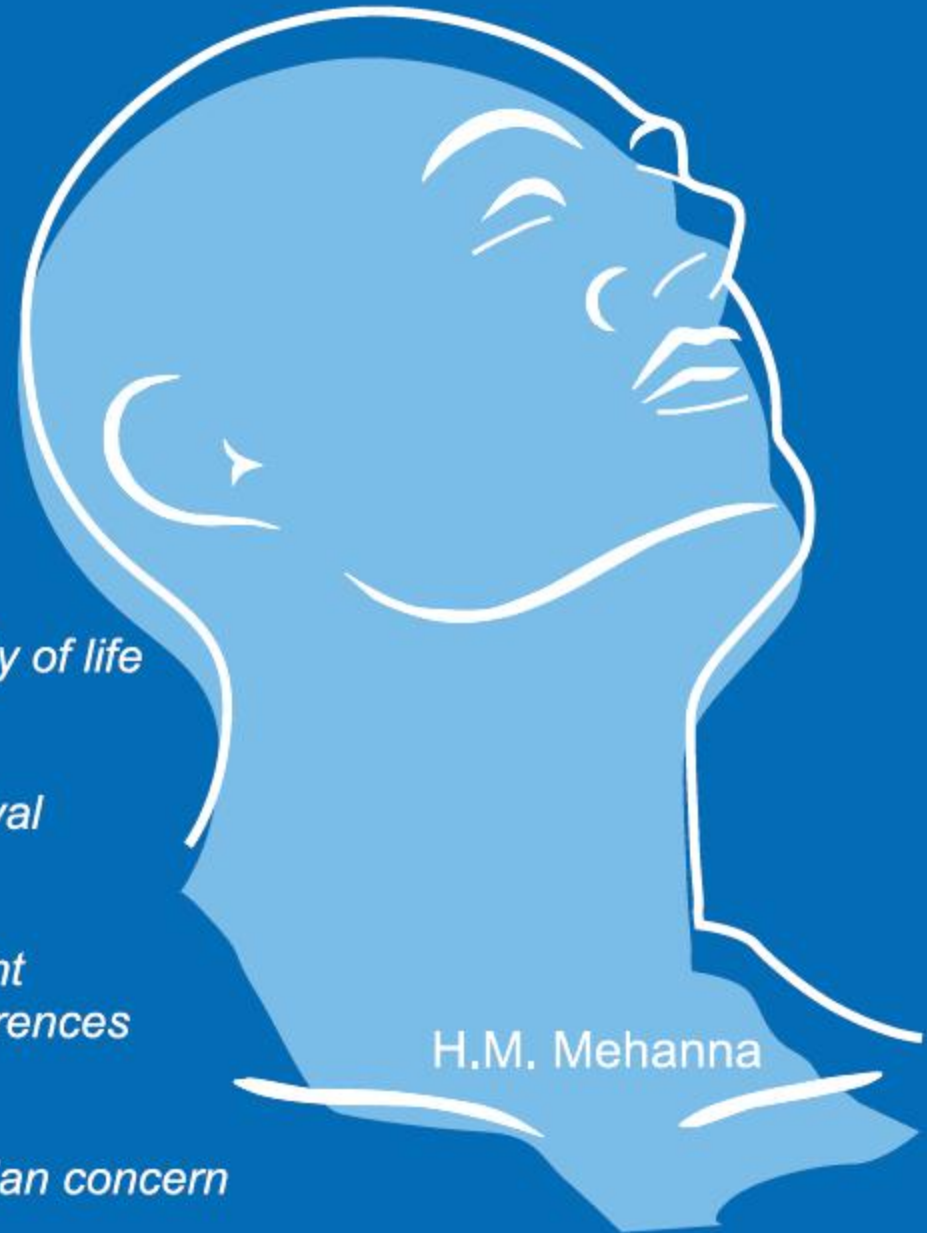


Towards effective assessment of the quality of life of head and neck cancer patients in the clinical setting



quality of life

survival

patient preferences

clinician concern

H.M. Mehanna

Towards effective assessment of the quality of life of head and neck cancer patients in the clinical setting

H.M. Mehanna



**Towards effective assessment of the
quality of life of head and neck cancer
patients in the clinical setting**

H.M. Mehanna

Towards effective assessment of the quality of life of head and neck cancer patients in the clinical setting

Thesis: Erasmus University Rotterdam, the Netherlands

Layout: R.M. Metselaar, M.F. de Boer

Cover design: M.F. de Boer, H Kneefel

Printed by Drukkerij Tripiti, Rotterdam (www.tripiti.nl)

ISBN 978-90-9025752-5

© 2010 H.M. Mehanna. All rights reserved. No part of this book may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission in writing from the proprietor.

TOWARDS EFFECTIVE ASSESSMENT OF THE QUALITY OF LIFE OF HEAD AND NECK CANCER PATIENTS IN THE CLINICAL SETTING

NAAR EFFECTIEVE EVALUATIE VAN DE KWALITEIT VAN LEVEN VAN HOOFD- HALSKANKERPATIENTEN IN DE KLINIEK

Thesis

to obtain the degree of doctor from the
Erasmus University Rotterdam

by command of the rector magnificus

Prof.dr. H.G. Schmidt

and in accordance with the decision of the Doctoral Board

The public defence shall be held on
Friday December the 10th of 2010 at 11.30 hours

by

Hisham Mohamed Hassan Mehanna

born in Cairo, Egypt



Doctoral committee

Promotors: Prof.dr. R.J. Baatenburg de Jong
Prof. R.P. Morton MB, BS, MSc, FRACS

Other members: Prof.dr. J.J. van Busschbach
Prof.dr. S.E.R. Hovius
Prof.dr. P.C. Levendag

Copromotor: Dr. M.F. de Boer

dedication

to my parents, Mohammed and Hoda and my wife Noha

Acknowledgements

The research for this thesis was financially supported by the Green Lane Research and Education Trust Fund, the NZ Lotteries Commission, and the Head and Neck Trust (NZ)

Publication of this thesis was financially supported by: The Institute of Head and Neck Studies and Education, UK and Atos Medical

CONTENTS

Chapter 1: Introduction	9
Chapter 2: Background in the Quality of life in head and neck cancer <i>[chapter In Scott Brown's Otolaryngology and head and neck surgery (7th Ed, ed. Michael Gleeson). Hodder Arnold, London, 2008]</i>	15
Chapter 3: Deterioration in the quality of life of late (10-year) survivors of head and neck cancer <i>[Clinical Otolaryngol. 2006; 31(3):204-11]</i>	51
Chapter 4: Does the quality of life predict long-term survival in head and neck cancer patients? <i>[Arch Otolaryngol Head Neck Surg. 2006;132 (1):27-31.]</i>	73
Chapter 5: The association of psychosocial factors and survival in head and neck cancer <i>[Clinical Otolaryngol 2008, 33, 83-89]</i>	91
Chapter 6: Why are head and neck cancer clinicians not measuring quality of life? <i>[J Laryngol Otol. 2006 Oct;120 (10):861-4.]</i>	109
Chapter 7: Patients' views on the utility of quality of life questionnaires in head and neck cancer <i>[Clin Otolaryngol. 2006 Aug;31 (4) :310-6]</i>	123
Chapter 8: Summary, discussion and conclusions	145
Samenvatting (Dutch summary)	161
Curriculum vitae	169
List of publications	171
Acknowledgements	175

Chapter 1

Introduction

Introduction

Head and neck cancer (HNC) is the 6th most common cancer worldwide, with 500,000 new cases a year. It is increasing in incidence in the UK (1). HNC affects several structures and sites in the head and neck, including the oral cavity, larynx, pharynx, nose, eye and skin. These sites are intimately involved in the essential functions of communication and eating, as well as the senses of smell, taste, vision and hearing.

Why is assessment of the QOL of HNC patients important?

Both HNC and its treatment have significant and often devastating effects on the function, appearance, psychological status, socialisation and individual quality of life of patients. As a result, patients with HNC have specific needs often beyond those of people diagnosed with other cancers (2-4). For example, when speech is affected, patients' ability to express themselves is impaired and can even be severely compromised. These effects and needs are ongoing, and manifest mostly in the post-treatment phase. For all these reasons, quality of life (QoL) and its assessment are of particular importance in head and neck cancer.

For patients with cancer, the outcome of primary importance to the patient is survival. However, despite new methods of treatment, survival from HNC has not improved greatly over the past 20 years (5). As a result, when deciding on the desirability of a recommended treatment for any particular patient, the quality of that survival becomes a major consideration (5). Such QoL effects should normally be weighed against the chances of survival and the likely QoL outcomes that other available treatment options might offer.

Survival statistics are normally based on 5-year data, and a proportion of patients live 10 years or more. Therefore, QoL measurement should be long-term, as well as prospective, in order to characterise the QoL, residual deficits and late side effects of treatment in patients who are cured, and to identify needs that they may have as a result of this.

One of the main aims of studying QoL in HNC is to work towards improving the outcomes of treatment. This may be achieved by gaining an understanding of the baseline state and post-treatment responses and their determinants so that interventions to improve outcomes can be devised.

Achieving effective QoL assessment in the clinical setting

To achieve efficient and effective QoL assessment within a clinical setting in HNC, two essential ingredients are required. The first is to understand the progression of QoL during a HNC patient's journey from diagnosis, through treatment and into long-term, together with the main determinants of QoL over the different phases of their treatment, and the association between QoL and survival. Whilst the short-medium term QoL journey has been well characterised, there has been little research in the HNC literature regarding long-term QoL and its impact on survival in HNC (6,7).

The second is to understand how best to utilise QoL assessment of HNC patients, and how to introduce it into routine clinical practice. It is now well-recognised that there are too many reported tools used to measure QoL in HNC. It is also well-recognised that further research into validating the tools, and identifying the most useful instruments from both the patients' and the clinicians' points of view is necessary (7) in order to facilitate routine quality of life measurement in the clinic.

Overall objectives

The objectives herein correspond to the two main sections of the thesis, and are:

1. To understand and quantify the association between time, survival and QoL in HNC, particularly in the long-term (Section One) , and
2. To explore means of improving QoL assessment, especially in a clinical setting, by determining the QoL tools most appropriate for use by HNC patients and by HNC clinicians (Section Two).

Specific aims

SECTION ONE [CHAPTERS 2 - 5]

Chapter 2: To review the current literature on QoL in HNC, and provide levels of evidence for the information and recommendations provided, according to the SIGN guidelines (8).

Chapter 3: (a) To report the first 10 year longitudinal study of QoL in HNC, describing the change over time of QoL of a group of long-term (10 year) survivors of HNC. (b) To study the association between prognostic indicators of quality of life, including socio-demographic factors (age, gender, smoking, alcohol), disease-related or medical factors (disease extent, disease site - mouth, larynx, pharynx-

chapter 1

treatment type, etc) and long-term quality of life measures (global QoL, depression, physical symptoms) in the aforementioned patient cohort.

Chapter 4: To study the association of QoL and psychosocial factors with long-term survival in a multivariate analysis of prognostic indicators of long-term survival from head and neck cancer

Chapter 5: To review the literature examining the association of QoL and psychosocial factors with long-term survival from head and neck cancer

SECTION TWO [CHAPTERS 6, 7 AND 8]

Chapter 6: To quantify and qualify the practices of clinicians regarding using QoL measurement and QoL tools, and impediments to their use, using a cross-sectional survey of HNC clinicians in Australia and New Zealand

Chapter 7: To identify which QoL HNC questionnaires HNC patients find most useful in expressing their QoL concerns.

Chapter 8: Summarise the main findings and conclusions, discuss clinical implications and suggest future avenues of research.

References

1. British Association of Otorhinolaryngology - Head Neck Surgery (BAO-HNS) (2002). Consensus document on the management of head and neck cancer. BAO-HN, London.
2. Radford K, Woods H, Lowe D, Rogers SN (2004). A UK multi-centre pilot study of speech and swallowing outcomes following head and neck cancer. *J.Clin Otolaryngol*, 29(4), 376-381.
3. Semple C (2001) The role of the CNS in head and neck oncology. *Nurs Stand.* -27;15:39-42.
4. Semple CJ, Allam C (2002) Providing written information for patients with head and neck cancer. *Prof Nurse.*;17:620-2.
5. Hammerlid E, Silander E, Hornestam L, Sullivan M. Health-related quality of life three years after diagnosis of head and neck cancer- a longitudinal study. *Head Neck* 2001;23: 113-125.
6. deBoer MF, McCormick L, Pruyn JFA, Ryckman RM: Physical and psychosocial correlates of head and neck cancer: A review of the literature. *Otolaryngol Head Neck Surg* 1999;120: 427-436.

7. Ringash J, Bezjak A. A structured review of quality of life instruments for head and neck cancer patients. *Head Neck* 2001;23: 201-213.
8. SIGN guidelines, www.sign.ac.uk, accessed 10.10.07.
9. Morton RP: Life-satisfaction in patients with head and neck cancer.
Clin Otolaryngol 1995;20: 499-503.
10. Morton R and Tandon D: Validation of Quality of life measures in head and neck cancer patients. *Aust. J. Otolaryng.* 2000;3: 479-487.

chapter 1

Section One

Chapter 2

Background: quality of life in head and neck cancer

Published: Morton RP, and Mehanna HM. Quality of Life in head and neck cancer. In Scott Brown's Otolaryngology and head and neck surgery (7th Ed, ed. Michael Gleeson). Hodder Arnold, London, 2008

Key points

- Patients' perceptions differ significantly from doctors'.
- QoL is an integral part of assessment of outcomes in head and neck cancer (HNC).
- QoL measurement should be routine, prospective, and long-term; using brief, patient-reported, validated tools, with both general and disease specific modules.
- QoL should be incorporated in to the management pathway of the patient to help improve patient care.
- QoL is the same after chemoradiotherapy or surgery for HNC, despite differences in functional deficits.
- QoL usually decreases immediately after treatment, then gradually increases to pre-treatment levels, usually by 12 months.
- Further research is required.

Introduction

“Just what constitutes ... quality of life for a particular patient and the therapeutic pathway to it often is extremely difficult to judge ...” J R Elkington, 1966.

In the latter half of the 20th century quality-of-life (QoL) emerged as an important outcome measure of medical treatment, especially for patients with chronic or incurable disorders. It is now common practice to include QoL outcomes when considering results of treatment, especially in clinical trials where alternative treatments are being compared. For patients with cancer, the quantity of survival is naturally the outcome of primary importance, but when deciding on the desirability of a recommended treatment for any particular patient, the quality of that survival is also a major consideration (1). Such QoL will also normally be weighed against the chances of survival and the likely QoL outcomes that other available treatment options might offer.

QoL has special relevance for head-and-neck cancer (HNC) patients because of the particular difficulties that they may encounter with everyday functioning. Whilst traditional outcome measures of HNC do not correlate with patient benefit, QoL correlates strongly with satisfaction. Moreover, since different treatment modalities give comparable survival, QoL after treatment becomes a major factor for deciding treatment modality. Formal QoL assessments in treatment of HNC should help to determine the balance between an optimal therapeutic effect on patient survival on

the one hand, and an acceptable QoL outcome on the other. Furthermore, it is now known that patients' and doctors' perspectives of the effects of HNC treatment differ considerably. Some patients do not want to trade survival for function. On the other hand, doctors consistently overestimate the mutilative effect of treatment on the patient, and consistently wrongly prioritise the aims of patients (1). QoL measurement helps the physician understand the patient's perspective and align themselves with that. It can also aid in identifying patients and families with psychosocial problems or risk factors, such as alcoholism or depression, needing active intervention. Finally, there is some evidence from studies of other cancers to suggest that optimising QoL may lead to more treatment - compliant patients, resulting in an increase in survival (2) [level 2&3].

Methods

We searched the following databases: MEDLINE, EMBASE, PubMed, Cochrane, CINAHL, and AMED, as well as cross checking with national guidelines, reference lists, textbooks and personal reference lists. We used the terms "quality of life" with "head and neck" or "larynx" "oral" or "pharynx". The identified abstracts were assessed for relevance. Original articles were assessed as to the quality of evidence according to guidelines published on Evidence-Based On-Call website (www.eboncall.org).

Results

THE QoL-CONCEPT: DEFINITION AND MEASUREMENT

GENERAL PERSPECTIVES

"... We should recognise that the effects of therapeutic strategies and of therapy itself on quality of life are not certain until they have been measured." David Osoba, 1991.

Most people probably have an intuitive understanding of the meaning of quality-of-life (QoL), as the term is frequently referred to and used in relation to health in general and cancer in particular. However QoL is often not measured and usually not specifically defined so that although it is well accepted as a concept, as a clinical outcome measure it represents a relatively new scientific paradigm. Social science research has led to the conclusion that QoL has four particular operational

Chapter 2

characteristics that are incontestable: that is, QoL is a self-reported, subjective, multidimensional phenomenon that changes over time (see table 1).

These characteristics provide a perspective of QoL and a basis for understanding the concept, but as they stand they do not provide a working definition. To conduct QoL research, a general, working definition for QoL is needed. It should incorporate the philosophy of patient-based measures and provide a basis for comparing patients' general well-being within and between studies.

DEFINITION

"Quality-of-life measures the difference between present experience and expectations and between perceived and actual goals." K C Calman, 1987.

The World Health Organisation (WHO) defines Health-related QoL (HRQoL) as: 'an individual's perception of their positioning in life in the context of the culture and value systems in which they live and in relation to their goals, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychosocial state, level of independence, social relationships, and their relationships to salient features of their environment' (3)

King et al (4) observed in their review of the "state-of-the-knowledge" of QoL in cancer patients that the lack of even a consensus definition of QoL may be related to the nature of the concept itself. They identified from the literature to 1995 ten descriptors or definitions of health-related QoL. A summary statement from these offerings is that QoL is a concept relating to the level of one's well-being and satisfaction and encompassing a range of physical and psychological characteristics and limitations that describe one's ability to function and derive satisfaction in doing so. In other words, QoL represents one's personal, subjective assessment of general well-being which can be regarded as a composite scale involving many contributing domains.

A key process in the personal integration of the various aspects of one's life is the perceived discrepancy between the reality of what one has, and what one wants, or expects, or has had (5). The concept embodied in this process has been called the "gap" theory and refers to the gap between reality on the one hand and expectations and desires on the other. This gap needs to be self-reported, because observers (eg doctors) cannot rate it accurately (1,5). Another key factor in the QoL construct is the individual's ability to adopt and employ various coping strategies

(6). A patient-rated global QoL measure will necessarily take account of the gaps between expectations and reality, the relative importance of those "gaps" to that individual, and how they cope with them.

Health-related QoL (HRQoL) has a disease as the focus. From King et al's review (4), it is apparent that QoL in adults is related to, but distinct from, health status. Terrel et al (7) refer to an "overall bother" score as a global QoL measure as a result of symptoms related to the HNC condition. They also employ a similar scale for patients' assessment of their response to treatment. Cohen et al (8) see HRQoL as a compromise which 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, and this is consistent with the definition, and the approach to measurement, of QoL that is used here.

CHARACTERISTICS OF QoL

Social science research has led to the conclusion that QoL has four particular operational characteristics that are incontestable: that is, QoL is a self-reported, subjective, multidimensional phenomenon that changes over time (see table 1).

FIRST OPERATIONAL CHARACTERISTIC: SELF-ADMINISTERED QUESTIONNAIRE

"... The patient's viewpoint of what constitutes a good quality of life is at least as valid as what a researcher or clinician might suggest." A John MacSweeney and Karen T Labuhn, 1990

An important issue in QoL research is the perspective from which it is defined. It is recognised that the patients' own perspective is the preferred source for QoL data. (1,9). An observer is effectively an onlooker of another's life situation and as such will have a limited, or at least different, perspective. Clinical observers have a perspective that usually relates to the on-going clinical management of the patient. As mentioned previously, there is a wealth of evidence now that shows that clinical impressions by observers can be misleading and that patients' priorities differ from health care workers' (1). Some observations may be quite well correlated between physicians and patients – such as degree of disfigurement– but the personal (QoL) impact of the observed variations cannot be anticipated (10).

Partners and other family members are observers who usually have specific and direct concerns about their relative's disability and deformity but who do not

Chapter 2

necessarily rate the patient's perception QoL accurately (11). Family members' concerns are likely to influence assessment of the patient's QoL, and this perspective may determine the quality and amount of support that patient receives (11). Society's view of QoL for HNC patients may very well also approximate a family's initial response. The net result may be a significant impact on the patient's own QoL assessment.

SECOND OPERATIONAL CHARACTERISTIC: SUBJECTIVE, BUT QUANTIFIABLE DATA

"... 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." John E Ware Jr, 1991.

Of course, objective measures can be used to monitor progress reliably and to validate subjective assessments. List et al (12) have produced a reliable performance scale which can discriminate among different levels of functioning across a broad spectrum of HNC. List et al's more recent (13) study of laryngeal cancer patients shows "virtually no relationship between [post-operative] performance outcome and emotional, social, functional or overall QoL." They found that patients cope "rather effectively with both acute and residual disease and treatment effects ... to the extent that these residuals do not globally interfere with life satisfaction". Ware (14) also points out that regression models of objective measures of function generally explain less than half of the variance in the patients' rating of that function.

Objective measures of functions such as swallowing, speech, shoulder movement and muscle strength measures are quantifiable and reliable. However the effect that any specific dysfunction may have on a patient will vary according to many factors, so that objective measures are not necessarily valid QoL scores. The use of objective measures is said to stem from a "beneficence model" of healthcare which assumes that health professionals know what promotes or protects the best interests of patients. It is more likely in fact that patients are in the better position than clinicians to define good and harm as it relates to them.

Clinicians have traditionally regarded subjective measures as unreliable. Despite some problems with inconsistency and difficulties with interpretation and measurement, guidelines (15) have emerged from research in several different fields of oncology. These guidelines are generally accepted and can be applied for the study of QoL in HNC (16) (see Table II). It is now understood that subjective

ratings of QoL can be both reliable and valid, and that patients should score their own QoL, rather than have it assessed for them by an observer. Several QoL instruments have been described for use in HNC. Rogers et al (17) and Ringash and Bejzak (9) summarise these very well. The most commonly used instruments are discussed later in this chapter.

From a practical standpoint researchers and clinicians should try to obtain information from as many perspectives as reasonably possible, but the patients' subjective assessment should form the most important data nucleus, while data from clinicians (e.g. the disfigurement scale), "significant others" and objective measures (e.g. measures of swallowing) will provide useful supplementary information.

THIRD OPERATIONAL CHARACTERISTIC: MULTIDIMENSIONAL NATURE

"Ultimately, the combination of quality-of-life domains assessed in a given study is a function of the patient population under consideration, the nature of the applied treatments and the specific research questions at hand." Neil K Aaronson, 1990.

The general principle that QoL is a multi-dimensional construct, with contributions from several different aspects, or "domains", of life has widespread agreement among QoL researchers (1). Certainly single-perspective, uni-dimensional, or single-instrument evaluations of QoL are now recognized as inadequate. The specific domains contributing to global QoL, or general well-being, will vary according to clinical and socio-cultural circumstances (6).

There are several advantages associated with the multidimensional approach in the measurement of QoL. These have been identified by Aaronson (18) as follows:

- 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.

While specific terminology may differ, the essential components of QoL can be divided broadly into four domains: physical function, psychological state, social interaction, and somatic sensation/symptoms (Table 1).

Chapter 2

Other domains are also accepted as contributory, but these are not normally included in routine QoL assessments. King et al (4) suggest that any comprehensive QoL measure should have a spiritual component. Only 1 of 18 studies in Gotay and Moore's (6) review of QoL in HNC included a spiritual dimension. Cella and Tulsky (19) also cite two other domains - sexuality/intimacy and occupational functioning - which have received rather more attention. Fraser (20) considers that QoL should incorporate not only physical, psychological and social well-being but also economic, occupational and domestic/family domains. Others regard the inclusion of the financial component as an "inappropriate and possible distorting addition". Although the financial consequences of an illness are clearly important, their effect upon a patient, and the community as a whole, is dependent on the structure of community social support programs rather than the biology of the disease. Which dimensions should be included in any study would depend on the aim of the study and the profile of the population under review. Regardless of the number of domain items, the effect on a patient's QoL will be expressed by way of a global measure.

FOURTH OPERATIONAL CHARACTERISTIC: VARIATION OVER TIME

"Ideally the data should describe the QoL of patients before, during and after treatment, giving a continuous picture of any changes." PM Fayers and DR Jones, 1990.

One of the major basic principles of research into QoL of HNC patients (see Table 2) is to design a longitudinal study. De Graeff et al (21) discuss the difficulties of interpretation of data relating to long-term QoL outcomes effects from cross-sectional studies of HNC, and King et al (4) state unequivocally that "there is no substitute for longitudinal assessment in QoL research" as there is an ebb and flow in global QoL in cancer patients. 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 – is not unusual. Therefore longitudinal studies are important so that patients may be used as their own internal controls.

The baseline study is essential if future assessments are to be weighed against the initial status. The pre-morbid characteristics that a patient brings to the initial consultation are clearly very important in relation to later events. The ideal first

assessment should probably therefore be after the time of diagnosis but before the beginning of treatment (it is interesting to note that non-cancer patients presenting for diagnostic biopsy are more distressed pre-diagnosis than patients who turn out to have HNC) (22). The critical QoL value is often not any particular score a patient provides at a specific time, but rather the change over time. This can be extrapolated to comparisons of groups of patients where the central issue is not necessarily whether the overall score is better in one group, but rather whether the change in scores observed over time is different in each group. In that way the dynamics controlling QoL outcomes for individual patients and groups of patients can be adequately understood.

Longitudinal studies of traditional HNC research differ from longitudinal QoL-outcomes research in that studies that select survival and disease-free curves as primary outcomes 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. 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. QoL data, because of its fluctuating nature, is not recoverable once lost. QoL studies require consistent and careful follow-up in order to promote meaningful comparisons and to avoid important loss of information. Given adequate data relating to each of the contributing domains, and sufficient time for follow-up, it is likely that the principle determinants of poor QoL in HNC patients will emerge. Only then may one purposefully pursue Aaronson's suggestion (18) that interventions to improve QoL status be introduced.

METHODOLOGICAL ISSUES SURROUNDING QoL-ASSESSMENT

"choosing an instrument is an exercise in trade offs" Moinpour et al ,1989

In principle, therefore, QoL measurement in cancer patients should use an instrument that not only accounts for likely disease- and treatment-related symptoms but also incorporates several other domains and an overall (global) QoL rating and follows them over time. These principles are central to any QoL enquiry and they lead to the major methodological issues that surround QoL assessment.

First, there is no "gold standard" measure against which any overall QoL score can be tested (9). This is not unusual in social science. In fact, when one considers the central role that coping strategies may play in determining QoL outcomes, it is no surprise that there is also no gold standard for coping ability, even though scales such as the 'Locus of Control' and the 'Sense of Coherence' (1) have been

Chapter 2

developed, and extensively investigated applied in HNC. Nevertheless, the absence of a gold standard should not dissuade one from seeking benchmark measures against which to compare any proposed new assessment tools.

The second issue relates to the need for both global and component measures. The principles regarding the component-versus-global QoL measurement issue have been discussed and developed by Cella and Tulsky (19), and Gotay and Moore (6) and reviewed more recently by others (23). While a 'global' score provides a ready means of comparison between treatments and between patient groups, it is also rather non-specific and difficult to interpret. Therefore QoL should also be assessed at the multidimensional, or component, level so that clinicians obtain the kind of information they require for understanding and interpretation. Ideally the functional measures most important in determining general well-being for any patient or group of patients will be determined thus enabling health-care workers to act upon the results.

In order to obtain an overall QoL score, some researchers have summed the assigned scores from several different QoL items (9). 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 QoL. A question on global QoL in which the patient rates his or her own overall QoL is more appropriate, as QoL is more than the sum of its parts (9). Each or any of the contributing domain items can then be examined for a correlation with the global QoL. Fries & Spitz (24) use the term "hierarchy 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. For example, while the EORTC questionnaire produces an aggregate score, it also contains a single-item, overall global QoL measure. This has recently also been recognised by the University of Washington group who developed one of the first head and neck cancer-specific questionnaires, and who have now added a global single-item question to their instrument (9).

A third problem for QoL instruments is that a comprehensive enquiry of all the likely contributing domains would result in a very arduous, time-consuming and unwieldy questionnaire. A short enquiry is likely to miss important contributory components, and indeed there is a functional dependence of reliability on the length of a test that serves to emphasise the importance of ensuring that a questionnaire is not too

short. The notional ideal length of a questionnaire is probably best described as one in which as much relevant information as possible is obtained without tiring or alienating the patient or interfering with the efficient delivery of clinical care. This is likely to differ for every clinical department and may take some time to determine for any specific situation. Hassan and Weymuller (25) regard the ideal QoL head and neck cancer questionnaire to be short, concise, easy to understand, minimise opportunity for health-worker bias, and be sensitive to changes in health status. As a general principle, one should probably try to gain a little 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.

The fourth major methodological issue relates to generic versus diagnosis-specific QoL instruments. 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. They contribute unique information about QoL that is not captured in disease-specific measures. Many, including Gliklich et al (23), believe that it is essential 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. These requirements should not discourage the clinician-researcher unduly: as Neil Aaronson (18) states, “we cannot ... afford to wait for the ‘ideal’ measure or the ‘state of the art’ infrastructure. Incremental improvement in the quality of our research can be expected only as we develop hands-on experience with the methods that are currently available to us.”

It is disappointing to see that, despite a plethora of publications, no consensus has yet emerged as to which specific parameters should be measured, or which methods should be used in HNC. One generic instrument that has attained widespread popularity and use is the SF-36. This has been applied to many different diseases as varied as sinusitis, hypertension, arthritis and gastro-intestinal disorders. It records data on 6 domains: physical functioning, role functioning, social functioning, mental health, health perceptions and bodily pain. This allows comparison between very different conditions providing data on health status across groups of patients. Although the result is rather non-specific however, because of its generic nature, it has been used for QoL assessment in HNC by several authors.

HISTORICAL DEVELOPMENT OF QoL IN HNC

“... since no-one has yet reported a cure by radical operation, there must be no basis for argument. It cannot increase comfort to add post-operative anemia to cancerous cachexia.” Chevalier Jackson, 1901.

QoL assessment as part of clinical practice in oncology had its beginnings about 50 years ago. Early QoL studies in HNC patients were narrative and cross-sectional; these were followed at first by simple quantitative measures of various parameters and later by longitudinal studies of greater complexity. Relatively few HNC studies have reported global QoL and only recently have prospective studies and the incorporation of QoL assessment in randomised HNC clinical trials emerged. As yet no studies have compared QoL measures from widely different socio-cultural groups.

Changing Attitudes

"In deciding the method of treatment we should not, in our eagerness to achieve cure, lightly disregard the crippling that may result from our surgical endeavours". M.R. Ewing & Hayes Martin, 1952

Although recognition of the importance of the patient's personal life-satisfaction or psychological well-being in the management of an illness goes back to Hippocrates' (c460 - 377 BC) time, the traditional focus of medical care has been on the treatment and control of disease, on the assumption that patient benefit will follow. So it is that in 1886 Jessett spoke of maxillary cancer "... the only hope we have of permanently benefiting the patient suffering from this disease is by free and extensive operations, i.e., thoroughly removing the whole of the cancerous tissues and getting to healthy structures."

Open concern from doctors treating HNC for patients' psychological well-being became increasingly evident in the latter half of the 20th century (26). In 1954, Ormerod described the standard practice of taking care before laryngectomy to explain to a patient what is entailed in the operation, including counselling by a speech therapist and interviews with previous patients. In 1983 Natvig confirmed the importance of this in his studies (27). Even so, those concerns were not universal: indeed, it was common for the diagnosis to be withheld from patients - a situation hardly conducive to systematic psycho-social enquiry. On occasions, psychological enquiry of cancer patients was even vigorously opposed (26).

Concern for the psycho-social aspects of patients facing death gathered momentum in the 1960s with the emergence of the Hospice movement pioneered by Cecily Saunders in Britain and Elizabeth Kubler-Ross in the U.S.A.. This phenomenon gave considerable impetus to the development of QoL assessment in oncology in general. Despite the interest in QoL outcomes after curative therapy, the study of effectiveness of palliation for patients with end-stage recurrent disease is likely to be one of the most important and useful applications of QoL research in head-and-neck cancer.

