

Prolonged Survival in Patients with Lung Cancer with Diabetes Mellitus

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Introduction: Patients with lung cancer have a high frequency of comorbidity. Data on the impact of diabetes mellitus, the most frequent endocrine disorder, on the prognosis of lung cancer are conflicting. The aim was to investigate the impact of diabetes mellitus on survival in lung cancer.

Method: We analyzed data from a cohort, the Nord-Trøndelag Health Study (HUNT study) linked to the Norwegian Cancer Registry and controlled the results using two lung cancer studies, the Pemetrexed Gemcitabine study and the Norwegian Lung Cancer Biobank. Survival in lung cancer with and without diabetes mellitus was compared using the Kaplan-Meier method and Cox regression model for each study and the studies combined.

Results: One thousand six hundred seventy-seven cases of lung cancer were included, 1031 from HUNT study, 436 from the Pemetrexed Gemcitabine study, and 210 from the Norwegian Lung Cancer Biobank registry, and among these 77 patients had diabetes mellitus. In the combined analysis, patients with lung cancer with diabetes mellitus had increased survival compared with those without ($p = 0.005$). The 1-, 2-, and 3-year survival in patients with lung cancer with and without diabetes mellitus were 43% versus 28%, 19% versus 11%, and 3% versus 1%, respectively. Adjusting for age, gender, histology, and stage of disease in the Cox regression model, the hazard ratio for survival in patients with lung cancer with diabetes mellitus was 0.55 (95% CI, 0.41–0.75) as compared with without.

Conclusion: Patients with lung cancer with diabetes mellitus have an increased survival compared with those without diabetes mellitus.

Key Words: Lung cancer, Diabetes mellitus, Survival.

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Lung cancer incidence is high in the western countries, and in Norway lung cancer ranks among all cancers as the second highest in males and the third highest in females.¹

Age, gender, tumor histology, stage of disease, and performance status (PS) are well-established prognostic factors in lung cancer.^{2–5} Patients with lung cancer have a high frequency of comorbidities. In clinical lung cancer studies, patients with comorbidities often are excluded, leading to a lack of information about the potential effect of comorbidity on survival, quality of life, or the possible interactions of the therapeutic agents on the comorbidity itself. One reason may be that there is no consensus on how to assess comorbidity or the impact of comorbidity on disease course or survival.⁶

Diabetes mellitus is the most prevalent endocrine disorder and the incidence is increasing. Results from studies on the impact of diabetes mellitus on lung cancer prognosis are to date conflicting. One report showed an increased survival,⁷ three authors referred no change in survival^{8–10} and two studies showed decreased survival^{11,12} (Table 1). Diabetes mellitus has been reported to be associated with increased mortality in cancers of colon, pancreas, endometrium, liver, and breast.^{13–16} Another concern is how targeted therapy like insulin-like growth factor-1 receptor (IGF-1R) inhibitor may influence the prognosis in patients with lung cancer with diabetes mellitus. The aim of the present study was to analyze the impact of diabetes mellitus on survival in patients with lung cancer in a large Norwegian cohort study.

PATIENTS AND METHODS

The main study population was recruited from a prospective cohort study, the Nord-Trøndelag Health study (HUNT). In this population, we found 1206 cases of lung cancer. Adding the 436 cases from the Pemetrexed Gemcitabine study (PEG study) and the 210 cases of lung cancer from the Norwegian Lung Cancer Biobank study (NLBCB registry study), we identified a total of 1852 cases of lung cancer that were evaluated for inclusion into our study.

