

ORIGINAL ARTICLE

Is diabetes mellitus a negative prognostic factor for the treatment of advanced non-small-cell lung cancer?



Ali Inal^{a,*}, M. Ali Kaplan^a, Mehmet Kucukoner^a, Zuhat Urakçı^a, Faruk kılinc^b, Abdurrahman Isikdogan^a

^a Dicle University, Department of Medical Oncology, Diyarbakir, Turkey

^b Dicle University, Division of Endocrinology, Diyarbakir, Turkey

Received 17 April 2013; accepted 5 September 2013

Available online 6 November 2013

KEYWORDS

Diabetes mellitus;
Non-small cell lung
cancer;
Prognostic factors

Abstract

Background: It has been demonstrated that there are a lot of different prognostic factors which are worthy of consideration whereas diabetes mellitus (DM) has not been clearly or consistently identified as a prognostic value in advanced non-small cell lung cancer (NSCLC). The aim of this study was to investigate the prognostic significance of the characteristics of patients in advanced NSCLC. Specifically, we investigated the impact of DM for progression-free survival (PFS) and overall survival (OS) in patients receiving first-line platinum-based doublets chemotherapy.

Methods: We retrospectively reviewed 442 patients with advanced NSCLC. DM and other potential prognostic variables were chosen for analysis in this study. Univariate and multivariate analyses were conducted to identify prognostic factors associated with survival.

Result: The results of univariate analysis for OS were identified as having prognostic significance: performance status ($p < 0.001$), stage ($p < 0.001$), DM ($p < 0.001$), liver metastasis ($p = 0.02$) and brain metastasis ($p < 0.001$). Stage, diabetes mellitus, and liver metastasis were identified as having prognostic significance for PFS.

Multivariate analysis showed that poor performance status, presence of DM and advanced stage were considered independent negative prognostic factors for OS ($p = 0.001$, $p < 0.001$ and $p < 0.001$ respectively). Furthermore, DM and stage were considered independent negative prognostic factors for PFS ($p = 0.005$ and $p = 0.001$ respectively).

Conclusion: In conclusion, DM at the time of diagnosis was associated with the negative prognostic importance for PFS and OS in the advanced stage patients who were receiving first-line platinum-based doublets chemotherapy. In addition poor performance status and advanced stage were identified as negative prognostic factors.

© 2013 Sociedade Portuguesa de Pneumologia. Published by Elsevier España, S.L. All rights reserved.

* Corresponding author.

E-mail addresses: dr.ainal@gmail.com, dr.ali33@mynet.com (A. Inal).

PALAVRAS-CHAVE

Diabetes mellitus;
Carcinoma pulmonar de células não pequenas;
Factores de prognóstico

Será a diabetes mellitus um fator de prognóstico negativo no tratamento do carcinoma pulmonar de não pequenas células em estadio avançado?**Resumo**

Antecedentes: Existem vários factores de prognóstico previamente estabelecidos no carcinoma pulmonar de não pequenas células (NSCLC) avançado. Até à presente data, a diabetes mellitus (DM) não foi identificada de forma consistente como potencial factor de prognóstico neste contexto. O objectivo do presentes estudo é investigar o significado prognóstico das diferentes características dos doentes com NSCLC avançada. Especificamente, investigámos o impacto da DM para a sobrevida livre de progressão (PFS) e sobrevida global (OS) em doentes em regime duplo de quimioterapia de primeira linha à base de platina.

Métodos: Analisámos retrospectivamente 442 doentes com NSCLC avançado. Foram escolhidas a DM e outras potenciais variáveis de prognóstico para a análise neste estudo. Foram realizadas análises univariadas e multivariadas para identificar os factores de prognóstico associados à sobrevida.

