Non-small Cell Lung Cancer in the Young: A Retrospective Analysis of Diagnosis, Management and Outcome Data

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Abstract. *Background: Non-small cell lung cancer (NSCLC) in young patients is uncommon and is thought to constitute a distinct oncological entity with characteristic clinicopathological patterns. Since the reported data are scant and discordant, the presentation, management and outcome data of NSCLC patients aged under 45 years of age were analyzed and compared with those of patients over 45 years old. Prognostic factors for risk classification were also evaluated. Materials and Methods: The data were abstracted from the Hellenic Cooperative Oncology Group (HeCOG) cancer registry database. The presentation, management and outcome data of patients with histologically confirmed NSCLC, managed from 1989 until 2004 in HeCOG participating centers, were retrospectively analyzed. The clinicopathological characteristics of patients aged < and > than 45 years old were compared and evaluated for prognostic significance regarding outcome. Results: The data for NSCLC patients (1906), of whom 115 were aged <45, were retrieved. In comparative analysis, the young patients were more frequently asymptomatic at diagnosis, while older patients presented significantly higher rates of thoracic pain, cough and fatigue ($p<0.01$). The young patients were more commonly diagnosed with adenocarcinoma and less frequently with squamous cancer than patients aged over 45. Although the stage distribution was distinct, with older patients presenting higher rates of stage IV disease (21.9% vs. 12.2%), the rates of early lung cancer (stages I-IIIa) were similar. The overall survival (OS) was not significantly different (median OS 12 vs. 11.5 months, $p=0.277$). Among patients who underwent first-line palliative chemotherapy, young individuals had a significantly shorter time to progression: 4.3 vs. 5.8 months ($p=0.0049$). Univariate and multivariate regression analyses established the prognostic usefulness of the performance status, disease stage and disease-free interval for the risk of death, both in the total number of patients (1906) and in young patients (115). Conclusion: This large retrospective series failed to present strong evidence that NSCLC among young individuals constitutes a distinct clinicopathological entity with differing biological behavior, since the same clinicopathological prognostic factors were valid in both age groups. Molecular phenotypic studies are needed to shed light on this controversial subject.*

Lung cancer is among the most common and lethal malignancies of developed countries, its etiological link to tobacco smoking being established beyond doubt. Accordingly, its prevalence is higher in the sixth and seventh decades of life, while occurrence of the disease in young adults is quite uncommon. This epidemiological observation has been explained by the time-period required for the environmental toxin (smoke) to induce genetic damage that will ultimately lead to cancer. Many studies have suggested that lung cancer in the young may constitute a distinct clinicopathological entity with different gender distribution, stage at diagnosis, pathological features and prognosis, although the reported data are frequently discordant (1-7). Estimates are rendered more difficult by the possibility of national patterns (*e.g.*, squamous histology in Italy (4, 8) and Poland (2)) and by the rarity of the disease in young people. To date, only five studies comparing lung cancer demographics in more than 100 young subjects have been published (2, 3, 7-9), but data on the patients' clinical outcome were presented in only three (2, 3, 8).

This report presents the patient and tumor characteristics, management and outcome data of 115 non-small cell lung cancer (NSCLC) patients, aged <45 years at diagnosis, registered in the HeCOG (Hellenic Cooperative Oncologic Group) cancer registry from 1989 until 2004, aiming to highlight differing patterns of malignant behavior, as well as generating testable hypotheses about the disease biology. Prognostic models, able to provide a risk calculation for NSCLC patients, were evaluated.

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Key Words: Non-small cell lung cancer, survival.

Materials and Methods

The data for analysis were abstracted from the HeCOG cancer registry, a Hellenic database that has been collecting nationwide clinicopathological data of NSCLC patients treated in participating centers since 1989. Considering that all registered patients had been enrolled in phase II/III studies of cytotoxic chemotherapy combinations, there was a bias against patients with low performance status (IV) and short life expectancy, commonly excluded from these studies. The standardized data relating to age, gender, demographics, smoking habits, performance status, histology, stage at diagnosis, presenting symptoms, number of metastatic sites, treatment (surgery, radiotherapy, chemotherapy), the administered regimen and outcome were collected and analyzed by a statistician and a physician in the first semester of 2005.

