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Differences in lung cancer care and related triggers - evidence from German claims data

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Julia Walter

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Mitberichterstatter:	Prof. Dr. Peter C. Scriba
	PD Dr. Gerhard Preissler
Mitbetreuung durch den promovierten Mitarbeiter:	PD Dr. Larissa Schwarzkopf
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List of abbreviations

WIdO	Wissenschaftliches Institut der AOK
SHI	statutory health insurance
SCLC	small cell lung cancer
NSCLC	non-small cell lung cancer
UICC	Union for Cancer Control
HSR	health services research
LASSO	least absolute shrinkage and selection operator

List of publications included in this thesis

Walter J, Tufman A, Leidl R, Holle R, Schwarzkopf L: Rural versus urban differences in end-of-life care for lung cancer patients in Germany. Supportive Care in Cancer (2018) 26: 2275. https://doi.org/10.1007/s00520-018-4063-y

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Zusammenfassung

Lungenkrebs trägt einen großen Anteil an der weltweiten Krankheitslast und gehört zu den häufigsten krankheitsbedingten Todesursachen. Die Erkrankung tritt in unterschiedlichen Histologien auf, welche unterschiedliche Prognosen und Therapieoptionen implizieren. Bei der Mehrheit der Patienten wird der Lungenkrebs erst in einem späten Stadium festgestellt, das mediane Erkrankungsalter liegt bei ca. 70 Jahren. Im frühen Stadium bestehen bei Durchführung einer Operation gute Heilungschancen. Im fortgeschrittenen Stadium ist meist nur eine Chemotherapie, oft kombiniert mit einer Bestrahlung und eher palliativem Ansatz, möglich. Aufgrund der hohen Mortalität der Erkrankung spielt die terminale Phase eine große Rolle, hier liegt der Fokus auf der Beibehaltung der Lebensqualität und der Sterbebegleitung. Vor diesem Hintergrund zielt der im Jahr 2008 ins Leben gerufene Nationale Krebsplan darauf ab, allen Krebspatienten in Deutschland, unabhängig von ihrem Geschlecht, Alter, Wohnort oder anderen Gegebenheiten, denselben Zugang zu effektiver, standardmäßiger aber auch innovativer, Krebstherapie zu ermöglichen.

Ziel dieser Arbeit ist es, anhand von Krankenkassendaten die aktuelle Versorgungssituation von Lungenkrebspatienten in Deutschland abzubilden und im Einklang mit den Zielen des Nationalen Krebsplanes, möglicherweise vorhandene Versorgungsunterschiede aufzudecken und benachteiligte Patientengruppen zu identifizieren. Hierzu wird eine Kohorte von ca. 17.500 Lungenkrebspatienten (diagnostiziert in 2009) aus Daten des Wissenschaftlichen Institut der AOK (WIdO), identifiziert. Diese Patienten werden bezüglich verschiedener Versorgungssituationen und in unterschiedlichen Patientengruppen deskriptiv und unter der Zuhilfenahme multivariabler Analysemethoden miteinander verglichen.

Die Untersuchungen zeigen, dass anders als bei der Ausgestaltung der Krebstherapie an sich, die Betreuung in der letzten Lebensphase unabhängig von einem eher städtischen oder eher ländlichen Wohnort ist. Faktoren die einen Einfluss auf die Leistungsinanspruchnahme am Lebensende haben, hängen meist mit

einer vorherigen Tumorbehandlung, Komorbiditäten und dem Alter der Patienten zusammen. Das Geschlecht und das Tumorstadium haben einen signifikanten Einfluss auf die unterstützende Behandlung in der Lebensendphase.

Die Ergebnisse dieser Untersuchung zeigen auch, dass ein Großteil der Lungenkrebspatienten in Deutschland im Krankenhaus verstirbt. Faktoren, die mit einem vorherigen Krankenhausaufenthalt bzw. einer vorherigen Behandlung im Krankenhaus und Komorbiditäten zusammenhängen, erhöhen die Wahrscheinlichkeit im Krankenhaus zu versterben. Wird ein Patient hingegen frühzeitig ambulant palliativ betreut, ist die Wahrscheinlichkeit im Krankenhaus zu versterben geringer. Zu bedenken ist hierbei, dass ein Versterben im Krankenhaus mit signifikant höheren Ausgaben für das Krankenversicherungssystem verbunden ist.

Die Mehrheit der Lungenkrebspatienten wird erst im Alter von über 65 Jahren diagnostiziert und unsere vorherigen Untersuchungen zeigen, dass das Alter auch einen Einfluss auf die Behandlung zum Lebensende hat. Eine weitere Untersuchung zeigt, dass sich sowohl in der Behandlung des Tumors selbst, als auch in der Schmerztherapie und der Gabe von Antidepressiva ein signifikanter altersabhängiger Unterschied zulasten der älteren Patienten ergibt.

Zusammenfassend unterstreicht die vorliegende Arbeit die Wichtigkeit des nationalen Krebsplanes und die hiermit in Verbindung stehende Notwendigkeit zur Verbesserung der Lungenkrebsversorgung. Zudem werden ältere Patienten als eine wichtige Personengruppe herausgestellt, die einerseits besonders stark von der Erkrankung betroffen ist und andererseits nicht immer ausreichend versorgt wird. In diesem Zusammenhang ist eine weitere wichtige Implikation dieser Arbeit, dass die frühzeitige und stärkere Einbindung der Palliativmedizin in die Lungenkrebsbehandlung ein wichtiger Ansatz für eine effiziente, gleichmäßige und gerechte Versorgung ist.

Summary

Lung cancer is a leading cause for morbidity and mortality worldwide. It presents in different histologies with differing prognosis and treatment options. A majority of lung cancer patients is diagnosed in an advanced stage and at a median age of around 70 years. The treatment option for early stage patients is lung cancer resection with curative intent. Patients with advanced stage are mostly treated with chemotherapy, often alongside radiotherapy, mostly focused on prolonging life and relief of symptoms. As mortality in lung cancer patients is high, the terminal phase is of great importance. The primary aim of therapy in this phase is maintaining quality of life and providing support in the last days of life. Therefore, in 2008 the national cancer plan was introduced in order to set goals for cancer care in Germany. The main fields of action in the national cancer plan are to provide effective and innovative, state-of-the art cancer care for all cancer patients in Germany, irrespective of age, gender, residence area and other basic characteristics.

The aim of this thesis is to assess lung cancer care in Germany using real world evidence from claims data. In particular, in line with the goals set in the national cancer plan, the aim is to identify possible inequity in cancer care or vulnerable patient groups. Using claims of around 17500 lung cancer patients (diagnosed in 2009) provided by WIdO the scientific institute of the AOK statutory health insurance (SHI) funds, in this thesis these patients are analyze in different healthcare settings and comparisons of healthcare provision in different patient groups are made, using descriptive and multivariable analysis methods.

The analyses show that, other than general cancer care, end-of-life care does not differ depending on the place of residence of the patient. Factors that do influence end-of- life care are aspects relating to prior anticancer treatment, comorbidities, and age. In addition, gender and stage of the disease at the time of diagnosis are significantly associated with supportive care in the terminal phase.

The results show that a large proportion of lung cancer patients die in a hospital setting. Factors that are associated with inpatient death mostly relate to prior contacts with the hospitals like prior hospitalizations

and treatment of the tumor or comorbidities. Factors that lower the likelihood of inpatient death relate to access to care settings, which are more focused on palliation than hospitals. Expenses for the health insurance fund are significantly higher for patients with inpatient death.

Age plays an important role in lung cancer as a majority of patients is diagnosed when they are 65 years and older. Additionally, age was identified as an important factor for end-of-life care. Therefore, it was assessed whether there are inequities in lung cancer care between younger and elderly patients. The results suggest that there is an age-dependent disparity in the frequency of anti-tumor treatment and in supportive care provided to young and elderly patients.

This thesis highlights the importance of the national cancer plans and efforts to improve lung cancer care in Germany. Additionally, it identifies elderly patients as a patient group that on the one hand is most vulnerable to the disease and, for whom on the other hand therapy not always fits their needs. In line with that, the thesis suggests that a bigger focus on, and an earlier integration of palliative care could be a crucial step to provide more equity in lung cancer care.

Chapter 1 General introduction

1.1. Epidemiology and Etiology

Across all types of cancer, in 2014, lung cancer had the second highest incidence in men and the third highest incidence in women in Germany [1]. Incidence rates in 2014 ranged from 57.2 per 100,000 in men and 28.9 per 100,000 in women [2]. Although incidence rates are stable in men and are even expected to decrease in the coming years, numbers in females are still on the rise [1]. Further, lung cancer was the fourth leading cause of death in Germany in 2015 [3], it accounted for the highest proportion of cancer-related deaths in total and in men, and the second highest in women [3]. Relative 5-year survival rates are around 16 to 21 % in males and females [4]. Lung cancer mostly develops at a higher age, with median age at diagnosis ranging between 68 and 70 years in developed countries [1, 5, 6].

The main risk factor for lung cancer is smoking. In men, 9 out of 10 lung cancer cases, and in women at least 6 out of 10 lung cancer cases are attributable to active smoking [1]. Passive smoking also increases the risk. There are two main types of lung cancer, small cell lung cancer (SCLC) which makes up around 10% to 15% of all lung cancers, and non-small lung cancers (NSCLC) which makes up around 80% to 85% [7]. NSCLC presents in several subtypes. Adenocarcinomas represent around 40% of all lung cancer cases, squamous cell carcinoma around 25% to 30%, and large cell carcinomas about 10% to 15% [7]. In NSCLC, staging according to the Union for Cancer Control (UICC) criteria includes stages 0, and I to IV, with substages Ia, Ib, II2, IIb, IIIa, IIIb, IIIc, and IVa and IVb [8]. Although the UICC criteria are also used in SCLC, a more commonly used definition is the Veterans Administration classification system [9], classifying the cancer by very limited, limited, and extensive disease. A study conducted across several European countries and Canada found that almost 70% of patients with SCLC are diagnosed with extensive disease [10]. In NSCLC the proportion diagnosed with advanced disease is around 50% [10] . According to data of cancer registries across Germany, in 2011 13% of lung cancer (SCLC and NSCLC) patients were diagnosed in stage

I, 8% in stage II, 23% in stage III and 55% of patients was diagnosed in stage IV [11]. The delay in diagnosis can in part be explained by a low and unspecific symptom load in the beginning of the disease [12]. It is also a major reason for the low 5-year survival rates, as potentially curative therapy options are often only available for early stage disease [8].

1.2. Treatment

Treatment options in lung cancer are highly dependent on the stage and the type of cancer. Additionally, the general condition of the patient including comorbidities are relevant factors in treatment decisions. A higher age alone should not be the sole reason to not pursue one of the treatments [8]. Therapies include surgical resection of the tumor, radiotherapy, cytostatic chemotherapy, and therapy with targeted agents, monoclonal antibodies and immunotherapy. In SCLC, tumor resection is often not indicated, as this type of cancer is generally fast growing and a complete resection is mostly not possible. Therefore, patients suffering from SCLC are mainly treated with chemotherapy [8]. In early stages of NSCLC when the tumor sizes are still small and the cancer has not spread to other parts of the body (mainly stages I, II, and IIIa), a resection of the tumor is the treatment of choice [8]. If a surgical resection of the tumor is possible, the most common approach is a lobectomy [13], which means that one or more lobes of the lung are resected. Lobectomy can be performed either thoracoscopic or as thoracotomy. Studies have shown that thoracoscopic lobectomy is associated with less postoperative pain, fewer complications, less surgical morbidity and equal or better long-term survival than thoracotomy [14-18]. Additionally, our own research showed that 3-year lung cancer-specific costs are significantly lower for thoracoscopic compared to open lobectomy from the perspective of German statutory health insurance (SHI) funds [19]. As a large part of lung cancer patients are not eligible for a resection, chemotherapy plays a major role in treatment. But also in patients with NSCLC who have undergone a resection of the tumor, often adjuvant chemotherapy is administered, sometimes accompanied by radiotherapy [8]. For all patients with non-resectable tumors

chemotherapy, often in combination with radiotherapy, is used for treatment. After years without a major breakthrough in therapy, treatment strategies with targeted therapies and immunotherapy have been recently approved in the treatment of NSCLC. Some of the targeted agents show promising results in second-line, third-line, and even in first-line therapy in patients with advanced stage NSCLC. These agents have shown to significantly improve progression free survival [20-28], cause less toxicity [23, 25-27], and show better quality-of-life [20-22, 28] compared to cytostatic chemotherapy. However, targeted agents are most effective in patients with certain mutations so-called driver mutations, and only around 13-40% of NSCLC patients have driver mutations for which a drug has already been approved [29, 30]. Regarding immune therapy, according to a recent study from the USA around 21.5% of patients with NSCLC could be eligible for therapy with immune checkpoint-inhibitors [31], which have shown survival benefits compared to cytostatic chemotherapy in several randomized controlled trials [32].

1.3. Treatment intent and treatment phases

In general, lung cancer is defined by different disease phases with differing treatment intents. In the beginning, the intent of therapy is to cure the patient of the disease. This phase is characterized by patients with very limited and limited disease in SCLC, and stages I, II, and IIIa, in NSCLC. In this phase, if possible, surgical resection is performed with curative intent. In SCLC 3-year survival rates in resected patients range from 50-70% in stage I N0 to 30-40% in stage II N1 and 20% in stage II N2 [8, 33]. In NSCLC 5-year survival for resected patients is 69% to 89% in stage Ia [34], 52% to 75% in stage Ib [35], 45% [34] to 52% [35] in stage IIa, 33% in stage IIb [34] and 24% [34] to 44% [35] in stage IIIa. When a curative surgical resection is not indicated, therapy intent in both SCLC and NSCLC is palliative and defined by the goal to prolong survival and relieve symptoms (stage IIIb and IV). Compared to best supportive care alone, classical chemotherapy alongside best supportive care results in a 9% higher 1-year survival [36]. When a targeted therapy or immune therapy is indicated and prescribed, this can result in significantly lower hazard ratios regarding

progression free survival compared to classical chemotherapy [20-28]. Symptom relief in this phase of the disease mainly refers to relief of dyspnea and pain, but also psycho-oncological aspect should be addressed [8]. The terminal phase, which is closely linked with the second phase, is characterized by a focus on maintaining quality of life and providing end-of-life [8]. According to treatment guidelines in this phase only measures that relate to symptom control should be applied [8].Quality measures of end-of-life include place of death (inpatient death unfavorable) and hospitalizations close to death, but also late onset of palliative care and chemotherapy closely before death [37-39]. In general, studies show that an early integration of palliative care into routine care can prolong life while maintaining a good quality of life [40-42].

1.4. Lung cancer care in Germany

To ensure adequate provision of cancer care in Germany as described above, in 2008 the German government defined goals concerning cancer care in the national cancer plan (Nationaler Krebsplan). The national cancer plan includes four key fields of action including several sub goals. The first field of action relates to cancer prevention, the second involves further development of structures in oncological health care, the third ensures provision of efficient oncological treatment, and the fourth has an emphasis on strengthening patient orientation. Prevention of lung cancer involves on the one hand initiatives to strengthen tobacco control, campaigns to stop smoking or prevent people to start smoking, as well as introducing non-smoking. On the other hand, it involves programs for lung cancer screening. So far, there is no population based screening program in Germany, however the guideline allows yearly low-dose CT scans for asymptomatic patients at risk [8]. The first goal of field of action number two is to have all cancer patients receive high quality care, notwithstanding their age, gender, origin, place of residence or insurance status. In line with this, a process of certifying hospital as cancer centers was introduced. These centers have to fulfill several criteria in order to receive accreditation as certified centers and have to maintain

these standards over time. Until the end of 2017, there were 49 certified lung cancer centers in Germany. The main aim in field of action three is to ensure that all patients have a fair and fast access to innovative and efficient cancer therapies. This includes a quick translation of results from basic research to real world treatment of patients. Patient orientation can be strengthened by offering comprehensive and easily accessible information to patients and their relatives. Additionally, communication skills of all service providers involved should be trained regularly, and patients should be included actively in treatment decisions.

1.5. Health Services Research and claims data

According to the German Centers for Health Research, health services research (HSR) represents the fourth pillar of health research besides basic research, pre-clinical research and clinical research [43]. It investigates how basic and clinical research is translated into routine care and how policy changes like the introduction of the national cancer plan affect everyday medical care. In line with the goals of the national cancer plan, additionally, it aims at detecting over- and underprovision of care. Data used in this kind of research mainly comes from physician records, hospital records, and claims of SHI funds.

Claims data, also called administrative data or secondary data, refer to data that is collected routinely by service providers and SHI funds mainly for the purpose of reimbursement. Analyses involving claims data often focus on access to healthcare e.g. disparities in treatment [44], quality of healthcare [44], but also the evaluation of interventions and policy changes [45].

A major challenge when analyzing claims data relates to the lack of clinical information, as information in claims data are restricted to the needs of reimbursement. For example, in lung cancer claims data does not provide direct information about the histology of the cancer or the stage of the cancer at the time of diagnosis. This information can only be derived indirectly by using diagnoses of metastases or procedural codes for therapies. Another weakness of claims data refers to underreporting and incorrect data. If a

specific test or diagnostic code is not relevant for reimbursement purposes it is less likely to be reported. Further, data can be entered incorrect e.g. by the administrative clerk.

Although there are some challenges to using claims data, they are a powerful tool to generate real world evidence in medical science. One major advantage of claims data is the aspect of external validity [46]. In Germany, around 86% of the population is insured through a SHI fund. Law regulates insurance contributions and healthcare services covered by the SHI and patient clientele differs only slightly between different SHI funds [47]. Therefore, analyzing German SHI claims can provide a comprehensive overview of nationwide routine healthcare practices and results can be generalized to the whole population. Additionally, compared to clinical trials these data help to study groups that are generally more difficult to observe because they are often not included in clinical trials, like children or elderly patients [48]. Therefore, it is possible to analyze if evidence from clinical trials and health policies are implemented in the broad population and whether there are disparities between patient groups regarding if and how this evidence and policies are administered. Furthermore, sample sizes in claims data analyses are typically large therefore, rare diseases, rare complications, and rare outcomes can be studied appropriately.

The dataset used in the analyses of the three papers included in this thesis contained anonymized health insurance claims for 17478 patients diagnosed with lung cancer in 2009. The dataset was provided by WIdO, the scientific institute of the AOK SHI funds, which covers around 30% of the German resident population. Basic data contained month and year of birth, month and year of death (if applicable), sex, and care level as well as nursing home residence status over the course of the disease. Additionally, it included claims for hospitalizations, outpatient hospital visits, outpatient physician visits, and medications.

