VOLUME 23 NUMBER 28 OCTOBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pretreatment Quality of Life and Functional Status Assessment Significantly Predict Survival of Elderly Patients With Advanced Non–Small-Cell Lung Cancer Receiving Chemotherapy: A Prognostic Analysis of the Multicenter Italian Lung Cancer in the Elderly Study

Paolo Maione, Francesco Perrone, Ciro Gallo, Luigi Manzione, FrancoVito Piantedosi, Santi Barbera, Silvio Cigolari, Francesco Rosetti, Elena Piazza, Sergio Federico Robbiati, Oscar Bertetto, Silvia Novello, Maria Rita Migliorino, Adolfo Favaretto, Mario Spatafora, Francesco Ferraù, Luciano Frontini, Alessandra Bearz, Lazzaro Repetto, and Cesare Gridelli

From the S Giuseppe Moscati Hospital, Avellino; National Cancer Institute; Medical Statistics, Second University of Napoli; Pneumology V, Monaldi Hospital, Napoli; S Carlo Hospital, Potenza; Mariano Santo Hospital, Cosenza; S Giovanni di Dio e Ruggi d'Aragona, Salerno; Civil Hospital, Noale, Venezia; Sacco Hospital; S Gerardo Hospital, Monza, Milano; Civil Hospital, Rovereto, Trento; Molinette Hospital; San Luigi Gonzaga Hospital, Orbassano, Torino; Forlanini Hospital; Instituto Nazionale Ripose e Cura Anziani, Roma; Civil Hospital, Padova; Pneumology, University of Palermo, Palermo; S Vincenzo Hospital, Taormina, Catania; Centro di Riferimento Oncologico, Aviano, Pordenone, Italy.

Submitted October 19, 2004; accepted June 8, 2005.

Supported in part by Associazione Italiana per la Ricerca sul Cancro (AIRC), Clinical Trials Promoting Group (CTPG), and Gruppo Italiano di Oncologia Geriatrica (GIOGer). P.M. is the recipient of an AIRC fellowship.

Presented in part at the 38th Annual Meeting of the American Society of Clinical Oncology, Orlando, FL, May 18-21, 2002 (poster).

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Cesare Gridelli, MD, c/o Unità Sperimentazioni Cliniche, Istituto Nazionale Tumori, Via Mariano Semmola, 80131 Napoli, Italy; e-mail: cgridelli@libero.it.

0732-183X/05/2328-6865/$20.00

DOI: 10.1200/JCO.2005.02.527

ABSTRACT

Purpose
To study the prognostic value for overall survival of baseline assessment of functional status, comorbidity, and quality of life (QoL) in elderly patients with advanced non–small-cell lung cancer treated with chemotherapy.

Patients and Methods
Data from 566 patients enrolled onto the phase III randomized Multicenter Italian Lung Cancer in the Elderly Study (MILES) study were analyzed. Functional status was measured as activities of daily living (ADL) and instrumental ADL (IADL). The presence of comorbidity was assessed with a checklist of 33 items; items 29 and 30 of the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30 (EORTC QLQ-C30) were used to estimate QoL. ADL was dichotomized as none versus one or more dependency. For IADL and QoL, three categories were defined using first and third quartiles as cut points. Comorbidity was summarized using the Charlson scale. Analysis was performed by Cox model, and stratified by treatment arm.

Results
Better values of baseline QoL ($P = .0003$) and IADL ($P = .04$) were significantly associated with better prognosis, whereas ADL ($P = .44$) and Charlson score ($P = .66$) had no prognostic value. Performance status 2 ($P = .006$) and a higher number of metastatic sites ($P = .02$) also predicted shorter overall survival.

Conclusions
Pretreatment global QoL and IADL scores, but not ADL and comorbidity, have significant prognostic value for survival of elderly patients with advanced non–small-cell lung cancer who were treated with chemotherapy. Using these scores in clinical practice might improve prognostic prediction for treatment planning.

J Clin Oncol 23:6865-6872. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Non–small-cell lung cancer (NSCLC) is a group of heterogeneous clinical entities with different clinical behaviors and prognoses. As is true for many other types of tumors, the proportion of NSCLC patients aged 70 years or older is constantly increasing in industrialized countries because of the gain in life expectancy observed in the second part of the last century, and this trend is expected to continue in the next decades.[1]

In addition to classical prognostic factors for advanced NSCLC including performance status (PS) and the extent of disease,[2] elderly cancer patients have peculiar characteristics that may affect prognosis. In this regard, a pretreatment geriatric assessment, including evaluation of comorbidity, functional status, depression, cognitive impairment, nutritional status, and social support, has been proposed to assess prognosis and predict toxicity.[3-5] However, the advantage of such a comprehensive assessment is probably outweighed by the disadvantage of its poor applicability in clinical practice.

