Original Article

Is In-Hospital Mortality Higher in Patients With Metastatic Lung Cancer Who Received Treatment in the Last Month of Life? A Retrospective Cohort Study

Adinda Mieras, MSc, H. Roeline W. Pasman, PhD, Bregje D. Onwuteaka-Philipsen, PhD, Anne-Marie M.C. Dingemans, MD, PhD, Edith V. Kok, MD, Robin Cornelissen, MD, PhD, Wouter Jacobs, MD, Jan-Willem van den Berg, MD, PhD, Alle Welling, MD, Brigitte A.H.A. Bogaarts, MD, Lemke Pronk, MD, and Annemarie Becker-Commissaris, MD, PhD

Department of Pulmonary Diseases (A.M., A.B.-C.), Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam; Department of Public and Occupational Health (A.M., H.R.W.P., B.D.O.-P.), Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Public Health Research Institute, Amsterdam; Amsterdam UMC (A.M., H.R.W.P., B.D.O.-P., A.B.-C.), Vrije Universiteit Amsterdam, Expertise Center for Palliative Care, Amsterdam; Department of Pulmonary Diseases (A.-M.M.C.D.), Maastricht University Medical Center+, Maastricht; Department of Pulmonary Diseases (E.V.K.), Streekziekenhuis Koning Beatrix, Winterswijk; Department of Pulmonary Diseases (R.C.), Erasmus MC Cancer Institute, Rotterdam; Department of Pulmonary Diseases (W.J.), Martini Ziekenhuis, Groningen; Department of Pulmonary Diseases (J.-W.v.d.B.), ISALA, Zwolle; Department of Pulmonary Diseases (A.W.), Noordwest Ziekenhuisgroep Alkmaar, Alkmaar; Department of Pulmonary Diseases (A.W.), Noordwest Ziekenhuisgroep Den Helder, Den Helder; Department of Pulmonary Diseases (B.A.H.A.B.), VieCuri Medical Center, Venlo; and Department of Pulmonary Diseases (L.P.), Flevoziekenhuis, Almere, The Netherlands

Abstract

Context. Metastatic lung cancer is an incurable disease that results in a high burden of symptoms, a poor quality of life, and an expected prognosis of less than one year after diagnosis. Treatment shortly before death may result in potential burdensome and inappropriate hospital admissions and hospital deaths. Dying at home is, at a population level, considered a quality for good end-of-life care.

Objectives. We examined what percentage of patients with metastatic lung cancer died inside the hospital and if hospital death, or other characteristics of the patient, oncologist or health care, were associated with treatment in the last month of life.

Methods. This retrospective cohort study evaluated the medical records of 1322 patients with metastatic lung cancer who received care at one of 10 hospitals across The Netherlands and died between 1/6/2013 and 31/7/2015. Demographic and clinical characteristics were obtained from the medical records.

Results. In total, 18% of the patients died during a hospital admission. This percentage was higher for patients who received chemotherapy (42%) or targeted therapy with tyrosine kinase inhibitors (25%) in the last month of life. Patients younger than 60 years of age, patients who received chemotherapy in the last month of life, and patients in whom tyrosine kinase inhibitors were started in the last month of life were more likely to die inside the hospital.

Conclusion. In The Netherlands, fewer than one in five patients with metastatic lung cancer died in the hospital and in-hospital death was associated with the relatively late use of chemotherapy or targeted therapy. Careful selection of patients for disease-modifying therapy might enhance the opportunity for patients to die at their preferred place. J Pain Symptom Manage 2019;58:805–811.

