Improving Dysphagia Quality of Life Outcomes in Patients Receiving Head and Neck Radiotherapy.

Nigel James Anderson

Bachelor Applied Science (Human Biology)

Bachelor of Medical Radiations Science (Radiation Therapy)

A thesis submitted for the degree of Doctor of Philosophy at

Monash University in 2019

Faculty of Medicine, Nursing and Health Sciences

Copyright notice

Conflict of interest

I, or any of the authors, have no actual or potential conflicts of interests arising from any studies undertaken that contribute to this thesis.

Table of Contents

Abstract

This thesis is comprised of a number of studies looking to better understand the debilitating effects of radiation induced dysphagia in head and neck cancer (HNC) patients.
Radiotherapy plays a critical role in the management of HNC, used as a primary modality, or often in combination with surgical and chemotherapeutic options. Dysphagia, best described as a difficulty in swallowing, is often a consequence of high dose radiation therapy. It is often further exacerbated when combined with toxic chemotherapeutic regimes.
Both acute and late dysphagia can compromise the clinical outcomes of HNC patients, with respect to control of their disease and ongoing, life-limiting toxicities. The opportunity to better understand dysphagia, its debilitative effects, and how to ultimately manage its onset is critical to achieving the optimal outcome for each HNC patient.

Early prediction of the onset of radiation-induced toxicities, in particular dysphagia, gives the patient and their clinical team the best chance of personalised, supportive care interventions. The first of the studies in this thesis (Chapter 3) investigated the validity of universally used late dysphagia dose/volume/outcome predictive metrics in the acute setting. At the time, little to no work had been undertaken in this space. Management of acute toxicities is not only paramount in ensuring the patient is capable of completing their intended course of treatment, but critical in facilitating the delivery of precision radiotherapy. The findings of Chapter 3 demonstrate a significant correlation between the late and acute dysphagia metrics. There was a significant reduction in the incidence of acute grade 3 toxicity across a number of QUANTEC reported guidelines for late toxicity. Larynx V50Gy < or > 27% group at week 5 (14.3% vs 45.2%, p=0.01) and 6 (25.9%, vs 65.9%, p<0.01) and Dmean <44Gy or > 44Gy at week 5 (14.7% vs 50.0, p=0.02) and 6 (32.4% vs 67.6%, p=0.01) presented a significant reduction in acute dysphagia, as did Dmean<40Gy or >40Gy (week 5: 5.6% vs 42.3%, p<0.01; week 6:23.5% vs 59.3%, p=0.01). A significant toxicity reduction at treatment week 6 (28.0% vs 63.0%, p=0<01) was seen from Dmax <66Gy to Dmax >66Gy.

Chapters 4 and 5 undertook a comprehensive review of a HNC patient radiotherapy cohort. Both studies looked to derive key variables that could be used to predict for a widely used surrogate of radiation induced dysphagia- enteral feeding. Chapter 4 uncovered both T-classification and level 2 lymphadenopathy as significant predictors of prolonged feeding tube dependence. Level 2 lymphadenopathy as a clinical predictor was a novel finding and has not previously been reported. These two clinical variables were subsequently used to develop a feeding tube risk stratification model, to assist in the identification of both high-risk patients at greatest need of dietetics and speech pathology intervention, and low-risk patients who don't require a feeding tube who may otherwise have one inserted. Patients presenting with neither of these variables had a mean feeding tube use of seven (0-59) days. Those with T-classification ≤ 2 and level 2 lymphadenopathy, T-classification ≥ 3 and No level 2-lymphadenopathy, and T-classification ≥ 3 and level 2-lymphadenopathy fed for a mean of 75 (56-90), 108 (68-173) and 170 (113-295) days, respectively.

Chapter 5 further extrapolated this analysis to include critical swallowing anatomy, and in particular, inadvertent dose that would further exacerbate risk of prolonged feeding tube use. Dose to cervical oesophagus (D50 > 36Gy), base of tongue (D50 > 61Gy) and superior pharyngeal constrictor muscle (D50 > 61Gy) were all deemed significantly important to varying levels.

Multivariate analysis showed T-classification ≥ 3 and level II lymphadenopathy as independent significant predictors of incidence and duration of feeding tube use in oral cavity, pharyngeal and supraglottic primaries. The mean dose deposited in the cervical oesophagus over 36Gy further increased the incidence and duration of feeding tube use. The mean dose deposited in the base of tongue and superior pharyngeal constrictor muscles affected incidence and duration of feeding tube use, respectively.

This created another layer of certainty to the already derived clinical variables, which remained significant predictors of feeding tube use, despite the presence of dosimetric variables.

Chapter 6 delved further into the objective measures of patient dysphagia, quantifying weight loss in each of the feeding tube risk stratified groups derived in Chapter4. Interestingly, at a low-intermediate risk (LIRi) of prolonged feeding tube use were those who lost significantly more weight than high-risk (HRi) and high-intermediate-risk (HIRi) counterparts (HRi=4.8% v LIRi=8.2%, p=0.002; HIRi=5.2% v LIRi=8.2%, p=0.006) Further investigations revealed that this group compromised a significantly higher incidence of patients with oropharyngeal carcinoma (OPC) (HRi: 71%, HIRi: 52%, LIRi: 81%, p=0.008) demonstrating a positive HPV status (88%, p=0.001), in combination with clinical features increasingly recognisable in this cohort i.e. younger, no history of smoking or alcohol abuse, and no pre-existing comorbidities. The findings from Chapter 6 add another layer of information to support the risk stratification tool of Chapter 4.

The works described in each of the chapters culminates into a body of work that is particularly relevant in the management of modern HNC. The incidence of HPV-associated HNC is rapidly growing, with the findings of this thesis providing some valuable insight into the optimal management of this distinctly different population. This thesis poses as many questions as it provides answers, yet provides a critical body of evidence to support a patient population that will demand a significant proportion of our multidisciplinary resources in the coming decades.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature: ……..……

Print Name: Nigel James Anderson

Date: 30th July 2019

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original papers published in peer reviewed journals. The overarching theme of this document/thesis is investigating acute and late dysphagia toxicities in patients undergoing a course of radiotherapy for the management of squamous cell carcinoma of the head and neck. Furthermore, there is a detailed focus on the optimal management of these patients through the development of predictive tools to guide clinical decision making with respect to optimal nutritional support pathways. The ideas, development and writing of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Faculty of Medicine, Nursing and Health Sciences under the supervision of Professor Michal Schneider; at the Olivia Newton-John Cancer Wellness and Research Centre under the supervision of Dr Morikatsu Wada; and at the Royal Marsden Hospital (London, UK) under the supervision of Dr Vincent Khoo.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers, with complementary clinical and technical skillsets, and acknowledges input into team-based research.

In the case of Chapters 3, 4, 5, 6, my contribution to the work involved the following:

Thesis Chapter	Publication title	Publication status	Nature and extent (%) of students contribution	Co-author names Nature and % of Co-author's contribution	Co-authors, Monash student Y/N
3	Dose Volume Response in Acute Dysphagia Toxicity: Validating QUANTEC Recommendations into Clinical Practice for Head and Neck Radiotherapy	Published	90% of data analysis, 90% of concept, design, data interpretation and manuscript writing, 100% of study conduct, data generation, and data collection.	Wada, input into manuscript; Schneider, data analysis input into manuscript; Rolfo, input into manuscript; Lim Joon, input into manuscript; Khoo, input into manuscript	N
4	Pre-treatment Risk Stratification of Feeding Tube Use in Patients Treated with IMRT for Head and Neck Cancer	Published (shared first authorship with James Jackson)	50% of data analysis, 50% of concept, design, data interpretation and manuscript writing, 50% of study conduct, data generation, and data collection	Jackson, data analysis, concept, design, data interpretation and manuscript writing, study conduct, data generation, and data collection; Smith, data analysis, input into manuscript; Wada, input into manuscript; Schneider, input into manuscript; Michael Poulsen, input into manuscript; Rolfo, input into manuscript; Fahandej, input into manuscript; Gan, input into manuscript; Lim Joon, input into manuscript; VKhoo, input into manuscript.	Y
5	Clinical and dosimetric risk stratification for patients at high-risk of feeding tube use during definitive IMRT for head and neck cancer	Submitted to Oral Oncology, June 2019 (shared first authorship with James Jackson)	50% of data analysis, 50% of concept, design, data interpretation and manuscript writing, 50% of study conduct, data generation, and data collection	Jackson, data analysis, concept, design, data interpretation and manuscript writing, study conduct, data generation, and data collection; Smith, data analysis, input into manuscript; Wada, input into manuscript; Schneider, input into manuscript; Poulsen, input into manuscript; Rolfo, input into	Y

				manuscript; Fahandej, input into manuscript; Gan, input into manuscript; Lim Joon, input into manuscript; VKhoo, input into manuscript.	
6	Increased, On-treatment Weight Loss Despite a Decreased Risk of Prolonged Feeding Tube Use: The Changing Landscape of Head and Neck Cancer Radiotherapy Patients	Published	100% of data analysis, 100% of concept, design, data interpretation and manuscript writing, 100% of study conduct, data generation, and data collection.	Jackson, input into manuscript; Wada, input into manuscript; Schneider, input into manuscript; Poulsen, input into manuscript; Rolfo, input into manuscript; Fahandej, input into manuscript; Gan, input into manuscript; Lim Joon, input into manuscript; Khoo. input into manuscript.	Y

Student signature:

……

Date: 30th July 2019

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student and co-authors' contributions to this work.

Main Supervisor signature:

……

Date: 30th July 2019

Publications during PhD enrolment

Chapter 3 (Anderson, First Author):

Nigel J Anderson, Morikatsu Wada, Michal Schneider, Maureen Rolfo, Daryl Lim Joon; Vincent Khoo.

Dose Volume Response in Acute Dysphagia Toxicity: Validating QUANTEC Recommendations into Clinical Practice for Head and Neck Radiotherapy

Acta Oncologica 2014 Oct; 53(10): pp 1305-11

Chapter 4 (Anderson & Jackson, Joint First Authors):

Nigel J Anderson, James E. Jackson, Jennifer G Smith, Morikatsu Wada, Michal Schneider, Michael Poulsen MBBS, Maureen Rolfo, Maziar Fahandej, Hui Gan, Daryl Lim Joon, Vincent Khoo.

Pre-treatment Risk Stratification of Feeding Tube Use in Patients Treated with IMRT for Head and Neck Cancer

Head & Neck 2018 Oct; 40(10): pp 2181-2192

Chapter 5 (Anderson & Jackson, Joint First Authors):

James E. Jackson, Nigel J Anderson, Morikatsu Wada, Michal Schneider, Michael Poulsen, Maureen Rolfo, Maziar Fahandej, Hui Gan, Daryl Lim Joon, Vincent Khoo.

Clinical and dosimetric risk stratification for patients at high-risk of feeding tube use during definitive IMRT for head and neck cancer

Oral Oncology, Submitted June 2019

Chapter 6 (Anderson, First Author):

Nigel J Anderson, James E. Jackson, Morikatsu Wada, Michal Schneider, Michael Poulsen, Maureen Rolfo, Maziar Fahandej, Hui Gan, Daryl Lim Joon, Vincent Khoo.

Increased, On-treatment Weight Loss Despite a Decreased Risk of Prolonged Feeding Tube Use: The Changing Landscape of Head and Neck Cancer Radiotherapy Patients

Journal of Medical Radiation Sciences, 2019, In Press (accepted for publication, July 2019)

Acknowledgements

The countless hours dedicated to the compilation of this thesis and its carefully planned chapters could not have taken place without the support and guidance of many amazing people. I can't thank each of them enough for their support in helping me achieve this milestone.

To my three supervisors, your support has been tremendous. Professor Michal Schneider, whose guidance, wisdom and honesty has made this journey both rewarding and enjoyable. Dr Morikatsu Wada, whose clinical expertise in the field of head and neck radiation oncology has been critical to the undertaking of this work in an ever-evolving field. Dr Vincent Khoo, whose vision, support and wealth of clinical, academic and research experience has provided clear direction over the many years of this thesis' undertaking.

Dr Jennifer Smith, who provided clear and concise direction in the application of complicated statistical analyses.

To my good friend and colleague, Jim Jackson. We've spent many, many hours combining our complementary skillsets to generate this significant body of work that will no doubt change the way head and neck patients are managed for the better. I look forward to seeing where this work takes us and our profession in the coming years.

Thank you to the radiation therapy teams at both the Olivia Newton-John Cancer Wellness and Research Centre and Peter MacCallum Cancer Centre for your direction, peer review and clinical back fill to support my endeavours of my research over the last 8 years.

I would also like to acknowledge the support from other members of the multidisciplinary team radiation oncology division within Austin Health Radiation Oncology- Dr Daryl Lim Joon, Dr Maziar Fahandej, Dr Hui Gan, Kate Kaegi, Fiona Sneyd, Michelle Cimoli and Trish Jenkins- who were instrumental in their contribution to vast aspects of this work.

In particular, I would like to acknowledge the unbelievable support of my friend and colleague, Ms Maureen Rolfo, who has been unwavering in her support of myself throughout

my entire career and the duration of this thesis, especially during some challenging times in 2014.

I would also like to thank my three beautiful children- Aidan, Lea and Jake- for your understanding when you really didn't understand why Dad was locked away in the study for long periods of time over a number of years.

Finally, there is one remarkable human being, who without her support, I would never be able to achieve what I have. Lisa Anderson has been there every step of the way, as a wife and mother to our three children, supporting me to reach this milestone. I couldn't have done this without your love and support and for that I'll be forever indebted to you.

Abbreviations

AACRT	Asia-Australasia Conference of Radiological Technologists
AEI	Adequacy of Enteral Intake
AJCC	American Committee on Cancer
ASCO	American Society of Clinical Oncology
ASMIRT	Australian Society of Medical Imaging and Radiation Therapy
ASMMIRT	Annual Scientific Meeting of Medical Imaging and Radiation Therapy
ASTRO	American Society for Radiation Oncology
BMI	Body Mass Index
BMJ	British Medical Journal
CECT	Contrast Enhanced Computed Tomography
CI	Confidence Intervals
CMS	Computerised Medical Systems
CRT	Chemo-radiation therapy
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DARS	Dysphagia/Aspiration at risk structures
DNA	Deoxyribonucleic acid
DVO	Dose/Volume/Outcome
ECOG	Eastern Cooperative Oncology Group
EGFR	Estimated Glomerular Filtration Rate
EORTC	European Organisation for Research and Treatment of Cancer
ESTRO	European Society for Radiotherapy & Oncology
FDG	Fluorodeoxyglucose
FEES	Fibreoptic Endoscopic Evaluation of Swallowing
FT	Feeding Tube
GORTEC	Phase III randomized trial of very accelerated radiation therapy compared with conventional radiation therapy in squamous cell head and neck cancer
GTV	Gross Tumour Volume
HIRi	High-Intermediate Risk (of prolonged Feeding Tube Use)

HN	Head and Neck
HPV	Human Papilloma Virus
HRi	High Risk (of prolonged Feeding Tube Use)
IAEA	International Atomic Energy Agency
ICCR	International Conference on the Use of Computers in Radiation Therapy
IGRT	Image Guided Radiation Therapy
IMRT	Intensity Modulated Radiation Therapy
IQR	Interquartile Range
ISRRT	International Society of Radiographers and Radiological Technologist
JCO	Journal of Clinical Oncology
LIRi	Low-Intermediate Risk (of prolonged Feeding Tube Use)
LRi	Low Risk (of prolonged Feeding Tube Use)
MDADI	M. D. Anderson Dysphagia Inventory
MO	Missouri
MPCM	Middle Pharyngeal Constrictor Muscle
MR	Median Rank
MRI	Magnetic Resonance Imaging
MV	Megavoltage
NCI	National Cancer Institute
NEMICS	North Eastern Melbourne Integrated Cancer Service
NGT	Nasogastric Tube
NHS	National Health Service
NS	Nutritional Status
NTCP	Normal Tissue Complication Probability
OAR	Organ at Risk
OO	Oral Oncology
OPC	Oropharyngeal Carcinoma
OR	Odds Ratio
PAEC	Pakistan Atomic Energy Commission
PARSPORT	Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer
PCM	Inferior Pharyngeal Constrictor Muscle
PCM	Pharyngeal Constrictor Muscle

PEG	Percutaneous Endoscopic Gastrostomy
PET	Positron Emission Tomography
PG-SGA	Patient-Generated Subjective Global Assessment
PORT	Post-operative Radiation Therapy
POS	Pharyngeal/oesophageal stricture
PRO	Patient Reported Outcome
PSS-HN	Performance Status Scale for Head and neck cancer
PTV	Planning Target Volume
QC	Quality Control
QLQ	Quality of life questionnaire
QoL	Quality of Life
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SGL	Supraglottic Larynx
SIB	Simultaneous Integrated Boost
SPCM	Superior Pharyngeal Constrictor Muscle
SPSS	Statistical Package for the Social Sciences
TCP	Tumour Control Probability
TNM	Tumour/Nodal/Metastases
TPS	Treatment Planning System
TROG	Trans-Tasman Radiation Oncology Group
UAE	United Arab Emirates
UK	United Kingdom
USA	United States of America
VF	Video Fluoroscopy

List of Figures

List of Tables

Chapter 1: Introduction

1.1 Incidence and mortality of head and neck cancer

Squamous cell carcinoma (SCC) of the head and neck presents as the sixth most common malignancy amongst all cancers diagnosed globally.[1, 2] Head and neck malignancies primarily originate in the upper aero-digestive tract, and more specifically, in the mucosa of the oral cavity, oropharynx, larynx, hypopharynx and nasopharynx. Additionally, head and neck malignancies may further originate in the paranasal sinus, salivary glands, and on occasion, present in the neck as SCC that are of an unknown primary origin.

While one third of patients present with limited, early stage disease, the large majority of patients will present with locally advanced disease at their initial cancer diagnosis including metastases into adjacent lymph nodes.[3] This has led to largely stagnant survival outcomes over a significant period of time, with only 40-50% of those diagnosed living beyond five years.[4] These relatively poor survival outcomes can be attributed to loco-regional recurrences, distant metastases and second sites of primary disease.

In recent years, human papilloma virus (HPV) infection has emerged as a significant risk factor for head and neck SCC, with incidence of HPV-associated cancers of the oropharynx growing considerably at the expense of more traditional risk factors, such as alcohol and tobacco abuse.[4] Early data suggests that HPV-associated head and neck cancers are associated with improved survival outcomes.[5] With incidence of HPV-associated malignancies forecast to significantly increase in the immediate and short term, head and neck cancer mortality will improve, underlining the importance of improved survivorship pathways for these patients beyond cure.

1.2 Development of head and neck cancer

With more than 95% of SCC origin, head and neck malignancies appear, on the surface, to present as a relatively homogenous disease type.[4] Despite this, head and neck cancers are in fact one of extreme heterogeneity. The two genetic subclasses of HPV-negative and HPV-positive disease can be further stratified at the histological level. Such heterogeneity has hindered personalised diagnosis and prognostications, potentially leading to suboptimal treatment pathways and ultimately, the relatively poor outcomes we see in head and neck cancer patients.

However, despite this sub-classified heterogeneity, the discovery of HPV associated SCC has been a critical game changer in the understanding of the aetiology of head and neck cancer, and subsequent therapeutic strategies. Cases of oropharyngeal carcinoma that were traditionally attributed to increasing age and excessive use of alcohol and/or tobacco are now further stratified into a HPV-positive disease cohort associated with a younger patient demographic and with a history of changing sexual habits, with little to no history of substance abuse. The improved prognosis of this cohort has led to significant changes in the way these patients are managed. This increase in HPV-associated cancers is rapidly increasing with the availability of specialised DNA testing, which in turn, is further exacerbated by the decrease in HPV-negative tumour types due to the reduction in tobacco use in the Western world.

1.3 Presentation of head and neck cancer

Disease origin will play a significant role in the presenting symptoms of a head and neck cancer patient. Patients presenting with laryngeal cancers will most frequently present with hoarseness, caused by the obstruction of vocal structures by the infiltrating malignancy. Where a cancer of the pharyngeal axis is present, patients will often present with persistent dysphagia.[6] Unilateral ear pain and painless neck nodes are also characteristic of a newly

presenting head and neck cancer patient. Well established practice guidelines detail common presenting symptoms that are, generally, persistent for in excess of three weeks, to maximise the opportunity for preliminary diagnosis leading to further diagnostic interventions for a head and neck cancer.[6]

Additionally, as we look to further stratify the presentation of specific disease sub-types, patients with HPV-associated oropharyngeal carcinoma more commonly report with neck lymphadenopathy as a presenting symptom, compared to the primary disease related symptoms of HPV-negative patients, including sore throat, dysphagia, and/or odynophagia.[7]

1.4 Staging of head and neck cancer

Patients presenting with suspicious lesions of the oral mucosa and any of the afore mentioned symptoms are recommended to undergo a number of clinical investigations to confirm and subsequently stage their cancer.[8] Physical examination of the entire neck and oral cavity, looking for suspicious nodes and lesions, respectively, should take place in the first instance.

Computed tomography (CT) provides preliminary diagnostic information regarding the size and location of the primary tumour, combined with the extent of nodal (if any) disease. Magnetic resonance imaging (MRI) is further indicated in circumstances of dental artefact interference, or when soft tissue extension is not definitive in CT (i.e. primary tumour extension in nasopharyngeal carcinoma).

The extent of locally advanced and distant nodal metastasis can be better understood via the use of positron emission tomography-computed tomography (PET-CT), together with ultrasound guided fine needle biopsy into regions of suspicious nodal activity. Fine needle biopsy provides cytological confirmation of nodal disease, and can also provide an appropriate sample for immunohistochemistry, to identify p16 expression and subsequent tumour HPV status- an indication of HPV DNA transcription.[9] Understanding HPV status plays a crucial role in disease staging and the development of subsequent management strategies.

Tumour (T), Nodal (N) and Metastases (M), traditionally referred to as the TNM staging system, has long been the recommended clinically staging tool for SCC of the head and neck. The American Joint Committee on Cancer (AJCC) Staging Manual (Eighth Edition) details each level.[10] Recent modifications, to reflect current practice in head and neck cancer diagnosis, further incorporate oral cavity depth invasion, HPV status determined by immune-histochemical staining, and extra-nodal extension as critical staging parameters.[11]

1.5 Treatment of head and neck cancer

Surgery and radiotherapy remain the modalities of choice in the primary care of early stage and locally advanced SCC of the head and neck cancer. Additionally, chemotherapy and targeted therapies, such as anti-EGFR monoclonal antibody Cetuximab, have contributed to improved survival outcomes in those with locally advanced disease when compared to surgery or radiotherapy in isolation.[12, 13] Surgery, with or without post-operative radiotherapy, remain the pillars of advanced disease management. Radiotherapy can also be delivered in conjunction with induction, concurrent and adjuvant chemotherapy regimens.

The technological capability to deliver an increased precision in head and neck radiotherapy has improved considerably in recent years, with the ability to integrate highly targeted dose sculpting into treatment planning.[14] We have witnessed a rapid progression from three-dimensional conformal radiation therapy to intensity modulated techniques across the duration of this thesis. Modulated arc treatments are now the standard of care in a large majority of clinical centres providing head and neck radiotherapy.

Modern head and neck cancer management pathways now equally consider both tumour control probability and treatment related toxicities, and their impact on quality of life beyond treatment. Greater understanding of radio-therapeutic interventions will considerably contribute to this knowledge base as head and neck cancer survivorship increases.

1.6 Purpose of this thesis

The purpose of this thesis is to investigate current radiotherapy practice in the management of head and neck cancers, to better understand treatment related dysphagia and the subsequent impact of our care on the patient's nutritional habits. Chapter 3 addresses recommendations for predicting late dysphagia that are indicative of modern practice (Quantitative Analyses of Normal Tissue Effects in the Clinic or QUANTEC), in an attempt to validate whether these dose/volume/outcome recommendations can act as a viable end-point in the prediction of acute dysphagia toxicity. It is such toxicity that will often compromise the quality of radiotherapy that can be delivered, and ultimately, the patient outcome.

Recognising the role of current guidelines in driving clinical practice, the thesis aims to revolutionise the approach to individualised patient care via the development of a feeding tube predictive model to be applied to future head and neck cancer radiotherapy patients. Feeding tubes are critical to optimal patient weight management throughout and beyond their care, to ensure precision radiotherapy is attained, and equally important, patient welfare is maintained throughout and following their care. Chapters 4 and 5 present the development and presentation of a novel feeding tube stratification tool, used to assist in identification of patients at high risk of prolonged feeding tube use. These tools will complement good clinical judgement, to ensure optimal supportive care pathways are instigated based on evidence-based practice.

Finally, Chapter 6 draws on the novel findings of earlier chapters, with the aim of providing currency of this work to the modern-day head and neck cancer patient. The explosion of HPV-associated head and neck cancers has occurred concurrently with the development of this thesis. An opportunity to give relevance to the already developed risk stratification tool provides an exciting opportunity to highlight the importance of this body of work in driving

practice change in the management of head and neck radiotherapy patients, now and into the foreseeable future.

Chapter 2: Literature Review

This chapter represents a comprehensive review of the management of radiation induced dysphagia based on the available literature until late 2013.

An update to the review based on literature published between 2014 and December 2018 has been included in section 2.8.

2.1 Introduction

Radiotherapy forms an integral part of the multidisciplinary approach to the treatment of head and neck cancer, and is a proven modality in improving local regional control and survival outcomes.[15, 16] Significant advances in radiotherapy treatment delivery technology have enabled unprecedented treatment intensification to this particular patient group.[17] This has enabled greater survival outcomes, yet often at the expense of increased acute and late treatment induced toxicities.[18] Outcomes pertinent to mucositis, odynophagia and dysphagia were also reported, highlighting the growing trend toward late toxicity awareness associated with improved survival outcome data.[19-21]

The addition of concurrent chemotherapy as the standard of care for head and neck cancer patients has seen an increase of radiation-induced dysphagia in both the acute and late setting. Early data reported significant increases in the incidence of dysphagia with the addition of chemotherapy, reporting an increase in dysphagia from 9% to 23% in chemo-radiation patients with laryngeal cancer when compared to radiation alone post induction chemotherapy. Persistent dysphagia among almost 50% patients was reported in a study of 55 patients in the United States which resulted in poor nutritional status, percutaneous endoscopic gastrostomy (PEG) tube dependence and aspiration pneumonia.[22, 23] In one study, 51% of patients had dysphagia that persisted for two years after chemo-radiation.[24] More recent literature further supports a high incidence of long-term dysphagia in patients receiving chemo-radiation.[25, 26] The Alabama group reported an incidence of 38.5% in those treated with chemo-radiation.[26]

Findings from the early 1990's reported that dysphagia and subsequent weight loss during treatment can have a detrimental effect on survival.[27] While the reporting of dysphagia and radiation induced swallowing complications is common, few clinical studies (until the early part of the last decade) have focused on swallowing dysfunction and its subsequent causes, and have focused mainly on survival data.[28] A subsequent review paper revealed that only 12% of head and neck squamous cell carcinoma studies reported on dysphagia outcomes, and 3% reported outcomes pertaining to the efficacy of enteral nutrition in the management of head and neck radiotherapy patients.[20]

The complex nature of the swallowing mechanism (which will be discussed in more detail later), with its intricate relationship between multiple voluntary and involuntary muscles and nerve pathways has been described in numerous publications.[29-31] The adverse effect to the swallowing mechanism, through the use of high dose radiation +/- chemotherapy, has long been recognised as the dose limiting toxicity for this therapeutic regime.[32, 33]

Advances in technology across the past decade for head and neck treatment delivery have facilitated significant change to standard radiotherapy practice. Intensity modulated radiation therapy (IMRT) reduces treatment related toxicities through the creation of steep dose gradients at the target and organ at risk (OAR) interface. Studies comparing past and present treatment planning techniques have reported the dosimetric benefits of IMRT planning.[34, 35] Multiple head and neck IMRT studies have addressed the role of IMRT in improving outcomes, inclusive of dysphagia.[28, 31, 36-38]

These developments in technology have reinvigorated the landscape for head and neck radiotherapy. While dysphagia may still remain an extremely critical dose-limiting toxicity, the profession's ability to understand and manage its causes and subsequent effect, is rapidly improving. This review will summarise the anatomy pertinent to the swallowing mechanism, how dysphagia is identified and measured in patients with head and neck cancer, and how a comprehensive understanding may facilitate dysphagia reduction, or, if not achievable,

optimal management strategies to ensure best possible outcomes for head and neck radiotherapy patients.

2.2 Swallowing Anatomy Delineation, Mechanism and Dysphagia

Understanding the complex anatomy of the swallowing mechanism, and the role of pertinent structures in its efficient coordination, is integral in identifying physiological and anatomical relationships in acute and late dysphagia. Multiple studies have reported on the anatomy of the swallowing mechanism, with one reporting that in excess of 30 pairs of muscles and six cranial nerves are involved in the mechanism.[31] This interpretation is supported by multiple publications.[29, 30]

While identifying the structures responsible for efficient and effective swallowing is important, the correlation of these structures to specific tasks within the mechanism is of utmost importance if knowledge of dysphagia anatomy and physiology is to be determined and understood while patients undergo treatment. Numerous publications provide evidence of radiation induced morbidity of multiple structures responsible for swallowing, including the base of tongue, posterior pharyngeal wall, larynx, vocal cord and upper oesophageal sphincter.[31, 39-44]

A 2013 study identified and discussed the anatomical and physiological changes of structures believed to facilitate radiation induced dysphagia in their editorial.[45] They made early reference to a supporting study that aimed to identify the pertinent muscles involved in active hyolaryngeal elevation- a key functional process required in aspiration prevention. This study, on the basis of functional MRI before and after hyolaryngeal elevation in healthy volunteers, identified the suprahyoid and longitudinal pharyngeal muscles as those crucial to the successful execution of this function.[39] Earlier work further supported these findings. [31] While highlighting the complexity of the swallowing process, the authors described those structures most pivotal to swallowing via post radiotherapy video-fluoroscopy and computed

tomography in patients experiencing late dysphagia toxicity. This study identified the pharyngeal constrictor muscles (PCM- superior, middle and inferior) and the glottis and supraglottic larynx as those structures that were crucial to radiation induced dysphagia. Thickening of the PCM, glottis and supraglottic larynx was reported after chemo-radiation, while not in any other muscles involved in swallowing.[31] Later, MRI-based interpretation of radiation induced damage of the PCM also supported these findings. Comparison of pre and three-months post chemo-radiation demonstrated changes suggestive of oedema and inflammation in the PCM.[40] Muscles that had received lower dose of radiation failed to demonstrate such thickening and did not demonstrate the characteristic increased T2 MRI signal.[40]

The findings of all the afore mentioned studies support the hypothesis that although many muscles involved in the swallowing mechanism receive high doses, it is those that lie directly beneath the mucosa and submucosa (PCM inclusive) that display major functional impairment during and after chemo-radiation, an area primarily affected by the processes responsible for acute mucositis and dysphagia during chemo-radiation.[45] This hypothesis is further supported via studies using FDG-PET identification of laryngeal inflammation and acute pharyngeal constrictor perfusion changes measured via computed tomography during and post chemo-radiation.[41, 42, 46]

More recently, the Groningen group explored a more specific identification of swallowing abnormalities, identifying the middle PCM (MPCM) and superior PCM (SPCM)/supraglottic larynx as pertinent to the swallowing of soft and solid foods respectively; supraglottic larynx for liquids; and supraglottic larynx and oesophageal inlet when assessing subjects most susceptible to choking on swallowing.[47] Studies such as these provide an exciting platform for further individualizing the management of acute and late dysphagia. A more comprehensive understanding of dysphagia and its predictive measures are pivotal in enabling prophylactic measures for greater individualized, supportive input into the care of head and neck patients.

2.3 How is dysphagia measured?

Dysphagia reported endpoints are imperative to consistent, robust evaluation of dysphagia in the clinic. Objective evaluations incorporating instrumental assessment, subjective evaluations requiring observer interpretation, and patient reported quality of life outcomes, have formed the foundation of dysphagia endpoints over an extended period of time.

Video fluoroscopy (VF) has formed the basis of multiple investigations, and involves a modified barium swallow and oesophagography to visualize the oral, pharyngeal, and oesophageal phases of swallowing.[48, 49]

Swallowing dysfunction pre and three months post radiotherapy, via the use of video-fluoroscopy, has been previously evaluated. Anterior-posterior and lateral planes were viewed while subjects were required to ingest foods of varying consistency. Irregularities in timing and duration of the swallow, beyond those of normal controls, were defined. Functional level of numerous structures, namely base of tongue (its contact with posterior pharyngeal wall), laryngeal (elevation and anterior movement), epiglottis (degree of movement from vertical to horizontal) and cricopharyngeus (premature closure) were measured objectively by two speech pathologists.[36]

Manometry and fibreoptic endoscopic evaluation of swallowing (FEES) are alternate measures capable of objective swallowing evaluation. Manometry measures pressures generated in the mouth and pharynx, yet it is more commonly utilized in the oesophagus and "pressures generated by sequential contraction of the esophagus musculature" (p.1220).[50] While providing important information on swallowing physiology, it is quite limited in its application.[50] FEES has the capability of pharynx visualization via transnasal insertion of an endoscopic tube to below the soft palate. The inability to visualize the oral stage of swallowing is a limitation of this procedure.[50] Another study undertook a FEES to understand the dysphagic characteristics of thirty-one nasopharyngeal cancer patients. This technique was used to report on multiple disorders within this patient cohort, in particular within the

pharyngeal phase of swallowing. Pharyngeal retention, post swallow aspiration, atrophic changes to the tongue, vocal cord palsy, velopharyngeal incompetence, delay or absence of the swallow reflex and poor pharyngeal constriction were amongst those dysfunctions measured.[51]

Subjective evaluation of dysphagia as an endpoint is commonly used to compliment an objective evaluation. The 'Common Terminology Criteria for Adverse Events' (CTCAE) was utilized to measure acute toxicity and the RTOG/European Organization for Research and Treatment of Cancer (EORTC) 'Late Radiation Morbidity Scale' to measure late effects from three months after radiation therapy- in addition to the objective VF evaluation.[52] CTCAE endpoints have also been utilized in multiple publications.[41] This EORTC late dysphagia assessment tool has also been used more recently as a primary endpoint of grade 2-4 swallowing dysfunction at six months post chemo-radiation.[47] Swallowing dysfunction at six months post chemo-radiation was utilised due to its value in predicting swallowing dysfunction at subsequent time points of 12, 18 and 24 months.[53]

Patient reported quality of life (QoL) outcomes have been indicative of the true extent of complication in the grading of xerostomia in head and neck radiotherapy.[54, 55] Although their application in the derivation of dysphagia related endpoints is less definitive, QoL measures still play an integral role in reporting of the dysphagia endpoint. Multiple studies have utilised various dysphagia-related QoL questionnaires in their correlation with dose to swallowing structures. [56, 57] Both studies reported a relationship between dosimetric and clinical variables and patient reported measures.

The EORTC H&N35 is a 35-question survey developed with input from participants from more than ten countries. It derives a patient reported scaled answer on topics including pain, swallowing, senses, speech, social eating, social contact and sexuality. In its entirety, a score ranging from 1-100 is accumulated. A higher score is symptomatic of dysphagia, with 10-point changes over time deemed clinically important.[58]

The Performance Status Scale for Head and Neck Cancer (PSS-HN) consists of three clinician rated subscales. Normalcy of diet, understandability of speech and eating in public are each scored on a scale of 1-100. A higher score is indicative of better performance.[59]

The final patient related questionnaire utilized is the M.D. Anderson Dysphagia Inventory (MDADI). A 20-question survey, the MDADI is used to assess how patients view their swallowing function/dysfunction, and how this affects their QoL post chemo-radiation. Like the PSS-HN, a scale of 1-100 is used, with 100 representative of optimal swallowing function and QoL outcomes.[60]

Objective evaluations not involving instrumental intervention (i.e. video-fluoroscopy) have been the subject of review in more recent literature. Patient weight loss and reliance on nutritional interventions provide dysphagia endpoints in multiple publications. One study took a nutritional counselling and needs based intervention approach in their assessment of weight loss and NGT endpoints in their study of 103 patients undergoing treatment for head and neck malignancies. Patient weight loss was recorded pre and post radiation +/- chemotherapy treatment, with weight loss in excess of 5% warranting investigation of potential swallowing complication.[61] Numerous other publications have reported on the prolonged use of nutritional intervention (via percutaneous endogastric (PEG) or nasogastric tube (NGT)) as a dysphagia endpoint.[62-64] Varying clinical and dosimetric endpoints were correlated with prolonged feeding tube use.

2.4 How is dysphagia managed?

Oral nutritional intervention is a requirement for nearly all patients undergoing head and neck radiotherapy, with a reported 50-70% presenting with severely impaired swallowing requiring enteral feeding interventions.[65, 66] Enteral feeding tubes are commonly used in the form of either a NGT or PEG. The choice of feeding tube, and their appropriate timing, and

subsequent effect on weight loss, quality of life and long term functional outcomes, still varies in clinical practice.[67]

PEG tube interventions are routinely utilised in a prophylactic approach to counteract treatment-induced weight loss and dehydration, which have the potential to instigate treatment breaks and adversely affect disease outcomes.[27, 68] The alternative, the NGT, adopts a reactive strategy, in which on-treatment nutritional supplements are utilised for nutritional management during treatment, until a point at which oral supplementation is inadequate to meet the nutritional demands of the patient. This is routinely determined by a patient's inability to meet pre-determined nutritional requirements (i.e. a percentage of one's nutritional requirements received orally) or a given percentage of weight loss.[67]

A critical review, published in 2012, provides a description of the advantages of tube feeding timing in the intervention timeline.[67] They suggest that prophylactic tube insertion promotes better weight preservation and fewer treatment induced hospitalisations, resulting in improved quality of life throughout and post chemo-radiation. Reactive tube insertion is suggestive of lower rates of long-term dysphagia, a shorter duration of PEG dependence, while sparing intervention in those few who don't require this invasive intervention. Reactive tube intervention can take the form of either NGT of PEG.

The review also outlines the benefits of both the NGT and PEG tubes. NGT has the benefits of ease of insertion, lower risk of complication and lower cost. This can be combined with the previously described benefits associated with reactive nutritional interventions. PEG tubes are more aesthetically appealing, and provide for less discomfort and fewer dislodgements. They also harness the prophylactic benefits, as they are most commonly used in this approach.

Two prospective randomized trials have addressed the prophylactic versus reactive question.[69, 70] In a cohort of 39 patients, one compared prophylactic PEG (P-PEG) and reactive PEG (R-PEG), reporting improved QoL outcomes at six months post radiotherapy in

the P-PEG group (p=0.001).[69] The larger of the two trials (N=134) compared P-PEG and reactive NGT. They reported the P-PEG group as using enteral feeding for a significantly longer period of time (177 days vs. 122 days. P<0.0001), yet a reduction in long term dysphagia at one-year post treatment (2% vs. 9%, p=0.047). Improved QoL was reported on a global health scale in the P-PEG group, based on multiple QoL variables (64 points vs. 52, p=0.02).[70] Of particular note was that both studies reported equivalent requirements for reactive intervention (73% v 72%), suggesting prophylactic intervention may have better suited a large number of these reactively managed patients.

Multiple other studies have reported lower rates of treatment-induced hospitalization when a prophylactic management plan has been adopted as opposed to a reactive approach.[71-74]

While the literature presents a strong argument for prophylactic feeding tube insertion, there remains conflicting data that suggests long term feeding outcomes may be hindered by prophylactic management strategies. An Australian group undertook a prospective study comparing PEG and NGT managed patients. They reported that PEG patients had a longer median duration of use (147 vs. 53 days, p<0.001). Furthermore, in disease free survivors, grade 3 dysphagia at six months post chemo-radiation was greater in the PEG managed cohort.[75] These findings have been subsequently supported by a study which investigated the role of prophylactic PEG insertion for head and neck chemo-radiation patients. They reported a significantly higher level of oesophageal stricture in patient with a P-PEG compared to those managed reactively (30% vs. 6%, p<0.001).[76] The before-mentioned review article hypothesised that NGT acts as a stent for the upper oesophagus and hypopharynx. However, this anatomy recovers via swallowing following removal of the NGT. On the other hand, PEG dependent patients avoid swallowing for weeks, which can result in endoscopic intervention to re-open fibrosed tissues post chemo-radiation.[67] Similar outcomes have also been reported, suggesting that P-PEG promotes a longer period of non-oral feeding, leading to the deconditioning of the muscles responsible for deglutition.[77] Both theories give weight to the findings of a later study, who reported that adherence to

swallowing exercises in P-PEG managed patients resulted in a reduction in decreased long term PEG dependence, suggestive of the importance of maintaining function of this musculature during treatment regardless of whether it is being actively used for swallowing or not.[78]

2.5 Radiation dose to swallowing anatomy and predicting dysphagia

Dysphagia endpoints have long been correlated with delivered dose and it is well known that the incidence of radiation induced toxicities is strongly linked to the delivered dose.[79] Acute and late treatment induced toxicities are extremely reliant on the ability of treatment planners to deliver optimal and clinically acceptable three-dimensional (3D) dose distributions. The ability to optimally manage this patient group has a heavy reliance on both prophylactic interventions and management strategies. Understanding expected dose consequences is integral to the development of such strategies on an individual case basis.

The Emami paper from 1991 has formed the basis for modern day dose-volume-outcome (DVO) data, and established the foundation for modern day dose guidance.[80] Inherent dysphagia DVO recommendations were included in this paper. Since then, multiple studies have reported on dose/volume/outcome correlation for numerous critical structures.[36, 46, 81] The QUANTEC series of articles summarizes this updated data, to better refine dose volume recommendations for the radiotherapy planner. With improved DVO data, improved access and effective utilization of more sophisticated planning, delivery and imaging systems, we will have improved capability for precision dose steering and dose deposition.[82]

Radiation induced dysphagia is strongly correlated with laryngeal dose in patients receiving definitive head and neck chemo-radiation. This was addressed by the QUANTEC report.[46, 48, 81, 83] Inadvertent dose deposition to adjacent high dose target volumes often hastens the onset of radiotherapy (RT) induced acute mucositis and laryngeal oedema, resulting in a disruption to the swallowing mechanism and its associated structures. Yet, as previously

highlighted, swallowing is a complex, multifaceted mechanism. The functional role of each anatomical structure is inter-related. Therefore, isolating the dosimetric consequence upon each anatomical structure in RT induced dysphagia can be somewhat challenging.

Dose parameters significantly associated with late laryngeal oedema and subsequent dysphagia were previously reported.[81] Their findings recommended a V50Gy of less than 27% and a dose mean of less than 43.5Gy to the larynx to minimize oedema incidence. Furthermore, an additional study generated dose variables for minimizing late aspiration, reporting that a dose mean to glottic/ supraglottic larynx should not exceed 50Gy.[52] This study also reported compromised swallowing outcomes when a mean dose of 60Gy and V65Gy of 50% to PCM were exceeded.

Findings out of Michigan in 2004 provide the impetus for modern day dysphagia and aspiration related structure (DARS) identification.[32] This identification of pertinent radiation sensitive swallowing anatomy provided direction for multiple DVO outcome publications such as those comprising the QUANTEC report. While reporting on a relatively small cohort (N=26), their identification of DARS tissue thickening via post radiotherapy video-fluoroscopy was instrumental for future DVO driven studies. They identified the PCMs, larynx and supraglottic larynx (SGL) as critical DARS with respective increases in thickness of 2.5mm to 7mm (PCMs) and 2mm to 4mm (larynx and SGL).The volume of these structures receiving in excess of 50Gy was reported as critical to the likelihood of swallowing complications.[32] Later work of this group suggested that the superior and middle PCMs, of the PCM muscle group, as those most critical for dose avoidance if integrity of the swallowing mechanism was to be maintained.[84]

Numerous institutions have incorporated the DARS identification concept to drive a wave of supporting DVO publications. A variety of dysphagia endpoints were utilized to correlate delivered dose to structures involved in the swallowing mechanism. One study performed post therapy video-fluoroscopy on their cohort (N=96) to establish a relationship between late dysphagia and volume of larynx and inferior PCM receiving in excess of 50Gy.[28] Dose

mean below 60Gy to both supraglottic and glottic larynx was reported to reduce the risk of aspiration. Those with a dose mean of less than 60Gy were more likely to present with low risk aspiration index, and those above 60Gy, a median risk index score. These scores were generated on the basis of post radiotherapy QoL questionnaire and FEES.[30]

Correlation of PCM dose and multiple dysphagia endpoints have contributed to multiple dose guidance recommendations. A steep dose effect relationship to the superior PCM and middle PCM was reported in 2007. Each increase of 10Gy in mean dose resulted in a 19% increase in probability of QoL reported dysphagia.[85] The critical role of both the superior and middle PCMs was shared in another study.[86] Endpoints of this study were based on three endpoints, PEG tube dependence, video-fluoroscopy and pharyngeal/oesophageal stricture (POS) requiring dilatation. They reported an increased risk of POS when superior PCM V65Gy was greater than 75% and middle PCM was V65 greater than 75%. Increased likelihood of long-term PEG dependence and aspiration were also correlated with inferior PCM V60Gy greater than12% and larynx Dmean greater than 41Gy and V60Gy greater than 24%.[86] An additional contribution to radiation induced dysphagia further supports the influence of superior and middle PCMs in long term PEG dependence. Of particular interest from this study, however, is the correlation of oral mucosa dose to acute PEG dependence. This study reported an increased risk of acute dysphagia complication when V9.5-10Gy/week was in excess of 50-60 cubic centimetres. Acute dysphagia DVO data is far less frequent in the literature, so contributions at this level are very important to inform clinical practice.[63]

Correlation of inferior PCM dose and swallowing complication is less frequently reported in the literature. Most recently, in a study of 55 patients, inferior PCM V60Gy and Dmean have been identified as significant predictors of video-fluoroscopy identified dysphagia at ten weeks post therapy.[87]

A potential caveat of many of these studies is the relatively low accrual in each study. However, two recent studies, with significantly higher patient accrual, give credence to

earlier findings.[47, 88] In a study of 259 patients, dosimetric indices from two dysphagia endpoints, patient reported QoL questionnaires and barium swallow video-fluoroscopy were derived. Barium swallow abnormalities were associated with increased dose to both superior PCM (Dmean<60Gy) and middle PCM (Dmean<60Gy). Patient reported QoL dysphagia increased to greater than 20% when Dmean to supraglottic larynx exceeded 55Gy.[88] A further study developed a series of predictive models for various dysphagia endpoints. This work (N=354) reported RTOG/EORTC reported dysphagia complication with dose escalation to both the superior PCM (SPCM) and supraglottic larynx (SGL) for multiple endpoints. Both structures were significant predictors in multivariate regression for late dysphagia (SPCM, $p<0.01$; SGL, $p<0.01$) and swallowing of solid foods (SPCM, $p<0.01$; SGL, $p<0.01$).[47] Outcomes of both of these studies support the importance of DARS in dysphagia risk reduction.

While there have been numerous studies reporting delivered dose to DARS as pertinent to swallowing outcomes, one study has demonstrated no significant relationship between PCM dose and patient and observer recorded endpoints. This work only comprised 37 patients, and represents one of only few reports in the literature on DVO outcome data reporting.[89]

2.6 Pre-treatment factors and dysphagia prediction

Delivered dose of radiation to swallowing anatomy continues to be reported as a significant cause of dysphagia in head and neck cancers. The role of pre-treatment factors and morbidities has received less attention in the literature, with many more publications reporting studies aimed at evaluating a relationship between dose and dysphagia endpoints. Age, tumour geometry and geography, concurrent chemotherapy, baseline (pre-treatment) swallowing performance, smoking and alcohol status, performance status, radiotherapy

technique and irradiated volume have been investigated as potential predisposing factors to varying dysphagia endpoints.

Multiple studies have combined dosimetric predictors with pre-treatment factor correlation. A 2012 study reported that older patients, with tumours located in the naso and oropharynx, treated with 3D conformal radiotherapy are most susceptible to poor dysphagia outcomes compared to younger patients, treated with IMRT, with geographic tumour locations caudal to those of the nasopharynx and oropharynx. Another study reported tumour geography as a significant predictor for dysphagia, in addition to geometry (T-Stage) and pre-treatment swallowing abnormality.[90]

A comprehensive review of PEG and nasogastric tube as predictors of long-term dysphagia was undertaken.[91] Toxicity data was prospectively collected on 350 patients as part of a phase III randomized trial (TROG 91:01) to develop a predictive enteral grading scoring (PEG Score) system to predict the likelihood of nutritional intervention via PEG/NGT. Planning target volume (PTV) length of the highest prescribed dose, in excess of 82mm, was found to be the most significant contributing factor. RTOG based staging greater than 1, altered radiotherapy dose fraction (i.e. higher dose per fraction than 2Gy standard fractionation) and ECOG performance status greater than 1 were also deemed predictive of an increased risk nutritional intervention. PTV length greater than 82mm was associated with three activation points. Other predictors were given one point. Patients were deemed to be at an increased risk of PEG/NGT feeding when the PEG score was greater than or equal to six.

Gross tumour and PTV size have been consistently recognized as those factors associated with long term dysphagia in studies reporting on pre-treatment factors alone. Williams et al (2012), using a multivariate analysis, reported an increased significant risk of enteral feeding with increased T-stage ($p=0.007$). Prophylactic PEG use was also a predictor of late swallowing complication at 12 months post treatment (P-PEG = 18% vs. NGT = 5%, $p<0.01$).[92] In another study, PTV size in excess of 235cc to the high dose PTV, and a total

PTV in excess of 615cc were predictors of patient weight loss and NGT requirement.[61] Greater than five percent weight loss, prescribed dose greater than 60Gy and concurrent chemotherapy were also significant predictors of these objective endpoints.[61] In one of the larger accrued studies in recent literature reporting on dysphagia outcomes (N=474), it was reported that 40% of non-surgical interventions for head and neck cancer can avoid PEG. Of those remaining 60%, this study also reported T-stage (T3-4) as a predisposing factor for long term PEG use. Concurrent chemotherapy (p=0.015), baseline swallowing dysfunction (p=0.001) and weight loss (p=0.0012) were also reported as significant predisposing factors. An adherence to swallowing exercise regimes was also reported as a significant contributor to decreased PEG dependence in both the acute and late settings.[93]

2.7 Discussion & Conclusion

Dysphagia related head and neck radiotherapy outcomes have been investigated at length over a long period of time. Multiple institutions and collaborative groups have published on all aspects of radiation-induced dysphagia, including identification of pertinent anatomy responsible for the swallowing mechanism, tools for dysphagia diagnosis, objective and subjective measurement tools, management strategies, and dosimetric and pre-treatment predictors of late dysphagia.

The radiation oncology profession sits at a critical point in time. Current practice in the planning and delivery of head and radiotherapy demands unprecedented precision. Intensity modulated radiotherapy (IMRT) has afforded unbridled conformality in treatment planning, where disparity in dose between high dose tumour and adjacent swallowing anatomy has been significantly improved. This precision is subsequently afforded to treatment delivery. Our ability to deliver a highly fatal dose of radiation to a tumour, while avoiding dose to adjacent swallowing anatomy, is greater than it has ever been. On the other hand, the

opportunity to significantly underdose a tumour and overdose swallowing anatomy, has never been higher.

Previous work from our group reported the significant dosimetric benefits afforded with modern treatment planning systems.[35] However, we rely on weight maintenance and precision image guided radiotherapy (IGRT) to ensure planned dose is equivocal to delivered dose, such that dose/volume/outcome data is accurate for future application.

The importance of acute toxicity management should not be underestimated, so as to ensure optimal delivery of planned dosimetry and to prevent the decrement in the quality of the IMRT plan. This has been the focus of current work from our group.