1.6. Objectives, and contents of this dissertation

The main objective of this dissertation is to study lung cancer care in Germany using claims data. In particular, relating to the goals in fields of action two defined in the national cancer plan, the thesis aims

to detect possible differences in lung cancer care between geographical regions and across patient populations with different characteristics. In consequence, the information gathered in this thesis can be used to identify aspects of care that need improvement and patient groups that are more vulnerable, or until now, do not get the best care to fit their needs.

Article 1 aims at detecting differences relating to geographical residence (rural or urban) in end-of-life care in lung cancer patients. As laid out in chapter 1.1, mortality rates in lung cancer are high, therefore the end-of-life phase is a phase that affects most patients during the course of the disease. As other studies found that active lung cancer treatment differs between rural and urban areas, this analysis aims to detect whether end-of-life care also differs according to the area of residence. Using the district types major city, urban area, rural area and remote rural area the analysis compares a variety of aspects of end-of-life care relating to healthcare utilization and supportive care. There were no differences relating to geographical residence of the patients, therefore the results reject the hypothesis of regional inequality in end-of-life care. Instead, the results show that trigger factors for high and low utilization of healthcare are mostly age, comorbidities, and prior anticancer treatment. Supportive care is mostly associated with gender and the stage of the disease at the time of diagnosis.

The analysis in article 1 also shows that, compared to other countries, quality indicators of end-of-life care have room for improvement in Germany. In particular, the majority of lung cancer patients in Germany die in a hospital setting, whereas in the USA only around 20% of patients do [49]. Previous research has found that irrespective of a cancer diagnosis, there is a preference for dying at home or in a hospice [50, 51]. Therefore, article 2 aims to identify factors associated to inpatient death in German lung cancer patients. Using a least absolute shrinkage and selection operator (LASSO) selection model, the analysis identifies factors relating to an increased and decreased likelihood of inpatient death. Factors associated with a higher likelihood of inpatient death are often related to previous contacts with hospitals like prior hospitalizations and treatment of the tumor or comorbidities. Factors associated with a lower likelihood of

inpatient death are related to access to care settings, which are more focused on palliation than hospitals. Additionally, expenses for the health insurance fund are significantly higher for patients with inpatient death. These findings suggest that a more thorough implementation of tools like palliative care might help patients to make self-determined decisions relating to their place of death.

Article 3 focuses on differences in therapy relating to the patients' age. Results from article 1 suggest that end-of-life care is associated directly with the age of the patient. As lung cancer is most commonly diagnosed in elderly patients with a median age of diagnosis of around 68-70 years in developed countries [1, 5, 6], these patients make up the majority of lung cancer cases. Therefore, this article studies differences in active tumor therapy, diagnostic measures, palliative care, and costs between non-elderly (≤ 65 years) and young-old (65-74 years), middle-old (75-84 years), and old-old (≥ 85 years) patients. Results show that the likelihood to receive any tumor-directed treatment is significantly associated with age. Elderly lung cancer patients receive significantly fewer resections and radiotherapy or antineoplastic therapy. Additionally, older patients are less likely to receive structured palliative care and increasing age is associated with reduced quotas for outpatient treatment with opioids and antidepressants. These results suggest the existence of an age-dependent care disparity with potential undertreatment of elderly patients. Adjustments to public health policies seem to be urgently needed to support equal access to care.

In conclusion, the three articles of this thesis highlight the importance of the national cancer plans and efforts to improve lung cancer care in Germany. It shows that end-of-life care is provided indiscriminately across Germany, without disadvantages for patients from rural areas. However, the research identifies elderly patients as an important patient groups that, on the one hand is most vulnerable to the disease, and on the other hand suffers from potential undertreatment. In line with that, the thesis suggests that a bigger focus on, and an earlier integration of palliative care could be a crucial step to provide more equity in lung cancer care.

1.7. Individual contribution of the author

The author of this thesis has contributed substantially to the concept of all included articles and the involved study question, and prepared the datasets for all analysis. Additionally, she performed the statistical analysis for the articles 1 and 3, wrote the original manuscript for these articles, and accompanied the publication process as the corresponding author. She has supervised the Master thesis, which formed the basis for article 2, and was the main contributor to editing and reviewing this article.

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Chapter 2 Article 1

Rural versus urban differences in end-of-life care for lung cancer patients in Germany

ORIGINAL ARTICLE

CrossMark

Rural versus urban differences in end-of-life care for lung cancer patients in Germany

Julia Walter [1,2] · Amanda Tufman [2,3] · Reiner Leidl [1,2,4] · Rolf Holle [1] · Larissa Schwarzkopf [1,2]

Abstract

Purpose To assess rural-urban differences in healthcare utilization and supportive care at the end-of-life in German lung cancer patients.

Methods We identified 12,929 patients with incident lung cancer in 2009 from claims data and categorized them to four district types (major city, urban, rural, remote rural). We compared site of death, unplanned hospitalizations, hospital days, outpatient doctor, general practitioner (GP) and home visits, structured palliative care, therapy with antidepressants, pain relief medication and chemotherapy, and therapeutic puncturing in the last 30 and 14 days of life using mixed models with logistic link function for binary outcomes and log link function for count data. We adjusted all models by age, sex, comorbidities, metastases location and presence of multiple tumors at diagnosis, survival in months, and type of tumor-directed treatment.

Results We found significant differences in two of the outcomes measured. The likelihood of > 14 hospital days in the last 30 days was significantly higher in rural districts than in remote rural districts (1.27 [1.05, 1.52], $p = 0.0003$). The number of visits to the GP in the last 30 days of life was significantly lower in urban districts than in remote rural districts ($\beta = -0.19$ [-0.32, -0.06], $p = <0.0001$). No other endpoints were associated with regional differences. Triggering factors for high and low utilization of healthcare were mostly age, comorbidities, and prior anticancer treatment.

Conclusion Healthcare utilization and supportive care did not differ significantly between different district types. Results reject the hypothesis of regional inequity in end-of-life care of lung cancer patients in Germany.

Keywords Rurality · Quality of care · Equality · Claims data · Death · Regional differences

✉ Julia Walter
julia.walter@helmholtz-muenchen.de

1 German Research Center for Environmental Health, Helmholtz Zentrum München, Institute for Health Economics and Health Care Management (IGM), Ingolstädter Landstraße 1, 85764 Neuherberg, Germany

2 German Center for Lung Research (DZL), Aulweg 130, 35392 Gießen, Germany

3 Medical Clinic – Pneumology, Hospital of the Ludwig-Maximilians-University (LMU) Munich, Ziemssenstr. 1, 80336 Munich, Germany

4 Munich Center of Health Sciences, Ludwig-Maximilians-University, Ludwigstr. 28, 80539 Munich, RG, Germany

Introduction

Five-year survival rates of lung cancer patients are one of the lowest across all types of cancer, at around 16–20% [1]. Therefore, the end-of-life phase is especially important for patients with this type of cancer. It poses one of the most challenging phases as, on the one hand, the quality of care and the possibility of passing away with dignity is of high importance. On the other hand, costs and healthcare utilization are highest in the year before death, matched only by those right after diagnosis [2].

Studies have shown that access to general cancer care varies between rural and urban areas, with more specialized care centers in central cities. There are significant differences between rural and urban areas concerning the type of onco-logical treatment (surgery, chemotherapy, or radiotherapy) patients receive [3–5]. Travel time also has a significant influence on access to specialists and treatment [6–8], and

furthermore poses an extra burden on patients. [9] This leads to a fear among cancer patients and their relatives living in rural settings of not getting the same quality of care, a fear underlined in a review considering the perspectives of patients, family, and caregivers [10].

End-of-life care differs from general treatment as it is not intended to be curative or to prolong life, but focuses on pain relief and symptom control. Guidelines recommend that in the terminal phase of lung cancer, only measures that relate to symptom control should be applied [11]. To this point, there have been only few studies assessing differences in end-of-life care between rural and urban areas. Ho et al. (2011) assessed trends in aggressiveness of end-of-life care in Canada as a composite endpoint and found that living in a rural area was a significant predictor for receiving aggressive care [12]. Other studies focusing on nursing home residents found that, on the one hand, in rural areas fewer feeding tubes were used, and the average length of hospitalizations was lower than in urban areas, but, on the other hand, the number of hospitalizations and inhospital deaths were lower in urban areas [13–15]. A study in elderly lung cancer patients found that rural residents had fewer emergency room (ER) admissions and a higher usage of hospice services, but more intensive care unit (ICU) days than urban residents [16].

However, to this point, no extensive study has assessed rural-urban differences on end-of-life care including also supportive care measures specifically in lung cancer patients. Therefore, the aim of this study was to compare differences in healthcare utilization and supportive care at the end-of-life between lung cancer patients from urban vs. rural areas and see whether patients in rural areas are at a disadvantage. All analyses were carried out using data from German statutory health insurance companies (SHI).

Material and methods

Study design and study population

We conducted a retrospective observational study of administrative claims data in Germany. Data came from the Scientific Institute of AOK SHI fund, covering around 30% of the German resident population, and included patients from all 402 districts in Germany. In total, around 86% of German citizens are insured in a SHI. Law regulates insurance contributions and healthcare services covered by the SHIs. Patient clientele differs only slightly between different SHIs. Data was completely anonymized and according to Swart et al. [17], the consultation of an ethics committee is not required for analysis of this kind of data. Data included patient-level data of inpatient and outpatient treatment costs, German International Classification of Diseases (ICD-10-GM) codes, and OPS codes (German Version of the International Classification of

Procedures in Medicine) from 2009 to 2012. A study population consisting of patients with incident lung cancer in 2009 was derived previously from this dataset. A detailed description of the methodology can be found elsewhere [18]. From the study population, we analyzed those who had died before the year 2013 but who had at least survived for more than 30 days after diagnosis. We also excluded patients with missing information about their area of residence.

Urban and rural areas

To distinguish between different types of residential areas, we used the district types defined by the German Federal Institute for Research on Building, Urban Affairs, and Spatial Development for 2014, which are based on both the population density and the proportion of the population living in large and medium-sized cities [19]. It distinguishes four district types:

> Major city: minimum 100,000 inhabitants
> Urban districts: districts with minimum 50% of population in large or medium-sized cities and population density > 150 inhabitants/km^2, or districts with population density of > 150 inhabitants/km^2 when excluding large or medium-sized cities
> Rural districts with population concentrations: districts with minimum 50% of population in large or medium-sized cities but population density < 150 inhabitants/km^2, or districts with less than 50% of population in large or medium-sized cities but population density > 100 inhabitants/km^2
> Remote rural districts with low population density: districts with less than 50% of population in large or medium-sized cities and population density < 100 inhabitants/km^2 when excluding large or medium-sized cities

Patients in our analysis were assigned to one of the district types according to the ZIP-code of the last known place of residence.

Healthcare utilization and supportive care

The following outcomes concerning healthcare utilization were compared between the four district types: site of death by determining inpatient deaths from the discharge status of the last hospitalization, more than one unplanned (admit status = emergency) hospitalization in the last 30 days of life, spending more than 14 days in the hospital in the last 30 days of life, and number of office (all doctors and general practitioner (GP)) and home visits by providers. Apart from that, we looked at palliative and supportive care during the last weeks of life by measuring the following: start of palliative care at least 30 days before death (taking into account inpatient and outpatient claims for structured palliative care measures),

treatment with antidepressants and with structured pain relief treatment during the last 30 days of life (indicated by outpatient claims for antidepressants and WHO stages 2 or 3 pain medication as well as inpatient claims for structured pain treatment), chemotherapy treatments in the last 2 weeks of life, and therapeutic puncturing (ascites, pleural, pericardial) in the last 2 weeks. We included chemotherapy treatment, as according to guidelines, all treatment not relating to symptom control should be ceased [11]. Also, palliative care is associated with reducing chemotherapy, and quality of life has been shown to increase with earlier onset of palliative care [20–22]. All above treatments were identified through ICD codes, OPS codes, and ATC codes from inpatient and outpatient records.

Covariates

Covariates for the analysis were sex, age at time of death, comorbidities at time of diagnosis, presence of multiple tumors at diagnosis, type of coded metastases at diagnosis (no metastases, metastases in lymph nodes or other metastases), survival after diagnosis in months, and the type of anticancer treatment (no treatment, surgery, chemotherapy, radiotherapy). Comorbidities and treatments were derived from inpatient and outpatient ICD and OPS codes as well as physician fee records. We included congestive heart failure, diabetes, chronic obstructive pulmonary disease (COPD), moderate or severe liver disease, and renal disease as they are negatively associated with survival in lung cancer and are also relevant when it comes to the choice of lung cancer therapy [11, 23, 24].

Statistical analysis

We calculated sample characteristics, healthcare utilization, and aspects of medical care as means and proportions in the four groups. We used generalized linear mixed models (GLMM) to account for cluster effects in each district by including the district number as random intercept. To estimate any binary indicator of medical service utilization, we used logistic regression in the GLMM; for indicators with count data, we used a log link function and the Poisson distribution.

Except for the outcome of chemotherapy in the last 14 days of life where the type of anticancer treatment was left out, all regression models were adjusted by the covariates mentioned above. To take into account multiple testing, we used a significance threshold of $\alpha <= 0.0045$ and calculated 99.55% confidence intervals for all outcomes (Bonferroni adjustment based on running 11 models).

In sensitivity analysis 1 (SA 1), we analyzed the above aspects in a subgroup of patients that survived at least 180 days after diagnosis, to exclude a potential bias from patients who died suddenly due to side effects during the initial treatment (e.g., during surgery) and therefore did not receive specific end-of-life care.

In a second sensitivity analysis (SA 2), we only used inpatient healthcare events (e.g., hospitalizations, hospital days) with a major diagnosis of lung cancer to calculate the outcomes. By this, we wanted to exclude a bias caused by inpatient healthcare utilization due to comorbidity.

All analyses were performed using SAS 9.3 (SAS software of the SAS System for Microsoft, Version 9.3 (c) 2002–2010 by SAS Institute Inc., Cary, NC, USA.); tables and figures were created in Microsoft Excel and PowerPoint.

Results

Study population and unadjusted outcomes

The study population comprised 12,929 patients. A patient flow diagram can be found in Fig. 1. In Table 1, the general demographic information of the study population is listed in total and in the four different district types.

The descriptive statistics of healthcare utilization and supportive care across the four district types are reported in Table 2. Concerning the percentage of patients spending more than 14 days in the hospital in the last 30 days of life, we found a gradient towards increasing percentages with increasing urbanization of the district. The number of doctor visits was lowest in major cities, highest in urban districts, and
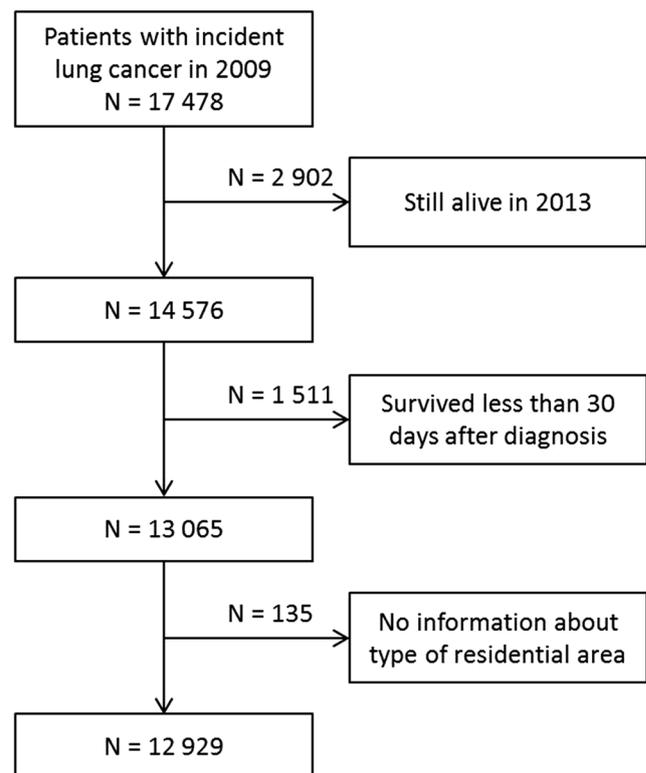
Fig. 1 Patient flow diagram of study population

Table 1 Sample characteristics

	Total (N = 12,929)	Major city (N = 3488)	Urban district (N = 4654)	Rural district (N = 2454)	Rural district with low population density (N = 2333)
Mean age in years (sd)	68.8 (10.1)	68.5 (10.0)	68.4 (10.1)	69.6 (10.1)	69.5 (9.8)
Male gender N (%)	9253 (71.6)	2323 (66.6)	3323 (71.4)	1848 (75.3)	1759 (75.4)
Diabetes mellitus N (%)	1832 (14.2)	480 (13.8)	619 (13.3)	391 (15.9)	342 (14.7)
Renal disease N (%)	294 (2.3)	84 (2.4)	93 (2.0)	68 (2.8)	49 (2.1)
Liver disease N (%)	225 (1.7)	70 (2.0)	79 (1.7)	38 (1.6)	38 (1.6)
COPD N (%)	6563 (50.8)	1886 (54.1)	2280 (49.0)	1235 (50.3)	1162 (49.8)
Congestive heart failure N (%)	4638 (35.9)	1150 (33.0)	1597 (34.3)	962 (39.2)	929 (39.8)
Multiple tumors at diagnosis N (%)	1904 (14.7)	490 (14.1)	723 (15.5)	343 (14.0)	348 (14.9)
Metastases at diagnosis N (%)	7845 (60.7)	2144 (61.5)	2807 (60.3)	1485 (60.5)	1409 (60.4)
Mean survival after diagnosis in months (sd)	11.0 (9.6)	11.0 (9.6)	10.9 (9.6)	11.3 (9.9)	10.5 (9.2)
Treatment					
No treatment N (%)	2392 (18.5)	612 (17.6)	850 (18.3)	463 (18.9)	467 (20.0)
Chemotherapy N (%)	8857 (68.5)	2444 (70.1)	3238 (69.6)	1642 (66.9)	1533 (65.7)
Surgery N (%)	1428 (11.0)	398 (11.4)	526 (11.3)	286 (11.7)	218 (9.3)
Radiotherapy N (%)	6310 (48.8)	1748 (50.1)	2290 (49.2)	1171 (47.7)	1101 (47.2)

Means and proportions of sample characteristics broken down by district type

sd, standard deviation; COPD, chronic obstructive pulmonary disease

decreasing again with higher rurality. The results for the number of GP visits and the number of home visits were similar.

