Mental Adjustment and Health-related Quality of Life in Laryngeal Cancer Patients: Quantitative and Qualitative Approaches

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Abstract

The overall aim of this thesis was to investigate mental adjustment and HRQL in patients treated for laryngeal cancer. Specific aims were to evaluate if either VAS or Likert response options was more suitable when assessing self-ratings of voice and speech; to investigate the sensitivity to change of the Swedish Self Evaluation of Communication Experiences after Laryngeal Cancer questionnaire (the S-SECEL); to investigate the relation between mental adjustment to cancer and HRQL, mood disorder and survival and to evaluate the content validity of the Swedish version of the Mini-MAC Scale.

Both inductive and deductive research methods were used. Quantitative methods were used in paper I – III, which are based on a prospective longitudinal study including 100 laryngeal cancer patients. Patients were assessed pre-treatment and 1, 2, 3, 6 and 12 months after start of treatment. Self-report instruments distributed were the S-SECEL, Mini-MAC, EORTC-QLQ-C30 with the QLQ-H&N35, HAD and one study specific instrument. Data were analysed primarily with non-parametric methods. Qualitative methods were used in paper IV where 18 patients with laryngeal cancer were interviewed shortly after end of treatment. Data were analysed using a constant comparison technique consistent with Grounded Theory.

Results demonstrated that communication dysfunction increased 1 month after start of treatment, followed by a continuous decrease throughout the year. The S-SECEL was well accepted by patients and demonstrated more sensitivity to change in communication dysfunction over time compared to more established instruments. Patients using the mental adjustment responses Helpless-Hopeless and Anxious Preoccupation reported more anxiety and depression, as well as decreased HRQL. Survival analysis indicated that use of a Helpless-Hopeless response was related to poorer survival; however, these results are based on a relatively small study sample. The results from paper IV showed the core category to be Setting Boundaries, concerning patients' attitude to information and thoughts about the cancer and a prerequisite for mental adjustment to diagnosis and treatment without major negative impact on mental health or HRQL. The results from paper IV largely confirmed the structure of the Mini-MAC Scale.

Conclusion: For assessment of self-rated voice and speech in laryngeal cancer patients, the Likert scale seems to be more suitable than the VAS, possibly due to the relatively high age of the patient population. The S-SECEL could be a valuable tool in clinical practice for identifying patients at risk for psychosocial problems and to help plan rehabilitation. Considering the relation between mental adjustment and HRQL, mood disorder and possibly survival, assessment of mental adjustment should be considered when planning treatment and rehabilitation in laryngeal cancer patients. The findings further emphasize the importance of adapting the information given and rehabilitation options to each individual patient.

Key words: laryngeal cancer, HRQL, Mental Adjustment to cancer, S-SECEL, Mini-MAC

List of publications

This thesis is based on the following papers, referred to in the text by their Roman numerals:

I.   Is a line the same as a box? Speech assessment by VAS is not superior to Likert scales in laryngeal cancer patients.
      Johansson M, Finizia C, Degl' Innocenti A, Rydén A
      Med Sci Monit 2007;13(11):CR481-487

II.   Self evaluation of communication experiences after laryngeal cancer – a longitudinal questionnaire study in patients with laryngeal cancer.
      Johansson M, Rydén A, Finizia C
      BMC Cancer, 2008;8:80

III. Mental adjustment to cancer and its relation to anxiety, depression, HRQL and survival in patients with laryngeal cancer.
      Johansson M, Rydén A, Finizia C
      Submitted

IV.   "Setting Boundaries" – Mental adjustment to cancer in laryngeal cancer patients: An interview study.
      Johansson M, Rydén A, Ahlberg K, Finizia C
      Submitted

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Abbreviations

EORTC	the European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	the EORTC Quality of Life Questionnaire Core 30
EORTC QLQ-H&N35	the EORTC Quality of Life Questionnaire Head and Neck Module
FDA	Food and Drug Administration
GT	Grounded Theory
HAD	the Hospital Anxiety and Depression Scale
H&N	Head and Neck
HPV	Human Papillomavirus
HRQL	Health-related Quality of Life
MAC	Mental Adjustment to Cancer Scale
Mini-MAC	Mini-Mental Adjustment to Cancer Scale
QoL	Quality of Life
SECEL	the Self-Evaluation of Communication Experiences after Laryngeal cancer
S-SECEL	the Swedish SECEL
SF-36	The Short Form (36) Health Survey
TNM	Classification system for malignant tumours: T = primary Tumour N = regional lymph Nodes M = distant Metastasis
VAS	Visual Analogue Scale
WHO	World Health Organization

Background

1.1 Laryngeal Cancer

Laryngeal cancer is one of the most common forms of head and neck (H&N) cancer, with approximately 200 new cases per year in Sweden [1]. Most patients are over 60 years of age at diagnosis. The disease has a large male-to-female predominance; during the last decade more than 80 % of Swedish patients diagnosed with laryngeal cancer were male. There are geographical differences in the worldwide incidence. In northern Europe, Australia and New Zeeland and most parts of East Asia and Africa the rates are low, while countries in southern and central Europe, as well as parts of Brazil and Uruguay, demonstrate far higher incidence [2]. Further, differences are found between rural and urban areas, with lower incidence in rural areas. There are also differences between socioeconomic groups, with decreasing incidence of laryngeal cancer with increasing social advantages, such as higher education level and more income [3].

Risk factors

The dominating risk factor for laryngeal cancer is cigarette smoking but there is growing evidence for alcohol drinking being an independent risk factor [4]. The role of human Papillomavirus (HPV) for development of laryngeal cancer has been debated. According to some studies the virus has been detected in approximately 25 % of laryngeal cancer tumours [5], while other conclude that HPV is of no importance for development of laryngeal cancer [6]. Furthermore, various occupational agents have been suggested as additional risk factors, for example polycyclic aromatic hydrocarbons [7]. A number of studies have also highlighted the possible effect of diet on development of different forms of upper aerodigestive tract tumours, including laryngeal [8].

Gastroeosophageal reflux has been suggested as a causative factor in laryngeal cancer but this connection, however, remains unresolved [9].

Anatomical regions of the larynx

For description of the localization of the tumour the larynx is divided into three anatomical regions:

- The supraglottic larynx includes the epiglottis, false vocal cords, ventricles, aryepiglottic folds and arytenoids.
- The glottis includes the true vocal cords and the anterior and posterior commissures.
- The subglottic region begins below the true vocal cords and extends to the lower border of the cricoid cartilage or the first tracheal cartilage.

When all three levels are involved, the tumour is depicted as transglottic. The anatomical regions of the larynx are pictured in figure 1. In Swedish patients, a majority of the laryngeal tumours are glottic. Second most common are supraglottic tumours, while subglottic ones are rare. However, there are geographical differences concerning what is the most common site of the tumour localization, for example, in our neighbouring country Finland supraglottic tumours are the most common [10].
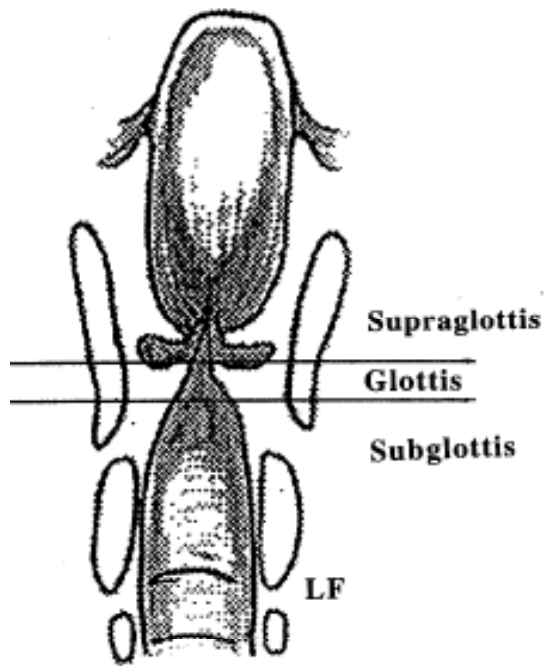
Figure 1. The anatomical regions of the larynx

Classification of laryngeal tumours

Laryngeal tumours are classified according to a global standard, the TNM-staging system developed by the International Union against Cancer. This classification describes tumour stage (TX-4), regional metastases (NX-3) and distant metastases (MX-1), tables I and II. Combinations of T, N and M are divided into stages, table III. Further classification is made of tumour tissue based on the keratinisation of epithelial cells. The tumour tissue is defined as well differentiated, moderately differentiated or undifferentiated [11].

