Mercedes Nicklasson Quality of Life Assessment in Patients with Lung Cancer – Clinical Implications 2013

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To Anders,
Amanda and Alexander

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ABSTRACT

Introduction. Lung cancer is the leading cancer-related cause of death worldwide. In Sweden, nearly 3,700 patients are diagnosed with lung cancer every year. The overall prognosis is poor with a 5-year relative survival rate of 13% for men and 19% for women. Malignant pleural mesothelioma is rare, with an annual incidence of 110 patients, and seldom curable. Most patients with lung cancer or mesothelioma are diagnosed with advanced-stage disease and experience multiple symptoms that have a negative impact on their health related quality of life (HRQL). In addition to increased survival, the goals of cancer care include symptom control, psychosocial support and improved or maintained HRQL. In current clinical practice, physicians may underestimate the patients´ HRQL problems and it has therefore been suggested that the incorporation of self-administered HRQL assessments in clinical practice could increase the focus on patient well-being.

Aims. To evaluate whether the prospective use of individual HRQL measures in oncology clinical practice would have any influence on patient-physician communication, clinical decision-making, HRQL and satisfaction with care.

Methods and results. We used the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) and lung cancer module (LC13) for screening of HRQL issues during consultations.

In Paper I, we investigated the psychometric properties and clinical relevance of the instrument in 112 patients with advanced-stage lung cancer or mesothelioma who were receiving palliative care, but not chemotherapy. The EORTC QLQ-C30 and LC13 proved to be valid, reliable and clinically relevant for evaluation of HRQL in the target population. The clinical validity of the instrument was demonstrated by the associations between specific questionnaire domains and tests commonly used in clinical practice, including lung function and a 6-minute walk test. In addition, most of the QLQ-C30 functioning scores were significantly associated with remaining survival time.

In Papers II-IV, 171 patients were randomized to one of two groups. Patients in the experimental group (EG) answered the QLQ-C30 and LC13 questionnaire using a digital table interface at scheduled outpatient visits, after which a printed summary of the HRQL results was presented to the physician during the consultation. Patients in the control group (CG) completed a paper version of the same questionnaire, which was not presented to the physician but stored for later analysis. When indicated, patients in both groups received palliative chemotherapy and/or palliative radiotherapy. Consultations were audio-recorded for quantitative content analysis. Information about medical and psychosocial interventions was retrieved from clinical records. Issues pertaining to emotional function were more frequently discussed during consultations in the EG ($p<0.05$). Similarly, interventions to alleviate emotional and social concerns were more common in the EG than in the CG ($p=0.013$ and $p=0.0036$, respectively). In addition, perceived psychosocial problems and general symptoms were more likely to be captured during consultations when self-reported HRQL measures were available to the physician. HRQL scores over time were similar across the groups. Emotional function and dyspnoea improved in the whole patient population, with no significant differences between the EG and the CG. In general, patients rated their satisfaction with care as high. Negative predictors included poor health status (most consistently appetite loss), younger age, living alone and older age of the physician at the last visit during the study period.

Conclusions. Access to HRQL measures increases the probability of psychosocial problems and general symptoms being captured during consultations, but does not influence patients´ HRQL or satisfaction with care.

Keywords: lung cancer, mesothelioma, health related quality of life, daily clinical practice, satisfaction with care

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SAMMANFATTNING PÅ SVENSKA

Lungcancer är den sjukdom som leder till flest dödsfall i cancer i världen. Ungefär 3700 patienter insjuknar i lungcancer varje år i Sverige. Den relativa 5-årsöverlevnaden är 13% för män och 19% för kvinnor. Malignt pleuramesoteliom (cancer i lungsäcken) är ovanlig och sällan botbar. I Sverige insjuknar ungefär 110 patienter i mesoteliom varje år. De flesta patienter med lungcancer eller mesoteliom har avancerad sjukdom vid diagnos och upplever flera symtom som påverkar deras hälsorelaterade livskvalitet negativt. Cancervården har som mål att förlänga överlevnaden, lindra symtom och förbättra eller bibehålla patienternas livskvalitet. Denna typ av vård brukar kallas palliativ vård. Vårdpersonalen kan dock underskatta patientens symtom och en fråga som ställs här är om användning av standardiserade frågeformulär kan öka uppmärksamheten på patientens välbefinnande.

Syftet med avhandlingsarbetet var att undersöka om tillgång till resultat av livskvalitetsmätningar vid läkarbesök påverkar kommunikationen mellan patienten och läkaren, åtgärder som vidtas, samt patientens livskvalitet över tid och tillfredställelse med vården.

Vi mätte patienternas livskvalitet vid läkarbesök med EORTC QLQ-C30 + LC13, som är ett frågeformulär framtaget av en europeisk organisation för cancerforskning och behandling. Frågeformuläret har 30 frågor om allmänna symtom och välbefinnande vid cancer och 13 frågor om vanliga symtom associerade med lungcancer och dess behandling.

I delarbete 1 studerades frågeformulärets mätegenskaper hos 112 patienter som fick palliativ vård, dock inte cellgiftbehandling. Studien visade att EORTC QLQ-C30 + LC13 mätte vad det är avsett att mäta och att det var tillförlitlig för denna patientgrupp. Den kliniska betydelsen av formuläret visades genom jämförelser mellan specifika frågor i formuläret och vanliga kliniska undersökningar, såsom andningstest och 6 minuters gångtest. Livskvalitetsresultatet hade dessutom samband med överlevnaden.

I delarbeten 2-4 fördelades 171 patienter genom randomisering i 2 grupper. Patienter i försöksgruppen (FG) svarade på en datorversion av EORTC QLQ-C30 + LC13 med hjälp av ett digitalbord vid planerade läkarbesök. En skriftlig sammanfattning av livskvalitetsresultat visades för läkaren vid besöket. Patienter i kontrollgruppen (KG) fyllde i en papperversion av samma frågeformulär, som inte visades för läkaren, utan sparades för senare analys. Patienter i båda grupper kunde få cellgift- och/eller strålbehandling. Samtalen mellan patienter och läkare spelades in för innehållsanalys. Information om vidtagna åtgärder togs fram ur patientens journal. Studien visade att emotionella besvär diskuterades oftare i FG jämfört med KG och att åtgärder inom psykosociala områden var fler i FG. Sannolikheten att upplevda psykosociala problem och allmänna symtom fångades upp under läkarbesöket ökade om livskvalitetsresultat var tillgängliga för läkaren. Emotionellt välbefinnande och andfåddhet förbättrades generellt, och livskvalitet över tid var lika i både grupperna. Patienterna rapporterade genomgående hög tillfredsställelse med vården, utan någon skillnad mellan FG och KG. Nedsatt hälsotillstånd, särskilt aptitlöshet, lägre patientålder, ensamboende, och högre läkarålder var faktorer som påverkade patientens tillfredställelse med vården negativt.

Sammanfattningsvis visar studien att tillgång till resultat av livskvalitetsmätningar under läkarbesöket ökar uppmärksamheten på patientens upplevda psykosociala problem och symtom, men påverkar inte patientens livskvalitet över tid eller tillfredsställelse med vården.

RESUMEN EN ESPAÑOL

Introducción: El cáncer de pulmón es la primera causa de muerte por cáncer en el mundo. En Suecia, el número de nuevos casos por año es de 3.700. La sobrevida es corta. El mesotelioma pleural maligno es una enfermedad poco común y raramente curable. En Suecia se diagnostican alrededor de 110 casos de mesothelioma por año. La mayoría de los pacientes con cáncer de pulmón o mesotelioma pleural reciben el diagnóstico en fases avanzadas de la enfermedad y presentan varios síntomas que influyen en forma negativa en la calidad de vida relacionada con la salud (CVRS). Los objetivos de la oncología clínica son prolongar la sobrevida de los pacientes, así como aliviar los síntomas y mejorar o mantener la calidad de vida.

Como los médicos usualmente subestiman los síntomas de los pacientes, la incorporación de cuestionarios que miden la CVRS durante las visitas médicas podría aumentar la atención sobre los mismos.

Objetivo: El objetivo de esta tesis fue investigar si el acceso a los resultados de la medición de la CVRS durante la visita médica influencia la comunicación entre el paciente y el médico y la toma de decisiones, así como la CVRS y la satisfacción de los pacientes con el servicio de salud.

Métodos y resultados: En el estudio medimos la CVRS de los pacientes con el EORTC QLQ-C30 + LC13, un cuestionario diseñado por la Organización Europea para la Investigación y el Tratamiento del Cáncer. El cuestionario tiene 30 preguntas sobres síntomas generales y el bienestar emocional y social de los pacientes con cáncer, y 13 preguntas sobre síntomas relacionados con el cáncer de pulmón o su tratamiento.

En la primera parte de la tesis, medimos las propiedades psicométricas del cuestionario en pacientes que recibieron cuidados paliativos, excepto quimioterapia. El estudio demostró que el cuestionario es válido y confiable. La relevancia clínica del cuestionario quedó demostrada por las asociaciones de preguntas específicas del mismo con estudios clínicos como la espirometría y la prueba de marcha de seis minutos. Además, la calidad de vida estuvo relacionada con la sobrevida de los pacientes.

La segunda parte de la tesis fue el estudio randomizado de 171 pacientes, los cuales fueron divididos en dos grupos. Los pacientes del grupo experimental (GE) respondieron una versión computarizada del cuestionario EORTC QLQ-C30 + LC13, durante las visitas al médico, quien tuvo acceso al resultado escrito de las mediciones de la CVRS. Los pacientes del grupo control (GC) completaron la versión en papel del mismo cuestionario, el cual no fue mostrado al médico, y fue guardado para ser analizado posteriormente. Los pacientes de ambos grupos pudieron recibir quimioterapia y/o radioterapia. La conversaciones entre el paciente y el médico se grabaron para poder analizar el contenido de las mismas. La información sobre tratamientos y estudios clínicos se obtuvieron de las historias clínicas. El estudio demostró que los problemas emocionales fueron tratados más frecuentemente en el GE comparado con el GC, y que en el GE se tomaron un mayor número de decisiones en el área psicosocial. La probabilidad de que los problemas psicosociales y síntomas sufridos por los pacientes fueran tratados durante la visita al médico aumentó cuando el médico tuvo acceso a los resultado de la CVRS. El bienestar emocional y la disnea mejoraron en ambos grupos, y la CVRS fue similar en los dos grupos. Los pacientes estuvieron conformes con la atención brindada por el servicio de salud, sin diferencias entre el GE y el GC. Los factores determinantes de menores niveles de satisfacción fueron el estado de salud deteriorado, especialmente la falta de apetito, vivir solo, la menor edad del paciente y la mayor edad del médico.

Conclusión: El acceso a los resultados de las mediciones de CVRS aumenta la atención sobre los problemas psicosociales que sufren los pacientes, pero no influencia la CVRS o la satisfacción de los pacientes.

LIST OF PAPERS

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

I. Nicklasson M, Bergman B. Validity, reliability and clinical relevance of EORTC QLQC30 and LC13 in patients with chest malignancies in a palliative setting. *Qual Life Res*2007;16:1019-1028

II. Nicklasson M, Elfström ML, Olofson J, Bergman B. The impact of individual quality-of-life assessment on psychosocial attention in patients with chest malignancies: A randomized study. *Supp Care Cancer* 2013;21:87-95

III. Nicklasson M, Elfström ML, Bergman B. Quality-of-life and interaction of self-reported symptoms on consultation contents in patients with chest malignancies. Results from a randomized trial. Submitted

IV. Nicklasson M, Elfström ML, Bergman B. Satisfaction with care in patients with chest malignancies: predictive factors and outcome of a randomized trial. Submitted

CONTENT

ABBREVIATIONS

AUC	Area under the curve
BPI	Brief pain inventory
CASC	Comprehensive assessment of satisfaction with care
CAT	Computerized adaptive test
CG	Control group
CT	Computed tomography
EBUS	Endobronchial ultrasound
ED	Extensive disease
EG	Experimental group
EORTC	European organization for research and treatment of cancer
EORTC IN-PATSAT32	In-patients´ satisfaction with care questionnaire
EORTC OUT-PATSAT35	Out-patients´ satisfaction with care questionnaire
EORTC QLQ-C30	Core quality of life questionnaire for cancer care
EORTC QLQ-C30 and LC13	Core quality of life questionnaire and lung cancer module
EORTC QLQ-C15-PAL	Core quality of life questionnaire for palliative care
EUS	Esophageal ultrasound
FACT	Functional assessment of cancer therapy scale
FLIC	Functional living index-cancer
HADS	Hospital anxiety and depression scale
HRQL	Health related quality of life
LCSS	Lung cancer symptom scale
LD	Limited disease
MID	Minimal important difference
MRI	Magnetic resonance imaging
NNT	Number needed to treat
NSCLC	Non small cell lung cancer
PASQOC	Patient satisfaction and quality in oncological care
PET-CT	Positron emission tomography-computed tomography
PS	Performance status
PSQIII	Patient satisfaction questionnaire

QL	Global quality of life scale
RIAS	Roter interaction analysis system
ROC	Receiver operating characteristic
SATDR	Satisfaction with doctor index
SATGEN	Overall satisfaction with care
SATTOT	Total satisfaction index
6MWT	6-minute walk test
SCLC	Small cell lung cancer
SD	Standard deviation
SF-36	Short-form health survey
SSQ	Subjective significant questionnaire
TBNA	Transbronchial needle aspiration
TNM	T:tumour, N:node, M:metastasis
WHO	World health organization

1 INTRODUCTION

1.1 Lung cancer

Lung cancer is one of the most common malignancies and the leading cancer-related cause of death worldwide (1, 2). In 2011, 3,652 new cases of lung cancer were diagnosed in Sweden, of which 49% were in women. The age standardised incidence rate for women was 34 per 100 000 in 2011, with an annual increase of 2.9 % over the last 20 years. In men the incidence was 42.7 per 100 000 in 2011, with an annual decrease of 0.5 % over the last two decades (3). In patients under 70 years, the disease is more common in women. Lung cancer occurs predominantly in the elderly and most patients in Sweden are 60-80 years old at the time of diagnosis (4).