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TABLE 1. Characteristics of Relevant Publications Analyzing or Commenting the Influence of Diabetes Mellitus on the Survival in Patients with Lung Cancer

Reference	Type of Publication/ Type of Study	Inclusion Criteria for LC	Definition of DM	Numbers of Patients: Total/LC with DM	Adjusted for	Statistical Method	Survival in Patients with LC and DM	Mean Age (yr)	Gender
De Giorgio et al. ⁷	Letter to the editor/ retrospective	NA	NA	50/25	None	χ^2 test; 1- and 3-yr survival	Increased	NA	NA
Hanbali et al. ⁸	Research letter/ retrospective	NSCLC	History of DM	566/n.a.	Stage	Multivariable model; RR <1.0, 95% CI 0.68–1.17	Equal	NA	NA
Satoh et al. ⁹	Letter to the editor/ retrospective	NA	History of DM	975/90	Stage, sex, PS	Wilcoxon test; Cox regression model $p = 0.94$	Equal	NA	NA
Tammemagi et al. ¹⁰	Cohort study/registry study	NA	History of DM	1155/NA	Stage, sex, age, smoking history, histology	Kaplan-Meier method Cox regression model HR 1.40, 95% CI 0.2–2.72	Equal	NA	NA
Seshasai et al. ¹¹	Meta-analyses/ retrospective	NA	History of DM, fasting glucose, DM medication, DM type 2	NA	Sex, age, smoking history, BMI	Cox regression model HR 1.27, 95% CI 1.13–1.43	Decreased	55 ± 9	Male: 51% Female: 49%
Vasic ¹²	Prospective clinical study	Stage III/IV NSCLC	History of DM DM type 2	87/11	Stage, sex, age Karnofsky status	Kaplan-Meier method Cox regression model $p = 0.007$	Decreased	63.7	Male: 86% Female: 14%

LC, lung cancer; DM, diabetes mellitus; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; NA, not available; PS, performance status; BMI, body mass index; RR, risk ratio.

The aim of the study was to assess the influence of diabetes mellitus on the mortality of lung cancer. Hence, we included in the analyses only lung cancer-related mortality. Additionally, in the 3-year follow-up period, 92% of all patients who died, died of lung cancer-related mortality and only 8% of other or unknown causes.

Study Populations

The HUNT study is a large population-based prospective cohort study in Norway having collected data in three waves, HUNT 1 (1984–1986), HUNT 2 (1995–1997), and HUNT 3 (2006–2008).¹⁷ Individuals aged 20 years or more were invited each time. In total 77,216 (88% of invited), 65,215 (69% of invited), and 50,810 (54% of invited) people participated in HUNT 1, 2, and 3, respectively. Many people participated two or three times, which reduces the total number of subjects to 106,456. Nord-Trøndelag is a county in the middle of Norway having 130,708 inhabitants in January 2009. This population is considered representative of the Norwegian population, but the county lacks larger cities, has a lower educational and income level, and the proportion of smokers is slightly below the mean in Norway.

In all of the study waves, data were collected from the following three areas: demographic, personal and family medical history, and clinical examinations. The control study 1 (the “PEG” study) was an open randomized multicenter phase III trial of 436 patients with stage IIIB/IV non-small cell lung cancer by the Norwegian Lung Cancer Group.¹⁸ The aim of the study was to compare pemetrexed plus carboplatin versus gemcitabine plus carboplatin as first line chemotherapy, with respect to health-related quality of life, survival, and toxicity. All patients received four cycles of chemotherapy. The study was conducted from April 2005 to July 2006.

The control study 2 (NLCB, a registry study) started March 15, 2006, and aims to collect tumor tissue, normal tissue, and blood samples from patients consecutively admitted to hospital and suspected to have lung cancer. Thus, patient with and without lung cancer are included. In the current study, we have only included patients with histological verified lung cancer (stage of disease I-IV) until October 15, 2010.

Data from the HUNT study were linked to the Cancer Registry of Norway and the Norwegian Cause of Death Registry at Statistics Norway.¹⁹ In the PEG study and in the NLCB registry, data were collected from the electronic patient records.

Patients with lung cancer were included, but if the cause of death was either unknown ($n = 77$) or other than lung cancer ($n = 98$), the patients were excluded. Six patients of these 175 excluded patients with lung cancer had diabetes mellitus.