Better understanding the acute dose/response/outcome correlation in head and neck radiotherapy could play a role in the development of safer treatment intensification protocols, with ultimately the potential for improved tumour control loco-regionally. Predictive dosimetric measures for expected treatment tolerance may provide a basis for inclusion/exclusion of treatment intensification protocols, or enable the implementation of suitable prophylactic measures to increase the likelihood of treatment tolerance. Further to radiotherapy dose intensification, the ability to deliver less toxic loco regional treatment may allow intensification of systemic treatments. The benefits of concurrent platinum based systemic therapy and biologic agents are well established.[94] A greater understanding of the acute response to radiotherapy, and the knowledge to implement individualized prophylactic measures, may optimize delivery of such potentially toxic programs and reduce associated toxicities. Various allied health professionals, including dietitians and speech pathologists, provide opportunity for on-treatment assistance to enable improved treatment tolerance.

On-treatment interventions and their early implementation have proven beneficial in enhancing treatment tolerance. Planned patient geometry and treatment tolerance is dependent on multiple contributing factors. A more comprehensive understanding of the role of dosimetric measures and their correlation to incidence of acute toxicity will allow for a

greater focus on treatment planning dose steering. Yet, perhaps of greater importance is the early instigation of supportive care intervention (i.e. dietetics, speech pathology) where dose avoidance is not possible. Such measures may be able to better maintain or achieve optimal treatment tolerance, weight management and treatment delivery.

However, two observations from the recent literature should guide the direction of future work. Both papers discuss the disparity in swallowing anatomy delineation and dysphagia endpoint interpretation respectively.[57, 95] Their respective observations highlight the importance of consistency in dose/volume/outcome data methodology and subsequent reporting. Increased precision in radiation therapy demands improvement in all areas of dysphagia management, from anatomy delineation through to outcome measure and interpretation. Slight discrepancies present greater consequence than ever before. The overwhelming theme of the recent literature has been focused on predicting dysphagia via both dosimetric and predisposing factors. Predicting dysphagia enables the implementation of individualised supportive care programs. Precision and consistency in all aspects of delineation, identification and management will encourage improved correlation with future predictive measures, ultimately leading to more effective dysphagia management strategies for head and neck radiotherapy patients.

2.8 Literature Review Update: Recent progress of dysphagia management in head and neck radiotherapy patients (2014-2018)

This section summarises recent developments in the literature that occurred concurrently with the published studies of this thesis and after the above review up until December 2018.

2.8.1 How is dysphagia measured?

Subjective tools used to evaluate and measure dysphagia and its consequence are still routinely utilised in current clinical practice. Previously described instruments such as CTCAE, RTOG and EORTC continue to complement FEES and barium swallow aided video fluoroscopy as the gold standard for dysphagia identification. Despite the reliance on- in particular, the physician measures such as CTCAE- there is evidence to suggest that these measures alone may not fully articulate the impact and nature of severity of radiation induced swallowing dysfunction when compared to instrumental evaluation alone e.g. modified barium swallow.[96] However, information derived from the standard reporting of the modified barium swallow can be difficult to correlate with well-defined endpoints of the CTCAE scale. The dynamic imaging grade of swallowing toxicity tool (DIGEST) is well described in a 2017 paper. DIGEST is described as an instrument capable of clarifying this discrepancy, through the standardisation of modified barium swallow reporting through the introduction of a five-point ordinal scale to evaluate the safety and efficacy of pharyngeal bolus clearance.[97] Further work attempts to better understand the relationship between the findings of both the CTACE and DIGEST methods of swallowing toxicity quantification.[96] They report that DIGEST can play an important role in complementing CTCAE toxicity scoring in both the acute and late phases of dysphagia. It has the capability for improved specificity for acute physiologic dysphagia and enhanced sensitivity of late phase dysphagia. This additional understanding provides valuable, complementary information to traditional CTCAE criteria such as patient reported symptoms, alterations to diet and feeding tube dependence for nutritional requirements.

While findings for clinician reported dysphagia outcomes and validated patient reported quality of life measures are well established, there remains a paucity of data exploring the relationship between each of these two critical dysphagia measures. The Eating Assessment Tool-10 (EAT-10) is a tool routinely used in the detection of aspiration in non-oncologic patient populations.[98-100] Measuring self-perceived swallowing impairment, EAT-10 is a validated tool with a symptom specific focus. EAT-10's utility in the previously undefined population of head and neck cancer patients, to ascertain its value as an additional tool in the detection of radiation-induced swallowing complication, has been previously undertaken.[101] A significant correlation between EAT-10 and physician reported scoring within 1-year post treatment was reported. However, no correlation was reported between the two measures in patients presenting beyond 1-year post-radiotherapy. While reporting encouraging early findings, the authors recognised the size of the studied population (N=44) and heterogeneity in patient follow-up as limiting factors in their data and recommended further validation in a controlled environment to further ascertain the congruence between EAT-10 and subjective physician measures.

Sarcopenia is described as the depletion of muscle mass, and is a condition that often has an adverse effect on cancer patient prognosis. Sarcopenia may play a role in the higher rates of toxicity, including dysphagia- often attributed in the HNC population. A 2016 paper addressed the lack of literature to support this theory in the HNC population.[102] Diagnostic abdominal CT-scans are routinely used in the diagnosis of sarcopenia. Previous work has demonstrated a correlation between depleted skeletal muscle mass at the level of the L3 vertebrae and total-body skeletal muscle mass, serving as a reliable prognostic marker in the diagnosis of sarcopenia.[103, 104] However, appropriate diagnostic imaging of this region is not routinely undertaken in head and neck cancer patients, limiting the identification of sarcopenia in these patients. The authors of this study assessed skeletal muscle mass on head and neck CT scans (a standard diagnostic evaluation in HNC), and reported that skeletal muscle mass at the level of the C3 vertebrae strongly predicted that at the level of

the L3 vertebrae (r=0.785, p<0.001), suggestive of C3 as a reliable surrogate for sarcopenia detection. Early identification of such patients may facilitate early nutritional intervention for patients demonstrating acute symptoms of dysphagia.[102]

The growing complexities of head and neck radiotherapy underline the importance of clinical expertise in the detection and subsequent management of radiation induced dysphagia. Multidisciplinary teams are a critical pillar in the care of HNC patients. Despite evidence of improved staging, management and outcomes, there is still data to suggest that there is low uptake in many environments treating HNC with radiotherapy.[105] This theory was further demonstrated in a study of multidisciplinary, specialised care in the management of dysphagia in post-radiotherapy patients in India (N=26).[106] In their cohort of patients, they introduced a specialised skillset from a highly skilled institution in the United States, to formalise a dysphagia management plan. The multidisciplinary teams comprised surgeons, radiation oncologists, radiologists and speech, swallowing and language pathologists in both regions. The consultation was undertaken via telemedicine. The functional oral intake score (FOIS) of this patient cohort improved from baseline to post-intervention, demonstrating the value of adding specialised multidisciplinary care into dysphagia management.

2.8.2 How is dysphagia managed?

Nutritional intervention

Weight management is becoming increasingly critical in the precision delivery of radiotherapy, due to the increased sensitivities to patient contour fluctuations afforded by modern radiotherapy techniques such as IMRT, VMAT and proton therapy. Prophylactic identification of at-risk patients, prior to radiotherapy commencing, is critical to the implementation of proactive nutritional interventions. As many as 20% of patients require long-term PEG use despite being in remission from their cancer diagnosis, as a consequence of increased weight loss afforded by chemo-radiotherapy.[107] Pre-treatment

body-mass index (BMI) has also been identified as a significant prognostic factor in HNC patients.[108] A low BMI at diagnosis (i.e. a patient who is underweight) was an adverse prognostic factor, compared to overweight patients, who had a better prognosis. Nutritional interventions for these patients, therefore, play a critical role in their management.

There remains conflicting data as to the validity of nutritional management strategies. A 2015 review article interrogated the literature, with a particular focus on the impact of prophylactic PEG (pPEG) use on swallowing-related outcomes.[109] Amongst the twenty studies that were included in their review, some were subject to selection bias due an inherent absence of non-randomised sampling.[109] Furthermore, the swallowing-related outcomes and dysphagia from each of these studies demonstrated a lack of clarity through inconclusive and varied results, indicative of current clinical practice.

Despite earlier studies reporting long term dependence when a pPEG is inserted, more recent work has demonstrated conflicting findings. One study investigated the impact of early PEG feeding on longer term feeding outcomes in a cohort of fifty-seven patients.[110] They reported that encouraging patients in the early use of PEG utilisation may prolong time to removal. Despite this, however, it doesn't increase long term dependency beyond 4 months. Further supporting these findings, in a randomised study of 134 patients, it was established that there was no significant difference in swallowing function between the pPEG and clinical nutritional support (control) assigned groups at one, two and eight years post diagnosis and treatment.[111] These swallowing outcomes were defined via the EORTC-QLQ-H&N35, the oral intake scale, PEG tube dependence, oesophageal intervention, weight, BMI and overall survival. Subsequently, they recommended the use of pPEG without an increased risk of long-term dysphagia.

The use of oral nutritional intervention, in the absence of artificial nutrition via tube means, has also been evaluated in a HNC population undergoing radiotherapy with or without chemotherapy.

A 2018 randomised study of 159 newly diagnosed HNC patients was undertaken to better understand the value of oral nutritional support (ONS) when combined with nutritional counselling, compared to nutritional counselling alone.[112] The addition of ONS resulted in significantly improved weight maintenance (p=0.006), driven by an improved protein-calorie intake, and an improved patient reported QoL. Furthermore, ONS reduced the requirement for suspension/cessation of anti-cancer treatments (i.e. suboptimal doses of radiotherapy and/or chemotherapy), indicative of a better tolerance to treatment.

2.8.3 Swallowing exercises/strength training of swallowing anatomy

While the use of instrumental intervention, such as those utilised in a 2018 study investigating the use of balloon dilation in radiation-induced oesophageal stricture, has demonstrated benefit in short term management of dysphagia, the literature is abundant with swallowing rehabilitation as a key strategy in this space.[113]

The antagonistic effects of radiotherapy (+/- chemotherapy) on swallowing strength have been long recognised, with subsequent strategies to support improved conditioning the subject of multiple studies. It has been previously recognised that chemo-radiotherapy affects tongue endurance and salivary flow rate, leading to an adverse impact on swallowing efficiency.[114] Appropriate consideration, as such, was recommended when planning dysphagia management strategies for these patients.

Expiratory function, following a course of radiotherapy for HNC, is significantly depressed in aspirating patients when compared to non-aspirators.[115] On the basis of these findings, the authors hypothesised that airway protection impairment (i.e. aspiration candidates) may

extend outside the radiation treatment field, beyond the already irradiated laryngopharyngeal structures, suggestive of an inter-dependency of structures critical in aspiration prevention. The impact of potential aspiration, however, can be minimised through the introduction of subglottic expiratory strengthening exercises. Further work from this group demonstrated a reduction in maximum expiratory pressures (a symptom indicative of increased aspiration risk) in 91% of participants (58/64, with an average improvement of 57%, $p<0.001$)) when expiratory muscle strength training was introduced via an 8-week, personalised program.[116] Additionally, swallowing safety (via Dynamic Imaging Grade of Swallowing Toxicity or DIGEST) ($p=0.03$) and MD Anderson Dysphagia Inventory (MDADI) ($p=0.13$) scores also reported significant improvement among patients enrolled in expiratory muscle strength training. These findings were further validated in a study reporting significant improvements in oro-motor function, pharyngeal impairment, oral pharyngeal swallow efficiency and incisal opening at three and six months post-radiotherapy.[117] Another study also reported the benefits of rehabilitative exercises in mitigating chronic dysphagia, through significant improvements to in chin tuck, jaw opening and anterior tongue strength. Sixteen of the seventeen patients in this study reported feeling a benefit from undertaking these exercises as part of their rehabilitation.[118]

2.8.4 Barriers to swallowing exercises

Despite multiple publications having demonstrated a significant benefit to swallowing outcomes when rehabilitative exercise is introduced into a patient's care pathway, there remain ongoing barriers to its effective utilisation. While a 2015 publication reported systematic swallowing exercises had no impact on swallowing outcomes in the first year following radiotherapy, they recognised poor adherence to recommended exercise (despite supervised sessions) as a significant barrier to success.[119] At 11 months, 49% of patients had withdrawn from the study, compromising the investigators ability to fully appreciate the

role of swallowing exercises in late dysphagia reduction. Equivalent, high rates of non-compliance were also demonstrated in other studies.[120, 121]

A possible rationale for non-adherence to swallowing exercises was proposed. The authors suggested that following chemoradiotherapy, patient responsiveness to swallowing function and physiology become less symptom-specific, and manifest as more general difficulty in swallowing, compromising their ability to articulate and recognise benefits.[122] Additional barriers to adherence were also explored, purporting that a lack of psychological capability to clearly clarify and understand exercise rationale was adversely affecting their adherence.[123] Furthermore, study participants reported a lack of systems in place to ensure compliance, being overwhelmed with information, and pain and fatigue associated with undertaking the exercises, as further barriers to optimal compliance. Social support and personal desire to prevent long-term adverse effects were recognised as facilitators of improved patient compliance.

Conversely, following a review of outcomes in non-compliant and compliant patients who have undergone dysphagia rehabilitation following HNC, another study demonstrated no benefit in the rehabilitative compliant group.[124] They questioned the proper dose of efficacy of swallowing exercises in the HNC population and the need to further optimise this regime.

2.8.5 Solutions to improve compliance

To address the proven inadequacies in patient adherence to swallowing rehabilitation, multiple strategies have been proposed to improve this compliance. One group established an automated swallow detection algorithm via mobile health technologies in order to minimise the complexities of patient interaction in this often misunderstood rehabilitative process.[125] This technology utilises electromyography to monitor access and adherence to swallowing therapy. Other examples of mobile technologies have also been generated to improve adherence to patient swallowing exercises.[126]

Additional strategies to improve patient understanding, and subsequently, improve compliance, were investigated.[127] A well-established, internationally recognised framework, which allows a user to describe consequences of condition on an individual in the context of their environment, was utilised in this study. The International Classification of Functioning Disability, and Health (ICF) is useful in detailing the complexity and impact of dysphagia, leading to a more holistic approach to dysphagia management.[127]

2.8.6 Organ at risk (OAR) delineation

Earlier described studies demonstrate the clinical value in avoiding structures critical to the complex nature of the swallowing mechanism.[37, 38, 70, 87, 92] With the precision afforded by modern radiotherapy treatment planning technologies, accurate delineation of these structures is paramount to optimal correlation of outcome to delivered dose. In a published review in 2018, the importance of accurate DARS delineation was highlighted in order to ensure that the radiotherapy therapeutic ratio is maximised and the risk of swallowing dysfunction is minimised.[128] The review further recommended, when possible, the utilisation of magnetic resonance imaging to support optimal anatomical DARS delineation. Additionally, the review highlighted that guidelines such as UMCG did not consider relevant structures, such as hard palate, soft palate, lateral and medial pterygoid muscles, genioglossus muscle and mylo/geniohyoid complex, as pertinent structures in dysphagia avoidance.[128] Similarly, international consensus guidelines for delineating OAR for HNC radiotherapy did not specifically define DARS. The need for consistency in OAR delineation was further supported by the MD Anderson head and neck cancer symptom working group, who, in a study of 300 oropharyngeal cancer patients, reported a number of pertinent dose volume outcome metrices.[129] They stressed the importance of accurate delineation to ensure effective translation of these recommendations into clinical practice.

2.8.7 Predicting dysphagia via clinical factors and radiation dose to swallowing anatomy

Studies in the preceding five years have demonstrated a particular focus on both clinical and dosimetric predictors of dysphagia. In publications with a sole dosimetry focus, a review was published on dose volume outcome data and reported mean dose to PCM as the most important dosimetric predictor of late swallowing disturbance.[130] Interestingly, in 2016, the value of parotid-sparing IMRT in contributing to a positive outcome on swallowing performance up to twelve months post radiotherapy was reported.[131]

The MD Anderson head and neck cancer symposium working group further added to the pool of structures contributing to adverse swallowing outcomes post radiotherapy, revealing that their dosimetric endpoints pointed to mylo/geniohyoid complex V69Gy (the volume receiving ≥69 Gy), genioglossus V35Gy, anterior digastric V60Gy as potential constraints to mitigate or minimise the risk of radiation induced dysphagia.[132]

The ability to predict for timely, prophylactic PEG insertion remains the primary focus of this thesis. Our work has demonstrated the novel finding that level 2 nodal lymphadenopathy is a clinical factor predictive of prolonged feeding tube use, in addition to tumour classification or T-stage.[133] Further studies have reported that mean dose to oropharynx, ECOG status and CRT are all predictive of need for pPEG insertion.[134]

Further works in the domain of clinical predictors of enteral feeding tube requirement have demonstrated similar results. Recent findings to determine if p16 status, chemo-radiotherapy and other nutritional markers could predict proactive gastrostomy, have found that low risk patients with oropharyngeal cancer who are p16 positive and at high malnutrition risk would benefit from pPEG. This is indicative of the growing HPV positive HNC population we are seeing in Western radiotherapy clinics, which will continue to grow as the incidence of HPV associated cancers peak.[135] These findings were similarly supported by a study that

demonstrated clinical factors- advanced nodal disease, chemoradiotherapy, good performance status- with an increased reliance on pPEG use.[136]

The two observations described as the key themes of future work (in the conclusions of 2.7) remained prominent in the recent literature. Both swallowing anatomy delineation and dysphagia endpoint interpretation have been investigated at length in the last five years, in addition to earlier works. Recognition of the important role of patient engagement in their care has also been widely reported. Barriers to swallowing exercise compliance, and subsequent methods to improve, demand a more holistic approach to care. With the changing landscape of the head and neck cancer patient demographic towards HPV-associated disease, each of these themes, in line with the contents of this thesis, will require ongoing investigation to ensure optimal management of this patient cohort moving forward.

Chapter 3: Dose Volume Response in Acute Dysphagia Toxicity: Validating QUANTEC Recommendations into Clinical Practice for Head and Neck Radiotherapy.

Nigel J Anderson[1,3], Morikatsu Wada[1], Michal Schneider-Kolsky[3], Maureen Rolfo[1], Daryl Lim Joon[1], Vincent Khoo[1,2,3,4].

[1]Department of Radiation Oncology, Austin Health, Heidelberg Heights, Victoria, AUSTRALIA

[2]Department of Clinical Oncology, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Chelsea, London, UK.

[3]Department of Medical Imaging and Radiation Sciences, Monash University, Victoria, AUSTRALIA

[4]Department of Medicine, University of Melbourne, Victoria, AUSTRALIA

Published: Acta Oncologica 2014 Oct; 53(10): pp 1305-11

3.1 Preface

This chapter replicated the manuscript that was peer reviewed and subsequently published in Acta Oncologica in 2014 (see full reference above).

The theme of this manuscript was to investigate the clinical applicability of the QUANTEC dose/volume/outcome recommendations for late dysphagia, in the acute setting. Precision radiotherapy, in particular in the head and neck domain, is becoming more reliant upon the maintenance of planned body habitus to ensure the delivery of planned radiotherapy. Steep dose gradients between target volumes and organs at risk mean that any deviations from planned radiotherapy can lead to an underdosage of the tumour and overdose of critical normal anatomy, leading to suboptimal tumour control and increased likelihood of radiation induced toxicities.

Dose to the larynx has long been regarded as a surrogate for late dysphagia following head and neck radiotherapy. However, dysphagia management and subsequent weight maintenance is critical to the precision delivery of head and neck radiotherapy. There are little to no dose recommendations for dysphagia prevention in the acute setting. This manuscript aimed to validate whether the QUANTEC dose/volume/outcome recommendations for dysphagia can be utilised to predict dysphagia in the acute setting.

3.2 Abstract

Purpose: To determine the validity of QUANTEC recommendations in predicting acute dysphagia using intensity modulated head and neck radiotherapy

Materials and Methods: Seventy-six consecutive patients with locally advanced squamous cell carcinoma (SCC) of the head and neck +/- systemic therapy were analyzed. Multiple dose parameters for the larynx (V50Gy, Dmean and Dmax were recorded. Acute dysphagia toxicity was prospectively scored in all treatment weeks (week 1- 6 or 1-7) using CTCAEv3 by three blinded investigators. QUANTEC larynx recommendations (V50Gy<27%, Dmean<44Gy, Dmean<40Gy, Dmax<66Gy) were used to group the cohort (i.e. V50Gy<27% v V50Gy>27%). The proportion of patients with Grade 3 dysphagia was compared within each group.

Results: There was a significant reduction in the incidence of grade 3 toxicity in the V50Gy < or > 27% group at week 5 (14.3% vs 45.2%, p=0.01) and 6 (25.9%, vs 65.9%, p<0.01). A significant reduction at week 5 (14.7% vs 50.0, p=0.02) and 6 (32.4% vs 67.6%, p=0.01) was seen in Dmean <44Gy when compared to Dmean > 44Gy.Dmean<40Gy also delivered a significant reduction at week 5 (5.6% vs 42.3%, p<0.01) and week 6 (23.5% vs 59.3%, p=0.01) A significant toxicity reduction at treatment week 6 (28.0% vs 63.0%, p=0<01) was seen from Dmax <66Gy to Dmax >66Gy.

Conclusions: QUANTEC late toxicity recommendations for dose to larynx during IMRT are a useful predictor for acute dysphagia toxicity in this patient cohort. Furthermore, this included chemoradiotherapy regimes and post-operative radiotherapy patients-allowing for prophylactic implementation of supportive care measures.

3.3 Introduction

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) series of articles provides a summary of updated dose/volume/outcome data to refine current dose volume recommendations, previously defined via the recommendations of Emami et al (1991). [80] The QUANTEC dose/volume/outcome data was generated to provide the radiotherapy planner with improved data to facilitate effective utilization of more sophisticated planning, delivery and imaging systems in steering precision dose deposition.[82]

Radiation induced dysphagia is strongly correlated to laryngeal dose in patients receiving definitive head and neck chemo-radiation. This was addressed by the QUANTEC report.[46, 81, 83] Inadvertent dose deposition to adjacent high dose target volumes often hastens the onset of radiotherapy (RT) induced acute mucositis and laryngeal edema, resulting in a disruption to the swallowing mechanism and its associated structures. However, swallowing is a complex, multifaceted mechanism. The functional role of each anatomical structure is inter-related. Therefore, isolating the role of each anatomical structure in RT induced dysphagia can be somewhat challenging. The QUANTEC report suggests that late dysphagia is often a consequence of acute oral mucositis, and that acute dysphagia may be a predictor of late swallowing complication.[137] Our study aimed to address these questions, by validating the recommendations of the QUANTEC report to determine their usefulness in predicting acute dysphagia, through an analysis of dose/volume/outcome in glottic/supraglottic larynx in definitive head and neck patients treated at our center. Furthermore, this study aimed to establish if systemic therapy and radiotherapy delivered post-operatively (PORT) affects this dose/volume/outcome relationship, and whether late QUANTEC recommendations are still relevant in predicting acute dysphagia within chemo-radiotherapy and PORT regimes.

3.4 Materials and Methods

Seventy-six consecutive patients with locally advanced squamous cell carcinoma (SCC) of the head and neck, treated with intensity modulated radiotherapy (IMRT- 60-70Gy) definitively or PORT +/- systemic therapy between 2008 and 2011, were analysed (table 1). Patients with primary laryngeal disease and re-irradiation were excluded from this review. The study was approved by our institutional ethics committee.

3.4.1 Treatment Planning

The prescribed doses were planned via a simultaneous integrated boost (SIB), to a gross tumor volume (GTV), high risk clinical target volume (CTV) and low risk CTV. Dose to GTV (60-70Gy), high risk CTV (60-63Gy) and low risk CTV (54-56Gy) was planned at five fractions per week over 6 to 7 weeks. Treatment regime (i.e. pre/post-operative radiotherapy, +/- systemic therapy) contributed to the radiotherapy treatment length. Each target was expanded with a departmental protocol margin (1cm GTV to CTV, 0.5cm CTV to PTV) to form PTV_1, PTV_2 and PTV_3 respectively.

Optimized IMRT plans, deliverable via seven to nine equally spaced step-and-shoot segmented beams on a 6MV linear accelerator (Elekta Synergy, Elekta Oncology, Crawley, UK), were generated using both the Elekta CMS XiO and Monaco treatment planning systems (TPS) (Elekta CMS Software, St Louis, MO, USA) on 0.25cm computed tomography (CT) slices.

Dose mean (Dmean), dose maximum (Dmax) and V50Gy of glottic and supraglottic larynx (referred to as ‘larynx’ for the remainder of article) were recorded for each patient dataset. A dose volume constraint of V50Gy<30% was used for all patients (if clinically achievable). The larynx was delineated by a single radiation oncologist (MW) for all patients. Larynx was defined by epiglottic tip superiorly, lower border of cricoid cartilage inferiorly, and laterally via the pharyngeal lumen/thyroid cartilage. Anterio-posterior boundaries were the posterior aspect of hyoid or laryngeal cartilage anteriorly, and encompassed pharyngeal constrictors

bounded by prevertebral fascia posteriorly. All QUANTEC recommendations for the larynx (V50Gy <27%, Dmean<40Gy, Dmean <44Gy, Dmax <66Gy) were utilized to categorize the patient cohort i.e. V50Gy <27% v V50Gy >27%; Dmean <40Gy v Dmean >40Gy, Dmean <44Gy v Dmean >44Gy; Dmax<66Gy v Dmax>66Gy. Biological equivalent larynx V50Gy, Dmean and Dmax was additionally calculated and applied to patients where dose per fraction was in excess of 2Gy per fraction (alpha/beta value of 4 was utilised for conversion). Equivalent biological doses have been analyzed in this paper.

3.4.2 Acute Toxicity Assessment

Patients were prospectively scored on a weekly basis (weeks 1-6 or 7) by three radiation oncologists (blinded to previous scores or other adverse effects) for acute dysphagia toxicity using the common toxicity criteria for adverse events version three (CTCAEv3) assessment tool. Grade 3 toxicity was deemed clinically significant, and its incidence recorded. Symptomatic and severely altered eating/swallowing- with an indication for percutaneous endogastric (PEG) tube intervention and intravenous fluids- was suggestive of Grade 3 dysphagia. QUANTEC defined dose volume categories were subsequently analyzed for grade 3 toxicity incidence within the cohort.

Several possible clinical risk factors were also recorded for analysis. These included:

i) Age

ii) Sex

iii) Chemoradiotherapy (CRT)

iv) Surgery (Post-Operative Radiotherapy (PORT) v Definitive

v) Pre-existing dysphagia

vi) Pre-existing nutritional status (Patient-Generated Subjective Global Assessment (PG-SGA) Tool)

vii) Pre-existing morbidity

3.4.3 Statistical Methods

The proportion of patients with grade 3 toxicity according to either V50Gy (< or > 27%), Dmean (< or > 40Gy), Dmean (< or > 44Gy) or Dmax (< or > 66Gy) were compared across the entire treatment using the Friedman test (overall change in proportion across entire treatment) and Chi Square test (change in the proportion of patients incidence between two groups at individual weeks of treatment i.e. Dmax <66% vs > 66%/week). These statistical methods were subsequently applied to the stratified data of the chemoradiotherapy, RT only, PORT and definitive cohorts. A Chi Square test was used to compare clinical risk factors across two groups (i.e. % CRT patients in V50Gy<27% vs V50Gy>27%). All analyses were carried out using SPSS (version 18.0, Chicago, USA). A p-level of < 0.05 was afforded significance.

3.5 Results

Patient demographics, tumor and treatment characteristics are shown in the supplementary material (Appendix i). Statistically significant toxicity reduction was observed on the basis of multiple larynx QUANTEC dose volume recommendations (refer to Tables 2-3 for all acute grade 3 dysphagia incidences) in the combined cohort.

V50Gy <27% resulted in a 68.4% reduction in grade 3 toxicity at treatment week 5 (p=0.01) and a 60.7% reduction at treatment week 6 (p<0.01) compared to V50 >27%. The reduction in toxicity from week 6 to 7 was not significant. Not all patients were prescribed a seven-week treatment course. This dose parameter was not significant at week 7 due to the reduced patient numbers at this time point.

Dmean <44Gy resulted in a 69.8% reduction of grade 3 toxicity at treatment week 5 (p=0.01) and 51.4% reduction at treatment week 6 (p<0.01) compared to Dmean >44Gy. Dmean <40Gy further supported Dmean as a key predictor of acute dysphagia, with significant reduction at week 5 (5.6% vs 42.3%, p<0.01) and week 6 (23.5% vs 59.3%, p=0.01).

Treatment with a Dmax <66Gy demonstrated a 55.6% reduction of toxicity at treatment week 6 ($p<0.01$) compared to Dmax >66Gy.

Furthermore, analysis of larynx Dmean for patients with CTCAEv3 grading above and below 3 supports the Dmean>44Gy as a useful predictor of acute dysphagia. (although statistically insignificant). Patients who peaked at grade 3 toxicity (n=47) reported an average larynx Dmean of 46.3Gy+/- 9.7Gy compared to those below grade 3 (n=29) who reported a Dmean of 42.5+/-6.8Gy ($p=0.07$).

Subsequent stratification of the total cohort into PORT (n=29) and Definitive (n=47) (Table 2) reports comparable trends to that of the entire cohort. Statistically significant toxicity disparity, however, is less frequent, due to the reduced numbers in the stratified cohorts

A comparable trend is also reported in the CRT (n=40) and RT Only (n=36) cohorts (Table 3). In the CRT cohort, all dose constraints are significant predictors at varying time points. The RT Only group (significant only at V50Gy>27%, week 6) reports comparable trends in toxicity incidence with the combined cohort. In the absence of more definitive dose/volume/outcome data, the QUANTEC recommendations appear a useful predictor of acute dysphagia in this RT Only cohort.

Further stratification reports an equivalent distribution of potential clinical risk factors across most QUANTEC defined groups (refer to table 4). There was a significantly greater proportion of CRT patients in the Dmax>66Gy cohort, compared to those Dmax<66Gy. A significantly greater proportion of PORT patients were in the Dmax<66Gy cohort. Both of these results can be in part explained by the prescribed dose levels to the CRT and PORT patients. CRT patients were predominantly prescribed in excess of 66Gy, whilst PORT patients less than 66Gy.

The peak toxicity of any patient throughout treatment was grade 3 (60.5% of all patients). 25.0% of patients reported a peak grade 2 toxicity and 13.2% a peak grade 1 toxicity.

3.6 Discussion

Our results have shown that the QUANTEC report dose recommendations for late dysphagia are a useful tool for predicting acute dysphagia in a typical group of head and neck cancers usually treated radically with radiotherapy. Reduction in the inadvertent dose delivery to laryngo-pharyngeal structures has been extensively investigated and reported.[52, 79] Our findings support the recommendations of the QUANTEC report.[137] These recommendations are based on the dose/volume/outcome data from multiple studies, which have been derived from late toxicity endpoints including edema and aspiration.

Other publications have attempted to validate the QUANTEC recommendations in various critical organs[138-140] Liu et al (2010) reported consistent rectal bleeding complications to those of the NTCP QUANTEC model in prostate radiotherapy. However, due to relative homogeneity of rectal dose distributions, this study warned of a low predictive power in their cohort.[138] Appelt et al (2014) combined the dose response function of radiation pneumonitis (based on QUANTEC recommendations) with known clinical risk factors, to increase confidence in predicting radiation pneumonitis and to individualize toxicity risk estimates.[139] Most recently, parotid dose recommendations were validated by Beetz et al (2014). Their work reported significantly lower rates of patient-rated xerostomia based on QUANTEC recommendations. However, this group warned of decreased reliability in the model in the elderly and patients with minor pre-existing xerostomia[140]

Dose parameters significantly associated with late laryngeal edema were previously reported by Sanguineti et al.[81] Their findings recommended a V50Gy of less than 27% and a dose mean of less than 43.5Gy to the larynx to minimize edema incidence. However, it should be recognized that only a small percentage of this cohort (n=12, 18.2%) underwent concurrent chemotherapy, with subsequent stratification eliminating chemotherapy as an edema predictor. Dose-volume relationships generated from this work may well be affected by this discrepancy. This should be considered when applying these constraints in the presence of systemic therapy. Furthermore, Feng et al (2007) generated dose variables for minimizing

late aspiration, reporting that a dose mean to glottic/ supraglottic larynx should not exceed 50Gy.[36, 52] The role of the laryngeal dose in late vocal dysfunction has also been reported. Dornfeld et al reported a steep decrease in vocal toxicity when the maximal laryngeal dose was kept below 66Gy.[46] A limitation of this particular study, however, was the absence of full three-dimensional dose metrics. Specified points within swallowing anatomy were identified for dose analysis. Limitations in their planning software didn't enable retrospective analysis of newly delineated structures.

While tumor control and late toxicity should and will always remain the primary outcome measure, treatment tolerance in the acute setting is becoming increasingly important.[141] The primary focus of this study was to address the current lack of acute dysphagia dose/ volume/ outcome data in the literature. The QUANTEC recommendations for reduction in late edema, aspiration and vocal dysfunction were shown to be clinically significant predictors of acute dysphagia in our study. The incidence of acute dysphagia toxicity was significantly higher in patient cohorts exceeding the specified dose goals.

There is an increasing awareness of the importance of minimizing the consequences of acute toxicities. Multiple publications emphasize the importance of maintaining planned patient geometry, to ensure optimal delivery of planned dosimetry and to prevent the decrement in the quality of the IMRT plan, in particular, in predicting parotid gland dose.[142, 143] The ability to predict, prevent and manage severe dysphagia may reduce the incidence and the magnitude of significant weight loss thus in our cohort. Better understanding the acute dose/response/outcome correlation in head and neck radiotherapy could play a role in the development of safer treatment intensification protocols, with ultimately, the potential for improved tumor control loco-regionally. This has been investigated via various radiotherapy dose escalation strategies.[144, 145] Increasing dose to sites of putative radiation resistance, as suggested by various PET substrates has been explored previously[146] Predictive dosimetric measures for expected treatment tolerance may provide a basis for inclusion/exclusion of treatment intensification protocols, or enable the implementation of suitable prophylactic

measures to increase the likelihood of treatment tolerance. Further to radiotherapy dose intensification, the ability to deliver less toxic loco regional treatment may allow intensification of systemic treatments. The benefits of concurrent platinum based systemic therapy and biologic agents are well established.[94] A greater understanding of the acute response to radiotherapy, and the knowledge to implement individualized prophylactic measures, can optimize delivery of such potentially toxic programs and reduce associated toxicities. Various allied health professionals, including dietetics and speech pathology, provide opportunity for on-treatment assistance to enable improved treatment tolerance.

On-treatment interventions, and their early implementation have proven beneficial in enhancing treatment tolerance. Studies have proven the benefit of enteral feeding (via PEG) in reducing weight loss and interrupted treatment, amongst many other acute toxicity incidents.[147] Yet, there is also data suggesting that a long term dependence on PEG feeding is detrimental to latter swallowing function, with increased risk of atrophy to masticatory and swallowing muscles.[21] The work of Sanguinetti et al addressed this concern through the development of predictive dosimetric parameters (to oral mucosa) for PEG insertion throughout IMRT for oropharyngeal cancer.[148] Planned patient geometry and treatment tolerance is dependent on multiple contributing factors. A more comprehensive understanding of the role of dosimetric measures and their correlation to incidence of acute toxicity will allow for a greater focus on treatment planning dose steering. Yet, perhaps of greater importance, is the early instigation of supportive care intervention (i.e. dietetics, speech pathology) where dose avoidance is not possible. Such measures may be able to better maintain or achieve optimal treatment tolerance, weight management and treatment delivery.

A limitation of this study is that the study population does encompass multiple tumor types and demographic characteristics, but this group is typically representative of the cases treated radically with radiotherapy. Despite this heterogeneity of disease sub-type entities, the outcome data were relatively consistent as reported. The role of systemic therapy or

radiotherapy given definitively or post-operatively in influencing acute dysphagia incidence was addressed. Our results showed that systemic therapy or surgical intervention did not significantly affect the incidence of grade 3 dysphagia in each of the groups (data not presented). This was performed to ascertain concurrent systemic therapy or surgery given in conjunction with radiotherapy in some patients was not a confounding factor in the outcome of our analysis. Multiple other demographic factors were not analyzed, such as tumor size and geography, pre-existing medical conditions and quality of life accompanying scoring during radiation therapy. Equivalent toxicity incidence was reported regardless of biological or physical laryngeal dose.

3.7 Conclusion

This study demonstrated the usefulness of the QUANTEC late toxicity recommendations in predicting acute dysphagia toxicity. Precision radiotherapy demands optimal maintenance of planned geometry through optimizing the opportunity for improved treatment tolerance. A more comprehensive understanding of acute dose/volume/outcome correlation enables individualized treatment programs to be developed, to facilitate improved treatment tolerance via measured prophylactic interventions.

Table 1. Demographic and tumor characteristics of head and neck IMRT patients (Total N = 76)

	Patients n/N (%)	
Sex		
Male	53	(69.7)
Female	23	(30.3)
Age (Mean, ± SD)		
Male	60.5 (± 9.4) years	
Female	60.7 (±13.1) years	
Primary Tumor Site		
Oropharynx	39	(51.3)
Floor of Mouth	11	(14.5)
Other	10	(13.2)
Unknown Primary	8	(10.5)
Nasopharynx	6	(7.9)
Oral Tongue	2	(2.6)
T Classification		
T0	2	(2.6)
T1	10	(13.2)
T2	22	(28.9)
T3	18	(23.7)
T4	12	(15.8)
Tx	12	(15.8)
N Classification		
N0	15	(19.7)
N1	11	(14.5)
N2a	12	(15.8)
N2b	19	(25.0)
N2c	13	(17.1)
N3	6	(7.9)
M Classification		
M0	70	(92.2)
M1	3	(3.9)
Mx	3	(3.9)
Post-Operative (PORT)	29	(38.2)
Definitive RT	47	(61.8)
Systemic Therapy		
Yes	39	(51.3)
Cisplatin	32	(82.1)
Cetuximab	4	(10.2)
Carboplatin	3	(7.7)

T= Tumor, N= Node, M = Metastases

Table 2. Incidence of CTCAEv3 grade 3 acute dysphagia (treatment weeks 1-6 /7) in ALL patients compared to Definitive and PORT*

All Patients (n=76)	**V50Gy<27% n/N (%)**	**V50Gy>27% n/N (%)**	**Dmean<44Gy n/N (%)**	**Dmean>44Gy n/N (%)**	**Dmean<40Gy n/N (%)**	**Dmean>40Gy n/N (%)**	**Dmax<66Gy n/N (%)**	**Dmax>66Gy n/N (%)**
Week 1	1/33 (3.0)	1/42 (2.4)	1/36 (2.8)	1/39 (2.6)	0/19 (0.0)	2/56 (3.6)	1/27 (3.7)	1/48 (2.1)
Week 2	3/34 (8.8)	2/41 (4.9)	3/36 (8.3)	2/39 (5.1)	1/19 (5.3)	4/56 (7.1)	3/28 (10.7)	2/47 (4.3)
Week 3	4/32 (12.5)	5/41 (12.2)	4/34 (11.8)	5/39 (12.8)	1/18 (5.6)	8/55 (14.6)	4/26 (15.4)	5/47 (10.6)
Week 4	4/30 (13.3)	5/41 (12.2)	3/33 (9.1)	6/38 (15.8)	0/17 (0.0)	9/54 (16.7)	3/24 (12.5)	6/47 (12.8)
Week 5	4/28 (14.3)	19/42 (45.2)^	5/34 (14.7)	18/36 (50.0)^	1/18 (5.6)	22/52 (42.3)#	6/26 (23.1)	17/44 (38.6)
Week 6	7/27 (25.9)	29/44 (65.9)#	11/34 (32.4)	25/37 (67.6)^	4/17 (23.5)	32/54 (59.3)^	7/25 (28.0)	29/46 (63.0)#
Week 7	9/14 (64.3)	21/26 (80.8)	13/19 (68.4)	17/21 (81.0)	3/7 (42.9)	27/33 (81.8)	3/6 (50.0)	27/34 (79.4)
PORT Only (n=29)								
Week 1	1/14 (7.1)	1/14 (7.1)	1/14 (7.1)	1/14 (7.1)	0/9 (0.0)	2/19 (10.5)	1/19 (5.3)	1/9 (11.1)
Week 2	3/15 (20.0)	2/14 (14.3)	3/15 (20.0)	2/14 (14.3)	1/9 (11.1)	4/20 (20.0)	3/20 (15.0)	2/9 (22.2)
Week 3	3/14 (21.4)	3/14 (21.4)	3/14 (21.4)	3/14 (21.4)	1/8 (12.5)	5/20 (25.0)	4/19 (21.1)	2/9 (22.2)
Week 4	3/12 (25.0)	2/14 (14.3)	3/13 (23.1)	2/13 (15.4)	0/7 (0.0)	5/19 (26.3)	3/17 (17.7)	2/9 (22.2)
Week 5	2/13 (15.4)	6/13 (46.2)	2/14 (14.3)	6/12 (50.0)	0/9 (0.0)	8/17 (47.1)	4/18 (22.2)	4/8 (50.0)
Week 6	4/12 (33.3)	9/13 (69.2)	5/13 (38.5)	8/12 (66.7)	2/8 (25.0)	11/17 (64.7)	6/17 (35.3)	7/8 (87.5)^
Week 7	N/A	3/3 (100.0)	1/1 (100.0)	2/2 (100.0)	N/A	3/3 (100.0)	N/A	3/3 (100.0)
Definitive Only (n=47)								
Week 1	0/19 (0.0)	0/28 (0.0)	0/23 (0.0)	0/24 (0.0)	0/10 (0.0)	0/37 (0.0)	0/9 (0.0)	0/38 (0.0)
Week 2	0/19 (0.0)	0/27 (0.0)	0/22 (0.0)	0/24 (0.0)	0/10 (0.0)	0/36 (0.0)	0/9 (0.0)	0/37 (0.0)
Week 3	1/18 (5.6)	2/27 (7.4)	1/21 (4.8)	2/24 (8.3)	0/10 (0.0)	3/35 (8.6)	0/8 (0.0)	3/37 (8.1)
Week 4	1/18 (5.6)	3/27 (1.1)	1/21 (4.5)	3/24 (12.5)	0/10 (0.0)	4/35 (11.4)	0/8 (0.0)	4/37 (10.8)
Week 5	3/18 (16.7)	12/26 (46.2)	4/21 (19.1)	11/23 (47.8)	1/9 (11.1)	14/35 (40.0)^	2/9 (22.2)	13/35 (37.1)
Week 6	4/18 (22.2)	19/28 (67.9)#	7/22 (31.8)	16/24 (66.7)^	2/9 (22.2)	21/37 (56.8)	1/9 (11.1)	22/37 (59.5)^
Week 7	9/14 (64.3)	18/23 (78.3)	12/18 (66.7)	15/19 (79.0)	3/7 (42.9)	24/30 (80.0)	3/6 (50.0)	24/31 (77.4)

Table 2 Key

CTCAEv3 = Common toxicity criteria for adverse events version three
*Treatment length dependent on treatment intent/concurrent treatments/pre or post-operative
n = no. of grade 3 recordings
N = no. of patients with recordings at treatment week
% = grade 3 dysphagia incidence
PORT = Post-Operative Radiotherapy
^ = $p<0.05$ following Chi Square test
# = $p<0.01$ following Chi Square test

Table 3. Incidence of CTCAEv3 grade 3 acute dysphagia (treatment weeks 1-6 /7) in ALL patients compared to CRT and RT Only*

All Patients (n=76)	**V50Gy<27% n/N (%)**	**V50Gy>27% n/N (%)**	**Dmean<44Gy n/N (%)**	**Dmean>44Gy n/N (%)**	**Dmean<40Gy n/N (%)**	**Dmean>40Gy n/N (%)**	**Dmax<66Gy n/N (%)**	**Dmax>66Gy n/N (%)**
Week 1	1/33 (3.0)	1/42 (2.4)	1/36 (2.8)	1/39 (2.6)	0/19 (0.0)	2/56 (3.6)	1/27 (3.7)	1/48 (2.1)
Week 2	3/34 (8.8)	2/41 (4.9)	3/36 (8.3)	2/39 (5.1)	1/19 (5.3)	4/56 (7.1)	3/28 (10.7)	2/47 (4.3)
Week 3	4/32 (12.5)	5/41 (12.2)	4/34 (11.8)	5/39 (12.8)	1/18 (5.6)	8/55 (14.6)	4/26 (15.4)	5/47 (10.6)
Week 4	4/30 (13.3)	5/41 (12.2)	3/33 (9.1)	6/38 (15.8)	0/17 (0.0)	9/54 (16.7)	3/24 (12.5)	6/47 (12.8)
Week 5	4/28 (14.3)	19/42 (45.2)^	5/34 (14.7)	18/36 (50.0)^	1/18 (5.6)	22/52 (42.3)#	6/26 (23.1)	17/44 (38.6)
Week 6	7/27 (25.9)	29/44 (65.9)#	11/34 (32.4)	25/37 (67.6)^	4/17 (23.5)	32/54 (59.3)^	7/25 (28.0)	29/46 (63.0)#
Week 7	9/14 (64.3)	21/26 (80.8)	13/19 (68.4)	17/21 (81.0)	3/7 (42.9)	27/33 (81.8)	3/6 (50.0)	27/34 (79.4)
CRT (n=40)								
Week 1	0/15 (0.0)	0/25 (0.0)	0/20 (0.0)	0/20 (0.0)	0/8 (0.0)	0/32 (0.0)	0/10 (0.0)	0/30 (0.0)
Week 2	0/15 (0.0)	1/24 (4.2)	0/19 (0.0)	1/20 (5.0)	0/8 (0.0)	1/31 (3.2)	0/10 (0.0)	1/29 (3.5)
Week 3	1/15 (6.7)	3/24 (12.5)	1/19 (5.3)	3/20 (15.0)	0/8 (0.0)	4/31 (12.9)	1/10 (10.0)	3/29 (10.3)
Week 4	1/15 (6.7)	2/24 (8.3)	1/19 (5.3)	2/20 (10.0)	0/8 (0.0)	3/31 (9.7)	0/10 (0.0)	3/29 (10.3)
Week 5	2/14 (14.3)	10/23 (43.5)	2/18 (11.1)	11/19 (57.9)#	0/7 (0.0)	13/30 (43.3)^	2/10 (20.0)	11/27 (40.7)
Week 6	4/13 (30.8)	18/25 (72.0)^	6/18 (33.3)	16/20 (80.0)#	1/6 (16.7)	21/32 (65.6)	2/9 (22.2)	20/29 (69.0)^
Week 7	8/10 (80.0)	15/18 (79.0)	10/13 (76.9)	12/14 (85.7)	3/5 (60.0)	19/2 (86.4)	2/3 (66.7)	21/25 (84.0)
RT Only (n=36)								
Week 1	1/18 (5.6)	1/17 (5.9)	1/17 (5.9)	1/18 (5.6)	0/11 (0.0)	2/24 (8.3)	1/18 (5.6)	1/17 (5.9)
Week 2	3/19 (15.8)	1/17 (5.9)	3/18 (16.7)	1/18 (5.6)	1/11 (9.1)	3/25 (12.0)	3/19 (15.8)	1/17 (5.9)
Week 3	3/17 (17.7)	2/17 (11.8)	3/16 (18.8)	2/18 (11.1)	1/10 (10.0)	4/24 (16.7)	3/17 (17.7)	2/17 (11.8)
Week 4	3/15 (20.0)	3/17 (17.7)	3/15 (20.0)	3/17 (17.7)	0/9 (0.0)	6/23 (26.1)	3/15 (20.0)	3/17 (17.7)
Week 5	3/17 (17.7)	8/16 (50.0)	4/17 (23.5)	6/16 (37.5)	1/11 (9.1)	9/22 (40.9)	4/17 (23.5)	6/16 (37.5)
Week 6	4/17 (23.5)	10/16 (62.5)^	6/17 (35.3)	8/16 (50.0)	3/11 (27.3)	11/22 (50.0)	5/17 (29.4)	9/16 (56.3)
Week 7	1/4 (25.0)	6/8 (75.0)	3/6 (50.0)	5/7 (71.4)	0/2 (0.0)	8/11 (72.7)	1/3 (33.3)	6/9 (66.7)

Table 3 Key

CTCAEv3 = Common toxicity criteria for adverse events version three
*Treatment length dependent on treatment intent/concurrent treatments/pre or post-operative
n = no. of grade 3 recordings
N = no. of patients with recordings at treatment week
% = grade 3 dysphagia incidence
CRT = Concurrent Cisplatin Chemotherapy + Radiotherapy
^ = $p<0.05$ following Chi Square test
# = $p<0.01$ following Chi Square test

Table 4. Distribution of Clinical Risk Factors

	V50Gy<27% (%)	V50Gy>27% (%)	Dmean<44Gy (%)	Dmean>44Gy (%)	Dmean<40Gy (%)	Dmean>40Gy (%)	Dmax<66Gy (%)	Dmax>66Gy (%)
Sex (Female)	35.5	26.7	31.6	28.9	42.1	26.3	34.5	27.7
Age (≥65)	48.4	51.1	55.3	44.7	36.8	54.4	48.3	51.1
CRT	45.2	62.2	52.6	57.9	42.1	59.6	34.5	68.1#
Dysphagia	19.4	20.0	26.3	13.2	10.5	22.8	10.3	25.5
Pre-Tx NS	38.7	24.4	39.5	21.1	36.8	28.1	27.6	31.9
Morb. Score	25.8	17.8	28.9	13.2	21.1	21.1	20.7	21.3
PORT	45.2	33.3	39.5	36.8	47.4	35.1	69.0	19.1#

Table 4 Key
Dysphagia = Pre-existing dysphagia
Pre-Tx NS = Pre-Treatment Nutritional Status identifying Malnourishment (PG SGA Score ≥B)
Morb. Score= Pre-Treatment morbidity Score ≥2
PORT = Post-Operative Radiation Therapy
# = $p<0.01$ following Chi Square test

Chapter 4: Pre-treatment Risk Stratification of Feeding Tube Use in Patients Treated with IMRT for Head and Neck Cancer

Nigel J Anderson[1,2,6]; James E. Jackson[1,3,4,6]; Jennifer G Smith[5]; Morikatsu Wada[1], Michal Schneider[6]; Michael Poulsen MBBS[7,8], Maureen Rolfo[1]; Maziar Fahandej[1,9] ; Hui Gan[10]; Daryl Lim Joon[1]; Vincent Khoo[1,6,11,12]

[1] Department of Radiation Oncology, Olivia Newton John Cancer Wellness & Research Centre, Austin Health, Heidelberg, Victoria, AUSTRALIA

[2] Department of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria, AUSTRALIA

[3] School of Medicine, Griffith University, Gold Coast, AUSTRALIA

[4] Faculty of Health Sciences and Medicine, Bond University, Gold Coast, AUSTRALIA

[5] Plain Statistics Pty Ltd, Horsham, Victoria, AUSTRALIA

[6] Department of Medical Imaging and Radiation Sciences, Monash University, Victoria, AUSTRALIA

[7] Radiation Oncology Centres, Gold Coast University Hospital, Queensland, AUSTRALIA

[8] Faculty of Medicine, The University of Queensland, Herston, Queensland, AUSTRALIA

[9] Department of Palliative Care, St Vincent's Hospital, Fitzroy, Victoria, AUSTRALIA

[10] Olivia Newton-John Cancer Research Institute, Austin Health, Heidelberg, Victoria, AUSTRALIA

[11] Department of Clinical Oncology, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Chelsea, London, UK.

