Development and Implementation of Quality of Life Measures in Head and Neck Cancer Patients

by

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Thesis

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ABSTRACT

Background:

A diagnosis of head and neck cancer (HNC) heralds a life-threatening event for patients. Quality of Life (QOL) assessment is an important outcome measure, as HNC treatment imposes enduring post-treatment difficulties for the survivors, often leading to a degree of psychological distress, and an adverse impact on physical, role, and social functioning. QOL status has a major impact on the extent to which patients need to access healthcare support services, and the degree to which they engage socially. Clinical research into QOL outcomes provides data that ensures that clinicians are uniquely placed to anticipate and plan for patient needs and to determine appropriate choice among different treatment options.

Patients and Method:

The research incorporated in this thesis includes publications spanning 28 years, from 1984 to 2012. The first research was a pilot, cross-sectional, observational study of previously treated HNC patients that demonstrated the substantial psychological impact of HNC treatment. This prompted further exploration of QOL assessment in which a valid and reliable QOL instrument was designed and subsequently used in a prospective observational study of a cohort of Auckland HNC patients. These studies were conducted at a time when understanding of QOL in HNC was in its infancy[i].

Indeed, the Auckland cohort study of 201 patients was one of the first[ii] large longitudinal studies of QOL outcomes in HNC patients. Life satisfaction was used as a multi-dimensional global QOL composite measure, and Calman's ***Gap Theory*** was invoked to explain the dynamics of perceived global QOL. The data

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[i] "*… thank you for being one of the ground-breakers in this field. I have found it very gratifying during my career to see QOL (which was seen as a bit "fringe" when I started to work on it) finally accepted as an integral part of patient-centred care and survivorship/de-escalation research in HNC. I have you have experienced the same pride in your work and foresight.*" (Professor Jolie Ringash, personal email communication, Feb 2, 2018)

[ii] refer section 2.2.1, table IV, page 36.

from this Auckland cohort were used in subsequent investigations to assess the impact of pain and time on global QOL, and the relationship between QOL and survival.

Results:

Important issues in this thesis include a discussion of: the role of an overall, or global, QOL measure as an important dependent variable for outcomes research; the central role of Calman's "*Gap Theory*" in the understanding and interpretation of QOL outcomes in cancer patients; and an appreciation of the "*response shift*" phenomenon, as manifest by a paradoxical relationship between perceived post-treatment QOL and reported functional measures.

Findings from the studies incorporated in this thesis have shown that the pattern of post-treatment QOL outcomes is determined by tumour site and stage, that post-treatment global QOL is significantly associated with survival, that culture has a significant impact on perceived global QOL, and that there is a significant late deterioration in global QOL for HNC survivors.

The consequence of these findings is that QOL outcomes are important to include in the process of shared clinical decision-making.

Conclusion:

The published works show how the phenomenon of QOL assessment has developed over the period in review, culminating in an appreciation of how the information from QOL outcomes has shaped clinical decision-making. The report of the relationship between culture and QOL outcomes has added significantly to the understanding of the dynamics of health-related QOL, while observations relating to long-term QOL outcomes, and the prognostic role of early of post-treatment QOL outcomes, have the potential to substantially influence future clinical practice.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed..
Date..

PUBLICATIONS INCLUDED IN THIS THESIS

Pilot Study of QOL Outcomes in HNC Patients

Morton RP, Davies ADM, Baker J, Baker GA, Stell PM (1984) Quality of life in treated head and neck cancer patients: a preliminary report. *Clin Otolaryngol* 9: 181-185.

Literature Review of Studies on QOL in HNC

Morton RP (1995) Evolution of quality-of-life assessment in head-and-neck cancer. *J Laryngol Otol* 109: 1029-1035.

Morton RP (1995) Quality-of-life measures in head-and-neck cancer: capabilities and caveats. *Curr Oncol* 2: 77-83.

Morton RP, Izzard M (2003) Quality of life outcomes in head and neck cancer patients. *World J Surg* 27: 884-889.

Development and Validation of the Auckland QOL Questionnaire

Morton RP, Witterick I (1995) Rationale and development of a quality of life instrument for head and neck cancer patients. *Am J Otolaryngol* **16**:284-293.

Morton RP, Tandon DA (2000) Validation of quality of life measures in head and neck cancer patients. *Aust J Otolaryngol* 3(5): 479-487.

Longitudinal Studies of the Auckland QOL Cohort

Morton RP (1995) Life satisfaction in head and neck cancer patients. *Clin Otolaryngol* 20:499-503

Morton RP (2003) Studies in the quality-of-life of head-and-neck cancer patients. Results of a 2-year Longitudinal Study and a Comparative Cross-sectional Cross-cultural Survey. *Laryngoscope* 113:1091-1103.

Mehanna HM, Morton RP (2006) Deterioration in quality-of-life of late (10-year) survivors of head and neck cancer. *Clin Otolaryngol* 31**(**3): 204-211.

Mehanna HM, Morton RP, West, TM (2006) Does quality of life predict long-term survival in head and neck cancer patients? *Arch Otolaryngol* 132: 27-31.

Studies of Targeted QOL Issues in HNC Patients

Spielman PM, Majumdar S, Morton RP (2010) Quality of life and functional outcomes in the management of early glottis carcinoma: a systematic review of studies comparing radiotherapy and transoral laser microsurgery. *Clin Otolaryngol* 35: 373–382.

Morton RP (1997) Laryngeal cancer: quality of life and cost-effectiveness. *Head & Neck* 19: 243-250.

Chaplin JP, Morton RP (1999) A prospective, longitudinal study of pain in head and neck cancer patients. *Head & Neck* 21: 531-537.

Kwok HCK, Morton RP, Chaplin JM, McIvor NP, Sillars HA (2002) Quality of Life after Parotid and Temporal Bone Surgery for Cancer. *Laryngoscope* 112: 820-833.

Eponymous Invited Lectures

Morton RP. *The 2009 Semon Lecture*[iii].; University of London, UK; Nov 2009*: “Changing Perceptions in Head and Neck Cancer Management caused by Quality of Life Issues”*[iv]. *ENT & Audiology News*2010;**19(4):**43-46.

Morton RP. *Th*e 2010 Eugene N Myers International Head & Neck Lecture.
Toward Comprehensive Multidisciplinary Care for Head and Neck Cancer Patients:
Quality of Life versus Survival. *Otolaryngol–Head Neck Surg* (2012) 147(3): 404–406.

The “Quality of Life” component of the **Introduction** in this thesis has been based partly on material published previously in a book chapter:

Morton RP, Mehanna H (2008) Quality of life in head and neck cancer. In: *Scott-Brown’s Otorhinolaryngology, Head and Neck Surgery.* 7th edition. Gleeson M (Ed) Hodder Arnold, vol 2 pp 2766-2780.

[iii] Being invited to deliver this lecture is considered to be the highest honour the University of London can confer on an Otolaryngologist (*personal communication;* Professor Michael Gleeson, Chair, Semon Lectureship Committee).

[iv] The original title proposed by the Semon Trust was ‘Changes in Quality of Life caused by Head and Neck Cancer Treatment’; the impact on patient care as a result of learning about QOL outcomes was, in my view, greater than the changes in QOL resulting from treatment, hence the minor adjustment in title, but major change in emphasis.

ACKNOWLEDGEMENTS

I acknowledge Professor Paul Worley, who initially suggested that I apply to Flinders University, to do a PhD by prior publication. Without his positive encouragement my thesis would not have even started.

My supervisors, Professor Ross McKinnon and Associate Professor Eng Ooi, have been marvellous. Ross's support, attention to detail, and succinct assurance have made the whole process more manageable than I had hoped. Eng's thoughtful reviews and advice have helped me to remain anchored to the task in hand; moreover, his timely encouragement assuaged my self-doubt at a critical point in time. I also acknowledge the encouragement and unstinting good advice that Professor Tara Brabazon has provided me.

Professor Philip Stell was my mentor; his disciplined approach to recording clinical data and his impeccable reporting of outcomes became my creed for my own clinical research.

I want to thank Keith Macky MSc, who taught me how to conduct a survey and gave me the tools for psychometric analysis. Also Ann Carter, the wonderful, retired charge nurse who conducted so many of the Quality of Life questionnaires that formed the basis for my quality of life research publications. Ann understood the patients and their concerns; they loved her, and so did I.

I am grateful to my colleague Nick McIvor FRACS, who believed in me, and helped me to see the value of a global, or overall, dependent variable outcome for quality of life. I also want to acknowledge Hisham Mehanna, who as an enthusiastic Clinical Fellow re-ignited my interest in Quality of Life outcomes for head and neck cancer patients at a time when I had begun to lose momentum.

I thank Professor Ernie Weymuller, who has become a firm friend and a strong supporter of me in the world of clinical research on quality of life in head and neck cancer patients. Comparing notes with Ernie has been a treasured bonus for me over the years.

My thanks also to Toronto’s Professor Bernie Cummings who challenged me in a way that made me re-think my early results and their implications; as a result I realised the potential for psychological intervention in patients before it was a published practice. Professors Pat Bradley, David Howard, Gene Myers, Jatin Shah and Ken McKenzie recognised the importance of my Quality of Life studies and provided speaking platforms for me to disseminate more widely the messages contained in my publications on that subject, for which I am grateful.

I thank the NZ Lotteries Commission, the Head and Neck Surgery Trust, and the Green Lane Research and Education Trust Fund for their financial support, at a time when it was ‘unfashionable’ to conduct quality of life research. The Garnett Passe and Rodney Williams Foundation provided the opportunity for me to pursue a sabattical to expand my studies and involve Toronto patients. Thanks to Professor Arnold Noyek who brokered that sabbatical for me, who insisted that I submit my Toronto quality of life research work as a dissertation to the ‘Triological Society’. This led to my election to membership of the Society, and the selection of the publication from this work as one of the ‘Head and Neck’ seminal articles of the 20th century.

I am also grateful to the Flinders University for admitting me as a Research Higher Degree candidate, and subsequently awarding me a Research Training Program fee offset, in the form of an Australian Government Research Training Program Scholarship.

I thank my courageous, remarkable, uncomplaining patients who have had to endure the tribulations of head and neck cancer and its treatment. They, together with their families, have given so generously of their time and their emotions in order for us to learn more and thereby hopefully help those that follow.

I also wish to make special mention of my co-authors who accepted and even embraced my vision for this research; graciously enduring in the process, my obsessive editing of large numbers of manuscript drafts.

And through it all, my family has selflessly accepted my passion for this work, and supported me through the difficult and demanding times. Their unconditional love of me, and belief in me has been phenomenal. Most especially, I have been greatly blessed with my wonderful wife Hanneke, without whom I would have been drifting and lost. She has been my pathfinder, my compass, and the wind beneath my wings. Words are not enough.

ABBREVIATIONS

AQLQ	Auckland Quality of Life Questionnaire
BAHA	Bone-Anchored Hearing Aid
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
CNS	Central Nervous System
C-RT	Chemotherapy-Radiotherapy (Combined modality)
EBV	Epstein-Barr Virus
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	30-item EORTC QOL questionnaire, core module
EORTC QLQ-H&N35	35-item EORTC QOL questionnaire, head and neck module
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-HN	Functional Assessment of Cancer Therapy-Head and Neck
FLIC	Functional Living Index-Cancer
GHQ-12	12-item General Health Questionnaire
HLA	Human Leukocyte Antigen
HNC	Head and Neck Cancer
HPV	Human Papilloma Virus
HR	Hazard Ratio
HRQOL	Health-Related Quality of Life
IMRT	Intensity-Modulated Radiotherapy
LASER	Light Amplification by Stimulated Emission of Radiation
LS	Life Satisfaction
NZ	New Zealand
NPC	Naso-pharyngeal Cancer
OR	Odds Ratio
PF	Physical Functioning
PI	Principle Investigator
PCS	Physical Component Scale
QL	Quality of Life

QLQ	Quality of Life Questionnaire
QOL	Quality of Life
RCT	Randomised Clinical Trial
RLH	Royal Liverpool Hospital
RSM	Royal Society of Medicine
RT	Radiotherapy
SF35	35-item Short Form (questionnaire)
S-RT	Surgery plus adjuvant Radiotherapy
TBR	Temporal Bone resection
TLM	Trans-oral LASER Microsurgery
TORS	Trans-oral Robot-assisted Surgery
UK	United Kingdom
UWQOL	University of Washington Quality of Life Questionnaire

CONTRIBUTIONS TO CONJOINT WORK INCLUDED IN PUBLISHED PAPERS IN THIS THESIS

For all studies included in this thesis I …

- Singly conceived the study
- Personally developed and wrote or co-wrote the submissions for all Ethics committee applications
- Conducted or oversaw the recruitment and interviews of patients included in the clinical studies
- Coordinated the clinical databases used in the clinical studies
- Contributed wholly or substantially to the recruitment of participants in each trial
- Personally conducted or supervised the data analysis for each study except for the 1983 Pilot study.
- Wrote the initial manuscript drafts for 13 of the 15 papers included in this thesis.
- Led the editing of all manuscripts prior to submission for publication, and oversaw the publication process as senior and (with one exception) corresponding author.

For most of the work I either published alone, or engaged one or two (mainly junior) colleagues, principally to provide experience for them in conducting a directed literature review, performing statistical analysis, and co-writing a manuscript. Most of the work was conducted at the Green Lane Hospital in Auckland, under the auspices of the department of Otolaryngology-Head and Neck Surgery, or at the Mt Sinai Hospital in Toronto, under the auspices of the University of Toronto, as part of my sabbatical (in the form of a Garnett Passe & Rodney Williams Memorial Foundation Advanced Fellowship). The pilot study published in 1984 was conducted at the Royal Liverpool Hospital under the auspices of the University of Liverpool and the RLH Head and Neck Surgery Department.

No outside scientific contributions were received for the five single-author publications included in this thesis.

For the multi-author publications, specific contributions to each study were:

Pilot Study of QOL Outcomes in HNC Patients

Morton RP, Davies ADM, Baker J, Baker GA, Stell PM (1984) Quality of life in treated head and neck cancer patients: a preliminary report. *Clin Otolaryngol* 9: 181-185.

Professor Stell was the Head of Department, and gave permission for access to his patients for this study. I was responsible for conducting the literature review, devised the concept, recruited the patients, assisted with the data management and analysis, and wrote the paper. Geoffrey Baker and Jenny Baker were psychology students under the supervision of Anne Davies, senior lecturer in the Psychology department of the University of Liverpool. These three were responsible for selection of the psychological tools included in the study. I wrote the initial draft and all co-authors contributed to editing of final draft before submitting the manuscript for publication.

Literature Review of studies on QOL in HNC

Morton RP, Izzard M (2003) Quality of life outcomes in head and neck cancer patients. *World J Surg* 27: 884-889.

Dr Izzard was my registrar at the time of the preparation of this manuscript; I invited him to join me as co-author and tasked him with conducting the literature search for the items in Table 1. He also contributed to the editing process of later drafts of the manuscript.

Development and Validation of the Auckland QOL Questionnaire

Morton RP, Witterick I (1995) Rationale and development of a quality of life instrument for head and neck cancer patients. *Am J Otolaryngol* 16: 284-293.

Dr Ian Witterick was a colleague in Toronto with an interest and higher degree in clinical epidemiology. I asked him to review my draft manuscript and offer editing suggestions, which he did, especially in respect of the definition of clinimetric measures.

Morton RP, Tandon DA (2000) Validation of quality of life measures in head and neck cancer patients. *Aust J Otolaryngol* 3(5): 479-487.

Dr Dev Tandon was a colleague who reviewed my draft manuscript and assisted with editing of that and subsequent versions, prior to submission for publication.

Longitudinal Studies of the Auckland QOL Cohort

Mehanna HM, Morton RP (2006) Deterioration in quality-of-life of late (10-year) survivors of head and neck cancer. *Clin Otolaryngol* 31(3): 204-211.

Dr Hisham Mehanna was a Clinical Fellow under my supervision. I provided him access to the database of the patients in the Auckland Quality of Life cohort. I had recruited all and interviewed most of the patients in the initial study, and managed the database. The concept to review the 10-year survivors was mine. David Goldsmith (a clinical assistant) and I conducted the 10-year follow-up interviews. Dr Mehanna wrote the initial draft manuscript under my supervision; we edited later drafts collaboratively.

Mehanna HM, Morton RP (2006) Does quality of life predict long-term survival in head and neck cancer patients? *Arch Otolaryngol* 132: 27-31

Dr Hisham Mehanna was a Clinical Fellow under my supervision. I provided him access to the material in the Auckland Quality of Life cohort database. I had recruited all and interviewed most of the patients and managed the data. The concept to review the 10-year survivors was mine. Statistician Tina West performed the multivariable statistical analysis of survival. Dr Mehanna and I co-wrote the manuscript; Tina West reviewed the manuscript prior to submitting for publication.

Studies of Targetted QOL Issues in HNC Patients

Spielmann PM, Majumdar S, Morton RP (2010) Quality of life and functional outcomes in the management of early glottic carcinoma: a systematic review of studies comparing radiotherapy and transoral laser microsurgery. *Clin Otolaryngol* 35: 373–382.

Dr Spielmann approached me for assistance with this study, which I had proposed in the 2009 Semon Lecture at the Laryngology Section of the Royal Society of Medicine. Dr Spielmann conducted the primary literature review and Dr Majumdar and I assisted with the review and selection of papers for inclusion in the systematic analysis, reviewed the results and contributed to writing the manuscript.

Chaplin JP, Morton RP (1999) A prospective, longitudinal study of pain in head and neck cancer patients. *Head & Neck* 21: 531-537.

Dr Chaplin was my registrar at the time of writing this manuscript. He assisted with the literature review and manuscript editing. I performed the data analysis from data already in the Auckland Quality of Life cohort database, and led the publication process.

Kwok HCK, Morton RP, Chaplin JM, McIvor NP, Sillars HA (2002) Quality of life after parotid and temporal bone surgery for cancer. *Laryngoscope* 112: 820-833

Drs McIvor, Chaplin and SIllars each contributed patients for inclusion in this study, and reviewed the final manuscript. Henry Kwok was a medical student who interviewed the patients, managed the database and collaborated with me in writing the manuscript.

FUNDING

Applications for funding were all submitted by me; the principle investigator (PI) for the Liverpool randomised clinical trial (RCT) protocol was Professor PM Stell. For all other grants I was the nominated Principle Investigator.

1. (1982-83) N-W Cancer Research Fund (UK) (NZ$) 40,000

   Randomised clinical trial, including related clinical Studies in Head & Neck Cancer

   (Investigators: PM Stell; RP Morton) This funding was granted for the purposes of conducting an RCT in Liverpool, UK, under the oversight of Professor Stell [PI]; the pilot study of QOL involved patients encountered in the course of the trial, and was effectively a spin-off from that trial, made possible by funding for the trial itself.

2. (1989) Lottery Medical Research (NZ) NZ$ 5,000

   Studies in Quality of Life in Head & Neck Cancer

   (RP Morton)

3. (1992) Lottery Medical Research (NZ) NZ$ 10,000

   Studies in Quality of Life in Head & Neck Cancer

   (RP Morton)

4. (1999) Auckland Deafness Research Foundation NZ$ 4,000

   Study of Quality of life after temporal bone resection for cancer

   (Investigators RP Morton [PI]; HCK Kwok)

5. (2000) Maurice and Phyllis Paykel Trust NZ$ 21,000

   Study of Long-term Quality of Life results in Head and Neck Cancer Patients

   (Investigators RP Morton [PI]; DA Goldsmith)

PORTIONS OF WORK SUBMITTED FOR RESEARCH HIGHER DEGREES AT OTHER UNIVERSITIES

The publications:

- *Mehanna HM, Morton RP, West, TM. Does quality of life predict long-term survival in head and neck cancer patients? Arch Otolaryngol (2005)* ***132****:27-31,* and
- *Mehanna HM, Morton RP. Deterioration in quality-of-life of late (10-year) survivors of head and neck cancer. Clin Otolaryngol (2006)* ***31****(3): 204-211*

were included in a thesis submitted by Dr Mehanna, entitled: "*Towards effective assessment of quality of life of head and neck cancer in the clinical setting*" to obtain the degree of doctor from the Erasmus University, Rotterdam.

Whilst Dr Mehanna led the literature review for that thesis, and assisted with updating of patient demographic and follow-up data, the work used original material from the Auckland Quality of Life cohort database collected across a 12 year period, under my supervision.

These studies were conceived, proposed and initiated by me and I co-wrote the published papers.

1. INTRODUCTION

Quality of life (QOL) is a universally recognised feature of everyday life. When an individual is confronted with stressful or dangerous circumstances, it is likely that the quality of that individual's life will be impacted or threatened. A cancer diagnosis is a situation wherein both survival and quality of life become major considerations.

Head-and-neck cancer (HNC) is not only life-threatening, it is also is a threat to one's ability to engage socially, or even function normally. Everyday functions such as breathing, speaking, eating and swallowing are especially likely to be compromised.

This thesis addresses the issue of quality of life outcomes for individuals diagnosed and treated for head and neck cancer, and its relevance to treatment options. The phenomenon of head and neck cancer is first discussed below, and is followed by a description of quality of life dynamics and measurement.

