Decision making in elderly patients with lung cancer

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DECISION MAKING IN ELDERLY PATIENTS WITH LUNG CANCER

Besluitvorming bij oudere patiënten met longkanker

(met een samenvatting in het Nederlands)

Proefschrift

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door

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CONTENTS

Chapter 1

Introduction and outline of thesis

INTRODUCTION

Every year over 12,000 patients are diagnosed with lung cancer in the Netherlands. It is predominantly a disease of the elderly: half of the patients are over 70 years of age and 30% is older than 75 years.[1] Due to the aging of Western society, the number of elderly patients with lung cancer has risen in the last twenty years and is expected to keep on rising in the next years (Figure 1).[1,2]

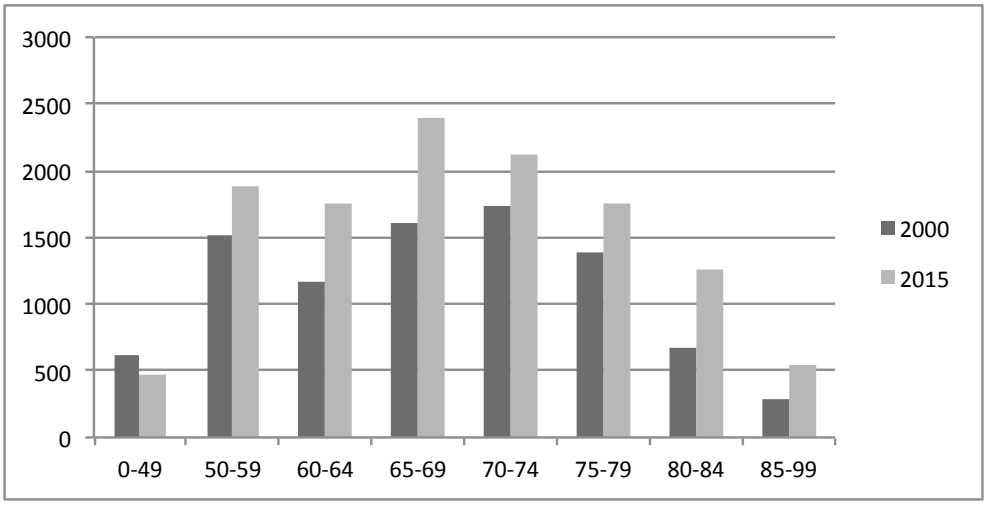

Figure 1. Incidence of lung cancer in the Netherlands, www.cijfersoverkanker.nl[1]

Lung cancer is frequently diagnosed at advanced stages because earlier stage disease does not cause any symptoms at all or only nonspecific symptoms.[1,3] At time of presentation, this type of malignancy often shows an aggressive course of disease and mortality rates are high, even with oncologic treatment.[1,4] It is a challenge to select the optimal treatment for each individual patient as benefit from therapy varies.[5–8] Toxic regimens to treat lung cancer require physical and emotional reserves. Differences in treatment success become even more apparent in the heterogeneous category of the elderly, because aging is an individual process that leads to a great variance in comorbidity, functional reserves and presence of geriatric syndromes.[9] In addition, treatment goals of the elderly might also differ from younger patients. Multiple studies have shown that older patients are in general less willing to undertake treatment for life extension at the cost of considerable toxicity, especially when this treatment negatively influences their quality of life or functional status.[10–12]

Current clinical practice

At the moment, evidence based guidelines regarding treatment of older patients with lung cancer are scarce. The existing available evidence may provide some guidance, but a

consensus on the optimal treatment is still lacking.[3,13–16] Due to the heterogeneity of older patients, it is incorrect to assume that a treatment regimen investigated in younger patients will also be the best option for the elderly. From other malignancies, for example in elderly patients with stage I to III colorectal cancer, we have seen that guideline adherence declines significantly with increasing age.[17] Optimal cancer care for the elderly must be tailored to the individual patient to balance between overtreatment of frail and undertreatment of fit older patients.[9] An important step in the improvement of clinical care for frail or elderly patients with lung cancer, is analyzing current clinical practice.

Geriatric assessment and screening tools

To quantify the health status and reserves of a patient with lung cancer, cancer specialists currently use tools such as the performance score (PS) designed by the World Health Organization (WHO) or pulmonary function tests. However, these tools do not appear to differentiate sufficiently between fit and potentially frail patients within the elderly population.[9] Thus, cancer specialists have looked to the field of geriatrics for other stratification methods. The concept of frailty is defined by geriatricians as a biological syndrome of decreased reserves and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes.[18] Care dependence, malnutrition, depressive symptoms or decreased mobility can be present even in patients with good performance score and are easy to miss for the cancer specialist.[19] For this reason, the International Society of Geriatric Oncology (SIOG) task force advised in 2005 to implement a geriatric assessment (GA) in standard care for elderly patients with cancer.[9] This GA is a systematic procedure to objectively appraise the health status of older people, focusing on somatic, functional and psychosocial domains, and is aimed at constructing a multidisciplinary treatment plan.[9,20]

In recent years the effects of a geriatric assessment were mainly analyzed in patient cohorts with various types of malignancies. In studies on elderly patients treated with chemotherapy, a GA was shown to be able to predict the risk of toxicity. In the Cancer and Aging Research Group model, which includes GA parameters such as mobility and falls, the lowest risk group had a 25% rate of grade III-V toxicity, while the highest risk group had an 89% risk of grade III-V toxicity (area under the curve 0.72).[21] In addition, the GA has shown to predict for six month mortality among the elderly treated with chemotherapy where a poor nutritional status and poor physicial performance each more than doubled the risk for early death.[22] Previous studies have also shown that a geriatric assessment is predictive of post-operative morbidity in older adults with cancer undergoing surgery, where increasing age alone did not seem to be associated with complications in the elective surgery setting.[23]

Although there are publications about the relevance of a geriatric assessment in other type of malignancies, it is important that this is also investigated in lung cancer because every type of malignancy has its own characteristics. For instance, lung cancer's rapid course of disease and poor overall prognosis will affect the additional impact that presence of geriatric impairments may have on outcome. The intense treatment regimens will require greater reserves than less toxic treatments and this may influence the relevance of certain impairments over others. Finally, given its association with lifestyle, lung cancer patients generally have a high prevalence of comorbid conditions that may be different compared to other kinds of cancer. Therefore, it is still difficult to formulate a recommendation regarding a specific approach for the implementation of this geriatric assessment in clinical or diagnostic work-up for patients with lung cancer.

Patient–reported outcome measures

To determine the efficacy of new treatments for lung cancer, the most frequently used parameters are survival, disease-free survival or response rate.[24] However, considering the overall poor prognosis of lung cancer, treatment objectives tend to shift from prolonging survival per se to maintaining quality of life and optimizing the number of days spent in acceptable health.[25,26] In a palliative treatment setting, factors other than survival or progression-free survival gain importance. Patients want to know: 'How long can I keep living in my own house?', 'What will be my quality of life?', 'Is it feasible for me to complete suggested treatments?' or 'How much time will I be spending in the hospital?'. Quality of life, overall functioning and healthcare utilization become increasingly important in this setting.

It would be helpful if this shift in priorities is mirrored in research objectives to be able to inform our patients about these aspects of treatment.[27] Incorporation of these so-called patient-reported outcome measures (PROMs) in research and current clinical practice has been advocated since several years, this will provide evidence that allows for a more holistic approach to patient care.[27,28] Besides, even in a curative setting, incorporation of PROMS in clinical trials can be useful. For instance, newer treatment strategies, such as targeted therapies or replacing major surgery with radiotherapy, are thought to have less disadvantageous side effects, be more patient-friendly and to allow for omission of invasive procedures.[29] PROMs could be an important factor in comparing the benefits and risks of novel treatment options with conventional therapy and between different types of new treatments.[26]

AIMS AND OUTLINE OF THIS THESIS

Many questions regarding the optimal treatment of frail or elderly with lung cancer still remain to be answered. This thesis focuses on three different aspects of decision-making. **Part I** addresses current clinical practice in lung cancer with special attention for the age-related differences. In **Part II**, we elaborate on the potential value of a geriatric assessment for patients with lung cancer, and in **Part III**, we review the use of patient-reported outcome measures of ongoing clinical trials and current clinical practice.

Part I consists of three chapters: in **Chapter 2**, the National Institutes of Health (NIH) trial registry is analyzed to assess the selection of patients in ongoing clinical trials on lung cancer: are frail and elderly patients also able to participate? Decision making in a single-center multidisciplinary team is explored in **Chapter 3** by making an aged based-comparison among patients aged <65 years, 65-75 years and older than 75 years. In addition, the subsequent clinical course in these different age categories is analyzed. **Chapter 4** describes data of the Netherlands Cancer Registry regarding outcomes of lung cancer care in patients aged 85 years and older regarding decision making, treatment and survival.

In **Part II**, the value of a geriatric assessment for elderly patients with lung cancer is reviewed. **Chapter 5** is a systematic review of all available evidence on the relevance of a geriatric assessment in elderly patients with lung cancer, with regards to prognostication and predicting treatment related toxicity. **Chapter 6** presents our results of geriatric assessments performed in patients with lung cancer diagnosed and treated in two large teaching hospitals in the Netherlands: the Diakonessenhuis Utrecht and the Haga hospital in the Hague. As some critics state that a geriatric assessment can be time- and manpower-consuming, physicians are seeking shorter tools to distinguish fit and frail patients. **Chapter 7** describes the prognostic value of two frailty screening tools for elderly patients with lung cancer. To analyze the use of geriatric assessments and frailty screening tools in current clinical practice in the Netherlands, we have conducted a survey among Dutch thoracic oncologists (pulmonologists specialized in oncology, **Chapter 8**).

In **Part III**, we analyzed if patient-reported outcome measures (PROMs) are research objectives of studies on lung cancer and other poor prognosis malignancies. In **Chapter 9**, we describe the use of PROMs in currently ongoing clinical trials on lung cancer registered at the National Institutes of Health (NIH) trial registry. **Chapter 10** addresses the evaluation and reporting of quality of life in phase III chemotherapy trials on malignancies with a poor prognosis. In **Chapter 11**, palliative chemotherapy and healthcare utilization in the last three months of life among patients treated with chemotherapy in our institution is described.

Part IV of this thesis consists of a general discussion (**Chapter 12**) and summary (**Chapter 13 and 14**), including an interpretation of main findings, conclusions, recommendations for current clinical practice and future research.

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PART I

CURRENT CLINICAL PRACTICE

Chapter 2

Selection of patients in ongoing clinical trials on lung cancer

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ABSTRACT

Background

Lung cancer is predominantly a disease of the elderly: half of all newly diagnosed patients are over 70 years old. Older patients and those with comorbidities are underrepresented in clinical trials; scientific communities have addressed this issue since the end of the 20th century. We set out to determine the characteristics of the selection of patients in lung cancer trials that are currently recruiting.

Methods

We searched The United States National Institutes of Health (NIH) clinical trial registry (www.clinicaltrials.gov) on April 23, 2015 for currently recruiting phase I, II, or III clinical trials in lung cancer. Trial characteristics and study objectives were extracted from the registry website.

Results

Of the 419 trails selected in this overview, 88 % explicitly or implicitly excluded elderly patients. Patients were excluded based on stringent organ selection in 76 % of the trials, based on performance status (57 %) and based on age (13 %). The median number of placed restrictions per trial was seven. In the 2 % of the trials that were exclusively designed for elderly patients only fit patients were included.

Conclusion

In this overview of current lung cancer trials registered in the NIH clinical trial registry, we found that elderly patients and those with comorbidities are often excluded from participation in clinical trials. Therefore, it is difficult for physicians and their frail patients to properly evaluate the efficacy and safety of current treatment options. More research that includes the elderly and those with comorbidities is urgently needed.

INTRODUCTION

In the Netherlands, over 12,000 cases of lung cancer occur annually.[1] Lung cancer generally has a poor prognosis and often progresses rapidly.[1] It is in fact the leading cause of cancer mortality worldwide.[1] Lung cancer is predominantly a disease of the elderly: half of all newly diagnosed patients are over 70 years old.[1] Survival rates are worse for patients older than 75 years.[1] Over the past years, new treatment strategies for lung cancer have been developed.[2,3] Important changes include the use of targeted therapies and the use of radiotherapy instead of surgery.[2] These new treatment strategies are expected to have fewer disadvantageous side effects, be more patient friendly, and allow for the omission of invasive procedures.[2-4]

Historically, older patients and those with comorbidities have been excluded from clinical trials.[5] Among the U.S. Food and Drug Administration-approved treatments for cancer, only 9 % of patients enrolled in registration trials were older than 75 years of age, whereas 31 % of patients with cancer are within that age group.[6] However, it is incorrect to assume that a treatment regimen investigated in younger patients will also be the best for the elderly. Elderly patients represent a heterogeneous population due to the differences in physiological reserves, in comorbidity, in functional capacity, and in the presence of geriatric syndromes.[7] As a result of these differences, the way that treatment affects them also differs. In addition, complications of therapy are common and are more likely to occur in patients with decreased physiological reserves.[8]

To help doctors and their patients select the optimal treatment, it is important to know if the results of investigated treatment strategies apply to them. However, this is only possible if these trials include older patients and patients with comorbidities that are representative for the general population with lung cancer. Since the end of the 20th century, scientific communities and research cooperative groups have addressed the underrepresentation of older patients in trials.[5,9-12] They all urged for the development of clinical trials that will facilitate or include older patients and those with comorbidities.[5,9-11]

To evaluate whether these recommendations are put into practice, we set out to evaluate the inclusion and exclusion criteria for currently recruiting clinical trials for patients with lung cancer.

METHODS

To identify currently ongoing clinical trials concerning pulmonary malignancies, we searched The United States National Institutes of Health (NIH) clinical trial registry (www.clinicaltrials.gov) on April 23, 2015 for 'lung cancer.' This search was limited to interventional phase I, II, or III trials, or mixed phase I/II or II/III trials that were recruiting on the date of the search or due to start recruiting within 6 months. We included trials that investigated oncological treatment of pulmonary malignancies and excluded those that investigated other types of malignancies as well.

For the included trials, the following data were extracted from the registry website: type of intervention, source of funding, primary or secondary study objectives, start year of the study, and inclusion or exclusion criteria that focus on age limits, performance status (PS), comorbidity, or organ function. Restrictions regarding organ function and comorbidity were classified into the following categories: ''bone marrow function,'' ''hepatic,'' ''renal,'' ''pulmonary,'' ''cardiac,'' ''other cardiovascular disease,'' ''prior oncologic history,'' and ''psychiatric history.'' For each category, restrictions were labeled as ''moderate,'' as ''strict,'' or as ''none'' if no exclusion criteria pertaining to that category were mentioned. This classification was previously used by Lewis et al.[13]; full details per category can be found in the Appendix. In summary, strict restrictions were those protocol exclusion criteria that required normal to nearly normal laboratory values or organ function, whereas moderate restrictions allowed for mildly abnormal values while still imposing some restrictions. To combine the data using the Karnofsky PS and the data using the World Health Organization (WHO) PS, we set a Karnofsky PS of 100 as equivalent to WHO PS 0, Karnofsky PS 80–90 equivalent to WHO PS 1, 60–70 to WHO PS 2, 40–50 to WHO PS 3, and <30 to WHO PS 4.[14]

Data were extracted from the registry website by CN and KJS. If the authors could not reach consensus, a third reviewer was asked to give her opinion (MH). We used the opinion of the third reviewer for trials in which the description of the inclusion and exclusion criteria per organ system were unclear and therefore subject of debate.

We considered trials as excluding elderly patients if they used an upper age limit of 75 years or younger, if they only allowed very fit patients with a WHO PS of 0 or 1, or if they placed strict restrictions on one or more organ systems.[15,16] Only descriptive data are presented, we did not perform statistical analysis.

RESULTS

We identified a total of 791 trials in the trial registry search and out of these we included 419 in this overview. Trials that did not address pulmonary malignancies (n = 168) or included other malignancies in addition to lung cancer (n = 164) were excluded from our selection. Trials that did not address oncological treatment (n = 40) were also excluded.

Characteristics of Included Trials

The characteristics of the included trials are summarized in Table 1. A lower age limit for inclusion from the trial was applied in 100 % of the trials: 21 years for 97 %, aged between 22–59 years for 1 % and 70 + years for 2 %. (Table 2). In 18 % of the trials, an upper age limit for exclusion was applied: in 4 % of the trials, this limit was set at 75 years or younger and in 14 % this limit was set at 76 + years. Patients with a WHO performance score (PS) of 0 or 1 were allowed in 90 % of the trials, with a WHO PS 2 were allowed in 38 %, with a WHO PS 3 in 2 %, and with a WHO PS 4 in 1 %. In 10 % of the trials, a clear description of allowed PS was lacking.

Table 1. Characteristics of selected trials

		All trials (*n*=419)	
		n	%
Diagnosis	NSCLC	362	86
	SCLC	48	11
	Mesothelioma	19	5
Start of inclusion	<2007	3	1
	2008-2009	22	5
	2010-2011	47	11
	2012-2013	179	43
	2014-2015	168	40
Intervention*	Chemotherapy	267	64
	Targeted therapy	132	31
	Radiotherapy	86	20
	Immunotherapy	61	15
	Chemoradiation	38	9
	Other interventions	33	8
	Surgery	23	5
	Surgery and chemotherapy	10	2
Phase	I	122	29
	II	273	65
	III	87	21
Industry-sponsored*		210	50

(N)SCLC (Non)small cell lung cancer

** Trials could have multiple interventions and multiple sponsors*

Table 2. Inclusion and exclusion criteria of selected trials

		All trials (*n*=419)	
		n	%
Lower age limits, years	<21	408	97
	22-59	2	1
	60-64	0	0
	65-69	0	0
	70+	9	2
Upper age limits, years	<50	0	0
	51-64	1	1
	65-69	3	1
	70-74	12	3
	75-79	39	9
	80-84	9	2
	85-95	10	2
	none	345	82
Performance status (PS)	PS 0 included	377	90
	PS 1 included	376	90
	PS 2 included	161	38
	PS 3 included	7	2
	PS 4 included	3	1
	PS unclear	40	10
Organ system restrictions	Bone marrow function	81	19
	No restrictions	316	75
	Moderate restrictions	22	5
	Stringent restrictions		
	Hepatic function	82	20
	No restrictions	149	36
	Moderate restrictions	188	45
	Stringent restrictions		
	Renal function	85	20
	No restrictions	199	48
	Moderate restrictions	135	32
	Stringent restrictions		
	Pulmonary function	112	27
	No restrictions	221	53
	Moderate restrictions	86	20
	Stringent restrictions		
	Cardiac function	96	23

Table 2. Inclusion and exclusion criteria of selected trials (continued)

		All trials (*n*=419)	
		n	%
	No restrictions	163	39
	Moderate restrictions	160	38
	Stringent restrictions		
	Other cardiovascular disease		
	No restrictions	138	33
	Moderate restrictions	249	59
	Stringent restrictions	32	8
	Oncological history		
	No restrictions	83	20
	Moderate restrictions	305	73
	Stringent restrictions	31	7
	Psychiatric history		
	No restrictions	300	72
	Moderate restrictions	99	24
	Stringent restrictions	20	5

Selection of Patients in Lung Cancer Trials

One or more restrictions on organ function were placed in 95 % of the included trials. As clarified in the method section, restrictions per organ system were categorized as strict, moderate, and none. Strict restrictions for one or more organ systems were placed in 71 % of the trials. Strict restrictions were most frequently applied to hepatic function (45 %), cardiac function (38 %), and renal function (32 %). Moderate restrictions for one or more organ systems were placed in 92 %. Moderate restrictions were most frequently applied to bone marrow function (75 %), oncological history (73 %), cardiovascular diseases other than cardiac function (59 %), pulmonary function (53 %), renal function (48 %), and cardiac function (39 %). One or more strict organ restrictions were placed in 73 % (194/267) of the trials that investigated chemotherapy, in 73 % (96/132) of the trials that investigated targeted therapies, as tyrosine kinase inhibitors, and in 78 % (67/86) of the trials that investigated radiotherapy. The median number of placed restrictions was seven (IQR25–75:4–7), the median number of strict restrictions was one (IQR25–75: 0–3), and the median number of moderate restrictions was four (IQR25–75: 2–6).

Trials Designed for Elderly Patients

Nine out of 419 trials used a lower age limit of 70 > years and were categorized asexclusively designed for elderly patients. Eight out of these nine studies applied one or more strict restrictions per organ system. One study did not place strict restrictions but only

placed moderate restrictions on prior oncological history. The other eight studies placed strict organ restrictions on renal function (7/8) or hepatic function (8/8). For all these nine trials, patients with a WHO performance score of 3 or 4 were not allowed for inclusion. The treatment focus of these studies included chemotherapy, targeted therapy, radiotherapy, and chemoradiotherapy.

Trials Excluding Elderly Patients

As clarified in the method section, we considered trials as excluding elderly patients, if they used an upper age limit of 75 years or younger, if they only allowed patients with a WHO PS of 0 or 1, or if they placed strict restrictions on one or more organ systems.[15] When we applied these criteria, 370 out of 419 trials (88 %), explicitly or implicitly, excluded elderly patients from their trials. Elderly patients were excluded on the basis of age in 55 trials (13%), on the basis of WHO PS in 239 trials (57 %), and on the basis of placing strict organ restrictions in 318 trials (76 %).

DISCUSSION

In this overview of current lung cancer trials registered in the NIH clinical trial registry, we found that elderly patients and those with comorbidities are often excluded from participation in clinical trials. Of the trails selected in this overview, 88 % explicitly or implicitly excluded elderly patients. Patients were excluded based on stringent organ selection in 76 % of the trials, based on PS (57 %) and based on age (13 %). The median number of restrictions per organ system per trial was seven. In the 2 % of the trials that were exclusively designed for elderly, patients with a WHO performance score of 3 or 4 were not allowed, and nearly all these trials applied one or more strict restrictions per organ system.

This study has several limitations. First, we have focused exclusively on the NIH clinical trial registry, and therefore, we do not have a full presentation of all clinical trials worldwide. However, the NIH trial registry is by far the largest; as a comparison, we have searched the second largest registry (the European Union clinical trial registry— www.clinicaltrialregister.eu) with the same query and it resulted in only a fraction of the trials included in this overview. The second limitation is that there is no consensus on which cut-off values represent strict or moderate restrictions in organ function. To circumvent this issue, we chose to use a classification that was previously used in a peer-reviewed and often cited publication by Lewis et al..[13] Finally, we only had access to the data reported on the primary website. It is possible that other inclusion or exclusion criteria were applied but not mentioned on the registry website. However, we believe that this is unlikely to have happened on a large scale.

In clinical practice, severe impairments in organ function will often be a reason to withhold certain treatment options for lung cancer, and rightfully so, as some level of physical reserves is required to endure the treatment. However, in general, treatment will be offered to a much broader scope of patients than was included in the clinical trials that were used to determine treatment benefit, with the underlying assumption that the results of these trials have sufficient external validity to allow for extrapolation to a more general lung cancer population. Particularly, the high median number of restrictions per organ system in the included trials was considered.

This assumption may not be correct. For instance, a recent publication compared outcome of patients included in the CAIRO trials with patients not included in the trial but fulfilling the inclusion criteria, and patients not included and not fulfilling the inclusion criteria.[17] All patients received the same treatment. Patients fulfilling the trial criteria achieved similar benefit, irrespective of trial participation. However, patients not fulfilling the trial criteria experienced little treatment benefit, compared to the other two groups. This illustrates that study results are primarily valid within a population that is comparable to the trial population and do not provide reliable evidence on what the effect would be in other patient groups.

As Western societies age, cancer in the elderly becomes an increasingly relevant topic, because the incidence of cancer increases with age. However, many questions regarding the outcome of various treatment options for lung cancer in older patients remain unanswered. Trials specifically addressing the elderly would perhaps provide the most superior solution, but as seen in this overview, these trials represent only 2 % of all ongoing lung cancer trials. A second option to increase our knowledge is to allow for participation of patients that are representative for the general lung cancer population by including also frail and elderly patients.

However, the desirability of including older or vulnerable patients in clinical trials is subject to debate.[13] Interestingly, the advocates of including these patients and their opponents use similar arguments to support their opinions. The first argument is that elderly or frail patients generally have reduced physiological reserves and will be more prone to interactions due to polypharmacy and altered pharmacodynamics in an aging body. These factors may limit their ability to tolerate treatment and as a result, they will be less likely to benefit from certain therapies compared to fit, younger patients.[18-22] In addition, comorbidities may form competing causes of death, decreasing overall survival. Thus, the results of clinical trials are expected to be less positive when older patients are allowed to participate or will be inconclusive due to smaller treatment effects.[20,23-25] Although these arguments are valid, they also underline the fact that results from trials focusing exclusively on young and fit lung cancer patients cannot simply be generalized to all lung cancer patients.[12,26]

To improve the evidence of treatment for patients that are not young and fit, several options should be taken into consideration when developing new clinical trials. First, all inclusion and exclusion criteria formulated in a trial protocol should be considered carefully to determine whether they are truly necessary or could perhaps be expanded to allow for the participation of a broader range of patients. Subgroup analyses could be undertaken to specifically describe the results for less fit or elderly patients. A second option is to develop trials which incorporate a treatment arm specifically designed for patients not fulfilling the inclusion criteria, for instance with a reduced intensity treatment plan. A third option is to develop trials specifically for the elderly. Finally, the observational data regarding patient characteristics including comorbidities and frailty data as well as treatment outcome could be used to determine treatment benefit in non-trial populations.

CONCLUSION

Elderly patients and those with comorbidities are underrepresented in currently ongoing clinical trials on lung cancer treatment, and many trials directly or indirectly limit their participation. As trial results cannot be simply be extrapolated to patients outside the trial population, many questions regarding optimal treatment for older patients remain unanswered. This should be taken into consideration in future trial designs.

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Appendix. Classification of inclusion and exclusion criteria for organ function[13]

Organ system	Moderate restrictions	Strict restrictions
Bone marrow	· Adequate bone marrow/hematologic function · Cut-off for white blood cell count ≥3500/mm^3 or lower · Cut-off for absolute neutrophil count ≥1000/mm^3 or lower · Cut-off for platelet count ≥125.000/mm^3 or lower	· Normal bone marrow/hematologic function · Cut-off for white blood cell count ≥4000/mm^3 or higher · Cut-off for absolute neutrophil count ≥1800/mm^3 or higher · Cut-off for platelet count ≥130.000/mm^3 or lower
Hepatic	· Adequate hepatic function · Cut-off for bilirubin 1.8 times upper limit of normal or higher · Cut-off for bilirubin 1.8 mg/dL or more · Cut-off for aspartate aminotransferase /alanine aminotransferase 1.8 times upper limit of normal or less · Prothrombin time within 25% of normal value	· Normal hepatic function · Normal bilirubin · Cut-off for bilirubin 1.7 times upper limit of normal or less · Cut-off for bilirubin 1.7 mg/dL or less · Normal aspartate aminotransferase / alanine aminotransferase · Cut-off for aspartate aminotransferase /alanine aminotransferase 1.7 times upper limit of normal or less
Renal	· Adequate renal function · Cut-off for creatinine clearance ≥ 60 ml/min or lower · Cut-off for creatinine 1.8 times upper limit of normal or higher · Cut-off for creatinine 1.8 mg/dL or more	· Normal renal function · Normal creatinine · Cut-off for creatinine clearance ≥ 61 ml/min or higher · Cut-off for creatinine 1.7 times upper limit of normal or lower · Cut-off for creatinine 1.7 mg/dL or less

Appendix. Classification of inclusion and exclusion criteria for organ function[13] (continued)

Organ system	Moderate restrictions	Strict restrictions
Cardiac	· Adequate cardiac function · No clinically evident congestive heart failure · No difficult to control congestive heart failure · Cut-off for left ventricular ejection fraction ≥40% or lower · Cut-off for shortening fraction ≥25% or lower · No clinically significant cardiac disease · No New York Heart Association (NYHA) grade III or IV disease · No myocardial infarction in past 12 months or shorter · No angina pectoris requiring medication · No unstable heart rhythm · No difficult to control heart rhythm · No symptomatic arrhythmia in past 6 months · Cut-off for QTc > 450ms or higher	· Normal cardiac function · No history of congestive heart failure · Cut-off for left ventricular ejection fraction ≥45% or higher · Cut-off for shortening fraction ≥27% or higher · No New York Heart Association (NYHA) grade II or more · No history of myocardial infraction or ischemic heart disease · No myocardial infarction in past 5 years or longer · No abnormal conduction disease · No arrhythmia requiring treatment
Other cardiovascular	· No poorly controlled hypertension · No systolic blood pressure > 200 mmHg · No diastolic blood pressure > 120 mmHg · No thrombo-embolic disease in past 6 months · No cerebrovascular events with persistent neurological deficits	· No history of hypertension · No hypertension requiring more than 2 antihypertensive drugs · No systolic blood pressure > 160 mmHg · No diastolic blood pressure > 100 mmHg No history of stroke · No history of transient ischemic attack · No prior thrombo-embolic disease (deep venous thrombosis and/or pulmonary embolism)

Appendix. Classification of inclusion and exclusion criteria for organ function[13] (continued)

Organ system	Moderate restrictions	Strict restrictions
Pulmonary	· Adequate pulmonary function · Cut-off for diffusing capacity for carbon monoxide (DLCO) ≥ 50% or lower · Cut-off for forced expiratory volume in 1 second (FEV1) ≥50% or lower · Cut-off for oxygen saturation (SaO2) at room air ≥93% or lower · Cut-off for total lung capacity ≥50% of normal or lower · No need for oxygen suppletion	· Normal pulmonary function · Cut-off for diffusing capacity for carbon monoxide (DLCO) ≥ 60% or higher · Cut-off for forced expiratory volume in 1 second (FEV1) ≥60% or higher · Cut-off for oxygen saturation (SaO2) at room air ≥94% or higher · No history of pulmonary disease
Psychiatric	· No active psychiatric disease · No mental illness making informed consent impossible · No psychiatric disease in past 5 years · No active substance abuse or addictions	· No history of psychiatric disease · No history of substance abuse
Prior malignancies	· No prior malignancy in past 5 years or shorter · No active/concurrent malignancy · No malignant disease likely to progress in next 5 years	· No prior malignancy · No prior malignancy in past 10 years or longer

* If multiple criteria per category are listed, then trials will be classified according to the most stringent restriction

Chapter 3

Multidisciplinary decision–making regarding chemotherapy for lung cancer patients: an age–based comparison

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ABSTRACT

Introduction

Optimising decision making in elderly patients is becoming increasingly urgent. We analysed treatment decisions and course of therapy for patients with lung cancer in different age categories: <65 years, 65-75 years and 75 years and older.

Methods

349 patients with lung cancer (median age 67.8 years), discussed at the multidisciplinary team meeting in the Diakonessenhuis Utrecht, the Netherlands, were reviewed. Multidisciplinary decision making and subsequent clinical course were extracted from medical files.

Results

We found that 39% of eligible patients older than 75 years of age started treatment with chemotherapy compared to 80% of the younger patients (<65 and 65-75). When patients did receive chemotherapy, primary and secondary treatment adaptations were effectuated in 58%: for patients aged <65 in 49%, for patients aged 65-75 and >75 years in 66%. For 44% of all patients treated with chemotherapy, unplanned hospital admissions were required: in 42% for the patients <65, in 52% for those aged 65-75 and in 27% for >75 years.

Conclusion

The decision-making process and course of treatment for lung cancer vary per age category. In particular, patients between 65-75 years of age might be more frail than initially thought. Age and frailty are important characteristics that need more attention.

INTRODUCTION

In the Netherlands, over 12,000 patients are newly diagnosed with lung cancer every year.[1] Lung cancer still remains the leading cause of cancer-related deaths globally.[2] Due to nonspecific symptoms, diagnosis is often made in advanced disease stages. For these patients, treatment is frequently with palliative intent and often consists of chemotherapy. For the advances disease stages, survival is generally poor, even with oncologic treatment.[1] The disease frequently occurs in elderly patients: approximately 30% of these patients are older than 75 years of age.[1]

Treating these older patients is a challenge. Given the heterogeneity of the elderly population in comorbidity, remaining functional capacity, and geriatric syndromes, it cannot be assumed that treatment regimens that are most beneficial for younger patients will also be the best choice for the elderly.[3] Among the Food and Drug Administration (FDA) approved treatments for cancer, only 9% of patients enrolled in the registration trials were older than 75 years of age, whereas 31% of patients with cancer are within that age group.[4,5] Much of the data on lung cancer therapies are also based on patients with a younger profile. Over the past fifteen years, a few trials have focused on the elderly patients, but these mainly included a subset with a good performance status. While these studies may provide some guidance on the management of older patients, a consensus on the optimal treatment is still lacking.[6–10] This means that cancer specialists must determine for themselves what the best treatment option will be in each individual case.

The decision-making process for oncologic treatment will often consist of several steps. In the Netherlands, over 95% of decisions regarding treatment for newly diagnosed lung cancer are first discussed in a multidisciplinary cancer team (MDT) meeting.[11–13] Guidelines recommend distinguishing fit and frail elderly by using the Eastern Cooperative Oncology Group performance score (ECOG PS) to quantify functional status together with clinical judgement.[11,12] The thoracic oncologist and the patient need to make a final decision on the eligibility and desirability of surgical, radiotherapeutical or chemotherapeutical treatment after critical evaluation and after the healthcare professionals inform the patient about the possible benefits and risks.[11–13]

With the imminent ageing of western societies[14], and the subsequent rise in the number of older lung cancer patients[1], optimising decision making for this patient population is becoming increasingly important. A first step is to become aware of current clinical practice for older patients. However, the age at which patients are being classified as ‘old’ has changed over time. The exact cut-off point might not be as strict, but classifying a patient as ‘old’ might be useful in identifying vulnerable patients. For lung cancer patients, where

comorbidities might be highly prevalent, the cut-off for 'old' is particularly unclear. In this audit of current treatment decision making for lung cancer patients we identified three age categories: <65 years, 65-75 and over 75 years. We sought to assess how treatment decisions for lung cancer in these age groups were made by the MDT, especially by the thoracic oncologist (a member of the MDT), and the patient. A secondary goal was to retrospectively analyse the course of treatment for these different age categories.

METHODS

The multidisciplinary lung cancer team (MDT) at the Diakonessenhuis – a large teaching hospital in Utrecht, the Netherlands – meets weekly to discuss treatment options for all newly diagnosed patients as well as for those in whom decisions need to be made regarding the next treatment step. In accordance with national guidelines[13], this team consists of specialists from the departments of pulmonology specialized in oncology (thoracic oncologist), surgery, radiology, pathology and a case manager from our centre as well as a thoracic oncologist, radiotherapist and thoracic surgeon from an affiliated tertiary referral centre (University Medical Centre Utrecht). In the Netherlands, in contrast to other countries, lung cancer is primarily treated by the pulmonologist specialized in oncology (thoracic oncologist). Patients are discussed on the basis of a case form, containing all information considered to be relevant to the case. Once a consensus is reached within the team, based on the presented information, the treatment recommendations are summarized on the case form and then double-checked with the team members. After the MDT meeting, the treating specialized pulmonologist (thoracic oncologist) and the patient decide whether they opt for the same treatment as suggested by the MDT or if they deviate from the suggested treatment regimen.

In this audit, we compared the recommendations of the MDT with guideline recommended treatment. An overview of Dutch guidelines for treatment of lung cancer can be found in Appendix 1.[11,12] In summary: surgical resection is advised for stage Ia and Ib non small cell lung cancer (NSCLC). Adjuvant chemotherapy is not recommended for stage Ia, but is stated to be a consideration for stage Ib.[12] For stage II, surgical resection with adjuvant chemotherapy is advised. Although surgical resection is the first treatment choice for stage I-II NSCLC, stereotactic body radiotherapy (SBRT) is considered to be a good alternative.[15] Concurrent chemoradiotherapy, or sequential chemoradiotherapy depending on the size and location of the tumor, is advised for stage III NSCLC, as well as for limited disease small cell lung cancer (SCLC). Chemotherapy is recommended for all patients with stage IV NSCLC and for all stages of SCLC. For patients with an ECOG PS of 3 or 4, best supportive care is recommended.[11,12]

For this audit, all patients with NSCLC or SCLC discussed at the team meetings between January 2012 and December 2014 were reviewed to select those patients for whom a treatment decision regarding a newly diagnosed pulmonary malignancy was discussed. Patients were excluded from our analysis if no case sheet was available in the medical file, if they had an ECOG performance score of 3 or 4, if they were not diagnosed with NSCLC or SCLC (for example mesothelioma, no or other histological diagnosis) or if they were treated elsewhere.

We divided our patients in three groups based on age: the first group consists of patients younger than 65 years of age (<65), the second group consists of patients aged between 65 and 75 years (65-75) and the last group consists of patients older than 75 years of age (>75).