Resultados: Os resultados de análise univariada para OS identificaram como tendo significância para o prognóstico: estado geral ($p < 0,001$), estádio ($p < 0,001$), DM ($p < 0,001$), metástases hepáticas ($p = 0,02$) e metástases no cérebro ($p < 0,001$). O estádio, diabetes mellitus e as metástases hepáticas foram identificadas como tendo significância de prognóstico para a PFS. A análise multivariada mostrou que um mau estado geral, a presença de DM e um estádio avançado foram considerados factores de prognóstico negativo independentes para OS ($p < 0,001$; $p < 0,001$ e $p < 0,001$; respectivamente). Além disso, a DM e estádio foram considerados factores de prognóstico negativo independentes para a PFS ($p = 0,005$ e $p < 0,001$; respectivamente).

Conclusões: Em conclusão, a DM na altura do diagnóstico comportou-se como um fator de prognóstico negativo para a PFS e OS nos doentes em estádio avançado que estavam em regime duplo de quimioterapia de primeira linha à base de platina. Além do mau estado geral, os estádios avançados foram identificados como factor de prognóstico negativo.

© 2013 Sociedade Portuguesa de Pneumologia. Publicado por Elsevier España, S.L. Todos os direitos reservados.

Introduction

Lung cancer is the most common of all cancer deaths in both men and women worldwide. NSCLC represents 80–85% of all diagnosed lung cancers cases.¹ Surgery is the only curative treatment option for patients with NSCLC. At the time of diagnosis, two-third of patients with lung cancer are diagnosed with locally advanced or metastatic disease. The median survival time for advanced disease is 5.8–12.6 months and the overall 5-year survival rate among this patient population is still less than 10%.^{2,3} Systemic chemotherapy with the platinum-based doublets are currently recommended as a standard of first-line chemotherapy for treatment of NSCLC.⁴

An increased incidence of the NSCLC is connected with aging,⁵ which explains why NSCLC frequently appears simultaneously with other age-related diseases such as diabetes mellitus (DM). Various studies have indicated that among patients with colorectal,⁶ pancreatic,⁷ breast,⁸ or liver⁹ cancer, existing DM was associated with a lower long-term survival. The prognostic significance of pre-existing DM in patients with lung cancer was evaluated.^{10–18} Three studies^{10–12} reported a decrease in survival in patients with DM compared to those without DM. On the other hand, several studies have shown that DM was associated with an equal^{13–15} or an increased chance of survival.^{16–18} The effect of DM on patients with NSCLC remains uncertain. In addition to this, DM has not been clearly or consistently identified

as a prognostic value for the recurrence or progression of advanced NSCLC.^{6,11–14} The aim of this study was to investigate the impact of DM for PFS and OS on the patients receiving first-line platinum-based doublets chemotherapy.

Methods

We retrospectively reviewed 442 patients with histological or cytological proven NSCLC who were receiving first-line platinum-based doublets chemotherapy between August 2002 and February 2012. They had to meet the following inclusion criteria; (1) they had a histological or cytological diagnosis of locally advanced and/or metastatic NSCLC; (2) they were 18 years of age or older; (3) they had had no previous chemotherapy or radiotherapy; (4) they had to have a measurable disease, as defined by Response Evaluation Criteria in Solid Tumors RECIST.

Patients were identified as having DM on the basis of elevated fasting glucose level (>126 mg/dL), and a history of DM or medication use, such as insulin or oral hypoglycemic agents. Prevalent hypertension was defined as systolic pressure ≥ 140 mm Hg and/or diastolic ≥ 90 diastolic and/or currently taking antihypertensive medications.

Twelve potential prognostic variables were chosen on the basis of previously published clinical trials.^{19–24} The variables were divided into categories: age (<70 or ≥ 70), gender (male or female), Eastern Cooperative Oncology

Group (ECOG) performance status (0–1 or 2–3), stage (III or IV), histology (squamous cell carcinoma or adenocarcinoma), weight loss $\geq 5\%$ within the previous 3 months (present or absent), DM (present or absent), hypertension (present or absent), smoking history (present or absent), second-line chemotherapy (present or absent), liver metastasis (present or absent) and brain metastasis (present or absent) at the time of first-line chemotherapy administration.