Key Words

End of life, lung cancer, chemotherapy, TKI, place of death

Address correspondence to: Adinda Mieras, MSc, Department of Pulmonary Diseases, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, de Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands. E-mail: a.mieras@vumc.nl

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Introduction

Metastatic lung cancer is an incurable disease and the leading cause of death from cancer worldwide. This disease results in a high burden of symptoms, a poor quality of life, and an expected prognosis of less than one year after diagnosis.[1,2] Treatment is focused on relieving symptoms, temporary disease control, and prolonging lifespan. According to international guidelines on lung cancer, palliative chemotherapy, immunotherapy (introduced in 2015), and/or targeted therapy with tyrosine kinase inhibitors (TKIs) directed toward specific targetable protein driver mutations (such as EGFR and ALK mutations) are treatments of choice.[3–6] Aggressive treatment shortly before death is increasing over time[7] and may result in potential burdensome and inappropriate hospital admissions and consequently hospital deaths, which could be a threat to good end-of-life care.[8–10]

In many countries, a substantial part of patients with cancer die in hospitals,[11,12] whereas most patients prefer to die at home.[13–17] In a study of Cohen et al. (2017), between 27.5% (New Zealand) and 86.5% (Korea) of patients with lung cancer died inside a hospital, with 28% of patients in The Netherlands.[18] For metastatic lung cancer patients with a poor prognosis, quality of death is an important factor and dying at home is considered, at population level, as a quality indicator.[19] Multiple studies present factors influencing the probability of death at home, with anticancer treatment in the last phase of life as one of the factors that may hinder patients to die at home.[20–22] Results from a systematic review about determinants of home and nursing home death indicate that there are no studies available on factors associated with hospital deaths specifically for patients with metastatic lung cancer.[23,24]

Therefore, we conducted a multicenter study in The Netherlands to examine what percentage of patients with metastatic lung cancer died inside the hospital, what percentage received a treatment for metastatic lung cancer, and what percentage received chemotherapy or TKIs in the last month of life. We also examined if hospital death is associated with receiving treatment in the last month of life and other patients, health care, and oncologists characteristics.

Methods

Study Design and Population

We conducted a patient medical file study in 10 hospitals across The Netherlands, 3 academic and 7 nonacademic hospitals. We gathered demographic and clinical characteristics from medical files of patients who died of metastatic lung cancer. Medical files were selected based on Diagnosis Treatment Combinations (DBC) codes (DBC 1303 = non−small cell lung cancer [NSCLC], DBC 1304 = small cell lung cancer [SCLC]) or International Classification of Diseases (ICD) codes, Ninth and Tenth Revision (ICD9 and ICD10 for (N)SCLC). Out of this selection, patients were included if they were diagnosed with metastatic lung cancer and died between the 1st of June 2013 and the 31st of July 2015. A two-year time frame was chosen to assure a sufficient sample size. We excluded patients who were referred to another hospital for a second opinion and therefore might receive a medical treatment elsewhere (n = 123), who were treated with an experimental drug for lung cancer (n = 6), or if the date of the end of treatment was not known (n = 18). A total of 1322 patients were included in this study, ranging from 70 to 200 patients per hospital.

Ethics, Consent, and Permission

This study was approved by the medical ethical committee (METc) of the VU University Medical Centre in Amsterdam, The Netherlands. According to the committee, obtaining informed consent from the family of the patients was not required because this study is based on medical files of patients who already died and data are handled anonymously.

Statistical Methods

Statistical analyses were conducted using IBM SPSS statistics 22 (Armonk, NY). Frequencies were used for the descriptive statistics in Table 1. Generalized estimated equation (GEE) was used to attain understanding of the association between patient, health care, and oncologist characteristics and the place of death. By using the 10 hospitals as a subject variable, GEE accounts for the cluster effect present in the commonly used logistic regression models.

