

A Population-based Study of the Pattern of Terminal Care and Hospital Death in Patients with Non-small Cell Lung Cancer

CARSTEN NIEDER^{1,2}, TERJE TOLLÅLI³, JAN NORUM^{2,4}, ADAM PAWINSKI¹ and ROY M. BREMNES^{2,5}

¹Department of Oncology and Palliative Medicine, Nordland Hospital, Bodø, Norway;

²Institute of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway;

³Department of Pulmonology, Nordland Hospital, Bodø, Norway;

⁴Northern Norway Regional Health Authority, Bodø, Norway;

⁵Department of Oncology, University Hospital of North Norway, Tromsø, Norway

Abstract. Non-small cell lung cancer (NSCLC) is a major cause of cancer-related death and utilization of health care resources worldwide. Significant costs are generated in the months before death, with hospitalization being a major cost driver. Moreover, hospital death causes physical and emotional distress. We analyzed factors predicting the likelihood of hospital death from NSCLC. Patients who died from NSCLC (any stage and treatment) during the recent 5-year interval up to 31.12.2010, within a defined geographical region of northern Norway, were included (n=112). Only 15% of all patients did not require any hospitalization during their last 3 months. A minority of patients (24%) died at home, 53% in hospital and 23% in nursing homes. The likelihood of hospital death was independent of initial management and time between diagnosis and death. Even 45% of patients treated with best supportive care died in hospital. Multivariate analysis showed that initial tumor stage of T4 (RR 1.64), systemic therapy during the last 3 months of life (RR 2.60) and any active therapy during the last 4 weeks (RR 1.63) significantly increased the likelihood of hospital death, while early discussion of resuscitation preferences reduced it (RR 0.21). These four parameters suggest that early focus on symptom palliation and resuscitation preferences are crucial components of strategies improving terminal care. Patients with T4 tumors might experience unsatisfactory symptom control and should be offered a part in prospective studies addressing these issues.

The survival of patients with lung cancer is limited. For 2005-2007, 1-year survival was around 30% in the UK, 35% in

Denmark, and 39-44% in Australia, Canada, Norway, and Sweden (1). Five-year survival was 9-11% in the UK and Denmark versus 15-20% in the other four countries. In the US, 5-year relative survival was 16% during the time period 1999-2005 (2). The number of estimated deaths from lung cancer in the US in 2010 was 157,300, with non-small cell lung cancer (NSCLC) being the largest contributor. As a consequence, a large number of NSCLC patients worldwide receive palliative oncological treatment, either at diagnosis or recurrence. These patients might experience a considerable symptom burden when their disease becomes refractory to a specific line of treatment and in the terminal phase. Ideally, it would be desirable to obtain symptom control without aggressive end-of-life care, thus avoiding overuse of costly, potentially toxic and distressing treatments (3, 4).

As described previously, significant costs are generated by oncological treatment during the final months of life, with hospitalization being a major cost driver (5, 6). It is at least equally important that patients with cancer who died in an intensive care unit or hospital experienced more physical and emotional distress and worse quality of life (QOL) at the end of their life compared with patients who died at home or at a hospice (7). Among caregivers of these patients, hospital deaths were associated with a significantly increased risk for prolonged grief disorder. Previous analyses of large NSCLC populations have often been limited by lacking detailed information on different aspects of treatment and sociodemographic parameters. In this study, we performed detailed population-based analyses of baseline and sociodemographic factors plus several management- and outcome-related variables that might predict the likelihood of hospital death in patients with NSCLC.

Patients and Methods

This retrospective population-based study included all patients who died from NSCLC in the part of the Norwegian county of Nordland where all in-patient health care is provided by the Nordland Hospital

Correspondence to: Carsten Nieder, MD, Department of Oncology and Palliative Medicine, Nordland Hospital, P.O. Box 1480, 8092 Bodø, Norway. Tel: +47 75578490, Fax: +47 75534975, e-mail: carsten.nieder@nlsh.no

Key Words: Non-small cell lung cancer, palliation, hospital death, best supportive care.