Eligible patients had histological or cytological diagnosis of NSCLC with adequate performance status (PS 0-2), hepatic, renal and bone marrow reserves. They were divided into two groups: young adults <45, and patients aged ≥45 years old. The patient/tumor epidemiological characteristics, as well as the management and outcome data of the two groups, were compared.

Overall survival (OS) was defined as the time between the date of diagnosis and the date of death or last follow-up. Disease-free survival (DFS) was defined as the time from diagnosis to malignant relapse among patients with early lung cancer who underwent curative surgery and adjuvant chemotherapy. Among patients with advanced NSCLC receiving palliative chemotherapy, the disease-free interval (DFI) was calculated from the initial diagnosis of localized tumor to relapse with unresectable disease. Time to progression (TTP) was defined as the time from the start of palliative treatment until disease progression or death without progression (TTP_1 for first-line chemotherapy and TTP_2 for second-line chemotherapy).

The comparison analyses within the two groups for all the aforementioned categorical variables were performed using the Chi-square and Fisher exact tests. All reported *p*-values are two-sided. The survival curves were plotted using the Kaplan-Meier product limit method and were compared with the log-rank test. Univariate and multivariate parameter analyses for the potential prognostic significance for overall survival used Cox's regression models; the 95% confidence intervals (95% CI) of the odds ratios were computed by the Wald statistic. Univariate and multivariate Cox regression analyses for survival were run only among the three following categories: a) all patients who underwent first-line palliative chemotherapy, b) young patients who underwent first-line palliative chemotherapy and c) all patients with early lung cancer (stages I-IIIa).

Results

From 1989 to 2004, 1906 patients with NSCLC were registered in the HeCOG cancer registry: 98.5% were enrolled in HeCOG clinical trials; 115 (6%) were aged less than 45 years. The characteristics of the patients and the clinicopathological and management data are reported in Table I.

In the entire cohort, 244 cases (12.8%) of NSCLC occurred in females and 1662 (87.2%) in males. When the two age groups were considered, there was a trend for an

Table I. *Patient characteristics with respect to age group (≤45, >45 years old).*

Variable	Young (115) %	Old (1791) %	*p*
Male/Female ratio	(N=94/21)	(N=1568/223)	0.071
Smoking status			0.326
Yes	77.4	74.7	
No	7.0	9.7	
Unknown	15.7	15.6	
Symptoms			
No symptoms	61.7	47.6	0.004
Hemoptysis	18.3	18.4	0.999
Pain	4.3	12.6	0.007
Dyspnea	3.5	8.4	0.075
Cough	7.0	16.0	0.007
Fever	2.6	5.2	0.275
Weight loss	12.2	15.9	0.354
Fatigue	0.9	8.0	0.002
Palpable mass	-	0.6	0.999
Vena cava	3.5	2.9	0.577
Unknown	-	0.6	
Histological type			0.004
Squamous	23.5	36.5	
Adenocarcinoma	48.7	42.7	
Large cell	10.4	4.9	
Other[1]	15.7	11.7	
Stage			0.016
I+II	1.8	3.4	
III	85.2	72.8	
IV	12.2	21.9	
Resectability			0.648
Resectable (I-IIIa)	10.5	11.7	
Unresectable (IIIb-IV)	89.5	86.4	
Unknown	0.9	1.9	
PS			0.634
0 or 1	82.6	81.6	
2 or 3	15.7	17.5	
Unknown	1.7	0.9	
No. of metastatic sites			0.421
0	13.0	15.4	
1-2	67.5	69.6	
More than 3	19.1	14.9	
Surgery			0.319
Yes	20.9	17.9	
No	68.7	74.8	
Unknown	10.4	7.4	
Radiotherapy			0.195
Yes	33.0	28.9	
No	53.9	62.1	
Unknown	13.0	8.9	
Chemotherapy *			0.275
Adjuvant	2.6	4.1	
First line	94.8	93.3	
None #	0.9	0.2	
Unknown	1.7	2.4	

[1]Category 'Other' included mixed, unclassified and undifferentiated tumors.

Patients with unknown data were not included in the Chi-square or Fisher's exact tests.

No treatment because of poor medical condition.

