013 (Ø) Wermker 2012 (Ø)	Beaver 2001 (Ø) Schweinfurth 2001 (Ø) Mekhail 2001 (Ø) Ringstrom 1999 (Ø) Jack 2012 (-)
Higher N stage	5			Mays 2014 (Ø) Locher 2013 (Ø) Wermker 2012 (Ø)	Beadle 2017 (Ø) Al-Othman 2003 (Ø)
Higher TNM stage	8		Lango 2016 (+) Ottosson 2013 (+)	Chepeha 2004 (+) Gardine 1988 (Ø)	Poulsen 2008 (Ø) Mangar 2006 (Ø) Cheng 2006 (-) Riera 2002 (-)
Moderate to poor histology	1				Schweinfurth 2001 (Ø)
Treatment Factors					
Chemotherapy	16		Barnhart 2017 (+) Lango 2016 (+) Brown 2016a (Ø)	Mallick 2013 (Ø) Locher 2013 (Ø) Strom 2013 (Ø) Walsh 2011 (Ø)	Bhayani 2013b (+) Beadle 2017 (Ø) Ishimaru 2016 (Ø) Yang 2016 (Ø) Nugent 2010a (Ø) Al-Othman 2003 (Ø) Mekhail 2001 (Ø) Matuschek 2016 (-) Cheng 2006 (-)
Multimodality treatments	7			Chepeha 2004 (+) Mays 2014 (Ø) Gardine 1988 (Ø)	Chen 2017 (+) Beaver 2001 (Ø) Schweinfurth 2001 (Ø) Jack 2012 (-)
Accelerated or hyper-fractionated RT	3		Ottosson 2013 (+)	Strom 2013 (Ø)	Poulsen 2008 (Ø)
Larger RT fields/oral mucosa	3			Mallick 2013 (Ø) Sanguineti 2011 (Ø)	Poulsen 2008 (Ø)
Higher RT dose >60gy/ Definitive RT	2			Locher 2013 (Ø)	Al-Othman 2003 (Ø)
Bilateral neck RT	2		Barnhart 2017 (+)	Wermker 2012 (Ø)	

Risk Factor	Total	Level I	Level II	Level III	Level IV
Surgical Factors					
Surgery to oral cavity	2				Chen 2017 (+) Schweinfurth 2001 (Ø)
Surgery to base of tongue or pharynx	4			Chepeha 2004 (+) Wermker 2012 (Ø)	Chen 2017 (+) Schweinfurth 2001 (Ø)
Surgery to larynx	2			Mays 2014 (Ø)	Chen 2017 (+)
Flap reconstruction	5			Chepeha 2004 (+) Mays 2014 (Ø)	Chen 2017 (+) Schweinfurth 2001 (Ø) Cheng 2006 (-)
Other factors					
Nutrition symptoms or opioid use pre-treatment	3	Trotti 2003 (+)	Ottosson 2013 (+)		Riera 2002 (Ø)
No prophylactic pain control (gabapentin)	1				Yang 2016 (Ø)
Non-adherent to swallow exercises	1				Bhayani 2013b (+)
Tracheostomy	2			Mays 2014 (Ø)	Cheng 2006 (-)
Fistula	1				Riera 2002 (-)

Abbreviations: BMI=Body Mass Index; TNM=Tumour, Nodal, Metastases Staging; RT=Radiotherapy. Quality rating: (+) = positive; (Ø) = neutral; (-) = negative.

2.2.3 Guidelines for high risk patients

Using evidence to predict patients at future risk of weight loss or tube feeding would help to select patients who may benefit from a prophylactic gastrostomy (proPEG). Pre-treatment insertion avoids the difficulties of undergoing the procedure when cytotoxic or once acute toxicities have developed e.g. mucositis, oesophagitis and neutropenia, and helps minimise the risk of complications (Garsed, Armstrong, & Scott, 2007).

There are currently three sets of guidelines published from the UK and Australia that identify high risk patients undergoing radiotherapy treatment. Two recommend high risk patients receive a proPEG (Brown et al., 2013b; Wood, 2005). The third classifies patients as high or low nutritional risk, but favours a reactive approach to tube placement (Kiss et al., 2012). All three sets of guidelines demonstrated significant clinical benefits following implementation such as less weight loss, fewer hospital admissions, reduced length of stay, fewer unplanned nasogastric tube (NGT) insertions, improved transition to oral diet post-treatment and reduced oncologist review at two weeks post-treatment (Brown, Ross, Jones, Hughes, & Banks, 2014a; Hughes et al., 2013; Kiss et al., 2012; Wood, 2005). The Australian protocol for proPEG insertion is the only validated version and following further review was subsequently revised (Brown et al., 2016a).

Guidelines for gastrostomy selection in the surgical population have also been developed in the UK (Jack, Dawson, Reilly, & Shoaib, 2012), and more recently a predictive model has been developed and validated in the USA (Mays et al., 2014). Despite the accuracy of this predictive model, it is quite complex and will be challenging to transfer into a clinical setting. A summary of each of the published guidelines/models described above are in Table 2-3.

This body of evidence has been considered in the internationally endorsed guidelines to provide evidence-based practical recommendations as follows:

“Prophylactic enteral feeding should be considered to improve nutritional status, cost and patient outcomes for patients who have: T4 tumours undergoing concurrent chemoradiotherapy; hypopharyngeal tumours undergoing concurrent chemoradiotherapy; Other patient groups should be considered by the multidisciplinary team on an individual basis dependent on other clinical factors such as tumour site, staging, effect of multi-modality treatments, radiotherapy treatment fields and dose, type of surgical procedure, nutritional status and dysphagia.” (Head & Neck Guideline Steering Committee, 2011).

However the recommendation is currently only weakly supported (Grade C), and so it is not surprising that practices remain varied worldwide, with discrepancies reported in Australia (Brown & Findlay, 2011), UK (Moor, Patterson, Kelly, & Paleri, 2010) America (Koyfman & Adelstein, 2012), Canada (Orphanidou et al., 2011) and Italy (Trignani et al., 2015).

The validated revised Australian protocol describing the risk factors which inform the high risk criteria for consideration of proPEG insertion (Brown et al., 2016b) was selected to be used for the studies included in this thesis.

Table 2-3: Summary of existing guidelines for gastrostomy selection

Citation	Country	Criteria for Gastrostomy
Wood 2005	UK	○ Radical radiotherapy/chemoradiation: Oral cavity, Nasopharynx, Oropharynx, Hypopharynx ○ Palliative radiotherapy/chemoradiation (radical length): Oral cavity, Nasopharynx, Oropharynx, Hypopharynx ○ Patients (including carcinomas of the larynx) with: ○ Advanced disease ○ ≥10% weight loss within 6 months ○ BMI < 20 ○ Over 70 years of age ○ Undergoing combined treatment ○ Patients with a small treatment field or reduced dose – Consider on an individual basis and discuss with the oncology dietitian and the ENT speech and language therapist
Kiss 2012	Australia	○ T3/T4 oral cavity ○ T3/T4 and/or N2/N3 oropharynx/hypopharynx/larynx/nasopharynx ○ Adjuvant chemoradiation ○ Infield boost ○ Severe malnutrition (PG-SGA C) ○ Moderate malnutrition (PG-SGA B) in the presence of dysphagia
Jack 2012	UK	○ Oral cavity, T3/T4, texture modified diet, surgery alone ○ Oral cavity, T3/T4, full diet, surgery and radiotherapy ○ Oral cavity, T1/T2, texture modified diet, surgery alone ○ Oral cavity, T1/T2, full diet, surgery and chemoradiotherapy ○ Mandible tumours, any stage or treatment ○ Oropharynx, T2/T3, fluid diet, surgery and radiotherapy
Brown 2013b	Australia	○ Oral cavity with bilateral chemoradiotherapy ○ Midline oropharyngeal with chemoradiotherapy ○ Hypopharyngeal or nasopharyngeal with chemoradiotherapy ○ Dysphagia at presentation or prior to radiotherapy/chemoradiotherapy ○ Severe malnutrition at presentation: ○ Unintentional weight loss >10% in 6 months ○ BMI <18.5 ○ BMI <20 with unintentional weight loss 5-10% in 6 months ○ Dietitian assessment SGA C ○ Poor oral intake (minimal intake >5days and/or unlikely to improve for >5 days)

Mays 2014	USA	Predictive probability = X/(1 + X) X= e [5.8517 − (0.6874 × A) − (0.8847 × B) − (0.4541 × C) − (1.4086 × D) − (0.6947 × E) − (0.9533 × F) − (0.6588 × G) − (3.7531 × H) − (0.5632 × I)] where A = Preoperative weight loss (No = 1, Yes = 0) B = Clinical node stage (N0 = 1,N1 = 0,N2 = 0) C = Clinical node stage (N1 = 1,N0 = 0,N2 = 0) D = Preoperative irradiation (No = 1, Yes = 0) E = Dysphagia (No = 1, Yes = 0) F = Tracheostomy (No = 1, Yes = 0) G = Reconstruction type; (primary closure or SSG = 1, microvascular free flap or pedicled rotation flap = 0) H = Supra-cricoid laryngectomy (No = 1, Yes = 0) I = T stage (T1 or T2=1, T3 or T4=0)
Brown 2016a	Australia	○ Oral/oropharyngeal with bilateral chemoradiotherapy ○ Hypopharyngeal or nasopharyngeal or unknown primary with chemoradiotherapy ○ Severe malnutrition at presentation: ○ Unintentional weight loss >10% in 6 months ○ BMI <20 with unintentional weight loss 5-10% in 6 months ○ Dietitian assessment SGA C

Abbreviations: BMI=Body Mass Index; ENT=Ear Nose Throat; TNM=Tumour, Nodal, Metastases Staging; PG-SGA=Patient-Generated Subjective Global Assessment; SGA=Subjective Global Assessment; SSG=Split Skin Graft.

2.3 Nutrition goals and prescription

Following nutrition screening, assessment and diagnosis, the first step of nutrition intervention is goal setting and nutrition prescription. In patients who have been identified at risk of malnutrition or malnourished, the aim is to maintain/prevent a decline/improve nutritional status (Watterson et al., 2009). Whilst this is the ideal goal for all patients commencing treatment, studies have shown that weight loss occurs despite nutrition intervention (Jager-Wittenaar et al., 2011b; Paccagnella et al., 2010; van den Berg et al., 2010), and thus the consensus goal for patients receiving CRT is to minimise a decline in nutritional status/weight (Head & Neck Guideline Steering Committee, 2011).

The number of studies investigating nutrition requirements in patients with HNC is very low. Only one study (level III-2 neutral quality) has measured resting energy expenditure with indirect calorimetry in patients undergoing CRT (n=18) and found that requirements were approximately 90-100kJ/kg/day throughout treatment, but were slightly more elevated at two weeks post-treatment at 105kJ/kg/day (Garcia-Peris et al., 2005).

Other studies have determined requirements based on energy/protein intakes from food records and assessed outcomes to determine adequacy. One level IV (positive quality) study found that patients with sufficient intakes (defined as >145kJ/kg/day and >1.5g protein/kg/day) lost less body weight/lean mass during treatment than those with insufficient intakes; and only those with sufficient intakes were able to achieve weight gain post-treatment (Jager-Wittenaar et al., 2011b). One level IV (neutral quality) study monitored energy intakes for a group of HNC patients (n=47) and found they were at 135kJ/kg/day pre/during treatment and increased to 160kJ/kg/day at six months post-treatment (van den Berg et al., 2006). However, patients who received CRT (n=3) intakes were only 80kJ/kg/day at the end of treatment resulting in the largest weight loss; which continued post-treatment despite increases in energy intake up to 155kJ/kg/day. A recent level IV neutral quality study in a larger sample (n=116) with approximately 60% receiving CRT had similar findings – with energy and protein intakes respectively at 115kJ/kg/day and 1.1g/kg/day at baseline, reducing to 95kJ/kg/day and 1.0g/kg/day at the end of treatment, and improving to 135kJ/kg/day and 1.3g/kg/day at two to three months post-treatment, however nutrition outcomes were not reported (Alvarez-Camacho et al., 2016).

One level IV (neutral quality) study (n=39) has investigated energy requirements at one year post-treatment based on how optimal BMI was achieved through long-term enteral feeding (Schattner et al., 2005). The authors concluded the following energy prescriptions were required for each goal; 145kJ/kg/day for weight maintenance, 185kJ/kg/day for weight gain and 115kJ/kg/day for weight loss.

Overall the evidence is limited and inconsistent, and there is a lack of longitudinal studies with sufficient sample size. Therefore the current consensus recommendation for the nutrition prescription in any cancer patient is to provide 105-125kJ/kg/day (low level of evidence) and 1.5g protein/kg/day (moderate level of evidence) (Arends et al., 2017).

2.4 Nutrition implementation

The second step of nutrition intervention is selection of the nutrition implementation method to meet these goals and prescription. The evidence for the following methods of implementation are described below and include dietary counselling, oral nutrition supplements and tube feeding.

2.4.1 Dietary counseling and oral nutrition supplements

There is level I evidence for the role of nutrition support for patients receiving radiotherapy from two positive quality systematic reviews (Garg, Yoo, & Winquist, 2010; Langius et al., 2013c). Garg et al. (2010) identified three RCT's in relation to dietary counselling (Isenring, Bauer, & Capra, 2007; Isenring, Capra, & Bauer, 2004; Ravasco et al., 2005a) and two RCT's in relation to oral nutrition supplements (Arnold & Richter, 1989; Nayel, el-Ghoneimy, & el-Haddad, 1992). The systematic review by Langius et al. (2013c) identified two additional RCT's for dietary counselling (Macia et al., 1991; van den Berg et al., 2010) and they also included Ravasco et al. (2005a) in the analysis of oral nutrition supplements as this study had a third arm of oral supplements alone for comparison. Both reviews concluded beneficial effects of dietary counselling in relation to improving nutritional status and QOL compared to usual care (ad lib diet / nurse education and nutrition booklet). Whilst the patient numbers in individual studies were small (less than 50 randomised per arm), they were well-designed and of high quality. The role of oral nutrition supplements was deemed to be inconsistent, however they have been shown to be a cost effective intervention in malnourished patients in both the acute and community settings (Elia, Normand, Laviano, & Norman, 2016a; Elia, Normand, Norman, & Laviano, 2016b).

Since the systematic reviews were completed, a prospective level IV (neutral quality) study has evaluated the effect of nutrition counselling and oral nutrition supplements on toxicity outcomes from CRT, and found a relatively low rate of grade three mucositis at 33%, however interpretation was limited due to a lack of control group (Valentini et al., 2012).

There has also been a quasi RCT (level III-1 neutral quality) that compared a daily oral nutrition supplement versus no supplement and reported improvements on QOL and less need for feeding tube placement (Trachootham et al., 2015). The supplement used was described as a novel type of oral supplement (Nutrijelly – semi solid texture) which was acceptable to the Thai population. It provides 230-260kcal and 10-11g protein per serve and thus is similar to other commercial liquid oral supplements. However, this study was severely limited by the lack of any nutritional outcome measures or details of nutrition interventions other than provision of a daily supplement. Finally a small cross-sectional study (n=32) in a post CRT treatment population with median follow-up of 44 months (range 14-68 months) is the first study to report on longer term nutritional needs of patients (van den Berg et al., 2014). The authors reported malnutrition risk and weight loss is still a concern, especially in females and patients with high BMI pre-treatment, and that a high degree of food modifications, and use of nutritional supplements and tube feeding are still required. It was also found that food group recommendations and alcohol intake were not meeting guidelines, and that dietary advice for survivorship management is also important.

2.4.2 Timing of intervention

It is now widely accepted, based on the findings above, that patients receiving radiotherapy for HNC should be automatically referred to the dietitian for individualised dietary counselling (with or without oral nutrition supplements as required), with a minimum of weekly review during treatment and for at least six weeks post-treatment (Head & Neck Guideline Steering Committee, 2011). The limitations from these systematic review findings are that the majority of studies were undertaken in patients receiving radiotherapy alone, compared to current standard of care which is concurrent CRT, and the requirement or benefit of longer term nutrition intervention beyond six weeks post-treatment is not known. Nutrition support has been widely investigated for the role of preoperative nutrition support (Bertrand, Piquet, Bordier, Monnier, & Roulet, 2002; Flynn & Leightty, 1987; Weimann et al., 2006) particularly in regards to the role of immunonutrition (Stableforth, Thomas, & Lewis, 2009), but there have been limited studies investigating the timing of nutrition support prior to oncological or radiotherapy treatment. Positive outcomes have recently been reported following pre-treatment nutrition intervention in lung cancer patients undergoing CRT (Kiss et al., 2016).

Two studies have reported the success of an early nutrition intervention in HNC patients undergoing (chemo) radiotherapy, with less weight loss, fewer treatment interruptions, less unplanned admissions and higher completion of chemotherapy (Paccagnella et al., 2010; Wang, Wang, Pang, & Yeh, 2012). The intervention groups both had a dietetic review pre-treatment, but also received regular contact throughout treatment. Paccagnella et al. (2010) also had regular dietitian review post-treatment and Wang et al. (2012) also had mandatory hospitalisation and NGT placement throughout treatment to supplement oral intake. Both were in comparison to usual care in which patients received a nutrition booklet and were only referred to a dietitian in severe cases of symptoms or weight loss. Given the increase in dietetic intervention as a whole, it is unlikely the positive outcomes were due to the pre-treatment counselling alone.

A post-hoc analysis of an RCT (Rabinovitch et al., 2006), found that patients who received pre-treatment nutrition support had less weight loss and less mucositis, however were also more likely to have reduced locoregional control and survival. However, patients who received this support had more severe weight loss/dysphagia and advanced disease, and were therefore more likely to have poorer clinical outcomes. A recent study also looked at the impact of feeding tube timing in a population of patients with HPV-related oropharyngeal cancer undergoing adjuvant (chemo) radiotherapy. They did not use proPEG tubes, but found that patients who had their feeding tube placed prior to treatment, for therapeutic reasons, had a reduced survival (Verma et al., 2015). Again this group of patients had poorer nutritional status pre-treatment with 10.1% weight loss compared to 1.2% weight loss in patients who had feeding tubes placed later. Thus the presence of the feeding tube prior to treatment is really a surrogate marker for poor nutritional status and this is more likely the reason for reduced survival (Martin et al., 2015).

2.4.3 Tube feeding: Optimal type and timing

As many patients are unable to maintain adequate oral intake during treatment tube feeding is often recommended (Arends et al., 2006). The selection of tube type (gastrostomy versus NGT) and the timing of placement (prophylactic versus reactive) are areas that are highly debated. A gastrostomy tube is preferred if anticipated duration of nutrition support is likely to be greater than four weeks (Arends et al., 2006). Historically, many centres favoured the proPEG method, however there has been a trend in recent times to move away from this approach and favour reactive management with an NGT (Clavel et al., 2011; Lawson et al., 2009; Madhoun, Blankenship, Blankenship, Krempl, & Tierney, 2011).

This section discusses the key evidence in the field with a detailed overview of the individual studies in the Appendices (Appendix A and Appendix B). For prophylactic tubes versus oral intake there were two level II neutral studies and five level III-2 studies (one positive, one neutral, three negative); for prophylactic tubes versus reactive tubes there were seven level III-2 studies (two positive, five neutral); for prophylactic tubes versus reactive management (oral intake +/- tube feeding as required) there were three level II studies (one positive, two neutral), twenty-five level III-2 studies (five positive, twenty neutral) and three level III-3 studies (two positive, one neutral). For reactive tubes versus oral intake there were four level III-2 studies (three neutral, one negative); and for comparison of reactive tubes there were two level II studies (one neutral, one negative) and four level III-2 studies (three neutral, one negative).

In 2014, the Canadian Agency for Drugs and Technologies in Health completed a review of systematic reviews and guidelines to determine the clinical effectiveness of NGT versus gastrostomy for patients with HNC. They identified four systematic reviews (Langius et al., 2013c; Nugent, Lewis, & O'Sullivan, 2013; Orphanidou et al., 2011; Wang, Liu, Liu, Ye, & Huang, 2014a) and four sets of clinical practice guidelines (Canada 2009, UK 2011, Australia 2014 and America 2014) and provided detailed critical appraisal of the evidence.

In summary, due to the lack of high level and high quality evidence to support one method over the other, no clear recommendations could be made from this review which was reflected in the other clinical guidelines available. Since this review, the UK guidelines have been updated although again no clear recommendations are made regarding feeding tube choice, other than consideration of gastrostomy if tube feeding is anticipated for greater than four weeks and that prophylactic feeding can be offered as part of locally agreed guidelines (Talwar et al., 2016).

Of the systematic reviews included above, the highest quality review (Level I positive) was based on four RCTs with heterogenic study designs (Langius et al., 2013c). The first was a prophylactic NGT intervention trial versus oral intake undertaken in the 1980’s and published in two papers (Daly et al., 1984; Hearne et al., 1985). This intervention achieved higher energy and protein intakes and less weight loss, with no differences in toxicities, treatment response or survival. The individual study provides level II evidence (neutral quality) that tube feeding has superior outcomes to oral intake alone, however applicability to contemporary practices thirty years later is limited.

The second RCT (neutral quality) compared reactive nutrition support with either gastrostomy or NGT (Corry et al., 2008). The gastrostomy group had less weight loss at six weeks post-treatment but this difference was not maintained six months later, and they had longer duration of tube use, although dysphagia outcomes were no different at six months. Overall QOL was no different between groups, but differences were seen for certain domains. This individual study provides level II evidence (neutral quality) that both gastrostomy and NGT provide similar outcomes when placed reactively, and thus tube selection should consider the acceptability to the patient in terms of the different impacts on QOL.

The final two RCT's were both comparisons of proPEG versus reactive management (oral +/- tube feeding as required). One study (positive quality) reported on QOL outcomes and BMI (Salas et al., 2009). There were no differences in BMI at six months, but the proPEG group had a higher QOL for some domains at some time points. The second study (neutral quality) had no difference in weight loss outcomes, treatment delays, unplanned admissions or survival between groups, but the proPEG group had better QOL at six months for a number of domains, and less swallow problems at one year (Silander et al., 2012). These two studies both provide level II evidence that the prophylactic approach does not improve clinical or nutrition outcomes (although weight change was only monitored from six months post-treatment) but can improve some aspects of QOL compared to the reactive approach, with no impact on long-term swallow. Due to the overall variations in study design and sources of bias, the conclusion of the systematic review was that the effect of tube feeding interventions was inconsistent.

Two additional systematic reviews have been completed since the Canadian Agency for Drugs and Technologies in Health review (Shaw et al., 2015; Zhang, Zhu, Ling, Zhang, & Wan, 2016). As no new RCT's have been published since those included in the reviews by Langius et al. (2013c) and Wang et al. (2014a), the new systematic reviews broadened their inclusion criteria to include prospective and retrospective comparative studies, and so have been graded as level III-I (both were considered high quality). Due to differences in inclusion criteria with respect to the intervention and outcomes, different papers were included for each review. A summary of all systematic reviews to date has been compiled (Table 2-4).

Zhang et al. (2016) concluded that proPEG may be the optimal tube feeding method in reducing the rate of treatment interruptions and unplanned hospital admissions, with no difference in terms of tube complications. Both proPEG and NGT were found to be superior to reactive gastrostomy in terms of minimising weight loss. However, it was acknowledged that this was based on limited high level evidence (two RCTs and 11 cohort studies all with risk of bias) and that further research is required to confirm these findings. The review also did not consider other relevant outcomes such as tube dependency, QOL and cost.

Tube dependency however was covered by Shaw et al. (2015). Five studies examined prevalence of tube use post-treatment (two were in favour of the reactive group, one found no difference, and two did not find any differences beyond three months). Seven studies examined duration of tube use (three studies were in favour of the reactive group, and four studies had no difference). Due to inconsistencies in results, no firm conclusions could be made.

Another RCT comparing NGT (n=50) and gastrostomy (n=50) has been completed in India (Sadasivan, Faizal, & Kumar, 2012) however was not identified for inclusion in any of the systematic reviews. Whilst nutritional and QOL outcomes were better in the gastrostomy group the trial was deemed to be of negative quality. The methodology was very unclear with respect to the timing of the tube placement and thus it was difficult to ascertain if tubes were placed before surgery or radiotherapy and prophylactically or reactively.

A well-designed RCT is currently underway in the UK (Paleri et al., 2016) which will hopefully start to address some of the uncertainty regarding optimal tube selection. This research group is comparing the proPEG approach to reactive management (oral nutrition with NGT as required) with outcomes of swallowing, QOL, nutritional parameters (BMI, weight and intake of enteral nutrition during treatment), admissions, dilatations, survival, and tube complications, with follow-up until 12 months post-treatment.

Table 2-4: Summary of systematic reviews on tube feeding interventions in head and neck cancer

Citation	Level & Quality	Study design	Interventions & Outcomes	Results	Comments/Limitations
Langius 2013c	I +	Systematic review of RCTs N=10 N=536 participants HNC with RT/CRT	6 RCT's (7 papers) of diet/ONS interventions - Dietary counselling (n=4) - Dietary counselling/ONS (n=1) - ONS (n=2) 4 RCT's (5 papers) of tube interventions - NGT vs oral (n=2) - NGT vs gastrostomy (n=1) - proPEG vs reactive (n=2) Outcomes: - Nutrition - QOL - Dysphagia	Dietary counselling beneficial on nutrition intake/status & QOL ONS/tube feeding effects inconsistent NGT beneficial on nutrition intake/wt vs oral intake Gastrostomy short-term benefit on wt loss vs NGT proPEG no difference for wt at 6mths, some benefit on short-term QOL (some domains), less dysphagia at 1 year vs reactive	All studies high risk of bias Small number of studies on ONS and tube feeding
Garg 2010	I +	Systematic review of RCT's N=10 N=585 participants HNC with RT/CRT	10 RCT/papers of: - Dietary counselling/ONS (n=5) - Drug interventions (n=4) - Prophylactic tube feeding (n=1) Outcomes: - Nutrition	Nutritional status appeared to be maintained or improved with dietary counselling, megesterol acetate and prophylactic tube feeding	Limited RCTs addressing clinical question of interest >95% of patients had RT alone vs usual CRT Tube feeding conclusion based on one study

Citation	Level & Quality	Study design	Interventions & Outcomes	Results	Comments/Limitations
Nugent 2013	I Ø	Systematic review of RCT's N=1 N=33 participants HNC with RT/CRT .	Compared tube feeding methods. Gastrostomy (n=15) vs NGT (n=18) – both reactive tube feeding. Outcomes: - Nutritional status - Tube complications - Timing tube placed - QOL/ Patient satisfaction - Health economics - RT delays - Duration tube feeding - Reason for ceasing	No conclusive evidence on which to base recommendations for the optimal method of enteral feeding during treatment and in the post-treatment period	Systematic review well written but overall neutral rating as only based on one article of low quality
Zhang 2016	III-I +	Systematic review and network meta-analysis of level II to III-2 papers N=13 (2 RCT) N=1631 participants HNC with RT/CRT	Compared one or more tube feeding method (proPEG vs reactive gastrostomy vs NGT vs oral) Outcomes: - Wt - Treatment delays - Admissions - Tube complications	proPEG and NGT had less wt loss vs reactive gastrostomy proPEG had less treatment delays and admissions vs others No differences in tube complications	Risk of bias appraised using Cochrane handbook (RCTs) and Newcastle-Ottawa scale (others) Did not include other outcomes such as cost, QOL and tube dependency

Citation	Level & Quality	Study design	Interventions & Outcomes	Results	Comments/Limitations
Shaw 2015	III-I +	Systematic review of level II to III-2 papers N=20 (2 RCT) N=3168 participants HNC with RT/CRT/POCRT	Compared proPEG with other nutrition interventions Outcomes: - Swallow - Wt	Inconclusive due to poor study quality, high risk of bias, wide variation in treatment, RT type and patient population and inconsistent methods to assess dysphagia Wt loss outcomes inconsistent: 6/15 had significant differences in favour of proPEG, 7/15 had no differences and 2/15 unclear	Included 5 conference abstracts Used Cochrane review procedures Focus on swallow outcomes which has not identified all studies with nutrition outcomes
Wang 2014a	III-1 Ø	Systematic review of level II to III-2 papers N=8 (1 RCT) N=818 participants HNC with RT/CRT (+/- surgery)	Compared tube feeding methods (NGT and gastrostomy) Outcomes: - Nutrition status - Complications - Survival - Duration tube feeding - Delays/admissions - QOL	No differences for nutrition status, infection, survival, RT delays NGT has higher dislodgements, admissions, length of stay Gastrostomy has higher dysphagia and duration tube feeding QOL benefits in both groups for different domains	Combination of reactive and proPEG studies Quality assessment tool graded all as good quality Different outcomes assessed in different studies

Citation	Level & Quality	Study design	Interventions & Outcomes	Results	Comments/Limitations
Orphanidou 2011	III-3 Ø	Systematic review of level III/IV papers N=7 N=435 participants HNC with CRT	Compared proPEG with other nutrition interventions - proPEG vs reactive (n=2) - proPEG with no control (n=5) Outcomes: - Adverse effects	Lack of high level evidence, no conclusions drawn Used to develop local guidelines in Canada	Due to small numbers, broadened search to include stage I/II and RT alone (n=13 extra papers) Lack of information on search strategy, quality assessment methods, what the outcomes were.

Abbreviations: RCT=Randomised Controlled Trial; HNC=Head and Neck Cancer; RT=Radiotherapy; CRT=Chemoradiotherapy; ONS=Oral Nutrition Supplements; NGT=Nasogastric Tube; proPEG=Prophylactic Gastrostomy; QOL=Quality of Life; Wt=Weight; POCRT=Post-operative Chemoradiotherapy. Quality rating: (+) = positive; (Ø) = neutral; (-) = negative.

2.5 Other considerations for nutrition interventions

2.5.1 Patient adherence, motivation and preferences

Patient motivation can also impact the effectiveness of nutrition care process (Splett & Myers, 2001), however adherence to dietary advice/recommendations is rarely captured. One of the key RCT's comparing dietary counselling and supplements to usual care did measure adherence with dietary recommendations on a weekly basis through a daily supplement consumption record maintained by the patient and verified by a carer/relative. It found that even at three months follow-up the nutrition intervention group had remained adherent with dietary recommendations, and this translated into positive patient outcomes (Ravasco et al., 2005a).

There has been only one other study (level IV neutral quality) that reported on clinical outcomes according to adherence and non-adherence with dietary recommendations (Capuano et al., 2008). Forty seven percent of patients were deemed non-adherent – defined as either not accepting nutritional counselling or refusing NGT or gastrostomy tubes during treatment (although reasons for refusal were not stated). Ninety percent of adherent patients maintained their weight and all of the non-adherent patients continued to lose weight during treatment (mean weight change 0% vs -11% respectively), and this trend continued in the 30-day follow-up period post-treatment. However, while this study accounted for adherence to the tube feeding recommendation or referral to a dietitian, it did not account for adherence to the recommendations given in the consultation.

It is known that treatment preferences can also affect patient participation and adherence to interventions in RCTs (King et al., 2005). A previous RCT comparing different feeding tubes found patients had a strong preference for feeding tube type and thus did not want to be randomised (Corry et al., 2008). Therefore feasibility testing of this type of trial is important for future studies and is currently being considered in the pilot study comparing proPEG to the reactive approach (Paleri et al., 2016). The patient experience with feeding tubes may also account for factors relating to patient adherence and four recent qualitative studies have investigated this. Merrick & Farrell (2012) reported three main themes emerged from their study on gastrostomy tube experience; positive adaptation to acceptance of tube feeding (n=9); ambivalence between acceptance and rejection of the tube (n=4); and anxiety and fear of the tube (n=2) (Merrick & Farrell, 2012). The positive cognitive approach towards the tube in the first group may have been a contributing factor to less weight loss (6.5% vs 10-15%).

Two studies reporting on patient experiences with gastrostomy tubes have been completed in the UK (Mayre-Chilton, Talwar, & Goff, 2011) and Canada (Osborne, Collin, Posluns, Stokes, & Vandenbussche, 2012). Both indicated primarily positive or neutral experiences with the tube with perceived benefits in preventing weight loss, however the impact of the tube on social and daily activities and intimacy were raised. A recent study in Sweden compared experiences of NGT and gastrostomy feeding, and whilst positive and negative experiences were reported, there were no clear preferences for tube type highlighting the importance of individual care (Ehrsson, Sundberg, Laurell, & Langius-Eklof, 2015). Cultural acceptance of tube feeding is also an important consideration, with low acceptance in Thailand (Pramyothin, Manyanont, Trakarnsanga, Petsuksiri, & Ithimakin, 2016) and long-term NGT feeding reported to be preferable to gastrostomy tubes in many Asian nations (Jaafar, Mahadeva, Morgan, & Tan, 2016).

2.5.2 Complications with gastrostomy placement

Patients also need to be informed of the potential complications of treatment recommendations so that they can make informed decisions regarding their healthcare. Gastrostomy insertion may be a common method of intervention, however it is a medical procedure which entails risks. There has been one systematic review and meta-analysis which has reported on complications following percutaneous endoscopic gastrostomy (PEG) or radiologically inserted gastrostomy (RIG) tube insertions in patients with HNC (Grant et al., 2009). They included 27 studies of retrospective case series or cohorts (n=2379) and found similar mortality rates (PEG 2.2% vs RIG 1.8%) but higher major complications (8.9% vs 7.4%) and minor complications (22.1% vs 19.5%) with RIG tubes. The results from this study found that in comparison to a meta-analysis on mixed or non-cancer patients (n=5752) (Wollman, D'Agostino, Walus-Wigle, Easter, & Beale, 1995), patients with HNC have similar PEG major complication rates but RIG procedure-related mortality and major complications are higher. However as the results are based on low levels of evidence with high risk of bias the authors are unable to firmly conclude or recommend the optimal method of gastrostomy tube placement.

Neoplastic seeding is also a concern following gastrostomy placement, and although the incidence is rare, with a large series (n=208) reporting a rate of 0.92% (Cruz, Mamel, Brady, & Cass-Garcia, 2005), the outcomes are poor; with overall mortality of 87% and one year survival of 35% (Huang et al., 2013).

A literature review of cases of neoplastic seeding from HNC identified 38 cases of metastases at the gastrostomy site and 13 cases of tracheostomy site seeding (Nisa, Khanfir, & Giger, 2013). A subsequent review identified an additional four patients with gastrostomy site metastasis (total accumulative cases n=42) (Huang et al., 2013). This updated review of gastrostomy site seeding reported that in 97% of cases the pull technique was used and that 89% occurred when the tube was placed prior to treatment A recent retrospective cohort study in Taiwan also reports an increased oesophageal cancer risk (HR=2.31, p=0.02) in their patients with a gastrostomy (n=1851) compared to a matched control group of patients without a gastrostomy (n=3702) (Lin, Lin, Lee, Huang, & Chang, 2016). Theories have been proposed on the possible mechanism by which seeding occurs such as swallowing of tumour cells or lymphatic spread, but it has also been suggested that direct implantation may occur with the pull technique from the endoscope, and thus debate on the optimal method continues.

Since the systematic review by Grant et al. (2009), a retrospective comparative cohort study (level III-2 neutral quality) was completed comparing PEG and RIG tubes. Although no statistical differences in major or minor complications were found, it was acknowledged there was a high number of tube dislodgements in the RIG group (McAllister et al., 2013). A second retrospective comparative cohort study (level III-2 neutral quality) was completed comparing pull PEG with push PEG, and whilst a higher incidence of complications (tube blockage and dislodgement) was reported with the push method, the findings were limited as the study was completed in a mixed patient population with a tube selection bias as all HNC patients had the push PEG (Kohler et al., 2015).

The first RCT in this area (level II positive quality) has examined outcomes following two methods of radiological insertion – traditional percutaneous placement (n=29) and per-oral placement (n=27), with no differences in pain scores, time and success of procedure, complications and QOL (Bernstein et al., 2015). There was only one major complication, overall infection rates were 8% and overall minor complications were 31-41%. Follow-up was limited to six months post insertion, and this may not have been long enough to observe cases of seeding, as previously reported to occur on average at eight months post insertion (Huang et al., 2013). Therefore the evidence remains unclear as to the optimal method of placement with the choice often dependent upon the institution and the skill of the staff available.

One study has suggested the “overtube-assisted PEG placement” technique could be an alternative method to reduce the risk of tumour seeding (Musumba et al., 2015). Other methods of tube feeding have also been reported in the literature such as cervical oesophagostomy (Wang et al., 2014b), but this was a small case series of nasopharyngeal cancer patients with severe dysphagia post-treatment in China and the advantage of this method over gastrostomy feeding is unclear. Due to the risks involved with any procedure, it is important to inform and select patients appropriately to minimise exposure to any unnecessary risks.

2.5.3 Predictors of prolonged tube feeding

Some patients may require prolonged or long-term tube feeding following treatment. It has been shown that the requirement for tube feeding for acute toxicity is not associated with the long-term need for tube feeding (Al-Othman, Amdur, Morris, Hinerman, & Mendenhall, 2003). There is still no accepted definition of the term “tube dependency”, however study designs have become more specific when investigating this phenomenon with clearer time points for outcome measures and definitions of tube use to classify true dependent cases. For the purposes of this literature review, prolonged tube feeding has been defined as requiring tube feeding beyond three months post-treatment. A summary of evidence from all studies is available in Table 2-5.

There have been two level II neutral quality studies (Wopken et al., 2014a; Wopken et al., 2014b) that provide the highest level of evidence to date for a number of predictive factors of prolonged tube feeding at six months post-treatment. These factors include: pre-treatment weight loss; higher T stage; higher N stage; chemotherapy; accelerated or hyperfractionated radiotherapy; bilateral neck radiation; and higher radiation doses to the pharyngeal constrictor muscles or larynx. This information was then used to develop a predictive model to determine the probability of tube dependency in patients. The factors with the largest body of additional evidence (level III/IV studies) to support their role in prolonged tube feeding duration include: higher T stage (n=8); higher N stage (n=6); the hypopharynx (n=6); older age (n=6); chemotherapy (n=4); and the dose to swallowing structures (n=5). Whilst some of these factors are similar to the predictors of tube feeding during treatment (i.e. increased stage, increased age and chemotherapy), the tumour site effects are noticeably different.

The oropharynx is more important in the acute phase due to the radiotherapy dose to the oral mucosa, resulting in mucositis (Sanguineti, Rao, Gunn, Ricchetti, & Fiorino, 2013). The hypopharynx is more important in the chronic phase due to the radiotherapy dose to the swallowing structures being in closer proximity, resulting in dysphagia (Bhayani et al., 2013a). Emerging research is also suggesting that it may be more important to identify tumour subsites as risk factors, such as the posterior wall in the hypopharynx (Bhayani et al., 2013a; Homma et al., 2016; Murono et al., 2015). Other social factors are also beginning to be identified such as smoking (Bhayani et al., 2013a; O'Shea et al., 2015), social supports (Jang et al., 2013; Magnuson et al., 2013) and the impact of patient adherence to swallowing exercises (Bhayani et al., 2013a; Bhayani et al., 2013b). Finally, in addition to pre-treatment weight loss identified in two studies by Wopken et al. (2014a, 2014b), low BMI at baseline (McRackan et al., 2008; Miyamoto et al., 2012) and greater than 10% weight loss during treatment (Bhayani et al., 2013b) have also been associated with prolonged tube feeding. This illustrates that patients with the greatest nutritional deficits are using their tubes for longer, which is an anticipated outcome of appropriate tube use to improve nutritional status.

Table 2-5: Summary of studies investigating predictive of tube feeding dependency (>3months post treatment).

Risk Factor	Total	Level II	Level III	Level IV
Patient Factors				
Pre-treatment weight loss	3	Wopken 2014a (Ø) Wopken 2014b (Ø)		Jang 2013 (+)
Low BMI	2		Miyamoto 2012 (Ø) McRackan 2008 (Ø)	
Pre-treatment dysphagia	1			Amin 2012 (Ø)
Nutrition symptoms or opioid use pre-treatment	2			Jang 2013 (+) Sanguineti 2013 (Ø)
High smoking	4			O'Shea 2015 (+) Bhayani 2013a (+) Setton 2015 (Ø) Amin 2012 (Ø)
Non smoking	1			Homma 2016 (Ø)
Poor baseline performance status	2			Homma 2016 (Ø) Pohar 2015 (Ø)
Older age	6		Machtay 2008 (Ø) Miyamoto 2012 (Ø)	Shinozaki 2014 (Ø) Setton 2015 (Ø) Kornguth 2005 (Ø) Lawson 2009 (Ø)
Female gender	3			Homma 2016 (Ø) Sanguineti 2013 (Ø) Al-Othman 2003 (Ø)
Single	2		Magnuson 2013 (Ø)	Jang 2013 (+)
Tumour Factors				
Hypopharynx	6		Machtay 2008 (Ø)	Bhayani 2013a (Ø) Homma 2016 (Ø) Murono 2015 (Ø) Ishiki 2012 (Ø) Al-Othman 2003 (Ø)
Larynx	2		Machtay 2008 (Ø)	Hurst 2016 (Ø)
Multiple synchronous primary	1			Al-Othman 2003 (Ø)

Risk Factor	Total	Level II	Level III	Level IV
Tumour Factors cont.				
Higher TNM stage	3			Akst (+) Homma 2016 (Ø) Lohia 2014 (Ø)
Higher T stage	10	Wopken 2014a (Ø) Wopken 2014b (Ø)	Machtay 2008 (Ø) Gokhale 2010 (Ø)	Lavo 2017 (Ø) Pohar 2015 (Ø) Amin 2012 (Ø) Lawson 2009 (Ø) Avery 2008 (Ø) Kornguth 2005 (Ø)
Higher N stage	7	Wopken 2014b (Ø)		Hurst 2016 (Ø) Lavo 2017 (Ø) Setton 2015 (Ø) Lawson 2009 (Ø) Avery 2008 (Ø) Kornguth 2005 (Ø)
Treatment Factors				
Chemotherapy	6	Wopken 2014a (Ø) Wopken 2014b (Ø)		Lavo 2017 (Ø) Setton 2015 (Ø) Sanguineti 2013 (Ø) Kornguth 2005 (Ø)
Multimodality treatments	4		Machtay 2008 (Ø) Magnuson 2013 (Ø) Miyamoto 2012 (Ø)	Avery 2008 (Ø)
Accelerated or hyperfractionated RT	2	Wopken 2014a (Ø) Wopken 2014b (Ø)		
Larger RT fields/oral mucosa	3		Sanguineti 2011 (Ø)	Gensheimer 2016 (Ø) Sanguineti 2013 (Ø)
3D conformal RT	3			Bhayani 2013b (+) Beadle 2017 (Ø) Lohia 2014 (Ø)
Higher RT dose >60Gy/ Definitive RT	1			Al-Othman 2003 (Ø)
Bilateral neck RT	3	Wopken 2014b (Ø)		Chen 2017 (+)
Higher dose to pharyngeal constrictor muscles or larynx	6	Wopken 2014a (Ø)	Gokhale 2010 (Ø)	Vlacich 2014 (Ø) Sanguineti 2013 (Ø) Amin 2012 (Ø) Li 2009 (Ø)
Pre-treatment CT Scan Gross Tumour Volume	1			Hurst 2016 (Ø)

Risk Factor	Total	Level II	Level III	Level IV
Surgical Factors				
Glossectomy or Maxillectomy	1			Avery 2008 (Ø)
Flap reconstruction	1			Chen 2017 (+)
Other factors				
Tracheostomy	1		Magnuson 2013 (Ø)	
>10% weight loss during treatment	1			Bhayani 2013b (+)
Non-adherence to swallow exercises	1			Bhayani 2013a (+) Bhayani 2013b (+)
Vocal cord paralysis	1			Lavo 2017 (Ø)
Laryngeal oedema	1			Lavo 2017 (Ø)

Abbreviations: BMI=Body Mass Index; TNM=Tumour, Nodal, Metastases Staging; RT=Radiotherapy. Quality rating: (+) = positive; (Ø) = neutral; (-) = negative.

2.5.4 Impact on quality of life

There are a number of patient and treatment factors that affect QOL outcomes including: type of treatment (Metreau, Louvel, Godey, Le Clech, & Jegoux, 2014; Payakachat, Ounpraseuth, & Suen, 2013); persistent smoking (Egestad & Emaus, 2014); higher baseline BMI (Egestad & Nieder, 2015); type of radiotherapy treatment (Vainshtein et al., 2015); socioeconomic factors and comorbidities (Wells et al., 2016). Tube feeding, with an NGT or gastrostomy, has been shown to cause psychosocial distress; although short-term significant improvements in QOL are seen indicating a degree of adaptation (Roberge et al., 2000). It is well known that a prolonged feeding tube is associated with reduced QOL (Rogers, Thomson, O'Toole, & Lowe, 2007; Terrell et al., 2004) as well as depression (Chen et al., 2013). A recent large cross-sectional study (n=280) in survivors up to five years post-treatment confirmed that presence of a feeding tube was an independent predictor of poorer cancer-specific QOL (Wells et al., 2016). Of note, as the feeding tube is most likely in-situ to improve a patient's nutritional status, malnutrition may actually be a confounding factor of reduced QOL (Ravasco et al., 2004). However, patients are generally keen to have their tube removed as soon as possible, with a recent qualitative study suggesting that patients appear to equate tube removal with a positive transitional stage in the recovery process towards cure from their cancer (Merrick & Farrell, 2012). Thus it is important for patients (and carers) to understand the potential impacts of tube feeding upon QOL and be provided with appropriate supports and counselling to develop coping strategies to adapt to the impact of tube feeding upon their personal lives (Brotherton, Abbott, & Aggett, 2006). Prevention of long-term tube dependence is also important and adherence to swallowing exercises has been shown to be beneficial (Hutcheson et al., 2013) as well as the evolution of treatment regimens (discussed in the next section).

2.5.5 Effect of evolving treatment regimens and p16/HPV status

Radiotherapy techniques have evolved from 3D conformal techniques to intensity-modulated radiotherapy (IMRT), which means the dose to surrounding tissues and/or organs at risk, such as the salivary glands, can be spared. This has resulted in a reduction in long-term dysphagia and xerostomia (Kam et al., 2007; Nutting et al., 2011; Pow et al., 2006), Consequently, it is anticipated that a patient's nutritional intake would improve, however the studies are yet to measure this as a specific primary outcome to demonstrate this theoretical benefit, and high rates of weight loss and tube feeding during and post-treatment have still been reported (Caudell et al., 2010; Gunn, Endres, Parker, Sormani, & Sanguineti, 2010; Studer et al., 2010). Therefore recommendations for nutrition intervention have not changed.

More recently helical-IMRT has been introduced, which is more targeted than IMRT, and raises the question as to whether the anticipated reduction in toxicities would reduce the need for intensive nutrition intervention. There are currently no studies that have specifically investigated the impact of helical-IMRT on nutrition outcomes. Level IV studies have reported weight or tube feeding as secondary outcomes, and significant weight loss still appears to be an issue (Capelle et al., 2012; Chao, Low, Perez, & Purdy, 2000; You et al., 2012). Details of tube feeding are minimal with one small case series (n=5) reporting that all patients had a proPEG placed (Loo et al., 2011); and one study (n=17) reported no–one required a gastrostomy (Chao et al., 2000); however use of tubes was not described and weight loss was prevalent.

Similarly, it has also been noted that proton therapy is another form of radiotherapy technique with reported reduced toxicity and improved efficacy (McKeever et al., 2016). Early reports published in the last year are indicating a reduction in the need for tube feeding (Blanchard et al., 2016; Gunn et al., 2016; McDonald, Liu, Moore, & Johnstone, 2016; Phan et al., 2016), although grade three mucositis was still reported at 58% (Gunn et al., 2016) and weight loss outcomes have not been studied.

Other new developing treatments include progress with targeted systemic agents such as anti-Epidermal Growth Factor Receptor therapies including monoclonal antibodies (e.g. Cetuximab). Early trials indicated that Cetuximab did not increase the toxicity of treatment compared to radiotherapy alone (Bonner et al., 2006), and a follow-up sub-analysis of the data according to p16 status (as a marker of HPV) found that this also had no effect on mucositis, dysphagia or feeding tube use (Bonner et al., 2016). At the time of commencement of this thesis there had only been two studies reporting a comparison of Cetuximab with Cisplatin, which showed higher rates of toxicity, weight loss and feeding tube use with Cetuximab (Walsh et al., 2011) and no significant differences with feeding tube dependence at nine months (Koutcher et al., 2011). Since then the studies have had mixed results with: one showing no difference in weight loss or feeding tube use (Ye, Hay, Laskin, Wu, & Ho, 2013); one showing higher rate of tube placement with Cisplatin (Levy et al., 2014); one showing higher need for nutrition support with Cetuximab (Magrini et al., 2015); and a small case series of patients receiving Cetuximab with a high use of feeding tubes (11/14 patients) and high rates of mucositis (Yokota et al., 2015). The most recent study (n=500) found use of nutrition support was higher in the Cisplatin group at 30 days post commencement of treatment, but no different on completion of treatment (Ishimaru et al., 2016).

Other studies comparing outcomes with weekly versus high dose Cisplatin also show no differences in weight loss, tube use during treatment or tube dependency at six months (Jagdis et al., 2014; Oosting et al., 2016). The role of induction or neoadjuvant chemotherapy is also an area of interest but a large number of variables within studies make interpretation of the data challenging (e.g. different lengths of treatment times, cycles, chemotherapy agents and control groups) (Dobrosotskaya et al., 2014; Jensen et al., 2011). Immunotherapy is also an emerging area of research that will need to be considered in the future (Ferris, 2015).

As patients with HPV-related disease have been found to have improved survival outcomes (Benson, Li, Eisele, & Fakhry, 2013), research has expanded to investigate whether current recommended treatments remain suitable for this sub-set of patients, with a greater focus on survivorship and long-term QOL (Rischin, Ferris, & Le, 2015). There is an increasing number of radiation and chemotherapy de-intensification trials, such as reducing radiation dose and avoiding or reducing Cisplatin, with the aim to reduce toxicity and long-term side effects (Bhatia & Burtness, 2015). There is also a renewed interest in surgical management with the advent of trans-oral robotic surgical techniques for early stage oropharyngeal cancers, which reduces long-term speech and swallowing dysfunction (Holsinger & Ferris, 2015). A recent systematic review reports reactive feeding tube placement rates of 18-39% following this surgical technique with long-term dependence of 0-7% (mean follow-up of 11-26 months) (Hutcheson, Holsinger, Kupferman, & Lewin, 2015). Although a recent Australian study has reported tube feeding outcomes acutely postoperatively with long-term data on tube dependency; nutritional status and weight outcomes remain unknown (Hirshoren et al., 2016).

In summary it can be seen that healthcare treatments and techniques continue to evolve for patients with HNC and it is important to re-assess the appropriateness of nutrition interventions and recommendations for practice accordingly.

Chapter 3 **Identified need for research**

3.1 Thesis aims and objectives

Malnutrition and weight loss remain a significant issue in patients with HNC, despite aggressive nutrition interventions with intensive dietetic counselling and insertion of proPEG tubes. Causes of malnutrition and weight loss from tumour burden and treatment side effects are well established (Figure 1-1). A number of additional causes have been generated from the literature and observations from clinical practice that require consideration (Figure 3-1).

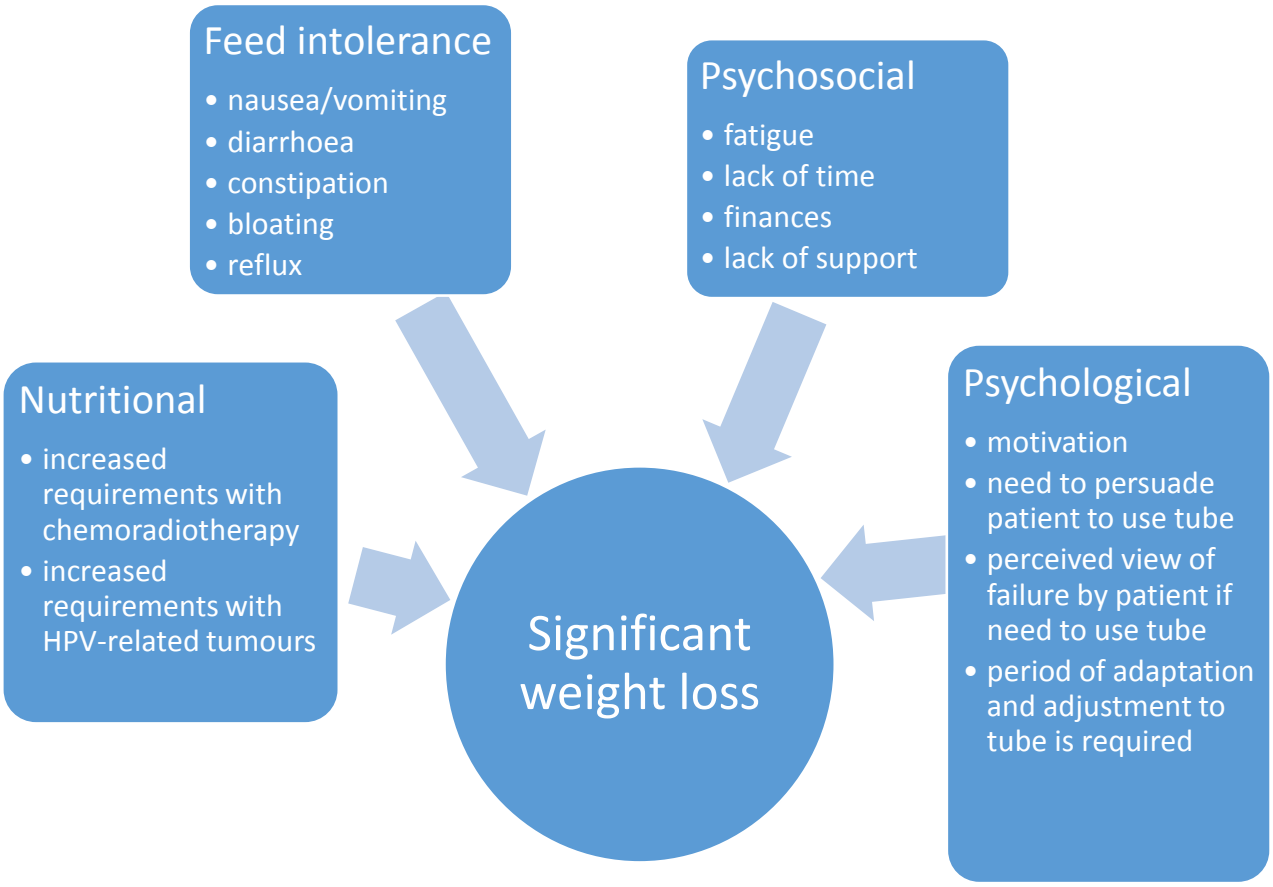


Figure 3-1: Additional causes of significant weight loss in head and neck cancer

Source: Developed by author Abbreviations: HPV=Human Papillomavirus

The overarching aim of the research from this thesis is to minimise this weight loss and improve nutrition outcomes, which will subsequently improve other clinical, cost and patient outcomes. This will be addressed by the following objectives: 1) to optimise the identification of patients for access to appropriate nutrition care; 2) to optimise the nutrition interventions that are implemented as part of the nutrition care process. Several novel areas of research will be considered across different aspects of the nutrition care model as outlined in Figure 3-2 and the remainder of this chapter.

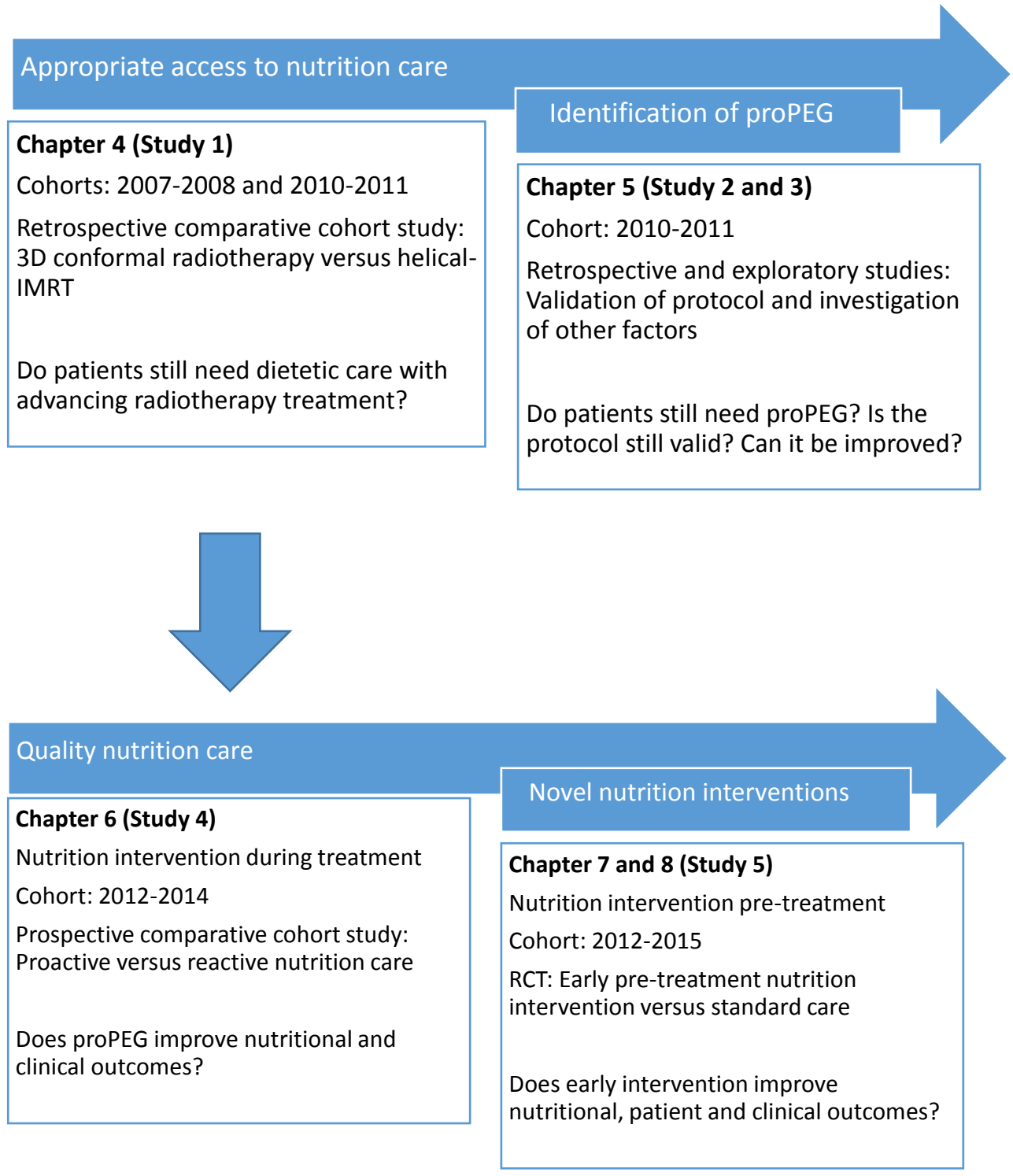


Figure 3-2: Outline of research in this thesis in the context of the nutrition care model

Abbreviations: IMRT=Intensity-Modulated Radiotherapy; proPEG=Prophylactic Gastrostomy; RCT= Randomised Controlled Trial

3.2 Appropriate access to nutrition care

3.2.1 The impact of evolving treatments on nutrition care

The first step in receiving quality nutrition care is to determine appropriate access through screening or assessment. Current clinical practice guidelines recommend routine referral to the dietitian for all patients receiving radiotherapy for HNC. The literature review identified that there is a lack of information regarding the impact of helical-IMRT on nutrition outcomes.

Therefore, this thesis (Chapter 4) will provide novel research to compare the nutrition outcomes between cohorts of patients receiving 3D conformal radiotherapy compared to helical-IMRT to understand the impact of advancing treatment on nutritional outcomes and nutrition interventions required. The findings will directly inform recommendations for clinical practice and determine whether referral procedures for appropriate access to nutrition care need to change.

3.2.2 The identification of patients for proactive gastrostomy

The protocol for proPEG at the Royal Brisbane and Women's Hospital is another method of identifying high risk patients for appropriate nutrition care. This protocol was previously validated in a patient cohort receiving 3D conformal radiotherapy (Brown et al., 2013b). Therefore, this thesis will provide novel research to validate this protocol in a new cohort receiving helical-IMRT.

As well as changes to radiotherapy techniques the literature review identified that there was a lack of information on whether new systemic therapies, such as Cetuximab, or a diagnosis of a HPV-related cancer can influence nutrition outcomes. Therefore this thesis will provide further novel research in these areas to determine the impact of these new factors on the requirement for proPEG.

Together these findings (Chapter 5) will provide a unique insight into the nutritional needs of patients in the evolving epidemiology of HNC and current treatment regimens and provide information on the optimal identification of patients for proPEG.

3.3 Quality nutrition care and outcomes

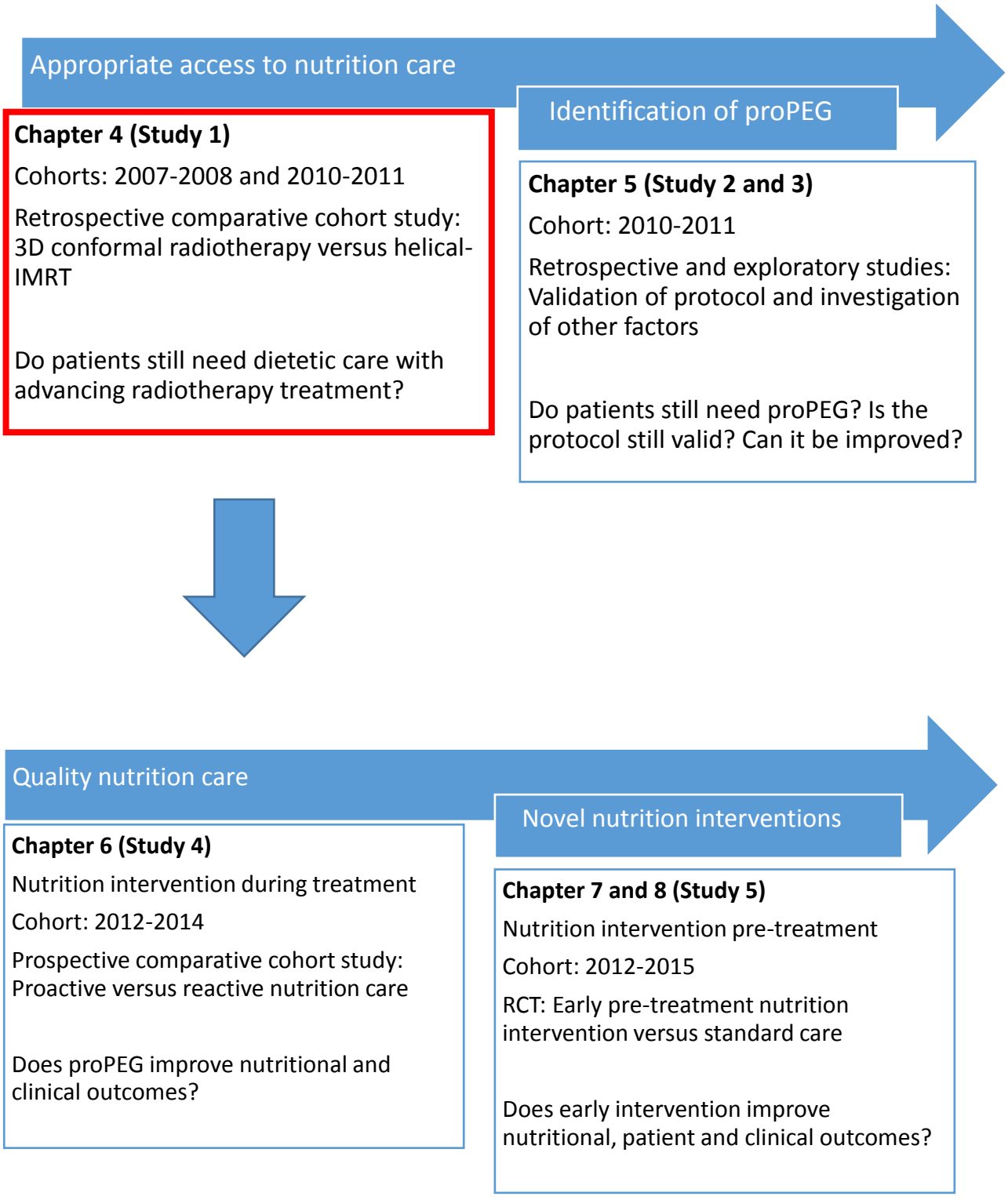
3.3.1 Optimising nutrition interventions during treatment

Once patients have obtained access to nutrition care, the quality nutrition care process can commence. Despite a significant body of literature on tube interventions during treatment, there is still a lack of consensus on the optimal method due to a lack of high quality RCT's. Only two studies have compared proPEG versus the reactive approach of tube feeding if and when required (Salas et al., 2009; Silander et al., 2012; Silander, Jacobsson, Berteus-Forslund, & Hammerlid, 2013) and this is the most applicable study design to informing current practice. Since work on this thesis commenced, a pilot RCT comparing these two methods of nutrition support is now underway (Paleri et al., 2016).

Meanwhile, this thesis (Chapter 6) reports on prospective clinical outcomes (weight) and cost outcomes (admissions) of high risk patients who receive a proPEG versus those who are managed reactively. This research will therefore provide additional evidence to add to the body of literature to help inform decision-making in clinical practice regarding timing of feeding tube placement until further high level evidence becomes available.

3.3.2 Early nutrition intervention pre-treatment

As prior research identified that patients continue to lose weight, despite proPEG and weekly dietetic counselling (Brown et al., 2014a), the final main study from this thesis (Chapters 7 and 8) investigates a novel early nutrition intervention that is commenced prior to treatment via the proPEG. There have been no studies in the literature to date that have investigated additional pre-treatment nutrition interventions in comparison to standard best practice care models of regular dietitian care during and post-treatment. Current studies which use proPEG tubes and report on the timing of commencement of nutrition support, do so when clinically indicated in response to deterioration in swallowing or nutritional status (Beer, Krause, Zuercher, & Stanga, 2005; Marcy et al., 2000; Nguyen et al., 2006; Nugent et al., 2010a; Raykher et al., 2009; Scolapio, Spangler, Romano, McLaughlin, & Salassa, 2001; Wiggenraad et al., 2007). A range of outcomes following the theoretical model will be assessed from this intervention study: clinical outcomes (weight, body composition, nutritional status, and treatment tolerance); cost outcomes (unplanned admissions); and patient outcomes (survival and QOL). The results of this research will directly inform future clinical practice and will provide more evidence on the role of pre-treatment nutrition support in this patient population.


Appropriate access to nutrition care
Identification of proPEG
Chapter 4 (Study 1)
Cohorts: 2007-2008 and 2010-2011
Retrospective comparative cohort study: 3D conformal radiotherapy versus helical-IMRT
Do patients still need dietetic care with advancing radiotherapy treatment?
Chapter 5 (Study 2 and 3)
Cohort: 2010-2011
Retrospective and exploratory studies: Validation of protocol and investigation of other factors
Do patients still need proPEG? Is the protocol still valid? Can it be improved?
Quality nutrition care
Novel nutrition interventions
Chapter 6 (Study 4)
Nutrition intervention during treatment
Cohort: 2012-2014
Prospective comparative cohort study: Proactive versus reactive nutrition care
Does proPEG improve nutritional and clinical outcomes?
Chapter 7 and 8 (Study 5)
Nutrition intervention pre-treatment
Cohort: 2012-2015
RCT: Early pre-treatment nutrition intervention versus standard care
Does early intervention improve nutritional, patient and clinical outcomes?

4.1 Chapter overview

The findings in this chapter have been published in the European Journal of Clinical Nutrition (Journal Impact Factor 2.935; Ranked 31/80 Nutrition & Dietetics category; Quartile 2). Section 4.2 and 4.3 are presented in their accepted format prior to publication.

The aim of this chapter was to investigate how the emerging technology in radiotherapy techniques has translated into clinical practice, specifically the impact on nutritional outcomes. As targeted radiotherapy techniques have been developed to minimise toxicity to normal tissues it was expected to see a reduction in treatment-related toxicities which in turn was expected to result in a reduction in nutrition impact symptoms and thus reduce weight loss and the decline in nutritional status. However there are very few studies which have investigated this hypothesis in relation to nutrition outcomes. Therefore the nutrition outcomes of patients receiving the new technique (helical-IMRT) were compared to patients who received the previous technique (3D conformal radiotherapy) via a retrospective clinical audit.

Results of this study were presented at the following international and national conferences: 6th European Congress on Head and Neck Oncology, Liverpool UK, 2014 (Appendix C - 11.3.2) and the Dietitians Association of Australia 31st National Conference, Brisbane, Australia, 2014 (Appendix C – 11.3.3).

Date submitted: 20/04/2015

Date accepted: 21/07/2015

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4.2 Abstract

Background/Objectives: Since 2007 our institution has used validated guidelines for the insertion of proactive gastrostomy feeding tubes in patients with head and neck cancer. Helical Intensity-Modulated Radiotherapy (H-IMRT) delivered by Tomotherapy™, is an advanced radiotherapy technique introduced at our centre in 2010. This form of therapy reduces long-term treatment-related toxicity to normal tissues. The aim of this study is to compare weight change and need for tube feeding following H-IMRT (n=53) with patients that would have previously been treated with 3D conformal radiotherapy (n=134).

Subjects/Methods: Patients with head and neck cancer assessed as high nutritional risk with recommendation for proactive gastrostomy were identified from cohorts from 2007-08 and 2010-11. Retrospective data were collected on clinical factors, weight change from baseline to completion of treatment, incidence of severe weight loss (>10%) and tube feeding. Statistical analyses to compare outcomes between the two treatments included Chi Square, Fishers Exact and Two Sample Wilcoxon tests ($p<0.05$).

Results: The H-IMRT cohort had higher proportions of patients with definitive chemoradiotherapy ($p=0.032$) and more advanced N stage ($p<0.001$). Nutrition outcomes were not significantly different between H-IMRT and conformal radiotherapy respectively: need for proactive gastrostomy (n=49, 92% versus n=115, 86%, $p=0.213$); median percentage weight change (-7.2% versus -7.3%, $p=0.573$); severe weight loss incidence (28% versus 27%, $p=0.843$).