The assessment of comorbidity and the evaluation of functional status are among the most important constituents of a comprehensive geriatric assessment. Comorbidity may be summarized according to several scales.[6,7] Functional status refers to the ability of the patient to perform daily functions. Assessment of PS is the most widely used functional score in oncology, however, it has been suggested that this score might underestimate the degree of functional impairment, particularly in the elderly subset of patients.[3] The most widely used functional impairment geriatric scales are Katz's basic Activities of Daily Living (ADL)[8] and Lawton's[9] Instrumental Activities of Daily Living (IADL). Although these geriatric scales may produce additional information on the functional assessment of elderly cancer patients, their prognostic role in elderly patients with advanced NSCLC is unknown.

The Multicenter Italian Lung Cancer in the Elderly Study–01 (MILES-01)[10] was a large prospective randomized trial of chemotherapy dedicated to elderly patients with advanced NSCLC. This study showed that polychemotherapy with gemcitabine plus vinorelbine was not more effective than gemcitabine alone and vinorelbine alone. A previous study by the same group of investigators,[11] the phase III Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) study, showed that vinorelbine was better than supportive care in elderly patients with advanced NSCLC. Also in that study, we found that the baseline scores of items 29 and 30 of the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30 predicted time to dropout from the study; patients with worse scores tended to drop out earlier than patients with higher scores.[11]

The current study was planned a priori in the MILES protocol to explore the possible prognostic role of ADL, IADL, and comorbidity. Following the reported results of the ELVIS study, we also included quality of life measured with items 29 and 30 of EORTC QLQ-C30 as a covariate of prognostic analysis.

PATIENTS AND METHODS

Patients and Treatment

Patients with advanced NSCLC enrolled onto the MILES study[10] were 70 years old or older, had stage IV or IIIB disease with supraclavicular metastatic nodes or malignant pleural effusion, and a baseline PS not worse than 2, according to the Eastern Cooperative Oncology Group (ECOG) scale. The MILES study compared the combination of vinorelbine and gemcitabine with the two drugs given singly. Patients were randomly assigned to receive vinorelbine (30 mg/m^2), gemcitabine (1,200 mg/m^2), or gemcitabine (1,000 mg/m^2) plus vinorelbine (25 mg/m^2). All treatments were administered on days 1 and 8 every 3 weeks for six cycles of 21 days. The primary end point of the study was overall survival. Of 707 patients randomly assigned between December 1997 and November 2000, 566 patients (80%) with complete information on baseline ADL, IADL, and quality of life were included in this prognostic analysis.

Global Health Status/Quality of Life

To assess quality of life, the EORTC QLQ-C30[12] and the EORTC lung cancer–specific module QLQ-LC13[13] were used. In the current analysis, only one score was used, the global health status/quality of life (QoL), calculated with responses to items 29 and 30 of EORTC QLQ-C30. In response to these two items, patients were asked to grade their global health status (item 29) and quality of life (item 30) during the previous week on a scale of 7 points. A raw score was calculated for each patient and linearly transformed in a percent scale ranging from 0 to 100, 0 representing the lowest level of global quality of life and 100 the highest. In this analysis, patients were grouped in three score categories using first and third quartiles as cut points: "better" (scoring $>$ 67%, roughly representing the highest quarter of the distribution), "intermediate" (scoring 43% to 67%, about half of subjects), and "worse" (scoring $\leq$ 42%, representing the lowest quarter of the distribution).

Geriatric Assessment

Concomitant pathologies were scored as absent/present using a predefined list of 33 possible diseases. Comorbidity was summarized by the Charlson score,[6] summing up data regarding myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, ulcer disease, mild liver disease and diabetes. The other pathologic conditions (hemiplegia, moderate or severe renal disease, diabetes with organ damage, any other cancer, moderate or severe liver disease, AIDS) used to calculate the Charlson score were not taken into account because they were precluded by exclusion criteria for the study. Consequently, higher scores were rarely attained, and just four categories were used in the analysis (0, 1, 2, $\geq$ 3).

Functional status of elderly patients was measured by ADL and IADL scores that were recorded at baseline, before randomization, by physicians.

ADL[8] includes bathing, dressing, using the bathroom, continence, getting up and being able to move around the house, and feeding. For each of the six items, two possible scores were assigned: 0 (dependent) or 1 (independent). Thus, the ADL score for each patient ranged from 0 (unable to perform any activity) to 6 (able to perform all activities). Because of the high prevalence of patients scoring 6, two groups were arbitrarily created for this analysis: fully independent (score 6) and $\geq$ 1 dependency (scores $<$ 6).