Table I. TNM-classification of laryngeal cancer, T-stage [12]

	Supraglottic	Glottic	Subglottic
T-stage (primary tumour)			
TX	Primary tumour can not be assessed		
T0	No evidence of primary tumour		
Tis	Carcinoma in situ		
T1	One subsite, normal vocal cord mobility	Limited to vocal cord (s), normal mobility T1a one vocal cord T1b both vocal cords	Limited to subglottis
T2	Mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis without fixation of the larynx	Extends to supraglottis and/or subglottis and/or impaired vocal cord mobility	Extends to vocal cord (s) with normal or impaired mobility
T3	Vocal cord fixation and/or invades any of: postcricoid area, pre-epiglottic tissues, paraglottic space and/or thyroid cartilage erosion	Vocal cord fixation, and/or invades paraglottic space and/or thyroid cartilage erosion	Vocal cord fixation
T4a	Through thyroid cartilage and/or invades tissues beyond the larynx	Through thyroid cartilage or invades tissues beyond the larynx	Through cricoid or thyroid cartilage and/or invades tissues beyond the larynx
T4b	Prevertebral space, mediastinal structures or encases carotid artery	Prevertebral space, mediastinal structures or encases carotid artery	Prevertebral space, mediastinal structures or encases carotid artery

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Table II. TNM-classification of laryngeal cancer, N- and M-stage [12]

N-stage (Regional lymph nodes)	
NX	Regional lymph nodes can not be assessed
N0	No regional lymph node metastasis
N1	Ipsilateral single $\leq$ 3 cm
N2 (a)	Ipsilateral single > 3 cm to 6 cm
N2 (b)	Ipsilateral multiple $\leq$ 6 cm
N2 (c)	Bilateral, contralateral $\leq$ 6 cm
M-stage (Distant metastasis)	
MX	Distant metastases can not be assessed
MO	No distant metastases
M1	Distant metastasis present

Table III. Staging of laryngeal cancer

	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3,	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Histopathology

The dominating histopathological type of laryngeal cancer worldwide is squamous cell carcinoma, while rarely seen types are verrucous carcinoma, adenocystic carcinoma, neuroendocrine carcinoma, oat cell carcinoma and lymphoma [10].

Treatment of laryngeal cancer

The primary aim of treatment of laryngeal cancer is of course survival, but since the larynx plays a fundamental role in voice production and hence communication, the preservation of a functional larynx is an important aspect to consider. In Sweden radiotherapy alone is the most common treatment of choice for early laryngeal cancer (T1 – T2). However, transoral laser microsurgery has been used for excision of benign lesions and early premalignancy in the larynx since the 1970's and has with time gained acceptance as treatment for glottic carcinoma in-situ and early cancers [13]. T3 tumours and selected T4 tumours are most often treated with primary radiotherapy and concurrent chemotherapy for patients with a decent performance status. Until recently chemotherapy was administrated as induction at Sahlgrenska University Hospital. However, several studies, including Forastiere et al, have showed concurrent administration of chemotherapy to be superior to induction [14] and the regimens have therefore been changed. Primary total laryngectomy with pre- or postoperative radiotherapy is used for T4 tumours with spread cartilage destruction, as well as in some T3 tumours. Furthermore, total laryngectomy is used for salvage in persistent or recurrent disease after radiotherapy. After total laryngectomy, where the entire larynx is removed and the pharynx is reconstituted, a permanent tracheostomy is required. The most common form of voice rehabilitation after total laryngectomy is a tracheoesophageal (TE) fistula, i.e. a fistula between the tracheal wall and oesophagus, which is then stented with a silicone rubber catheter functioning as a voice prosthesis. Except total laryngectomy other available surgical treatments are chordectomy and partial laryngectomy.

Prognosis of laryngeal cancer

The prognosis of laryngeal cancer is dependent on the size of the tumour and the presence of metastases. Furthermore, the prognosis differs between the

different tumour locations; glottic tumours are highly curable since the location on the vocal cord causes hoarseness, leading to early discovery of these tumours. The relatively good prognosis of the glottic tumours is also due to the lack of extensive lymphatics giving a low incidence of lymph node metastases. For tumours in the supraglottic or subglottic areas, on the other hand, the risk of lymphatic spread or spread by involvement of adjacent organs such as the hypopharynx is greater.

1.2 Voice and Speech

Laryngectomy causes serious impaired speech function. Impaired voice function is however also a common side effect when patients are treated with radiotherapy or transoral laser surgery [15, 16]. Dysfunction in voice and speech affects the ability to communicate and hence disrupt interaction with others, which in turn often results in social and psychological dysfunction. To what extent patients perceive their voice impairment to affect their health-related quality of life (HRQL), however, varies greatly [15]. Furthermore, objective voice analyses often do not correlate with subjective assessments. According to Benninger et al, the patient's impression of the quality of his/her own voice seems to be one of the most important variables to consider when evaluating treatment effects [17]. It is therefore important that HRQL instruments used in laryngeal cancer patients include items addressing voice and communication dysfunction.

1.3 Patient Reported Outcomes and Self-Report Instruments

The concept patient-reported outcome (PRO) is defined as any report coming directly from the patient regarding his/her health condition and hence should be without interpretation by a clinician, family member or anyone else [18]. The experiences of disease and symptoms are highly subjective, why it can

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be argued that the patient is the only reliable source of such data. Therefore, traditionally used observer-reported measures are not optimal since they are an interpretation of the experience and therefore often affected by inter-observer variability.

The most common way to assess PROs is with self-report instruments. PROs have grown in importance, illustrated by the fact that the American Food and Drug Administration (FDA) recommend drug companies to use PRO instruments in clinical trials when measuring a concept best known by the patient or best measured from the patient perspective. FDA has also presented a set of guidelines for the development, modification and evaluation of self-report instruments used as endpoints in clinical trials [19]. The use of self-report instruments has some advantages compared to other methods of collecting PRO, it is e.g. less time consuming than doing interviews. The use of self-report instruments also guarantees that the questions are asked in a standardized manner, facilitating comparisons within and between groups.

Self-report instruments are used in clinical trials to measure impact of an intervention on one or more aspects of patients' health status, ranging from symptoms to more complex concepts such as effect on activities of daily living or HRQL. Self-report instruments can also be used in clinical practice for estimation of symptoms or treatment effects.

PRO instruments are constituted of a number of questions or statements (items), grouped together in domains (factors), measuring the same concept. Most PRO instruments are either generic or disease specific, while some are constituted of two parts; one generic and one disease specific. Generic instruments are designed to measure domains of general health, overall disability and general HRQL, and render comparisons across patient populations and with norm populations possible. The drawback is their weakness in responsiveness to disease specific changes that may be

clinically relevant. Disease-specific instruments, on the other hand, measure attributes of symptoms, mental health and functional status relevant to a particular disease or condition and hence are more responsive to changes in the target condition [20].

Response alternatives in self-report instruments

One important aspect to consider when constructing an instrument is which type of response alternative to use. One of the most common forms used is the continuous Visual Analogue Scale (VAS), typically consisting of a 100 mm horizontal line anchored at the ends with for example "no pain" to "unbearable pain". It has been argued that the VAS is more sensitive to change than the discrete points of categorical scales like the Likert (described below) [21], while other studies have indicated that respondents may find it difficult to understand [22].

Another commonly used response alternative is the categorical Likert scale, consisting of statements, positive and negative, for which the patient must state to what degree he or she agree. Likert scales generally comprise three to eleven response alternatives [23]; however, opinions differ as to what the optimal number of response alternatives is [24-27]. The more steps the higher the sensitivity, but it has been claimed that respondents are unable to discriminate beyond seven levels [22], which might increase the risk of guessing. An advantage of Likert scales is the ease of administration and interpretation [28], whereas a drawback may be that a more comprehensive vocabulary is required to be able to distinguish between the different categories [29].

Evaluation of PRO instruments: a psychometric process

Once a self-report instrument has been developed, to ensure accuracy its psychometric properties have to be evaluated. Some central notions in this process will be described below.

Validity

The validity of an instrument refers to whether the instrument is actually measuring what it is intended to measure, e.g. that an instrument intended for measuring depression really is measuring depression and not some related state. There are several terms included in the validity notion, which will be described below.

Content validity concerns whether the items are reflecting what is intended to be measured. High content validity implies that the instrument is covering all the relevant aspects. Furthermore, it is just as important that all items not relevant are excluded. Content validity can not be computed with statistical methods, but is established through literature review, assessments by experts and input by patients. Since the purpose of the PRO instruments is to capture the subjective experiences of patients, the input from patients is fundamental. The most common qualitative method for gathering patient input is through interviews with individual patients or focus groups. The information gathered can be used to generate items, adapt the language used in items to suit the intended population and to receive information about suitable response alternatives. Qualitative methods are often used for analysing interview data. Qualitative methodology focus on the understanding of human experiences and describes subjective values, emotions, states of mind and ethical values. It aims to capture the overall picture, coherence and meaningfulness. These research methods have a long history in the social sciences, while in medicine the use of such methods traditionally have been scarce and they are sometimes even regarded with scepticism by the medical community, accused of its subjective nature and the absence of facts [30]. In the mid 1990's, however, a debate on qualitative research in medicine began, with the British Medical Journal dedicating a series to this issue. In one of the papers included in this series, Pope et al conclude that "qualitative methods can, and do, enrich our knowledge of health and health care. It is not that qualitative methods are somehow superior to quantitative ones--such a

position merely perpetuates the quantitative-qualitative dichotomy--but that we need a range of methods at our fingertips if we are to understand the complexities of modern health care" [31]. Consequently, qualitative and quantitative methods should be thought of as being complementary rather than conflicting. Malterud et al argue that qualitative inquiry could contribute to a broader understanding of medical science [32] and the use of qualitative methods in medicine has increased, for example in the area of oncology and palliative medicine [33].

