Prolonged progression-free survival and overall survival are associated with diabetes mellitus but inversely associated with levels of blood glucose in patients with lung cancer

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Abstract

Background: Previous studies have provided conflicting evidence about the increased overall survival (OS) in lung cancer patients with diabetes mellitus (DM) compared with those without DM. This study assessed progression-free survival (PFS)/OS in lung cancer patients with or without DM and tentatively analyzed the impact of blood glucose levels on PFS/OS in lung cancer patients.

Methods: Data were collected from lung cancer patients based upon admission records from January 2010 to January 2012 and follow-up records from January 2010 to January 2015 in the Department of Pulmonary Medicine, Zhongshan Hospital, Fudan University, Shanghai. The data included patient sex, age, body mass index (BMI), smoking status, history of DM, level of blood glucose, pathological type, clinical stage of cancer, chemotherapy regimen, and history of anti-DM drugs. The Cox regression model and Kaplan-Meier method were used for the analysis of hazard factors and PFS/OS. For comparison of PFS/OS in lung cancer with or without DM, patients were divided into three groups: lung cancer with DM, lung cancer without DM but with elevated level of blood glucose, lung cancer without DM or elevated level of blood glucose.

Results: In total, the data from 200 lung cancer patients (138 males/62 females, aged 29.0 to 78.0 years, mean 60.0 ± 8.6 years) were collected. For the comparison of PFS/OS in lung cancer patients with or without DM, patients were divided into three groups: lung cancer with DM ($n = 31$); lung cancer without DM but with elevated levels of blood glucose ($n = 40$); and lung cancer without both DM and elevated levels of blood glucose ($n = 128$), whereas 1 patient dropped out of the study. All the patients underwent complete chemotherapy and were followed up for 36.0 to 60.0 months. Kaplan-Meier survival analysis showed that lung cancer patients with DM had increased PFS and OS compared with those without DM (log-rank, $P < 0.05$, $P < 0.01$); the median PFS in lung cancer with DM was 12.0 months (95% confidence interval [CI], 4.0–16.0) *vs.* 6.0 months in those without DM (95% CI, 5.8–6.3); and the median OS in lung cancer patients with DM was 37.0 months (95% CI, 29.0–46.6) *vs.* 12.0 months in those without DM (95% CI, 10.9–13.1). For the other two groups of patients without DM, there was a trend toward a shorter PFS and OS in patients with elevated blood glucose compared with those without elevated blood glucose. Cox regression showed that PFS in lung cancer patients was favorably associated with the usage of anti-DM drugs, BMI, clinical stage of cancer, and chemotherapy regimen (all $P < 0.05$) but was inversely associated with the level of blood glucose ($P < 0.05$).

Conclusions: Lung cancer patients with DM have prolonged PFS and OS compared with those without DM, and the level of blood glucose was inversely associated with PFS. The current results indicate that PFS may be a meaningful intermediate endpoint for OS and that the levels of blood glucose hopefully represent a prognostic factor in lung cancer patients.

Keywords: Diabetes mellitus; Lung cancer; Overall survival; Progression-free survival; Serum glucose level

Introduction

Epidemiological studies have demonstrated that lung cancer has become the leading cause of cancer-related death worldwide.[1] Although the diagnosis and treatment of lung cancer have improved in recent years, the 5-year survival rate of lung cancer patients is still very low.[2] However, the survival of lung cancer patients may involve many aspects. In clinical lung cancer studies, patients with lung cancer have a high frequency of comorbidities, among which diabetes mellitus (DM) is the most common comorbidity with lung cancer. An increasing number of studies have revealed that DM is an important risk factor for lung cancer in which there is a higher prevalence of DM in lung cancer patients,[3] but the relationship between the two diseases is still unclear, especially the impact of DM on lung cancer survival, results of which have been conflicting to date. The results from studies have shown increased

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survival,[4] no change in survival[5-7] and decreased survival[8] in lung cancer patients with DM. Therefore, it is necessary to provide further evidence for the potential effect of DM on the survival of lung cancer patients.