[12] Department of Medicine, University of Melbourne, Victoria, AUSTRALIA

Published: Head & Neck 2018 Oct; 40(10): pp 2181-2192

4.1 Preface

This chapter represents the manuscript that was peer reviewed and subsequently published in Head & Neck in 2018 (see full reference above).

The study presented in Chapter 3 successfully validated the QUANTEC larynx dose/volume/outcome recommendations for late dysphagia in the acute setting i.e. dose values that predict late dysphagia were also found to be predictive of acute clinician scored dysphagia. While it provided valuable data, toxicities, both acute and late, are very much dependent on a vast array of clinical variables. The theme of this manuscript was to investigate clinical predictors of feeding tube use in patients undergoing a radical/curative course of radiotherapy for head and neck cancer. A series of potential predictors, all of which were available at a multidisciplinary tumour board meeting whereby the patient treatment pathway is decided, were reviewed in a large series of patients. The prevalence of each of these variables was analysed with feeding tube utilisation, in an attempt to derive significant clinical variables that were predictive of prolonged feeding tube use.

Being able to predict for likelihood and duration of feeding tube use has multiple benefits for both the patient and heath service provider. It provides data for greater transparency in the feeding tube requirement informed consent process for the patient. With respect to the health service provider, it facilitates greater transparency in resource allocation to individualise patient pathways, while providing grounds for prophylactic toxicity management to minimise the risk of long-term radiation-induced complications.

4.2 Abstract

Purpose: To establish a risk stratification model for feeding tube (FT) use in head and neck IMRT patients.

Methods: 139 patients treated with definitive IMRT (+/- concurrent chemotherapy) for head and neck mucosal cancers were included. Patients were recommended a prophylactic FT and followed up by a dietician for at least eight weeks post-radiotherapy. Potential prognostic factors were analysed for risk and duration of FT use for at least 25% of dietary requirements.

Results: Many variables had significant effects on risk and/or duration of FT use in univariate analyses. Subsequent multivariable analysis showed that T-classification ≥ 3 and level 2-lymphadenopathy were the best independent significant predictors of higher risk and duration of FT use respectively in oral cavity, pharynx and supraglottic primaries.

Conclusions: In patients treated with definitive IMRT, T-classification ≥ 3 and level 2-lymphadenopathy can potentially stratify patients into four risk groups for developing severe dysphagia requiring FT use.

4.3 Introduction

Head and neck cancer and its treatment with radiation therapy (RT), with or without concurrent chemotherapy, are associated with dysphagia and associated malnutrition and weight loss.[149-152] Enteral feeding via a feeding tube (FT) is a common method of providing patient nutrition during and immediately following RT in as many as 80% of patients.[153-157] Patients at high risk of prolonged, severe dysphagia may benefit from a prophylactic gastrostomy tube to minimize hospitalisations, while maximising convenience and short term quality of life.[67, 75, 158]

However, the insertion of a gastrostomy tube is an invasive procedure which can be associated with major complications and occasionally death.[159] Prolonged use of gastrostomy tubes has been associated with long-term swallow dysfunction and a potential risk of late mortality.[67, 120] Considering these risks, the insertion of prophylactic gastrostomy tubes should be reserved for those patients likely to derive the most benefit, namely patients at highest risk of prolonged, severe dysphagia. Furthermore, identification of high-risk patients is critical in developing patient pathways and appropriate allocation of allied health resources. The main objective of this study was to develop a risk stratification model for anticipated duration of FT use, using the clinical and radiological information available at a patient's initial discussion at a Multidisciplinary Tumor Board.

4.4 Methods and Materials

4.4.1 Patients

Following Institutional Ethics Committee approval, the patient population was retrospectively accrued from the institution's radiation oncology database. To be eligible for inclusion, patients were required to receive primary and definitive intensity-modulated radiotherapy (IMRT) (with or without concurrent systemic treatment) for mucosal cancers of the head and neck. Patients with stage II–IVB disease were included. Patients were excluded if they underwent therapeutic surgery to the primary site or neck dissection prior to commencing RT. Patients were required to have been offered a prophylactic FT prior to treatment, as per

departmental policy- laryngeal and pharyngeal tumors planned to receive ≥64Gy with bilateral nodal irradiation, or having a pre-existing nutritional deficiency. All included patients had to be followed up by a dietician for a minimum of eight weeks post radiotherapy completion.

4.4.2 Pre-treatment evaluation

Prior to treatment, each patient underwent diagnostic contrast-enhanced computed tomography (CECT) of the face, neck and chest, as well as whole-body positron emission tomography with low dose CT for co-registration (PET/CT). Selected patients underwent magnetic resonance imaging (MRI) through the face and neck, when it was thought clinically beneficial to assist in optimal target delineation, e.g. nasopharyngeal primary disease.

4.4.3 RT planning and treatment

Target volumes were outlined on the planning CECT by one radiation oncologist. The PET/CT and MRI (if available) were co-registered with the planning CECT on the treatment planning system (TPS). The elective (prophylactic) nodes were defined according to consensus guidelines.[160] All patients received bilateral, elective irradiation of levels 2 to 4 nodes. Patients with oropharynx or nasopharynx cancers had bilateral, elective irradiation of level 1B nodes. In patients with oropharynx or hypopharynx cancers elective irradiation of ipsilateral level 5 nodes and the retrostyloid space was delivered to clinically node positive hemi-necks. In patients with cancer of the nasopharynx, bilateral retrostyloid space lymph nodes were treated to an elective dose. All T0 patients in this cohort were treated electively to bilateral nodal basins, including level 1B, while bilateral tonsils and tongue base were treated as high risk clinical target volume (CTV).

Clinically and radiologically involved nodes were contoured individually. The prescribed doses were planned with a simultaneous integrated boost to a gross tumor volume (GTV), high risk CTV and low risk CTV. In 137 cases, the dose to GTV (66–70Gy), high risk CTV (63Gy) and elective CTV (56Gy) was planned at five fractions per week over six to seven

weeks. The remaining two patients were prescribed 60 or 64Gy in 30 fractions. Medically fit patients were considered for concurrent systemic therapy based on disease stage and comorbidities.

Optimized IMRT plans, deliverable via seven to nine equally spaced step-and-shoot segmented beams on a 6 MV linear accelerator (Elekta Synergy, Elekta, Crawley, UK), were generated using either the Elekta CMS XiO or Monaco treatment planning systems (TPS) (Elekta, St Louis, MO, USA) on 0.25 cm CT slices.

4.4.4 Nutritional Assessment and Follow-Up

All patients had a complete pre-therapy consultation with a dietician followed by weekly nutritional reviews while on therapy. Following therapy, dietetic review, whether by phone or in person, was conducted at least every two weeks following therapy until cessation of enteral feeding.

Adequacy of Enteral Intake (AEI) was recorded at each review using the scale: AEI 0 = 0–24%, AEI 1 = 25–49%, AEI 2 = 50–74% and AEI 3 = 75–100% of daily nutritional needs. All patients were followed until their AEI was less than 1.

Speech pathology services were offered to all patients with oropharyngeal dysphagia to minimize aspiration and malnutrition risk. Video fluoroscopy and Fibreoptic Endoscopic Evaluation of Swallowing were available for at-risk patients. Swallowing rehabilitation was not available to this patient cohort.

4.4.5 Statistical Analyses

Outcomes measured were 1) the risk of FT use for at least 25% of nutritional requirements (AEI ≥ 1) and 2) the duration of such use measured in days from the first date the AEI was recorded at 1 or higher to the date when it dropped to AEI 0 or the tube was removed.

Potential patient and tumor related prognostic variables were subdivided according to previously reported cut-off points.[47, 61, 91, 161] Only variables which would be known at the pre-therapy multidisciplinary tumor board were considered. For analysis of risk of FT use (Yes or No) we used the Fisher exact test if there were only two subgroups (eg. age ≤ or > 65 years), the Cochran-Armitage test for trend if there were three or more ordered subgroups (eg. ECOG performance status) or the Pearson chi square test for three or more unordered subgroups (eg. cancer site).[162] For analysis of duration of FT use, Kaplan-Meier analysis was carried out and subgroups were compared using the Mantel-Cox log rank test for differences or the Tarone-Ware test for trend.[163, 164] As all patients were followed up to cessation of AEI ≥ 1 tube feeding, no durations were censored. All P values reported were two-sided and 95% confidence intervals (CI) were calculated. The significance criterion was $P < 0.05$ for previously reported prognostic factors or $P < 0.005$ for new prognostic factors (to adjust for multiple hypotheses).

Prognostic factors which were significant in the univariate analyses were tested in multivariable models to find the smallest number of independent prognostic factors which had a significant effect on the risk and duration of FT use. For risk of FT use, exact logistic regression with conditional maximum likelihood inference was used for the multivariable analyses with P values obtained from the exact conditional scores test (20).[162] For duration of FT use, Cox proportional hazards regression was used and the exponentials of the coefficients (e^{β}) from the final model were interpreted as “Recovery rate ratios”.

Both backwards and forwards stepwise regression was performed and variables were retained in the model if the P value was < 0.05. Patients with unknown values for a particular

factor were omitted from any models containing that factor, except for Human Papilloma Virus (HPV) where “unknown” was treated as a separate level of the factor.

4.5 Results

Between January 2007 and December 2013, 139 eligible patients were treated with radical intent IMRT. Their median age at commencement of RT was 61 years (range 20 to 91) and 78% were male. The most common cancer site was oropharynx (78 patients, 56%). The other primary sites were nasopharynx (16, 12%), supraglottis (15, 11%), glottic larynx (14, 10%), hypopharynx (5, 4%), oral cavity, (2, 1%) and unknown primary (9, 7%). Forty-one of the 78 oropharynx patients (53%) and five of the nine with unknown primaries (56%) had known HPV positive disease. Patient demographic and tumor characteristics are shown in the "Total" column in Table 5.

Altogether, 101 patients (73%) used a FT for at least 25% of their nutritional requirements, for at least 48 hours. The Kaplan-Meier curve of duration of FT use at AEI ≥ 1 is shown in Figure 1. Patients who did not use the FT at this level are represented in the Figure with 0 days duration; hence the curve starts at 73% on the vertical axis. The median duration of FT use for all patients was 70 days (CI 55–81 days). Twenty-four patients (17%) used it for at least six months, ten (7%) for at least 12 months and two (1%) for more than two years but the curve was curtailed at 24 months for the purpose of clarity.

Ninety patients (65%) used the FT for at least 75% of their requirements (AEI 3) at some stage and 18 (13%) used it at this level for more than six months.

4.5.1 Univariate analyses

Results of the univariate analyses on all 139 patients are shown in Table 5. Patients with cancer of the oral cavity or pharynx needed a feeding tube for longer than patients with cancers of supraglottis, glottic larynx or unknown primary (Figure 2). The other statistically significant prognostic factors for risk and duration of FT use were T-classification, N-

classification, level 2 lymphadenopathy, bilateral neck lymphadenopathy, concurrent chemotherapy, prior dysphagia and prior malnutrition. BMI < 18.5 and negative HPV status in oropharynx or unknown primary patients were significantly associated only with longer duration of FT use. Retropharyngeal and level 3 nodal disease were not considered to be statistically significant factors, despite having P values less than 0.05, because they did not meet our criterion of $P < 0.005$ for new hypotheses and either risk or duration of FT use was not significant. Patients older than 65 years were less likely to use the FT than younger patients, yet there was no significant difference in duration of FT use. This was contrary to most previous studies. There were no significant associations between the risk or duration of tube feeding and tobacco or alcohol use, comorbidities scaled using the Charlson co-morbidity index, ECOG performance status, or levels 1, 4 or 5 lymphadenopathy.

4.5.2 Multivariable analyses

Cancer site was a significant prognostic factor, therefore, nine patients with unknown primaries were excluded from the multivariable analyses. Only one of the fourteen patients with glottic larynx cancer needed to use a FT, so these patients were considered to be very low risk and also excluded from the multivariable analyses.

The remaining 116 patients with cancers in the pharynx, oral cavity or supraglottis were included in multivariable analyses for risk and duration of FT use for at least 25% of dietary needs. Factors with more than two subgroups were collapsed into two, specifically cancer site (pharynx and oral cavity versus supraglottis), T-classification (T3–4 versus T<3) and N-classification (N1–3 versus N0).

In the final models T-classification 3–4 ($P = 0.0018$ and $P < 0.0001$ respectively) and level 2 nodal disease ($P = 0.0030$ and $P = 0.0001$ respectively) were the only independent significant predictors of risk and duration of FT use respectively (Table 6). The recovery rate (rate of ceasing FT use at AEI ≥ 1) with T3–4 disease was estimated to be 25% of the rate in patients with T<3 disease (CI 16% – 39%) and with level 2 nodal disease it was estimated to

be 45% of the rate in patients with no level 2 nodes involved (CI 30% – 67%). Patients with both T-classification 3–4 and level 2 nodal disease were predicted to recover at approximately 11% of the rate of patients with neither factor (i.e. T<3 and no level 2 nodal disease) (CI 5% – 26%). Table 7 and Figure 3 display the observed duration of FT use in the presence of neither, one or both of these two significant factors.

None of the other factors, which were significant in the univariate analyses, was statistically significant in the multivariable analyses after taking into account T-classification 3–4 and level 2 lymphadenopathy.

4.6 Discussion

This analysis introduces a clinically useful and simple screening tool for both risk and duration of significant FT use, which is relevant when IMRT is used. Stratifying pharynx, oral cavity and supraglottis patients by two variables – T-classification (3–4) and presence of involved level 2 lymph nodes – separates patients into four distinct groups. Low risk patients have neither risk factor, low–intermediate risk patients have T<3 tumors with level 2 lymph nodes involved, high-intermediate risk patients have T3–4 tumors without level 2 nodes and high-risk patients have T3–4 tumors and level 2 lymphadenopathy. This information is readily available when a patient is first presented at a Multidisciplinary Tumor Board and the model described could be used to guide decisions regarding insertion of prophylactic tubes. It does not take dosimetric factors into consideration.

In our experience, all but the lowest risk group had at least an 85% chance of requiring enteral feeding for at least 25% of their diet, for at least 48 hours, at some stage during therapy or convalescence. Patients with glottic larynx cancer had a very low risk of needing a feeding tube (approximately 7% in our limited data). The risk for patients with unknown primaries in the head and neck is likely to depend on the volume of pharyngeal mucosa and constrictor muscles irradiated and whether patients had level 2 nodal involvement. These patients received elective mucosal irradiation, predominantly base of tongue and tonsillar

fossae, to 63Gy and often concurrent chemotherapy, but did not suffer physical obstruction from macroscopic tumor.

There still remains substantial controversy as to whether patients are best managed via reactive or prophylactic FT for RT related dysphagia.[67] However, even departments that adhere to strict reactive FT protocols insert prophylactic tubes in a subset of high risk patients, and, conversely, departments with policies of liberal prophylactic FT use will choose to spare a low risk subset of patients from undergoing the insertion procedure.

Apart from cancer site, we found advanced T-classification to be the most significant prognostic factor for duration of FT use. This is not a new finding and is consistent with the observations of numerous published studies.[161, 165-168] The most common dichotomy of T-classification in the published literature has been T1–2 versus T3–4 with the more advanced classifications universally having higher rates of acute and long term FT use.[161, 168, 169] The findings of our study support this.

The impact of level 2 lymph nodes on patient dysphagia is a novel finding. Lymph node positivity has been associated with increased FT dependence at six months (OR 7.08; $P < 0.001$).[168] We are able to report specifically on this subset of node positive patients owing to the careful and consistent target delineation under the direction of a single radiation oncologist. The causality of this finding remains unclear. Level 2 lymph nodes have a strong association with primary cancers of the oropharynx and, in the current series, 69% of both oropharynx and nasopharynx cancers had level 2 adenopathy.[170] Numerous studies have shown that radiotherapy for oropharynx malignancy is associated with high rates of symptomatic dysphagia.[65, 71, 161, 168] In this study, all patients with oropharyngeal and nasopharyngeal cancer had elective, bilateral irradiation of neck level 1B. This would lead to high dose deposition in the region of the patient's submandibular glands, which has been documented to increase the risk of both xerostomia and dysphagia.[168, 171] Anatomically, level 2 nodes are close to the parotid glands. Like the submandibular glands, the risk and severity of both xerostomia and dysphagia have been associated with increasing dose to parotid

glands.[76, 172-174] The level 2 region lies lateral to the base of tongue for its entire cranio-caudal length.[160] The tongue base has been described as a crucial organ in swallowing and an increasing risk of dysphagia has been documented with increasing dose to this organ.[168]

Level 2 node involvement is associated with more advanced disease and thus more aggressive therapy, such as altered fractionation or use of concurrent systemic therapy. However, this is only by virtue of node positivity and a similar relationship was not seen in this study with adenopathy at other stations.

Regarding our univariate analysis, the finding that patients with pharyngeal and oral cavity carcinomas suffered more dysphagia than those with laryngeal primaries has been previously well documented.[168] Our finding that older patients were less likely to use FT is consistent with that of Wopken et al but is inconsistent with other published studies.[86, 167, 168] We did not observe any effect of alcohol abuse on FT use, as seen by Frowen et al.[166]

The results of this study differ from several others in the duration of FT use for at least 25% of dietary needs. The median duration was over two months and at six months, 17% percent of patients were still using their FT. While earlier series have reported significantly higher rates of prolonged FT use, many modern studies, that have included patients treated with IMRT, have cited lower rates of long-term FT.[63, 66, 67, 76, 86, 153, 168]

It is important to distinguish FT use from FT dependence. A proportion of patients in this study who were using their FT at six months were also taking food and supplements orally. Eighteen patients (13%) were using their FT for more than 75% of daily needs for more than six months, which is consistent with recently published prophylactic cohorts, such as Wopken et al (10.7%). Regardless of nutritional intervention, it is common for patients with head and neck cancer to lose more than 10% of their bodyweight during and immediately following therapy.[146, 147] In many cases, an in situ gastrostomy tube provides a convenient way to optimize patient nutrition, even when they are eating. These patients have already avoided or suffered the potential complications associated with gastrostomy insertion, so it is

not surprising that dieticians and nutritional counsellors sometimes encourage ongoing nutritional supplementation in patients still eating.

In the short term, gastrostomies are more comfortable and convenient than nasogastric tubes and have less negative impact on body image and family life.[75] For this reason, it is not surprising that the medical literature almost universally reflects longer duration of FT use with gastrostomy as opposed to reactive nasogastric tubes.[70, 74, 75, 175] In reports where FT use at six months is less than 5%, a nasogastric tube was inserted as a reaction to failure of oral nutrition. It is not surprising that nasogastric tubes were not kept in-situ or repeatedly re-inserted for the purpose of nutritional optimisation, given the poor acceptability of this FT on body image psychosocial function.[66, 67, 75, 176]

Undoubtedly, long term FT dependence has a striking negative impact on many domains of quality of life.[136, 177-180] A considerable amount of published data suggests that patients with prophylactic FT's are less likely to maintain an oral, or partial oral, diet during RT and that this can negatively affect short and long-term diet outcomes, as well as duration of FT dependence.[67, 181, 182] Despite the majority of reported studies showing higher FT use at six months with prophylactic FT, Salas et al found no difference and Silander et al reported lower rates of grade 3 dysphagia in patients with a prophylactic gastrostomy tube (2% vs 9%).[69, 70]

The high risk and duration of FT use in this study can also be explained by the high-risk patients enrolled. All patients had bilateral neck irradiation, and gross disease was treated to an equivalent dose of 70Gy. Many series have included patients who were treated with ipsilateral and postoperative RT, who are not expected to use FTs routinely. In this series, 84 patients were treated with concurrent systemic therapy. This is known to increase acute toxicity, including severe dysphagia, although it did not affect FT use in our series.[183] Whilst concurrent chemotherapy did not retain significance following multivariable analyses, there may be some co-linearity with both T- and N-classification and the role it plays in more advanced disease.

Tumors of the glottic larynx had low risk of FT dependence and were excluded from the multivariable regression analyses. While earlier studies by Eisbruch, Caudell and Caglar have shown the larynx to be an important RT avoidance structure, a recent study by Wopken shows that patients with laryngeal primaries are the least likely to suffer FT dependence at six months (OR 1.00 vs. 13.82 for oropharynx and 16.19 for hypopharynx; $p<0.001$).[52, 84, 86, 168, 184] Treatment of salivary gland tumors is very rarely associated with dysphagia and therefore, this patient cohort was not included in this study.

In this study, no patient had access to swallowing rehabilitation. A randomized controlled trial reported by Carnaby-Mann et al. showed that swallowing exercises led to less deterioration of swallowing muscles and functional swallowing ability during chemoradiotherapy for head and neck cancers.[120] Patients randomised to swallowing exercises were more likely to maintain an oral diet and were less likely to use a FT.[120] Hutcheson et al. reported that adherence to swallowing exercises was similarly effective to maintenance of an oral, or partial oral, diet during chemoradiotherapy for better long term diet and shorter FT use.[182] The lack of swallowing exercises in this study may limit the ability the applicability of our data to patients who are exercising. However, the complete absence of swallowing exercises in this cohort, contributes to the uniformity of our data and possibly the internal validity of our findings. Swallowing exercises have definite patient benefits, but not all patients are adherent to prescribed swallowing exercises and many patients are partially adherent, making these benefits difficult to quantify.[120, 182]

Furthermore, every effort was made to minimize patient pain, as analgesia has been associated with a shorter duration of FT use.[136] All patients were reviewed at least weekly by a medical doctor to prescribe analgesia in a stepwise fashion: mouthwashes and anti-thrush measures, simple analgesia (e.g. soluble paracetamol), local anaesthetic mouthwashes (e.g. xylocaine and cocaine), and ultimately titration of opioids. Prophylactic gabapentin was not administered, as it is not registered for this use in Australia, though it has been associated with reduced FT use in a previously published study.[136]

This study possesses all the limitations inherent to a single-institution, retrospective analysis. We are unable to provide data on patients' functional swallowing ability, however, we are able to accurately report on patients having oral, or partial oral, diet at various time points due to comprehensive, prospectively recorded nutritional data. All of the patients were treated by a single radiation oncologist, however, it must be acknowledged that these patients were treated over eight years, a sufficient time period for even individual practice to vary. All patients were treated in the FDG PET and IMRT era, without swallowing exercises. This lends to uniformity in staging, volume delineation, and treatment delivery across the cohort. This study proposes a simple and novel clinical risk stratification tool that warrants prospective validation.

4.7 Conclusion

In patients with pharynx or supraglottic larynx cancers treated with definitive, bilateral IMRT, with or without concurrent systemic therapy, two clinical risk factors, namely T-classification 3–4 and level 2 lymphadenopathy, can potentially stratify patients into four distinct risk groups for developing severe dysphagia requiring FT use for at least 25% of their dietary requirements. This stratification may be useful in the clinic prior to radiotherapy planning and treatment so that patients at risk may have a FT inserted early prior to further nutritional status deterioration.

Table 5. Univariate analyses of prognostic factors for feeding tube use (Yes/No) and duration in 139 patients.

Prognostic factor	Subgroup	Feeding tube used*			Days of feeding tube use*		
		Yes/Total	%	P value†	Median	(95% CI)	P value‡
Cancer site	Pharynx or oral cavity	86/101	85%	< 0.0001	89	(70 – 120)	< 0.0001
	Larynx, supraglottis	10/15	67%		16	(0 – 79)	
	Larynx, glottis	1/14	7%		0	(0 – 0)	
	Unknown primary	4/9	44%		0	(0 – 66)	
Human papilloma virus (HPV)	Negative	22/23	96%	0.13	163	(81 – 233)	0.004
(for 87 oropharynx/unknown 1°)	Positive	35/46	76%		61	(31 – 90)	
	Unknown	13/18	72%		59	(0 – 77)	
T stage	X, 0	4/10	40%	0.0007	0	(0 – 66)	< 0.001
	1	15/23	65%		50	(0 – 77)	
	2	31/47	66%		44	(7 – 75)	
	3	34/40	85%		119	(79 – 173)	
	4	17/19	89%		150	(57 – 262)	
N stage	0	22/44	50%	0.0004	7	(0 – 59)	0.006
	1	16/20	80%		75	(44 – 120)	
	2	60/70	86%		86	(70 – 122)	
	3	3/5	60%		45	(0 – >295)	
Bilateral neck node disease	No	70/104	67%	0.016	59	(28 – 75)	0.025
	Yes	31/35	89%		118	(57 – 170)	
Retropharyngeal node disease	No	93/131	71%	0.11	66	(50 – 79)	0.025
	Yes	8/8	100%		153	(14 – >834)	
Level 1 node disease	No	85/120	71%	0.28	70	(57 – 83)	0.58
	Yes	16/19	84%		55	(18 – 113)	
Level 2 node disease	No	36/62	58%	0.0010	37	(0 – 68)	0.0054
	Yes	65/77	84%		83	(65 – 120)	
Level 3 node disease	No	72/107	67%	0.012	65	(31 – 79)	0.53
	Yes	29/32	91%		86	(57 – 136)	

Level 4 node disease	No	90/127	71%	0.18	68	(49 – 79)	0.14
	Yes	11/12	92%		124	(45 – 393)	
Level 5 node disease	No	92/128	72%	0.73	70	(49 – 81)	0.55
	Yes	9/11	82%		58	(0 – 393)	
Concurrent chemotherapy	No	30/55	55%	0.0002	16	(0 – 59)	0.0048
	Yes	71/84	85%		86	(75 – 118)	
Dysphagia or odynophagia	No	75/110	68%	0.020	59	(42 – 77)	0.009
	Yes	26/29	90%		133	(70 – 200)	
Nutrition (PG-SGA)	Well-nourished	72/106	68%	0.012	58	(42 – 75)	0.001
(1 missing)	Malnourished	29/32	91%		147	(77 – 211)	
Body Mass Index	Underweight (<18.5)	10/12	83%	0.51	208	(81 – 479)	0.002
(15 missing)	Not underweight (≥18.5)	80/112	71%		65	(45 – 77)	
Age on commencing RT	≤ 65 years	70/88	80%	0.019	75	(58 – 90)	0.74
	> 65 years	31/51	61%		31	(0 – 106)	
ECOG Performance Status	0	43/58	74%	0.87	58	(35 – 79)	0.17
	1	53/74	72%		70	(50 – 116)	
	2	5/7	71%		128	(0 – >303)	
Charlson Comorbidity Index	0	55/72	76%	0.23	70	(45 – 101)	0.85
	1	16/22	73%		59	(10 – 108)	
	2	19/27	70%		77	(16 – 170)	
	3, 4, 5	11/18	61%		17	(0 – 136)	
Tobacco smoking	Never or minimal	39/46	85%	0.13	70	(50 – 101)	0.53
(4 missing)	Past	27/42	64%		55	(0 – 90)	
	Current	33/47	70%		70	(42 – 128)	
Alcohol drinker	Never or social	69/94	73%	0.73	66	(44 – 90)	0.46
(5 missing)	Past	8/11	73%		120	(0 – 200)	
	Current	20/29	69%		57	(14 – 77)	

* “Feeding tube use” means feeding tube was used for at least 25% of nutritional requirements.

† Two-sided P value from Fisher exact test for difference between 2 subgroups, Pearson chi square test for difference between 3 or more unordered subgroups, or Cochran-Armitage test for trend across 3 or more ordered subgroups.

‡ Two-sided P value from Mantel-Cox log rank test for differences between subgroups or Tarone-Ware test for trend across 3 or more ordered subgroups.

*Table 6. Final multivariable models for feeding tube use (Yes/No) and duration (n = 116)**

Feeding tube use (exact logistic regression with conditional maximum likelihood inference) †

					Odds ratio		Exact
Factor	Reference	Level	β	s.e.$_\beta$	OR	95% CI	P value
T stage	T0–T2	T3–T4	1.867	0·633	6.47	1·73–31.4	0·0018
Level 2 nodes	No	Yes	1.640	0·559	5.15	1·56–19.0	0·0030

Duration of feeding tube use (Cox proportional hazards regression) †

					Recovery ratio		Exact
Factor	Reference	Level	β	s.e.$_\beta$	RR	95% CI	P value
T stage	T0–T2	T3–T4	-1.388	0·230	0.25	0.16–0.39	<0·0001
Level 2 nodes	No	Yes	-0.795	0·205	0.45	0.30–0.67	0·0001

* "Feeding tube use" means feeding tube was used for at least 25% of nutritional requirements.

† β = coefficient for each Level relative to the Reference category, based on 116 patients with cancers of pharynx, oral cavity or supraglottis. s.e.$_\beta$ = estimated standard error of β. OR or RR = e^{β}. 95% CI = 95% confidence interval for the OR or RR = $e^{\beta \pm 1{\cdot}96\ (\text{s.e.}\beta)}$.

‡ Other factors which were not significant when added individually to the models were: body mass index (<18.5 vs ≥18.5), nutrition (PG-SGA mal-nourished vs well nourished), dysphagia (Yes vs No), cancer (pharynx/oral cavity vs supraglottic larynx), human papilloma virus status (positive/unknown vs negative), N stage (N1–3 vs N0), bilateral neck nodes (Yes vs No), and planned concurrent chemotherapy. When added individually to the above models, the P values for these factors were all >0.3 for incidence and >0.1 for duration of feeding tube use.

Table 7. Prognostic groups based on T stage and Level 2 lymphadenopathy: data from 116 patients with cancers of pharynx, oral cavity or supraglottis.

			Feeding tube used*			Days of feeding tube use*	
Group	**T stage**	**Level 2 nodal disease**	**Yes/Total**	**%**	**(95% CI)**	**Median**	**(95% CI)**
1	T0–2	No	10/20	50%	(27 – 73)	7	(0 – 59)
2		Yes	36/42	86%	(70 – 95)	75	(56 – 90)
3	T3–4	No	24/27	89%	(71 – 98)	108	(68 – 173)
4		Yes	26/27	96%	(81 – 100)	170	(113 – 295)
All pharynx, oral cavity, supraglottis patients			96/116	83%	(75 – 89)	79	(68 – 106)

* “Feeding tube use” means feeding tube was used for at least 25% of nutritional requirements.

Figure 1. Duration of feeding tube use for at least 25% of nutritional requirements for all 139 patients. Kaplan-Meier analysis.

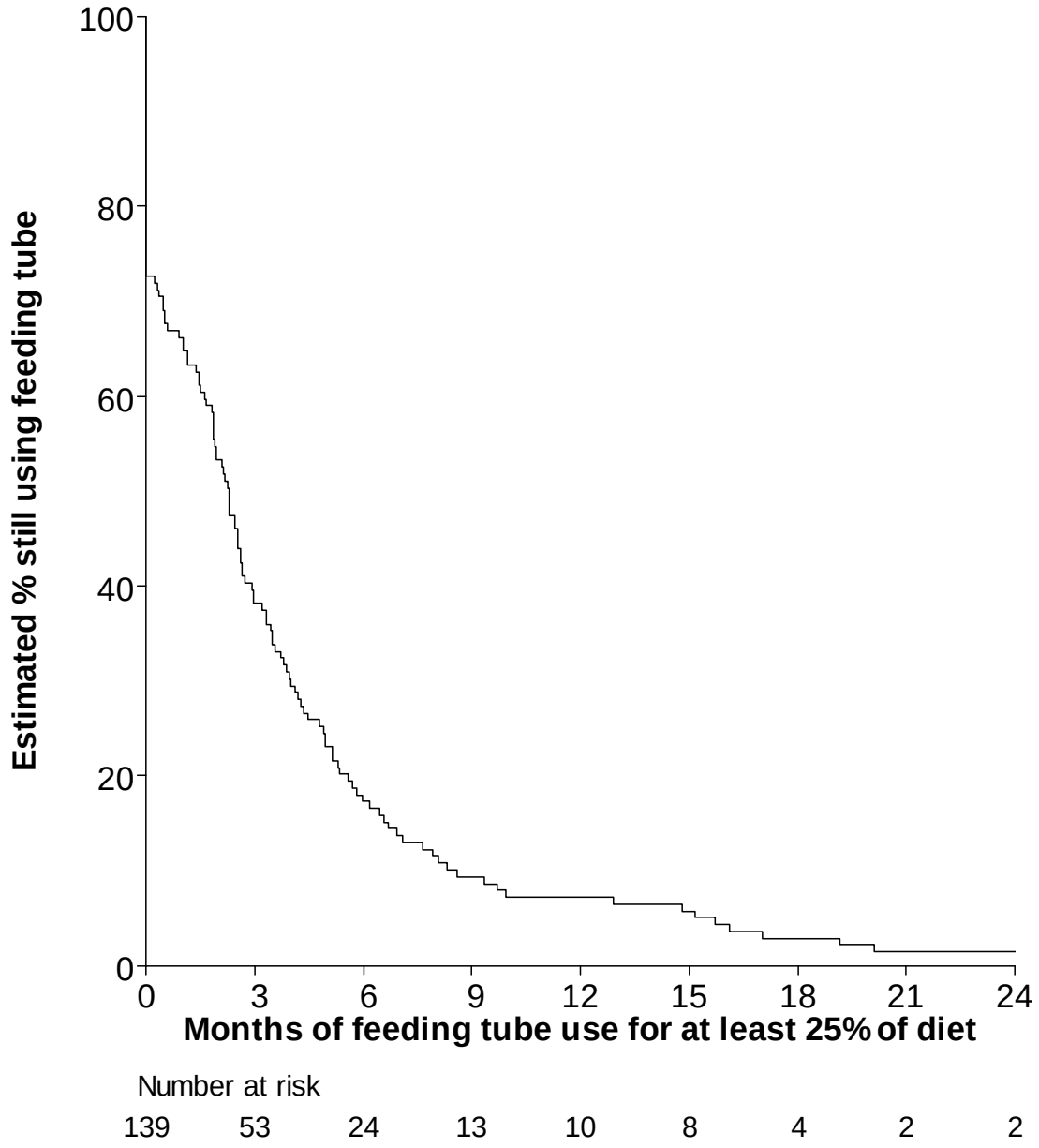
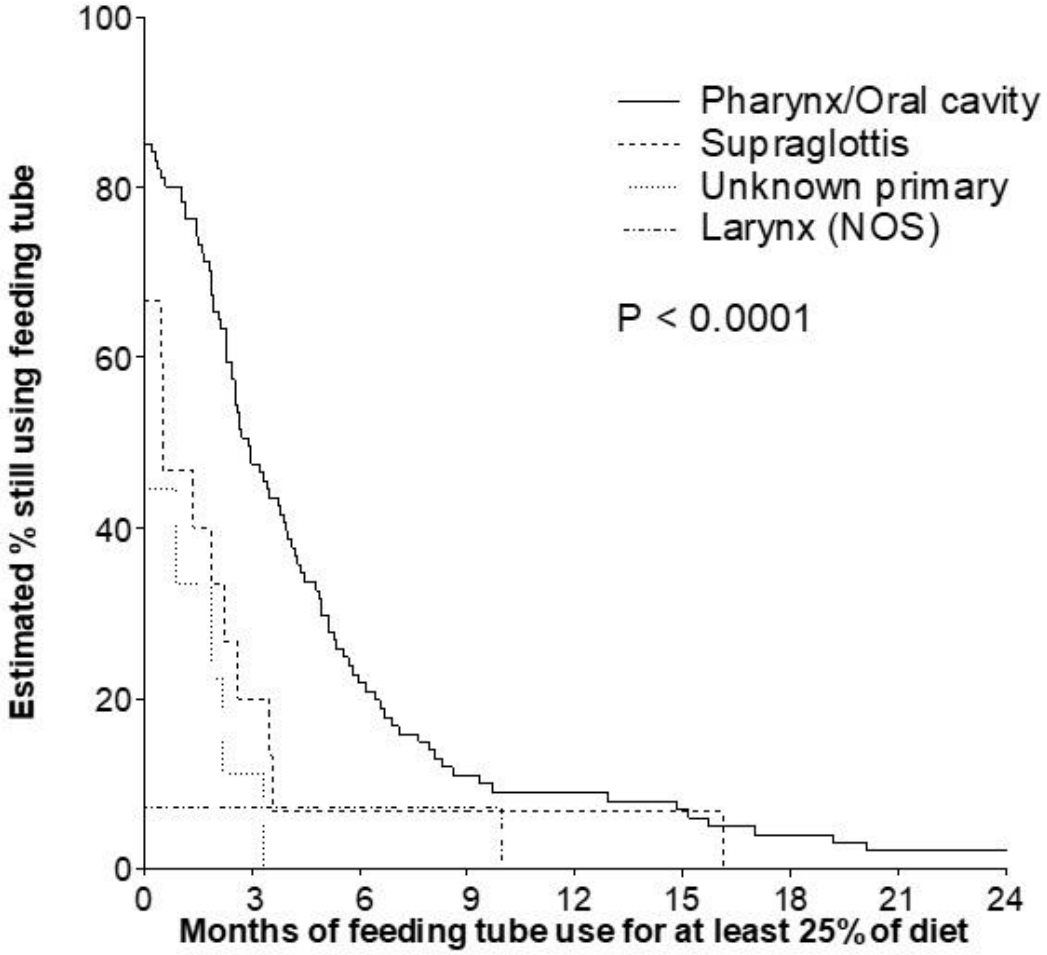
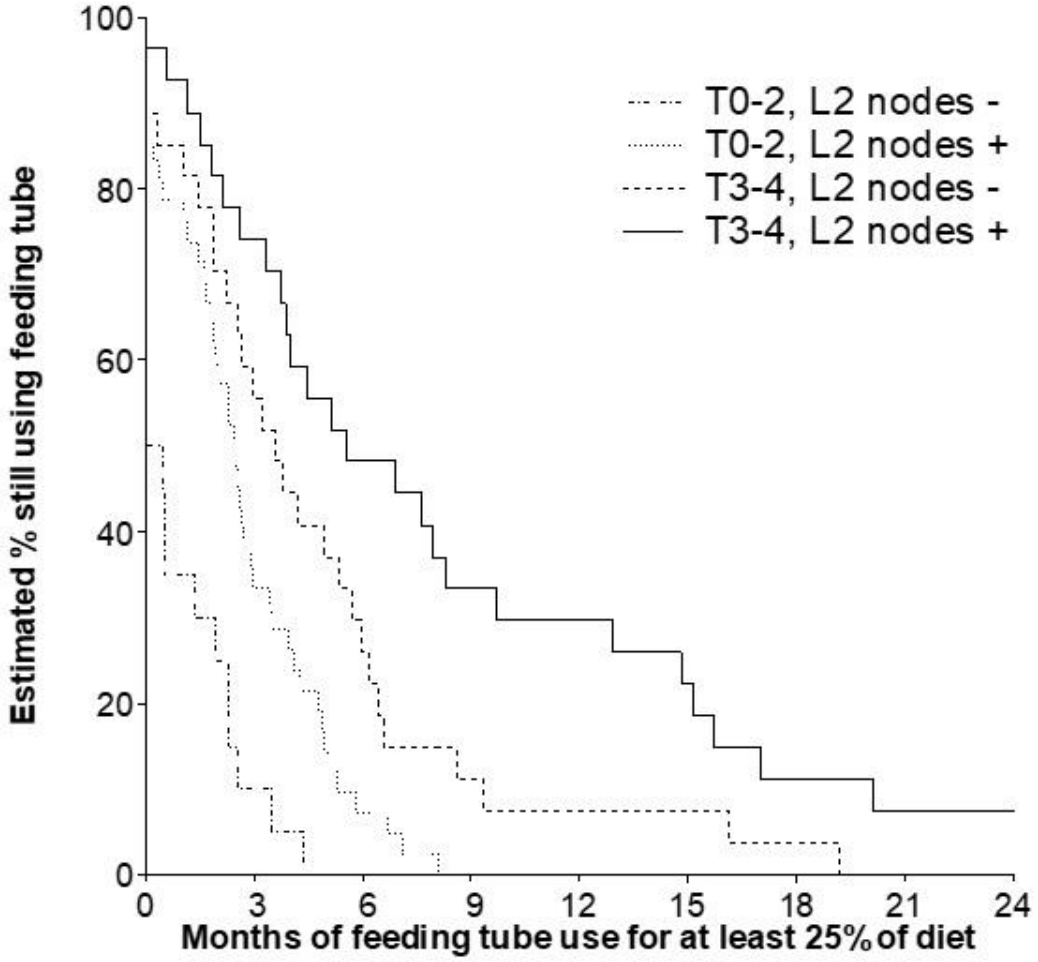


Figure 2. Duration of feeding tube use for at least 25% of nutritional requirements by primary cancer site. Kaplan-Meier analysis, 139 patients.



	Number at risk								
Pharynx/OC	101	48	22	11	9	7	4	2	2
Supraglottis	15	3	1	1	1	1	0	0	0
Unknown	9	1	0	0	0	0	0	0	0
Larynx (NOS)	14	1	1	1	0	0	0	0	0

Figure 3 . Duration of feeding tube use for at least 25% of nutritional requirements by prognostic group according to T-stage and level 2 lymphadenopathy. Kaplan-Meier analysis, 116 patients with pharynx, oral cavity or supraglottis cancers.



Number at risk

T0-2, L2 -	20	2	0	0	0	0	0	0	0
T0-2, L2 +	42	14	3	0	0	0	0	0	0
T3-4, L2 -	27	15	7	3	2	2	1	0	0
T3-4, L2 +	27	20	13	9	8	6	3	2	2

Chapter 5: Clinical and dosimetric risk stratification for patients at high-risk of feeding tube use during definitive IMRT for head and neck cancer

James E. Jackson MBBS, FRANZCR[1,3,4,5,6]; Nigel J Anderson, BAppSc[1,2,5,]2; Morikatsu Wada MBBS, FRANZCR[1], Michal Schneider, PhD[5]; Michael Poulsen MBBS, FRANZCR, MD[6,7], Maureen Rolfo, DipAppSc[1]; Maziar Fahandej, BMBS FRACGP[1,8] ; Hui Gan, MBBS, FRACP, PhD[9]; Daryl Lim Joon, MBBS FRANZCR[1,6]; Vincent Khoo, MD[1,5,10,11]

1. Department of Radiation Oncology, Olivia Newton John Cancer Wellness & Research Centre, Austin Health, Heidelberg, Victoria, AUSTRALIA
2. Department of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria, AUSTRALIA
3. School of Medicine, Griffith University, Gold Coast, AUSTRALIA
4. Faculty of Health Sciences and Medicine, Bond University, Gold Coast, AUSTRALIA
5. Department of Medical Imaging and Radiation Sciences, School of Primary and Allied Health Sciences, Monash University, Victoria, AUSTRALIA
6. Icon Cancer Centres, Gold Coast University Hospital, Queensland, AUSTRALIA
7. Faculty of Medicine, The University of Queensland, Herston, Queensland, AUSTRALIA
8. Department of Palliative Care, St Vincent's Hospital, Fitzroy, Victoria, AUSTRALIA
9. Olivia Newton-John Cancer Research Institute, Austin Health, Heidelberg, Victoria, AUSTRALIA
10. Department of Clinical Oncology, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Chelsea, London, UK.
11. Department of Medicine, University of Melbourne, Victoria, AUSTRALIA

Key words: Radiotherapy, intensity-modulated, enteral nutrition, head and neck neoplasms, radiation dosage.

Corresponding Author: Nigel Anderson (nigel.anderson@petermac.org)

Department: Peter MacCallum Cancer Centre

305 Grattan St

Melbourne, VIC 3000 AUSTRALIA

5.1 Preface

This chapter represents the manuscript that has been submitted for peer review at Oral Oncology in June 2019 (currently under review).

The study presented in Chapter 4 discovered two critical clinical variables- T-classification and level 2 lymphadenopathy- to enable risk stratification of feeding tube use in radically treated HNC patients. Level 2, in particular, was a novel finding, that had not previously been reported. The theme of this Chapter 5 was to investigate dosimetric predictors, in addition to the previously investigated clinical predictors of feeding tube, to ascertain whether additional dosimetric data could be used to further risk stratify feeding tube use. Although this detail was not known at the multidisciplinary tumour board, as it was derived after radiotherapy planning, there remained am opportunity to better understand the needs of this patient cohort with respect to feeding tube use.

As detailed prior to Chapter 4, being able to predict for likelihood and duration of feeding tube use has multiple benefits for both the patient and heath service provider.

5.2 Abstract

Background: To identify organs to which dose limitation using IMRT can potentially modify the incidence and duration of feeding tube use, during and immediately following therapy for HNC.

Methods: One hundred and fourteen patients treated with definitive IMRT (+/- concurrent chemotherapy) for head and neck mucosal cancers were included. Patients were recommended a prophylactic FT and followed up by a dietician for at least eight weeks post-radiotherapy. Salivary and swallowing organs were delineated for each patient. Tumor and dosimetric variables were recorded for all patients and analysed for incidence and duration of FT use for at least 25% of dietary requirements.

Results: Multivariate analysis showed T-classification ≥ 3 and level II lymphadenopathy as independent significant predictors of incidence and duration of feeding tube use in oral cavity, pharyngeal and supraglottic primaries. Mean dose deposited in the cervical esophagus over 36Gy further increased the incidence and duration of feeding tube use. Mean dose deposited in the base of tongue and superior pharyngeal constrictor muscles affected incidence and duration of feeding tube use, respectively.

Conclusions: In patients treated with definitive IMRT, T-classification and Level II lymphadenopathy, combined with a mean cervical esophagus dose over 36Gy can stratify patients into eight distinct risk groups for using feeding tubes for at least 25% of their dietary requirements.

5.3 Introduction

Intensity modulated radiotherapy (IMRT) is a radiotherapy (RT) technique that can be used to intentionally spare normal structures essential to alimentation.[31, 43, 52, 84, 168, 177, 185-187] Reducing dose deposition in these organs may lessen RT-induced swallowing difficulties during head and neck RT. Enteral feeding via a feeding tube (FT) is a method of providing patient nutrition during and immediately following RT in as many as 80% of patients who are unable to maintain a sufficient oral diet.[153-157] While FT's are a convenient way to optimize patient nutrition and impact positively on patients' short-term quality of life[69, 70, 75, 188], gastrostomy tubes can be associated with severe short and long-term complications.[67, 75, 159, 182] Hence, patient selection is crucial to insert gastrostomy tubes in only patients whom are likely to benefit, while sparing a larger population the risk of harm.

We have previously described a risk assessment tool for identifying patients needing FT's for more than 25% of their nutritional requirements. This tool stratifies patients into four risk groups based on two clinical variables: T-classification[189] (TC) and presence of cervical level II adenopathy (LTA).[190] While these disease-related variables are not modifiable, the risk of FT-use may be modifiable by constraining dose deposited in nominated aerodigestive and salivary structures. The purpose of this study was to identify organs to which dose limitation using IMRT can potentially modify the incidence and duration of FT-use, during and immediately following therapy for HNC.

5.4 Methods and Materials

5.4.1 Patients

Following Institutional Ethics Committee approval, the patient population was retrospectively accrued from the institution's radiation oncology database. To be eligible, patients were required to receive primary, definitive IMRT (with or without concurrent systemic treatment) for mucosal cancers of the head and neck. Patients with stage II–IVB disease were included. Patients were excluded if they underwent therapeutic surgery to the primary site or neck

dissection prior to commencing RT. Patients were required to have been offered a prophylactic FT prior to treatment, as per departmental policy, which consist of laryngeal and pharyngeal tumors planned to receive ≥64Gy with bilateral nodal irradiation or having a pre-existing nutritional deficiency. All patients had nutritional assessment and follow-up.

5.4.2 RT planning and treatment

Target volumes were delineated by one radiation oncologist. Pre-treatment evaluation, planning, and delivery have been described previously. The elective (prophylactic) nodes were defined according to consensus guidelines.[160] All patients received bilateral, elective irradiation of levels II to IV nodes. Patients with oropharynx or nasopharynx cancers had bilateral, elective irradiation of level IB nodes. In patients with oropharynx or hypopharynx cancers, elective irradiation of ipsilateral level V nodes and the retrostyloid space was delivered to clinically node positive hemi-necks. In patients with cancer of the nasopharynx, bilateral retrostyloid space lymph nodes were treated to an elective dose. All T0 patients in this cohort were treated electively to bilateral nodal basins, including level IB, while bilateral tonsils and base of tongue (BOT) were treated as high-risk clinical target volume (CTV).

Clinically and radiologically involved nodes were contoured individually. The prescribed doses were planned with a simultaneous integrated boost to a gross tumor volume (GTV), high-risk CTV and low-risk CTV. Dose to GTV (66–70Gy), high-risk CTV (63Gy) and elective CTV (56Gy) was planned at five fractions per week over six to seven weeks. Medically fit patients were considered for concurrent systemic therapy based on disease stage and comorbidities.

Swallowing organs at risk (SWOARs) were delineated on each of the included patients by four investigators, as per the University of Groningen, CT-based delineation guidelines for radiation induced swallowing dysfunction.[95] Contoured SWOARs were the superior (SPCM), middle (MPCM) and inferior (IPCM) pharyngeal constrictor muscles, cricopharyngeal muscle (CP), esophagus inlet muscles (EI), cervical esophagus (CE), BOT, supraglottic larynx

(SGL) and glottic larynx (GL). Additionally, bilateral parotid glands and bilateral submandibular glands (SMGs) were delineated as recognition of their pertinent role in salivary production. An extended oral cavity (OC) was delineated as per Eisbruch et al[191] and the BOT was excluded from this structure for analysis.

5.4.3 Nutritional Assessment and Follow-Up

All patients had a complete pre-therapy consultation with a dietician followed by weekly nutritional reviews while on therapy. Following therapy, dietetic review, whether by phone or in person, was conducted at least every two weeks following therapy until cessation of enteral feeding.

Adequacy of Enteral Intake (AEI) was recorded at each review using the scale: AEI 0 = 0–24%, AEI 1 = 25–49%, AEI 2 = 50–74% and AEI 3 = 75–100% of daily nutritional needs. All patients were followed until their AEI was less than 1.

Speech pathology services were offered to all patients with oropharyngeal dysphagia to minimize aspiration and malnutrition risk. Videofluoroscopy and Fibreoptic Endoscopic Evaluation of swallowing were available for at-risk patients. Swallowing rehabilitation was not available to this patient cohort.

5.4.4 Statistical Analyses

Dosimetric parameters underwent univariate analysis, where values were subdivided into approximate quartiles to the nearest Gy. Potential patient and tumor related prognostic variables were subdivided according to previously reported cut-off points.[190] To explore the risk of FT-use (Yes or No) we used the Fisher exact test if there were only two subgroups (e.g. combined parotid gland mean dose ≤ or > 25 Gy). For analysis of duration of FT-use, Kaplan-Meier analysis was carried out and subgroups were compared using the Mantel-Cox log rank test for differences or the Tarone-Ware test for trend.

Outcomes measured were 1) the risk of FT-use for at least 25% of nutritional requirements

(AEI ≥ 1) and 2) the duration of such use measured in days from the first date the AEI was recorded at 1 or higher to the date when it dropped to AEI 0 or the tube was removed.

As all patients were followed up to cessation of AEI ≥ 1 tube-feeding, no durations were censored. All P values reported were two-sided and 95% confidence intervals (CI) were calculated. The significance criterion was $P < 0.05$ for previously reported prognostic factors or $P < 0.005$ for new prognostic factors (to adjust for multiple hypotheses).

Prognostic factors which were found to have a significant effect on the use of FT (Yes or No) and duration of FT-use for ≥25% of diet in the univariate analyses were tested in multivariable models to find the smallest number of independent prognostic factors. Swallowing structures that were included in the multivariate model were dose dichotomized at the approximate median values for these patients, except for the combined parotid glands, where the QUANTEC dose constraints (dose mean of combined bilateral parotid glands) were used as the point of dichotomization instead (refer to Table 9 for values). For risk of FT-use, exact logistic regression with conditional maximum likelihood inference was used for the multivariable analyses with P values obtained from the exact conditional scores test. For duration of FT-use, Cox proportional hazards regression was used and the exponentials of the coefficients (e^{β}) from the final model were interpreted as “Recovery rate ratios”.