IADL[9] includes the ability to use the telephone, shopping, food preparation, housekeeping, handyman work, laundry, the ability to get around outside the home, responsibility for own medications, and the ability to handle finances. For each item four responses are available, three representing varying degrees of dependency (all assigned score 0) and one representing full

independency (score 1). Some of the explored domains (eg, cooking, washing clothes, and so on) are fully applicable only to women, considering the advanced age of the population. Thus, missing data within the forms were frequent among men. To accommodate this phenomenon, a raw score was calculated considering only questions that had been answered by the patients, on the assumption that missing values were primarily due to inapplicability of the question. Such score was linearly transformed in a percent scale ranging from 0 to 100, 0 representing the lowest level of ability and 100 the highest. For prognostic and correlation analyses, patients were arbitrarily grouped in three score categories: "better" (scoring 100%, roughly representing the best quarter), "intermediate" (scoring 51% to 99%, about half of the subjects), and "worse" (scoring 0% to 50%, representing the worst quarter).

Statistical Methods

Associations between baseline ADL, IADL, and QoL categories and characteristics of patients were studied by contingency tables and the χ^2 test.

Overall survival was defined as the time elapsed from the date of randomization to the date of death or the date of the last follow-up for patients alive at the end of the study. Multivariate survival analysis was done using the Cox model,[14] and was stratified by treatment arm. Because of the high number of events, a simple strategy was undertaken by a single model including all known or potential prognostic factors (age, sex, stage, histotype, number of sites of disease, baseline QoL, ADL, IADL, and Charlson score) and a variable representing institutions by number of patients enrolled ($<$ 10, 10-29, $\geq$ 30) as a possibly confounding covariate. The likelihood ratio test was used to test the contribution of each variable to the model when added last, that is after adjustment for all of the other covariates. *P* values less than .05 were considered statistically significant. Overall survival curves were drawn by the Kaplan-Meier method.[15]

RESULTS

Patient Characteristics

Median age of the patients was 74 years (range, 70 to 84 years); 229 patients (40%) were 75 years old or older (Table 1). Men represented 82% of the population. Institutions that enrolled more than 30 patients comprised about one fourth of the patients; those that enrolled between 10 and 29 patients comprised about half the patients.

More patients with stage IV disease than stage III disease were enrolled, representing 69% of the sample (Table 2). Squamous cell carcinoma was the most prevalent histologic type (45% of patients), followed by adenocarcinoma (34%). Patients had a median of three organs affected by cancer. Nineteen percent of patients had a deteriorated baseline PS (ECOG category 2). Approximately 90% of the patients had at least one and approximately 40% had three or more comorbidities; only 11% of patients had no comorbidity. According to the Charlson score, 42% of patients were in the lowest category (score 0).

QoL, ADL, IADL, and Charlson score

Distribution of baseline QoL, ADL, and IADL in the population is illustrated in Figure 1. QoL was distributed symmetrically, with the majority of patients reporting intermediate scores. Conversely, both ADL and IADL distributions were highly skewed, the best score being most frequent (85% and 33% for ADL and IADL, respectively).

PS was significantly correlated with QoL, ADL, and IADL scores. All the scores were worse among patients with PS2 (Table 2; all *P* values $<$ .0001), whereas Charlson score

Table 1. Distribution of Baseline ADL, IADL, and QoL by Characteristics of Patients, Size of Institution, and Assigned Treatment

	QoL						ADL				IADL							
	Worse (n = 153)		Intermediate (n = 294)		Better (n = 119)		≥ 1 Dependency (n = 84)		Fully Independent (n = 482)		Worse (n = 161)		Intermediate (n = 217)		Better (n = 188)		Total (n = 566)	
Variable	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years																		
$<$ 75	89	58	177	60	71	60	51	61	286	59	88	55	136	63	113	60	337	60
75-79	56	37	109	37	45	38	28	33	182	38	66	41	72	33	72	38	210	37
≥ 80	8	5	8	3	3	2	5	6	14	3	7	4	9	4	3	2	19	3
Sex																		
Male	117	77	244	83	104	87	71	85	394	82	**145**	**90**	**176**	**81**	**144**	**77**	465	82
Female	36	23	50	17	15	13	13	15	88	18	**16**	**10**	**41**	**19**	**44**	**23**	101	18
Center by No. of patients																		
$<$ 10	**31**	**20**	**91**	**31**	**26**	**22**	15	18	133	28	**43**	**27**	**40**	**18**	**65**	**35**	148	26
10-29	**77**	**50**	**119**	**40**	**63**	**53**	41	49	218	45	**71**	**44**	**111**	**51**	**77**	**41**	259	46
≥ 30	**45**	**30**	**84**	**29**	**30**	**25**	28	33	131	27	**47**	**29**	**66**	**30**	**46**	**24**	159	28
Assigned treatment																		
Vinorelbine	49	32	102	35	41	34	35	42	157	33	57	35	74	34	61	32	192	34
Gemcitabine	54	35	95	32	38	32	20	24	167	35	53	33	70	32	64	34	187	33
Combination	50	33	97	33	40	34	29	34	158	33	51	32	73	34	63	34	187	33

NOTE. Boldfaced numbers are statistically significant.
Abbreviations: ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; QoL, Quality of Life.

