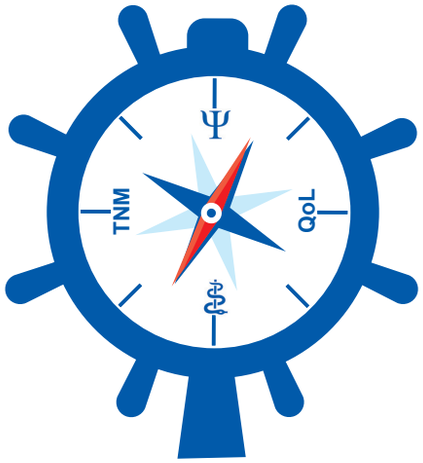

PATIENT REPORTED OUTCOMES IN LUNG CANCER

Mark de Mol

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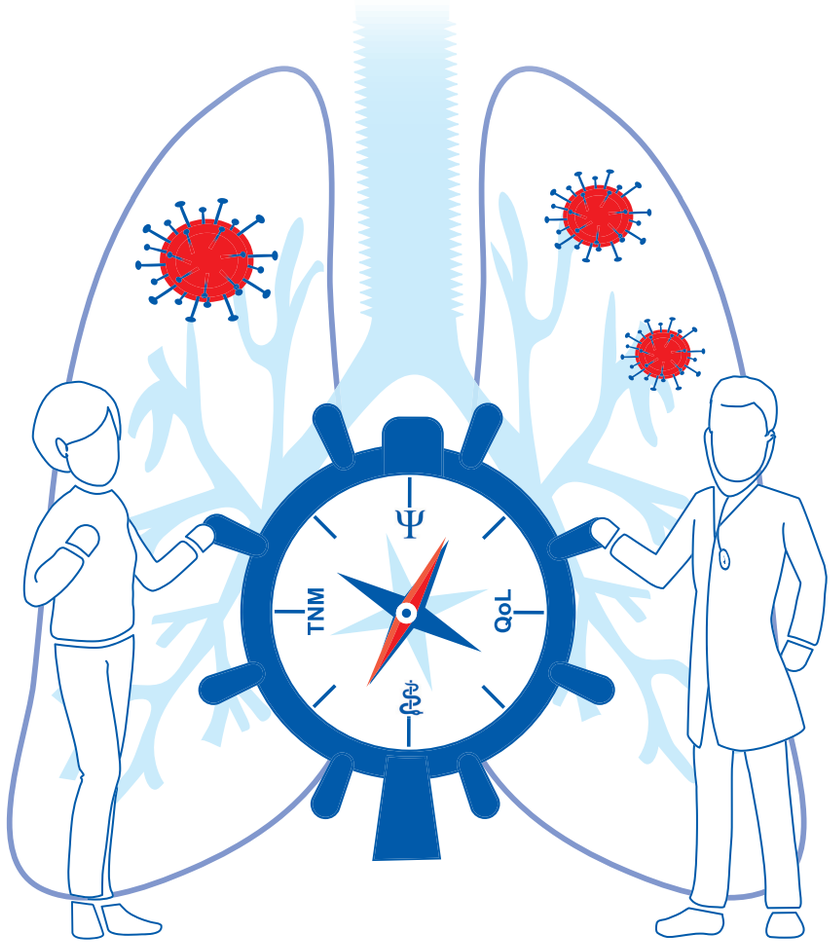

Mark de Mol

Patient Reported Outcomes in Lung Cancer

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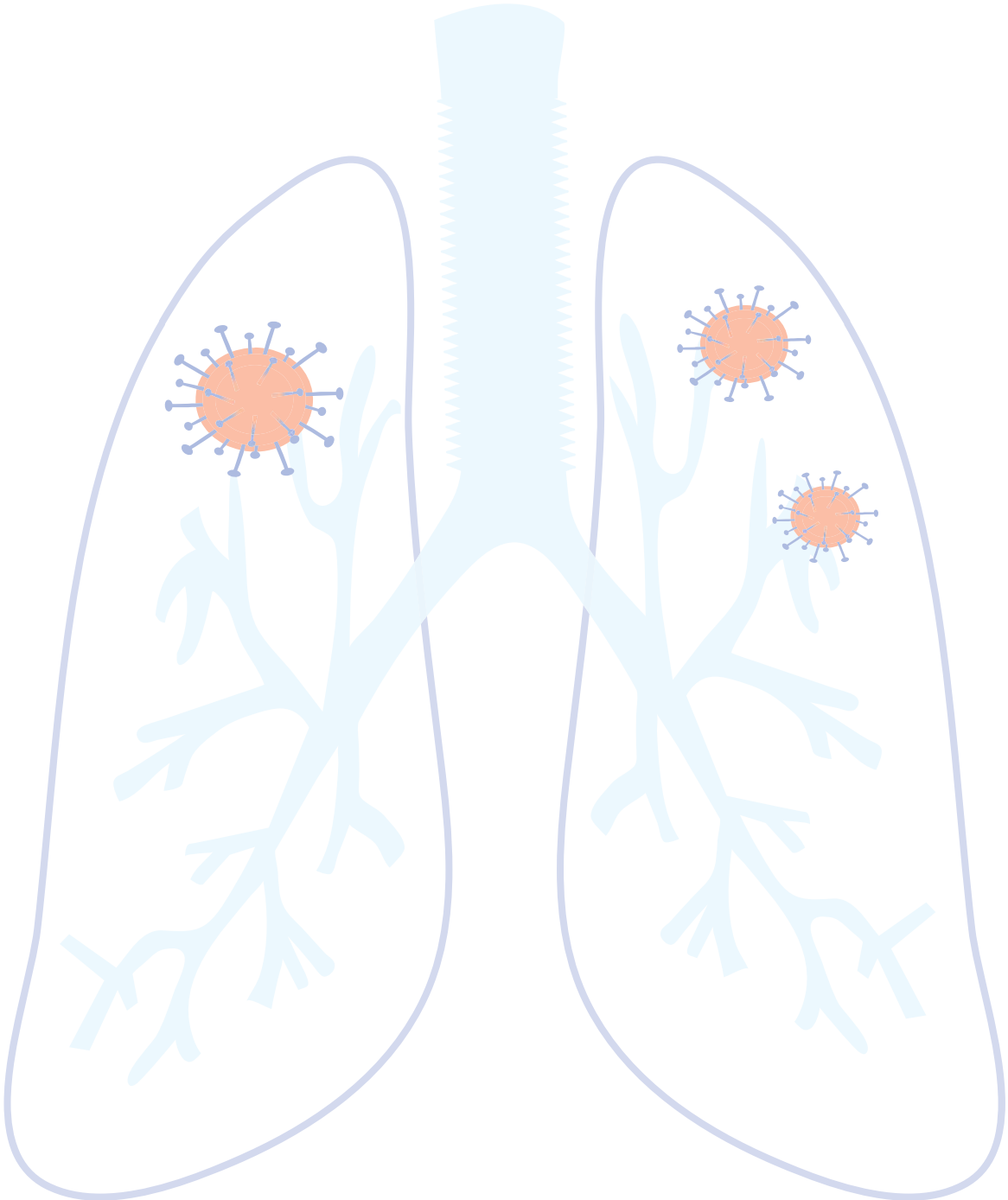


INTRODUCTION

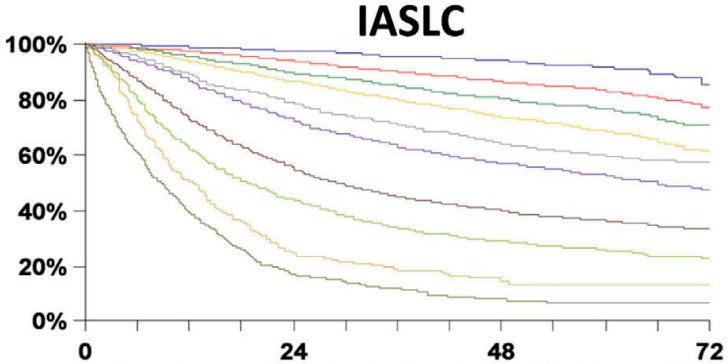
LUNG CANCER

Epidemiology

Lung cancer has the highest incidence among cancers with 2.1 million newly diagnosed patients in 2018 globally [1]. In the Netherlands, more than 13,000 patients were diagnosed with this disease in 2017 [2]. Lung cancer is also the leading cause of cancer-related mortality due to its high incidence [1] and poor prognosis [1,3,4]. An estimated number of 1.8 million persons in the world died in 2018 as a result of lung cancer, which is about three times the mortality associated with breast and colon cancer and almost five times the mortality related to prostate cancer [1]. In the Netherlands, more than 10,000 lung cancer deaths were reported in 2017 [2]. Figure 1 demonstrates the prognosis of patients with lung cancer according to the stage of disease based upon the data of the lung cancer staging project executed by the International Association for the Study of Lung Cancer.

Trends in incidence and mortality of lung cancer in men and women follow the geographic, temporal, and gender-related development of the tobacco epidemic in the 20th century [6]. Incidence and mortality rates in males are declining in countries where the smoking rate in men have dropped (i.e., United Kingdom, Australia, United States, Canada). However, they increase in countries in which the tobacco epidemic started later (i.e., low- and middle-income countries in South America and Asia) [6] and in women [7].

Fig. 1 Overall survival in patients with lung cancer staged according to the eighth edition stage groups in the IASLC data set. Adapted from Chansky et al., 2017 [5]



cTNM	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IV	664 / 882	8.8	17%	6%

cTNM, clinically staged tumors

Abbreviations: IASLC, International Association for the Study of Lung Cancer; N, number of patients; MST, median survival time (months)

Etiology

Multiple risk factors contribute to the development of lung cancer. Smoking is responsible for 85% of lung cancer cases [8] and is considered to be the most important risk factor [8-10]. Men and women who smoke have a 23 and 13 times higher chance to develop lung cancer compared to non-smokers [9,10] with the duration of smoking and the intensity of smoking significantly related to the risk of developing lung cancer [11,12]. Most patients with lung cancer are male with the highest risk to develop the disease from the age of sixty years or older [13]. In addition, women who smoke have a higher risk for lung cancer than males [14]. Passive smoking results in an increased risk for (lung) cancer as well [15]. Although, other causes of lung cancer are known, like exposure to ionizing radiation (e.g., radon [16-18], radiotherapy [19,20], and the radiation caused by atomic bombs [21]), asbestos [22,23], genetic predisposition [24,25], indoor air pollution [26,27], and chronic obstructive pulmonary disease [28,29], in a substantial proportion of patients causes are yet undetermined.

Clinical manifestation

About 70% of patients present with advanced-stage disease [30] with distant metastasis often occurring in bone, lung, brain, liver, adrenal glands, extra thoracic lymph nodes, and pleura/pericard [31,32]. This late-stage presentation of lung cancer may be explained by several reasons. For instance, primary tumors located in periphery of the lung and not associated with a blood vessel or airway may not demonstrate symptoms early in the course of the disease. In addition, the presence of non-specific systemic symptoms, associated with metastatic disease, may lead to a significant delay in specialist referral [33]. Lastly, lung cancer metastasizes early in its development, which also contributes to that a majority of patients is diagnosed with an advanced-stage of disease.

Histology

The uncontrolled proliferation of epithelial cells of the respiratory tract leads to the development of lung cancer [34]. A rough categorization into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) can be made [35,36]. NSCLC represents 80-85% and SCLC 10-15% of the cases [30]. SCLC and NSCLC derive their names from the microscopic morphological aspects of the tumor cells. This thesis is focused on patients with NSCLC.

Depending on the original cells that develop into cancer, four main types of lung cancer can be distinguished, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and neuroendocrine tumors. The latter includes SCLC and large cell neuroendocrine carcinoma [37,34,36]. Discrimination between these types and categories of lung cancer is of importance given the consequences for treatment and survival.

Adenocarcinomas develop from epithelial cells of the lower respiratory tract and are mostly located in the periphery of the lung [34,36]. Histologically, these tumors may

demonstrate a lepidic, acinar, papillary, or micropapillary growth pattern. Solid adenocarcinoma show sheets of cells that lack the mentioned growth patterns [36]. The nuclei are located in the periphery of the cytoplasma with prominent nucleoli [36]. Glandular arrangements of cells may demonstrate highly variable morphological features [34,36]. Immunohistochemical markers expressed by cells of adenocarcinomas are TTF-1 and TTF-1 and/or Napsin A [34-36].

According to the degree of differentiation, squamous cell carcinomas are tumors that demonstrate intracellular bridging and keratinization. In addition, undifferentiated carcinomas that express markers of squamous cell differentiation are also part of these group of tumors [36]. Squamous cell carcinomas are often centrally located in a lobar or main bronchus [34]. They consist of a proliferation of atypical polygonal cells that invade desmoplastic stroma as single cells or solid nests and trabeculae [34,36]. Keratinization of the cytoplasm of these cells is often focal in tumors. Nuclei and nucleoli do not have prominent features. In these tumors inflammation and necrosis is often present [36]. Markers that are frequently used for immunohistochemistry are CK 5 and 6 and p63 or p40 [34,36]. In squamous cell carcinoma TTF-1 should be negative [36].

Large cell carcinomas are part of the group of undifferentiated non-small cell carcinomas [34]. Cells are cohesive and demonstrate evident malignant cytological features[36]. Tumors demonstrate sheets or nests of large polygonal cells with vesicular nuclei and prominent nucleoli with moderate cytoplasm [34,36]. Specimens should not demonstrate morphologic or immunohistochemical characteristics of other tumors [34,36].

Small cell carcinomas belong to the group of the neuroendocrine tumors [38]. They often present as bulky disease due to extensive hilar and mediastinal lymph node involvement [34]. At tissue level, small cell carcinomas consist of small to medium sized cells with scant cytoplasm and with round to spindled nuclei without prominent nucleoli [34,36]. The cells demonstrate a sheet-like growth pattern. A nested or trabecular pattern, peripheral palisading or rosette formation is less common. Necrosis is often present [34,36]. Napsin A is negative in all neuroendocrine tumors. TTF-1, chromogranin A, synaptophysin and NCAM/ CD-56 may be positive [34,36].

Large cell neuroendocrine carcinomas demonstrate histologic characteristics of neuroendocrine morphology (e.g., nested, trabecular, rosette-like, and peripheral palisading growth patterns) and neuroendocrine markers [36]. They are typically situated in peripheral regions of the upper lobes [34] and often demonstrate necrosis [37]. Cells are large and atypical with prominent nucleoli and abundant cytoplasm [34,36]. Mitosis are counted more than 10 per mm^2 [34,36]. Tumors are positive for markers NCAM/CD56, chromogranin A, synaptophysin [34,36].

Table 1. TNM 7th edition for staging lung cancer. Adapted from: Goldstraw et al., 2007 [40].

T (primary tumor)	
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1a	Tumor ≤ 2 cm in greatest dimension
T1b	Tumor > 2cmbut ≤ 3 cm in greatest dimension
T2	Tumor > 3cm but ≤ 7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm): involves main bronchus, ≥ 2 cm distal to the carina invades visceral pleura associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor > 3cmbut ≤ 5 cm in greatest dimension
T2b	Tumor > 5cm but ≤ 7 cm in greatest dimension
T3	Tumor > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium or tumor in the main bronchus 2cm distal to the carina but without involvement of the carina or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe
N (Regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion
M1b	Distant metastasis

Staging

The International Association for the Study of Lung Cancer (IASCL) has developed a Tumor Node Metastasis (TNM) staging system to stage lung cancer. Staging of lung cancer is of importance as treatment and prognosis is determined according to the stage of disease. Recently, the eight edition of this system was introduced to stage newly diagnosed lung cancer in patients [39]. However, patients described in this thesis are still staged according to the IASCL TNM 7th edition (Tables 1 and 2) [40-42]. For most of the studies in this thesis, the aim was to include patients with advanced-stage disease (i.e., stage IIIB and IV according to TNM 7th edition). Although in TNM 8th edition stage IIIB is divided into stage IIIB and IIIC and stage IV is divided into stage IV A and IV B, this aim to include patients with advanced-stage disease is still assured.

Table 2. Stages according to TNM 7th edition. Adapted from: Goldstraw et al., 2007 [40]

T and M stage	N stage			
	N0	*N1*	*N2*	*N3*
T1a,b	IA	IIA	IIIA	IIIB
T2a	IB	IIA	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIA	IIIB
T4	IIIA	IIIA	IIIB	IIIB
M1a	IV	IV	IV	IV
M1b	IV	IV	IV	IV

Treatment

This paragraph discusses the therapy options available for patients with NSCLC. As patients with SCLC were not included in the studies of this thesis, treatment for this patient group will not be discussed.

Treatment for lung cancer depends on disease stage and patient and disease-related factors (e.g., performance score, comorbidity, type of tumor). Some patients with lung cancer can be treated with curative intent with surgery, radiotherapy, platinum-based chemotherapy or a combination of these modalities (i.e., patients with stage I to III disease). A surgical resection of the tumor (e.g., lobectomy, segmentectomy) combined with a mediastinal lymphadenectomy is, in general, the treatment modality of choice for patients with stage I and II disease [43,44]. It is recommended to treat patients after a surgical resection with adjuvant chemotherapy in case of stage II disease [45,46,43,44], unexpected positive N2 lymph node(s) [43], resectable locally advanced NSCLC with single station N2 disease [43,47], or if the resection of the tumor is irradical [44]. Patients that are not able to receive surgery, for instance due to low performance status or compromised lung function, can be treated with stereotactic radiotherapy [48,43,44].

Patients with stage III disease are recommended to be treated with concurrent chemoradiotherapy over sequential chemoradiotherapy [49,50,43,44]. In those patients compromised by decreased performance status, older age or comorbidities sequential chemoradiotherapy may be preferred [43].

Despite the above mentioned curative options, even in stage I lung cancer metastatic disease does develop often as micro metastatic disease, which remains undiagnosed with present staging methods, or local disease was not cured by the original intervention. Moreover, the majority of patients are diagnosed with advanced-stage disease at first presentation and cannot be treated with curative intent. Treatment in these patients is often confined to platinum-based chemotherapy and associated with small survival benefits [51-53]. However, novel therapies, such as the first, second, and third generation of Endothelial Growth Factor Receptor tyrosine kinase inhibitors [54-58], Anaplastic Lymphoma Kinase inhibitors [59-62], and more recently Programmed Death-1 and Programmed Death-Ligand 1 inhibitors [63-66] have demonstrated significant improvement in progression free and overall survival in patient with NSCLC. It is recommended for patients with an targetable genetic abnormality to start with first line treatment with protein kinase inhibitors directed against this abnormality [44,56,60,67-73]. In addition to the screening for mutations, PD-L1 status of the tumor should be determined. In the absence of mutations and depending on PD-L1 expression, recently PD-L1 inhibitors as monotherapy or PD-1/PD-L1 inhibitors in combination with chemotherapy have been registered as first line treatment [44,67,74].

Besides the poor prognosis of advanced-stage disease, lung cancer and treatment-related adverse events can have a considerable impact on a patient's well-being [75]. Therefore, prolongation of survival with the preservation of a patient's well-being is an important goal of treatment [76].

PATIENT REPORTED OUTCOMES IN LUNG CANCER

Patients' well-being can be evaluated with the use of patient reported outcomes (PROs). A PRO reflects a patient's subjective perceptions and evaluation of elements related to their health and well-being. This information can primarily be provided by the patient and often not obtained by other means [77]. Evaluation of PROs is increasingly incorporated [78-86] and recommended [87] as an outcome parameter in (lung) cancer. Clinical trials investigating new therapies include PROs alongside the traditional endpoints of treatment (i.e., response and overall and progression free survival) to monitor the effects of treatment on patients well-being and to facilitate drug approval and legislation. However, although it is often claimed that Quality of Life (QoL) is incorporated, Health Status (HS) or Health-Related Quality of Life (HRQoL) are the concepts that are usually assessed in

studies, [76,85,79,82,78,81,86]. In contrast, in clinical practice patients' distress is often evaluated instead of HS, HRQoL, or QoL.

Besides the assessment of distress, HS, and HRQoL, it may be worthwhile to evaluate patients' Quality of Life (QoL) and feelings about their treatment. Insight in patients' QoL, expectations of treatment, feelings about side effects, and satisfaction with therapy may be of importance upon making treatment decisions and to monitor the impact of side effects on patients. The next sections will discuss the conceptualization and characteristics of these constructs, their intended use, and explore the implementation of them in shared treatment decision making.

HS, HRQoL, and QoL

Although there is some overlap between HS, HRQoL and QoL, they describe different concepts.

HS is functioning orientated and refers to limitations in physical abilities, mental status, and social activities [88]. For instance, a HS measure measures walking, as a derivative of physical activity, to the extent in which a patient is (un)able to perform this ability. In lung cancer, the EuroQoL-five dimensions (EQ-5D) [89] is the most frequently used in studies. The EQ-5D can be used to monitor patients' HS over time. Moreover, whereas other instruments are primarily developed for clinical research purposes, the EQ-5D health state index is also used for economic purposes (i.e., providing information regarding resource allocation, medical effectiveness in drug approval processes).

HRQoL represents the impact of disease and treatment on the feelings patients have about their functional capabilities and well-being [88]. In this thesis, the EORTC QLQ-C30 will be used to evaluate HRQoL as it is a cancer-specific HRQoL instrument [90]. However, considering the limited items discussing HRQoL, the focus on functioning, the negatively phrasing of almost all of the individual items, the EORTC QLQ-C30 could be perceived as an instrument that measures mostly HS and to a lesser extent HRQoL. The EORTC QLQ-C30 is primarily used in research to assess the effects of cancer and treatment on patients' functioning. In this thesis, the EORTC QLQ-C30 is used to assess the impact of disease and treatment on patients.

QoL, according to the definition of the WHO, is 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' [91]. 'It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs, and their relation to salient features of their environment' [91,92]. Thus, QoL evaluates patients' feelings (i.e., satisfied or bothered) about their functioning and well-being in at least three key areas (i.e., physical, psychological and social well-being). In addition, there is also room for domains like the environment (e.g., satisfaction with living conditions) or spirituality (e.g., mean-

ingfulness of personal life). HRQoL is QoL, but focusses on health. In that sense, it is less broadly defined as QoL. Moreover, HRQoL and QoL measures include negative as well as positive aspects (e.g., the possibility to meet people, to recreate or to learn new things) [88]. Considering that HS instruments do not provide information about patients' opinions and feelings, QoL measures offer additional valuable information as they ask patients to consider these. The World Health Organization Quality of Life group developed specific questionnaires to assess QoL [91-94]. In 1998, the WHOQOL-100 was published [92] and six years later an abbreviated version, the World Health Organization Quality of Life-BREF questionnaire (WHOQOL-BREF), to enable rapid assessment of QoL in epidemiological surveys and clinical studies in a wide range of disease areas [95,96].

Unfortunately, measures aimed to assess patients' QoL are not routinely utilized. It is possible that cancer researchers and physicians are not acquainted with QoL measures and their interpretation given the small amount of studies that have reported the results and use of these instruments in cancer patients. This thesis aims to to enhance the knowledge of physicians, researchers, and other health care professionals about the concept, definition, and application of QoL in lung cancer. Furthermore, considering the additional value of QoL assessment in relation to HS and HRQoL, a psychometric evaluation of the WHOQOL-BREF may be necessary to stimulate the incorporation of QoL assessment in lung cancer studies and daily practice. This may facilitate the comparison of QoL outcomes between treatment arms in studies investigating new therapies in lung cancer. In addition, validation and application of the WHOQOL-BREF may also help to determine which clinical and patient-related factors are associated with QoL. Knowledge of these factors may provide opportunities to improve lung cancer patients' QoL.

Distress

Distress reflects to the psychological (i.e., cognitive, emotional), social, and spiritual experience associated with a diagnosis and treatment of cancer [97-99]. In patients with cancer, the Distress Thermometer (DT) is used to screen for distress. The DT is a visual analogue scale [97] and is often completed by patients with its associated problem list that assesses the occurrence of practical, social, emotional, spiritual, and physical problems. As such, the DT and its problem list may share, at first glance, some similarities with HRQoL. Considering that HRQoL is a factor associated with survival, it may be worthwhile to investigate if a fast and efficient instrument as the DT can provide prognostic information as well. Especially in lung cancer patients with a limited prognosis and who are prone to a decrease in HRQoL due to cancer and treatment-related adverse events, this may be of importance. Therefore, in this thesis the relation between distress and survival will be explored.

Feelings about treatment

Insight in patients' treatment-related opinions may provide physicians with opportunities to improve therapy compliance, personalize treatment, treat side effects, but also to enlarge patients' role in treatment decision making. The Cancer Therapy Satisfaction Questionnaire (CTSQ) evaluates patients' treatment perspectives by assessing their expectations of therapy, feelings about side effects, and satisfaction with therapy [100-102]. Although the CTSQ has been validated before [100,102], a psychometric study in patients treated with chemotherapy has not been performed. Considering the impact of chemotherapy-related side effects on a patient's well-being, a validation study may provide opportunities to facilitate its clinical application and to further study the use of the CTSQ in patients with lung cancer treated with chemotherapy.

PROS IN TREATMENT DECISION MAKING AND CARE MANAGEMENT

Despite their potential use in clinical practice, results of PRO (e.g., HS, HRQoL and QoL) analyses in trials are often not discussed with patients upon making treatment decisions. In addition, PROs seem to play a relatively minor role in decisions regarding adaptation or the stop of palliative chemotherapy [103]. This is unfortunate as a study investigating patient participation in treatment decision making in patients with advanced-stage lung cancer, reported that 21.9% of patients were less involved in treatment decisions than they actually preferred. Of the patients that preferred some input in doctor's decision making or shared treatment decision making, 53.1% reported this was not achieved for treatment decisions [104].

These results suggest that improvements in shared treatment decision making are required. Knowledge of patients' opinions about this process may be helpful. Several systematic reviews demonstrated that PROs could affect treatment decisions in cancer patients [105-107]. PROs and their corresponding PROMs may also provide more reliable information regarding the burden of adverse events experienced by patients than observations performed by health care professionals [108,109]. A study which reported results of three randomized trials (i.e., one breast cancer, and two lung cancer trials) showed that treatment-related toxicities (i.e., anorexia, nausea, vomiting, constipation, diarrhea, and hair loss) were underreported by physicians in 40.7% to 74.4% of the patients who reported these toxicities by means of the EORTC QLQ-C30 [109]. Considering that in daily practice toxicities are often not systematically scored according to standardized methods, under-recognition of toxicities in daily practice may be even more distinct. Moreover, in patients receiving palliative chemotherapy in an outpatient setting, PRO-related issues were discussed significantly more often with those patients that completed the EORTC QLQ-C30 before consultation with their doctor and when both patients and physicians had

taken knowledge of the results before the actual consultation [110]. Similar results were reported by Velikova et al. [111].

Given the need for improved patient participation in treatment decision making and that PROs could facilitate this process, this thesis aims to stimulate the use of PROs in treatment decision making. Results of a study are reported that assesses patients' level of participation and factors (e.g., level of patients' decisional conflict, feeling uninformed) related to patients' opinions about their participation. Moreover, PROs will be related to clinical outcomes of treatments (e.g., side effects) and patient's opinions about their treatment. Our results could provide opportunities to improve patient participation in shared treatment decision making.

AIMS OF THIS THESIS

The aims of this thesis were: 1) to improve the knowledge of physicians, researchers, and other health care professionals about the concepts, definitions, and application of some of the most frequently used patient reported outcomes (PROs) in lung cancer, 2) to stimulate the use of QoL measurement in lung cancer by testing the psychometric properties of the World Health Organization Quality of Life-BREF instrument (WHOQOL-BREF), 3) to identify clinical and sociodemographic variables that are related to HRQoL and QoL in lung cancer, 4) to investigate the association between patients' feelings about treatment and HRQoL and QoL in lung cancer, and 5) to explore the process of treatment decision making in patients with lung cancer.

The following research questions are addressed:

- Chapter 1: Is the DT a predictor for overall survival after correction for variables such as age, gender, comorbidity, and histology in patients with lung cancer?
- Chapter 2: Is the WHOQOL-BREF a reliable and valid patient reported outcome measure (PROM) to evaluate QoL in patients with lung cancer and mesothelioma?
- Chapter: 3: Which factors (e.g., depressive symptoms, personality traits, age, gender, performance status, education) are associated with HRQoL and QoL in patients with lung cancer at the start of treatment?
- Chapter 4: Is the CTSQ a reliable and valid PROM to evaluate patients' treatment opinions in patients with lung cancer treated with chemotherapy?
- Chapter 5: Which CTSQ domains (i.e., expectations of therapy, feelings about side effects, and satisfaction with therapy) are associated with HRQoL and QoL in patients with lung cancer?
- Chapter 6: What is the added value of patients' satisfaction with therapy alongside outcomes as HRQoL, QoL, adverse events in patients with lung cancer?
- Chapter 7: What is the role of the patient in clinical decision making in lung cancer?

OUTLINE OF THIS THESIS

First, background information is provided regarding the research questions that are explored in the chapters of this thesis (**introduction**). The concepts of distress, HS, HRQoL, QoL, distress, and patients' treatment opinions are discussed. As the DT is often completed by patients with lung cancer, and may have some common grounds with HRQoL, **chapter 1** explores if the DT is associated with survival similarly as HRQoL is. **Chapter 2** reports about the psychometric properties of the WHOQOL-BREF. In addition, minimal clinically important differences were provided to stimulate the use of the WHOQOL-BREF in clinical practice. As HRQoL and QoL are often affected in patients, knowledge about which factors are related to these concepts might provide opportunities to enhance them. In **chapter 3**, potential factors that may be associated with HRQoL and QoL are explored among known factors in multivariable analyses. **Chapter 4** addresses the validation of a PROM that evaluates patients' feelings about treatment, while **chapter 5** assesses which of these feelings are related with HRQoL and QoL. Relating patients' perspectives about treatment with HRQoL and QoL may be of importance for shared treatment decision making and to improve patients' HRQoL and QoL. The role of patients' perspectives about treatment is further explored in **chapter 6** in which the additional value of patients' satisfaction with therapy is determined next to QoL, HRQoL, and adverse events. **Chapter 7** reports how patients value their role in treatment decision making in lung cancer and relates this to the experience of decisional conflict and information provision. This thesis concludes with a **general discussion**, in which the clinical implications of the results of the studies that form this thesis and future perspectives are discussed.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians 68 (6):394-424. doi:10.3322/caac.21492
2. IKNL (2019) https://www.cijfersoverkanker.nl. Accessed August 1, 2019
3. Hayat MJ, Howlader N, Reichman ME, Edwards BK (2007) Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. The oncologist 12 (1):20-37. doi:10.1634/theoncologist.12-1-20
4. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, Kunkler I, Group E-W (2007) Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. The Lancet Oncology 8 (9):784-796. doi:10.1016/S1470-2045(07)70246-2
5. Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallieres E, Groome P, Kennedy C, Krasnik M, Peake M, Shemanski L, Bolejack V, Crowley JJ, Asamura H, Rami-Porta R, Staging I, Prognostic Factors Committee AB, Participating I (2017) The IASLC Lung Cancer Staging Project: External Validation of the Revision of the TNM Stage Groupings in the Eighth Edition of the TNM Classification of Lung Cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 12 (7):1109-1121. doi:10.1016/j.jtho.2017.04.011
6. Torre LA, Siegel RL, Jemal A (2016) Lung Cancer Statistics. Advances in experimental medicine and biology 893:1-19. doi:10.1007/978-3-319-24223-1_1
7. Torre LA, Siegel RL, Ward EM, Jemal A (2014) International variation in lung cancer mortality rates and trends among women. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 23 (6):1025-1036. doi:10.1158/1055-9965.EPI-13-1220
8. Warren GW, Cummings KM (2013) Tobacco and lung cancer: risks, trends, and outcomes in patients with cancer. American Society of Clinical Oncology educational book American Society of Clinical Oncology Annual Meeting:359-364. doi:10.1200/EdBook_AM.2013.33.359
9. Thun MJ, Day-Lally CA, Calle EE, Flanders WD, Heath CW, Jr. (1995) Excess mortality among cigarette smokers: changes in a 20-year interval. American journal of public health 85 (9):1223-1230
10. (2004). In: The Health Consequences of Smoking: A Report of the Surgeon General. Reports of the Surgeon General. Atlanta (GA),
11. Remen T, Pintos J, Abrahamowicz M, Siemiatycki J (2018) Risk of lung cancer in relation to various metrics of smoking history: a case-control study in Montreal. BMC cancer 18 (1):1275. doi:10.1186/s12885-018-5144-5
12. Doll R, Peto R, Boreham J, Sutherland I (2004) Mortality in relation to smoking: 50 years' observations on male British doctors. Bmj 328 (7455):1519. doi:10.1136/bmj.38142.554479.AE
13. Siegel RL, Miller KD, Jemal A (2019) Cancer statistics, 2019. CA: a cancer journal for clinicians 69 (1):7-34. doi:10.3322/caac.21551
14. Hansen MS, Licaj I, Braaten T, Langhammer A, Le Marchand L, Gram IT (2018) Sex Differences in Risk of Smoking-Associated Lung Cancer: Results From a Cohort of 600,000 Norwegians. American journal of epidemiology 187 (5):971-981. doi:10.1093/aje/kwx339
15. Kim AS, Ko HJ, Kwon JH, Lee JM (2018) Exposure to Secondhand Smoke and Risk of Cancer in Never Smokers: A Meta-Analysis of Epidemiologic Studies. International journal of environmental research and public health 15 (9). doi:10.3390/ijerph15091981

16. Malinovsky G, Yarmoshenko I, Vasilyev A (2019) Meta-analysis of case-control studies on the relationship between lung cancer and indoor radon exposure. Radiation and environmental biophysics 58 (1):39-47. doi:10.1007/s00411-018-0770-5
17. Lorenzo-Gonzalez M, Ruano-Ravina A, Torres-Duran M, Kelsey KT, Provencio M, Parente-Lamelas I, Leiro-Fernandez V, Vidal-Garcia I, Castro-Anon O, Martinez C, Golpe-Gomez A, Zapata-Cachafeiro M, Pineiro-Lamas M, Perez-Rios M, Abal-Arca J, Montero-Martinez C, Fernandez-Villar A, Barros-Dios JM (2019) Lung cancer and residential radon in never-smokers: A pooling study in the Northwest of Spain. Environmental research 172:713-718. doi:10.1016/j.envres.2019.03.011
18. Kreuzer M, Fenske N, Schnelzer M, Walsh L (2015) Lung cancer risk at low radon exposure rates in German uranium miners. British journal of cancer 113 (9):1367-1369. doi:10.1038/bjc.2015.324
19. Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, Dodwell D, Ewertz M, Gray R, Jagsi R, Pierce L, Pritchard KI, Swain S, Wang Z, Wang Y, Whelan T, Peto R, McGale P, Early Breast Cancer Trialists' Collaborative G (2017) Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 35 (15):1641-1649. doi:10.1200/JCO.2016.72.0722
20. Lorigan P, Radford J, Howell A, Thatcher N (2005) Lung cancer after treatment for Hodgkin's lymphoma: a systematic review. The Lancet Oncology 6 (10):773-779. doi:10.1016/S1470-2045(05)70387-9
21. Cahoon EK, Preston DL, Pierce DA, Grant E, Brenner AV, Mabuchi K, Utada M, Ozasa K (2017) Lung, Laryngeal and Other Respiratory Cancer Incidence among Japanese Atomic Bomb Survivors: An Updated Analysis from 1958 through 2009. Radiation research 187 (5):538-548. doi:10.1667/RR14583.1
22. Nielsen LS, Baelum J, Rasmussen J, Dahl S, Olsen KE, Albin M, Hansen NC, Sherson D (2014) Occupational asbestos exposure and lung cancer--a systematic review of the literature. Archives of environmental & occupational health 69 (4):191-206. doi:10.1080/19338244.2013.863752
23. Leveque E, Lacourt A, Luce D, Sylvestre MP, Guenel P, Stucker I, Leffondre K (2018) Time-dependent effect of intensity of smoking and of occupational exposure to asbestos on the risk of lung cancer: results from the ICARE case-control study. Occupational and environmental medicine 75 (8):586-592. doi:10.1136/oemed-2017-104953
24. Liu C, Cui H, Gu D, Zhang M, Fang Y, Chen S, Tang M, Zhang B, Chen H (2017) Genetic polymorphisms and lung cancer risk: Evidence from meta-analyses and genome-wide association studies. Lung cancer 113:18-29. doi:10.1016/j.lungcan.2017.08.026
25. Wang J, Liu Q, Yuan S, Xie W, Liu Y, Xiang Y, Wu N, Wu L, Ma X, Cai T, Zhang Y, Sun Z, Li Y (2017) Genetic predisposition to lung cancer: comprehensive literature integration, meta-analysis, and multiple evidence assessment of candidate-gene association studies. Scientific reports 7 (1):8371. doi:10.1038/s41598-017-07737-0
26. Gordon SB, Bruce NG, Grigg J, Hibberd PL, Kurmi OP, Lam KB, Mortimer K, Asante KP, Balakrishnan K, Balmes J, Bar-Zeev N, Bates MN, Breysse PN, Buist S, Chen Z, Havens D, Jack D, Jindal S, Kan H, Mehta S, Moschovis P, Naeher L, Patel A, Perez-Padilla R, Pope D, Rylance J, Semple S, Martin WJ, 2nd (2014) Respiratory risks from household air pollution in low and middle income countries. The Lancet Respiratory medicine 2 (10):823-860. doi:10.1016/S2213-2600(14)70168-7
27. Kurmi OP, Arya PH, Lam KB, Sorahan T, Ayres JG (2012) Lung cancer risk and solid fuel smoke exposure: a systematic review and meta-analysis. The European respiratory journal 40 (5):1228-1237. doi:10.1183/09031936.00099511

28. Wang H, Yang L, Zou L, Huang D, Guo Y, Pan M, Tan Y, Zhong H, Ji W, Ran P, Zhong N, Lu J (2012) Association between chronic obstructive pulmonary disease and lung cancer: a case-control study in Southern Chinese and a meta-analysis. PloS one 7 (9):e46144. doi:10.1371/journal.pone.0046144
29. Mouronte-Roibas C, Leiro-Fernandez V, Fernandez-Villar A, Botana-Rial M, Ramos-Hernandez C, Ruano-Ravina A (2016) COPD, emphysema and the onset of lung cancer. A systematic review. Cancer letters 382 (2):240-244. doi:10.1016/j.canlet.2016.09.002
30. Travis WD (2011) Pathology of lung cancer. Clinics in chest medicine 32 (4):669-692. doi:10.1016/j.ccm.2011.08.005
31. Popper HH (2016) Progression and metastasis of lung cancer. Cancer metastasis reviews 35 (1):75-91. doi:10.1007/s10555-016-9618-0
32. Torok JA, Gu L, Tandberg DJ, Wang X, Harpole DH, Jr., Kelsey CR, Salama JK (2017) Patterns of Distant Metastases After Surgical Management of Non-Small-cell Lung Cancer. Clinical lung cancer 18 (1):e57-e70. doi:10.1016/j.cllc.2016.06.011
33. Buccheri G, Ferrigno D (2004) Lung cancer: clinical presentation and specialist referral time. The European respiratory journal 24 (6):898-904. doi:10.1183/09031936.04.00113603
34. Konopka KE (2016) Diagnostic Pathology of Lung Cancer. Seminars in respiratory and critical care medicine 37 (5):681-688. doi:10.1055/s-0036-1592172
35. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, Geisinger K, Hirsch FR, Ishikawa Y, Kerr KM, Noguchi M, Pelosi G, Powell CA, Tsao MS, Wistuba I, Panel WHO (2015) The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 10 (9):1243-1260. doi:10.1097/JTO.0000000000000630
36. Travis WD, Brambilla E, Burke A, Marx A, Nicholson AG (2015) WHO classification of tumours of the lung, pleura, thymus and heart. 4th edition. Lyon : International Agency for Research on Cancer:26-50
37. Sholl LM (2016) The Molecular Pathology of Lung Cancer. Surgical pathology clinics 9 (3):353-378. doi:10.1016/j.path.2016.04.003
38. Chuang SC, Fanidi A, Ueland PM, Relton C, Midttun O, Vollset SE, Gunter MJ, Seckl MJ, Travis RC, Wareham N, Trichopoulou A, Lagiou P, Trichopoulos D, Peeters PH, Bueno-de-Mesquita HB, Boeing H, Wientzek A, Kuehn T, Kaaks R, Tumino R, Agnoli C, Palli D, Naccarati A, Aicua EA, Sanchez MJ, Quiros JR, Chirlaque MD, Agudo A, Johansson M, Grankvist K, Boutron-Ruault MC, Clavel-Chapelon F, Fagherazzi G, Weiderpass E, Riboli E, Brennan PJ, Vineis P, Johansson M (2014) Circulating biomarkers of tryptophan and the kynurenine pathway and lung cancer risk. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 23 (3):461-468. doi:10.1158/1055-9965.EPI-13-0770
39. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, Nicholson AG, Groome P, Mitchell A, Bolejack V, International Association for the Study of Lung Cancer S, Prognostic Factors Committee AB, Participating I, International Association for the Study of Lung Cancer S, Prognostic Factors Committee Advisory B, Participating I (2016) The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 11 (1):39-51. doi:10.1016/j.jtho.2015.09.009
40. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, Postmus PE, Rusch V, Sobin L, International Association for the Study of Lung Cancer International Staging C, Participat-

ing I (2007) The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 2 (8):706-714. doi:10.1097/JTO.0b013e31812f3c1a

41. Groome PA, Bolejack V, Crowley JJ, Kennedy C, Krasnik M, Sobin LH, Goldstraw P, Committee IIS, Cancer R, Biostatistics, Observers to the C, Participating I (2007) The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 2 (8):694-705. doi:10.1097/JTO.0b013e31812d05d5
42. Rami-Porta R, Crowley JJ, Goldstraw P (2009) The revised TNM staging system for lung cancer. Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia 15 (1):4-9
43. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, Escriu C, Peters S, Committee EG (2017) Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 28 (suppl_4):iv1-iv21. doi:10.1093/annonc/mdx222
44. NCCN (2019) Non-Small Cell Lung Cancer (Version 5.2019). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed July 30, 2019
45. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, Spiro SG, Rolland E, Fossati R, Aubert D, Ding K, Waller D, Le Chevalier T, Group LC (2008) Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26 (21):3552-3559. doi:10.1200/JCO.2007.13.9030
46. Artal Cortes A, Calera Urquizu L, Hernando Cubero J (2015) Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. Translational lung cancer research 4 (2):191-197. doi:10.3978/j.issn.2218-6751.2014.06.01
47. Tsitsias T, Boulemden A, Ang K, Nakas A, Waller DA (2014) The N2 paradox: similar outcomes of pre- and postoperatively identified single-zone N2a positive non-small-cell lung cancer. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 45 (5):882-887. doi:10.1093/ejcts/ezt478
48. Verstegen NE, Lagerwaard FJ, Hashemi SM, Dahele M, Slotman BJ, Senan S (2015) Patterns of Disease Recurrence after SABR for Early Stage Non-Small-Cell Lung Cancer: Optimizing Follow-Up Schedules for Salvage Therapy. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 10 (8):1195-1200. doi:10.1097/JTO.0000000000000576
49. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC, Uitterhoeve A, Wang X, Stewart L, Arriagada R, Burdett S, Pignon JP (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 28 (13):2181-2190. doi:10.1200/JCO.2009.26.2543
50. Zatloukal P, Petruzelka L, Zemanova M, Havel L, Janku F, Judas L, Kubik A, Krepela E, Fiala P, Pecen L (2004) Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung cancer 46 (1):87-98. doi:10.1016/j.lungcan.2004.03.004
51. Group NM-AC (2008) Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from

16 randomized controlled trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26 (28):4617-4625. doi:10.1200/JCO.2008.17.7162

52. Non-Small Cell Lung Cancer Collaborative G (2010) Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. The Cochrane database of systematic reviews (5):CD007309. doi:10.1002/14651858.CD007309.pub2
53. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group (1995). Bmj 311 (7010):899-909
54. Morita S, Okamoto I, Kobayashi K, Yamazaki K, Asahina H, Inoue A, Hagiwara K, Sunaga N, Yanagitani N, Hida T, Yoshida K, Hirashima T, Yasumoto K, Sugio K, Mitsudomi T, Fukuoka M, Nukiwa T (2009) Combined survival analysis of prospective clinical trials of gefitinib for non-small cell lung cancer with EGFR mutations. Clinical cancer research : an official journal of the American Association for Cancer Research 15 (13):4493-4498. doi:10.1158/1078-0432.CCR-09-0391
55. Costa DB, Kobayashi S, Tenen DG, Huberman MS (2007) Pooled analysis of the prospective trials of gefitinib monotherapy for EGFR-mutant non-small cell lung cancers. Lung cancer 58 (1):95-103. doi:10.1016/j.lungcan.2007.05.017
56. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 31 (27):3327-3334. doi:10.1200/JCO.2012.44.2806
57. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, Zhou C, Hu CP, O'Byrne K, Feng J, Lu S, Huang Y, Geater SL, Lee KY, Tsai CM, Gorbunova V, Hirsh V, Bennouna J, Orlov S, Mok T, Boyer M, Su WC, Lee KH, Kato T, Massey D, Shahidi M, Zazulina V, Sequist LV (2015) Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. The Lancet Oncology 16 (2):141-151. doi:10.1016/S1470-2045(14)71173-8
58. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, Shepherd FA, He Y, Akamatsu H, Theelen WS, Lee CK, Sebastian M, Templeton A, Mann H, Marotti M, Ghiorghiu S, Papadimitrakopoulou VA, Investigators A (2017) Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. The New England journal of medicine 376 (7):629-640. doi:10.1056/NEJMoa1612674
59. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, De Pas T, Besse B, Solomon BJ, Blackhall F, Wu YL, Thomas M, O'Byrne KJ, Moro-Sibilot D, Camidge DR, Mok T, Hirsh V, Riely GJ, Iyer S, Tassell V, Polli A, Wilner KD, Janne PA (2013) Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. The New England journal of medicine 368 (25):2385-2394. doi:10.1056/NEJMoa1214886
60. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Iyer S, Reisman A, Wilner KD, Tursi J, Blackhall F, Investigators P (2014) First-line crizotinib versus chemotherapy in ALK-positive lung cancer. The New England journal of medicine 371 (23):2167-2177. doi:10.1056/NEJMoa1408440
61. Shaw AT, Kim TM, Crino L, Gridelli C, Kiura K, Liu G, Novello S, Bearz A, Gautschi O, Mok T, Nishio M, Scagliotti G, Spigel DR, Deudon S, Zheng C, Pantano S, Urban P, Massacesi C, Viraswami-Appanna K, Felip E (2017) Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. The Lancet Oncology 18 (7):874-886. doi:10.1016/S1470-2045(17)30339-X
62. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SI, Perol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T, Investigators AT (2017) Alectinib

versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. The New England journal of medicine 377 (9):829-838. doi:10.1056/NEJMoa1704795

63. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, Powderly JD, Heist RS, Carvajal RD, Jackman DM, Sequist LV, Smith DC, Leming P, Carbone DP, Pinder-Schenck MC, Topalian SL, Hodi FS, Sosman JA, Sznol M, McDermott DF, Pardoll DM, Sankar V, Ahlers CM, Salvati M, Wigginton JM, Hellmann MD, Kollia GD, Gupta AK, Brahmer JR (2015) Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33 (18):2004-2012. doi:10.1200/JCO.2014.58.3708
64. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhaufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crino L, Blumenschein GR, Jr., Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR (2015) Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. The New England journal of medicine 373 (17):1627-1639. doi:10.1056/NEJMoa1507643
65. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Aren Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. The New England journal of medicine 373 (2):123-135. doi:10.1056/NEJMoa1504627
66. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M, Fidler MJ, de Castro G, Jr., Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M, Garon EB (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 387 (10027):1540-1550. doi:10.1016/S0140-6736(15)01281-7
67. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, Mok TS, Reck M, Van Schil PE, Hellmann MD, Peters S, Committee EG (2018) Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 29 (Supplement_4):iv192-iv237. doi:10.1093/annonc/mdy275
68. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M (2009) Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. The New England journal of medicine 361 (10):947-957. doi:10.1056/NEJMoa0810699
69. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, Li W, Hou M, Shi JH, Lee KY, Xu CR, Massey D, Kim M, Shi Y, Geater SL (2014) Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. The Lancet Oncology 15 (2):213-222. doi:10.1016/S1470-2045(13)70604-1
70. Lim SM, Kim HR, Lee JS, Lee KH, Lee YG, Min YJ, Cho EK, Lee SS, Kim BS, Choi MY, Shim HS, Chung JH, La Choi Y, Lee MJ, Kim M, Kim JH, Ali SM, Ahn MJ, Cho BC (2017) Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring ROS1 Rearrangement. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 35 (23):2613-2618. doi:10.1200/JCO.2016.71.3701
71. Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, Riely GJ, Varella-Garcia M, Shapiro GI, Costa DB, Doebele RC, Le LP, Zheng Z, Tan W, Stephenson P, Shreeve SM, Tye LM, Christensen JG,

Wilner KD, Clark JW, Iafrate AJ (2014) Crizotinib in ROS1-rearranged non-small-cell lung cancer. The New England journal of medicine 371 (21):1963-1971. doi:10.1056/NEJMoa1406766