Trust (NHT). NHT is owned by the Ministry of Health and Care services and administered through a regional trust (North Norway Regional Health Authority trust). It provides specialist-level health care services to approximately 112,000 inhabitants, *i.e.* roughly 50% of the population of the county (a geographically widespread, largely rural area) including its main city Bodø. NHT is the exclusive oncology care provider for the county where no private pulmonology or oncology services are available. As previously described, this fact and the structure of the Norwegian health care system allows for evaluation of unselected patient groups almost comparable to large population-based registries, albeit with limited size (8). We used the electronic databases of the Departments of Oncology and Palliative Medicine, Pulmonology, Thoracic Surgery and the Division of Internal Medicine, NHT, to identify all patients treated for histologically confirmed NSCLC and selected those who died during the 5-year time period from January 1st 2006 to December 31st 2010. The initial diagnosis of NSCLC could have been made earlier. Of 174 patients with NSCLC, 112 died from the disease and were included in this study. We excluded the remaining 62 patients; because they were alive at the date of data collection (January 1st 2011, $n=54$), because they had died from intercurrent disease with their NSCLC in remission ($n=6$), or because they had died within 30 days after surgery ($n=2$, pneumonectomy in both cases). All medical records including co-morbidity and medication use, death certificates and demographic data were available in the hospital's electronic patient record (EPR) system and were reviewed retrospectively starting from the first referral for suspected lung cancer until death. Our cohort was divided into 2 subgroups, *i.e.* patients who died in the hospital and those who died at home or in primary public health care facilities, *i.e.* nursing homes. No dedicated hospice services are available in the region but the primary health care sector also employs registered oncology nurses and cooperates closely with the multidisciplinary palliative team at NHT, *e.g.* by means of regular weekly meetings and telephone consultation. Hospital oncologists or pulmonologists might refer patients to the multidisciplinary palliative team. No consistent criteria for referral were used during the study period. All patients were Caucasians, born in Norway and covered by the national public insurance system. Their treatment was based on national guidelines developed by the Norwegian Lung Cancer Group (www.nlcg.no) (TT and RMB are members of this group) and discussed by a multidisciplinary tumor board which also meets on a weekly basis. TNM staging was applied as described in (9).

Statistical analysis and ethics. Patients were selected from the hospitals EPR system and the PASW Statistics 18 software package (IBM SPSS Statistics, Somers, NY, USA) was employed for the database and statistical analyses. For comparison of dichotomous variables the Chi-square test and Fisher's exact test, where applicable, were employed, and for continuous variables the Mann-Whitney *U*-test. For multivariate prediction of the primary study endpoint (likelihood of dying in hospital), Cox regression analysis was used (forward stepwise data selection method). Only variables with a significant *p*-value in the univariate tests were included in the multivariate analysis. The following variables were analyzed: age, sex, weight loss, co-morbidity, prescription drug use, smoking status, immediate family network, distance between hometown and hospital, T stage, N stage, TNM stage (seventh edition), initial pattern of metastatic disease (if any), pattern of metastases before death (if any), histology, time from diagnosis to death, initial

management strategy, clinical trial participation, number of lines of systemic treatment, timing of systemic treatment, use and timing of thoracic radiotherapy, active treatment during the last four weeks of life, referral to palliative team, patients' resuscitation preferences. Significance level was set to 5% and all tests were carried out as two-sided. The study was performed as a retrospective analysis of end of life care for NSCLC. As a quality of care analysis, no approval from the Regional Committees for Medical and Health Research Ethics (REK) was necessary.