On the other hand, DM is known to be the most prevalent endocrine disorder, and the fluctuation of blood glucose is absolutely an influential factor on the prognosis of DM. Although age, sex, tumor histology, disease stage, and performance status are well-established prognostic factors in lung cancer,[9-12] the impact of blood glucose fluctuations on the prognosis of lung cancer patients is still a key point that needs to be clarified. In lung cancer patients with or without DM, fluctuations in blood glucose frequently exist due to DM itself, the usage of chemotherapy and corticosteroids, surgery, or other factors. Therefore, a question arises as to whether blood glucose levels can represent a prognostic factor for survival in lung cancer. Unfortunately, few studies have examined this issue, and the epidemiological evidence is limited.[13]

The present study aimed to assess progression-free survival (PFS)/overall survival (OS) in lung cancer patients with or without DM and to tentatively analyze the impact of blood glucose levels on PFS/OS in lung cancer patients.

Methods

Ethical approval

This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University, China, and obtained informed consent from the patients.

Data collection

Data were collected from lung cancer patients based upon admission records from January 2010 to January 2012 and follow-up records from January 2010 to January 2015 in the Department of Pulmonary Medicine, Zhongshan Hospital, Fudan University. The data included patient sex, age, body mass index (BMI), smoking status, history of DM, level of blood glucose, pathological type, clinical stage of cancer, chemotherapy regimen, and history of anti-DM drugs. The inclusion criteria were as follows: newly diagnosed with lung cancer based on pathological type and clinical stage; pre-existing DM before the diagnosis of lung cancer; completed chemotherapy regimens (including surgical treatment before chemotherapy for all stage I and stage II patients); and follow-up after treatment. The exclusion criteria were as follows: insufficient clinical or pathological data; incomplete follow-up records; and other concurrent comorbidities (except DM).

Basic characteristics of clinical stage and chemotherapy regimens of lung cancer patients

The pathological types of lung cancer were squamous-cell carcinoma, adenocarcinoma, and small cell lung cancer types. The clinical stage of cancer was determined according to the International Association for the Study of Lung Cancer criteria.[11] The chemotherapy regimens included cisplatin/pemetrexed (PP), cisplatin/docetaxel (DP), cisplatin/vinorelbine (NP), cisplatin/paclitaxel (TP), and cisplatin/gemcitabine (GP). All stage I and stage II patients underwent surgical treatment before chemotherapy. Some patients received 5 mg intravenous dexamethasone on the day of chemotherapy.

Diagnosis of DM and monitoring of blood glucose

Pre-existing DM was diagnosed according to information on DM and/or the use of anti-diabetic medication in the hospital medical records. The levels of blood glucose were monitored at the points of each chemotherapy cycle and lasted for 36.0 to 60.0 months with a total of four to six chemotherapy cycles and follow-up periods.

Evaluation of the association of DM and levels of blood glucose with PFS/OS in lung cancer patients

Kaplan-Meier survival analysis was used to compare the survival curves of lung cancer patients with or without DM. Cox proportional hazard regression models were used for analyses of the association of PFS/OS with levels of blood glucose and other influential factors. The primary endpoint was OS, which was defined as the time from chemotherapy initiation to the date of death from any cause or was censored at the last follow-up. PFS was defined as the time from chemotherapy initiation to the time of disease progression or death or was censored at the last follow-up. We defined disease progression according to the standard Response Evaluation Criteria in Solid Tumors.[14]

Statistical analysis

All statistical analyses were performed using SPSS statistical software (version 19.0 for Windows; IBM Corporation, Armonk, NY). χ^2 tests and independent-samples *t*-tests were used to compare categorical variables and continuous variables, respectively. Normally distributed data are shown as the mean ± standard deviation. The statistical significance level was set at a P value < 0.05.

