INTRODUCTION

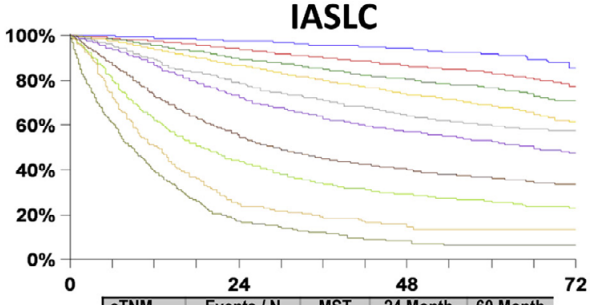
LUNG CANCER

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