Terminology

“What kind of a device would you call this?’ asked one of his scientific friends present. ‘I call it an X ray,’ said Roentgen.” Donald T Atkinson, 1958

The term "Quality-of-life", was first used in an essay submitted to the Dwight Eisenhower's Presidential Commission on National Goals by A.L. Heckscher (26). In 1977 "quality-of-life" became a 'key word' by which journal articles could be retrieved by the United States National Library of Medicine Medline Computer Search program. Since then, there has been a steadily increasing body of QoL-related clinical research, including work related to HNC, as evidenced in recent reviews.

QoL Measurements and Measurers

“Opinions vary as to the usefulness and interpretation of various quality of life instruments (but) the need to consider the possible impact of treatment on QoL is widely recognized” Trotti, et al, 1998.

The history of QoL measurement follows the history of the development of the QoL concept, and the evolution of the science of psychometric analysis. Quantitative assessment of QoL in cancer patients had its beginnings in the latter half of the 1940s (26), although the psycho-social impact of treatment was regarded at that time as not generally quantifiable.

Before 1980 the validity and range of QoL measurement devices was such that few useful studies emerged. The patient interviews that formed the basis of many reports were usually not defined, and those psychometric instruments that were described were directed at only one or two QoL aspects, such as emotional state. Only very limited information could be derived with these study designs.

Chapter 2

In 1981, McNeil et al (28) provided some insight to society's values in their analysis of the trade-offs that different groups within the community were prepared to consider in respect of treatment alternatives for advanced laryngeal cancer. They concluded that (healthy) people were prepared to trade 2 or 3 years of life in return for preservation of the larynx when considering treatment options for a theoretical advanced laryngeal cancer.

In the 1980s, it became possible to test the psychometric properties of QoL instruments. Several cross-sectional studies developed and tested the reliability and validity of modern QoL instruments devised using Guyatt's principles (9). The most comprehensive cross-sectional study of HNC patients from the early studies was reported by Natvig (27). The research was confined to patients in Norway who had had a total laryngectomy between 6 months and 18 years previously, and represented a valiant effort to cover all aspects of the impact of the surgery, including physical, social, psychological and occupational aspects of life. In general, the early cross-sectional studies were concerned with laryngeal cancer and laryngectomy. Those reports relating to oral and pharyngeal cancers indicated that rehabilitative concerns were often greater than those generally encountered after laryngectomy.

Social scientists (e.g. Gotay and Moore [6]) see that HNC is ideally suited to QoL measurement and that "the development and application of vigorous scientific research in this field holds enormous promise". Although the potential importance of QoL outcomes in HNC research is probably still not fully appreciated by many clinical otolaryngologists, there is considerable interest in the QoL paradigm from both disciplines. In 1983, a paper from Sweden was the first collaborative effort between an otolaryngologist and a social scientist, and the first to provide a quantified QoL index in head-and-neck cancer. Since then there have been many examples.

The most recent step in the evolution of QoL measurement has been the longitudinal studies - where patients act as their own 'controls' - and data from clinical trials where like groups can be legitimately compared. These provide a much more reliable basis upon which to reliably determine those factors which influence QoL outcomes.

Pruyn et al (11) searched the literature for studies of psychosocial aspects of HNC and found 117 studies to 1984, of which only 13 "chose a longitudinal approach". Most of those studies were limited in scope – such as voice rehabilitation following

total laryngectomy – and were not very sophisticated from a psychometric perspective. Pruyn's group have produced a further, similar review for the period 1984 to 1995 (29). There was a clear increase in the proportion of prospective studies (16 out of 50 selected studies). Several of the longitudinal studies used instruments with good psychometric properties and somewhat broader parameters than earlier reports. Most of the studies were of rather limited duration (3-6 months) although studies of 2 and 3 years' duration are now appearing. Longitudinal studies of less than 12 months' duration have probably been too short to draw conclusions regarding overall QoL outcomes after treatment for HNC.

Nowadays it is standard practice to include QoL considerations in clinical research, to the extent that QoL has become a recommended end-point in clinical trials, and the National Cancer Institute of Canada Clinical trials Group now incorporate QoL data in all their clinical trials.

CURRENT QoL INSTRUMENTS FOR HNC

“It is hard properly to evaluate human suffering: the blind say they would rather be blind than deaf; whilst the patient without a voice considers himself fortunate that he is neither blind nor deaf.” Leroy A Schall, 1954.

Guidelines for development of QoL questionnaires

‘researchers should undertake comprehensive literature searches to ascertain whether a suitable measure is available before they decide to develop a new [measure]’ Garratt et al, 2002.

The science of psychometric and clinimetric measures has developed to the stage where a considerable degree of confidence in reliability and validity can be generated in the data from self-administered questionnaires. Kirshner and Guyatt (15) have developed a framework for evaluating health indices such as QoL assessment, in which they describe the basic steps for the development of an instrument (Table 2). Kirschner & Guyatt's (15) requirements for development of QoL questionnaire items are: selection of item pool, item scaling, item reduction, reliability, validity, and responsiveness. The issue of questionnaire validity is a notion that is not traditionally familiar to clinicians. Bombardier and Tugwell (30) provide guidelines for assessing questionnaire validity, in terms that can be readily understood by medical readers (Table 3).

Chapter 2

The principles embodied in those steps have been incorporated and developed into a guideline for the study of QoL by the European Organisation for Research and Treatment of Cancer (EORTC) (16). The EORTC QoLQ-30 core questionnaire has been through this development process (16). It represents a generic QoL instrument and, to it has been added an 'Head and Neck' site-specific module designed for HNC patients. An instrument subjected to this kind of rigor will be robust and able to provide meaningful data for analysis.

Summary of commonly used QoL instruments

"Choosing which instrument to use poses a challenge for investigators of QoL in head and neck cancer. No one instrument is ideal for all purposes." Ringash and Bezjak, 2001

There are now many instruments in use for assessing QoL in cancer patients and several (71 were identified in a recent review [9]) have been developed or adapted specifically for head and neck cancer. Many studies have conducted cross-validation of HNC-specific instruments with various generic instruments, and between HNC-specific questionnaires, so that the validity and reliability of many instruments has now been determined (6,9). The most commonly used measures of QoL have been summarised in Tables 4 and 5. The information presented has been adapted mainly from the excellent structured review of commonly used QoL instruments in head and neck cancer by Ringash and Bezjak (2001) (9).

All the instruments included have their particular strengths and weaknesses, and it is acknowledged that no one measure exists for all purposes. The informed selection of a measure appropriate for a specific requirement is essential, and may be guided by structured reviews, consensus and expert opinion. To take the situational examples mentioned by Ringash and Bezjak in their review (9), the EORTC or FACT may be useful for studies comparing HNC patients to those with other cancers, as these tools have general as well as specific modules, and have been used extensively to assess different cancers. If, on the other hand, the aim was to study very specific patient groups, then a very specific tool eg HNRQ for radiotherapy patients and UoWQoL of surgical patients, may be more sensitive. For international or multi-cultural studies, the EORTC or FACT may be most appropriate as they have been translated into several languages, and the EORTC has been assessed cross-culturally.

Garratt et al (31) suggest that "researchers should undertake comprehensive literature searches to ascertain whether a suitable measure is available before they

decide to develop a new (measure)". Aaronson (26) advocates that energy be spent searching for existing instruments to suit (perhaps with some modification) rather than expended on generating new instruments. This is a view supported by many. Future efforts should be directed at completing the assessment of reliability, responsiveness and validity of current measures, concentrating on direct comparisons between measures, and on determining the most appropriate tools for particular situations. [Grade B].

WHAT DO WE KNOW ABOUT QoL IN HNC?

There are many apparent inconsistencies in QoL research in HNC patients that are probably related to many different factors, such as patient case-mix, local treatment, and method of voice rehabilitation after laryngectomy (oesophageal voice versus tracheo-oesophageal puncture), available social support, and cultural and ethnic issues. Measuring QoL outcomes using clinical trial methodology can control some of these factors.

Impact of Time on QoL

"there was a significant improvement between diagnosis and the 3 year assessment for global QoL" Hammerlid et al, 2001.

The longitudinal studies of QoL in HNC reported to date have generally used different instruments to measure QoL. In those studies where different instruments are compared, it has been shown consistently that the different QoL measures correlate strongly with each other, which suggests that the different questionnaires are measuring the same phenomenon, but in slightly different ways.

In general, studies show that QoL at diagnosis is lower for HNC patients than for the population in general (32). This worsens during and immediately after treatment. In Hammerlid et al's study (33), QoL reached its worst level one month after radiotherapy treatment, and three months after total laryngectomy. Schliepake et al (2002) found the same was true for reconstructed oral cancer resections (34). QoL then starts improving, so that by one year after treatment QoL returns to pre-treatment levels (32,35). There appears to be slight further improvement between the first and third years, as reported by Hammerlid et al (35). Morton (5) showed no significant drop in general well-being (global QoL) at 3 months after treatment, but a significant improvement, compared with pre-treatment levels, after 12 and 24 months. By three years, although patients still suffer significant functional deficits,

Chapter 2

their global QoL shows no significant differences to the general population. (35) [Level 2]

Impact of Site and Stage of Disease on QoL

"Patients with large tumours were more affected by their disease than patients with small tumours" Hammerlid et al, 1998.

QoL is positively correlated with the stage and site of the disease (36, 38). The effect of stage of the primary tumour on QoL may seem as a surrogate for the effects of treatment, as one determines the other. However, even at diagnosis, stage III and IV laryngeal tumours have lower global QoL scores than stage I and II (33). Furthermore, QoL improved after treatment for all stages, but still remained lower for the more advanced tumours. De Graeff et al found that the same was true for oral cancers (36), and Rogers et al found that tumour size for oral cancer was a significant predictor of post-treatment QoL at 1 year (37). Therefore it would appear that the stage of the disease independently affects QoL. Interestingly, Hammerlid et al found that the difference in QoL due to stage appears to increase with time after treatment, so that it was greater at three years than at diagnosis (35). [level 2]

The site of the primary tumour not only affects functions specific to that site, but also appear to affect global QoL. Weymuller et al in their prospective study of 210 patients found that hypopharyngeal tumours have the worst global scores and laryngeal tumour patients have the best (38). Other studies have found the same. Moreover, within one site, subsites differ in their effect on QoL, eg tongue base tumours have the worst QoL amongst oral cancers (37). [level 2&3].

Impact of Treatment on QoL

"Results suggest that total laryngectomy is not necessarily a disastrous event for most patients" Morton, 1997.

Many HNC patients do not want to trade off survival for function (39). Therefore, survival is the consideration that should be of primary importance whenever cancer treatments are compared and the QoL aspects of care need to be reviewed in the light of the eventual survivorship.

There appears to be a perception amongst some clinicians that because radiotherapy does not result in tissue loss, it must lead to a better QoL. This is not

supported by data. It is important when counselling patients and deciding on treatment options to bear in mind that any treatment modality in HNC, whether it be surgery, radiotherapy or a combination of both, results in significant morbidity and a negative impact on QoL.

It is also important to remember that current evidence suggests that QoL is primarily not determined by treatment modality. Furthermore, functional limitations caused by treatment do not necessarily translate into worse QoL. In other words, QoL does not correlate with physiologic measures of function. List et al (13) found no difference in global QoL between total laryngectomy, hemi-laryngectomy and radiotherapy treatment groups in their study of 21 laryngeal cancer patients. They however demonstrated quite marked differences between these treatment groups in respect of symptoms and physical functioning scores related to speech and deglutition. They stated that their findings “contradicted expectations that functional restrictions ... would have a negative impact on overall QoL”.

Another report, by Morton (39), comparing QoL outcomes of laryngeal cancer patients treated either by radiotherapy or total laryngectomy showed similar apparently counter-intuitive results in which patients treated surgically had greater dysfunction than patients treated by radiotherapy, and yet had similar global QoL scores. Weymuller et al in their prospective study of 210 patients also found that there was no difference in QoL between the chemoradiotherapy and laryngectomy treatment groups (38). Furthermore, Stoeckli et al compared patients with early laryngeal disease treated by laser with those treated by radiotherapy and found no significant differences in global QoL (40). This seems to suggest that at least some groups of patients can learn to cope with and adapt to dysfunction, given time and appropriate support measures. It should be remembered that longitudinal studies of 2-years or more have less than 50% of the initial patient group surviving to contribute to the 2-year assessment. However, those that do survive seem to have adapted remarkably well to their disability or handicap. (Level 2).

Survivors from the widely reported “VA study” of laryngeal cancer where patients were randomly assigned to combined surgery and radiotherapy or induction chemotherapy prior to radiotherapy or surgery have recently been reviewed for QoL outcomes (41). While the study was not designed to monitor QoL, the prominence of this particular study means that the results are viewed with great interest. Only 46 of 93 ‘known survivors’ were assessed, and speech function was found to be similar irrespective of laryngectomy status. Pain scores were less and emotion/depression scores were better in the patients in whom the larynx was

Chapter 2

preserved. The results indicated that pain and psychosocial function were more important to patients' QoL than speech. Unfortunately the cross-sectional nature of the QoL data and the incomplete follow-up raises many questions.

Another important aspect of the effect of treatment on QoL is the impact of the mode of reconstruction (mainly in oral cancers) has on QoL. Because of the considerably greater effort and cost involved in revascularised tissue reconstruction, it is important to establish its efficacy and superiority over less complex reconstruction techniques to justify its routine use. Schliepake et al (34) has recently shown that revascularised fasciocutaneous flaps produced the greatest improvement in QoL, when compared to local flaps and myocutaneous revascularised flaps. Moreover, at 12 months, revascularised forearm flaps resulted in a higher QoL than at diagnosis. Myocutaneous revascularised flaps for large volume defects produced the lowest QoL scores, with QoL being significantly lower at 1 year than at diagnosis. [Level 2]

Impact of Premorbid Patient Characteristics on QoL

"Psychological interventions in patients with head and neck cancer that fail to take pre-existing problems into account may incorrectly focus on adjustment to illness". Walter Baile, et al, 1993.

It is likely that, if survivorship and QoL outcomes are similar between treatments, economic factors will become major determining factors in the treatment decision-making process. One variable that may moderate that process, however, is the pre-morbid QoL profile of any particular patient. Very little information is available in relation to the premorbid characteristics of HNC patients.

Demographic characteristics

"Studies do not show a consistent difference between men and women [in QoL]... With regard to age, it is often assumed that elderly patients fare worse but few data support this view" de Graeff et al, 2000.

Demographic information such as age, gender, vocation, work profiles, level of education and marital status is often reported but it is not clear what importance to place on these factors from the QoL point of view. At this stage there is no consistent evidence for any inter-group differences in QoL at diagnosis or as an outcome based on the aforementioned demographic patient variables (32,35) [Level 3].

Alcohol and Tobacco

“... Alcohol consumption ...may not be perceived by the patients as having as much of an effect on health status as does medication ...” Erin M. McDonough, et al, 1996.

The life-time alcohol and tobacco consumption of HNC patients has been widely reported, but these life-style parameters of social functioning do not necessarily reflect QoL or general well-being; and they often change (by choice) after treatment for HNC. This suggests that patients’ priorities alter after they discover that they have developed a malignancy. However, if patients are instructed to alter dietary habits (including reduction of alcohol consumption) after treatment for head and neck cancer, their compliance is not predictable (42). Some research suggests that the individuals who have less disruption to their lives – for example those who have less advanced disease or who undergo less invasive treatment – are the ones more likely to continue smoking (42), despite an increased risk of recurrence and death. Importantly there is evidence that alcohol intake ‘can provide important prognostic information’ in HNC, and that abstinence amongst alcoholic patients can lead to prolonged survival. (43) [Level 2&3]

Sexual Functioning

“As for sex, I didn’t think of my cancer of the larynx patients in terms of their sexuality.” Lawrence W. DeSanto. 1994.

Some authors have investigated pre-treatment sexual functioning in HNC patients. De Santo et al (44) found that about two thirds of laryngeal cancer patients treated surgically cited no change or only a slight decrease in sexual interest after surgery but that about 20% of all patients reported serious sexual performance problems post-operatively. Presumably not all of the patients reporting ‘no-change’ were sexually active pre-operatively. Herranz and Gavilan (45) using the same instrument as DeSanto et al reported 55-60% of patients and their spouses had no change in their interest in sex and about 40% had no change in sexual activity. It is uncertain from these reports how sexual functioning – or a change in functioning – correlates with overall QoL or whether it should be recorded at the time of diagnosis. [Level 3]

Coping Skills

“From a clinical perspective, (the first area to) be considered in determining patient risk for psychological disturbance includes patient variables such as ... coping

Chapter 2

resources. It is likely that laryngeal cancer patients are at increased risk for psychological disturbance.” Richard P McQuellon and Gail J Hurt. 1997.

There is a gathering body of evidence to suggest that pre-existing abilities in relation to coping skills and stress management may well be important (1). The retrospective nature of most of the studies of coping means that only survivors are assessed and that the evidence is potentially biased or non-representative of the total population being studied. Baile et al (46) noted that HNC patients showed a more “repressive” coping style than non-cancer patients, with high scores on dependency and social conformity among the HNC group. This would explain the observation that married patients fare better than unmarried patients, and that over 80% of laryngectomy patients who retain their circle of friends develop oesophageal speech whereas only 10% of those who lose all their friends regain speech. [Level 3]

Langius et al (47) followed a group of oral and pharyngeal cancer patients prospectively for 12 months and found a strong positive correlation between patients' inherent coping ability - as measured by the sense of coherence - and psychosocial, physical, and home functioning, and eating disturbance. De Boer et al (48) also showed in a cross-sectional study that the important factor in rehabilitation seemed to be not so much the treatment received - or the site of tumour (oral cavity versus larynx) - but rather the innate ability of patients to cope. This issue of patients' coping abilities is quite pivotal, as the ability of an individual to adjust is determined at least in part by that person's coping ability. Support for this notion comes from Italy (49) where it was found that the single most important factor in determining patients' mental coping with disease was, after multivariate analysis, the time since treatment (less than, or more than 12 months).

Psychological Factors

“Heightened attention to the psycho-social concerns of patients treated for head and neck cancer will serve to ... increase levels of compliance and maximize patient outcomes.” Erin M McDonough et al. 1996.

Davies et al (22) examined the psycho-social aspects of patients prior to endoscopy for diagnostic biopsy and found that patients with cancer had a significantly higher rate of depression (29%) before biopsy than the group of patients whose biopsies were negative. Baile et al (46) also found a high rate (about 40%) of pathological anxiety and depression among HNC patients prior to biopsy, but found that patients with benign lesions were slightly more emotionally

disturbed and significantly more stressed. Baile et al suggested that cancer patients may minimise the seriousness of their problems, and that there is "a need to assess psychological status of these patients before treatment". The very few prospective studies in this field show that depressive symptoms may be one of the significant pre-treatment predictors of QoL (36) [level 2]. For example, the psychological preparation pre-operatively also appears to be a major factor for post-operative adaptation and adjustment (50). Moreover there is evidence now emerging that psychosocial intervention (in the form of long term psychological therapy) may result in significant improvements in QoL of HNC patients compared to controls (33,51,52). These findings have led several authors to suggest that the identification of patients with depression should be routinely carried out, and interventions instituted as part of the rehabilitation program [Grade B].

Cultural, religious and spiritual factors

"75% of patients surveyed thought that their physicians should address spiritual issues as part of their medical care" Matthews et al, 1998.

For many years QoL in HNC has been reported from different centres by authors who each used their own particular measure to record QoL. In recent years there has been wider utilisation of some of the QoL instruments by different centres which allows comparison between populations. Even so, there has been little or no attempt by authors to examine or explain differences between populations according to cultural differences. Some studies have reported multi-centre studies of QoL in HNC patients, but still there is a degree of cultural homogeneity in the study groups.

The impact of religion and spirituality has recently been studied more closely. Studies show that they have a positive role in maintaining physical and mental health in times of stress and grief, and that 75% of HNC patients want doctors to address spiritual issues (53) [Level 3]. Doctors are not trained in enquiring about non-medical concerns of patients, and therefore may find it alien. However, routine questioning about the role of religion in the patient's coping mechanism, and how to support that, is to be encouraged [Grade B] (1).

Social support

"Social support ...is thought to be a good predictor of subsequent well being" Collins, 2000.

Chapter 2

As noted above, HNC patients appear to be more dependent on family and social support. Stam et al (54) found that satisfaction with social support and pre-operative counselling by a laryngectomee predicted later satisfaction and higher QoL. They found that Natvig (27) identified 3 areas that were important QoL determinants. These were: individual patient coping skills, family support, and pre-operative counselling of the patient and his family. Other studies have found similar findings. [Level 3]

Performance status, Symptoms and Co-Morbidity

"[Pre-operative] functional status ...has been shown to be positively correlated with QoL" de Graeff, 2000.

In the very good study by de Graeff et al (36), the baseline pre-treatment performance status (as measured by the Karnofsky performance status) was one of the significant predictors of QoL after treatment. Similar findings were reported by Hammerlid et al (55) in their study which found that physical functioning at diagnosis was an independent predictor of global QoL at three years post-treatment. [Level 2]

Symptoms, whether from the tumour or from its treatment, may also determine QoL. Pain is a commonly reported correlate of QoL, and pain may be predictably related to treatment. For example, if the neck has been surgically treated, shoulder pain and discomfort will be worse than if no neck dissection is performed. Chaplin and Morton (56) showed that the prevalence of pain and discomfort was no different with the type of neck dissection although Kuntz et al (57) reported that the degree of discomfort and pain was more with radical neck dissections [level 3].

Co-morbidity in the context of cancer is defined as a patient's medical condition which is in addition to and distinct from their index cancer. Patients with head and neck cancer are likely to have co-morbidities, because they are usually older and have usually had high consumptions of tobacco and alcohol. Co-morbidities significantly affect head and neck cancer patient's outcomes and survival (58-61) [Level 2]. This is partly because these co-morbidities interact with the patient's cancer and its treatment, eg whether a patient is fit enough for a certain treatment. Co-morbidities can also affect survival independently- eg a patient may be cured from the HNC but die of heart failure. Co-morbidity may also be an independent determinant of QoL, especially the longer a patient survives (61).

Areas for future research

- Clearer definition of QoL and consensus on how to measure it.
- Randomised prospective trials with large numbers of patients with same site primaries, and the emergence of long-term prospective data
- Assessment of impact of ethnicity, culture and spirituality.
- Evaluation of reproducibility of disease – specific measures instead of development of new tools, and identification of best tools for particular circumstances.
- More structured QoL assessment of organ preservation methods.
Is QoL enhanced by the following: selective neck dissections, organ preservation surgery, organ preservation chemoradiotherapy?
- Clearer understanding and more regular assessment (eg by specialist counsellor) of contributing factors to well-being and determination of effects of intervention in these on QoL.

Conclusions

Assessment of quality of life in patients with head and neck cancer has improved our understanding of patients' priorities and the patient journey during and after treatment. This has improved clinicians' ability to provide patients with appropriate information regarding their condition and treatment, and to aid patients during the decision making process.

There are further, potentially greater, benefits to come in future however – these include better reporting formats of QoL studies, improving the follow-up consultation, screening patients for problems and initiating interventions to improve QoL.

References

1. Collins SL. Quality of life issues in head and neck cancer management. in Penzak M(ed): Current Controversies in Otorhinolaryngology. Thieme; 2000:101-115.
2. Stockler M, Osaba D, Goodwin P, et al. Validation of the PROSQoLI: a pragmatic outcome measure for clinical trials in advanced prostate cancer. *Proc Am Soc Clin Oncol* 1995; 14:244.
3. World Health Organisation. Rehabilitation after cardiovascular diseases, with special emphasis on developing countries: Report of a WHO expert committee. Geneva: WHO; 1993. WHO Technical Report series 831.
4. King CR, Haberman M, Berry DL, et al: Quality of life and the cancer experience: the state of the knowledge. *Oncol Nurs Forum* 1997;24:27-41.
5. Morton RP: Life-satisfaction in patients with head and neck cancer. *Clin Otolaryngol* 1995;20:499-503.
6. Gotay CC, Moore TD: Assessing quality of life in head and neck cancer. *Qual Life Res* 1992;1:5-17.
7. Terrell JE, Nanavati KA, Esclamado RM, Bishop JK, Bradford CR, Wolf GT: Head and neck cancer-specific quality of life. *Arch Otolaryngol Head Neck Surg* 1997;123:1125-1132.
8. Cohen SR, Mount BM, Tomas JJN, Mount LF: Existential well-being is an important determinant of quality of life. *Cancer* 1996;77:576-586.
9. Ringash J, Bezjak A. A structured review of quality of life instruments for head and neck cancer patients. *Head Neck* 2001;23:201-213.
10. Stewart M, Chen A, Stach CB. Outcome analysis of voice and quality of life in patients with laryngeal cancer. *Arch Otolaryngol Head Neck Surg* 1998,124:143-148.
11. Pruyn JFA, deJong PC, Bosman LJ, et al: Psychosocial aspects of head and neck cancer. A review of the literature. *Clin Otolaryngol* 1986;11:469-474.
12. List MA, Ritter-Sterr C, Lansky SB: A performance status scale for head and neck cancer patients. *Cancer* 1990;66:564-569.
13. List MA, Ritter-Sterr CA, Baker TM, et al. Longitudinal assessment of quality of life in laryngeal cancer patients. *Head Neck* 1996;18:1-10.

14. Ware JE: Measuring functioning, well-being, and other generic health concepts. in Osoba D (ed): Effect of cancer on quality of life. Boston, CRC press; 1991:7-22.
15. Kirshner B, Guyatt GH: A methodological framework for assessing health indices. *J Chronic Dis* 1985;38:27-36.
16. Bjordal K, Hammerlid E, Ahlner Elmqvist M, et al: Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - H&N35. *J Clin Oncol* 1999;17:1008-1019.
17. Rogers SN, Fisher SE, Woolgar JA: A review of quality of life assessment in oral cancer. *Int J Oral Maxillofac Surg* 1999;28:99-117.
18. Aaronson NK: Methodologic issues in assessing the quality of life of cancer patients. *Cancer* 1991;67:844-850.
19. Cella DF, Tulsky DF: Measuring quality of life today: methodological aspects. *Oncology* 1990;4:29-38.
20. Fraser SCA: Quality-of-life measurement in surgical practice. *Br J Surg* 1993;80:163-169.
21. deGraeff A, deLeeuw RJ, Ros WJ, et al: A prospective study on quality of life of laryngeal cancer patients treated with radiotherapy. *Head & Neck* 1999;21:291-296.
22. Davies ADM, Davies C, Delco MC: Depression and anxiety in patients undergoing diagnostic investigations for head and neck cancer. *Br J Psychiat* 1986;149:491-493.
23. Gliklich RE, Goldsmith TA, Funk GF. Are Head and neck specific quality of life measures necessary? *Head Neck*,1997;19:474-480.
24. Fries JF, Spitz PW: The heirarchy of patient outcomes. in Spilker B (ed): Quality of life assessment in clinical trials. New York, Raven Press; 1970:25-35.
25. Hassan SJ, Weymuller EA: Assessment of quality of life in head and neck cancer patients. *Head & Neck* 1993;15:485-496.
26. Aaronson NK: Quality of life research in cancer clinical trials: a need for common rules and language. *Oncology* 1990;4:59-66.
27. Natvig K: Laryngectomees in Norway. Study no. 1: social, personal and

Chapter 2

- behavioural factors related to present mastery of the laryngectomy event. *J Otolaryngol* 1983;12:155-162.
28. McNeil BJ, Weichselbaum R, Pauker SG: Tradeoffs between quality and quantity of life in laryngeal cancer. *N Engl J Med* 1981;305:982-987.
 29. de Boer MF, McCormick L, Pruyn JFA, Ryckman RM: Physical and psychosocial correlates of head and neck cancer: A review of the literature. *Otolaryngol Head Neck Surg* 1999;120:427-436.
 30. Bombardier C, Tugwell PX: A methodological framework to develop and select indices for clinical trials: statistical and judgemental approaches. *J Rheumatol* 1982;9:753-757.
 31. Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Quality of life measurement; bibliographic study of patient assessed health outcome measures. *BMJ* 2002;324:1417-20.
 32. Armstrong E, Isman K, Dooley P, Brine D, Riley N, Dentice R, King S, Khanbhai F. An investigation into quality of life of individuals after laryngectomy. *Head Neck* 2001; 23:16-24.
 33. Hammerlid E, Mercke C, Sullivan M, Westin T. A prospective quality of life study of patients with laryngeal carcinoma by tumour stage and different radiation therapy schedules. *Laryngoscope* 1998;108:747-759.
 34. Schliepcke H, Jamil MU. Impact of intraoral soft-tissue reconstruction on the development of quality of life after ablative surgery in patients with oral cancer. *Plast Reconstr. Surg.* 2002;109:421-431.
 35. Hammerlid E, Silander E, Hornestam L, Sullivan M. Health-related quality of life three years after diagnosis of head and neck cancer- a longitudinal study. *Head Neck* 2001;23:113-125.
 36. de Graeff A, de Leeuw JRJ, Ros WJG, Hordijk G-J, Blijham GH, Winnubust JAM. Pretreatment factors predicting quality of life after treatment for head and neck cancer. *Head Neck*; 2000;22:398-407.
 37. Rogers SN, Lowe D, Fisher SE, Brown JS, Vaughan ED. Health-related quality of life and clinical function after primary surgery for oral cancer. *Br J Oral Max Surg* 2002;40:11-18.
 38. Weymuller EA, Yeuh B, Deleyiannis WB, Kuntz AL, Alsarraf R, Coltrera MD. Quality of life in patients with head and neck cancer – lessons learned from 549 prospectively evaluated patients. *Arch Otolaryngol Head Neck Surg* 2000;126:329-335.

39. Morton RP. Laryngeal cancer: quality of life and cost-effectiveness. *Head Neck* 1997;19:243-250. **
40. Stoeckli SJ, Guidicelli M, Schneider A, Huber A, Schnid S. Quality of life after treatment for early laryngeal carcinoma. *Eur Arch Otorhinolaryngol* 2001;258:96-99.
41. Terrell JE, Fisher SG, Wolf GT. Long-term quality of life after treatment for laryngeal cancer. *Arch Otolaryngol Head Neck Surg* 1998;124:964-971.
42. McDonough EM, Boyd JH, Varvares MA, Maves MD: Relationship between psychological status and compliance in a sample of patients treated for cancer of the head and neck. *Head & Neck* 1996;18:269-276.
43. Deleyiannis FWB, Thomas DB, Vaughan TL, Davis S. Alcoholism: Independent predictor of survival in patients with head and neck cancer. *J Natl Cancer Inst* 1996;88:542-549.
44. DeSanto LW, Olsen KD, Perry PA, Rohe DE, Keith RL: Quality of life after surgical treatment of cancer of the larynx. *Ann Otol Rhinol Laryngol* 1995;104:763-769.
45. Herranz J, Gavilan J: Psychosocial adjustment after laryngeal cancer surgery. *Ann Otol Rhinol Laryngol* 1999;108:990-997.
46. Baile WF, Gibertini M, Scott L, Endicott J: Prebiopsy assessment of patients with suspected head and neck cancer. *J Psychosoc Oncol* 1993;10:79-91.
47. Langius A, Bjorvell H, Lind MG. Functional status and coping in patients with oral and pharyngeal cancer before and after surgery. *Head & Neck* 1994;16:559-68.
48. de Boer MF, Pruyn JFA, van den Borne B, Kneegt PP, Ryckman RM, Verwoerd CDA. Rehabilitation outcomes of long-term survivors treated for head and neck cancer. *Head & Neck* 1995;17:503-15.
49. Mosconi P, Cifani S, Crispino S, Fossati R, Apolone G: The performance of SF-36 health survey in patients with laryngeal cancer. *Head Neck* 2000;22:175-82.
50. Strauss RP. Psychosocial responses to oral and maxillofacial surgery for head and neck cancer. *J Oral Maxillofac Surg* 1989;47:343-8.
51. Semple C, Sullivam K, Dunwoody L et al. Psychosocial interventions for patients with head and neck cancer. *Cancer Nursing* 2004, 27:434-441.