The *published works* in this thesis have been taken from a larger body of work encompassing 33 years (1984-2017) by the author. The publications here have been frequently cited by others, and widely recognised as comprising pioneering work in the field. The initial pilot study identified some of the difficulties confronting patients treated for HNC; and identified a need to explore QOL outcomes further, in order to gain insight into, and understanding of, patient-based outcomes. The subsequent publications include reviews of the literature pertaining to QOL in HNC patients, detailed description of the nature and dynamics of QOL as a clinical outcome, and a series of observational prospective studies involving QOL in HNC patients.

Overall, the publications provide a basis for the understanding of the dynamics of QOL in individuals, information for use in patient decision-making and on-going care, and data for hypothesis generation for future interventional studies[v].

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[v] the findings from the research publications in this thesis was incorporated and effectively summarized in the Eugene N Myers lecture [Appendix 2, page 162]

1.1 Background: A Synopsis of Head and Neck Cancer

The term "Head and Neck Cancer" (HNC) is used to describe cancers that arise in the structures of the head and neck – specifically skin, lips and oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses, salivary glands, and cervical oesophagus (*Argiris et al, 2008*) – excluding thyroid, eyes and brain[vi]. HNCs are virtually all epithelial in origin, and predominantly squamous cell carcinoma in type. HNC tumours involve or threaten the basic and essential functions of breathing, communication and eating, and the treatment may also impact on cosmesis, as well as the special senses (smell, taste, vision and hearing). Patients with HNC often have specific needs beyond those of people diagnosed with other cancers (*Semple, 2001; Radford et al, 2004*), and taken together, the disruption to every waking moment of everyday life makes HNC one of the most distressing forms of cancer for patients and their families (*List & Bilir, 2004; Abendstein et al, 2005*).

1.1.1 Incidence

Head and neck cancer is the 6th most common cancer worldwide, with 500,000 new cases – and around 300,000 deaths – each year (*Chaturvedi et al 2013*). Traditionally, the HNC patient profile has been dominated by elderly male patients with alcohol/ tobacco-associated cancers of the oral cavity, pharynx and larynx. In recent times, the incidence of tobacco-related HNCs has declined noticeably, in association with a decrease in tobacco consumption (*Chaturvedi et al, 2011; Stenmark et al, 2017*). Other HNCs have increased in incidence, especially oro-pharyngeal cancer which has increased markedly in the past three decades. This is particularly evident in developed countries, notably among white men less than 60 years of age

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[vi] HNCs may involve thyroid, eye and brain, but clinicians primarily involved in the care of patients with cancer of the thyroid, eye/orbit or brain generally recognize that these tumours are distinct from the broad category of HNC because of unique clinical issues and distinctly different tumour behaviour.

(*Chaturvedi et al, 2013*; *McCarthy et al, 2015; Marur & Forastiere, 2016*).

1.1.2 Aetiology

Life-style choices figure prominently among the factors that carry increased risk of HNC. These include recreational activity such as alcohol and tobacco consumption, and sexually transmitted HPV (*Rettig et al, 2015*). There are also contributing occupational, environmental, and hereditary factors. The major factors are summarized below.

1.1.2.1 *Tobacco and Alcohol.*

The primary risk factors traditionally associated with HNC are tobacco use and alcohol consumption; high tobacco and alcohol consumption is associated with poorer response to treatment, as well as reduced survival (*Pytynia et al, 2004*). The principle sites of alcohol and tobacco-related HNC are oral cavity, larynx and hypopharynx, with an average age at presentation of 60-65 years. The rate of HNC is six times greater in smokers than in non-smokers (*Do et al., 2003*), with a dose-response relationship between the incidence of HNC and the frequency, amount and duration of smoking (*Hashibe et al, 2007*). Alcohol consumption and cigarette smoking often co-occur in patients with HNC (*Mayne et al, 2009*) and these two agents have been found to act synergistically to increase risk of the disease (*Maasland et al, 2014)* but, high levels of alcohol consumption carry increased risk of HNC, even in individuals who have never smoked (*Moyses et al, 2013*).

1.1.2.2. *Hereditary Factors.*

A family history of HNC is associated with about a 70% increased relative risk (i.e. OR 1.68; 95% CI 1.23-2.29) of developing the disease in first-degree relatives (*Negri et al,* 2009). There is evidence of ethnic disparity for some tumours, especially nasopharyngeal cancer (NPC) which is particularly prevalent among Chinese and Polynesian people (*Goldsmith et al, 2002*). High incidence rates persist in Chinese migrants moving to low incidence areas (*Buell, 1974; Yu et al,* *1981*); specific HLA haplotypes are associated with the risk of NPC (*Goldsmith et al, 2002*), and studies based on sibling pairs have shown the presence of an NPC "susceptibility gene" in the HLA region (*Hildesheim et al*, 2002).

1.1.2.3 *Viral Infection*.

Epstein-Barr virus (EBV), and human papillomavirus (HPV) comprise two major aetiologic factors for HNC.

EBV is linked to NPC (*Popat et* al, 2000; *Goldsmith et al, 2002*) and, as noted above, is associated with a genetic predisposition in in the HLA genetic region.

HPV is linked to both laryngeal and oropharyngeal cancer (*Rettig et al, 2015; Boscolo-Rizzo et al, 2018*). Molecular studies have established that the oncogenic HPV subtype 16 is related to oropharyngeal cancer (*Gillison, 2000; Mehanna et al 2010*). The proportion of oropharyngeal cancers testing positive for, and attributable to, the HPV subtype 16 has risen from less than 40% before 2000, to more than 65% by 2010 (*Marur et al 2008; Stenmark et al, 2017*). These HPV-related cancers of the head and neck have been attributed to sexual practices (*Rettig et al, 2015)* and are presenting in patients that are younger and fitter than non-HPV-related HNC (*Stenmark et al, 2017; Howlader N et al, 2017*).

1.1.2.4 *Diet.*

Aside from genetic susceptibility there is case-control evidence of a link between diet and HNC. A diet high in animal fats and low in fruits and vegetables increases risk of HNC (*Maasland et al, 2015*). There is an increased risk of NPC in people that have a childhood diet that contains salted fish (*Morton & Benjamin, 1989*), thought to be related to early exposure to a high content of mutagenic chemicals such as N-nitrosamines (*Yu et al, 1981*).

1.1.2.5 *Other Factors*

Occupational exposure to hazards, such as those associated with leather-work, nickel workers, furniture manufacture and furniture repair, and those exposed to cutting oils, have been shown to have an increased risk of cancer of the nose and sinus cavities (*Roush et al, 1980*). Exposure to wood dust also confers a risk for paranasal sinus cancer, and applies especially to adenocarcinoma of the naso-ethmoid region (*Acheson et al, 1984*).

1.1.3 Treatment and Prognosis

The overall 5-year survival rate for treated HNC is between 50% and 60%. While this is comparable with some cancers (e.g. bladder 50%, Colon 57%, cervix 63%) it is relatively low compared with other cancers, such as breast (78%), uterus (78%), and prostate (84%) (*Cancer Research UK, 2018*). The primary treatment modalities for HNC are surgery and radiotherapy; these are used either singly or as a dual modality regimen. Adjuvant chemotherapy may be combined with radiotherapy. The treatment-associated morbidity generally increases as treatment modalities are added.

Treatment options need to be considered in light of the extent (stage) of disease at presentation, because about 30% of patients present with early (stage I-II) disease and can be managed with single modality treatment (surgery and/or radiotherapy). Advanced disease (stage III-IV at presentation) is more common than early stage disease, perhaps partly because the disease can be difficult to detect in primary care settings, and may be overlooked until the clinical signs are more apparent (*Woollons & Morton, 1995; Alho et al, 2006*). Advanced HNC receives more ‘aggressive’ multi-modality treatment and carries a poorer prognosis (*Keir et al 2007; van der Schroeff et al, 2012*), and is associated with greater post-treatment morbidity

(*Nordgren et al, 2008*). This substantial morbidity related to everyday functioning has made post-treatment care of the HNC patient a very important issue (*Ringash, 2014*), with multidisciplinary input required to try to mitigate the adverse effects of radical surgery and chemo-radiotherapy (C-RT) [vii] (*Chin et al, 2006; Bressan et al 2017*). The introduction of new technological advances has also allowed clinicians to refine their therapeutic endeavours in an attempt to reduce morbidity.

The impetus to obtain better QOL outcomes after surgery was, to a large degree, a driver for the development of an '***organ preservation***' philosophy (*Tufano RP, 2002*).

1.1.3.1 *Minimally Invasive Surgery and Organ Preservation.*

In the 1980s technical advances in endoscopy led to the introduction of the concept of '*Minimally Invasive Surgery*' (*Wickham, 1987*) and '*Minimal Access Surgery*' (Cushieri, 1990). Since that time, endoscopic surgery has evolved further, to be applied for the management of HNC, especially with the aid of the LASER (via '*Trans-oral LASER Microsurgery*' - TLM) (*Steiner & Ambrosch, 2000; Haughey et al, 2011*). More recently, the introduction of a sophisticated endoscopic approach - trans-oral robot-assisted surgery (TORS) - has been added (*Weinstein et al, 2010*). Over the past decade or so, these endoscopic techniques have facilitated widespread involvement of an organ preservation approach in HNC treatment protocols.

Radiation oncologists adopted protocols for advanced tumours, using sequential and concomitant radio-chemotherapy in an effort to avoid the need for radical surgery (*Wang & Knecht, 2011*). Clinical studies have since reported that survival with organ preserving chemo-radiotherapy is not significantly compromised when compared with surgery

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[vii] *See also section 4.2 (Appendix 2), page 173.*

followed by radiotherapy (e.g. *El-Deiry et al, 2005; Chen et al, 2014*). There has been a tendency for organ preservation to be considered a convenient measure for better QOL, but the reality is that treatment-related morbidity, especially following chemo-radiotherapy (*Calais et al, 1999*), can be severe. Thus organ preservation as an outcome is at best only a *surrogate* measure for QOL.

Rather than preserving structure, preservation of function should be the goal (*el-Diery et al, 2005*), as the perceived benefit of a retained organ that has no useful function is probably minimal. Throughout this process, patients' priorities need also to be considered, as some may in fact value appearance or structure over function.

For practical purposes, the issue of organ preservation in HNC has in effect focused predominantly on two anatomical stuctures: the larynx, and the oropharynx. These two structures merit special consideration, as follows.

1.1.3.2 *Organ Preservation: Laryngeal Cancer.*

Total laryngectomy has been the traditional standard of care for advanced laryngeal cancer (*Tufano, 2002*). The pathway to organ preservation in the treatment of HNC was paved in relation to advanced laryngeal cancer, where preserving the larynx using radical chemo-radiotherapy (C-RT) was proposed for stage III and IV tumours, instead of removing the larynx surgically (*Wolf et al, 1991; Genden et al, 2007*).

A principal assumption by the advocates for C-RT is that tissue preservation results in preservation of function (*Gillespie et al, 2004*). Preservation of a normal swallow, retention of a natural airway, and a functioning voice are critical components for laryngeal function (*Greco et al, 2018*); a preserved but non-functioning larynx will be different, but may be no better for the patient than the reality of an absent larynx.

Thus the trade-off becomes one between an absent larynx - with a permanent tracheal end-stoma that carries a dramatic impact for the patient (*Krouse et al, 2004*) - versus a preserved - but often painful and dysfunctional - larynx (*Machtay et al, 2008*). Treatment by C-RT may well be able to avoid a tracheostomy but often a gastrostomy feeding tube is required because dysphagia is such that oral intake is rendered impossible by radiation-induced fibrosis of the pharynx (*List et al, 1999*), and swallowing function has been shown to have the largest impact on overall QOL (DeSanto et al, 1995; Murray et al, 1998).

By comparison, early glottic (laryngeal) cancer has generally been able to be treated with organ preservation using traditional external beam radiotherapy, delivered over several weeks. This treatment can cause discomfort and inconvenience for the patient but preserves an intact, functioning larynx. If radiotherapy fails, total laryngectomy is the traditional default option for salvage although in recent years minimally invasive larynx-preservation surgery has become an option, using trans-oral LASER micro-surgery (*Steiner, 1993*). Here the advent of LASER surgery has enabled small laryngeal tumours to be removed endoscopically without resorting to the previous open surgical partial laryngectomy (*Tufano 2002*).

Minimal access trans-oral laser micro-surgery is now established as a primary treatment option for early laryngeal cancers; this surgery usually has patients reasonably able to go home the following day and resuming normal activities within a week (*Steiner & Ambrosch, 2000*). These treatment alternatives for early laryngeal cancer carry comparable survival outcomes (*Back & Sood, 2008*)[viii].

Just as with early laryngeal cancer, the different treatment options for advanced laryngeal cancer also generally confer comparable survival outcomes, although the pattern of *symptom* outcomes differs more markedly between treatment options for the advanced tumours than the early tumours. Given the comparable survival rates between RT and C-RT on the one hand, and surgery plus adjuvant RT (S-RT) on the other, QOL outcome studies have the potential to facilitate decision-making between competing treatment strategies (*Schwartz et al, 2001*).

1.1.3.3 *Organ Preservation: Oropharyngeal Cancer.*

Traditionally, oropharyngeal cancer treatment has involved radical, open surgery; this is usually associated with substantial morbidity as a result of extensive dissection, massive tissue resection and micro-vascular free flap reconstruction (*Parsons et al, 2002; Bozek et al, 2008*). In an attempt to avoid the morbidity associated with the major surgery, non-surgical treatment protocols for oropharyngeal cancers have been developed (*Dawe et al, 2016*). The initial non-surgical treatment was based on radiotherapy alone, but with disappointing tumour control rates.

With the introduction of C-RT for oropharyngeal cancer, there was improved survival outcomes (*Chen et al 2014*). The C-RT treatment regimen became seen as a preferable option despite substantial associated morbidity (*Calais et al, 1999*). With the advent of transoral LASER microsurgery (TLM) (*Steiner & Ambrosch 2000; Haughey et al 2011*), and

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[viii] This issue is addressed further in a systematic review of the literature that is reproduced in this thesis (section 2.5.1), page 121.

endoscopic-assisted transoral robotic surgery (TORS) (*Weinstein et al, 2010*) a minimal access surgical approach was established that allowed tumour resection without the wholesale trauma of the external approach (*Dawe et al, 2016*).

The refinement of surgical techniques has been matched by advances in radiotherapy (such as intensity-modulated radiotherapy IMRT), that are designed to reduce radiation to tissue that is uninvolved with tumour. Given the distinct treatment options for oropharyngeal cancer, it becomes important to consider patients' concerns about voice and swallowing, while allowing for prognosis (*Wilson et al, 2011; Adelstein et al, 2012*).

Survival outcomes from oropharyngeal cancer treatment appear similar between the non-surgical C-RT and the trans-oral surgery (TLM/TORS) (*Lawson et al, 2008; Monier & Simon 2015; Nichols et al, 2019*), but there is evidence that TLM confers better short-term QOL than C-RT (*O'Hara et al, 2015*). The short-term QOL differences do not seem to persist, as seen in Mowry et al's (*2006*) report where there are no significant difference between C-RT and S-RT in long-term (2-year) overall QOL.

1.1.3.4 *Treatment Outcomes: QOL*

Early studies of QOL in HNC patients emerged in the 1980s, and coincided with the introduction of micro-vascular free-flap reconstruction (*Futran, 2000*) and IMRT techniques (*Intensity Modulated Radiation Therapy Collaborative Working Group,* 2001). Until then, the patients really struggled to cope with the effects of major surgical resection and radical RT[ix].

[ix] *A Pilot Study of QOL Outcomes in HNC Patients from 1984* reported 39% incidence of depression. (See section *2.1; page 25*)

Opportunities to reduce treatment-related morbidity emerged with the advent of:

- refined RT - designed to limit tissue trauma from radiation (*Graff et al, 2007*)
- sophisticated surgical flap reconstruction - designed to improve cosmesis and restore physical functioning (*Bozek et al, 2008*), and
- the principles of Minimal Access Surgery/ Minimally Invasive Surgery (*Cushieri, 1990*) - to avoid the added morbidity resulting from trauma to normal neighbouring tissue and structures in the process of an open access surgical approach

Given the intimate relationship between HNC treatment and the essential functioning of airway, communication, swallowing, and appearance, it has become clear that the assessment and measurement of QOL outcomes is an essential component of the future management of patients with HNC (*Ringash 2017*).

Indeed, once it became evident that survivorship was not being unduly compromised by these new techniques (*Rodrigo et al, 2008; Moore et al, 2009; Arens, 2012*), the focus turned even more to QOL as a tool to assist with 'informed consent' and the decision-making process when considering treatment options.

Notwithstanding the increased number and sophistication of treatment options, many advanced tumours still require multi-modality treatment - including major ablative surgery - with consequential dysfunction and disfigurement (*Hagedoorn & Molleman, 2006*), chronic pain (*Krebber et al, 2016*), and often detrimental effects on the physical, emotional, and social functioning of patients (*Bjordal & Kaasa, 1995; Bjordal et al, 1999; Ringash 2015*).

1.2 Background: A Synopsis of Quality of Life Assessment in HNC

> *"Of all human cancers, (head and neck cancer) is the most distressing, since the head and neck is the site of the most complex functional anatomy in the human body. Its areas of responsibility include breathing, the CNS, vision, hearing, balance, olfaction, taste, swallowing, voice, endocrine and cosmesis. … Consequently, in treating cancers of the head and neck, the effects of the treatment on the functional outcome of the patient need the most serious consideration".* (*Chin et al, 2014*)

1.2.1 QOL as an Outcome.

Survival and cure is the outcome of primary importance for patients with HNC, as reflected in a survey of HNC patients (*List et al, 2000*) which showed that, at the time of diagnosis, 93% of patients considered cure to be the most important outcome, while 56% identified wanting to live as long as possible as a priority. A series of QOL issues (pain, energy, swallowing, voicing, appearance) were also of concern, but at the time of diagnosis it is the threat to life that dominates. As Maas (*1991*) pointed out

> *" ... patients often only think of how to get rid of the tumor, and do not consider the possible consequences of (alternative treatments) on a longer term".*

Only when survival seems assured (or, indeed, if early death becomes inevitable) does the quality of survival assume priority (*Hammerlid et al, 2001*). However, QOL as a clinical outcome measure represents a relatively recent scientific paradigm (*Schipper, 1990*). As such, QOL assessment has not yet been generally incorporated into routine clinical practice (*Mehanna & Morton, 2006a; Browman et al, 2009)* .

1.2.2. *Definition of QOL.*

QOL has been frequently referred to as a concept, and mentioned in relation to health in general and cancer in particular, but it was not specifically defined until the latter half of the 20th century.

By 1995, ten descriptors or definitions of health-related QOL had been identified (*King et al, 1997*). This apparent lack of consensus may have been related to the complex nature of the concept itself, but a relatively simple defining statement that pertains in this thesis is:

> "*QOL is a multi-dimensional construct that represents one's personal, subjective, integrated perception of general well-being*".

Health-related QOL (HRQOL) has a disease as the focus; the QOL impact of a specific disease depends chronicity, the degree to which the disease is perceived as a threat, and the disruption, disability and dysfunction created by the disease and its treatment. Llewellyn et al (*2006*) studied the impact of HNC and its treatment in relation to how patients' perceived QOL is related to their belief systems and coping strategies. They also noted that HRQOL is distinct from individualised QOL, as indeed did King et al (*1997*) who report that HRQOL in adults is related to, but actually distinct from, health status. Cohen et al (*1996*) consider HRQOL as a compromise that reflects pre-occupation with the disease rather than the patients' experience of illness. Their preferred approach is to focus on "existential well-being" rather than HRQOL, especially in cancer patients. This is quite consistent with the definition of QOL used in this thesis.

1.2.3 *Early QOL Studies in HNC Patients.*

A history of QOL assessment in HNC patients was published in 1995 and forms part of this thesis[x]. Stated simply, early QOL measures were basic, and slow to evolve and it was not generally appreciated that the patient was the best person to assess and self-report on their QOL status. Priestman and Baum (*1976*) published a landmark study that used a simple 10-

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[x] see section 2.2.1: *Evolution of quality-of-life assessment in head-and-neck cancer (page 32)*

item linear analogue scale for recording patient-based results of breast cancer treatment.

In 1983 the first reports of multi-dimensional QOL-related patient-based outcomes for HNC patients appeared (*Drettner & Ahlbom, 1983; Natvig 1983a, 1983b*). In 1984, a study of QOL in HNC patients in Liverpool, UK was published by the author and is included in this thesis[xi], and was one of the first quantitative studies of QOL in HNC to appear in the literature. This work provided the stimulus to embark on a program to further explore the nature and dynamics of QOL outcomes in HNC patients and the relevance for clinical practice. This thesis contains the series of studies and reviews published as part of that process.