The dependent variable was the place of death. This variable was dichotomized as follows: 'died in hospital (yes/no)'. The independent variables were patient, health care, and oncologist characteristics. Patient characteristics were sex (male/female), age (≤60, 61-70, ≥71), marital status (married/unmarried), comorbidity (yes/no), and histology of the tumor (SCLC, NSCLC with targetable driver mutation [NSCLC+], NSCLC without targetable driver mutation [NSCLC-]). Health care characteristics were type of medical treatment for metastatic lung cancer (none/chemotherapy/TKIs), received medical treatment in the last month of life (no/yes; chemotherapy/yes; TKIs), started medical treatment in the last month of life (no/yes; chemotherapy/yes; TKIs), line of medical treatment (first, second, third, and more), and hospital type (academic/nonacademic). Oncologist characteristics were sex (male/female) and age (≤40, 41-50, ≥51). Hospital type and

Table 1
Demographic Characteristics of Study Participants ($N = 1322$)

Variable	*n* (%)
Gender	
Male	791 (60)
Female	531 (40)
Age (yrs)	
≤60	307 (23)
61–70	487 (37)
≥71	528 (40)
Marital status[a]	
Married	863 (76)
Not married	276 (24)
Comorbidity	
Yes	982 (74)
No	337 (26)
Tumor histology	
SCLC	264 (21)
NSCLC with targetable mutation	182 (14)
NSCLC without targetable mutation	843 (65)
Treatment for metastatic lung cancer	
Chemotherapy	692 (52)
TKI	121 (9)
None[b]	509 (39)
Treatment received in the last month	
Yes; chemotherapy	145 (11)
Yes; TKIs	87 (7)
No	1090 (82)
Treatment started in the last month	
Yes; chemotherapy	79 (6)
Yes; TKIs	15 (1)
No	1228 (93)
Line of treatment	
1st	490 (37)
2nd	185 (14)
≥3rd	134 (10)
Hospital type	
Academic	414 (31)
Nonacademic	908 (69)

SCLC = small cell lung cancer; NSCLC = non–small cell lung cancer; TKIs = tyrosine kinase inhibitors.
[a]>5% missing values: marital status (14%).
[b]None is defined as receiving no medical treatment for metastatic lung cancer.

oncologists characteristics were included in the analyses because policies and treatment preferences may very between academic, nonacademic hospitals and oncologists characteristics, respectively.

Each statistically significant variable in the univariate GEE analyses ($P < 0.10$) was entered into a multivariate GEE model. The final model was derived using the backward selection method, with a *P*-value of <0.05 considered as statistically significant. Results of the GEE analyses are presented as odds ratios and associated 95% confidence intervals.

Results

Patient Characteristics

From the 1322 patients with metastatic lung cancer, 692 patients (52%) received chemotherapy, 121 patients (9%) received TKIs, and 509 patients (39%) received neither. From the patients who did receive chemotherapy or TKIs, 232 patients (18%) received this in the last month of life. A total of 79 patients (6%) and 15 patients (1%) started chemotherapy or TKIs in the last month of life (Table 1).

Percentage of Patients Who Died Inside the Hospital or at Any Other Place

From all 1322 patients with metastatic lung cancer, 239 patients (18%) died inside the hospital (Fig. 1a). No difference was found, stratified for patients receiving any treatment or no treatment (Fig. 1b). Patients receiving TKIs showed a larger percentage (21%) of hospital deaths compared to patients receiving chemotherapy (18%) (not shown). However, a difference was seen when patients received any treatment in the last month of life; 36% of these patients died inside the hospital (Fig. 1c). From the 145 patients who received chemotherapy in the last month of life, 61 patients (42%) died in the hospital (Fig. 1d). From the 87 patients who received TKIs in the last month of life, 22 patients (25%) died inside the hospital (Fig. 1d).

Association Between the Characteristics of the Population and Hospital Death

Age, treatment in the last month of life, and treatment started in the last month of life were associated with death inside the hospital. Patients ≤60 years had a 1.233 times higher odds ($P = 0.039$) for death inside the hospital compared to patients with an age of ≥71 years. Patients who received chemotherapy in the last month of life had a 3.355 times higher odds ($P < 0.001$) for death inside the hospital compared to patients who did not receive a treatment in the last month of life. Patients in whom TKIs were started in the last month of life had a 9.911 times higher odds ($P < 0.001$) for death inside the hospital compared to patients who did not start a treatment in the last month of life (Table 2). From these patients in whom TKIs were started in the last month of life and died inside the hospital, one patient received this treatment in the first line, five patients in the second line, and four patients in the third line or more.