Adjusted outcomes

We found significant differences in two aspects of healthcare utilization between the different district types; the results can be found in Table 3. The odds ratio of spending more than 14 days in the hospital in the last 30 days of life was significantly higher in rural districts than in remote rural districts (1.27 [1.05, 1.52], p = 0.0003), and the number of visits to the general practitioner (GP) in the last 30 days of life was significantly lower in urban districts than in remote rural districts ($\beta = -0.19$ [−0.32, −0.06], p = < 0.0001. Concerning

Table 2 Unadjusted proportions and means of healthcare utilization and supportive care

	Total (N = 12,929)	Major city (N = 3488)	Urban district (N = 4654)	Rural district (N = 2454)	Rural district with low population density (N = 2333)
Mean number of doctor visits in last 30 days	5.3	4.9	5.7	5.5	5.1
Mean number of GP visits in last 30 days	2.9	2.4	3.1	3.0	3.0
Mean number of home visits in last 30 days	1.7	1.6	1.8	1.7	1.7
Proportion in %					
More than 1 unplanned hospital visit in last 30 days	9.6	11.0	8.8	9.4	9.6
Spending more than 14 days in the hospital in last 30 days	42.8	46.5	42.1	40.9	40.5
Death in acute care hospital	55.8	57.3	55.0	54.8	56.3
Chemotherapy in last 14 days[a]	18.6	18.5	18.9	17.5	19.2
First palliative care contact at least 30 days before death	16.3	15.3	16.5	15.8	17.6
Prescription of antidepressants in last 30 days[b]	10.5	9.78	11.56	10.68	9.52
Structural pain medication in last 30 days	33.34	31.79	33.05	35.09	34.42
Therapeutic puncture in last 14 days	3.5	2.9	3.7	3.3	4.2

Unadjusted proportions and means of healthcare utilization and medical care in relation to district type

GP, general practitioner

[a] Calculated only for patients that were treated with chemotherapy over the course of the disease (N = 3941)

[b] Calculated for patients without a prior diagnosis of depression (N = 11,040)

Table 3 Adjusted odds ratios and parameter estimates of healthcare utilization and supportive care

	Major city vs. rural district with low population density			Urban district vs. rural district with low population density			Rural district vs. rural district with low population density		
	β	CI	P value	β	CI	P value	β	CI	P value
No. of doctor visits in last 30 days	0.07	[−0.04, 0.18]	0.06	−0.07	[−0.20, 0.06]	0.12	0.06	[−0.06, 0.17]	0.16
No. of GP visits in last 30 days	0.01	[−0.10, 0.12]	0.80	−0.19	[−0.32, −0.06]	< 0.0001	−0.02	[−0.14, 0.10]	0.61
No. of home visits in last 30 days	0.11	[−0.06, 0.29]	0.07	−0.11	[−0.32, 0.10]	0.13	0.02	[−0.17, 0.21]	0.76
	OR	CI	P value	OR	CI	P value	OR	CI	P-value
More than 1 unplanned hospital visit in last 30 days	1.21	[0.99, 1.48]	0.01	0.98	[0.73, 1.31]	0.82	0.90	[0.69. 1.17]	0.26
Spending more than 14 days in the hospital in last 30 days	1.03	[0.86, 1.25]	0.62	1.06	[0.90, 1.26]	0.31	1.27	[1.05, 1.52]	0.0003
Death in acute care hospital	0.94	[0.77, 1.15]	0.40	0.92	[0.77, 1.10]	0.18	1.03	[0.84, 1.27]	0.65
Chemotherapy in last 14 days[a]	0.95	[0.70, 1.27]	0.59	1.03	[0.79, 1.33]	0.76	0.89	[0.67, 1.19]	0.24
First palliative care at least 30 days before death	0.90	[0.65, 1.24]	0.33	0.88	[0.66, 1.19]	0.23	0.83	[0.59, 1.17]	0.13
Prescription of antidepressants in last 30 days[b]	0.93	[0.66, 1.29]	0.51	1.18	[0.88, 1.58]	0.11	1.05	[0.75, 1.47]	0.68
Structural pain medication in last 30 days	0.85	[0.71, 1.02]	0.01	0.91	[0.77, 1.08]	0.13	1.03	[0.85, 1.24]	0.71
Therapeutic puncture in last 14 days	0.78	[0.50, 1.21]	0.11	0.87	[0.60, 1.27]	0.30	0.68	[0.44, 1.04]	0.01

Odds ratios for each district type from logistic regression of binary healthcare utilization and medical care and parameter estimates β from Poisson regression for healthcare utilization with count data

[a] Calculated only for patients that were treated with chemotherapy over the course of the disease ($N = 8857$)

[b] Calculated for patients without a prior diagnosis of depression ($N = 11,040$)

OR, odds ratio; *CI*, confidence interval; *GP*, general practitioner

all other measures of healthcare utilization and supportive medical treatment, we did not find significant differences.

As the differences in healthcare utilization and supportive care of the adjusted analysis were mostly not significantly associated with the district type, we looked a bit further into the covariates that did have a significant influence in the multivariate model. A summary of the significant covariates and the direction of their influence can be found in Table 4. Concerning outpatient healthcare utilization, male gender and comorbidities were significantly associated with lower numbers of doctor visits. Age was associated with a higher number. A higher inpatient healthcare utilization was mostly driven by comorbidities and all types of anticancer treatments during the course of the disease. Older age and longer survival after diagnosis were associated with less inpatient healthcare use. Supportive care was given to males significantly less often than to females. And a lower stage of the disease at diagnosis was associated with receiving more structured supportive care measures.

As quality of care also relates to survival, in an additional analysis, we compared the adjusted length of survival in months between the four district types and did not find any significant differences.

Sensitivity analysis

When we excluded patients who did not survive for at least 180 days after diagnosis in SA 1, the study population included 7707 patients. By and large, the effects in this sensitivity analysis remained stable. We found several odds ratios with a reversed direction; however, all were non-significant in the complete sample as well as in the subsample. Concerning GP visits, the difference between urban and remote rural areas was not significant anymore, but the difference between major cities and the reference group was, with fewer visits in major cities. When we only included hospitalizations with a major diagnosis of lung cancer in SA 2, the effects of comorbid conditions were not significant anymore; prior anticancer treatment remained as the main triggering factor. Results from the sensitivity analysis can be found in Online Resources 1 to 3.

Discussion

This study sought to evaluate possible differences between end-of-life care in urban and rural areas of Germany to see if patients in rural areas are at a disadvantage concerning their quality of end-of-life care. Our results show that the utilization of healthcare services and supportive care does not differ significantly depending on the area of residence. We only found two aspects with significant differences. Patients in urban districts tended to have fewer GP visits, and patients in rural districts were less likely to spend more than 14 days in the hospital in their last weeks of life than in remote rural districts with low population density. In addition, in the sensitivity analysis, we only found a few significant differences. This

Table 4 Predictors of healthcare utilization and supportive care from regression analysis

	Male gender	Age	DM	LD	RD	HI	COPD	Prior Cancer	None vs. distant mets	Lymph-node vs. distant mets	CH	RT	SU	Surv month
No. of doctor visits in last 30 days		+	(+)	(−)	+	−				(−)	+	+	−	−
No. of GP visits in last 30 days	−	+	+	−	−				+			(−)	−	
No. of home visits in last 30 days	−	+		−	−	−			+		−		−	
Chemotherapy in last 14 days[a]		−			(+)	(+	)				(+)			−
More than 1 unplanned hospital visit in last 30 days	(+)	−			+		(+)				+			−
Spending more than 14 days in the hospital in last 30 days		−		(+)	+	+	(+)			+		+	+	−
Death in acute care hospital		−	(+)	+	+	+	+			(−)	+	(+)	+	−
First palliative care at least 30 days before death	−							+		+	+	+	+	
Prescription of antidepressants in last 30 days[b]	−									+			+	
Structural pain medication in last 30 days	−	(−)		(−)	−					+				+
Therapeutic puncture in last 14 days		−											−	

Significance (at $\alpha < 0.0045$) and direction of parameter estimates from regression of healthcare utilization and supportive care. "+" indicates increasing number/likelihood, "−" indicates decreased number/likelihood. Brackets indicate predictors with significance $\alpha < 0.05$

[a] Calculated only for patients that were treated with chemotherapy over the course of the disease ($N = 8857$)

[b] Calculated for patients without a prior diagnosis of depression ($N = 11{,}040$)

DM, diabetes mellitus; *LD*, liver disease; *RD*, renal disease; *HI*, heart insufficiency; *COPD*, chronic obstructive pulmonary disease; *CH*, chemotherapy; *RT*, radiotherapy; *SU*, surgery; *GP*, general practitioner

leads to the conclusion that although access to anticancer treatment might be different depending on the area of residence, end-of-life care does not generally differ significantly. A reason for this finding could be that specialists mostly carry out anticancer care and often these specialists are centered in and around bigger cities, whereas end-of-life care can be provided by GPs and hospice services, which can be found in every district type. Therefore, regional differences in end-of-life care are not an issue in a German setting.

As the district type did not trigger differences seen in the univariate analysis, we looked into which other covariates mostly contributed to differences in healthcare utilization and supportive care. Contrary to outpatient care, the utilization of inpatient healthcare significantly decreased with increasing age. Therefore, with increasing age, there seems to be a shift from inpatient to outpatient end-of-life care. The opposite effect was found concerning comorbidities. Having a comorbid condition was associated with increasing inpatient and decreasing outpatient healthcare utilization. Most of the comorbidities in the study like COPD and heart insufficiency are comorbid conditions that can usually be handled in an outpatient setting leading to the question whether these conditions are managed appropriately in the outpatient sector in Germany. When we only included hospitalizations with a major diagnosis of lung cancer in the sensitivity analysis, the effects of comorbid conditions were not significant anymore. Interestingly, prior treatments with chemotherapy, radiotherapy, or lung cancer surgery

were significant indicators of inpatient treatment at the end-of-life but in the case of prior lung cancer surgery, a predictor of decreased outpatient treatment. This could indicate that patients with prior hospital treatment are more likely to use hospital services again at the end-of-life.

Concerning supportive care at the end-of-life, we found that male gender was significantly associated with lower use. Male patients were less likely to receive structured palliative care at an earlier stage and to be treated with structured pain medication and antidepressants. This finding is likely due to patient preferences and different opinions regarding the need of supportive care. A less advanced stage and longer survival were significantly associated with a higher likelihood of supportive care. Patients with less advanced stages at diagnosis have more time to prepare themselves and arrange their living and treatment conditions at the end-of-life.

A study from Canada using a composite endpoint of receiving at least one of the four indicators of aggressive care in cancer patients (chemotherapy in last 14 days, more than one ER visit, more than one hospitalization, and at least one ICU admission in the last 30 days), found that rurality was a significant predictor of the likelihood of experiencing one or more of these indicators [12]. However, we cannot evaluate the extent to which each of the single indicators was predicted by rurality so a direct comparison to our results is not feasible.

Nayar et al. studied healthcare utilization of elderly lung cancer patients in the last 90 days of life in 2014 [16]. They

found significant differences between metropolitan areas compared to micropolitan, rural, and rural remote areas in the United States of America (USA). Residents of metropolitan areas had significantly more inpatient admissions compared to micropolitan areas and significantly fewer visits to the ER than in all other areas. In contrast to that, we did not find a significant difference between the likelihood of an unplanned hospital visit between remote rural districts with low population density and the other district types.

Other studies comparing rural-urban differences have focused on end-of-life care in nursing-home residents and in contrast to our study found that rural residence was significantly associated with a higher likelihood of inpatient death, hospitalization, and a lower risk of ICU admissions [14, 15]. Despite the differences in the characteristics of the study-populations (nursing home residents vs. all lung cancer patients), there were also some similar results to our data. In line with a German study that compared the 5-year survival rates of cancer and also specifically lung cancer patients between rural and urban districts, we did not find significant differences in the length of survival [25].

Disregarding effects of the district type, compared to studies analyzing the quality of end-of-life care of cancer patients in other countries, we found higher percentages of patients receiving chemotherapy in the last 14 days in Germany (19%) and in the USA (18%) [26] than in Canada (3–16%) [12, 27] and Korea (6%) [28]. Further, the percentage of patients dying in the hospital was higher in Germany (56%) compared to for instance the USA (20%). A reason for this result is that in the USA, hospice care is paid for by Medicare, and patients with a life expectancy of less than 6 months are encouraged to visit such a facility [29].

Earle et al. developed upper benchmarks for some of the aspects of care which we used for our study [30]. Healthcare systems with numbers below these benchmarks would be considered as not providing aggressive or intense treatment at the end-of-life. Compared to these benchmarks, the number of unplanned hospital visits and the proportion of inpatient deaths in our study were above the suggested upper benchmarks. However, these benchmarks were set based on 11 regions in the USA, so differences between the healthcare systems of the two countries may restrict a direct transfer of the benchmarks to the results found in our study.

A limitation of this study is that in our data, it was not feasible to distinguish between small cell lung cancer and non-small cell lung cancer or to identify the stage of the disease. However, the effect of these variables on the end-of-life care is small, and palliative treatment strategies are similar across histology.

Also, the term district describes areas with a wide variety of sizes (35–3000 km^2) and populations (34,000–1.8 million) [19]. In defining the four different district types, these factors are taken into account by categorizing according to population density and the percentage of the population living in cities, yet this does not rule out the possibility that districts with the same district type are not similar in terms of other influencing factors. However, by using a mixed model, we adjusted for cluster effects in each district in order to minimize this possible bias.

Another limitation is that by using claims data, the patient burden and preferences at the end-of-life cannot be directly measured, and possible differences in patient-reported outcomes cannot be analyzed. The same is true for information about the availability and access to different care settings. Generally, inpatient and outpatient hospice services are available to all citizens. They are covered under SHI and the compulsory long-term care insurance. Unfortunately, from the codes in our dataset, we could only derive whether structured palliative care services were provided but not if they were provided in a hospice or by hospice services. Information on socioeconomic status was not available in the dataset. However, the same as hospice services, home care, and nursing home care are covered by SHIs and the long-term care insurance, which is compulsory for all citizens. Albeit, in some cases, costs for home or nursing home care can be higher than the reimbursement. Therefore, financial reasons can influence end-of-life care decision making; however, these could not be assessed fully in our study.

The biggest strength of our study is the sample size of our dataset. It covers around 30% of the German residents, and our study population includes patients from all 402 districts in Germany. Further, in Germany, around 86% of the population is insured through SHIs similar to AOK, and 90–95% of all services provided are defined by law. Therefore, our results are generalizable to the whole German population. Another strength is the comprehensive picture of the treatment process that can be derived from the insurance data.

Equality in the access to high quality healthcare depending on the area of living has been researched in different studies [31, 32]. Concerning the end-of-life phase, to this point, there has been little evidence presented on this topic, especially for the case of lung cancer. Therefore, our study contributes to forming a picture on how end-of-life care is undertaken depending on the area of residence and lowers the fear of not getting the best quality of care.

Conclusion

In contrast to studies from other countries, our results show that lung cancer patients receive the same kind of supportive care at the end-of-life regardless of whether they live in a big city, a smaller town, or in the countryside in Germany. In addition, healthcare utilization does not differ significantly between different area types. Triggering factors for high and low utilization of healthcare are mostly age, comorbidities, and prior anticancer treatment. Receiving supportive care was mostly predicted by male gender and the disease stage at diagnosis.

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Compliance with ethical standards

Conflict of interest The study was carried out on behalf of Helmholtz Zentrum München (German Research Center for Environmental Health), an independent organization funded by the German and Bavarian government and the German Center for Lung Research (DZL) which is an association of the leading university and non-university institutions dedicated to lung research in Germany. The authors do not have a conflict of interest with regard to this project.

The authors confirm that the data utilized in this study cannot be made available in the manuscript, the supplemental files, or in a public repository due to German data protection laws ('Bundesdatenschutzgesetz', BDSG). Therefore, they are stored on a secure drive in the senior author's institution to facilitate replication of the results.

Generally, access to data of statutory health insurance funds for research purposes is possible only under the conditions defined in German Social Law (SGB V § 287). Requests for data access can be sent as a formal proposal specifying the recipient and purpose of the data transfer to the appropriate data protection agency. Access to these data is only provided through a data use agreement (DUA) with the data owner. Interested researchers may access these data by submitting their own DUA contract if required. They may additionally contact the corresponding author to request paperwork necessary to be added to the project DUA.

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Chapter 3 Article 2

Factors related to and economic implications of inhospital death in German lung cancer patients - results of a Nationwide health insurance claims data based study

BMC Health Services Research

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Factors related to and economic implications of inhospital death in German lung cancer patients - results of a Nationwide health insurance claims data based study

Karina Deckert[1,2]* , Julia Walter[2] and Larissa Schwarzkopf[2]

Abstract

Background: When patients die in a hospital their quality of life is lower than when they die at home or in a hospice. Despite efforts to improve palliative care supply structures, still about 60% of lung cancer patients die in a hospital. Studies have examined factors related to inhospital death in lung cancer patients, yet none used data of a representative German population, additionally including economic aspects. This study aimed to identify factors related to inhospital death in German lung cancer patients and analysed resulting costs.

Methods: We analysed a dataset of health insurance claims of 17,478 lung cancer patients (incident 2009) with 3 year individual follow-up. We grouped patients into inhospital death and death elsewhere. Studied factors were indicators of healthcare utilization, palliative care, comorbidities and disease spread. We used logistic regression models with LASSO selection method to identify relevant factors. We compared all-cause healthcare expenditures for the last 30 days of life between both groups using generalized linear models with gamma distribution.

Results: Twelve thousand four hundred fifty-seven patients died in the observation period, thereof 6965 (55.9%) in a hospital. The key factors for increased likelihood of inhospital death were receipt of inpatient palliative care (OR = 1.85), chemotherapeutic treatments in the last 30 days of life (OR = 1.61) and comorbid Congestive Heart Failure (OR = 1.21), and Renal Disease (OR = 1.19). In contrast, higher care level (OR = 0.16), nursing home residency (OR = 0.25) and receipt of outpatient palliative care (OR = 0.25) were associated with a reduced likelihood. All OR were significant (*p*-values< 0.05). Expenditures in the last 30 days of life were significantly higher for patients with inhospital death (€ 6852 vs. € 33,254, *p*-value< 0.0001).

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* Correspondence: karina.deckert@web.de
[1]Institute for Medical Information Processing, Biometry, and Epidemiology, Ludwig-Maximilians-University (LMU), Marchioninistr. 15, 81377 Munich, Germany
[2]Helmholtz Zentrum München GmbH, German Center for Environmental Health, Institute of Health Economics and Health Care Management, Member of Comprehensive Pneumology Center Munich (CPC-M), Member of German Center for Lung Research (DZL), Ingolstaedter Landstrasse 1, 85764 Neuherberg, Germany

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Conclusion: Findings suggest that factors associated with inhospital death often relate to previous contact with hospitals like prior hospitalizations, and treatment of the tumour or comorbidities. Additionally, factors associated with dying elsewhere relate to access to care settings which are more focused on palliation than hospitals. From these results, we can derive that implementing tools like palliative care into tumour-directed therapy might help patients make self-determined decisions about their place of death. This can possibly be achieved at reduced economic burden for SHIs.