Results

Basic characteristics of the data collection

In total, all the data from lung cancer patients admitted to our hospital were reviewed from January 2010 to January 2012, and the data from 200 newly diagnosed lung cancer patients were ultimately included (138 males/62 females, age 29.0–78.0 years, mean 60.0 ± 8.6 years), including 31 lung cancer patients with pre-existing type 2 DM who met the inclusion criteria. For Kaplan-Meier survival analysis, enrolled patients were divided into three groups based on the study purpose: lung cancer with DM ($n = 31$); lung cancer without DM but with elevated levels of blood glucose ($n = 40$); and lung cancer without both DM and elevated levels of blood glucose ($n = 128$), whereas 1 patient dropped out of the study. Based on the endpoint, there were 176 patients who completed the follow-up period. The basic characteristics of the enrolled patients with lung cancer are summarized in Table 1.

Table 1: Basic characteristics of enrolled patients with lung cancer.

Variables	With DM ($n = 31$)	Without DM, elevated blood glucose ($n = 40$)	Without DM, no elevated blood glucose ($n = 128$)
Age (years), mean ± SD	62.2 ± 6.2	59.4 ± 7.6	58.1 ± 9.3
<60 years, *n* (%)	9 (29.0)	20 (50.0)	68 (53.1)
≥60 years, *n* (%)	22 (71.0)	20 (50.0)	60 (46.6)
Sex, *n* (%)			
Male	22 (71.0)	27 (67.5)	88 (68.7)
Female	9 (29.0)	13 (32.5)	40 (31.3)
Blood glucose (mmol/L)			
Before chemotherapy	7.2 ± 0.9	5.5 ± 0.7	5.0 ± 0.7
During chemotherapy	7.2 ± 1.7	5.8 ± 0.9	4.8 ± 0.4
After chemotherapy	8.2 ± 0.8	6.2 ± 0.6	4.9 ± 0.7
Smoking history, *n* (%)			
Yes	18 (58.1)	21 (52.5)	70 (54.7)
No	13 (42.0)	19 (47.5)	57 (44.5)
Body mass index (kg/m^2), mean ± SD	25.3 ± 3.9	23.9 ± 3.0	22.4 ± 3.1
Clinical Stage, *n* (%)			
I	7 (22.6)	2 (5.0)	11 (8.6)
II	4 (12.9)	2 (5.0)	10 (7.8)
IIIa	3 (9.7)	7 (17.5)	23 (18.0)
IIIb	5 (16.1)	5 (12.5)	21 (16.4)
IV	12 (38.7)	24 (60.0)	62 (48.4)
Pathological type of lung cancer, *n* (%)			
Squamous-cell carcinoma	11 (35.5)	16 (40.0)	40 (31.3)
Adenocarcinoma	16 (51.6)	21 (52.5)	79 (61.7)
Small cell lung cancer	4 (12.9)	3 (7.5)	9 (7.0)
Chemotherapy regimes, *n* (%)			
Cisplatin/gemcitabine (GP)	18 (58.1)	17 (42.5)	48 (37.5)
Cisplatin/paclitaxel (TP)	3 (9.7)	11 (27.5)	28 (21.9)
Cisplatin/vinorelbine (NP)	6 (19.4)	6 (15.0)	34 (26.6)
Cisplatin/docetaxel (DP)	3 (9.7)	3 (7.5)	11 (8.6)
Cisplatin/pemetrexed (PP)	1 (3.2)	3 (7.5)	7 (5.5)
Usage of dexamethasone, *n* (%)			
Yes	28 (90.3)	13 (32.5)	34 (26.6)
No	3 (9.7)	26 (65.0)	89 (69.5)
Not available	0	1 (2.5)	5 (3.9)
Death during follow-up, *n* (%)	13 (41.9)	31 (77.5)	92 (71.9)
Completion of follow-up, *n* (%)	25 (80.6)	35 (87.5)	116 (90.6)

DM: Diabetes mellitus; SD: Standard deviation.