Study Variables

Lung Cancer Diagnosis and Stage of Disease

Lung cancer diagnosis was based on traditional histological classification (World Health Organization. Histological Typing of Lung Tumors, from the 2nd edition in 1981 to date). Lung cancer was classified as non-small cell lung cancer (NSCLC) or small cell lung cancer. Based on the

TNM classification system for lung cancer (International Association for the Study of Lung Cancer, IASLC) the Cancer Registry of Norway has categorized lung cancer into nonmetastatic and metastatic disease for the whole period. No tumor invasion of organ or neighbor structures, no lymph node metastasis other than local lymph node metastasis was defined as nonmetastatic disease. Patients with all other metastatic features, including organ and lymph node metastasis, were defined as metastatic disease.

We have no information about what treatment the patients in the HUNT study and the NLCB registry received. However, as in the PEG study where we have that information, there are no recommendations in our guidelines indicating that patients with diabetes mellitus should be treated differently from other patients.

Diabetes Mellitus

In the HUNT study, diabetes mellitus was defined by the answer “yes” to the question “Do you have or have you had diabetes.” Based on the age of the patients, use of medication and the duration of diabetes mellitus, the majority of the patients were classified as diabetes mellitus type 2. In the PEG study and the NLCB registry, diabetes mellitus was diagnosed according to information of diabetes mellitus and/or the use of antidiabetic medication in the hospital medical record.

Confounders

Gender, age (≥ 70 or < 70 years), PS, stage of disease, histology, and smoking status were tested in the regression models. PS was accessible only for the PEG study. All except for smoking contributed significantly and were included in the models.

Statistical Analysis

All analyses were performed for each study and combined to increase the power of the study. First, the Kaplan-Meier method was used to compare the median overall survival (OS) rate for patients with and without diabetes mellitus, and we added the 1, 2, and 3-year survival rates in both groups. Second, between groups differences in known prognostic factors were tested with the χ^2 test. Third, when the Log-rank test showed statistically significant differences, we used the adjusted Cox regression model to adjust survival for age, gender, tumor histology, and the stage of disease of disease. In the PEG study, we adjusted also for PS. Hazard ratio (HR) is reported with 95% confidence interval (CI), and statistical significance was defined as $p \leq 0.05$. Two-sided test was used in all statistical procedures. Statistical analyses were performed using PASW version 17 (Predictive Analytics Soft Ware IBM Corporation, New York, NY).

Ethical Considerations

The Regional Committee for Medical and Health Research Ethics have approved both the current study (REK no. 2010/1081) and the two control studies.

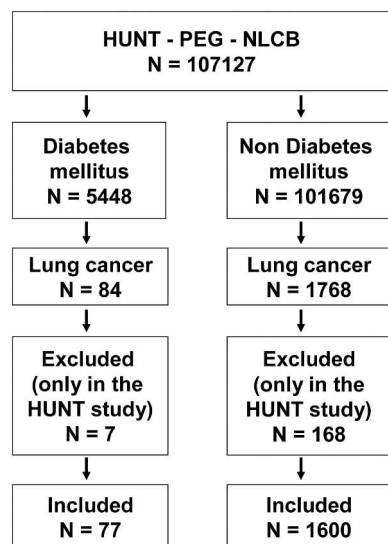


FIGURE 1. Flow sheet of the number of eligible patients included in the study.