Construct validity refers to whether an instrument actually measures the intended construct/s, e.g. if the Hospital Anxiety and Depression Scale (HAD) actually measures anxiety and depression. Two concepts used in these analyses are *convergent validity* and *discriminant validity*.
Convergent validity examines how well constructs that theoretically should be related to each other are, in fact, observed to be related, e.g. pain and depression. Convergent validity is typically estimated with correlation coefficients and should preferably be >0.40. However, if the correlation between two constructs is very high, this might imply a possible redundancy, i.e. that they actually measure the same construct.
Discriminant validity can be viewed as the counterpart to convergent validity and is based on the assumption that constructs theoretically *not* related to each other should demonstrate low correlations.

Performing factor analysis is a common step in the validation process and primarily a test of construct validity. Factor analyses are based on relations and examine the relation between items and underlying constructs. There are two types of factor analyses, explorative and confirmatory. The exploratory computes the correlation coefficients, i.e. factor loadings, between items and latent constructs that are not prespecified. It also indicates how many factors the instrument should be constituted of and which items possibly could be removed. The confirmatory factor analysis, on the other hand, serves to test whether the anticipated picture of how items are related to factors can be

supported. The notion "Eigenvalue" is central in the area of factor analysis. It is a measure of how much variance each factor can measure. A common rule of thumb is that factors with an Eigenvalue >1 should be retained [34].

Reliability

The reliability of an instrument refers to the precision and stability of an instrument. A reliable instrument should reproduce similar results when used at repeated measurements when conditions are stable. Reliability can be assessed by a test-retest procedure using correlation analyses. The most common method for measuring reliability is, however, the statistical measure of Cronbach's alpha [35]. This measures internal consistency, i.e. to what extent items are correlated to each other, actually a form of validity. Cronbach's alpha coefficients >0.70 are usually judged as acceptable, while >0.80 is recommended. The formula for Cronbach's alpha is constructed in such a way that the more items included in an instrument the higher the Cronbach's alpha, implying that the measure must be cautiously interpreted for instruments with a larger number of items.

Sensitivity

Sensitivity is the ability of an instrument to detect differences between patients or groups of patients. The more sensitive an instrument, the smaller the number of patients needed to detect a difference. The sensitivity is often evaluated in cross-sectional studies. If differences between groups are statistically significant the instrument is often regarded to be sensitive.

Responsiveness

Responsiveness is closely related to sensitivity. But while sensitivity is examining inter-personnel differences, responsiveness is the ability of an instrument to detect intra-personnel differences over time and is hence evaluated in longitudinal studies. A common measure of responsiveness is effect size (ES). ES involves translating differences into a standard unit of measurement, enabling comparisons with internal and external benchmarks.

Furthermore, ES offers an alternative to statistical significance testing to interpret results. Disease-specific PRO instruments are commonly more responsive than generic instruments.

1.4 Mental Adjustment vs. Coping

Mental adjustment is related to the more widely spread theories of coping, which in turn springs from research on stress. The interest in how humans handle stressful events goes back to the beginning of the last century, when focus was primarily on unconscious mechanisms. For example, Freud used the concept of defence mechanism to describe unconscious processes used to deal with internal threats and conflicts [36]. One of the most widely spread theories of coping has been proposed by Lazarus and Folkman. They define coping as "constantly changing cognitive and behavioural efforts to manage specific external or internal demands that are appraised as taxing or exceeding the resources of a person" [37]. The theory of Lazarus and Folkman contains three processes: primary appraisal; secondary appraisal; and coping. Primary appraisal is the perception of something as a threat. Secondary appraisal involves the process of bringing to mind a correct response to the threat, while coping is the process of executing that specific response. According to Lazarus and Folkman, what is perceived as stressful is dependent on both the environment and the characteristics of the individual. By defining coping as *constantly changing*, Lazarus and Folkman imply that coping is oriented towards the situational context, and therefore changes within this context. That is, coping is process-oriented and therefore their theory is often called the transactional theory of coping.

The term 'adjustment' or 'mental adjustment' is often used in cancer and general health psychology literature to describe the absence of psychological morbidity. Adjustment has been defined in a number of ways, but one theory that has gained attention is that of mental adjustment to cancer, defined by Watson and Greer as "the cognitive and behavioural responses the patient

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makes to the diagnosis of cancer" [38]. Mental adjustment comprises (1) appraisal, - i.e. how the patient perceives the implications of cancer and (2) the ensuing reactions – i.e. what the patient thinks and does to reduce the threat posed by the disease [39]. Even if the concepts of coping and mental adjustment often are used synonymously, there is one predominant difference: mental adjustment includes the ensuing emotional reactions to a threatening event, while the transactional theory of coping regards the emotional reactions as the outcome of a coping strategy. In conformity with the transactional theory of coping, some authors argue that the term adjustment should exclusively describe the processes of adaptation that occur over time as the individual manages, learns from and accommodates to the multitude of changes following changed life circumstances [40].

Measuring mental adjustment

The use of self-report instruments has been criticised when measuring coping and mental adjustment, e.g. for rendering an incomplete and distorted portrait of coping [41]. However, it is important to note that self-report instruments are to be viewed as an *initial* step towards understanding the patient. The use of self-report instruments has also been defended by e.g. Lazarus, who refers to the advantages of these instruments: "they can be used as screening instruments since they are easy to administrate and respond to and furthermore, they permit testing of larger samples, which is useful in study settings" [42].

At what point to measure adjustment responses is a matter of discussion. The most common opinion is that the evaluation should be made in as close relation to the stressful event as possible. This is stressed by e.g. Coyne et al, who argue that the longer the time between an incident and its evaluation, the greater the risk for response biases [41]. Conversely, Mehanna et al [43] argue that when examining the association of psycho-social factors (not coping and mental adjustment solely) on survival in head and neck cancer it

is more appropriate to measure one year after treatment, when most patients have reached a steady-state psycho-social status.

The research on coping and mental adjustment has received some criticism, mainly regarding the fact that many studies are cross-sectional. Most researchers are in agreement that coping is changeable and therefore repeated assessments and longitudinal designs are advocated. Criticism has further been raised regarding measuring mental adjustment at time points without direct connection to specific stressors, rendering comparisons between studies harder.

Mental adjustment to cancer

Over the years coping and mental adjustment has become an important part of health-related research and the interest in how people cope with or adjust to cancer has increased. This research has mainly examined the relation between adjustment responses and psychological distress. To some extent the research has also been concerned with identifying possible factors predisposing certain coping responses [44]. Furthermore, it has been advocated that this research should also cover psychological well-being and supportive coping processes [39].

Already in the 1950's studies on coping with cancer were published [44] and during the 1980's the number of publications boomed [45]. Since then there has been a steady rise in the number of publications on this theme, and in many of these studies cancer is treated as a uniform state. However, it is important to bear in mind that cancer is a multifaceted disease with a variety of challenges and problems depending on diagnosis and treatment, and hence give rise to a variety of adjustment responses.

Both mental adjustment and coping have been identified as important factors for HRQL in general and psychological state in particular in cancer patients

[38, 46-48]. Furthermore, there is an ongoing debate on the possible impact of mental adjustment on the outcome of cancer, where e.g. Pettingale et al appoint mental adjustment responses to be the single most significant factor in determining both death and recurrence [49]. Yet other studies, including one systematic review by Petticrew et al, have found no or little evidence of any effect of coping or mental adjustment on survival [50]. These diverse findings concerning the effect of mental adjustment on outcome leave the question a matter for discussion.

Mental adjustment to laryngeal cancer

Despite the enormous amounts of publications on coping or mental adjustment and cancer, and a growing interest regarding mental adjustment to cancer in patients with H&N cancer [46, 51-53], in the area of laryngeal cancer the interest has been scarce. For H&N cancer patients most studies have indicated an association between an avoidance response and decreased HRQL [52, 54, 55], but also an inverse relation between the coping/adjustment strategy Fighting Spirit and depression [46]. Due to the multi-factorial and multi-site nature of H&N cancer some authors have expressed the need to investigate adjustment responses in patients with different sites of H&N cancer, like laryngeal cancer, separately [43, 51].

1.5 Health-Related Quality of Life (HRQL)

The topic of quality of life (QoL) seems to have been discussed already in ancient Greece, e.g. by Aristotle [18]. But despite the concept's long history, no consensus on the definition of QoL has been reached. It is a multidimensional concept and a majority of the abundant definitions include aspects of happiness and satisfaction with life. In 1948 the World health Organization (WHO) defined health as 'a state of complete physical, mental and social well-being and not merely the absence of disease' [56]. This

definition opened up for a multi-dimensional view of health and since then QoL has become more important in health care practice and research [57]. Due to the lack of a clear definition of QoL and to distinguish between QoL in its more general sense and the requirements of clinical medicine and clinical trials, the term 'health-related quality of life' (HRQL) is frequently used. HRQL refers to the physical, psychological and social domains of health that are unique to each individual [57] and describes HRQL as a consequence of illness, injury or treatment. HRQL can further be divided into two aspects: well-being and function.

HRQL and laryngeal cancer

During the last decades treatment options for cancer have changed, resulting in increased survival rates for many cancer diagnoses, but also with new types of both acute as well as delayed side effects. The changes in treatment and survival have extended the focus on endpoints for clinical research studies to not only include survival and treatment toxicity, but also the patients' subjective experiences such as HRQL.