Both backwards and forwards stepwise regression was performed, and variables were retained in the model if the P value was < 0.05.

5.5 Results

Between January 2007 and December 2013, 114 eligible, consecutive patients were treated with radical intent IMRT. Their median age at commencement of RT was 61 years (*Range:* 20 - 91) and 78% were male. The most common cancer site was oropharynx (60 patients, 53%). The other primary sites were nasopharynx (15, 13%), supraglottis (13, 11.5%), glottic larynx (14, 12.5%), hypopharynx (4, 3.5%), oral cavity, (2, 1.5%) and unknown primary (6,

5%). Twenty-nine of the 60 oropharynx patients (48%) had known HPV positive disease. Sixty-eight patients received concurrent systemic therapy (59.6%): 65 patients (57%) received cisplatin (100mg/m^2 three weekly), and three patients (2.6%) received weekly cetuximab. The previously reported univariate analysis of patient demographic and tumor characteristics can be found in Table 5 (in Chapter 4).

5.5.1 Univariate analyses

Results of the univariate analysis on all 114 patients are shown in Table 8. Increasing size of tumor and target volumes were significantly associated for both incidence and duration of feeding tube use. The incidence and duration of FT-use was associated with increasing dose to the OC (D2% and D50%), SPCM (D2% and D50%), MPCM (D2% and D50%), combined parotid glands (Dmean), and combined SMGs (Dmean). Increasing dose to the CP (D2% and D50%) and GL (D2% and D50%) were significantly associated with an increased incidence of FT-use. EI (D50%), CE (D50%) and BOT (D50%) were significantly associated with a longer duration of FT-use. There were no significant associations between the incidence or duration of tube-feeding and dose to IPCM and SGL.

5.5.2 Multivariable analyses

Ninety-four patients with dosimetry/tumor volume data and cancers in the pharynx, oral cavity or supraglottis were included for multivariable analyses for risk and duration of FT-use for at least 25% of dietary needs.

As per our previous study, cancer site was a significant prognostic factor, therefore, six patients with unknown primaries were excluded from the multivariable analyses. Furthermore, only one of the fourteen patients with glottic larynx cancer needed to use a FT, so these 14 patients were considered to be very low-risk and also excluded from the multivariable analyses.

Our previous study found both TC (T3-4) and LTA to be strongly associated with risk and duration of FT-use.[190] Additional tumor volume and dosimetric prognostic factors found to be

significant for risk/and or duration of FT-use at univariate analysis were tested in this multivariable analysis, alongside TC and LTA.

In the final models, TC (T3–4) (p= 0.0099), CE D50% (P=0.0002) and BOT D50% (p=0.022) were significant predictors of risk of FT-use. LTA was of borderline significance (p= 0.051) in the multivariable model once BOT D50% was included, although it was highly significant (P= 0.0032) without BOT D50% in the model. This indicates partial confounding between LTA and median dose to the BOT. TC (T3–4) (P < 0.0001), LTA (P= 0.0040), CE D50% (P=0.0002) and SPCM (p=0.0089) were significant predictors of duration of FT-use (Table 9). Figure 4 displays the observed duration of FT-use when CE D50% is above or below the median of 36Gy. A mean dose of at least 25Gy to the combined parotid glands was of borderline significance when added to this model (P= 0.048) but it was partly confounded with LTA and the median dose to the SPCM, increasing their P values to 0.026 and 0.018 respectively. It added to the complexity of the model while it increased the likelihood ratio by only 1.7, which was insufficient to justify its inclusion.

Several of the raw dosimetry variables were moderately correlated with each other, particularly SPCM D50% and OC D50% (r = 0.74), BOT D50% and OC D50% (r = 0.64), and BOT D50% and SPCM D50% (r = 0.62), so the inclusion of one of a pair in the model made the other factor non-significant. The CE was correlated with EI D50% (r = 0.67), but not with SPCM D50 (r = -0.09), OC D50% (r = -0.10) or BOT D50% (r = -0.11).

The recovery rate of a patient with cancer of the supraglottis, pharynx or oral cavity with T3–4 disease, LTA, CE D50 > 36Gy and SPCM D50 > 64Gy is estimated to be $e^{-1.248 - 0.702 - 0.834 - 0.600} = e^{-3.384} = 0.034$ times the recovery rate of a patient with TC T1–2, no LTA and lower median doses to the CE and SPCM (Table 9).

None of the other factors, which were significant in the univariate analyses were statistically significant in the multivariable analyses, after taking into account advanced TC and presence of LTA.

The outcomes observed for patients in eight prognostic groups derived from the first three prognostic factors (TC, LTA and CE D50%) are shown in Table *10* and were used to generate FT prognostic groups like those generated from both TC and LTA in our previous study. While SPCM was a significant prognostic factor for duration of feeding, incorporating this as an additional factor would result in 16 prognostic groups with very small numbers of patients, providing unreliable estimates.

5.6 Discussion

Our group has previously published a risk stratification model for FT-use, based on clinical TC and presence of metastatic LTA.[190] This model stratified patients into four distinct risk groups. Through further analysis of RT dosimetry to SWOARS, the OC, and parotid and submandibular salivary glands, we have developed three models to further stratify risk of FT-use. The overarching model in this study produces eight main prognostic groups for both the incidence, for more than 48 hours, and duration of FT-use. This model includes the two above clinical values and the mean dose to the CE. Two more sophisticated models are presented for both FT-use and duration. Both include TC, LTA, and mean dose to CE. The additional variables of mean dose to BOT and SPCM are significant for FT-use and duration, respectively. This is shown diagrammatically in Figure 5.

The CE, like other SWOARS, is intimately associated with the physical passage of food in deglutition. An association with poorer swallowing outcomes with increasing dose to this organ has been described previously.[168] This current study shows a significant impact of a mean dose exceeding 36Gy on both incidence and duration of FT-use on patients already stratified by TC and LTA. While this impact was most pronounced in the lower risk patients for FT incidence, the median (range) FT duration for patients with advanced TC, LTA present, and mean dose to CE over 36Gy was 170 (113 – 479) days compared to 101 (55 - 393) days in similar patients with CE mean doses of 36Gy or less. While this association, obtained from retrospective data, does not prove causality, it represents a promising variable for future, prospective studies. Limiting dose to the CE is particularly appealing, as the

majority of patients in this study (53%), and in contemporary western cohorts[192], were treated for oropharyngeal cancers. Modern helical IMRT techniques should easily be able to achieve doses well under 36Gy, without compromising target coverage, in the majority of these patients.

The BOT is a SWOAR that a considerable amount of HNC primaries arise from, or directly invade.[95] Increasing dose to this organ has been associated with poor swallowing outcomes.[168] In this cohort, patients who received a mean dose of over 61Gy to their BOT were more likely to use a FT than those who received lower doses, and this effect was additive to the TC, LTA and CE mean dose. Not surprisingly, a partial confounding effect was seen between BOT dose and LTA. The P-value for FT-use associated with LTA rose from 0.0032 to 0.05 with the addition of BOT dose. As previously described, there are both anatomical and disease-related reasons for this confounding effect.[95, 190, 193]

Prospective evaluation of the impact of dose limitation to the BOT would not be as straightforward as it would be for CE. Tumors arise in the BOT and invade into it from other sites and the BOT possesses rich lymphatics. Despite ongoing advances, many radiation oncologists doubt the sensitivity of three dimensional and molecular imaging for detecting the full extent of disease spread in this region. Treatment failure in the BOT portends a poor prognosis and surgical salvage has traditionally been difficult and debilitating[194]. For these reasons, many clinicians would likely be reluctant to reduce margins around gross disease in the BOT in pursuit of a swallowing outcome.

The model for FT duration in this manuscript incorporates TC, LTA, CE mean dose and mean dose to the SPCM above 64Gy. Like BOT, SPCM dose is also partially confounded by LTA, albeit to a lesser degree. Similar anatomical and disease related (tonsillar and BOT primaries tend to metastasize to level II) mechanisms for this interaction likely hold. In this model, we also see partial confounding with mean parotid gland dose. This makes intuitive sense based on the above reasoning, as parotid glands sit immediately lateral to level II.[160] Prospective evaluation of dose limitation to the SPCM would be difficult in patients with

tonsillar primaries, particularly with advancing TC. This may be more appropriate for patients with BOT and other non-tonsillar primaries. Conversely, BOT is a more appealing avoidance structure in patients with tonsillar primaries.

SMGs produce 65-90% of mucin rich saliva and 95% of salivary flow during a 24-hour period.[171] Studies have shown that a mean dose of less than 39Gy to SMGs results in both patient and observer reported xerostomia.[171] Wopken et al have observed a significant increase in 6-month FT dependence with every increasing Gy of mean dose to the ipsilateral (OR 1.13; $p<0.001$) and contralateral SMG (OR 1.10; $p<0.001$).[168] Our univariate analysis showed increasing incidence and duration of FT-use with increasing mean dose to SMGs over 61Gy. In this patient cohort, bilateral level IB nodal regions were electively irradiated in all patients with naso or oropharyngeal primaries, and SMGs are contained in this region.[160] This has led to universally higher SMG doses in this study compared to other cohorts with selective IB omission. This higher overall dose likely contributes to the non-significance of SMG dose in our multivariate models. There is ample retrospective data supporting the safety of submandibular sparing techniques[171, 195-197] and this should be pursued where appropriate.

In our univariate analysis, limiting the mean dose to bilateral parotid glands to under 25Gy was associated with reduced incidence and duration of FT-use. This is consistent with previously published data.[168] Other studies have shown that mean dose to the contralateral parotid gland alone is associated with xerostomia and use of FT, six months following RT.[168, 174] It is well known that avoiding the irradiation of parotid glands can reduce the incidence and severity of xerostomia[168, 172-174] and as such is already a priority in IMRT plans worldwide.

This study reports on two dependent variables, the incidence and duration of FT-use. Regarding incidence, 70% of patients with early TC, with no LTA and a low mean CE dose were able to avoid any tube-feeding. This represents a truly low-risk population and this risk is lower still in patients with low mean BOT dose. These findings may have implications for

resource allocation, certainly with regards to avoiding gastrostomy tubes, and perhaps regarding less intensive speech therapy and dietetic support.

The duration of FT-use is a particularly valuable endpoint with regards to selecting patients who may benefit from a prophylactic gastrostomy. Substantial controversy exists as to whether HNC patients are best managed via reactive or prophylactic FTs[67], and a thorough discussion of same is beyond the scope of this manuscript. However, even departments that adhere to strict reactive FT protocols insert prophylactic tubes in a subset of high-risk patients, and, conversely, departments with policies of liberal, prophylactic FT-use will choose to spare a low-risk subset of patients from undergoing the insertion procedure. All patients in this study were recommended a prophylactic FT and this potentially affected the overall duration of FT-use seen. Many studies have previously shown higher FT-use at six months with prophylactic use of a FT.[75, 76, 175] However, Salas et al found no difference between reactive and prophylactic FT and Silander et al reported lower rates of grade 3 dysphagia in patients with a prophylactic gastrostomy tube (2% vs 9%).[69, 70]

In this study, no patient had access to swallowing rehabilitation. A randomized controlled trial has shown that swallowing exercises led to less deterioration of swallowing muscles and functional swallowing ability during chemoradiotherapy for HNC.[120] Patients randomized to swallowing exercises were more likely to maintain an oral diet and were less likely to use a FT.[120] Adherence to swallowing exercises can improve maintenance of an oral, or partial oral, diet during chemoradiotherapy. This appears to be associated with better long-term diet and shorter FT-use.[182] The lack of swallowing exercises in this study may limit the applicability of our data to patients who are performing swallowing exercises. However, the complete absence of these exercises in this cohort contributes to the uniformity of our data and possibly adds to the internal validity of our findings. Swallowing exercises have definite patient benefits, but not all patients are adherent to prescribed swallowing exercises and many patients are partially adherent, making these benefits difficult to quantify.[120, 182]

This study possesses all the limitations inherent to a single-institution, retrospective analysis.

We are unable to provide data on patients' functional swallowing ability; however, we were able to accurately report on patients having oral, or partial oral diet at various time points due to comprehensive, prospectively recorded nutritional data. All patients were treated by a single radiation oncologist; however, it must be acknowledged that these patients were treated over seven years, a sufficient time period for individual practice to vary. All patients were treated in the FDG-PET and IMRT era. This lends to uniformity in staging, volume delineation and treatment delivery across the cohort. This study expands upon a simple and novel clinical risk stratification tool and identifies the CE, BOT and SPCM as avoidance structures for further prospective study.

5.7 Conclusion

In patients with pharynx or supraglottic larynx cancers treated with definitive, bilateral IMRT, with or without concurrent systemic therapy, two clinical risk factors, namely T-classification (T3–4) and level II lymphadenopathy, combined with a mean cervical esophagus dose over 36Gy, can potentially stratify patients into eight distinct risk groups for using feeding tubes for at least 25% of their dietary requirements. This stratification may be useful in the clinic prior to commencing radiotherapy, so that patients at risk may have a FT inserted early prior to further nutritional status deterioration. Prospective studies on dose limitation to the cervical esophagus, base of tongue and superior pharyngeal constrictor muscles are warranted.

Table 8. *Univariate analyses of additional prognostic factors for feeding tube use (Yes/No) and duration, following radiotherapy planning.*

Prognostic factor	**Subgroup**	**Feeding tube used***			**Days of feeding tube use***		
		Yes/Total	**%**	**P value†**	**Median**	**(95% CI)**	**P value‡**
Cranio-caudal Length of PTV High	≤ 6.5cm	18/41	44%	<0.0001	0	(0-28)	<0.0001
	>6-8cm	23/31	74%		79	(14-130)	
	>8-11cm	35/38	92%		112	(75-157)	
	>11cm	25/29	86%		81	(55-149)	
GTV Primary	≤ 10cc	15/40	38%	<0.0001	0	(0-16)	<0.0001
	>10–20cc	26/34	76%		58	(35 – 79)	
	>20-40cc	28/32	88%		86	(70 – 120)	
	>40cc	32/33	97%		170	(118-233)	
GTV Nodes	0cc	24/46	52%	0.0019	15	(0-59)	0.017
	>0–10cc	19/24	79%		113	(44 – 161)	
	>10-30cc	33/37	89%		77	(64 – 90)	
	>30cm	25/32	78%		78	(44 – 149)	
GTV Total	≤ 20cc	15/40	38%	<0.0001	0	(0-16)	<0.0001
	>20–40cc	23/28	82%		69	(35 – 101)	
	>40-70cc	36/40	90%		90	(75 – 130)	
	>70cm	27/31	87%		149	(57 – 204)	
Oral Cavity (D2%)	≤ 54Gy	10/26	38%	<0.0001	0	(0 - 68)	<0.0001
	>54–70Gy	17/28	61%		51	(0 – 77)	
	>70-74Gy	30/34	88%		79	(50 – 120)	
	>74Gy	25/25	100%		136	(77 – 182)	
Oral Cavity (D50%)	≤ 27Gy	12/28	43%	<0.0001	0	(0 - 42)	<0.0001
	>27–37Gy	19/29	66%		58	(0 – 70)	
	>37-51Gy	24/28	86%		92	(57 – 163)	
	>51Gy	27/28	96%		129	(90 – 204)	
SPCM (D2%)	≤ 65Gy	9/29	31%	<0.0001	0	(0 - 0)	<0.0001
	>65–72Gy	20/25	80%		70	(57 – 101)	

	>72-75Gy	22/24	92%		60	(35 – 105)	
	>75Gy	32/35	91%		130	(90 – 182)	
SPCM (D50%)	≤ 52Gy	10/26	38%	<0.0001	0	(0 - 58)	<0.0001
	>52–64Gy	24/34	71%		47	(11 – 70)	
	>64-69Gy	21/24	88%		90	(57 – 120)	
	>69Gy	28/29	97%		149	(101 – 200)	
MPCM (D2%)	≤ 67Gy	13/28	46%	<0.0001	0	(0 - 70)	0.0001
	>67–71Gy	17/25	68%		66	(0 – 106)	
	>71-74Gy	28/36	78%		64.5	(44 – 97)	
	>74Gy	25/25	100%		161	(90 – 204)	
MPCM (D50%)	≤ 56Gy	12/25	48%	<0.0001	0	(0 - 105)	0.024
	>56–62Gy	21/33	64%		70	(0 – 101)	
	>62-68Gy	26/31	84%		68	(35 – 125)	
	>68Gy	24/25	96%		79	(59 – 233)	
IPCM (D2%)	≤ 58Gy	19/26	73%	0.55	89	(18 - 120)	0.15
	>58–64Gy	25/31	81%		75	(55 – 125)	
	>64-71Gy	17/26	65%		33	(0 – 65)	
	>71Gy	22/31	71%		77	(14 – 170)	
IPCM (D50%)	≤ 44Gy	21/28	75%	0.11	70	(10 - 106)	0.86
	>44–51Gy	26/29	90%		77	(58 – 113)	
	>51-66Gy	20/32	63%		62	(0 – 118)	
	>66Gy	16/25	64%		42	(0 – 108)	
CPM (D2%)	≤ 52Gy	22/27	81%	0.012	77	(49 - 106)	0.56
	>52–57Gy	25/31	81%		81	(45 – 122)	
	>57-66Gy	22/28	79%		72.5	(31 – 149)	
	>66Gy	13/26	50%		8	(0 – 108)	
CPM (D50%)	≤ 38Gy	23/29	79%	0.009	66	(35 - 101)	0.065
	>38–43Gy	20/24	83%		76	(45 – 113)	
	>43-57Gy	27/32	84%		92	(57 – 157)	
	>57Gy	12/27	44%		0	(0 – 68)	

EIM (D2%)	≤ 45Gy	21/28	75%	0.060	68	(10 - 101)	0.10
	>45–51Gy	22/26	85%		81	(58 – 161)	
	>51-57Gy	25/31	81%		77	(44 – 157)	
	>57Gy	15/29	52%		16	(0 – 70)	
EIM (D50%)	≤ 35Gy	18/28	64%	>0.99	52	(0 - 97)	0.042
	>35–41Gy	24/31	77%		65	(18 – 83)	
	>41-48Gy	23/26	88%		123	(68 – 177)	
	>48Gy	18/29	62%		57	(0 – 133)	
CE (D2%)	≤ 43Gy	17/28	61%	0.51	17	(0 - 90)	0.18
	>43–49Gy	23/30	77%		77	(44 – 130)	
	>49-55Gy	25/29	86%		77	(57 – 113)	
	>55Gy	18/27	67%		77	(0 – 133)	
CE (D50%)	≤ 28Gy	17/30	57%	0.060	16	(0 - 70)	0.039
	>28–36Gy	20/28	71%		62	(7 – 97)	
	>36-42Gy	26/29	90%		101	(77 – 130)	
	>42Gy	20/27	74%		77	(16 – 149)	
BOT (D2%)	≤ 64Gy	9/28	32%	0.51	0	(0 - 42)	0.18
	>64–71Gy	22/29	76%		68	(16 – 81)	
	>71-74Gy	21/24	88%		94.5	(50 – 125)	
	>74Gy	31/33	94%		105	(59 – 182)	
BOT (D50%)	≤ 46Gy	11/28	39%	0.060	0	(0 - 58)	0.039
	>46–61Gy	17/27	63%		45	(0 – 77)	
	>61-79Gy	30/33	91%		101	(70 – 136)	
	>79Gy	25/26	96%		101	(55 – 200)	
SGL (D2%)	≤ 66Gy	20/27	74%	0.78	70	(35 – 113)	0.43
	>66–71Gy	19/29	66%		59	(0 – 79)	
	>71-73Gy	19/23	83%		90	(57 – 120)	
	>73Gy	25/34	74%		66	(31 – 130)	
SGL (D50%)	≤ 45Gy	18/27	67%	0.63	77	(0 - 120)	0.77
	>45–56Gy	27/30	90%		82	(65 – 116)	

	>56-68Gy	19/28	68%		53.5	(0 – 122)	
	>68Gy	19/28	68%		45.5	(0 – 108)	
GL (D2%)	≤ 48Gy	24/30	80%	0.011	77	(44 – 101)	0.37
	>48–54Gy	24/26	92%		94	(58 – 150)	
	>54-71Gy	19/30	63%		63.5	(0 – 113)	
	>71Gy	16/28	57%		16	(0 – 108)	
GL (D50%)	≤ 34Gy	27/32	84%	0.0016	80	(35 - 106)	0.42
	>34–41Gy	22/27	81%		75	(57 – 118)	
	>41-66Gy	21/27	78%		77	(59 – 128)	
	>66Gy	13/28	46%		0	(0 – 106)	
Both Parotids (Dmean)	< 25Gy	22/33	67%	0.0021	35	(0 – 70)	<0.0001
	≥25Gy	55/59	93%		113	(79 – 150)	
Both SMGs (Dmean)	≤ 61Gy	11/19	58%	0.0013	16	(0 - 106)	0.0003
	>61–64Gy	16/21	76%		70	(11 – 79)	
	>64-67Gy	18/18	100%		89	(57 – 149)	
	>67Gy	15/16	94%		202	(77 – 451)	

Abbreviations: SPCM, superior pharyngeal constrictor muscle; MPCM, middle pharyngeal constrictor muscle; IPCM, inferior pharyngeal constrictor muscle; CPM. crycopharyngeal muscle; EIM, esophageal inlet muscle; CE, cervical esophagus; BOT, base of tongue; SGL, supraglottic larynx; GL, glottic larynx; SMG, submandibular gland.

* "Feeding tube use" means feeding tube was used for at least 25% of nutritional requirements.

† Two-sided P value from Fisher exact test for difference between 2 subgroups, Pearson chi square test for difference between 3 or more unordered subgroups, or Cochran-Armitage test for trend across 3 or more ordered subgroups.

‡ Two-sided P value from Mantel-Cox log rank test for differences between subgroups or Tarone-Ware test for trend across 3 or more ordered subgroups.

Table 9. Final multivariable models for feeding tube use[*] (Yes/No) and duration (n = 94) after planning CT (i.e. including GTV, PTV and dosimetric variables)

Feeding tube use (exact logistic regression with conditional maximum likelihood inference) †

					Odds ratio		Exact
Factor	Reference	Level	β	s.e.$_\beta$	OR	95% CI	P value
T stage	T1–T2	T3–T4	2.314	0·925	10.1	1·4–124.4	0·0099
Level 2 nodes	No	Yes	1.707	0·866	5.5	0.8–51.4	0·051[#]
CE D50	≤ 36Gy	> 36Gy	3.466	1.162	32.0	3.3-1811.0	0·0002
BOT D50	≤ 61Gy	> 61Gy	1.930	0·810	6.9	1·2–55.0	0·022[#]

Duration of feeding tube use (Cox proportional hazards regression) †

					Recovery ratio		Exact
Factor	Reference	Level	β	s.e.$_\beta$	RR	95% CI	P value
T stage	T1–T2	T3–T4	-1.248	0·258	0.287	0.17–0.48	<0·0001
Level 2 nodes	No	Yes	-0.702	0·244	0.495	0.31–0.80	0·0040
CE D50	≤ 36Gy	> 36Gy	-0.834	0.222	0.434	0.28–0.67	0·0002
SPCM D50	≤ 61Gy	> 61Gy	-0.600	0·229	0.549	0.35–0.86	0·0089

Abbreviations: CE, cervical esophagus; BOT, base of tongue; SPCM, superior pharyngeal constrictor muscle

* "Feeding tube use" means feeding tube was used for at least 25% of nutritional requirements.

[#] Level 2 nodal involvement was of borderline significance (P = 0.051) once BOT D50 was included. However, it was highly significant (P = 0.0032) without BOT D50 in the model. This indicates partial confounding between Level 2 nodes and median dose to the base of the tongue.

† β = coefficient for each Level relative to the Reference category, based on 116 patients with cancers of pharynx, oral cavity or supraglottic larynx. s.e.$_\beta$ = estimated standard error of β. OR or RR = e^{β}. 95% CI = 95% confidence interval for the OR or RR = $e^{\beta \pm 1{\cdot}96\ (\text{s.e.}\beta)}$.

‡ Other factors which were not significant when added individually to the models were: body mass index (<18.5 vs ≥18.5), nutrition (PG-SGA mal-nourished vs well nourished), dysphagia (Yes vs No), cancer (pharynx/oral cavity vs supraglottic larynx), human papilloma virus status (positive/unknown vs negative), N stage (N1–3 vs N0), bilateral neck nodes (Yes vs No), planned concurrent chemotherapy, PTV length (≤8cm vs >8cm), GTV primary size

(≤20cc vs >20cc), GTV nodal size (≤ 10cc vs > 10cc), GTV total size (≤40cc vs >40cc), oral cavity D50 (≤37Gy vs >37Gy), superior PCM D50 (≤64Gy vs >64Gy), middle PCM D50 (≤62Gy vs >62Gy), esophageal inlet muscle D50 (≤41Gy vs >41Gy), both parotids Dmean (<25Gy vs ≥20Gy) and both submandibular gland Dmean (<64Gy vs ≥64Gy). When added individually to the above models, the P values for these factors were all >0.1 for incidence and >0.1 for duration of feeding tube use.

Table 10. *Prognostic groups based on T stage and Level 2 lymphadenopathy: data from 94 patients with cancers of pharynx, oral cavity or supraglottis.*

			PEG feeding ≥ 25% of diet		*Duration of PEG feeding*	
T stage	*Level 2 nodes*	*CE D50*	*Yes/Total*	*%*	*Median days*	*(95% CI)*
T1–2	No	≤ 36 Gy	3/10	30%	0	(0 – 42)
		> 36 Gy	6/7	86%	70	(0 – 133)
	Yes	≤ 36 Gy	12/16	75%	65	(0 – 120)
		> 36 Gy	15/15	100%	83	(70 – 157)
T3–4	No	≤ 36 Gy	10/13	77%	90	(0 – 150)
		> 36 Gy	11/11	100%	116	(57 – 491)
	Yes	≤ 36 Gy	9/9	100%	101	(55 – 393)
		> 36 Gy	13/13	100%	170	(113 – 479)
All supraglottic/pharynx/OC patients with dosimetry			79/94	84%	79	(68 – 106)

Abbreviations: CE, cervical esophagus

Figure 4. *Duration of feeding tube use for at least 25% of nutritional requirements by D50%of cervical oesophagus. Kaplan-Meier analysis, 94 patients.*

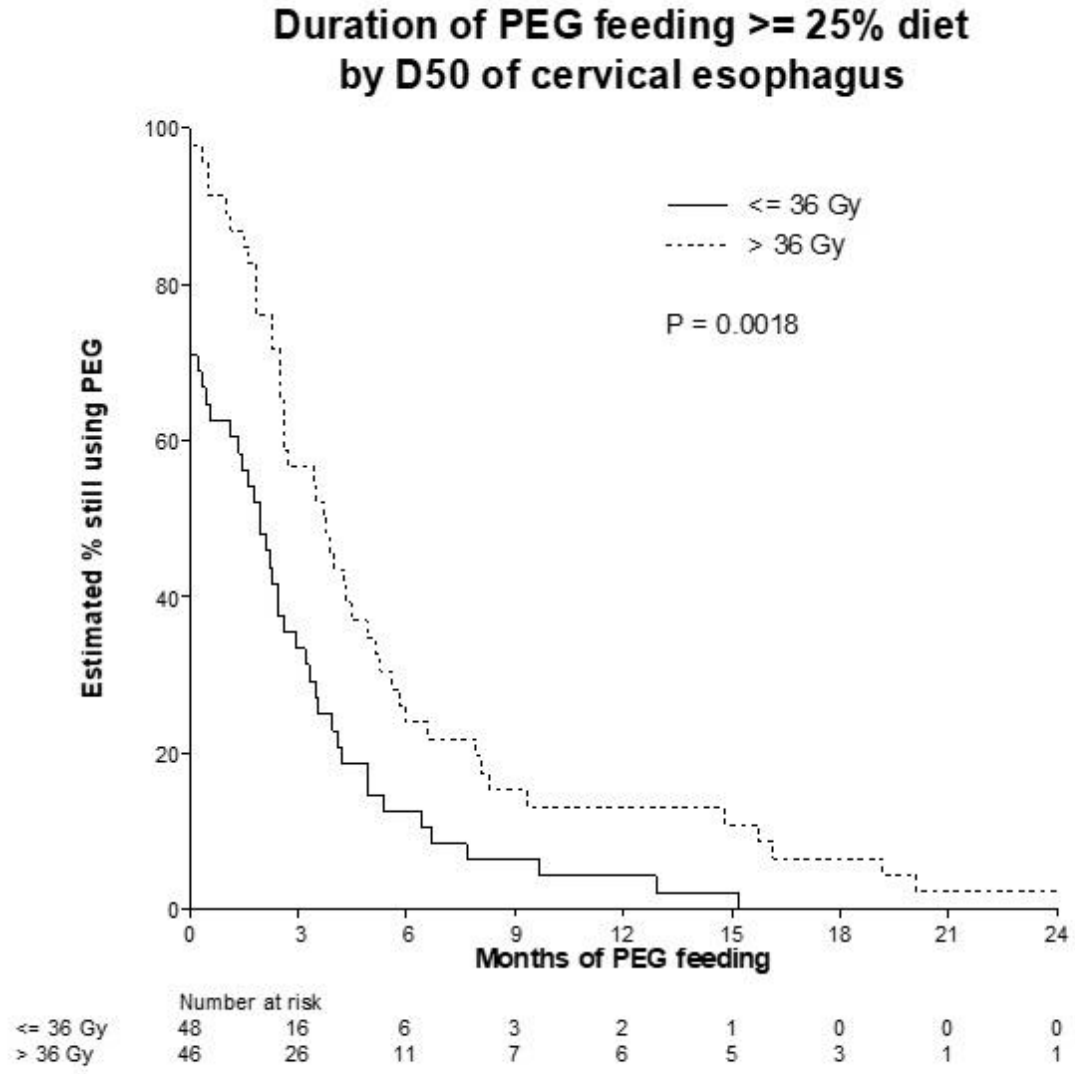
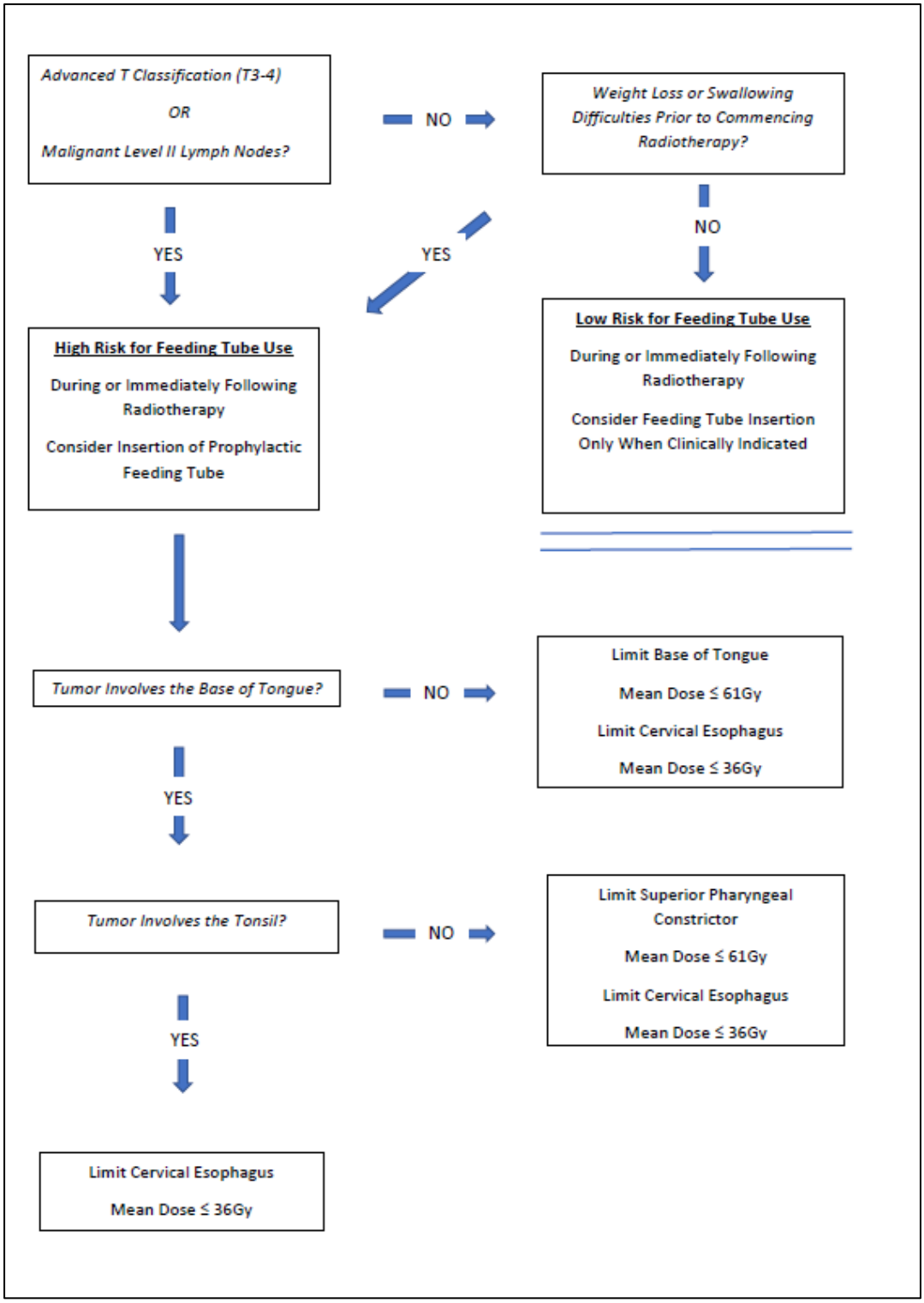


Figure 5. Proposed treatment approach for patients for patients receiving definitive, bilateral (chemo) radiotherapy for cancers of the head and neck.



Chapter 6: Increased, On-treatment Weight Loss Despite a Decreased Risk of Prolonged Feeding Tube Use: The Changing Landscape of Head and Neck Cancer Radiotherapy Patients

Nigel J Anderson[1,2,5], James E. Jackson MBBS[1,3,4,5], Morikatsu Wada[1], Michal Schneider[5], Michael Poulsen[6,7], Maureen Rolfo[1], Maziar Fahandej[1,8], Hui Gan[9,11,12], Daryl Lim Joon[1], Vincent Khoo[1,5,10,12]

[1] Department of Radiation Oncology, Olivia Newton John Cancer Wellness & Research Centre, Austin Health, Heidelberg, Victoria, AUSTRALIA

[2] Department of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria, AUSTRALIA

[3] School of Medicine, Griffith University, Gold Coast, AUSTRALIA

[4] Faculty of Health Sciences and Medicine, Bond University, Gold Coast, AUSTRALIA

[5] Department of Medical Imaging and Radiation Sciences, Monash University, Victoria, AUSTRALIA

[6] Radiation Oncology Centres, Gold Coast University Hospital, Queensland, AUSTRALIA

[7] Faculty of Medicine, The University of Queensland, Herston, Queensland, AUSTRALIA

[8] Department of Palliative Care, St Vincent's Hospital, Fitzroy, Victoria, AUSTRALIA

[9] Department of Medical Oncology, Austin Health and Olivia Newton-John Cancer Research Institute, Melbourne, Victoria, Australia.

[10] Department of Clinical Oncology, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Chelsea, London, UK.

[11] School of Cancer Medicine, La Trobe University School of Cancer Medicine, Melbourne, Australia.

[12] Department of Medicine, University of Melbourne, Victoria, AUSTRALIA

Published: Journal of Medical Radiation Sciences, 2019 (in press)

6.1 Preface

This chapter replicates the manuscript that was peer reviewed and subsequently published in Journal of Medical Radiation Sciences in 2019 (currently In Press, following acceptance for publication in June 2019).

The theme of this manuscript was to further investigate the patient cohort that was analysed for clinical predictors of prolonged feeding tube use in Chapter 4. Two significant clinical predictors of prolonged feeding tube, namely T-classification and level 2 lymphadenopathy, were derived in Chapter 4. This enabled four distinct groups to be categorized for the risk of feeding tube use on the basis of a T-classification and level 2 lymphadenopathy.

Feeding tubes are a critical tool in the weight management of head and neck radiotherapy patients, to mitigate the debilitating effects of toxic radiotherapy and its effect on delivering precision treatment. This chapter, however, delved deeper, to ascertain whether a higher risk of prolonged feeding tube use translated to greater weight loss over a course of radiotherapy. Chapters 4 and 5 looked purely at feeding tube use as a surrogate for dysphagia. In addition, this chapter investigated weight loss within each of the previously risk stratified HNC patient cohorts.

6.2 Abstract

Introduction: Precision radiotherapy relies heavily on optimal weight management. Our group previously developed a risk stratification model for patients at risk of prolonged feeding tube (FT) intervention. The study objective was to assess on-treatment weight loss according to stratified risk of prolonged FT use.

Methods: One-hundred and one (n=101) definitive head and neck radiotherapy patients were included in this study. Patients were stratified into High-Risk (HRi: T-classification≥3 with Level 2 Nodal disease), High-Intermediate-Risk (HIRi: T-classification≥3 without Level 2 Nodes), and Low-Intermediate-Risk (LIRi: T-classification<3 with Level 2 Nodes) of prolonged FT use. Demographic variables and on-treatment weight loss were evaluated according to risk status.

Results: Oropharyngeal carcinoma (OPC) was present in a larger proportion in the LIRi cohort (HRi: 71%, HIRi: 52%, LIRi: 81%, p=0.008). LIRi patients were more likely to have human papilloma virus (HPV) associated disease (88%, p=0.001). Never/minimal smoking (p=0.003), good performance status (p<0.001), healthy BMI (p=0.050) and no pre-existing dysphagia (p<0.001) were predominant within the LIRi prognostic group.

LIRi patients lost significantly more weight in total (HRi=4.8% v LIRi=8.2%, p=0.002; HIRi=5.2% v LIRi=8.2%, p=0.006) and when using a FT (HRi=4.6% v LIRi=8.8%, p<0.001; HIRi=5.3% v LIRi=8.8%, p=0.002).

Conclusions: Patients identified as low-intermediate-risk of prolonged, ≥25% FT use report significantly increased weight loss compared to patients at higher risk of FT use. This cohort is typical of the increasing number of patients presenting with HPV-associated OPC. Results of this study suggest we should closely observe such patients throughout treatment, to ensure optimal weight maintenance, facilitating precision radiotherapy.

Keywords: Feeding Tube, Head & Neck Cancer, IMRT, Toxicity, Weight Loss.

6.3 Introduction

Radiotherapy (RT) for head and neck cancer is associated with the debilitating toxicities of malnutrition and weight loss.[149, 151, 152] It has been long established that dysphagia and subsequent weight loss during treatment can have a detrimental effect on survival outcomes.[198] Weight maintenance is critical to optimal treatment tolerance and paramount to the delivery of precision radiotherapy, as changes in patient contour will impact on the design and delivery of radiotherapy. Enteral feeding via a feeding tube (FT) is a common method of minimising weight loss by providing patient nutrition during and immediately following RT in as many as 80% of head and neck cancer patients.[155-157] Despite the demonstrated benefits of FT for nutritional support, conflicting evidence remains as to the most effective strategy for optimal weight management.[158] Previous work from our group proposed a risk stratification model for patients at risk of requiring prolonged FT use for ≥25% of nutritional requirement, to ensure insertion of prophylactic FT is reserved for those patients likely to derive the most benefit.[133] Multivariate regression was undertaken on clinical variables previously recognised in the literature. Additional variables that were deemed to be of potential importance (i.e. specific levels of macroscopic nodal involvement) or where little to no published data was available as to their role in feeding tube risk stratification, warranting further investigation (i.e. Human Papilloma Virus or HPV-status) were also included for analysis.[47, 61, 90, 91, 161]T-classification and level 2 lymphadenopathy were found to be highly predictive of feeding tube use. Four levels of prolonged feeding tube use risk were derived from these two prognostic variables:

i) High Risk (HRi)- T-classification ≥3 and Level 2 Lymphadenopathy
ii) High-Intermediate Risk (HIRi)- T-classification ≥3 and No Level 2 Lymphadenopathy
iii) Low-Intermediate Risk (LIRi)- T-classification <3 and Level 2 Lymphadenopathy
iv) Low Risk (LRi)- T-classification <3 and No Level 2 Lymphadenopathy

The main objective of this study was to assess acute weight loss (i.e. weight lost during the radiotherapy treatment course) among the high, high-intermediate and low-intermediate risk

cohorts, to better understand if the known risk of prolonged FT use for ≥25% of nutritional requirement is indicative of on-treatment weight loss outcomes, and consequently, optimal FT utilisation is occurring to ensure weight maintenance during radiotherapy. Subsequently, identification of high frequency clinical variables (beyond T-classification and level 2 lymphadenopathy) in the increased weight loss cohort will enable a greater understanding of the feeding tube use/weight loss relationship, and its impact on the management of the head and neck radiotherapy patient population.

6.4 Methods and Materials

6.4.1 Patients

Following Institutional Ethics Committee approval, one-hundred and one patients, treated between January 2007 and December 2013 who were previously incorporated into the already-published FT risk stratification model, were included for further analysis in this retrospective study. As this study was a retrospective review of data captured as part of routine patient care, which is de-identified, a waiver of consent was approved by the institutional ethics committee. LIRi, HIRi and HRi patients are defined as patients who have a median FT use of greater than or equal to 25% of their nutritional requirement for 75, 108 and 170 days, respectively.[133] Patients at Low Risk (LRi) of FT use (i.e. median feeding tube use of ≥25% of nutritional requirement of 7 days) were excluded from the analysis due to negligible likelihood of FT insertion as derived from our previous work. Patients were included in the weight loss analysis based on their risk-stratified status alone, regardless of FT insertion or not (eg. a HRi patient may have declined a FT insertion, yet still be included in the analysis as a ‘high risk’ patient due to having a T-classification ≥3 and level 2 lymphadenopathy).

As per our previous study, to be eligible for inclusion in the database, patients were required to receive primary and definitive intensity-modulated radiotherapy (IMRT) (with or without concurrent systemic treatment) for mucosal cancers of the head and neck.[133] Patients with

stage II–IVB disease were included. Patients were excluded if they underwent therapeutic surgery to the primary site or neck dissection prior to commencing RT. Patients were required to have been offered a prophylactic FT prior to treatment (as per departmental policy), have a tumour of supraglottic, oral cavity or pharyngeal origin, planned to receive ≥64Gy with bilateral nodal irradiation, with or without current chemotherapy. 'FT Only' patients are defined as those who had a FT inserted and utilised it for greater than 25% of nutritional needs (for at least 48 hours), as opposed to those who didn't have a FT inserted (declined) and/or patients who had a FT inserted and didn't use it (i.e. failed to utilise their FT for more than 25% of their nutritional needs for at least 48 hours). Patients with unknown primary and glottic laryngeal cancers were excluded from the risk stratification model. All included patients had to be followed up by a dietician for a minimum of 8 weeks post radiotherapy completion.

6.4.2 RT planning and treatment

Uniform delineation of all radiotherapy target volumes was performed by a (one) radiation oncologist on a radiotherapy planning contrast enhanced computed tomography (CECT) scan. The PET/CT and MRI (if available) were co-registered with the planning CECT on the treatment planning system. A comprehensive narrative detailing target delineation, radiation dose, radiotherapy planning and treatment methodology is described in Anderson et al (2018).[133]

6.4.3 Nutritional Assessment and Follow-Up

All patients had a complete pre-therapy consultation with a dietician followed by weekly nutritional reviews while on therapy. Following therapy, dietetic review, by phone or in person, was conducted at least every two weeks following therapy until cessation of enteral feeding.

Adequacy of Enteral Intake (AEI) was recorded at each review using the scale: AEI 0 = 0–24%, AEI 1 = 25–49%, AEI 2 = 50–74% and AEI 3 = 75–100% of daily nutritional needs i.e.

the contribution of enteral feeding to daily nutritional requirement. All patients were followed until their AEI was less than 1.

Speech pathology services were offered to all patients with oropharyngeal dysphagia to minimize aspiration and malnutrition risk. Video fluoroscopy and Fibreoptic Endoscopic Evaluation of Swallowing were available for at-risk patients. Swallowing rehabilitation was not available to this patient cohort.

6.4.4 Outcome Measures

1) Weight loss during RT* between:

i) HRi and HIRi patients (All patients and FT only patients)

ii) HRi and LIRi patients (All patients and FT only patients)

iii) HIRi and LIRi patients (All patients and FT only patients),

*Weight Loss during RT = % weight change between RT commencement and recorded weight in final week of RT

2) Number of days from the commencement of radiation therapy until the commencement of Adequacy of Enteral Nutrition (AEI1) (i.e. enteral feeding reliance for 25-49% of nutritional needs) and AEI3 (i.e. enteral feeding reliance for 75-100% of nutritional needs) FT use between:

i) HRi and HIRi patients

ii) HRi and LIRi patients

iii) HIRi and LIRi patients

6.4.5 Statistical Analyses

Statistical analysis was carried out using GraphPad Prism v7.02 (GraphPad Software Inc, California). Descriptive statistics were calculated for baseline demographic characteristics, disease stage, treatment characteristics and potential prognostic factors that were analysed in the generation of the risk stratification model (Table 11). Each of these variables was

available at the time of multidisciplinary tumour board meeting prior to radiotherapy to allow timely risk stratification.

For categorical variables, the frequency distribution between patients with HRi, HIRi and LIRi of prolonged feeding tube use was evaluated using Fisher's Exact test, the Cochran-Armitage test for trend if there were three or more ordered subgroups (eg. ECOG performance status) or the Pearson chi square test for three or more unordered subgroups (eg. cancer site). All p-values were 2-sided with a 0.05 α level of significance. Patients with unknown values for a particular factor were omitted from any models containing that factor.

6.5 Results

One hundred and one patients- treated with radical intent IMRT were eligible for inclusion in this study. They were categorised into HRi (n=28), HIRi (n=31) and LIRi (n=42) of prolonged FT use prognostic groups. One (3.6%), seven (22.6%) and six (14.3%) patients didn't have a FT inserted/adequately utilise their FT in the HRi, HIRi and LIRi risk groups, respectively. The majority of patients across each prognostic group were ≤65 years of age, with significantly more under 65-years old in the LIRi cohort (HRi: 64%; HIRi: 52%; LIRi: 88%, p=0.014). Males were represented at a ratio of approximately 3:1 in each group. The most common cancer site was oropharynx, with a significantly larger proportion in the LIRi cohort (HRi: 71%, HIRi: 52%, LIRi: 81%, p=0.008). 84% (59/70) of OPC patients had a known human papilloma virus (HPV) status, with those in the LIRi cohort more likely to have HPV associated disease (88%, p=0.001). Patients with never/minimal smoking history (p=0.003), good performance status (p<0.001), healthy body mass index (BMI) (p=0.050) and no pre-existing dysphagia (p<0.001) were significantly more frequent within the LIRi prognostic group when compared to the HRi and HIRi cohorts. All patient demographic and tumour characteristics are shown in their entirety in the 'Total' column in Table 11.

There was no significant difference in weight loss between HRi or HIRi patients in total (HRi=4.8% v HIRi=5.2%, p=0.813) or when using a FT (HRi=4.6% v HIRi=5.3%, p=0.641). However, when compared with both the HRi and HIRi prognostic groups, LIRi patients lost

significantly more weight in total (HRi=4.8% v LIRi=8.2%, p=0.002; HIRi=5.2% v LIRi=8.2%, p=0.006) and when using a FT (HRi=4.6% v LIRi=8.8%, p<0.001; HIRi=5.3% v LIRi=8.8%, p=0.002) (table 12). No significant differences in days to commencement of AEI Levels 1 and 3 FT use were observed between each of the prognostic groups (Table 13).

6.6 Discussion

Our previous body of work introduced a clinically useful risk stratification tool for both the requirement for and duration of significant FT use. The tool stratifies pharynx, oral cavity and supraglottic patients by two easily-attainable clinical variables – T-classification (<3 v ≥3) and presence/absence of involved level 2 lymph nodes –into four distinct risk classifications for the likelihood/intensity of FT use.[133] This information is readily available when a patient is first presented at a Multidisciplinary Tumour Board, with the model described capable of guiding decisions regarding prophylactic insertion of FTs. It does not take radiation dose factors into consideration.

Apart from cancer site, Anderson et al (2018) found advanced T-classification to be the most significant prognostic factor for duration of FT use. This is not a new finding and is consistent with the observations of numerous published studies.[133, 161, 165-168] However, the contribution of level 2 lymphadenopathy to prolonged feeding tube use is a novel finding. The possible causality of level 2 nodal lymphadenopathy is detailed at length in this manuscript.[133]

Treatment induced weight loss and dehydration can lead to episodes of hospitalisation and treatment breaks, which adversely affect disease outcomes.[68, 198, 199] Weight loss and deviations from planned body habitus have the potential to cause deviations in planned radiotherapy i.e. less dose to the tumour and increased dose to healthy tissue. Greater sophistication in radiotherapy planning and delivery means less room for error, such as patient contour change as a result of weight loss. With the increasing conformality and subsequent precision of modern treatment techniques, such deviations from planned treatment geometry have potential for greater consequence to planned doses of radiation.[200] Current practice dictates that such scenarios are often dealt with via adaptive radiotherapy

protocols (i.e. radiotherapy planning is repeated to account for patient anatomical change), yet this is often not clinically feasible in busy, clinical departments where resources are stretched and modern technologies not always readily available.[201, 202] Prevention of weight loss not only assists in patient well-being, but also as reduces the potential need for resource intensive adaptive radiation therapy. Optimal identification of at-risk patients via a simple to use prognostic tool provides an opportunity to minimise the need for weight loss driven adaptation via instigation of timely, robust nutritional interventions.

The LIRi group were identified as patients with small primary tumours with level 2 nodal disease, so intuitively, presented with more OPC cases. Furthermore, an overwhelming majority presented with HPV-associated disease (88%). Despite having a FT inserted, this patient cohort lost significantly more weight than those at higher risk of FT dependence. These findings are consistent with recent published data, who describe increased weight loss in HPV-associated OPC patients at a similar magnitude to our work.[203] Patients were also significantly younger, of good performance status, with a healthy BMI and no history of pre-existing co-morbidities such as underlying dysphagia. These patients reported to have never had or had a limited history of tobacco use. Of the 85% of patients with a known HPV status across the entire cohort, the presence of HPV-associated disease was significantly higher in the LIRi group (LIRi: 88%; HRi: 37%; HIR: 57%).

Therefore, despite being a valuable resource in stratifying FT use, the findings of this weight loss analysis may necessitate the need for additional consideration (beyond the FT risk stratification tool) when a LIRi patient is identified. The risk stratification tool, alone, may be insufficient to fully characterise the FT requirements of this select patient cohort. This group loses more weight across their course of radiotherapy than those with a far more extensive disease burden. Sub-optimal patient compliance to recommended FT use could provide an explanation for such weight-loss.