Cox proportional hazard regression for the association of PFS/OS with prognostic factors

Multivariable Cox proportional hazard regression showed that PFS was favorably associated with the usage of anti-DM drugs (hazard ratio [HR] = 0.126, $P < 0.05$), BMI (HR = 0.882; $P < 0.05$), clinical stage of cancer (HR = 0.174, $P < 0.05$), and chemotherapy regimens (HR = 0.188, $P < 0.05$) but was inversely associated with the levels of blood glucose (HR = 1.363, $P < 0.05$) [Table 2].

On the other hand, multivariable Cox proportional hazard regression showed that OS was favorably associated with BMI (HR = 0.860, $P < 0.05$), clinical stage of cancer (HR = 0.292, $P < 0.001$), and usage of dexamethasone (HR = 1.954, $P < 0.05$), whereas levels of blood glucose showed a weak inverse association with OS (HR = 1.346; $P = 0.094$) [Table 3].

Table 2: Cox proportional hazard regression for the association of PFS with prognostic factors.

Parameters	HR	*P* values	95% CI
Sex	1.365	0.4221	0.605–2.125
Age	0.980	0.1985	0.950–1.010
Smoking history	0.564	0.1206	0.400–1.288
History of DM	2.553	0.1727	1.206–3.900
Usage of anti-DM drugs	0.126	**0.0106**	0.105–0.157
Body mass index	0.882	**0.0070**	0.791–0.973
Clinical stage	0.174	**0.0134**	0.140–0.229
Chemotherapy regimes	0.188	**0.0317**	0.146–0.264
Usage of dexamethasone	1.464	0.1829	0.903–2.025
Pathological type	0.981	0.9505	0.369–1.593
Blood glucose	1.363	**0.0434**	1.062–1.664

PFS: Progression-free survival; HR: Hazard ratio; CI: Confidence interval; DM: Diabetes mellitus.

Table 3: Cox proportional hazard regression for association of OS with prognostic factors.

Parameters	HR	*P* values	95% CI
Sex	0.966	0.9318	0.164–1.768
Age	0.982	0.2409	0.951–1.013
Smoking history	0.530	0.0943	0.380–1.274
DM history	1.799	0.4352	0.324–3.274
Usage of anti-DM drugs	0.307	0.1464	0.206–1.901
Body mass index	0.860	**0.0040**	0.757–0.963
Clinical stage	0.292	**<0.0001**	0.773–0.934
Chemotherapy regimes	0.497	0.2992	0.300–1.817
Usage of dexamethasone	1.954	**0.0328**	1.339–2.569
Pathological type	0.995	0.9875	0.386–1.604
Levels of blood glucose	1.346	0.0944	0.998–1.694

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; DM: Diabetes mellitus.

Table 4: Logistic regression analysis of the influential factors on levels of blood glucose.

Parameters	OR	Standard error	*P* values
Sex	1.14	0.18	0.4522
Age	1.02	0.01	**0.0159**
Smoking history	1.11	0.16	0.5276
History of DM	7.32	0.22	**<0.0001**
Body mass index	1.04	0.02	**0.0211**
Clinical stage	1.03	0.04	0.5576
Chemical therapy regimes			
Cisplatin/docetaxel (DP)	1.84	0.31	**0.0494**
Cisplatin/vinorelbine (NP)	1.21	0.30	0.5146
Cisplatin/paclitaxel (TP)	1.17	0.28	0.5639
Cisplatin/gemcitabine (GP)	1.13	0.28	0.6690
Cisplatin/pemetrexed (PP)	–	–	–
Usage of dexamethasone	1.31	0.19	0.1458
Pathological type			
Adenocarcinoma	0.79	0.22	0.2964
Squamous-cell carcinoma	1.06	0.13	0.6368
Other pathologic types	–	–	–

OR: Odds ratio; DM: Diabetes mellitus.