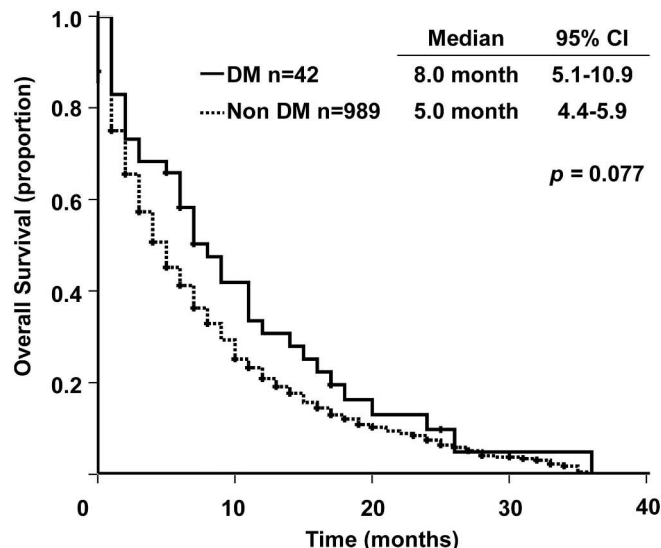


FIGURE 2. Kaplan-Meier survival curve for patients with and without diabetes mellitus in the HUNT study.

RESULTS

We analyzed the data from 1677 patients with lung cancer (Figure 1). The number of patients with lung cancer in the HUNT study, in the PEG study, and NLCB registry and their demographical characteristics are given in Table 2.

Results from the Lung Cancer Population in the HUNT Study

The Kaplan-Meier survival analysis showed a nonsignificant trend toward increased survival in patients with lung

cancer with diabetes mellitus compared with those without diabetes mellitus (*p* = 0.077). Median OS was 8.0 months (95% CI, 5.1–10.9) and 5.0 months (95% CI, 4.4–5.6), respectively (Figure 2).

The 1, 2, and 3-year survival for patients with and without diabetes mellitus were 33% versus 28%, 13% versus 8%, and 5% versus 1%, respectively. Patients with lung cancer were equal in age (*p* = 0.88), smoking history (*p* = 0.29), and tumor histology (*p* = 0.48), although the frequency

TABLE 2. Characteristics of Patients with Lung Cancer in the HUNT, PEG, and NLCB Study and These Cohorts When Merged

	HUNT 1984–2008 (n = 1206)				PEG 2005–2006 (n = 436)				NLCB 2006–2010 (n = 210)				Total (n = 1852)			
	DM (n = 49)		Non-DM (n = 1157)		DM (n = 17)		Non-DM (n = 419)		DM (n = 18)		Non-DM (n = 192)		DM (n = 84)		Non-DM (n = 1768)	
	n	%	N	%	N	%	N	%	N	%	N	%	N	%	n	%
Age (yr) ^a	71.0 ± 8.2		70 ± 10.9		73 ± 7.0		64 ± 9.8		68 ± 8.0		68 ± 9.7		70.1 ± 7.7		67.3 ± 10.1	
Gender																
Male	39	80	749	65	12	70	239	57	10	56	112	58	61	73	1100	62
Female	10	20	408	35	5	30	180	43	8	44	80	42	23	27	668	38
Smoking history																
Never	9	18	182	16	0	0	32	8	0	0	5	3	9	11	219	12
Ever	40	82	975	84	17	100	387	92	18	100	187	97	75	89	1549	88
Stage of disease																
Non-metastatic	28	57	507	44	—	—	—	—	8	44	80	42	36	43	587	33
Metastatic	11	22	520	45	17	100	419	100	9	50	110	57	37	44	1049	59
Unknown	10	21	130	11	—	—	—	—	1	6	2	1	11	13	132	8
Histology																
NSCLC	35	71	806	70	17	100	419	100	14	78	157	82	66	78	1382	78
SCLC	6	12	201	17	—	—	—	—	3	17	27	14	9	11	228	13
Unknown	8	17	150	13	—	—	—	—	1	5	8	4	9	11	158	9

n, number; HUNT, Health Study of Nord-Trøndelag; PEG, Pemetrexed Gemcitabine study; NLCB, Norwegian Lung Cancer Bio Bank; LC, lung cancer; DM, diabetes mellitus; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

^a Values given as median ± SD.