1.2.4. *Rationale for QOL Assessment.*

For a QOL assessment to be clinically valid, it needs to be broad-based, patient-generated and sensitive to patients' current and changing status. This is the basis for conducting a QOL enquiry, but the rationale for doing so involves more[xii]. With a reliable, valid and responsive QOL measure, one can assess the success of treatment, aside from survival. In Osoba's words (*1991*):

> *"... the effects of therapeutic strategies and of therapy itself on quality of life are not certain until they have been measured".*

Thus QOL becomes the benchmark for comparing patient outcomes from two alternative treatments that produce equivalent survivorship; the treatment that is associated with the preferred post-treatment QOL profile will be favored (*Efficace et al, 2003*). Issues arise when a

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[xi] see section 2.1: *Quality of life in treated head and neck cancer patients: a preliminary report (p age 25)*

[xii] see section 2.3.1: *Rationale and development of a quality of life instrument for head and neck cancer patients (page 57).*

treatment provides a superior survival, but produces considerably more disability or dysfunction. Much effort has been directed at improving the reconstruction techniques to aid rehabilitation and lessen the adverse consequences of intensive, ablative, "heroic" surgery. The assumption is that repairing tissue defects will reduce dysfunction and disfigurement, and thereby improve QOL. Certainly there is evidence that at least some function is restored if appropriate reconstruction measures are taken (*Vaughan, 2009*).

Survival is the appropriate primary outcome measure for a life-threatening condition such as HNC, and post-treatment survival curves are generated on the assumption that each patient contributes equally to the curve for as long as they remain alive. In fact, *not all patients are surviving equally well*. Thus physical and psychological functioning may be compromised to the extent that an individual's life-utility is markedly impaired. Barofsky and Sugarbaker (*1990*) note that "… *death and complete health are not extremes of a linear continuum for quality of life states*", but rather that there is considerable variance in global QOL among cancer patients as they progress over time.

QOL assessment allows the *qualitative* aspect of survival to be considered, such that quality outcomes can be compared between treatments, and between patient groups. This information can be used to inform patients as part of their preparation for treatment. When an alternative treatment carries equivalent survivorship prospects but varying life-utility, QOL becomes an important factor in clinical decision-making; here the likely QOL outcomes can be weighed together with information about prognosis (*Rathod et al, 2015*). This touches on the need for clinicians to set realistic expectations for patients, and in doing so, to prepare patients for managing the potential gap[xiii] between expectations and experience.

Another intriguing aspect of the rationale for assessing QOL in HNC patients relates to its emerging role for QOL in determining prognosis. Browman et al (*2009*) discuss the finding of QOL measurement as an independent prognostic indicator for survival in patients with early-stage (I and II) squamous cell head and neck cancer, based on data from randomised HNC trials. An earlier report from the Auckland observational QOL cohort study had also reported a similar correlation between post-treatment QOL and survival [xiv].

In summary, the *rationale* for measuring QOL comes down to: obtaining and providing data on outcome from a patient's perspective; furnishing a basis for treatment preference (thereby assisting in the informed consent process); monitoring progress after treatment to identify patients potentially at risk; and providing data to assist with comparison of patient-reported outcomes (PROMS) between centres and between different treatment protocols.

1.2.5 *The "Gap theory" and Global QOL*

One's overall, or 'global', QOL is an important dependent variable. The key to this personal integration of overall QOL is the perceived discrepancy between the reality of what one has on the one hand, and what one wants, expects, or has had on the other hand (*Padilla et al, 1988; Gough, 1994; Fisher SE 2009; Rathod et al, 2015*). Calman (*1984, 1987*) refers to the concept embodied in this process as the *"gap theory"*, being the gap between reality and expectations.

[xiii] This concept of the 'gap' is a very important consideration in the understanding of QOL dynamics *(see next section; 1.2.5, overleaf).*

[xiv] *the publication concerned ("Does Quality of Life predict long-term survival in head and neck cancer patients?") is included in this thesis; see section 2.4.4* (page 113).

This gap needs to be self-reported, because observers cannot rate it accurately (*Deschler et al, 1999*). A patient-rated global QOL measure will take account of the gaps between expectations and reality, the relative importance of those gaps to the individual, and how the individual copes with these[xv].

1.2.6 *Principles of QOL Measurement*.

QOL measurement in cancer patients should involve self-report by the patient and not only account for disease- and treatment-related symptoms, but also incorporate several other domains as well as a global QOL rating (*Sprangers et al, 1993*), and follow the QOL ratings over time. It is important to recognize that QOL is *more than the sum of its parts* (*Gourin 2008*), and that no single contributing domain item should be used as a surrogate for overall QOL. If, say, swallow function is the outcome of interest when comparing different treatments (e.g. *Gillespie et al, 2004*), then this outcome measure relates to swallowing, but not necessarily to overall quality of life. Another example is 'voice-related quality of life' where in fact the subject of interest is voice, rather than overall QOL as such.

There are several instruments that have been described for measuring QOL in HNC (*DeBoer et al, 1999; Ringash & Bezjak, 2001*). Silveira et al's (*2010*) analysis shows that different instruments may measure similar things but in somewhat different ways. This is also reported in other studies (e.g. List et al (*1996*), Hassan and Weymuller (*1993*) and D'Antonio et al, (*1996*)) where support emerges for the view that various tools are effectively different routes to the same destination.

Nevertheless, there is a minimum data checklist that covers essential parameters to be

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[xv] See also discussion in section 1.2.6.1: Global *versus* Component measures

included for a QOL instrument to be suitable (*Ringash & Bezjak 2001, Sprangers et al, 2002; Efficace et al, 2003; de Almeida et al, 2013; Rathod et al, 2015*). Indeed, a QOL assessment instrument should attend to several important operational requirements, and these are described in section 1.2.7 below.

There are also basic Principles of QOL Assessment that underscore the phenomenon - namely, the issue of Global versus Component measures, the length of Questionnaire, and the distinction between Generic and Disease-specific instruments:

1.2.6.1 Global *versus* Component measures

The issue of overall (global) QOL was introduced above in section 1.2.5. Some authors (e.g. *Cella & Tulsky, 1990; Gotay & Moore, 1992*) have discussed and developed the principles regarding component-versus-global QOL measures. A 'global' score can be considered a dependent variable and a ready means of comparison between treatments and between patient groups. Assessment at the multidimensional, or component, level is required to assist with understanding and interpretation of overall QOL scores.

Studies of QOL outcomes have described an 'aggregate score' or summation of component parts, but this is not necessarily a patient-generated global QOL score. An aggregate QOL score is likely to best reflect global QOL if the items from the domains represent good content and construct validity.

Ideally the component QOL measures most important in determining general well-being – or global QOL - would be identified if both component and global data are captured, thus enabling health-care workers to act upon the results (*Aaronson, 1990*). For example, pain and depression can be managed with medication, and measures that incorporate allied healthcare workers (physiotherapy, health psychology) can be introduced to manage physical and psycho-social concerns.

Fries & Spitz (*1970*) use the term "heirarchy of patient outcome" to describe the relationship between global QOL, its contributing domains and the component measures, and emphasise the importance of recording both global and component scores. One such example is the EORTC-QLQ30/ QLQ-H&N35, which is a popular outcome measure for many researchers of QOL in HNC patients. It has several questions that relate to important domains, and two items on overall QOL that are summed to produce a global QOL score. A slightly different approach to deriving a measure of overall QOL has been favoured by Coyne et al (*2007*) who used the 5-item Emotional Well-Being subscale of the FACT-G 27-item QOL instrument to generate a surrogate global QOL.

King et al (*1996*) compared global QOL in a group of 98 cancer patients using two different validated questionnaires. One instrument (the EORTC QLQ-C30) had a single item global QOL question, the other (FLIC) used a 'total' score generated from 7 sub-scores. The correlation between QLQ-C30 global QOL versus the FLIC total score was 0.76. FLIC also has a 3-item scoring for "current health", (a global perspective concept) and the correlation between the two FLIC items ('total' and 'current') was high, at 0.79. King et al (*2014*) also examined the correlation between QLQ-C30 global QOL and the FACT-G total score (27 items) and found a correlation of 0.69.

The EORTC group recently examined so-called 'higher order' scoring for their QLQ-C30, and generated a single score from 27 items, leaving out global health and financial concerns questions *(Geisinger et al, 2016)*. Their conclusion was that a summary score is "robust".

Given the above considerations, the issue of "component-versus-global QOL measures" is contentious to a degree and, at this stage, somewhat unresolved[xvi].

1.2.6.2 Questionnaire Length

In general, one should try to gain information about as many different domains as possible, rather than to obtain a great deal of information and data from a small number of domains (*Moinpour et al, 1989*).

A comprehensive enquiry into all contributing domains can result in a very arduous, time-consuming and unwieldy questionnaire, but the risk of a short enquiry is that it may omit important components. Grant et al's review (*1990*) of 14 different QOL evaluation tools revealed a range from 1 to 235 items. Single-item measures – such as the functional status scale of Karnofsky (*1948*) and the linear analogue self-assessment scale of global QOL - demonstrate the limited information available from such instruments.

There has since been several analyses of QOL instruments (*McSweeney & Labuhn,1990; Ringash & Bezjak 2001; Pusic etal, 2007; de Almeida et al, 2013; Ojo et al, 2012; Rathod et al, 2015*). Most questionnaires cover several domains although Mehanna and Morton (*2006*) studied patients' views on 4 validated QOL questionnaires for HNC patients and found that whilst almost half preferred a particular specific questionnaire, no single preferred instrument was consistently identified by the patients. When prompted, most

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[xvi] *"Agreed - it's psychometrically contentious to include such a mixed bag of concepts into a single summary score. However, empirically there's a lot of correlation ... The EORTC held off for many years on calls for a 'higher order' summary score – they are conservative and cautious group. But eventually it happened ... A systematic review would be interesting, but a lot of work".*

(Professor Madeleine T. King, *personal email communication, Feb 21, 2018*) would prefer a short questionnaire (<20 items). Depending on the instrument, between 11% and 18% of responders considered the questionnaire to be too long, but the length of the instrument apparently did not affect perceived usefulness.

1.2.6.3 Generic *versus* Disease-specific Instruments

It is agreed that no single instrument is appropriate for all QOL HNC studies (*Gourin 2008; Deschler et al, 1999*) and that "*choosing an instrument is an exercise in trade-offs*" (*Moinpour et al, 1989*).

Generic questionnaires cover a broad range of items in different domains, but tend to lack important questions specific to any cancer site or type so that sensitivity and responsiveness to important clinical change may be lacking. Generic scales assess concepts that are relevant to everyone, but are not specific to any age, disease or treatment group. D'Antonio et al (*1998*) consider that a generic QL instrument contributes unique information about QOL that is not captured in disease-specific measures.

"Disease-specific" instruments are tailored to the clinical situation and designed for sub-sets of HNC patients, such as those involving skull-base pathology (de Almeida et al, 2013). Ware (*1991*) believes that "*the overwhelming answer ... is to use both generic and disease-specific measures and to analyse them together*". In any event, to ensure content validity, questionnaires in cancer patients need to be at least to some degree site-specific, to accommodate the widely varying nature of disease- and treatment-related symptoms.

1.2.7 Operational Characteristics

There are three factors that represent the principle requirements for conducting a QOL research: self-reporting, subjective but quantifiable data, and multidimensional enquiry.

1.2.7.1 Self-administered [*'Self-Reported'*] Questionnaire

Patients' subjective assessment should form the preferred source for primary data, while objective measures (e.g. measures of swallowing; *Logemann et al, 1989*) and observer data (e.g. the disfigurement scale (*Katz et al 2000*)) can provide important useful supplementary information. Data from family or partners can also be useful, but it should be recognised that the perception of others is different from that of the patients themselves. (*McSweeney & Labuhn, 1990, Richardson et al, 2015a, 2015b; Richardson et al 2016*).

Clinical observers have a perspective that usually relates to the on-going clinical management of the patient but there is evidence that clinical impressions by observers can be misleading (*Collins, 2000*), and that patients' perception of their health priorities are different from those of health care workers (*Demez & Moreau, 2008*). Research-oriented observers are often interested in objective measures that can be used to monitor progress reliably and validate subjective assessments, but Ware is unequivocal: *"... biologic indicators are not adequate proxies for measures of functional status, well-being or other quality-of-life concepts or to changes in these variables over time."* (*Ware, 1991*).

Indeed, the use of objective measures stems from a "beneficence model" of healthcare which assumes that health professionals know what promotes or protects the best interests of patients (*Kinsinger, 2009*). It is likely that patients are in a better position than clinicians to define good and harm as it relates to them and that objective measures should be regarded as only surrogate indicators of QOL.

1.2.7.2 Subjective, but Quantifiable Data

The science of psychometric and clinimetric measures has developed to the stage where there can be a considerable degree of confidence in validated self-administered questionnaires. Kirshner and Guyatt (*1985*) have developed a framework for evaluating health indices such as QOL assessment, in which they describe the basic steps for developing an instrument. A questionnaire subjected to this kind of rigor will be robust and able to provide meaningful data for analysis.

Objective measures of functions such as swallowing, speech, shoulder movement and muscle strength measures are quantifiable and reliable. However the impact that a specific dysfunction may have on a patient will vary according to many factors, so that objective measures are not necessarily valid indicators of patients' perceived global QOL. Ware (*1991*) points out that regression models of objective measures of function generally explain less than half of the variance in the patients' qualitative rating of that function.

List et al (*1990*) produced a reliable performance scale that can discriminate among different levels of functioning across a broad spectrum of HNC although List et al's subsequent (*1996*) study of laryngeal cancer patients shows "*virtually no relationship between performance outcome and emotional, social, functional or overall QOL.*" Rather, patients cope "… effectively with both acute and residual disease and treatment effects … to the extent that these residuals do not globally interfere with life satisfaction".

1.2.7.3 Multidimensional Nature.

A critical feature of QOL is that it is a multi-dimensional construct, and according to McSweeney & Labuhn (*1990*), single-perspective, uni-dimensional, or single-instrument evaluations of QOL are not adequate.

The multidimensional QOL construct has contributions from several different aspects of life ("domains") (*Gotay & Moore, 1992; Aaronson 1991*). The major domains may be considered in four groups: physical function, psychological state, social interaction, and somatic sensation (*Schipper, 1990; Ware, 1991*), although there is a potential for several more distinct QOL domains, such as:

- sexuality/intimacy (*Cella & Tulsky, 1990*)
- domestic/ family domains (*Fraser, 1993*)
- occupational functioning (*Cella & Tulsky, 1990; Fraser, 1993*)
  Schipper et al (*1990*) regard occupational functioning as a sub-set of physical functioning.
- economic (*Fraser, 1993*)
  Schipper (*1990*) regard the inclusion of the financial component as an "*inappropriate and possible distorting addition*" because financial consequences are dependent on the structure of community social support programs rather than the biology of the disease.
- spiritual (*King, 1997*)
  only 1 of 18 studies in Gotay and Moore's (*1992*) review of QOL in HNC included a spiritual dimension.

In practice, the specific domains that contribute to overall, or global, QOL will vary according to clinical and socio-cultural circumstances (*Aaronson 1990*). The dimensions to be included in any study would depend on the study aims, and the profile of the population under review. Regardless of the number of domain items, the net effect of those scores on a patient's QOL will be expressed by way of a global measure.

Advantages of the multidimensional approach are: (*Aaronson, 1990*)

- the positive and negative effects of a given treatment can be disentangled;
- different effects at different stages may be identified, even in the presence of a constant global QOL score which would be insensitive to such changes;
- both anticipated and unexpected effects can be documented by monitoring the different components of QOL

As mentioned in section 1.2.6.1, summed or aggregate scores can produce a “total” QOL score, but not necessarily a valid global QOL score, because there may be items of importance to the patient that have not been accounted for and which can have an impact on general well-being (*Gourin, 2008*). The impact of specific ratings can be weighed against the global QOL and their relative importance for any individual patient can readily be assessed. In other words, in an ‘integrated’ global measure, the patients can assign their own weighting to the various domain functioning.

1.2.8 *Variation Over Time*

An essential feature of research into QOL of HNC patients should be the importance of longitudinal studies (*Sprangers et al, 1993*). De Graeff et al (*2000*) have discussed the difficulties of interpretation of data relating to long-term QL outcomes effects from cross-sectional studies of HNC, and King et al (*1997*) state unequivocally that “*there is no substitute for longitudinal assessment in QOL research*”.

It is also well recognised that QOL and health status may not be congruent. This apparent paradox – where patients can be severely disabled by treatment and recurrent tumour, yet exhibit a relatively good QOL while other patients who are free of disease and who have minor treatment-related symptoms may be very distressed with a poor QOL (*Gough, 1994*) – is not unusual. This paradox has been referred to as “response shift” (*Breetveldt et al 1991; Sprangers et al, 1999; Rathod et al, 2015; Ringash 2015*), a term initially coined by Howard et al (*1979*). This phenomenon is an important dynamic in patients with cancer, and emphasises the importance of longitudinal studies in which patients can be used as their own internal controls (*Schipper et al, 1990*).

A baseline study is essential so that future assessments can be weighed against the initial status. The pre-morbid characteristics that a patient brings to the initial consultation are very important in relation to later events (*de Graeff et al, 2001*). Ideally, a first assessment should be after the time of diagnosis but before the beginning of treatment (*Davies et al, 1986*). The critical QOL value is often not any particular score a patient provides at a specific time, but rather the change in that patient's score *over time*.

Traditional longitudinal HNC studies differ from those that have QOL-outcomes as the focus, in that the former select survival and disease-free curves as primary outcomes and derive a single data point from each patient entered in the study. That data point is only acquired when the patient either dies or fails therapy (Schipper et al, 1990). Thus a patient can be lost for many years and yet all the survival data can be retrieved if he appears in the clinic one day for follow-up. On the other hand QOL data - because of its fluctuating nature and given the issue of recall bias (*Coughlin SS, 1990*) - cannot be reliably recovered once time has passed. As a consequence, information on the determinants of later QOL is lacking.

With validated QOL data, followed over time, one may add materially to the information on outcomes from randomised clinical trials (*Browman et al, 2009; Ringash, 2017*). Moreover, one may purposefully pursue interventions to improve QOL status after treatment (*Aaronson, 1990; Richardson et al, 2017*), and possibly also survivorship.

2. PUBLISHED WORKS

2.1 Pilot Study of QOL Outcomes in HNC Patients

Morton RP, Davies ADM, Baker J, Baker GA, Stell PM (1984) Quality of life in treated head and neck cancer patients: a preliminary report" *Clin Otolaryngol* 9:181-185.

This publication was one of the early studies to investigate QOL outcomes in HNC Patients[xvii]. The sample was especially selected, in order to reduce patient variation, and comprised male patients of a similar age that previously had been successfully treated for bucco-pharyngeal cancer. At the time that this study was conducted we had no reliable information regarding how age and gender might affect perceived QOL, so we chose to reduce variation in these two factors at least.

The results showed that half of the subjects had dysphoric mood, and 40% were clinically depressed. We had anticipated some degree of psychological distress may be evident, so we ensured that reliable and valid psychometric instruments were included in our assessment. The results were more striking than we expected, and this study has been cited frequently[xviii] because of the high rate of clinical depression.

We examined several other domains and showed construct validity in relation to functional disability and the Karnofsky score, both of which were significantly related to treatment. This early study demonstrated the multi-dimensional nature of QOL[xix] and confirmed the importance of including psycho-social assessment as well as symptom-based measures in QOL outcomes research, at a time when there was very little information in the literature.

This work also identified the need for long-term longitudinal studies of QOL in HNC at a time when most publications were cross-sectional, or short-term prospective studies.

The author set about planning a longitudinal study, after returning to Auckland in1984; the result can be seen from the four publications included in section **2.4** of this thesis**.**

[xvii] see **2.2.1**: Morton RP. "Evolution of quality-of-life assessment in head-and-neck cancer".

[xviii] 131 citations, excluding self-citation (*Researchgate 2018*).

[xix] See section **1.2.7**, specifically 1.2.7.3 (page 24)

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2.2 Review of the Literature on QOL in HNC

This section comprises the three publications that address the history and the nature of QOL assessment in HNC patients as reported in the literature prior to 2000:

- "Evolution of Quality of Life Assessment in Head and Neck Cancer"
- "Quality-of-life measures in head-and-neck cancer: capabilities and caveats"
- "Quality of life outcomes in head and neck cancer patients"

2.2.1 Morton RP. "Evolution of quality-of-life assessment in head-and-neck cancer". *J Laryngol Otol* (1995) **109**:1029-1035 [xx].

This paper is the first publication to comprehensively review the development of QOL assessment in HNC patients. It was published 10 years after our initial pilot study[xxi] and helps to place that first pilot study in context.

The historical review shows how assessment of QOL began in clinical oncology practice about 50 years ago. Early QOL studies in HNC patients were narrative accounts and cross-sectional studies; these were followed initially by simple quantitative measures of various parameters or isolated QOL domains, and only later were prospective longitudinal multi-dimensional studies pursued.

More recently the incorporation of QOL assessment has been included (as a secondary outcome) in randomised HNC clinical trials (*Browman et al, 2009; Ringash, 2015; Ringash, 2017*).

[xx] This publication has been cited in the literature by others 64 times (*Researchgate, 2018*)

[xxi] see section **2.1,** page 25

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2.2.2 Morton RP. "Quality-of-life measures in head-and-neck cancer: capabilities and caveats." *Curr Oncol* (1995) **2**: 77-83.

This paper comprises a review of the nature and variance of QOL domains and a critical appraisal of the strengths and weaknesses of QOL assessment in HNC patients, using previously published QOL studies as examples.