More often than not, LIRi patients have a prophylactic FT inserted. Despite this, there remains some obvious, unmet needs with respect, but not limited to, dietetic counselling,

optimal FT utilisation and psychological factors in the HPV-associated head and neck cancer population, hindering FT utilisation and compromising optimal weight management. Similar studies suggest unmet needs, indicating the need for further investigation of underlying contributing factors.[204, 205] This is further supported by the insignificant finding of days from the start of radiotherapy to the commencement of both AEI1 and AEI3 FT use- suggesting that LIRi patients are either using their FT, albeit inadequately, or providing an inaccurate account of their use upon weekly dietetic review. Additionally, a possible underlying clinician and allied health assumption of a well-educated patient group capable of appropriate self-management may further exacerbate the consequence of this non-compliance. Conversely, despite the perception of increased self-management capabilities, HPV-associated cancer patients have higher levels of psychosocial and informational needs. If such needs become unmet, there is the potential to further complicate treatment and recovery.[206, 207] All of these possible contributing factors must be the subject of further research, so that we, as the multidisciplinary team members responsible for the care of HPV-associated OPC patients, can better understand their needs and attitudes towards their treatment and subsequent compliance to recommended nutritional advice. A push for future prospective studies is also supported by Vangelov et al.[203] Further investigations may, perhaps, recommend nutritional support and guidance to the same level we apply to those patients we deem at highest risk of radiation induced dysphagia.

OPC has had a major demographic shift over the past two decades. The evolution of HPV-associated OPC has introduced a paradigm shift in the traditionally atypical head and neck cancer patient (i.e. a patient that presents with a history of heavy alcohol and/or tobacco abuse).[208, 209] Many western countries have witnessed a rise in the number of HPV-associated cancers, compared to a previous population that included patients with predominantly carcinogen (tobacco and alcohol) associated disease.[210] The United States reported a population-level incidence increase of 225% in HPV-positive OPC from 0.8 per 100,000 in 1988 to 2.6 per 100,000 in 2004. Alternatively, the incidence of HPV-negative

OPC decreased by 50% over the same period, from 2.0 per 100,000 to 1.0 per 100,000. This was further supported with a shift towards younger, white individuals.[209, 211] HPV-associated OPC has played a critical role in this demographic shift in disease incidence.[212] The LIRi cohort identified in this study is representative of this growing number of OPC patients presenting to radiotherapy departments. This particular cohort will continue to grow as HPV-associated OPC numbers peak in the coming years.

A striking clinical feature of the HPV-associated OPC patient is their excellent prognosis, with their risk of death halved in comparison to HPV-negative patients.[193, 213, 214] The concept of treatment de-escalation is currently being reviewed at length, in order to minimise the risk of chronic treatment related toxicities in a patient cohort that, in general, has a favourable prognosis.[212] Multiple treatment de-intensification strategies are being investigated in each of the surgical, chemotherapy and radiotherapy (and combinations, thereof) disciplines. Reduced doses of radiation (to as low as 54Gy) are being investigated, minimising the risk of FT dependence that is often seen in patients receiving high doses of radiation to critical swallowing structures (i.e. pharyngeal constrictor muscles) that are in close proximity to macroscopic disease.[215] Often, such regimens are coupled with less toxic cetuximab chemotherapy, compared to traditional cisplatin-based regimes.[152]

The concept of radiation dose de-escalation is relatively well established and accepted globally in low-risk HPV-associated OPC. Recent studies have reported equivalent outcomes to standard dose regimes.[216] High tech, radiotherapy has the capability for phenomenal dose sculpting, creating rapid dose fall off between target/tumour volumes and critical normal structures. Cautiously, we must therefore recognise that error apportioned to small uncertainties in radiotherapy treatment planning and delivery is higher than ever before. On-treatment weight loss is one of these uncertainties that has the potential to alter the planned dose of radiotherapy via a change in patient geometry.[200] In an era of radiation dose de-escalation, it is incredibly important that the reduced dose being delivered is being delivered with precision. We are at a very real risk of further ‘de-escalating’ dose that has

already been ‘de-escalated’ through variations apportioned to weight loss. Our study demonstrates that with weight loss at a heightened risk in the patient cohort most likely to be afforded such dose de-escalation (i.e. HPV-associated OPC or LIRi patients), we must recognise the extra supportive care measures required to ensure optimal weight maintenance is afforded this unique patient group.

In this cohort, no patient had access to swallowing rehabilitation. Furthermore, every effort was made to minimize patient pain. All patients were reviewed at least weekly by a medical doctor to prescribe analgesia in a stepwise fashion: mouthwashes and anti-thrush measures, simple analgesia (e.g. soluble paracetamol), local anaesthetic mouthwashes (e.g. xylocaine and cocaine), and ultimately titration of opioids[133].

This study has limitations inherent to a single-institution, retrospective analysis. The authors recognise that the cohort of HPV associated patients is relatively small (38/70 OPC patients), due to the availability of emerging technology enabling HPV diagnosis at the time this cohort received radiotherapy. Therefore, despite the identification of key clinical variables of HPV-associated disease within the LIRi cohort, any conclusions must be interpreted with caution. We are unable to provide data on patients’ functional swallowing ability, however, we are able to accurately report on patients having oral, or partial oral, diet at various time points due to comprehensive, prospectively recorded nutritional data. All patients were treated by a single radiation oncologist; however, it must be acknowledged that these patients were treated over eight years, a sufficient time period for even individual practice to vary. All patients were treated in an era with equitable access to FDG-PET and IMRT, without swallowing exercises. This lends to uniformity in staging, volume delineation and treatment delivery across the cohort.

6.7 Conclusion

Patients typically identified as low-intermediate risk (LIRi) of prolonged FT use for ≥25% of nutritional requirement (T-classification <3, Level 2 node lymphadenopathy) report significantly increased weight loss compared to patients at higher risk of prolonged FT use

undergoing definitive head and neck radiotherapy. This patient cohort demonstrates the demographic and diagnostic parameters of a stereotypical HPV-associated OPC patient-characteristic of the changing landscape of the modern-day head and neck radiotherapy patient. Results of this study suggest we should closely observe such patients throughout treatment, ensuring optimal weight maintenance, and in turn, facilitating precision radiotherapy. Larger, prospective studies are warranted to validate this finding, and to examine any additional contributing factors- either physical or psychosocial- that may be contributing to the sub-optimal weight management outcomes reported in this study.

Table 11. Description of prognostic factors in patients with high, high-intermediate and low-intermediate risk for prolonged feeding tube use (n=101)

Prognostic factor	**Subgroup**	**High Risk (HRi) FT Use***		**High-Intermediate Risk (HIRi) FT Use#**		**Low-Intermediate Risk (LIRi) FT Use$**		
		Yes/Total	**%**	**Yes/Total**	**%**	**Yes/Total**	**%**	**P value†**
Cancer site	Oropharynx	20/28	71%	16/31	52%	34/42	81%	0.008
	Pharynx (other) or oral cavity	6/28	22%	6/31	19%	7/42	17%	
	Larynx, supraglottis	2/28	7%	9/31	29%	1/42	2%	
Human papilloma virus (HPV)+	Negative	12/19	63%	6/14	43%	3/26	12%	0.001
(1 missing HR, 2 HIR, 8 LIR)	Positive	7/19	37%	8/14	57%	23/26	88%	
T stage	X, 0	0/28	0%	0/31	0%	1/42	2%	<0.001^
	1	0/28	0%	0/31	0%	17/42	41%	
	2	0/28	0%	0/31	0%	24/42	57%	
	3	19/28	68%	21/31	68%	0/42	0%	
	4	9/28	32%	10/31	32%	0/42	0%	
N stage	0	0/28	0%	18/31	58%	0/42	0%	<0.001
	1	3/28	11%	4/31	13%	12/42	28%	
	2	23/28	82%	9/31	29%	28/42	67%	
	3	2/28	7%	0/31	0%	2/42	5%	

Bilateral neck node disease	No	13/28	46%	24/31	77%	32/42	76%	0.014
	Yes	15/28	54%	7/31	23%	10/42	24%	
Retropharyngeal node disease	No	22/28	79%	31/31	100%	40/42	95%	0.008
	Yes	6/28	21%	0/31	0%	2/42	5%	
Level 1 node disease	No	21/28	75%	25/31	81%	38/42	90%	0.215
	Yes	7/28	25%	6/31	19%	4/42	10%	
Level 2 node disease	No	0/28	0%	31/31	100%	0/42	0%	<0.001^
	Yes	28/28	100%	0/31	0%	42/42	100%	
Level 3 node disease	No	15/28	54%	25/31	81%	32/42	76%	0.047
	Yes	13/28	46%	6/31	19%	10/42	24%	
Level 4 node disease	No	19/28	68%	30/31	97%	41/42	98%	<0.001
	Yes	9/28	32%	1/31	3%	1/42	2%	
Level 5 node disease	No	24/28	86%	31/31	100%	36/42	86%	0.086
	Yes	4/28	14%	0/31	0%	6/42	14%	
Concurrent chemotherapy	No	4/28	14%	14/31	45%	8/42	19%	0.011
	Yes	24/28	86%	17/31	55%	34/42	81%	
Dysphagia or odynophagia (pre-existing)	No	17/28	61%	19/31	61%	41/42	98%	<0.001
	Yes	11/28	39%	12/31	39%	1/42	2%	
Nutrition (PG-SGA)	Well-nourished	23/28	82%	22/31	71%	35/42	83%	0.395
	Malnourished	5/28	18%	9/31	29%	7/42	17%	

Body Mass Index	Underweight (<18.5)	5/22	23%	5/31	16%	1/38	3%	0.049
(6 missing HR, 4 LIR)	Not underweight (≥18.5)	17/22	77%	26/31	84%	37/38	97%	
Age on commencing RT	≤ 65 years	18/28	64%	16/31	52%	35/42	83%	0.014
	> 65 years	10/28	36%	15/31	48%	7/42	17%	
Sex	Male	21/28	75%	24/31	77%	33/42	79%	0.941
	Female	7/28	25%	7/31	23%	9/42	21%	
ECOG Performance Status	0	9/28	32%	7/31	23%	26/42	62%	<0.001
	1	18/28	64%	18/31	58%	16/42	38%	
	2	1/28	4%	6/31	19%	0/42	0%	
Charlson Comorbidity Index	0	12/28	43%	14/31	46%	30/42	71%	0.151
	1	4/28	14%	6/31	19%	4/42	10%	
	2	7/28	25%	5/31	16%	6/42	14%	
	3, 4, 5	5/28	18%	6/31	19%	2/42	5%	
Tobacco smoking	Never or minimal	9/28	32%	7/30	23%	24/40	60%	0.003
(1 missing HIR, 2 LIR)	Past	6/28	21%	13/30	44%	11/40	28%	
	Current	13/28	47%	10/30	33%	5/40	12%	
Alcohol drinker	Never or social	19/28	68%	20/29	69%	32/39	82%	0.683
(2 missing HIR, 3 LIR)	Past	3/28	11%	3/29	10%	2/39	5%	
	Current	6/28	21%	6/29	21%	5/39	13%	

* “High Risk (HRi) Feeding Tube use” are patients with both T-Stage≥3 and Level 2 node disease, with risk of feeding tube use for at least 25% of nutritional requirements.

“High-Intermediate Risk (HIRi) Feeding Tube use” are patients with T-Stage≥3 without Level 2 node disease, with risk of feeding tube use for at least 25% of nutritional requirements.

& “Low-Intermediate Risk (HIRi) Feeding Tube use” are patients without T-Stage≥3 with Level 2 node disease, with risk of feeding tube use for at least 25% of nutritional requirements.

+ HPV status is restricted to patients with a diagnosis of cancer of the oropharynx only

^ Statistical significant difference due to variable dichotomisation contributing to generation of prognostic group i.e. T-stage and level 2 node disease

† Two-sided P value from Fisher exact test for difference between 2 subgroups, Pearson chi square test for difference between 3 or more unordered subgroups, or Cochran-Armitage test for trend across 3 or more ordered subgroups.

Table 12. Comparison of weight loss across High Risk (HR), High-Intermediate Risk (HIR) and Low-Intermediate Risk (LIR) patients

	*High Risk (HRi) of FT Use v High-Intermediate Risk (HIRi) of FT Use			#High Risk (HRi) of FT Use v Low-Intermediate Risk (LIRi) of FT Use			&High-Intermediate Risk (HIRi) of FT Use v Low-Intermediate Risk (LIRi) of FT Use		
	HRi (n= 28)	**HIRi (n= 31)**	**p-value**	**HRi (n= 28)**	**LIRi (n= 42)**	**p-value**	**HIRi (n= 31)**	**LIRi (n= 42)**	**p-value**
% Weight Loss (All)	4.8 +/- 4.8	5.2 +/- 5.4	0.813	4.8 +/- 4.8	8.2 +/- 3.8	0.002	5.2 +/- 5.4	8.2 +/- 3.8	0.006
	HRi (n=27)	**HIRi (n=24)**		**HRi (n=27)**	**LIRi (n=36)**		**HIRi (n=24**	**LIRi (n=36)**	
% Weight Loss (with FT)	4.6 +/- 4.8	5.3 +/- 5.0	0.641	4.6 +/- 4.8	8.8 +/- 3.6	<0.001	5.3 +/- 5.0	8.8 +/- 3.6	0.002

* % Weight loss (i.e. % weight change between commencing radiotherapy and recorded weight in final week of radiotherapy) comparing patients at High Risk (HR) and High-Intermediate Risk (HIR) of feeding tube (FT) use (all patients and FT inserted only patients)

\# % Weight loss comparing patients at High Risk (HR) and Low-Intermediate Risk (LIR) of feeding tube (FT) use (all patients and FT inserted only patients)

& % Weight loss comparing patients at High-Intermediate Risk (HIR) and Low-Intermediate Risk (LIR) of feeding tube (FT) use (all patients and FT inserted only patients)

Table 13. Days (mean) from the commencement of radiation therapy until the commencement of feeding tube (FT) use[$]

	*High Risk (HRi) of FT Use v High-Intermediate Risk (HIRi) of FT Use			#High Risk (HRi) of FT Use v Low-Intermediate Risk (LIRi) of FT Use			&High-Intermediate Risk (HIRi) of FT Use v Low-Intermediate Risk (LIRi) of FT Use		
	HRi (n=27)	**HIRi (n=24)**	**p-value**	**HRi (n=27)**	**LIRi (n=36)**	**p-value**	**HIRi (n=24**	**LIRi (n=36)**	**p-value**
Days to AEI1 (+/- SD)	23.4 +/- 10.9	21.3 +/- 15.2	0.568	23.4 +/- 10.9	26 +/- 11.8	0.378	21.3 +/- 15.2	26 +/- 11.8	0.183
Days to AEI3 (+/- SD)	30 +/- 14.6	31.5 +/- 33.9	0.840	30 +/- 14.6	36.6 +/- 13.3	0.075	31.5 +/- 33.9	36.6 +/- 13.3	0.441

* Days from commencement of radiation therapy until the commencement of feeding tube (FT) use (AEI1 and AEI3)- High Risk (HR) vs High-Intermediate Risk (HIR) of feeding tube (FT) use

\# Days from commencement of radiation therapy until the commencement of feeding tube (FT) use (AEI1 and AEI3)-High Risk (HR) vs High-Intermediate Risk (HIR) of feeding tube (FT) use

& Days from commencement of radiation therapy until the commencement of feeding tube (FT) use (AEI1 and AEI3)- High Risk (HR) vs High-Intermediate Risk (HIR) of feeding tube (FT) use

$ “Feeding tube (FT) use” means feeding tube was used for at least 25% of nutritional requirements (AEI1) and 75% of nutritional requirements (AEI3).

Chapter 7: Discussion

7.1 Introduction

Radiation therapy plays an integral role in the palliative, definitive and post-operative management of head and neck cancer. Approximately 890,000 new cases of head and neck cancer (HNC) were estimated to have been diagnosed globally in 2018, a near 30% increase from similar figures captured in 2015.[217, 218] Of these patients, 93,000 (10.4%) present with a primary diagnosis of oropharyngeal carcinoma (OPC). Over the equivalent period of time, HNC-specific mortality decreased by 5%.[217] Proportionately to new cancer diagnoses, HNC patients are living beyond their diagnosis and treatment in greater numbers than ever before.[217]

A 2017 review of management of radiation induced toxicities in HNC details the importance of new technologies and novel therapeutic approaches in minimising the effect of radiation-induced toxicities, in particular the role of intensity modulated radiotherapy techniques in reducing dose to pertinent swallowing structures.[219] The management of HNC has undergone a rapid transformation, with a demographic shift in recent years in patients presenting to oncology departments globally. This is of increasing importance when we consider the improved survival of these patients.[209] Traditional contributory variables, such as a long history of tobacco and alcohol abuse and pre-existing co-morbidities, are being replaced in an otherwise healthy, younger cohort, who present with an increased BMI, little to no comorbidities, smaller primary tumours and larger nodal disease.[7, 209] This more contemporary presentation of disease is indicative of HPV-associated OPC. Presentation of this subtype of HNC has grown by 225% in the United States alone since the 1980s. Conversely, we have seen a halving of HPV-negative associated HNC.[209]

With this onset of HPV-associated disease, combined with the rapid developments in radiotherapeutic, chemotherapeutic and surgical treatment options, there is a renewed confidence in the prognosis of HNC patients. Therefore, while an extreme focus has rightly

remained on optimal disease management strategies, there has been a significant accompanying paradigm shift towards toxicity-related risk mitigation, induced by these highly effective- yet toxic- treatment regimes. HNC patients are living beyond their initial cancer diagnosis, yet are at significant risk of life long complications of their treatment which can have significant implications on their quality of life.

Dysphagia or compromised swallowing leading to difficulties in oral nutrition is one of the most, if not the most, life altering treatment-induced complication associated with a course of radiotherapy (with or without concurrent chemotherapy). Intensive, coordinated multidisciplinary management is necessary to optimise treatment and quality of life outcomes. Despite these complexities, there lies an exciting opportunity to individualise patient management strategies to ensure patient outcomes are optimised and side effects minimised as much as possible.

The research outlined in this thesis takes a systematic approach to improving the available evidence, aiming to further individualise and optimise the standard of care that can be delivered to HNC radiotherapy patients. Chapter 1 provides an overview of head and neck cancer, including its incidence and mortality, aetiology, presentation, staging and treatment options. Chapter 2 delivers a comprehensive literature review of the management of radiation induced dysphagia, inclusive of how it is measured and managed, combined with recent literature detailing clinical and dosimetric variables used to predict the likelihood and severity of prolonged dysphagia. Late dysphagia, a consequence of curative radiotherapy, has been the subject of multiple publications over many decades. Dose/Volume/Outcome (DVO) data has been published at length, providing a critical resource to drive clinical practice and moderate the risk of late dysphagia.[43, 47, 63, 220] However, until the last decade, the DVO resources utilised were somewhat outdated, derived from clinical outcomes and not reflective of modern precision radiotherapy. The American Society of Radiation Oncology (ASTRO) responded accordingly, updating the recommendations based on a compilation of DVO resources indicative of not only all modern radiotherapy practice, but all treatment

sites.[172] The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) report, however, recognised the limitations in providing meaningful data beyond late radiation induced toxicities. With the rapid onset of precision radiotherapy and the need for acute toxicity management to enable optimal treatment tolerance, the QUANTEC reports called for DVO outcome data to guide acute toxicity management.[172]

Chapter 3 of this thesis (Dose Volume Response in Acute Dysphagia Toxicity: Validating QUANTEC Recommendations into Clinical Practice for Head and Neck Radiotherapy) addresses this gap in the literature as described by ASTRO in the QUANTEC Report.[172, 221] In this study of 76 patients with locally advanced squamous cell carcinoma of the head and neck (+/- systemic therapy), we reported that multiple QUANTEC larynx dose parameters (Dmean<44Gy, Dmean<40Gy, V50Gy<27% and Dmax<66Gy) predictive of late dysphagia, were also suggestive of dysphagia in the acute setting (treatment weeks 5 and 6). This novel finding, in an area of recognised need by ASTRO, is critical in the current radiotherapy landscape, where acute toxicity prophylaxis and subsequent management is imperative to precision radiotherapy. Acute toxicity management is paramount to optimal weight management, ensuring not only the delivery of precision radiotherapy, but adherence and completion of prescribed, predetermined treatment regimens demonstrating best patient outcomes. The significance of these findings was recognised by ASTRO and selected for an oral presentation at the 2011 ASTRO Annual Meeting in Miami. The findings were subsequently published in Acta Oncologica.[221]

The findings published in Chapter 3 offer a complementary set of acute dysphagia dosimetric findings to the late DVO data of the QUANTEC Reports.[172, 221] Yet, while DVO outcome data is imperative to a comprehensive risk stratification strategy for each HNC radiotherapy patient, understanding clinical risk factors is equally important. Perhaps of greatest importance is the identification of appropriate clinical risk factors which can enable the introduction of early prophylactic measures to best manage the anticipated onset of acute dysphagia symptoms, prior to radiotherapy treatment planning. Appropriate nutritional

management strategies are a critical component of optimal weight management throughout a course of HNC radiotherapy. Multidisciplinary integration and different nutritional interventions, namely NGT and pPEG, have been described at length throughout this thesis. Marrying of both clinical and dosimetric dysphagia endpoints forms a critical component of Chapters 4 and 5 of this thesis, aiming to better understand the role of treatment variables contributing to prolonged feeding tube use. While Chapter 3 looks to validate existing late dysphagia dosimetric endpoints in an acute setting, it fails to address the value of critical clinical endpoints such as, but not limited to, tumour staging, systemic therapies and patient demographic variables. Chapter 4 addresses this need, investigating the value of these clinical variables in feeding tube use identification and stratification. Chapter 5 looks to further extrapolate these findings, to better appreciate the value of dosimetric end points in the complex anatomy of the swallowing axis.

Chapter 4 describes a comprehensive review of pPEG feeding outcomes in a cohort of 139 patients. Multiple other studies have also been undertaken in this domain, reporting on a series of variables predictive of prolonged feeding tube reliance. All tumour staging was performed using the American Joint Committee on Cancer (AJCC) staging system.[10] While our study detailed T-classification as a significant predictor of prolonged feeding tube use (T-classification ≥3), consistent with previous findings, our results highlighting the role of level 2 nodal lymphadenopathy as predictive of prolonged feeding tube reliance is a novel finding.[133, 161, 165-168, 222] The presence of malignancy in the level 2 lymph nodes increases the likelihood of contralateral disease, in particular, in cancers of the oropharynx.[223] As far as the authors are aware, no other studies have reported on the predictive significance of individual neck nodal levels in feeding tube risk stratification. In a period of time where radiotherapy treatment planning, treatment delivery and image guidance facilitates highly conformal radiotherapy, such detail in the identification of feeding tube risk factors is incredibly important. Perhaps, of greater importance, however, is the relative ease in which this level 2 lymphadenopathy (and T-classification) can be diagnosed via preliminary patient diagnostic

workup (i.e. CT, PET and MRI imaging modalities), allowing early identification of these key predictive variables and timely risk stratification of anticipated feeding tube reliance. Prophylactic insertion of a pPEG tube can take place prior to radiotherapy, ensuring a seamless transition to utilisation at the onset of acute dysphagia requiring nutritional intervention. Additionally, this knowledge can assist in the appropriate prioritisation of multidisciplinary support (namely, dietetics and speech pathology) in clinical scenarios where demand for such intervention is high and workload distribution must be prioritised. As described throughout this thesis, dietetic/nutritional and speech therapy interventions demonstrate a significant benefit when adherence is sustained. Identification of patients at highest risk of prolonged dysphagia, requiring feeding tube intervention, can ensure a greater evidence-based, data-driven distribution of multidisciplinary resources to ensure appropriate adherence to nutritional and swallowing exercise advice in such patients. The potential impact to associated departmental costs is profound, enabling optimal care pathways for those at highest need, without the need to draw on additional, costly resources.

The ability to stratify the risk of feeding tube use on the basis of clinical factors alone provides an obvious clinical benefit for the timely, prophylactic intervention in HNC patients, prior to the commencement of their radiotherapy. Despite this demonstrated benefit in the Chapter 3 cohort, further analysis of radiotherapy treatment planning variables was required.

The swallowing mechanism is particularly complex and requires multiple interactions between many structures. Dose to pertinent swallowing anatomy has the potential to complement the clinical predictors (T-classification and level 2 lymphadenopathy) demonstrated in Chapter 3. Chapter 5 presents such an analysis, introducing dosimetric variables for ten pertinent swallowing structures in addition to the clinical variables. The swallowing structures are described comprehensively in published guidelines.[95] This analysis was undertaken to ascertain if any additional dosimetric variables could be attributed to an increased risk of prolonged feeding tube use. The findings of Chapter 4 were

exclusive to dosimetry and variables pertinent with the radiotherapy treatment planning pathway.

Chapter 5 built on the novel findings of Chapter 4. A base of tongue D50>61Gy and a superior PCM D50>61Gy was found to be predictive of the need for prolonged feeding tube use. Cervical oesophagus D50>36Gy was a significant predictor of both the need for and prolonged duration of feeding tube use. These dosimetric endpoints facilitated the addition of a dosimetric arm to the feeding tube risk stratification model. While these dosimetric findings provide another layer of clarity to the risk stratification model, perhaps the most important conclusion from this study was that, despite the addition of a dosimetric analysis, both T-classification and level 2 lymphadenopathy remained significant predictors of prolonged feeding tube use. While dosimetry provides additional justification, it is not mandatory to initiate supportive care strategies in high-risk patients. The HNC radiotherapy pathway relies heavily on uninterrupted delivery to facilitate optimal therapeutic outcomes.[198, 199] However, this pathway risks being interrupted by an unscheduled, invasive surgical pPEG insertion during radiotherapy. If we are to put this finding into a clinical context, the dosimetric predictors may act as a complimentary addition to the risk stratification model described in Chapter 4, due to the highly predictive significance of the two clinical variables in both versions of the feeding tube risk stratification model. Yet, if the cervical oesophagus can be avoided in treatment planning due to favourable tumour geography and geometry, this has the potential to lead to more favourable feeding tube outcomes. What remains to be undertaken is the validation of each of these significant findings in an independent, larger cohort of HNC patients, via a prospective, longitudinal study, further consolidating this body of evidence, and its applicability to the wider HNC population.

The findings derived in Chapter 6 build upon the novel clinical parameters unearthed in the risk stratification model of Chapter 4. The risk stratification model demonstrates a simple tool to identify patients at high risk of prolonged feeding tube use, based purely on duration of

use. Chapter 6, however, presents an additional set of circumstances that must be considered when forecasting the shifting demographic characteristics of current and future HNC patients. With the significant paradigm shift towards HPV-associated cancers of the oropharynx, in particular in the western world, the results of Chapter 6 must be used to complement clinical decisions apportioned to the risk stratification model. The findings present a clear divide between predicted feeding tube use and demonstrated weight loss, suggestive of underlying contributing factors to poor adherence to nutritional advice.

While the differing physical attributes of an HPV-associated HNC patient are well known (when compared to those of the traditional HPV-negative patient), there is still little published data on HPV-associated patient reported barriers to nutritional recommendations. Despite a decreased disease burden and a lower stratified risk of prolonged feeding tube use, a significant increase in weight loss is witnessed in this cohort. When observing physical (clinical and dosimetric) factors alone, this finding is contradictory to what would routinely be expected when apportioning responsibility to prolonged feeding tube use.

While not definitive and requiring further investigation, these findings are suggestive of an underlying patient consideration that has to date been otherwise under-appreciated, posing a number of questions that demand further investigations. Why are these patients losing more weight? Are they underreporting feeding tube use/compliance? Previous work has demonstrated a greater psychosocial and informational need in HPV-associated HNC patients, that has potential to complicate treatment and recovery if not met.[206, 207] These are questions that all remain unanswered in this particular cohort of HNC patients. Future prospective studies validating the findings of Chapters 4 and 5 would benefit from patient reported endpoints being embedded in the methodology. The mechanisms behind patient non-compliance must be better understood so that we can continue to evolve to the individualised needs of HPV-associated HNC patients. Patient reported barriers and subsequent strategies to enable optimal nutritional compliance are critical to further complement the clinical value of tools such as the pPEG risk stratification model.

The body of work detailed in this thesis has further added to the growing evidence base in the management of radiation-induced dysphagia. However, like any body of work detailing a DVO and/or clinical variable predictive relationship, we must recognise the inherent limitations of the era in which the data was acquired, to ensure results are interpreted in the appropriate relevant clinical context. Ongoing recommendations must endeavour to align themselves with best practice, such that DVO data is representative of current, precision radiotherapy. As previously detailed, an opportunity to validate these findings prospectively, in a current clinical setting among a large cohort of patients, would further add value to the recommendations derived from this body of work and presented in this thesis. Knowledge based planning and proton therapy are just two examples of improved dose sculpting capability that could further build on this body of work.

Additionally, it should be recognised that all of the data utilised in this thesis was collected at a single institution. We recognise the significant benefits of utilising a single institution cohort, which are uniform in target and OAR delineation and provide consistency in treatment plan interpretation. Furthermore, this patient cohort was afforded equitable access to multidisciplinary care (e.g. dietetics and speech pathology) and uniform, consistent patient follow-up. However, there remains an exciting opportunity to validate these findings in an external cohort. With the uniform methodology that was adhered to in each of these studies, extrapolation to an equivalent external patient cohort in a single or multi-centre study should be achievable with relative ease, regardless of the technology available.

7.2 Multidisciplinary Management of the Head and Neck Cancer Patient

In contrast to other cancer patients, the HNC patient demands a truly multidisciplinary approach to their care pathway. Beyond the radiation oncologist, radiation therapist and specialised radiation oncology nursing, HNC patients engage the services of an extensive team of allied health professionals. Dietitians and speech pathologists are critically important

to the management of treatment-induced dysphagia and subsequent return to a good quality of life beyond their cancer treatment and cure. In Australia, we are extremely fortunate to have access to such skilled, multidisciplinary professionals providing world-leading care for HNC patients. However, this is not necessarily the case globally. The findings presented in this thesis emphasise the importance of the multidisciplinary team in the optimal management of HNC patients. We must continue to investigate strategies to provide equitable care to this patient cohort.

Despite the rapid advances in radiotherapy treatment planning, our ability to sculpt dose around critical, healthy structures is limited by complex tumour/OAR geographic relationships in the head and neck. Subsequently, radiation induced dysphagia will continue to demand significant allied health intervention to improve outcomes and optimise care. Therefore, identification of patients at highest need of support remains a critical factor.

Treatment-induced dysphagia is chronic in nature for patients undergoing chemoradiation for HNC. In a prospective cohort of 96 patients, a number of persistent, dysphagia- related toxicities were identified as being present for up to three years post treatment and were considered a barrier to oral food intake.[224] Odynophagia and dysgeusia demonstrated significant improvements in the six months following radiotherapy. However, xerostomia was still reported in over 80% of cases at three years post treatment and seen as a barrier to oral intake in more than 20% of the cohort.[224] These findings highlight the importance of ongoing speech therapy and dietetics counselling beyond radiotherapy, to ensure appropriate management of these chronic toxicities.

The multidisciplinary relationship of HNC clinicians are fast becoming better understood. Multiple review papers have demonstrated a dose/volume/outcome relationship between

pertinent swallowing structures and key swallowing/nutritional outcome measures.[225, 226] Pertinent swallowing anatomy, including but not limited to base of tongue, pharyngeal constrictor muscles and oesophageal inlet, were associated with a number of key swallowing endpoints six months post radiotherapy.[225] End points (described in full by Cartmill et al, 2012) included Common Toxicity Criteria for Adverse Events (CTCAE) relating to dysphagia and xerostomia; full diet versus modified diet following clinical swallow evaluation (CSE); functional status using the Royal Brisbane Hospital Outcome Measure for Swallowing (RBHOMS) following CSE; and patient-rated swallowing function using the MD Anderson Dysphagia Inventory (MDADI) global score.[225] A more recent review also demonstrated a relationship between both objective and subjective swallowing endpoints and dose to swallowing anatomy.[226] Findings reported by both of these reviews demonstrate the critical relationship that exists between the radiation oncology and speech/nutritional clinical teams. Our novel clinical finding of level 2 lymphadenopathy and dosimetric relationships of cervical oesophagus, base of tongue and superior PCM to feeding tube use, add further, valuable contributions to the field. Further prospective studies investigating their relationship with a greater myriad of swallowing/nutritional outcomes will further embed their value into the HNC multidisciplinary decision-making pathways.

Despite comprehensive data highlighting the critical role of speech pathologists in the optimal care of HNC radiotherapy patients, many clinics offering HNC radiotherapy are unable to access adequate speech pathology services.[114-117, 227] Conversely, many services are unable to offer complex HNC radiotherapy due to the unavailability of these critical allied health services. This can lead to an increased strain on the service due to a saturation of HNC patients in appropriately resourced clinics.[228] As a consequence, available resources are stretched. Risk stratification models that can better identify patients at high-risk of prolonged feeding tube risk are crucial for enabling timely, personalised intervention. The ability to appropriately distribute allied health resources to those at highest-need is pivotal to

ensuring optimal toxicity outcomes are afforded all HNC patients. Additionally, evidence-based risk stratification may actually enable low-risk patients to have their care closer to home. If the appropriate, modified allied health support could be incorporated in their local setting, the potential benefits to the patient and health care system are significant. A patient may have the opportunity to remain at home throughout their treatment without their care being compromised. The potential health and financial benefits are far reaching.

Another critical factor compromising optimal swallowing outcomes is patient adherence to prescribed swallowing exercise programs. Two publications have highlighted poor adherence across varying HNC populations (27% and 58% adherence).[182, 229]. A reliance on patients to engage in self-directed swallowing rehabilitation regimens is a recognised barrier to adherence.[229] In a randomised study (n=79) of clinician-directed, patient-directed and tele-practice-directed swallowing programs, overall adherence was poor (27%) over the six-weeks of chemo-radiation therapy. Adherence was particularly poor in the latter half of treatment (weeks 4-6), compared to the first three weeks (p=0.036). However, of particular value in this study was the finding that adherence to swallowing exercises was significantly worse in the patient-directed cohort in weeks 1-3 of treatment, when compared to the clinician-directed cohort (26% v 43%, p=0.014) cohort. A trend towards significance was also witnessed when comparing the patient directed cohort and the tele-practice directed cohorts (26% v 36%, p=0.064). These results present an interesting conundrum, whereby data clearly demonstrates improved adherence when clinicians are engaged with the patient, whether by direct or ‘tele’ interactions. However, with speech pathology resources stretched, this doesn’t appear feasible for all patients. While the economic value of a tele-practice swallowing program has been shown to demonstrate a significant cost saving, additional data to optimise HNC patient triage would only further minimise the economic footprint of such a program.[228] Further qualitative work, exploring patients’ perception of tele-practice, enhances understanding of the value of the service. This has the potential to build further evidence of value on top of the demonstrated clinical benefit. The findings presented in this

thesis can provide immediate impact to enable optimal resource distribution in both conventional practice and across innovative platforms such as tele-practice.

Finally, when detailing the many members of the multidisciplinary team responsible for shaping the treatment journey for a HNC patient, perhaps one of the most important elements is often overlooked. Carers play a critical role in dysphagia management. They are present more than any member of the multidisciplinary team and are paramount in ensuring that patients adhere to nutritional advice and interventions. However, carers often feel ill-prepared for their role as a key member of the 'multidisciplinary' dysphagia management team.[230] The findings of this study successfully describe the impact of dysphagia on the everyday lives of carers, not only with respect to meal preparation and nutritional maintenance of the HNC patient, but the implications for social engagement and maintaining normality in family life.[230] In the study of twelve carers, four key themes were derived- the role of dysphagia in disrupting daily life, the need for carers to make adjustments, the disconnect that lies between carers' expectations and the reality of dysphagia, and carers' experiences of available supports and services.[225] Each of these themes describe the ill-preparedness carers felt with regard to their dysphagia management responsibilities. We, as a treating team, must undertake further work to better understand the role of the carer in the patient journey. They are the 'unsung hero' in the multidisciplinary care of the patient to ensure complex management strategies are adhered to and acute toxicities managed. Their 'worth' is perhaps best understood in their absence, where a dearth of identifiable support networks demonstrates inferior treatment related outcomes. In a study of race-based HNC outcomes in the United States, African-American patients who were unmarried, unemployed and had inferior access to healthcare, demonstrated poorer local regional control ($p=0.033$) and overall survival ($p=0.004$) compared to equivalent Anglo-Saxon Americans.[231] The findings of this thesis, and in particular Chapter 6, demonstrate a disconnect between feeding tube utilisation and optimal weight management. We have hypothesised an underlying patient consideration to dysphagia management beyond physical, clinical patient

attributes. The role of the carer was not investigated in any of our studies. Existing evidence suggests that their experiences and preparedness are vitally important to optimal patient care during a course of radiation therapy. In addition to risk stratification models and a better patient education, identification and integration of the carer into optimal care pathways appears vitally important to complement the key findings from our work. More work needs to be done to further our understanding in this area.

7.3 Dosimetric/Clinical Considerations in Head and Neck Radiotherapy: Where to from here?

The underlying theme throughout the large majority of the studies performed in this thesis has been the development of clinically useful risk stratification models to better predict the need for feeding tube intervention in head and neck cancer patients. Not only does timely risk stratification enable a proactive approach to toxicity management, but it also allows resource distribution to enable appropriate care for those patients with the highest needs.

The rapidly-evolving field of radiation oncology will ensure that predictive/risk-stratification models such as those developed and described in this thesis, will need to constantly evolve with changing practice. Evolution is imperative to ensure we remain at the cutting edge of care we can afford our patients.

Feeding tube risk stratification models currently exist that drive informed decision making with respect to the need for feeding tube insertion. Guidelines developed at the Royal Brisbane and Women's Hospital were derived via a combination of available clinical evidence and expert consensus.[232] Type of cancer, treatment approach and the presence of pre-existing dysphagia and/or malnutrition are all utilised to help appropriately identify a patient's likelihood of feeding tube dependence. Subsequent validation of this model in a prospective model has demonstrated good swallowing outcomes in the majority of patients, depicting the value of their proactive treatment strategy.[233] The findings described in this

thesis further add to and complement this earlier body of work. There should not be a need to use one model in favour of another, but an opportunity to derive the prominent features of each to enable a better-informed decision. The addition of pertinent clinical and dosimetric variables provides greater clarity to decision making, and in particular for those patients undergoing a course of definitive radiotherapy (+/- chemotherapy).

Multiple groups continue to add to the literature in the realm of radiation-induced dysphagia management, describing what clinical and dosimetric factors continue to be of particular relevance in predicting and minimising the impact of this debilitating toxicity. A 2017 study demonstrated a significantly longer duration of feeding tube placement (1.18 times longer, p=0.03) when three-dimensional conformal radiotherapy (3DCRT) was used instead of intensity modulated radiotherapy (IMRT).[234] Malnutrition risk and a HPV-associated disease were significant predictors of a need for proactive feeding tube placement, demonstrating a 4.5 and 4.4 times greater risk for feeding tube placement, respectively.[135] Furthermore, more recent work has reported on a number of critical factors linked to persistent feeding tube use at six-month follow-up.[222, 235] In a systematic review of prognostic factors for feeding tube dependence post curative chemoradiation, advanced tumour and nodal stage, pre-treatment weight loss, bilateral neck irradiation, (concomitant) chemotherapy and a prophylactic gastrostomy policy were prognostic for tube feeding dependence for patients up to six months post-radiotherapy, as well as beyond six months. Interestingly, additional variables such as narcotics abuse and living alone at time of treatment were predictors of increased feeding tube requirement for the 6-month period post-treatment.[222] A number of key dosimetric findings indicative of both acute and late feeding dependence were also reported in the literature.[222] Dose to the larynx, the pharyngeal constrictor muscle inferior and superior and the contralateral parotid gland were all significant predictors of acute and late feeding tube dependence as detailed in the systematic review. Additionally, dose and volume of irradiated oral mucosa was critical in the development of acute complications such as mucositis, especially when combined with the toxic effects of chemotherapy. Radiation

induced mucositis may in fact lead to periods of feeding tube use due to the pain it generates when eating. Mucositis may not directly affect the swallowing structures. However, it can play a secondary role in the deconditioning of swallowing muscles when it affords feeding tube use.

Finally, as investigated in Chapter 6 of this thesis, a reduction in salivary gland dose, in particular the submandibular glands (SMG), can have a positive impact on patient reported outcomes.[236, 237] While the results of our study did not demonstrate a definitive benefit for SMG dose reduction with respect to tube dependence, the impact on patient reported QoL was not measured, and therefore, not evaluated in our patient cohort. Most recently, a mean dose of less than 39Gy to the SMG was demonstrated to improve patient reported outcomes with regard to patient reported xerostomia.[236] An additional study reported similar findings, suggesting that a mean dose of less than 39Gy to SMG could be attained with a slight compromise of target coverage in low risk, neck nodal target volumes.[237] In doing so, the authors recommended further validation of SMG sparing in a randomised clinical trial.

As witnessed throughout this chapter (7) and Chapter 2 of this thesis, there is a wealth of data depicting a wide array of clinical and dosimetric variables predictive of objective (i.e. feeding tube dependence, weight loss) and subjective clinician (i.e. CTCAE scoring) outcome measures. This evidence base will continue to evolve, considering the multitude of tools we currently have available clinically to precisely sculpt dose to complex radiotherapy target volumes. However, there remains a paucity of good, robust clinical data correlating patient reported outcomes with these heavily reported objective and clinician subjective measures. This view is supported in a recent review, which recognises the lack of current, readily available evidence inclusive of patient reported outcome measures.[238]

To ensure high quality outcome data, extensive follow-up for up to two years post radiotherapy, must be included in all longitudinal studies. While feeding tube use is likely to have ceased within this two-year period, it is important to understand persistent patient barriers to optimal QoL, regardless of severity. All prospective HNC clinical trials must, at the

very least, incorporate patient reported outcomes and QoL measures as part of the methodology during and beyond treatment/follow up. This thesis has demonstrated the potentially valuable role of such data in complementing clinically useful predictive tools like those generated in our studies.

7.4 The head and neck cancer patient: Now and the future

The body of work and patient population comprising the analysis in this thesis has taken place over a number of years. As previously described, throughout this time, there has been a quantum shift in the stereotypical head and neck patient who presents for radiotherapy. Furthermore, and perhaps the best recognition of the growing burden of HPV-associated disease in HNC (and all HPV-associated malignancies), is the inclusion of HPV-related cancers in the most recently published global cancer registry- figures that were not captured in previous iterations.[217]

Recognition of HPV-associated cancers as a significant development in the immediate future of cancer diagnoses was the consequence of a deeper analysis of cancers attributable to infections.[239] Nearly two million cancers were attributed to infection in 2012, of which 30% (or 640,000) were attributed to HPV, second only to helicobacter pylori (35.4%), an infection commonly associated with high frequency gastrointestinal malignancies of the liver and stomach. Of the 96,000 cases of reported oropharyngeal cancer, 30.8% were attributed to HPV-associated disease.[239] It should be noted that these figures are inclusive of geographical regions with typically low incidence of HPV-associated oropharyngeal carcinoma (e.g. India and China), resulting in a markedly higher incidence in western countries, including Australia (refer to Table 14 for the frequencies of HPV attributable oropharyngeal carcinoma, by country/region). With HPV-associated cancer incidence yet to peak, the prevalence of HPV-associated oropharyngeal cancer will continue to grow in the immediate and short term placing increased burden on cancer services.

Table 14. Frequency of HPV attributable oropharyngeal carcinoma, by country/region[239]

HPV (high-risk type)	Region	HPV-attributable fraction (95% CI)
Carcinoma of the oropharynx, including tonsils and base of tongue	North America	51% (47-55)
	North-West Europe	42% (34-47)
	East Europe	50% (39-57)
	South Europe	24% (17-30)
	China	23% (17-27)
	Japan	46% (39-59)
	India	22% (5-44)
	South Korea	60% (46-70)
	Australia	41% (32-47)
	Elsewhere	13% (5-23)

Apart from this demographic shift, HPV-associated HNC patients are also presenting with different symptoms of their disease compared to their HPV-negative HNC counterparts. As described in chapter 1, preliminary data to support the increased prevalence of neck mass and sore throat as early symptoms of patients with squamous cell carcinoma (SCC) of the oropharynx has been reported.[7] However, it is patients with HPV-associated oropharyngeal carcinoma who more commonly report with neck lymphadenopathy as a presenting symptom, compared to the primary disease related symptoms of HPV-negative patients, including sore throat, dysphagia, and/or odynophagia.[7]

Incidence and severity of acute, radiation induced toxicities of the HPV-associated HNC population are only beginning to be better understood. An increase in incidence of treatment-related early toxicities has been reported, with HPV-positive and non-smoking status correlating with increased risk of high-grade mucositis and associated outcomes. Such outcomes often contribute to the need for nutritional intervention.[240] Furthermore, and similar to the findings of Chapter 6, others have reported a correlation between acute weight loss and HPV-associated oropharyngeal disease.[203] The reasons for a spike in acute toxicities in the HPV-associated HNC population is not fully understood, considering the relative equipoise in radiation therapy (and concurrent chemotherapy) regimens with HPV-unrelated disease. Better appreciating this link is critical to the optimal application of lessons learnt from this thesis, so that they can be modified to meet the individual patient needs.

Notwithstanding the marked physical discrepancies between these two distinct, HPV-distinguished patient cohorts, we are also only beginning to better appreciate the psychological hurdles of a HNC patient, regardless of HPV status. In 2018, it was reported that HNC patients (in their entirety) present with a three-fold increase in depressive disorders when compared to a comparative healthy patient cohort.[241] These findings were further supported by another study, suggestive of an association between patient eating and pain reported outcomes and depression.[242] This study reported that changes in depressive

symptoms over time were associated with same-months changes in weight loss (p=0.041), and further, changes in weight loss were associated with same-month changes in depressive symptoms (p=0.15).[242] Both studies suggest that a link between depressive symptoms, poor patient reported outcomes and associated weight loss exists, regardless of HPV-status, albeit, more commonly seen as a late sequalae.[242] While there is no available data that we are aware of describing an equivalent association in HPV-associated HNC alone, our findings demonstrate a significant discrepancy in weight loss between HPV-associated cancers and those without. Is depression playing a pronounced role in this patient cohort, in the acute setting, contributing to increased on-treatment weight loss? This question remains unanswered and would benefit from further investigation in a prospective study. A greater understanding of the link between HPV-associated HNC and depression (if any) would certainly assist in formulating more personalised strategies to weight management to complement predictive models established in this thesis.

There is limited data to support a contributory role of HPV-status to patient wellbeing. Recent findings have reported HPV status as an important marker of appropriate symptom management strategies.[243] HNC patients with HPV-unrelated disease reported significantly higher levels of fatigue at baseline (p=0.001) and three months post radiotherapy (p=0.002), suggestive of persistent fatigue, unrelated to their diagnosis. On the other hand, fatigue from baseline to one-month post radiotherapy demonstrated was significantly elevated among HPV-associated HNC patients (p=0.001). A correlation between treatment and increased levels of fatigue was subsequently reported in the HPV-associated cohort. As a consequence, acute fatigue symptom management strategies were recommended for HPV-associated oropharyngeal cancer patients undergoing chemoradiotherapy. The Radiation Therapy Oncology Group (RTOG) 0129 also reported similar findings for patient reported QoL and performance status.[244] HPV-associated HNC patients reported a significant decrease in patient reported QoL/performance status (p<0.0001) from baseline to the final two weeks of radiotherapy, despite having a higher relative reported QoL at baseline.[244] While an association between fatigue and psychological conditions such as depression in

HPV-associated HNC has not been reported to date, the findings in each of these studies, combined with those of this thesis, warrant further investigation. Is fatigue a symptom of depression, which has a previously demonstrated relationship with weight loss in HNC patients? It is reasonable to hypothesise that there may be an underlying alliance, which may help us better understand the findings of Chapter 6 of this thesis. Were our HPV-associated HNC patients losing more weight because they have increased levels of fatigue, leading to depressive symptoms? Without patient reported outcomes in this study, we are unable to validate such relationships. Alternatively, are we placing too great an emphasis on the relationship between HPV-related disease, depression and weight loss? Recent findings have reported that radiation induced toxicities have a significant impact on oral intake.[224] Considering HPV-associated malignancies are primarily in the oropharynx, in close proximity to dysphagia-associated structures, is it this relationship that is the main contributor to increased weight loss in this cohort? Both theories described in the literature would suggest that it may be a complex mix of both. We must therefore delve further into the patient experience to better understand patient barriers inhibiting effective nutritional management throughout the course of radiotherapy, while also considering the toxicity inducing location of these tumours. Subsequently, the independent findings of this thesis and each of these studies demand further investigation in a combined prospective study to ascertain definitively whether an association exists.

The value of QoL in HNC patients is well recognised, due to the debilitating side effects of treatment.[245] However, despite the availability of multiple disease specific validated QoL tools, until recently, there remains a paucity of evidence in the QoL literature for HNC.[245] The RTOG 0129 trial comparing standard radiation versus accelerated radiation plus cetuximab, introduced a study design that was appropriately powered to elucidate any differences between the cancer specific measures of Performance Status Scale for the Head and Neck (PSS-HN), Head and Neck Radiotherapy Questionnaire (HNRQ), and the Spitzer Quality of Life Index (SQLI). These measures were captured at eight time points from pre-

treatment to five years post radiotherapy, providing extensive 5-year QoL follow-up.[244] While this study demonstrated no difference in QoL between the two cohorts, it set a framework for future HNC QoL studies, demonstrating a valuable and feasible platform to collect high quality QoL data. Consequently, multiple publications purport that patient reported outcomes (PRO) should be used to complement QoL in the setting of future randomised clinical trials.[245, 246]

Further studies which built upon the framework established back in 2002 at the commencement of RTOG 0129, have subsequently demonstrated the value of good quality QoL studies in HNC. Each reported that a good QoL prior to the commencement of treatment was an independent prognostic variable for improved survival post treatment.[247-249] Furthermore, HPV-associated HNC was correlated with a better QoL life before and after treatment, but with a significant reduction in QoL during treatment itself. The Trans-Tasman Radiation Oncology Group (TROG) further supported these results, demonstrating equivalent findings linking a positive HPV status with a good QoL pre and post treatment, and a reduction in QoL during radiotherapy, in a cohort of 200 patients during and after chemoradiation.[250] Such compelling evidence propagates a strong case for deescalating treatment strategies in the favourable prognosis of HPV-associated oropharyngeal cancer cohort, while also facilitating an improved QoL during the widely reported decline in quality of life experienced while undergoing treatment.[245] Subsequent recommendations for treatment de-escalation, whist providing a platform for improved QoL, place greater significance on the findings presented in Chapter 6, with a risk of increased weight loss demonstrated in this patient cohort.

7.5 Treatment de-intensification and radiation dose de-escalation

The concept of radiotherapy dose de-escalation was first introduced in Chapter 6. Dose de-escalation aims to minimise radiation induced toxicities such as dysphagia, at the same time

as maintaining equivalent disease control. As discussed, this places an even greater importance on optimal on-treatment weight maintenance, as the opportunity for 'double' dose de-escalation is increased with a lower delivered dose, coupled with a patient at higher risk of geometric uncertainty due to their increased risk of on-treatment weight loss. Although this approach is very much in its infancy, the preliminary clinical data is promising. In a study of dose de-escalation to the elective neck, the reported actuarial rate of lymph node recurrence (3.9% at 2 years, N=233) in a cohort receiving a lower prescribed dose (40Gy) to the elective neck was comparable to equivalent cohorts receiving a standard 50Gy, albeit, in different cohorts.[251-253] Despite these promising findings, this study only presented a single, dose de-escalated arm. A prospective, randomisation of both of these dose cohorts (40Gy v 50Gy) would further validate the purported benefit of this dose de-escalation. These findings suggest that a lower dose to elective nodal stations does not necessarily lead to a higher rate of regional recurrence. This was supported in a cohort receiving elective nodal dose prescriptions at 15-20% lower than standard of care.[254] Lower doses were associated with a comparable incidence of progression-free survival to a cohort receiving historical regimens, while demonstrating an improved toxicity profile as a consequence of the lower therapeutic dose. Only one of 44 patients (2%) undertaking this modified regimen was feeding tube reliant at three months post-radiotherapy. None were dependent at six months. These early findings suggest that this regimen is extremely tolerable with respect to radiation induced dysphagia. Furthermore, disease control is not compromised as a result of this toxicity reduction. Another group also demonstrated favourable QoL outcomes in patient delivered de-escalated radiotherapy compared to historical controls, further adding to the evidence base supporting wider application of de-intensification treatment strategies.[255] A compelling counter argument to the double de-escalation risk which was earlier hypothesised, may well be based on the assumption that by reducing dose, you are in fact reducing treatment related toxicities, and in turn, minimising the risk of acute toxicity leading to weight loss. Do they effectively cancel each other out? We are yet to uncover the answer to this question.