72. Planchard D, Besse B, Groen HJM, Souquet PJ, Quoix E, Baik CS, Barlesi F, Kim TM, Mazieres J, Novello S, Rigas JR, Upalawanna A, D'Amelio AM, Jr., Zhang P, Mookerjee B, Johnson BE (2016) Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. The Lancet Oncology 17 (7):984-993. doi:10.1016/S1470-2045(16)30146-2
73. Planchard D, Smit EF, Groen HJM, Mazieres J, Besse B, Helland A, Giannone V, D'Amelio AM, Jr., Zhang P, Mookerjee B, Johnson BE (2017) Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. The Lancet Oncology 18 (10):1307-1316. doi:10.1016/S1470-2045(17)30679-4
74. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR, Investigators K- (2016) Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. The New England journal of medicine 375 (19):1823-1833. doi:10.1056/NEJMoa1606774
75. Al-Batran SE, Hozaeel W, Tauchert FK, Hofheinz RD, Hinke A, Windemuth-Kieselbach C, Hubner A, Burmester M, Koenigsmann M, Wiegand J, Zur Hausen G, Linsse B, Kuhl R, Pauligk C, Arbeitsgemeinschaft Internistische O (2015) The impact of docetaxel-related toxicities on health-related quality of life in patients with metastatic cancer (QoliTax). Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 26 (6):1244-1248. doi:10.1093/annonc/mdv129
76. Belani CP, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M, Fossella F, group TAXs (2006) Effect of chemotherapy for advanced non-small cell lung cancer on patients' quality of life. A randomized controlled trial. Lung cancer 53 (2):231-239. doi:10.1016/j.lungcan.2006.05.003
77. Rothman ML, Beltran P, Cappelleri JC, Lipscomb J, Teschendorf B, Mayo FDAP-ROCMG (2007) Patient-reported outcomes: conceptual issues. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 10 Suppl 2:S66-75. doi:10.1111/j.1524-4733.2007.00269.x
78. Spiro SG, Rudd RM, Souhami RL, Brown J, Fairlamb DJ, Gower NH, Maslove L, Milroy R, Napp V, Parmar MK, Peake MD, Stephens RJ, Thorpe H, Waller DA, West P, Big Lung Trial p (2004) Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life. Thorax 59 (10):828-836. doi:10.1136/thx.2003.020164
79. Gridelli C, de Marinis F, Pujol JL, Reck M, Ramlau R, Parente B, Pieters T, Middleton G, Corral J, Winfree K, Melemed S, Zimmermann A, John W, Beyrer J, Chouaki N, Visseren-Grul C, Paz-Ares LG (2012) Safety, resource use, and quality of life in paramount: a phase III study of maintenance pemetrexed versus placebo after induction pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 7 (11):1713-1721. doi:10.1097/JTO.0b013e318267cf84
80. Yang JC, Hirsh V, Schuler M, Yamamoto N, O'Byrne KJ, Mok TS, Zazulina V, Shahidi M, Lungershausen J, Massey D, Palmer M, Sequist LV (2013) Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 31 (27):3342-3350. doi:10.1200/JCO.2012.46.1764
81. Chen G, Feng J, Zhou C, Wu YL, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu CP, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, Zhang L, You C (2013) Quality of life (QoL) analyses from OPTIMAL (CTONG-0802), a phase III, randomised, open-label study of first-line

erlotinib versus chemotherapy in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC). Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 24 (6):1615-1622. doi:10.1093/annonc/mdt012

82. Spigel DR, Patel JD, Reynolds CH, Garon EB, Hermann RC, Govindan R, Olsen MR, Winfree KB, Chen J, Liu J, Guba SC, Socinski MA, Bonomi P (2015) Quality of life analyses from the randomized, open-label, phase III PointBreak study of pemetrexed-carboplatin-bevacizumab followed by maintenance pemetrexed-bevacizumab versus paclitaxel-carboplatin-bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 10 (2):353-359. doi:10.1097/JTO.0000000000000277
83. Rittmeyer A, Gorbunova V, Vikstrom A, Scherpereel A, Kim JH, Ahn MJ, Chella A, Chouaid C, Campbell AK, Barlesi F (2013) Health-related quality of life in patients with advanced nonsquamous non-small-cell lung cancer receiving bevacizumab or bevacizumab-plus-pemetrexed maintenance therapy in AVAPERL (MO22089). Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 8 (11):1409-1416. doi:10.1097/JTO.0b013e3182a46bcf
84. Novello S, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krzakowski M, von Pawel J, Gottfried M, Bondarenko I, Liao M, Barrueco J, Gaschler-Markefski B, Griebsch I, Palmer M, Reck M, Group LU-LS (2015) Analysis of patient-reported outcomes from the LUME-Lung 1 trial: a randomised, double-blind, placebo-controlled, Phase III study of second-line nintedanib in patients with advanced non-small cell lung cancer. European journal of cancer 51 (3):317-326. doi:10.1016/j.ejca.2014.11.015
85. Pujol JL, Paz-Ares L, de Marinis F, Dediu M, Thomas M, Bidoli P, Corral J, San Antonio B, Chouaki N, John W, Zimmermann A, Visseren-Grul C, Gridelli C (2014) Long-term and low-grade safety results of a phase III study (PARAMOUNT): maintenance pemetrexed plus best supportive care versus placebo plus best supportive care immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. Clinical lung cancer 15 (6):418-425. doi:10.1016/j.cllc.2014.06.007
86. Di Maio M, Leighl NB, Gallo C, Feld R, Ciardiello F, Butts C, Maione P, Gebbia V, Morgillo F, Wierzbicki R, Favaretto A, Alam Y, Cinieri S, Siena S, Bianco R, Riccardi F, Spatafora M, Ravaioli A, Felletti R, Fregoni V, Genestreti G, Rossi A, Mancuso G, Fasano M, Morabito A, Tsao MS, Signoriello S, Perrone F, Gridelli C, Investigators T (2012) Quality of life analysis of TORCH, a randomized trial testing first-line erlotinib followed by second-line cisplatin/gemcitabine chemotherapy in advanced non-small-cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 7 (12):1830-1844. doi:10.1097/JTO.0b013e318275b327
87. Basch E, Abernethy AP, Mullins CD, Reeve BB, Smith ML, Coons SJ, Sloan J, Wenzel K, Chauhan C, Eppard W, Frank ES, Lipscomb J, Raymond SA, Spencer M, Tunis S (2012) Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 30 (34):4249-4255. doi:10.1200/JCO.2012.42.5967
88. De Vries J. DOBL (2014) The choice determines the success. Nederlands tijdschrift voor Orthopaedie 21 (2):39-42
89. TheEuroQolGroup (1990) EuroQol-a new facility for the measurement of health-related quality of life. Health policy 16 (3):199-208
90. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 85 (5):365-376

91. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization (1995). Social science & medicine 41 (10):1403-1409
92. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties (1998). Social science & medicine 46 (12):1569-1585
93. Power MJ, Green AM, Group WH-D (2010) Development of the WHOQOL disabilities module. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 19 (4):571-584. doi:10.1007/s11136-010-9616-6
94. Power M, Quinn K, Schmidt S, Group W-O (2005) Development of the WHOQOL-old module. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 14 (10):2197-2214. doi:10.1007/s11136-005-7380-9
95. Skevington SM, Lotfy M, O'Connell KA, Group W (2004) The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 13 (2):299-310
96. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group (1998). Psychological medicine 28 (3):551-558
97. Holland JC (1997) Preliminary guidelines for the treatment of distress. Oncology 11 (11A):109-114; discussion 115-107
98. Ugalde A, Aranda S, Krishnasamy M, Ball D, Schofield P (2012) Unmet needs and distress in people with inoperable lung cancer at the commencement of treatment. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 20 (2):419-423. doi:10.1007/s00520-011-1296-4
99. NCCN (2019) Distress Management (Version 3.2019). https://www.nccn.org/professionals/physician_gls/pdf/distress.pdf. Accessed July 30, 2019
100. Trask PC, Tellefsen C, Espindle D, Getter C, Hsu MA (2008) Psychometric validation of the cancer therapy satisfaction questionnaire. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 11 (4):669-679. doi:10.1111/j.1524-4733.2007.00310.x
101. Abetz L, Coombs JH, Keininger DL, Earle CC, Wade C, Bury-Maynard D, Copley-Merriman K, Hsu MA (2005) Development of the cancer therapy satisfaction questionnaire: item generation and content validity testing. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 8 Suppl 1:S41-53. doi:10.1111/j.1524-4733.2005.00073.x
102. Park SJ, An SM, Kim SH (2013) Development of a Korean version of the Cancer Therapy Satisfaction Questionnaire (CTSQ): cross-cultural adaptation, reliability, and validity. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 22 (2):431-436. doi:10.1007/s11136-012-0164-0
103. Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK (2002) Role of health-related quality of life in palliative chemotherapy treatment decisions. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 20 (4):1056-1062
104. Pardon K, Deschepper R, Vander Stichele R, Bernheim J, Mortier F, Schallier D, Germonpre P, Galdermans D, Van Kerckhoven W, Deliens L (2011) Are patients' preferences for information and participation in medical decision-making being met? Interview study with lung cancer patients. Palliative medicine 25 (1):62-70. doi:10.1177/0269216310373169
105. Blazeby JM, Avery K, Sprangers M, Pikhart H, Fayers P, Donovan J (2006) Health-related quality of life measurement in randomized clinical trials in surgical oncology. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 24 (19):3178-3186. doi:10.1200/JCO.2005.05.2951

106. Efficace F, Feuerstein M, Fayers P, Cafaro V, Eastham J, Pusic A, Blazeby J, Group EQoL (2014) Patient-reported outcomes in randomised controlled trials of prostate cancer: methodological quality and impact on clinical decision making. European urology 66 (3):416-427. doi:10.1016/j.eururo.2013.10.017

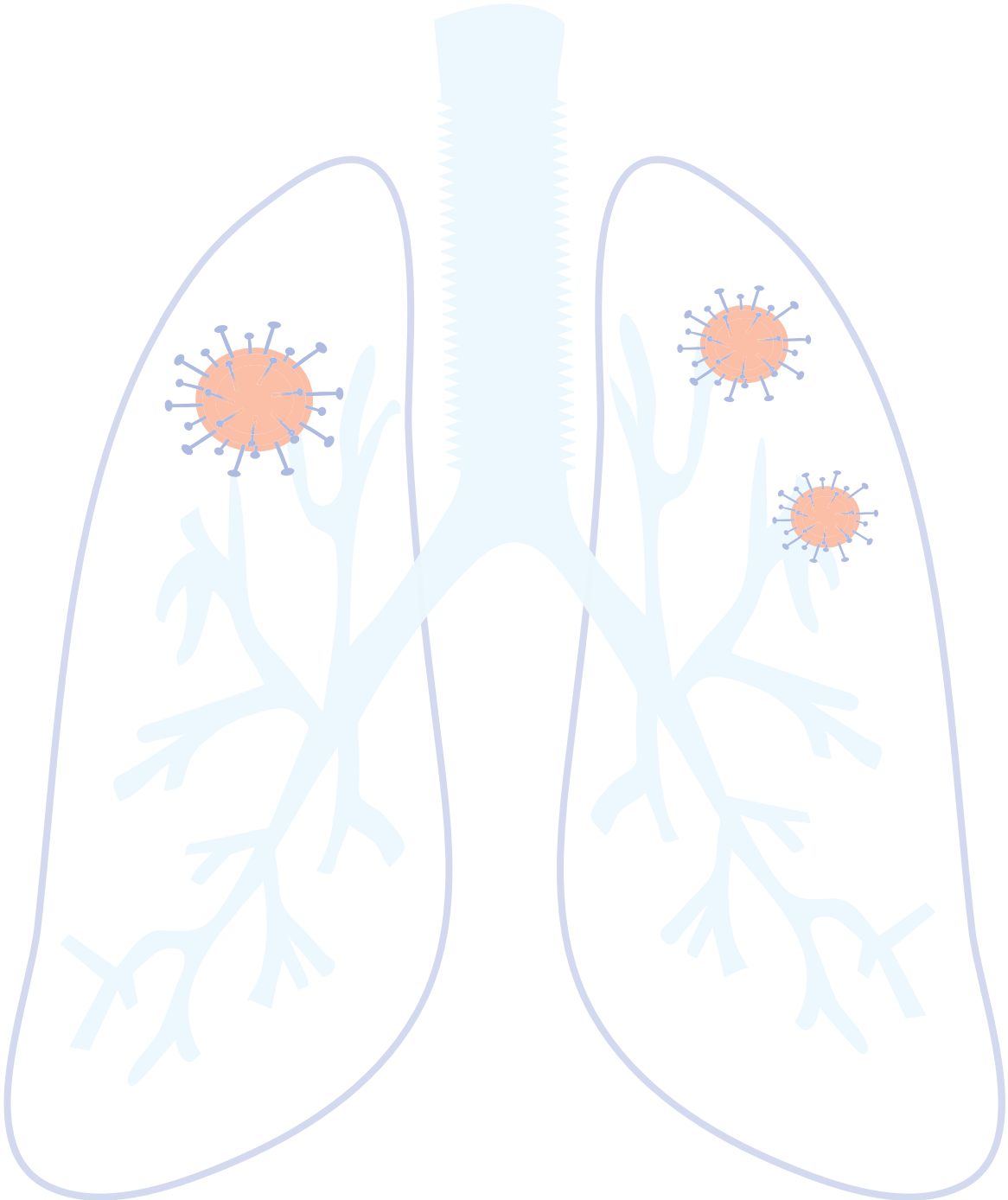
107. Efficace F, Jacobs M, Pusic A, Greimel E, Piciocchi A, Kieffer JM, Gilbert A, Fayers P, Blazeby J, Registry EQoLGPROMOTIO-P (2014) Patient-reported outcomes in randomised controlled trials of gynaecological cancers: investigating methodological quality and impact on clinical decision-making. European journal of cancer 50 (11):1925-1941. doi:10.1016/j.ejca.2014.04.005

108. Butler L, Bacon M, Carey M, Zee B, Tu D, Bezjak A (2004) Determining the relationship between toxicity and quality of life in an ovarian cancer chemotherapy clinical trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 22 (12):2461-2468. doi:10.1200/JCO.2004.01.106

109. Di Maio M, Gallo C, Leighl NB, Piccirillo MC, Daniele G, Nuzzo F, Gridelli C, Gebbia V, Ciardiello F, De Placido S, Ceribelli A, Favaretto AG, de Matteis A, Feld R, Butts C, Bryce J, Signoriello S, Morabito A, Rocco G, Perrone F (2015) Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33 (8):910-915. doi:10.1200/JCO.2014.57.9334

110. Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK (2002) Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. Jama 288 (23):3027-3034

111. Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, Selby PJ (2004) Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 22 (4):714-724. doi:10.1200/JCO.2004.06.078



CHAPTER 1

The Distress Thermometer as a predictor for survival in stage III lung cancer patients treated with chemotherapy

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ABSTRACT

Background: Depression and Health-Related Quality of Life have been associated with prognosis in lung cancer. As the Distress Thermometer (DT) measures emotional problems and may share similarities with aspects of Health Related Quality of Life, we aimed to retrospectively assess the prognostic value of the Distress Thermometer in lung cancer patients treated with chemotherapy.

Methods: Patients with stage III lung cancer who were treated at the day-care oncology unit with chemotherapy containing carboplatin from 2009 to 2014 and in whom a DT was performed at the time of the first cycle of chemotherapy were included in this study.

Results: In total, one hundred and thirteen patients were included in the analysis. In the simple Cox regression analysis, overall survival did not significantly differ according to DT score. No significant differences in DT score according to stage, histology, (intended) treatment, age, sex, and comorbidity were observed. Also in a multivariable model the DT was not prognostic for overall survival, whereas sex and (intended) treatment was.

Conclusions: In this study no prognostic value of the DT could be established in patients with stage III lung cancer treated with carboplatin. Further research is warranted to address this issue.

INTRODUCTION

Distress reflects the spectrum of psychological problems (i.e., cognitive, emotional, social, and spiritual) associated with a diagnosis and treatment of cancer and can be measured by the Distress Thermometer (DT) [1-3]. In general, the DT is completed together with a problem list. The clinical application of the DT has been extensively investigated in patients with different forms and stages of malignancies demonstrating acceptable to good accuracy in detecting distress [4-7] as well as change in distress [8]. One study in patients diagnosed with breast cancer demonstrated that moderate to severe distress was related to a significant decrease in Health-Related Quality of Life (HRQoL) and that for the HRQoL scales for which a minimally important difference has been established this decrease ranged from two to three and a half times the established minimally important difference [9]. According to the results of this study, the DT could address aspects of distress beyond psychological problems and is therefore linked to HRQoL. Furthermore, the resemblance of items of the problem list with items of HRQoL questionnaires (e.g., the European Organization for Research and Treatment of cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)), and the good to moderately strong relation of the problem list with the DT [6] support an association with HRQoL.

To date, multiple studies have evaluated HRQoL as a predictor of survival in lung cancer patients [10-16]. Overall/global HRQoL is often observed to be a prognostic factor in these studies [10,13-16]. Considering that depression has been associated with a decreased survival in patients with lung cancer [17,18] and the considerable overlap between the problem list and HRQoL, the DT may be utilised as a fast, efficient, and promising tool to provide prognostic information similar as overall/global HRQoL does. Especially in lung cancer patients with a limited prognosis and who are at risk for cancer and treatment-related adverse events and thus a decline in HRQoL this may be of importance. As the relation of the DT with survival has not been investigated before in lung cancer, we hypothesized that the DT is a predictor for overall survival (OS) after correction for age, gender, comorbidity, and histology.

METHODS

Patient selection

Patients diagnosed with lung cancer treated at the day-care oncology unit of a large teaching hospital (Amphia Hospital, Breda, The Netherlands) specialized in lung cancer care from August 2009 until August 2014 were retrospectively enrolled in our study if they met the following criteria: they were aged 18 years or older, were diagnosed with stage III non-small cell lung carcinoma (NSCLC) or stage III small cell lung carcinoma (SCLC) according

to TNM 7th edition [19], were treated with first line chemotherapeutic regiments containing carboplatin, had a level of functioning which indicated that completion of the DT could be beneficial to optimize care, and had completed the DT at least at the time of the first cycle of treatment. We limited our inclusion to patients treated with carboplatin as the DT was more consistently performed in the day-care clinic of our department than at the clinical oncology unit. To optimize homogeneity of the patient sample only patients with stage III disease were analyzed as this was the largest population in our series. Patients with cisplatin treatment were not included as they require hospitalization. If no information on clinical treatment or survival was available, patients were excluded. As the included patients received standard care and were not exposed to additional interventions this study did not fall under the Medical Research Involving Human Subjects Act (WMO). In addition, informed consent of each patient was not required as the all data was handled to Dutch privacy law Therefore, permission of a medical ethics committee was not necessary.

The Distress Thermometer

The DT is a visual analogue scale originally developed to describe the level of distress that patients experience. Its scale ranges from 0 (no distress) to 10 (extreme distress) [1]. The DT is completed together with the problem list by patients at the time of the first, third, and fourth cycle of chemotherapy at our department. The Dutch version of the problem list comprises 47 items. It addresses practical, social, emotional, spiritual, and physical problems. The psychometric properties of the DT combined with the Dutch problem list have been investigated by Tuinman et al. [6]. They observed a good internal consistency, except for practical problems ($\alpha = 0.60$) and spiritual problems ($\alpha = 0.64$). In addition, a strong correlation between the DT and emotional problems ($r = 0.61$), physical problems ($r = 0.64$), and the total problem list ($r = 0.68$) was found. Tuinman et al. reported a sensitivity of 0.85 and a specificity of 0.69 of the DT at a cut-off value of five after performing receiver operator characteristics analysis with a Hospital Anxiety Depression Scale score of ≥ 15 as a gold standard [6].

Additional information

Sociodemographic information (i.e., age, gender), comorbidity, histological tumor type (i.e., adenocarcinoma, squamous cell carcinoma, NSCLC otherwise not differentiated or adenocarcinoma in situ, and SCLC), cancer stage according to TNM 7th edition (i.e., IIIA and IIIB; patients originally staged according to TNM 6th edition were restaged using TNM 7th edition) [19], treatment (i.e., chemotherapy, surgery in combination with (neo)adjuvant chemotherapy or chemotherapy in combination with radiotherapy (i.e., concurrent or sequential), and OS was retrieved from the electronic patient information system and the cancer registration of the Netherlands Comprehensive Cancer Organisation.

Statistical analysis

The Mann-Whitney U test and one-way ANOVA were used to compare DT scores obtained at the time of the first cycle of chemotherapy.

Patient's OS was defined as the time between date of histological diagnosis and date of death from any cause or date of last contact/last known to be alive**.** Patients who were still alive at the time of analysis were censored at 31 December 2014.

Survival probabilities were estimated and expressed by Kaplan-Meier curves. Curves were compared with the log rank test. Univariable Cox proportional hazards models were used to evaluate the DT at the first cycle of chemotherapy to be a predictor for OS. In addition, univariable Cox proportional hazards models were built to evaluate the individual significance of the pretreatment covariates as a predictor of OS. Covariates (i.e., age, gender, comorbidity, histology, Charlson Comorbidity Index and (intended) treatment) were chosen as based on previous studies.

The DT score was then entered in a multivariable Cox proportional hazards model with the remaining determinants after univariable analyses. Models were used in which the DT was analyzed as a continuous variable, and as a dichotomous variable. Dichotomous variables were created by categorizing patients into two groups based on the DT cut-off value of five as proposed by Tuinman et al. [6].

P-values of $p \leq 0.05$ were regarded as significant. Data were analyzed with the use of IBM SPSS Statistics for Windows version 21.0.

RESULTS

Patients and results of the DT

Table 1 describes the included patients. Of the 495 identified patients treated with carboplatin chemotherapy, 281 were discarded from the analyses since the DT was not completed at the first cycle of chemotherapy. Of the remaining 214 patients, 113 patients were diagnosed with stage III disease. The age of these patients ranged from 37 to 79 years, with a mean of 63.3 (SD 8.7). Forty-six percent of the patients were diagnosed with adenocarcinoma. The majority of the patients received a combination of chemotherapy and radiotherapy. Thirty-nine patients (34.5%) demonstrated DT scores higher than the cut-off score of ≥ 5. No significant differences were observed between distributions of scores or mean scores of the DT for different patient characteristics.

Table 1. Characteristics of study population and distribution of DT scores

Characteristic	Overall sample (N=214)	Mean DT score (SD)	Median (range)	P	DT < 5	DT ≥ 5
Age, years						
Mean (SD)	63.3 (8.7)					
Min, max	37, 79					
Sex[a]						
Male	64 (56.6)	3.3 (2.7)	3.0 (0.0-9.0)	0.91	43 (38.1)	21 (18.6)
Female	49 (43.4)	3.3 (2.4)			31 (27.4)	18 (15.9)
DT						
Median	3.0					
Range	0.0-9.0					
Histology[b]						
Adenocarcinoma	52 (46.0)	3.3 (2.5)	3.0 (0.0-9.0)	0.18	34 (30.1)	18 (15.9)
Squamous cell carcinoma	41 (36.3)	3.1 (2.4)	3.0 (0.0-8.0)		29 (25.7)	12 (10.6)
NSCLC otherwise not specified, adenocarcinoma in situ	6 (5.3)	5.4 (2.9)	6.0 (0.0-8.0)		1 (0.9)	5(4.4)
SCLC	14 (12.4)	2.8 (2.9)	2.1 (0.0-9.0)		10 (8.8)	4 (3.5)
CCI						
Median	1.0					
Min, max	0, 5					
0-1[a]	98 (86.7)	3.2 (2.4)	3.0 (0.0-9.0)	0.42	67 (59.3)	31 (27.4)
>2	15 (13.3)	4.0 (3.3)	5.0 (0.0-9.0)		7 (6.2)	8 (7.1)
Treatment[b]						
Chemotherapy	9 (8.0)	4.2 (2.7)	5.0 (0.0-8.0)	0.34	4 (3.5)	5 (4.4)
Surgery and (neo) adjuvant chemotherapy	14 (12.4)	3.9 (2.7)	4.0 (0.0-9.0)		9 (8.0)	5 (4.4)
Chemotherapy and sequential/concurrent radiotherapy	90 (79.6)	3.1 (2.5)	3.0 (0.0-9.0)		61 (54.0)	29 (25.7)

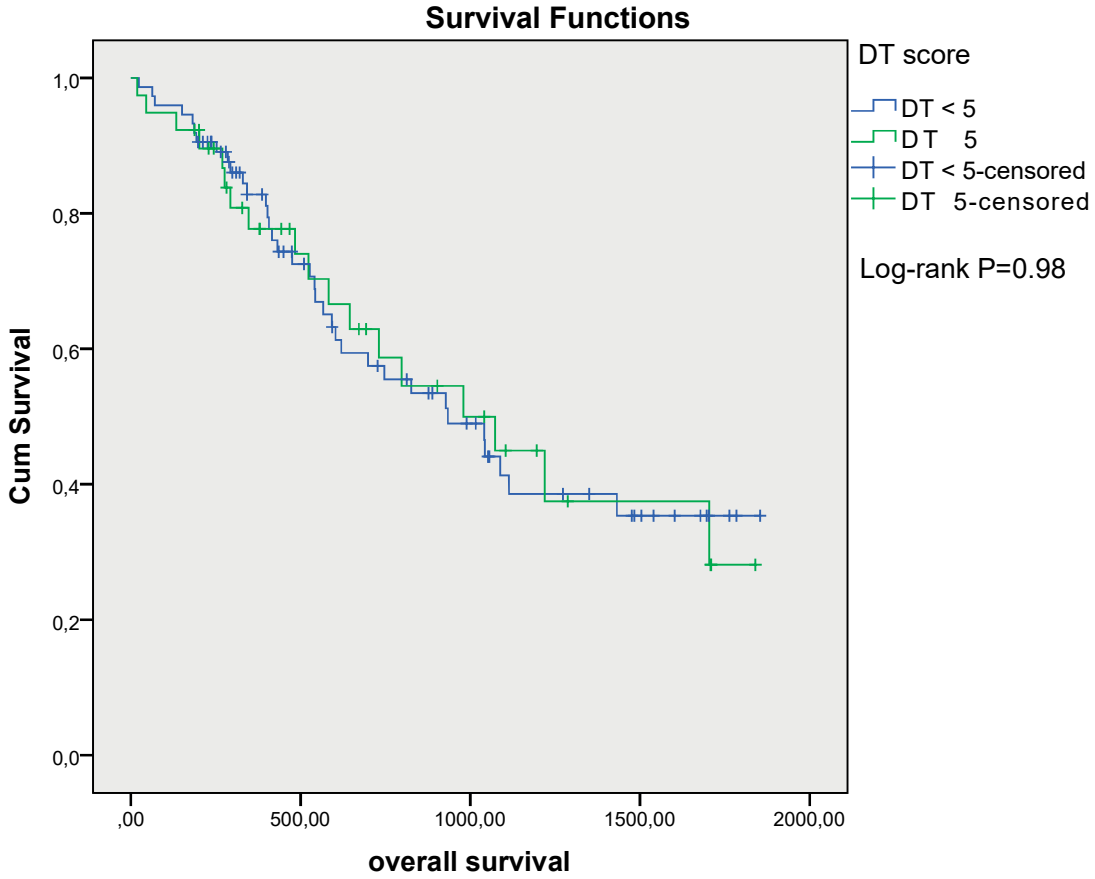
Values are given in numbers (percentages) and means unless stated otherwise.
[a]P-values calculated with the Mann-Whitney U test.
[b]P-values calculated with one-way ANOVA.
Abbreviations: N, number of patients; SD, standard deviation; DT, distress thermometer score at first cycle of chemotherapy; NSCLC, non-small cell lung carcinoma; SCLC, small cell lung carcinoma, CCI, Charlson Comorbidity Index.

Survival estimates and Cox proportional hazards models

Patients with a DT score < 5.0 did not differ to patients with a score of ≥ 5.0 with regard to age, sex, histology, comorbidity, and (intended) treatment. Figure 1 shows the Kaplan-Meier curves of the patients dichotomized by a cut-off score ≥ 5.0. No significant differences were observed (p = 0.98). Age and (intended) treatment independently predicted OS (Table 2). The DT score at the first cycle of chemotherapy as a continuous variable was

in the univariable analysis not prognostic for OS. Utilizing a dichotomized DT (cut-off ≥ 5) in the univariable analysis revealed similar results. The multivariable model with age and (intended) treatment as variables demonstrated only (intended) treatment to be a significant factor for decreased OS.

Fig. 1 Overall survival based on Distress Thermometer (DT) score at first cycle of chemotherapy



DISCUSSION

To the best of our knowledge, the present study is the first in which the association between distress as measured by the DT and OS in cancer is studied. Although the DT and its problem list have some common grounds with generic HRQoL instruments, we were not able to identify it as a prognostic factor for OS in lung cancer.

It is possible that our negative results are explained by the inability of the DT to measure all aspects of HRQoL. Validity of the DT has been demonstrated by comparison with questionnaires investigating aspects related to cognitive and emotional functioning [20], but not with generic HRQoL questionnaires. Tuinman et al. demonstrated that the DT had a high correlation with the physical ($r = 0.64$) domain and was moderately associated with

Table 2. Results of the univariable and multivariable[a] analyses for OS

Covariates	**Univariable analyses**		**Multivariable analysis**	
	HR	95% CI	HR	95% CI
DT	1.02	0.91-1.14		
DT				
<5	0.99	0.56-1.76		
≥5[b]				
Age	**1.04**	**1.00-1.07**	1.03	1.00-1.07
Sex				
Male	0.71	0.41-1.22		
Female[b]				
Histology				
Adenocarcinoma[b]				
Squamous cell carcinoma	1.72	0.95-3.13		
NSCLC otherwise not specified, adenomatous hyperplasia	1.33	0.31-5.71		
SCLC	1.01	0.43-2.39		
CCI				
0-1	0.98	0.44-2.18		
> 2[b]				
Treatment				
Surgery and (neo)adjuvant chemotherapy[b]				
Chemotherapy	1.45	0.57-3.71	1.43	0.56-3.66
Chemotherapy and sequential/concurrent radiotherapy	**6.87**	**2.16-21.85**	**6.34**	1.99-20.19

[a]All variables entered together in one block.
[b]Reference group.
Abbreviations: OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; DT, distress thermometer score at first cycle of chemotherapy as a continuous variable; NSCLC, non-small cell lung carcinoma; SCLC, small cell lung carcinoma, CCI, Charlson Comorbidity Index.

the practical (r = 0.39) and family/social domain (r = 0.31) of the problem list [6]. Generic HRQoL questionnaires, such as the EORTC QLQ-C30, address similar aspects of a patient's well-being (e.g., physical functioning/symptoms, social functioning). It would be interesting to explore whether the validity of the DT and its problem list can be established by comparing them with such instruments [6].

Similar to the study of Tuinman et al. we had to exclude identified large number of patients [6]. This may be explained by several reasons. First, patients may refuse to complete the DT and the problem list due to the length of the instrument (47 problems). Moreover, as the items of the problem list can only be answered by YES or NO, patients may not recognize their situation in these options, or may consider some of the items as irrelevant. Secondly, health care personnel may not have provided the DT to patients on a regularly basis as the score of the DT would not likely result in adjustment of care. This holds true for

patients considered not to experience any distress but also in patients experiencing high levels of distress in whom already extra measures are taken.

Given the previous considerations, the included patients are likely to represent a population in which patients with the best and those with the worst clinical status were not selected. It is likely this selection bias contributed to the negative results of this study. For future studies, it might be of interest to include a broader patient population and to investigate whether completion of patient outcome measures (such as the DT) is influenced by a reduced HRQoL at the start of treatment or due to treatment related side effects.

We found the mean DT score in our patients to be comparable with other studies in lung cancer [3,21] but lower as seen in patients with cancer from other sites [6,7]. This finding is in contrast with the knowledge that many lung cancer patients have a bad prognosis and considerable diagnosis and treatment related stress. An explanation for this observation could be the in general low socio-economic status of lung cancer patients which could prevent them from adequately expressing their distress. Moreover, distress may also be influenced by age. Recently, it has been demonstrated that an increased age is related to the experience of decreased distress in cancer [22]. As lung cancer patients, in general, have a higher age at diagnosis, this may also explain the relatively low mean DT score. Thirdly, a considerable part of lung cancer patients have severe comorbidity (e.g., cardiac and pulmonary disease) [23] so that they are familiar with a certain amount of distress.

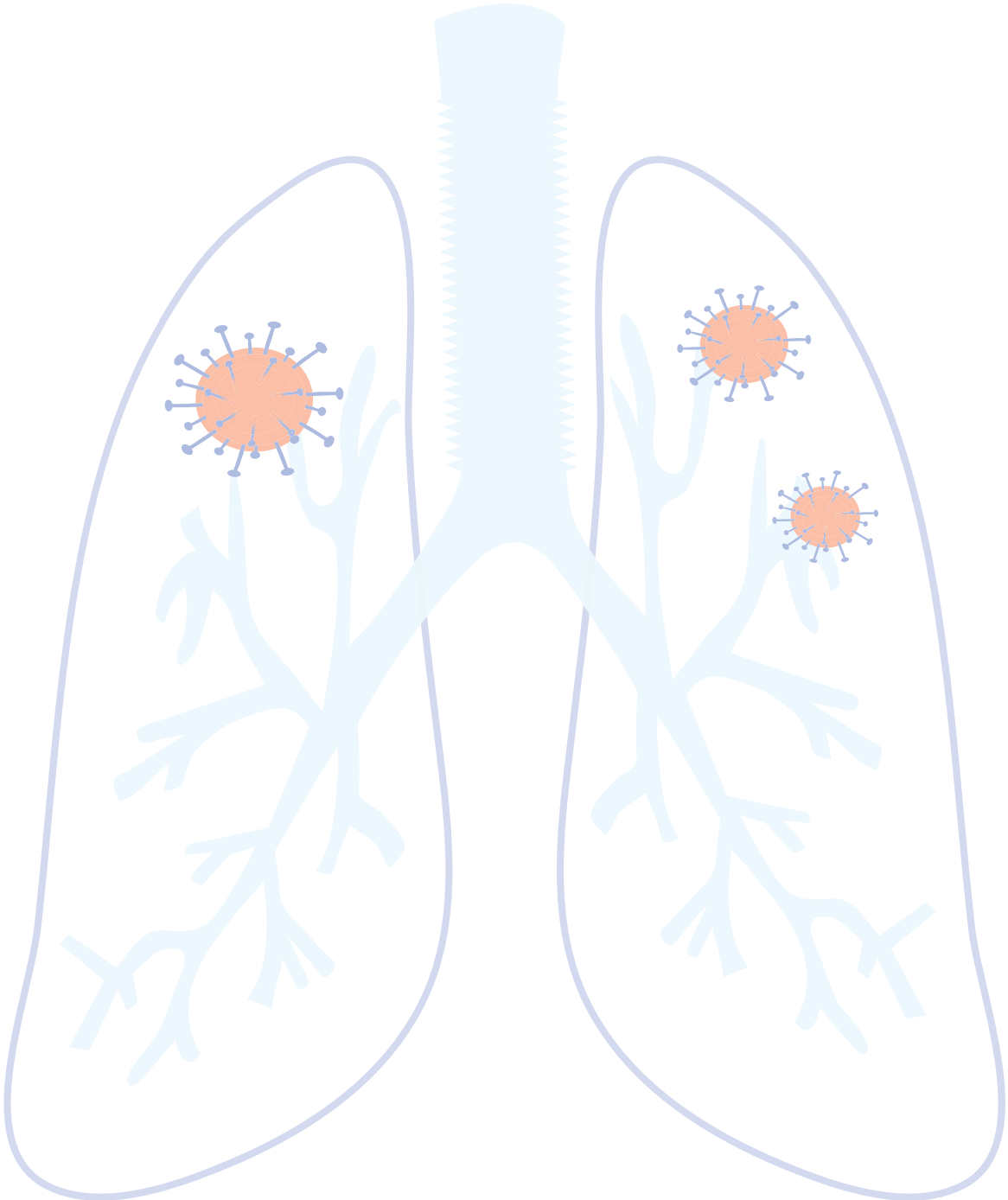
Given the potential relationship of the DT with global/overall HRQoL, we used only the DT without the problem list to perform the calculations in this report. However, the negative results of our study should not prevent further prospective research of the DT and the problem list beyond their intended use. The role of the DT and the problem list should be more extensively evaluated in studies investigating patient reported outcome measures to determine its concurrent validity with generic HRQoL questionnaires, to evaluate its validity and reliability in lung cancer and to assess its prognostic relevance. Such studies may offer opportunities to enhance the implementation of the DT and problem list in daily practice, to recognize patients who are prone to a negative change in HRQoL during treatment and to identify even those patients at risk for a poorer prognosis.

In conclusion, the DT was not found to be prognostic in a cohort of patients with stage III disease treated with Carboplatin. Further prospective investigations are warranted incorporating a large patient cohort with a broader treatment regimen.

REFERENCES

1. Holland JC (1997) Preliminary guidelines for the treatment of distress. Oncology 11 (11A):109-114; discussion 115-107
2. NCCN (2014) NCCN clinical practice guideline Distress Management version 2.
3. Ugalde A, Aranda S, Krishnasamy M, Ball D, Schofield P (2012) Unmet needs and distress in people with inoperable lung cancer at the commencement of treatment. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 20 (2):419-423. doi:10.1007/s00520-011-1296-4
4. Ma X, Zhang J, Zhong W, Shu C, Wang F, Wen J, Zhou M, Sang Y, Jiang Y, Liu L (2014) The diagnostic role of a short screening tool--the distress thermometer: a meta-analysis. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 22 (7):1741-1755. doi:10.1007/s00520-014-2143-1
5. Mitchell AJ (2007) Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 25 (29):4670-4681. doi:10.1200/JCO.2006.10.0438
6. Tuinman MA, Gazendam-Donofrio SM, Hoekstra-Weebers JE (2008) Screening and referral for psychosocial distress in oncologic practice: use of the Distress Thermometer. Cancer 113 (4):870-878. doi:10.1002/cncr.23622
7. Hoffman BM, Zevon MA, D'Arrigo MC, Cecchini TB (2004) Screening for distress in cancer patients: the NCCN rapid-screening measure. Psycho-oncology 13 (11):792-799. doi:10.1002/pon.796
8. Gessler S, Low J, Daniells E, Williams R, Brough V, Tookman A, Jones L (2008) Screening for distress in cancer patients: is the distress thermometer a valid measure in the UK and does it measure change over time? A prospective validation study. Psycho-oncology 17 (6):538-547. doi:10.1002/pon.1273
9. Head BA, Schapmire TJ, Keeney CE, Deck SM, Studts JL, Hermann CP, Scharfenberger JA, Pfeifer MP (2012) Use of the Distress Thermometer to discern clinically relevant quality of life differences in women with breast cancer. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 21 (2):215-223. doi:10.1007/s11136-011-9934-3
10. Qi Y, Schild SE, Mandrekar SJ, Tan AD, Krook JE, Rowland KM, Garces YI, Soori GS, Adjei AA, Sloan JA (2009) Pretreatment quality of life is an independent prognostic factor for overall survival in patients with advanced stage non-small cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 4 (9):1075-1082. doi:10.1097/JTO.0b013e3181ae27f5
11. Jacot W, Colinet B, Bertrand D, Lacombe S, Bozonnat MC, Daures JP, Pujol JL, Onco LRhn (2008) Quality of life and comorbidity score as prognostic determinants in non-small-cell lung cancer patients. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 19 (8):1458-1464. doi:10.1093/annonc/mdn064
12. Efficace F, Bottomley A, Smit EF, Lianes P, Legrand C, Debruyne C, Schramel F, Smit HJ, Gaafar R, Biesma B, Manegold C, Coens C, Giaccone G, Van Meerbeeck J, Group ELC, Quality of Life U (2006) Is a patient's self-reported health-related quality of life a prognostic factor for survival in non-small-cell lung cancer patients? A multivariate analysis of prognostic factors of EORTC study 08975. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 17 (11):1698-1704. doi:10.1093/annonc/mdl183

13. Montazeri A, Milroy R, Hole D, McEwen J, Gillis CR (2001) Quality of life in lung cancer patients: as an important prognostic factor. Lung cancer 31 (2-3):233-240
14. Braun DP, Gupta D, Staren ED (2011) Quality of life assessment as a predictor of survival in non-small cell lung cancer. BMC cancer 11:353. doi:10.1186/1471-2407-11-353
15. Movsas B, Moughan J, Sarna L, Langer C, Werner-Wasik M, Nicolaou N, Komaki R, Machtay M, Wasserman T, Bruner DW (2009) Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 27 (34):5816-5822. doi:10.1200/JCO.2009.23.7420
16. Langendijk H, Aaronson NK, de Jong JM, ten Velde GP, Muller MJ, Wouters M (2000) The prognostic impact of quality of life assessed with the EORTC QLQ-C30 in inoperable non-small cell lung carcinoma treated with radiotherapy. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 55 (1):19-25
17. Chen J, Li W, Cui L, Qian Y, Zhu Y, Gu H, Chen G, Shen Y, Liu Y (2015) Chemotherapeutic Response and Prognosis among Lung Cancer Patients with and without Depression. Journal of Cancer 6 (11):1121-1129. doi:10.7150/jca.11239
18. Arrieta O, Angulo LP, Nunez-Valencia C, Dorantes-Gallareta Y, Macedo EO, Martinez-Lopez D, Alvarado S, Corona-Cruz JF, Onate-Ocana LF (2013) Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Annals of surgical oncology 20 (6):1941-1948. doi:10.1245/s10434-012-2793-5
19. Rami-Porta R, Crowley JJ, Goldstraw P (2009) The revised TNM staging system for lung cancer. Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia 15 (1):4-9
20. Donovan KA, Grassi L, McGinty HL, Jacobsen PB (2014) Validation of the distress thermometer worldwide: state of the science. Psycho-oncology 23 (3):241-250. doi:10.1002/pon.3430
21. Schofield P, Ugalde A, Gough K, Reece J, Krishnasamy M, Carey M, Ball D, Aranda S (2013) A tailored, supportive care intervention using systematic assessment designed for people with inoperable lung cancer: a randomised controlled trial. Psycho-oncology 22 (11):2445-2453. doi:10.1002/pon.3306
22. VanHoose L, Black LL, Doty K, Sabata D, Twumasi-Ankrah P, Taylor S, Johnson R (2015) An analysis of the distress thermometer problem list and distress in patients with cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 23 (5):1225-1232. doi:10.1007/s00520-014-2471-1
23. Aarts MJ, Aerts JG, van den Borne BE, Biesma B, Lemmens VE, Kloover JS (2015) Comorbidity in Patients With Small-Cell Lung Cancer: Trends and Prognostic Impact. Clinical lung cancer 16 (4):282-291. doi:10.1016/j.cllc.2014.12.003



CHAPTER 2

Satisfactory results of a psychometric analysis and calculation of minimal clinically important differences of the World Health Organization Quality of Life-BREF questionnaire in an observational cohort study with lung cancer and mesothelioma patients

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ABSTRACT

Background: To determine the psychometric properties and minimal clinically important differences (MCIDs) of the World Health Organization Quality of Life-BREF (WHOQOL-BREF) in advanced-stage lung cancer patients.

Methods: Patients (n=153) completed the WHOQOL-BREF and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). Confirmatory factor analysis (CFA) was performed and reliability and construct validity determined. MCIDs were estimated with two distribution-based methods (0.5 standard deviation (SD) and 1 standard error of measurement (1 SEM)).

Results: CFA confirmed WHOQOL-BREF domain structure. All domains demonstrated good internal consistency ($\alpha > 0.70$), except social relationships ($\alpha = 0.57$). Nineteen of the 24 WHOQOL-BREF items had correlations of ≥ 0.40 with their intended domain. Four items had higher correlations with a domain other than their intended domain. Moderate to strong correlations were observed for corresponding domains of the two questionnaires, except for the social domains ($r = 0.07$). For 0.5 SD, MCIDs ranged from 0.88 to 1.55, and for 1 SEM MCIDs ranged from 1.76 to 2.72.

Conclusions: The WHOQOL-BREF has satisfactory psychometric properties in patients with advanced-stage lung cancer, whereas the observed MCIDs provide a method for interpretation of scores.

BACKGROUND

In general, chemotherapy in patients with advanced-stage lung cancer is associated with small survival benefits [1,2]. In addition, Quality of Life (QoL) may be reduced in patients with lung cancer [3].This emphasizes the importance of maintaining patients' QoL at an acceptable level by early identification of treatment-induced changes. QoL is evaluated by questionnaires of which the European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire (EORTC QLQ-C30) is one of the most frequently applied in cancer [4]. However, this instrument is considered to be a Health-Related Quality of Life (HRQoL) questionnaire (i.e., it focusses on those aspects of QoL related to the disease and its treatment) and measures to a lesser extent patients' opinions of the other aspects of QoL [4]. Therefore, the WHO formulated a comprehensive definition of QoL based on extensive research. In 2004, they released the World Health Organization Quality of Life instrument-BREF (WHOQOL-BREF) to enable rapid QoL assessment in epidemiological surveys and clinical studies [5].

Recently, a study performed in Taiwanese patients diagnosed with stage I to IV lung cancer reported satisfactory psychometric properties of the WHOQOL-BREF. However, the 28-item Taiwanese version of the WHOQOL-BREF (the original WHOQOL-BREF holds 26 items [5]) was used and specific results concerning patients with advanced-stage lung cancer were not reported. Therefore, further psychometric validation of the WHOQOL-BREF in this group may be mandatory for several reasons. First, patients with advanced-stage lung cancer form a well-defined group due to their poor prognosis compared to patients with stage I or II lung cancer and the population in the WHOQOL-BREF field trial [5]. Second, apart from the symptoms of lung cancer, treatment is in most patients with advanced-stage lung cancer associated with substantial adverse events which can directly influence (HR)QoL. Third, although some studies have reported results of the WHOQOL-BREF in lung cancer [6,7], the application of this questionnaire in patients starting treatment with chemotherapy was not reported. Fourth, as correct interpretation of the minimal clinically important difference (MCID) depends on the psychometric characteristics of the instrument and the patient population from which it is derived, the determination of a reliable MCID in lung cancer ideally requires evaluation of the reliability and validity of the WHOQOL-BREF in these patients.

Given these considerations, additional research is needed to enable implementation of the WHOQOL-BREF in future trials investigating therapeutic regimens in lung cancer and to facilitate the interpretation of individual scores. To contribute to these goals the objective of our study focused on two main aspects of the WHOQOL-BREF: 1) to test the reliability and validity of the WHOQOL-BREF in patients with advanced-stage lung cancer, and 2) to assess the MCIDs of the WHOQOL-BREF domain scores. We expected that the 4-domain structure of the WHOQOL-BREF would be confirmed and that the internal consistencies

of all domains were at least acceptable, except for social relationships [5]. Moreover, we hypothesized that all items of the WHOQOL-BREF would have an acceptable positive correlation (i.e., correlation coefficient ≥ 0.40) with their intended domains and that all items would have higher positive correlations with their intended domain than with the other three domains [8]. Considering construct validity, we expected significant differences in mean domain scores between known groups according to ECOG performance score and EORTC QLQ-C30 global Health Status/QoL score [9]. In addition, construct validity was assessed by correlating the domains of the WHOQOL-BREF with the scales of the EORTC QLQ-C30 [9]. We hypothesized that all domains would have at least moderate correlations (i.e., correlation coefficient ≥ 0.50) with their corresponding scales of the EORTC QLQ-C30 [10]. In this study, we expected no floor or ceiling effects for domain scores of the WHOQOL-BREF.

METHODS

Study population

PERSONAL is a prospective observational multi-center cohort study of patients with non-squamous non-small cell lung carcinoma (NSCLC) and unresectable mesothelioma receiving pemetrexed. Patients were recruited from October 2012 to November 2014 from three teaching hospitals (Erasmus University Medical Center, Amphia Hospital, and Sint Franciscus Gasthuis hospital) and a regional hospital (Bravis hospital) in the Netherlands. For this study, which is part of an ongoing analysis of PERSONAL, data of 191 enrolled patients was available. Patients were enrolled if they met the following criteria: were aged eighteen years or older, had a cytological or histological confirmed diagnosis of non-squamous NSCLC or unresectable malignant pleural mesothelioma and started treatment with pemetrexed monotherapy or in combination with a platinum compound. Patients were excluded when they were not able to read Dutch or could not complete the questionnaires because of a physical or mental condition. A sample size of at least 50 patients was needed in order to perform a validation study [9]. Informed consent was obtained from all individual participants included in the study. This multi-center study was approved by the Institutional Review Board of the Erasmus University Medical Center in Rotterdam, the Netherlands.

Study measures

The WHOQOL-BREF [5,11] is a well-established generic QoL instrument intended for use in a wide range of chronic diseases and cancer [5]. It comprises 24 items divided over four domains plus two items of the general facet describing overall QoL and general health. The domains represent physical health (seven items), psychological health (six items), social

relationships (three items), and environment (eight items) and are scored on a 4-20 scale with higher scores indicating a better QoL [11]. The general facet is scored on a 2-10 scale. Previous studies have demonstrated good psychometric properties of the WHOQOL-BREF in patients with lung cancer [12] and in patients with chronic diseases or different forms of cancer [5].

The EORTC QLQ-C30 is a cancer-specific HRQoL instrument with demonstrated psychometric properties [13]. It consists of 30 items and incorporates a global Health Status/QoL scale, five functional scales and several single items assessing additional symptoms or problems. The functional scales represent physical functioning (five items), cognitive functioning (two items), emotional functioning (four items), role functioning (two items), and social functioning (two items). EORTC QLQ-C30 scales are scored on a 0-100 scale, with higher scores on the functional scales being indicative of better HRQoL, whereas higher scores on the symptom scales are reflective of worse symptoms [4].

All questionnaires were completed after diagnosis and before the first cycle of chemotherapy. In addition to completing the questionnaires, we collected sociodemographic information (i.e., age, gender, educational level, ethnicity, employment, partner status) and clinical information (i.e., cancer stage, type of tumour, line of therapy and the Eastern Cooperative Oncology Group (ECOG) performance status). At day 1 of the first cycle of chemotherapy we assessed, according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, the severity and number of different cancer related and, if applicable, treatment related adverse events that patients experienced.

