PHYSICIANS’ VIEWS ON PALLIATIVE CARE AND ASSESSMENT OF SYMPTOMS OF NON-SMALL CELL LUNG CANCER PATIENTS

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You can't go back and change the beginning, but you can start where you are and change the ending.

C.S. Lewis
ABSTRACT

Maria Silvoniemi

Physicians’ Views on Palliative Care and Assessment of Symptoms of Non-Small Cell Lung Cancer Patients

University of Turku, Faculty of Medicine, Department of Pulmonary Diseases and Clinical Allergology, Doctoral Programme in Clinical Research (DPCR), Department of Oncology and Radiotherapy - Annales Universitatis Turkuensis, Turku, Finland, 2018

This study examined physicians’ views on palliative care and assisted dying and assessed non-small cell lung cancer (NSCLC) patients’ symptoms and quality of life (QOL) during chemotherapy.

Finnish physicians expressed uncertainty about the management of end-of-life (EOL) situations and advanced cancer symptoms. Additional training needs were recognized. At the time the survey was carried out, 10% of oncologists and 19% of other physicians supported the legalization of euthanasia. Most physicians believed that proper palliative care might reduce requests for euthanasia.

A six-month symptom survey was conducted among NSCLC patients receiving chemotherapy. The patients had several comorbidities, most frequently cardiovascular diseases and lung diseases. The most severe symptoms were pain, cough, dyspnea, fatigue and insomnia. The lowest scores for functional scales were at the baseline for physical and role functioning. The patients' global QOL was relatively low at the baseline. Women had a better QOL and suffered less from pain than men during the study. Pain intensity increased during the study, especially in men, and physical functioning deteriorated. A high level of pain and low social and role functioning predicted poorer survival. The Edmonton Symptom Assessment Scale (ESAS) was found to be a reliable tool to accomplish frequent symptom assessment for real time use.

In conclusion, symptom assessment and control and quality-of-life issues are an important focus in the treatment of advanced lung cancer. The quality of care could be improved with better training of health care professionals, and symptom assessment could improve the awareness and recognition of the symptoms.

Keywords: palliative care, physicians’ perceptions, end-of-life care, non-small cell lung cancer, symptom assessment, quality of life, chemotherapy, ESAS
TIIVISTELMÄ

Maria Silvoniemi

Lääkäreiden näkemyksiä palliatiivisesta hoidosta ja oireiden arviointi eipi-enisoluista keuhkosyöpää sairastavilla potilailla

Turun yliopisto, Lääketieteellinen tiedekunta, Keuhkosairausoppi ja kliininen allergologia, Turun kliininen tohtorihjelma (TKT), Kliininen syövätautioppi - Annales Universitatis Turkuensis, Turku, Suomi, 2018

Tämä tutkimus kartoitti lääkäreiden näkemyksiä palliatiivisesta hoidosta ja eutanasiasta sekä eipi-enisoluista keuhkosyöpää sairastavien potilaiden oireita ja elämänlaatua solunsalpaajahoidon aikana.

Suomalaiset lääkärit kokivat epävarmuutta syöpään liittyvien oireiden hoidossa ja elämän loppuvaiheen kysymysten käsittelemisessä. Oirehoidon toteuttamiseen toivottiin lisäkoulutusta. Eutanasian laillistamista kannatti 10% syövätaulaisia erikoislääkäriä ja 19% muista tutkimuskyselyyn vastanneista lääkäreistä. Suurin osa lääkäreistä arvioi asianmukaisen palliatiivisen hoidon vähentävän mahdollisia eutanasiaapyntöjä.


Keuhkosyövän hoitoa tulisi arvioida elinaikahyödyn lisäksi oireiden lievittymisen ja elämänlaadun näkökulmasta. Hoidon laatua voitaisiin parantaa lääkäreiden koulutuksen lisäämisellä ja säännöllisen oirekartoituksen avulla.

Avainsanat: palliatiivinen hoito, lääkärin näkemys, oirehoito, elämänlaatu, eipi-enisoluinen keuhkosyölä, oirekysely, solunsalpaajahoito, ESAS
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<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
</tr>
<tr>
<td>ALK</td>
<td>Anaplastic lymphoma kinase</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
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<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
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<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CRF</td>
<td>Cancer-related fatigue</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>DNR</td>
<td>Do-not-resuscitate</td>
</tr>
<tr>
<td>EAPC</td>
<td>European Association for Palliative Care</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency departments</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
</tr>
<tr>
<td>EOL</td>
<td>End-of-life</td>
</tr>
<tr>
<td>ESAS</td>
<td>Edmonton Symptom Assessment Scale</td>
</tr>
<tr>
<td>ESAS-r</td>
<td>Revised Edmonton Symptom Assessment Scale</td>
</tr>
<tr>
<td>ESMO</td>
<td>European Society for Medical Oncology</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organization of Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Fluorodeoxyglucose positron emission tomography</td>
</tr>
<tr>
<td>IAHPC</td>
<td>International Association for Hospice and Palliative Care</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NOS</td>
<td>Not otherwise specified</td>
</tr>
<tr>
<td>NRS</td>
<td>Numeric rating scale</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
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<tr>
<td>NSCLC</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>PAS</td>
<td>Physician-assisted suicide</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Programmed death ligand 1</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient-reported outcome</td>
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<td>PS</td>
<td>Performance status</td>
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Abbreviations

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<tr>
<td>QLQ-C30</td>
<td>EORTC Quality of Life Questionnaire</td>
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<tr>
<td>QLQ-LC13</td>
<td>EORTC Lung Cancer-Specific Questionnaire</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>ROS1</td>
<td>ROS1 proto-oncogene receptor tyrosine kinase</td>
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<tr>
<td>SABR</td>
<td>Stereotactic ablative radiotherapy</td>
</tr>
<tr>
<td>TNM</td>
<td>The classification of malignant tumors (Tumor-Node-Metastasis)</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>Zubrod/Z</td>
<td>Scoring system of the performance status of the patient</td>
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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which are referred to in the text by the Roman numerals I-IV. Some unpublished data are also presented.


IV. Silvoniemi M, Vasankari T, Löyttyniemi E, Valtonen M, Salminen E. Quality of life and symptom development among NSCLC patients receiving chemotherapy. [manuscript]

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1 INTRODUCTION

Substantial advancements in cancer treatment have been introduced during recent decades. However, advanced cancer disease often turns out to be incurable, leading to a need for palliative and end-of-life (EOL) care. The importance of effective symptom control and high-quality EOL care for cancer patients was brought to discussion by Cicely Saunders, the pioneer of palliative care. In 1967, she founded St Christopher's Hospice, the world’s first modern hospice, in London. Palliative care has taken quantum leaps forward since then and has gained a central role globally in the developing fields of health care (Clark 1999, Clark 2007, Sepúlveda et al. 2002, Kelley et al. 2015). Brennan stated in 2007 that palliative care should be considered a human right (Brennan 2007).

The management of progressive cancer disease tends to be challenging, since a growing need typically exists for more intensive interventions during the course of treatment. Some patients may experience insufficient symptom alleviation. Furthermore, overwhelming suffering may even lead one to wish for death. Palliative care professionals are mainly against legalizing euthanasia or physician-assisted suicide (PAS), although the debate on legalizing them is actively ongoing especially in Western European countries. Palliative care is defined neither to hasten nor postpone death and therefore euthanasia and PAS are excluded from palliative care. The European Association for Palliative Care (EAPC) and the International Association for Hospice and Palliative Care (IAHPC) have both given statements that patients requesting euthanasia or PAS should first be offered appropriate palliative care (Miccinesi et al. 2005, Radbruch et al. 2016, De Lima et al. 2017).

The encountering of cancer patients and discussions concerning treatment options, symptoms and EOL care can be challenging to health care professionals. Adequate communication skills are needed in these situations and physician training has been shown to reduce emotional stress in these situations (Ramirez et al. 1995, Bousquet et al. 2015).

Lung cancers are the leading causes of cancer-related deaths in the world (Cheng et al. 2016). Non-small cell lung cancer (NSCLC), as a major subgroup of lung cancers, is often inoperable at the time of diagnosis due to local advancement or distant metastases (Kocher et al. 2015). No curative treatment is available in those situations. New treatments have emerged in recent years, and the treatment outcomes have improved, but survival rates for the general lung cancer population remain low. Five-year survival rates of 10 % for men and of 16% for women have been reported in Finland (Finnish Cancer Registry 2018).
The focus of the treatment of locally advanced or metastatic NSCLC is to prolong survival and alleviate symptoms. A minority of the patients are suitable for targeted treatments that generally have fewer toxicities and better response rates than other systemic treatments. Immunotherapy is a therapy of choice in specific situations, yet chemotherapy is still the backbone of treatment for the majority of metastatic and advanced NSCLC patients at some point of the disease (Hanna et al. 2017, Ettinger et al. 2018).

NSCLC patients are frequently symptomatic at the time of diagnosis since the metastatic disease contributes to multiple symptoms (Barbera et al. 2010a). Therefore, it is of utmost importance that the modest 9% absolute increase in 1-year survival gained with chemotherapy is obtained without jeopardizing the patient’s quality of life (QOL) (Novello et al. 2016). Chemotherapy causes toxicity, but if the tumour burden decreases the symptoms typically improve concomitantly. Thus, minor toxicity can be accepted if the symptoms caused by the cancer are alleviated and QOL maintained.

The response to chemotherapy is mainly evaluated using radiological imaging (mainly computed tomography). Nevertheless, the reasonableness to continue the treatment should also be based on the QOL, symptoms, and preferences of the patient. The QOL should not deteriorate too much during chemotherapy. Patients have reported the improvements gained for survival as valuable only if their symptoms are mild. Patients with severe symptoms may consider even minor survival benefits harmful (Bridges et al. 2012).

Patients’ symptoms and QOL must be assessed regularly to gain this patient perspective. This repeated assessment is the only reliable way to observe the response of symptoms to chemotherapy. Health care professionals may easily underestimate the patient’s symptoms without regular assessment (Laugsand et al. 2010).

Most patients are symptomatic and have a poor prognosis as the median survival is still 12–13 months in advanced NSCLC (Noonan et al. 2015) despite developments in the treatment modalities. The patients need information regarding the disease, treatment options, symptom management, and prognosis, while their personal needs should also be taken into consideration. Better knowledge of these essential facts has been shown to improve patients’ adherence to the treatment (Lin et al. 2014).

This study’s focus was to assess the physicians’ knowledge of symptom management and evaluate NSCLC patients’ symptoms. The study evaluated the views, fears, and training needs among Finnish physicians representing different specialities responsible for EOL care. The goal of the patient-focused approach
Introduction

was to evaluate the symptoms experienced by the patients during chemotherapy, which could optimally lead to improvements in the management of symptoms of NSCLC patients, and to understand the comprehensive benefit and feasibility of chemotherapy in advanced NSCLC.
2 REVIEW OF LITERATURE

2.1 Palliative care and end-of-life care

The World Health Organization (WHO) defines palliative care as “an approach that improves the QOL of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care intends neither to hasten nor postpone death” (WHO 2014).

Palliative care should be given to patients based on need, not only based on diagnosis or the disease’s prognosis (Higginson et al. 1999). Parallel with cancers, comprising the largest group of patients requiring palliative care, there are also several other diseases that create a remarkable need for palliative care efforts. These include many chronic pulmonary diseases, cardiovascular diseases, neurological diseases and kidney failure (Traue et al. 2005).

The current recommendation is to offer palliative care already in the early course of the disease and to integrate palliative care into standard oncologic care during the whole disease trajectory (Bakitas et al. 2009, Ferrell et al. 2017, Gaertner et al. 2017). Early palliative care in NSCLC has been shown to lead to better QOL, longer survival, lower rates of symptoms including depression, and less aggressive EOL treatment compared to standard care (Temel et al. 2010, Ferrell et al. 2015).

The core of palliative care is to maintain a good QOL for patients with a severe disease. The QOL concept is complex but is usually understood as a patient’s overall satisfaction with life and state of well-being. It comprises physical, psychological, emotional and social factors (Bottomley 2002, Camps et al. 2009). An improved QOL and survival have become important goals for cancer therapies during the past two decades.

Palliative care near death is called end-of-life (EOL) care. The alleviation of the patient’s physical, emotional and spiritual suffering is of utmost importance as the patient and the family are preparing for death. Discussions with the patient concerning EOL issues are essential to good EOL care; these should cover a patient’s fears and hopes concerning EOL care and dying and treatment preferences (Osinski et al. 2017).
2.2 Euthanasia and physician assisted suicide

The European Association for Palliative Care (EAPC) defines euthanasia as “a physician (or other person) intentionally killing a person by the administration of drugs, at that person’s voluntary and competent request” (Radbruch et al. 2016). The legalization of euthanasia has recently been at the center of an ongoing discussion; it is legal in the Netherlands, Belgium, Luxembourg, Colombia and Canada (Steck et al. 2013, Emanuel et al. 2016).

Passive euthanasia is an occasionally used term for withholding or withdrawing a futile treatment, in other words, when “letting the patient die” in a hopeless situation. EAPC has recommended that the term passive euthanasia should not be used as it is “a contradiction in words” and such a term actually cannot exist (Materstvedt et al. 2003, Gesang 2008, Radbruch et al. 2016). IAHPC uses instead the term “nontreatment decisions” for these situations (De Lima et al. 2017).

Physician-assisted suicide (PAS) is defined by EAPC as “a physician intentionally helping a person to terminate his or her life by providing drugs for self-administration, at that person’s voluntary and competent request” (Radbruch et al. 2016). Switzerland first decriminalized assisted suicide and PAS has subsequently been legalized in the Netherlands, Belgium, Luxembourg, Canada, Colombia and in the US states of Oregon, Washington, Montana, Vermont, California, Colorado and in the District of Columbia (Washington, D.C.). In addition, the legal status of PAS is somewhat unclear in several countries (Emanuel et al. 2016, Snyder Sulmasy et al. 2017). Terms PAS and euthanasia are often called together as assisted dying (Boudreau et al. 2013).

Palliative sedation means a “monitored use of medications intended to induce a state of decreased or absent awareness to a patient to relieve the burden of otherwise intolerable suffering”. This is used to relieve severe symptoms in the EOL situation and does not impact the patient’s survival. Thus, it is part of palliative care, contrary to assisted dying, which directly conflicts with the palliative care definition (Cherny et al. 2014, De Lima et al. 2017).

The debate on legalizing euthanasia or PAS is ongoing, especially in the Western European countries (Emanuel et al. 2016). The public’s acceptance of euthanasia or PAS differs among the European countries, mainly depending on the cultural and social factors and religiousness of the country (Miccinesi et al. 2005). A study published in 2002 demonstrated that 48% of the public would accept euthanasia in Finland (Ryynänen et al. 2002). It has recently been reported that 70–80% of the Finnish public support the legalization of euthanasia (www.hs.fi/kotimaa/art-2000005476276.html). The results vary depending on the study design. A web-
based survey reported that 43% of the general public strongly agreed that Finland would benefit from legalizing euthanasia (Terkamo-Moisio et al. 2017).

2.3 Physicians’ perspectives on palliative care and assisted dying

Seriously ill patients have benefitted from the evolution of palliative care practice in recent decades. However, professional challenges have been incompletely met among health-care employees working in this field. A majority of health-care professionals and students in all fields have expressed a need for advanced expertise in palliative care and a requirement for more training in this field. EOL discussions are especially felt difficult and effective training in communication skills seems to be required (Goel et al. 2014, Chiu et al. 2015, Kelley et al. 2015).

Studies indicate that physicians frequently oppose the legalisation of assisted dying, despite the common public acceptance (McCormack et al. 2012, Snyder Sulmasy et al. 2017). The American College of Physicians has stated that PAS is not a solution or a therapy to difficult EOL questions and that the care of the dying and their families must be developed instead (Snyder Sulmasy et al. 2017). Nevertheless, in recent years, the attitudes of physicians in Finland have become more supportive of assisted dying (Louhiala et al. 2015), and euthanasia is regarded as less reprehensible (Piili et al. 2018). This conforms to the public’s growing acceptance of assisted dying.

Professionals of palliative care have been found to be mainly against legalising assisted dying. The IAHPC has stated that “no country should consider the legalization of assisted dying until it ensures universal access to palliative care services and to appropriate medications, including opioids for pain and dyspnea” (De Lima et al. 2017). The EAPC also recommends that patients requesting euthanasia or PAS should first be offered palliative care (Radbruch et al. 2016). However, among different cultures, agreement on assisted dying varies strongly, and former experience in the field of assisted dying is proven to affect the willingness to be involved with it. Other factors influencing a physician’s willingness to perform assisted dying are not clearly known (Zenz et al. 2015, Radbruch et al. 2016).
2.4 Non-small cell lung cancer (NSCLC)

2.4.1 NSCLC epidemiology and risk factors

Lung cancer is the leading cause of cancer-related deaths in the world (Ferlay et al. 2013, Pukkala et al. 2013, Cheng et al. 2016). It is the second most common cancer among men in Finland and third most common among women. In 2015, 1690 men and 936 women were diagnosed with lung cancer in Finland (Finnish Cancer Registry, 2018).

Lung cancer is a large, heterogenic group of thoracic malignancies, but generally divided into two categories by histology: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The NSCLC group accounts for approximately 80% of all lung cancers and comprises of three main histologies: adenocarcinoma, squamous cell carcinoma and large cell carcinoma (Travis et al. 2015).

Adenocarcinoma, with multiple different subtypes, has the highest incidence of all lung cancer subtypes, affecting one-third of men and almost half of the cases in women. Adenocarcinoma is the most prevalent type of non-smokers’ lung cancers but is also associated with smoking. In approximately 10% of adenocarcinoma cases, an activated epidermal growth factor receptor (EGFR) mutation not related to tobacco carcinogenesis is found. Chromosomal rearrangements of the genes encoding anaplastic lymphoma kinase (ALK) and ROS1 proto-oncogene receptor tyrosine kinase (ROS1) are found in 3-4% and 1-2% of adenocarcinomas, respectively, mainly in non-smokers (Bergethon et al. 2012, Govindan et al. 2012, Kerr et al. 2014).

Squamous cell carcinoma comprises approximately one-third of NSCLC patients, and the incidence of large cell carcinoma is 15% (Wahbah et al. 2007, Fan et al. 2011).

The most important risk factor for lung cancer is cigarette smoking which accounts for 80-90% of lung cancers (Doll 1998, Boyle 1997, Shopland et al. 1991). The risk is increased even if a person is exposed to environmental tobacco smoke or so-called passive smoking (Taylor et al. 2007). Smoking also increases the risk for secondary malignancies, even a second lung cancer, and can worsen the efficacy of the lung cancer treatments leading to recurrence of the cancer and poorer survival and QOL. Consequently, smoking cessation is highly advisable at any time of smoking history (Peto et al. 2000, Florou et al. 2014, Parsons et al. 2010).

In addition to tobacco smoking, other etiologic factors for lung cancer have been identified, many of them related to occupational factors (Subramanian et al. 2007,
Pukkala et al. 2009, McCarthy 2012). Asbestos is an important risk factor for lung cancer, increasing its risk by 5-fold, and together with smoking the risk is strongly multiplied (Lee 2001, Frost et al. 2011). From non-occupational factors, indoor radon is shown to increase the risk of lung cancer, especially for smokers. Up to 9% of lung cancers have been estimated to be due to radon exposure in Europe (Darby et al. 2006, Krewski et al. 2006). A family history of the disease is also a risk factor as individuals with a first-degree relative with lung cancer have shown a 1.5-fold increase in lung cancer risk (Coté et al. 2012). Additionally, human papilloma virus (HPV) infection has been suggested to play a role in the development of lung cancer (Syrjänen et al. 2012, Xiong et al. 2017).

2.4.2 Clinical characteristics in NSCLC

NSCLC is typically found in an advanced stage as it has a tendency to metastasize early and is usually symptomless for a long time from the initiation of the disease (Popper 2016). As a result, only approximately one-sixth of NSCLC patients are operable at the time of diagnosis (Gunn et al. 2018). The mean age at diagnosis of NSCLC is 64–70 years (Kocher et al. 2015, Finnish Cancer Registry 2018). Most patients (nearly 70%) are male, as cigarette smoking was previously more popular among men (Kocher et al. 2015).

Smoking, which is the main risk factor for NSCLC (see chapter 2.4.1.) also increases the risk for comorbidities, such as pulmonary diseases, cardiovascular diseases, other cancers, infections and renal failure (Carter et al. 2015). Aging contributes to these patients’ higher risk of comorbidity as well (Janssen-Heijnen et al. 1998). Chronic obstructive pulmonary disease (COPD) is the most common comorbid disease in NSCLC with a prevalence of 40-50% (Young et al. 2009, Gould et al. 2017). The other common comorbid conditions in a patient sample of over 6000 lung cancer patients were peripheral vascular disease (12%), cerebrovascular disease (12%), heart failure (11%), myocardial infarction (11%), prior cancer (15%), renal disease (21%) and diabetes (24%) (Gould et al. 2017).