Conclusions: Both groups had median weight loss >5% and high incidences of tube feeding and severe weight loss. Nutrition intervention remains critical in this patient population, despite advances in radiotherapy techniques, and no changes to current management are recommended.

4.3 Manuscript

INTRODUCTION

Patients with mucosal squamous cell carcinoma cancer of the head and neck have a high incidence of malnutrition and frequently require enteral tube feeding. Since 2007 our institution has used validated local hospital guidelines: The RBWH Swallowing and Nutrition Management Guidelines for Patients with Head and Neck Cancer (S&N Guidelines), for a proactive approach to the insertion of enteral feeding tubes (Brown et al., 2013b). Implementation of the S&N Guidelines has reduced unplanned hospital admissions and length of stay (Hughes et al., 2013) and adherence to the S&N Guidelines has improved nutrition outcomes (Brown et al., 2014a). There is no international consensus for the optimal method of tube feeding (Nugent et al., 2013), and centres have adapted either a proactive or reactive approach. The majority of studies supporting prophylactic gastrostomy insertion have been undertaken in patients receiving treatment with conformal radiotherapy or radiotherapy alone (Lee et al., 1998; Senft, Fietkau, Iro, Sailer, & Sauer, 1993; Tyldesley et al., 1996). As radiotherapy techniques and treatment regimens evolve, nutrition support recommendations also require ongoing review.

Intensity-Modulated Radiotherapy (IMRT) is a targeted form of radiotherapy. When compared to three-dimensional (3D) conformal radiotherapy, IMRT allows better preservation of organs and tissue in close proximity to the cancer being treated (e.g. parotid glands), and so reduces late side effects such as xerostomia and thereby improves quality of life (Vergeer et al., 2009). Although, some authors have postulated this may lead to a reduced need for a gastrostomy (Sanguineti et al., 2011), there are studies that continue to support the role of a prophylactic gastrostomy with IMRT, particularly with concurrent treatment (Romesser et al., 2012). There have been concerns that prophylactic gastrostomy insertion increases the risk of gastrostomy dependency, with longer duration of tube usage and increased dysphagia post-treatment (Corry et al., 2008; Kramer, Newcomb, Hessler, & Siddiqui, 2014; Mekhail et al., 2001), although some studies with IMRT have not found this to be of concern (Amin et al., 2012; de Arruda et al., 2006; Rusthoven et al., 2008).

Since 2010 the majority of patients with squamous cell carcinoma of the head and neck in our centre have been treated with Helical-IMRT (H-IMRT) using Tomotherapy™. Several studies have suggested H-IMRT can achieve superior dose sparing to organs at risk versus other forms of IMRT (Fiorino et al., 2006; Lee et al., 2008a; Ruchala, Olivera, Schloesser, & Mackie, 1999; Sheng, Molloy, & Read, 2006).

This has strengthened the hypothesis that intensive nutrition support with a feeding tube may no longer be warranted. However the extent of nutrition outcomes and requirement for tube feeding following H-IMRT has not been widely reported. Therefore the aim of this study was to investigate weight change and the requirement for tube feeding in a cohort of high risk patients receiving H-IMRT compared to a high risk cohort receiving standard conformal radiotherapy to see if any change to nutrition management is warranted.

SUBJECTS AND METHODS

Study design and data collection

This was a retrospective comparative cohort study. Data collection was via retrospective chart audit and the use of existing clinical databases in the patient administration systems of the hospital. Independent variables included: gender; age; clinical factors (tumour site, tumour stage, and treatment); and adherence to the S&N Guidelines recommendations for proactive gastrostomy insertion. Dependent variables included: percentage weight change from diagnosis to the end of radiotherapy treatment, the incidence and use of proactively placed gastrostomy tubes and the incidence, type and duration of use of reactive feeding tubes.

Study Population

Patients attending the multidisciplinary Combined Head & Neck Clinic for cancer treatment over two time periods at a large metropolitan tertiary referral hospital were screened for inclusion in the study. The first cohort (January 2007 to December 2008) was treated with 3D conformal radiotherapy and the second cohort (July 2010 to June 2011) received either 3D conformal radiotherapy or H-IMRT. Patients were excluded if they had: benign disease; a non-head and neck tumour; palliative intent treatment; refused treatment; treatment at another hospital; incomplete/missing data; or no access to the medical chart. The remaining eligible patients were classified as high risk or non-high risk according to the S&N Guidelines (Figure 4-1). For the purposes of this study, only high risk patients receiving definitive or adjuvant radiotherapy as part of their treatment were included to provide a final comparative sample of patients who received either H-IMRT or 3D conformal radiotherapy (Figure 4-2).

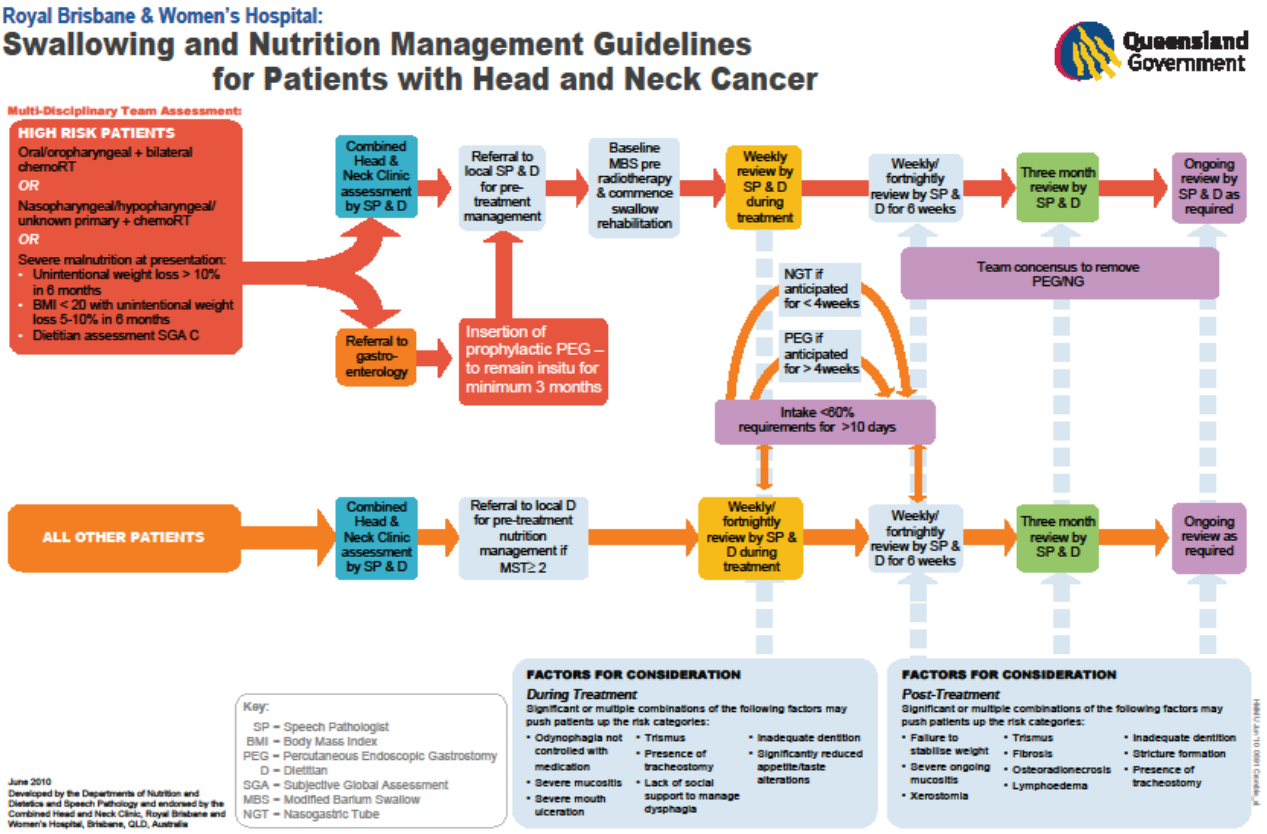

Figure 4-1: Royal Brisbane and Women's Hospital Swallowing and nutrition management guidelines for patients with head and neck cancer – revised version 2010

Original Source: Brown et al., 2016a

These guidelines have minor alterations to the high risk definition compared with the original version used from 2007 to 2009. They previously included the diagnosis of dysphagia at baseline. This has now been removed and unknown primary tumours added.

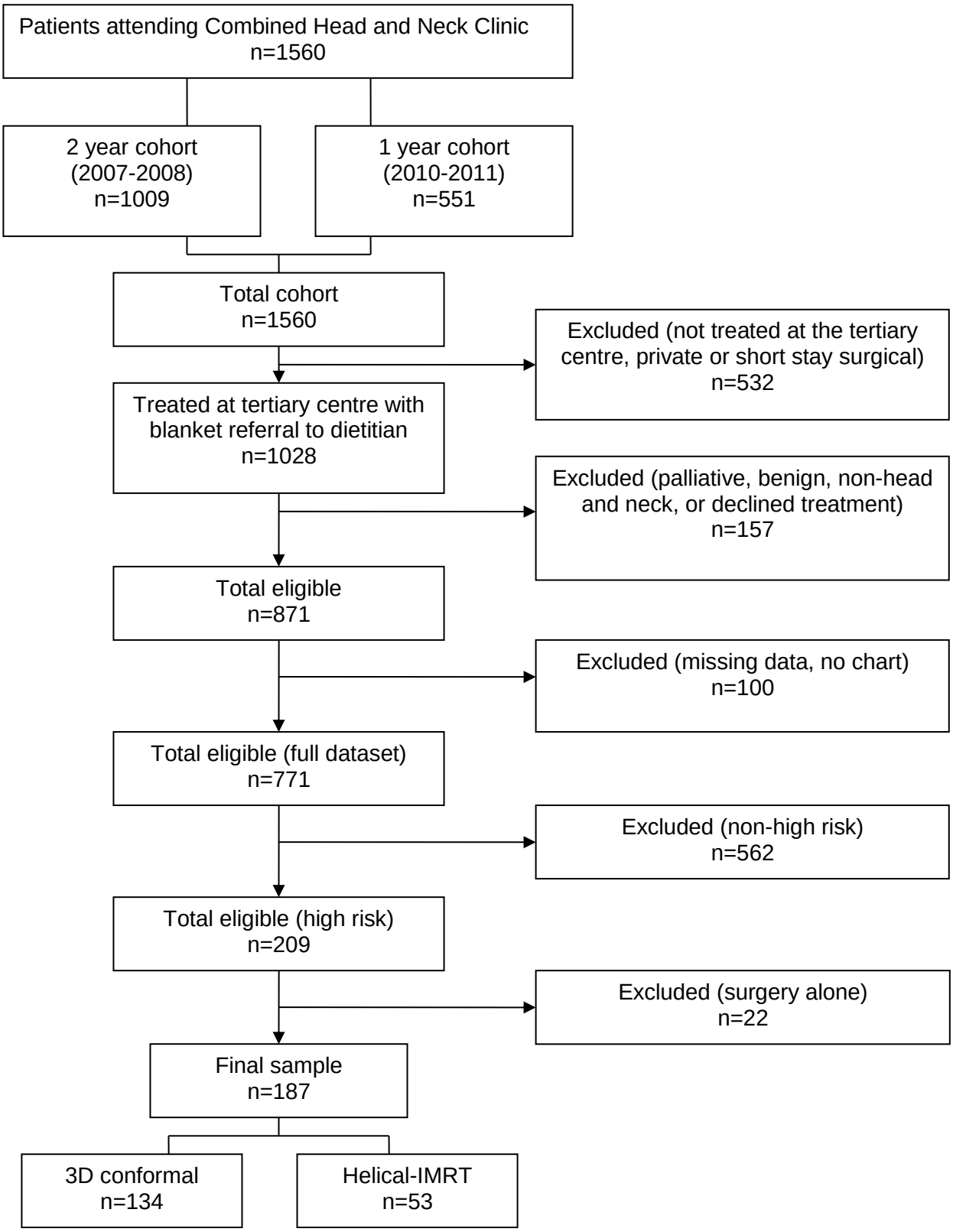

Figure 4-2: Cohort inclusion and exclusion criteria

Nutrition Intervention

High risk patients were recommended for gastrostomy placement prior to treatment (proactive gastrostomy tube placement). This guideline recommendation encompasses those who would benefit from immediate nutrition support due to poor nutritional status or significant dysphagia at diagnosis (a therapeutic gastrostomy) as well as those who would benefit from future nutrition support due to predicted treatment side effects (a prophylactic gastrostomy). All other patients who may require tube feeding during treatment have either a nasogastric or gastrostomy tube placed depending on predicted duration of need (reactive tube placement).

All patients were screened at baseline by the dietitian using the validated Malnutrition Screening Tool (Ferguson et al., 1999a). Patients who were identified at risk of malnutrition (score 2-5) were provided with dietary advice or referred to their local dietitian service pre-treatment. Patients were referred routinely to the surgical dietitian and/or radiotherapy dietitian respectively according to their treatment plan. Outpatients were seen on a weekly basis during treatment and inpatients were seen daily to weekly as clinically indicated as part of standard care.

Weight was recorded at diagnosis and at the end of radiotherapy treatment and percentage weight change calculated. Nutrition requirements were calculated by the dietitian using the ratio method (Isenring et al., 2013). Energy requirements (125kJ/kg/day or 30kcal/kg/day) and protein requirements (1.2g/kg/day) were based on actual body weight, unless the patient was overweight (body mass index >25kg/m^2), and then adjusted body weight was used. Adjusted body weight was calculated using the following equation (IBW+ [(actual body weight-IBW)*25%]), whereby ideal body weight (IBW) was the weight at body mass index 25kg/m^2. At each dietetic review, weight was monitored, and energy and protein intakes were estimated using a 24 hour recall method. The dietitian estimated actual intake against standard portion sizes and revised nutrition requirements and prescriptions as clinically indicated.

Initiation of tube feeding for all patients was recommended if oral intake fell to <60% of estimated energy requirements and was not anticipated to improve in the next 10 days. Patients continued on tube feeding until they were able to establish a minimum of 60% of their nutrition requirements orally and maintain their weight. All patients were referred to their local dietitian service on completion of treatment.

Outcomes

Percentage weight change was chosen as the primary nutrition outcome for this study as it has been widely used and accepted in the literature. Unintentional weight loss of ≥10% within the previous six months signifies a substantial nutritional deficit (Rivadeneira, Evoy, Fahey, Lieberman, & Daly, 1998). It has been associated with moderate-severe malnutrition and therefore is considered a simple valuable measure to use for this purpose (Attar et al., 2012). Significant weight loss has also been shown to negatively impact on patient and clinical outcomes, such as quality of life (Langius et al., 2013a) and survival (Langius et al., 2013b; Martin et al., 2015), and thus is a clinically significant measure readily available from retrospective data collection.

The nutrition outcome data were used to retrospectively determine the validity of the S&N Guideline recommendation for proactive gastrostomy. For each patient the outcome of whether they were deemed to "need or not need a proactive gastrostomy" was calculated. A patient was deemed to truly "need a proactive gastrostomy" if the following clinical outcomes occurred:

- Patient had a proactive gastrostomy placed as per the S&N Guidelines and it was used for nutrition support
- Patient had a reactive feeding tube placed and it was used for >4 weeks
- Patient had an unused proactive gastrostomy, or a reactive feeding tube for <4 weeks, or no feeding tube, AND lost ≥10% body weight

These outcome definitions are described fully elsewhere when they were used to originally validate the S&N Guidelines (Brown et al., 2013b), and are deemed to confirm the prediction that the patient required a proactive gastrostomy as per the S&N Guidelines.

Statistical Analysis

Based on the sample size from the two cohorts there was an approximate ratio of 1:2.5 patients in each treatment group. In a previous study the response within each group had a standard deviation of 5. If the true difference in the treatment groups' mean weight loss is 2.3%, we will be able to reject the null hypothesis that the population means treatment groups are equal with probability (power) 0.804. The Type I error probability associated with this test of this null hypothesis is 0.05.

Statistical analysis was performed to determine any baseline differences between the treatment groups. Categorical variables were collapsed when necessary for the Chi-square test as per details in Table 4-1. Continuous variables were assessed for normal distribution using the Shapiro-Wilk test and non-parametric tests were used when the data were not normally distributed. To compare outcomes the Two Sample Wilcoxon test was used for continuous variables and the Chi-square test or Fishers exact test for the categorical variables. Statistical significance was set at $p<0.05$ for all analyses. Data were analysed using R Commander Version 1.8-3 and R version 2.14.2 (2012-02-29).

Ethics

The study was deemed a quality improvement study and exempt from full ethical review by the Human Research Ethical Committee at the Hospital. Patients received standard nutritional care during their treatment and were not subject to any experimental intervention. All data used is routinely collected for ongoing quality assurance and available in the patient administration systems of the hospital.

RESULTS

Sample population

There were 187 high risk patients eligible for the study after applying inclusion and exclusion criteria (Figure 4-2). Reasons for high risk rating were as follows: oral cavity cancer and bilateral chemoradiotherapy (n=42); oropharyngeal cancer and bilateral chemoradiotherapy (n=108); nasopharyngeal cancer and chemoradiotherapy (n=6); hypopharyngeal cancer and chemoradiotherapy (n=13); unknown primary and chemoradiotherapy (n=6); severe malnutrition at presentation (n=12); severe dysphagia at presentation (n=0).

Of those presenting with severe malnutrition (defined as either unintentional weight loss >10% in six months, body mass index <20 kg/m^2 with unintentional weight loss 5-10% in six months, or Subjective Global Assessment C); four patients had postoperative radiotherapy for oral cavity (n=1) or laryngeal (n=3) tumours; five patients had radiotherapy for oropharyngeal (n=3), hypopharyngeal (n=1) or laryngeal (n=1) tumours; and the remaining three patients had chemoradiotherapy for a laryngeal tumour. High risk patients who received H-IMRT (n=53) were compared to high risk patients who received 3D conformal radiotherapy (n=134) (Table 4-1). None of the patients had metastatic disease and all received curative intent treatment.

Whilst there were no statistically significant differences for age, gender, site or T stage; the H-IMRT cohort had more advanced nodal disease (N2 or N3 stage), 85% versus 57% ($p<0.001$), as well as a higher proportion treated with definitive chemoradiotherapy, 94% versus 78% ($p=0.017$).

S&N Guideline adherence and method of tube feeding

Overall adherence with the S&N Guidelines high risk category recommendations was high with 157/187 patients (84%) receiving a proactive gastrostomy. Two patients in the H-IMRT group had a reactive tube placed versus 14 patients in the 3D conformal group. The overall method of tube feeding was no different between the two groups ($p=0.172$) (Table 4-2).

Nutrition Outcomes - weight

The mean weight at baseline was not significantly different between the two groups ($p=0.272$). There were no significant differences between the two types of treatment with regards to the outcome of weight change from diagnosis to the end of radiotherapy treatment (Table 4-2). Median percentage weight change was -7.2% (range: -19.1, 8.5) in the H-IMRT group versus -7.3% (range: -20.1, 22.9) in the conformal group ($p=0.573$). Incidence of severe weight loss (≥10%) was 28% in the H-IMRT group versus 27% in the conformal group ($p=0.843$).

Table 4-1: Patient characteristics: Demographics and clinical data

	Helical-IMRT (n=53)	3D conformal (n=134)	P values
	N (%)		
Age (years) [a]			0.324
Median (range)	59 (32,85)	61 (26,86)	
Gender [b]			0.756
Male	43 (81)	106 (79)	
Female	10 (19)	28 (21)	
Site [b]			0.132
Oral cavity	7 (13)	36 (27)	
Oropharynx	36 (68)	75 (56)	
Nasopharynx	4 (7)	2 (1)	
Hypopharynx	3 (6)	11 (8)	
Larynx	1 (2)	6 (5)	
Unknown primary	2 (4)	4 (3)	
T Classification [b]			0.103
T1	11 (21)	12 (9)	
T2	14 (26)	34 (25)	
T3	14 (26)	32 (24)	
T4	12 (23)	52 (39)	
Tx	2 (4)	4 (3)	
N Classification [b]			<0.001 [c]
N0	3 (6)	30 (22)	
N1	5 (9)	28 (21)	
N2	44 (83)	68 (51)	
N3	1 (2)	8 (6)	
Treatment [b]			0.032 [c]
RT	0 (0)	5 (4)	
ChemoRT	50 (94)	105 (78)	
Surgery + RT	1 (2)	3 (2)	
Surgery & ChemoRT	2 (4)	21 (16)	

Abbreviations: IMRT=Intensity-Modulated Radiotherapy; 3D=Three-Dimensional; RT=Radiotherapy; ChemoRT=Chemoradiotherapy. [a] Two sample Wilcoxon test. [b] Chi Square test (site: oral vs oropharyngeal vs all others; T stage: T1/T2 vs T3/T4/Tx; N stage: N0/N1 vs N2/N3; treatment: definitive RT +/- chemo vs adjuvant RT +/- chemo). [c] Statistical significance p<0.05.

Table 4-2: Comparison of nutrition outcomes for helical-IMRT and 3D conformal radiotherapy treatments

	Helical-IMRT (n=53)	3D conformal (n=134)	P values
	Median (range)		
	Weight [a]		
Baseline (kg)	78 (46,126)	74 (42,150)	0.276
End of radiotherapy (kg)	76 (44,116)	69 (37, 137)	0.277
Weight change (kg)	-4.8 (-18.0, 4.1)	-5.35 (-21.3, 10.3)	0.873
	Weight Loss [a]		
Weight loss (%)	-7.2 (-19.1, 8.5)	-7.3 (-20.1, 22.9)	0.573
	N (%)		
≥10% weight loss [b]			0.843
Yes	15 (28)	36 (27)	
No	38 (72)	98 (73)	
Tube outcomes [c]			0.172
Proactive tube	49 (92)	108 (81)	
Reactive tube	2 (4)	14 (10)	
Nil tube	2 (4)	12 (9)	
Met criteria [d] **"needed a proactive gastrostomy"** [b]			0.213
Yes	49 (92)	115 (86)	
No	4 (8)	19 (14)	

Abbreviations: IMRT=Intensity-Modulated Radiotherapy; 3D=Three dimensional. Statistical significance p<0.05. [a] Two Sample Wilcoxon Test. [b] Chi Square test. [c] Fishers exact test. [d] Definition of criteria for "needed a proactive gastrostomy" according to Brown et al., 2013b

Nutrition outcomes – "need a proactive gastrostomy"

Both groups had a high proportion of patients who met the positive prediction "need a proactive gastrostomy" based on their actual clinical outcomes; with 92% in the H-IMRT group (n=49) versus 86% in the 3D group (n=115) (p=0.213) (Table 4-2). There were nine unused proactive tubes overall, of which three patients had severe weight loss (≥10%); and 14 patients that did not receive any form of tube feeding, however six of these also had severe weight loss (≥10%) (Table 4-3).

Table 4-3: Description of tube feeding and nutrition outcomes to determine the need for proactive gastrostomy tube following helical-IMRT and 3D conformal radiotherapy treatments

Positive prediction [a] **"needed a proactive gastrostomy"**	**Helical-IMRT (n=53)**	**3D conformal (n=134)**
Met criteria	**49 (92%)**	**115 (86%)**
Proactive PEG used	46	102
Reactive NGT and PEG	1	2
Reactive PEG	1	1
Reactive NGT ≥ 4 weeks	0	1
Reactive NGT < 4 weeks + ≥10% wt loss	0	1
Unused proactive PEG + ≥10% wt loss	1	2
Nil tube + ≥10% wt loss	0	6
Did not meet criteria	**4 (8%)**	**19 (14%)**
Reactive NGT < 4 weeks + <10% wt loss	0	9
Unused proactive PEG + <10% wt loss	2	4
Nil tube + <10% wt loss	2	6

Abbreviations: IMRT=Intensity-Modulated Radiotherapy; 3D=Three dimensional. PEG=gastrostomy tube; NGT=nasogastric tube. [a] Definition of criteria for "needed a proactive gastrostomy" according to Brown et al., 2013b.

DISCUSSION

The results from this study demonstrate that despite advances in radiotherapy techniques which reduce long-term toxicity and side effects (Vergeer et al., 2009), this has not translated into improved early nutritional outcomes. We have found no statistical difference in the mean weight loss during treatment and in the need for tube feeding, with a large proportion of patients still meeting the positive prediction for proactive gastrostomy placement. Whilst acknowledging there were differences in clinical characteristics between the two groups (higher rates of advanced N stage disease and more patients receiving definitive chemoradiotherapy in the H-IMRT group) which could possibly be attributed to the increasing incidence of human papillomavirus-related oropharyngeal cancers (Hocking et al., 2011); ultimately there was still a high incidence of weight loss and requirement for tube feeding in both groups.

Research relating to impact of H-IMRT on nutrition outcomes and tube feeding requirements is sparse (Chatterjee et al., 2011), although there are some studies reporting on outcomes following linear accelerator based IMRT (Caudell et al., 2010; Gunn et al., 2010; Studer et al., 2010). The current evidence indicates that weight loss is a recurring problem, despite advancing radiotherapy techniques, which supports the ongoing essential need for nutrition intervention. Maintaining and improving nutritional status has been shown to improve quality of life (Langius et al., 2013a; van den Berg et al., 2008) and other clinical outcomes (Capuano et al., 2008). Capelle et al. (2012) reported a median loss of 6% of pre radiotherapy weight (with a maximum weight loss of 13.6%) in a small case series (n=20) of patients receiving definitive or adjuvant chemoradiotherapy (Capelle et al., 2012). You et al. (2012) reported 23% of their patients (7/31) lost >5% of their body weight and these weight changes and anatomical contour changes impacted on severity of side effects such as xerostomia (You et al., 2012). Duma et al. (2012) were investigating the dosimetric effect of adaptive radiotherapy and they reported re-planning usually occurred by the end of the third week of treatment, at which point there was a median weight loss of 2.3kg (0 to -10.7kg), however overall weight change was not reported (Duma, Kampfer, Schuster, Winkler, & Geinitz, 2012). There is even less data in the literature on the usage of feeding tubes with H-IMRT. In one small study (n=5), all patients had a proactive gastrostomy tube placed however nutritional outcomes or tube use were not reported (Loo et al., 2011). Another small study (n=17) reported that no patients in their case series received a gastrostomy (although the use of nasogastric tubes was not reported), however 29% (n=5) had severe weight loss ≥10% (Chao et al., 2000).

Multidisciplinary team adherence to the S&N Guideline recommendations for high risk patients improved over time, with adherence of 80% (2007-08) increasing to 89% (2010-11). Despite a high rate of tube feeding and therefore nutrition intervention in this patient group, the weight loss outcomes remain sub optimal. Both groups had median weight loss ≥5% and a high incidence of severe weight loss (≥10%) which is consistent with the literature (Capelle et al., 2012; Chao et al., 2000; Silander et al., 2013).

Further research is required to investigate why patients continue to lose significant weight, despite intensive nutrition interventions, and investigate strategies to overcome this weight loss (Brown et al., 2014b). The aetiology of patients' weight loss is likely multi-factorial, and not simply related to the radiotherapy dosimetry. Patients receiving concurrent chemoradiotherapy often experience additional chemotherapy induced side effects such as nausea, vomiting, taste changes, loss of appetite and fatigue. Silander et al. (2013) demonstrated patients were not able to meet their recommended energy and protein intakes despite prophylactic gastrostomy, hypothesising treatment side effects as the main barrier (Silander et al., 2013).

Patient adherence to recommendations is also an important consideration, as we have shown in this study that despite proactive gastrostomy insertion, there were three patients that chose not to use their tube when it was recommended to do so, resulting in clinically significant weight loss. Capuano et al. (2008) reported 47% of patients were deemed non-adherent – either not accepting nutritional counselling or refusing nasogastric or gastrostomy tubes during treatment, and this had a significant impact on their outcomes (Capuano et al., 2008). Further research to develop our understanding of factors which impact upon weight loss and adherence is required to enable the development of effective strategies to ultimately improve nutrition outcomes.

A retrospective study design results in limitations such as patient exclusions due to difficulties accessing charts and missing data. It also limits the ability to measure other clinical outcomes which are not part of routine practice such as quality of life, blood results, body composition and toxicity profiles. Whilst reduced late toxicity has been demonstrated with IMRT (Vergeer et al., 2009), the research with H-IMRT remains limited with studies only reporting the reduction in doses to organs at risk compared to IMRT (Fiorino et al., 2006; Lee et al., 2008a; Ruchala et al., 1999; Sheng et al., 2006). A prospective observational study is currently in progress to determine acute and late toxicity profiles following H-IMRT and will be reported on separately.

The duration of gastrostomy use should be more carefully considered in future studies. If duration of gastrostomy use is <4 weeks, a nasogastric tube may be more appropriate (Arends et al., 2006), as long as there is no compromise to the ultimate nutrition outcome and degree of weight loss. Whilst the high risk definition for the S&N Guidelines actually changed slightly over the period of data collection for the two cohorts (Brown et al., 2016a), this had a negligible impact on results due to small numbers in the categories affected by change, (no patients classified as high risk due to dysphagia alone and only six patients with an unknown primary treated with chemoradiotherapy).

Additional outcome measures such as nutritional status using validated tools (Bauer, Capra, & Ferguson, 2002) or a combination of standardised characteristics to diagnose malnutrition (White et al., 2012) would have been useful to include in this study, however the detail required for these types of assessment were usually only routinely recorded at baseline. Therefore percentage weight loss was used as the primary nutrition outcome as this was a convenient measure available through retrospective chart audit. Given ≥10% weight loss has been shown to impact on patient and clinical outcomes (Langius et al., 2013b; Langius et al., 2013a; Martin et al., 2015), this was considered a suitable nutrition outcome measure for this study design.

The strength of this study is it is the largest cohort to date with adequate statistical power to report on nutrition outcomes following H-IMRT. We were fortunate to able to compare patients receiving the two types of treatment over a similar period of time at one centre with no other contemporaneous changes in practice at our institution that may have confounded these results. Concurrent comparative cohort studies will become increasingly difficult to perform as centres migrate to the use of advanced techniques as their new standard of care. Our study also benefits from minimal selection bias with the use of validated guidelines to clearly identify high risk patients for proactive tube feeding, with a high rate of adherence by the multi-disciplinary team.

In conclusion, although H-IMRT has been shown to deliver reduced doses to normal tissue, there are no significant differences in incidence of tube feeding or weight loss during treatment when compared to conformal 3D radiotherapy techniques. Therefore the placement of a proactive gastrostomy tube is still warranted in high risk patients and nutrition intervention remains critical.

ACKNOWLEDGEMENTS

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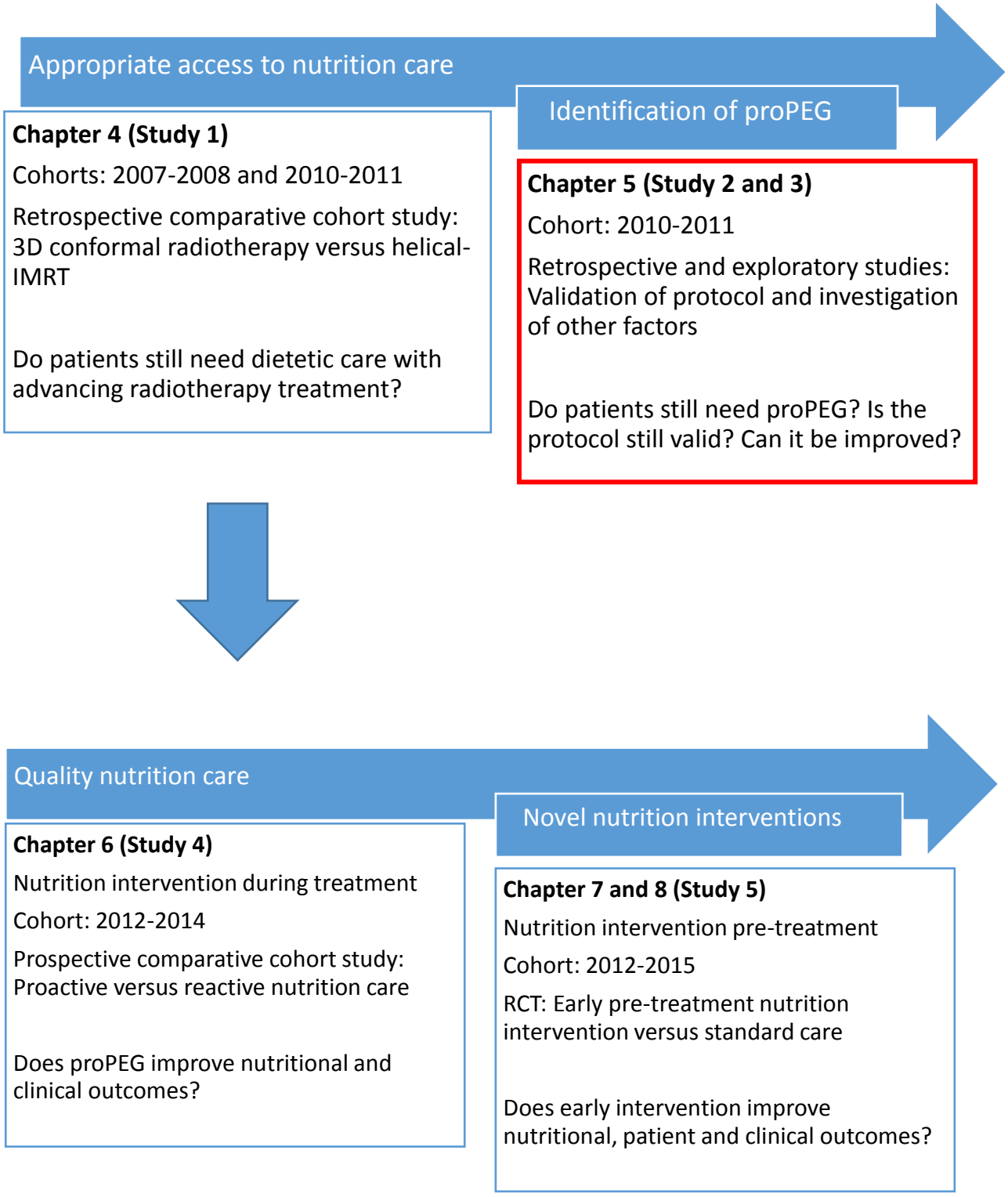
4.4 Chapter summary

This is the first study of its kind to report fully on nutrition outcomes following treatment with helical-IMRT in a large sample size (n=187). The results of this study have demonstrated that despite advances in radiotherapy techniques, nutrition intervention remains critical in this patient population. There were no clinical or statistical differences between the two treatment groups in regards to any of the nutrition outcome measures. Both groups lost a median of 7% weight loss during treatment, and approximately a quarter to a third of patients in each group had a severe weight loss of 10% or greater. This implies that radiotherapy dosimetry and the improved target precision with these advancing techniques are not the only factors that influence nutrition outcomes in this population. The majority of all patients in the study also met the criteria for proPEG placement. The rate was slightly higher in the helical-IMRT group at 92% vs 86%, which may have been due to the higher rates of chemoradiotherapy and advanced N stage disease in this group. These clinical characteristics are likely to have influenced decision-making in the selection of patients to receive helical-IMRT and created some sample bias. However, overall the findings from this study have demonstrated that weight loss and tube feeding remain significant issues in this patient population.


Appropriate access to nutrition care
Identification of proPEG
Chapter 4 (Study 1)
Cohorts: 2007-2008 and 2010-2011
Retrospective comparative cohort study: 3D conformal radiotherapy versus helical-IMRT
Do patients still need dietetic care with advancing radiotherapy treatment?
Chapter 5 (Study 2 and 3)
Cohort: 2010-2011
Retrospective and exploratory studies: Validation of protocol and investigation of other factors
Do patients still need proPEG? Is the protocol still valid? Can it be improved?
Quality nutrition care
Novel nutrition interventions
Chapter 6 (Study 4)
Nutrition intervention during treatment
Cohort: 2012-2014
Prospective comparative cohort study: Proactive versus reactive nutrition care
Does proPEG improve nutritional and clinical outcomes?
Chapter 7 and 8 (Study 5)
Nutrition intervention pre-treatment
Cohort: 2012-2015
RCT: Early pre-treatment nutrition intervention versus standard care
Does early intervention improve nutritional, patient and clinical outcomes?

5.1 Chapter overview

As the previous chapter demonstrated a need for ongoing nutrition intervention in patients receiving helical-IMRT, placement of proPEG is still an important consideration. The protocol used to identify patients at the Royal Brisbane and Women's Hospital (RBWH) was originally validated in a cohort of patients who received three-dimensional conformal radiotherapy (Brown et al., 2013b). The aim of the first study in this chapter was to review the protocol to ensure it remained valid in a new cohort of patients receiving helical-IMRT.

The first study is presented in section 5.2 as the accepted format prior to publication in the European Journal of Clinical Nutrition (Journal Impact Factor 2.935; Ranked 31/80 Nutrition & Dietetics category; Quartile 2). Preliminary results were presented at the 15th Australia and New Zealand Head and Neck Cancer Society Annual Scientific Meeting, Melbourne, Australia, 2013 (Appendix C – 11.3.4).

Date submitted: 26/04/2015

Date accepted: 19/12/2015

Citation: Brown, T., Getliffe, V., Banks, M., Hughes, B., Lin, C., Kenny, L., Bauer, J. (2016). Validation of an updated evidence-based protocol for proactive gastrostomy tube insertion in patients with head and neck cancer. *Eur J Clin Nutr*, *70*(5), 574-81. doi:10.1038/ejcn.2015.230.

Meanwhile other clinical factors not previously taken into account had also emerged including: p16 status (an immunohistological marker for HPV-related tumours); type of systemic therapy (Cetuximab was a newly approved monoclonal antibody); and albumin and C-reactive protein (CRP) (biomarkers of pre-cachexia). The aim of the second study in this chapter was to explore whether these additional clinical factors should be considered and incorporated into the protocol.

The second study is presented in section 5.3 as the accepted format prior to publication in Head and Neck (Journal Impact Factor 2.760; Ranked 3/43 Otorhinolaryngology category; Quartile 1). This study was presented at the Multinational Association of Supportive Care in Cancer Annual Meeting, Adelaide, Australia, 2016 (Appendix C – 11.3.5).

Date submitted: 23/03/2016

Date accepted: 07/10/2016

Citation: Brown, T., Wittholz, K., Way, M., Banks, M., Hughes, B., Lin, C., Kenny, L., Bauer, J. (2017). Investigation of p16 status, chemotherapy regimen and other nutrition markers for predicting gastrostomy in patients with head and neck cancer. *Head Neck*, *39*(5), 868-875. doi:10.1002/hed.24630

Section 5.4 provides an overall summary of the findings from these two studies.

5.2 Validation of protocol

5.2.1 Abstract

Background/Objectives: Evidence-based practice guidelines are available to assist in the decision-making for nutrition interventions in patients with head and neck cancer. Re-assessment of guideline recommendations is important with changing demographics, new treatment regimens, advancing radiotherapy techniques, such as helical intensity-modulated radiotherapy, and the emergence of new literature. The aim of this study was to validate the updated high risk category definition in our local hospital protocol for the swallowing and nutrition management of patients with head and neck cancer to determine the ongoing predictive ability for identifying proactive gastrostomy requirement in a new cohort.

Subjects/Methods: Patients attending a major tertiary hospital for head and neck cancer treatment from 2010 – 2011 were included (n=270). Data were collected on; patient demographics (age, gender), clinical factors (tumour site, staging and treatment), nutrition outcome measures (weight, enteral feeding), and protocol adherence. Sensitivity and specificity were calculated and compared to the original validation study.

Results: Proactive gastrostomy tubes were inserted in 86 patients. Overall protocol adherence was 93%. Sensitivity improved to 72% (increase of 18%) and specificity improved to 96% (increase of 3%) compared to the original validation study where patients received three-dimensional (3-D) conformal radiotherapy.

Conclusion: The results of this study confirm the updated high risk category in the protocol for the swallowing and nutrition management of patients with head and neck cancer remains valid to predict proactive gastrostomy in a mixed population receiving helical intensity-modulated radiotherapy and 3-D conformal radiotherapy. The protocol has an improved sensitivity and specificity and hence remains just as relevant for advanced techniques of radiation treatment delivery.

5.2.2 Manuscript

INTRODUCTION

Patients with squamous cell carcinoma of the head and neck frequently experience dysphagia as a result of cancer treatment or the tumour itself, which often results in a need for tube feeding to provide adequate nutritional intake. The optimal form of tube feeding remains controversial in the literature, with inadequate high level evidence to enable any firm recommendations (Langius et al., 2013c; Nugent et al., 2013; Wang et al., 2014a). Risks of gastrostomy placement in the selection of feeding tube need to be considered (Grant et al., 2009). Some studies have shown benefits with prophylactic gastrostomy placement compared to a reactive approach to nutrition support including reduced weight loss/improved nutritional status (Chang et al., 2009; Lewis, Brody, Touger-Decker, Parrott, & Epstein, 2014; Rutter et al., 2011; Silander et al., 2012), improved quality of life (Salas et al., 2009), and reduced admissions and healthcare costs (Baschnagel et al., 2014; Hughes et al., 2013). Other studies have shown no difference in outcomes with feeding tube selection and suggest a reactive approach may be more favourable to reduce duration of feeding tube use (Kramer et al., 2014; Sheth, Sharp, & Walters, 2013). Whilst there are concerns that gastrostomy placement may result in gastrostomy dependency and increased dysphagia post-treatment (Corry et al., 2008; Ward et al., 2016), other studies have not supported this finding (Crombie et al., 2015; Prestwich et al., 2014).

A hospital protocol for the swallowing and nutrition management of patients with head and neck cancer was developed at our institution in order to help clinicians identify high risk patient groups who would benefit from proactive gastrostomy placement. The risk categories in the protocol have been validated for their ability to predict the need for proactive gastrostomy placement in a patient population receiving three-dimensional (3-D) conformal radiotherapy (Brown et al., 2013b). Implementation of the protocol has been shown to reduce unplanned hospital admissions and length of stay (Hughes et al., 2013) and adherence to the protocol has been demonstrated to improve nutrition outcomes (Brown et al., 2014a). The protocol was subsequently modified following availability of new evidence (Isenring et al., 2008) and further internal evaluation to improve their accuracy and validity (Brown et al., 2016a) which resulted in some changes to the high risk category definition (Figure 5-1).

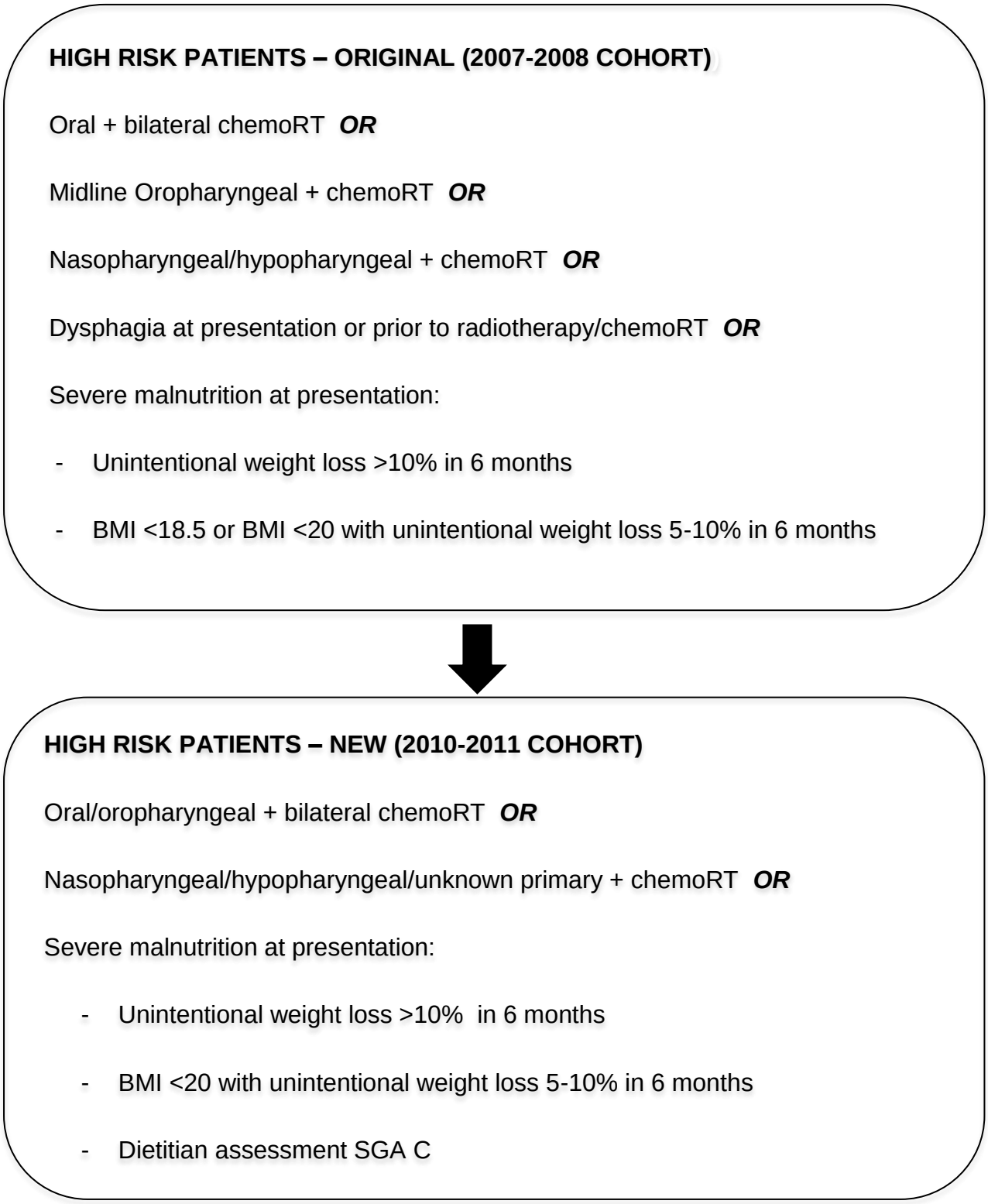


Figure 5-1: Comparison of the high risk category of the Royal Brisbane and Women's Hospital protocol for the swallowing and nutrition management of patients with head and neck cancer for each cohort

Abbreviations: chemoRT=chemoradiotherapy; BMI=body mass index; SGA=subjective global assessment. Adapted from Brown et al., 2013b.

Evolving radiotherapy techniques, such as conformal radiotherapy or linear accelerator-based intensity-modulated radiation therapy (IMRT), have been used in recent years with the aim of limiting the radiation dose to healthy tissues and organs to minimise unwanted side effects. Around the same time of implementation of the updated protocol, a new radiotherapy technique Helical-IMRT (H-IMRT) was also introduced at our hospital. This is a relatively new type of IMRT delivery system using a Tomotherapy™ machine. It further limits radiation damage to normal tissue compared to IMRT and thereby results in less long-term side effects of radiation (Capelle et al., 2012; van Vulpen et al., 2005). To date the majority of studies investigating nutrition outcomes and tube feeding requirements have been undertaken in patients receiving 3-D conformal radiotherapy or IMRT, and therefore the nutritional needs of patients following H-IMRT are largely unknown.

Additionally in recent years there has been an increasing incidence of human papillomavirus (HPV)-related head and neck tumours (Jemal et al., 2013). These patients present with distinct carcinogenesis, risk factors, clinical presentation and prognosis compared to HPV-negative patients (Benson et al., 2013; Bonilla-Velez, Mroz, Hammon, & Rocco, 2013; Evans et al., 2013; Gillison et al., 2008; Petrelli, Sarti, & Barni, 2014; Ramqvist & Dalianis, 2010) resulting in a change of clinical and demographical profile of the population. Patients with HPV-positive tumours show better response to treatment, overall survival, and progression-free survival (Benson et al., 2013), and therefore research into alternative treatment protocols to reduce toxicities without compromising oncological outcomes are underway (Rischin & Corry, 2013).

As treatment methods evolve through technology and further research to optimise patient outcomes, it is important to continue to re-evaluate the evidence for supportive cares such as the nutrition management of this patient population. Therefore the main aim of this study was to validate the updated high risk category definition in the protocol for the swallowing and nutrition management of patients with head and neck cancer to determine the ongoing predictive ability for identifying proactive gastrostomy requirement in a new cohort to account for any changes in treatment and population characteristics that are likely to have occurred over the recent years. The second aim was to determine if there was any impact specifically from the use of H-IMRT treatment on the applicability of the protocol.

SUBJECTS AND METHODS

Study Setting

This is a single institution study where all patients with head and neck cancer attend a multidisciplinary clinic at a tertiary hospital for diagnosis, staging and planning of treatment. All patients are assessed by: surgical and medical specialists (Ear, Nose and Throat Surgeons; Plastic and Reconstructive Surgeons; Oral and Maxillofacial Surgeons; Radiation Oncologists and Medical Oncologists); a dentist; speech pathologist; dietitian; and nursing staff. The protocol for the swallowing and nutrition management of patients with head and neck cancer is applied to each patient to assist in the planning of their nutrition management as part of their treatment.

Study population

Patients were eligible for the study if they attended our hospital for assessment and treatment between July 2010 and June 2011. Inclusion criterion was a referral to a dietitian at our hospital, which occurs as part of standard care during curative intent surgical and/or oncological treatment for head and neck cancer. Patients were therefore ineligible if they had: benign disease; a non-head and neck tumour; treatment of palliative intent; treatment privately or at another facility or on the short stay surgical unit. Patients were excluded if there was: incomplete data (i.e. weight was not recorded or the patient did not complete treatment); or no access to the medical chart (i.e. patients did not consent for chart to be used for audit/research purposes or the medical chart was destroyed) The study was deemed a quality improvement study and exempt from full ethical review by the Human Research Ethical Committee at the Hospital.

Study design and data collection

Data collection was via retrospective chart audit and the use of existing clinical databases. Independent variables included: gender, age, clinical factors (tumour site, tumour stage, and treatment location), patient risk rating from the protocol (high or low), and adherence to the protocol risk category recommendations. Dependent variables included: nutrition outcome measures (percentage weight loss from baseline at diagnosis to the end of cancer treatment); incidence of proactive tube placement and use of this tube; and the incidence of reactive tube placement, including type of tube and duration of use.

Use of the tube was recorded by the dietitian in the medical notes as part of standard assessment on each review during and after treatment. Data on gastrostomy complications rates were also collected for the 30-day period post insertion. Major complications were defined as those requiring surgical intervention, blood transfusion or IV antibiotics. Admissions or prolonged admissions relating to gastrostomy complications were noted.

Outcomes

The dependent variables were used to assess the primary outcome of whether each patient was deemed to require or not require a proactive gastrostomy. Patients were confirmed as high risk, and therefore requiring a proactive gastrostomy, if significant weight loss (≥10% baseline body weight) had occurred by the end of the acute-phase cancer treatment, or a proactive tube was placed and used or a reactive tube was placed and used for more than four weeks. These outcome definitions are described fully elsewhere (Brown et al., 2013b), and were previously used to confirm the need for intensive early nutrition support intervention, and thus placement of a proactive gastrostomy. A contingency table was used to compare these patient outcomes with the protocol risk category and determine sensitivity, specificity, positive predictive value and negative predictive value. The results were compared to data from the original validation study.

Statistical Analysis

Statistical analysis was performed between the current cohort and the historical cohort (used to previously validate the protocol) to determine if there were any differences between the cohorts' categorical variables and continuous variables, using the Chi-square test and the Independent Samples T-test respectively. Categories were collapsed to enable statistical comparison as follows: Treatment Site (oropharynx and nasopharynx), T Classification (T0 and Tx; recurrent and other), N Classification (other and unknown), and Treatment Type (radiotherapy alone and chemotherapy alone). Age was a continuous variable (years) and presented as mean $\pm$ sd. Levene's test was applied to check assumption of equal population variance prior to the Independent Samples T-test. Statistical significance was set at $p<0.05$. Data were analysed using R Commander Version 1.8-3 and R version 2.14.2 (2012-02-29).

RESULTS

Patient Characteristics

There were 551 patients who attended the hospital for assessment during the one year study period. After inclusion and exclusion criteria were applied this gave a final sample size of n=270 for analysis (Figure 5-2). Patients had a median age of 63 years (range 15-90 years) and were mainly men (77%). The most frequent squamous cell carcinoma of the head and neck sub sites were oral cavity (30%) and oropharynx (24%). Tumour classification was distributed evenly, and 14% of patients presented with recurrent disease. Seventy five percent of all patients received multimodality treatment. There were 75 patients who received H-IMRT, accounting for 33% of all patients receiving radiotherapy (n=230), with the remainder receiving 3-D conformal radiotherapy.

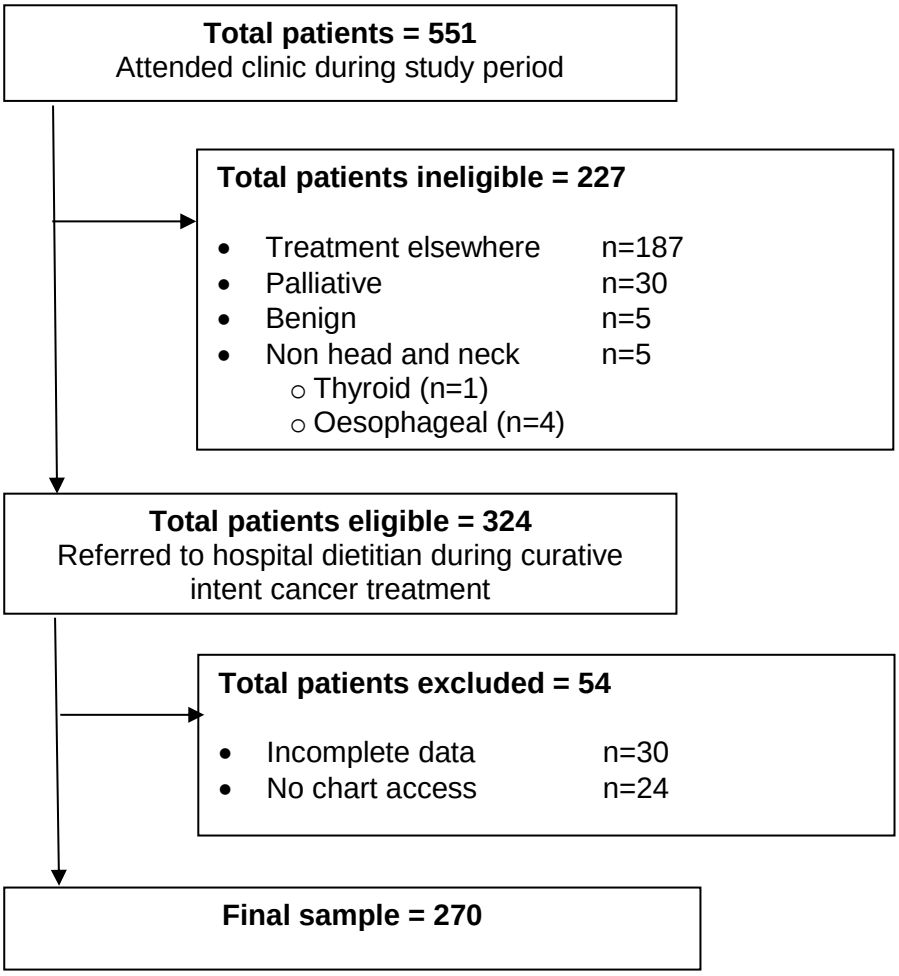


Figure 5-2: CONSORT diagram to illustrate eligible patient sample with inclusion and exclusion criteria

The patient demographics and clinical characteristics are summarised (Table 5-1), and compared to the cohort from the original validation study (n=501). There were no significant differences between the two cohorts with respect to gender, or age, however there were a number of statistically significant differences with respect to tumour site, staging and treatment. In the current cohort there was a lower proportion of patients with laryngeal cancer, fewer patients with recurrent disease, more patients with N2 disease and fewer patients that received radiotherapy alone.

Assessment using the protocol identified 88 patients as high risk accounting for 33% of the cohort. Reasons for high risk rating are shown (Figure 5-3). Of those presenting with severe malnutrition; one patient had radiotherapy for laryngeal cancer, another had radiotherapy for oral cavity cancer, and the third had salvage surgery for recurrent disease.

Overall a gastrostomy tube or nasogastric tube was inserted in 37% (*n=100*) of patients at some stage during cancer treatment (Table 5-2). This was very similar to the cohort from the original validation study where it was required in 34% of patients (n=173), (p=0.488).

Gastrostomy Complications

Gastrostomy data complications were available for 79/92 patients (12 patients had their tubes placed privately, and one patient had an existing tube in-situ). The rate of major complications from gastrostomy insertion was 3.8% (n=3); one patient required surgical intervention for a laparoscopy and bowel drain; one patient require IV antibiotics for suspected bowel perforation; one patient developed an ileus. An additional three patients had a prolonged admission post insertion managed conservatively and a further six patients required an admission for IV antibiotics for a site infection.

Table 5-1: Comparison of patient demographics and clinical characteristics

Patient Characteristics	**Previous 2 year cohort (2007-2008) N=501**		**New 1 year cohort (2010-2011) N=270**		***P Value***
	n	**%**	**n**	**%**	
Age years (Mean ± SD)	63.51 ± 12.40		63.15 ± 12.91		*P=0.708*
Gender					*P=0.948*
Male	387	77%	208	77%	
Female	114	23%	62	23%	
Site [a]					*P=0.004*
Oral cavity	139	28%	81	30%	
Oropharynx	101	20%	65	24%	
Nasopharynx	5	1%	4	2%	
Hypopharynx	16	3%	14	5%	
Larynx	78	16%	18	7%	
Unknown primary	28	6%	9	3%	
Other	134	27%	79	29%	
T Classification [b]					*P=0.080*
T0	0	0%	13	5%	
T1	93	19%	45	17%	
T2	102	20%	69	26%	
T3	71	14%	34	13%	
T4	87	17%	60	22%	
Tx	37	7%	9	3%	
Recurrent	110	22%	38	14%	
Other	1	0%	2	1%	
N Classification [c]					*P<0.001*
N0	176	35%	93	34%	
N1	79	16%	45	17%	
N2	100	20%	88	33%	
N3	14	3%	4	1%	
Recurrent	110	22%	38	14%	
Other	1	0%	2	1%	
Unknown	21	4%	0	0%	
Treatment [d]					*P=0.023*
Surgery	73	15%	40	15%	
Radiotherapy	85	17%	28	10%	
ChemoRT	143	29%	91	34%	
Surgery + RT	153	31%	96	36%	
Surgery & ChemoRT	46	9%	15	6%	
Chemotherapy	1	0%	0	0%	
Additional Treatment Details					
Tomotherapy	0	0%	75	28%	*P<0.001*
Cetuximab	34	7%	16	6%	*P=0.538*

Abbreviations: RT=radiotherapy. Statistical methods: continuous variables analysed using independent samples t-test; categorical variables analysed using chi-squared test; p<0.05 significant. [a] Owing to small cell size; combined oropharynx and nasopharynx. [b] Owing to small cell size; combined T0 and Tx; combined recurrent and other. [c] Owing to small cell size; combined other and unknown. [d] Owing to small cell size; combined radiotherapy alone and chemotherapy alone. Adapted from Brown et al., 2013b.

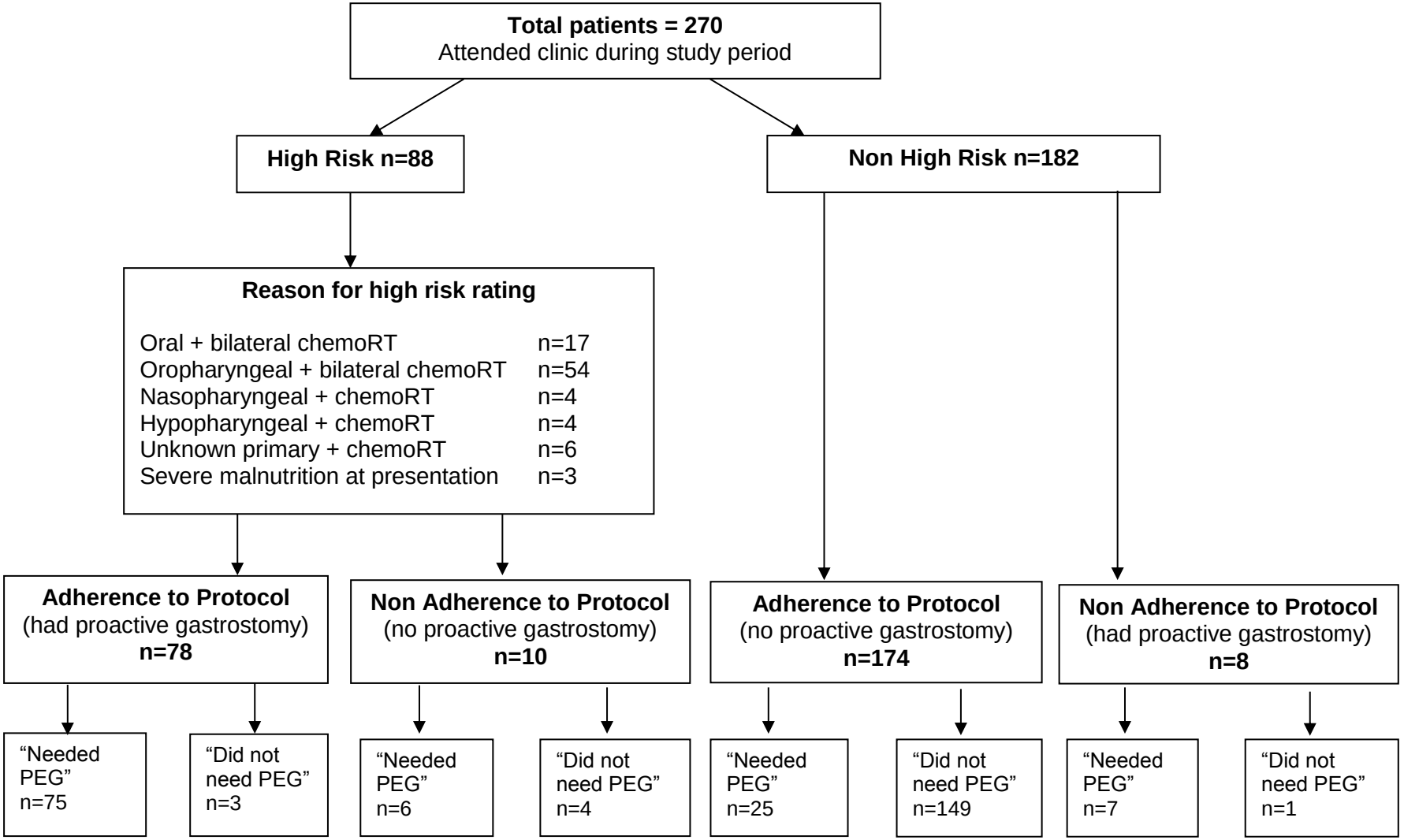


Figure 5-3: Adherence to the Royal Brisbane and Women's Hospital protocol for the swallowing and nutrition management of patients with head and neck cancer and associated outcomes

Abbreviations: chemoRT=chemoradiotherapy; PEG=proactive gastrostomy.

Table 5-2: Method of nutrition support utilised during treatment in the 2010-2011 patient cohort

Type of Nutrition Support	**n**	**%**
Nil tube feeding	**170**	**63**
Proactive gastrostomy tube [a]	**86**	**32**
Used	80	93
Unused	6	7
Reactive tube	**14**	**5**
NGT < 4 weeks	5	36
NGT > 4weeks	3	21
NGT & PEG	3	21
PEG	3	21

Abbreviations: PEG=gastrostomy tube; NGT=nasogastric tube. [a] Proactive gastrostomy tube indicates therapeutic or prophylactic gastrostomy placed prior or within first 2 weeks of treatment.

Adherence to the protocol

Overall adherence with the protocol risk category recommendations by the treating medical team was high (93% compared to 87% in the original cohort for validation). Of the 88 high risk patients, 89% (*n=78*) received a proactive gastrostomy as per the protocol recommendation (Figure 5-3). Only three of these patients ended up not meeting the final criteria for proactive gastrostomy, as they did not use their tube and had less than 10% weight loss. Two patients did not use their tube against recommendations and thus lost more than 10% weight. All other patients used their tube. A proactive gastrostomy was not placed in the remaining 10 high risk patients because the procedure was medically contraindicated (n=1), was refused by the patient or treating Consultant (n=2), or other reasons such as scheduling difficulties (n=7). Six of these patients did end up meeting the final outcome criteria for proactive gastrostomy insertion based on their individual outcomes (Figure 5-3). Of the 182 non high risk patients, eight did have a proactive gastrostomy tube inserted, despite no recommendation in the protocol. Seven of these patients did use their tube (one patient had >10% weight loss despite tube use) and therefore selection for placement was deemed appropriate. Only one patient did not use the tube as predicted by the risk rating and was able to minimise weight loss to <10%. Of the remaining 174 low risk patients without a tube, three patients had a gastrostomy placed during treatment, three patients had a nasogastric tube for more than four weeks, and 19 patients had more than 10% weight loss. Therefore in total 25 patients did end up meeting the final outcome criteria for proactive gastrostomy insertion based on their individual outcomes.

Validation of the protocol

Of the 270 patients, 113 (42%) met the predefined positive prediction “did need a proactive gastrostomy” based on patient outcomes. Of these, 32 patients (28%) failed to be identified as high risk using the protocol. An exploration of this group was undertaken to see if any common factors could be identified. Overall seven patients had surgery alone and all others had unilateral radiotherapy (either adjuvant or definitive +/- chemotherapy). There were seven patients the Consultants identified for proactive gastrostomy which were mainly T3, T4 or N2 staging (n=5) and oral cavity tumours (n=5). There were seven patients who required a reactive feeding tube, four of which had surgery alone, but otherwise there were no other common factors with site or staging. The remaining 18 patients who all lost >10% body weight had no other common sites but the majority had T3, T4 or N2 staging (n=10/18).

Of the 270 patients, the remaining 157 patients, all of whom lost <10% body weight, met the predefined alternative patient outcome "did not need a proactive gastrostomy". Of these, seven (4%) patients were identified as false positives (i.e. a result that indicates the patient is high risk when they are not). Therefore, sensitivity of the protocol risk categories to predict patients' need for a proactive gastrostomy was 72%, specificity was 96%, positive predictive value was 92%, and negative predictive value was 82% (Table 5-3).

Table 5-3: Sensitivity and specificity of the risk categories in the Royal Brisbane and Women's Hospital protocol for the swallowing and nutrition management of patients with head and neck cancer to predict requirement for proactive gastrostomy insertion in a mixed cohort of patients receiving 3-D conformal radiotherapy and helical-IMRT

		Prediction for proactive gastrostomy [a] (defined from patient outcomes at end of acute cancer treatment)		Positive and negative predictive values
		Positive: Did need a proactive gastrostomy [b] (*n*)	Negative: Did not need a proactive gastrostomy [c] (*n*)	
Determined from protocol risk criteria	High risk [d]	81 (TP)	7 (FP)	**PPV**=TP/(TP+FP) **92%**
	All other patients [e]	32 (FN)	150 (TN)	**NPV**=TN/(FN+TN) **82%**
Sensitivity and specificity		**Sensitivity** =TP/(TP+FN) **72%**	**Specificity** =TN/(FP+TN) **96%**	

Abbreviations: FN=false negative; FP=false positive; IMRT=intensity-modulated radiotherapy; NPV=negative predictive value; PPV=positive predictive value; TN=true negative; TP=true positive. [a] Proactive gastrostomy indicates therapeutic or prophylactic gastrostomy placed prior or within first 2 weeks of treatment. [b] Positive prediction = met the predefined primary patient outcome. "A patient did not have an active gastrostomy or long-term NGT and had ≥10% weight loss or patient had an active gastrostomy or long-term NGT". [c] Negative prediction = met the predefined alternative patient outcome. "A patient did not have an active gastrostomy or long-term NGT and had <10% weight loss". [d] Recommended for proactive gastrostomy insertion. [e] No recommendation for proactive gastrostomy insertion.

DISCUSSION

This study aimed to validate the updated protocol for the swallowing and nutrition management of patients with head and neck cancer in relation to the new high risk category definition for proactive gastrostomy insertion. The study was undertaken in a new cohort, with patients receiving standard 3-D conformal radiotherapy and H-IMRT. Compared to data collected in the validation of the original protocol where patients only received 3-D conformal radiotherapy (Brown et al., 2013b), this study found both the sensitivity and specificity improved and that indication for proactive gastrostomy using the updated high risk category definition was appropriate.

The increased sensitivity of 72% (compared to previous results of 54%) meant that there were a lower percentage of false negatives and more patients were likely to be correctly identified for a gastrostomy when required. When the characteristics of the false negatives were investigated to see if any improvements could be made to the guidelines; advanced staging (such as T3 and T4) appeared to be an important factor to consider, which is also widely supported in the literature (Chang et al., 2009; Jack et al., 2012; Strom et al., 2013). A number of patients also received surgery alone or postoperative radiotherapy, and so more consideration should perhaps be given the surgical procedure. Other guidelines have since been developed specifically for this (Jack et al., 2012) and they could be used to further inform decision-making in this population.

The specificity remained high at 96% (compared to previous results of 93%) indicating a lower percentage of false positives and fewer patients were likely to receive a gastrostomy unnecessarily. The improvement in the sensitivity and specificity compared to the previous study is attributed to the minor changes to the criteria used to identify high risk patients in the protocol (Figure 5-1) and the clinical and treatment differences noted between the cohorts which may possibly be explained by the increasing incidence of HPV oropharyngeal tumours (Jemal et al., 2013).

In regards to the advances in treatment techniques over time, research relating specifically to H-IMRT and its' impact on nutrition outcomes and tube feeding requirements is sparse, with the majority of the studies to date reporting on outcomes following linear accelerator based IMRT. Long-term benefits following IMRT are well documented with reduced xerostomia and improved quality life, due to reduced radiation dose to the parotid glands (Vergeer et al., 2009).