Statistical analysis

The response distributions of item and domain scores of the WHOQOL-BREF were assessed by using two methods. As proposed in the validation paper of the WHOQOL-BREF, skewness was observed if less than 10% of responses fell in each of two adjacent scale points of an item at the extreme ends of the scale [5]. Floor and ceiling effects of domain scores of the WHOQOL-BREF were considered to be present if more than 15% of the respondents achieved the lowest (i.e., floor effect) or highest (i.e., ceiling effect) possible score [9].

The multi-trait/multi-method methodology, as proposed by Campbell and Fiske [14] and later adapted by Ware et al., was used to study item-domain relations [15]. Analyses were performed with MAP-R software which examines the correlations between items and domains and corrects the correlation of each item with its intended domain for overlap [15]. For the multi-trait/multi-item analyses, missing values are replaced by the mean score of the other items of the corresponding domain if at least half of the items are completed. According to Trask et al., item-convergent validity was defined as a correlation coefficient ≥ 0.40 between questionnaire items and their intended domains [8]. Item-divergent validity was supported when items had higher correlations with their intended domain than with other domains of the questionnaire [8].

Construct validity was evaluated by correlating the WHOQOL-BREF domains with the corresponding scales of the EORTC QLQ-C30 using Pearson's correlation coefficient. According to Hinkle, correlations of 0.00 to 0.30 were regarded as negligible, 0.30 to 0.50 as low, 0.50 to 0.70 as moderate, 070 to 0.90 as high, and correlations of 0.90 to 1.00 as very high [10]. In addition, known-groups validity comparisons were made for the WHOQOL-BREF domains in relation to the total number of different adverse events, the number of different grade 3 or 4 adverse events, the ECOG performance status and the global Health Status/QoL score of the EORTC QLQ-C30 to assess construct validity. One-way ANOVA was used to determine whether there were any significant differences between the means of the groups.

Internal consistency reflects the capability of items within a domain to measure the same concept. To evaluate internal consistency, first the four-factor design of the WHOQOL-BREF was analysed with confirmatory factor analysis (CFA) using structural equation modelling. Missing values were replaced by expectation-maximization imputation for the CFA. The original model is demonstrated in Figure 1. Goodness of fit was assessed by the Comparative Fit Index (CFI) and the Root Mean Square Error Approximation (RMSEA). A satisfactory to good fit is defined when CFI > 0.90 and RMSEA < 0.06 [16,17]. For the resulting domains, Cronbach's coefficient alpha was calculated to express internal consistency. A coefficient of 0.70 or higher was considered to be acceptable [9].

For each WHOQOL-BREF domain, the MCID was calculated using two distribution-based methods (i.e., the 0.5 SD [18] and 1 standard error of measure (SEM) [19-21]). MCID is the smallest change in an outcome that a patient would identify as important. The 0.5 SD benchmark of an outcome measure means that patients improving more than 0.5 of the outcome score's SD have reached a minimal clinically important difference [22]. As we lacked a test-retest reliability coefficient, we used the conservative lower bound of the 95% confidence intervals of the Cronbach's alphas of the four domains to calculate the SEM. Thus, the SEM was calculated with an altered version of the SEM formula [23]: SD x $\sqrt{(2x\ (1 - \text{lower bound 95\% Confidence Interval Cronbach's alpha}))}$.

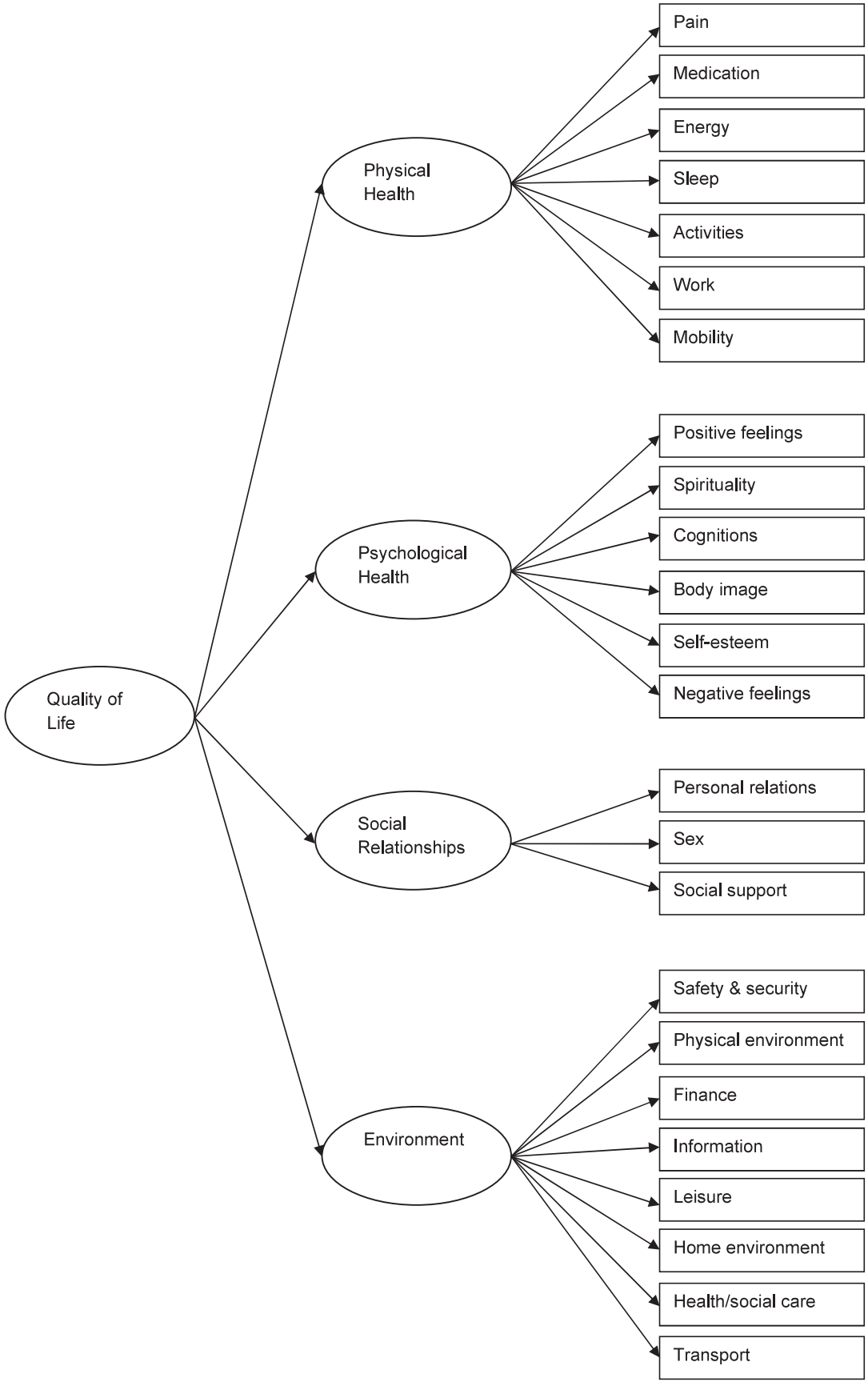
A p-value of $p < 0.05$ was considered to be statistically significant. Analyses were performed using SPSS version 21.0, except for the CFA (AMOS version 22.0) and the calculation of the 95% confidence intervals of the four domains of the WHOQOL-BREF (R, version 3.2.5).

RESULTS

Patient characteristics

Of the 191 enrolled patients, 153 patients (80.1%) completed the questionnaires to a sufficient degree. Table 1 summarizes the patient characteristics of these patients.

Fig. 1 Four factor model of the WHOQOL-BREF



Abbreviations: WHOQOL-BREF, World Health Organization Quality of Life-BREF questionnaire.

Table 1. Characteristics of study population

Characteristic	Overall sample (N=153)
Age, years	
Mean (SD)	63.4 (9.2)
Min, max	37, 83
Sex	
Male	83 (54.2)
Ethnicity	
White/Caucasian	143 (93.5)
Asian	3 (2.0)
Negroid	2 (1.3)
Other	5 (3.3)
Education[a]	
Low	113 (73.9)
High	33 (21.6)
Unknown	7 (4.6)
Employment	
Yes	40 (26.1)
No	112 (73.2)
Unknown	1 (0.7)
Partner status	
Married/cohabiting	116 (75.8)
Unmarried partners/not cohabiting	6 (3.9)
Divorced/separated	14 (9.2)
Widowed/partner died	10 (6.5)
Single	6 (3.9)
Unknown	1 (0.7)
Cancer stage[b]	
Locally advanced (IIIB)	19 (12.4)
Metastatic (IV)	119 (77.8)
Other	14 (9.2)
Unknown	1 (0.7)
Type of tumor[b]	
Adenocarcinoma	141 (92.2)
Large cell carcinoma	4 (2.6)
Mesothelioma	7 (4.6)
Large cell neuroendocrine carcinoma	1 (0.7)
Line of therapy	
First line	134 (87.6)
Second line	10 (6.5)
Third line	1 (0.7)

Table 1. Characteristics of study population (continued)

Characteristic	Overall sample (N=153)
Adjuvant	8 (5.2)
ECOG performance status[a]	
Grade 0	39 (25.5)
Grade 1	99 (64.7)
Grade 2	11 (7.2)
Grade 3	2 (1.3)
Unknown	2 (1.3)

Values are given in numbers (percentages) unless stated otherwise.
[a]Low education: persons whose highest level of education is primary education, lower general education or lower vocational education. High education: persons whose highest level of education is higher general education, higher vocational education or university.
[b]Measured at baseline.
Abbreviations: N, number of patients; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group.

Mean scores, floor and ceiling effects, and skewness

The WHOQOL-BREF domain scores are shown in Table 2. The mean general facet score was 5.9 (1.8). Mean scores of the four domains ranged from 12.9 (SD 3.1; physical health) to 16.2 (SD 2.6; social relationships). Floor and ceiling effects of the domain scores were below the limit of 15%. Fourteen of the 26 items demonstrated skewed response distributions with responses <10% in each of two adjacent scale points at the extreme lower end of the scale indicating that most of the information was distributed over the other scale points (Table 2). These items were positive feelings, spirituality, cognitions, self-esteem, and body image for the psychological health domain and personal relations and social support for the social relationships domain. In addition, all items of the environment domain, except leisure, demonstrated few responses at the extreme lower end of the scale. One item, negative feelings exhibited responses <10% in each of two adjacent scale points at the extreme upper end of its scale.

Confirmatory Factor Analysis

CFA with the use of structural equation modelling was conducted to analyse the four-factor structure of the WHOQOL-BREF. Inspection of the modification indices revealed two possible modifications to improve the model fit of the original model. After adding error covariances between the measurement error of the items 1 (pain) and 2 (medication) and between 8 (positive feelings) and 9 (spirituality) model fit improved. The CFI increased from 0.854 to 0.896 whereas the RMSEA decreased from 0.069 to 0.058 approaching both of the criteria for a satisfactory to good fit (CFI > 0.90 and RMSEA < 0.06).

Table 2. Frequency responses for items of the WHOQOL-BREF

Items/ domains	Description	N	Mean (SD)	Floor effect (%)	Ceiling effect (%)	Scale points[a]				
						1	2	3	4	5
General facet										
	overall QoL	150	5.9 (1.8)	4 (2.7)	3 (2.0)	3.3	14.4	24.2	44.4	12.4
	general health					21.6	35.9	26.1	13.1	2.6
Physical health										
3	pain	153	12.9 (3.1)	1 (0.7)	1 (0.7)	28.1	28.8	19.0	20.3	3.3
4	medication					11.8	26.8	25.5	24.8	10.5
10	energy					3.9	19.6	35.9	25.5	14.4
15	sleep					8.5	23.5	26.1	26.1	15.0
16	activities					7.8	34.6	24.8	26.8	5.9
17	work					12.4	39.2	21.6	20.3	6.5
25	mobility					4.6	11.8	13.1	35.3	35.3
Psychological health										
5	positive feelings	153	14.4 (2.5)	0 (0.0)	2 (1.3)	**3.9**	**7.8**	39.2	41.2	7.8
6	spirituality					**2.6**	**5.2**	32.7	43.8	15.0
7	cognitions					**4.6**	**9.8**	44.4	22.2	19.0
11	body image					**0.7**	**4.6**	28.1	26.1	39.9
18	self esteem					**0.7**	**9.8**	30.7	43.8	13.7
26	negative feelings					14.4	32.7	43.1	**9.8**	**0.0**
Social relationships										
19	personal relations	153	16.2 (2.6)	0 (0.0)	20 (13.1)	**0.7**	**0.7**	**6.5**	40.5	50.3
20	sex					5.9	13.7	36.6	24.8	16.3
21	social support					**0.7**	**1.3**	**9.2**	34.0	54.9
Environment										
8	safety & security	153	15.9 (2.3)	0 (0.0)	1 (0.7)	**0.7**	**3.9**	26.8	32.0	36.6
9	physical environment					**0.7**	**2.0**	26.8	35.3	34.0
12	finance					**2.0**	**6.5**	37.3	21.6	32.0
13	information					**0.0**	**0.7**	36.6	37.3	24.8
14	leisure					3.9	13.1	24.2	35.3	23.5
22	home environment					**2.6**	**5.2**	12.4	39.9	39.9
23	health/social care					**1.3**	**2.0**	15.7	49.0	32.0
24	transport					**1.3**	**2.0**	**9.2**	43.8	43.8

[a]Values are given in percentages.

Values in bold represent skewed distributions of the frequency of responses of patients.

Abbreviations: WHOQOL-BREF, World Health Organization Quality of Life-BREF questionnaire; N, number of patients; SD, standard deviation; QoL, Quality of Life.

Multi-trait/multi-item analyses and internal consistency

Multi-trait/multi-item analyses demonstrated that all items, except those representing sleep, body image, sex, physical environment, and finance had a correlation of ≥ 0.40 with their intended domain (Table 3). Four items showed higher correlations with other domains than their own. The item sleep of the physical health domain had a higher positive correlation with the psychological health domain, whereas the items body image and self-esteem of the psychological health domain had higher positive correlations with the environment domain and the physical health domain respectively. In addition, the item personal relationships of the social relationships domain showed a higher positive correlation with the environment domain than its intended domain. For all domains, except the social relationships domain, Cronbach's alpha was higher than 0.70 (i.e., physical health: 0.81, 95% CI 0.76-0.85; psychological health: 0.77, 95% CI 0.71-0.83; environment: 0.77, 95% CI 0.70-0.82; social relationships: 0.57, 95% CI 0.43-0.68).

Construct validity

Table 4 presents the correlations between the domains of the WHOQOL-BREF and the EORTC QLQ-C30 domains/symptom scales. In general, low correlations were observed between WHOQOL-BREF domains and EORTC QLQ-C30 domains/symptom scales. Only for physical health, moderate to high correlations were observed with the EORTC QLQ-C30 domains except for the correlation with cognitive functioning. The lowest correlations were found between social relationships and the EORTC QLQ-C30 domains/symptom scales. The observed negative correlations between the WHOQOL-BREF and EORTC QLQ-C30 symptom scales indicate that a higher score of the WHOQOL-BREF domains corresponded with less worse symptoms.

Table 5 shows the known-groups validity comparisons for the WHOQOL-BREF domains and general facet in relation to the number of different adverse events, the number of different grade 3 or 4 adverse events, the ECOG performance status and the global Health Status/QoL score. Significant differences were detected regarding the general facet score, physical health, and psychological health among ECOG grades 0, 1, and 2 or higher. Similar results were observed for the general facet and the WHOQOL-BREF domain scores according to global Health Status/QoL as measured by the EORTC QLQ-C30 except for social relationships. For all of the observed significant differences except one (i.e., psychological health based on ECOG performance score), effect sizes were medium to large.

Minimal clinically important differences

Table 6 demonstrates the distribution-based estimates of the MCIDs for the different domains of the WHOQOL-BREF.

Table 3. Multi-trait/Multi-item item-domain correlation for the WHOQOL-BREF (N=153)

Items/domains	Description	Physical health	Psychological health	Social relationships	Environment
Physical health					
3R	pain	.53*	.41	**.20**	**.35**
4R	medication	.40*	**.24**	**.01**	**.21**
10	energy	.57*	.53	**.13**	.42
15	sleep	.27*	.32	**.06**	.27
16	activities	.72*	.56	**.17**	**.46**
17	work	.70*	**.54**	**.17**	**.43**
25	mobility	.61*	.47	**.24**	**.45**
Psychological health					
5	positive feelings	.52	.67*	**.33**	**.47**
6	spirituality	**.34**	.53*	**.24**	**.36**
7	cognitions	.44	.48*	**.20**	.48
11	body image	.32	.34*	.30	.45
18	self esteem	.60	.58*	**.38**	.49
26R	negative feelings	.43	.52*	**.21**	.43
Social relationships					
19	personal relations	**.16**	.30	.43*	.47
20	sex	**.15**	.31	.32*	.31
21	social support	**.16**	.28	.43*	.42
Environment					
8	safety & security	.46	.57	**.36**	.60*
9	physical environment	**.12**	.35	.31	.38*
12	finance	.23	.29	.26	.30*
13	information	**.24**	**.33**	**.36**	.53*
14	leisure	.41	.34	**.19**	.46*
22	home environment	.46	.55	.41	.56*
23	health/social care	.36	.41	.32	.41*
24	transport	**.39**	.44	.43	.57*

*Pearson item-scale correlations corrected for overlap.
Correlations in bold represent correlations between items and domains that differ more than two standard errors from their correlations with their own domains.
Abbreviations: SD, standard deviation; N, number of patients; QoL, Quality of Life; WHOQOL-BREF, World Health Organization Quality of Life-BREF questionnaire.

DISCUSSION

Patients with advanced-stage lung cancer are prone to a decrease in QoL due to poor prognosis and cancer and treatment-related adverse events. Unfortunately, trials investigating

Table 4. Correlations of the WHOQOL-BREF with the EORTC QLQ-C30 domains (N=153)

EORTC QLQ-C30 domains/ Items	WHOQOL-BREF domains/items				
	General facet	Physical health	Psychological health	Social relationships	Environment
Physical functioning	0.43*	0.73*	0.37*	0.04	0.26*
Role functioning	0.46*	0.73*	0.46*	0.08	0.26*
Emotional functioning	0.49*	0.51*	0.61*	*0.19***	0.43*
Cognitive functioning	0.33*	0.49*	0.47*	0.08	0.40*
Social functioning	0.42*	0.59*	0.47*	0.07	0.32*
Global Health Status/QoL	0.67*	0.73*	0.58*	0.12	0.39*
Fatigue	-0.39*	-0.69*	-0.44*	-0.06	-0.33*
Nausea and vomiting	-0.32*	-0.29*	-0.24*	-0.16	-0.05
Pain	-0.32*	-0.62*	-0.28*	-0.06	-0.26*
Dyspnea	-0.28*	-0.30*	-0.15	0.05	-0.10
Insomnia	-0.29*	-0.49*	-0.35*	-0.04	-0.32*
Appetite loss	-0.36*	-0.38*	-0.22*	0.02	-0.05
Constipation	*-0.17***	-0.23*	*-0.18***	-0.06	-0.24*
Diarrhea	0.00	-0.08	-0.04	-0.10	-0.06
Financial problems	-0.03	-0.34*	-0.22*	-0.11	-0.36*

Pearson correlation coefficients.

*P < 0.01.

**P < 0.05.

Abbreviations: WHOQOL-BREF, World Health Organization Quality of Life-BREF questionnaire; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; N, number of patients; QoL, Quality of Life.

new therapies and treatment modalities in lung cancer often assess the impact on QoL with the use of HRQoL instruments [2,24-26]. This is unfortunate as the WHOQOL-BREF may facilitate a more comprehensive evaluation of QoL. Given the importance of a comprehensive evaluation of QoL, the present study assessed the psychometrics and MCIDs of the WHOQOL-BREF in patients with advanced-stage lung cancer to facilitate adequate QoL monitoring in clinical practice and lung cancer trials. In general, our study demonstrated that the WHOQOL-BREF is a reliable and valid instrument in patients with advanced-stage lung cancer.

We found that the general health item of the general facet was more positively skewed in our study compared with the WHOQOL-BREF field trial reflecting higher frequencies of patients with worse general health [5]. This is as expected given the frequent occurrence of adverse events and poor prognosis of advanced-stage lung cancer. However, the patients in this study indicated better QoL for several items of the psychological health, social relationships and environment domains than the patients included in the field trial. Moreover, an additional seven items of these three domains were negatively skewed in our patients

Table 5. Known-groups comparisons for the WHOQOL-BREF general facet and domain scores (n=153)

	General facet			Physical health			Psychological health			Social relationships			Environment		
	N	Mean (SD)	P-value (effect size)*	N	Mean (SD)	P-value (effect size)*	N	Mean (SD)	P-value (effect size)*	N	Mean (SD)	P-value (effect size)*	N	Mean (SD)	P-value (effect size)*
Number of different adverse events[a]															
0-5	84	6.1 (1.7)	0.10	87	13.6 (3.1)	<0.001 (0.08)	87	14.5 (2.5)	0.47	87	16.1 (2.7)	0.37	87	15.8 (2.2)	0.81
more than 5	66	5.6 (1.8)		66	11.8 (2.9)		66	14.2 (2.6)		66	16.4 (2.4)		66	15.9 (2.4)	
Number of different adverse events with CTCAE grade 3 or 4[a]															
0	112	6.0 (1.8)	0.16	115	13.1 (3.1)	0.06	115	14.4 (2.4)	0.93	115	16.1 (2.6)	0.36	115	15.8 (2.3)	0.82
1	27	6.0 (1.8)		27	12.8 (3.0)		27	14.4 (2.8)		27	16.5 (2.6)		27	16.0 (2.3)	
2 or more	11	4.9 (1.4)		11	10.8 (2.6)		11	14.7 (2.9)		11	17.1 (2.2)		11	16.1 (2.6)	
ECOG performance score[b]			< 0.001 (0.08)			< 0.001 (0.23)			0.04 (0.04)			0.05			0.38
0	37	6.6 (1.5)		39	15.1 (2.3)		39	15.1 (2.2)		39	16.3 (2.5)		39	16.1 (1.8)	
1	98	5.7 (1.8)		99	12.3 (3.0)		99	14.3 (2.6)		99	16.5 (2.3)		99	15.9 (2.5)	
2 or more	13	4.8 (1.1)		13	10.2 (2.0)		13	13.1 (2.2)		13	14.7 (3.5)		13	15.1 (2.3)	
Global Health Status/QoL EORTC QLQ-C30 score															
0-50	67	4.9 (1.5)	< 0.001 (0.30)	69	10.8 (2.7)	< 0.001 (0.36)	69	13.1 (2.6)	< 0.001 (0.22)	69	16.0 (2.8)	0.28	69	15.1 (2.4)	< 0.001 (0.10)
more than 50	79	6.8 (1.4)		80	14.6 (2.3)		80	15.5 (1.9)		80	16.5 (2.3)		80	16.6 (2.0)	

P-values calculated with one-way ANOVA unless stated otherwise.

*Effect sizes (η^2) were only shown where one-way ANOVA was significant ($P < 0.05$).

[a]Reported adverse events: as reported at and before day 1 of the first cycle of chemotherapy.

[b]Post hoc analyses with Tukey HSD test of significant differences: for the general facet, between ECOG 0 and 1 and also 0 and 2 or higher; for physical health, between all ECOG categories; for psychological health, between ECOG 0 and ECOG 2 or higher.

Abbreviations: WHOQOL-BREF, World Health Organization Quality of Life-BREF questionnaire; SD, standard deviation; N, number of patients who completed the questionnaire; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; QoL, Quality of Life; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.

Table 6. Estimates of minimal clinically important differences on WHOQOL-BREF domains

Domains	0.5 SD	1 SEM
General facet	0.876	
Physical health	1.545	2.155
Psychological health	1.259	1.914
Social relationships	1.274	2.716
Environment	1.142	1.761

Abbreviations: WHOQOL-BREF, World Health Organization Quality of Life-BREF questionnaire; SD, standard deviation; SEM, standard error of measure.

indicating also better QoL. One item (i.e., negative feelings) was positively skewed demonstrating that most patients rarely experienced negative feelings while the WHOQOL-BREF field trial observed higher frequencies in the scale points that corresponded with increased negative feelings. As this higher level of QoL was not related to physical QoL, which is in general determined by universal factors (i.e., the cancer and its treatment), but rather to the other domains of the WHOQOL-BREF, this may be explained by several reasons. Given the negative skewness of seven of the eight items of the environment domain, it is likely that the high standard of care and the high level of prosperity in the Netherlands may be, at least in part, responsible for this observation. In addition, patients with lung cancer may experience less psychological distress compared to patients with other types of cancer. A meta-analysis by Krebber et al. found that the prevalence of depression as diagnosed by a structural interview was the lowest (3%) in lung cancer patients compared with other forms of cancer. The prevalence of depression as diagnosed by self-report instruments (20%) was also lower or comparable with other forms of cancer [27].

Prior to testing the reliability and validity of the WHOQOL-BREF, we performed a first order CFA to analyse if the proposed four-factor model matched with the patients in the present study. Before (i.e., RMSEA) and after (i.e., CFI and RMSEA) adding error covariances between the measurement errors of items pain and medication and between items positive feelings and spirituality, the observed fit indices indicated a slightly better model fit than the field trial of the WHOQOL-BREF [5]. However, as we were not able to calculate 95% confidence intervals for the observed fit indices and Skevington et al. did not report them [5], we could not determine if the CFI and RMSEA observed in the present study were significantly different. Moreover, if they are different, it is likely that the differences in fit indices are explained by the differences between patient populations of both studies. In the present study a homogeneous sample of patients with advanced-stage lung cancer was used whereas the patient population of the WHOQOL-BREF field trial consisted of patients with different diseases [5]. Also the statistical differences between the present study and that of Skevington et al. impair the direct comparison of model fit.

Similarly as observed by Skevington et al., the internal consistency of the social relationships domain was below the commonly accepted value of 0.7 [5] whereas the other domains all had a Cronbach's alpha > 0.70. As Cronbach's alpha is in part dependent of the number of items of a domain, a reason for this low alpha possibly lies in the fact that the social relationships domain consists of just three items. In a recent Taiwanese validation study of the WHOQOL-BREF which did not report specific results of patients with advanced-stage lung cancer (i.e., overall results of Rasch analyses of patients with stage I to IV disease were reported), the inclusion of one extra item (i.e., being respected) in the social relationship domain resulted in a Cronbach's alpha of 0.67 [12], which is higher than observed in this study, although comparable with the alpha found in the field trial (0.68) [5]. Explanations for the lower observed internal consistency of the social relationships domain in our study in contrast with the other two reports could be the homogeneity of the patient sample or the decreased ability of the combined items to reflect the underlying construct in patients with advanced-stage lung cancer compared to those with limited disease stage or other forms of cancer or chronic diseases. Furthermore, one of the three items (i.e., personal relations) had a higher correlation with the environment domain then with its own hypothesized domain in this study which indicates that this item may not be completely representative for the construct of social relationships. In addition to the relatively low Cronbach's alpha, this result further hampers the interpretation of analyses with this domain and raises the question if the three items should be assessed separately.

After performing multi-trait/multi-item analyses we observed similar cross domain correlations as the field trial did. While the self-esteem item of the psychological health domain in the field trial was strongly related with the other three domains [5], we observed a stronger correlation with the physical health domain than with its own domain. This is not only in contrast with the results of the field trial [5], but also with patients with other forms of cancers. One study in cervical cancer survivors reported that self-esteem was related to the mental component summary score and not with the physical component summary score of the Short Form 36 QoL questionnaire [28]. A reason for this result could be the considerable impact advanced-stage lung cancer can have on physical abilities. This may lead to dependence of others which could affect self-esteem. In the field trial of the WHOQOL-BREF the centre specific analyses revealed that the items safety & security and energy often had higher correlations with domains other than their own [5] whereas we found that this was the case for the items sleep, body image, self-esteem, and personal relations. These differences in cross-correlation could be explained by some reasons. For instance, as the sample size of this study was relatively small, the observed differences may reflect mere chance than a true observation. Also methodological differences and the specific characteristics of patients with advanced disease (e.g., poor prognosis, prone to cancer-related adverse events) are, at least in part, responsible for these findings.

In general, low correlations were observed between WHOQOL-BREF domains and EORTC QLQ-C30 domains/symptom scales. This is probably related to differences in constructs and concepts between the questionnaires. Whereas the WHOQOL-BREF is a generic questionnaire, the EORTC QLQ-C30 is a cancer specific questionnaire. Moreover, items of the WHOQOL-BREF are positively phrased while those of the EORTC QLQ-C30 are often negatively phrased. In this regard, the EORTC QLQ-C30 may not be regarded as a gold standard to evaluate construct validity of the WHOQOL-BREF. In addition, this also points to the additional value of the WHOQOL-BREF in QoL analyses in cancer patients.

Both the field trial of the WHOQOL-BREF and the recent Taiwanese study did not report MCIDs to facilitate the clinical application of the WHOQOL-BREF [5,12]. In the present study, we were able to report statistically derived MCIDs for the four WHOQOL-BREF domains. Because we were not able to perform a test-retest reliability analysis, we used the conservative lower bound of the 95% confidence intervals of each of the Cronbach's alphas of the WHOQOL-BREF domains for the calculation of the 1 SEM MCIDs. Considering the vulnerability of patients with advanced-stage lung cancer for treatment and cancer-related adverse events and the short period of three weeks between chemotherapy cycles, we expected it to be difficult to define an appropriated interval between completions of the WHOQOL-BREF for two reasons. 1) If the interval between completions of the WHOQOL-BREF would be too short, patients could recall their earlier answers. 2) If the interval between completions of the WHOQOL-BREF would be too long, it is likely that the occurrence of therapy and cancer-related adverse events would have biased WHOQOL-BREF scores. However, by taking the lower bound of the confidence interval, we expected that patients who experience a larger difference over time than the observed SEM estimates are likely to have a true change. Considering that the 0.5 SD MICDs depend on the variance of test scores, which are expected to be relatively small in a homogenous patient population as in the present study, the larger 1 SEM MCIDs may provide a more conservative method for the interpretation of individual scores. However, 1 SEM MCIDs depend on the reliability of a questionnaire. A questionnaire with a limited reliability may result in a relatively large 1 SEM. This could result in an overestimation of the true MCID which decreases sensitivity. Given these considerations, we calculated MCIDs according to both methods and recommended to base the choice for either of the two approaches on the homogeneity of the patient sample and the reliability of the questionnaire in the particular population.

Another limitation is that the present study used CFA in combination with the multi-trait/multi-method methodology [14,15] which is in contrast with the increased application of Rasch analysis in recent years to assess psychometric properties of QoL questionnaires in cancer [29-32]. However, we chose the same methodology for the analyses to enable precise comparisons of the psychometric properties observed in this study with those reported by the original field trial of the WHOQOL-BREF.

Lastly, the sample size of our study could be considered a limitation. Although we included less than recommended 200 patients by Boomsma and Hoogland [33], we still observed an acceptable model fit which demonstrated that our data suited the simple design of the model [34].

CONCLUSIONS

This study demonstrated that the WHOQOL-BREF has satisfactory reliability and validity in patients diagnosed with advanced-stage lung cancer. Moreover, we identified and proposed MCIDs to facilitate application of the WHOQOL-BREF not only in studies investigating new therapies and treatment modalities, but also in daily clinical practice.

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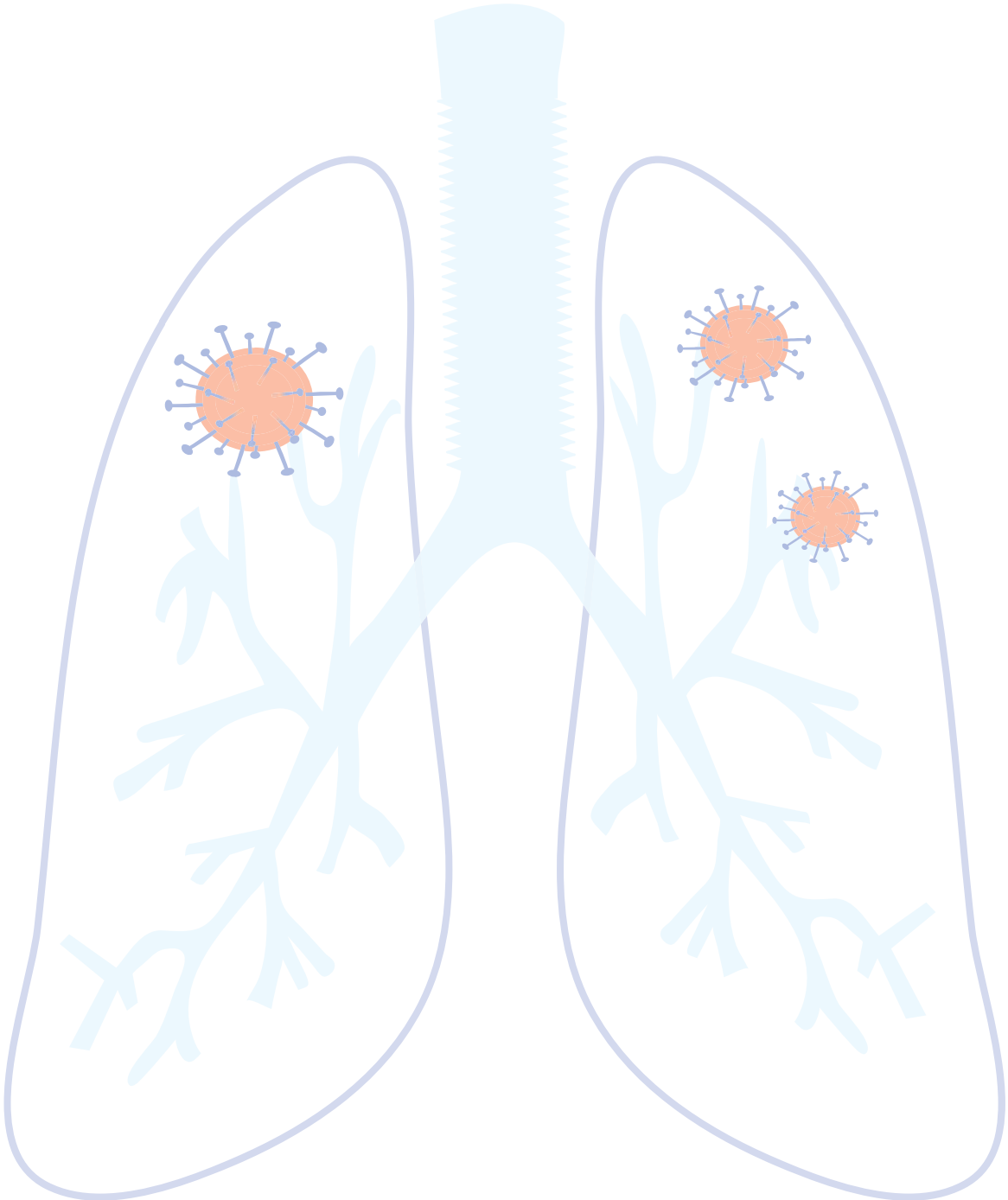
REFERENCES

1. Group NM-AC (2008) Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26 (28):4617-4625. doi:10.1200/JCO.2008.17.7162
2. Spiro SG, Rudd RM, Souhami RL, Brown J, Fairlamb DJ, Gower NH, Maslove L, Milroy R, Napp V, Parmar MK, Peake MD, Stephens RJ, Thorpe H, Waller DA, West P, Big Lung Trial p (2004) Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life. Thorax 59 (10):828-836. doi:10.1136/thx.2003.020164
3. Chabowski M, Polanski J, Mazur G, Janczak D, Rosinczuk J (2017) Sociodemographic and Clinical Determinants of Quality of Life of Patients with Non-small Cell Lung Cancer. Adv Exp Med Biol 1022:1-10. doi:10.1007/5584_2017_36
4. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 85 (5):365-376
5. Skevington SM, Lotfy M, O'Connell KA, Group W (2004) The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 13 (2):299-310
6. Mohan A, Mohan C, Bhutani M, Pathak AK, Pal H, Das C, Guleria R (2006) Quality of life in newly diagnosed patients with lung cancer in a developing country: is it important? European journal of cancer care 15 (3):293-298. doi:10.1111/j.1365-2354.2006.00654.x
7. Mohan A, Mohan C, Pathak AK, Pandey RM, Guleria R (2007) Impact of chronic obstructive pulmonary disease on respiratory status and quality of life in newly diagnosed patients with lung cancer. Respirology 12 (2):240-247. doi:10.1111/j.1440-1843.2006.01038.x
8. Trask PC, Tellefsen C, Espindle D, Getter C, Hsu MA (2008) Psychometric validation of the cancer therapy satisfaction questionnaire. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 11 (4):669-679. doi:10.1111/j.1524-4733.2007.00310.x
9. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC (2007) Quality criteria were proposed for measurement properties of health status questionnaires. Journal of clinical epidemiology 60 (1):34-42. doi:10.1016/j.jclinepi.2006.03.012
10. Hinkle DE WW, Jurs SG (2003) Applied statistics for the behavioral sciences. 5th ed Boston, Mass: Houghton Mifflin;
11. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group (1998). Psychological medicine 28 (3):551-558
12. Lin CY, Yang SC, Lai WW, Su WC, Wang JD (2015) Rasch models suggested the satisfactory psychometric properties of the World Health Organization Quality of Life-Brief among lung cancer patients. Journal of health psychology. doi:10.1177/1359105315603474
13. Luckett T, King MT, Butow PN, Oguchi M, Rankin N, Price MA, Hackl NA, Heading G (2011) Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: issues, evidence and recommendations. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 22 (10):2179-2190. doi:10.1093/annonc/mdq721
14. Campbell DT, Fiske, D. W. (1959) Convergent and discriminant validation by the multitrait-multimethod matrix. Psychological bulletin 56 (2):81-105

15. Ware JE, Harris, W.J., Gandek, B., et al. (1997) MAP-R for Windows: Multitrait./Multi-Item Analysis Program-Revised User's Guide. Health Assessment Lab; Boston, MA:
16. Den Oudsten BL, Van Heck GL, Van der Steeg AF, Roukema JA, De Vries J (2009) The WHOQOL-100 has good psychometric properties in breast cancer patients. Journal of clinical epidemiology 62 (2):195-205. doi:10.1016/j.jclinepi.2008.03.006
17. Hu L BP (1999) Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Equ Model 6:1-55
18. Norman GR, Sloan JA, Wyrwich KW (2003) Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 41 (5):582-592. doi:10.1097/01.MLR.0000062554.74615.4C
19. Wyrwich KW, Nienaber NA, Tierney WM, Wolinsky FD (1999) Linking clinical relevance and statistical significance in evaluating intra-individual changes in health-related quality of life. Med Care 37 (5):469-478
20. Wyrwich KW, Tierney WM, Wolinsky FD (1999) Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. J Clin Epidemiol 52 (9):861-873. doi:S0895435699000712 [pii]
21. Wyrwich KW, Tierney WM, Wolinsky FD (2002) Using the standard error of measurement to identify important changes on the Asthma Quality of Life Questionnaire. Qual Life Res 11 (1):1-7
22. King MT (2011) A point of minimal important difference (MID): a critique of terminology and methods. Expert Rev Pharmacoecon Outcomes Res 11 (2):171-184. doi:10.1586/erp.11.9
23. Beaton DE, Bombardier C, Katz JN, Wright JG (2001) A taxonomy for responsiveness. Journal of clinical epidemiology 54 (12):1204-1217
24. Rittmeyer A, Gorbunova V, Vikstrom A, Scherpereel A, Kim JH, Ahn MJ, Chella A, Chouaid C, Campbell AK, Barlesi F (2013) Health-related quality of life in patients with advanced nonsquamous non-small-cell lung cancer receiving bevacizumab or bevacizumab-plus-pemetrexed maintenance therapy in AVAPERL (MO22089). Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 8 (11):1409-1416. doi:10.1097/JTO.0b013e3182a46bcf
25. Gridelli C, de Marinis F, Pujol JL, Reck M, Ramlau R, Parente B, Pieters T, Middleton G, Corral J, Winfree K, Melemed S, Zimmermann A, John W, Beyrer J, Chouaki N, Visseren-Grul C, Paz-Ares LG (2012) Safety, resource use, and quality of life in paramount: a phase III study of maintenance pemetrexed versus placebo after induction pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 7 (11):1713-1721. doi:10.1097/JTO.0b013e318267cf84
26. Spigel DR, Patel JD, Reynolds CH, Garon EB, Hermann RC, Govindan R, Olsen MR, Winfree KB, Chen J, Liu J, Guba SC, Socinski MA, Bonomi P (2015) Quality of life analyses from the randomized, open-label, phase III PointBreak study of pemetrexed-carboplatin-bevacizumab followed by maintenance pemetrexed-bevacizumab versus paclitaxel-carboplatin-bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 10 (2):353-359. doi:10.1097/JTO.0000000000000277
27. Krebber AM, Buffart LM, Kleijn G, Riepma IC, de Bree R, Leemans CR, Becker A, Brug J, van Straten A, Cuijpers P, Verdonck-de Leeuw IM (2014) Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psycho-oncology 23 (2):121-130. doi:10.1002/pon.3409

28. Bartoces MG, Severson RK, Rusin BA, Schwartz KL, Ruterbusch JJ, Neale AV (2009) Quality of life and self-esteem of long-term survivors of invasive and noninvasive cervical cancer. Journal of women's health 18 (5):655-661. doi:10.1089/jwh.2008.0959
29. Ashley L, Smith AB, Jones H, Velikova G, Wright P (2014) Traditional and Rasch psychometric analyses of the Quality of Life in Adult Cancer Survivors (QLACS) questionnaire in shorter-term cancer survivors 15 months post-diagnosis. Journal of psychosomatic research 77 (4):322-329. doi:10.1016/j.jpsychores.2014.07.007
30. Shih CL, Chen CH, Sheu CF, Lang HC, Hsieh CL (2013) Validating and improving the reliability of the EORTC qlq-c30 using a multidimensional Rasch model. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 16 (5):848-854. doi:10.1016/j.jval.2013.05.004
31. Winstanley JB, Saw R, Boyle F, Thompson J (2013) The FACT-Melanoma quality-of-life instrument: comparison of a five-point and four-point response scale using the Rasch measurement model. Melanoma research 23 (1):61-69. doi:10.1097/CMR.0b013e32835c7dd9
32. Holzner B, Bode RK, Hahn EA, Cella D, Kopp M, Sperner-Unterweger B, Kemmler G (2006) Equating EORTC QLQ-C30 and FACT-G scores and its use in oncological research. European journal of cancer 42 (18):3169-3177. doi:10.1016/j.ejca.2006.08.016
33. Boomsma A, Hoogland, J.J. (2001) The robustness of LISREL modeling revisited. In Cudeck, R., Du Toit, S., Sörbom D. (Eds.), Structural equation modelling: Present and future (pp. 139-168). Chicago: Scientific Software.
34. Byrne BM (2005) Factor analytic models: viewing the structure of an assessment instrument from three perspectives. Journal of personality assessment 85 (1):17-32. doi:10.1207/s15327752jpa8501_02



CHAPTER 4

Reliability and validity of the Cancer Therapy Satisfaction Questionnaire in Lung Cancer

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ABSTRACT

Purpose: To test the reliability and validity of the Cancer Treatment Satisfaction Questionnaire (CTSQ), to assess its relation with Quality of Life (QoL), and to assess the interpretability of the domain scores in patients with lung cancer receiving intravenous chemotherapy.

Methods: Patients with stage IIIB and IV non-squamous non-small cell lung carcinoma treated with pemetrexed were enrolled in our study. They completed the 16-item CTSQ and two other (HR)QoL questionnaires. Information about sociodemographic characteristics, cancer stage, the Eastern Cooperative Oncology Group performance status, and the experience of adverse events was collected. Internal consistency, construct validity, and clinical interpretability were calculated.

Results: Fifty-five patients completed the CTSQ. Correlations of the CTSQ items with its domain were all above 0.40. A high correlation between item 8 and the expectations of therapy and satisfaction with therapy domain was observed (0.50 and 0.48, respectively). The CTSQ domains demonstrated good internal consistency and low to moderate correlations of the CTSQ with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and World Health Organization Quality of Life-BREF. No significant differences in mean domain scores were observed in relation to the number and severity of different adverse events and chemotherapy-related adverse events.

Conclusions: The Dutch version of the CTSQ was found to be a reliable and valid instrument to assess satisfaction and expectations of treatment in patients with lung cancer receiving intravenous chemotherapy. Furthermore, the CTSQ proved to be of additional informative value as not all of its domains correlated positively with the various domains of the existing HRQoL instruments.

INTRODUCTION

Anti-cancer therapies mostly offer modest improvements in survival, making the occurrence of adverse events an important outcome parameter in studies and clinical practice. It is well established that adverse events impair Health-Related Quality of Life (HRQoL) [1] and that (change of) HRQoL acts as a prognostic factor in (lung) cancer patients [2-7].

Questionnaires evaluating HRQoL offer valuable information about the impact of cancer and therapy related adverse events. However, they do not address patients' satisfaction, expectations and preferences concerning the occurrence and management of adverse events, the choice and type of therapy, and the efficacy of treatment. Such information provides opportunities for physicians to improve therapy compliance, personalize the course of treatment and to develop interventions designed to prevent or effectively treat adverse events and thus improve HRQoL. Certainly in diseases with a poor prognosis (e.g., advanced-stage lung cancer) where the treatment is associated with only limited increases in survival and elevated risks for adverse events, insight into patients' expectations and satisfaction is of upmost importance.

In 2005, the CTSQ was developed to assess patients' opinions and feelings concerning their cancer therapy and associated adverse events [8]. A psychometric validation study of this questionnaire was performed, which resulted in an optimized and more brief version ensuring its reliability for research purposes [9]. Since then, the CTSQ has only been validated in a Korean study in which just four patients were treated with chemotherapy [10].

Given these considerations the objective of our study was focused on three main aspects of the CTSQ: (1) to test the reliability and validity of the Cancer Treatment Satisfaction Questionnaire (CTSQ) in patients with lung cancer intravenous chemotherapy, (2) to assess its relation with Health-Related Quality of Life (HRQoL), and (3) to assess the interpretability of the domain scores.

MATERIALS AND METHODS

Study population

This study was approved by the Institutional Review Board of the Erasmus University Medical Center in Rotterdam, The Netherlands. Patients were recruited from a university hospital (Erasmus University Medical Center) and a large teaching hospital (Amphia hospital) specialized in lung cancer care located in the western part of the Netherlands. Patients were enrolled in our study if they met the following criteria: they provided written informed consent, were aged eighteen years or older, and were treated with at least four cycles of pemetrexed monotherapy or in combination with cisplatin or carboplatin as either first or second line. Patients were excluded if they met the following criteria: they

were not able to read Dutch or could not complete the questionnaire because of a physical or mental condition (which prohibited participation in the study). A sample size of at least 50 patients was needed in order to perform a validation study [11].

Study measures

The CTSQ contains three domains covering 16 items: expectations of therapy (ET; 5 items), feelings about side effects (FSE; 4 items) and satisfaction with therapy (SWT; 7 items). Each item was scored on a scale from one to five with a value of one corresponding with the worst response and a value of five representing the best response. Four items are reverse coded. Domain score was calculated by the formula: (mean of completed item scores -1) x 25. This results in a domain score ranging from 0 to 100, with a higher score representing a better outcome on each domain.

The original CTSQ was translated into Dutch by TransPerfect Translations Inc. according to the forward/backward methodology following international guidelines [12]. Questions were translated in a forward manner (English to Dutch) by two independent native-speaking linguists of the target language experienced in the translation of quality of life instruments. A third independent native speaker reviewed these translations and selected the most appropriate translation of the items or provided an alternative version. Discrepancies, linguistic limitations or cultural differences were addressed. Back translation was performed by a fourth independent native-speaker with proficiency in English. An oncologist determined whether the Dutch translation was in line with the medical terminology as used in the Netherlands. Finally, five respondents who received cancer treatment in the past 18 months asked to provide feedback on the Dutch CTSQ during an interview. The respondents' overall impression of the instrument was that it was ''easy to complete''. The respondents' answers corresponded with the intended meanings of the items. During the translation process some questions were slightly changed (i.e., not literally translated) to ensure conceptual equivalence and cultural relevance to facilitate correct use of Dutch grammar. Permission of use was granted by Pfizer Inc. the current owner of the intellectual rights of the CTSQ. A pre-assessment of the Dutch version was conducted in 14 patients with lung cancer (not included in this study) to assess whether the questions were understandable and acceptable for use in the study.

The European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire- Core 30 (EORTC-QLQ-C30) is a cancer-specific HRQoL instrument with demonstrated psychometric properties [13]. It consists of 30 items and incorporates a global Health Status/Quality of Life scale, five functional scales and a number of single items assessing additional symptoms or difficulties. Each of the QLQ-C30 domains is scored on a 0-100 scale, with higher scores on the functional scales being indicative of better HRQoL, whereas higher scores on the symptom scales are reflective of worse symptoms [14,15].

The World Health Organization Quality of Life-BREF (WHOQOL-BREF) is a shorter version of the original WHOQoL-100 questionnaire. It is a generic QoL instrument and comprises 26 items divided over 4 domains: physical health, psychological health, social relationships, and environment and one facet: overall Quality of Life and general health. The WHOQOL-BREF domains are scored on a 4-20 scale and the facet on a 2-10 scale with higher scores indicating a better Quality of Life [16]. The WHOQOL-BREF is a well-established instrument that was developed for use in a wide range of disease areas and health problems [17].

