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Geriatric assessment may help decision-making in elderly patients with inoperable, locally advanced non-small-cell lung cancer

Maite Antonio[1,2], Juana Saldaña[1,2], Jennifer Linares[1], José C Ruffinelli[1], Ramón Palmero[1], Arturo Navarro[3], Maria Dolores Arnaiz[3], Isabel Brao[1], Samantha Aso[4], Susana Padrones[4], Valentí Navarro[5], Jesús González-Barboteo[6], Josep Maria Borràs[7], Felipe Cardenal[1] and Ernest Nadal*[,1,8]

[1]Thoracic Oncology Unit, Department of Medical Oncology, Institut Català d'Oncologia, Hospital Duran i Reynals, Avinguda Gran via 199-203. L'Hospitalet, Barcelona 08908, Spain; [2]Geriatric Oncology Unit, Department of Medical Oncology, Institut Català d'Oncologia, Avinguda Gran via 199-203. L'Hospitalet, Barcelona 08908, Spain; [3]Thoracic Oncology Unit, Department of Radiation Oncology, Institut Català d'Oncologia. Avinguda Gran via 199-203. L'Hospitalet, Barcelona 08908, Spain; [4]Department of Respiratory Medicine, Hospital Universitari de Bellvitge, Feixa Llarga, s/n, 08907. L'Hospitalet, Barcelona 08907, Spain; [5]Clinical Research Unit, Institut Català d'Oncologia, Avinguda Gran via 199-203. L'Hospitalet, Barcelona 08908, Spain; [6]Palliative Care Unit, Institut Català d'Oncologia, Avinguda Gran via 199-203. L'Hospitalet, Barcelona 08908, Spain; [7]Department of Clinical Sciences, IDIBELL, University of Barcelona, Feixa Llarga, s/n, 08908. L'Hospitalet, Barcelona 08907, Spain and [8]Clinical Research in Solid Tumors (CReST) Group, OncoBell Program, IDIBELL, Avinguda Gran via 199-203. L'Hospitalet, Barcelona 08908, Spain

Background: Although concurrent chemoradiotherapy (cCRT) increases survival in patients with inoperable, locally advanced non-small-cell lung cancer (NSCLC), there is no consensus on the treatment of elderly patients. The aim of this study was to determine the prognostic value of the comprehensive geriatric assessment (CGA) and its ability to predict toxicity in this setting.

Methods: We enrolled 85 consecutive elderly (⩾75 years) participants, who underwent CGA and the Vulnerable Elders Survey (VES-13). Those classified as fit and medium-fit by CGA were deemed candidates for cCRT (platinum-based chemotherapy concurrent with thoracic radiation therapy), while unfit patients received best supportive care.

Results: Fit (37%) and medium-fit (48%) patients had significantly longer median overall survival (mOS) (23.9 and 16.9 months, respectively) than unfit patients (15%) (9.3 months, log-rank $P=0.01$). In multivariate analysis, CGA groups and VES-13 were independent prognostic factors. Fit and medium-fit patients receiving cCRT ($n=54$) had mOS of 21.1 months (95% confidence interval: 16.2, 26.0). In those patients, higher VES-13 (⩾3) was associated with shorter mOS (16.33 *vs* 24.3 months, $P=0.027$) and higher risk of G3-4 toxicity (65 *vs* 32%, $P=0.028$).

Conclusions: Comprehensive geriatric assessment and VES-13 showed independent prognostic value. Comprehensive geriatric assessment may help to identify elderly patients fit enough to be treated with cCRT.

As a result of population ageing and increasing incidence of lung cancer in the elderly, oncologists commonly face the challenge of effectively managing older adults with lung cancer (Wingo *et al*, 2003). Non-small-cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers, and 25–30% of NSCLC patients are diagnosed with locally advanced disease (Walters *et al*, 2013).