The 'Gap Theory' (*Calman, 1984, 1987*), was mentioned earlier[xxii], and is discussed and expanded upon in this paper, emphasising how this concept is central to the core understanding of QOL dynamics. Indeed, the Gap Theory forms the basis for much of the rationale regarding the manifestation of patients' perceived global QOL (*Ferrans, 2007*). Hence most of the QOL outcomes that are reported in sections 2.4 and 2.5 of this thesis can be explained by the application of the Gap Theory.

In principle, QOL can be improved if a patient's gap between expectations and experience is reduced (or, ideally, closed). Efforts to close the gap may involve strategies to enhance or improve functional status, or modify behaviour to avoid specific dysfunction (e.g. adjusting diet). On the other hand various forms of education and psychotherapy - where patients learn to engage positive coping strategies – may also reduce the gap. There is a growing body of scientific evidence to support both the former (*Greco et al, 2018*) and the latter processes (*Semple et al, 2013*).

[xxii] see **2.2.1**: Morton RP. "Evolution of quality-of-life assessment in head-and-neck cancer".

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2.2.3 Morton RP, Izzard M (2003) Quality of life outcomes in head and neck cancer patients" *World J Surg* 27: 884-889.

This paper[xxiii] reviews how QOL instruments may be utilized, given the heterogeneous nature of HNC and the importance of allowing for differences in relevant QOL domains according to tumour site. The principles of QOL assessment are described in some detail, emphasizing the importance of longitudinal studies, and disease-specific multidimensional instruments.

Oral cancer and ***Laryngeal cancer*** are used as examples of how QOL outcomes may vary by tumour site. A potential pivotal role is identified for QOL assessment in relation to *organ-preservation* in laryngeal cancer, and to *surgical reconstruction* in oral cancer.

The issue of laryngeal organ preservation was very topical at the time of this publication (*Ferlito et al, 2000; 2002) and* has since also been the subject of much discussion in the literature (e.g. *Loughran et al, 2005; Goor et al, 2006; Genden et al, 2007; Hutchison et al, 2008*). Organ preservation has also been discussed earlier in the Introduction to this thesis[xxiv].
The QOL impact of surgical reconstruction in oral cancer has also been the subject of studies by several authors since this paper was published (*Van Cann et al, 2005; Nordgren et al, 2008; Bozek et al, 2009; Chang et al, 2013; Ling et al, 2016*).

Another dimension to QOL assessment was also discussed in this paper, namely *utility* of QOL as it relates to survivorship. This gives rise to the concept of life-utility, or Quality-Adjusted Life-Years (QALYs). The QALY measure is used as a moderator for reporting survival outcome; utility scores have been described in relation to HNC by other authors, subsequent to this

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[xxiii] The final publication is available at Springer Nature via http://dx.doi.org/DOI: 10.1007/s00268-003-7117-2.

[xxiv] See section **1.1.3.2**

publication (*Ringash et al 2007; Konski et al 2009; Ringash 2015*).[xxv]

The principles expressed in this paper have been cited and generally accepted by many others[xxvi]. In this paper we have stated that, at that time of publication, QOL assessment in HNC was still "***in it's infancy***". For example, only one systematic review of QOL outcomes in HNC had been published up to that time (*Ringash & Bezjak, 2001*). In that review of the literature 114 papers were found that used the terms QOL and HNC in the text. A minority (42) described a QOL questionnaire, and 8 HNC-specific QOL instruments were found[xxvii].

In the 15 years following this publication, several systematic reviews have been published (*Pusic et al, 2007; Ojo et al, 2012; Lang et al, 2013; Semple et al, 2013; de Almeida et al 2014; Humphris et al 2014; Rathod et al, 2015; Dawe et al, 2016; Maggiore et al, 2017; Bressan et al, 2017; Smith et al, 2017; Verma et al, 2018; Greco et al, 2018; Richardson et al, 2018*).

[xxv] In addition, an earlier study by Ringash et al (2000) used the Time trade-off technique to address the issue of quality-of-life-adjusted survival times in a cohort of 120 laryngeal cancer patients, patients, but this work was overlooked at the time.

[xxvi] This publication has been cited in the literature by others 82 times (*Researchgate, 2018*)

[xxvii] one of the QOL questionnaires reported was the Auckland instrument, first published in 1995 (see section **2.3.1;** page 57)

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2.3 **Development and Validation of the Auckland QOL Questionnaire**

This section contains two publications concerned with the initial analysis of the Auckland QOL Instrument. The clinimetric and/or psychometric characteristics of the various items and scales are reviewed and the reliability and validity of the questionnaire is examined.

- Rationale and development of a quality of life instrument for head and neck cancer patients
- Validation of quality of life measures in head and neck cancer patients

2.3.1 Morton RP, Witterick I (1995) Rationale and development of a quality of life instrument for head and neck cancer patients. *Am J Otolaryngol* 16: 284-293.

This paper describes the rationale[xxviii], domains and essential characteristics of QOL questionnaires together with clinimetric and psychometric properties required for QOL study[xxix]. Clinical scenarios are used to illustrate the trade-off between survival and QOL.

This paper also introduces the General Health Questionnaire (GHQ), as applied to HNC research. The GHQ is a validated screening tool for psychological distress, and this paper is the first to have applied this to HNC patients. Aarstad et al (*2014*) more recently reported an analysis of the use of GHQ in a QOL questionnaire for a cohort of successfully treated HNC patients, and found that the GHQ sum scores uniquely predicted survival when adjusted by health-related QOL[xxx].

The second part of this paper describes the initial work on validation of the Auckland QOL instrument in a pilot study of 84 patients. This work was included in a structured review of QOL instruments for HNC patients (*Ringash & Bezjak, 2001*). In that review, the small number for test-re-test reliability analysis was noted, and the limited information regarding the various non-psychosocial domain items was considered to restrict assessment of face validity and content validity.

[xxviii] It is worth noting here, when considering the clinical rationale for studying QOL issues, that table 1 is a composite of informal opinion conveyed to the authors by colleagues, when discussing QOL issues in relation to HNC management. As such, the table should be viewed as an unattributed narrative account of prevailing attitudes.

[xxix] The appendix to this paper also provides an aide-memoire for the taxonomy used in QOL research.

[xxx] The relationship between QOL measures and survival is also reported in a publication that forms part of this thesis (see section **2.4.4**). GHQ was included in that analysis, and discussed further in the preamble discussion, to that paper (pages 111-2)

Those issues were addressed in our subsequent validation study (section 2.3.2). Ringash and Bezjak (*2001*) also noted some inconsistent scaling of domain items that they considered might confuse patients, but the results in this initial report, and the later longitudinal studies (section 2.4) support the construct validity of this instrument, thus mitigating the response scaling issue.

Current Reviews

Rationale and Development of a Quality-of-Life Instrument for Head-and-Neck Cancer Patients

Randall P. Morton, MBBS, MSc, FRACS, and Ian J. Witterick, MD, FRCSC

> *The ordinary patient goes to his doctor because he is in pain or some other discomfort and wants to be comfortable again. . . . The doctor on the other hand wants to discover the pathological condition and control it . . . The two are thus to some degree at cross purposes. . . . The good doctor therefore has to learn to serve two objects at the same time—the diagnosis and treatment of the patient's ailment on one hand, and to keep him comfortable on the other.*
>
> —*Wilfred Trotter (1872-1939)*[1]

It is a paradox that a patient is treated on the basis of the nature of presenting symptoms, but that success is generally measured in terms of control of the underlying pathology. If the underlying process is adequately controlled, then the outcome is traditionally recorded as "successful," regardless of the patient's satisfaction with the results. In fact, the physicians' assessment of treatment outcome and patient satisfaction is frequently different from the patients' perceptions.[2-5]

With the present trend of increasing requirements for quality assurance and clinical audit, it is likely that some measure of patient satisfaction will be required of clinicians in the future—especially for those patients undergoing radical and expensive treatment for conditions such as head-and-neck cancer.[6-8]

Quality of life (QL), which may be regarded as subjective well-being (defined further in part II of this article), has become an important patient-oriented outcome measure in cancer treatment today,[4,7-9] attracting hundreds of publications in the medical literature each year.[5] The only situation in head-and-neck oncology where QL issues may be unimportant is when a treatment is very likely to be curative and also promptly restores the patient to his or her premorbid state of "normal living."[9]

Many clinicians regard QL data as "soft" and therefore unreliable.[8,10,11] The reality is that QL measurement lies within the realm of "clinimetrics," which is the science of arbitrary scales as measures for clinical phenomena that cannot be expressed in the customary dimensions of laboratory data.[12,13] The APGAR score is an example of clinimetrics, which now has universal acceptance among clinicians. Most QL instruments that have been used in cancer patients show sound psychometric properties, and their usefulness in cancer sites other than the head and neck has already been established.[4,14] Even given that QL can be measured with instruments that are reliable, valid, and sensitive, there are varying opinions about the application of QL assessment in cancer patients. They include two somewhat conflicting views: (1) enhancing the QL of patients is a part of the treatment process, and (2) the proper goal is to cure the disease, and to do research on the QL, one must choose between QL or survivorship.[15] A third position is the following: QL assessment is important, but physicians are only respon-

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sible for treatment-related items within the QL construct, and enquiry of such things as economic factors or psychological well-being, is inappropriate unless one intends or is able to act on the results (B. J. Cummings, personal communication, March 1995).[16]

In the first part of this article, we examine the rationale behind QL measures in head-and-neck oncological practice and address the opinions detailed above in that light. In the second part of this article, we discuss the technicalities of developing a QL instrument for head-and-neck cancer and report results from a pilot study in which such an instrument was tested.

Terms used in this article that the reader may be unfamiliar with are explained in the Appendix (page 291).

RATIONALE

The Clinical Problem

Survival is the appropriate primary outcome measure for a life-threatening condition such as head-and-neck cancer. Considerable dysfunction and disability may follow the treatment, but this is often regarded as a compromise, or "price to pay" for a cure. Of course, survival "at any cost" has always been inappropriate,[17] and if two treatments produce equivalent survivorship, then the treatment which is associated with a better QL, or lower morbidity, will be favored.[18]

Concern arises when a treatment provides a superior survival, but produces considerably more disability or dysfunction.[7,11,15,19,20] Therefore, recent developments in head-and-neck surgery have been directed at improving the reconstruction techniques to aid rehabilitation and lessen the adverse consequences of the more intensive, ablative, "heroic" surgical efforts. The assumption is that replacing excised tissue will reduce dysfunction and disfigurement, and thereby improve QL. There is good evidence that function is restored if appropriate reconstruction measures are taken,[21,22] but little evidence at this stage to demonstrate whether QL improves or not as a result.

On the other hand, radiotherapy initiatives have focused on organ preservation by using more aggressive regimens for advanced disease.[18,23,24] The assumption again is related to presumed better function, and therefore (assumed) better QL, if the organ remains intact rather than if it is excised. This concept is intuitively appealing but again is not yet proven. Clearly, QL assessment is relevant but considerably more research needs to be done before it can be used with confidence as a determinant for treatment. Unfortunately, much of the literature relating to QL research in head-and-neck cancer has been poorly defined or of limited scope and generally has not tested several commonly held assumptions that many head-and-neck surgical and radiation oncologists hold today.

The Assumptions

Assumptions in common use in head-and-neck oncological practice today are generally based on personal bias, or on impressions or invalid deductions taken from limited data. The prevalent assumptions are summarized in Table 1. Some of them will be valid, but confirmatory evidence from clinical research is lacking so far. Nevertheless, head-and-neck cancer reports continue to invoke the term "quality of life" in support of a particular treatment or reconstructive option.[25-27]

The controversy surrounding the management of advanced laryngeal cancer is an example of this debate.

TABLE 1. Assumptions That Prevail Among Clinicians Treating Head-and-Neck Cancer

1. Ablative, disabling surgery is justified because of the devastating effects of uncontrolled head-and-neck cancer.
2. Impairment of functional status, such as speech and swallowing, will adversely affect QL.
3. Patients will accept and cope with considerable disfigurement and disability in return for a chance of survival, or relief of pain and discomfort.
4. The effects of major ablative surgery are so severe that it cannot be justified.
5. If a patient can return to work his QL will be better.
6. A poor general condition represents a poor QL.
7. Giving a patient the diagnosis of cancer will lower his or her QL.
8. Treating minimal (T_1) disease will not have any substantial impact on QL.

Advanced laryngeal cancer example. There is evidence that a combination chemotherapy-radiotherapy regimen for advanced laryngeal cancer confers a survivorship equivalent to that obtained by surgery (laryngectomy) alone.[23] Some patients treated initially with chemoradiotherapy will go on to have a laryngectomy, but a moderate proportion of the patients will not require surgery at all.[23,24] Therefore, the chemotherapy-radiotherapy is preferred because more people retain their larynx. This assumes that the adverse effects of chemoradiotherapy on a patient's QL are less than those incurred after laryngectomy. However, there are no reliable data to compare the QL of a laryngectomee with an equivalent patient treated by radiotherapy. The only report to compare radiotherapy with surgery as treatment for laryngeal cancer[28] was seriously flawed, and its conclusions in favor of radiotherapy cannot be supported on the data provided.[29]

Stam et al[30] recently reviewed the literature relating to QL status after laryngectomy and concluded that it is unclear what one is to make of the various claims about the importance of medical and surgical interventions, speech therapy, communication factors, and social support on the outcome of laryngeal surgery. There is an increasing body of evidence to indicate that psychological well-being is associated with adequate preoperative counseling and a preoperative visit from a laryngectomee.[30-32]

McNeil et al[33] conducted an inquiry of healthy volunteers (most of whom were not typical of the laryngeal cancer patient profile) who were given a hypothetical diagnosis of advanced laryngeal cancer. They wanted to determine how much survival people would be prepared to sacrifice in return for retaining their voice. The results showed that people were prepared to forgo some survival time in favor of larynx preservation. However, laryngeal cancer patients' priorities have been shown to be different from healthy observers' priorities.[2] Although surveys such as that by McNeil et al may be suitable for planning and evaluating public policy, producing what Morreim[34] refers to as "Consensus Quality of Life" measures, they are arguably inappropriate for clinical care where "Personal Quality of Life" is the focus.[34] Moreover, many QL measures of psychological well-being are higher in cancer patients than in healthy "controls,"[35,36] so the opinions of subjects in the study of McNeil et al do not necessarily reflect those of patients, and firm conclusions cannot be made.

Until QL measures for head and neck cancer are standardized and their clinical value proven, dilemmas such as that which exists for the management of advanced laryngeal cancer cannot be resolved. Nevertheless, it is very likely that QL measures carry considerable usefulness in head-and-neck oncology, and that obtaining an efficient QL instrument for head-and-neck cancer is a goal worth pursuing. Research in other cancer sites provides examples to support this view.

Examples of clinical value of QL measures in cancer.

1. In patients with advanced breast cancer undergoing chemotherapy ". . . no single factor before treatment predicted survival or response more accurately than initial quality-of-life scores."[8]
2. "Radiation therapy (RT) has led to significantly more depression than in surgery alone . . . although more radical surgery patients are significantly less satisfied with their body image than partial mastectomy patients. RT could well be more frightening to breast surgery patients than had been anticipated by doctors."[37]
3. Counseling patients with metastatic breast cancer to improve their psychological well-being has resulted in a survival, which was not only of better quality, but also significantly longer than patients who received no counseling.[38]
4. Results after total gastrectomy for cancer have shown that patients whose operation was palliative (ie, lived less than a year) never regained their preoperative quality of life. The conclusion was that "unless our treatments improve the quality of life we are probably doing our patients more good by not operating on them."[39]
5. Patients who were disease-free 6 months after undergoing a Whipple's procedure for periampullary carcinoma recorded mean util-

ity scores of 0.98 to 1.00, suggesting that they considered their well-being to be near-normal to normal.[40]

There is no real conflict between survival and QL when treatment is palliative, because no patient is expected to survive the disease, and quality becomes the natural primary outcome measure of interest.[41] Therefore, the "choice" between survival and QL does not apply, although sometimes even quite radical treatment may qualify as palliative if it will counter the effects of uncontrolled disease.

At the other end of the therapeutic spectrum, treatment for small (T_1) tumors generally provides a high chance of cure and the lasting effects of the treatment are probably minimal (assumption 8, Table 1). Here also, therefore, there is no conflict between QL and survival considerations. In fact, in such circumstances, monitoring QL is probably not warranted.[41]

The Dilemma

The dilemma is the following: if a treatment provides a superior chance of survival but is likely to lead to greater measurable dysfunction and disability, does one need to choose between QL or radical treatment?

There is very little research relating to the question of whether QL issues should dominate over survival considerations when treating head-and-neck cancer for cure. Rather, head-and-neck cancer studies of QL generally have been descriptive, attempting to quantify and characterize QL and its contributory domains as much as possible. Many of the studies not only have small numbers, but also contain widely diverse clinical material. Therefore, one is unable to generalize or draw conclusions at this stage, regarding QL outcomes and priorities for specific patient subgroups within head-and-neck cancer. Many treated patients may have a disability or dysfunction that a clinician regards as unacceptable, but which may be quite acceptable to the patient who is grateful to be alive and participating.[40] Thus for individual patients, in respect to specific treatment options, QL issues affecting choice of treatment should be taken back to the patient as much as possible.

It is likely that major QL problems will arise if the tumor recurs despite radical treatment. The patient must then contend not only with the problem of a progressive, fatal disease process, but also with the situation that his or her reserves may have been severely compromised by the underlying residual treatment-related morbidity.

DEVELOPMENT

QL Characteristics and Definition

QL is a broad concept encompassing an extensive range of physical and psychological characteristics and limitations that describe an individual's ability to function and derive satisfaction in doing so, and thus applies to the level of well-being and satisfaction.[42] Therefore it is a multidimensional construct of many facets of life and may be defined as the difference between one's perceived reality and one's expectations or wishes. This is referred to as the "gap" theory and is explained in more detail elsewhere.[6,43]

There is universal agreement among QL researchers that data must be self-reported by patients, and that physical, social, and psychological functioning should be assessed. Generic QL instruments cover a broad range of items in different domains, but tend to lack important questions specific to any cancer site or type, so that sensitivity and responsiveness to important clinical change may be lacking. To ensure content validity, therefore, questionnaires for cancer patients need to be site-specific to accommodate the widely varying nature of disease- and treatment-related symptoms. A patient-generated global measure of QL, or general well-being, should always be included.[13] An ideal QL head-and-neck cancer questionnaire would be short, concise, easy to understand, as unbiased as possible with respect to health-worker interpretions, and be sensitive to changes in health status.[42,44,45]

A Comprehensive Head-and-Neck Questionnaire

Several papers have reported the use of questionnaires to examine the QL of head-and-neck cancer patients, but few have been prospective studies, and many have involved only small numbers.[46] The process of developing and validating a QL questionnaire has been reported by others[47,48] and the present status of QL instruments in current use in head-and-neck cancer patients has been reviewed elsewhere.[29,49]

Development of the head-and-neck questionnaire described in this article began with a preliminary cross-sectional study of buccopharyngeal cancer patients 10 years ago.[50] The measures of psychological function in those patients were interesting, but the process of obtaining the data was unwieldy and impractical, taking up to 90 minutes per patient to complete. Nevertheless the results were useful[19,35,51,52] and identified areas of concern that needed to be incorporated in the next questionnaire. A question item list was generated and reduced using a judicious approach, following consultation with head-and-neck cancer patients and surgeons and a psychologist with special interest and acknowledged expertise in population surveys. Difficulties with the wording and understanding of the items was tried in a group of previously treated head-and-neck cancer patients.

Deciding on which instruments to assess psychological functioning and psychological well-being proved to be the most difficult task. Most instruments were long, time-consuming, and exhausting. After a review of the literature to that time, and preliminary field-testing for patient acceptability, two psychological instruments were chosen: the General Health Questionnaire and the Life Satisfaction Scale.

The general health questionnaire (GHQ-12). The GHQ is an instrument with items that inquire how the respondent perceives his or her present cognitive, social, role and emotional functioning. Different versions of the GHQ have been reported by several investigators studying health-related QL, and have shown it to be psychometrically sound in cancer patients,[53-55] including head-and-neck cancer patients.[56] It is a self-administered screening test designed for detecting nonpsychotic psychiatric disorders using a 4-point Likert-type scale. Scoring of each question uses either a 2- or 4-point scale, and a total score is obtained by simply summing each of the 12 item scores. High scorers report more symptoms, and thus have a greater probability of being diagnosed with mental disturbance or psychological distress than low scorers. The original instrument had 60 items. A number of shorter versions have been developed using the "best" questions from the GHQ-60, which are balanced for overall agreement set, which exclude items that select false positives on the basis of physical (rather than mental) illness, and which contain the most discrimination items. This questionnaire uses the 12-item version of the GHQ.

Life satisfaction (LS-10). Life satisfaction can be viewed as a component of psychological well-being and has been regarded as representing a patient's global QL.[57] The scale used in the questionnaire was developed by Warr et al,[58] with life satisfaction being operationally defined as "the degree to which a person reports satisfaction with (his or her) life and life-space." The original instrument had 15 items with three identifiable subscales. A trial of this scale showed that patients found little relevance in one of the subscales. Therefore, only the satisfaction with lifestyle and personal life have been retained, resulting in a 10-item measure. Responses are on a 7-point scale from "Extremely dissatisfied" (1) through "Not sure" (4) to "Extremely satisfied" (7). Total life satisfaction is the sum of the scores for each of these items. The higher the score, the more satisfied the respondent is with their lifestyle and personal life.