Keywords: Lung carcinoma, Place of death, End of life care, Terminal care, Routine data, Palliative care, Health care supply structures,

Background

In Germany, around 51% of all-cause and tumour-related deaths occur in a hospital setting, whereupon males (♂ 57% vs. ♀ 45%) and patients with tumours in respiratory organs (60% vs. 50%) are affected above average [1]. Previous research has found that irrespective of a cancer diagnosis, there is a preference for dying at home or in a hospice; dying in a hospital setting is favoured only by few (Gomes 2012, Gomes 2013, Pinzon 2011 and Higginson 2013) [2–5]. A palliative care setting may help patients express preferences about their place of death and their preferred treatment based on extensive information. Thus, patients in palliative care settings may more likely achieve their preferred end of life choices which supposed to improve their Quality of life (QoL) at the end of life. Although the number of inhospital deaths has declined in recent years, there is still an obvious discrepancy between the preferred and the actual place of death, especially in patients with respiratory tumours. Furthermore, this patient group is of high public health relevance, as respiratory tumours were the fourth leading cause of death in Germany in 2015 [6]. Two studies from the US and the UK found that, patients' QoL at the end of life tends to be worse when they die in a hospital compared to when they die elsewhere, because they are more likely to experience physical and emotional distress and feel less at peace [7, 8]. Owing to different framework conditions, generalizing findings from one health care system to another is a sensitive issue. Of course, the results of the US-based study might not be fully replicable in the German setting, but since both systems are strongly "curatively" oriented and pay subordinate attention to palliative care, similar results can be expected for German populations. Additionally, inpatient care at the end of life generates higher expenditures than outpatient care as shown by Gaertner et al. (2013) [9] and Schwarzkopf et al. (2015) [10]. Thus, reducing the share of inhospital death in lung cancer patients is in the interest of both the patients concerned and health care service payers.

Costa (2014) published a systematic review on determinants influencing the place of death of terminally ill patients [11]. Interprofessional home palliative care and early referral to palliative services, inter alia, increased the number of home deaths. Based on these results, the German palliative care system has been improved, as Cremer-Schaeffer and Radbruch (2012) reported [12]. Since 2007, every German citizen has a legal claim to palliative home care. Furthermore, palliative care was implemented in educational programs for health professionals and the number of hospices increased overall. Consequently, Dasch et al. (2016) showed that the number of inhospital deaths in German lung cancer patients decreased between 2001 and 2011 (from 68,1% to 60,3% in men and from 70,7% to 49,6% in women) [1]. While trying to determine further factors influencing the place of death, Escobar Pinzón et al. (2011) found that nonworking relatives and a high care level are associated with home deaths in the German general population [4]. A study by Leak et al. (2013) describes characteristics of 104 lung cancer patients dying in emergency departments in North Carolina (USA) [13]. 71% of those patients died on their first visit and 65% of them were male. The most common chief complaint was respiratory distress. Considerably more patients ($n = 143.627$) were included in a UK nationwide study of O'Dowd et al. (2016) [14]. They identified sex, increasing age and social deprivation as factors associated with inpatient death.

To our knowledge, there is no representative nationwide study for a German population investigating multiple factors related to inhospital death as well as related to healthcare expenditures in German lung cancer patients as of yet.

Therefore, our study aimed to improve the evidence available by:

a) Defining factors related to inhospital death based on statutory health insurance (SHI) claims data,

b) using logistic regression models to identify factors associated with inpatient deaths, and

c) comparing healthcare expenditures in the terminal phase between patients dying in a hospital and patients dying elsewhere.

Methods

Structure of the dataset

For our retrospective claims data analysis, we used nationwide insurance claims data by the AOK Research Institute (WIdO) [15] covering about 30% of the German population. According to the German Guidelines for Secondary Data Analysis [16] ethical approval is generally not required for this type of study. The German Reporting Standards for Secondary Data Analyses (STROSA) were considered in the preparation and implementation of this study [17].

The basic dataset contained anonymized data of 17,478 patients diagnosed with lung cancer in 2009, with patient-individual three-year follow-up (2009–2012). Details about the sample collection are described elsewhere [10]. Data included year and month of birth, sex, federal state of residence, care level (reflecting impairment in activities of daily living) and nursing home status over the course of the disease. Additionally, we had information on health care service utilization in the in- and out-patient setting, as well as on corresponding diagnosis codes (German International Classification of Diseases/ICD-10-GM) and medical procedures undertaken (OPS/German Version of the International Classification of Procedures in Medicine respectively GONR/outpatient billing codes).

Owing to data protection laws, date of death was only provided per month. For the purposes of this analyses we set date of death to the 15th of each month for any individual observed. Thus, there is an admitted imprecision of up to 2 weeks. To increase precision of date of death we subsequently checked the discharge status of hospital stays. Whenever death was documented here, we replaced the fictive data of death (15th of x) by the real date of death, which is date of discharge. Regarding the remainders, we searched for service provision after the 15th in the month of death. In case of service provision in the second half of the month, this date was assumed to be the date of death.

Sample selection

As we compared place of death (inhospital or elsewhere) in our analysis, we excluded all patients who did not die within the individual three year follow-up period (n = 3247). One individual was excluded due to implausible data. To avoid a bias from patients with fulminant presentations and to focus on patients likely medically stable enough to have a choice regarding their place of death, we excluded patients who lived for less than 30 days after diagnosis (n = 1511). We further excluded any patients who died during the hospital stay of diagnosis (n = 115) and those with an implausible date of death, as they had claims for ambulant palliative treatments after date of death (n = 23). There are two possible reasons for claims of treatments after death. Firstly, out-patient palliative care also includes grief counselling for the relatives of the deceased. Secondly, as mentioned above date of death in our study can differ from actual date of death by a maximum of 2 weeks. Lastly, we excluded patients with unknown district type of residence at the time of diagnosis (n = 124). Our final study sample contained 12,457 patients (Fig. 1).

We assigned patients to the group inhospital death if the discharge status was 'death' in the last hospital visit. All other patients were assigned to the group of dying elsewhere.

Factors related to inhospital death

We conducted a literature search in Pubmed in order to identify factors possibly associated with inhospital death. Search terms used included "place of death", "end of life care", "quality at the end of life", and "factors influencing place of death" preferred for German lung cancer populations. We considered a potential association between inhospital death and following factors: age at time of death, gender, length of survival after diagnosis, nursing home residency, need for care, residence in Eastern vs. Western Germany, residence in rural vs. urban area, palliative care, previous healthcare utilization and treatment pattern, comorbidity burden and disease stage at diagnosis [4, 11, 13, 14].

Survival was measured as months survived after diagnosis. Nursing home residency (yes / no) and need for care defined as the patient's care level refer to the last quarter before death. At the time of data collection, the German SHI system accounted for three care levels reflecting the patient's capabilities to independently perform activities of daily living. The three levels of dependency were distinguished by how often assistance is needed and how long it takes a non-professional caregiver to help the dependent person. Higher care levels indicate increased need for assistance (i.e. greater physical or psychological impairment[1]) [18]. Living in Eastern or Western Germany as well as living in an urban or rural district was defined based on the ZIP code of the last documented residential address. We used the district types defined by the Federal Institute for Research on Building, Urban Affairs and Spatial Development for 2014, to classify the patients' residential area as urban (district type 1 and 2) or rural (district type 3 and 4) [19].

Palliative care was included as a binary variable indicating whether palliative care measurements were administered at least once in an inpatient or outpatients setting. Information for this came from claims relating to palliative care codes (OPS for inpatient, GONR for outpatient palliative care).

Fig. 1 Patient flow diagram
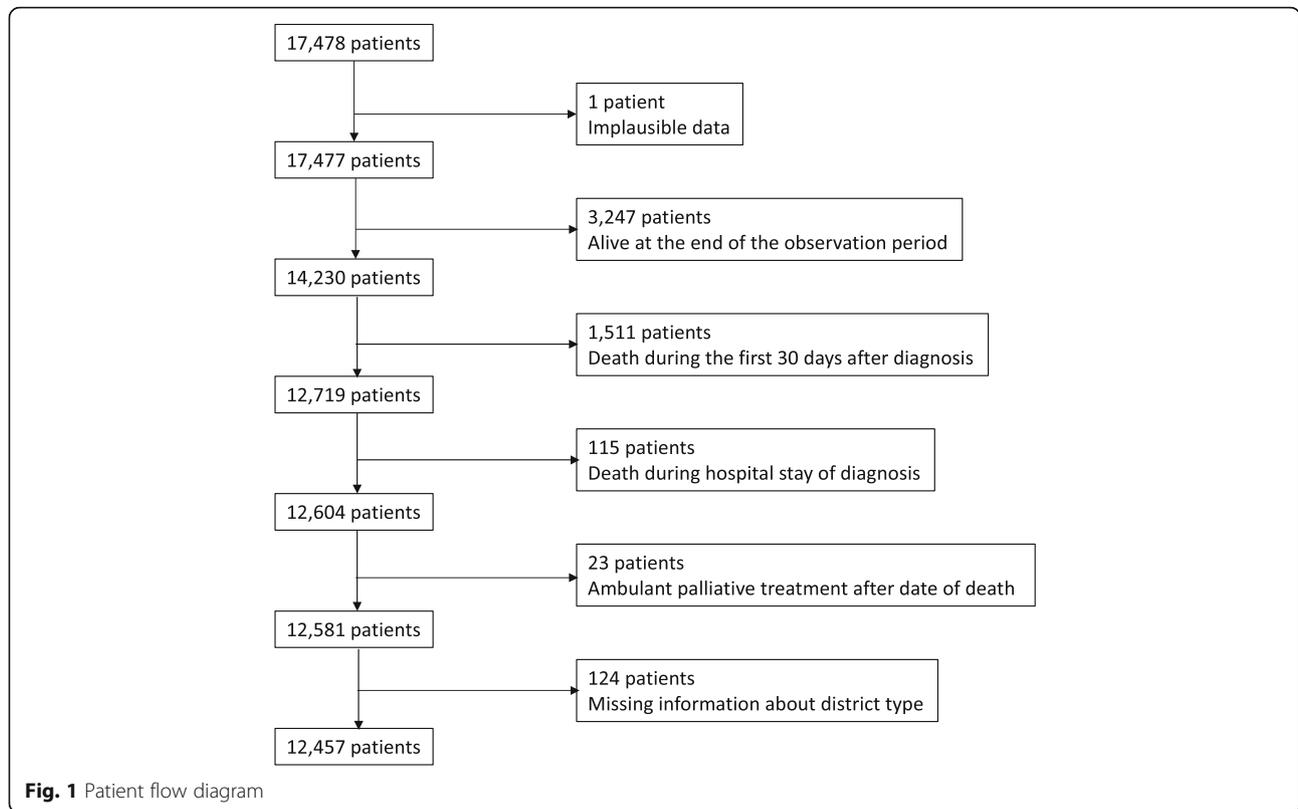
We assessed previous healthcare utilization by calculating the number of days patients spent in a hospital, the number of outpatient hospital visits and of outpatient doctor visits (based on the number of days with a claim for a GONR) between diagnosis and death. To factor in collinearity with survival time we divided all those aspects by survival in months, resulting in utilization of healthcare by month survived.

To best possibly account for tumour stage at diagnosis –which is not documented within claims data– we used the type of tumour-directed therapy patients received and the location of metastases at baseline. We grouped patients using inpatient and outpatient ICD-10, OPS, billing and ATC codes into 'no tumour-directed therapy', 'surgical resection', 'radiotherapy', 'chemotherapy' and combinations of chemotherapy, radiotherapy and surgical resection. We identified patients with metastases at baseline using inpatient and verified outpatient ICD 10 codes in the quarters before and after the diagnosis of lung cancer and grouped them according to location; into thoracic, cerebral and bone metastases.

To reflect treatment intensity at the end of life, we reported chemotherapy given in the last 30 days before death as binary variable. This indicator of aggressive treatment has been used previously in end-of-life research [20].

To assess the patients' comorbidity burden, we calculated the Charlson comorbidity index using the coding algorithm described by Sundararajan et al. (2004) [21] on all ICD-10 codes in claims in the 2 years prior to the diagnosis of lung cancer and included the distinct Charlson conditions as binary variables (comorbidity yes / no). As slight modifications from the initial algorithm, lung cancer was excluded from the condition 'cancer'. Furthermore, we disregarded the condition 'metastatic carcinoma' to avoid a multicollinearity issue with the variable metastases location at baseline.

Economic implications

To assess the economic implications of inhospital death we calculated expenditures for the health insurance company in the last 30 days before death. We compared total all-cause expenditures for hospitalizations, doctor visits and medications between patients with inhospital death to those who died elsewhere.

Statistical methods

To investigate potential differences between lung cancer patients dying in a hospital and those dying elsewhere, we compared means, standard derivations (SD) medians and frequencies of basic variables like, gender, age and need for care. Categorical variables were compared using the χ^2-test. Only age was approximately normally distributed (visual inspection) and compared using t-test (pooled test for equal variances). All other categorical

variables were compared with Wilcoxon U-test for non-normal distributions. We compared survival trends of both groups via Kaplan-Meier curves and Log-Rank tests.

To examine the relationship between the related factors described above and inhospital death we used a multivariate logistic regression model and chose LASSO ("least absolute shrinkage and selection operator") as the selection method [22]. LASSO selection combines some of the favourable properties of stepwise regression (ease of interpretation) and ridge regression (robustness) [22] while additionally performing better concerning multi-collinearity [23, 24]. The first part of the LASSO loss function is equal to an ordinary least square regression, whereas the second part constrains the absolute value of the sum of the regression estimates by the parameter. It can be written as

$$ L^{Lasso}\left(\beta_1,...,\beta_p\right) = \left\|Y - \sum_{j=1}^{p} X_j \beta_j\right\|^2 + \lambda \sum_{j=1}^{p}\left|\beta_j\right| $$

where L is the loss function, X is an $n \times p$ design matrix for predictors, Y is an $n \times 1$ vector of responses, β is a $p \times 1$ vector of regression coefficients, and $\lambda \geq 0$ is the regularization parameter that controls the degree of shrinkage. Because the penalty term $(\lambda \sum_{j=1}^{p} |\beta_j|)$ is based on the sum of the absolute values of the regression estimates, some estimates can be shrunken to exactly zero, which results in their exclusion from the model. That enables LASSO to be used for selection of predictor variables [25]. The LASSO loss function is not differentiable because of the unknown parameter λ. Thus, we used the method proposed by Nesterov (2013) to minimize the function while optimizing λ [26]. Age and sex were considered as pre-fixed covariates. To calculate odds ratios (ORs), 95%-confidence intervals (CIs) and *p*-values, we ran a logistic regression model with the covariates identified by LASSO selection. In this regard, it should be noted that all variables chosen by LASSO selection have an important influence on the outcome variable, irrespective of their statistical significance within the subsequent logistic regression model.

As expenditures did not show a normal Gaussian distribution using linear regression (OLS) was not possible. Therefore, we used a Generalized Linear Model (GLM) with gamma distribution and log link function. This kind of model is able to handle data that are right-skewed and eliminates heteroscedasticity [27]. The derivate of the parameter estimates from gamma regression represent the additive effect (in expenditures) that a change in this variable would cause. To interpret these results more easily, healthcare expenditures were reported as recycled predictions with confidence intervals and *p*-values. Recycled predictions are used to understand the marginal effect of independent variables on a dependent variable. They are obtained from the gamma regression model by averaging predicted scores, after fixing the value of one independent variable (either inhospital death, or death elsewhere), and using observed values on the remaining independent variables. The recycled predictions then provide adjusted means for both groups [28]. All recycled prediction models were adjusted by the factors identified as being associated with inhospital death earlier. The parameter estimates obtained from this gamma GLM are provided as Additional file 1.

Confidence intervals and *p*-values of the adjusted means and difference were based on non-parametric bootstrapping (1000 bootstrap repetitions, percentile method). We used a significance level of 5% for all analyses.

To examine the robustness of the model we ran three sensitivity analyses (SA). For SA1 we extended the definition of inhospital death to include patients who were discharged from the hospital in the week before death and spent at least 2 days in the hospital in that week (additional 825 patients in inhospital death group). We chose the last week of life because it is defined as phase of death and we assumed that hospitalization in that final phase might correlate particularly strong with a decreased QoL [29]. Because our definition of inhospital death did not reflect whether a patient died on a general ward or on a palliative ward we ran SA2. Here, we reassigned 572 patients with inhospital death who had palliative treatments during the hospital stay of death to the group with death elsewhere. To avoid missing important information about patients with fulminant presentation (death during the first 30 days after diagnosis) we did not exclude these patients in SA 3 and performed the analysis with a sample of 13,090 patients.

All statistical analyses were performed using SAS version 9.4. Figures and tables were created with Microsoft Word, Power Point and Excel.

Results
Patient population and univariate analysis of factors related to inhospital death
Of the final study sample, 6965 individuals (55.9%) died in a hospital (Table 1). Patients with inhospital death were significantly younger than patients who died outside a hospital. Most of the patients were male (71.7%) with a significantly higher proportion of males in the inhospital death group. The residential setting was comparable in both groups regarding regional (Eastern vs. Western Germany) as well as structural (urban vs. rural) aspects. Nursing home residency was significantly less common in the inhospital death group, even though only few patients (7.7%) lived in a nursing home at all.