Table 2. Distribution of Baseline ADL, IADL, and QoL by Characteristics of Disease, Performance Status, and Charlson Score

	QoL						ADL				IADL							
	Worse (n = 153)		Intermediate (n = 294)		Better (n = 119)		≥ 1 Dependency (n = 84)		Fully Independent (n = 482)		Worse (n = 161)		Intermediate (n = 217)		Better (n = 188)		Total (n = 566)	
Variable	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Stage																		
IIIB	41	27	95	32	42	35	24	29	154	32	52	32	75	35	51	27	178	31
IV	112	73	199	68	77	65	60	71	328	68	109	68	142	65	137	73	388	69
Histology																		
Squamous	58	38	148	50	46	39	37	44	215	45	69	43	98	45	85	45	252	45
Adenocarcinoma	59	39	90	31	45	38	34	41	160	33	57	35	70	32	67	36	194	34
Other histology	36	23	56	19	28	23	13	15	107	22	35	22	49	23	36	19	120	21
No. of metastatic sites																		
1	4	3	8	3	3	3	2	2	13	3	4	2	6	3	5	3	15	3
2	42	27	100	34	45	38	27	32	160	33	46	29	77	35	64	34	187	33
3	63	41	121	41	33	28	38	45	179	37	71	44	75	35	71	38	217	38
4	29	19	49	17	25	21	10	12	93	19	29	18	41	19	33	18	103	18
≥ 5	15	10	16	5	13	11	7	8	37	8	11	7	18	8	15	8	44	8
Performance status																		
0-1	**111**	**73**	**236**	**80**	**113**	**95**	**47**	**56**	**413**	**86**	**101**	**63**	**190**	**88**	**169**	**90**	460	81
2	**42**	**27**	**58**	**20**	**6**	**5**	**37**	**44**	**69**	**15**	**60**	**37**	**27**	**12**	**19**	**10**	106	19
Charlson score																		
0	67	44	111	38	59	50	35	42	202	42	**54**	**34**	**85**	**39**	**98**	**52**	237	42
1	50	33	121	41	39	33	27	32	183	38	**64**	**40**	**84**	**39**	**62**	**33**	210	37
2	30	20	47	16	15	13	17	20	75	16	**37**	**23**	**35**	**16**	**20**	**11**	92	16
≥ 3	6	4	15	5	6	5	5	6	22	54	**6**	**4**	**13**	**6**	**8**	**4**	27	5

NOTE. Boldfaced numbers are statistically significant.
Abbreviations: QoL, Quality of Life; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living.

was only associated with IADL, being lower in patients with higher IADL scores ($P = .005$).

Overall Survival

Of 566 patients eligible for prognostic analysis, 462 patients (82%) died. Median overall survival for patients was 30 weeks (95% CI, 28 to 34), and 6-month and 1-year probabilities of overall survival were 0.56 and 0.32, respectively.

Results of multivariate analysis are reported in Table 3. After adjusting for the other covariates, QoL and IADL were associated with prognosis ($P = .0003$ and $P = .04$, respectively), whereas ADL was not ($P = .44$). A low PS (ECOG score 2) and the number of metastatic sites also independently predicted worse overall survival rates ($P = .006$ and $P = .02$, respectively). Charlson score was not associated with prognosis; the results were superimposible if the total number of comorbidities was used instead of the Charlson score. Kaplan-Meier–estimated overall survival curves for QoL and IADL are shown in Figure 2.

DISCUSSION

A significant amount of both clinical and basic research has focused on the prognostic factors for patients with NSCLC. Although the prognosis of patients with advanced NSCLC is ominous overall, the identification of prognostic factors can be useful, not only for providing important information to the patients, but also for the correct choice of treatment. The latter issue is particularly relevant for elderly patients, because of the concerns about generalizability of treatment effects demonstrated in younger patients[16] and poor tolerability of treatments.

Within a secondary analysis of the MILES study, we looked for new tools to predict the prognosis of elderly patients at the time of diagnosis and before chemotherapy treatment. Specifically, we studied the prognostic value of the patient's self-assessment of QoL and physician's assessment of functional scales (ADL and IADL) and comorbidity.