The following data were collected: age at inclusion, sex, prior medical history (assessed using the Charlson comorbidity index (CCI)[16]), date of the meeting, date of oncologic diagnosis and the treatment decision to be discussed at meeting. The content of the case form was reviewed to determine what data were presented at the meeting, both regarding the patient and the malignancy. Patient-related data were classified as comorbidity, functional status, nutritional status, psychosocial status and patient's preference regarding treatment choice.

Subsequently, the patient's medical files were reviewed to retrieve the recommendation of the multidisciplinary team regarding treatment and to determine to what extend these recommendations were implemented. Reasons for deviating from guideline recommended treatment or MDT recommendations were also retrieved from the medical file and subdivided in the following categories: comorbidity, physical condition, age, patient's preference, insufficient expected benefit and unclear.

For patients receiving chemotherapy, the following data were collected: intended chemotherapy regimen, dosage, number of cycles and interval. The intended regimen was compared to the standard regimen according to treatment guidelines.[11,12] Adaptations from guideline-recommended treatment were classified as primary adjustments when changes were made upfront, prior to the first treatment cycle, and as secondary adjustments when they were made after chemotherapy had commenced.

Additional data were collected regarding the course of treatment, assessment of completion of all intended cycles, secondary dose reductions, interruption of cycles, increased time-interval between cycles and the reasons for treatment adjustments as well as unforeseen hospital admissions during therapy. The reasons were classified as fever/infections,

nefrotoxicity, neurotoxicity, hematological toxicity, gastro-intestinal toxicity, vascular disorders, subjective/constitutional symptoms or other.

The medical ethics committee reviewed the research protocol and provided a written statement that this study was exempt from full ethical review given its retrospective nature.

Statistical analysis

All analyses were performed in SPSS Statistics version 23.0. For comparisons between groups, the chi-square test was used for nominal and ordinal variables; the ANOVA test was used for continuous variables. P-value smaller than 0.05 was considered as statistically significant.

RESULTS

In the weekly multidisciplinary lung cancer meetings that took place between January 2012 and December 2014, a total of 431 unique patients were discussed. Of these, 349 patients were included for analysis. Reasons for exclusion are listed in Figure 1.

Treatment of stage Ia and Ib

According to the guidelines, for 53 patients with stage Ia or Ib NSCLC surgical resection was indicated. Median age of these patients was 71 years (range 44-86) and 39.6% (n= 21) was male. In nine of these patients the MDT recommended treatment with curative stereotactic body radiotherapy instead of surgery. The median age of the patients treated with radiotherapy was 74 years (range 59 - 86 years). Reasons to recommend curative radiotherapy instead of surgical resection varied from comorbidity/physical condition (n=4), lung function (n=3) to age (n=2). The reason 'age' was mentioned in patients of 85 and 86 years old. The oldest patient that underwent surgical treatment was 81 years old.

Baseline characteristics of patients with an indication for chemotherapy

Table 1 shows baseline characteristics of patients with an indication for adjuvant or palliative chemotherapy (n=293), of which 75% had NSCLC and the remaining 25% had SCLC. A curative treatment intent was suggested for 31% of all patients: 32% of youngest patients, 37% of middle group (65-75 years) and 21% of the oldest group.

The median age at diagnosis was 67.2 years (range 39.7 – 93.7); 42% (n=124) was younger than 65 years of age, 31% (n=92) was aged between 65 and 75 years, 26% (n=77) was

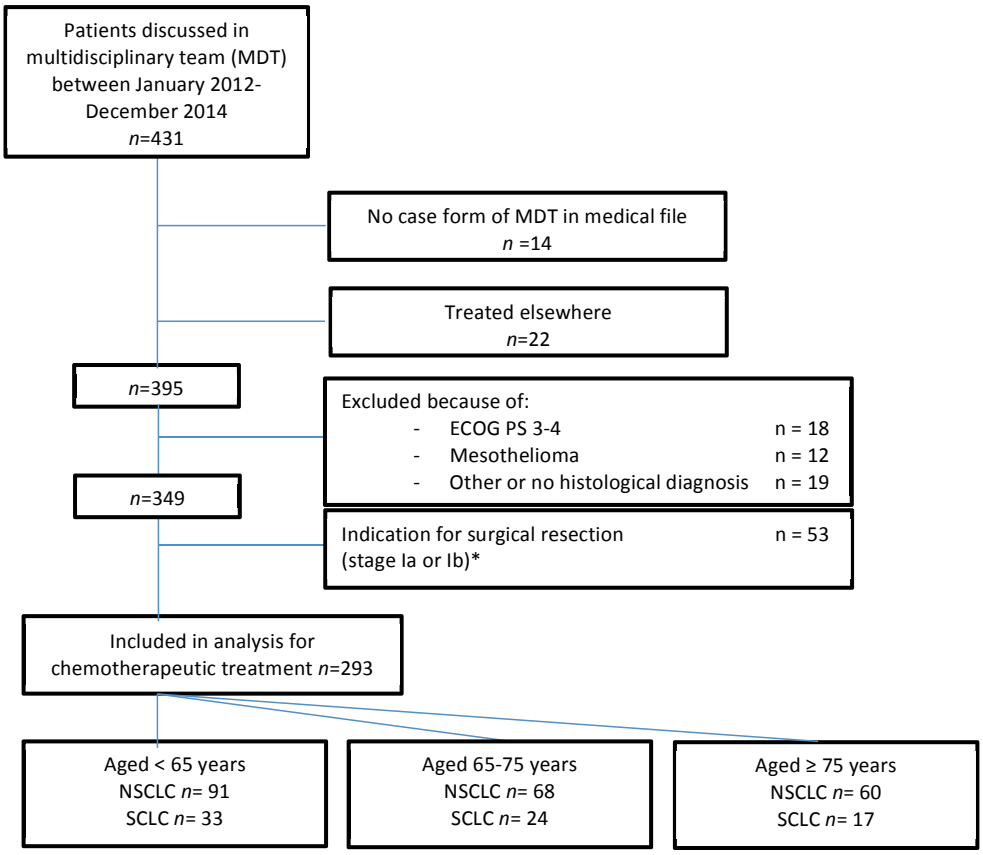

Figure 1. Patient selection

*Guidelines are ambivalent regarding chemotherapy for stage Ib NSCLC

older than 75 years of age, 48% was male. Approximately half (49%) of the patients had a Charlson Comorbidity Index of 1 or higher. Older patients had a higher comorbidity burden ($p<0.001$).

On the case form, cancer-related data were presented for nearly all patients (98%). Comorbid diseases were reported for 83% of patients, nutritional status for 44%, psychosocial status in 17% and patient's preference regarding therapy in 14%. The preference of the patients was presented at the MDT more frequently in the elderly: 26% (75+) versus 9% (<65 years) and 10% (65-75 years) ($p<0.001$).

Decision making process

Figure 2 shows the steps taken in decision-making regarding chemotherapy per age category. The MDT chose not to suggest treatment with chemotherapy in 4% of patients aged younger than 65 years (Fig 2A) (n=5), in 4% of patients aged 65-75 years (Fig2B) (n=4) and

Table 1. Baseline characteristics

	All patients (n = 293)	<65 years (n=124)	65-75 years (n=92)	≥75 years (n=77)	p value
Median age in years (range)	67.2 (39.7 – 93.7)				
Female	151 (51%)	74 (60%)	45 (49%)	32 (42%)	**0.04**
Male	145 (49%)	50 (40%)	47(51%)	45 (58%)	
Charlson comorbidity index ≥1	146 (49%)	46 (37%)	48 (52%)	51 (66%)	**0.001**
Type of malignancy					
NSCLC	222 (75%)	91 (73%)	68 (74%)	60 (78%)	0.8
SCLC	74 (25%)	33 (27%)	24 (26%)	17 (22%)	
Treatment intent					
Curative	93 (31%)	40 (32%)	34 (37%)	16 (21%)	0.07
Palliative	203 (69%)	84 (68%)	58 (63%)	61 (79%)	
Data presented at cancer team meeting					
Cancer-related data	291 (98%)	122 (98%)	90 (98%)	77 (100%)	0.5
Comorbidity	245 (83%)	97 (78%)	78 (85%)	68 (88%)	0.2
Nutritional status	128 (43%)	53 (43%)	49 (53%)	26 (34%)	**0.04**
Functional status	64 (22%)	21 (17%)	22 (24%)	21 (27%)	0.2
ECOG sheet	233 (79%)	104 (84%)	73 (79%)	55 (71%)	0.1
Psychosocial status	50 (17%)	23 (19%)	11 (12%)	16 (21%)	0.3
Patient's preference	40 (14%)	11 (9%)	9 (10%)	20 (26%)	**0.001**

Bold values indicate significance at p≤ 0.05

in 14% (Fig2C) (n=11) of patients aged 75 years and older. The reason to advise against chemotherapy was most often comorbidity or physical condition (n=17; 85%) and in the oldest category (75+), age itself was mentioned in four patients (5%). Multiple reasons were possible for each patient.

After the MDT meeting, the pulmonologists opted not to start chemotherapy despite the advice of the MDT in 8% (n=10) of the youngest, 10% (n=9) of the middle and in 16% (n=12) of the oldest patients, mostly because of poor physical condition (n=22; 71%) or lack of expected benefit (n=4; 13%).

Additionally, in 8% (n=10) of the youngest, 7% (n=6) of the middle category and in 31% (n=24) of the oldest, patients chose best supportive care instead of chemotherapy. Ultimately, treatment with chemotherapy was started in 80% (n=99) of patients aged <65 years, in 79% of patients aged 65-75 years (n=73) and in 39% of patients aged >75 years (n=30). The oldest patient that underwent treatment with chemotherapy was 86 years.

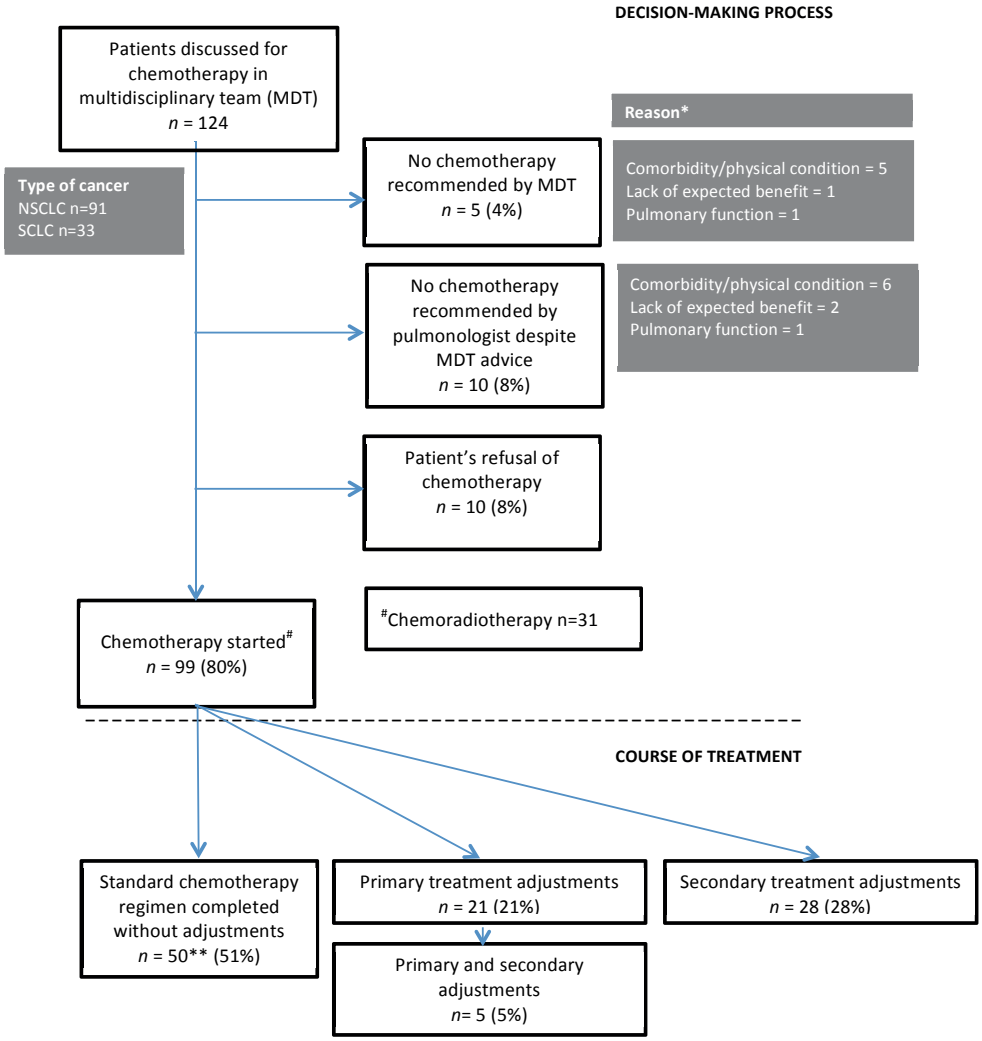

Figure 2 A. Patients aged younger than 65 years
DECISION-MAKING PROCESS
*Multiple reasons were possible for each patient
**4 patients were treated with TKI

According to the guidelines, chemoradiotherapy was indicated in 87 patients (30%). The MDT advised this treatment in 74 patients (85%) and in the other thirteen patients (15%) the MDT deviated from the guidelines. Of these thirteen patients one was aged younger than 65 years, one was aged between 65 and 75 years and eleven were aged older than 75 years. In nine of these thirteen patients, the MDT recommended only supportive care, because of physical condition/comorbidity (n=7), patient's preference (n=1) or age (n= 1, 94 years old). In three patients (23%) stereotactic radiotherapy was the recommended alternative for the

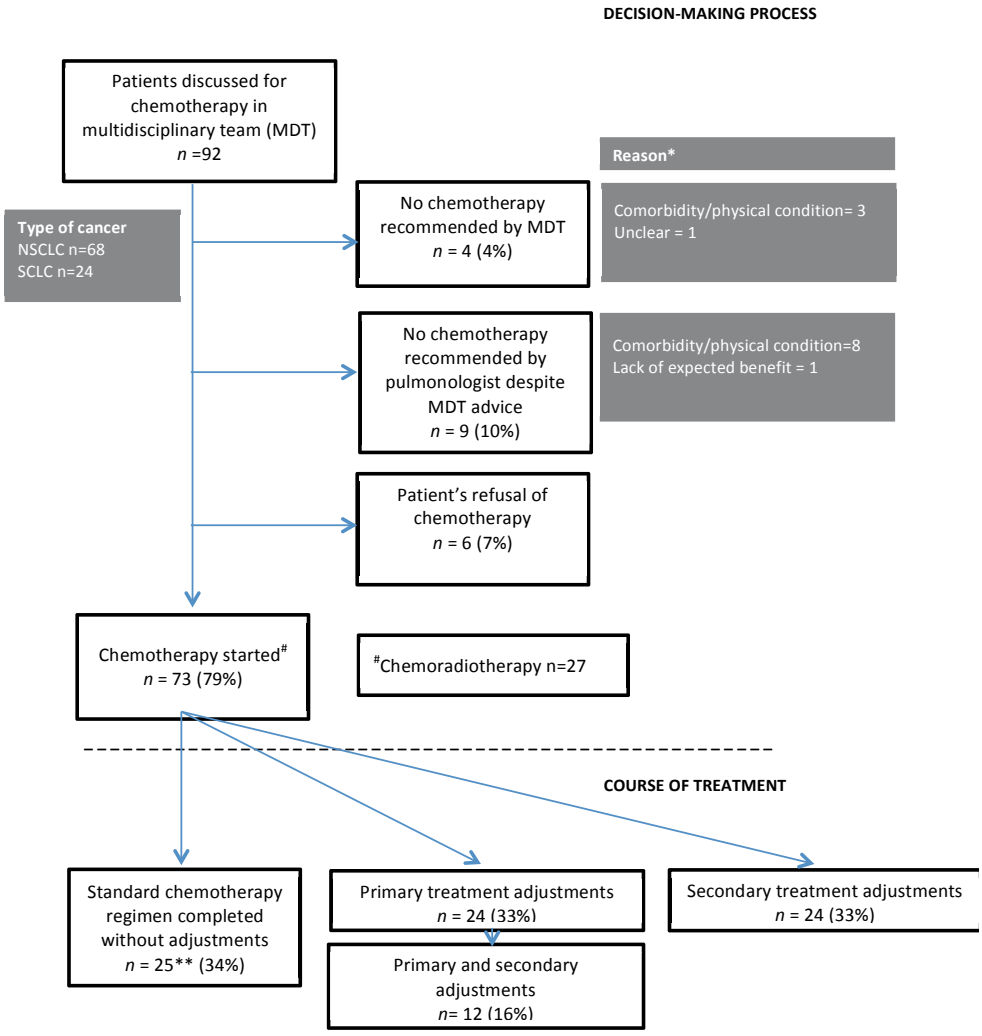

Figure 2 B. Patients aged 65–75 years
*Multiple reasons were possible for each patient
**3 patients were treated with TKI

MDT because of poor physical condition (n=3) and remaining pulmonary function (n=2). In one patient (8%) chemotherapy instead of chemoradiotherapy was recommended because of the patient's preference. Multiple reasons were possible for each patient.

After the MDT recommendations, three patients decided that they only wanted supportive care and for two patients the pulmonologists decided not to start with chemoradiotherapy despite the advice of the MDT because of comorbidity and poor physical condition.

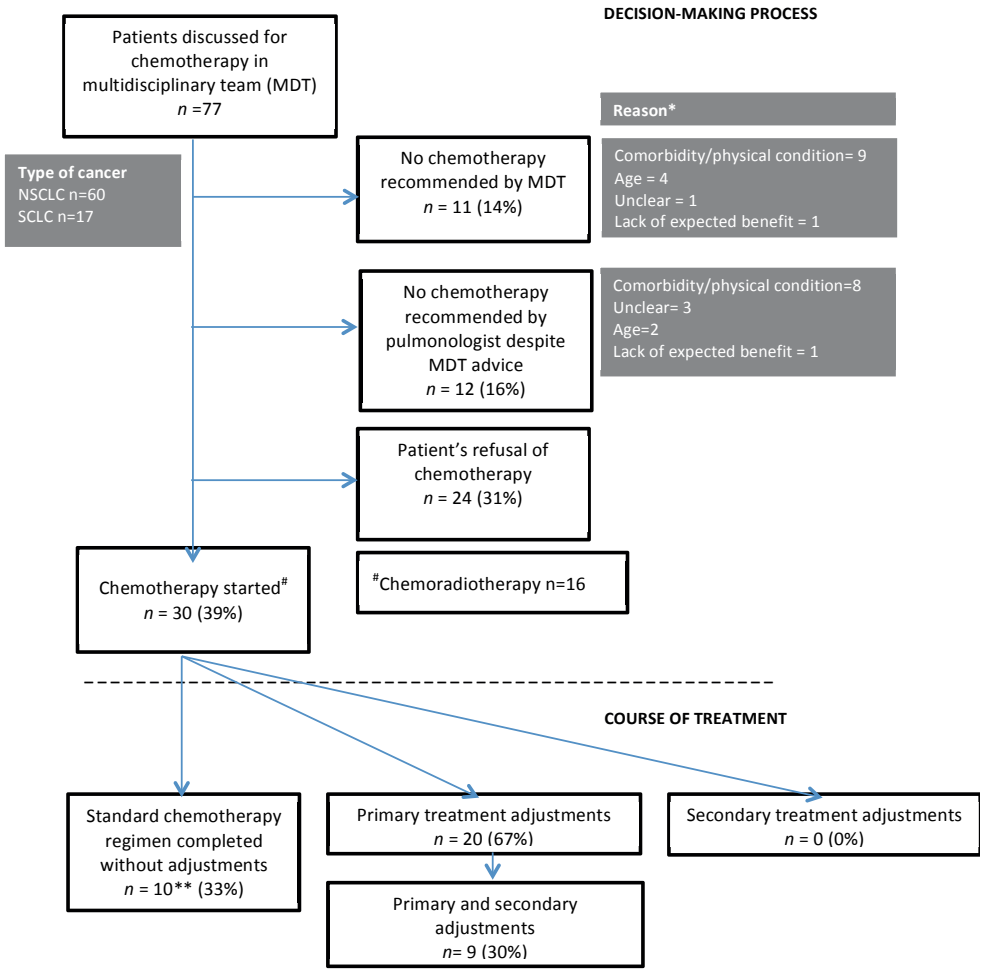

Figure 2 C. Patients aged 75 years and older
*Multiple reasons were possible for each patient
**5 patients were treated with TKI

The median age of the patients treated with chemoradiotherapy was 68 years (range 46.4 – 83.8). The oldest patient that underwent a concurrent regimen was 74 years.

Course of treatment

In 51% (n=50) of the 99 patients aged <65 years receiving chemotherapy, the guideline recommended treatment regimen could be followed without treatment adaptations, in comparison to 34% of patients aged 65-75 years (n=25/73) and 33% of patients aged 75 years and older (n=10/30). The treatment consisted of tyrosine kinase inhibitor (TKI) in four (4%) patients aged <65 years, in three (4%) patients aged 65-75 years and in five (17%) patients aged >75 years.

Primary treatment adjustments - upfront changes prior to the first treatment cycle - were made in 21% (n=21) of patients younger than 65 years, in 33% (n=24) of patients aged 65-75 years and in 67% (n=20) of patients aged 75 years or older. Secondary treatment adjustments - adaptations made after chemotherapy was commenced - were made in 28% (n=28), in 33% (n=24) and in none, respectively, for patients without primary treatment adjustments. Both primary and secondary treatment adaptations were made in 5% (n=5) of patients <65 years, in 16% (n=12) of patients aged 65-75 years and in 30% (n=9) of patients aged 75+.

In 22 of 69 patients (32%) that were treated with chemoradiotherapy, this regimen was started and finished without treatment adaptations. For 13 patients (32%) primary adaptations were made, for 16 (23%) patients secondary treatment adaptations were made and for 18 (26%) patients both primary and secondary adaptations were made.

Details of treatment adjustments are shown in Table 2 divided per treatment intent (curative or palliative). The main primary treatment adjustment for patients treated with a curative intent was sequential instead of concurrent chemoradiotherapy (n=30), which occurred significantly more in patients aged 75 years and older (p<0.001). For 17% of the patients (n=12) with an indication for chemoradiotherapy, a concurrent regimen was not an option due to the location or the size of the tumor. For the patients treated with a palliative intent, the main adaptation was change in type of chemotherapy (n=30; 24%).

Secondary treatment adjustments, for both palliative and curative treatment, consisted mainly of interruption of a treatment cycle (n=36; 18%) delay between cycles (n=32; 16%) and change in type of chemotherapy (n=34; 17%). Reasons for secondary treatment adjustments per age category are shown in Table 3. Main reasons in patients aged <65 years were infections (n=12; 36%) or nephrotoxicity (n=9; 27%), for patients aged 65-75 years nephrotoxicity (n=13; 36%) or constitutional symptoms (n=12; 33%) and for patients aged 75+ the reason was mainly constitutional symptoms (n=4; 44%).

Unplanned hospital admissions

Unplanned hospital admissions during the course of therapy were needed for 49% of the patients treated with a curative intent (n=39) and for 40% of the patients treated with a palliative intent (n=49). For the patients in the youngest category (<65 years), these admissions were required for 43% (n=15) of the curatively treated and for 42% (n=27) of the palliatively treated. In the age category 65-75 years 55% (n=17) of the curatively treated and 50% (n=21) of the palliatively treated had unplanned admissions. For the oldest patients, these percentages were 54% of the curatively and 6% of the palliatively treated patients.

Table 2. Course of treatment

	Total group	<65 years	65-75 years	>75 years	p- value*
Curative					
N of patients had chemotherapy with ***curative*** intent	79 (39%)	35 (35%)	31 (42%)	13 (43%)	0.6
Primary adjustment	33 (42%)	8 (23%)	12 (39%)	13 (100%)	**<0.001**
Primary dose reduction	2 (2.5%)	1 (3%)	1 (3%)	0	0.8
Sequential instead of concurrent chemoradiotherapy	31 (39%)	6 (17%)	12	13 (100%)	**<0.001**
Type of chemotherapy	4 (5%)	1 (3%)	1 (3%)	2 (15%)	
Reduced number of cycles	1 (1.3%)	0	1 (3%)	0	
Prolonged interval between cycles	1 (1.3%)	1 (3%)	0	0	
Secondary adjustment	38 (48%)	14 (40%)	7 (55%)	7 (54%)	0.4
Reduced number of cycles	9 (11%)	3 (9%)	6 (19%)	0	
Reduction of dosage	10 (13%)	4 (11%)	5 (16%)	1 (8%)	
Interruption of treatment cycle	18 (23%)	8 (23%)	5 (16%)	5 (39%)	
Delay between cycles	17 (22%)	8 (23%)	3 (10%)	6 (46%)	
Type of chemotherapy	15 (19%)	5 (14%)	8 (26%)	2 (15%)	
Unforeseen hospital admissions during course of therapy	39 (49%)	15 (43%)	17 (55%)	7 (54%)	
Palliative					
N of patients had chemotherapy with ***palliative*** intent	123 (61%)	64 (65%)	42 (58%)	17 (57%)	0.6
Primary adjustment	34 (28%)	13 (20%)	13 (31%)	8 (47%)	0.08
Primary dose reduction	3 (2%)	0	2 (5%)	1 (6%)	
Type of chemotherapy	30 (24%)	13 (20%)	11 (26%)	6 (36%)	0.4
Reduced number of cycles	1 (1%)	0	0	1 (6%)	
Secondary adjustment	40 (33%)	19 (30%)	19 (45%)	2 (12%)	
Reduced number of cycles	12 (10%)	5 (8%)	7 (17%)	0	
Reduction of dosage	4 (3%)	1 (2%)	3 (7%)	0	
Interruption of treatment cycle	18 (15%)	8 (13%)	9 (21%)	1 (6%)	
Delay between cycles	15 (12%)	7 (11%)	6 (14%)	2 (12%)	
Type of chemotherapy	19 (15%)	11 (17%)	8 (19%)	0	
Unforeseen hospital admissions during course of therapy	49 (40%)	27 (42%)	21 (50%)	1 (6%)	

* Bold values indicate significance at p≤ 0.05. P-values were not calculated if n < 5

Table 3. Reasons for secondary treatment adaptations and unplanned hospital admissions

		n of patients with chemotherapy	*n*	Constitutional symptoms	Vascular toxicity	Neurotoxicity	Hematological toxicity	Gastrointestinal toxicity	Infections	Nephrotoxicity	Other
Reasons for secondary treatment adjustment*		202	78	20	8	4	12	7	20	23	11
Age category (years)	<65	99	33	4	4	2	5	1	12	9	6
	65-75	73	36	12	4	2	5	5	6	13	4
	≥ 75 years	30	9	4	0	0	2	1	2	1	1
Unplanned hospital admissions*		202	88	12	8	1	12	13	35	2	9
Age category (years)	<65	99	42	6	3	1	4	3	19	0	6
	65-75	73	38	6	2	0	6	8	13	1	2
	≥ 75 years	30	8	0	1	0	2	1	2	1	1

* Multiple adjustments and reasons in each category were possible per patient

Reasons for admissions, regardless of age and treatment intent, were mainly infections (n=35), gastrointestinal toxicity (n=13) or hematologic toxicity (n=12).

For 51% (35 out of 69) patients treated with chemoradiotherapy, unplanned hospital admissions were needed during course of therapy.

DISCUSSION

In this audit of multidisciplinary decision making and course of chemotherapeutic treatment in NSCLC and SCLC, we found that decision making and course of therapy vary per age category. 39% of eligible patients older than 75 years of age received chemotherapy compared to 79% of the patients aged 65-75 years and 80% of patients younger than 65 years. When patients did receive chemotherapy, primary and secondary treatment adaptations were effectuated in 58%: in 49% of the youngest patients, adjustments were effectuated and for both the category of 65-75 and for older than 75 years, treatment adjustments needed to be made in 66%. For 44% of the patients, treatment resulted in unforeseen hospital admissions. The guideline recommended treatment regimen was commenced and completed without treatment adaptations in only 29% (n=85) of all patients; for the youngest patients in 40% (n=50), for the middle category in 27% (n=25) and in 13% (n=10) of the elderly. For the patients treated with chemoradiotherapy, 22 patients (32%) started and finished without treatment adaptations.

This study has several limitations. Because of the retrospective study design, it was not possible to comprise all nuances and details of the discussion in the multidisciplinary meeting. To investigate motivations behind treatment recommendations, we had to rely on the information available on the case form or medical file. However, most decisions were clearly and explicitly motivated. Another weakness of our study is the single-centre study design. Despite the fact that dilemmas regarding cancer treatments for frail patients are universal, decisions made in the MDT can depend mainly on opinions and preconceptions of individual team members, because of the difficulty of distinguishing fit and frail patients. This means that a comparable audit in another centre could lead to different results. Despite these limitations, our study highlights the complexity of patient selection and course of treatment in pulmonary cancer care. In addition, performing this analysis with a multicentre design would lead to an increased heterogeneity of data complicating analysis and generalization.

Currently, 95% of the decisions regarding treatment of pulmonary cancer are made in a multidisciplinary team (MDT). The little available research on this topic shows that MDT meetings increase guideline adherence.[17,18] Whether this is a good thing depends on the quality of the guideline and its interpretation.[19] Collective decision making is known to reduce the sense of individual responsibility and to encourage taking riskier decisions.[20] In our study, data regarding the patient's functional and general health status presented to the multidisciplinary team were limited and mostly subjective rather than based on objective measures or validated assessment tools. Considering the high percentage of unforeseen hospital admissions during the course of treatment and the number of treatment adjustments, lung cancer care can be improved by tailoring care to the individual patient and not only to the tumor characteristics. A potential improvement would be the integration of the patient's attitude and preference regarding treatment in this multidisciplinary decision-making process, in addition to the availability of a more detailed description of the general health status and overall frailty at the MDT meetings.[19]

The decision regarding start of chemotherapy should be based on careful weighing of risks and benefits. To make this selection process more objective, guidelines obligate to quantify functional status by using ECOG performance score, and recommend to withhold chemotherapy in patients with ECOG 3 or 4.[11–13] However, distinguishing fit and frail patients will require a thorough knowledge of the patient's health status and it can be questioned if the one dimensional ECOG performance status suffices.[21] Especially in a heterogeneous population such as the elderly, there is a great variety in physiological reserves, comorbidity, functional capacity and presence of geriatric syndromes which cannot all be captured in a single dimension.[22] Previous research has shown that multiple geriatric impairments can be present in patients with a good performance status.[23-28] In addition, for elderly

patients (aged 80 years and older), poorer ECOG score is not as clearly related to worse overall survival as it is in younger patients.[29] Furthermore, previous research has shown that relying on ECOG scores can result in both overtreatment and undertreatment of older patients, with all subsequent consequences for patients and society.[30]

Our results demonstrate that decisions regarding start and course of chemotherapy vary per age. Regarding the selection process, patients aged between 65 and 75 years start chemotherapeutic treatment as often as patients aged younger than 65 (80% in both groups). This is significantly more often than the patients in the category aged 75 years and older (39%). However, when comparing the course of chemotherapy, patients aged 65 – 75 years need comparable primary and secondary treatment adaptations as the elderly aged 75 + (66% in both) compared to 49% of the patients younger than 65 years. This is an important finding, because it raises questions about the identification of vulnerable patients in the category between 65 and 75 years. In recent years, due to prolonged life expectancy and improved health care the age at which patients are classified as 'old' has changed. However, it can be questioned if this change is also correct for lung cancer patients, where comorbidities are highly prevalent, even in younger age categories.

In malignancies with a poor overall prognosis, treatment objectives tend to shift from survival per se to maintaining quality of life and optimising number of days spent in acceptable health. In our analysis, 47% (n=80) of the patients younger than 75 years had unplanned hospital admissions during treatment and in 40% (n=69), secondary treatment adaptations needed to be made due to toxicity. In a treatment setting that is primarily palliative, it is important to make patients aware of the effect the treatment might have on their quality of life, as this might affect their treatment preferences.[31–33] A remarkable finding was the 6% hospital admissions of elderly patients treated with a palliative intent in comparison to higher rates for the younger categories. Though this concerned only limited numbers of patients, a possible explanation might be the anticipation of toxicity in this age group resulting in primary and secondary treatment adjustments.

To be able to adequately inform our patients about these aspects of lung cancer treatment, incorporation of patient-related outcome measures (PROMs) into trials is needed. However, at the moment these PROMs are included only in a minority of lung cancer trials, for example, only 20% of currently ongoing trials incorporate quality of life as outcome measure.[34] In addition, an evaluation of the reporting of quality of life in phase III clinical trials, concerning chemotherapy for patients suffering from a solid malignancy with a poor prognosis, showed that 57% of trials did not include quality of life as a study objective.[35] Of the trials that did, these results were left out of 50% of full text publications or only presented as a single sentence statement.[35] These outcome measures should be included

in and reported for future trials to increase our knowledge of the optimal treatment of lung cancer patients.

In conclusion, this audit demonstrated that multidisciplinary decision-making regarding chemotherapy in patients with pulmonary malignancies is still a challenge. After selecting patients eligible for chemotherapy, treatment adaptations were often effectuated and unplanned hospital admissions were common during course of treatment. The decision-making process and course of treatment for lung cancer varied per age category. Especially the patients between 65-75 years of age were at risk of overestimation at start of treatment and might be more frail than initially thought. Given the poor prognosis of lung cancer in general and the limited research that includes the elderly patients, more data are urgently needed. We need to be able to inform our patients about these aspects of disease and the limitations of treatment.

Abbreviations

ECOG PS	Eastern Cooperative Oncology Group Performance Score
MDT	Multidisciplinary cancer team
NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
TKI	Tyrosine kinase inhibitor
SBRT	Stereotactic body radiotherapy

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APPENDIX

Table 1. Summary of Dutch guidelines for treatment of pulmonary malignancies according to tumor stage.

	Summary of Dutch guidelines for treatment of pulmonary malignancies according to tumor stage	
NSCLC		
	Stage Ia	Surgical resection
	Stage Ib	Surgical resection and adjuvant chemotherapy to be considered*
	Stage II	Surgical resection with adjuvant chemotherapy
	Unforseen pN2 or pN3	Surgical resection with adjuvant radiotherapy
	Tumor cells in resection	Adjuvant radiotherapy
	Stage III	Concurrent chemoradiation therapy
	Stage IV	Palliative chemotherapy**
SCLC		
	Limited disease	Chemoradiation therapy
	Extensive disease	Palliative chemotherapy
	In case of response to chemotherapy	Profylactic cranial irradiation
NSCLC and SCLC	ECOG PS 3 or 4	Best supportive care

(N)SCLC: (non) small cell lung cancer
ECOG PS: Eastern Cooperative Oncology Group Performance Score
* Guideline is ambivalent according treatment with adjuvant chemotherapy in stage IB
** Targeted therapy with tyrosine kinase inhibitor if mutation in EGFR or ALK is found

Chapter 4

Lung cancer in the oldest old: a nation–wide study in the Netherlands

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ABSTRACT

Introduction

An important step in improving research and care for the oldest patients with lung cancer is analyzing current data regarding diagnostic work-up, treatment choices and survival.

Methods

We analyzed data on lung cancer from the Netherlands Cancer Registry (NCR –IKNL) regarding diagnostic work-up, treatment and survival in different age categories; the oldest old (≥85 years of age) versus those aged 71-84 (elderly) and those aged ≤70 years (younger patients).

Results

47,951 patients were included in the 2010-2014 NCR database. 2,196 (5%) patients were aged ≥85years. Histological diagnosis was obtained significantly less often in the oldest old (38%, p<0.001), and less standard treatment regimen was given (8%, p<0.001) compared to elderly and younger patients. 67% of the oldest old received best supportive care only versus 38% of the elderly and 20% of the younger patients (p<0.001). For the oldest old receiving standard treatment, survival rates were similar in comparison with the elderly patients. In the oldest old, no survival differences were found when comparing standard or adjusted regimens for stage I and IV NSCLC; for stage III, oldest old receiving standard treatment had longer survival. No oldest old patients with stage II received standard treatment.

Conclusion

Clinicians make limited use of diagnostics and invasive treatment in the oldest old; however selected oldest old patients experienced similar survival rates as the elderly when receiving some form of anticancer therapy (standard or adjusted). More research is needed to further develop individualized treatment algorithms.

INTRODUCTION

In the Netherlands, over 12,000 patients are diagnosed with lung cancer annually.[1] Lung cancer is predominantly a disease of the elderly, as half of the patients are over 70 years of age at time of diagnosis and 30% are older than 75 years.[1] This proportion is expected to rise even further in the coming decades due to ageing of Western societies and increasing quality of medical care.[1,2]

It is a challenge to select the optimal treatment for elderly patients.[3–5] They represent a heterogeneous population due to the individual process of aging, resulting in a great variety in comorbidity, physiological reserves, geriatric syndromes and functionality.[6] In addition, due to stringent restrictions per organ system, the (especially frail) elderly are often excluded from participation in clinical trials.[7] The assumption that trial results are also valid in a population other than the studied population may not be correct.[8] Therefore, decision-making in frail or elderly patients often depends on opinions of individual team members of the multidisciplinary team.[9] This could both lead to overtreatment and undertreatment of individual patients.[10] Specific guidelines regarding treatment of lung cancer in frail and elderly patients are scarce.[11]

An important step in improvement of clinical care in the oldest patients with lung cancer is analyzing current clinical practice and outcomes in this population. For this purpose, we analyzed patient data on lung cancer from a nationwide registry in the Netherlands, regarding diagnostic work-up, treatment choices and survival in different age categories: the oldest old (≥85 years of age), the elderly (71-84 years) and younger patients (18-70 years).