All questionnaires were completed after patients finished their 4-cycle therapy of chemotherapy. In addition to completing the instruments, respondents were asked to provide information about the frequency and severity of adverse events they have experienced (cancer or therapy-related). We also collected sociodemographic information (age, gender, educational level, ethnicity, smoking status and clinical history) and information about cancer stage, hospitalization (due to cancer or adverse effect of therapy), and the Eastern Cooperative Oncology Group (ECOG) performance status.

Statistical analysis

Floor and ceiling effects were calculated in our study and were considered to be present if more than 15% of the respondents achieved the lowest (floor effect) or highest (ceiling effect) possible domain score [11].

Construct validity was evaluated using Pearson's rank correlation coefficient between questionnaire items and domains. Correlations of 0.40 or higher indicate a good correlation between items and domains [11].

Internal-consistency reliability measures to which extent items within a domain correlate with each other to form a (multi-item) domain. Reliability coefficients for the CTSQ domains were estimated using Cronbach's coefficient alpha where a reliability coefficient of 0.70 or higher was considered to be acceptable [11].

Known-groups validity comparisons were made for the CTSQ domains in relation to the number of different adverse events and its severity. Also the impact of therapy-related adverse events compared to cancer-related adverse events on CTSQ domain score was evaluated. For this analysis, the one-way ANOVA was used to determine whether there are any significant differences between the means of two or more independent groups.

The association between the CTSQ domains with domains of the EORTC QLQ-C30 and WHOQOL-BREF was assessed using Spearman's correlation coefficients.

We assessed interpretability, which is defined as the degree to which one can assign qualitative meaning to quantitative scores. For each CTSQ domain, the MCID was calculated using the approach of 0.5 SD [18] and 1 standard error of measure (SEM) [19-21]. MCID is the smallest change in an outcome that a patient would identify as important. The 0.5 SD benchmark of an outcome measure entails that patients improving more than 0.5 of the outcome score's SD have achieved a minimally clinically important difference

[22]. For the 1 SEM approach we have used the internal consistency reliability estimates. In addition, results of the known-groups comparison were used to derive the MCID using the number of adverse events with Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 as an anchor.

A p-value below 0.05 was considered to be statistically significant. All analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY).

RESULTS

Patient characteristics

Table 1 describes the characteristics of our study population. A total of 55 patients completed the questionnaires. The age of these patients ranged from 45 to 79 years, with a mean of 55.0 (SD 8.6). Forty-four patients indicated they had received a low level of education (80.0%), and 32.7% stated to be employed. The majority of these patients were diagnosed with adenocarcinoma of the lung (94.5%) and 85.5% had stage IV NSCLC. Almost all patients (98.2%) had a good ECOG performance score (grade 0 or 1). The majority of patients received pemetrexed chemotherapy as a first line treatment (85.5%).

Table 1. Characteristics of study population

Characteristic	Overall sample (N=55)
Age, years	
Mean (SD)	55 (8.6)
Min, max	45, 79
Sex	
Male	27 (49.1)
Ethnicity	
White / Caucasian	52 (94.5)
Asian	1 (1.8)
Negroid	1 (1.8)
Other	1 (1.8)
Education[a]	
Low	44 (80.0)
High	8 (14.5)
Unknown	3 (5.5)
Employment	
Yes	18 (32.7)
Marital status	
Married/ cohabiting	44 (80.0)

Table 1. Characteristics of study population (continued)

Characteristic	Overall sample (N=55)
Unmarried partners/ not cohabiting	3 (5.5)
Divorced/ separated	2 (3.6)
Widowed/ partner died	4 (7.3)
Single	1 (1.8)
Unknown	1 (1.8)
Cancer stage[b]	
Locally advanced (IIIB)	4 (7.3)
Metastatic (IV)	47 (85.5)
Other	4 (7.3)
Type of tumor[b]	
Adenocarcinoma	52 (94.5)
Large cell carcinoma	1 (1.8)
Mesothelioma	1 (1.8)
Large cell neuroendocrine carcinoma	1 (1.8)
Line of therapy	
First line	47 (85.5)
Second line	5 (9.1)
Adjuvant	3 (5.5)
ECOG performance status[a]	
Grade 0	17 (30.9)
Grade 1	38 (69.1)

Values are given in numbers (percentages) unless stated otherwise.
[a]Low education: persons whose highest level of education is primary education, lower general education or lower vocational education. High education: persons whose highest level of education is higher general education, higher vocational education or university.
[b]Measured at baseline
Abbreviations: N, number of patients; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group (ECOG)

Mean scores and floor and ceiling effects

The mean scores of the ET and FSE domain were 55.6 (SD 22.5) and 52.2 (SD 23.8), respectively. The SWT domain had a mean score of 79.7 (SD 13.9), which was much higher compared to the mean scores of the other domains. No patients demonstrated the lowest possible domain score of 0.0. The floor effects for all domains were therefore zero. The FSE domain did not reach the highest possible score of 100, resulting in a negligible ceiling effect for this domain. For the ET and SWT domain we observed a ceiling effect of 5.5% and 9.1% respectively, which is below the common accepted limit of 15% (Table 2).

Table 2. Summary statistics for CTSQ domains

CTSQ domain	N	Mean (SD)	Median	Observed range (min, max)	Floor effect n(%)	Ceiling effect n(%)
Expectations of therapy (ET)	55	55.6 (22.5)	55.0	15.0, 100.0	0 (0.0)	3 (5.5)
Feelings about side effects (FSE)	54	52.2 (23.8)	56.3	12.5, 93.8	0 (0.0)	0 (0.0)
Satisfaction with therapy (SWT)	55	79.7 (13.9)	82.1	42.9, 100.0	0 (0.0)	5 (9.1)

Abbreviations: SD, standard deviation; N, number of patients; CTSQ, cancer therapy satisfaction questionnaire

Construct validity

Construct validity was supported for all 16 items as we observed a correlation of 0.40 or higher with their own hypothesized domain. However, we found that item 8, (chemotherapy would help you live longer) had a good correlation with its own hypothesized domain (0.50), and with the competing SWT domain (0.48). All other comparisons showed good results, as these items correlated better with their own hypothesized domain than with competing domains (Table 3).

Internal consistency

The internal consistency of the CTSQ domains is shown in Table 4. All three domains met the reliability coefficient of 0.70 or higher. Cronbach's alpha of the ET and FSE domains were both above 0.80 (0.83), except for the SWT domain (0.77). As presented in Table 3, we observed that item 8 had a similar correlation with the SWT domain as with the ET domain. For this reason we decided to move item 8 from the ET domain to the SWT domain and calculated Cronbach's alpha for the revised CTSQ domains. We found a slight increase of the alpha coefficients of both domains (ET: 0.86, SWT: 0.79).

Known-groups comparisons

Table 5 shows the known-groups validity comparisons for the CTSQ domains in relation to the number of different adverse events, its severity and chemo-related adverse events. None of these results were found to be significant. We observed an increasing number of grade 3 and 4 adverse events that corresponded with a decreasing mean score of the FSE domain. The same observation was found in the analysis where we looked at the percentage of adverse events that were related to chemotherapy. Also, frequency and severity of adverse events were not related to satisfaction with therapy.

Minimally clinically important differences

The estimates of the MCIDs are given in Table 6. Estimates of the MCID for the ET and FSE domain were almost the same (0.5 SD: 11.75; 1 SEM: 9.69 and 0.5 SD: 12.4; 1 SEM: 9.28, respectively). The calculated estimates using the 0.5 SD approach were higher for both

Table 3. Construct validity of the CTSQ (n=55)

Item number	Description	ET correlation coefficient (sig.)	FSE correlation coefficient (sig.)	SWT correlation coefficient (sig.)
Expectations of therapy (ET)				
1	CT would help you to return to a normal life	**0.73** (<0.001)	-0.20 (0.16)	-0.04 (0.77)
2	CT would get rid of the cancer	**0.87** (<0.001)	0.07 (0.61)	-0.006 (0.97)
3	CT would help prevent the cancer from coming back	**0.89** (<0.001)	0.13 (0.33)	0.20 (0.15)
4	CT would stop the cancer from spreading	**0.81** (<0.001)	-0.04 (0.80)	0.34 (0.01)
8	CT would help you live longer	**0.50** (<0.001)	0.15 (0.39)	**0.48** (<0.001)
Feelings about side effects (FSE)				
5R*	CT limited your daily activities	0.002 (0.99)	**0.68** (<0.001)	0.23 (0.09)
6R*	Upset about side effects	0.02 (0.91)	**0.80** (<0.001)	0.14 (0.30)
11R*	Overall, was taking CT as difficult as expected	-0.05 (0.70)	**0.91** (<0.001)	0.20 (0.14)
13	Overall, were side effects as expected	0.12 (0.38)	**0.87** (<0.001)	**0.41** (0.002)
Satisfaction with therapy (SWT)				
7	CT was worth taking even with side effects	0.37 (0.006)	0.08 (0.56)	**0.70** (<0.001)
9R*	How often did you think about stopping CT	-0.08 (0.56)	0.30 (0.03)	**0.42** (0.002)
10	Overall, how worthwhile was your CT	0.29 (0.03)	0.02 (0.89)	**0.63** (<0.001)
12	Overall, how well did the benefits of CT meet your expectations	0.27 (0.05)	0.25 (0.06)	**0.79** (<0.001)
14	How satisfied were you with the form of your CT	-0.11 (0.45)	0.19 (0.17)	**0.57** (<0.001)
15	How satisfied were you with your most recent CT	0.09 (0.51)	**0.40** (0.003)	**0.64** (<0.001)
16	If given choice again, would you decide to take this CT treatment	0.02 (0.87)	0.28 (0.04)	**0.74** (<0.001)

Correlations of CTSQ domains with CTSQ items of 0.40 or larger are in bold.
*These items were reverse-coded by subtracting the original value from 6, where a value of 1 represents the worst response and a value of 5 represents the best response.
Abbreviations: sig., significance (2-tailed); CT, chemotherapy; CTSQ, cancer therapy satisfaction questionnaire

domains compared to the estimates using the 1 SEM approach. We observed a much lower estimate for the SWT domain (0.5 SD: 6.55; 1 SEM: 6.14) and a smaller difference between the estimates of the 0.5 SD and 1 SEM. The anchor-based MCID was estimated by calculating the average change in CTSQ score. For the ET domain, the estimate that was obtained using the number of grade 3 or 4 adverse events as an anchor was higher than the observed estimates using the 0.5 SD and 1 SEM approach (14.3). For the other two domains, we observed lower estimates when using the anchor- based method (SE: 8.5 and SWT: 5).

Table 4. Internal consistency of CTSQ domains

CTSQ domain	Internal consistency	Internal consistency (revised)
	Cronbach's alpha	Cronbach's alpha*
	N=55	N=55
Expectations of Therapy (ET)	0.83	0.86
Feelings about Side Effects (FSE)	0.83	0.83
Satisfaction with Therapy (SWT)	0.77	0.79

*Item 8 was moved from the ET domain to the SWT domain
Abbreviations: N, number of patients who completed the CTSQ questionnaire; CTSQ, cancer therapy satisfaction questionnaire

Table 5. Known-groups comparisons (n=55)

Description	CTSQ Expectations of therapy			CTSQ Feelings about side effects			CTSQ Satisfaction with therapy		
	N	Mean (SD)	P-value (effect size)*	N	Mean (SD)	P-value (effect size)*	N	Mean (SD)	P-value (effect size)*
Number of different adverse events[a]									
0-10	27	56.2 (24.7)	0.86	26	55.3 (22.9)	0.36	27	79.1 (13.2)	0.77
more than 10	28	55.1 (20.6)		28	49.3 (24.7)		28	80.2 (14.7)	
Number of adverse events with CTCAE grade 3 or 4[a]									
0	25	57.1 (22.7)	0.17	24	53.6 (23.6)	0.41	25	77.5 (14.4)	0.47
1	10	42.3 (16.3)		10	51.9 (23.0)		10	80.0 (14.4)	
2 or 3	12	63.3 (27.2)		12	57.8 (26.1)		12	85.1 (11.0)	
more than 3	8	56.3 (16.4)		8	39.8 (21.6)		8	77.7 (15.8)	
% of adverse events that are related to chemotherapy									
0-25	6	63.3 (23.2)	0.35	6	56.3 (22.7)	0.56	6	84.5 (14.0)	0.65
26-50	11	61.6 (23.8)		10	55.0 (22.6)		11	76.0 (9.5)	
51-75	23	49.5 (21.4)		23	54.9 (25.7)		23	80.7 (14.1)	
76-100	15	57.7 (22.6)		15	44.6 (22.5)		15	78.8 (16.5)	

*Effect sizes were only shown where one-way ANOVA was significant (P<0.05)
[a]reported adverse events: 2 weeks prior to last chemo until 4 weeks after last chemo
Abbreviations: CTSQ, cancer therapy satisfaction questionnaire; SD, standard deviation; N, number of patients who completed the questionnaire; CTCAE, Common Terminology Criteria for Adverse Events

Correlation of CTSQ domains with quality of life

The correlation between the CTSQ domains and domains of the EORTC QLQ-C30 is shown in Table 7. We found the FSE domain correlated more strongly with the EORTC QLQ-C30 domains than the other two CTSQ domains. The highest correlations ($r \geq 0.40$) were observed with global Health Status, role functioning, emotional functioning and the symptom domains fatigue, nausea and vomiting, and appetite loss. No correlation of 0.40 or higher was observed between the ET domain and the HRQoL domains. The SWT

Table 6. Estimates of minimally clinically important differences on CTSQ domains

CTSQ domain	0.5 SD[a]	1 SEM[b]	Known-groups differences[c]
Expectations of therapy	11.25	9.28	A difference of 14.8 points between 0 and 1 AE, 21 points difference between 1 and 2/3 AEs and a difference of 7 points between 2/3 and >3 AEs. The average difference is 14.3 points
Feelings about side effects	11.9	9.81	A difference of 1.7 points between 0 and 1 AE, 5.9 points difference between 1 and 2/3 AEs and a difference of 18 points between 2/3 and >3 AEs. The average difference is 8.5 points.
Satisfaction with therapy	6.95	6.37	A difference of 2.5 points between 0 and 1 AE, 5.1 points difference between 1 and 2/3 AEs and a difference of 7.4 points between 2/3 and>3 AEs. The average difference is 5 points.

[a]0.5 SD of CTSQ domain scores
[b]using internal consistency reliability estimates
[c]using the known-group criterion 'number of adverse events with CTCAE grade 3 or 4'
Abbreviations: n, number of patients who completed the CTSQ questionnaire; CTSQ, cancer therapy satisfaction questionnaire; CTCAE, Common Terminology Criteria for Adverse Events; SD, standard deviation; SEM, standard error of measure

Table 7. Correlations of CTSQ with EORTC QLQ-C30 domains

	CTSQ domains		
N=55	Expectations of therapy	Feelings about side effects	Satisfaction with therapy
EORTC QLQ-C30 domains			
Global Health Status/ Quality of Life	0.01	**0.40****	0.27*
Physical functioning	0.18	0.34*	0.20
Role functioning	0.13	**0.48****	0.09
Emotional functioning	-0.011	**0.51****	0.17
Cognitive functioning	0.006	0.18	-0.03
Social functioning	-0.080	0.32*	0.02
Fatigue	-0.10	**-0.52****	-0.22
Nausea and vomiting	-0.04	**-0.53****	**-0.41****
Pain	-0.006	-0.26	-0.17
Dyspnea	0.018	-0.23	0.07
Insomnia	-0.16	0.10	-0.06
Appetite loss	-0.07	**-0.60****	-0.30*
Constipation	-0.20	-0.39**	-0.11
Diarrhea	-0.15	-0.11	0.04
Financial difficulties	-0.09	-0.04	0.04

Spearman correlations. Correlations of CTSQ domains with EORTC QLQ-C30 domains of r ≥ 0.40 or larger are in bold.
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).
Abbreviations: CTSQ, cancer therapy satisfaction questionnaire; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; N, number of patients who completed the questionnaire

domain only significantly correlated with nausea and vomiting (r = -0.41). The negative correlations between the CTSQ and HRQoL domains indicate that higher scores of the CTSQ domains are associated with worse symptoms.

Results of the association between the CTSQ and WHOQOL-BREF domains are presented in Table 8. The domains of WHOQOL-BREF had the strongest correlations with the FSE domain. However, only the psychological domain had a correlation above 0.40 (r = 0.52).

Table 8. Correlations of CTSQ with WHOQOL-BREF domains

	CTSQ domains		
N=55	Expectations of therapy	Feelings about side effects	Satisfaction with therapy
WHOQOL-BREF domains			
Overall Quality of Life and general health	0.20	0.28*	0.14
Physical health	0.10	0.36**	0.10
Psychological health	0.21	**0.52****	0.24
Social relationships	0.07	0.12	0.12
Environment	0.04	0.15	0.04

Spearman correlations. Correlations of CTSQ domains with WHOQOL-BREF domains of r ≥ 0.40 or larger are in bold.
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).
Abbreviations: CTSQ, cancer therapy satisfaction questionnaire; WHOQOL-BREF, World Health Organization Quality of Life-BREF; N, number of patients who completed the questionnaire

DISCUSSION

Although HRQoL questionnaires inform health care professionals about the well-being of their patients, they do not address patients' expectations and satisfaction with therapy. Brown et al. demonstrated that expectations of therapy and adverse events are important determinants for patient compliance [1]. In addition, satisfaction is likely to express contentment with therapy and may also be influenced by the occurrence of adverse events. The CTSQ could be used as a tool to monitor the management of therapy and adverse events to improve HRQoL. Especially in cancer patients with a limited prognosis, this may be of importance. Therefore, our objective was to evaluate the reliability and validity of the CTSQ. Our study showed good results and hence supports the construct validity and internal consistency reliability of the CTSQ.

The previous psychometric validation study demonstrated a positively skewed score distribution of the ET domain with a substantial ceiling effect (20.5) [9]. Even higher ceiling effects were observed in the study by Park et al. for the ET and FSE domains (21.6 and 36.3, respectively) [9]. No floor or ceiling effects were found in our study, which indicates

that no extreme items are missing in the lower or upper end of the scale. This might be explained by the fact that all patients in our study had advanced-stage lung cancer of whom all have a limited survival compared to those with a curable disease. As lung cancer patients in general demonstrate information seeking behavior to cope with their disease [23] and the patients in our study were already informed about their limited survival prior to the start of therapy, we assume that the patients enrolled in our study did not have such high expectations. Moreover, disease stage may also influence the FSE and SWT domains. Simultaneously with disease progression, patients may experience more and severe cancer-related adverse events. These adverse events may be attributed by patients to chemotherapy probably resulting in a lower FSE domain score and decreased satisfaction with therapy.

All items correlated better with their own domains than with the other domains, which is in line with the results of the psychometric validation study. However, the correlations between the items and domains were found to be higher in our study compared with the previous study, which might be explained by the homogeneity of the population in our study. We observed that item 8 of the CTSQ (cancer therapy would help you live longer) had strong correlations with the SWT domain and with its own ET domain. Moreover, when we moved item 8 from the ET to the SWT domain, it resulted in a slight increase of alpha coefficients for both the ET and SWT domains. Although our results are in line with the results of the previous CTSQ studies [9,10], the sample size in our study was small. Therefore, we suggest further research to be conducted in a larger population to confirm this finding.

In 2004, a validation study of another patient satisfaction questionnaire (TSQM) was performed and showed significant differences in patient satisfaction and convenience of treatment between different treatment modalities (e.g., oral, topical, injectable, inhaler) [24]. As patients in our study received only intravenously administered chemotherapy, we expect this may have affected the generalizability of our results. In addition, all patients in our study were diagnosed with advanced-stage lung cancer whereas patients with various diseases were included in the TSQM validation study [24]. This may also hamper broad application of the CTSQ. However, when we compare our study with the study of Trask et al., which was conducted in a more heterogeneous population, we observed similar results with respect to construct validity and internal consistency reliability. Therefore, we assume that the single route of administration and the disease stage of the included patients in our study did not have a major impact on our results in terms of generalizability.

As for the estimates of the MCIDs, we observed similar results for the FSE and SWT domains when we compare our results (FSE 11.9, 9.81; SWT 6.95, 6.37) with the results of the previous psychometric validation study (FSE 11.0, 10.55; SWT 6.88, 5.84). However, we found a clear difference of the MCIDs of the ET domain between both studies as in our study a larger change of domain score is needed for it to be considered clinically relevant

(MCIDs in our study: 11.25, 9.28; Trask et al.: 9.59, 6.92). A possible explanation for this is the ceiling effect of 20.5%, which was observed in the study by Trask, which was not observed in our study [9]. Consequently, they were not able to detect such a difference, because this change would then exceed the range of the scale.

We observed an increasing number of severe and chemotherapy-related adverse events that corresponded with a decreasing mean FSE domain score. According to Grutters et al. this may be due to the impact of adverse events on HRQoL as they showed in their study that already moderate adverse events resulted in a significant decrease in HRQoL [25]. To assess this relation between patient satisfaction and expectations regarding treatment and HRQoL in more detail, we correlated the CTSQ domains with the HRQoL domains and items. No positive correlations were found between the ET domain and any of the HRQoL domains or items indicating that not all concepts of the CTSQ are identified by HRQOoL questionnaires. This finding may be due to the relevance of adverse events for patients. For instance, certain laboratory abnormalities may not result in the experience of symptoms, while these symptoms are being regarded as an adverse event according to the Common Terminology Criteria for Adverse Events (CTCAE). As argued before, expectations of therapy are likely to be influenced by the information patients have received. However, satisfaction seems also to be influenced by patients' opinions regarding the received information as several studies investigating patient satisfaction reported increased satisfaction when adequate information was provided by health care professionals [26-28]. Moreover, satisfaction with information has been associated with better HRQoL [29]. Therefore, we assume the CTSQ may give additional clinically relevant information that is not provided by HRQoL questionnaires regarding patients' expectations and satisfaction with information provision and possibly also other aspects of cancer care.

Terwee et al. suggested that a sample size of at least 50 patients would be sufficient for a validation study [11]. Nevertheless, for the clinical interpretation of the scores, a larger sample size may be needed to get more reliable results as we were not able to calculate the effect size in the known-groups comparison. For this reason, the small sample size may be considered as a limitation in our study.

We were not able to evaluate test-retest reliability since the questionnaire was only given once after the fourth cycle of chemotherapy. If patients fill in the CTSQ a second time after the first completion, it will be hard to define an appropriate interval between those two completions as we included patients who have a relatively poor prognosis. If the interval between these completions is too short, the difficulty may be that they recall their earlier answers upon filling in the CTSQ for a second time. Moreover, when the interval is too long, patients may have progressed in their disease experiencing more adverse events, which may bias our results. However, we do not expect this to be a major problem as this part has already been validated in the psychometric validation study, showing good results [9].

In conclusion, we were able to support the internal consistency reliability and construct validity of the Dutch version of the CTSQ in lung cancer patients treated with intravenous chemotherapy. Only a few aspects of HRQoL were significantly correlated to items of the CTSQ, indicating the need of using the CTSQ in studies evaluating satisfaction and expectations of patients on cancer chemotherapy. Since patients with disseminated cancer often have a limited prognosis, considering patients' motivations and needs is of importance to improve HRQoL. We therefore believe that our results may encourage researchers to use the CTSQ to investigate patients' expectations and satisfaction with therapy in future studies.

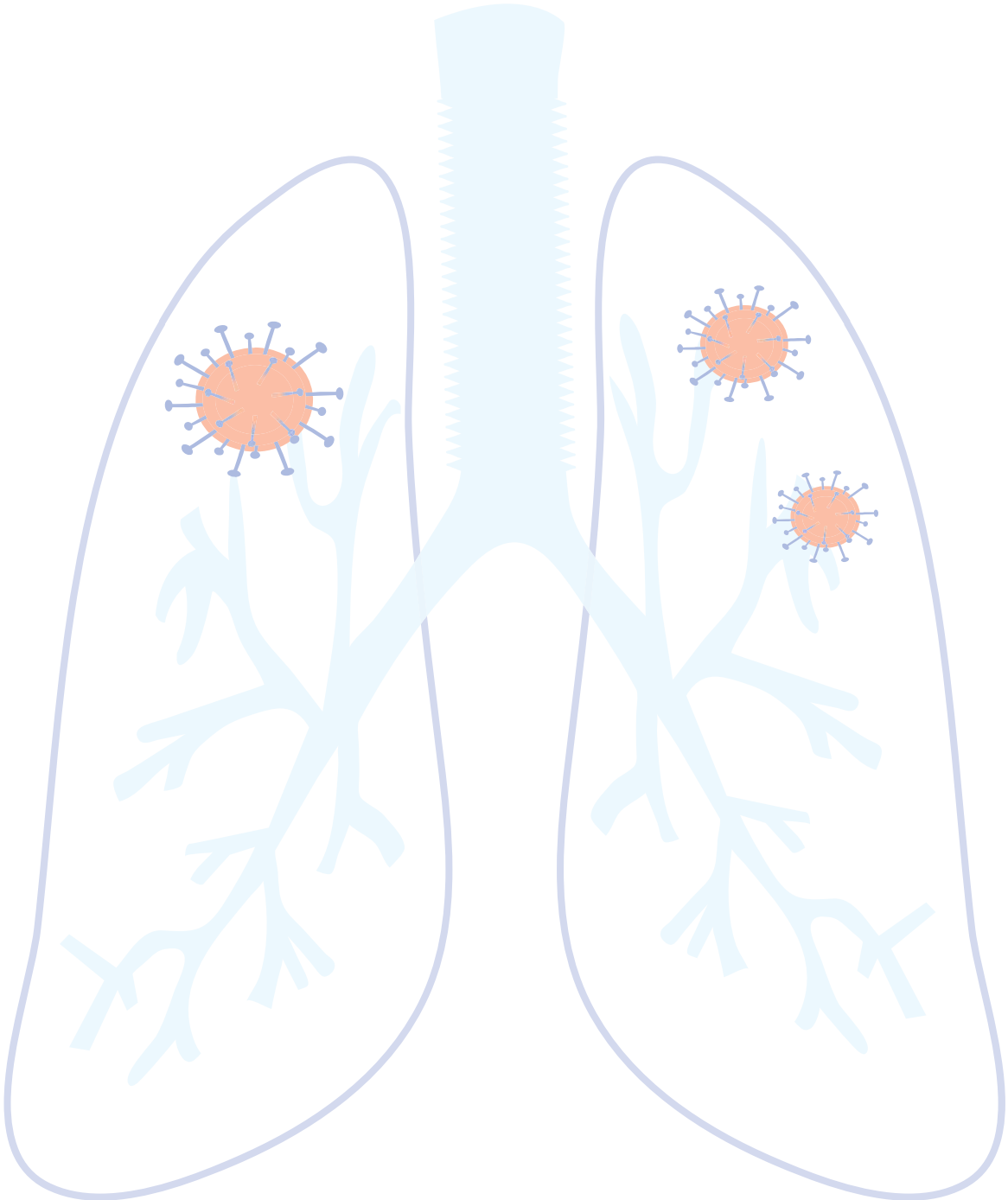
REFERENCES

1. Brown LF, Kroenke K, Theobald DE, Wu J, Tu W (2010) The association of depression and anxiety with health-related quality of life in cancer patients with depression and/or pain. Psychooncology 19 (7):734-741. doi:10.1002/pon.1627
2. Gotay CC, Kawamoto CT, Bottomley A, Efficace F (2008) The prognostic significance of patient-reported outcomes in cancer clinical trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26 (8):1355-1363. doi:10.1200/JCO.2007.13.3439
3. Staren ED, Gupta D, Braun DP (2011) The prognostic role of quality of life assessment in breast cancer. The breast journal 17 (6):571-578. doi:10.1111/j.1524-4741.2011.01151.x
4. Qi Y, Schild SE, Mandrekar SJ, Tan AD, Krook JE, Rowland KM, Garces YI, Soori GS, Adjei AA, Sloan JA (2009) Pretreatment quality of life is an independent prognostic factor for overall survival in patients with advanced stage non-small cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 4 (9):1075-1082. doi:10.1097/JTO.0b013e3181ae27f5
5. Movsas B, Moughan J, Sarna L, Langer C, Werner-Wasik M, Nicolaou N, Komaki R, Machtay M, Wasserman T, Bruner DW (2009) Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. J Clin Oncol 27 (34):5816-5822. doi:JCO.2009.23.7420 [pii] 10.1200/JCO.2009.23.7420
6. Langendijk H, Aaronson NK, de Jong JM, ten Velde GP, Muller MJ, Wouters M (2000) The prognostic impact of quality of life assessed with the EORTC QLQ-C30 in inoperable non-small cell lung carcinoma treated with radiotherapy. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 55 (1):19-25
7. Ediebah DE, Coens C, Zikos E, Quinten C, Ringash J, King MT, Schmucker von Koch J, Gotay C, Greimel E, Flechtner H, Weis J, Reeve BB, Smit EF, Taphoorn MJ, Bottomley A (2014) Does change in health-related quality of life score predict survival? Analysis of EORTC 08975 lung cancer trial. British journal of cancer 110 (10):2427-2433. doi:10.1038/bjc.2014.208
8. Abetz L, Coombs JH, Keininger DL, Earle CC, Wade C, Bury-Maynard D, Copley-Merriman K, Hsu MA (2005) Development of the cancer therapy satisfaction questionnaire: item generation and content validity testing. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 8 Suppl 1:S41-53. doi:10.1111/j.1524-4733.2005.00073.x
9. Trask PC, Tellefsen C, Espindle D, Getter C, Hsu MA (2008) Psychometric validation of the cancer therapy satisfaction questionnaire. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 11 (4):669-679. doi:10.1111/j.1524-4733.2007.00310.x
10. Park SJ, An SM, Kim SH (2013) Development of a Korean version of the Cancer Therapy Satisfaction Questionnaire (CTSQ): cross-cultural adaptation, reliability, and validity. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 22 (2):431-436. doi:10.1007/s11136-012-0164-0
11. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC (2007) Quality criteria were proposed for measurement properties of health status questionnaires. Journal of clinical epidemiology 60 (1):34-42. doi:10.1016/j.jclinepi.2006.03.012
12. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P, Translation ITFf, Cultural A (2005) Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health 8 (2):94-104. doi:VHE4054 [pii] 10.1111/j.1524-4733.2005.04054.x

13. Luckett T, King MT, Butow PN, Oguchi M, Rankin N, Price MA, Hackl NA, Heading G (2011) Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: issues, evidence and recommendations. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 22 (10):2179-2190. doi:10.1093/annonc/mdq721
14. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M (1994) The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. European journal of cancer 30A (5):635-642
15. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85 (5):365-376
16. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group (1998). Psychol Med 28 (3):551-558
17. Skevington SM, Lotfy M, O'Connell KA, Group W (2004) The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 13 (2):299-310
18. Norman GR, Sloan JA, Wyrwich KW (2003) Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 41 (5):582-592. doi:10.1097/01.MLR.0000062554.74615.4C
19. Wyrwich KW, Nienaber NA, Tierney WM, Wolinsky FD (1999) Linking clinical relevance and statistical significance in evaluating intra-individual changes in health-related quality of life. Med Care 37 (5):469-478
20. Wyrwich KW, Tierney WM, Wolinsky FD (1999) Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. J Clin Epidemiol 52 (9):861-873. doi:S0895435699000712 [pii]
21. Wyrwich KW, Tierney WM, Wolinsky FD (2002) Using the standard error of measurement to identify important changes on the Asthma Quality of Life Questionnaire. Qual Life Res 11 (1):1-7
22. King MT (2011) A point of minimal important difference (MID): a critique of terminology and methods. Expert Rev Pharmacoecon Outcomes Res 11 (2):171-184. doi:10.1586/erp.11.9
23. Ellis J, Lloyd Williams M, Wagland R, Bailey C, Molassiotis A (2013) Coping with and factors impacting upon the experience of lung cancer in patients and primary carers. Eur J Cancer Care (Engl) 22 (1):97-106. doi:10.1111/ecc.12003
24. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, Rowland CR (2004) Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes 2:12. doi:10.1186/1477-7525-2-121477-7525-2-12 [pii]
25. Grutters JP, Joore MA, Wiegman EM, Langendijk JA, de Ruysscher D, Hochstenbag M, Botterweck A, Lambin P, Pijls-Johannesma M (2010) Health-related quality of life in patients surviving non-small cell lung cancer. Thorax 65 (10):903-907. doi:65/10/903 [pii] 10.1136/thx.2010.136390
26. Gilbert SM, Sanda MG, Dunn RL, Greenfield TK, Hembroff L, Klein E, Saigal CS, Pisters L, Michalski J, Sandler HM, Litwin MS, Wei JT (2014) Satisfaction with information used to choose prostate cancer treatment. J Urol 191 (5):1265-1271. doi:S0022-5347(13)06090-4 [pii]10.1016/j.juro.2013.12.008
27. Temple-Oberle C, Ayeni O, Webb C, Bettger-Hahn M, Ayeni O, Mychailyshyn N (2014) Shared decision-making: Applying a person-centered approach to tailored breast reconstruction informa-

tion provides high satisfaction across a variety of breast reconstruction options. J Surg Oncol. doi:10.1002/jso.23721

28. Nicolaisen M, Muller S, Patel HR, Hanssen TA (2014) Quality of life and satisfaction with information after radical prostatectomy, radical external beam radiotherapy and postoperative radiotherapy: a long-term follow-up study. J Clin Nurs. doi:10.1111/jocn.12586
29. Husson O, Oerlemans S, Mols F, Smeets RE, Poortmans PM, van de Poll-Franse LV (2014) Satisfaction with information provision is associated with baseline but not with follow-up quality of life among lymphoma patients: Results from the PROFILES registry. Acta Oncol 53 (7):917-926. doi:10.3109/0284186X.2013.879201



CHAPTER 5

Frequency of low-grade adverse events and Quality of Life during chemotherapy determine patients' judgement about treatment in advanced-stage thoracic cancer

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ABSTRACT

Purpose: In lung cancer, the preservation of well-being is warranted given the limited prognosis. Chemotherapy may negatively influence Health Related Quality of Life (HRQoL) due to adverse events. However, patients' judgement about this negative impact is not well understood. We examined the relationship between expectations, feelings about side effects and satisfaction with therapy and (HR)QoL in advanced-stage thoracic cancer and investigated which of these factors has the highest impact on (HR)QoL.

Methods: 69 patients completed the Cancer Therapy Satisfaction Questionnaire (CTSQ), the World Health Organization Quality of Life-BREF (WHOQOL-BREF), and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). Multiple regression analyses were performed to investigate the relation of the CTSQ domains (i.e., expectations of therapy, feelings about side effects, satisfaction with therapy) with (HR)QoL and simple regression analyses to identify the factors of the CTSQ domain that was most often associated with (HR)QoL.

Results: feelings about side effects were associated with the (HR)QoL domain/scale scores, (i.e., WHOQOL-BREF domains: $\beta = 0.36$ to 0.58; EORTC QLQ-C30 scales: $\beta = 0.33$ to 0.61) except social relationships of the WHOQOL-BREF. Low-grade adverse events were related to feelings about side effects ($\beta = -0.326$; $p = 0.007$).

Conclusions: Patients experiencing negative feelings about side effects have worse (HR) QoL. Additional care should be provided to prevent low-grade adverse events.

INTRODUCTION

In patients with advanced-stage lung cancer, the preservation of their well-being is warranted given their, in general, limited prognosis [1,2]. Chemotherapy may have a negative impact on patients' Health Related Quality of Life (HRQoL) due to side effects [3]. However, it is not well understood what aspect of chemotherapy causes this potential negative effect on QoL. The Cancer Therapy Satisfaction Questionnaire (CTSQ) is an instrument that assesses patients' expectations, their feelings about side effects and their satisfaction with therapy. Application of this questionnaire gives more insight in patients view on treatment.

Although several publications reported about patients' satisfaction with care [4-6], patients' opinions related to side effects were not evaluated in these studies. Moreover, in a study by Rha et al. it was observed that clinicians underestimated the impact of side effects compared to patients. In addition, physicians rated different symptoms (i.e., nausea and vomiting) as most problematic than patients (i.e., fatigue and anorexia) did [7]. The CTSQ assesses the feelings patients have about treatment [8]. As such, the CTSQ could inform physicians about patients' treatment related opinions, which may facilitate the management of (HR)QoL. For instance, if a patient scores low on the feelings about side effects domain of the CTSQ, this is a clear indicator that they are bothered by side effects. Subsequent identification and adequate management of the experienced side effects may offer opportunities to maintain (HR)QoL at an acceptable level.

However, the CTSQ may also be useful in the process of clinical decision making. In many patients with advanced cancer, a physician's decision to start with treatment is related to a patient's functional status, co-morbidity and potential toxicity [9,10], whilst patients often focus on survival benefits [10,11] and may accept a decrease in QoL [12]. Moreover, patients with cancer would like to be involved in treatment decisions [13]. A considerable proportion (38.3%; n= 49) of patients with lung cancer preferred to have some input in treatment decision making or would like shared treatment decisions. However, this was achieved in only 46.9% (n=23) of the 49 cases [14]. Therefore, exploring a patient's treatment-related opinion is important as they could have a different understanding of survival rates and the impact of side effects on (HR)QoL than their physicians.

In previous studies we and others have shown that the domains of the CTSQ (i.e., expectations of therapy, feelings about side effects, satisfaction with therapy) are related to (HR)QoL [15,16]. In this study, we investigate which of the CTSQ domains are associated with (HR)QoL at the end of treatment in patients with advanced-stage lung cancer and mesothelioma. In addition, we assess which underlying factors (i.e., sociodemographic and clinical variables) are associated with the CTSQ domain that is most often significantly related with (HR)QoL.

METHODS

Study population

PERSONAL is a prospective observational multi-center cohort study of patients with locally advanced or metastatic (i.e., stage IIIB or IV) non-squamous non-small cell lung carcinoma (NSCLC) and unresectable mesothelioma treated with pemetrexed. Patients were recruited from October 2012 to November 2014 from three teaching hospitals (i.e., Erasmus University Medical Center, Amphia Hospital and Sint Franciscus Gasthuis hospital) and a regional hospital (i.e., Bravis hospital). Patients were enrolled if they met the following criteria: they were aged eighteen years or older, had a cytological or histological confirmed diagnosis of advanced or metastatic (i.e., stage IIIB and IV) NSCLC or unresectable malignant pleural mesothelioma and were treated with at least four cycles of pemetrexed in combination with a platinum compound as first line therapy or with at least four cycles of pemetrexed monotherapy as second line. Patients were excluded if they were not able to read Dutch or could not complete the questionnaires due to a physical or mental condition. Informed consent was obtained from all individual participants included in the study. All procedures were in accordance with the ethical standards of the institutional review board of the Erasmus University Medical Center in Rotterdam, The Netherlands (approval number MEC-2012-232) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Procedures

The WHOQOL-BREF and EORTC QLQ-C30 were completed by patients before the first cycle of chemotherapy, after the second (day 7 to 14) and after the fourth cycle (day 14 to 21). The CTSQ was completed by patients after the fourth cycle of chemotherapy simultaneously with the (HR)QoL questionnaires. In addition, we collected sociodemographic information (i.e., age, sex, educational level, ethnicity, employment, partner status (i.e., living or not living together with a partner)), and clinical information (i.e., Eastern Cooperative Oncology Group (ECOG) performance status and cancer stage, type of tumor, line of therapy and tumor response). In the four weeks before completion of the CTSQ, the severity and number of different chemotherapy-related clinical adverse events that patients experienced were assessed at a weekly basis according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The information regarding these adverse events was collected directly form patients during patient interviews and from medical records in the hospital information system.

Study measures

The CTSQ contains three domains covering 16 items: expectations of therapy (five items), feelings about side effects (four items) and satisfaction with therapy (seven items) [15,8].

Each item is scored on a Likert-scale from 1 (worst response) to 5 (best response). Four items are reverse coded. Domain scores range from 0 to 100, with a higher score representing a better outcome. All patients completed the Dutch translation of the original English CTSQ [16]. Previous studies have assessed the psychometric properties in patients with different forms of cancer, including advanced-stage lung cancer, and demonstrated good results [15,16].

The WHOQOL-BREF [17,18] is a short version of the original WHOQOL-100 [19,20]. It consists of a general facet (two items) and four domains that represent physical health (seven items), psychological health (six items), social relationships (three items), and environment (eight items). Each item is scored on a Likert-scale from 1 (worst response) to 5 (best response). Domains of the WHOQOL-BREF are scored on a 4-20 scale and the general facet on a 2-10 scale with higher scores indicating a better Quality of Life [17]. Previous studies have demonstrated satisfactory psychometric properties of the WHOQOL-BREF in patients with lung cancer [21] and in patients with chronic diseases or different forms of cancer [18] except for the social relationships domain [21,18].

The EORTC QLQ-C30 is a cancer specific HRQoL instrument with demonstrated psychometric properties [22] and was originally developed with lung cancer patients [23]. It consists of 30 items and incorporates a global Health Status/QoL scale, five functional scales and a number of items assessing additional symptoms or problems. The functional scales represent physical functioning (five items), cognitive functioning (two items), emotional functioning (four items), role functioning (two items), and social functioning (two items). Each of the EORTC QLQ-C30 domains is scored on a 0-100 scale, with higher scores on the functional scales being indicative of better HRQoL, whereas higher scores on the symptom scales are reflective of worse symptoms [23].

Statistics

Patient characteristics were analyzed with descriptive statistics. Fisher's exact test was used to compare patients that completed the CTSQ and (HR)QoL questionnaires with those that did not on a selection of categorical clinical and sociodemographic variables. For the variables 'age' and 'grade 1 or 2 chemotherapy related clinical adverse events' the independent T-test was used. The Mann-Whitney U test was used for the variable 'grade 3 or 4 chemotherapy related clinical adverse events'.

Multiple linear regression analyses were performed to identify the relationship between expectations of therapy, feelings about side effects and satisfaction with therapy with (HR)QoL without prior simple linear regression analyses given the low number of independent variables. As no specific data has been reported in lung cancer, we expected each potential factor to show a medium effect size. According to Cohen, a correlation of 0.3 (or $R^2 = 0.09$) constitutes a medium effect [24]. Thus, given an effect size of $R^2 = 0.09$, a power of 0.80 and an alpha of 0.05, 69 patients were needed for our main analyses.

Subsequently, simple linear regression analyses were performed to assess the relationship between sociodemographic (i.e., age, sex, ethnicity, education, employment, and partner status) and clinical variables (i.e., type of tumor, ECOG performance status, cancer stage, and treatment response) and expectations of therapy, feelings about side effects or satisfaction with therapy. Regression analyses were performed only on the independent variable (i.e., expectations of therapy, feelings about side effects or satisfaction with therapy) that was most often significantly associated with (HR)QoL in the previous multiple regression analyses.

A p-value of 0.05 or lower was considered to be statistically significant. All analyses were performed with IBM SPSS Statistics for Windows version 21.0.

RESULTS

Patient selection and characteristics

Of the 177 patients eligible for inclusion, 95 patients (54%) with stage IIIB or IV NSCLC or mesothelioma completed all four cycles of chemotherapy (figure 1). Twenty-six of these patients (26%) did not complete the (HR)QoL questionnaires and/or the CTSQ. These patients did not differ with the 69 patients (73%) according to age, sex, ethnicity, education, employment, partner status, cancer stage, type of tumor, line of therapy, ECOG performance status, and number of different grade 1 or 2 or grade 3 or 4 adverse events. Table 1 summarizes the characteristics of all 177 patients and the 69 patients used for the analyses.

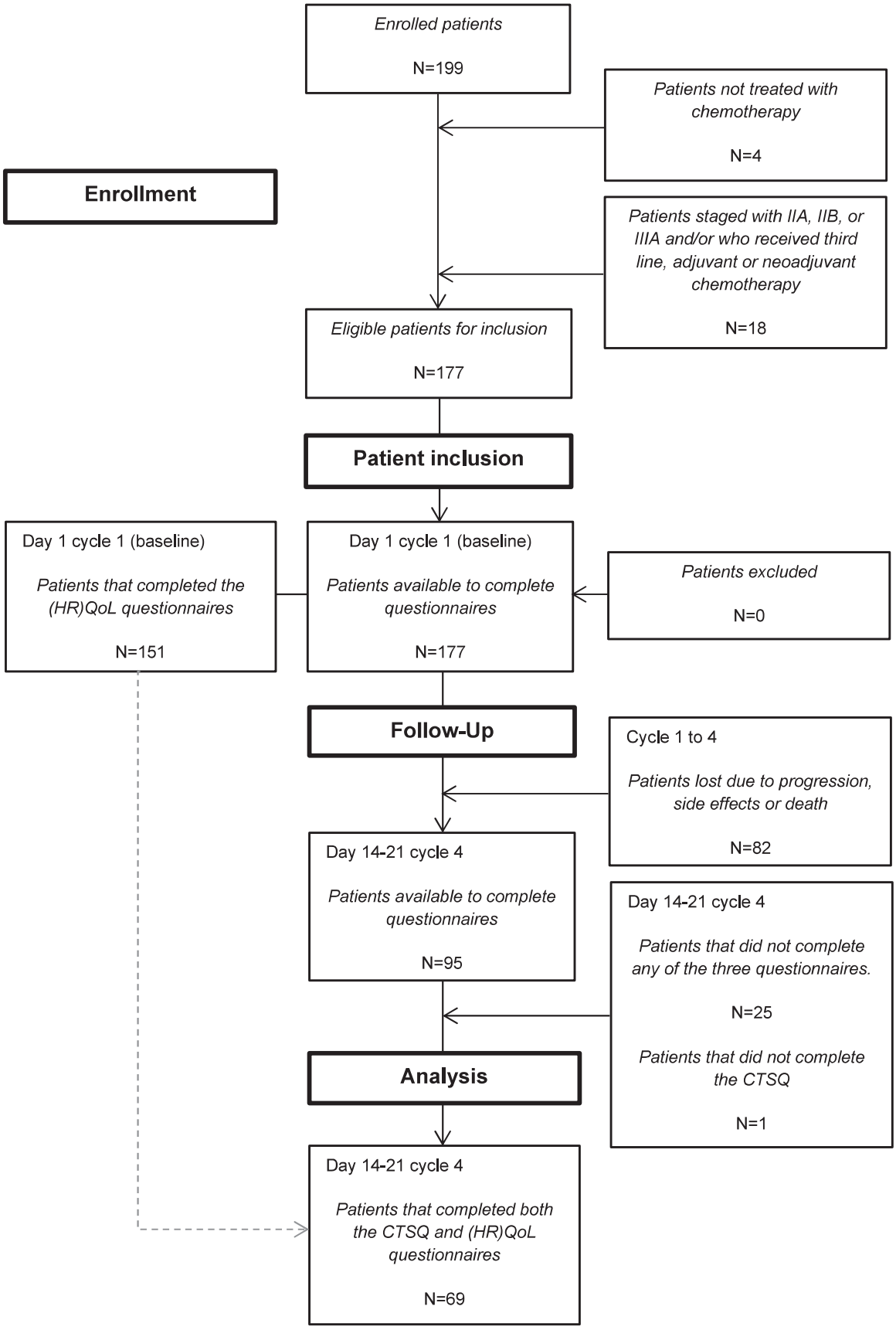
CTSQ domain scores

The median score of the expectations of therapy domain was 55.0 (Inter Quartile Range (IQR) 38.8) and that of the feelings about side effects domain was 56.3 (IQR 42.2). Satisfaction with therapy had a median score of 82.1 (IQR 17.9).

(HR)QoL scale and domain scores

Table 2 demonstrates the scores of the different scales and domains of the EORTC QLQ-C30 and WHOQOL-BREF. For the WHOQOL-BREF, mean domain scores of the normally distributed domains were 13.6 (SD 3.1) for physical health and 16.1 (SD 2.1) for environment. Median scores of the non-normally distributed domains were 13.7 (IQR 4.0) and 15.3 (IQR 2.7) for, respectively, psychological health and social relationships. The median score of the general facet was 6.0 (IQR 3.0). Median scores for the different scales of the EORTC QLQ-C30, including the global Health Status/QoL scale, ranged from 50.0 (IQR 50.0) to 83.3 (IQR 33.3).