As for comorbidity, we recognize that a limitation of the present study consists of the use of a qualitative yes/no checklist, which does not result in information about the severity of concomitant diseases. This choice was pragmatically based on the principle of reducing the time needed to assess patients at baseline. A similar scale has been used previously by Repetto et al.[5] The Charlson score,[6] which was used as a summary measure of comorbidity, revealed no prognostic value in the MILES study. Although the potential prognostic role of the Charlson score was limited by the fact that eligibility criteria of the study excluded patients with higher scores, this finding is consistent with those recently reported by Janssen-Heijnen et al [17] showing that among 4,072 patients diagnosed with NSCLC in the

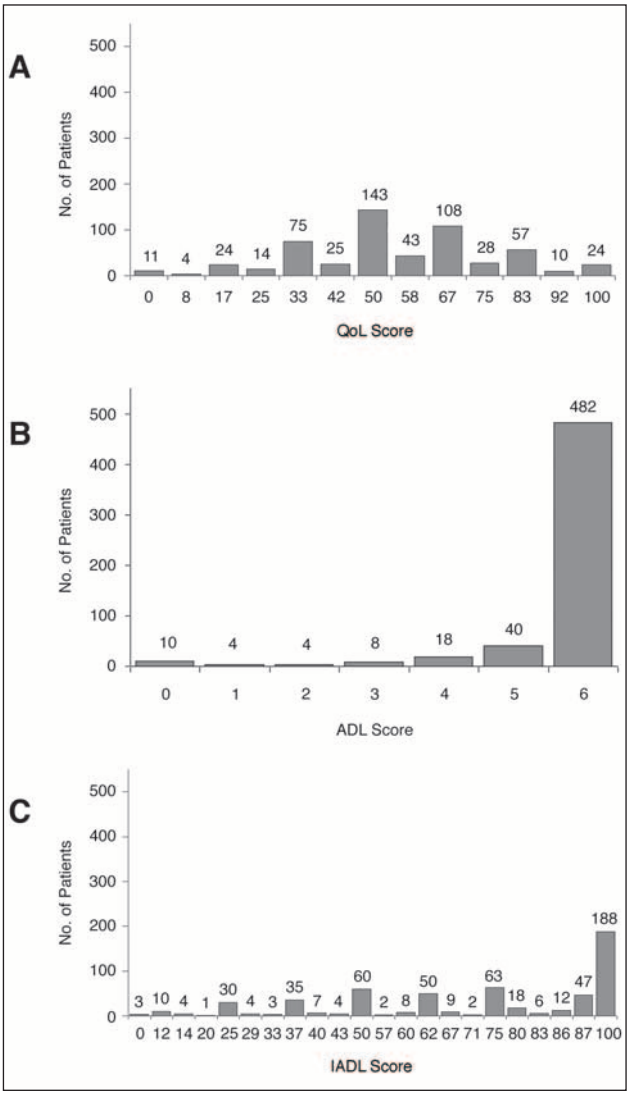

Fig 1. Distribution of (A) quality of life (QoL), (B) Activities of Daily Living (ADL), and (C) instrumental ADL (IADL). QoL and IADL values are linear transformations of the raw scores.

Table 3. Multivariate Analysis

Variable	HR	95% CL Upper	95% CL Lower	*P**
Sex				.07
Male (n = 465)	Ref			
Female (n = 101)	0.78	0.59	1.02	
Age, years				.69
< 75 (n = 337)	Ref			
75-79 (n = 210)	1.09	0.89	1.32	
≥ 80 (n = 19)	0.96	0.57	1.64	
Performance status				.006
0-1 (n = 460)	Ref			
2 (n = 106)	1.46	1.12	1.88	
Charlson score				.66
0 (n = 237)	Ref			
1 (n = 210)	1.06	0.85	1.32	
2 (n = 92)	1.12	0.85	1.48	
≥ 3 (n = 27)	0.84	0.52	1.36	
ADL				.44
No dependence (n = 482)	Ref			
One or more dependence (n = 84)	1.12	0.85	1.47	
IADL				.04
Better (n = 188)	Ref			
Intermediate (n = 217)	0.97	0.76	1.22	
Worse (n = 161)	1.31	1.00	1.71	
Quality of Life				.0003
Better (n = 119)	Ref			
Intermediate (n = 294)	1.62	1.24	2.10	
Worse (n = 153)	1.76	1.29	2.39	
Stage				.71
IIIb (n = 178)	Ref			
IV (n = 388)	1.04	0.85	1.28	
Histotype				.17
Other (n = 314)	Ref			
Squamous (n = 252)	1.14	0.94	1.39	
No. of sites of disease				.02
For each added site	1.13	1.02	1.24	
Center by No. of enrolled patients				.09
< 10 (n = 148)	Ref			
10-29 (n = 259)	1.19	0.94	1.52	
≥ 30 (n = 159)	1.34	1.03	1.74	

Abbreviations: HR, Hazard ratio of death; CL, confidence limits; Ref, reference category; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living.
*Likelihood ratio test.