Etiology

Tobacco smoking is the main risk factor for lung cancer. Almost 90% of patients have a history of previous or present tobacco smoking (4). Other known risk factors are exposure to asbestos and radon, particularly in conjunction with tobacco smoking. Arsenic, nickel and nickel compounds, hexavelant chromium, bischloromethyleter and vinyl chloride used in chemicals and industrial processes have also been identified as lung carcinogens (5).

Prognosis

The overall prognosis is poor with 5-year relative survival rates of 13.6% for men and 19.4% for women in Sweden (2). Approximately 30% of patients can receive a potentially curative treatment but for the majority, lung cancer is not curable because of the advanced stage of the disease at diagnosis or comorbidity that limits curative treatment options such as surgery or chemo-radiotherapy (4).

Diagnostic procedure

The purpose of the diagnostic procedure is to establish the tumour type and extent of tumour growth, which are prerequisites for determining the best treatment modality for each patient. The image diagnostic tools for tumour staging include computed tomography (CT) scans of the thorax and abdomen, positron emission tomography with CT (PET-CT) and CT or magnetic resonance imaging (MRI) of the brain. Bronchoscopy is performed to obtain samples for histopathological and/or cytological analysis. Biopsies from central or peripheral tumour tissue enable analysis of molecular biological changes, which may be of significance for treatment selection. Cytology specimens are obtained from bronchoalveolar fluid and transbronchial needle aspiration (TBNA). In recent years, endobronchial ultrasound–guided (EBUS) and esophageal ultrasound-guided (EUS) needle aspiration have been increasingly used. Another diagnostic method is CT-guided transthoracic biopsy or fine-needle aspiration. In addition, biopsies or cytology specimens may be obtained from metastases.

Histological classification

Lung cancer can be divided into two main groups: small cell lung cancer (SCLC) and non small cell lung cancer (NSCLC). SCLC accounts for 15% of cases and has histological, clinical and therapeutic characteristics that differ from the other lung cancer types. NSCLC includes various subtypes, the three major being adenocarcinoma (40%), squamous cell carcinoma (20%) and large cell carcinoma (14%) (4).

Staging

At diagnosis, the tumours are classified according to the TNM (T: tumour, N: node, M: metastasis) staging system that assesses the anatomic tumour extent. The tumours in this study were classified in accordance with the 6th edition of the TNM classification (6). After this study was conducted, the TNM classification was updated to the 7th edition (7). One major change relevant to this study is the reclassification of pleural dissemination as M1 (metastasis) in the 7th edition (T4 in the previous edition). Thus, in the papers included in this thesis, tumours with

malignant pleural effusion were classified as IIIb (IV in the 7th edition). The updated TNM classification was adopted in Sweden in 2010.

According to the 6th edition of the classification system used in the present study, SCLC was divided into two categories, namely limited and extensive disease. Limited disease (LD) indicates tumour growth limited to one lung, the mediastinum and supraclavicular lymph nodes. Extensive disease (ED) is defined as distant metastases outside the thorax or pleural carcinosis. The updated TNM system should now be applied for the staging of SCLC, where LD corresponds to stages I-III and ED to stage IV (8).

Symptoms

Patients with lung cancer usually experience multiple disease-related symptoms, especially in the advanced disease stage. The most common symptoms are fatigue, dyspnoea, cough, appetite loss, pain and insomnia. Emotional problems such as anxiety and depression are also common (9-14). Cancer treatment may alleviate the disease-related symptoms, whereas they may cause other symptoms such as nausea/vomiting, hair loss, neuropathy and dysphagia. Symptoms increase in severity and frequency as the cancer progresses.

Treatment

The treatment of choice for patients with NSCLC is surgery. However, less than 20% of such patients can be operated, i.e. patients with early stage disease and acceptable heart-lung function. Despite the curative intention of surgical treatment and the documented beneficial effects of adjuvant chemotherapy, nearly 50% of operated patients experience tumour recurrence, generally 1-2 years after surgery (15-17).

The majority of patients with NSCLC have advanced stage disease at diagnosis. In these patients, the purpose of the treatment is palliative or life-prolonging. Chemotherapy increases short-term survival in patients with good performance status and no significant comorbidities. The treatment options usually include platinum-based combinations. In recent years and after this study was finished, new treatment concepts were introduced, namely targeted therapy with biological agents and

maintenance therapy (18-23). In addition, early integration of palliative care with standard cancer treatment is suggested to improve both quality of life and survival of patients with advanced NSCLC (24).

SCLC is characterized by aggressive growth with metastases at diagnosis and high sensitivity to chemotherapy and radiotherapy. Disease stage is one of the most important prognostic factors. With standard treatment the median survival for patients with limited disease is 15-20 months. The prognosis for patients with extensive disease is worse, the median survival with standard treatment being 8-13 months (25). Chemotherapy is the standard therapy for SCLC. Patients with limited stage disease are also treated with thoracic irradiation. Patients with limited or advanced disease stage with good partial or complete response after chemotherapy are offered prophylactic cranial irradiation (25-27).

1.2 Malignant pleural mesothelioma

Malignant pleural mesothelioma is often related to previous asbestos exposure. This malignancy is rare and seldom curable. In 2011, 111 patients with malignant pleural mesothelioma were diagnosed, of which 93 were men. The 5-year relative survival rates (95% CI) in 2004-2008 were 9% for men and 17% for women (28). Dyspnoea, chest pain and general symptoms such as appetite loss are common. As the disease progresses, symptoms usually worsen (29). Palliative chemotherapy is the treatment option for most patients (30, 31), while surgery combined with chemotherapy and radiotherapy has been proposed for patients in the early disease stage (32, 33). New treatment modalities, such as immunotherapy and gene therapy, are in the experimental phase (33).

1.3 Health related quality of life (HRQL)

Most patients with advanced lung cancer and mesothelioma experience multiple symptoms, the number and severity of which increase as the disease progresses (9, 10). These physical symptoms in combination with psychological distress have a negative impact on the patients' HRQL. Thus, the goals of cancer care in patients with advanced disease are symptom control, psychosocial support and improved or maintained HRQL, as well as increased short-term survival (34).

There is no gold standard definition of HRQL. 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 or infirmity". HRQL represents the influence of an illness and its treatment on physical and psychological functioning, as perceived by the patient. It has been defined as "patients' appraisal of and satisfaction with their current level of functioning compared with what they perceived to be possible or ideal" (35). HRQL is a multidimensional concept. Most investigators agree that it includes four dominant dimensions: 1) physical/occupational function, 2) psychological state, 3) sociability and 4) somatic comfort. HRQL is also a dynamic parameter and changes over time (36).

1.3.1 Modes of administration of HRQL measures

HRQL questionnaires are *interviewer* or *self administered*. In addition, alternative versions can be completed by *substitute respondents*, e.g. close relatives.

The collection of HRQL data by trained interviewers prevents missing items, but requires administrative resources such as training for the interviewers and allocation of time necessary for an interviewer to administer the instrument.

Self-administered instruments need less administrative resources, but require time and effort on the part of patients and there is an increased risk of missing data, misunderstanding instructions and of a low response rate due to poor health or language barriers.

Substitute respondents can provide HRQL information on behalf of patients who are too old and/or ill to concentrate on questionnaires. However, a weakness of this method is that substitute respondents´ perceptions of patients´ problems can differ from those of the patient her/himself (37, 38).

1.3.2 Psychometric properties of standardized HRQL measurement instruments

Evaluation based on standardized HRQL questionnaires allows comparison between groups of patients and has been widely implemented in clinical trials. The psychometric properties of such questionnaires are important for allowing the drawing of conclusions.

Validity refers to whether the instrument actually measures what it is intended to measure. The approaches to evaluating validity include content, construct and criterion validity. Content validity refers to the extent to which the domain of interest is comprehensively sampled by the items or questions in the instrument. Construct validity involves comparisons between measures and examinations of the logical relationships that should exist between a measure and characteristics of patients and patient groups. A method for testing construct validity is multitrait-multimethod analysis, which allows correlations between two or more measures tested by two or more methods. Convergent validity concerns whether a measure has a strong association with a related measure. Discriminative validity means identifying properties that can distinguish between two measures or groups of patients that are not related to each other. When testing criterion validity, the results of a measurement are compared with those of a standard measurement (37-40).

Reliability refers to the consistency of an instrument. It can be evaluated by measuring the degree of association among the items, e.g. by calculating the Cronbach alpha coefficient (41). Another method for establishing the reliability of an instrument is test-retest, which measures the correlation between the results obtained in the same individual on different occasions. In HRQL assessment, this method can only be used if the patient is clinically stable between measurements.

Responsiveness is the ability of the instrument to detect changes in patient HRQL over time. In the case of instruments used in clinical studies, it is important that the changes they demonstrate are not only statistically significant but also clinically relevant. Two approaches for testing responsiveness are evaluation of effect-size and minimal important difference (MID) (40). Distribution-based methods concern the statistical distribution of the study results. The most common approach is the use of effect-size, which is the mean difference between two measures over time, e.g. baseline and follow-up, divided by standard deviation at baseline, or between two groups, divided by standard deviation for the control group. Although originally used for estimating sample size, Cohen's recommendations for small (0.2-0.5), medium (>0.5-0.8) and large (>0.8) effect sizes are also employed for evaluating the responsiveness of HRQL data (42). MID estimates rely on information about threshold values from studies of minimal clinically meaningful changes and will be explained in more detail later in the thesis.

Interpretability. Different approaches have been proposed to help clinicians to attribute an easily understandable meaning to any given quantitative score. Distribution-based effect sizes can be used to interpret HRQL changes. With the anchor-based method, quality of life measures are compared with other measures, such as reference values from specific patient groups or the general population. One approach is to relate HRQL scores to known clinical parameters, e.g. the impact of pain on aspects of daily living. In addition, estimates of the minimal important difference provide information for the clinical interpretation of results (38, 43-46).

Feasibility refers to the patient and administrative burden. The former burden is the time and effort required to complete the self-administered questionnaire. The feasibility of an instrument can be assessed by measuring the time required to complete it and evaluating the extent of as well as the reasons for missing data. Administrative burden refers to the resources needed for administration of the instrument, e.g. a paper-and-pencil questionnaire or a computer-based instrument. Computer versions facilitate automatic analysis of the HRQL results and presentation of scale scores.

1.3.3 Types of HRQL measure

Generic instruments include health profiles and utility measures. Generic health profiles, such as the SF-36 Health Survey (47) measure a wide range of important HRQL aspects and facilitate comparison between diseases. However, generic profiles may not cover all aspects of a specific condition. The utility method, which indicates how much patients value or prefer different states of health, originated in economic and decision theory.

Specific instruments contain questions that are relevant to a disease, population or problem of primary interest, with greater responsiveness to HRQL changes compared to generic measures (37).

1.4 Assessment of HRQL in cancer patients

1.4.1 Use of HRQL assessment in clinical trials

The traditional clinical measures of cancer treatment outcomes are tumour response, progression free survival, toxicity and overall survival (48). During recent decades, increasing attention has been paid to the patients´ physical and psychosocial well-being during cancer therapy. Patients´ perceptions of treatment effects play a central role, particularly when the expected impact on improved survival is small and when the aim is to alleviate symptoms. HRQL is now considered an important outcome in clinical trials and its use recommended by oncology clinical research groups (49-52).

Several instruments such as the Functional Living Index-Cancer (FLIC) (53), the Functional Assessment of Cancer Therapy scale (FACT) (54) and the Lung Cancer Symptom Scale (LCSS) (55) have been developed to assess HRQL in patients with cancer in clinical trials.

The instrument most frequently used in cancer patients is the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life questionnaire (QLQ-C30), which was designed primarily for use in oncology clinical trials. The QLQ-C30, which is a “core questionnaire”, comprises 30 items that measure aspects

of functioning (physical, emotional, cognitive, social and role) and symptoms (fatigue, pain, dyspnoea, sleep problems, constipation, diarrhoea, appetite loss and nausea/vomiting) commonly reported by cancer patients, as well as financial problems and global health/quality of life.

Version I of the QLQ-C30 was validated in 305 patients with non-resectable lung cancer. The results were published in 1993 and demonstrated the good psychometric properties of the questionnaire (56). In the present study, we used updated versions of the questionnaire (57, 58).

In addition to the core questionnaire, a number of diagnosis-specific questionnaire modules have been developed (59, 60). A lung cancer specific module, the LC13, includes complementary measures of symptoms and side effects (dyspnoea, cough, site-specific pain, peripheral neuropathy, sore mouth, alopecia) related to lung cancer or its standard treatment (61).

The EORTC QLQ-C30 has been found to be reliable, valid and sensitive to change, thus is widely used in clinical trials (62).

1.4.2 Use of HRQL assessment in daily clinical practice

While frequently employed in clinical trials, patients´ self-reported HRQL is not routinely used in most cancer units and symptom assessment is generally made by healthcare professionals asking questions about symptoms and problems (63).

Is this the optimal method for obtaining information about patients´ physical and psychosocial concerns? Two studies revealed poor (64) or low to moderate (65) levels of agreement between patients´ self-reported HRQL ratings and those made by physicians and nurses. A comparison of data extracted from medical records regarding physicians' documentation of cancer symptoms in patients with different primary malignancies and the symptoms reported by the patients in the EORTC QLQ-C30 revealed that the only area of agreement was pain, whereas other symptoms and psychosocial problems were more frequently reported by patients than by physicians (66). In another study of the concordance between lung cancer symptoms rated by patients by means of a disease specific questionnaire and

physicians' ratings of the symptoms, the authors found that the physicians underestimated symptoms, particularly appetite loss and fatigue (67).

Furthermore, Levinson and Roter revealed that the frequency with which patients expressed psychosocial concerns during the encounters varied depending on physicians´ attitudes. Patients discussed more emotional and social problems with physicians who exhibited a positive attitude towards psychosocial issues (68).