Fig. 1 Selection of patients



Abbreviations: N, number of patients; CTSQ, Cancer Therapy Satisfaction Questionnaire; (HR)QoL, (Health-Related) Quality of Life

Table 1. Patient characteristics

Characteristic	All patients (N=177)	Patients that completed all questionnaires (N=69)	Patients that did not complete (all) questionnaires (N=26)	P-value*
Age, years				
Mean (SD)	63.5 (9.0)	62.7 (8.0)	64.4 (9.8)	0.38
Min, max	37, 83	45, 79	37, 78	
Sex				
Male	94 (53.1)	38 (55.1)	13 (50.0)	0.82
Female	83 (46.9)	31 (44.9)	13 (50.0)	
Ethnicity				
Caucasian	167 (94.4)	64 (92.8)	24 (92.3)	1.00
Other	10 (5.6)	5 (7.2)	2 (7.7)	
Education[a]				
Low	113 (63.8)	51 (73.9)	18 (69.2)	0.75
High	32 (18.1)	13 (18.8)	3 (11.5)	
Unknown	32 (18.1)	5 (7.2)	5 (19.2)	
Employment				
Yes	39 (22.0)	20 (29.0)	4 (15.4)	0.41
No	112 (63.3)	48 (69.6)	17 (65.4)	
Unknown	26 (14.7)	1 (1.4)	5 (19.2)	
Partner status[b]				
Yes	123 (69.5)	59 (85.5)	15 (57.7)	0.18
No	28 (15.8)	9 (13.0)	6 (23.1)	
Unknown	26 (14.7)	1 (1.4)	5 (19.2)	
Cancer stage[c]				
Locally advanced (IIIB)	21 (11.9)	5 (7.2)	2 (7.7)	0.89
Metastatic (IV)	147 (83.1)	60 (87.0)	22 (84.6)	
Other	9 (5.1)	4 (5.8)	2 (7.7)	
Type of tumor[c]				
Adenocarcinoma	160 (90.4)	63 (91.3)	21 (80.8)	0.17
Large cell carcinoma, mesothelioma, other	17 (9.6)	6 (8.7)	5 (19.2)	
Line of therapy				
First line	161 (91.0)	64 (92.8)	24 (92.3)	1.00
Second line	16 (9.0)	5 (7.2)	2 (7.7)	
ECOG performance status				
Grade 0 or 1	155 (87.6)	66 (95.7)	26 (100.0)	0.20
Grade 2 or higher	21 (11.9)	1 (1.4)		
Unknown	1 (0.6)	2 (2.9)		

Table 1. Patient characteristics (continued)

Characteristic	All patients (N=177)	Patients that completed all questionnaires (N=69)	Patients that did not complete (all) questionnaires (N=26)	P-value*
Grade 1 or 2 chemotherapy related clinical adverse events				
Mean		9.2 (3.2)	8.5 (4.0)	0.33
Min, max		3, 19	1, 18	
Unknown		1 (1.4)		
Grade 3 or 4 chemotherapy related clinical adverse events				
Median		0.0	0.0	0.93
Min, max		0, 4	0, 5	
Unknown		1 (1.4)		

Values are given in numbers (percentages) unless stated otherwise.
*P-values describe differences observed with Fisher's exact test for all categorical variables and with the independent T-test and Mann-Whitney U test for the variables 'age' and 'grade 1 or 2 chemotherapy-related clinical adverse events' and the variable 'grade 3 or 4 chemotherapy-related clinical adverse events', respectively.
[a]Low education: persons whose highest level of education is primary education, lower general education or lower vocational education. High education: persons whose highest level of education is higher general education, higher vocational education or university.
[b]Partner status: living or not living together with a partner
[c]Measured at baseline
Abbreviations: SD, standard deviation; N, number of patients; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group

Adverse events

Table 3 describes the occurrence of different chemotherapy related clinical adverse events according to their grade. Fatigue was the most frequently experienced adverse event with 87.0% of patients reporting fatigue followed by nausea (71.0%) and anorexia (63.8%).

The association of the CTSQ with (HR)QoL

For all domains and scales of the (HR)QoL questionnaires, except for the WHOQOL-BREF domain social relationships, the feelings about side effects domain was significantly associated with (HR)QoL (Table 4). Positive feelings about side effects were associated with higher (HR)QoL scores whereas negative feelings about side effects related with lower(HR)QoL. In contrast, high expectations of therapy were only significantly associated with increased psychological health and high satisfaction with therapy with solely increased global Health Status/Quality of Life. No other associations between the (HR)QoL questionnaires and the expectations of therapy and satisfaction with therapy domain were found.

Table 2. Results of the WHOQOL-BREF and EORTC QLQ-C30

Questionnaires	N	Min, Max	Mean	SD	Median	IQR
WHOQOL-BREF						
Overall QoL/general health	69	3.0, 10.0	6.2	1.7	6.0	3.0
Physical health	67	6.9, 20.0	13.6	3.1	13.7	4.1
Psychological health	68	10.0, 18.7	14.1	2.2	13.7	4.0
Social relationships	68	6.7, 20.0	15.5	2.4	15.3	2.7
Environment	67	11.0, 20.0	16.1	2.1	16.3	3.5
EORTC QLQ-C30						
Global Health Status/QoL	67	8.3, 100.0	57.3	24.6	66.7	41.7
Physical functioning	69	13.3, 100.0	65.1	22.4	66.7	33.3
Role functioning	69	0.0, 100.0	53.1	33.9	50.0	50.0
Emotional functioning	68	16.7, 100.0	75.1	21.5	75.0	25.0
Cognitive functioning	68	0.0, 100.0	77.0	24.4	83.3	33.3
Social functioning	67	0.0, 100.0	74.6	26.8	83.3	33.3
CTSQ						
Expectations of therapy	68	15.0, 100,0	58.1	23.8	55.0	38.8
Feelings about side effects	69	12.5, 100	53.7	25.3	56.3	42.2
Satisfaction with therapy	69	42.9, 100	79.6	13.1	82.1	17.9

Abbreviations: WHOQOL-BREF, World Health Organization Quality of Life-BREF questionnaire; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; CTSQ, Cancer Therapy Satisfaction Questionnaire; N, number of patients; SD, standard deviation; IQR, interquartile range

Table 3. 10 most frequently reported adverse events according to CTCAE 3.0

Adverse events	N	Grade 1 or 2	Grade 3 or 4
Total	69		
fatigue	60	53 (76.8)	7 (10.1)
nausea	49	46 (66,7)	3 (4.3)
anorexia	44	42 (60.9)	2 (2.9)
Altered taste	38	38 (55.1)	0 (0.0)
mucositis	34	33 (47.8)	1 (1.4)
Dry skin	30	30 (43.5)	0 (0.0)
constipation	30	29 (42.0)	1 (1.4)
Neuropathy sensory	25	25 (36.2)	0 (0.0)
dizziness	24	24 (34.8)	0 (0.0)
rash	21	21 (30.4)	0 (0.0)

Values are given in numbers (percentages)
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients

Table 4. Results of the multiple regression analyses for the WHOQOL-BREF and EORTC QLQ-C30 domains/scales with the CTSQ domains as variables

Variables	N	B	SE	β	P-value	95% CI for B	R^2
WHOQOL-BREF							
Overall QoL/general health							
ET	68	0.010	0.008	0.143	0.199	-0.005, 0.026	0.258
FSE		0.031	0.008	0.472	<0.001*	0.016, 0.046	
SWT		0.003	0.015	0.026	0.824	-0.027, 0.033	
Physical health							
ET	66	0.017	0.014	0.135	0.217	-0.010, 0.045	0.309
FSE		0.063	0.014	0.527	<0.001*	0.036, 0.090	
SWT		0.005	0.027	0.022	0.851	-0.048, 0.059	
Psychological health							
ET	67	0.020	0.009	0.212	0.032*	0.002, 0.038	0.439
FSE		0.050	0.009	0.578	<0.001*	0.033, 0.068	
SWT		0.015	0.017	0.091	0.377	-0.019, 0.050	
Social relationships							
ET	67	0.015	0.013	0.144	0.256	-0.011, 0.041	0.044
FSE		0.014	0.013	0.141	0.286	-0.012, 0.039	
SWT		0.002	0.025	0.013	0.925	-0.048, 0.052	
Environment							
ET	66	0.011	0.011	0.121	0.310	-0.010, 0.032	0.166
FSE		0.031	0.010	0.364	0.004*	0.010, 0.052	
SWT		0.008	0.021	0.052	0.682	-0.033, 0.050	
EORTC QLQ-C30							
Global Health Status/Quality of Life							
ET	66	-0.018	0.109	-0.017	0.869	-0.237, 0.200	0.339
FSE		0.425	0.106	0.442	<0.001*	0.212, 0.637	
SWT		0.478	0.210	0.257	0.026*	0.059, 0.898	
Physical functioning							
ET	68	0.154	0.103	0.162	0.142	-0.053, 0.360	0.275
FSE		0.376	0.101	0.421	<0.001*	0.174, 0.577	
SWT		0.237	0.200	0.137	0.240	-0.162, 0.635	
Role functioning							
ET	68	0.179	0.147	0.125	0.227	-0.114, 0.472	0.360
FSE		0.817	0.143	0.607	<0.001*	0.531, 1.102	
SWT		-0.192	0.283	-0.074	0.499	-0.758, 0.373	
Emotional functioning							
ET	67	0.027	0.105	0.030	0.795	-0.182, 0.237	0.190
FSE		0.347	0.102	0.412	<0.001*	0.144, 0.550	
SWT		0.085	0.201	0.052	0.672	-0.316, 0.487	

Table 4. Results of the multiple regression analyses for the WHOQOL-BREF and EORTC QLQ-C30 domains/scales with the CTSQ domains as variables (continued)

Variables	N	B	SE	β	P-value	95% CI for B	R^2
				Cognitive functioning			
ET	67	-0.043	0.126	-0.041	0.737	-0.295, 0.209	0.099
FSE		0.315	0.122	0.329	0.012*	0.071, 0.559	
SWT		-0.222	0.242	-0.120	0.361	-0.705, 0.260	
				Social Functioning			
ET	66	0.019	0.135	0.017	0.887	-0.251, 0.290	0.149
FSE		0.414	0.131	0.395	0.003*	0.151, 0.677	
SWT		-0.061	0.260	-0.030	0.815	-0.581, 0.459	

*P-values of ≤ 0.05

Abbreviations: CTSQ, Cancer Therapy Satisfaction Questionnaire; WHOQOL-BREF, World Health Organization Quality of Life-BREF questionnaire; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; N, number of patients; B, unstandardized beta; SE, standard error; β, standardized beta; CI, confidence interval; R^2, explained variance; ET, expectations of therapy; FSE, feelings about side effects; SWT, satisfaction with therapy

Factors associated with feelings about side effects

In the simple regression analyses, only low grade chemotherapy related clinical adverse events (i.e., grade 1 or 2 adverse events) were significantly associated with feelings about side effects (P< 0.01) (Table 5). No other relationship was observed.

Table 5. Results of the simple regression analyses for the CTSQ FSE domain score

	FSE						
	N	B	SE	β	P-value	95% CI for B	R^2
Age	69	-0.134	0.383	-0.043	0.728	-0.899, 0.631	0.002
Sex	69	-4.968	6.132	-0.099	0.421	-17.206, 7.271	0.010
Ethnicity: Caucasian/other	69	-8.092	11.780	-0.084	0.494	-31.606, 15.421	0.007
Type of tumor: adenocarcinoma/other	69	14.368	10.734	0.161	0.185	-7.058, 35.795	0.026
ECOG performance score: 0 or 1/higher	69	-23.878	12.787	-0.222	0.066	-49.400, 1.644	0.049
Cancer stage: IIIB/IV	69	9.896	9.020	0.133	0.277	-8.108, 27.899	0.018
Education: low/high	64	0.129	7.730	0.002	0.987	-15.323, 15.581	0.000
Employment: yes/no	68	8.238	6.659	0.151	0.220	-5.056, 21.532	0.023
Partner status: yes/no	68	-6.128	9.025	-0.083	0.499	-24.147, 11.890	0.007
Tumor response: complete and partial response/stable or progressive disease	69	5.525	6.466	0.104	0.396	-7.382, 18.432	0.011
Grade 1 or 2 chemotherapy clinical AE's	68	-2.543	0.907	-0.326	0.007*	-4.354, -0.733	0.107
Grade 3 or 4 chemotherapy clinical AE's	68	1.527	2.984	0.063	0.610	-4.430, 7.484	0.004

*P-values ≤0.05

Abbreviations: CTSQ, Cancer Therapy Satisfaction Questionnaire; FSE, feelings about side effects; N, number of patients; B, unstandardized beta; SE, standard error; β, standardized beta, CI, confidence interval; R^2, explained variance; ECOG, Eastern Cooperative Oncology Group; AE, adverse event

DISCUSSION

Preservation of (HR)QoL is an important goal during chemotherapy considering that patients with advanced-stage lung cancer have a limited prognosis [1,2]. Therefore, identification of patients at risk for decreases in (HR)QoL due to treatment may offer opportunities for improvement. We observed, using a validated scoring system to determine patients' judgement about therapy in different domains, that negative feelings about side effects were associated with decreased (HR)QoL. Especially for patients experiencing low-grade adverse events at a regularly basis, this seems important.

Of the three CTSQ domains, expectations of therapy, satisfaction with therapy and feelings about side effects, the last one was associated with (HR)QoL. In contrast, satisfaction with therapy was only related with the global Health Status/QoL scale of the EORTC QLQ-C30. A reason for this may be that none of the seven items of the satisfaction with therapy domain except one (i.e., chemotherapy was worth taking even with side effects), refer to adverse events or (HR)QoL. Moreover, patients may associate satisfaction with therapy with treatment response and survival and not with particular aspects of (HR)QoL. Since the feelings about side effects domain was most often related to (HR)QoL, we studied the underlying factors of this domain. It appeared that the number of different grade 1 or 2 chemotherapy-related clinical adverse events were significantly associated. As these were often experienced on a regularly basis over longer periods of time, vigorous management of them is warranted. Therefore, it is recommended that health care providers have high awareness and consequently check the occurrence and impact of low-grade adverse events as our results clearly demonstrate that patients are bothered by them. In contrast, no relation with chemotherapy-related clinical grade 3 or 4 adverse events was found. This may be because high grade toxicities were much less experienced in this patient cohort and that the study lacked power. In addition, patients completed the CTSQ after four cycles of chemotherapy. Patients that experienced severe complications may have interrupted chemotherapy and were therefore not included.

Earlier, it was found that HRQoL issues were more often discussed between doctors and patients when the EORTC QLQ-C30 was completed by patients than when this was not the case [13]. All participating physicians and 87% of patients were interested in the persistent use of the questionnaire. These results demonstrated the value of questionnaires in oncological practice. However, application of such an instrument does not provide information about what people think and feel about their treatment. Moreover, (HR)QoL instruments are often more extended than the sixteen items of the CTSQ and require more time to be completed which hampers their application during clinical practice. Also, simply the registration of adverse events does not provide information about the extent to which patients are bothered by them. Therefore, considering the results of this study, we advocate the

use of the four items of the feelings about side effects domain of the CTSQ as this seems more time efficient and patient friendly.

In the present study, feelings about side effects were more often significantly associated with (HR)QoL than satisfaction with therapy. This is an important observation that may be used by physicians and patients when making treatment decisions. Although several reports reported that patients may accept a decrease in QoL or treatment related toxicity given a possible survival benefit [11,12], a systematic review demonstrated that most cancer patients (>50%) in the included studies required moderate survival benefits to make chemotherapy and its risk for toxicity acceptable [25]. Given that, according to our results, patients with negative feelings about side effects could have low (HR)QoL and that prognosis is limited in advanced-stage lung cancer, we propose that the CTSQ results of previously treated patients may be used to help newly diagnosed patients at risk for adverse events (i.e., decreased performance score, significant comorbidity) in making treatment decisions. For instance, if a considerable proportion of patients who received chemotherapy were often hampered by adverse events according to their CTSQ results, newly diagnosed patients with a limited prognosis could take knowledge of these results and make a more considered treatment decision. In such a way, CTSQ results are handled in a similar manor during decision making as response and survival rates.

Satisfaction with therapy was significantly associated with the global Health Status/QoL scale of the EORTC QLQ-C30 whereas this was not observed for the general facet of the WHOQOL-BREF. It is possible this observation is merely due to the idiosyncrasies of the data at hand or simply chance. Also, the relatively small number of patients or selection bias may be responsible for this. In addition, patients may consider occurrence and management of adverse events when they evaluate satisfaction (although this is not directly described by the items that form the Satisfaction with Therapy domain). Given that adverse events can directly affect a patient's HRQoL, the interest of health care professionals for adverse events could influence the relation of satisfaction with therapy score with the global Health Status/QoL scale. For instance, adequate management of adverse events may lead to high patient satisfaction with their care. This may result in increased satisfaction with therapy scores. Given that treatment of adverse events could also enhance HRQoL, increased patient satisfaction with care may result in the observation of an association between satisfaction with therapy and global Health Status/QoL. Expectations of therapy were significantly associated with psychological health. Besides the possibility of related constructs, reasons for this may be related to coping. For instance, in patients with advanced stage lung cancer coping capacity three months after baseline was a predictor for HRQoL [26]. Patients with good coping capacity may have high expectations and may value (HR)QoL more positively than those with few coping capabilities. In addition, coping style may also be of influence as patients that demonstrate 'a fighting spirit' may report higher expectations than those that have no hope of a good outcome. Moreover,

non-acceptance of the diagnosis and/or prognosis could result in a paradoxical expression of high expectations.

Some limitations of this study have to be addressed. First, the included patients were not asked for their motivation to receive chemotherapy, nor was determined which factors could influence patients' treatment preferences and opinions. This limited us, together with the observational design of this study and the calculation of associations, to investigate causal relationships between the CTSQ and the (HR)QoL questionnaires. As the present study is part of a larger project in which patients' motivations were not routinely assessed, we could not provide this information. However, a review that evaluated cancer patients' preferences for adjuvant therapy reported that in addition to treatment benefit and toxicity, personal experience of the treatment and having dependents (e.g., children) were important determinants of patients' preferences [27]. Acquiring such information is of importance as it may help physicians to plan their communication strategy towards patients and provides opportunities for personalized treatment.

Second, patients treated with less than four cycles of chemotherapy were not included in this study. These patients dropped out due to progression or adverse events. Given that they had to discontinue treatment with chemotherapy earlier than expected, it is possible they could have valued satisfaction with therapy more often as important. This could have confounded our results and may explain why satisfaction with therapy in our study was not associated with (HR)QoL. However, other observational studies in patients with advanced-stage lung cancer have experienced similar difficulties with patients dropping out during treatment. In addition, we observed consistent findings regarding the associations of the CTSQ domains with (HR)QoL. Therefore, the findings of the present study contribute to the results of the limited number of reports that discussed the relation of patients' disease and treatment related opinions with (HR)QoL.

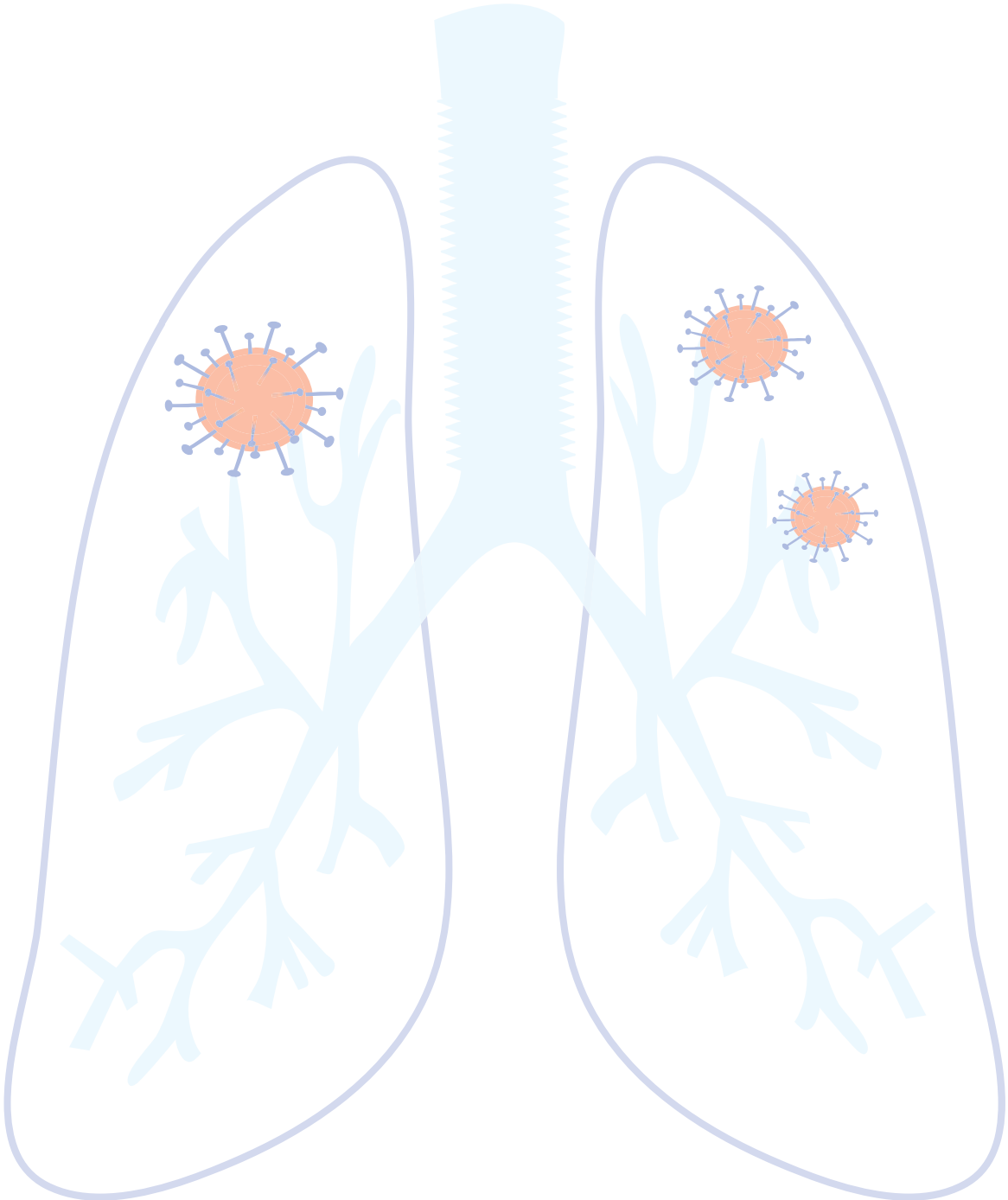
Third, the observed R squares of the simple regression analyses for the feelings about side effects domain in Table 5 were relatively small. To demonstrate with reasonable power that the other predictors were truly not a determinant of feelings about side effects domain score would require the inclusion of many more patients. Given that the R square of the analysis in which low-grade adverse events were associated with feelings about side effects score was relatively high, suggesting an acceptable power, the result of this analysis remains of importance.

In conclusion, we demonstrated that patients with advanced stage lung cancer who experience strong negative feelings about side effects have a decreased (HR)QoL. Our findings demonstrate that low-grade adverse events are of importance for patients' feelings about side effects. Therefore, it is recommended that in clinical practice, physicians facilitate vigorous management of low grade adverse events to enhance the (HR)QoL of patients. In addition, the observed results may aid physicians and patients in making treatment decisions.

REFERENCES

1. Hayat MJ, Howlader N, Reichman ME, Edwards BK (2007) Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. The oncologist 12 (1):20-37. doi:10.1634/theoncologist.12-1-20
2. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, Kunkler I, Group E-W (2007) Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. The Lancet Oncology 8 (9):784-796. doi:10.1016/S1470-2045(07)70246-2
3. Al-Batran SE, Hozaeel W, Tauchert FK, Hofheinz RD, Hinke A, Windemuth-Kieselbach C, Hubner A, Burmester M, Koenigsmann M, Wiegand J, Zur Hausen G, Linsse B, Kuhl R, Pauligk C, Arbeitsgemeinschaft Internistische O (2015) The impact of docetaxel-related toxicities on health-related quality of life in patients with metastatic cancer (QoliTax). Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 26 (6):1244-1248. doi:10.1093/annonc/mdv129
4. Kleeberg UR, Tews JT, Ruprecht T, Hoing M, Kuhlmann A, Runge C (2005) Patient satisfaction and quality of life in cancer outpatients: results of the PASQOC study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 13 (5):303-310. doi:10.1007/s00520-004-0727-x
5. Nguyen TV, Anota A, Bredart A, Monnier A, Bosset JF, Mercier M (2014) A longitudinal analysis of patient satisfaction with care and quality of life in ambulatory oncology based on the OUT-PATSAT35 questionnaire. BMC cancer 14:42. doi:10.1186/1471-2407-14-42
6. Hagedoorn M, Uijl SG, Van Sonderen E, Ranchor AV, Grol BM, Otter R, Krol B, Van den Heuvel W, Sanderman R (2003) Structure and reliability of Ware's Patient Satisfaction Questionnaire III: patients' satisfaction with oncological care in the Netherlands. Medical care 41 (2):254-263. doi:10.1097/01.MLR.0000044904.70286.B4
7. Rha SY, Song SK, Lee CE, Park Y, Lee J (2016) Gaps exist between patients' experience and clinicians' awareness of symptoms after chemotherapy: CINV and accompanying symptoms. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 24 (11):4559-4566. doi:10.1007/s00520-016-3295-y
8. Abetz L, Coombs JH, Keininger DL, Earle CC, Wade C, Bury-Maynard D, Copley-Merriman K, Hsu MA (2005) Development of the cancer therapy satisfaction questionnaire: item generation and content validity testing. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 8 Suppl 1:S41-53. doi:10.1111/j.1524-4733.2005.00073.x
9. Wan-Chow-Wah D, Monette J, Monette M, Sourial N, Retornaz F, Batist G, Puts MT, Bergman H (2011) Difficulties in decision making regarding chemotherapy for older cancer patients: A census of cancer physicians. Critical reviews in oncology/hematology 78 (1):45-58. doi:10.1016/j.critrevonc.2010.02.010
10. Davidson PM, Jiwa M, Goldsmith AJ, McGrath SJ, Digiacomo M, Phillips JL, Agar M, Newton PJ, Currow DC (2011) Decisions for lung cancer chemotherapy: the influence of physician and patient factors. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 19 (8):1261-1266. doi:10.1007/s00520-011-1176-y
11. Chu DT, Kim SW, Kuo HP, Ozacar R, Salajka F, Krishnamurthy S, Damyanov D, Altug S, Reece WH, Wang L (2007) Patient attitudes towards chemotherapy as assessed by patient versus physician: a prospective observational study in advanced non-small cell lung cancer. Lung cancer 56 (3):433-443. doi:10.1016/j.lungcan.2007.01.028
12. Koedoot CG, de Haan RJ, Stiggelbout AM, Stalmeier PF, de Graeff A, Bakker PJ, de Haes JC (2003) Palliative chemotherapy or best supportive care? A prospective study explaining patients' treatment preference and choice. British journal of cancer 89 (12):2219-2226. doi:10.1038/sj.bjc.6601445

13. Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK (2002) Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. Jama 288 (23):3027-3034
14. Pardon K, Deschepper R, Vander Stichele R, Bernheim J, Mortier F, Schallier D, Germonpre P, Galdermans D, Van Kerckhoven W, Deliens L (2011) Are patients' preferences for information and participation in medical decision-making being met? Interview study with lung cancer patients. Palliative medicine 25 (1):62-70. doi:10.1177/0269216310373169
15. Trask PC, Tellefsen C, Espindle D, Getter C, Hsu MA (2008) Psychometric validation of the cancer therapy satisfaction questionnaire. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 11 (4):669-679. doi:10.1111/j.1524-4733.2007.00310.x
16. Cheung K, De Mol M (2015) Reliability and validity of the Cancer Therapy Satisfaction Questionnaire in Lung Cancer. Quality of Life Research
17. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group (1998). Psychological medicine 28 (3):551-558
18. Skevington SM, Lotfy M, O'Connell KA, Group W (2004) The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 13 (2):299-310
19. Group W (1995) The World Health Organization Quality of Life assessment (WHOQOL): Position paper from the World Health Organization Soc Sci Med 41:1403-1409
20. Group W (1998) The World Health Organization Quality of Life assessment (WHOQOL): Development and general psychometric properties. Social science & medicine 46:1569-1585
21. Lin CY, Yang SC, Lai WW, Su WC, Wang JD (2015) Rasch models suggested the satisfactory psychometric properties of the World Health Organization Quality of Life-Brief among lung cancer patients. Journal of health psychology. doi:10.1177/1359105315603474
22. Luckett T, King MT, Butow PN, Oguchi M, Rankin N, Price MA, Hackl NA, Heading G (2011) Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: issues, evidence and recommendations. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 22 (10):2179-2190. doi:10.1093/annonc/mdq721
23. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 85 (5):365-376
24. Cohen J (1992) A power primer. Psychological bulletin 112 (1):155-159
25. Blinman P, Alam M, Duric V, McLachlan SA, Stockler MR (2010) Patients' preferences for chemotherapy in non-small-cell lung cancer: a systematic review. Lung cancer 69 (2):141-147. doi:10.1016/j.lungcan.2010.05.001
26. Henoch I, Bergman B, Gustafsson M, Gaston-Johansson F, Danielson E (2007) The impact of symptoms, coping capacity, and social support on quality of life experience over time in patients with lung cancer. Journal of pain and symptom management 34 (4):370-379. doi:10.1016/j.jpainsymman.2006.12.005
27. Jansen SJ, Otten W, Stiggelbout AM (2004) Review of determinants of patients' preferences for adjuvant therapy in cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 22 (15):3181-3190. doi:10.1200/JCO.2004.06.109



CHAPTER 6

Treatment satisfaction of patients with advanced-stage non-small-cell lung cancer receiving platinum-based chemotherapy: results from a prospective cohort study (PERSONAL)

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ABSTRACT

Introduction: In patients with advanced-stage non-small-cell lung cancer (NSCLC) treatment benefits and risks need to be constantly weighed. We explored patient reported satisfaction with therapy (SWT) and assessed its added value alongside Quality of Life (QoL) and adverse events (AEs).

Patients and methods: In a prospective multi-center cohort study, patients with stage IIIB/IV NSCLC received platinum-pemetrexed chemotherapy. They completed the World Health Organization Quality of Life-BREF (WHOQOL-BREF) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) before and during chemotherapy. After the last cycle, patients reported on SWT, expectations of therapy (ET) and feelings about side effects (FSE) using the Cancer Therapy Satisfaction Questionnaire (CTSQ). Explained variance (R^2) of QoL after treatment by SWT was calculated. Using (multivariable) linear regression, we examined the association of SWT with patient and treatment-related variables, FSE and AEs.

Results: Eighty-nine patients finished four cycles of chemotherapy, of whom 65 completed the CTSQ. Fifty-six patients (86.2%) would probably/definitely decide to undergo the same treatment again, regardless of a deterioration/improvement of QoL or high/low frequency of AEs during chemotherapy. Explained variance of QoL by SWT was highest for the EORTC QLQ C-30 global Health Status/QoL scale (R^2=0.170). Patients' age (β=0.43; 95%CI 0.05-0.82), FSE (β=0.17; 95%CI 0.06-0.29) and tumor response (β=7.93; 95%CI (1.64-14.22) were independently associated with SWT.

Conclusion: SWT may provide important supplementary information besides QoL and treatment toxicities. Tumor response, higher age and FSE score were associated with better SWT. These insights may impact decision making during palliative chemotherapy.

INTRODUCTION

Chemotherapy has shown to improve overall survival and Quality of Life (QoL) of patients with advanced-stage non-small-cell lung cancer (NSCLC) [1,2]. However, survival gain remains limited and treatment is often accompanied by adverse events (AEs) varying in number and severity depending on the different chemotherapy regimens and patients' individual characteristics [1,3]. Therefore, decisions whether to start or continue with treatment are complex and require that patients' expectations, preferences, and values with regard to benefits and risks are taken into account.

The implementation of patient reported outcomes in clinical practice has shown to improve assessment of and communication about symptoms and QoL [4]. AEs can have a considerable impact on Health-Related (HR)QoL [5]. In turn, change of (HR)QoL provides prognostic information with regard to (lung) cancer survival [6–9]. HRQoL has gained importance in treatment decision making in addition to clinical effectiveness of treatment, since it incorporates the influence of AEs (treatment or cancer-related) and acts as a prognostic factor for survival. However, considering treatment decisions in this manner ignores patients' reflection on treatment harms and benefits.

Another challenge in clinical decision making is the considerable variability in how patients value the importance of survival benefit and symptom relief offered by chemotherapy [10–12]. In general, patients with metastatic lung cancer consider even a small increase in life expectancy as worthwhile, yet 10-25% of patients would not choose chemotherapy if additional survival is less than 12 months [13]. Younger patients tend to accept a much smaller treatment benefit compared to older patients [13,14]. Patients' preferences are also affected by their understanding of prognosis. Many patients receiving chemotherapy for metastatic (lung) cancer overestimate their life expectancy, which might explain the discordance between the treatment decisions they make and their actual preferences [15–17].

To date, there is little insight into which patient or treatment-related factors are associated with treatment satisfaction. Taking into account patients' perceptions of prognosis and treatment satisfaction could offer a patient-centered view on the impact of negative and positive treatment effects and therefore may have added value in decision making.

In this prospective multi-center study from a real-world's perspective, we explored the association between SWT and patient and treatment-related factors and (feelings about) AEs in patients with advanced-stage NSCLC treated with chemotherapy and we aimed to assess the added value of SWT alongside generally accepted clinical outcomes (HR)QoL and AEs.

PATIENTS AND METHODS

Pemetrexed and biomarkers: an observational study (PERSONAL) is a prospective multicenter cohort study of adult patients with locally advanced or metastatic (stage IIIB/IV) non-squamous NSCLC and unresectable mesothelioma receiving platinum-combined pemetrexed as first-line and pemetrexed monotherapy as second-line treatment. Patients were recruited from October 2012 until November 2014 from a university hospital (Erasmus University Medical Center), two large teaching hospitals specialized in lung cancer care (Amphia hospital; Franciscus Gasthuis) and a regional hospital (Bravis hospital) located in the southwestern part of the Netherlands. Patients with unresectable mesothelioma were excluded from analyses in the present study. All patients provided written informed consent. This study was approved by the Institutional Review Board of the Erasmus University Medical Center in Rotterdam, The Netherlands.

Data collection

The validated Cancer Therapy Satisfaction Questionnaire (CTSQ) consists of 16 items covering three domains: satisfaction with therapy (SWT; seven items), feelings about side effects (FSE; four items) and expectations of therapy (ET; 5 items) [18]. Items were scored on a scale from one (worst score) to five (best score). Four items were reverse coded. Each domain score was calculated by linear transformation of the mean of the corresponding item scores, resulting in a domain score range from 0 to 100. A higher score represents a better outcome on each domain, for instance a higher domain score of SWT corresponds with better treatment satisfaction. Items of special interest from the ET and SWT domain were the following: “How often do you think the chemotherapy can cure the disease?” (ET domain) and two items from the SWT domain; “The chemotherapy was worth it, even with side effects?”; “Would you decide to take the chemotherapy again, if given the choice?”.

The World Health Organization Quality of Life-BREF (WHOQOL-BREF) is a generic QoL instrument developed to use in a wide range of disorders and health problems, including oncological diseases [19]. The questionnaire comprises 26 items covering four domains (physical health, psychological health, social relationships, and environment) and one facet, including one item to assess overall QoL and one item to measure general health. The domain scores range between 4 to 20 and the facet is scored on a 2 to 10 scale, with a higher score indicating a better QoL.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) is a HRQoL questionnaire, which is internationally used in clinical studies [20]. The questionnaire consists of 30 items and incorporates a global Health Status/QoL scale and five functional scales. Each of the QLQ-C30 scales is scored on a 0 to 100 scale, with a higher score being representative of a better HRQoL.

Patients completed (HR)QoL questionnaires before the start of chemotherapy (baseline). Follow-up assessments were performed during the 2nd cycle (day 7-14) and during the 4th cycle (day 14-21) of chemotherapy. At the latter moment, patients were also requested to complete the CTSQ. We collected sociodemographic information (age, sex, ethnicity), Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, disease stage and treatment. After the start of chemotherapy, all clinical and laboratory AEs (cancer or therapy-related) were weekly registered according to Common Terminology Criteria for Adverse Events (CTCAE 4.0). Tumor response measurements were obtained according to RECIST 1.1 after the 2nd and 4th cycle of chemotherapy.

Statistical analysis

Sociodemographic and clinical variables were compared between patients who completed the CTSQ questionnaires and patients who did not. We used the independent-samples *t*-test and the χ^2-test or Fisher's exact test for continuous and categorical variables respectively.

Patients were categorized into two groups using the median number of all grades clinical AEs and into three groups with regard to alteration of QoL during treatment, based on known minimal clinically important differences (MCID) of the EORTC QLQ-C30 and WHOQOL-BREF [21,22] [de Mol M, Visser S, Aerts JG et al. Satisfactory results of a psychometric analysis and calculation of minimal clinically important differences of the WHOQoL-BREF questionnaire in lung cancer patients. *Submitted for publication*]: deterioration, no change or improvement (Supplemental Appendix A1).

Using the Mann-Whitney U and Kruskal-Wallis test, differences in response distributions to individual items of the SWT domain were examined across mentioned groups according to alteration of QoL and frequency of AEs. Differences in mean SWT domain scores were described for the three groups based on alteration of QoL. The Pearson's correlation coefficients (ρ) were used to calculate the explained variance (R^2) of QoL after four cycles of chemotherapy by SWT.

Patient and treatment-related variables and (feelings about) AEs associated with SWT ($P < 0.05$) in univariable analyses, were analyzed with the use of multivariable linear regression (method: Enter). These regression analyses were restricted to patients treated with first-line platinum-based treatment to ensure a more homogeneous population.

All statistical analyses were performed with the use of SPSS, version 22.0 (IBM Corporation, Armonk, NY).

RESULTS

In total, 165 patients with advanced-stage NSCLC were enrolled in this study (Figure 1). All patients included for analyses received pemetrexed-based chemotherapy as first or second-line treatment. Of these patients, 85.5% completed the (HR)QoL questionnaires at baseline. Eighty-nine (53.9%) patients finished four cycles of chemotherapy, of whom 73.0% completed the CTSQ and (HR)QoL questionnaires. Reasons for non-completion of the questionnaires are reported in Supplemental Table A1. Seventy-six patients stopped chemotherapy preliminary due to intolerable toxicities (42.1%), progressive disease (38.2%) or preplanned sequential radiotherapy or surgery (19.7%).

Patient characteristics

Patient characteristics are outlined in Table 1. The mean age in this population was 63.3±9.2 years and slightly more than half of the patients were male (50.9%). The majority of patients had metastatic NSCLC (87.3%) and received pemetrexed as first-line treatment (90.3%), mostly combined with cisplatin (61.8%) or carboplatin (36.4%). The patients who completed the CTSQ questionnaires after four cycles of chemotherapy had a significantly lower ECOG performance score at baseline ($P = 0.001$), a better tumor response ($P < 0.001$), and a higher frequency of treatment- or cancer-related AEs ($P < 0.001$) than patients who did not complete the CTSQ.

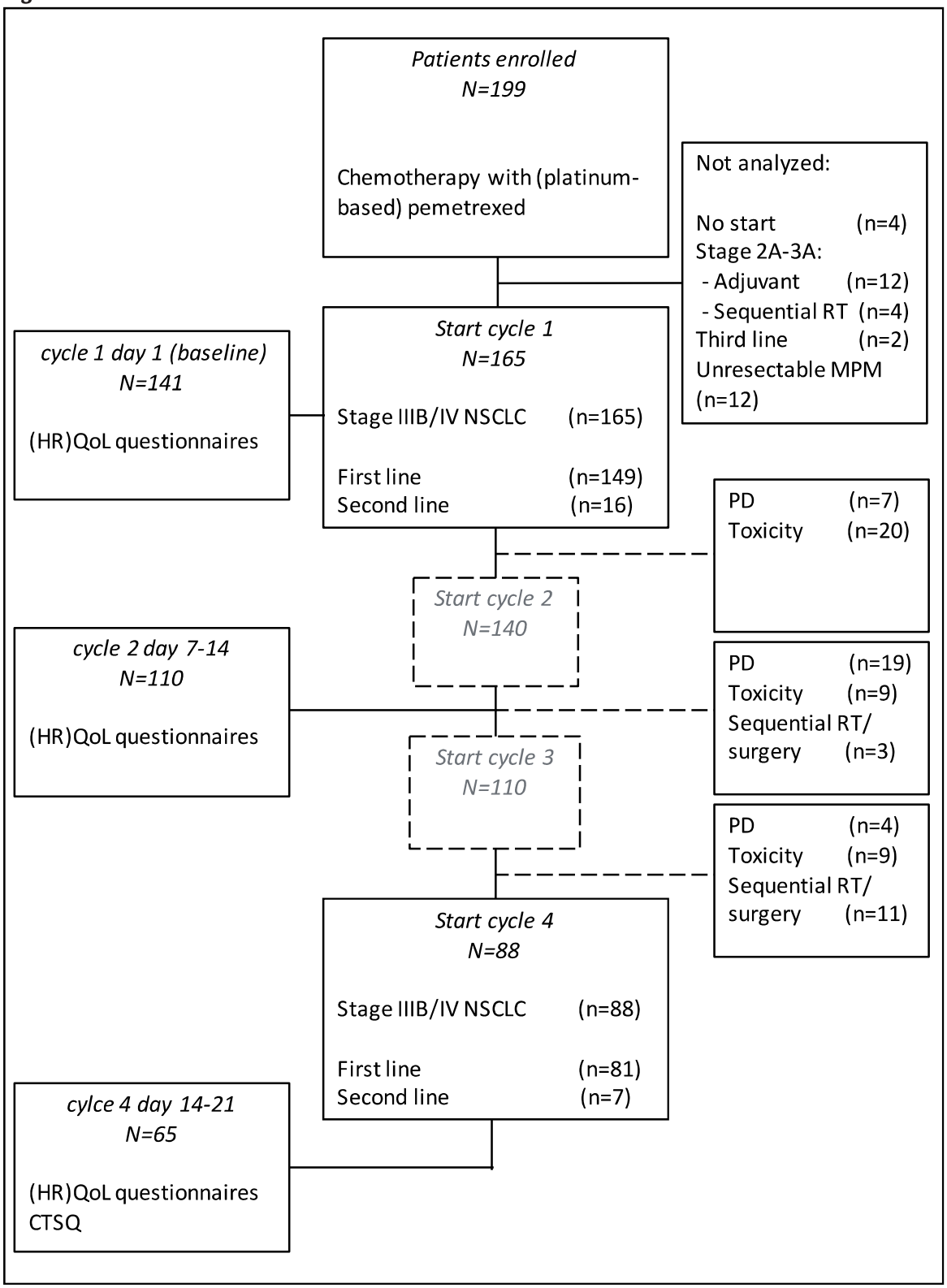
Treatment satisfaction

The median domain scores of SWT, FSE and ET were 82.1 (Interquartile range [IQR]: 71.4-89.3), 56.3 (IQR: 37.5-75.0), and 55.0 (IQR: 40.0-78.8), respectively. Of the patients who completed the CTSQ, 26.1% often or always expected chemotherapy could cure their disease. During treatment, patients experienced 20.5 ± 5.0 all grades AEs, 13.5 ± 3.7 all grades clinical AEs, and 1.8 ± 1.7 grade ≥ 3 AEs, both treatment and cancer-related. Detailed information about treatment-related clinical and laboratory AEs is provided in Table 2.

Responses to individual items within the SWT domain are shown in Figure 2. Of the patients who completed the item whether chemotherapy was worth taking even with side effects (*N*=64), 81.3% answered positively. Twelve patients responded negatively (*N*=3, 4.7%) or were in doubt (*N*=9, 14.1%). Fifty-six of the 65 patients (86.2%) would probably or definitely decide to undergo the same treatment again. Distributions of the answers of both items were not significantly different for patients with a deterioration in QoL compared to patients with no change or improvement of QoL and between patients with a high (≥14) or low (<14) frequency of clinical AEs (both treatment and cancer-related).

Table 3 shows the distribution of SWT scores across different groups based on alteration of QoL during treatment. Patients with an improved WHOQOL-BREF facet score had a statistically higher (p=0.008) SWT domain score (84.1±10.5) than patients without change

Fig. 1 Flowchart



Abbreviations: (HR)QoL, (health-related) quality of life; NSCLC, non-small cell lung cancer; MPM, malignant pleural mesothelioma; CTSQ, Cancer Therapy Satisfaction Questionnaire; PD, progressive disease; RT, radiotherapy.

Table 1. Characteristics of patients who started treatment with pemetrexed

Characteristic	Total (N=165)	Completion CTSQ questionnaire (N=65)	No completion CTSQ questionnaire (N=100)	P-value
Age, mean (SD)	63.3 (9.2)	62.1 (7.9)	64.1 (9.8)	0.174
Gender, male	84 (50.9)	34 (52.3)	50 (50.0)	0.874
Ethnicity, Caucasian	155 (93.9)	60 (92.3)	95 (95.0)	0.814
ECOG performance score				0.001
0 or 1	145 (87.8)	64 (98.5)	81 (81.0)	
≥ 2	20 (12.2)	1 (1.5)	19 (19.0)	
Type of tumor				0.577
Adenocarcinoma	160 (97.0)	63 (96.9)	97 (97.0)	
Large cell carcinoma	5 (3.0)	2 (3.1)	3 (3.0)	
Cancer stage				0.153
Locally advanced (IIIB)	21 (12.7)	5 (7.7)	16 (16.0)	
Metastatic (IV)	144 (87.3)	60 (92.3)	84 (84.0)	
Combination therapy				0.665
Cisplatin	102 (61.8)	39 (60.0)	63 (63.0)	
Carboplatin	60 (36.4)	24 (36.9)	36 (36.0)	
Monotherapy	3 (1.8)	2 (3.1)	1 (1.0)	
Line of therapy				0.595
1st line	149 (90.3)	60 (92.3)	89 (89.0)	
2nd line	16 (9.7)	5 (7.7)	11 (11.0)	
Best tumor response				<0.001
PR	44 (26.7)	24 (36.9)	20 (20.0)	
SD	76 (46.1)	40 (61.5)	36 (36.0)	
PD	17 (10.3)	0 (0.0)	17 (17.0)	
not evaluable*	28 (16.9)	1 (1.5)	27 (27.0)	
Mean number of adverse events per cycle (SD)†				
All grades	7.4 (4.1)	5.1 (1.2)	8.7 (4.6)	<0.001
Grade 1 and 2	6.3 (3.2)	4.7 (1.2)	7.2 (3.5)	<0.001
Grade 3 and 4	1.0 (1.4)	0.5 (0.4)	1.4 (1.7)	<0.001
Comorbidity				
Cardiovascular disease	71 (43.0)	25 (38.5)	46 (46.0)	0.421
COPD	25 (15.2)	7 (10.8)	19 (18.0)	0.268
Diabetes	22 (13.3)	5 (7.7)	17 (17.0)	0.217

Data are expressed as numbers (%) unless stated otherwise.

*Not evaluable due to early progression/death or systemic deterioration.

† Distinct treatment or cancer-related adverse events according to CTCAE 4.0.

Abbreviations: CTSQ, Cancer Therapy Satisfaction Questionnaire; PR, partial response; SD, stable disease; PD, progressive disease; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; N, number of patients.

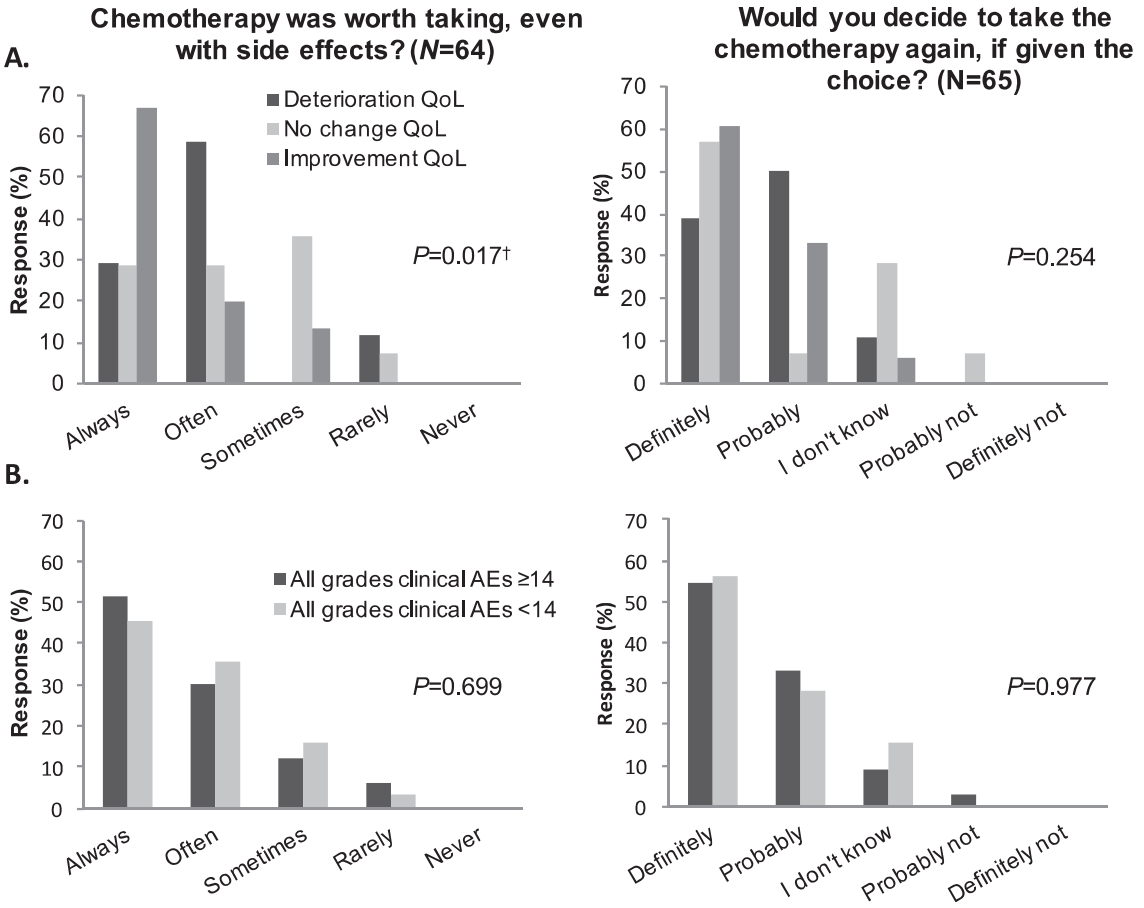
Table 2. Adverse events in patients who completed the CTSQ (N=65)

	Frequency (%)	
Adverse event	All grades	Grade ≥ 3
Treatment-related*		
Any	69 (100)	32 (49)
Clinical		
Fatigue	61 (94)	7 (11)
Anemia	57 (88)	8 (12)
Nausea	46 (71)	3 (5)
Decreased appetite	44 (68)	2 (3)
Taste alteration	37 (57)	0
Oral mucositis	33 (51)	1 (2)
Dry eyes/watering eyes	31 (48)	0
Dry skin	29 (45)	0
Constipation	26 (40)	1 (2)
Rash	19 (29)	0
Diarrhea	15 (23)	1 (2)
Vomiting	13 (20)	0
Dizziness	13 (20)	0
Alopecia	13 (20)	0
Dysphagia	12 (18)	0
Dyspepsia	10 (15)	0
Pruritus	10 (15)	0
Abdominal bloating	9 (14)	0
Weight loss	8 (12)	0
Laboratory		
Decreased white cell count	43 (66)	9 (14)
Decreased neutrophil count	42 (65)	18 (28)
Decreased thrombocyte count	33 (51)	6 (9)
Alanine aminotransferase elevation	32 (49)	0
Aspartate aminotransferase elevation	25 (38)	0
Alkaline phosphatase elevation	22 (34)	0
Blood creatinine level elevation	15 (23)	0

Listed are adverse events that are reported in at least 10% of the patients.