Both sides of the argument, however, require further, prospective investigation to provide definitive data before even approaching an answer to this theory.

Despite the early clinical evidence supporting treatment de-intensification in favour of a reduced toxicity profile, patients with HNC still overwhelmingly prioritise cure over survival and swallowing outcomes.[256] Regardless of HPV status, there is a demonstrated preference for the prioritisation of oncologic outcomes (i.e. disease related) over non-oncologic outcomes (i.e. treatment-induced toxicities). Patients included in the above study prioritised cure over survival and toxicity. Seventy-five percent of the one-hundred and fifty survey respondents ranked cure as their highest priority.[256] However, as age was incrementally increased per decade, survival was deemed less important (odds ratio, 0.72; 95% CI, 0.52-1.00). Patients over the age of 75 frequently reported survival and/or cure as a lower priority over toxicity (median rank, 6; interquartile range, 2-11). Considering that HPV-associated HNC is predominantly seen in younger patients, this finding is of limited value.

We must therefore, in the knowledge that the large majority of the available clinical data is not subject to long-term follow-up, proceed with treatment de-intensification with cautious optimism and engage the patient in a comprehensive model of shared decision making. This view is shared by many. The American Society of Clinical Oncology (ASCO), has very recently provided a commentary on de-escalation strategies across the three main modalities for OPC- surgery, chemotherapy and radiation therapy. They stipulate that, although preliminary data is encouraging, de-escalation must only occur under the strict governance of a well-designed clinical trial.[257] Another study concluded that de-intensification of treatment from chemoradiotherapy to radiotherapy or surgery alone, in cases of HPV1 AJCC eighth edition stage I or stage II disease, may in fact compromise patient safety.[258] Furthermore, a third study concluded that “until mature results from prospective phase 3 clinical trials are available, we recommend caution in the de-intensification of therapy particularly as current therapy achieves high rates of long-term

disease control".[259] All of these studies don't dismiss the demonstrated early gains of dose de-escalation to patient disease and toxicity outcomes. However, they provide a voice of reason that must be considered in the absence of demonstrated, repeatable, highest quality clinical data that can only mature with time. To ensure robust clinical trial outcome data, optimal nutritional management must be integrated into such well-designed clinical trials, to mitigate the contribution of confounding variables (such as weight loss) when analysing the effectiveness of treatment deintensification. Risk stratifying HNC patients for feeding tube use can play a key role in ensuring this.

7.6 HPV vaccination and screening programs

Despite the rapid onset of HPV-associated oropharyngeal cancers in the western world (including Australia), HNC still remains rare when compared to other tumour sites. Subsequently, national screening initiatives like we see in breast, bowel and prostate cancer, are difficult to institute. The demographic shift towards HPV-associated disease also minimises openings for conventional screening opportunities such as pre-cancerous plaques in the oral mucosa.[260]

Yet, the biggest opportunity for management of not only HPV-associated HNC, but other sites of HPV-associated disease including the cervix, is via globally supported HPV vaccination programs. In the previous 10-15 years, most countries across Europe, North America and Australia have adopted local HPV vaccination programs, with a primary target population of adolescent girls, the most susceptible to HPV-associated cervical cancer, where 100% of cases are associated with HPV infection.[239] Despite vaccination uptake ranging from 30 to 80% across these countries, there remains a substantial opportunity for HPV vaccination programs to play a critical role in the field of HNC cancers.[261] If HPV vaccination via a standardised and well organised program is a continued priority amongst

adolescents, both female and male, there lies an opportunity to make a dent into the incidence of HPV-associated HNC.

A recent commentary takes a well measured view with respect to the efficacy of HPV vaccination for HNC.[260] The authors suggest that it is still a little premature to consider a HPV vaccination program as the definitive solution to reduce the global burden of HNC. However, there are grounds for optimism if we are to extrapolate the significant gains of the cervical cancer vaccination experience.[260] With time, and the anticipated benefits of coverage or 'herd' immunity, we can be quietly confident of making an impact into the global HPV-associated cancer footprint for all affected tumour sites. An excellent safety profile accompanies HPV and many other vaccinations, allowing for extensive roll out and thorough, longitudinal follow up.[262] This, however, may take many years to come to fruition. Recent projections from the US cancer registry paint a comprehensive forecast for the incidence of HPV-associated cancers in the US over the next decade. Based on forecasts from birth cohorts ranging from 1939 to 1969, a rapid increase in HPV-associated cancers is predicted in older white men (65 to 74 years- 40.7 to 71.2 per 100,000; 75 to 84 years- 25.7 to 50.1 per 100,000).[263] With a predicted 50% increase in US citizens aged 65 years or older leading into the year 2029, a significant shift in disease burden is anticipated.[263] This shift is thought to be primarily apportioned to the change in sexual behaviours in cohorts born between the 1930s and 1950s.[264] While the cohorts that have been the subject of early investigations have been primarily younger, this demographic is shifting. These affected birth cohorts are getting older, and consequently, are presenting with HPV-associated HNC later in life. Subsequently, although modest forecasts for HPV-associated HNC are predicted for birth cohorts post the 1960s, this is not fully understood.[263] The introduction of vaccination programs, together with time, limit the quality of this data at this point in time. The true benefits of a quality vaccination program won't be realised until those vaccinated are at highest risk of disease expression. Although younger, this cohort is still generally older than

50 years of age. In the interim, we must continue to develop strategies to counter the growing- and yet to peak- HPV-associated HNC population.

One of the aims of this thesis was to develop a tool to assist risk stratify feeding tube use in HNC patients. The value of such a tool is in its complementary use with good multidisciplinary, clinical judgement, reflective of the individual patient. The contents of this thesis not only provide a series of clinical findings to better stratify feeding tube risk, but aim to give them clinical currency. Understanding both the current and projected patterns of HNC incidence is imperative to extracting maximum value from the risk stratification tool. This is very much inclusive of the patterns of HPV-associated disease. The intricacies of the HPV-associated cohort, in particular, the predicted shift towards an older population, will need to be considered in an evolving risk stratification tool. The framework established in the development of the risk stratification tool provides an ongoing, valuable contribution to the field. It is not only valid in the present, but is able to be modified with due consideration for future HNC populations.

Chapter 8: Conclusion and future directions

Radiation induced dysphagia is arguably the most debilitating of toxicities associated with a course of head and neck radiotherapy. It has been the subject of extensive investigation, with respect to contributary clinical and dosimetric variables, acute and late management strategies, and more recently, its impact on the quality of life of patients throughout and beyond their cancer diagnosis.

The title of this thesis, “Improving Dysphagia Quality of Life Outcomes in Patients Receiving Head and Neck Radiotherapy”, formed the foundation for each of the chapters that encapsulate this body of work, with each chapter aiming to build on the established evidence base by providing a valuable contribution to a group of patients who , endure toxicities which affect their quality of life - both in the short and the long term. Chapter 3 adds immediate value to a set of DVO recommendations that are only validated for late dysphagia, by giving them applicability in the understanding of acute radiation-induced dysphagia. This understanding is critical in modern, precision radiotherapy, where acute toxicity management, treatment tolerance and subsequent weight management are pertinent to optimal treatment delivery and patient outcomes. Furthermore, it answered a recognised gap in the literature as detailed in the QUANTEC reports.[172] Chapters 4 and 5 performed a comprehensive analysis of clinical and dosimetric variables to better appreciate the key prognostic variables that predict prolonged feeding tube use, both in the acute (on-treatment) phase and extending beyond into post-radiotherapy side effect management. The risk stratification tool, propagated from the key findings of T-classification and level 2 lymphadenopathy, makes a significant contribution to the literature, and more importantly, provides a tool for immediate clinical value. Not only does it support evidence based nutritional intervention decision making and appropriate allied health resource prioritisation, it also facilitates an improved patient/clinician informed consent process, where patients are better equipped and educated to rightfully contribute to complex, medical decisions. Finally, Chapter 6 provides a valuable insight into the modern-day HNC radiotherapy patient,

whereby HPV-associated disease has transformed the patient demographic that presents for treatment. This chapter reported some significant outcomes with respect to weight loss in this HPV-associated patient cohort. However, it perhaps raised even more questions that must be at the forefront of future prospective trials as we look to better understand both the physical and mental attributes of our patients that help or hinder our ability to provide optimal patient care.

The yet-to-peak HPV epidemic within our society provides many exciting opportunities for ongoing research in the space of HNC dysphagia management. Like the majority of tumour sites, there are rapid developments in all facets of HNC radiotherapy- complementary diagnostic imaging, treatment planning and delivery and image guidance. However, it is the unique opportunity to combine this development with a changing HNC patient demographic, that provides a challenging, yet exciting, platform for clinical research. Will DVO data further evolve with the recent adoption of dose de-escalation strategies? Will we be capable of avoiding exposing critical swallowing anatomy that were otherwise unavoidable with previous dose regimes and technologies? One of the single biggest questions that requires immediate attention, as recognised in these thesis findings, is how can we better manage radiation-induced dysphagia (and other toxicities) in a cohort of patients that presents as a polar opposite to the traditional HNC patient, on which the large majority of our clinical evidence base is derived from.

We are at the forefront of many new technologies that could change the way we deliver HNC radiotherapy. Proton therapy has the potential to be a real ‘game changer’ with respect to toxicity reduction, especially in Australia where proton therapy clinical operations will commence in the very near future. The evolution of the magnetic resonance imaging (MRI) linear accelerator, while very much in its clinical infancy, provides a dynamic platform for improved radiotherapy practice. Image guidance, with potential for margin reduction and radiotherapy plan adaptation, leading to possible gains in toxicity profiles, is one such possibility. Will soon-to-accrue local clinical trials investigating the role of immunotherapy in

HPV-associated head and neck cancers revolutionise the role of radiotherapy like it has in other malignancies? Furthermore, will the somewhat forgotten art of brachytherapy make a renaissance in the treatment of HNC?

With each of these variations in practice, the role of the multidisciplinary team must evolve. It must be driven by clinical, patient reported and QoL outcome data, so that radiation-induced dysphagia management strategies can be continually adapted to meet the individual needs of each and every patient. Available DVO data on radiation dose de-escalation is also in its infancy and will no doubt continue to shape future research methodologies, and subsequently, clinical practice.

Finally, what we don't currently fully appreciate is what we don't know. Over the course of this thesis, eight years, the field of HNC radiotherapy has significantly evolved. This has impacted the rapidly evolving profession of radiation oncology. However, unlike many other cancer profiles, the way in which we understand HNC, and most importantly, its patient population, has changed significantly. This understanding, constantly improving as new data is published, poses many challenges. These are exciting challenges and opportunities to further improve optimised quality of life outcomes for HNC radiotherapy patients for many years to come.

Chapter 9: References

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol.* 2006;24:2137-2150.

2. Rischin D, Ferris RL, Le QT. Overview of Advances in Head and Neck Cancer. *J Clin Oncol.* 2015;33:3225-3226.

3. Braakhuis BJ, Brakenhoff RH, Leemans CR. Treatment choice for locally advanced head and neck cancers on the basis of risk factors: biological risk factors. *Ann Oncol.* 2012;23 Suppl 10:x173-177.

4. Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. *Nat Rev Cancer.* 2011;11:9-22.

5. Ragin CC, Taioli E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. *Int J Cancer.* 2007;121:1813-1820.

6. Mehanna H, Paleri V, West CM, Nutting C. Head and neck cancer--Part 1: Epidemiology, presentation, and prevention. *BMJ.* 2010;341:c4684.

7. McIlwain WR, Sood AJ, Nguyen SA, Day TA. Initial symptoms in patients with HPV-positive and HPV-negative oropharyngeal cancer. *JAMA Otolaryngol Head Neck Surg.* 2014;140:441-447.

8. Paleri V, Staines K, Sloan P, Douglas A, Wilson J. Evaluation of oral ulceration in primary care. *BMJ.* 2010;340:c2639.

9. Singhi AD, Westra WH. Comparison of human papillomavirus in situ hybridization and p16 immunohistochemistry in the detection of human papillomavirus-associated head and neck cancer based on a prospective clinical experience. *Cancer.* 2010;116:2166-2173.

10. Huang SH, O'Sullivan B. Overview of the 8th Edition TNM Classification for Head and Neck Cancer. *Curr Treat Options Oncol.* 2017;18:40.

11. Lydiatt W, O'Sullivan B, Patel S. Major Changes in Head and Neck Staging for 2018. *Am Soc Clin Oncol Educ Book.* 2018;38:505-514.

12. Seiwert TY, Cohen EE. State-of-the-art management of locally advanced head and neck cancer. *Br J Cancer.* 2005;92:1341-1348.

13. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol.* 2010;11:21-28.

14. Gregoire V, Langendijk JA, Nuyts S. Advances in Radiotherapy for Head and Neck Cancer. *J Clin Oncol.* 2015;33:3277-3284.

15. Daly ME, Chen AM, Bucci MK, et al. Intensity-modulated radiation therapy for malignancies of the nasal cavity and paranasal sinuses. *Int J Radiat Oncol Biol Phys.* 2007;67:151-157.

16. Rusthoven KE, Raben D, Chen C. Improved Survival in Patients With Stage III-IV Head and Neck Cancer Treated With Radiotherapy as Primary Local Treatment Modality. *International Journal of Radiation Oncology*Biology*Physics.* 2008;72:343-350.

17. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol.* 2011;12:127-136.

18. Denis F, Garaud P, Bardet E, et al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. *Int J Radiat Oncol Biol Phys.* 2003;55:93-98.

19. Rosenthal DI, Lewin JS, Eisbruch A. Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. *J Clin Oncol.* 2006;24:2636-2643.

20. Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiother Oncol.* 2003;66:253-262.

21. Murphy BA, Gilbert J. Dysphagia in head and neck cancer patients treated with radiation: assessment, sequelae, and rehabilitation. *Semin Radiat Oncol.* 2009;19:35-42.

22. Nguyen NP, Moltz CC, Frank C, et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. *Ann Oncol.* 2004;15:383-388.

23. Nguyen NP, Sallah S, Karlsson U, Antoine JE. Combined chemotherapy and radiation therapy for head and neck malignancies: quality of life issues. *Cancer.* 2002;94:1131-1141.

24. Staar S, Rudat V, Stuetzer H, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy--results of a multicentric randomized German trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2001;50:1161-1171.

25. Nuyts S, Dirix P, Clement PM, et al. Impact of adding concomitant chemotherapy to hyperfractionated accelerated radiotherapy for advanced head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys.* 2009;73:1088-1095.

26. Caudell JJ, Schaner PE, Meredith RF, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2009;73:410-415.

27. Mick R, Vokes EE, Weichselbaum RR, Panje WR. Prognostic factors in advanced head and neck cancer patients undergoing multimodality therapy. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 1991;105:62-73.

28. Caglar HB, Tishler RB, Othus M, et al. Dose to Larynx Predicts for Swallowing Complications After Intensity-Modulated Radiotherapy. *International Journal of Radiation Oncology*Biology*Physics.* 2008;72:1110-1118.

29. Batth SS, Caudell JJ, Chen AM. Practical considerations in reducing swallowing dysfunction following concurrent chemoradiotherapy with intensity-modulated radiotherapy for head and neck cancer. *Head Neck.* 2013.

30. Jensen K, Lambertsen K, Grau C. Late swallowing dysfunction and dysphagia after radiotherapy for pharynx cancer: Frequency, intensity and correlation with dose and volume parameters. *Radiotherapy and Oncology.* 2007;85:74-82.

31. Eisbruch A, Schwartz M, Rasch C, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? *Int J Radiat Oncol Biol Phys.* 2004;60:1425-1439.

32. Eisbruch A. Dysphagia and aspiration following chemo-irradiation of head and neck cancer: major obstacles to intensification of therapy. *Ann Oncol.* 2004;15:363-364.

33. Robbins KT. Barriers to winning the battle with head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2002;53:4-5.

34. Semenenko VA, Reitz B, Day E, Qi XS, Miften M, Li XA. Evaluation of a commercial biologically based IMRT treatment planning system. *Med Phys.* 2008;35:5851-5860.

35. Anderson N, Lawford C, Khoo V, Rolfo M, Joon DL, Wada M. Improved normal tissue sparing in head and neck radiotherapy using biological cost function based-IMRT. *Technology in cancer research & treatment.* 2011;10:575-583.

36. Feng FY, Kim HM, Lyden TH, et al. Intensity-Modulated Radiotherapy of Head and Neck Cancer Aiming to Reduce Dysphagia: Early Dose-Effect Relationships for the Swallowing Structures. *International Journal of Radiation Oncology*Biology*Physics.* 2007;68:1289-1298.

37. Lin A, Kim HM, Terrell JE, Dawson LA, Ship JA, Eisbruch A. Quality of life after parotid-sparing IMRT for head-and-neck cancer: A prospective longitudinal study. *International Journal of Radiation Oncology*Biology*Physics.* 2003;57:61-70.

38. Feng M, Jabbari S, Lin A, et al. Predictive factors of local-regional recurrences following parotid sparing intensity modulated or 3D conformal radiotherapy for head and neck cancer. *Radiotherapy and Oncology.* 2005;77:32-38.

39. Pearson WG, Jr., Hindson DF, Langmore SE, Zumwalt AC. Evaluating swallowing muscles essential for hyolaryngeal elevation by using muscle functional magnetic resonance imaging. *Int J Radiat Oncol Biol Phys.* 2013;85:735-740.

40. Popovtzer A, Cao Y, Feng FY, Eisbruch A. Anatomical changes in the pharyngeal constrictors after chemo-irradiation of head and neck cancer and their dose-effect relationships: MRI-based study. *Radiother Oncol.* 2009;93:510-515.

41. Truong MT, Lee R, Saito N, et al. Correlating computed tomography perfusion changes in the pharyngeal constrictor muscles during head-and-neck radiotherapy to dysphagia outcome. *Int J Radiat Oncol Biol Phys.* 2012;82:e119-127.

42. Dornfeld K, Hopkins S, Simmons J, et al. Posttreatment FDG-PET uptake in the supraglottic and glottic larynx correlates with decreased quality of life after chemoradiotherapy. *Int J Radiat Oncol Biol Phys.* 2008;71:386-392.

43. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. *J Clin Oncol.* 2010;28:2732-2738.

44. Schwartz DL, Hutcheson K, Barringer D, et al. Candidate dosimetric predictors of long-term swallowing dysfunction after oropharyngeal intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys.* 2010;78:1356-1365.

45. Vainshtein J, Eisbruch A. Function, muscles, and sparing by IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2013;85:577-578.

46. Dornfeld K, Simmons JR, Karnell L, et al. Radiation doses to structures within and adjacent to the larynx are correlated with long-term diet- and speech-related quality of life. *Int J Radiat Oncol Biol Phys.* 2007;68:750-757.

47. Christianen ME, Schilstra C, Beetz I, et al. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study. *Radiother Oncol.* 2012;105:107-114.

48. Rancati T, Schwarz M, Allen AM, et al. Radiation dose-volume effects in the larynx and pharynx. *Int J Radiat Oncol Biol Phys.* 2010;76:S64-69.

49. Kendall KA, McKenzie S, Leonard RJ, Goncalves MI, Walker A. Timing of events in normal swallowing: a videofluoroscopic study. *Dysphagia.* 2000;15:74-83.

50. Mittal BB, Pauloski BR, Haraf DJ, et al. Swallowing dysfunction--preventative and rehabilitation strategies in patients with head-and-neck cancers treated with surgery, radiotherapy, and chemotherapy: a critical review. *Int J Radiat Oncol Biol Phys.* 2003;57:1219-1230.

51. Wu CH, Hsiao TY, Ko JY, Hsu MM. Dysphagia after radiotherapy: endoscopic examination of swallowing in patients with nasopharyngeal carcinoma. *The Annals of otology, rhinology, and laryngology.* 2000;109:320-325.

52. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. *Int J Radiat Oncol Biol Phys.* 2007;68:1289-1298.

53. Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Leemans CR, Slotman BJ. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. *Radiother Oncol.* 2009;90:189-195.

54. Meirovitz A, Murdoch-Kinch CA, Schipper M, Pan C, Eisbruch A. Grading xerostomia by physicians or by patients after intensity-modulated radiotherapy of head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2006;66:445-453.

55. Dirix P, Nuyts S, Van den Bogaert W. Radiation-induced xerostomia in patients with head and neck cancer: a literature review. *Cancer.* 2006;107:2525-2534.

56. Teguh DN, Levendag PC, Noever I, et al. Treatment Techniques and Site Considerations Regarding Dysphagia-Related Quality of Life in Cancer of the Oropharynx and Nasopharynx. *International Journal of Radiation Oncology*Biology*Physics.* 2008;72:1119-1127.

57. Dirix P, Abbeel S, Vanstraelen B, Hermans R, Nuyts S. Dysphagia After Chemoradiotherapy for Head-and-Neck Squamous Cell Carcinoma: Dose-Effect Relationships for the Swallowing Structures. *International Journal of Radiation Oncology*Biology*Physics.* 2009;75:385-392.

58. Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *European journal of cancer.* 2000;36:1796-1807.

59. List MA, D'Antonio LL, Cella DF, et al. The Performance Status Scale for Head and Neck Cancer Patients and the Functional Assessment of Cancer Therapy-Head and Neck Scale. A study of utility and validity. *Cancer.* 1996;77:2294-2301.

60. Chen AY, Frankowski R, Bishop-Leone J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. *Arch Otolaryngol Head Neck Surg.* 2001;127:870-876.

61. Mallick I, Gupta SK, Ray R, et al. Predictors of weight loss during conformal radiotherapy for head and neck cancers - how important are planning target volumes? *Clin Oncol (R Coll Radiol).* 2013;25:557-563.

62. Rutter CE, Yovino S, Taylor R, et al. Impact of early percutaneous endoscopic gastrostomy tube placement on nutritional status and hospitalization in patients with head and neck cancer receiving definitive chemoradiation therapy. *Head Neck.* 2011;33:1441-1447.

63. Sanguineti G, Gunn GB, Parker BC, Endres EJ, Zeng J, Fiorino C. Weekly dose-volume parameters of mucosa and constrictor muscles predict the use of

percutaneous endoscopic gastrostomy during exclusive intensity-modulated radiotherapy for oropharyngeal cancer. *Int J Radiat Oncol Biol Phys.* 2011;79:52-59.

64. Sanguineti G, Rao N, Gunn B, Ricchetti F, Fiorino C. Predictors of PEG dependence after IMRT+/-chemotherapy for oropharyngeal cancer. *Radiother Oncol.* 2013;107:300-304.

65. Nugent B, Parker MJ, McIntyre IA. Nasogastric tube feeding and percutaneous endoscopic gastrostomy tube feeding in patients with head and neck cancer. *J Hum Nutr Diet.* 2010;23:277-284.

66. Clavel S, Fortin B, Despres P, et al. Enteral feeding during chemoradiotherapy for advanced head-and-neck cancer: a single-institution experience using a reactive approach. *Int J Radiat Oncol Biol Phys.* 2011;79:763-769.

67. Koyfman SA, Adelstein DJ. Enteral feeding tubes in patients undergoing definitive chemoradiation therapy for head-and-neck cancer: a critical review. *Int J Radiat Oncol Biol Phys.* 2012;84:581-589.

68. Capuano G, Grosso A, Gentile PC, et al. Influence of weight loss on outcomes in patients with head and neck cancer undergoing concomitant chemoradiotherapy. *Head Neck.* 2008;30:503-508.

69. Salas S, Baumstarck-Barrau K, Alfonsi M, et al. Impact of the prophylactic gastrostomy for unresectable squamous cell head and neck carcinomas treated with radio-chemotherapy on quality of life: Prospective randomized trial. *Radiother Oncol.* 2009;93:503-509.

70. Silander E, Nyman J, Bove M, Johansson L, Larsson S, Hammerlid E. Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer: a randomized study. *Head Neck.* 2012;34:1-9.

71. Beaver ME, Matheny KE, Roberts DB, Myers JN. Predictors of weight loss during radiation therapy. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2001;125:645-648.

72. Lee JH, Machtay M, Unger LD, et al. Prophylactic gastrostomy tubes in patients undergoing intensive irradiation for cancer of the head and neck. *Arch Otolaryngol Head Neck Surg.* 1998;124:871-875.

73. Piquet MA, Ozsahin M, Larpin I, et al. Early nutritional intervention in oropharyngeal cancer patients undergoing radiotherapy. *Support Care Cancer.* 2002;10:502-504.

74. Tyldesley S, Sheehan F, Munk P, et al. The use of radiologically placed gastrostomy tubes in head and neck cancer patients receiving radiotherapy. *Int J Radiat Oncol Biol Phys.* 1996;36:1205-1209.

75. Corry J, Poon W, McPhee N, et al. Prospective study of percutaneous endoscopic gastrostomy tubes versus nasogastric tubes for enteral feeding in patients with head and neck cancer undergoing (chemo)radiation. *Head Neck.* 2009;31:867-876.

76. Chen AM, Li BQ, Lau DH, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2010;78:1026-1032.

77. Baredes S, Behin D, Deitch E. Percutaneous endoscopic gastrostomy tube feeding in patients with head and neck cancer. *Ear Nose Throat J.* 2004;83:417-419.

78. Bhayani MK, Hutcheson KA, Barringer DA, et al. Gastrostomy tube placement in patients with oropharyngeal carcinoma treated with radiotherapy or chemoradiotherapy: Factors affecting placement and dependence. *Head Neck.* 2013.

79. Caudell JJ, Schaner PE, Desmond RA, Meredith RF, Spencer SA, Bonner JA. Dosimetric Factors Associated With Long-Term Dysphagia After Definitive Radiotherapy for Squamous Cell Carcinoma of the Head and Neck. *International Journal of Radiation Oncology*Biology*Physics.*In Press, Corrected Proof.

80. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys.* 1991;21:109-122.

81. Sanguineti G, Adapala P, Endres EJ, et al. Dosimetric predictors of laryngeal edema. *Int J Radiat Oncol Biol Phys.* 2007;68:741-749.

82. Marks LB, Ten Haken RK, Martel MK. Guest editor's introduction to QUANTEC: a users guide. *Int J Radiat Oncol Biol Phys.*76:S1-2.

83. Rancati T, Fiorino C, Sanguineti G. NTCP modeling of subacute/late laryngeal edema scored by fiberoptic examination. *Int J Radiat Oncol Biol Phys.* 2009;75:915-923.

84. Eisbruch A, Levendag PC, Feng FY, et al. Can IMRT or brachytherapy reduce dysphagia associated with chemoradiotherapy of head and neck cancer? The Michigan and Rotterdam experiences. *Int J Radiat Oncol Biol Phys.* 2007;69:S40-42.

85. Levendag PC, Teguh DN, Voet P, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. *Radiother Oncol.* 2007;85:64-73.

86. Caudell JJ, Schaner PE, Desmond RA, Meredith RF, Spencer SA, Bonner JA. Dosimetric factors associated with long-term dysphagia after definitive radiotherapy for squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys.* 2010;76:403-409.

87. van der Molen L, Heemsbergen WD, de Jong R, et al. Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures. *Radiother Oncol.* 2013;106:364-369.

88. Mortensen HR, Jensen K, Aksglaede K, Behrens M, Grau C. Late dysphagia after IMRT for head and neck cancer and correlation with dose-volume parameters. *Radiother Oncol.* 2013;107:288-294.

89. Bhide SA, Gulliford S, Kazi R, et al. Correlation between dose to the pharyngeal constrictors and patient quality of life and late dysphagia following chemo-IMRT for head and neck cancer. *Radiother Oncol.* 2009;93:539-544.

90. Dirix P, Abbeel S, Vanstraelen B, Hermans R, Nuyts S. Dysphagia after chemoradiotherapy for head-and-neck squamous cell carcinoma: dose-effect

relationships for the swallowing structures. *Int J Radiat Oncol Biol Phys.* 2009;75:385-392.

91. Poulsen MG, Riddle B, Keller J, Porceddu SV, Tripcony L. Predictors of acute grade 4 swallowing toxicity in patients with stages III and IV squamous carcinoma of the head and neck treated with radiotherapy alone. *Radiother Oncol.* 2008;87:253-259.

92. Williams GF, Teo MT, Sen M, Dyker KE, Coyle C, Prestwich RJ. Enteral feeding outcomes after chemoradiotherapy for oropharynx cancer: a role for a prophylactic gastrostomy? *Oral Oncol.* 2012;48:434-440.

93. Bhayani MK, Hutcheson KA, Barringer DA, Roberts DB, Lewin JS, Lai SY. Gastrostomy tube placement in patients with hypopharyngeal cancer treated with radiotherapy or chemoradiotherapy: Factors affecting placement and dependence. *Head Neck.* 2013.

94. Pignon JP, le Maitre A, Maillard E, Bourhis J, Group M-NC. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol.* 2009;92:4-14.

95. Christianen ME, Langendijk JA, Westerlaan HE, van de Water TA, Bijl HP. Delineation of organs at risk involved in swallowing for radiotherapy treatment planning. *Radiother Oncol.* 2011;101:394-402.

96. Goepfert RP, Lewin JS, Barrow MP, et al. Grading Dysphagia as a Toxicity of Head and Neck Cancer: Differences in Severity Classification Based on MBS DIGEST and Clinical CTCAE Grades. *Dysphagia.* 2018;33:185-191.

97. Hutcheson KA, Barrow MP, Barringer DA, et al. Dynamic Imaging Grade of Swallowing Toxicity (DIGEST): Scale development and validation. *Cancer.* 2017;123:62-70.

98. Belafsky PC, Mouadeb DA, Rees CJ, et al. Validity and reliability of the Eating Assessment Tool (EAT-10). *Ann Otol Rhinol Laryngol.* 2008;117:919-924.

99. Cheney DM, Siddiqui MT, Litts JK, Kuhn MA, Belafsky PC. The Ability of the 10-Item Eating Assessment Tool (EAT-10) to Predict Aspiration Risk in Persons With Dysphagia. *Ann Otol Rhinol Laryngol.* 2015;124:351-354.

100. Rofes L, Arreola V, Mukherjee R, Clave P. Sensitivity and specificity of the Eating Assessment Tool and the Volume-Viscosity Swallow Test for clinical evaluation of oropharyngeal dysphagia. *Neurogastroenterol Motil.* 2014;26:1256-1265.

101. Arrese LC, Carrau R, Plowman EK. Relationship Between the Eating Assessment Tool-10 and Objective Clinical Ratings of Swallowing Function in Individuals with Head and Neck Cancer. *Dysphagia.* 2017;32:83-89.

102. Swartz JE, Pothen AJ, Wegner I, et al. Feasibility of using head and neck CT imaging to assess skeletal muscle mass in head and neck cancer patients. *Oral Oncol.* 2016;62:28-33.

103. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol (1985).* 2004;97:2333-2338.

104. Prado CM, Birdsell LA, Baracos VE. The emerging role of computerized tomography in assessing cancer cachexia. *Curr Opin Support Palliat Care.* 2009;3:269-275.

105. Badran KW, Heineman TE, Kuan EC, St John MA. Is multidisciplinary team care for head and neck cancer worth it? *Laryngoscope.* 2018;128:1257-1258.

106. Mayadevi M, Thankappan K, Limbachiya SV, et al. Interdisciplinary Telemedicine in the Management of Dysphagia in Head and Neck. *Dysphagia.* 2018.

107. Moleiro J, Faias S, Fidalgo C, Serrano M, Pereira AD. Usefulness of Prophylactic Percutaneous Gastrostomy Placement in Patients with Head and Neck Cancer Treated with Chemoradiotherapy. *Dysphagia.* 2016;31:84-89.

108. Gama RR, Song Y, Zhang Q, et al. Body mass index and prognosis in patients with head and neck cancer. *Head Neck.* 2017;39:1226-1233.

109. Shaw SM, Flowers H, O'Sullivan B, Hope A, Liu LW, Martino R. The effect of prophylactic percutaneous endoscopic gastrostomy (PEG) tube placement on

swallowing and swallow-related outcomes in patients undergoing radiotherapy for head and neck cancer: a systematic review. *Dysphagia.* 2015;30:152-175.

110. Brown T, Banks M, Hughes BGM, Lin C, Kenny LM, Bauer JD. Impact of early prophylactic feeding on long term tube dependency outcomes in patients with head and neck cancer. *Oral Oncol.* 2017;72:17-25.

111. Axelsson L, Silander E, Nyman J, Bove M, Johansson L, Hammerlid E. Effect of prophylactic percutaneous endoscopic gastrostomy tube on swallowing in advanced head and neck cancer: A randomized controlled study. *Head Neck.* 2017;39:908-915.

112. Cereda E, Cappello S, Colombo S, et al. Nutritional counseling with or without systematic use of oral nutritional supplements in head and neck cancer patients undergoing radiotherapy. *Radiother Oncol.* 2018;126:81-88.

113. Park JH, Kim KY, Song HY, et al. Radiation-induced esophageal strictures treated with fluoroscopic balloon dilation: clinical outcomes and factors influencing recurrence in 62 patients. *Acta Radiol.* 2018;59:313-321.

114. Rogus-Pulia NM, Larson C, Mittal BB, et al. Effects of Change in Tongue Pressure and Salivary Flow Rate on Swallow Efficiency Following Chemoradiation Treatment for Head and Neck Cancer. *Dysphagia.* 2016;31:687-696.

115. Hutcheson KA, Barrow MP, Warneke CL, et al. Cough strength and expiratory force in aspirating and nonaspirating postradiation head and neck cancer survivors. *Laryngoscope.* 2017.

116. Hutcheson KA, Barrow MP, Plowman EK, et al. Expiratory muscle strength training for radiation-associated aspiration after head and neck cancer: A case series. *Laryngoscope.* 2018;128:1044-1051.

117. Messing BP, Ward EC, Lazarus CL, et al. Prophylactic Swallow Therapy for Patients with Head and Neck Cancer Undergoing Chemoradiotherapy: A Randomized Trial. *Dysphagia.* 2017;32:487-500.

118. Kraaijenga SAC, Molen LV, Stuiver MM, et al. Efficacy of a novel swallowing exercise program for chronic dysphagia in long-term head and neck cancer survivors. *Head Neck.* 2017;39:1943-1961.

119. Mortensen HR, Jensen K, Aksglaede K, Lambertsen K, Eriksen E, Grau C. Prophylactic Swallowing Exercises in Head and Neck Cancer Radiotherapy. *Dysphagia.* 2015;30:304-314.

120. Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. *Int J Radiat Oncol Biol Phys.* 2012;83:210-219.

121. Ahlberg A, Engstrom T, Nikolaidis P, et al. Early self-care rehabilitation of head and neck cancer patients. *Acta Otolaryngol.* 2011;131:552-561.

122. Rogus-Pulia NM, Pierce MC, Mittal BB, Zecker SG, Logemann JA. Changes in swallowing physiology and patient perception of swallowing function following chemoradiation for head and neck cancer. *Dysphagia.* 2014;29:223-233.

123. Govender R, Wood CE, Taylor SA, Smith CH, Barratt H, Gardner B. Patient Experiences of Swallowing Exercises After Head and Neck Cancer: A Qualitative Study Examining Barriers and Facilitators Using Behaviour Change Theory. *Dysphagia.* 2017;32:559-569.

124. Krisciunas GP, Castellano K, McCulloch TM, et al. Impact of Compliance on Dysphagia Rehabilitation in Head and Neck Cancer Patients: Results from a Multi-center Clinical Trial. *Dysphagia.* 2017;32:327-336.

125. Constantinescu G, Hodgetts W, Scott D, et al. Electromyography and Mechanomyography Signals During Swallowing in Healthy Adults and Head and Neck Cancer Survivors. *Dysphagia.* 2017;32:90-103.

126. Starmer HM, Abrams R, Webster K, et al. Feasibility of a Mobile Application to Enhance Swallowing Therapy for Patients Undergoing Radiation-Based Treatment for Head and Neck Cancer. *Dysphagia.* 2018;33:227-233.

127. Nund RL, Scarinci NA, Cartmill B, Ward EC, Kuipers P, Porceddu SV. Application of the International Classification of Functioning, Disability and Health (ICF) to people with dysphagia following non-surgical head and neck cancer management. *Dysphagia.* 2014;29:692-703.

128. De Felice F, de Vincentiis M, Luzzi V, et al. Late radiation-associated dysphagia in head and neck cancer patients: evidence, research and management. *Oral Oncol.* 2018;77:125-130.

129. Head MDA, Neck Cancer Symptom Working G. Beyond mean pharyngeal constrictor dose for beam path toxicity in non-target swallowing muscles: Dose-volume correlates of chronic radiation-associated dysphagia (RAD) after oropharyngeal intensity modulated radiotherapy. *Radiother Oncol.* 2016;118:304-314.

130. Duprez F, Madani I, De Potter B, Boterberg T, De Neve W. Systematic review of dose--volume correlates for structures related to late swallowing disturbances after radiotherapy for head and neck cancer. *Dysphagia.* 2013;28:337-349.

131. Roe JW, Carding PN, Drinnan MJ, Harrington KJ, Nutting CM. Swallowing performance and tube feeding status in patients treated with parotid-sparing intensity-modulated radiotherapy for head and neck cancer. *Head Neck.* 2016;38 Suppl 1:E1436-1444.

132. Head MDA, Neck Cancer Symptom Working G, Kamal M, et al. Patient reported dry mouth: Instrument comparison and model performance for correlation with quality of life in head and neck cancer survivors. *Radiother Oncol.* 2018;126:75-80.

133. Anderson NJ, Jackson JE, Smith JG, et al. Pretreatment risk stratification of feeding tube use in patients treated with intensity-modulated radiotherapy for head and neck cancer. *Head Neck.* 2018.

134. Matuschek C, Bolke E, Geigis C, et al. Influence of dosimetric and clinical criteria on the requirement of artificial nutrition during radiotherapy of head and neck cancer patients. *Radiother Oncol.* 2016;120:28-35.

135. Brown TE, Wittholz K, Way M, et al. Investigation of p16 status, chemotherapy regimen, and other nutrition markers for predicting gastrostomy in patients with head and neck cancer. *Head Neck.* 2017;39:868-875.

136. Yang W, McNutt TR, Dudley SA, et al. Predictive Factors for Prophylactic Percutaneous Endoscopic Gastrostomy (PEG) Tube Placement and Use in Head and Neck Patients Following Intensity-Modulated Radiation Therapy (IMRT) Treatment: Concordance, Discrepancies, and the Role of Gabapentin. *Dysphagia.* 2016;31:206-213.

137. Rancati T, Schwarz M, Allen AM, et al. Radiation dose-volume effects in the larynx and pharynx. *Int J Radiat Oncol Biol Phys.*76:S64-69.

138. Liu M, Moiseenko V, Agranovich A, et al. Normal Tissue Complication Probability (NTCP) modeling of late rectal bleeding following external beam radiotherapy for prostate cancer: A Test of the QUANTEC-recommended NTCP model. *Acta Oncol.* 2010;49:1040-1044.

139. Appelt AL, Vogelius IR, Farr KP, Khalil AA, Bentzen SM. Towards individualized dose constraints: Adjusting the QUANTEC radiation pneumonitis model for clinical risk factors. *Acta Oncol.* 2013.

140. Beetz I, Steenbakkers RJ, Chouvalova O, et al. The QUANTEC criteria for parotid gland dose and their efficacy to prevent moderate to severe patient-rated xerostomia. *Acta Oncol.* 2013.

141. Strigari L, Pedicini P, D'Andrea M, et al. A new model for predicting acute mucosal toxicity in head-and-neck cancer patients undergoing radiotherapy with altered schedules. *Int J Radiat Oncol Biol Phys.* 2012;83:e697-702.

142. Lee C, Langen KM, Lu W, et al. Assessment of Parotid Gland Dose Changes During Head and Neck Cancer Radiotherapy Using Daily Megavoltage Computed Tomography and Deformable Image Registration. *International Journal of Radiation Oncology*Biology*Physics.* 2008;71:1563-1571.

143. O'Daniel JC, Garden AS, Schwartz DL, et al. Parotid Gland Dose in Intensity-Modulated Radiotherapy for Head and Neck Cancer: Is What You Plan What You Get? *International Journal of Radiation Oncology*Biology*Physics.* 2007;69:1290-1296.

144. Zhou J, Fei D, Wu Q. Potential of intensity-modulated radiotherapy to escalate doses to head-and-neck cancers: What is the maximal dose? *International Journal of Radiation Oncology*Biology*Physics.* 2003;57:673-682.

145. Bhide S, Urbano TG, Clark C, et al. Results of intensity modulated radiotherapy (IMRT) in laryngeal and hypopharyngeal cancer: a dose escalation study. *Radiotherapy and Oncology.* 2007;82:S74-S75-S74-S75.

146. La TH, Filion EJ, Turnbull BB, et al. Metabolic Tumor Volume Predicts for Recurrence and Death in Head-and-Neck Cancer. *International Journal of Radiation Oncology*Biology*Physics.* 2009;74:1335-1341.

147. Raykher A, Correa L, Russo L, et al. The role of pretreatment percutaneous endoscopic gastrostomy in facilitating therapy of head and neck cancer and optimizing the body mass index of the obese patient. *JPEN J Parenter Enteral Nutr.* 2009;33:404-410.

148. Sanguineti G, Gunn GB, Parker BC, Endres EJ, Zeng J, Fiorino C. Weekly dose-volume parameters of mucosa and constrictor muscles predict the use of percutaneous endoscopic gastrostomy during exclusive intensity-modulated radiotherapy for oropharyngeal cancer. *Int J Radiat Oncol Biol Phys.*79:52-59.

149. De Luis DA, Izaola O, Aller R. Nutritional status in head and neck cancer patients. *Eur Rev Med Pharmacol Sci.* 2007;11:239-243.

150. Ng K, Leung SF, Johnson PJ, Woo J. Nutritional consequences of radiotherapy in nasopharynx cancer patients. *Nutr Cancer.* 2004;49:156-161.

151. Silver HJ, Dietrich MS, Murphy BA. Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck

cancer treated with concurrent chemoradiation after low-dose induction chemotherapy. *Head Neck.* 2007;29:893-900.

152. van Wayenburg CA, Rasmussen-Conrad EL, van den Berg MG, et al. Weight loss in head and neck cancer patients little noticed in general practice. *J Prim Health Care.* 2010;2:16-21.

153. Ang KK, Harris J, Garden AS, et al. Concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: radiation therapy oncology group phase II trial 99-14. *J Clin Oncol.* 2005;23:3008-3015.

154. Beckmann GK, Hoppe F, Pfreundner L, Flentje MP. Hyperfractionated accelerated radiotherapy in combination with weekly cisplatin for locally advanced head and neck cancer. *Head Neck.* 2005;27:36-43.

155. Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol.* 2012;13:145-153.

156. Driessen CM, Janssens GO, van der Graaf WT, et al. Toxicity and efficacy of accelerated radiotherapy with concurrent weekly cisplatin for locally advanced head and neck carcinoma. *Head Neck.* 2015.

157. Ho KF, Swindell R, Brammer CV. Dose intensity comparison between weekly and 3-weekly Cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: a retrospective comparison from New Cross Hospital, Wolverhampton, UK. *Acta Oncol.* 2008;47:1513-1518.

158. Bossola M. Nutritional interventions in head and neck cancer patients undergoing chemoradiotherapy: a narrative review. *Nutrients.* 2015;7:265-276.

159. Grant DG, Bradley PT, Pothier DD, et al. Complications following gastrostomy tube insertion in patients with head and neck cancer: a prospective multi-institution study, systematic review and meta-analysis. *Clin Otolaryngol.* 2009;34:103-112.

160. Gregoire V, Ang K, Budach W, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol.* 2014;110:172-181.

161. Bhayani MK, Hutcheson KA, Barringer DA, et al. Gastrostomy tube placement in patients with oropharyngeal carcinoma treated with radiotherapy or chemoradiotherapy: factors affecting placement and dependence. *Head Neck.* 2013;35:1634-1640.

162. Waser M, Siebenhaar C, Zampese J, et al. Novel grafting procedure of ruthenium 2,2':6',2''-terpyridine complexes with phosphonate ligands to titania for water splitting applications. *Chimia (Aarau).* 2010;64:328-329.

163. Wei QK, Fang TJ, Chen WC. Development and validation of growth model for Yersinia enterocolitica in cooked chicken meats packaged under various atmosphere packaging and stored at different temperatures. *J Food Prot.* 2001;64:987-993.

164. Williams TM, Flecha AR, Keller P, et al. Cotargeting MAPK and PI3K signaling with concurrent radiotherapy as a strategy for the treatment of pancreatic cancer. *Mol Cancer Ther.* 2012;11:1193-1202.

165. Cheng SS, Terrell JE, Bradford CR, et al. Variables associated with feeding tube placement in head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2006;132:655-661.

166. Frowen J, Cotton S, Corry J, Perry A. Impact of demographics, tumor characteristics, and treatment factors on swallowing after (chemo)radiotherapy for head and neck cancer. *Head Neck.* 2010;32:513-528.

167. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol.* 2008;26:3582-3589.

168. Wopken K, Bijl HP, van der Schaaf A, et al. Development of a multivariable normal tissue complication probability (NTCP) model for tube feeding dependence after

curative radiotherapy/chemo-radiotherapy in head and neck cancer. *Radiother Oncol.* 2014;113:95-101.

169. Mangar S, Slevin N, Mais K, Sykes A. Evaluating predictive factors for determining enteral nutrition in patients receiving radical radiotherapy for head and neck cancer: a retrospective review. *Radiother Oncol.* 2006;78:152-158.

170. Sanguineti G, Califano J, Stafford E, et al. Defining the risk of involvement for each neck nodal level in patients with early T-stage node-positive oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2009;74:1356-1364.

171. Little M, Schipper M, Feng FY, et al. Reducing xerostomia after chemo-IMRT for head-and-neck cancer: beyond sparing the parotid glands. *Int J Radiat Oncol Biol Phys.* 2012;83:1007-1014.

172. Bentzen SM, Constine LS, Deasy JO, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys.* 2010;76:S3-9.

173. Dawes C. Rhythms in salivary flow rate and composition. *Int J Chronobiol.* 1974;2:253-279.

174. Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA. Unilateral versus bilateral irradiation in squamous cell head and neck cancer in relation to patient-rated xerostomia and sticky saliva. *Radiother Oncol.* 2007;85:83-89.

175. Mekhail TM, Adelstein DJ, Rybicki LA, Larto MA, Saxton JP, Lavertu P. Enteral nutrition during the treatment of head and neck carcinoma: is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube? *Cancer.* 2001;91:1785-1790.

176. Roberge C, Tran M, Massoud C, et al. Quality of life and home enteral tube feeding: a French prospective study in patients with head and neck or oesophageal cancer. *Br J Cancer.* 2000;82:263-269.

177. El-Deiry MW, Futran ND, McDowell JA, Weymuller EA, Jr., Yueh B. Influences and predictors of long-term quality of life in head and neck cancer survivors. *Arch Otolaryngol Head Neck Surg.* 2009;135:380-384.

178. Gurney TA, Eisele DW, Orloff LA, Wang SJ. Predictors of quality of life after treatment for oral cavity and oropharyngeal carcinoma. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2008;139:262-267.

179. Nguyen NP, Frank C, Moltz CC, et al. Impact of dysphagia on quality of life after treatment of head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2005;61:772-778.

180. Rogers SN, Thomson R, O'Toole P, Lowe D. Patients experience with long-term percutaneous endoscopic gastrostomy feeding following primary surgery for oral and oropharyngeal cancer. *Oral Oncol.* 2007;43:499-507.

181. Langmore S, Krisciunas GP, Miloro KV, Evans SR, Cheng DM. Does PEG use cause dysphagia in head and neck cancer patients? *Dysphagia.* 2012;27:251-259.

182. Hutcheson KA, Bhayani MK, Beadle BM, et al. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. *JAMA Otolaryngol Head Neck Surg.* 2013;139:1127-1134.

183. Trotti A, Pajak TF, Gwede CK, et al. TAME: development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group. *Lancet Oncol.* 2007;8:613-624.

184. Caglar HB, Tishler RB, Othus M, et al. Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys.* 2008;72:1110-1118.

185. Amin N, Reddy K, Westerly D, Raben D, DeWitt P, Chen C. Sparing the larynx and esophageal inlet expedites feeding tube removal in patients with stage III-IV oropharyngeal squamous cell carcinoma treated with intensity-modulated radiotherapy. *Laryngoscope.* 2012;122:2736-2742.

186. Eisbruch A, Kim HM, Feng FY, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. *Int J Radiat Oncol Biol Phys.* 2011;81:e93-99.

187. van der Laan HP, van de Water TA, van Herpt HE, et al. The potential of intensity-modulated proton radiotherapy to reduce swallowing dysfunction in the treatment of head and neck cancer: A planning comparative study. *Acta Oncol.* 2013;52:561-569.

188. Senft M, Fietkau R, Iro H, Sailer D, Sauer R. The influence of supportive nutritional therapy via percutaneous endoscopically guided gastrostomy on the quality of life of cancer patients. *Support Care Cancer.* 1993;1:272-275.

189. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010;17:1471-1474.

190. Anderson NJ, Jackson JE, Smith JG, et al. Pretreatment risk stratification of feeding tube use in patients treated with intensity-modulated radiotherapy for head and neck cancer. *Head Neck.* 2018;40:2181-2192.

191. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2001;50:695-704.

192. Porceddu SV, Pryor DI, Burmeister E, et al. Results of a prospective study of positron emission tomography-directed management of residual nodal abnormalities in node-positive head and neck cancer after definitive radiotherapy with or without systemic therapy. *Head Neck.* 2011;33:1675-1682.

193. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med.* 2010;363:24-35.

194. White H, Ford S, Bush B, et al. Salvage surgery for recurrent cancers of the oropharynx: comparing TORS with standard open surgical approaches. *JAMA Otolaryngol Head Neck Surg.* 2013;139:773-778.

195. Collan J, Kapanen M, Makitie A, et al. Submandibular gland-sparing intensity modulated radiotherapy in the treatment of head and neck cancer: sites of locoregional relapse and survival. *Acta Oncol.* 2012;51:735-742.

196. Doornaert P, Verbakel WF, Rietveld DH, Slotman BJ, Senan S. Sparing the contralateral submandibular gland without compromising PTV coverage by using volumetric modulated arc therapy. *Radiat Oncol.* 2011;6:74.

197. Gensheimer MF, Liao JJ, Garden AS, Laramore GE, Parvathaneni U. Submandibular gland-sparing radiation therapy for locally advanced oropharyngeal squamous cell carcinoma: patterns of failure and xerostomia outcomes. *Radiat Oncol.* 2014;9:255.

198. Ohri N, Rapkin BD, Guha C, Kalnicki S, Garg M. Radiation Therapy Noncompliance and Clinical Outcomes in an Urban Academic Cancer Center. *Int J Radiat Oncol Biol Phys.* 2016;95:563-570.

199. Russo G, Haddad R, Posner M, Machtay M. Radiation treatment breaks and ulcerative mucositis in head and neck cancer. *Oncologist.* 2008;13:886-898.