METHODS

Design and patients

To analyze lung cancer care in the oldest old, we retrieved data from patients with non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) or SCLC aged 18 years and older from the Netherlands Cancer Registry (NCR) between 2010 and 2014. The NCR is a nationwide cancer registry that contains information on tumor characteristics and initial treatment of all newly diagnosed malignancies in the Netherlands. Data come from a national pathology database supplemented by data from medical records, collected by trained registry personnel. Survival data are available through linkage of the Cancer Registry data with municipal population registries.[1] Follow-up was completed until February 1, 2016.

Data analysis

The NCR provided information per patient on: age, sex, histological diagnosis (non-small cell lung cancer [NSCLC], small cell lung cancer [SCLC] or no histological diagnosis), clinical tumor staging according to Tumor Node Metastasis classification (cTNM)[12,13], acquired initial treatment (surgery, [stereotactic body] radiotherapy, chemoradiotherapy, chemotherapy, targeted therapy or best supportive care), follow-up (in days) and vital status (alive or not).

In this audit, we compared treatment as recorded at the NCR with guideline recommended treatment. An overview of Dutch guidelines for treatment of lung cancer can be found in the Appendix.[12,13] In summary: surgical resection is advised for stage Ia and Ib NSCLC. Adjuvant chemotherapy is not recommended for stage Ia, but is advised to consider for stage Ib. For stage II surgical resection with adjuvant chemotherapy is advised. Concurrent chemoradiotherapy, or sequential chemoradiotherapy depending on the size and location of the tumor, is advised for stage III NSCLC, as well as for limited disease SCLC. For selected patients with stage III surgical resection in combination with (neo)-adjuvant chemo- or radiotherapy is stated to be considered as standard treatment. Chemotherapy alone is recommended for all patients with stage IV NSCLC and for extended disease SCLC. For patients with NSCLC and an ECOG PS of 3 or 4 best supportive care only is recommended, for SCLC guideline recommend best supportive care only in case of an ECOG PS of 4. In the present guidelines, age and frailty are not considered to be determinants for choice or adjustment of therapy.[12,13]

Diagnostic work-up was classified as according to guidelines if the disease stage was known and if a histological diagnosis was available. We classified therapy as 'standard treatment' when in line with guideline recommended treatment. Treatment was classified as 'adjusted treatment' when patients received some form of oncologic therapy, but adapted from the guideline recommendation. Treatment was classified as 'best supportive care only' (BSC) when patients received best supportive care only or no treatment at all. Patients were excluded from further analyses when it was impossible to categorize treatment due to lack of information. Unfortunately, no information about ECOG PS was available.

Statistical analysis

To assess outcomes regarding diagnostic work-up, treatment choices and survival of lung cancer care in the oldest old (85 years and older), a comparison was made between these patients, those aged between 71 and 84 years ('elderly') and those aged between 18 and 70 years ('younger'). Overall survival analyses are described as proportion of patients alive after one, two and three years. When groups consisted of less than 10 patients, no further survival analyses were performed.

All analyses were performed in SPSS Statistics version 23.0. For comparisons between groups, the chi-square test was used for nominal and ordinal variables, and the ANOVA test was used for continuous variables. Normally distributed data are presented as mean with standard deviation and non-normally distributed numbers are presented as median with interquartile range (IQR). A p-value smaller than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 47,951 patients with lung cancer were included in the 2010-2014 NCR database (Table 1). The oldest old (≥85 years) consisted of 2,196 (5%) patients, 18,686 (39%) were aged between 71-84 years and 27,069 (57%) were younger than 70 years of age. The median age of included patients was 69 years (interquartile range: 61-76 years) and 60% were male.

Table 1. Baseline characteristics of patients with lung cancer according to age category

		≤70 years		71-84 years		≥85 years		p-value
	Number of patients (%)	27,069	(57%)	18,686	(39%)	2,196	(5%)	
Sex	Male, n (%)	14,716	(54%)	12,569	(67%)	1,461	(67%)	<0.001
Age	Median (IQR)	62	(57-66)	76	(73-80)	87	(86-88)	
Diagnosis, n (%)	NSCLC	21,567	(80%)	13,556	(73%)	1,197	(55%)	<0.001
	SCLC	4,250	(16%)	2,605	(14%)	168	(8%)	
	No histological diagnosis	1,252	(5%)	2,525	(14%)	831	(38%)	
Disease stage, n (%)	I	3660	(14%)	2782	(15%)	205	(9%)	<0.001
	II	1975	(7%)	1451	(8%)	149	(7%)	
	III	6,719	(25%)	4,251	(23%)	404	(18%)	
	IV	13,927	(51%)	8,614	(46%)	957	(44%)	
	Unknown	788	(3%)	1,588	(9%)	481	(22%)	
Treatment for NSCLC and SCLC*, n (%)	Standard treatment	17,041	(66%)	6,283	(39%)	105	(8%)	<0.001
	Adjusted treatment	3,617	(14%)	3,710	(23%)	348	(25%)	<0.001
	Best supportive care only	5,141	(20%)	6,155	(38%)	912	(67%)	<0.001

*Patients with no histological diagnosis were excluded from analyses
IQR: interquartile ranges, (N)SCLC: (non)small cell lung cancer

Diagnosis

Figure 1 shows differences in diagnostic work-up for lung cancer among the oldest old (≥85), elderly (71-84) and younger patients (≤70). For the oldest old, no histological diagno-

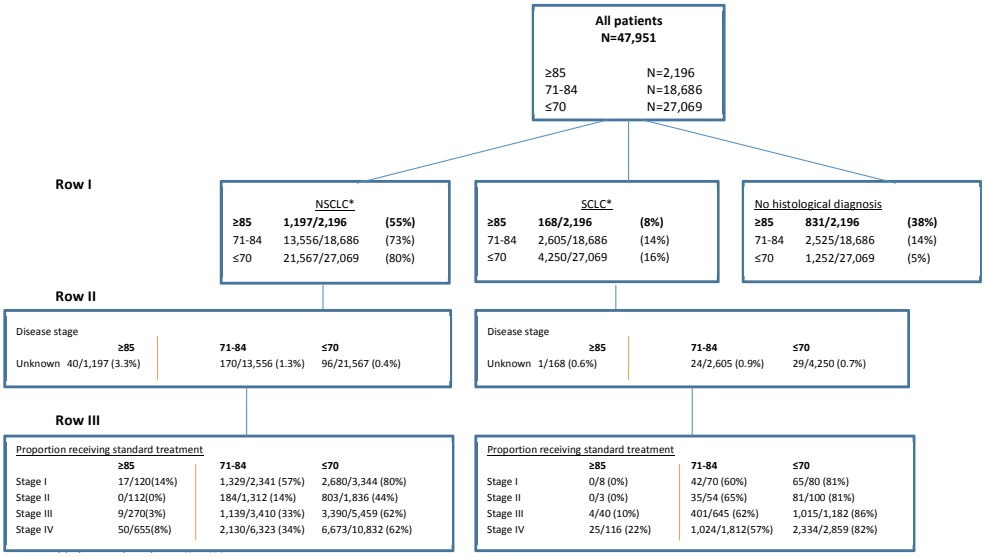


Figure 1. Flowchart diagnostic work-up and treatment choice. Percentages in Row I represent the proportion of patients within each age group with that particular diagnosis. In Row II, percentages represent the proportion of patients with particular diagnosis per age group with unknown stage of disease. Percentages in Row III represent the proportion of patients within each age group that received standard treatment as recommended for that particular diagnosis and disease stage.
*(N)SCLC: (non) small cell lung cancer

sis was obtained in 38% of patients, versus 14% in the elderly and 5% in the younger group (p<0.001). Of the 2,196 oldest old, 1,197 (55%) patients were diagnosed with NSCLC and 168 (8%) with SCLC.

Tumor staging was also significantly more often incomplete in the oldest old (Figure1): the NSCLC disease stage was unknown in 3.3% of the patients aged 85+ versus 1.3% of the elderly and 0.4% of the younger patients (p<0.001) For patients with SCLC, numbers of oldest old patients were too small for analyses.

Standard treatment according to guidelines

Patients without a histological diagnosis (4,608 out of 47,951 patients, 9.6%) were excluded from analyses regarding treatment guideline adherence. Of these patients, 68% received best supportive care only.

In those with a histological diagnosis (NSCLC or SCLC), standard treatment was given significantly more often to the elderly and younger patients than to the oldest old (Fig. 1 and Table 1): only 8% received standard treatment compared to 39% of the elderly and 66% of the younger patients (p<0.001). In addition, regardless of tumor type or disease stage, 67% of the oldest old received best supportive care only versus 38% of the elderly, and 20% of

the younger patients (p<0.001). The remaining patients received an adjusted treatment regimen: 25% of the oldest old, 23% of the elderly and 14% of the younger patients.

Targeted therapy for stage IV NSCLC was given to 45 oldest old patients, which is 7% of this category with stage IV, to 379 elderly and to 733 younger patients.

Overall survival

Survival analyses were performed separately for each histological subgroup (NSCLC, SCLC, no histological diagnosis). For patients without a histological diagnosis, survival after one year was 23% in the oldest old, 35% in the elderly and 45% in the younger patients (p<0.001). Survival after two years for patients without a histological diagnosis was 13% in the oldest old, 22% in the elderly and 34% in the younger patients (p<0.001).

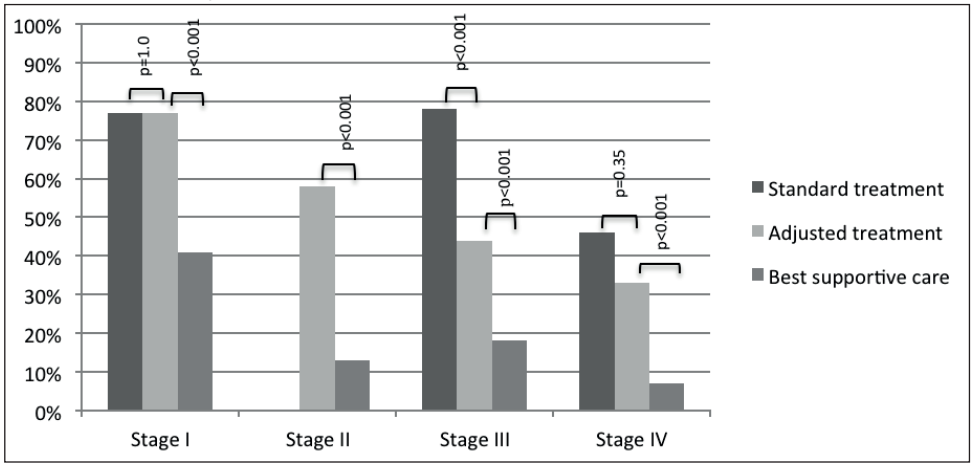
One and two year survival analyses of the oldest old with NSCLC according to treatment strategy and tumor stage are visualized in Figure 2a and 2b, respectively. One year survival in the oldest old with stage I NSCLC receiving standard treatment was 76% (13/17) compared to 95% (2,509/2,655) in younger patients with stage I NSCLC (p=0.02), while no significant difference could be observed comparing the oldest old with the elderly (89%, 1,175/1,321; p=0.2). No analyses could be performed for stage II due to limited numbers of patients receiving standard treatment. For stage III in the oldest old, 7 out of 9 patients (78%) receiving standard treatment were alive after one year, 4 out of 9 (44%) were alive after two years. For stage IV NSCLC, no significant differences in survival among the different age categories for patients receiving standard treatment were observed either: for the oldest old, one year survival with standard treatment was 46% (23 out of 50), compared to 36% (770 out of 2,131) for the elderly and 36% (2,372 out of 6,680) for the younger patients (p=0.35).

As visualized in Figure 2a and b, one and two year survival did not differ significantly for stage I NSCLC between the oldest old receiving standard treatment and oldest old receiving adjusted treatment – i.e. radiotherapy instead of surgical resection (both 77% and 57-65%, respectively). For the oldest old with stage I, after three years 47% of patients (8 out of 17) were alive compared to 42% of patients who received adjusted treatment (32 out of 76).

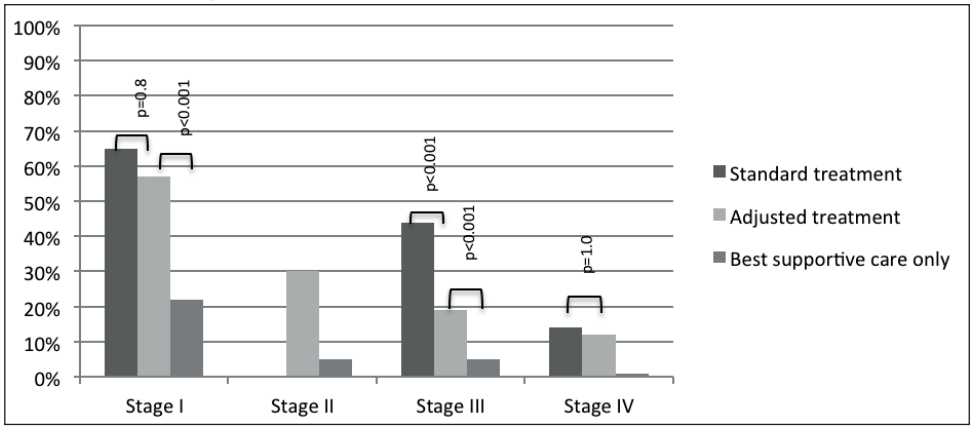
For stage IV, no significant differences were observed between patients receiving standard treatment versus adjusted treatment – i.e. radiotherapy or surgical resection instead of palliative chemotherapy (two year survival 14% and 12%, respectively; p=1.0). No significant differences could be found after three years either (4% and 2%, p=0.6). Due to limited

Figure 2.

A. NSCLC One year survival of the oldest old (85+)



B. NSCLC Two year survival of the oldest old (85+)



numbers of patients receiving standard treatment these analyses could not be performed for stage II and III.

For all disease stages, best supportive care only resulted in a significantly poorer survival (Figure 2A), with similar survival rates compared to other age groups (data not shown).

For the SCLC population, numbers of patients were too small for meaningful subgroup analyses per disease stage, one year survival was 9% (15 out of 168) in the oldest old, 21% (545 out of 2,605) in the elderly and 40% (1,703 out of 4,249) for younger patients (p<0.001).

DISCUSSION

In this study, using the 2010-2014 Netherlands Cancer Registry (NCR) database, a total of 2,196 patients of 85 years and older were identified, which makes this study one of the first describing clinical practice in such a large cohort of oldest old patients with lung cancer. It was found that in this population, physicians generally limited diagnostic work-up and use of invasive treatment. More often no histological diagnosis was obtained and, regardless of disease stage, the majority received best supportive care only (67%) or an adjusted treatment regimen (25%). However, for the selected minority of oldest old who did receive standard treatment, survival rates were similar in comparison with elderly patients. Of note, no differences were observed in one and two year survival between the oldest old with NSCLC who received standard treatment in comparison to an adjusted regimen (stage I and IV); however, survival was significantly worse in those receiving best supportive care only.

Due to the large nation-wide coverage of the NCR, over 95% of the patients diagnosed with lung cancer within the 2010 and 2014 timeframe from the Netherlands are included in this database. Our results regarding diagnostic work-up and treatment are largely in line with previous research, focusing on clinical practice in the older lung cancer patients.[14–16] Comparing treatment choices in older patients showed international differences. A Canadian study, in which 29,515 patients with lung cancer younger than 70 years were compared with 32,131 patients older than 70 years, concluded that microscopic information of the disease lacked more frequently in the elderly and referral to an oncologist occurred significantly less often.[17] Studies performed in Sweden and Japan among octogenarians (patients aged 80 years and older) with lung cancer found that 46% received no treatment or best supportive care only[18–20]. This proportion was lower in a retrospective American study among 111 octogenarians with stage I-IV lung cancer, where only 11% received best supportive care.[21] A possible explanation for the higher proportion of administered best supportive care only (74%) among the oldest old, could be the age limit of 85 years instead of 80 used in the other studies. In addition, cultural aspects regarding medical care late in life could also be an important factor for this inequality.[22,23]

Analyzing current clinical practice can aid in identifying aspects of lung cancer care and research that are amenable for improvement. We found that in the minority of the oldest old patients who receive some form of anticancer therapy (be it standard treatment or an adjusted regimen), survival rates were comparable to those in patients aged 71-84 years demonstrating that selected oldest old are able to benefit from oncologic therapy. This subsequently leads to the important question of how to identify these individuals within the heterogeneous oldest old population, with its extensive variety in comorbidities, physi-

ological reserves and frailty.[24,25] Treatment guidelines and currently available research give little support as to the criteria on which this selection should ideally be based.

Unfortunately, the NCR database does not contain data regarding patient specific factors such as comorbidity, functional reserves, quality of life, presence of geriatric syndromes or ECOG PS. These factors are key-issues in the decision-making process regarding diagnosis and treatment as well as for outcome.[6,14,15,25–28] Due to lack of this information, it was not possible to identify which patient characteristics are associated with receiving standard treatment or having longer survival. We have to keep in mind that this is a selected population. In addition, no information was available about quality of life, toxicity, treatment completion or the patients' perspective regarding satisfaction with treatment. As a result of these limitations, we are unable to translate our findings into individual treatment algorithms or stratification models. Another limitation of this study is that when comparing treatment regimens (standard vs. adjusted), we are comparing selected patient populations, particularly in the oldest old, where a significant proportion had no histological diagnosis or inadequate staging. While this is a reflection of actual clinical practice, and the data are real life data, it is important to keep this selection in mind when interpreting these results. In addition, survival rates are total rates and not cancer specific. However, because lung cancer generally has a poor prognosis we do think that subsequent overall survival rates are significantly influenced by this disease.

Despite these limitations, data do suggest two important areas of future research. First of all, research should focus on identifying those patient-related factors that differentiate between those who are able to benefit from treatment from those for whom best supportive care is the best option. For this purpose, the International Society of Geriatric Oncology has suggested the use of a geriatric assessment, [26] which is a systematic procedure for detecting previously undiagnosed medical conditions and geriatric syndromes, such as care dependence, mobility issues, cognitive impairments or malnutrition.[5,26] Prior research in lung cancer demonstrated that using geriatric assessment for selecting treatment intensity resulted in less aggressive treatment and less toxicity without affecting survival.[29]

Another area for improvement would be the incorporation of patient reported outcome measures (PROMs) in clinical research.[30,31] Especially for the oldest old, PROMS such as maintaining independence, cognitive function and quality of life are highly relevant when trying to balance risks and benefits.[32,33] Multiple previous studies have demonstrated that older patients with cancer are generally less willing to accept toxicity for additional survival time, especially when therapy negatively influences their quality of life or functional status.[14,15,30,31,34] At the moment PROMs are incorporated only in a minority of clinical trials,[33] despite the fact that, nearly two decades ago, the Federal Drug Administration (FDA) and

European Organization for Research and Treatment of Cancer (EORTC) guidelines made inclusion of quality of life mandatory in all new clinical trial proposals in diseases with a poor prognosis.[35–37] Improving lung cancer care needs to be accomplished by multidimensional changing; incorporation of these suggested interventions can lead to great progress in current clinical practice and will be helpful for advising patients prior to the treatment start.

In conclusion, lung cancer is primarily a disease of older patients, although only a minority is older than 85 years; this is one of the first studies describing a cohort of over 2,000 oldest old with lung cancer. Clinicians make limited use of diagnostics and invasive treatment in this patient population. However, selected patients experienced survival rates similar to the elderly when receiving some form of anticancer therapy (standard or adjusted). More research is needed to be able to identify key-issues for the development of individualized treatment algorithms to help improve the complex decision making process for patients with lung cancer.

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Appendix. Summary of Dutch lung cancer guideline recommended treatment

	Summary of Dutch guidelines for standard treatment of pulmonary malignancies according to tumor stage	
NSCLC		
	Stage Ia	Surgical resection
	Stage Ib	Surgical resection *
	Stage II	Surgical resection with adjuvant chemotherapy
	Unforeseen pN2 or pN3	Surgical resection with adjuvant radiotherapy
	Tumor cells in resection	Adjuvant radiotherapy
	Stage III	Concurrent chemoradiation therapy, for selected patients surgical reseection with adjuvant therapy is stated to be considered
	Stage IV	Palliative chemotherapy**
SCLC		
	Limited disease	Chemoradiation therapy
	Extensive disease	Palliative chemotherapy
	In case of response to chemotherapy	Prophylactic cranial irradiation
NSCLC	WHO PS 3 or 4	Best supportive care
SCLC	WHO PS 4	Best supportive care

(N)SCLC: (non) small cell lung cancer
WHO PS: World Health Organization Performance Score
* Guideline is ambivalent according treatment with adjuvant chemotherapy in stage IB
** Targeted therapy with tyrosine kinase inhibitor if mutation in EGFR or ALK is found

PART II

VALUE OF A GERIATRIC ASSESSMENT

Chapter 5

The relevance of a geriatric assessment for elderly patients with lung cancer – A systematic review

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ABSTRACT

Background

Lung cancer is predominantly a disease of the elderly: half of all newly diagnosed patients are over 70 years old. In the Netherlands over 12,000 new cases are diagnosed annually. We set out to assemble all available evidence on the relevance of a geriatric assessment for lung cancer patients.

Methods

A systematic Medline and Embase research was performed for studies in which a geriatric assessment was used to detect health issues or which addressed the association between baseline geriatric assessment (composed of at least two of the following domains: cognitive function, mood/depression, nutritional status, activities of daily living, instrumental activities of daily living, polypharmacy, objectively measured physical capacity, social support and frailty) and outcome.

Results

23 publications from 18 studies were included. The median age of patients was 76 years (range 73-81). Despite generally good ECOG performance status, the prevalence of geriatric impairments was high with medians ranging from 29% of cognitive impairments to 70% of IADL impairments. Objective physical capacity and nutritional status, as items of the geriatric assessment had a consistent association with mortality. The information revealed by a geriatric assessment lead to changes in oncologic treatment choices and non-oncologic interventions.

Conclusion

This review demonstrates that a geriatric assessment can detect multiple health issues that are not reflected in the ECOG performance status. Impairments in geriatric domains have predictive value for mortality and appear to be associated with completion of treatment. It seems useful to develop and validate an individualised treatment algorithm that includes these geriatric domains.

INTRODUCTION

In the Netherlands, over 12,000 new cases of lung cancer are diagnosed annually.[1] Lung cancer is predominantly a disease of the elderly: half of all newly diagnosed patients are over 70 years old.[1] Due to nonspecific symptoms, diagnosis is often made in advanced disease stages. Lung cancer usually shows an aggressive course of disease and mortality rates are high. In fact, lung cancer is a leading cause of cancer mortality worldwide.[1] Survival rates are even worse in the elderly, with one and five year survival of 33 and 10% for all patients diagnosed with lung cancer aged 75 years and older.[1]

Given these data, selecting the optimal treatment can be a challenge. Benefit from lung cancer treatment varies, particularly in the heterogeneous group of the elderly.[2–4] Complications are common and more likely to occur in patients with decreased physiological reserves.[2–4] Currently used measures for quantifying a lung cancer patient's health status and reserves, such as performance status, do not appear to differentiate sufficiently within the elderly population.[5] Geriatric impairments, such as care dependence, depressive symptoms, malnutrition or decreased mobility can be present even in patients with good performance status. These factors are easy to miss if one is not aware of that pitfall.[6–8]

For this reason, a 2005 International Society of Geriatric Oncology task force recommended that a geriatric assessment (GA) should be implemented for older cancer patients.[5] This is a systematic procedure used to objectively appraise the health status of older people, focusing on somatic, functional and psychosocial domains, and aimed at constructing a multidisciplinary treatment plan.[5] In 2005 it was not possible for the task force to formulate a recommendation with a specific approach, due to lack of cancer-specific evidence. Now, ten years later, this recommendation is yet to be implemented in general practice. Despite numerous publications on this subject, many questions still remain to be clarified.

Therefore, we set out to assemble all available evidence on the relevance of geriatric assessment in treatment decisions, prediction of outcomes and prevalence of geriatric conditions in older lung cancer patients.

METHODS

Search strategy and article selection

We set out to identify cohort studies of patients with lung cancer in which a geriatric assessment was used to detect geriatric conditions or which addressed the association between baseline geriatric assessment and outcome. For this purpose, a geriatric assessment was

defined as an assessment using validated tools, composed of at least two of the following domains: cognitive function, mood/depression, nutritional status, activities of daily living (ADL), instrumental activities of daily living (IADL), polypharmacy, objectively measured physical capacity (for instance hand grip strength, gait speed or balance tests), social support and frailty. As prior medical history, comorbidity and performance status are a routine part of the oncologic work up, these were not considered as part of the geriatric assessment for this particular systematic review. For outcomes, the following items were defined: prevalence of geriatric conditions, survival, response to treatment, toxicity, treatment completion, impact on treatment or decision making, functional or cognitive status during or after treatment, and quality of life.

On January 1st 2016, we performed a search in both Medline and Embase using synonyms of geriatric assessment or frailty combined with synonyms of lung cancer. The full search can be found in Appendix 1. We did not apply limits in age, language or publication date in the search.

One investigator (MH) assessed titles and abstracts of all studies retrieved by the search and determined which were eligible for further investigation. Studies that assessed less than two geriatric domains and studies that used only non-validated assessment tools or non-validated subscales of validated assessment tools were excluded, as were studies that included other conditions in addition to lung cancer.

All potentially relevant articles were subsequently screened as full text by two authors (KS and MH). In case only an abstract was available, we attempted to find a final report of the study when we searched Embase and Medline and used the names of first, second and/or final authors as well as key words from the title. Also, in case of insufficient data in the original manuscript, the authors were contacted for additional information, for example on the tools used in the geriatric assessment. Finally, citations of included publications were cross-referenced to retrieve any additional relevant studies.

Data extraction

Two investigators (KS and MH) independently extracted data about the study design and results of each eligible study. Items that were extracted included the type of study, study setting, study population (number of patients, median age, malignancy subtype, stage, treatment), content of geriatric assessment and assessment tools used, outcome measures examined, prevalence of geriatric conditions, and the reported results on the association between the geriatric assessment and the outcome measures.

Quality assessment

The methodological quality of each of the studies was independently assessed by two reviewers (MH, KS), using the Newcastle-Ottowa Scale adapted to this subject (Appendix 2a).[9] In case the reviewers could not reach consensus, a third reviewer (LvE) was asked to give her opinion.

Data synthesis and analysis

As a result of heterogeneity in study designs, diversity of patient populations and the wide variety in content of the geriatric assessment, a formal meta-analysis was not possible. Therefore, we summarized the study results to describe our main outcomes of interest.

RESULTS

Study characteristics

The literature search identified 1479 citations (490 from Medline and 989 from Embase), of which 296 were duplicates. Details on the search and reasons for exclusion can be found in Figure 1. After exclusion of 1161 studies, 21 eligible publications were identified. Cross-referencing yielded two additional studies.[10,11] These studies were not found with our initial search because there was no synonym for geriatric assessment or frailty in their title or abstract. Ultimately, 23 publications from 18 studies were included in this review.

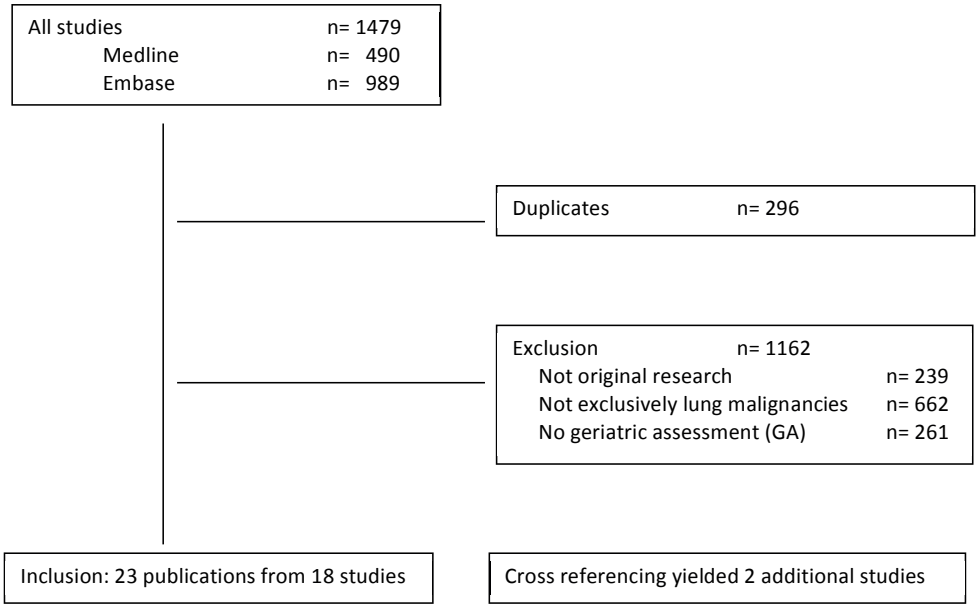

Figure 1. Search results and study selection

Table 1. Characteristics of studies on the association between the geriatric assessment and outcome measures

Publication			Patients			Treatment
Author	Year of publication	Full text (F) or abstract (A)	Patient population	Number of patients	Me(di)an age in years*	Treatment
Agemi[12,32]	2015	A	NSCLC and SCLC, receiving chemotherapy, ≥70 years	101	79 (?)	Chemotherapy or radiotherapy or combination
Aliamus[13]	2011	F	Lung cancer, ≥70 years	49	78.6 (70-91)	Various
Biesma[14,15]	2011	F	NSCLC stage III-IV ≥70 years, PS 0-2	181	74 (70-87)	Chemotherapy
Borget [16–18,20]	2013	A	NSCLC, stage IIIB/IV	195	77 (?)	Chemotherapy
Cheng[29]	2011	A	Lung cancer, ≥70 years	120	75.6 (?)	Various
Corre[19]	2016	F	NSCLC Stage IV, ≥70 years, PS 0-2,	493	77 (70-91)	Chemotherapy
Cudennec[21]	2009	F	Lung cancer, ≥75 years	57	80.8 (±5.7)	Various
Dal Molin[22]	2013	A	Lung cancer, ≥70 years	73	75 (?)	Various
Dujon[23]	2006	F	Lung cancer	41	75.7 (±6.6)	Unknown
Gajra[24]	2012	A	Stage IV NSCLC	100	73 (65-89)	Chemotherapy
Girones[25]	2012	F	Lung cancer	83	77 (±5.1)	Various
Karampeazis[26]	2011	A	NSCLC, ≥65 years	131	74 (65-92)	Chemotherapy
Katayama[27]	2012	A	NSCLC, ≥70 years, PS 0-1	331	Unknown	Chemotherapy
Maestu[28]	2007	F	NSCLC stage IIIB-IV, ≥70 years	59	74 (70-83)	Chemotherapy
Maione[10]	2005	F	NSCLC stage IIIB-IV, ≥70 years	556	74 (70-84)	Chemotherapy
Quoix[11]	2011	F	NSCLC stage IIIB-IV, ≥70 years, PS 0-2	451	77 (70-89)	Chemotherapy
Vanacker[30]	2013	A	Lung cancer ≥70 years	73	76 (?)	Various
Xue[31]	2015	F	NSCLC stage IIIB/IV, ≥65 years	24	73 (65-83)	Chemotherapy

* Reported as median (range) or mean (standard deviation - SD) in accordance with available data± Assessment was not performed with a validated assessment tool or the method of assessment was not reported ** Based on self-assessment of multiple geriatric domains.

Content of geriatric assessment										Outcome measures						
Activities of daily living	Instrumental activities of daily living	Cognition	Mood	Objective physical capacity	Nutritional state	Social support	Medication issues	Frailty	Prevalence geriatric conditions	Survival	Response	Treatment toxicity	Treatment completion	Impact on treatment or decision-making	Functional or cognitive status during or after treatment
		±						+		+		+	+		
+		+	+	+	+									+	
+	+	+	+	+				+		+		+	+		+
+	+	+		+	+	+			+	+					
								+**		+			+	+	
+	+		+	±										+	
-	+	+	+	+	±	±	+		+						
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+	+	+	+	±	+			+						+	
±	±				±				+						

An overview of the included studies can be found in Table 1. All studies focused exclusively on patients with lung cancer. Overall, the median number of included patients was 101 (range 24- 556), with a median age of 76 years (range 73 – 81).[10–32] Seven studies included only patients with a performance score (PS) of 0-2 (World Health Organisation WHO) .[10–12,15,20,27–2910,11,14,19,26–28] The number of domains addressed in the geriatric assessment ranged from two to eight, with 67% examining at least four domains.[10,12–19,21–29] These included activities of daily living (ADL) in fifteen[10,11,14,16,19,21–28,30,31] (83%) and instrumental activities of daily living (IADL) in fourteen studies (78%).[10,14,16,19,21–28,30,31] Cognition[11–14,21,23–27,30–32] and mood[13,14,19,21,22,24–27,30] were investigated in 67% and 55% of the included studies, objectively measured physical capacity was included in eight studies (44%).[13,14,16,19,21,23,24,30] Nutritional state was used in eleven studies (61%),[11,13,16,21–25,28,30,31] social support in three studies (17%),[16,24,25] medication issues in one (6%)[21] and a frailty screening instrument in four studies (22%).[12,14,29,30,32]

Eight studies (44%) [10,11,16,21,23,25,28,31] addressed the prevalence of geriatric conditions and ten (55%) studied the association between geriatric conditions at baseline and survival.[10–12,14,16,22,25,27–29] The association of the geriatric condition on toxicity was investigated in five studies (28%),[12,14,26–28] while four studies (22%) described the influence of geriatric conditions on treatment completion[12,14,24,29] and two (11%) on treatment response.[27,28] Three studies (17%) addressed the impact of geriatric assessment on treatment or decision-making.[13,19,29] Only two studies (11%) investigated quality of life during treatment for lung cancer, however they study did not investigate the correlation between (any item) of a CGA and this outcome measurement.[11,15] Unfortunately none of the included studies focused on overall functioning or quality of life.