Due to the reduced dose-volume achieved with IMRT some authors have postulated this may lead to a reduced need for a gastrostomy when treated with IMRT alone (Sanguineti et al., 2011). However, there are studies that also continue to support the role of a proactive gastrostomy with IMRT, particularly with concurrent treatment (Romesser et al., 2012), and rates of gastrostomy dependence have not been found to be any different with IMRT (Rusthoven et al., 2008).

Several studies suggest that H-IMRT can achieve superior dose sparing to organs at risk versus other forms of IMRT (Fiorino et al., 2006; Lee et al., 2008a; Sheng et al., 2006; van Vulpen et al., 2005), strengthening the rationale that intensive nutrition support with a feeding tube may no longer be warranted with this advanced treatment technique. However there is very limited data on the usage of feeding tubes with H-IMRT. In one small study (n=5), all patients had a proactive gastrostomy tube placed however nutritional outcomes or tube use were not reported (Loo et al., 2011). Another small study (n=17) reported that no patients in their case series received a gastrostomy however 29% (n=5) had severe weight loss >10% (Chao et al., 2000).

Weight loss secondary to acute radiation toxicity is a well-recognised side effect of radical treatment for head and neck cancer (Chatterjee et al., 2011) and a number of studies support that weight loss is a recurring problem with H-IMRT(Capelle et al., 2012; Duma et al., 2012; You et al., 2012). Similarly we found 64% of patients experienced clinically significant weight loss during treatment; 46% (123/270) lost $\geq$5% and 18% (49/270) lost $\geq$10% of their body weight. Of the patients that received H-IMRT (n=75), 25% lost $\geq$5% and 23% lost $\geq$10%. Weight loss remains prevalent, despite advances in treatment techniques (Brown et al., 2015), and therefore nutrition support is essential to assist with maintaining nutritional status which has been shown to improve quality of life (Langius et al., 2013a; van den Berg et al., 2008) and other clinical outcomes (Capuano et al., 2008). The protocol for proactive gastrostomy placement hence remains just as relevant for advanced techniques of radiation treatment delivery.

There are limitations in the interpretation of these results due to the study being undertaken at a single site and therefore limiting the applicability to other centres not using the protocol. The retrospective study design also results in a number of patients being excluded due to access issues to the medical chart and missing outcome weight data.

There was a smaller sample size compared to the previous cohort used (one year versus two years data collection), and the study only had a small subset of radiotherapy patients that actually received H-IMRT (75/230). This introduced some selection bias as patients were generally prioritised for H-IMRT if they had extensive fields, high risk tumour sites such as the base of tongue or required bilateral irradiation rather than ipsilateral irradiation.

The strength of this study is the favourable sample size compared to other published studies to date which have reported on nutrition outcomes and tube feeding requirements with H-IMRT, which therefore helps to develop our knowledge in this field. Studies with IMRT have shown median gastrostomy use of three months (de Arruda et al., 2006) and benefits in expediting gastrostomy removal with the dose constraints formulated during planning (Amin et al., 2012), however we do not fully understand the impact of H-IMRT on the duration of gastrostomy use. According to the evidence-based European Society of Clinical Nutrition and Metabolism non-surgical oncology guidelines (Arends et al., 2006) a nasogastric tube is recommended for nutrition support that is required for <4 weeks and therefore this may be a more appropriate method of tube feeding if indeed the duration of gastrostomy use is <4 weeks. Therefore determining the duration of gastrostomy use will be an important consideration in future studies with H-IMRT.

In summary the results of this study confirm the protocol's updated high risk category is valid to predict proactive gastrostomy placement with a higher sensitivity and specificity. The revised version is therefore preferable for clinical use and has been shown to be appropriate for a mixed patient cohort receiving both 3-D conformal radiotherapy and H-IMRT.

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5.3 Investigation of other factors.

5.3.1 Abstract

Background: The study aim was to determine if p16 status, chemotherapy regimen or other nutrition markers could improve protocol accuracy in predicting proactive gastrostomy in patients with head and neck cancer.

Methods: Patients who received curative treatment from July 2010 to June 2011 were included (n=269). Associations between dependent variables (age, gender, tumour site, staging, treatment, p16 status, albumin, Malnutrition Screening Tool (MST) score), the protocol risk rating and requirement for proactive gastrostomy were examined.

Results: Current protocol correctly identified 81/88 (92%) high risk patients for gastrostomy, but incorrectly classified 32/181 (18%) low risk patients. Analysis of low risk patients with oral or oropharyngeal cancers, found p16-positive disease had 4.4 times greater odds (p=0.049), and those at risk of malnutrition had 4.5 times greater odds (p=0.019), of requiring gastrostomy.

Conclusions: Malnutrition risk and p16 status could be used to identify further patients who may benefit from proactive gastrostomy.

5.3.2 Manuscript

INTRODUCTION

Malnutrition and swallowing dysfunction are common among patients with head and neck cancer. This is linked to the aggressive nature and location of the disease and treatment side effects which include odynophagia, nausea and vomiting, xerostomia, poor appetite and dysphagia which in turn leads to weight loss and dehydration (Head & Neck Guideline Steering Committee, 2011; Kramer et al., 2014; Nicolini et al., 2013). Extensive research supports nutritional intervention, specifically enteral nutrition, to help patients meet their nutritional requirements and mitigate these side effects (Brown et al., 2014a; Brown et al., 2013b; Isenring et al., 2004; Jeffery, Sherriff, & Langdon, 2012). Although the optimal form of nutrition support is yet to be identified (Moor et al., 2010; Nugent et al., 2013), proactive gastrostomy placement (insertion of a feeding gastrostomy tube prior to treatment) in anticipation of adverse outcomes that may lead to malnutrition, has gained popularity (Orphanidou et al., 2011). As previous observational studies (Locher et al., 2013; Strom et al., 2013) have identified, predicting the requirement for proactive gastrostomy placement is often complicated by confounding factors and selection bias.

At our facility, the decision for proactive gastrostomy placement is based on a validated protocol (Figure 5-4) to categorise patients' level of predicted nutritional risk as high or medium/low based on risk factors which have been shown in the literature to increase dysphagia, weight loss and the need for tube feeding during treatment (Brown et al., 2013b). The protocol helps guide decision-making by the multidisciplinary team to determine appropriate nutrition and swallowing management, including recommendations for proactive gastrostomy placement and tube feeding, but the final decision also considers the individual patient circumstances such as the extent of dysphagia at presentation, any medical contraindications for tube placement and patient choice. Adoption of this protocol locally has shown improved nutritional outcomes (Brown et al., 2014a) and decreased unplanned hospital admissions and length of stay (Hughes et al., 2013). However since their development nearly 10 years ago, additional factors have emerged in clinical practice that have the potential to impact on patient outcomes during treatment for head and neck cancer that were not previously considered.

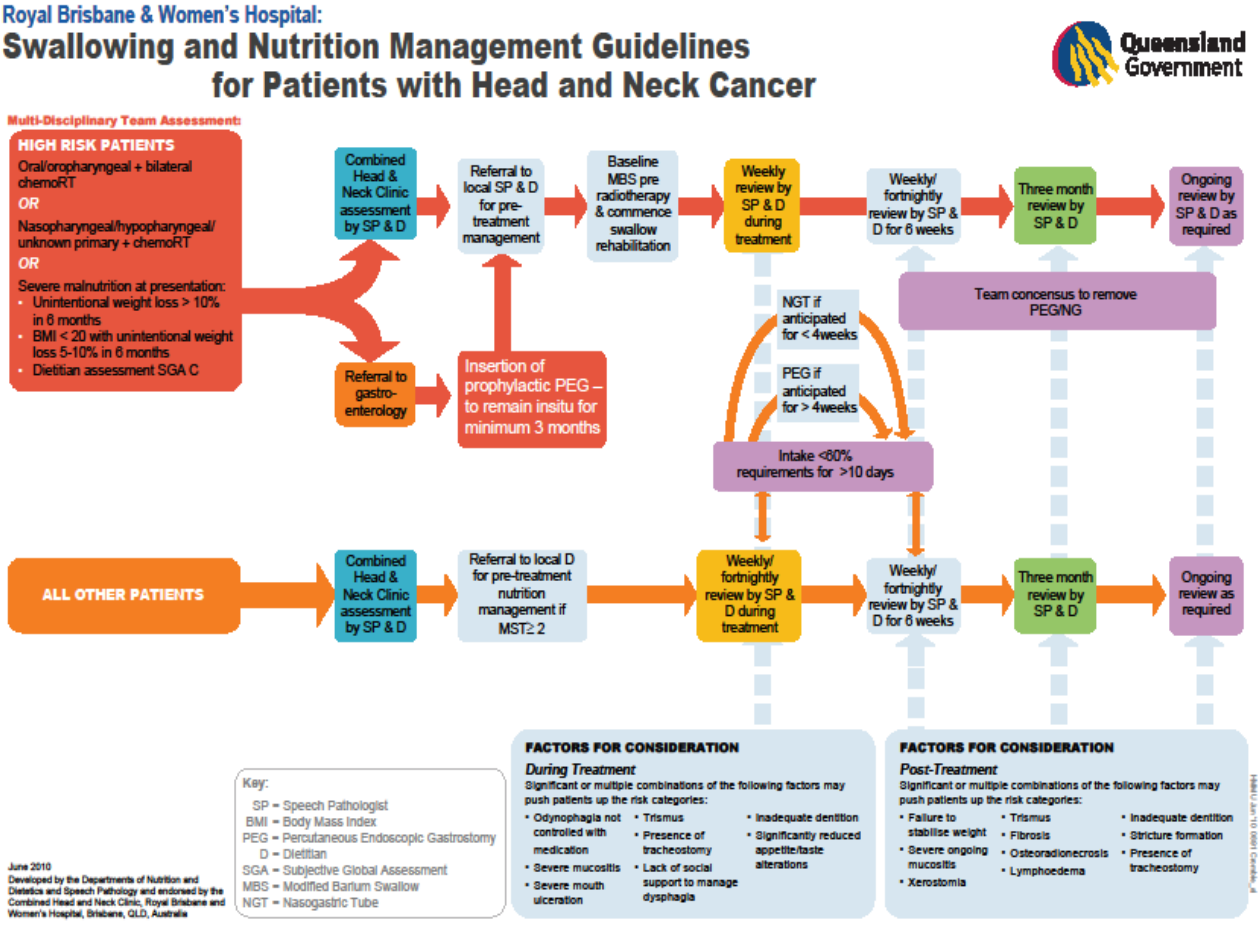

Figure 5-4: Royal Brisbane and Women's Hospital Swallowing and nutrition management guidelines for patients with head and neck cancer – revised version 2010

Original Source: Brown et al., 2016a

Firstly, a new international definition and classification of cancer cachexia was released in 2011, which is now defined in three stages – pre-cachexia, cachexia and refractory cachexia (Fearon et al., 2011). Initially, identification of cachexia was through the chief diagnostic criterion of non-oedematous weight loss of ≥5% in the last 12 months (Evans et al., 2008) and screening tools such as the Malnutrition Screening Tool (MST) have been previously recommended for use in cancer patients to detect this (Isenring et al., 2013).

Early identification of the pre-cachexia phase (weight loss of <5%) is now deemed important to enable early interventions (Couch et al., 2014; Lucia, Esposito, Rossi Fanelli, & Muscaritoli, 2012). However it has been suggested that significant biochemical and molecular changes may occur before any weight loss is evident (Couch et al., 2014; Lucia et al., 2012) and therefore markers such as C-reactive protein (CRP) and serum albumin which are linked to the inflammatory process in cachexia may also be useful as an early diagnostic indicator of this condition (Couch et al., 2007; Gupta & Lis, 2010).

Secondly, whilst chemoradiotherapy (CRT) has been linked with weight loss and the need for tube feeding (Silander et al., 2012; Strom et al., 2013), there are different types, doses and delivery schedules of chemotherapy used in treatment of HNC which have altered toxicity profiles (Espeli et al., 2012; Frenkel et al., 2013; Geeta et al., 2006; Ley et al., 2013; Walsh et al., 2011).

Cetuximab, a monoclonal antibody targeting the epithelial growth factor receptor (EGFR) was approved for use in Australia in 2007, following the pivotal results of the combination demonstrating superior response rates and survival compared to radiotherapy alone (Bonner et al., 2006) and therefore was a suitable alternative for patients unable to have chemotherapy. Consequently, the planned chemotherapy agent and dose used may have differing effects on inhibiting patients from meeting their nutritional requirements and so may be appropriate for inclusion in the criteria for determining placement of proactive feeding tubes.

Finally, in recent years there has been an increasing incidence of human papillomavirus (HPV)-associated oropharyngeal tumours (Jemal et al., 2013). These patients present with distinct carcinogenesis, risk factors, and clinical presentation compared to HPV-negative disease (Benson et al., 2013; Bonilla-Velez et al., 2013; Evans et al., 2013; Gillison et al., 2008; Petrelli et al., 2014; Ramqvist & Dalianis, 2010). This unique disease subset demonstrates a better response to treatment, overall survival, and progression-free survival (Benson et al., 2013) compared to HPV-negative head and neck cancer.

As such, research into the de-intensification of treatment in order to reduce toxicities without compromising oncological outcomes are underway. However, the impact of HPV (specifically p16 status; an immunochemistry marker) on nutrition outcomes in head and neck cancer populations is unknown.

Whilst our previous research has indicated that the protocol has a high sensitivity and specificity in predicting patients that would benefit from a proactive gastrostomy (Brown et al., 2016b), the aim of this study was to explore whether any of these other newly identified relevant clinical factors should also be considered and incorporated into the protocol to improve the validity even further.

MATERIALS AND METHODS

Study Setting

In this single institutional cohort study, a convenience sample was used from a previous quality improvement project. This sample was taken from patients who attended the tertiary hospital for surgical or oncological curative treatment from July 2010 to June 2011. All patients are seen by the dietitian automatically during their surgical admissions or radiotherapy treatment. Patients are classified as a high or low nutrition risk according to our local protocol (Figure 5-4) (Brown et al., 2016b). Patients in the high risk category are those recommended for a proactive gastrostomy placement prior to treatment. The criteria is primarily based on tumour site and planned treatment, as well as the degree of weight loss or malnutrition at baseline. Full details are available in Figure 5-4. The risk rating was determined at the multidisciplinary meeting based on clinical staging for those treated definitively and on pathological staging based on those treated adjuvantly. This ensured patients were appropriately classified following upstaging or down staging after surgery. Exclusion criteria included non-head and neck tumours, benign disease, treatment of palliative intent or patients who declined treatment, and those less than 18 years old (Figure 5-5). Those participants with missing weight data or no medical chart access were also excluded. All participants provided previous consent for their medical charts to be used in quality improvement projects. Ethics approval for this study was granted by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/14/QRBW/92) who approved this project for Low and Negligible Risk Research as set out in the National Health and Medical Research Statement.

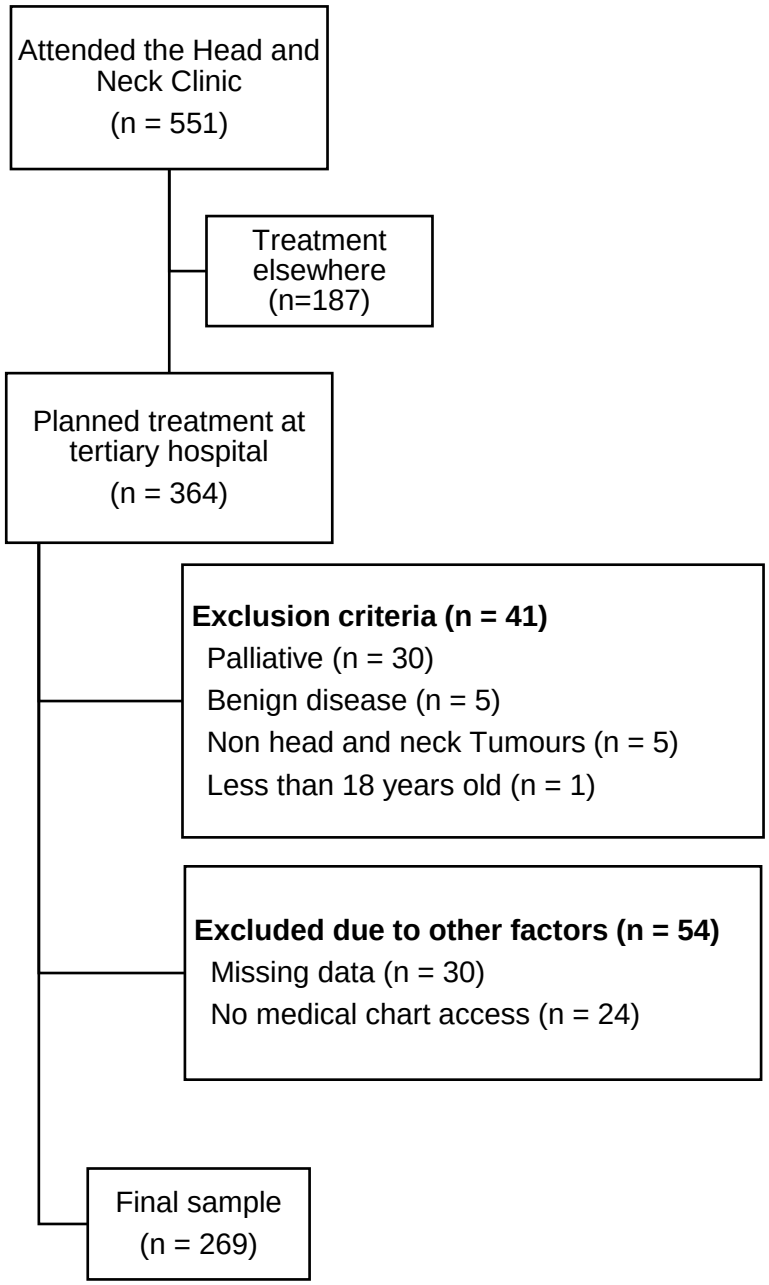

Figure 5-5: Exclusion criteria applied to cohort

Data collection

Information was gathered through retrospective chart audits and electronic medical data base review. The following variables were collected and grouped as follows: age, gender, tumour sites (oral = oral cavity; oropharyngeal = oropharynx, nasopharynx, hypopharynx and unknown primary; other = larynx and other sites), T-classification (T0 and TX; T1 and T2; T3 and T4; recurrent), N-classification (N0; N1, N2a and N2b; N2c and N3; recurrent), overall treatment which was then categorised according to surgical status (yes or no) and radiation status (surgery alone; radiotherapy and postoperative radiotherapy; CRT and postoperative CRT), intended chemotherapy treatment (high-dose cisplatin, low-dose weekly cisplatin or cetuximab), radiotherapy technique (helical intensity-modulated radiotherapy (H-IMRT) or 3D conformal) and the MST score (a malnutrition screening tool validated in radiation oncology patients which considers recent nutritional intake and weight loss (Ferguson et al., 1999a)). The following pathology tests were also reviewed: pre-treatment serum albumin, pre-treatment CRP and the results from immunochemistry to determine p16 status (a surrogate marker for HPV) as either positive or negative. Blood results were included if they were taken within one month prior to treatment commencement. Tumour sites and classifications were coded using the International Classification of Disease-Version 10-Australian Modification, (National Centre for Classification in Health, 2010) and the Union for International Cancer Control Tumour, Node, and Metastasis (TNM) staging system.

Outcome measures

The outcome variables in the dataset were; percentage weight loss during treatment (from baseline at diagnosis to the end of treatment), type of feeding tube inserted, and then where applicable, the use of gastrostomy (actively used for any period of time or unused), and duration of nasogastric tube use (short-term <4 weeks, or long-term >4 weeks). These variables were used to determine the primary outcome of whether each patient was deemed to require or not require a proactive gastrostomy according to the following criteria. Patients were deemed to meet the criteria ‘needed a proactive gastrostomy’ when; a) a patient had an actively used gastrostomy OR b) a patient had a long-term nasogastric feeding tube for greater than four weeks OR c) a patient did not have an actively used gastrostomy or a long-term nasogastric feeding tube for greater than four weeks AND had ≥10% weight loss.

Conversely patients were deemed to meet the criteria 'did not need a proactive gastrostomy' when; a patient did not have an active gastrostomy or long-term feeding tube AND had <10% weight loss. Specifics of this definition have been described elsewhere (Brown et al., 2013b).

Statistical Analysis

The analysis was organised into three distinct stages for this study. (1) Determine which baseline independent patient variables are associated with the protocol risk category rating. (2) Determine if any of the baseline independent patient variables not already associated with the protocol risk category rating are associated with the primary outcome of proactive gastrostomy requirement. (3) Determine if any of the baseline independent patient variables are useful in discriminating between those patients that were deemed low risk but would have benefited from a proactive gastrostomy and those that were correctly deemed low risk.

Descriptive characteristics were determined using frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Pearson's chi-squared test, or Fisher's Exact test when necessary, were used to test associations between categorical variables. Logistic regression was used to investigate the outcome "needed a proactive gastrostomy", and variables were entered into the multivariate model if $p<0.2$ on univariate analysis. Overall statistical significance was set at $p<0.05$. Data was analysed using IBM SPSS database and statistical package (version 22, SPSS Inc., Chicago).

RESULTS

Of the total 269 patients in this study, the majority were males (77%) and greater than 65 years old (42%). The tumour sites were evenly distributed with oral cavity (30%), oropharyngeal (34%) and other (36%). The oropharyngeal group consisted primarily of oropharynx (n=65), followed by hypopharynx (n=14), nasopharynx (n=4) and unknown primary (n=9). The other group consisted of larynx (n=18) and all other salivary and skin tumours (n=78).The majority of all patients received multi-modality treatment (75%), including 34% treated with definitive CRT, 41% surgery and adjuvant (chemo)radiotherapy and only 15% surgery alone. Additional patient characteristics are summarised in Table 5-4. Given the low proportion of patients with a recorded pre-treatment CRP value (n = 6), this variable was excluded from further statistical analyses.

Table 5-4: Patient demographics and clinical characteristics including comparison between high and low risk groups using current protocol definitions

Variable name	Variable categories	Total (n=269)	High Risk (n=88)	Low Risk (n=181)	p-value
		N (%)			
Gender	Male	208 (77.3)	70 (79.5)	138 (76.2)	0.544
	Female	61 (22.7)	18 (20.5)	43 (23.8)	
Age (years)	<50	32 (11.9)	14 (15.9)	18 (9.9)	0.069
	50-65	123 (45.7)	45 (51.1)	78 (43.1)	
	>65	114 (42.4)	29 (33.0)	85 (47.0)	
Tumour Site	Oral	81 (30.1)	18 (20.5)	63 (34.8)	<0.001
	Oropharynx	92 (34.2)	68 (77.3)	24 (13.3)	
	Larynx & other	96 (35.7)	2 (2.3)	94 (51.9)	
T Classification (n=267)	T0 & TX	20 (7.5)	4 (4.5)	16 (8.9)	0.001
	T1 & T2	114 (42.7)	43 (48.9)	71 (39.7)	
	T3 & T4	94 (35.2)	38 (43.2)	56 (31.3)	
	Recurrent	39 (14.6)	3 (3.4)	36 (20.1)	
N Classification (n=267)	N0	95 (35.6)	9 (10.2)	86 (48.0)	<0.001
	N1, N2a, N2b	103 (38.6)	51 (58)	52 (29.1)	
	N2c, N3	30 (11.2)	25 (28.4)	5 (2.8)	
	Recurrent	39 (14.6)	3 (3.4)	36 (20.1)	
Radiotherapy type (n=229)	H-IMRT	75 (32.8)	53 (60.9)	22 (15.5)	<0.001
	3D Conformal	154 (67.2)	34 (39.1)	120 (84.5)	
MST score (n=184)	0-1	135 (73.4)	52 (73.2)	83 (73.5)	0.975
	2 to 5	49 (26.6)	19 (26.8)	30 (26.5)	
Serum Albumin (n=193)	>35	168 (87.0)	64 (80.0)	104 (92.0)	0.014
	<35	25 (13.0)	16 (20.0)	9 (8.0)	
Overall treatment	RT	28 (10.4)	0 (0)	28 (15.5)	<0.001
	CRT	91 (33.8)	77 (87.5)	14 (7.7)	
	Surgery + RT	95 (35.3)	2 (2.3)	93 (51.4)	
	Surgery + CRT	15 (5.6)	8 (9.1)	7 (3.9)	
	Surgery	40 (14.9)	1 (1.1)	39 (21.5)	
Radiation Status	Surgery alone	40 (14.9)	1 (1.1)	39 (21.5)	<0.001
	Radiotherapy	123 (45.7)	2 (2.3)	121 (66.9)	
	CRT	106 (39.4)	85 (96.6)	21 (11.6)	
Surgery Status	No	119 (44.2)	77 (87.5)	42 (23.2)	<0.001
	Yes	150 (55.8)	11 (12.5)	139 (76.8)	
Chemotherapy Type (n=106)	Cisplatin (weekly)	40 (37.7)	29 (34.1)	11 (52.4)	0.278
	Cisplatin (high dose)	50 (47.2)	43 (50.6)	7 (33.3)	
	Cetuximab	16 (15.1)	13 (15.3)	3 (14.3)	
p16 status (n=163)	Positive	59 (36.1)	45 (57.7)	14 (16.5)	<0.001
	Negative	104 (63.8)	33 (42.3)	71 (83.5)	
Smoking Status (n=145)	Non Smoker	33 (22.8)	8 (14.8)	25 (27.5)	0.080
	Current Smoker	45 (31.0)	22 (40.7)	23 (25.3)	
	Ex-smoker	67 (46.2)	24 (44.4)	43 (47.3)	

Abbreviations: H-IMRT=Helical Intensity-Modulated Radiotherapy; MST=Malnutrition Screening Tool; RT=Radiotherapy; CRT= Chemoradiotherapy.

Based on the current protocol 88 patients were deemed high risk; of those 88 patients 92% (n=81) were correctly identified as high risk (true positives) whilst only 8% (n=7) were false positives. Of the 181 that were deemed low risk, 18% (n=32) were deemed to have been candidates for a proactive gastrostomy and 82% (n=149) were correctly identified to not require a proactive gastrostomy (true negatives). Thus the protocol has a high sensitivity and specificity and a high positive predictive value (92%) in classifying those who would benefit from a proactive gastrostomy (Brown et al., 2016b). Age was not found to be associated with the outcome “met criteria for proactive gastrostomy” (p=0.463), however smoking status was associated (p=0.041). Current smokers were more likely to meet the criteria for proactive gastrostomy (38% vs 25%) and non-smokers were less likely to meet the criteria (14% vs 30%).

On exploration of the characteristics associated with protocol risk rating, it was found that patients classified as high risk tended to have oropharyngeal tumours (p<0.001), were receiving concurrent chemotherapy (p<0.001), were receiving H-IMRT (p<0.001), were not undergoing surgery (p<0.001), and had higher T-classification (p=0.001) and N-classification cancers (p<0.001). They also were more likely to have p16-positive cancers (p<0.001), and had serum albumin levels greater than 35 (p=0.014). There was no association with age, gender, or MST or with the new variable of interest - chemotherapy type (p=0.278) (Table 5-4).

As there is a high potential for confounding associations between all these variables, and as tumour site and treatment are the primary variables used for the current protocol, further investigation was carried out to see if these two variables were correlated with any other dependent variables. All variables were found to be correlated to tumour site and/or treatment, with the exception of MST and serum albumin (Table 5-5). However neither of these were subsequently found to be associated with the primary outcome “met criteria for proactive gastrostomy” (MST, p=0.271 and serum albumin, p=0.126), and so would not be beneficial in adding into the protocol high risk category definition. Overall this shows the current two variables used in the protocol (site and treatment) incorporate almost all other clinical factors and are therefore good proxies for all these other factors that may contribute to the predicted need for a gastrostomy.

On review of the low risk patients only (n=181) to determine which characteristics are common to those that “met criteria for proactive gastrostomy” (n=32), we found that the only variable associated was MST, p=0.039. Logistic regression indicates that the odds of requiring a proactive gastrostomy when identified at risk of malnutrition (MST = 2 – 5) are 2.7 times greater than those not at risk of malnutrition (MST = 0 – 1) (p=0.044). This is based on the 113 low risk patients who had MST recorded (Table 5-6).

To determine the role of p16 status, sub group analysis was performed on patients that were deemed low risk and had an oral or oropharyngeal tumours (n=87), as p16 status is not routinely available to those with other cancers (i.e. laryngeal, skin, salivary). In this sub group, 19 patients met the criteria for proactive gastrostomy, and this was again only significantly associated with MST (p=0.030), and moderately associated with p16 status (p=0.074). Therefore MST and p16 status were eligible to be entered into a logistic regression model. In this sub group of low risk patients with an oral or oropharyngeal tumours, patients with p16-positive disease had 4.4 times greater odds of requiring a proactive gastrostomy than those who were p16-negative (p=0.049), and those at risk of malnutrition (MST = 2-5) had 4.5 times greater odds of requiring a proactive gastrostomy than those not at risk of malnutrition (MST= 0-1) (p=0.019) (Table 5-6).

Table 5-5: Statistical associations (p values) between all clinical variables and two of the variables that inform the current protocol high risk definition

Other Variables	Variables which inform current high risk definition	
	Tumour site	**Radiation Status**
Gender	<0.001	0.255
Age	0.004	0.03
Tumour site	N/A	<0.001
T Classification	<0.001	<0.001
N Classification	<0.001	<0.001
Radiotherapy type	<0.001	<0.001
MST	0.142	0.3
Serum Albumin	0.116	0.129
Radiation Status	<0.001	N/A
Surgery Status	<0.001	<0.001
Chemotherapy type	0.061	N/A
p16 status	<0.001	<0.001
Risk Rating	<0.001	<0.001

Abbreviations: N/A=not applicable; MST=Malnutrition Screening Tool.

Table 5-6: Logistic regression models for predicting proactive gastrostomy

Cohort	Variable	B	P value	Exp(B)	95% C.I. for Exp(B)	
					Lower	**Upper**
All low risk patients (n=113)	**MST**					
	0-1	0	reference	1		
	2-5	0.99	0.044	2.69	1.03	7.05
Low risk patients with oral or oropharyngeal tumour only (n=67)	**p16 status**					
	Negative	0	reference	1		
	Positive	1.48	0.049	4.41	1.01	19.31
	MST					
	0-1	0	reference	1		
	2-5	1.50	0.019	4.48	1.29	15.64

Abbreviations: CI=confidence interval; MST=Malnutrition Screening Tool.

DISCUSSION

This study aimed to investigate potential new clinical markers on their ability to predict the requirement of a proactive gastrostomy for patients with head and neck cancer. This included; albumin as a marker of pre-cachexia, p16 as a marker of HPV status and the prescribed chemotherapy regimen. The current protocol primarily use tumour site and treatment (either oral cavity or oropharynx with bilateral CRT or nasopharynx, hypopharynx or unknown primary with CRT) as the current clinical factors to predict the need for proactive gastrostomy. Severe malnutrition is also part of the current high risk definition but is rarely used as a sole indicator, as it is often seen in conjunction with the tumour site and/or with the TNM stage which determines when CRT, rather than radiotherapy alone, is required. The use of tumour site and treatment to determine the risk rating also explains a number of the other associations seen with the high risk category. Tumours of larger size and/or in difficult locations where functional outcomes cannot be safely preserved are often recommended for definitive radiotherapy over surgery. Similarly patient selection for H-IMRT is based on whether the tumour site is critical to the swallowing functionality, or if extensive fields or bilateral neck irradiation is required. Therefore tumour site and staging has a great influence on overall treatment selection and helps explain the characteristics of the high risk population.

Whilst we have previously shown the guidelines in their current format have a high validity (Brown et al., 2016b), this study has confirmed that the two key variables of tumour site and treatment are strongly associated to a number of other clinical variables, thus eliminating the need to include any additional variables which would unnecessarily add to the complexity of the high risk criteria definition. The significance of tumour site is expected given the role of the pharynx in the swallowing process. This supports findings from previous studies which also documented tumour site to be a significant independent predictive factor for the requirement of proactive tube placement (Habib et al., 2014; Wermker, Jung, Huppmeier, Joos, & Kleinheinz, 2012).

Concurrent CRT has also consistently been reported in the literature to increase the need for nutritional support and enteral tube feeding (Locher et al., 2013) due to the enhancement of radiation side effects such as mucositis and dysgeusia as well as other severe toxicities associated with different chemotherapy agents which impact on a patients' ability to consume adequate nutrition orally.

The type of chemotherapy regimen has not been found to be a factor to assist predicting the need for proactive gastrostomy insertion in this study. This was also the case in the study by Wopken et al. (2014b) who reported that chemotherapy (regardless of the regimen) was a predictor of tube feeding at six months after treatment (Wopken et al., 2014b), and despite different toxicity profiles from different chemotherapy agents, the impact on weight loss and tube feeding is similar (Ye et al., 2013). Some studies suggest that the need for nutritional support is even greater in patients receiving Cetuximab treatment (Magrini et al., 2015; Walsh et al., 2011; Yokota et al., 2015). As such, it appears that CRT overall, regardless of dose or type, is most important for consideration.

This study also did not find a role for baseline serum albumin levels in predicting a patients' need for proactive gastrostomy, and the limitations of retrospective data collection meant that CRP could not be fully investigated. However the early identification of patients at risk of malnutrition remains an important consideration. A recent review focused on nutrition support in cancer patients, highlighted that malnourished patients have a poorer response to chemotherapy and higher risk of toxicity (Bozzetti, 2013) indicating that consideration of pre-treatment risk of malnutrition is important.

The MST is an appropriate validated malnutrition screening tool and has also been recommended for assisting in the identification of cachexia (Bauer et al., 2006). Further research into the ability of the MST or other tools to identify the pre-cachexia state would be of interest, and provide a simpler and less invasive approach than reliance on blood samples for albumin or other inflammatory markers that are not routinely measured.

This study did find that low-risk patients with an oral or oropharyngeal tumour, with p16-positive disease had 4.4 times greater odds of requiring a proactive gastrostomy than those who were p16-negative. This subset of patients are likely to be those undergoing unilateral radiotherapy treatment and therefore not identified as a high risk patient who receives bilateral treatment. This finding of positive p16 status increasing the need for proactive gastrostomy may be explained by other studies which have reported that patients with p16-positive disease have a higher acute toxicity than p16-negative disease (Becker-Schiebe, Sperling, Pinkert, & Hoffmann, 2015), and rates of dysphagia and organ toxicity are higher in patients with p16-positive disease (Tehrany et al., 2015).

We also found that current smoking status had an association with the need for a proactive gastrostomy, which is in line with other studies (Mangar et al., 2006). However as p16-positivity is generally associated with non-smoking (Marur, D'Souza, Westra, & Forastiere, 2010), (although it is possible to see in current smokers), this suggests some potential contradiction of our finding of p16-positive disease also being associated with need for proactive gastrostomy. There are likely multifactorial reasons for this. Due to the different demographics and clinical presentation of the p16-positive and negative populations a difference in quality of life has been reported, with a higher baseline quality of life and a larger decrease in quality of life immediately post-treatment for patients with p16-positive disease (Maxwell et al., 2014; Sharma et al., 2012). This may be explained by the increased toxicity seen, or may be due to other psychosocial factors yet to be fully explored, such as differences in coping strategies and levels of psychological distress. These may all be other important variables to consider in the prediction of proactive gastrostomy requirement.

The main limitations of this study were the retrospective study design and the large amounts of missing data, in particular smoking status and immunochemistry for p16 (not routinely requested in patients with non-mucosal tumour sites at this facility). Therefore there were only 67 patients included in the final model due to missing data, and only 16 of which met the outcome for proactive gastrostomy. As such, these results should be interpreted with caution due to small sample sizes in some groups resulting in large confidence intervals.

Dysphagia at presentation was not included as a variable for investigation, although the consideration of tumour site and volume may also account for this as a surrogate marker (Colangelo, Logemann, & Rademaker, 2000). Furthermore, this study did not consider social status which has been reported as a significant predictor for proactive gastrostomy placement in a prior study (Locher et al., 2013) and may be an important variable to improve the predictive ability of these guidelines. Another variable to also consider for future studies is the radiotherapy dose to the pharyngeal constrictor muscles and mylo/geniohyoid complex, as it has been shown that the dose and volume to these are associated with dysphagia and gastrostomy tube dependence (Dale et al., 2016; Li et al., 2009). Multivariate analysis including these variables would then help determine any confounding relationships between radiotherapy dose, tumour site and p16 status, or indeed if p16 status could be used as a surrogate marker of the oropharynx and thus constrictor dose.

Overall, the findings support the current high risk criteria in the swallowing and nutrition guidelines which currently consider treatment type, tumour site and nutritional status. These results suggest that the current guidelines, whilst only made up of three variables, act as proxies for almost all other clinical factors. The findings do not support the addition of serum albumin, p16 status or chemotherapy type or dose in the high risk criteria. However using the MST (and p16 status in oral or oropharyngeal tumours) may help identify other low risk patients that do actually require a proactive gastrostomy, and thus improve the guidelines' sensitivity.

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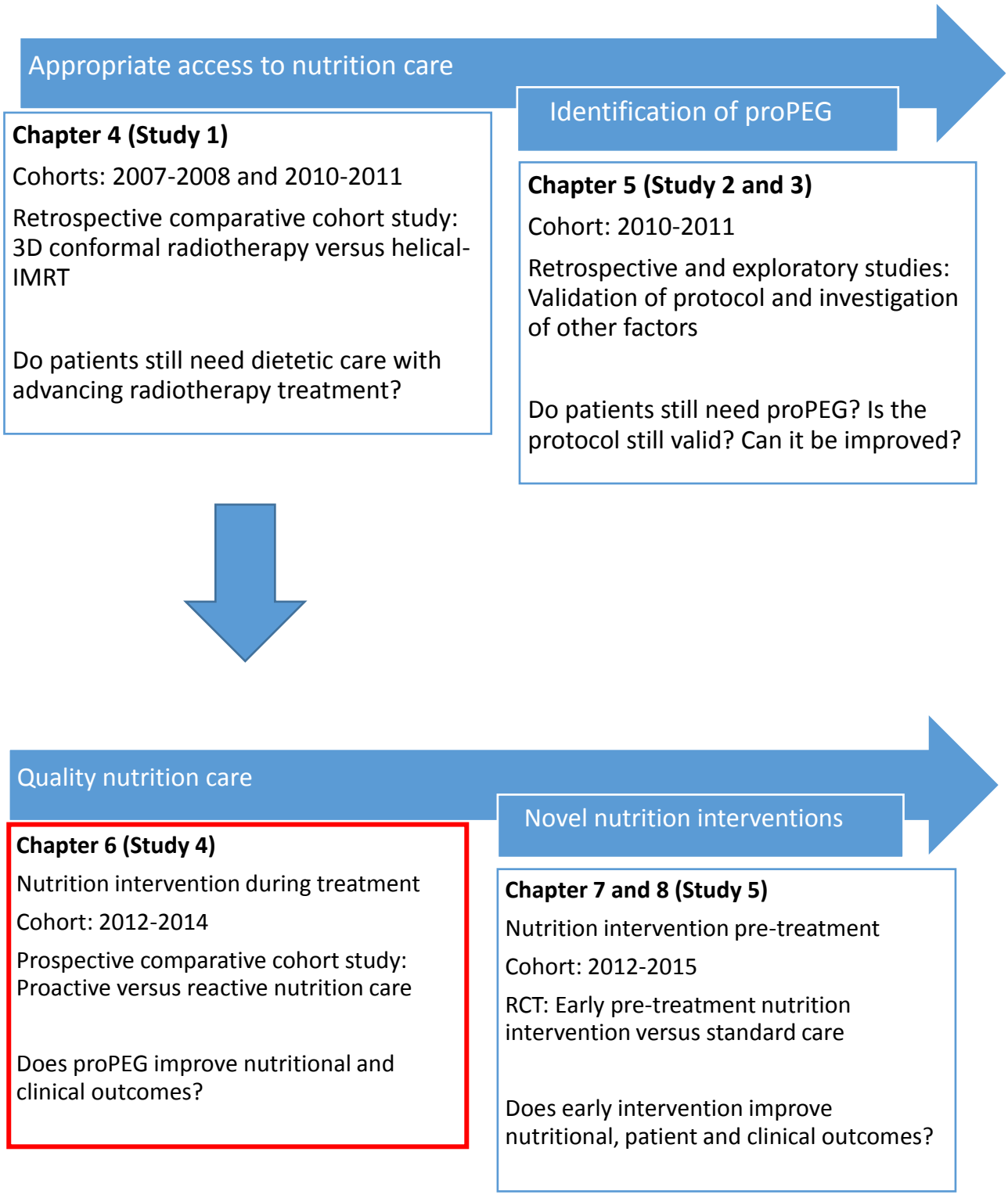
5.4 Chapter summary

The results of this study have demonstrated that the updated protocol remains valid for predicting who would benefit from proPEG in a mixed cohort of patients receiving 3D conformal and helical-IMRT. In comparison to the original validation study, there is an improvement in sensitivity (from 54% to 72%) and a slight increase in specificity (from 93% to 96%). There were a few other clinical differences noted between the cohorts such as a reduction in laryngeal cancers and recurrent tumours, an increase in advanced N stage disease and a reduction in treatment with radiotherapy alone. It is possible that these changes may be attributed to reduction in smoking behaviours (Luke, Yeoh, & Roder, 2008) as well as the increasing incidence of HPV-related oropharyngeal tumours (Jemal et al., 2013) which are usually treated with multimodality treatment due to more extensive nodal involvement (Mallen-St Clair et al., 2016).

There was no additional benefit of adding the other factors under investigation (p16 status, chemotherapy type, albumin or CRP) to the high risk definition, as the two key variables currently used (tumour site and treatment) were found to be related to almost all other variables and thus were sufficient predictors on their own. This retains a simple predictive model which is highly effective with a positive predictive value of 92%.

To improve the low risk definition and identify patients who would have benefited from proPEG (n=32, 18%) a baseline malnutrition screening tool (MST) score of two or more increased the odds 2.7 fold of requiring a tube. The role of p16 status in the low risk definition was inconclusive as whilst it potentially helped to identify the need for tube feeding in a sub-group of patients with oral or oropharyngeal cancer (p16-positive disease had a 4.4 increased odds compared to p16-negative disease), this was based on a limited sample size of patients who had a p16 test completed, and findings need to be confirmed in a larger sample size.

In summary it was concluded to continue with the current protocol in its current format. This research illustrates the importance of quality improvement work to continually re-evaluate procedures and interventions to ensure they remain relevant in dynamic healthcare environments with changing disease profiles and evolving treatments.


Appropriate access to nutrition care
Identification of proPEG
Chapter 4 (Study 1)
Cohorts: 2007-2008 and 2010-2011
Retrospective comparative cohort study: 3D conformal radiotherapy versus helical-IMRT
Do patients still need dietetic care with advancing radiotherapy treatment?
Chapter 5 (Study 2 and 3)
Cohort: 2010-2011
Retrospective and exploratory studies: Validation of protocol and investigation of other factors
Do patients still need proPEG? Is the protocol still valid? Can it be improved?
Quality nutrition care
Novel nutrition interventions
Chapter 6 (Study 4)
Nutrition intervention during treatment
Cohort: 2012-2014
Prospective comparative cohort study: Proactive versus reactive nutrition care
Does proPEG improve nutritional and clinical outcomes?
Chapter 7 and 8 (Study 5)
Nutrition intervention pre-treatment
Cohort: 2012-2015
RCT: Early pre-treatment nutrition intervention versus standard care
Does early intervention improve nutritional, patient and clinical outcomes?

6.1 Chapter overview

The findings in this chapter have been published in the Journal of the Academy of Nutrition and Dietetics (Journal Impact Factor 3.609; Ranked 19/80 Nutrition & Dietetics category; Quartile 1). Section 6.2 and 6.3 are presented in their accepted format prior to publication.

Despite the evidence outlined in previous chapters to demonstrate the critical need for nutrition intervention and the validity of the protocol to identify patients who would benefit from proPEG, we observed that adherence to the protocol by the multidisciplinary team started to decline over time. Adherence rates to the high risk category recommendation to place a proPEG had fallen to just 60% in 2015 (Appendix C – 11.3.6). Therefore the aim of the study in this chapter was to compare the nutritional and clinical outcomes of all patients classified as high risk who were having treatment at the RBWH based on whether they received a proPEG (adherence to local protocol recommendation) or whether they were managed reactively (non-adherence to local protocol recommendation).

Results of this study were presented at the following international conference: World Congress of Larynx Cancer, Cairns, Australia, 2015 (Appendix C – 11.3.7).

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6.2 Abstract

Background: The optimal method of tube feeding for patients with head and neck cancer remains unclear. A validated protocol is available which identifies high nutritional risk patients who would benefit from prophylactic gastrostomy tube placement. Adherence to this protocol is ultimately determined by clinical team discretion or patient decision.

Objective: The study aim was to compare outcomes following adherence and non-adherence to this validated protocol thus comparing a prophylactic and reactive approach to nutrition support in this patient population.

Design: Prospective comparative cohort study. Patients were observed during routine clinical practice over two years.

Participants/setting: Patients with head and neck cancer having curative intent treatment between August 2012 and July 2014 at a tertiary hospital in Queensland, Australia, were included if assessed as high nutrition risk according to the validated protocol (n=130). Patients were grouped according to protocol adherence as to whether they received prophylactic gastrostomy as per protocol recommendation (proPEG, n=69) or not (noPEG, n=61).

Main outcome measures: Primary outcome was percentage weight change during treatment. Secondary outcomes were feeding tube use and hospital admissions.

Statistical analysis performed: Chi-square, Fishers Exact and Two Sample T tests were performed to determine differences between the groups. Linear and logistic regression were used to examine weight loss and unplanned admissions respectively.

Results: Patient characteristics; 88% male, median 59 years old, with predominantly stage IV oropharyngeal cancer receiving definitive chemoradiotherapy. Statistically significantly less weight loss in the proPEG group (7.0% versus 9.0%, p=0.048) and more unplanned admissions in the noPEG group (82% versus 75%, p=0.029). In the noPEG group 26 patients (43%) required a feeding tube or had ≥10% weight loss.

Conclusion: Prophylactic gastrostomy improved nutrition outcomes and reduced unplanned hospital admissions. Further investigation of characteristics of patients with minimal weight loss or feeding tube use could help refine and improve the protocol.

6.3 Manuscript

INTRODUCTION

The role of dietary counselling in improving nutrition outcomes for patients with head and neck cancer has been well documented (Garg et al., 2010; Langius et al., 2013c), but the optimal management with patients requiring enteral tube feeding remains unclear and so no firm recommendations can be made (Langius et al., 2013c; Nugent et al., 2013). The debate in the literature continues as to whether patients with head and neck cancer should have a nasogastric tube or gastrostomy tube (Corry et al., 2008; Wang et al., 2014a) and the optimal timing of gastrostomy placement (Bradley, Brown, & Paleri, 2015; Talwar & Findlay, 2012). Enteral feeding tubes can either be placed prior to the commencement of treatment in anticipation of the need for tube feeding later on (prophylactic) or they can be placed during treatment when deemed required (reactive).

Studies comparing prophylactic versus reactive gastrostomy tube placement have mixed findings with some reporting less weight loss and fewer unplanned admissions (Lewis et al., 2014; Romesser et al., 2012) and others reporting no difference in nutrition outcomes, disease control or survival (Kramer et al., 2014; Williams et al., 2012). However rates of weight loss despite prophylactic gastrostomy placement were still clinically significant with approximately 10% weight loss or more at three months post-treatment (Brown et al., 2014a; Romesser et al., 2012) and at six months post-treatment (Kramer et al., 2014; Williams et al., 2012). The detrimental impact of malnutrition is well documented in terms of increased complications and healthcare costs in surgical patients (Gourin, Couch, & Johnson, 2014).The impact of poor nutrition outcomes has also recently been shown to have a significant prognostic effect on reducing survival outcomes for patients with head and neck cancer receiving radiotherapy (Langius et al., 2013b) and reducing their quality of life (Langius et al., 2013a), and thus is a key outcome measure to consider.

A validated protocol has been developed in Australia (Brown et al., 2016b) to identify patients who would benefit from gastrostomy insertion prior to treatment (Figure 6-1) and form part of the local hospital's procedure on the "Swallowing and Nutrition Management Guidelines for Patients with Head and Neck Cancer". The published protocol has been included as part of internationally endorsed dietetic guidelines on the nutritional management of patients with head and neck cancer (Head & Neck Guideline Steering Committee, 2011).

The true extent of protocol implementation is unknown, however the literature continues to report the approach to prophylactic gastrostomy selection remains varied between hospitals in Australia (Brown & Findlay, 2011) and worldwide (Koyfman & Adelstein, 2012; Moor et al., 2010; Orphanidou et al., 2011). The protocol uses clinical information at diagnosis based on tumour site and treatment plan and nutritional status to determine the patients' future nutrition risk rating and pathway of care. Patients classified as high risk are recommended for prophylactic gastrostomy placement and all other patients are managed reactively as required. This protocol has shown a number of positive outcomes with reduced unplanned admissions and length of stay (Hughes et al., 2013), improved nutrition outcomes with protocol adherence (Brown et al., 2014a), and no detrimental impact on swallowing function (Crombie et al., 2015).

Following local implementation at the tertiary hospital where the protocol was developed, initial adherence to the recommendation of prophylactic gastrostomy placement for high risk patients was 75% in 2008 (Brown et al., 2013b) which improved to 89% in 2010 (Brown et al., 2016b), however since then it has fallen to 60% in 2015 (unpublished data).This decline appeared to coincide with the introduction of helical intensity-modulated radiotherapy at this hospital site in 2010. The reason for the healthcare teams' decline in adherence to this recommendation has been based on the premise that helical intensity-modulated radiotherapy has improved dose reduction for organs at risk (Sheng et al., 2006), therefore reducing radiotherapy toxicities and potential nutrition impact symptoms which may imply aggressive nutrition support via a gastrostomy may no longer be required. However recent studies in this limited area of research to date have not supported this hypothesis reporting feeding tube use and weight loss is still high (Brown et al., 2015).

Using the validated protocol to identify a cohort of high nutrition risk patients, the aim of this study was to compare the nutritional and clinical outcomes of high nutrition risk patients who received a prophylactic gastrostomy tube (healthcare team adherence to the protocol recommendation) versus the outcomes of high nutrition risk patients who did not receive a prophylactic gastrostomy tube (healthcare team non-adherence to the protocol recommendation). These two groups thus enabled a comparison between a prophylactic and reactive approach to nutrition support in a similar group of patients within one institution. The hypothesis being that the prophylactic gastrostomy group would have less weight loss and fewer unplanned admissions than the group that did not receive a prophylactic gastrostomy and were managed reactively.

MATERIALS AND METHODS

Study design

This was a prospective cohort study to monitor the outcomes of high nutrition risk patients with head and neck cancer. On attendance at the multidisciplinary clinic for diagnostic staging and treatment planning, patients were assessed using the protocol (Brown et al., 2016a) to assign a nutrition risk rating of high or low, whereby high risk patients are recommended for prophylactic gastrostomy insertion (Figure 6-1). Patients were grouped as follows: those who received a prophylactic gastrostomy prior to commencement of radiotherapy, as per the protocol recommendation (proPEG) and those who did not receive a prophylactic gastrostomy prior to radiotherapy, against the protocol recommendation (noPEG), either due to a patient or Consultant decision. A prophylactic tube placement was defined as placement of a gastrostomy prior to commencement of treatment. Any feeding tubes (nasogastric or gastrostomy) placed after commencement of treatment were defined as reactive tube placement. Key outcome variables of interest were weight change during treatment, requirement for enteral tube feeding and incidence of unplanned hospital admissions and associated length of stay. Predictor variables included patient demographics and clinical characteristics such as tumour site, staging and treatment. Other covariates considered were the treating radiation oncologist.

Study population

Patients attending a tertiary hospital for treatment for head and neck cancer between August 2012 and July 2014 were assessed for inclusion in the study. The tertiary hospital provides specialist cancer care services for a wide geographical region of Australia. Patients were included in this study if they were assigned a high nutrition risk rating and received curative intent treatment at the tertiary hospital. The high nutrition risk group included patients with a diagnosis of oral or oropharyngeal cancer receiving bilateral chemoradiotherapy, patients with nasopharyngeal or hypopharyngeal cancers or unknown primaries receiving chemoradiotherapy and patients with severe malnutrition on presentation (Figure 6-1).

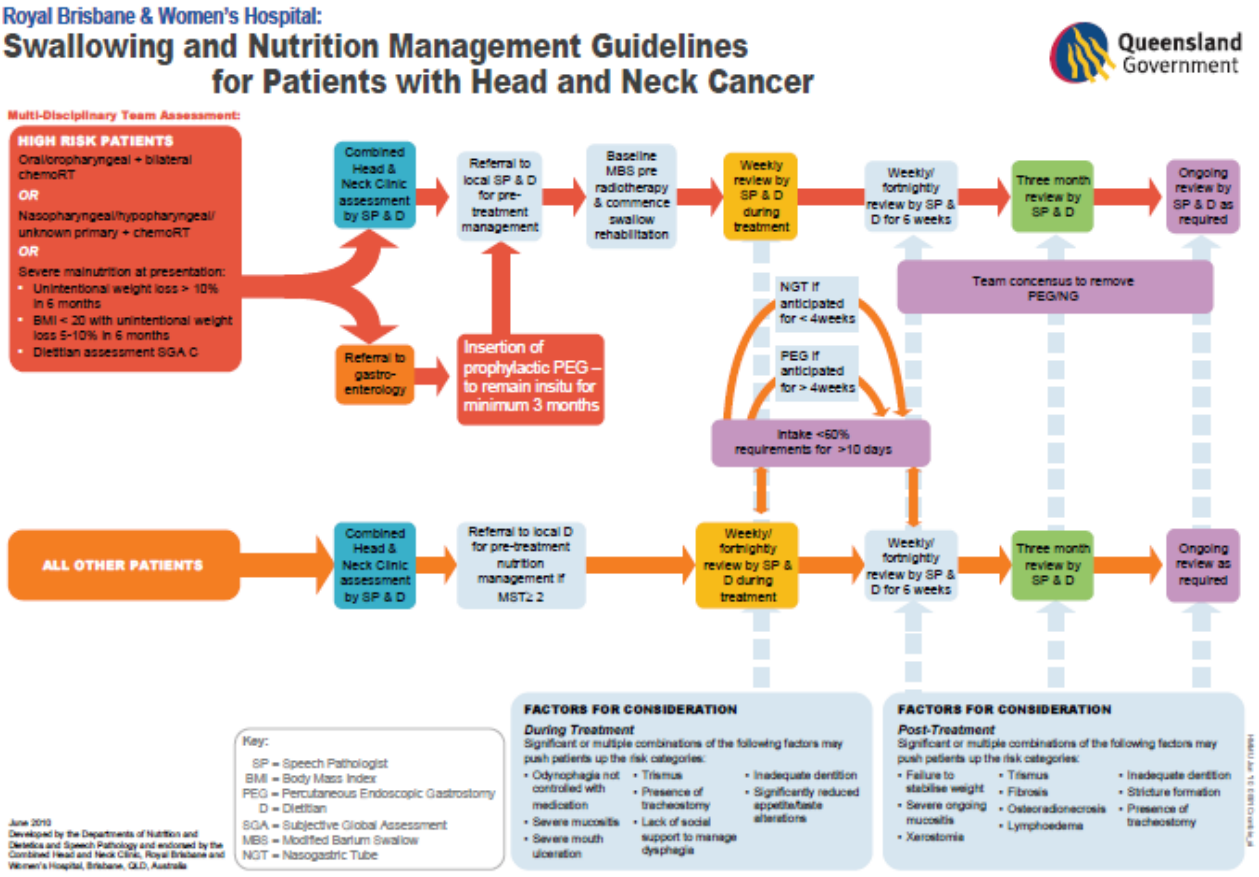

Figure 6-1: Royal Brisbane and Women's Hospital Swallowing and nutrition management guidelines for patients with head and neck cancer – revised 2010

Original Source: Brown et al., 2016a

Patients were excluded if they did not complete treatment or were unable to have a gastrostomy due to medical contraindications to the procedure. Treatment for this patient group consisted of helical intensity-modulated radiotherapy at a dose of 2Gy/day for five days/week, to total doses of 70Gy (definitive) or 60Gy (adjuvant). Chemotherapy was prescribed according to clinician discretion and consisted of either high dose Cisplatin, weekly Cisplatin or Cetuximab. The sample size was based on a convenience sample of eligible patients over the study time period.

Nutrition Management

All patients were screened at diagnosis using the recommended validated Malnutrition Screening Tool (Isenring et al., 2013) and at risk patients were referred to their local dietitian pre-treatment. During treatment, the dietitian and speech pathologist saw all patients weekly and the patient was referred to their local dietetic and speech pathology service in their home town for ongoing review post-treatment. Nutritional requirements were calculated using 1.2g protein/kg/day and 30kcal/kg/day (125 kilojoules/kg/day) (Isenring et al., 2013), using actual body weight unless the patient had a body mass index >25kg/m^2, and then adjusted body weight was used.

Patients were advised on a high protein, high energy diet with or without oral nutrition supplements to meet these requirements. Tube feeding was initiated in either group if patients were unable to maintain weight on oral intake alone (continued weight loss on weekly reviews) or diet history indicated oral intake was <60% of nutritional requirements and it was anticipated there would be no improvement over the next 10 days. Tube feeding was usually initiated as supplementary bolus feeding using a 1.5kcal/ml polymeric fibre containing feed unless there were concerns with tolerance in which case pump feeding was used, and feeding rates/volumes were titrated to meet nutritional requirements according to level of oral intake. The decision relating to tube type in the noPEG group was based on the anticipation of duration of enteral feeding (Arends et al., 2006). Full details of the nutritional management pathway is illustrated in Figure 6-1.

Outcome measures

Data were prospectively collected from medical charts during standard clinical care for the following predictor variables; baseline patient demographics (age, sex), and clinical characteristics (tumour site, cancer staging, treatment, and p16 status as an immunohistological marker of human papillomavirus-related tumours).The treating radiation oncologist (Consultant A, B, C or other) was also recorded as a covariate to account for any potential individual variations in decision-making or treatment planning. Outcome variables were also prospectively collected as described below and included: weight change during treatment; feeding tube use; hospital admissions and length of stay. Weight was measured in kilograms on standard scales at diagnosis and weekly during treatment as part of usual clinical care. Weight change during treatment was the difference in weights from diagnosis to the last week of radiotherapy and percentage weight change was calculated.

Feeding tube use was a binary outcome variable (yes or no) and defined as follows: for the proPEG group this was determined by whether patients actually used their gastrostomy tube for enteral feeding during treatment or not; for the noPEG group this was determined by whether patients required insertion of a reactive enteral feeding tube or not. This data was prospectively recorded by the clinical dietitian during weekly clinical reviews in assessing oral and enteral intakes. These feeding tube use outcomes were then taken into consideration with weight loss outcomes to determine retrospectively whether the patient met the final outcome criteria for truly requiring a prophylactic gastrostomy. These predefined criteria have been described fully elsewhere (Brown et al., 2013b), but essentially if a patient used a gastrostomy feeding tube or had a nasogastric feeding tube for more than four weeks or had 10% weight loss or more, they were deemed in retrospect to have met the criteria and would have benefited from placement of a prophylactic gastrostomy.

All admissions to the tertiary hospital from diagnosis to one month post-treatment were recorded prospectively by the dietitian during routine clinical care (this therefore excluded any admissions to private hospitals or those outside of the health service district). The dietitian was responsible for seeing patients routinely in weekly outpatient clinics and whenever admitted as an inpatient. The data were verified by checking the electronic hospital admission database systems and any missing data were collected by medical chart review. Admission type (planned or unplanned) and the timing of admission (pre/during treatment or post-treatment) were recorded. An unplanned admission was defined as an unexpected admission or a prolonged planned admission. Length of stay (LOS) was recorded in days for each admission type and any prolonged length of stays greater than seven days were noted. The reasons for unplanned admissions were coded as either a medical admission or a nutrition-related admission - sub divided into either: gastrointestinal disturbances (nausea, vomiting, diarrhoea, constipation); pain related to mucositis; enteral tube management issues (gastrostomy complications or insertion/management of a nasogastric tube); or other nutrition reasons (general poor intake, lack of appetite, dehydration, fatigue, or other social factors affecting nutritional intake/meal preparation e.g. temporary accommodation or social isolation from partners/family). Planned admissions were for administration of chemotherapy.

Ethical statement

The study was deemed exempt by the Human Research Ethical Committee at the Royal Brisbane and Women's Hospital according to the "National Statement on Ethical Conduct in Human Research (2007)".

Statistical considerations

Statistical analysis was performed between the proPEG and noPEG groups to determine if there were any baseline differences between the demographics and clinical characteristics. Categorical variables were summarized as counts and frequencies and compared using the Chi-square test. If the assumptions of the Chi-square test could not be met due to small expected cell counts, variables were collapsed if clinically meaningfully to do so, otherwise Fishers Exact test was used. Continuous variables were summarized as means and standard deviations and compared using the Two Sample T test (following assessment of normal distribution using the Shapiro-Wilk test).

The null hypothesis stated that there was no difference in outcomes (weight loss or unplanned admissions) between the proPEG and noPEG groups. Multivariate analysis was performed to adjust for any baseline differences or confounding effects. Percentage weight loss (as a continuous variable) was calculated from diagnosis to last week of radiotherapy and was examined using linear regression. Unplanned admissions and length of stay greater than seven days (as categorical variables) were examined using logistic regression. Predictor or covariate variables with a $p<0.2$ on bivariable analysis were entered into the multivariable models. Final variable selection for each multivariable model used Akaike's Information Criteria (AIC) with a backward stepwise algorithm. The final models reported were with the smallest objective AIC.

Statistical significance was set at $p<0.05$ for all analyses. Data were analysed using R Commander Version 2.1-7 and R version 3.1.3 (2015-03-09) (R Foundation for Statistical Computing, Vienna, Austria) (R Core Team, 2014).

Table 6-1: Summary of characteristics of patients with head and neck cancer receiving chemoradiotherapy – a comparison between patients with and without a prophylactic gastrostomy

Patient Characteristics	**All Patients (n=130)**		**proPEG [a] (n=69)**		**noPEG [b] (n=61)**		***P value* [c]**
	n (%)						
Age (years)							*P=0.64*
Mean ± SD	59.1 ± 9.7		59.5 ± 10.0		58.7 ± 9.5		
Median (range)	59 (37-83)		60 (40-83)		59 (37-81)		
Sex							*P=0.43*
Male	114	88%	62	90%	52	85%	
Female	16	12%	7	10%	9	15%	
Tumor Site [d]							*P=0.006*
Oral cavity	12	9%	5	7%	7	12%	
Oropharynx	100	77%	59	86%	41	67%	
Nasopharynx	4	3%	1	1%	3	5%	
Hypopharynx	6	5%	4	6%	2	3%	
Unknown primary	8	6%	0	0%	8	13%	
Tumor Classification [e]							*P=0.003*
T0	8	6%	0	0%	8	13%	
T1	22	17%	8	12%	14	23%	
T2	45	35%	25	36%	20	33%	
T3	31	24%	20	29%	11	18%	
T4	24	18%	16	23%	8	13%	
Nodal Classification [f]							*P=0.27*
N0	9	7%	4	6%	5	8%	
N1	7	5%	6	9%	1	2%	
N2a	8	6%	2	3%	6	10%	
N2b	65	50%	31	45%	34	56%	
N2c	35	27%	24	35%	11	18%	
N3	6	5%	2	3%	4	6%	
Overall Cancer Stage [g]							*P=0.17*
II	1	1%	0	0%	1	2%	
III	10	8%	8	12%	2	3%	
IV	119	91%	61	88%	58	95%	
Treatment							*P=0.10*
ChemoRT [h]	115	88%	64	93%	51	84%	
Adj ChemoRT [h]	15	12%	5	7%	10	16%	
p16 Status [i]							*P=0.58*
Positive	96	77%	52	79%	44	75%	
Negative	29	23%	14	21%	15	25%	
Treating Radiation Oncologist							*P<0.001*
Consultant A	40	31%	14	20%	26	43%	
Consultant B	36	28%	15	22%	21	34%	
Consultant C	33	25%	25	36%	8	13%	
Other	21	16%	15	22%	6	10%	

Abbreviations: [a] proPEG=prophylactic gastrostomy tube placed according to protocol. [b] noPEG=no prophylactic gastrostomy tube against protocol recommendation. [c] Continuous variables analysed using T tests and categorical variables analysed using Chi Square (unless stated otherwise) with statistical significance set at $p<0.05$. [d] Tumor site analysed with Fishers Exact test as following categories = Oropharynx/Nasopharynx vs Oral vs Hypopharynx vs Unknown Primary. [e] Tumor classification analysed as following categories = T0/T1 vs T2/T3 vs T4. [f] Nodal classification analysed as following categories = N0/N1/N2a vs N2b vs N2c/N3. [g] Overall cancer stage analysed as following categories = II/III vs IV. [h] ChemoRT=chemoradiotherapy. [i] p16= immunohistological marker of human papillomavirus-related tumors.

RESULTS

Patient characteristics

Over the two years, 139 patients were identified as high risk using the protocol and of these 130 were eligible for inclusion. The cohort characteristics were typical for a head and neck cancer profile and reflective of the criteria of the local protocol to determine the high risk rating. There were 69 patients who received a prophylactic gastrostomy according to the protocol recommendation (proPEG group) and 61 patients who did not receive a prophylactic gastrostomy (noPEG group). Protocol adherence to the high risk pathway is therefore 53% in this cohort. Statistically significant differences were seen between these two groups with respect to tumour site, tumour stage, and treating radiation oncologist (Table 6-1). All patients completed treatment and had follow-up data.

Weight outcomes

On bivariable analysis the variables associated with the outcome of weight loss (age $p=0.006$, site $p=0.033$, group $p=0.112$) and the differences between the groups (see Table 6-1 for variables with $p<0.2$) were entered into the model for multivariate analysis. Four variables remained significant in the final model (group, age, tumour site and treating Consultant) where AIC=403. The difference in weight loss between groups when adjusted for age, tumour site and treating Consultant was significant, with the noPEG group losing approximately 2% more weight than the proPEG group (ß = -1.95, 95% CI [-3.77, 1.76], $p=0.04$). Other associations with less weight loss on multivariate analysis were hypopharyngeal ($p=0.01$) or unknown primary tumours ($p=0.01$) compared to oropharyngeal/nasopharyngeal tumours, and increasing age ($p=0.002$).

Tube feeding

Overall 91% of patients used their prophylactic gastrostomy (n=63). Of the six patients who did not use their gastrostomy, three were non adherent to recommendations to use it resulting in one patient losing more than 10% body weight and two patients losing more than 5% weight. In the noPEG group, 13 patients required a reactive feeding tube (one patient had a gastrostomy and all others had a nasogastric tube) and 13 patients on oral nutrition support lost more than 10% of their body weight. Therefore overall 26 patients (43%) met the pre-determined criteria for prophylactic gastrostomy insertion on the basis of their outcomes (i.e. had reactive feeding tube or more than 10% weight loss) and therefore may have benefited from prophylactic tube feeding (Table 6-2).

Table 6-2: Summary of tube feeding outcomes in patients with head and neck cancer receiving chemo-radiotherapy – a comparison between patients with and without a prophylactic gastrostomy

Outcome	proPEG [a] (n=69)		noPEG [b] (n=61)	
	n	%	n	%
Tube use [c]	63	91%	13	21%
No tube use and ≥10% weight loss	1	1%	13	21%
No tube use and <10% weight loss	5	7%	35	57%
Met predefined outcome criteria for prophylactic gastrostomy [d]	64	93%	26	43%
Did not meet predefined outcome criteria for prophylactic gastrostomy	5	7%	35	57%

Abbreviations: [a] proPEG=prophylactic gastrostomy tube placed according to protocol. [b] noPEG=no prophylactic tube against protocol recommendation. [c] Tube use=use of prophylactic gastrostomy in the proPEG group or use of a reactive feeding tube in the noPEG group. [d] Met predefined outcome criteria for prophylactic gastrostomy = used a prophylactic gastrostomy feeding tube or reactive feeding tube or had ≥10% weight loss.

Sub analysis of the noPEG group to compare any differences between the patients that met the predefined outcome criteria for prophylactic gastrostomy (n=26) and those that didn't (n=35), found no statistically significant differences with respect to age, sex, tumour site, stage, treatment or p16 status (Table 6-3). Exploratory analysis found patients who met the criteria for prophylactic gastrostomy had a higher incidence of T3 and T4 tumours and nasopharyngeal tumours. The patients that did not meet the predefined outcome criteria for prophylactic gastrostomy had more unknown primary tumours, and more adjuvant rather than definitive chemoradiotherapy.

Comparison of outcomes within the proPEG group to compare any differences between the patients that met the predefined outcome criteria for prophylactic gastrostomy (n=64) and the five patients that didn't, found definitive chemoradiotherapy compared to adjuvant chemoradiotherapy (p=0.04) was associated with meeting the criteria, however analysis in this group was limited due to a small sample size of only five patients not meeting the criteria.

Admission outcomes

Approximately 50% of patients in each group were affected by an unplanned admission (p=0.877). Weight loss was the only other variable found to be associated with unplanned admissions for inclusion in multivariate analysis (p=0.110) and entered into the model with the differences between the groups (see Table 6-1 for variables with p<0.2) to give a final model with AIC=187. Logistic regression found no association with group and unplanned admissions (odds ratio (OR) 1.12, 95% CI [0.5, 2.6], p=0.803) or indeed any other independent predictors in the model.