In the case of H&N cancer, in spite of an increase in treatment intensity during the last decade, with the development of higher doses of radiotherapy, accelerated and hyperfractionated radiotherapy and concurrent chemotherapy and radiotherapy, the improvements in overall survival have been modest [58]. However, the new treatment modalities can have a substantial effect on the HRQL. Regarding laryngeal cancer patients, results have repeatedly demonstrated HRQL levels to decrease following diagnosis, as well as during and immediately after treatment but one year post-treatment an improvement in HRQL is often seen. Patients might, however, still suffer from symptoms probably caused by side-effects from treatment such as communication, trismus and swallowing problems [59-61]. The numbers of long-term follow up studies are scarce, but Nordgren et al followed laryngeal cancer patients until five years post-diagnosis and

Hammerlid and Taft followed patients with H&N cancer for three years, both using the EORTC QLQ-C30 and QLQ-H&N35. When HRQL scores in H&N cancer survivors three years after diagnosis were compared with normative data, the results were comparable when measured with more general HRQL-instruments like the SF-36 and the EORTC QLQ-C30 [62, 63]. However, when an instrument specific for H&N cancer were used, laryngeal cancer patient scored significantly worse both at follow-up at three [63] and five years [62] after diagnosis, probably reflecting long-term or permanent side effects of treatment.

Many of the studies examining HRQL in laryngeal cancer are performed on mixed groups of H&N cancer sites. Compared to other H&N cancers, laryngeal cancer patients face communication dysfunction, an important aspect to consider when evaluating HRQL in this patient group.

1.6 Anxiety and Depression in Cancer Patients

Numerous studies have demonstrated the high prevalence of anxiety and depression in cancer patients in general. However, the reported prevalence differs widely with figures ranging from 5% to 50% [64, 65]. This variety might be due to methodological differences such as use of instrument, cut-off points, type of cancer diagnoses and point of assessment. Although seemingly contradictory some studies, including meta-analyses, have demonstrated that in comparison to a norm population the prevalence of anxiety in cancer patients is not higher [66, 67]. For depression, however, the prevalence seems to be somewhat higher.

Anxiety and depression in laryngeal cancer patients

Data on mental disorders in patients with laryngeal cancer are rather scarce, but the results available indicate that the prevalence is comparable to a

general cancer population [59, 68]. Although several studies have demonstrated high levels of anxiety and/or depression these figures are reported at diagnosis and decreases over the year following diagnosis [59, 60, 69]. It should, however, be noted that few studies with a longitudinal design and long-term follow up have been performed.

Aims of the thesis

The overall aim of this thesis was to investigate the mental adjustment and HRQL in patients treated for laryngeal cancer, as well as the psychometric properties of PRO instruments intended to measure these notions.

Specific aims:

Paper I: Primary aim of this paper was to assess if either VAS or Likert was relatively more suitable when assessing self-ratings of voice and speech in patients treated for laryngeal cancer. An additional aim was to investigate whether the scales differed in measuring change after treatment.

Paper II: Aim of this study was to investigate the sensitivity to change of the Swedish Self Evaluation of Communication Experiences after Laryngeal Cancer questionnaire (the S-SECEL), addressing communication dysfunction in patients treated for laryngeal cancer.

Paper III: Aim of this longitudinally designed study was to investigate the relation between mental adjustment to cancer and HRQL, anxiety, depression and survival in patients treated for laryngeal cancer.

Paper IV: Primary aims of this study were to increase the understanding of mental adjustment responses in laryngeal cancer patients and the outcome of these responses. Secondary aim was to evaluate the content validity of the Swedish version of the Mini-MAC Scale with regard to findings from the patient interviews.

Subjects and methods

2.1 Study design

Table IV. Studies included in the thesis

	Study design	Subjects	Time frame	Instruments used
Paper I	Descriptive, prospective, longitudinal	71 of the 100 included laryngeal cancer patients	Before and 12 months after start of treatment	Study specific instruments
Paper II	Descriptive, prospective, longitudinal	100 laryngeal cancer patients	Before, during and up to 12 months after start of treatment	EORTC QLQ C-30, H&N-35, S-SECEL, HAD
Paper III	Descriptive, prospective, longitudinal	95 of the 100 included laryngeal cancer patients	1 and 12 months after start of treatment	EORTC QLQ C-30, H&N-35, S-SECEL, HAD, Mini-MAC
Paper IV	Cross sectional	18 laryngeal cancer patients	0 – 8 weeks after end of treatment	Interviews

Paper I - III

These papers were all performed with quantitative methodology and data were retrieved from a prospective longitudinal study. Patients were recruited at a weekly tumour conference at Sahlgrenska University Hospital to which all patients with laryngeal cancer in the western part of Sweden are admitted. The inclusion period was 1998 to 2005 with a discontinuation for two years. Data was collected with PRO instruments on six occasions during a follow-up time of one year (for more information se table V). Before start of treatment instruments were distributed to patients at the tumour conference and mailed-back. A mail-out/mail-back procedure was used for follow-up assessments at 1, 2, 3, 6 and 12 months after start of treatment. Patients who had not returned their questionnaires within 2-3 weeks were reminded once by mail. 12 months after treatment start patients were also followed up with a visit to the outpatient clinic, with recording of received treatment and evaluation of performance status and residual tumour.

Table V. Instruments used at baseline and follow-up assessments

Measurement point	Instruments distributed
Before treatment	S-SECEL, EORTC QLQ-C30, QLQ-HN35, HAD, study specific instrument
1 month after start of treatment	S-SECEL, EORTC QLQ-C30, QLQ-HN35, HAD, Mini-MAC
2 months after start of treatment	S-SECEL, EORTC QLQ-C30, QLQ-HN35, HAD
3 months after start of treatment	S-SECEL, EORTC QLQ-C30, QLQ-HN35, HAD
6 months after start of treatment	S-SECEL, EORTC QLQ-C30, QLQ-HN35, HAD
12 months after start of treatment	S-SECEL, EORTC QLQ-C30, QLQ-HN35, HAD, study specific instrument, Mini-MAC

Paper IV

This was a multi-centre study performed with qualitative methodology. The design was cross-sectional. Participants were recruited from Ear, Nose and Throat-departments at five Swedish university hospitals of which three were located in urban-suburban cities and two in middle-sized towns. Participants were selected according to the grounded theory idea of theoretical sampling. Patients who had recently been diagnosed with laryngeal cancer and finished treatment not more than eight weeks prior to the interview were eligible for the study. Patients with poor knowledge of the Swedish language or who were unable to take part due to dementia, psychiatric disease or alcohol abuse were not asked to participate, neither were patients previously diagnosed with any type of cancer. The study period was June 2009 to April 2010. Data was collected by semi-structured face-to-face interviews and the material was analysed by a constant comparison technique consistent with Grounded Theory (GT) created by Glaser and Strauss [70] and further developed by Corbin and Strauss [71].

2.2 Participants

Paper I - III

During the study period 210 patients were admitted to the tumour conference. Of these 63 patients were regarded not eligible and reasons for exclusion were: participation in other studies (19), insufficient knowledge in Swedish language (10), second primary cancer tumour (9), psychiatric disorder (12), dementia (4) and alcohol addiction (9). Of the remaining 147 patients deemed eligible 47 declined while 100 patients accepted participation. Of the patients who declined participation, 22 stated that they were not feeling well enough, three declined due to family reasons and another 22 did not give any reason. A flow chart of participants is presented in figure 2.

All patients included received radiotherapy as part of their treatment. The majority of the patients with T1 disease received conventionally fractionated radiation therapy, a few received hyper fractionated radiation therapy. Patients with T2-T4 disease received either hyper fractionated or conventionally fractionated radiotherapy, in a majority the regional nodes were irradiated as well. Chemotherapy was given to 9 patients with stage III-IV tumours. One patient was laryngectomised before inclusion, two patients were treated with primary laryngectomy and four patients were treated with laryngectomy as salvage surgery during the study year. For further information on participants and non-participants, see table VI.

Twenty-nine participants dropped out during the study year, yielding a response rate of 100% at baseline, 95% at one month, 86% at two months, 81% at three months, 75% at six months and 71% at one year. At the end of the study year five patients had active disease or were deceased. The 29 drop-out patients missing at follow-up did not differ from the participants completing the study regarding gender, age, civil status or educational level but significantly more were smokers and had a supraglottic localisation.