Netherlands between 1995 and 1999, the number of comorbidities (collected according to a slightly modified version of the Charlson score) had no prognostic value for overall survival. A possible explanation of the lack of prognostic relevance of comorbidity in advanced lung cancer is reported in a recent paper by Read et al.[18] The authors found that among 11,558 cancer patients, concurrent comorbidities had no relevant prognostic impact for groups of patients with the lowest overall survival rates, including 1,005 patients with advanced lung cancer. Whether different and more detailed definitions of comorbidity can produce useful prognostic information in the setting of advanced NSCLC remains to be seen.[19,20] However, a study by Piccirillo et al[21] of elderly patients with head and neck cancer suggests that general comorbidity indexes (like the Charlson score) perform similarly to disease-specific comorbidity indexes, and both types of scores are only able to weakly predict prognosis.

In contrast with the established prognostic value of ADL in nononcologic geriatric patients,[22] baseline ADL had no prognostic value in the MILES population. A possible explanation could be that the prognostic value of ADL, as that of comorbidity,[18] may only be truly effective in populations with a life expectancy longer than that of patients with advanced NSCLC. In addition, we should consider that dependencies in ADL represent quite severe deficiencies that probably prevent patients from being considered

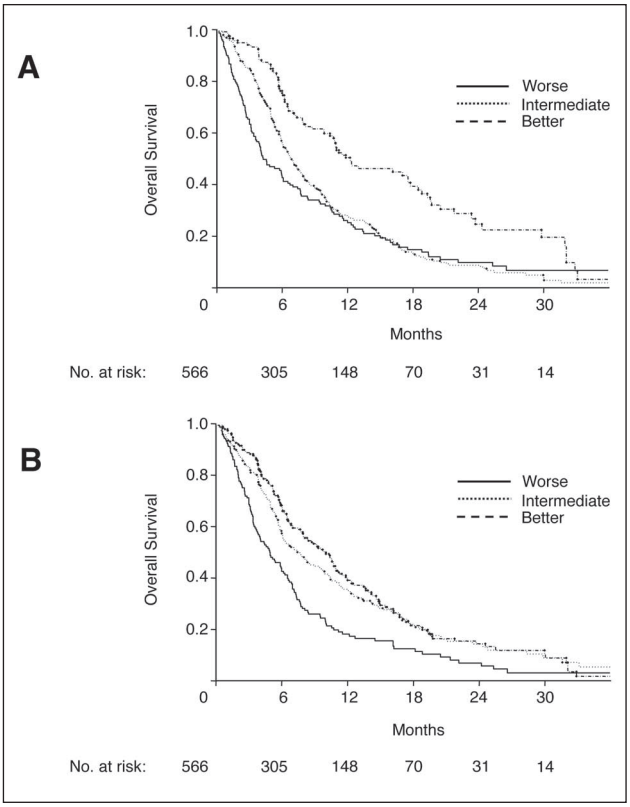

Fig 2. Kaplan-Meier–estimated overall survival curves according to pretreatment (A) quality of life (QoL) and (B) intermediate Activities of Daily Living (IADL) categories.

eligible for chemotherapy and for clinical trials. On the contrary, we found that baseline IADL had an independent prognostic role, that appears mostly relevant for the lower quarter, ie, the worse category. IADL is a quite easy-to-use instrument, but its application is limited by the fact that some domains (eg, cooking, washing clothes, and so on) are not effectively applicable to male patients, particularly if they are elderly. To accommodate this phenomenon, we ignored missing data and calculated a raw score based on available answers; this might reduce reproducibility of the present result.

Another important observation of our study was that baseline self-assessment of QoL, with two simple questions, was the strongest prognostic factor among elderly patients with advanced NSCLC enrolled onto the MILES trial; the major difference being evident between the upper quarter (ie, the better category) and the other categories that appear to have similar prognosis. To our knowledge, the present study reports the largest analysis on the prognostic role of QoL score in advanced NSCLC and the first analysis on the important subset of elderly patients. Indeed, Ganz et al[23] reported on the importance of the Functional Living Index–Cancer[24] in 40 patients. Montazeri et al[25] reported that in a series of 129 patients global QoL measured by the EORTC C-30 questionnaire was significantly lower among the 30 patients who died within 3 months, as compared with the rest of the patients in the study. Langendijk et al[26] reported similar results with the EORTC C-30 questionnaire with patients with lung cancer undergoing potentially curative radiation therapy. These results are in slight contrast with the observations of Herndon et al[27] on 206 patients enrolled onto the Cancer and Leukemia Group B 8931 trial; they found that although several items of the EORTC C-30 questionnaire (including the overall QoL score) were correlated with prognosis at univariate analysis, only the pain score was retained in the final multivariate model.