Chapter 2

52. Semple CJ, Dunwoody L, Sullivan K, Kernohan WG. Patients with head and neck cancer prefer individualized cognitive behavioural therapy. *Eur J Cancer Care*. 2006; 15: 220-7.
53. Matthews DA, McCullough ME, Larson DB, et al. Religious commitment and health status. *Arch Fam Med* 1998;7:118-124.
54. Stam HJ, Koopmans JP, Mathieson CM: The psychosocial impact of a laryngectomy: a comprehensive assessment. *J Psychosoc Oncol* 1991;9:37-58.
55. Hammerlid E, Taft C. Health-related quality of life in long-term head and neck cancer survivors; a comparison with general population norms. *B J Cancer* 2001;84:149-156.
56. Chaplin JC, Morton RP. A prospective, longitudinal study of pain in head and neck cancer patients. *Head & Neck* 1999;21:531-7.
57. Kuntz AL, Weymuller EA. Impact of neck dissection on quality of life. *Laryngoscope* 1999;109:1334-8.
58. Singh B, Bhaya M, Zimble M, Stern J, Roland JT, Rosenfeld RM et al. Impact of comorbidity on outcome of young patients with head and neck squamous cell carcinoma. *Head & Neck Surgery* 1998; 20(1):1-7.
59. Sabin SL, Rosenfeld RM, Sundaram K, Har-El G, Lucente FE. The impact of comorbidity and age on survival with laryngeal cancer. *Ear Nose Throat J*. 1999; 78(8):578, 581-4.
60. Reid BC, Alberg AJ, Klassen AC, Samet JM, Rozier RG, Garcia I et al. Comorbidity and survival of elderly head and neck carcinoma patients. *Cancer* 2001; 92(8):2109-2116.
61. Piccirillo JF. Importance of comorbidity in head and neck cancer. *Laryngoscope*. 2000; 110(4):593-602.
62. Morton RP. Evolution of quality of life assessment in head and neck cancer, *J Laryngol Otol*. 1995,109:1029-35.

Figure 1: Best research practice.

- It is important to have a clear definition.
- QoL studies should use patient self-reported data, which account for at least the four main domains, and which provide a patient-rated global QoL score, as well as disease-specific measures.
- Studies should use existing validated instruments, and should follow patients longitudinally from the time of diagnosis.
- Additional information may be gathered from patients' family members; and objective assessments of function - such as swallowing and speech - may be useful.
- Future research to concentrate on validation of current measures, and on determining the most appropriate tools for particular situations.

Figure 2: Best clinical practice

- Identification of patients with depression and alcoholism should be routinely carried out, and interventions instituted as part of the rehabilitation program
- Routine questioning about the role of religion in the patient's coping mechanism, and how to support that, is to be encouraged
- Pre-operative counselling by a laryngectomee is important.

Figure 3: Practical points to enhance QoL of your HNC patients ⁺

- Assess QoL before cancer treatment instituted.
- Screen for depression and alcoholism , and develop a treatment plan since this has positive effect on QoL.
- Consider the impact of religion and spirituality.
- Empower patients - give patients sense of control by involving them in decision-making.
- Set realistic expectations, and avoid over-optimistic outlooks.
- Offer patients opportunity to talk to pts who had treatment- found to be one of the most effective interventions to increase QoL.
- Use the most oncologically effective treatment first, then make modifications that can optimise QoL, eg parotid sparing post-op radiotherapy.
- Get involved in patient groups and post-treatment educational and support groups.

⁺ adapted from Collins (1)

Table 1: Features of the QoL phenomenon in cancer patients.

Operational Characteristics	Essential Components/ Domains
QoL assessments must be self-administered	Physical function
QoL is subjective, but quantifiable	Psychological state
QoL is multifactorial, or multidimensional	Social interaction
Overall QoL (and each dimension's value) varies over time	Somatic sensation

Table 2: Guidelines for the development and implementation of QoL questionnaires in cancer patients (15,54).

1	Decide the Hypothesis to be tested	
2	Decide on definition of Quality-of-life to be used	
3	Disease-specific questionnaire to include:	Disease and Treatment-related symptom scores; Health and Disease-status
4	Patient data to be self-reported	
5	Enquiry on domains of functional status to include:	Psychological functioning Socio-sexual functioning Physical functioning Global QoL measure (patient-generated)
6	Field testing and fine-tuning of questionnaire	
7	Instruments should have proven, or be checked for:	Reliability Validity Responsiveness/Sensitivity
8	Design longitudinal study	

Table 3: Terms used to describe the various forms of validation that a QoL questionnaire must exhibit (30,62)

Psychometric criterion	Biomedical terminology	meaning
Content validity	Comprehensiveness	Questions cover relevant issues
Face validity	Credibility	Questions are clear
Criterion validity	Accuracy	Performance of instrument in comparison to a 'gold standard'
Discriminant validity	Responsiveness	Ability and sensitivity to detect change.
Construct validity	Biological sense	Ability of instrument to behave in a fashion consistent with a theoretical framework
Reliability	Reproducibility	Ability to produce similar results on retesting

Table 4: characteristics of commonly used QoL instruments #

	EORTC QoLQ C30/ H&N35	FACT- G/H&N	HNRQ	QoL- H&N	QoLQ	QoL- RTI/HN	HN QoL	UW QoL
General (G) or specific (S)	both	both	S	both	S	both	S	S
Validated	+	+	+/-	+/-	+/-	+/-	+/-	+
No of items	65	27	22	29	19	39	21	12
No of domains	6	4	6	3	4	5	4	9
Self- administer	+	+	-	+	+	+	-	+
Global measure	+	-	-	+	-	+	+	+
Summary score	-	+	+	-	?	+	-	+
Cross-cultural validation/ translation	+ several languages	+/- ongoing	-	-	-	+/- Japanese , German, Spanish	-	-
Scoring	C30- B HN35-W	B	B	B	?	?	B	B
Time to complete	18	5	10	15	?	?	11	short

adapted from review by Ringash and Bezjak (9)

+ means criterion present or proven, - means not present or not yet proven; +/- means limited or partial proof available; ? means not assessable;

B means the higher the score, the better the QoL; W means the higher the score, the worse the QoL or symptom.

EORTC QoLQ C30/H&N35: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Head and Neck Cancer C30/H&N35; FACT – G/H&N : Functional Assessment of Cancer Therapy-General/Head and Neck

HNRQ : Head and Neck Radiotherapy Questionnaire; QoL-H&N: Quality of Life Instrument for Head and Neck Cancer; QoLQ: Quality of Life Questionnaire for Advanced Head and Neck Cancer; QoL-RTI/H&N: Quality of Life –Radiation Therapy instrument Head & Neck Module; HNQoL: University of Michigan Head and Neck Quality of Life; UWQoL: University of Washington Quality of Life Questionnaire

Table 5: purpose and uses for which instrument was developed. #

Instrument	Stated Purpose	Uses
EORTC QoLQ C30/ H&N35	D, E	For use in HNC patients in all stages, acute or chronic, treated or untreated
FACT-G/H&N	D, E	For descriptive, discriminative and evaluative use.
HNRQ	E	To measure radiation induced acute morbidity and QoL in HNC patients.
QoL-H&N	D, E	To be a short sensitive, disease specific questionnaire with emphasis on psychological factors.
QoLQ	E	To discriminate between patients with advanced HNC undergoing radiotherapy alone or surgery and radiotherapy
QoL-RTI/HN	E	Very specific for measuring QoL in patients undergoing radiotherapy
HNQoL	D, E	Overall assessment of disease specific QoL in HNC patients
UW QoL	D	Intended primarily for patients undergoing surgery

adapted from review by Ringash and Bezjak (9)

D means discriminative purpose, E means evaluative purpose.

EORTC QoLQ C30/H&N35: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Head and Neck Cancer C30/H&N35; FACT – G/H&N :

Functional Assessment of Cancer Therapy-General/Head and Neck

HNRQ : Head and Neck Radiotherapy Questionnaire; QoL-H&N: Quality of Life Instrument

for Head and Neck Cancer; QoLQ: Quality of Life Questionnaire for Advanced Head and

Neck Cancer; QoL-RTI/H&N: Quality of Life –Radiation Therapy instrument Head & Neck

Module; HNQoL: University of Michigan Head and Neck Quality of Life; UWQoL: University

of Washington Quality of Life Questionnaire.

Chapter 3

Deterioration in the quality of life of late (10-year) survivors of head and neck cancer

Published: Mehanna HM, Morton RP. Deterioration in quality of life of late (10–year) survivors of head and neck cancer patients. *Clin Otolaryngol.* 2006; 31(3):204-11

Presented at the 6th International Conference on Head and Neck Cancer (sponsored by the American Head and Neck Society), Washington DC, USA on 8th August 2004

Chapter 3

Abstract

Objectives:

1. Determine 10 year Quality of life (QoL) in head and neck cancer (HNC) patients
2. Examine the potential predictors of *late* QoL

Design: prospective 10 year (QoL) assessment in a cohort of HNC patients.

Setting: tertiary referral head and neck cancer centre in Auckland, New Zealand

Participants: 200 patients diagnosed and treated for HNC. Exclusion criteria were blindness, learning difficulties or inability to understand or read English.

Main outcome measures: QoL at 10 years measured by Auckland QoL questionnaire, and analyzed for associations with the following co-variables: age, gender; co-morbidities (alcohol intake and smoking), type and stage of disease; treatment modality; and QoL measures.

Results: At 10 years following diagnosis, overall QoL (Life Satisfaction score) decreased significantly by an average of 11% (95% CI -5%, -17%) compared to before treatment, and by 15% when compared to years one and two. Pre-treatment QoL significantly predicted late QoL, whilst QoL 1 year after treatment did not. None of the socio-demographic, disease or treatment related factors predicted long-term QoL on univariate analysis, but this may be due to the small sample size.

Conclusions: This observed late drop in the QoL of HNC patients requires further corroboration and investigation. Due to small sample sizes associated with long-term studies in HNC cohorts, studies of predictors of long-term QoL will only be likely to succeed if done as multi-centre studies. As there is some evidence to suggest that psychosocial interventions improve the QoL of HNC patients, it may be appropriate to consider screening for risk of a late deterioration in QoL in order to plan appropriate psychosocial intervention.

Introduction

The importance of health-related quality of life measurement in patients with head and neck cancer is now well recognised, due to the significant effect of the disease and its treatment on their functional and psychological states. Since the different

treatment modalities may result in similar survival rates but different types of functional effects (1,2), health-related quality of life also plays a role in differentiating and choosing between treatment modalities.

Over the past two decades, there has been a rapid increase in studies on health – related quality of life in head and neck cancer (3). Initially studies of quality of life were retrospective and cross-sectional, using non-validated measures with the inherent methodological inadequacies. More recently, we (4) and others (5-8) have reported prospective quality of life studies with medium-term (2-3 years) follow-up. These have demonstrated that patients' quality of life usually decreases during treatment, but that generally, it starts improving 3-6 months after treatment to reach or exceed the pre-treatment level by the end of the first year. Quality of life appears to continue to improve slightly for the following two - three years (4-11).

It is recognised however that quality of life measurement has to be long-term, as well as prospective, since clinical follow-up and survival statistics for head and neck cancer are normally based on five - year data, and a proportion of patients live 10 years or more. Therefore, long-term measurement is necessary to characterise the quality of life, residual deficits and the late side effects of treatment in those who are cured. Some cross-sectional quality of life outcomes in long-term head and neck cancer survivors have been published (12-15), but these had no pre-treatment or early post-treatment measures for comparison – thereby considerably limiting the utility of the data. To date, no *longitudinal* quality of life data beyond 5 years is available in the literature. This is in part due to the difficulties encountered in conducting long-term trials in head and neck cancer, and in part due to the effect of patient attrition on small sample sizes.

For the same reasons, predictors of *long-term or late* quality of life (5 years or more after diagnosis) have remained largely undefined. Determination of these predictors is important to attempt to identify means of improving the long-term quality of life of the patient, not only for the patients' wellbeing, but also because there is increasing evidence that there may be a survival benefit (16). There are a large number of potential predictors or risk factors under study. The literature demonstrates associations between quality of life following treatment for head and neck cancer and tumour site (17,18), size (17-19) and type of treatment (19-23). Some researchers have also demonstrated that patient related factors (age, gender [21-23]), employment (24,25), marital status (18), and co- morbidities (26) predict quality of life. Patient behaviour, namely alcohol intake and smoking, has also been shown to be associated with quality of life in head and neck cancer by

Chapter 3

some (27-28), but not by others (29-31). Understandably, psychosocial factors, especially depression, have also been shown to be associated with quality of life in head and neck cancer (29-32).

The conflicting nature of the literature on predictors of quality of life in head and neck cancer is the result of several factors that complicate research in head and neck cancer in general. These complicating factors are:

- a. small sample sizes due to a low incidence rate and a large number of primary sites. Due to the small sample sizes, multi-variate analysis is usually not possible, and
- b. the need to analyse multiple potential predictors, some of which are related and hence suffer from confounding, and finally
- c. the duration of follow-up varies considerably between studies, and since time of measurement may have a significant influence on the quality of life being studied, this confounds the situation further.

This study reports quality of life data from a *prospective ten-year* follow-up of a cohort of head and neck cancer patients, and examines the potential predictors of *late* quality of life, including demographic and patient related factors, disease and treatment related factors, and quality of life / psychosocial factors.

Methods

PATIENTS

Two hundred patients with primary epithelial head and neck cancer, attending a head and neck clinic in tertiary referral centre in Auckland, New Zealand, were recruited to a two year prospective quality of life study from 1989 – 1992 (4). Patients with blindness, learning difficulties or inability to understand or read English were excluded. The survivors of this cohort were traced 10 years after diagnosis through a national hospital tracking system, through contact with their family doctors and by using their last known address and / or next of kin.

DATA COLLECTION AND ETHICAL CONSIDERATIONS

Appropriate approval from the local ethics committee was obtained. Consenting was performed by a trained clinic nurse, who also gave assistance with completion of the questionnaire if required.

Patients completed the Auckland Quality of Life Questionnaire at diagnosis, and at three, twelve and 24 months as part of the two year prospective quality of life study from 1989 – 1992 (4). At 10 years, the surviving patients were asked to complete the Auckland Quality of Life Questionnaire again to provide the 10 year follow-up data.

AUCKLAND QUALITY OF LIFE QUESTIONNAIRE

The Auckland Quality of Life Questionnaire (4) is a validated, patient-reported, composite health-related quality of life measure, comprised of the three the instruments detailed below:

LIFE SATISFACTION SCORE (LS)

This is a well established psychometric tool measuring general well being. It is self-reported and consists of two parts:

- a. Single item 'life as a whole these days' representing overall (global) score of life satisfaction. This has a 7 point Likert scale, ranging from extremely dissatisfied (scores 1) to extremely satisfied (score 7).
- b. Aggregated 10 item score relating to social, family and general physical function. The individual items are scored using the same seven point Likert scale above, and the scores are then summated to form an aggregated score (minimum 10, maximum 70). The higher the score, the greater the satisfaction. Further validation has suggested that the aggregated score is more sensitive measure of global quality of life than the single item measure, and hence has been used as the dependent variable in the analysis of this study (4,33).

GENERAL HEALTH QUESTIONNAIRE (GHQ)-12

This is a well established, patient self-reported, psychometric instrument that measures psychological distress. It is often used as a screening tool for unmet psychosocial needs, and has previously been used in studies of head and neck cancer (4, 33). The GHQ focuses on interruptions in normal psychological function, rather than on lifelong traits. The GHQ was scored using the 4-point Likert scale rather than the alternate condensed 2-point option, with each of the 12 items being a question with a four point Likert response (score 0-3). The item scores are summated (score range 0-36).

Chapter 3

HEAD AND NECK SYMPTOM QUESTIONNAIRE

This consists of 5 items concerning disease and treatment related symptoms - head and neck pain, shoulder and arm pain, speech difficulty, swallowing difficulty and cough. Scores range from 1 to 5, with 1 being most severe symptoms, and 5 being no symptoms at all.

ANALYSIS

The dependent variable for this study was overall quality of life (as measured by the aggregate Life Satisfaction score) at 10 years following diagnosis. This was analyzed for associations with the following co-variables: socio-demographic factors (age, gender); co-morbidities (alcohol intake and smoking), tumour characteristics (type and stage of disease); treatment modality; and quality of life measures. The latter included overall quality of life, psychological disability and physical disability measures, both at diagnosis and 12 months later. For ease of interpretation, continuous risk factors in the final models eg Life Satisfaction score and GHQ in Table 4, were expressed using categorical classifications, since it had been established that the results were not sensitive to continuous or categorical expression. These categorical classifications were selected using the score of the upper quartile as the cut-off point, so that the upper quartile group was compared with the rest of the sample. The Mann Whitney U test was used to examine statistical differences ($p < 0.05$) between subgroups in co-variate analyses. Due to the small sample size, multi-factorial analyses were not performed.

RESULTS

PATIENTS CHARACTERISTICS

At ten years, 136 (68%) patients were deceased, and 50 (25%) patients were confirmed alive, of whom 43 were successfully contacted. Two had moved overseas, 2 could not be contacted, 2 declined participation, and one was excluded due to dementia. The status of 14 (7%) was unknown. All 43 contacted patients were disease free.

The ten-year survivors were on average four years ($SD \pm 1.7$) younger at recruitment than non-survivors, and were more likely to be male (86% in 10 year survivors versus 76% in the inception cohort), have glottic carcinoma and have early (stage I) disease (37% vs. 18% respectively) [See table 1]. Only 9% of

survivors had advanced stage IV disease at presentation compared to 35% of original cohort.

MAIN QUALITY OF LIFE PARAMETERS

At 10 years following diagnosis, overall quality of life (Life Satisfaction), had decreased significantly by an average of 7 points (95% CI $-3,-11$), that is a drop of 11% for the 10 year survivors compared to baseline before treatment, and a decline of 15% when compared to years one and two scores (see figure 1). Psychological distress (as measured by General Health Questionnaire) had worsened on average by 3 points (95% CI $-1,-5$), or a 9% decrease, and by more (15%) when compared to the one and two year scores (see figure 2). All head and neck symptoms deteriorated by 0.4 to 0.8 points, representing 10-20% change, compared to baseline; the largest declines occurring for shoulder/arm pain, head and neck pain and coughing (see table 2 and 3). All the above changes in Life Satisfaction, GHQ and symptom scores are mirrored to a similar, but slightly lesser degree, by the changes reported by the overall cohort (see tables 2 and 3).

PREDICTORS OF QUALITY OF LIFE 10 YEARS FOLLOWING TREATMENT

None of the socio-demographic (gender, age, smoking and alcohol status), disease (stage and site) or treatment related factors predicted long-term quality of life. Pre-treatment quality of life significantly predicted late quality of life, whilst quality of life 1 year after treatment did not (see table 4). Psychological distress prior to treatment did not predict long-term quality of life, whereas psychological distress after treatment had a significant association with poorer long-term quality of life (see table 4). Pre-treatment speech was the only symptom measure to significantly predict long-term health-related quality of life, where those with better speech pre-treatment showed larger deteriorations in their long-term health-related quality of life.

Discussion

KEY FINDINGS

Considering that in the first two years, patients' quality of life recovered and often exceeded baseline, the late deterioration in quality of life among long-term survivors of head and neck cancer has not been previously reported and is

Chapter 3

unexpected, especially when taking into account that these patients had generally presented with early stage disease that was controlled by single modality therapy.

This late decrease in quality of life and worsening of psychological status may be related to a late anxiety or anger reaction, as has been previously reported in a cross-sectional study (12). Alternatively, it may be a reflection of a perceived loss of interest in, attention to, or sympathy with, the patient from medical staff or family after the patient's discharge from follow-up (usually at five years after treatment). Furthermore, patients did report deterioration of their head and neck symptoms, possibly due to late effects of treatment or deteriorating health and increasing co-morbidities with advancing age. Although there was no significant association detected in the study, this worsening of symptoms may possibly have resulted in the deterioration in quality of life and psychological status. Other possible explanations may include regression to the population mean quality of life, following early post-treatment euphoria at tumour control.

LIMITATIONS OF STUDY

Several factors should be taken into consideration. Due to the large gap between the time points investigated, the study fails to identify the point at which the patients' quality of life starts to deteriorate. Is it gradual, or precipitous? Secondly, as with all prospective trial in cancer, there is an inherent selection as the study only involves survivors, whom, as one might expect, had better quality of life at every point compared to the remainder who did not survive (figure 1).

Furthermore, most of the survivors are patients who had early stage disease which was controlled by single modality treatment, and therefore findings, especially comparisons between subgroups, may be biased by this predominance. In addition, due to the nature of the disease, only 25% of patients are alive by 10 years. This has a bearing on the number of surviving participants in such a long-term trial, and may result in analysis bias due to sample size being too small to show significant differences in sub-group factorial analyses. Therefore the results of the analysis of possible predictors should be interpreted with caution. This is also the reason that a multivariate analysis of possible predictors was not performed, as it would have been meaningless with small numbers.

COMPARISON WITH OTHER STUDIES

The above reasons may also explain some of the variable findings of our study. For example, demographic, disease and treatment factors did not predict long-term

quality of life. This is at variance with *some* of the published literature (18-23) as discussed previously. However, these studies mainly looked at short- and medium - term quality of life, and hence the variance with our study may be explained by the length of follow-up. Our study examines quality of life at *10 years*, which may be determined by new factors that developed in later years (for example co-morbidities and unmet needs), and which were not present before treatment or in the early post-treatment phase. Analysis bias should also be considered, since as expected, most surviving patients were a homogeneous group – early laryngeal disease treated by radiotherapy- and hence there may be no significant differences between such a homogeneous group.

Many longitudinal studies of quality of life and other factors in head and neck cancer patients show deterioration in the quality of life of patients at 3 months (5-8). In our study, psychological distress worsened at 3 months, but the overall quality of life did not deteriorate. We are unable to explain this difference, but the issues discussed above may be contributing to this. However, the changes in quality of life at the other time points (1 and 2 years – which are the ones that we have used in our analysis) reflect the findings of the other studies.

We had hypothesised that long-term quality of life was likely to be influenced more by the steady state quality of life that the patient reaches after experiencing and adapting to their disease and subsequent treatment than by their quality of life before treatment. Hence, we had postulated that quality of life one year after treatment may be a stronger determinant of *long-term* quality of life than pre-treatment quality of life. While the study did show an association between psychological state at 1 year and long-term quality of life, the findings regarding overall quality of life did not confirm our hypothesis. The reasons for these findings are not obvious, but again all the above arguments may be potential explanations.

CLINICAL RELEVANCE

There is emerging evidence that quality of life may be associated with long-term survival in head and neck cancer (34), and some evidence that psychosocial interventions may improve patients quality of life (35). Therefore it may be appropriate to consider screening long-term survivors for quality of life deterioration so as to enable detection and appropriate intervention.

Conclusions

This late drop in the quality of life of head and neck cancer patients has not been observed previously, and requires further corroboration and investigation. Due to small sample sizes associated with long-term studies in head and neck cancer cohorts, studies of predictors of long-term quality of life will only be likely to succeed if done as multi-centre studies (with consideration for the effects of culture on quality of life (4)).

Acknowledgements

The authors would like to thank Ms Teena West, Biostatistician, for all her patience and help with the statistics and analysis.

The authors would also like to thank the following for their generous support in funding this research: the Green Lane Research and Education Trust Fund, the NZ Lotteries Commission, and the Head and Neck Trust (NZ)

The authors would also like to thank Dr Nicholas McIvor, Consultant, Dept of head and neck surgery, Auckland City Hospital, New Zealand for allowing access to his patients for the purposes of this study

References

1. El-Deiry M, Funk GF, Nalwa S, Karnell LH, Smith RB, Buatti JM, Hoffman HT, Clamon GH, Graham SM, Trask DK, Dornfeld KJ, Yao M. Long-term quality of life for surgical and nonsurgical treatment of head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2005;131:879-85
2. Hanna E, Sherman A, Cash D, Adams D, Vural E, Fan CY, Suen JY. Quality of life for patients following total laryngectomy vs chemoradiation for laryngeal preservation. *Arch Otolaryngol Head Neck Surg*. 2004;130:875-9.
3. Ringash J, Bezjak A. A structured review of quality of life instruments for head and neck cancer patients. *Head Neck*. 2001, 23:201-213.
4. Morton R. Studies in the Quality of life of head and neck cancer patients: results of a two year longitudinal study and a comparative cross-sectional cross-cultural survey. *Laryngoscope*, 2003;113:(7): 1091-103.
5. Hammerlid E, Silander E, Hornestam I, Sullivan M. Health – related quality of life three years after diagnosis of head and neck cancer – a longitudinal study. *Head Neck*, 2001;23:113-125.
6. List MA, Ritter-Sterr CA, Baker TM, Colangelo LA, Matz G, Pauloski BR, Logemann JA. Longitudinal assessment of quality of life in laryngeal cancer patients. *Head Neck*, 1996;18:1-10.
7. Terrell JE, Fisher SG, Wolf GT . Long-term quality of life after treatment of laryngeal cancer. *Arch Otolaryngol Head Neck Surg*, 1998;24:964-71.
8. de Graeff A, de Leeuw R, Ros WJG, Hordijk G-A, Bettermann JJ, Blijham GH, Winnubst JAM. A prospective study on quality of life of laryngeal cancer patients treated with radiotherapy. *Head Neck*, 1999, 21: 291-6.
9. Weymuller EA, Yueh B, Deleyiannis FW, Kuntz AL, Alsarraf R, Coltrera MD. Quality of life in patients with head and neck cancer: lessons learned from 549 prospectively evaluated patients. *Arch Otolaryngol Head Neck Surg*. 2000; 126(3):329-35
10. Ackerstaff AH, Lindeboom JA, Balm AJ, Kroon FH, Tan IB, Hilgers FJ. Structured assessment of the consequences of composite resection. *Clin Otolaryngol*, 1998, 23:339-44.
11. Ackerstaff AH, Tan IB, Rasch CR, Balm AJ, Keus RB, Schornagel JH, Hilgers FJ. Quality-of-life assessment after supradose selective intra-arterial cisplatin and concomitant radiation (RADPLAT) for inoperable stage IV head and neck

Chapter 3

- squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg.* 2002;128:1185-90.
12. Bjordal K and Kaasa S. Psychological distress in head and neck cancer patients 7-11 years after curative treatment. *Br J Cancer*, 1995;71: 592-7
 13. D'Antonio L, Long S, Zimmerman G, Peterman AH, Petti GH, Chonkich GD. Relationship between quality of life and depression in patients with head and neck cancer. *Laryngoscope*, 1998;108:806-11.
 14. Magne N, Marcy PY, Chamorey E, Guardiola E, Pivot X, Schneider M, Demard F, Bensadoun RJ. Concomitant twice-a-day radiotherapy and chemotherapy in unresectable head and neck cancer patients; a long-term quality of life analysis. *Head Neck*, 2001;23:678-682.
 15. de Graeff A., de Leeuw JR, Ros WJ, Hordijk G-A, Bettermann JJ, Blijham GH, Winnubst JAM. Sociodemographic factors and quality of life as prognostic indicators in head and neck cancer. *Eur. J. Cancer*, 2001;37:332-339
 16. Hammerlid E, Mercke C, Sullivan M, Westin T. A prospective quality of life study of patients with laryngeal carcinoma by tumour stage and different radiation schedules. *Laryngoscope* 1998;108:747-759
 17. Morton RP. Life satisfaction in patients with head and neck cancer. *Clin Otolaryngol* 1995;20:499-503
 18. Long SA, D'Antonio LL, Robinson EB, Zimmerman G, Petti G, Chonkich G. Factors related to quality of life and functional status in 50 patients with head and neck cancer. *Laryngoscope*, 1998;106:1084-88.
 19. Rogers S.N., Lowe D., Fisher S.E., Brown JS, Vaughan ED. Health – related quality of life and clinical function after primary surgery for oral cancer. *Br. J. Oral Maxillofac. Surg.* 2002;40:11-18
 20. Harrison LB, Zelefsky MJ, Armstrong JG, Carper E, Gaynor JJ, Sessions RB. Performance status after treatment for squamous cell cancer of the base of tongue – a comparison of primary radiotherapy versus surgery. *Int J Radiat Oncol Biol Phys*, 1994;30:953-57.
 21. Rogers S.N., Lowe D. & Humphris G. Distinct patient groups in oral cancer: a prospective study of perceived health status following primary surgery. *Oral Oncol.* 2000;36:529-538
 22. Ledebøer QCP, van der Velden LA, de Boer MF, Feenstra L, Pruyn JFA. Physical and psychosocial correlates of head and neck cancer: an update of

- the literature and challenges for the future (1996-2003). *Clin Otolaryngol*, 2005, 30: 303-19.
23. List MA, Mumby P, Haraf D, Siston A, Mick R, MacCracken E, Vokes E. Performance status and quality of life outcomes in patients completing concomitant chemoradiotherapy protocols for head and neck cancer. *Qual Life Res*; 1997;6:274-284.
 24. Sehlen S, Hollenhorst h, Lenk M, Schymura B, Herschbach P, Aydemir U, Duhmke E. (2002) Only sociodemographic variables predict quality of life after radiotherapy in patients with head and neck cancer. *Int J Radiation Oncology Biol Phys*, 2002;52:779-783
 25. Kugaya A., Akechi T., Okamura H. et al. Correlates of depressed mood in ambulatory head and neck cancer patients. *Psychooncology*, 1999;8:494-499
 26. Terrell JE, Ronis DL, Fowler KE, Bradford CR, Chepeha DB, Prince ME, Teknos TN, Wolf GT, Duffy SA. Clinical predictors of quality of life in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2004;130:401-8.
 27. Duffy SA, Terrell JE, Valenstein M, Ronis DL, Copeland LA, Connors M. Effect of smoking, alcohol and depression on the quality of life of head and neck cancer patients. *Gen Hospital Psychiatry*, 2002;24:140-7.
 28. Rogers SN, Humphris G, Lowe D, Brown JS, Vaughan ED. The impact of surgery on quality of life as measured by the Medical Outcomes Short Form 36. *Oral Oncol Eur J Cancer* 1998;34:171-9.
 29. Allison P.J., Guichard C. & Gilain L. A prospective investigation of dispositional optimism as a predictor of health –related quality of life in head and neck cancer patients. *Qual. Life Res*. 2000;9:951-960.
 30. de Graeff A., Leeuw J.R., Ros W.J., Hordijk G-A, Bettermann JJ, Blijham GH, Winnubst JAM. Pretreatment factors predicting quality of life after treatment for head and neck cancer. *Head Neck* 22,398-40.
 31. Hassanein K.A., Musgrove B.T. & Bradbury E. Functional status of patients with oral cancer and its relation to style of coping, social support and psychological status. *Br J Oral Maxillofac Surg*. 2001;39:340-5.
 32. Hammerlid E, Persson L-O, Sullivan M, Westin T. Quality of life effects of psychosocial intervention in patients with head and neck cancer. *Otolaryngol Head Neck Surg* 1999;120:507-16.

Chapter 3

33. Morton R and Tandon D. Validation of quality of life measures in head and neck patients. *Aust J Otolaryngol*, 2000;3:479-487.
34. Mehanna HM, Morton RP. Does quality of life predict long-term survival in head and neck cancer patients? *Arch Otolaryngol Head Neck Surg*. 2006;132(1):27-31.
35. Semple C J, Sullivan K, Dunwoody L, Kernohan WG. Psychosocial Interventions for Patients with Head and Neck Cancer: Past, Present, and Future. *Cancer Nursing*. 2004;27:434-441.

Table 1. Baseline characteristics of study group and 10 year survivors.

	All patient cohort n=200	10 yr survivors n=43
Demographics and co-morbidites		
Male	152 (76%)	37 (86%)
Age	64 ± 11.9	60 ± 10.5
Alcohol consumption nearly/every day	67 (34%)	13 (31%)
Ever smoked	170 (85%)	35 (83%)
Disease Status		
AJCC Stage		
I	35 (18%)	15 (36%)
II	30 (15%)	8 (19%)
III	45 (22%)	12 (23%)
IV	69 (35%)	4 (9%)
unknown	21 (10)	4 (9)
Nodal involvement	86 (43%)	10 (24%)
Tumour Site		
Supraglottis	29 (15%)	3 (7%)
Glottis	47 (24%)	19 (45%)
Oro/naso/hypopharyx	64 (32%)	7 (17%)
Oral	26 (13%)	6 (14%)
Other	34 (17%)	7 (17%)
Treatment		
Surgery	32 (16%)	9 (21%)
Radiotherapy	64 (32%)	16 (38%)
Surgery & Radiotherapy	81 (41%)	16 (38%)
unknown	23 (11%)	2 (5%)
Neck dissection	64 (32%)	10 (24%)

Table 2: All patient cohort symptom scores and change over time

Mean baseline \pm standard deviation and change (95% confidence interval) in symptom scores.