Discussion

Our study showed that 18% of patients with metastatic lung cancer died inside the hospital, which was independent of receiving treatment or not. Furthermore, 42% of patients who received chemotherapy and 25% of patients who received TKIs in the last month of life died inside the hospital. Patients younger than 60 years, patients who received chemotherapy in the last month of life, and patients in whom TKIs were started in the last month of life had higher odds to die inside the hospital.

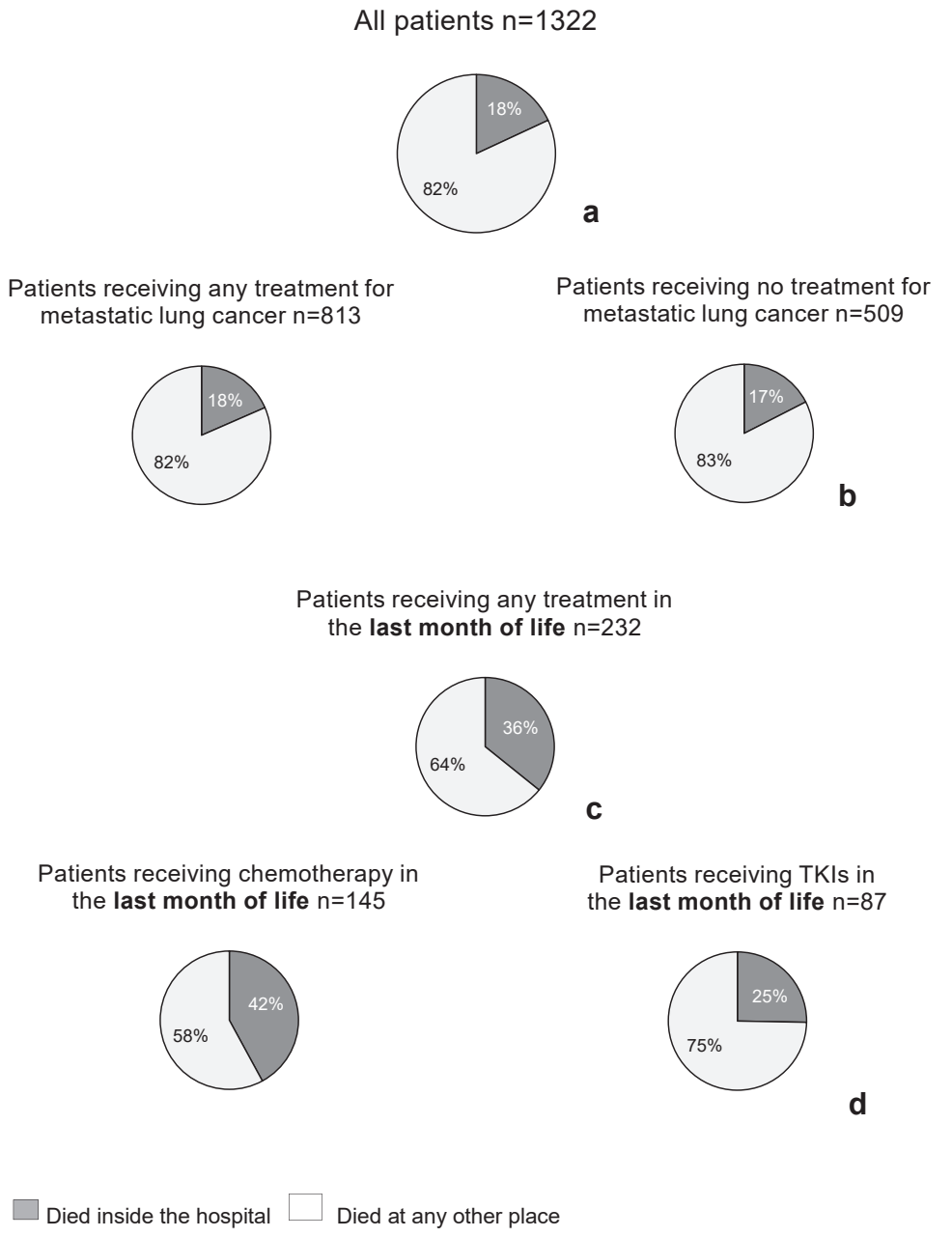

Fig. 1. (a–d) Percentages of patients with metastatic lung cancer who died inside the hospital or at any other place, specified in receiving treatment at any time (a and b) and in the last month of life (c and d).

In 2008, 28% of lung cancer patients died inside the hospital in The Netherlands.[18] This is a higher percentage compared to the results of our study where we show that in 2013–2015, 18% of patients with metastatic lung cancer died inside the hospital. This decrease in hospital deaths in five to eight years of time may be explained by the increased awareness of palliative care in general and the developments in home care.

In total, 18% of patients received a medical treatment for metastatic lung cancer within the last month of life and 7% started this treatment in the last month of life. This is comparable to the work of Earle et al.[7]

Our finding that patients receiving chemotherapy in the last month of life have higher odds for hospital death confirms findings from earlier studies that receiving chemotherapy in the last month of life is associated with a reduced likelihood of home death.[6,19,25] In interpreting this result, it is important to realize the fact that a high percentage of home deaths is considered a quality indicator of care at the end of life and does not mean that all hospital deaths