Quality assessment

All studies were assessed on quality by two authors and used the Newcastle-Ottowa Scale adapted to this subject. The results per study are described in Appendix 2b. The overall quality, based on the adapted Newcastle- Ottowa Scale, of the studies was good, as depicted in Figure 2.[10–14,16,19,21–32] However, in six of the included studies, the content of the geriatric assessment was not well described.[12,16,19,24,29,31] Because no full text publication was available in eight studies, some data applicable to evaluating the adequacy of follow-up were lacking.[12,16,22,24,26,27,29,30,32] One study did not clarify their method of patient selection and could therefore not be assessed regarding its risk of selection bias.[21]

Prevalence of geriatric conditions

To determine the diagnostic yield of supplementing the standard pulmonary work-up with a geriatric assessment, the prevalence of geriatric impairments was compared to the prevalence of poor performance status. In seven studies that described the prevalence of

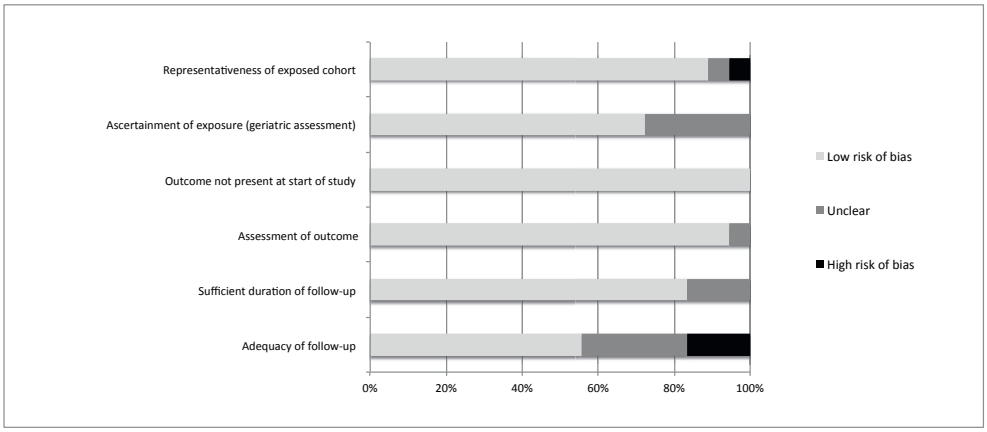

Figure 2. Overview of quality and risk of bias of the included studies

geriatric impairments, the proportion of patients with a poor WHO performance status (2 or higher) varied between 19% and 63% with a median of 39%.[10,16,21,23,25,28,31] By comparison, ADL impairment was described in five studies with a prevalence of 49%, 48%, 20%, 17% and 15% respectively.[10,11,23,25,31] IADL impairment was described in six studies with a median prevalence of 70% (range 29- 95%),[10,16,21,23,25,31] cognitive impairment in 29% (range 8-51%)[11,17,22,24,26] and mood 31% (10-47%).[16,21,25] Cudennec et al. studied elderly patients (75 years or older) with lung cancer and found impaired physical capacity in 68%.[21] Assessment of the nutritionals status found malnutrition or weight loss in half of the patients.[11,11,16,21,23,25,29,31]

Mortality

The predictive value of a geriatric assessment for mortality was reported in ten studies (Table 2).[10-12,14,22,25,27–29,32] Objective physical capacity and nutritional status, as items of the geriatric assessment, demonstrated a consistent association with mortality, both in univariate and multivariable analyses.[11,14,16,22,25,28] Basic and instrumental activities of daily living were associated with mortality, although most of these performed only univariate analyses.[10,11,14–16,22,25,27,28] Results for mood and cognition were varying, while social support and medication issues did not show an association with mortality.[11,11,12,14–16,22,25,27,32]

Many studies also included previously identified risk factors associated with death. Of these, performance status was strongly associated with death, while comorbidity provided varied results and age was not associated with mortality.[11,14–16,22,25,27,28]

Toxicity

Five studies assessed the association between geriatric assessment and chemotherapy-related toxicity.[12,14,26–28,32] Overall, few significant associations were found. In one study

Table 2. Association of age, performance status, comorbidity and geriatric conditions with mortality

Study				Results for univariate and multivariable analyses‡												
Author	**Year of publication**	**Number of patients**	**Type of malignancy**	**Age**	**Performance status**	**Comorbidity**	**ADL**	**IADL**	**Cognition**	**Mood**	**Objective physical capacity**	**Nutritional status**	**Social Support**	**Medication issues/ polypharmacy**	**Frailty**	**Summarised geriatric assessment score**
Agemi	2015	101	NSCLC or SCLC						-						+	
Biesma	2010	181	NSCLC receiving chemotherapy		+	-	+	+	-	+	+				+	
Borget	2013	195	NSCLC		+ +	+ +	--	--	--	--	+ +	+ +	- -			
Cheng	2011	120	Lung cancer													+
Dal Molin	2013	73	Lung cancer	-	+	-	+	+				+		-		
Girones	2012	83	Lung cancer	-	+	-	-	+	+	+		+	-			
Katayama	2012	331	NSCLC		+		-	-	+	-						
Maestu	2007	59	NSCLC		++	--	++	++			(++)					
Maione	2005	556	NSCLC				-	+							+	
Quoix	2011	451	NSCLC	-	++	-	++		+			++				
Proportion of studies with a significant association				**0/3**	**7/7**	**1/5**	**4/8**	**5/7**	**3/6**	**2/4**	**3/3**	**4/4**	**0/2**	**0/1**	**3/3**	

† No studies reported on the association between

‡ There was little uniformity across studies in the confounders and variables included in the multivariable analyses

+ /- significant / no association in the analysis.

++/-- significant/ no association after multivariate analysis. Parentheses indicate that a non-validated assessment tool was used to determine the presence of the geriatric domain

dependency in IADL correlated with grade 3-4 neutropenia.[28] Another study found that patients with depressive symptoms according to the geriatric depression scale (GDS) were more likely to experience grade 2 neuropsychiatric toxic effects.[14]

Completion of treatment

Four studies analysed the predictive value of the likelihood of completing all planned courses of chemotherapy in relation to geriatric assessment.[12,14,24,29,32] One study found that patients with better ADL, IADL or physical functioning scores were more likely to finish all chemotherapy cycles, but no association for cognition or mood.[14] One study did not find a significant association between frailty or cognition and completion of treatment.[12,32] A third study found an association between the need for assistance in IADL and early discontinuation of chemotherapy but no association for cognition, mood, nutritional status, physical capacity or social support.[24] In the fourth study, a summarized score for the geriatric assessment was not associated with treatment completion.[29]

Other outcome measures

The correlation between response on treatment and different items of the GA was investigated by two studies, but neither found a significant relation.[27,28]

Two studies described the impact of a geriatric assessment on treatment choices.[29,30] The first study reported that after geriatric assessment 75% of the patients were referred for non-oncologic interventions aimed at optimizing the patient's health status or quality of life. For these interventions they were referred to: dieticians, social workers, palliative care team, geriatricians or occupational therapists.[29] In the second study, the geriatric assessment identified previously unknown problems in 26% of the patients; this led to change of treatment for 4% of the patients and resulted in non-oncologic interventions in 10%.[30] None of these studies reported on outcomes of non-oncologic interventions.[29,30]

One study focussed on the impact of a GA on the treatment decisions made at a multidisciplinary oncology team meeting for elderly patients with lung cancer aged 70 and above. Based on the results of the geriatric assessment, 45% of treatment decisions were modified.[13]

Finally, one study compared standard treatment allocation based on performance status and age to a geriatric assessment-based treatment allocation.[19] Overall, the patients in the GA-based arm received less aggressive treatment and experienced significantly less all grade toxicity.[19] Furthermore, there was no significant difference between these two groups in terms of time to treatment failure, defined as progression or death.[19]

DISCUSSION

The relevance of geriatric assessment in lung cancer has not been extensively researched. This review demonstrates that geriatric impairments are highly prevalent, even in patients with good performance status, and are of prognostic significance.[10,11,16,21,23,25,28] In particular, impairments in objectively measured physical capacity and nutritional status are predictive of mortality.[10,11,14,16,22,25,28] Furthermore, the information revealed by a geriatric assessment can lead to changes in oncologic treatment choices as well as non-oncologic interventions.[29,30] Finally, a GA-stratified treatment allocation did not improve efficacy but showed comparable survival and in addition this selection process appears to be able to decrease overall toxicity and aggressiveness of treatment.[19] Experiencing less all grade toxicity and receiving less aggressive treatment without losing efficacy can be seen as an important argument to advocate treatment allocation of the basis of a geriatric assessment.

This review has several limitations. First, the included studies were heterogeneous in their patient populations, study design, treatment regimens, content of the geriatric assessment and reported outcomes; as a result, we were unable to perform a formal meta-analysis and draw more definitive conclusions. Second, we focused only on studies addressing multiple geriatric domains. Therefore, we may have missed studies focussing on a single geriatric domain or studies that used multiple domains, but did not label this as being a geriatric assessment. In addition, for eight included studies there was no full text publication available.

Despite these limitations, this is the first review providing an overview of currently available evidence regarding the prognostic value of geriatric conditions in the population of the elderly patient treated for lung cancer. Although there are publications about the relevance of a geriatric assessment in other type of malignancies, it is important that this is also investigated in lung cancer because every type of malignancy has its own characteristics. For instance, lung cancer's rapid course of disease and poor overall prognosis will affect the additional impact that presence of geriatric impairments may have on outcome. The intense treatment regimens will require greater reserves than less toxic treatments and this may influence the relevance of certain impairments over others. Finally, given its association with lifestyle, lung cancer patients generally have a high prevalence of comorbidities that may be different compared to other kinds of cancer.

At the moment, treatment decisions are based on clinical assessment in combination with age and performance status. However, as ageing is an individual process, chronological age does not necessarily reflect one's biological age.[33] This is also demonstrated in this review, where age is not found to be predictive for survival of elderly lung cancer patients.[22,25] On

Table 3. Association between geriatric condition and toxicity of treatment, treatment completion or response.

Study				Results for univariate and multivariable analyses‡							
Author	Year of publication	Number of patients	Type of malignancy	ADL	IADL	Cognition	Mood	Objective physical capacity	Nutritional status	Social Support	Frailty
Toxicity											
Agemi	2015	101	NSCLC or SCLC			-					trend
Biesma	2010	181	NSCLC receiving chemotherapy	-	-	-	trend	trend			-
Karampeazis	2011	131	NSCLC	-	-	-	-				
Katayama	2012	331	NSCLC	- -	- -	- -	- -				
Maestu	2007	59	NSCLC	-	+						
Treatment completion											
Agemi	2015	101	NSCLC or SCLC			-					-
Biesma	2010	181	NSCLC receiving chemotherapy	+	+	-	-	-			-
Cheng	2011	120	Lung cancer								-
Gajra	2012	100	Stage IV NSCLC >65 years		(++)	- -	- -	--	--	--	
Response											
Katayama	2012	331	NSCLC	- -	- -	- -	- -				
Maestu	2007	59	NSCLC	- -	- -						

† No studies reported on the association between

‡ There was little uniformity across studies in the confounders and variables included in the multivariable analyses

+ /- significant / no significant association in the analysis.

++/-- significant/ no significant association after multivariate analysis. Parentheses indicate that a non-validated assessment tool was used to determine the presence of the geriatric domain.

the other hand, while performance status has a significant association with survival (Table 2), it has been suggested that within the elderly population, performance status alone is insufficient in discriminating between fit and vulnerable patients.[5]

Based on our review, in addition to performance status, physical capacity and nutritional status are the most important factors associated with overall survival.[14,16,22,25,28] Both factors are closely related to the phenotype of frailty, defined by Fried et al.[34] Objectively measured physical capacity has been demonstrated to be relevant to prognosis and treatment outcome across a range of studies in various malignancies.[35–38] Physical capacity could be considered as a summary indicator of a patient's vitality because it is an integrated summary of multiple organ systems. Reduced physical capacity could reflect damage in one of the organ systems and be the result of reduced physical activity and deconditioning that has a direct effect on health and survival.[39] In addition to being a component of the frailty concept, nutritional status appears to reflect the severity of disease.[33]

Interestingly, this review also demonstrates that multiple geriatric impairments can be present in patients with a good performance status. Even if not particularly relevant for prognostication, these impairments could significantly affect treatment choices by informing the clinician on the overall health status of an older patient across multiple domains.[40,41] For instance, while cognition is not associated with survival or toxicity, cognitive impairments and a lack of sufficient social support could significantly limit the feasibility of treatment with new oral targeted therapies.

Furthermore, impairments detected by a geriatric assessment can form the starting point for interventions aimed at optimising the patient's well-being and quality of life.[30] Rao et al showed that adding geriatric care to standard in-patient care for hospitalized elderly cancer patients resulted in a significant decrease in the amount of emotional limitations, social dysfunction and bodily pain experienced at three months, and the effect on pain was still significant after one year.[42] However, this was the only study published on this subject.

Despite the importance of the CGA in the evaluation of elderly patients, a CGA can be a time and manpower consuming procedure. For some patients a CGA might not be necessary and to reduce the time and manpower consuming aspects of treatment, it would be helpful if screening tools could be used to identify individuals for whom the CGA would be the most beneficial. Several screening tools have been investigated, however uncertainty remains about the discriminative power in selecting patients for further assessment. A review about the use of screening tools in geriatric oncology showed that Geriatric 8 (G8) and Triage Risk Screening Tool (TRST) demonstrated the highest sensitivity for frail patients, but had a poor specificity and negative predictive value. The currently available screening

tools gave insufficient discriminative power in selecting patients for further assessment.[43] More research on the use of screening tools is necessary.

Despite promising new treatment strategies prognosis and survival rates are still poor, especially in advanced lung cancer. Therefore a thorough assessment, especially in the elderly population, is of utmost importance to carefully weigh the advantages and risks of treatment for this form of cancer. To further increase our knowledge on the ways in which geriatric assessment could be applied in the lung cancer practice, more research is urgently needed. An important concern is that current cancer trials generally have age limitations in addition to strict exclusion criteria per organ system. As a consequence, the average elderly cancer patient will generally not be allowed to participate.[8,44] In addition, most trials focus almost entirely on cancer-related outcome measures such as survival, response rate and safety,[8,44] while the outcome measures that are also of major importance for elderly patients, such as quality of life, functional decline and cognitive functioning, are hardly being studied. Improving lung cancer care for the elderly will only be possible if trials conduct a more patient-centred approach instead of being merely disease-centred.

In conclusion, this review demonstrates that a geriatric assessment in lung cancer patients can detect multiple health issues, even in patients with good performance status. Outcomes of this assessment can be used in prognostication, treatment decisions, optimizing health status and quality of life. More research with clinical trials that incorporate a geriatric assessment is urgently needed to confirm and extend these findings. This should consist of determinants of frailty by the assessment of nutritional status and objective physical capacity next to evaluation of the effect of non-oncologic interventions.

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Appendix 1. Search syntax for Medline and Embase

Medline:

("frailty"[tiab] OR "Geriatric Assessment"[Mesh] OR geriatric assessment*[tiab] OR geriatric*[tiab]) OR (frail*[tiab]) AND ((cancer OR carcinoma) AND (lung[tiab] OR pulmonary[tiab] OR bronch*[tiab]) OR lung cancer[MeSH Terms] OR NSCLC OR SCLC OR non small cell lung cancer[MeSH Terms])

Embase:

(frailty:ab,ti OR (geriatric AND assessment:ab,ti) OR geriatric:ab,ti OR 'geriatric assessment'/exp OR frail*:ab,ti) AND (((cancer OR carcinoma) AND (lung:ab,ti OR pulmonary:ab,ti OR bronch*:ab,ti)) OR nsclc:ab,ti OR nsclc OR 'lung cancer'/exp OR slcl:ab,ti)

Appendix 2a. Quality assessment, based on the Newcastle–Ottowa Scale[5]

Selection	1. Representativeness of the exposed cohort	+	truly representative of the average elderly patient with lung cancer
		+	somewhat representative of the average older patient with lung cancer
		+	in studies using a geriatric assessment to select patients for inclusion: if no
		-	other issues resulting in potential inclusion bias were encountered selected group of users, mixed cohort of younger and older patients or
		?	a mixed cohort with lung cancer no description of the derivation of the cohort
Outcome	2. Ascertainment of exposure (geriatric assessment)	+	clearly described and using validated assessment tools
		-	using non-validated assessment tools for > 40% of investigated geriatric conditions
		?	no description
	3. Demonstration that outcome of interest was not present at start of study	+	yes
		-	no
		na	not applicable in studies addressing the prevalence of geriatric conditions or using the geriatric assessment for patients selection or treatment assignment
	1. Assessment of outcome (treatment alterations)	+	clear description of method of assessment
		?	unclear description of method of assessment
		?	no description
		na	not applicable in studies addressing the prevalence of geriatric conditions or using the geriatric assessment for patients selection or treatment assignment
	2. Was follow-up long enough for outcome to occur?	+	yes
		-	no
		na	not applicable in studies addressing the prevalence of geriatric conditions or using the geriatric assessment for patients selection or treatment assignment
	3. Adequacy of follow-up of cohorts	+	complete follow-up: all subjects accounted for
		+	subjects to follow-up unlikely to introduce bias: loss to follow-up less than 10%
		-	follow-up rate less than 90%
		?	no statement
		na	not applicable in studies addressing the prevalence of geriatric conditions or using the geriatric assessment for patients selection or treatment assignment

Appendix 2b. Quality assessment of included studies

Publication		Quality assessment: Selection			Quality assessment: Outcome		
Author	Publication year	Representativeness of exposed cohort	Ascertainment of exposure (geriatric assessment)	Outcome not present at start of study	Assessment of outcome	Sufficient duration of follow-up	Adequacy of follow-up
Agemi	2015	+	?	+	?	?	-
Aliamus	2011	+	+	+	+	+	+
Biesma	2010	+	+	+	+	+	-
Borget	2013	+	?	+	+	+	+
Cheng	2011	+	?	+	+	+	?
Corre	2016	+	?	+	+	?	?
Cudennec	2010	?	+	na	na	na	na
Dal Molin	2013	+	+	+	+	+	+
Dujon	2006	+	+	na	na	na	na
Gajra	2012	+	?	+	+	+	?
Girones	2012	+	+	+	+	+	+
Karampeazis	2011	+	+	+	+	+	?
Katayama	2012	-	+	+	+	?	?
Maestu	2007	+	+	+	+	+	+
Maione	2005	+	+	+	+	+	+
Quoix	2011	+	+	+	+	+	+
Vanacker	2013	+	+	+	+	+	-
Xue	2015	+	+	na	na	na	na

na: not applicable

Chapter 6

The effect of a geriatric assessment on treatment decisions for patients with lung cancer

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ABSTRACT

Background

Decision-making for older patients with lung cancer can be complex and challenging. A geriatric assessment (GA) may be helpful and is increasingly being used since 2005 when SIOG advised to incorporate this in standard work-up for the elderly with cancer. Our aim was to evaluate the value of a geriatric assessment in decision-making for patients with lung cancer.

Methods

Between January 2014 and April 2016 data on patients with lung cancer from two teaching hospitals in the Netherlands were entered in a prospective database. Outcome of geriatric assessment, non-oncologic interventions and suggested adaptations of oncologic treatment proposals were evaluated.

Results

83 patients (median age 79 years) were analyzed with a geriatric assessment, 59% were treated with a curative intent. Half of the patients were classified as ECOG PS 0 or 1. The majority of the patients (78%) suffered from geriatric impairments and 43% (n=35) of the patients suffered from three or more geriatric impairments (out of 8 analyzed domains). Nutritional status was most frequently impaired (52%). Previously undiagnosed impairments were identified in 58% of the patients and non-oncologic interventions were advised for 43%. For 33% of patients, adaptations of the oncologic treatment were proposed. Patients with higher number of geriatric impairments more often were advised a reduced or less intensive treatment ($p<0.001$).

Conclusion

A geriatric assessment uncovers previously unknown health impairments and provides important guidance for tailored treatment decisions in patients with lung cancer. More research on GA-stratified treatment decisions is needed.

INTRODUCTION

In the Netherlands, over 12,000 new cases of lung cancer are diagnosed every year.[1] Lung cancer is predominantly a disease of the elderly: half of all newly diagnosed patients are over 70 years old.[1] Lung cancer usually shows an aggressive course of disease and mortality rates are high. It is the leading course of cancer mortality worldwide.[2] Survival rates are even worse in elderly patients (>75), with one- and five year survival rates of 33% and 10%, respectively.[1]

Older patients represent a heterogeneous population due to differences in physiological reserves, comorbidity, functional capacity, and the presence of geriatric impairments.[3] As a result of these differences, benefit from lung cancer treatment varies.[4–6] In addition, complications of therapy are common and are more likely to occur in patients with decreased physiological reserves.[7]

Currently used measures for quantifying health status and reserves in patients with lung cancer, such as performance status or pulmonary function testing, do not appear to differentiate sufficiently within the elderly population.[3] Even in patients with good performance status, geriatric impairments can be present because impairments in cognitive functioning, depressive symptoms and malnutrition are easy to miss.[7–9]

Therefore, in 2005 a task force of the International Society of Geriatric Oncology (SIOG) recommended that a geriatric assessment should be used to detect these unaddressed problems, improve functional status, and possibly survival.[3] This systematic procedure can be used to objectively appraise the health status, focusing on somatic, functional and psychosocial domains.[3,10]

Although a myriad of publications have propagated its use, the actual implementation of geriatric assessments in clinical practice has thus far been limited.[3,11–13] In the Diakonessenhuis and Haga hospital, two large teaching hospitals in the Netherlands, geriatric assessments for patients with lung cancer have been implemented in the standard care for patients over 70 years of age since 2014. In this analysis, we have assessed the yield of this assessment and its effect on treatment decisions.

METHODS

Between January 2014 and April 2016, all consecutive patients with lung cancer aged 70 years and older referred for a geriatric assessment at the Haga hospital in The Hague

were included in a prospective database for quality control purposes. No patients were excluded for this initial database. Selection of patients for a geriatric assessment was done if the patient was considered to be potentially frail based on the Geriatric8 (G8)[14] and Identification of Seniors at Risk (ISAR-HP)[15] screening tools or by the referring physician/ thoracic oncologist based on clinical judgment. The maximum score of the G8 is 17 points, with a score of 14 or less being defined as impaired.[14] The maximum score of the ISAR-HP is 4, and a score of 2 or more is defined as impaired.[15] Oncologic treatment options were formulated by the thoracic oncologist, based on a complete oncologic work-up, prior to referral for the geriatric assessment.

The geriatric consultations assessments were performed by three geriatricians specialized in geriatric oncology. Patients were seen together with their family or caregivers if possible. The geriatric assessment was partly performed by a specialized nurse and included an evaluation across eight geriatric domains: comorbid diseases, medication use, diagnosis and, if applicable, treatment of cognitive impairments, mood disorders, nutritional status, functional impairments (mobility, basic and (instrumental) activities of daily living ((I)ADL)) and social network or supportive care status. Specific geriatric tools per geriatric domain were used on indication: Charlson Comorbidity Index[16] to score comorbidity (a score of ≥2 was defined as impaired), medication use was defined as an impaired geriatric domain if patients used three or more drugs or in case of inappropriate prescription, mini nutritional assessment (maximum 27 points, impaired≤23)[17], mini mental state examination (maximum 30 points, impaired ≤23.5)[18], geriatric depression scale (maximum 15 points, possible depression ≥6)[19], timed-up-and-go-test (impaired ≥12 seconds) [20,21], hand grip strength (age related cutoff values, no adjustment from the original research)[22], Katz index (6 items scored, impaired ≥2)[23] and Lawton (maximum 8 points, 0 indicating fully dependency, impaired ≥2)[24] were used for scoring ADL en IADL respectively. The geriatrician interpreted the assessment outcomes, reflected on them with patient and caregivers, proposed interventions for optimization impairments that were found and discussed the patients' preferences and expectations.

Based on this assessment and consultation, the geriatrician evaluated the patient's capacity to tolerate treatment within the multidisciplinary lung cancer team and if needed, proposed an adaptation of oncologic treatment, tailored to the patient's capacities, health limitations and preferences. If applicable, advance care planning was initiated.

The treatment adaptations were labeled as 'no change' if the geriatrician agreed with the treatment plan of the oncologist. If the geriatrician advised for a different regimen than suggested by the oncologist, these changes were categorized as 'more intensive' or 'less intensive'.

Data collection

The regional ethics committee and institutional review board of both hospitals approved this study. The primary endpoint was the effect of the geriatric assessment on (adaptation of) oncologic and non-oncologic treatment decisions. Secondary endpoints were the prevalence of geriatric impairments, the incidence of newly diagnosed geriatric syndromes or medical conditions, and the additional yield of the assessment in terms of advance care planning, managing the patients' expectations and clarifying the patients' priorities and preferences.

The following data were collected from the medical record: patient demographics (age, sex, Eastern Cooperative Oncology Group Performance Status (PS)[25], comorbidity measured by the Charlson Comorbidity Index (CCI)[16]), tumor data (tumor type, staging), initial oncologic treatment plan and alternative options prior to geriatric assessment, final oncologic treatment following geriatric assessment. In addition, we collected information on outcome of the geriatric assessment: prevalence of geriatric impairments, incidence of newly diagnosed medical conditions, non-oncologic interventions, suggestions regarding oncologic treatment choices, discussions on advance care planning, clarification of patients' priorities and expectations regarding oncologic treatment.

Statistical analysis

For the analysis of our primary outcome, treatment decisions following geriatric assessment were classified as: no change, intensified oncologic treatment, less intensive treatment or supportive care only. Numbers are presented as medians with interquartile ranges (IQR) if not normally distributed. Statistical analyses were performed using SPSS 24.0 (SPSS, Inc., Chicago, IL, USA). A p-value <0.05 was considered statistically significant. The chi-square test was used to compare categorical variables between groups.

RESULTS

Patient characteristics

Eighty-three patients were included in the present analysis. Patient demographics can be found in Table 1. The median age of the patients was 79 years (IQR: 74 – 82 years) and 65% were male (n=54). The Charlson Comorbidity Index (CCI) was 0 or 1 for 23 patients (28%), the remaining 73% (n=60) had a CCI of 2 or higher. The majority of the patients (n=49, 59%) were diagnosed with non-small cell lung cancer (NSCLC), nine patients (11%) were diagnosed with small cell lung cancer (SCLC), two patients (2%) were diagnosed with mesothelioma and for 23 patients (28%) no histological diagnosis was obtained. Most patients had options for treatment with a curative intent (n=49, 59%) for the remaining

Table 1. Patient characteristics

		Total (n=83)
Male (%)		54 (65)
Median age in years (IQR25-75*)		79 (74 -82)
Diagnosis (%)		
	NSCLC**	49 (59)
	SCLC**	9 (11)
	Mesothelioma	2 (2)
	No histological diagnosis	23 (28)
Disease stage (%)	I	22 (27)
	II	10 (12)
	III	15 (18)
	IV	22 (27)
	Unknown	14 (17)
Curative treatment options (%)		49 (59)
Charlson Comorbidity Index (%)	0 or 1	23 (28)
	≥2	60 (72)
ECOG PS*** (%)	0	14 (17)
	1	28 (34)
	2	11 (13)
	3	5 (6)
	Unknown	25 (30)

*IQR25-75: Interquartile ranges 25th and 75th percentile
**ECOG PS: Eastern Cooperative Oncology Group Performance Status
***(N)SCLC: non-small cell lung cancer

patients the treatment intent was only palliative at time of diagnosis and assessment. For 25 patients (30%) the PS was unknown, of the remaining patients were 42 (72%) classified as PS 0 or 1, eleven (19%) patients had a PS of 2 and five (9%) patients had a PS of 3.

Geriatric assessment

The majority of the patients (n=66, 80%) were referred for a geriatric assessment after risk identification by using Geriatric8 (G8≤14) or Identification of Seniors at Risk (ISAR-HP≥2) and the remaining seventeen patients (20%) were referred by the treating physician based on clinical judgment. For all patients the GA was performed prior to initiation of oncologic treatment.

Results of geriatric assessments are depicted in Table 2. The majority of the patients (78%; n=65) suffered from one or more geriatric impairments: in 43% (n=35) ≥3 geriatric impairments were identified. Nutritional status was most frequently impaired (52%; n=43),

Table 2. Outcome of geriatric assessment

	Prevalence of geriatric impairments	Suggestion for non-oncologic interventions
(Risk of) malnutrition	43 (52%)	21 (25%)
Impaired mobility	32 (39%)	12 (15%)
Cognitive impairments	28 (34%)	6 (7%)
Care dependence in IADL*	26 (31%)	8 (10%)
Comorbidity	26 (31%)	4 (5%)
Insufficient social network	20 (24%)	6 (7%)
Care dependence in ADL*	17	6 (7%)
Medication issues	9 (11%)	1 (1%)
Psychological issues**	5 (6%)	3 (7%)

*(I)ADL: (instrumental) activities of daily living
Impaired score on geriatric depression scale

followed by mobility (39%; n=32) and cognitive function (34%; n=28). For 58% of the patients (n=48) the geriatric assessment revealed previously unknown geriatric impairments. Non-oncologic interventions aimed to optimize health status before and during cancer treatment were proposed for 36 patients (43%). Domains that were most frequently amenable for intervention were nutritional status (25%; n=21), followed by impaired mobility based on an impaired Timed-up and Go or low handgrip strength (14%; n=12) and care dependency in IADL (10%; n=8). A total of 5 patients had an impaired GDS and 3 were subsequently referred for further counseling. Other suggested non-oncologic interventions are described in detail in the Appendix 1.[26]

In addition, for 69% (n=57) of patients, the geriatric assessment aided in clarifying patients preferences and expectations or initiating advance care planning.

Treatment decisions

Based on the geriatric assessment, suggestions for change of the oncologic treatment were proposed in 27 out of 83 patients (33%); the thoracic oncologists adopted all suggestions. These results are shown in Figure 1 and Appendix 2. A more intensive treatment regimen was suggested for one patient (1%): the geriatrician advised for stereotactic radiotherapy (SBRT) instead of the suggested best supportive care (BSC) of the oncologist. A less intensive treatment regimen was suggested for twenty-six patients (31%). A less intensive treatment suggestion included SBRT instead of surgical resection (n=6) or BSC instead of palliative chemotherapy (n=11), chemoradiotherapy (n=5) or surgical resection (n=4).

We did not find a significant difference in change of treatment based on the geriatric assessment between patients treated with a palliative or curative intent.

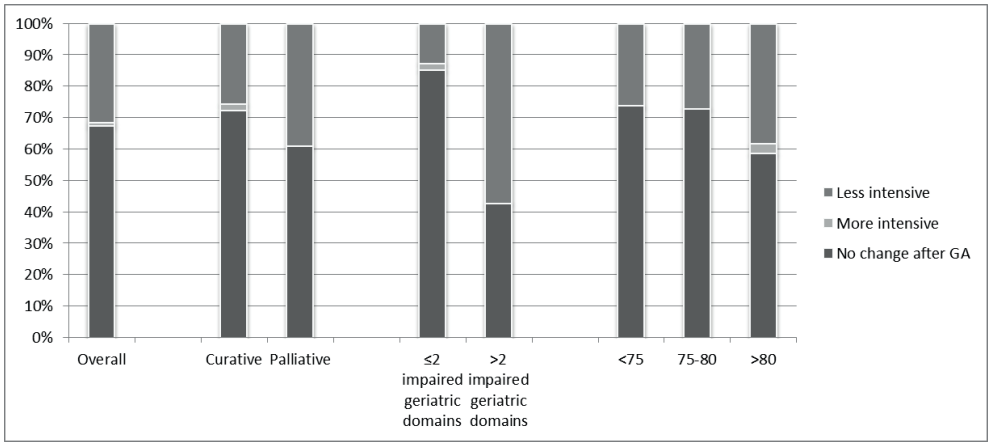

Figure 1. Oncologic treatment suggestions based on geriatric assessment
Less intensive: the geriatrician advised for a less intensive treatment than suggested by the oncologist
More intensive: the geriatrician advised for a more intensive treatment than suggested by the oncologist
No change after GA: there was no difference in oncologic treatment after the geriatric assessment

For patients with a higher number of geriatric impairments more often an adapted treatment plan was advised: a less intensive treatment was suggested for 13% of patients (n=6) with ≤2 geriatric impairments versus 57% (n=20) for the patients with >2 geriatric impairments ($p<0.001$).

No significant difference could be observed by analyzing treatment decisions comparing different age categories (<75, 75-80 and older than 80 years) ($p=0.56$).

DISCUSSION

This study shows results of geriatric assessments and consultations in patients with lung cancer in two teaching hospitals in the Netherlands. The prevalence and number of geriatric impairments was high in the investigated elderly population (78%), especially considering that half of the patients had an ECOG PS of 0 or 1. The geriatric assessment identified previously undiagnosed impairments in 58% of the patients and non-oncologic interventions were advised for 43%. Nutritional status was most frequently impaired, followed by impairments in mobility and cognitive function. For 34% of the patients adaptations in the oncologic treatment were suggested after the geriatric assessment. With increasing numbers of observed geriatric impairments, less aggressive treatment was more often advised. In addition, the geriatric assessment was often used as a moment to start discussions about preferences and expectations of treatment or initiating advance care planning.

This analysis has several limitations. First, in this type of observational cohort study, a direct comparison of survival and oncologic outcomes between groups is hampered by selection bias and confounding by indication. This could subsequently mean that differences in outcome are incorrectly attributed to the treatment decision, rather than to confounding factors such as poor general health, which affects both treatment choice and outcome. We have no data on health status or treatment decisions in older patients who were not referred. Second, we only reported on the alteration in treatment, but limited data were available about follow-up of how patients subsequently fared. Furthermore, as no control group was available, we were unable to ascertain whether the changes made for the treatment plan resulted in overall better outcomes. Despite these limitations, this analysis provides insight in current clinical practice and the variety of elderly patients with lung cancer that are being referred for a geriatric assessment.

Our findings are in line with prior research that emphasized the importance of a geriatric assessment in the care of elderly patients with cancer.[27,10] A study among 49 patients with lung cancer in France also showed a high number (45%) of modifications of treatment decisions after a geriatric assessment.[28] Another study, performed in Belgium reported the presence of one or more geriatric impairments in 71% of patients with lung cancer.[29] In a Dutch study among patients with various cancer types, previously undiagnosed impairments were identified in 49% and non-oncologic interventions were initiated in 56%.[30]

Our study demonstrates that geriatric assessment can be helpful in the complex decision-making process for elderly patients with lung cancer. Decisions in this heterogeneous population can be complex, particularly because evidence regarding treatment of frail patients is scarce as they patients are frequently excluded from participation in clinical trials.[31] As was previously demonstrated, study results are primarily valid within a population that is comparable to the trial population, and do not provide reliable evidence on what the effect would be in other patient groups.[32] As a result, treatment decisions for the elderly will mainly depend on opinions and preconceptions of individual oncologists.

The effect of GA-stratified treatment allocation has not been extensively investigated. A GA-stratified treatment allocation in patients with lung cancer did not improve efficacy but showed comparable survival and appeared to be able to decrease overall toxicity and aggressiveness of treatment.[33] Experiencing less all grade toxicity and receiving less aggressive treatment without losing efficacy can be seen as an important argument to advocate treatment allocation on the basis of a geriatric assessment. More research is urgently needed to further extent these findings.

The incorporation of a routine geriatric assessment in standard oncologic care for all elderly patients with cancer is currently hampered by the time- and resource-consuming nature of these assessments.[12,13] Furthermore, while there is general consensus that they can be beneficial, there is no clear guideline on when, how and by whom they should be performed.[12,13] The presented method of geriatric screening followed by full geriatric consultation and assessment for selected patients may be adequately time efficient. Importantly, it is still a matter of debate whether cancer specialists themselves should take more time to assess patients across multiple (geriatric) domains instead of introducing geriatric consultation by a geriatrician into the care pathway of older patients with cancer. Keeping in mind that the latter requires geriatricians with specific expertise in oncology.

An important yield of the geriatric assessment was clarifying patient's priorities and expectations concerning the proposed treatment options. It appears that this is mostly due to a greater amount of time available for the assessment and not necessarily require expertise specific to the geriatrician.[13] In an age where the amount of time spent on staging and exploring disease characteristics is rapidly increasing, and more and more money is spent on increasingly sophisticated anti-cancer treatments, taking the time to sit down with a patient and explore what they want and whether or not they will be able to benefit from and tolerate cancer treatment should not be a matter of discussion.[34] However, this will require the incorporation of more elaborate training in the specific needs of frail elderly patients in oncologic study curricula.

CONCLUSION

This analysis shows that a geriatric assessment can aid in tailoring treatment decisions, by identifying previously unknown geriatric impairments. Our findings are in line with the SIOG advise that a geriatric assessment should be used in the evaluation of elderly patients with cancer.[11] There is a significant relation between the number of geriatric impairments and the advice for less aggressive treatment. A geriatric assessment is often used as moment to start discussions about preferences and expectations of treatment. Collaboration between geriatricians and oncologists is required to optimize treatment for patients with cancer.[30] More research on GA-stratified treatment decisions in patients with lung cancer is needed.

Abbreviations

BSC	Best Supportive Care
CCI	Charlson Comorbidity Index

G8	Geriatric 8
(I)ADL	(Instrumental) Activities of Daily Living
ISAR-HP	Identification of Seniors at Risk Hospitalized Patients
NSCLC	Non-Small Cell Lung Cancer
PS	Eastern Cooperative Oncology Group Performance Status
SCLC	Small Cell Lung Cancer
SBRT	Stereotactic Body Radiotherapy
SIOG	International Society of Geriatric Oncology

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APPENDIX 1 Examples of suggested non-oncologic interventions

	Examples of suggested non-oncologic interventions[26]
(Risk of) malnutrition	Referral to dietician, supplemental nutrician drinks
Impaired mobility	Home care, referral occupational therapist, physiotherapist
Cognitive impairments	Home care, start medication, update medication list, referral to specialized nurses
Care dependence in (I)ADL	Home care, occupational therapist, physical therapist
Comorbidity	Update medication list, diagnose and treat comorbidities
Insufficient social network	Home care, specialized nurses, consulting general practitioner
Medication issues	Update medication list
Psychological issues	Referral to general practitioner, referral to psychologist

*(I)ADL: (instrumental) activities of daily living

APPENDIX 2 Change in oncologic treatment after geriatric consultation

Advise oncologist	**Advise geriatrician**	**Number of patients**
	More intensive	
Best supportive care	SBRT*	1
	Less intensive	
SBRT*	Surgical resection	6
Palliative chemotherapy	Best supportive care	11
Chemoradiotherapy	Best supportive care	5
Surgical resection	Best supportive care	4

SBRT: Stereotactic body radiotherapy

Chapter 7

Prognostic value of Geriatric 8 (G8) and Identification of Seniors at Risk for Hospitalized Patients (ISAR–HP) screening tools for patients with lung cancer

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ABSTRACT

Background

Due to the time-consuming aspect of a geriatric assessment cancer specialists are seeking for shorter screening tools to distinguish fit and frail patients. We analyzed the predictive value of the G8 (geriatric8) and ISAR-HP (identification of seniors at risk) in elderly patients with lung cancer.

Patients and methods

Between January 2014 and April 2016, patients with lung cancer older than 70 years of age diagnosed at two teaching hospitals in the Netherlands were included in a database. Patients were classified as potentially frail with a G8≤14 or ISAR-HP ≥2.

