Lung Cancer in the Oldest Old

Lung (2017) 195:627–634
DOI 10.1007/s00408-017-0026-1

Lung Cancer in the Oldest Old: A Nation-Wide Study in The Netherlands

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Received: 20 March 2017 / Accepted: 12 June 2017 / Published online: 19 June 2017

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. 2196 (5%) patients were aged ≥85 years. 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.

Keywords Frail · Geriatric · IKNL · NCR · NKR · Pulmonary malignancies

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Abbreviations

NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
IKNL	Integraal Kankercentrum Nederland
NCR	Netherlands Cancer Registry

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 aging 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 nation-wide 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 nation-wide 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 Table 2 in 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, guidelines 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 1, 2, and 3 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 χ^2 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 2196 (5%) patients, 18,686 (39%) were aged between 71 and 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.

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 diagnosis was obtained in 38% of patients, versus 14% in the elderly and 5% in the younger group ($p < 0.001$). Of the 2196 oldest old, 1197 (55%) patients were diagnosed with NSCLC and 168 (8%) with SCLC.

Tumor staging was also significantly more often incomplete in the oldest old (Fig. 1): 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 (4608 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; 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 1 year was 23% in the oldest old, 35% in the elderly, and 45% in the younger patients ($p < 0.001$). Survival after 2 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 2-year survival analyses of the oldest old with NSCLC according to treatment strategy and tumor stage are visualized in Fig. 2a, b, respectively. 1-year survival in the oldest old with stage I NSCLC receiving standard treatment was 76% (13/17) compared to 95% (2509/2655) 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%, 1175/1321; $p = 0.2$). 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 1 year, and 4 out of 9 (44%) were alive after 2 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, 1-year survival with standard treatment was 46% (23 out of 50), compared to 36% (770 out of 2131) for the elderly and 36% (2372 out of 6680) for the younger patients ($p = 0.35$).

As visualized in Fig. 2a, b, 1- and 2-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 3 years, 47% of patients (8

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%)	2196	(5%)	
Sex							
Male, *n* (%)	14,716	(54%)	12,569	(67%)	1461	(67%)	<0.001
Age							
Median (IQR)	62	(57–66)	76	(73–80)	87	(86–88)	
Diagnosis, *n* (%)							
NSCLC	21,567	(80%)	13,556	(73%)	1197	(55%)	<0.001
SCLC	4250	(16%)	2605	(14%)	168	(8%)	
No histological diagnosis	1252	(5%)	2525	(14%)	831	(38%)	
Disease stage, *n* (%)							
I	3660	(14%)	2782	(15%)	205	(9%)	<0.001
II	1975	(7%)	1451	(8%)	149	(7%)	
III	6719	(25%)	4251	(23%)	404	(18%)	
IV	13,927	(51%)	8614	(46%)	957	(44%)	
Unknown	788	(3%)	1588	(9%)	481	(22%)	
Treatment for NSCLC and SCLC[a], n (%)							
Standard treatment	17,041	(66%)	6283	(39%)	105	(8%)	<0.001
Adjusted treatment	3617	(14%)	3710	(23%)	348	(25%)	<0.001
Best supportive care only	5141	(20%)	6155	(38%)	912	(67%)	<0.001