*Correspondence: E Nadal; E-mail: esnadal@iconcologia.net

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Concurrent chemoradiotherapy (cCRT) is the standard treatment for good performance status patients with inoperable locally advanced NSCLC (Furuse *et al*, 1995; Aupérin *et al*, 2010; O'Rourke *et al*, 2010; Ramnath *et al*, 2013; Bezjak *et al*, 2015; Eberhardt *et al*, 2015). Chemoradiotherapy is considered a reasonable standard of care for fit elderly patients (Pallis *et al*, 2014; Dawe *et al*, 2016). However, as a result of misperceptions about poorer survival and higher risk of toxicity, oncologists are often reluctant to treat older patients using conventional therapy at standard doses (Schild *et al*, 2007; Cardenal *et al*, 2015). In addition, it remains unclear whether cCRT is suitable for unselected elderly patients due to the limited data available from clinical trials (Werner-Wasik *et al*, 2000; Rocha Lima *et al*, 2002; Firat *et al*, 2006; Schild *et al*, 2007; Davidoff *et al*, 2011; Pang *et al*, 2016). Consequently, undertreatment and overtreatment bias in older adults with inoperable locally advanced NSCLC is a concern.

Ageing is characterised by great heterogeneity, so advanced age alone should not prevent people from accessing the most appropriate treatment (Hung and Mullins, 2013). In all patients, treating physicians have to balance the risk of death due to lung cancer against the potential survival benefit of treatment, but in the elderly they should pay particular attention to the risk of treatment-related adverse events and the patient's life expectancy irrespective of cancer (Pallis *et al*, 2014; Antonio *et al*, 2017). Comprehensive geriatric assessment (CGA) is considered the gold standard for characterising elderly patients according to their frailty profile (Balducci and Beghe, 2000a; Solomon *et al*, 2003; Extermann *et al*, 2005; Handforth *et al*, 2014). Comprehensive geriatric assessment is a multidimensional tool based on several scales that estimates physiological reserves and helps predict poor treatment outcomes, including toxicity, morbidity, and mortality (Extermann and Hurria, 2007). Comprehensive geriatric assessment includes assessment with standardised tools, an intervention plan and follow-through. Because CGA is time consuming and requires expertise to interpret the results and implement the appropriate interventions, screening tools like the Vulnerable Elders Survey (VES-13) are used to preselect the fittest patients from the rest of the elderly population for whom a full CGA might be indicated (Decoster *et al*, 2015).

The main objective of this prospective pilot study is to examine the prognostic value of CGA and its ability to predict toxicity in elderly patients with inoperable, locally advanced NSCLC. A secondary objective was to explore the clinical value of the VES-13 in this clinical setting.

MATERIALS AND METHODS

Study design and participants. This prospective study was conducted at the Institut Català d'Oncologia in L'Hospitalet de Llobregat, Barcelona. Since 2008 all newly diagnosed lung cancer patients aged 75 years or older who are deemed candidates for chemotherapy (with or without radiotherapy) have been systematically referred to the Geriatric Oncology Unit to undergo CGA. Eligible patients for this study were aged 75 years or older, had histological or cytological confirmation of locally advanced NSCLC based on clinical assessments (cardiopulmonary function, contrast thoracic computed tomography (CT) and positron-emitted tomography-CT (PET-CT) scan, and selective mediastinal staging with endobronchial ultrasonography and/or oesophageal ultrasonography), and were considered candidates for nonsurgical cancer treatment by the Multidisciplinary Thoracic Oncology Tumour Board. We prospectively collected the following data: age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, histology, and clinical stage according to the 7th edition of TNM, regimen of chemotherapy and radiotherapy, treatment-related toxicity, CGA variables, and VES-13 scores.

All data related to patients, tumour characteristics, and CGA results were recorded anonymously by the study investigators at the Geriatric Oncology Unit. As the study was based on current clinical practice, all patients signed the standard informed consent form for receiving cCRT. The Institutional Review Board approved the study.