All of the analyses were performed using the SPSS statistical software program package (SPSS version 11.5 for windows). The differences in the clinical characteristics between the two groups were analyzed by a chi-square test and a student t test. OS was calculated from the start of the first cycle of chemotherapy to the date of death from any cause or the date of the last follow-up. PFS was defined as the time from the first day of chemotherapy till progression or death. OS and PFS were estimated using the Kaplan–Meier

method. The Cox proportional hazards regression model was used to determine statistical significant variables related to survival. Differences were assumed to be significant when P value was less than 0.05.

Results

Between August 2002 and February 2012, 442 patients with advanced NSCLC were enrolled in this study. There were 66 patients (M: 56, F: 10) on DM side and 376 patients (M: 328, F: 48) on the non-diabetic side. DM patients were older than the non-diabetic patients (median 60 versus 58, $P > 0.05$). HT was more common on the DM side than on the non-diabetic one (22.7% versus 8.2%, $p < 0.0001$). There was no statistical difference between patients with the DM and the non-diabetic group in terms of gender, performance status, stage, histology, weight loss, smoking history, first-line

Table 1 Characteristics of diabetic and non-diabetic NSCLC patients.

Characteristic	With DM		Without DM		p
	No	(%)	No	(%)	
Enrolled patients.	66	14.9	376	85.1	
<i>Sex</i>					
Male	56	84.8	328	87.2	$P > 0.05$
Female	10	15.2	48	12.8	
<i>Age, years</i>					
<70	54	81.8	327	87.0	$P > 0.05$
≥ 70	12	18.2	49	13.0	
<i>Performance status (%)</i>					
0–1	30	45.5	218	58.0	$P > 0.05$
2–3	16	24.2	100	26.6	
Unknown	20	30.3	58	15.4	
<i>Smoking history</i>					
Current or former	40	60.6	250	66.5	
Never	6	9.1	55	14.6	$P > 0.05$
Unknown	20	30.3	71	18.9	
<i>Weight loss</i>					
Yes	5	7.6	77	20.5	
No	40	60.6	238	63.3	$P > 0.05$
Unknown	21	31.8	61	16.2	
<i>Metastatic sites (%)</i>					
Liver	10	15.1	43	11.4	$P > 0.05$
Brain	11	16.7	56	14.9	
<i>Stage (%)</i>					
III	28	42.4	160	42.6	
IV	38	57.6	216	57.4	$P > 0.05$
<i>Hypertension</i>					
Yes	15	22.7	31	8.2	
No	51	77.3	345	91.8	$P < 0.001$
<i>First-line chemotherapy</i>					
GemCis	19	28.8	115	30.5	
DocCis	23	34.8	132	35.0	$P > 0.05$
PacCis	19	28.8	93	24.7	
Other	13	7.6	37	9.8	
<i>Second-line chemotherapy</i>	19	28.6	107	28.7	$P > 0.05$

Table 2 Univariate analysis of OS by categorical variable.

Variable	Log-rank test value	Degrees of freedom	p-Value
Sex	0.87	1	0.35
Age	1.23	1	0.26
Stage	52.5	1	<0.001
Smoking history	2.12	1	0.14
Performance status	14.8	1	<0.001
Histology	0.18	1	0.66
Weight loss	0.32	1	0.85
DM	15.1	1	<0.001
Hypertension	2.5	1	0.10
Second-line chemotherapy	3.0	1	0.08
<i>Metastatic sites</i>			
Liver	5.3	1	0.02
Brain	29.4	1	<0.001

Table 3 Univariate analysis of PFS by categorical variable.