IQR interquartile ranges, *(N)SCLC* (non)small cell lung cancer

[a] Patients with no histological diagnosis were excluded from analyses

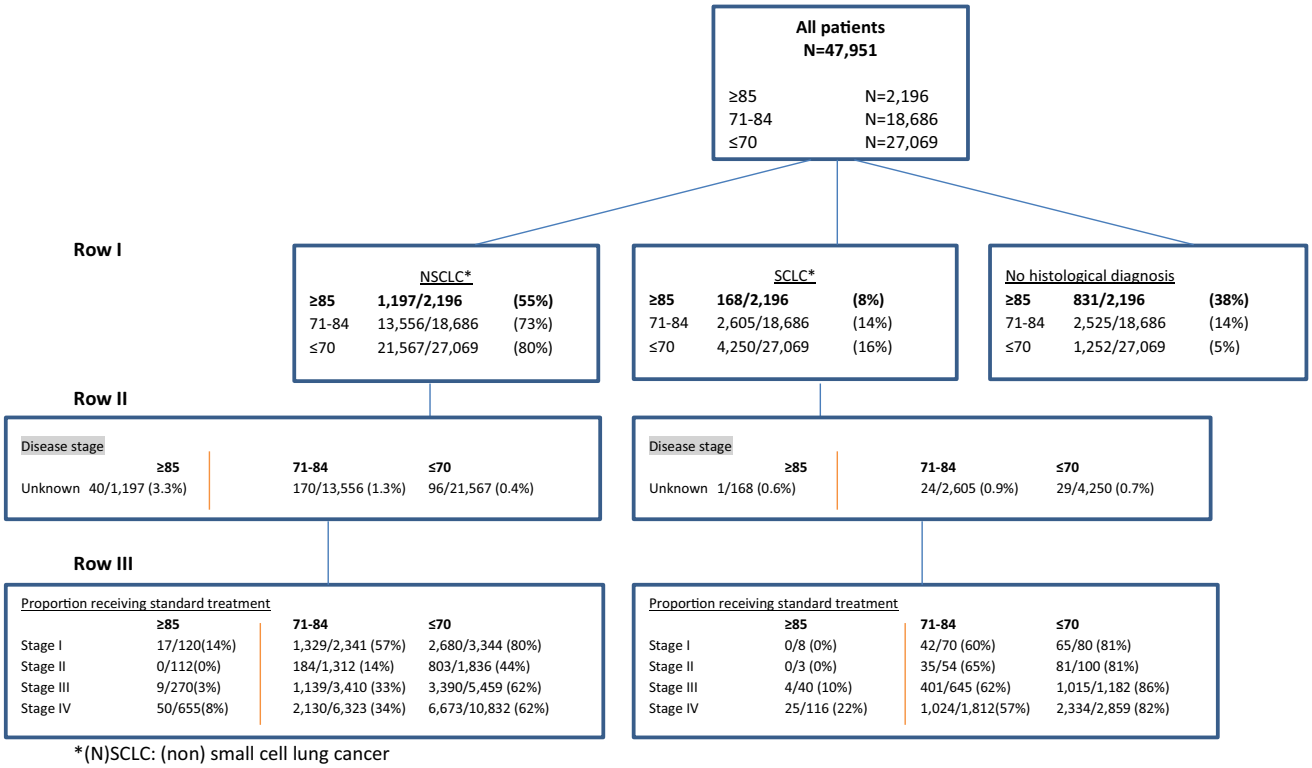

Fig. 1 Flowchart diagnostic work-up and treatment choice. *Percentages* in *Row I* represent the proportion of patients within each age group with that particular diagnosis. In *Row II*, *percentages* represent the proportion of patients with particular diagnosis per age group with unknown stage of disease. *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