	Baseline	Mean Change from Baseline (95% CI) at			
	N=200 (mean \pm sd)	3 months n=173	12 months n=139	24 months n=95	10 years n=43
Coughing	7 \pm 1.3	-0.2 (-0.42, 0.07)	0.1 (-0.05, 0.49)	0.1 (-0.04, 0.59)	-0.4 (-1.17, -0.21)
Speaking difficulty	4.6 \pm 0.8	-0.5 (-0.64, -0.26)	-0.4 (-0.55, -0.14)	-0.1 (-0.34, 0.09)	-0.4 (-0.81, -0.46)
Head and neck pain	4.1 \pm 1.1	0.1 (-0.11, 0.27)	0.2 (0.02, 0.41)	0.4 (0.10, 0.61)	-0.3 (-0.76, 0.05)
Shoulder and arm pain	4.8 \pm 0.6	-0.4 (-0.55, -0.26)	-0.4 (-0.55, -0.24)	-0.3 (-0.48, -0.07)	-0.8 (-0.15, -0.46)
Swallowing difficulty	4.2 \pm 1.2	-0.2 (-0.40, -0.02)	-0.2 (-0.42, -0.02)	-0.1 (-0.32, 0.15)	-0.6 (-0.93, -0.21)

sd = standard deviation, CI = confidence interval

Symptom scores range from 1 to 5 where 1 indicates severe pain/difficulty and 5 no pain/difficulty.

Change calculated as: time period – baseline scores.

A negative mean change indicates a deterioration in symptoms, a positive mean change indicates an improvement in symptoms.

Table 3: Quality of Life outcomes of 10 year survivors over time (n=43).

Life Quality Measure (score range)	Mean score (95% CI)			
	Baseline	1 year	2 year	10 year
Life Satisfaction (10-70)	60.8 (59,62.7)	64.1 (62.1,66)	63.2 (60.9, 65.6)	53.6 (50.7,56.6)
Global Satisfaction (1-7)	6.21 (6.1, 6.4)	6.4 (6.5,6.9)	6.41 (5.9,7.0)	5.7 (5.2,6.2)
GHQ (0-36)	21.44 (19.1,22.6)	19.9 (18.6, 20.1)	19.0 (16.6, 21.7)	21.14 (19.34, 20.04)
Head and Neck symptoms				
Coughing (1-5)	4.0 (3.6,4.3)	4.0 (3.7,4.4)	4.1 (3.7,4.4)	3.3 (3.0,3.6)
Speaking (1-5)	4.6 (4.4,4.8)	4.5 (4.2, 4.8)	4.7 (4.5,4.8)	4.1 (3.8,4.6)
Head/Neck pain (1-5)	4.3 (4.0,4.6)	4.5 (4.2,4.7)	4.6 (4.4,4.8)	3.9 (3.6,4.2)
Shoulder/arm pain (1-5)	4.7 (4.6,4.9)	4.4 (4.2,4.7)	4.7 (4.5,4.9)	3.9 (3.6,4.3)
Swallowing (1-5)	4.7 (4.4,4.9)	4.5 (4.2,4.7)	4.4 (4.1,4.7)	4.1 (3.8,4.4)

GHQ scores range from 0-36, where 0 is most least distress and 36 is most distress.

Symptom scores range from 1 to 5 where 1 indicates severe pain/difficulty and 5 no pain/difficulty.

Chapter 3

Table 4. Association between long-term QoL and QoL measures before treatment and one year after diagnosis for 10 year survivors (n=43).

	Median Change in LS	p value*
Quality of Life Status		
Life Satisfaction Score		
Pre treatment		
> 64	-11.5 (-17, -8)	0.001
<= 64	-3 (-9, 6)	
1- year		
> 64	-5 (-13, 2)	0.417
<= 64	-8 (-16.5, -1.5)	
General Health Questionnaire		
Pre treatment		
> 24	-7.5 (-11, 4.5)	0.717
<= 24	-6 (-13, 1)	
1- year		
> 24	-11.5 (-16.5, -4.5)	0.015
<= 24	-5 (-10, 2)	
Cough		
Pre treatment		
Occasionally/rarely	-8 (-15, -3)	0.058
Constantly/most days	2 (-9, 6)	
1-year		
Occasionally/rarely	-5.5 (-11.5, 1)	0.753
Constantly/most days	-6 (-11, 6)	
Speaking		
Pre treatment		
No/little difficulty	-8 (-13, -2)	0.033
Moderate/great difficulty	4 (-1, 8.5)	
1-year		
No/little difficulty	-5 (-10, 2)	0.300
Moderate/great difficulty	-9 (-18, 1)	
Head/Neck Pain		
Pre treatment		

Deterioration of QOL of late survivors

	Nil/slight	-8 (-14, 1)	
	moderate/extreme	-4 (-5, 7)	0.078
1-year			
	Nil/slight	-5 (-10, 2)	
	moderate/extreme	-11 (-18, -4)	0.142
Shoulder/Arm Pain			
Pre treatment			
	Nil/slight	-6 (-13, 1)	
	moderate/extreme	-2 (-10, 6)	0.672
1-year			
	Nil/slight	-5 (-10, 2)	
	moderate/extreme	-10 (-18, 6)	0.638
Swallowing Difficulty			
Pre treatment			
	Nil/slight	-7 (-13, 1)	
	moderate/extreme	1 (-8, 9.5)	0.210
1-year			
	Nil/slight	-5 (-11, 2)	
	Moderate/extreme	-9 (-18, 2)	0.598

Key (table 4):

*p value comparing two subgroups, using Mann Whitney U test.

LS = aggregated life satisfaction score, compares upper quartile group (with LS score over 64) to rest of sample (LS 64 or under)

General health questionnaire (GHQ) score compares upper quartile group (with GHQ score over 24) to rest of sample (GHQ 24 or under)

Chapter 3

Figure 1: Average Life satisfaction (overall QL) scores for study cohort (—) and ten year survivors (- - -) over time.

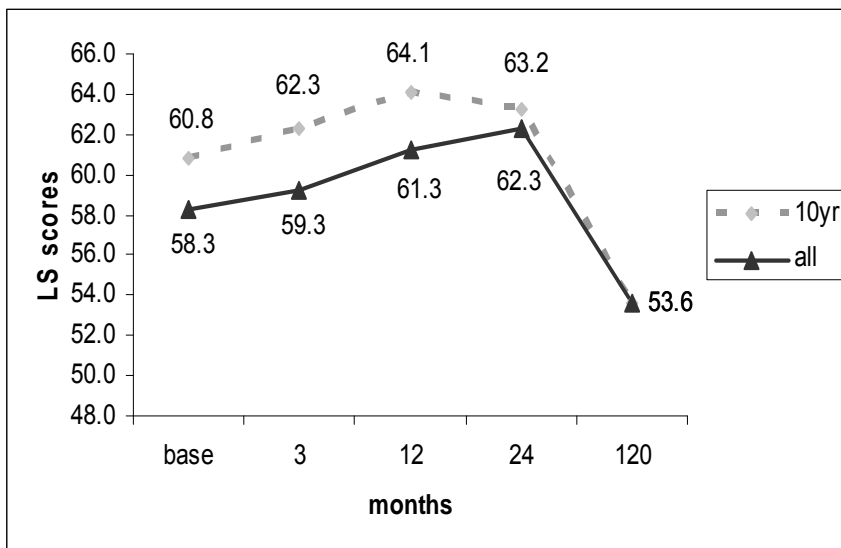
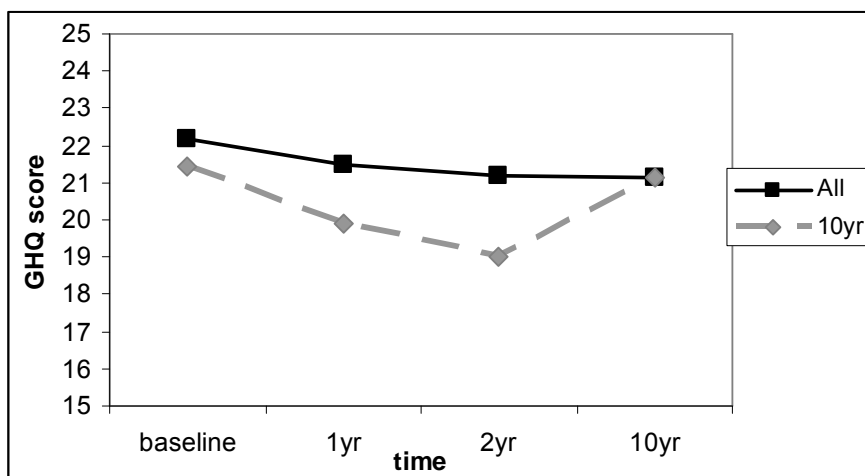


Figure 2: Psychological distress (measured by average General Health Questionnaire (GHQ) scores) for study cohort (—) and ten year survivors (- - -) over time.



Chapter 4

Does quality of life predict long-term survival in head and neck cancer patients?

Published: Mehanna HM, Morton RP. Does quality of life predict long-term survival in head and neck cancer patients? Arch Otolaryngol Head Neck Surg. 2006;132 (1):27-31.

Presented at the 6th International Conference on Head and Neck Cancer (sponsored by the American Head and Neck Society), Washington DC, USA on 8th August 2004

Abstract

Objective: Assess whether pre-treatment and post treatment quality of life (QOL) was associated with long-term survival in head and neck cancer (HNC) patients.

Design: 10-year follow-up of inception cohort.

Setting: Regional tertiary referral centre.

Participants: 200 consecutive patients with primary epithelial head and neck cancer.

Methods: Quality of life and several recognized risk factors for mortality were assessed prospectively, using the Auckland QOL questionnaire, prior to treatment and 12 months post treatment, and survival was determined at 10 years.

Outcome measures: survival, odds of mortality (hazards ratio).

Results: At 10 years 136 (68%) were deceased, 48 (24%) were confirmed alive and the status of 16 (8%) was unknown. Median survival: 6 years (IQR 4.4, 7.7). Prior to treatment those with low quality of life had no significantly increased odds of mortality (hazard ratio [HR] 1.4 (95% CI 0.8, 2.4)). In contrast, post-treatment, those with low quality of life at 1 year had significantly increased odds of mortality [2.5 (95% CI 1.4, 4.3, $p=0.001$)] even after adjustment for co-variates.

Conclusions: The findings suggest potential survival benefits from improvements in QoL. However, the observed associations between survival benefit and 1 year QoL may be confounded by co-morbidity, which was not measured, and this deserves further investigation.

Introduction

Over past 20 years there has been an increased awareness of quality-of-life (QoL) as an outcome measure of cancer management (1). More recently, there has been a lot of interest in QoL as a predictor of survival. Strong associations between overall quality of life, a variety of QoL variables and short-term mortality have been reported in patients with a variety of advanced palliative-intent cancers (2), including breast (3), lung cancer (4,5,6) and melanoma (7). However, QoL variables predicting survival in such patients may not be relevant when considering long-term survival in patients treated with curative intent.

Does QoL predict long-term survival in HNC-patients?

Therefore, studies evaluating the relationship of QoL with long-term mortality have been published. They are however much fewer in number due to the difficulties associated with conducting long-term longitudinal studies (8). These studies have shown variable and sometimes contradicting results, with some demonstrating a strong clear association between overall QoL and long-term survival (9,10,11), whilst others demonstrate no relationship at all (4) or a relationship with only one component QoL variable (13,14,15).

For head and neck cancer, the limited evidence available suggests that *pretreatment* overall QoL and long-term survival are not associated (16). However, studies have found associations between long-term survival and individual variables, such as cognitive functioning (16), fatigue (17) and perceived self-efficacy (18). To date, no studies have examined the role of QoL after treatment, once patients have adapted to their diagnosis and treatment effects, in predicting long-term survival.

These apparent inconsistencies in quality of life research in HNC patients raise important questions. Does poor quality of life increase the risk of mortality in the long term, or is it a surrogate for other risk factors, such as tumour site and stage? And since quality of life significantly changes after treatment, would quality of life post treatment be a more accurate prognosticator for long-term survival?

This report describes an analysis of the association between quality of life prior to and one year post treatment with long-term survival in a cohort of HNC patients. Several other factors that could impact on this relationship were also analyzed. These included socio-demographic factors, alcohol intake and smoking history, disease characteristics, treatment, and psychological and functional disability.

Methods

STUDY POPULATION

A cohort of 200 patients with primary epithelial HNC were recruited for a prospective QoL study after written informed consent was obtained by a trained nurse, as approved by the local ethics committee. The exclusion criteria were inability to understand or read English, blindness and learning disabilities. The cohort was followed up for ten years.

DATA COLLECTION

Patients completed a quality of life questionnaire at diagnosis. Twelve months later, those patients free of recurrence completed the same QoL questionnaire again. At diagnosis, the following risk factor data was also collected: age, gender, alcohol intake, smoking status, disease type and stage (according to the American Joint Committee on Cancer Classification [19]) and subsequent treatment.

QUALITY OF LIFE MEASURES

The Auckland Quality of Life Questionnaire (AQLQ) was used in this study. It is self-reported, patient-oriented and validated (see previous publications for further details - 20-22), and is a composite of 3 questionnaires. The first, the Life Satisfaction Score (LSS), is a measure of general well-being, and is considered a reliable measure of overall QoL (20). It consists of ten questions, each with a Likert 1-7 scale. The ten scores are summated to give an aggregated score, with a range of 10 (poorest) to 70 (best QoL).

The second component is the General Health Questionnaire (GHQ). This is a well-validated instrument that measures psychological distress (20,21). We used the 12-item version with an aggregated score, ranging between 0 (no distress) to 36 (maximum distress). The final component of the Auckland QoL questionnaire is the Functional Ability Questionnaire (FAQ), which enquires about the severity of several important HNC physical symptoms: cough, speech and swallowing difficulties, head and neck pain, and shoulder pain. For the purposes of clarity during the reporting of this study, some FAQ scores have been reversed where appropriate, so that the direction of all scores measuring physical symptoms coincide, that is, higher scores denote *better* function and *less* severe symptoms.

END POINTS

The primary outcome measure for this study was all cause mortality. This was determined from patients' clinical notes, a centralized national clinic booking system, the patient's last recorded address, family doctor or next of kin.

STATISTICAL ANALYSIS

Associations between quality of life and other baseline characteristics were examined with logistic regression (with low/not low quality of life as the outcome measure). Cox proportional hazards regression analysis with time-constant

Does QoL predict long-term survival in HNC-patients?

covariate were used to examine associations between baseline variables and all cause mortality, as well as QoL one year after diagnosis and all cause mortality. The proportionality of hazards was assessed by plotting Schoenfeld residuals (23) against each covariate, and no significant departures from the base model were discovered. The results are reported as hazard ratios and 95% confidence intervals. The nature of the associations between low quality of life (at both baseline and at one year) and mortality were examined using a linear term, quintiles and a binary measure in the models. For ease of interpretation, continuous risk factors in the final models were expressed using categorical classifications since it had been established that the results were not sensitive to continuous or categorical expression. When analyzing the association between one year QoL and mortality (Table 4), patients who had died before 12 months were of course excluded.

Results

OVERALL SURVIVAL

At 10 years, 136 (68%) of the 200 patients were deceased. Of the remaining 64, 48 participants were confirmed alive and the status of 16 could not be determined. The overall median survival was 6 years (95%CI 4.4, 9.1) (Figure 1). For the one year assessment, three patients had recurrent disease and received palliative treatment, and data was available for 137 out of 140 patients who were alive at one year without recurrence. Patients' baseline characteristics are detailed in table 1.

The associations between baseline characteristics and both low quality of life (LSS <55) prior to treatment and mortality are presented in Table 2. Participants who smoked, had nodal involvement, underwent neck dissection and those reporting swallowing difficulties were more likely to have low quality of life before treatment.

Age, disease severity measures, pretreatment low quality of life and high psychological disability were all strongly associated with mortality, as was reported shoulder and arm pain and swallowing difficulty (Table 2). However, the association between *pretreatment* quality of life and mortality decreased substantially after adjustment for co-variables, and became statistically insignificant (Table 3).

In contrast, the association between low quality of life *post treatment* and mortality remained strong even after adjustment for demographic and disease severity

measures (Table 3). The only other post treatment quality of life measure to remain significant after adjustment was head and neck pain.

Discussion

KEY FINDINGS

The results of this prospective study demonstrate a strong independent association between long-term survival and quality of life *after* treatment for head and neck cancer. This is the first time this has been reported in the head and neck literature.

Prior to treatment, *overall* or *global* QoL was not strongly associated with long-term survival once adjustment for disease severity had been performed, supporting the findings of the few other substantive studies on this area in the head and neck cancer literature (16,17,18). During the pre-treatment phase, classical predictors of survival (age, tumour stage and site) were found to be more important in determining long-term mortality. This is consistent with existing literature (16,18), further supporting the validity of our findings.

COMPARISON WITH OTHER STUDIES

In contrast to previous studies, which only examined QoL before or just at the start of treatment (2-18), we also examined QoL one year after diagnosis. We hypothesized that, intuitively, it is more likely that the steady state QoL - after patients had adjusted to the impact of their diagnosis and effects of treatment, and had mobilised their coping strategies accordingly - that would be the determinant of long-term survival (24,25), rather than pre-treatment QoL. This was based on the observations that QoL status usually decreases noticeably during and in the period immediately after treatment, and that patients return to a steady state QoL around one year after diagnosis (26,27). The findings of this study appear to corroborate this premise, and to our knowledge, this is the first time this relationship between *post-treatment* QoL and *long-term survival* has been demonstrated in the HNC literature. It would also explain why a strong association between pre-treatment overall QoL and long-term survival could not be demonstrated in our and other studies (16-18), as the pretreatment QoL may be strongly confounded by disease severity and uncertainty regarding treatment.

LIMITATIONS OF THE STUDY

We are aware of potential limitations of this kind of study:

All cause mortality was used as the end point, as we were unable to always accurately define cause of death, because we frequently used death certificates for information, with the accompanying unreliability of this source as an indicator of true cause of death in cancer patients. In any event, it is our experience that patients are interested in their overall survival prognosis, rather than disease specific survival.

As with most studies of HNC, due to the relatively low incidence of the disease and the heterogeneity of the tumour sites, there are small numbers of patients in each tumour site sub-group. This may lead to analysis bias because significant associations may not be detected due to low sample numbers. Furthermore, there was incomplete data for all included patients leading to attrition of patients available for analysis. Confidence intervals were provided to adjust for this.

We did not collect data on co-morbidities (apart from smoking and alcohol consumption), as at the time of inception of the cohort and at 1 year after diagnosis, the idea of 10 year QoL follow-up and the role of co-morbidities as a determinant of long-term QoL were not widely contemplated or considered by the authors or the literature at that time. Therefore we have not adjusted for co-morbidities in our study. This raises the possibility that the association between QoL and long-term survival may be confounded by co-morbidity and may be in fact a reflection of it, as some authors have found co-morbidity to be a significant prognostic indicator of survival. On the other hand, there are others, including some examining HNC (17), who have found that co-morbidity does *not* play a role.

We excluded patients with recurrent disease undergoing palliative treatment when re-assessing QoL at 1 year. These patients are known to have both a poor quality of life and a short survival duration (2,4,5). Since this study was examining long-term survival, the authors felt that including these patients in the analysis was inappropriate as it would bias the results by strengthening the association between QoL and survival.

This line of research in other cancers, such breast and lung cancers (10-11) has demonstrated some strong associations between pre-treatment overall QoL and survival, which is at variance with our findings in HNC. However there have been other long-term studies, which have not found this relationship, or only found limited associations with single component variables (13-15). The reasons for these inconsistencies are unclear, and are likely to be multiple – including

Chapter 4

methodological differences, small study numbers, differences in tumour types and behaviour, and confounding by other factors.

There are also conflicting findings in the literature regarding the role of psychological factors, such as depression, in determining survival from cancer. Some report that psychosocial complaints are independent prognostic factors of survival following cancer (2), including HNC (18). Others (4,13,16), however, have not demonstrated such a relationship. This study did not find a strong association between psychological distress (as measured by GHQ) and long-term survival. Hence, it would seem that the relationship between QoL and survival may be in some, possibly large, part independent of psychological state.

CLINICAL RELEVANCE

Notwithstanding the difficulties with data and analysis, we believe we have produced sufficient evidence to warrant further investigation of the association between global QoL and survival in HNC patients. Whilst no causative relationship can be proven from this study, our findings may mean that interventions to improve QoL can potentially improve survival. Elucidating and understanding these associations, as well as the prognostic role of co-morbidities, more clearly would be important in establishing whether QoL can be manipulated to enhance survival. Ultimately, the relationship between QoL and long-term survival will only be considered useful if interventions can effect any actual therapeutic or survival advantage.

Conclusions

This study has demonstrated, for the first time, an independent and strong association between quality of life *after* treatment and long-term survival in head and neck cancer patients. Whilst a weak association between pre-treatment QoL and survival was demonstrated, recognized risk factors (age, disease site and extent) were found to be the main prognostic factors in the pre-treatment period. The findings suggest potential survival benefits from improvements in QoL. However, the observed associations between survival benefit and one year QoL may be confounded by co-morbidity, which was not measured, and this deserves further investigation.

Does QoL predict long-term survival in HNC-patients?

Acknowledgments

The authors would like to thank the following organizations for their generous support in funding this research: the Green Lane Research and Education Trust Fund, the NZ Lotteries Commission, and the Head and Neck Trust (NZ)

References

1. Morton RP. Evolution of quality of life assessment in head and neck cancer. *J Laryngol Otol*. 1995;109(11):1029-35.
2. Coates A, Porzsolt f, Osoba D. Quality of life in oncology practice/ prognostic value of EORTC QLQ-C30 scores in patients with advanced malignancy. *Eur J Cancer* 1997;33:1025-30.
3. Coates A, GebSKI v, Signorini D, Murray P, McNeil D, Byrne M, Forbes J , Australian New Zealand Cancer Trials Group. Prognostic value of quality of life scores during chemotherapy for advanced breast cancer. *J Clin Oncol* 1992;10:1833-8.
4. Herndon JE, Fleishman S, Kornblith AB, Kosty M, Green MR, Holland J. Is quality of life predictive if survival of patients with advanced nonsmall cell lung carcinoma? *Cancer* ,1999;85:333-40.
5. Langedijk H, Aaronson NK, de Jong JM, ten Velde GP, Muller MJ, Wouters M. The prognostic impact of quality of life assessed with EORTC QLQ-C30 in inoperable non-small cel lung carcinoma treated with radiotherapy. *Radiother Oncol*. 2000;55:19-25.
6. Buccheri GF, Ferringo D, Tamburini M, Brunelli C. The patient's perception of his own quality of life might have an adjunctive prognostic significance in lung cancer. *Lung Cancer*, 1995,12:45-58.
7. Coates A, Thomson D, McLeod GRM, Hersey P, Gill PG, Olver IN, Kefford R, Lowenthal RM, Beadle G, Walpole E. Prognostic value of quality of life scores in a trial of chemotherapy with or without interferon in patients with metastatic malignant melanoma. *Eur J Cancer* 1993;29:1731-34.
8. De Boer MF, McCormick LK, Pruyn JF, Ryckman RM, van den Borne BW. Physical and psychosocial correlates of head and neck cancer: a review of the literature. *Otolaryngol Head Neck Surg*. 1999 Mar;120(3):427-36.
9. Dancey J, Zee B, Osaba D, Whitehead M, Lu F, Kaizer L, Latreille J, Pater JL. Quality of life score: an independent prognostic variable in a general population of cancer patients receiving chemotherapy. *Quality Life Res* 1997;6: 151-158.
10. Ringal GI, Ringdal K, Kvinnsland S, Gotestam KG. Quality of life of cancer patients with different prognoses *Quality Life Res* 1994,3;143-154.
11. Chau I, Norman AR, Cunningham D, Waters JS, Oates J, Ross P J. Multivariate Prognostic Factor Analysis in Locally Advanced and Metastatic

Does QoL predict long-term survival in HNC-patients?

Esophago-Gastric Cancer-Pooled Analysis From Three Multicenter, Randomized, Controlled Trials Using Individual Patient Data.. *J Clin Oncol*. 2004;22:2395-2403.

12. Herndon JE, Fleishman S, Kornblith AB, Kosty M, Green MR, Holland J. Is quality of life predictive of the survival of patients with advanced nonsmall cell lung carcinoma? *Cancer* 1999;85:333-40.
13. Ringal GI, Gotestam KG, Kaasa S, Kvinnsland S, Ringdal K. Prognostic factors and survival in a heterogeneous sample of cancer patients. *B J Cancer* 1996;73:1594-99.
14. Blazeby JM, Brookes ST, Alderson D. The prognostic value of quality of life scores during treatment for oesophageal cancer. *Gut* 2001, 49: 227-230.
15. Chang VT, Thaler HT, Polyak TA, Kornblith AB, Lepore JM, Portenoy RK. Quality of life and survival – the role of the multidimensional symptom assessment. *Cancer*, 1998;83:173-9.
16. de Graeff A, de Leeuw JRJ, Ros WJG, Hordijk GJ, Blijham GH, Winnubst JAM. Sociodemographic factors and quality of life as prognostic indicators in head and neck cancer. *Eur J Cancer* 2001,37:332-9.
17. Fu-Min Fang, Yi-Tien Liu, Yeh Tang, Chong-Jong Wang, Sheung-Fat Ko. Quality of life as a survival predictor for patients with advanced head and neck carcinoma treated with radiotherapy. *Cancer* 2004;100:425-32.
18. de Boer MF, van den Borne B, Pruyn JFA, Ryckman RM, Volovics L, Knegt PP, Meeuwis CA, Mesters I, Verwoerd CD. Psychosocial and physical correlates of survival and recurrence in patients with head and neck cancer. *Cancer* 1998;83:2567-79.
19. American Joint Committee on Cancer Classification. AJCC Cancer Staging Manual, Fourth Edition. Springer-Verlag 1994, New York.
20. Morton RP, Witterick IJ. Rationale and development of a quality of life instrument for head and neck cancer patients. *Am J Otolaryngol* 1995, 16; 284-93.
21. Morton RP. Life satisfaction in patients with head and neck cancer. *Clin Otolaryngol* 1995, 20, 499-503.
22. Morton R and Tandon D. Validation of quality of life measures in head and neck patients. *Aust J Otolaryng* 2000;3:479-487.

Chapter 4

23. W.N. Venables WN and Ripley BD. *Modern Applied Statistics with S-Plus*. Third edition Springer 1999, New York.
24. Owen C, Watkinson JC, Pracy P, Glaholm J. The psychosocial impact of head and neck cancer. *Clin Otolaryngol* 2001;26:351-6.
25. List MA, Rutherford JL, Stracks J, Haraf D, Kies MS, Vokes EE. An exploration of the pretreatment coping strategies of patients with carcinoma of head and neck. *Cancer*, 2002; 95:98-104.
26. Hammerlid E, Silander E, Hornestam I, Sullivan M. Health – related quality of life three years after diagnosis of head and neck cancer – a longitudinal study. *Head Neck* 2001;23:113-125.
27. de Graeff, de Leeuw JRJ, Wyand JG, Hordijk G-J, Blijham GH, Winnubst JAM. Long-term quality of life of patients with head and neck cancer. *Laryngoscope* 2000;110:98-106.

Does QoL predict long-term survival in HNC-patients?

Figure 1. Kaplan-Meier plot of survival with 95% confidence interval

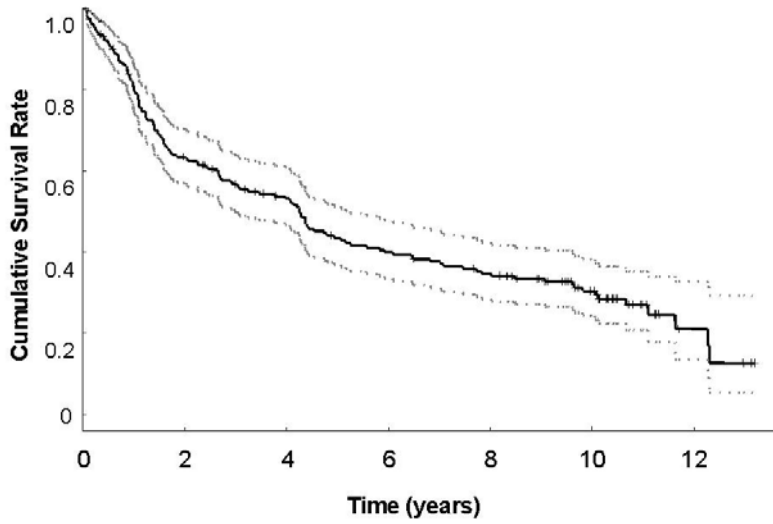


Table 1: Characteristics of study group at baseline and at 1 year.

	Baseline	Cohort at 1 year
	n=200	n=137
Demographics and co-morbidities		
Male	152 (76%)	108 (79%)
Age	64 ± 11.9	63 ± 11.9
Alcohol consumption nearly/every day	67 (34%)	48 (35%)
Ever smoked	170 (85%)	117 (85%)
Disease Status		
AJCC Stage		
I	35 (18%)	28 (20%)
II	30 (15%)	22 (16%)
III	45 (23%)	35 (26%)
IV	69 (35%)	40 (29%)
Nodal involvement	86 (43%)	53 (39%)
Tumour Site		
Supraglottis	29 (15%)	21 (15%)
Glottis	47 (24%)	41 (30%)
Oro/naso/hypopharynx	64 (32%)	34 (25%)
Oral	26 (13%)	19 (14%)
Other	34 (17%)	22 (16%)
Treatment		
Surgery	32 (16%)	26 (19%)
Radiotherapy	64 (32%)	44 (32%)
Surgery & Radiotherapy	81 (41%)	67 (49%)
Neck dissection	64 (32%)	51 (37%)

Does QoL predict long-term survival in HNC-patients?

Table 2: Association between pre-treatment characteristics, all cause mortality and overall quality of life at baseline (univariate analyses)

	Hazard ratio (95% CI) for all cause mortality		Odds ratio (95% CI) for low quality of life at baseline	
	HR (95% CI)	P value	OR (95% CI)	P value
Demographics and co-morbidites				
Male	0.74 (0.50, 1.08)	0.119	2.0 (0.81, 4.72)	0.137
Age >72 (Highest Quartile)	1.76 (1.23, 2.50)	0.002	0.6 (0.28, 1.42)	0.265
Smoker	0.95 (0.58, 1.56)	0.830	4.7 (1.08, 20.7)	0.039
Alcohol consumption nearly/every day	1.04 (0.73, 1.48)	0.847	1.1 (0.54, 2.19)	0.803
Disease status				
Disease Stage				
Stage III & IV vs I & II	2.5 (1.66, 3.78)	<0.001	2.1 (0.93, 4.53)	0.074
Nodal Involvement	2.2 (1.52, 3.05)	<0.001	2.2 (1.12, 4.39)	0.023
Tumour Site				
Supraglottis vs glottis	2.5 (1.66, 3.78)	0.001	1.3 (0.44, 4.11)	0.783
Oral vs glottis	1.6 (0.82, 3.09)	0.175	1.9 (0.62, 5.67)	0.242
Oro/naso/hypopharynx vs glottis	3.0 (1.82, 4.88)	<0.001	1.4 (0.56, 3.54)	0.598
Other vs glottis	2.5 (1.39, 4.33)	0.002	0.7 (0.22, 2.41)	0.224
Treatment				
Surgery vs surgery & radiotherapy	0.6 (0.35, 1.06)	0.078	0.4 (0.14, 1.39)	0.162
Radiotherapy vs Surgery & radiotherapy	1.0 (0.64, 1.42)	0.814	0.5 (0.24, 1.26)	0.157
Neck dissection	1.7 (1.19, 2.51)	0.004	2.5 (1.18, 5.33)	0.017

Chapter 4

QoL and disability measures

Life satisfaction < 55 (Lowest Quartile)	1.5 (1.02, 2.22)	0.038
GHQ >23 (Highest Quartile)	1.6 (1.10, 2.39)	0.015	2.1 (1.00, 4.35)	0.051
Head and neck pain	1.6 (1.11, 2.23)	0.012	1.7 (0.88, 3.48)	0.112
Shoulder and arm pain	0.9 (0.41, 1.87)	0.122	1.3 (0.34, 5.26)	0.679
Cough constantly/most days	1.2 (0.87, 1.74)	0.233	1.6 (0.80, 3.08)	0.185
Speaking difficulty	0.9 (0.52, 1.71)	0.842	1.8 (0.64, 5.16)	0.260
Swallowing difficulty	2.0 (1.42, 2.92)	0.001	2.3 (1.13, 4.63)	0.022

Key:

Poor quality of life is indicated by a life satisfaction score < 55.; CI indicates confidence interval.