Table 1 Description of the study sample

	Entire sample	Inhospital death	No Inhospital death	*p*-value[c]
n (%)	12,457 (100)	6965 (55.9)	5492 (44.1)	
Mean age at death (SD)	69.9 (10.0)	68.8 (10.0)	71.4 (9.9)	< 0.0001
Sex				
Male N (%)	8930 (71.7)	5070 (72.8)	3860 (70.3)	0.002
Survival				
Median survival in months	7	7	8	< 0.0001
Living in a nursing home [a] (%)	958 (7.7)	188 (2.7)	770 (14.0)	< 0.0001
Care level [a]				
No care level N (%)	4958 (39.8)	3769 (54.1)	1189 (21.7)	< 0.0001
1 N (%)	2451 (19.7)	1324 (19.0)	1127 (20.5)	0.0351
2 N (%)	3416 (27.4)	1376 (19.8)	2040 (37.1)	< 0.0001
3 N (%)	1632 (13.1)	496 (7.1)	1136 (20.7)	< 0.0001
State				
Western Germany N (%)	9724 (78.1)	5478 (78.7)	4246 (77.3)	0.0732
Urban district [b] N (%)	7829 (62.9)	4380 (62.9)	3449 (62.8)	0.922
Mean Charlson Comorbidity Score (SD)	3.77 (2.65)	3.81 (2.66)	3.72 (2.63)	0.0777
Body regions with Metastases				
Cerebal N (%)	2271 (18.2)	1237 (17.8)	1034 (18.8)	0.1256
Bones N (%)	2845 (22.8)	1630 (23.4)	1215 (22.1)	0.0912
Thoracic N (%)	4207 (33.8)	2406 (34.5)	1801 (32.8)	0.0402

[a] Data of the last quarter before death were used
[b] Urban district is based on the district types defined by the Federal institute for Research on Building, Urban Affairs and Spatial Development for 2014. Urban district contains district type 1 and 2, the reference category rural district contains district type 3 and 4
[c] *p*-values were calculated with t-test for age at death, Wilcoxon U-test for Charlson Comorbidity Score and Chi^2 test for sex, living in a nursing home, care level, state and urban district

Further, need for care was significantly less severe in those dying in a hospital. Mean Charlson comorbidity score did not differ significantly between the two groups. Patients dying in a hospital significantly more often had thoracic metastases (34.5% vs. 32.8%), other metastases locations did not differ.

Median survival was lower in patients dying in the hospital and the log-rank test showed significantly different survival between the two groups (Fig. 2).

Patients dying in a hospital were hospitalized significantly more often (10.9 vs. 8.4 days per month survived, *p*-value < 0.0001) and visited outpatient doctors significantly more frequently (3.1 vs. 2.8 visits per month survived, *p*-value < 0.0001).

The proportion of patients with inpatient palliative care was significantly higher in patients with inhospital death (18.0% vs. 13.4%, *p*-value < 0.0001) and the proportion of patients with outpatient palliative care was significantly higher in patients who died elsewhere (7.7% vs 1.6%, *p*-value < 0.0001).

The proportion of patients receiving chemotherapy in the last 30 days of life was significantly higher in the inhospital death group (30.0% vs. 16.7%, *p*-value < 0.0001). Overall, almost one-fifth of patients did not receive any tumour-directed therapy between diagnosis and death (*n* = 2.124, 17.1%). The proportion of patients not receiving cancer-directed therapy was significantly lower in the inhospital death group (12.9% vs 22.4%, *p*-value < 0.0001). Descriptive statistics of healthcare utilization, palliative care and therapy are displayed in Table 2.

Regarding comorbidity burden, dementia was significantly less prevalent in the inpatient death group, whereas the prevalence of peripheral vascular disease, diabetes with complications and renal disease was significantly higher (Fig. 3).

Multivariate analysis of factors related to inhospital death

The LASSO method selected the following as factors related to inpatient death: length of survival in months, nursing home residency, care level, number of hospital days, inpatient and outpatient palliative care, chemotherapy in the last 30 days of life, presence of congestive heart failure (CHF), and renal disease, as well as cerebral metastases (Table 3). Longer survival since diagnosis increased the odds of inhospital death. Nursing home residency, and increasing need for care reflected by higher care levels decreased the odds. Having spent
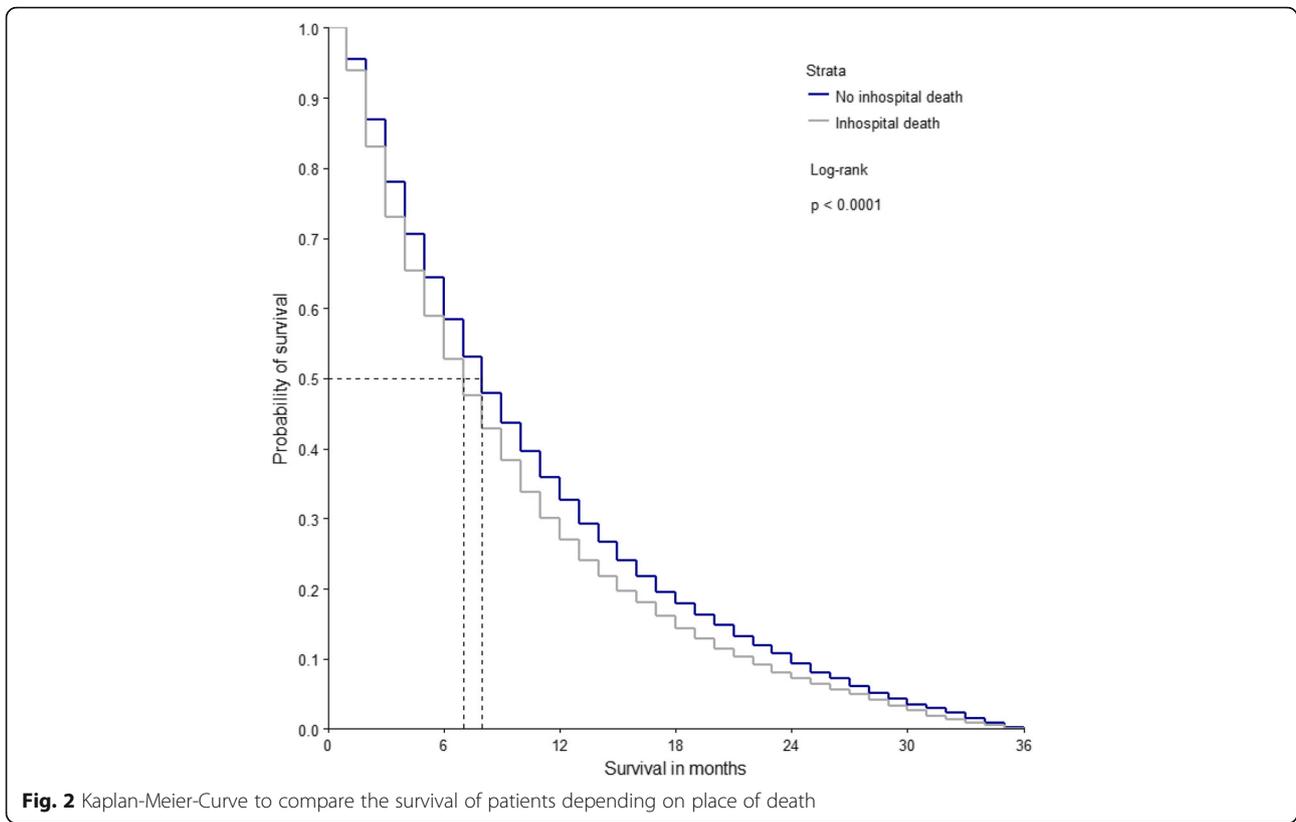
Fig. 2 Kaplan-Meier-Curve to compare the survival of patients depending on place of death

Table 2 Descriptive statistics of healthcare utilization, palliative care and therapy

	Entire sample	Inhospital death	No Inhospital death	*p*-value[c]
n (%)	12,457 (100)	6965 (55.9)	5492 (44.1)	
Healthcare utilization [a]				
Number of hospital days (SD)	9.8 (8.2)	10.9 (8.7)	8.4 (7.3)	< 0.0001
Number of outpatient doctor visits (SD)	3.0 (2.4)	3.1 (2.6)	2.8 (2.2)	< 0.0001
Number of outpatient hospital visits (SD)	0.01 (0.1)	0.01 (0.1)	0.02 (0.1)	0.0559
Palliative Care				
Inpatient palliative care N (%)	1994 (16.0)	1256 (18.0)	738 (13.4)	< 0.0001
Outpatient palliative care N (%)	2388 (4.3)	111 (1.6)	425 (7.7)	< 0.0001
Chemotherapy in last 30 days of life (%)	3009 (24.2)	2090 (30.0)	919 (16.7)	< 0.0001
Treatment [b]				
No treatment N (%)	2124 (17.1)	896 (12.9)	1228 (22.4)	< 0.0001
Chemotherapy N (%)	2990 (24.0)	1745 (25.1)	1245 (22.7)	0.002
Radiotherapy N (%)	967 (7.8)	512 (7.4)	455 (8.3)	0.0532
Surgery N (%)	715 (5.7)	421 (6.0)	294 (5.4)	0.0996
Chemotherapy and Radiotherapy N (%)	3169 (25.4)	1867 (26.8)	1302 (23.7)	< 0.0001
Chemotherapy and Surgery N (%)	1016 (8.2)	632 (9.1)	384 (7.0)	< 0.0001
Radiotherapy and Surgery N (%)	301 (2.4)	158 (2.3)	143 (2.6)	0.2263
All three types N (%)	1175 (9.4)	734 (10.5)	441 (8.0)	< 0.0001

[a] Healthcare utilization by month survived between diagnosis and death
[b] Information if patients received this combination of treatments at any time of the observation period. Number or order of treatments was not considered
[c] *p*-values from Wilcoxon U-test for healthcare utilization, and from Chi² test for treatment and palliative care

Fig. 3 Prevalence of Charlson comorbidity groups depending on place of death
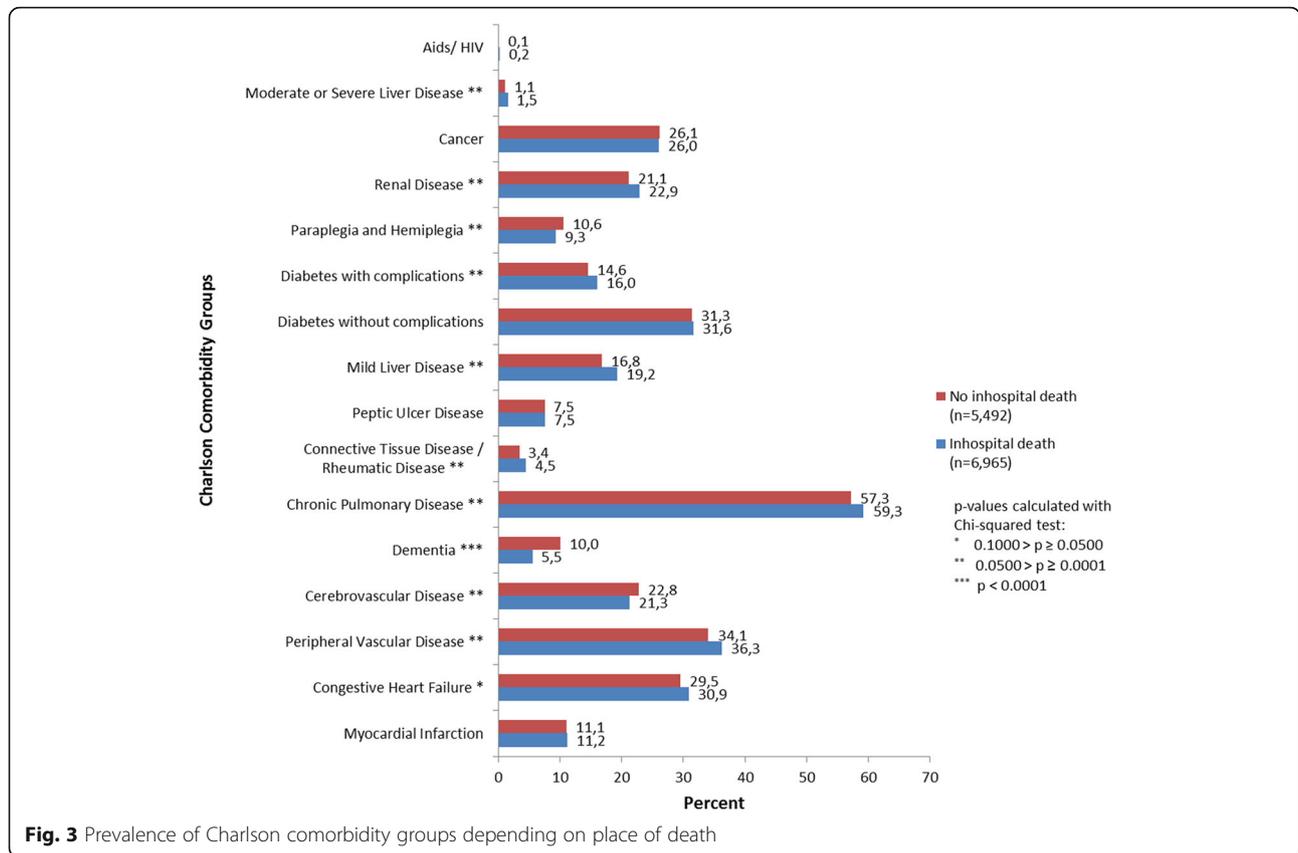
more days in a hospital and receiving inpatient palliative care increased the likelihood for inhospital death whereas receiving outpatient palliative care resulted in a lower risk for inhospital death. If a patient received chemotherapy in the last 30 days of life, he was more likely to die in a hospital setting. Patients with CHF, or renal disease had an increased risk of inhospital death. Furthermore, patients with cerebral metastases had a decreased risk of inhospital death.

Multivariate analysis of expenditures

All-cause total costs were significantly higher for patients dying in a hospital (€ 6852 vs. € 3.254, *p*-value < 0.0001). Hospitalizations made up the biggest part of expenditures and were significantly higher in patients with inhospital death (€ 5895 vs. € 2321, *p*-value < 0.0001). Expenditures for doctor visits were significantly higher in patients who did not die in a hospital (€ 358 vs. € 245, *p*-value < 0.0001), as were expenditures for medications (€ 691 vs. € 585, *p*-value < 0.0001).

Sensitivity analyses

The results of SA1 (Additional file 2) and the main analyses were similar, however the LASSO method did not result in an inclusion of renal disease as an important factor anymore. The results of SA2 (Additional file 2)

and the main analyses differed in two aspects. First, chronic pulmonary disease (CPD) was selected as important factor additionally, increasing the odds of inhospital death. Second, inpatient palliative care now decreased the likelihood of inhospital death.

The model in SA3 was almost the same as in the main analysis, some effect sizes changed in decimal places only.

Discussion

In our study, we sought to identify factors related to inhospital death in German lung cancer patients. We found that especially the patients' age and frailty, as measured in the need for care and nursing home residency, were important factors related to not dying in a hospital. In addition, patients with cerebral metastases had a decreased risk of inhospital death. The utilization of outpatient palliative care also reduced the likelihood of inhospital death but receiving inpatient palliative care increased the likelihood of inhospital death. Furthermore, a higher number of days spent in a hospital, CHF and renal disease, as well as receiving chemotherapy in the last 30 days of life were associated with an increased risk of inpatient death.

Total healthcare expenditures were about twice the expenditures of dying elsewhere, with expenditures for hospitalizations predominantly responsible for these

Table 3 Results of the logistic regression

	OR [a, b]	95% CI [a, c]	*p*-value
Age at death	0.985	0.98–0.989	< 0.0001
Sex			
Male vs female	0.95	0.87–1.04	0.2533
Survival in months	1.01	1.006–1.02	< 0.0001
Living in a nursing home	0.25	0.21–0.30	< 0.0001
Care level (reference = no care level)			
1	0.47	0.42–0.53	< 0.0001
2	0.26	0.24–0.29	< 0.0001
3	0.16	0.14–0.19	< 0.0001
Healthcare utilisation			
Number of hospital days [d]	1.04	1.036–1.05	< 0.0001
Palliative Care			
Inpatient palliative care	1.85	1.66–2.08	< 0.0001
Outpatient palliative care	0.25	0.20–0.32	< 0.0001
Chemotherapy in last 30 days of life	1.61	1.46–1.77	< 0.0001
Charlson Comorbidities Groups			
Congestive Heart Failure	1.21	1.11–1.33	< 0.0001
Renal Disease	1.19	1.08–1.32	0.0006
Body regions with Metastases			
Cerebral metastases	0.86	0.77–0.96	0.0050

[a] Values are rounded to two decimals except if they would be rounded to exactly 1 then they are rounded to three decimals
[b] Odds ratio
[c] 95% confidence interval
[d] Healthcare utilization by month survived between diagnosis and death

differences. Although expenditures for outpatient care and medications were higher in patients not dying in the hospital, the sum of these differences were negligible compared to the differences in inpatient expenditures.

Evidence, in which direction age affects inhospital death is inconclusive: Dasch et al. found a negative association for the general population in a North Rhine-Westphalia-based study (< 60 versus > 80 years: OR 1.41, *p*-value 0.001) [30], but O'Dowd et al. observed a positive association among lung cancer patients in the UK (> 85 year vs. 70–74 years OR 1.16; 95% CI 1.08–1.24) [14]. Finally, Escobar Pinzón et al. (2011) found no association at all between age and place of death in a population of Rhineland-Palatinate, however this study was not focused on lung cancer patients but referred to the general population [4]. We believe that our observation of negative association is plausible: Younger patients may be subject to more aggressive inpatient therapy. Therefore, their primary clinical relationship is rather with an oncologist than with a palliative care team. Moreover, they might have more social/familial obligations than older patients and death at home may not be desirable if they have a young family at home. Consequently, younger patients have an increased risk of inpatient death.

Longer survival after diagnosis increased the risk of inhospital death. This was a surprising result at first as we assumed that patients with shorter survival have less time to come to terms with impending death, and therefore to organize their final days in a preferred and comfortable place. However, if a patient is diagnosed in a late stage of the disease the focus of care is more likely to be on palliation and organizing end-of-life care rather than curative therapy. In line with that, patients with cerebral metastases at time of diagnosis died in the hospital less frequently.

In our study nursing home residency was associated with a reduced likelihood of dying in a hospital. This might be explained by the fact that continuous nursing care — as often required at end of life — is already available in this setting, whilst it can often not be guaranteed in an ambulatory setting. Even though dying in a nursing home or in a hospice is not the same as dying at home, most patients prefer those places to hospitals [2]. Relatives who are not able to arrange care of the patients at home due to financial or other reasons, thus should be supported more relating organization of accommodation in a hospice or a palliative care facility in order to increase the patient's QoL during the last days. Wye et al. (2014) describe that arranging care outside the hospital is a very tough task for the relatives [31]. For this reason, the UK has implemented end of life care services, which provide nurses who support relatives with organizational services, as well as assistance with decision-making. These nurses are supposed to offer time for conversations with the patients and the relatives about death, as well as the practical aspects of caring for the dying. This concept works especially for cancer patients who are close to death and should be considered as a developing concept to further improve end of life care in Germany. Actually, at the time this study was conducted, there was study ongoing to evaluate establishing a system of 'social care nurses' in cancer therapy in Germany funded by the German Ministry of health.