200. Mali SB. Adaptive Radiotherapy for Head Neck Cancer. *J Maxillofac Oral Surg.* 2016;15:549-554.

201. Dawson LA, Sharpe MB. Image-guided radiotherapy: rationale, benefits, and limitations. *Lancet Oncol.* 2006;7:848-858.

202. Brouwer CL, Steenbakkers RJ, Langendijk JA, Sijtsema NM. Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in head and neck organs at risk during radiotherapy provide information to help? *Radiother Oncol.* 2015;115:285-294.

203. Vangelov B, Kotevski DP, Williams JR, Smee RI. The impact of HPV status on weight loss and feeding tube use in oropharyngeal carcinoma. *Oral Oncol.* 2018;79:33-39.

204. Fang CY, Heckman CJ. Informational and Support Needs of Patients with Head and Neck Cancer: Current Status and Emerging Issues. *Cancers Head Neck.* 2016;1.

205. Reich M, Leemans CR, Vermorken JB, et al. Best practices in the management of the psycho-oncologic aspects of head and neck cancer patients: recommendations from the European Head and Neck Cancer Society Make Sense Campaign. *Ann Oncol.* 2014;25:2115-2124.

206. Gold D. The psychosocial care needs of patients with HPV-related head and neck cancer. *Otolaryngol Clin North Am.* 2012;45:879-897.

207. Hendry M, Pasterfield D, Gollins S, et al. Talking about human papillomavirus and cancer: development of consultation guides through lay and professional stakeholder coproduction using qualitative, quantitative and secondary data. *BMJ Open.* 2017;7:e015413.

208. Pytynia KB, Dahlstrom KR, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. *Oral Oncol.* 2014;50:380-386.

209. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29:4294-4301.

210. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol.* 2010;11:781-789.

211. Zumsteg ZS, Cook-Wiens G, Yoshida E, et al. Incidence of Oropharyngeal Cancer Among Elderly Patients in the United States. *JAMA Oncol.* 2016;2:1617-1623.

212. D'Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. *PLoS One.* 2014;9:e86023.

213. Mirghani H, Blanchard P. Treatment de-escalation for HPV-driven oropharyngeal cancer: Where do we stand? *Clin Transl Radiat Oncol.* 2018;8:4-11.

214. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst.* 2008;100:261-269.

215. Sturgis EM, Ang KK. The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms? *J Natl Compr Canc Netw.* 2011;9:665-673.

216. Gabani P, Lin AJ, Barnes J, et al. Radiation therapy dose de-escalation compared to standard dose radiation therapy in definitive treatment of HPV-positive oropharyngeal squamous cell carcinoma. *Radiother Oncol.* 2019;134:81-88.

217. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer.* 2019;144:1941-1953.

218. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136:E359-386.

219. Siddiqui F, Movsas B. Management of Radiation Toxicity in Head and Neck Cancers. *Semin Radiat Oncol.* 2017;27:340-349.

220. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). *Int J Radiat Oncol Biol Phys.* 2010;76:1333-1338.

221. Anderson NJ, Wada M, Schneider-Kolsky M, Rolfo M, Joon DL, Khoo V. Dose-volume response in acute dysphagia toxicity: Validating QUANTEC recommendations into clinical practice for head and neck radiotherapy. *Acta Oncol.* 2014;53:1305-1311.

222. Wopken K, Bijl HP, Langendijk JA. Prognostic factors for tube feeding dependence after curative (chemo-) radiation in head and neck cancer: A systematic review of literature. *Radiother Oncol.* 2018;126:56-67.

223. Paleri V, Urbano TG, Mehanna H, et al. Management of neck metastases in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol.* 2016;130:S161-S169.

224. Barnhart MK, Robinson RA, Simms VA, et al. Treatment toxicities and their impact on oral intake following non-surgical management for head and neck cancer: a 3-year longitudinal study. *Support Care Cancer.* 2018;26:2341-2351.

225. Cartmill B, Cornwell P, Ward E, et al. Emerging understanding of dosimetric factors impacting on dysphagia and nutrition following radiotherapy for oropharyngeal cancer. *Head Neck.* 2013;35:1211-1219.

226. Hutchison AR, Cartmill B, Wall LR, Ward EC. Dysphagia optimized radiotherapy to reduce swallowing dysfunction severity in patients undergoing treatment for head and neck cancer: A systematized scoping review. *Head Neck.* 2019;41:2024-2033.

227. Hutcheson KA, Barrow MP, Lisec A, Barringer DA, Gries K, Lewin JS. What is a clinically relevant difference in MDADI scores between groups of head and neck cancer patients? *Laryngoscope.* 2016;126:1108-1113.

228. Wall LR, Kularatna S, Ward EC, et al. Economic Analysis of a Three-Arm RCT Exploring the Delivery of Intensive, Prophylactic Swallowing Therapy to Patients with Head and Neck Cancer During (Chemo)Radiotherapy. *Dysphagia.* 2018.

229. Wall LR, Ward EC, Cartmill B, Hill AJ, Porceddu SV. Adherence to a Prophylactic Swallowing Therapy Program During (Chemo) Radiotherapy: Impact of Service-Delivery Model and Patient Factors. *Dysphagia.* 2017;32:279-292.

230. Nund RL, Ward EC, Scarinci NA, Cartmill B, Kuipers P, Porceddu SV. Carers' experiences of dysphagia in people treated for head and neck cancer: a qualitative study. *Dysphagia.* 2014;29:450-458.

231. Naghavi AO, Echevarria MI, Strom TJ, et al. Treatment delays, race, and outcomes in head and neck cancer. *Cancer Epidemiol.* 2016;45:18-25.

232. Brown TE, Spurgin AL, Ross L, et al. Validated swallowing and nutrition guidelines for patients with head and neck cancer: identification of high-risk patients for proactive gastrostomy. *Head Neck.* 2013;35:1385-1391.

233. Crombie JM, Ng S, Spurgin AL, Ward EC, Brown TE, Hughes BG. Swallowing outcomes and PEG dependence in head and neck cancer patients receiving

definitive or adjuvant radiotherapy +/- chemotherapy with a proactive PEG: a prospective study with long term follow up. *Oral Oncol.* 2015;51:622-628.

234. Beadle BM, Liao KP, Giordano SH, et al. Reduced feeding tube duration with intensity-modulated radiation therapy for head and neck cancer: A Surveillance, Epidemiology, and End Results-Medicare Analysis. *Cancer.* 2017;123:283-293.

235. Barnhart MK, Ward EC, Cartmill B, et al. Pretreatment factors associated with functional oral intake and feeding tube use at 1 and 6 months post-radiotherapy (+/- chemotherapy) for head and neck cancer. *Eur Arch Otorhinolaryngol.* 2017;274:507-516.

236. Hawkins PG, Lee JY, Mao Y, et al. Sparing all salivary glands with IMRT for head and neck cancer: Longitudinal study of patient-reported xerostomia and head-and-neck quality of life. *Radiother Oncol.* 2018;126:68-74.

237. Jackson WC, Hawkins PG, Arnould GS, Yao J, Mayo C, Mierzwa M. Submandibular gland sparing when irradiating neck level IB in the treatment of oral squamous cell carcinoma. *Med Dosim.* 2019;44:144-149.

238. Brodin NP, Kabarriti R, Garg MK, Guha C, Tome WA. Systematic Review of Normal Tissue Complication Models Relevant to Standard Fractionation Radiation Therapy of the Head and Neck Region Published After the QUANTEC Reports. *Int J Radiat Oncol Biol Phys.* 2018;100:391-407.

239. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Health.* 2016;4:e609-616.

240. Vatca M, Lucas JT, Jr., Laudadio J, et al. Retrospective analysis of the impact of HPV status and smoking on mucositis in patients with oropharyngeal squamous cell carcinoma treated with concurrent chemotherapy and radiotherapy. *Oral Oncol.* 2014;50:869-876.

241. Fan CY, Chao HL, Lin CS, et al. Risk of depressive disorder among patients with head and neck cancer: A nationwide population-based study. *Head Neck.* 2018;40:312-323.

242. Van Liew JR, Brock RL, Christensen AJ, Karnell LH, Pagedar NA, Funk GF. Weight loss after head and neck cancer: A dynamic relationship with depressive symptoms. *Head Neck.* 2017;39:370-379.

243. Xiao C, Beitler JJ, Higgins KA, et al. Associations among human papillomavirus, inflammation, and fatigue in patients with head and neck cancer. *Cancer.* 2018;124:3163-3170.

244. Xiao C, Zhang Q, Nguyen-Tan PF, et al. Quality of Life and Performance Status From a Substudy Conducted Within a Prospective Phase 3 Randomized Trial of Concurrent Standard Radiation Versus Accelerated Radiation Plus Cisplatin for Locally Advanced Head and Neck Carcinoma: NRG Oncology RTOG 0129. *Int J Radiat Oncol Biol Phys.* 2017;97:667-677.

245. Bjordal K, Bottomley A. Making Advances in Quality of Life Studies in Head and Neck Cancer. *Int J Radiat Oncol Biol Phys.* 2017;97:659-661.

246. Ringash J. Quality of Life in Head and Neck Cancer: Where We Are, and Where We Are Going. *Int J Radiat Oncol Biol Phys.* 2017;97:662-666.

247. Cramarossa G, Chow E, Zhang L, et al. Predictive factors for overall quality of life in patients with advanced cancer. *Support Care Cancer.* 2013;21:1709-1716.

248. van Nieuwenhuizen AJ, Buffart LM, Brug J, Leemans CR, Verdonck-de Leeuw IM. The association between health related quality of life and survival in patients with head and neck cancer: a systematic review. *Oral Oncol.* 2015;51:1-11.

249. Quinten C, Maringwa J, Gotay CC, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. *J Natl Cancer Inst.* 2011;103:1851-1858.

250. Ringash J, Fisher R, Peters L, et al. Effect of p16 Status on the Quality-of-Life Experience During Chemoradiation for Locally Advanced Oropharyngeal Cancer: A

Substudy of Randomized Trial Trans-Tasman Radiation Oncology Group (TROG) 02.02 (HeadSTART). *Int J Radiat Oncol Biol Phys.* 2017;97:678-686.

251. Nevens D, Duprez F, Daisne JF, et al. Recurrence patterns after a decreased dose of 40Gy to the elective treated neck in head and neck cancer. *Radiother Oncol.* 2017;123:419-423.

252. van den Bosch S, Dijkema T, Verhoef LC, Zwijnenburg EM, Janssens GO, Kaanders JH. Patterns of Recurrence in Electively Irradiated Lymph Node Regions After Definitive Accelerated Intensity Modulated Radiation Therapy for Head and Neck Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys.* 2016;94:766-774.

253. Kjems J, Gothelf AB, Hakansson K, Specht L, Kristensen CA, Friborg J. Elective Nodal Irradiation and Patterns of Failure in Head and Neck Cancer After Primary Radiation Therapy. *Int J Radiat Oncol Biol Phys.* 2016;94:775-782.

254. Chen AM, Felix C, Wang PC, et al. Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study. *Lancet Oncol.* 2017;18:803-811.

255. Hegde JV, Shaverdian N, Daly ME, et al. Patient-reported quality-of-life outcomes after de-escalated chemoradiation for human papillomavirus-positive oropharyngeal carcinoma: Findings from a phase 2 trial. *Cancer.* 2018;124:521-529.

256. Windon MJ, D'Souza G, Rettig EM, et al. Increasing prevalence of human papillomavirus-positive oropharyngeal cancers among older adults. *Cancer.* 2018;124:2993-2999.

257. Adelstein DJ, Ismaila N, Ku JA, et al. Role of Treatment Deintensification in the Management of p16+ Oropharyngeal Cancer: ASCO Provisional Clinical Opinion. *J Clin Oncol.* 2019;37:1578-1589.

258. Cheraghlou S, Yu PK, Otremba MD, et al. Treatment deintensification in human papillomavirus-positive oropharynx cancer: Outcomes from the National Cancer Data Base. *Cancer.* 2018;124:717-726.

259. Choi KJ, Cheng T, Cobb MI, Sajisevi MB, Gonzalez LF, Ryan MA. Recurrent post-tonsillectomy bleeding due to an iatrogenic facial artery pseudoaneurysm. *Acta Otolaryngol Case Rep.* 2017;2:103-106.

260. De Felice F, Polimeni A, Tombolini V. Human papillomavirus (HPV) vaccine and HPV-related head and neck cancer: What's next? *Oral Oncol.* 2019.

261. Hanson CM, Eckert L, Bloem P, Cernuschi T. Gavi HPV Programs: Application to Implementation. *Vaccines (Basel).* 2015;3:408-419.

262. D'Souza G, Dempsey A. The role of HPV in head and neck cancer and review of the HPV vaccine. *Prev Med.* 2011;53 Suppl 1:S5-S11.

263. Tota JE, Best AF, Zumsteg ZS, Gillison ML, Rosenberg PS, Chaturvedi AK. Evolution of the Oropharynx Cancer Epidemic in the United States: Moderation of Increasing Incidence in Younger Individuals and Shift in the Burden to Older Individuals. *J Clin Oncol.* 2019;37:1538-1546.

264. Frisch M, Hjalgrim H, Jaeger AB, Biggar RJ. Changing patterns of tonsillar squamous cell carcinoma in the United States. *Cancer Causes Control.* 2000;11:489-495.

Chapter 10: Appendices

10.1 Appendix A: Dissemination of Findings

Achievements during candidature (2011-2019)

10.1.1 Published Abstracts

Anderson NJ, Wada M, Schneider-Kolsky, M, Rolfo M, Lim Joon D, Khoo V (2012) Correlation of oral cavity dose, acute mucositis, and PEG dependency for head and neck IMRT. Int J Radiat Oncol Biol Phys 84 (3):s518

Anderson NJ, Wada M, Schneider-Kolsky M, Rolfo M, Lim Joon D, Khoo V (2012) Dose volume response in acute dysphagia and PEG dependence: Validating QUANTEC recommendations for head and neck IMRT. Int J Radiat Oncol Biol Phys 84 (3):s529

Anderson NJ, Jackson J, Wada M, Schneider-Kolsky M, Rolfo M, Gan H, Kaegi K, Sneyd F, Lim Joon D, Khoo V (2013) Creating guidelines for reactive and prophylactic enteral feeding in definitive (chemo) IMRT for head and neck cancer. Int J Radiat Oncol Biol Phys 87 (2):s471

Anderson NJ, Jackson J, Khoo V, Schneider M, Rolfo M, Gan H, Kaegi K, Sneyd F, Lim Joon D, Wada M (2014) Gross tumor volume size and oral cavity dose drive dysphagia in definitive (chemo) IMRT for head and neck cancer. Int J Radiat Oncol Biol Phys 90 (1):s566-67

Anderson NJ, Jackson J, Wada M, Schneider M, Rolfo M, Fahandej M, Lim Joon D, Khoo V (2018) Prediction of feeding tube needs in head and neck radiation therapy patients: Independent validation of a feeding tube prognostic tool. Int J Radiat Oncol Biol Phys 100 (5):1397

10.1.2 Oral Presentations

September 2011	Oral Presentation, 2011 Australasian Elekta Users Meeting, Sydney "Acute Xerostomia and Dysphagia: Do QUANTEC Dose Volume Recommendations Translate to Current Clinical Practice?"
October 2011	Oral Presentation, ASTRO Annual Meeting, Miami, USA Dose Volume Response in Acute Dysphagia Toxicity: Validating QUANTEC Recommendations into Clinical Practice for Head and Neck Radiotherapy,
April 2012	Oral Presentation, 2012 ASMMIRT, Sydney "Maintaining Planned Patient Geometry Through the Utilization of Robust Nutritional Support Interventions"
August 2012	Oral Presentation, 2012 Australasian Elekta Users Meeting, Fremantle "Understanding the Impact of Two Pharyngeal Axis Delineation Guidelines for Planning Definition and Discrepancy in Head & Neck IMRT"
May 2013	Oral Presentation, Victorian Integrated Cancer Services Conference, Melbourne "Creating Guidelines for Reactive and Prophylactic Enteral Feeding in Definitive (Chemo) IMRT for Head and Neck Cancer"

August 2013	Oral Presentation, 2013 Australasian Elekta Users Meeting, Melbourne
	"Profile of a Feeder: Utilising Elekta TPS and Mosaiq Record & Verify to Identify PEG Feeding Characteristics in Head and Neck IMRT patients"
March 2017	Oral Presentation, ASMMIRT 2017, Perth
	Predictive modelling to personalise management of head and neck cancer patients
March 2018	Oral Presentation, ASMIRT 2018 Annual Meeting, Canberra
	Independent Validation of a Feeding Tube Prognostic Application (App) for Head and Neck Radiotherapy Patients
April 2018	Oral Presentation, ISRRT World Congress, Port of Spain. Trinidad
	Predicting Feeding Tube Needs in Head and Neck Radiotherapy Patients: Independently Validating a Feeding Tube Prognostic Tool
March 2019	Oral Presentation, ASMIRT/AACRT 2019 Combined Meeting, Adelaide
	The Modern-Day Head and Neck Radiotherapy Patient: Can we be positive that high-risk of feeding tube use results in poorer weight loss outcomes?

10.1.3 Poster Presentations

October 2012	Poster Presentation, ASTRO Annual Meeting, Boston, USA "Correlation of Oral Cavity Dose, Acute Mucositis and PEG Dependency for Head and Neck IMRT"
October 2012	Poster Presentation, ASTRO Annual Meeting, Boston, USA "Dose Volume Response in Acute Dysphagia and PEG Dependence: Validating QUANTEC Recommendations for Head and Neck IMRT"
April 2012	Poster Presentation, ESTRO Annual Meeting, Geneva, Switzerland "Understanding the Impact of Two Pharyngeal Axis Delineation Guidelines for Planning Definition and Discrepancy in Head & Neck IMRT"
September 2013	Poster Presentation, ASTRO Annual Meeting, Atlanta, USA "Creating Guidelines for Reactive and Prophylactic Enteral Feeding in Definitive (Chemo) IMRT for Head and Neck Cancer"
September 2014	Poster Presentation, ASTRO Annual Meeting, San Francisco, USA Gross Tumor Volume Size and Oral Cavity Dose Drive Dysphagia in Definitive (Chemo) IMRT for Head & Neck Cancer

June 2016	Poster Presentation, ICCR, London, UK Predicting Intensity and Duration of Enteral Nutrition Intervention in Head and Neck Radiotherapy
February 2018	Poster Presentation, ASTRO Multidisciplinary Cancers Symposium, Scottsdale, USA (Monash Travel Grant) Predicting Feeding Tube Needs in Head and Neck Radiotherapy Patients: Independently Validating a Feeding Tube Prognostic Tool

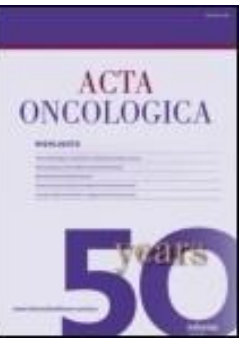
10.1.4 Invited Presentations

September 2011	Invited Speaker, Singapore & Malaysia Radiographers Conference
May 2016	Invited Speaker, ESTRO Teaching Course, Tokyo, Japan
October 2017	Invited International Atomic Energy Agency (IAEA) Expert, UAE National Training Course on Radiotherapy, Abu Dhabi, UAE
March 2018	Invited IAEA Expert, PAEC-IAEA International Conference on Advances in Radiation Oncology & Nuclear Medicine, Islamabad, Pakistan
February 2019	Invited IAEA Expert, National Training Course on planning, treatment delivery and QC for IMRT for prostate and nasopharynx cancer, Tehran, Iran

10.1.5 Awards

April 2012	Awarded “Best Paper Presentation” at ASMMIRT 2012
September 2015	Recipient of NEMICS Grant to further develop and implement a Head & Neck PEG Predictive Tool
March 2017	Awarded “Best Paper Presentation” at ASMMIRT 2017

10.2 Appendix B: Publications (as published)



Taylor & Francis
Taylor & Francis Group

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

Dose-volume response in acute dysphagia toxicity: Validating QUANTEC recommendations into clinical practice for head and neck radiotherapy

Nigel J. Anderson, Morikatsu Wada, Michal Schneider-Kolsky, Maureen Rolfo, Daryl Lim Joon & Vincent Khoo

To cite this article: Nigel J. Anderson, Morikatsu Wada, Michal Schneider-Kolsky, Maureen
Rolfo, Daryl Lim Joon & Vincent Khoo (2014) Dose-volume response in acute dysphagia toxicity:
Validating QUANTEC recommendations into clinical practice for head and neck radiotherapy, Acta
Oncologica, 53:10, 1305-1311, DOI: 10.3109/0284186X.2014.933874

To link to this article:
https://doi.org/10.3109/0284186X.2014.933874

Acta Oncologica, 2014; 53: 1305–1311

informa
healthcare

ORIGINAL ARTICLE

Dose-volume response in acute dysphagia toxicity: Validating QUANTEC recommendations into clinical practice for head and neck radiotherapy

NIGEL J. ANDERSON [1], MORIKATSU WADA [1], MICHAL SCHNEIDER-KOLSKY[3], MAUREEN ROLFO[1], DARYL LIM JOON[1] & VINCENT KHOO [1,2,4]

[1] Department of Radiation Oncology, Austin Health, Heidelberg Heights, Victoria, Australia, [2] Department of Clinical Oncology, Royal Marsden Hospital and Institute of Cancer Research, London, UK, [3] Department of Medical Imaging and Radiation Sciences, Monash University, Victoria, Australia and [4] Department of Medicine, University of Melbourne, Victoria, Australia

ABSTRACT

Purpose. To determine the validity of QUANTEC recommendations in predicting acute dysphagia using intensitymodulated head and neck radiotherapy.

Material and methods. Seventy-six consecutive patients with locally advanced squamous cell carcinoma (SCC) of the head and neck / systemic therapy were analyzed. Multiple dose parameters for the larynx (V50Gy, Dmean and Dmax) were recorded. Acute dysphagia toxicity was prospectively scored in all treatment weeks (week 1– 6 or 1– 7) using CTCAEv3 by three blinded investigators. QUANTEC larynx recommendations (V50Gy 27%, Dmean 44 Gy, Dmean 40 Gy, Dmax 66 Gy) were used to group the cohort (i.e. V50Gy 27% vs. V50Gy 27%). The proportion of patients with Grade 3 dysphagia was compared within each group.

Results. There was a signifi cant reduction in the incidence of grade 3 toxicity in the V50Gy or 27% group at week 5 (14.3% vs. 45.2%, p 0.01) and 6 (25.9% vs. 65.9%, p 0.01). A signifi cant reduction at week 5 (14.7% vs. 50.0, p 0 .02) and 6 (32.4% vs. 67.6%, p 0.01) was seen in Dmean 4 4 Gy when compared to Dmean 44 Gy. Dmean 40 Gy also delivered a signifi cant reduction at week 5 (5.6% vs. 42.3%, p 0.01) and week 6 (23.5% vs. 59.3%, p 0.01). A signifi cant toxicity reduction at treatment week 6 (28.0% vs. 63.0%, p 0 01) was seen from Dmax 66 Gy to Dmax 66 Gy. V50Gy 27% (p 0.01), Dmean 40 Gy (p 0.01) and Dmax 66 Gy (p 0.01) were also predictors of Grade 3 dysphagia when analyzed with multiple clinical risk factors.

Conclusions. QUANTEC late toxicity recommendations for dose to larynx during IMRT are a useful predictor for acute dysphagia toxicity in this patient cohort. Furthermore, this included chemoradiotherapy regimes and post-operative radiotherapy patients, allowing for prophylactic implementation of supportive care measures.

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) series of articles provides a summary of updated dose/volume/outcome data to refi ne current dose-volume recommendations, previously defi ned via the recommendations of Emami et al. [1]. The QUANTEC dose/volume/outcome data was generated to provide the radiotherapy planner with improved data to facilitate effective utilization of more sophisticated planning, delivery and imaging systems in steering precision dose deposition [2].

Radiation-induced dysphagia is strongly correlated to laryngeal dose in patients receiving defi nitive head and neck chemo-radiation. This was addressed by the QUANTEC report [3– 5]. Inadvertent dose deposition to adjacent high dose target volumes often hastens the onset of radiotherapy (RT)-induced acute mucositis and laryngeal edema, resulting in a disruption to the swallowing mechanism and its associated structures. However, swallowing is a complex, multifaceted mechanism. The functional role of each anatomical structure is inter-related. Therefore, isolating the role of each anatomical structure in RT-induced dysphagia can be somewhat challenging. The QUANTEC report suggests that late dysphagia is often a consequence of acute oral mucositis, and that acute dysphagia may be a predictor of late swallowing complication [6]. Our study aimed to address these questions, by validating the recommendations of the QUANTEC report to determine their usefulness in predicting acute dysphagia, through an analysis of dose/volume/outcome in glottic/supraglottic larynx in defi nitive head and neck patients treated at our center. Furthermore, this study aimed to establish if systemic therapy and RT delivered post-operatively (PORT) affects this dose/volume/outcome relationship, and whether late QUANTEC recommendations are still relevant in predicting acute dysphagia within chemo-radiotherapy and PORT regimes.

Material and methods

Seventy-six consecutive patients with locally advanced squamous cell carcinoma (SCC) of the head and neck, treated with intensity modulated radiotherapy (IMRT 60– 70 Gy) defi nitively or PORT / systemic therapy between 2008 and 2011 were analyzed. Patients with primary laryngeal disease and reirradiation were excluded from this review. The study was approved by our institutional ethics committee.

Treatment planning

The prescribed doses were planned via a simultaneous integrated boost (SIB), to a gross tumor volume (GTV), high risk clinical target volume (CTV) and low risk CTV. Dose to GTV (60 – 70 Gy), high risk CTV (60 – 63 Gy) and low risk CTV (54– 56 Gy) was planned at fi ve fractions per week over 6– 7 weeks. Treatment regime (i.e. pre/post-operative RT, / systemic therapy) contributed to the RT treatment length. Each target was expanded with a departmental protocol margin (1 cm GTV to CTV, 0.5 cm CTV to PTV) to form PTV_1, PTV_2 and PTV_3, respectively.

Optimized IMRT plans, deliverable via 7– 9 equally spaced step-and-shoot segmented beams on a 6 MV linear accelerator (Elekta Synergy, Elekta Oncology, Crawley, UK), were generated using both the Elekta CMS XiO and Monaco treatment planning systems (TPS) (Elekta CMS Software, St Louis, MO, USA) on 0.25cm computed tomography (CT) slices.

Dose mean (Dmean), dose maximum (Dmax) and V50Gy of glottic and supraglottic larynx (referred to as ‘ larynx’ for the remainder of article) were recorded for each patient dataset. A dose-volume constraint of V50Gy 30% was used for all patients (if clinically achievable). The larynx was delineated by a single radiation oncologist (MW) for all patients. Larynx was defi ned by epiglottic tip superiorly, lower border of cricoid cartilage inferiorly, and laterally via the pharyngeal lumen/thyroid cartilage. Anterioposterior boundaries were the posterior aspect of hyoid or laryngeal cartilage anteriorly, and encompassed pharyngeal constrictors bounded by prevertebral fascia posteriorly. All QUANTEC recommendations for the larynx (V50Gy 27%, Dmean 40 Gy, Dmean 44 Gy, Dmax 66 Gy) were utilized to

Correspondence: V. Khoo, Department of Clinical Oncology, The Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK. Tel: 44 20 78082911. Fax: 44 20 78118017. E-mail: Vincent.khoo@rmh.nhs.uk

(Received 3 F ebruary 2 014 ; accepted 23 M ay 2 014)

ISSN 0284-186X print/ISSN 1651-226X online © 2014 Informa Healthcare
DOI: 10.3109/0284186X.2014.933874

categorize the patient cohort, i.e. V50Gy 27% vs. V50Gy 27%; Dmean 40 Gy vs. Dmean 40 Gy, Dmean 44 Gy vs. Dmean 44 Gy; Dmax 66 Gy vs.

Dmax 66 Gy. Biological equivalent larynx V50Gy, Dmean and Dmax was additionally calculated and applied to patients where dose per fraction was in excess of 2 Gy per fraction (alpha/beta value of 4 was utilized for conversion). Equivalent biological doses have been analyzed in this paper.

Acute toxicity assessment

Patients were prospectively scored on a weekly basis (weeks 1 – 6 or 7) by three radiation oncologists (blinded to previous scores or other adverse effects) for acute dysphagia toxicity using the common toxicity criteria for adverse events version three (CTCAEv3) assessment tool. Grade 3 toxicity was deemed clinically signifi cant, and its incidence recorded. Symptomatic and severely altered eating/swallowing – with an indication for percutaneous endogastric (PEG) tube intervention and intravenous fl uids – was suggestive of Grade 3 dysphagia. QUANTEC defi ned dosevolume categories were subsequently analyzed for grade 3 toxicity incidence within the cohort.

Several possible clinical risk factors were also recorded for analysis. These included:

1. Age;
2. Sex;
3. Chemo-radiotherapy (CRT);
4. Surgery [post-operative radiotherapy (PORT) vs. defi nitive];
5. Pre-existing dysphagia (CTCAEv3);
6. Pre-existing nutritional status [PatientGenerated Subjective Global Assessment (PG-SGA) Tool];
7. Pre-existing comorbidity (Charlson Comorbidity Measuring Tool) [7].

Statistical methods

The proportion of patients with grade 3 toxicity according to either V50Gy (or 27%), Dmean (or 40 Gy), Dmean (or 44 Gy) or Dmax (or 66 Gy) were compared across the entire treatment using the Friedman test (overall change in proportion across entire treatment) and χ^2-test (change in the proportion of patients incidence between two groups at individual weeks of treatment, i.e. Dmax 6 6% vs. 6 6%/week). These statistical methods were subsequently applied to the stratifi ed data of the CRT, RT only, PORT and defi nitive cohorts. A χ^2-test was used to perform a univariate analysis of dosimetric and clinical risk factors associated with grade 3 acute dysphagia. All analyses were carried out using SPSS (version 18.0, Chicago, IL, USA). A p-level of 0.05 was afforded signifi cance.

Results

Patient demographics, tumor and treatment characteristics are shown in the Supplementary Appendix (available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.933874). Statistically signifi cant toxicity reduction was observed on the basis of multiple larynx QUANTEC dose-v olume recommendations (refer to Tables I and II for all acute grade 3 dysphagia incidences) in the combined cohort.

V50Gy 27% resulted in a 68.4% reduction in grade 3 toxicity at treatment week 5 (p 0.01) and a 60.7% reduction at treatment week 6 (p 0.01) compared to V50 27%. The reduction in toxicity from week 6 – 7 was not signifi cant. Not all patients were prescribed a seven-week treatment course. This dose parameter was not signifi cant at week 7 due to the reduced patient numbers at this time point.

Dmean 44 Gy resulted in a 69.8% reduction of grade 3 toxicity at treatment week 5 (p 0.01) and 51.4% reduction at treatment week 6 (p 0.01) compared to Dmean 44 Gy. Dmean 40 Gy further supported Dmean as a key predictor of acute dysphagia, with signifi cant reduction at week 5 (5.6% vs. 42.3%, p 0.01) and week 6 (23.5% vs. 59.3%, p 0.01). Treatment with a Dmax 66 Gy demonstrated a 55.6% reduction of toxicity at treatment week 6 (p 0.01) compared to Dmax 66 Gy.

Furthermore, analysis of larynx Dmean for patients with CTCAEv3 grading above and below 3 was undertaken. Patients who peaked at grade 3 toxicity (n 47) reported an average larynx Dmean of 46.3 Gy 9.7 Gy compared to those below grade 3 (n 29) who reported a Dmean of 42.5 6.8 Gy

(p 0.07).

Subsequent stratifi cation of the total cohort into PORT (n 29) and Defi nitive (n 47) (Table I) reports comparable trends to that of the entire cohort. Statistical signifi cant toxicity disparity, however, is less frequent. A comparable trend is also reported in the CRT (n 40) and RT Only (n 36) cohorts (Table II). In the CRT cohort, all dose constraints are signifi cant predictors at varying time points. The RT Only group (signifi cant only at V50Gy 27%, week 6) reports comparable trends in toxicity incidence

Table I. Incidence of CTCAEv3 grade 3 acute dysphagia (treatment weeks 1– 6 /7 *) in ALL patients compared to Defi nitive and PORT.

	V50Gy n/N (%)	27% V50Gy n/N (%)	27% Dmean n/N (%)	4 4Gy Dmean n/N (%)	4 4Gy Dmean	4 0Gy Dmean	4 0Gy Dmax	6 6Gy Dmax	6 6Gy n/N (%)	n/N (%)	n/N (%)
All Patients (n 76)											
Week 1	1/33 (3.0)	1/42 (2.4)	1/36 (2.8)	1/39 (2.6)	0/19 (0.0)	2/56 (3.6)	1/27 (3.7)	1/48 (2.1)			
Week 2	3/34 (8.8)	2/41 (4.9)	3/36 (8.3)	2/39 (5.1)	1/19 (5.3)	4/56 (7.1)	3/28 (10.7)	2/47 (4.3)			
Week 3	4/32 (12.5)	5/41 (12.2)	4/34 (11.8)	5/39 (12.8)	1/18 (5.6)	8/55 (14.6)	4/26 (15.4)	5/47 (10.6)			
Week 4	4/30 (13.3)	5/41 (12.2)	3/33 (9.1)	6/38 (15.8)	0/17 (0.0)	9/54 (16.7)	3/24 (12.5)	6/47 (12.8)			
Week 5	4/28 (14.3)	19/42 (45.2) ^	5/34 (14.7)	18/36 (50.0) ^	1/18 (5.6)	22/52 (42.3) #	6/26 (23.1)	17/44 (38.6)			
Week 6	7/27 (25.9)	29/44 (65.9) #	11/34 (32.4)	25/37 (67.6) ^	4/17 (23.5)	32/54 (59.3) ^	7/25 (28.0)	29/46 (63.0) #			
Week 7	9/14 (64.3)	21/26 (80.8)	13/19 (68.4)	17/21 (81.0)	3/7 (42.9)	27/33 (81.8)	3/6 (50.0)	27/34 (79.4)			
PORT Only (n 29)											
Week 1	1/14 (7.1)	1/14 (7.1)	1/14 (7.1)	1/14 (7.1)	0/9 (0.0)	2/19 (10.5)	1/19 (5.3)	1/9 (11.1)			
Week 2	3/15 (20.0)	2/14 (14.3)	3/15 (20.0)	2/14 (14.3)	1/9 (11.1)	4/20 (20.0)	3/20 (15.0)	2/9 (22.2)			
Week 3	3/14 (21.4)	3/14 (21.4)	3/14 (21.4)	3/14 (21.4)	1/8 (12.5)	5/20 (25.0)	4/19 (21.1)	2/9 (22.2)			
Week 4	3/12 (25.0)	2/14 (14.3)	3/13 (23.1)	2/13 (15.4)	0/7 (0.0)	5/19 (26.3)	3/17 (17.7)	2/9 (22.2)			
Week 5	2/13 (15.4)	6/13 (46.2)	2/14 (14.3)	6/12 (50.0)	0/9 (0.0)	8/17 (47.1)	4/18 (22.2)	4/8 (50.0)			
Week 6	4/12 (33.3)	9/13 (69.2)	5/13 (38.5)	8/12 (66.7)	2/8 (25.0)	11/17 (64.7)	6/17 (35.3)	7/8 (87.5) ^			
Week 7	N/A	3/3 (100.0)	1/1 (100.0)	2/2 (100.0)	N/A	3/3 (100.0)	N/A	3/3 (100.0)			
Defi nitive Only (n 47)											
Week 1	0/19 (0.0)	0/28 (0.0)	0/23 (0.0)	0/24 (0.0)	0/10 (0.0)	0/37 (0.0)	0/9 (0.0)	0/38 (0.0)			
Week 2	0/19 (0.0)	0/27 (0.0)	0/22 (0.0)	0/24 (0.0)	0/10 (0.0)	0/36 (0.0)	0/9 (0.0)	0/37 (0.0)			
Week 3	1/18 (5.6)	2/27 (7.4)	1/21 (4.8)	2/24 (8.3)	0/10 (0.0)	3/35 (8.6)	0/8 (0.0)	3/37 (8.1)			
Week 4	1/18 (5.6)	3/27 (1.1)	1/21 (4.5)	3/24 (12.5)	0/10 (0.0)	4/35 (11.4)	0/8 (0.0)	4/37 (10.8)			
Week 5	3/18 (16.7)	12/26 (46.2)	4/21 (19.1)	11/23 (47.8)	1/9 (11.1)	14/35 (40.0) ^	2/9 (22.2)	13/35 (37.1)			
Week 6	4/18 (22.2)	19/28 (67.9) #	7/22 (31.8)	16/24 (66.7) ^	2/9 (22.2)	21/37 (56.8)	1/9 (11.1)	22/37 (59.5) ^			
Week 7	9/14 (64.3)	18/23 (78.3)	12/18 (66.7)	15/19 (79.0)	3/7 (42.9)	24/30 (80.0)	3/6 (50.0)	24/31 (77.4)			

CTCAEv3, Common toxicity criteria for adverse events version three; n, no. of grade 3 recordings; N, no. of patients with recordings at treatment week; %, grade 3 dysphagia incidence; PORT, post-operative radiotherapy. * Treatment length dependent on treatment intent/ concurrent treatments/pre or post-operative; ^ p 0.05 following χ^2 -test; # p 0.01 following χ^2 -test.

Table II. Incidence of CTCAEv3 grade 3 acute dysphagia (treatment weeks 1– 6 /7 *) in ALL patients compared to CRT and RT Only.

	V50Gy (%)	27% V50Gy n/N (%)	27% Dmean n/N (%)	44Gy Dmean n/N (%)	44Gy Dmean	40Gy Dmean	40Gy Dmax	66Gy Dmax	66Gy n/N (%)	n/N (%)	n/N (%)	n/N
All Patients (n 76)												
Week 1	1/33 (3.0)	1/42 (2.4)	1/36 (2.8)	1/39 (2.6)	0/19 (0.0)	2/56 (3.6)	1/27 (3.7)	1/48 (2.1)				

Week 2	3/34 (8.8)	2/41 (4.9)	3/36 (8.3)	2/39 (5.1)	1/19 (5.3)	4/56 (7.1)	3/28 (10.7)	2/47 (4.3)
Week 3	4/32 (12.5)	5/41 (12.2)	4/34 (11.8)	5/39 (12.8)	1/18 (5.6)	8/55 (14.6)	4/26 (15.4)	5/47 (10.6)
Week 4	4/30 (13.3)	5/41 (12.2)	3/33 (9.1)	6/38 (15.8)	0/17 (0.0)	9/54 (16.7)	3/24 (12.5)	6/47 (12.8)
Week 5	4/28 (14.3)	19/42 (45.2) ^	5/34 (14.7)	18/36 (50.0) ^	1/18 (5.6)	22/52 (42.3) #	6/26 (23.1)	17/44 (38.6)
Week 6	7/27 (25.9)	29/44 (65.9) #	11/34 (32.4)	25/37 (67.6) ^	4/17 (23.5)	32/54 (59.3) ^	7/25 (28.0)	29/46 (63.0) #
Week 7	9/14 (64.3)	21/26 (80.8)	13/19 (68.4)	17/21 (81.0)	3/7 (42.9)	27/33 (81.8)	3/6 (50.0)	27/34 (79.4)
CRT (n 40)								
Week 1	0/15 (0.0)	0/25 (0.0)	0/20 (0.0)	0/20 (0.0)	0/8 (0.0)	0/32 (0.0)	0/10 (0.0)	0/30 (0.0)
Week 2	0/15 (0.0)	1/24 (4.2)	0/19 (0.0)	1/20 (5.0)	0/8 (0.0)	1/31 (3.2)	0/10 (0.0)	1/29 (3.5)
Week 3	1/15 (6.7)	3/24 (12.5)	1/19 (5.3)	3/20 (15.0)	0/8 (0.0)	4/31 (12.9)	1/10 (10.0)	3/29 (10.3)
Week 4	1/15 (6.7)	2/24 (8.3)	1/19 (5.3)	2/20 (10.0)	0/8 (0.0)	3/31 (9.7)	0/10 (0.0)	3/29 (10.3)
Week 5	2/14 (14.3)	10/23 (43.5)	2/18 (11.1)	11/19 (57.9) #	0/7 (0.0)	13/30 (43.3) ^	2/10 (20.0)	11/27 (40.7)
Week 6	4/13 (30.8)	18/25 (72.0) ^	6/18 (33.3)	16/20 (80.0) #	1/6 (16.7)	21/32 (65.6)	2/9 (22.2)	20/29 (69.0) ^
Week 7	8/10 (80.0)	15/18 (79.0)	10/13 (76.9)	12/14 (85.7)	3/5 (60.0)	19/2 (86.4)	2/3 (66.7)	21/25 (84.0)
RT Only (n 36)								
Week 1	1/18 (5.6)	1/17 (5.9)	1/17 (5.9)	1/18 (5.6)	0/11 (0.0)	2/24 (8.3)	1/18 (5.6)	1/17 (5.9)
Week 2	3/19 (15.8)	1/17 (5.9)	3/18 (16.7)	1/18 (5.6)	1/11 (9.1)	3/25 (12.0)	3/19 (15.8)	1/17 (5.9)
Week 3	3/17 (17.7)	2/17 (11.8)	3/16 (18.8)	2/18 (11.1)	1/10 (10.0)	4/24 (16.7)	3/17 (17.7)	2/17 (11.8)
Week 4	3/15 (20.0)	3/17 (17.7)	3/15 (20.0)	3/17 (17.7)	0/9 (0.0)	6/23 (26.1)	3/15 (20.0)	3/17 (17.7)
Week 5	3/17 (17.7)	8/16 (50.0)	4/17 (23.5)	6/16 (37.5)	1/11 (9.1)	9/22 (40.9)	4/17 (23.5)	6/16 (37.5)
Week 6	4/17 (23.5)	10/16 (62.5) ^	6/17 (35.3)	8/16 (50.0)	3/11 (27.3)	11/22 (50.0)	5/17 (29.4)	9/16 (56.3)
Week 7	1/4 (25.0)	6/8 (75.0)	3/6 (50.0)	5/7 (71.4)	0/2 (0.0)	8/11 (72.7)	1/3 (33.3)	6/9 (66.7)

CRT, Concurrent Cisplatin Chemotherapy Radiotherapy; CTCAEv3, Common toxicity criteria for adverse events version three; n, no. of grade 3 recordings; N, no. of patients with recordings at treatment week; %, grade 3 dysphagia incidence. * Treatment length dependent on treatment intent/concurrent treatments/pre or post-operative; ^ p 0.05 following χ^2-test; # p 0.01 following χ^2-test.

with the combined cohort. In the absence of more defi nitive dose/volume/outcome data, the QUANTEC recommendations appear a useful predictor of acute dysphagia in this RT Only cohort.

A univariate analysis of dosimetric and clinical risk factors supports the use of QUANTEC recommendations across the majority of head and neck RT patients. OnlyV 50 27% (p 0 .01), Dmean 4 0 Gy (p 0 .01) and Dmax 66 Gy (p 0 .01) predicted for grade 3 dysphagia. No clinical risk factors – including PORT or CRT – signifi cantly predicted grade 3 dysphagia (Table III).

The peak toxicity of any patient throughout treatment was grade 3 (60.5% of all patients). In total 25.0% of patients reported a peak grade 2 toxicity and 13.2% a peak grade 1 toxicity.

Discussion

Our results have shown that the QUANTEC report dose recommendations for late dysphagia are a useful tool for predicting acute dysphagia in a typical group of head and neck cancers usually treated radically with RT. Reduction in the inadvertent dose delivery to laryngo-pharyngeal structures has been extensively investigated and reported [8,9]. Our fi ndings support the recommendations of the QUANTEC report [6]. These recommendations are based on the dose/volume/outcome data from multiple studies, which have been derived from late toxicity endpoints including edema and aspiration.

Other publications have attempted to validate the QUANTEC recommendations in various critical organs [10– 12]. Liu et al. reported consistent rectal bleeding complications to those of the NTCP QUANTEC model in prostate RT. However, due to

Table III. Dosimetric and clinical risk factors affecting incidence of CTCAEv3 Grade 3 acute dysphagia (Total Grade 3 patients, N 47).

	CTCAEv3 G3 n/N (%)	Univariate (p-value)
V50Gy 27%	34/47 (72.3)	0.004*
Dmean 44Gy	27/47 (57.4)	0.156
Dmean 40Gy	40/47 (85.1)	0.014*
Dmax 66Gy	36/47 (76.6)	0.001*
Sex (Female)	16/47 (34.0)	0.445
Age (65)	27/47 (57.4)	0.156
CRT	30/47 (63.8)	0.063
Dysphagia	11/47 (23.4)	0.383
Pre-Tx NS	13/47 (27.7)	0.610
Morb. Score	12/47 (25.5)	0.261
PORT	14/47 (29.8)	0.088

CTCAEv3 G3, Common toxicity criteria for adverse events version three grade 3 acute dysphagia toxicity; Dysphagia, Pre-existing dysphagia; Morb. Score, pre-treatment morbidity score 2; PORT, post-operative radiation therapy; Pre-Tx NS, pre-treatment nutritional status identifying malnourishment (PG SGA Score B). p-value determined via χ^2-test. * Statistically signifi cant risk factors (p 0.05).

relative homogeneity of rectal dose distributions, this study warned of a low predictive power in their cohort [10]. Appelt et al. combined the dose response function of radiation pneumonitis (based on QUANTEC recommendations) with known

clinical risk factors, to increase confi dence in predicting radiation pneumonitis and to individualize toxicity risk estimates [11]. Most recently, parotid dose recommendations were validated by Beetz et al. Their work reported signifi cantly lower rates of patient-rated xerostomia based on QUANTEC recommendations. However, this group warned of decreased reliability in the model in the elderly and patients with minor pre-existing xerostomia [12].

Dose parameters signifi cantly associated with late laryngeal edema were previously reported by Sanguineti et al. [4]. Their fi ndings recommended a V50Gy of less than 27% and a dose mean of less than 43.5 Gy to the larynx to minimize edema incidence. However, it should be recognized that only a small percentage of this cohort (n 12, 18.2%) underwent concurrent chemotherapy, with subsequent stratifi cation eliminating chemotherapy as an edema predictor. Dose-volume relationships generated from this work may well be affected by this discrepancy. This should be considered when applying these constraints in the presence of systemic therapy.

Furthermore, Feng et al. generated dose variables for minimizing late aspiration, reporting that a dose mean to glottic/ supraglottic larynx should not exceed 50 Gy [9,13]. The role of the laryngeal dose in late vocal dysfunction has also been reported. Dornfeld et al. reported a steep decrease in vocal toxicity when the maximal laryngeal dose was kept below 66 Gy [3]. A limitation of this particular study, however, was the absence of full three-dimensional dose metrics. Specifi ed points within swallowing anatomy were identifi ed for dose analysis. Limitations in their planning software did not enable retrospective analysis of newly delineated structures.

While tumor control and late toxicity should and will always remain the primary outcome measure, treatment tolerance in the acute setting is becoming increasingly important [14]. The primary focus of this study was to address the current lack of acute dysphagia dose/volume/outcome data in the literature. The QUANTEC recommendations for reduction in late edema, aspiration and vocal dysfunction were shown to be clinically signifi cant predictors of acute dysphagia in our study. The incidence of acute dysphagia toxicity was signifi cantly higher in patient cohorts exceeding the specifi ed dose goals.

There is an increasing awareness of the importance of minimizing the consequences of acute toxicities. Multiple publications emphasize the importance of maintaining planned patient geometry, to ensure optimal delivery of planned dosimetry and to prevent the decrement in the quality of the IMRT plan, in particular, in predicting parotid gland dose [15,16]. The ability to predict, prevent and manage severe dysphagia may reduce the incidence and the magnitude of signifi cant weight loss thus in our cohort. Better understanding the acute dose/response/outcome correlation in head and neck RT could play a role in the development of safer treatment intensifi cation protocols, with ultimately, the potential for improved tumor control loco-regionally. This has been investigated via various RT dose escalation strategies [17,18]. Increasing dose to sites of putative radiation resistance, as suggested by various PET substrates has been explored previously [19]. Predictive dosimetric measures for expected treatment tolerance may provide a basis for inclusion/exclusion of treatment intensifi cation protocols, or enable the implementation of suitable prophylactic measures to increase the likelihood of treatment tolerance. Further to RT dose intensifi cation, the ability to deliver less toxic loco regional treatment may allow intensifi cation of systemic treatments. The benefi ts of concurrent platinum based systemic therapy and biologic agents are well established [20]. A greater understanding of the acute response to RT, and the knowledge to implement individualized prophylactic measures, can optimize delivery of such potentially toxic programs and reduce associated toxicities. Various allied health professionals, including dietetics and speech pathology, provide opportunity for on-treatment assistance to enable improved treatment tolerance.

On-treatment interventions and their early implementation have proven benefi cial in enhancing treatment tolerance. Studies have proven the benefi t of enteral feeding (via PEG) in reducing weight loss and interrupted treatment, amongst many other acute toxicity incidents [21]. Yet, there is also data suggesting that a long-term dependence on PEG feeding is detrimental to latter swallowing function, with increased risk of atrophy to masticatory and swallowing muscles

[22]. The work of Sanguinetti et al. addressed this concern through the development of predictive dosimetric parameters (to oral mucosa) for PEG insertion throughout IMRT for oropharyngeal cancer [23]. Planned patient geometry and treatment tolerance is dependent on multiple contributing factors. A more comprehensive understanding of the role of dosimetric measures and their correlation to incidence of acute toxicity will allow for a greater focus on treatment planning dose steering. Yet, perhaps of greater importance, is the early instigation of supportive care intervention (i.e. dietetics, speech pathology) where dose avoidance is not possible. Such measures may be able to better maintain or achieve optimal treatment tolerance, weight management and treatment delivery.

A limitation of this study is that the study population does encompass multiple tumor types and demographic characteristics, but this group is typically representative of the cases treated radically with RT. Despite this heterogeneity of disease sub-type entities, the outcome data were relatively consistent as reported. The role of systemic therapy or RT given defi nitively or post-operatively in infl uencing acute dysphagia incidence was addressed. Our results showed that systemic therapy or surgical intervention did not signifi cantly affect the incidence of grade 3 dysphagia. This was performed to ascertain concurrent systemic therapy or surgery given in conjunction with RT in some patients was not a confounding factor in the outcome of our analysis (in conjunction with multiple other clinical risk factors). Quality of life accompanying scoring was not used in this study. Equivalent toxicity incidence was reported regardless of biological or physical laryngeal dose.

Conclusion

This study demonstrated the usefulness of the QUANTEC late toxicity recommendations in predicting acute dysphagia toxicity. Precision RT demands optimal maintenance of planned geometry through optimizing the opportunity for improved treatment tolerance. A more comprehensive understanding of acute dose/volume/outcome correlation enables individualized treatment programs to be developed, to facilitate improved treatment tolerance via measured prophylactic interventions.

Declaration of interest: The authors report no confl icts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Emami B, Lyman J , B rown A , C oia L , G oitein M, Munzenrider JE , et a l . T olerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991; 21 : 109 – 22 .

[2] Marks LB, Ten Haken R K , Martel M K . Guest editor's introduction to QUANTEC: A users guide. Int J Radiat Oncol Biol Phys 2010; 76(3 Suppl): S1– 2 .

[3] Dornfeld K , Simmons JR, Karnell L , Karnell M, Funk G , Yao M , e t al . Radiation doses to structures within and adjacent to the larynx are correlated with long-term diet- and speech-related quality of life. Int J Radiat Oncol Biol Phys 2007; 68 :7 50 –7 .

[4] Sanguineti G , Adapala P , E ndres E J , B rack C , F iorino C , Sormani M P , e t a l . Dosimetric predictors of laryngeal edema. Int J Radiat Oncol Biol Phys 2007; 68 :7 41 – 9 .