High psychological distress as indicated by GHQ (general health questionnaire) score >23 (highest quartile).

All above are univariate analyses.

Does QoL predict long-term survival in HNC-patients?

Table 3: Association between quality of life measures at baseline and at 1 year and mortality unadjusted and adjusted for potential confounders.

	Hazard ratio (95% CI) for mortality		Hazard ratio (95% CI) for mortality adjusted for age, gender, smoking, alcohol consumption, disease stage, nodal involvement and tumour site	
	HR (95% CI)	P value	HR (95% CI)	P value
Quality of life measures at baseline				
Life satisfaction <55 (LQ)	1.7 (1.1, 2.5)	0.010	1.4 (0.9, 2.4)	0.145
Other quality of life measures [†]	1.2 (0.8, 1.9)	0.337	1.4 (0.8, 2.4)	0.223
Quality of life measures at 1 year				
Life satisfaction <55 (LQ)	3.0 (2.1, 4.2)	<0.001	2.5 (1.4, 4.3)	0.001
General health >23 (HQ)	0.9 (0.5, 1.4)	0.263	1.1 (0.6, 2.1)	0.724
Head and neck pain	1.9 (1.2, 3.1)	0.008	1.9 (1.1, 3.4)	0.024
Shoulder and arm pain	1.6 (1.0, 2.6)	0.066	1.5 (0.84, 2.7)	0.166
Cough constantly/most days	1.4 (0.9, 2.2)	0.133	1.1 (0.6, 1.7)	0.835
Speaking difficulty	1.1 (0.6, 1.8)	0.780	0.8 (0.5, 1.5)	0.428
Swallowing difficulty	1.4 (0.9, 2.2)	0.140	1.3 (0.7, 2.2)	0.399

Key

LQ indicates lower quartile; HQ highest quartile.

[†]includes GHQ, head and neck pain, shoulder pain, cough, speaking and swallowing difficulties.

CI indicates confidence interval.

Chapter 5

The association of psychosocial factors and survival in head and neck cancer (a review)

Published: Mehanna HM, De Boer MF, Morton RP. The association of psychosocial factors and survival in head and neck cancer. *Clinical Otolaryngol* 2008, 33, 83-89

Presented at First International Conference on the Prognosis of Head and Neck Cancer, Amsterdam, Nov 2004

Updated 17.04.10

Chapter 5

Abstract

Objective: Update a previous review examining associations between psychosocial factors and survival in head and neck cancer patients.

Data Sources: Searched Cochrane, Psych info and Embase for the period from 1 January 1995 to 1 April 2010, as well as personal and article reference lists and article archives.

Study Selection: Identified articles assessed by consensus for eligibility using following criteria: survival as outcome measure; psychosocial factors as prognostic indicators; results specifically for head and neck cancer patients, not including oesophageal or thyroid cancer. Seven of 74 articles fulfilled criteria.

Data Extraction: Data abstracted independently by two reviewers using predetermined proformas. Quality was also rated using Scottish Intercollegiate Guidelines Network 50 tool.

Data Synthesis: At baseline, expression of intense psychosocial complaints, higher self-perceived physical ability, self-reported high physical functioning and the Short Form-36 physical component score were significantly associated with increased survival.

Uncertainty about the diagnosis and treatment was found to be a negative prognostic indicator, as was being single, poor cognitive function, baseline fatigue, pessimism and alcoholism.

Overall quality of life and head and neck pain, eating score, speech and SF-36 physical functioning post treatment were found to be significantly associated with survival. However, overall quality of life and depression at the time of diagnosis were not.

Conclusions. There appears to be some association between selected psychosocial factors and long term survival from head and neck cancer. However this relationship is currently neither strong nor proven, requiring examination by multi centred trials with standardisation of research definitions and methodologies, and examination of post treatment psychosocial factors.

Introduction

The link between the psyche and cancer has intrigued researchers throughout the ages. Hypocrites, two thousand years ago, noted that women with excess black bile were more melancholic and were more prone to cancer than those who had excess blood and were more sanguine (1) and Galen in 200AD stated in his *Tumoribus* that cancer was more common in melancholic women (2). Naturally, these comments were not the result of scientific experiments. It was not until 1893 that the first scientific study on the subject was published by Snow. He reported a statistical analysis of the association between psychological factors and cancer in 250 patients, and concluded that stressful life events were associated with the development of cancer in the majority of patients (3).

In the second half of 20th century, there was a considerable increase in interest in the field of cancer psychology, with a consequent increase in research in the field. This activity was to mark the start of psycho-oncology as a discipline (4). These studies from the 1950s and 1960s showed that emotional expression was associated with survival (5-7). Furthermore, patients with poor social support or loss of social support, for example through death of a spouse, were also shown to have a lower survival rate from cancer.

In the latter part of the century, experiments were performed to examine the possible mechanisms that may be involved in this association – especially concentrating on the role of corticosteroid levels and immune factors (8 -9). As a result, several models of the interaction of psychological, social factors and cancer appeared, some of which also included biological mechanisms. These included the Andersen Biobehavioural Model of Cancer Stress and Disease Course (9), the Van de Borne and Pruyn Coping model (10), The Dirksen Well Being model (11) and Thomas' model of distress (12). The Andersen model is especially interesting as it incorporates interactions between psychological behaviour and biological factors to explain their effects on disease course and progression (9).

The importance of establishing an association between psychosocial factors and long-term survival lies in the fact that psychosocial interventions have recently been found to improve quality of life and the psychological status of head and neck cancer patients (13,14). If there is an identifiable relationship between psychosocial factors and long term survival, then improving patients' psychosocial state could improve the long term survival in susceptible patients.

Chapter 5

In 1998, one of the authors (MdB) published a review of the available literature to 1995, on the association of psychosocial factors and survival in cancer (15). He concluded that there were often contradictory findings in the literature regarding the associations between different psychosocial factors and long-term survival in cancer. Some of the problems identified were: the multitude of definitions and psychosocial measures used, different methodologies, small populations under study with mixed cancer sites, different follow up durations and different analysis strategies. Despite the heterogeneous nature of the research, it is noteworthy that till 1995 there had been no studies examining the relationship between psychosocial factors and survival from head and neck cancer.

The aim of the current review is to update the previous review (15) by examining subsequent research that has addressed the possible association between psychosocial factors and survival in head and neck cancer patients.

Methods

An electronic literature search of the Cochrane, Psych info and Embase databases was performed for the period from 1 January 1995 to 1 April 2010. The search strategy began with a search of the terms in Table 1 as key words, and/or words in the abstract or title. These were then cross-referenced with the following terms: head and neck, cancer, neoplasm, larynx, pharynx, oral, upper aero digestive tract, survival, mortality and recurrence. A search of personal reference lists and article archives was also performed, as was an inspection of the reference lists from the articles identified by the literature review.

The identified articles were then assessed for eligibility according to the following criteria:

1. Survival as the outcome measure
2. Psychosocial factors as prognostic indicators
3. Results reported specifically for head and neck cancer patients
4. Exclude studies that report only on oesophageal or thyroid cancer

The quality of the papers was also rated, using the Scottish Intercollegiate Guidelines Network (SIGN) 50 tool, which is a validated instrument used to assess quality of studies (particularly their internal validity) in a structured manner according to pre-determined criteria – examining aims, selection of subjects, assessment statistical analysis and confounding (16). The instrument results in a rating of overall quality that varies from ++ “high quality” that fulfils most (i.e. more than 50%) of the quality criteria, to + “average quality” that fulfils some (i.e. 20-

50%) of the criteria, or – “poor” that fulfils few or none (i.e. less than 20%) of the criteria.

Results

There were 76 articles initially identified that related to head and neck cancer. The psychosocial factors that were reported by the various studies, and the instruments used are listed in table two. Only 13 studies fulfilled the eligibility criteria and these studies, including quality assessment, are summarised in table three.

BASELINE ASSESSMENT

At baseline, expression of intense psychosocial complaints (17), physical self-efficacy (that is, higher self-perceived physical abilities) (17), self-reported high physical functioning (24) and the Short Form-36 physical component score (47) were associated with increased survival.

Uncertainty about the diagnosis and treatment was found to be a negative prognostic indicator (17), as was being single (17, 18, 43), poor cognitive function (19), baseline fatigue (20, 24), pessimism (45) and alcoholism (21).

Overall, or global, quality of life at the time of diagnosis was not associated with survival in any of the studies. Depression at presentation was not associated with survival except in Aarsted et al's small study (23), and then only through an association with stage (i.e. not an independent risk factor).

ASSESSMENT AFTER TREATMENT

Overall quality of life - as represented by Life Satisfaction Score - was significantly and independently associated with subsequent survival (22) in one large 10-year study. Global quality of life – by EORTC - at 6 months post-treatment and a deterioration of quality of life between 6 months and baseline were also found to be significant predictors of long-term survival by another study (43). A smaller, 5-year study mentioned briefly that they did not appear to find an association. Its results for this particular aspect were excluded however due to insufficient information being provided and inadequate methodology used to determine the association (24).

Chapter 5

Other specific symptoms following treatment were also found to be associated with survival. These included pain (22,44), eating (44), speech (44) and physical functioning (44)

Discussion

KEY FINDINGS

There are several psychosocial factors that may be associated with long-term survival such as post-treatment global quality of life, physical self-efficacy, expression of complaints and emotions, cognitive function, marital status and alcoholism. Some of these factors may be confounded by – or surrogates for - other factors or causes. Indeed, the findings are inconsistent and at times contradictory. This lack of consistency may reflect an absence of an actual association between psychosocial factors and quality of life. However it may also be a reflection of several methodological shortcomings.

One important shortcoming of most studies is that they are single centre experiences, many with relatively small sample sizes and of cancers from several head and neck sites. These factors will impact on the power and sensitivity of such studies. Another contributing factor may be that definitions of psychosocial factors and the methods for their measurement are far from standardised. There is also a lack of homogeneity in outcomes reporting. Even when the instruments are the same, the studies have different methodological designs - for example retrospective versus prospective cohorts versus case control studies (Table 3). Indeed, whilst using the same instrument (the EORTC QLQ C30) four studies each found a different psychosocial factor to be significantly associated with survival (19,20,23,24).

Considerable effort needs to be directed toward obtaining consensus and achieving standardisation of definitions, designs and methodologies, preferably in the context of multi centre, and possibly international, trials. When considering such studies, the role of culture as an important confounding factor in quality of life assessments would need to be taken into account (25).

Consideration should be given to the timing of the assessment and measurement of the psychosocial factors under study. It would appear that most studies examine the association of baseline psychosocial factors with long-term survival. Indeed there may be personality traits that are best measured, or identified, at diagnosis,

Association of psychosocial factors and survival

before treatment. This may allow psychosocial intervention to start at the same time as the medical treatment. Fawzy et al (26) concludes in a review that 'early stage interventions that encourage active behavioural coping and active cognitive coping rather than avoidance or passive acceptance of the illness can attenuate distress, decrease the amount of psychosocial adjustment to the illness needed, improve quality of life, and may also be associated with longer survival time'.

However it has been clearly shown that patients' quality of life varies during the course of the disease. Several studies have demonstrated that patients' quality of life drops significantly during treatment, and then begins to rise again, about 3-6 months after diagnosis. By the end of the first year, patient's quality of life usually has returned to its pre-treatment levels (24, 25, 27-29). Most studies indicate that quality of life then reaches a plateau for at least the next two years. This variation during the course of the disease may also apply to some of the other psychosocial factors such as anxiety and psychological distress (24), although other factors (e.g. smoking) may not change at all. Late deterioration in quality of life and psychological distress has been described (27), but the point at which such decline begins is not clear.

Intuitively, it seems to us more likely that the steady-state psychosocial status *after* treatment would be a more significant determinant of long-term survival than the psychosocial status *before* treatment. A few studies have now examined post treatment factors in detail (22,43,44), and there was indeed a strong correlation between post-treatment quality of life and long-term survival. Therefore, we would suggest that future studies should also examine psychosocial factors after treatment at the point when a steady state has been achieved. The evidence is that patients' quality of life begins to plateau at one year post diagnosis (24,27-29), and this may be a good time-point to use.

Certainly, there is sufficient data emerging to support future research on the potential role of psychosocial factors in head and neck cancer prognosis, including examining existing psychosocial parameters (such as coping strategies) that have not generally been captured in studies so far. Clearly, more work needs to be done in this area.

Conclusions

Long-term survival from head and neck cancer appears to be related, both at baseline and after treatment, to some psychosocial factors, such as cognitive function, fatigue, self-efficacy and expressed uncertainty. However this relationship

Chapter 5

is not currently clear in the literature. There is significant variability and sometimes contradiction in the reported result, and this may suggest the lack of any real association. It may also reflect the considerable heterogeneity in definitions, methodologies, and designs, and sizes of the studies. Standardisation of these in the context of multi centred trials and the examination of post treatment psychosocial factors should be undertaken in an effort to elucidate this relationship further.

References

1. Rigatos GA, Scarlos DB. Psychosomatic concepts in writings of ancient Greek philosophers. In G Christodoulou (ed.) *Psychosomatic medicine. Past and Future*. New York/London: plenum Press, 1987: 43-46.
2. Goldfarb C, Driesen j, Cole D. Psychophysiologic aspects of malignancy. *American Journal of Psychiatry* 1967;123:1545-1552.
3. Bleiker EMA. Personality factors and breast cancer: A prospective study of relationship between psychological factors and the development of breast cancer. Academic Thesis, Amsterdam, 1995.
4. Morton RP. Evolution of quality-of-life assessment in head-and-neck cancer. *J Laryngol Otol*.1995;109:1029-1035.
5. Bacon CL, Renneker R, Cutler M. A psychosomatic survey of cancer of the breast. *Psychosomatic Medicine* 1952;14:453.
6. Blumberg EM, West PM, Ellis FW. A possible relationship between psychological factors and human cancer. *Psychosomatic Medicine* 1954;4: 277-286.
7. Stavrazy KM, Buck CN, Lott JS, Worklin JM. Psychological factors in the outcome of human cancer. *Journal of Psychosomatic Research* 1968;12:251-259.
8. Solomon GF, Amkraut AA. Pseudoneuroendocrinological effects on the immune response. *Ann Rev Microbiol* 1981;35:155-84.
9. Andersen BL. Biobehavioural outcomes following psychological interventions for cancer patients. *J Consult Clin Psych* 2002;70;3:590-610.
10. Pruyt JFA. Coping with stress in cancer patients. *Patient Education Counseling* 1983;5:57-62.
11. Dirksen SR. Theoretical modelling to predict subjective well being. *Western J Nursing Research*, 1990;12:629-643.
12. Thomas BC, Pandey M, Ramdas K, Nair MK. Psychological distress in cancer patients: hypothesis of a distress model. *Eur J Cancer Prevention* 2002;11: 179-185.
13. Meyer TJ, Mark MM. Effects of psychosocial interventions in adult cancer patients: a met-analysis of randomized experiments. *Health Psychology* 1995;14:101-8.

Chapter 5

14. Semple C, Sullivan K, Dunwoody L, Kernohan WD. Psychosocial interventions for patients with head and neck cancer. *Cancer Nursing* 2004;27:434-441.
15. De Boer MF, McCormick LK, Pruyn JF, Ryckman RM, van den Borne BW. Physical and psychosocial correlates of head and neck cancer: a review of the literature. *Otolaryngol Head Neck Surg.* 1999;120:427-36.
16. Scottish Intercollegiate Guidelines Network (SIGN) 50 tool www.sign.ac.uk - accessed 04.09.06.
17. De Boer MF, Van den Borne B, Pruyn JF, et al. Psychosocial and physical correlates of survival and recurrence in patients with head and neck carcinoma: results of a 6 year longitudinal study. *Cancer* 1998;83:2567-79.
18. Yeole BB, Sankaranarayanan R, Sunny M Sc L, Swaminathan R, Parkin DM.. Survival from head and neck cancer in Mumbai (Bombay), India. *Cancer.* 2000;89(2):437-44.
19. de Graeff A., de Leeuw J.R., Ros W.J., Hordijk G-A, Bettermann JJ, Blijham GH, Winnubst JAM. Sociodemographic factors and quality of life as prognostic indicators in head and neck cancer. *Eur. J. Cancer* 2001;37:332-339.
20. Fang FM, Liu YT, Tang Y, Wang CJ, Ko SF. Quality of life as a survival predictor for patients with advanced head and neck carcinoma treated with radiotherapy. *Cancer* 2004;100:425-32.
21. Deleyiannis FW, Thomas DB, Vaughan TL, Davis S. Alcoholism: independent predictor of survival in patients with head and neck cancer. *J Natl Cancer Inst.* 1996; 88(8):542-9.
22. Mehanna HM, Morton RP. Does quality of life predict long-term survival in head and neck cancer patients? *Arch Otolaryngol Head Neck Surg.* 2006;132(1):27-31.
23. Aarstad AK, Aarstad HJ, Bru E, Olofsson J. Mood, anxiety and sense of humor in head and neck cancer patients in relation to disease stage, prognosis and quality of life. *Acta Otolaryngol.* 2005;125(5):557-65.
24. Nordgren M, Jannert M, Boysen M, et al. Health-related quality of life in patients with pharyngeal carcinoma: a five-year follow-up. *Head Neck.* 2006; 28(4):339-49.
25. Morton R. Studies in the quality of life of head and neck cancer patients: results of a two year longitudinal study and a comparative cross-sectional cross-cultural survey. *Laryngoscope*, 2003,113: (7): 1091-103.

Association of psychosocial factors and survival

26. Fawzy FI, Fawzy NW, Hyun CS. Short-term psychiatric intervention for patients with malignant melanoma: effects on psychological state, coping, and the immune system In Lewis CE, O'Sullivan C, Barraclough J. *The psychoimmunology of cancer, mind and body in the fight for survival*, Oxford: Oxford Medical Publications, 1994; 291-319.
27. Mehanna HM, Morton RP. Deterioration in quality of life of late (10 –year) survivors of head and neck cancer patients. *Clin Otolaryngol*. 2006;31(3):204-11.
28. Hammerlid E, Silander E, Hornestam I, Sullivan M. Health – related quality of life three years after diagnosis of head and neck cancer – a longitudinal study. *Head Neck* 2001;23:113-125.
29. List MA, Ritter-Sterr CA, Baker TM, et al. Longitudinal assessment of quality of life in laryngeal cancer patients. *Head Neck* 1996;18:1-10.
30. Terrell JE, Fisher SG, Wolf GT. Long-term quality of life after treatment of laryngeal cancer. *Arch Otolaryngol Head Neck Surg*, 1998;24:964-71.
31. De Boer MF, Pruyn JFA, Van den Borne HW, et al. Rehabilitation outcomes of long-term survivors treated for head and neck cancer. *Head Neck* 1995;17: 503-15.
32. Pruyn JFA, Van der Borne HW, Stringer P. Theories , methods and some results on coping with cancer and contact with fellow-sufferers. In: Watson M, Greer S. *Psychosocial Issues in Malignant Disease*. Oxford, Pergamon Press, 1986:41-52.
33. Van den Borne HW, Pruyn JFA. Contacts between fellow cancer patients [Lotgenotencontact bij kankerpatiënten] [thesis]. Assen/Maastricht:Van Gorcum, 1985.
34. Ryckman RM, Robbins MA, Thornton B, Cantrell P. Development and validation of a Physical Self-Efficacy Scale. *J Pers Soc Psychol* 1982;42:891-900.
35. Pruyn JFA, Van den Borne HW, Reuver RSM et al. The Locus of Control Scale for Cancer Patients. [De Locus of Control-schaal voor Kankerpatiënten.] *Tijdschr Soc Gezondheidszorg* 1988;66:404-8.
36. Wallston KA, Wallston BS. Development of the Multidimensional Health Locus of Control Scales (MHLC). *Health Educ Monogr* 1978;6:160-70.
37. Bjordal K, Ahnler-Elmqvist M, Tolleson E, et al on behalf of EORTC quality of life study group. Development of a European for Research and Treatment of

Chapter 5

- Cancer (EORTC) questionnaire module to be used in quality of life assessment in head and neck cancer. *Acta Oncol* 1994;33:879-885.
38. Radloff LS. The CES-D Scale: a self – report depression scale for research in a general population. *Appl Psychol Measurement* 1977;1:385-401.
 39. Beck AT. Depression. Clinical, experimental, and theoretical aspects. New York: Harper & Row; 1967.
 40. Spielberger CD, Gorsuch RL, Lushene RE. *STAI manual for the state anxiety questionnaire (“Self-evaluation questionnaire”)*. Palo Alto, CA: Consulting Psychologist Press; 1970.
 41. Svebak S. Revised questionnaire on the sense of humor. *Scand J Psychol* 1974;15:328-31.
 42. Eysenck HJ, Eysenck SBG. *Manual of the Eysenck personality inventory*. London: University of London Press; 1964.
 43. Oskam IM, Verdonck-de Leeuw IM, Aaronson NK, et al. Quality of life as predictor of survival: a prospective study on patients treated with combined surgery and radiotherapy for advanced oral and oropharyngeal cancer. *Radiotherapy and Oncology*, 2010 Feb 26. [Epub ahead of print]
 44. Karvonen-Gutierrez CA, Ronis DL, Fowler KE, Terrell JE, Gruber SB, Duffy SA. Quality of life scores predict survival among patients with head and neck cancer. *J Clin Oncol* 2008;26:2754–60.
 45. Allison PJ, Guichard C, Fung K, et al: Dispositional optimism predicts survival status 1 year after diagnosis in head and neck cancer patients. *J Clin Oncol* 2003;21:543-548,.
 46. Siddiqui F, Pajak TF, Watkins-Bruner D, et al. Pretreatment quality of life predicts for locoregional control in head and neck cancer patients: a radiation therapy oncology group analysis. *Int J Radiation Oncology Biol Phys* 2008;70: 353–60.
 47. Grignon LM, Jameson MJ, Karnell LH, Christensen AJ, Funk GF. General health measures and long-term survival in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2007;133:471–76.

Association of psychosocial factors and survival

Table 1: Psychosocial terms and definitions used in electronic search strategy

anxiety, coping strategy, depression, dispositional optimism, emotional support, employment, extroversion, fighting spirit, hopelessness, hostility, locus of control, loss of control, marital status, negative feelings, positive life evaluation, psychosocial well being, self esteem, social involvement, social network, social support, social ties, trait anxiety, quality of life

Chapter 5

Table 2: Psycho-social factors examined in the literature with scales used for assessment.

Measure	Instrument(s)	Refs that used it
<i>QOL measures:</i>		
Global or overall QOL	EORTC QLQ C30	37,43
	LSS, AQLQ	22,27
	SF-36	44
Post-treatment quality of life	LSS, AQLQ	22,37
General psycho-social well-being	RSCL	32
<i>Physical status indicators:</i>		
Head and neck specific complaints	EORTC QLQ C30	Several
	Bespoke scales	Several
	EORTC HN35	37
	HNQOL	44
	AQLQ	22,27
	FACT HN	46
Physical self efficacy	Ryckman scale	34
Cognitive function	EORTC QLQ C30	37
Fatigue	EORTC QLQ C30	37
<i>Psychological disability measures:</i>		
Depression	CES-D	30,38
	Beck depression inventory	39
Anxiety	STAI	40
Psychological distress	GHQ	22,27
<i>Personality trait indicators:</i>		
Coping	LOC/MHLOC	32,35,36
	van de Borne scale LOC	33
	Cancer locus of control	35
	Wallston and Wallston	36
Self esteem	CPI	31
Uncertainty	Bespoke	31
Dispositional optimism	Bespoke	31,45
Humour	Svebak humor	41
Neuroticism	EPI	42
<i>Other factors:</i>		
Marital status	Several	
Alcoholism	MAST	21

Key : AQLQ, Auckland Quality of Life Questionnaire; CES-D, Centre for Epidemiological Studies-depression; CPI, California Psychological Inventory; EORTC HN 35, EORTC head and neck specific questionnaire; EORTC QLQ C30, European Organisation of Radiation and Treatment of Cancer QLQ C30 general questionnaire; EPI, Eysenck personality inventory; GHQ, General Health Questionnaire; LOC, locus of control; LSS, Life satisfaction score; MAST, Michigan alcoholism screening test; MHLOC, Multidimensional health locus of control; QLQ, quality of life questionnaire; QOL, quality of life; RSCL, Rotterdam symptom check list; STAI, Spielberger trait anxiety inventory; HNQOL, Head neck Quality of Life questionnaire; SF-36, short form quality of life 36 questionnaire; FACT HN, Functional Assessment of Cancer Therapy Head and Neck.

Table 3: Summary of studies showing positive association between psychosocial factors and survival of head and neck cancer patients.

Author	Quality	Sample size (exclusions)	Study design	Follow up	Statistical tests	Psycho-social Factor(s) HR/RR mortality (CI)
Aarstad et al 2005, Bergen (23)	+	78 (51) Only 27 analysed	Case control;	72 mth	Pearsons rho, Cox regression, ANOVA	Anxiety and depression - NS Svebak humour NS
Balkrishna <i>et al</i> 2000 Mumbai (18)	-	6311 (15% missing data)	Retrospective	60mth		Single status HR 1.2 (1.0-1.4) Religion - Christian HR 1.3 (1.1 – 1.5)
De Boer et al, 1998, Rotterdam (17)	++	133 (58)	Prospective	72 mth	Kaplan-Meier / log rank tests.	High intensity of complaints-improved survival Perceived self –efficacy-improved survival Uncertainty - decreased survival
De Graeff, et al 2001, Utrecht (19)	++	208 (58 refused)	Prospective	62 mth	Cox regression, Kaplan-Meier, log rank	Poor cognitive function on EORTC– RR 1.85 (1.06-3.33). Unmarried RR 1.82 (1.03-3.23)
Deleyiannis et al 1996 Seattle (21)	++	649 (159)	Retrospective	84mth	Cox proportional hazards	Alcoholism HR 2.06 (1.43-2.98) History of alcohol related health problems HR 2.76 (1.69 – 4.49)
Fang et al 2004, Taiwan (20)	+	102 (N/A)	Prospective	36mth	Cox proportional hazards	Baseline fatigue on EORTC – HR 1.0174 (1.0081-1.027)

Mehanna & Morton, 2006, Auckland (22)	++	200 (4) [130 at 12 months]	Prospective	120mth	Cox proportional hazards ratio	QoL at diagnosis NS. QoL 1 year after diagnosis, poor life satisfaction score <55) - HR 2.5 (95% CI 1.4, 4.3) Head and neck pain – HR 1.9 (1.1, 3.4)
Nordgren et al 2006,(24) Sweden/Norway	+	89 (N/A) [65 at 12 months]	Prospective	60 mth	Cox proportional hazards	Physical function scale on EORTC - HR 0.98 (0.97-0.99), advanced stage - HR 5.59 (1.68-18.6) Similar global QoL at 12months in survivors over 5 years and those who died between 1-5 years.
Allison PJ 2003 (45), France	++	101(1) [51 at 1 year]	Prospective	12 mnth	odds ratio	<i>Baseline:</i> Dispositional optimism - pessimistic subjects (OR 1.12; 95% CI 1.01 -1.24) living alone (OR, 4.14; 95% CI 1.21 - 14.17)
Siddiqui F 2008 (46), USA	+	1093 (417)	Prospective	49mnth	???	<i>Baseline:</i> no association of FACT HN score with overall survival but associated with locoregional control
Grignon, 2007, (47), USA	+	919 (415)	Prospective	60mnth	Cox proportional hazards	<i>Baseline:</i> SF-36 physical component score predicts OS (risk ratio 0.97) and DSS (0.98). Comorbidity also predicts OS and DSS. Mental

						component o SF-36 does not.
Karvonen-Gutierrez ,2008 (44), Michigan , USA	+	973 (588) post-treatment	Retrospective, cross-sectional	61 mnth	Cox proportional hazards ratio	<i>Post treatment (median 4mnth): SF-36 physical component score (0.86, 95CI 0.80 to 0.93); HRQOL pain (0.92, 95CI 0.87 to 0.98), eating (0.94, 95CI 0.89 to 0.99), speech (0.92, 95 CI 0.87 to 0.96), Married (0.68, 95 CI 0.50 to 0.92)</i>
Oskam et al, 2010 (43), Netherlands	++	80 (12) [55 at 6mnth]	Prospective	58mnth	Cox regression relative risk	<i>Baseline: partner (3.10; CI 1.36-7.06) predicted DSS 6 months: EORTC global QoL (0.96, CI 0.94-0.98) and deterioration of global QoL (5.08, CI 2.3-14.6) predicted both DSS and OS.</i>

Key:

EORTC: EORTC Quality of life questionnaire , CES-D : , HR : hazards ratio for mortality, RR: relative risk of mortality, N/A : not available, , mth: months; NS – not significant , QoL -quality of life, DSS – disease specific survival

HNQOL – Head neck Quality of Life questionnaire, SF-36 – short form quality of life 36 questionnaire FACT HN – Functional Assessment of Cancer Therapy Head and Neck

Section Two

Chapter 6

Why are head and neck cancer clinicians not measuring quality of life?

Published: Mehanna HM, Morton RP. Why are head and neck cancer clinicians not measuring quality of life? *J Laryngol Otol.* 2006 Oct;120 (10):861-4.

Presented: Why head and neck cancer clinicians not measuring quality of life? 4th International Head and Neck Cancer Quality of Life Workshop, Liverpool, Nov 2004.

Abstract

Aim: to quantify and qualify the use of QoL measures by head and neck cancer (HNC) clinicians and to identify any impediments to their use.

Methods: questionnaire survey of members of Australia and New Zealand HN society

Results: 128 of 187 (68.5%) responded. Only 43 (34%) had ever used a QLQ, and only 17 (13%) were currently using one. Impediments to use included too time consuming and no proven benefit for clinical management. Nevertheless 113 (88%) indicated willingness to use a minimum core QoL questionnaire – for routine clinical use and for research – but indicated a preference for short (10-15 questions), quick (less than 10 minutes) questionnaires.

Conclusions: most HNC clinicians did not use a QoL measure routinely, with impediments to routine use being mainly clinician based. Most respondents would use a minimum core QL measure, especially if it were a short quick consensus questionnaire.

Introduction

Quality of life (QoL) measurement is now widely considered to be integral to best patient care (1). Indeed the most recent BAO HNS consensus document states that QoL measures are an essential outcome measure of HN surgery and should be included in the minimum HN dataset (2). Furthermore QoL measures have been included in the BAHNO advisory dataset and the British National HN cancer dataset (3). Despite these recommendations, a recent survey of head and neck cancer clinicians in the U.K. indicated that most were not engaged in any QoL data accrual (4).

This study sought to determine whether the UK experience was reflected elsewhere and to enquire further regarding reasons for clinicians' choices regarding QoL data. To achieve this, head and neck oncologic physicians and surgeons in Australia and New Zealand were surveyed, specifically to quantify and qualify the use of QoL measures and identify any impediments to the use of such measures.

Methods

The Australian and New Zealand Head and Neck Society (ANZHNS) consists of 187 professionals involved in the care of head and neck cancer in Australia and New Zealand. Most members are consultant medical practitioners, with the following backgrounds: otorhinolaryngology (33%), plastic surgery (20%), radiation oncology (21%), maxillofacial surgery (11%), head and neck surgery (7%), medical oncology (2%), general surgery (1%), and others (1%). Their principal objectives are 'to promote the practice of head and neck oncology, to educate medical colleagues and the public about our specialty, to foster research and to seek optimal treatment outcomes for our patients' (5).

All members of the ANZHNS were surveyed using an anonymised postal questionnaire (appendix A) enquiring about their use of QoL questionnaires (QLQ), reasons for this and their criteria for an acceptable minimum consensus QLQ. Non-responders were sent a follow-up survey.