Our study indicated that patients with lower care levels are more likely to die in a hospital. Escobar Pinzón et al. (2011) found similar results in his study (care level 3 vs no care level: OR (death elsewhere vs inhospital death) 4.95, *p*-value < 0.0001) [4]. The higher the care level the higher the need for support in various aspects of everyday life. Thus, comprehensively dealing with the organization of the required care has already taken place. If a home-care setting for a person with high nursing needs has been organized previously, it is far easier to enable the patients dying outside a hospital – as hospitalization is necessary less frequently, and relatives are able to handle complications outside a hospital (with assistance of professionals).

According to our study, CHF and renal diseases increased the probability of inhospital death. These comorbid conditions tend to require intense treatments and are associated with a high likelihood of complications. Managing these complications often requires further inpatient hospital care [32]. However, it should be examined whether it is possible to further train formal and informal care-givers to manage these conditions outside the hospital.

If a patient in our study received inpatient palliative care, he was more likely to die in a hospital setting. This finding was unsurprising as inpatient palliative care is administered in a hospital for example on a palliative care ward. Our SA 2 supports this assumption as in this analysis we regrouped patients from the inhospital death group, if they had an inpatient palliative care treatment in the hospital stay of death. Resulting in the effect of inpatient palliative care changing direction and now reducing the likelihood of inpatient death.

Given, that outpatient palliative care was per se provided on a low level among patients of the inhospital death group, a conclusive interpretation of these results is limited to some extent. By trend, our analyses support the study of Purdy et al. (2015), which reported that patients receiving outpatient palliative care for a longer duration were less likely to die in a hospital. Patients and relatives using palliative care have usually already confronted the fact of impending death. Most families feel overburdened in this situation. The providers of palliative care are in a better position to assist the family with decision-making and to help them with enabling the patient's death in a preferred place – mainly because there is sufficient time and opportunity for such conversations. Furthermore, palliative care providers have a broad base of knowledge about the health care system as well as local supply structures. In addition, engaging with outpatient palliative care may define a population who are more determined to die at home. Purdy et al. (2015) [33] demonstrated that an end of life coordination centre that aims to help patients under palliative care be cared for in their preferred place, can reduce the number of inhospital deaths significantly (OR 0.33, p-value < 0.001).

In contrast to receiving palliative care, the administration of chemotherapy in the last 30 days of life was associated with an increased likelihood of inhospital death. Receiving chemotherapy shortly before death can be considered as an aggressive treatment and deemed undesirable by some clinicians [34, 35], even though it needs to be kept in mind that palliative care could to some extent also include chemo-therapeutic measures. That these patients more often die in a hospital could be explained by the close relationship between the patient and the oncologist who is often located in a hospital.

Furthermore, death might be associated with the treatment itself while in the hospital.

Similar reasons could play into the finding that patients with a higher number of hospital days also have a higher likelihood of inpatient death. A higher number of hospitalizations may indicate a more aggressive or longer tumour-directed treatment. Therefore, patients have an established relationship with the hospital and its clinicians and associate them rather than a palliative care team with the primary point of contact.

Despite higher comorbidity burden, patients in the inhospital death group were less frail as measured in care level and nursing home residency. Therefore, we can deduct that it's not the patients' frailty that has an impact on the place of death as these patients are already cared for at diagnosis, but more importantly specific comorbidities. Therefore, these comorbidities are important aspects to consider when lung cancer is diagnosed.

As expected, we found that expenditures for inpatient care were around double in the inhospital death group. However importantly, we could see that the excess costs in the outpatient sector for patients who did not die in the hospital were almost negligible. From this, we can conclude that not only costs for hospitalizations are much higher, but also additional expenditures for outpatient care are extremely low.

Thus, extending outpatient palliative care services as it currently happens in Germany will probably create a win-win situation for patients and the SHI system, since the expected decline in expenditures for inpatient care would compensate for the additional expenses in the outpatient sector. Our results are supported by the studies of Faßbender (2005) [36] and Smith et al. (2012) [37] who found that palliative care might have a cost-cutting effect because of fewer therapeutic interventions not primarily aiming at improving QoL for terminally ill patients. Thereby the need for inpatient treatments might be reduced and patients remain in a stable condition while still receiving sufficient medical and non-medical care.

Most limitations in our study stem from the use of claims data, which are primarily documented by healthcare providers for billing purposes with health insurance funds. The exact place of death is not important for these parties and is therefore not documented. This is the reason that within this study we have only been able to distinguish between inhospital death and death elsewhere. We do not know if patients in the inhospital death group died on a palliative ward or on a normal ward, nor can we differentiate between various places of death outside a hospital such as a hospice or the family home. Owing to data protection laws, data contained only year and month of death for those who died in an

outpatient setting. We used rules to define a more valid date of death but there are still possible differences to the actual date of death of up to 2 weeks for each individual. As O'Malley et al. (2005) described, the coding of ICD- and OPS-codes is a source of error in itself [38] which can e.g. arise out of unintentional and intentional coder errors, such as misspecification, unbundling, and up-coding. This should be considered when interpreting variables based on those codes like Charlson comorbidity groups. For historical reasons, the average income and the family structure of AOK-insured people may differ from the general German population. When there was no free choice of health insurance provider, the AOK as a Local Health Care Funds insured the general population (workers, retirees, family members) in contrast to company-provided health insurance funds, which for example insured predominantly persons with higher incomes and who tends to be healthier. Even now when all members of the population are in the position to choose their own health insurance provider, this structure is still visible. However, Jaunzeme et al. (2013) have shown that these differences are small enough to assume that the population of AOK-insured and herewith our results are representative for the German resident population [39].

Our study represents the first nationwide examination of factors possibly related to inhospital death in German lung cancer patients such as the patients' care needs, comorbidity burden, lung cancer-related treatments, and regional aspects. More importantly, we could provide expenditures for inhospital death not only as total but also for different aspects of care and therefore provide evidence that investments in palliative care can nevertheless reduce expenditures in total. As an innovative methodological approach, we applied the LASSO selection method which combines the easy interpretability and robustness. LASSO selection has been shown to outperform other selection methods like stepwise selection [40]. Finally, our analyses are automatically based on a multicentre study, whereby biases resulting from specific documentation rules and approaches of single healthcare providers are avoided. Thus, we are convinced that these analyses create a sound starting point for conditions that need to be considered when trying to create an environment supporting terminally ill-patients to make a more self-determined decision on where to spend their last days of life.

Conclusion

This study provides further evidence about factors related to inhospital death in German lung cancer patients. Findings suggest that factors associated with inhospital death often relate to previous contacts with hospitals. This includes prior hospitalizations, tumour-directed

treatment and treatment of comorbidities. Additionally, factors associated with dying elsewhere relate to access to other care settings than hospitals where therapy is focused more on palliation. From these results we can implicate that an early or earlier integration of palliative care into tumour-directed therapy might be a useful tool in helping patients to make informed decisions in the last phase of their life, by using established relationships e.g. with the oncologist. Additionally, further expanding the palliative supply network, can be achieved while still reducing costs for SHIs.

Endnotes

[1]Care level I: People who need assistance with personal hygiene, feeding or mobility for at least two activities from one or more areas at least once a day, and who additionally need help in the household several times a week for at least 90 min a day with 45 min attributable to basic care.Care level II: People who need assistance in at least two basic activities of daily living (ADLs) at least three times a day at various times and additional help in I ADLs several times a week for at least 3 h a day, with 2 h attributable to basic care.Care level III: People who need assistance in at least two ADLs around the clock and additional help in an IADL several times a week for at least 5 h per day, with 4 h attributable to basic care.

Additional files

Additional file 1: Parameter estimates from gamma regression costs. The table shows the parameter estimates from the gamma regression of costs in the last 30 days of life. Costs comprise total all-cause expenditures for hospitalizations, doctor visits and medications and are compared between patients with inhospital death to those who died elsewhere. (PDF 68 kb)

Additional file 2: Results of the logistic regression in SA 1 and SA 2. We ran the logistic regression with lasso selection method for SA 1 and SA 2 to proof the robustness of the main analysis. (DOCX 20 kb)

Abbreviations
AOK: A Local Health Care Funds; CHF: Congestive heart failure; CI: Confidence level; CPD: Chronic pulmonary disease; MLD: Mild liver disease; OR: Odds ratio; PVD: peripheral vascular disease; QoL: quality of life; SA: Sensitivity analysis; SD: Standard deviation; SHI : Statutory health insurance; WIdO: AOK Research Institute

helped to draft the manuscript. All authors read and approve the final manuscript.

Ethics approval and consent to participate

According to the German Guidelines for secondary data analysis ethical approval is generally not required for a retrospective analysis of claims data like this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Chapter 4 Article 3

"Age matters"—German claims data indicate disparities in lung cancer care between elderly and young patients

"Age matters"—German claims data indicate disparities in lung cancer care between elderly and young patients

Julia Walter [1,2] *, Amanda Tufman[2,3], Rolf Holle[1], Larissa Schwarzkopf[1,2]

1 German Research Center for Environmental Health, Institute for Health Economics and Health Care Management (IGM), Helmholtz Zentrum München, Germany, 2 German Center for Lung Research (DZL), Gießen, Germany, 3 Ludwig-Maximilians-University Hospital (LMU) Munich, Medical Clinic V–Pneumology, Munich, Germany

* Julia.Walter@helmholtz-muenchen.de

Abstract

Background

Although lung cancer is most commonly diagnosed in elderly patients, evidence about tumor-directed therapy in elderly patients is sparse, and it is unclear to what extent this affects treatment and care. Our study aimed to discover potential disparities in care between elderly patients and those under 65 years of age.

Methods

We studied claims from 13 283 German patients diagnosed with lung cancer in 2009 who survived for at least 90 days after diagnosis. We classified patients as "non-elderly" ($\leq$ 65), "young-old" (65–74), "middle-old" (75–84), and "old-old" ($\geq$ 85). We compared receipt of tumor-directed therapy (6 months after diagnosis), palliative care, opioids, antidepressants, and pathologic diagnosis confirmation via logistic regression. We used generalized linear regression (gamma distribution) to compare group-specific costs of care for 3 months after diagnosis. We adjusted all models by age, nursing home residency, nursing care need, comorbidity burden, and area of residence (urban, rural). The age group "non-elderly" served as reference group.

Results

Compared with the reference group "non-elderly", the likelihood of receiving any tumor-directed treatment was significantly lower in all age groups with a decreasing gradient with advancing age. Elderly lung cancer patients received significantly fewer resections and radiotherapy than non-elderly patients. In particular, treatment with antineoplastic therapy declined with increasing age ("young-old" (OR = 0.76, CI = [0.70,0.83]), "middle-old" (OR = 0.45, CI = [0.36,0.50]), and "old-old" (OR = 0.13, CI = [0.10,0.17])). Patients in all age groups were less likely to receive structured palliative care than "non-elderly" ("young-old" (OR = 0.84, CI = [0.76,0.92]), "middle-old" (OR = 0.71, CI = [0.63,0.79]), and "old-old" (OR = 0.57, CI = [0.44,0.73])). Moreover, increased age was significantly associated with reduced

quotas for outpatient treatment with opioids and antidepressants. Costs of care decreased significantly with increasing age.

Conclusion

This study suggests the existence of age-dependent care disparities in lung cancer patients, where elderly patients are at risk of potential undertreatment. To support equal access to care, adjustments to public health policies seem to be urgently required.

Introduction

Lung cancer was the fourth leading cause of death in Germany in 2016 [1]. Among all types of cancer, lung cancer accounted for the highest proportion of cancer-related deaths in men and the second highest in women [1]. Lung cancer is most commonly diagnosed in elderly patients with median age at diagnosis of around 68–70 years in developed countries [2–4]. In Germany in 2013, incidence rates ranged from 125 per 100 000 in 55- to 59-year-old men to 423 in 100 000 in 80- to 84-year-old men, and from 64 to 106 per 100 000 in women [5]. Despite these numbers, historically, elderly patients are underrepresented in clinical trials [6]; therefore, evidence on treatment effects in this relevant patient group is insufficient. Efforts to address this issue by enrolling more elderly patients in clinical trials have been made [7] and, since the 1990s, numbers have improved [8]. However, most elderly trial participants are enrolled in age-unspecific trials [9]. In these trials, only patients who meet the strict eligibility criteria concerning comorbidities and performance status are included [6, 9, 10]; therefore, they most probably do not represent the average elderly patient [10]. Recent guidelines include recommendations for elderly patients (>70 years), for example relating to performance status, but do not further differentiate between subgroups of elderly patients, for instance young-old, middle-old, and old-old [11]. However, clinical experience suggests that differences exist between age-based subgroups of elderly patients, and that both chronological and biological age can be relevant to treatment decisions in the setting of lung cancer [12]. Numerous studies have shown that treatments effective in younger adults can be of similar benefit to elderly patients [13, 14]; however, there is also evidence that treatment approaches in elderly patients are considerably different [15, 16]. Furthermore, survival in lung cancer is significantly associated with age as well [17, 18]. A study from Turkey found that patients over the age of 70 years had 1-year survival rates of 42.5% compared with 67.3% in patients 70 years or younger [17]. Similarly, in an analysis of Surveillance, Epidemiology and End Results data, an age gradient of 7.4% vs. 12.3% vs. 15.5% was found concerning 5-year survival rates in lung cancer patients aged younger than 70 years, between 70 und 79 years, and 80 years or older respectively [18].

Although most of the trials and studies concerning the treatment of elderly lung cancer patients focus on tumor-directed therapy, and some include pain management, no study has yet looked at differences in therapy comprehensively. Although access to tumor-directed treatment is certainly of importance, access to diagnostic tests and palliative care is also crucial and should be available to all affected patients regardless of age. Too little is known about care provided to elderly patients in various age subgroups.

Therefore, this study comparing non-elderly and elderly lung cancer patients in Germany aimed to:

1. evaluate whether tumor-directed treatment differs depending on age,

2. investigate whether delivery of diagnostic and palliative care measures is different across age groups, and

3. compare the costs of initial treatment and care after diagnosis across three elderly age groups.

Materials and methods

Dataset and sample selection

We analyzed anonymized health insurance claims from 17 478 patients with a first diagnosis of lung cancer in 2009—identified via ICD10 code C34—provided by the Scientific Institute of the AOK health insurance trust (WIdO), covering about 30% of the German population. As our dataset contained only retrospectively achieved and anonymized information on patients, meaning that the person in charge of this examination cannot make any inference to the individual person's data, the Ethics Committee of the Medical Faculty of the Ludwig-Maximilians-University of Munich approved exhaustive analyses of the data (Votum-Number 88–15). Additionally, consultation of an ethics committee is generally not required for this kind of study [19]. Basic data contained birth date, sex, postal codes, care level, and nursing home residency status over the course of the disease. Care level indicates the intensity of assistance needed to complete activities of daily living (higher care level = more assistance) [20]. Additionally, we used claims for hospitalization, outpatient hospital care, outpatient doctor visits, and medications including German International Classification of Diseases (ICD-10-GM) codes, OPS codes (German version of the International Classification of Procedures in Medicine), billing codes (GONR), and Anatomical Therapeutic Chemical (ATC) codes.

We identified 17 478 patients with incident lung cancer in 2009 according to a three-step process. First, we selected all patients with a diagnosis of lung cancer (ICD-C34) in 2009. In a second step, to avoid false positives, we included only patients with at least one inpatient principal diagnosis or at least two confirmed outpatient diagnoses in two distinct quarters of the year 2009. Third, we excluded all patients with a history of lung cancer or lung metastases in the 2 years prior to 2009. Further detailed information about this process can be obtained elsewhere [21]. From the sample of patients with incident lung cancer, we excluded patients with missing postal code of residence (n = 176). Additionally, we excluded those who died within the first 3 months after diagnosis (n = 4 019), as treatment options for them are limited and time to organize care is short. The proportion of these patients increased by age group, which we considered a source of bias, leading to an overestimation of treatment disparities. The remaining 13 283 patients were considered to be medically stable enough to qualify for some type of care.

We classified our sample according to age at time of diagnosis into "non-elderly" (≤ 65 years), "young-old" (65–74 years)," middle-old" (75–84 years), and "old-old" (≥ 85 years), a definition regularly used in gerontology [22].

Claims data do not include information about the stage of lung cancer, but the stage impacts on eligibility for therapeutic procedures [23]. Therefore, we stratified our sample into patients with advanced stage (with metastases) and patients with early stage (without metastases) disease, using the ICD codes for metastases within the 3 months after lung cancer diagnosis.

Outcome parameters

We compared the type of tumor-directed therapy in the 6 months after diagnosis by identifying antineoplastic therapy (cytostatic chemotherapy and targeted therapy), radiotherapy, and surgical lung resections from claims in the hospital (ICD and OPS codes), outpatient doctor visits (ICD and GONR codes), and prescribed medications (ATC codes). For information on specific codes, please refer to Schwarzkopf et al. [21].

In patients not receiving any tumor-directed treatments, we analyzed whether they received further invasive diagnostic measures (biopsy) to confirm the histological diagnosis.

To measure palliative care treatments, we first compared the proportion of patients who had claims for either inpatient (OPS codes) or outpatient (GONR codes) multimodal, structured palliative care, among patients who were deceased during the observation period. Second, we calculated the number of days between the first diagnosis and the first structured palliative care treatment for patients receiving structured palliative care. Third, as pain management and treatment of psychosocial aspects are an integral part of palliative care, we assessed the proportion of patients receiving opioids or antidepressants through claims for outpatient medications (ATC codes).

Additionally, we assessed all-cause and lung cancer-specific total, inpatient, outpatient, and medication expenditures within the 3 months after diagnosis to reflect the immediate treatment and care intensity. Lung cancer-specific expenditures related to inpatient visits with a primary diagnosis of lung cancer, medications used in antineoplastic therapy or as supportive drugs (e.g., antiemetics, antianemics), and outpatient cases with a diagnosis of lung cancer.

Confounders

We included the following variables as confounders in all analyses based on strong evidence in the literature: baseline information on sex, nursing home residency, and need for nursing care (care level) as a measure of performance status, comorbidity burden (Charlson index) [24], and residential area (rural/urban) [25].

Sex may influence the biology of lung cancer and, therefore, treatment options and outcomes [26, 27]. Also, we expected that the proportions of males and females in each age group may differ. Care level in combination with nursing home residency and Charlson index reflects the patients' frailty, which has been shown to influence treatment choice and outcomes in lung cancer specifically in elderly patients [28–30]. The Charlson index was calculated based on all inpatient ICD and all confirmed outpatient diagnoses in the 2 years prior to lung cancer diagnosis (excluding diagnoses of lung cancer and metastases). The area of residence has also been shown to influence treatments and survival in lung cancer [31, 32]. We identified the type of district of residence in our dataset based on the postal code of residence, using district types defined by the German Federal Institute for Research on Building, Urban Affairs and Spatial Development for 2014 [33].