Several investigators have advocated some form of personal satisfaction measure for assessment of QL,[13,30,42,59] although Atkinson[60] has suggested that life-satisfaction (LS) is a response to the perceived QL rather than a measure of it. The results of a longitudinal study of head-and-neck cancer patients using LS analysis is reported elsewhere.[61]

Social functioning. Social functioning items are contained within the GHQ-12 and LS-10. Additional questions relating to hobbies, membership of clubs, eating out socially, general leisure, and recreational activities are also included as separate items. There are also separate questions relating to perceived adequacy of family support and social circumstances (living alone, with partner, with family) in addition to a LS-10 question on satisfaction with family life.

Demographics. An occupational history is obtained using open questions, and there are specific questions on tobacco, alcohol, and caffeine consumption. Items relating to racial background, age, and gender are also included.

Physical functioning. Items relating to general health, daily activities, and role functioning are contained within the GHQ-12 and LS-10. An additional item enquires about patients' concern with their appearance.

Disease- and treatment-related symptoms. There are several questions regarding voice, swallowing, coughing, breathing, and pain. Pain severity and degree of dysphagia is assessed using visual analogue scales anchored by words and numbers; pain in the shoulder and arm region is distinguished from pain in the head and neck. Additional information about difficulties with specific food is obtained with an open question.

Global index. The single-item overall life-satisfaction measure of Warr et al[58] is used as a single, global measure of psychological well-being. A global life-satisfaction measure can also be obtained by using the total (summed) life-satisfaction score. One question within the GHQ-12 may also be extracted for analysis inquiries of the patient: "Over the past few weeks have you been feeling reasonably happy, all things considered?"

No system of summing scores from each of the physical, social, and psychological domains to provide an "overall QL score" is used.

Psychometric Analysis

To determine the content and face validity of the head-and-neck questionnaire, a pilot study was conducted.

Patients. The questionnaire was field-tested on a group of 84 patients at various stages of treatment for head-and-neck cancer, including terminal, end-stage disease. The profile of these patients are summarized in Table 2. All patients had a diagnosis of squamous carcinoma of the oral cavity, pharynx, larynx, or paranasal sinuses. There were four clinical categories defined, based on status of disease at the time the questionnaire was completed: (1) at diagnosis, (2) at 6 months or more after treatment (no active disease evident), (3) at time of re-presentation with salvageable tumour recurrence, and (4) when previously treated patients had unsalvageable (end-stage) recurrent disease.

Methods. Informed consent was obtained, and the patient asked to complete a questionnaire by the nurse research assistant. The nurse was not part of the treatment team, but was responsible for approaching each patient, explaining any areas of confusion regarding the questionnaire, and maintaining data records. The data were entered into a MS/DOS-based computer using a software statistical program package entitled SPSS/PC+.[62]

Results. The internal consistency of the LS-10 and GHQ-12 were conducted on the first 43 patients. Cronbach's alpha[63] was 0.8272 for the GHQ-12 and 0.8299 for the LS-10. The scores were sufficiently high for the measures to be used as unidimensional scales.[64]

The test-retest reliability was assessed in a smaller group of 10 patients, where the questionnaires were administered up to 8 days apart in patients whose clinical status was stable. Mean correlation coefficient relating to pain, swallowing, breathing, and speaking

TABLE 2. Profile of Patients in QL Questionnaire Pilot Study

Clinical Status	Men	Women	Total
New patients	25	6	31
Treated patients—no recurrence	27	8	35
Recurrent tumor (salvageable)	7	2	9
Recurrent tumor (unsalvageable—terminal)	4	5	9
Total	63	21	84

TABLE 3. Mean GHQ-12 Scores for Patients in Each of the Disease-Status Categories

	Men	Women	Total
New patients	10.1 (4.7)*	10.6 (2.2)	10.1 (4.1)
Treated: NED	10.2 (4.1)	11.5 (4.1)	10.5 (4.3)
Treatable Recurrence	12.4 (3.8)	14.5 (2.0)	13.1 (3.5)
Recurrent, end-stage disease	13.2 (4.5)	18.4 (5.3)	16.2 (5.3)

Abbreviation: NED, no evidence of disease.
* Values in parentheses are 1 SD from the mean.

was 0.896 (range 0.612 to 1.0). The coefficient for the global life satisfaction single item was 0.612, and for the aggregated measure (LS-10), 0.9417. For the aggregated GHQ-12, the coefficients were 1.00 for the 2-point scale, and 0.57 for the 4-point scale.

Construct validity was tested by observing changes in the items within the instrument, according to clinical status. Mean GHQ-12 and LS-10 scores for patients in each of the four clinical categories are shown in Tables 3 and 4. In the GHQ-12 (Table 3), there are noticeable gender differences, and the measures are worse with recurrent and end-stage disease as expected. The LS-10 (Table 4) showed a lower satisfaction score with recurrent end-stage disease but did not show any difference between the other three categories. Patterns of social activity (as recorded in responses to changes in the frequency with which patients continued eating out with friends, at restaurants, and so on), appetite, and concern with appearance is shown in Table 5. Patients with recurrent disease had poorer appetite, and diminished social activity when compared with earlier phases of the disease process.

TABLE 4. Mean LS-10 Scores for Patients in Each of the Disease-Status Categories

	Men	Women	Total
New patients	53 (7)*	58 (4)	54 (7)
Treated: NED	53 (8)	55 (10)	54 (8)
Treatable recurrence	55 (5)	46 (1)	54 (6)
Recurrent, end-stage disease	46 (9)	46 (7)	46 (7)

Abbreviation: NED, no evidence of disease.
* Values in parentheses are 1 SD from the mean.

TABLE 5. Number (%) of Patients Reporting a Poor Appetite, Decreased Social Function as Measured by Eating Out, or Concern With Appearance

	Appetite	Eating Out	Appearance
New patients	4 (13%)	8 (27%)	2 (6%)
Treated: NED	6 (17%)	10 (30%)	3 (8%)
Treatable recurrence	2 (29%)	3 (29%)	– (0%)
Recurrent, end-stage disease	4 (44%)	7 (75%)	5 (55%)

Abbreviation: NED, no evidence of disease.

Prevalence of pain and mean pain scores are shown in Table 6. A similar pattern to that seen for appetite and social activity is evident.

Discussion

The results of this pilot study of a head-and-neck questionnaire show that it is responsive to changes in patients' clinical status, in the presence of psychological stress. The QL measurements move in the expected direction, according to deterioration in the patient's general condition. The two principle psychologic indices, GHQ-12 and LS-10 have very good internal consistency, and the test-retest reliability coefficients are high. These results indicate that the questionnaire has good construct and face validity; that is, it distinguishes between disease states, and exhibits changes that we would expect, given the clinical circumstances.

There are several weaknesses of this analysis. First, the patients were a rather disparate group, even within each clinical status category, and there was no record of physical status (such as Karnofsky score).[48] Second, the

TABLE 6. Number (%) of Patients Recording Pain in Each of the Disease-Status Categories, and Mean Pain Scores

	Prevalence	Mean Score (SD)
New patients	12 (41%)	1.6 (1.5)
Treated: NED	16 (45%)	2.1 (2.0)
Treatable recurrence	7 (78%)	4.4 (3.1)
Recurrent, end-stage disease	7 (78%)	3.8 (2.9)

Abbreviation: NED, no evidence of disease.

numbers of patients in the "recurrent" tumor groups were small, especially if subdivided by gender. Third, a larger number of patients would be needed for the test-retest analysis results to be entirely convincing.

However, the purpose of the pilot study was to confirm the likely clinimetric reliability of the instrument, and in this respect the exercise was successful. The results are certainly good enough to warrant using this questionnaire for a larger, prospective, longitudinal study of head-and-neck cancer patients, which is in progress.

There are some QL domain items that are not covered in this questionnaire. These include questions relating to changes in patients' spiritual life, sex life, occupational status, and economic circumstances as a result of their illness. It is difficult to know how many questions are too many for the patients. The longitudinal study will provide information about which questions are most sensitive to changes in the patients' clinical status, and any irrelevant questions can be discarded, to be replaced with others relating to the missing domains. Other items may not be responsive enough to be relevant for each of the different categories of tumor site or disease status. Concern with appearance is one such item. Indeed, this question may more closely apply to social or psychological functioning than physical functioning. The University of Washington[48] and the European Organisation for Research and Treatment of Cancer (EORTC)[56] have conducted psychometric analyses using their own questionnaires. We see benefits in different instruments being tested, so that they may then be compared, and the best items taken to be incorporated into a composite instrument.

A dimension that may have some prognostic or other predictive value in subjective well-being of head-and-neck cancer patients[65,66] is patient coping skills. This is a relative newcomer into QL assessment, and the current "coping" measures are rather long and time-consuming and do not generally conform with the "ideal" questionnaire strategy outlined earlier. Therefore, at this stage this aspect has not been incorporated.

It is likely that QL parameters in head-and-neck cancer are subsite- and treatment-specific, so that a craniofacial resection for ethmoidal cancer should not be incorporated in the same analysis as a gastric transposition for post-cricoid carcinoma.[67] Until the difficulties relating to QL assessment in the more common tumors and treatments are resolved, it is unlikely that these "special cases" will be adequately studied.

The need for further research on QL in head-and-neck cancer is indisputable. With more data, decisions regarding treatment selection will be able to be based on reliable information rather than on assumption or bias.[68] Aaronson[69] states that there is a need "of primary importance . . . to develop multidimensional quality of life instruments that are brief and psychometrically robust." Hassan and Weymuller[48] expand on this theme; the questionnaire described here shows sufficient promise to go some way towards fulfilling that need. We intend to report in more detail on the clinimetric characteristics of this questionnaire after data from an ongoing longitudinal study become available. This will enable more complete scrutiny of associations between QL measures and anatomic subsites, treatment categories, and questionnaire subscales. The aim is to generate confidence in an instrument so that interventional studies can be planned to indicate its value in clinical management.

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APPENDIX

Clinimetrics: The term proposed for the field of study concerned with the construction of clinical indices.

Consistency: See "Internal Consistency" and "Reliability."

Construct Validity: When no "gold standard" (see 'criterion validity') is available for comparison, hypotheses ("minitheories") are proposed regarding how an index will perform under different clinical circumstances. How well the index compares with the anticipated performance, as predicted by the hypothesis, is a measure of its construct validity.

Content Validity: A judgmental assessment of the underlying components of an index, including the quality of the basic data, the omission of important variables, the inclusion of unsuitable variables, and the weighing of variables.

Criterion Validity: An external reference that is a "gold standard" against which the measure in question can be compared. There are few "gold-standards" when dealing with symptom scales because the ultimate source of "truth" is the individual patient's subjective state (see also "construct validity").

Face Validity: Combines basic common sense and a reasonable knowledge of the clinical disease to see if the index overall represents and measures the intended attributes or disease process.

Internal Consistency: A index of trend or relatedness that measures the interdependency of two variables.

Psychometrics: The term proposed for the study concerned with the measurement of psychological phenomena or educational achievement.

Quality-of-Life **(QL):** A multi-dimensional construct of subjective well-being. May be regarded as the difference, or "gap," between one's perceived reality and one's expectations or wishes.

Reliability **(Consistency, Accuracy):** The ability of a measuring system to yield the same result when the measurement is repeated using the same method and observer (intraobserver) or other observer (interobserver).

Responsiveness **(Discriminative Validity):** The ability of the instrument to detect clinically important change when it has occurred.

Utility: A quantitative measure of the strength of an individual's preference for a given outcome. Utility scales are arbitrarily set but generally range from 0 to 1.0. Zero represents very poor health or death and 1.0 represents "normal" or perfect health.

Validity: A rating of the ability of an index to measure what it is supposed to be measuring. See also "Responsiveness," and "Criterion," "Construct," "Content," and "Face" validity.

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"Validation of quality of life measures in head and neck cancer patients". *Aust J Otolaryngol* (2000) **3**(5): 479-487.

This paper reports the results of the formal validation analysis of the Auckland QOL questionnaire. The Questionnaire was one of "*12 … instruments (that) satisfied (their) inclusion criteria*" and was noted to be "*well-validated from a quantitative standpoint and … psychometrically sound*" in an independent review of 233 articles of QOL outcomes studies for HNC patients (*Pusic et al, 2007*).

The absence of a factor analysis in the item reduction process of questionnaire development was deemed to be a weakness (*Ringash & Bezjak 2001; Rathod et al, 2015*), but when patients' views were explored in a randomised trial of 4 validated QOL instruments (including this present questionnaire, no statistically significant differences were found in respect of understanding of questions and usefulness in communicating health problems (*Mehanna & Morton 2006b*)[xxxi]. Indeed, no single instrument was favoured significantly more than any other.

The potential for rationalisation of QOL questionnaires, is discussed at some length in this paper[xxxii].

[xxxi] see also section 1.2.6.2, above.

[xxxii] Professor Jolie Ringash commented in an email to me, after reading this paper:

"*Your paper is prescient in suggesting, "a QL screening instrument in which key areas are included… a subsequent, more detailed questionnaire" (if problems noted); this is of course what computer-adaptive testing (CAT) is designed to do, and I do believe that is most likely the future for QOL measurement.*" (*Ringash, personal email communication, 2 Feb 2018*)

VALIDATION OF QUALITY-OF-LIFE MEASURES IN HEAD AND NECK CANCER PATIENTS

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Assessment of patients' quality of life is a complex issue, and any questionnaire designed to record quality of life needs to be validated. This paper reports the results of the development and validation process of a quality of life questionnaire designed for use in patients diagnosed with head and neck cancer in Auckland. The questionnaire proved to be generally reliable, valid, and sensitive to change in clinical status. The implications for clinicians wishing to monitor quality of life in their head and neck cancer patients are discussed.

The phenomenon of Quality of Life (QL) is well recognised and frequently referred to in the medical literature. It may be defined as a personal, subjective assessment of an individual's general well-being and is thought to reflect the gap between reality, on the one hand, and one's expectations or desires on the other (Padilla et al 1988). As such, it needs to be self-reported, because observers cannot rate it accurately (Deschler et al 1998, Karnell et al 1999).

Measurement of QL is quite complex (Cohen et al 1996); it is a multi-dimensional construct, and several domains need to be assessed before a reasonably comprehensive perspective can be obtained (Morton 1995a). Domains that are generally accepted as major contributors to health-related QL include physical, social, and psychological functioning; family and social support; and disease- and treatment- related symptoms (Cohen et al 1996, Morton 1995b). Examples of symptom measures include pain and discomfort, dysphagia, coughing and sputum production. Many of these outcome measures will impact on and even correlate with the patients' perceived QL, but no single item can necessarily reflect the QL outcome for any particular patient. Other domains – such as body image, sexuality, spiritual and occupational functioning, and economic status – are also accepted as contributory, but these are not normally included in routine QL assessments.

There are many instruments in use for assessing QL in cancer patients and several have been developed or adapted specifically for head and neck cancer (Hassan and Weymuller 1993, Bjordal and Kaasa 1995, Morton 1995b, List et al 1996, Terrell et al 1997, Trotti et al 1998). A specific instrument should be used for each major site (Morton 1995a, Gliklich et al 1997) because individual patient profile, the nature of the disease, and the impact of treatment, each differ considerably with different cancer sites. Any questionnaire which is to be used for QL assessment needs to be reliable and consistent, sensitive to change in clinical circumstances, and a fair representation of patients' actual perceptions of QL and its composite domains. The process by which these characteristics are established is called *validation.*

In order to obtain an overall QL score, some researchers have summed the assigned scores from several different QL items (Hassan and Weymuller 1993, List et al 1996). This approach presupposes that the method of scoring each item actually represents the weighting, or importance, that patients generally ascribe to that item, and that there is no confounding between items. It also assumes that the selected items represent virtually all the important factors that contribute significantly to a patient's overall QL. A question on global QL in which the patient rates his or her own overall QL is more appropriate (Cohen et al 1996), as QL is more than the sum of its parts (Trotti et al 1998). Each or any of the contributing domain items can then be examined for a correlation with the global QL.

The present paper reports the process of development and validation of a QL instrument that has been used in Auckland to assess QL in head and neck cancer patients.

Patients and Method

Questionnaire Development

After consultation with colleagues and patients regarding which items could be included, a questionnaire was designed with the assistance of a clinical psychologist.

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This draft questionnaire was trialed with several patients, after which some items were re-worded and others were removed. Specific items within this amended version of the questionnaire included a 12-item measure of psychological distress – the General Health Questionnaire (GHQ-12) – and a 10-item measure of general well-being – the Life Satisfaction measure (LS-10) – as well as a single-item overall (global) life-satisfaction score. Within the GHQ-12 and the LS-10 were items relating to social, family and general physical functioning. These scales are described in more detail elsewhere (Morton and Witterick 1995). Additional questions relating to pain and dysphagia used a visual analogue scale – anchored by words and numbers – while other questions used a 4 to 5 point Likert-type scale.

It was felt initially that the questionnaire had satisfactory face and content validity but as the results of new QL studies appeared it became apparent that, for content validity requirements to be fulfilled, additional items needed to be included. Questions on physical functioning, ability to communicate, and sexuality, were therefore added using the same format as that used for items in the LS-10 module. Items on occupational history and consumption of hot drinks were omitted because they showed no correlation with other items in the instrument and were unrelated to the global QL measure.

Initial validation of this Auckland QL questionnaire (AQLQ) focussed principally on the internal consistency of the questionnaire and its responsiveness by way of ability to reflect differences between clinical disease states. The AQLQ was employed at first in patients at different stages of disease. The instrument was shown to be consistent, with the specific sub-scales LS-10 and GHQ-12 having especially good internal consistency (Morton and Witterick 1995). The results also pointed to satisfactory discriminative validity, that is, the ability to detect clinically important change when it has occurred. For example, patients with terminal disease had lower life satisfaction (LS-10 score) and greater psychological distress (GHQ-12) than other patient categories, while patients with recurrent tumour were more distressed – and pain prevalence and severity was higher – than those with no evidence of recurrence. Subsequently, a longitudinal study design was used to assess how QL measures changed over time (Morton 1995b). Inter-group comparison yielded good construct validity, with differing clinical status and social circumstances reflected in expected changes in QL scores. For example, laryngeal cancer patients who had had a laryngectomy reported more difficulty with speech than those patients treated by radiotherapy (Morton 1997) and patients with pain 3 months after treatment were very likely to report on-going pain at 2 years (Chaplin and Morton 1999).

Thus far the AQLQ had only been tested in isolation, and not validated against other measures, nor subjected to adequate reliability testing. Further analysis was required, and the results form the subject of this present paper.

Validation Analysis

Patients attending the outpatient clinic at Green Lane Hospital and having been treated for head and neck cancer were asked to participate in the study. All had been treated at least 12 months previously and had no signs of active disease. Each patient had information recorded regarding diagnosis, staging and treatment as well as general condition (Karnofsky score), current disease status, date of birth, gender and hospital identification number.

The patients were asked to complete the AQLQ. For purposes of comparison, the University of Washington QL instrument (UWQOL) (Hassan and Weymuller 1993) and two global items on "overall health", and "overall quality of life" from the European Organisation for Research and Treatment of Cancer (EORTC) head and neck QL instrument (Bjordal and Kaasa 1995) were also included. This combined questionnaire was completed while the patient was at the hospital. A second (identical) questionnaire was completed at home 7 days later and returned by mail. All questionnaires were self-administered and took less than 10 minutes to complete.

No patient refused to enter this study initially; a total of 42 patients were recruited. Thirty-six (86%) returned the second questionnaire at 7 days, as requested. There were 11 men and 25 women, and the average age was 62 years (S.D. 13.1 years).

Forty-one percent had had laryngeal or hypo-pharyngeal tumours and 43% had had oral or oro-pharyngeal tumours. The remaining 16% had been treated for sino-nasal, nasopharyngeal or metastatic skin cancer. Most (60%) patients had been treated once only for their tumour, 32% had been treated twice, and 8% had been treated 3 times. Six patients had received surgery alone, and 7 radiotherapy alone; the other 23 patients had received both surgery and radiotherapy, either as a planned combined treatment (9 patients) or as salvage surgery following failed radiotherapy (12 patients) for recurrent disease. No patients had been treated with chemotherapy.

Most (92%) of the patients were non-smokers at the time of the data collection although more than 88% had been smokers at some stage, and 30% were non-drinkers while only 11% admitted to drinking alcohol every day. The median BMI score was 22.8 (range: 18.1 – 37.6): 9% had a BMI above 30 and 15% were below a BMI of 20. The majority (85%) of patients were deemed to have only minor signs or symptoms of disease (Karnofsky score of 90 or greater).

Analysis of Results

Data was entered onto a personal computer and statistical analysis was performed using SPSS (Norussis 1993). There were three aspects to the analysis. The first examined the reliability by way of test-retest reproducibility using Pearson product coefficients of correlation. The second assessed the degree to which the AQLQ correlated with the validated UWQOL and EORTC measures. The third aspect was a review of the spread of responses to each question and the proportion of unanswered questions.