Results

The study population included 112 patients, with a median age of 72 years. The majority were males (60%) and had stage IIIB (24%) or IV (40%) disease. Clinical and demographic characteristics are presented in Table I. The initial management consisted of surgical resection in 14 patients (12.5%), combined chemoradiotherapy in 14 (12.5%), palliative systemic treatment in 25 (22%), palliative thoracic radiotherapy in 39 (35%) and best supportive care (BSC) alone in 20 (18%) as displayed in Table II. During the last 3 months of life, systemic treatment was provided to 28% and thoracic radiotherapy to 23% of patients, respectively. During the last 4 weeks of life, 27% ($n=30$) of the patients received some type of active oncological therapy, *i.e.* radiotherapy and/or chemotherapy including tyrosine kinase inhibitors. Among these 30 cases, treatment was administered in an attempt to palliate brain metastases ($n=4$), thoracic disease progression ($n=18$), or other metastases ($n=6$). Two patients died unexpectedly from chemotherapy toxicity. Only a minority of the patients (23%) were referred to the multidisciplinary palliative team at NHT. The issue of resuscitation was discussed some time during treatment for 80% of the patients but for 45%, discussion took place during the last 2 weeks of life. During their last 3 months, the patients spent a median of 20 days in hospital. Only 17 patients (15%) were not hospitalized during their last 3 months.

Only 27 patients (24%) died at home, 59 (53%) in the hospital and 26 in nursing homes (23%, the median length of stay in nursing homes was 30 days). The patients who died in hospital also spent significantly greater number of days as in-patients during the last 3 months of life (median 22 *versus* 10, $p=0.0025$). Further details about the last hospital stay until death are shown in Table III. The likelihood of dying in hospital was not significantly influenced by the time from diagnosis to death (different cut-off points defining short or long survival were tested), or initial management strategy. Even 45% of the patients managed with BSC eventually died in hospital. Neither initial presence of brain metastases, bone metastases or any other specified organ metastases nor development of such metastases before death significantly influenced the likelihood of hospital death. Overall 14% of patients had brain metastases, 16% liver metastases, 29% bone metastases

Table I. Baseline parameters at lung cancer diagnosis.

Variable	All patients n=112	Patients who died in hospital n=59	Patients who died in other places n=53	p-Value
Age, years (median, range)	72, 47-89	69, 47-85	73, 48-89	0.24
Gender				
Male	67 (60%)	32 (54%)	35 (66%)	0.25
Female	45 (40%)	27 (46%)	18 (34%)	
Distance to hospital				
Short ^a	58 (52%)	33 (56%)	25 (47%)	0.45
Long ^b	54 (48%)	26 (44%)	28 (53%)	
Family status				
Relationship±children	68 (61%)	37 (63%)	31 (58%)	0.10
Children only	28 (25%)	17 (29%)	11 (21%)	
Single, no children	16 (14%)	5 (8%)	11 (21%)	
Smoking status				
Never smoker	5 (4%)	1 (2%)	4 (8%)	0.34
Quit ≥1 year	34 (30%)	20 (34%)	14 (26%)	
Quit <1 year	26 (23%)	16 (27%)	10 (19%)	
Active smoker at diagnosis	47 (42%)	22 (37%)	25 (47%)	
Comorbidity				
No serious comorbidity	54 (48%)	30 (51%)	24 (45%)	0.58
Previous other cancer	23 (21%)	12 (20%)	11 (21%)	
Other serious comorbidity ^c	35 (31%)	17 (29%)	18 (34%)	
Diabetes mellitus	8 (7%)	5 (8%)	3 (6%)	0.84
Prescription drug use				
None	32 (29%)	18 (31%)	14 (26%)	0.68
Use	80 (71%)	41 (69%)	39 (74%)	
Number of drugs (median, range)	3, 0-10	3, 0-10	2, 0-8	0.45
Weight loss				
0-5%	69 (62%)	38 (64%)	31 (58%)	0.56
>5%	43 (38%)	21 (36%)	22 (42%)	
Histology				
Squamous cell cancer	41 (37%)	23 (39%)	18 (34%)	0.83
Adenocarcinoma	42 (38%)	25 (42%)	17 (32%)	
Large cell anaplastic	8 (7%)	2 (3%)	6 (11%)	
Other or not specified	21 (19%)	9 (15%)	12 (23%)	
Disease stage				
T1 ^d	7 (6%)	4 (7%)	3 (6%)	0.01
T2	35 (32%)	15 (25%)	20 (38%)	
T3	37 (33%)	16 (27%)	21 (40%)	
T4	33 (29%)	24 (41%)	9 (17%)	
N0 ^d	27 (24%)	15 (25%)	12 (23%)	0.31
N1	12 (11%)	6 (10%)	6 (11%)	
N2	56 (50%)	27 (46%)	29 (55%)	
N3	17 (15%)	11 (19%)	6 (11%)	0.046
I ^d	6 (5%)	3 (5%)	3 (6%)	
II	9 (8%)	5 (8%)	4 (8%)	
IIIA	25 (22%)	10 (17%)	15 (28%)	
IIIB	27 (24%)	19 (32%)	8 (15%)	
IV	45 (40%) ^e	22 (20%)	23 (43%)	