TABLE 3. Multivariate Analysis (Cox Regression) for Survival in Patients with Lung Cancer

	HUNT			PEG			NLCB			Total		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age (≥70 yr vs. <70 yr)	1.47	1.27–1.69	<0.001	1.05	0.84–1.31	0.652	1.62	1.12–2.36	0.011	1.39	1.24–1.56	<0.001
Gender (male vs. female)	1.15	0.99–1.34	0.071	0.72	0.58–0.89	0.003	1.68	1.13–2.48	0.01	1.32	1.18–1.50	<0.001
Stage of disease (metastatic vs. non-metastatic)	1.85	1.59–2.15	<0.001	1.22	0.96–1.55	0.102	2.94	1.92–4.49	<0.001	1.67	1.47–1.89	<0.001
Tumor histology (SCLC vs. NSCLC)	1.05	0.89–1.25	0.54	—	—	—	0.92	0.71–1.18	0.512	1.33	1.14–1.55	<0.001
DM vs. non-DM	0.69	0.46–1.04	0.08	0.51	0.27–0.96	0.037	0.74	0.38–1.44	0.381	0.55	0.41–0.75	<0.001

All available known prognostic factors for survival in lung cancer were entered in the Cox-model.
 HUNT, Health Study of Nord-Trøndelag; PEG, Pemetrexed Gemcitabine study; NLCB, Norwegian Lung Cancer Bio Bank; HR, hazard ratio; CI, confidence interval; LC, lung cancer.

of males was higher ($p < 0.029$) and the frequency of metastatic disease was lower ($p = 0.011$) among patients with diabetes mellitus. In the Cox regression model, adjusting for confounders, the nonsignificant trend of survival benefit persisted (HR, 0.69; 95% CI, 0.46–1.04) (Table 3).

Results from the PEG Study

The Kaplan-Meier survival analysis showed an increased 3-year survival in patients with lung cancer with diabetes mellitus compared with those without diabetes mellitus ($p = 0.048$). Median OS was 16.0 months (95% CI, 5.7–26.3) and 7.1 months (95% CI, 6.3–7.8), respectively (Figure 3).

The 1-, 2-, and 3-year survival for patients with and without diabetes mellitus were 53% versus 31%, 21% versus 12%, and 0% versus 0%, respectively. Patients with lung cancer with and without diabetes mellitus were equal in age ($p = 0.73$), gender ($p = 0.27$), smoking history ($p = 0.23$), and PS ($p = 0.453$), whereas the frequency of metastatic disease was lower ($p = 0.022$) in the diabetes mellitus group. Difference in histology could not be studied because all patients in this study had NSCLC. In the adjusted Cox regression model, diabetes mellitus showed increased survival in patients with lung cancer (HR, 0.51; 95% CI, 0.27–0.96).

When entering PS in the Cox model (together with age, gender, and stage of lung cancer), diabetes mellitus remained an independent prognostic factor for survival (HR, 0.48; 95% CI, 0.25–0.91).

Results from the NLCB Registry

The Kaplan-Meier survival analysis showed equal 3-year survival in patients with and without diabetes mellitus ($p = 0.93$). Median OS was 14.0 months (95% CI, 8.2–19.8) and 11.0 months (95% CI, 8.0–14.0), respectively (Figure 4).

The 1-, 2-, and 3-year survival for patients with and without diabetes mellitus were 52% versus 53%, 31% versus 38% and 0% versus 29%, respectively. Patients with lung cancer with and without diabetes mellitus were equal in age ($p = 0.98$), smoking history ($p = 0.49$), gender ($p = 0.68$), stage of disease ($p = 0.64$), and tumor histology ($p = 0.17$). In the Cox regression model, adjusting for confounders dia-