The complete AQLQ questionnaire and the additional QL items used for comparison are included in the Appendix.

Results

Reliability

The results of the test-retest reliability analysis are shown in Table 1. The reliability of the UWQOL scale was confirmed. The Life Satisfaction scale (LS-10), the GHQ-

12 scale and the EORTC QLQ items also rated very well on test-retest correlation, although the single item on global Life Satisfaction did not rate as well as the EORTC single item on QL. The single items recording symptoms and physical functioning were also generally very reliable measures, and the questions on alcohol and tobacco consumption were extremely reliable. The items relating to difficulty with speaking, global life-satisfaction, and frequency of head and neck pain, were the only questions with a correlation coefficient less than 0.65.

Table 1
Test-Retest Pearson product reliability coefficients.

Global LS	0.59**	Concern with Appearance	0.70**
LS-10	0.81***	Appetite	0.75**
EORTC QL	0.74**	Cough	0.73**
EORTC Health	0.65**	Pain severity (head, neck)	0.70**
GHQ-12	0.78***	Pain severity (shoulder, arm)	0.65**
UWQOL	0.85***	Amount of saliva	0.95***
Dyspnoea	0.67**	Alcohol consumption	0.94***
Dysphagia	0.79***	Cigarette consumption	0.98***
Eating Out	0.71**	Limited in activities	0.68**
Difficulty with food	0.90***	Pain frequency (head, neck)	0.61**
Difficulty with speaking	0.43*	Pain frequency (shoulder, arm)	0.75***

* $p < 0.05$; ** $p < 0.005$; *** $p < 0.0001$

Validity
There was generally a good correlation between the different questions that addressed the same QL domain. These comparisons involved some single items from within the UWQOL, GHQ-12 and LS-10 scales and some single items from the body of the AQLQ. Similar questions on the same subject were available for speech function, swallowing, pain, shoulder function, disfigurement, recreation, and energy levels. Each of these areas was examined to test for construct validity. The results are detailed in matrix form in Tables 2-7 according to various QL domains.

Global QL. There was strong correlation (Table 2) between the single-item overall Life Satisfaction measure, and the two composite scales LS-10 and the GHQ-12. There was also strong correlation between the two EORTC single-item measures of general health and overall QL. The EORTC QL measure also correlated very well with the LS-10 ($r = 0.62$, $p < 0.0001$), the GHQ-12 and the single item overall Life Satisfaction. There was moderate correlation between the EORTC QL measure and the UWQOL score. The observer-rated Karnofsky score generally correlated with the other global QL measures, except for the single-item LS score.

Table 3
Matrix to show the correlation coefficients between items relating to speech and communication

Speech	Difficulty Speaking	Satis. with Ability to Communicate	UW Speech
Difficulty Speaking	1.0		
Satisfaction with Communication	0.12	1.00	
UW Speech	0.51*	0.26	1.0

* $p < 0.01$

Speech. The question on satisfaction with the ability to communicate did not correlate with the question on difficulty with speaking or the UWQOL item relating to intelligibility (Table 3). The latter items correlate with each other somewhat ($r = 0.51$; $p < 0.005$) although the responses to the UWQOL speech question were limited to 2 values only (see Table 8). The item on satisfaction with communication ability seems to be measuring something different from the other 2 items on speech.

Swallowing. Eating out socially is moderately correlated ($r = 0.43$; $p < 0.01$) with items inquiring specifically about dysphagia and presumably in accounting for factors other than dysphagia. Table 4 shows that the other specific dysphagia questions all correlated very well with each other.

Table 2
Matrix to show the Correlation coefficients between similar items relating to general QL measures

'Global' rating scale	Karnofsky	UWQOL	GHQ-12	LS-10	LS Overall	EORTC QL	EORTC Health
Karnofsky	1.0						
UWQOL	0.57**	1.0					
GHQ-12	0.38*	0.53**	1.0				
LS-10	0.51**	0.22	0.63***	1.0			
LS Overall	0.33	0.32	0.68***	0.71***	1.0		
EORTC QL	0.60***	0.57***	0.67***	0.63***	0.68***	1.0	
EORTC Health	0.58**	0.42*	0.57***	0.55**	0.56***	0.87***	1.0

* $p < 0.05$; ** $p < 0.005$; *** $p < 0.0001$

Table 4
Matrix to show the Correlation coefficients between similar items relating to swallowing and eating.

Swallowing	Dysphagia score	Eat out socially	Food type	UW chewing	UW swallowing
Dysphagia Score	1.0				
Eat out socially	0.43*	1.0			
Food type	0.73***	0.43**	1.0		
UW chewing	0.67***	0.45**	0.82***	1.0	
UW swallowing	0.72***	0.37*	0.81***	0.80***	1.0

* $p < 0.05$; ** $p < 0.005$; *** $p < 0.0001$

Table 5
Matrix to show the Correlation coefficients between similar items relating to swallowing and eating.

Pain	Frequency (head/neck)	Severity (head/neck)	Frequency (shoulder/arm)	Severity (shoulder/arm)	UW pain
Frequency (head, neck)	1.0				
Severity (head, neck)	0.57***	1.0			
Frequency (shoulder, arm)	0.77***	0.42*	1.0		
Severity (shoulder, arm)	0.53**	0.54**	0.77***	1.0	
UW Pain	0.47**	0.50**	0.43*	0.46**	1.0

* $p < 0.05$; ** $p < 0.005$; *** $p < 0.0001$

Table 6
Matrix to show the Correlation coefficients between similar items relating to shoulder function

Shoulder Problems	Frequency (shoulder pain)	Severity (shoulder pain)	UW shoulder	UW pain
Pain frequency (shoulder/arm)	1.0			
Pain severity (shoulder/arm)	0.77**	1.0		
UW shoulder	0.75***	0.63***	1.0	
UW pain	0.37	0.17	0.11	1.0

* $p < 0.05$; ** $p < 0.005$; *** $p < 0.0001$

Pain. There is moderate correlation (Table 5) between the UWQOL pain measure and the other questions on pain ($r = 0.43, 0.5$; $p < 0.01$); the correlation between the AQLQ items on pain frequency and pain severity is quite strong ($r = 0.58, 0.77$; $p < 0.005$).

Shoulder function. In Table 6 a correlation is seen ($r = 0.77, 0.75, 0.37$; $p < 0.0001$, $p = 0.02$) between the AQLQ item on frequency of shoulder and arm pain, and the AQLQ severity of shoulder/arm pain, the UWQOL item on shoulder discomfort and the UWQOL overall pain score.

Appearance. There was significant, moderate, correlation ($r = 0.46$; $p < 0.01$) between the two items regarding patients' concern about their body image.

Energy/Leisure/Recreation. There was a mild correlation (Table 7) between AQLQ satisfaction with leisure activity and the UWQOL items on recreation and general activity ($r = 0.36, 0.38$, $p < 0.5$). There was a generally good correlation between satisfaction with energy levels and the GHQ-12 item on activity and tiredness ($r = 0.48$ to $r = 0.66$). Patients' leisure activities satisfaction score correlated very well with satisfaction with energy levels ($r = 0.66$, $p < 0.001$).

Sensitivity
Each of the patient-generated variables was examined for variation and spread within the scale for each variable.

Table 7
Matrix to show the Correlation coefficients between similar items relating to energy and leisure activity.

Energy Levels	Limited Activity	Satisfaction with energy	Satisfaction with leisure	Normal Activities	UW Activity	UW Recreation
Limitation of Activity	1.0					
Satisfaction with energy	0.55***	1.0				
Satisfaction with leisure	0.31	0.66***	1.0			
Normal Activities	0.65***	0.48**	0.24	1.0		
UW Activity	0.73***	0.60***	0.36*	0.48**	1.0	
UW Recreation	0.77***	0.52**	0.38*	0.64***	0.69***	1.0

* $p < 0.05$; ** $p < 0.005$; *** $p < 0.0001$

Table 8
Outline of those questions to which fewer than 4 values were reported, and the proportion of respondents in each value.

Question	Value 1	Value 2	Value 3
Eating out socially	54%	17%	29%
Saliva sufficiency	51%	46%	3%
UW chewing	8%	36%	56%
UW disfigurement	19%	53%	28%
UW pain	11%	36%	50%
UW recreation	3%	14%	53%
UW speech	56%	44%	-
UW shoulder	11%	19%	69%

There were 11 of 21 AQLQ variables and 7 of 9 UWQOL variables in which more than 50% of the patients were represented by a single specific value. Table 8 summarises the 8 questions (2 in the AQLQ, and 6 in the UWQOL) in which the spread of response was limited to 3 values and the question (from the UWQOL) in which only 2 values were recorded. Although the items in Table 8 were reliable on test-retest analysis, many responses clustered such that 2 adjoining ratings comprised 70% or more of the total responses. The AQLQ item on saliva was one of these.

Acceptability

Some questions were not answered by all respondents. Within the life-satisfaction scale, 5 patients (14%) did not complete the question relating to satisfaction with sex life and one failed to respond to the question on what the future holds. Two patients did not complete the composite GHQ-12 scale, addressing psychological distress. Two general questions also had 2 non-responders. These related to limitation of work or other activities, and thinking about personal appearance. Nine questions had one missing response each. These were questions on eating out socially, family support, difficulty eating food, overall (global) life satisfaction, sufficiency of saliva, frequency of pain in the head and neck region, frequency of shoulder and arm pain, a severity of shoulder and arm pain, and the UWQOL pain item.

Discussion

The reliability of the UWQOL and the global items in the EORTC-QLQ instrument is confirmed, and this study establishes reliability for most of the items in the AQLQ. This study therefore adds to the choice of questions for head and neck oncologists seeking to monitor various QL domains. There is probably enough choice in the literature for head and neck surgical oncologists to derive QL instruments of their own without the need for further questionnaire development. Most QL questions that address similar issues and meet basic requirements of reliability and validity are well correlated. This suggests that they measure similar things, and are probably interchangeable.

Although the setting was different from the first and second questionnaire, the test-retest reliability of the items from established instruments was in accordance with that reported elsewhere. This suggests that the different setting does not compromise the reliability analysis, and that a postal survey may be a valid means of conducting a QL assessment.

The AQLQ as used here has some duplication and redundancy. Some overlap of questions seems inevitable as the UWQOL, despite its brevity, has questions that correlate very closely with each other. Perhaps more importantly, the UWQOL has a limited ability to identify social and psychological dysfunction. A pragmatic approach would see an amalgamation of various items from the various available validated head and neck QL instruments. However, this approach should be used with care when dealing with composite scales, such as the LS-10 and GHQ-12, as it may lead to the use of an instrument that was not originally intended. In that event, the 'new' instrument would need to be validated. Other, single, items do not carry that risk, and therefore can be considered with alternative items from other questionnaires for inclusion, as required.

The high non-response rate (14%) to the question on satisfaction with sex-life suggests that this item is unacceptable for routine inclusion. The items on global life-satisfaction, frequency of head and neck pain, and difficulty with speech, may not be sufficiently reliable to retain, and the lack of variation in response to the AQLQ item on saliva would indicate that this question is not sufficiently sensitive to retain. Alternatively, this question, together with the other items may appear limited because there are no major differences in the population surveyed (for example, no patients had active disease). If these items can be shown in further studies to be predictive of or associated with important changes in global QL or disease status then they may be included in future questionnaires. As a composite measure, the UWQOL is reportedly responsive to changes in clinical status (Hassan and Weymuller 1993). In the present study the responses to the UWQOL item on speech were probably too clustered for that question to be sensitive enough for use as a single measure.

In any QL survey of head and neck cancer patients, a global measure is needed. The EORTC global QL score and the composite life-satisfaction scale correlate very well with each other and based on this study, either measure would be preferable to the single-item global life-satisfaction. The EORTC global QL scale also correlates well with psychological distress as measured by the GHQ-12. This correlation does not eliminate the need for monitoring the psychological domain, however, as QL is in large part related to psychological well-being. The GHQ has proven to be a useful screening instrument for identifying patients who have unmet psychosocial needs (Bjordal et al 1995, Kaasa et al 1993). By regular use of the GHQ-12, counselling resources could be directed specifically to where they may be most useful and cost-effective.

A head and neck cancer QL survey should also have specific disease- and treatment-related symptom scores. In the present study, there is obvious similarity between the UWQOL items and most of the corresponding AQLQ items in respect of pain, and difficulties with swallowing, speech, and shoulder function. For example, any item on dysphagia in Table 2 correlates well with all the others except for the item on eating out socially. Clearly, dysphagia is not the only reason that patients chance their social eating patterns.

Several authors have recommended a combination of a short, disease-specific questionnaire and a broad, generic questionnaire (Gliklich et al 1997, Terrell et al 1997, Bjordal and Kaasa 1995). This concept is most explicit in the approach taken by the EORTC which has a 30-item core questionnaire and a 35-item head and neck "module" (Bjordal and Kaasa 1995). Gliklich et al (1997) suggest that their 11-item "head and neck survey" (H&NS) disease-specific instrument could be used in conjunction with the Medical Outcomes Study Short-Form 36-item Health Survey (SF-36) generic instrument. They regard swallowing, speech and appearance as the only important head and neck specific aspects that need to be monitored. While this may be true, it has not yet been clearly established. The rather narrow perspective, the duplication of questions on specific symptoms, and the lack of a global QL measure all detract from their proposal. Terrell et al's (1997) analysis of their 20-item "head and neck quality of life" (HNQOL) questionnaire suggests that it is a coherent disease-specific QL instrument. However, it has not been tested for sensitivity to change in health status as a result of treatment or recurrence of disease, nor does it have a global QL item. The HNQOL uses composite scales that involve some overlap and duplication, and does not address the area of speech or communication difficulty. Nevertheless, there is good correlation with the mental and physical components of the SF-12, a shortened version of the SF-36.

There is little doubt that the downsizing of surveys, and in particular the time required to complete questionnaires, is desirable (Hassan and Weymuller 1993, Terrell et al 1997) and important if they are to be utilised more widely. The questions that exhibit some variation of response between patients and that have an important impact on general well-being or lifestyle will be favoured. While omission of important items may become an issue with the future rationalising of questionnaires, unnecessary duplication needs to be avoided. The UWQOL instrument has two items on eating and two on recreation/activity, which tends to bias the resultant composite score toward these items in such a short questionnaire. To an extent this has been corrected by the subsequent inclusion of a global QL score and an item on global health (Deleyiannis et al 1997). These added items are very similar to the EORTC items used in this present study and they can be used as dependent variables in any analysis. Terrell et al's (1997) HNQOL is derived from an initial 47-item head and neck cancer-specific questionnaire in which so-called " 'bother' questions", and identified 4 final domains of interest: communication (4 items), eating (6 items), emotion (6 items) and pain (4 items), are used. Gliklich et al's (1997) H&NS uses 5 questions to address eating/swallowing, 2 to survey speech/communication, and 4 for appearance. These items produce a disease-specific QL score that is the sum of the 2 symptom fields. Because both the H&NS and the HNQOL instruments involve composite sub-scales, it is not appropriate to use individual questions from these domains directly in a separate questionnaire. Instead, each sub-scale should be used until it is clear that fewer questions do not result in loss of important information and that each item retains reliability and validity.

It seems likely that only one or two of the questions would be needed in a routine questionnaire, to provide sufficient information about each symptom domain. In Table 1, the item on difficulty with food is seen to be more reliable than the dysphagia visual analogue scale, and this would lead one to favour the former. The same principle applies to general activity and energy levels. Table 6 compares the various questions that touch on this aspect of QL and it is apparent that there is a close relationship between them all, each measuring something similar, but also reflecting slight differences.

It has not yet been established which items or scales are required for a head and neck cancer QL measure and which items can be omitted. A practical approach may be to have a QL screening instrument in which key areas are included. If a screening questionnaire indicates the potential for problems that may require attention, a subsequent, more detailed questionnaire could be administered. Other items that should probably be included in a 'core' QL questionnaire might include questions that relate to energy, pain and dysphagia. Pain experienced by patients should be monitored because pain impacts on QL (Chaplin and Morton 1999) and most pain can be successfully managed. All questions relating to pain in this study proved to be reliable and valid. Some measures of dysphagia should be included as this also significantly affects QL (Morton 1995b). Most patients with difficulty in swallowing or eating can benefit from the specific assistance of a voice-language therapist or nutritionist.

Summary

The present study has provided options for inclusion of items in a QL questionnaire. The rationale behind the implementation of a QL assessment has been discussed. It is likely that regular use of a brief, relevant, valid questionnaire can identify patients with unmet and otherwise unexpressed needs that may be effectively managed by appropriate and timely interventions. An underlying basic assumption is that, by improving the specific area or life domain that requires attention, QL for that patient will be enhanced. There is circumstantial evidence in support of this concept, but it has yet to be tested in a prospective, interventional study.

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Appendix

I. Auckland Quality of Life Questionnaire

1. Do you have cough?
a: Constantly.
b: Every day.
c: Most days.
d: Occasionally/rarely.

2. Do you have difficulty speaking or communicating because of your illness?
a: No difficulty speaking.
b: A little difficulty.
c: Moderate difficulty.
d: Great difficulty/cannot speak at all.

3. When did you last have pain in:
– the head and neck region?
a: Today.
b: Yesterday.
c: Within past week.
d: Within past month.
e: More than a month ago/no pain.

– your shoulder or arm?
a: Today.
b: Yesterday.
c: Within past week.
d: Within past month.

e: More than a month ago/no pain.

4a. The last time you had pain in the head or neck region, how bad was it?

0 1 2 3 4 5 6 7 8 9 10

Nil Slight Moderate Severe Extreme

4b. The last time you had pain in the shoulder or arm, how bad was it?

0 1 2 3 4 5 6 7 8 9 10

Nil Slight Moderate Severe Extreme

4c. How much difficulty do you have swallowing?

0 1 2 3 4 5 6 7 8 9 10

Nil Slight Moderate Severe Extreme

4d. How much difficulty do you have breathing?

0 1 2 3 4 5 6 7 8 9 10

Nil Slight Moderate Severe Extreme

Over the past week, have you:

5. Been limited doing your work or other activities?
a: Not at all.
b: A little.
c: Quite a bit.
d: Very much.

6. Been thinking about your personal appearance?
a: Not at all.
b: A little.
c: Quite a bit.
d: Very much.

Diet:

7. Do you have a good appetite?
a: All or most of the time.
b: A good deal of the time.
c: About half the time.
d: Occasionally.
e: Seldom or never.

8. Do you have sufficient saliva to make eating comfortable?
a: Not enough saliva.
b: About the right amount.
c: Too much/dribbling.

9. Compared to before your illness, how often do you eat out (e.g. at restaurants, coffee bars, with friends, etc.)?
a: More often than usual.
b: Same as usual.
c: Less often than usual.
d: Much less often.

10. Do you have any difficulty eating food?
a: Not at all.
b: Difficulty with some types of food.
c: Restricted to soft food only.
d: Restricted to liquid diet only.
e: Unable to take oral diet of any kind.

Alcohol/Tobacco Consumption

11. How often to you drink alcohol?
a: Every day.
b: Nearly every day.
x: 2-4 days a week.
d: Weekly, or less.
e: Not at all.

12. How much do you smoke?
a: More than 40 cigs/day.
b: Between 20 and 40 cigs/day.
c: Between 10 and 20 cigs/day.
d: Between 1 and 10 cigs/day.
e: Not at all.

Psychological Well-being ('General Health Questionnaire')

Over the past few weeks, have you:

1. Been able to concentrate on whatever you are doing?
a: Better than usual.
b: Same as usual.
c: Less than usual.
d: Much less than usual.

2. Felt that you were playing a useful part in things?
a: Not at all.
b: Same as usual.
c: Less useful than usual.
d: Much less useful.

3. Felt constantly under strain?
a: Not at all.
b: No more than usual.
c: Rather more than usual.
d: Much more than usual.

4. Been able to enjoy your normal day-to-day activities?
a: More so than usual.
b: Same as usual.
c: Less so than usual.
d: Much less than usual.

5. Been feeling unhappy and depressed?
a: Not at all.
b: No more than usual.
c: Rather more than usual.
d: Much more than usual.

6. Been thinking of yourself as a worthless person?
a: Not at all.
b: No more than usual.
c: Rather more than usual.
d: Much more than usual.

7. Been feeling reasonably happy, all things considered?
a: More so than usual.
b: Same as usual.
c: Less so than usual.
d: Much less than usual.

8. Lost much sleep over worry?
a: Not at all.
b: No more than usual.
c: Rather more than usual.
d: Much more than usual.

9. Felt capable of making decisions about things?
a: More so than usual.
b: Same as usual.
c: Less so than usual.
d: Much less capable.

10. Felt you couldn't overcome your difficulties?
a: Not at all.
b: No more than usual.
c: Rather more than usual.
d: Much more than usual.

11. Been able to face up to your problems?
a: More so than usual.
b: Same as usual.
c: Less able than usual.
d: Much less able.

12. Been losing confidence in yourself?
a: Not at all.
b: No more than usual.
c: Rather more than usual.
d: Much more than usual.

Current Life Situation ('Life Satisfaction')

Please consider the following aspects of your life at the present moment. Indicate how satisfied you feel about each one using the following scale.

1: Extremely dissatisfied.
2: Very dissatisfied.
3: Moderately dissatisfied.
4: Not sure.
5: Moderately satisfied.
6: Very satisfied.
7: Extremely satisfied.