Variable	Log-rank test value	Degrees of freedom	p-Value
Sex	1.65	1	0.19
Age	2.47	1	0.11
Stage	19.8	1	<0.001
Smoking history	0.19	1	0.65
Performance status	0.005	1	0.94
Histology	0.16	1	0.68
Weight loss	0.29	1	0.58
DM	14.5	1	<0.001
Hypertension	1.57	1	0.20
Second-line chemotherapy	0.62	1	0.43
<i>Metastatic sites</i>			
Liver	3.88		0.04
Brain	2.85	1	0.09

chemotherapy, first-line chemotherapy cycles, second-line chemotherapy ($p > 0.05$). The patients' baseline characteristics are listed in **Table 1**.

The results of univariate analysis for OS are summarized in **Table 2**. Among the twelve variables of univariate analysis, five variables were identified as having prognostic significance: Performance status ($p < 0.001$), stage ($p < 0.001$), diabetes mellitus ($p < 0.001$), liver metastasis ($p = 0.02$) and brain metastasis ($p < 0.001$).

The results of univariate analysis for PFS are summarized in **Table 3**. Three variables were identified as having prognostic significance: stage ($p < 0.001$), diabetes mellitus ($p < 0.001$), and liver metastasis ($p = 0.04$).

Multivariate analysis included the prognostic significance factors in univariate analysis. The results of multivariate analysis are shown in **Table 4**. Multivariate analysis by Cox proportional hazard model showed that poor performance status, presence of DM and advanced stage were considered independent negative prognostic factors for OS ($p = 0.001$, $p < 0.001$ and $p < 0.001$ respectively) (**Figs. 1–3**). Furthermore, DM and stage were considered as independent negative prognostic factors for PFS ($p = 0.005$ and $p = 0.001$ respectively).

Discussion

In this retrospective study, we set out to clarify the impact of DM on the prognosis of patients with NSCLC. The aim of this study was to investigate the impact of DM for PFS and OS on the patients receiving first-line platinum-based doublets chemotherapy.

The prevalence of DM and cancer is increasing in current society. In our study, the prevalence of DM in NSCLC patients was 14.9%, about twice as high as the global

Table 4 Multivariate analysis of prognostic factors.

Factors	OR	%95 CI	p-Value
<i>PFS</i>			
DM	1.83	1.20–2.79	0.005
Stage	1.69	1.25–2.30	0.001
<i>OS</i>			
DM	2.38	1.48–3.81	<0.001
Stage	3.76	2.45–5.77	<0.001
Performance status	1.92	1.32–2.79	0.001

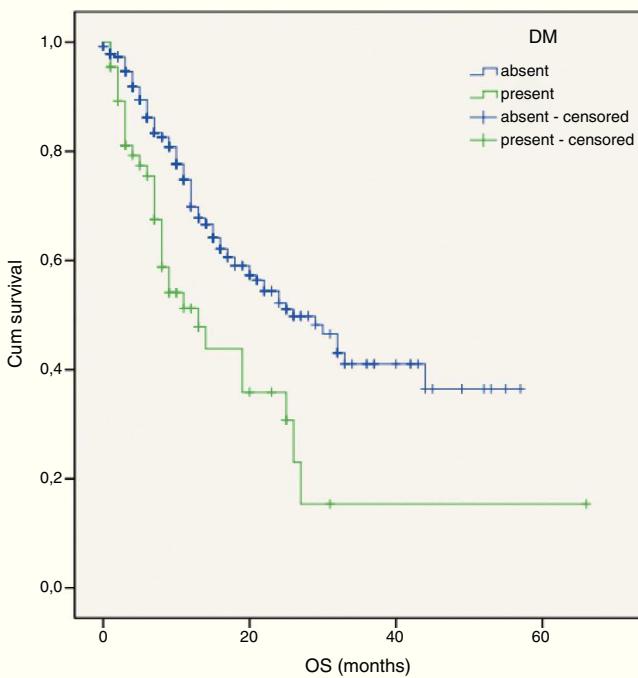


Figure 1 Survival of patients according to DM.