Results

142 patients (median age of 77 years (IQR: 73 -82)) were included, 76% (n=108) were potentially frail. After correction for possible confounders, potentially frail patients had a significant higher risk for one-year mortality (Hazard ratio (HR) 4.08 (95%CI 1.67 – 9.99; p=0.02). A higher disease stage (HR: 1.72; 95%CI 1.40 – 2.12; p<0.001) was also a significant predictor for mortality, initial treatment (standard or not) and age were not. When using both screening instruments separately, impaired score on G8 and higher disease stage were the remaining variables in regression analyses (HR impaired G8: 3.01; 95% CI: 1.35 – 6.72; p<0.001). Patients with an impaired score on ISAR-HP and G8 had more geriatric impairments compared to patients with only impaired G8.

Conclusion

Screening with G8 is useful for prognostication of elderly patients with lung cancer and might be used in combination with ISAR-HP to increase specificity at the cost of sensitivity. Using ISAR-HP as only screening tool would be insufficient.

INTRODUCTION

Predicting the success rate of lung cancer treatment is difficult, particularly for older patients.[1–4] Differences in physiological reserves, comorbidity, functional capacity, and the presence of geriatric syndromes have a great impact on treatment effects and toxicity and hence cancer outcomes.[1,5] Lung cancer treatment guidelines are less applicable to the general elderly lung cancer population as they are based on clinical trials from which elderly and those with comorbidity have often been excluded.[6,7] Therefore, there is a great need for individual algorithms to help predicting if a certain treatment will be beneficial or not.[8]

In 2005, the International Society of Geriatric Oncology (SIOG) advised to incorporate a geriatric assessment in the clinical work-up for elderly patients with cancer.[9] Geriatric assessments can detect multiple health issues, even in lung cancer patients with good performance status.[10] Outcomes of this assessment can be used for prognostication, treatment decisions, optimizing health status and quality of life.[10] However, these geriatric assessments are often seen as too time-consuming and therefore cancer specialists are seeking for a shorter screening tool that can separate fit older patients with cancer, who are able to receive standard cancer treatment, from vulnerable patients that should subsequently receive a full assessment to guide tailoring of their treatment.[11,12]

Two instruments that have been suggested are the Geriatric 8 (G8, Table 1)[13] and Identification of Seniors At Risk-Hospital Patients (ISAR-HP, Table 2).[14] The G8 screening tool was developed specifically for older cancer patients.[13] It places significant weight on nutritional status (46% of the total score), while also focusing on mobility, neuropsychological problems, medication use, self-rated health status and age. It has shown a good sensitivity for geriatric impairments across multiple domains, meaning that most patients with geriatric impairments were identified using this screening tool.[13,15,16] However, some concerns were raised regarding its specificity, as many patients without geriatric impairments were incorrectly identified as requiring further assessment.[16] The ISAR-HP was initially developed for the emergency department, and later revised for hospitalized patients. It is a four-item questionnaire that has proven beneficial in identifying older patients at risk of functional decline following hospital admission.[14]

The prognostic value of the G8 and ISAR-HP screening tools have not been evaluated specifically in patients with lung cancer. Since pulmonary malignancies generally have a rapid course of disease and a poor overall prognosis, previous study results in other types of cancer may not be applicable to patients with lung cancer.[17]

Table 1. Geriatric–8 (G–8) screening tool

Items	Possible responses (score)
1. Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = Severe decrease in food intake 1 = Moderate decrease in food intake 2 = No decrease in food intake
2. Weight loss during the last 3 months?	0 = Weight loss >3kg 1 = Does not know 2 = Weight loss between 1 and 3kg 3 = No weight loss
3. Mobility?	0 = Bed or chair bound 1 = Able to get out of bed/chair but does not go out 2 = Goes out
4. Neuropsychological problems?	0 = Severe dementia or depression 1 = Mild dementia 2 = No psychological problems
5. Body mass index (BMI)? (weight in kilograms) / (height in square metres)	0 = BMI <19 1 = BMI 19 to <21 2 = BMI 21 to <23 3 = BMI ≥23
6. Takes more than three prescription drugs per day?	0 = Yes 1 = No
7. In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = Not as good 0.5 = Does not know 1.0 = As good 2.0 = Better
8. Age	0 = >85 1 = 80–85 2 = <80
Total score 0–17	Cut-off ≤ 14 : potentially frail

Table 2. Identification of seniors at risk for hospitalized patients (ISAR–HP) screening tool

Items	Possible responses (scores)
1. Before hospital admission, did you need assistance for IADL (e.g., assistance in housekeeping, preparing meals, shopping, etc.) on a regular basis?	Yes = 1, No = 0
2. Do you use a walking device (e.g., a cane, walking frame, crutches, etc.)?	Yes = 2, No = 0
3. Do you need assistance for traveling?	Yes = 1, No = 0
4. Did you pursue education after age 14?	Yes = 0, No = 1
Total score (0-5)	Cut-off ≥ 2: potentially frail

IADL: instrumental activities of daily living

In two large teaching hospitals in the Netherlands, these two screening tools are routinely obtained for older patients with lung cancer. In this analysis, we set out to determine the value of the tools in patient prognostication, selection of patients for a geriatric assessment and prediction of treatment completion.

METHODS

Between January 2014 and April 2016, all patients with lung cancer aged 70 years of age or older, diagnosed at the Haga hospital in The Hague and the Diakonessenhuis Utrecht were included in a database for quality control purposes.

Specialized nurses, pulmonologists (thoracic oncologists) or geriatricians obtained the G8 and ISAR-HP screening tools from these patients prior to start of treatment. The maximum score of the G8 is 17 points, with a score of 14 or less being defined as impaired.[13] The maximum score of the ISAR-HP is 4, and a score of 2 or more is defined as impaired.[14]

If patients had a normal score on both G8 and ISAR-HP, they were classified as 'fit'. Patients were classified as 'potentially frail' if they had an impaired score on G8, ISAR-HP or both, and these patients were subsequently referred for a geriatric assessment.

We set out to analyze the predictive value of the G8 and ISAR-HP in prognostication of one-year survival and the relation between impaired screening and the outcome of a geriatric assessment. One year survival was defined from diagnosis of cancer. Additional analyses were done to assess if G8 and ISAR-HP should both be used or if it is sufficient to use one, and if so, which tool performs best. The treating physicians were aware of the results of screening prior to start of treatment.

To answer these questions, the following data were collected from the medical records: patient demographics (age, sex, vital state, date of death, comorbidity measured by the Charlson Comorbidity Index[18], World Health Organization Performance Status (PS)[19]), oncologic data (tumor type, staging, initial oncologic treatment plan (standard or adjusted), course of treatment (if adjustments needed to be made after treatment had commenced) and, if available, information on the outcome of geriatric assessment (prevalence of geriatric impairments). On the basis of tumor type, stage, size and location treatment intent was considered either curative or with a palliative intent. Initial oncologic treatment was classified as standard if it was in line with Dutch guideline recommended therapy (Appendix)[20,21], and treatment was classified as adapted if these recommendations were not followed.

Median duration of follow-up was 489 days. In addition to follow-up via the medical record, date of death was also retrieved through linkage with the Municipal Personal Records Database.

The regional ethics committee and institutional review board at both hospitals approved this study.

Statistical analysis

Statistical analyses were performed using SPSS 24.0 (SPSS, Inc., Chicago, IL, USA). The chi-square was used for comparisons between groups for categorical variables and the ANOVA was used continuous variables. A p-value <0.05 was considered as statistically significant.

Cox regression analyses were performed to assess the prognostic value of the frailty screening. Sex, diagnosis, disease stage, age (categorized as <75 years, 75-80 years, > 85 years) and intended treatment (standard or adjusted) were considered as potential confounders. For each of these factors, the proportional hazards assumption was tested using a log minus log plot. Next, the outcome of the frailty screening (potentially frail or fit) and all potential confounders were entered into a multivariable Cox regression analysis. To detect the additive value of the two screening instruments, this analysis was repeated using a new variable based on 0, 1 or 2 impaired score on screening tools,

To assess the relative value of G8 and ISAR-HP, this analysis was also performed using both instruments (normal/impaired) as separate variables. A backward conditional stepwise procedure was done, followed by a forward conditional analysis.

RESULTS

Patient characteristics

A total of 142 patients were included, of which 62% (n=88) were male. Baseline characteristics are depicted in Table 3. The median age of patients was 77 years (IQR: 73 -82) and 63% was older than 75 years of age. The performance score was unknown in 41 patients (29%); of the remaining patients 29 (29%) had a PS 0, a PS 1 was scored in 41 (41%) patients, PS 2 in 21 (21%) and a PS 3 in 10 patients (10%). The majority of patients (n= 84; 59%) was diagnosed with non-small cell lung cancer (NSCLC), 24 (17%) with small cell lung cancer (SCLC), 5 (4%) with mesothelioma, and in 29 patients (13%) no histological diagnosis was obtained. Of all included patients, 54% had a malignancy that could be treated with a curative intent at time of diagnosis (on the basis of tumor type, stage, location and size);

Table 3. Baseline characteristics

		Total	Fit*	Potentially frail**	p-value
Number of patients		142	34	108	
Median age		77 (73 - 82)	76 (72 - 81)	77 (73 - 82)	
Percentage male		88 (62%)	25 (74%)	63 (58%)	0.11
Diagnosis	*NSCLC*	84 (59%)	25 (74%)	59 (55%)	0.07
	SCLC	24 (17%)	4 (12%)	20 (19%)	
	Mesothelioma	5 (4%)	2 (6%)	3 (3%)	
	No histological diagnosis	29 (13%)	3 (9%)	26 (24%)	
Treatment intent	*Curative*	72 (51%)	23 (32%)	49 (68%)	**0.03**
	Palliative	70 (49%)	11 (16%)	59 (84%)	
WHO Performance status	*0*	29 (20%)	12 (35%)	17 (16%)	**0.01**
	1	41 (29%)	11 (32%)	30 (28%)	
	2	21 (15%)	1 (3%)	20 (19%)	
	3	10 (7%)	0 (0%)	10 (9%)	
	Unknown	41 (29%)	10 (29%)	31 (29%)	
Standard initial treatment		38 (27%)	16 (47%)	22 (20%)	**0.01**
Unplanned hospital admissions during treatment		41 (35%)	12 (36%)	29 (35%)	0.39
Charlson Comorbidity Index	*≥1*	115 (81%)	26 (77%)	89 (82%)	0.44

*Patients were classified as fit if they a normal score on both G8(≤14) and ISAR-HP(≥2)
**Patients were classified as potentially frail if they had an impaired G8 or ISAR-HP (or both)
Bold values indicate statistical significance p-value <0.05
Percentages between () account for proportion of total population of column.

the remaining 46% could only be treated with a palliative intent. 81% of the patients had a Charlson comorbidity index (CCI) of 1 or higher.

Screening tools and course of treatment

Overall, 24% (n=34) had a normal frailty screening and were classified as fit, while 76% (n=108) had an impaired screening score on G8 (score ≤14), ISAR-HP (score ≥2) or both and were classified as potentially frail.

No significant differences were seen in age, sex or CCI ≥1 between fit and potentially frail patients. Of the patients with lung cancer that could be treated with a curative intent (on the basis of tumor characteristics) 67% was labeled as potentially frail compared to 85%

of the patients that could only be treated with a palliative intent (p=0.01). Of the NSCLC patients, 70% (59 out of 84) were classified as potentially frail, compared to 83% (20 out of 24) in SCLC and 90% (26 out of 29) of patients without a histologically confirmed diagnosis (p=0.07).

67% of patients with a PS 0 or 1 (47 out of 70) were considered potentially frail while only one patient with a poor PS (2 or 3) had a normal score on both screening instruments ('fit') (p=0.01) (Table 3).

Standard oncologic treatment was offered to 27% (n=38) of all included patients; this proportion was 47% (16 out of 34) for fit patients versus 20% (22 out of 108) for potentially frail patients (p=0.01). For the 18 fit patients receiving adjusted treatment regimens, this consisted of stereotactic bodyradiotherapy instead of surgical resection (n=8), adjustments in type or intensity of chemotherapy regimen (n=4), best supportive care only on request of the patient (n=4), sequential instead of concurrent chemoradiotherapy (n=1) or the omission of adjuvant chemotherapy after surgical resection (n=1).

There was no difference in treatment adjustments during course of therapy (after treatment had commenced) between fit and potentially frail patients: 33% versus 28% (p=0.6). For patients who started standard treatment, there was no significant difference in treatment adjustments during therapy (after treatment had commenced) between fit and potentially frail patients either: 43% versus 40% (p=0.8).

One–year mortality in relation to frailty screening

After one year, 46% of the patients (65 out of 142) had died; 21% (7 out of 34) of the fit and 54% (58 out of 108) of the potentially frail patients (p=0.01).

Results of the Cox regression are shown in Table 4. After correction for potential confounders, being scored as potentially frail was significantly associated with worse one-year mortality, with a hazard ratio (HR) of 4.08 (95%CI 1.67 – 9.99; p=0.02) (Figure 1A). In addition, a higher disease stage (HR: 1.72; 95%CI 1.40 – 2.12; p<0.001) was also a significant predictor for mortality.

Of note, age and initial treatment (standard or not) were not associated with one-year mortality (Fig 1C and D).

Prognostic value of screening tools for presence of geriatric impairments

Out of 108 patients with an impaired screening, 69% (n=75) were analyzed with a geriatric assessment. For the remaining patients no geriatric assessment was performed because

Table 4. Multivariable survival analysis

	Hazard Ratio	95% confidence interval (lower-upper)	Significance (p-value)
Potentially frail patients	4.08	1.67 – 9.99	**0.002**
No histological diagnosis	1.99	0.85 – 4.61	0.11
Disease stage	1.72	1.40 – 2.12	**<0.001**
Standard initial treatment	1.22	0.59 – 2.53	0.6
Male	0.64	0.36 – 1.15	0.13
Age category*	0.92	0.59 – 1.41	0.92

Bold values indicate statistical significance p-value <0.05
*<75 versus 75-85 and >85 years of age

they were already in a terminal stage of disease at time of analysis (n=28) or the geriatric assessment was not performed before start of treatment (n=5). The median number of geriatric impairments was two (IQR: 1-4); one or more geriatric impairments were found in 80% (n=59) of all assessed patients and 43% (n=32) had three or more geriatric impairments.

A more detailed analysis of the geriatric assessments is described elsewhere.[22]

G8 versus ISAR–HP

Out of 142 patients, G8 was impaired in 70% (n=100) and ISAR-HP in 41% (n=58). 46 patients had an impaired score on G8 but a normal score on ISAR-HP; two patients had an impaired ISAR-HP but a normal G8 screening and 60 patients had an impaired score on both G8 and ISAR-HP.

The prevalence of geriatric syndromes was significantly higher in the patients with two impaired screening tools compared to patients with only an impaired G8: 22% of patients with only an impaired G8 score but normal ISAR-HP score had three or more geriatric problems versus 74% of patients with an impaired score on both screening tools (p<0.001). The proportion of patients with any impairment did not differ significantly between patients with only an impaired G8 score and patients with an impaired score on both screening tools (78% versus 87% respectively, p=0.48). Of note, 26 out of 35 patients (74%) with a normal ISAR-HP score had one or more geriatric problems and 17% had three or more geriatric problems. The two patients with an normal G8 but impaired ISAR-HP score had two and zero geriatric problems respectively.

An impaired score on both screening tools was not associated with a worse one-year mortality compared to an impaired score on only one screening tool (Figure 1E).

When using both screening instruments separately, an impaired score on G8 and higher disease stage were the only remaining variables in the backward conditional regression analysis (HR for impaired G8: 3.01; 95% CI: 1.35 – 6.72; p<0.001) and the forward conditional

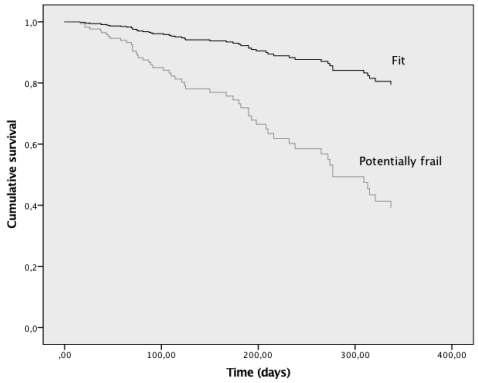

Figure 1A Fit versus potentially frail patients (p=0.02)

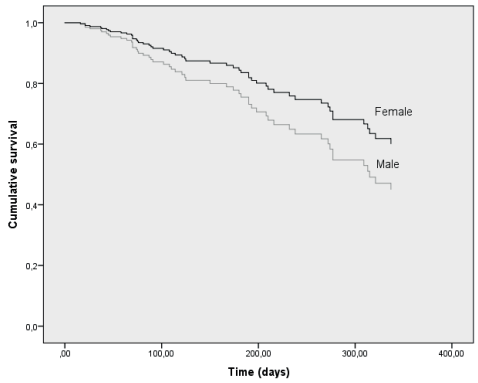

Figure 1B Male versus female (p=0.13)

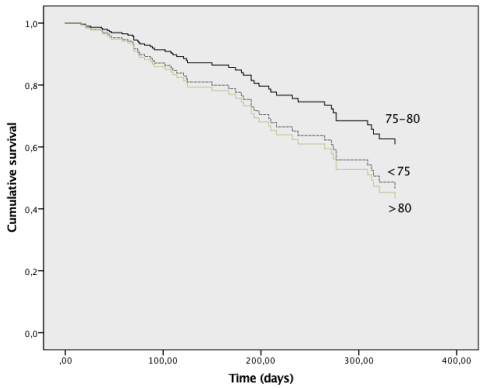

Figure 1C. Comparing age categories (<75, 75–80 and >80) (p=0.92)

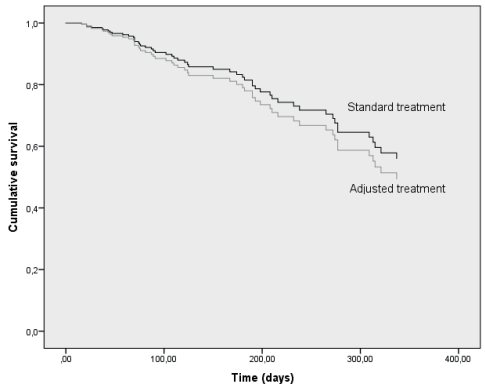

Figure 1D Standard versus adjusted initial treatment (p=0.6)

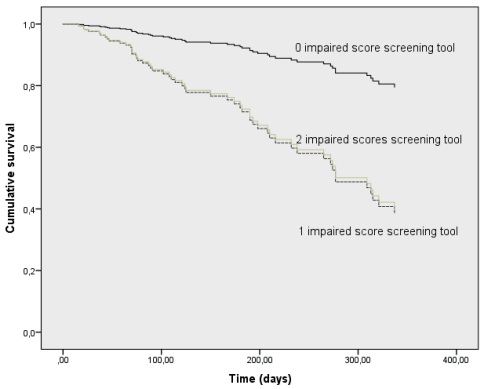

Figure 1E Number of impaired scored screening tools

Figure 1. Multivariable cox regression analyses

analysis confirmed this finding. ISAR-HP was not independently associated with mortality (HR: 1.09; 95%CI: 0.59 – 2.00; p=0.79).

DISCUSSION

Our study demonstrates that G8 and ISAR-HP screening tools can be used in the prognostication of elderly patients with lung cancer. Potentially frail patients, as defined by an impaired score on G8 or ISAR-HP, have a significant higher risk of one year mortality compared to fit patients. When analyzing both screening instruments separately, G8 was independently associated with one year mortality and ISAR-HP was not. Patients with an impaired score on both ISAR-HP and G8 had more geriatric impairments in comparison with patients who had only an impaired score on G8. Using ISAR-HP as only screening tool would be insufficient, but can be used in combination with G8 to increase specificity at the cost of sensitivity.

This study has several limitations. With regards to the proportion of patients that had a geriatric assessment: patients with a normal score on G8 and ISAR-HP did not have a geriatric assessment. Therefore, we were not able to identify the number of impaired geriatric domains for these patients or to calculate diagnostic accuracy of the investigated screening tools for impairments in the extended geriatric assessment. As the geriatric assessment was only performed in patients who were deemed potentially frail after the screening, we could not formally calculate the specificity and sensitivity of these instruments. Thus, while we can see that the sensitivity would decrease if the combination of both instruments was used, as a significant percentage of patients with impairments would no longer be screened as potentially frail, we were unable to give the exact numbers. In addition, only 69% of the potentially frail patients had a geriatric assessment. For some patients, no referral for a geriatric assessment was made because they were already in a terminal stage of disease or because they had already started oncologic treatment. With regards to the duration of follow-up, we were only able to calculate one year survival. However, the median survival for the whole group was within this period.

Despite these limitations, the results of our study can contribute to current lung cancer practice and encourage the integration of a geriatric evaluation in current practice. We performed this study in two large teaching hospitals in the Netherlands, using a two-stepped model where patients were referred for a geriatric assessment in case they were classified as potentially frail. Because we have analyzed both G8 and ISAR-HP, our results can help developing this model depending on the availability of geriatric oncologic expertise in each hospital. If this specific knowledge is easily accessible and available, G8 can be used

as only screening tool to refer patients for a geriatric assessment in case a patient has an impaired score. If geriatric oncologic expertise is more scarce, adding ISAR-HP to screening with G8 would lead to a higher chance of selecting patients with multiple geriatric impairments and thereby increasing specificity at the cost of sensitivity.

Our findings are in line with previous research, where also a significant relation between an impaired G8 and survival was found.[15,23] However, these studies did not specifically investigate lung cancer patients. We think that it is important that the prognostic value of these screening tools is also analysed specifically for lung cancer because every type of malignancy has its own characteristics. Pulmonary malignancies generally have a rapid course of disease and a poor overall prognosis.[17] These aspects of this disease will affect the additional impact that presence of geriatric impairments may have on outcome.[10] The intense treatment regimens for beating lung cancer will require greater reserves than less toxic treatments and this may influence the relevance of certain impairments over others. This was also emphasized by the limited effect on one-year survival of standard versus adjusted initial treatment.

On the basis of this study, patients who are potentially frail do not appear to benefit from standard treatment as we have seen that being potentially frail a significant impact on one year survival, while the initiation of standard treatment did not affect outcome. However, we do not know what the outcome would have been if all potentially frail patients did receive an adjusted regimen; therefore, it is too early to translate our findings into a treatment recommendation. Future research could focus on a stratification of treatment based on the outcome of a frailty screening to determine if this strategy can aid in optimizing benefit while limiting risks and toxicity.

In the past years, multiple screening tools have been analysed and adapted with the aim to increase the diagnostic accuracy.[24] For example, in the revised version the G8 was modified to a six item screening tool, which included PS and a history of heart failure or coronary artery disease and excluded age, mobility, body mass index and decline of food intake due to loss of appetite.[24] We have to keep in mind that screening tools are inferior in comparison to a geriatric assessment, which is assumed to be the golden standard with regard to detecting impairments in geriatric domains.[23,25] By using screening tools, we make sacrifices regarding sensitivity or specificity.[23] However, when individual research teams continue to adapt existing screening tools or develop new ones rather than exploring the usefulness of those already in use, it is impossible to fully establish and validate the diagnostic accuracy of the investigated screening tools. Thus, we think that the aim should be to validate the current best available screening tools in different clinical settings or populations[15,16,26].

CONCLUSION

This study shows that the G8 and ISAR-HP screening tools can be used for prognostication in elderly patients with lung cancer. Potentially frail patients, as identified with an impaired G8 or ISAR-HP screening, had a significant higher risk for one-year mortality irrespective of the treatment they received or the stage of their disease. The prevalence of geriatric impairments was high among potentially frail patients and increased further if patients had an impaired score on both screening tools. Analyzing the screening instruments separately showed that G8 had an independent relation with one-year mortality and ISAR-HP not. Using ISAR-HP as only screening tool would therefore be insufficient, however an impaired score on ISAR-HP in addition to an impaired score on G8 would lead to fine-tuning of selection of patients with multiple geriatric impairments and can be helpful is geriatric oncologic expertise is scarce.

Abbreviations

G8	Geriatric 8
GA	Geriatric Assessment
ISAR-HP	Identification of Seniors at Risk for Hospitalized Patients
NSCLC	Non Small Cell Lung Cancer
PS	World Health Organization Performance Status
SCLC	Small Cell Lung Cancer

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APPENDIX

	Summary of Dutch guidelines for standard treatment of pulmonary malignancies according to tumor stage	
NSCLC		
	Stage Ia	Surgical resection
	Stage Ib	Surgical resection *
	Stage II	Surgical resection with adjuvant chemotherapy
	Unforeseen pN2 or pN3	Surgical resection with adjuvant radiotherapy
	Tumor cells in resection margins	Adjuvant radiotherapy
	Stage III	Concurrent chemoradiation therapy
	Stage IV	Palliative chemotherapy**
SCLC		
	Limited disease	Chemoradiation therapy
	Extensive disease	Palliative chemotherapy
	In case of response to chemotherapy	Prophylactic cranial irradiation
Mesothelioma	All stages	Palliative chemotherapy
NSCLC, SCLC, and mesothelioma	WHO PS 3 or 4	Best supportive care

(N)SCLC: (non) small cell lung cancer
WHO PS: World Health Organization Performance Score
* Guideline is ambivalent according treatment with adjuvant chemotherapy in stage IB
** Targeted therapy with tyrosine kinase inhibitor if mutation in EGFR or ALK is found

Chapter 8

Geriatric evaluation in lung cancer care – A survey of daily practice in the Netherlands

Submitted

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ABSTRACT

Background

To identify ways to improve care for older lung cancer patients, we set out to examine how older lung cancer patients in the Netherlands are currently being analysed prior to oncological treatment and to explore the potential obstacles in the incorporation of a routinely performed geriatric evaluation.

Methods

We sent a web-based survey to 138 Dutch pulmonologists specialized in lung cancer care between April and September 2015.

Results

The response rate was 37%. According to the answers of the responding pulmonologist, a geriatric evaluation was available in 90% of the hospitals. This was performed routinely in a minority of the hospitals (45%) on the basis of age (18%), with use of some form of screening tool (27%), however mostly performed on ad hoc basis (56%). More than half (52%) of the respondents answered to be not, or not completely, satisfied with current geriatric evaluation. The main obstacles for implementing geriatric evaluation in standard care were lack of a structured format for this evaluation and lack of geriatric oncologic expertise.

Conclusion

There is interest in the incorporation of a geriatric evaluation in the care for the heterogeneous elderly population with lung cancer. However, at the moment the optimal set-up for geriatric oncologic care is lacking. There seems to be no consensus about the optimal design in terms of patient selection, timing and use of screening tools. A closer collaboration between pulmonologists specialized in lung cancer care and geriatricians could help to improve appropriate care for elderly patients with lung cancer.

INTRODUCTION

In the Netherlands, over 12,000 patients are diagnosed with lung cancer annually.[1] Like elsewhere, half of these patients are over 70 years old, making lung cancer predominantly a disease of the elderly.[1] The numbers of elderly patients are expected to rise in the next years due to prolonged life expectancy.[2]

Many questions still remain unanswered regarding optimal lung cancer treatment for older patients. As ageing is an individual process that varies in comorbidity, remaining functional capacity, disabilities and geriatric conditions, treatment regimens investigated in fit, younger patients cannot automatically be extrapolated to older patients.[3] Tailoring of care is mandatory, based on a thorough evaluation of the patient's overall health status in addition to tumour characteristics and preference of the patient. However, most physicians have never received specific training on the particular needs of older patients with cancer.[4] Lack of this specific training can make them uncomfortable in decision-making for this population.[4] In addition, elderly cancer patients have reported that their individual situation, including concurrent diseases and psychosocial status should receive more attention in the decision-making process.[5]

Over the past years, international research groups have addressed this issue by advocating the incorporation of a geriatric evaluation into the standard oncological work-up to improve cancer care for older patients.[3,6] A geriatric evaluation is used to assess the patient's health status across multiple domains.[7] It can be used to identify previously unrecognized health issues which may guide treatment decisions and which can possibly be modified to improve quality of life and outcomes.[8–10]

However, a geriatric evaluation in lung cancer practice is not yet implemented in standard care. It is unclear whether this is due to logistical issues such as insufficient time or personnel for performing the evaluation or insufficient support or priority among the involved professionals. Identifying these underlying obstacles could provide more clarity on the next steps that can be taken to improve lung cancer care for older patients.

The goal of our study was to examine how older patients with lung cancer are currently being evaluated prior to initiation of oncological treatment in the Netherlands and to explore the potential obstacles in the incorporation of a routinely performed geriatric evaluation.

MATERIALS AND METHODS

We developed an anonymous web-based survey and used software developed by SurveyMethods, Inc. (http://www.surveymethods.com). This questionnaire focused on the main issues related to geriatric evaluation in lung cancer care. The content of this survey is shown in Figure 1. Briefly, the first part of the questionnaire focused on the current methods of evaluating older lung cancer patients prior to oncological treatment. The second part focused on satisfaction with current practices in this treatment, possibilities for improvement and potential barriers for the incorporation of a geriatric evaluation. Questions ranged from multiple choices to open answers.

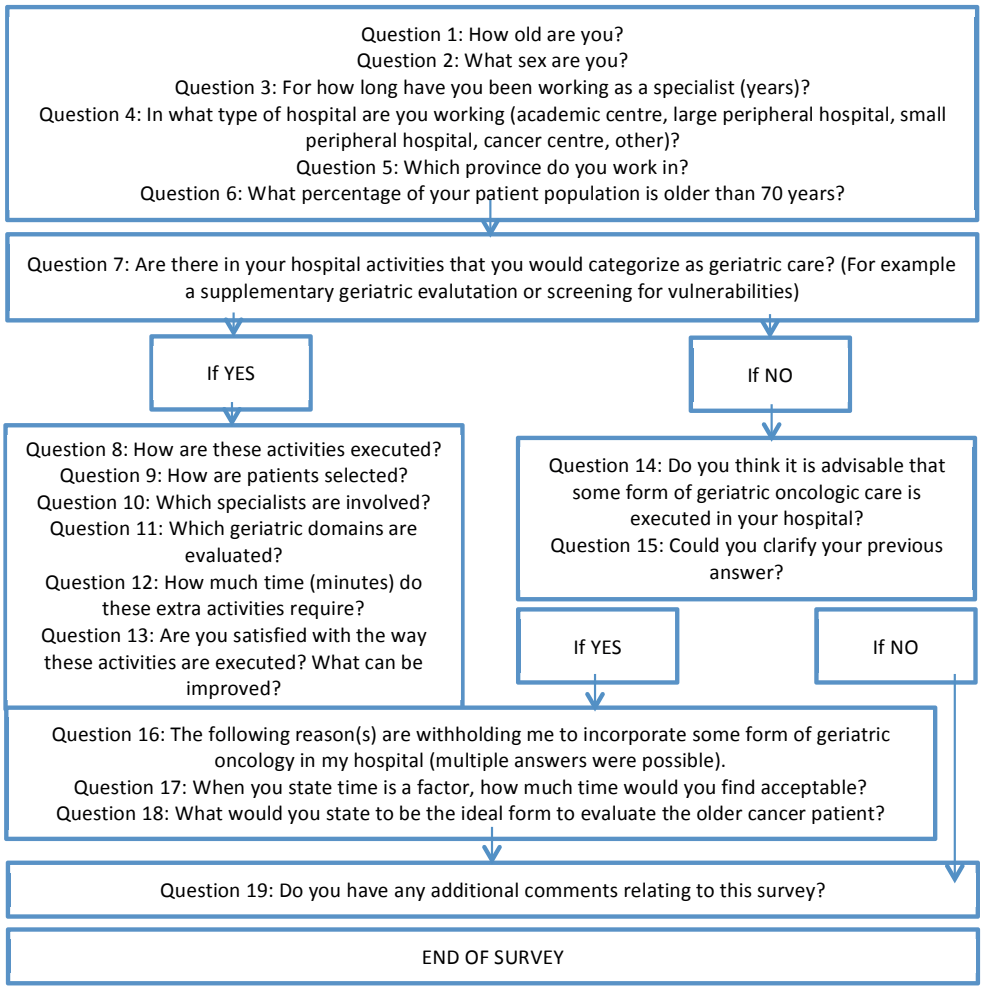

Figure 1. Content of survey (translated from Dutch)

Between April 2015 and September 2015, this survey was sent to all 138 members of the Dutch Taskforce for Pulmonary Malignancies of the Dutch Lung Society (NVALT). The NVALT is the professional association for pulmonologists in the Netherlands. This taskforce consists of all NVALT members specialized in pulmonary malignancies.

No statistical analyses were performed only descriptive data are presented.

RESULTS

Response rate and respondent characteristics

The overall response rate to the questionnaire was 37% (51/138). Characteristics of the respondents are listed in Table 1. Responses came from all over the country, covering 12 provinces of the Netherlands and a range of hospital types, including primary, secondary and tertiary referral centres were represented.

Table 1. Characteristics of respondents

	Total (n=51)
Response rate	51/138 (37%)
Median age of respondent (range)	49 (33-61)
Years of experience as medical specialist (range)	11 (0-28)
%female	30%
Type of hospital	
Academic	12%
Large peripheral	64%
Small peripheral	22%
Tertiary/categorical	2%
Median % patients over 70 years old	50% (20-80)

Geriatric evaluation in daily lung cancer practice

According to the answers of the respondents to this survey, in 90% of the hospitals some form of geriatric evaluation is performed, ranging from an occasional, ad hoc assessment to a routine assessment of all oncologic patients aged 70 years or older. As visualized in Figure 2, the way that patients are selected for a geriatric assessment differs. In 56% the pulmonologists or oncologic specialized nurses refer patients as needed based on their own clinical judgement or based on the opinion of the multidisciplinary team for lung cancer treatment. On the other hand, 18% of the respondents answered that patients are routinely referred when reaching a particular age. Other methods for patient selection

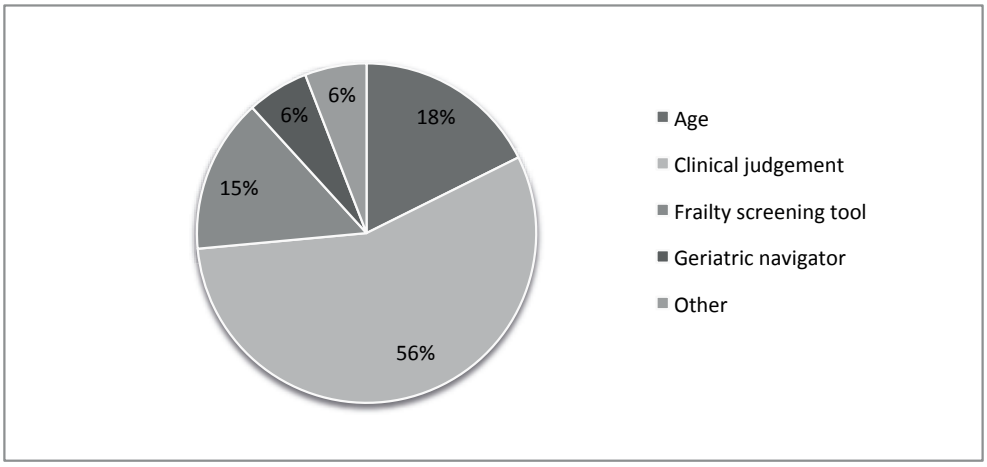

Figure 2. Selection of patients for geriatric assessment

include some form of frailty screening tool (15%), the Geriatric Navigator (6%)[11] – a Dutch web-based instrument for assessing overall health status and the presence of particular geriatric impairments, developed specifically for older cancer patients – and 6% used a combination of these tools. In addition, in some hospitals non-specialized nurses or were involved in this selection.

As the way that patients are selected for a geriatric evaluation differs, the involved health-care professionals for the geriatric evaluation selection process differ as well. There is a wide range of professionals involved in this process ranging from geriatricians (74%), oncologic specialized nurses (68%), geriatric specialized nurses (32%), physiotherapists (6%) to psychiatrists and psychiatric nurses (9%).

When geriatric evaluations are being performed – routinely or ad hoc – 45% of the respondents reported that at least four different geriatric domains are examined and 35% examine eight domains or more. Domains that are most frequently investigated, besides comorbidity and polypharmacy, are nutritional status (81%), activities of daily living (71%), cognition (68%) and social network (68%). Instrumental activities of daily living (32%) and mood (48%) were the least examined domains. The median time that a geriatric evaluation requires is reported as 20 minutes, with a range between 1 and 120 minutes.

Satisfaction with current practices

The respondents who reported to have implemented a form of geriatric evaluation for their elderly cancer patients were asked how satisfied they are with current practice. One-quarter stated to be completely satisfied. Over half (52%) answered that they are not, or not completely, satisfied with the way the geriatric evaluation is performed in their hospital

at the moment .The primary issue – as reported by 2/3 of these respondents – is the lack of a consistent, structured set-up for the geriatric evaluation. Many pulmonologists declared that they struggled with finding the right format and a lack of experience with available screening tools. There seems to be no consensus about the design of this evaluation, about the patient selection, the timing, the focus of geriatric domains, the use of screening tools and the required action that need to be taken following the geriatric evaluation.