^a0-30 km from home to hospital; ^bmore than 30 km from home to hospital;

^cfor example cardiovascular, cerebrovascular, liver diseases, COPD (exceeds 100% because of multiple comorbidities); ^dseventh edition of the TNM classification (based on imaging); ^eno significant impact of metastases location was found, *i.e.* neither patients with brain metastases, liver metastases, nor other patterns of spread were more likely to die in hospital.

and 25% pleural or contralateral lung metastases before death. Among all variables shown in Tables I and II and evaluated in univariate tests, only two baseline and three management-associated parameters were significantly associated with the likelihood of dying in hospital (Table IV). In the multivariate analysis, initial T4 stage significantly increased the likelihood of dying in hospital, while early discussion of resuscitation preferences decreased the likelihood (Table IV). The other two significant parameters were less useful in clinical practice because the actual survival of a given patient was unpredictable. The impact of T4 stage was unrelated to the recent changes in the TNM stage grouping because the patients staged T4 for separate tumor nodules in a different ipsilateral lobe, had comparably high rates of death in hospital (70%) than those with 'classical' T4 invading other structures (74%).

Cause of death was documented reliably and in sufficient detail only for patients who died in hospital. The prevailing cause of death of these 59 patients was thoracic NSCLC progression (47%), infection (22%), extrathoracic metastases (17%), myocardial infarction (5%), apoplexy (3%) and other causes (6%). The latter causes were considered directly or indirectly treatment-related (consequences of anemia, thrombocytopenia, steroid-induced complications *etc.*). In patients who died at home or in nursing homes, death was typically attributed to NSCLC without discriminating between intra- or extrathoracic causes.

Discussion

Comparable to the results of the present NSCLC study, other studies have shown that hospital death is more common than death outside hospital among patients with lung cancer of any histological type. Sharp *et al.* evaluated 18,078 deaths from lung cancer in Ireland (1994-2005) (10). The majority (53%) of deaths occurred in a hospital, 29% at home, 12% in hospices and 4% in nursing homes. The percentage of hospital deaths did not change over time. In Ontario, Canada, 59.5% of patients with lung cancer died in hospitals (analysis limited to the year 2002) (11). As in our study, age, gender and extent of metastatic disease did not significantly influence the likelihood of hospital death. However, progressive chest malignancy did. We also found a high proportion of deaths from thoracic cancer progression. Moreover, initial tumor stage of T4 was the only clinical disease-related parameter predictive of hospital death in the multivariate analysis.