In addition to providing crucial prognostic information, QoL assessment may be useful to improve communication with the patient and help the clinician to design tailored supportive treatments based on the correct identification of the overall burden of symptoms, the relative importance given to each of them by the patient, and his or her expectations regarding treatment's efficacy. As an example of poor patient-physician communication, even in the setting of randomized clinical trials, we have recently reported[28] that pain measured by the pain scores included in the EORTC C-30 and LC-13 questionnaires is frequently undertreated by physicians, particularly when instrumental staging is negative for bone metastases. Thus, we suggest that the use of QoL instruments in clinical practice could help physicians improve their control of the patient's symptoms. Indeed, the feasibility and utility of a comprehensive assessment of elderly cancer patients, also when based on self-report methodology like QoL questionnaires, has been proven.[29]

In conclusion, quality of life and functional status assessment, by items 29 and 30 of the EORTC C-30 questionnare and the IADL scale, respectively, could be used in clinical practice as prognostic factors to aid the selection of elderly patients with advanced NSCLC for chemotherapy.

Acknowledgment

We thank Federika Crudele, Giuliana Canzanella, Fiorella Romano, and Assunta Caiazzo for data management and secretarial assistance; Alfonso Savio for hardware and software assistance; and the Gruppo Oncologico Italia Meridionale (GOIM) for promoting the study among its associated centers.

Appendix

List of institutions and coauthors. National Cancer Institute, Napoli: *Medical Oncology B (Cesare Gridelli,† Emiddio Barletta, Maria Luisa Barzelloni,‡ Rosario Vincenzo Iaffaioli) and Clinical Trials Unit (Francesco Perrone, Paolo Maione,† Ermelinda De Maio, Massimo Di Maio, Gianfranco De Feo). Medical Statistics, Second University of Napoli (Ciro Gallo, Giuseppe Signoriello, Paolo Chiodini). *III Internal Medicine, University Federico II of Napoli (Silvio Cigolari,**