There were 25% in each group affected by a LOS greater than seven days (p=0.995). Weight loss and N stage were the only other variables found to be associated with LOS for inclusion in multivariate analysis (p=0.050 and p=0.191 respectively) and were entered into the model with the baseline differences between the groups as before (see Table 6-1 for variables with p<0.2) to give a final AIC=154. Logistic regression found no association with group and LOS (OR 0.91, 95% CI [0.3, 2.6], p=0.859), however less weight loss had a reduced odds of a LOS greater than seven days and this was statistically significant (OR 0.91, 95% CI [0.8-1.0], p=0.036)

Table 6-3: Summary of characteristics of patients with head and neck cancer receiving chemoradiotherapy who did not receive a prophylactic gastrostomy as per protocol according to their final actual tube feeding and weight loss outcomes

Patient Characteristics	**Met predefined outcome criteria for prophylactic gastrostomy [a] (n=26)**		**Did not meet predefined outcome criteria for prophylactic gastrostomy (n=35)**		***P value*** [b]
	n (%)				
Age (years)					*P=0.64*
Mean ± SD	58.0 ± 11.2		59.2 ± 8.1		
Median (range)	59 (37-81)		59 (38-74)		
Sex [c]					*P=1*
Male	22	85%	30	86%	
Female	4	15%	5	14%	
Tumor Site [d]					*P=0.77*
Oral cavity	4	15%	3	9%	
Oropharynx	18	69%	23	66%	
Nasopharynx	3	12%	0	0%	
Hypopharynx	0	0%	2	6%	
Unknown primary	1	4%	7	20%	
Tumor Classification [e]					*P=0.39*
T0	1	4%	7	20%	
T1	6	23%	8	23%	
T2	9	35%	11	31%	
T3	5	19%	6	17%	
T4	5	19%	3	9%	
Nodal Classification [f]					*P=0.84*
N0	3	12%	2	6%	
N1	1	4%	0	0%	
N2a	2	8%	4	11%	
N2b	14	54%	20	57%	
N2c	5	19%	6	17%	
N3	1	4%	3	9%	
Treatment [c]					*P=0.49*
ChemoRT [g]	23	88%	28	80%	
Surgery & ChemoRT [g]	3	12%	7	20%	
p16 Status [h]					*P=0.25*
Positive	16	67%	28	80%	
Negative	8	33%	7	20%	

Abbreviations: [a] Met predefined outcome criteria for prophylactic gastrostomy = used a prophylactic gastrostomy feeding tube or reactive feeding tube or had ≥10% weight loss. [b] Continuous variables analysed using T tests and categorical variables analysed using Chi Square (unless stated otherwise) with statistical significance set at $p<0.05$. [c] Analysed using Fishers Exact test. [d] Tumor site analysed as following categories = Oropharyngeal vs all others. [e] Tumor classification analysed as following categories = T0/T1 vs T2 vs T3/T4. [f] Nodal classification analysed as following categories = N0/N1/N2a vs N2b vs N2c/N3. [g] ChemoRT=chemoradiotherapy. [h] p16 = immunohistological marker of human papillomavirus-related tumors.

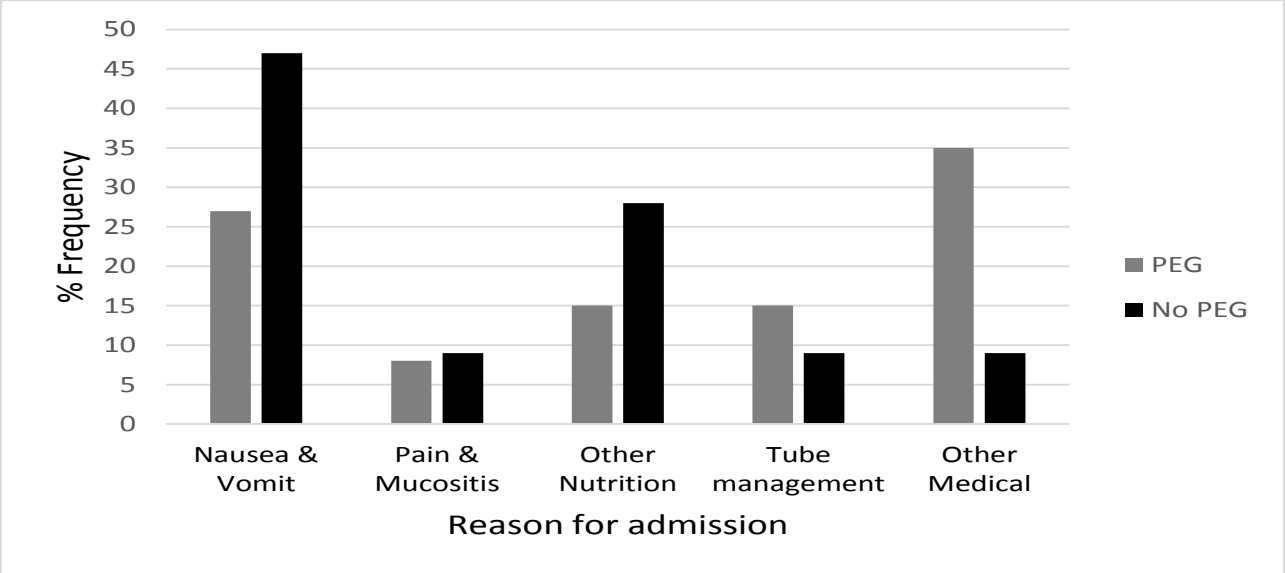

Figure 6-2: Reasons for unplanned nutrition related admissions in patients with head and neck cancer receiving chemoradiotherapy – a comparison between patients with a prophylactic gastrostomy (proPEG) and those managed reactively (noPEG)

Nutrition-related unplanned admissions were significantly higher in the noPEG group (91% vs 65%, p=0.0008). The reasons for unplanned admissions are summarized in Figure 6-2. While gastrostomy complications accounted for 15% of unplanned admissions, mainly due to prolonged admission post insertion for pain management, 9% of unplanned admissions in the noPEG group was for insertion and management of a nasogastric tube, and this was not statistically different. There was no procedure-related mortality in this cohort. The proportion of unplanned admissions during treatment (82% vs 74%, p=0.006) and post-treatment (40% vs 24%, p=0.006) was significantly higher in the noPEG group. The mean LOS per unplanned admission event was lower in the proPEG group (4.2 $\pm$ 5.1 days versus 6.2 $\pm$ 7.6 days, p=0.084). Overall the proPEG group had 106 admission events (excluding routine overnight admissions for insertion of gastrostomy) with total LOS of 374 days (46 days planned and 328 days unplanned), and the noPEG group had 107 admissions with total LOS of 355 days (63 days planned and 292 days unplanned).

Outcomes of patients excluded for gastrostomy placement

Of the eight patients who were medically contraindicated for gastrostomy placement, four required a nasogastric tube, one had ≥10% weight loss during treatment, one had 5.5% weight loss, and the other two patients died during treatment. One patient did not receive a gastrostomy due to scheduling difficulties and lost 16.5% body weight. In total, these nine patients had 226 days of unplanned admissions.

DISCUSSION

This comparative cohort study was initiated to determine the outcomes of patients who had reactive nutrition management as they did not receive a prophylactic gastrostomy as per protocol recommendations, and compare it to those that were managed prophylactically. In this study, the 2.0% difference in weight loss between groups in favour of the proPEG group was statistically significant following multivariate analysis (p=0.04). A number of studies have shown similar benefits with less weight loss with a prophylactic approach (Lewis et al., 2014; Silander et al., 2012), but others have found no difference (Kramer et al., 2014; Olson et al., 2013; Williams et al., 2012). Although the difference may appear small it is clinically significant, with a recent large prospective cohort study (n=8160) showing that even subtle weight loss is an independent predictor of survival (Martin et al., 2015).

A number of studies have compared prophylactic versus reactive approaches to nutrition support with mixed results and outcomes, but there are limitations and variations in methodology. Some studies have compared prophylactic gastrostomy to reactive gastrostomy (Kramer et al., 2014; Olson et al., 2013), or to a reactive nasogastric tube (Prestwich et al., 2014) or to either type of reactive feeding tube or no feeding tube (Lewis et al., 2014; Silander et al., 2012; Williams et al., 2012). Many of these historical cohort studies are deemed to have a high degree of selection bias, as patients with most advanced disease or nutritional deficits are often those selected for prophylactic gastrostomy. One study hoped to avoid this issue by comparing approaches across two different centres, with one using prophylactic gastrostomy placement and the other using the reactive approach (Olson et al., 2013), but this also resulted in clinical differences between groups. The current study had hoped to avoid this problem by the use of a validated protocol for patient selection for gastrostomy (Brown et al., 2013b), but due to non-adherence from the healthcare team, a selection bias was again created with different clinical characteristics between the two groups. As per other authors, this study adjusted for these group differences in multivariate analysis, with the additional strength of also including the treating Consultant as a covariate to adjust for any selection bias from the medical team. Indeed this was found to be an important variable in the final model, although there was no impact of the treating Consultant per se on weight loss outcomes. As high level randomized controlled trials have been shown to be challenging in this population to address this question of optimal tube feeding type (Corry et al., 2008), this current study adds to the existing body of evidence from other prospective cohort trials, and therefore provides further information to assist in the decision-making for the selection of feeding tubes for this patient population.

Interestingly one of the few randomized controlled trials in this field found significantly less weight loss at six months in the prophylactic group (11.4%) compared to the reactive group (13.6%), with the nadir of weight loss up to six months post-treatment (Silander et al., 2012). Therefore a limitation of the current study is that weight was only recorded to the end of treatment and so any differences beyond the end of treatment cannot be accounted for. Weight loss >10% during and up to 12 weeks post-treatment has been associated with worse quality of life outcomes (Langius et al., 2013a), and >5% weight loss during treatment or >7.5% weight loss up to 12 weeks post-treatment has been shown to be associated with worse survival outcomes (Langius et al., 2013b). In this era of chemoradiotherapy treatment a number of studies are reporting significant weight loss of 9-12% despite prophylactic gastrostomy placement (Brown et al., 2014a; Rutter et al., 2011), and so it is important to consider approaches to improve nutritional outcomes. A randomized controlled trial is currently underway to evaluate if an early nutrition intervention using the prophylactic gastrostomy can optimize and improve a patient's nutrition outcome (Brown et al., 2014b).

There are concerns that gastrostomy placement may result in feeding tube dependency and increased dysphagia post-treatment (Corry et al., 2008), however several studies have shown that prophylactic gastrostomy placement does not impact on long-term swallow function (Crombie et al., 2015; Prestwich et al., 2014; Silander et al., 2012). Although not collected specifically as part of this study, additional research is being carried out locally to determine swallow function and incidence of dysphagia during and post-treatment, as this remains an important area of research and will be reported on separately.

In line with the findings of this study, a reduction in unplanned admissions with the prophylactic approach has also been reported in a number of studies (Hughes et al., 2013; Lewis et al., 2014; Olson et al., 2013; Rutter et al., 2011; Williams et al., 2012), although was not supported in the randomized controlled trial previously mentioned (Silander et al., 2012). A strength of this study was looking at unplanned admissions for up to a month post-treatment, however this only captured patients living in the local area (which typically accounts for approximately half of the patients treated at the tertiary hospital), and not those that may have returned home to remote, rural or regional areas, who may have had admissions locally. Although unplanned nutrition-related admissions were higher in the noPEG group it was interesting to see patients in the proPEG group were still admitted for a range of nutritional reasons.

While a gastrostomy may not mitigate against an admission for additional medical management for nausea, vomiting or pain, it was unexpected to see admissions for poor appetite and intake. However patient adherence to nutrition recommendations was not collected as part of this study, and is likely to be a contributing factor for these type of admissions, as patient adherence with nutrition advice is known to have an impact on outcomes (Capuano et al., 2008). The higher rate of other medical admissions in the proPEG group was not attributable to the tube placement. These type of admissions were similar in each group and included medical conditions such as cellulitis, hyperglycaemia, chest pain, hypotension, neutropenia, non-neutropenic fevers, dyspnoea, liver failure and other systemic infections.

This study has shown that a review of the current protocol to determine gastrostomy tube placement is required, as 57% of patients in the noPEG group, did not have significant weight loss or require a feeding tube as expected, and therefore it was the correct decision not to place a gastrostomy. Unfortunately in comparing the sub groups within this group, who subsequently met the criteria for prophylactic gastrostomy versus those that didn't, no statistical differences were found, which is likely limited by the small sample size.

The selection bias results from this study imply T stage and tumour site are the most important factors which influence decision-making. It is not known how much baseline nutritional status or swallowing function impacted on the team decision, or what other factors radiation oncologists may take into account in their decision-making e.g. radiation field size and dose to the pharyngeal constrictor muscles (Vlacich et al., 2014), or other social factors (Magnuson et al., 2013) or comorbidities (Blanchford et al., 2014). These factors will require further investigation to inform updates to the protocol to more accurately identify the patients who will benefit most from prophylactic gastrostomy placement and minimise exposure to unnecessary clinical risks.

CONCLUSIONS

This study has demonstrated improved nutritional outcomes and less unplanned nutrition-related admissions with prophylactic gastrostomy placement in a high risk group of patients with head and neck cancer, compared to those who had reactive management. As approximately half of the high risk patients managed reactively were appropriately identified to not require a prophylactic gastrostomy the protocol requires further review to improve the specificity.

ACKNOWLEDGEMENTS

The authors would like to thank the staff from the Combined Head and Neck Clinic for their support and ongoing access to their patients, and staff from the department of Nutrition and Dietetics for their assistance with data collection.

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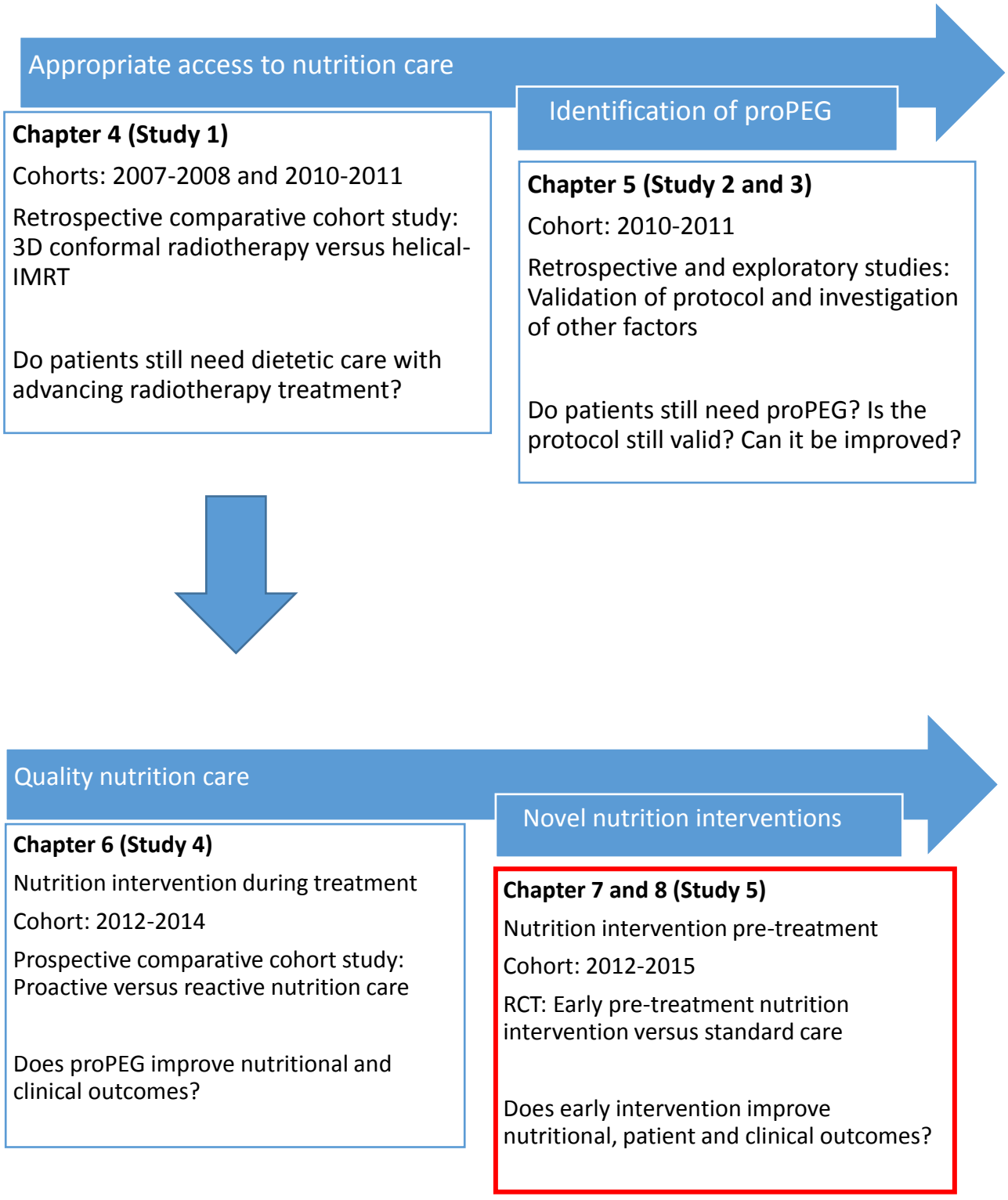
6.4 Chapter summary

This chapter reported on outcomes following non-adherence to the local protocol for proPEG placement. A significant proportion of patients in the reactive group (protocol non-adherence) ended up with a feeding tube or more than 10% weight loss (43%), and thus implied a proPEG was warranted. Conversely 57% of patients in this group actually had reasonably nutrition outcomes with <10% weight loss, and thus non-adherence to the protocol was the right decision. It is unclear whether these cases were a Consultant-initiated decision or a patient-initiated decision as this information could not be distinguished from the medical chart. Positive outcomes from a patient-led decision may have been due to strong motivation to maintain weight and oral intake to avoid a feeding tube. A Consultant-led decision was likely to be based on other clinical factors beyond the current scope of the protocol which implies that other factors may be influencing decision-making and further investigation of the protocol high risk definition would be beneficial.

In addition this chapter has provided further evidence to support that the proPEG approach does result in less weight loss and unplanned admissions than the reactive nutrition support approach. Our proPEG group had 2% less weight loss during treatment than the reactive group (p=0.048), and the rate of unplanned admissions overall was lower at 75% vs 82% in the reactive group (p=0.029). However mean weight loss during treatment is still clinically significant at 7-9% and further optimisation of nutrition outcomes is required.


Appropriate access to nutrition care
Identification of proPEG
Chapter 4 (Study 1)
Cohorts: 2007-2008 and 2010-2011
Retrospective comparative cohort study: 3D conformal radiotherapy versus helical-IMRT
Do patients still need dietetic care with advancing radiotherapy treatment?
Chapter 5 (Study 2 and 3)
Cohort: 2010-2011
Retrospective and exploratory studies: Validation of protocol and investigation of other factors
Do patients still need proPEG? Is the protocol still valid? Can it be improved?
Quality nutrition care
Novel nutrition interventions
Chapter 6 (Study 4)
Nutrition intervention during treatment
Cohort: 2012-2014
Prospective comparative cohort study: Proactive versus reactive nutrition care
Does proPEG improve nutritional and clinical outcomes?
Chapter 7 and 8 (Study 5)
Nutrition intervention pre-treatment
Cohort: 2012-2015
RCT: Early pre-treatment nutrition intervention versus standard care
Does early intervention improve nutritional, patient and clinical outcomes?

7.1 Chapter overview

The findings in this chapter have been published in the BMC Nursing Open Access Journal. (Journal Impact Factor 0.561; Ranked 16/65 Nursing Open Access category; Quartile 1). Section 7.2 and 7.3 are presented in their accepted format prior to publication.

The results from previous chapters have shown that weight loss during treatment remains significant despite proPEG placement. Previous research at the RBWH has also shown that weight loss continues post-treatment with approximately 9% weight loss by three months post-treatment (Brown et al., 2014a) and other studies have reported a nadir of weight loss at six months post-treatment at 11% (Silander et al., 2012). The aim of this chapter is to describe the methodology used for a novel nutrition intervention approach which aims to improve nutrition outcomes in patients receiving a proPEG. This study forms the main phase of the research for this thesis.

This protocol has been presented at the following conference: Clinical Oncological Society of Australia 39th Annual Scientific Meeting, Brisbane, Australia, 2012 (Appendix C – 11.3.8).

Date submitted: 05/05/2013

Date accepted: 26/06/2014

Citation: Brown, T., Banks, M., Hughes, B., Kenny, L., Lin, C., Bauer, J. (2014). Protocol for a randomized comparison of early prophylactic feeding via gastrostomy versus standard care in high risk patients with head and neck cancer. *BMC Nursing*, *13*, 17. doi:10.1186/1472-6955-13-17

7.2 Abstract

Background: Patients with head and neck cancer are at high risk of malnutrition and dysphagia. Enteral tube feeding via a gastrostomy or nasogastric tube is often required in response to dysphagia, odynophagia or other side effects of treatment that lead to dehydration and/or weight-loss during or after cancer treatment. A recent systematic review concluded that the optimal method of tube feeding remains unclear; however prophylactic placement of a gastrostomy, in anticipation of its use during and after treatment, is common practice. A number of benefits have been demonstrated with a prophylactic gastrostomy tube; however the majority of these studies have been undertaken in patients receiving radiotherapy alone. More recent studies in patient populations receiving concurrent chemoradiotherapy are showing that despite prophylactic gastrostomy placement significant weight loss still occurs, placing the patient at risk of the consequences of malnutrition. Therefore we set out to investigate innovative prophylactic nutrition support via the gastrostomy to optimise the nutritional outcomes of patients with head and neck cancer.

Methods/design: Patients with head and neck cancer will be eligible for this single centre randomised controlled trial if they are identified for referral for a prophylactic gastrostomy using local guidelines. Patients will be excluded if they are: under the age of eighteen; pregnant; unable to give informed consent; or severely malnourished or moderately malnourished with significant dysphagia requiring a liquid or puree diet. All eligible patients who consent for the study will be allocated randomly to either the intervention or control group (usual care). The intervention group will commence prophylactic supplementary nutrition support via the gastrostomy immediately following placement compared to usual care where nutrition support is commenced via the gastrostomy when clinically indicated during treatment. Key outcome measures will be percentage weight loss, body composition, nutritional status and quality of life, measured at baseline and three months post-treatment.

Discussion: To our knowledge this is the first study to evaluate the effectiveness of early prophylactic tube feeding compared to commencement of feeding during treatment, as per current standard practice, in patients undergoing prophylactic gastrostomy prior to treatment for head and neck cancer.

Trial registration: Trial has been registered in the Australian New Zealand Clinical Trials registry as ACTRN12612000579897.

7.3 Manuscript

BACKGROUND

Patients with head and neck cancer are at high risk of malnutrition and dysphagia. Evidence-based guidelines are available to provide optimal nutrition care to this patient group throughout the treatment trajectory (Brown et al., 2013a). There is good evidence to support the role of dietetic counselling to improve nutrition outcomes in patients with head and neck cancer receiving radiotherapy (Garg et al., 2010). Enteral tube feeding via a gastrostomy or nasogastric tube is often required in response to dysphagia, odynophagia or other side effects of treatment that lead to dehydration and/or weight-loss during or after cancer treatment. A recent systematic review concluded that the optimal method of tube feeding remains unclear (Nugent, Lewis, & O'Sullivan, 2010b), although this was based on only one eligible randomised controlled trial (RCT) comparing the use of nasogastric tubes and gastrostomy tubes placed when required during treatment (Corry et al., 2008). Since then a new RCT has been published (Sadasivan et al., 2012) which supports the use of gastrostomy over nasogastric tubes, however the actual timing of the tube placement in relation to the treatment is unclear. Two further RCTs have compared proactive to reactive enteral feeding approaches, and while less weight loss is seen with the proactive approach, the differences are not statistically significant (Salas et al., 2009; Silander et al., 2012)

There are benefits and disadvantages to both types of enteral feeding and their timing (Koyfman & Adelstein, 2012). Prophylactic placement of a gastrostomy, in anticipation of its use during and after treatment, is common practice. Consideration must be given to the risks associated with the procedure of gastrostomy placement (Grant et al., 2009) and there is increasing concern that gastrostomy placement leads to prolonged tube dependency and long-term dysphagia (Corry et al., 2008; Langmore, Krisciunas, Miloro, Evans, & Cheng, 2012; Mekhail et al., 2001). Although one additional study comparing two different centre's approaches with reactive gastrostomy placement versus proactive gastrostomy placement found a higher rate of gastrostomy dependency in the proactive placement group at three months there was no difference at six or 12 months (Olson et al., 2013). The risks of gastrostomy placement are often outweighed by the number of benefits that have been demonstrated with a prophylactic gastrostomy tube with, earlier commencement of nutrition support (Scolapio et al., 2001), reduced weight loss (Beaver et al., 2001; Tyldesley et al., 1996), improved quality of life (Fietkau, Iro, Sailer, & Sauer, 1991; Salas et al., 2009; Senft et al., 1993), and reduced admissions and healthcare costs (Hughes et al., 2013; Lee et al., 1998; Piquet et al., 2002).

Of note the majority of these studies have been undertaken in patients receiving radiotherapy alone. As concurrent chemoradiotherapy is the generally accepted non-surgical standard of care for many of these patients, the additional toxicities associated with this dual modality treatment place the patient at greater nutritional risk. More recent studies are showing that despite prophylactic gastrostomy placement significant weight loss still occurs (Li et al., 2009; Rutter et al., 2011; Silander et al., 2012), placing the patient at risk of the consequences of malnutrition.

One large study of patients receiving chemoradiotherapy which compared reactive (n=279) and proactive (n=166) gastrostomy placement reported no difference in weight loss outcomes between the two groups but the proportion of patients with weight loss >10% at the end of treatment was 37-42%, and by 12 months post-treatment is was 42-53% (Olson et al., 2013). A separate study utilising a reactive feeding approach with nasogastric tubes also reported a mean weight loss of 10.4% during treatment, with a weight loss of >10% affecting over half of their patients (54%) (Clavel et al., 2011).

Similar to the literature, our current clinical practice guidelines with prophylactic gastrostomy tubes (Brown et al., 2013b), whilst effective in reducing unplanned hospital admissions and length of stay (Hughes et al., 2013), did not appear to be effective in achieving positive nutrition outcomes (Brown et al., 2014a). We have hypothesised from clinical observation that this may be due to: poor tolerance to nutrition support during treatment due to the side effects; difficulties adhering to nutrition recommendations secondary to other barriers such as time, finance or fatigue; increased nutritional requirements during treatment; and/or reluctance of patients to engage with utilising the tube for nutrition support. Therefore it was hypothesised as to whether earlier nutrition intervention can improve these patient's nutritional outcomes.

The majority of studies published in the literature utilising prophylactic gastrostomy tubes generally commence nutrition support when clinically indicated in response to deterioration in swallowing or nutritional status (Nugent et al., 2010a; Raykher et al., 2009; Scolapio et al., 2001). Some studies have reported on commencement of enteral feeds prior to treatment (Beer et al., 2005; Marcy et al., 2000; Nguyen et al., 2006; Wiggenraad et al., 2007) however these study designs are quite different to our proposal, with their patients often having a poor nutritional status or dysphagia at baseline therefore requiring immediate or therapeutic nutrition support, in comparison to our target population being primarily well-nourished with minimal dysphagia.

Whilst this innovative pre-treatment nutrition intervention strategy of prophylactic feeding may not address all our concerns or barriers experienced with current practice with gastrostomy feeding, the intervention is intended to particularly aid the psychological aspects. Anecdotally in practice, we have seen that patients who have a gastrostomy placed for surgery and then require nutrition support again during radiotherapy, appear to be better adapted to the tube, than patients who have had the tube placed for definitive chemoradiotherapy. This observation was supported by recent studies in the literature where Salas et al. (2009) reported a negative physical effect of the gastrostomy just after the beginning of treatment, but also a positive mental effect over time as patients became used to the tube (Salas et al., 2009). Merrick& Farrell (2012) also recently explored patient experiences with a gastrostomy tube through a qualitative study design, and three themes were found (Merrick & Farrell, 2012). The majority of patients demonstrated “constructive cognitive appraisal” whereby they positively adapted to the tube and accepted tube feeding. However some patients were described as displaying “cognitive affective dissonance”, whereby although they experienced no physical concerns with the tube, there was a negative mental reaction to the tube. Smaller numbers of patients were found to have “emotion focused appraisal” so while accepting the necessity of the tube, there was a lot of anxiety and fear. Therefore part of the rationale for this current study design is to also assist patients with adapting to their tube by commencement of earlier tube feeding, so that when tube feeding becomes absolutely necessary during treatment, there is less anxiety and it becomes easier to adapt to and manage.

This study aims to compare the outcomes of early prophylactic tube feeding compared to commencement of feeding during treatment, as per current standard practice, in patients undergoing prophylactic gastrostomy prior to treatment for head and neck cancer. The research will directly inform future clinical practice and will provide more evidence on the role of pre-treatment nutrition support in this patient population.

METHODS/DESIGN

Study design and setting

This study is a single centre randomised controlled trial. Recruitment will be from patients attending the Combined Head and Neck Clinic at the Royal Brisbane and Women’s Hospital, a tertiary hospital for cancer care services in Queensland, Australia.

The study has been approved by the Royal Brisbane and Women's Hospital Human Research Ethics Committee on 19th July 2012 (HREC/12/QRBW/162) and The University of Queensland Medical Research Ethics Committee on 8th August 2012 (2012000890).

Participants and recruitment

Patients will be eligible for the study if they are identified as high risk patients and referred for a prophylactic gastrostomy as per the Royal Brisbane and Women's Hospital Swallowing and Nutrition Management Guidelines for Patients with Head and Neck Cancer (Brown et al., 2013b). A patient would be deemed high risk at the multidisciplinary combined head and neck clinic if they meet the following criteria: oral cavity or oropharyngeal cancer receiving bilateral chemoradiotherapy; nasopharyngeal or hypopharyngeal cancer receiving chemoradiotherapy; or an unknown primary tumour receiving chemoradiotherapy; or if they have severe malnutrition. The final decision of tube placement is made by the treating team. Patients will be excluded if they: are under the age of eighteen; are pregnant; have cognitive impairment, an intellectual disability or a mental illness; or are receiving non-curative intent treatment.

Patients meeting these criteria will be identified by a member of the treating team (radiation oncologist, medical oncologist or surgeon) who will discuss the study and provide a copy of the Patient Information and Consent Form if they are interested. The research dietitian (author TB) will be notified of these patients and a follow-up telephone call will be made to provide full details of the study and to answer any patient questions. If the patient wishes to enrol the research dietitian will assess the patient when they attend for their gastrostomy procedure to complete eligibility criteria. A full nutritional assessment will be undertaken using the Patient Generated Subjective Global Assessment (PG-SGA) tool (Bauer et al., 2002). This is a validated tool recommended to assess nutritional status in patients with cancer (Isenring et al., 2013), and encompasses assessment of weight history, dietary intake, nutrition impact symptoms, function/activity, and physical assessment of muscle/fat stores. The tool provides a subjective global assessment (SGA) rating of well-nourished (SGA A), moderate malnutrition (SGA B) or severe malnutrition (SGA C). A numerical score is also generated indicating the level of nutritional risk. A score >9 indicates a referral to the dietitian for management. Patients will be excluded if they are found to have either: severe malnutrition or moderate malnutrition with significant dysphagia requiring a liquid or puree texture modified diet. Remaining eligible patients will provide written consent and baseline data will be collected.

Interventions

All eligible patients who consent for the study will be allocated randomly to either the intervention or control group (usual care). All patients will receive education from the dietitian and nursing staff on the care of their gastrostomy tube pre-treatment and will receive joint dietetic and speech pathology review on a weekly basis during treatment.

In the hospital's usual care, patients will commence enteral nutrition via their prophylactic gastrostomy when required during treatment following assessment by the clinical dietitian. Indicators for commencing enteral nutrition are: oral intake less than 60% of estimated energy requirements (based on 125-145kJ/kg) for a period of or anticipated to be, greater than 10 days; or the patient is unable to maintain weight; or the patient requires significant texture modification of diet; or the patient has increased or uncontrolled nutrition impact symptoms. The regimen will be determined by the clinical dietitian to suit the patients' individual requirements and adapted as required during treatment. All patients are encouraged to maintain oral intake as much as possible during treatment and as long as it remains safe to do so as advised by the speech pathologist.

The intervention group will commence prophylactic nutritional support via their gastrostomy at the time of tube placement (pre-treatment) in addition to their current oral intake. The supplementary enteral nutrition will consist of a 200ml bolus feed (1.5kcal/ml polymeric formula) to be administered twice a day between meal times, and will continue until completion of treatment. The enteral nutrition products for this intervention will be provided to the patient by the Department of Nutrition and Dietetics. Adherence will be monitored by the patient completing a self-reporting diary and verified by the clinical dietitian. If during treatment the patient displays any of the clinical indicators described above in usual care, the enteral feeding regimen will be increased by the clinical dietitian to suit the patients' individual requirements.

All patients will be referred to their local dietitian service on completion of treatment for ongoing care as required. The research dietitian will provide monthly telephone review with all patients to determine ongoing use of the gastrostomy tube for a maximum of six months post-treatment.

Objectives

The aim of this study in patients undergoing prophylactic gastrostomy prior to treatment for head and neck cancer is to compare the nutritional, clinical and patient outcomes following an early prophylactic tube feeding approach versus our standard care of commencing tube feeding via the prophylactic gastrostomy as required. It is anticipated that the intervention group will have improved nutritional outcomes, which in turn is expected to improve patient outcomes, such as quality of life, and clinical outcomes, due to the earlier commencement of nutritional support. The null hypothesis is that there is no difference in the outcomes between the two groups.

Outcomes

The primary endpoint is percentage weight change from baseline (pre-treatment) to three months post-treatment. Secondary endpoints will also be measured at baseline and three months post completion of treatment and include: nutritional status using the Patient-Generated Subjective Global Assessment tool (PG-SGA), body composition using Bioelectrical Impedance Analysis (BIA), and quality of life using the European Organisation for Research and Treatment of Cancer (EORTC) tools. The questionnaires to be used include the quality of life of cancer patients (EORTC QLQ-C30) and the module for head and neck (EORTC QLQ-H&N35). Additional qualitative data will be collected through the patient diary to assess adherence to the intervention. If patients are unable to meet the recommended goal intake, the reason why will be recorded by the patient e.g. nausea, lack of time, too tired etc. Tertiary endpoints will include: tolerance to chemotherapy and radiotherapy (dose received, changes to treatment, interruptions); unplanned hospital admissions; gastrostomy complications; and treatment response. Follow-up to assess gastrostomy use (duration and degree of tube use post-treatment) will occur monthly for six months post-treatment or until tube is removed. If the tube is still in-situ at six months, then follow-up would also occur at 12 months post-treatment to assess long-term gastrostomy dependency. Survival will also be measured at one year and five years.

The primary and secondary outcomes have been set at three months to ensure maximum follow-up and prevent attrition from the study. As the centre is a major tertiary hospital in Queensland which covers an area of 715 309 square miles, many patients do not receive ongoing follow-up at the tertiary centre, but at regional cancer centres or local health services.

In addition the aim of this study is to see whether an early nutrition intervention can minimise weight loss in the acute period of treatment. Other studies have shown the nadir of weight loss occurs around this time point (Brown et al., 2014a; Paccagnella et al., 2010), and looking at weight outcomes beyond this time point can be impacted upon by so many other variables such as the effect of recurrent disease or a change in the nutrition management goals from weight maintenance during treatment to achieving a healthy weight through lifestyle and dietary changes as recommended for cancer survivorship. Therefore the aim of this study was to investigate the effect of an early nutrition intervention on minimising this nadir of weight loss.

To enhance the quality of the measurements and to reduce any inter-rater variability in assessment the data will be collected by the designated research dietitian. The research dietitian is responsible for recruitment and data collection only, and is not providing any dietetic patient care.

Adverse Events

A data monitoring committee will meet quarterly to review and collate serious adverse events. Any serious adverse events resulting from the study intervention will be reported to the RBWH Human Research and Ethical Committee as per standard procedures, and would be appropriately managed by the medical team to minimise or eliminate the effect of the adverse event on the patient.

Intervention Team Roles

The study intervention team consists of: one research dietitian (author TB) who is responsible for the recruitment and outcome assessments at baseline and follow-up, and a second research dietitian (author MB) who is responsible for the randomisation process. The dietetic care is provided by two different treating clinicians (not blinded): one is allocated to the care of the standard arm; the second is allocated to the care of the intervention arm. This is to prevent any cross contamination between the cares given in each arm of the study. The multidisciplinary treatment team is also notified of the randomisation outcome so that there is reinforcement of the nutrition protocol from all professions involved in the patient care. The research dietitians are not involved in the clinical care of the patient. The research dietitian responsible for recruitment and outcome assessment is blinded to the randomisation sequence but not to the randomisation outcome, as they also provide support and encouragement to the intervention group to maximise adherence to the protocol.

Sample size

The primary outcome in this study is a continuous response variable (% weight loss) from independent control and intervention patients, which have been randomised in a ratio 1:1. In a previous study we have found high risk patients recommended for a prophylactic gastrostomy (i.e. the target population for this RCT) to experience a mean 9% weight loss at three months post-treatment with standard deviation 9.4 (Brown et al., 2014a). The aim of this intervention is to reduce this weight loss; however there are no other studies which have investigated the impact of prophylactic enteral tube feeding on which we can draw an anticipated response for this study for the sample size calculation. Ideally the goal for the intervention group is a mean weight loss of <5% as this is not deemed to be clinically significant, and thus a positive nutrition outcome. Therefore to detect a 5% true difference in % weight loss between the intervention and control groups, 56 patients in each group will be required to be able to reject the null hypothesis that the population means of the intervention and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. Given that mortality during treatment is low and good follow-up at three months is expected, as patients are returning to the hospital for their treatment scans and appointment with the oncologist, an attrition rate of 10% is used. Therefore the total sample required is 123 patients (62 patients in each group).

There is a study to consider, of patients receiving chemoradiotherapy, in which an early pre-treatment nutrition intervention of dietary counselling with or without oral supplements or tube feeding was compared to patients without a pre-treatment nutrition assessment and intervention. They found a mean weight loss at three months post-treatment of 9.75% $\pm$ 5.75 in their standard care group compared to a mean weight loss of 2.77% $\pm$ 7.93 (Paccagnella et al., 2010).

The sample size was calculated based on this demonstrated difference of 7% and examples of multiple sample sizes based on varying assumptions are illustrated in Table 7-1. Therefore sample size could be reduced to 39 patients per arm, with an attrition rate of 10%, which then results in total sample size of 86 (43 patients in each group), at a power of 90%.

Table 7-1: Examples of sample sizes with varying assumptions (Type I Error 0.05)

Power	Number of patients required in each arm			
	SD = 9.4 (Brown et al., 2014a)		SD = 5.34 (Paccagnella et al., 2010)	
	5% difference*	7% difference**	5% difference	7% difference**
80%	56	29	19	10
90%	75	39	25	13

Abbreviations: *Difference to reach clinically significant target weight loss of <5% (as studies have shown weight loss of 9.3-9.75% (Brown et al., 2014a; Paccagnella et al., 2010). ** Difference seen with pre-treatment dietary counselling intervention (Paccagnella et al., 2010)

Both of these sample sizes are deemed feasible from historical data at our institute. Each year approximately 500-550 patients attend the Combined Head and Neck Clinic at our institution. In a sample year (2010-11) 270 patients went on to have curative treatment with a standard referral to the dietitian. Of these; 106 patients were planned for adjuvant or definitive concurrent chemoradiotherapy with 88 categorised as high risk. The majority of these proceeded with a prophylactic gastrostomy as per the guideline recommendation (n=86), and nil were considered high risk due to severe malnutrition. Based on 86 eligible patients per year, factors such as patients not giving consent (20%) and other factors such as scheduling difficulties (5%) were considered, resulting in an estimated 64-65 patients per year (or approximately five patients per month). Therefore recruitment is anticipated to be achievable in two years from a single centre.

Randomisation

The research dietitian (author TB) will inform the clinical treating dietitian of newly recruited patients following consent and baseline data collection. The clinical dietitian will provide patient details to an independent member of the research team (author MB) for randomisation. The random allocation sequence is generated by computer and stratified according to baseline nutritional status (well-nourished versus moderate or suspected malnutrition).

Additional stratification based on tumour site or treatment was not undertaken, as the high risk category of the guidelines used to determine prophylactic gastrostomy placement has been based on these factors. As the guidelines have been found to be highly specific at predicting the requirement for a gastrostomy (Brown et al., 2013b) it was not deemed necessary that additional stratification was required. It is not possible for this study to be double-blinded; however the allocation sequence is concealed to the participants, their health care providers, and the research dietitian responsible for recruitment, as it is undertaken by an independent member of the research team not involved in patient care or data collection.

Statistical methods

To determine whether there are any differences between the two groups at baseline - participant characteristics will be summarised using mean and standard deviation for continuous variables and analysed using student t-tests, and categorical variables will be summarised using frequencies and percentages and analysed using chi-squared tests of association. If the data is not normally distributed and found to be skewed, then the data can be transformed using log transformation before applying the appropriate parametric test. If this is not successful, then alternative non parametric tests can be applied, such as the Wilcoxon-Mann-Whitney test for continuous variables.

Analysis will be undertaken on an intention-to-treat basis. To determine the effect of the nutrition intervention group versus the control group (the independent categorical variable) on the primary outcome of % weight loss (the dependent continuous variable), analysis of variance (ANOVA) will be used. For the secondary outcomes, % fat free mass, PG-SGA score and quality of life score, the change over time from baseline to three months will be analysed between groups using the repeated measures ANOVA. Univariate analysis will be used to determine the association of any other independent variables on the outcome measures. Any statistically significant associations found will then be used to add each variable into a normal regression model to enable adjusting for any confounding effects. The regression model will also enable adjusting for any important clinical differences found between the intervention and control group at baseline. All tests will assume normal distribution; otherwise alternative non parametric tests will be applied for non-normal distributed data. Statistical significance will be set at $p<0.05$. For any results that are not statistically significant, any relevant clinically significant results will be reported.

Table 7-2: Comparison of key studies which report on timing of commencement of enteral feeding during treatment

Citation	Study population	N	Type and timing of tube placement	Commencement of feeds (no. days after start of treatment)	Outcomes
Nugent 2010a	HNC with radical chemoradiotherapy requiring tube feeding	50	Prophylactic PEG (before start of treatment) n=21	Range: 1-33 days	Mean weight loss: -4.6%
			Late PEG (during treatment) n=11	Range: 14-30 days	Mean weight loss: -8.7%
			NG tube n=18	Range: 10-34 days	Mean weight loss: -8.5%
Raykher 2009	HNC with definitive or adjuvant chemoradiotherapy or radiotherapy requiring PEG	163	Prophylactic PEG (before start of treatment) n=161	Mean 21 days	○ PEG used by n=160 (98%) due to severe dysphagia (mean duration of use 251 ± 317 days) ○ Treatment interruptions in 7% ○ Strictures requiring dilatation in 12% ○ BMI optimised in obese/overweight patients through individual regimens
			Late PEG (during treatment) n=2		
Scolapio 2001	HNC with definitive or adjuvant radiotherapy requiring PEG	54	Prophylactic PEG (before start of treatment) n=41	Mean 10 days	Mean wt loss 2.7kg Nil nutrition-related admissions
			Late PEG (during treatment) n=13	Mean 23 days	Mean wt loss 4.5kg Nutrition-related admissions n=4

Abbreviations: HNC=head and neck cancer; PEG=gastrostomy; NG=nasogastric; BMI=body mass index.

Table 7-3: Comparison of key studies which commence enteral feeding via a prophylactic gastrostomy immediately

Citation	Study population (N)	Study design	Nutrition characteristics at baseline	Timing of PEG tube placement	Commencement of PEG feeds	Oral intake	Outcomes
Marcy 2000	Stage IV HNC treated with CRT and prophylactic PEG (n=50)	Retrospective case series	34% had BMI <20kg/m2	Within 5 days before treatment (n=38) or within 5 days after treatment started (n=12)	All patients started 48 hours post insertion Tube feeds were increased over 4 days to provide goal of 2000 kcal/day	Unknown	Mean weight increase of 2.5kg by 3 weeks
Beer 2005	HNC with radical radiotherapy or CRT and PEG tube feeding (n=151)	Retrospective comparative cohort	Group A – 49% malnourished Group B – 47% malnourished	Group A (n=78, 52%) early PEG: before or within 2 weeks of radiotherapy. Group B (n=73, 48%) delayed PEG: after 2 weeks of radiotherapy.	All patients started 12 hours post insertion Tube feeds were increased over 3 days to provide individual goal	Clear fluids only	Mean weight loss 1.03 kg Group A vs. 4.0 kg Group B (P=0.004) Radiotherapy interruptions (>3 days) 10% Group A vs. 25% Group B (P=0.02)
Wiggenraad 2007	Stage III and IV HNC treated with CRT and prophylactic PEG (n=50)	Retrospective case series	48% on puree or liquid diet 78% had weight loss	Mostly 1-2 weeks before treatment commenced (N=3 had placed >3 weeks prior)	26% commenced prior to treatment (tube feeding initiated if reduced food intake or weight loss)	Unknown	Mean loss of weight during treatment 2.8%

Abbreviations: HNC=head and neck cancer; CRT=chemoradiotherapy; PEG=gastrostomy; BMI=body mass index.

DISCUSSION

This study will evaluate the effectiveness of prophylactic nutrition support via a gastrostomy compared to current standard practices of commencing nutrition support in a reactive way during treatment. To our knowledge this is the first study to trial this approach of prophylactic nutrition support in a formal research setting. Of those studies that report specific details on the actual timing of the commencement of nutrition support, all commence a number of days after the commencement of treatment: 1-33 days (Nugent et al., 2010a), 21 days (Raykher et al., 2009) and 10 days (Scolapio et al., 2001). See Table 7-2.

The studies which have reported on the early commencement of tube feeding have quite a different study design and intent to our protocol (Table 7.3). Nguyen et al. (2006) stated criteria in their study for the initiation of enteral feeds prior to treatment being; poor oral intake prior to treatment, or aspiration on pre-treatment Modified Barium Swallow assessment (Nguyen et al., 2006). However the authors did not describe the number of patients in their study that met these criteria. Wiggenraad et al. (2007) reported 26% of their patients commenced enteral feeds prior to treatment (Wiggenraad et al., 2007), however this was likely in response to poor swallowing or nutritional status, with 48% of patients already requiring a puree or liquid diet and 78% of patients with weight loss prior to treatment. It was also found that when there was dysphagia at baseline, tube feeding was commenced earlier (day 2) compared to when there was no dysphagia at baseline (day 17).

There have been two other studies which have looked at initiating tube feeding immediately following prophylactic placement (Beer et al., 2005; Marcy et al., 2000). Both of these studies also had a significant proportion of patients who were nutritionally compromised at baseline and therefore the characteristics of the patients commencing early nutrition support are likely to be quite different to the patient characteristics we are anticipating studying. Both also appear to provide the majority of nutrition via the gastrostomy tube, with minimal oral intake. This is a very different approach to our proposed intervention where we are providing supplementary nutrition via the tube and advocate patients maintain/continue with oral intake for as long as possible to minimise the risk of long-term dysphagia and prolonged rehabilitation post-treatment (Rosenthal, Lewin, & Eisbruch, 2006).

Salas et al. (2009) reports on a randomised controlled trial on the quality of life in patients with a systematic gastrostomy (n=21) versus no systematic gastrostomy (n=18) (Salas et al., 2009). In the control group 13 patients later receive an insertion of a gastrostomy and the other five patients remained on oral intake alone.

There are no details in the methodology on the nutrition interventions provided to either group and the results do not include information on the actual timing of gastrostomy placement or the timing for the commencement of feeding. Therefore it is difficult to ascertain whether prophylactic nutrition support was utilized or whether it was prophylactic (systematic) tube placement.

Some of the anticipated problems with this current study protocol will be patient adherence to recommendations. Capuano et al. (2008) have shown that patients who adhere to dietary recommendations have improved outcomes compared to those that do not adhere (Capuano et al., 2008). Therefore patients have been asked to keep a record of the number of feeds they have each day so that adherence can be considered as a confounding variable. Patients have also been asked to record any reasons why they have not had the recommended amount. This may be due to feeling full or bloating, or from side effects of treatment such as nausea, or from practical issues such as not having enough time in the day due to treatment schedules/appointments, being fatigued or financial difficulties to purchase the recommended feeds. This additional information from the study will provide evidence for the feasibility of implementing the early intervention into clinical practice, and will also assist in identifying factors that patients experience during treatment so that alternative strategies can be found.

With the advent of evolving techniques using intensity-modulated radiotherapy and helical Tomotherapy, the dose to surrounding tissues (pharyngeal constrictor muscles) and salivary glands can be spared due to steeper dose gradient outside target volumes, and as a consequence there are less reports of long-term dysphagia and xerostomia (Kam et al., 2007; Nutting et al., 2011; Pow et al., 2006). Therefore it is hypothesized that patients may be less likely to require feeding tubes. The guidelines for prophylactic gastrostomy at our institution were previously validated in a patient cohort receiving standard 3D conformal radiotherapy (Brown et al., 2013b) and so additional research is also planned to retrospectively re-validate these guidelines in patients now receiving helical Tomotherapy to see whether the requirement for a feeding tube has changed.

However it should be noted there are a range of other reasons why patients may have an inadequate oral intake other than dysphagia and xerostomia. Therefore these patients are still susceptible to weight loss and malnutrition, and the adverse consequences. So despite the reduction of some side effects in this population with evolving treatments, nutrition support can still be indicated for other reasons.

Patients in this study protocol are being asked to record the main reason they are using the gastrostomy for nutrition support e.g. pain on swallowing (odynophagia), difficulty swallowing (dysphagia), painful ulcers (mucositis), difficulty chewing/dry mouth (xerostomia), taste changes (dysgeusia), nausea/vomiting or general poor appetite. These nutrition impact symptoms can all lead to a decline in nutritional status and weight loss, both of which have been associated with poor quality of life (Langius et al., 2013a; Ravasco, Monteiro-Grillo, & Camilo, 2003).

In conclusion the results from this study will aim to address the questions regarding the optimal nutrition interventions required to manage patients with head and neck cancer and will also assist in our understanding of the impact of the new treatment regimens. Together this will inform future clinical practice for the nutritional management of this patient population to achieve positive outcomes.

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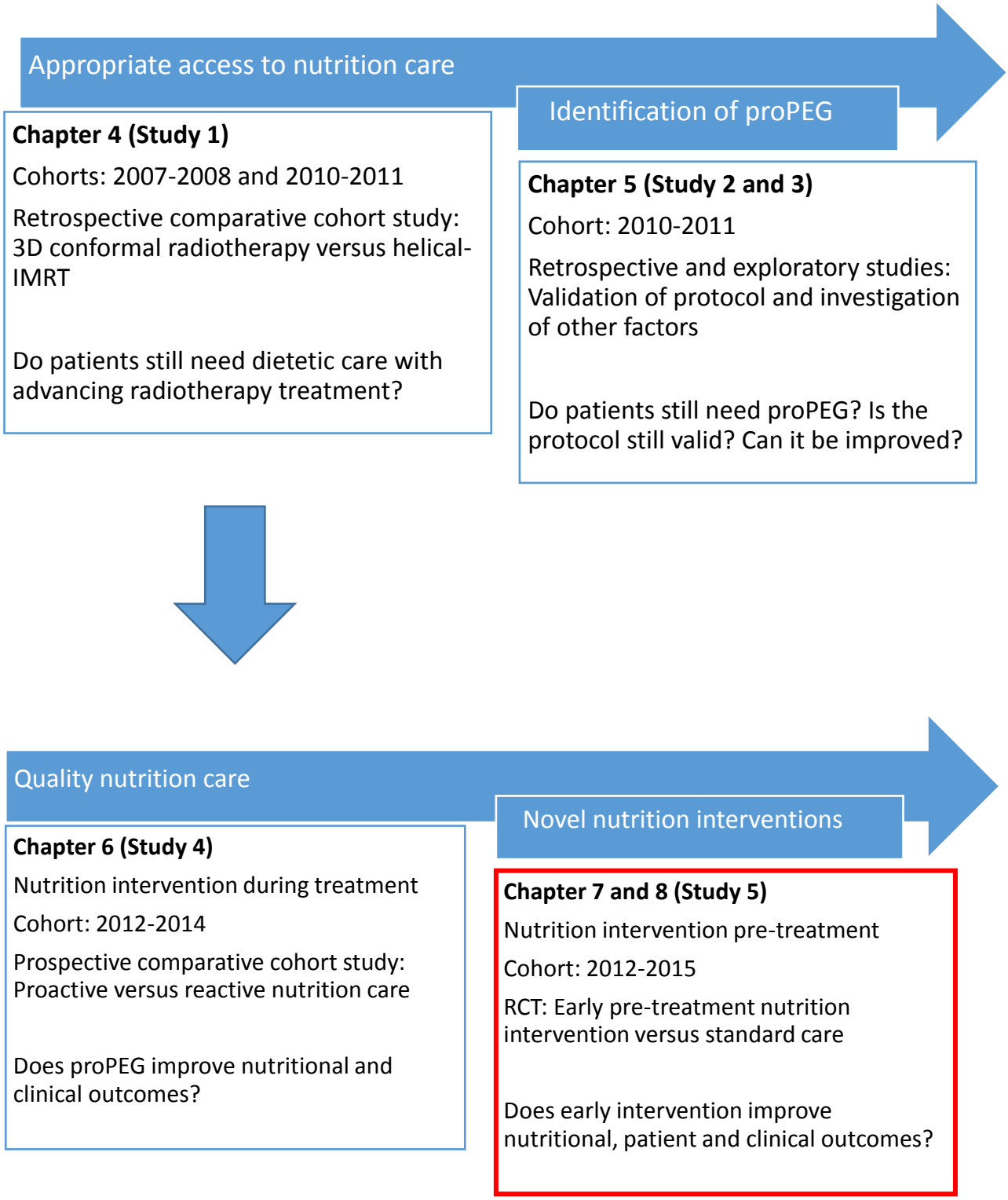
7.4 Chapter summary

This chapter has outlined the methodology for the proposed RCT to investigate the impact of an early nutrition intervention versus standard care in patients who receive a proPEG prior to treatment. Current standard care practice commences use of the gastrostomy tube when it is clinically indicated during treatment and this has resulted in clinically significant weight loss as previously reported. The proposed early intervention will commence patients using their gastrostomy immediately following placement to supplement their usual meal intake, and will then increase the volume of feeding as it becomes clinically necessary during treatment. This is the first study to investigate such an approach. The primary outcome is weight loss, but a number of other nutritional, patient and clinical outcome measures have also been included as secondary outcomes.


Appropriate access to nutrition care
Identification of proPEG
Chapter 4 (Study 1)
Cohorts: 2007-2008 and 2010-2011
Retrospective comparative cohort study: 3D conformal radiotherapy versus helical-IMRT
Do patients still need dietetic care with advancing radiotherapy treatment?
Chapter 5 (Study 2 and 3)
Cohort: 2010-2011
Retrospective and exploratory studies: Validation of protocol and investigation of other factors
Do patients still need proPEG? Is the protocol still valid? Can it be improved?
Quality nutrition care
Novel nutrition interventions
Chapter 6 (Study 4)
Nutrition intervention during treatment
Cohort: 2012-2014
Prospective comparative cohort study: Proactive versus reactive nutrition care
Does proPEG improve nutritional and clinical outcomes?
Chapter 7 and 8 (Study 5)
Nutrition intervention pre-treatment
Cohort: 2012-2015
RCT: Early pre-treatment nutrition intervention versus standard care
Does early intervention improve nutritional, patient and clinical outcomes?

8.1 Chapter overview

This chapter summarises the results from the RCT described in the previous chapter. Relevant information for this trial is available in the appendices including: ethical approvals (Appendix D, Appendix E, and Appendix F); nutrition and quality of life (QOL) outcome assessment tools (Appendix G, Appendix H); and data collection tools (Appendix I). The findings in this chapter have been published as three manuscripts as outlined below.

The main results from the trial, including the nutrition, patient and clinical outcomes, are presented in section 0 as a manuscript published in the British Journal of Cancer (Journal Impact Factor 5.569; Ranked 28/213; Oncology category; Quartile 1). Section 8.2.1 and 8.2.2 are presented in their accepted format prior to publication. The results have been presented at two international conferences: 18th Australia and New Zealand Head and Neck Cancer Society ASM, Auckland, New Zealand, 2016 (Appendix C – 11.3.9) and the 10th International Head and Neck Cancer Quality of Life Conference, Liverpool, UK, 2016 (Appendix C – 11.3.10).

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The longer term results from the trial in relation to gastrostomy outcomes are presented in section 8.3 as a manuscript published in Oral Oncology (Journal Impact Factor 4.286; Ranked 52/213; Oncology category; Quartile 1). Section 8.3.1 and 8.3.2 are presented in their accepted format prior to publication. The results have been presented at the following international conference: 10th International Head and Neck Cancer Quality of Life Conference, Liverpool, UK, 2016 (Appendix C– 11.3.11).

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The results on patient adherence and barriers to tube feeding are presented in section 8.4 as a manuscript published in Oral Oncology (Journal Impact Factor 4.286; Ranked 52/213; Oncology category; Quartile 1). Section 8.4.1 and 8.4.2 are presented in their accepted format prior to publication. The results have been presented at the following conference: Clinical Oncological Society of Australia 43rd Annual Scientific Meeting, Gold Coast, 2016 (Appendix C – 11.3.12).

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Finally section 8.5 provides an overall summary of the findings from this trial.

8.2 RCT: Nutritional, patient and clinical outcomes

8.2.1 Abstract

Background: Weight loss remains significant in patients with head and neck cancer, despite prophylactic gastrostomy and intensive dietary counseling. The aim of this study was to improve outcomes utilising an early nutrition intervention.

Methods: Patients with head and neck cancer at a tertiary hospital in Australia referred for prophylactic gastrostomy prior to curative intent treatment were eligible for this single centre randomised controlled trial. Exclusions included severe malnutrition or dysphagia. Patients were assigned following computer-generated randomisation sequence with allocation concealment to either intervention or standard care. The intervention group commenced supplementary tube feeding immediately following tube placement. Primary outcome measure was percentage weight loss at three months post treatment.

Results: Recruitment completed June 2015 with 70 patients randomised to standard care (66 complete cases) and 61 to intervention (56 complete cases). Following intention-to-treat analysis, linear regression found no effect of the intervention on weight loss (10.9% $\pm$ 6.6 standard care vs 10.8% $\pm$ 5.6 intervention, p=0.930) and this remained non-significant on multivariable analysis (p=0.624). No other differences were found for quality of life or clinical outcomes. No serious adverse events were reported.

Conclusion: The early intervention did not improve outcomes but poor adherence to nutrition recommendations impacted on potential outcomes.

8.2.2 Manuscript

INTRODUCTION

Treatments for head and neck cancer (HNSCC) including surgery, radiotherapy and chemotherapy have a number of side effects which can impact on nutritional intake (Talwar & Findlay, 2012), with multi-modality therapy having higher toxicity (Moroney et al., 2017). As a consequence many patients experience significant weight loss and develop malnutrition during the course of treatment (Hebuterne et al., 2014). This is associated with a number of detrimental outcomes including reduced physical functioning, quality of life, and immune function, and increased treatment interruptions, toxicities, hospital admissions, and mortality (Gorenc, Kozjek, & Strojan, 2015). Critical weight loss of 5% or more during treatment has been associated with worse survival outcomes (Langius et al., 2013a) demonstrating the importance of optimal nutrition to minimise weight loss. Improvements in nutritional status have also been linked to improved aspects of quality of life (Isenring et al., 2004, Ravasco et al., 2004).

A number of systematic reviews have recommended the importance of dietary counselling to improve nutritional and patient outcomes (Langius et al., 2013c, Garg et al., 2010), however the role of tube feeding remains unclear due to a lack of well-designed clinical trials to inform optimal tube type and timing of placement (Nugent et al., 2013, Wang et al., 2014a, Orphanidou et al., 2011). A recent meta-analyses comparing outcomes with nasogastric tubes and either prophylactic or reactive gastrostomy tubes, found the prophylactic tubes resulted in a reduction in treatment interruptions and nutrition related hospital admissions, but had no superiority in managing nutritional status (Zhang et al., 2016). Either way, clinically significant weight loss of greater than 10% occurs with either the prophylactic or reactive approach (Silander et al., 2012, Chang et al., 2009, Rutter et al., 2011, Clavel et al., 2011, Olson et al., 2013).

Of those studies that report specific details on the actual timing of the commencement of nutrition support through the prophylactic gastrostomy, the majority are after the commencement of treatment when it becomes clinically indicated in response to deterioration in swallowing or nutritional status (Nugent et al., 2010a, Raykher et al., 2009, Scolapio et al., 2001). Hence it is not surprising that there are similar nutrition outcomes with reactive tube use; as although the prophylactic tube is in situ and ready for access, the initiation and indication for nutrition support is reactive in both groups.

Some studies have reported the commencement of enteral feeds prior to treatment (Nguyen et al., 2006, Wiggenraad et al., 2007, Marcy et al., 2000, Beer et al., 2005) but these patients had poor nutritional status or dysphagia at baseline and therefore nutrition support was clinically indicated immediately.

This is the first study to our knowledge to trial an early prophylactic tube feeding intervention prior to treatment in a target population who are primarily well-nourished with minimal dysphagia. This group may be considered to have low motivation to use their tube as there is no current obvious problem with eating, but despite good baseline nutritional and swallowing status, these patient have still been shown to have high rates of tube feeding and weight loss during treatment (Brown et al., 2015). The validation of the protocol used at our institute to identify patients for prophylactic gastrostomy also supports this finding (Brown et al., 2016b). The criteria used in this protocol are primarily based on tumour site and treatment, and so the majority of patients selected are those receiving chemoradiotherapy for unresectable tumours or as organ-preserving treatment. By increasing nutritional intake through prophylactic supplementary tube feeding it was assumed this would assist in reducing weight loss. The additional rational for this interventional approach was based on the psychological impact of gastrostomy tube placement, including anxiety and fear associated with tube use (Salas et al., 2009, Merrick & Farrell, 2012). Therefore this period of early tube feeding could assist patients to adapt to the tube more easily.

The aim of this study is to compare nutritional, clinical and patient outcomes following an early tube feeding approach via the prophylactic gastrostomy versus standard care of commencing tube feeding via the prophylactic gastrostomy when clinically indicated. The null hypothesis being no difference in the outcomes between the two groups. It is anticipated that the intervention group will have improved nutritional outcomes, according to an established nutrition framework, which in turn is expected to improve patient outcomes, such as quality of life, and other clinical outcomes (Splett, 1996).

MATERIALS AND METHODS

This was a single centre randomised controlled trial conducted in Queensland, Australia. The full protocol is published (Brown et al., 2014b). The study design was a parallel group study using equal randomisation (1:1). No changes occurred to the study design or outcome measures following commencement.

Participants and Study Setting

Patients with HNSCC were eligible for the study if referred for a prophylactic gastrostomy prior to treatment. A local protocol was used by the multidisciplinary clinic to identify high nutrition risk patients suitable for prophylactic gastrostomy (Brown et al., 2016b), however the final decision of tube placement was made by the treating team. Excluded patients included; age < 18; pregnant; cognitively impaired or with an intellectual disability or mental illness; planned for non-curative intent treatment; or if diagnosed as severely or moderately malnourished with significant dysphagia requiring a liquid or puree texture modified diet.

The study was approved by the Royal Brisbane and Women's Hospital Human Research Ethics Committee on 19th July 2012 (HREC/12/QRBW/162) and The University of Queensland Medical Research Ethics Committee on 8th August 2012 (2012000890). All patients provided written informed consent to participate. This trial has been registered in the Australian New Zealand Clinical Trials registry as ACTRN12612000579897. Available at http://www.anzctr.org.au.

Patients were recruited from the Royal Brisbane and Women's Hospital from September 2012 to June 2015. This is a major tertiary/quaternary hospital providing specialist cancer care services to patients throughout Queensland, Australia. All patients see the dietitian and speech pathologist as part of routine care, with access to other allied health services as required.

Dependent on the patient's home address and local health service district location, follow up care post treatment may continue at the tertiary centre or be transferred to a regional cancer centre. Level of allied health services and thus access to follow up care at each regional centre may vary, particularly for patients from rural or remote areas.

Interventions

All patients received education on the care of their feeding tube during their overnight elective admission for gastrostomy placement. Prior to discharge patients were randomly allocated to either the standard care or intervention arm and booked into the joint dietitian and speech pathology clinic for weekly review during treatment.

In the standard care arm, patients were commenced on enteral nutrition via their prophylactic gastrostomy by the dietitian when indicated. Indicators included: oral intake less than 60% of estimated energy requirements (based on 125-145kJ/kg) for a period of, or anticipated to be, greater than 10 days; the patient was unable to maintain weight; the patient required significant texture modification of diet; or the patient had increased or uncontrolled nutrition impact symptoms. The regimen was determined by the clinical dietitian to suit the patients' individual requirements and adapted as required during treatment.

For patients in the intervention group, this meant initiation of enteral nutrition via their prophylactic gastrostomy immediately following tube placement prior to commencement of treatment. The prophylactic enteral nutrition was in addition to their current oral intake and consisted of 2x 200ml bolus feeds (1.5kcal/ml polymeric formula with fibre) per day. Patients were provided with weekly supplies and were given guidance and suggestions on how to incorporate the enteral feeding into their daily routine (e.g. behavioural strategies and reminders; appropriate timings for administration, such as between meals). This enteral nutrition recommendation was continued until completion of treatment, and was increased as necessary during treatment if the patient had any of the clinical indicators for starting enteral nutrition as described in standard care. If patients required an increase in enteral nutrition they were converted to a home enteral nutrition prescription and were required to pay a co-payment for the product as per standard care. If patients described enteral feed intolerance, an alternative non-fibre formula was trialled.

To monitor adherence, patients in both arms were asked to maintain a self-reporting diary of their daily prescribed enteral nutrition intake, and any barriers to this prescription. These were verified by the clinical dietitian on weekly review. Overall adherence was defined as achieving $\geq$75% of prescribed enteral nutrition intake (Hubbard, Elia, Holdoway, & Stratton, 2012). All patients were encouraged to maintain oral intake as much as possible during treatment and as long as it remained safe to do so as per the speech pathologist. On completion of treatment all patients were referred to their local dietitian service for ongoing care as required.

Outcomes

The primary endpoint was percentage weight change with additional nutrition outcomes including body composition (fat mass and fat free mass) and nutritional status. Weight and body fat percentage were measured on digital Bioelectrical Impedance Analysis (BIA) scales (Tanita Body Composition Monitor BC-582, Manufacturer Tanita Corporation, Japan) at recruitment (baseline) and three months post treatment. Patients were asked to remove shoes, socks and outer clothing and to empty their pockets. Nutritional status was assessed by the Patient-Generated Subjective Global Assessment tool (PGSGA) (Bauer et al., 2002), a validated tool recommended to assess nutritional status in patients with cancer (Isenring et al., 2013).

The secondary endpoint was quality of life, which was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) tools (Aaronson et al., 1993). The questionnaires included the quality of life of cancer patients (EORTC QLQ-C30) and the module for head and neck (EORTC QLQ-H&N35). The raw data was transformed into scores ranging from 0-100, following established procedures (Fayers et al., 2001). A higher score for global quality of life and functioning scales was indicative of higher quality of life and function. A higher score for symptom scales was indicative of a higher level of symptom burden. Guidelines for interpretation of longitudinal changes in quality of life scores for EORTC QLQ-C30 were used to determine clinical impact (Cocks et al., 2012) and these were graded as either an improvement or deterioration, with trivial, small, medium or large clinical effect.

Tertiary endpoints included tolerance to chemotherapy and radiotherapy, rate of unplanned hospital admissions and gastrostomy complications. Dose of chemotherapy and radiotherapy received were recorded. Delays to radiotherapy were recorded as days beyond expected finish date and a prolonged treatment time was defined as those greater than seven days. Completion of planned chemotherapy was defined as either completion of three cycles of high dose cisplatin, seven cycles of weekly cisplatin or eight cycles of cetuximab. Completion of target dose was defined as $\geq$200mg/m2 cisplatin or $\geq$ six cycles of cetuximab. Reasons for changes to chemotherapy were coded as toxicities (gastrointestinal, haematological, renal, or other).

Unplanned hospital admissions and length of stay were prospectively recorded during treatment and classified as either a medical admission, or management of gastrostomy complications or management of nutrition impact symptoms.

Gastrostomy complications were recorded during the first three months post insertion. Major complications were defined as those requiring hospital admission. Minor complications were defined as site infections or other stoma issues such as hypergranulation, excoriation, erythema, pressure injury or leakage. Monthly follow up was completed via the telephone to assess gastrostomy use and date of removal for up to six months post treatment. If the tube was still in-situ at six months, then follow up was repeated at 12 months. Day of gastrostomy removal was recorded in relation to the day of treatment completion.

Treatment response was assessed via the three month post treatment PET/CT scan and defined as either complete metabolic response, or persistent disease requiring salvage surgery or persistent disease requiring palliative care. Survival outcomes were assessed at 12 months post treatment and time (in months) to disease relapse and/or death were recorded.

To enhance the quality of the measurements and to reduce any inter-rater variability in assessment the data was collected by the designated research dietitian. If patients failed to attend their follow up appointment, quality of life data were obtained by telephone interview and/or completion of postal surveys, and weight and PGSGA data were obtained following face to face assessment by the local dietitian.

Sample Size

The primary outcome for the study was a continuous response variable of percentage weight loss. The aim was to reduce the absolute amount of percentage weight loss by 5% in the intervention group compared to the percentage weight loss seen in the standard care group. A sample size of 123 patients was required to detect a 5% difference in percentage weight loss between the intervention and control groups, with a two sided 5% significance level, power of 80% and an attrition factor of 10%. Recruitment continued until sample size was attained.

Randomisation

Patients were stratified according to baseline nutritional status (well nourished (PGSGA A) versus moderate/suspected malnutrition (PGSGA B)), and then randomly assigned to one of two groups (with an allocation ratio 1:1) following simple randomisation procedures. The randomisation sequence was computer generated using MS Excel. This allocation sequence was concealed to the researcher enrolling participants but the participants, healthcare team or outcome assessor were not able to be blinded to the allocation.