Logistic regression models for the analysis of influential factors on levels of blood glucose

Logistic regression analysis showed that sex, smoking status, pathological type, clinical stage of cancer, and use of dexamethasone did not reveal influential effects on the levels of blood glucose in patients ($P > 0.05$), but a history of DM (odds ratio (OR) = 7.32, $P < 0.05$), BMI (OR = 1.04, $P < 0.05$), and age (OR = 1.02, $P < 0.05$) significantly influenced the levels of blood glucose. Additionally, DP regimens (OR = 1.84, $P < 0.05$) significantly influenced the levels of blood glucose compared with the GP, TP, NP, and PP regimens [Table 4].

Kaplan-Meier survival analysis for the association of PFS and OS with DM and elevated levels of blood glucose in lung cancer patients

Kaplan-Meier survival analysis showed that lung cancer patients with DM had increased PFS and OS compared with those without DM (log-rank, $P < 0.05$, $P < 0.01$); the median PFS in lung cancer patients with DM was 12.0 months (95% confidence interval [CI], 4.0–16.0) *vs.* 6.0 months in those without DM (95% CI, 5.8–6.3); and the median OS in lung cancer patients with DM was 37.0 months (95% CI, 29.0–46.6) *vs.* 12.0 months in those without DM (95% CI, 10.9–13.1). For the other two groups of patients without DM, there was a trend toward a shorter PFS and OS in patients with elevated blood glucose compared with those without elevated blood glucose [Figure 1].

Discussion

In the present study, we found a significant survival benefit for lung cancer patients with DM. Kaplan-Meier survival analysis showed that lung cancer patients with DM had increased PFS and OS compared with those without DM, and the median PFS was 12.0 months in lung cancer patients with DM *vs.* 6.0 months in those without DM; the median OS was 37.0 months in lung cancer patients with DM *vs.* 12.0 months in those without DM. Our results were in agreement with those of the previous HUNT and PEG study,[13] but the HUNT and PEG study only demonstrated increased OS in patients with lung cancer with DM compared with those without DM. Compared with previous studies, the present study preliminarily revealed that there was prolonged PFS in lung cancer patients with DM in addition to OS. In fact, the relationship between PFS and OS has been evaluated in other tumor types, and PFS could be either a predictor of OS[15] or a surrogate endpoint of OS in patients with metastatic renal cell carcinoma.[16] Therefore, there are some advantages in clinical lung cancer studies to set PFS as a valid intermediate endpoint for OS in lung cancer patients with comorbidities due to its shorter prognostic observation periods.

It is known that patients with lung cancer have a high frequency of comorbidities, and the most common comorbidity of lung cancer is DM. Clinically, DM is closely related to the prognosis of many kinds of tumors. Previous epidemiological evidence has demonstrated that patients with DM have a significantly high risk for liver, pancreatic, and endometrial cancer, and DM has also been associated with a poor prognosis in breast, prostate, and colorectal cancer.[3] Although the role of DM in the development, growth, and prognosis of lung cancer still needs to be further illustrated, an increasing number of studies support the survival benefit of DM in lung cancer. The underlying mechanisms may involve a low frequency of metastasis because the majority of patients with lung cancer die due to metastasis and not due to the primary tumor, in which the microvessel changes caused by DM may play a protective role against the metastasis of lung cancer cells.[17] In addition, it may be argued that the survival benefit seen in patients with DM depends on additional frequent and regular consultations that lead to an early diagnosis of comorbidities and thereby a survival benefit.

Another interesting finding in our study was the inverse association of the levels of blood glucose with PFS in