In an observational study of patient-physician communication in a palliative setting, the authors found that the greater part of the conversations addressed medical/technical issues and only 23% of the visit was devoted to HRQL concerns. Furthermore, physicians did not discuss HRQL issues in 20-54% of the encounters with patients who experienced serious problems in this area. In particular, emotional issues and fatigue were not discussed (69). Concordant with these results, other recently published studies have demonstrated that a relatively small part of patient-physician encounters were devoted to emotional and social problems. One study illustrated that while HRQL issues were raised to some degree in every encounter and accounted for 25% of the conversation, only limited attention was paid to psychosocial areas (70). In another study, psychosocial issues were discussed in 27% of the consultations, regardless of the severity of emotional problems reported by patients. Furthermore, such discussions were generally initiated by the patients (71).

Benefits of assessing the patients´ HRQL in clinical practice

According to the research results discussed above, current clinical practice may underestimate patients' health problems. Systematic HRQL evaluation can enhance the likelihood that the physician will identify relevant issues as well as help patients to articulate their concerns and enhance patient-physician communication (69). In a study using pre-test/post-test intra-individual comparisons, the availability of HRQL ratings during consultations resulted in physicians posing an increased number of questions about daily activities, emotional problems and work related issues (72).

It has been suggested that real time HRQL assessment could facilitate the clinical management of patients´ symptoms and problems as well as symptom monitoring

and evaluation of responses to medical treatment and other interventions aimed at alleviating such problems (63, 73).
Finally, evaluation of HRQL can help physicians to predict patient survival. Using the FLIC questionnaire, Ganz et al. demonstrated a significant relationship between HRQL scores and survival time in patients with lung cancer (74). When studying patients with inoperable loco-regional NSCLC, psychosocial well-being and general symptoms emerged as the best predictors of survival (75).

Barriers to be overcome

Although HRQL evaluation may have the potential to improve patient-physician interactions as well as cancer care, most oncology units have not yet implemented it (63).

One of the barriers is that *physicians´ attitudes* towards HRQL assessment vary. While most physicians recognize the importance of assessing HRQL in randomized clinical trials, they can be reluctant to formally collect HRQL data in clinical practice and question the clinical validity of the assessment instruments (76). Other reasons for limited acceptance are lack of time and resources, concerns about patient compliance and the assumption that physicians can adequately assess patient HRQL (77). In addition, physicians generally expect that patients will raise psychosocial concerns themselves (78). As a result of these attitudes, psychosocial problems may be overlooked. Therefore, one of the aims of this thesis is to investigate whether the use of HRQL data can lead to greater focus on psychosocial concerns.

Practical aspects. Although a prerequisite for HRQL assessment in clinical trials is research logistics that facilitate data collection and analysis, the lack of such resources in clinical practice makes the routine use of HRQL evaluation challenging.
Pragmatic strategies are required to facilitate the incorporation of HRQL assessment in routine clinical patient-physician encounters, without increasing the burden for patients and healthcare professionals.
Collection of HRQL data by means of traditional paper questionnaires does not allow a quick analysis of the results or calculation of the scale/item scores for presentation

to the physician in the form of a summary, which is indispensable for her/his evaluation of the HRQL ratings. In contrast, computer-based systems can automatically translate the patients´ responses to scores, producing graphics or reports that can be printed out and presented to the physicians "in real time" at consultations. For the purpose of this study we developed a digital response system, which is described in Paper II.

Interpretation of HRQL data. Although clinicians are used to interpreting the results of laboratory tests and radiographic methods as well as pathological tests as clinical relevant or not, they experience difficulties when trying to interpret HRQL ratings. Two methods for overcoming this barrier have been described. The first relates the HRQL scores to clinical variables (anchors) that are familiar to the physicians, i.e. radiographic findings or blood tests. The second assesses whether HRQL changes are not only statistically but also clinically meaningful. The minimal important difference (MID) has been defined as the smallest score difference in a HRQL scale/item perceived as beneficial by patients (44). From the clinicians´ perspective, clinical significance is the smallest effect size that leads to a recommendation of treatment or a change therein (79).

Osoba et al. studied the MID in the EORTC QLQ-C-30 using a subjective significance questionnaire (SSQ) as an independent measure in patients with breast cancer or SCLC who participated in clinical trials. The SSQ was developed to assess the patients´ perception of change in physical, emotional and social functioning as well as global quality of life since they last completed the QLQ-C30. The response alternatives comprise a 7 category scale ranging from "very much worse" to "very much better". In the case of patients who perceived small changes in the SSQ, the mean change in scores in the corresponding QLQ-C30 domains was about 5 to 10, for moderate changes about 10 to 20 and for large changes >20. However, the magnitude of change varied with the diagnosis, e.g. in the global QL domain, one-category difference in the SSQ rating was associated with a 6.9 change in the mean score of patients with breast cancer and 10.2 in patients with SCLC (80). A later study of patients receiving treatment for lung cancer demonstrated that the MID varied depending on whether the health status improved or worsened as well as on

the scale itself. As the MID values were in the same range as in the earlier study, it was proposed that they can be used to compare treatment effects (81).
Whereas MID has been studied in patients undergoing cancer treatment in clinical trials, the usefulness of these results in clinical practice remains to be proven (82-84). Furthermore, results presented as mean score changes are somewhat difficult to interpret. Additional ways of describing HRQL results can be used. Cut-off points for MID can be established in order to determine the proportion of patients who improve as a consequence of a therapeutic intervention, thus rendering the data easier to understand. Consequently, the number of patients needed to treat (NNT) in order for one patient to benefit can be calculated (85, 86).

It has been suggested that even when cut-off values are not available, repeated HRQL measures that monitor symptoms and functioning problems as well as specific treatment effects could facilitate an intuitive analysis of clinical significance (84).

When this study was commenced, no randomized studies investigating the usefulness of HRQL data in routine clinical practice were published. In one smaller, controlled but non-randomized study, patients in the control group completed a paper version of an HRQL questionnaire after the encounter with the physician, while those in the experimental group completed a computerized version of the HRQL questionnaire, with a report being presented to the physician and nurse before the consultation. The results indicated that HRQL topics were discussed more frequently in the experimental group compared to the control group (87).

1.5 Satisfaction with care

The assessment of patient perceptions of quality of care has gained increasing importance in oncology (88-92). Patient satisfaction can be defined as the degree to which their expectations of medical care are fulfilled (93-95). Feedback from patients

can also be used as a measure of quality of care and help to identify areas where improvements are warranted (91, 96). Aspects of the care process, such as healthcare professionals' performance and communication skills as well as the attention paid to patients´ psychosocial needs, have been related to patient satisfaction with care (90, 97, 98). However, satisfaction can vary in line with the patients´ health status (99, 100), demographic characteristics (88, 94, 98, 101), tumour stage (102) and tumour type (103) .

When this study was started, data on satisfaction with care in patients with lung cancer were sparse. A few descriptive, non-interventional studies with mixed cancer diagnoses including lung cancer were reported (89, 104, 105). The effects of HRQL assessment on physician behaviour and satisfaction with care in patients with lung cancer were investigated in a smaller controlled study (87). No intervention effects on patient satisfaction were observed.

Instruments for evaluation of patient satisfaction with cancer care in clinical trials include multidimensional questionnaires such as the Patient Satisfaction Questionnaire (PSQIII) (106), the Patient Satisfaction and Quality in Oncological Care (PASQOC) (107), the EORTC IN-PATSAT32 (108) and the OUT-PATSAT35 (109), as well as study-specific instruments (100).

The EORTC IN-PATSAT32 was developed by the EORTC Quality of Life Group for assessing cancer patients´ perception of the quality of hospital-based care. At the start of the present study, this questionnaire was known as the Comprehensive Assessment of Satisfaction with Care (CASC) and was the only internationally validated instrument available in Swedish for assessment of patient satisfaction with care (110).

The EORTC IN-PATSAT32 comprises 32 items, which are aggregated into eleven multi-item and three single-item scales. It assesses cancer patients´ perception of the quality of doctors´ and nurses´ technical and interpersonal skills, information and availability, aspects of care organization (exchange of information, hospital access and waiting time), hospital environment (comfort) and general satisfaction with the

care. Each item has five response alternatives (poor, fair, good, very good and excellent). All scores are linearly transformed into a 0-100 scale, where a higher score indicates a greater level of satisfaction.

After this study was conducted, an adapted version of the EORTC IN-PATSAT32, the EORTC OUT-PATSAT35, was developed to assess cancer patients´ satisfaction with their ambulatory care. Validation studies of the French and Spanish versions of the instrument have been published (109, 111).

2 AIM

The general aim was to evaluate whether the prospective use of individual HRQL measures in oncology clinical practice would have any influence on patient-physician communication, clinical decision-making, HRQL and satisfaction with care.

Methodological research aim

- To determine the psychometric properties and clinical relevance of the EORTC QLQ-C30 and LC13 in a palliative care population of patients with chest malignancies

Clinical research aims

- To establish a basis for clinical interpretation of HRQL measures in the target population
- To investigate whether the prospective use of individual HRQL data has an impact on patient-physician communication
- To determine whether the prospective use of individual HRQL measures has an influence on diagnostic and therapeutic interventions
- To study the association between patient-reported HRQL and the topics discussed during patient-physician consultations
- To examine whether access to patient-reported HRQL has an effect on patient HRQL over time
- To establish whether access to patient-reported HRQL influences patient satisfaction with care
- To identify predictors of patient satisfaction with care

3 STUDY POPULATION

The study population comprised two sub-sets of patients with incurable chest malignancies who received medical care at Sahlgrenska University Hospital in Gothenburg. Overall, 283 patients were included, of whom 202 had NSCLC, 56 SCLC and 23 malignant pleural mesothelioma. The latter were included due to the fact that their disease-related symptoms, prognosis and palliative treatment options are to some extent similar to those of patients suffering from lung cancer. In addition, 2 patients with lung metastases caused by colon cancer diagnosed during the course of the study were retained in the analysis (Paper I). The patients who participated in the study were included during two subsequent periods between November 1999 and May 2005.

Paper I: The first 112 consecutively included patients were studied regarding the clinical validity of the EORTC QLQ-C30 and LC13 in patients not receiving chemotherapy. The inclusion criteria were: a diagnosis of lung cancer or malignant pleural mesothelioma not amenable to curative or life prolonging treatment, a period of six or more weeks without chemotherapy, ability to understand and respond to questionnaires and signed informed consent. Both out and in-patients were included. Palliative radiotherapy and supportive care including pharmacological treatment for symptom control were accepted.

Papers II-IV: 171 consecutive out-patients participated in a randomised trial to study the impact of individual HRQL assessment on the topics discussed during consultations, clinical decision making, HRQL over time and patient satisfaction with care. The inclusion criteria were: advanced-stage lung cancer or mesothelioma, expected survival time of at least 3 months, ability to understand and respond to questionnaires and signed informed consent. When indicated, patients in this sub-sample received palliative chemotherapy and/or palliative radiotherapy.

4 METHODS

4.1 Study design

4.1.1 Paper I

Patients with chest malignancies that were not amenable to curative or life prolonging treatment were consecutively enrolled. The main purpose of the study was the clinical evaluation of the EORTC QLQ-C30 in the target population. At baseline, the patients completed the Swedish version of the EORTC QLQ-C30 (version 2.0) and LC13. Symptom questionnaires as well as laboratory and exercise tests were also employed as specified in Paper I.

After the encounter with the physician, the patients were assessed by the social worker who conducted a semi-structured interview in order to evaluate the quantity and quality of their social activity and support. Quantity was scored on a five point scale ranging from “no support/activity” to “much support/activity”, while quality was scored on a five point scale ranging from “very poor support/activity” to “very good support/activity”.

Three weeks after the baseline assessment, patients with a stable performance status completed the EORTC QLQ-C30 and LC13 a second time.

In addition, remaining survival times for the patients were estimated.

4.1.2 Papers II-IV

Patients with chest malignancies were recruited consecutively at their first appointment in the outpatient clinic and randomised to one of two groups with different HRQL assessment strategies and methods.

Patients in the experimental group (EG) completed a computerized version of the EORTC QLQ-C30 (version 3.0) and LC13 using a digital table interface (Figure 1). When necessary, the research nurse assisted the patients. Response data were automatically saved in a commercially available database application (File Maker

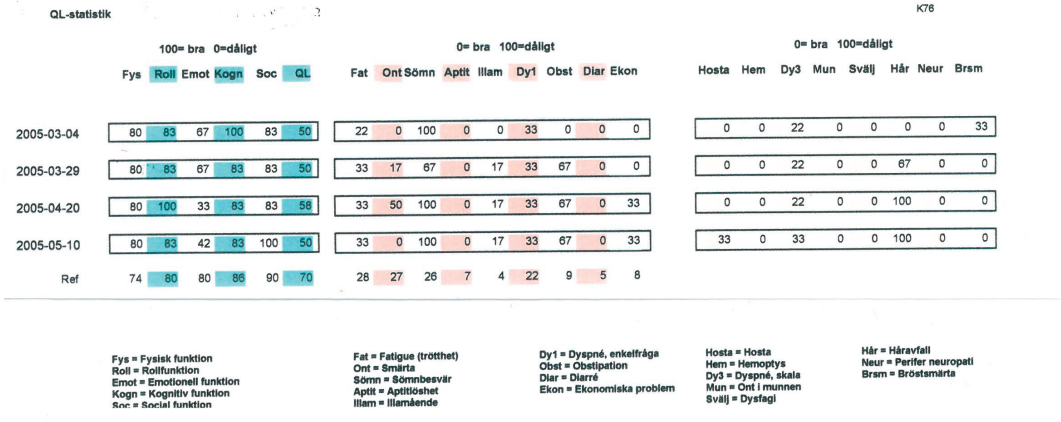
Pro®), which was adapted to calculate aggregated scale scores. A summary of the scores was printed out and presented to the consulting physician before her/his encounter with the patient. Results of measurements at subsequent patient-physician encounters were added to the previous reports in order to facilitate evaluation of the patients´ symptoms and functioning over time (Figure 2). The reports also included age and gender specific reference scores from a large sample of the Swedish population (112). Prior to the study, all participating physicians underwent a brief education on the dimensionality of the EORTC questionnaire and interpretation of the scores. In the course of the study, they were reminded to take account of the HRQL reports during consultations, although it was left to their discretion to decide on the actions necessary.