Statistical Methods

Baseline participant characteristics were summarised using mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Differences between groups were assessed using Chi-squared tests for categorical variables (or Fishers Exact test if assumptions could not be met due to small expected cell counts) and two sample t –tests for continuous variables (or two sample Wilcoxon tests if assumptions could not be met for normally distributed data and homogeneity of variance). Normal distribution was formally assessed using Shapiro-Wilk test and variance assessed using Levene's test. Analysis was performed on an intention to treat basis. To determine the effect of the nutrition intervention group versus the control group (the independent categorical variable) on the primary outcome of % weight loss (the dependent continuous variable), analysis of variance (ANOVA) was used. For the secondary outcomes (% fat free mass, % fat mass, PGSGA score and quality of life scores), the mean change over time from baseline to three months was also analysed between groups using ANOVA. Bivariate analysis determined the association of any other independent variables on the outcome measures. Any variables with statistically significant associations ($p<0.1$) were entered into a linear regression model (or logistic regression for any binary outcome variables). Any variables with baseline differences between groups were also added into the model as covariates to adjust for any confounding effects. Final variable selection for each multivariable model used Akaike's Information Criteria (AIC) with a backward stepwise algorithm. The final models reported were those with the smallest objective AIC. Time to event outcomes (gastrostomy removal, disease relapse, death) were analysed using the Kaplan Meier method with the log rank test. Statistical significance was set at $p<0.05$. Data were analysed using R Commander Version 2.1-7 and R version 3.1.3 (2015-03-09) (R Foundation for Statistical Computing, Vienna, Austria). For any results that were not statistically significant, any relevant clinically significant results were reported.

RESULTS

Eligible patients (n=174) were invited to participate in the study between September 2012 to June 2015 with 131 patients recruited and randomised (Figure 8-1). The final 12 month outcomes were completed in August 2016 and all patients were analysed on an intention-to-treat basis. Patient, clinical and treatment characteristics and their baseline nutrition measures are summarised in Table 8-1 and baseline quality of life measures are available in Supplementary Table 1 (Table 8-4).

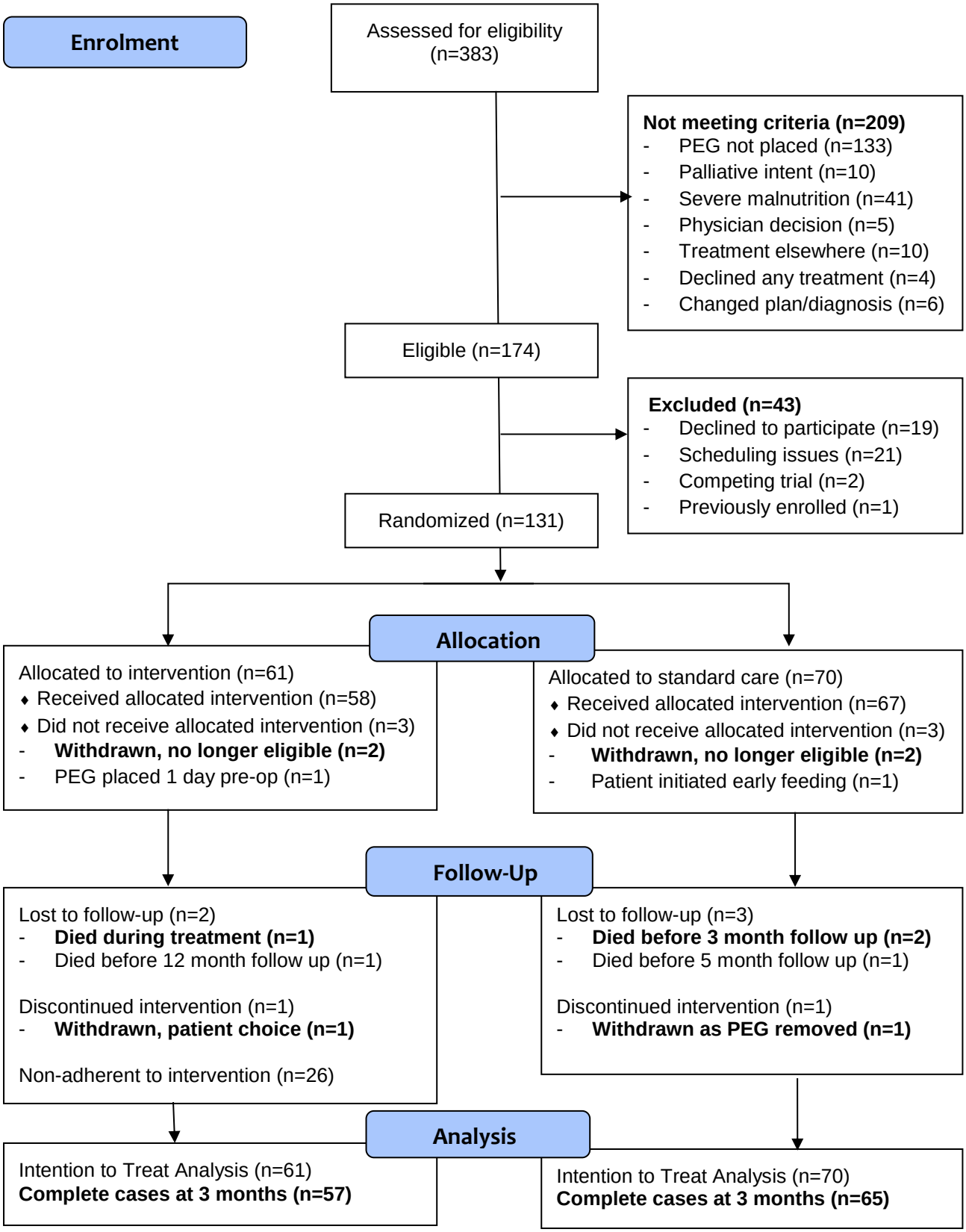


Figure 8-1: CONSORT Flow Diagram

Abbreviations: PEG=gastrostomy.

Table 8-1: Summary of patients enrolled in the trial and comparison of baseline characteristics between standard care and intervention groups

Variable	Total (n=131)	Standard Care (n=70)	Intervention (n=61)	P value
Age				
Years (mean ± sd)	60.5 ± 10.1	60.0 ± 10.9	61.1 ± 9.1	0.558
Sex				
Male	115 (88)	59 (84)	56 (92)	0.19
Female	16 (12)	11 (16)	5 (8)	
Smoking history				
Non smoker	26 (20)	14 (20)	12 (20)	
Former	81 (62)	39 (56)	42 (69)	0.147
Current	24 (18)	17 (24)	7 (11)	
Tumour Site				
Oral cavity	14 (11)	7 (10)	7 (11)	0.885
Oropharynx	101 (77)	56 (80)	45 (74)	
Nasopharynx	4 (3)	2 (3)	2 (3)	
Hypopharynx	8 (6)	3 (4)	5 (8)	
Larynx	2 (1)	1 (1)	1 (2)	
UKP	1 (1)	0 (0)	1 (2)	
Other	1 (1)	1 (1)	0 (0)	
T Stage				
T0	1 (1)	0 (0)	1 (2)	0.111
T1	8 (6)	4 (5)	4 (7)	
T2	44 (34)	20 (29)	24 (39)	
T3	37 (28)	26 (37)	11 (18)	
T4	41 (31)	20 (29)	21 (34)	
N Stage				
N0	12 (9)	7 (10)	5 (8)	0.629
N1	13 (10)	8 (11)	5 (8)	
N2a	4 (3)	1 (1)	3 (5)	
N2b	55 (42)	30 (43)	25 (41)	
N2c	42 (32)	20 (29)	22 (36)	
N3	5 (4)	4 (6)	1 (2)	
p16 status				
Positive	85 (69)	43 (65)	42 (72)	0.385
Negative	39 (31)	23 (35)	16 (28)	
Treatment				
ChemoRT	123 (94)	67 (96)	56 (92)	0.472
Other	8 (6)	3 (4)	5 (8)	
Chemotherapy				
HD cisplatin	68 (58)	36 (56)	32 (60)	0.382
Weekly cisplatin	25 (21)	12 (19)	13 (25)	
Cetuximab	24 (21)	16 (25)	8 (15)	

Weight Loss 6mths				
Nil	51 (39)	22 (31)	29 (48)	0.266
<5%	43 (33)	27 (39)	16 (26)	
5-10%	22 (17)	12 (17)	10 (16)	
>=10%	15 (11)	9 (13)	6 (10)	
Nutritional status				
PG-SGA A	99 (76)	50 (71)	49 (80)	0.237
PG-SGA B	32 (24)	20 (29)	12 (20)	
PG-SGA C	0 (0)	0 (0)	0 (0)	
Diet				
Full	87 (66)	47 (67)	40 (66)	0.579
Soft	35 (27)	20 (29)	15 (25)	
Minced	8 (6)	3 (4)	5 (8)	
Puree	1 (1)	0 (0)	1 (1)	
Anthropometry				
Weight (kg)	82.6 $\pm$ 18.7	79.7 $\pm$ 18.7	85.8 $\pm$ 18.4	0.063
Fat free mass (kg)	59.2 $\pm$ 10.4	57.6 $\pm$ 10.5	60.9 $\pm$ 10.1	0.073
BMI (kg/m2)	27.2 $\pm$ 5.5	26.4 $\pm$ 5.7	28.1 $\pm$ 5.2	0.078
Nutrition Risk				
PG-SGA score (median, range)	6 (1-21)	6 (1-21)	5 (1-20)	0.052

Abbreviations: UKP=Unknown primary; ChemoRT=Chemoradiotherapy; HD=High Dose; PG-SGA=Patient Generated Subjective Global Assessment; BMI=Body Mass Index.

In the standard care group two patients received surgery alone and one patient had radiotherapy alone. There were five patients in the intervention group who had post-operative radiotherapy. All other patients in the study received definitive or adjuvant chemoradiotherapy (94%), of which five also had neoadjuvant chemotherapy. Radiotherapy was delivered by helical intensity modulated radiotherapy for 98% of patients, with definitive doses at >66Gy (n=111) and adjuvant doses at 60-66Gy (n=12). Most patients had their gastrostomy placed via endoscopy (93%) versus radiologically (7%), a median of five days prior to treatment in each group (p=0.277).

Nutrition Outcomes

There were no significant differences for weight loss, body composition or nutritional status once adjusted for any differences at baseline or any other confounding variables in multivariable models (Table 8-2). The only predictors of weight loss in the multivariate model were baseline BMI and P16 status; with every 10 unit increase in BMI there was approximately 4% more weight loss, and patients with p16 negative disease had approximately 4% less weight loss than those with p16 positive disease. No variables were identified to predict loss of fat free mass loss. Predictors of other nutritional outcomes (fat mass and PGSGA) from multivariable models are summarised in Supplementary Table 2 (Table 8-5).

Quality of Life Outcomes

There were no statistical differences in any of the domains of quality of life or functional scales after adjusting for any baseline differences. See Supplementary Table 3 (Table 8-6). Multivariable models were created for global quality of life, functioning scales and selected symptoms scales for which the intervention may have impacted on (e.g. fatigue, appetite, gastrointestinal symptoms, dysphagia and social eating), however no significant effects of the intervention were found following adjustment for other confounding variables. See Supplementary Table 4 (Table 8-7). On review of the clinical impact of quality of life (EORTC QLQ-C30) the majority of domains showed some degree of deterioration over time (particularly loss of appetite, role functioning and fatigue) but comparisons between groups was limited due to baseline differences. The only exception was social functioning which was similar at baseline, but clinical differences were seen with a medium deterioration in the intervention group and no change in the standard group. See Supplementary Table 5 (Table 8-8).

Table 8-2: Summary of unadjusted and adjusted linear regression analysis for the effect of the early nutrition intervention on nutrition outcomes in patients with head and neck cancer compared to standard care

Outcome Variable	Comparison of Outcomes Between Groups		Summary of Regression Analysis (Ref: Standard Care)								
	Standard Care	Intervention	Unadjusted		Adjusted for baseline differences		Adjusted in full multivariable model				
	Mean ± sd		β	P value	β	P value	β	SE	95% CI		P value
Weight (% change)	-10.9 ± 6.6	-10.8 ± 5.6	0.1	0.93	1.01	0.326	0.48	0.98	-1.46	2.43	0.624
Fat Free Mass (% change)	- 4.2 ± 4.9	-6.3 ± 5.4	-2.06	0.036*	-1.51	0.104	-1.22	0.92	-3.03	0.6	0.187
Fat Mass (% change)	-28.5 ± 16.7	-22.7 ± 15.2	5.85	0.056	NA	NA	1.72	2.64	-3.52	6.96	0.515
PG-SGA score (change)	3.2 ± 6.0	3.7 ± 5.3	0.45	0.665	-0.52	0.534	-0.28	0.86	-1.98	1.42	0.743
SGA nutritional status (% decline)	31%	26%	OR 0.79	0.551	NA	NA	OR 0.78	1.55	0.33	1.83	0.569

Abbreviations: PG-SGA=Patient Generated Subjective Global Assessment; SGA=Subjective Global Assessment.

Radiotherapy tolerance

The proportion of patients completing planned radiotherapy treatment was 100% in standard care (n=65/65) and 95% in the intervention group (n=55/58) (p=0.102). Two patients in the intervention failed to attend scheduled treatment (one patient completed 62/70Gy and one patient completed 66/70Gy) and one further patient died during treatment from liver failure due to complications of chemotherapy. There was no difference in rates of treatment re-planning (22% standard care vs 19% intervention, p=0.723) or delays to radiotherapy treatment (n=9 standard care vs n=7 intervention, p=0.381). Three patients in the intervention and one patient in standard care had a prolonged treatment time which were due to: admission for myocardial infarction; admission to a regional hospital for neutropenia and infection; admission to manage severe mucositis and secretions; and identification of a new node requiring re-scanning and planning.

Chemotherapy tolerance

Although only approximately half of patients completed their planned chemotherapy prescription (59% standard care vs 51% intervention, p=0.361), almost all completed the target dose of chemotherapy (95% standard care vs 98% intervention, p=0.407). Overall there was no statistical difference in the changes to the planned chemotherapy (45% standard care vs 53% intervention, p=0.418). The toxicity reasons for deviations from the prescribed chemotherapy plan were similar in each group: haematological (42%), renal (27%), gastrointestinal (5%) and other (22%).

Unplanned Admissions

Unplanned admissions affected approximately half of all patients in each group (47% standard care vs 57% intervention, p =0.270) with no statistical differences for reasons for admissions or associated length of stay (Table 8-3). Nutrition-related admissions accounted for 47% of all admission events in the standard care group (n=20/43) and 53% in the intervention group (n=20/38).

Table 8-3: Summary of the effect of the early nutrition intervention on unplanned admissions and LOS in patients with head and neck cancer

	Standard Care	Intervention	P value
Total number of patients with an unplanned admission	31	33	0.27
Reason for unplanned admission	**n (%)**		
Clinical	15 (48)	12 (36)	0.33
Nutrition	20 (65)	20 (61)	0.747
G tube	8 (26)	6 (18)	0.461
LOS per unplanned admission	**Median (range)**		
Clinical	3 (1-23)	6 (1-36)	0.182
Nutrition	4 (1-24)	5 (2-25)	0.981
G tube	3 (1-22)	1 (1-2)	0.154

Abbreviations: LOS=Length of Stay; G tube=Gastrostomy tube.

Gastrostomy Outcomes

There was no gastrostomy placement associated mortality. Major tube complications were similar in each group (12% standard care vs 10% intervention, p=0.775). Pain management accounted for 45% of all major complications (n=9/20). Minor tube complications affected 40% of patients in both groups (p=0.995), and events included: site infections requiring oral antibiotics (n=27), other site/stoma complications (n=29). Fifty percent of all patients had commenced clinically indicated tube feeding by week three. Tube use was high at the end of treatment with no differences between groups (88% standard care and 86% intervention, p=0.776). The mean day of tube removal from completion of treatment was 104.7 +/- 54.0 days in the standard care group vs 115.5 +/- 62.5 days in the intervention group (p=0.333).

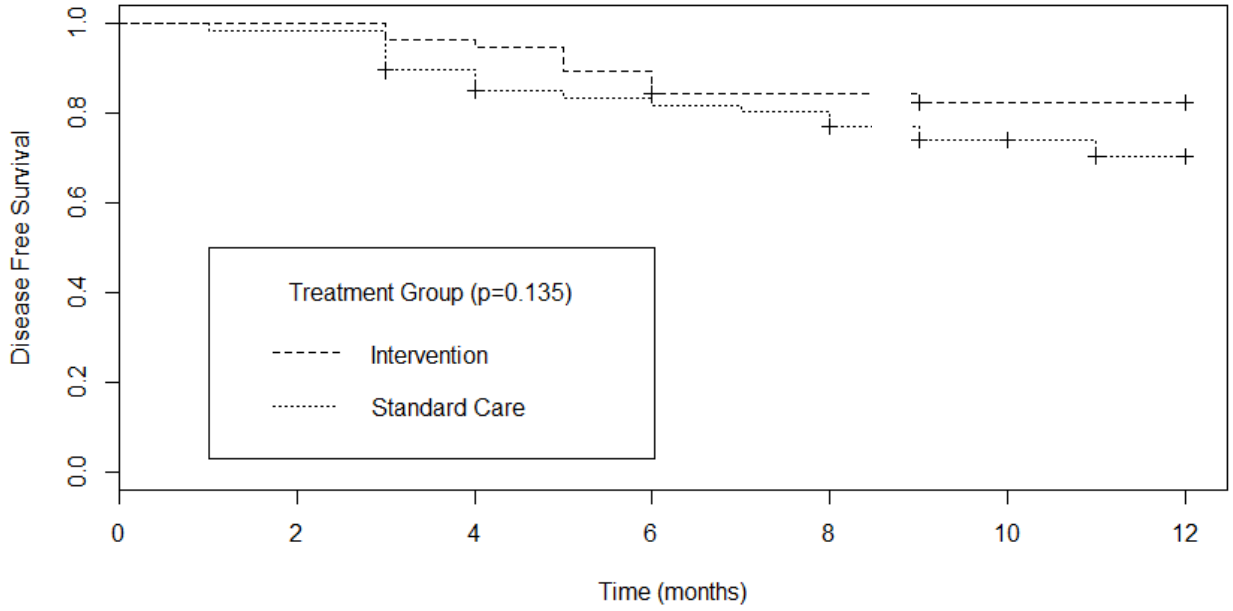
Survival and Disease outcomes

The outcomes on PET at three months post treatment were no different between groups (p=0.661). A complete response was seen in 78% of patients in standard care (n=49) and 81% in the intervention (n=42). Salvage surgery for persistent disease was carried out for six patients in each group, and palliative care was required for eight patients in standard care and four patients in the intervention. At 12 months there were no differences in disease free survival or overall survival, with 19 cases of disease relapse in the standard care group and 10 cases in the intervention group (p=0.135) (Figure 8-2a) and six and five deaths in the standard care and intervention group respectively (p=0.946) (Figure 8-2b).

Additional analysis

Adherence to the intervention was defined as consuming $\geq$75% of the prescribed enteral feeding and unfortunately this was only achieved by 51% of patients. Due to this poor adherence, a per-protocol analysis was also performed to compare those patients who adhered to the intervention (n=29) to standard care (n=57) but no significant differences were found for any outcomes. When adherence to the therapeutic phase of feeding was compared (i.e. when tube feeding became clinically indicated in each group) the intervention group had a higher adherence (58% vs 38%, p=0.037). Adherent patients (n=49) had less weight loss than non-adherent patients (n=55) (-10.3% vs -12.6%, p=0.038).

Weight outcomes at the end of treatment were reviewed using routine clinical data. Weight loss was -6.7% +/- 5.3 in standard care versus -6.1% +/- 4.5 in the intervention group on an intention-to-treat basis (p=0.466) and -5.6% +/- 4.6 in the adherent intervention group on a per-protocol basis (p=0.299).



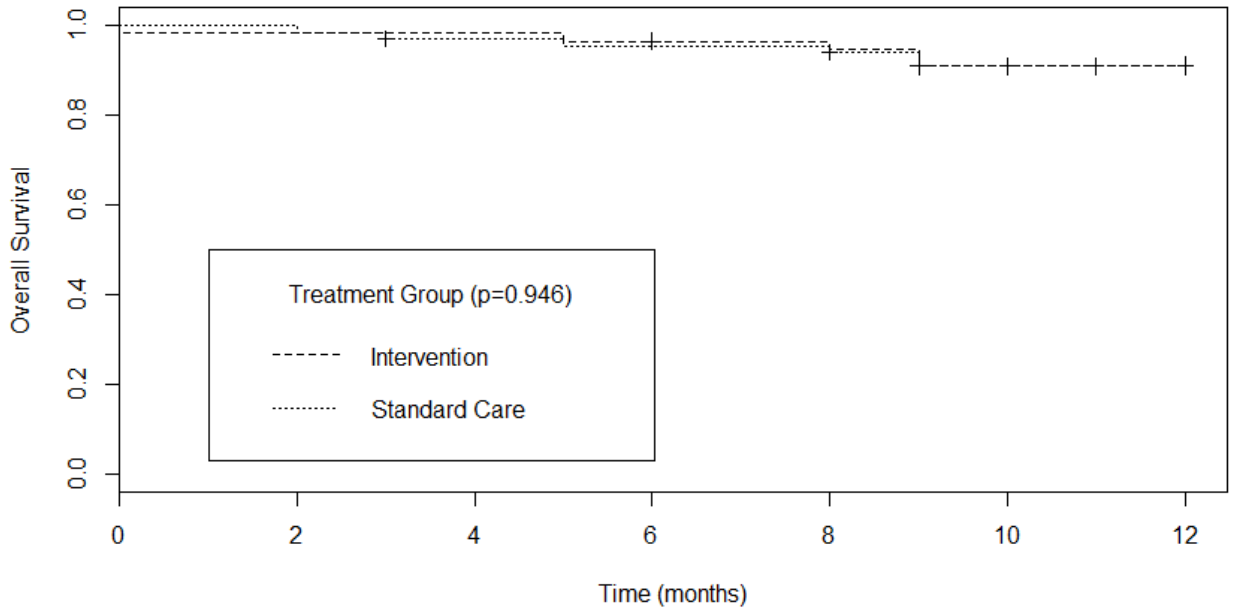


Figure 8-2: Kaplan Meier curves to compare disease free survival (a) and overall survival (b) at twelve months post-treatment between standard care and intervention groups

DISCUSSION

This randomised controlled trial investigating an early tube feeding intervention was primarily conducted in a well-nourished group of patients with HNSCC who had a prophylactic gastrostomy placed prior to treatment without any significant dysphagia. The results from the intention-to-treat analysis found no impact on weight loss outcomes at three months post treatment, with both groups losing approximately 10% of their body weight. Consequently there were no statistical differences in any of the other secondary outcomes in regards to nutritional status, body composition, quality of life or other clinical outcomes.

The overall body composition results are very similar to a recent report (although they measured outcomes at one month post treatment), with an absolute percentage fat mass loss of 3.9% and a FFM loss of 2.4kg, versus our measures of 4.3% and 3.3kg (de Carvalho et al., 2015). One study has reported lean mass accounts for 62% of weight loss mass (Jager-Wittenaar et al., 2011b), however this present study found the reverse with fat mass accounting for 67% of weight loss. The preservation of fat free mass with nutrition intervention has been reported in other studies (Isenring, Capra, Bauer, & Davies, 2003). Further research is required on changes in body composition during and post treatment to understand any long term implications. Meanwhile routine monitoring of body composition is suggested as this provides more information than body weight alone.

This is the first study to report on outcomes following an early prophylactic tube feeding intervention. There has been one other study which has described an early nutrition intervention of dietary counseling pre-chemoradiotherapy compared to a historical control group, which found statistically significantly less weight loss, fewer breaks in radiotherapy and less unplanned admissions (Paccagnella et al., 2010). However their early nutrition intervention was essentially equivalent to our control group. A similar style of study has recently been undertaken in patients with lung cancer (Kiss et al., 2016). Our current study design initiates supplementary prophylactic tube feeding prior to commencement of treatment and so could be described as an even more intensive early intervention. The only other study to our knowledge which has looked at early nutrition interventions in patients with HNSCC is a secondary analysis in patients undergoing definitive radiotherapy as part of a larger prospective RCT (n=1073) (Rabinovitch et al., 2006). Their results showed that although patients who received nutrition support prior to treatment had benefits in terms of less weight loss and less grade three or four mucositis, they ultimately had poorer overall survival (Rabinovitch et al., 2006).

Their patients who received pre-treatment nutrition support had more advanced stage tumours, lower performance status, more weight loss in last six months and more grade three and four dysphagia at baseline, and the detrimental impact of malnutrition at diagnosis on overall survival is well known (Datema, Ferrier, & Baatenburg de Jong, 2011). The methodological limitations of these exploratory findings are acknowledged by the authors and they recommend that RCT's are required to explore how nutrition support in the malnourished patient may negatively impact upon treatment outcomes (Rabinovitch, Berkey, Raben, & Cooper, 2007), however there have been no further studies in this field.

Other factors also need to be taken into consideration in interpretation of these findings such as evolving treatment and disease, with patients now primarily receiving chemoradiotherapy (compared to radiotherapy alone) and a higher incidence of human papilloma virus (HPV) associated tumours (Hocking et al., 2011). The profile of patients selected for our study was also quite different as the eligibility criteria focused on well-nourished patients with minimal dysphagia. Given critical weight loss during treatment is also an independent prognostic indicator of worse disease-specific and overall survival rates (Langius et al., 2013a) and even subtle weight loss of 2.4% is related to decreased survival (Martin et al., 2015), these studies highlight the importance of including mortality as an outcome for any nutrition intervention studies. Our one year survival outcomes to date have not demonstrated any differences with respect to the timing of nutrition intervention, although this was not the primary outcome and sample size may be a limiting factor to draw any firm conclusions. Further survival analysis is planned at five years post treatment.

One of the potential reasons for the negative findings from this trial was the poor adherence to the prescribed nutrition intervention (51%) which was much lower than expected. A study in hospitalised patients found 87% of prescribed tube feedings were met, however this was in a group of patients that were entirely dependent on enteral nutrition (van den Broek, Rasmussen-Conrad, Naber, & Wanten, 2009). A systematic review on adherence to prescribed oral nutrition supplements, which is perhaps more akin to the supplementary bolus feeds used in this study, found a mean adherence of 79% (Hubbard et al., 2012). The prescribed daily tube feeds for the intervention were provided to the patients at no extra cost to facilitate adherence, as it has been shown that provision of complimentary nutritional supplements can improve outcomes (Lee et al., 2008b), but this did not appear to help in this case.

Key barriers patients encountered to tube feeding recommendations were nausea and early satiety, as well as a perception that the extra tube feeding was not required as patients felt they were eating normally. Further qualitative research is recommended to investigate these barriers in depth, as they are potentially modifiable and can be addressed. Improving adherence to dietary recommendations has been shown to result in improved outcomes both within this study and others (Capuano et al., 2008, Hopanci Bicakli et al., 2017). The characteristics of this patient population also suggest that adherence may be particularly challenging given the high rate of mental health problems, substance use and social issues which increases psychologic distress and depression (Kugaya et al., 2000, DiMatteo, Lepper, & Croghan, 2000). Adherence to other aspects of clinical management, such as adherence to radiotherapy protocols by the clinician, has also been shown to influence patient outcomes (Peters et al., 2010).

The main limitation of this study is that, despite a motivated patient cohort, poor adherence to the intervention impacted on the power of the study which may also explain why no significant differences were found on the post-hoc per-protocol analysis. Steps were taken through the study by the research dietitian to improve adherence such as; increased communication to the multidisciplinary team and more regular contact with the intervention patients. The clinician staff did change over the course of the study period which may have led to variations in clinical practice, however this is reflective of the pragmatic nature of nutrition care delivery in healthcare settings, and was minimised as much as possible, particularly for the intervention care arm. Whilst attrition from the study was generally very low, geographical location of patients did inhibit some follow up care for the study, particularly for physical measurement of BIA.

Our study identified P16 status as a strong confounding variable associated with a number of outcomes which was adjusted for in the multivariate models, however, given the impact of HPV status on survival outcomes (Ang et al., 2010) it is increasingly being suggested that clinical trials should stratify for smoking, staging and HPV (P16) status. Differences in quality of life related to tube feeding may also not have been addressed with the tools used, however they are the most widely accepted tools used in this population (Ojo et al., 2012). Future studies could consider additional tools specifically related to tube feeding, such as the QOL-EF (Stevens et al., 2011). Finally swallowing outcomes were not measured using a validated assessment tool in this study, but there was no impact of long term gastrostomy dependency as a surrogate measure of dysphagia.

This interventional approach is not only restricted to hospitals which utilise prophylactic gastrostomy placement. Although designed as a tube feeding intervention, it could still be used by sites who prefer the reactive approach to nutrition management during treatment, as the supplements could be prescribed orally, and this is actually what some of our patients preferred to do. They were still included in the study as their nutritional intake was still being supplemented whether it was by the oral or enteral route. Only 11% of eligible patients (19/174) declined to participate which demonstrated a high acceptability of the trial, although this did not translate into adherence.

The use of prophylactic gastrostomy tubes remained high in this cohort of pre-defined high nutritional risk patients, with 87% of all study patients using their tube at the end of treatment, which confirms appropriate decision-making regarding tube placement. Although the early nutrition intervention did not minimise weight loss or improve other associated outcomes, this study has highlighted the significant barriers that patients encounter. Given the finding that patients who followed the early nutrition intervention had higher levels of adherence to nutrition recommendations later on in treatment, which did reduce weight loss, it is planned to introduce this approach into practice.

In conclusion this research demonstrates the high complexity of managing patients with head and neck cancer, as desired outcomes have not been attained even with intensive intervention and support. Whilst this novel early nutrition intervention can be considered to assist adherence, it is but one of many potential strategies. A multi-component intervention by the multidisciplinary team is recommended to adequately address and overcome patient barriers to healthcare recommendations before further improvements in nutrition outcomes are realised.

Table 8-4: Supplementary Table 1 - Comparison of baseline quality of life in patients with head and neck cancer in the early nutrition intervention and standard care groups

Variable	Baseline Quality of Life (QOL) scores		
	Standard Care (n=70)	**Intervention (n=61)**	**Wilcoxon Two Sample Test**
	Mean +/- sd **Median (range)**	**Mean +/- sd** **Median (range)**	**p value**
EORTC-QLQ C30			
Global Health Status/QOL	65.2 ± 22.8 67 (0-100)	73.9 ± 20.0 83 (17-100)	0.025*
Physical functioning	86.7 ± 17.9 93 (20-100)	93.6 ± 9.0 100 (60-100)	0.085
Role functioning	79.1 ± 27.3 92 (0-100)	89.1 ± 21.5 100 (0-100)	0.011*
Emotional functioning	73.3 ± 18.9 75 (8-100)	78.7 ± 19.0 83 (17-100)	0.071
Cognitive functioning	80.9 ± 21.3 83 (0-100)	87.6 ± 14.6 83 (50-100)	0.089
Social functioning	77.4 ± 26.9 83 (0-100)	83.3 ± 22.8 100 (0-100)	0.257
Fatigue	28.9 ± 23.6 22 (0-89)	17.2 ± 17.0 22 (0-67)	0.004*
Nausea and vomiting	5.0 ± 10.4 0 (0-33)	3.3 ± 9.0 0 (0-50)	0.301
Pain	30.7 ± 30.1 25 (0-100)	18.4 ± 24.3 17 (0-100)	0.017*
Dyspnoea	11.1 ± 20.3 0 (0-67)	10.4 ± 17.8 0 (0-67)	0.94
Insomnia	36.2 ± 30.4 33 (0-100)	24.6 ± 26.5 33 (0-100)	0.024*
Appetite loss	21.4 ± 30.1 0 (0-100)	9.3 ± 18.4 0 (0-100)	0.017*
Constipation	12.4 ± 22.1 0 (0-100)	11.2 ± 21.2 0 (0-100)	0.763
Diarrhoea	7.1 ± 14.9 0 (0-67)	2.2 ± 8.3 0 (0-33)	0.026*
Financial difficulties	27.4 ± 36.1 0 (0-100)	21.9 ± 30.4 0 (0-100)	0.498

Variable	Baseline Quality of Life (QOL) scores		
	Standard Care (n=70)	Intervention (n=61)	Wilcoxon Two Sample Test
	Mean +/- sd Median (range)	Mean +/- sd Median (range)	p value
EORTC-QLQ H&N35			
Pain	31.1 ± 27.5 25 (0-100)	19.9 ± 19.8 17 (0-67)	0.017*
Swallowing	13.6 ± 18.1 4 (0-67)	11.8 ± 16.4 0 (0-58)	0.708
Senses Problems	12.6 ± 21.1 0 (0-100)	8.2 ± 13.8 0 (0-50)	0.324
Speech Problems	19.2 ± 19.2 11 (0-78)	13.5 ± 18.5 11 (0-78)	0.035*
Social eating	16.2 ± 18.9 8 (0-67)	11.8 ± 17.7 0 (0-92)	0.147
Social contact	8.00 ± 13.4 0 (0-60)	5.1 ± 10.4 0 (0-40)	0.098
Less sexuality	15.7 ± 27.5 0 (0-100)	22.8 ± 33.6 0 (0-100)	0.278
Teeth	14.3 ± 28.1 0 (0-100)	14.2 ± 23.9 0 (0-100)	0.618
Opening mouth	23.3 ± 31.8 0 (0-100)	12.6 ± 28.0 0 (0-100)	0.006*
Dry mouth	26.7 ± 26.4 33 (0-100)	19.1 ± 26.8 0 (0-100)	0.048*
Sticky saliva	21.4 ± 27.8 0 (0-100)	19.1 ± 26.9 0 (0-100)	0.61
Coughing	25.2 ± 26.3 33 (0-100)	19.7 ± 25.4 0 (0-100)	0.171
Felt ill	11.9 ± 19.7 0 (0-67)	9.6 ± 17.9 0 (0-67)	0.494
Pain killer	70.0± 46.2 100 (0-100)	47.5 ± 50.4 0 (0-100)	0.009*
Nutritional supplements	21.4 ± 41.3 0 (0-100)	18.0 ± 38.8 0 (0-100)	0.631
Feeding tube	0 ± 0 0 (0-0)	0 ± 0 0 (0-0)	NA
Weight loss	30.0 ± 46.2 0 (0-100)	26.2 ± 44.4 0 (0-100)	0.636
Weight gain	25.7 ± 44.0 0 (0-100)	26.2 ± 44.4 0 (0-100)	0.949

Table 8-5: Supplementary Table 2 - Summary of multivariable models for effects on nutrition outcomes in patients with head and neck cancer

Linear Regression	**Unadjusted**				**Adjusted**				
Variable	**β**	**SE**	**95% CI**	**P value**	**β**	**SE**	**95% CI**		**P value**
Model for % weight loss (F(4,104)=14.3, p<0.001, R^2 = 0.354)									
Neoadjuvant chemo (Reference: no)									
- Yes	-5.21	2.71	-10.58	0.15	0.057	-3.00	2.41	-7.77	1.78	0.216
Age	0.14	0.05	0.03	0.25	0.011*	0.10	0.05	0.00	0.19	0.056
p16 (Reference: positive)									
- Negative	6.04	1.17	3.72	8.35	<0.001*	4.36	1.11	2.15	6.56	<0.001*
Baseline BMI	-0.55	0.09	-0.73	-0.37	<0.001*	-0.43	0.09	-0.61	-0.24	<0.001*
Model for % FFM loss (F(4,103)=7.7, p<0.001, R^2 = 0.230)									
Age	0.09	0.05	0.00	0.18	0.061	0.05	0.05	-0.04	0.14	0.264
Gender (Reference: male)									
- Female	2.91	1.58	-0.21	6.04	0.067	0.74	1.86	-2.95	4.44	0.690
p16 (Reference: positive)									
- Negative	3.19	1.09	1.03	5.35	0.004*	1.90	1.06	-0.21	4.01	0.077
Baseline FFM	-0.19	0.04	-0.28	-0.11	<0.001*	-0.18	0.06	-0.29	-0.07	0.002*

Model for % FM loss (F(9,92)=5.78, p<0.001, R^2 = 0.361) – *only significant variables shown*										
Age	0.26	0.15	-0.03	0.55	0.077	0.26	0.13	0.00	0.51	0.048*
Current Smoking (Reference: none)										
- High >20/day	-18.4	6.13	-30.55	-6.27	0.003*	-13.06	5.46	-23.91	-2.22	0.019*
p16 (Reference: positive)										
- Negative	9.93	3.35	3.29	16.56	0.004*	9.06	3.11	2.89	15.23	0.004*
Social support (Reference: Yes)										
- No	-10.4	3.46	-17.24	-3.54	0.003*	-11.37	3.07	-17.46	-5.27	<0.001*
Model for change in PG-SGA score (F(4,110)=18.6, p<0.001, R^2 = 0.403)										
Usual residence (Reference: City)										
- Regional	-2.58	1.06	-4.68	-0.47	0.017*	-0.89	0.90	-2.67	0.89	0.323
- Remote	-3.81	1.70	-7.18	-0.44	0.027*	-1.89	1.45	-4.76	0.98	0.194
p16 (Reference: positive)										
- Negative	-4.69	1.09	-6.84	-2.54	<0.001*	-2.36	0.99	-4.32	-0.41	0.018*
Baseline PG-SGA	-0.66	0.08	-0.82	-0.50	<0.001*	-0.57	0.09	-0.75	-0.39	<0.001*
Logistic Regression	**Unadjusted**					**Adjusted**				
Variable	OR	SE	95% CI		P value	OR	SE	95% CI		P value
Model for change in nutritional status (SGA)										
Gastrostomy tube (Reference: PEG)										
- RIG	3.42	2.02	0.85	14.62	0.081	6.85	2.62	1.13	59.0	0.046*
p16 (Reference: positive)										
- Negative	0.24	1.79	0.07	0.68	0.014*	0.21	1.84	0.06	0.63	0.011*

Abbreviations: BMI=Body mass index; FFM=Fat free Mass; FM=Fat mass; PG-SGA=Patient generated subjective global assessment; SGA=Subjective global assessment; PEG=percutaneous endoscopic gastrostomy; RIG=radiological inserted gastrostomy.

Table 8-6: Supplementary Table 3 - Comparison of change in quality of life scores over treatment in patients with head and neck cancer for the early nutrition intervention and standard care groups

Variable	Change in QOL scores		Linear Regression model			
	Standard Care (n=70)	Intervention (n=61)	Unadjusted (ANOVA)		Adjusted for baseline differences (ANCOVA)	
	Mean (sd)	Mean (sd)	β	p value	β	p value
EORTC-QLQC30						
Global Health Status/QOL	-2.9 + 22.7	-6.2 + 20.3	-3.28	0.405	0.8	0.818
Physical functioning	-5.5 + 14.1	-9.4 + 16.8	-3.93	0.164	-1.77	0.505
Role functioning	-4.7 + 31.6	-14 + 30.7	-9.35	0.102	-3.66	0.435
Emotional functioning	2.5 ± 18.9	2.3 ± 21.5	-0.13	0.971	2.14	0.526
Cognitive functioning	-5.7 + 23.6	-6.9 + 19.6	-1.14	0.775	-34.92	0.061
Social functioning	-2.1 + 27.1	-12.1 + 31.7	-10.05	0.063	NA	NA
Fatigue	8.4 ± 23.2	17.0 ± 22.4	8.63	0.040*	2.77	0.46
Nausea and vomiting	1.6 ± 15.1	4.7 ± 18.3	3.12	0.307	NA	NA
Pain	-8.3 + 29.7	-0.7 + 30.8	7.61	0.17	1.6	0.731
Dyspnoea	3.7 ± 25.5	0.6 ± 22.2	-3.12	0.479	NA	NA
Insomnia	-2.6 + 34.8	0.0 ± 37.3	2.61	0.691	-6.1	0.288
Appetite loss	19.8 ± 34.5	18.7 ± 28.2	-1.08	0.852	-6	0.282
Constipation	-0.5 + 21	2.6 ± 22.2	3.15	0.425	NA	NA
Diarrhoea	0.0 ± 20.6	1.8 ± 11.6	0	0.571	-3.87	0.131
Financial difficulties	1.8 ± 31.7	4.1 ± 35.7	2.27	0.712	NA	NA

Variable	Change in QOL scores		Linear Regression model			
	Standard Care (n=70)	Intervention (n=61)	Unadjusted (ANOVA)		Adjusted for baseline differences (ANCOVA)	
	Mean (sd)	Mean (sd)	β	p value	β	p value
EORTC-QLQ H&N35						
Pain	-5.1 + 27.6	-2.7 + 26.3	2.37	0.631	-4.93	0.202
Swallowing	6.2 ± 22.5	8.8 ± 28.1	2.66	0.564	NA	NA
Senses Problems	21.6 ± 27.2	19.6 ± 22.7	-2.03	0.659	NA	NA
Speech Problems	3.1 ± 20.6	8.2 ± 25.2	5.06	0.228	8.47	0.082
Social eating	13.7 ± 27.0	18.8 ± 31.2	5.12	0.335	NA	NA
Social contact	1.2 ± 15.8	6.1 ± 16.5	4.93	0.096	3.6	0.187
Less sexuality	13.0 ± 39.0	9.1 ± 38.6	-3.88	0.589	NA	NA
Teeth	1.0 ± 30.8	6.1 ± 38.7	5.1	0.421	NA	NA
Opening mouth	-1.6 + 31.1	4.1 ± 29.6	5.65	0.309	-0.38	0.939
Dry mouth	41.1 ± 38.4	55.6 ± 32.9	14.42	0.030*	8.95	0.094
Sticky saliva	32.3 ± 39.8	35.1 ± 44.7	2.79	0.717	NA	NA
Coughing	0.0 ± 31.4	4.7 ± 23.9	4.68	0.363	NA	NA
Felt ill	-0.5 + 19.2	-0.3 + 21.9	0.23	0.952	NA	NA
Pain killer	-29.7 + 60.9	-14 + 51.5	15.65	0.132	-0.04	0.997
Nutritional supplements	31.3 ± 61.4	31.6 ± 60.2	0.33	0.976	NA	NA
Feeding tube	26.6 ± 44.5	36.8 ± 48.7	10.28	0.227	NA	NA
Weight loss	-4.7 + 60.2	10.5 ± 67.3	15.21	0.192	NA	NA
Weight gain	10.9 ± 62.0	7.0 ± 67.8	-3.92	0.74	NA	NA

Abbreviations: QOL=Quality of Life; ANOVA=analysis of variance; ANCOVA=analysis of co-variance; EORTC=European Organisation for Research and Treatment of Cancer; QLQC30=QOL of Cancer Patients; QLQ H&N35=QOL module for Head and Neck Cancer.

Table 8-7: Supplementary Table 4 - Summary of multivariable linear regression models for selected Quality of Life outcome measures from the EORTC QLQ-C30 and EORTC H&N35 questionnaires in patients with head and neck cancer

	Unadjusted					Adjusted				
Variable	**β**	**SE**	**95% CI**		**P value**	**β**	**SE**	**95% CI**		**P value**
Model for Global QOL (F(6,108)=10.1, p<0.001, R^2 =0.360)										
Baseline FFM	-0.51	0.19	-0.89	-0.14	0.008*	-0.17	0.18	-0.53	0.18	0.333
Weight loss history 6mths (Reference: nil)										
- <5%	-5.91	4.34	-14.51	2.69	0.176	-6.26	3.76	-13.71	1.19	0.099
- >5%	-6.01	5.41	-16.72	4.70	0.268	-12.11	5.13	-22.29	-1.93	0.020*
- >10%	20.59	6.56	7.59	33.59	0.002*	8.45	6.39	-4.21	21.12	0.189
p16 (Reference: positive)										
- Negative	13.54	4.18	5.25	21.83	0.002*	8.79	3.80	1.26	16.32	0.022*
Baseline global QOL	-0.56	0.09	-0.73	-0.39	<0.001*	-0.47	0.09	-0.64	-0.30	<0.001*
Model for Physical Functioning (F(4,116)=7.6, p<0.001, R^2 =0.209)										
Current ETOH (Reference: nil)										
- low	3.17	3.27	-3.29	9.64	0.333	3.05	3.04	-2.97	9.07	0.318
- high	-0.97	4.59	-10.05	8.11	0.833	-0.36	4.27	-8.82	8.09	0.932
- very high	-9.41	4.16	-17.64	-1.18	0.025*	-7.30	3.90	-15.02	0.42	0.064
Baseline physical function	-0.49	0.10	-0.69	-0.28	<0.001*	-0.45	0.10	-0.65	-0.25	<0.001*
Model for Role Functioning (F(5,103)=13.8, p<0.001, R^2 =0.401)										
Baseline SGA (Reference: A – well nourished)										
- B (malnourished)	14.81	7.06	0.83	28.79	0.038*	-0.21	6.41	-12.92	12.50	0.974

Synchronous Primary (Reference: No)										
- Yes	24.81	12.07	0.92	48.70	0.042*	12.20	10.66	-8.95	33.34	0.255
Neoadjuvant chemotherapy (Reference: No)										
- Yes	30.34	12.81	2.97	57.71	0.030*	14.51	11.62	-8.54	37.56	0.215
p16 (Reference: positive)										
- Negative	19.88	3.28	7.74	32.02	0.002*	10.53	5.69	-0.75	21.82	0.067
Baseline role function	-0.80	0.10	-1.00	-0.61	<0.001*	-0.73	0.12	-0.97	-0.50	<0.001*
Model for Emotional Functioning ($F(2,112)=15.4$, $p<0.001$, $R^2=0.215$)										
p16 (Reference: positive)										
- Negative	8.44	4.16	0.19	16.68	0.045*	7.61	3.77	0.13	15.08	0.046*
Baseline emotional function	-0.46	0.09	-0.64	-0.28	<0.001*	-0.47	0.09	-0.65	-0.28	<0.001*
Model for Cognitive Functioning ($F(4,110)=8.1$, $p<0.001$, $R^2=0.229$)										
p16 (Reference: positive)										
- Negative	8.94	4.47	0.09	17.80	0.048*	5.00	4.14	-3.20	13.20	0.230
Current Smoking (Reference: None)										
- Low	14.51	6.54	1.56	27.46	0.028*	3.75	6.35	-8.83	16.32	0.556
- High	8.27	7.87	-7.31	23.84	0.295	1.73	7.79	-13.71	17.16	0.825
Baseline cognitive function	-0.54	0.10	-0.73	-0.34	<0.001*	-0.52	0.11	-0.74	-0.31	<0.001*

Model for Social Functioning (F(1,113)=9.7, p=0.002, R^2 =0.079)										
p16 (Reference: positive)										
- Negative	18.05	5.80	6.55	29.54	0.002*	18.05	5.80	6.55	29.54	0.002*
Model for Fatigue (F(6,108)=9.7, p<0.001, R^2 =0.349)										
Baseline SGA (Reference: A – well nourished)										
- B (malnourished)	-9.51	5.22	-19.85	0.83	0.071	-1.18	4.79	-10.67	8.31	0.806
Current ETOH (Reference: Nil)										
- Low	-10.01	4.93	-19.78	-0.24	0.045*	-8.50	4.33	-17.08	0.08	0.052
- High	-8.81	6.93	-22.53	4.91	0.206	-6.26	5.85	-17.85	5.33	0.287
- Very high	3.61	6.28	-8.82	16.04	0.567	5.72	5.41	-5.01	16.45	0.293
p16 (Reference: positive)										
- Negative	-11.94	4.56	-20.96	-2.91	0.010*	-9.33	3.99	-17.23	-1.43	0.021*
Baseline fatigue	-0.59	0.09	-0.77	-0.42	<0.001*	-0.52	0.09	-0.70	-0.34	<0.001*
Model for Nausea and Vomiting (F(3,117)=2.9, p=0.038, R^2 =0.069)										
Current ETOH (Reference: Nil)										
- Low	2.53	3.54	-4.47	9.53	0.476	2.53	3.54	-4.47	9.53	0.476
- High	2.68	4.97	-7.16	12.51	0.591	2.68	4.97	-7.16	12.51	0.591
- Very high	12.94	4.50	4.03	21.85	0.005*	12.94	4.50	4.03	21.85	0.005*

Model for Appetite (F(3,117)=5.7, p=0.001, R^2 =0.134)										
p16 (Reference: positive)										
- Negative	-15.90	6.35	-28.48	-3.31	0.014*	-10.01	6.43	-22.76	2.74	0.122
Overall Stage (Reference: II/III)										
- IV	17.41	8.35	0.88	33.94	0.039*	14.60	8.27	-1.79	30.98	0.080
Baseline SGA (Reference: A – well nourished)										
- B (malnourished)	-22.32	6.93	-36.03	-8.60	0.002*	-20.11	7.17	-34.33	-5.90	0.006*
Model for Constipation (F(5,113)=3.9 p=0.003, R^2 =0.146)										
RT technique (Reference: Tomotherapy)										
- Other	21.77	12.59	-3.17	46.71	0.087	17.98	12.38	-6.54	42.51	0.149
Weight loss history 6mth (Reference: Nil)										
- <5%	8.18	4.48	-0.69	17.04	0.070	7.38	4.43	-1.39	16.14	0.098
- >5%	0.68	5.57	-10.35	11.72	0.903	2.32	5.80	-9.16	13.80	0.690
- >10%	-11.81	6.77	-25.21	1.59	0.084	-12.70	6.64	-25.87	0.46	0.058
Synchronous Primary (Reference: No)										
- Yes	-21.22	8.19	-37.45	-5.00	0.011*	-21.62	8.36	-38.18	-5.06	0.011*

Model for Diarrhoea (F(10,108)=8.4 p<0.001, R^2 =0.439)										
N stage (Reference: N0)										
- N1	-3.03	6.95	-16.79	10.73	0.664	-7.96	6.93	-21.70	5.78	0.254
- N2a	3.03	9.51	-15.81	21.87	0.751	-10.48	8.74	-27.81	6.84	0.233
- N2b	2.37	5.42	-8.36	13.10	0.662	-8.20	5.96	-20.01	3.60	0.171
- N2c	10.52	5.55	-0.46	21.51	0.060	-0.92	5.96	-12.74	10.90	0.878
- N3	-13.62	9.51	-32.46	5.22	0.155	-15.00	8.79	-32.42	2.42	0.091
RT technique (Reference: Tomotherapy)										
- Other	-23.64	9.77	-42.99	-4.28	0.017*	-12.95	10.41	-33.59	7.69	0.216
Treatment (Reference: Surgery)										
- RT	-33.3	19.70	-72.31	5.71	0.094	NA	NA	NA	NA	NA
- PORT	-6.66	13.45	-33.31	19.99	0.622	6.23	16.03	-25.55	38.01	0.698
- CRT	2.86	11.48	-19.88	25.59	0.804	11.56	14.44	-17.06	40.18	0.425
- POCRT	-16.66	12.71	-41.84	8.52	0.193	6.85	14.76	-22.40	36.11	0.643
Baseline diarrhoea	-0.84	0.10	-1.05	-0.64	<0.001*	-0.73	0.12	-0.97	-0.49	<0.001*
Model for Swallowing (F(5,109)=6.1 p<0.001, R^2 =0.218)										
Current Smoking (Reference: None)										
- Low	-11.68	7.56	-26.65	3.30	0.125	-2.39	7.27	-16.79	12.00	0.742
- High	16.46	9.10	-1.56	34.47	0.073	21.30	8.94	3.58	39.00	0.019*
Guideline Risk rating (Reference: High)										
- Low	14.47	8.67	-2.69	31.63	0.098	23.20	9.17	5.01	41.38	0.013*
Baseline FM	0.58	0.21	0.17	1.00	0.006*	0.47	0.21	0.05	0.90	0.029*

p16 (Reference: positive)										
- Negative	-18.13	4.88	-27.79	-8.46	<0.001*	-18.11	4.93	-27.89	-8.33	<0.001*
Model for Social Eating ($F(2,112)=9.2$ $p<0.001$, $R^2=0.141$)										
Baseline SGA (Reference: A – well nourished)										
- B (malnourished)	-18.55	6.43	-31.27	-5.82	0.005*	-14.87	6.43	-27.60	-2.14	0.022*
p16 (Reference: positive)										
- Negative	-19.82	5.60	-30.92	-8.73	<0.001*	-17.50	5.59	-28.56	-6.43	0.002*
Model for Mouth Opening ($F(5,115)=11.8$ $p<0.001$, $R^2=0.340$)										
Baseline Diet (Reference: General)										
- Soft	-14.62	6.28	-27.06	-2.19	0.022*	-6.77	5.54	-17.74	4.20	0.224
- Minced	-22.69	12.61	-47.66	2.28	0.075	-14.60	10.88	-36.16	6.95	0.182
- Puree	-6.02	30.00	-65.45	53.40	0.841	30.46	26.59	-22.22	83.13	0.254
Days G Tube inserted pre treatment	-1.23	0.32	-1.85	-0.61	<0.001*	-0.91	0.29	-1.48	-0.34	0.002*
Baseline Mouth opening	-0.51	0.08	-0.67	-0.35	<0.001*	-0.45	0.09	-0.62	-0.28	<0.001*

Abbreviations: QOL=quality of life; FFM=Fat free mass; ETOH=alcohol; SGA=subjective global assessment; RT=radiotherapy; PORT=post-operative radiotherapy; CRT=chemoradiotherapy; POCRT=post-operative chemoradiotherapy; FM=fat mass; G tube=gastrostomy.

Table 8-8: Supplementary Table 5 - The clinical importance of change in quality of life scores from baseline to three months post treatment in patients with head and neck cancer – comparison between standard care group (prophylactic gastrostomy used as clinically indicated) and intervention group (early prophylactic gastrostomy use to supplement oral intake)

	Score change	Direction of change	Size of clinical effect	Score change	Direction of change	Size of clinical effect	Differences between groups
Global Health Status/QOL	-2.9 ± 22.7	Deterioration	Trivial	-6.2 ± 20.3	Deterioration	Small	Yes
Physical functioning	-5.5 ± 14.1	Deterioration	Small	-9.4 ± 16.8	Deterioration	Small	No
Role functioning	-4.7 ± 31.6	Deterioration	Trivial	-14.0 ± 30.7	Deterioration	Small/Medium	Yes*
Emotional functioning	2.5 ± 18.9	Improvement	Trivial	2.3 ± 21.5	Improvement	Trivial	No
Cognitive functioning	-5.7 ± 23.6	Deterioration	Small	-6.9 ± 19.6	Deterioration	Small	No
Social functioning	-2.1 ± 27.1	Deterioration	Trivial	-12.1 ± 31.7	Deterioration	Medium	Yes*
Fatigue	8.4 ± 23.2	Deterioration	Small	17.0 ± 22.4	Deterioration	Large	Yes*
Nausea and vomiting	1.6 ± 15.1	Deterioration	Trivial	4.7 ± 18.3	Deterioration	Trivial	No
Pain	-8.3 ± 29.7	Improvement	Small	-0.7 ± 30.8	Improvement	Trivial	Yes
Dyspnoea	3.7 ± 25.5	Deterioration	Trivial	0.6 ± 22.2	Deterioration	Trivial	No
Insomnia	-2.6 ± 34.8	Improvement	Trivial	0.0 ± 37.3	Neutral	Trivial	No
Appetite loss	19.8 ± 34.5	Deterioration	Medium	18.7 ± 28.2	Deterioration	Medium	No
Constipation	-0.5 ± 21.0	Improvement	Trivial	2.6 ± 22.2	Deterioration	Trivial	No
Diarrhoea	0.0 ± 20.6	Neutral	Trivial	1.8 ± 11.6	Deterioration	Trivial	No
Financial difficulties	1.8 ± 31.7	Deterioration	Trivial	4.1 ± 35.7	Deterioration	Small	Yes

Abbreviations: EORTC=European Organisation for Research and Treatment of Cancer; QLQC30=QOL of Cancer Patients; QOL=Quality of Life. Methodology: Interpretation of clinical effect following Guidelines for interpretation of longitudinal QOL differences (Cocks et al., 2012). *difference between groups over two levels of clinical effect (i.e. trivial to medium or small to large).

8.3 RCT: Gastrostomy outcomes

8.3.1 Abstract

Objectives: Prophylactic gastrostomy tube (PGT) is frequently used in patients with head and neck cancer (HNSCC). There are concerns this leads to tube dependency but this phenomena is not well defined. This study aimed to determine whether early feeding via PGT impacted on longer term tube feeding outcomes.

Materials and Methods: Patients with HNSCC with PGT were observed monthly post-treatment regarding tube use and time to removal up to twelve months. Patients were from a randomised controlled trial comparing an early feeding intervention via the PGT (n=57) versus usual care which commenced feeding when clinically indicated (n=67).

Results: Patient characteristics; male (88%), mean age 60±10.1 years, oropharyngeal tumours (76%), receiving chemoradiotherapy (82%). Tubes were used by 87% (108/124) on completion of treatment and 66% (83/124) one month post. No differences in tube use between groups at any time point or tube removal rates over 12 months (p=0.181). In patients free of disease (n=99), the intervention had higher tube use at 4 months (p=0.003) and slower removal rates (p=0.047). Overall ten patients had their tube in-situ at 12 months (8%) but five were awaiting removal (4% true dependency rate). Of the five patients legitimately using the tube, only one (<1%) was from severe dysphagia post definitive chemoradiotherapy.

Conclusion: PGT use is high in the acute phase post-treatment. Encouraging early use may prolong time to tube removal but it does not increase long term dependency rates beyond four months post treatment. Monitoring tube use is important to prevent over-estimation of dependency rates.

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8.3.2 Manuscript

INTRODUCTION

Prophylactic gastrostomy tube (PGT) placement is a common method of nutrition support in patients with mucosal head and neck cancer (HNSCC), however there are concerns this leads to dysphagia and long term tube dependency (Chen et al., 2010; Corry et al., 2008; Langmore et al., 2012; Mekhail et al., 2001). Some studies have reported nil impact on swallowing function (Crombie et al., 2015; Silander et al., 2010), and the most recent systematic review on this topic remains inconclusive (Shaw et al., 2015). As there is no agreed definition of the term gastrostomy dependency, its use can therefore be misunderstood (Talwar & Findlay, 2012). Although many investigators are now reporting rates of gastrostomy retention it is unclear if patients are legitimately so because of dysphagia, other nutrition impact symptoms or poor nutritional status, or if patients elect to continue gastrostomy use despite no physical barriers to oral nutrition.

Several studies document the predictive factors for long term tube feeding, or gastrostomy dependency, such as tumour sites (Caudell et al., 2010; Ishiki et al., 2012), tumour stage (Akst et al., 2004; Avery et al., 2008; Gokhale et al., 2010; Kornguth et al., 2005; Lawson et al., 2009), treatment modality (Avery et al., 2008; Kornguth et al., 2005; Lango et al., 2010), radiotherapy treatment fields and dose (Caudell et al., 2010; Gokhale et al., 2010; Li et al., 2009; Sanguineti et al., 2011), smoking (Li et al., 2009), age (Kornguth et al., 2005; Lango et al., 2010; Lawson et al., 2009), and pre-treatment weight loss or low body mass index (BMI) (Lango et al., 2010; McRackan et al., 2008). These types of clinical factors are often considered for the prediction of patients who may benefit from PGT placement (Brown et al., 2013b; Jack et al., 2012; Wood, 2005), as they are anticipated to require a feeding tube for longer than four weeks and thus a gastrostomy is the most suitable long term feeding device (Arends et al., 2006). It is therefore little surprise that these characteristics are also associated with prolonged use.

However prolonged feeding tube use can also be influenced by psychosocial factors (Magnuson et al., 2013) as well as ongoing nutrition impact symptoms which continue to effect the patient's nutritional status and intake (Bressan et al., 2016). Many studies which report on gastrostomy dependency outcomes fail to report adequate information on the patient's nutritional status (Hatoum et al., 2009; Sanguineti et al., 2013) which may be the key reason for prolonged tube feeding.

Another limitation of historical studies is the lack of information on the level of allied health input they have received both during and post-treatment for swallowing and nutritional rehabilitation. Maintenance of oral intake during treatment has been shown to reduce the duration of feeding tube use (Ames et al., 2011). The role of the dietitian has been identified as important in assisting patients wean from their feeding tube (Mayre-Chilton et al., 2011) and the prophylactic swallowing exercises prescribed by the speech pathologist are also important to maintain or improve long term swallow outcomes (Duarte, Chhetri, Liu, Erman, & Wang, 2013; Hutcheson et al., 2013).

Likewise there is also insufficient detail on the criteria used for decision making regarding gastrostomy removal. Whilst some guidelines advocate a multidisciplinary team decision (Brown et al., 2013b), there is still minimal information in the literature on when it is appropriate to remove a gastrostomy. One study addressed predictors of gastrostomy removal and reported patients with localised HNSCC and those under 65 years old were independent predictors, however this was in a mixed population of HNSCC, other malignancies and neurological indications (Naik, Abraham, Roche, & Concato, 2005). Further limitations of this study were that oral intake resumption was used as the reason for gastrostomy removal however there was no additional information on the adequacy of the oral intake or the patients' nutritional status at the time of removal. The lack of evidence in this area means that evidence based guidelines (Head & Neck Guideline Steering Committee, 2011; Talwar et al., 2016) are unable to provide clear recommendations to guide clinical practice on gastrostomy removal indications and report the patient should be able to maintain their nutritional status with safe swallowing prior to tube removal (Head & Neck Guideline Steering Committee, 2011).

A recent randomised controlled trial comparing an early feeding intervention versus standard care in patients with HNSCC and a PGT prior to treatment has been completed to determine the effectiveness of this early intervention on minimising weight loss (Brown et al., 2014b) with the main outcomes reported elsewhere (Brown et al., 2017a). This current study is a planned secondary analysis from this trial to determine whether this early feeding intervention had any impact on longer term tube feeding outcomes. In addition, patterns of tube use post treatment and their role in providing nutrition support will be described.

PATIENTS AND METHODS

Participants and Study Setting

Adult patients with HNSCC were recruited from a tertiary hospital in Queensland, Australia from September 2012 to June 2015 if referred for a PGT prior to treatment based on a validated protocol (Brown et al., 2016b). Patients identified as high risk from this protocol and recommended a PGT typically received definitive or adjuvant chemoradiotherapy. Other patients may be considered for a PGT based on a consultant decision.

Radiotherapy was delivered using helical-intensity modulated radiotherapy at a standard 2Gy per fraction, five fractions per week, to a total maximal dose of 60-66Gy for adjuvant treatment (to the surgical bed) and 70Gy (to the gross disease) for definitive treatment. Elective nodal irradiation was delivered to bilateral neck using the same technique. Cervical lymph node levels at risk of harbouring subclinical disease were electively irradiated simultaneously to a total dose of 52-54Gy in 33-35 fractions delivered at 5 fractions per week. Concurrent chemotherapy was prescribed at the discretion of the medical oncologist and usually consisted of high dose cisplatin, weekly cisplatin or cetuximab.

Patients were excluded from the study if: planned for non-curative intent treatment; or were severely malnourished; or were moderately malnourished with significant dysphagia requiring a liquid or puree texture modified diet.

The study was approved by the Royal Brisbane and Women's Hospital Human and The University of Queensland Medical Research Ethics Committees. All patients provided written informed consent to participate. This trial is listed in the Australian New Zealand Clinical Trials registry (ACTRN12612000579897) and the protocol is published for further information (Brown et al., 2014b).

Randomisation

Patients were stratified according to baseline nutritional status and randomly assigned to either the intervention or standard care (allocation ratio 1:1). Simple randomisation procedures were followed with a computer-generated randomisation sequence concealed to the researcher enrolling participants.

Interventions

All patients were seen by the dietitian during overnight admission for PGT placement and then reviewed weekly by the dietitian and speech pathologist in a joint clinic as part of routine care. All patients were encouraged to maintain some level of oral intake during treatment as long as it remained safe to do so.

Patients in the standard care group were commenced on enteral nutrition following assessment by the dietitian during treatment. Patients in the intervention group were commenced on supplemental enteral nutrition immediately following PGT placement prior to commencement of treatment in addition to their current oral intake. The prophylactic enteral nutrition consisted of 2x 200ml bolus feeds (1.5kcal/ml polymeric formula with fibre) per day and was continued until completion of treatment, increasing as necessary during treatment. Indicators for commencing or increasing enteral nutrition in both groups followed local protocol recommendations (Brown et al., 2016b).

On completion of treatment all patients were referred to their local health service district dietitian and speech pathology service either at the tertiary centre itself or a regional cancer centre in Queensland, Australia. The research dietitian maintained monthly telephone contact with the patient to determine degree of tube use for up to six months post-treatment or until the tube was removed. If the tube was still in situ at six months, then follow up was repeated at 12 months post-treatment.

Outcomes

The primary outcome for this sub-study was the day of tube removal in relation to the day of completion of treatment. The null hypothesis being no difference in time to tube removal between the two groups. The use of the tube at each month was assessed as either: tube removed; tube in situ but not using; tube in situ and using for either 25% or 50% or 75% of nutrition requirements (supplementary nutrition); or tube in situ and using for 100% of nutrition requirements (with either oral intake as tolerated or nil by mouth due to aspiration risk). Diet texture, classified as either full, soft, minced, puree, or liquids, was recorded at baseline and at three months post treatment. Gastrostomy complications were recorded prospectively as part of routine care for the first three months the tube was in-situ. Major complications were defined as any complication necessitating hospital admission for management, including prolonged admissions post insertion. Minor complications were defined as stoma issues including site infections managed with oral antibiotics.

Statistical Methods

Baseline participant characteristics for continuous variables were summarised using means and standard deviations and differences between groups assessed with two sample t–tests or Wilcoxon tests. For categorical variables at baseline and tube outcomes, frequency and percentages were calculated and group difference assessed using Chi-squared or Fishers Exact tests. Normal distribution was assessed using Shapiro-Wilk test and variance assessed using Levene's test. Time to tube removal was analysed using the Kaplan Meier method and the log rank test. Statistical significance was set at $p<0.05$. Data were analysed using R Commander Version 2.1-7 and R version 3.1.3 (2015-03-09).

RESULTS

Participant Flow

Overall 131 patients were randomised (61 intervention and 70 standard care). Seven patients were excluded and there were four deaths from persistent disease in the follow up phase (all died with their tube in-situ). There was one protocol deviation in each group. All patients that completed treatment were analysed on an intention-to-treat basis (n=124) and subsequent analysis was performed following exclusion of patients with persistent disease at three months (n=99) (Figure 8-3).

Patient Characteristics

There were no differences in patient, clinical and treatment characteristics between groups at baseline (Table 8-9). Patients were predominantly male, median age 60 years, with oropharyngeal tumours, and non-metastatic stage IV disease. The majority of patients received definitive or adjuvant chemoradiotherapy (n=116), five of whom had neoadjuvant chemotherapy, and the remaining patients received surgery alone (n=2), radiotherapy alone (n=1), and post-operative radiotherapy (n=5). There was a higher proportion of current smokers in the standard care group although this did not reach statistical significance (24% vs 9%, p=0.072)

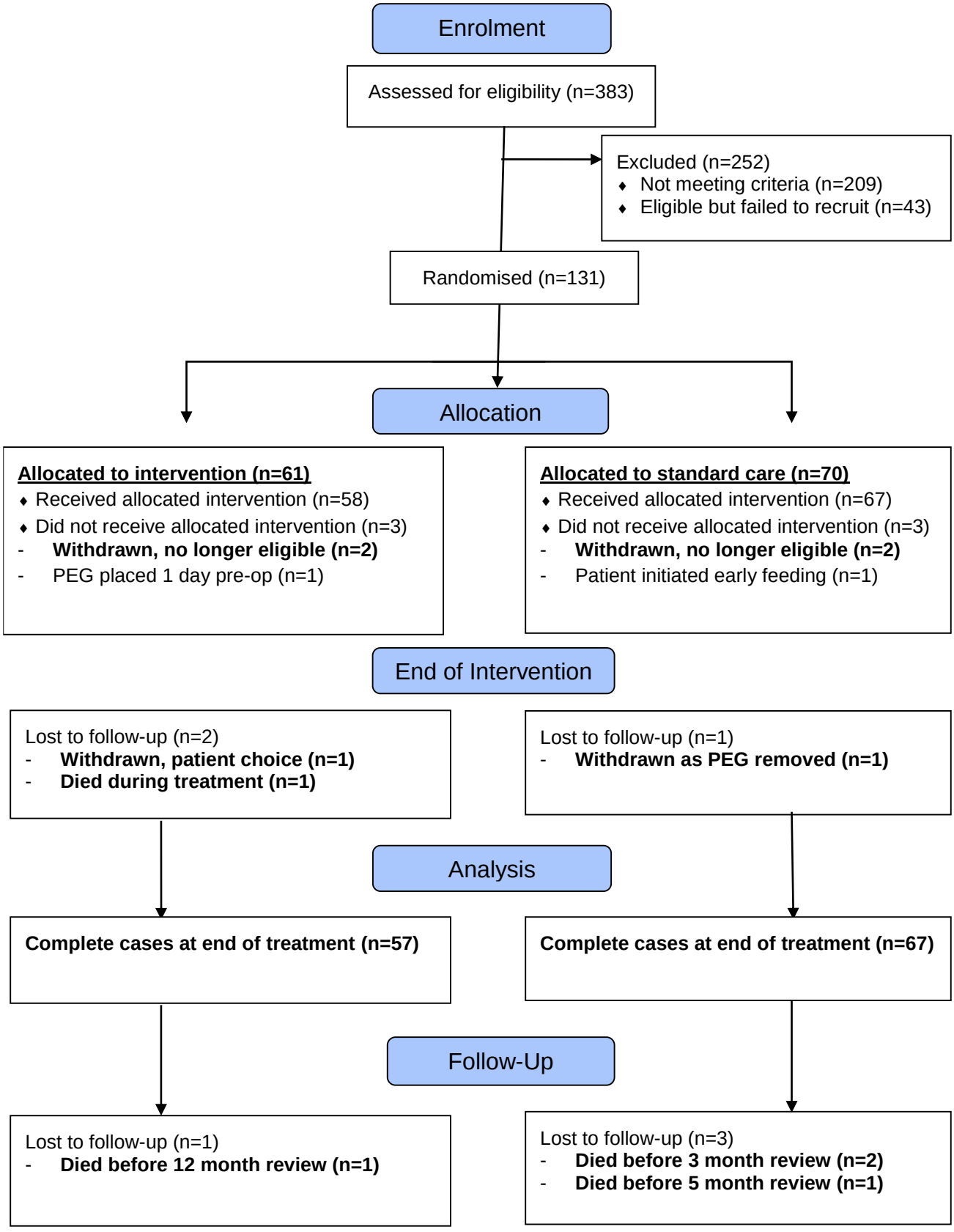

Figure 8-3: CONSORT Diagram of Patient Flow

Abbreviations: PEG=gastrostomy tube.