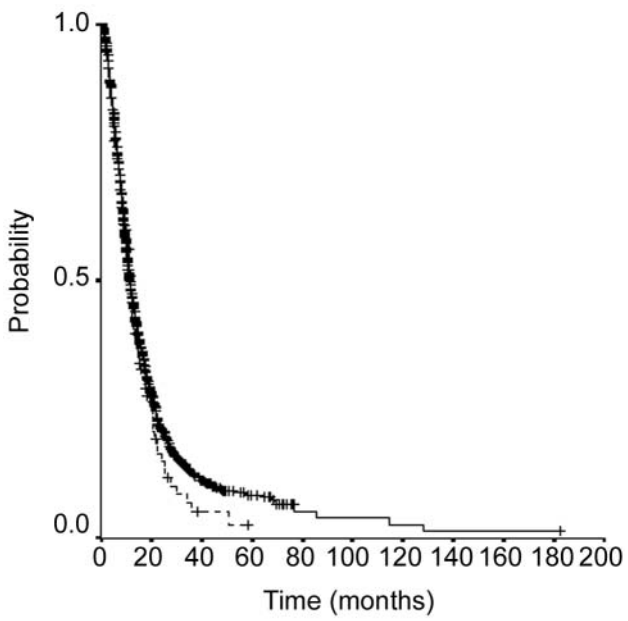

Figure 1. *Overall survival curves for younger (- - - - -) and older (_____) patients.*

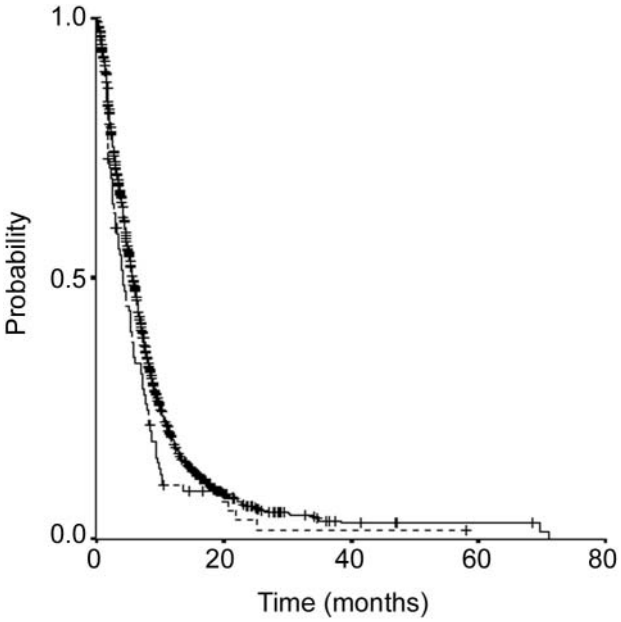

Figure 2. *Time to disease progression curves after first-line chemotherapy for younger (- - - - -) and older (_____) patients.*

increased proportion of females with lung cancer among the younger individuals (18.2% in the younger *vs.* 12.4% in the older age group), although this difference was not significant. A large proportion of the patients had been asymptomatic (48.5%), with the most commonly reported symptoms being hemoptysis (18.3%), weight loss (15.6%), cough (15.4%) and thoracic pain (12.1%). In comparative analysis, the young patients had been more frequently asymptomatic at diagnosis, while older individuals had presented significantly higher rates of thoracic pain, cough and fatigue ($p<0.01$). Adenocarcinoma was the leading cell type, accounting for more than 40% of tumors in each group. Statistical differences were encountered when the proportion of histological type per group was analyzed. The rates of adenocarcinomas and large cell tumors had been higher in the younger patients, while the older patients had presented higher rates of squamous cell carcinoma.

More than 90% of the patients in both groups had had advanced disease at presentation (stage III or IV). The stage distribution among the groups had differed ($p=0.016$), with older patients presenting a larger proportion of stage IV tumors (21.9% *vs.* 12.2%). However, the proportion of patients with early lung cancer (I-IIIa *vs.* ≥ IIIb) had been similar. No differences were found for smoking history, performance status, number of metastatic sites or type of treatment provided.

Seventy-six patients had received adjuvant chemotherapy, of whom 75 (99%) had received carboplatin-paclitaxel in the context of a HeCOG randomized trial. The median number of administered cycles had been six per patient. 1832 patients had been enrolled in clinical trials evaluating first-line palliative chemotherapeutic regimens, 1639 (89.5%) patients were given the programmed regimen and, overall, 1787 received a form of first-line chemotherapy. Among those treated with the programmed protocol, 1054 (64.3%) received a platinum-based regimen (cisplatin or carboplatin) and 585 (35.7%) a non-platinum-based scheme. The median number of cycles per patient was five (range 1-14). Second-line palliative chemotherapy administration was documented in 98 patients, among whom 18% were given a platinum-based regimen (cisplatin or carboplatin) and 79% a non-platinum regimen. The median number of administered cycles per patient was four (range 1-17).