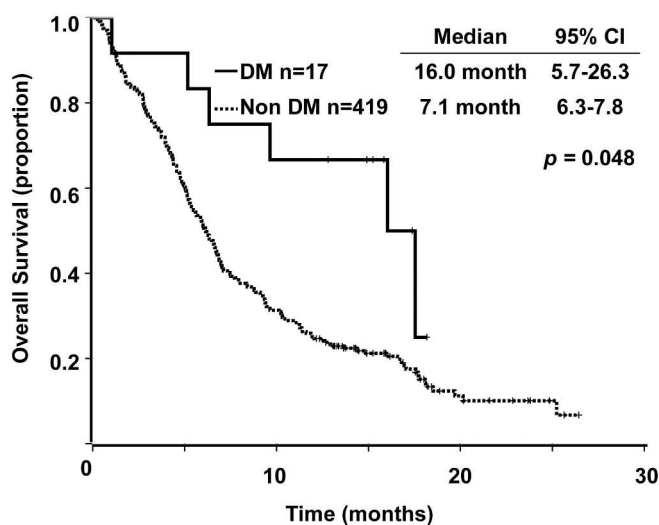


FIGURE 3. Kaplan-Meier survival curve for patients with and without diabetes mellitus in the PEG study.

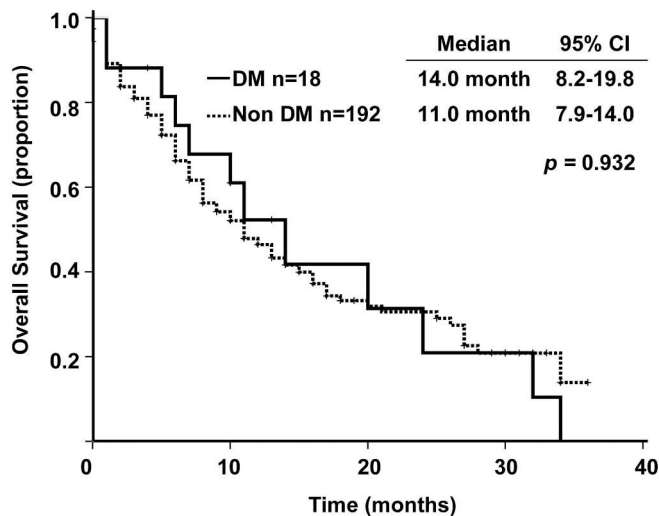


FIGURE 4. Kaplan-Meier survival curve for patients with and without diabetes mellitus in the NLCB registry.

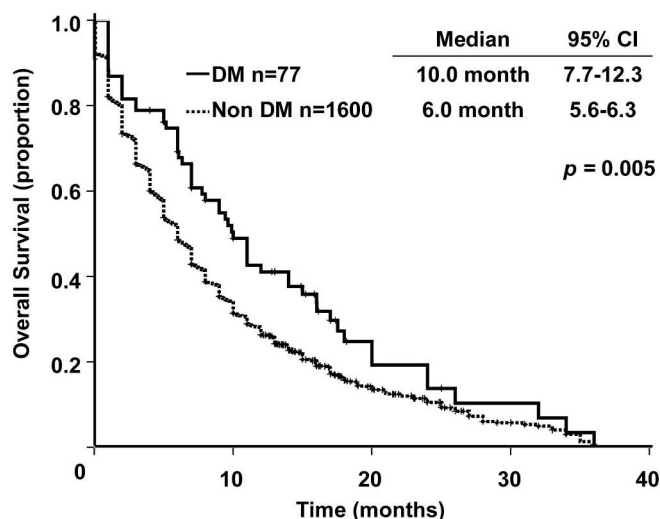


FIGURE 5. Kaplan-Meier survival curve for patients with and without diabetes mellitus in the HUNT and PEG study and NLCB registry all combined.

betes mellitus was not significantly associated with survival (HR, 0.74; 95% CI, 0.38–1.44).