Another issue that was mentioned was the oncologic expertise of the geriatricians in their hospital: 19% of the dissatisfied respondents answered that the geriatricians only provide general recommendations but are lacking specific expertise in the treatment or decision-making for older cancer patients.

A third issue is the extra costs of this evaluation, as described by 10% of the dissatisfied respondents. They answered that they are worried about the efficacy and economic issues of health care.

DISCUSSION

Lung cancer is often diagnosed in advanced stages, generally progresses rapidly, and is mainly a disease of elderly patients.[1] As the elderly represent a heterogeneous population, special attention and tailoring of care is needed for this patient population.[12] This study provides an insight in the current use of geriatric evaluation of lung cancer patients in the Netherlands and describes the encountered obstacles for implementation of standard geriatric oncologic care in patients with pulmonary malignancies. According to the answers of the responding pulmonologist, a geriatric evaluation is available in 90% of the hospitals. This is performed routinely in a minority of the hospitals on the basis of age (18%) or with use of some form of screening tool (27%) and mostly performed on ad hoc basis (56%). More than half (52%) of the respondents answered to be not, or not completely, satisfied with current geriatric evaluation of their patients. The main issue is the lack of a structured format, which is considered mandatory for incorporation of a geriatric evaluation in oncologic care and the decision making process.

A recent survey about geriatric oncologic care among Dutch cancer specialist (surgeons, radiotherapist, medical oncologist and geriatricians) showed comparable outcomes as described in our study.[13,14] They declared that the use of geriatric evaluations in elderly cancer care was confirmed by half of the respondents, varying from 65% of medical oncologist tot 27% of radiation oncologists.[13] It was routinely performed in one third of the patients; in another third the geriatric evaluation was performed on an ad hoc basis only and the

remaining third did not elaborate on its execution. Cancer specialists seem to be interested in introducing a geriatric oncology program and a closer collaboration with geriatricians.[15] However, a lack of priority and uncertainty of the optimal set-up for a geriatric oncology program remain important obstacles.[13–15]

At the moment, treatment decisions in lung cancer care are based on clinical assessment in combination with age and performance status discussed at the multidisciplinary tumour board meeting. However, as ageing is an individual process, chronological age does not necessarily reflect one's biological age.[12] In addition, age is not found to be predictive for survival of elderly lung cancer patients.[16,17] While performance status has a significant association with survival, it has been suggested that within the elderly population, performance status alone is insufficient in discriminating between fit and vulnerable patients.[3]

The identification of frail patients can be improved by using a geriatric assessment. However, the relevance of a geriatric assessment in lung cancer care has not been extensively researched. Geriatric impairments are highly prevalent, even in patients with good performance status, and are of prognostic significance.[17–23] In particular, impairments in objectively measured physical capacity and impairments in nutritional status are predictive of early mortality.[16–18,21,22,24] Furthermore, the information revealed by a geriatric assessment can lead to changes in oncologic treatment choices as well as non-oncologic interventions.[25,26] In addition, a geriatric assessment-stratified treatment allocation can potentially decrease overall toxicity and aggressiveness of treatment without decreasing efficacy.[27] Thus, there are sustainable arguments for the implementation of geriatric assessments in pulmonary oncology.

At the moment little is known about the effects of applying guideline recommended treatment in elderly cancer patients. An analysis of the NIH trial registry showed that elderly patients and those with comorbidities are often excluded from participation in clinical trials.[28] We do take a risk when we apply these treatments on frail and elderly patients. More research that includes these patients is urgently needed.

This study has several limitations. First, we used open-ended questions to give the respondents the opportunity to freely provide their input. However, this required a secondary interpretation and categorization of answers. We tried to make this interpretation as objective as possible by using a mix between open-ended and pre-formulated answers. Second, the response rate was only 37%, which is a well-known issue in survey-based studies. In addition, it is not unlikely that those pulmonologists with special interest for geriatric oncology answered this survey, which makes it unclear if these answers are representative for all oncologic pulmonologists. Despite these limitations, this is the first study that provides

information about the use and the encountered obstacles for a geriatric evaluation in lung cancer patients.

A suggestion to improve geriatric evaluation in lung cancer patients would be an intensified cooperation between lung cancer specialists and geriatricians, for example by including a geriatrician in the multidisciplinary tumour board meetings. At these meetings patient centred information is often lacking and the available information is mainly disease specific.[29] Knowledge on physiological ageing, remaining functional capacity in combination with comorbidity is of major importance for the assessment of a patient's ability to tolerate treatment.[29] The presence of geriatricians at the MDT can lead to increased patient-centred decision-making.[30] However, in addition to the urge of specific training of oncologists on the particular needs of elderly cancer patients, geriatricians need a specialized training in oncological care as well.[4] Only a quarter of the responding geriatricians in the survey among Dutch cancer specialists reported that elderly cancer patients received a routinely performed geriatric evaluation prior to the initiation of oncologic treatment, and unfortunately many geriatricians reported that optimising cancer care for elderly patients was currently not a priority at their centre.[14] Given the significant burden and complexity of cancer for the elderly, geriatricians are encouraged to share their expertise with other specialists to be able to optimise care for elderly cancer patients.[14] The cooperation between pulmonologists and geriatricians only has an additional value if they both exactly know what their role is and if there is a format of what may be expected from their consultation.[15]

CONCLUSION

There is interest among oncologic pulmonologists in the incorporation of a geriatric evaluation in the care for the heterogeneous elderly population with lung cancer. However, at the moment a structured format of a geriatric evaluation for this category of patients is lacking. There is no consensus about the optimal design of this evaluation in terms of patient selection, timing, use of screening instruments and the required action that need to be taken following the geriatric evaluation. A closer collaboration between lung cancer specialists and geriatricians could help in bridging the gap between geriatrics and oncologic care to optimize the treatment of lung cancer in elderly patients.

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PART III

PATIENT–REPORTED OUTCOME MEASURES

Chapter 9

Patient–centered outcome measures in lung cancer trials

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ABSTRACT

Background

Scientific communities focusing on cancer research have urged for the development of trials that address patient-centered outcome measures instead of solely focusing on cancer as a disease-centered process. This is important for patient with lung cancer because of the rapid course of disease and generally poor prognosis. We set out to determine the characteristics and study objectives of the current clinical trials in pulmonary malignancies.

Methods

The United States National Institutes of Health clinical trial registry was searched on April 23rd 2015, for currently recruiting phase I, II or III clinical trials in lung cancer. Trial characteristics and study objectives were extracted from the registry website.

Results

Of the 419 clinical trials included in this review, patient-centered outcome measures are investigated in a minority of the trials. Outcome measures as quality of life, functional capacity and health care utilization are included in a small number of trials (20%, 4% and 2% respectively). Treatment completion is included in 1% of the trials. Research goals are most frequently toxicity (78%) and progression-free survival (76%).

Conclusion

Patient-centered outcome measures are included in a minority of the currently recruiting clinical trials in pulmonary malignancies. If we do not investigate these outcome measures, it is not possible to increase our knowledge of the optimal treatment, as this should aim to optimize the patient's well-being as well as the course of disease. One option could be to incorporate combinations of patient- and disease-centered endpoints, for instance by using overall treatment utility or quality-adjusted outcome measures.

INTRODUCTION

In a palliative treatment setting, factors other than survival or progression-free survival gain importance. Patients want to know: 'How long can I keep living in my own house?', 'What will be my quality of life?', 'Is it feasible for me to complete suggested treatments?' or 'How much time will I be spending in the hospital?'. Quality of life, overall functioning and healthcare utilization become increasingly important in this setting.[1–3] To provide patients with answers to these questions, it would be helpful if this shift in priorities is mirrored in research objectives. In recent years, cancer societies and patient advocacy groups have urged for the development of trials that can provide information regarding these so called patient-related outcome measures (PROMS),[1,4,5] and multiple validated tools have been developed to incorporate PROMs in clinical research.[6–9] Incorporating these in clinical trials will provide evidence that allows for a more holistic approach to patient care.

In the Netherlands, over 12,000 cases of lung cancer occur every year.[10] Due to nonspecific symptoms, diagnosis is usually made in advanced disease stages where cure is no longer possible.[10] Survival for patients with advanced disease is generally poor, even with oncologic treatment.[10] For this reason, PROMS are quite relevant to lung cancer treatment.[2,11] Besides, even in a curative setting, incorporation of PROMS in clinical trials can be useful. For instance, newer treatment strategies, such as targeted therapies or replacing major surgery with radiotherapy, are thought to have less disadvantageous side effects, be more patient-friendly and to allow for omission of invasive procedures.[12] PROMs could be an important factor in comparing the benefits and risks of novel treatment options with conventional therapy and between different types of new treatments.[13]

In current clinical practice, many complex questions remain to be answered concerning patient-centered problems. Given the time that transpires between the first conceptualization of a study and the actual publication of final results, any progress in the next years is most likely to come from currently ongoing clinical trials. Therefore, we set out to determine the characteristics and study objectives of current clinical trials in lung cancer.

METHODS

We searched the United States National Institutes of Health (NIH) clinical trial register (www.clinicaltrails.gov)[14] on April 23rd 2015 and used the term 'lung cancer' to identify currently on-going clinical trials concerning pulmonary malignancies. This search was limited to interventional phase I, II or III trials, or mixed phase I/II of II/III trials which were recruiting on the date of the search, or due to start recruiting within the next six months. We included

trials focusing on oncologic treatment of pulmonary malignancies. Studies that also investigated other type of malignancies were excluded.

For the included trials the following data were extracted from the registry website: type of intervention, inclusion and exclusion criteria with regard to age and performance status (PS), source of funding, primary and secondary study objectives and start year of the study.

To combine data of the Karnofsky PS and World Health Organization (WHO) PS, Karnofsky PS of 100 was considered equivalent of WHO PS 0, Karnofsky PS 80-90 equivalent to PS 1, 60-70 as WHO PS 2, 40-50 as WHO PS 3 and <30 as WHO PS 4.[15]

Study objectives (primary and secondary) were classified into ten categories (Appendix 1): overall survival, progression-free survival, toxicity, efficacy, completion of treatment, pharmacological parameters, health care utilization, biological parameters, quality of life and functioning. Of these, completion of treatment, health care utilization, quality of life and functioning were labeled as patient-centered outcome measures. Overall survival, progression-free survival, toxicity, efficacy, pharmacological parameters and biological parameters were considered as disease-centered outcome measures.

Statistical analysis

To assess differences between categories, the χ^2 test was used. A P-value of <0.05 was considered significant.

RESULTS

A total of 791 trials were identified in the trial registry search and out of these we included 419 in this overview. Trials that did not address pulmonary malignancies (*n*=168) or included other (solid) malignancies in addition to lung cancer (n=164) were excluded from our selection, as were trials that did not address oncologic treatment (*n*=40).

The characteristics of the included trials are summarized in Table 1. The majority (86%) of the trials focused on non-small cell lung cancer (NSCLC), 11% of the trials focused on small cell lung cancer (SCLC) and 5% of the trials on mesothelioma. Phase I trials comprised 29% of the included trials, phase II trials 65% and phase III trials 21%. Trials could include multiple trial phases. The treatment under investigation was chemotherapy in 64%, targeted therapies in 31% and immunotherapy in 15%. Radiotherapy was investigated in 20% of the trials, and 5% included surgical treatment. Overall, 50% of the trials were industry-sponsored. Most trials (97%) had a lower age limit for inclusion of 21 years of age and 82%

Table 1. Characteristics of selected trials

		All trials (*n*=419)	
		n	%
Diagnosis	NSCLC	362	86
	SCLC	48	11
	Mesothelioma	19	5
Start of inclusion	<2007	3	1
	2008-2009	22	5
	2010-2011	47	11
	2012-2013	179	43
	2014-2015	168	40
Intervention*	Chemotherapy	267	64
	Targeted therapy	132	31
	Radiotherapy	86	20
	Immunotherapy	61	15
	Chemoradiation	38	9
	Other interventions	33	8
	Surgery	23	5
	Surgery and chemotherapy	10	2
Phase	I	122	29
	II	273	65
	III	87	21
Industry-sponsored*		210	50
Lower age limits, years	<21	408	97
	22-59	2	1
	60-64	0	0
	65-69	0	0
	70+	9	2
Upper age limits, years	<50	0	0
	51-64	1	1
	65-69	3	1
	70-74	12	3
	75-79	39	9
	80-84	9	2
	85-95	10	2
	none	345	82
Performance status (PS)	PS 0 included	377	90
	PS 1 included	376	90
	PS 2 included	161	38
	PS 3 included	7	2
	PS 4 included	3	1
	PS unclear	40	10

(N)SCLC (Non-)small cell lung cancer

* Trials could have multiple interventions and multiple sponsors

have no upper age limit. Patients with a performance score of 0 or 1 were allowed in 90% of the included trials, in 38% a PS of 2. A performance score of 3 and 4 was allowed in 2% and 1% of trials respectively.

Study objectives

The most frequently used study objectives were all categorized as disease-centered outcome measures. Toxicity was investigated in 78% of the trials, progression-free survival in 76% of the trials, efficacy and overall survival were both investigated in 71% of the trials. Patient-related outcome measures were studied in 96 of 419 trials (23%). Of all trials, 20% addressed quality of life, 4% functioning, 2% healthcare utilization and 1% completion of treatment. Of trials including PROMs, the majority (89%) addressed quality of life. Biological parameters were included in 27% of all trials and pharmacological parameters in 19%. Outcome measures varied per trial phase (Table 2). Patient-centered outcome measures were included in <10% of the phase I trials, 21% of phase and 44% of phase III trials (p=<0.001).

Table 2. Study objectives

	All trials (*n*=419) (%)	Phase I (*n*=122)(%)	Phase II (*n*=273) (%)	Phase III (*n*=87) (%)
Toxicity	325 (78)	118 (97)	205 (75)	55 (63)
Progression-free survival	318 (76)	68 (56)	213 (78)	76 (87)
Efficacy	299 (71)	86 (70)	203 (74)	59 (68)
Overall survival	299 (71)	56 (46)	208 (76)	78 (78)
Biological parameters	115 (27)	41 (34)	76 (28)	16 (18)
Quality of life	85 (20)	11 (9)	46 (17)	37 (43)
Pharmacological parameters	79 (19)	49 (40)	44 (16)	8 (9)
Functioning	18 (4)	5 (4)	12 (4)	6 (7)
Health care utilization	7 (2)	0 (0)	1 (0)	6 (7)
Completion of treatment	6 (1)	2 (2)	6 (2)	0 (0)

There was no change in the use of patient-related outcome measures over time and no difference between types of diagnosis (Table 3). Industry-sponsored trials were less likely to address PROMs (19% versus 27% in other trials, p=0.03). Chemotherapeutic trials addressed PROMs significantly less in comparison to all other type of interventions (p=0.01). Radiotherapeutic trials addressed one or more PROMs in 30% of the trials versus 21% in non-radiotherapeutic trials. No difference could be observed in use of PROMs in trials that used targeted therapies versus other interventions.

Table 3. Use of PROM per study characteristic

		No PROM *n* (%)	Any PROM *n* (%)	p-value
Diagnosis	NSCLC	278 (77)	84 (23)	0.7
	SCLC	38 (79)	10 (21)	0.7
	Mesothelioma	15 (79)	4 (21)	0.8
Start of inclusion	<2007	2 (67)	1 (33)	0.8
	2008-2009	16 (73)	6 (27)	
	2010-2011	36 (77)	11 (23)	
	2012-2013	138 (77)	41 (23)	
	2014-2015	131 (78)	37 (22)	
Intervention*	Chemotherapy	216 (81)	51 (19)	**0.01**
	Targeted therapy	106 (80)	26 (20)	0.3
	Radiotherapy	60 (70)	26 (30)	0.07
	Immunotherapy	51 (84)	10 (16)	0.2
	Chemoradiation	30 (79)	8 (21)	0.8
	Other interventions	24 (73)	9 (27)	0.5
	Surgery	20 (87)	3 (13)	0.247
	Surgery and chemotherapy	10 (100)	0 (0)	0.07
Phase	I	107 (88)	15 (12)	**0.01**
	II	217 (79)	56 (21)	0.1
	III	49 (56)	38 (44)	**<0.001**
Industry-sponsored*		171 (81)	39 (19)	**0.03**
Other		152 (73)	57 (27)	

PROM Patient-related outcome measure
(N)SCLC (Non-)small cell lung cancer
* Trials could have multiple interventions and multiple sponsors
Bold values indicate significance with p<0.05

DISCUSSION

In this overview of currently recruiting clinical lung cancer trials registered in the National Institutes of Health (NIH) clinical trial registry, patient centered outcome measures were included in a minority of the trials. Even in phase III trials, PROMs were addressed in only 44% of the trials. As far as we know, this analysis is the first to demonstrate that these outcome measures are still not used on a regular basis in pulmonary cancer research. When these outcome measures are not investigated, improving lung cancer care will stagnate at some point. We will not be able to inform our patients about important aspects of treatment as for example functional capacity or expected days to spend in the hospital.

Agencies as the US Department of Health and Human Services Food and Drug Administration and the Institute of Medicine, have urged for a shift from a disease-centered towards a more patient-centered system.[1,2,16–19] To facilitate this process, Federal Drug Administration (FDA) and European Organization for Research and Treatment of Cancer (EORTC) guidelines have made inclusion of quality of life mandatory for all new clinical trial proposals in diseases with a poor prognosis.[18,20,21] In addition, cancer patients themselves have stated that the highest research priorities for them are 'the impact of cancer on life, how to live with cancer and related support issues', while research on treatment and toxicity were given a much lower priority.[22,23] PROMs become even more relevant in elderly patients,[24 25] as the limited disease-centered evidence for this age group shows inferior results for survival and toxicity compared to younger patients. In addition, multiple studies have demonstrated that elderly cancer patients are generally less willing to accept toxicity for additional survival time, especially when therapy negatively influences their quality of life or functional status.[26 27 28] Thus, questions regarding PROMs will become increasingly urgent with imminent ageing of society. It is important for phase I-III trials that not only effects of the treatment on the tumor are investigated, by analyzing safety and efficacy, in addition, it is important in diseases with a poor prognosis, as lung cancer, that effects of treatment on the patients are incorporated as end-points in clinical trials. Treatment perspectives can be changed from disease-centered to a more patient-centered view. To be able to inform our patients about all different aspects of treatment, it would be of great importance if these outcome measures will be incorporated in clinical trials.

However, as this overview demonstrates, at the moment patient-centered outcome measures are only incorporated in a minority of ongoing clinical trials, and there seems to be little increase of incorporation of PROMs over time. For newer treatment options, in particular for trials that address radiotherapy, there has been a small increase in the use of quality of life and other patient-centered outcome measures. In contrast, in the trials selected for this overview, PROMS are addressed in a minority of the trials on targeted therapies with tyrosine kinase inhibitors (TKIs). An explanation might be, that many of these treatments are still in early phases of investigation. However, TKIs have now been in use for several years, so also other aspects of these therapies could be investigated. In this context, PROMs can also be useful in detecting a positive influence of treatment on cancer symptoms,[13,29] particularly when comparing different types of TKIs or other types of novel combination therapies.

Although there is general support for the incorporation of PROMs in clinical research, it should be noted that it is not always straightforward how this should be done, as the assessment and analysis of PROMs in a clinical trial can be complicated. While there is no lack of validated options for measuring PROMs,[6,30–32] these instruments often yield a

whole range of parameters that can make interpretation difficult. Furthermore, in studies with poor prognosis, high mortality rates can result in missing data and selective loss-to-follow-up that can bias results.[6] Furthermore, weighing quality of life and survival effects of treatment can be difficult and prone to subjective interpretation, particularly when results are conflicting.[9] One option could be to use combined end-points such as overall treatment utility or therapeutic success[30], which incorporates efficacy, toxicity and acceptability of the treatment to the patient. Selecting these outcome measures with a multidisciplinary team, consisting of patients and varying professional disciplines would strengthen the study protocol by encouraging the incorporation of PROMs. A second option would be to use quality-adjusted treatment outcomes such as the Q-TWIST (quality-adjusted time without symptoms of disease or toxicity of treatment)[31], which integrates multiple relevant but potentially conflicting outcome measures into one end point. Another option would be to encourage the development of prospective randomized controlled trials dedicated to assess patient-centered aspects of treatment.

This study has several limitations. First of all, we have focused exclusively on the NIH clinical registry, and therefore we do not have a full presentation of all clinical trials worldwide. However, the NIH trial registry is by far the largest registry; as a comparison, a cursory search of the second largest registry (the European Union clinical trial registry - www.clinicaltrialregister.eu) using the same search resulted in only a fraction of the number included in this overview. Another limitation is that we only had access to the data reported on the primary website. It is possible that other study outcomes or objectives are included but not mentioned on the website. However, we believe that this is unlikely to have happened on a large scale, as the NIH asks for detailed and specific information of primary and secondary outcome measures, and think that this overview gives the best available information about the outcome measures of currently recruiting trials.[14] In addition, it is plausible and likely that patient report their symptoms and side effects when they visit their oncologist. However, to analyze trends and changes on the outcome measures and to be able inform other patients about these aspects of treatment it would be helpful if patient-centered outcome measures were incorporated in clinical trials using validated assessment tools.

In conclusion, patient-related outcome measures are included in a minority of the currently recruiting clinical trials in pulmonary malignancies. Given the time that transpires between conceptualization of research and the publication of their results and subsequent incorporation in treatment guidelines, it is important that these questions are addressed in clinical research. Using combinations of endpoints can facilitate the inclusion of patient-centered outcome measures in trials and will broaden in the available information that physicians can give their patients about different treatments. The scientific community

should actively participate in taking the steps to improve the delivery of evidence-based, tailor-made and patient-focused cancer care.

Abbreviations

FDA	Food and Drug Administration
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
PS	Performance Status
PROM	Patient-related outcome measures
SCLC	Small cell lung cancer
WHO	World Health Organization

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e– Appendix 1

Study objective	Classified as
Overall survival	Overall survival
Mortality at a particular time point during follow-up	
Progression-free survival	Progression-free survival
Event-free survival	
Disease-free survival	
Time-to-progression	
Duration of response	
Toxicity	Toxicity
Safety	
Feasibility	
Maximum-tolerated dose	
Response	Efficacy
Efficacy	
Time-to-responde	
Engraftment	
Completion of planned treatment	Completion of treatment
Achieved dose intensity	
Compliance to treatment	
Pharmacokinetics	Pharmacological parameters
Pharmacodyamics	
Health care utilization	Health care utilization
Health economics	
Laboratory parameters	Biological parameters
Genetic parameters	
Tumor biology	
Quality of life	Quality of life
Care dependence	Functioning
Institutionalization	

Chapter 10

Evaluation and reporting of quality of life outcomes in phase III chemotherapy trials registered at the National Institutes of Health clinical trial registry

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ABSTRACT

Background

Quality of life (QoL) should be included in trials where treatment is expected to have a limited impact on long-term survival. We set out to determine whether phase III chemotherapy trials addressing solid malignancies with a poor prognosis include QoL as a study objective and to assess the extent to which these data have been published.

Methods

We performed a search of the National Institutes of Health clinical trial registry website to identify phase III chemotherapy trials for poor prognosis solid malignancies. The retrieved protocols were subsequently reviewed, to assess whether QoL was included as an outcome measure. Subsequently, a Medline, Embase and world-wide-web search was performed to identify any full text publication or conference abstract regarding the outcome of trials including QoL, which were then reviewed to determine whether and to what extend quality of life results were included.

Results

For the 201 included studies, we found that 57 % of trials did not include QoL as a study objective. Of the remaining trials, 50 % have not reported the QoL results in a full text publication, or presented these only as a single sentence statement.

Conclusion

Evaluation and publication of QoL results of phase III chemotherapy trials for poor prognosis solid malignancies remains limited. This must be improved in order to provide patients suffering from these malignancies with adequate information regarding the benefits and risks of the treatment in terms of both prolongation and quality of life.

INTRODUCTION

In oncology, parameters usually taken into consideration in determining the efficacy of new treatments are overall survival, disease- or progression-free survival and response rate. However, when a disease has a poor prognosis or can no longer be cured, treatment objectives tend to shift from optimizing survival per se to relieving symptoms, maintaining quality of life and optimizing the number of days spent in acceptable health.[1] This shift in clinical treatment goals should be mirrored in research objectives. In particular, randomized controlled trials have the potential to offer high-quality information regarding health-related quality of life to both practitioners and patients, by providing the scientific rigor necessary for valid outcome interpretation.[2]

Over the past 40 years, multiple quality of life assessment tools have been developed for incorporation in clinical research.[3,4,5] Moreover, in the late '90s, organizations such as the Food and Drug Administration, the European Organization for Research and Treatment of Cancer, the United Kingdom Medical Research Council and the National Cancer Institute of Canada have all recommended that quality of life outcomes are considered in new clinical trials proposals.[6,7] In particular, quality of life should be included in trials where the (new) treatment is expected to have only a small impact on long-term survival, or where the disease course in both arms is expected to be similar but quality of life benefits of treatment might differ.[8]

However, to utilize these data in clinical practice, they must first be adequately analyzed and published. In this study, we set out to determine whether phase III chemotherapy trials addressing solid malignancies with a poor prognosis include quality of life as a study objective, and to assess the extent to which these data have been published.

METHODS

The objective of this analysis is to determine the extent of quality of life evaluation and reporting in randomized phase III chemotherapy trials (including biologicals and targeted therapies), which were registered at the National Institutes of Health (NIH) Clinical Trial Registry, and focused on adult patients suffering from a solid tumor with a poor prognosis. This NIH registry is by far the largest clinical trial registries in the world.[9]

For this analysis, we considered a trial to be focusing on a poor prognosis malignancy if they allowed for inclusion of advanced stages of melanoma, sarcoma, upper gastrointestinal, urological, head and neck or pulmonary cancer, as well as any solid malignancy that is

metastatic, recurrent or progressive under primary treatment. On June 26th, 2015, we performed a search of the trial registry on the clinicaltrials.gov website using the search term ''chemotherapy''. The registry search engine allows for incorporation of various limitations. Our search included the following four criteria: interventional studies, phase III studies, studies for adults or seniors, and studies registered as being completed.

We subsequently reviewed the online data regarding the study protocol published on the clinicaltrials.gov website of the trials yielded by this search. These data were downloaded from the website on the day of the search. Only studies that were started in the year 2000 or after were included. Trials were excluded if they did not focus exclusively on adult cancer patients and chemotherapy, if the start date was prior to 2000, if the start and/or completion date was not provided, if they were not exclusively phase III with a randomized design, if no study objectives were listed or if they focused only on treatment of chemotherapy-related side effects or one specific cancerrelated symptoms.

For each of these trials, data were extracted and if necessary recoded according to predefined database by one author (MH). The following data were downloadable form the clinicaltrials.gov website: type of cancer, primary agent under examination (classified as targeted therapy or chemotherapy), number of arms in the trial, type of treatment in each arm, start year and year of completion, and the study sponsor (classified as industry, National Institutes of Health or other). We classified treatment type per arm as combination, single-agent or no treatment. In addition, the trial registry website was explored to assess the reported study objectives and to determine the inclusion of health-related quality of life as an outcome measure. We judged any study which mentioned health-related quality of life as a primary or secondary study objective as including quality of life, irrespective of the primary purpose of the study. We did not set any criteria with regard to the formulation of a specific hypothesis regarding quality of life or power calculations addressing this outcome measure. For trials including a quality of life assessment, two subsequent searches were done in August 2015. First, the trial registry was explored to determine whether any study results were posted, and if so, whether these included quality of life results. Second, a Medline, Embase and internet search was done using the trial registry number, the study acronym if available as well as any other study identification numbers or names, to identify any full text publication or conference abstract regarding the outcome of the trial. Each of these publications was reviewed to determine whether quality of life results were included, and for full text publications, the extent to which these were described. This extent was classified as: a single sentence, paragraph, subsection, separate publication or primary focus of the main publication. In addition, the impact factor of the journal in the year the full text publications came out was determined using the citefactor-website (http://www.citefactor.org/journal-impact-factor-list-2014.html) which contains the impact factor for

over 9000 journals. The highest ranking publication per trial was considered the primary publication. If no publication of any of the trial results was found (n = 15), an attempt was made to contact the primary investigator to verify that trial results were (thus far) unpublished. For four studies, no investigator could be tracked down. For the other 13 studies, only two investigators responded to the query.

Statistical analysis

For comparisons between groups, the Chi-square test was used. Analyses were done using SPSS Version 23. A p value<0.05 was considered statistically significant.

RESULTS

Search and selection

The search of the National Institutes of Health clinical trial registry yielded 16,922 trial protocols. After applying the additional search limitations (interventional studies, phase III and/or IV studies, studies for adults or seniors, and studies registered as being completed), 1563 trials protocols remained for more detailed examination. This resulted in the exclusion of 1362 trials (Fig. 1), leaving 201 trial protocols for inclusion in this analysis. These 201 studies can be found in Webappendix 1.

Trial characteristics

Details of these 201 trials can be found in Table 1. The trials commenced from 2000 onwards and covered a wide range of cancer types, with lung cancer being the most frequent (74 trials, 37 %). The primary focus was a targeted therapy in 86 trials (43 %); the remaining protocols addressed only chemotherapy. Most studies compared two or more types of combination treatment (41 %) or combination therapy versus single-agent therapy (29 %). Twothirds of trials were industry-sponsored.

Examination of the study objectives showed that for two trials health-related quality of life was the primary study objective (1 %) and another 84 (42 %) included it as a secondary objective (Fig. 2). Thus, 57 % of trials did not include quality of life as an objective in the trial protocol published in the registry. There was a decrease in the incorporation of quality of life as an outcome variable over time (45 % in 2000–2004, 43 % in 2005–2009 and 27 % in 2010–2014) but this change was not statistically significant (p = 0.53). Of industry-sponsored trials, 38 % included quality of life as a study objective compared to 50 % of those not sponsored by industry (p=0.09).

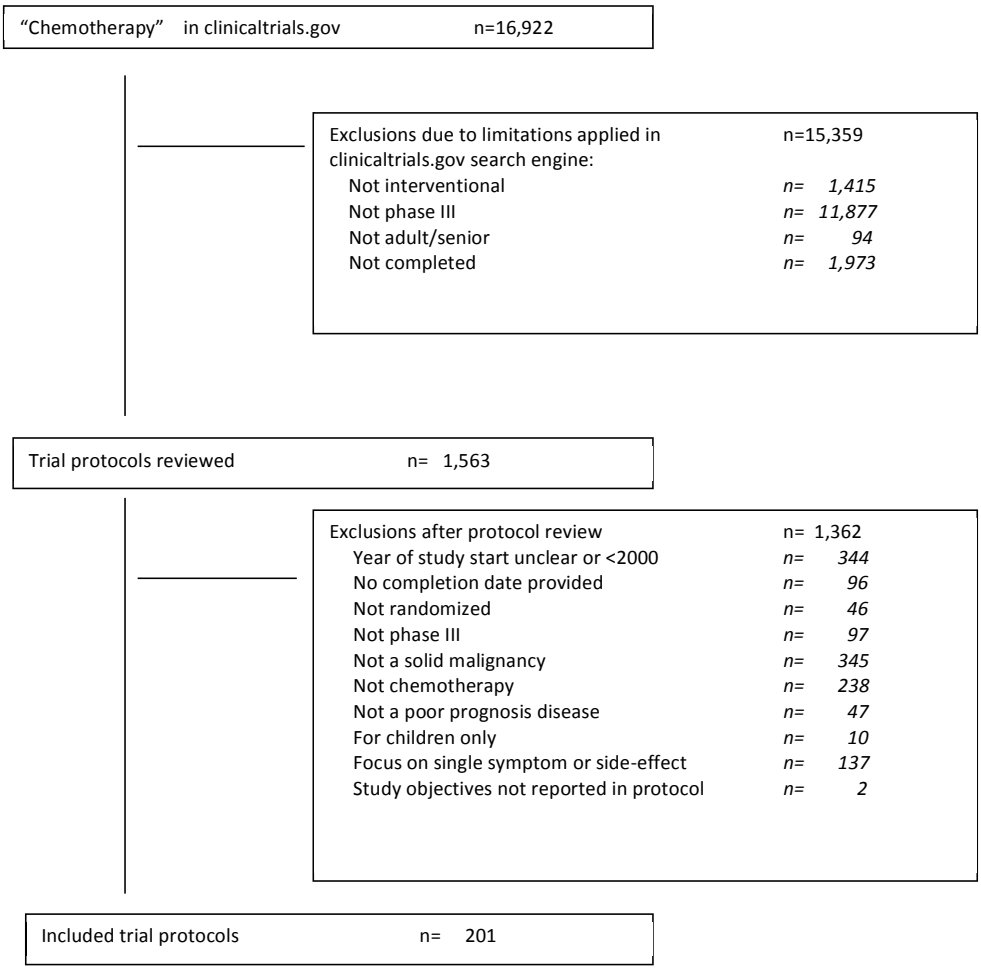

Figure 1. Search results and study selection

Publication of quality of life results

Of the 86 trials that included quality of life as a study objective, 26 have reported trial results on the registry

website. In three cases (12 %), the quality of life data were omitted from these reports. Full text publications were found for 66 of the 86 trials (77 %) that included quality of life as a study objective. The mean number of full text publications per trial was 1.9 (range 0–7); additionally, a mean of 0.8 conference abstract per trial was retrieved (range 0–10). Of these 66 trials, 24 did not publish their quality of life results in any of their publications (36 %, Fig. 2). Quality of life was the main focus of the study and subsequent primary publication in two cases (3 %) and of a secondary publication in seven (11 %). Twenty-five trials (38

Table 1. Characteristics of the 201 selected trials

		n=	%
Diagnosis	Breast cancer	20	10%
	Colorectal cancer	21	10%
	Gynecological cancer	11	5%
	Lung cancer	74	37%
	Melanoma	10	5%
	Pancreas cancer	13	6%
	Prostate cancer	9	4%
	Stomach cancer	21	10%
	Other/various	22	11%
Primary agent under examination	Chemotherapy	115	57%
	Targeted therapy	86	43%
Type of comparison	Combination vs. combination treatment	83	41%
	Combination vs. single agent treatment	58	29%
	Combination vs. no treatment	3	1%
	Combination vs. single agent vs. no treatment	2	1%
	Single agent vs. single agent treatment	28	14%
	Single agent vs. no treatment	27	13%
Number of arms	Two	187	93%
	Three	12	6%
	Four	2	1%
Start year	2000-2004	83	41%
	2005-2009	107	53%
	2010-2014	11	5%
Sponsor*	Industry	131	65%
	National Institutes of Health	15	7%
	Other	86	43%
Quality of life assessment	Primary objective	2	1%
	Secondary objective	84	42%
	Not included	115	57%

* Trials could have multiple sponsors.

%) presented the quality of life data as a paragraph or separate subsection in the primary publication, while for seven trials (11 %), the reporting of these data consisted of a single sentence in the primary report. Two studies (3 %) reported these data only in a conference abstract but not in the primary publication. The median impact factor of the primary publications of the 66 trials was 17.9 (range 2.8–54.4). For the publications in which quality of life was the primary focus, the median impact factor was significantly lower (median

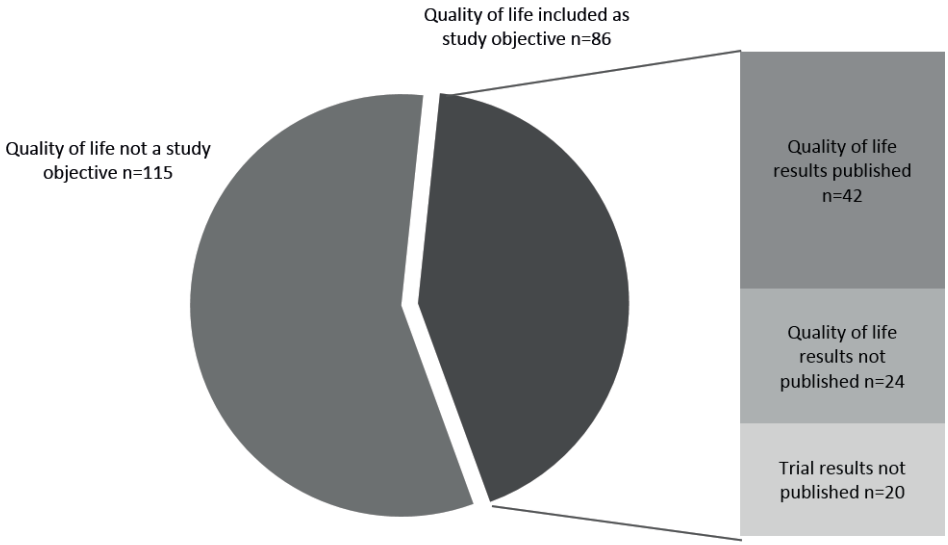

Figure 2. Inclusion and reporting of quality of life for the 201 included trials

impact factor 5.7 (range 4.5–24.7), p=0.05). There was no difference in the median impact factors of primary publications that did and did not report quality of life results (medians 18.0 vs. 17.9, respectively). There was no difference between industry- and non-industry-sponsored trials with regard to publication of quality of life results (any quality of life result published in 64 and 61 %, respectively, p = 0.8).