Performance status (PS) is a measurement describing a patient’s level of functioning (daily activity, physical activity, ability to care for themselves). The scale was developed by the Eastern Cooperative Oncology Group (ECOG) and is also called the WHO or Zubrod score. PS is assessed at baseline when planning treatments and regularly thereafter during treatments and follow-up (Oken et al. 1982) (Table 1). Lung cancer patients have several comorbidities affecting their well-being and PS at the time of diagnosis and NSCLC is frequently diagnosed in an advanced stage with metastatic lesions already present. Therefore, these patients typically suffer from several symptoms and have a poor PS. Approximately 20%
of NSCLC patients planned for chemotherapy have a PS of 2 or worse (NSCLC Meta-Analyses Collaborative Group 2008, Kocher et al. 2015).

Table 1. WHO performance status. (Oken et al. 1982)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Explanation of activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

2.4.3 Prognosis and prognostic factors

Survival rates have improved during the last three decades for advanced (stage IIIB/IV) NSCLC. The median survival was five months during the early years of this period, with only the best supportive care as the treatment. Currently, survival is longer, up to 12–13 months (Noonan et al. 2015). The five-year survival time for all lung cancer patients (all stages, including operated patients) in Finland is currently 10% for men and 16% for women (Cheng et al. 2016, Finnish Cancer Registry 2018).

The histologic type of NSCLC is also an independent predictor of survival. Survival is highest for patients with adenocarcinoma and lowest for those with large cell tumors. Adenocarcinoma is classified into five subtypes (lepidic, acinar, solid, papillary, and micropapillary), and the survival rates also vary between these groups: the highest survival rates are reported in the lepidic adenocarcinoma subtype and the lowest in the micropapillary subtype (Cetin et al. 2011, Warth et al. 2012).

Good PS is associated with better prognosis of NSCLC patients and the stage of the disease is also associated with survival. Expectedly, a later stage corresponds
to poorer prognosis. Other factors associated with prolonged survival include female sex, never smoker status and lower co-morbidity (Bauml et al. 2013, Detterbeck et al. 2017). Symptom distress has also been described as a factor influencing survival. The more symptomatic a patient is, the lower the survival rates (Degner et al. 1995).

### 2.4.4 Diagnostics and staging of NSCLC

Lung cancer diagnosis is based on tumor tissue samples from primary tumor or from metastatic site where histopathological diagnosis and molecular markers are established. The least invasive method is used to perform the tissue biopsy. The biopsy is usually taken with a flexible video-bronchoscopy or with a CT-guided coaxial core needle biopsy from the tumor or the metastasis. A tissue biopsy through mediastinoscopy, video-assisted thoracoscopy or thoracic surgery should be performed if these procedures are unfeasible or the results are uninformative (Stamatis 2015).

Several specific immunohistochemical staining methods may be utilized to further characterize the disease. Genotyping NSCLC is recommended when making treatment plans. The detection of the EGFR mutation and possible ALK and ROS1 rearrangements is essential (Dietel et al. 2016).

A contrast-enhanced computed tomography (CT) scan is the primary method for the staging purpose. For additional information on staging, a metabolic positron emission tomography imaging with fluorodeoxyglucose (FDG-PET) is sometimes accomplished (Salminen et al. 2002, Ambrosini et al. 2012). Of imaging modalities, FDG-PET/CT scan offers the highest sensitivity for mediastinal lymph nodes and distant metastases assessment, yet all imaging modalities may produce false positive or negative findings (Darling et al. 2011). Therefore, invasive techniques providing cytological and/or histopathological samples remain the most accurate methods for the evaluation of mediastinal lymph nodes in staging and/or restaging (Stamatis 2015).

The stage of the cancer is the main factor in treatment decisions. The staging system involving tumor, nodes, and metastases of NSCLC was revised in the 8th edition of the Tumor-Node-Metastasis (TNM) classification (Detterbeck et al. 2017). It divides NSCLC into four stages based on tumor size, nodal involvement, and distant metastases.
2.4.5 Disease specific treatment of NSCLC

2.4.5.1 Treatment decisions

Decision-making for the treatment of advanced NSCLC is complex. The treatment goal is to prolong survival but also to improve the QOL and relieve the symptoms of the patients. The treatment strategy should be individual for each NSCLC patient based on stage, PS, age, histology, co-morbidities, molecular pathology, and the patient’s preferences. Sufficient pulmonary function is mandatory if surgery or radiotherapy is considered. Management plans for each patient should be discussed in multidisciplinary teams (Ung et al. 2016).

The patient’s opinions of the treatments should be regarded, as they differ depending on patients’ values and preferences (Zafar et al. 2009). This shared decision-making is increasingly supported in Western countries and has been shown to improve the patients’ QOL in some studies (Kashaf et al. 2015). Cancer patients’ preferences for chemotherapy have been shown to vary considerably as some patients accept chemotherapy only for a long survival gain and some patients for any small chance of benefit (Matsuyama et al. 2006). Sung et al. (2017) found that only 46% of patients preferred a treatment associated with increased survival if it caused greater toxicity.

Opportunities to enroll NSCLC patients in cancer clinical trials should be enhanced. The general intention has been to seek otherwise healthy subjects to be enrolled in these trials (Hanna et al. 2017). This is often problematic in the case of NSCLC since the patients frequently have a poor PS and simultaneous additional diseases. Pragmatic trials accepting the inclusion of patients with those limitations are required for the development of new therapies for patients with NSCLC (Horn et al. 2013).

Treatment modalities include surgery, radiotherapy and systemic therapy. Systemic therapy comprises chemotherapy, different targeted therapies and immunotherapy. These treatment modalities are described in the following subchapters and reported in detail in the European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines for NSCLC (Novello et al. 2016, Hanna et al. 2017, Postmus et al. 2017, Ettinger et al. 2018).
2.4.5.2 Surgery

Surgery should be considered for stage I and II diseases, and lobectomy is the preferred surgical procedure (Ginsberg et al. 1995, Rosen et al. 2016). A systematic lymph node dissection should be performed to achieve complete resection of the cancer and a comprehensive staging (Rami-Porta et al. 2005, Gagliasso et al. 2017). Only a minority of NSCLC are operable at the time of diagnosis. According to a retrospective study in Finland, 14% of lung cancer patients were operated on during the 2010-2014 period (Gunn et al. 2018). Adjuvant chemotherapy with four cycles of cisplatin and vinorelbine is recommended after surgery for patients with stage IIA, IIB or IIIA disease giving an absolute increase in survival of 4% at five years (Kris et al. 2017, Burdett et al. 2015).

2.4.5.3 Radiotherapy

In NSCLC, radiotherapy (RT) is applied for both curative and palliative purposes. The thoracic region is a challenging area to implement RT considering respiratory movements as well as the organs at risk, such as the lung, heart, and spinal cord. RT in NSCLC may cause acute toxicity such as esophagitis or pneumonitis, the latter being potentially fatal. Late toxicity comprises fibrosis, esophageal stricture, and cardiac toxicity (Baker et al. 2016).

Stereotactic ablative body radiotherapy (SABR) is considered the treatment of choice in stage I or II for patients who are unsuited for surgery (Siva et al. 2016). SABR is more effective and safer than surgery in some patient groups, and the performance of these two treatment modalities is currently being actively evaluated (Chen H et al. 2018). SABR’s efficacy was demonstrated in a study by Sun et al. (2017), which showed a remarkable local control after the treatment. Only 8.1% of the NSCLC patients with clinical stage I disease treated with SABR developed local recurrence after seven years of follow-up, and regional or distant disease recurrence was seen in only 13.6% and 13.8% of patients, respectively.

Concurrent chemoradiotherapy is the main treatment modality recommended for unresectable stage III disease, and it outperforms RT alone (Albain et al. 2009). The combination of cisplatin and etoposide currently appears to be the most favorable choice for radiosensitizing purposes in the treatment of advanced NSCLC (Tam et al. 2017). An anti-programmed death ligand 1 antibody durvalumab recently showed superior efficacy as a consolidation therapy compared to placebo after platinum-based chemoradiotherapy of stage III NSCLC.
(progression-free survival of 16.8 months vs. 5.6 months, respectively) (Antonia et al. 2017).

Palliative radiotherapy may be applied in the management of symptoms from brain metastases (headache, neurologic dysfunction, seizures), skeletal metastases (pain, spinal cord compression), or the primary tumor in the lung (pain, hemoptysis, superior vena cava syndrome) (Jones et al. 2014).

### 2.4.5.4 Chemotherapy

Chemotherapy forms the basis of the treatment in locally advanced or metastatic NSCLC (stage III and IV diseases). The relative increase in 1-year survival gained with chemotherapy has been reported to be 23% and the absolute increase 9% (increasing 1-year survival from 20% to 29%) compared to best supportive care (NSCLC Meta-Analyses Collaborative Group 2008, Novello et al. 2016). Chemotherapy was invented to prolong survival which was the main focus of the first studies on these therapies (Grilli et al. 1993). Symptom alleviation and patients’ QOL during the treatments has gradually received more attention (Anderson et al. 2000, Robinson et al. 2012) and at present the goal of treatment of advanced NSCLC is to both alleviate the symptoms and to prolong survival (Jassem et al. 2002, Langendijk et al. 2000, Ford et al. 2013).

A platinum-based doublet is recommended for first-line treatment for patients without major comorbidities and with PS 0-2 and EGFR-, ALK- and ROS1-negative disease who are not indicated for immunotherapy. A third-generation cytotoxic agent, such as gemcitabine, vinorelbine, taxanes or pemetrexed, is used in combination with a platinum (cisplatin or carboplatin) from four up to six cycles, resulting in a three-to-four-month treatment duration (Pujol et al. 2006, Novello et al. 2016). These cytotoxic agents are recommended as a single-agent therapy similarly from four to six cycles for the second line or third line treatment of NSCLC (Di Maio et al. 2009).

Pemetrexed maintenance therapy is recommended as a treatment option for non-squamous NSCLC after first-line chemotherapy if response or stable disease is achieved with the induction treatment (Novello et al. 2016). A prolonging of progression-free survival (4.4 months for pemetrexed vs. 2.8 months for placebo) and overall survival (13.9 months vs. 11.0 months, respectively) was achieved with pemetrexed for patients with good PS after induction therapy with cisplatin (Paz-Ares et al. 2012, Paz-Ares et al. 2013). The therapy’s possible worsening of patients’ QOL was initially a concern (Petrelli et al. 2013) but it was shown not to deteriorate patients’ QOL or PS (Gridelli et al. 2012).
Chemotherapy can be burdensome and causes toxicity. The side effects are graded by the international Common Terminology Criteria for Adverse Events (CTCAE) (National Cancer Institute, 2017). The main adverse effects from NSCLC chemotherapy are hematologic toxicities (neutropenia, thrombocytopenia and anaemia), weakness, nausea and vomiting and alopecia. Possible side effects also include neuropathy, febrile infections and pain. Platinum-based therapies are recommended in the first line treatment of NSCLC. Cisplatin has shown higher overall response rates compared to carboplatin, though survival rates are comparable (Jiang et al. 2007). Nevertheless, cisplatin causes significantly more toxicity than carboplatin, such as nephrotoxicity, infections, ototoxicity and nausea, leading to more hospitalizations. Therefore, it is important to weigh the pros and cons when choosing between these platinum regimens; that is, a higher response rate versus toxicity and QOL of the patient (D’Addario et al. 2005, Santana-Davila et al. 2014, Snee 2018).

2.4.5.5 *Immunotherapy*

A current treatment option for selected, advanced NSCLC patients, either in first or second line as monotherapy, is immunotherapy that consists of the immune checkpoint inhibitors (ICI) pembrolizumab, nivolumab or atezolizumab. They target the key signalling pathways of programmed cell death protein-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) (Herzberg et al. 2017, Ramos-Esquível et al. 2017). The high PD-L1 expression rate and high mutation burden of the tumor both predict a better response rate to ICIs, but responses can still occur in some PD-L1 negative tumors. Substantial efforts are being made to find a more specific biomarker for ICIs (Sacher et al. 2016, Giroux Leprieur et al. 2017, Goodman et al. 2017).

The median overall survival for these therapies has been demonstrated to be better than for the standard chemotherapy docetaxel (12–13 months vs. 9 months), and adverse effects were less common than during docetaxel treatment (Ramos-Esquível et al. 2017). The adverse effects are related to the mechanism of the action of immunotherapies and differ from other systemic therapies. They are relatively rare, but severe adverse effects may even be fatal. These toxicities require early detection and proper management, usually with corticosteroids (Brahmer et al. 2018).

A novel promising treatment for NSCLC is ICI and chemotherapy given in combinations. In a recent study, pembrolizumab combined with a standard chemotherapy resulted in significantly longer overall survival than chemotherapy alone (estimated rate of overall survival at 12 months was 69% vs. 49%,
respectively). The rates of adverse effects were similar in these groups, though the discontinuation rate of the treatment was higher in the pembrolizumab group (Gandhi et al. 2018). Atezolizumab in combination with bevacizumab plus chemotherapy has also shown some promising results in improving survival compared to standard treatment combinations (Socinski et al. 2018).

2.4.5.6 Targeted therapies

Chemotherapy has mainly been guided by the tumor’s histological classification. However, the genetic heterogeneity of NSCLC allows for the detection of distinct subgroups of the disease, harboring different malignant mutations (Gallant et al. 2018). The so-called “driver mutations” transform normal cells into malignant cells (Vogelstein et al. 2013), and different targeted therapies are available if a driver mutation is found. Compared to standard chemotherapy, these targeted therapies have a better efficacy and are more convenient for the patient, as they are taken orally and are most often well tolerated.

An EGFR receptor-tyrosine kinase inhibitor (EGFR-TKI) is recommended for the first-line treatment for advanced NSCLC with known, activating EGFR mutations. The available EGFR-TKIs are gefitinib, erlotinib, and afatinib, which have shown superior efficacy compared to standard chemotherapy, with a median survival of 20 months (Riely et al. 2006, Gao et al. 2012, Sequist et al. 2013). A T790M mutation of the EGFR gene can evolve during this first-line EGFR-TKI therapy, causing resistance to the therapy and progression of the disease. Osimertinib, a third-generation EGFR-TKI, is preferable for patients with a T790M mutation (Mok et al. 2017).

Patients with an ALK (anaplastic lymphoma kinase) fusion gene–positive NSCLC have been demonstrated to significantly benefit from treatment with crizotinib (Shaw et al. 2013), alectinib (Shaw et al. 2016), or ceritinib (Shaw et al. 2014a). Crizotinib has also been found to inhibit ROS1, showing remarkable efficacy in this setting. It is now recommended in the treatment of ROS1-positive NSCLC patients (Shaw et al. 2014b).

Emerging targeted treatments of NSCLC mainly include therapies for other novel molecular targets. These comprise, for example, inhibitors of activated BRAF, MEK1, and proto-oncogene MET mutations (Jordan et al. 2017, Gallant et al. 2018).
2.4.5.7 Monitoring treatment response

CT imaging is most frequently used to monitor the tumor’s response to treatment. Response evaluation criteria in solid tumors (RECIST) is a commonly used classification in categorizing treatment outcomes in four different classes: complete response, partial response, stable disease, and progressive disease (Eisenhauer et al. 2009). Specific criteria are needed to monitor tumor response to treatment when administering immunotherapy agents (Kim et al. 2017).

In advanced NSCLC, the evaluation of patient-reported outcome (PRO) plays an important role in monitoring the therapy response. This is thoroughly described in the following chapters.

2.4.6 Palliative care in NSCLC

The treatments of metastatic NSCLC must have a palliative approach, and the patients’ QOL during treatment must be considered carefully in addition to attempts in prolonging survival. Additionally, as previously stated, palliative care should be offered to patients already in the early course of the disease and integrated into standard oncologic care during the whole disease trajectory (Bakitas et al. 2009, Ferrell et al. 2017, Gaertner et al. 2017). This integrated palliative care improves the QOL and symptoms of NSCLC patients. It is shown to lead to less aggressive EOL treatment and longer survival of NSCLC patients compared to standard care. In the study of Temel et al. (2010), the survival of NSCLC patients in the early palliative care group was significantly longer than in the standard care group (median 11.6 vs. 8.9 months, respectively).

The use of systemic cancer treatments, such as chemotherapy, near death is not beneficial. Earle et al. (2005) have suggested criteria for avoidance of “overly aggressive cancer care near end of life”. These include that less than 10% of patients are offered chemotherapy in the last two weeks of life and less than 2% of patients initiate a new chemotherapy regimen within one month before death. Maintaining good QOL is important in EOL care and the QOL can worsen with chemotherapy, even in patients with good PS (Prigerson et al. 2015).

Patients with an advanced lung cancer become more symptomatic closer to death (Tishelman et al. 2007, Zeng et al. 2011). These symptoms often require immediate treatment and, therefore, easily induce visits to emergency departments (ED) if proper palliative care is unavailable. Barbera et al.’s (2010b) study reported that one of the largest groups visiting the ED during the final six months of life was the group of lung cancer patients with various disruptive symptoms. Moreover,
patients with advanced cancer often visit ED and are admitted to hospital due to different severe symptoms some of which could be treated with simple interventions (Hjermstad et al. 2013). Avoiding aggressive cancer care may be evaluated by determining the number of those who have been admitted to intensive care unit or ED in the last month of life. Earle et al.’s study suggested that the proportion of those patients should be less than 4 % (Earle et al. 2005).

However, these burdensome ED visits near death can be reduced by developing the implementation of palliative care for the NSCLC patients. The ED visits can be diminished if symptom assessment is used in patient care and, thereby, symptom management improved (Dudgeon et al. 2008). Furthermore, integrating palliative care early in the course of NSCLC treatment reduces these futile ED visits leading to better outcome of the patient (Smith et al. 2012).

The most common symptoms of lung cancer patients are pain, fatigue, dyspnea, insomnia, coughing, and loss of appetite (Cooley 2000, Iyer et al. 2013). Symptom management in NSCLC is discussed in chapter 2.5.

Psychological interventions, such as behavior therapy or meaning-centered, hope-centered, and stress-reduction interventions have shown positive effects on the QOL of cancer patients. The observation and proper treatment of the existential questions and concerns of cancer patients is an essential part of high-quality palliative care (Uitterhoeve et al. 2004, Best et al. 2015).

Existential concerns are common among cancer patients and are described to consist of components of self-control, meaning, identity, relationships, dignity, hope and spiritual well-being (Henoch et al. 2009). These existential concerns may lead to holistic suffering impairing the patients’ ability to cope with the burden of being a cancer patient.

2.4.7 End-of-life care in NSCLC

EOL care is the final phase of palliative care, which is provided near death at home, hospital, different nursing homes or inpatient hospices. It consists of an interdisciplinary team alleviating the patient’s physical, emotional and spiritual suffering (Kelley et al. 2015). High-quality EOL care has been shown to improve the QOL of the patients and caregivers (Wright et al. 2008). It also provides patients the possibility to discuss and prepare for death (Kehl 2015). Offering aggressive anticancer treatments until very near death might cause delay in the initiation of EOL care and entering hospice care (Saito et al. 2011).
2.5 Pain and other symptoms in cancer patients with an emphasis on NSCLC

Symptoms such as fatigue, pain, weakness, dyspnea, lack of appetite, nausea, insomnia, and depression have been commonly observed among patients with advanced cancer (Walsh et al. 2000, Salminen et al. 2008, Barbera et al. 2010a). The five most frequently observed symptoms (lack of appetite, pain, fatigue, lack of energy, weakness) have been reported in more than 50% of patients with different types of incurable cancer (Teunissen et al. 2007) (Table 2). Older cancer patients have a slightly different spectrum of frequently reported symptoms, such as fatigue, pain, excretory symptoms, urinary incontinence, constipation, weakness, and anxiety (Van Lancker et al. 2014).

Table 2. Commonly observed symptoms of patients with incurable cancer. Adapted from Teunissen et al. 2007.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>74%</td>
</tr>
<tr>
<td>Pain</td>
<td>71%</td>
</tr>
<tr>
<td>Lack of energy</td>
<td>69%</td>
</tr>
<tr>
<td>Weakness</td>
<td>60%</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>53%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>46%</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>39%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>36%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>35%</td>
</tr>
<tr>
<td>Nausea</td>
<td>31%</td>
</tr>
<tr>
<td>Cough</td>
<td>28%</td>
</tr>
</tbody>
</table>

2.5.1 Symptoms in NSCLC

Lung cancer patients have been the most symptomatic of all cancer patients in studies comparing patients with different types of cancer (Degner et al. 1995, Barbera et al. 2010a, Isaac et al. 2012). The most common symptoms identified during the disease trajectory are fatigue, dyspnea, pain, insomnia, coughing, and appetite loss (Cooley 2000, Iyer et al. 2013). Other symptoms are weakness, hemoptysis, anorexia, fever, hoarseness, and weight loss (Chute et al. 1985, Spiro
et al. 2007). Lung cancer patients have named their most distressing symptoms to be pain, fatigue, and problems with breathing (Tishelman et al. 2007).