Table VI. Sociodemographic and demographic characteristics of informants
in paper I - III

	Participants (n=100)	Non-participants (n=110)	p-value[†]
Age, median years (range)	67 (27-92)	71 (44-87)	Ns
Sex			Ns
Female	17 (17 %)	22 (20 %)	
Male	83 (83 %)	88 (80 %)	
Tumour site			
Glottic	72 (72 %)	61 (55 %)	0.0188
Supraglottic	20 (20 %)	37 (34 %)	0.0382
Subglottic	4 (4 %)	3 (3 %)	Ns
Transglottic	4 (4 %)	9 (8 %)	Ns
Stage			
0	3 (3 %)	2 (2 %)	
I	57 (57 %)	43 (39 %)	
II	22 (22 %)	24 (22 %)	
III	9 (9 %)	17 (15 %)	
IV	9 (9 %)	24 (22 %)	0.0010
WHO-Index			
0	77 (77 %)	62 (59 %)	
1	18 (18 %)	25 (24 %)	
2	4 (4 %)	13 (12 %)	
3	1 (1 %)	4 (4 %)	
4		1 (1 %)	0.0016
Married/Cohabitant	70 (70 %)	62 (56 %)	Ns
Smokers	50 (50 %)	70 (64 %)	Ns
Loss of weight	21 (21 %)	35 (32 %)	Ns
Residual disease	2 (2 %)	2 (2 %)	Ns
Cardiovascular disease	45 (45 %)	38 (35 %)	Ns
Other previous malignancy	8 (8 %)	11 (10 %)	Ns

[†]p-value significant at ≤0.05, ns=not significant
The participants were classified as N0M0, except one patient classified as
N2M0 and two classified as N2M1. Among non-participants 10 patients were
classified as N1M0, six as N2M0, one as N3M0 and one patient as N2M1.
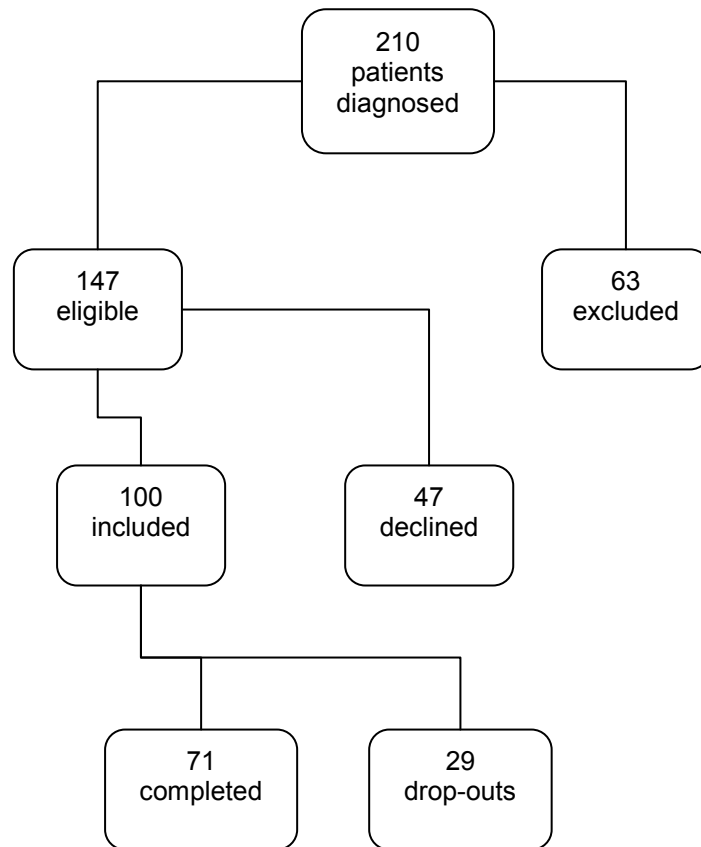
Figure 2. Flowchart of participants in papers I – III

Paper IV

During the inclusion period of this study 22 patients were asked to participate.
Four declined participation; three of them due to feeling too weak to
participate and one did not give any reason. Remaining number of
participants was 18 and 16 of these were men. Median age of the
interviewees was 64 years. For information about demographic and clinical
characteristics, see table VII.

Table VII. Sociodemographic and clinical characteristics of informants in
        paper IV

Sex	N (%)
Male	16 (89)
Female	2 (11)
Age, median (range)	64 (50 – 78)
Stage of cancer*	
T1	11 (61)
T2	6 (33)
T3	1 (6)
Treatment	
Radiotherapy	15 (83)
Laser	2 (11)
Laryngectomy	1 (6)
Marital status	
Married/Partner	12 (67)
Widowed	2 (11)
Single	4 (22)
Children	
Yes	16 (89)
No	2 (11)

*All patients were classified as N0M0, except one patient classified as N0Mx.

2.3 PRO Instruments

S-SECEL

The original Self Evaluation of Communication Experiences after
Laryngectomy (SECEL) was developed to assess communication dysfunction
in patients with laryngectomies and has demonstrated satisfactory
psychometric properties [72]. The SECEL has been used as a screening tool
to develop recommendations for intensive counselling, and for evaluating the
effects of voice therapy and rehabilitation on the patients' daily living
activities. For identifying the patients in need of further rehabilitation and in-

depth counselling, the original authors have recommended a specific cut off value [73, 74]. The Swedish version of the SECEL was adapted for use in patients who receive different treatments for laryngeal cancer. Two items in the original SECEL, specifically addressing experiences after laryngectomy, were re-worded in the S-SECEL. Otherwise the S-SECEL is congruent with the original SECEL in both its format and content. The S-SECEL has proved reliable and shown both convergent and discriminant validity and satisfactory internal consistency [75, 76].

The instrument consists of 35 items addressing communication experiences and dysfunction. 34 of the items are aggregated into three subscales:

- The General subscale (5 items), describes general attitudes about being relaxed or calm and acknowledgement of the sickness and treatment. Examples of questions are:
  - "Do you think that your speech improves with practice?"
  - "Would you describe yourself as outgoing and talkative?"
- The Environmental subscale (14 items), focuses on how the patient experiences his/her voice in different environments. Questions are for example;
  - "Do you have trouble speaking in a large room?"
  - "Do you have difficulty yelling or calling out to people?"
- The Attitudinal subscale (15 items), describes attitudes about speech, feelings about self-perceptions and perceptions of others, for example:
  - "Do you avoid speaking because of your voice?"
  - "Do you feel that people get annoyed with you because of your voice?"

Each item is rated on a 4-point Likert scale ranging from 0 (never) to 3 (always), and addresses the last 30 days. Scoring of subscales and a total scale is carried out by simple addition. Thus, the summary scale scores range from 0-15 for General, 0-42 for Environmental, 0-45 for Attitudinal and 0-102 for Total, respectively. A higher score indicates greater perceived

communication dysfunction. The 35th item "Do you talk the same amount now as before your laryngeal cancer" has three response categories; Yes/More/Less, and is not included in the scoring system.

Mini-MAC

The Mini- Mental Adjustment to Cancer scale (Mini-MAC) is a revised version of the widely used Mental Adjustment to Cancer scale (MAC) [38], developed for measuring mental adjustment to cancer in a general cancer population. According to the creators, The MAC, as well as the Mini-MAC, were designed to measure a predefined set of psychological responses to a cancer diagnosis, and not intended to measure every possible response to the diagnosis of cancer. It was designed for use in busy oncology clinics with large numbers of patients. They claim its main usefulness to be as a screening device, providing an aid or tool for the doctor or nurse which allows recognition of patients' attitudes to their diagnosis. If the score on negative attitudes is high, this may be an indication that supportive intervention is needed [38]. The instrument does not specify the stressors, other than the ways of adaptation to different aspects of the "illness".

The Mini-MAC contains 29 items and the psychometric properties of the instrument have proved satisfactory [77]. The Swedish version of the Mini-MAC has been obtained by standard translation procedures with forward/backward translation, pre-tested on different cancer patients and reviewed by clinicians and patient focus groups. The Mini-MAC items are rated on a four-point Likert scale ranging from "Definitely does not apply to me" (1) to "Definitely applies to me" (4) and measures patients experiences at present. The Mini-MAC has five domains:
- Helpless-Hopeless, e.g. "I feel completely at a loss about what to do" (8 items)
- Cognitive Avoidance, e.g. "I distract myself when thoughts about my illness come into my head" (4 items)

- Fighting Spirit, e.g. "I try to fight the illness" (4 items)
- Anxious Preoccupation, e.g. "I worry about the cancer returning or getting worse" (8 items)
- Fatalism, e.g. "I've had a good life; what's left is a bonus" (5 items).

The domains can be scored separately through simple addition. Since the domains consist of different number of items we also calculated mean scores by dividing the sum with number of items.

The Mini-MAC was chosen over the MAC due to the fewer numbers of items, making it easier for participants to fill out. Also, the Mini-MAC's extended focus on Avoidance as adjustment response was judged as important.

EORTC QLQ-C30 and QLQ-H&N35

The EORTC Study Group on Quality of Life has developed a modular measurement system for evaluating quality of life in cancer patients participating in clinical trials [78]. A 30-item core instrument, the EORTC QLQ-C30, assesses the physical and psychosocial functioning and symptom experiences of cancer patients in general [79]. To address additional symptoms associated specifically with H&N cancer and its treatment, a complementary 35-item module can be used, the QLQ-H&N35 [80, 81]. When tested in large, cross-cultural samples of patients with cancer, both the core instrument [79] and the H&N cancer-specific module [81] have demonstrated satisfactory to excellent reliability and validity for most factors. Exceptions were however found for the domains measuring Speech and Senses, that demonstrated low internal consistency [82]. The EORTC instruments are widely used, for example in a structured review on HRQL in H&N cancer EORTC was the most commonly used measure [83]. Of particular importance is the ability of these instruments to distinguish between patient groups differing in clinical status and to detect changes in patients' clinical status over time.

Calculated scale scores range from 0-100. For the Functioning scales and Global quality of life scale a higher score corresponds to higher functioning, whereas on the Symptom scales and single items a higher score represents higher levels of symptoms [84]. A change in score over time of >10 points could be interpreted as clinically significant [85]. A one-week frame is employed.