Patients in the control group (CG) completed a standard paper version of the same questionnaire before the consultation with the doctor. These questionnaires were not presented to the physicians, but stored for analysis.

The patients´ HRQL was assessed by means of the EORTC QLQ-C30 and LC13 at scheduled visits over a 2-3 month period. When the study was initiated, an evaluation period of 8 weeks was stipulated, but after 6 months, the evaluation period was extended to 12 weeks in order to enhance the responsiveness of outcome measures to the study intervention and better match the standard treatment duration in patients receiving chemotherapy. For the purpose of comparing HRQL across the randomization groups and over time, completed questionnaires were ordered and labelled based on the time from randomization. Four time intervals were established, i.e. T1: baseline, T2: day15-42, T3: day 43-63 and T4: day 64-84. If two questionnaires were completed within the same interval, the first was generally used for the analysis.

The physicians were not randomized, but saw patients in both groups.

Figure 1. *The digital table interface*



QL-statistik

K76

	100= bra 0=dåligt						0= bra 100=dåligt								0= bra 100=dåligt							
	Fys	Roll	Emot	Kogn	Soc	QL	Fat	Ont	Sömn	Aptit	Illam	Dy1	Obst	Diar	Ekon	Hosta	Hem	Dy3	Mun	Svälj	Hår	Neur	Brsm
2005-03-04	80	83	67	100	83	50	22	0	100	0	0	33	0	0	0	0	0	22	0	0	0	0	33
2005-03-29	80	83	67	83	83	50	33	17	67	0	17	33	67	0	0	0	0	22	0	0	67	0	0
2005-04-20	80	100	33	83	83	58	33	50	100	0	17	33	67	0	33	0	0	22	0	0	100	0	0
2005-05-10	80	83	42	83	100	50	33	0	100	0	17	33	67	0	33	33	0	33	0	0	100	0	0
Ref	74	80	80	86	90	70	28	27	26	7	4	22	9	5	8								

Fys = Fysisk funktion
Roll = Rollfunktion
Emot = Emotionell funktion
Kogn = Kognitiv funktion
Soc = Social funktion

Fat = Fatigue (trötthet)
Ont = Smärta
Sömn = Sömnbesvär
Aptit = Aptitlöshet
Illam = Illamående

Dy1 = Dyspné, enkelfråga
Obst = Obstipation
Diar = Diarré
Ekon = Ekonomiska problem

Hosta = Hosta
Hem = Hemoptys
Dy3 = Dyspné, skala
Mun = Ont i munnen
Svälj = Dysfagi

Hår = Håravfall
Neur = Perifer neuropati
Brsm = Bröstsmärta

Figure 2. *Example of a HRQL report*

Patient-physician conversations during planned study visits were recorded on disk and analysed in order to evaluate the focus on symptoms and psychosocial functioning. The statements made by the physicians and the patients were categorized into predefined content categories as described in Paper II and analysed quantitatively. We used an adapted version of the Roter Interaction Analysis System (RIAS) (113). The content categorization method was validated by an independent coder (psychologist) in a sub-sample of patients.

Data on diagnostic and therapeutic interventions initiated during the study period were collected from the medical records and coded into predefined categories corresponding to the conversation content categories. This coding method was validated by a senior physician who was not involved in the care of the participants.

The patients completed the EORTC IN-PATSAT32 questionnaire after the last consultation in the study.

4.2 Statistical methods

Scale scores in the EORTC QLQ-C30 and EORTC IN-PATSAT32 questionnaires were calculated and transformed into a 0-100 scale in accordance with the EORTC guidelines (114). For functioning scales and the global quality of life scale in the EORTC QLQ-C30, a higher score corresponds to better functioning. In the case of symptom scales, a higher score represents worse symptoms. In the EORTC IN-PATSAT32, a higher score indicates a greater level of satisfaction with care.

Statistical methods are summarized in Table 1. When normal distributions could not be found or anticipated, non-parametric methods were used for analysis. P-values of <0.05 were considered statistically significant in all papers.

Table 1. Statistical methods used in the papers

Methods	Papers			
	I	II	III	IV
Parametric				
Cronbach´s alpha	X			X
Repeated ANOVA measurements	X			
Pearson correlation coefficient	X			
Multitrait analysis	X			
Non-parametric				
Spearman correlation analysis			X	X
Mann Whitney U-test	X	X	X	X
Kruskal-Wallis test	X	X		
Mantel-Haenszel test		X		X
Fisher's exact test				X
Signed rank test			X	X
Bivariate logistic regression				X
Multiple regression	X			X
Multiple logistic regression				X
ROC curve				X

Paper I

The reliability of the multi-item scales was tested by calculating the Cronbach´s alpha coefficient (41). In addition, test-retest for reliability was established using repeated ANOVA.

Construct validity was determined by means of multitrait analysis. Evidence of item convergent validity was defined as a correlation between an item and its own hypothesized scale of at least .40 (corrected for overlap).

Correlations with known clinical parameters and established questionnaires for symptom assessment were described as strong (>.60), substantial (>.40) or moderate (>.20), based on assumed effect size and modified from Cohen (42).

Non-parametric statistics were used for comparison of differences between groups.

It was expected that conceptually related measures (e.g. the EORTC physical functioning scale and a standardised 6-minute walk test or the EORTC emotional

function scale and the HADS) would correlate more strongly with each other than with measures that were not directly related.

Sample size calculation (Papers II-IV)

The EORTC QLQ-C30 global quality of life (QL) scale was used for sample size calculations, the hypothesis being that a score difference of >10 corresponds to a clinically relevant group difference (80). A minimum of 162 patients were required based on 0.8 power and a *p*-value of 0.05 (two-sided) to detect this difference, with an assumed standard deviation of 22 (56) and a 20% dropout rate.

Paper III

Correlations between HRQL measures and the corresponding conversation content categories were calculated in two ways. First, an *inter-individual* correlation analysis between the mean individual values for each HRQL category over time and the mean number of coded statements made by the patients and the physicians over time was performed. An interaction analysis of inter-individual correlations by randomization group was undertaken. All patients, irrespective of the number of assessments over time, were included in this evaluation.

Second, *intra-individual* correlation slopes were estimated, using pairwise comparisons between a specific HRQL domain and the occurrence of the corresponding conversation category at each time of assessment. Mean values for individual slopes were calculated. This analysis included all patients who had at least two paired QLQ-C30 and LC13 measures and audio-recorded consultations over time.

Paper IV

In the exploratory prediction analysis, a number of variables (54 in all) were screened as independent variables (predictors), including demographic and clinical factors in addition to those that mirrored the care process, as described in Paper IV.

We used three measures based on the IN-PATSAT32 questionnaire as dependent variables in the prediction analysis. First, we employed the original overall quality

rating item (hereafter called SATGEN). In addition, we calculated two aggregated score indices: one satisfaction-with-doctor index (SATDR), summarising the four physician-related scales (physicians' technical and interpersonal skills, information and availability) and one total satisfaction index (SATTOT) summarising the entire questionnaire, with the exception of the overall quality rating item to avoid conceptual overlap.
The rationale for creating the two summary indices was to limit the number of comparisons in order to avoid random significance effects and to increase the variance in the dependent measures.

Parametric stepwise regression was used for multivariate analysis of the SATTOT index, which could be transformed to normal distribution by replacing the original values with rank orders.
As the SATDR and SATGEN measures could not be transformed to normal distribution, the response scores were dichotomised and logistic regression analysis was performed. Cut-off scores were defined by the distribution of score values aimed at distinguishing between satisfied and less satisfied patients and ensuring at least 30 individuals in the less satisfied category. As the SATGEN measure score distribution was highly skewed, only top scores (100) were defined as "high satisfaction", while scores of <100 were deemed "less satisfied". As regards the SATDR index, scores of ≥80 were defined as "high satisfaction", while values of <80 were classified as "less satisfied".

An area under the ROC-curve (AUC-statistics) was calculated for describing the goodness of predictors. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular cut off value for prediction of the outcome. The area under the curve (AUC) is a measure of how well a parameter can discriminate between two groups. An AUC value between 0.7 and 0.9 is considered acceptable and sufficiently strong in most cases, while an AUC of >0.9 indicates a very strong model (115).

5 RESULTS

5.1 Psychometric properties of the EORTC QLQ-C30 and LC13 in a palliative setting (Paper I)

5.1.1 Patients

112 outpatients and hospitalized patients with advanced lung cancer or malignant pleural mesothelioma were consecutively enrolled. Patients´ demographic and clinical characteristic are presented in Table 2. Compare to previously published data from lung cancer patients receiving chemo-and/or radiotherapy, the patients in the present study had worse scores on almost all scales and symptom items (116).

5.1.2 Reliability

Internal consistency

With the exception of cognitive functioning, all the multi-item scales had an internal consistency of .70 or more, which is generally accepted as the minimum required reliability level for group comparisons (117). The alpha-coefficient for the cognitive functioning scale, which comprises two items that assess memory and concentration difficulties was only .57. An analysis of individual questionnaires revealed contradictory responses (with a maximum difference of 3 item score points) from four patients to the above-mentioned two items.

Test-retest

Forty eight patients who were deemed to have maintained their performance status completed the EORTC questionnaire three weeks after the start of the study. No statistically significant differences were observed in the functioning scale scores between baseline and three weeks, indicating the reproducibility of the questionnaire in clinically stable patients.

Table 2. Patient characteristics at baseline, sub-population I (n=112)

Sex, proportion females	40%
Age, median (years)	68.5 (44-87)
≥70 years	53 (48%)
Performance status (WHO)	
0	4 (4%)
1	35 (31%)
2	43 (38%)
3	30 (27%)
Diagnosis	
SCLC	16 (24%)
NSCLC	85 (76%)
Mesothelioma	9 (8%)
Lung metastases	2 (2%)
Previous treatment	
Chemotherapy	28 (25%)
Radiotherapy	22 (20%)
Chemo- and radiotherapy	22 (20%)
Surgery	10 (9%)
None	30 (27%)
Time from diagnosis, median (range)	31 weeks (12-229)

5.1.3 Validity

Construct validity

The multi-trait analysis demonstrated satisfactory item-scale correlations, with the exception of five scaling errors in the item measuring difficulty concentrating in the cognitive functioning scale.

Criterion validity

Gender had no significant interaction effect on any of the measures in the HRQL questionnaire. Patients <70 years of age reported lower social functioning scores and more financial impact of the disease and treatment compared to older patients.

In general, patients with poor performance status reported lower levels of functioning and more symptoms. A difference of one score level in the WHO performance scale

corresponded to a mean score difference of 27.6 in the QLQ-C30 physical functioning scale and 16.5 in the global QL scale.

During a standardised 6-minute walk test (6MWT), 58 patients walked a distance >200 m, 30 walked a distance ≤200 m, while 24 did not manage to walk at all, the distance being recorded as 0. In general, patients who performed better during the walk test had more favourable scores in both the functioning and symptom scale of the HRQL questionnaire, in particular physical functioning, followed by fatigue, role functioning, global QL and social functioning. The relationship between the 6MWT and variance of dyspnoea was of borderline significance (p =0.053). A similar pattern was seen in a correlation analysis that employed walking distance as a continuous variable, where there was a strong correlation (r = .77) with EORTC physical functioning and substantial correlations (r > .4) with fatigue, role functioning and global QL. A modest correlation was seen with dyspnoea (r = .21; p =0.037).

Spirometry was performed in 96 patients. In general, patients with an *FEV1* < 50% predicted (n = 27) scored worse in functioning and symptom scales than did those with an FEV1 ≥ 50% predicted (n = 61), particularly physical functioning and global QL.
Variance analysis revealed no significant FEV1 interaction effect on the QLQ-C30 single-item dyspnoea measure (p =0.054), although such an effect was seen with regard to the QLQ-LC13 three-item dyspnoea scale (p =0.03). In concordance with these results, correlations with the QLQ-C30 and LC13 dyspnoea measures were modest, although statistically significant (r = .33; p < .01, and r = .24; p < .05, respectively).

Patients with a haemoglobin level (Hb) of <120 g/l experienced significantly worse fatigue, appetite loss, dyspnoea, nausea/vomiting, global QL and role, physical and social functioning compared to patients with a Hb of ≥ 120 g/l.

Patients with a percutaneous oxygen saturation of <92% scored significantly worse in the physical, role and social functioning scales and reported more dyspnoea,

fatigue, appetite loss, pain, sleep disturbances and constipation than those with a percutaneous oxygen saturation of ≥ 92%.

QLQ-C30 functioning scores (with the exception of cognitive functioning) significantly predicted the remaining survival time. Overall survival was significantly worse in patients reporting functioning scores of <60 or global QL scores of <50 compared to those with higher scores. QLQ-C30 scores were related to the remaining survival time, with scores worsening especially during the last 30 days (Figure 3).