Only 6–13% of patients have been reported as asymptomatic at diagnosis. The disease is already widely spread in many cases. Thus, physical deterioration may be so severe that the patient might not be fit for any antitumor therapy, and the best supportive care is sometimes the only care possible (Spiro et al. 2007, Hamilton et al. 2005, Kocher et al. 2015).

The symptom burden of NSCLC patients is frequently heavier due to simultaneous diseases, such as COPD or cardiovascular diseases, as previously stated (Gould et al. 2017). These comorbidities should also be properly treated to decrease the symptom burden.

### 2.5.2 Cancer pain

Pain is a common symptom among cancer patients. In a meta-analysis of cancer patients, 38% reported moderate to severe pain, and 39% of cancer patients expressed pain after curative treatment, 55% during anticancer treatment, and 66% in advanced, metastatic, or terminal phases of cancer (van den Beuken-van Everdingen et al. 2016). In lung cancer, pain is also reported as one of the most distracting and common symptoms, estimated to affect 27% of outpatients and 76% of patients in palliative care (Potter et al. 2004).

The primary tumor is reported to be the main cause of pain in advanced cancer, but the sites of metastases and cancer treatments can also lead to severe pain. Cancer pain is mainly caused by the progression of the disease to the bones, visceral organs, or nerve roots. In many cancer patients, pain is related to several of these origins (Gutgsell et al. 2003, Mercadante et al. 2010).

Neuropathic pain is caused by damage to a nerve or to the spinal cord (WHO 1986). Of patients with cancer pain, 20–40% have been reported to experience neuropathic pain (Bennett et al. 2012, Roberto et al. 2016), mainly caused by the tumor itself or by the treatment received for the cancer, mainly chemotherapy. Pain with neuropathic characteristics tends to be more intense and has a greater impact on functioning and QOL than pain without neuropathic characteristics (Bennett et al. 2012, Bouhassira et al. 2017). NSCLC is often treated with cisplatin, docetaxel, or vinorelbine, which can cause peripheral neuropathy resulting in pain, sensory loss, or sometimes sensory ataxia. Up to 30–40 % of these patients have reported symptoms of neuropathy temporarily or permanently (Nurgalieva et al. 2010, Velasco et al. 2015, Staff et al. 2017).
Acute postoperative pain is common in cancer patients, and chronic postoperative pain has been reported in approximately one-fifth of patients for up to 10 years after lung cancer surgery (Mercadante et al. 2010, Grosen et al. 2013). Radiotherapy can also result in acute pain, for example through oral mucositis, skin burns, or chronic pain resulting from radiation fibrosis of a nerve plexus or radiation myelopathy (WHO 1996).

Cancer pain can be divided into continuous, intermittent, or breakthrough pain. Breakthrough pain, described as intermittent exacerbations of otherwise controlled pain, is reported to occur in 75% of cancer patients suffering from pain (Gutgsell et al. 2003).

### 2.5.2.1 Treatment of cancer pain

A highly important part of good symptom management is adequate pain assessment and treatment. Pain has multidimensional features that influence patients’ emotional, spiritual, physical, and psychosocial well-being, thus decreasing the overall QOL (Serlin et al. 1995, Kroenke et al. 2010). Cicely Saunders was one of the first people to emphasize this multidimensional nature of pain with the concept of “total pain” (Clark 1999).

The WHO Cancer Pain Relief Program was established in 1982 to upgrade the inadequate treatment of cancer pain. The “pain ladder,” which describes the basics of pain treatment, was subsequently introduced in the WHO publication “Cancer Pain Relief” (WHO 1986). WHO released the second reviewed edition of this publication “Cancer Pain Relief – with a Guide to Opioid Availability” in 1996 (WHO 1996). These guidelines are still used worldwide and form the basis of pain medication (Carlson 2016). The EAPC published evidence-based guidelines for cancer pain treatment based on the WHO recommendations of the pain ladder in 2012 (Caraceni et al. 2012).

This conception of the pain ladder refers to a three-step approach in pain treatment. The lowest step of the ladder is for mild pain and non-opioid pain medication in the form of paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) is recommended for treatment. The second step is for moderate pain, and the treatment recommendation is a non-opioid, in combination with an opioid (codeine or another weak opioid) for mild/moderate pain. The third and highest step is for severe pain; it involves strong opioids (morphine, oxycodone, hydromorphone, fentanyl, methadone) (Figure 1). When treating moderate pain, a pain medication shift from the first step straight to the third step is also feasible and often performed (Bandieri et al. 2016).
The WHO guidelines recommend adjuvant drugs for the treatment of neuropathic pain, such as tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, gabapentin, and corticosteroids (WHO 1996, Finnerup et al. 2015). No preventive treatment is available against chemotherapy-induced neuropathic pain. Thus, the only prophylactic approach is a decrease of the dose or duration of the cytotoxic agent (Hershman et al. 2014).

The WHO publications on pain medication also recommend that the medication be given regularly (“by the clock”), primarily by mouth. Some patients also suffer from intermittent or breakthrough pain. It is strongly recommended to treat this pain with additional doses of oral immediate-release opioids and to perform an appropriate titration of the around-the-clock opioid therapy (Caraceni et al. 2012). Every single patient needs an individual dose prescription as well as thorough and understandable information regarding the pain medication. This is essential for the implementation of pain management.

![The WHO pain ladder](image)

**Figure 1.** The WHO pain ladder. See text for details. (Modified from WHO’s “Cancer Pain Relief”; WHO, 1986.)
In more complicated cases, consulting an anesthesiologist or a pain management specialist allows for possible additional procedures to be utilized in pain management. Nerve blocks, for example, may offer an immediate relief of pain. Radiotherapy of painful bone tumors or metastases also relieves pain effectively, often for months (Smith et al. 2015).

2.5.2.2 Current state of cancer pain treatment

The treatment of cancer patients’ pain has often been shown to be inadequate (Breivik et al. 2009, Constantini et al. 2009, van den Beuken-van Everdingen et al. 2016). A review by Deandrea et al. (2008) showed that nearly half of cancer patients had insufficient pain treatment 10 years ago.

Insufficient pain management can originate from health care professionals, patients, or the health care system. In a review by Kwon (2014), the professional-related barriers were mainly lack of knowledge and skill in pain management, poor pain assessment, and physicians’ reluctance to prescribe opioids. The main areas of physicians’ poor knowledge in cancer pain treatment have been regular medication of chronic cancer pain, management of breakthrough pain, dose titration, use of adjuvant medications, and aspects of tolerance or addiction (Wolfert et al. 2010, Kwon 2014). Patient-related barriers include adherence to analgesic regimens and cognitive or affective factors. The poor availability of pain and palliative care specialists and limits on access to opioids present possible system-related barriers.

Opioids are often used in the treatment of cancer pain, but many patients develop adverse effects from them. The main adverse effects are constipation, central nervous system toxicity (such as cognitive impairment, confusion, drowsiness, hallucinations), nausea, and vomiting. These should be properly assessed and managed to achieve an optimal state of pain treatment (Jost et al. 2010). Novel analgesics have been developed in recent years, but better analgesic performance compared to traditional opioids has not been found (Mercadante 2017).

Cancer pain management needs to be improved by randomized controlled studies to provide better treatment modalities including new pain medications. Health care professionals as well as patients and their family members need more education on pain treatment. In addition, the systematic assessment of pain is of the utmost importance (Schug et al. 2015).
2.5.3 Dyspnea

Dyspnea is a more prevalent symptom in lung cancer than in other cancers (Vainio et al. 1996, Dudgeon et al. 2001, Bruera et al. 2000). It is an unpleasant symptom that often interferes with the activities of daily living (Kathiresan et al. 2010); it is defined by the American Thoracic Society (ATS) as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations varying in intensity” (Parshall et al. 2012). Almost half of the patients with newly diagnosed NSCLC report dyspnea, which is reported to induce panic disorder symptoms in every tenth patient (Shin et al. 2014).

Possible treatable reasons for dyspnea include pulmonary embolism, pleural effusion, congestive heart disease, exacerbation of COPD or asthma or obstruction of the major airways. These should be observed and treated in the most preferred way (Kvale et al. 2007). Distressing symptoms of dyspnea in advanced cancer can be alleviated with opioids administrated orally or parentally (Bruera et al. 1993, Ripamonti et al. 2002, Jennings et al. 2002). Some patients may benefit from oral steroids as well (Kvale et al. 2007). The guidelines for treatment of dyspnoea in lung cancer also recommend the use of oxygen in a case of hypoxemia, patient education, fans, psychosocial support, relaxation techniques, and breathing control (Kvale et al. 2007, Parshall et al. 2012, McCannon et al. 2012).

2.5.4 Cough

Together with dyspnea, cough is a common and distressing symptom for many lung cancer patients (Harle et al. 2012). It is associated with symptoms of dyspnea, fatigue, and sleep disturbance and also has major social and psychological effects (Molassiotis et al. 2011).

Cough treatment is often challenging as there is no strong evidence for any treatment modality, and the existing antitussive drugs lack evidence of their effectiveness (Young et al. 2011). The antitumor treatment of NSCLC may improve symptoms including cough (Jassem et al. 2002, Bezjak et al. 2006), and this is evidently primarily recommended. A recent guideline recommends that the palliative treatment for cough in patients with lung cancer should consist of nonpharmacologic treatment modalities such as diaphragmatic breathing and cough suppression techniques and pharmacologic modalities such as demulcents, opioids, peripherally acting antitussives, or local anesthetics. Peripherally acting antitussives include levodropropizine, guaifenesin, benzonatate, moguisteine, levocloperastine, gamma-aminobutyric acid (GABA) agonists, theobromine, and drugs affecting eicosanoids. Radiotherapy might be effective for selected patients.
in the alleviation of cough and dyspnea, mainly in cases of endobronchial obstruction (Reinfuss et al. 2011). Overall, new treatment options for the treatment of cough in cancer patients are urgently needed (Dicpinigaitis 2006, Molassiotis et al. 2017).

2.5.5 Depression

NSCLC is a very burdensome disease, both physically and mentally, and depression is very common among these patients, affecting around one-third or even half of the patient population (Hopwood et al. 2000, Shi et al. 2015). Insomnia and other sleep disturbances are also frequently reported; the quality of sleep has been described as poor for lung cancer patients, significantly affecting their QOL (Palesh et al. 2010, Savard et al. 2011, Chen D et al. 2018).

There is no strong evidence for the efficacy of any specific treatment modalities of depression in lung cancer patients. Thus, the customary medication for depression is recommended. Integrated collaborative care for depression delivered by a team of cancer nurses and psychiatrists in collaboration with primary care physicians is shown to be more effective than the usual care (Walker et al. 2013, Walker et al. 2014).

The symptoms of fatigue, insomnia and loss of appetite may occur together with depression or anxiety or sometimes with several other symptoms. First, it is important to try to address the different symptoms individually and treat them sequentially. For example, the treatment of depression with antidepressants might relieve many other symptoms or adequate treatment of pain can improve insomnia and fatigue. These symptoms have adequate pharmacological and nonpharmacologic treatments that are reported in detail in the guidelines (Dy et al. 2008, Levy et al. 2016, Simoff et al. 2013).

2.5.6 Cancer-related fatigue

Cancer-related fatigue (CRF) is defined by the NCCN as a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that interferes with usual functioning (Berger et al. 2015). Primary CRF can be caused by the tumor itself or by alterations caused by cytokines, changes in the central nervous serotonenergic system, disturbance of the hypothalamic regulatory circuits, or disturbance of circadian melatonin secretion. Secondary CRF is linked to disease-related factors such as possible infections, malnutrition, use of medications, sleep disturbance, anemia, emotional
distress, or comorbidities (Carnio et al. 2016). The term “weakness” is often used to imply the physical dimension of fatigue and the term “tiredness” to the cognitive dimension. “Lack of energy” refers to the reduced resources of energy resulting from the disease. Weakness, tiredness, and lack of energy can be regarded as different subdimensions of fatigue, but are often included in the term “fatigue” for simplicity (Radbruch et al. 2008).

2.5.7 Nausea and vomiting

One-third of advanced cancer patients suffer from nausea, and vomiting is often related to it. In one-fourth of nausea episodes, there is more than one underlying cause. The most common causes in patients with advanced cancer are impaired gastric emptying and metabolic or chemical factors. Impaired gastric emptying is mainly caused by opioids or other medication, tumor invasion, ascites, hepatomegaly, or splenomegaly, while chemical causes for nausea include certain medications or metabolic abnormalities such as hypercalcemia, hyponatremia, or uremia. Intracranial metastases or leptomeningeal carcinomatosis can also induce nausea (Ang et al. 2010, Gordon et al. 2014). The proportion of cancer patients suffering from loss of appetite varies between 39% to 82%. This generally leads to weight loss, which is an adverse prognostic factor (Poole et al. 2002).

2.5.8 Insomnia

Insomnia is caused by sleep and wake disturbances from several reasons. Cancer patients may have sleep-disordered breathing or a periodic limb movement disorder which should be treated accordingly. Fears and anxiety regarding disease and death often cause insomnia, along with other possible reasons such as pain, nausea, depression, and anxiety (Levy et al. 2016).

2.6 Assessment of symptoms and quality of life in lung cancer

The assessment of a patient’s condition was traditionally limited to the documentation of PS and adverse effects using the CTCAE. These are still valid methods but inadequate for gaining a comprehensive view of the patient’s situation. It is recommended that an instrument for QOL and symptom assessment should be included in lung cancer studies to improve the quality of treatment outcome assessment (Huschka et al. 2007, Basch et al. 2009, Prigerson et al. 2015).
2.6.1 Assessment of symptoms

Regular symptom assessment among cancer patients is important. A detailed evaluation of symptoms enables one to acquire an extensive and comprehensive view of patients’ well-being. Mercadante et al. (2010) stated in their study of lung cancer patients’ pain management that “an adequate assessment is required to plan a successful treatment.” Without this assessment, the physician is unaware of the patient’s symptoms and the symptom management cannot be accomplished properly. Symptom assessment is regularly emphasized in palliative care guidelines, as it leads to better symptom management (WHO 1986, WHO 1996, Sung et al. 2017).

One perspective emphasizing the importance of symptom assessment is that health-care professionals may underestimate the severity of patients’ symptoms. The difference between the estimates of symptom severity assessed by patients and by professionals has been demonstrated in different studies. Laugsand et al. (2010) found that professionals underestimated patients’ symptoms and frequently reported the percentages of moderate to severe symptoms as lower than the patients’. Several other studies have indicated the same. Williams et al.’s (2016) study showed that health care providers underrate the prevalence of cancer patients’ pain and fatigue. Rhondali et al. (2012) revealed that the nurses’ clinical impression of patients’ symptoms, even in a palliative care unit, showed a poor association with patient-reported symptom intensity. Opioid-induced constipation is a common adverse effect of opioid treatment for cancer pain and is important to detect and treat. LoCasale et al.’s (2016) study demonstrated that physicians regularly underestimate this problem during opioid treatment, which evidently complicates pain management.

2.6.2 Assessment of quality of life

Along with symptom assessment, an evaluation of the individual patient’s QOL is important in cancer care (Chapter 2.1, Palliative care and end-of-life care previously defined the QOL concept). The goal of assessing lung cancer patients’ QOL is to observe the aspect of the disease and their individual opinion of their own well-being. Doctors have medical expertise concerning the treatment options, but patients are the experts on their own illness and might not have the same views the doctors have regarding the disease and its treatments (Joyce 1994). This patient-focused approach is important, particularly concerning the commonly dismal prognosis of advanced lung cancer.
Tanvetyanon et al. (2007) were the first to systematically review the QOL outcomes of standard chemotherapy of NSCLC. They concluded that QOL assessment was not on a satisfactory level with regard to compliance with QOL assessment, standardization of the analyses or the overall reporting of QOL variables. Subsequently, symptom and QOL assessment of cancer patients has become more emphasized. Today, it is even a crucial part of clinical trials by bringing in the important patient perspective of benefits and risks of the treatment (Bottomley et al. 2007, Cleeland et al. 2013). A good QOL is recommended today as the primary endpoint for clinical trials and an important goal of treatments in lung cancer (Mannion et al. 2014).

This patient perspective has been named patient reported outcome (PRO) and there is growing interest in it. It is defined as an “outcome reported directly by patients themselves” and consists of patients’ assessments of their health status, QOL, satisfaction with care, and experience of the treatment and disease itself (Calvert et al. 2013). Measuring PROs has been shown to improve patient satisfaction and communication between patients and health care professionals. PROs also help to identify unrecognized symptoms and to observe treatment responses (Chen et al. 2013).

2.6.3 Instruments for the assessment

Several validated instruments and methods exist to assess cancer patients’ symptoms and QOL. Generic instruments are designed to be applicable in different populations and interventions. These are, for example, the Medical Outcomes Study 36-Item Short Form (SF-36) health survey, the EuroQol-5D Instrument (EQ-5D), the European Organization of Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, the Health Utilities Index (HUI), and the 15D (Sintonen 2001, Coons et al. 2000, Fayers et al. 2002).

Disease-specific questionnaires are designed specifically for a certain cancer type. For symptom assessment in lung cancer patients there are questionnaires such as the Lung Cancer Symptom Scale (LCSS), the Functional Assessment of Cancer Therapy (FACT-L) questionnaire, and the EORTC LC-13 questionnaire (Gridelli et al. 2001).

No totally ideal or comprehensive instrument is available, and the choice of the instrument should be based on the study’s purpose. For example, certain instruments are appropriate for assessing only one symptom or only QOL, and some are valid for concurrently assessing several symptoms together with QOL. Some instruments assess only a shorter timeframe, such as “today,” and some a
longer timeframe, such as “the past two weeks” (Kirkova et al. 2006, Ganz et al. 2007).

An emerging field in symptom assessment consists of electronic techniques for collecting PROs. This electronic monitoring has many advantages compared to traditional methods of measuring PROs, including being easier to manage, score and interpret (Jones et al. 2007). Recent results from a clinical randomized trial have shown that integrating routine electronic PROs into oncology practice prolongs survival, reduces hospitalization and results in better patient QOL (Basch et al. 2016, Basch et al. 2017).

2.6.3.1 EORTC QLQ-C30 and QLQ-LC13 questionnaires

The European Organization of Research and Treatment of Cancer (EORTC) assembled a Quality of Life Group in 1980 to enhance the assessment of QOL in clinical trials. This work resulted in the development of a core questionnaire, QLQ-C30, which can be supplemented with disease-specific questionnaires, such as the lung cancer-specific questionnaire (QLQ-LC13) (Fayers et al. 2002). These questionnaires are reliable and well-validated instruments for measuring cancer patients’ symptoms and QOL (Aaronson et al. 1993). QLQ-C30 combined with the QLQ-LC13 especially assesses disease- and treatment-specific symptoms in lung cancer patients (Bergman et al. 1994). They can be used for cancer patients participating in clinical trials as well as in palliative care (Brasel 2007).

The core QLQ-C30 questionnaire comprises five functional scales (physical, role, cognitive, emotional, social), one item on health-related QOL, five single items (constipation, diarrhea, sleep, dyspnea, financial problems) and three symptom scales (fatigue, pain, nausea/vomiting). The QLQ-LC13 comprises 13 questions that evaluate symptoms associated especially with lung cancer (cough, haemoptysis, dyspnea, site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy, alopecia), and pain medication.

These EORTC questionnaires are currently widely used around the world (Fayers et al. 2002) and have been chosen as standard instruments assessing PROs as outcome indicators for lung cancer (Koller et al. 2015). Compared to different self-assessment questionnaires used in palliative care, EORTC QLQ-C30 covers the most frequent symptoms, is easy to fill out and gives a more reliable measurement of the symptoms using multi-item scales for some symptoms (Strömgren et al. 2002). QLQ-LC13 is recommended as a standard tool for measuring lung cancer patients’ QOL in clinical trials (Salvo et al. 2009).
2.6.3.2 Edmonton Symptom Assessment Scale (ESAS)

The Edmonton Symptom Assessment Scale (ESAS) is an easy-to-use assessment tool originally based on a visual analogue scale (VAS) but more recently used with an 11-point numerical rating scale (NRS). It was invented in 1991 by the Edmonton Regional Palliative Care Program (Bruera et al. 1991) for an easy and daily symptom assessment, especially in the palliative care setting. It was subsequently validated in several studies (Dudgeon et al. 1999, Chang et al. 2000, Nekolaichuk et al. 2008, Richardson et al. 2009) and translated into many languages (Hui et al. 2017). It is routinely and globally used in many clinics for the assessment of symptom intensity among cancer patients (Bruera et al. 2013).