prevalence of diabetes.¹⁹ Epidemiological evidence indicates that DM was found to be common in some cancers such as breast, colorectum, liver, endometrium, and pancreas cancer.^{24–28} The prevalence of DM in newly diagnosed cancer patients is reported to be 8–18% in the United States.²⁹ Diabetes is generally characterized by insulin resistance and hyperinsulinemia.³⁰ It has been claimed that hyperinsulinemia can lead to increases in the level of growth

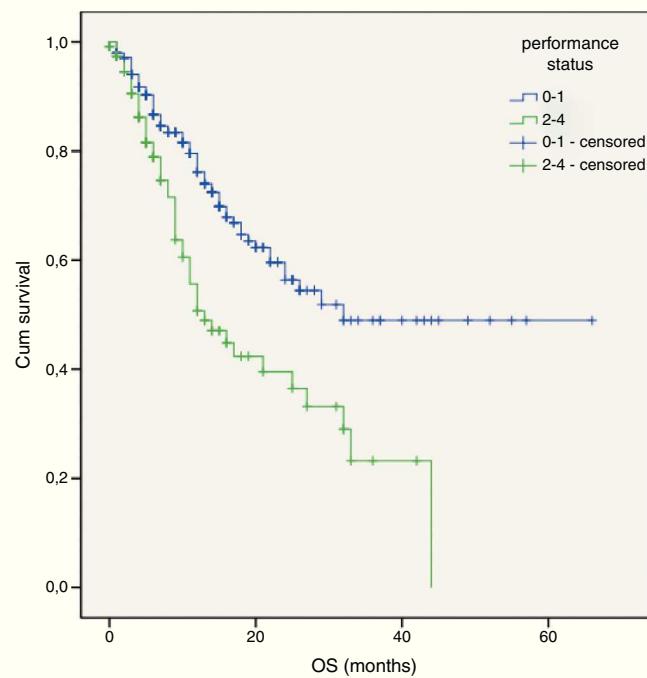


Figure 3 Survival of patients according to performance status.

hormones for malignant tumors, which often over-express insulin receptors and insulin-like growth factor.^{11,31}

A number of very different trials have linked pre-existing DM at the time of diagnosis with an increased mortality rate for patients with pancreatic,⁸ hepatocellular,⁹ or breast¹⁰ cancer. However, there are few studies about the impact of diabetes mellitus for survival in lung cancer.^{10–18} The evidence is limited and conflicting, although prior studies^{16–18} have shown that pre-existing DM at the time of diagnosis is strongly associated with an increase in OS. On the other hand, other studies have shown the association between DM and an equal^{13–15} or an increased survival rate.^{16–18}

The current study demonstrated that patients with DM ($n=66$) exhibited a significant increase in mortality and recurrence compared with those without DM ($n=376$). Our retrospective study review suggests that DM is associated with independent risk factors for survival. There may be several reasons for this. First, patients with DM may present with more advanced NSCLC.³² Because of concomitant treatment of the chronic diseases associated with DM, patients may not undergo routine screening for lung cancer.³³ Second, pre-existing diabetes may have a greater risk of chemotherapy-related toxicity such as febrile neutropenia, infection.³² Third, patients with DM may receive less aggressive treatment, (including chemotherapy, radiotherapy, and/or surgery).³²

A poor PS is usually accepted as a negative prognostic factor for all cancer patients.^{34,35} The importance of PS was also confirmed in advanced NSCLC patients.^{21,22} Our results demonstrated that PS is associated with independent negative risk factors for survival.