1. The house or flat that you live in.
2. The local district that you live in.
3. Your standard of living; the things that you can buy and do.
4. The way you spend your leisure time.
5. Your present state of health.
6. The education you have received.
7. What you are accomplishing in life.
8. What the future seems to hold for you.
9. Your social life.
10. Your family life.
11. Your energy level.
12. Your sex life.
13. Your ability to communicate with others.

II. EORTC General Health Questions

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

0 1 2 3 4 5 6 7
Very poor Excellent

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

0 1 2 3 4 5 6 7
Very poor Excellent

III. University of Washington Quality of life Questionnaire

Pain
a. I have no pain
b. There is mild pain not needing medication
c. I have moderate pain – requires regular medication
d. I have severe pain controlled only be narcotics
e. I have severe pain not controlled by narcotics

Disfigurement
a. There is no change in my appearance
b. The change in my appearance is minor
c. My appearance bothers me but I remain active
d. I feel significantly disfigured and limit my activities due to my appearance
e. I cannot be with people, due to my appearance

Activity
a. I am as active as I have ever been
b. There are times when I can't keep up my old pace, but not often
c. I am often tired and have slowed down my activities although I still get out
d. I don't go out because I don't have the strength
e. I am usually in a bed or chair and don't leave home

Recreation/Entertainment
a. There are no limitations to recreation at home and away from home
b. There are a few things I can't do but I still get out and enjoy life
c. There are many times when I wish I could get out more but I'm not up to it
d. There are several limitations to what I can do, mostly I stay home and watch TV
e. I can't do anything enjoyable

Employment
a. I work full time
b. I have a part-time but permanent job
c. I only have occasional employment
d. I am unemployed
e. I am retired – not related/due to cancer treatment

Chewing
a. I can chew as well as ever
b. I can eat soft foods but cannot chew some foods
c. I cannot even chew soft foods

Swallowing
a. I can swallow as well as ever
b. I cannot swallow certain solid foods
c. I can only swallow liquid food
d. I cannot swallow because it goes down the wrong way and chokes me

Speech
a. My speech is the same as always
b. I have difficulty with saying some words but I can be understood over the phone
c. Only my family and friends can understand me
d. I cannot be understood.

Shoulder disability
a. I have no problem with my shoulder
b. My shoulder is stiff but it has not affected my activity or strength
c. Pain or weakness in my shoulder has caused me to change my work
d. I cannot work due to problems with my shoulder.

2.4 Longitudinal Studies of the Auckland QOL Cohort

This section contains four publications that report on the experience over time from a large cohort of Auckland HNC patients, and includes a unique cross-cultural matched-pairs study that compares QOL perceptions from two different cultures (Auckland, New Zealand, and Toronto, Canada).

It also includes unique analyses of 10-year QOL outcomes, reporting on late effects and QOL impact on survivorship.

- Morton RP (1995) Life satisfaction in head and neck cancer patients. *Clin Otolaryngol* 20: 499-503
- Morton RP (2003) Studies in the Quality-Of-Life of Head-And-Neck Cancer Patients. Results of a 2-year Longitudinal Study and a Comparative Cross-sectional Cross-cultural Survey**.** *Laryngoscope* 113:1091-1103
- Mehanna HM, Morton RP (2006) Deterioration in quality-of-life of late (10-year) survivors of head and neck cancer. *Clin Otolaryngol* 31(3): 204-211.
- Mehanna HM, Morton RP (2006) Does quality of life predict long-term survival in head and neck cancer patients? *Arch Otolaryngol* 132:27-31

2.4.1 Morton RP (1995) Life satisfaction in head and neck cancer patients. *Clin Otolaryngol* 20:499-503

This study was the first to publish 2-year follow-up longitudinal QOL data in HNC[xxxiii]. The patients in this report form the basis of the long-term follow-up and comparative studies that follow, later in this thesis.

Life Satisfaction is described in some detail and was proposed as a dependent overall outcome measure for **Global QOL**. Kreitler et al (*1993*) had previously used life satisfaction in cancer patients, and Ferrans (2007) supported the concept of life satisfaction as a single or multiple-item measure where she discussed how best to monitor and report overall QOL using a Global QOL measure[xxxiv].

Individual QOL domain items become worse after treatment, but paradoxically the global QOL is improved. This probably reflects a ***response shift*** (i.e. changing internal standards) [xxxv] by patients as they learn to cope with their symptoms, and gain satisfaction from surviving their cancer. This report of changing life satisfaction in HNC patients pre-dates the publication by Sprangers & Schwartz (*1999*), where a rationale for the apparent paradox was proposed. Ringash (*2015*) describes the response shift phenomenon as follows:

> *"… After diagnosis with a critical illness, an individual may modify his or her values, standards of measurement, or conception of QOL. Response shift may be viewed as a beneficial adaptive process …"*

List et al (*2002*) and others (*Hassanein et al, 2001; Llewellyn et al, 2006*) provide data to

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[xxxiii] This publication has been cited in the literature by others 54 times (*Researchgate, 2018*)

[xxxiv] Also discussed in the Introduction to this thesis (*see section **1.2.6.1***)

[xxxv] The response shift phenomenon is also discussed in section ***1.2.8** (see pages 27-8)*

support the concept that patients’ coping strategies are instrumental in the adaptation expressed in the response shift phenomenon.

Not only was this study the first to provide 2-year follow-up QOL outcomes in HNC patients, it also provides data that are ahead of most reports of QOL in HNC. Although the term ‘response shift’ was not used, the phenomenon was evident in the reporting of the results, and although ‘global QOL’ was not a term mentioned in the paper, the whole publication effectively promoted life-satisfaction as a global QOL measure in HNC.

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2.4.2 Morton RP (2003) Studies in the Quality-Of-Life of Head-And-Neck Cancer Patients. Results of a 2-year Longitudinal Study and a Comparative Cross-sectional Cross-cultural Survey. *Laryngoscope* 113: 1091-1103

This paper[xxxvi] provides a more detailed analysis of long-term outcomes from the Auckland Cohort, together with a cross-sectional cross-cultural matched-pairs analysis to compare Auckland and Toronto HNC patients.

With the exception of pain and psychological distress (GHQ) there was no observed strong correlation between post-treatment physical functioning and overall, or global, QOL in the Auckland cohort. This may reflect a form of response shift[xxxvii] (*Ringash, 2015*).

When comparing the two population groups, the treatment outcomes (i.e. physical functioning, symptom scores, etc) were remarkably congruent between patients matched for age, gender and time since treatment. Even so, their global QOL was notably different. This can only be explained if the two population groups have differing expectations, differing unmet needs, or different value systems. Effectively, each group perceives that expectations or needs have not been met, or values have not been addressed following treatment. This can be considered a further expression of the earlier mentioned Calman's **Gap Theory** (see section 1.2.5).

[xxxvi] This publication has the distinction of being chosen as one of the "***seminal articles***" on Head and Neck Cancer in the 20th Century. The process for this selection was that prominent international leaders were approached to submit a list of the best ten published articles in their opinion, on their area of special expertise in Head and Neck Cancer. A list of over 2100 articles was generated. An appointed editorial committee selected the ten best articles per topic, producing a 'short' list of 200 publications. The Editor and Associate Editors then selected 100 best articles, to include in the publication:
'*A Century of Progress in Head and Neck Cancer*' (Jaypee Pubishers, 2014).

[xxxvii] refer also to introduction; section 2.4.1, page 79

This report is one of the first to demonstrate the influence of cultural factors on QOL in HNC[xxxviii]. Vilela et al (*2006*) subsequently made a similar observation, noting that their study group - comprising French Canadians - had lower depression and anxiety scores at baseline than that reported by a Swedish group (*Hammerlid et al, 1999*), using the same QOL instrument (the 'Hospital Anxiety and Depression Scale'). Allison (*2001*) found some disparity in symptom scores (especially pain) between 3 cultural groups, but very little correlation with global QOL. Several other more recent cross-cultural studies have focussed on reliability and validity of QOL instruments in various languages and cultures (e.g. *Vartanian et al 2006; Adnane et al, 2016*) without actually conducting a cross-cultural analysis of global QOL. Vartanian et al's study (*2006*) showed that cultural factors were associated with post-treatment work disability. One 12-country validation study of the EORTC QOL Instrument (*Bjordal et al, 2000*) signalled an intention to examine cross-cultural differences in QOL outcomes, but there is no sign of such an analysis having been published[xxxix].

A recent variation on cultural perceptions of QOL in HNC has been published by Demez & Moreau (*2008*). These authors conducted a survey of physicians from two distinct cultures; one a French-speaking "Latin" culture, the other Dutch-speaking with a "Germanic and Anglo-Saxon" culture. Various health states (e.g. the presence of a feeding tube, gastrostomy, xerostomia, or tracheostomy) were proposed to the interviewees, and there was a very significant cultural group difference in the perceived 'acceptability' of each of the health states. It may be assumed that similar cultural variation exists among patients, in relation to the same issues. The perceived acceptability of any specific health-state outcome seems very likely to impact on global QOL.

[xxxviii] This paper has been cited in the literature 84 times by others (*Researchgate, 2018*)

[xxxix] my attempt by email to obtain further information from Professor Bjordal on this issue received no response

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2.4.3 Mehanna HM, Morton RP (2006) Deterioration in quality-of-life of late (10-year) survivors of head and neck cancer. *Clin Otolaryngol* 31(3): 204-211

This paper is the first long-term longitudinal follow-up study of HNC patients to report QOL outcomes at 10 years. A marked, significant deterioration in perceived QOL is described. The *effect size* of this change is 0.72, which can be considered a moderate-to-strong effect (Ferguson, 2009). This finding reinforces earlier observations in the literature from cross-sectional analysis where 'late anger', etc., is reported among long-term survivors (Terrell et al. 1998).

Some cross-sectional studies have published results of QOL in long-term (8-12 years) HNC survivors (*Ruhl et al, 1997; Vartanian et al, 2004; Grignon et al, 2007; Rogers et al 2006*), although the study groups are not strictly comparable because of the cross-sectional study design.

Rathod et al's (*2015*) systematic review of QOL in HNC discussed the reported QOL changes over time. In 9 longitudinal studies, information regarding global QOL was available for the first 12-24 months following treatment. Of these, 2 showed significant deterioration in global QOL, 4 studies showed stable QOL, or marginal improvement QOL and 3 reported marginal (non-significant) QOL deterioration. This can be compared with significant improvement in global QOL over the first 12-24 months in the Auckland study[xl]. This recorded variation between studies, in QOL changes over time may reflect differences in post-treatment support regimens (i.e. a function of unmet needs), or culture (i.e. different value systems).

[xl] *see* section ***2.4.2***

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2.4.4 Mehanna HM, Morton RP (2006) Does quality of life predict long-term survival in head and neck cancer patients? *Arch Otolaryngol* 132: 27-31

This paper is one of the first to identify an association between post-treatment QOL and long-term survival. Only Abendstein et al (*2005*) pre-dates this publication. In recent years, there has been a growing body of evidence in support of the phenomenon that QOL is predictive of survival.

Studies reporting a ***pre***-treatment prognostic QOL measure include Fang et al (*2004*) who showed that baseline fatigue was predictive of overall survival, De Boer et al (*1998*) who found the related perceived "physical self-efficacy" was predictive of survival and de Graeff et al (*2001*) who reported that "less optimal cognitive functioning" carried a two-fold relative risk of dying. Other studies (e.g. *Grignon et al, 2007*) have reported baseline physical functioning to be correlated with later survival; this has also been identified in studies of ***post***-treatment QOL measurement (*Jameson et al, 2008; Meyer et al, 2009*; *Oskam et al, 2010;* see also table below). Siddiqui et al (*2008*) reported that the total (summed) score of the FACT-HN instrument was correlated with loco-regional tumour control, but not related to overall survival.

In addition to global QOL (as measured by life-satisfaction), this Auckland study identified pain as a significant factor for survival (multivariate analysis, p=0.02). Karvonen-Gutierrez et al (*2008*) also found that post-treatment pain scores were negatively associated with 8-year survival.

The most recent report of the prognostic impact of post-treatment QOL (*Aarstad et al, 2014*) found that psychological distress (GHQ score) was predictive of survival in a Norwegian cohort. They used a Guttman scale to score the GHQ and converted this to a dichotomous variable (cut-off > 6). The Auckland study also measured GHQ using a Likert scale and the upper quartile as the cut-off. This latter methodology also revealed a significant effect on survival with univariate analysis, but this did not persist with multivariate analysis, because of confounding with the strong relationship between life satisfaction and survival[xli]. The differences between the studies' results may be the global QOL 10-item 'Life Satisfaction' measure (scale 0-70) used in the Auckland study[xlii]. The Norwegian study (*Aarstad et al, 2014*) used the 2-item EORTC global measure (scale 0-10) which is less likely to be as sensitive a measure, because of lower granularity[xliii],.

Grignon et al (*2007*), Jameson et al, *(2008);* Oskam et al, *(2010);* and Meyer et al, *(2009*), all show a physical subscale (PCS from the SF35, and PF from EORTC-QLQC-30) to be predictive of survival. The physical component is a QOL domain item, distinct from psycho-social and emotional functioning. The Auckland QOL Questionnaire has three rather dispersed[xliv], items that measure physical functioning (PF). In view of the later reports that identify physical functioning as a potential prognostic factor it is unfortunate that the Auckland study did not examine this aspect. It is possible that PF and Life Satisfaction are confounding variables; given the very strong association between Life Satisfaction and survival, it seems unlikely that PF as a separate variable would have prevailed in the regression analysis; certainly some research has found that PF is not associated with prognosis (*de Graeff et al, 2001*). This clearly requires further research, in order to clarify the relationship between PF, Life Satisfaction and Survival.

[xli] The QOL studies in the Auckland cohort, using the Auckland QOL questionnaire, showed signficant correlation between global QOL (Life Satisfaction) and GHQ (see table 2, section 2.3.2 Morton RP, Tandon DA. Validation of quality of life measures in head and neck cancer patients).

[xlii] see section **2.4.1**

[xliii] https://en.oxforddictionaries.com/definition/granularity - granularity: "The scale or level of detail in a set of data".

[xliv] Question 5: "Have you been limited doing your work or other activities?". Item 4 in the GHQ and Item 5 in the Life Satisfaction scale are also similar items.

Author/ year	n	Post-Rx QOL	Sur-vival	HR (CI)	p
Abendstein et al, 2005	357	QOL @ 1 yr	5 yrs	n.a.	0.01
Mehanna/Morton 2006	200	QOL @ 1 year	10 yrs	2.5 (1.4,3.4)	0.001
Goldstein et al, 2007	479	Decrease in QOL @ 1 yr	3 yrs	n.a.	< 0.001
Nordgren et al, 2008	122	Decrease in QOL *domains* @ 1 yr (no QOL incl)	5 yrs	n.a.	< 0.001
Jameson et al, 2008	403	Decr in PCS @ 12mths	5 yrs	0.97 (RR)	0.003
Karvonen-Gutierrez et al, 2008	495	PCS, pain, eating, speech	8 yrs	0.86, 0.92, 0.92, 0.94	≤ 0.005
Meyer et al, 2009	540	Decrease in PF @ 6 mths	5 yrs	0.67 (0.53,0.8)	0.0007
Scharpf et al, 2009	157	Pain at 12 months	5 yrs	2.46 (n.a.)	0.04
Oskam et al, 2010	92	Decrease in PF @ 6 mths; QOL @ 6 mths	5 yrs	5.1 (2.1,14.2) 1.3 (1.1,*2.3*)	< 0.0001 <0.01
Aarstad et al, 2014	162	GHQ @ 12 months	10 yrs	3.4 (1.6,7.6)	0.002

TABLE: Studies that have demonstrated a relationship between post-treatment QOL measures and survival.

HR = hazard ratio; RR = risk ratio; CI = confidence interval;
PCS = Physical Component Scale (SF36); PF = Physical Functioning (EORTC-QLQ);
n = number of patients; n.a. = not available

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2.5 Studies of Targeted QOL Issues in HNC Patients

Four publications have been selected to illustrate the importance of recognising QOL outcomes from a site-specific perspective. The HNC spectrum is rather heterogeneous, and each tumour site relates in specific, particular ways to the various QOL domains (*Hammerlid et al, 2001*).

In this section it can be seen how larynx and skull-base tumours represent different ends of the HNC spectrum and how within one site (larynx) the dynamics may vary according to stage of disease at presentation. A fourth publication focuses not on one tumour site, but rather on one specific domain (pain) and how it may be experienced or expressed differently, according to tumour site and type of treatment.

- Quality of life and functional outcomes in the management of early glottis carcinoma: a systematic review of studies comparing radiotherapy and transoral laser microsurgery
- Laryngeal cancer: quality of life and cost-effectiveness.
- A prospective, longitudinal study of pain in head and neck cancer patients.
- Quality of Life after Parotid and Temporal Bone Surgery for Cancer.

2.5.1 Spielmann PM, Majumdar S, Morton RP (2010) Quality of life and functional outcomes in the management of early glottic carcinoma: a systematic review of studies comparing radiotherapy and transoral laser microsurgery. *Clin. Otolaryngol*. 35: 373–382

HNC is a heterogeneous group of tumours, and within this grouping specific tumour sites have particular QOL issues. This paper focuses on early laryngeal (glottis) cancer, in order to examine the issues relating to this relatively common but rather particular head and neck cancer. With cancer of the larynx, overall survival from different treatment regimens (surgical and nonsurgical) is not materially different (*Dey et al, 2002*), so the focus has been turned to relative QOL outcomes and comparative cost of treatment (*Luscher et al, 2001; Goor et al, 2006; Tschiesner, 2012*). This systematic review[xlv] addresses QOL outcomes following treatment of early laryngeal cancer, including both global QOL and two major specific physical functions implicated in treatment of laryngeal cancer: voice and swallowing.

The provisional finding here, given the absence of any randomised clinical trials (RCTs), is that QOL outcomes are comparable, irrespective of whether the primary treatment is surgery or radiotherapy.

Dey et al (*2002*) considered that a large international RCT here was warranted, but that:

> *"… successful completion (of an RCT) may require international collaboration (and) should … measure complication rates, cost, voice outcomes and patient quality of life as well as mortality and morbidity*".

[xlv] This paper was adjudged the best systematic review to be published in the journal for the year 2010

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2.5.2 Morton RP (1997) Laryngeal cancer: quality of life and cost-effectiveness. *Head & Neck* 19: 243-250.

This paper addresses the question of how different treatments (ablative surgery or non-surgical 'organ-preservation' treatment) for advanced laryngeal cancer might be rationalised when examined from a cost-effectiveness and QOL outcome perspective.

This paper was written after the introduction of chemotherapy plus radiotherapy (C-RT) as an alternative to total laryngectomy plus radiation (S-RT) for advanced laryngeal cancer (*Wolf et al, 1991; Genden et al, 2008*). The non-surgical option was based on the findings that C-RT could achieve survival rates comparable to primary surgery (total laryngectomy), and an assumption that laryngeal preservation would provide better better QOL than an absent larynx and tracheal stoma.

The results from this Auckland cohort indicate that the presence of a permanent tracheal stoma is not necessarily associated with worse global QOL (despite some worse physical functioning with speech, etc.), and provided support for primary surgery as a viable option. In the event - despite preservation of the larynx - C-RT may create major problems with dysphagia and aspiration that can be potentially devastating for the patient. (*Browman et al, 1993; Hutcheson et al, 2008*).

Findings similar to the Auckland results, namely no significant difference in perceived self-reported global quality of life between groups of patients treated by C-RT or S-RT have subsequently been published (*Hanna et al, 2004; LoTempio et al, 2005*). Generally, it has been found that patients treated surgically have worse scores for speech and shoulder function whereas the C-RT patients have worse scores for pain, swallowing, and chewing (*Vartanian &*

Kowalski, 2009).

It is important for patients to know the pattern of QOL outcomes when making decisions about treatment. As stated earlier[xlvi], different cultural groups may regard the acceptability of some health states to be less than others.

As for the cost of care, once the down-stream cost-impact of recurrence is factored in, the Auckland data showed that surgery is less expensive than radiotherapy[xlvii]. This paper challenges oncologists to examine their own local data on outcomes and costs, and not assume automatically that organ preservation provides superior results.

[xlvi] see section 2.4.2, page 90

[xlvii] This paper employs a moderately simplistic approach that lacks the sophisticated modelling techniques relating to healthcare economics that are in use by highly specialised authors (eg. see Blumenschein & Johannesson, 1996).

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2.5.3. Chaplin JP, Morton RP (1999) A prospective, longitudinal study of pain in head and neck cancer patients. *Head & Neck* 21: 531-537.

This paper reports the pain experience reported by HNC patients from the Auckland cohort and is the first long-term longitudinal study of its kind.

This is no doubt that pain is an issue for HNC patients: a systematic literature review of pain prevalence in cancer patients noted that, of all cancer sites, HNC had the highest prevalence of pain (70%; CI 51-88%) (*van den Beuken-van Everdingen, et al, 2007; Zhu et al, 2012*).