DISCUSSION

In this analysis of the evaluation and reporting of quality of life in phase III chemotherapy for patients suffering from a solid malignancy with a poor prognosis, we found that 57 % of trials did not include quality of life as a study objective. Of the trials that did, 50 % have not reported the quality of life results in a full text publication, or presented these only as a single sentence statement. Furthermore, the median impact factor of publications of which the primary focus was quality of life was significantly lower than for the publications of which the primary focus was treatment efficacy (17.9 vs. 5.7, respectively, p = 0.05).

When patients are confronted with an incurable illness, the majority will be motivated to receive life-prolonging treatment if this is available.[10] However, they need to weigh the potential survival benefits against the possibility of suffering severe side effects that could limit their quality of life or their ability to function independently in their daily tasks.[11,12] For

many, prolongation of active life expectancy is much more important than prolongation of life expectancy as such.[12] If the prospects of life during or after treatment do not meet the individual's required minimum level of quality of life, this may render the treatment unacceptable to that person, regardless of the potential survival benefits.[13] For this reason, there is general consensus among policy makers and cancer research organizations that quality of life assessments should be included in trials where the (new) treatment is expected to have only a small impact on long-term survival, such as in the palliative treatment setting, or where the disease course in both arms is expected to be similar but quality of life benefits of treatment might differ.[8] Thus, in clinical trials where the primary aim is the prolongation of life or the course of disease, but the overall prognosis is likely to remain poor—as is the case in the majority of the trials included in this overview—quality of life should still be included as a relevant outcome measure.

However, these recommendations are only scarcely being put into general practice, as is demonstrated by the present overview. Our study is the first to address the use of quality of life assessments throughout the trajectory from trial conceptualization to publication. Previous studies have addressed the fact that many currently ongoing cancer trials still do not include quality of life or other patient-centered outcome measures.[14,15] Other researchers have addressed the inadequacy of the evaluation and reporting of quality of life in randomized trials.[2,16] This was most apparent for the absence of power analyses regarding quality of life outcomes, with one review reporting that only 15 % of the clinical trials they assessed had calculated the number of patients required for a reliable evaluation of differences in quality of life between treatment arms.[2] However, in recent years, much work has been undertaken to standardize patient-reported outcome (PRO) reporting in clinical trials, which will hopefully salvage some of these issues.[17,18] Even when quality of life data is collected, the evaluation and reporting is subject to multiple difficulties. Performing statistical analysis of quality of life can be complicated, as studies with poor prognosis malignancies are inherently faced with high attrition rates due to the natural course of the illness, resulting in missing data.[19]

However, there are various accepted methods available to address this issue. In addition, there is no standardized method of analyzing and/or reporting of quality of life instruments.[2] The choice of method will depend on the expected effects of treatment on quality of life. However, as previously demonstrated, few studies formulate aspecific hypothesis pertaining to this aspect of treatment outcome.[16] Furthermore, several reviews have addressed the fact that only a minority of trials addressing quality of life elaborate on the clinical meaningfulness of these results. Trials studying both quality of life and prolongation of life generally base their overall conclusions on the survival results, even when quality of life results demonstrated an opposite pattern of benefit between the two treatment arms.[20,21]

Particularly when the primary trial results are negative, the results regarding quality of life may be considered irrelevant in terms of selecting from available options.

A further question that has been raised in quality of life research is whether the currently available instruments sufficiently address the issues that are most relevant to cancer patients. Most commonly used tools, such as the European Organization for Research and Treatment of Cancer's QLQ-C30[3], have been designed predominantly for use in research.[22] These instruments have undergone comprehensive psychometric validation in cancer trial patients receiving intensive treatment, but they may miss some of the psychosocial and care-related issues that are most relevant to patients across various disease stages.[22] For this reason, rather than routinely using a prespecified quality of life instrument, researchers should select an instrument that is likely to capture the domains most likely to be affected by the disease and/or the treatment[23], once again underlining the need for a specific hypothesis with regard to quality of life.

Although we believe our study results are a reflection of actual research practice in phase III chemotherapeutic trails, it has several limitations. First of all, we have focused exclusively on the National Institutes of Health (NIH) clinical trial registry and therefore, we do not have a full representation of all clinical trials worldwide. However, the NIH trial registry is by far the largest; as a comparison, a search of the second largest registry (the European Union clinical trial registry—www.clinicaltrialregister.eu) using the same search term yields only 3100 trials, one-fifth of the number included in this overview. Given that there is significant overlap between these two registries, we believe that the NIH registry contains a good representation of phase III chemotherapy trials worldwide. Another potential limitation is that for determining the study objectives of the studies under investigation, we only examined the data as reported by the primary investigators on the registry website; the full study protocol was not reviewed. Although the National Institutes of Health website has stated that the data regarding primary and secondary outcome measures ''be as specific as possible''[24], it is possible that other study objectives were formulated in the study protocol that were not mentioned on the registry website. Finally, we made every possible effort to find all available publications; however, it is possible that publications were missed if they did not mention the study acronym or any of the reported study identification numbers and had a significantly different title than the reported study title.

In conclusion, this analysis of the evaluation and reporting of quality of life in phase III chemotherapy for patients suffering from a solid malignancy with a poor prognosis shows that despite the recommendations of the most important organizations for cancer research worldwide, the majority of these trials do not include quality of life as a study objective. Furthermore, only half of those that do have not reported the quality of life results in a full

text publication or presented it only as a single sentence statement. Obstacles with regard to the evaluation and reporting of quality of life in clinical trials can occur on many levels in the process from initial trial concept to the final publication. In order to enable patients suffering from a poor prognosis malignancy to make an informed decision whether or not to start a specific treatment, adequate information regarding the benefits and risks of the treatment in terms of both prolongation as well as quality of life is indispensable. Therefore, these issues need to be resolved.

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Chapter 11

Chemotherapy and health care utilization near the end of life in patients with cancer

Submitted

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ABSTRACT

Introduction

The quality of medical care delivered to patients with cancer near the end of life is a significant issue. Previous studies have defined several areas suggestive of aggressive cancer treatment as potentially representing poor quality care. The primary objective of current analysis was to examine chemotherapy and health care utilization in the last three months of life among patients with cancer that received palliative chemotherapy.

Methods

Patients were selected from the hospital administration database of the Diakonessenhuis Utrecht, the Netherlands. Data were extracted from the medical files. 604 patients were included for analysis (median age: 64 years).

Results

For 300 patients (50%) chemotherapy was given in the last three months (CT+). For 76% (n=229) of CT+patients unplanned hospital admissions were made in these last three months, compared to 44% (n=133) of CT–patients ($p<0.001$). Visits to the Emergency Room in last three months were made by 67% (n=202) of CT+patients compared to 43% (n=132) of CT–patients ($p<0.001$).

Conclusion

Healthcare consumption was significantly higher in patients who received chemotherapy in the last three months of life. Being able to inform our patients about these aspects of treatment can help to optimize both the quality of life and the quality of dying in patients with cancer.

INTRODUCTION

Many issues faced at the end of life by patients dying of cancer will be similar, regardless of their initial type of cancer.[1] Previous studies have defined several areas suggestive of overly aggressive cancer treatment and potentially representing poor quality of care, including use of chemotherapy in the last period before death, use of treatment resulting in high rates of emergency room (ER) visits, hospitalization or intensive care units (ICU), admission for terminal patients and underuse of hospice services.[2–4] Quality of medical care delivered to cancer patients near the end of life is therefore of significant concern.

Trends over time suggest that the utilization of aggressive cancer care near the end of life is increasing, without rendering significant benefits in terms of disease control, quality of life or survival.[5] Possible explanations are the expanding range of chemotherapeutic options, increasing optimism amongst cancer specialists, anecdotal experiences of late-line treatment success, higher expectations and demands from patients and their families and also the complexities of truthfully communicating a patient's poor prognosis whilst not wanting to take away hope.[1,5]

Reversely, interventions aimed at improving quality of care at the end of life, such as offering palliative care early in a disease trajectory when cure is not an option, have been shown to result in significant improvement in quality of life.[6] In some cases, such as in a large randomized trial of metastatic lung cancer patients, the improvements caused by advance care planning were similar to what can be expected among patients who have a response to cisplatinum-based chemotherapy. In addition to improved quality of life, these patients received less aggressive end-of-life care and even experienced longer survival.[6]

In this time of increasingly sophisticated anti-cancer treatments and subsequently mounting health care costs, judicious use of treatment options and tailor-made care is of paramount importance. A first step in improving the quality of care provided at the end of life for patients diagnosed and treated for cancer is to become aware of our own treatment practices. Therefore, the primary objective of this audit was to examine the use of chemotherapy in the last three months of life among patients with cancer treated with palliative chemotherapy at the Diakonessenhuis Utrecht, the Netherlands. Secondary outcome measures included healthcare utilization during the last three months of life.

METHODS

This audit was performed in the Diakonessenhuis Utrecht – a large teaching hospital in the Netherlands. We selected all patients who had received chemotherapy with a palliative intent for a solid malignancy between February 2011 and August 2015 and were deceased at the time of analysis, from the Diakonessenhuis hospital administration data. Patients were excluded if they only received topical chemotherapy (for example intravesical in bladder malignancies). Patients were also excluded if they were (partially) treated elsewhere, because this resulted in missing data regarding healthcare utilization, including chemotherapy, in the last three months of life.

Patients were classified as CT+ if they received palliative chemotherapy in the last three months of life and as CT– if they did not.

For all patients, the following data were collected from the medical charts: date of birth, sex, diagnosis, date of (palliative) diagnosis, last known date of chemotherapy, date and location of death, details about known healthcare utilization (data about admission to hospital or the ICU and ER-visits) in the last three months of life. In addition, for CT+ patients we also collected data on comorbidity (assessed using the Charlson comorbidity index[7] (CCI)), Eastern Cooperative Oncology Group Performance Status (ECOG PS) at the time of initiation of last line of treatment, first date of chemotherapy, last known date of chemotherapy, and treatment line of chemotherapy.

The medical ethics committee reviewed the research protocol and provided a written statement that this study was exempt from full ethical review given its retrospective nature.

Statistical analysis

All analyses were performed in SPSS Statistics version 23.0. A p-value smaller than 0.05 was considered statistically significant. For comparisons between groups, the chi-square test was used for nominal and ordinal variables, and the ANOVA test was used for continuous variables. Subgroup analyses were performed according to primary diagnosis: lung cancer, colorectal cancer, breast cancer, malignancies of upper gastro-intestinal tract (GI), including malignancies of the esophagus, gastric cancer, cholangiocarcinoma and pancreascarcinoma) and the remaining diagnoses were grouped together (‘other’).

RESULTS

Patient selection

A total of 1461 individual patients were treated with palliative chemotherapy in our hospital between February 2011 and August 2015 and therefore selected from the hospital administration data. The patient selection is depicted in Fig 1: 698 patients were still alive and therefore excluded; their diagnoses can be viewed in the Appendix. Sixty-two patients were excluded because they were treated elsewhere and another 97 patients because they were treated with a curative intent (n=74) or received topical chemotherapy only (n=23). Ultimately, 604 patients were selected for further analyses.

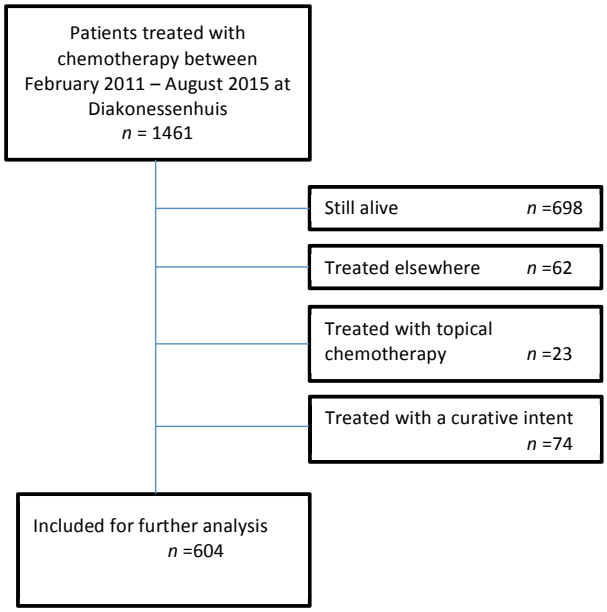

Figure I. Patient selection

Baseline characteristics

The 604 included patients received palliative chemotherapy for a wide range of diagnoses (Table 1). The most frequent diagnoses were lung cancer (38.6%; n=233), colorectal cancer (24.2%; n=146), breast cancer (14.1%; n=85) and malignancies of the upper GI tract (8.6%; n=52). The remaining 14.6% (n=88) were treated for other malignancies: ovarian (n=32), prostate (n=25), urothelium (n=20), endometrial (n=4), adenocarcinoma of unknown primary (ACUP (n=6)) or angiosarcoma (n=1).

Half of all included patients (n=300) received chemotherapy in the last three months of life (CT+). Patients who did not receive chemotherapy in the last three months of life (CT–;

Table 1. Diagnoses

Type of malignancy	n (total n=604)	% of total (n= 604)
Lung	233	38.6
Colorectal	146	24.2
Breast	85	14.1
Upper gastro-intestinal tract*	52	8.6
Other**	88	14.6

*Upper gastro-intestinal tract: cholangio, gastric, pancreatic, esopaghus
**Ovarian, prostate, urothelium, adenocarcinoma of unknown primary, endometrial, angiosarcoma

n=304) had a median time between death and the last chemotherapy of 170 days (IQR 25 -75: 123 – 278), compared to a median of 39 days for the CT +patients (IQR25- 75: 21- 63 days) (Table 2).

Out of all patients treated with chemotherapy for lung cancer (n=233), 47.6% (n=111) were treated with chemotherapy in the last three months of life (CT+ patients with lung cancer). This was 46.6% for patients with colorectal cancer (n=68), 58.8% for breast cancer (n=50), 59.6% for upper GI tract malignancies and 45.4% for other malignancies (n=40). There was no significant difference between these subgroups (p=0.17).

The median age of all included patients was 63.8 years (IQR25 -75: 56.5-70.6) and did not differ significantly between CT+ patients (median 63.5 years) and CT– patients (median 64.7 years, p=0.17). Among the subgroups, the median age did not differ significantly between CT+ and CT– patients (Table 2).

For CT+ patients, the ECOG PS at the time of initiation of the last line of chemotherapy was not recorded in 40.7%. Of the patients for whom ECOG was documented, 61% had an ECOG PS of 0, 30% had an ECOG PS 1, 7% had an ECOG PS 2, and 3% ECOG PS4, respectively. The Charlson Comorbidity Index at this time was ≥1 for 36.3% (n=109), the remaining 64% had a CCI of 0.

The median time between diagnosis and death was 454 days, this was significantly lower in the CT+ patients compared to the CT– patients with medians of 345 days and 595 days, respectively (p<0.001). The median time between diagnosis and death ranged from 260 days (IQR25-75: 137-451) for patients with lung cancer to 1930 days (IQR25-75: 1032-4170) for patients with breast cancer. The CT+ patients had a significantly shorter time period between diagnosis and death in all subgroups, although this difference was not statistically significant for patients with breast cancer.

Table 2. Baseline characteristics

	All patients	CT + *	CT – *	p-value
Number of patients (%)				
- Total	604	300	304	
- Lung	233	111	122	
- Colorectal	146	68	78	
- Breast	85	50	35	
- Upper GI	52	31	21	
- Other	88	40	48	
			Median age at diagnosis in years (IQR25-75)	
- Total	63.8 (56.5 – 70.6)	63.5 (56.5 – 70.1)	64.7 (56.3 – 71.4)	0.17
- Lung	65.3 (58.9 – 72.0)	65.2 (58.5 – 72.1)	65.4 (59.0– 72.0)	0.84
- Colorectal	64.8 (57.1 – 71.4)	63.8 (55.0 – 70.2)	66.5 (58.8 – 73.7)	0.28
- Breast	57.4 (48.8 – 64.9)	59.4 (56.5 – 64.7)	53.7 (48.9 – 65.5)	0.59
- Upper GI	61.7 (50.8 – 68.0)	61.4 (50.8 – 69.3)	2.0 (50.5 – 67.9)	0.90
- Other	64.0 (58.7 – 70.8)	62.8 (59.3 – 68.4)	67.8 (56.3 – 72.4)	0.37
			Median time between primary diagnosis and death in days (IQR25-75)	
- Total	454 (215 – 1087)	346.5 (119 – 846)	595 (323 – 1157)	**<0.001**
- Lung	260 (137 – 451)	127 (73 – 315)	377.5 (250 – 551)	**0.04**
- Colorectal	642 (358 – 1126)	424.5 (207 – 839)	843.5 (543 – 1512)	**<0.001**
- Breast	1930 (1032 – 4170)	1823.5 (833 – 3985)	1932 (1156 – 5208)	0.59
- Upper GI	225 (110 – 403)	162 (80 – 307)	401 (260 – 563)	**<0.001**
- Other	822 (400 – 1662)	673 (169 – 1498)	1039 (490 – 1888)	**0.04**
			Median time between last chemotherapy and death in days (IQR25-75)	
- Total	91 (39 – 170)	39 (21-63)	170 (123-278)	**<0.001**
- Lung	99 (38 – 180)	37 (18 – 63)	170 (127 – 271)	**<0.001**
- Colorectal	99 (40 – 177)	36.5 (20 – 62)	170 (127 – 235)	**<0.001**
- Breast	75 (29 – 140)	35 (14 – 63)	169 (119 – 295)	**<0.001**
- Upper GI	69 (39 – 123)	43 (28 – 63)	144 (111 – 264)	**<0.001**
- Other	99 (51 – 216)	46 (30 – 68)	173 (125 – 342)	**<0.001**
			Patients for whom last course was first line chemotherapeutic treatment	
- Total		161 (53.7)		
- Lung		75 (67.6)		
- Colorectal		22 (32.4)		
- Breast		16 (32.0)		
- Upper GI		25 (81.0)		
- Other		21 (52.5)		

Bold values indicate significance at $p < 0.05$

Single numbers displayed between brackets represent percentages (%), other numbers: IQR25-75: interquartile ranges 25th and 75th percentile

*CT+ Patients that received palliative chemotherapy in the last three months of life

**CT– Patients that did not receive chemotherapy in the last three months of life

***ER Emergency Room

**** GI Gastro-intestinal

For 53.7% of the CT+ patients, the last course of chemotherapy consisted of first line treatment. This percentage was 67.6% for lung cancer, 32.4% for patients with colorectal cancer, and 48.4 % for upper GI tract malignancies. For CT+ patients with breast cancer, the last course of chemotherapy was first line treatment for 31% of the patients, second line for 20%, third line for 16% and fourth line for 12%.

Healthcare utilization in the last 90 days of life

For the total group, unplanned hospital admissions in the last three months of life were made for 362 out of 604 patients (59.9%). (Table 3) This percentage was significantly higher for CT+ patients than for CT– patients (76.3% n = 229 versus 43.8% n =113), ($p<0.001$). For CT+ patients this ranged from 68.0% for breast cancer patients to 84.6% of lung cancer patients.

For CT– patients this ranged from 28.2% (colorectal cancer) to 53.3% (lung cancer).

Visits to the Emergency Room in the last three months of life were made by 55.3% of the total group (n=334), significantly more often by CT+ patients (67.3%; n=202) compared to CT–patients (43.4%; n=132) ($p<0.001$). In the subgroups, this ranged from 28.6% in CT–patients with breast cancer to 79.3% in CT+ patients with lung cancer (Table 3).

End of life/ Place of death

The place of death was unknown for 33.5% (n=203) of all patients. Of the remaining, 217 patients died at home (35.9%), comprising 28.0% of the CT+ patients (n=84) and 43.8% of the CT– patients (n=133) (Table 3). Of all included patients, 18.4% died in hospital (n=111), and this occurred significantly more often in CT+ patients (29.0%; n=87) compared to CT– patients (7.9%; n=24) ($p<0.001$). The percentages were similar among all subgroups. In addition, 12.2% (n=74) of the patients died in a hospice. There was no statistical difference between admission in a hospice or unknown place of death between CT+ and CT– patients.

DISCUSSION

We found that as many as half of the patients received chemotherapy in the last three months of life in this audit on chemotherapy and healthcare utilization among patients receiving palliative chemotherapy. For patients treated for breast cancer or for malignancies of the upper GI tracts this was even higher, reaching up to 60%. In CT+ patients, the last course of chemotherapy was first line treatment in 54% and the median time between the initiation of the last line of chemotherapy and death was 39 days. More than half of patients had unplanned hospital admissions and visited the ER in the last three months

Table 3. Healthcare utilization in the last 3 months of life

		Unplanned hospital admissions	Visits ER***	Death in hospital	Death at home
Total (n=604)		362 (59.9)	334 (55.3)	111 (18.4)	217 (35.9)
	CT+*	229 (76.3)	202 (67.3)	87 (29)	84 (28)
	CT –**	133 (43.8)	132 (43.4)	24 (7.9)	133 (43.8)
	p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Lung (n=233)		160 (68.7)	156 (67.0)	50 (21.5)	93 (39.9)
	CT+	95 (85.6)	88 (79.3)	34 (30.6)	30 (27.0)
	CT–	65 (53.3)	68 (55.7)	16 (13.1)	63 (51.6)
	p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Colorectal (n=146)		72 (49.3)	62 (42.5)	26 (17.8)	50 (34.2)
	CT+	50 (73.5)	38 (55.9)	22 (32.4)	19 (27.9)
	CT–	22 (28.2)	24 (30.8)	4 (5.1)	31 (37.9)
	p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Breast (n=85)		45 (52.9)	38 (45.2)	16 (18.8)	34 (40.0)
	CT+	34 (68.0)	28 (57.1)	14 (28.0)	17 (34.0)
	CT–	11 (31.4)	10 (28.6)	2 (5.7)	17 (48.6)
	p-value	**<0.001**	**<0.001**	**0.05**	**0.05**
Upper GI**** (n=52)		34 (65.4)	32 (61.5)	8 (15.4)	16 (30.8)
	CT+	23 (74.2)	23 (74.2)	8 (25.8)	9 (29.0)
	CT–	11 (52.4)	9 (42.9)	0 (0)	7 (33.0)
	p-value	0.11	**0.02**	n.a.	**0.02**
Other (n=88)		51 (58)	46 (52.3)	11 (12.5)	24 (11.1)
	CT+	27 (67.5)	26 (62.5)	9 (22.5)	9 (22.5)
	CT–	24 (50.0)	21 (43.8)	2 (4.2)	15 (31.3)
	p-value	0.106	0.08	0.07	0.07

Bold values indicate significance at $p < 0.05$

Numbers displayed between brackets represent percentages (%)

*CT+ Patients that received palliative chemotherapy in the last three months of life

**CT– Patients that did not receive chemotherapy in the last three months of life

***ER Emergency Room

**** GI Gastro-intestinal

of life. Both occurred significantly more often in CT+ patients than in CT-patients and this finding was consistent among all predefined subgroups. In addition, we found that the risk of dying in the hospital was significantly higher for CT+ patients.

There is a long-held perception of death resulting from treatment failure rather than disease progression and as a result, initiation or continuation of treatment is the 'the default option' for patients presenting to emergency departments or other places of the hospital.[3,8,9] On the other hand, chemotherapy and healthcare utilization in the last three months of life have both been suggested as determinants of overly aggressive or poor quality end-of-life care.[2-4] In the course of disease, clinicians, patients and their caregivers must continually weigh the potential benefits of treatment against their negative effects and find the balance between hope and realism.

Our study shows that the use of chemotherapy in the last three months of life is high. However, it is difficult to place these results into clinical perspective and to determine if this does indeed represent suboptimal cancer care. Because of the retrospective nature of our study, we are not informed about details leading to the decision to start or to continue chemotherapy in individual patients. Legitimate reasons for starting chemotherapy late in the disease trajectory do exist; for instance, the aim of chemotherapy might have been to treat specific symptoms and thereby improve quality of life.[3,10]

As demonstrated in a large randomized controlled trial in patients with metastatic lung cancer, early integration of palliative care with standard oncologic care resulted in less aggressive treatment at the end of life and clinically meaningful improvements in quality of life and mood.[6] However, most remarkably, early integration of palliative care prolonged survival by two months, despite patients receiving less chemotherapy. A possible explanation for this finding seems to be in line with earlier data that showed that a lower quality of life and depressed mood are associated with shorter survival among patients with metastatic non-small-cell lung cancer.[11,12] Early integration of palliative care will also lead to well-timed advance care planning and allow patients and their caregivers to express their preferences and concerns regarding the end of life.[13,14]

Our study has several limitations. Firstly, our results are only descriptive and therefore it is difficult to determine whether or not individual treatment decisions should be considered overly aggressive or non-beneficial. Second, our study has a single-center study design. Despite the fact that dilemmas regarding cancer treatments in a palliative setting are universal, the opinions and preconceptions of individual physicians may have an impact on treatment decisions. In addition, intercultural differences, as for example informing the patient about the disease status, are not universal.[15,16] Therefore, a similar audit in another center might yield different results.

Nevertheless, our findings are in line with prior research, which has shown that treatment towards the end of life is becoming more aggressive over time.[1] One review demonstrated

that the prevalence of non-beneficial treatment at the end-of-life in patients with cancer ranged from 33% to 38%.[3] Reported rates of the start of chemotherapy at the end of life ranged from 8.8% within fourteen days of death[17] to 76% within six weeks of death.[18] Due to differences in healthcare systems around the world, data about healthcare utilization (e.g. emergency department visits or unplanned hospitalization), are more difficult to compare. One study reported that up to 48% of patients with advanced lung cancer visited the emergency ward within 30 days preceding death.[19] In an Australian study, up to 74% of the patients with cancer made unplanned hospital visits in the six months after chemotherapeutic treatment.[20]

In addition to healthcare utilization at the end of life, place of death should be regarded as an essential goal in end-of-life care.[21] Most people prefer to stay at home in the last phase of life.[22] Yet, a survey among Dutch general practitioners revealed that potentially 25% of the hospital admissions could have been avoided.[23] Our data show that receiving chemotherapy near the end of life is associated with a lower chance of dying at home. Similarly, one study found that more than half of the patients whose death was expected, were transferred from home to a hospital in the last three months of life.[24,25]

Given the palliative treatment intent, it is important to be able to inform our patients about other aspects of treatment, as for example the likelihood of requiring emergency hospital admission or the impact it will have on quality of life, physical functioning and care dependency. However, at the moment these patient-centered outcome measures (PROMs) are only incorporated into a minority of the ongoing clinical trials.[26] In addition, a recent study showed that 57% of phase III clinical trials for solid malignancies with a poor prognosis did not include quality of life as a study objective.[27] Of the trials that did, these results were omitted in 50% of full text publications or only presented as a single sentence statement.[27]

This analysis was performed as a first step in improving the quality of care our center offers patients with cancer in the last phase of life. As a next step, efforts need to be made to more routinely incorporate advance care planning for patients in the palliative treatment setting, particularly as they near the end of life. One important issue is that it is not simple to recognize when the last three months or the final of life has started. No validated tools currently exist to aid clinicians in this process. Additionally, it would be helpful if better predictors for therapeutic response were available. This could be an important line of future research.

In conclusion, in this retrospective study half of all patients with cancer treated with palliative chemotherapy received chemotherapy in the last three months of life. Use of healthcare, including unplanned hospital admissions and ER visits was high among all patients,

but significantly higher for patients receiving chemotherapy in the last three months than for those who did not. Additionally, the risk of dying in the hospital was higher for CT+ patients, whereas CT– patients more often died at home. For diseases with a poor prognosis we need to inform our patients about these aspects of treatment as well. Although it is difficult to generalize our results, we have made a first step to give insight in these often overlooked aspects of treatment. Expanding research on which treatments may be non-beneficial in the last phase of life can contribute to improving both quality of life and quality of death in patients suffering from cancer.

Abbreviations

CCI	Charlson Comorbidity Index
CT+	Patients that received chemotherapy in the last three months of life
CT–	Patients that did not receive chemotherapy in the last three months of life
ER	Emergency Room
GI	Gastro-intestinal
ICU	Intensive Care Unit

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Appendix. Type of malignancy of patients treated with chemotherapy (curative or palliative intent) at Diakonessenhuis Utrecht not deceased

Type of malignancy	n (%)
Lung	63 (9)
Colorectal	157 (22.5)
Mamma	418 (59.8)
Ovarian	29 (4.1)
Prostate	11 (1.6)
Urothelium	4 (0.6)
Pancreas	2 (0.3)
Gastric	8 (1.1)
Esophagus	4 (0.6)
Endometrium	2 (0.3)

PART IV

GENERAL DISCUSSION AND SUMMARY

Chapter 12

General discussion

Introduction

It remains a challenge to select the optimal treatment for each individual patient with lung cancer. Differences in treatment success become even more apparent in the heterogeneous category of the elderly, because aging is an individual process that leads to a great variance in comorbidity, functional reserves, presence of geriatric syndromes and treatment goals. Due to demographic developments the number of elderly patients with lung cancer is increasing. The management of this specific population with lung cancer therefore is a challenge. With the results of the research presented in this thesis we have tried to clarify several issues concerning decision making in elderly patients with lung cancer.

Part I addressed current clinical practice in lung cancer with special attention to age-related differences. In **Part II**, we elaborated on the potential value of a geriatric assessment for patients with lung cancer, and in **Part III**, we reviewed the use of patient-reported outcome measures (PROMs) in ongoing clinical trials and in current clinical practice. In this chapter, the results of the studies of this thesis are discussed and placed in a wider perspective. In addition, directions for future research will be given.

Treatment of lung cancer is not uniform

The issue of guidelines or recommendations specific to elderly patients with cancer was barely addressed until the nineties of the previous century. It was generally accepted that elderly or frail patients received an adapted treatment regimen or that study results obtained in fit younger patients were extrapolated to the elderly. In the last decades of the twentieth century, cancer specialists began to realize that these assumptions were incorrect.[1] Given the heterogeneity of the elderly population in comorbidity, physiological reserves and geriatric syndromes, one must be cautious about potential undertreatment of the fit elderly or overtreatment of frail patients (Chapter 3 and 4).[2]

Currently, over 95% of decisions regarding a new treatment for lung cancer are first discussed in meetings of a multidisciplinary treatment team (MDT). After the advice of the MDT, the cancer specialist and the patient need to make a final decision on the best treatment modality for each individual patient.[3–5] However, given the fact that the majority of the information discussed at the MDT meeting is disease-specific, rather than patient-specific,[6] one can question if the current MDT meetings are the right platform for treatment decisions in elderly patients with lung cancer (Chapter 3). It is known that collective decision making improves guideline adherence, but also encourages taking riskier decisions.[7–9] Whether these treatment decisions turn out to be beneficial for the patient also depends on the quality of the guidelines and its interpretation.[6] We think that several aspects of decision making and care for elderly patients with lung cancer are amenable to improvement.

First, treatment should be tailored to the ability of patients to tolerate treatment. It is of major importance to identify factors that will affect treatment outcome and hence showed influence decision making (Chapter 3, 5 and 6). In addition, the availability of more detailed information about the general health status, overall frailty of patients and the patients' and their caregivers' attitude regarding treatment at the meetings of a MDT will further increase the quality of the treatment advise (Chapter 5 and 6). At the moment the distinction between fit and potentially frail patients is often based on the clinical judgment of the patient's treating physician. This judgment is not always able to discriminate sufficiently between fit and frail patients within the elderly population. Even in patients with good performance status, geriatric impairments can be present because impairments in cognitive functioning, depressive symptoms and malnutrition are easy to miss.

Having more detailed information available about the patient at the MDT meeting, such as care dependency, cognitive status, nutritional status or overall functioning, will lead to a more tailored treatment recommendation for fit or frail patients. In addition, research is being performed on the incorporation of the opinion of the general practitioner in this decision-making process, because they have generally known their patients for an extended period of time and have a good holistic view of the patient.[10]

Despite the obviously positive development that chronological age is no longer considered a valid criterion on which to base treatment decisions, it would be unfair to say that age does not matter at all. In addition to the process of physiological aging resulting in decreased organ function over time, treatment of cancer in general is often aimed at preventing problems in the future. As aging limits life expectancy, it may also limit the efficacy of such treatments. Competing causes of death should also be taken into account (Chapter 5 and 6).[2]

Geriatric assessment and screening tools need to be incorporated in current practice

Decision making regarding start or discontinuation of treatment should be a careful weighing of risks and benefits. In general, treatment for lung cancer is toxic and can lead to serious side effects that may result in frequent hospitalization. Therefore, treatment requires physical and emotional reserves. At the moment, guidelines or recommendations for treatment of frail or elderly patients are scarce and elderly-specific evidence based models for predicting success rate of therapy for lung cancer still need to be developed.[11–14] Especially in a palliative treatment setting, when the goal of treatment is not just survival benefit but also the prevention or alleviation of cancer-related symptoms and prolonged self-support, treatment decisions should be based on reliable sources to prevent doing more harm.

In 2005, the International Society of Geriatric Oncology (SIOG) recommended to incorporate a geriatric assessment (GA) in the work-up for all elderly patients with cancer.[2] As presented in Chapter 5 and 6, a geriatric assessment can aid in identifying previously unknown geriatric impairments, such as care dependency, impaired cognitive function, poor nutritional status or decreased overall functioning, that can guide treatment decisions. Now, more than ten years after the initial recommendation, the actual implementation of these assessments is still limited (Chapter 8). Several obstacles that hamper a smooth integration of a geriatric assessment in standard clinical practice can be identified.

First, there is limited clinical data on the possible effect of treatment adjustments based on geriatric assessments for patients with lung cancer. Only one study, published in 2016, reported on the results of geriatric assessment-allocated treatment.[15] In this study, patients who where treated on the basis of a geriatric assessment in general received less intensive treatment and experienced less toxic side effects, while survival rates did not differ from the patients who received usual lung cancer care. Unfortunately, it will take some time before advice resulting from this trial is incorporated in current guidelines, especially as critics and also the authors of this study themselves consider this a negative study result, since it failed to show superior survival with GA-allocated treatment.[16]

Another important obstacle for implementation of geriatric assessment is lack of a structured format of how, when, where and by whom this assessment needs to be done. This is emphasized by the results described in Chapter 8.[17] There is no consensus on the format of the GA, resulting in limited comparability of study results (Chapter 5). Because this subject is relatively new in the field of oncology and in the field of geriatric medicine as well, specialized knowledge needs to be further acquired. Until recently, the special needs of elderly patients received limited attention within medical and nursing education. Fortunately, it is increasingly being incorporated in various curricula at medical schools of different universities. Hopefully, the overall knowledge of the needs of frail elderly will improve in the near future. Conversely, for adequate collaboration in geriatric oncology, geriatricians need to receive some form of training about several aspects of cancer treatment. Thus, if a cancer specialist refers their patients to a geriatrician, the latter need to be able to formulate a tailored and pragmatic recommendation before start of treatment, during course of treatment and follow-up (Chapter 8), rather than only a more general summary of the patient's overall health status.

A further practical issue in implementing geriatric assessment is that it is difficult to define a strict age criterion as a basis for patient selection. As outlined in Chapter 3, patients with lung cancer aged between 65 and 75 years of age are often more frail than initially thought because they started treatment as often as patients younger than 65 years but treatment

adjustments were needed as often as in the oldest (>75 years of age). Therefore, we may conclude that benefit of a geriatric assessment can be significant for this age category to prevent overtreatment of the more vulnerable patients. For the oldest patients (75+ years), physicians limit the start of standard treatment (Chapter 3). This could lead to the conclusion that a geriatric assessment is not necessary for these patients because physicians were already cautious of potentially overtreatment of these frail elderly patients. On the other hand, one can also argue that for these patients a geriatric assessment might subsequently result in the identification of those patients more fit than initially thought. Therefore geriatric assessments could potentially prevent undertreatment. As we have described in Chapter 4, a selected group of these oldest old patients (85 years and older) can have similar benefit from treatment as younger patients.

A frequently found statement when reviewing literature regarding incorporation of geriatric assessment in standard care is that this systematic procedure is too time-consuming. However, we think that it is difficult to maintain that this argument regarding time still holds true. In the Netherlands, the maximum hourly salary for a specialized nurses is €35. It is hard to explain that it is easier to start an intensive toxic treatment costing thousands than to have a nurse spend half an hour examining if there are patient characteristics that will hamper treatment success or predict unacceptable toxicity. Therefore, we think that the adagio should change from 'a geriatric assessment is too time-consuming' to the motto 'a geriatric assessment is time well-spent'.[18]

Furthermore, we think that a prefixed lead-time from diagnosis to start of treatment should be omitted from current guidelines for elderly patients. In the Netherlands, criteria regarding lead-time are often formulated as a mean of assessing quality of care. Taking high quality decisions needs time, for example to perform an extensive (multidimensional) or geriatric assessment, to discuss treatment decisions in a more extensive multidisciplinary team or to allow the patient and the family sufficient time to come to a decision.