The strengths of the present study are the completeness and comprehensiveness of data and the unselected patient population. Even patients of advanced age, those with previous malignant diseases and those managed with BSC were included. The limited patient population is, however, a weakness. Another weakness is that population-based studies,

Table II. *Patterns of care and general outcomes.*

Variable	All patients n=112	Patients who died in hospital n=59	Patients who died in other places n=53	p-Value
Initial management				
Best supportive care	20 (18%)	9 (15%)	11 (21%)	0.47
Primary systemic therapy	25 (22%)	11 (19%)	14 (26%)	
Surgical resection	14 (13%)	10 (17%)	4 (8%)	
Primary chemoradiation	14 (13%)	7 (12%)	7 (13%)	
Palliative thoracic radiotherapy	39 (35%)	22 (37%)	17 (32%)	
Clinical trial participation				
Included in prospective clinical trial	15 (13%)	8 (14%)	7 (13%)	0.9
Lines of systemic therapy				
Number (median, range)	1, 0-4	1, 0-4	1, 0-4	0.8
Timing of systemic therapy				0.002
Never received	50 (45%)	26 (44%)	24 (45%)	
During last 3 months before death	31 (28%)	23 (39%)	8 (15%)	
Stopped before last 3 months	31 (28%)	10 (17%)	21 (40%)	
Timing of thoracic radiotherapy (RT)				
Never received	39 (35%)	21 (36%)	18 (34%)	0.73
During last 3 months before death	26 (23%)	13 (22%)	13 (25%)	
Before last 3 months	47 (42%)	25 (42%)	22 (42%)	
Active treatment during last 4 weeks of life				
Any systemic or radiotherapy	30 (27%)	22 (37%)	8 (15%)	0.01
No active treatment	82 (73%)	37 (63%)	45 (85%)	
Palliative team utilization				
None	86 (77%)	47 (80%)	39 (74%)	0.51
≥3 Months before death	8 (7%)	4 (7%)	4 (8%)	
<3 Months before death	18 (16%)	8 (14%)	10 (19%)	
Resuscitation preference				
Discussed >2 weeks before death	40 (36%)	2 (3%)	38 (72%)	0.0005
Discussed during last 2 weeks	50 (45%)	45 (76%)	5 (9%)	
Not discussed	22 (37%)	12 (20%)	10 (19%)	
Other				
Days in hospital during the last 3 months of life (median, range)	20, 0-50	22, 1-50	10, 0-46	0.0025
Survival, months (median, range)	8.5, 0.7-56.8	8.7, 0.7-56.8	7.7, 1.3-30.5	0.29

regardless of size, always include patients staged by various modalities, exhibiting different levels of accuracy. Also in the present study surgically staged, positron emission tomography –computed tomography (PET-CT) staged and purely anatomical imaging staged patients were included. These differences might, however, influence N status more than T status, and hence are unlikely to explain the significant impact observed for patients with T4 stage tumor. Our presented demographic data and patterns of care appear both plausible and comparable to other larger studies. For example, the majority of patients who died from NSCLC had stage III or IV disease, while lower stages with secondary development of metastases were comparably underrepresented. Furthermore, most patients had received both systemic treatment and thoracic radiotherapy or surgery. In 715,330 patients with lung cancer analyzed by Coleman *et al.* (1), the mean age at diagnosis was 70 years, *i.e.* in accordance to our results.

If we take a critical look at our patterns of care during the terminal phase of the disease, in order to improve our future strategies, the findings of most practical relevance are that too many patients received active oncological treatment during the last 4 weeks of their life (27%) and antibiotics during their final hospitalization. NHT's palliative team may have been underutilized. Current efforts aim at improving access to the team, better cooperation with the primary public health care sector and opening of hospice facilities in the region. Besides that, communication regarding attempts for symptom relief, resuscitation preferences and other patient or caregiver expectations started too late. These findings, which were confirmed by other groups (12-14), highlight that aggressive end-of-life care and delayed focus on symptom palliation are highly important issues (15-17).

Even though one acknowledges that i) prediction of treatment toxicities and prognosis in individual patients still

Table III. Details regarding the final hospital stay of patients who died in hospital (n=59).