The original ESAS had eight scales, one for each symptom assessed, but currently several modified versions of the original questionnaire exist (Hui et al. 2017). Mainly, nine or ten symptoms are addressed: pain, depression, shortness of breath, anxiety, appetite, tiredness, nausea and drowsiness, in addition to total well-being. Sometimes a blank scale is available on the list to add one’s own symptom. These symptoms are rated from 0 (no symptom) to 10 (worst possible symptom) on NRS.

A revised version of ESAS (ESAS-r) was introduced in 2011 (Watanabe et al. 2009, Watanabe et al. 2011, Hui et al. 2017). This updated version organizes the symptoms in a new way, includes explanations for some of the symptoms, defines the timeframe as “now” and revises the format.

2.6.3.3 Beck Depression Inventory (BDI)

The Beck Depression Inventory (BDI) is one of the most commonly used, global questionnaires designed to assess depression. Its advantages are a good sensitivity to change and high validity in differentiating between depressed and non-depressed patients. (Beck et al. 1961, Richter et al. 1998). BDI is indicated as a reliable, well validated and sensitive tool among the longer questionnaires used to screen patients for emotional distress (Vodermaier et al. 2009).

The BDI comprises 21 multiple-choice questions regarding different symptoms related to depression. The scores from each of the questions are added together, with the total score indicating the severity of the depression (Beck et al. 1988).
3 AIMS OF THE STUDY

This doctoral study’s aims were to

1. assess the views and fears concerning palliative care, euthanasia and PAS of Finnish physicians representing different specialities responsible for EOL care;

2. evaluate the skills in cancer pain management and survey possible training needs in palliative care among physicians in Finland;

3. evaluate symptoms and QOL of advanced NSCLC patients prior to, during, and after chemotherapy based on their own recordings by using different assessment tools, and compare these findings with the patients’ characteristics, disease stage, and histopathological findings;

4. examine factors affecting survival in this NSCLC patient study population; and

5. introduce a symptom assessment tool applicable in clinical practice for lung cancer patients.
4 SUBJECTS AND METHODS

4.1 Study subjects

4.1.1 Studies I and II

An anonymously filled questionnaire surveying the attitudes on euthanasia, PAS and palliative care issues and needs for palliative care training was sent to practising clinical oncologists in Finland in November-December 2006 through the webpage of the Finnish Society for Oncology and their address list. Additionally, the survey was handed out during their meeting in January 2007 for the trainers aiming to specialize in oncology and radiotherapy. These two groups of physicians formed the study group named as “oncologists.” According to the statistics of the Finnish Medical Association 129 physicians were practicing clinical oncology or specializing in the field at that time.

The survey was next sent by mail to 2055 general practitioners and specialists in internal medicine and geriatrics working in the Hospital Districts of Helsinki and Uusimaa and the Hospital District of Southwestern Finland between January 2007 and January 2008. This group of physicians formed the group of “other physicians” in this study.

4.1.2 Studies III and IV

Studies III and IV were conducted at Turku University Hospital in the Department of Pulmonary Diseases. All consecutive patients with newly diagnosed NSCLC prior to their first chemotherapy were asked to join the study between August 2008 and August 2011. Patients diagnosed over a year earlier, patients not consenting to participate in the study and patients not able to communicate in Finnish were excluded. Written informed consent had to be signed before inclusion.
4.2 Methods

4.2.1 Studies I and II

A questionnaire to survey Finnish physicians’ opinions and knowledge of euthanasia, PAS and palliative care was distributed to 2184 physicians, in all. This questionnaire was previously used in the Centre of Palliative Medicine in Bonn to evaluate medical students’ opinions (Clemens et al. 2008a, Clemens et al. 2008b). The questions were translated in Finnish and pre-tested for fluency and understandability with medical students in the Faculty of Medicine, Turku University, Finland.

The first part of the questionnaire surveyed the respondents’ characteristics: gender, age, speciality, place of work and year of graduation from medical school. The other parts of the questionnaire evaluated the physicians’ knowledge, opinions and attitudes on euthanasia, PAS, palliative care and cancer pain management. Perception of own skills and possible needs in training in palliative medicine were also assessed (see Appendix 1). One reminder letter was sent after the questionnaire’s delivery.

4.2.2 Studies III and IV

QOL and symptoms of advanced NSCLC patients planned for chemotherapy recruited for this study were measured with three different questionnaires in the beginning of the treatment (baseline) and again at three and six months (see Appendix 2). The patients filled out the questionnaires without staff assistance.

The three different questionnaires on each measurement point were

- European Organization of Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) combined with the EORTC lung cancer –specific questionnaire (QLQ-LC13)
- Edmonton Symptom Assessment Scale (ESAS)
- Beck Depression Inventory (BDI)

The responses are documented on a four- or seven-point Likert scale in the EORTC QLQ-C30 and QLQ-LC13 questionnaires. These scores are calculated to range from 0 to 100 in the analysis. A high score for a functional scale represents a high level of functioning, and a high score for QOL represents a high QOL, while a high score for an individual symptom item represents a high severity of a symptom. The
Subjects and methods

questionnaire data in study III were also compared to the reference data obtained from the EORTC reference values manual (Scott et al. 2008). Reference mean values for NSCLC patients representing all stages of the disease and values for patients representing all cancer patients were taken for comparison.

ESAS is an easy-to-use assessment tool based on the visual analogue scale (VAS) or numeric rating scale (NRS) (Dudgeon et al. 1999). The original ESAS questionnaire was translated into Finnish and slightly modified to gather a separate perception of pain at rest and pain at effort. Symptoms of insomnia and constipation were also added. Consequently, the questionnaire had 11 items comprising 10 symptoms. The symptoms were assessed with an NRS based questionnaire. A symptom was considered as mild with ESAS scores of 1-3, moderate with scores of 4-6 and severe with scores of 7-10. The score of 0 was considered as absence of the symptom in question. Similar scoring has been used also by other authors (Hui et al. 2017, Selby et al. 2010, Oldenmenger at al. 2013). The association between the results of the EORTC questionnaire and the results from ESAS were evaluated.

Depressive symptoms were assessed with BDI. In this questionnaire, the score of 0–9 corresponds to no depression, 10–18 to mild depression, 19–29 to moderate depression, and ≥30 to severe depression (Beck et al. 1961).

All demographic and clinical patient data were collected from the hospital records. This data included age, gender, PS at the beginning of the study, histopathological diagnosis, TNM classification at the time of diagnosis, sites of metastases, smoking status and concurrent diseases.

4.3 Statistics

4.3.1 Studies I and II

Gender, age distribution, years of practicing physician, occupation site, if the respondent had taken care of a seriously ill relative and physicians’ specialty were cross-tabulated with the questions concerning knowledge and views on euthanasia, fears when meeting a dying patient and education needs. Statistical significance of these associations was tested with Pearson’s chi-square test.

Binary logistic regression was used to create models to explain the importance of the background variables in the answers. Any variable significantly associated (p<0.05) with the questions in the univariable logistic regression analysis was
included in the multivariate logistic regression analysis. The variable “years of practicing physician” had to be excluded from the analysis to avoid multicollinearity due to high correlation existing between the age and the years of practicing physician in the multivariate logistic regression analysis.

Results are expressed using odds ratios (OR) with their 95% confidence intervals (CI). P-values less than 0.05 were considered statistically significant. Statistical analysis was carried out using SAS System for Windows, release 9.2 (SAS Institute Inc., Cary, NC).

### 4.3.2 Studies III and IV

Units and percentages were calculated to describe the categorical data. Quantitative data were summarized by median with range or IQR (Interquartile range Q1-Q3; Q1=lower quartile, Q3=upper quartile) or means together with a standard deviation.

Patient characteristics were compared between females and males using Fisher’s exact test. Comparisons of symptoms (EORTC questionnaires) between females and males were performed for each time point with a Wilcoxon rank sum test since the data were not normally distributed. The Pearson correlation was calculated using age, EORTC QLQ-C30 and QLQ-LC13 scores. Association between the global QOL score and several specific factors [sex, stage, pathological diagnosis, age class (≤60, 60-70, >70 years), the number of pack years of smoking (≤10 years, 11 – 40 years, > 40 years), metastases in bone or brain] were examined using multi-way analysis of variance. A similar model was performed for the association between QOL and lung cancer-specific questionnaire scores. Modelling was performed separately because of the multi-co-linearity aspects. The severity of dyspnea was compared by the number of pack years of smoking (≤10 years, 11 – 40 years, > 40 years) using the Kruskal–Wallis test. The association between the scores from EORTC and ESAS questionnaires and different symptoms were tested by Spearman correlation coefficient.

Pain and QOL over six months were analyzed using linear mixed models for repeated measures. These models addressed gender, diagnosis, smoking status, stage, bone metastases, brain metastases, age (classified into three classes reported previously) and time. The interaction between time and all these factors was also included in the model to examine whether changes were different in the categories. Square root transformation was performed on the pain score to achieve normal distribution assumption for residuals. Changes in symptoms and QOL over time were tested using the Wilcoxon Signed Rank Test for two time points.
A log-rank test and Kaplan-Meier curve were executed on each variable separately (gender, age, PS at baseline, stage of the disease, sites of metastases, smoking status, baseline comorbidities and EORTC QLQ-C30 questionnaire’s baseline symptoms, global QOL and functional scales) to observe the association between them and survival time. In addition, Cox’s proportional hazard model was executed to be able to estimate hazard ratios (with 95% confidence interval) for these explanatory variables.

A p-value of less than 0.05 (two-tailed) was considered statistically significant. The statistical analyses were performed using SAS® software (Version 9.3 for Windows; SAS Institute Inc. Cary, NC, USA).

4.4 Ethics

Studies I and II were survey-based studies for physicians and did not require consent from the Ethics Committee.

The protocol of studies III and IV was approved by the Ethical Committee of the Hospital District of South West Finland. The studies were performed in accordance with the Declaration of Helsinki (2008). Clinical trial information: NCT00818402.
5 RESULTS

5.1 Survey of physicians’ perceptions on assisted dying and aspects of palliative care in Finland (studies I and II)

5.1.1 Respondents’ characteristics

Originally, the questionnaire was distributed to 129 physicians practicing clinical oncology or specializing in the field. Fifty-nine physicians answered the questionnaire giving a response rate of 46%. These respondents formed the study group of 59 physicians named “oncologists” consisting of 47 oncology specialists and 12 physicians specializing in clinical oncology. The mean age of the oncologists was 44.4 years (SD 9.2), and the mean amount of working years was 16.8 (SD 9.7). Forty-seven (80 %) of the respondents were female.

In the other group, the questionnaire was sent to 2055 general practitioners and specialists in internal medicine and geriatrics. The total number of respondents from this group named as other physicians was 661 and the response rate 32%. They represented general practitioners (n=302), geriatricians (n=33) and specialists in internal medicine (n=159) but there were also specializing physicians (n=113) and few other specialised physicians from other fields (n=54). The mean age of the other physicians was 46.2 years (SD 11.5) and the mean amount of working years was 18.5 (SD 11.5). Females represented 432 (65 %) of the respondents (Table 3).
Table 3. Characteristics of the respondents in studies I and II. (Table adopted from Study II)

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<td>47</td>
<td>432</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;36 years</td>
<td>10</td>
<td>144</td>
</tr>
<tr>
<td>36-50 years</td>
<td>37</td>
<td>251</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>12</td>
<td>266</td>
</tr>
<tr>
<td>Speciality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal medicine</td>
<td>-</td>
<td>159</td>
</tr>
<tr>
<td>General practice</td>
<td>-</td>
<td>302</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>Specialising</td>
<td>12</td>
<td>113</td>
</tr>
<tr>
<td>Other c</td>
<td>-</td>
<td>54</td>
</tr>
<tr>
<td>Oncology</td>
<td>47</td>
<td>-</td>
</tr>
<tr>
<td>Years of practicing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>as a physician</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4 years</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>5-9 years</td>
<td>10</td>
<td>83</td>
</tr>
<tr>
<td>10-19 years</td>
<td>17</td>
<td>152</td>
</tr>
<tr>
<td>20-29 years</td>
<td>20</td>
<td>164</td>
</tr>
<tr>
<td>30-45 years</td>
<td>7</td>
<td>159</td>
</tr>
</tbody>
</table>

a information missing from one respondent in the group of other physicians (n=660)
b specialising in oncology
c This group consisted of seven pediatricians, three surgeons, three psychiatrists, three occupational health physicians, two pediatric neurology physicians and one physician from each of the following specialities: anesthesiology, clinical physiology, gynecology, neurology, physical and rehabilitation medicine, otorhinolaryngology, and respiratory medicine. Information missing from twenty-nine respondents.
d information missing from three respondents in the group of other physicians (n=658)

5.1.2 Views on euthanasia and PAS (study I)

In the group of other physicians, 87% of the respondents, recognized the concept of active euthanasia, while 84% knew passive euthanasia, 80% palliative sedation and 71% assisted suicide. Oncologists were also familiar with the concepts as 95% knew active euthanasia, 86% knew passive euthanasia and 82% recognized assisted suicide.
Only 19% of other physicians and 10% of the oncologists supported legalization of euthanasia in Finland. Among the group of other physicians, male physicians accepted the legalization of euthanasia more often than females (23% vs. 17%) (p=0.012). The respondents’ age in this group did not influence their opinion.

If active help in dying was legalized, only 14% of the oncologists and 17% of other physicians would practice it.

Forty-three (73%) of the oncologists and 449 (68%) of the other physicians considered misuse of euthanasia a probable risk. The majority of both groups (97% and 96%, respectively) had the opinion that patients’ demands for active euthanasia would be reduced with proper palliative care.

### 5.1.3 Views on end-of-life care

Twenty-six percent of the respondents in the group of other physicians and 17% of oncologists expressed any fears when meeting patients with incurable diseases or dying patients.

Significant predictors for feeling fears when meeting dying or incurably ill patients were characterized only in the group of other physicians. These were female gender (p=0.0039), age less than 36 years (p=0.0010) and no previous experience in taking care of seriously ill relatives (p=0.0058) (Table 4).

### 5.1.4 Knowledge and views of pain and dyspnea treatment (study II)

The knowledge of the WHO analgesic principles differed between oncologists and other physicians (Table 5). Sixty-eight percent of the oncologists and 13% of the other physicians had the opinion that they knew the WHO analgesic ladder in detail. When their knowledge of the number of steps in the WHO analgesic ladder was asked, 32% of the other physicians and 46% of the oncologists could recall that the ladder consists of three steps. Eighty percent of the oncologists had the opinion that medication should be used only when needed compared with 2% of the other physicians (p <0.0001). Sixty-nine percent of the oncologists preferred enteral dosing compared with 40% of the other physicians (p <0.0001).
Table 4. Views among the group of other physicians when meeting dying patients. Assessed with a question: “Do you have any fears in a situation when meeting a dying patient or a patient with incurable disease?” The question was answered by 649 physicians (n=649).

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Yes</th>
<th>Univariate</th>
<th>Multivariate&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>%</td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Sex&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>423</td>
<td>133</td>
<td>31</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>male</td>
<td>225</td>
<td>36</td>
<td>16</td>
<td>0.42 (0.28–0.63)</td>
<td><strong>&lt;0.0001</strong></td>
<td>0.52 (0.33 – 0.81)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>257</td>
<td>41</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>36-50 years</td>
<td>249</td>
<td>66</td>
<td>27</td>
<td>1.90 (1.23–2.94)</td>
<td><strong>0.004</strong></td>
<td>1.48 (0.92 – 2.37)</td>
</tr>
<tr>
<td>&lt; 36 years</td>
<td>143</td>
<td>62</td>
<td>43</td>
<td>4.03 (2.52–6.45)</td>
<td><strong>&lt; 0.0001</strong></td>
<td>2.65 (1.49 – 4.74)</td>
</tr>
<tr>
<td><strong>Speciality&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal medicine</td>
<td>156</td>
<td>23</td>
<td>15</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>General practice</td>
<td>298</td>
<td>75</td>
<td>25</td>
<td>1.95 (1.16–3.25)</td>
<td><strong>0.011</strong></td>
<td>1.59 (0.93 – 2.72)</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>33</td>
<td>7</td>
<td>21</td>
<td>1.56 (0.61–4.00)</td>
<td>0.358</td>
<td>1.10 (0.42 – 2.92)</td>
</tr>
<tr>
<td>Specialising physician</td>
<td>113</td>
<td>47</td>
<td>42</td>
<td>4.12 (2.31–7.35)</td>
<td><strong>&lt;0.0001</strong></td>
<td>1.81 (0.92 – 3.54)</td>
</tr>
<tr>
<td>Other</td>
<td>29</td>
<td>10</td>
<td>34</td>
<td>3.04 (1.26–7.37)</td>
<td><strong>0.014</strong></td>
<td>2.70 (1.07 – 6.75)</td>
</tr>
<tr>
<td><strong>Taken care of a seriously ill relative&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>447</td>
<td>137</td>
<td>31</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>198</td>
<td>31</td>
<td>16</td>
<td>0.42 (0.27–0.65)</td>
<td><strong>&lt;0.0001</strong></td>
<td>0.52 (0.33 – 0.83)</td>
</tr>
<tr>
<td><strong>Attitude towards euthanasia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no/dnk&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes&lt;sup&gt;d&lt;/sup&gt;</td>
<td>124</td>
<td>25</td>
<td>20</td>
<td>0.67 (0.41–1.08)</td>
<td>0.099</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Those significant in univariate analysis included in the model.
<sup>b</sup> Information missing from one respondent (n=648)
<sup>c</sup> Information missing from 32 respondents (n=629)
<sup>d</sup> Information missing from 16 respondents (n=645)
<sup>e</sup> Physicians answering ‘no or do not know’ to the question: “Should active euthanasia be permitted in Finland?”
<sup>f</sup> Physicians answering ‘yes’ to the question: “Should active euthanasia be permitted in Finland?”
Table 5. The expertise with the WHO analgesic principles among the responding physicians. Table adopted from Study II.

<table>
<thead>
<tr>
<th></th>
<th>Other physicians</th>
<th>Oncologists</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How do you grade your knowledge of the WHO analgesic ladder?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I know it in detail</td>
<td>87 (13%)</td>
<td>40 (68%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I know the principle but not the details</td>
<td>260 (40%)</td>
<td>12 (20%)</td>
<td></td>
</tr>
<tr>
<td>I know the concept only partly</td>
<td>145 (22%)</td>
<td>7 (12%)</td>
<td></td>
</tr>
<tr>
<td>I do not know it</td>
<td>160 (25%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>How many steps are there in the WHO analgesic ladder?</strong></td>
<td>463 (b)</td>
<td>58 (c)</td>
<td></td>
</tr>
<tr>
<td>1 or 2 steps</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.0014</td>
</tr>
<tr>
<td>three steps</td>
<td>150 (32%)</td>
<td>27 (46%)</td>
<td></td>
</tr>
<tr>
<td>four steps</td>
<td>246 (53%)</td>
<td>29 (49%)</td>
<td></td>
</tr>
<tr>
<td>five steps</td>
<td>67 (14%)</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Which of the following principles correspond to the guidelines of WHO?</strong></td>
<td>658 (e)</td>
<td>59 (0%)</td>
<td></td>
</tr>
<tr>
<td>Medication only when needed</td>
<td>15 (2%)</td>
<td>47 (80%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medication regularly by the clock</td>
<td>124 (19%)</td>
<td>8 (14%)</td>
<td>0.3156</td>
</tr>
<tr>
<td>Parenteral dosing preferred</td>
<td>69 (11%)</td>
<td>41 (69%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Enteral dosing preferred</td>
<td>265 (40%)</td>
<td>41 (69%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Combining the different steps</td>
<td>480 (73%)</td>
<td>23 (39%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* information missing from nine respondents in the group of other physicians (n=652)
* information missing from 198 respondents in the group of other physicians (n=463)
* information missing from one respondent in the group of oncologists (n=58)
* multiple alternatives possible to choose
* information missing from three respondents in the group of other physicians (n=658)
Results

In the treatment of neuropathic pain respondents recommended anti-convulsants (100% of the oncologists and 70% of others, $p<0.0001$) or anti-depressants (90% and 67%, respectively, $p=0.0003$) together with opioids. Oncologists favoured steroids (76%), NSAIDs (69%) and neuroleptic drugs (61%) in the treatment of neuropathic pain significantly more often than other physicians who were not so acquainted with these medications (13%, 30% and 24% respectively, $p<0.0001$ for each).