Combined Survival Analysis in the HUNT and PEG Study and NLCB Registry

The Kaplan-Meier survival analysis showed an increased 3-year survival in patients with lung cancer with diabetes mellitus compared with patients with lung cancer without diabetes mellitus ($p = 0.005$). Median OS was 10.0 months (95% CI, 7.7–12.3) compared with 6.0 months (95% CI, 5.6–6.3) (Figure 5).

The 1-, 2-, and 3-year survival for patients with and without diabetes mellitus were 43% versus 28%, 19% versus 11%, and 3% versus 1%, respectively. Patients with lung cancer with and without diabetes mellitus were equal in age ($p = 0.88$), smoking history ($p = 0.92$), and tumor histology ($p = 0.88$), whereas there were more males ($p = 0.048$) and lower stage of disease ($p = 0.034$) among patients with diabetes mellitus. In the Cox regression model, adjusting for confounders, diabetes mellitus was an independent predictor (HR, 0.55; 95% CI, 0.41–0.75) of increased survival in lung cancer.

DISCUSSION

The HUNT study showed a trend toward increased survival in patients with lung cancer with diabetes mellitus, compared with patients without diabetes mellitus. In the PEG study, but not in the NLCB study, we found a significant survival benefit for those with diabetes mellitus. When pooling the patients with lung cancer from all three study populations, increased OS was found in patients with lung cancer with diabetes mellitus, both in the univariate and in the multivariate analyses when adjusting for known prognostic factors for survival among patients with lung cancer. Except for gender and stage of disease, there was no imbalance in other known prognostic factors between the two groups of

interest. The difference in stage-distribution is in our opinion not the reason for this unexpected observation. Patients with diabetes mellitus had longer survival also in the PEG study that included only patients with advanced disease. In addition, the hazard ratio was consistent in all three studies, also when adding PS in the analysis in the PEG study.

We found only one previous report showing increased survival in patients with lung cancer and diabetes mellitus.⁷ This report did not adjust for confounders and the patient number (lung cancer and diabetes mellitus) was as low as 25. Thus, this report supports our outcome results, but the report has obvious limitations that are also commented by others.⁹ Two studies reported decreased survival.^{11,12} The first study was a recently published meta-analysis consisting of 97 studies including patients based on either increased fasting blood glucose levels (≥ 7 mmol/l), medical records that confirmed the use of antidiabetics, or the diagnosis of diabetes mellitus. The mean age was about 55 years, compared with a median age of 71 years of patients with lung cancer reported by the National Cancer Institute,²⁰ which is in accordance with our study. The design and inclusion criteria in The Emerging Risk Factors (TERF) Collaboration study were different to our study. The diverging mean age, inclusion criteria, and design may explain the different results and the study populations and results are not directly comparable with our study. The second study was a prospective study of 87 patients with advanced lung cancer, of them 11 patients with diabetes mellitus, included over 1.5 years with 6 months follow-up. There were 86% men, and no exact definition of diabetes mellitus. The results were not adjusted for histology. The fact that men were highly overrepresented and the lack of precise definition of diabetes mellitus may explain the diverging results, compared with our study. A research letter, a comment and reanalysis of a study and one study showed no significant association between diabetes mellitus, lung cancer, and survival.^{8–10} However, despite no such association, it is noteworthy that Hanbali et al., like we did, reported a lower frequency of metastasis in lung cancer with diabetes mellitus. Tammemagi et al.¹⁰ studied patients in a private health care system using a retrospective design. Patients were either black or white people and were included during a 3-year period and were followed up for 2 more years. The Charlson index of comorbidity was used and the authors performed the same analyses as we did. Diabetes mellitus with end-organ damage showed an elevated adjusted HR of 1.4 for survival in patients with lung cancer and diabetes mellitus, but it was not significant (95% CI, 0.2–2.72), as for diabetes mellitus without end-organ damage.