Hospital Anxiety and Depression Scale (HAD)

The HAD is an instrument developed for detection of mood disorders in somatically ill patients [86] and has frequently been used in cancer studies, including H&N cancer [87, 88]. The two factor structure for anxiety and depression has been confirmed repeatedly [89, 90]. The Swedish version has been documented in several studies [91]. HAD consists of 14 items on a four-point Likert scale ranging from 0-3. The summary scale scores for anxiety (7 items) and depression (7 items) thus range from 0-21. Each person is also grouped according to a clinically tested classification of psychiatric morbidity. The constructors have calculated cut off scores where a scale score < 8 is in the normal range, a score 8-10 indicates possible and a score >10 indicates probable anxiety or depression. Some authors have however discussed the possible need for different cut off values for different populations [92, 93]. For example Zöger et al used HAD for patients with tinnitus, and found the optimal cut-off score for these patients to be ≥ 5 [94].

Study specific instruments

Two study specific short forms about speech intelligibility, voice quality and speech acceptability were used in paper I. The questions included in these instruments were:

- Is your speech easy to understand?
- Is your voice of good quality?
- Is your speech socially acceptable?

These questions were answered twice at each measurement point, once with VAS assessments, once with Likert assessment. VAS assessments were made by marking an appropriate place on the 100 mm line anchored at either end to represent normal speech vs. severely disturbed speech, i.e. never vs. always easy to understand, never vs. always of good quality and never vs. always socially acceptable. Each patient's response was measured to the nearest mm giving a number between 0 and 100 for each patient, where a higher value represented better self-rated voice and speech.

The categorical Likert response alternatives consisted of four word descriptions: Never / Sometimes / Often / Always. Responses were rated 0 – 3 and the figures were included with the word description where a higher value represented better self-rated voice and speech.

The World Health Organization Functional Scale

This is not a PRO instrument, but a physician-completed 5-point scale developed by the World Health Organization, where:
- 0 = Able to carry out all normal activity without restriction
- 2 = Ambulatory and capable of all self-care but enable to carry out any work; up and about more than 50 per cent of waking hours
- 4 = Completely disabled, cannot carry on any self-care; totally confined to bed or chair [95].

The Karnofsky Performance Index

Like the WHO functional scale, the Karnofsky index is a physician-completed instrument. It emphasizes physical performance and dependency. Although

not designed as a QoL-measure, it is frequently used as one [96]. The index has 11 descriptions ranging from 0 (dead) to 100 (normal) per cent [97].

2.4 Statistics

Descriptive statistics were calculated according to standard procedures. Level of significance was set at 5% throughout. Differences within groups were tested with the Wilcoxon paired signed ranks test and between-group analyses were carried out using the Mann-Whitney *U* test. For measuring changes over time Wilcoxon's signed rank test was used. Test-retest reliability was assessed by Spearman's correlation.

In paper I a statistical method designed to evaluate the inter-scale concordance between discrete and continuous scaling of the same item was used [98, 99] to evaluate the order consistency between our Likert and VAS paired data. The data is viewed as paired since each individual answered the same questions on two scales. The concordance between two different scales is a measure of their interchangeability, i.e., to what extent one scale can be replaced by the other. A high inter-scale concordance between different scale assessments means that they produce the same ordering of individuals, i.e. a high level of order-consistency and few disordered pairs. Example of ordered pairs is Likert/VAS responses "1/30" and "2 /50", while "2 /30" and "1/50" represent disordered pairs. The measure of disorder, D, defines the number (%) of disordered pairs out of all possible different pairs.

In paper II, besides statistical significance, clinical significance was calculated for EORTC, i.e. a score difference of >10 points. Magnitude of group differences was further analyzed by means of effect sizes (ES). ES of within-group change was calculated as mean change between assessments divided by the standard deviation of change [100]. ES were judged against standard criteria proposed by Cohen: trivial (0 to <0.2), small (0.2 to <0.5), moderate

(0.5 to <0.8) and large (≥0.8) [101]. This method supplements usual significance testing and provides standardized effect levels regardless of sample size and scaling properties.

In paper III correlations between Mini-Mac domains and domains measuring mood disorder and HRQL were calculated using Spearman's correlation and cases of missing data were handled by imputation, i.e. if less than 50 % of items in a domain were missing the calculated mean value replaced missing items. Cronbach's alpha was calculated in order to examine the internal reliability of the five original Mini-Mac domains when assessing present data. Due to multiple testing number of false significances was calculated as ((number of tests-number of significant tests)*alfa)/(1-alfa) [102].

The survival analysis in paper III was performed in order to predict death. Survival was calculated from date of diagnosis. Endpoint chosen for the analysis was all-cause mortality, since the validity of the more commonly used end point disease-specific mortality has been questioned [103]. For ordered categorical or continuous variables Cox's PH-regression was used. Hazard ratios were calculated for descriptive purposes. For multivariate purposes a stepwise Cox's PH-regression was performed. Only variables that affected survival time at univariate tests (p<0.1) were included as possible predictors in the multivariate analysis.

2.5 Grounded Theory

For analyses of the qualitative data in paper IV a constant comparison technique consistent with Grounded Theory (GT) was used. GT is a research method that uses a systematic set of procedures to generate an inductively derived grounded theory about a phenomenon. GT was originally not developed for analysis of qualitative data solely, but has with time become the most frequently used qualitative research method [104]. GT was

developed in medical sociology and has its roots in the philosophies of symbolic interactionism and pragmatism [71]. The creators of GT were Glaser and Strauss [70] who developed GT through their first work "Awareness of dying" from 1965 [105], in which they studied how the awareness of the fact that a patient was dying influenced the interactions with the patient. GT was later further developed by Corbin and Strauss [71]. GT is especially suitable when studying areas that have not previously been studied, when there are no or almost no theories developed or to give voice to the informants.

Characteristic for GT is the technique of simultaneous data collection and analysis. The core of the analysis according to GT is constant comparisons. Data analysed is most often constituted of transcribed interviews, but can be any kind of information that comes in the researcher's way. Data is collected until so called theoretical saturation is reached, i.e. when no new information can be obtained, implying that one cannot decide in advance the number of informants to be included in the study.

The analysis constitutes of three types of coding; open, axial and selective coding. Open coding means repeatedly readings of the transcripts and an in-depth, line-by-line analysis, breaking the text into individual units of meaning and labelling them to identify concepts. These concepts are then constantly compared and hereby confirmed or modified and grouped in order to form more abstract categories. Axial coding implies relating concepts and categories to each other, hereby elaborating them and adding depth and complexity to the interpretation. The third level of analysis, selective coding, is the process of choosing a core category, representing the main theme of the research, and relating the descriptive categories to the core category.

2.6 Ethics

Both studies included in this thesis were conducted in accordance with the Declaration of Helsinki and approved by the ethical committee at Sahlgrenska University Hospital, Gothenburg, Sweden.

Summary of main results

3.1 Paper I

Purpose of this study was to evaluate whether VAS or Likert was the more suitable response alternative for assessment of laryngeal cancer patients' self-ratings of voice and speech. Results showed that although test-retest reliability was acceptable for both response alternatives, it was stronger for the Likert scale. Furthermore, the VAS responses all deteriorated significantly between the two pre-treatment assessments, not corresponding to any clinical deterioration, indicating a possible instability in VAS response patterns. Mean changes from baseline to follow-up were statistically significant for all items irrespective of response scale. On a group level, the two response formats were in agreement with regard to the direction of change between assessments. However, on an individual level a considerable overlap was noted. The measure of disorder, indicating the level of inter-scale concordance between the VAS and Likert pairs, was 11 – 16 % at baseline and 6 – 8 % at follow-up. When comparing the results of the first and fourth age quartiles, a lower concordance was observed in the older group.

3.2 Paper II

Aim of this longitudinal study was to investigate the sensitivity to change of the S-SECEL, addressing communication dysfunction in patients treated for laryngeal cancer. Results demonstrated that the S-SECEL was well accepted with a cumulative response rate of 76% and an item response rate on 99.5%. Communication dysfunction increased at 1 month, followed by a continuous decrease throughout the year. The mean S-SECEL total and subscale scores at the different measurement points are shown in Figure 2. Changes were statistically significant at most measurement points, demonstrating the sensitivity of the S-SECEL to changes in communication over time. The S-SECEL was more sensitive regarding communication dysfunction than the EORTC QLQ-C30 and QLQ-H&N35, with the largest changes found in disease specific items.
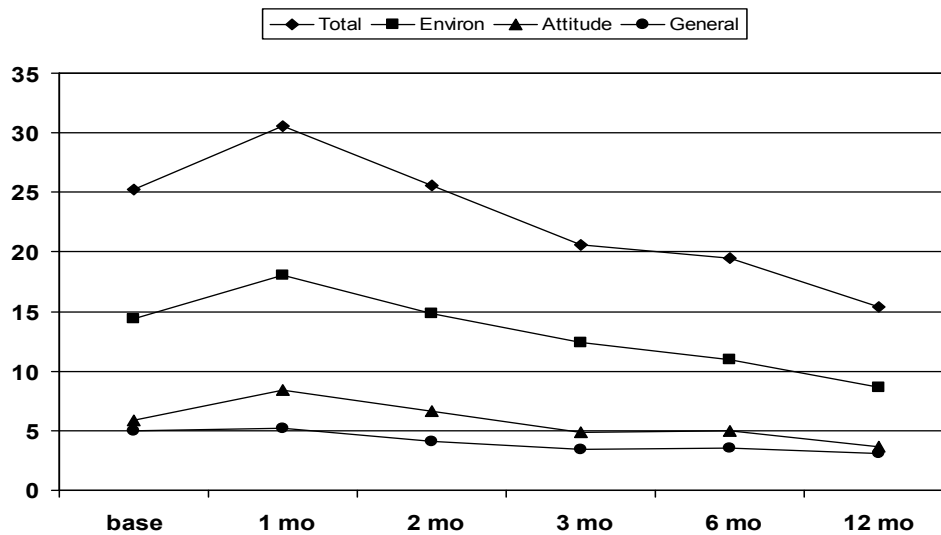