One of the questions assessed the palliative management of dyspnoea with opioids. Nearly all oncologists (98%) knew that if there is no curable treatment for dyspnea symptoms can be alleviated with opioids. The proportion of other physicians giving this same answer was 73% ($p<0.0001$). A majority of the respondents knew that opioids are not contraindicated for treating a severe, incurable dyspnoea (98% and 93%, respectively).

The physicians evaluated if the following treatments would be valid for relieving symptoms of advanced cancer: radiation therapy, chemotherapy or surgery. All the oncologists and 96% of the other specialists recommended radiation therapy ($p=0.10$), 83% of oncologists and 76% of other physicians recommended surgery ($p=0.25$), and 78% and 65% considered chemotherapy acceptable ($p=0.041$).

5.1.5  *Perceptions of the status of cancer pain treatment in Finland among respondents (study II)*

Sixty-one percent of the other physicians and 47% of the oncologists considered that most of the cancer patients in Finland receive good pain treatment.

Both groups of respondents named similar main factors for insufficient cancer pain control. Underestimation of pain severity and physicians’ inadequate skills in pain treatment were identified to be the most essential elements. Additionally, causing possible drug addiction to opioids was estimated to be one of the main reasons for inadequate pain treatment (Table 6).
Table 6. Respondents estimation of state of cancer pain management in Finland and reasons for inadequate treatment of pain. Table adopted from Study II.

<table>
<thead>
<tr>
<th>What is your estimation of the state of pain treatment of cancer patients in Finland?</th>
<th>Other physicians</th>
<th>Oncologists</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most of the cancer patients receive good pain treatment</td>
<td>401 61</td>
<td>28 47</td>
<td>0.1143</td>
</tr>
<tr>
<td>Most of the cancer patients’ pain is undertreated</td>
<td>229 35</td>
<td>28 47</td>
<td></td>
</tr>
<tr>
<td>I can’t say</td>
<td>24 4</td>
<td>3 5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What are the reasons for inadequate treatment of pain?</th>
<th>Other physicians</th>
<th>Oncologists</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underestimation of pain</td>
<td>509 77</td>
<td>47 80</td>
<td>0.6697</td>
</tr>
<tr>
<td>Inadequate skills of physicians</td>
<td>457 69</td>
<td>43 73</td>
<td>0.5717</td>
</tr>
<tr>
<td>Fear of drug addiction</td>
<td>268 41</td>
<td>32 54</td>
<td>0.0429</td>
</tr>
<tr>
<td>Prescribing pain medicine to be used only when needed</td>
<td>258 39</td>
<td>31 53</td>
<td>0.0445</td>
</tr>
<tr>
<td>Requirement of special prescription forms for opioids</td>
<td>229 35</td>
<td>16 27</td>
<td>0.2363</td>
</tr>
<tr>
<td>Wrong diagnosis of pain</td>
<td>167 25</td>
<td>13 22</td>
<td>0.5744</td>
</tr>
<tr>
<td>Other</td>
<td>80 12</td>
<td>9 15</td>
<td>0.4867</td>
</tr>
</tbody>
</table>

*a information missing from seven respondent in the group of other physicians (n=654)

*b multiple alternatives possible to choose

5.1.6 Perceptions of training in palliative care (study II)

Only 24% of the other physicians and 58% of the oncologists considered the education on pain treatment to be adequate (p<0.0001). Furthermore, the status of training in palliative care was considered unsatisfactory by 95% of the other physicians and 76% of the oncologists (p<0.0001).

The other physicians group stated pain management and palliative care basics to be the most important fields requiring more training. Nearly two thirds of the oncologists expressed needs for training in interaction and communication skills. Education on palliative home care and ethical questions in palliative care were also named as essential (Table 7).
Table 7. Three fields on training needs. The respondents were asked to name three fields in which they wish to have more training. Table adopted from Study II.

<table>
<thead>
<tr>
<th></th>
<th>Other physicians</th>
<th>Oncologists</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Interaction and communication</td>
<td>192</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>Ethical questions in end-of-life care</td>
<td>178</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Developing end-of-life care at home</td>
<td>157</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Treatment of pain</td>
<td>349</td>
<td>53</td>
<td>12</td>
</tr>
<tr>
<td>Basics of palliative care</td>
<td>328</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>End-of-life care in general</td>
<td>251</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>Examination and treatment of symptoms</td>
<td>156</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Sedation</td>
<td>140</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Legislation concerning euthanasia</td>
<td>100</td>
<td>15</td>
<td>8</td>
</tr>
</tbody>
</table>

*Information missing from seven respondents in the group of other physicians (n=654)*

5.2 Survey of NSCLC patients’ symptoms and quality of life (studies III and IV)

5.2.1 Patient characteristics

Altogether 154 consecutive patients planned for chemotherapy were asked to participate the study. Ten patients did not meet the inclusion criteria and 22 patients refused. Finally, 122 patients (79% of total addressed) were included in the study.

Forty-six (38%) of the patients were females. The mean age of the whole patient population was 67 years (range 45-86 years). The majority of the patients were smokers or former smokers (87%). More than a half of the patients had a diagnosis of adenocarcinoma (54%), 36% had a squamous cell carcinoma, and 10% formed the group of “other” including the diagnoses of a large cell carcinoma, a poorly differentiated carcinoma, or a NSCLC not otherwise specified (NOS).

Twenty-eight percent of patients had a Stage III and 65% a Stage IV NSCLC. The main metastasis site was lymph nodes: 19 patients (16%) had N1 disease, 46 patients (38%) N2 disease and 31 patients (25%) N3 disease. Twenty-eight percent...
of the patients had pleural metastases, 16% had bone metastases, 6% liver metastases, 12% brain metastases and 15% adrenal gland metastases. Nine patients (7%) had a stage I or II disease at the time of diagnosis and six of them were operated before the study. At the time of the beginning of the study they had showed a local or mediastinal recurrence of the disease.

No significant differences existed in the baseline characteristics between males and females, apart from smoking status (Table 8). About half (51%) of the patients had a cardiovascular disease, and one fifth (21%) had a diagnosis of COPD (Table 9).

No patient had received cancer chemotherapy before the study. Fourteen patients (11%) had undergone lung surgery but experienced progressive disease and were treated with chemotherapy. Eighteen (15%) patients had received radiotherapy, 17 patients mainly for palliation of symptoms such as brain metastases, vena cava syndrome or pain and one patient for a curative intent (Table 10).

The first-line chemotherapy mainly consisted of carboplatin or cisplatin combined with gemcitabine (n=46, 37%), pemetrexed (n=27, 22%) or vinorelbine (n=12, 10%). Some patients received only single-agent chemotherapy with gemcitabine (n=26, 21%) or pemetrexed (n=9, 7%). Sixty-three percent of men (n=48) and 70% of women (n=32) had a partial response or a stable disease after first line chemotherapy. No significant difference existed in the response rates between men and women (p=0.4704).

Erlotinib was given for second line treatment for thirteen (17%) men and twelve (26%) women. The EGFR mutation status was not known.

Ninety-three patients (76%) remained in the study at the three-month study point and 71 patients (58%) at six months. The reason for this decline in the number of patients was mainly due to the patients’ death by six months (n=40). Four patients were admitted to another institution during the study, and five patients dropped out because they were too weak to complete the questionnaire.

At three-month timepoint, 54 patients (58% of remaining study patients) received chemotherapy; 46 patients as a first line, seven patients as a second line and one patient as a third line treatment. Two patients were on erlotinib treatment. At six months, 14 patients (20% of remaining study patients) had ongoing chemotherapy and five patients received erlotinib.
Table 8. Patient characteristics by gender, and p-values showing statistical significance of differences between the groups (n=122). Table modified from Study III.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male n (%)</th>
<th>Female n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>76 (62.3)</td>
<td>46 (37.7)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60 years</td>
<td>14 (18.4)</td>
<td>8 (17.4)</td>
<td>0.9684</td>
</tr>
<tr>
<td>60-70 years</td>
<td>38 (50.0)</td>
<td>22 (47.8)</td>
<td></td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td>24 (31.6)</td>
<td>16 (34.8)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adenocarcinoma</td>
<td>39 (51.3)</td>
<td>27 (58.7)</td>
<td>0.4034</td>
</tr>
<tr>
<td>SCC</td>
<td>31 (40.8)</td>
<td>13 (28.3)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>6 (7.9)</td>
<td>6 (13.0)</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>3 (4.0)</td>
<td>13 (28.9)</td>
<td>0.0004*</td>
</tr>
<tr>
<td>Former</td>
<td>42 (56.0)</td>
<td>16 (35.6)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>30 (40.0)</td>
<td>16 (35.6)</td>
<td></td>
</tr>
<tr>
<td>Total pack years:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>under 10 years</td>
<td>1 (1.4)</td>
<td>4 (12.5)</td>
<td>0.0070*</td>
</tr>
<tr>
<td>11 – 40 years</td>
<td>40 (55.6)</td>
<td>22 (68.8)</td>
<td></td>
</tr>
<tr>
<td>over 40 years</td>
<td>31 (43.1)</td>
<td>6 (18.8)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (2.6)</td>
<td>2 (4.4)</td>
<td>0.2200</td>
</tr>
<tr>
<td>II</td>
<td>5 (6.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>23 (30.3)</td>
<td>11 (23.9)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>46 (60.5)</td>
<td>33 (71.7)</td>
<td></td>
</tr>
<tr>
<td>Metastases at the time of diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lymph nodes</td>
<td>60 (80.0)</td>
<td>38 (82.6)</td>
<td>0.8146</td>
</tr>
<tr>
<td>pleura</td>
<td>20 (26.3)</td>
<td>14 (30.4)</td>
<td>0.6792</td>
</tr>
<tr>
<td>bone</td>
<td>12 (15.8)</td>
<td>7 (15.2)</td>
<td>1.0000</td>
</tr>
<tr>
<td>liver</td>
<td>4 (5.3)</td>
<td>3 (6.5)</td>
<td>1.0000</td>
</tr>
<tr>
<td>brain</td>
<td>9 (11.8)</td>
<td>6 (13.0)</td>
<td>1.0000</td>
</tr>
<tr>
<td>adrenal gland</td>
<td>11 (14.5)</td>
<td>7 (15.2)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Performance status (Zubrod)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12 (15.8)</td>
<td>14 (30.4)</td>
<td>0.1684</td>
</tr>
<tr>
<td>1</td>
<td>53 (69.7)</td>
<td>28 (60.9)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10 (13.2)</td>
<td>3 (6.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (1.3)</td>
<td>1 (2.2)</td>
<td></td>
</tr>
</tbody>
</table>

*a statistically significant difference
SCC = squamous cell carcinoma
Table 9. Concurrent diseases of the NSCLC patients at the beginning of the chemotherapy. Table modified from Study III.

<table>
<thead>
<tr>
<th>Disease</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>62 (50.8)</td>
</tr>
<tr>
<td>Lung*</td>
<td>29 (23.7)</td>
</tr>
<tr>
<td>COPD**</td>
<td>26 (21.3)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>18 (14.8)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>17 (13.9)</td>
</tr>
<tr>
<td>Gastrointestinal/hepatic</td>
<td>9 (7.4)</td>
</tr>
<tr>
<td>Kidney</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Neurological</td>
<td>6 (4.9)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>6 (4.9)</td>
</tr>
<tr>
<td>Rheumatic</td>
<td>7 (5.7)</td>
</tr>
<tr>
<td>Urological</td>
<td>8 (6.6)</td>
</tr>
<tr>
<td>Previous cancer</td>
<td>21 (17.2)</td>
</tr>
</tbody>
</table>

* All lung diseases included.
** Chronic obstructive pulmonary disease

Table 10. Treatment of NSCLC patients before the study. Table modified from Study III.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Surgery with curative intent</td>
<td>14 (11.5)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>11</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>1</td>
</tr>
<tr>
<td>Wedge resection</td>
<td>2</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>18 (14.8)</td>
</tr>
<tr>
<td>Radical RT</td>
<td>1</td>
</tr>
<tr>
<td>Brain metastases RT</td>
<td>10</td>
</tr>
<tr>
<td>Vena cava SDR RT</td>
<td>3</td>
</tr>
<tr>
<td>Bone metastases RT</td>
<td>2</td>
</tr>
<tr>
<td>Other palliative RT</td>
<td>2</td>
</tr>
</tbody>
</table>

RT = Radiotherapy, SDR = Syndrome
5.2.2 Baseline symptoms

The median EORTC QLQ-C30 questionnaire score for global QOL was 54.2 at baseline, i.e. in the beginning of chemotherapy. In the functional scales, cognitive, emotional and social functioning had the highest scores (83.3, for each), while the lowest scores were for physical and role functioning (66.7, for both).

The EORTC symptom scales showed that the most prominent symptoms at baseline were coughing, dyspnea, fatigue, insomnia and pain (Table 11).

Gender, age, number of pack years, pathological diagnosis, stage or the location of the metastases (brain or bone) were not significantly associated with global QOL or the symptoms in the study population at baseline.

Nevertheless, decreased cognitive functioning (p=0.003), emotional functioning (p=0.041) and physical functioning (p=0.013), in addition to increased dyspnea (p=0.0002), diarrhea (p=0.020) and insomnia (p=0.037) had all a significant negative influence on global QOL at baseline in the multivariate analysis.

Dyspnea was observed to have a significant negative effect on physical function (p<0.0001), but the number of pack years was not significantly associated with the symptom of dyspnea.
Table 11. Symptoms during the study: At baseline and at 3 and 6 months after the baseline. Table adopted from Study IV manuscript.

a) Symptoms of the whole patient group

<table>
<thead>
<tr>
<th>EORTC QLQ-C30(^1)</th>
<th>Baseline n=122</th>
<th>3 months n=93</th>
<th>6 months n=71</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mdn  M  IQR</td>
<td>Mdn  M  IQR</td>
<td>Mdn  M  IQR</td>
</tr>
<tr>
<td>Global Quality of Life</td>
<td>54.2 56.9 33.3-79.2</td>
<td>58.3 59.2 41.7-83.3</td>
<td>54.2 56.7 33.3-83.3</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>66.7 64.4 46.7-83.3</td>
<td>60.0 60.2 40.0-80.0</td>
<td>66.7 61.8 40.0-86.7</td>
</tr>
<tr>
<td>Role functioning</td>
<td>66.7 63.5 33.3-83.3</td>
<td>83.3 64.9 33.3-100.0</td>
<td>66.7 66.4 50.0-100.0</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>83.3 82.8 66.7-100.0</td>
<td>83.3 83.7 66.7-100.0</td>
<td>83.3 83.1 66.7-100.0</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>83.3 75.2 66.7-91.7</td>
<td>75.0 76.4 66.7-91.7</td>
<td>83.3 77.3 66.7-100.0</td>
</tr>
<tr>
<td>Social functioning</td>
<td>83.3 81.1 66.7-100.0</td>
<td>83.3 78.1 66.7-100.0</td>
<td>100.0 83.3 66.7-100.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33.3 31.9 22.2-44.4</td>
<td>33.3 39.1 22.2-55.6</td>
<td>33.3 34.7 22.2-55.6</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>0.0 5.0 0.0-0.0</td>
<td>0.0 13.1 0.0-16.7</td>
<td>0.0 7.7 0.0-16.7</td>
</tr>
<tr>
<td>Pain</td>
<td>16.7 21.8 0.0-33.3</td>
<td>16.7 26.9 0.0-50.0</td>
<td>16.7 27.5 0.0-50.0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>33.3 33.9 0.0-66.7</td>
<td>33.3 35.5 0.0-66.7</td>
<td>33.3 34.7 0.0-66.7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>33.3 30.3 0.0-33.3</td>
<td>33.3 26.1 0.0-33.3</td>
<td>33.3 27.7 0.0-33.3</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>0.0 19.3 0.0-33.3</td>
<td>0.0 23.8 0.0-33.3</td>
<td>0.0 23.9 0.0-33.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.0 16.0 0.0-33.3</td>
<td>0.0 21.4 0.0-33.3</td>
<td>0.0 16.7 0.0-33.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.0 5.8 0.0-0.0</td>
<td>0.0 9.8 0.0-0.0</td>
<td>0.0 9.5 0.0-0.0</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>0.0 23.1 0.0-33.3</td>
<td>0.0 17.0 0.0-33.3</td>
<td>0.0 17.9 0.0-33.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EORTC QLQ-LC13(^2)</th>
<th>Baseline n=122</th>
<th>3 months n=93</th>
<th>6 months n=71</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mdn  M  IQR</td>
<td>Mdn  M  IQR</td>
<td>Mdn  M  IQR</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22.2 32.7 11.1-44.4</td>
<td>33.3 35.0 22.2-44.4</td>
<td>22.2 30.1 22.2-44.4</td>
</tr>
<tr>
<td>Coughing</td>
<td>33.3 41.7 33.3-66.7</td>
<td>33.3 31.5 33.3-33.3</td>
<td>33.3 39.0 33.3-66.7</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>0.0 7.2 0.0-0.0</td>
<td>0.0 4.3 0.0-0.0</td>
<td>0.0 4.3 0.0-0.0</td>
</tr>
<tr>
<td>Sore mouth</td>
<td>0.0 9.5 0.0-0.0</td>
<td>0.0 9.9 0.0-0.0</td>
<td>0.0 11.4 0.0-33.3</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0.0 8.3 0.0-0.0</td>
<td>0.0 6.9 0.0-0.0</td>
<td>0.0 6.1 0.0-0.0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0.0 11.9 0.0-33.3</td>
<td>0.0 20.3 0.0-33.3</td>
<td>33.3 21.1 0.0-33.3</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0.0 10.3 0.0-0.0</td>
<td>33.3 38.5 0.0-66.7</td>
<td>33.3 31.4 0.0-66.7</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0.0 17.8 0.0-33.3</td>
<td>33.3 21.0 0.0-33.3</td>
<td>0.0 18.4 0.0-33.3</td>
</tr>
<tr>
<td>Arm pain</td>
<td>0.0 18.6 0.0-33.3</td>
<td>33.3 20.1 0.0-33.3</td>
<td>0.0 18.8 0.0-33.3</td>
</tr>
<tr>
<td>Other pain</td>
<td>0.0 22.6 0.0-33.3</td>
<td>33.3 25.9 0.0-33.3</td>
<td>33.3 23.7 0.0-33.3</td>
</tr>
</tbody>
</table>

Mdn = median, M = Mean, IQR = Interquartile range

\(^1\) EORTC Quality of Life Questionnaire QLQ-C30

\(^2\) EORTC Lung cancer-specific questionnaire EORTC QLQ-LC13.