All previous studies and reports are based on diverging designs and/or a limited number of patients that may be the cause of the inconsistent results (Table 1). With the introduction of individualized treatment using targeted therapy, comorbidity seems to be an important consideration. Reviewing studies using IGF-1R antagonists have shown results that are even more difficult to interpret.²¹ Serious adverse events such as hyperglycemia and dehydration were seen in the patients treated with IGF-1R antagonist (figitumumab).^{22,23} In addition, low body mass index and reduced creatinine clearance

were predictive of early death for patients receiving figitumumab plus chemotherapy versus only chemotherapy as shown by Jassem et al. in an Abstract no. 7500 ASCO 2010. This result underlines the importance of studying host-related factors like comorbidity and the influence on the prognosis, like serious adverse events related to the antitumor drug itself or its impact on comorbidity. Like in this case, IGF-1R antagonists may mask the positive prognostic effect of diabetes mellitus.

The fact that patients with diabetes mellitus showed a lower frequency of metastatic diseases may partly explain the survival benefit in patients with diabetes mellitus, because the majority of the patients with lung cancer die of metastasis and not of the primary tumor. However, as we adjusted for stage of disease in our analyses this potential advantage can hardly explain the observed increased survival in patients with diabetes mellitus. In addition, increased survival in patients with diabetes mellitus was clearly demonstrated in the PEG study where all patients had advanced lung cancer.

It can be argued that the survival benefit seen in patients with diabetes mellitus depends on more frequent and regular consultations that lead to an earlier diagnosis and thereby a survival benefit. However, the fact that the survival benefit was even more pronounced among the patients in the PEG study, where only patients with advanced lung cancer were included, contradicts the view that frequent consultation as the cause of increased survival.²⁴ Most likely the majority of the diabetic patients had diabetes mellitus type 2, so it is unclear whether the result can be transferred to patients with diabetes mellitus type 1.

The present study has some strengths and probably advantages compared with the previous studies discussed earlier. It is the first cohort study from a well-defined geographical area, with a stable and large number of inhabitants, investigating lung cancer, diabetes mellitus, and survival. The participation in the HUNT study was very high and indicates that we have investigated a representative study population. All previous studies are either clinical studies or letters or reports that briefly described survival in patients with lung cancer and diabetes mellitus, apart from the meta-analysis.¹¹ In contrast to the previous studies, the present study included patients with lung cancer without regard to histological classification or stage of disease, and that means minimal selection bias. Another advantage is the number of patients, 1600 patients with lung cancer without diabetes mellitus and 77 patients with lung cancer with diabetes mellitus.

In our study population (the HUNT study), the prevalence of lung cancer (1.9%), and diabetes mellitus (4%) is comparable with what is seen in western countries. The median age of the patients with lung cancer in the HUNT study was 71 years and indicates good external validity of the present study.

The three studies (HUNT, PEG, and NLCB study) recruited patients from the same geographical part in Norway (North or South Trøndelag in the middle of Norway). They represent different time periods, and the HUNT and the NLCB study included all diagnosed patients with lung can-

cer, whereas the PEG study included only advanced NSCLC (IIIB/IV). Thus, these patients are hardly highly selected.

A potential shortcoming is that we had no exact information about treatment in the HUNT study. On the other hand, we have no reason to believe that the treatment indication and chosen therapy for lung cancer in the three studies differ between patients with and without diabetes mellitus during the study period. In Norway, we practice very similar treatment indications and treatment modalities for the lung cancer population in accordance to the national guidelines, both with and without diabetes mellitus. In sum, we have found a rather consistent pattern with increased survival in patients with lung cancer with diabetes mellitus compared with those without diabetes mellitus.

CONCLUSION

In the patients with lung cancer, diabetes mellitus associates with increased survival compared with patients without diabetes mellitus. Standard therapy should not be withheld from patients with diabetes mellitus provided they are otherwise fit: even if it may be considered a significant comorbidity. The survival benefit may be of clinical importance and should be focused on in future studies.

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