Previous findings by a number of authors^{22,23} have shown that the tumor stage at initial presentation was the most important prognostic factor for survival in patients with NSCLC. Similarly, stage of disease was found to be an

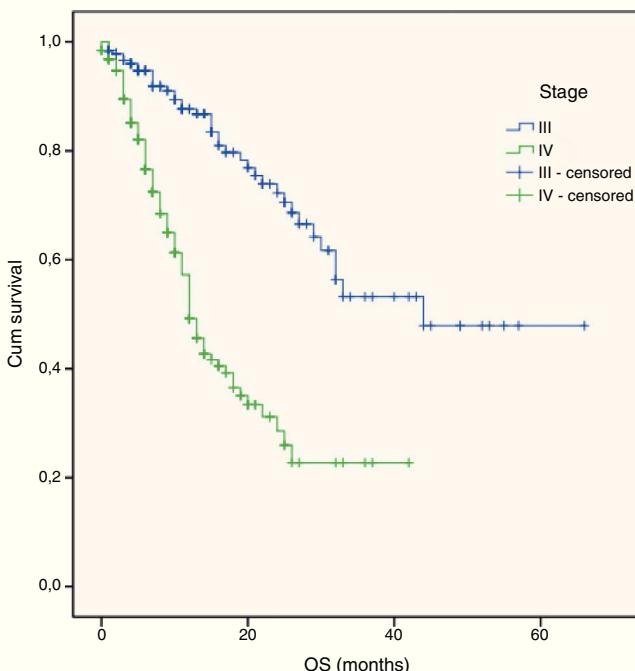


Figure 2 Survival of patients according to stage.

independent negative prognostic factor of survival in the present retrospective study.

The present study has got some limitations. First it is a retrospective study. Second, we did not evaluate the type of DM, duration of diabetes and the types of diabetic therapy used. Third, our findings may have a selection bias because of the possibilities of undiagnosed DM among patients classified as not having DM.