All the scales and single-item measures ranged in score from 0 to 100. A high score for a functional scale represented a high level of functioning, and a high score for QOL represented a high QOL, while a high score for a symptom item represented a high level of symptomatology and problems.
b) Symptoms of male patients during the study

<table>
<thead>
<tr>
<th>EORTC QLQ-C30¹</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mdn M IQR</td>
<td>Mdn M IQR</td>
<td>Mdn M IQR</td>
</tr>
<tr>
<td>Global Quality of Life</td>
<td>50.0 54.6 33.3-75.0</td>
<td>58.3 56.9 41.7-66.7</td>
<td>50.0 50.4 33.3-66.7</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>66.7 63.8 46.7-80.0</td>
<td>53.3 54.9 33.3-80.0</td>
<td>60.0 58.5 40.0-80.0</td>
</tr>
<tr>
<td>Role functioning</td>
<td>66.7 61.7 33.3-83.3</td>
<td>66.7 59.8 33.3-83.3</td>
<td>66.7 63.6 50.0-83.3</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>83.3 81.6 66.7-100.0</td>
<td>83.3 83.9 66.7-100.0</td>
<td>83.3 80.6 66.7-100.0</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>83.3 77.4 66.7-91.7</td>
<td>77.8 78.1 66.7-91.7</td>
<td>83.3 78.7 66.7-100.0</td>
</tr>
<tr>
<td>Social functioning</td>
<td>83.3 78.6 66.7-100.0</td>
<td>83.3 75.1 66.7-100.0</td>
<td>83.3 81.0 66.7-100.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33.3 33.6 22.2-44.4</td>
<td>33.3 41.3 22.2-55.6</td>
<td>33.3 38.6 22.2-55.6</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>0.0 5.0 0.0-0.0</td>
<td>16.7 12.1 0.0-16.7</td>
<td>0.0 7.8 0.0-16.7</td>
</tr>
<tr>
<td>Pain</td>
<td>16.7 23.8 0.0-33.3</td>
<td>25.0 28.7 0.0-50.0</td>
<td>33.3 29.5 0.0-50.0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>33.3 36.0 0.0-66.7</td>
<td>33.3 38.5 0.0-66.7</td>
<td>33.3 38.0 0.0-66.7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>33.3 24.9 0.0-33.3</td>
<td>33.3 24.1 0.0-33.3</td>
<td>33.3 24.8 0.0-33.3</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>0.0 20.0 0.0-33.3</td>
<td>33.3 25.7 0.0-33.3</td>
<td>33.3 28.7 0.0-66.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.0 16.0 0.0-33.3</td>
<td>0.0 21.1 0.0-33.3</td>
<td>0.0 15.5 0.0-33.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.0 5.3 0.0-0.0</td>
<td>0.0 10.5 0.0-0.0</td>
<td>0.0 11.6 0.0-0.0</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>0.0 18.7 0.0-33.3</td>
<td>0.0 14.9 0.0-33.3</td>
<td>0.0 13.8 0.0-33.3</td>
</tr>
</tbody>
</table>

EORTC QLQ-LC13²

| Dyspnea | 33.3 35.3 22.2-50.0 | 33.3 38.1 22.2-50.0 | 33.3 33.9 22.2-44.4 |
| Coughing | 33.3 42.8 33.3-66.7 | 33.3 35.1 33.3-33.3 | 33.3 41.9 33.3-66.7 |
| Hemoptysis | 0.0 6.7 0.0-0.0 | 0.0 1.7 0.0-0.0 | 0.0 5.6 0.0-0.0 |
| Sore mouth | 0.0 7.6 0.0-0.0 | 0.0 8.2 0.0-33.3 | 0.0 11.6 0.0-33.3 |
| Dysphagia | 0.0 7.6 0.0-0.0 | 0.0 7.0 0.0-0.0 | 0.0 7.0 0.0-0.0 |
| Peripheral neuropathy | 0.0 12.0 0.0-33.3 | 0.0 21.3 0.0-33.3 | 33.3 22.5 0.0-33.3 |
| Alopecia | 0.0 7.6 0.0-0.0 | 33.3 32.2 0.0-33.3 | 33.3 29.4 0.0-33.3 |
| Chest pain | 33.3 19.6 0.0-33.3 | 33.3 20.7 0.0-33.3 | 16.7 19.8 0.0-33.3 |
| Arm pain | 0.0 20.3 0.0-33.3 | 33.3 21.4 0.0-33.3 | 0.0 17.1 0.0-33.3 |
| Other pain | 0.0 22.9 0.0-33.3 | 0.0 25.2 0.0-33.3 | 33.3 24.2 0.0-33.3 |

Mdn = median, M = Mean, IQR = Interquartile range

¹ EORTC Quality of Life Questionnaire QLQ-C30
² EORTC Lung cancer-specific questionnaire EORTC QLQ-LC13.

All the scales and single-item measures ranged in score from 0 to 100. A high score for a functional scale represented a high level of functioning, and a high score for QOL represented a high QOL, while a high score for a symptom item represented a high level of symptomatology and problems.
c) Symptoms of female patients during the study

<table>
<thead>
<tr>
<th>EORTC QLQ-C30</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=46</td>
<td>n=35</td>
<td>n=28</td>
</tr>
<tr>
<td></td>
<td>Mdn</td>
<td>M</td>
<td>IQR</td>
</tr>
<tr>
<td>Global Quality of Life</td>
<td>58.3</td>
<td>60.5</td>
<td>41.7-83.3</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>73.3</td>
<td>65.4</td>
<td>46.7-86.7</td>
</tr>
<tr>
<td>Role functioning</td>
<td>66.7</td>
<td>66.3</td>
<td>50.0-100.0</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>91.7</td>
<td>84.8</td>
<td>66.7-100.0</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>75.0</td>
<td>71.5</td>
<td>58.3-83.3</td>
</tr>
<tr>
<td>Social functioning</td>
<td>100.0</td>
<td>85.1</td>
<td>66.7-100.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22.2</td>
<td>29.2</td>
<td>22.2-33.3</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>0.0</td>
<td>5.1</td>
<td>0.0-0.0</td>
</tr>
<tr>
<td>Pain</td>
<td>16.7</td>
<td>18.5</td>
<td>0.0-33.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>33.3</td>
<td>30.4</td>
<td>0.0-33.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>33.3</td>
<td>39.1</td>
<td>33.3-66.7</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>0.0</td>
<td>18.1</td>
<td>0.0-33.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.0</td>
<td>15.9</td>
<td>0.0-33.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.0</td>
<td>6.7</td>
<td>0.0-0.0</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>33.3</td>
<td>30.3</td>
<td>0.0-50.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EORTC QLQ-LC13</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=46</td>
<td>n=35</td>
<td>n=28</td>
</tr>
<tr>
<td></td>
<td>Mdn</td>
<td>M</td>
<td>IQR</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22.2</td>
<td>28.2</td>
<td>11.1-44.4</td>
</tr>
<tr>
<td>Coughing</td>
<td>33.3</td>
<td>40.0</td>
<td>33.3-66.7</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>0.0</td>
<td>8.1</td>
<td>0.0-0.0</td>
</tr>
<tr>
<td>Sore mouth</td>
<td>0.0</td>
<td>12.9</td>
<td>0.0-33.3</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0.0</td>
<td>9.6</td>
<td>0.0-0.0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0.0</td>
<td>11.9</td>
<td>0.0-33.3</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0.0</td>
<td>14.8</td>
<td>0.0-0.0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0.0</td>
<td>14.7</td>
<td>0.0-33.3</td>
</tr>
<tr>
<td>Arm pain</td>
<td>0.0</td>
<td>15.9</td>
<td>0.0-33.3</td>
</tr>
<tr>
<td>Other pain</td>
<td>33.3</td>
<td>22.2</td>
<td>0.0-33.3</td>
</tr>
</tbody>
</table>

Mdn = median, M = Mean, IQR = Interquartile range

1 EORTC Quality of Life Questionnaire QLQ-C30
2 EORTC Lung cancer-specific questionnaire EORTC QLQ-LC13.

All the scales and single-item measures ranged in score from 0 to 100. A high score for a functional scale represented a high level of functioning, and a high score for QOL represented a high QOL, while a high score for a symptom item represented a high level of symptomatology and problems.
5.2.3  *Symptom severity comparison with EORTC reference values (study III)*

Physical functioning scores in this study were noticeably lower (mean score 64.4) than the reference scores for NSCLC patients (mean 78.4) and for all cancer patients (76.7) (Figure 2). Dyspnea was regarded as a distressing symptom, with a mean score of 33.9, which was nearly at the same level as the NSCLC reference score (38.5) but still considerably higher than the score for all cancer patients (21.0). Additionally, coughing was one of the most disturbing symptoms (41.7), corresponding to the reference value of NSCLC patients (38.4). The global QOL score was nearly similar for all groups (56.9 for the study group, 58.8 for the NSCLC reference group and 61.3 for all cancer patients).
Figure 2. Mean baseline scores for functional and symptom domains of the (a) European Organisation for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30) and (b) lung cancer-specific questionnaire (QLQ-LC13) for study patients compared to a reference population of all-cancer patients and a reference population of patients with non-small cell lung cancer (NSCLC) at all stages. Figure adopted from Study III.
5.2.4 Pain progression during the study period (study IV)

The patients expressed pain throughout the entire study period, and the pain intensity of the whole patient group increased from baseline to the 6-month follow-up point (p=0.0014) (Table 11).

In a multivariate analysis, pain was found to increase more for men with a significant difference compared to women (p=0.0240) (Table 11).

Patients with bone metastases also had significantly more pain (median at baseline 33.3, IQR 16.7-50.0 vs. median at six months 66.7, IQR 0.0-83.3) than patients without them (16.7, IQR 0.0-33.3 vs. 16.7, IQR 0.0-41.7, respectively) (p=0.0052).

Among patients in the diagnosis group of “other”, including the diagnoses of a large cell carcinoma, a poorly differentiated carcinoma or NOS, pain increased significantly (median at baseline 33.3, IQR 0.0-41.7 vs. median at six months 83.3, IQR 50.0-83.3) (p=0.0167) compared to patients with adenocarcinoma or squamous cell carcinoma whose pain intensity stayed mainly on the same level during these six months (at baseline and at six months, median 16.7, IQR 0.0 - 33.3).

All the other factors studied were not significantly associated with pain in the multivariate analysis.

5.2.5 Other symptoms and QOL during the study period (study IV)

The whole patient group experienced no significant changes in the global QOL during the study period. However, in a multivariate analysis global QOL was significantly better among women compared to men during the six-month period (p=0.0049).

The patients’ physical functioning declined from the baseline to the 3-month time point (p=0.0064) and between the baseline and the 6-month time point (p=0.0355).

The symptoms of nausea and vomiting were more intense at three months than at baseline (p<0.0001). The intensity of fatigue (p=0.0002), and the intensity of constipation (p=0.0213) increased, as well. The level of nausea and vomiting remained more intense after six months compared to baseline (p=0.0469), but all the other symptoms decreased nearly to the same level as at the baseline.
5.2.6 ESAS results

The median ESAS scores of the study patients stayed mainly under the score of three and did not change significantly during the study period. Fatigue and dyspnea were the most prominent symptoms (Figure 3).

![ESAS scores graph](image)

*Figure 3. The median ESAS scores of the study patients.*

5.2.7 Depression

At the baseline 43% of patients represented with no depression, 40% had mild depression and 15% had moderate depression measured by BDI. Only two patients (2%) expressed severe depression (Figure 4). The status of depression did not change significantly during the six-month study period and did not affect survival. One patient expressing severe depression at the baseline committed suicide during the study.
Figure 4. Depression of NSCLC patients during the study.

5.2.8 Symptom assessment comparison between EORTC and ESAS questionnaires (study III)

A strong positive correlation between EORTC QLQ-C30 and ESAS questionnaires was found for all symptoms except nausea and vomiting (Table 12). Most of the correlation coefficients were over 0.7 (range 0.546–0.865, p<0.0001 for all symptoms). Only global QOL measured with QLQ-C30 compared to total well-being measured with ESAS had a lower correlation coefficient 0.577. This was also seen between QLQ-C30 symptom “nausea and vomiting” and ESAS symptom “nausea”.

Table 12. The association of Edmonton Symptom Assessment Scale (ESAS) to the European Organisation for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30). Table adopted from Study III.

<table>
<thead>
<tr>
<th>EORTC QLQ-C30</th>
<th>ESAS Correlation coefficient p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOL Total well-being</td>
<td>0.577 &lt;0.0001</td>
</tr>
<tr>
<td>Pain Pain at rest or upon effort</td>
<td>0.763 &lt;0.0001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.704 &lt;0.0001</td>
</tr>
<tr>
<td>Nausea and vomiting Nausea</td>
<td>0.546 &lt;0.0001</td>
</tr>
<tr>
<td>Dyspnea Dyspnea</td>
<td>0.800 &lt;0.0001</td>
</tr>
<tr>
<td>Loss of appetite Loss of appetite</td>
<td>0.761 &lt;0.0001</td>
</tr>
<tr>
<td>Insomnia Insomnia</td>
<td>0.819 &lt;0.0001</td>
</tr>
<tr>
<td>Constipation Constipation</td>
<td>0.865 &lt;0.0001</td>
</tr>
</tbody>
</table>

5.2.9 Patient characteristics’ and symptoms’ influence on survival (study IV)

The follow-up period for survival of the study patients was up to March 2018. The median survival was 259 days (IQR 133-607 days) and at this timepoint four patients were alive.

Gender, concurrent diseases or smoking status did not have any significant association with survival. However, high PS at baseline (p<0.0001), high tumor stage (p=0.0199) and bone metastases (p=0.0096) were significant negative predictive factors in the univariate model.

The global QOL score at baseline did not influence survival, yet, patients with severe pain at the baseline had a poorer survival (p=0.0296).

Two of the functional scales at baseline had a significant effect on survival, namely, role functioning (p<0.0001) and social functioning (p=0.0005). The survival was worse if the functioning was low (Figure 5).
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</tr>
</thead>
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Figure 5. The Kaplan-Meyer curves of overall survival time for study patients, by the EORTC QLQ-C30 questionnaire’s subscale scores of pain (a), social functioning (b) and role functioning (c). Survival was compared between the groups using the Log-Rank test with p-values shown in the figure text. Figures adopted from Study IV manuscript.

(a) EORTC QLQ-C30 pain. Subscale score divided into two groups by the median score at baseline (n=121) (p=0.0296). Hazard ratio (HR) for death: 1.85 (95% CI, 1.1-3.2).

<table>
<thead>
<tr>
<th>No/little pain</th>
<th>Severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>49</td>
</tr>
<tr>
<td>72</td>
<td>47</td>
</tr>
<tr>
<td>65</td>
<td>40</td>
</tr>
<tr>
<td>60</td>
<td>39</td>
</tr>
<tr>
<td>56</td>
<td>36</td>
</tr>
<tr>
<td>53</td>
<td>30</td>
</tr>
<tr>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>17</td>
<td>2</td>
</tr>
</tbody>
</table>

No/little pain = Baseline scores below median (n=72).
Severe pain = Baseline scores over median (n=49).
(b) EORTC QLQ-C30 social functioning. Subscale score divided into four groups by quartiles at the baseline (n=120) (p=0.0005).

HR for death:  
- Group 1 vs. Group 4: HR 3.4 (95% CI, 1.8-6.6)
- Group 1 vs. Group 3: HR 1.70 (95% CI, 0.8-3.6)

Group 1 = Social functioning scores from the first quartile (scores 0-66.7) (n=39)
Group 2 = Social functioning scores from the second quartile (scores 66.7-83.3) (n=0)
Group 3 = Social functioning scores from the third quartile (scores 83.3-100.0) (n=22)
Group 4 = Social functioning scores from the fourth quartile (score of 100.0) (n=59)
(c) EORTC QLQ-C30 role functioning. Subscale score divided into four groups by quartiles at the baseline (n=120) (p<0.0001).

HR for death: Group 1 vs. Group 2: HR 4.6 (95% CI, 2.3 – 9.4)
Group 1 vs. Group 4: HR 5.4 (95% CI, 2.5 – 11.7)

Discussion

6.1 Views on euthanasia and physician-assisted suicide

A minority (19% of other physicians and 10% of the oncologists) of physicians supported the legalization of euthanasia in study I, with male physicians being more supportive than females. A review by Emanuel et al. (2016) on attitudes toward euthanasia and PAS revealed that the public support for euthanasia has increased in the Western European countries in recent decades, but physicians’ support for assisted dying remains remarkably lower. Generally, fewer than half of the physicians in these countries support legalizing assisted dying. Miccinesi et al. (2005) found that the attitudes of physicians towards EOL decisions varied mainly according to country among seven different European countries: physicians in the Netherlands, Belgium and Switzerland support assisted dying significantly more often than in other European countries where assisted dying is not legal. Like in our study, they found that male physicians supported assisted dying more often than female physicians.

The respondents’ views in our study are more critical than in other reports from Finland and reflect their opinions at the time the study was conducted. A study in 1998 found that 34% of Finnish physicians agreed that euthanasia would be acceptable in some situations (Ryynänen et al. 2002). A more recent study of Finnish physicians’ attitudes towards active euthanasia reported a change in their views during the recent decade. In 2003, 29% of Finnish physicians supported active euthanasia, and in 2013, already 46% supported it (Louhiala et al. 2015). Importantly, no significant change in the proportion of those willing to practice active euthanasia was found between these two surveys. This proportion was approximately one-fifth of physicians in both studies, which is in line with our study results. The physicians in these Finnish studies were not characterized by different specialities, which hampers the comparison to our study representing physicians engaged more with the care of dying patients.

Physicians involved more with palliative and EOL care have been found to oppose assisted dying more strongly than those in other specialities (Marini et al. 2006, Lee et al. 2009, Zenz et al. 2015). This was also found in a recent Finnish survey on attitudes towards euthanasia where only 17% of physicians engaged with palliative care (oncologists, geriatrics, pulmonologists and palliative care specialists) supported the legalization of euthanasia and 15% the legalization of PAS (https://www.laakariliitto.fi/site/assets/files/1270/saattohoito_ja_eutanasia_kysely_tuloksia_13022017.pdf).
6 DISCUSSION

6.1 Views on euthanasia and physician-assisted suicide

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Discussion

Approximately two-thirds of all respondents (study I) feared the possible misuse of euthanasia if it was legalized. The “slippery slope” concept is frequently used, referring to the expansion of intentionally ending the life of patients who do not make an explicit request (Emanuel et al. 2016). The majority had the opinion that the requests for euthanasia would be reduced with proper palliative care. Interestingly, in accordance with our study, Miccinesi et al. (2005) found that the majority of physicians in all seven countries, even in the Netherlands and Belgium, had the opinion that sufficient palliative care could prevent almost all requests for active help for dying. This supports the recommendation of the EAPC that the patients requesting active help in dying should first be offered adequate palliative care (Radbruch et al. 2016). Patients with progressive diseases asking for hastening of death have expressed that this wish is often a strategy to cope with the upcoming death; they may be more in a need of psychological support and overall information on EOL care and the dying process (Pestinger et al. 2015).

The difference in attitudes among the general public, physicians of all specialities and palliative care physicians can be partly explained by the amount of information and education on the subject. People often become more opposed to euthanasia or PAS when they gain more experience with the care of the dying and information on the complex aspects of assisted dying (Wolfe et al. 1999, Clemens et al. 2008b, Raisio et al. 2015). Thorough information regarding this issue would be important for the policymakers in the ongoing debate on legalization of assisted dying.

However, little is also known about the potential difference in attitudes toward this issue between male and female physicians working in palliative care. This would be important to evaluate in detail to be able to better characterize the factors affecting physicians’ attitudes.

6.2 Cancer pain and its management

Our study patients who planned to undergo chemotherapy (studies III and IV) experienced pain at the beginning of the study, though the median level of pain was low. Levels of fatigue, dyspnea, insomnia, and coughing were more severe than pain. The pain intensity of men increased significantly more than women’s during the study period. The findings are in line with the previous literature indicating that pain is one of the most common symptoms reported by lung cancer patients (Cooley 2000, Isaac et al. 2012, Iyer et al. 2013). NSCLC patients have even reported pain to be one of the most important symptoms associated with distress (Tishelman et al. 2007). Contrary to our results, previous studies have indicated that women might be in greater risk of cancer pain, although the findings have varied (Huhti et al. 1980, Fillingim et al. 2009). Our finding of men suffering...
more from pain is interesting and would be essential to be evaluated in detail. This difference between men and women may partly be due to patient-related barriers that have been found in some studies (Ward et al. 1993, Jacobsen et al. 2009). Men can be more unwilling to discuss pain matters based, for example, on concerns about addiction or tolerance to pain medication, fatalism that pain is unavoidable in cancer or a belief that “good patients avoid talking about pain.”

The severity of pain had an influence on the NSCLC patients’ survival in our study. A recent review of the impact of pain on overall survival revealed that in most of the previous studies on lung cancer patients, pain was not a significant prognostic factor for overall survival (Zylla et al. 2017). This finding needs more exploration. Additionally, it should be investigated whether survival could be prolonged with proper cancer pain management.

Thirty-nine percent of other physicians and 53% of the oncologists regarded pain treatment not to be on an adequate level in Finland. Furthermore, our study patients did suffer from pain, though the median intensity was low. A recent meta-analysis of cancer pain prevalence referred that patients still suffered from untreated pain globally (van den Beuken-van Everdingen et al. 2016) though its prevalence should have declined during the last decades as the education on pain treatment and awareness of its importance have been emphasized. In Finland, physicians’ knowledge and practices in the management of cancer pain have been previously measured in a three-series survey in the years 1985, 1990 and 1995. An improvement in the treatment of cancer pain was observed during these 10 years as the daily doses of opioids increased and the physicians were more familiar with the use of the WHO analgesic ladder. A quarter of the Finnish physicians used the analgesic ladder in 1995 (Vainio et al. 1988, Vainio et al. 1992, Kaasalainen et al. 1997). Comparing our results (study II) to these, the knowledge of the analgesic ladder among physicians seems to have improved, though it is still not adequate.

Current pain medications are mainly effective, but sufficient palliation of pain is sometimes hard to achieve with them. In addition, pain medication can occasionally lead to severe adverse effects, which can result in unsatisfactorily low doses of medication. These may be some of the reasons for inadequate pain treatment, and novel and better-tolerated drugs are needed to be investigated in the future (Jost et al. 2010, Mercadante 2017).

Physicians’ skills in the treatment of neuropathic pain in cancer patients were not satisfactory. Primary care physicians especially were unfamiliar with neuropathic pain treatments. In our study of NSCLC patients, symptoms of neuropathy increased during the six-month study period, but the possible proportion of neuropathy-induced pain was not defined. Neuropathic cancer pain, however, has been frequently reported in previous studies. Neuropathy can be due to the disease
itself but is mainly caused by chemotherapy, especially the chemotherapy regimens cisplatin and docetaxel, which are commonly used in the treatment of NSCLC (Nurgalieva et al. 2010, Roberto et al. 2016). Our findings call for better management of neuropathy symptoms, since neuropathic pain is shown to worsen cancer patients’ QOL (Mols et al. 2014, Oh et al. 2017). Therefore, the importance of paying attention to the occurrence of neuropathy symptoms should be obvious. Recent studies have shown that neuropathic pain is still undertreated, and adjuvant analgesics in the treatment are especially rarely prescribed (Piano et al. 2013, Oh et al. 2017). Thus, more training in this field is needed.