Table 8-9: Summary of patient characteristics at baseline with comparison of standard care group and intervention group

Variable		Standard Care (n=67)	Intervention (n=57)	P value
Age (years)	Mean ± sd	59.6 ± 10.7	61.1 ± 9.4	0.424
	Median (range)	59 (36-83)	60 (40-83)	
Gender	Male	58, 87%	52, 91%	0.414
	Female	9, 13%	5, 9%	
Smoking history	Non smoker	14, 21%	12, 21%	0.072
	Former	37, 55%	40, 70%	
	Current	16, 24%	5, 9%	
Tumour Site	Oral cavity	6, 9%	7, 12%	0.899
	Oropharynx	54, 81%	43, 75%	
	Nasopharynx	2, 3%	2, 4%	
	Hypopharynx	3, 5%	4, 7%	
	Larynx	1, 1%	0, 0%	
	Unknown Primary	0, 0%	1, 2%	
	Other	1, 1%	0, 0%	
T Stage	T0	0, 0%	1, 2%	0.175
	T1	4, 6%	4, 7%	
	T2	20, 30%	23, 40%	
	T3	25, 37%	11, 19%	
	T4	18, 27%	18, 32%	
N Stage	N0	7, 10%	4, 7%	0.561
	N1	7, 10%	4, 7%	
	N2a	1, 2%	3, 5%	
	N2b	29, 43%	24, 42%	
	N2c	19, 28%	21, 37%	
	N3	4, 6%	1, 2%	
Overall Stage	II	1, 1%	0, 0%	0.409
	III	10, 15%	5, 9%	
	IV	56, 84%	52, 91%	
P16 status	Positive	43, 68%	41, 76%	0.358
	Negative	20, 32%	13, 24%	
Treatment [a]	Chemoradiotherapy	59, 88%	49, 86%	0.468
	Adj chemoradiotherapy	5, 8%	3, 5%	
	Radiotherapy	1, 1%	0, 0%	

	Adj radiotherapy	0, 0%	5, 9%	
	Definitive surgery	2, 3%	0, 0%	
Chemotherapy	High dose cisplatin	36, 56%	31, 60%	0.395
	Low dose cisplatin	12, 19%	13, 25%	
	Cetuximab	16, 25%	8, 15%	
Weight loss history	Nil	21, 31%	28, 49%	0.193
(in last 6 months)	<5%	26, 39%	16, 28%	
	5-10%	11, 16%	9, 16%	
	>=10%	9, 13%	4, 7%	
Nutritional status	Well-nourished	49, 73%	48, 84%	0.136
	Malnourished	18, 27%	9, 16%	
Diet	Full	46, 69%	38, 67%	0.778
	Soft	18, 27%	14, 25%	
	Minced	3, 4%	4, 7%	
	Puree	0, 0%	1, 1%	

[a] For statistical analysis compared chemo based treatments (high risk) vs non-chemo based treatments (non-high risk). Risk rating as per validated protocol for prophylactic gastrostomy selection (Brown et al., 2016b).

Gastrostomy Tube Insertion and Complications

Most patients had their PGT placed via endoscopy (93%) versus radiologically (7%), with no difference in method of placement between groups (p=0.505). The tubes were placed a median of five days prior to treatment in each group (p=0.334). There was no mortality associated with placement. There was no difference in major complications (10% standard care vs 11% intervention, p=0.989), or minor complications (40% standard care vs 40% intervention, p=0.995) between groups. The major complications included: peritonitis (n=3); IV antibiotics for site infection (n=1); blood transfusion for bleeding (n=1); failed endoscopic placement (n=2); and prolonged admission for pain management post insertion (n=7). Site infections accounted for approximately half of the minor complications (n=27/50).

Gastrostomy Tube Use

On assessment of the whole cohort, the PGT was used for full nutrition by 72% of patients (89/124) on completion of treatment, with 15% (19/124) using the tube for supplementary nutrition (Table 8-10). There were eight patients in standard care who did not use their PGT at all during treatment and eight patients in the intervention group that did not increase their feeds above the prescribed intervention amount (13%). Half of these had a less than desirable outcome of ≥10% weight loss or malnutrition. Five of these patients used their tube post-treatment and three were clearly non-adherent with recommendations to use.

Patterns of PGT use and removal over time for each group can be seen in Figure 8-4. At one month post-treatment approximately two thirds of patients were still using their tube, and a third were requiring the tube for full nutrition. At two months tube use was predominantly for supplementary nutrition (27%) versus full enteral feeding (15%), and by three months this dropped slightly to 22%. By four months, just over half of the tubes had been removed (57%). There was no statistical difference between groups at any time point (Table 8-10). At four months, there was a trend to higher rates of supplementary feeding in the intervention group (21% vs 6%, p=0.052) (Table 8-10). The pattern of tube use was similar when only patients free of disease at three months post treatment were considered, although the differences observed at four months were significant (p=0.003). See Supplementary Table 1 (Table 8-13).

Diet Texture Outcomes

Just over half the patients in each group had returned to a full diet texture at three months post-treatment and there were no differences in diet texture between groups (p=0.727) (Table 8-11).

Gastrostomy Tube Removal

Median time (range) to tube removal was no different in each group: standard care group 100 days (28-276) versus intervention group 110 days (21-280) (p=0.339). The Kaplan Meier curve shows that there was no statistical difference in the rate of removal over the 12 month follow up period (p=0.181) (Figure 8-5). However the rate of removal was slower in the intervention arm when patients with persistent disease were excluded (p=0.047). See Supplementary Figure 1 (Figure 8-6).

Table 8-10: Comparison of gastrostomy use and tube outcomes for twelve months post-treatment between standard care and intervention group

Months post treatment	Tube use or Outcome	Standard Care (n=67)	Intervention (n=57)	Total (n=124)	Fishers Exact
		N (%)	N (%)	N (%)	P value
0	Nil	8 (12)	8 (14)	16 (13)	0.737
(N=124)	Supplementary	9 (13)	10 (18)	19 (15)	
	Full	50 (75)	39 (68)	89 (72)	
1	Nil	22 (33)	15 (26)	37 (30)	0.857
(N=124)	Supplementary	22 (33)	22 (39)	44 (35)	
	Full	21 (31)	18 (32)	39 (31)	
	Removed	2 (3)	2 (4)	4 (3)	
2	Nil	27 (40)	18 (32)	45 (36)	0.710
(N=124)	Supplementary	18 (27)	16 (28)	34 (27)	
	Full	8 (12)	10 (18)	18 (15)	
	Removed	14 (12)	13 (23)	27 (22)	
3	Nil	26 (39)	21 (37)	47 (38)	0.477
(N=124)	Supplementary	11 (16)	16 (28)	27 (22)	
	Full	6 (9)	3 (9)	9 (7)	
	Removed	22 (33)	17 (30)	39 (31)	
	Died tube in situ	2 (3)	0 (0)	2 (2)	
4	Nil	18 (28)	10 (18)	28 (23)	0.052
(N=122)	Supplementary	4 (6)	12 (21)	16 (13)	
	Full	3 (5)	5 (9)	8 (7)	
	Removed	40 (62)	30 (53)	70 (57)	
5	Nil	8 (12)	9 (16)	17 (14)	0.331
(N=122)	Supplementary	2 (3)	5 (9)	7 (6)	
	Full	2 (3)	4 (7)	6 (5)	
	Removed	52 (80)	39 (68)	91 (74)	
	Died tube in situ	1 (2)	0 (0)	1 (1)	
6	Nil	6 (9)	7 (12)	13 (11)	0.239
(N=121)	Supplementary	1 (2)	5 (9)	6 (5)	
	Full	2 (3)	3 (5)	5 (4)	
	Removed	55 (86)	42 (74)	97 (80)	
12	Nil	3 (4)	2 (3)	5 (4)	0.526
(N=121)	Supplementary	0 (0)	2 (3)	2 (2)	
	Full	1 (2)	2 (3)	3 (2)	
	Removed	60 (94)	50 (88)	110 (91)	
	Died tube in situ	0 (0)	1 (2)	1 (1)	

Abbreviations: *Statistically significant ($p<0.05$)

Table 8-11: Comparison of diet texture outcomes at three months post treatment between standard care and intervention group

Diet Texture at 3 months post treatment	Standard Care (n=64)[a]	Intervention (n=57)	P value
Full	33, 51%	30, 53%	0.727
Soft	21, 33%	14, 25%	
Minced	4, 6%	4, 7%	
Puree	3, 5%	4, 7%	
Liquid	3, 5%	3, 5%	
NBM	0, 0%	2, 3%	

Abbreviations: *Statistically significant ($p<0.05$), a n=2 died before 3 month follow up and n=1 missing data (patient too unwell to attend follow up appointment)

Gastrostomy Outcomes at 12 months

At 12 months there were ten patients overall with tubes in-situ giving an apparent gastrostomy dependency rate of 8%; however only five were using the tube, giving a true gastrostomy dependency rate of 4% (Table 8-10). Of those not using the tube; two were waiting appointments for removal and three were delayed decision-making due to suspected recurrent disease. Patients still using the tube at 12 months were all legitimate cases (Table 8-12). When patients with persistent disease in the 12 month follow up period were excluded there were only three patients overall using the tube at one year post-treatment. Two of these were due to post-operative functional dysphagia and one was due to severe dysphagia following definitive chemoradiotherapy.

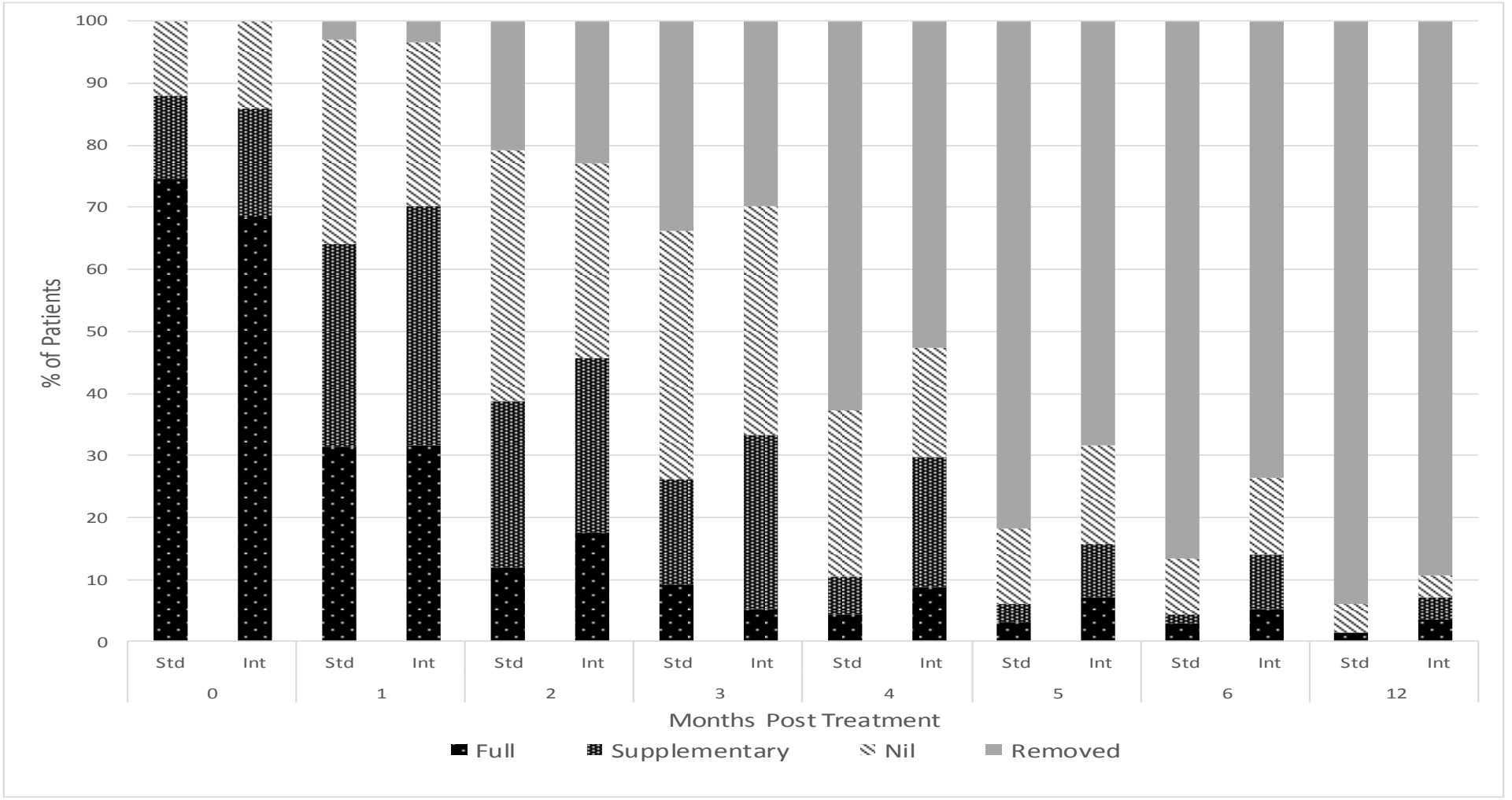

Figure 8-4: Patterns of gastrostomy use over twelve month's post-treatment with comparison between standard care and intervention group

Abbreviations: Std=standard care group; Int=intervention group.

Table 8-12: Characteristics of patients who are still tube dependent at twelve months post-treatment

Patient	Diagnosis	PET response at 3 months	Clinical outcome at 12 months	Diet textures before and during treatment	Diet outcomes at 12 months	Tube use at 12 months
1	T1N2b oropharynx SCC P16+ Chemoradiotherapy	Full response	Disease free	Dysphagia diagnosed from week 2 of treatment, placed NBM from end of treatment to 6 months post treatment	Recommended to remain NBM, but eating and drinking as tolerated	Supplementary (75%)
2	T4N2b oropharynx SCC P16+ Chemoradiotherapy	Persistent disease	Disease free following salvage surgery	Dysphagia diagnosed from week 6 of treatment, thick fluids only at end of treatment, and NBM between 4-6 months post treatment	Liquids/puree as tolerated	Full
3	T4N0 oropharynx Adenoid cystic carcinoma Adjuvant radiotherapy	N/A as primary resection	Disease free	NBM from surgery to 6 months post treatment	Commenced thick fluids only	Full
4	T4N2b oropharynx SCC P16- Chemoradiotherapy	Persistent disease	Palliative with lung metastases	Dysphagia pre-treatment – requiring soft diet. Modified texture diet as tolerated throughout treatment – with full tube use at end of treatment	Liquids/puree as tolerated	Full
5	T2N1 oral cavity SCC Adjuvant chemoradiotherapy	N/A as primary resection	Disease free	Dysphagia post op – requiring puree diet. Modified texture diet as tolerated throughout treatment – with full tube use at end of treatment	Puree	Supplementary (25%)

Abbreviations: PEG=gastrostomy tube; SCC=squamous cell carcinoma; NBM=nil by mouth.

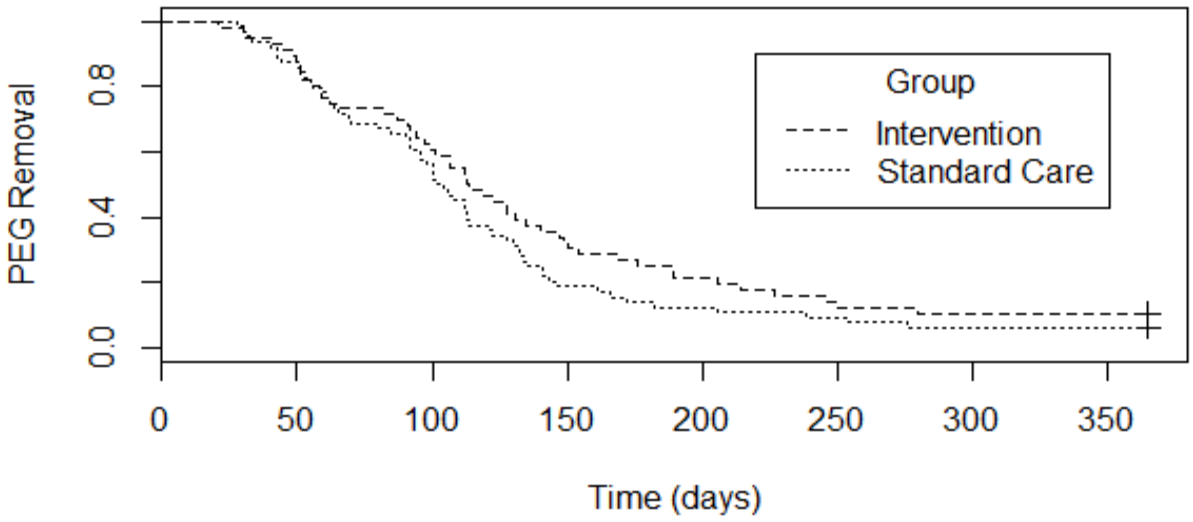

Figure 8-5: Kaplan Meier curves to compare the rate of gastrostomy tube removal over twelve months post-treatment between standard care and intervention group

DISCUSSION

This study reports on PGT use in the post-treatment period in a group of patients with advanced HNSCC predominantly receiving chemoradiotherapy. This study demonstrated that tube use remains important in the immediate acute phase post-treatment despite the predominate use of helical-IMRT in this trial. The majority of patients then recover relatively quickly prior to their three month outcome assessment with the oncologist and there is a low incidence of long term tube dependency at 12 months. The early intervention which encouraged early PGT use to supplement oral intake may have prolonged time to tube removal in this heterogeneous study cohort but it did not increase long term dependency rates beyond four months post treatment.

On completion of treatment, 87% of patients utilised their tube, with the majority entirely dependent for their full nutritional needs. This is higher than previous reports in the literature at 75% (Akst et al., 2004), but may be attributable to the increasing incidence of human papillomavirus (HPV) related tumours (Hocking et al., 2011). These p16 positive tumours (as a marker for HPV status) appear to have increased acute toxicities compared to p16 negative tumours (Becker-Schiebe et al., 2015), and thus the need for nutrition support is likely to be higher. A recent study has confirmed that p16 status can be used as a predictor of PGT requirement (Brown et al., 2017b).

Overall usage is still high at one month post-treatment at 66% and then drops to 29% at three months. This compares favourably to other studies with rates of 66% of patients requiring a feeding tube at three months (Akst et al., 2004) and 62-65% at six months in a study where patients received accelerated or hyper fractionated chemoradiotherapy (Hatoum et al., 2009). This improvement is potentially attributed to advanced radiotherapy techniques such as helical-IMRT which further minimise doses to organs at risk and thus reduce long term toxicities such as xerostomia and dysphagia (Lee et al., 2008a; Sheng et al., 2006), thus allowing patients to recover more quickly.

When cumulative tube use is considered both during and post-treatment, this highlights that the majority of patients do require nutrition support via a feeding tube for greater than four weeks and therefore selection of a gastrostomy over a nasogastric tube is appropriate based on this outcome (Arends et al., 2006). Given the ultimate reason for placing a PGT is to ensure provision of adequate nutrition and to minimise the negative sequelae of malnutrition, longer term use should not be negatively viewed.

Malnutrition is common post-treatment (Jager-Wittenaar, et al., 2011a; Silander et al., 2012; van den Berg et al., 2008), and poor nutrition indicators such as low BMI and pre-treatment weight loss have also been associated with gastrostomy dependence (McRackan et al., 2008; Wopken et al., 2014b). This suggests that gastrostomy use can be appropriate to assist improving long term nutritional status. It is acknowledged there were 16 patients that did not use their PGT by the end of treatment, however some patients went on to use their PGT post-treatment, whilst others were non-adherent to recommendations and would have benefited from using the PGT based on their poorer nutritional outcomes.

The median removal time following completion of treatment was 110 days (range 21-280) for the whole cohort. This is similar to another study where the median duration of tube feeding after completion of treatment was 110 days, although the range was much wider from 0-592 days (Silander et al., 2010), and more favourable than a study that reported a median duration of tube use at 192 days in a group of patients receiving chemoradiotherapy with IMRT (Li et al., 2009). However it is difficult to compare results across other studies due to variations in how authors define the time period of tube use/duration. Limitations of several studies which report on gastrostomy dependency have not considered appropriate nutritional outcome data including degree of tube use, or the intensity and frequency of dietary counselling (Talwar & Findlay, 2012).

This study has illustrated that using the presence of a gastrostomy as a measure of gastrostomy dependency is not an accurate indicator due to potential non-use of the tube, and thus leads to over-estimation of dependency rates. For future study designs it is recommended that gastrostomy use is recorded to determine whether patients are truly dependent on their tube or not.

Dysphagia is a major long term toxicity in many patients, even in those without enteral feeding tubes (Oozeer et al., 2011; Sethugavalar et al., 2016). There are concerns in the literature that gastrostomy insertion can lead to dysphagia and tube dependency (Chen et al., 2010; Corry et al., 2008; Langmore et al., 2012; Mekhail et al., 2001), although other studies have shown no detrimental impact on swallowing function (Crombie et al., 2015; Silander et al., 2010) and the body of literature remains inconclusive from a recent systematic review (Shaw et al., 2015). Whilst the data from this current study suggests there may have been more tendency for the intervention group to use the tube for supplementary feeding for longer, with an increased use at four months post-treatment, there were no other statistical differences at any other time point. Overall encouraging early use of the PGT before treatment and before nutrition impact symptoms develop did not result in an increase in long term dependency, with the only differences observed at four months. Post-hoc analysis in patients free of disease indicated that the intervention group may have had slower rates of removal; however this was largely attributed to patients who underwent primary surgical resection of their tumour which increases the risk of dysphagia.

A limitation of this study was that swallowing outcome measures were not included. However both groups had similar outcomes in terms of diet texture tolerance at three months post-treatment, with half of all patients in each group resuming full diet texture. At this time point, 31% of patients had their tube removed and 38% were no longer using it. This is similar to a previous study which reported that half of all patients had resumed a full diet by the time of PGT removal (Crombie et al., 2015). Whilst PGT placement has been reported to show improvements in quality of life during the acute treatment phase (Salas et al., 2009; Silander et al., 2012), the presence of a long term feeding tube has the greatest negative impact on quality of life (Terrell et al., 2004), particularly in the domains of interference with family life, relationships, social activities and hobbies (Rogers et al., 2007). It has also been associated with clinical depression (Chen et al., 2013). One study also reported that two thirds of patients were longing to have the tube removed (Roberge et al., 2000) and similar comments were seen in a qualitative study (Merrick & Farrell, 2012).

This current study has shown that as patients recover post-treatment many have tubes in-situ which are no longer being used and thus has the potential to impact on quality of life, mental health and their recovery from their cancer experience. As there are no general guidelines as to when gastrostomy removal should occur when the tube is no longer required, many clinicians opt to wait for the outcome of the post-treatment scans to ensure no further treatment or salvage surgery is required for persistent disease. One study has reported that the relative risk of feeding tube dependence at 18 and 24 months was 4.74 and 7.66 respectively in patients who have undergone a post-treatment neck dissection (Lango et al., 2010). This risk needs to be outweighed with the potential benefit of tube removal on the patient's quality of life, and should be discussed with the individual patient to inform decision making.

CONCLUSION

PGT use continues to play a significant role in the nutritional management of patients with HNSCC in the acute phase post-treatment and long term dependence rates are low. Encouraging early use of the PGT may prolong time to tube removal but it does not increase long term dependency rates beyond four months post treatment. However prolonged gastrostomy use is a complex multifaceted phenomena and consideration must be given to the patient's nutritional status to assist understanding of the reasons for long term tube use as it may be appropriate.

ACKOWLEDGEMENTS

The authors would like to thank: the staff from the Combined Head and Neck Clinic at the Royal Brisbane and Women's Hospital for their support, and a number of dietitians throughout Queensland for their assistance with data collection.

Table 8-13: Supplementary Table 1 - Comparison of gastrostomy use and tube outcomes for twelve months post-treatment between standard care and intervention groups in patients clear of disease at three months

Months post treatment	Tube use or Outcome	Standard Care (n=52)	Intervention (n=47)	Total (n=99)	P value
0	Nil	5 (10)	7 (15)	12 (12)	0.477
	Supplementary	6 (11)	8 (17)	14 (14)	
	Full	41 (79)	32 (68)	73 (74)	
1	Nil	18 (34)	13 (28)	31 (31)	0.919
	Supplementary	15 (29)	15 (32)	30 (30)	
	Full	17 (33)	17 (36)	34 (34)	
	Removed	2 (4)	2 (4)	4 (4)	
2	Nil	22 (42)	15 (32)	37 (37)	0.305
	Supplementary	16 (31)	12 (26)	28 (28)	
	Full	4 (8)	9 (19)	13 (13)	
	Removed	10 (19)	11 (23)	21 (21)	
3	Nil	21 (40)	15 (32)	36 (36)	0.581
	Supplementary	11 (21)	15 (32)	26 (26)	
	Full	2 (4)	3 (6)	5 (5)	
	Removed	18 (35)	14 (30)	32 (32)	
4	Nil	14 (27)	5 (11)	19 (19)	0.003*
	Supplementary	4 (8)	12 (26)	16 (16)	
	Full	0 (0)	4 (8)	4 (4)	
	Removed	34 (65)	26 (55)	60 (61)	
5	Nil	5 (10)	7 (15)	12 (12)	0.082
	Supplementary	2 (4)	5 (11)	7 (7)	
	Full	0 (0)	3 (6)	3 (3)	
	Removed	45 (86)	32 (68)	77 (78)	
6	Nil	3 (6)	5 (11)	8 (8)	0.166
	Supplementary	1 (2)	5 (11)	6 (6)	
	Full	1 (2)	2 (4)	3 (3)	
	Removed	47 (90)	35 (74)	82 (83)	
12	Nil	1 (2)	2 (4)	3 (3)	0.244
	Supplementary	0 (0)	2 (4)	2 (2)	
	Full	0 (0)	1 (2)	1 (1)	
	Removed	51 (98)	42 (89)	93 (94)	

*Statistically significant ($p<0.05$)

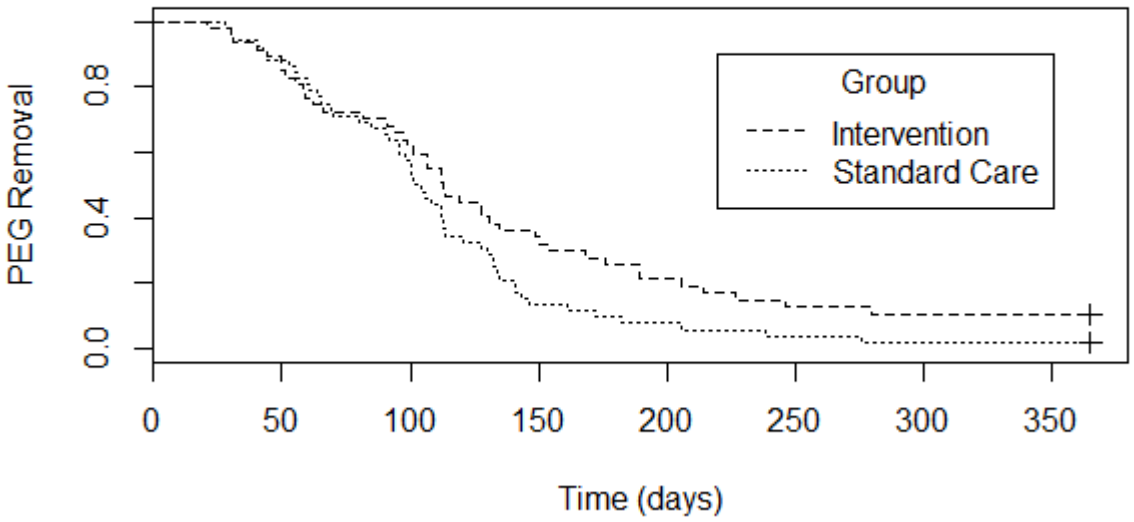

Figure 8-6: Supplementary Figure 1 - Kaplan Meier curves to compare the rate of gastrostomy tube removal over twelve months post-treatment between standard care and intervention group in patients clear of disease at three months

8.4 RCT: Patient adherence and barriers

8.4.1 Abstract

Objectives: The main aim was to investigate the incidence of patient adherence to nutritional tube feeding recommendations in patients with head and neck cancer and to determine patient barriers to meeting tube feeding prescription.

Materials and Methods: This was an observational study from a randomised controlled trial in patients with head and neck cancer deemed at high nutritional risk with prophylactic gastrostomy (n=125). Patients were randomised to receive early tube feeding prior to treatment (intervention group) or standard care. All patients in the intervention and standard care groups then commenced clinical tube feeding as required during treatment. Patients maintained a daily record of gastrostomy intake, main nutrition impact symptom necessitating gastrostomy use, and reasons for not meeting nutrition prescription. Adherence was defined as meeting ≥75% of total prescribed intake.

Results: Patients were predominantly male (89%), median age 60, with oropharyngeal tumours (78%), stage IV disease (87%) treated with chemoradiotherapy (87%). Primary reasons for gastrostomy use were poor appetite/dysgeusia (week 2-3) and odynophagia/mucositis (week 4-7). Early tube feeding adherence was 51%. Clinical tube feeding adherence was significantly higher in the intervention group (58% vs 38%, p=0.037). Key barriers to both phases of tube feeding were; nausea, early satiety and treatment factors (related to hospital healthcare processes).

Conclusions: Early tube feeding can improve patient adherence to clinically indicated tube feeding during treatment. Low adherence overall is a likely explanation for clinically significant weight loss despite intensive nutrition interventions. Optimising symptom management and strategies to overcome other barriers are key to improving adherence.

8.4.2 Manuscript

INTRODUCTION

Treatment fidelity is important to assess in intervention research trials as it refers to the extent to which interventions are delivered as intended according to the study protocol (Gearing et al., 2011). It is particularly important for intervention research trials which encompass behavioural change, so that the efficacy of the intervention can be considered in the correct context and inappropriate rejection of potentially effective interventions can be minimised (Beck et al., 2015). Treatment fidelity has been described as having at least four core components including: study design and protocol to outline how the intervention should be organised and delivered; training and supervision of those delivering the intervention to ensure consistency; monitoring of intervention delivery to determine whether the intervention was delivered as intended; and monitoring of intervention receipt to determine whether the intervention was received and understood (Bellg et al., 2004; Gearing et al., 2011). A recent systematic review identified that monitoring of intervention delivery is currently the most widely reported component in the literature, with monitoring of intervention receipt having the least focus (Gearing et al., 2011). Assessment of intervention receipt can include considerations to patient comprehension, engagement and adherence to the intervention (Beck et al., 2015).

Patient adherence alone is a complex area of treatment fidelity affecting many aspects of healthcare. A number of studies have investigated patient adherence in different aspects of generic multidisciplinary cancer care and their impact on clinical outcomes such as; oral chemotherapy (Greer et al., 2016; Muluneh et al., 2016), analgesics (Oldenmenger, Sillevis Smitt, de Raaf, & van der Rijt, 2016; Meghani & Knafl, 2016), and anti-emetic medication (Vidall et al., 2015). Patient characteristics have been shown to influence adherence to clinical practice guidelines in the critical care setting (Cahill, Suurdt, Ouellette-Kuntz, & Heyland, 2010). It has been reported that patients with head and neck squamous cell carcinoma (HNSCC) have a high rate of mental health problems, substance use and social issues which increases psychologic distress and depression (Kugaya et al., 2000), which in this population, can predict malnutrition outcomes (Britton et al., 2012). Depression has also been shown to reduce adherence to medical treatment recommendations (DiMatteo et al., 2000) and so the characteristics of this patient population suggests that adherence may be particularly challenging. Indeed a recent systematic review on swallowing preservation exercises reported low adherence rates in all trials reporting on this outcome (n=4) (Perry, Lee, Cotton, & Kennedy, 2016).

Adherence to dietary advice in patients with HNSCC has rarely been studied. One study defined adherence as patient acceptance of dietary counselling or tube feeding as part of their nutrition program, and found non-adherence resulted in more weight loss (Capuano et al., 2008). However this did not account for adherence to the dietary advice actually provided. This has been addressed more recently, where a study defined adherence to dietary counselling as consuming ≥75% of recommended energy and protein intake, and this confirmed favourable outcomes on body composition parameters with adherence (Hopanci Bicakli et al., 2017).

Nutrition support and intervention is considered an integral component of HNSCC management and includes regular nutrition screening and assessment, dietary counselling and tube feeding interventions, including consideration to prophylactic gastrostomy placement (Talwar et al., 2016). However despite these intensive recommended nutrition interventions, significant weight loss still occurs (Brown et al., 2014a; Silander et al., 2010). A randomised controlled trial (RCT) was initiated to further intensify nutrition intervention through commencement of an early supplementary tube feeding phase via the prophylactic gastrostomy before there were any clinical indicators for tube feeding during treatment (Brown et al., 2014b). It was hypothesised that this “early tube feeding phase” would reduce fear and anxiety associated with the tube (Merrick & Farrell, 2012), assist patients to adapt to using the tube for when it was required during the “clinical tube feeding phase” to meet nutritional requirements (Salas et al., 2009), and thus result in less weight loss. There was no difference in the primary outcome of weight loss or secondary outcomes including quality of life, nutritional status, body composition, clinical outcomes and survival (Brown et al., 2017a).

The primary aim of this sub study from the RCT described above was to report on patient adherence to nutritional tube feeding recommendations, as a measure of one component of treatment fidelity, and to determine if there were any differences in adherence following the early tube feeding intervention versus standard care. The second aim was to determine any patient barriers to meeting the prescribed level of tube feeding, during both the early and clinical phases of tube feeding. Once the clinical phase of tube feeding had commenced the final aim was to explore reasons why patients felt they needed the tube for nutrition support, to gain a greater understanding of their experience and perspective.

PATIENTS AND METHODS

Participants and Study Setting

Patients with HNSCC were recruited from the Royal Brisbane and Women's Hospital (RBWH), a tertiary/quaternary hospital in Queensland, Australia from September 2012 to June 2015. They were included if referred for a prophylactic gastrostomy prior to treatment based on a validated protocol (Brown et al., 2016b). Patients were randomly assigned using a computer generated concealed allocation sequence to either the early intervention or standard care (1:1).

The full trial protocol has been published and describes the full eligibility criteria, randomisation procedures, primary outcome measures and sample size calculation in more detail (Brown et al., 2014b). The study had ethical approval by the RBWH Human Research Ethics Committee and The University of Queensland Medical Research Ethics Committee. All patients provided written informed consent to participate.

Interventions

Patients were reviewed weekly by the dietitian, speech pathologist, radiation oncologist and medical oncologist, and had access to nursing support and other allied health services as required. Radiotherapy was delivered using helical-intensity modulated radiotherapy at doses of 2Gy per day to a total 60-70Gy. Chemotherapy was prescribed at the discretion of the medical oncologist.

Patients in the intervention group had supplemental tube feeding commenced immediately following gastrostomy placement (prior to treatment/surgery) in addition to their current oral intake. The prescription consisted of two bolus feeds (1.5kcal/ml polymeric formula with fibre) per day (total 400ml) which continued as a minimum until completion of treatment. This was defined as the "early tube feeding phase" and was only prescribed in the intervention arm. Weekly supplies were provided to the patient and they were all encouraged to maintain oral intake as much as possible. Once treatment commenced, patients were assessed weekly by the dietitian and in response to clinical criteria, were commenced on tube feeding (standard care) or had tube feeding increased (intervention). Indicators for commencing or increasing enteral nutrition in both groups were stated in the local protocol (Brown et al., 2016b) and included factors such as reduced oral intake, weight loss and/or uncontrolled symptoms. This was defined as the "clinical tube feeding phase" and was possible in both groups.

When this phase commenced the patient was given a script requiring co-payment to obtain supplies through pharmacy or home delivery. The regimen was determined by the dietitian to suit the patients' individual requirements and adjusted weekly as required. If tolerance was a concern, alternative feed formulas and delivery methods were negotiated and trialled.

On commencement of either phase of tube feeding all patients were provided with weekly diary log books. Patients were asked to record the main reason necessitating gastrostomy use each week, which may have been for the study intervention itself. A checklist of nutrition impact symptoms was provided and included free text space for any other reasons. Patients were asked to complete this step to determine the underlying cause of the triggers for the recommendation to commence clinical tube feeding (i.e. the resultant weight loss or poor oral intake). This patient reported information would also prevent any bias from clinician interpretation of the reasons. Secondly patients were asked to maintain a daily record of gastrostomy intake with any reasons for not meeting nutrition prescription if applicable (free text space). The dietitian collected the diaries from the patients at each weekly review and if incomplete assisted with completion as able with information obtained from interview/assessment.

Outcomes

Daily percentage adherence to tube feeding was calculated from patient diaries based on prescribed versus actual recorded intake and mean adherence for the duration of tube feeding was calculated as the primary outcome. So that all diaries were complete, retrospective chart audits were undertaken if required to obtain any missing data from the documented weekly dietitian assessments which were based on patient reported intake data. Daily and overall adherence was then classified as a binary variable (adherent vs non-adherent) which was defined as ≥75% of prescribed intake.

Days that patients were non-adherent based on this definition were identified from patient diaries and any stated barriers were extracted. If patients recorded multiple barriers for any one day, all were included. If no barriers were stated on non-adherent days this was also recorded to calculate adherence to diary completion. Due to the qualitative and individual nature of this outcome, any missing data was accepted as missing and not statistically imputed. Barriers were then classified according to: nutrition impact symptoms as per the Patient-Generated Subjective Global Assessment (PG-SGA) (Ottery, 2005); other physical symptoms; patient factors and environmental factors. The rationale for these classifications and examples of entries from patient diaries are shown in Table 8-14.

The date the dietitian recommended initiating the clinical tube feeding phase was recorded and classified as week of treatment according to fractions of radiotherapy received (5# per week). Reasons for gastrostomy tube use each week were collated from patient diaries.

Weight was measured in kilograms using digital scales at baseline, end of radiotherapy treatment and at three months post radiotherapy, and percentage weight loss was calculated.

Statistical Methods

Baseline participant characteristics and outcomes between groups (where relevant) were summarised using mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Differences between groups were assessed using Chi-squared or Fishers Exact tests for categorical variables and two sample t–tests for continuous variables. The Shapiro-Wilk test was used to test normality and Levene's test was used to assess variance. Adherence and barriers to feeding were assessed as either the early tube feeding phase (intervention group only) or the clinical tube feeding phase (both groups) and outcomes reported using descriptive statistics. Statistical significance was set at $p<0.05$. Data were analysed using Excel 2013 and R Commander Version 2.1-7 and R version 3.1.3 (2015-03-09).

RESULTS

Patient Characteristics

One hundred and thirty one patients entered the RCT. The flow through the study is illustrated in Figure 8-7. Of the eligible patients, 58 were in the intervention and 67 were in the standard care group. The early tube feeding phase was completed by 57/58 patients in the intervention group. The clinical tube feeding phase was completed by 50/58 eligible patients in the intervention group and 58/65 eligible patients in standard care. Two patients were excluded in standard care as they received surgery alone. The patient demographic and clinical characteristics are shown in Table 8-15. Patients were predominantly male (89%), median age 60 (range 36-83), with oropharyngeal tumours (78%), stage IV disease (87%) treated with chemoradiotherapy (87%), with no statistically significant differences between groups. Clinically there was a higher proportion of patients with advanced T stage in the standard care group and a higher mean BMI in the intervention group.

Table 8-14: Classification of patient reported barriers to tube feeding during definitive/adjuvant (chemo) radiotherapy for head and neck cancer

Category	Individual barriers	Examples from diaries
Nutrition Impact Symptoms	No problems eating	Eating normally Still eating and drinking orally Not needing PEG
	Constipation	Constipated since chemo Problems with constipation
	Diarrhoea	Had loose bowel Pump reduced due to diarrhoea
	Feel full quickly	Too full and unable to eat other meals Bloated feeling – too full
	Nausea	Have felt nauseous for a few days I feel like I want to throw up every meal
	No appetite	Appetite down Not hungry
	Pain	Too much pain Using Endone for pain and headaches
	Smells Bother me	Smells make me feel ill Smell sensitivity
	Vomiting	Had two feeds but threw one up Vomiting after PEG feed
Other physical symptoms	Reflux	Bad reflux in the evening couldn't eat Hiccups all day
	Fatigue	Too fatigued Very tired, asleep by 6pm
	Malaise	Felt unwell Not well
Patient factors	Psychosocial (e.g. mood, motivation, support)	Not bothered Feeling very low – no get up and go Wife not there to encourage
	Script (e.g. ordering, delivery, supply)	Not ordered script due to finances Haven't got script yet Ran out of supply
	Time (e.g. lack of time)	Not enough time Out all day Home late
	Other alternatives (e.g. choosing other food/drink)	Tried Weetabix and Sustagen Ate fruit 2L water
Environmental factors	Treatment (e.g. appointments, admissions)	On drip at hospital for 2hours Stopped doing feeds when admitted Interrupted by chemo & rad treatment
	Medical (e.g. tube/feeding complications)	Nil by tube for endoscopy Advised no feeds until review by doctor Having trouble with tube

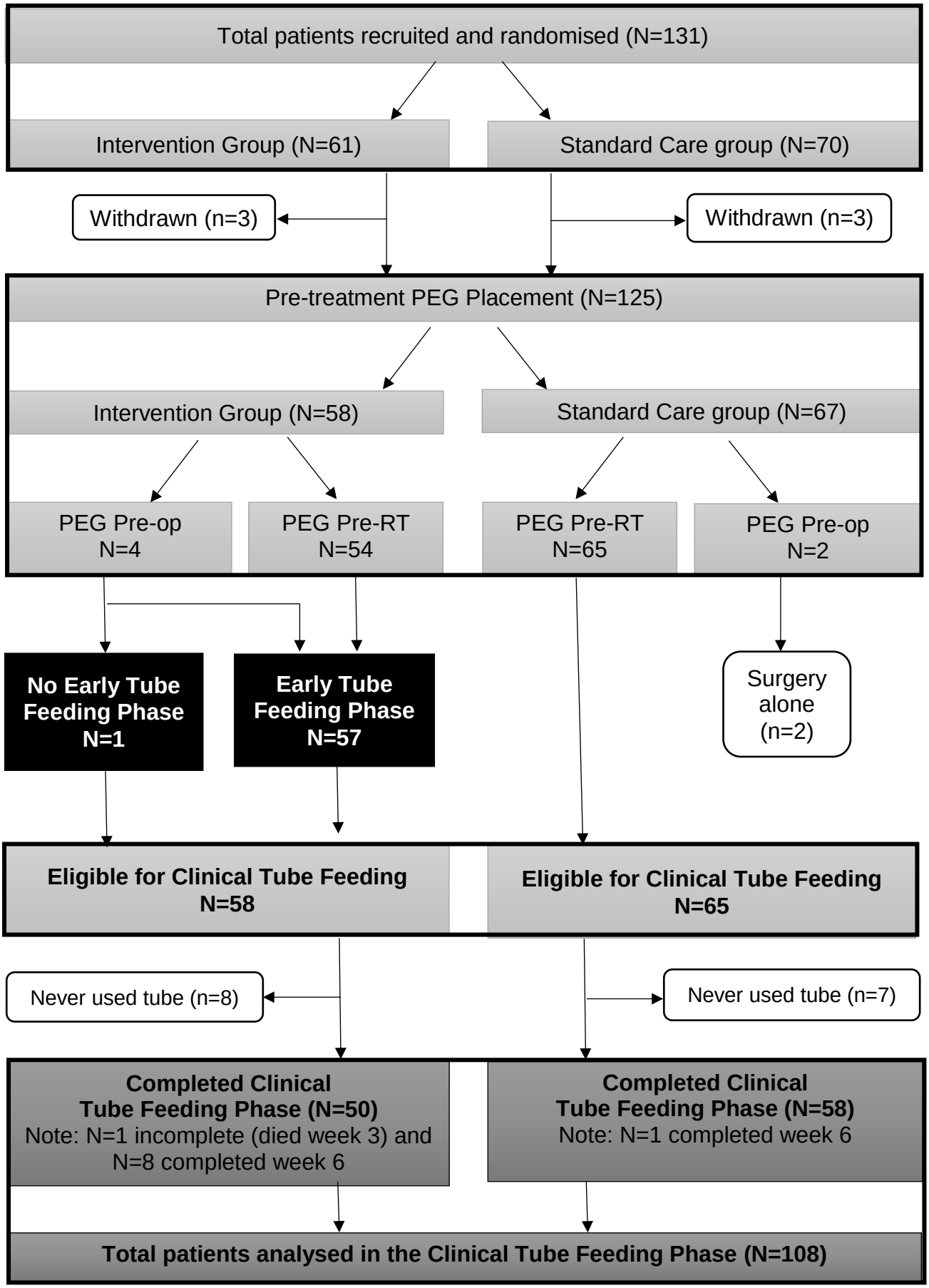

Figure 8-7: Patient Flow through Study Phases

Abbreviations: PEG=gastrostomy; Pre-op=pre-operatively; Pre-RT=pre- radiotherapy.

Table 8-15: Summary of demographic and clinical characteristics of patients with head and neck cancer (n=125)

Variable		Total (n=125)	Standard (n=67)	Intervention (n=58)	p value
Age (years)	Mean ± sd	60.3 ± 10.1	59.6 ± 10.7	61.0 ± 9.3	0.439
BMI (kg/m2)	Mean ± sd	27.4 ± 5.5	26.5 ± 5.7	28.4 ± 5.2	0.063
			N (%)		
Gender	Male	111 (89)	58 (87)	53 (91)	0.395
	Female	14 (11)	9 (13)	5 (9)	
Tumour Site	Oral cavity	13 (10)	6 (9)	7 (12)	0.770
	Oropharynx	97 (78)	54 (81)	43 (74)	
	Nasopharynx	4 (3)	2 (3)	2 (3)	
	Hypopharynx	8 (6)	3 (5)	5 (9)	
	Other	3 (3)	2 (2)	1 (2)	
T Stage	T0	1 (1)	0 (0)	1 (2)	0.153
	T1	8 (6)	4 (6)	4 (7)	
	T2	44 (35)	20 (30)	24 (41)	
	T3	36 (29)	25 (37)	11 (19)	
	T4	36 (29)	18 (27)	18 (31)	
N Stage	N0	11 (9)	7 (10)	4 (7)	0.567
	N1	11 (9)	7 (10)	4 (7)	
	N2a	4 (3)	1 (2)	3 (5)	
	N2b	54 (43)	29 (43)	25 (43)	
	N2c	40 (32)	19 (28)	21 (36)	
	N3	5 (4)	4 (6)	1 (2)	
Overall Stage	II-III	16 (13)	11 (16)	5 (9)	0.344
	IV	109 (87)	56 (84)	53 (91)	
p16 status (n=118)	Positive	84 (71)	43 (68)	41 (75)	0.452
	Negative	34 (29)	20 (32)	14 (25)	
Treatment	Surgery +/- RT	8 (7)	3 (4)	5 (9)	0.617
	CRT	109 (87)	59 (88)	50 (86)	
	Adj CRT	8 (6)	5 (8)	3 (5)	

Abbreviations: BMI=body mass index; RT=radiotherapy; CRT=chemoradiotherapy.

Weight Outcomes

Both groups experienced similar levels of weight loss during radiotherapy (6.7±5.3% standard care vs 6.1±4.5% intervention, p=0.471, 95% CI [-2.4, 1.1]) as well as up to three months post treatment (10.9±6.7% standard care vs 10.8±5.6% intervention, p=0.930, 95% CI [-2.3, 2.1]).

Adherence to tube feeding

Overall mean adherence to the early tube feeding phase was 67.9±29.6%. Adherence to the early tube feeding phase improved over time, and was consistently above 70% from week 3 onwards (Figure 8-8), although the number of patients in this phase decreased over time as patients progressed to the clinical tube feeding phase (Table 8-16).

Overall mean adherence to clinical tube feeding was higher in the intervention group at 77.4±18.7% compared to 69.0±20.2% in the standard care group (p=0.028, 95% CI [0.9, 15.9]). Adherence to the clinical tube feeding phase in the intervention group was consistently high throughout treatment at approximately 70% or more, but only reached this level after week four of treatment in standard care (Figure 8-8). This illustrates a period of adaptation is required following commencement of tube feeding irrespective of whether it was prophylactic or clinically indicated.

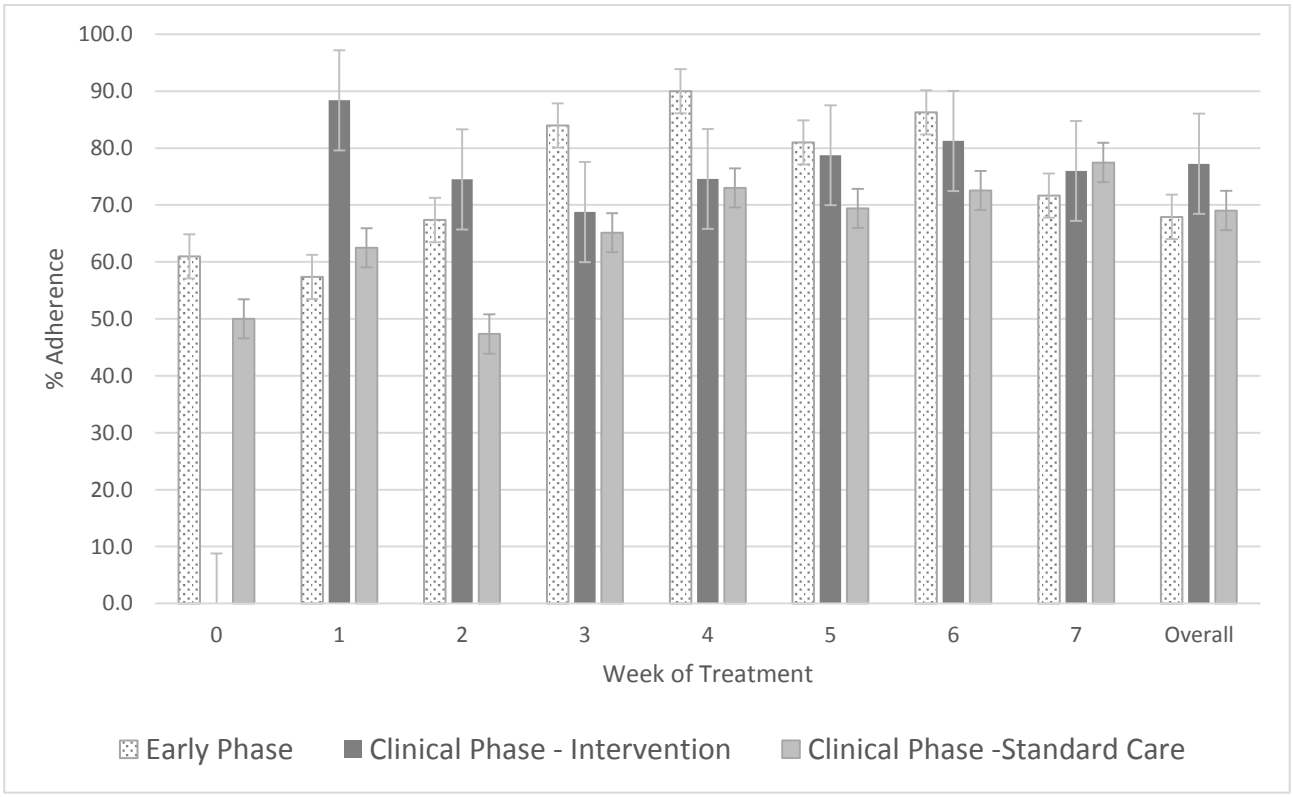

Figure 8-8: Mean adherence to tube feeding recommendations over time for patients with head and neck cancer receiving definitive/adjuvant (chemo) radiotherapy

Table 8-16: Timing of commencement and reason for clinical tube feeding in patients with head and neck cancer receiving definitive/adjuvant (chemo) radiotherapy

Week of Treatment	Number of patients commencing clinical tube feeding			Accumulative use of tube	Patient reason for clinical tube feeding			
	Standard (n=60)	Intervention (n=50)	Total (n=110)	Total (n=125)		Standard (n=60)	Intervention (n=50)	Total (n=110)
	n			n (%)		n		n (%)
Week 0	3	4	7	7 (6)	Odynophagia	0	0	0 (0)
					Nausea	0	0	0 (0)
					Appetite/taste	1[a]	0	1 (14)
					Dysphagia	2	4	6 (86)
Week 1	3	1	4	9 (7) [b]	Odynophagia	1	0	1 (11)
					Nausea	1	0	1 (11)
					Appetite/taste	1	1	2 (22)
					Dysphagia	1	4	5 (56)
Week 2	16	9	25	34 (28)	Odynophagia	2	0	2 (6)
					Nausea	5	3	8 (23)
					Appetite/taste	11	7	18 (53)
					Dysphagia	2	4	6 (18)
Week 3	12	16	28	62 (50)	Odynophagia	13	7	20 (32)
					Nausea	2	3	5 (8)
					Appetite/taste	15	13	28 (45)
					Dysphagia	2	7	9 (15)
Week 4	15	12	27	88 (72) [c]	Odynophagia	22	12	34 (39)
					Nausea	3	7	10 (11)
					Appetite/taste	16	14	30 (34)
					Dysphagia	6	8	14 (16)
Week 5	6	4	10	98 (80)	Odynophagia	25	17	42 (43)
					Nausea	7	6	13 (13)
					Appetite/taste	16	14	30 (31)
					Dysphagia	5	8	13 (13)

Week of Treatment	Number of patients commencing clinical tube feeding			Accumulative use of tube	Patient reason for clinical tube feeding			
	Standard (n=60)	Intervention (n=50)	Total (n=110)	Total (n=125)		Standard (n=60)	Intervention (n=50)	Total (n=110)
	n			n (%)		n		n (%)
Week 6	4	3	7	105 (86)	Odynophagia	30	24	54 (51)
					Nausea	5	6	11 (10)
					Appetite/taste	15	8	23 (22)
					Dysphagia	7	10	17 (16)
Week 7	1	1	2	98 (87) [d]	Odynophagia	35	26	61 (62)
					Nausea	4	4	8 (8)
					Appetite/taste	11	5	16 (16)
					Dysphagia	6	7	13 (13)

Abbreviations: a Patient request to start pre radiotherapy. b Patients discontinued as had surgery alone (n=2). c Patient discontinued as died during treatment (n=1). d Patients discontinued as completed treatment in week 6 (n=9).

Classification of overall tube feeding adherence in the early and clinical phases between groups is shown in Figure 8-9. The proportion of patients classified as adherent to the early phase was 51% (n=29). Adherent patients were older (64.4±7.9yr vs 57.8±9.7yr, p=0.006, 95% CI [2.0, 11.4]) but no other differences in patient characteristics/demographics were seen. The proportion of patients classified as adherent to the clinical phase was higher in the intervention group at 58% compared to 38% in standard care (p=0.037). There were no differences in patient characteristics/demographics between the adherent and non-adherent patients for this phase. The group differences for clinical tube feeding were more evident at higher adherence rates, with more patients in the intervention achieving ≥75% adherence, and more patients in standard care achieving 50-75% adherence. If patients were adherent to the clinical phase, they had less weight loss at three months post treatment (-10.3±5.7% vs -12.6±5.7%, p=0.038, 95% CI [0.1, 4.6]).

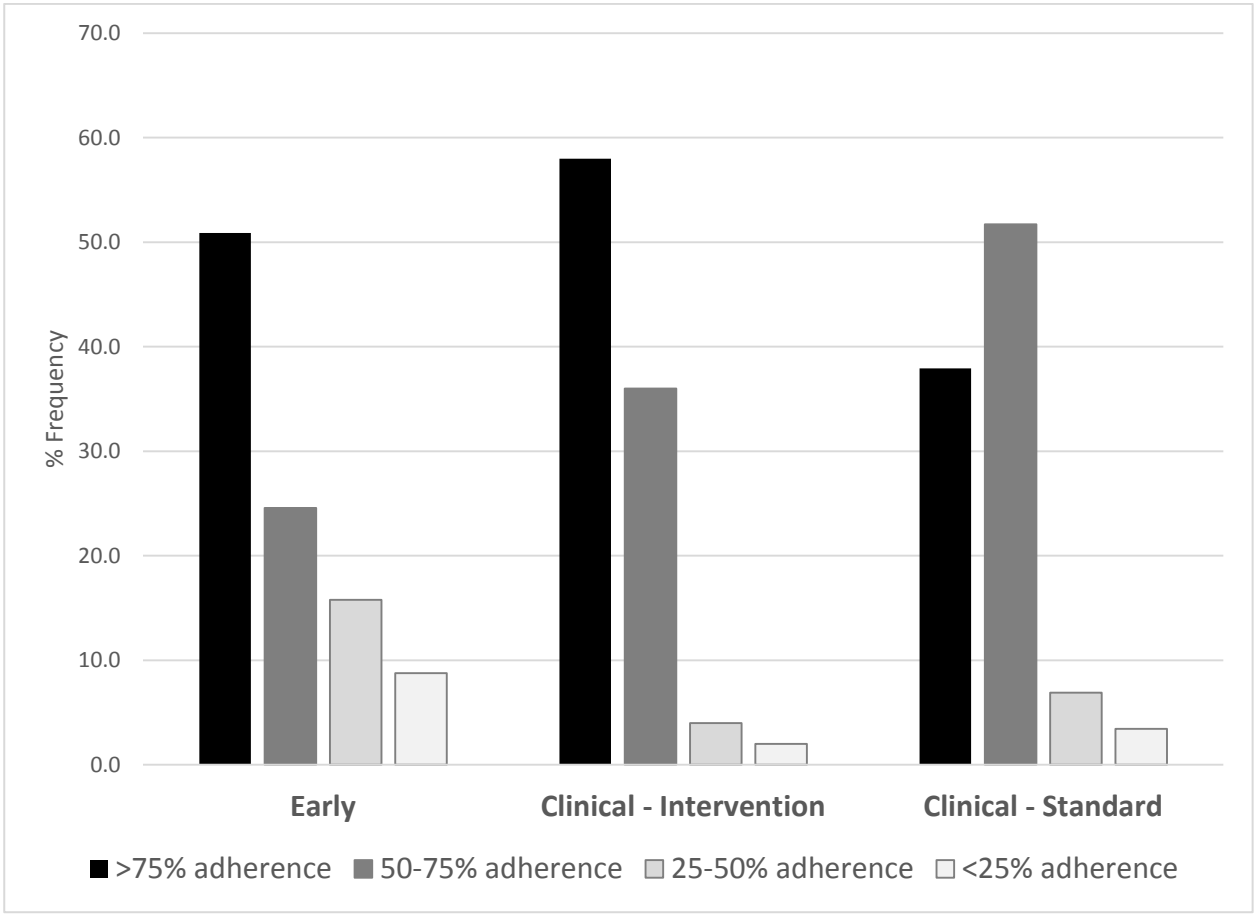

Figure 8-9: Comparison of overall adherence to tube feeding recommendations during the early and clinical phases in patients with head and neck cancer receiving definitive/adjuvant (chemo) radiotherapy

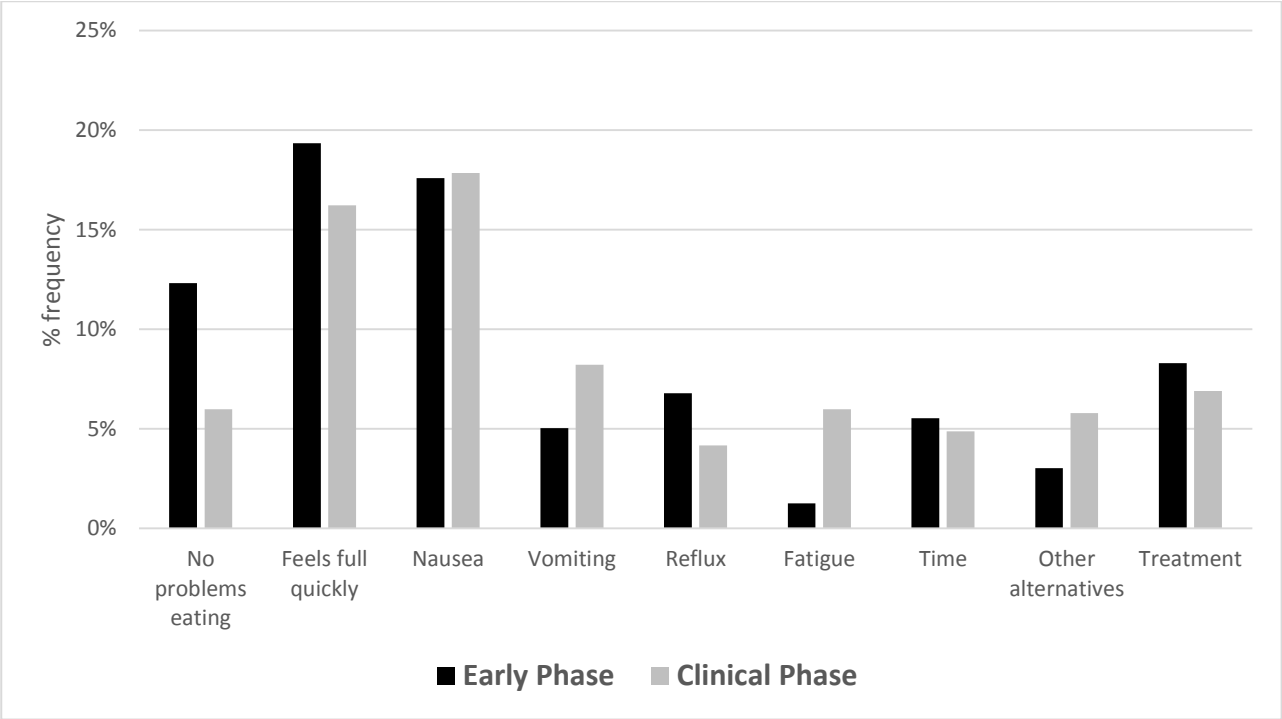

Figure 8-10: Summary of the main barriers to tube feeding recommendations during the early and clinical phases in patients with head and neck cancer receiving definitive/adjuvant (chemo) radiotherapy

Barriers to tube feeding

The most common reasons for non-adherence to the early tube feeding phase included; feels full quickly (19%), nausea (18%), no problems eating (12%), treatment factors (8%), reflux (7%) and time available to administer feeds (6%) (Figure 8-10). The number of reported barriers decreased over time (especially in week 6 and 7) as patients progressed to the clinical tube feeding phase. Overall the most common reasons for non-adherence to the clinical tube feeding phase were; nausea (18%), feels full quickly (16%), vomiting (8%), treatment factors (7%), fatigue (6%), other alternatives (6%) and no problems eating (6%) (Figure 8-10). The number of reported barriers was very low in week 0 and 1, as most patients progressed to the clinical tube feeding phase from week 2 onwards.

Mean adherence to diary completion for recording barriers was 52.5±35.4% overall, with no differences between groups (49.3±33.4% intervention vs 55.7±37.4% standard care, p=0.333, 95% CI [-6.6, 19.4]). When the groups were compared in the clinical phase, common key barriers were; nausea, vomiting, feels full quickly and treatment factors. Only minor differences were observed; with patients in standard care more frequently reporting no problems eating, fatigue and psychosocial reasons, whereas patients in the intervention stated using other alternatives more often.

Commencement of Clinical Tube Feeding

There was no difference in the time to commencement of clinical tube feeding between the groups (p=0.825) with the majority (74%) commencing between weeks 2-4. Patients using the tube prior to treatment were due to post-operative dysphagia (n=6) or poor appetite (n=1, standard care). Loss of appetite/taste were primary reasons for tube use in weeks 2-3 and odynophagia became the most predominant factor from week 4-7. The timing and reasons for commencing this phase are summarised in Table 8-16.

DISCUSSION

This study has investigated the reasons for initiation of tube feeding and the adherence and barriers to tube feeding prescriptions both before and during treatment in a group of patients with HNSCC who had a prophylactic gastrostomy placed prior to treatment. The findings provide a unique insight into understanding tube use and barriers to tube feeding prescriptions from a patient perspective.

Adherence to the early tube feeding phase for this trial was only 51%, which was lower than expected given other nutrition intervention trials with oral supplements report much higher adherence rates of 79% (Hubbard et al., 2012). However the intervention group did have significantly higher adherence rates to subsequent clinical tube feeding compared to standard care (58% vs 38%, p=0.037), and this in itself led to less weight loss. This confirmed our secondary hypothesis that by promoting and encouraging early use of the tube, this allowed patients to develop a habit of accessing the gastrostomy on a daily basis, thus promoting behavioural change resulting in better adaptation to the tube and feeding management in the later stages of treatment.

Three common barriers were identified across all phases/groups and included nausea, feels full quickly and treatment factors. Nutrition impact symptoms such as nausea and feels full quickly, have been reported as highly prevalent in a large HNSCC cohort (n=635) prior to treatment at 14% and 28% respectively (Farhangfar et al., 2014), however as they excluded patients being tube fed it is unclear how these findings compare to this current study. Vomiting also became a more important factor in the clinical phase, highlighting that optimising symptom management is a key area to address.

Treatment barriers included healthcare system processes interfering with their ability to administer tube feedings e.g. time spent for appointments or treatment, and the hospital admission, transfer and discharge processes. Clinician knowledge and healthcare systems have been identified previously as key themes in barriers and enablers to nutrition care in HNSCC (Martin, de van der Schueren, Blauwhoff-Buskermolen, Baracos, & Gramlich, 2016). Another study on the impact of tube feeding upon daily life found that that finding "a place to feed" and "negative attitudes of others towards feeding" were challenges experienced (Brotherton et al., 2006), which may influence how patients cope in the hospital (and their social) environment. This will be important to investigate further to understand how the environment can be improved to better support patients' needs.

Another key barrier in the early phase of tube feeding, although it was also one of the main barriers in the standard care group during the clinical tube feeding phase, was the patient perception that they had "no problems eating" and thus did not see the need for tube feeding. Choosing "other alternatives" tended to occur more in the clinical phase of tube feeding and was more frequently reported in the intervention group. Although some of these alternatives appeared to be reasonable high protein/energy options (e.g. cheese, chicken, smoothies, custard), portion sizes were not determined to assess overall nutritional adequacy, and there was also a high number that reported nutritionally inadequate alternatives such as fruit, tea, coffee and water.

Both of these barriers highlight that there may be a gap in patient knowledge and underestimation of their nutritional needs, which are increased during treatment (Arends et al., 2017). It may also reflect conflicting goals of weight management between the patient and clinician. The patient desire for weight loss has been observed anecdotally in clinical practice and confirmed in some qualitative studies which have reported patients found perceived benefits of weight loss; "I lost weight when I was on my PEG…a little benefit" (Mayre-Chilton et al., 2011) and "I haven't been able to eat, and have lost between 10 and 12kg. I'm pleased with my weight reduction" (Ehrsson et al., 2015). This observation may also be a reflection of the changing demographic of HNSCC patients with a greater proportion of over-weight patients with p16 positive disease rather than the classical underweight/malnourished patient with p16 negative disease (Albergotti et al., 2016). In the current study the mean (SD) BMI was 27.4 $\pm$ 5.5 kg/m^2.

This current study identified the loss of appetite/dysgeusia as important factors necessitating tube use in the earlier stages of treatment, but also highlighted their importance in the final weeks of treatment accounting for 16-22% of cases. Traditionally requirement for gastrostomy in patients with HNSCC has been associated with dysphagia (Lango et al., 2016) or odynophagia from mucositis (Trotti et al., 2003), as these symptoms present as the physical inability to eat or drink. A review of the influence of nutrition impact symptoms on nutritional status, weight loss, and oral intake found most studies report on dysphagia and xerostomia (Bressan et al., 2016), with loss of appetite shown to have the greatest reduction on oral intake (Farhangfar et al., 2014). This study has demonstrated that patients perceive loss of appetite/dysgeusia as severe enough to necessitate feeding tube use, which supports recommendations that lack of appetite should be used as a clinical indicator for initiation of nutrition support in cancer care (Arends et al., 2006).

The limitation to this current study is the poor adherence to diary completion for reporting barriers to tube feeding recommendations (49-56%), despite prompting by the dietitian at weekly appointments, which means that only half the days in which patients were non-adherent are accounted for. This in itself may be a reflection of the overall impact of treatment on even motivated patients. It was not recorded how often patients required prompting by the dietitian at weekly reviews but even this strategy did not fully assist diary completion, highlighting inadequate appointment time may also have been a barrier. It also creates bias in patient reported symptoms from those that were adherent. For example if one patient suffered from reflux and diligently recorded this reason daily, this may have overestimated the true frequency of this barrier within the population.

The accuracy and reliability of the patient diaries to calculate tube feeding adherence rates is also a limitation, as if incomplete, data had to be estimated from recall or obtained retrospectively from charts. Future studies should consider how adherence could be more accurately recorded. Dedicated research assistant time to allow for daily contact with the patient is one option or smartphone app technology could be considered as this has been successful at improving self-monitoring in weight loss trials (Carter, Burley, Nykjaer, & Cade, 2013; Wharton, Johnston, Cunningham, & Sterner, 2014) and so perhaps may be effective at self-monitoring intake. Other studies have also reviewed service delivery models (Wall, Ward, Cartmill, Hill, & Porceddu, 2016), and utilised a novel telepractice application (Wall, Ward, Cartmill, Hill, & Porceddu, 2017) to improve adherence to prophylactic swallowing exercises which could also be methods to apply to improving dietary adherence.

Finally, as the focus was on adherence to tube feeding, other sources of dietary intake and adherence to dietary advice were not assessed.

The strength of this study is that it is the first to investigate and identify reasons for patient non-adherence to tube feeding prescriptions in this population which will help to inform future research and models of care. It is acknowledged that other outcomes which may have impacted on motivation and adherence, such as psychosocial distress and depression were not assessed in this study, and these would also be useful to consider for future studies in this field. Further qualitative research is suggested to develop an in-depth understanding of the physical, practical and psychological barriers patients face to inform the design of appropriate multidisciplinary models of care, ideally with a focus on patient and carer empowerment and ownership of care.