Statistical analysis

In the univariate analysis, we calculated care as proportions and costs as means for the four age groups. We compared proportions using Chi^2 test and means using Kruskal–Wallis test.

For our multivariate analysis, we used logistic regression models for the binary outcomes palliative care, opioid medication, antidepressant medication, biopsy, no tumor-directed treatment, antineoplastic therapy, radiotherapy, and tumor resection, all reported as odds ratios (OR).

For count data (time until first palliative care), we used generalized linear regression models with negative-binomial distribution and reported results as incidence rate ratios (IRR). To model costs, we used a generalized linear model with gamma distribution and calculated age group-specific average costs based on recycled predictions. We applied non-parametric bootstrapping (1 000 bootstrap repetitions, percentile method) to obtain confidence intervals (CI) and p-values. Recycled predictions were obtained from the gamma regression model by averaging predicted scores, after fixing the value of one independent variable (here, age group "non-elderly") and using observed values on the remaining independent variables (age groups

"young-old", "middle-old", "old-old"). The recycled predictions then provide adjusted means for all age groups [34].

We used the age group "non-elderly" as reference in all regression models and adjusted them by the confounders mentioned above. We used a significance threshold of $\alpha \leq 0.05$ with 95% CI for all outcomes.

All analyses were performed using SAS 9.3 (SAS software from the SAS System for Microsoft, Version 9.3 (c) 2002–2010 by SAS Institute Inc., Cary, NC, USA); tables and figures were created in Microsoft Excel and R Studio using the graphical package *forestplot* [35].

Sensitivity analysis

To address a bias from possible misclassification of patients to the strata of no metastases, we conducted a sensitivity analysis. A misclassification could happen if, after the initial diagnosis of lung cancer, no further diagnostic procedures to investigate the extent of the disease (presence of metastases) were performed, due to either patient refusal or other concerns. Therefore, in this sensitivity analysis, we only included patients who did not have a diagnosis of metastases, but who had received further diagnostic procedures, including but not limited to, PET-CT, abdominal or cranial CT, and MRI.

Results

Sample characteristics and univariate analysis

Of the 13 283 patients, 4 595 (34.6%) were classified as "non-elderly", 5 195 (39.1%) as "young-old", 3 107 (23.4%) as "middle-old", and 386 (2.9%) as "old-old". Within all four age groups, the majority of patients were male, with the highest proportion among "young-old" (74.4%) and the lowest among "old-old" (55.7%). Patients' frailty, as reflected in comorbidity burden, nursing home status, and care level, increased by age group. In all age groups, most patients lived in urban areas, with the highest proportion of urban dwellers among "non-elderly". Around 60% of all patients had a diagnosis of metastases in the 3 months after diagnosis. In these patients, the proportion of "non-elderly" patients was around 10% points higher compared with patients without metastases. In consequence, in patients without metastases, a higher proportion of patients was in the age groups "middle-old" and "old-old" than in the stratum of patients with metastases. Further characteristics of patients with metastases compared with those without metastases did not differ. Table 1 displays sample characteristics of the whole study population, as well as for patients with and without metastases.

Within the pooled cohort of patients with and without metastases, proportions and means of all unadjusted outcomes differed significantly between the age groups, with higher age indicating lower treatment intensity. Additionally, domain-specific unadjusted expenditures differed significantly between the distinct age groups, with highest expenditures in "non-elderly" and gradually decreasing expenditures among more advanced age groups.

In patients without metastases, the proportion of patients receiving palliative care was higher than in patients with metastases across all age groups. Patients in higher age groups were less likely to receive palliative care than younger patients in both metastases strata. Prescription of opioids and antidepressants decreased with increasing age group independent of whether patients had metastases at diagnosis or not. The proportion of patients receiving opioids was higher in patients with metastases; the proportion of antidepressant prescriptions was similar. Regarding tumor-directed treatment, the share of patients receiving no tumor-directed therapy was higher in patients without metastases than in patients with metastases and increased with increasing age group. Diagnosis confirmation through biopsy was higher in patients with metastases than in patients without metastases and decreased with increasing

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Table 1. Sample characteristics of lung cancer patients diagnosed in 2009 in Germany.

All patients					
Means and proportions	Young (n = 4 595)	Young-old (n = 5 195)	Middle-old (n = 3 107)	Old-old (n = 386)	p-value
Male (%)	66.5	74.4	68.9	55.7	< 0.0001
Mean Charlson index at diagnosis	1.7	2.7	3.2	3.1	< 0.0001
Nursing home residency (%)	1.1	1.8	2.6	12.4	< 0.0001
Care level (%)					
No care level	91.7	86.8	77.2	53.9	< 0.0001
Care level 1	5.1	8.1	14.9	26.4	
Care level 2	2.7	4.4	6.9	16.8	
Care level 3	0.5	0.8	1.0	2.9	
Urban residence area (%)	66.4	61.8	60.6	60.1	< 0.0001
Patients with metastases					
Means and proportions	Young (n = 1 616)	Young-old (n = 2 077)	Middle-old (n = 1 492)	Old-old (n = 225)	p-value
Male (%)	65.0	75.6	68.8	55.1	<0.0001
Mean Charlson index at diagnosis	1.7	2.9	3.3	3.3	< 0.0001
Nursing home residency (%)	1.3	1.5	3.2	13.3	<0.0001
Care level (%)					
No care level	93.4	88.9	77.6	52.4	<0.0001
Care level 1	4.3	7.1	14.8	26.7	
Care level 2	1.9	3.5	6.6	18.7	
Care level 3	0.4	0.5	1.0	2.2	
Urban residence area (%)	66.7	62.5	60.5	58.7	0.001
Patients without metastases					
Means and proportions	Young (n = 2 979)	Young-old (n = 3 118)	Middle-old (n = 1 615)	Old-old (n = 161)	p-value
Male (%)	67.2	73.7	69.0	56.5	<0.0001
Mean Charlson index at diagnosis	1.7	2.6	3.1	2.9	<0.0001
Nursing home residency (%)	1.0	1.9	2.1	11.2	<0.0001
Care level (%)					
No care level	90.8	85.3	76.8	55.9	<0.0001
Care level 1	5.4	8.7	15.0	26.1	
Care level 2	3.2	4.9	7.2	14.3	
Care level 3	0.6	1.0	1.0	3.7	
Urban residence area (%)	66.3	61.4	60.7	62.1	0.0001

Notes: Means and proportions of sample characteristics in all patients and both metastases strata, in age groups "non-elderly"($\leq$ 65 years)," young-old" (65–74 years), "middle-old" (75–84 years), and "old-old" ($\geq$ 85 years). P-values from Chi^2 test for binary variables and Kruskal–Wallis test for continuous variables.

age. Therapy with antineoplastic agents decreased with increasing age group irrespective of the presence of metastases. Although there was no clear trend of radiotherapy treatment in patients without metastases, the proportion of patients with radiotherapy treatment decreased with increasing age in patients with a metastases diagnosis at diagnosis of lung cancer. Regarding lung cancer resection, there was no significant difference related to age in patients with metastases. In patients without metastases, the share of patients with a tumor resection decreased with increasing age group.

Results of the univariate analysis in the whole sample and in both metastases strata are displayed in Table 2.

Table 2. Unadjusted means and proportions of care and expenditures of lung cancer patients diagnosed in 2009 in Germany.

	All patients				
	Young (n = 4 595)	Young-old (n = 5 195)	Middle-old (n = 3 107)	Old-old (n = 386)	p-value
Structured palliative care in deceased patients (%) (n)	29.8 (1 368)	27.0 (1 402)	25.6 (795)	23.8 (92)	0.0001
of these, mean time until structured palliative care (sd)	369.1 (294)	356.8 (306)	312.2 (278)	253.4 (223)	<0.0001
Opioid medication (%) (n)	70.8 (3 255)	65.3 (3 393)	63.5 (1 974)	58.8 (227)	<0.0001
Antidepressants in patients without prior diagnosis of depression (%) (n)	30.8 (1 198)	25.8 (1 178)	22.4 (605)	18.2 (55)	<0.0001
No tumor-directed treatment (%) (n)	4.4 (200)	7.8 (403)	20.2 (626)	54.7 (211)	<0.0001
of these, patients with biopsy (%) (n)	61.5 (123)	60.3 (243)	56.2 (352)	43.6 (92)	0.0003
Antineoplastic therapy (%) (n)	65.9 (3 030)	58.3 (3 027)	44.3 (1 376)	17.1 (66)	<0.0001
Radiotherapy (%) (n)	23.7 (1 090)	21.9 (1 139)	21.4 (664)	17.1 (66)	0.004
Tumor resection (%) (n)	34.7 (1 595)	35.4 (1 839)	27.8 (864)	15.3 (59)	<0.0001
Mean all-cause total expenditures (€)	12 822	11 954	10 125	6 695	<0.0001
Mean all-cause hospital expenditures	10 393	9 790	8 411	5 491	<0.0001
Mean all-cause outpatient expenditures	101	906	780	670	<0.0001
Mean all-cause medication expenditures	1 418	1 258	934	534	<0.0001
Mean lung cancer-specific total expenditures	10 168	9 371	7 669	4 330	<0.0001

	No metastases				
	Young (n = 1 616)	Young-old (n = 2 077)	Middle-old (n = 1 492)	Old-old (n = 225)	p-value
Structured palliative care in deceased patients (%) (n)	19.9 (322)	19.6 (407)	19.4 (289)	26.7 (60)	0.08
of these, mean time until structured palliative care (sd)	488.0 (327)	441.1 (326)	373.8 (304)	300.3 (239)	<0.0001
Opioid medication (%) (n)	64.7 (1 045)	59.6 (1 237)	59.5 (887)	56.0 (126)	0.002
Antidepressants in patients without prior diagnosis of depression (%) (n)	31.2 (424)	25.5 (461)	20.3 (261)	18.8 (33)	<0.0001
No tumor-directed treatment (%) (n)	7.1 (114)	10.4 (215)	25.5 (381)	65.8 (148)	<0.0001
of these, patients with biopsy (%) (n)	62.3 (71)	58.6 (126)	54.9 (209)	39.9 (59)	0.001
Antineoplastic therapy (%) (n)	45.1 (728)	39.6 (823)	30.9 (461)	12.0 (27)	<0.0001
Radiotherapy (%) (n)	13.7 (221)	16.4 (341)	18.5 (276)	13.3 (30)	0.002
Tumor resection (%) (n)	54.6 (882)	50.8 (1 054)	34.3 (511)	11.6 (26)	<0.0001
Mean all-cause total expenditures (€)	11 381	10 645	9 181	5 920	<0.0001
Mean all-cause hospital expenditures	9 515	8 856	7 612	4 718	<0.0001
Mean all-cause outpatient expenditures	812	812	793	724	0.37
Mean all-cause medication expenditures	1 016	950	760	478	0.20
Mean lung cancer-specific total expenditures	9 000	8 126	6 583	3 708	<0.0001

	Metastases				
	Young (n = 2 979)	Young-old (n = 3 118)	Middle-old (n = 1 615)	Old-old (n = 161)	p-value
Structured palliative care in deceased patients (%) (n)	35.1 (1 046)	31.9 (995)	31.3 (506)	19.9 (32)	<0.0001
of these, mean time until structured palliative care (sd)	332.5 (273)	322.3 (290)	277.1 (256)	165.5 (158)	<0.0001
Opioid medication (%)(n)	74.2 (2 210)	69.2 (2 156)	67.3 (1 087)	62.7 (101)	<0.0001
Antidepressants in patients without prior diagnosis of depression (%) (n)	30.6 (774)	26 (717)	24.4 (344)	17.3 (344)	<0.0001
No tumor-directed treatment (%) (n)	2.9 (86)	6.0 (188)	15.2 (245)	39.1 (63)	<0.0001
of these, patients with biopsy (%) (n)	60.5 (52)	62.2 (117)	58.4 (143)	52.4 (33)	0.56
Antineoplastic therapy (%) (n)	77.3 (2 302)	70.7 (2 204)	56.7 (915)	24.2 (39)	<0.0001
Radiotherapy (%) (n)	29.2 (869)	25.6 (798)	24.0 (388)	22.4 (36)	0.0003
Tumor resection (%) (n)	23.9 (713)	25.2 (785)	21.9 (353)	20.5 (33)	0.06
Mean all-cause total expenditures (€)	13 604	12 826	10 997	7 778	<0.0001
Mean all-cause hospital expenditures	10 849	10 395	9 135	6 571	<0.0001
Mean all-cause outpatient expenditures	1 120	969	767	596	<0.0001

(Continued)

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Table 2. (Continued)

Mean all-cause medication expenditures	1 635	1 463	1 094	611	<0.0001
Mean lung cancer-specific total expenditures	10 422	9 823	8 440	5 127	<0.0001

Notes: Means and proportions of care and expenditures in age groups "non-elderly" ($\leq$ 65 years)," young-old" (65–74 years), "middle-old" (75–84 years), and "old-old" ($\geq$ 85 years). All-cause and lung cancer-specific total, inpatient, outpatient, and medication expenditures within the 3 months after diagnosis. Lung cancer-specific expenditures relate to inpatient visits with a primary diagnosis of lung cancer, medications used in antineoplastic therapy or as supportive drugs (e.g., antiemetics, antianemics), and outpatient cases with a diagnosis of lung cancer.

P-values from Chi^2 test for binary variables and Kruskal–Wallis test for continuous variables.

Multivariate analysis

Results of the multivariate analysis of the whole sample can be found in S1 (care) and S2 (costs) Figs in the supplementary material.

Patients without metastases. No clear trend was observed in patients without metastases concerning structured palliative care. Compared with the reference group "non-elderly", only "middle-old" patients showed a significantly lower likelihood of receiving structured palliative care (OR = 0.72, CI = [0.58, 0.88]). Time until palliative care was significantly shorter in "non-elderly" patients compared with "middle-old" (IRR = 0.80, CI = [0.69, 0.92]) and "old-old" patients (IRR = 0.71, CI = [0.56, 0.91]). All elderly age groups had a significantly lower chance of receiving opioids and antidepressants compared with "non-elderly" patients. Compared with "non-elderly" patients, the likelihood of receiving any tumor-directed treatment was significantly lower in all age groups with a decreasing gradient with advancing age. Referring to patients with no tumor-directed treatment, diagnostic biopsies were performed significantly less often in "old-old" than in "non-elderly" patients (OR = 0.49, CI = [0.29, 0.83]). The odds of receiving antineoplastic therapy were significantly lower and decreased with increasing age group. Receiving radiotherapy was significantly more likely in "middle-old" patients than in "non-elderly" patients (OR = 1.32, CI = [1.08, 1.16]). The likelihood of tumor resection was significantly higher in "non-elderly" patients compared with "middle-old" and "old-old" patients. All results from the multivariate analysis of patients without metastases are available in Fig 1.

Patients with metastases. The likelihood of receiving palliative care was significantly lower in all age groups compared with "non-elderly" patients in the group of patients with metastases ("young-old": OR = 0.83, CI = [0.74, 0.93], "middle-old": OR = 0.76, CI = [0.66, 0.88], "old-old": OR = 0.38, CI = [0.25, 0.56]). Similar to patients without metastases, in patients with metastases, the odds of receiving opioid and antidepressant medication was also significantly lower and decreased with increasing age group. Patients in all age groups were less likely to receive any kind of tumor-directed therapy compared with "non-elderly" patients, but the likelihood of diagnosis confirmation in untreated patients did not differ. Patients in all age groups were less likely to receive antineoplastic therapy than "non-elderly" patients ("young-old": OR = 0.75, CI = [0.67, 0.85], "middle-old": OR = 0.42, CI = [0.37, 0.48], "old-old": OR = 0.11, CI = [0.08, 0.16]). Additionally, the odds of receiving radiotherapy were lower in the "middle-old" and "old-old". The likelihood of receiving a resection was not associated with age in patients with metastases. Adjusted odds ratios and incidence rate ratios of patients with metastases are shown in Fig 2.

Figs 3 and 4 show age group-specific expenditures as recycled predictions with CIs. All types of expenditures decreased by age group, with "non-elderly" patients incurring significantly higher expenditures in all domains than the three more advanced age groups in patients with metastases. In patients without metastases, outpatient all-cause expenditures did not
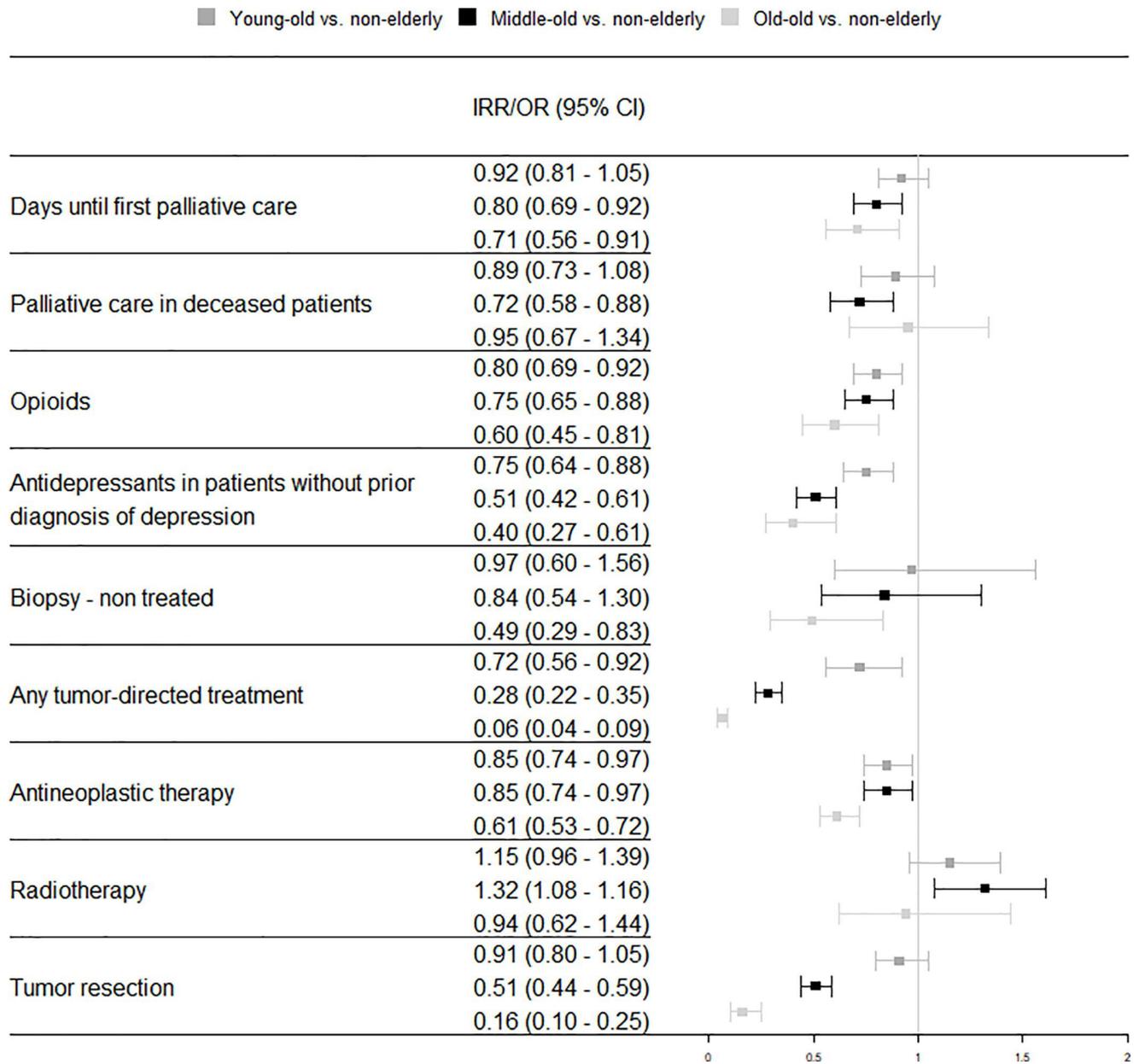
Fig 1. Adjusted odds ratio and incidence rate ratio of care among age groups of lung cancer patients with metastases diagnosed in 2009 in Germany. Time until first palliative care is reported as incidence rate ratio (IRR); all other outcomes are reported as odds ratios (OR). All IRR and ORs are adjusted for sex, nursing home residency, care level, Charlson comorbidity index, and rural vs. urban residence. CI = confidence interval, OR = odds ratio.

differ significantly between "non-elderly" and "young-old" as well as "old-old" patients. Additionally, all-cause medication expenditures did not differ between "non-elderly" and "old-old" patients. Other than that, the results were the same as in patients without metastases.