The median overall survival for the group of young patients (n=115) was 12 months (95% CI: 10.5-13.1), compared to 11.5 months (95% CI, 10.9-12.2) for the older individuals (n=1791). The survival difference between the two groups was not significant in log-rank test analysis ($p=0.277$) (Figure 1). The median disease-free survival (DFS) in radically-treated adult patients with localized tumors (stage I-IIIA) receiving adjuvant chemotherapy was 30 months (95% CI 0.6-52.6). A comparison of the DFS between younger and older individuals was not feasible since only three young patients had received adjuvant treatment and all had died within 13.2 months. Among patients with advanced NSCLC who had undergone first-line palliative chemotherapy, the median time to progression (TTP_1) had been 4.3 months (95% CI 3.2-5.3) and 5.8 months (95% CI 5.4-6.1), respectively, for the younger

Table II. *Univariate analysis for relative risk of death.*

Analyzed variables	All patients Palliative chemotherapy N=1787			Young patients Palliative chemotherapy N=109			All early lung cancer patients Adjuvant chemotherapy N=222		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Age									
<45	1.000			-			1.000		
≥45	0.894	0.720-1.11	0.311	-	-	-	0.689	0.350-1.358	0.282
Performance status									
0+1	1.000			1.000			1.000		
2+3	1.701	1.486-1.948	<0.001	1.072	0.591-1.943	0.820	2.162	1.009-4.631	0.047
Stage									
I+II	1.000						-		
III	2.421	1.549-3.784	<0.001	1.000#			-	-	-
IV	2.737	1.734-4.318	<0.001	0.941	0.470-1.883	0.864	-	-	-
Resectable stages									
I	-			-			1.000		
II	-	-	-	-	-	-	1.364	0.651-2.855	0.411
IIIa	-	-	-	-	-	-	2.765	1.437-5.320	0.002
Gender									
Male	1.000			1.000			1.000		
Female	0.936	0.795-1.102	0.429	0.976	0.559-1.704	0.932	1.372	0.741-2.541	0.314
Histology									
Adenocarcinoma	1.000			1.000			1.000		
Squamous	1.070	0.948-1.209	0.273	1.611	0.927-2.797	0.091	0.861	0.595-1.246	0.428
Other	1.325	1.138-1.542	<0.001	1.126	0.608-2.085	0.707	0.951	0.583-1.550	0.840
Metastatic sites									
0	1.000			1.000			-		
1-2	1.065	0.903-1.255	0.455	1.502	0.743-3.036	0.257	-	-	-
3 or more	1.568	1.286-1.912	<0.001	1.613	0.731-3.558	0.237	-	-	-
Adjuvant chemotherapy	-			-					
Yes	-	-	-	-	-	-	1.000		
No	-	-	-	-	-	-	1.364	0.651-2.855	<0.001
Palliative chemotherapy							-		
Platinum-based	1.000			1.000			-	-	-
Non-platinum-based	0.96	0.854 -1.08	0.501	0.706	0.411- 1.21	0.208	-	-	-
DFI									
Up to 12 months	1.000			1.000			-		
>12 months	0.212	0.175-0.258	<0.001	0.153	0.047-0.493	0.002	-	-	-

# Stages I+II+III *vs.* IV.
DFI = disease-free interval.
95% CI = 95% confidence interval.
HR = hazard ratio.

and older groups, the difference being statistically significant (p=0.0049) (Figure 2). Among patients who underwent second-line palliative chemotherapy, the median TTP_2 from the start from the start of second-line treatment had been 2.7 (95% CI 0-6.5) and 4.4 months (95% CI 3.2-5.5), respectively, for younger and older individuals. The difference did not reach statistical significance (p=0.2622).