Angela Cioffi, Vincenzo Guardasole, Valentina Angelini). *S Carlo Hospital, Potenza (Luigi Manzione, Antonio Rossi, Domenico Bilancia, Domenico Germano). Pneumology V, Monaldi Hospital, Napoli (Francovito Piantedosi, Alfredo Lamberti, Vittorio Pontillo, Luigi Brancaccio). Mariano Santo Hospital, Cosenza (Santi Barbera, Francesco Renda, Francesco Romano). Sacco Hospital, Milan (Elena Piazza, Gabriella Esani, Anna Gambaro). Medical Oncology, Noale–VE (Orazio Vinante, Francesco Rosetti, Giuseppe Azzarello). S Giuseppe Hospital, Milano (Maurizia Clerici, Roberto Bollina, Paolo Belloni). S Maria del Carmine Hospital, Rovereto–TN (Sergio Federico Robbiati, Mirella Sannicolò). Molinette Hospital, Torino (Oscar Bertetto, Libero Ciuffreda, Giuseppe Parello). S Paolo Hospital, Milano (Luciano Frontini,§ Mary Cabiddu[#]). S Maria della Misericordia Hospital, Udine (Cosimo Sacco, Angela Sibau). San Lazzaro Hospital, Alba–CN (Gianfranco Porcile, Federico Castiglione, Oliviero Ostellino). Civil Hospital, Padova (Silvio Monfardini, Adolfo Favaretto, Micaela Stefani). San Luigi Gonzaga Hospital, Orbassano–TO (Giorgio Scagliotti, Silvia Novello, Giovanni Selvaggi). Forlanini Hospital, Roma (Filippo De Marinis, Maria Rita Migliorino, Olga Martelli). Medical Oncology, Az Ospedaliera "Bianchi-Melacrino-Morelli", Reggio Calabria (Giampietro Gasparini,¶ Alessandro Morabito,¶ Domenico Gattuso). *Experimental Medical Oncology, Oncologic Institute, Bari (Giuseppe Colucci, Domenico Galetta, Francesco Giotta). *Medical Oncology, University of Palermo (Vittorio Gebbia). *La Maddalena Hospital, Palermo (Nicola Borsellino, Antonio Testa). *S Vincenzo Hospital, Taormina–CT (Francesco Ferraù, Emilia Malaponte). Thoracic Surgery, University of Foggia (Matteo A. Capuano, Michele Angiolillo, Francesco Sollitto). Medical Oncology, CRO, Aviano–PN (Umberto Tirelli, Alessandra Bearz, Simona Spazzapan). Medical Oncology, University of Messina (Vincenzo Adamo, Giuseppe Altavilla, Antonino Scimone). Pneumology, University of Palermo (Mario Spatafora, Maria Raffaella Hopps, Francesco Tartamella). G. Rummo Hospital, Benevento (Giovanni Pietro Ianniello, Vincenza Tinessa). S Luigi and S.S. Currò Gonzaga Hospital, Catania (Giuseppe Failla, Roberto Bordonaro). Chemotherapy, University of Palermo (Nicola Gebbia, Maria Rosaria Valerio). *S Maria Goretti Hospital, Latina (Modesto D'Aprile, Enzo Veltri), Latina. Medical Oncology, University of Perugia (Maurizio Tonato, Samir Darwish). *Cardarelli Hospital, Campobasso (Sante Romito, Francesco Carrozza). S Gerardo Hospital, Monza–MI (Sandro Barni,[#] Antonio Ardizzoia). USSL 33, Rho–MI (Giuliana Mara Corradini, Gianfranco Pavia). *Civil Hospital, Avellino (Mario Belli, Giuseppe Colantuoni). S Chiara Hospital, Trento (Enzo Galligioni, Orazio Caffo). Medical Oncology, Spedali Riuniti, Bergamo (Roberto Labianca, Antonello Quadri). Medical Oncology, University La Sapienza, Roma (Enrico Cortesi, Giuliana D'Auria). Civil Hospital, Legnano– MI (Sergio Fava, Anna Calcagno). S Carlo Borromeo Hospital, Milano (Gino Luporini, M. Cristina Locatelli). S Maria Hospital, Terni (Francesco Di Costanzo, Silvia Gasperoni). Serbelloni Hospital, Gorgonzola–MI (Luciano Isa, Paola Candido). USSL 15, Camposampiero–PD (Fernando Gaion, Giovanni Palazzolo). *Miulli Hospital, Acquaviva delle Fonti–BA (Giuseppe Nettis, Anselmo Annamaria). *Medical Oncology II, "Regina Elena" Institute, Roma (Massimo Rinaldi, Massimo Lopez). S Martino Hospital, Genova (Raffaella Felletti, Giorgio Bernabò Di Negro). *Civil Hospital, Polla–SA (Nestore Rossi, Antonio Calandriello). San Gennaro Hospital, Napoli (Luigi Maiorino). S Croce Hospital, Fano–PS (Rodolfo Mattioli). S Giovanni Hospital, Torino (Alfredo Celano). S Bortolo Hospital, Vicenza (Stefania Schiavon). Oncology, Monaldi Hospital, Napoli (Alfonso Illiano). Cottolengo Hospital, Torino (Carlo Alberto Raucci). *Oncologic Center, Catania (Michele Caruso). Medical Oncology, University of Milano (Paolo Foa‖). Medical Oncology, Biomedical Campus, Roma (Giuseppe Tonini). Thoracic Surgery, Ascalesi Hospital, Napoli (Carlo Curcio††). Civil Hospital, Treviglio–BG (Marina Cazzaniga). Pneumology, Spedali Riuniti, Bergamo. Medical Oncology I, IST, Genova. *Fatebenefratelli Hospital, Benevento. *Medical Oncology, University of Cagliari. Businco Hospital, Cagliari. Agnelli Hospital, Pinerolo– TO. SS Trinità Hospital, Sora–FR. S Andrea Hospital, Vercelli. Civil Hospital, Gorizia. Medical Oncology, University of Sassari. Civil Hospital, Bolzano. Fortunato Hospital, Rionero in Vulture–PZ. *Da Procida Hospital, Salerno. C Cantù Hospital, Abbiategrasso–MI. Pugliese Ciaccio Hospital, Catanzaro. Civil Hospital, Rovigo. S Maria delle Grazie Hospital, Pozzuoli–NA. Civil Hospital, S Felice a Cancello–CE. *Galateo Hospital, S.Cesareo–LE. Civil Hospital, Lagonegro–PZ. *Civil Hospital, Sciacca–AG.

NOTE: (*) denotes Institutions that participate in the activities of the Gruppo Oncologico Italia Meridionale; (†) S Giuseppe Moscati Hospital, Avellino; (‡)DaProcida Hospital, Salerno; (§) S Gerardo Hospital, Monza; (‖) S Paolo Hospital, Milano; (¶) S Filippo Neri Hospital, Roma; (#) Civil Hospital, Treviglio (BG); (**) S Giovanni di Dio e Ruggi d'Aragona, Salerno; (††) Monaldi Hospital, Napoli.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Francesco Perrone					Eli Lilly (A); Pierre Fabre (A)			
Cesare Gridelli					Eli Lilly (A); Pierre Fabre (A)			
Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required								

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