Table 2
Univariate and Multivariate GEE Analyses of Factors Associated With Hospital Death

$N = 1322$ Variable (n)	Patients Who Died in the Hospital (Row %)	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Gender					
Female (531)	17	1.0			
Male (791)	19	1.161 (0.927–1.454)	0.193		
Age (yrs)					
≤60 (307)	20	1.346 (1.140–1.590)	**<0.001**	1.233 (1.011–1.503)	**0.039**
61–70 (487)	20	1.348 (1.048–1.732)	**0.020**	1.229 (0.978–1.544)	0.077
≥71 (528)	15	1.0		1.0	
Marital status					
Married (863)	18	1.0			
Not married (276)	20	1.105 (0.697–1.754)	0.671		
Comorbidity					
No (337)	19	1.0			
Yes (982)	17	1.139 (0.878–1.477)	0.328		
Tumor histology					
SCLC (264)	21	1.0			
NSCLC with targetable mutation (182)	16	0.574 (0.302–1.092)	**0.091**		
NSCLC without targetable mutation (843)	18	0.791 (0.575–1.089)	0.150		
Treatment received for metastatic lung cancer					
None (509)	18	1.0			
Chemotherapy (692)	18	1.064 (0.788–1.438)	0.686		
TKI (121)	22	1.221 (0.761–1.959)	0.408		
Treatment in the last month of life					
No (1090)	14	1.0		1.0	
Yes; chemotherapy (145)	42	4.406 (2.796–6.944)	**<0.001**	3.355 (2.332–4.827)	**<0.001**
Yes; TKI (87)	25	2.038 (0.975–4.258)	**0.058**	1.159 (0.634–2.090)	0.623
Treatment started in the last month of life					
No (1228)	16	1.0		1.0	
Yes; chemotherapy (79)	47	4.626 (2.471–8.662)	**<0.001**	1.534 (0.936–2.515)	0.089
Yes; TKI (15)	67	11.878 (4.012–35.169)	**<0.001**	9.911 (3.960–24.801)	**<0.001**
Line of treatment					
1st (490)	19	1.0			
2nd (185)	20	1.091 (0.540–2.206)	0.808		
≥ 3rd (134)	16	0.807 (0.504–1.293)	0.373		
Hospital type					
Nonacademic (908)	16	1.0			
Academic (414)	22	1.429 (0.900–2.270)	0.130		
Sex oncologist					
Female (327)	16	1.0			
Male (919)	18	1.215 (0.714–2.065)	0.473		
Age category oncologist					
≤40 (181)	20	1.158 (0.717–1.870)	0.548		
41–50 (479)	17	1.082 (0.655–1.788)	0.757		
≥51 (585)	17	1.0			