Figure 2. S-SECEL scores

3.3 Paper III

Aim of this study was to investigate the relation between mental adjustment to cancer and HRQL, anxiety, depression and survival in patients treated for laryngeal cancer. Patients were assessed at one and 12 months after start of treatment, respectively, using the Mini-MAC, the Attitudinal domain of the S-SECEL, the EORTC QLQ-C30 supplemented with the QLQ-H&N35, and the HAD scale. For survival analyses patients were followed up for a median time of 4.22 years from inclusion. Results demonstrated that the most commonly used adjustment response at both occasions was Fighting Spirit and that the use of adjustment responses was relatively stable over time. Correlation analyses showed that patients using Helpless-Hopeless and Anxious Preoccupation responses reported more anxiety and depression, as well as decreased HRQL. Survival analysis indicated that use of a Helpless-Hopeless response was related to poorer survival (HR 1.17, p 0.008), however, it should be noted that these results are based on a relatively small study sample.

3.4 Paper IV

Primary aim of this study was to increase the understanding of mental adjustment responses in laryngeal cancer patients, as well as the outcome of these responses. Secondary aim was to evaluate the content validity of the Swedish version of the Mini-MAC Scale with regard to findings from the patient interviews. Results demonstrated that the core category arising was "Setting boundaries", concerning above all patients' attitude to information and thoughts about the cancer and seeming to be a prerequisite for mental adjustment to diagnosis and treatment without major negative impact on mental health or HRQL. Furthermore, five descriptive categories emerged: Fighting Spirit; Avoidance; Comparisons; Anxious Preoccupation; and Social Interactions. When comparing these results with the domains of the Mini-MAC Scale, the Fighting Spirit, Cognitive Avoidance and Anxious Preoccupation domains were clearly represented. Concerning the Fatalism and the Hopeless-Helpless domains the support was somewhat weaker.

General discussion

4.1 Mental Adjustment in Patients with Laryngeal Cancer

In both paper III and paper IV, Fighting Spirit was the dominating adjustment response being mentioned by a majority of the participants. The Fighting Spirit response is widely acknowledged and frequently present in instruments measuring coping and mental adjustment. Although Fighting Spirit was the most reported response, in paper III we could not find any significant relation to mood disorders, HRQL or survival. One contributing factor to these results could be the somewhat low internal consistency of this domain with the item "I feel highly optimistic" not fitting the model in the factor analysis. Previous studies have demonstrated a connection between Fighting Spirit and optimism [106, 107]. Furthermore, optimism has been shown to be inversely related to distress when measured at baseline and at 12 months follow-up [108]. The psychometric weakness of this item in the Swedish version might be explained by shortcomings in the translation or that Fighting Spirit and optimism actually are two separate concepts that sometimes co-vary.

4.2 Effects of Mental Adjustment to Cancer

Results from paper III further demonstrated that, at both measurement points, the Helpless-Hopeless and Anxious Preoccupation responses were associated with mood disorder and HRQL; findings in line with what has previously been demonstrated in other cancer diagnoses [77, 109, 110]. The relation between these adjustment responses and psychiatric morbidity was even more transparent when analysis demonstrated that the use of both Helpless-Hopeless and Anxious Preoccupation was significantly more common among patients with a possible/probable mood disorder. This

relation seems to be stable over time; results of correlation analyses at one and 12 months are more or less unchanged, demonstrating that a Helpless-Hopeless or an Anxious Preoccupation response has a negative impact on well-being, irrespective of phase of illness. In paper IV, however, feelings of helplessness or hopelessness were scarcely mentioned but, in spite of this, we argue that the Helpless-Hopeless domain is an important response to evaluate in laryngeal cancer patients due to its potentially detrimental effects.

Yet another finding from paper III was that the survival analysis suggested a slightly increased risk of death for patients using a Helpless-Hopeless response. The role of adjustment responses and coping on survival has been questioned [50], but our finding is in line with what Watson et al have demonstrated in a large number of breast cancer patients, at 5 as well as 10 years follow-up [111, 112].

4.3 Changes in Mental Adjustment Over Time

There seems to be stability in the use of adjustment responses, both for the Fighting Spirit response and the Helpless-Hopeless response. This might seem surprising, since the situation at the two measurement points were very different: one month after start of treatment a majority of patients were still under treatment and were suffering from side effects, while 11 months later most patients had recovered well and received reassuring information about their health status. It could therefore be assumed that patients would appraise their situation at follow-up as less stressful and hence the pattern of adjustment responses should change over time with, in particular, a decreased use of both Anxious Preoccupation and Helpless-Hopeless responses. However, of the two, only Anxious Preoccupation obtained statistical significance while Helpless-Hopeless, together with Fighting Spirit and Cognitive Avoidance, remained stable. This impression of stability has previously been demonstrated by Nordin et al [109] and it can possibly be

argued that it reflects an aspect of personality [109, 113] or life experience, given the relative homogeneity in age and gender for the laryngeal cancer group. Regarding the Helpless-Hopeless response, the stability could also possibly be due to a tendency for a floor effect leaving little room for improvement.

Adjustment responses expressed in paper IV, but not represented in the Mini-MAC, were Comparisons (the use of inter-individual or inter-individual comparisons for making the participants' own situation seem more optimistic and, thus, more manageable) and Social Interactions. Even though Social interactions are generally deemed as beneficial for both mental health [114] and survival [115] in cancer patients, this adjustment response seems to be more complex than others. While for most participants in paper IV, Social Interaction was described as beneficial and seemed to enhance good adjustment responses for others the effect of Social Interaction seemed to be linked to the participant's relation to the person he/she turned to. This has previously been described also by Cicero et al, where the patient's perception of social support from friends was predictive of Fighting Spirit, whereas support from family members was not [116]. Furthermore, some participants described fear of rejection and disappointment regarding the perceived social support, a finding supported by results from a review on experiencing cancer in old age by Hughes et al [117]. Social Interaction was however frequently mentioned, indicating importance for the mental adjustment of laryngeal cancer patients. Watson's and Greer's definition of mental adjustment has previously received some criticism for failing to include several dimensions of adjustment, such as the social [40].

The results from paper III and IV raise the question of a need for further investigation of the content validity of the Swedish version of the Mini-MAC Scale. Even though the findings largely support the Swedish version of the Mini-MAC, some deviations were found which should be considered. They do not automatically imply that the instrument is invalid or must be revised,

rather that it is important to be aware of the unique features of the laryngeal cancer population and how they adjust to cancer and to take this into consideration when evaluating results.

4.4 HRQL and Communication Dysfunction

In order to properly assess the impact of disease on patients, self-report instruments are important tools. Generic instruments have their advantages, e.g. for comparisons between groups, such as different cancer diagnoses. However, by being so general, they may not be sensitive enough to capture the specific troubles of diagnose groups. The use of diagnose specific, or situation-tailored, instruments has previously been advocated by e.g. Coyne [41]. In the case of laryngeal cancer patients it is of great importance that HRQL instruments include items on voice, speech and communication, since these have been demonstrated to be issues of importance. Instruments for assessing HRQL in H&N cancer patients in general have been developed, as for example the EORTC QLQ-C30 with H&N35. Previous works have however indicated that they are not specific enough for use in laryngeal cancer patients. For example, Müller et al argue that the QLQ-H&N35 is not specific enough and stress that questionnaires should be more precise when used on patients with laryngeal cancer [118]. In the case of laryngectomees, Op de Coul et al have underlined the necessity to develop and use more specific additional questionnaires as an adjunct to the existing EORTC questionnaires when studying specific symptoms in these patients [119]. There do exist other instruments for assessment of voice impairment and it's psychosocial implication, such as the often used Voice Handicap Index [120]. These instruments are, however, not developed specifically for patients with cancer, which is likely to influence how patients assess their communication and psychosocial dysfunction.

Results from our study proved the S-SECEL to be sensitive to changes in communication and psychosocial dysfunction longitudinally. The response

pattern over time, when compared to the EORTC QLQ-C30 with H&N35 and the HAD, lent further support to the construct validity of the S-SECEL. The response rate for the used set of questionnaires was high, supporting the feasibility of assessment method in clinical settings. These findings indicate that the S-SECEL could be a more suitable instrument than the EORTC QLQ-C30 with QLQ-H&N35 when measuring communication experiences in patients with laryngeal cancer.

4.5 Anxiety and Depression

Baseline results of the HAD scale corresponds well to other comparable studies [75, 121], both regarding anxiety and depression. The decrease in anxiety reported at the one month follow-up may seem contradictory to the increased dysfunction according to the S-SECEL. However, this could be due to a feeling of relief having been diagnosed and receiving treatment. This improvement, however, was not found in the Emotional scale of the EORTC QLQ-C30.