Physical pain is an important symptom: it has been used as a dependent outcome variable in QOL research (*Hammerlid et al, 2001*). Moreover, as was found in the Auckland study (see section **2.4.4**) others have reported that pain is a significant negative correlate for long-term survival (*Scharpf et al, 2009; Karvonen-Gutierrez et al, 2008*), and it is well recognised that it has an adverse effect on global QOL. A statement from a Swedish study of QOL in HNC patients describes this latter phenomenon from their findings:

> "*patients with … the worst social and role functioning … were the group of patients with the highest pain score (OLQ-C30) and highest use of painkillers …*" (*Hammerlid et al, 2001*)

This present Auckland study reveals that pain early in the patients' course is predictive of on-going later pain, a phenomenon also noted by Keefe et al, (*1986*). Notwithstanding this, the overall pattern is that after treatment for HNC, the prevalence of pain is lower, and less severe than at the time of presentation. Nevertheless, it is important to monitor pain levels in HNC patients, especially given its association with global QOL outcomes, and survival.

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2.5.4 Kwok HCK, Morton RP, Chaplin JM, McIvor NP, Sillars HA (2002) Quality of Life after Parotid and Temporal Bone Surgery for Cancer. *Laryngoscope* 112: 820-833

This study examines a disease very different from upper aerodigestive tract HNCs and further illustrates the importance of using disease-specific QOL instruments. The effects on appearance and ability to hear and communicate after temporal bone resection (TBR) are quite profound. No other studies have reported on the QOL sequelae from the complex and disfiguring surgery involved in TBR.

Using a case-control methodology, the TBR group is compared with cancer patients having less radical surgery for malignancy in the same region of the body (ie the parotid gland), but with preservation of facial nerve function, facial contour, appearance and hearing.

The results are quite striking, in that the dramatic nature of observer-based assessment (audiometric “dead-ear”; severe facial palsy, and gross disfigurement) did not correlate with the patients’ own concerns. Rather, the factors to adversely impact on patients’ global QOL were: communication difficulty, physical symptoms, and disturbed social functioning. These results suggest that tailored interventions - such as bone-anchored hearing aids (BAHAs) – would address communication and social function unmet needs, and should be considered. Indeed, this approach (i.e. BAHA insertion in patients having had TBR) has been recommended in later publications (*Bibas & Gleeson, 2006; Littlefield et al, 2015*).

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3. CONCLUSIONS

The published works span 25 years of research into Quality of Life outcomes in Head and Neck Cancer patients. The initial work was conducted at a time when research into and knowledge of QOL outcomes in HNC patients was in an early phase. Indeed, there was little appreciation that QOL assessment had a significant role in surgical practice. The first study was a cross-sectional design that confirmed the multi-dimensional nature of QOL, and reported substantial psycho-social dysfunction among HNC survivors. It concluded that longitudinal studies were required to monitor and record patients' progress through their journey from diagnosis, and treatment and into the follow-up period.

Twenty years ago, when the Auckland QOL instrument was developed, there were very few validated QOL assessment instruments. The Auckland questionnaire was piloted, then validated and implemented in a cohort of Auckland HNC patients that were recruited for the purpose. The patients were then followed for 10 years, thus providing a *unique dataset* of QOL outcomes, setting the scene for several unique clinical studies.

3.1. *Landmark Research in this Thesis*.

The Auckland instrument was used to conduct a large matched pairs analysis for *cross-cultural study* - the first study of its kind for HNC - demonstrating an intriguing correlation between culture and global QOL, when other factors are controlled.

The description of *pain experience* in HNC patients, also represents unique published work in this thesis, as does the *QOL impact of temporal bone resection* for large metastatic cutaneous SCC of the head and neck.

The long-term outcomes data provide new insight into the significant adverse impact of *late effects* of HNC diagnosis and treatment; and while the *prognostic relationship* between QOL measures and survivorship is not unique (i.e. that global QOL and pain are significant predictors of survival) the work published here is one of the first 2 papers to bring attention to this effect, and is now become accepted as an established feature of HNC patient survival (see, for example, *Aarstad et al, 2014*).

3.2 *QOL as a Primary Outcome*

The quality of survival becomes of paramount importance when different treatments confer the same survival but a different QOL pattern. The papers on laryngeal cancer in this thesis provide clear illustrations for this phenomenon, and discuss the implications for patients and clinicians alike. Indeed, probable QOL outcome is a major driver for decision-making today, when considering treatment options.

3.3 QOL and Survival

The observation of the relationship between QOL and survival, and the discovery of late deterioration in QOL for long-term survivors has prompted a host of research into how psych-social intervention may improve QOL in HNC patients, and thereby pre-empt late QOL deterioration, and promote better survivorship.

4. IMPACT OF THESE PUBLISHED WORKS ON LATER RESEARCH

The multiple citations of the Publications in this thesis have been cited many times, and is testimony to the influence of this work. Key methodological messages that are reflected in current understanding of QOL in HNC patients include (a) the importance of longitudinal studies, and (b) the need for tailored QOL instruments for unique clinical scenarios. The importance of patients' coping strategies (and the 'gap') has been emphasised, and the need for clinical services to provide survivorship resources, has been referred to in the discussion. The importance on patient self-report was emphasised by the author at a time when beneficent clinicians often did not seek patient input on outcomes; this approach to gathering QOL data has become accepted practice today. Similarly, the effect of culture on perceived QOL (which has become a massive focus of work for the EORTC in recent years) had not been greatly explored at the time of the cross-cultural study reported here.

The *future role* of QOL outcomes assessment in the management of HNC patients has been identified in the published works and includes the role for QOL outcomes assessment in *randomised clinical trials* (RCTs); the role of *psycho-social intervention* in improving QOL and survivorship; and the role of the *multi-disciplinary* clinic in providing quality care for HNC patients,

4.*1* *QOL as an Outcome in RCTs*:

The medical and radiation oncologists have pre-empted surgeons in this task: in the past 10 years there have been 7 RCTs published that included QOL comparisons (*Ringash, 2017*)

4.2 Psycho-social Intervention:

A recent Auckland-based RCT (*Richardson et al, 2017*) - instigated because of the findings reported in the published works in this thesis - has demonstrated that a self-regulatory intervention (targeting illness perceptions and coping) increases social QOL at 6 months after treatment.

A current systematic review of the literature, examining other controlled studies of psycho-social intervention in HNC patients (*Richardson et al, 2018*) has identified 21 studies (10 RCTs), reporting that Cognitive Behavioural Therapy (CBT) and psychoeducation, have the greatest empirical support. Further research is needed to investigate the late effects of psychological interventions among patients with head and neck cancer, using randomised controlled designs, adequately powered samples, and long term follow-up.

4.3 Multi-disciplinary Care:

QOL was largely overlooked as an outcome of interest by most head and neck surgeons when the early papers in this thesis were published. The publications in this thesis have served to bring the issue forward, such that QOL outcomes are now acknowledged as important considerations for both patients and clinicians (*Ringash, 2014*). The *multidisciplinary care* of patients with HNC[xlviii] has also been the subject of several studies (*Birchall et al, 2003; Fleissig et al, 2006; Dingman et al, 2008; Humphris, 2008; Gill et al 2011; Ringash et al. 2017*).

The three aspects of ORL assessment identified above represent components of HNC patient care that are developing today, and will be features of future QOL research. The published works here have made a substantial contribution to this pathway.

[xlviii] this was the theme for the 2010 Eugene N Myers lecture (see ***Appendix 2***)

5. APPENDICES

1. ***The 2009 Semon Lecture***[xlix]
RSM Laryngology Section; University of London, UK Nov 2009

“Changes in Head and Neck Cancer Management caused by Quality of Life Issues”

[xlix] Being invited to deliver this lecture is considered to be the highest honour the University of London can confer on an Otolaryngologist (*personal communication, Prof M Gleeson,* chair, Semon Lecture Committee).

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None declared.

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Changing Perceptions in Head and Neck Cancer Management Caused by Quality of Life Issues

Sir Felix Semon was an outstanding clinician and exceptional laryngologist. The money raised by donations from his colleagues on his retirement in 1909 was used to establish the London University's Semon Lecture. Semon's Obituary in the BMJ, reads: *"In Semon's own hands a lasting cure was obtained in over 80% of the cases he operated on for malignant laryngeal growths, and… his work has proved of immense and lasting benefit to humanity. Furthermore… by avoiding the necessity for more drastic and maiming operations… a large number of patients who have undergone a radical operation for laryngeal cancer are restored… to a useful and happy life."* [1] Today's topic reflects these sentiments and is also reminiscent of the 1989 Semon Lecture, delivered by my mentor, Philip Stell, entitled *'Head and Neck Cancer: can we do any better?'*

Points of tension between QoL and cure

The *primary* outcome of head and neck cancer (HNC) treatment is *cure*; treatment that gives the best chance of cure should be the preferred option and quality of life (QoL) issues will be secondary. But this does not necessarily equate to cure at *any* cost; the time trade-off technique has shown that there are people who would rather be dead than to continue as they are.

The so-called 'Andy Gump' deformity is an early, extreme example of QoL compromise in pursuit of cure. Such adverse QoL outcomes have driven the search for better reconstructive techniques. Now heroic surgery can be attempted – in the name of cure – and followed by prodigious reconstruction aimed at restoring form and function. Such spirited surgery has more recently been matched by equally belligerent chemoradiotherapy, with the aim of *preserving* form and function rather than restoring it. This has led in turn to conservation ('organ preservation') surgery such as TLM (trans-oral laser microsurgery) and TORS (trans-oral robotic surgery).

organ preservation has become something of a surrogate for QoL. Sadly, organ preservation does not always mean organ function

Thus 'organ preservation' has become something of a surrogate for QoL. Sadly, organ preservation does not always mean organ function. Hoffman *et al.*[2] refer to this when discussing treatment of advanced layngeal cancer, *"Organ preservation should only be considered when survival and function (is) equivalent to total laryngectomy and postoperative radiotherapy…"*

Demez *et al.*'s survey[3] found that 75% of Belgian otolaryngologists would withhold curative treatment if it led to impaired QoL. About 40% considered oral diet limited to liquids to be unacceptable but only 25% considered gastrostomy feeding unacceptable. Clinical research suggests that patients do not carry the same values.

Personal research on QoL

My first paper on QoL appeared in 1984 while working with Stell in Liverpool; I reported a 39% incidence of depression in previously treated bucco-pharyngeal cancer patients.[4] This study pre-dated free flaps and IMRT, and the patients were all struggling to cope with the effects of major surgical resections and radical RT. Added to that they were living in Liverpool after all, where the evidence of the Toxteth riots was a constant reminder of how things were.

I was struck by the plight of these patients; I subsequently conducted a two-year observational study in Auckland patients; QoL scores two years after treatment were better than at the time of diagnosis.[5]

In Toronto, using the same QoL instrument, I found that patients of the same age, gender, tumour type and tumour stage, had a *worse* QoL than the Auckland patients, at the equivalent time after treatment, despite having virtually *identical* dysfunction and symptom scores.[5] This comparative study reflects both the resilience of the New Zealand character and the good common sense of our nurses, who were advising the patients. As explained by Calman (1984): *"Quality of Life measures the difference, or the gap, … between the hopes and expectations of the individual and that individual's present experiences"*[6]… which implies that Toronto patients had a generally higher expectation than the Auckland group, and were more dissatisfied even though they had comparable clinical outcomes.

Calman was a student of Immanuel Kant, who wrote: *"Our perception is shaped by our previous experiences."* Kant also said: "We see things not as they are, but as we are" which may explain why clinicians rate patient quality of life differently from the patients. Using Calman's 'gap' approach, we can influence a person's QoL by:

1. Enhancement: optimise function and minimise symptoms wherever possible,
2. Modification: all members of the MDT should present the patient with a consistent picture of what to expect, and avoid unrealistic expectations,
3. Guidance: consider counselling or psychotherapy, to provide patients with the tools with which to cope with change.

When I repeated the QoL questionnaire on the 10 year survivors from my original QoL cohort, the earlier 'good' QoL scores had deteriorated materially.[7] Most of the survivors originally had stage I and II tumours, and should have had relatively few symptoms. So, why the deterioration?

My hypothesis is that they were no longer the focus of attention. Everyone – the doctors, the nurses, and their family – had moved on. The patients were 'locked in' to a life that they hadn't prepared for. Most of them had not expected to survive this long, and the euphoria of having 'beaten the disease' had long gone. This 'time-since-treatment' effect is not related to age, because at no time is age correlated with QoL.[5,7,8]

I also hypothesised that QoL after treatment would be more important than QoL before treatment. Before treatment patients are full of hope and generally pleased that their tumour is being attended to. After 12 months, the therapeutic dust will have settled, and patients know what to expect. Our analysis showed that QoL was clearly the strongest determinant of subsequent survival.[8] In 2005 a Swedish group reported QoL in 357 HNC patients using the EORTC QoL instrument.[9] Five year survival was 54%, and the five year survivors reported better HRQoL at 12 months than those who died. There are four other relevant studies:

1. Goldstein *et al*. (2007)[10] reviewed QoL scores in 479 patients of whom 60% survived three years or more. There was a consistent relationship between several quality of life domain scores and survival, especially in QoL scores at six and 12 months ($p<0.001$). Only long-term survivors showed a positive slope between six and 12 months for all QoL domains and global QoL.
2. Nordgren *et al.* (2008)[11] studied 122 patients with oral cancer; the survival at five years was 52%. They found that the *change* at 12 months in some EORTC QoL items was significantly correlated with survival ($p<0.001$). Unfortunately they did not study the *global* quality of life scores at 12 months.
3. Meyer *et al.* (2009)[12] studied 540 stage I and stage II cancers treated by radiotherapy. Survival was 75% at five years, the change between baseline and six months global QoL was significantly related to survival ($p=0.00047$). The change in the EORTC Physical Functioning also carried very strong statistical significance ($p<0.0000046$) and was an independent predictor of survival.
4. Oskam *et al.* (2009)[13] is an unpublished Dutch study of 75 patients where a deterioration in quality of life at six months carried a HR of 5.08; this, and global QoL was the sole predictor of survival at six years.

Research shows that baseline 'perceived physical self-efficacy' is a strong correlate of six year survival.[14] This is a clue to QoL dynamics. Physical self-efficacy refers to patients' ability to generate and test alternative forms of behaviour and strategies that possibly could influence the course of the illness. Also, *"patients who expressed a higher intensity of negative feelings in regard to their illness… were more likely to survive… than those patients who were unable to express such feelings"*.[14] An inability to express negative emotions is known to be related to the progression of cancers elsewhere in the body.

This begs the question: could we improve survival if we improve QoL after treatment? So far, this aspect of QOL in HNC remains in the research domain.

surveys show that virtually all clinicians think QoL should be measured, but rather few of them actually do it

QoL impact on HNC management

At large international meetings where there are several concurrent sessions, the audiences at QoL sessions tend to be very small; the 'hands-on' subjects seem to be more appealing. Nevertheless, surveys show that virtually all clinicians think QoL should be measured, but rather few of them actually do it. Many clinicians consider that QoL assessment does not affect HNC management, even though HNC treatment affects QoL. Presumably, those clinicians do not understand QoL measures or do not know how to use the results. Perhaps they don't have the resources to collect or analyse the data or they believe that they have sufficient information without a QoL enquiry. Even so, most *research* funding bodies require – and professional bodies such as the British Association of Head & Neck Oncologists (BAHNO) recommend – that a quality of life component be included in the dataset for head and neck cancer.

Perceived role of QoL assessment

Authors reporting on QoL in HNC often do not define what they mean by QoL yet always define HNC. The net result is that the term 'quality of life' has come to be applied very loosely to all kinds of measures and observations.

Ferrans (2007)[15] uses the Wilson-Cleary model to examine what added value may be obtained by measuring health-related QOL. There are both objective measures and patient-generated data. Factors external to the main health stream can contribute substantially to overall QoL which Ferrans calls *'the quintessential element of the model'.* While symptom scores and functional status are important (indeed, often these outcomes are of are specific interest), they are really only components.

Some say that global QoL is too far 'downstream' to be sensitive to treatment-related symptoms and outcomes, and is anyway unrelated to the symptom functioning scores. This is true, but does not invalidate the value of measuring both. There are many examples where QoL has improved even when symptom scores have deteriorated, and it is well recognised that symptom severity scores are not reflected in patients' symptom 'importance' ratings.

Irrespective of whether QoL is measured, one should in practice address patient expectations; inform and advise patients about what to expect not only at the time of diagnosis but also into the 'on-going surveillance' phase. In addition patients' dysfunction and pain must be treated, to minimise symptoms.

The case of laryngeal cancer

Early glottic cancer

If we were to look for a classic tumour for which QoL is a core consideration it would be T1 glottic cancer. Just as QoL is a primary outcome in *palliative care* because survival is not the concern (as everyone dies at the end of treatment), so it is that if virtually everyone survives – as we expect with T1 glottic cancer – then QoL again should be a prime consideration.

A 2009 consensus statement on trans-oral laser assisted surgery for early glottic cancer, was focussed on local control, which was 91-100%, and disease-specific survival which was 91-98%, irrespective of how the tumours were treated.[16]

I submit that if long-term QoL is not being examined in T1 glottic cancer care, then we are missing the point. The above consensus document states that *"there is no universally accepted functional measure to assess the impact of treatment on voice".*[16] That may be so, but we do have a way of assessing the impact of treatment on QoL. Even if voice outcomes differ between treatments, it is not clear how those differences might relate to QoL or patients' perception of their treatment outcome.

Thus, cure rates do not change with treatment, but QoL outcomes might. If QoL proves to be no different, then personal preference – and maybe cost – becomes the issue. Currently, there is an increased awareness of QoL as an issue in T1 glottic cancer, but we cannot say if one treatment or another affects it materially.

Advanced laryngeal cancer

QoL in advanced laryngeal cancer is probably even more important than in early tumours. Alternate treatments for advanced laryngeal cancer exist: chemoradiotherapy or total laryngectomy, followed by radiotherapy. A review[17] of treatment options for advanced laryngeal cancer shows survival outcomes to be effectively the same. On QoL outcomes, the authors state that: *"both chemoradiation and laryngectomy impact negatively on quality of life in different ways. Although differences in quality of life could be detected by functional and subscale analyses, the overall quality of life scores of both groups was similar."* I came to the same conclusion in my analysis of Auckland laryngeal cancer patients.

A cautionary note comes from a study of the National Cancer Database (2006)[2] which reported that *"increase in use of chemoradiotherapy has parallelled increased mortality of patients with laryngeal cancer… the most notable decline in survival occurred among advanced glottic cancer".* So there are questions being asked about the efficacy of chemoradiotherapy.

The quality of life paradox

Because QoL is a composite, complex integrated measure that is not generally reflected in symptom scores, there is a paradox: after treatment patients improve their QoL, even though they have increased difficulty with (say) swallowing, breathing, speaking or with secretions. Patients seem to accept these symptoms as a trade-off for being alive.

Meanwhile, doctors perceive QoL outcomes differently from patients, very often focussing on one or other function and thinking of that as a *surrogate* for QoL. This kind of thinking must be discouraged.

QoL surrogacy; QoL utility

QoL is more than the sum of its parts, and no single item should be used as a surrogate for QoL. If we consider, say, swallow function to be the outcome of interest, when comparing different treatments, then we should call that outcome swallowing, and not 'quality of life'. Hybrid terms are now creeping into the QoL taxonomy, such that we now read of 'voice-related quality of life' when in fact the subject of interest is voice, not QoL. This slippage in terminology is not helping.

Demez *et al.*'s survey[3] indicates that doctors are willing to consider offering a treatment that has a lower survival probability, to preserve patients' QoL. However, Demez *et al.* state: *"in a majority of cases, physicians underestimate the quality of life of their patients", and ask: "should the physician allow his choice of treatment to be influenced by his own perception of quality of life?"* This strikes at the very core of the subject of this lecture. The wealth of patient-generated QoL data in the literature has increased physician awareness of QoL outcomes. The problem is that the quality of much of the reporting is poor, which confuses the issue.

Routine use of QoL measures in the clinical setting continues to be questioned, presumably because functional outcome and symptom scores do not correlate with QoL. However, patient surveys in both Auckland and Liverpool suggest that at least patients find it useful as an *aide-memoire* prior to their consultation.[18]

Quality-adjusted survival is a focus of my current interest together with investigation of unmet needs and the role of psychological enquiry and intervention.

Summary

Overall, there is increased awareness of QoL as an outcome today, and there is increased expectation that QoL will be taken into account when planning treatment. However, most clinicians don't collect or analyse QoL data.

Nevertheless, when reporting survival outcomes, increasingly more papers refer to QoL, even if the data are not available.[19] Ultimately, some form of quality-adjusted survival may become the norm when assessing results of treatment for HNC.

A recent paper states that *"the evaluation of QoL… in cancer is critical to optimal patient care, comprehensive evaluation of treatment alternatives and the development of informed rehabilitation and patient education services"*.[20] I agree. The problem for many is that until we have a unified and meaningful understanding of QoL, what comprises QoL domains, and how they could be measured, reported and interpreted, our perceptions of how HNC management is affected by QoL issues will remain disparate and confused. ■

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American Academy of Otolaryngology-Head and Neck Surgery. Boston, Aug 2010

"Quality of Life Assessment in Head and Neck Cancer patients: Observations and Implications"

Morton RP.
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