[5] Rancati T, Fiorino C , Sanguineti G . NTCP modeling of subacute/late laryngeal edema scored by fi beroptic examination. Int J Radiat Oncol Biol Phys 2009; 75 :9 15 – 23.

[6] Rancati T, Schwarz M, Allen A M , Feng F, Popovtzer A , Mittal B, et al . R adiation dose-volume effects in the larynx and pharynx. Int J Radiat Oncol Biol Physs 2010; 76 (3 Suppl): S64 – 9.

[7] Charlson ME , Pompei P , Ales KL , MacKenzie CR . A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987; 40 :3 73 – 83 .

[8] Caudell JJ , S chaner P E , D esmond R A , M eredith R F , Spencer SA, Bonner J A . D osimetric factors associated with long-term dysphagia after defi nitive radiotherapy for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2010; 76 :4 03 – 9.

[9] Feng FY, Kim HM, Lyden TH, Haxer MJ, Feng M , Worden F P , et al . Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: Early doseeffect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 2007; 68 :1 289 – 98 .

[10] Liu M, Moiseenko V, Agranovich A , K arvat A , Kwan W, Saleh Z H , e t a l . N ormal tissue complication probability (NTCP) modeling of late rectal bleeding following external beam radiotherapy for prostate cancer: A test of the QUANTEC-recommended NTCP model. Acta Oncol
2010; 49 :1 040 – 4.

[11] Appelt A L , V ogelius I R , F arr K P , K halil A A , B entzen SM.
Towards individualized dose constraints: Adjusting the QUANTEC radiation pneumonitis model for clinical risk factors. Acta Oncol
2014; 53 :6 05 – 12 .

[12] Beetz I , S teenbakkers R J , C houvalova O , L eemans CR , Doornaert P, van der Laan BF, et al . The QUANTEC criteria for parotid gland dose and their effi cacy to prevent moderate to severe patient-rated xerostomia. Acta Oncol
2014; 53 :5 97 – 604.

[13] Feng FY , K im H M , L yden TH, Haxer MJ, Feng M , Worden F P , et al . Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: Early doseeffect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 2007; 68 :1 289 – 98 .

[14] Strigari L, Pedicini P, D'Andrea M, Pinnaro P, Marucci L , Giordano C, et al . A new model for predicting acute mucosal toxicity in head-and-neck cancer patients undergoing radiotherapy with altered schedules. Int J Radiat Oncol Biol Phys
2012; 83 :e 697 – 702.

[15] Lee C , Langen KM , Lu W , Haimerl J , Schnarr E , Ruchala KJ, et al . Assessment of parotid gland dose changes during head and neck cancer radiotherapy using daily megavoltage computed tomography and deformable image registration. Int J Radiat Oncol Biol Phys 2008; 71:
1563– 71 .

[16] O'Daniel JC, Garden AS, Schwartz DL, Wang H, Ang KK , Ahamad A , e t al . P arotid gland dose in intensitymodulated radiotherapy for head and neck cancer: Is what you plan what you get? I nt J Radiat Oncol Biol Phys 2007;
69 :1 290 – 6.

[17] Zhou J , F ei D , W u Q . P otential of intensity-modulated radiotherapy to escalate doses to head-and-neck cancers: What is the maximal dose? Int J Radiat Oncol Biol Phys
2003; 57 :6 73 – 82 .

[18] Bhide S , U rbano TG, Clark C , H ansen V , Adams E ,
Miles E, et al . Results of intensity modulated radiotherapy (IMRT) in laryngeal and hypopharyngeal cancer: A dose escalation study. Radiother Oncol 2007 ;8 2(Suppl 1) :
S74– 5.

[19] La TH, Filion EJ, Turnbull BB, Chu JN , Lee P, Nguyen K , et al . Metabolic tumor volume predicts for recurrence and death in head-and-neck cancer. Int J Radiat Oncol Biol Phys
2009; 74 :1 335 – 41 .

[20] Pignon JP, le Maitre A , M aillard E , B ourhis J . M eta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009; 92 :4 – 14 .

[21] Raykher A, Correa L , R usso L , B rown P, Lee N, Pfi ster D , et a l . T he role of pretreatment percutaneous endoscopic gastrostomy in facilitating therapy of head and neck cancer and optimizing the body mass index of the obese patient. JPEN J Parenter Enteral Nutr 2009; 33 :4 04 – 10 .

Supplementary material available online

Supplementary Appendix to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.933874.

[22] Murphy BA , G ilbert J . D ysphagia in head and neck cancer patients treated with radiation: Assessment, sequelae, and rehabilitation. Semin Radiat Oncol 2009 ;1 9 :3 5 – 42.

[23] Sanguineti G , Gunn G B , Parker B C , Endres EJ, Zeng J , Fiorino C . W eekly dose-volume parameters of mucosa and constrictor muscles predict the use of percutaneous endoscopic gastrostomy during exclusive intensity-modulated radiotherapy for oropharyngeal cancer. Int J Radiat Oncol
Biol Phys 2 011 ;7 9 :5 2 – 9.

Received: 26 January 2017 | Revised: 7 January 2018 | Accepted: 3 April 2018

DOI: 10.1002/hed.25316

ORIGINAL ARTICLE

WILEY

Pretreatment risk stratification of feeding tube use in patients treated with intensity-modulated radiotherapy for head and neck cancer

Nigel J. Anderson BAppSc[1,2] | James E. Jackson MBBS, FRANZCR[1,3,4] | Jennifer G. Smith PhD[5] | Morikatsu Wada MBBS, FRANZCR[1] | Michal Schneider PhD[6] | Michael Poulsen MBBS, FRANZCR[7,8] | Maureen Rolfo DipAppSc[1] | Maziar Fahandej BMBS, FRACGP[1,9] | Hui Gan MBBS, FRACP, PhD[10] | Daryl Lim Joon MBBS, FRANZCR[1] | Vincent Khoo MD[1,6,11,12]

[1]Department of Radiation Oncology, Olivia Newton John Cancer Wellness and Research Centre, Austin Health, Heidelberg, Victoria, Australia

[2]Department of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

[3]School of Medicine, Griffith University, Gold Coast, Australia

[4]Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia

[5]Plain Statistics Pty Ltd, Horsham, Victoria, Australia

[6]Department of Medical Imaging and Radiation Sciences, Monash University, Victoria, Australia

[7]Radiation Oncology Centres, Gold Coast University Hospital, Queensland, Australia

[8]Faculty of Medicine, The University of Queensland, Herston, Queensland, Australia

[9]Department of Palliative Care, St Vincent's Hospital, Fitzroy, Victoria, Australia

[10]Olivia Newton-John Cancer Research Institute, Austin Health, Heidelberg, Victoria, Australia

[11]Department of Clinical Oncology, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Chelsea, London, UK [12]Department of Medicine, University of Melbourne, Victoria, Australia

Correspondence
James Jackson, Department: Radiation Oncology Centres, Gold Coast University Hospital, 1 Hospital Boulevard, Southport, Queensland, 4215 Australia.,
Email: jimejackson@gmail.com

Abstract

Background: The purpose of this study was to establish a risk stratification model for feeding tube use in patients who undergo intensity-modulated radiotherapy (IMRT) for head and neck cancers.

Methods: One hundred thirty-nine patients treated with definitive IMRT (1/- concurrent chemotherapy) for head and neck mucosal cancers were included in this study. Patients

were recommended a prophylactic feeding tube and followed up by a dietician for at least 8 weeks postradiotherapy (post-RT). Potential prognostic factors were analyzed for risk and duration of feeding tube use for at least 25% of dietary requirements.

Results: Many variables had significant effects on risk and/or duration of feeding tube use in univariate analyses. Subsequent multivariable analysis showed that T

classification 3 and level 2 lymphadenopathy were the best independent significant predictors of higher risk and duration of feeding tube use, respectively, in oral cavity, pharyngeal, and supraglottic primaries.

Conclusion: In patients treated with definitive IMRT, T classification 3 and level 2 lymphadenopathy can potentially stratify patients into 4 risk groups for developing severe dysphagia requiring feeding tube use.

KEYWORDS

enteral nutrition, feeding tube, head and neck cancer, intensity-modulated radiotherapy (IMRT), toxicity

1 | INTRODUCTION

Head and neck cancer and its treatment with radiotherapy (RT), with or without concurrent chemotherapy, are associated with dysphagia and associated malnutrition and weight loss.[1–4] Enteral feeding via a feeding tube is a common method of providing patient nutrition during and immediately after RT in as many as 80% of patients.[5–9] Patients at high risk of prolonged, severe dysphagia may benefit from a prophylactic gastrostomy tube to minimize hospitalizations, while maximizing convenience and short-term quality of life.[10–12]

However, the insertion of a gastrostomy tube is an invasive procedure that can be associated with major complications and occasionally death.[13] Prolonged use of gastrostomy tubes has been associated with long-term swallow dysfunction and a potential risk of late mortality.[11,14] Considering these risks, the insertion of prophylactic gastrostomy tubes should be reserved for those patients likely to derive the most benefit, namely patients at highest risk of prolonged, severe dysphagia. Furthermore, identification of high-risk patients is critical in developing patient pathways and appropriate allocation of allied health resources. The main purpose of this study was to develop a risk stratification model for anticipated duration of feeding tube use, using the clinical and radiological information available at a patient's initial discussion at a multidisciplinary tumor board.

2 | MATERIALSAND METHODS

2.1 | Patients

After institutional ethics committee approval, the patient population was retrospectively accrued from the institution's radiation oncology database. To be eligible for inclusion, patients were required to receive primary and definitive intensity-modulated radiotherapy (IMRT; with or without concurrent systemic treatment) for mucosal cancers of the head and neck. Patients with stages II to IVB disease were included. Patients were excluded if they underwent therapeutic surgery to the primary site or neck dissection before commencing RT. Patients were required to have been offered a prophylactic feeding tube before treatment, as per departmental policy, laryngeal and pharyngeal tumors planned to receive 64 Gy with bilateral nodal irradiation, or having a preexisting nutritional deficiency. All included patients had to be followed up by a dietician for a minimum of 8 weeks post-RT completion.

2.2 | Pretreatment evaluation

Before treatment, each patient underwent diagnostic contrastenhanced CT of the face, neck, and chest, as well as wholebody positron emission tomography (PET) with low dose CT for coregistration (PET/CT). Selected patients underwent MRI through the face and neck, when it was thought clinically beneficial to assist in optimal target delineation (eg, nasopharyngeal primary disease).

2.3 | Radiotherapy planning and treatment

Target volumes were outlined on the planning contrastenhanced CT by one radiation oncologist. The PET/CT and MRI (if available) were coregistered with the planning contrast-enhanced CT on the treatment

planning system. The elective (prophylactic) nodes were defined according to consensus guidelines.[15] All patients received bilateral, elective irradiation of levels 2 to 4 nodes. Patients with oropharyngeal or nasopharyngeal cancers had bilateral, elective irradiation of level 1B nodes. In patients with oropharyngeal or hypopharyngeal cancers, elective irradiation of ipsilateral level 5 nodes and the retrostyloid space were delivered to clinically nodepositive hemi-necks. In patients with cancer of the nasopharynx, bilateral retrostyloid space lymph nodes were treated to an elective dose. All patients with T0 classification disease in this cohort were treated electively to bilateral nodal basins, including level 1B, whereas bilateral tonsils and tongue base were treated as high-risk clinical target volume (CTV).

Clinically and radiologically involved nodes were contoured individually. The prescribed doses were planned with a simultaneous integrated boost to a gross tumor volume, high-risk CTV and low-risk CTV. In 137 cases, the dose to gross tumor volume (66-70 Gy), high-risk CTV (63 Gy), and elective CTV (56 Gy) was planned at 5 fractions per week over 6 to 7 weeks. The remaining 2 patients were prescribed 60 or 64 Gy in 30 fractions. Medically fit patients were considered for concurrent systemic therapy based on disease stage and comorbidities.

Optimized IMRT plans, deliverable via 7 to 9 equally spaced step-and-shoot segmented beams on a 6 MV linear accelerator (ElektaSynergy, Elekta, Crawley, UK),weregenerated using either the Elekta CMS XiO or Monaco treatment planning systems (Elekta, St Louis, MO) on 0.25 cm CT slices.

2.4 | Nutritional assessment and follow-up

All patients had a complete pretherapy consultation with a dietician followed by weekly nutritional reviews while on therapy. After therapy, dietetic review, whether by telephone or in person, was conducted at least every 2 weeks after therapy until cessation of the enteral feeding.

Adequacy of enteral intake was recorded at each review using the scale: adequacy of enteral intake 0 5 0%-24%; adequacy of enteral intake 1 5 25%-49%; adequacy of enteral intake 2 5 50%-74%, and adequacy of enteral intake 3 5 75%-100% of daily nutritional needs. All patients were followed until their adequacy of enteral intake was <1.

Speech pathology services were offered to all patients with oropharyngealdysphagiatominimizeaspirationandmal nutrition risk. Video fluoroscopy and fiberoptic endoscopic evaluation of swallowing were available for at-risk patients. Swallowing rehabilitationwas not available tothis patient cohort.

2.5 | Statistical analyses

Outcomes measured were: (1) the risk of feeding tube use for at least 25% of nutritional requirements (adequacy of enteral intake 1); and (2) the duration of such use measured in days from the first date the adequacy of enteral intake was recorded at 1 or higher to the date when it dropped to adequacy of enteral intake 0 or the tube was removed.

Potential patient and tumor-related prognostic variables were subdivided according to previously reported cutoff points.[16–19] Only variables that would be known at the pretherapy multidisciplinary tumor board were considered. For analysis of the risk of feeding tube use (yes or no) we used the Fisher exact test if there were only 2 subgroups (eg, age or >65 years), the Cochran-Armitage test for trend if there were 3 or more ordered subgroups (eg, Eastern Cooperative Oncology Group [ECOG] performance status) or the Pearson chi-square test for 3 or more unordered subgroups (eg, cancer site).[20] For analysis of duration of feeding tube use, Kaplan-Meier analysis was carried out and subgroups were compared using the Mantel-Cox log-rank test for differences or the Tarone-Ware test for trend.[21,22] As all patients were followed up to cessation of adequacy of enteral intake 1 tube feeding, no durations were censored. All P values reported were 2-sided and 95% confidence intervals (CIs) were calculated. The significance criterion was $P < .05$ for previously reported prognostic factors or $P < .005$ for new prognostic factors (to adjust for multiple hypotheses).

Prognostic factors that were significant in the univariate analyses were tested in multivariable models to find the smallest number of independent prognostic factors, which had a significant effect on the risk and duration of feeding tube use. For risk of feeding tube use, exact logistic regression with conditional maximum likelihood inference was used for the multivariable analyses with P values obtained from the exact conditional scores test.[20] For duration of feeding tube use, Cox proportional hazards regression was used and the exponentials of the coefficients (e^b) from the final model were interpreted as "recovery rate ratios."

Both backward and forward stepwise regressions were performed and variables were retained in the model if the P value was < .05. Patients with unknown values for a particular factor were omitted from any models containing that factor, except for human papillomavirus (HPV), in which "unknown" was treated as a separate level of the factor.

3 | RESULTS

Between January 2007 and December 2013, 139 eligible patients were treated with radical intent IMRT. Their median age at commencement of RT was 61 years (range 20-91 years) and 78% were men. The most common cancer site was the oropharynx (78 patients; 56%). The other primary sites were the nasopharynx (16; 12%), supraglottis (15; 11%), glottic larynx (14; 10%), hypopharynx (5; 4%), oral cavity, (2; 1%) and unknown primary (9; 7%). Forty-one of the 78 patients with oropharyngeal cancer (53%) and 5 of the 9 with unknown primaries (56%) had known HPV-positive disease. Patient demographic and tumor characteristics are shown in the "Total" column in Table 1.

Altogether, 101 patients (73%) used a feeding tube for at least 25% of their nutritional requirements, for at least 48 hours. The Kaplan-Meier curve of duration of feeding tube use at adequacy of enteral intake 1 is shown in Figure 1. Patients who did not use the feeding tube at this level are represented in Figure 1 with 0 days duration; hence, the curve starts at 73% on the vertical axis. The median duration of feeding tube use for all patients was 70 days (CI 55-81 days). Twenty-four patients (17%) used it for at least 6 months, 10 patients (7%) for at least 12 months, and 2 patients (1%) for >2 years but the curve was curtailed at 24 months for the purpose of clarity.

Ninety patients (65%) used the feeding tube for at least 75% of their requirements (adequacy of enteral intake 3) at some stage and 18 (13%) used it at this level for >6 months.

TABLE 1 Univariate analyses of prognostic factors for feeding tube use (yes/no) and duration in 139 patients

	Feeding tube used[a]			Days of feeding tube use[a]		
Prognostic factor	Yes/total	%	P value[b]	Median, %	(95% CI)	P value[c]
Cancer site						
Pharynx or oral cavity	86/101	85	< .0001	89	(70-120)	< .0001
Larynx, supraglottis	10/15	67		16	(0-79)	
Larynx, glottis	1/14	7		0	(0-0)	
Unknown primary	4/9	44		0	(0-66)	
HPV						
Negative (for 87 oropharynx/unknown 1)	22/23	96	.13	163	(81-233)	.004
Positive	35/46	76		61	(31-90)	

Unknown	13/18	72		59	(0-77)	
T classification						
X, 0	4/10	40	.0007	0	(0-66)	< .001
1	15/23	65		50	(0-77)	
2	31/47	66		44	(7-75)	
3	34/40	85		119	(79-173)	
4	17/19	89		150	(57-262)	
N classification						
0	22/744	50	.0004	7	(0-59)	.006
0	16/20	80		75	(44-120)	
2	60/70	86		86	(70-122)	
3	3/5	60		45	(0->295)	
Bilateral neck node disease						
No	70-104	67	.016	59	(28-75)	.025
Yes	31/35	89		118	(57-170)	
Retropharyngeal node disease						
No	93/131	71	.11	66	(50-79)	.025
Yes	8/8	100		153	(14->834)	
Level 1 node disease						
No	85/120	71	.28	70	(57-83)	.58
Yes	16/19	84		55	(18-113)	
Level 2 node disease						
No	36/62	58	.0010	37	(0-68)	.0054
Yes	65/77	84		83	(65-120)	
Level 3 node disease						
No	72/107	67	.012	65	(31-79)	.53
Yes	29/32	91		86	(57-136)	
Level 4 node disease						
No	90/127	71	.18	68	(49-79)	.14
Yes	11/12	92		124	(45-393)	
Level 5 node disease						
No	92/128	72	.73	70	(49-81)	.55
Yes	9/11	82		58	(0-393)	

(Continues)

TABLE 1 (Continued)

Prognostic factor	Feeding tube used[a] Yes/total	%	P value[b]	Days of feeding tube use[a] Median, %	(95% CI)	P value[c]
Concurrent chemotherapy						
No	30/55	55	.0002	16	(0-59)	.0048
Yes	71/84	85		86	(75-118)	
Dysphagia or odynophagia						
No	75/110	68	.020	59	(42-77)	.009
Yes	26/29	90		133	(70-200)	
Nutrition, PG-SGA						
Well nourished, 1 missing	72/106	68	.012	58	(42-75)	.001
Malnourished	29/32	91		147	(77-211)	
BMI						
Underweight, <18.5, 15 missing	10/12	83	.51	208	(81-479)	.002
Not underweight, 18.5	80-112	71		65	(45-77)	
Age on commencing RT						
65 y >65 y	70/88	80	.019	75	(58-90)	.74
	31/51	61		31	(0-106)	
ECOG Performance Status						
0	43/58	74	.87	58	(35-79)	.17
1	53/74	72	70	(50-116)		
2	5/7	71	128	(0->303)		
Charlson Comorbidity Index						
0	55/72	76	.23	70	(45-101)	.85
1	16/22	73		59	(10-108)	
2	19/27	70		77	(16-170)	
3, 4, 5	11/18	61		17	(0-136)	
Tobacco smoking						
Never or minimal, 4 missing	36/46	85	.13	70	(50-101)	.53
Past	27/42	64		55	(0-90)	
Current	33/47	70		70	(42-128)	
Alcohol drinker						
Never or social, 5 missing	69/94	73	.73	66	(44-90)	.46
Past	8/11	73		120	(1-200)	

Current	20/29	69	57	(14-77)

Abbreviations: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; PG-SGA, Patient Generated Subjective Global Assessment; RT, radiotherapy. [a]"Feeding tube use" means that the feeding tube was used for at least 25% of nutritional requirements.

[b]Two-sided P value from Fisher exact test for difference between 2 subgroups, Pearson chi-square test for difference between 3 or more unordered subgroups, or Cochran-Armitage test for trend across 3 or more ordered subgroups.

[c]Two-sided P value from Mantel-Cox log rank test for differences between subgroups or Tarone-Ware test for trend across 3 or more ordered subgroups.

3.1 | Univariate analyses

Results of the univariate analyses on all 139 patients are shown in Table 1. Patients with cancer of the oral cavity or pharynx needed a feeding tube for longer than patients with cancers of the supraglottis, glottic larynx, or unknown primary (see Figure 2). The other statistically significant prognostic factors for risk and duration of feeding tube use were T classification, N classification, level 2 lymphadenopathy, bilateral neck lymphadenopathy, concurrent chemotherapy, prior dysphagia, and prior malnutrition. The body mass index <18.5 and negative HPV status in patients with new hypotheses and either risk or duration of feeding tube use was not significant. Patients older than 65 years were less likely to use the feeding tube than younger patients, yet there was no significant difference in duration of feeding tube use. This was contrary to most previous studies. There were no significant

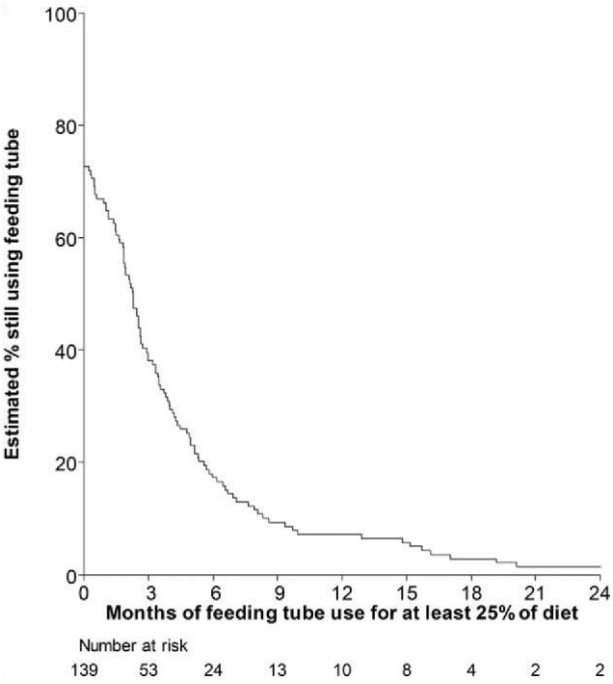


FIGURE 1 Duration of feeding tube use for at least 25% of nutritional requirements for all 139 patients using the Kaplan-Meier analysis

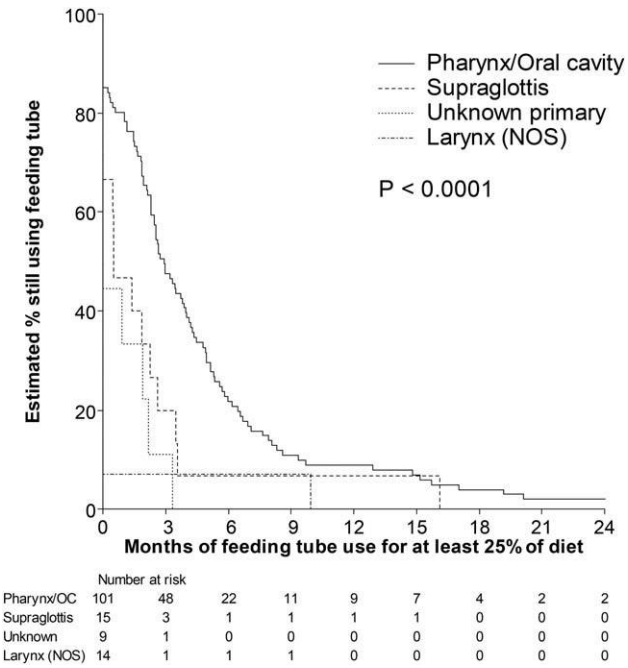


FIGURE 2 Duration of feeding tube use for at least 25% of nutritional requirements by primary cancer site. Kaplan-Meier analysis, 139 patients. NOS, not otherwise specified; OC, oral cavity

oropharyngeal cancer or unknown primary were significantly associated only with longer duration of feeding tube use. Retropharyngeal and level 3 nodal disease were not considered to be statistically significant factors, despite having P values < .05, because they did not meet our criterion of P < .005 for

associations between the risk or duration of tube feeding and tobacco or alcohol use, comorbidities scaled using the Charlson comorbidity index, ECOG performance status, or levels 1, 4, or 5 lymphadenopathy.

3.2 | Multivariable analyses

Cancer site was a significant prognostic factor; therefore, 9 patients with unknown primaries were excluded from the multivariable analyses. Only 1 of the 14 patients with glottic laryngeal cancer needed to use a feeding tube, so these patients were considered to be very low risk and were also excluded from the multivariable analyses.

The remaining 116 patients with cancers in the pharynx, oral cavity, or supraglottis were included in multivariable analyses for risk and duration of feeding tube use for at least 25% of dietary needs. Factors with >2 subgroups were collapsed into 2, specifically cancer site (pharynx and oral cavity vs supraglottis), T classification (T3-4 vs T <3) and N classification (N1-3 vs N0).

In the final models, T classifications 3 and 4 (P 5 .0018 and P < .0001, respectively) and level 2 nodal disease (P 5 .0030 and P 5 .0001, respectively) were the only independent significant predictors of risk and duration of feeding tube use, respectively (Table 2). The recovery rate (rate of ceasing feeding tube use at adequacy of enteral intake 1) with T3 to T4 disease was estimated to be 25% of the rate in patients with T classification <3 disease (CI 16%-39%) and with level 2 nodal disease was estimated to be 45% of the rate in patients with no level 2 nodes involved (CI 30%-67%). Patients with both T classifications 3 and 4 and level 2 nodal disease were predicted to recover at approximately 11% of the rate of patients with neither factor (ie, T classification <3 and no level 2 nodal disease; CI 5%-26%). Table 3 and Figure 3 display the observed duration of feeding tube use in the presence of neither, 1, or both of these 2 significant factors.

None of the other factors, which were significant in the univariate analyses, was statistically significant in the multivariable analyses after taking into account T classifications 3 and 4 and level 2 lymphadenopathy.

4 | DISCUSSION

This analysis introduces a clinically useful and simple screening tool for both risk and duration of significant feeding tube use, which is relevant when IMRT is used. Stratifying patients with pharyngeal, oral cavity, and supraglottis cancers by 2 variables – T classifications 3 and 4 and presence of involved level 2 lymph nodes – separates patients

TABLE 2 Final multivariable models for feeding tube use (yes/no) and duration (n 5 116)[a]

Feeding tube use (exact logistic regression with conditional maximum likelihood inference)[b]							
					OR		
Factor	Reference	Level	b	SE_b	OR	95% CI	Exact P value
T classification	T0-T2	T3-T4	1.867	0.633	6.47	1.73-31.4	.0018
Level 2 nodes	No	Yes	1.640	0.559	5.15	1.56-19.0	.0030
Duration of feeding tube use (Cox proportional hazards regression)[b]							
					Recovery ratio		
Factor	Reference	Level	b	SE_b	OR	95% CI	Exact P value
T classification	T0-T2	T3-T4	-1.388	0.230	0.25	0.16-0.39	<.0001
Level 2 nodes	No	Yes	-0.795	0.205	0.45	0.30-0.67	.0001

Abbreviations: 95% CI, 95% confidence interval for the OR or RR 5 eb6 1.96 (s.e.b); OR, odds ratio; RR, relative risk; SE_b, estimated standard error of b.

[a]"Feeding tube use" means feeding tube was used for at least 25% of nutritional requirements.

[b] b, coefficient for each level relative to the reference category, based on 116 patients with cancers of pharynx, oral cavity or supraglottis.

[c] Other factors which were not significant when added individually to the models were: body mass index (<18.5 vs 18.5), nutrition (Patient Generated Subjective Global Assessment malnourished vs well nourished), dysphagia (yes vs no), cancer (pharynx/oral cavity vs supraglottic larynx), human papillomavirus status (positive/unknown vs negative), N classification (N1-3 vs N0), bilateral neck nodes (yes vs no), and planned concurrent chemotherapy. When added individually to the above models, the P values for these factors were all > .3 for incidence and > .1 for duration of feeding tube use.

OR or RR 5 e^b.

into 4 distinct groups. Low-risk patients have neither risk factor, low-intermediate risk patients have T<3 tumors with level 2 lymph nodes involved, high-intermediate-risk patients have T3 to T4 tumors without level 2 nodes, and high-risk patients have T3 to T4 tumors and level 2 lymphadenopathy. This information is readily available when a patient is first presented at a multidisciplinary tumor board and the model described could be used to guide decisions regarding insertion of prophylactic tubes. However, it does not take dosimetric factors into consideration.

In our experience, all but the lowest-risk group had at least an 85% chance of requiring enteral feeding for at least 25% of their diet, for at least 48 hours, at some stage during therapy or convalescence. Patients with glottic laryngeal cancer had a very low risk of needing a feeding tube (approximately 7% in our limited data). The risk for patients with unknown primaries in the head and neck is likely to depend on the volume of pharyngeal mucosa and constrictor muscles irradiated and whether patients had level 2 nodal involvement. These patients received elective mucosal irradiation, predominantly to the base of the tongue and tonsillar fossae, to 63 Gy and often concurrent chemotherapy but did not incur physical obstruction from macroscopic tumors.

There still remains substantial controversy as to whether patients are best managed via reactive or prophylactic feeding tube for RT-related dysphagia.[11] However, even departments that adhere to strict reactive feeding tube protocols insert prophylactic tubes in a subset of high-risk patients, and, conversely, departments with policies of liberal prophylactic feeding tube use will choose to spare a low- risk subset of patients from undergoing the insertion procedure.

Apart from cancer site, we found advanced T classification to be the most significant prognostic factor for duration of feeding tube use. This is not a new finding and is consistent with the observations of numerous published studies.[16,23–26] The most common dichotomy of T classification in the published literature has been T1 to T2 versus T3 to T4 with the more advanced classifications universally having higher rates of acute and long-term feeding tube use.[16,26,27] The findings of our study support this.

TABLE 3 Prognostic groups based on T classification and level 2 lymphadenopathy: data from 116 patients with cancers of the pharynx, oral cavity, or supraglottis

			Feeding tube used[a]			Days of feeding tube use[a]	
Group	T classification	Level 2 nodal disease	Yes/total	%	(95% CI)	Median	(95% CI)
1	T0-2	No	10/20	50	(27-73)	7	(0-59)
2		Yes	36/42	86	(70-95)	75	(56-90)
3	T3-4	No	24/27	89	(71-98)	108	(68-173)
4		Yes	26/27	96	(81-100)	170	(113-295)
All patients with pharyngeal, oral cavity, supraglottis cancers			96/116	83	(75-89)	79	(68-106)

Abbreviation: 95% CI, 95% confidence interval.

[a]"Feeding tube use" means feeding tube was used for at least 25% of nutritional requirements.

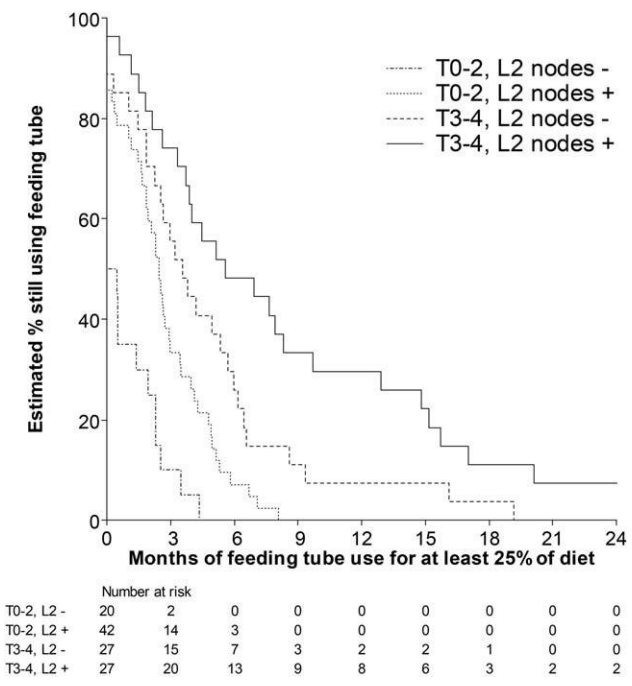


FIGURE 3 Duration of feeding tube use for at least 25% of nutritional requirements by prognostic group according to T classificationand level 2 lymphadenopathy. Kaplan-Meier analysis, 116 patients with pharyngeal, oral cavity, or supraglottis cancers

The impact of level 2 lymph nodes on patient dysphagia is a novel finding. Lymph node positivity has been associated with increased feeding tube dependence at 6 months (odds ratio [OR] 7.08; $P < .001$).[26] We are able to report specifically on this subset of patients with node-positive disease owing to the careful and consistent target delineation under the direction of a single radiation oncologist. The causality of this finding remains unclear. Level 2 lymph nodes have a strong association with primary cancers of the oropharynx and, in the current series, 69% of both oropharyngeal and nasopharyngeal

cancers had level 2 adenopathy.[28] Numerous studies have shown that RT for oropharyngeal malignancy is associated with high rates of symptomatic dysphagia.[16,26,29,30] In this study, all patients with oropharyngeal and nasopharyngeal cancers had elective, bilateral irradiation of neck level 1B. This would lead to high-dose deposition in the region of the patient's submandibular glands, which has been documented to increase the risk of both xerostomia and dysphagia.[26,31] Anatomically, level 2 nodes are close to the parotid glands. Like the submandibular glands, the risk and severity of both xerostomia and dysphagia have been associated with increasing doses to the parotid glands.[32–35]The level 2 region lies lateral to the base of the tongue for its entire craniocaudal length.[15] The tongue base has been described as a crucial organ in swallowing and an increasing risk of dysphagia has been documented with increasing doses to this organ.[26]

Level 2 node involvement is associated with more advanced disease and, thus, more aggressive therapy, such as altered fractionation or use of concurrent systemic therapy. However, this is only by virtue of node positivity and a similar relationship was not seen in this study with adenopathy at other stations.

Regarding our univariate analysis, the finding that patients with pharyngeal and oral cavity carcinomas incurred more dysphagia than those with laryngeal primaries has been previously well documented.[26] Our finding that older patients were less likely to use feeding tubes is consistent with that of Wopken et al[26] but is inconsistent with other published studies.[25,36] We did not observe any effect of alcohol abuse on feeding tube use, as seen by Frowen et al.[24]

The results of this study differ from several others in the duration of feeding tube use for at least 25% of dietary needs. The median duration was over at 2 months and at 6 months, with 17% of the patients still using their feeding tubes. Although earlier series have reported significantly higher rates of prolonged feeding tube use, many modern studies, which have included patients treated with IMRT, have cited lower rates of long-term feeding tube use.[5,11,26,35–38]

It is important to distinguish feeding tube use from feeding tube dependence. A proportion of patients in this study who were using their feeding tubes at 6 months were also taking food and supplements orally. Eighteen patients (13%) were using their feeding tube for >75% of daily needs for >6 months, which is consistent with recently published prophylactic cohorts, such as Wopken et al[26] (10.7%). Regardless of nutritional intervention, it is common for patients with head and neck cancer to lose >10% of their bodyweight during and immediately after therapy.[2,3] In many cases, an in situ gastrostomy tube provides a convenient way to optimize patient nutrition, even when they are eating. These patients have already avoided or incurred the potential complications associated with gastrostomy insertion, so it is not surprising that dieticians and nutritional counselors sometimes encourage ongoing nutritional supplementation in patients still eating food orally.

In the short term, gastrostomies are more comfortable and convenient than nasogastric tubes and have less negative impact on body image and family life.[12] For this reason, it is not surprising that the medical literature almost universally reflects longer duration of feeding tube use with gastrostomy as opposed to reactive nasogastric tubes.[12,39–41] In reports in which feeding tube use at 6 months is <5%, a nasogastric tube was inserted as a reaction to failure of oral nutrition. It is not surprising that nasogastric tubes were not kept in situ or repeatedly reinserted for the purpose of nutritional optimization, given the poor acceptability of this feeding tube on body image psychosocial function.[11,12,38,42]

Undoubtedly, long-term feeding tube dependence has a striking negative impact on many domains of quality of life.[43–47] A considerable amount of published data suggest that patients with prophylactic feeding tubes are less likely to maintain an oral, or partially oral, diet during RT and that this can negatively affect short-term and long-term diet outcomes, as well as duration of feeding tube dependence.[11,48,49] Despite the majority of reported studies showing higher feeding tube use at 6 months with prophylactic feeding tube, Salas et al[50] found no difference and Silander et al[40] reported lower rates of grade 3 dysphagia in patients with a prophylactic gastrostomy tube (2% vs 9%).

The high risk and duration of feeding tube use in this study can also be explained by the high-risk patients enrolled. All patients had bilateral neck irradiation, and gross disease was treated to an equivalent dose of 70 Gy. Many series have included patients who were treated with ipsilateral and postoperative RT who are not expected to use feeding tubes routinely. In this series, 84 patients were treated with concurrent systemic therapy. This is known to increase acute toxicity, including severe dysphagia, although it did not affect feeding tube use in our series.[51] Although concurrent chemotherapy did not retain significance after multivariable analyses, there may be some co-linearity with both T classification and N classification and the role it plays in more advanced disease.

Tumors of the glottic larynx had low risk of feeding tube dependence and were excluded from the multivariable regression analyses. Although earlier studies by Caglar et al,[52] Eisbruch et al,[53] and Caudell et al[36] have shown the larynx to be an important RT avoidance structure, a recent study by Wopken et al[26] shows that patients with laryngeal primaries are the least likely to incur feeding tube dependence at 6 months (OR 1.00 vs 13.82 for oropharyngeal cancer and 16.19 for hypopharyngeal cancer; $P < .001$).[26,54] Treatment of salivary gland tumors is very rarely associated with dysphagia and, therefore, this patient cohort was not included in this study.

In this study, no patient had access to swallowing rehabilitation. A randomized controlled trial reported by Carnaby-Mann et al[14] showed that swallowing exercises led to less deterioration of swallowing muscles and functional swallowing ability during chemoradiotherapy for head and neck cancers. Patients randomized to swallowing exercises were more likely to maintain an oral diet and were less likely to use a feeding tube.[14] Hutcheson et al[49] reported that adherence to swallowing exercises was similarly effective to maintenance of an oral, or partial oral, diet during chemoradiotherapy for better long-term diet and shorter feeding tube use. The lack of swallowing exercises in this study may limit the ability the applicability of our data to patients who are exercising. However, the complete absence of swallowing exercises in this cohort contributes to the uniformity of our data and possibly the internal validity of our findings. Swallowing exercises have definite patient benefits but not all patients are adherent to prescribed swallowing exercises and many patients are partially adherent, making these benefits

difficult to quantify.[14,49]

Furthermore, every effort was made to minimize patient pain, as analgesia has been associated with a shorter duration of feeding tube use.[47] All patients were reviewed at least weekly by a medical doctor to prescribe analgesia in a stepwise fashion: mouthwashes and anti-thrush measures, simple analgesia (eg, soluble paracetamol), local anesthetic mouthwashes (eg, xylocaine and cocaine), and ultimately titration of opioids. Prophylactic gabapentin was not administered, as it is not registered for this use in Australia, although it has been associated with reduced feeding tube use in a previously published study.[47]

This study possesses all the limitations inherent to a single-institution retrospective analysis. We are unable to provide data on patients' functional swallowing ability, however, we are able to accurately report on patients having oral, or partial oral, diet at various time points due to comprehensive, prospectively recorded nutritional data. All of the patients were treated by a single radiation oncologist; however, it must be acknowledged that these patients were treated over 8 years, a sufficient time period for even individual practice to vary. All patients were treated in the fluorodeoxyglucose-PET and IMRT era, without swallowing exercises. This lends to uniformity in staging, volume delineation, and treatment delivery across the cohort. This study proposes a simple and novel clinical risk stratification tool that warrants prospective validation.

5 | CONCLUSION

In patients with pharyngeal or supraglottic laryngeal cancers treated with definitive, bilateral IMRT, with or without concurrent systemic therapy, 2 clinical risk factors, namely T classifications 3 to 4 and level 2 lymphadenopathy, can potentially stratify patients

into 4 distinct risk groups for developing severe dysphagia requiring feeding tube use for at least 25% of their dietary requirements. This stratification may be useful in the clinic before RT planning and treatment so that patients at risk may have a feeding tube inserted early before further nutritional status deterioration.

ACKNOWLEDGMENTS

The authors thank the Departments of Nutrition and Dietetics & Speech Pathology, Austin Health, Heidelberg, Victoria, Australia, for their help with this study.

ORCID

Nigel J. Anderson BAppSc http://orcid.org/0000-0002-4826-2339

REFERENCES

[1] De Luis DA, Izaola O, Aller R. Nutritional status in head and neck cancer patients. Eur Rev Med Pharmacol Sci. 2007;11:239243.

[2] Ng K, Leung SF, Johnson PJ, Woo J. Nutritional consequences of radiotherapy in nasopharynx cancer patients. Nutr Cancer. 2004;49:156-161.

[3] Silver HJ, Dietrich MS, Murphy BA. Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck cancer treated with concurrent chemoradiation after low-dose induction chemotherapy. Head Neck. 2007;29:893-900.

[4] van Wayenburg CA, Rasmussen-Conrad EL, van den Berg MG, et al. Weight loss in head and neck cancer patients little noticed in general practice. J Prim Health Care. 2010;2:16-21.

[5] Ang KK, Harris J, Garden AS, et al. Concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: radiation Therapy Oncology Group phase II trial 99-14. J Clin Oncol. 2005;23:3008-3015.

[6] Beckmann GK, Hoppe F, Pfreundner L, Flentje MP. Hyperfractionated accelerated radiotherapy in combination with weekly cisplatin for locally advanced head and neck cancer. Head Neck. 2005;27:36-43.

[7] Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol. 2012;13:145-153.

[8] Driessen CM, Janssens GO, van der Graaf WT, et al. Toxicity and efficacy of accelerated radiotherapy with concurrent weekly cisplatin for locally advanced head and neck carcinoma. Head Neck. 2016;38 Suppl 1:E559-E565.

[9] Ho KF, Swindell R, Brammer CV. Dose intensity comparison between weekly and 3-weekly cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: a retrospective comparison from New Cross Hospital, Wolverhampton, UK. Acta Oncol. 2008;47:1513-1518.

[10] Bossola M. Nutritional interventions in head and neck cancer patients undergoing chemoradiotherapy: a narrative review. Nutrients. 2015;7:265-276.

[11] Koyfman SA, Adelstein DJ. Enteral feeding tubes in patients undergoing definitive chemoradiation therapy for head-and-neck cancer: a critical review. Int J Radiat Oncol Biol Phys. 2012;84: 581-589.

[12] Corry J, Poon W, McPhee N, et al. Prospective study of percutaneous endoscopic gastrostomy tubes versus nasogastric tubes for enteral feeding in patients with head and neck cancer undergoing(chemo) radiation. Head Neck. 2009;31:867-876.

[13] Grant DG, Bradley PT, Pothier DD, et al. Complications following gastrostomy tube insertion in patients with head and neck cancer: a prospective multi-institution study, systematic review and meta-analysis. Clin Otolaryngol. 2009;34:103-112.

[14] Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2012;83(1):210-219.

[15] Gregoire V, Ang K, Budach W, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSQ, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. Radiother Oncol. 2014;110:172181.

[16] Bhayani MK, Hutcheson KA, Barringer DA, et al. Gastrostomy tube placement in patients with oropharyngeal carcinoma treated with radiotherapy or chemoradiotherapy: factors affecting placement and dependence. Head Neck. 2013;35:1634-1640.

[17] Christianen ME, Schilstra C, Beetz I, et al. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study. Radiother Oncol. 2012;105:107-114.

[18] Mallick I, Gupta SK, Ray R, et al. Predictors of weight loss during conformal radiotherapy for head and neck cancers - how important are planning target volumes? Clin Oncol (R Coll Radiol). 2013;25:557-563.

[19] Poulsen MG, Riddle B, Keller J, Porceddu SV, Tripcony L. Predictors of acute grade 4 swallowing toxicity in patients with stages iii and

iv squamous carcinoma of the head and neck treated with radiotherapy alone. Radiother Oncol. 2008;87:253259.

[20] Cytel studio (2005). Cytel Software Corporation, Cambridge, MA, USA. http://www.cytel.com/. Accessed November 1, 2016.

[21] R core team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2014.

[22] VSN International (2013). Genstat for Windows 16th edition, VSN International, Hemel Hempstead, UK. http://www.vsni.co. uk. Accessed November 1, 2016.

[23] Cheng SS, Terrell JE, Bradford CR, et al. Variables associated with feeding tube placement in head and neck cancer. Arch Otolaryngol Head Neck Surg. 2006;132:655-661.

[24] Frowen J, Cotton S, Corry J, Perry A. Impact of demographics, tumor characteristics, and treatment factors on swallowing after (chemo)radiotherapy for head and neck cancer. Head Neck. 2010;32:513-528.

[25] Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol. 2008;26:3582-3589.

[26] Wopken K, Bijl HP, van der Schaaf, et al. Development of a multivariable normal tissue complication probability (NTCP) model for tube feeding dependence after curative radiotherapy/ chemo-radiotherapy in head and neck cancer. Radiother Oncol. 2014;113:95-101.

[27] Mangar S, Slevin N, Mais K, Sykes A. Evaluating predictive factors for determining enteral nutrition in patients receiving radical radiotherapy for head and neck cancer: a retrospective review. Radiother Oncol. 2006;78:152-158.

[28] Sanguineti G, Califano J, Stafford E, et al. Defining the risk of involvement for each neck nodal level in patients with early Tstage node-positive oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2009;74:1356-1364.

[29] Beaver ME, Matheny KE, Roberts DB, Myers JN. Predictors of weight loss during radiation therapy. Otolaryngol Head Neck Surg. 2001;125:645-648.

[30] Nugent B, Parker MJ, McIntyre IA. Nasogastric tube feeding and percutaneous endoscopic gastrostomy tube feeding in patients with head and neck cancer. J Hum Nutr Diet. 2010;23:
277-284.

[31] Little M, Schipper M, Feng FY, et al. Reducing xerostomia after chemo-IMRT for head-and-neck cancer: beyond sparing the parotid glands. Int J Radiat Oncol Biol Phys. 2012;83:10071014.

[32] Bentzen SM, Constine LS, Deasy JO, et al. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys. 2010; 76:S3-S9.

[33] Dawes C. Rhythms in salivary flow rate and composition. Int J Chronobiol. 1974;2:253-279.

[34] Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA. Unilateral versus bilateral irradiation in squamous cell head and neck cancer in relation to patient-rated xerostomia and sticky saliva. Radiother Oncol. 2007;85:83-89.

[35] Chen AM, Li BQ, Lau DH, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys.
2010;78:1026-1032.

[36] Caudell JJ, Schaner PE, Desmond RA, Meredith RF, Sepncer SA, Bonner JA. Dosimetric factors associated with long-term dysphagia after definitive radiotherapy for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 2010; 76:403-409.

[37] Sanguineti G, Gunn GB, Parker BC, Endres EJ, Zeng J, Fiorino C. Weekly dose-volume parameters of mucosa and constrictor muscles predict the use of percutaneous endoscopic gastrostomy during exclusive intensity-modulated radiotherapy for oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2011; 79:52-59.

[38] Clavel S, Fortin B, Despres P, et al. Enteral feeding during chemoradiotherapy for advanced head-and-neck cancer: a singleinstitution experience using a reactive approach. Int J Radiat Oncol Biol Phys. 2011;79:763-769.

[39] Mekhail TM, Adelstein DJ, Rybicki LA, Larto MA, Saxton JP, Lavertu P. Enteral nutrition during the treatment of head and neck carcinoma: Is a percutaneous endoscopic gastrostomy

tube preferable to a nasogastric tube? Cancer. 2001;91:17851790.

[40] Silander E, Nyman J, Bove M, Johansson L, Larsson S, Hammerlid E. Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer: a randomized study. Head Neck. 2012;34: 1-9.

[41] Tyldesley S, Sheehan F, Munk P, et al. The use of radiologically placed gastrostomy tubes in head and neck cancer patients receiving radiotherapy. Int J Radiat Oncol Biol Phys. 1996;36:
1205-1209.

[42] Roberge C, Tran M, Massoud C, et al. Quality of life and home enteral tube feeding: a French prospective study in patients with head and neck or oesophageal cancer. Br J Cancer. 2000;82:
263-269.

[43] El-Deiry MW, Fultran ND, McDowell JA, Weymuller EA Jr, Yueh B. Influences and predictors of long-term quality of life in head and neck cancer survivors. Arch Otolaryngol Head Neck Surg. 2009;135:380-384.

[44] Gurney TA, Eisele DW, Orloff LA, Wang SJ. Predictors of quality of life after treatment for oral cavity and oropharyngeal carcinoma. Otolaryngol Head Neck Surg. 2008;139:262267.

[45] Nguyen NP, Frank C, Moltz CC, et al. Impact of dysphagia on quality of life after treatment of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2005;61:772-778.

[46] Rogers SN, Thomson R, O'Toole P, Lowe D. Patients experience with long-term percutaneous endoscopic gastrostomy feeding following primary surgery for oral and oropharyngeal cancer. Oral Oncol. 2007;43:499-507.

[47] Yang W, McNutt TR, Dudley SA, et al. Predictive factors for prophylactic percutaneous endoscopic gastrostomy (PEG) tube placement and use in head and neck patients following intensitymodulated radiation therapy (IMRT) treatment: concordance, discrepancies, and the role of gabapentin. Dysphagia. 2016;31(2):
206-213.

[48] Langmore S, Krisciunas GP, Miloro KV, Evans SR, Cheng DM. Does PEG use cause dysphagia in head and neck cancer patients? Dysphagia. 2012;27(2):251-259.

[49] Hutcheson KA, Bhayani MK, Beadle BM, et al. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. JAMA Otolaryngol Head Neck Surg.
2013;139(11):1127-1134.

[50] Salas S, Baumstarck-Barrau K, Alfonsi M, et al. Impact of the prophylactic gastrostomy for unresectable squamous cell head and neck carcinomas treated with radio-chemotherapy on quality of life: prospective randomized trial. Radiother Oncol. 2009;93:
503-509.

[51] Trotti A, Pajak TF, Gwede CK, et al. TAME: Development of a new method for summarising adverse events of cancer treatment by the radiation therapy oncology group. Lancet Oncol. 2007;8:
613-624.

[52] Caglar HB, Tishler RB, Othus M, et al. Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys. 2008;72:11101118.

[53] Eisbruch A, Levendag PC, Feng FY, et al. Can IMRT or brachytherapy reduce dysphagia associated with chemoradiotherapy of head and neck cancer? The Michigan and Rotterdam experiences. Int J Radiat Oncol Biol Phys. 2007;69:S40S42.

[54] Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys. 2007;68:1289-1298.

How to cite this article: Anderson NJ, Jackson JE, Smith JG, et al. Pretreatment risk stratification of feeding tube use in patients treated with intensitymodulated radiotherapy for head and neck cancer. Head & Neck. 2018;00:1–12. https://doi.org/10.1002/ hed.25316