*Adverse events were scored as treatment-related if investigator defined relatedness as probably or definitely.

Fig.2 A. Distribution of responses to two items of the SWT domain across patients with a deterioration, no change and improvement of the facet score (global QoL/general health) of the WHOQOL-BREF using minimal clinical important differences. B. Distribution of responses to two items of the SWT domain across patients with more (≥ 14) or less (< 14) clinical adverse events.



†Distribution of answers to this item was significantly different between patients with no change and an improvement of QoL (*P = 0.010*).
Abbreviations: AE, adverse event; QoL, Quality of Life.

(71.2±17.1) or a deterioration (75.8±9.5). The SWT domain scores did not differ between groups across the WHOQOL-BREF domains. No significantly different SWT domain scores were found between groups based on EORTC QLQ C-30 global Health Status/QoL scale and the other scales (Supplemental Table A2). Likewise, the SWT scores did not differ across QoL groups between the 2nd and 4th chemotherapy cycle assessed with the WHOQOL-BREF and EORTC QLQ-C30 respectively (Supplemental Table A3 and A4). The explained variance of (HR)QoL after chemotherapy by SWT ranged from 0.002 (Cognitive scale) to 0.170 (global Health Status/QoL scale) using the EORTC QLQ C-30 and from 0.009 (social relationships) to 0.125 (psychological health) assessed with the WHOQOL-BREF (Table 4).

If we restricted all above mentioned analyses to patients with first-line treatment, no significantly different results were found (data not shown).

Table 3. Mean SWT domain scores across groups regarding change in WHOQOL-BREF facet and domain scores between baseline and after 4th cycle of pemetrexed treatment (N=62)

WHOQOL-BREF facet/ domains	Δ QoL group	N (%)	Mean change in facet/ domain scores†	Domain score SWT	P-value*
Overall QoL/general health	Deterioration	17 (27)	-2.1 (1.1)	75.8 (9.5)	
	No change	14 (23)	0.0 (0.0)	71.2 (17.1)	*0.008*
	Improvement	31 (50)	1.7 (0.9)	84.1 (10.5)	
Physical health	Deterioration	16 (26)	-4.2 (2.6)	76.3 (15.9)	
	No change	24 (39)	0.0 (0.7)	78.1 (13.1)	0.455
	Improvement	20 (32)	3.7 (2.1)	82.0 (10.9)	
	Missing	2 (3)			
Psychological health	Deterioration	26 (42)	-3.0 (1.6)	78.0 (12.7)	
	No change	25 (40)	0.0 (0.5)	79.2 (14.5)	0.853
	Improvement	10 (16)	2.7 (1.3)	80.0 (11.8)	
	Missing	1 (2)			
Social relationships	Deterioration	29 (47)	-3.2 (2.3)	78.6 (13.0)	
	No change	17 (27)	0.0 (0.2)	75.6 (15.1)	0.309
	Improvement	15 (24)	2.2 (1.8)	82.9 (10.6)	
	Missing	1 (2)			
Environment	Deterioration	18 (29)	-2.4 (1.2)	81.3 (9.8)	
	No change	28 (45)	-0.1 (0.8)	76.0 (15.4)	0.428
	Improvement	14 (23)	2.8 (1.3)	82.1 (11.2)	
	Missing	2 (3)			

Data are expressed as means (SD).
†Minimal clinical important differences were used to determine deterioration, no change and improvement of QoL per domain/facet.
*Distributions of SWT scores across change in QoL groups were compared using the Kruskal-Wallis test.
Abbreviations: WHOQOL-BREF, World Health Organization Quality of Life-BREF; SWT, satisfaction with therapy; SD, standard deviation; N, number of patients.

Factors associated with satisfaction with therapy

Results of the regression analyses performed in patients treated with first-line platinum-based pemetrexed treatment (*N*=60) with the SWT domain score as dependent variable and patient and treatment-related factors as independent variables are shown in Table 5. In the univariable analyses patients' age (*P* = 0.042), tumor response (*P* = 0.014), sex (*P = 0.048)* and the domain score FSE (*P* = 0.004) were significantly related to SWT. In the multivariable analysis (R^2 = 32.6%), only age (β = 0.43; 95% CI 0.05-0.82), FSE (β = 0.17;

95% CI 0.06-0.29) and tumor response (β = 7.93; 95% CI 1.64-14.22) showed independent relations with SWT. No associations were found between SWT and the frequency of grade 1/2 or grade 3/4 AEs. Similarly, recent AEs (within four weeks before completion of CTSQ) and clinical AEs were not related with SWT (data not shown).

Table 4. QoL scores after 4 cycles of chemotherapy and its explained variance by SWT domain score of the CTSQ

WHOQOL-BREF					EORTC QLQ-C30				
Facet/domains	N	Mean (SD)	ρ	R^2	Scales	N	Mean (SD)	ρ	R^2
Overall QoL/ general health	65	6.3 (1.6)	0.203	0.041	Global Health Status/QoL	63	58.6 (23.8)	0.412	0.170
Physical health	63	13.7 (3.0)	0.240	0.058	Physical functioning	65	65.7 (21.8)	0.279	0.078
Psychological health	64	14.2 (2.2)	0.354	0.125	Role functioning	65	54.9 (33.6)	0.155	0.024
Social relationships	64	15.5 (2.5)	0.094	0.009	Emotional functioning	64	76.0 (21.5)	0.191	0.036
Environment	63	16.2 (2.1)	0.179	0.032	Cognitive functioning	64	78.1 (23.9)	-0.042	0.002
					Social functioning	63	75.4 (26.8)	0.128	0.016

ρ is the Pearson's correlation coefficient between the SWT domain score and the QoL score.
Abbreviations: SWT, satisfaction with therapy; WHOQOL-BREF, World Health Organization Quality of Life-BREF; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QoL, Quality of Life; SD, standard deviation; N, number of patients; R^2, explained variance

Table 5. Linear regression analyses of factors associated with satisfaction with therapy (N=60)

	Univariable analysis		Multivariable analysis	
	β coefficient (95% CI)	P-value	β coefficient* (95% CI)	P-value
Age	0.51 (0.10, 0.93)	*0.042*	0.43 (0.05, 0.82)	*0.028*
Sex				
female vs. male	-6.74 (-13.42, -0.06)	*0.048*	-3.90 (-9.98, 2.17)	0.203
ECOG performance score				
0 vs. ≥1	-1.61 (-9.14, 5.92)	0.670		
Tumor response (4th cycle)				
PR vs. SD or PD	-8.94 (-15.99, -1.90)	*0.014*	7.93 (1.64, 14.22)	*0.014*
No. of grade 1/2 AEs†	-0.13 (-0.86, 0.60)	0.731		
No. of grade 3/4 AEs†	1.27 (-0.77, 3.30)	0.217		
FSE domain score	0.19 (0.06, 0.32)	*0.004*	0.17 (0.06, 0.29)	*0.005*

*Adjusted for all factors statistically significant $p < 0.05$ in the univariable model.
†Cancer or treatment related adverse events during total treatment period.
Abbreviations: β, standardized beta; ECOG, Eastern Cooperative Oncology Group; N, number of patients; PR, partial response; SD, stable disease; PD, progressive disease; QoL, quality of life; AE, adverse event; FSE, feelings about side effects.

DISCUSSION

As shared decision making becomes increasingly important nowadays, the need for clinically useful patient reported outcomes increases likewise. It has been recently demonstrated that shared decisions were positively associated with a higher patient-reported quality of care [23], which may be particularly important in cancer patients with poor prognosis. Therefore, our objective was to assess the value of patient reported SWT alongside widely accepted clinical outcomes of therapy. To our knowledge, this is the first study to have extensively assessed and characterized patients' satisfaction with chemotherapy.

Our results propose that SWT covers different aspects of patient-centered and reported impact of treatment effects than QoL and adverse events and therefore SWT could be useful in decision making, as it offers important supplementary information from a patients' perspective. SWT described < 10% of the variance of the functional scales and domains from both (HR)QoL questionnaires, except for global Health Status/QoL (17%) and the psychological domain (13%). Accordingly, our group [18] already suggested the additional informative value of patients' SWT as the different aspects of (HR)QoL showed a low correlation (<0.3) to items of the CTSQ. Although symptomatic adverse events may substantially contribute to QoL in NSCLC [5], the frequency of (severe) treatment and cancer-related adverse events was not associated with treatment satisfaction. However, patients with better feelings about these side effects appeared to be more content with therapy. Therefore, patients' education about and management of adverse events may have added value in maintaining patients' well-being during chemotherapy, ultimately resulting in higher treatment satisfaction.

In our study, >80% of the patients valued pemetrexed and platinum-based chemotherapy as worth taking and would probably or definitely decide to take the chemotherapy again regardless of the presence of chemotherapy-related adverse events or deterioration in QoL. As ~75% of the patients correctly expected no or unlikely cancer cure, expressed satisfaction with therapy in our study is not solely a reflection of inaccurate expectations. Previous studies evaluating treatment preferences in a variety of oncological populations have reported that patients value even small benefits greatly and judge toxicity as less important [10,24]. More recently, Peeters et al. [12] and Pacchiana et al. [25] assessed patients' perceptions on future maintenance treatment for advanced NSCLC and they showed a generally favorable attitude towards treatment continuation at foresight, even if the expected gain of overall survival would be minimal. In agreement with our findings, mild-to-moderate side effects would be accepted by most patients [12]. Blinman et al [10] noticed that smaller benefits were judged sufficient for metastatic compared to locally advanced NSCLC. Furthermore, pemetrexed has been shown to be associated with relatively mild toxicity profiles and is generally well tolerated [3,26]. In our study population, these

considerations may have contributed to the highly valued merits of treatment despite side effects and the large willingness to undergo treatment again at hindsight.

Older patients showed a higher treatment satisfaction than younger patients, which offers no support to restrained prescription of pemetrexed and platinum-based chemotherapy in the elderly. Although recent studies have shown that palliative platinum-based doublet treatments result in improved survival rates comparable to younger patients, they often receive no chemotherapy or only single-agent regimens resulting in risk of undertreatment [27–29]. However, adequate information about other important treatment outcomes as toxicity, symptom relief and costs are scarce. In general, younger patients are more socially active compared to elderly. Moreover, it is commonly accepted that senescence is associated with an increased risk of morbidity and mortality. Therefore, higher hopes and demands of chemotherapy and worse coping with a shorter life expectancy may explain the finding in our study that younger patients are less easily satisfied with treatment.

Importantly, patients in our study represent a real-life study population, which significantly differs from populations generally included in clinical trials. Many patients in our population had (multiple) comorbidities, which occurs more frequently in unselected cancer populations [30]. However, this is in contrast to earlier clinical trials where patients with significant comorbidities or organ dysfunction were excluded from enrolment [3,31]. Additionally, higher median age and the inclusion of patients with a high (≥ 2) ECOG performance score compared to previous clinical trials could have led to lower tolerability of treatment and higher number of (severe) adverse events. Grutters et al. already showed that (even mild) adverse events might negatively influence QoL outcomes [5].

A major limitation of our study is imposed by the study design, which prevented us to evaluate treatment satisfaction (and its relation with change of QoL) in patients who did not complete the full treatment of four cycles chemotherapy. Therefore, our results were obtained in a group of patients who had a good performance score and who mainly established disease stabilization. These factors could have led to an overestimation of the level of treatment satisfaction and underestimation of the associations between SWT with QoL and (feelings about) adverse events and between treatment response and SWT. In future research, we would recommend to assess SWT earlier during therapy to increase knowledge with respect to treatment satisfaction in patients with clinically important toxicities, poor treatment response and worse QoL. Finally, we cannot exclude the possibility of unmeasured false hope and social desirability bias in our results. Since patients completed the questionnaires by self-report and the questionnaires were collected by their care providers, it is possible patients responded with greater optimism than they actually felt.

CONCLUSION

In conclusion, the CTSQ is a useful tool to extensively assess SWT in research as well as in daily clinical decision making. The results of this study justify further exploration of SWT in patients with advanced NSCLC treated with chemotherapy. In shared decision making on palliative treatment, knowledge about patients' treatment satisfaction may provide important supplementary information besides patients' QoL and treatment toxicities.

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REFERENCES

1. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. Cochrane database Syst Rev. 2010;(5):CD007309. doi:10.1002/14651858.CD007309.pub2.
2. Mannion E, Gilmartin JJ, Donnellan P, Keane M, Waldron D. Effect of chemotherapy on quality of life in patients with non-small cell lung cancer. Support Care Cancer. 2014;22(5):1417-1428. doi:10.1007/s00520-014-2148-9.
3. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543-3551. doi:10.1200/JCO.2007.15.0375.
4. Howell D, Molloy S, Wilkinson K, et al. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. Ann Oncol. 2015;26(9):1846-1858. doi:10.1093/annonc/mdv181.
5. Grutters JPC, Joore MA, Wiegman EM, et al. Health-related quality of life in patients surviving non-small cell lung cancer. Thorax. 2010;65(10):903-907. doi:10.1136/thx.2010.136390.
6. Movsas B, Moughan J, Sarna L, et al. Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. J Clin Oncol. 2009;27(34):5816-5822. doi:10.1200/JCO.2009.23.7420.
7. Staren ED, Gupta D, Braun DP. The prognostic role of quality of life assessment in breast cancer. Breast J. 17(6):571-578. doi:10.1111/j.1524-4741.2011.01151.x.
8. Ediebah DE, Coens C, Zikos E, et al. Does change in health-related quality of life score predict survival? Analysis of EORTC 08975 lung cancer trial. Br J Cancer. 2014;110(10):2427-2433. doi:10.1038/bjc.2014.208.
9. Qi Y, Schild SE, Mandrekar SJ, et al. Pretreatment quality of life is an independent prognostic factor for overall survival in patients with advanced stage non-small cell lung cancer. J Thorac Oncol. 2009;4(9):1075-1082. doi:10.1097/JTO.0b013e3181ae27f5.
10. Blinman P, Alam M, Duric V, McLachlan S-A, Stockler MR. Patients' preferences for chemotherapy in non-small-cell lung cancer: a systematic review. Lung Cancer. 2010;69(2):141-147. doi:10.1016/j.lungcan.2010.05.001.
11. Bridges JFP, Mohamed AF, Finnern HW, Woehl A, Hauber AB. Patients' preferences for treatment outcomes for advanced non-small cell lung cancer: a conjoint analysis. Lung Cancer. 2012;77(1):224-231. doi:10.1016/j.lungcan.2012.01.016.
12. Peeters L, Sibille A, Anrys B, et al. Maintenance Therapy for Advanced Non–Small-Cell Lung Cancer: A Pilot Study on Patients' Perceptions. J Thorac Oncol. 2012;7(8):1291-1295. doi:10.1097/JTO.0b013e31825879ea.
13. Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. BMJ. 1998;317(7161):771-775. http://www.ncbi.nlm.nih.gov/pubmed/9740561. Accessed June 24, 2016.
14. Brundage MD, Feldman-Stewart D, Cosby R, et al. Cancer patients' attitudes toward treatment options for advanced non-small cell lung cancer: implications for patient education and decision support. Patient Educ Couns. 2001;45(2):149-157. http://www.ncbi.nlm.nih.gov/pubmed/11687329. Accessed June 24, 2016.
15. Weeks JC, Cook EF, O'Day SJ, et al. Relationship Between Cancer Patients' Predictions of Prognosis and Their Treatment Preferences. JAMA. 1998;279(21):1709. doi:10.1001/jama.279.21.1709.

16. Temel JS, Greer JA, Admane S, et al. Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: results of a randomized study of early palliative care. J Clin Oncol. 2011;29(17):2319-2326. doi:10.1200/JCO.2010.32.4459.
17. Weeks JC, Catalano PJ, Cronin A, et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med. 2012;367(17):1616-1625. doi:10.1056/NEJMoa1204410.
18. Cheung K, de Mol M, Visser S, Den Oudsten BL, Stricker BH, Aerts JGJ V. Reliability and validity of the Cancer Therapy Satisfaction Questionnaire in lung cancer. Qual Life Res. 2016;25(1):71-80. doi:10.1007/s11136-015-1062-z.
19. Skevington SM, Lotfy M, O'Connell KA, WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res. 2004;13(2):299-310. http://www.ncbi.nlm.nih.gov/pubmed/15085902. Accessed June 24, 2016.
20. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-376. http://www.ncbi.nlm.nih.gov/pubmed/8433390. Accessed June 26, 2016.
21. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of- life scores. J Clin Oncol. 1998;16(1):139-144. doi:10.1200/jco.1998.16.1.139.
22. Maringwa JT, Quinten C, King M, et al. Minimal important differences for interpreting health-related quality of life scores from the EORTC QLQ-C30 in lung cancer patients participating in randomized controlled trials. Support Care Cancer. 2011;19(11):1753-1760. doi:10.1007/s00520-010-1016-5.
23. Kehl KL, Landrum MB, Arora NK, et al. Association of Actual and Preferred Decision Roles With Patient-Reported Quality of Care: Shared Decision Making in Cancer Care. JAMA Oncol. 2015;1(1):50-58. doi:10.1001/jamaoncol.2014.112.
24. Duric VM, Stockler MR, Heritier S, et al. Patients' preferences for adjuvant chemotherapy in early breast cancer: what makes AC and CMF worthwhile now? Ann Oncol. 2005;16(11):1786-1794. doi:10.1093/annonc/mdi370.
25. Pacchiana MV, Capelletto E, Carnio S, et al. Patients' Attitudes and Physicians' Perceptions Toward Maintenance Therapy for Advanced Non–Small-cell Lung Cancer: A Multicenter Italian Survey. Clin Lung Cancer. 2016. doi:10.1016/j.cllc.2016.10.002.
26. Pujol J-L, Paz-Ares L, de Marinis F, et al. Long-Term and Low-Grade Safety Results of a Phase III Study (PARAMOUNT): Maintenance Pemetrexed Plus Best Supportive Care Versus Placebo Plus Best Supportive Care Immediately After Induction Treatment With Pemetrexed Plus Cisplatin for Advanced Nonsquamou. Clin Lung Cancer. 2014;15(6):418-425. doi:10.1016/j.cllc.2014.06.007.
27. Quoix E, Zalcman G, Oster J-P, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet (London, England). 2011;378(9796):1079-1088. doi:10.1016/S0140-6736(11)60780-0.
28. Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(13):2191-2197. doi:10.1200/JCO.2009.25.4052.
29. Paz-Ares LG, Zimmermann A, Ciuleanu T, et al. Meta-analysis examining impact of age on overall survival with pemetrexed for the treatment of advanced non-squamous non-small cell lung cancer. Lung Cancer. 2017;104:45-51. doi:10.1016/j.lungcan.2016.12.007.

30. Aarts MJ, Aerts JG, Van Den Borne BE, Biesma B, Lemmens VEPP, Kloover JS. Comorbidity in patients with small-cell lung cancer: Trends and prognostic impact. Clin Lung Cancer. 2015;16(4):282-291. doi:10.1016/j.cllc.2014.12.003.
31. Paz-ares L, Marinis F De, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind , phase 3 , randomised controlled trial. Lancet Oncol. 2012;13(3):247-255. doi:10.1016/S1470-2045(12)70063-3.

SUPPLEMENTAL TABLES

Table A1. Reasons for non-completion of questionnaires by patients who started chemotherapy

	baseline ***N*=165**	**2nd cycle (day 7-14)** ***N*=141**	**4th cycle (day 14-21)** ***N*=89**
	EORTC QLQ-C30 WHOQOL-BREF	*EORTC QLQ-C30 WHOQOL-BREF*	*EORTC QLQ-C30 WHOQOL-BREF CTSQ*
Non-completion, total	24 (14.5)	31 (21.9)	24 (27.0)
Not able to read Dutch	1 (0.6)	1 (0.7)	1 (1.1)
Physical disabilities	3 (1.8)	1 (0.7)	1 (1.1)
Poor condition	8 (4.2)	6 (4.3)	2 (2.2)
Mental burden	7 (4.2)	4 (2.8)	4 (4.5)
Stop study, death	N/A	3 (2.1)	1 (1.1)
Stop study, PD	N/A	3 (2.1)	1 (1.1)
Stop study, toxicity	N/A	1 (0.7)	0
Logistic failure	5 (3.0)	10 (7.1)	10 (11.2)
Unknown	1 (0.6)	2 (1.4)	4 (4.5)

Data are expressed as frequencies (percentage). Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; WHOQOL-BREF, World Health Organization Quality of Life-BREF; CTSQ, Cancer Therapy Satisfaction Questionnaire; PD, progressive disease; N/A, not applicable

Table A2. CTSQ domains in relation with change in EORTC QLQ C-30 QoL and functional scale scores between before and after treatment with pemetrexed (N=63)

EORTC QLQ C-30 scales	Δ QoL group	N (%)	Mean change in scale score†	Domain score SWT	P-value*
Global Health Status/QoL	Deterioration	21 (33)	-24.6 (24.4)	78.4 (13.2)	0.801
	No change	11 (17)	-0.76 (24.6)	77.3 (14.8)	
	Improvement	31 (49)	13.9 (22.5)	80.0 (12.5)	
Physical functioning	Deterioration	36 (57)	-23.3 (17.0)	76.6 (14.5)	0.346
	No change	6 (10)	0.0 (0.0)	83.8 (8.6)	
	Improvement	21 (33)	20.3 (17.8)	81.8 (10.5)	
Role functioning	Deterioration	33 (52)	-38.9 (120.2)	78.7 (12.4)	0.965
	No change	9 (14)	0.0 (0.0)	77.0 (20.0)	
	Improvement	21 (33)	41.3 (22.7)	80.4 (10.6)	
Emotional functioning	Deterioration	21 (33)	-22.4 (18.2)	77.9 (14.5)	0.818
	No change	8 (13)	0.0 (0.0)	79.9 (19.6)	
	Improvement	32 (51)	22.4 (18.3)	79.2 (10.6)	
	Missing	2 (3)			
Cognitive functioning	Deterioration	21 (33)	-29.4 (22.3)	76.0 (13.9)	0.441
	No change	28 (45)	0.0 (0.0)	80.4 (11.6)	
	Improvement	12 (19)	25.0 (16.7)	80.1 (15.4)	
	Missing	2 (3)			
Social functioning	Deterioration	21 (33)	-30.2 (25.6)	78.5 (13.1)	0.904
	No change	19 (31)	0.0 (0.0)	78.2 (15.0)	
	Improvement	20 (32)	33.3 (18.7)	80.0 (12.1)	
	Missing	3 (5)			

Data are expressed as means (SD).

†Minimal clinical important difference=5, > 5 in positive or negative direction were considered as having an improvement or deterioration in QoL respectively

*Distributions of data across groups were compared using the Kruskal-Wallis test.

Abbreviations: EORTC QLQ-C30; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SD, standard deviation; N, number of patients; QoL, Quality of Life; SWT, satisfaction with therapy.

Table A3. CTSQ domains in relation with change in WHOQOL-BREF QoL and domain scores between 2nd and 4thcycle of chemotherapy (after treatment) with pemetrexed (N=55)

WHOQOL-BREF facet/domains	Δ QoL group	N (%)	Mean change in overall QoL/ domain score†	Domain score SWT	P-value*
Overall QoL/ general health	Deterioration	15 (27)	-2.2 (1.2)	78.1 (15.0)	0.230
	No change	16 (29)	0.0 (0.0)	76.1 (12.4)	
	Improvement	24 (44)	1.8 (0.9)	83.2 (9.8)	
Physical health	Deterioration	15 (27)	-3.6 (1.8)	78.5 (15.3)	0.883
	No change	22 (40)	0.0 (0.7)	79.2 (11.3)	
	Improvement	16 (29)	3.0 (1.1)	81.7 (11.7)	
	Missing	2 (4)			
Psychological health	Deterioration	20 (36)	-2.4 (1.2)	75.0 (12.1)	0.132
	No change	20 (36)	0.1 (0.6)	81.8 (13.8)	
	Improvement	14 (25)	2.3 (0.7)	83.2 (9.0)	
	Missing	1 (2)			
Social relationships	Deterioration	22 (40)	-2.6 (2.2)	81.1 (11.0)	0.404
	No change	15 (27)	0.0 (0.2)	75.7 (12.5)	
	Improvement	17 (31)	2.1 (0.9)	81.1 (14.0)	
	Missing	1 (2)			
Environment	Deterioration	13 (24)	-2.8 (1.1)	81.8 (10.2)	0.847
	No change	31 (56)	0.0 (0.6)	79.6 (13.1)	
	Improvement	9 (16)	1.9 (0.6)	78.2 (13.5)	
	Missing	2 (4)			

Data are expressed as means (SD).

†Minimal clinical important differences were used to determine deterioration, no change and improvement of QoL per domain/facet.

*Distributions of data across groups were compared using the Kruskal-Wallis test.

Abbreviations: WHOQOL-BREF, World Health Organization Quality of Life-BREF; QoL, Quality of Life; SD, standard deviation; N, number of patients; SWT, satisfaction with therapy.

Table A4. CTSQ domains in relation with change in EORTC QLQ C-30 QoL and functional domain scores between 2nd and 4thcycle of chemotherapy (after treatment) with pemetrexed (N=60)

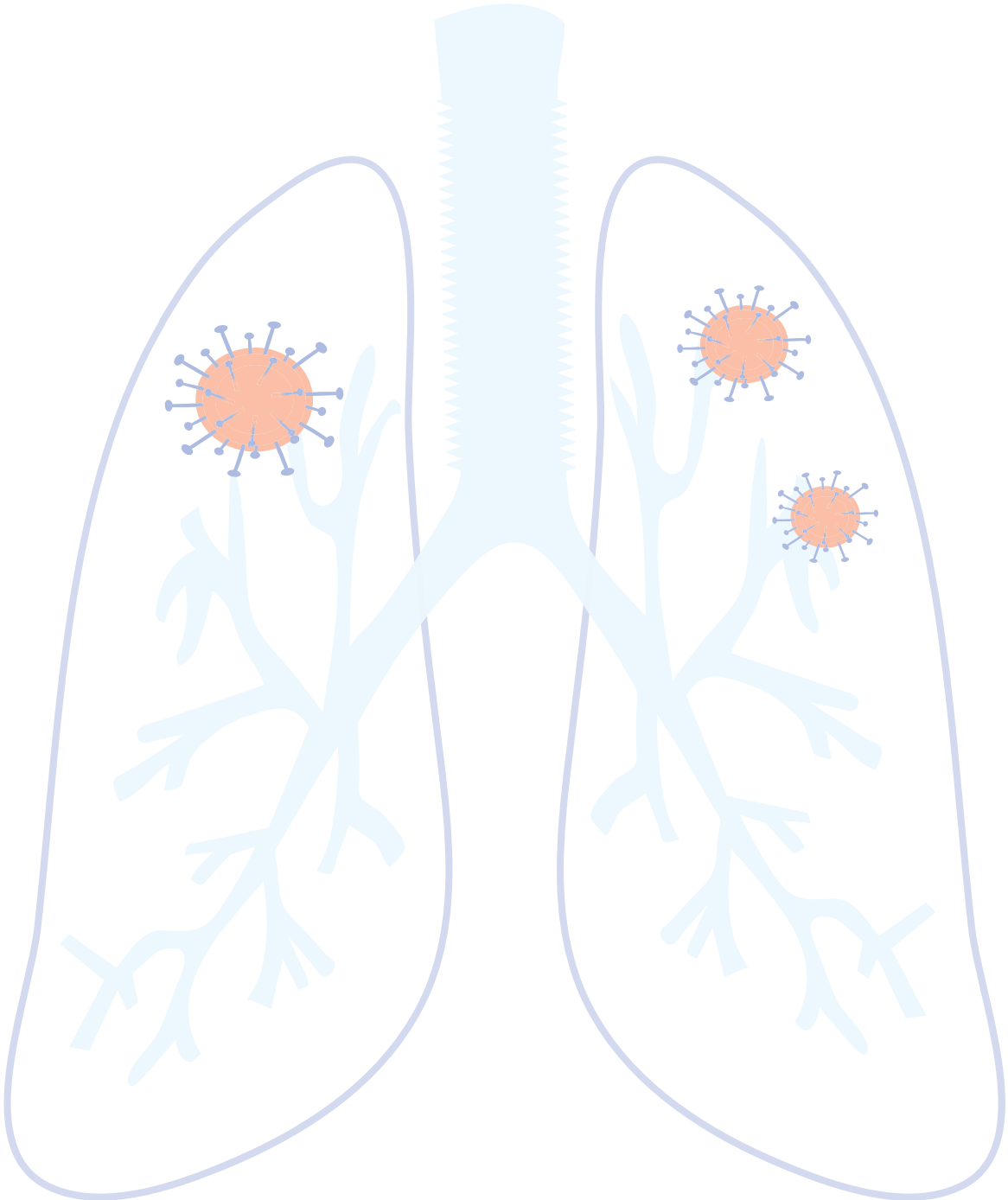
EORTC QLQ C-30 scales	Δ QoL group	N (%)	Mean change in scale score†	Domain score SWT	P-value*
Global Health Status/QoL	Deterioration	21 (35)	-26.2 (15.0)	78.2 (11.9)	0.191
	No change	11 (18)	0.0 (0.0)	86.0 (11.8)	
	Improvement	21 (35)	18.3 (13.3)	78.1 (12.9)	
	Missing	7 (12)			
Physical functioning	Deterioration	29 (48)	-20.2 (16.2)	76.9 (15.7)	0.855
	No change	12 (20)	0.0 (0.0)	81.3 (7.2)	
	Improvement	20 (33)	21.0 (11.9)	81.4 (11.6)	
Role functioning	Deterioration	26 (43)	-32.7 (16.0)	78.9 (12.8)	0.980
	No change	19 (32)	0.0 (0.0)	89.1 (13.4)	
	Improvement	15 (25)	36.7 (16.9)	80.2 (14.1)	
Emotional functioning	Deterioration	21 (35)	-22.2 (14.8)	77.9 (14.8)	0.699
	No change	15 (25)	0.0 (0.0)	78.3 (10.0)	
	Improvement	18 (30)	15.7 (7.5)	82.7 (11.2)	
	Missing	6 (10)			
Cognitive functioning	Deterioration	19 (32)	-26.3 (12.8)	77.6 (14.4)	0.670
	No change	21 (35)	0.0 (0.0)	79.6 (10.8)	
	Improvement	14 (23)	26.2 (12.6)	82.4 (12.2)	
	Missing	6 (10)			
Social functioning	Deterioration	20 (33)	-30.0 (23.3)	77.3 (14.3)	0.807
	No change	17 (28)	0.0 (0.0)	80.2 (11.7)	
	Improvement	16 (27)	34.4 (15.5)	82.4 (10.9)	
	Missing	7 (12)			

Data are expressed as means (SD).

†Minimum clinical important difference = 5, > 5 in positive or negative direction was considered as having an improvement or deterioration in QoL, respectively.

*Distributions of data across groups were compared using the Kruskal-Wallis test.

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SD, standard deviation; N, number of patients; QoL, Quality of Life; SWT, satisfaction with therapy.



CHAPTER 7

Treatment selection of early-stage non-small cell lung cancer: the role of the patient in clinical decision making

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ABSTRACT

Background: The objective of this study is to investigate the role and experience of early-stage non-small cell lung cancer (NSCLC) patients in the decision making process concerning treatment selection in the current clinical practice.

Methods: Stage I-II NSCLC patients (surgery 55 patients, stereotactic body radiotherapy (SBRT) 29 patients, median age 68) were included in this prospective study and completed a questionnaire that explored: (1) perceived patient knowledge of the advantages and disadvantages of the treatment options, (2) experience with current clinical decision making, and (3) the information that the patient reported to have received from their treating physician. This was assessed by multiple-choice, 1-5 Likert scale, and open questions. The Decisional Conflict Scale was used to assess the decisional conflict. Health-Related Quality of life (HRQoL) was measured with SF-36 questionnaire.

Results: In 19% of patients, there was self-reported perceived lack of knowledge about the advantages and disadvantages of the treatment options. Seventy-four percent of patients felt that they were sufficiently involved in decision making by their physician, and 81% found it important to be involved in decision making. Forty percent experienced decisional conflict, and one-in-five patients to such an extent that it made them feel unsure about the decision. Subscores with regard to feeling uninformed and on uncertainty, contributed the most to decisional conflict, as 36% felt uninformed and 17% of patients were not satisfied with their decision. HRQoL was not influenced by patient experience with decision making or patient preferences for shared decision making.

Conclusions: Dutch early-stage NSCLC patients find it important to be involved in treatment decision making. Yet a substantial proportion experiences decisional conflict and feels uninformed. Better patient information and/or involvement in treatment decision making is needed in order to improve patient knowledge and hopefully reduce decisional conflict.

BACKGROUND

Surgical resection is considered the preferred treatment for patients with early-stage non-small cell lung cancer (NSCLC). A less invasive option for patients with comorbidities is stereotactic body radiotherapy (SBRT) [1, 2]. Several studies have demonstrated that SBRT may be as effective as surgery in potentially operable patients, however, randomized trials with larger patient populations and longer follow-up are still lacking [3–5]. In this setting it is important to provide adequate information to allow patients to take an active role in treatment decision making.

Shared decision making (SDM) is a process in which physician and patient work together in making a health decision after discussing the options, the benefits and harms, and considering the patients' values, preferences, and circumstances [6, 7]. SDM is seen as the middle ground between informed choice, where the patient makes the decision based on information received from the physician, and traditional paternalistic decision making, where the physician makes the decision based on best available evidence [8, 9]. Patients who are active participants in the process of their care, for example asking questions, expressing their opinions and preferences, have better health outcomes, more knowledge regarding the disease and they are less anxious than patients who do not participate in the decision making [7, 10–12]. SDM supports patients to understand the disease and weigh advantages and disadvantages of treatment options in their own context, which will result in an informed treatment decision making with patients' needs and values incorporated. Although SDM has gained increased awareness among the healthcare community, it has not been widely incorporated into routine clinical practice in lung cancer care. This can be explained by the fact that there is lack of familiarity with SDM [13, 14], and also because the care of lung cancer patients can be complex due to multiple treatment types over an extended period of time and often includes a guideline-driven treatment [15]. Furthermore, there are a number of factors that complicate the implementation of SDM in current clinical practice such as guideline based treatments, patient knowledge, time constrains, and care settings [16, 17].

This study assesses among Dutch early-stage NSCLC patients: (1) perceived patient knowledge of the advantages and disadvantages of treatment options, (2) experience with current clinical decision making, and (3) perceived understanding of information regarding their disease and the treatment.

METHODS

Patient population

Between December 2012 and December 2014, 155 consecutive patients with stage I or II NSCLC were recruited for this prospective observational study. These patients were subsequently treated surgically or with SBRT at Erasmus University Medical Center, Erasmus MC Cancer Institute, or Amphia Hospital Breda. Consecutive patients were contacted by telephone to explain the purpose of the study and obtain their consent to receive a questionnaire. Only patients who agreed to participate and provided written informed consent were eligible for the inclusion in this study (n = 84). The overall response rate was 54%. No significant differences were found between responders and non-responders in terms of baseline characteristics. This study was approved by the institutional review board of Erasmus University Medical Center (MEC 2012-462).

Clinical staging of patients treated surgically (n= 55) or with SBRT (n = 29) was done with CT-scan, 18FDG-PET imaging and/or using (minimally invasive) endoscopic techniques when appropriate. Clinical and pathological staging was based on American Joint Committee on Cancer 7th edition staging manual [18]. Chronic obstructive pulmonary disease (COPD) was defined according to the GOLD criteria [19]. Comorbidity scores were recorded using the Charlson Comorbidity Index (CCI) [20]. Treatment planning of patients who received SBRT have been described previously [21]. All patients were discussed in a multidisciplinary team meeting before being accepted for treatment.

Data collection

Baseline characteristics of patients were collected by reviewing the patients' medical records and hospital information system. After the treatment decision was made but before the actual start of the treatment, patients completed a questionnaire. The aim of this questionnaire is to investigate: (1) perceived patient knowledge of the advantages and disadvantages of treatment options, (2) experience with current clinical decision making (this includes the preferences, patient experience and involvement in treatment decision making using the Decisional Conflict Scale (DCS) and Control Preferences Scale (CPS), and (3) perceived understanding of information regarding their disease and the treatment. These components are measured at baseline using multiple choice questions, a 1-5 Likert scale, and open questions. Health-Related Quality of Life (HRQoL) was measured before the treatment, 6 months and 12 months after the treatment using the Short-Form 36-Item Health Survey (SF-36). For details regarding the questionnaire see Additional file 1.

Control preference scale

The patients' preferred decisional role was assessed using a modified version of the CPS. The CPS is an instrument that assesses preferences regarding patient participation in

health care decisions. Patients were asked to select one of the five statements on roles in treatment decision making; (A) the physician makes the decision about the treatment alone, (B) the physician makes the decision after considering the patient's opinion, (C) the patient makes the decision together with the clinician, (D) the patient makes the decision after considering the doctor's opinion, and (E) the patient makes the decision about the treatment alone [22–24]. This scale has been widely used in previous studies [25, 26]. To investigate the potential association between education level and CPS patients were asked to indicate their educational attainment.

Decisional conflict scale

The DCS was used to assess the level of 'decisional conflict' that patients experience while making health care decisions. This scale has been extensively validated and has been widely used. The DCS measures decision uncertainty that leads to decision delay and quantifies modifiable factors which contribute to uncertainty. It contains 16 items, each using a five-point Likert response format (i.e., completely agree, agree, neither agree nor disagree, disagree, completely disagree). These items are combined to form a total score and five subscales (i.e., uncertainty, informed, values clarity, support, and effective decision subscore). Scores lower than 25 are associated with implementing decisions and scores exceeding 37.5 are associated with delay or feeling unsure about implementation [27, 28]. In case of missing values (< 6%) we used a multiple imputation technique to impute missing values in order to avoid them being depicted as 'unknown' in incomplete observations. We have used 5-fold multiple imputation using SPSS for Windows version 21 [29]. In the surgery group 32 and 19 patients were alive at 6 and 12 months without tumor progression, respectively. In the SBRT group this was 9 and 4 patients at 6 and 12 months, respectively. Due to the low response rates at 6 and 12 months we could not explore decisional conflict over time.

Health-Related Quality of Life assessment

HRQoL was measured with the SF-36. The SF-36 is the most extensively used and evaluated health outcomes measure and has shown to be valid and reliable in multiple populations. The SF-36 assess eight self-reported aspects of HRQoL (i.e., physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health). It also yields physical (PCS) and mental (MCS) health summary measures. Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores and then transforming the scores to a scale from 0 to 100 [30]. The mean score of the PCS and MCS is 50 with a standard deviation of 10 and wherein a higher score means a better health status. Furthermore, a higher score on the SF-36 subdomains represents a better functioning; a high score on the bodily pain scale indicates the absence of pain. The scale has good reliability, with

Cronbach α ranging from 0.65 to 0.96 for all subscales [31]. We used the Dutch adaptation of the SF-36 health status scale [32]. Patients were asked to complete the SF-36 form after treatment decision was made but before the treatment (baseline), at 6 and 12 months to all surviving patients. In case of missing values we applied simple imputation [33, 34]. HRQoL was assessed in 84 patients at baseline (surgery = 55, SBRT = 29). Due to the low response rates at 6 and 12 months (surgery group 32 and 19 patients were alive at 6 and 12 months and this was in the SBRT group 9 and 4 patients, respectively) the effect of time could not be analyzed.

Local control and the presence of metastases were defined according to the guidelines of ACCP and STS [35]. Twelve patients were diagnosed with tumor recurrence after the treatment, four of these patients had both locoregional and distant recurrence.

Statistical analysis

Continuous data are reported as mean ± SD or median with range, and categorical data are reported as proportions. Normally distributed continuous variables were compared by using Student t tests, and not normally distributed (Kolmogorov-Smirnov) data were compared by using the Mann-Whitney U test. Discrete variables were compared by using the Chi-Square test or the Fisher Exact test where appropriate. Aim 1 and 3 of this manuscript were analyzed using simple statistics by counting the 'yes' and 'no' answers. Components measured with 1-5 Likert-scale were not categorized.

A general linear model (GLM) with the bootstrap method was used to assess the association between HRQoL measured at baseline and (1) patients' experience with involvement in treatment selection, (2) patients' preferences for SDM, and (3) patients' preferred decisional role in treatment decision making (assessed with CPS). The purpose behind the use of bootstrapping is to account for skewed distribution of residuals of SF-36 variables [36, 37] and to obtain valid and reliable p-values.

All statistical tests were two-tailed and a p-value of < 0.05 was regarded as statistical significant. The statistical software package SPSS for Windows version 21 (SPSS Inc., Chicago, IL) was used for data analysis. GraphPad Prism5.00 for Windows (GraphPad software, San Diego, CA) was used to obtain graphs of QoL.

RESULTS

The baseline characteristics of all 84 patients are listed in Table 1. In 55 patients surgical treatment was chosen (median age = 65), in 29 patients SBRT (median age = 73). In this cohort of patients the education level was in accordance with the education level of the general Dutch population [38].

Table 1. Patient characteristics

Characteristics	Total (N=84)	Surgery (N=55)	Radiotherapy (N=29)	P-value
Sex				*0.406*
Male (%)	44 (52)	27 (49)	17 (59)	
Female (%)	40 (48)	28 (51)	12 (41)	
Age, median (range)	68 (50-87)	65 (50-81)	73 (52-87)	*0.001*
Education level (%):				*0.875*
Primary education	12 (14)	8 (15)	4 (14)	
Secondary education	21 (55)	29 (53)	17 (59)	
Higher education	46 (27)	15 (27)	8 (27)	
other	3 (4)	3(5)		
Smoking habits				
Nonsmoker (%)	3 (4)	2 (4)	1 (3)	*0.588*
Current or former smoker (%)	60 (71)	38 (69)	22 (76)	
Unknown, N (%)	21 (25)	15 (27)	6 (21)	
FEV_1% mean±SD	80 (24)	87 (20)	67 (26)	*0.001*
Unknown, N (%)	3 (4)	2 (4)	1 (3)	
DLCO (%) mean±SD	76 (24)	83 (22)	61 (22)	*<0.001*
COPD (%)				*0.001*
No COPD	38 (45)	31 (56)	7 (24)	
GOLD I	17 (20)	10 (18)	7 (24)	
GOLD II	19 (23)	13 (24)	6 (21)	
GOLD III	8 (10)	1 (2)	7 (24)	
GOLD IV	2 (2)	-	2 (7)	
Charlson comorbidity index (%)				*0.026*
≤ 1	47 (56)	33 (60)	14 (48)	
2-3	26 (31)	17 (31)	9 (32)	
4	6 (7)	3 (5)	3 (10)	
≥ 5	5 (6)	2 (4)	3 (10)	
Clinical stage (%)				*0.001*
IA	47 (56)	22 (40)	25 (86)	
IB	14 (17)	12 (22)	2 (7)	
IIA	17 (20)	15 (27)	2 (7)	
IIB	6 (7)	6 (11)		
Pathological stage (%)				
IA	17 (31)	17 (31)		
IB	18 (33)	18 (33)		
IIA	9 (16)	9 (16)		
IIB	7 (13)	7 (13)		
IIIA/B	4 (7)	4 (7)		

Table 1. Patient characteristics (continued)

Characteristics	Total (N=84)	Surgery (N=55)	Radiotherapy (N=29)	P-value
Histology (%)				*0.262*
Squamous cell carcinoma	18 (21)	14 (26)	4 (14)	
Adenocarcinoma	21 (25)	15 (27)	6 (21)	
Large cell carcinoma	8 (10)	6 (11)	2 (7)	
NSCLC	37 (44)	20 (36)	17 (58)	
Clinical tumor diameter (mm), median (range)	25 (7-130)	29 (7-130)	22 (9-41)	*<0.001*
Unknown, N (%)		11 (5)		
Pathological tumor diameter (mm), median (range)	28 (1-90)	28 (1-90)		

Abbreviations: FEV_1%, forced expiratory volume in 1 second expressed as a percent of predicted; DLCO, diffusion capacity of the lung for carbon monoxide; COPD, chronic obstructive pulmonary disease; N, number of patients; SD, standard deviation; NSCLC, non-small cell lung cancer.

Perceived patient knowledge regarding the treatment

Self-reported lack of knowledge about the advantages and disadvantages of the treatment options was present in 18% of patients in the surgery group and in 22% of patients in the SBRT group. Self-reported lack of knowledge about the treatment risks was present in 6% of patients in the surgery group and in 21% of patients in the SBRT group.

Experience with current clinical decision making

Patient preferences for SDM

The majority (85%) of patients agreed that ideally decision making should be done together with the physician. Twelve percent of patients wanted to leave the decision about the appropriate treatment to their treating physician and 3% indicated that the decision should be done mainly by patients. No association was found between the education level and the control preference scale.

Experience in treatment decision making

On average, patients in this cohort discussed their treatment with three physicians. The majority of patients in the surgery and SBRT group involved a family member in making the choice for a treatment, 75 and 68%, respectively. Most of patients thought that they had enough time to make an informed decision (80% in the surgery group and 79% in the SBRT group). Patients indicated that several subjects were discussed during the conversation with their treating physician. Two percent of patients in the surgery group had the feeling that not every aspect of the treatment was discussed during the conversation with their treating physician. This was 11% in the SBRT group.

In the surgery group, 40% of patients experienced decisional conflict (score > 25), and 22% to such an extent that they felt unsure about their decision (score > 37.5). Thirty-two percent felt uncertain about the best choice, and 39% felt uninformed. Twenty-nine percent felt unclear about personal values for benefits and side effects of the treatment. Twenty-one percent felt unsupported in decision making, and 21% of patients were not satisfied with their decision.

In the SBRT group, 48% of patients experienced decisional conflict, and 7% to such an extent that they felt unsure about their decision. Thirty-five percent felt uncertain about the best choice, and 29% felt uninformed. Thirty-two percent felt unclear about personal values for benefits and side effects of the treatment. Fourteen percent felt unsupported in decision making, and 7% of patients were not satisfied with their decision. Subscores on feeling uninformed and on uncertainty contributed the most to decisional conflict. Scores exceeding 37.5 are described here, details of the total score and five subscales for the two treatment groups are illustrated in Fig. 1.

Fig. 1 Decisional conflict in patients treated surgically or with stereotactic body radiotherapy (SBRT). Scores <25 (green color) are associated with implementing decisions and scores <37.5 (red color) are associated with delay or feeling unsure about implementation. Orange color represent scores between 25 and 37.5

Involvement in treatment decision making

Seventy-four percent of patients felt that they were sufficiently involved in decision making by their physician, 73% felt that they had a choice between different treatment

options, 81% found it important to be involved in decision making, 6% reported that alternative treatment options and complementary treatments were not discussed during the conversation about their treatment. Patients mentioned immunotherapy, diet and vitamin supplements as an example. Involvement in treatment decision making for the two treatment groups can be found in Table 2.

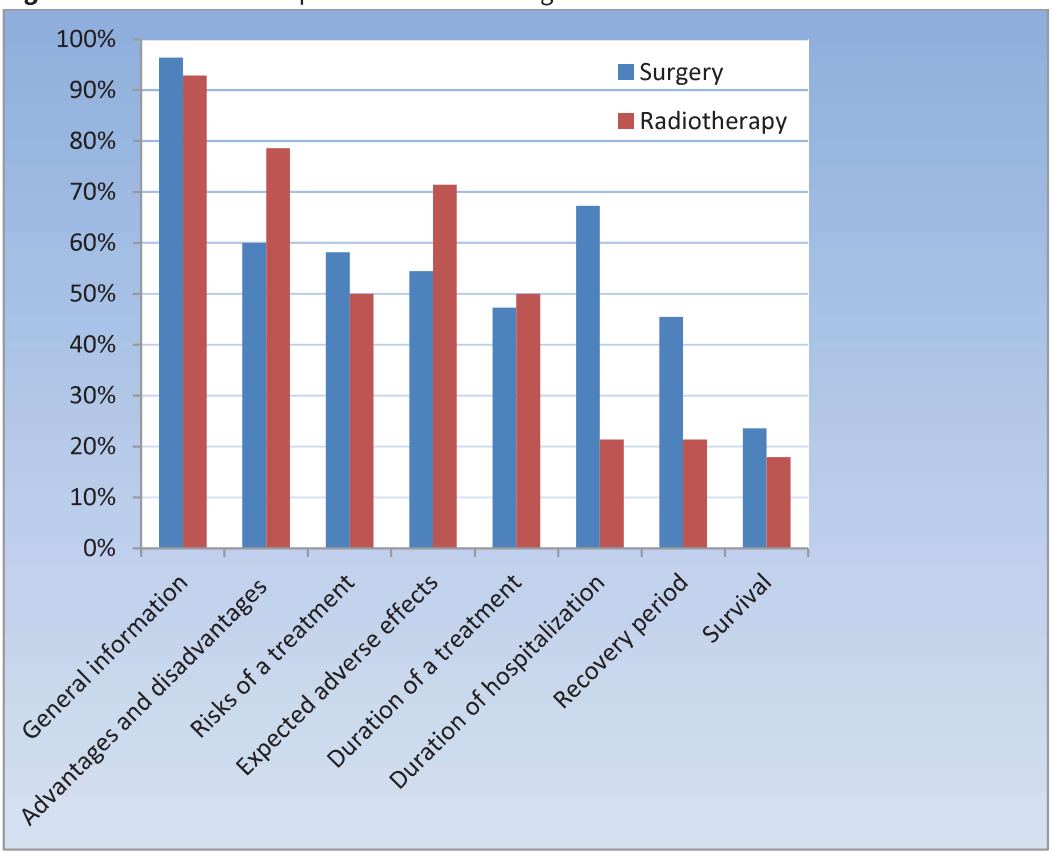
Table 2. Involvement in treatment decision making for the two treatment groups

Involvement in decision making	Surgery (%)	Radiotherapy (%)
Felt sufficiently involved	78	68
Found important to be involved	78	89
Having a choice	71	79
Not having a choice	18	7

Perceived understanding of information regarding the disease and the treatment

Patients were asked to report which topics were discussed during the conversation about their treatment. Figure 2 illustrates that the minority of patients who undergone surgery or radiation therapy received information about the survival, 24 and 18%, respectively.