When all advanced NSCLC patients who had received first-line palliative chemotherapy were considered, univariate analyses (Table II) established that low performance status (2-3), high tumor stage (III and IV), more than three metastatic sites at diagnosis and disease-free interval from the initial diagnosis of localized disease to metastatic relapse of less than 12 months were associated with inferior survival. In multivariate analysis (Table III), the characteristics predictive of adverse outcome were stages III (hazard ratio (HR) 1.981; 95% CI: 1.126-3.102) and IV (HR 2.173; 95% CI: 1.373-3.439), as well as poor performance status (PS 2-

Table III. *Multivariate analysis for relative risk of death.*

Analyzed variables	All patients Palliative chemotherapy N=1257			Young patients Palliative chemotherapy N=92			Early lung cancer patients Adjuvant chemotherapy N=213		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Performance status									
0+1	1.000			-			-		
2+3	1.690	1.447-1.974	<0.001	-	-	-	-	-	-
Stage									
I+II	1.000						-		
III	1.981	1.266-3.102	0.003	-			-	-	-
IV	2.173	1.373-3.439	0.001	-	-	-	-	-	-
Resectable stages									
I	-			-			1.000		
II	-	-	-	-	-	-	1.308	0.624-2.741	0.477
IIIa	-	-	-	-	-	-	1.968	1.008-3.843	0.047
Histology									
Adenocarcinoma	1.000			-			-		
Squamous	0.992	0.869-1.133	0.911	-	-	-	-	-	-
Other	1.292	1.098-1.521	0.002	-	-	-	-	-	-
Metastatic sites									
0	1.000			-			-		
1-2	1.046	0.847-1.292	0.675	-	-	-	-	-	-
3 or more	1.386	1.082-1.774	0.010	-	-	-	-	-	-
Adjuvant chemotherapy	-			-					
Yes	-	-	-	-	-	-	1.000		
No	-	-	-	-	-	-	2.177	1.432-3.331	<0.001
DFI									
Up to 12 months	1.000			1.000			-		
>12 months	0.204	0.163-0.256	<0.001	0.135	0.032-0.567	0.006	-	-	-

DFI = disease-free interval.
95% CI = 95% confidence interval.
HR = hazard ratio.

3, HR 1.690; 95% CI: 1.447-1.974). A disease-free interval longer than 12 months seemed to reflect indolent tumor biology associated with superior outcome (HR 0.204, 95% CI 0.163-0.256). Conversely, among young patients who had received first-line chemotherapy, a disease-free interval longer than 12 months still seemed to show a protective effect on their survival in both univariate (Table II) and multivariate analyses (Table III). In univariate analysis, a non-significant trend for a higher risk of death was found for squamous histology (Table II).

Among all early lung cancer patients with stage I-IIIa disease, the univariate analysis (Table II) indicated a higher probability of death for individuals with stage IIIa tumors (HR 2.765; 95%CI: 1.437-5.320), absence of adjuvant chemotherapy (HR 2.461 95%CI: 1.648-3.673) and poor performance status (PS 2-3, HR 2.162; 95%CI: 1.009-4.631). In multivariate analysis (Table III), stage IIIa and the absence of adjuvant chemotherapy were confirmed as prognostic factors of poor survival.

Discussion

The occurrence of lung cancer among young adults is uncommon. Although it has been hypothesized that its clinicopathological characteristics may differ from those of older individuals, the matter has not been thoroughly investigated in the literature. To date, only five studies comparing lung cancer patterns in young and adult patients had a sample size larger than 100 young individuals in the data analysis (2, 3, 7-9) (Table IV). Unfortunately, survival data were only reported in three studies (2, 3, 8) since the other two studies (7, 9) were focused on the risk of developing lung cancer rather than on the patients' treatment outcome. This study, therefore, represents one of the largest series of young patients with lung cancer reported (6), and is the first report analyzing the characteristics of the disease among the Greek population (any age group considered).

Our results confirmed that young patients were represented by a higher proportion of females (1-3, 6, 7)

Table IV. *Studies comparing young and older lung cancer patients that involved more than 100 young subjects in the data comparison: clinicopathological characteristics and patients' outcome.*

Clinicopathological characteristics

Author	Year	Country	Young (N)	Age cut-off	Leading cell type				Male /Female		% Early stages	
					Young	%	Old	%	Young	Old	Young	Old
Roviaro *et al.* (8)	1985	Italy	155	45	SQ	46	SQ	46	13.0	13.6	36	43
McDuffie *et al.* (7)	1989	Canada	187	50	AC	33	SQ	37	1.2	3.5	NA	NA
Kreuzer *et al.* (9)	1998	Germany	251	45	AC	42	AC	31	2.6	5.6	NA	NA
Ramalingam *et al.* (3)	1998	US	2840	50	AC	45	SQ	38	1.5	2.2	19	25
Radzikowska *et al.* (2)	2001	Poland	757	50	SQ	35	SQ	42	2.9	6.9	32	32
Our study	2005	Greece	115	45	AC	49	AC	43	4.5	7.0	2	3