Underestimation of pain was named as one of the most important reasons for inadequate pain management among physicians in our study (study II) and has also been expressed as one of the main reasons in other studies (Laugsand et al. 2010, Salminen et al. 2013). The publication of WHO’s ‘Cancer pain relief’ in 1986 already underlined that physicians and other staff must “Believe the patients’ complaint of pain” (WHO 1986) and that the assessment of pain is critically important in pain management. A clinical practice guideline on the treatment of cancer pain was published in 2008 in the Netherlands with an expectation of better pain registration, evaluation and treatment but the guidelines were shown to not be implemented into practice. The reasons for this were inadequate assessment of pain, physicians focusing excessively on the specific treatment of cancer, and poor information exchange between the physician and the patient (Besse et al. 2016). Other physician-related barriers to inadequate cancer pain management have been found to be physicians’ lack of skills and the reluctance of physicians to prescribe opioids (Davis et al. 2004, Kwon 2014). The effort needed to overcome these previously described challenges does not seem to be overwhelming. Therefore, it is of utmost importance to focus on improving cancer pain management in the future.

6.3 Other symptoms and quality of life

The most severe symptoms among our NSCLC patients were cough, dyspnea, fatigue and insomnia. The lowest scores for the functional scales were at the baseline for physical and role functioning. The symptom profile was quite similar to the findings of previous studies among NSCLC patients (Cooley 2000, Iyer et al. 2013). Compared to EORTC reference scores (Scott et al. 2008), they also were mainly alike, but the physical functioning scores of our patients were lower. Dyspnea was expressed more often among our NSCLC patients and the reference group of NSCLC patients compared to a group of all cancer patients. Because of the heterogeneity of patient characteristics in these reference groups, statistical
Discussion

Comparison with them was not possible. However, it has been previously demonstrated that a mean change of 10-20 in the scores of EORTC QLQ-C30 domains indicates a moderate change in symptoms (Osoba et al. 1998). The difference in the scores of physical functioning between these groups may be explained by the differences between the groups of cancer patients, as our study patients mainly had an advanced disease (stage III and IV) compared to the reference group of NSCLC patients of all stages.

Health-related QOL is determined by our expectations of health in relation to our experience of it. It can differ between people and change within time (Carr et al. 2001). The study patients’ QOL did not change during the six months. However, a notable part of the patients died during the study probably affecting this finding as these patients’ QOL was assumingly lowered. Chemotherapy has been shown to improve QOL (Anderson et al. 2000, Belani et al. 2006) but not in our study. However, it is important that our study patients’ QOL did not deteriorate.

Nevertheless, when separating the groups by genders, the women’s QOL was found to be significantly better during the six-month study period compared to the men’s. The reason for this difference was unclear. The response rates were similar for both genders and no significant differences exist between the treatment modalities. The only difference in the patients’ characteristics between men and women was the number of pack years, but it had no effect on the symptoms at the baseline. As previously told, the severity of pain was also lower among women, which might have an influence on QOL. Gender can also affect the way patients cope with NSCLC and possible occurrence of emerging symptoms. Some differences in the coping strategies between the genders have been found in previous studies that might also have influenced the study patients, but these coping strategies are still unclear and under research (Loscalzo et al. 2018). Nevertheless, according to our results, when tailoring treatments for NSCLC cancer patients, men should be focused more on inquiring about symptoms and being given more information on possible management possibilities to improve their QOL.

The treatment of NSCLC frequently causes adverse effects, and it is very important not to worsen the QOL of the patients too much. Our patients had an increase in the symptoms suggested to be induced by chemotherapy at the three-month study point, but these had no influence on QOL. Still, the side-effects should be better focused on and treated adequately. The emerging immune therapy for NSCLC is giving hope, as its side effects are more infrequent than those of chemotherapy. Brahmer et al. (2017) found that immune therapy improved or maintained QOL better than chemotherapy parallel with a better overall survival when comparing
Discussion

The ESAS scores in our study did not change significantly during the study period, the PS is insufficient (Yogananda et al. 2018). Detection and that the physician's estimate of patients' well-being based only on ESAS-r also indicated the feasibility of using ESAS-r for patients' symptom management. A recent study with evidence in the group of breast cancer patients that routine symptom screening symptoms are associated to the number of visits in EDs. They subsequently found (2013) showed in their study of 45 118 cancer patients that patient-reported symptoms were associated to the number of visits in EDs. They subsequently found (2011), and in a study of cancer pain management in Finnish hospices reported that, pain medication increased prior to death (Koivu et al. 2014). These results are in line with our findings concerning patients with advanced NSCLC during disease modifying therapy identifying important targets for future symptom-based management.

The factors affecting survival in our study were the baseline scores of pain, role functioning and social functioning. Global QOL at baseline did not have an influence on survival. In previous studies, the pre-diagnosis QOL was mainly found to be a significant prognostic factor among patients with lung cancer (Braun et al. 2011, Sloan et al. 2012, Pinheiro et al. 2017). Degner et al. (1995) found that even a single measure of symptom distress was a significant survival predictor. The symptom intensity of cancer patients measured with ESAS has been presented to increase during the last month before death, thus predicting survival (Zeng et al. 2011), and in a study of cancer pain management in Finnish hospices reported that, pain medication increased prior to death (Koivu et al. 2014). These results are in line with our findings concerning patients with advanced NSCLC during disease modifying therapy identifying important targets for future symptom-based management.

Routine symptom assessment is evidently beneficial. It allows physicians to identify and treat the symptoms earlier to achieve good palliation. Barbera et al. (2013) showed in their study of 45 118 cancer patients that patient-reported symptoms are associated to the number of visits in EDs. They subsequently found evidence in the group of breast cancer patients that routine symptom screening with ESAS diminished these visits (Barbera et al. 2015). A recent study with ESAS-r also indicated the feasibility of using ESAS-r for patients’ symptom detection and that the physician’s estimate of patients’ well-being based only on the PS is insufficient (Yogananda et al. 2018).

The ESAS scores in our study did not change significantly during the study period, and the mean scores stayed mainly under the score of three. However, it is evident...
that at least minor changes do occur. ESAS was shown to be a reliable tool for symptom assessment in a review of Richardson et al. (2009), but, alike in our study the scores were skewed.

ESAS was tested in our study for the first time with lung cancer patients to compare it with the results of the simultaneously completed EORTC questionnaire: They proved to be in good correlation with each other. ESAS forms were simple and rapid to fill out. During the study period, ESAS was introduced to routine use for symptom assessment at the Departments of Pulmonary diseases, Oncology and Radiotherapy and Palliative care at the Turku University Hospital. ESAS was proved in our study, as well as other previous studies, to be a useful tool in the daily assessment of symptoms, but often needing interpretation by the staff and discussion with patients to fully reveal the status of their symptoms (Garyali et al. 2006, Richardson et al. 2009).

6.4 Physicians’ training needs

The majority of physicians (study I and II) considered the education in palliative care as inadequate in Finland. The oncologists reported mostly of a need for education in communication skills and ethical questions, and the group of other physicians reported mostly the need for education on the basics of palliative care and pain management. Several studies have reported similar findings of insufficient training in the field of palliative care, especially pain management and communication skills. A review by Charlton et al. (2008) illustrated that the training in palliative care, especially communication skills, is inadequate globally. A survey of physicians in Australia and Europe revealed that only half of the physicians representing different specialities had any formal training in palliative care, and 87-98% of the physicians wanted more training in palliative care (Löfmark et al. 2006). Cherny et al. (2003) found that 42% of ESMO members, mainly medical oncologists, regarded their EOL care training as inadequate. A study among consultants in acute clinical specialities revealed that they frequently must break bad news for the patients but only half of them have received some training in this area (Barnett et al. 2007).

Younger (under 36 years) and female physicians especially had fears when meeting dying or seriously ill patients (study I). This indicates a need for more training and support in these situations. The caring for the seriously ill patient is burdensome for the health-care professionals, especially for young physicians (Charlton et al. 2008). Female physicians have also been shown to participate more actively in patient communication and to use more emotionally focused talk in these conversations (Roter et al. 2002). Conveying bad news to a patient provokes
Discussion

clear physiological and psychological stress particularly in inexperienced physicians (Hulsman et al. 2010). A Japanese study surveyed the burden on oncologists when communicating discontinuation of anticancer treatment; 47% of oncologists expressed having a high level of burden in these situations (Otani et al. 2011). A review by Trufelli et al. (2008) revealed that the prevalence of burnout syndrome is elevated among physicians taking care of cancer patients. Shanafelt et al. (2014) found that oncologists who were working more among patient care were in the greatest risk for burnout.

Further education in palliative care seems generally to be required. Studies have shown that physicians with better training in palliative care discuss options for palliative care and EOL subjects more often than physicians without training (Löfmark et al. 2006). These discussions of EOL subjects have been reported to prevent overly aggressive EOL care and increase family satisfaction (Kelley et al. 2015).

Different educational models have been developed to improve physician communication skills, and the training in this field has been associated with improved quality of care and less stress and burnout of physicians (Back et al. 2005, Barth et al. 2011). A recent review of the impact of training in communication skills of generalist palliative care providers showed an improvement in the physicians’ ability to show empathy and discuss emotions (Selman et al. 2017). ASCO published guidelines in 2017 for patient-clinician communication for oncology clinicians (Gilligan et al. 2017). These guidelines recommend that the training in communication skills should be based on skills practice and experiential learning such as role-play sessions or direct observation of patient encounters.

Education in palliative care has gradually improved in Finland. The undergraduate education on palliative medicine was recently evaluated at Tampere University, and it complied well with the EAPC recommendations. University of Helsinki also has an undergraduate curriculum in palliative medicine, while the other three Finnish Universities with a Faculty of Medicine are in the process of planning their formal curriculum for future students (Elsner et al. 2013, Lehto et al. 2017). An official program for special competency in palliative medicine started in Finland in 2007 and over 100 physicians have accomplished this education (Centeno et al. 2015). The Finnish Ministry of Social Affairs and Health published a report in 2015 that described the recommendations for palliative treatment and EOL care and emphasized the need for proper training in palliative care (Saarto et al. 2017). All these improvements are urgently needed to fill the gaps between the needs and supplies of training in Finland.


6.5 The strengths and limitations of this study

A limitation of studies I and II is the low response rate to the physicians’ survey. This has been a frequent problem in many other physician surveys and studies (Kellerman et al. 2001, Fischer et al. 2006). It can be assumed that the physicians who responded may represent more of those who are interested in this study subject; thus, the real knowledge of Finnish physicians on EOL care and symptom management can be even lower.

Studies III and IV were prospective studies in which all consecutive NSCLC patients subjected for chemotherapy were asked to participate. Thus, all potentially eligible patients were included in the study and they represented the “real-life” patients in our clinic. The patient characteristics were analogous to those in previous NSCLC studies in regard to age, smoking status and comorbidities thus allowing direct comparison between the studies.

Our study patients’ symptoms were assessed with three different questionnaires to gain a comprehensive view of the patients’ conditions. The results can, thus, be compared between these instruments that extensively cover the important symptoms. Strömgren et al. (2002) found in their study that using EORTC QLQ-C30 and ESAS together covered the 12 most frequent symptoms of palliative care patients. The important symptom of cough is also included when combining these questionnaires with the QLQ-LC13 questionnaire.

The NSCLC patients’ subjective experiences were registered for the first time in Finland (studies III and IV) and Finnish physicians have not been to our knowledge surveyed before on the perceptions and skills of symptom management (studies I and II). This brings important new information for Finnish health-care professionals and policymakers and helps to form a basis for developing symptom management and palliative care in Finland.

A limitation in studies III and IV is that our study population of NSCLC patients is reasonably small. Distinct subgroups of patients with advanced NSCLC can be recognized in regard to several factors, such as tumor histopathology and stage, the implementation of chemotherapy, and patient’s comorbidities. This leads to a need for a large enough patient cohort when performing a study intended to provide results that would be generalizable to the whole group of patients with advanced NSCLC. Nevertheless, the patient characteristics in our study appeared comparable to other corresponding studies. We did not find any results conflicting with other existing literature that would obviously be attributed to the constitution of our study population.
Several advancements in palliative care have been seen since the time of the data acquisition in our studies. Fortunately, general knowledge of these issues has been increased, and the physicians’ focus has been addressed more closely to the quality of palliative care. The number of studies conducted and published in this field after the initiation of this thesis work has gratifyingly increased. Among these studies, our work provides an additional perspective on the treatment of these incurably ill patients.

### 6.6 Future

There are still many unmet needs in the field of cancer patients’ symptom management. WHO has classified countries into different groups regarding the state of palliative care in the country; Finland is classified into a group of “countries where hospice and palliative care services are at a stage of preliminary integration into mainstream service provision” (WHO 2014). Woitha et al. (2016) ranked palliative care development in the European Union, and Finland was situated quite low, at level 21 out of 28 countries. The Finnish Ministry of Social Affairs and Health has published a report that points out the targets for development of cancer treatment and palliative care for the years 2010–2020” (Reports of the Ministry of Social Affairs and Health, 2010). The Finnish Ministry of Social Affairs and Health also published a report and plan in 2017 for implementing adequate and organized palliative treatment and EOL care in Finland (Reports and Memorandums of the Ministry of Social Affairs and Health, 2017). These plans include the improvement of palliative training of health care professionals. This is a very important beginning to develop sufficient palliative care in Finland.

Symptom assessment should be integrated into every-day clinical work and accomplished regularly for all NSCLC patients to achieve a better understanding of the symptoms and, thus, treat them properly. Electronic patient-reported assessment tools for cancer patients’ symptoms have emerged along with the development of new technological applications. The patient-reported outcomes (PROs) can be collected by different electronic devices in the clinic or at home with these electronic patient-reported outcome (ePRO) methods. A frequent evaluation of symptoms is possible with electronic diaries. This is a totally new and promising way to optimize symptom control. Recent studies on an electronic assessment tool for patients with cancer presented an improvement in survival as the symptoms were detected earlier. It also improved QOL and decreased the amount of ED visits and hospitalizations (Basch et al. 2016, Basch et al. 2017).
These findings are central, as we can diminish human suffering and the use of resources by focusing on regular symptom monitoring.

Advancements in palliative medicine due to digitalization are not supposed to be limited only to the remotely implemented acquisition of symptom data. State-of-the-art techniques such as Big Data analytics and machine learning are also assumed to offer several additional approaches, such as models to identify those who need palliative care (Nwosu et al. 2018). The use of linked data among patients in palliative care will obviously help to better understand this multidimensional entity more precisely identifying the need and delivery of palliative care in real-life health care (Tanuseputro 2017). Furthermore, it is of special interest to also be able to link this knowledge to the data on treatment response and patient survival. This will probably make it possible to achieve evidence to be exploited in the guiding of the oncological treatment of patients with advanced cancer.

In conclusion, modern tools combined with humanity offer a highly promising approach for scientific research intended to provide patients with incurable cancer with comprehensive palliative care.
CONCLUSIONS

1. The majority of physicians did not support active help in dying and every fourth expressed some fears when meeting dying or incurably ill patients.

2. Physicians expressed a need to develop palliative care and improve the state of cancer pain management in Finland.

3. The advanced or metastatic NSCLC patients in our study, especially men, were symptomatic, and their QOL was not at an optimal level. Global QOL was better among women compared to men during chemotherapy. The reason for this was unclear and needs further study.

4. A high level of pain and low social and role functioning of NSCLC patients at the baseline predicted poorer survival.

5. The ESAS forms were useful in the daily assessment of symptoms, and are applicable to the clinical practice. The results correlated well with the EORTC QLQ-C30 questionnaire.

In conclusion, symptom management should be improved in the future by developing further education for physicians involved in palliative and cancer care as well as by providing better facilities for high-quality practice in this field. An adequate symptom assessment tool plays a key role in the satisfactory implementation of symptom control for patients with advanced cancer.
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Turku, September 2018

Maria Silvoniemi
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References


References


References


References


APPENDICES

Appendix 1. Questionnaire of studies I and II.

Taustatiedot:

1. Ikä (vuosia): _______  Kyselyn vastauspvm: pv _____ kk _____200_
2. Sukupuoli:
   [ ] Mies
   [ ] Nainen

3. Valmistunut lääkäriksi vuonna: _________________

4. Lääketieteen opiskelupaikkasi:
   [ ] Turku
   [ ] Helsinki
   [ ] Tampere
   [ ] Oulu
   [ ] Kuopio
   [ ] Muu, mikä_____________________

5. Uskonto (esim. luterilainen, kreikk. katolinen, room. katolinen muu): _________________

6. Kuinka monta vuotta olet toiminut kliinisessä lääkärintyössä       _______v

7. Nykyinen
   a) toimenkuvasi
      [ ] Kliininen työ
      [ ] Hallinto
      [ ] Muu, mikä: __________________________
   b) toimipaikkasi
      [ ] Terveyskeskus vastaanotto
      [ ] Terveyskeskus vuodeosasto
      [ ] Aluesairaala
      [ ] Keskiusairaala
      [ ] Yo-sairaala
      [ ] Muu, mikä: __________________________
   c) toimialueesi sairaanhoitopiiri: __________________________

8. Oletko hoitanut itselle läheistä vaikeasti sairasta, joka menehtynyt sairauteensa
   [ ] Kyllä (isä, sisko, isoäiti tms.): ____________________
   [ ] En

9. Erikoistumisalasi
   [ ] Sisätautien erikoislääkäri
   [ ] Yleislääkäri
   [ ] Syöpätautien erikoislääkäri
   [ ] Erikoistuva lääkäri, ala: __________________________
   [ ] Muu, mikä_______________________________________
Käsityksiä kuolinapuun liittyen:

1. Mitkä oheisista kuolinapuun liittyvistä termeistä ovat Sinulle tuttuja määritelmiltään? Tunnen...
   - ...aktiivin eutanasian
   - ...passiivin eutanasian
   - ...avustetun itsemurhan
   - ...palliatiivisen sedaation
   ylläolevista käsitteistä ei mikään ole minulle tuttu.

2. Mikä kuolinapu on Suomessa rangaistava teko? (useampi oikea vastaus on mahdollinen)
   - Aktiivi eutanasia
   - Passiivi eutanasia
   - Avustettu itsemurha

3. Hollannissa aktiivi eutanasia on tietyissä tapauksissa sallittua. Tulisiko mielestäsi Suomessa sallia aktiivi eutanasia?
   - Kyllä
   - Ei
   - En osaa sanoa

4. Ottaisitko määräytyssä tilanteessa vastuullesi aktiivin eutanasian toteuttamisen?
   - Kyllä
   - Ei
   - En osaa sanoa.