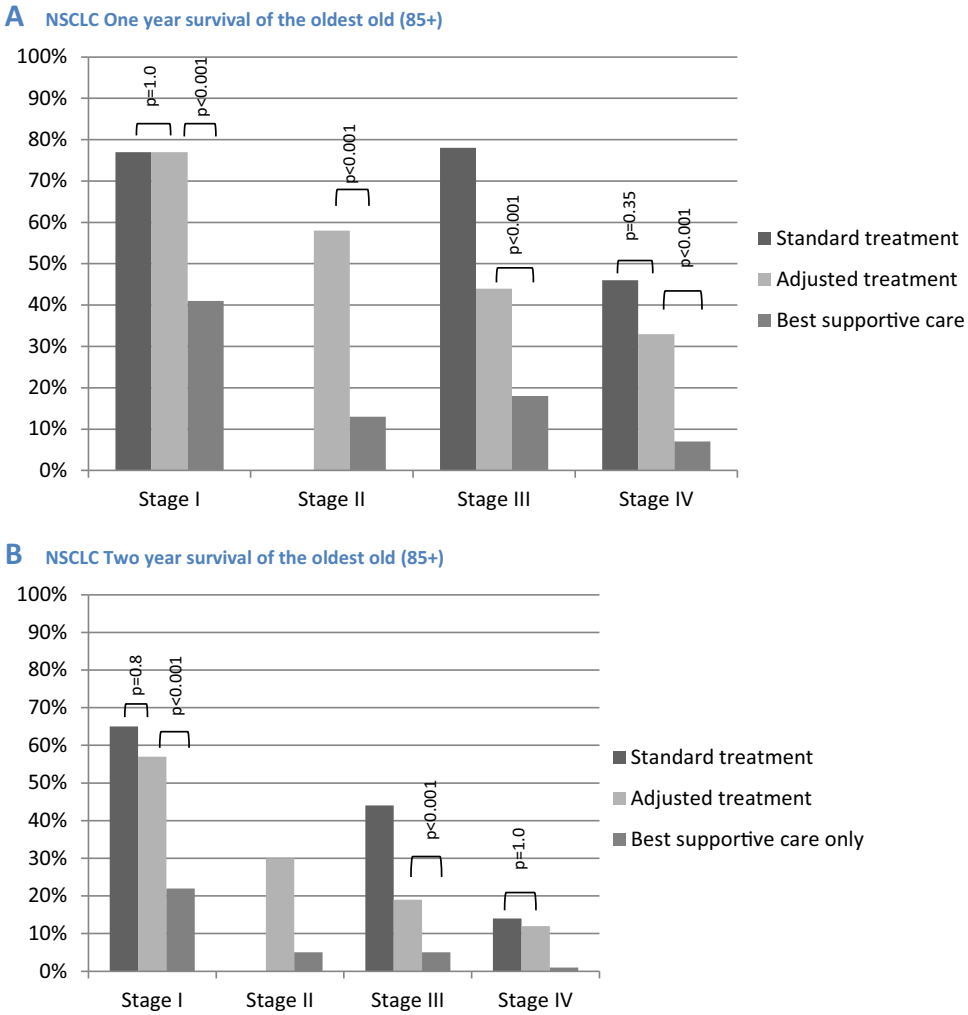

Fig. 2 **a** 1-year survival of patients with NSCLC older than 85 years according to treatment. **b** 2-year survival of patients with NSCLC older than 85 years according to treatment

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 (2-year survival 14 and 12%, respectively; $p = 1.0$). No significant differences could be found after 3 years either (4 and 2%, $p = 0.6$). Due to limited 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 (Fig. 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, 1-year survival was 9% (15 out of 168) in the oldest old, 21% (545 out of 2605) in the elderly, and 40% (1703 out of 4249) for younger patients ($p < 0.001$).

Discussion

In this study, using the 2010–2014 Netherlands Cancer Registry (NCR) database, a total of 2196 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 2-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 the 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 anti-cancer therapy (be it standard treatment or an adjusted regimen), survival rates were comparable to those in patients aged 71–84 years demonstrating that the 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, physiological reserves, and frailty [5, 24]. 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 [5, 6, 14, 15, 25–27]. 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, [25] 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, 25]. 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 [28].

Another area for improvement would be the incorporation of patient-reported outcome measures (PROMs) in clinical research [29, 30]. 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 [31, 32]. 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, 29, 30, 33]. At the moment, PROMs are incorporated only in a minority of clinical trials [32], 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 [34–36]. 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 2000 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.

Acknowledgements The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data for the Netherlands Cancer Registry as well as IKNL staff for scientific advice.

Financial Support This study was supported by the Aart Huisman Scholarship for research in geriatric oncology and the Cornelis Visser Foundation.

Compliance with Ethical Standards

Conflict of interest No potential conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Appendix

See Table 2.

Table 2 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[a]
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 resection with adjuvant therapy is stated to be considered
Stage IV	Palliative chemotherapy[b]
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

[a] Guideline is ambivalent according treatment with adjuvant chemotherapy in stage IB

[b] Targeted therapy with tyrosine kinase inhibitor if mutation in EGFR or ALK is found

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