The role of psychosocial care appears paramount to improving outcomes, with one study already showing the benefits of a psychological intervention on nutrition outcomes and mortality (Britton et al., 2016). The impact of a dietitian-delivered health behaviour intervention is currently underway based on motivational interviewing and cognitive behavioural therapy (Britton et al., 2015) and has considered treatment fidelity across all key components (Beck et al., 2015). Other potential models include using social cognitive theory to improving dietary adherence (Cases, Fruge, & Daniel, 2015), following beneficial application on exercise adherence post treatment (Rogers et al., 2015). Current apps targeting areas of behaviour change however are not based on behavioural theories which is a potential limitation to their application in this context and thus require further research and development (DiFilippo, Huang, Andrade, & Chapman-Novakofski, 2015).

CONCLUSION

The observed low adherence to tube feeding recommendations overall is a likely explanation for clinically significant weight loss in patients with HNSCC during chemoradiotherapy. Whilst several barriers have been identified to tube feeding recommendations in this study, the early tube feeding approach is one strategy which has been shown to improve patient adherence to clinically indicated tube feeding during treatment. The implications of this in clinical practice is that routine encouragement of early tube feeding should be considered purely for behavioural purposes to improve adherence. Optimising symptom management will also be key; with nausea, vomiting and early satiety identified as primary barriers for patients.

As adherence was found to be lower in the earlier stages of treatment, this presents opportunities for increased dietetic and psychological interventions prior to treatment to improve patient understanding of nutritional needs and develop additional behavioural change strategies to overcome any environmental and psychosocial barriers. A collaborative multidisciplinary approach to addressing these factors will ultimately improve adherence to dietary recommendations, resulting in less clinically significant weight loss and thus improving other associated clinical outcomes.

ACKNOWLEDGMENTS

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8.5 Chapter summary

The results from the RCT did not show any benefit of the early nutrition intervention in relation to the planned outcomes. There were no significant differences in nutritional outcomes (weight, body composition, and nutritional status), QOL outcomes, or clinical outcomes (radiotherapy tolerance, chemotherapy tolerance, unplanned admissions, gastrostomy complications, and overall disease and survival outcomes). The early intervention did not show an increased dependency on the gastrostomy tube with most tubes removed between 3-4 months post treatment, with only five patients remaining dependent on their tubes at 12 months (4%).

The main explanation for the negative outcomes from the trial were likely due to the poor adherence to the intervention component of the trial, with only 29/57 patients (51%) adhering to the protocol. However one of the benefits that this study found was the intervention group had better adherence to tube feeding during the treatment phase compared to the standard care group (58% vs 38%, p=0.037). Sub analysis between adherent patients (n=49) and non-adherent patients (n=55) found the adherent group had less weight loss (-10.3% vs -12.6%, p=0.038). However the adherence rates are still low in general which implies nutritional requirements are frequently not being met, offering a hypothesis as to why patients continue to lose such a large amount of weight, despite what appears to be very intensive dietetic input with prophylactic gastrostomy (proPEG) tube placement prior to treatment. A number of potential barriers to tube feeding recommendations have been identified that warrant further investigation.

Chapter 9 **Discussion**

9.1 Chapter overview

This chapter summarises the results of the research in this thesis in relation to the aims and hypotheses, and discusses the strengths and limitations of the studies. The significance of the thesis and how the original research contributes to the field of dietetics are summarised, including implications for clinical practice and application of the results to the theoretical model. Finally opportunities for future research are identified, followed by concluding remarks.

9.2 Discussion of results in relation to aims and hypothesis

Study 1 (Chapter 4)

This study aimed to compare the outcomes of weight change and the requirement for tube feeding across two types of radiotherapy treatment – 3D conformal and helical-IMRT.

H_0 - There would be no difference in weight loss or tube feeding outcomes between the two treatment groups (helical-IMRT and 3D radiotherapy)

H_1 - The helical-IMRT group would experience less weight loss and need for tube feeding due to the more targeted nature of treatment which would reduce toxicities and nutrition-impact symptoms

The sample size (n=187) was sufficient to detect a 2.3% difference in weight loss between the two groups with 80% power and a Type I error 0.05. No differences in nutritional outcome measures were seen between the two groups. Median weight loss during radiotherapy was 7.3% (-20.1% to 22.9%) in the 3D group and 7.2% (-19.1% to 8.5%) in the helical-IMRT group (p=0.573). Incidence of severe weight loss ($\geq$10%) was 27% in the 3D group and 28% in the helical-IMRT group (p=0.843). Requirement for proPEG was 86% in the 3D group and 92% in the helical-IMRT group (p=0.213). The alternative hypothesis was refuted and the null hypothesis retained.

Study 2 (Chapter 5 Section 0)

This study aimed to validate the updated Royal Brisbane and Women's Hospital (RBWH) protocol to identify patients for proPEG insertion in a new cohort of patients (n=270) following the introduction of helical-IMRT.

H_0 - There would be no difference in protocol specificity between the two cohorts following the introduction of helical-IMRT

H_1 - The specificity of the protocol would reduce as it was anticipated there would be a reduced need for tube feeding with helical-IMRT

The results indicated an improvement in all validity measures compared to the original validation study (Brown et al., 2013b). The sensitivity improved from 54% to 72% and the specificity improved from 93% to 96%. The positive predictive value improved from 82% to 92% and the negative predictive value improved from 77% to 82%. The alternative hypothesis was refuted and the null hypothesis retained. The protocol remains valid for use.

Study 3 (Chapter 5 Section 5.3)

This was a hypothesis generating study to determine if any other variables, not previously considered, could be used to improve the predictive ability of the RBWH protocol to identify patients for proPEG. Four variables were investigated in a cohort of 269 patients.

1-H_0 – Systemic therapy agent or regimen does not improve the protocol's ability to identify patients for proPEG

1-H_1 – Systemic therapy agent or regimen does improve the protocol's ability to identify patients for proPEG

Since the protocol was originally developed, the choice of systemic therapy agents has increased. The newly approved monoclonal antibody (Cetuximab) had different toxicity profiles (Bonner et al., 2006), which were expected to influence nutrition impact symptoms and thus the need for tube feeding. The results from the study found the choice of systemic therapy agent or regimen was not associated with meeting the criteria for proPEG, and so the null hypothesis was retained.

2-H_0 – MST score does not improve the protocol's ability to identify patients for proPEG

2-H_1 – MST score does improve the protocol's ability to identify patients for proPEG

The second factor investigated was the Malnutrition Screening Tool (MST) which detects patients at risk of malnutrition based on two questions related to weight loss and appetite (Ferguson, Capra, Bauer, & Banks, 1999b). It is routinely completed to identify those who would benefit from dietetic intervention before treatment, but is not currently used in the protocol definitions. A score of two or more identifies patients at risk of malnutrition and this score was found to identify additional patients for proPEG in the low risk group. The alternative hypothesis was accepted.

3-H_0 – Nutritional biochemical markers (CRP/albumin) do not improve the protocol's ability to identify patients for proPEG

3-H_1 – Nutritional biochemical markers (CRP/albumin) do improve the protocol's ability to identify patients for proPEG

The third factor investigated was the role of albumin and C-reactive protein (CRP), as these biochemical markers are associated with the pre-cachectic state (Couch et al., 2014).

It was anticipated that abnormal albumin or CRP levels may be able to predict patients who are likely to lose weight/develop cachexia and thus an increased need for tube feeding. The current method of nutrition screening using the MST relies on weight loss to have already occurred, and thus these biochemical markers may be able to help identify patients earlier. Unfortunately CRP was not routinely measured in our clinic and only available in six patients (out of 269), therefore this could not be explored. Albumin data were more readily available, although still limited to 72% of the cohort. The results from this study showed that albumin was not associated with the criteria for proPEG and the null hypothesis was retained.

4-H_0 – p16 status does not improve the protocol's ability to identify patients for proPEG

4-H_1 – p16 status does improve the protocol's ability to identify patients for proPEG

The final factor investigated was p16 status (an immunohistological marker for human papillomavirus-related tumours), which has become increasingly important to clinicians due to influences on treatment recommendations (Rischin et al., 2015). Routine testing of p16 status was not completed during the data collection period and was limited to 61% of the cohort. Despite these sample size limitations, a p16-positive status was found to identify additional patients for proPEG in the low risk group. The alternative hypothesis was accepted.

Study 4 (Chapter 6)

This study was commenced following observation of increasing clinician non-adherence to the RBWH protocol for proPEG in routine annual audits. During the time period of the previous three studies (2010-2011) the clinician adherence to the protocol was high at 89%, but this dropped to 53% during 2012-2014 (Appendix C – 11.3.7). This was attributed to the evolving changes in treatments described in preceding studies, despite a lack of supporting evidence to change practice. The aim of this study was to compare the outcomes of high risk patients who received a proPEG (protocol adherence) (n=69) to those that did not receive a proPEG and were managed reactively (protocol non-adherence) (n=61).

H_0 – There would be no difference in weight loss or unplanned admissions between high risk patients managed with a proPEG and those managed reactively

H_1 – Patients who were managed with a proPEG would have less weight loss and less unplanned admissions

The results found that patients with a proPEG had 2% less weight loss (7% vs 9%, p=0.04). Overall unplanned admissions rates were no different between groups (50% vs 50%, p=0.803) but the proPEG group had fewer unplanned admissions for nutrition-related reasons (65% vs 91%, p=0.008). Therefore the alternative hypothesis was accepted.

Study 5 (Chapter 8)

Study 5 (Chapter 8)

Although the previous study demonstrated proPEG was beneficial compared to reactive management, the overall nutrition outcomes were still poor. Mean weight loss was still deemed critical and at a level associated with reduced survival (Langius et al., 2013b). The final study in this thesis aimed to minimise this weight loss through an early tube feeding intervention in high risk patients with HNC who had a proPEG placed pre-treatment.

H_0 – There would be no difference in weight loss (or other secondary outcomes) between the intervention group (early tube feeding) and the standard care group (clinical tube feeding when indicated)

H_1 – There would be less weight loss (and thus improvements in other secondary outcomes) between the intervention group (early tube feeding) and the standard care group (clinical tube feeding when indicated)

By minimising weight loss, it was hypothesised that this would translate into other benefits with: reduced loss of lean body mass; improved nutritional status; improved QOL; less unplanned admissions; improved tolerance to radiotherapy and chemotherapy treatment (with higher completion rates of target/planned doses); which may then improve treatment response and survival outcomes. The sample size (n=131) was adequate to detect a 5% difference in weight loss with 80% power and two-sided 5% significance. There was no effect of the early intervention on the primary outcome of percentage weight loss (10.8% vs 10.9% p=0.930). On multivariable analysis the intervention group had 0.5% less weight loss but this remained non-significant (p=0.624). The alternative hypothesis was refuted and the null hypothesis retained.

9.3 Strengths and limitations

Study 1 (Chapter 4)

The major strength of this study, investigating weight loss and tube feeding requirement following helical-IMRT, is the primary focus on nutrition outcome measures in the largest cohort size to date (n=53). Other studies have only: reported nutrition outcomes as secondary measures; had smaller sample size (11 to 31 patients) for weight loss (Capelle et al., 2012; Chao et al., 2000; Duma et al., 2012; You et al., 2012); and only five to 17 patients for tube feeding (Chao et al., 2000; Loo et al., 2011). As the change to helical-IMRT at the hospital was a gradual process, this enabled a comparison of patients receiving the two different treatments (helical-IMRT vs 3D conformal) over a concurrent period of time. The advantage of this study design over a historical cohort comparison is less confounding variables or changes in practice which may have also affected outcomes. The adherence with the protocol for proPEG selection was also high at this time (84%), which minimised any selection bias issues and meant comparable patient groups (defined as high or low nutrition risk) were managed in a similar manner.

Study 2 and 3 (Chapter 5)

The limitations of Study 2 to validate the protocol for proPEG selection (Chapter 5) included a smaller sample size (n=270) compared to the original validation study (n=501) (Brown et al., 2013b), as the data were collected over one year rather two years. It was also a single site study, which reduces generalisation to other centres. Retaining the methodology from the original validation study was important to enable a direct comparison of outcomes, however, it was recognised this also provided some drawbacks. The definition for determining proPEG requirement did not consider duration of gastrostomy use, as if used for less than four weeks and nutritional status was not compromised, then a nasogastric tube would suffice. Whilst the gradual transition to helical–IMRT was an advantage in the previous study, this did present some limitations for this study. Only 60% of the high risk patients actually received helical-IMRT (53/88), which translated to only 33% of the whole cohort who received radiotherapy as part of their treatment (75/230). Ideally repeating the study with all high risk patients receiving helical-IMRT would more accurately determine the true requirement of proPEG. The disadvantages of all of the retrospective study designs (Chapter 4 and Chapter 5) were limitations of missing data, as a number of cases needed to be excluded due to no access to medical charts, or variables of interest were not routinely collected or recorded.

Study 4 (Chapter 6)

The strength of comparative Study 4 between proactive and reactive nutrition support, based on adherence and non-adherence to the protocol for proPEG selection, was the prospective concurrent study design (level III-2 evidence). The statistical analysis was thorough to account for the differences between groups and this was the first study to control for any selection bias in the decision-making processes by including the treating Consultant as a co-variate in the multivariable models. Despite prospective data collection, it was difficult to distinguish whether non-adherence to the protocol was attributed to either the Consultant or the patient. This is an important consideration as a patient-led decision may be based on attitudes or motivation towards the role of nutrition in treatment and thus influence outcomes. Weight was only measured until the end of radiotherapy. Routine assessment post-treatment, particularly for patients from rural or regional areas, is difficult to implement as part of standard practice. Therefore the true extent of weight loss may not have been captured as the nadir has been reported to occur up to six months post-treatment (Ehrsson et al., 2012). A surrogate measure was the collection of unplanned admission data for one month post-treatment, as unplanned admissions are usually attributed to weight loss, dehydration or other treatment toxicities. However, it was recognised admissions in local/regional areas when patients returned home may have been missed.

Study 5 (0 and Chapter 8)

The strength of Study 5 was the RCT study design (level II evidence), which included: robust design and implementation; attainment of target sample size; intention-to-treat analysis; statistical adjustments for any baseline differences; and full disclosure of outcomes. The target sample size (n=123) was exceeded (n=131), which provided 80% power at a two-sided 5% significance level, to detect a 5% difference in weight loss between groups.

Although treatment fidelity was not formally assessed, a number of components were considered to strengthen the study (Beck et al., 2015). In regards to the first component of fidelity (study design), the intervention was based on theory from the literature review regarding the behaviours associated with feeding tubes (Merrick & Farrell, 2012; Salas et al., 2009) and the role of pre-treatment nutrition interventions in other cancer patients (Kiss et al., 2016). The study ensured minimising contamination between treatment arms by designating different dietitians to each arm of the trial.

For the second component of fidelity (training providers), steps were taken to ensure the dietitian providing the intervention was appropriately skilled and experienced, and a checklist was provided to standardise education and information given to the patient. Steps were also taken to minimise workload rotations whilst the study was in place so that the intervention was delivered as consistently as possible. The research dietitian completed all outcome measures to ensure standard assessment.

In the third component of fidelity (delivery of treatment), weekly discussions were held between the research dietitian and the intervention dietitian to ensure the intervention was being provided as planned. Communication was also developed with the multidisciplinary team (MDT) to provide additional support in promoting the intervention and communicating any problems with the delivery. Finally, the fourth component of fidelity (receipt of treatment) was monitored via patient self-reported diaries to record adherence to the intervention, however this methodology could have been strengthened through pilot testing of the diaries prior to implementation to ensure that patients knew how to define their symptoms.

The main limitation of the RCT was the unexpected poor patient adherence to the early feeding intervention. Some other difficulties were encountered in relation to the recruitment, randomisation process and outcome measurements. Some patients were recruited who were technically low risk but had a proPEG as per Consultant decision (n=10). Four were due to late changes to treatment plans (e.g. cancellation of chemotherapy or change to unilateral field treatment) and the other six had primary surgery and required their tube for functional postoperative dysphagia rather than to manage side effects of CRT, and thus created a more heterogeneous sample.

In retrospect, the stratification procedure should also have included p16 status, as HPV-related tumours have been recognised as a distinct clinical entity (Mallen-St Clair et al., 2016), and should be controlled for from the onset. An independent outcome assessor blinded to the randomisation allocation would have been useful to strengthen the study, but was not deemed practical within resources available.

An extension of nutrition and QOL outcome measurements at the end of treatment or one to two weeks post-treatment would also have strengthened the study. Three months post-treatment was selected to minimise attrition, however by this point most patients were recovering and so any group differences may have been more evident earlier.

Additional outcome measures such as the Performance Status Scale (List, Ritter-Sterr, & Lansky, 1990) or the MD Anderson Dysphagia Inventory (Chen et al., 2001) for swallowing function and the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) for psychosocial distress, would have also enhanced the study.

Some body composition outcomes were missing due to patients not returning to the tertiary centre for follow-up, and so additional body composition equipment at regional cancer centres would have been useful. Otherwise, efforts were made to ensure all other data collection was complete by contacting patients by telephone/mail or liaising with the local dietitian, and so overall attrition and missing data were of minimal concern.

Finally the quality of life tools selected for this study, although widely used and validated, do not adequately address QOL issues arising from tube feeding. The QLQ-H&N35 has recently been reviewed and updated to the QLQ-H&N43, however the only question relating to feeding tubes has been removed, and no new questions have been added on this topic (Singer et al., 2015). Future studies should consider additional QOL tools specifically related to enteral feeding, such as the QOL-EF (Stevens et al., 2011), although this has rarely been used in clinical practice with only six citations to date, and only one of which is for a clinical trial (Bernstein et al., 2015).

9.4 Significance of the thesis

9.4.1 Contribution to the field

The research in this thesis has made a significant contribution to the field of nutrition and cancer care with five manuscripts (Chapters 4-7) accepted for publication in high impact international journals (Journal of the Academy of Nutrition and Dietetics, Head and Neck, European Journal of Clinical Nutrition, and BMC Nursing), with a further three submitted and under review.

The work of the candidate has been widely recognised with invitations to present at one international conference (World Congress of Larynx Cancer, 2015) and two national conferences (Australian and New Zealand Head and Neck Cancer Society, 2013 and the Advanced Symposium for Health Professionals working in Head and Neck Cancer, 2016). The candidate was also invited to present at a Patient Reported Research Forum as part of the 10th International Head and Neck Cancer Quality of Life Conference, 2016. The candidate has also presented peer reviewed abstracts at a number of national and international conferences, as well as locally within the Metro North Health Service District and Queensland Health.

The thesis comprises a number of areas of original research to contribute to and advance the knowledge of nutrition management of patients with HNC. Dietitians working in this field currently refer to *"Evidence-based practice guidelines for the nutritional management of patients receiving radiation therapy and/or chemotherapy"* (Isenring et al., 2013) and internationally endorsed *"Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer"* (Head & Neck Guideline Steering Committee, 2011) which are maintained through an online wiki format to ensure they remain current (Brown et al., 2013a). The publications arising from this thesis will enable ongoing updates to be made and will gain international exposure through the link of these guidelines to *"Practice-based Evidence in Nutrition"* – a global resource for nutrition recognised in Canada, United Kingdom, South Africa, Australia, New Zealand and Spain. Evaluation of the online guidelines demonstrated even broader international exposure with access recorded in 33 countries following their initial launch in 2011 (Brown et al., 2013a).

The next section maps the research from this thesis to the nutrition care model and this is followed by a discussion of the results in the context of the current literature and how they can inform clinical practice recommendations within the guidelines (Head & Neck Guideline Steering Committee, 2011).

9.4.2 Nutrition care model in the context of head and neck cancer

In summary, the results from this study can be used to update the nutrition care model in relation to the care of patients with HNC (Figure 9-1). Appropriate access to necessary care relies on routine referral processes for all patients and identification of high risk patients to implement proPEG insertion. Both of which are dependent on patient and clinician adherence. Additional components of quality nutrition care have been added to include strategies to help overcome barriers to nutrition care and improve adherence to nutrition care recommendations. This should then achieve improved nutrient intake, and allow the cascade of events to continue resulting in improved clinical, cost and patient outcomes.

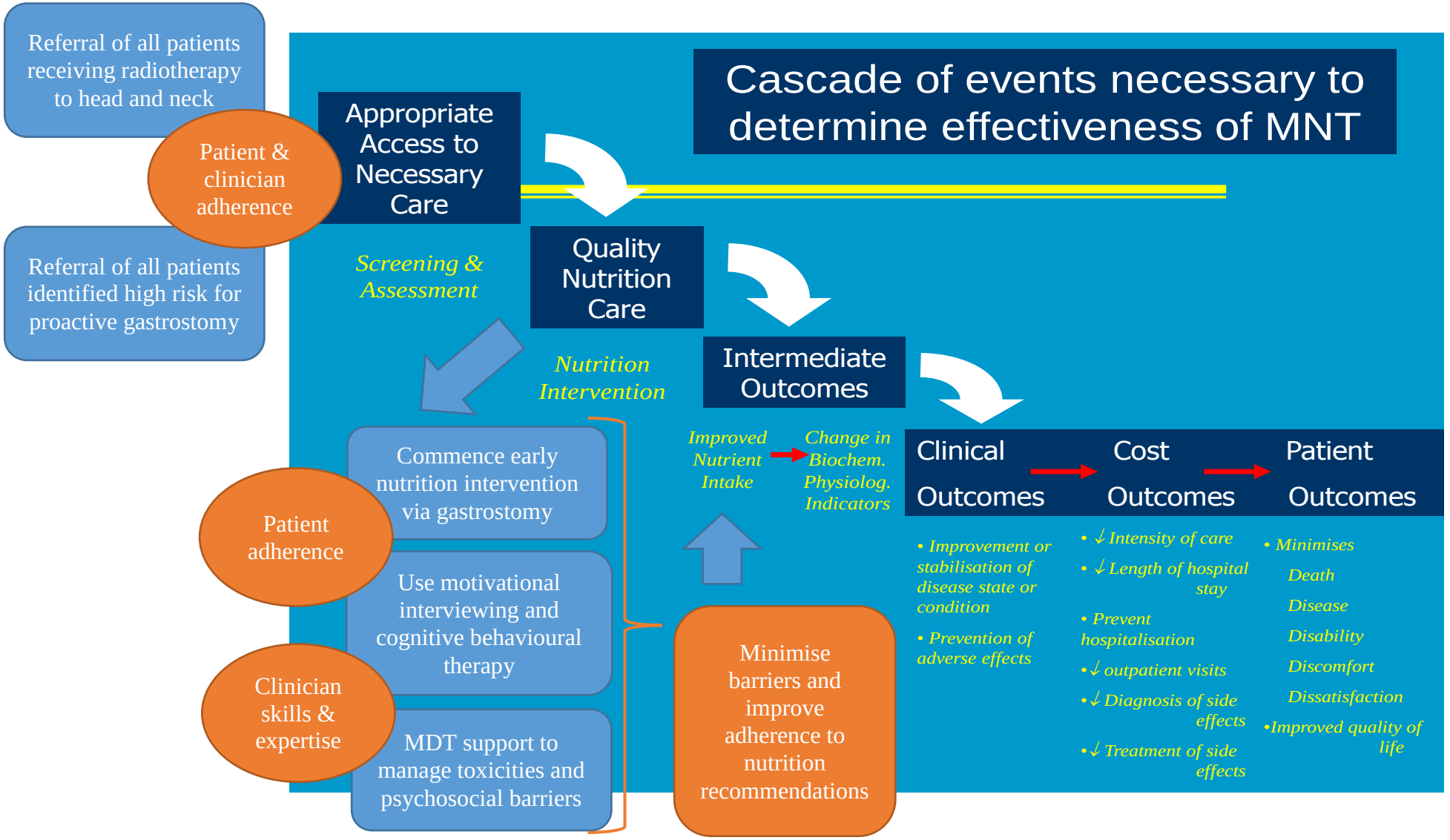

Figure 9-1: Updated Theoretical Model of the Nutrition Care Model in the context of head and neck cancer

Source: Adapted from Splett, 1996. Abbreviations: MNT=Medical Nutrition Therapy; MDT=Multidisciplinary Team

9.4.3 Recommendations for clinical practice

Appropriate Access to Nutrition Care

The first phase of this thesis (Study 1-3 in Chapter 4 and Chapter 5) explored if current procedures for appropriate access to nutrition care remain valid in the context of evolving treatments/disease. Study 1 identified that weight loss and requirement for tube feeding are no different in patients receiving helical-IMRT (n=53) compared to patients previously treated with 3D conformal radiotherapy (n=134). This is the first study to report detailed nutrition outcomes in patients receiving helical-IMRT in the largest cohort to date. Other studies have reported varying degrees of weight loss, with minimal details on tube feeding if at all, but sample sizes are small and nutrition was not the primary focus (Capelle et al., 2012; Chao et al., 2000; Duma et al., 2012; You et al., 2012). No previous studies have investigated the requirement for tube feeding with helical-IMRT treatment and so Study 2 is the first to confirm that the current protocol used at the RBWH to identify patients for proPEG remains valid in the era of helical-IMRT treatment.

Study 3 reviewed the protocol for proPEG insertion in the context of other evolving aspects of disease and treatment. The chemotherapy agent was not found to be predictive of proPEG requirement, supporting other studies in the literature in which regardless of chemotherapy agent, the impact on weight loss and tube feeding is similar (Wopken et al., 2014b; Ye et al., 2013). The role of pre-cachectic nutrition markers such as albumin, although potentially useful at predicting development of cachexia and associated weight loss and survival (Couch et al., 2007; Gupta & Lis, 2010), was not found to be useful in predicting proPEG need. The established MST for identifying patients at risk of malnutrition (Ferguson et al., 1999a) was for the first time found to be associated with predicting proPEG in the low risk group of patients. As the MST identifies patients with baseline weight loss this supports other studies which have identified baseline weight loss to be predictive of proPEG (Beaver et al., 2001; Gardine et al., 1988; Mangar et al., 2006; Mays et al., 2014; Orphanidou et al., 2011). Finally a positive p16 status was also found to be predictive of proPEG in the low risk group of patients. This is a novel finding with no other studies previously investigating the role of p16 status on nutrition-related outcomes. It is possibly explained by patients with p16-positive status having higher levels of acute and long-term toxicity (Hanasoge et al., 2016).

Clinical Questions

Q. What are the impacts of new developing treatment regimens on nutritional status and outcomes?

The current recommendation (Grade C) for IMRT states *"Patients should be managed in the same way as for conventional radiotherapy"* (Head & Neck Guideline Steering Committee, 2011). The results from this thesis provide level III-2 evidence to support this recommendation in relation to treatment with helical-IMRT.

The current recommendation (Grade C) for targeted therapy treatments states *"Patients should be managed in the same way as for conventional CRT"* (Head & Neck Guideline Steering Committee, 2011). The results from this thesis provide additional level IV evidence to support this recommendation.

Q. Which patients should be identified for prophylactic enteral feeding?

The current recommendation (Grade C) states that "Prophylactic enteral feeding should be considered to improve nutritional status, cost and patient outcomes, for patients with T4 or hypopharyngeal tumours undergoing concurrent CRT. Other patient groups should be considered by the MDT on an individual basis dependent on other clinical factors" (Head & Neck Guideline Steering Committee, 2011). The RBWH protocol referred to in this thesis is not included as part of the recommendation as it is level IV evidence. However, it is the only validated protocol published and its use is increasing at other centres across Australia (e.g. Gold Coast, Darwin) as well as receiving seven citations from the UK, Spain, Netherlands, Korea and Morocco demonstrating international impact (Source: Scopus 13/02/2017) .

The results from this thesis provide further level IV evidence that the protocol remains a valid method of identifying patients for proPEG in the era of helical-IMRT, and so can continue to be used as a tool to aid decision-making in other centres. The information from the updated literature review in this thesis also suggests this recommendation should be reviewed. There is now a clearer distinction and difference between predictors of tube requirement for treatment and predictors of prolonged tube dependence, particularly with tumours of the hypopharynx (Bhayani et al., 2013a).

Quality Nutrition Care and Outcomes – during treatment

The second phase of the thesis (Study 4 in Chapter 6) explored different methods of nutrition implementation during treatment in the nutrition intervention phase of the quality nutrition care process. Proactive nutrition care (adherence to proPEG protocol) versus reactive nutrition care (non-adherence to proPEG protocol) was compared in relation to nutrition-related and cost-related outcomes.

The benefit of the proactive approach seen in this study with reduced weight loss and reduced unplanned admissions has been supported in other studies (Lewis et al., 2014; Romesser et al., 2012), although disputed by others (Olson et al., 2013). The most recent systematic review suggests the proPEG approach is preferred (Zhang et al., 2016), although it is acknowledged further high level evidence is required to fully validate this recommendation. The research in this chapter also confirms barriers to achieving appropriate access to quality nutrition care can arise from both clinician adherence to protocols (Lacey & Pritchett, 2003) and patient adherence to recommendations (Capuano et al., 2008).

Clinical Questions

Q. What are the effective methods of implementation to ensure positive outcomes?

The current recommendation (Grade B) states that “Prophylactic tube feeding compared to reactive tube feeding demonstrates improves nutrition outcomes (weight loss), quality of life and clinical outcomes (reduced hospital admissions, length of stay and treatment interruptions) during the treatment phase” (Head & Neck Guideline Steering Committee, 2011). The results from this thesis provide additional level III-2 evidence to support this recommendation.

Quality Nutrition Care and Outcomes – pre- treatment

The final phase of the thesis (Study 5 in Chapter 7 and Chapter 8) explored a new pre-treatment nutrition intervention as part of the quality nutrition care process and monitored how this impacted on nutritional, clinical, cost and patient outcomes. All components of nutrition intervention were considered. Both groups had the same method of implementation with proPEG and weekly dietetic counselling scheduled during treatment. The nutrition prescription was altered in the intervention group with an early tube feeding phase consisting of two bolus feeds per day to supplement oral intake. Both groups had the same overarching goal as per current evidence-based guidelines, although the aim of the intervention was to minimise weight loss further.

As this was the first study in this field, there were no studies with which to compare results. There was no difference in weight loss between groups, and as such there was no cascade of events to then influence the other clinical, cost and patient outcomes. However, patient adherence to the intervention was poor due to a range of nutrition impact symptoms including; nausea and early satiety, which are known to be prevalent pre-treatment (Farhangfar et al., 2014). Another common barrier was that patients frequently reported “no problems with eating” which implied they didn’t perceive the need for tube feeding and/or their oral intake was adequate. Improving patient education may be one strategy that could assist in overcoming this barrier. Patient factors have been identified in the literature as affecting the nutrition care process and outcomes and these include motivation, lifestyle, disease acuity and socioeconomic status (Splett & Myers, 2001) as well as depression (Britton et al., 2012). Therefore this highlights a role for improving or increasing psychological supports and interventions.

Likewise the skills of the healthcare professional delivering the nutrition care process can also influence outcomes, such as the skills of communication and collaboration (Lacey & Pritchett, 2003), which are essential for symptom management in conjunction with the MDT. The healthcare professional’s expertise in behavioural change has also been recognised (Splett & Myers, 2001). A psychological intervention incorporating motivational interviewing and cognitive behavioural therapy has been shown to improve nutrition outcomes (Britton et al., 2016) and the role of a dietitian-led similar psychological intervention is currently being studied (Britton et al., 2015). The results of this may well provide guidance on future models of care by allied health professionals and highlights the potential importance of training dietitians to deliver psychological-based interventions to facilitate behaviour change.

The other key finding from this study was that the early tube feeding phase did improve adherence to the clinical tube feeding phase later in treatment when indicated. This early approach appeared to have a psychological benefit in helping patients adjust to their feeding tube which has been reported in other qualitative studies (Merrick & Farrell, 2012; Salas et al., 2009).

Clinical Questions

A new question for quality nutrition care in the pre-treatment phase is proposed. Following identification of patients for prophylactic enteral tube placement, it is suggested to add:

Q. When should tube feeding through the prophylactic tube commence?

The results from this thesis provide level II evidence that commencement of early tube feeding immediately following placement improves adherence to clinical tube feeding later in treatment. Routine encouragement of early supplementary feeding is recommended to enhance behavioural change to facilitate adaptation to the tube and improve overall adherence.

Q. What is the impact of patient adherence with dietary advice to their outcomes?

The current recommendation (Grade B) states “the role of the MDT is essential to ensure management of treatment side effects and other psychosocial factors to enable patients to follow dietary advice” (Head & Neck Guideline Steering Committee, 2011). The results from this thesis provide level IV evidence on the types of barriers patient encounter with tube feeding recommendations, including nutrition impact symptoms, psychosocial factors and environmental factors, and thus provides ongoing support for this recommendation to help address these barriers and improve adherence.

9.5 Recommendations for future research

Opportunities for research on appropriate access to care and quality nutrition care

The first opportunity is ongoing improvements of the protocol for proPEG selection. Chapter 5 identified a number of other variables that are worthy of further investigation such as p16 status, MST score at baseline, smoking status, T stage and a review of the tumour sites. The literature also suggests other parameters could include; baseline dysphagia, poor performance status, older age, and higher TNM stage (Lango et al., 2016; Ottosson et al., 2013). Consideration needs be given to the surgical population, as there is increasing evidence that patients undergoing certain surgical procedures may also warrant proPEG (Jack et al., 2012; Mays et al., 2014). Revalidation of the protocol in a patient cohort with a larger proportion of patients receiving helical-IMRT is currently underway, and will address previous limitations by accounting for duration of gastrostomy use. Finally, new research to demonstrate the external validity of the protocol in other centres would help enhance generalisability and applicability in a broader clinical setting. Translational research could also investigate similar protocol development in other relevant patient populations such as oesophageal cancer and motor neurone disease.

The optimal method of tube feeding remains unknown and although results are pending from the RCT comparing proactive and reactive approaches in the UK (Paleri et al., 2016), nutrition was not considered a primary outcome. High level evidence may well be difficult to obtain, as patients often do not want to be randomised in tube feeding trials (Corry et al., 2008). The research from Chapter 6 has already been expanded to compare nutrition outcomes across hospital sites using proPEG versus reactive management. This will provide additional level III-2 evidence with less bias, as tube placement will be according to protocol rather than physician discretion as per a previous study (Olson et al., 2013).

The main barrier from the RCT in Chapter 8 was poor adherence to the intervention. A qualitative study is recommended to further investigate the patient barriers to tube feeding in more detail. This type of research has only been completed in mixed patient populations with long-term feeding tubes (Jaafar et al., 2016) and so the findings are not applicable to patients with HNC during an acute period of treatment when the tube is deemed temporary. This information could be used to inform and evaluate new models of care delivered by the MDT. This area of research could also be applied to other patient groups requiring temporary enteral feeding to determine if adherence and barriers to tube feeding was exclusive to the HNC population.

Opportunities for research in causes and management of nutrition impact symptoms

The research from this thesis in Chapter 8 identified nausea and early satiety to be the key barriers to tube feeding, with loss of appetite and dysgeusia common reasons for initiating tube feeding in the earlier weeks of treatment. These nutrition impact symptoms have not been as widely studied as other common symptoms such as dysphagia and xerostomia (Bressan et al., 2016) and thus provide various opportunities for further research as described below.

The high prevalence of poor appetite prior to treatment (Farhangfar et al., 2014) suggests cachexia is already present. Appetite pathways are affected by the complex interaction of inflammatory cytokines and hormones associated with cancer cachexia (Couch et al., 2015). Fish oils and omega-3 fatty acids have been widely studied in other cancer populations (de Aguiar Pastore Silva, Emilia de Souza Fabre, & Waitzberg, 2015). This intervention proposes to counteract this inflammatory state (Talvas et al., 2015), but has only recently been studied in HNC. Two RCTs (level II, one neutral, one positive quality) compared an omega-3 fatty acid enhanced enteral feed (with or without arginine/nucleotides) versus a standard enteral feed, resulting in improvements to nutritional status (Fietkau et al., 2013) and functional outcome measures (Vasson et al., 2014). However, both studies were predominantly in malnourished patients at baseline and in mixed populations of HNC and oesophageal cancer. It is questionable whether the findings would translate into well-nourished HNC patients and so a trial in this population is recommended. Likewise, it is unknown if cachexia pathways are similar in HPV-related tumours due to different metabolic features (Couch et al., 2015), and this presents further areas to research.

Another potential area to investigate is the role of the cephalic phase response, which occurs as a result of the thought of food, including sensory stimuli such as sight, smell and taste, triggering the parasympathetic nervous system to produce digestive enzymes (Power & Schulkin, 2008). Therefore the loss of appetite related to cachexia and the loss of appetite associated with taste changes will also reduce the natural cephalic phase response. Additionally when patients are tube fed they completely bypass this sensory phase (Stratton & Elia, 1999). This reduces the cephalic phase response and a decrease in gastric emptying results (Morey, Shafat, & Clegg, 2016) which has the potential to affect satiety, and may explain this symptom particularly in the later stages of treatment.

A comparison of the modes of enteral feeding delivery (pump versus bolus) could be undertaken to determine tolerance. A slower feed delivery system via a pump may help to minimise nutrition impact symptoms such as nausea and early satiety. It may also help patients who reported lack of time as a factor in administering feeds, as the pump could be connected and left to run overnight.

Finally dysgeusia is an area of limited research in HNC despite being highly prevalent. The incidence of grade two dysgeusia in patients receiving CRT has been reported at 94% at the end of treatment and approximately 20% at 12 weeks post-treatment (Moroney et al., 2017). Some research has been completed in the chemotherapy setting, in patients with breast cancer (Boltong et al., 2014) and colorectal cancer (Boltong, Keast, & Aranda, 2012). These studies demonstrate the negative impact taste dysfunction has on dietary intake and nutritional outcomes, although symptoms were transient and had resolved by eight weeks post-treatment. In comparison radiotherapy-induced dysgeusia can take months to years to fully resolve (Maes et al., 2002; Sandow, Hejrat-Yazdi, & Heft, 2006). Research to investigate patient experiences and consequences of taste changes resulting from HNC treatment is required.

Opportunities for research across the continuum of care

The research from this thesis in Chapter 8 was one of the first studies to investigate a pre-treatment nutrition intervention. Poor patient adherence to the intervention was potentially due to a lack of understanding of increased nutritional needs. A trial of earlier dietary counselling may be beneficial to develop patient engagement and self-management, as this has been successful in a pilot study in lung cancer (Kiss et al., 2016).

While historical studies provided evidence to support weekly dietetic review (Isenring et al., 2004; Ravasco et al., 2005a), they were compared to nil dietetic intervention and thus it is difficult to ascertain whether less frequent intervention would have still been beneficial. They were also undertaken in cohorts receiving radiotherapy alone and as standard treatment is now concurrent CRT, with some patients having triple modality treatment, increased toxicity during treatment is seen compared to radiotherapy alone (Moroney et al., 2017). More intensive dietetic care may be required and a study comparing twice weekly reviews versus weekly could be completed.

Likewise, this historical evidence for fortnightly review post-treatment may no longer be sufficient. Moroney et al. (2017) reported continual improvement of toxicities post-treatment, however, the first measurement was at two weeks and so it is unknown what occurs during that initial acute period post-treatment. It has been identified as a time when patients feel most vulnerable as they are “entering the unknown”, with the post-treatment period described as “probably the worst part” in a recent qualitative study (Nund et al., 2014). Thus a more intensive review period in the first two weeks post-treatment could be trialled.

Finally, further research is required into the appropriate time to transition into the provision of nutrition advice for survivorship. To reduce the risk of secondary cancers developing or other chronic health diseases, it is strongly recommended that cancer survivors strive to maintain an optimal weight and maintain a healthy lifestyle (Arends et al., 2017). Given patients are recovering more quickly from treatment side effects due to advances in technology (Beadle et al., 2017) and the increasing incidence of HPV-related tumours is resulting in younger patients with improved survival outcomes (Mallen-St Clair et al., 2016), the transition into survivorship is becoming increasingly important to address. However, when designing education programs, long-term toxicities, which either persist post-treatment (e.g. xerostomia) or potentially develop over time (e.g. trismus, fibrosis, and dysphagia) still need to be taken into consideration for this population (Kraaijenga et al., 2015).

9.6 Conclusions

The findings from this thesis have contributed to the body of knowledge of the nutritional management of patients with HNC across several aspects of the nutrition care process. The thesis includes original research on the nutritional outcomes of patients receiving helical-IMRT and refutes claims that advancing treatment techniques reduces nutrition impact symptoms and weight loss. The research has added to the literature supporting the benefits of proPEG over reactive tube feeding, with less weight loss and unplanned admissions. The updated protocol for proPEG selection has been validated in a contemporary patient cohort with a high positive predictive value thus minimising unnecessary tube placement. There are opportunities to improve the protocol classification further in a subset of low risk patients.

The thesis also contains results from an early tube feeding intervention, which is the first study of its kind in this patient population. There was no improvement in nutritional, quality of life or clinical outcomes, however adherence to the intervention was poor, which limited the power of the study. It was identified that patient barriers to tube feeding were a significant issue, even when tube feeding was clinically indicated. This was a novel finding to perhaps explain why patients continue to lose weight, despite intensive nutrition interventions. The early tube feeding approach significantly improved patient adherence to clinically indicated tube feeding later in treatment. Routine encouragement of early tube feeding could therefore be a method purely to facilitate behavioural change, and allow the patient to adapt to and become accustomed with the tube.

In summary, the research demonstrates the high complexity of patient management within a health service environment. Patients currently receive significant input from the dietitian and healthcare team but even this does not achieve desired outcomes. The additional nutrition intervention of commencing early tube feeding to prevent weight loss was not effective to achieve this on its own. The research has highlighted the many intricacies of patient care including barriers to healthcare recommendations. The role of the MDT is imperative for the design and implementation of multi-component interventions to overcome these barriers before improvements in nutrition outcomes can be seen.

Chapter 10 **Bibliography**

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Chapter 11 **Appendices**

11.1 Appendix A: Summary of studies on prophylactic tube feeding

Citation	Level & Quality	Study design	Interventions & Outcomes	Results	Comments/Limitations
Prophylactic tube versus Oral Intake					
Daly 1984	II Ø	Prospective RCT, USA N=35 Stage III/IV HNC with RT	Intensive NGT feeding (n=22) vs Oral diet + dietetic counselling (n=18) Outcomes: Energy & Protein Intake Wt Albumin Treatment response Survival	NGT had: • higher mean energy intake during RT • higher mean protein intake during RT • lower mean weight loss for all sites except NPC No significant differences for: • albumin • weight loss in NPC patients • survival/treatment response	Lack of clarity for the randomisation method Inadequate statistical reporting & protocol violations in each arm Intervention group had greater duration of toxicity, despite same RT field/dose Radiotherapy alone
Hearne 1985	II Ø	Prospective RCT, USA N=31 Stage III/IV HNC with RT	Intensive NGT feeding (n=18) vs Oral diet + dietetic counselling (n=13) Outcomes: Energy & Protein Intake Wt Albumin Toxicities Treatment response Survival	NGT had: • higher mean energy intake • higher mean protein intake • less wt loss for oropharyngeal and *recurrent* nasopharyngeal No significant differences for: • Toxicities • Albumin • weight loss in NPC patients	Patients were stratified according to tumour site, previous treatments and surgery and so similar at baseline Good explanation of randomisation, drop outs and changes to protocol (2 refused NGT and 2 had late NGT in oral group) Intention to treat analysis used Lack of significance levels Blinding not possible
Zogbaum 2004	III-2 +	Comparative cohort, USA N=34 HNC with RT +/- chemo +/- surgery	ProPEG (n=17) vs Oral diet (n=17) Outcomes: Wt and BMI Missed treatment days	ProPEG had: • stable BMI compared to reduced BMI in oral intake • less missed treatment days	Additional 4 patient excluded from intervention arm (n=21) Small study numbers Indications and decision making for tube feeding were not clear

Anwander 2004	III-2 Ø	Prospective comparative cohort, Germany N=30 Oropharynx with pre-op CRT	ProPEG (n=15) vs Oral diet and post-op NGT (n=15) Outcomes: Wt & Anthropometry (TSF, MAC)	Oral diet had: • Decrease TSF No significant differences for: • weight • MAC	Control group due to PEG refusal, which was more common in men Unusual treatment with pre-op CRT Both groups had post-op tube feeding (PEG vs NGT in control)
Mercuri 2009	III-2 -	Comparative cohort, Australia N=20 HNC with RT (3D)	PEG (N=10) vs Oral diet (n=10) Outcomes: Wt RT set up variations	PEG had: • less weight loss during RT • reduction in set-up variation in the superior-inferior and anterior-posterior planes	PEG placed according to local guidelines: 1) dysphagia pre-RT 2) ≥10% wt loss pre-RT 3) CRT 4) Bilateral neck RT Small study, with no Dietitian or nutrition assessment parameters
Fietkau 1991	III-2 -	Prospective comparative cohort, Germany N=212 HNC with RT ± chemo or surgery	ProPEG (n=47) vs oral diet (n=134) Outcomes: Wt & Anthropometry (MAMC, TSF)	ProPEG had: • wt gain 2kg during RT (compared to wt loss of 3kg in oral group) • less wt loss post RT • increase TSF No significant differences for: • MAMC	Excluded n=31 who had late PEG Wide range of treatment regimens with low numbers of patients having CRT (n=13) which is more relevant to current practice Nil PEG complications observed
Senft 1993	III-2 –	Prospective comparative cohort, Germany N=212 HNC with RT ± chemo or surgery	ProPEG (n=28) vs oral diet (n=81) Outcomes: QOL	ProPEG had: • maintained QOL during RT (whereas oral group dropped) • higher QOL at 6/52	Probable bias due to poor response rate to QOL questionnaire (only 60%)

Prophylactic tube versus Reactive tube					
Prestwich 2014	III-2 +	Retrospective comparative cohort, UK N=56 Oropharynx with CRT/POCRT (3D)	ProPEG (n=43) vs NGT (n=13) Outcomes: Swallow (MDADI) >2yr post treatment Median follow up 36mth	ProPEG had: • Longer tube use (161d vs 53d) but NS (p=0.68) No significant differences for: • MDADI	Tube placement at discretion of clinician or patient preference with diet/speech input as required Good response rate 89% (n=63 eligible) BMI higher in NGT group at baseline and higher Cisplatin use in proPEG group
Kramer 2014	III-2 +	Retrospective comparative cohort, USA N=86 HNC with CRT /POCRT (IMRT)	ProPEG (n=56) vs Reactive PEG (n=30) Outcomes: Wt Tube duration Survival	ProPEG had: • longer duration in situ (227 vs 139d, p<0.01) No significant differences for: • wt loss at 2,6,12mths • survival when adjusted for HPV and TNM stage	Tube placement at discretion of clinician or patient preference Full MDT support Unclear if measured time tube in place or being used. Had to be on oral for 1 month with stable wt before tube removed
Ward 2016	III-2 Ø	Retrospective comparative cohort, USA N=78 HNC with CRT (3D/IMRT) 5 years post treatment with no disease relapse	NGT (n=36) vs reactive PEG (n=17) vs proPEG (n=25) Outcomes: Severe late dysphagia SLD = stricture, aspiration pneumonia, or 2nd feeding tube after 3mths post treatment or tube fed at 1 year	ProPEG had: • Higher 5yr cumulative SLD than NGT (61% vs 31%, p=0.016) PEG use associated with SLD (HR 3.195) on multivariate analysis	Long study period (1996-2012) led to variations in treatment practices, tube selection practices and group differences (IMRT and smoking) – mostly accounted for in multivariate but tube selection bias. Excluded oropharyngeal HPV+ due to potential treatment de-intensification Patients only seen by speech as required when developed dysphagia
Morton 2009	III-2 Ø	Retrospective comparative cohort, New Zealand N=36 HNC with CRT	ProPEG (n=30) vs Reactive PEG (n=6) Outcomes: Swallow (PSS) QOL Wt Diet	ProPEG had: • less wt loss at 12mth (p=0.049) No significant differences for: • diet texture at end of treatment or 12mth • PSS • QOL	All patients offered proPEG, so reactive group is patients who declined ProPEG was placed before or in first month of treatment Outcomes at 12-18mths post diagnosis Small sample size

Beer 2005	III-2 Ø	Retrospective comparative cohort, Switzerland N=151 HNC with RT/CRT	ProPEG (n=78) vs reactive PEG (n=73) Outcomes: Wt/BMI Malnutrition RT delays	ProPEG had: • Less wt loss (1.03kg vs 3.58kg) • Decreased malnutrition at end RT (31% vs 60%) • Less RT delays (10% vs 25%)	Malnutrition not defined Significantly higher smoking and alcohol intake in proPEG group Planned for PEG on the basis of unable to meet energy needs by oral intake so full enteral feeding with oral clear fluids if tolerated
Scolapio 2001	III-2 Ø	Retrospective comparative cohort, USA N=54 HNC with RT +/- surgery +/- chemo	ProPEG (n=41) vs reactive PEG (n=13) Outcomes: Wt RT delays Unplanned admissions	ProPEG had: • Earlier commencement of nutrition support (day 10 vs day 23) • Less wt loss (2.7kg vs 4.5kg) • Less admissions for dehydration (0 vs 4) Other results: • Median duration of tube use 165d • 90% of patients lost wt (mean wt loss 3.4kg) despite goal intakes of 25-30kcal/kg, and attributed to bloating/nausea/tube malfunction	Selection bias in those selected for PEG placement: no clearly defined criteria Groups were not similar at baseline, no randomization and poor statistics 95% of pts used the proPEG and tubes removed when consuming >50% orally Commenced nutrition support 24hr post placement to goal, but unclear if oral intake allowed
Magne 2001	III-2 Ø	Retrospective comparative cohort, France N=90 Stage IV oropharynx or hypopharynx with CRT (bd)	ProPEG (n=50) vs NGT (n=40) Outcomes: Complications Duration of feeding QOL BMI/Wt	ProPEG had: • Better weight gain (+2.5kg vs +0.7kg) but no difference in BMI at week 1,3,6 • No major tube complications • Less aspiration pneumonia (n=6 vs n=21) • Less mechanical failure (n=5 vs n=32) • Longer duration of use (605d vs 89d) • Better cosmesis and more mobility • Improved global QOL (67% vs 27%)	Commenced nutrition support 48hr post tube placement to goal 8400kJ/d + clear fluids/additional oral diet (oral intake not accounted) Groups similar at baseline with equal treatment regimens No statistics for complications Limited QOL results presented – only completed in 33 survivors (n=15 NG, n=18 PEG)

Prophylactic tube versus Reactive care (i.e. oral intake with tube feeding as required)					
Salas 2009	II +	RCT, multicentre, France N= 39 HNC with CRT ,	ProPEG (n=21) vs Reactive Care (n=18) Reactive: PEG (n= 13) Oral (n=5) **Outcomes**: BMI QOL	ProPEG had: • Higher QOL at 6/12 No significant differences for: • BMI at end of RT or 6/12 Other results: • Higher BMI & lower KPS score at baseline were significantly related to higher QOL at 6/12	Reactive care: PEG placed when indicated (dysphagia/ severe odynophagia, dehydration, wt loss **>**15%)**.** Unclear what/when nutrition support was given in ProPEG group Median PEG use was 1.5mths post-RT but effect reported at 6mths Inclusion criteria: BMI≥20, wt loss<10% previous 6/12, KPS≥70
Silander 2013	II Ø	RCT, Sweden N=127 HNC with CRT/PORT	ProPEG (n=62) vs Reactive care (n=65) Outcomes: Energy/protein intakes Wt Dysphagia (EORTC35 QOL single item)	No significant differences for: • Energy and protein intakes or their source (oral, ONS, EN, PN) • Wt loss • Dysphagia (eating difficulty) Other results: • Energy and protein intakes did not meet requirements until after 6mths • Wt loss was 7% at 3mth, peaked at 11-12% at 6mths, then stabilised or improved • EN and difficulty with eating was highest at 2-3mths	Intakes measured with 3d food record (compliance 88%) with 7 non complaint patients excluded from original study Reactive care had oral or tube feeding as required – unable to determine exact tubes received due to extra exclusions PN use was low in both groups but exact use unknown and indications unclear No information on speech pathology input Malnutrition defined: >10% wt loss 6mth
Silander 2012	II Ø	RCT, Sweden N=134 HNC with CRT/PORT	ProPEG (n=64) vs Reactive care (n=70) Reactive: Tube (n=51) Oral (n=19) Outcomes: Wt/BMI Admissions QOL Survival Tube use & dependency Dysphagia	ProPEG had: • Better QOL at 6mth (10 domains) • Less patients unable to swallow at 1yr (2% vs 9% p=0.047) • Less patients with >10% wt loss at 2mth (6% vs 19% p=0.059) • Longer tube use (177d vs 122d p<0.001) but started 23d earlier No significant differences for: • Survival, RT delays, Admissions • Mean wt loss at 6mth,1 or 2yr	Reactive care had oral or tube feeding as required (overall 6 had PEG – but some may have converted from NGT as many placed months post treatment) No information on speech pathology input Malnutrition defined: >10% wt loss 6mth

Quon 2015	III-2 +	Comparative cohort, Canada N=178 HNC with RT/CRT (3D/IMRT)	ProPEG (n=92) vs Reactive care (n=86) Reactive: Tube (n=24) Oral (n=62) Outcomes: Swallow (RBHOMS, PSS, ESAS)	No significant differences for: • Swallow outcome • Tube dependency	Tube placement at discretion of oncologist and practices changed after IMRT commenced Reactive care had tubes usually placed for wt loss 5-10% and were usually PEG (96%) vs NGT (4%) No baseline differences between tube groups, but the oral group had lower T-stage/overall stage, less CRT, less baseline dysphagia/wt loss Lack of information on MDT care
Williams 2012	III-2 +	Retrospective comparative cohort, UK N=104 Oropharynx with CRT/POCRT (3D)	ProPEG (n=71) vs Reactive care (n=21) vs Therapeutic PEG (n=12) Outcomes: Time to start feeds LOS Unplanned admission Wt Diet Tube dependence Survival	ProPEG vs reactive NGT had: • Earlier commencement (24d vs 41d, p<0.001) • Less unplanned admission days (6 vs 14, p<0.01) • Longer tube duration (181d vs 64d, p<0.01) No significant differences for: • Wt loss (end RT or 6mths) • Diet texture • RT delays • Survival Other results: • Tube duration associated with proPEG and T stage	Significant baseline differences: -Therapeutic PEG had lower wt/BMI, more modified diet, higher T stage and more surgery -ProPEG group had higher dose RT Tube selection bias at discretion of clinician and patient choice Regular MDT care during/post treatment Therapeutic PEG started feeds immediately post placement

Romesser 2012	III-2 +	Retrospective comparative cohort, USA N=400 Oropharynx with CRT (IMRT)	ProPEG (n=325) vs Reactive care (n=75) Reactive: PEG (n=29) Oral (n=46) Outcomes: Wt Albumin Toxicities Admissions RT delays Survival	ProPEG had: • Less wt loss at 3mth (12% vs 14.3%, p=0.05) • Less admissions (p=0.026) • Less rehydration (p=0.004) Shorter time to tube removal (3.4mths vs 5.1mths p=0.004) No significant difference for: • Albumin, toxicities, RT delays or survival Other results: • Predictors of prolonged PEG were older age, female, T3/T4	Large sample but long study period of 11 years may have influenced treatment and service provision with lack of information on diet/speech roles/input Intention-to-treat analysis completed All patients offered proPEG so reactive group is from patients who declined Differences at baseline: age, follow up time, tumour site, chemo type Only 7/325 did not use proPEG
Bahl 2004	III-2 +	Retrospective comparative cohort, Canada N=75 NPC with CRT + adjuvant chemo	ProPEG (n=23) vs Reactive care (n=52) Reactive: Tube (n=17) Oral (n=35) Outcomes: Compliance to CRT Toxicity Weight change Feeding tube use	ProPEG had: • Slowest decline to nadir wt (186d vs. 117d and 129d) • Greatest recovery of baseline wt by 1yr (94% vs 87% and 92%) • Longer duration of tube use (145d vs 116d) Other results: CRT compliance associated with: • Higher baseline wt and proPEG CRT non-compliance associated: • lower baseline wt, female, non-Asian, Stage III	Main aim of paper was compliance to CRT regimen Type of feeding tubes used reactively and prophylactically (ProPEG) unclear - described as feeding tube only. Confounding factors regarding tube insertion decision was acknowledged No criteria for feeding tube placement but weight loss, stomatitis, and pharyngeal dysfunction were cited as most common No details regarding dietetic intervention
Pramyothin 2016	III-2 Ø	Prospective comparative cohort, Thailand N=95 HNC with CRT	ProPEG (n=25) vs Reactive care (n=70) Reactive: NGT (n=16) Oral (n=54) Outcomes: Treatment Delays Wt QOL	ProPEG had: • Less wt loss (5% vs 8%, p=0.05) • Less with >10% wt loss (4% vs 24%, p=0.03) No significant differences for: • QOL • Treatment delays	Patient selection of study group led to baseline differences with more women in ProPEG group and better performance status in reactive care. Overall high proportion of cohort with NPC and mean age younger which may affect generalisability Only 16/53 patients consented to NGT when met reactive tube feeding criteria

Yamazaki 2016	III-2 Ø	Retrospective comparative cohort, Japan N=27 HNC with CRT (Cetuximab and IMRT)	ProPEG (n=15) vs Reactive care (n=12) Outcomes: Toxicity Treatment delays Admissions Survival Wt	ProPEG had: • Less leukopenia (7% vs 68%, p=0.002) • Less Grade 3 mucositis (47% vs 83%, p=0.058) • Less RT delays (5 vs 0) • Less with >10% wt loss (27% vs 75%, p=0.013) • Better overall survival (93% vs 73%, p=0.055) No significant differences for: • Unplanned admissions (8 vs 9) • Progression-free survival (33% vs 33%, p=0.934)	Small sample size Decision process regarding ProPEG placement unclear – became mandatory but unclear when Unplanned admissions in proPEG group mainly for worsening nutrition (due to non-use of PEG) Unknown if anyone had NGT placed in reactive care
Sethugavalar 2016	III-2 Ø	Comparative cohort matched pair analysis, UK N=52 Oropharynx with CRT (IMRT)	ProPEG (n=26) vs Reactive care (n=26) Reactive: NGT (n=17) Oral (n=9) Outcomes Swallow (MDADI) at >2years post treatment	ProPEG had: • Worse total swallow scores (59.4 vs 68.1, p=0.04) • Worse global, emotional and functional swallow scores No significant differences for: • Physical swallow scores	Tube selection bias as per Consultant or patient decision No measures of: nutritional status at baseline or post; adherence to diet/speech appointments; whether prophylactic swallow exercises used
Lewis 2014	III-2 Ø	Retrospective comparative cohort, USA N=109 HNC with CRT	ProPEG (n=25) vs Reactive care (n=84) Reactive: Tube (n=34) vs Oral (n=50) Outcomes: Wt loss Admissions/DEM Completion chemo Tube dependency	ProPEG had: • Less wt loss at 12mth (2% vs 10% reactive, 15% oral, p<0.001) • Less DEM visits (p<0.001) • Less admissions (p<0.001) • Completed more chemo cycles (p<0.001) No significant differences for: • Mean duration of tube use (319d vs 277d, p=0.492) • Tube use at 12mth	Type of feeding tubes used reactively and prophylactically (ProPEG) unclear - described as feeding tube only Tube placement on case by case basis Race differences between groups - ProPEG group had lower BMI and more wt loss at baseline (adjusted in analysis)

Baschnagel 2014	III-2 Ø	Retrospective comparative cohort, USA N=193 HNC with CRT (IMRT)	ProPEG (n=139) vs Reactive care (n=54) Reactive: PEG (n=22) Oral (n=32) Outcomes: Admissions & Costs Tube dependence Complications/Toxicities	ProPEG had: • Less strictures and aspiration • Less admissions • Reduced costs No significant differences for: • Tube dependence at 1 or 2yr	Tube placement at discretion of clinician or patient preference Placed proPEG in outpatients No baseline difference between groups (Tumour site and N stage different in those without tube)
Olson 2013	III-2 Ø	Comparative cohort, USA N=445 HNC with CRT (3D/IMRT)	ProPEG centre (n=166) • 88% had PEG Reactive centre (n=279) • 31% had PEG Outcomes: Wt (end RT and 1yr) Tube complication Late toxicity Tube dependency	ProPEG centre had: • Higher tube dependence at 3mth No significant differences for: • Wt • Admissions • Complications • Survival • Late toxicity • Tube dependence at 6 or 12mths	Several differences between centres; site, stage, chemo type, baseline wt. No mention of speech pathology input Secondary analysis removed NPC and Cetuximab – did not change results Reports higher rate of complications when whole cohort compared, but when you only compare patients with PEG there is no difference
Peerawong 2012	III-2 Ø	Retrospective comparative cohort, Thailand N=219 NPC with CRT (3D)	ProPEG (n=77) vs Reactive care (n=142) Outcomes: Wt Toxicities Treatment completion	ProPEG had: • Less wt loss • Less severe wt loss (>10%) at 3rd, 4th and 5th cycle of chemo • Less hypokalaemia (p=0.002) No significant differences for: • Haematological toxicities • Completion of CRT	Excluded patients with altered fractionation and IMRT ProPEG group had better ECOG but more co-morbidity at baseline Unclear what decision criteria used for proPEG placement and not clear if any patient in reactive care needed tube
Langmore 2012	III-2 Ø	Retrospective comparative cohort, USA N=59 HNC with RT/CRT-3D/IMRT	ProPEG (n=27) vs Reactive care (n=32) Reactive: PEG (n=6) Oral (n=26) Outcomes: Wt & Diet at 3, 6, 12mth	No difference in wt loss, but reactive group had better diet (p=0.002) No difference in wt loss, but partial/oral diet at end of RT had better diet vs NBM groups (p<0.001)	Author noted limitations: retrospective study design; did not include formal swallow studies, standardized diet score, or QOL scale. No comparison of differences between groups at baseline

Oozeer 2011	III-2 Ø	Retrospective case control, UK N=44 HNC with CRT >2years post treatment	ProPEG (n=16) vs Reactive care (n=15) Outcomes: Swallow (MDADI score)	ProPEG had: • Worse swallow with lower MDADI score in all domains (emotional, functional, physical, and global) P=0.001	Groups poorly matched re: time since treatment (ProPEG assessed on average 7 month later). Tube selection bias as per patient or clinician preference Lack of swallowing and nutritional status at baseline. No swallow exercise given. Unclear if proPEG maintained oral intake Small sample size and drop out n=13
Rutter 2011	III-2 Ø	Retrospective comparative cohort, USA n=111 HNC with CRT (3D/IMRT)	ProPEG (n=59) vs Reactive care (n=52) Reactive: PEG (n=31) Oral (n=21) Outcomes: Wt Admissions Complications Tube dependency	Any PEG (vs Oral) had: • 2.6% less wt loss during CRT (p=0.064), at 6 weeks post (p=0.02), and 3 months post (p=0.008) • No difference in wt loss at 6 months post or admissions ProPEG (vs reactive PEG) had: • Less wt loss at 6 weeks (p=0.003) and 6 months post (p=0.011) • Decreased LOS (p=0.012) • Lower risk of nutrition admissions (p =0.01) • No difference in survival, tube dependence, or complications	Varied treatment protocols Good MDT input but no information on speech pathology until post treatment Study investigated timing of PEG placement (only 59% were pre-treatment and true proPEG). Greatest effects seen if placed before week 3. All patients offered proPEG prior to treatment Disease control was the only predictor of tube dependence.
McLaughlin 2010	III-2 Ø	Retrospective comparative cohort, USA N=91 HNC with CRT/POCRT	ProPEG (n=15) vs Reactive care (n=76) Reactive: PEG (n=21) Oral (n=55) 0utcomes: Duration tube Complications	ProPEG had: • Longer tube duration (12mth vs 5mth) No significant differences for: • Tube complications (n=2 in each group) Other results: • Tube duration associated: T3-4	ProPEG offered if wt loss >10%, progressive dysphagia, aspiration risk, poor nutritional status, therefore likely reason for longer use Reactive PEG not initiated until 10-15% wt loss or dysphagia or aspiration No information on nutritional status or dietitian interventions. Tube dependency used as surrogate measure of dysphagia.

Chen 2010	III-2 Ø	Retrospective comparative cohort, USA N=120 HNC with CRT (3D/IMRT)	ProPEG (n=70) vs Reactive care (n=50) Reactive: PEG (n= 16) Oral (n=34) Outcomes: Wt Admissions Tube dependence Survival RT delays Dysphagia Strictures	ProPEG had: • Less wt loss during CRT (-8% vs -14%) • Less IV fluids (17% vs. 54%) • More dysphagia at 3mths (46% vs 27%) and 6mths (34% vs 5%) • More tube dependence at 6mths (41% vs 8%) and 12mths (21% vs 0%) • More strictures (30% vs 6%) No significant differences for: • RT delays • Admissions • Survival • Wt loss at 3 and 6mths	ProPEG at the discretion of physician Patients with proPEG were encouraged to feed by mouth for as long as possible Decisions to initiate tube feeds were based on individual patient and toxicities Dysphagia assessed using validated tool
Nugent 2010a	III-2 Ø	Retrospective comparative cohort, UK N=196 HNC with RT/CRT	ProPEG (n=27) vs Reactive care (n=169) Reactive: PEG (n=17), NGT (n=35), Oral (n=117) Outcomes: Wt RT delays	ProPEG had: • Less wt loss compared to each reactive care group across all treatments (RT, CRT, induction) but not statistically significant Other results: • oropharyngeal cancer associated with wt loss • pre-treatment wt loss and dual modality treatments associated with tube feeding	Consultant decision on type of tube Included only patients who were seen by dietitian within 1st week of treatment. Tube feeding commenced when oral intake <60% and/or wt loss >5% No statistical results presented
Chang 2009	III-2 Ø	Retrospective cohort, New Zealand N=71 HNC with RT ± surgery or chemo	ProPEG (n=7) vs Reactive care (n=64) Reactive: NGT (n=28) Oral (n=36) Outcomes: • Wt • Admissions • RT delays	ProPEG had: • Less wt loss (P=0.016) No significant differences for: • Admissions • RT delays	Selection bias as no criteria for proPEG so group had more stage III/IV, CRT and 6mth wt loss (controlled for in analysis) Criteria for reactive NGT if inadequate oral intake or significant wt loss (5%) Commenced PEG feeding when required - threshold seemed lower than for NGT

Allen 2007	III-2 Ø	Comparative cohort, USA N=46 HNC with CRT (3D) – hyper fractionated	ProPEG (n=22) vs Reactive care (n=24) Reactive: PEG (n= 14) Oral (n=10) Outcomes: Wt	ProPEG had: • Less wt loss (-3.8% vs -7.9%, p=0.08)	Clear criteria for proPEG (pharynx in the high-dose treatment volumes) but 20/42 patients refused or unable to schedule (14/20 ended up with reactive PEG) Late referral to speech - Patients with dysphagia >3mths post therapy
Mangar 2006	III-2 Ø	Retrospective comparative cohort, UK N=160 HNC with RT	ProTube (n=30) vs Reactive care (n=130) ProTube: PEG n=6 NGT n=24 Reactive: Tube n=20 Oral n=110 Outcomes: Wt	ProTube had: • Less wt loss than reactive tube Other results: • Any tube feeding (n=50) associated with: stage III/IV, smoking >20/d, poor performance status	Comparison of tube timing not primary outcome No criteria for proactive tube placement, but all had 5-10% wt loss
Beaver 2001	III-2 Ø	Retrospective comparative cohort, USA N=249 HNC with RT/PORT +/- chemo	ProTube (n=33) vs Reactive care (n=192) Reactive: Tube (n=72) Oral (n=120) Outcomes: Wt Admissions DEM visits	ProTube had: • Less severe wt loss (14% vs reactive 60% oral 25%, p<0.05) • Less admissions and DEM visits Other results: • Need for tube associated with T3-T4, oral, oropharynx, pre-treatment severe wt loss, PORT • No need for tube associated with T1-T2, nasopharynx, RT alone	Comparison of tube not primary outcome Long study period (11 years) which may influence practice/treatment delivery with tube selection dependent on clinician Data in tables/text not consistent and 24 patients not accounted for Severe wt loss defined as >10% 6mth, >5% 1mth, 2% 1wk, >7% of BMI 6mth
Lee 1998	III-2 Ø	Retrospective comparative cohort, USA N=88 HNC with RT +/- chemo/surgery	ProPEG (n=36) vs Reactive care (n=52) Reactive: PEG (n= 16) Oral (n=36) Outcomes: • Wt • Admissions • RT delays	ProPEG had: • Less nutrition-related admissions (13% vs. 34%) • Less wt loss (3.1kg vs. 7kg) • Less wt loss >5% (n=15 vs n=37) No significant differences for: • RT delays • All-cause admissions • Survival or local control	Selection criteria for proPEG dependent on clinician (generally expected toxicity) No randomization, groups not similar at baseline Incomplete data on pre-treatment wt loss 70% of hospitalizations overall were due to malnutrition or dehydration

Tyldesley 1996	III-2 Ø	Retrospective comparative cohort, Canada N=64 HNC with RT	ProPEG (n = 12) vs Reactive care (n=52) Reactive: PEG (n=22) NGT (n=1) Oral (n=29) Outcomes: Wt Admission/LOS RT delays	ProPEG had: • Less wt loss during RT (3% vs 6%) • Shorter LOS (4.9d vs 19d) • Longer duration tube in situ (20.9 weeks vs 13.8 weeks) • No RT delays Any PEG had: • Less wt loss 4-6wk (3-5% vs 9%) • Less wt loss 3mth (3-4% vs 12%)	Selection criteria for proPEG dependent on clinician – factors considered included tumour size, RT volume, age, medical status, nutritional status PEG group matched to no PEG control group using age, sex, RT volume & dose N=3 in PEG group were palliative intent Small study, lacking power
Pezner 1987	III-2 Ø	Comparative cohort, Canada N=89 HNC with RT	ProTube (n=17) vs Reactive care (n=72) ProTube: NGT n=4, cervical oesophagostomy n=4, gastrostomy n=9 Reactive: NGT n=3, gastrostomy n=6, Oral n=63 Outcomes: Wt	ProTube had: • Less wt loss during RT (4.8% vs 9.4% and 7.1%) • Less pts with >10% wt loss (6% vs 44% and 24%) Other results: • Well-nourished patients tended to lose more weight than those malnourished at baseline, however not statistically significant due to small numbers	Old study using data and older RT technology >30 years ago Tube selection bias based on clinician and patient acceptance Does not appear to be prophylactic tube placement but early tube feeding - more likely ProTube if malnourished at baseline
Hughes 2013	III-3 +	Retrospective comparative cohort, Australia N=165 HNC with CRT/POCRT (3D)	Pre 2005 (n=77) -ProPEG n=5 (6%) -Reactive n=18 -Oral n=54 Post 2007 (n=88) -ProPEG n=39 (44%) -Reactive n=4 -Oral n=45 Outcomes: Admissions LOS 30d mortality	Post guidelines (proPEG): • Less admissions (p<0.001) • Less unplanned admissions (p<0.001) • Shorter LOS (p<0.001) No significant differences for: • Mortality Other results: • Associations with admission - male and reactive tube	Study evaluating impact of proPEG guidelines in pre and post phase Cohorts differences for tumour site and chemo regimen Nutritional outcomes and PEG complications only collected for 2007 cohort

Piquet 2002	III-3 +	Retrospective comparative cohort, Switzerland N=90 Oropharynx with RT	Early intervention (n=45) -ProPEG n=33 (74%) -NGT n=6 -Oral n=6 Historical control (n=45) -ProPEG n=5 (11%) -NGT n=12 -Oral n=28 Outcomes: Wt Admissions	Post early intervention (proPEG): • Less wt loss (3.5kg vs 6.1kg p<0.01) • Less hospital admission for dehydration (0% vs 8% p<0.01)	Study evaluating impact of early nutrition intervention (including proPEG) in pre and post phase Clear PEG insertion criteria: wt loss >10%, BMI< 20, age >70 Those without proPEG received counseling and ONS, but nutrition interventions in historical group less clear Groups matched so similar for age and TNM staging Assumed QOL is better for PEG patients (not measured)
Assenat 2011	III-3 Ø	Retrospective comparative cohort, France N=139 HNC with CRT (3D)	ProPEG (n=61) vs Reactive care (n=78) Reactive: PN (n=45), oral (n=33) Outcomes: Wt RT delays Admissions/LOS Survival	ProPEG had: • Less wt loss (1kg vs 5kg, p<0.0001) • Less RT delays (38% vs 59%, p=0.01) • Shorter RT delays (100d vs 236d, p=0.03) No significant differences for: • Survival	Tube selection based on time period of study ProPEG had worse baseline nutrition status and more hyper-fractionated RT Inappropriate measures of nutritional status (NRI, albumin and/or wt loss) Indications for PN not clear

Abbreviations: BMI=body mass index; CRT=chemoradiotherapy; DEM=Department of Emergency Medicine; EN=enteral nutrition; ESAS=Edmonton Symptom Assessment System; HPV=human papilloma virus; HNC=head and neck cancer; IMRT=intensity-modulated radiotherapy; KPS=Karnofsky performance scale; LOS=length of stay; MAC=mid-arm circumference; MAMC=mid-arm muscle circumference; MDADI=MD Anderson Dysphagia Inventory; MDT=multidisciplinary team; NGT=nasogastric tube; NPC=nasopharynx; NRI=nutritional risk index; ONS=oral nutrition supplements; PEG=gastrostomy tube; PN=parenteral nutrition; POCRT=post-operative chemoradiotherapy; PORT=post-operative radiotherapy; proPEG=prophylactic gastrostomy; ProTube=prophylactic feeding tube; PSS=performance status scale; QOL=quality of life; RCT=randomised controlled trial; RBHOMS =Royal Brisbane Hospital Outcome Measure for Swallowing; RT=radiotherapy; TNM=tumour, nodal, metastases staging; TSF=triceps skinfold; Wt=weight.