In conclusion, DM at the time of diagnosis was associated with the negative prognostic importance for PFS and OS in advanced stage patients receiving first-line platinum-based doublets chemotherapy. In addition, poor performance status and advanced stage were identified as negative prognostic factors. It may be concluded that these findings may also facilitate pretreatment prediction of survival and can be used for selecting patients for the correct choice of treatment. Therefore, a prospective trial and larger clinical trials are needed.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe 2004. *Ann Oncol*. 2005;16:481–8.
2. Shepherd FA. Screening, diagnosis, and staging of lung cancer. *Curr Opin Oncol*. 1993;5:310–22.
3. Hotta K, Fujiwara Y, Kiura K, Takigawa N, Tabata M, Ueoka H, et al. Relationship between response and survival in more than 50,000 patients with advanced non-small cell lung cancer treated with systemic chemotherapy in 143 phase III trials. *J Thoracic Oncol*. 2007;5:402–7.
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: lung cancer version 2.2012. Fort Washington, PA: National Comprehensive Cancer Network; 2012.
5. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol*. 2006;24:2137–50.
6. Huang YC, Lin JK, Chen WS, Lin TC, Yang SH, Jiang JK, et al. Diabetes mellitus negatively impacts survival of patients with colon cancer, particularly in stage II disease. *J Cancer Res Clin Oncol*. 2011;137:211–20.
7. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Survival after resection for ductal adenocarcinoma of the pancreas. *Br J Surg*. 1996;83:625–31.
8. Kaplan MA, Pekkolay Z, Kucukoner M, Inal A, Urakci Z, Ertugrul H, et al. Type 2 diabetes mellitus and prognosis in early stage breast cancer women. *Med Oncol*. 2011.
9. Toyoda H, Kumada T, Nakano S, Takeda I, Sugiyama K, Kiriyama S, et al. Impact of diabetes mellitus on the prognosis of patients with hepatocellular carcinoma. *Cancer*. 2001;91:957–63.
10. Seshasai SR, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011;364:829–41.
11. Luo J, Chen YJ, Chang LJ. Fasting blood glucose level and prognosis in non-small cell lung cancer (NSCLC) patients. *Lung Cancer*. 2012;76:242–7.
12. Vasic L. Locally advanced non-small cell lung cancer pretreatment prognostic factors: disease stage, tumor histopathological characteristics, the patient-related factors. *Arch Oncol*. 2007;15:19–23.
13. Nakazawa K, Kurishima K, Tamura T, Ishikawa H, Satoh H, Hizawa N. Survival difference in NSCLC and SCLC patients with diabetes mellitus according to the first-line therapy. *Med Oncol*. 2013;30:367. March.
14. Satoh H, Ishikawa H, Kurishima K, Ohtsuka M, Sekizawa K. Diabetes is not associated with longer survival in patients with lung cancer. *Arch Intern Med*. 2001;161:485.
15. Hanbali A, Al-Khasawneh K, Cole-Johnson C, Divine G, Ali H. Protective effect of diabetes against metastasis in patients with non-small cell lung cancer. *Arch Intern Med*. 2007;167:513.
16. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. Impact of comorbidity on lung cancer survival. *Int J Cancer*. 2003;103:792–802.
17. Hatlen P, Grønberg BH, Langhammer A, Carlsen SM, Amundsen T. Prolonged survival in patients with lung cancer with diabetes mellitus. *J Thorac Oncol*. 2001;6:1810–7.
18. De Giorgio R, Barbara G, Cecconi A, Corinaldesi R, Mancini AM. Diabetes is associated with longer survival rates in patients with malignant tumors. *Arch Intern Med*. 2000;160:2217.
19. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27:1047–53.
20. Wheatley-Price P, Blackhall F, Lee SM, Ma C, Ashcroft L, Jitlal M, et al. The influence of sex and histology on outcomes in non-small-cell lung cancer: a pooled analysis of five randomized trials. *Ann Oncol*. 2010;21:2023–8.
21. Paralkar VR, Li T, Langer CJ. Population characteristics and prognostic factors in metastatic non-small-cell lung cancer: a fox chase cancer center retrospective. *Clin Lung Cancer*. 2008;9:116–21.
22. Jeremic B, Milicic B, Dagovic A, Aleksandrovic J, Nikolic N. Pretreatment clinical prognostic factors in patients with stage IV non-small cell lung cancer (NSCLC) treated with chemotherapy. *J Cancer Res Clin Oncol*. 2003;129:114–22.
23. Tibaldi C, Vasile E, Bernardini I, Orlandini C, Andreuccetti M, Falcone A. Baseline elevated leukocyte count in peripheral blood is associated with poor survival in patients with advanced non-small cell lung cancer: a prognostic model. *J Cancer Res Clin Oncol*. 2008;134:1143–9.
24. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer*. 2007;121:856–62.
25. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst*. 2005;97:1679–87.
26. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia*. 2007;50:1365–74.
27. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review

- of epidemiologic evidence. *Clin Gastroenterol Hepatol.* 2006;4:369–80.
28. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer.* 2005;92: 2076–83.
29. Ko C, Chaudhry S. The need for a multidisciplinary approach to cancer care. *J Surg Res.* 2002;105:53–7.
30. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA.* 2005;293:194–202.
31. Dawson SL. Long-term risk of malignant neoplasm associated with gestational glucose intolerance. *Cancer.* 2004;100: 149–55.
32. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, et al.: Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. *Int J Cancer.* 1992;120:1986–92.
33. Maruthur NM, Bolen S, Brancati FL, et al. Obesity and mammography: a systematic review and meta-analysis. *J Gen Intern Med.* 2009;24:665–77.
34. Kim JG, Ryoo BY, Park YH, Kim TY, Im YH, et al. Prognostic factors for survival of patients with advanced gastric cancer treated with cisplatin-based chemotherapy. *Cancer Chemother Pharmacol.* 2008;61:301–7.
35. Mitry E, Douillard JY, Van Cutsem E, Cunningham D, Magherini E, Mery-Mignard D, et al. Predictive factors of survival in patients with advanced colorectal cancer: an individual data analysis of 602 patients included in irinotecan phase III trial. *Ann Oncol.* 2004;15:1013–7.