Results

Of the 187 members, 128 (68.5%) responded. Of these, otorhinolaryngologists comprised 47 (37%), radiation oncologists 30 (23%), plastic surgeons 26 (20%), maxillofacial surgeons 9 (7%), head and neck/general surgeons 9 (7%), medical oncologists 4 (3%) and speech pathologists 3 (3%). Most (122 - 95%) were consultants. Figure 1 shows the respondents as a proportion of members by specialty.

Of the 128 respondents, only 43 (34%) had ever used a QLQ, and only 17 (13%) were currently using one, of whom only 2 (1.5%) were using it in routine clinical practice, either as an outcome measure or for follow-up. The remainder (i.e. 11.5% of all respondents) were using QLQ as part of QL research or as part of a clinical trial. Radiation (47%) and medical oncologists (50%) were proportionately more likely to have used a QLQ than surgeons [maxillofacial surgeons (44%), otolaryngologists (36%), general surgeons (22%)], and almost exclusively used it for research purposes. Only 1 (4%) of 26 plastic surgeon respondents had used a QLQ.

Of those 27 respondents who had ceased using a QLQ, almost half (13, or 48%) stopped because they thought it did not add value to clinical management or that it

Chapter 6

was too intrusive in a clinical setting. Other reasons for stopping included: - clinical trial ending (5; 19%); patients did not want it (2; 7%); questionnaires did not fulfil their needs (4; 15%); and did not know what to do with the information (3; 11%).

When asked about the desirability of a short screening questionnaire for identifying patient complaints, 85 (66%) indicated somewhat or extremely desirable, with 31 (24%) indicating it would be undesirable, with no differences between oncologists and surgeons.

Most [113 (88%)] of the 128 respondents indicated that they would use a consensus minimum head and neck cancer QLQ. Of those, 46 (40%) would use it for clinical purposes only, such as routine follow-up, screening for problems and as a clinical outcome measure, whilst 24 (21%) would use it for research purposes only, and 43 (38%) would use it for both (figure 2). Over 90% indicated that a questionnaire with up to 10 -15 questions taking 10 minutes to complete would be an acceptable format.

Of the 15 (12%) respondents who would not consider using a core questionnaire, only 3 thought that patients did not like questionnaires. The remainder indicated physician based reasons, such as not adding value to patient management, too time consuming in a clinic or not knowing what to do with the information (figure 3).

Discussion

KEY FINDINGS

Although research interest in HN QoL is at its highest (1), and professional and governmental bodies have stipulated the need for routine QoL measurement (2-4), the vast majority of head and neck clinicians in our study were not measuring QL as a clinical outcome measure. Only a third of our respondents had ever used QLQ, and only a small proportion of these were currently using one, mainly as part of research or a clinical trial. Oncologists were more likely to have used a QLQ than surgeons, primarily because of their increased involvement in clinical trials. Interestingly, both those who had stopped using QLQ and those who do not want to use QLQ at all did so because of physician related reasons, mainly because it was too time consuming, they did not find QLQ of any benefit to patient care, or that the QLQs did not fulfil the clinicians' needs.

COMPARISON WITH OTHER STUDIES

These findings are very similar to those of a UK survey carried out on British head and neck oncologists (4). That survey had also found that only 29% of respondents had used QLQ, and that the main reasons for not using them were 'lack of resource and proven value'. Furthermore, respondents in both studies indicated that the main problem with QLQ was that they were too time consuming in a clinic setting.

Yet most clinicians in our survey indicated that they would consider using a consensus minimum dataset QLQ, with the great majority indicating that they would use it in routine clinical practice, either as an outcomes measure or for problem identification. However the respondents also indicated that the QLQ should be short, taking upto 10 minutes to complete. Furthermore, two thirds indicated their desire for a short questionnaire to screen for patient complaints and problems, such as pain, physical and psychological dysfunction.

LIMITATIONS OF STUDY

There are limitations in our study. The main one is that the response rate, while good for postal questionnaires, is still only modest, and will carry response bias. Also, the membership of ANZHNS is not a complete register of professionals involved in the management of head and neck cancer in Australia and New Zealand, which may lead to sample bias. Furthermore, the surgical respondents' backgrounds are biased towards otolaryngology. Interestingly the UK study was sourced from a maxillofacial unit, and respondents' backgrounds were biased towards maxillofacial surgery, and this may reflect a tendency for members to respond better when the authors are from their own specialty. However, it is reassuring that the findings of both studies are very similar despite the possible biases, and the different geographies and healthcare systems.

CLINICAL RELEVANCE

There appears to be a significant gap between the current status of QoL measurement in clinical practice and the ideal, or even what the clinicians themselves aspire to. This gap would seem to exist because current QLQs do not appear to address the needs of the head and neck clinician, who would like a short consensus QLQ, and which ideally could also be used to assist patient management. Further assessment of current QLQs is needed to identify which of these would best fulfil these criteria, and whether modification of existing

questionnaires is required to achieve these aims. It is also important that the assessment ensures that the selected QLQ also fulfils the needs of the patients. Finally, better funding and the utilisation of data managers, who would be responsible for the distribution, collection and analysis of QLQ in the clinic, may address some of the resource issues, and make routine collection of QL data more feasible in clinical practice.

Conclusions

Most head and neck clinicians do not currently collect quality of life data, mainly due to time and resource constraints, or because these questionnaires are not perceived to have relevance to patient management. However, most clinicians surveyed indicated a readiness to use a short consensus QLQ questionnaire for routine clinical practice and for research, if that was available. Therefore, further assessment and modification of existing questionnaires is required to satisfy these needs, and encourage the measurement of QL outcomes in clinical practice.

Acknowledgements

Our thanks to members of the Australian and New Zealand Head and Neck Society who responded to the survey, and to Ms Karen Wright, the ANZHNS administrator, for her help in the distribution of the survey.

References

1. Weymuller EA, Yueh B, Deleyiannis FW, Kuntz AL, Alsarraf R, Coltrera MD. Quality of life in patients with head and neck cancer: lessons learned from 549 prospectively evaluated patients. *Arch Otolaryngol-Head Neck Surg* 2000;126:329-335.
2. BAO HNS. Effective head and neck cancer management – third consensus document. 2002 p6.
3. <http://www.nhsia.nhs.uk/cancer/pages/dataset/docs/dataset.pdf>, accessed 6 April 2004
4. Kanatas AN, Rogers SN. A national survey of health-related quality of life questionnaires in head and neck oncology. *Ann R Coll Surg Engl* 2004;86:6-10
5. Australia and New Zealand Head and Neck Society. www.anzhns.org, accessed 30 May 2004.

Figure 1: Respondents as a proportion of members of ANZHNS by specialty.

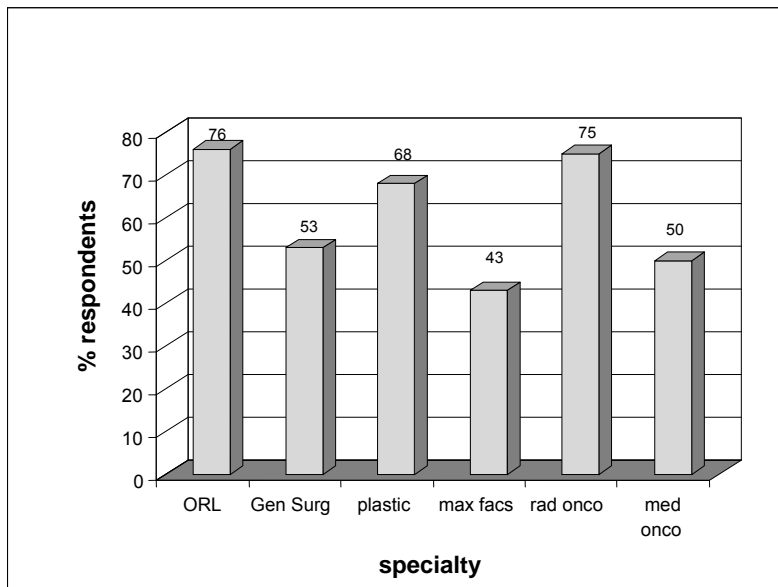
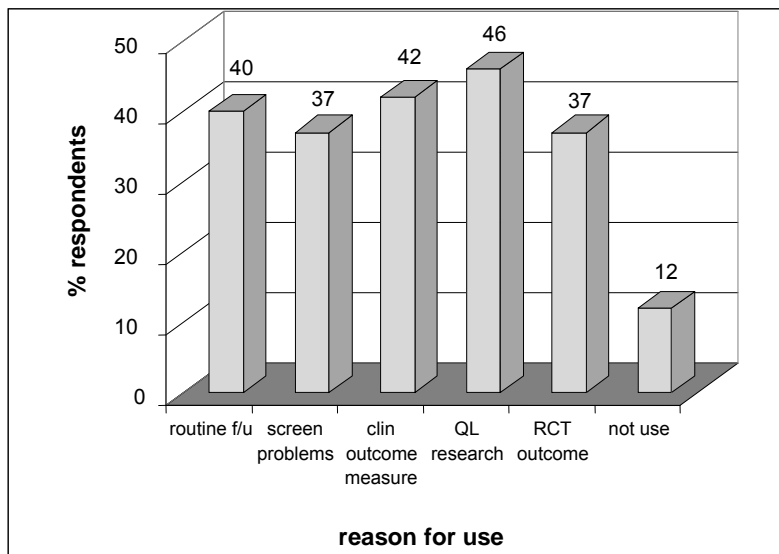


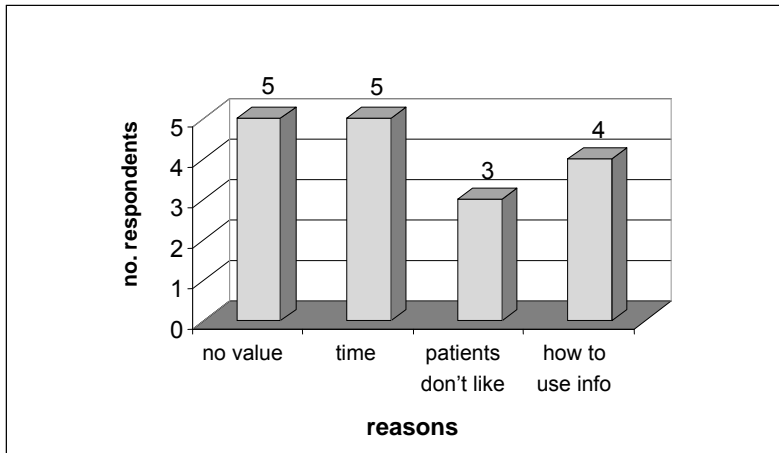
Figure 2: Reasons for use of a consensus minimum HNC QLQ



Note: respondents could choose more than one response to this question

Why are HNC clinicians not measuring QoL?

Figure 3: Reasons for not using a consensus QLQ



Chapter 6

Appendix A

The Australian and New Zealand Head and Neck Society

Survey on the use of Head and neck cancer Quality of life Questionnaires

We would be grateful if you would fill out this questionnaire, and fax it back to us on (+64) 9 631 0770

It will take **less than 5 minutes** to complete

1. Which speciality do you belong to?
 - i. Maxillofacial
 - ii. ORL.
 - III Plastics
 - vii. Other: please state.....
 - iv. General surgery
 - v. medical oncology
 - vi. Radiation oncology
2. What is your grade?
 - i. Consultant or equivalent
 - ii. Registrar or trainee
 - iii. Non-medical
3. Have you ever used a head and neck Quality of Life questionnaire(HNQLQ):
 - a. Yes
 - b. No – then **please go to question 7**
4. Do you still use a HNQLQ?
 - a. Yes
 - b. No – then **please go to question 6**
5. What do you use the HNQLQ for? (*you may mark more than one choice*)
 - a. routine clinical follow-up of patients
 - b. routine screening of patients for problems eg pain, psychosocial
 - c. routine outcome measure of treatment in clinical practice
 - d. Quality of life (QoL) research
 - e. Outcome measure as part of a clinical trial
 - f. Other: please state.....

Now please go to question 7

6. Why did you stop using a HNQLQ? (*you may mark more than one choice*)
 - a. does not add value to clinical management of patient
 - b. too time consuming or intrusive in a clinic setting
 - c. not wanted by patients
 - d. current questionnaires do not fulfil my needs
 - e. did not know what to do with the information
 - f. other: please state.....

7. How desirable do you think it is to have a short screening questionnaire for identifying problems eg pain, psychosocial, physical dysfunction?
 - a. extremely undesirable
 - b. somewhat undesirable
 - c. indifferent – neither desirable or undesirable
 - d. somewhat desirable
 - e. extremely desirable

8. Would you consider using a consensus core (minimum) head and neck cancer quality of life questionnaire? (*you may mark more than one choice*)
 - a. No – **please go to question 10**
 - b. Yes – for routine clinical follow-up of patients
 - c. Yes – for routine screening of patients for problems eg pain, psychosocial
 - d. Yes – for routine outcome measure of treatment in clinical practice
 - e. Yes – for quality of life (QoL) research
 - f. Yes – for outcome measure as part of RCT
 - g. Yes – other: please state.....

9. Which of the following would be acceptable to you for a consensus core questionnaire, :
 - a. Time required to complete questionnaire (please select only one choice)
 - i. <1 min
 - ii. <5 mins
 - iii. 6-10 mins
 - iv. 11-15 mins
 - v. 16-20
 - vi. >20 min
 - vii. Duration does not matter
 - viii. Other: please state.....

 - b. number of questions included in questionnaire (please select only one choice):
 - i. <5 questions
 - ii. 5-10
 - iii. 11-15
 - iv. 16-20
 - v. 21-25
 - vi. >25 questions
 - vii. number of questions does not matter
 - viii. Other: please state.....

Chapter 6

NOW Please go to comments section below

10. Why would you NOT use a consensus core questionnaire? (*you may mark more than one choice*)
- a. questionnaires do not add value to clinical management
 - b. too time consuming in a clinic
 - c. patients do not like it
 - d. I already use a questionnaire that I am happy with
 - e. I would not know what to do with the information
 - f. other: please state.....

Comments section:

If you have any comments or suggestions, we would be grateful if you would include them in the space below

Chapter 7

Patients' views on the utility of quality of life questionnaires in head and neck cancer: a randomised trial

Published: Mehanna HM, Morton RP. Patients' views on the utility of quality of life questionnaires in head and neck cancer: a randomised trial. *Clin Otolaryngol*. 2006 Aug;31 (4) :310-6.

Presented Patients' views on the utility of quality of life questionnaires in head and neck cancer. ORS spring meeting 2006, Bath April 2006

Abstract

Objectives:

1. Evaluate head and neck cancer (HNC) patients' perspectives regarding the usefulness of quality of life questionnaires (QLQ) in communicating their health problems to clinicians
2. Identify the QLQ that HNC patients find most useful.

Design: randomized questionnaire study. Patients completed all four validated HNC QLQs – EORTC , FACT HN35, University of Washington QLQ, Auckland QLQ. Order of questionnaire presentation was randomized to counterbalance for order effects

Setting: tertiary referral HNC centre, Auckland, New Zealand

Participants: 80 patients diagnosed and treated for HNC. Exclusion criteria: blindness, learning difficulties or inability to understand or read English.

Main outcome measures: patient ratings of perceived usefulness and preferences of studied questionnaires .

Results: Patients reported high relevance to their problems and high ease of understanding of all questionnaires, with FACT scoring highest (79% and 89% respectively). 58% participants (67% respondents) would like to complete a questionnaire in clinic, as it would help them describe their health problems to their doctors; 28% of participants did not. Almost half preferred a particular QLQ, FACT being most preferred. Length of questionnaire did not affect reported usefulness, but most would prefer a short questionnaire (<20 items).

Conclusions: Patients report that HNC QLQs effectively describe their health concerns. Most are in favour of completing QLQs in clinic, as an aid for describing health problems to clinicians. There appears to be a difference between clinicians and patients regarding the perceived usefulness of QLQs in the clinic setting, which needs to be highlighted to clinicians.

Introduction

Routine measurement of quality of life in head and neck cancer practice has been strongly recommended by several professional bodies (1). There are several

extensively-validated quality of life questionnaires currently available for this purpose (2). Furthermore most head and neck cancer clinicians report being in favour of health-related quality of life assessment and questionnaires in the clinic (3,4).

Despite this, *less than a third* of head and neck cancer clinicians have carried out quality of life assessments (usually in a research setting) (3). The main impediments are reported to be a combination of resource limitations, confusion regarding which questionnaire to use and a perceived lack of proven clinical usefulness (no impact on patient care) (3,4).

One clinically relevant use of quality of life questionnaires may be as a communication aid for patients to describe their health problems to their clinicians. Use of quality of life measurement in a clinical oncological setting has been shown to improve patient - clinician communication and is associated with an improved quality of life and emotional functioning of patients (5). Detmar et al also concluded in another randomised trial that use of quality of life questionnaires in routine clinical oncological use facilitated patient – clinician communication, and improved clinician awareness of their patients' quality of life issues (6). The same was found by Taenzer et al (7). No such work has been done in head and neck cancer to date.

It should also be noted that the available validated quality of life questionnaires correlate moderately with each other (2), and therefore probably measure similar aspects of quality of life. However no assessment or comparison of acceptability of different head and neck cancer quality of life questionnaires for use in this setting has been attempted. This poses a problem when deciding which questionnaire to use in the clinical setting. For example, which questionnaire to use for oral versus laryngeal patients or for patients with early disease versus advanced disease.

The aims of this study were:

1. To examine patient perspectives regarding the usefulness of head and neck cancer quality of life questionnaires in communicating their health problems to clinicians,
2. To identify patient reported characteristics of an “ideal” questionnaire for this purpose,
3. To identify which of four validated, widely used head and neck cancer quality of life questionnaires patients most prefer to use for this purpose.

Methods

Patients

Consecutive new and follow-up patients attending the head and neck clinic at the Auckland Regional Head and Neck cancer unit were recruited, after informed consent, to complete the study survey. The exclusion criteria were inability to read or understand English, blindness and learning disability. In total, 80 patients were approached to participate: 76 consented, but two subsequently withdrew because they felt too unwell to complete the long questionnaire. Of the four patients who refused to participate, three declined due to lack of time to complete the questionnaire, and one because he was unwell.

Ethical considerations

Approval was obtained from the local ethics committee as part of a programme of quality of life studies, and patients were consented using a customised patient information leaflet and consent form by the clinic nurse.

Quality of life questionnaires

All patients were asked to complete the study survey. This consisted of the four commonly used, validated, patient-reported quality of life questionnaires: The University of Washington quality of life questionnaire v3 (12 questions and a free text area), the FACT Head and neck questionnaire v4 (38 questions), the EORTC HN35 questionnaire (34 questions), and the Auckland Quality of Life Questionnaire (41 questions).

Value of completion of a quality of life questionnaire

After each questionnaire, there were four questions enquiring about its acceptability and usefulness to the participant (appendix S1).

Comparison between quality of life questionnaires

At the end of the survey, there were eight questions asking participants to compare all four questionnaires, and to rank the questionnaires in terms of most and least useful, as well as enquiring about the characteristics of the ideal questionnaire from the point of view of the patient (appendix S2).

In order to adjust for the effects of fatigue and /or boredom, due to the large number of questions and their somewhat repetitive nature, patients were randomised (using a computer generated model) to complete one of four versions

of the study survey, in which the quality of life questionnaires were presented in different order (see Table 1). Neither investigators nor participants knew or could influence the version that any participant received. Subjects could request assistance in completing the questionnaire from a clinic nurse who had been trained in administering them.

The study survey was piloted on a group of 10 patients and their comments were used to amend the final versions as necessary.

Analysis

Data was input into an excel database, and data were verified by a second person then analysed using SAS system. The chi squared test was applied to determine statistically significant differences (set at $p < 0.05$) between different questionnaires and also between randomisation arms.

In the ideal characteristics section of the results, the response rates to each of the 4 questions varied considerably with the potential for bias occurring as discussed subsequently in the section on Limitations of the study. Missing data can be reported in several ways; either excluded from the analysis or included in the analysis as the best and worst case scenarios with a range of values. We have elected to perform the latter as it gives a more accurate representation of the possible ranges. Routine measurement of quality of life in head and neck cancer practice has been done.

Results

Study population

Patients were predominantly male (68 %), with a mean age of 65 years. Over 80% had squamous carcinomas, with the most common site being oral cancer, and with a predominance of advanced disease. Over half the patients had been previously treated by surgery and/ or radiotherapy and occasionally chemotherapy (see table 1). The mean duration since treatment for the follow-up patients was 21 months (range 1- 120 months). As noted earlier, three patients refused participation due to lack of time and one because they were too ill. Two patients withdrew after consent due to being too ill.

Chapter 7

Characteristics of Questionnaires under study

There was no significant difference between the quality of life questionnaires in respect of ease of comprehension, perceived length of questionnaire, relevance, or preference, but the following specific features and trends for the various instruments were observed:

Ease of comprehension & questionnaire length

Patients reported a high and similar ease of understanding for each of the questionnaires, with the FACT scoring highest (89% respondents) (table 2 and figure 1). A small proportion (10-17%) of patients found questionnaires too long irrespective of the actual number of questions.

Relevance to health problems and fulfilment of needs

Patients reported a high relevance of all questionnaires to their problems, with FACT again being most relevant (74% of respondents) (table 2 and figure 1). Most patients felt that the questionnaires helped them to describe their problems to their doctors, with FACT again being reported as the most useful in that regard.

Approximately a third of patients found that questionnaires helped them to concentrate on their problems, with the UW QoL scoring highest (37%) and the Auckland quality of life questionnaire scoring lowest (22%). Approximately a quarter of respondents found no advantage to using the questionnaires, and this was consistent between questionnaires with no significant differences (table 2).

Comparison of Patient Preferences of Questionnaires

When asked to compare questionnaires, almost half of patients identified a specific questionnaire that they felt most helped them to describe their problems; FACT was the most commonly identified, followed by UWQoL 22 (30%) of 70 respondents felt that any of the questionnaires would help them describe their problems (table 3). The most commonly cited reasons were that the questionnaire was relevant to their health problems (53%), that it was easy to understand (39%), and that it would help them state their problems to their doctor (30%). The order in which the component questionnaires appeared to the subjects in the survey questionnaire did not appear to affect their rating of usefulness (table 3). This was also not affected by whether they were new (untreated), or treated patients.

When asked to rate the questionnaire least useful, most (approximately 60%) respondents indicated 'not sure'. Although the UW QoL was most cited, this only accounted for approximately 15% of respondents. The main reason for lack of

usefulness of a questionnaire was that it was not relevant to their health problems. Again responses did not vary significantly depending on whether patients were treated or new (untreated).

Ideal questionnaire characteristics

60% of respondents (with a range of 43% to 71% when non-respondents were accounted for) would like to complete a questionnaire in the clinic, as they felt it would help them describe their health problems to their doctors (table 4). 40% of respondents (range 29%-57%) did not want to fill in a questionnaire, because they felt that it was not relevant to their health problems or that it took too long.

Over half of respondents (range 47%-59% when non-respondents are accounted for) would prefer a short brief questionnaire, up to 20 questions long, and requiring less than 10 minutes to complete. Approximately a quarter were not concerned about the length of questionnaires or time taken to complete it.

There were no significant differences in characteristics reported by new (untreated) and treated patients

Discussion

Key findings

A majority (60%) of head and neck cancer patients favoured using quality of life questionnaires as a method of communicating their problems to their doctors and of helping them concentrate on their problems, while a minority (about 25%) did not consider quality of life questionnaires to be of any major advantage. Most patients found the questionnaires easy to understand and relevant, and this applied to both new and treated patients. This has important implications for the use of quality of life questionnaires in routine clinical practice.

It is reassuring that most patients felt that the quality of life questionnaires were generally easy to understand and relevant to their health problems and that length of questionnaire did not seem to affect patients' perception of utility. Hence, the choice of questionnaire probably does not matter. Overall however, the FACT instrument appeared to be the most preferred.

For the time being, the choice of questionnaire may be best left to the clinician involved, taking into consideration the aim for which quality of life is being

Chapter 7

measured and what specific outcomes are of interest. While long questionnaires are likely to be used for research purposes, a shorter quality of life questionnaire option may be preferred for general clinical practice, and is consistent with the wishes of head and neck oncologists (6), as well as those of the patients.

Limitations of study

Due to the need to compare four questionnaires, the number of questions in the study questionnaire was large, and the possible resultant fatigue or boredom may have impacted on the participants' responses. The design of the study attempted to address this issue by randomisation to four groups each with a different order of questionnaire presentation. However, because of the resultant four groups, numbers in each group are relatively low, and therefore may not have sufficient power to detect statistically significant differences between the sub-groups.

Furthermore, although the questions on usefulness and comparison of questionnaires were straightforward and were piloted, they have not been validated in large scale studies, and may be a source of bias. In addition, some patients did not respond to some questions on preferences (table 4), either in the positive or negative, and this should be considered when interpreting the data, as potentially they may have had a negative view but did not want to express it. Alternatively, they may have had a positive view or they omitted the question in error.

Small sample size also prevented subgroup analysis by site and treatment modality which may have a bearing on patient preference. For example, could the UWQOL be more suited for oral cancer (or surgical) patients and FACT better for laryngeal cancer (or radiotherapy) patients?

Clinical applicability

The majority of respondents would like to complete a questionnaire in the clinic, mainly because it assists them to describe their condition to their doctor. This is in contrast to the findings of clinician surveys, which show that doctors do not use quality of life questionnaires because of a combination of resource limitations and a perceived lack of proven clinical usefulness (5,6). It would therefore appear that there is a gap between the perceptions of the patients and their clinicians regarding the direct benefit of the use of quality of life questionnaires in routine clinical practice, and this needs to be addressed further.

Furthermore, this study provides the basis for further research to evaluate the effects of using quality of life questionnaires in the consultation in head and neck

practice on improving communication and clinical outcomes. A mixed methods multi-centre trial to examine this is currently in the advanced stages of planning.

Conclusions

Patients report that HNC QLQs effectively describe their health concerns. Most are in favour of completing QLQs in clinic, as an aid for describing health problems to clinicians. There appears to be a difference between clinicians and patients regarding the perceived usefulness of QLQs in the clinic setting, which needs to be highlighted to clinicians.

Acknowledgements

We would like to thank Dr Nicholas Mclvor, FRACS, and Dr John Chaplin, FRACS, consultants at the Auckland Regional Head and Neck Unit, for allowing us access to their patients for this study.

We would also like to thank Ms Teena West, Biostatistician, for her considerable assistance with the statistical analysis.

References

1. British Association of Otorhinolaryngology- Head Neck Surgery. Consensus document on the management of head and neck cancer. BAO-HNS, London 2002.
2. Ringash J, Bezjak A. A structured review of quality of life instruments for head and neck cancer patients. *Head Neck* 2001;23:201-213.
3. Kanatas AN, Rogers SN. A national survey of health-related quality of life questionnaires in head and neck oncology. *Ann R Coll Surg Engl* 2004;86:6-10.
4. Mehanna HM, Morton RP, West T. Why are head and neck cancer clinicians not measuring quality of life ? *J Laryngol Otol*. 2006 Oct;120(10):861-4.
5. Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, Selby PJ. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. *J Clin Oncol*. 2004, Feb 15;22(4):714-24.

Chapter 7

6. Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK
Health-related quality-of-life assessments and patient-physician
communication: a randomized controlled trial. *JAMA*. 2003;288:3027-34.
7. Taenzer P, Bultz BD, Carlson LE, Specca M, DeGagne T, Olson K, Doll R,
Rosberger Z.. Impact of computerized quality of life screening on physician
behaviour and patient satisfaction in lung cancer outpatients. *Psychooncology*.
2000 May-Jun;9(3):203-13.

Table 1: Patient Characteristics

		Total n=74	Order of QLQ Presentation			
			1,2,3,4 n=18	2,3,4,1 n=18	3,4,1,2 n=19	4,3,1,2 n=19
Male		50(68%)	16(89%)	10(56%)	8 (42%)	16(84%)
Age, years , mean (sd)		65 (15)	69 (18)	63 (17)	62 (11)	66 (13)
Patient Type	New/Untreated	36(49%)	8 (44%)	9 (50%)	9 (47%)	10(53%)
	Follow-up/Treated	38(51%)	10(56%)	9 (50%)	10 (53%)	9 (47%)
Tumour Type	Squamous	60(81%)	14(78%)	14(78%)	14 (74%)	18(95%)
	Glandular	9 (12%)	2 (11%)	3 (17%)	3 (16%)	1 (5%)
	Other	5 (6%)	2 (11%)	1 (6%)	2 (10%)	0
Stage	I	13(18%)	4 (22%)	2 (11%)	4 (21%)	3 (16%)
	II	9 (12%)	0	4 (22%)	2 (11%)	3 (16%)
	III	11(15%)	1 (6%)	2 (11%)	1 (5%)	7 (37%)
	IV	22(30%)	4 (22%)	6 (33%)	7 (37%)	5 (26%)
	No staging system	19(26%)	9 (50%)	4 (22%)	5 (26%)	1 (5%)
Site	Oral	24(32%)	5 (28%)	9 (50%)	6 (32%)	4 (21%)
	Oropharynx	9(12%)	0	2 (11%)	3 (16%)	4 (21%)
	Glottis	9 (12%)	2 (11%)	2 (11%)	1 (5%)	4 (21%)

	Other (incl hypo/nasopharynx)	29(39%)	9 (50%)	5 (28%)	9 (47%)	6 (31%)
Follow Up Patients Only						
Surgery (<i>Primary</i>)	Laryngectomy	3 (4%)	1 (6%)	0	1 (5%)	1 (5%)
	Maxillectomy	2 (3%)	0	1 (6%)	1 (5%)	0
	Mandibulectomy	1 (1%)	0	1 (6%)	0	0
	Glossectomy	11(15%)	3 (17%)	5 (28%)	1 (5%)	2 (11%)
<i>Flap</i>	Local					
	Free flap single	28(38%)	6 (33%)	8 (44%)	8 (42%)	6 (32%)
	Combination free flaps	3 (4%)	1 (6%)	0	2 (11%)	0
Neck dissection	Unilateral	29(39%)	8 (45%)	9 (50%)	5 (27%)	7 (37%)
	Bilateral	5 (7%)	3 (17%)	1 (6%)	1 (5%)	0
Radiotherapy	None	24(32%)	3 (17%)	6 (7%)	8 (42%)	7 (37%)
	Curative	14(19%)	2 (11%)	4 (22%)	7 (37%)	1 (5%)
	Adjunct	16(22%)	5 (28%)	8 (44%)	3 (16%)	0
Chemotherapy	No	36(49%)	15(83%)	17(94%)	16 (84%)	18 (95%)
	Yes	6 (8%)	2 (12%)	0	3 (16%)	1 (5%)

Table 2: Questionnaire characteristics as perceived by patients

n (%)	Questionnaire1 UW QLQ	Questionnaire2 AQLQ	Questionnaire3 EORTC	Questionnaire 4 FACT HN
	72 (100)	74 (100)	72 (100)	73
Relevant to my health problems	43 (60)	43(58)	49 (68)	54(74)
Easy to understand	57 (79)	57(77)	62 (86)	65(89)
Helps me to concentrate on the problems I have	28 (39)	16(22)	1926	27(37)
Neither helpful or unhelpful	17 (24)	19(26)	1724	18(25)
Too long	10 (14)	13 (18)	8 (11)	12 (16)
Difficult to understand	1	0	0	0
Too short	1	0	0	0
Annoying/intrusive because too long	1	2 (3)	1	1
Annoying/intrusive because difficult to understand	2 (3)	1	1	1
Annoying/intrusive because not relevant to my health problems	0	0	1	0

No statistically significant differences between questionnaires were found using chi-squared test ($p < 0.05$).