Patient survival analyses

Author	Survival data (younger *vs.* older)	
Roviaro *et al.* (8)	No 5-year overall survival differences No survival differences were found even when patients surgically resected and not resected were independently considered	$p>0.05$
McDuffie *et al.* (7)	No survival data	NA
Kreuzer *et al.* (9)	No survival data	NA
Ramalingam *et al.* (3)	Statistically significant 5-year overall survival benefit in younger patients (16.1% *vs.* 13.4 %)	$p<0.01$
Radzikowska *et al.* (2)	Statistically significant 1-year overall survival benefit in younger patients (32.6% *vs.* 28.9%)	$p<0.049$
Our study	No survival differences	$p=0.891$

Early stages = stage I and II; SQ = squamous carcinoma; AC = adenocarcinoma; NA = not assessed.

and more often presented with adenocarcinoma histology (1, 3-8) and advanced stage of disease (3-5). As previously reported, the young adults were fitter (2) and, when the disease was localized, more commonly underwent potentially curative surgery (2, 3, 6), radiotherapy (3) or combined-modality management (2, 3) in comparison to older patients. Still, these differences were not statistically significant in our study, though this may be due to a patient-selection bias since the majority of patients who had entered the HeCOG database had been enrolled in HeCOG clinical trials (good PS, life expectancy more than 3 months).

Our report highlights some strikingly different findings in comparison to those previously reported. Our results on the presenting symptomatology of the disease are in contrast with those reported by Bourke *et al.* (4), who found statistically higher rates of cough and chest pain among young patients and of asymptomatic presentation among older individuals. Furthermore, the proportion of asymptomatic subjects was higher in our study than in that of Bourke *et al.*, any age-group considered (young patients: 7% *vs.* 62%; old patients 17% *vs.* 48%). These differences may, in part, be explained by a screening-reporting bias, due to the high proportion of Greek primary care physicians who screen their asymptomatic patients with chest radiography (10).

Although it has been suggested that young patients with lung cancer have a better prognosis than older ones (2-4, 6), the outcome of the young adults in our series was similar to that of the older patients, while the duration of response to first-line palliative chemotherapy was shorter. This may, in part, be explained by a co-morbidity reporting bias in previous reports. Patients in the sixth and seventh decades of life probably have a worse PS, poorer general condition and co-morbid conditions such as diabetes, heart failure, ischemic vascular disease, all of which are confounding factors affecting survival. In this setting, it is clear that young patients are more likely to undergo surgical interventions and combined-modality treatments than

elderly individuals. In contrast, the majority of patients in our study had been included in clinical trials; both younger and older patients therefore presented similar baseline conditions (*e.g.*, PS) and co-morbidity-related bias was minimized. We may therefore hypothesize that, among the overall group of older individuals, the prognosis might be worst; but when co-morbidity patterns are balanced, treatment modalities in the two groups may be equally tolerated and the outcome may be similar.

Another peculiarity is that Greeks of any age group more often present with adenocarcinomas than squamous carcinomas. Whether this had any impact on our patients' outcome is debatable. In any case, a similar distribution of lung cancer histology had been described in the literature (1, 4).

Univariate and multivariate regression analyses evidenced that among patients undergoing first-line chemotherapy (independent of the age group analyzed), the relative risk of death was mainly correlated to low PS (2+3), higher stages (III and IV) and a disease-free interval of less than 12 months. These three parameters reflect host and tumor factors, such as organ system integrity, disease bulk, tumor biology and aggressive malignant behavior.

In conclusion, we failed to establish that NSCLC in young individuals unequivocally presents distinct clinicopathological characteristics, or that it is biologically more aggressive. The same prognostic factors as for older individuals defined the disease course. Insights into the molecular biology of the malignancy (11, 12) with high-throughput technologies may better serve the goal of identifying patient subgroups with distinct molecular signatures and clinical behavior.

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Received November 14, 2005
Revised February 15, 2006
Accepted May 8, 2006