Sensitivity analysis

Results of the sensitivity analysis are provided in S1 and S2 Tables in the supplementary material. Results differed only marginally from the analysis in the original sample.
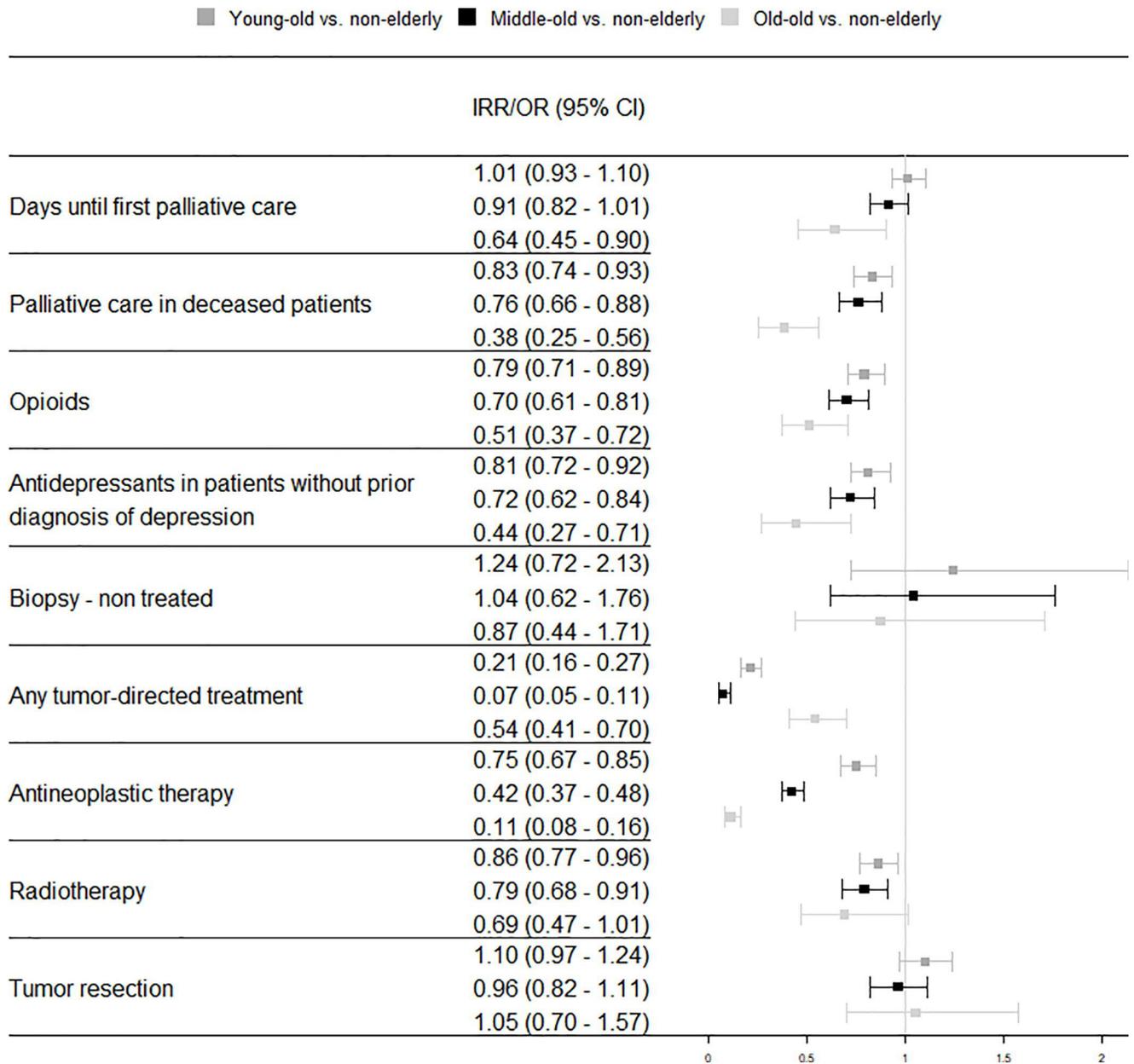
Fig 2. Adjusted odds ratio and incidence rate ratio of care among age groups of lung cancer patients without metastases diagnosed in 2009 in Germany. Time until first palliative care is reported as incidence rate ratio (IRR); all other outcomes are reported as odds ratios (OR). All IRR and ORs are adjusted for sex, nursing home residency, care level, Charlson comorbidity index, and rural vs. urban residence. CI = confidence interval, OR = odds ratio.

Discussion

Care for elderly lung cancer patients differs widely from care for patients under the age of 65 years, regardless of the presence of metastases at the time of lung cancer diagnosis. Elderly lung cancer patients receive fewer lung cancer-directed treatments than non-elderly patients. The proportion of patients not receiving any treatment in our study was around 40%, and even 66% among "old-old" patients with and without metastases, but only between 3% and 7% among "non-elderly" patients. An interesting finding was that the proportions of patients not

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|	Non-elderly (n=1 616)		Young-old (n=2 077)		Middle-old (n=1 492)		Old-old (n=225)	
■ Total all-cause	11 533 €		10 590 €	***	9 116 €	***	5 969 €	***
■ Total lung-cancer related	8 905 €		8 093 €	***	6 659 €	***	3 884 €	***
■ Inpatient all-cause	9 612 €		8 850 €	**	7 606 €	***	4 772 €	***
▨ Outpatient all-cause	871 €		796 €		758 €	**	715 €	
▨ Medication all-cause	1 045 €		943 €		749 €	***	488 €	***

Fig 3. Adjusted mean expenditures in the 3 months after diagnosis among age groups in lung cancer patients with metastases diagnosed in 2009 in Germany. All-cause and lung cancer-specific total, inpatient, outpatient, and medication expenditures within the 3 months after diagnosis reported as recycled predictions with 95% confidence intervals. Significance levels (* <0.05, ** <0.01, *** < 0.0001) indicate significant differences between the age groups "young-old" (65–74 years), "middle-old" (75–84 years), and "old-old" ($\geq$ 85 years) and the reference group "non-elderly" ($\leq$ 65 years). Lung cancer-specific expenditures relate to inpatient visits with a primary diagnosis of lung cancer, medications used in antineoplastic therapy or as supportive drugs (e.g., antiemetics, antianemics), and outpatient cases with a diagnosis of lung cancer.

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receiving any tumor-directed treatments were higher in the group of patients without metastases. We hypothesized that a reason for this was a problem of misclassification of patients to this stratum. By refining our sample in the sensitivity analysis, we believe we were able to address this issue appropriately, as now proportions in the younger age groups were similar. In particular, the use of antineoplastic therapy declined with increasing age in both metastases strata. Recent studies and guidelines support the use of carboplatin-based doublets in fit elderly patients and single-agent treatment in less fit patients [14]. However, for patients aged 80 years and older, there are limited data from trials; therefore, specific recommendations for this age group are lacking [36]. The extreme drop seen between the "middle-old" and "old-old" might be related to the reluctance of patients and physicians to administer antineoplastic therapy in a setting with little evidence from trials.

Although rates of tumor resections in patients with metastases were comparable in all age groups, the share of patients receiving tumor resection dropped from 55% in the "non-elderly" to less than 12% in "old-old" patients. This drop was still apparent in the refined sample from the sensitivity analysis. As we adjusted for comorbidities, care level, and nursing home status, increasing frailty of older patients cannot fully justify this observation. In the early stages of lung cancer, tumor resection is also recommended in elderly patients [14] and should not be denied just because of calendar age. There is evidence that outcomes of tumor resection in lung cancer patients are similar irrespective of age, even in patients older than 80 years [13, 37].

The results of our study underline previous findings about less comprehensive tumor-directed treatment in elderly patients. Costa et al. found that the likelihood of patients $\geq$ 70

|	Non-eldery (n=2 979)		Young-old (n=3 118)		Middle-old (n=1 615)		Old-old (n=161)	
■ Total all-cause	13 750 €		12 798 €	***	10 870 €	***	7 570 €	***
■ Total lung-cancer related	10 357 €		9 850 €	***	8 488 €	***	5 188 €	***
■ Inpatient all-cause	10 995 €		10 363 €	**	9 007 €	***	6 348 €	***
▨ Outpatient all-cause	1 113 €		969 €	***	774 €	***	614 €	***
▨ Medication all-cause	1 638 €		1 464 €	**	1 091 €	***	613 €	***

Fig 4. Adjusted mean expenditures in the 3 months after diagnosis among age groups in lung cancer patients without metastases diagnosed in 2009 in Germany. All-cause and lung cancer-specific total, inpatient, outpatient, and medication expenditures within the 3 months after diagnosis reported as recycled predictions with 95% confidence intervals. Significance levels (* <0.05, ** <0.01, *** < 0.0001) indicate significant differences between the age groups "young-old" (65–74 years), "middle-old" (75–84 years), and "old-old" (≥ 85 years)and the reference group "non-elderly" (≤ 65 years). Lung cancer-specific expenditures relate to inpatient visits with a primary diagnosis of lung cancer, medications used in antineoplastic therapy or as supportive drugs (e.g., antiemetics, antianemics), and outpatient cases with a diagnosis of lung cancer.

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years of age receiving tumor resection, antineoplastic therapy, and radiotherapy was significantly lower than for younger patients [38]. Additionally, Palma et al. reported that age was a significant predictor of receiving tumor resection but not a significant factor influencing overall survival after this surgical procedure [39].

In addition to tumor-directed care, we found significant differences in the rate of palliative care in elderly lung cancer patients in Germany. Experts from the "European Organization for Research and Treatment of Cancer elderly task force" recommend that palliative care should be integrated into lung cancer therapy shortly after diagnosis in patients with advanced disease [14]. Also, Temel et al. show in their study that palliative care alongside usual oncologic care results in prolonged survival, improved health-related quality of life, and reduced depression [40]. However, in our sample, only between 20% and 35% of patients received any structured palliative care.

Further, we found that the likelihood of patients being treated with opioids declines significantly by age group. This might indicate insufficient pain management at more advanced age. A systematic review reports that pain in cancer is prevalent in 39–66% of patients depending on the stage of the disease [41]. It also suggests that experiencing pain from cancer or cancer treatment does not depend on age; therefore, differences in the prevalence of pain management should not occur. In contrast to our results, the review by Deandrea et al. found no consistent role of age and sex concerning low-level pain treatment in cancer patients [42]. However, other studies have shown that older patients are at a disadvantage when it comes to pain management [43].

Similar results were found in the treatment of depression. Studies report that female sex, severe illness, as well as poor functional and performance status predominantly predict depression in cancer patients [43–46]. Therefore, we would not expect significant age-related differences in the treatment of depression. Concerning treatment with antidepressants, Findley et al. report reduced treatment in elderly patients with cancer and depression [47], and Ashbury et al. found that cancer patients in general are insufficiently treated for depression [48].

Expenditures in our study refer to health insurance expenditures in the first 3 months after diagnosis and reflect the intensity of measures taken up right after diagnosis. Total expenditures were on average €6 000–14 000 with a significant decrease the higher the age group. This was true for almost all cost components. The biggest cost component was expenditures for hospitalizations. These results emphasize at the monetary level how the intensity of treatment decreases with advancing age.

A limitation of our study is that our data did not include information about the histology or stage of the tumor at diagnosis. Therefore, we cannot exclude that lower treatment intensity in elderly patients might result from more advanced stages in our age categories. However, a study from the UK found that patients in their 50s and 60s are more likely to be diagnosed with advanced lung cancer than older patients [49]. Furthermore, by stratifying our study sample by the presence of metastases and refining this definition in our sensitivity analysis, we believe we were able to approximate stage at diagnosis. All the above analyses showed stable results of differences in therapy with increasing age.

Another limitation is that we had no access to any measures of patient preferences. Previous research has shown that the desire for aggressive therapy is as high in octogenarians as in younger patients [36]. In addition, when patients did not receive guideline-recommended therapy, this was due to refusal in only 26% of cases, whereas 48% were not offered the therapy because of comorbidities or poor performance status, and 26% were not offered therapy because of their age [36]. Further, while patient preference may play a role in the use of tumor-directed therapy, it does not seem plausible that elderly patients prefer to receive less palliative care or pain relief. Previous research has found that elderly patients are at risk of undertreatment for pain, as their sensitivity to pain is underestimated, they are expected to be able to tolerate pain well, and there is a misconception about their ability to benefit from the use of opioids [43, 50]. Management of pain and depression are integral parts of palliative care and closely interlocked according to the concept of "total pain" in cancer by Cecily Saunders [51]. Therefore, a strength of our study is including palliative measures in addition to active tumor treatment. Furthermore, by also comparing expenditures in the phase directly following diagnosis, we reflect overall differences in the intensity of initial care. The outstanding feature of our analysis is the direct comparison of different age groups, with a classification algorithm established in gerontology. So far, studies have investigated differences in treatment given to elderly patients mostly by either including age as a continuous variable in a logistic regression or studying cohorts only including elderly patients [15, 52, 53]. Stratification for age has been done previously, but mostly specifying one large group as elderly patients, for example all patients > 70 years [28, 36]. Thus, non-linear effects of aging might not have been comprehensively addressed within previous work. Another strength of our study is the sample size of our dataset. It covers around 30% of German residents, and our study population includes patients from all 402 districts in Germany. The AOK SHI funds are part of the German SHI system, which covers around 86% of the population. Some 95% of all SHI services are defined by law and offered by all the distinct SHI funds. Therefore, our results are generalizable to at least the whole German population insured under SHI.

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Conclusion

In conclusion, our study describes a significant age gradient across all care aspects studied, affecting tumor-directed therapies as well as palliative care and the treatment of pain and depression. Evidence from this study suggests that this effect cannot be explained completely by patient preferences and a certain degree of undertreatment in elderly patients is plausible. As a majority of lung cancer patients are over the age of 65 years, this is of great public health concern. Although efforts to enhance palliative care in Germany have been made, lawmakers should further adjust public health policies to address these disparities.

Supporting information

S1 Fig. Adjusted odds ratio and incidence rate ratio of care among age groups of lung cancer patients diagnosed in 2009 in Germany. Days until first palliative care is reported as incidence rate ratio (IRR); all other outcomes are reported as odds ratios (OR). All IRR and ORs are adjusted for sex, nursing home residency, care level, Charlson comorbidity index, and rural vs. urban residence. CI = confidence interval, OR = odds ratio.
(TIFF)

S2 Fig. Adjusted mean expenditures in the 3 months after diagnosis among age groups in lung cancer patients diagnosed in 2009 in Germany. All-cause and lung cancer-specific total, inpatient, outpatient, and medication expenditures within the 3 months after diagnosis reported as recycled predictions with 95% confidence intervals. Significance levels (* <0.05, ** <0.01, *** < 0.0001) indicate significant differences between the age groups "young-old" (65–74 years), "middle-old" (75–84 years), and "old-old" ($\geq$ 85 years) and the reference group "non-elderly" ($\leq$ 65 years). Lung cancer-specific expenditures relate to inpatient visits with a primary diagnosis of lung cancer, medications used in antineoplastic therapy or as supportive drugs (e.g., antiemetics, antianemics), and outpatient cases with a diagnosis of lung cancer.
(TIF)

S1 Table. Unadjusted means and proportions of care among age groups of lung cancer patients with metastases and diagnosis confirmation, diagnosed in 2009 in Germany. Notes: Means and proportions of care in age groups "non-elderly"($\leq$ 65 years), "young-old" (65–74 years), "middle-old" (75–84 years), and "old-old" ($\geq$ 85 years). P-values from Chi^2 test for binary variables and Kruskal–Wallis test for continuous variables.
(DOCX)

S2 Table. Adjusted odds ratio and incidence rate ratio of care among age groups of lung cancer patients with metastases and diagnosis confirmation, diagnosed in 2009 in Germany. Notes: Days until first palliative care are reported as incidence rate ratio (IRR); all other outcomes are reported as odds ratios (OR). All IRR and ORs are adjusted for sex, nursing home residency, care level, Charlson comorbidity index, and rural vs. urban residence. CI = confidence interval, OR = odds ratio.
(DOCX)

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Author Contributions

Conceptualization: Julia Walter, Rolf Holle.

Data curation: Julia Walter.

Formal analysis: Julia Walter.

Investigation: Julia Walter.

Methodology: Julia Walter, Rolf Holle, Larissa Schwarzkopf.

Supervision: Amanda Tufman, Rolf Holle, Larissa Schwarzkopf.

Validation: Julia Walter.

Writing – original draft: Julia Walter.

Writing – review & editing: Julia Walter, Amanda Tufman, Rolf Holle, Larissa Schwarzkopf.

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