Fig. 2 Information that the patient received during the consultation



Health-Related Quality of Life assessment

At baseline, patients in the surgery group scored higher on physical component summary (mean 42.4 ± 12.3) than patients in the SBRT group (mean 34.4 ± 10.1), Fig. 3. No major differences could be found between the HRQoL in the surgery and SBRT group for the other measured SF-36 scales, except for physical functioning and general health (Fig. 4). Recurrence rates and death rates are illustrated in Table 3.

Fig. 3 Scatterplot of physical component summary (PCS) and mental component summary (MCS) at baseline in the surgery and stereotactic body radiotherapy (SBRT) group

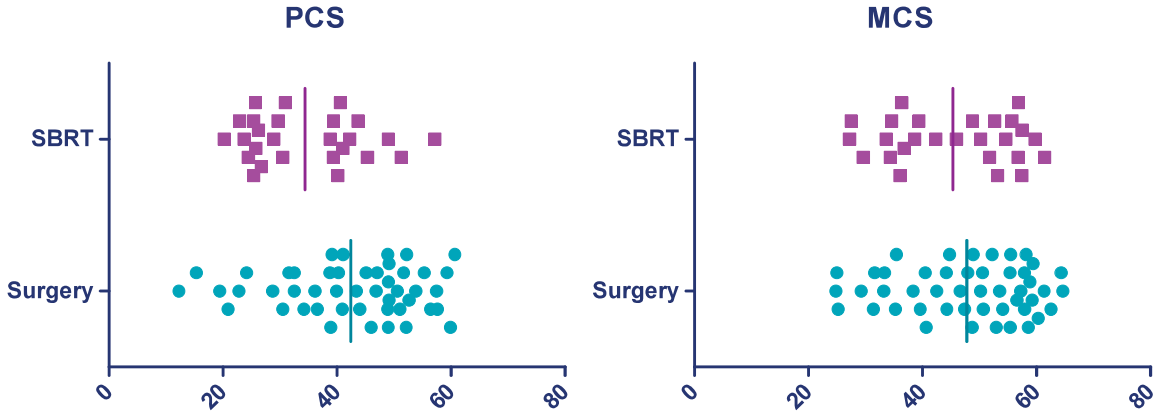
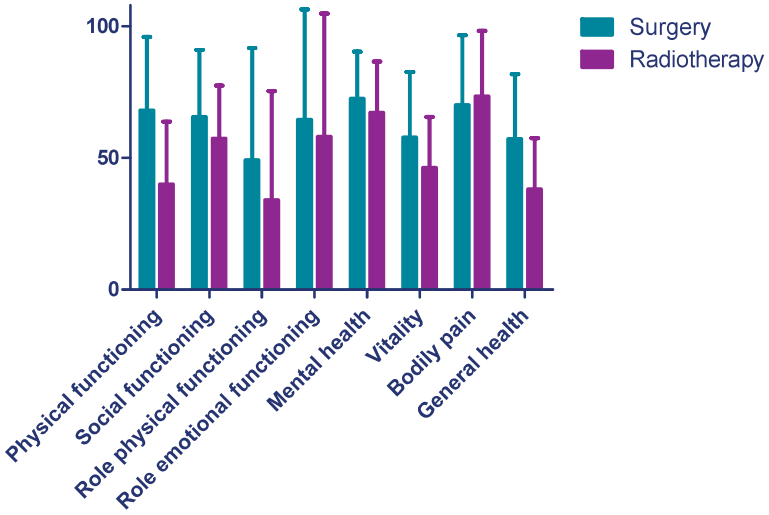


Fig. 4 Eight self-reported aspects of HRQoL measured at baseline. The scores are expressed as the mean score with a standard deviation stratified by treatment group. A high score indicates better HRQoL, with a high score on bodily pain representing absence of pain



SDM and HRQoL at baseline

No significant association could be found between HRQoL and patient experience with involvement in treatment selection (PCS p-value = 0.398, MCS p-value = 0.341), patient preferences for SDM (PCS p-values = 0.439, MCS p-value = 0.580), and final decision in lung cancer treatment selection (PCS p-value = 0.402, MCS p-value = 0.662).

Table 3. Recurrence rate of patients treated surgically or with SBRT. Four patients had both loco-regional recurrence and distant recurrence.

	Surgery (%)	Radiotherapy (%)
All recurrence	9 (16)	3 (10)
Time till all recurrence(mean ± SD)	1.1 ± 0.7 months	0.4 ± 0.06 months
Local recurrence	1 (2)	-
Loco-regional recurrence	4 (7)	1 (3)
Distant recurrence	9 (16)	2 (7)
Death	5 (9)	8 (28)

Abbreviations: SD, standard deviation

DISCUSSION

This study illustrate that in the current clinical practice lung cancer patients experience decisional conflict and suboptimal information provision regarding the treatment and survival which highlights the need of improvement of information conveyance, and involvement of patients with early-stage NSCLC in treatment decision making.

Perceived patient knowledge regarding the treatment and communication with the patient

Up to one-fifth of patients reported lack of knowledge about the advantages and disadvantages of the treatment options and one-tenth of patients reported lack of knowledge about the treatment risks. These results illustrate that providing information needs to improve, particularly in an early stage of diagnosis and treatment because lung cancer patients are emotionally unstable and could be overloaded with information about their disease [39]. Numerous studies explored different strategies to improve and adopt SDM in clinical practice [40]. One of the main topics of improving cancer communication is 'health literacy' which involves the ability of the patient to read, understand, and use health information to make an appropriate decision. In order to achieve an effective communication it is essential to describe health state in language that is accessible to the patient and discuss the benefits and risks of treatment options in a balanced way [41, 42]. In the field of breast cancer it is illustrated that deciding on a cancer treatment without fully understanding the associated risks and benefits could lead to overuse or underuse of cancer treatments [43, 44].

Additionally, the majority of patients felt sufficiently involved in treatment decision making and indicated that they had enough time to make an informed decision. It was interesting to see that the minority of patients reported to have received information on survival. It is crucial to discuss survival and prognosis with the patient in a way that the patient will understand this information because previous studies have shown that cancer

patients overestimate their life expectancy and probabilities of cure when compared to their physicians' perspective [45–47]. This will lead to unrealistic high expectations about the medical treatment, which is a common phenomenon in oncology patients [48, 49].

Experience with current clinical decision making

The majority of patients had a strong desire to participate in treatment decision making and preferred the decision to be the outcome of a SDM-process. This is in line with previous studies showing that more patients preferred to participate rather than delegate decisions [50]. One of the challenges of SDM is knowing how much involvement a patient wants and needs. It is even more difficult when patients vary in the amount of control that they prefer to have over the treatment decision making at the time of diagnosis [26]. Using tools such as decision aids prior to the consultation or during the visit will improve the communication between the patient and physician and there will be more time for the patient to absorb health care information and ask questions during the consultation [51, 52].

Forty percent of patients experienced decisional conflict, and one-in-five patients to such an extent that it made them feel unsure about the decision. Decisional conflict was most evident in the uncertainty and informed subscale, suggesting that improvement of patient uncertainty and better informing the patient before the treatment will improve the quality of decision making [27]. The same rates has been reported by patients treated for other type of cancer [53, 54]. Various factors can play a role in high levels of decisional conflict in cancer patients. First, most cancer patients want as much information as possible, however, they could be overloaded with information when it is offered 'all at once' or when the information is not provided to the patients' family [55]. As we have illustrated in this study, an inadequate level of perceived information contributes the most to decisional conflict. Second, periodic assessment of a cancer patient's information requirements is also crucial, considering the complexity of cancer care. Finally, in our previous study we have illustrated that patients who receive SBRT differ significantly from the surgical patients [56]. It is important to appreciate these differences and realize that SBRT patients do not always have a choice between treatment options.

Although decisional conflict is about what patients go through when confronted with a difficult decision, the idea of decisional conflict is also to help patients to think about participation in decision making and motivate them to engage in treatment decision making [57]. Furthermore, these scales also illustrate how patients are informed and where the improvements are needed.

Health-Related Quality of Life and shared decision making

In general, lung cancer patients have poor HRQoL compared to the general population or patients without lung cancer [58, 59]. In this study, patients in the SBRT group scored at

baseline lower on physical component summary compared to patients treated surgically. No differences could be found regarding the mental component summary. An explanation for the observed differences in HRQoL between the two groups could be the significant differences in baseline characteristics [2, 56]. No association could be found between HRQoL and different aspects of SDM meaning that in this study HRQoL was not positively or negatively influenced by patient experiences with SDM. Our findings are comparable with a number of studies concluding that there is weak evidence that aspects of SDM are positively or negatively associated with QoL outcomes [60].

Strengths and limitations

The present study is a prospective observational cohort study allowing for new insights into the process of SDM and information conveyance in lung cancer patients. Although many articles have been written on SDM and patient participation in treatment decision making in cancer patients, to our knowledge little research has been done on the role of early-stage lung cancer patients -treated surgically or with SBRT- in treatment decision making and patients experiences and preferences regarding SDM. Also, the lung cancer patients were surveyed after diagnosis but before the treatment which allow us to investigate the unbiased perception of the patient regarding the treatment decision making.

Potential limitations need to be addressed regarding the present study. First, the conceptual design of this study was not built on a specific theory. We explicitly chose to include all patients with stage I or II NSCLC who were planned for a surgical treatment or SBRT. We wanted to illustrate patient participation in treatment decision making, since there is little research about the role of early-stage lung cancer patients -treated surgically or with SBRT- in treatment decision making. Second, overall response rate was 54% thus making the sample size of this study small. The non-responders were contacted to ask why they would not be part of the study. The following major reasons were given: (1) they were shocked by the diagnosis and therefore they did not want to complete the questionnaire; (2) they were too preoccupied with their illness and therefore they had no time for the questionnaire; (3) the questionnaire was too confrontational. However, no significant differences were found between responders and non-responders in terms of baseline characteristics. Third, we are aware of the shortcomings of using GLM. By using the bootstrap method we have tried to account for this inadequacy. However, no differences were observed between the results of GLM and results of GLM with bootstrapping. Finally, the response rate at 6 and 12 months was low due to recurrences rates and death rates in both treatment groups making analyses of HRQoL at 6 and 12 months difficult.

CONCLUSIONS

Shared decision making (SDM), where patients are involved as active partners with the physician in treatment decisions, is an important part of patient centered cancer care as it weighs the pros and cons of treatment options while taking patients values and preferences into account.

Dutch early-stage NSCLC patients find it important to be involved in treatment decision making. The majority of patients in this study found it important to be involved in decision making and reported that they felt sufficiently involved by their treating physician. Yet a substantial proportion of patients experiences decisional conflict and feels uninformed. HRQoL was not influenced by patient experiences with SDM. Better patient information, and patient involvement in treatment decision making is needed in order to improve patient knowledge and hopefully reduce decisional conflict.

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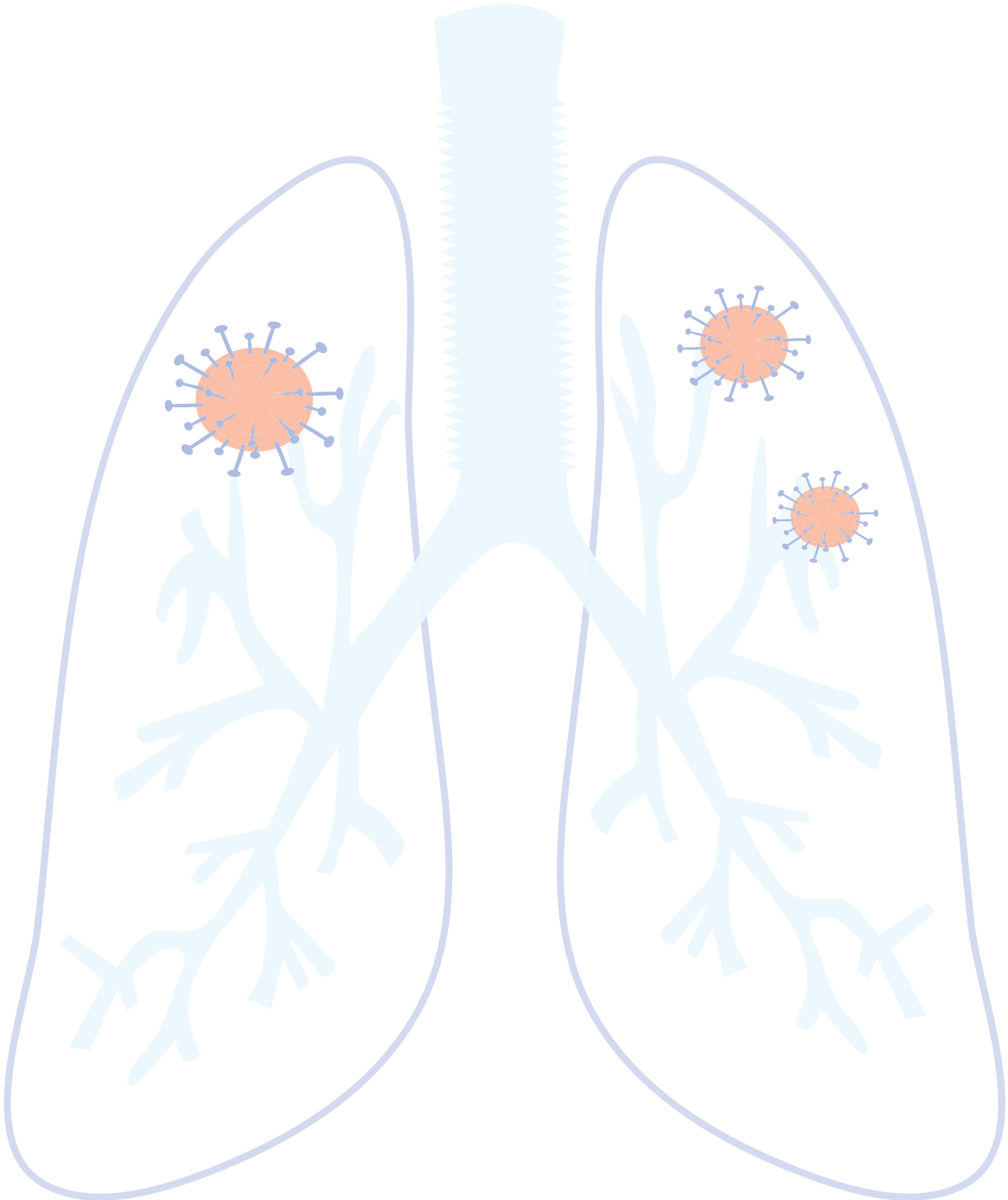
REFERENCES

1. Vansteenkiste J, Crino L, Dooms C, Douillard JY, Faivre-Finn C, Lim E, Rocco G, Senan S, Van Schil P, Veronesi G, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. Ann Oncol. 2014;25(8):1462–74.
2. Mokhles S, Verstegen N, Maat AP, Birim O, Bogers AJ, Mokhles MM, Lagerwaard FJ, Senan S, Takkenberg JJ. Comparison of clinical outcome of stage I nonsmall cell lung cancer treated surgically or with stereotactic radiotherapy: results from propensity score analysis. Lung Cancer. 2015;87(3):283–9.
3. Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, Groen HJM, McRae SE, Widder J, Feng L, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015;16(6):630–7.
4. Solda F, Lodge M, Ashley S, Whitington A, Goldstraw P, Brada M. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort. Radiother Oncol. 2013;109(1):1–7.
5. Treasure T, Rintoul RC, Macbeth F. SABR in early operable lung cancer: time for evidence. Lancet Oncol. 2015;16(6):597–8.
6. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, Cording E, Tomson D, Dodd C, Rollnick S, et al. Shared decision making: a model for clinical practice. J Gen Intern Med. 2012;27(10):1361–7.
7. Oshima Lee E, Emanuel EJ. Shared decision making to improve care and reduce costs. N Engl J Med. 2013;368(1):6–8.
8. Emanuel EJ, Emanuel LL. Four models of the physician-patient relationship. JAMA. 1992;267(16):2221–6.
9. Jordan JL, Ellis SJ, Chambers R. Defining shared decision making and concordance: are they one and the same? Postgrad Med J. 2002; 78(921):383–4.
10. Fowler FJ Jr, Gallagher PM, Drake KM, Sepucha KR. Decision dissonance: evaluating an approach to measuring the quality of surgical decision making. Jt Comm J Qual Patient Saf. 2013;39(3):136–44.
11. Ryan J, Sysko J. The contingency of patient preferences for involvement in health decision making. Health Care Manag Rev. 2007;32(1):30–6.
12. Murray E, Pollack L, White M, Lo B. Clinical decision-making: Patients' preferences and experiences. Patient Educ Couns. 2007;65(2):189–96.
13. Gravel K, Legare F, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: a systematic review of health professionals' perceptions. Implement Sci. 2006;1:16.
14. Friedberg MW, Van Busum K, Wexler R, Bowen M, Schneider EC. A demonstration of shared decision making in primary care highlights barriers to adoption and potential remedies. Health Aff (Millwood). 2013;32(2):268–75.
15. Hoffmann TC, Montori VM, Del Mar C. The connection between evidencebased medicine and shared decision making. JAMA. 2014;312(13):1295–6.
16. Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: a systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. Patient Educ Couns. 2014;94(3):291–309.
17. Mokhles S, Maat A, Aerts J, Nuyttens J, Bogers A, Takkenberg JJM. Opinions of lung cancer clinicians on shared decision making in early-stage non-small-cell lung cancerdagger. Interact Cardiovasc Thorac Surg. 2017;25:278–84.
18. Goldstraw P. IASLC staging manual in thoracic oncology. 1st ed. Orange Park: Editorial Rx Press; 2009.

19. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532–55.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
21. Nuyttens JJ, van de Pol M. The CyberKnife radiosurgery system for lung cancer. Expert Rev Med Devices. 2012;9(5):465–75.
22. Degner LF, Sloan JA, Venkatesh P. The control preferences scale. Can J Nurs Res. 1997;29(3):21–43.
23. Salkeld G, Solomon M, Short L, Butow PN. A matter of trust—patient's views on decision-making in colorectal cancer. Health Expect. 2004;7(2):104–14.
24. Janz NK, Wren PA, Copeland LA, Lowery JC, Goldfarb SL, Wilkins EG. Patientphysician concordance: preferences, perceptions, and factors influencing the breast cancer surgical decision. J Clin Oncol. 2004;22(15):3091–8.
25. Wallberg B, Michelson H, Nystedt M, Bolund C, Degner LF, Wilking N. Information needs and preferences for participation in treatment decisions among Swedish breast cancer patients. Acta Oncol. 2000;39(4):467–76.
26. Mallinger JB, Shields CG, Griggs JJ, Roscoe JA, Morrow GR, Rosenbluth RJ, Lord RS, Gross H. Stability of decisional role preference over the course of cancer therapy. Psychooncology. 2006;15(4):297–305.
27. O'Connor AM. Validation of a decisional conflict scale. Med Decis Mak. 1995; 15(1):25–30.
28. Koedoot N, Molenaar S, Oosterveld P, Bakker P, de Graeff A, Nooy M, Varekamp I, de Haes H. The decisional conflict scale: further validation in two samples of Dutch oncology patients. Patient Educ Couns. 2001;45(3): 187–93.
29. Rubin DB. Multiple imputation for non-response in surveys. New York: Wiley; 1997.
30. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473–83.
31. Smith HJ, Taylor R, Mitchell A. A comparison of four quality of life instruments in cardiac patients: SF-36, QLI, QLMI, and SEIQoL. Heart. 2000; 84(4):390–4.
32. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998;51(11):1055–68.
33. Bandayrel K, Johnston BC. Recent advances in patient and proxy-reported quality of life research. Health Qual Life Outcomes. 2014;12(1):110.
34. Coste J, Quinquis L, Audureau E, Pouchot J. Non response, incomplete and inconsistent responses to self-administered health-related quality of life measures in the general population: patterns, determinants and impact on the validity of estimates - a population-based study in France using the MOS SF-36. Health Qual Life Outcomes. 2013;11:44. Mokhles et al. BMC Cancer (2018) 18:79 Page 9 of 10
35. Donington J, Ferguson M, Mazzone P, Handy J Jr, Schuchert M, Fernando H, Loo B Jr, Lanuti M, de Hoyos A, Detterbeck F, et al. American College of Chest Physicians and Society of Thoracic Surgeons consensus statement for evaluation and management for high-risk patients with stage I non-small cell lung cancer. Chest. 2012;142(6):1620–35.
36. Efron B. Better bootstrap confidence-intervals. J Am Stat Assoc. 1987;82(397): 171–85.
37. Efron B. An introduction to the bootstrap method. New York: Chapmann and Hall/CRC; 1993.

38. Dutch population better educated. https://www.cbs.nl/en-gb/news/2013/40/dutch-population-better-educated.
39. Jensen JD, Carcioppolo N, King AJ, Scherr CL, Jones CL, Niederdieppe J. The cancer information overload (CIO) scale: establishing predictive and discriminant validity. Patient Educ Couns. 2014;94(1):90–6.
40. Legare F, Ratte S, Stacey D, Kryworuchko J, Gravel K, Graham ID, Turcotte S. Interventions for improving the adoption of shared decision making by healthcare professionals. Cochrane Database Syst Rev. 2010;5:CD006732.
41. Katz SJ, Belkora J, Elwyn G. Shared decision making for treatment of cancer: challenges and opportunities. J Oncol Pract. 2014;10(3):206–8.
42. Thorne S, Oliffe JL, Stajduhar KI. Communicating shared decision-making: cancer patient perspectives. Patient Educ Couns. 2013;90(3):291–6.
43. Katz SJ, Hawley ST. From policy to patients and back: surgical treatment decision making for patients with breast cancer. Health Aff (Millwood). 2007;26(3):761–9.
44. Bickell NA, Weidmann J, Fei K, Lin JJ, Leventhal H. Underuse of breast cancer adjuvant treatment: patient knowledge, beliefs, and medical mistrust. J Clin Oncol. 2009;27(31):5160–7.
45. Mackillop WJ, Stewart WE, Ginsburg AD, Stewart SS. Cancer-patients perceptions of their disease and its treatment. Br J Cancer. 1988;58(3):355–8.
46. Weeks JC, Cook EF, O'Day SJ, Petersen LM, Wenger N, Reding D, Harrell FE, Kussin P, Dawson NV, Connors AF, et al. Relationship between cancer patients' predictions of prognosis and their treatment preferences. JAMA. 1998;279(21):1709–14.
47. Reuben DB, Naeim A. Perspectives, preferences, care practices, and outcomes in late-stage cancer patients: connecting the dots. J Clin Oncol. 2004;22(24):4869–71.
48. Weeks JC, Catalano PJ, Cronin A, Finkelman MD, Mack JW, Keating NL, Schrag D. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med. 2012;367(17):1616–25.
49. Rosenberg SM, Tracy MS, Meyer ME, Sepucha K, Gelber S, Hirshfield-Bartek J, Troyan S, Morrow M, Schapira L, Come SE, et al. Perceptions, knowledge, and satisfaction with contralateral prophylactic mastectomy among young women with breast cancer: a cross-sectional survey. Ann Intern Med. 2013; 159(6):373–81.
50. Chewning B, Bylund CL, Shah B, Arora NK, Gueguen JA, Makoul G. Patient preferences for shared decisions: a systematic review. Patient Educ Couns. 2012;86(1):9–18.
51. O'Connor AM, Bennett CL, Stacey D, Barry M, Col NF, Eden KB, Entwistle VA, Fiset V, Holmes-Rovner M, Khangura S, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2009; 3:CD001431.
52. Elwyn G, O'Connor AM, Bennett C, Newcombe RG, Politi M, Durand MA, Drake E, Joseph-Williams N, Khangura S, Saarimaki A, et al. Assessing the quality of decision support technologies using the International Patient Decision Aid Standards instrument (IPDASi). PLoS One. 2009;4(3):e4705.
53. Sim JA, Shin JS, Park SM, Chang YJ, Shin A, Noh DY, Han W, Yang HK, Lee HJ, Kim YW, et al. Association between information provision and decisional conflict in cancer patients. Ann Oncol. 2015;26(9):1974–80.
54. Taylor BA, Hart RD, Rigby MH, Trites J, Taylor SM, Hong P. Decisional conflict in patients considering diagnostic thyroidectomy with indeterminate fine needle aspirate cytopathology. J Otolaryngol Head Neck Surg. 2016;45:16.
55. Hope S, Williams AE, Lunn D. Information provision to cancer patients: a practical example of identifying the need for changes in practice from the Dorset cancer Centre. Eur J Cancer Care (Engl). 2000;9(4):238–42.

56. Mokhles S, Nuyttens JJ, Maat AP, Birim O, Aerts JG, Bogers AJ, Takkenberg JJ. Survival and treatment of non-small cell lung cancer stage I-II treated surgically or with stereotactic body radiotherapy: patient and tumor-specific factors affect the prognosis. Ann Surg Oncol. 2015;22(1):316–23.
57. Janis IL. Decision making:a psycological analysis of conflict, choice, and commitment. New York: Free Press; 1977.
58. Poghosyan H, Sheldon LK, Leveille SG, Cooley ME. Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: a systematic review. Lung Cancer. 2013;81(1):11–26.
59. Myrdal G, Valtysdottir S, Lambe M, Stahle E. Quality of life following lung cancer surgery. Thorax. 2003;58(3):194–7.
60. Kashaf MS, McGill E. Does shared decision making in cancer treatment improve quality of life? A systematic literature review. Med Decis Mak. 2015; 35(8):1037–48.



GENERAL DISCUSSION

PATIENT REPORTED OUTCOMES IN LUNG CANCER

To this date lung cancer has the highest incidence of all major cancer types and is the main cause of cancer-related mortality worldwide [1]. Despite recent advancements in the treatment of advanced-stage lung cancer with Endothelial Growth Factor Receptor tyrosine kinase inhibitors [2-6], Anaplastic Lymphoma Kinase inhibitors [7-10], and more recently PD-1 and PD-L1 inhibitors [11-14], the survival benefits of these treatments often apply to relatively few patients. Therefore, to further assess if these treatments are worthwhile, patient reported outcomes (PROs), such as Quality of Life (QoL), are included as an outcome parameter to monitor the impact of side effects on patients' well-being and to facilitate drug approval and legislation.

Unfortunately, different definitions of QoL are often used in studies that report the consequences of new treatments. According to the definition of QoL, as formulated by the World Health Organization, QoL is 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns' [15]. 'It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs, and their relation to salient features of their environment' [15,16]. However, considering the questionnaires (i.e., patient reported outcome measures (PROMs)) that are used in studies that assess novel therapies, QoL is conceptually equated with Health-Related Quality of Life (HRQoL) and Health Status (HS). As a result, differences exist between the concepts these studies aim to measure and those that are actually measured, which hampers comparison of outcomes and may lead to doubtful conclusions. Therefore, prior to the start of a study that investigates patient-reported outcomes (PROs) (i.e., HS, HRQoL, and QoL), it is highly recommended to first define the concept of interest (i.e., PRO), subsequently to search for PROMs that claim to asses this concept and inspect their items and psychometric properties, and, lastly, to choose the PRO and associated PROM that bests reflects the concept of interest and the study requirements [17].

In the introduction of this thesis examples of PROMs that are commonly used in patients with lung cancer (i.e., Distress Thermometer [18], EQ-5D [19], EORTC QLQ-C30 [20], WHO-QOL-BREF [21]) are mentioned. These instruments assess different concepts (i.e., distress, HS, HRQoL, and QoL) and, in general, have satisfactory psychometric properties and can be used in patients with lung cancer. Application of PROs may be worthwhile during daily clinical practice. For instance, PRO outcomes observed in studies or in previously treated patients may be used to compare treatments with similar survival benefits to aid patients and physicians in making personalized treatment decisions. During treatment, results of individual patients may be used to monitor the effects of therapy on a patient's well-being

so that additional care can be provided if needed [22]. This is of importance given that few patients with advanced-stage lung cancer benefit from new treatments.

INTERPRETATION OF MAIN FINDINGS AND FUTURE PERSPECTIVES

Distress in patients with lung cancer

A PROM that is frequently applied in lung cancer patients treated with chemotherapy to monitor the effects of disease and treatment on a patient's well-being is the Distress Thermometer (DT). The DT measures the unpleasant psychological (i.e., cognitive, emotional, and behavioral), social, and spiritual experience associated with a diagnosis and treatment of cancer [23,18]. Previously, in patients with breast cancer, moderate to severe distress was related to a decrease in HRQoL [24]. Furthermore, several studies demonstrated that HS and HRQOL are predictive for survival [25-32]. In addition, depressive symptoms have been associated with decreased survival in patients with lung cancer [33,34]. These results could indicate that a relation may exist between distress and survival independent of HRQoL. Therefore, it was hypothesized that the DT would have similar prognostic significance as HS and HRQoL. However, a relationship between the DT and overall survival was not observed in patients with stage III lung cancer [35]. At the first cycle of chemotherapy, the DT-score was not prognostic for overall survival. This may be explained by the inability of the DT to measure the concept of HRQoL. Moreover, the included patients could represent a population in which patients with the best and those with the worst clinical status were not included resulting in selection bias. This could also have contributed to the negative results. Remarkably, the reported distress was less than observed in patients with other types of cancer [36,37]. This seems unexpected given the, in general, limited prognosis and the high burden of disease and side effects in patients with lung cancer. Patients' increased age could be an explanation for the lower observed levels of distress as increased age is previously related with the experience of less distress in cancer [38]. In the described study, a large number of patients (n= 214) was excluded since they did not complete the DT. This may be due to experience of side effects and deterioration of patients' well-being. For future studies, it may be worthwhile to determine whether completion of PROMs (e.g., the DT) is influenced by a reduced HS, HRQoL, and QoL or the experience of side effects. This may provide health care professionals with new insights in patients' willingness to complete PROMs. Knowledge about these insights may help physicians and nurses in aiding patients with the completion of PROMs by providing additional care.

Quality of Life in lung cancer

PROMs need to be reliable and valid given the patient population of interest. Since patients with advanced-stage lung cancer, in general, have a limited prognosis compared to other patients with cancer, and that their disease and treatment comes with a significant burden of adverse events, psychometric analysis of PROMs may be mandatory in these patients. For clinical purposes, it may be interesting to determine which patient-related factors (i.e., both clinical and demographic) are related to these PROs. For instance, some factors (e.g., older age, low performance status) could be used to identify patients prone to decreases in their well-being. In addition, treatment of other factors such as anxiety or depressive symptoms may provide opportunities to enhance a patient's well-being.

To stimulate the evaluation of QoL in studies next to HS and HRQoL we tested the psychometric properties of the WHOQOL-BREF in patients with advanced-stage lung cancer and mesothelioma [39]. A Taiwanese study by Lin et al. also reported results of a psychometric analysis of the WHOQOL-BREF. This study included patients with stage I to IV lung cancer [40]. Validation of a QoL instrument in patients with advanced-stage lung cancer was important since patients with stage I or II cancer patients differ from advanced-stage cancer patients. In general, patients with advanced-stage disease have a limited prognosis and experience a substantial burden of disease and treatment-related adverse events. Also an adapted version of the WHOQOL-BREF was used in the study by Lin et al. whereas the study reported in this thesis used the Dutch translation of the original WHOQOL-BREF [40]. Based on our results, the WHOQOL-BREF demonstrated satisfactory psychometric characteristics. These results are comparable to those observed by Lin et al. [40] and the WHOQOL group [41]. Compared to the WHOQOL-BREF field trial, patients in our study scored lower on general health [41]. This finding illustrates the large impact of lung cancer on patients compared with the general population and patients with other diseases and cancer types. In addition to the field trial [41] and the Taiwanese study [40], we reported the minimal clinically important differences (MCIDs) for the WHOQOL-BREF domain scores using two distribution-based methods [39]. These MCIDs further enable the application of the WHOQOL-BREF in research and clinical practice. Future studies should elaborate on these findings by calculating MCIDs with the use of other methods (e.g., anchor-based method).

Several sociodemographic and clinical factors have been associated with (HR)QoL in lung cancer. Increased age, higher performance status, and higher education were positively related to (HR)QoL, while female gender and having a spouse were negatively related [42-44]. Furthermore, in patients with cancer, depressive symptoms are negatively associated with HRQoL [45,46]. Contemplating on these findings, a study describing the relationships between sociodemographic and clinical variables and personality traits with (HR)QoL is reported in this thesis. It was observed that especially depressive symptoms were negatively related to (HR)QoL besides the Eastern Cooperative Oncology Group

performance score [47]. This observation provides opportunities to enhance (HR)QoL in patients with advanced-stage cancer. It may be worthwhile to screen patients for the presence of depressive symptoms. Adequate management of these symptoms (e.g., referral to a psychologist) could possibly increase patients' QoL. In a recent meta-analysis, supportive care interventions (i.e., psychotherapy, exercise program) reduced depressive symptoms [48]. In addition, it would be interesting to explore if depressive symptoms also have a role in shared decision making. In patients with diffuse large B-cell non-Hodgkin lymphoma it was observed that depression reduced the chance of being treated with curative intent with chemotherapy by hematologists [49]. Given that patients with advanced-stage lung cancer may also experience depressive symptoms and are treated with chemotherapy, depressive symptoms could also play a part in decision making in these patients.

The role of patients' perspectives about treatment in shared decision making and clinical practice

Although analysis of patients' (HR)QoL in studies and clinical practice may be beneficial , it does not evaluate how patients value their treatment. Given that chemotherapy may have a negative impact on a patients' HRQoL due to its side effects [50], in potential, this could affect patients' satisfaction with care. Several studies have reported about patients' satisfaction with care [51-53], but none of these studies reported on patients' opinions related to side effects. This is unfortunate as in a study by Rha et al. it was observed that clinicians did not correctly estimate the impact of side effects (i.e., nausea and vomiting) on patients [54]. Patients' feelings about treatment can be assessed with the Cancer Therapy Satisfaction Questionnaire (CTSQ) [55]. Completion of this questionnaire by patients may facilitate clinical decision making and in the end patients' (HR)QoL. In this thesis, results of a validation study of the CTSQ in patients with advanced-stage lung cancer was described. The CTSQ is a reliable and valid instrument to assess satisfaction, feelings about side effects, and expectations of treatment in patients with lung cancer [56]. Validation of the CTSQ in these patients seemed legitimate as the questionnaire has not extensively been evaluated in patients treated with chemotherapy [57,58]. In the same study, MCIDs were proposed with the use of two distribution-based methods and one anchor-based approach. These results stimulate the application of the CTSQ not only in studies but also in clinical practice.

In another study in this thesis, the relationship between patients' treatment satisfaction and feelings about side effects with their well-being was analyzed by relating CTSQ domain scores with (HR)QoL. Patients' feelings about side effects and not satisfaction with treatment were associated with (HR)QoL. Especially low-grade side effects (e.g., nausea, constipation, fatigue, anorexia) were related with feelings about side effects [59]. According to these results, it is recommended to have high awareness for the occurrence of low-grade side effects since patients are clearly bothered by them. Given the observed

associations, adequate management of low-grade side effects may offer opportunities to improve, maintain or prevent deterioration of (HR)QoL.

Earlier, it was found in a prospective, randomized cross-over trial that HRQoL-related issues (i.e., social functioning, dyspnea, and fatigue) were more often discussed between doctors and patients when the EORTC QLQ-C30 was completed by patients [60]. These observations demonstrate the value of such questionnaires in oncological practice. In addition, their application may also be worthwhile due to other reasons. The CTSQ is used as an example to illustrate these advantages, although other items, domains/scales or questionnaires (e.g., general facet of WHOQOL-BREF, global Health Status/QoL scale of the EORTC QLQ C30) may also be suitable. For instance, by asking patients to complete the feelings about side effects domain of the CTSQ, this identifies if they are bothered by side effects or not. If the results indicate that they are bothered, additional care can then be provided to treat these side effects. Also patients' CTSQ responses could facilitate the process of making shared treatment decisions. This is of importance, since it is known that shared decisions are related to better patient-reported quality of care [61]. Given that, according to our results, patients with negative feelings about side effects could have low (HR)QoL (i.e., WHOQOL-BREF domains: $\beta = 0.36$ to 0.58, $P < 0.005$; EORTC QLQ-C30 scales: $\beta = 0.33$ to 0.61, $P < 0.013$) and that prognosis is limited in advanced-stage lung cancer, it is proposed that the CTSQ results of previously treated patients can be used to help newly diagnosed patients at risk for adverse events in making treatment decisions. For instance, if a considerable proportion of patients who received chemotherapy were often hampered by adverse events according to their CTSQ results, newly diagnosed patients with a limited prognosis could take knowledge of these results and make a more considered treatment decision. In such a way, CTSQ results are handled in a similar manor during decision making as response and survival rates. This role of the CTSQ should be further explored in future studies that aim to analyze treatment decision making.

In addition to the feelings about side effects domain of the CTSQ, it is recommended to use also the results of the satisfaction with therapy domain upon making treatment decisions. Knowledge about patients' treatment satisfaction may provide important supplementary information besides patients' QoL and treatment toxicities'. Moreover, many patients receiving chemotherapy for metastatic (lung) cancer overestimate their life expectancy [62-65], which might explain the discordance between the treatment decisions they make and their actual preferences. Given these considerations, information about treatment satisfaction may help patients to formulate their actual treatment preferences (e.g., the continuation or stop of treatment with chemotherapy). This thesis describes a study on the CTSQ in patients with advanced-stage lung cancer treated with palliative chemotherapy [66]. Eighty-six percent of the included patients reported that they probably or definitely would like to receive the same treatment again despite side effects or deterioration of their well-being. Satisfaction with therapy explained less than 10% of

the observed variance of the functional scales and domains of the EORTC QLQ-C30 and the WHOQOL-BREF, except for the global Health Status/QoL scale of the EORTC QLQ-C30 and the psychological health domain of the WHOQOL-BREF. Furthermore, it was observed that patients who experienced increases in global Health Status/QoL during treatment were more satisfied than those that did not or experienced a decrease in that scale. These results contribute to previous findings [56] and demonstrate that the assessment of satisfaction with therapy offers supplementary information about the impact of therapy on patients next to (HR)QoL. In addition, patients' feelings about side effects were associated with their satisfaction with therapy. This may imply that adequate management of side effects could result in higher patients' satisfaction with care. Future studies should evaluate satisfaction with therapy at an earlier stage during treatment (e.g., after the first or second cycle of therapy), which could increase our understanding about satisfaction in patients who experience significant side effects, poor response to treatment, and decreases in (HR) QoL.

As mentioned earlier, implementation of PROs in clinical practice may facilitate shared treatment decision making. To determine if this may be worthwhile in patients with lung cancer, their role in clinical decision making was assessed [67]. Most patients felt themselves to be sufficiently involved in treatment decision making, although 26% of the patients experienced no involvement or felt insufficiently involved. About 80% of the included patients thought that treatment decisions were ideally taken together with physicians. In addition, about 40% of patients experienced decisional conflict (i.e., 40% of the surgically treated patients and 48% of the patients treated with stereotactic body radiotherapy). Uncertainty about chosen treatment and the feeling to be insufficiently informed explained decisional conflict mostly. The results demonstrated that improvements have to be made if shared treatment decision making in clinical practice truly wants to play a role of significance. Better patient information and patient involvement in treatment decision making is warranted in order to improve patient knowledge and reduce decisional conflict. This can be facilitated by inviting patients to complete PROMs before making treatment decisions as this gives patients more insight about which factors are of influence on their disease and treatment-related opinions.

CONCLUSION

The acquirement and implementation of PRO data holds much promise for the management of a cancer patient's well-being. According to the results in this thesis, it is recommended that all patients with advanced-stage lung cancer complete the CTSQ. Given that it directly evaluates patients' feelings about side effects and that it is associated with HRQoL and QoL, its role may be of more importance than that of the DT. In addition, new

approaches are recommended with an increasing role of PROs (e.g., (HR)QoL, feelings about side effects, satisfaction with therapy) in the process of shared decision making and as an equal outcome parameter next to response rates and survival. This work aimed to contribute to these developments. However, as is demonstrated, there are multiple controversies regarding the definition and the interpretation of these PROs, which impedes their use in research and clinical practice. To enable an optimal use of PROs in these settings, standardized procedures for PRO management and use have to be followed.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians 68 (6):394-424. doi:10.3322/caac.21492
2. Morita S, Okamoto I, Kobayashi K, Yamazaki K, Asahina H, Inoue A, Hagiwara K, Sunaga N, Yanagitani N, Hida T, Yoshida K, Hirashima T, Yasumoto K, Sugio K, Mitsudomi T, Fukuoka M, Nukiwa T (2009) Combined survival analysis of prospective clinical trials of gefitinib for non-small cell lung cancer with EGFR mutations. Clinical cancer research : an official journal of the American Association for Cancer Research 15 (13):4493-4498. doi:10.1158/1078-0432.CCR-09-0391
3. Costa DB, Kobayashi S, Tenen DG, Huberman MS (2007) Pooled analysis of the prospective trials of gefitinib monotherapy for EGFR-mutant non-small cell lung cancers. Lung cancer 58 (1):95-103. doi:10.1016/j.lungcan.2007.05.017
4. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 31 (27):3327-3334. doi:10.1200/JCO.2012.44.2806
5. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, Zhou C, Hu CP, O'Byrne K, Feng J, Lu S, Huang Y, Geater SL, Lee KY, Tsai CM, Gorbunova V, Hirsh V, Bennouna J, Orlov S, Mok T, Boyer M, Su WC, Lee KH, Kato T, Massey D, Shahidi M, Zazulina V, Sequist LV (2015) Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. The Lancet Oncology 16 (2):141-151. doi:10.1016/S1470-2045(14)71173-8
6. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, Shepherd FA, He Y, Akamatsu H, Theelen WS, Lee CK, Sebastian M, Templeton A, Mann H, Marotti M, Ghiorghiu S, Papadimitrakopoulou VA, Investigators A (2017) Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. The New England journal of medicine 376 (7):629-640. doi:10.1056/NEJMoa1612674
7. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, De Pas T, Besse B, Solomon BJ, Blackhall F, Wu YL, Thomas M, O'Byrne KJ, Moro-Sibilot D, Camidge DR, Mok T, Hirsh V, Riely GJ, Iyer S, Tassell V, Polli A, Wilner KD, Janne PA (2013) Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. The New England journal of medicine 368 (25):2385-2394. doi:10.1056/NEJMoa1214886
8. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Iyer S, Reisman A, Wilner KD, Tursi J, Blackhall F, Investigators P (2014) First-line crizotinib versus chemotherapy in ALK-positive lung cancer. The New England journal of medicine 371 (23):2167-2177. doi:10.1056/NEJMoa1408440
9. Shaw AT, Kim TM, Crino L, Gridelli C, Kiura K, Liu G, Novello S, Bearz A, Gautschi O, Mok T, Nishio M, Scagliotti G, Spigel DR, Deudon S, Zheng C, Pantano S, Urban P, Massacesi C, Viraswami-Appanna K, Felip E (2017) Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. The Lancet Oncology 18 (7):874-886. doi:10.1016/S1470-2045(17)30339-X
10. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SI, Perol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T, Investigators AT (2017) Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. The New England journal of medicine 377 (9):829-838. doi:10.1056/NEJMoa1704795

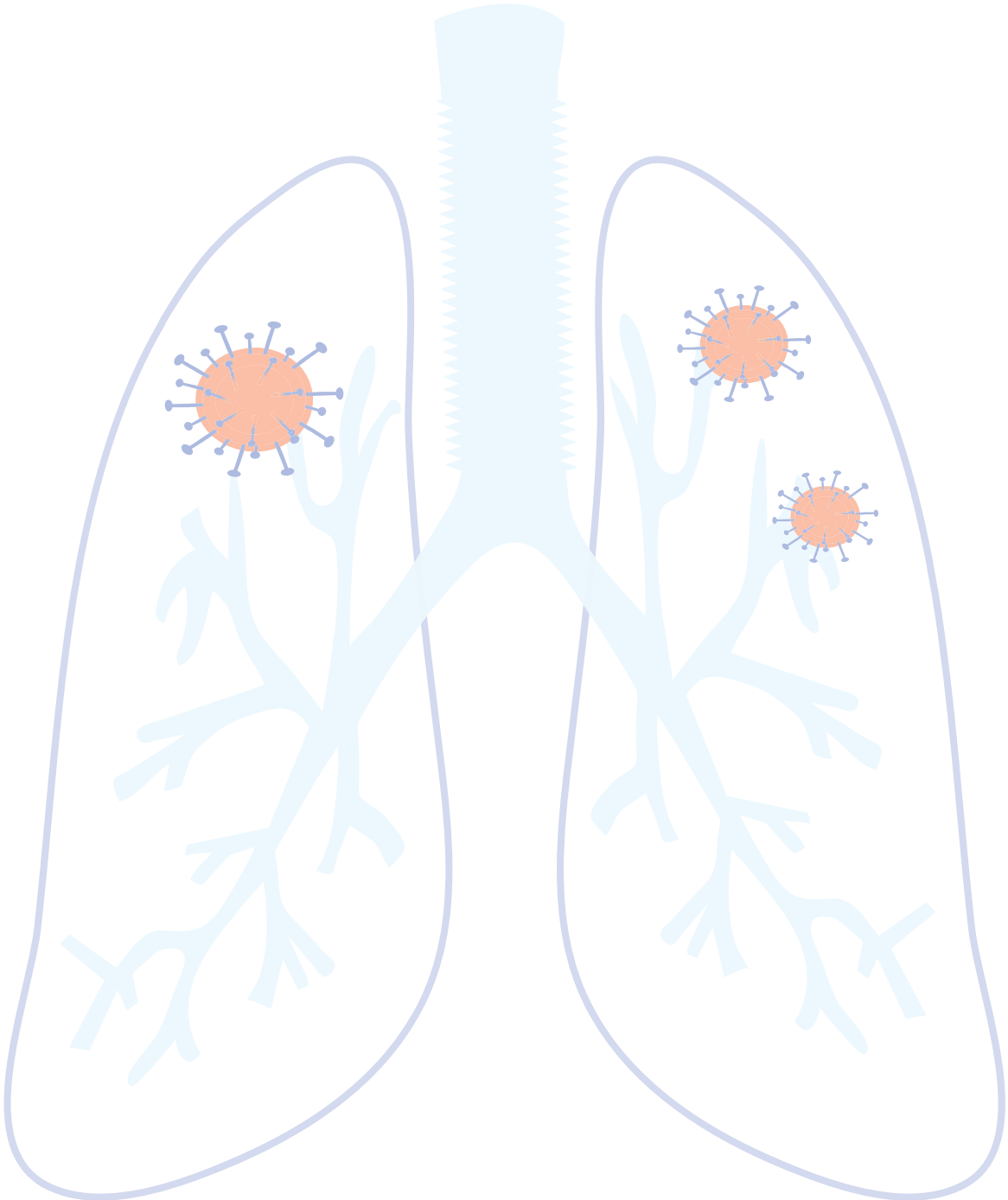
11. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, Powderly JD, Heist RS, Carvajal RD, Jackman DM, Sequist LV, Smith DC, Leming P, Carbone DP, Pinder-Schenck MC, Topalian SL, Hodi FS, Sosman JA, Sznol M, McDermott DF, Pardoll DM, Sankar V, Ahlers CM, Salvati M, Wigginton JM, Hellmann MD, Kollia GD, Gupta AK, Brahmer JR (2015) Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33 (18):2004-2012. doi:10.1200/JCO.2014.58.3708
12. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhaufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crino L, Blumenschein GR, Jr., Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR (2015) Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. The New England journal of medicine 373 (17):1627-1639. doi:10.1056/NEJMoa1507643
13. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Aren Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. The New England journal of medicine 373 (2):123-135. doi:10.1056/NEJMoa1504627
14. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M, Fidler MJ, de Castro G, Jr., Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M, Garon EB (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 387 (10027):1540-1550. doi:10.1016/S0140-6736(15)01281-7
15. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization (1995). Social science & medicine 41 (10):1403-1409
16. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties (1998). Social science & medicine 46 (12):1569-1585
17. De Vries J. DOBL (2014) The choice determines the success. Nederlands tijdschrift voor Orthopaedie 21 (2):39-42
18. NCCN (2014) NCCN clinical practice guideline Distress Management version 2.
19. TheEuroQolGroup (1990) EuroQol-a new facility for the measurement of health-related quality of life. Health policy 16 (3):199-208
20. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 85 (5):365-376
21. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group (1998). Psychological medicine 28 (3):551-558
22. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, Rogak L, Bennett AV, Dueck AC, Atkinson TM, Chou JF, Dulko D, Sit L, Barz A, Novotny P, Fruscione M, Sloan JA, Schrag D (2016) Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34 (6):557-565. doi:10.1200/JCO.2015.63.0830
23. Holland JC (1997) Preliminary guidelines for the treatment of distress. Oncology 11 (11A):109-114; discussion 115-107