On the basis of current best available evidence, we think that all lung cancer patients aged 70 years or older need some form of geriatric evaluation. Not all patients need an extensive geriatric assessment. For the patients who have a normal score on a screening tool, as for example the G8 (Chapter 7), a geriatric assessment can be omitted. To implement this in current care, we think that a two-stepped model with a screening tool as G8 and in case of an impaired score a subsequent referral for a geriatric assessment (Figure 1), would be a great step forward in tailored treatment of older patients with lung cancer. The G8 screening tool was developed specifically for older patients with cancer. It places significant weight on nutritional status (46% of the total score), while also focusing on mobility, neuropsychological problems, medication use, self-rated health status and age. It has

shown a good sensitivity for geriatric impairments across multiple domains, meaning that most patients with geriatric impairments were identified using this screening tool.[19,20] In addition, an impaired score on G8 was independently associated with a higher risk for one year mortality (Chapter 7).

With the research we have performed, we have shown the potential benefit of multidisciplinary collaboration between thoracic oncology and geriatric medicine. We think that this is an optimal form of patient-centered medicine. Decision making in geriatric oncology needs to be done by well-informed patients together with doctors that are also optimally informed about the multidimensional patient's health status. This is paramount for optimal decision making in elderly patients with lung cancer.

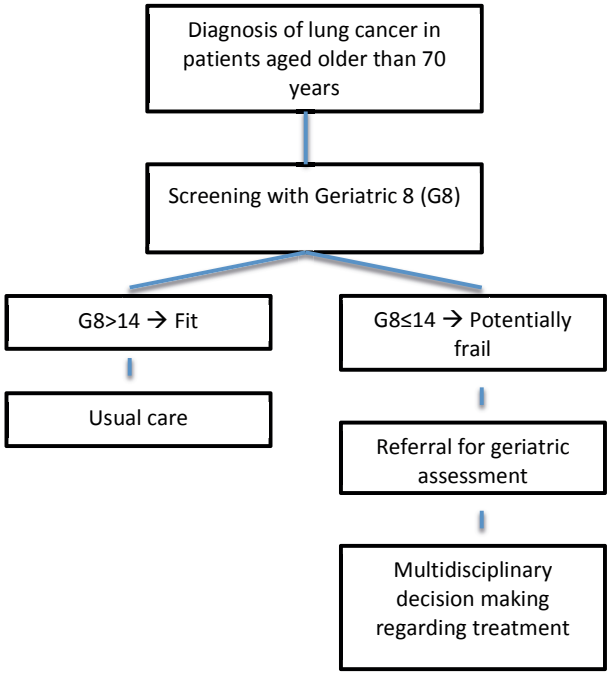

Figure 1. Two stepped geriatric screening model

Optimizing research for elderly patients

While retrospective analysis of clinical practice in elderly patients with lung cancer can reveal important findings regarding current decision making and course of treatment, data on potential confounders such as comorbidity, geriatric syndromes or decreased functional capacity are often not retrievable retrospectively. A next step to improve care and decision making is repeating studies with a prospective design.

By analyzing currently ongoing clinical trials on lung cancer, we have found that due to stringent restrictions per organ system, elderly patients were still disproportionately excluded from trial participation (Chapter 2). This is partly in line with the expected toxicity of treatment and impaired organ function can be a good reason to withhold treatment in daily clinical practice. However, at the moment we are inclined to offer therapy to a more heterogeneous population than initially included in clinical trials. The assumption that these study results can easily be extrapolated may not be correct.[21]

External validity of a trial is the extent to which trial results are a true reflection of what may be expected of a certain intervention in the target population, outside of the study population. Due to the disproportional exclusion of frail and elderly patients in current clinical trials, the effect of treatment in the study might be overestimated and risks of treatment might be underestimated when looking at the general target population. Therefore, recommendations for treatment of frail elderly patients remain limited due to the insufficient external validity of current clinical practice.

Another important factor amenable to improvement are currently used outcome measures in trials on lung cancer and other malignancies with a poor prognosis (Chapter 9,10 and 11): especially for elderly patients, quality of life might be more important than quantity of life. Previous studies have shown that elderly are generally less willing to accept toxicity for a limited amount of additional survival time and in previous conducted surveys patients gave highest priority to functional independency and quality of life.[22,23] For the majority of patients with lung cancer, quality of life is the highest goal and should be aspired to for as long as possible. However, this shift is not reflected in currently ongoing clinical trials on lung cancer (Chapter 9). Furthermore we have shown that even if these research objectives are incorporated in trials they are often not reported in trial publications or only mentioned as a single-sentence statement (Chapter 10).

Future perspectives

Despite the increasing awareness of the high prevalence of frailty in elderly patients with cancer, major challenges lie ahead in improving clinical practice. There are several possible ways to further improve current and future clinical research.[24]

First, a logical step would be the inclusion of elderly patients in clinical trials. However, although randomized controlled trials generally give the highest level of evidence, one can question if this also true for the elderly patients. Given the heterogeneity of the population, it might be difficult to generalize results for the whole population of frail elderly. Additionally, elderly patients might be hesitant to participate in a trial, especially in the case of randomization.[24] In addition, to be able to increase the external validity of trials, in addition

to the internal validity, we need to be realistic in the development of new trials for our frail and elderly patients. An important step for trial designers is critically reviewing if inclusion and exclusion criteria for a certain study are really necessary or if they can be broadened to be able to reach a wider population. In addition, this problem can be solved by reviewing a prospective cohort of elderly patients. However, this can lead to confounding by indication if non-randomized chosen treatments are directly compared. Another option would be to perform subgroup analyses, to establish the efficacy of a treatment for a certain population. Next, trials can be developed with a less intensive treatment arm for patients who did not fulfill all inclusion or exclusion criteria or to design trials especially for frail and older patients.

Second, in addition to increasing the external validity of the trials, we need to have some critisicm regarding currently used outcome measures such as toxicity or progression-free survival. Quality of life and care dependency are of major importance, especially in treatment of frail and elderly patients. To be able to analyze treatment success, we need to focus on overall treatment success or for example days spent in good health (Q-TWIST).[25]

Third, in addition to improving research, current education can also be developed further. By increasing awareness of the differences in care between fit and frail patients, we can improve quality of care delivered to the frail and elderly. Incorporating these learning goals in current education programs for medical students and physicians in training is of paramount importance.

Fourth, in this thesis we have discussed the value of a geriatric assessment. One can debate about who needs to perform the geriatric, or multidimensional, assessment. We do think that the most important aspect of decision making is that this needs to be done by well informed patients, together with optimally informed doctors. Having knowledge about the multidimensional patient's health status is therefore of paramount importance, especially for (doctors of) potentially frail patients. This multidimensional view of the patient's health status can also be obtained by another physician or health care worker instead of the geriatrician, however time for and specific knowledge about this assessment are important. The additional value of a geriatrician is for example that a summary of results of this assessment lead to increased information for the cancer specialist, such as patient characteristics and treatment preferences instead of receiving only separate results of validates tools to score different geriatric domains.

Finally, important next steps for future research are further analyzing the effect of a geriatric assessment for patients with lung cancer. In addition to the effect of a geriatric assessment on treatment decisions, the focus should be on the effect of GA-based care, with a multidis-

ciplinary intervention plan addressing the issues revealed by the geriatric assessment or geriatric nurse during treatment for lung cancer. Assessing the benefits of such care should include patient-reported outcome measures instead of only disease centered outcome measures as toxicity or survival. It would be of paramount importance to integrate the perspective of multiple disciplines, cancer specialists together with general practitioners, in the decision-making process but also on the effect of geriatric support during treatment and after completion of treatment.

Changing decision making in elderly patients with lung cancer

- Selected elderly patients can receive standard oncologic treatment
- Decision making at MDT should include more patient characteristics
- Do not only use ECOG performance status
- Implement a two stepped geriatric evaluation
- Incorporate patient reported outcome measures in daily practice and current clinical trials

In conclusion, decision making in elderly patients lung cancer remains complex and challenging. In this thesis we have addressed important aspects of this problem and possibly have contributed to our knowledge on the value of a geriatric assessment and on the use of patient reported outcome measures.

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Chapter 13

Summary

SUMMARY

In the Netherlands, over 12.000 patients are diagnosed with lung cancer annually. Lung cancer is mainly a disease of the elderly as half of the patients are over 70 years of age and 30% is older than 75 years. Lung cancer care in the elderly is therefore an important burden, especially since the number of older patients with lung cancer will keep on rising in the future due to the aging of Western societies. Moreover, the benefit of treatment for lung cancer varies, especially in the heterogeneous population of older patients because aging is an individual process determined by a great variety in comorbidity, functional reserves and presence of geriatric syndromes in the elderly.

The principal aim of this thesis was to evaluate decision making in elderly patients with lung cancer by analyzing current clinical practice (**Part I**), to analyze the value of a geriatric assessment for these patients (**Part II**) and to review the shift from a disease-centered to a patient-centered approach in outcome measures of ongoing trials and current clinical practice (**Part III**).

In **Part I**, we analyzed current clinical practice of care for older patients with lung cancer. In **Chapter 2**, we described the results of an evaluation we performed on the National Institutes of Health (NIH) trial registry. When assessing the inclusion and exclusion criteria of currently ongoing clinical trials on lung cancer, we concluded that in 88% of the trials elderly patients were explicitly or implicitly excluded. Although the number of trials excluding patients solely on the basis of age is decreasing over time, applying strict selection on organ functions before inclusion resulted in exclusion of elderly patients in the majority of the trials.

At the moment, there is a lack of elderly-specific evidence. Therefore, treatment of individual patients is often dependent on the opinions of the members of the multidisciplinary treatment team (MDT). The decision-making process for oncologic treatment consists of several steps. In the Netherlands, over 95% of decisions regarding a new treatment for lung cancer are first discussed in a MDT. After the recommendation of the MDT, the thoracic oncologist and the patient need to make a final decision on the eligibility and desirability of surgical, radiotherapeutical or chemotherapeutical treatment after critical evaluation and after the healthcare professionals inform the patients about the potential risks and benefits.

Results of analyzing this decision-making process in our institution are described in **Chapter 3**. We found that decision making and course of therapy varied per age category. 39% of eligible patients older than 75 years of age started treatment with chemotherapy, com-

pared to 80% of the patients aged 65-75 years and <65 years. When analyzing the course of therapy, treatment adjustments before start of therapy or and during treatment were effectuated for 58% of patients: for 66% of patients older than 75 years, for 66% of patients aged 65-75 years and for 49% of patients younger than 65 years. Given these numbers we have concluded that especially patients aged between 65-75 years of age might be more frail than initially thought because treatment is started as often as in the younger patients, but adaptations are needed as often as those aged older than 75 years.

In **Chapter 4**, we analyzed the oldest old (85 years and older) with lung cancer. A comparison of nationwide data of the Netherlands Cancer Registry (NCR – IKNL) was made among these patients, those aged younger (18-70 years) and those aged 71-84 years (elderly) diagnosed between 2010 and 2014. 47,951 patients (median age 69 years) were included in the 2010-2014 NCR database. 2,196 (5%) patients were aged ≥85years. In 38% of the oldest old, no histological diagnosis was obtained, which was significantly higher than in the elderly (14%) and younger patients (5%). Regardless of tumor type and stage, a standard treatment regimen was given significantly more often to the elderly and younger patients than to the oldest old. 67% of the oldest old received best supportive care only versus 38% of the elderly and 20% of the younger patients, respectively ($p<0.001$). For the oldest old with standard treatment, survival rates were similar in comparison with the elderly patients. Unfortunately, in the NCR database no patient-specific factors as comorbidity, functional reserves or presence of geriatric syndromes are included.

Selecting the optimal treatment for elderly patients can be a challenge. The elderly represent a heterogeneous population and currently used measures for quantifying a patient's health status and reserves, such as performance status or pulmonary function testing, do not appear to differentiate sufficiently within the elderly population. Care dependency, malnutrition, depressive symptoms or decreased mobility can be present in patients with normal performance status. Therefore, the International Society of Geriatric Oncology (SIOG) task force recommended in 2005 that a geriatric assessment should be implemented for all elderly patients with cancer. This systematic procedure is used to objectively appraise the health status across multiple domains, focusing on somatic, functional and psychosocial domains aimed at constructing a multidisciplinary treatment plan. **Part II** focuses on the role of a geriatric assessment in lung cancer care for the elderly.

In **Chapter 5** we systematically reviewed all available evidence on the relevance of a geriatric assessment for elderly patients with lung cancer. Our review of 23 publications from 18 studies demonstrated that a geriatric assessment can detect multiple health issues that are not reflected in the ECOG performance status. In addition, impairments in geriatric domains (especially objective physical capacity and nutritional status) had predictive value

for mortality and appeared to be associated with completion of treatment. Unfortunately, the actual implementation of these geriatric assessments in clinical practice has thus far been limited.

In two large teaching hospitals in the Netherlands, these systematic procedures have been implemented in the care for elderly patients with lung cancer since 2014 and results of these assessments are described in **Chapter 6**. Our findings support that a geriatric assessment can reveal previously unknown health impairments and may be an important tool for tailored treatment decisions in elderly patients with lung cancer. The majority of the patients we have analyzed suffered from geriatric impairments (78%) and 43% suffered from three or more impairments (out of eight assessed domains). Nutritional status was most frequently impaired. Previously undiagnosed impairments were identified in 58% of the patients and for 43% of all patients non-oncologic interventions were advised. For 33% of the studied patients, suggestions for change of the oncologic treatment were proposed and the oncologist adopted all these suggestions. A reduced or less intensive treatment was more often recommended for patients with a higher number of geriatric impairments.

Due to time and manpower consuming aspects of the geriatric assessment, cancer specialists are seeking a shorter screening tool to distinguish fit and frail patients. Two instruments that have been suggested in this respect are the Geriatric 8 (G8) and the Identification of Seniors at Risk for Hospitalized Patients (ISAR-HP) questionnaires. The G8 was specifically designed for older patients with cancer. It places significant weight on nutritional status (46% of total score), while also focusing on mobility, neuropsychological problems, medication use, self-related health status and age. The ISAR-HP was initially developed for elderly patients presenting at the emergency department, and later revised for hospitalized patients. The ISAR-HP is a four-item questionnaire that has proven to be helpful in identifying older patients at risk of functional decline following hospital admission. We studied the performance of both instruments in 142 patients with lung cancer (**Chapter 7)**. We found that both the G8 and the ISAR-HP screening tools can be used in the prognostication of elderly patients with lung cancer. Potentially frail patients, as defined by an impaired score in the G8 (≤14) or the ISAR-HP (≥2), have a significantly higher risk of one year mortality compared to fit patients with a score in the normal range on both screening instruments. When analyzing both screening instruments separately, G8 was independently associated with one-year mortality but ISAR-HP was not. However, adding the ISAR-HP tool to screening with G8 did select patients with a higher number of geriatric impairments.

The aim of **Chapter 8** was to analyze how older patients with lung cancer are currently being evaluated prior to initiation of oncological treatment in the Netherlands and to

explore the potential obstacles for incorporation of a routinely performed geriatric assessment. We found that there is interest among Dutch lung cancer specialists (thoracic oncologists) in the incorporation of a geriatric evaluation in standard care. However, at the moment, a structured format of how to perform a geriatric assessment is lacking: there is no consensus on the optimal design in terms of patient selection, timing, use of screening instruments and the required actions that need to be taken following an assessment. A closer collaboration between geriatric specialists and thoracic oncologists will probably help to optimize the treatment of lung cancer in elderly patients.

Part III of this thesis addressed the use of patient-reported outcome measures (PROMs) in current clinical practice and in the research of malignancies with a poor prognosis, including lung cancer. In a palliative treatment setting, factors other than survival or toxicity are becoming increasingly important. Quality of life, overall functioning or healthcare utilization are major topics of interest. Over the past 40 years, multiple quality of life assessment tools have been developed for incorporation in clinical research, and several organizations, such as the Federal Drug Administration (FDA) and European Organization for Research and Treatment of Cancer (EORTC), have demanded that PROMs should be incorporated in all new clinical trial proposals, particularly when expected disease prognosis is poor.

In **Chapter 9** we described results of our analysis of the National Institutes of Health (NIH) trial registry focusing on currently ongoing clinical trials on lung cancer. The most frequently used outcome measures were toxicity (78%) and progression-free survival (76%). PROMs, however, were only incorporated in a minority of the trials: of the 419 analyzed trials, outcome measures as quality of life, functional capacity and healthcare utilization were only included in 20%, 4% and 2% of trials, respectively.

In **Chapter 10** we used the NIH trial registry to analyze to which extent PROMs were included as study objectives of phase III clinical trials on poor prognosis malignancies and to which extent these data have been published. We found that for the 201 included studies in poor prognosis malignancies, 57% of the trials did not include quality of life as outcome measure and of the remaining trials, 50% had not reported the quality of life results in a full text publication or presented these only as a single sentence statement.

Many issues faced at the end of life by patients dying of cancer will be similar, regardless of their initial type of cancer. We analyzed potential areas representing poor quality of end of life care in deceased patients who had received palliative chemotherapy, such as commencing or continuing chemotherapy into the very last period of life and the use of treatment resulting in a high rates of emergency room visits, hospitalization or intensive care unit admissions (**Chapter 11**). Half of the 604 analyzed patients received chemotherapy

in the last three months of life. Healthcare utilization in the last three months of life was high for all patients, but significantly higher for those patients who received palliative chemotherapy in the last three months of life. Being able to inform our patients about these aspects of treatment can help to optimize both the quality of life and the quality of dying in patients with cancer.

In **Chapter 12** main findings of the performed research are discussed and future perspectives in care for elderly patients with lung cancer, and other poor prognosis malignancies, were addressed.

In conclusion, decision making in patients with lung cancer remains complex and challenging. We have concluded that treatment of lung cancer is not uniform and that selected elderly patients with lung cancer can experience similar benefit from therapy as younger patients. In addition, we have suggested a two-stepped geriatric or multidimensional evaluation for all elderly patients with lung cancer. Besides, we have stated that PROMs should be incorporated more frequently in research and clinical practice on lung cancer and other poor prognosis malignancies.

Chapter 14

Summary in Dutch – Samenvatting in het Nederlands

Samenvatting

In Nederland worden per jaar ongeveer 12.000 patiënten gediagnosticeerd met longkanker. Longkanker is voornamelijk een ziekte van de oudere patiënt, omdat de helft van hen op het moment van diagnose ouder is dan 70 jaar en ongeveer 30% ouder is dan 75 jaar. Het aantal oudere patiënten met longkanker zal in de komende jaren alleen maar toenemen vanwege de vergrijzing van de Westerse samenleving. Longkanker bij ouderen is een belangrijk en lastig probleem, omdat naast de toename van het aantal ouderen met kanker het effect van de behandeling van longkanker met name varieert binnen deze heterogene populatie. Veroudering is een individueel proces dat leidt tot een grote variatie in comorbiditeit, funtionele reserves en aanwezigheid van geriatrische problemen.

In dit proefschrift worden verschillende aspecten van besluitvorming bij longkanker in oudere patiënten geëvalueerd. In **Deel I** werd gekeken naar hoe oudere patiënten met longkanker op dit moment worden behandeld, in **Deel II** werd de waarde van een geriatrische assessment bij deze patiënten onderzocht, en in **Deel III** werd gekeken of er een verschuiving is opgetreden van ziektegerichte naar patientgerichte uitkomstmaten in onderzoek en klinische praktijk (**Deel III**).

In **Deel I** hebben we de huidige klinische praktijk bij ouderen patiënten met longkanker geanalyseerd. In **hoofdstuk 2** beschrijven we de resultaten van een evaluatie die is uitgevoerd met gegevens van het National Institutes of Health (NIH) trialregister. Het NIH is een van de grootste trialregisters waarin het merendeel van alle huidige lopende klinische studies zijn ingeschreven. Bij het beoordelen van de in- en exclusie criteria van de studies naar longkanker geregistreerd in het NIH, bleek dat in 88% van de studies oudere patienten expliciet of impliciet werden uitgesloten van deelname. Hoewel het aantal studies dat patiënten alleen op basis van leeftijd excludeert de laatste jaren is afgenomen, zorgt het toepassen van (zeer) strenge criteria voor orgaanfunctie voor impliciete exclusie van oudere patiënten in het merendeel van de studies.

Op dit moment is er beperkte specifieke wetenschappelijke kennis over longkanker bij oudere patiënten. Daardoor is de huidige behandeling van individuele patiënten veelal afhankelijk van de opinie van de verschillende leden van het multidisciplinaire team. Het proces van besluitvorming voor oncologische behandeling bestaat uit verschillende stappen. In Nederland worden meer dan 95% van de beslissingen over het starten van een nieuwe behandeling voor longkanker eerst besproken in het multidisciplinaire team. Na de aanbeveling van het team moet de behandelaar, veelal longarts, samen met de patiënt een definitieve beslissing nemen over de mogelijkheid en wenselijkheid van behandeling middels chirurgie, radiotherapie of chemotherapie.

Resultaten van dit besluitvormingsproces in het Diakonessenhuis Utrecht zijn beschreven in **hoofdstuk 3**. Wij zagen dat besluitvorming en verloop van behandeling varieerden per leeftijdscategorie. 39% van de patiënten ouder dan 75 jaar, die op papier geschikt waren voor chemotherapie en op basis van de richtlijn hiervoor in aanmerking kwamen, startte met behandeling met chemotherapie in vergelijking met 80% van de 'geschikte' patiënten tussen 65 en 75 jaar en jonger dan 65 jaar (ook 80%). Bij de analyse van het verloop van therapie zagen wij dat er bij 58% van de patiënten aanpassingen gedaan werden voor de start of tijdens de therapie: bij 66% van de patiënten ouder dan 75 jaar, ook voor 66% van de patiënten tussen de 65 en 75 jaar en voor 49% van de patiënten jonger dan 65 jaar. Op basis van deze getallen hebben wij geconcludeerd dat met name de patiënten tussen de 65 en 75 jaar mogelijk kwetsbaarder zijn dan in eerste instantie wordt gedacht, omdat behandeling even vaak gestart wordt als bij de jongste categorie patiënten, maar behandelaanpassingen even vaak nodig waren als bij de patiënten ouder dan 75 jaar.

In het laatste hoofdstuk van **Deel 1** (**hoofdstuk 4**) hebben we gekeken naar een specifieke categorie van oudere patiënten met longkanker, namelijk de oudste ouderen: patiënten ouder dan 85 jaar. Met data van het Integraal Kankercentrum Nederland (IKNL) uit de periode 2010-2014 hebben wij een vergelijking gemaakt tussen de oudste ouderen (85+ers), ouderen (71-84 jaar) en de jongeren (18 tot 70 jaar). In totaal hebben wij 47,951 patiënten (mediane leeftijd 69 jaar) in de database geïncludeerd, waarvan er 2,196 (5%) ouder waren dan 85 jaar. Bij 38% van de oudste ouderen werd geen histologische diagnose verkregen, dat was significant vaker dan in de groep met leeftijd tussen 71 en 84 jaar (14%) en jonger dan 70 jaar (5%). Ongeacht het tumortype en stadium werd een standaard behandeling, conform de richtlijn, significant vaker gegeven aan patiënten tussen 71 en 84 en jonger dan 70 jaar in vergelijking met patiënten ouder dan 85 jaar. 67% van de oudste ouderen (85+ers) kreeg alleen best supportive care versus 38% van de patiënten tussen 71 en 84 jaar en 20% van de patiënten jonger dan 70 jaar ($p<0.001$). Voor de oudste ouderen die standaard behandeling kregen was de overleving vergelijking met patienten tussen de 71 en 84 jaar die standaard behandeling kregen. Helaas zijn in de IKNL-database geen patiëntkenmerken als comorbiditeit, functionele reserves of aanwezigheid van geriatrische syndromen opgenomen.

Het is een uitdaging om voor oudere patiënten met longkanker de optimale behandeling te kiezen. De oudere patiënten vormen een heterogene populatie en de op dit moment gebruikte maten om de gezondheisstatus en reserves van een patiënt te kwantificeren, zoals Eastern Cooperative Oncology Group performance status (ECOG of World Health Organization PS) en longfunctietesten, zijn niet voldoende in staat gebleken om te differentieren tussen kwetsbare en fitte patiënten binnen deze groep ouderen. Zorgafhankelijkehid, depressieve symptomen en verminderde mobiliteit kunnen aanwezig zijn in patiënten met

een normale ECOG performance score. Mede daarom, heeft SIOG (International Society for Geriatric Oncology) in 2005 geadviseerd dat alle ouderen met kanker een vorm van geriatrische beoordeling moeten krijgen voor start van oncologische behandeling. Deze systematische procedure wordt gebruikt om de gezondheidsstatus objectief te beoordelen op verschillende domeinen: somatisch, functioneel en psychosociaal, met als doel het formuleren van een multidisciplinair behandelplan. **Deel II** van dit proefschrift richt zich op de rol van het geriatrisch assessment in longkankerzorg voor de oudere patiënt.

In **hoofdstuk 5** hebben we resultaten beschreven van de systematische review naar de relevantie van een geriatrisch assessment bij ouderen patiënten met longkanker. Onze review van totaal 23 publicaties uit 18 studies liet zien dat een geriatrisch assessment multipele gezondheidsproblemen kan identificeren, die niet worden weerspiegeld in de ECOG performance score. Daarnaast hadden aangedane geriatrische domeinen, met name objectieve fysieke capaciteit en voedingsstatus, een voorspellende waarde voor mortaliteit en bleken tevens geassocieerd met de kans op het afronden van de behandeling. Helaas wordt het geriatrisch assessment in de klinische praktijk nog maar beperkt toegepast.

In twee opleidingsziekenhuizen in Nederland, het Diakonessenhuis Utrecht en het Hagaziekenhuis in Den Haag, is het geriatrische assessment sinds 2014 opgenomen in de zorg voor oudere patiënten met longkanker. Resultaten hiervan zijn beschreven in **hoofdstuk 6**. Bij de analyse van het effect van een geriatrisch assessment bij 83 patiënten met longkanker, zagen we dat een geriatrisch assessment in staat is om nog onbekende gezondheidsgebreken te detecteren en belangrijke informatie oplevert om richting te geven aan de besluitvorming over start van behandeling. In onze studie had de meerderheid van de patiënten (78%) een of meerdere geriatrische problemen en had 43% meer dan 3 aangedane geriatrische domeinen (van de 8 beoordeelde domeinen). Hiervan was voedingsstatus het meest aangedane geriatrische domein. Nog niet-gediagnosticeerde problemen kwamen aan het licht bij 58% van de patiënten en voor 43% van de patiënten van de totale groep werden niet-oncologische interventies geadviseerd. Voor 33% van de patiënten werd een suggestie gedaan om de oncologische behandeling te veranderen, in alle gevallen nam de longarts dit advies over. Een minder intensieve behandeling werd vaker aanbevolen naarmate er meer geriatrische problemen waren.

Vanwege tijds- en arbeidsintensieve aspecten van het geriatrisch assessment zijn oncologen opzoek gegaan naar een kortere screeningstool om onderscheid te kunnen maken tussen fitte en kwetsbare patiënten. Twee voorgestelde instrumenten hiervoor zijn de Geriatric 8 (G8) en Identification of Seniors at Risk for Hospitalized Patients (ISAR-HP). De G8 was specifiek ontworpen voor oudere patiënten met kanker, hierbij is veel aandacht voor voedingsstatus (46% van de totaal score), maar wordt er ook gekeken naar mobi-

liteit, neuropsychologische problemen, medicatiegebruik, een eigen beoordeling van de gezondheid en leeftijd. De ISAR-HP was initieel ontworpen voor de spoedeisende hulp en later aangepast voor patiënten opgenomen in het ziekenhuis. ISAR-HP is een vragenlijst bestaande uit vier items die bewezen effectief is in het identificeren van patiënten die risico lopen op functionele achteruitgang na een ziekenhuisopname. Deze beide instrumenten, G8 en ISAR-HP is geanalyseerd in 142 patiënten met longkanker en resultaten hiervan zijn beschreven in **hoofdstuk 7**. Op basis van deze analyses kunnen wij concluderen dat G8 en ISAR-HP bruikbare screeningstools zijn in het onderscheiden van fitte en mogelijk kwetsbare ouderen patiënten met longkanker. Mogelijk kwetsbare patiënten, met een G8 score van ≤14 of ISAR-HP≥2, hebben een significant hoger risico om binnen een jaar te overlijden in vergelijking met fitte patiënten, die een normale score hebben op beide screeningsinstrumenten. Als we beide screeningsinstrumenten apart analyseerden, bleek dat G8 onafhankelijk was geassocieerd met éénjaarsoverleving en ISAR-HP niet. Echter, het toevoegen van ISAR-HP aan screening met G8 leidde tot selectie van patiënten met een groter aantal geriatrische problemen.

Het doel van **hoofdstuk 8** was het analyseren van hoe ouderen patiënten met longkanker op dit moment worden geëvalueerd voor de start van een oncologische behandeling, en te exploreren welke potentiele obstakels er zijn voor het routinematig opnemen van een geriatrisch assessment in het diagnostisch proces. Er bleek bij de Nederlandse longartsen met oncologie als aandachtsgebied duidelijk interesse te zijn voor het routinematig opnemen van een geriatrische evaluatie in de zorg voor oudere patiënten met longkanker. Echter, op dit moment is er nog geen duidelijk format over hoe deze geriatrische evaluatie er uit zou moeten zien en wie dit zou moeten uitvoeren. Er is geen consensus over het optimale design in termen van patiëntselectie, timing, gebruik van screeningsinstrumenten en nodige acties die moeten volgen op een assessment. Een betere samenwerking tussen geriaters en (longarts)oncologen kan helpen om de behandeling van oudere patiënten met longkanker te optimaliseren.

In **Deel III** van dit proefschrift wordt aandacht besteed aan het gebruik van patiënt gerapporteerde uitkomstmaten (PROMs) in wetenschappelijk onderzoek en klinische praktijk van maligniteiten met een slechte prognose, waaronder longkanker. Met name in een palliatieve behandelsetting worden andere factoren dan overleving of toxiciteit steeds belangrijker. Kwaliteit van leven, algemeen functioneren, behoud van zelfredzaamheid en gebruik van gezondheidszorg kunnen op een dergelijk moment veel belangrijker zijn. Verschillende organisaties, zoals de Federal Drug Administration (FDA) en European Organization for Research and Treatment of Cancer (EORTC) hebben opdracht gegeven om PROMs op te nemen als uitkomstmaten in alle nieuwe onderzoeksvoorstellen, met name wanneer het gaat om aandoeningen met een slechte prognose.

In **hoofdstuk 9** staan de resultaten beschreven van de analyse naar gebruikte uitkomstmaten in huidige studies naar longkanker, geregistreerd in het National Institutes of Health (NIH) trial register. De meest gebruikte uitkomstmaten waren toxiciteit (78%) en progressievrije overleving (76%). PROMs werden in het merendeel van de studies niet geanalyseerd: van de 419 geanalyseerde trials werden uitkomstmaten als kwaliteit van leven, functionele capaciteit en gebruik van gezondheidszorg slechts in respectievelijk 20%, 4% en 2% meegenomen.

In **hoofdstuk 10** hebben we gekeken in het NIH trialregister of PROMs werden meegenomen als uitkomstmaten in phase III klinische studies bij maligniteiten met een slechte prognose en in welke mate deze data uiteindelijk werden gepubliceerd. Van de 201 studies naar maligniteiten met een slechte prognose werd in 57% van de studies kwaliteit van leven niet meegenomen als uitkomstmaat en van de resterende studies werd in 50% in het uiteindelijke artikel kwaliteit van leven niet genoemd of slechts beschreven in een enkele zin.

Als we kijken naar de problemen die we tegenkomen bij patiënten die doodgaan aan kanker zijn er veel overeenkomsten tussen de diverse type maligniteiten. In **hoofdstuk 11** hebben we verschillende aspecten onderzocht die mogelijke betrekking hebben op slechte kwaliteit van leven in de laatste drie maanden van het leven bij patiënten die palliatief chemotherapie ontvingen. Hierbij hebben we gekeken naar gebruik van chemotherapie in de laatste 3 maanden, ongeplande ziekenhuisopnames en plaats van overlijden. Uit onze analyse bleek dat de helft van de 604 geanalyseerde patiënten palliatieve chemotherapie had gekregen in de laatste 3 maanden van hun leven. Gebruik van gezondheidszorg in de laatste 3 maanden was hoog voor alle patiënten, maar significant hoger voor die patiënten die de palliatieve chemotherapie ook in de laatst 3 maanden van hun leven hadden gekregen. Om in staat te zijn om onze patiënten in de toekomst ook informatie te kunnen geven over deze aspecten van behandeling is het van belang dat deze items worden meegenomen in wetenschappelijk onderzoek, daardoor hebben we mogelijk een ingang om zowel de kwaliteit van leven als de kwaliteit van sterven te optimaliseren bij patiënten met kanker.

In **hoofdstuk 12** zijn de belangrijkste bevindingen van het gedane onderzoek bediscussieerd en toekomstvisies over de zorg van oudere patiënten met longkanker, en andere maligniteiten met een slechte prognose, besproken.

Concluderend, besluitvorming bij oudere patiënten met longkanker is complex en blijft een uitdaging. Wij hebben kunnen concluderen dat behandeling van longkanker niet uniform is en dat geselecteerde oudere patiënten met longkanker een vergelijkbaar voor-

deel kunnen ondervinden van therapie als jongere patiënten. Bovendien, hebben wij een tweetraps geriatrisch model voorgesteld ter implementatie in de richtlijn voor alle oudere patiënten met longkanker. Daarnaast hebben wij beschreven dat patiënt gerapporteerde uitkomstmaten (PROMs) op dit moment nog te weinig worden gebruikt in onderzoek en klinische praktijk. Dit moet veranderen om in de toekomst onze patiënten beter te kunnen informeren en zodoende de besluitvorming bij ouderen patiënten met longkanker en andere maligniteiten met een slechte prognose te verbeteren.

APPENDICES

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List of publications
Acknowledgments in Dutch – Dankwoord
Curriculum Vitae in Dutch

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Chapter in book

Compendium 'Behandeling van kanker bij ouderen' by dr. M.E. Hamaker and prof. dr. J.E.A. Portielje,
Chapter 'Longkanker bij ouderen' - **Karlijn Schulkes,** Leontine van Elden
Publisher: Academic Pharmaceutical Productions

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CURRICULUM VITAE

Karlijn Schulkes werd op 6 augustus 1988 geboren in Geldrop, zij groeide op in het Brabantse Asten waar zij in 2006 haar atheneumdiploma behaalde aan het Varendonck College. Eveneens in 2006 verhuisde zij naar Utrecht om met de studie Geneeskunde te beginnen aan de Universiteit Utrecht. In het vierde jaar van haar opleiding werd de interesse voor wetenschap gewekt op de afdeling allergologie van het UMC Utrecht, alwaar zij meerdere wetenschappelijke keuzestages heeft gedaan (begeleiding dr. A.C. Knulst). Tijdens haar semi-arts stage op de afdeling longziekten en tuberculose van het Diakonessenhuis Utrecht (begeleiding dr. A. Bossink en dr. R. Van Snippenburg) raakte zij meer en meer geïnteresseerd in de longziekten. Na het behalen van haar artsenbul in 2012, ging Karlijn aan de slag als arts-assistent niet in opleiding (ANIOS) interne geneeskunde in het Diakonessenhuis Utrecht (begeleiding dr. A. Muller), na korte tijd kwam zij erachter dat haar passie meer bij de longziekten lag en is zij in het UMC Utrecht als ANIOS longziekten aan de slag gegaan. In de tijd als ANIOS in het Diakonessenhuis was zij al begonnen met het doen van onderzoek binnen de geriatrische oncologie met dr. Hamaker, maar dit kwam weer op een lager pitje te staan door de werkzaamheden in het UMC Utrecht. Na een korte periode te hebben gewerkt als ANIOS longziekten solliciteerde zij met succes voor de opleiding tot longarts. Per januari 2014 startte zij met het deel interne geneeskunde van de opleiding tot longarts, opnieuw in het Diakonessenhuis onder supervisie van dr. A. Muller en dr. T. Tobé. In deze periode was zij wederom door Marije Hamaker geënthousiasmeerd voor onderzoek naar (long)kanker bij ouderen. Hiervoor kreeg zij de Aart Huisman Beurs, die projecten ondersteunt ter verbetering van de geriatrisch oncologische zorg. Per januari 2016 heeft zij haar opleiding onderbroken om fulltime onderzoek te doen. Vanaf januari 2017 is zij weer in het UMC Utrecht aan het werk omdat zij haar opleiding tot longarts (opleider dr. R. Schweizer) weer heeft hervat. Karlijn is in 2016 getrouwd met Erik Kleemans, samen wonen zij in Utrecht.