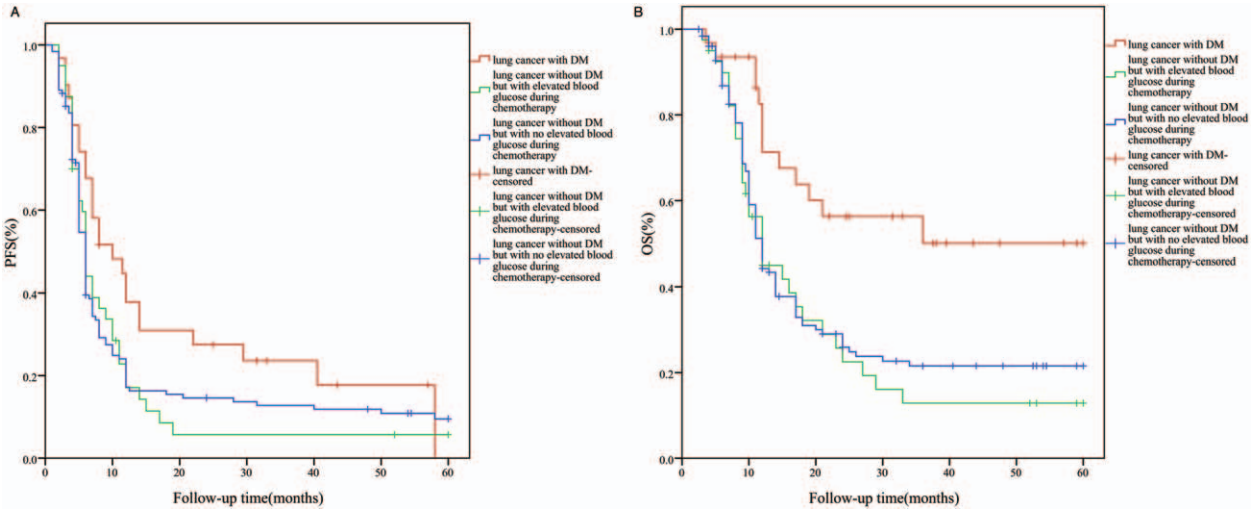

Figure 1: Kaplan-Meier analysis of PFS (A) and OS (B) in lung cancer patients with DM during the follow-up (in red), without DM but with elevated levels of blood glucose during the follow-up (in green), and without DM as well as without elevated blood glucose during the follow-up (in blue). DM: Diabetes mellitus; OS: Overall survival; PFS: Progression-free survival.

patients with lung cancer. When pooling all the data from patients with lung cancer together, multivariable Cox proportional hazard regression showed that PFS of lung cancer patients was favorably associated with the usage of anti-DM drugs, BMI, clinical stage of cancer, and chemotherapy regimens but was inversely associated with the levels of blood glucose. Furthermore, Kaplan-Meier survival analysis showed a trend of a shorter PFS and OS in lung cancer patients with elevated levels of blood glucose compared with those without elevated levels of blood glucose. It is suggested that blood glucose fluctuations may influence the prognosis of lung cancer patients.

Blood glucose fluctuations are absolutely known to be an unfavorable factor in the prognosis of DM. Clinically, in lung cancer patients with or without DM, fluctuations in blood glucose are frequently encountered due to DM itself, the usage of chemotherapy and corticosteroids, surgery, or other factors. How the levels of blood glucose influence the survival of lung cancer patients remains unknown. In the present study, logistic regression analysis showed that sex, smoking status, pathological type, clinical stage of cancer, and use of dexamethasone did not reveal influential effects on the levels of blood glucose, but a history of DM, BMI, age, and DP chemotherapeutic regimens significantly influenced the levels of blood glucose. These results could weakly explain the potential effects of fluctuations in blood glucose on the shorter PFS in patients with lung cancer. Thus, although the history of DM is favorable with prolonged PFS and OS in lung cancer patients, if events such as the irregular use of anti-DM drugs, late stage of cancer, lower BMI, and the use of DP chemotherapeutic regimens occur in lung cancer patients with or without DM, in whom the levels of blood glucose are constantly fluctuating, the survival benefit may go in the reverse direction.

The limitations of the present study include its small clinical sample size and retrospective nature, for which case selection bias may have been encountered. However, standardized data collection templates were used, follow-up records consistently lasted for 60 months, and suitable statistical methods were adopted to correct deviation. Conclusively, this study presented further evidence for the association of PFS/OS with DM and with the levels of blood glucose in lung cancer patients, suggesting that PFS may be a meaningful intermediate endpoint for OS, and the levels of blood glucose hopefully represent a prognostic factor for survival in lung cancer patients.

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Conflicts of interest

None.

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