24. Head BA, Schapmire TJ, Keeney CE, Deck SM, Studts JL, Hermann CP, Scharfenberger JA, Pfeifer MP (2012) Use of the Distress Thermometer to discern clinically relevant quality of life differences in women with breast cancer. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 21 (2):215-223. doi:10.1007/s11136-011-9934-3
25. Gotay CC, Kawamoto CT, Bottomley A, Efficace F (2008) The prognostic significance of patient-reported outcomes in cancer clinical trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26 (8):1355-1363. doi:10.1200/JCO.2007.13.3439
26. Movsas B, Moughan J, Sarna L, Langer C, Werner-Wasik M, Nicolaou N, Komaki R, Machtay M, Wasserman T, Bruner DW (2009) Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 27 (34):5816-5822. doi:10.1200/JCO.2009.23.7420
27. Qi Y, Schild SE, Mandrekar SJ, Tan AD, Krook JE, Rowland KM, Garces YI, Soori GS, Adjei AA, Sloan JA (2009) Pretreatment quality of life is an independent prognostic factor for overall survival in patients with advanced stage non-small cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 4 (9):1075-1082. doi:10.1097/JTO.0b013e3181ae27f5
28. Jacot W, Colinet B, Bertrand D, Lacombe S, Bozonnat MC, Daures JP, Pujol JL, Onco LRhn (2008) Quality of life and comorbidity score as prognostic determinants in non-small-cell lung cancer patients. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 19 (8):1458-1464. doi:10.1093/annonc/mdn064
29. Lemonnier I, Guillemin F, Arveux P, Clement-Duchene C, Velten M, Woronoff-Lemsi MC, Jolly D, Baumann C (2014) Quality of life after the initial treatments of non-small cell lung cancer: a persistent predictor for patients' survival. Health and quality of life outcomes 12:73. doi:10.1186/1477-7525-12-73
30. Efficace F, Bottomley A, Smit EF, Lianes P, Legrand C, Debruyne C, Schramel F, Smit HJ, Gaafar R, Biesma B, Manegold C, Coens C, Giaccone G, Van Meerbeeck J, Group ELC, Quality of Life U (2006) Is a patient's self-reported health-related quality of life a prognostic factor for survival in non-small-cell lung cancer patients? A multivariate analysis of prognostic factors of EORTC study 08975. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 17 (11):1698-1704. doi:10.1093/annonc/mdl183
31. Montazeri A, Milroy R, Hole D, McEwen J, Gillis CR (2001) Quality of life in lung cancer patients: as an important prognostic factor. Lung cancer 31 (2-3):233-240
32. Braun DP, Gupta D, Staren ED (2011) Quality of life assessment as a predictor of survival in non-small cell lung cancer. BMC cancer 11:353. doi:10.1186/1471-2407-11-353
33. Chen HM, Tsai CM, Wu YC, Lin KC, Lin CC (2015) Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer. British journal of cancer 112 (3):438-445. doi:10.1038/bjc.2014.612
34. Arrieta O, Angulo LP, Nunez-Valencia C, Dorantes-Gallareta Y, Macedo EO, Martinez-Lopez D, Alvarado S, Corona-Cruz JF, Onate-Ocana LF (2013) Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Annals of surgical oncology 20 (6):1941-1948. doi:10.1245/s10434-012-2793-5
35. de Mol M, den Oudsten BL, Aarts M, Aerts J (2017) The distress thermometer as a predictor for survival in stage III lung cancer patients treated with chemotherapy. Oncotarget 8 (22):36743-36749. doi:10.18632/oncotarget.14151

36. Tuinman MA, Gazendam-Donofrio SM, Hoekstra-Weebers JE (2008) Screening and referral for psychosocial distress in oncologic practice: use of the Distress Thermometer. Cancer 113 (4):870-878. doi:10.1002/cncr.23622
37. Hoffman BM, Zevon MA, D'Arrigo MC, Cecchini TB (2004) Screening for distress in cancer patients: the NCCN rapid-screening measure. Psycho-oncology 13 (11):792-799. doi:10.1002/pon.796
38. VanHoose L, Black LL, Doty K, Sabata D, Twumasi-Ankrah P, Taylor S, Johnson R (2015) An analysis of the distress thermometer problem list and distress in patients with cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 23 (5):1225-1232. doi:10.1007/s00520-014-2471-1
39. de Mol M, Visser S, Aerts J, Lodder P, de Vries J, den Oudsten BL (2018) Satisfactory results of a psychometric analysis and calculation of minimal clinically important differences of the World Health Organization quality of life-BREF questionnaire in an observational cohort study with lung cancer and mesothelioma patients. BMC cancer 18 (1):1173. doi:10.1186/s12885-018-4793-8
40. Lin CY, Yang SC, Lai WW, Su WC, Wang JD (2015) Rasch models suggested the satisfactory psychometric properties of the World Health Organization Quality of Life-Brief among lung cancer patients. Journal of health psychology. doi:10.1177/1359105315603474
41. Skevington SM, Lotfy M, O'Connell KA, Group W (2004) The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 13 (2):299-310
42. Jordhoy MS, Fayers P, Loge JH, Saltnes T, Ahlner-Elmqvist M, Kaasa S (2001) Quality of life in advanced cancer patients: the impact of sociodemographic and medical characteristics. British journal of cancer 85 (10):1478-1485. doi:10.1054/bjoc.2001.2116
43. Lundh Hagelin C, Seiger A, Furst CJ (2006) Quality of life in terminal care--with special reference to age, gender and marital status. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 14 (4):320-328. doi:10.1007/s00520-005-0886-4
44. Zimmermann C, Burman D, Swami N, Krzyzanowska MK, Leighl N, Moore M, Rodin G, Tannock I (2011) Determinants of quality of life in patients with advanced cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 19 (5):621-629. doi:10.1007/s00520-010-0866-1
45. Skarstein J, Aass N, Fossa SD, Skovlund E, Dahl AA (2000) Anxiety and depression in cancer patients: relation between the Hospital Anxiety and Depression Scale and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire. Journal of psychosomatic research 49 (1):27-34
46. Mystakidou K, Tsilika E, Parpa E, Katsouda E, Galanos A, Vlahos L (2005) Assessment of anxiety and depression in advanced cancer patients and their relationship with quality of life. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 14 (8):1825-1833. doi:10.1007/s11136-005-4324-3
47. de Mol M, Visser S, Aerts JG, Lodder P, van Walree NC, Belderbos HN, Den Oudsten BL (2019) Depressive symptoms and performance status are associated with (Health-Related) Quality of Life in patients with advanced-stage lung cancer: an observational multi-center cohort study. Submitted to BMC Cancer
48. Hsieh CC, Hsiao FH (2017) The effects of supportive care interventions on depressive symptoms among patients with lung cancer: A metaanalysis of randomized controlled studies. Palliative & supportive care 15 (6):710-723. doi:10.1017/S1478951517000335

49. van der Poel MW, Mulder WJ, Ossenkoppele GJ, Maartense E, Hoogendoorn M, Wijermans P, Schouten HC (2015) Factors that influence treatment decision-making in elderly DLBCL patients: a case vignette study. Annals of hematology 94 (8):1373-1379. doi:10.1007/s00277-015-2358-3
50. Al-Batran SE, Hozaeel W, Tauchert FK, Hofheinz RD, Hinke A, Windemuth-Kieselbach C, Hubner A, Burmester M, Koenigsmann M, Wiegand J, Zur Hausen G, Linsse B, Kuhl R, Pauligk C, Arbeitsgemeinschaft Internistische O (2015) The impact of docetaxel-related toxicities on health-related quality of life in patients with metastatic cancer (QoliTax). Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 26 (6):1244-1248. doi:10.1093/annonc/mdv129
51. Kleeberg UR, Tews JT, Ruprecht T, Hoing M, Kuhlmann A, Runge C (2005) Patient satisfaction and quality of life in cancer outpatients: results of the PASQOC study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 13 (5):303-310. doi:10.1007/s00520-004-0727-x
52. Nguyen TV, Anota A, Bredart A, Monnier A, Bosset JF, Mercier M (2014) A longitudinal analysis of patient satisfaction with care and quality of life in ambulatory oncology based on the OUT-PATSAT35 questionnaire. BMC cancer 14:42. doi:10.1186/1471-2407-14-42
53. Hagedoorn M, Uijl SG, Van Sonderen E, Ranchor AV, Grol BM, Otter R, Krol B, Van den Heuvel W, Sanderman R (2003) Structure and reliability of Ware's Patient Satisfaction Questionnaire III: patients' satisfaction with oncological care in the Netherlands. Medical care 41 (2):254-263. doi:10.1097/01.MLR.0000044904.70286.B4
54. Rha SY, Song SK, Lee CE, Park Y, Lee J (2016) Gaps exist between patients' experience and clinicians' awareness of symptoms after chemotherapy: CINV and accompanying symptoms. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 24 (11):4559-4566. doi:10.1007/s00520-016-3295-y
55. Abetz L, Coombs JH, Keininger DL, Earle CC, Wade C, Bury-Maynard D, Copley-Merriman K, Hsu MA (2005) Development of the cancer therapy satisfaction questionnaire: item generation and content validity testing. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 8 Suppl 1:S41-53. doi:10.1111/j.1524-4733.2005.00073.x
56. Cheung K, de Mol M, Visser S, Den Oudsten BL, Stricker BH, Aerts JG (2015) Reliability and validity of the Cancer Therapy Satisfaction Questionnaire in lung cancer. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. doi:10.1007/s11136-015-1062-z
57. Trask PC, Tellefsen C, Espindle D, Getter C, Hsu MA (2008) Psychometric validation of the cancer therapy satisfaction questionnaire. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 11 (4):669-679. doi:10.1111/j.1524-4733.2007.00310.x
58. Park SJ, An SM, Kim SH (2013) Development of a Korean version of the Cancer Therapy Satisfaction Questionnaire (CTSQ): cross-cultural adaptation, reliability, and validity. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 22 (2):431-436. doi:10.1007/s11136-012-0164-0
59. de Mol M, Visser S, den Oudsten BL, Lodder P, van Walree N, Belderbos H, Aerts JG (2019) Frequency of low-grade adverse events and quality of life during chemotherapy determine patients' judgement about treatment in advanced-stage thoracic cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. doi:10.1007/s00520-019-4659-x
60. Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK (2002) Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. Jama 288 (23):3027-3034

61. Kehl KL, Landrum MB, Arora NK, Ganz PA, van Ryn M, Mack JW, Keating NL (2015) Association of Actual and Preferred Decision Roles With Patient-Reported Quality of Care: Shared Decision Making in Cancer Care. JAMA oncology 1 (1):50-58. doi:10.1001/jamaoncol.2014.112
62. Weeks JC, Cook EF, O'Day SJ, Peterson LM, Wenger N, Reding D, Harrell FE, Kussin P, Dawson NV, Connors AF, Jr., Lynn J, Phillips RS (1998) Relationship between cancer patients' predictions of prognosis and their treatment preferences. Jama 279 (21):1709-1714
63. Temel JS, Greer JA, Admane S, Gallagher ER, Jackson VA, Lynch TJ, Lennes IT, Dahlin CM, Pirl WF (2011) Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: results of a randomized study of early palliative care. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 29 (17):2319-2326. doi:10.1200/JCO.2010.32.4459
64. Weeks JC, Catalano PJ, Cronin A, Finkelman MD, Mack JW, Keating NL, Schrag D (2012) Patients' expectations about effects of chemotherapy for advanced cancer. The New England journal of medicine 367 (17):1616-1625. doi:10.1056/NEJMoa1204410
65. Rose JH, O'Toole EE, Dawson NV, Lawrence R, Gurley D, Thomas C, Hamel MB, Cohen HJ (2004) Perspectives, preferences, care practices, and outcomes among older and middle-aged patients with late-stage cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 22 (24):4907-4917. doi:10.1200/JCO.2004.06.050
66. Visser S, de Mol M, Cheung K, van Toor JJ, van Walree NC, Stricker BH, Den Oudsten BL, Aerts J (2018) Treatment Satisfaction of Patients With Advanced Non-Small-cell Lung Cancer Receiving Platinum-based Chemotherapy: Results From a Prospective Cohort Study (PERSONAL). Clinical lung cancer 19 (4):e503-e516. doi:10.1016/j.cllc.2018.03.003
67. Mokhles S, Nuyttens J, de Mol M, Aerts J, Maat A, Birim O, Bogers A, Takkenberg JJM (2018) Treatment selection of early stage non-small cell lung cancer: the role of the patient in clinical decision making. BMC cancer 18 (1):79. doi:10.1186/s12885-018-3986-5



SUMMARY

In general, patients with advanced-stage lung cancer have a limited prognosis and are prone to a decrease in Health Status, Health-Related Quality of Life, and Quality of Life due to disease and treatment-related symptoms. As such, the preservation of their well-being is an important treatment goal. In studies in lung cancer, the effect of treatment on Quality of Life is often analyzed next to the traditional endpoints of disease progression and survival. However, if the definition of Quality of Life as formulated by the World Health Organization is used, these studies merely describe Health Status and Health-Related Quality of Life and not Quality of Life. As a result, the interpretation of studies that use Health Status, Health-Related Quality of Life, and Quality of Life as outcome parameters is hampered by the lack of consensus about the definitions of these concepts.

The main objectives of this thesis are: 1) to enhance the knowledge of physicians, researchers, and other health care professionals about the conceptualization and application of some of the most frequently used patient reported outcomes in lung cancer, 2) to stimulate the use of Quality of Life measurement by testing the psychometric properties of the World Health Organization Quality of Life-BREF instrument (WHOQOL-BREF), 3) to identify clinical and sociodemographic variables that are related to (Health-Related) Quality of Life, 4) to investigate the association between patients' feelings about treatment and (Health-Related) Quality of Life, and 5) to explore the role of Quality of Life in the process of treatment decision making in patients with advanced-stage lung cancer.

In the **introduction** background information about lung cancer and the concepts of Health Status, Health-Related Quality of Life, and Quality of Life is provided. Although these concepts demonstrate some overlap, their focus differs. While Health Status describes at least physical, psychological and social functioning, Health-Related Quality of Life evaluates patients' perception about their functioning and well-being in the above mentioned areas. Quality of Life may also reflect domains like the environment or spirituality. Health-Related Quality of Life is Quality of Life, but focusses on health and is less broadly defined as Quality of Life. In addition, the role of patient reported outcomes in treatment and decision making is discussed. Their role seems to be underestimated given their limited use in clinical practice. This is unfortunate as patient reported outcomes may identify aspects of a patient's well-being that need extra attention during treatment and may provide information regarding the burden of adverse events.

Given that distress refers to a patient's unpleasant psychological (i.e., cognitive, emotional, and behavioral), social, and spiritual experiences**,** Health Status and Health-Related Quality of Life have some overlap with the items measured with the Distress Thermometer. Earlier it was demonstrated that Health Status and Health-Related Quality of Life are associated with survival. In **chapter 1**, the association between the Distress Thermometer and overall survival is investigated**.** The Distress Thermometer score does not appear to be a significant predictor for overall survival. We demonstrate, however, that patients with lung cancer experience less distress compared with patients diagnosed with other types

of cancer. This seems rather unexpected considering the limited prognosis in lung cancer and the severity and number of side effects of treatment these patients experience.

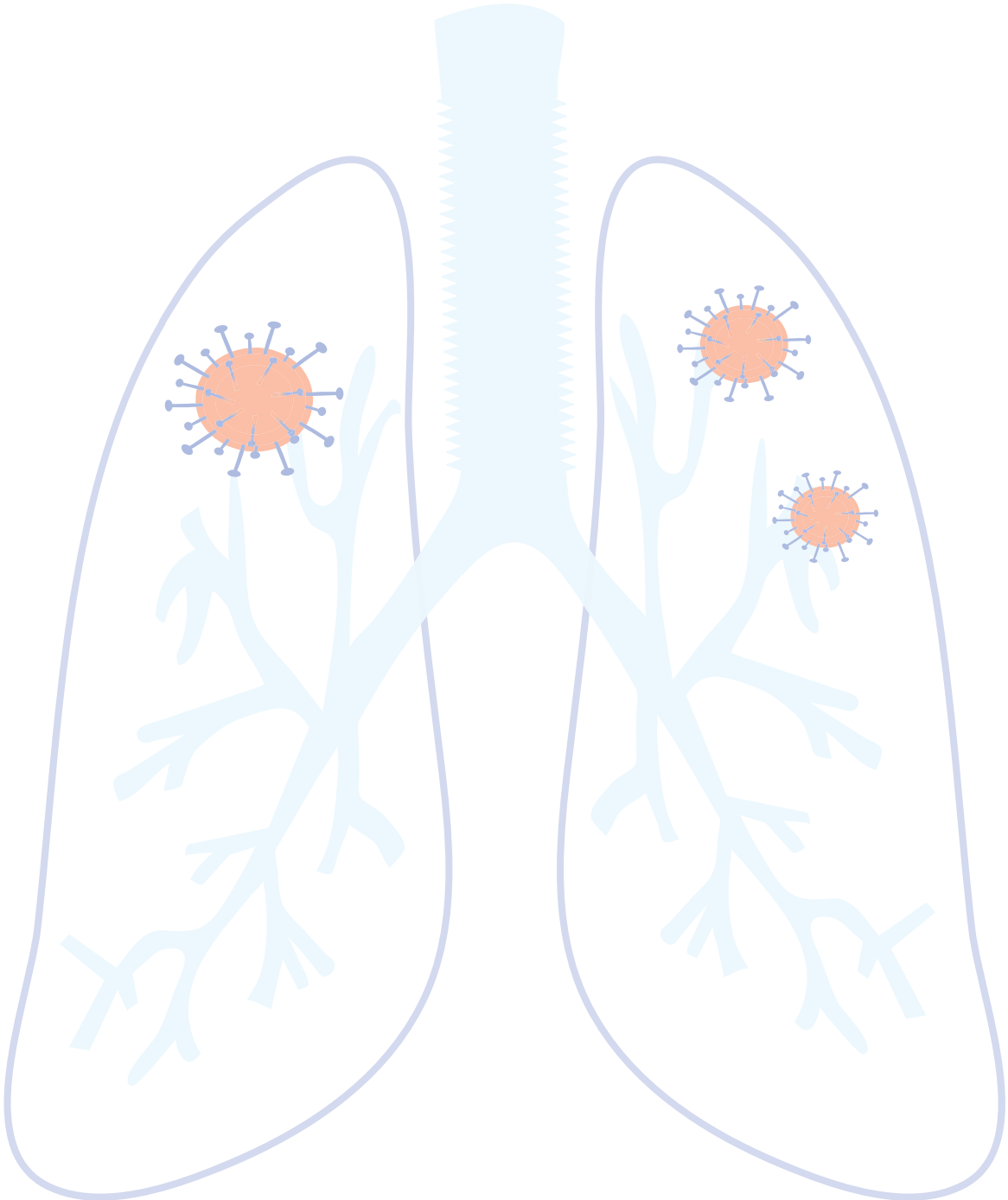
Chapter 2 reports the results of a study in which we investigated the psychometric properties of a Quality of Life instrument, the WHOQOL-BREF. It is demonstrated that this instrument has satisfactory psychometric properties. Moreover, minimal clinically important differences (MCIDs) are calculated which facilitate not only the interpretation of results but also the use of this questionnaire in clinical practice and scientific studies in patients with advanced-stage lung cancer. The association of patient and disease-related factors with (Health-Related) Quality of Life is also investigated. Besides a low Eastern Cooperative Oncology Group performance status, high scores on depressive symptoms are associated with decreased (Health-Related) Quality of Life **(chapter 3)**.

In this thesis three studies that have examined the association of treatment satisfaction with Quality of Life are reported. In the first study, we present results of a psychometric analysis of the Cancer Therapy Satisfaction Questionnaire (CTSQ; **chapter 4**). The CTSQ evaluates the expectations, feelings about side effects, and satisfaction of patients with their treatment. It is demonstrated that application of the CTSQ in patients with advanced-stage lung cancer is reliable and valid. **Chapter 5** describes the associations between CTSQ domains with (Health-Related) Quality of Life. Remarkably, not patients' satisfaction with treatment, but the domain that measures feelings about side effects (CTSQ) is most often associated with (Health-Related) Quality of Life. In addition, patients seem to be especially bothered by low-grade side effects (e.g., nausea, constipation, mucositis, anorexia, fatigue). This emphasizes the need for continuous screening and management of these side effects during treatment. Given the relation with (Health-Related) Quality of Life, the four CTSQ items that evaluate patients' feelings about side effects may be used to screen for decreases in (Health-Related) Quality of Life. Those patients that experience negative feelings about their side effects subsequently could complete a Health-Related Quality of Life and Quality of Life instrument to analyze which areas are affected or not. Knowledge of patients' satisfaction with treatment may provide important supplementary information for shared treatment decision making besides information about patients' treatment toxicities and (Health-Related) Quality of Life. In **chapter 6**, 86% of the patients reported that they probably or definitely will decide to undergo the same treatment again despite experienced side effects or decreases in their well-being. Moreover, it is demonstrated that satisfaction with therapy has a strong relation with the global Health Status/Quality of Life scale of the EORTC QLQ C-30 and the psychological health domain of the WHOQOL-BREF. Age, feelings about side effects, and tumor response appear to be related with satisfaction with therapy. In addition, patients that experienced increases in WHOQOL-BREF facet score (i.e., overall Quality of Life/general health) are more satisfied with treatment than those that reported no changes or decreases in Quality of Life. Considering the results of these two studies, it is proposed that CTSQ data may be used in a similar manor as survival

data of treatments in making shared treatment decisions. For instance, if a considerable proportion of patients who received chemotherapy were often hampered by side effects according to their CTSQ results, newly diagnosed patients with a limited prognosis could take knowledge of these results and make a more considered treatment decision.

Chapter 7 discusses our findings in a study regarding shared decision making in patients with stage I or II lung cancer. It is observed that 81% of patients ideally will make a treatment decision together with their physician and that 74% thinks they are sufficiently involved in this process. About 40% of patients experiences decisional conflict. Feeling to be uninformed and uncertainty about their treatment choice contributes most to the experience of decisional conflict. We advocate that patients need to be adequately informed and that their involvement in treatment decision making is needed in order to improve patient knowledge and reduce decisional conflict.

In the **general discussion** the interpretation of our findings is presented and they are placed into context. Contemplating on our findings, suggestions for future research with patient reported outcomes in patients with lung cancer are provided. In addition, recommendations are made to enable their implementation in clinical practice.



SAMENVATTING

Over het algemeen hebben patiënten met vergevorderde longkanker een beperkte prognose en zijn ze vatbaar voor een afname van hun Gezondheidstoestand, Gezondheidsgerelateerde Kwaliteit van Leven en Kwaliteit van Leven door ziekte en behandeling gerelateerde symptomen. Het waarborgen van hun welzijn is daarom een belangrijk doel van behandeling. Naast de traditionele eindpunten van ziekteprogressie en overleving wordt in studies vaak het effect van de behandeling op Kwaliteit van Leven onderzocht. Echter, wanneer de definitie van Kwaliteit van Leven opgesteld door de Wereldgezondheidsorganisatie wordt gehanteerd beschrijven deze studies met name Gezondheidstoestand en Gezondheidsgerelateerde Kwaliteit van Leven en niet Kwaliteit van Leven. Dit gebrek aan consensus over de definities van deze concepten heeft als gevolg dat de interpretatie van studies met Gezondheidstoestand, Gezondheidsgerelateerde Kwaliteit van Leven en Kwaliteit van Leven als uitkomstmaten wordt belemmerd.

De belangrijkste doelen van dit proefschrift zijn: 1) het verbeteren van de kennis van artsen, onderzoekers en andere gezondheidszorgprofessionals betreffende de conceptualisering en toepassing van enkele van de meest gebruikte patiënt-gerapporteerde uitkomsten in longkanker, 2) het stimuleren van het meten van Kwaliteit van Leven door de psychometrische eigenschappen van de World Health Organization Quality of Life-BREF instrument (WHOQOL-BREF) te testen, 3) het identificeren van klinische en sociodemografische variabelen gerelateerd aan (Gezondheidsgerelateerde) Kwaliteit van Leven, 4) het onderzoeken van de associatie tussen de gevoelens van patiënten over hun behandeling en (Gezondheidsgerelateerde) Kwaliteit van Leven en 5) het verkennen van de rol van Kwaliteit van Leven in het proces van het nemen van behandelbeslissingen bij patiënten met vergevorderde longkanker.

In de **introductie** wordt achtergrondinformatie gegeven over longkanker en de concepten van Gezondheidstoestand, Gezondheidsgerelateerde Kwaliteit van Leven en Kwaliteit van Leven. Hoewel deze concepten inhoudelijk enige overlap vertonen, verschilt de focus. Terwijl Gezondheidstoestand ten minste fysiek, psychologisch en sociaal functioneren beschrijft, evalueert Gezondheidsgerelateerde Kwaliteit van Leven de beleving van patiënten over hun functioneren en welzijn met betrekking tot bovenstaande gebieden. Kwaliteit van Leven kan ook domeinen zoals de omgeving of spiritualiteit reflecteren. Gezondheidsgerelateerde Kwaliteit van Leven is Kwaliteit van Leven, maar focust op gezondheid en is minder breed gedefinieerd als Kwaliteit van Leven. Daarnaast wordt de rol van patiënt-gerapporteerde uitkomsten tijdens de behandeling en in het nemen van beslissingen besproken. Hun rol lijkt te worden onderschat afgaande op het beperkte gebruik in de klinische praktijk. Dat is jammer, want patiënt-gerapporteerde uitkomsten kunnen aspecten van een patiënt zijn/haar welzijn identificeren die extra aandacht vereisen tijdens de behandeling en informatie geven over de belasting van bijwerkingen.

Gezondheidstoestand en Gezondheidsgerelateerde Kwaliteit van Leven hebben enige overlap met de items van de Distress Thermometer, omdat distress de onplezierige psy-

chologische (d.w.z. cognitieve, emotionele en gedragsmatige), sociale en spirituele ervaringen van patiënten beschrijft. Het werd eerder vastgesteld dat Gezondheidstoestand en Gezondheidsgerelateerde Kwaliteit van Leven geassocieerd zijn met overleving. In **hoofdstuk 1** wordt de associatie tussen de Distress Thermometer en overleving onderzocht. De Distress Thermometer score blijkt geen significante voorspeller voor overleving te zijn. Echter, we tonen wel aan dat patiënten met longkanker minder distress ervaren dan patiënten die gediagnosticeerd zijn met een andere vorm van kanker. Dit is een tamelijk onverwachte uitkomst gezien de beperkte prognose van longkanker en de ernst en het aantal bijwerkingen van de behandeling die patiënten ervaren.

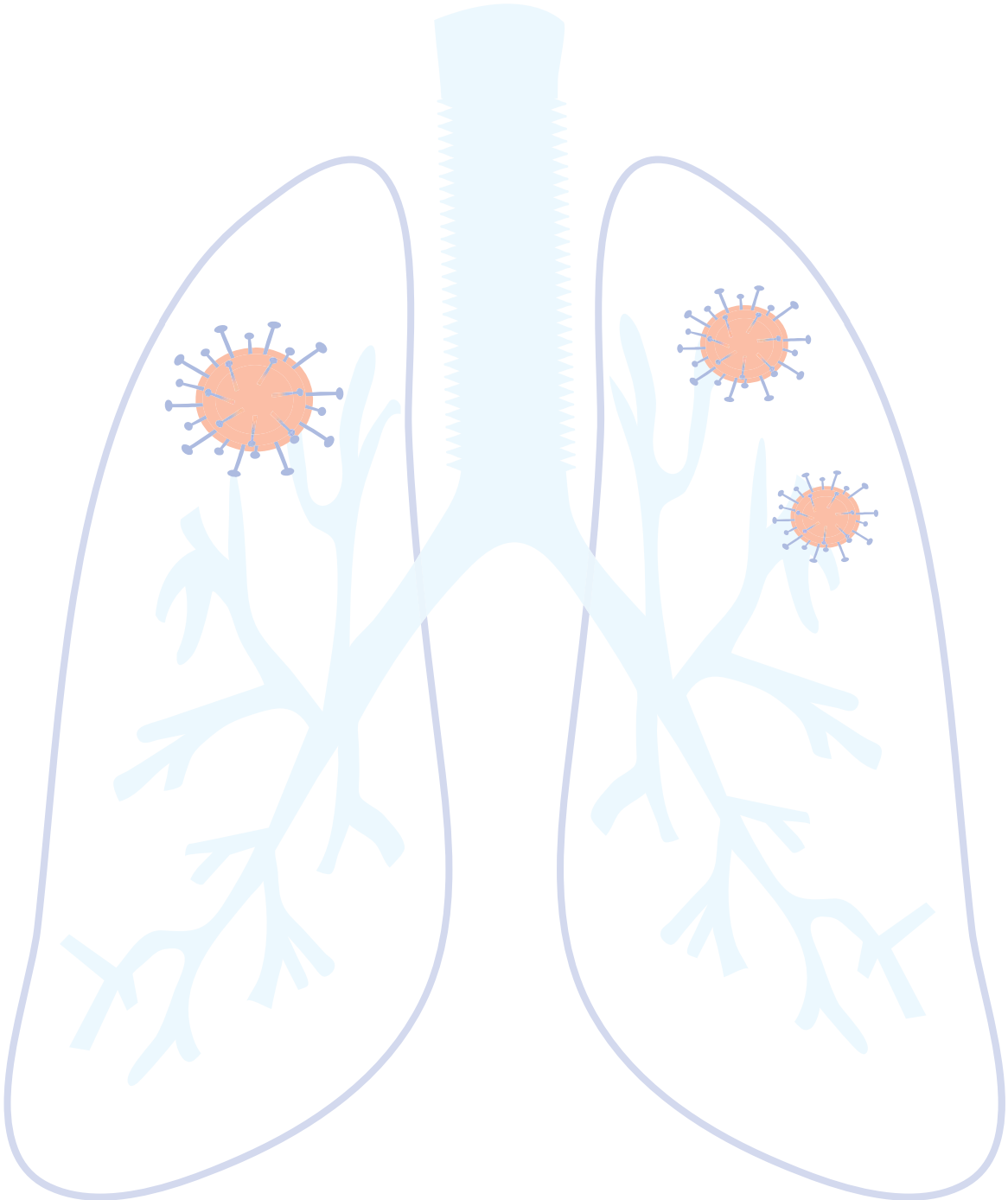
Hoofdstuk 2 rapporteert de resultaten van een studie waarin we de psychometrische eigenschappen van een Kwaliteit van Leven instrument, de WHOQOL-BREF, hebben onderzocht. Er wordt aangetoond dat dit instrument beschikt over adequate psychometrische eigenschappen. Bovendien worden minimaal klinisch belangrijke verschillen berekend die niet alleen de interpretatie van resultaten faciliteren, maar ook het gebruik van deze vragenlijst in de klinische praktijk en in wetenschappelijke studies bij patiënten met vergevorderde longkanker. De associatie tussen patiënt en ziekte gerelateerde factoren en (Gezondheidsgerelateerde) Kwaliteit van Leven wordt ook onderzocht. Naast een lage Eastern Cooperative Oncology Group performance status zijn ook hoge scores voor depressieve symptomen gerelateerd aan verminderde (Gezondheidsgerelateerde) Kwaliteit van Leven **(hoofdstuk 3)**.

In dit proefschrift worden drie studies beschreven die de associatie tussen tevredenheid met behandeling en Kwaliteit van Leven hebben onderzocht. In de eerste studie presenteren we de resultaten van een psychometrische analyse van de Cancer Therapy Satisfaction Questionnaire (CTSQ; **hoofdstuk 4**). De CTSQ beoordeelt de verwachtingen, gevoelens omtrent bijwerkingen en tevredenheid van patiënten over hun behandeling. Er wordt aangetoond dat toepassing van de CTSQ in patiënten met vergevorderde longkanker betrouwbaar en valide is. **Hoofdstuk 5** beschrijft de relaties tussen de CTSQ domeinen en (Gezondheidsgerelateerde) Kwaliteit van Leven. Opmerkelijk genoeg is niet de tevredenheid van patiënten met de behandeling, maar het domein dat de gevoelens omtrent bijwerkingen meet het vaakst geassocieerd met (Gezondheidsgerelateerde) Kwaliteit van Leven. Bovendien lijken patiënten met name last te hebben van laaggradige bijwerkingen (bijv. misselijkheid, constipatie, mucositis, anorexie, vermoeidheid). Dit benadrukt de waarde van het continu screenen op en behandelen van deze bijwerkingen tijdens de behandeling. Vanwege de relatie met (Gezondheidsgerelateerde) Kwaliteit van Leven zouden de vier CTSQ items die de gevoelens van patiënten over bijwerkingen evalueren gebruikt kunnen worden om te screenen op een afname van (Gezondheidsgerelateerde) Kwaliteit van Leven. Patiënten die negatieve gevoelens over bijwerkingen ervaren zouden vervolgens een Gezondheidsgerelateerde Kwaliteit van Leven en Kwaliteit van Leven vragenlijst kunnen invullen om te bepalen in welke domeinen zij problemen ervaren.

Naast informatie over bijwerkingen van behandelingen en de (Gezondheidsgerelateerde) Kwaliteit van Leven van patiënten, zou ook kennis van de tevredenheid van patiënten met de behandeling belangrijke aanvullende informatie kunnen geven. Uit **hoofdstuk 6** blijkt dat 86% van de geïncludeerde patiënten waarschijnlijk dan wel zeker zullen beslissen om dezelfde behandeling nogmaals te ondergaan ondanks de ervaren bijwerkingen of afname in hun welzijn. Daarnaast wordt aangetoond dat tevredenheid met behandeling een sterke relatie heeft met de globale Gezondheidstoestand/Kwaliteit van Leven/ Kwaliteit van Leven schaal van de European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 en het psychologische gezondheid domein van de WHOQOL-BREF. Leeftijd, gevoelens over bijwerkingen en tumor respons blijken gerelateerd te zijn aan tevredenheid met behandeling. Bovendien zijn patiënten met een toename van de WHOQOL-BREF facet score (d.w.z. algehele Kwaliteit van Leven/algemene gezondheid) meer tevreden over de behandeling dan de patiënten die geen verschil of een afname in Kwaliteit van Leven aangaven. We stellen voor, gelet op de resultaten van deze twee studies, CTSQ data op een vergelijkbare wijze te gebruiken als overlevingsdata van behandelingen bij het nemen van gedeelde behandelbeslissingen. Bijvoorbeeld, als een redelijk groot deel van de patiënten die behandeld zijn met chemotherapie afgaande op hun CTSQ resultaten vaak werden belemmerd door bijwerkingen dan zouden nieuw gediagnosticeerde patiënten met een beperkte prognose hier kennis van kunnen nemen en een meer overwogen behandelbeslissing kunnen nemen.

Hoofdstuk 7 bediscussieert onze resultaten van een studie betreffende het nemen van gedeelde behandelbeslissingen bij patiënten met stadium I of II longkanker. Er wordt geobserveerd dat 81% van de patiënten idealiter een behandelbeslissing samen met hun dokter zal willen maken en dat 74% vindt dat ze voldoende betrokken zijn bij dit proces. Ongeveer 40% van de patiënten ervoer een innerlijk conflict over hun behandelbeslissing. Het gevoel niet geïnformeerd te zijn en onzekerheid over de juistheid van de behandelkeuze droeg het meest bij aan het innerlijk conflict over hun behandelbeslissing. We bevelen het adequaat informeren van patiënten en hun betrokkenheid bij het nemen van behandelbeslissingen daarom aan ten einde de kennis van patiënten en hun innerlijk conflict over de behandelbeslissing te verminderen

In de **algemene discussie** wordt een interpretatie van onze bevindingen gepresenteerd en worden deze in context geplaatst. Onze bevindingen in overweging nemende worden suggesties gegeven voor toekomstig onderzoek met patiënt-gerapporteerde uitkomsten bij patiënten met longkanker. Bovendien worden aanbevelingen gedaan voor hun implementatie in de klinische praktijk.



PHD PORTFOLIO

PhD candidate	: Mark de Mol
Erasmus MC department	: respiratory medicine
Amphia Hospital department	: respiratory medicine
PhD period	: 2014 – 2020
Promotor	: prof. dr. J.G.J.V. Aerts
Copromotor	: dr. B.L. den Oudsten

PHD TRAINING

General courses

2014 Statistics course I: SPSS and describing statistics
Statistics course II: Variance analysis and linear regression analysis in SPSS
Statistics course III: Survival analysis, logistic regression analysis, and sensitivity and specificity
Tilburg University, department of medical psychology, Center of Research on Psychology in Somatic diseases (CORPS), Tilburg, The Netherlands

2015 Basic Course on Regulations and Organisation for clinical investigators
Erasmus MC, Rotterdam, The Netherlands

2016 English writing course: Effective scientific writing in English for publication in biomedical journals
Lisette van Hulst, Text and Training

2019 Integrity in Science course, Erasmus MC, Rotterdam, The Netherlands

Poster presentations

2016 European Lung Cancer Conference, Geneva, Switzerland
Title: 'Depressive symptoms, performance score, and personality traits as predictors of (health related) quality of life in patients with advanced stage lung cancer'
Title: 'Patients' feelings about side-effects are predictive for (health related) quality of life in patients with advanced stage lung cancer treated with chemotherapy'

International Conferences

2014 VESTA Investigators meeting, Frankfurt, Germany

2016 European Lung Cancer Conference, Geneva, Switzerland

2016 Springer Lung Cancer International Preceptorship, Vienna, Austria

TEACHING ACTIVITIES

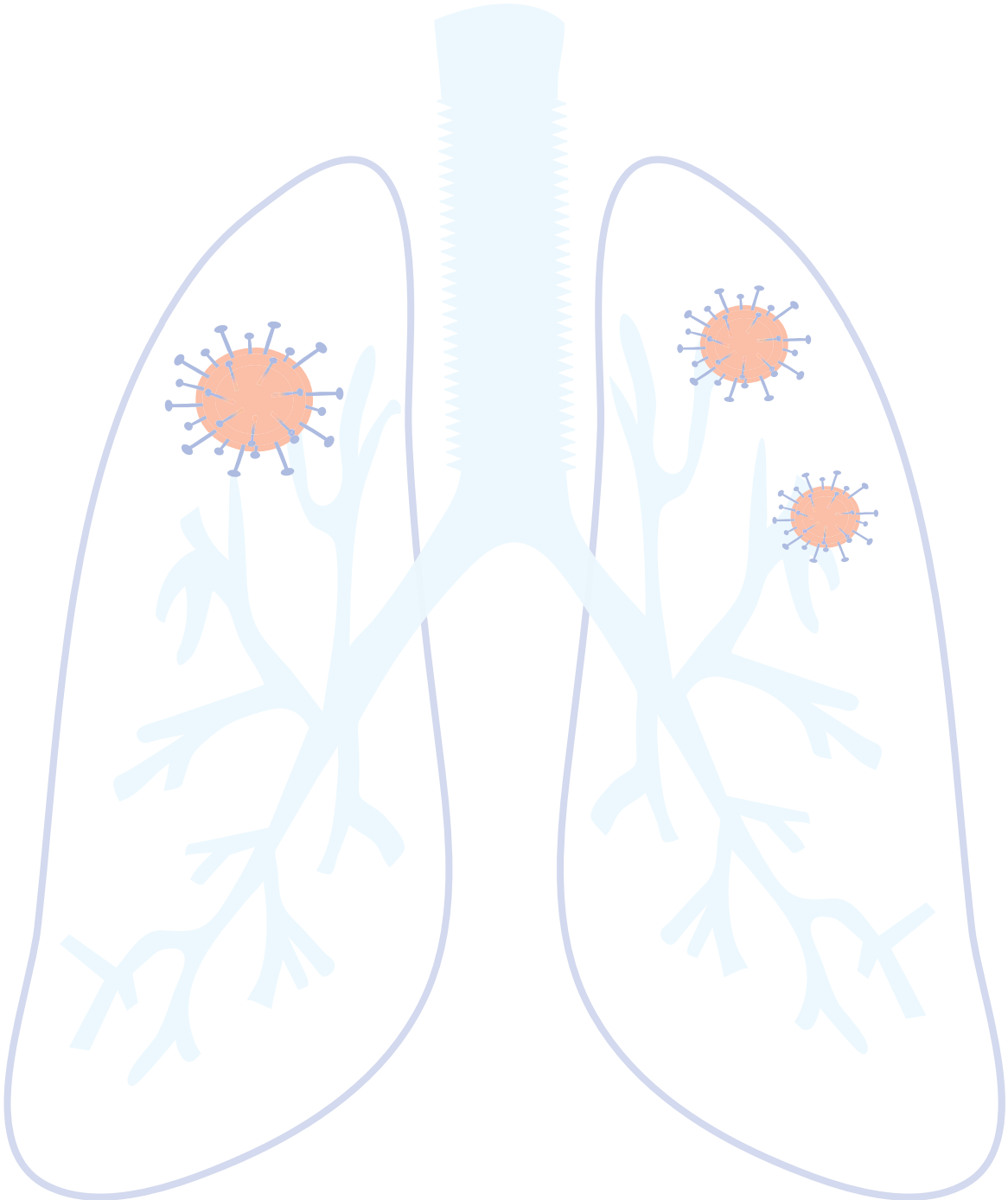
Lectures

2017 Tilburg University: Astma and Quit Smoking, Tilburg, The Netherlands

2018 Tilburg University: Astma and Quit Smoking, Tilburg, The Netherlands

Supervising students

2014 Master student, research internship, Amphia Hospital, Breda, The Netherlands



LIST OF PUBLICATIONS

MANUSCRIPTS IN THIS THESIS

de Mol M, Visser S, den Oudsten BL, Lodder P, van Walree N, Belderbos H, Aerts JG
Frequency of low-grade adverse events and Quality of Life during chemotherapy determine patients' judgement about treatment in advanced-stage thoracic cancer.
Support Care Cancer. 2019 Jan; doi: 10.1007/s00520-019-4659-x. [Epub ahead of print]

de Mol M, Visser S, Aerts JGJV, Lodder P, de Vries J, den Oudsten BL
Satisfactory results of a psychometric analysis and calculation of minimal clinically important differences of the World Health Organization Quality of Life-BREF questionnaire in an observational cohort study with lung cancer and mesothelioma patients.
BMC Cancer. 2018 Nov; 18(1): 1173

Visser S, **de Mol M**, Cheung K, van Toor JJ, van Walree NC, Stricker BH, Den Oudsten BL, Aerts JGJV
Treatment satisfaction of patients with advanced non-small-cell lung cancer receiving platinum-based chemotherapy: results from a prospective cohort study (PERSONAL).
Clin Lung Cancer. 2018 Jul; 19(4): e503-e516

Mokhles S, Nuyttens JJME, **de Mol M**, Aerts JGJV, Maat APWM, Birim Ö, Bogers AJJC, Takkenberg JJM
Treatment selection of early-stage non-small cell lung cancer: the role of the patient in clinical decision making.
BMC Cancer. 2018;18(1): 79

de Mol M, den Oudsten BL, Aarts M, Aerts JGJV
The Distress Thermometer as a predictor for survival in stage III lung cancer patients treated with chemotherapy.
Oncotarget. 2017 May; 8(22): 36743-36749

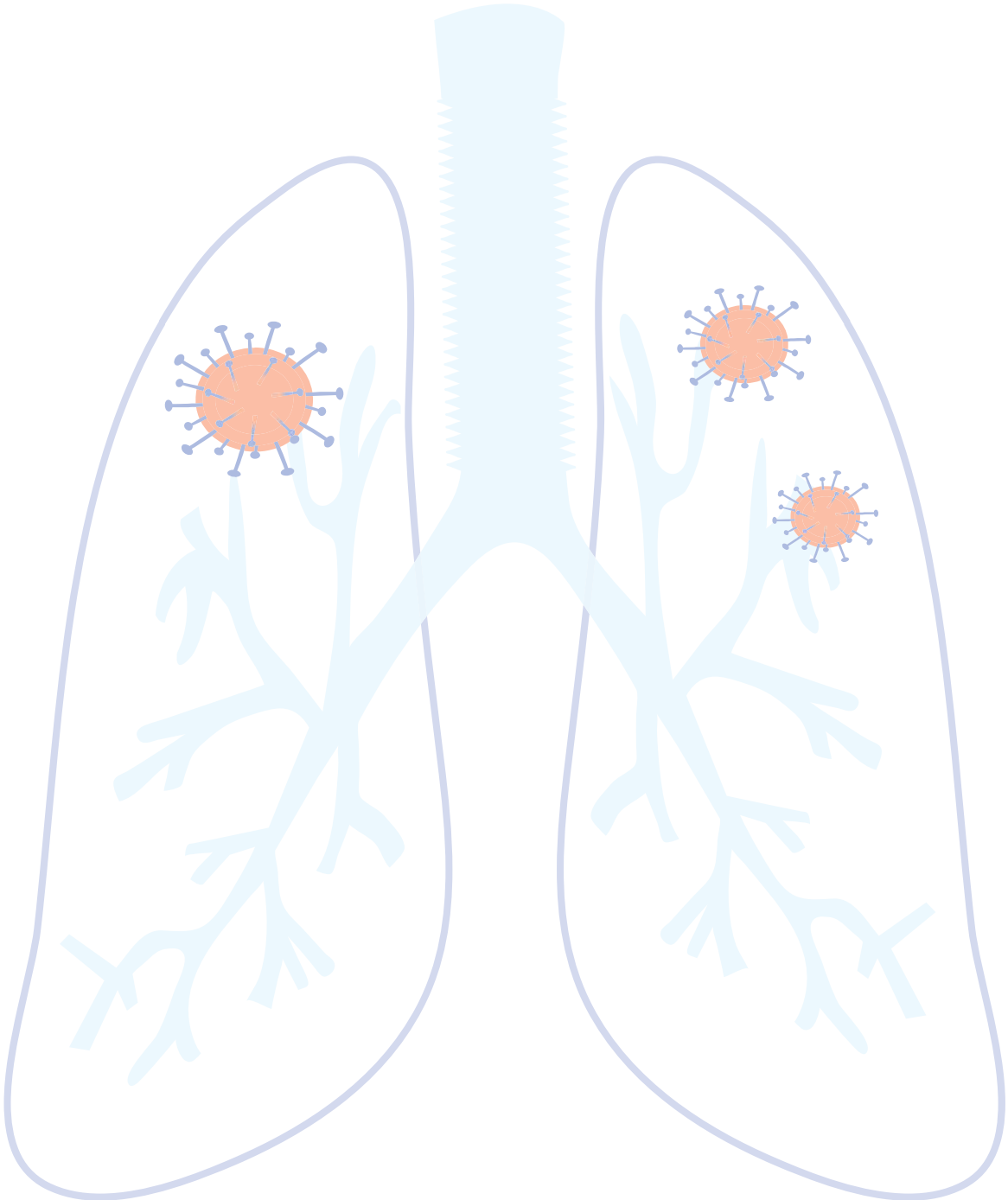
Cheung K*, **de Mol M***, Visser S, Den Oudsten BL, Stricker BH, Aerts JG
Reliability and validity of the Cancer Therapy Satisfaction Questionnaire in lung cancer.
Qual Life Res. 2016 Jan; 25(1): 71-80

SUBMITTED MANUSCRIPTS

de Mol M, Visser S, Aerts JGJV, Lodder P, van Walree NC, Belderbos H, den Oudsten BL.
Depressive symptoms and performance status are associated with (Health-Related) Quality of Life in patients with advanced-stage lung cancer: an observational multi-center cohort study.

OTHER PUBLISHED MANUSCRIPTS

de Goeie PL, Smit EF, Waasdorp C, Schram MTB, Kaijen-Lambers MEH, Bezemer K, **de Mol M**, Hartemink KJ, Nuyttens JJME, Maat APWM, Hegmans JPJJ, Hendriks RW, Senan S, Aerts JGJV.
Stereotactic Ablative Radiotherapy Induces Peripheral T-Cell Activation in Patients with Early-Stage Lung Cancer.
Am J Respir Crit Care Med. 2017 Nov; 196(9): 1224-1227



ABOUT THE AUTHOR

Mark de Mol was born on august 22th 1985, in Dordrecht, The Netherlands. He graduated in 2004 from Insula College Gymnasium in Dordrecht and started medical school in Rotterdam. He completed his studies with a clinical research project about the diagnostic value of the measurement of galactomannan in bronchoalveolar lavage fluid in diagnosing invasive pulmonary aspergillosis in immunocompromised pediatric patients at the department of pediatric respiratory medicine of the Sophia Children's Hospital under the supervision of H.M. Janssens, MD, PhD. After receiving both his 'doctorandus' degree in Medicine as well as his medical degree in 2010, he started to work as a resident not in training at the department of internal medicine of the former Havenziekenhuis hospital in Rotterdam supervised by P.J. Wismans, MD, PhD. A year later, he started working as a resident not in training at the department of respiratory medicine of the Amphia hospital in Breda under the supervision of R.S. Djamin, MD, PhD. In 2014, he started the work described in this thesis under the supervision of prof. J.G.J.V. Aerts, MD, PhD and B.L. den Oudsten, PhD at the department of respiratory medicine of the Erasmus University Medical Center and Amphia hospital and the department of Medical and Clinical Psychology, Centre of Research on Psychological and Somatic Disorders (CoRPS) of the Tilburg University. As of 2016, he is working as a resident in training at the department of respiratory medicine of the Amphia hospital in Breda supervised by M.J.J.H. Grootenboers, MD, PhD.