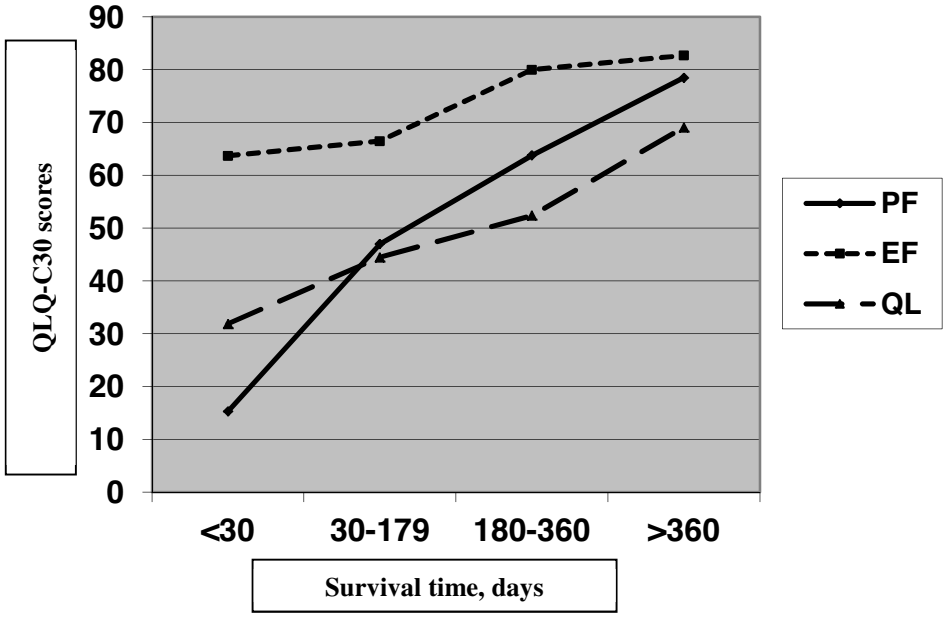


Figure 3. *QLQ-C30 functioning and global quality of life by remaining survival time. Abbreviations: PF-physical functioning, EF-emotional functioning, QL-global quality of life*

Concurrent validity

A strong correlation was seen between emotional functioning and the Hospital Anxiety and Depression scale (HADS) (118) anxiety scale. The HADS depression scale correlated with all functioning scales in the QLQ-C30.

The Brief Pain Inventory (BPI) (119) intensity sub-scale correlated strongly with the QLQ-C30 pain scale and BPI function sub-scale correlated substantially with all functioning scales and the global QL scale.

There were no significant associations between the social workers' ratings of social support and social activity and self-reported social functioning in the QLQ-C30.

5.2 Impact of individual assessment of HRQL on attention to symptoms and psychosocial problems (Papers II-III)

5.2.1 Patients

During a 28-month period, 335 consecutive patients with advanced lung cancer or pleural mesothelioma were assessed for eligibility. Of these, 173 (75% of eligible patients) were randomized to either the experimental group (EG; n=85) or the control group (CG; n=88). Two patients were later excluded due to withdrawal of consent and changed diagnosis.

No significant differences were found between groups in terms of patients' baseline characteristics and treatment (Table 3).

5.2.2 Study visits

740 encounters were documented for the 171 randomized patients, of which 650 were planned outpatient visits (EG 327; CG 323) and 90 emergency care visits (EG: 47 visits by 19 patients; CG: 43 visits by 11 patients).

Figure 4. *Flow chart of study participants*

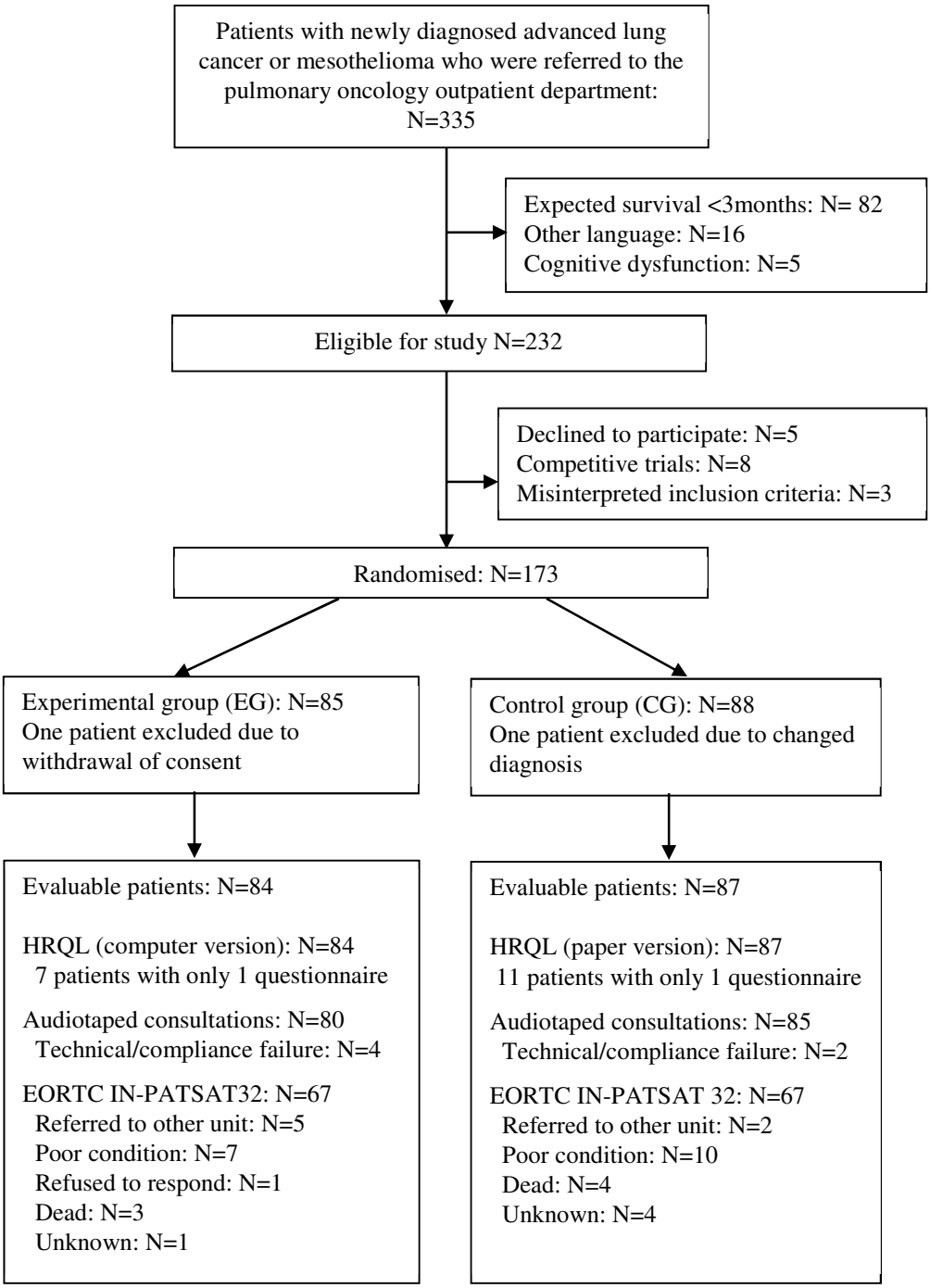


Table 3. Baseline characteristics and treatment, sub-population II (n=171)

Variables	EG (n=84)	CG (n=87)
Age, median (years)	68	67
Gender, proportion females	37%	39%
Tumour type, proportion with NSCLC	73%	65%
Performance status (WHO)		
0	14%	18%
1	51%	47%
2	22%	25%
3	13%	8%
Treatment		
Chemotherapy	77%	78%
Radiotherapy	43%	40%
Supportive care only	10%	9%

5.2.3 HRQL questionnaires

595 sets of EORTC QLQ-C30 and LC13 questionnaires were completed by the patients (EG: 300 computerized questionnaires presented to the physician; CG: 295 paper questionnaires stored for analysis). Each patient completed between one and six sets of questionnaires.

Self-reported symptoms and functioning in the EORTC QLQ-C30 and LC13 at baseline revealed no significant differences between the two groups, with the exception of the dyspnoea item in the QLQ-C30. Patients in the CG reported a higher level of dyspnoea compared to patients in the EG. However, there was no difference between the two groups regarding dyspnoea scores in the LC13. The functioning and symptoms scores are presented in Tables 4 and 5.

Table 4. Mean QLQC30 functioning and symptom scores (SD) by randomization group at baseline.

Domain	Experimental group N=84 Mean (SD)	Control group N=87 Mean (SD)	*p* value EG vs CG
Physical function	64.3 (26.4)	64.0 (20.6)	0.94
Role function	46.0 (36.0)	52.3 (33.9)	0.24
Social function	71.0 (29.4)	71.3 (29.4)	0.95
Cognitive function	77.8 (24.2)	82.9 (21.0)	0.14
Emotional function	64.3 (23.5)	66.1 (24.5)	0.62
Global QL	51.7 (26.6)	50.2 (20.9)	0.69
Dyspnoea	50.0 (33.3)	60.3 (28.6)	0.03*
Pain	29.6 (29.5)	28.7 (29.2)	0.85
Fatigue	46.6 (29.9)	46.8 (25.9)	0.95
Sleep disturbance	37.3 (37.1)	37.9 (34.5)	0.90
Appetite loss	34.9 (36.5)	24.9 (29.7)	0.05
Nausea/vomiting	9.9 (19.4)	8.2 (15.4)	0.53
Constipation	23.8 (32.5)	14.9 (27.3)	0.06
Diarrhoea	9.1 (22.2)	8.4 (19.2)	0.83
Financial problems	7.1 (19.4)	10.7 (24.9)	0.30

Table 5. Mean QLQ LC13 symptom scores (SD) by randomization group at baseline.

Domain	Experimental group N=84 Mean (SD)	Control group N=87 Mean (SD)	*p* value EG vs CG
Cough	41.3 (33.4)	42.7 (28.0)	0.76
Haemoptysis	6.3 (16.7)	6.0 (15.5)	0.89
Dyspnoea	39.9 (26.8)	42.4 (23.5)	0.53
Sore mouth	4.0 (12.0)	7.0 (18.7)	0.20
Problems swallowing	8.3 (18.6)	5.4 (14.3)	0.25
Periph. Neuropathy	13.5 (24.3)	9.0 (18.1)	0.18
Hair loss	2.8 (12.9)	5.2 (20.2)	0.35
Chest pain	25.0 (29.7)	23.5 (25.6)	0.73
Arm pain	25.3 (31.4)	22.0 (31.1)	0.50
Pain elsewhere	26.7 (31.5)	27.4 (33.2)	0.88

HRQL over time

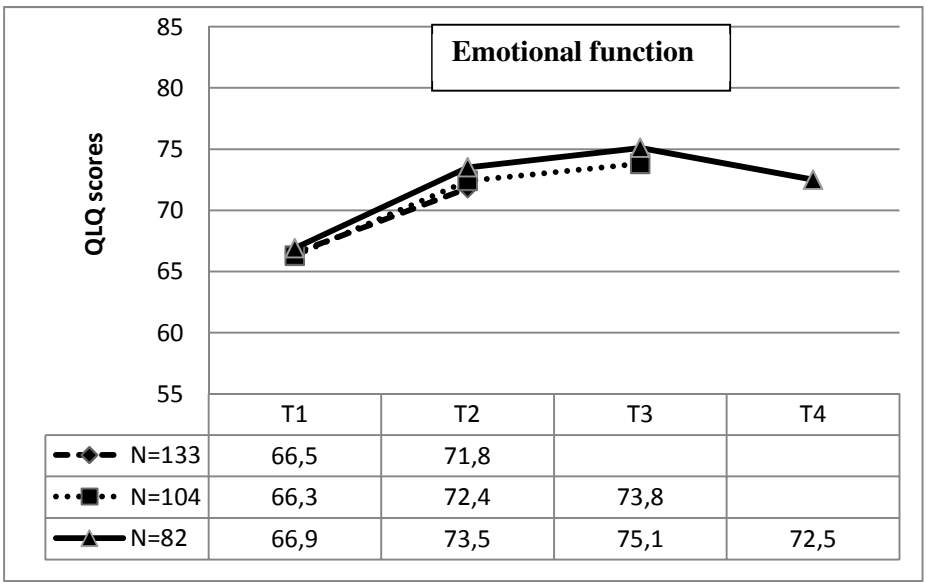
In order to reduce the risk of random significances due to multiple comparisons, and to adequately match the defined conversation content categories, selected core HRQL dimensions and symptoms (i.e. physical, emotional and social function, global quality of life, pain, dyspnoea, fatigue and appetite loss) were used for the longitudinal analysis. The mean values of these core functioning and symptom scores at baseline and at intervals up to 12 weeks for each randomisation group are presented in Table 6. No significant group differences were observed at any point.

Table 6. Mean QLQC30 and LC13 functioning and symptom scores (SD) for each randomization group at various time intervals up to 12 weeks.