Table 3: Head and neck cancer patient preferences of quality of life questionnaires

	Total	Order of QLQ Presentation			
		1,2,3,4	2,3,4,1	3,4,1,2	4,1,2,3
	n=70	n=16	n=17	n=19	n=18
<i>Which questionnaire helped most to describe health problems</i>					
Questionnaire 1 (UWQLQ)	10	4	2	3	1
Questionnaire 2 (AQLQ)	2	1	0	1	0
Questionnaire 3 (EORTC)	9	2	2	5	0
Questionnaire 4 (FACT HN)	13	3	3	2	5
Any of them	22	4	4	5	9
None of them	6	1	2	2	1
Not sure	4	1	3	0	0
A specific questionnaire	34	10	7	11	6
<i>Why was this the most useful?</i>					
Short	4	0	1	2	1
Easy to understand	27	5	5	8	9
Relevant to my health problems	37	9	11	6	11
Will help me state my health problems	21	4	7	4	6
Not sure	8	2	1	3	2

Other	2	1	0	1	0
<i>Which questionnaire helped least to describe health problems</i>					
Questionnaire 1 (UWQLQ)	10	2	3	4	1
Questionnaire 2 (AQLQ)	2	1	1	0	0
Questionnaire 3 (EORTC)	8	2	0	3	3
Questionnaire 4 (FACT HN)	4	1	2	1	0
All of them	3	1	1	0	1
Not sure	30	6	8	8	8
<i>Why did you not like it?</i>					
Too long	6	1	2	2	1
Hard to understand	1	0	1	0	0
Not relevant to my health problems	17	6	6	3	2
Too intrusive	6	1	3	1	1
Not sure	19	5	6	6	2
Other	4	2	0	0	2

No statistically significant differences between randomization groups were found using chi-squared test ($p < 0.05$).

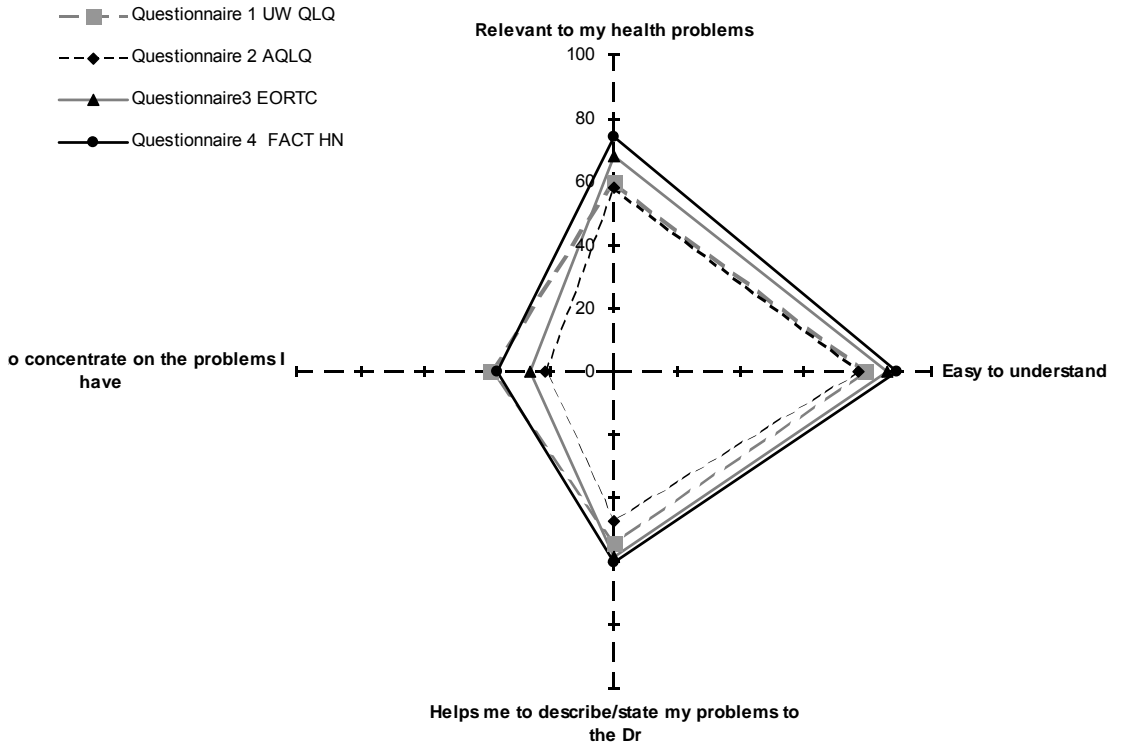
Chapter 7

Table 4: Ideal questionnaire characteristics as reported by head and neck cancer patients (n=70).

<i>If given a choice, would you like to fill in a questionnaire at the clinic?</i>	
Yes - helps me to state/describe health problems to the doc	25
Yes - helps me to concentrate on problems I have	5
No - questionnaire takes too long	9
No - questionnaire difficult to understand	0
No - questionnaire not relevant	11
No response	20
<i>Would you prefer a short brief questionnaire or a long detailed one?</i>	
Short brief	36
Long detailed	5
Either	22
Neither	4
No response	3
<i>Time required to complete questionnaire?</i>	
<60 seconds	2
<5 mins	18
6-10 mins	17
11-20 mins	18
>20 mins	0
Doesn't matter	12
Other	0
No response	3
<i>Number of questions in a questionnaire?</i>	
<5	2
5 to 10	14
11 to 15	8
16 to 20	9
> 20	8
Doesn't matter	21
No response	8

No significant differences were found between the randomization arms for any of the above factors using chi square test.

Figure 1: Questionnaire characteristics as perceived by head and neck cancer patients.



Appendix 1

Comparison between quality of life measures

Quality of Life Questionnaire Study Questionnaire 1

1. Regarding questionnaire 1, how would you describe this questionnaire?

Circle one

- | | | |
|-----------------------------------|-----|----|
| a. Relevant to my health problems | Yes | No |
| Not sure | | |
| b. Easy to understand | Yes | No |
| Not sure | | |
| c. Too long | Yes | No |
| Not sure | | |
| d. Difficult to understand | Yes | No |
| Not sure | | |
| e. Too short | Yes | No |
| Not sure | | |

2. How did you find questionnaire 1? You CAN circle MORE than one choice, if you wish

- A) Helps me to state/ describe my health problems to the doctor.
- B) Helps me to concentrate my mind on the health problems I have.
- C) Neither helpful or unhelpful.
- D) Annoying / intrusive because it is too long.
- E) Annoying / intrusive because it is difficult to understand.
- F) Annoying / intrusive because it is not relevant to my health problems or complaints.

3. Any additional comments about the questionnaire you wish to make?

Appendix S2:

Value of completion of a quality of life questionnaire

Quality of Life Questionnaire Study

Now please think back to all 4 questionnaires

1. Of the 4 questionnaires, which ONE do you think would help you MOST to state / describe your health problems to the doctor?

- A) Questionnaire 1
- B) Questionnaire 2
- C) Questionnaire 3
- D) Questionnaire 4
- E) ANY of them
- F) NONE of them
- G) Not sure

2. Why did you find the questionnaire you identified above in **question 1** helpful? You can circle MORE than one choice if you wish.

- A) Short
- B) Easy to understand
- C) Relevant to my health problems/complaints
- D) Will help me state / describe my health problems to the doctor
- E) Not sure
- F) Other - please state

3. Of the 4 questionnaires which ONE do you think would help you LEAST to state / describe your health problems to the doctor ?

- A) Questionnaire 1
- B) Questionnaire 2
- C) Questionnaire 3
- D) Questionnaire 4
- E) All of them
- F) Not sure

4. Why do you **not like** the questionnaire you identified above in **question 3**? You can circle MORE than one choice if you wish.

- A) Too long
- B) Hard to understand
- C) Not relevant to my health problems
- D) Too intrusive
- E) Not sure
- F) Other - please state _____

Chapter 7

5. If given a choice, would you like to fill in a questionnaire at the clinic, and why?
- A) YES - Helps me to state/ describe my health problems to the doctor.
 - B) YES - Helps me to concentrate my mind on the health problems I have.
 - C) NO - because questionnaire takes too long.
 - D) NO - because questionnaires are difficult to understand.
 - E) NO - because questionnaires are often *not* relevant to my health problems or complaints
6. Would you prefer a short brief questionnaire or a long detailed one?
- A) Short brief questionnaire asking a few questions.
 - B) Long detailed questionnaire asking a few questions.
 - C) Either is fine.
 - D) Neither - I do not want to fill any questionnaires.
7. Which of the following would be acceptable to you as a questionnaire about your health filled in clinic?
- c. Time required to complete questionnaire (please select only one choice)
- i. less than 1 minute
 - ii. Less than 5 minutes
 - iii. 6-10 minutes
 - iv. 11-15 minutes
 - v. 16-20 minutes
 - vi. more than 20 minutes
 - vii. duration does not matter
 - viii. Other: please state.....
- d. number of questions included in questionnaire (please select only one choice):
- i. less than 5 questions
 - ii. 5-10 questions
 - iii. 11-15 questions
 - iv. 16-20 questions
 - v. 21-25 questions
 - vi. more than 25 questions
 - vii. number of questions does not matter
 - viii. Other : please state...

Chapter 8

Summary, discussion and conclusions / samenvatting

Parts published as: Mehanna HM. Will measuring quality of life in head and neck cancer alter individuals' treatment? *Curr Opin Otolaryngol Head Neck Surg.* 2007 Apr;15(2):57-62.

Summary of main findings

I have provided detailed discussion and conclusions for each study in its own chapter. In this chapter, I discuss and summarise the main conclusions of the research thesis as a whole. I then provide suggestions as to how the findings of this research may be utilised and applied to clinical practice. Finally, I discuss the areas of important further research that are suggested by the findings of this research.

For this thesis, we set out to achieve two main objectives. The first was to attempt to characterise the QoL of HNC patients over time, especially in the longer term, and to understand its determinants and its association with survival. The second was to begin to explore means of improving QoL assessment, especially routinely in a clinical setting. This was to be examined by exploring the reasons for poor adoption of QoL tools in the clinical setting and by attempting to determine the QoL tools most appropriate for use by HNC patients and by HNC clinicians.

To achieve these objectives, we started by reviewing the current knowledge base on QoL in HNC in Chapter 2. We found that QoL usually decreases immediately after treatment for HNC, then gradually increases to pre-treatment levels, usually by 12 months. QoL appears to be similar following chemoradiotherapy or surgery for HNC, despite differences in functional deficits.

Many clinicians, researchers and professional bodies have called for QoL to be an integral part of assessment of outcomes in head and neck cancer (HNC). Its measurement should be routine, prospective, and long-term; using brief, patient-reported, validated tools, with both general and disease specific modules. As patients' perceptions differ significantly from doctors', QoL should be incorporated in to the management pathway of the patient to help improve patient care. We also identified a considerable need for more research into QoL in head and neck cancer to enable the above to happen.

In Chapter 3, we then examined the change over time of the quality of life of long-term (10 year) survivors of a cohort of patients that had had assessments of short-term QoL. We also studied the association between prognostic indicators of quality of life, including socio-demographic factors (age, gender, smoking, alcohol), disease-related or medical factors (disease extent, disease site - mouth, larynx, pharynx- treatment type, etc) and long-term quality of life, assessed by measures of global QoL, depression and physical symptoms in the aforementioned patient cohort.

Summary, discussion and conclusions

Our findings demonstrated that long-term (10 year) survivors of head and neck cancer report decreases of 11-15% in the level of their overall QoL, despite having improved above their baseline QoL in the short-term. This was, as far as we know, the first report of such long-term follow-up and of such a drop. We could not from the design of the study, determine when that drop actually occurred, and whether it was related to any new co-morbidities that have developed in the interim. This will require further work. It was clear, however, that baseline QoL was significantly associated with long-term QoL, whereas QoL at one year post-treatment, and tumour stage and treatment were not.

We were also interested in the relationship between QoL and psychosocial factors with long-term survival from head and neck cancer. Studies had shown an association between quality of life and survival of sufferers of several types of cancer, including breast, lung cancer and melanoma (1-3). This was mainly demonstrated in patients undergoing palliative treatment. We aimed to explore whether a similar association between QoL and psychosocial factors exists with long-term survival in head and neck cancer.

In Chapter 4, we therefore undertook a study (4) to examine the association of QoL and psychosocial factors with long-term survival. We too found that baseline QoL in our cohort of 200 patients was not associated with long-term survival. In contrast, post-treatment, those with low quality of life at one year had significantly increased odds of mortality [2.5 (95% CI 1.4, 4.3, $p=0.001$)] and with head neck pain, even after adjustment for co-variables. Survival was not associated with the psychological status of the patient.

We then undertook a systematic review of the literature in Chapter 5. We found that the above findings have since been confirmed in other cohorts (5-14). In all studies, at baseline, overall QoL was not associated with survival. However, expression of intense psychosocial complaints, higher self-perceived physical ability and self-reported high physical functioning were significantly associated with increased survival. Uncertainty about the diagnosis and treatment was found to be a negative prognostic indicator, as was being single, poor cognitive function, baseline fatigue, pessimism and alcoholism. The relationship is currently neither strong nor proven. It may be that this is because there is no real association. However the multiplicity of studies confirming similar types of relationships suggest that there is likely to be an association. Therefore the difficulties in establishing this association may be due to methodological inconsistencies - because of small

Chapter 8

sample sizes under study, and the considerable variability in definitions and methodologies. More work is needed to standardise the definitions and designs used, before multicentre studies can examine this topic more fully.

It is not known whether an association between quality of life and survival is simply a reflection of the patient's physical and psychological state when they have a recurrence that is impairing their function, and also causing stress and depression. Alternatively it may be that there are more involved physiological processes, such as

tumour related factors eg Insulin growth factor-1, which may be secreted by the tumour which may result in fatigue, pain and subsequent impairments of quality of life. Finally, there may be a different explanation and causative mechanism – the effect of psychology and quality of life on behaviour and physiological processes may result in better immunity and other tumour control mechanisms, resulting in better survival. This is suggested by some studies that have found that baseline personal traits eg pessimism (12) may be related to survival from head and neck cancer.

In the second section of the thesis, we have aimed to examine clinicians' views on the routine use of QoL in the clinical setting, and to identify any impediments to the implementation of routine qoL assessment in the clinic. To do this, in Chapter 6, we undertook a cross-sectional survey of HNC clinicians in Australia and New Zealand. We found that most (88%) head and neck clinicians were in favour of the routine use of a short QoL assessment tool in the clinic. Yet, only a minority (13%) were currently using any - mainly for research purposes. The main impediments to routine use in a clinical setting were lack of time and manpower resource, and lack of relevance for clinical practice. These findings were confirmed by a survey of UK head neck clinicians that we later undertook with colleagues (15).

As there are two partners in the consultation and clinical process, we also felt that it was important to explore the patients' perspective on the use of QoL assessment in the clinic. If patients were not willing to use the QoL instruments or did not find them useful, then there would be little imperative to introduce them into routine clinical practice. In Chapter 7, our study showed that most (74%) of patients felt the questionnaires were relevant to their medical problems and would help them describe their problems to their clinicians. Most (89%) found the questionnaires easy to understand. Half of the patients preferred a specific questionnaire, with FACT questionnaire being the most commonly identified. 60% of respondents would like to complete questionnaires in the clinic as they felt it would help them

describe their health problems to their clinicians. However 40% did not want to use questionnaires as they felt it was not relevant to their condition or took too long.

Conclusions

- QoL is a self-reported, subjective, multidimensional phenomenon that changes over time
- QoL is an integral part of assessment of outcomes in head and neck cancer (HNC).
- QoL usually decreases immediately after treatment, then gradually increases to pre-treatment levels, usually by 12-18 months.
- A significant drop in late QoL is observed at 10 years following diagnosis, which was predicted by pre-treatment QOL. None of the socio-demographic, disease or treatment related factors predicted long-term QOL on univariate analysis, but this may be due to the small sample size.
- Post treatment QoL appears to be a strong and significant predictor of long-term survival from head and neck cancer. Some pretreatment personality traits and some other post-treatment psychosocial factors (eg head and neck pain, eating score, speech and SF-36 physical functioning) appear to be also significantly associated with long term survival.
- Most HNC clinicians do not use a QoL measure routinely, as they feel that it is too time consuming and has no proven benefit for clinical management.
- Patients report that HNC quality of life questionnaires effectively describe their health concerns. Most are in favour of completing these questionnaires in clinic, as an aid for describing health problems to clinicians.

Discussion and applications of this research

Providing patients with better information on course of disease and prognosis.

Patients need and want information regarding their illness and treatment options. Evidence suggests that by providing them with effective information regarding their condition and treatment, patients' satisfaction and quality of life is improved and their anxiety is reduced (16). Yet most head and neck cancer patients still feel that the information they receive from multi-disciplinary teams is inadequate, especially during the 3-6month of the post-operative period (17).

Early literature reports on QoL in HNC were retrospective cross-sectional studies of groups of patients who had received treatment. These studies gave us some insight into the problems that these patient groups, eg laryngectomees, were experiencing post-operatively. However, the information was lacking in that it did not inform us of how their symptoms and QoL had developed or changed during and after treatment. In the early 1990s, prospective longitudinal studies started appearing in the literature (17,18). These and subsequent studies (19-21) describe the journey of HNC patients through treatment and for several years beyond. Such studies have been invaluable in enabling clinicians to gain an objective insight into the effects that their treatments were having on their patients. Importantly, this information is essential to enable the provision of better information and informed consent to patients. In addition, by identifying the 'critical' periods during the patient journey when they are most likely to have problems and their nature, clinicians are more able to anticipate these problems and intervene when they occur. More recently, long-term (10 year) QoL follow-up has been reported, thus beginning to complete the picture, with other cohorts soon to report their long term results.

Consider a patient who is about to embark on a course of chemoradiotherapy. One knows from the studies above that their QoL will drop precipitously over the next three months. This QoL deterioration will 'bottom out' at about 3-6 months from diagnosis, during which patients require the greatest support. Their QoL will then start improving at about 6 months, and continue to improve for the next six months. QoL will then usually start to plateau, and may improve at a much slower rate over the next couple of years. When discussing treatment and prognosis with patients at our clinic, we often present them with a graph of the likely course of symptoms and quality of life (see Figure 1). Anecdotally, it is our experience that patients find this information very valuable, as they know what to expect. Importantly when they are experiencing their worst symptoms, they are aware that this is likely to be transient, and that their QoL is likely to improve in the future.

Assessing new and existing treatments and techniques

In the curative setting, QoL considerations are especially important when choosing between treatments with similar survival rates, or when comparing new treatments to established ones in a research setting (25). Indeed, most research funding bodies now require that QoL data be collected routinely in trials examining new treatments.

By assessing patients' QoL, we are able to assess whether existing and new management interventions result in improved patient-reported outcomes and QoL. Such findings can be utilised to direct technical considerations when options present. For example, several studies have shown that for oropharyngeal resections, primary closure, when feasible, results in better swallowing outcomes than reconstruction with a free flap (22). Intensity modulated radiotherapy is another such instance where evaluation of QoL is essential. The multi-centre randomised study of parotid sparing intensity-modulated radiotherapy in patients with head and neck cancer (PARSPORT) study examined the effects of IMRT to spare the contra-lateral parotid compared to normal radiotherapy for oropharyngeal tumours (23). Its outcome measures are functional and QoL-based due to the potential significant effects on patients' well being.

Improving the consultation and follow-up

HNC patients spend the largest proportion of their time with us attending the follow-up clinic after their treatment. It is clear from both anecdotal reports and the limited research available (16, 30) that HNC clinics are often aimed at 'cancer surveillance'. They are mainly concerned with treating cancer and detecting recurrence, with less or little emphasis on addressing and improving patients' health related QoL. Furthermore the quality and outcomes of consultations can vary considerably. This is of concern when, as mentioned previously, HNC and its treatment can cause frequent and sometimes devastating effects on patients QoL, which may improve if detected and addressed.

Use of routine health-related QoL assessment in a clinical oncological setting has been shown to improve patient- clinician communication and is associated with a concomitant improvement in health-related QoL and emotional functioning of patients (31). Detmar et al (32) also concluded from a randomised trial that use of questionnaires in a routine clinical oncological setting facilitated patient – clinician communication, and improved clinician awareness of their patients' HRQoL issues

Chapter 8

(31). The same was found by Taenzer (33). To date, no such work has been done in HNC.

Furthermore, several studies have examined the use of health-related QoL data collection by 'touch –screen' technology and have found it to be widely accepted and easy to use by patients (32,34), including those with HNC in a pilot study by Millsopp (34). These tools can be utilised to facilitate routine HRQoL assessment in the clinic, to provide clinicians with timely longitudinal QoL information about the patient and to overcome some of the resource restrictions preventing clinicians' participation.

From this research, we now know that most head and neck cancer patients do find the routine use of QoL tools in the clinical setting useful. We have also explored which tools they most prefer. Furthermore we have explored the views of clinicians and identified the main impediments to using QoL tools in clinical practise. This paves the way for further research into better integration of these tools in the clinical setting in head and neck cancer/

Screening and Interventions to improve quality of life and psychosocial well-being

The ultimate aim of measuring QoL must be to improve or at least to prevent the deterioration of quality of life in HNC patients. One obvious target would be the psychosocial domain as it is heavily affected by head and neck cancer and its treatment. Many patients exhibit high levels of persistent psychological and emotional distress. There has been some research into the causes and predictors of psychosocial well-being and their impact on overall quality of life of patients with head and neck cancer. However, contradictory findings are often reported and few conclusions can be drawn from the literature. This is mainly attributable to the variety of definitions and methodologies used, the small sample sizes examined and the often retrospective nature of the studies. By identifying the predictors of long-term QoL in this research, we may be able to help focus research to particular areas in this field.

There are a few interventional studies that have aimed to improve psychosocial well-being and overall quality of life in patients with head and neck cancer. These have included social rehabilitation programs (34), group psychological therapy (using a combination of cognitive and behavioural techniques) (35) and a one week psycho-educational program. Some of these programmes have shown benefit. Recent evidence suggests that patients prefer individualised forms of psychosocial intervention (mainly cognitive behavioural therapy) (36). Findings are not consistent

however, as the largest study, evaluating a psychosocial support program in Sweden, showed no benefit (37).

The field of screening and intervention for dysfunction and disabilities holds a lot of promise, as does the design and evaluation of interventions to improve QoL in head and cancer. Knowledge of the determinants of long-term quality of life and the risk factors for poor QoL, as explored by this research, may aid clinicians in identifying patients who are at risk of poor quality of life earlier, and targeting them with more support and rehabilitation. However, much more work is needed in this field to standardize study designs and outcome measures and to evaluate the different interventions.

Future research avenues

Quality of life research has included research into patient preferences and priorities, which only a few decades ago, were never considered by physicians. List et al showed in 2000 (24) that patients' priorities lie in achieving cure, followed by survival for as long as possible, *then* followed by QoL issues. This understanding has helped clinicians recommend management to patients, and has been used to support the development of more aggressive treatment modalities in the hope that they would improve survival. However, List's study also showed that there was significant variability between patients and that it was important to seek patients' views and not to make assumptions. Furthermore, it has been long been established that patients' and clinicians' aims and priorities from treatment diverge considerably (25). Thus quality of life research has also helped teach us to become more patient-focused, and to defer to our patients' wishes, as esoteric as some of those wishes may seem to us clinicians.

In the palliative scenario, QoL is usually the most important treatment goal. Both patients and clinicians report wanting to discuss QoL issues, but also report that confusion regarding who should initiate the discussion appears to hamper this process (26). By measuring these patients' QoL routinely using patient-centred tools, this confusion can be overcome, and the issues important to the patient and their family can be addressed.

In the curative setting, QoL considerations are especially important when choosing between treatments with similar survival rates. Within our multi-disciplinary meetings and clinics, we regularly encounter decisions on which treatments to recommend. These often (should) include quality of life issues, and the decision is

Chapter 8

often to recommend either treatment and enable the patient to decide according to their preferences.

One problem frequently faced is that there is a distinct lack of high quality prospective comparisons of QoL outcomes for different treatments providing equivalent cure rates. Such difficult situations including comparing radiotherapy to conservation laryngeal surgery for a T1/T2 laryngeal tumour; or considering surgery compared to chemoradiotherapy for a T3 tonsillar tumour. The literature consists mainly of retrospective and some prospective reports on small groups of patients treated by one or other treatment option, with all the inherent selection and other biases. Indeed, despite all the studies on chemoradiotherapy, there is little prospective comparative evidence between the QoL of patients with laryngectomies compared to those receiving organ sparing treatment, especially with regards swallowing (27,28). This is partly due to the understandable difficulty in running randomized trials of these treatments. By prospectively collecting QoL outcome measures routinely and pooling them between centres, we may be in a better position to provide our patients with the necessary information to make these choices. Needless to say that much more comparative work is required in this area, although there are certainly some good efforts currently directed in this field.

Our research showed that patients appear to show a drop in QoL in the long-term. When and why this occurs is not yet known. Validation of these findings by other long-term cohorts is necessary. Further elucidation of the determinants of long-term QoL, including examination of the role of co-morbidity in this process, would also be important.

Long-term survival from head and neck cancer appears to be related to some psychosocial factors such as cognitive function, fatigue, self efficacy and expressed uncertainty. However this relationship is not currently clear in the literature. There is significant variability and sometimes contradiction in the reported results, and this may suggest the lack of any real association. It may also reflect the considerable heterogeneity in definitions, methodologies, and designs, and sizes of the studies. Standardisation of these in the context of multi centred trials and the examination of post treatment psychosocial factors should be undertaken in an effort to elucidate this relationship further.

There appears to be a significant gap between the current status of QoL measurement in clinical practice and the ideal, or even what the clinicians themselves aspire to. This gap seems to exist because current quality of life

Summary, discussion and conclusions

questionnaires do not appear to address the needs of the head and neck clinician, who would like a short consensus QLQ, and which ideally could also be used to assist patient management. Further assessment of current quality of life questionnaires is needed to identify which of these would best fulfil these criteria, and whether modification of existing questionnaires is required to achieve these aims. It is also important that the assessment ensures that the selected quality of life questionnaire also fulfils the needs of the patients.

More work needs to be undertaken to address the impediments to use of QoL tools in routine clinical practice in head and neck. Data capture techniques are already in development in the head and neck to improve the incorporation of QoL tools in the clinic. However, more research is required to make process of acquisition of the data quicker and less laborious for the patients. Furthermore, research is needed to evaluate the effects of using quality of life questionnaires on improving communication and clinical outcomes in the consultation. A mixed methods multi-centre trial to examine this is currently in progress.

The majority of patients appeared to favour the use of quality of life assessment in the clinic. Those who did not favour its use feel that it takes too long or may not be relevant to their condition. This would suggest therefore that there are several opportunities for research and improvement in this field. Firstly, identification of the quality of life tool most preferred particular specific head neck patient groups is necessary, especially for the most frequent sites – oral and laryngeal cancer. This is currently in progress. Secondly, refinement and better understanding of meaning of the results of quality of life scores is needed. This understanding will better guide clinicians and researchers as to how to better utilise these scores for the improvement of patients' quality of life. Specifically, more work is needed on the clinical relevance of the scores of common quality of life tools and the meaning of changes on these scores. To date, the majority of studies have been reported as changes in units of the quality of life measurement used to assess the patients, along with the statistical significance of the difference. For example, a new intervention A demonstrates a benefit of a mean difference of 5 units over the current treatment, when assessed by quality of life tool X. This may be statistically significant difference compared to the current treatment eg $p=0.03$. However, this does not provide information on the clinical significance of the changes detected, making QoL studies difficult to understand and translate into every day clinical practice. This, in my view, is a significant flaw in QoL studies in HNC that only recently has started being addressed (29).

Chapter 8

To understand the implications of the minimum clinically important difference, consider further the above example, which was given in a lecture by Jay Piccirillo (personal communication) at the British Academic Conference of Otorhinolaryngology. If the minimum clinically important difference for QoL tool X used above is 10 units, then actually the QoL advantage from this new intervention A is probably not clinically relevant, and thus unlikely to benefit most patients. Studies reporting QoL outcomes should therefore be reported using the MCID of the QoL tool used and the percentage of patients achieving a difference equal to or larger than the minimum clinically important difference .

Let's consider the above example further. If the study reports that the above intervention A resulted in a mean benefit of 20 units, which is twice the minimum clinically important difference, over the existing treatment then we can be more confident that this new intervention A is more beneficial than the current treatment. Even more reassuring would be a report that for example, 80% of patients receiving the new intervention A achieved a benefit of more than 10 units (the minimum clinically important difference), compared to 50% of patients receiving the existing treatment. This format is easily understood by clinicians and more relevant to clinical practice. Indeed, it is also easier to communicate to patients – one can confidently say to their patients that intervention A in the above study provides 80% of patients with benefit, and that it is more effective than the current treatment. However, to enable this to occur, more work is needed to identify the minimum clinically important differences for each of the commonly used QoL tools.

Work is also needed on how scores of different questionnaires compare to each other, and whether they are examining similar aspects. This is especially important in understanding and comparing the results of different studies that use different QoL measures. We have instituted a multicentre randomised study to examine this. As part of the refinement of the use of quality of life tools, better understanding is needed of the significance of life utility tools eg time trade off and health utilities index, and their role in head and neck cancer.

References

1. Coates A, GebSKI v, Signorini D, Murray P, McNeil D, Byrne M, Forbes J , Australian New Zealand Cancer Trials Group. Prognostic value of quality of life scores during chemotherapy for advanced breast cancer. *J Clin Oncol* 1992; 10: 1833-8.
2. Herndon JE, Fleishman S, Kornblith AB, Kosty M, Green MR, Holland J. Is quality of life predictive if survival of patients with advanced nonsmall cell lung carcinoma? *Cancer*,1999; 85; 333-40.
3. Coates A, Thomson D, McLeod GRM, Hersey P, Gill PG, Olver IN, Kefford R, Lowenthal RM, Beadle G, Walpole E. Prognostic value of quality of life scores in a trial of chemotherapy with or without interferon in patients with metastatic malignant melanoma. *Eur J Cancer* 1993; 29: 1731-34.
4. Mehanna HM, Morton RP. Does quality of life predict long-term survival in head and neck cancer patients? *Arch Otolaryngol Head Neck Surg.* 2006;132 (1):27-31.
5. de Graeff A., de Leeuw J.R., Ros W.J., Hordijk G-A, Bettermann JJ, Blijham GH, Winnubst JAM. Sociodemographic factors and quality of life as prognostic indicators in head and neck cancer. *Eur. J. Cancer* 2001; 37, 332-339.
6. Fang FM, Liu YT, Tang Y, Wang CJ, Ko SF. Quality of life as a survival predictor for patients with advanced head and neck carcinoma treated with radiotherapy. *Cancer* 2004;100:425-32.
7. Deleyiannis FW, Thomas DB, Vaughan TL, Davis S. Alcoholism: independent predictor of survival in patients with head and neck cancer. *J Natl Cancer Inst.* 1996; 88(8):542-9.
8. Aarstad AK, Aarstad HJ, Bru E, Olofsson J. Mood, anxiety and sense of humor in head and neck cancer patients in relation to disease stage, prognosis and quality of life. *Acta Otolaryngol.* 2005; 125(5):557-65.
9. Nordgren M, Jannert M, Boysen M, et al. Health-related quality of life in patients with pharyngeal carcinoma: a five-year follow-up. *Head Neck.* 2006; 28(4):339-49.
10. Oskam IM, Verdonck-de Leeuw IM, Aaronson NK, et al. Quality of life as predictor of survival: a prospective study on patients treated with combined surgery and radiotherapy for advanced oral and oropharyngeal cancer. *Radiotherapy and Oncology*, 2010 Feb 26. [Epub ahead of print]

Chapter 8

11. Karvonen-Gutierrez CA, Ronis DL, Fowler KE, Terrell JE, Gruber SB, Duffy SA. Quality of life scores predict survival among patients with head and neck cancer. *J Clin Oncol* 2008;26:2754–60.
12. Allison PJ, Guichard C, Fung K, et al: Dispositional optimism predicts survival status 1 year after diagnosis in head and neck cancer patients. *J Clin Oncol* 2003;21:543-548.
13. Siddiqui F, Pajak TF, Watkins-Bruner D, et al. Pretreatment quality of life predicts for locoregional control in head and neck cancer patients: a radiation therapy oncology group analysis. *Int J Radiation Oncology Biol Phys* 2008;70: 353–60.
14. Grignon LM, Jameson MJ, Karnell LH, Christensen AJ, Funk GF. General health measures and long-term survival in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2007;133:471–76.
15. Kanatas AN, Mehanna HM, Lowe D, Rogers SN. A second national Survey of health-related quality of life questionnaires in head and neck oncology. *Ann R Coll Surg Engl*, 2009;91:420-5.
16. Semple CJ, Allam C. Providing written information for patients with head and neck cancer. *Prof Nurse* 2002;17: 620-2.
17. Ziegler L, Newell R, Stafford N, Lewin R. A literature review of head and neck cancer patients information needs, experiences and views regarding decision-making. *Eur J Cancer Care*; 2004; 13:119-26.
18. Morton RP. Life-satisfaction in patients with head and neck cancer. *Clin Otolaryngol*. 1995; 20(6):499-503.
19. Hassan SJ, Weymuller EA: Assessment of quality of life in head and neck cancer patients. *Head & Neck* 1993;15:485-496.
20. Hammerlid E, Silander E, Hornestam I, Sullivan M. Health – related quality of life three years after diagnosis of head and neck cancer – a longitudinal study. *Head Neck* 2001;23:113-125.
21. El-Deiry M, Funk GF, Nalwa S, et al. Long-term quality of life for surgical and nonsurgical treatment of head and neck cancer. *Arch Otolaryngol Head Neck Surg.*, 2005;131:879-85.
22. Hanna E, Sherman A, Cash D, et al. Quality of life for patients following total laryngectomy vs chemoradiation for laryngeal preservation. *Arch Otolaryngol Head Neck Surg*. 2004;130:875-9.