	Patients (n=20, 34%) with ongoing active treatment	Patients (n=39, 66%) who no longer received active treatment	p-Value
Median length of hospital stay, days (range)	12, 2-36	9, 1-26	0.36
Admitted to intensive care unit	1 (5%)	1 (3%)	1
Antibiotic therapy	10 (50%)	24 (62%)	0.42

Table IV. Multivariate Cox regression analysis of the five parameters with significant p-value in univariate tests.

Parameter	p-Value	Risk ratio (95% confidence interval)
T4 stage vs. all other T stages	0.007	1.64 (1.19-2.27)
Stage IIIB vs. all other stages	0.09	1.44 (0.98-2.12)
Making a resuscitation plan early vs. within the last 2 weeks, or not at all	0.008	0.21 (0.06-0.75)
Active radiation or systemic treatment during the last 4 weeks vs. no active therapy	0.04	1.63 (1.18-2.24)
Systemic treatment during the last 3 months vs. earlier, or not at all	0.01	2.60 (1.40-5.00)

are imperfect (18), ii) occasionally patients will die unexpectedly, and iii) one does not want to despire patients of hope while providing active treatment, there is a potential for improved, individually adjusted strategies of palliative care during the last months of life in these patients. Recently Yun *et al.* (19) reported that patients informed of their terminal diagnosis had a significantly better QOL, fewer symptoms, and had a lower rate of emotional distress than patients deducing it from their worsening condition. Clearly, reasonably accurate estimates of the remaining survival time are prerequisites for individually tailored communication and care. Both individual physicians and tumor boards were shown to overestimate the survival of patients with very limited prognosis, *i.e.* those who died in less than one month (20). More accurate prediction of short survival might be possible by assessing dyspnea, serum lactate dehydrogenase level and leukocytosis.

In our study, the number of hospital deaths was high and so was the proportion of deaths from locally progressive thoracic disease. Together with the fact that patients with T4 NSCLC had higher rates of hospital death, this suggests that airway obstruction, atelectasis, pneumonia, pleural effusion, pericardiac effusion, superior vena cava syndrome, fatal bleeding and chest pain from thoracic wall or spine infiltration, are challenging situations at the end of one's life.

To estimate how much the frequency of hospital deaths can be reduced, prospective studies are pivotal. Such data may result in better management strategies for symptom palliation in these patients with very limited life expectancy. In this context, interventions such as tracheobronchial stent insertion and endoluminal brachytherapy might be explored (21). Future efforts should also focus on ways of empowering

families and public education, as well as intensifying home care and training practitioners in end of life care (22).

Recently, a randomized trial of early palliative care for patients with metastatic NSCLC was published (23). This trial included 151 patients with defined performance status (ECOG 0-2) who were younger than the general NSCLC population (mean age 65 years). Early palliative care integrated with standard oncologic care led to significant improvements in QOL and mood from baseline to 12 weeks. Moreover, more patients assigned to early palliative care had their resuscitation preferences documented. Fewer patients received aggressive end-of-life care, yet median survival was longer among patients receiving early palliative care. Whereas 54% of the patients in the standard oncologic care arm were admitted to a hospital within 30 days of death, the rate was reduced to 37% in the early palliative care arm. However, this study included selected patients with metastatic NSCLC and therefore confirmation from unselected, more representative patient populations is required. A weakness of this study is the lack of data on treatment beyond first-line and pattern of disease progression before death.

Nevertheless, the heightened focus on palliative interventions and terminal care as well as improved communication and shared decision-making will clearly result in more published data within this field. This avenue of research has the potential to improve QOL and satisfaction of patients and their caregivers and optimize resource utilization. Resources saved by less active therapy at the end of life may be allocated to curative and early treatment efforts for other cancer patients (24, 25). Time spent on active therapy at the end of life may be better used on communication with patients and their relatives, as well as preparation for the final steps of life.

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Received October 6, 2011

Revised November 17, 2011

Accepted November 18, 2011