	T1 (n=171)	T2 (n=136)	T3 (n=116)	T4 (n=104)
Physical function				
CG	64.0 (20.6)	65.7 (23.2)	68.6 (2.8)	66.5 (22.6)
EG	64.3 (26.4)	62.8 (24.0)	67.8 (25.9)	65.2 (24.7)
Emotional function				
CG	66.1 (24.5)	74.2 (20.6)	75.2 (20.3)	75.5 (18.7)
EG	64.3 (23.5)	69.6 (27.4)	72.7 (24.4)	72.0 (28.3)
Social function				
CG	71.3 (29.4)	75.9 (26.5)	73.1 (27.4)	74.1 (238)
EG	71.0 (29.4)	69.6 (31.9)	70.1 (30.1)	70.3 (31.2)
Global QL				
CG	50.2 (20.9)	57.3 (21.2)	56.3 (23.5)	51.4 (23.3)
EG	51.7 (26.6)	53.6 (24.8)	57.3 (20.9)	55.3 (22.9)
Pain				
CG	28.7 (2.2)	23.8 (26.0)	21,0 (26,6)	24.1 (27.7)
EG	29.6 (29.5)	25.5 (28,9)	26.4 (30.3)	23.9 (25.4)
Fatigue				
CG	46.8 (25.9)	43.2 (25.4)	41.0 (23.9)	44.2 (33.5)
EG	46.6 (29.9)	48.4 (26.8)	41.0 (28.5)	42.4 (26.3)
Appetite loss				
CG	24.9 (29.7)	27.9 (30.8)	27.6 (31.9)	26.5 (31.2)
EG	34.9 (36.6)	28.4 (33.7)	22.4 (30.2)	26.7 (34.2)
Dyspnoea LC13				
CG	42.4 (23.5)	35.2 (23.3)	34.8 (20.2)	36.6 (22.8)
EG	39.9 (26.8)	35.9 (24.7)	29.7 (22.1)	31.5 (22.4)

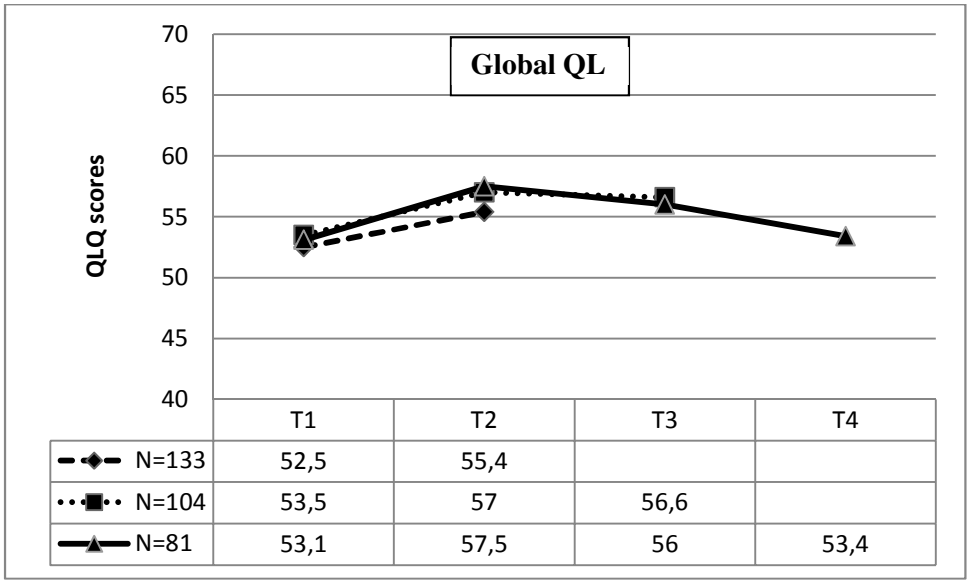
T1= baseline assessment, T2=follow-up assessment day 15-42, T3= follow-up assessment day 43-63, T4=follow-up assessment day 64-84

In the whole study population, significant improvements were observed in emotional functioning (p<0.01 at all follow-up measurements) (Figure 5), but there were no significant interaction effects of randomization on changes over time. As for global QL, no significant changes over time (Figure 6) or group differences were seen. Of the symptoms measured with the QLQ-LC13, significant improvements in dyspnoea were evident in the total study population (p<0.05 at T2 and T4, p=0.0002 at T3) (Figure 7), with no difference between the randomized groups. Similarly, significant improvements were observed in cough, haemoptysis and chest pain at all follow-up measurements, again without any interaction effects of randomization. Patients in both randomized groups reported hair loss (p<0.0001 for all follow-up measurements) and worsening of nausea/vomiting (p<0.05 at T3 and T4) without any difference between the CG and the EG.



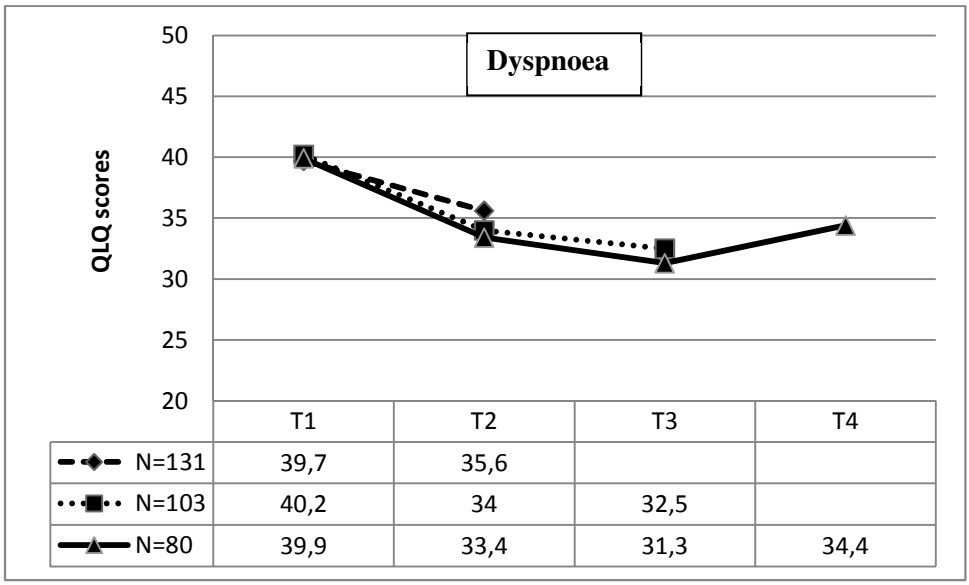
	T1	T2	T3	T4
N=133	66,5	71,8		
N=104	66,3	72,4	73,8	
N=82	66,9	73,5	75,1	72,5

Figure 5. *T1= baseline assessment, T2=follow-up assessment day 15-42 p<0.01, T3= follow-up assessment day 43-63 p<0.01, T4=follow-up assessment day 64-84 p<0.01*



	T1	T2	T3	T4
N=133	52,5	55,4		
N=104	53,5	57	56,6	
N=81	53,1	57,5	56	53,4

Figure 6. *T1= baseline assessment, T2=follow-up assessment day 15-42 p=0.17, T3= follow-up assessment day 43-63 p=0.24, T4=follow-up assessment day 64-84 p=0.31*



	T1	T2	T3	T4
N=131	39,7	35,6		
N=103	40,2	34	32,5	
N=80	39,9	33,4	31,3	34,4

Figure 7. *T1= baseline assessment, T2=follow-up assessment day 15-42 p<0.05, T3= follow-up assessment day 43-63 p=0.0002, T4=follow-up assessment day 64-84 p<0.05*

5.2.4 Physicians

All 22 physicians who worked at the outpatient clinic participated in the study. The number of visits per physician ranged between 1 and 148 (median 15). Eighteen physicians were specialists in respiratory medicine, while four were in training. Seven of the senior physicians who had more than 5 years of experience in pulmonary oncology accounted for 74% of scheduled visits. Each patient encountered between 1 and 6 different physicians (median 3), excluding emergency visits.

5.2.5 Audio-recorded patient-physician consultations

Of 593 audio-recordings, 443 were evaluable for content analysis (EG: 218 recordings of 80 patients; CG: 225 recordings of 85 patients).

In the experimental group, issues regarding emotional functioning were significantly more frequently discussed compared to the control group, both by physicians (mean, 1.5 vs. 0.9 statements; p=0.018) and by physicians and patients together (mean, 3.9 vs. 2.4 statements; p=0.015). The sum total of function-related statements was also higher in the EG than in the CG, both by physicians (mean 3.7 vs. 2.9; p=0.049) and by physicians and patients (mean 9.2 vs. 6.9; p=0.0096). In contrast, discussions about treatment, follow-up and prognosis, categorized as medical-technical, were more common in the CG than in the EG. There were no group differences regarding the mean duration of the encounters.

Analysis of the whole study population demonstrated significant inter-individual correlations between the EORTC scores and corresponding conversation content categories measuring emotional and physical functioning, pain, dyspnoea, appetite loss and fatigue. As for emotional functioning (p=0.010), fatigue (p=0.038) and appetite loss (p=0.0022), correlations were significantly stronger in the EG compared to the CG.

Significant intra-individual correlations between HRQL scores and corresponding conversation content categories were seen for dyspnoea, pain and fatigue in the combined CG and EG . Comparison between groups revealed significantly stronger

intra-individual correlations between scores for social functioning and discussion on social issues in the EG compared to the CG (p=0.026).

5.2.6 Medical and psychosocial interventions

The number of diagnostic and therapeutic interventions focused on emotional (mean, 0.43 vs. 0.15 per patient; p=0.0036) and social concerns (mean 1.17 vs. 0.74 per patient; p=0.013) was significantly higher in the EG compared to the CG. Similarly, actions directed towards dyspnoea were more frequent in the EG than in the CG (mean 1.08 vs. 0.53; p=0.017).

5.3 Satisfaction with care (Paper IV)

134 patients completed the EORTC IN-PATSAT 32 at their last study visit, 67 in each group. Overall, the patients reported high levels of satisfaction with care. The scores for most scales were above 80 and for general satisfaction above 90. There were no significant differences between the two randomization groups of patients.

Determinants of satisfaction

General satisfaction

SATGEN

Overall, 97 patients (76%) had top SATGEN scores of 100, while 30 (24%) had scores of <100. Only 5 (out of 54) variables were identified as significant independent predictors of the distribution of the dichotomized SATGEN scale. These were: age and marital status of the patients, age of the physicians, reported appetite loss in the HRQL questionnaire at baseline and the frequency with which appetite loss was discussed during the encounters. Older patients rated their overall

satisfaction higher than younger ones, as did those living with a partner. The age of the consulting physician at the last visit was negatively associated with the SATGEN score. Appetite loss at baseline was the only HRQL measure that significantly negatively predicted satisfaction. The mean number of statements on problems concerning appetite documented on audio recordings was also negatively associated with SATGEN scores.

In the logistic multiple regression model with SATGEN (dichotomised) as a dependent variable, several final models had similar explanation levels, with AUC values of 0.76-0.77. The model most frequently selected as the final model included the following independent variables: patient's marital status, physician's age at last visit and patient-reported appetite loss at baseline. The area under the ROC curve for this model was 0.76 (95% CI 0.66 - 0.87) in the study population.

SATTOT

In the univariate analysis, twelve variables were significantly associated with the distribution of the SATTOT index scores. The patients´ performance status at the last visit was negatively associated with satisfaction. Patients who required emergency care visits and younger patients had less favourable scores. Self-reported social and emotional functioning and global quality of life assessed by means of the QLQ-C30 were positively correlated with satisfaction scores, while self-reported fatigue and appetite loss at baseline correlated negatively with the SATTOT scores. As before, the mean number of statements on problems pertaining to appetite documented by means of audio recordings was negatively associated with SATTOT scores.

In the final multiple regression model of SATTOT as a dependent variable, four independent variables were retained: age of physician, QLQ-C30 social functioning at baseline and QLQ-C30 appetite loss both at baseline and at last visit. The adjusted R^2 for this solution was 0.24, whereby 24% of the variance in the SATTOT index could be determined by these four variables combined.

Satisfaction with doctor

Ninety-nine patients (74%) had SATDR scores of ≥80 indicating "high satisfaction", while 35 (26%) had scores of <80. Five out of 54 variables showed significance at $p<0.05$. Patients who required emergency care visits scored less favourably compared to those who only attended scheduled appointments. The age of the consulting doctor at the last visit was also negatively associated with the SATDR score. In the EORTC QLC-C30, low scores for emotional functioning at the last visit and high levels of appetite loss at baseline predicted less satisfaction with the doctor. The mean number of statements on appetite problems in the audio-recorded patient-doctor consultations was also negatively associated with SATDR scores.
These five variables were selected as independent variables in the multivariate analysis, with SATDR (dichotomised) as the dependent variable. In the final logistic multiple regression model, three independent explanatory variables were selected: emergency consultations, doctors´ age at last visit and mean number of statements on problems pertaining to appetite, documented by means of audio recordings. The area under the ROC curve for this model was 0.74 (95% CI 0.64 - 0.85) in the study population.

Neither the total number of doctors involved with each patient, nor the calculated continuity index significantly predicted the SATDR index score ($p=0.062$ and $p=0.29$, respectively).

6 DISCUSSION

6.1 Methodological strengths and weaknesses

Selection of HRQL questionnaire

The EORTC QLQ-C30 and LC13 was chosen as a model HRQL instrument in this study, based on our own experience of it both during the development phase (56, 61) and in clinical trials (120-124). The instrument has been widely used in international chemotherapy trials and its psychometric properties are well-documented (125). The Swedish versions of both the QLQ-C30 and LC13 have been validated in large studies and found to have comparable reliability and construct validity with other major language versions.

As HRQL data in palliative settings were sparse when this study was initiated, we first aimed to investigate the psychometric properties of the EORTC questionnaire in patients receiving palliative treatment, excluding chemotherapy (sub-sample I), before considering its use in the randomized study, which can constitute a methodological strength. However, employing the EORTC questionnaire both as an intervention instrument and an outcome measure for investigating the impact of available HRQL data on the care process and patients´ HRQL (sub-sample II) may also be a limitation, as repeated HRQL assessment may train patients, thus influencing their scores, which could weaken the effects of the study intervention. Employing a different instrument as an outcome measure could have reduced this problem.

While the information obtained from standardized HRQL questionnaires is useful for comparing groups in clinical trials, it may be insufficient for the evaluation of individual HRQL. In a Swedish study, 343 patients with inoperable lung cancer completed the EORTC QLQ-C30 and LC13, the Memorial symptom Assessment

Scale and the modified Distress screening tool as well as answering the question "What do you find most distressing at present?" A qualitative analysis of the responses to this question was performed, which demonstrated that the dimensions of symptom intensity and symptom distress differed. Only 55-59% of the concerns described as the most distressing were clearly assessed by the three questionnaires (126). In addition, increasing dependence on others was not detected by the EORTC (127). Furthermore the use of semi-structured interviews contributes meaning to individual patient scores (128) and adds information about perceived problems (129). In the course of the disease, patients´ perception of their health status usually changes due to deterioration as the tumour progresses, but also as a result of adaptation, as patients often adopt new internal standards. This phenomenon is known as response shift and is not easily observed by physicians (130, 131).

Nevertheless, the objective of the present study was not to determine the optimal method for individual HRQL measurement, but to investigate the possibility of employing a standardised questionnaire that can capture important aspects of patients' HRQL problems and use it in clinical practice without the need for a great deal of extra resources.