5. Jos vastasit edelliseen myöntävästi, mistä syystä?
   - Merkityksetön ja sietämätön kärsimys
   - Arvottomat olosuhteet (ihmisarmoton elämä)
   - Toive ettei olisi taakaksi perheelle
   - Kivun välttäminen
   - Sukulaiset ovat täysin uupuneita ja pyytävät apuani.
   - Potilaan elämänlaatu on olematon.
   - Haluan antaa potilaalle arvokkaan kuoleman.
   - Muu, mikä: _____________________________________________________________

6. Jos Suomessa laki sallisi aktiivin kuolinavun, toteuttaisitko sitä potilaan pyytäessä?
   - Kyllä
   - Ei
   - En osaa sanoa

7. Jos kyllä, miten perustelisit sen, että noudatat potilaan toivomusta?
   - En voi muutoin auttaa potilasta (avuttomuus)
   - En näe mitään mahdollisuutta tilanteen parantumiseen
   - Sukulaiset ovat täysin uupuneita ja pyytävät apuani.
   - Potilaan elämänlaatu on olematon.
   - Haluan antaa potilaalle arvokkaan kuoleman.
   - Muu, mikä: _____________________________________________________________
8. Pelkäätkö aktiivin eutanasian laillistamisen voivan johtaa väärinkäytöksiin?
   - Kyllä
   - Ei
   - En osaa sanoa

9. Uskotko, että hyvällä palliaatiivisella kivunhoidolla ja oirehoidolla voidaan vähentää potilaan toivomuksia aktiivista eutanasiasta?
   - Kyllä
   - Ei
   - En osaa sanoa

**Kivunhoito**

10. Miten arvioi WHO-kipuportaiden tuntemuksesi?
   - Tunnen niiden yksityiskohtat
   - Tunnen periaatteet, mutta en yksityiskohtia (lääkkeitä ja annostuksia)
   - Tunnen käsitteet pinnallisesti
   - En tunne sitä

11. Kuinka monta porrasta on WHO-kipuportaissa?
   - 1
   - 2
   - 3
   - 4
   - 5

12. Pitäisikö mielestäsi aina aloittaa 1-portaalta? (onko parasetamoli/tulehduskipulääke aina aloituslääke?)
   - Kyllä
   - Ei
   - En osaa sanoa

13. Arvioi miten suurella osalla syöpäpotilaista kipu voidaan lievittää hyvin?
   Arvioisin n. _____%

14. Miten arvioit suomalaisten syöpäpotilaiden kivunhoidon tason?
   - Luulen että Suomessa valtaosa syöpäpotilailta saa hyvän kivunhoidon.
   - Luulen että suuri osa syöpäpotilaiden kivusta alihoidetaan.
   - En osaa sanoa

15. Mitkä ovat mielestäsi syyt riittämättömäänä kivunhoitoon? (usea vaihtoehto mahdollinen)
   - Väärrä kipudiagnoosi
   - Kivun aliarviointi
   - Pelko lääkeriippuvuudesta
   - Erityisreseptivaatimus opiaattireseptien kirjoittamisessa
   - Lääkärin riittämätön taito
   - Kipulääkkeen määrääminen vain tarvittaessa käytettäväksi
   - Muu: ___________________________________________________________________

- Kyllä
- Ei
- En osaa sanoa

17. Jos opioidia käytetään neuropaattisen kivun hoidossa, minkä seuraavien lääkkeiden kanssa se kannattaisi yhdistää (voit valita useita vaihtoehtoja)

- Masennuslääkkeet
- Neuroleptiset lääkkeet
- Epilepsialääkkeet
- Tulehduskipulääkkeet
- Pahoinvointilääkkeet
- Kortikoidit

18. Onko mielestäsi aikaisempi koulutuksesi antanut riittävästi tietotaitoa seuraavasta:

19. Miten oleellisia ovat mielestäsi asianmukaisen opioidilääkityksen yhteydessä seuraavat ei-toivotut vaikutukset?

20. Mitkä seuraavista lääkityksen periaatteista vastaavat WHO:n suosituksesta:

- Lääkettä vain tarvittaessa
- Lääkettä säännöllisesti kellon mukaan
- Suositaan parenteraalista annostelua
- Suositaan enteraalista annostelua
- Eri portaitten yhdistäminen portaittaisessa annostelussa
- Kakkosporrasta ja kolmosporrasta ei voi yhdistää
- En osaa sanoa
Appendices

Oireiston hallinta

21. Monilla edennytä syöpää sairastavilla on ongelmana ruokahaluttomuus. Mitä suositat heille?
   (useampi vaihtoehto mahdollinen)
   ☐ Heille kuuluu aina laittaa ruokintaletku, esim. PEG, jotta vältytään kakeksialta
   ☐ Tulisi pyrkiä selvittämään ruokahaluttomuuden syyt.
   ☐ Ravitsemusneuvonta on tarpeen, jotta löydettäisiin sellaisia ravintovalmisteita, joita potilas
   voisi nauttia.
   ☐ Ruokahaluttomuutta voidaan aina parantaa lääkityksellä.
   ☐ Syöminen on osa elämänlaatua, kaikki mahdollinen pitäisi tehdä sen mahdollistamiseksi.

22. Jos syöpäpotilaalle on kehittynyt hoitoresistentti ileus eli suolilama, voidaan asentaa
   ravitsemusletku (PEG) helpottamaan pahoinvointia ja tyhjentämään vatsalaukun sisältöä.
   Potilas voi halutessaan silloin syödä suun kautta mutta ruoka saattaa tulla heti letkun kautta
   ulos. Olisiko tämä toimenpide Sinusta järkevä oksentelun helpottamiseksi?
   ☐ Kyllä
   ☐ Ei
   ☐ En ole varma

23. Mikä/mitkä seuraavista toimenpiteistä on/ovat mielestäsi vielä perusteltuja pitkälle
    edenneessä oireiston lievittämistarkoituksella (useammat vaihtoehdot mahdollisia)
   - Solunsalpaajahoito ☐ kyllä: __________________________ ☐ ei
   - Sädehoito ☐ kyllä: __________________________ ☐ ei
   - Leikkaushoito ☐ kyllä: __________________________ ☐ ei

24. Arvioisitko oheiset väittämät:

<table>
<thead>
<tr>
<th>Olen samaa mieltä</th>
<th>En ole varma</th>
<th>Olen eri mieltä</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jos hengenahdistukseen ei ole syytä poistavaa hoitoa voidaan oireita lievittää opioidilääkyksellä</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Hengenahdistuspotilailla opioidilääkykisyys on kontraindisoitu uhkaavasta hengityslamasta johtuen</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Happihoito happiviiksilla tai maskilla on tarpeen vain selvässä hapenpuutteessa ja hengitysvaikeudessa?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Happenanto ei hyödyta kuolevan potilaan hengenahdistusta</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Ruokahalua voidaan parantaa lääkkeillä</td>
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</table>

25. 40-70%:lla pitkälle edennytä syöpää sairastavista on ongelmana pahoinvointi ja oksentelu.
    Miten tätä oireita pitäisi mielestäsi hoitaa?
    ☐ Tarvittaessa pahoinvointilääkettä
    ☐ Säännöllinen pahoinvoinnin estolääkitys kellon mukaan ja vielä tarvittaessa
    ☐ Muu, mikä ________________________________
    ☐ En osaa sanoa
26. Miđä palliatiivisesta lääketieteestä toivoisit oppivasi enemmän (enintään kaksi vastausta)

☐ Kivunhoito

☐ Oirekontrolli

☐ Vuorovaikutus vaikeissa tilanteissa

☐ Potilaan omaisten kohtaaminen

☐ Eettiset kysymykset

☐ Muuta: __________________________________________________________

27. Miten arvioisi seuraavilla alueilla koulutuksen riittävyyden?

<table>
<thead>
<tr>
<th>Kivunhoito</th>
<th>Liian vähäinen</th>
<th>Puuttua</th>
<th>En osaa sanoa</th>
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<th>Oirehoito</th>
<th>Liian vähäinen</th>
<th>Puuttua</th>
<th>En osaa sanoa</th>
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<tr>
<th>Palliatiivinen LT</th>
<th>Liian vähäinen</th>
<th>Puuttua</th>
<th>En osaa sanoa</th>
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<th>Liian vähäinen</th>
<th>Puuttua</th>
<th>En osaa sanoa</th>
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<tr>
<th>Eettiset kysymykset</th>
<th>Liian vähäinen</th>
<th>Puuttua</th>
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28. Minkälaista koulutusta/opetusta toivoisit palliatiivisessa lääketieteessä (useampi vaihtoehto mahdollinen)

☐ Nykyinen riittävä

☐ Käytännön harjoittelua

☐ Enemmän luentoja

☐ Teoreettista seminaariopetusta

☐ Ei tarvitse opettaa erillisenä

☐ Muuta: __________________________________________________________

29. Pelkäätkö jotain mikä liittyy parantumattomasti sairaan/kuolevan potilaan kohtaamiseen?

☐ Kyllä

☐ En

☐ En osaa sanoa

30. Jos kyllä, mitkä asiat/tehtävät pelottaisivat eniten: (enintään 2 vastausta)

☐ Diagnoosin kertominen

☐ Olla paikalla, kun potilas kuolee

☐ Joutua keskustelemaan eksiistentiaalisista kysymyksistä??

☐ Joutua kohtaamaan kysymyksiä, joihin en osaa vastata

☐ Potilaan ja omaisten kohtaaminen

☐ Asianmukaisen kivunhoidon ja oirehoidon toteuttaminen

☐ Avuttomuus kun potilas ei ole parannettavissa

☐ Muu:  __________________________________________________________

31.  Miïten suuri osa syöpäpotilaista käsii depressiosta, arvioisin ________ %

Rintasyöpäpotilaista vastaava luku on mielestäni ________ %
32. Kenen mielestä tulisi tehdä ei elvytetä (DNR) päätös? (usea vaihtoehto mahdollinen)
- Potilasta hoitava lääkäri
- Erikoislääkäri ylikierrolla
- Lääkäri neuvoteltuaan omahoitajan kanssa
- Lääkäri yhteistyössä potilaan kanssa
- Lääkäri neuvoteltuaan omaisen kanssa
- Lääkäri yhteistyössä potilaan ja omaisen kanssa
- Muu vaihtoehto, mikä: ________________________________

33. Mitä ei elvytetä (DNR) tarkoittaa? (usea vaihtoehto mahdollinen)
- Älä aloita elvytystä
- Ei painantaelvytystä
- Ei aktiivihoitoa
- Saattohoitoon
- Ei mitään invaiviivisia hoitoja
- Voi tarkoittaa milloin mitäkin
- Hyvää oireenmukaisen hoitoa

34. Miten suhtaudut pitkälle dementoituneen potilaan keuhkoembolia epäilyyn hoitoon seuraavassa tilanteessa
- päävystyspolilla. Potilas on tuotu vanhainkodista hyvin sekavaan ja hengenahdistuksen kourissa
- päivystykseen, omainen vaatii aktiivia hoitoa. Hengitysfrekvenssi 36/min, potilas on ahdistunut ja levoton.
- (usea vaihtoehto mahdollinen)
- Lähetän potilaan spiraali-CT:hen, ja määrään tarvittaessa liuotuksen
- Sidon potilaan lepositeisiin ja aloitan Serenase ja morfiinihoidon
- Pyrin neuvottelemaan omaisen kanssa hoitolinjoista, ja ehdottamaan näin sopivan
- oireenmukaisen hoitolinjan
- Asetan DNR-päätöksen
- Muu vaihtoehto: _________________________________________________________

35. Millaiseksi arvioit oman suhtautumisesi epävarmuuteen lääketieteellisessä
- päättöksentekotilanteessa?
- Minun on vaikea sietää epävarmuutta diagnostiikan ja/tai hoitopäätöksien suhteen
- Pystyn sietämään kohtalaisesti epävarmuutta diagnostiikan ja/tai hoitopäätöksien suhteen
- Pystyn sietämään hyvin epävarmuutta diagnostiikan ja/tai hoitopäätöksien suhteen

36. Ovatko omaisten vaatimukset kuolevan potilaan hoidossa lisääntyneet viime vuosina?
- Kyllä
- Ei, ne ovat samanlaisia kuin aina ennenkin
- Ei, ne ovat vähentyneet
- En osaa sanoa
Appendices

37. **Jatkokoulutuksen tarve.** Nimeä alla olevasta listasta 3 kehitysaluetta, joista toivoisit lisää koulutusta

- Vuorovaikutus ja kommunikaatio
- Oireiden tutkimus ja hoito // erityisesti ______________________ oireen
- Psykososiaaliset kysymykset
- Saattinhoito yleensä
- Kotisaattohoidon kehittäminen
- Sedaatio
- Ettinen pohdinta saattohoidossa
- Lainsäädäntö euthanasiaan liittyen
- Kivunhoito
- Palliatiivisen hoidon perusteet
- Muu, mikä: ______________________________________________________
Appendix 2. Questionnaires of studies III and IV.

EDMONTON SYMPTOM ASSESSMENT SCALE (ESAS)

TYKS
Oirekyselykaavake /E.Salminen

Nimi:
Syntymäaika:
Pvm:

Kuinka voitte tänään?

1. Kipu- levossa
   Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

2. Kipu – liikkuesa
   Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

3. Väsymys, uupumus
   Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

4. Pahoinvointi
   Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

5. Masennus
   Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

6. Hengenahdistus
   Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

7. Ruokahalu
   Tavallinen 0 1 2 3 4 5 6 7 8 9 10 Huonoin mahdollinen

8. Ahdistuneisuus
   Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

9. Ummetus
   Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

10. Unettomuus
    Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

11. Millaisena koette vointinne kokonaisuudessaan tänään?
    Hyvä 0 1 2 3 4 5 6 7 8 9 10 Huonoin mahdollinen

12. Alleviivatkaa Teitä tällä hetkellä eniten häiritsevä oire!

13. Haluatteko tavata erityistyöntekijän (sosiaalihoitaja/psykologi/pastori/muu)?

14. Kipulääkitys: ________________________________
**EORTC QLQ-C30 QUESTIONNAIRE**

**EORTC QLQ-C30** (version 3.0.)

Selvitämme kyselyssämme joitakin teitä ja terveyttänne koskevia asioita. Pyydämme teitä vastaamaan itse kaikkiin kysymyksiin ympyröimällä parhaiten sopivan numeron. Tässä kyselyssä ei ole "oikeita" eikä "väärää" vastauksia. Pidämme antamanne tiedot ehdottoman luottamuksellisina.

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<tr>
<th>Syntymäaika (päivä, kk, vuosi):</th>
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<thead>
<tr>
<th>Kyselyn täyttöpaivä (päivä, kk, vuosi):</th>
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<th>Täyttääkö tähän nimikirjaimenne:</th>
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<tr>
<th>Tuntuvatko rasittavat työt kuten painavan ostoskassitin tai matkalaukun kantaminen teistä työläiltä?</th>
<th>1 2 3 4</th>
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<tbody>
<tr>
<td>Tuntuvatko rikat kävelymatkat työläiltä?</td>
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<tr>
<td>Tuntuvatko lyhyet kävelymatkat kotineen ulkopuolella työläiltä?</td>
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<tr>
<td>Pitääkö teidän pysytellä levossa tai istumassa päivän mittaan?</td>
<td>1 2 3 4</td>
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<tr>
<td>Tarvitsitteko apua ruokaillessanne, pukeutuessanne, peseytyessanne tai WC:n käytössä?</td>
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</table>

<table>
<thead>
<tr>
<th>1. Tuntuvatko rasittavat työt kuten painavan ostoskassitin tai matkalaukun kantaminen teistä työläiltä?</th>
<th>Ei lainkaan</th>
<th>Melko paljon</th>
<th>Hyvin paljon</th>
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<td>3. Tuntuvatko lyhyet kävelymatkat kotineen ulkopuolella työläiltä?</td>
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<td>4. Pitàäkö teidän pysytellä levossa tai istumassa päivän mittaan?</td>
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<tr>
<td>5. Tarvitsitteko apua ruokaillessanne, pukeutuessanne, peseytyessanne tai WC:n käytössä?</td>
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**Kuluneella viikolla:**

<table>
<thead>
<tr>
<th>Oliko teillä vaikeuksia suorittaa työstämme tai muista päivittäisistä toimistamme?</th>
<th>Ei lainkaan</th>
<th>Melko paljon</th>
<th>Hyvin paljon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliko teillä rajoituksia harrastusten tai muissa vapaa-ajan toimistamme?</td>
<td>1 2 3 4</td>
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<tr>
<td>Oliko teillä hengenahdistusta?</td>
<td>1 2 3 4</td>
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<td>Oliko kiinni?</td>
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<td>Tunsitteko levontarvetta?</td>
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<tr>
<td>Oliko unettomuutta?</td>
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<tr>
<td>Tunsitteko heikotusta?</td>
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<tr>
<td>Oliko ruokahalottomuutta?</td>
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<tr>
<td>Oliko pahoinvointia?</td>
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<tr>
<td>Oksensitteko?</td>
<td>1 2 3 4</td>
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<tr>
<td>Oliko ummetusta?</td>
<td>1 2 3 4</td>
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</table>

Jatkuu seuraavalle sivulle
### Kuluneella viikolla:

<table>
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<tr>
<th>Kysymys</th>
<th>Ei lainkaan</th>
<th>Vähän</th>
<th>Melko paljon</th>
<th>Hyvin paljon</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Oliko ripulia?</td>
<td>1</td>
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<td>18. Olitko väsynyt?</td>
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<tr>
<td>19. Häiritsikö kipu päivittäisiä toimianne?</td>
<td>1</td>
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<tr>
<td>20. Oliko teillä keskittymisvaikeuksia esim. sanomalehteni lukiessanne tai televisiota katsellessanne?</td>
<td>1</td>
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<td>21. Olitko jännittynyt?</td>
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<td>22. Olitko huolestunut?</td>
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<tr>
<td>23. Olitko ärtynyt?</td>
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<td>24. Olitko masentunut?</td>
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<tr>
<td>25. Oliko teidän vaikea muistaa asioita?</td>
<td>1</td>
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<tr>
<td>26. Häiritsikö hoito tai fyysinen kuntonne perhe-elämänpäällä?</td>
<td>1</td>
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<tr>
<td>27. Häiritsikö hoito tai fyysinen kuntonne sosiaalista kanssakäymisiä?</td>
<td>1</td>
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<tr>
<td>28. Aihettaako fyysinen kuntonne tai hoito taloudellisia vaikeuksia?</td>
<td>1</td>
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### Vastatkaa seuraaviin kysymyksiin ympyröimällä numerosarjasta 1-7 teihin parhaiten sopiva vaihtoehto

29. Millainen yleinen terveydentila oli kuluneella viikolla?
   - Erittäin huono
   - Erinomainen
   - | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
   - Erinomainen

30. Millainen yleinen elämänlaatu oli kuluneella viikolla?
   - Erittäin huono
   - Erinomainen
   - | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
   - Erinomainen


EORTC QLQ-LC13 QUESTIONNAIRE**

Toisinaan potilaat kertovat, että heillä esiintyy seuraavia oireita. Olkaa hyvä ja merkitkää miten paljon näitä oireita teillä on esiintynyt viime viikon aikana. Rengastakaa numero, joka parhaiten kuvaavat oireen laatu.

| 31. | Miten paljon yskitte? | 1 | 2 | 3 | 4 |
| 32. | Yskittekö verta? | 1 | 2 | 3 | 4 |
| 33. | Olitteko hengästynyt, kun lepäsitte? | 1 | 2 | 3 | 4 |
| 34. | Olitteko hengästynyt, kun kävelitte? | 1 | 2 | 3 | 4 |
| 35. | Olitteko hengästynyt, kun nousitte portaita? | 1 | 2 | 3 | 4 |
| 36. | Onko kielinen tai suunne ollut kipeä? | 1 | 2 | 3 | 4 |
| 37. | Onko teillä ollut nielemisvaikeuksia? | 1 | 2 | 3 | 4 |
| 38. | Onko käsänne tai jalkojanne kihelmöinyt? | 1 | 2 | 3 | 4 |
| 39. | Onko teillä lähtenyt hiuksia? | 1 | 2 | 3 | 4 |
| 40. | Oletteko tuntanut rintakipuja? | 1 | 2 | 3 | 4 |
| 41. | Oletteko tuntanut kipua käsi- tai jalkaan vai kahdella? | 1 | 2 | 3 | 4 |
| 42. | Onko teillä ollut kipuja muualla vartalossanne? | 1 | 2 | 3 | 4 |
| 43. | Oletteko ottanut mitään kipulääkettä? | 1 Ei | 2 Kyllä |

Jos olette, miten paljon siitä oli apua? 1 2 3 4
## THE BECK DEPRESSION INVENTORY

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### Appendices

| 18 | 0 | Ruokahaluni on ennaltaan |
|    | 1 | Ruokahaluni on aiempaa huonompi |
|    | 2 | Ruokahaluni on nyt paljon huonompi |
|    | 3 | Minulla ei ole lainkaan ruokahalua |

| 19 | 0 | Painoni on pysynyt viime aikoina ennaltaan |
|    | 1 | Olen laihtunut yli 2½ kiloa |
|    | 2 | Olen laihtunut yli 5 kiloa |
|    | 3 | Olen laihtunut yli 7½ kiloa |

| 20 | 0 | En ajattele terveyttäni tavallista enempää |
|    | 1 | Kiinnitän tavallista enemmän huomiota särkyihin ja kipuihin, vatsavaivoihin ja ummetukseen |
|    | 2 | Tarkkailen ruumiintuntemuksiani niin paljon, ettei muille ajatuksille jää aikaa |
|    | 3 | Terveyteni ja tuntemusteni ajatteleminen on kokonaan vallannut mieleni |

| 21 | 0 | Kiinnostukseni seksiin on pysynyt ennaltaan |
|    | 1 | Kiinnostukseni seksiin on vähentynyt |
|    | 2 | Kiinnostukseni seksiin on huomattavasti vähäisempää kuin aikaisemmin |
|    | 3 | En ole lainkaan kiinnostunut seksistä |

| 22 | 0 | Olen jossakin vaiheessa elämässä saanut psykiatrista hoitoa (psyykkelääkettä, psykoterapiaa, keskustelukäyntejä psykologin luona, sairaalahoitoa) |
|    | 1 | masennuksen takia |
|    | 2 | ahdistuneisuuden takia |
|    | 3 | muun syyyn takia. |

| 23 | 0 | Olisin halunnut saada psykososiaalista tukea enemmän syövän toteamisen jälkeen |

| 24 | 0 | Jos vastasit kyllä, niin millaisissa asioissa: |