The increase in depression at the second measurement point is in line with previous studies [122] and could be due to adverse effects during treatment. After one year, and terminated treatment, the prevalence was lower than at baseline.

4.6 Which Response Alternative to Choose - VAS *vs.* Likert

The lay-out of a self-report instrument, including the type of response alternative, is important for how patients interpret and understand the instrument. The self-report instruments used in this thesis all have the Likert-type response alternative. Many have argued for the advantages of the VAS alternative; since it is believed to be more sensitive [21] and more closely

assess the patients' experiences [123]. The results from paper I, however, indicate that for assessment of self-rated voice and speech in laryngeal cancer patients, the Likert scale seems to be more suitable than the VAS. The test-retest analyses indicated that both response alternatives were reliable; however, the VAS seemed to produce instability in response pattern not corresponding to a clinical change. The findings from paper I further demonstrated that for some Likert scores the associated VAS values varied across a very wide range. This pattern has previously been demonstrated by other authors, for example Bolognese [23], and might indicate that the VAS is hard to cognitively grasp [23, 124]. Laryngeal cancer patients as a group have a relatively high median age and our findings from paper I demonstrated lower concordance in the older patient group compared to the younger. It has been proposed that elderly patients find the VAS more troublesome, maybe due to handicaps that are more common in elderly such as tremor and impaired vision [125].

4.7 Clinical Implementation

During the last decades the trend towards a more patient-focused care, where patients' subjective experiences and opinions are considered, has been growing stronger. A central theme in this process is the theory of patient-centred, or person-centred, care. One important aspect of patient-centred care, as defined by Mead and Bower in their review [126], is the biopsychosocial perspective, broadening the perspective on illness to include social and psychological factors. Furthermore, Mead and Bower argue that according to the 'patient-as-person'-perspective, the patient is to be viewed as an experiencing individual rather than the object of some disease entity. It is hence important to understand the individual's experience of illness. Within the theory of person-centred care lays also the ideal of an egalitarian doctor-patient relationship. Even though these ideas are generally honoured, they

are not yet implemented into clinical practice, where focus to a large extent is on technical issues and signs of disease.

The work of this thesis is to large extent in line with the theories of person-centred care, with focus on the patients' subjective experiences of the laryngeal cancer diagnosis and especially the social and psychological aspects of the disease. Furthermore, in order to implement the theories of person-centred care into clinical practice, the use of self-report instruments can be important, providing an effective manner to collect the subjective experience of the patient. The aim of these studies is to highlight these issues and possibly help improve the care of laryngeal cancer patients.

The findings from paper II indicate that if the S-SECEL was used as a routine screening instrument, it could be a valuable tool for identifying patients at risk for psychosocial problems and help plan rehabilitation. It is therefore recommended for clinical use in evaluation of communication dysfunction for all patients with laryngeal cancer irrespective of treatment. Compared to more well-known HRQL-instruments, such as the EORTC QLQ-C30 with QLQ-H&N35, the S-SECEL seem to be a more suitable instrument in patients with laryngeal cancer since it is more sensitive, is shorter and can be used on an individual basis.

The relation between adjustment responses Helpless-Hopeless and Anxious Preoccupation and anxiety, depression, HRQL and possibly poorer survival indicate that it is desirable that clinicians become aware of the use of negative adjustment. Assessments of mental adjustment should be considered when planning treatment and rehabilitation in laryngeal cancer patient, in order to offer patients using maladaptive adjustment responses further support, e.g. psychotherapy. The findings regarding Social Interactions might indicate that relations outside the closest family, e.g. patient support groups, should be encouraged. The results of paper IV further emphasize the importance of adapting the information given and

rehabilitation options to each individual patient. The results also indicate that an avoidant adjustment response is not necessarily harmful, and we must not force information upon patients showing an avoidant attitude towards their diagnosis in the initial phase.

4.8 Limitations

A shortcoming of the longitudinal study (papers I – III) is that non-participants had more advanced disease and lower performance status than participants. This might have lead to an underestimation of the prevalence of psychiatric morbidity and communication dysfunction.
In the interview study (paper IV) three of the four patients who declined participation stated that they were not feeling well enough to participate. This might possibly have led to an underestimation of poor adjustment responses. Only two of 18 interviewees were women, which might seem like a small number. However, this reflects the actual constitution of the laryngeal cancer population in Sweden.

4.9 Future research and goals

A randomised study is ongoing in our department, aiming to evaluate the effect of rehabilitation with speech language pathologist on voice and speech in laryngeal cancer patients treated with radiotherapy. In this work the S-SECEL is used for evaluation of HRQL and communication dysfunction. We plan to do further psychometric testing of the S-SECEL with calculation of a cut-off score to be used in clinical practice. Furthermore, the Swedish version of the Mini-MAC is to be further validated and tested on a larger set of patients with various cancer diagnoses.

Conclusions

- For assessment of self-rated voice and speech in laryngeal cancer patients, the Likert scale seems to be more suitable than the VAS. Our results imply that the VAS might produce an instability in response patterns that does not necessarily imply a true change.

- The S-SECEL is sensitive to change over time and shows convergent results when compared to established HRQL questionnaires. The findings further indicate that the S-SECEL could be a more suitable instrument than the EORTC QLQ-C30 with QLQ-H&N35 in patients with laryngeal cancer; it is more sensitive, it is shorter and can be used on an individual basis.

- As a routine screening instrument, the S-SECEL could be a valuable tool for identifying patients at risk for psychosocial problems to help plan rehabilitation. It is therefore recommended for clinical use in evaluation of communication dysfunction for all patients with laryngeal cancer irrespective of treatment.

- Mental adjustment is related to HRQL, anxiety and depression and possibly survival. These findings indicate that assessments of mental adjustment should be considered when planning treatment and rehabilitation in laryngeal cancer patients.
  The most commonly used mental adjustment response at all measurement points was Fighting Spirit. The use of adjustment responses was relatively stable between over time.

- Results from paper IV showed the central theme of mental adjustment responses in laryngeal cancer patients to be 'Setting Boundaries', concerning above all patients attitude to information and thoughts about the cancer. The results emphasize the importance of adapting the information given and rehabilitation options to each individual patient.

- The findings of paper III and IV largely support the Swedish version of the Mini-MAC. However, some deviations were found which should be considered when interpreting results from the Mini-MAC in laryngeal cancer patients.

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Summary in Swedish (Svensk sammanfattning)

Patienters subjektiva upplevelser tillmäts allt större betydelse inom både klinisk forskning samt inom sjukvården. Sådan information samlas enklast in med frågeformulär och det ställs idag allt högre krav på att dessa frågeformulär är tillförlitliga. Diagnosspecifika frågeformulär skall vara framtagna och testade för att passa den aktuella patientgruppen. Patienter med struphuvudcancer har i allmänhet god prognos, men många lider av nedsatt röst- och talfunktion med negativ effekt på hälsorelaterad livskvalitet (HRQL). Det är därför av vikt att frågeformulär framtagna för patienter med struphuvudcancer innehåller frågor om dessa funktioner. De formulär som har utvecklats för att mäta HRQL hos patienter med huvud-halscancer inkluderar dock få frågor om röst och tal. Därför har frågeformuläret Self Evaluation of Communication Experiences after Laryngeal Cancer (SECEL), speciellt framtaget för att mäta HRQL hos larynxcancerpatienter, översatts till svenska (S-SECEL).

Coping, det vill säga förmågan att hantera stressfulla händelser, har identifierats som en viktig faktor för HRQL, psykisk ohälsa och eventuellt överlevnad hos cancerpatienter. Det saknas dock kunskap kring coping hos patienter med struphuvudcancer. Frågeformuläret Mini-MAC är framtaget för att undersöka coping hos en generell cancerpopulation, men har inte tidigare utvärderats på patienter med struphuvudcancer.

Resultaten i denna avhandling baseras på såväl kvantitativ som kvalitativ metodik och visar att S-SECEL accepterades väl av patienterna och uppvisade god tillförlitlighet. Jämfört med EORTC QLQ-C30 samt QLQ-H&N35 är S-SECEL mer känsligt för att fånga problem relaterade till kommunikation. Vad gäller copingstrategier visade resultaten att de flesta patienter uppvisade en vilja att besegra sin sjukdom. Dock uppvisade de patienter som under pågående behandling reagerar med ett ältande eller en

känsla av hopplöshet och hjälplöshet i högre grad psykisk ohälsa och nedsatt HRQL. En känsla av hopplöshet och hjälplöshet tycks även ha en negativ effekt på överlevnad.

De slutsatser som kan dras av dessa resultat är att det är av stor vikt att frågeformulär för att skatta HRQL hos struphuvudcancerpatienter även mäter patientens upplevda röst- och talfunktion. Coping är ytterligare en faktor av betydelse för struphuvudcancerpatienters HRQL och som även påverkar risken för psykisk morbiditet, eventuellt också överlevnad. En bedömning av patientens copingstrategier bör därför ingå som en del i det övriga omhändertagandet.

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Appendix I   S-SECEL

Appendix II   Mini-MAC

Appendix III   EORTC QLQ-C30 and QLQ-H&N35

Appendix IV   HAD

Appendix V   Study specific instrument