Compliance and selection bias

In the initial validation study (paper I), we did not document the number of patients who declined to participate or those who did not meet the inclusion criteria. However, 65% of the patients in this sub-sample had WHO PS 2 or 3 and some were hospitalized when they completed the questionnaires, indicating that HRQL assessment with the EORTC QLQ-C30 and LC13 is feasible also in very ill patients.

In sub-sample II, most patients agreed to participate, although 43 were missed and not invited. The questionnaires were completed by the patients in >90% of the scheduled consultations, with no difference in completion rates between the computerized and the paper version of the questionnaires. These results confirm the feasibility of the computer-based questionnaire, which was also demonstrated in a previous pilot study.

Missing data and drop-outs

In sub-sample II, 18, 6 and 37 patients had missing HRQL data over time, consultation content and satisfaction with care respectively, for the reasons specified in Fig 4. As regards the evaluation of satisfaction with care, 37 patients (17 in the EG and 20 in the CG) were lost to follow up (non-responders). The most frequent reason was poor health. The baseline PS of the non-responders was worse than that of the total sample. Of the patients who dropped out, 65% had a PS 2 or 3 vs. 26% of those who completed the study. Patient selection due to drop-outs may therefore, partly explain the high level of satisfaction with care in the EORTC INPATSAT32, as it was the fittest patients who completed the questionnaire, while those in poor condition were over-represented among the non-responders.

Attrition of ill patients is a common problem in clinical longitudinal studies in oncology (132, 133). However, the attrition rate in the present study (21.6%) was lower than in similar studies, which suggests that repeated HRQL assessment is feasible even in patients with poor health status.

Bias due to the study design (Papers II-III)

Patients in the EG and the CG completed the EORTC set of questionnaires, although in different response modes, which probably made all patients more aware of HRQL issues and may have weakened the effects of the randomization. Furthermore, as all the patient-physician conversations were audio-recorded, physicians may have been 'triggered' to discuss HRQL issues in both groups irrespective of their access to specific HRQL information in the EG.

Reversely as the physicians were not randomized for practical reasons and we did not collect information about the extent to which they actually used the prospectively presented HRQL results during the consultations, a hypothetical low physician compliance could have reduced the difference between the EG and the CG. Nevertheless, the results in Paper III demonstrated that the probability of discussing specific, patient-reported HRQL issues during the consultations was increased when the physicians received the HRQL information.

Data collection using the study specific digital table interface

This method proved feasible as there was high patient compliance and it took only a few minutes to analyse the HRQL responses and produce printouts for the physicians. The method was intended to be easy for patients to use. The table showed the whole questionnaire in A3 size and the patients marked the response alternatives with a digital pen, similar to completing a paper and pen question form, something that was familiar to the patients. Missing data was avoided as the electronic method indicated when a question had not been answered. Within a few minutes, a summary of the scale scores including previous results and reference values from the general population was presented to the physicians. A previous pilot study confirmed the feasibility of the electronic method, although some patients required the assistance of the research nurse.

Several studies exploring other methods of automated data collection, in particular "touch screen" questionnaires, have been reported. Some comparisons between paper-based versus computer-based touch screen questionnaires indicated that the latter were well accepted by patients and no responses were left out. In general, the electronic versions of questionnaires have proved feasible for most patients, although older people or those with poor performance status may require assistance (134-141). Recently, the EORTC Quality of Life Group developed an electronic version of the QLQ-C30 for general use (142).

6.2 Statistical considerations

Multiple comparisons increase the risk of random significances (type 1 error).
We sought to limit this risk by reducing the number of variables analysed in Paper III and selecting core HRQL dimensions and symptoms that matched the defined conversation content categories, i.e. physical, emotional and social functioning, global quality of life, pain, dyspnoea, fatigue and appetite loss.

For the same reason, two composite indices, i.e. SATTOT and SATDR, were defined as dependent variables in Paper IV in addition to the original SATGEN item, instead of analysing all 14 sub-scales in the EORTC IN-PATSAT32.
Nevertheless, a large number of comparisons were made within the project and some positive findings may be due to random effects. To avoid overestimation of associations, our interpretation of the results focused on patterns rather than on single outcomes.

6.3 HRQL profile in the study patients

As expected, patients in sub-sample I reported lower levels of physical functioning and worse symptoms compared with reference results obtained from patients in clinical trials (116). However, emotional functioning was better in our study population, which may be explained by a higher degree of acceptance of the disease related to longer time since diagnosis, compared to patients receiving treatment in clinical trials.

There were no significant HRQL differences between the EG and the CG in sub-sample II. As most patients in sub-sample II had a better PS and were amenable to oncological treatment, they had higher physical functioning scores compared to the patients in sub-sample I. In contrast, emotional functioning scores were lower in sub-sample II than in sub-sample I. As the patients in sub-sample II were informed of their incurable cancer diagnosis shortly before entering the study, this probably accounts for the difference in emotional functioning between the two sub-samples.

6.4 Psychometric properties and clinical relevance of the EORTC QLQ-C30 and LC13 in a palliative setting

The EORTC QLQ-C30 showed acceptable reliability in patients receiving palliative care for advanced lung cancer or mesothelioma. Generally, internal consistency expressed as an alpha-coefficient of >0.70 is considered acceptable for group comparisons. Except for cognitive functioning the internal consistency was >0.70 for all multi-item scales and in several cases >0.80. The lower consistency of the cognitive functioning scale was due to the contradictory responses provided by some patients to the items about concentration problems and memory difficulties. One may therefore consider analysing these two items separately in palliative settings.

After the conclusion of the present study, a short version of the QLQ-C30, the EORTC QLQ-C15-PAL, was developed for use in palliative care (143). Item response theory methods were applied to shorten multi-item scales and only scales/items rated most important by patients and healthcare professionals were retained (144). Interestingly, only a minority of patients rated items from the cognitive scale among the most important.

A test-retest after three weeks confirmed the reproducibility of the questionnaire in patients in a stable condition.

The clinical validity of the QLQ-C30 and LC13 questionnaire was supported by the association between its domains and clinical tests commonly used in clinical practice, such as FEV1, pulse oxymetry, haemoglobin levels and 6MWT. We also confirmed that physical symptoms, functioning and global quality of life are associated with performance status. To the best of our knowledge, we are the first to demonstrate the strong correlation between physical function and the 6MWT, which independently predicted patient-reported physical function in a multivariate analysis.

Patient-reported social functioning did not correlate well with the social worker's rating of social support and activity. A reasonable explanation is that the QLQ-C30 social function scale refers to the influence of disease and treatment on social function rather than the level of social support and activity, thus only partly covering the dimensionality of this complex domain. In a qualitative study, patients with lung cancer mentioned family and social support as important aspects of HRQL, in addition to physical well-being, functional independence and spirituality (145). Interestingly, in the EORTC QLQ-C15-PAL evaluation study, patients receiving palliative care rated the relevance of the social function scale as low, because they considered that the items refer to normal social activities and contact with family, which are interrupted for patients in hospital or palliative units (143). The EORTC QLQ-C30 social functioning scale may not sufficiently reflect the experience of patients with advanced cancer. Consequently, complementary methods, such as semi-structured interviews including evaluation of social support may be needed to provide a more accurate assessment of these patients' social functioning.

In recent years, item response theory, item banking and computerized adaptive testing (CAT) techniques have been increasingly used in quality of life research. These methods allow the development of brief, individually tailored instruments with a precise estimate of symptom burden and functional status, in addition to minimized floor and ceiling effects. The EORTC Quality of Life Group has initiated a project to develop a CAT version of the QLQ-C30. The results pertaining to physical functioning and fatigue, for which an item pool of 31 and 34 items respectively was employed, have been presented, demonstrating high levels of measurement precision and efficiency in both scales (146-148).

6.5 Prognostic importance of HRQL measurement

QLQ-C30 functioning scores (excluding cognitive function) significantly predicted the remaining survival time in sub-sample I.

Concordant with our findings, other studies of lung cancer in different settings have identified global quality of life as the most significant predictor of survival (149, 150). In one study, every 10-point increase in physical function and global QL was associated with a 10% and 9% increase in survival time, respectively (151).

In studies of patients with malignant pleural mesothelioma undergoing chemotherapy, the strongest predictors of survival were fatigue and physical functioning or pain and appetite loss, respectively (152, 153) .

Based on these and our own findings, we suggest that HRQL data be used as a complement to the widely established WHO-PS when evaluating survival prognosis in lung cancer or mesothelioma.

6.6 Contribution of individual HRQL assessment to patient-physician communication

The results of the intervention study (Papers II and III) indicate that emotional concerns were more frequently discussed in the patient group for which HRQL reports were available to the physicians without prolonging the duration of the consultations. As the number of statements regarding medical-technical issues was lower in this group compared to the control group, the results indicate that the availability of HRQL reports contributed to changing the focus of patient-physician conversations. There were no group differences in the mean emotional function scores that could explain the between-group difference in the focus on emotional concerns. However, there was a stronger correlation between the HRQL scores

reported and the frequency with which these problems were discussed during the patient-physician conversations in the EG compared with the CG (Paper III). The association between the magnitude of psychosocial concerns, general symptoms and the probability that such issues would be discussed during consultations was stronger in the EG (Paper III), confirming the hypothesis of this thesis that access to HRQL ratings could increase the attention paid to problems within these domains.

During the present work, a few randomized studies reported the impact of HRQL evaluation on patient-physician communication and also demonstrated that it increased awareness about HRQL issues (132, 133, 154). However, category analysis of the HRQL topics discussed revealed that the increased focus was to a large extent limited to physical symptoms. Only one reported more frequent discussion of social functioning (133), while cognitive functioning was discussed in greater detail in another (154). In one study, no effects of HRQL monitoring on discussion of functioning were found. The severity of the symptoms predicted the likelihood that these problems were discussed, but no interaction effect of randomization on this association was evident (155).

Thus, and to the best of our knowledge, this study is the first to demonstrate that assessment of patients´ self-reported HRQL and the presentation of the results to the doctors increases the probability that perceived psychosocial problems and general symptoms will be captured during patient-physician conversations.

The positive effects of HRQL assessment on patient-physician communication can be considered sufficient evidence of the value of the intervention in routine cancer care, as increased patient involvement in the care process is a goal of health care policy (156).

6.7 Impact of HRQL assessment on decision-making

The availability of individual HRQL assessment increased the number of interventions for psychosocial concerns and dyspnoea in the EG.
A variety of diagnostic and therapeutic actions were taken to address dyspnoea, such as spirometry, blood gases, radiographic and other visualizing methods, endoscopic investigations, oxygen treatment, pleural drainage, pleurodesis, pharmacological treatment and referral to palliative radiotherapy. Psychosocial interventions included referral to the social worker or psychiatrist, supportive conversations, information and/or referral to subsidies from the welfare system and foundations as well as medical treatment for symptoms of anxiety and depression.

This is the first study to demonstrate that the use of HRQL measures influences the decision-making process, thus highlighting the significance of such assessment in clinical practice. However, it remains to be demonstrated the increased measures taken meet the patients' real needs.

6.8 Impact of HRQL assessment on quality of life

The increased attention paid to psychosocial concerns in the EG did not result in improved quality of life , as there were no randomization group differences regarding the changes in HRQL over time.

A limitation of the study is that the outcome HRQL questionnaire was the same as the intervention instrument. This means that patients may have experienced a training effect as they completed the intervention questionnaire on several occasions, which could have influenced the assessment of HRQL over time, thus weakening the effects of the intervention on the reported quality of life.

However, several studies that employed a separate HRQL outcome questionnaire also failed to demonstrate significant effects of HRQL assessment on quality of life (154, 157). Only one trial indicated an improvement in self-reported well-being related to HRQL assessment (132). In one study, the regular completion of a structured HRQL diary by patients with inoperable lung cancer could have had a negative impact on well-being (158). In the latter study, however, there was no formal feedback of HRQL ratings to physicians.

Thus, while HRQL assessment improves patient-physician communication, it has little impact on patients´ HRQL. This raises the question as to whether other interventions are necessary. Measures that facilitate the interpretation of HRQL scores, such as linking cut-off and MID scores to treatment guidelines, may enhance the effects of HRQL assessment on the quality of cancer care and thereby patients' quality of life.

The importance of identifying sub-groups of patients who may benefit from specific treatment interventions is illustrated by one randomized study that investigated the effects of coordinated psychosocial interventions on HRQL. All patients completed questionnaires assessing HRQL, care needs and psychosocial concerns, the results of which were only presented to the physicians and nurses who encountered the experimental group. Based on the available information and pre-specified guidelines, an individualized management plan was produced. There were no overall significant differences between the groups regarding HRQL outcome, but a sub-group analysis suggested that the psychosocial intervention was beneficial in patients who suffered from moderate to severe depression at baseline (159).

Clinical significance of changes in HRQL over time

Overall, patients in sub-sample II experienced statistically significant improvements in emotional functioning, dyspnoea, cough, haemoptysis, chest pain and arm/shoulder pain over time. These improvements might also have been clinically significant, despite the fact that several were of a magnitude of less than 10 points. While a change of 10 points on a scale of 0-100 has been stated to be clinically meaningful, Maringwa et al. demonstrated in their study of MID from EORTC QLQ-

C30 scores in patients with lung cancer that meaningful improvement requires a smaller degree of change compared to meaningful deterioration (81). Similar findings were recently reported for the EORTC QLC-C15 (160).

The symptom alleviation experienced by patients in the present study may be explained by palliative treatment including chemotherapy, while improvements in emotional functioning can be a result of gradually increased acceptance of the disease over time.

6.9 Impact of HRQL assessment on satisfaction with care

The patients in sub-sample II reported high levels of satisfaction with care with no differences between the EG and CG. Neither the availability of HRQL measures nor the subsequent increased focus on psychosocial problems in the EG resulted in an increased level of perceived satisfaction with care. These results are consistent with several other studies that also failed to show any impact of access to HRQL assessment on patient satisfaction (157-159). One study demonstrated an improvement in patients´ perception of continuity of care by assessing HRQL and providing feedback to physicians, but no influence on general satisfaction with care was found (161). An overall problem with measures of satisfaction with care is that patients tend to report high levels of satisfaction, resulting in ceiling effects that limit the usefulness of such measures for analysis of group differences.