11.2 Appendix B: Summary of studies on reactive tube feeding

Citation	Level & Quality	Study design	Interventions and Outcomes	Results	Comments/Limitations
Comparison of reactive feeding tubes (PEG vs NGT)					
Corry 2008	II Ø	RCT, Australia N=33 HNC with RT/CRT	PEG (n=15) vs NGT (n=18) Outcomes: Performance status Wt Anthropometry (MAC, TSF) QOL Dysphagia Treatment response	PEG had: • less wt loss 6/52 (p<0.001) • less tube dislodgement (p=0.0001) but more pain at 1/52 (p=0.03) • less body image concern (p=0.05) • more tube convenience at 1/52 (p=0.02) • less interference with social activities (p=0.04) • longer duration of use in those with no evidence of disease (n=26) (p=0.0004) • higher costs No significant differences for: • Performance status or QOL • Treatment response • Wt or dysphagia at 6mth • Complication rates	Slow recruitment as 37% refused to be randomised and study closed early. Did not use intention-to-treat analysis: 9 excluded as did not receive tube to which they were randomised Feeding tubes placed when intake <50% and/or >5 kg wt loss from start of treatment Cost analysis excluded admission costs
Sadasivan 2012	II -	RCT, India N=100 HNC with PORT or CRT/POCRT	PEG (n=50) vs NGT (n=50) Outcomes: Wt Anthropometry (MAC) Haemoglobin Albumin Complications Patient satisfaction	PEG had: • Less wt loss 6wk (3% vs 11% p<0.001) and better haemoglobin and MAC • Less infections (4% vs 64% p<0.001) • Less dislodgements (0% vs 36% p<0.001) • Better QOL (p<0.01) No significant differences for: • Albumin	PEG group had lower baseline wt and more surgery No report of pre-treatment wt loss or dysphagia Tube placement timing unclear Did not use intention-to-treat analysis: 6 NGT excluded as opted for PEG at 6 weeks

Sobani 2011	III-2 Ø	Retrospective cohort, Pakistan N=32 Oral cavity with surgery ± RT	PEG (n=16) vs NGT (n=16) Outcomes: Wt Psychosocial acceptance Tube complications	PEG had: • Less wt loss (1.3 vs 5.4kg, p=0.025) • Longer mean tube use (6mths vs 15d) • Less complications • Better patient acceptance (100% recommend vs 0%) • Higher patient rating of tube as good/excellent (7 vs 1)	Tube selection based on patient preference Timing of tube placement, duration of follow-up and outcome time-points unclear No discussion of limitations - small sample size with limited statistical analysis
Corry 2009	III-2 Ø	Prospective comparative cohort, Australia N=105 HNC with RT/CRT 81% CRT (including Tirapazamine)	PEG (n=32) (Randomised n=22) vs NGT (n=73) (Randomised n=20) Outcomes: Wt Anthropometry (MAC) Complications Patient satisfaction Cost Mucositis Performance status Dysphagia Treatment response	PEG had: • Less wt loss 6/52 (p<0.001) • Less severe wt loss >10% 6/52 (p=0.05) • Higher infections (p=0.001) • Longer duration of use (p<0.001) • Less tube dislodgements (p<0.001) • More pain but less body image concerns • Less severe wt loss 6mth (13% vs 35%, p=0.09) No significant differences for: • Performance status or QOL • Treatment response • Grade 3 dysphagia at 6mth	Continued observation from study after RCT ceased early enabling patients to choose tube type Feeding tubes usually placed ~wk5 when intake <50% and/or >5 kg wt loss from start of treatment Did not discuss tube complications beyond 6mths when NGT used up to 396d Higher incidence Grade 3 dysphagia could explain higher chest infections in PEG group Toxicity scale uses tube feeding as measure of dysphagia
Mekhail 2001	III-2 Ø	Retrospective comparative cohort, USA n=91 HNC with RT/CRT	PEG (n=62) vs NGT (n=29) Outcomes: Dysphagia Tube duration Dilatations	PEG had: • More dysphagia at 3 and 6 months (p=0.015) • Longer feeding duration (28 vs 8 weeks, p<0.001) • More dilatations (p=0.022) No significant differences for: • dysphagia at 12 months	Tube selection bias as based on clinician or patient preference with PEG more likely if malnourished or expected longer feeding Unclear if NGT patients are more motivated with rehab due to tube discomfort & appearance

Lees 1997	III-2 -	Prospective comparative cohort, UK N=100 HNC with RT	PEG (n=32) vs NGT (n=68) Outcomes: Wt Tube use and duration QOL Survival	PEG had: • More bolus feeds than pump • Longer duration (28 vs 21d) • Better QOL No significant differences for: • Wt • Survival	Included radical and palliative treatment Tube selection criteria: PEG if enteral feeding >21d and does not interrupt RT QOL assessment did not use validated tool and limited reporting and statistics
Reactive feeding tube vs oral intake					
Sanguinetti 2013	III-2 Ø	Retrospective comparative cohort, USA N=59 Oropharynx with RT (IMRT)	Reactive PEG (n=22) vs Oral (n=37) Outcomes: Toxicity Admissions Wt	Reactive PEG had: • More mucositis (0.032) • More dysphagia (p<0.001) • More admissions (p=0.001) • More wt loss (p=0.031) Other results: • Reduced need for PEG if <50-60cm3 of oral mucosa has <9.5-10 Gy/week	Main aim was to determine predictive factors for PEG Tube placement as per physician based on criteria: >10% wt loss during RT, protracted symptoms and inadequate pain control
Clavel 2011	III-2 Ø	Retrospective comparative cohort, Canada N=253 HNC with CRT	Reactive NGT (n=126) vs Oral (n=127) 2% were prophylactic Outcomes: Wt Tube use and duration Admissions Survival	No significant differences for: • Wt (data not shown) • 3yr survival (83.7% vs 82.0%) Other results: • Overall mean weight loss 10.4% • Median NGT duration 40d • Nutrition admissions 15% of total	NGT placement criteria: wt loss >5-10%, uncontrolled odynophagia and/or risk of aspiration. No criteria for prophylactic placement Good MDT care and follow up Baseline characteristics similar in groups >50% of patients had wt loss >10%
Ahmed 2005	III-2 Ø	Retrospective comparative cohort, USA N=477 HNC with CRT	Any PEG (n=220) vs Oral (n=257) Outcomes: Wt Mucositis Nausea	No significant differences for: • Wt/ nausea/ mucositis Other results: • PEG associated with T4, oral, oropharynx, hypopharynx • No need for PEG associated with T2, larynx & paranasal sinus	Combined proPEG (n=52) and reactive PEG (n=129) Tube placement as per clinician decision No baseline nutritional status/dysphagia information

Goda 2015	III-2 -	Retrospective comparative cohort, Japan N=44 HNC with CRT	Reactive PEG "adherent" (n=13) vs Oral "non-adherent" (n=20) Additional 11 patients in oral group who did not meet criteria for tube insertion Outcomes: Total serum protein RT delays	Reactive PEG had • Less RT delays (0% vs 50%) No significant differences for: • Total serum protein	PEG placed if Grade 3 mucositis and inadequate oral intake (<1/3 usual) but exact timing of PEG placement unknown High refusal of tube feeding (NGT or PEG) when indicated (20/31) Role of MDT input unknown Inappropriate measure of nutritional status and wt loss outcomes not known High proportion of hypopharynx/larynx

Abbreviations: CRT=chemoradiotherapy; HNC=head and neck cancer; IMRT=intensity-modulated radiotherapy; MAC=mid-arm circumference; MDT=multidisciplinary team; NGT=nasogastric tube; PEG=gastrostomy tube; POCRT=post-operative chemoradiotherapy; PORT=post-operative radiotherapy; proPEG=prophylactic gastrostomy; QOL=quality of life; RCT=randomised controlled trial; RT=radiotherapy; TNM=tumour, nodal, metastases staging; TSF=triceps skinfold; Wt=weight.

11.3 Appendix C: Peer-reviewed conference abstracts/posters

11.3.1 Enteral Feeding & Nutritional Management in Head and Neck Cancer: Current Best Practice

Australian & New Zealand Head & Neck Cancer Society ASM, Melbourne, Australia. July 2013 (oral)

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The prevalence of malnutrition, weight loss and dysphagia is common in patients in with head and neck cancer. Several studies have demonstrated beneficial effects of dietary counselling during radiotherapy treatments, with improvements in weight, nutritional status and quality of life. Many patients also require nutrition support through enteral tube feeding, however the evidence remains unclear as to the optimal form of tube feeding. Prophylactic gastrostomy has been recommended in some patient groups due to the beneficial effects on maintaining nutritional status or weight as well as other benefits such as improved quality of life and reduced hospital admissions. However, many of these studies were undertaken in patients receiving radiotherapy alone, and now as chemoradiotherapy treatments become standard of care; the same results for nutrition outcomes in more recent trials are not seen. On overview of the current evidence in this area will be presented. At the Royal Brisbane and Women's Hospital, we are using validated guidelines to predict which patients may require prophylactic gastrostomy, and despite this proactive intervention, we have found that high risk patients can still lose 6-7% of body weight during treatment and up to 9-10% by three months post treatment. Weight loss and malnutrition can impact on the patients' quality of life, functional ability and other clinical outcomes. This presentation will also discuss current research underway to investigate novel approaches of nutrition intervention through prophylactic nutrition support and to determine whether early tube feeding improves nutrition outcomes.

11.3.2 Nutrition outcomes in patients with mucosal squamous cell carcinoma of the head and neck (HNSCC): Tomotherapy compared to 3D conformal radiotherapy

European Congress of Head & Neck Oncology, Liverpool, UK, April 2014 (oral)

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Background: Patients with HNSCC have a high incidence of malnutrition and frequently require enteral tube feeding. Since 2007 our institution has used validated local hospital guidelines for the insertion of prophylactic gastrostomy feeding tubes. Tomotherapy treatment was introduced in 2010; therefore this study investigated whether associated reduced treatment toxicity impacted weight loss and tube feeding requirements.

Methods: Patients with HNSCC attending a major tertiary hospital in 2010 – 2011 were included in the study. Patients assessed as high nutrition risk requiring a prophylactic gastrostomy were compared according to treatment received; Tomotherapy (n=53) versus 3D conformal radiotherapy (n=34). Data on clinical factors, weight change from baseline to completion of treatment, and utilisation of tube feeding were collected. Severe weight loss defined as >10%.

Results: The Tomotherapy cohort had higher proportions of patients with definitive chemoradiotherapy (p=0.043) and more advanced N stage (p=0.003). Nutrition outcomes were not significantly different between the two groups: prophylactic gastrostomy insertion (Tomotherapy: 87% versus conformal: 76%, p=0.473); mean percentage weight loss (Tomotherapy: 6.3% + 5.6 versus conformal: 8.6% + 5.8, p=0.07); incidence of severe weight loss (Tomotherapy: 28% versus conformal: 35%, p=0.492). Two patients in each group required later placement of a feeding tube. Five patients did not use their prophylactic tube (n=3, Tomotherapy; n=2, conformal) with one patient in each group non-adherent to recommendations to use their tube resulting in >10% weight loss.

Conclusion: The clinical significance of mean weight loss and high incidences of tube feeding and severe weight loss in both groups warrants no change to current practice regarding prophylactic gastrostomy insertion. While statistical significance of results is limited by inadequate sample size, a possible trend for less weight loss was noted in patients receiving Tomotherapy. Further research with adequate sample size and strategies to improve nutrition outcomes and adherence to recommendations are required.

11.3.3 Do advancing radiotherapy techniques impact on our nutrition management of patients with head and neck cancer?

Dietitians Association of Australia 31st National Conference, Brisbane, Australia. May 2014 (oral)

Teresa Brown[1,2], Merrilyn Banks[2], Brett Hughes[3], Charles Lin[3], Lizbeth Kenny[3], Judith Bauer[1]

[1]Centre for Dietetics Research (C-DIET-R), University of Queensland, [2]Department of Nutrition and Dietetics, Royal Brisbane and Women's Hospital, [3]Cancer Care Services, Royal Brisbane and Women's Hospital

Patients with head and neck cancer have a high incidence of malnutrition and frequently require enteral tube feeding. Since 2007 our institution has used validated local hospital guidelines for the insertion of prophylactic gastrostomy feeding tubes. Tomotherapy (an advanced radiotherapy technique) was introduced in 2010; therefore this study investigated whether associated reduced treatment toxicity from Tomotherapy impacted nutrition outcomes. Patients with head and neck cancer assessed as high nutritional risk with recommendation for prophylactic gastrostomy were included in the study from 2010-2011. Retrospective data were collected on clinical factors, weight change from baseline to completion of treatment, incidence of severe weight loss ($\geq$10%) and tube feeding. Outcomes were compared according to treatment; Tomotherapy (n=53) versus 3D conformal radiotherapy (n=34). The Tomotherapy cohort had higher proportions of patients with definitive chemoradiotherapy (p=0.043) and more advanced N stage (p=0.003). Nutrition outcomes were not significantly different between the two groups: prophylactic gastrostomy insertion (Tomotherapy: 87% versus conformal: 76%, p=0.473); mean percentage weight loss (Tomotherapy: 6.3% $\pm$ 5.6 versus conformal: 8.6% $\pm$ 5.8, p=0.07); severe weight loss incidence (Tomotherapy: 28% versus conformal: 35%, p=0.492). Both groups had mean weight loss >5% and high incidences of tube feeding and severe weight loss, which are clinically significant results supporting no change to current nutrition management for Tomotherapy. While statistical significance of results is limited by inadequate sample size, a possible trend for less weight loss was noted in patients receiving Tomotherapy. Further research is required with strategies to improve nutrition outcomes and adherence to recommendations.

11.3.4 A retrospective validation of the criteria for proactive gastrostomy tube insertion in patients with head and neck cancer in the era of Tomotherapy

Australian & New Zealand Head & Neck Cancer Society ASM, Melbourne, Australia. July 2013 (oral)

Vanessa Getliffe[1], Teresa Brown[1,2], Merrilyn Banks[2], Brett Hughes[3], Charles Lin[4], Lizbeth Kenny[4], Judy Bauer[1]

[1]School of Human Movement Studies, University of Queensland, [2]Department of Nutrition and Dietetics, Royal Brisbane and Women's Hospital, [3]Department of Medical Oncology, Royal Brisbane and Women's Hospital, [4]Cancer Care Services, Royal Brisbane and Women's Hospital.

Aim. The "Swallowing and Nutrition Guidelines for Patients with Head and Neck Cancer" were developed in response to the high risk of malnutrition and dysphagia that patients experience as a result of cancer treatment. The purpose of this study was to retrospectively re-validate the guidelines' assessment criteria in the era of Tomotherapy and compare these results to a previous two year cohort where the treatment modality was standard 3D conformal radiotherapy.

Methods. Patients (*n=271*) attending a Combined Head and Neck Clinic at a major tertiary hospital in 2010 - 2011 were assessed using the guidelines, with high-risk category patients recommended for proactive gastrostomy. Data were collected on clinical factors, nutrition outcome measures, type and duration of enteral tube feeding, and guideline adherence. Sensitivity, specificity, and positive predictive value were calculated. These results were compared to a previous validation cohort from 2007 - 2008 (*n=502*).

Results. The only significant difference between the two cohorts was the number of patients receiving Tomotherapy (*P*=<0.001). Proactive gastrostomy tubes were inserted in 87 of 271 patients (32%). Overall guideline adherence was 91% (vs. previous cohort results of 87%). High risk category adherence was 81% (compared to 75%). Validation outcomes were sensitivity 75% (compared to 54%), and specificity 90% (compared to 93%).

Conclusion. The results of this study confirm the Head and Neck Guideline's criteria and categories remain valid in the era of Tomotherapy to aid risk assessment and to guide early decision making for the suitability and timing of tube feeding in patients with head and neck cancer.

11.3.5 Investigation of p16 status, chemotherapy regimen and other nutrition markers for predicating gastrostomy in patients with head and neck cancer

Multinational Association of Supportive Care in Cancer, Adelaide, Australia. June 2016 (poster)

Investigation of p16 status, chemotherapy regimen and other nutrition markers for predicting gastrostomy in patients with head and neck cancer

Teresa Brown[1,2], Kym Wittholz[2], Leesa Wockner[3], Merrilyn Banks[1], Brett Hughes[1,2], Charles Lin[1,2], Lizbeth Kenny[1,2], Judith Bauer[2]

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Introduction

Various factors have been identified as predictors of gastrostomy in patients with head and neck cancer[1]. At our facility, the decision for proactive gastrostomy placement is based on a validated protocol *(see Figure)* to categorise patients' level of predicted nutritional risk as high or low based on risk factors which have been shown in the literature to increase dysphagia, weight loss and the need for tube feeding during treatment[2].

The aim of this study was to determine if factors yet to be investigated, such as p16 status, chemotherapy regimen and nutrition markers of pre cachexia, could improve the accuracy of this existing protocol to predict proactive gastrostomy placement.

Methods

269 patients (77% male: 23% female, mean age 63 years) who received curative oncological or surgical treatment from July 2010 to June 2011 at a tertiary hospital were included in this retrospective study.

Data collection included patient demographics, tumour and treatment details, malnutrition risk using the Malnutrition Screening Tool (MST), albumin as a pre cachexia marker, P16 status as a surrogate marker for HPV (Human Papillomavirus) and protocol risk category (high or low). The outcomes of weight loss during treatment and the use of a feeding tube were used to determine the primary outcome criteria of whether each patient was deemed to truly require or not require a proactive gastrostomy.

Patients were deemed to meet the criteria 'needed a proactive gastrostomy' when; **a)** a patient had an actively used gastrostomy OR **b)** a patient had a long-term nasogastric feeding tube for greater than four weeks OR **c)** a patient did not have an actively used gastrostomy or a long-term nasogastric feeding tube for greater than four weeks AND had ≥10% weight loss.

Statistical analysis involved the following steps:

1. Determine which baseline independent patient variables are associated with the protocol high risk category rating
2. Determine if any of the baseline independent patient variables are useful in the low risk category to discriminate between those patients that would have benefited from a proactive gastrostomy and those that were correctly deemed low risk.
3. Undertake logistic regression to identify independent predictors of gastrostomy placement.

Overall statistical significance was set at $p<0.05$. Data was analysed using IBM SPSS database and statistical package (version 22, SPSS Inc., Chicago).

Results

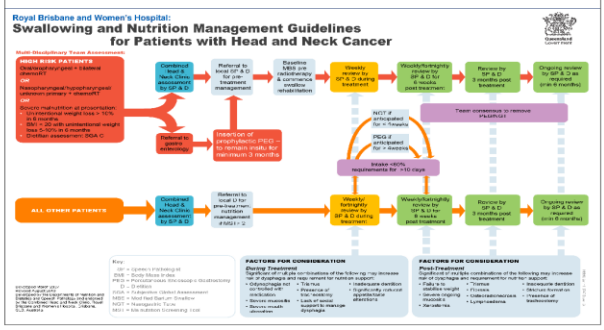
Using the current protocol 81/88 (92%) high risk patients were correctly identified, but 32/181 (18%) low risk patients were incorrectly classified.

On exploration of the characteristics associated with protocol risk rating, it was found that patients classified as high risk tended to have oropharyngeal tumours ($p<0.001$), were receiving concurrent chemotherapy ($p<0.001$), were not undergoing surgery ($p<0.001$), and had higher T-stage ($p=0.001$) and N-stage cancers ($p<0.001$).

They also were more likely to have p16 positive cancers ($p<0.001$), and had serum albumin levels greater than 35 ($p=0.014$). There was no association with age, gender or MST or with the new variable of interest - chemotherapy type ($p=0.249$)

On review of the low risk patients only (n=181) to determine which characteristics are common to those that "met criteria for proactive gastrostomy" (n=32), we found that the only new variable associated was MST, $p=0.039$.

The odds of gastrostomy in the low risk group were 2.7 times greater when at risk of malnutrition (MST = 2 – 5) ($p=0.044$). Sub group analysis of low risk patients with oral or oropharyngeal cancers, found p16 positive disease had 4.4 times greater odds ($p=0.049$), and those at risk of malnutrition (MST=2-5) had 4.5 times greater odds ($p=0.019$), of requiring a gastrostomy.



Conclusions

Overall, the findings support the current high risk criteria in the swallowing and nutrition guidelines which currently consider treatment type, tumour site and nutritional status. These results suggest that the current guidelines, whilst only made up of three variables, act as proxies for almost all other clinical factors. The findings do not support the addition of serum albumin, p16 status or chemotherapy type or dose in the high risk criteria. However using the MST (and p16 status in oral or oropharyngeal tumours) may help identify other low risk patients that do actually require a proactive gastrostomy, and thus improve the guidelines' sensitivity.

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c-diet-r CENTRE FOR DIETETICS RESEARCH · Queensland Government · The University Of Queensland AUSTRALIA

11.3.6 Validation of a protocol to predict proactive gastrostomy tube placement in patients with head and neck cancer receiving helical-IMRT

Australia & New Zealand Head & Neck Cancer Society, Auckland, New Zealand. Oct 2016 (poster)

Metro North Hospital and Health Service *Putting people first*

Validation of a protocol to predict proactive gastrostomy tube placement in patients with head and neck cancer receiving Helical-Intensity Modulated Radiotherapy

Teresa Brown[a,b] | Aaron Chan[a] | Kathleen Dwyer[b] | Merrilyn Banks[b] | Brett Hughes[c,d] | Charles Lin[c,d]
Lizbeth Kenny[c,d] | Jane Crombie[e] | Ann-Louise Spurgin[e,f] | Judith Bauer[a]

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PURPOSE

The "RBWH Swallowing and Nutrition Management Guidelines for Patients with Head and Neck Cancer (HNC)" identifies patients at *"high risk"* of dysphagia and nutrition decline and recommends proactive feeding tube placement *(see Figure 1)*. The protocol was originally validated in a two year cohort following implementation in 2007-2008[1]. Following review the protocol was revised and re-validated in 2010-2011[2]. This study aimed to validate the protocol in a new cohort with a larger proportion of *"high risk"* patients now receiving helical-intensity modulated radiotherapy (H-IMRT).

METHODOLOGY

Patients were eligible if they had curative intent treatment of a HNC between July 2013 and June 2014, and were seen by the Dietitian. Data were prospectively collected during standard dietetic care. Patients were confirmed as *"high risk"* if they experienced significant weight loss at the end of treatment (≥10% baseline body weight), or used any enteral feeding tube for >4 weeks and this outcome was then compared to the protocol risk classification.

RESULTS

The final sample included 315 patients (76% male, mean age 65) with primarily oral cavity/oropharyngeal tumours (51%). Compared to the previous validation cohort, there were no significant differences in patient characteristics, other than nodal disease (p=0.006) and the proportion treated with H-IMRT (p<0.001). The comparison of validation results over time are shown in Table 1.

CONCLUSION

Whilst remaining valid, a decrease in specificity of the protocol suggests over-estimation of the need for proactive tubes. This is possibly due to the increase in proportion of patients who receive H-IMRT which results in better sparing of normal tissues and structures compared with 3D conformal radiotherapy. Further modification of the protocol is recommended to optimise *"high risk"* identification whilst minimising the risk of unnecessary tube placement.

FIGURE 1

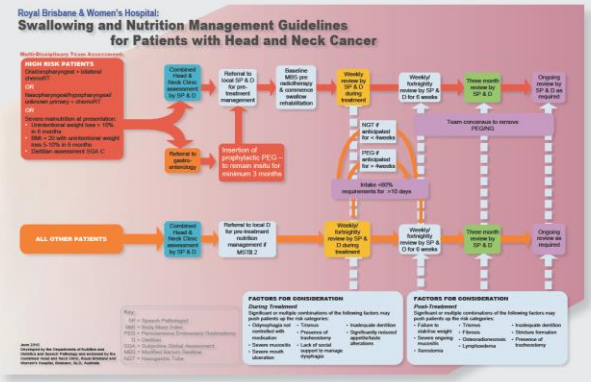

TABLE 1

	Comparison of Validation Studies Over Time		
Cohort	2013-2014 (N=315)	2010-2011 (N=270)[2]	2007-2008 (N=501)[1]
Radiotherapy treatment	H-IMRT (61%)	H-IMRT (28%)	3D conformal
Protocol version	Version 2 (2010)	Version 2 (2010)	Version 1 (2007)
Adherence to high risk pathway	60%	89%	75%
Sensitivity	73%	72%	54%
Specificity	86%	96%	93%
Positive predictive value	71%	92%	82%
Negative predictive value	87%	82%	77%

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11.3.7 Outcomes following proactive vs reactive nutrition support in patients undergoing chemoradiotherapy

World Congress of Larynx Cancer, Cairns, Australia July 2015 (oral)

Teresa Brown[1,2], Merrilyn Banks[2], Brett Hughes[3], Charles Lin[3], Lizbeth Kenny[3], Judith Bauer[1]

[1]Centre for Dietetics Research (C-DIET-R), University of Queensland, [2]Department of Nutrition and Dietetics, Royal Brisbane and Women's Hospital, [3]Cancer Care Services, Royal Brisbane and Women's Hospital

Purpose: The optimal method of tube feeding for patient with head and neck cancer remains unclear. Our institution uses validated local hospital guidelines for the insertion of prophylactic gastrostomy feeding tubes. The aim of this study was to investigate the outcomes of patients following non adherence to these recommendations.

Methodology: Patients assessed as high nutrition risk according to local guidelines were included from August 2012 – July 2014. Patients were grouped according to adherence to guideline recommendation for gastrostomy placement. Clinical outcomes were: weight change from diagnosis to the end of radiotherapy; use of feeding tubes; and admissions for up to one month post treatment.

Results: Over two years there were 130 high nutrition risk patients with the following characteristics - 88% male, median 59 years old, 77% oropharyngeal tumours, 91% stage IV disease, and 88% chemoradiotherapy treatment. Group 1 received a gastrostomy (n=69). Group 2 were managed reactively (n=61), with 26 patients (43%) requiring a feeding tube or with weight loss >=10%. Mean weight loss during treatment was 7.0% (gastrostomy group) versus 8.4% (reactive group) (p=0.114), which was significant when adjusting for T stage, tumour site, and age (p=0.048). Unplanned admissions accounted for 75% of total length of stay in the gastrostomy group and 82% in the reactive group (p=0.029).

Conclusion: Nutritional and clinical outcomes were improved in the group receiving gastrostomy when adjusting for clinical differences between the groups. Some selection bias was evident in patients without a gastrostomy and further investigation of this group could help to assist to improve the guidelines for gastrostomy selection.

11.3.8 Optimising nutrition outcomes for patients with head and neck cancer through innovative pre-treatment intervention strategies

Clinical Oncological Society of Australia, Brisbane, Australia. Nov 2012 (oral)

Teresa Brown[1, 2]

[1]Royal Brisbane & Women's Hospital, [2]Centre of Dietetics Research (C-DIET-R), The University of Queensland

There is high level evidence to support the role of the dietitian in the multidisciplinary team for the management of patients with head and neck cancer. Several studies have demonstrated the beneficial effects of dietary counselling during radiotherapy treatments, with improvements in weight, nutritional status and quality of life (Garg et al., 2010). Many patients also require nutrition support through tube feeding, however the evidence remains unclear as to the optimal form of tube feeding (Nugent et al 2010b). Prophylactic gastrostomy has been recommended in some patient groups due to the beneficial effects on maintaining nutritional status or weight (Tyldesley et al 1996, Lee et al 1998), as well as other benefits such as improved quality of life (Senft et al 1993) and reduced hospital admissions (Piquet et al 2002, Lee et al 1998). Many of these studies were undertaken in patients receiving radiotherapy alone, and now as chemoradiotherapy treatments become standard of care, the same results for nutrition outcomes in more recent trials are not seen (Silander et al 2010). At the Royal Brisbane and Women's Hospital, we are using validated guidelines to predict which patients may require prophylactic gastrostomy, and despite this proactive intervention, we have found that high risk patients can still lose 6-7% of body weight during treatment and up to 9-10% by three months post treatment. Weight loss and malnutrition can impact on the patients' quality of life, functional ability and other clinical outcomes. Therefore the aim of this research is to investigate novel approaches of nutrition intervention through prophylactic nutrition support and to determine whether early tube feeding improves nutrition outcomes.

11.3.9 Early feeding via a prophylactic gastrostomy – Preliminary findings from a RCT in high risk HNSCC patients undergoing chemoradiotherapy

Australia & New Zealand Head & Neck Cancer Society, Auckland, New Zealand. Oct 2016 (poster)

Metro North Hospital and Health Service *Putting people first*

Early feeding via a prophylactic gastrostomy – Preliminary findings from a randomised controlled trial in high risk head and neck mucosal SCC (HNSCC) patients undergoing chemoradiotherapy

Teresa Brown[a,b] | Merrilyn Banks[b] | Brett Hughes[c,d] | Charles Lin[c,d] | Lizbeth Kenny[c,d] | Judith Bauer[a]

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PURPOSE

Patients with HNSCC are at high risk of malnutrition and dysphagia, and enteral tube feeding is often required, however significant weight loss is still seen despite prophylactic gastrostomy placement. The aim of this study was to improve nutrition outcomes utilising an early feeding approach via the prophylactic gastrostomy.

METHODOLOGY

Patients were eligible if they were identified for a prophylactic gastrostomy prior to treatment for head and neck cancer (between September 2012 to June 2015) and were randomly allocated to the intervention (n=61) or usual care (n=70) *(see Figure 1)*. The intervention recommended supplementary feeding via the gastrostomy immediately compared to usual care where feeding was commenced when clinically indicated. Key measures at three months post treatment included percentage weight loss as the primary outcome, and body composition (using bioelectrical impedance), nutritional status (using Patient Generated Subjective Global Assessment – PGSGA), quality of life (using EORTC-QLQ30 and EORTC-H&N35) and chemotherapy/radiotherapy completion rates as secondary outcomes. Full methods available.[1]

FIGURE 1

Summary of recruitment and randomisation

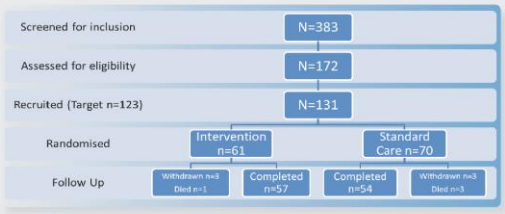
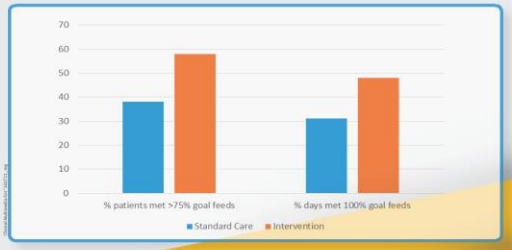


FIGURE 2

Impact of Early Feeding on Improving Enteral Intake during Treatment



RESULTS

Patients were predominantly male (88%), mean age 60.5, with oropharyngeal tumours (76%), stage IV disease (86%), and receiving chemoradiotherapy (82%). There were no significant differences for demographics, clinical characteristics or baseline nutritional status. The intervention group had slightly higher baseline BMI (28.1 vs 26.4, p=0.078) and fat free mass (60.9kg vs 57.6kg, p=0.073), and a slightly lower nutritional risk PGSGA score (5.8 vs 7.7, p=0.052). The standard care group had a lower quality of life (QOL) in a number of domains including global quality of life (p=0.025), fatigue (p=0.004) and dry mouth (p=0.048). No differences were seen in regards to nutrition or quality of life outcomes after adjusting for any baseline differences in multivariable analysis *(see Table 1)*.

Completion of target dose chemotherapy was similar in each group (95% standard care vs 98% intervention, p=0.407) as was completion of planned radiotherapy (100% standard care vs 95% intervention, p=0.102). Unplanned admissions affected 47% in the standard care group and 57% in the intervention group (p=0.102). Complete metabolic response on PET at three months also showed no differences in clinical outcomes (78% standard care vs 81% intervention, p=0.661).

Only 29/57 (51%) patients adhered to the intervention (consuming >75% of the prescribed supplements). Sub-analysis of this adherent group versus standard care still found no statistical differences. However the early feeding group did have improved adherence to tube feeding recommendations later in treatment when it became clinically necessary, with a higher proportion of patients meeting >75% of goal enteral feeds (p=0.037) and a higher proportion of days in which patients met 100% of goal enteral feeds (p<0.001) *(see Figure 2)*.

CONCLUSION

The early nutrition intervention improved adherence to recommended enteral feeding during treatment, however overall adherence to nutrition recommendations remains low and therefore this has not translated into improved outcomes overall. Further research is required to explore patient barriers to nutrition interventions to develop multidisciplinary models of care to improve adherence and optimise outcomes.

TABLE 1: *Summary of main nutrition and quality of life outcomes*

Outcome	Standard Care (n=70)	Intervention (n=61)	Differences observed at baseline	Significance following multivariable analysis*
Mean % weight change	-10.9	-10.8	NO	NO
Mean % fat free mass change	-4.2	-6.3	YES	NO
% decline nutritional status (SGA)	31%	26%	NO	NO
Mean change in Global QOL **	-2.9	-6.2	YES	NO
Mean change in fatigue ***	8.4	17.0	YES	NO
Mean change in dry mouth ***	41.1	55.6	YES	NO

KEY:
* Multivariable analysis using regression models adjusting for baseline differences
** Greater negative score for Global QOL = greater deterioration
*** Greater positive score for QOL symptoms = greater symptom burden

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11.3.10 Does early feeding via a prophylactic gastrostomy improve quality of life in patients with HNSCC?

10th International Quality of Life in Head & Neck Cancer Conference, Liverpool, UK. Nov 2016 (oral)

Teresa Brown[1,2], Merrilyn Banks[2], Brett Hughes[3,4], Charles Lin[3,4], Lizbeth Kenny[3,4], Judith Bauer[1]

[1]Centre for Dietetics Research (C-DIET-R), University of Queensland, [2]Department of Nutrition and Dietetics, RBWH, [3]Cancer Care Services, RBWH, [4]School of Medicine, University of Queensland

Background: Patients with HNSCC are at high risk of malnutrition and weight loss which is associated with reduced quality of life. Enteral tube feeding is often required, however even with prophylactic gastrostomy placement significant weight loss still occurs. The aim of this study was to improve nutrition outcomes utilising an early feeding approach via the prophylactic gastrostomy and thus improve quality of life.

Patients and Methods: Patients with HNSCC were eligible if identified for prophylactic gastrostomy prior to treatment and randomly allocated to the intervention (n=61) or usual care (n=70). The intervention recommended gastrostomy feeding immediately post placement to supplement oral intake. Usual care commenced gastrostomy feeding when clinically indicated. Key outcome measures were percentage weight loss and quality of life (EORTC-QLQ30, HN35) at three months post treatment.

Results: Patients were predominantly male (88%), mean age 60+10.1, with oropharyngeal tumours (76%), receiving chemoradiotherapy (82%). Adherence to the early intervention was poor (51%). There were no significant baseline differences for demographics, clinical or nutritional status variables, but a reduced quality of life in the usual care group. Weight loss outcomes were no different in each group (10.9% usual vs 10.8% intervention, p=0.930). Following adjustment of baseline differences in quality of life no statistical differences were observed for functional or symptom scales. The intervention group had a clinically important decline in social functioning (p=0.065). Both groups had clinically important deteriorations in; fatigue, appetite, senses, dry mouth, sticky saliva and social eating.

Clinical Implications: Symptoms impacting on quality of life persist post treatment and highlight the role of allied health support. There were no improvements in nutrition or quality of life measures following the early feeding approach. Poor adherence was explained by several clinical, environmental and psychosocial barriers which can be addressed to improve clinical practice, patient adherence and future outcomes.

11.3.11 Prophylactic gastrostomy use in patients with HNSCC post treatment – is there really a problem?

10th International Quality of Life in Head & Neck Cancer Conference, Liverpool, UK. Nov 2016 (poster)

Metro North Hospital and Health Service *Putting people first*

Prophylactic gastrostomy use in patients with head and neck cancer (HNSCC) post treatment *– is there really a problem?*

Teresa Brown[a,b] | Merrilyn Banks[b] | Brett Hughes[c,d] | Charles Lin[c,d] | Lizbeth Kenny[c,d] | Judith Bauer[a]

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BACKGROUND

Prophylactic gastrostomy placement is a common method of nutrition support in patients with HNSCC, however there are concerns this approach leads to dysphagia and long term tube dependency[1]. Whilst rates of gastrostomy retention are frequently reported as outcomes in studies, there is a lack of nutritional information regarding the reason for their ongoing use, and thus the term gastrostomy dependency can be misunderstood[2].

AIM

The aim of this study was to determine patterns of gastrostomy use post treatment to increase the understanding of patients' nutritional needs during this time and to determine associations with tube removal/retention.

PATIENTS AND METHODS

Patients with HNSCC with prophylactic gastrostomy were observed monthly post treatment to six and twelve months to determine tube use and removal time. Patients were part of a randomised controlled trial[3] comparing an early feeding intervention via the gastrostomy (n=61) versus usual care which commenced feeding when clinically indicated (n=70). Nutrition outcomes were collected at three months post treatment (weight change from baseline and nutritional status using the Patient Generated Subjective Global Assessment). Gastrostomy removal was recorded in days following completion of treatment. If the tube was in situ at time of review tube use was defined as either nil, full (meeting 100% of estimated nutritional requirements) or supplementary to oral intake. Factors associated with time to tube removal were explored using linear regression.

RESULTS

Patients were predominantly male (88%), mean age 60±10.1, with oropharyngeal tumours (76%), receiving chemoradiotherapy (82%). Seven patients were excluded from the study due a change in eligibility criteria (n=4), patient withdrawal (n=1), gastrostomy removal due to complication (n=1) and death during treatment due to liver failure (n=1). Therefore providing final sample for analysis as follows: standard care (n=67) and intervention (n=57).

Tubes were fully used by 72% (89/124) on completion of treatment, with only 16 patients not using their tube (13%). Patterns of gastrostomy use and removal over time for each group can be seen in Figure 1 and 2. There was no statistical difference between groups at any time point except at 4 months, which was attributed to higher rates of supplementary feeding in the intervention group (21% vs 6%, p=0.044).

Median time (range) to gastrostomy removal: usual care 100 days (28-276) versus intervention 110 days (21-280) (p=0.333). No differences in 12 month gastrostomy retention rates (p=0.181), with ten patients overall with tubes in situ. Only half were using the tube, two were waiting appointments for removal and three were delayed decision-making due to suspected recurrent disease. The true gastrostomy dependency rate is therefore 4%. Patients with poorer nutritional status at three months post treatment, as well as increasing age, current smoking and lack of social support, were associated with increased time to removal.

CLINICAL IMPLICATIONS

There is a high rate of gastrostomy use in the acute phase post treatment. Encouraging early use does not lead to increased dependency. Appropriate use enables the provision of adequate nutrition while the patient recovers from treatment side effects.

However as patients recover many have tubes in situ which are no longer being used. This can contribute to the over estimation of gastrostomy dependency rates. It is recommended that "tube use" rather than "tube in situ" is used in future studies to determine whether patients are truly dependent or not.

The presence of a long term feeding tube also has the greatest negative impact on quality of life[4]. Therefore procedures should be developed to ensure timely removal of unused tubes.

FIGURE 1

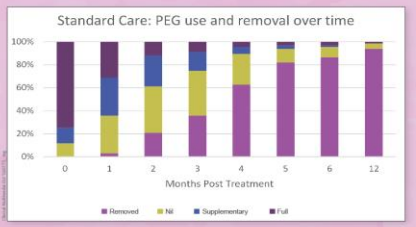
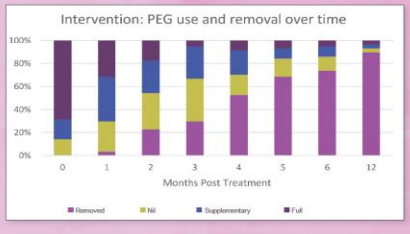
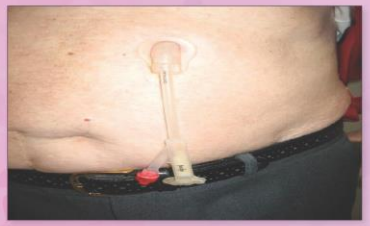


FIGURE 2





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[3] Brown T, Banks M, Hughes B, Kenny L, Lin C, Bauer J. Protocol for a randomized controlled trial of early prophylactic feeding via gastrostomy versus standard care in high risk patients with head and neck cancer. BMC Nursing. 2014;13:17.

[4] Terrell J, Ronis D, Fowler K, Bradford C, Chepeha D, Prince M, et al. Clinical predictors of quality of life in patients with head and neck cancer. Archives of Otolaryngology-Head & Neck Surgery. 2004;130(4):401-8.

Queensland Government

11.3.12 Understanding initiation of nutrition support in patients with HNSCC and adherence to recommendations – a patient perspective

Clinical Oncology Society of Australia ASM, Gold Coast, Australia. Nov 2016 (poster)

Metro North Hospital and Health Service *Putting people first*

Understanding initiation of nutrition support in patients with head and neck cancer (HNC) and adherence to recommendations – *a patient perspective*

Teresa Brown[a,b] | Merrilyn Banks[b] | Brett Hughes[c,d] | Charles Lin[c,d] | Lizbeth Kenny[c,d] | Judith Bauer[a]

Centre for Dietetics Research (C-DIET-R), School of Human Movement Studies and Nutrition Sciences, University of Queensland, Queensland, Australia
Department of Nutrition and Dietetics, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia
Cancer Care Services, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia
School of Medicine, University of Queensland, Queensland, Australia

The University Of Queensland AUSTRALIA

c-diet-r CENTRE FOR DIETETICS RESEARCH

AIMS

Patients undergoing treatment for HNC often require tube feeding, however weight loss remains prevalent. The aim of this study was to investigate the impact of patient adherence to nutrition recommendations on weight loss and understand patient barriers to meeting goal enteral feeding.

METHODS

Observational study in patients with HNC (n=125) deemed at high nutritional risk with prophylactic gastrostomy placed prior to treatment following local protocol. Weight was recorded at placement of gastrostomy and three months post treatment. Time of recommended commencement of gastrostomy feeding by the dietitian was recorded. Patients were asked to maintain a daily record of gastrostomy intake during treatment, main nutrition impact symptom necessitating gastrostomy use, and the reasons for not meeting nutrition prescription if applicable. Adherence was defined as actual intake >75% of prescribed intake. Patient consuming >100% of prescribed tube feeds were also considered adherent.

RESULTS

Patients were predominantly male (88%), median age 60, with oropharyngeal tumours (77%), non-metastatic stage IV disease (87%) treated with chemoradiotherapy (87%). Gastrostomy was placed a median 5 days prior to start of treatment and commenced use by week 4 in 83% of patients. The primary reason for gastrostomy use in weeks 2-3 was poor appetite/dysgeusia and in week 4-7 it was odynophagia/mucositis. Patients only met 100% of goal nutrition on 36% (range, 0-100%) of prescribed enteral feeding days. Key barriers to intake were; nausea/vomiting (23%), feeling full, bloated or no appetite (17%), lack of time, support or motivation (11%) and substituting with nutritionally inadequate oral intake (11%) *(see Figure 1)*. Other barriers included other symptoms such as reflux, constipation, diarrhoea, generally feeling unwell or in pain, specific feed intolerances and fatigue or sleeping too much. Environmental factors relating to hospital appointments or treatment were also reported. The incidence over time is reported for each of the main barriers identified *(see Figure 2a-2d)*. Adherent patients (n=49) had less weight loss than non-adherent patients (n=55) (-10.3% vs -12.6% respectively, p=0.038).

FIGURE 1

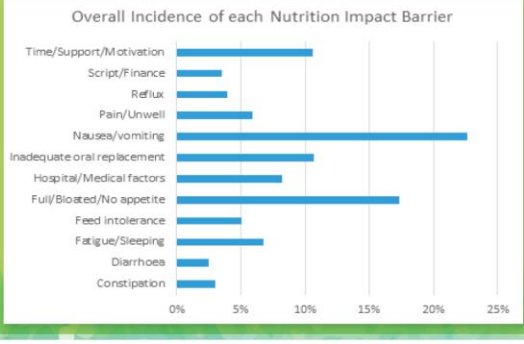

FIGURE 2a

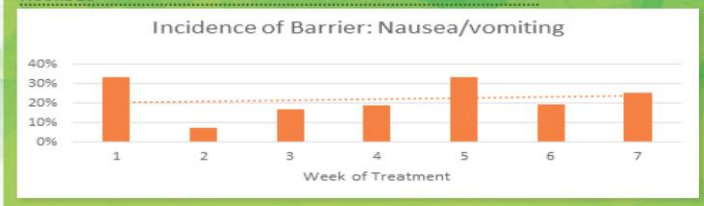

FIGURE 2b

FIGURE 2c

FIGURE 2d

CONCLUSIONS

Despite prophylactic gastrostomy placement, patients still have clinically significant weight loss >10% and only achieve goal nutritional intake for a third of the duration tube feeding is prescribed. Improving adherence to nutrition recommendations will assist in improving nutritional outcomes by minimising severe weight loss and malnutrition. Key areas to target have been identified to overcome barriers, including optimising symptom management, improving nutrition counselling in regards to the requirement for enteral nutrition and developing appropriate psychosocial supports. Nausea and vomiting was the most common barrier reported, and while cisplatin may be a major cause, it is likely multifactorial, as patients treated with non-emetogenic cetuximab still report symptoms. Other possible causes are from the oropharyngeal secretions from mucositis, side effects of opioids for pain control, and constipation. Future research should be considered to further explore and understand these barriers, including assessment of other psychological factors such as patient mood and depression, to help better support patients in the future.

Queensland Government

11.4 Appendix D: RBWH Human Research Ethics Committee Approval

Royal Brisbane and Women's Hospital
Metro North Hospital and Health Service

Office of the Human Research Ethics Committees

Queensland Health

Enquiries to: Ann-Maree Gordon
Assistant Coordinator
Phone: 07 3646 6132
Fax: 07 3646 5849
Our Ref: HREC/12/QRBW/162
E-mail: RBWH-Ethics@health.qld.gov.au

Mrs Teresa Brown
Department of Nutrition and Dietetics
Level 2, Dr James Mayne Building
Royal Brisbane & Women's Hospital
Herston Q 4029

Dear Mrs Brown,

Re: Ref N^{o}: HREC/12/QRBW/162: A randomized controlled trial to compare early prophylactic feeding via gastrostomy versus standard care in high risk patients with head and neck cancer

Thank you for submitting the above research project for single ethical review. This project was considered by the Royal Brisbane & Women's Hospital Human Research Ethics Committee (RBWH HREC) **(EC00172)** meeting held on 18 June, 2012.

I am pleased to advise that the RBWH Human Research Ethics Committee has granted ethical approval of this research project.

The nominated participating site for this project is:

- Royal Brisbane & Women's Hospital, QLD

This letter constitutes ethical approval only. This project cannot proceed until separate research governance authorisation has been obtained from the CEO or Delegate of the Royal Brisbane & Women's Hospital under whose auspices the research will be conducted.

It is noted that a Data Monitoring Committee will be established. Annual Reports should include any reports by this Committee.

The approved documents include:

Document	*Version*	*Date*
Covering Letter		25 May 2012
Application: NEAF *(Submission Code: AU/1/ED7D05)*	2.0 (2008)	25 May 2012
Protocol	8	25 May 2012
Patient PEG FEED Diary	2	25 May 2012
EORTC QLQ-C30 Questionnaire	3.0 English	
EORTC QLQ - H&N35 Questionnaire	1.0	
RBWH Research Advisory Committee approval of 2012 Research Scholarship		05 August 2011
Curriculum Vitae of Teresa Brown		
Curriculum Vitae of Charles Lin		
Curriculum Vitae of Liz Kenny		
Response to Request for Further Information		17 July 2012
Participant Information Sheet & Consent Form	4	22 June 2012

Approval of this project from the RBWH HREC is valid from **19.07.2012** to **19.07.2015** subject to the following conditions being met:

- The Coordinating Principal Investigator will immediately report anything that might warrant review of ethical approval of the project.
- The Coordinating Principal Investigator will notify the RBWH HREC of any event that requires a modification to the protocol or other project documents and submit any required amendments in accordance with the instructions provided by the HREC. These instructions can be found at http://www.health.qld.gov.au/rbwh/research/hrec.asp.
- The Coordinating Principal Investigator will submit any necessary reports related to the safety of research participants in accordance with the RBWH HREC policy and procedures. These instructions can be found at http://www.health.qld.gov.au/rbwh/research/hrec.asp.
- In accordance with Section 3.3.22 (b) of the National Statement the Coordinating Principal Investigator will report to the RBWH HREC annually in the specified format, the first report being due on **19.07.2013** and a final report is to be submitted on completion of the study. These instructions can be found at http://www.health.qld.gov.au/ohmr/html/regu/reporting_templates.asp.
- The Coordinating Principal Investigator will notify the RBWH HREC if the project is discontinued before the expected completion date, with reasons provided.
- The Coordinating Principal Investigator will notify the RBWH HREC of any plan to extend the duration of the project past the approval period listed above and will submit any associated required documentation. Instructions for obtaining an extension of approval can be found at http://www.health.qld.gov.au/rbwh/research/hrec.asp.

- The Coordinating Principal Investigator will notify the RBWH HREC of his or her inability to continue as Coordinating Principal Investigator including the name of and contact information for a replacement.
- A copy of this ethical approval letter together with completed Site Specific Assessment (SSA) and any other requirements must be submitted by the Coordinating Principal Investigator to the Research Governance Office at the Royal Brisbane & Women's Hospital in a timely manner to enable the institution to authorise the commencement of the project at its site.
- Should you have any queries about the RBWH HREC's consideration of your project please contact the HREC Coordinator on 07 3646 5490. The RBWH HREC's Terms of Reference, Standard Operating Procedures, membership and standard forms are available from http://www.health.qld.gov.au/rbwh/research/hrec.asp.

The RBWH HREC wishes you every success in your research.

Yours sincerely,

Dr Conor Brophy
Chairperson RBWH Human Research Ethics Committee
Metro North Hospital and Health Service
19.07.2012

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*. The processes used by this HREC to review research proposals have been certified by the National Health and Medical Research Council.

11.5 Appendix E: UQ Medical Research Ethics Committee Approval

THE UNIVERSITY OF QUEENSLAND
Institutional Approval Form For Experiments On Humans Including Behavioural Research

Chief Investigator:	Mrs Teresa Brown
Project Title:	A Randomised Controlled Trial To Compare Early Prophylactic Feeding Via Gastrostomy Versus Standard Care In High Risk Patients With Head And Neck Cancer
Supervisor:	A/Prof Judith Bauer, Dr Merrilyn Banks, Dr Brett Hughes
Co-Investigator(s):	Dr Liz Kenny, Dr Charles Lin
Department(s):	School of Human Movement Studies; Dept of Nutrition and Dietetics, RBWH; Cancer Care Services, RBWH
Project Number:	2012000890
Granting Agency/Degree:	RBWH Research Scholarship
Duration:	30th September 2018

Comments:

Expedited review on the basis of approval from the Royal Brisbane and Women's Hospital HREC dated 19/07/2012.

Name of responsible Committee:-
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:-
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Date: 8 AUG 2012 Signature:

11.6 Appendix F: Patient Information and Consent Form

Metro North Health Service District

Enquiries to: Teresa Brown
Phone: 07 3646 7995
Fax: 07 3646 1874

Participant Information and Consent Form
Version4, Dated 22 June 2012

EARLY TUBE FEEDING IN H&N CANCER

Principal Researcher(s): Teresa Brown, Dept Nutrition & Dietetics, A/Prof Judith Bauer, University of Queensland, Dr Merrilyn Banks, Dept Nutrition & Dietetics, Dr Brett Hughes, Cancer Care Services

Associate Researcher: Dr Liz Kenny, Cancer Care Services, Dr Charles Lin, Cancer Care Services

You are invited to take part in this research project.

Please read this information carefully. Feel free to ask questions. You may wish to discuss the project with a relative or friend. If you agree to participate, you will be asked to sign a Consent Form and you will be given a copy of this Participant Information and the Consent Form to keep as a record.

What is the study about?

The study is being carried out as part of a PhD research study at the University of Queensland. The study is to investigate the best time to start providing extra nutrition to patients receiving treatment for head and neck cancer. During treatment, many patients have difficulty eating enough food. The side effects of the radiotherapy or chemotherapy often reduce appetite or make it hard to chew and swallow food. A feeding tube is often used to provide enough nutrition whilst you are not eating well.

Currently we identify patients who may need a feeding tube during their treatment using hospital guidelines. This tube is usually placed a week or so before treatment starts. Once patients start to have difficulty eating, we advise they start using the feeding tube. While this approach has reduced complications during treatment and prevented unexpected hospital admissions, many patients still can lose a large amount of weight.

Office	Postal	Phone	Fax
Butterfield St Herston Q 4006	Post Office RBWH Queensland 4029	07 3636 8111 ISD + 61 7 3636 8111	07 3636 4240

The aim of this study is to see whether starting tube feeding earlier will improve patients' nutrition and weight. Improved nutrition is likely to have other positive benefits on quality of life with better energy levels and strength for everyday activities. We are also looking at whether it will improve your outcome to treatment.

What will it involve for me?

You are invited to take part in the study because you have been identified as needing a feeding tube (PEG tube) before your treatment for head and neck cancer. We are aiming to include 100 people like you. Participation will involve collecting information about your medical diagnosis and treatment, your weight and your nutrition intake from the PEG tube, both before, during and after treatment

You will need to attend an extra appointment with a research dietitian before you start treatment and 3 months after you finish treatment. At the appointment the dietitian will do an assessment/interview, check your weight on special scales that measure weight and body fat, and you will be asked to complete a survey to assess your quality of life. Each appointment will take approximately 30 minutes.

You will see the hospital dietitian as part of usual care when you come for your PEG tube to be placed. They will teach you how to care for your PEG tube. You will have an equal chance of being allocated to the standard care group or the intervention group.

- If you are in the standard care group, you are required to care for your PEG tube and flush water through it twice each day.
- If you are in the intervention group - you will also be asked to take two extra nutrition supplement drinks each day through your PEG tube in addition to the food you usually eat. Each supplement drink is about 200ml (less than 1 cup).

Both groups see their hospital dietitian throughout treatment as part of usual care. The hospital dietitian provides support and advises you on your diet and foods to eat. They will let you know if you need to start or have more tube feeds as treatment progresses. Once treatment finishes you are referred to your local dietitian for ongoing care.

After treatment, the research dietitian will contact you monthly by phone for a period of 6 months to check how you are eating and drinking and if still using the PEG. When you return to the hospital for your PET scans at 3 months, you will be seen by the research dietitian again to re-measure your weight, body fat, nutrition and quality of life survey.

If you have a family member or carer who you would like to be with you during these appointments, they are welcome to attend.

Your medical records will be reviewed for progress at 1 and 5 years post treatment.

Office	Postal	Phone	Fax
Butterfield St Herston Q 4006	Post Office RBWH Queensland 4029	07 3636 8111 ISD + 61 7 3636 8111	07 3636 4240

How will this study help me?

The study will not change the level of care you are currently receiving. You will have an equal chance of being allocated to either standard care or the intervention.

It is hoped that the extra nutrition in the intervention group will reduce any weight loss during treatment and maintain your nutrition. This should help your energy levels and strength during treatment. It may also assist you being well enough to receive optimal treatment from the chemotherapy and radiotherapy, and prevent emergency admissions to the hospital for complications.

Whilst we have good evidence from other research studies that nutrition advice during treatment is beneficial (our standard care), there is very little evidence for giving nutrition before treatment. This study will give us information we need to plan improvements to our service to other patients with head and neck cancer in the future and whether pre treatment nutrition is beneficial.

Is there any harm to me taking part?

The placement of a gastrostomy tube is associated with risks which your doctor will have explained to you to obtain your consent for the procedure. This risk applies to all patients receiving this procedure as part of standard care and so is the same for each group in this research project.

There may be inconveniences which include;

- having an extra appointment with the research dietitian pre treatment (after you see the medical oncologist) and then at 3 months post treatment (when you attend for your medical PET scans)
- keeping a simple diary record of how many PEG feeds you take each day and any symptoms
- experiencing some feelings of fullness with the extra nutrition

Your participation is voluntary, and your medical care will not be affected by whether you decide to participate or not. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

How can I find out more?

If you require further information or have any problems concerning this project, please contact the principle investigator, Teresa Brown on 3646 7995 (Dept Nutrition & Dietetics 3646 7997).

Office	Postal	Phone	Fax
Butterfield St Herston Q 4006	Post Office RBWH Queensland 4029	07 3636 8111 ISD + 61 7 3636 8111	07 3636 4240

If you would like to know the results of the project, please let the research dietitian know. They will record your name and address, and we will send a summary of the project results when they are available.

The Ethical Conduct of this Research

This study has been reviewed and approved by the Royal Brisbane & Women's Hospital Human Research Ethics Committee. Should you wish to discuss the study in relation to your rights as a participant, or should you wish to make an independent complaint, you may contact the Coordinator or Chairperson, Human Research Ethics Committee, Royal Brisbane & Women's Hospital, Herston, Qld, 4029 or telephone (07) 3646 5490, email: RBWH-Ethics@health.qld.gov.au.

Privacy Statement

The conduct of this research involves the collection, access and/or use of your identified personal information. The information collected is confidential and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. A de-identified copy of this data will be used for purpose of publishing research results. Your anonymity and confidentiality will at all times be safeguarded.

Office	Postal	Phone	Fax
Butterfield St Herston Q 4006	Post Office RBWH Queensland 4029	07 3636 8111 ISD + 61 7 3636 8111	07 3636 4240

Metro North Health Service District

Enquiries to: Teresa Brown
Phone: 07 3646 7995
Fax: 07 3646 1874

Participant Information and Consent Form
Version 4, Dated 22 June 2012

EARLY TUBE FEEDING IN H&N CANCER

Principal Researcher(s): Teresa Brown, Dept Nutrition & Dietetics, A/Prof Judith Bauer, University of Queensland, Dr Merrilyn Banks, Dept Nutrition & Dietetics, Dr Brett Hughes, Cancer Care Services

Associate Researcher: Dr Liz Kenny, Cancer Care Services Dr Charles Lin, Cancer Care Services

---

I have read, or have had read to me, and I understand the Participant Information version ..... dated.....

I freely agree to participate in this project according to the conditions in the Participant Information.

I will be given a copy of the Participant Information and Consent Form to keep.

The researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

Participant's Name (printed) .....

Signature Date

Declaration by research assistant and witness: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Research assistant's name (printed) .....

Signature Date

If participant is not able to consent for themselves, impartial witness is then required.

Witness name (printed) .....

Signature Date

Office	Postal	Phone	Fax
Butterfield St Herston Q 4006	Post Office RBWH Queensland 4029	07 3636 8111 ISD + 61 7 3636 8111	07 3636 4240

11.7 Appendix G: Nutrition Assessment Tool – PG-SGA

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID Information

History (Boxes 1-4 are designed to be completed by the patient.)

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____ kg
I am about _____ cm tall

One month ago I weighed about _____ kg
Six months ago I weighed about _____ kg

During the past two weeks my weight has:
☐ decreased (1) ☐ not changed (0) ☐ increased (0)

Box 1 ☐

2. Food Intake: As compared to my normal intake, I would rate my food intake during the past month as:
☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (1)
I am now taking:
☐ *normal food* but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritonal supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0)

Box 2 ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):
☐ no problems eating (0)
☐ no appetite, just did not feel like eating (3)
☐ nausea (1)
☐ vomiting (3)
☐ constipation (1)
☐ diarrhea (3)
☐ mouth sores (2)
☐ dry mouth (1)
☐ things taste funny or have no taste (1)
☐ smells bother me (1)
☐ problems swallowing (2)
☐ feel full quickly (1)
☐ pain; where? (3)_____
☐ other** (1) _____

** Examples: depression, money, or dental problems

Box 3 ☐

4. Activities and Function: Over the past month, I would generally rate my activity as:
☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
☐ pretty much bedridden, rarely out of bed (3)

Box 4 ☐

Additive Score of the Boxes 1-4 ☐ **A**

The remainder of this form will be completed by your doctor, nurse, or therapist. Thank you.

5. Disease and its relation to nutritional requirements *(See Worksheet 2)*

All relevant diagnoses (specify) _____

Primary disease stage (circle if known or appropriate) I II III IV Other _____

Age _____

Numerical score from Worksheet 2 ☐ **B**

6. Metabolic Demand *(See Worksheet 3)*

Numerical score from Worksheet 3 ☐ **C**

7. Physical *(See Worksheet 4)*

Numerical score from Worksheet 4 ☐ **D**

Global Assessment *(See Worksheet 5)*
☐ Well-nourished or anabolic (SGA-A)
☐ Moderate or suspected malnutrition (SGA-B)
☐ Severely malnourished (SGA-C)

Total PG-SGA score
(Total numerical score of A+B+C+D above) ☐
(See triage recommendations below)

Clinician Signature _____ RD RN PA MD DO Other ___ Date _____

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage). First line nutrition intervention includes optimal symptom management.

0-1	No intervention required at this time. Re-assessment on routine and regular basis during treatment.
2-3	Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and laboratory values as appropriate.
4-8	Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms survey (Box 3).
≥ 9	Indicates a critical need for improved symptom management and/or nutrient intervention options.

Worksheets for PG-SGA Scoring

Boxes 1-4 of the PG-SGA are designed to be completed by the patient. The PG-SGA numerical score is determined using 1) the parenthetical points noted in boxes 1-4 and 2) the worksheets below for items not marked with parenthetical points. Scores for boxes 1 and 3 are additive within each box and scores for boxes 2 and 4 are based on the highest scored item checked off by the patient.

Worksheet 1 - Scoring Weight (Wt) Loss

To determine score, use 1 month weight data if available. Use 6 month data only if there is no 1 month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point score in Box 1 of the PG-SGA.

Wt loss in 1 month	Points	Wt loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10 -19.9%
3-4.9%	2	6 - 9.9%
2-2.9%	1	2 - 5.9%
0-1.9%	0	0 - 1.9%

Score for Worksheet 1 ☐
Record in Box 1

Worksheet 2 - Scoring Criteria for Condition

Score is derived by adding 1 point for each of the conditions listed below that pertain to the patient.

Category	Points
Cancer	1
AIDS	1
Pulmonary or cardiac cachexia	1
Presence of decubitus, open wound, or fistula	1
Presence of trauma	1
Age greater than 65 years	1

Score for Worksheet 2 = ☐
Record in Box B

Worksheet 3 - Scoring Metabolic Stress

Score for metabolic stress is determined by a number of variables known to increase protein & calorie needs. The score is additive so that a patient who has a fever of > 102 degrees (3 points) and is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	>99 and <101	≥101 and <102	≥102
Fever duration	no fever	<72 hrs	72 hrs	> 72 hrs
Corticosteroids	no corticosteroids	low dose (<10mg prednisone equivalents/day)	moderate dose (≥10 and <30mg prednisone equivalents/day)	high dose steroids (≥30mg prednisone equivalents/day)

Score for Worksheet 3 = ☐
Record in Box C

Worksheet 4 - Physical Examination

Physical exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid status. Since this is subjective, each aspect of the exam is rated for degree of deficit. Muscle deficit impacts point score more than fat deficit. Definition of categories: 0 = no deficit, 1+ = mild deficit, 2+ = moderate deficit, 3+ = severe deficit. Rating of deficit in these categories are *not* additive but are used to clinically assess the degree of deficit (or presence of excess fluid).

Fat Stores:				
orbital fat pads	0	1+	2+	3+
triceps skin fold	0	1+	2+	3+
fat overlying lower ribs	0	1+	2+	3+
Global fat deficit rating	0	1+	2+	3+

Muscle Status:				
temples (temporalis muscle)	0	1+	2+	3+
clavicles (pectoralis & deltoids)	0	1+	2+	3+
shoulders (deltoids)	0	1+	2+	3+
interosseous muscles	0	1+	2+	3+
scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3+
thigh (quadriceps)	0	1+	2+	3+
calf (gastrocnemius)	0	1+	2+	3+
Global muscle status rating	0	1+	2+	3+

Fluid Status:				
ankle edema	0	1+	2+	3+
sacral edema	0	1+	2+	3+
ascites	0	1+	2+	3+
Global fluid status rating	0	1+	2+	3+

Point score for the physical exam is determined by the overall subjective rating of total body deficit.

No deficit	score = 0 points
Mild deficit	score = 1 point
Moderate deficit	score = 2 points
Severe deficit	score = 3 points

Score for Worksheet 4 = ☐
Record in Box D

Worksheet 5 - PG-SGA Global Assessment Categories

	Stage A	Stage B	Stage C
Category	Well-nourished	Moderately malnourished or suspected malnutrition	Severely malnourished
Weight	No wt loss OR Recent non-fluid wt gain	~5% wt loss within 1 month (or 10% in 6 months) OR No wt stabilization or wt gain (i.e., continued wt loss)	> 5% wt loss in 1 month (or >10% in 6 months) OR No wt stabilization or wt gain (i.e., continued wt loss)
Nutrient Intake	No deficit OR Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms	None OR Significant recent improvement allowing adequate intake	Presence of nutrition impact symptoms (Box 3 of PG-SGA)	Presence of nutrition impact symptoms (Box 3 of PG-SGA)
Functioning	No deficit OR Significant recent improvement	Moderate functional deficit OR Recent deterioration	Severe functional deficit OR recent significant deterioration
Physical Exam	No deficit OR Chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of SQ fat &/or muscle mass &/or muscle tone on palpation	Obvious signs of malnutrition (e.g., severe loss of SQ tissues, possible edema)

Global PG-SGA rating (A, B, or C) = ☐

11.8 Appendix H: Quality of Life Assessment Tools – EORTC

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - H&N35

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

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

Please go on to the next page

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

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

11.9 Appendix I Patient PEG Diary – example page

DATE OF DIETITIAN APPOINTMENT……..RADIATION #.....

RECOMMENDED DAILY FEEDS BY DIETITIAN = ...PER DAY

Main reason this week for using PEG **(tick one only)**	Using PEG as part of study □	Poor appetite/ no taste □
	Pain on eating and drinking □	Difficulty chewing/swallowing □
	Nausea □	Easier than cooking/shopping □
	Other – please state	

Please complete the chart below from the day you see the dietitian until your appointment the following week. If it is your last week, please discuss with the dietitian the best way to return your final weeks' diary.

DAY	DATE	Tick box for each PEG feed you have each day								Total feeds per day	Reasons you are unable to have the recommended amount e.g. too full, nausea, no time, too tired, constipation etc.
1											
2											
3											
4											
5											
6											
7											
You should have your next appointment with the dietitian by now. If not, please continue to keep the diary until your next appointment. Add extra lines if required.											
8											
9											
10											
11											

PLEASE BRING THIS SHEET TO YOUR DIETITIAN APPOINTMENT