GEE = generalized estimated equation; SCLC = small cell lung cancer; NSCLC = non–small cell lung cancer; TKIs = tyrosine kinase inhibitors.
Bold values indicate a *P*-value <0.1 for univariate analyses and a *P*-value <0.05 for multivariate analysis.

should be avoided. On an individual level, it is possible that dying in a hospital is an informed decision. Although most patients prefer to die at home,[16] hospital death may not always equal poor quality of death. A recent study showed that family members were satisfied with the quality of care patients received when they died inside the hospital. Symptoms were well managed overall and their loved ones were treated with kindness and respect.[26] There are several possible explanations for the relation between treatment in the last month of life and hospital death. Potentially, the aggressive character of the treatment increases the risk of hospitalization for the treatment of side effects.[5] Another explanation may be that when a patient is treated for lung cancer, the oncologist is still the main care provider and the patient has to come to the hospital now and then, making it more natural to go and stay in the hospital when problems occur. Patients in whom treatment for lung cancer is not started or stopped are referred back to the general practitioner. In an evaluation study from England, general practitioners mentioned that when one of their patients was hospitalized, they were rarely contacted by the hospital physicians about the patients' medical situation. Palliative care in the home setting becomes more difficult to accomplish in this scenario.[27]

Previous studies showed that patients with metastatic cancer who were receiving palliative chemotherapy and died inside the hospital are more likely to be

younger compared to patients who did not receive chemotherapy.[6,28,29] One possible explanation may be that oncologists and/or patients do not want "to give up" when patients are relatively younger resulting in starting and/or continuing treatment in the last month of life leading to a higher chance of hospital deaths.

To our knowledge, studies showing higher odds of hospital deaths in patients in whom TKIs were started in the last month of life have not yet been published. Our data set does contain patients in whom TKIs are started in the last month of life and died inside the hospital. However, this is only a small number ($n = 15$). The use of TKIs might have increased over the past years due to rapid developments in this field while our data stems from 2013 to 2015. To draw firm conclusions from this outcome, more research is needed.

The high number of patients analyzed in this study ($n = 1322$) among 10 different hospital sites makes the generalizability of the results large. By including three academic hospitals and seven nonacademic hospitals distributed across the North, East, South, and West of The Netherlands, we assume that it is a representative sample of the Dutch population with metastatic lung cancer. Because all patients diagnosed with metastatic lung cancer were included in this study, selection bias is minimized. To our knowledge, this is the first study that shows factors associated with hospital death in patients with metastatic lung cancer. At the same time, this study has some limitations. First, because of the retrospective study design, we are not informed on the preferred place of death. Second, we had information on several possible covariates or confounders, but it would have been good to have information on more. This is related to the limitations of a patient medical file study. For instance, data on performance status could not always be retrieved from medical records owing to absence of documentation. Patients with a poor performance status might have a higher risk to be hospitalized with death inside the hospital as a consequence. Other potentially relevant covariates or confounders are among others symptom burden, date of diagnosis, ethnicity, and socioeconomic circumstances.

In conclusion, our study shows that a substantial percentage of patients who received chemotherapy or TKIs in the last month of life died inside the hospital. Patients in whom TKIs were started in the last month of life even had a higher odds ratio of dying inside the hospital compared to patients who did not start in the last month of life. Although these treatments can be started with a palliative intent, a reluctant attitude toward treatment for metastatic lung cancer at the end of life might enhance the opportunity for patients to die at home, the preferred place of most people.[13–17] Although this study describes the Dutch situation, the percentages of hospital deaths for patients with metastatic lung cancer are informative for other countries.

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