6.10 Predictors of satisfaction with care

Despite high levels of patient satisfaction with care and low variance in the scores, several predictors, namely the patients´ age and marital status, symptoms and

functioning, the age of the physicians who encountered the patient at her/his last visit and need for emergency care visits were identified. In the multivariate analysis, several models with an AUC of 0.74 or higher, i.e. with good discriminating properties, were demonstrated.

This study confirms an association between patient satisfaction and health status. Patients with worse symptoms and functioning levels appear to experience less satisfaction with care (96, 99). Several explanations have been suggested to explain this relationship. Unmet needs of more seriously ill patients may be the cause of dissatisfaction, but it might also reflect general mood changes in patients with cancer due to their deteriorating health status (100, 162).

Requiring emergency care visits was negatively associated with satisfaction. Although the reasons for such visits were not analysed, clinical experience indicates that they were probably due to a worsening of the patients´ condition.

Of the symptoms, appetite loss was consistently negatively associated with patient satisfaction. Others have also identified appetite loss as a predictor of satisfaction, but only by means of univariate analysis (100) or in relation to the sub-scale that assesses physicians' interpersonal skills (163). Appetite loss is one of the most distressing symptoms in patients with lung cancer as well as a quality of life predictor (67, 164). In our study, a relatively high level of attention was paid to appetite loss, as it was the second most common symptom discussed during the consultations. It was also in second place in terms of the number of medical interventions aimed at symptom relief. The impact of the actions taken during the study, including referrals to a dietician, nutritional counselling, prescription of steroids and nutritional support, was not specifically evaluated, but in general, loss of appetite is difficult to alleviate and current treatment approaches only provide modest benefit (165, 166). Thus, in this context, the relationship between appetite loss and dissatisfaction may reflect both the burden of the disease and unmet needs due to the failure to provide effective palliative treatment, rather than a lack of attention to the problem.

In 2011, the European Palliative Care Research Collaborative produced guidelines for symptom management of cancer cachexia in patients with an advanced level of cancer and stressed the need for more clinical research in this area (167).

To the best of our knowledge, this is the first oncology study to propose a direct association between the age of the physician and patient satisfaction. However, as the physicians were not randomized, this finding must be treated with caution. We can assume a selection bias in view of the fact that in many cases 'dissatisfied' patients might have been scheduled to see a more experienced physician.

We found no relationship between patient satisfaction and the continuity of doctors. Only 7% of the patients saw the same doctor during all study visits, while 38% saw different doctors each time. To some degree, a change of doctor may be positively experienced as a "second opinion" on the care provided. However, feed-back from patients and proxies on a day-to-day basis indicated that patients experienced discontinuity as a problem. In addition, meeting the same physician at every visit was considered very important by patients with cancer in several studies (168, 169). Nevertheless, a vast majority of the patients in our study reported high levels of satisfaction with the care in general and with doctors, which may reflect that they were appreciated the medical care, and that the team of nurses was consistent through the course of the study.

After this study was conducted, predictors of satisfaction were investigated by means of the EORTC OUT-PATSAT35, where it was found that global health status was a main determinant of satisfaction (170). In this questionnaire, which is an adapted version of the EORTC IN-PATSAT32 for assessment of out-patient satisfaction with ambulatory cancer treatment, items specific to hospitals were excluded and other items relevant to out-patients added. A Swedish version of the EORTC OUT-PATSAT35 has not yet been validated, which is necessary given that this instrument is more suitable for out-patients than the EORTC IN-PATSAT32.
Finally, future research should investigate whether longitudinal assessment data can better determine predictors of patient satisfaction (171).

7 CONCLUSION

- The EORTC QLQ-C30 is a feasible, valid and clinically relevant instrument for assessing the HRQL of patients with advanced-stage lung cancer or mesothelioma receiving palliative care
- Prospective use of HRQL assessment influences patient-physician encounters and increases the focus on emotional concerns
- The availability of HRQL measures increases the probability that experienced psychosocial problems and general symptoms will be captured during consultations
- The prospective use of HRQL measures has an impact on the decision-making process and increases the number of interventions directed towards HRQL issues, especially in psychosocial areas
- Access to HRQL measures does not influence patient HRQL over time, nor patient satisfaction with care
- Patient satisfaction with care is predicted by age, marital status, health status, appetite loss in particular, as well as the age of the physician

8 FUTURE PERSPECTIVES

The results presented herein demonstrate that the patients´ assessment of their HRQL using the EORTC QLQ-C30 as well as feedback to physicians increases the focus on psychosocial problems during patient-physician encounters. Future research should investigate whether individually tailored questionnaires, such as the CAT version of the QLQ-C30, which is being developed at present, are superior to the original versions for following-up patients´ HRQL in daily oncology practice.

Studies on the interpretation of HRQL scores are required in order to establish cut-off values that can be linked to treatment recommendations, thereby supporting physicians in the decision-making process. Further research can investigate the effects of treatment or care interventions for specific self-reported problems on patient outcomes, such as HRQL and satisfaction with care. In addition, HRQL data formats need to be developed to facilitate interpretation by both caregivers and patients and promote the incorporation of HRQL assessment during consultations.

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APPENDIX QUESTIONNAIRES

EORTC QLQ-C30 (version 3)

Vi är intresserade av några saker som har med Dig och Din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på Dig. Det finns inga svar som är "rätt" eller "fel". Den information Du lämnar kommer att hållas strikt konfidentiell.

Var vänlig fyll i Dina initialer: |_|_|_|_|
När är Du född? (Dag, Månad, År): |_|_|_|_|_|_|_|_|
Dagens datum (Dag, Månad, År): |_|_|_|_|_|_|_|_|

		Inte alls	Lite	En hel del	Mycket
1.	Har Du svårt att göra ansträngande saker, som att bära en tung kasse eller väska?	1	2	3	4
2.	Har Du svårt att ta en lång promenad?	1	2	3	4
3.	Har Du svårt att ta en kort promenad utomhus?	1	2	3	4
4.	Måste Du sitta eller ligga på dagarna?	1	2	3	4
5.	Behöver Du hjälp med att äta, klä Dig, tvätta Dig eller gå på toaletten?	1	2	3	4

Under veckan som gått:

		Inte alls	Lite	En hel del	Mycket
6.	Har Du varit begränsad i Dina möjligheter att utföra antingen Ditt förvärvsarbete eller andra dagliga aktiviteter?	1	2	3	4
7.	Har Du varit begränsad i Dina möjligheter att utöva Dina hobbys eller andra fritidssysselsättningar?	1	2	3	4
8.	Har Du blivit andfådd?	1	2	3	4
9.	Har Du haft ont?	1	2	3	4
10.	Har Du behövt vila?	1	2	3	4
11.	Har Du haft svårt att sova?	1	2	3	4
12.	Har Du känt Dig svag?	1	2	3	4
13.	Har Du haft dålig aptit?	1	2	3	4
14.	Har Du känt Dig illamående?	1	2	3	4
15.	Har Du kräkts?	1	2	3	4
16.	Har Du varit förstoppad?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått:

		Inte alls	Lite	En hel del	Mycket
17.	Har Du haft diarré?	1	2	3	4
18.	Har Du varit trött?	1	2	3	4
19.	Har Dina dagliga aktiviteter påverkats av smärta?	1	2	3	4
20.	Har Du haft svårt att koncentrera Dig, t.ex. läsa tidningen eller se på TV?	1	2	3	4
21.	Har Du känt Dig spänd?	1	2	3	4
22.	Har Du oroat Dig?	1	2	3	4
23.	Har Du känt Dig irriterad?	1	2	3	4
24.	Har Du känt Dig nedstämd?	1	2	3	4
25.	Har Du haft svårt att komma ihåg saker?	1	2	3	4
26.	Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Ditt familjeliv?	1	2	3	4
27.	Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Dina sociala aktiviteter?	1	2	3	4
28.	Har Ditt fysiska tillstånd eller den medicinska behandlingen gjort att Du fått ekonomiska svårigheter?	1	2	3	4

Sätt en ring runt den siffra mellan 1 och 7 som stämmer bäst in på Dig för följande frågor:

29. Hur skulle Du vilja beskriva Din hälsa totalt sett under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

30. Hur skulle Du vilja beskriva Din totala livskvalitet under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

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EORTC QLQ - LC13

Patienter berättar ibland att de har följande symptom. Markera i vilken utsträckning som Du har haft dessa symptom under den senaste veckan. Svara genom att ringa in den siffra som bäst passar in på Dig.

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
31. Hur mycket har Du hostat ?	1	2	3	4
32. Har det kommit blod när Du hostat ?	1	2	3	4
33. Har Du varit andfådd även när Du vilat ?	1	2	3	4
34. Har Du blivit andfådd när Du tagit en promenad ?	1	2	3	4
35. Har Du blivit andfådd när Du gått i trappor ?	1	2	3	4
36. Har Du haft ont i munnen eller tungan ?	1	2	3	4
37. Har Du haft svårt att svälja ?	1	2	3	4
38. Har Du haft stickningar i händer och fötter ?	1	2	3	4
39. Har Du tappat något hår ?	1	2	3	4
40. Har Du haft ont i bröstet ?	1	2	3	4
41. Har Du haft ont i armen eller skuldran ?	1	2	3	4
42. Har Du haft ont på andra ställen i kroppen?	1	2	3	4
Om ja, var ? _____				
43. Har Du tagit smärtstillande medicin ?				
1. Nej **2. Ja**				
Om Ja , hur mycket har det hjälpt?	1	2	3	4

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LIVIA

Pat-ID: _____
Datum: _____

CASC-SF 4.0

Besvaras av patienter

Det här frågeformuläret handlar om Din uppfattning om vården Du erhållit vid den Lungonkologiska enheten på Sahlgrenska universitetssjukhuset. Avsikten med att ställa frågorna i formuläret är att med hjälp av Dina svar avgöra om vården och annan service på sjukhuset kan förbättras. Även om Du anser att sjukhuset ger Dig en vård av hög kvalitet kan vissa aspekter kanske förbättras. Därför är vi angelägna om att få ta del av Din uppfattning, oavsett om den är negativ eller positiv. Den information Du lämnar kommer att behandlas konfidentiellt.

Var vänlig och markera den siffra som bäst överensstämmer med Din uppfattning med ett kryss. Det är viktigt att Du, och ingen annan, besvarar frågorna.

I. När det gäller läkarna på Lungonkologiska mottagningen, hur bedömer Du det följande?

		Mycket dåligt	**Dåligt**	**Ganska bra**	**Bra**	**Utmärkt**
1.	Den kunskap och förståelse de hade för Din sjukdom	1	2	3	4	5
2.	Den behandling och den uppföljning de gav	1	2	3	4	5
3.	Den uppmärksamhet de visade Dina fysiska problem	1	2	3	4	5
4.	Deras villighet att lyssna på alla Dina bekymmer	1	2	3	4	5
5.	Det intresse de visade Dig som person och inte endast Din sjukdom	1	2	3	4	5
6.	Den tröst och det stöd de gav Dig	1	2	3	4	5
7.	Den information de gav Dig om Din sjukdom	1	2	3	4	5
8.	Den information de gav Dig om Dina provtagningar	1	2	3	4	5
9.	Den information de gav Dig om Din behandling	1	2	3	4	5
10.	Antalet besök/konsultationer de gjorde	1	2	3	4	5
11.	Den tid de ägnade Dig vid besök/konsultationer.	1	2	3	4	5

II. När det gäller vårdpersonalen på Lungonkologiska mottagningen, hur bedömer Du det följande?

	Mycket dåligt	Dåligt	Ganska bra	Bra	Utmärkt
12. Hur de utförde de fysiska undersökningarna av Dig (tog Din temperatur, Din puls,...).	1	2	3	4	5
13. Den omvårdnad de gav (hur de gav mediciner, och injektioner,…).	1	2	3	4	5
14. Den uppmärksamhet de visade Ditt fysiska välbefinnande.	1	2	3	4	5
15. Det intresse de visade Dig som person och inte endast Din sjukdom.	1	2	3	4	5
16. Den tröst och det stöd de gav Dig.	1	2	3	4	5
17. Deras medmänskliga egenskaper (artighet, respekt, förståelse, vänlighet, tålamod,...).	1	2	3	4	5
18. Den information de gav Dig om Dina provtagningar.	1	2	3	4	5
19. Den information de gav Dig om Din vård.	1	2	3	4	5
20. Den information de gav Dig om Din behandling.	1	2	3	4	5
21. Deras snabbhet/villighet att svara på Dina ringningar.	1	2	3	4	5
22. Den tid de ägnade Dig.	1	2	3	4	5

III. När det gäller annan service och organisation av vården på Lungonkologiska enheten, hur bedömer Du det följande?

	Mycket dåligt	Dåligt	Ganska bra	Bra	Utmärkt
23. Den information som vidarebefordrades från läkarna till Din husläkare.	1	2	3	4	5
24. Den vänlighet och hjälpsamhet som teknisk personal, receptions personal, laboratoriepersonal,….visade.	1	2	3	4	5
25. Om Du varit inlagd: Den information som gavs vid Din inskrivning på sjukhuset.	1	2	3	4	5
26. Om Du varit inlagd: Den information som gavs vid Din utskrivning från sjukhuset.	1	2	3	4	5
27. Väntetiden för att få provsvar.	1	2	3	4	5
28. Den snabbhet med vilken medicinska undersökningar och/eller behandlingar genomfördes.	1	2	3	4	5
29. Tillgängligheten (parkering, kommunikationer,…).	1	2	3	4	5
30. Möjligheten att hitta på sjukhuset.	1	2	3	4	5
31. Byggnadens trevnad (renlighet, utrymme lugn,…).	1	2	3	4	5

IV. Totalt sett:

32. Hur bedömer Du kvaliteten på den vård Du fått vid Lungonkologiska enheten?	1	2	3	4	5

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