23. Zuydam AC, Lowe D, Brown JS, et al. Predictors of speech and swallowing function following primary surgery for oral and oropharyngeal cancer. *Clin Otolaryngol.* 2005;30(5):428-37.
24. National Cancer Research Network Trials Portfolio.
<http://www.ncrn.org.uk/portfolio/data.asp?ID=1283> accessed 12 Dec 2006.
25. List MA, Stracks J, Colangelo L, et al. How do head and neck cancer patients prioritize treatment outcomes before initiating treatment? *J Clin Oncol.* 2000;18(4):877-84.
26. Collins SL. Quality of life issues in head and neck cancer management. in Penzak M(ed): *Current Controversies in Otorhinolaryngology.* Thieme; 2000:101-115.
27. Detmar SB, Aaronson NK, Wever LD et al. How are you feeling? Who wants to know? Patients' and oncologists' preferences for discussing health-related quality-of-life issues. *J Clin Oncol.*2000,18:3295-301.
28. Weymuller EA, Yeuh B, Deleyiannis WB, et al. Quality of life in patients with head and neck cancer – lessons learned from 549 prospectively evaluated patients. *Arch Otolaryngol Head Neck Surg* 2000;126:329-335.
29. Fung K, Lyden TH, Lee J, et al. Voice and swallowing outcomes of an organ-preservation trial for advanced laryngeal cancer. *Int J Radiat Oncol Biol Phys.* 2005 ;63(5):1395-9. **
30. Funk G; Karnell LH. Smith RB, Christensen A . Clinical Significance of Health Status Assessment Measures in Head and Neck Cancer: What Do Quality-of-Life Scores Mean? *Arch Otolaryngol Head Neck Surg,* 2004, 130;825–829.
31. Newell R, Ziegler L, Stafford N, Lewin RJ. The information needs of head and neck cancer patients prior to surgery. *Ann R Coll Surg Engl,* 2004;86:407-10.
32. Velikova G, Booth L, Smith AB, et al Measuring Quality of Life in Routine Oncology Practice Improves Communication and Patient Well-Being: A Randomized Controlled Trial. *J Clin Oncol,* 2004,22:714-724.
33. Detmar SB, Muller MJ, Schornagel JH, et al Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. *JAMA.* 2003;289:1636-7.
34. Taenzer P, Bultz BD, Carlson LE, et al. Impact of computerized quality of life screening on physician behaviour and patient satisfaction in lung cancer outpatients *Psychooncology* 2000;9:203–1.

Chapter 8

35. Velikova G, Brown JM, Smith AB, Selby PJ. Computer-based quality of life questionnaires may contribute to doctor-patient interactions in oncology. *Br J Cancer*. 2002;7(86):51-9.
36. Millsopp L, Frackleton S, Lowe D, Rogers SN. A feasibility study of computer-assisted health-related quality of life data collection in patients with oral and oropharyngeal cancer. *Int J Oral Maxillofac Surg*. 2006;35(8):761-4.
37. Clarke A. Resourcing and training head and neck cancer nurse specialists to deliver a social rehabilitation programme to patients. London, City University, 2001.
38. Hammerlid E, Persson LO, Sullivan M, Westin T. Quality-of-life effects of psychosocial intervention in patients with head and neck cancer. *Otolaryngol Head Neck Surg*. 1999;120(4):507-16.

Samenvatting

Het in dit proefschrift beschreven onderzoek heeft twee doelstellingen. In de eerste plaats is getracht de kwaliteit van leven van patiënten met hoofd-halskanker in de tijd (in het bijzonder op de lange termijn) te schetsen en de determinanten hiervan, ook in relatie tot de overleving, te doorgronden. Het tweede doel was initieel onderzoek te doen naar mogelijkheden om de meting van kwaliteit van leven te verbeteren, in het bijzonder de periodieke meting in de kliniek. Daartoe werd onderzocht waarom de meetinstrumenten van kwaliteit van leven in de kliniek weinig worden gebruikt en tegelijkertijd werd nagegaan welke instrumenten het meest geschikt zijn voor gebruik door patiënten en hulpverleners.

In het kader van deze doelstellingen werd allereerst een inventarisatie verricht van wat er tot nu toe bekend is over kwaliteit van leven bij hoofd-halskanker. Dit wordt beschreven in hoofdstuk 2. Hieruit kwam naar voren dat de kwaliteit van leven doorgaans direct na de behandeling afneemt en daarna, geleidelijk in 12 maanden, weer toeneemt tot het niveau van voor de behandeling. Ondanks verschillen in functieverlies blijkt de kwaliteit van leven na chemoradiotherapie en na chirurgie gelijk te zijn.

Veel klinici, onderzoekers en professionele instellingen hebben ervoor gepleit voor meting van kwaliteit van leven als integraal onderdeel bij het beoordelen van het resultaat van de behandeling van hoofd-halskanker. De evaluatie van de kwaliteit van leven zou routinematig, prospectief en ook op lange termijn moeten worden gedaan. Hiervoor moeten gevalideerde meetinstrumenten, met zowel algemene als ziekte-specifieke modules worden gebruikt, die kort zijn en de mening van de patiënt zelf weergeven. Aangezien de perceptie van de patiënt aanzienlijk verschilt van die van de arts, moet kwaliteit van leven worden betrokken bij het behandelplan van de patiënt om zo de zorg te verbeteren. Om bovenstaande te kunnen verwezenlijken is meer onderzoek naar kwaliteit van leven bij hoofd-halskankerpatiënten noodzakelijk.

In hoofdstuk 3 wordt verslag gedaan van een onderzoek naar de verandering van de kwaliteit van leven in de tijd bij lange termijn overlevers (10 jaar) van een cohort patiënten, bij wie ook een meting was verricht kort na de behandeling,. Bovendien werd het verband tussen prognostische factoren voor kwaliteit van leven, inclusief sociodemografische factoren (leeftijd, geslacht, roken, alcohol gebruik), ziekte gerelateerde factoren of medische factoren (tumor uitbreiding, de plaats van de tumor – mond, larynx, farynx – aard van de behandeling, etc.) en kwaliteit van

Chapter 8

leven op lange termijn, gemeten door middel van de globale kwaliteit van leven, depressie en lichamelijke klachten bij het boven genoemde cohort.

Onze bevindingen laten zien dat lange termijn (10 jaar) overlevers van hoofd-halskanker een vermindering van 11- 15% in niveau van kwaliteit van leven rapporteren, ondanks het feit dat zij op korte termijn een verbetering aangaven ten opzichte van de nulmeting. Dit is, voor zover wij weten, de eerste rapportage van een lange termijn follow-up met een dergelijke daling in niveau van kwaliteit van leven. De aard van het onderzoek laat een bepaling van het tijdstip van optreden van de niveaudaling niet toe. Ook was het niet mogelijk een relatie vast te stellen met eventueel nieuw ontwikkelde co-morbiditeit, die zich in de tussentijd voordeed. Dit vereist verder onderzoek. Het was echter duidelijk dat de uitgangswaarde van kwaliteit van leven significant was geassocieerd met de kwaliteit van leven op lange termijn, terwijl de kwaliteit van leven een jaar na de behandeling en het tumor stadium geen associatie vertoonden.

Wij waren ook geïnteresseerd in de relatie tussen kwaliteit van leven en psychosociale factoren met de lange termijn overleving bij hoofd-halskanker. Literatuuronderzoek laat zien dat er een relatie bestaat tussen kwaliteit van leven en overleving bij verschillende kankersoorten, waar onder borstkanker, longkanker en melanoom (1-3). Dit verband werd vooral aangetoond bij patiënten die palliatief werden behandeld. Wij wilden onderzoeken of een dergelijk verband tussen kwaliteit van leven en psychosociale factoren met lange termijn overleving bij hoofd-halskanker bestaat.

In hoofdstuk 4 wordt dit onderzoek beschreven (4) waarin het verband tussen kwaliteit van leven en psychosociale factoren met lange termijn overleving is bestudeerd. Ook wij vonden dat de uitgangswaarde van kwaliteit van leven in een cohort van 200 patiënten geen associatie vertoont met lange termijn overleving. Dit is niet in lijn met de meting na de behandeling: degenen met een lage van kwaliteit van leven 1 jaar na de behandeling hadden een significant verhoogde odds ratio voor overlijden [2,5 (95% BI 1,4; 4,3; p=0,001)] en voor pijn in het hoofd-halsgebied, ook na correctie voor co-variabelen. Overleving was niet geassocieerd met de psychosociale status van de patiënt.

De in hoofdstuk 5 beschreven systematische literatuurstudie toonde aan dat de in hoofdstuk 4 gerapporteerde resultaten sindsdien zijn bevestigd in andere cohort studies (5-14). In vrijwel alle artikelen was de kwaliteit van leven bij de nulmeting niet geassocieerd met de overleving. Echter, het uiten van psychosociale klachten,

een beter lichamelijk zelfbeeld en het subjectief beter lichamelijk functioneren vertoonden een significant verband met een langere overleving. Onzekerheid met betrekking tot diagnose en behandeling bleek een negatief prognostische waarde te hebben, zoals ook het niet hebben van een partner, een slechte cognitieve functie, vermoeidheid voor de behandeling, pessimisme en alcoholisme. Deze relatie is tot op heden noch sterk, noch bewezen. De reden hiervan kan zijn dat er geen echte associatie is. Het aantal studies dat dergelijke verbanden bevestigen suggereert echter dat er waarschijnlijk wel een relatie is. Het probleem om dit verband vast te aan te tonen is mogelijk toe te schrijven aan methodologische tekortkomingen – kleine steekproef omvang in de studie en de aanzienlijke variabiliteit in definities en methoden. Er moet meer aandacht worden besteed aan het standaardiseren van de definities en de studieopzet die worden gebruikt voordat in ‘multicentre’ verband dit onderwerp meer in extenso kan worden onderzocht.

Het is niet bekend of een verband tussen kwaliteit van leven en overleving eenvoudigweg een weerspiegeling is van de lichamelijke en psychologische toestand van een patiënt die een recidief heeft waardoor het functioneren wordt belemmerd en ook stress en depressieve gevoelens optreden. Anders gezegd is het mogelijk dat er meer psychologische processen bij zijn betrokken, zoals tumorgerelateerde factoren, zoals Insuline groeifactor-1, die mogelijk door de tumor wordt afgescheiden en resulteert in vermoeidheid en pijn met een negatieve invloed op de kwaliteit van leven. Ten slotte is er een mogelijk andere verklaring en oorzakelijk mechanisme: het effect van de psyche en kwaliteit van leven op gedrag en psychologische processen zou een betere immuniteit en andere tumorcontrolemechanismen tot gevolg hebben en kunnen resulteren in een betere overleving. Dit wordt ingegeven door een aantal onderzoeken waarin werd gevonden dat bepaalde persoonlijkheidskenmerken gemeten voor de behandeling, zoals pessimisme, gerelateerd zijn aan de overleving van hoofd-halskanker.

In het tweede deel van dit proefschrift wordt beschreven hoe de mening van artsen over routine kwaliteit van leven meting in de kliniek werd gepeild en wat de hindernissen zijn die systematische evaluatie hiervan in de weg staan. In hoofdstuk 6 wordt een transversaal onderzoek onder hoofd-halskankerspecialisten beschreven, dat werd uitgevoerd in Australië en Nieuw Zeeland. Hierbij werd gevonden dat de meeste hoofd-hals specialisten positief staan tegenover het routine gebruik van een kwaliteit van leven meetinstrument dat weinig tijd in beslag neemt. De praktijk is echter dat slechts een minderheid (13%) een dergelijk meetinstrument gebruikt en dan nog voornamelijk voor onderzoeksdoeleinden. De

Chapter 8

belangrijkste reden om er van af te zien was een gebrek aan tijd en mankracht. Daarbij werd ook de relevantie voor de dagelijkse praktijk niet gezien. Deze bevindingen werden bevestigd in een onderzoek onder collega hoofd-hals specialisten in Engeland, dat wij in een latere fase deden. (15).

Aangezien er in de consultatie en het klinisch beloop twee partners zijn, was het in onze ogen ook belangrijk het gebruik van kwaliteit van leven meetinstrumentarium vanuit patiënten perspectief te bekijken. In het geval dat patiënten het nut van kwaliteit van leven evaluatie niet zien en er geen gebruik van zouden willen maken, zou er weinig noodzaak zijn dit in de dagelijkse praktijk te gaan opnemen. In hoofdstuk 7 staat beschreven dat de meeste patiënten (74%) vonden dat de vragenlijsten relevant waren voor hun medische problemen en zouden bijdragen deze aan de hulpverleners duidelijk te maken. De meesten (89%) vonden de vragenlijsten gemakkelijk te begrijpen. De helft gaf de voorkeur aan één specifieke vragenlijst, waarbij de FACT (Functional Assessment of Cancer Therapy) vragenlijst meestal werd aangegeven. Van de respondenten wilde 60% graag de vragenlijst in de klinische setting invullen omdat het hen zou helpen hun problemen aan hun specialisten duidelijk te maken. Daarentegen wilde 40% van de patiënten de vragenlijsten niet gebruiken omdat ze het gevoel hadden dat deze niet relevant voor hun toestand waren en het invullen teveel tijd in beslag nam.

Conclusies

- Kwaliteit van leven is een subjectief fenomeen, door de patiënt zelf gerapporteerd, dat aan verandering in de tijd onderhevig is.
- Kwaliteit van leven is een integraal onderdeel van de evaluatie van de behandelingsresultaten bij hoofd-halskanker.
- Kwaliteit van leven neemt gewoonlijk af direct na de behandeling; neemt daarna geleidelijk weer toe tot het niveau van voor de behandeling, doorgaans in een tijdsbestek van 12-18 maanden.
- Een significante daling kwaliteit van leven op lange termijn wordt waargenomen 10 jaar na het stellen van de diagnose. De kwaliteit van leven van voor de behandeling blijkt een voorspeller van deze niveaudaling. Geen enkele van de demografische factoren en ziekte - of behandeling gerelateerde factoren kon

kwaliteit van leven op lange termijn in de univariate analyses voorspellen, maar dat berustte mogelijk op een te kleine steekproefomvang.

- De kwaliteit van leven na de behandeling blijkt een krachtige, significante voorspeller van lange termijn overleving bij hoofd-halskanker. Enkele persoonlijkheidskenmerken gemeten voor de behandeling en een aantal andere psychosociale factoren na de behandeling gemeten (b.v. pijn in het hoofd-halsgebied, de score van eten, spreken en SF-36 lichamelijk functioneren) blijken significant geassocieerd te zijn met lange termijn overleving.
- De meeste hoofd-halskanker specialisten evalueren niet routinematig de kwaliteit van leven door middel van een vragenlijst omdat zij menen dat het te veel tijd in beslag neemt en geen bewezen bijdrage levert aan het klinisch beleid.
- Patiënten geven aan dat kwaliteit van leven vragenlijsten bij hoofd-halskanker effectief hun gezondheidsaspecten weergeven. De meesten geven er de voorkeur aan deze vragenlijsten in het ziekenhuis in te vullen als ondersteuning bij het meedelen van hun klachten aan de arts bij het polikliniekbezoek.

Literatuur

1. Coates A, GebSKI v, Signorini D, Murray P, McNeil D, Byrne M, Forbes J , Australian New Zealand Cancer Trials Group. Prognostic value of quality of life scores during chemotherapy for advanced breast cancer. *J Clin Oncol* 1992; 10:1833-8.
2. Herndon JE, Fleishman S, Kornblith AB, Kosty M, Green MR, Holland J. Is quality of life predictive of survival of patients with advanced nonsmall cell lung carcinoma? *Cancer*,1999;85; 333-40.
3. Coates A, Thomson D, McLeod GRM, Hersey P, Gill PG, Olver IN, Kefford R, Lowenthal RM, Beadle G, Walpole E. Prognostic value of quality of life scores in a trial of chemotherapy with or without interferon in patients with metastatic malignant melanoma. *Eur J Cancer* 1993;29: 1731-34.
4. Mehanna HM, Morton RP. Does quality of life predict long-term survival in head and neck cancer patients? *Arch Otolaryngol Head Neck Surg.* 2006;132 (1):27-31.
5. de Graeff A., de Leeuw J.R., Ros W.J., Hordijk G-A, Bettermann JJ, Blijham GH, Winnubst JAM. Sociodemographic factors and quality of life as prognostic indicators in head and neck cancer. *Eur. J. Cancer* 2001;37,332-339.
6. Fang FM, Liu YT, Tang Y, Wang CJ, Ko SF. Quality of life as a survival predictor for patients with advanced head and neck carcinoma treated with radiotherapy. *Cancer* 2004;100:425-32.
7. Deleyiannis FW, Thomas DB, Vaughan TL, Davis S. Alcoholism: independent predictor of survival in patients with head and neck cancer. *J Natl Cancer Inst.* 1996;88(8):542-9.
8. Aarstad AK, Aarstad HJ, Bru E, Olofsson J. Mood, anxiety and sense of humor in head and neck cancer patients in relation to disease stage, prognosis and quality of life. *Acta Otolaryngol.* 2005;125(5):557-65.
9. Nordgren M, Jannert M, Boysen M, et al. Health-related quality of life in patients with pharyngeal carcinoma: a five-year follow-up. *Head Neck.* 2006; 28(4):339-49.
10. Oskam IM, Verdonck-de Leeuw IM, Aaronson NK, et al. Quality of life as predictor of survival: a prospective study on patients treated with combined surgery and radiotherapy for advanced oral and oropharyngeal cancer. *Radiotherapy and Oncology*, 2010 Feb 26. [Epub ahead of print]

11. Karvonen-Gutierrez CA, Ronis DL, Fowler KE, Terrell JE, Gruber SB, Duffy SA. Quality of life scores predict survival among patients with head and neck cancer. *J Clin Oncol* 2008;26:2754–60.
12. Allison PJ, Guichard C, Fung K, et al: Dispositional optimism predicts survival status 1 year after diagnosis in head and neck cancer patients. *J Clin Oncol* 2003; 21:543-548.
13. Siddiqui F, Pajak TF, Watkins-Bruner D, et al. Pretreatment quality of life predicts for locoregional control in head and neck cancer patients: a radiation therapy oncology group analysis. *Int J Radiation Oncology Biol Phys* 2008;70: 353–60.
14. Grignon LM, Jameson MJ, Karnell LH, Christensen AJ, Funk GF. General health measures and long-term survival in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2007;133:471–76.
15. Kanatas AN, Mehanna HM, Lowe D, Rogers SN. A second national Survey of health-related quality of life questionnaires in head and neck oncology. *Ann R Coll Surg Engl*, 2009 ; 91 : 420-5.

Curriculum vitae

Name Hisham M. Mehanna
Date of birth 1st September, 1969
Marital status Married with 3 children

Undergraduate qualifications

M.B., Ch.B. (hons) University of Glasgow, July 1994
(Sept 1991-June 1994)
Bachelor of Medical Sciences (hons) University of Kuwait, July 1990
(Sept 1986-June 1990)

Postgraduate qualifications

F.R.C.S. (ORL-HNS) Glasg. April 2002
Otorhinolaryngology- Head & Neck Surgery
F.R.C.S. (Glasg.) Feb 1998
Clinical Surgery in General

Present appointment

Consultant Head and Neck Surgeon, Departments of Head & Neck Surgery, University Hospitals Coventry and Warwickshire, Coventry, and Heart of England Foundation Trust, Birmingham, UK

Honorary Associate Clinical Professor, Warwick Medical School, Warwick, UK.

Director, Institute of Head and Neck Studies and Education (InHANSE), University Hospital, Coventry, UK.

Summary of clinical and academic experience

Hisham Mehanna took up post as a full-time Consultant Otorhinolaryngologist and Head and Neck surgeon at University Hospitals Coventry and Warwickshire in 2004. His subspecialties are head and neck and thyroid surgery. He is also an honorary associate clinical professor at Warwick Medical School. Hisham Mehanna is the Clinical Lead for Head and Neck Cancer at University Hospitals Coventry. He is also the Chair of the Joint Arden Head and Neck Cancer Centre.

Hisham holds over £3m in research grants. He is the chief investigator of PET NECK, a multicentre RCT examining the role of PET CT in the management of advanced head and neck cancer. He led a multi-institution consortium to secure a large grant from the Health Technology Assessment Unit, and has set-up the trial in 24 head and neck centres around the UK. Mr Mehanna is also the chief investigator of PET NECK Collect, which is a tissue bank that is funded by Cancer Research UK. He is also the chief investigator of a Macmillan Cancer-funded project examining a new concept in delivery of head and neck cancer care in the clinic. He is second investigator in a Cancer Research–UK LiNHCS trial. He has also attracted contract research work from several large multinational pharmaceutical companies.

Hisham supervises several PhD, MD and MSc students. He also runs an annual international postgraduate 'Masters' courses in head and neck surgery (since 2004). He has also organised several national meetings including those for the Otorhinolaryngological Research Society and the British Association of Otorhinolaryngologists-Head Neck surgeons. He has been a faculty member on several national and international courses. He is also the Higher Surgical Training Representative for Otorhinolaryngology-Head and Neck surgery at University Hospital Coventry.

In addition, he is a member of the National Clinical Research Institute head & neck clinical studies group that reviews funding applications for clinical trials and makes recommendations to research charities. He is also chair of its surgery & localised therapies sub-group. He also sits on the Interventional Technologies advisory panel of the Health Technology Assessment Unit. He is also Honorary Secretary of the Otorhinolaryngological Research Society, and Chair of the Research Committee of the British association of Head and Neck Oncologists.

List of publications

Book

Management of recurrence in head and neck cancer. Mehanna H, Ang KK (eds). Thieme, USA, publication date Oct 2010.

Chapters

Mehanna HM. The role of neck dissection in patients receiving chemoradiotherapy. In *Key Advances in Head Neck Cancer* (ed. A Miles) – in print

MacKenzie K, Mehanna H. Management of laryngeal carcinoma. In *Stell and Maran's Head and Neck Cancer* (ed John Watkinson) . Hodder Arnold, in print

Morton RP, and Mehanna HM. Quality of Life in head and neck cancer. In *Scott Brown's Otolaryngology and head and neck surgery* (7th Ed, ed. Michael Gleeson). Hodder Arnold, London, 2008

Morton RP and Mehanna HM. Psychology and quality of life. In *Prognostic factors in head and neck cancer* (ed. Robert J. Baatenburg de Jong). Taylor Francis, London, 2006.

Articles accepted in print

Mehanna H , Paleri V, West C, Nutting C. Head neck cancer – diagnosis and management. *BMJ* (review).

Mehanna H , Paleri V, West C, Nutting C. Head neck cancer – epidemiology and prevention. *BMJ* (review).

Chan A, Sanghera P, Choo BA, McConkey C, Mehanna H, Parmar S, Pracy P, Glaholm J, Hartley A. Hypofractionated Accelerated Radiotherapy with Concurrent Carboplatin for Locally Advanced Squamous Cell Carcinoma of the Head and Neck. *Clin Oncol*.

Weller MD, Nankivell PC, McConkey CC, Paleri V, Mehanna H .The risk and interval to malignancy of patients with laryngeal dysplasia; a systematic review of case series and meta-analysis. *Clin Otolaryngol*.

Mehanna H, Paleri V, Robson A, Wight R , Helliwell T. Joint consensus statement by otorhinolaryngologists and pathologists on the diagnosis and management of laryngeal dysplasia. *Clin Otolaryngol*.

Articles published

Mehanna H, Jones TM, Gregoire V, Ang KK. Oropharyngeal carcinoma related to human papillomavirus (editorial). *BMJ*, 2010 Mar 25;340:c1439. doi: 10.1136/bmj.c1439.

Hartley A, Sanghera P, Glaholm J, Mehanna H, McConkey C, Fowler J. Radiobiological Modeling of the Therapeutic Ratio for the Addition of Synchronous Chemotherapy to Radiotherapy in Locally Advanced Squamous Cell Carcinoma of the Head and Neck. *Clin Oncol*, 2010 Mar;22(2):125-30.

Mehanna HM, Jain A, Randeva H, Watkinson J, Shaha A. Postoperative hypocalcemia-The difference a definition makes. *Head Neck*. 2010 Mar;32(3):279-83.

McLarnon C, Kulloo P, Mehanna H, Kelly C, Paleri V. Quality-of-life considerations in treatment of unresectable, recurrent head and neck cancer. *Expert Rev Anticancer Ther*. 2010 Mar;10(3):345-52.

Paleri V, Mackenzie K, Wight RG, Mehanna H, Pracy P, Bradley PJ; ENT-UK Head and Neck Group. Management of laryngeal dysplasia in the United Kingdom: a web-based questionnaire survey of current practice. *Clin Otolaryngol*. 2009 Aug;34(4):385-9.

Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia - A systematic review and meta-analysis. *Head Neck*. 2009 Dec;32(12):1600-9

Smith J, Rattay T, McConkey C, Helliwell T, Mehanna H. Biomarkers in dysplasia of the oral cavity: A systematic review. *Oral Oncol*. 2009 Aug;45(8):647-53

Kanatas AN, Mehanna HM, Lowe D, Rogers SN. A second national survey of health-related quality of life questionnaires in head and neck oncology. *Ann R Coll Surg Engl*. 2009 Jul;91(5): 420-5

Wong WL, Nutting C, Dunn J, Fisher S, MacLennan K, MacCabe C, Mehanna H. Advanced head and neck cancer: is there a role for fluorodeoxyglucose PET/computed tomography? *Nucl Med Commun*. 2009 Jan;30(1):2-4.

Mehanna HM, Jain A, Morton RP, Watkinson J, Shaha A. Investigating the thyroid nodule. *BMJ*. 2009 Mar 13;338:b733. doi: 10.1136/bmj.b733 .

Mehanna H, Nankivell PC, Moledina J, Travis J. Refeeding syndrome - awareness, prevention and management. *Head Neck Oncol*. 2009 Jan 26;1(1):4.

Mehanna HM, Abdelrahim A, Sankar S, Randeve H, Lehnert H. Setting up a minimally invasive, endoscopically assisted parathyroidectomy service in the UK on a shoe-string: how we do it. *Clin Otolaryngol*. 2008 Oct;33(5):491-4.

Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. *BMJ*. 2008 Jun 28;336(7659):1495-8.

Isles MG, McConkey C, Mehanna HM. A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. *Clin Otolaryngol*. 2008 Jun;33(3):210-22.

Rattay, T, Mehanna HM Multidisciplinary team meetings –what, where, when, and why? *Student BMJ*, accepted April 2008.

Mehanna HM, De Boer MF, Morton RP. The association of psychosocial factors and survival in head and neck cancer. *Clin Otolaryngol*. 2008 Apr;33(2):83-9.

Mehanna HM. Will measuring quality of life in head and neck cancer alter individuals' treatment? *Curr Opin Otolaryngol Head Neck Surg*. 2007 Apr;15(2):57-62.

Morton RP, Mehanna H, Hall FT, Mclvor NP. Prediction of pharyngocutaneous fistulas after laryngectomy. *Otolaryngol Head Neck Surg*. 2007 Apr;136(4 Suppl):S46-9.

Mehanna HM, John S, Morton RP, Chaplin JM, Mclvor NP. Facial palsy as the presenting complaint of perineural spread from cutaneous squamous cell carcinoma of the head and neck. *ANZ J Surg*. 2007 Mar;77(3):191-3.

Mehanna HM, Morton RP. Patients' views on the utility of quality of life questionnaires in head and neck cancer: a randomised trial. *Clin Otolaryngol*. 2006 Aug;31(4):310-6.

Mehanna HM, Morton RP. Deterioration in quality-of-life of late (10-year) survivors of head and neck cancer. *Clin Otolaryngol*. 2006 Jun;31(3):204-11.

Mehanna HM, Morton RP. Why are head and neck cancer clinicians not measuring quality of life? *J Laryngol Otol*. 2006 Oct;120(10):861-4. Epub 2006 May 17.

Mehanna HM, Morton RP. Does quality of life predict long-term survival in patients with head and neck cancer? *Arch Otolaryngol Head Neck Surg*. 2006 Jan;132(1):27-31.

Mehanna H, Rejali D, Murray A. Suspending tonsillectomy: the effects on primary

and secondary acute care in Scotland. *Scott Med J.* 2004 Nov;49(4):144-5.

Mehanna HM, Kuo T, Chaplin J, Taylor G, Morton RP. Fungal laryngitis in immunocompetent patients. *J Laryngol Otol.* 2004 May;118(5):379-81.

O'Reilly BF, Mehanna H, Kishore A, Crowther JA. Growth rate of non-vestibular intracranial schwannomas. *Clin Otolaryngol Allied Sci.* 2004 Feb;29(1):94-7.

Mehanna H, Mills J, Kelly B, McGarry GW. Benefit from endoscopic sinus surgery. *Clin Otolaryngol Allied Sci.* 2002 Dec;27(6):464-71.

Mehanna HM, Al-Bahnasawi L, White A. National audit of the management of peritonsillar abscess. *Postgrad Med J.* 2002 Sep;78(923):545-8.

Mehanna HM, Kelly B, Browning GG. Benefit following day-case tonsillectomy. *J One Day Surg*, Nov 2002.

Mehanna HM, Hattie K, McLintock TTC, MacKenzie K. Adult daycase tonsillectomy – a prospective pilot. *J One Day Surg* 2001, 18, 8: 102-104.

Mehanna H, Abdelkader M, Albahnasawy L, Johnston A. Early discharge following nasal pack removal: is it feasible? *Clin Otolaryngol Allied Sci.* 2002 Jun;27(3):153-5.

Stallard S, Hole DA, Purushotham AD, Hiew LY, Mehanna H, Cordiner C, Dobson H, Mallon EA, George WD. Ductal carcinoma in situ of the breast – among factors predicting for recurrence, distance from the nipple is important. *Eur J Surg Oncol.* 2001 Jun;27 (4):373-7.

Mehanna HM, MacGregor FB. The case of the missing carotid artery--a well aimed knife! *J Laryngol Otol.* 1998 Apr;112(4):387-8.

Acknowledgements

I would like to thank

God for all the blessings that He has given me.

My parents Mohammed and Hoda for their constant love, concern and sacrifices, and many many more things that to list them would fill a thesis in its self.

My long-suffering wife, Noha, for her love and undying support – you are my solace and moral compass.

My children Sarah, Kareem and Adam – you are the ornaments of my world.

My brothers, Omar and Hussein, sister, Maryam, and my lifetime friend, Samer, for their love and friendship – I know that I will never walk alone.

Randall Morton for being my friend, mentor and advisor in all matters professional, clinical and personal – some things money cannot buy.

Maarten de Boer and Rob Baatenburg de Jong for their advice, friendship and support

My colleagues Darius, Raj, Peter, Piyush, Gary, Lydia, Mark and Paul, for their support and patience throughout.

Nick McIVor, John Chaplin, Kenneth MacKenzie, George Browning, Iain Swan and Gerry McGarry for their mentorship

My research collaborators Janet Dunn, David Snead, Chris McConkey, Vin Paleri and Kian Ang and all my other collaborators for putting up with all my antics

My research team and my PAs, Lauren and Gemma, for their hard work and patience

All the collaborators on my trials for their help and all the patients who participated in these studies

And finally to all my patients who make this work all worth while