Geriatric assessment. A team including a geriatrician and a geriatric oncologist assessed all patients by means of a CGA that incorporated validated instruments to explore eight domains: functional status, nutritional status, cognitive status, psychological status, comorbidities, medication, social support, and geriatric syndromes (Supplementary Table S1). Functional status was measured using two instruments: (a) the Barthel Activities of Daily Living (ADL) (Mahoney and Barthel, 1965), which uses a 0–100 scale to assess 10 basic self-care abilities (e.g., transfer, bathing, toileting, dressing, feeding); and (b) the Lawton Index of Instrumental Activities of Daily Living (IADL) (Lawton and Brody, 1969), an instrument assessing individuals' ability to independently interact with the external environment in eight complex daily activities: shopping, cooking, using the telephone, handling finances, housekeeping, laundry, self-managing medication, and using transportation; the summary score ranges from 0 (low function, dependent) to 8 (high function, independent). To assess nutritional status, participants were asked if they had unintentionally lost over 5% of their body weight in the previous 3 months. The team assessed cognitive status using the Short Portable Mental Status Questionnaire (Pfeiffer's test), which assigns a score from 0 to 10 based on the number of incorrect answers (Pfeiffer, 1975); mood was examined using the four-item Mini-Geriatric Depression Scale (D'Ath *et al*, 1994); and comorbidity using the Cumulative Illness Rating Scale for Geriatrics, with relevant comorbid conditions defined as those scoring three or more (Linn *et al*, 1968). We collected data on current medication according to self-report and the participants' medical charts, defining polypharmacy as taking five or more oral medications each day. We considered that participants had a good social environment if they had a primary caregiver, support at home, or a strong circle of friends and family capable of meeting the patient's needs. We determined the presence of a geriatric syndrome by self-reported number of falls in the previous 6 months, cognitive impairment, delirium, and urinary and/or faecal incontinence. If Pfeiffer's test indicated cognitive impairment, we referred the participant to a neuropsychologist for further assessment, classifying significant cognitive impairment as a geriatric syndrome rather than a comorbid condition to avoid overlap between comorbidity and geriatric syndrome domains. We considered only incontinence other than stress incontinence to be a geriatric syndrome.

Using the modification of the CGA proposed by Balducci and Beghe (2000b), we classified participants as 'fit', 'medium-fit', and 'unfit' (Supplementary Table S2). We defined fit as being able to independently perform all ADLs and IADLs, having no more than one clinically significant comorbid condition, and not having any geriatric syndromes. Medium-fit participants could have up to two clinically significant comorbid conditions and up to three IADL impairments, but no ADL disabilities or geriatric syndromes. Unfit participants were those with any ADL disability, more than three IADL disabilities, more than two clinically significant comorbidities, or any geriatric syndrome.

In addition to CGA, we incorporated the Vulnerable Elders Survey (VES-13), a vulnerability screening tool consisting of four groups of questions related to age, self-perceived health, difficulties to perform six specific activities, and difficulties to perform daily living tasks (Saliba *et al*, 2001). Vulnerability was defined as a VES-13 score of 3 or more on a 0–9 scale.

Treatment and follow-up. Treatment plan was based on CGA classification, and patients considered fit or medium-fit based on CGA were deemed candidates for cCRT. Radiotherapy was administered concurrently from the first day of chemotherapy up to a total dose of 60–66 Gy in daily fractions of 2 Gy over 6 weeks using a 3D technique. A specific CT scan of the thorax was performed using intravenous contrast. A PET-CT scan was used to contour the gross tumour volume (GTV). Only lymph node areas with suspicious uptake, pathological CT findings, or pathological confirmation of malignancy were included in the GTV (selective nodal irradiation) following international recommendations (De Ruysscher *et al*, 2010; Ramnath *et al*, 2013). No prophylactic nodal irradiation was performed. Organs at risk, such as the lungs, trachea, spinal cord, and oesophagus were contoured as per international guidelines (Kong *et al*, 2011). The following dose constraints were applied: for the lungs, V_{20} (volume of the healthy lung receiving <20 Gy) lower than 35%; for the oesophagus, mean dose of <34 Gy; and for the spinal cord, mean dose of <45 Gy. None of the patients received intensity-modulated radiation therapy. The mean GTV for patients treated with thoracic radiotherapy was 149.23 cm^3.

The treating physician used distinct platinum-based chemotherapy regimens (Supplementary Table S3), none of which included consolidation chemotherapy. Fit and medium-fit patients not undergoing cCRT for any reason were followed up. None of the participants classified as unfit received any active therapy and were assigned to best supportive care and followed up.

Statistical analysis. We expressed patient characteristics and geriatric variables as percentages for qualitative variables and as mean and standard deviation (s.d.) for quantitative variables. Toxicity was scored according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events version 4.0 before each cycle. We recorded data on treatment adherence and cause of discontinuation for any reason. Overall survival (OS) was defined as the time from pathological diagnosis until the date of death due to any cause or the last date the patient was known to be alive. Survival curves were plotted using the Kaplan–Meier method, and differences were assessed using the log-rank test. We constructed univariate and multivariate Cox proportional hazards models and analysed data using SPSS Statistics for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Participant characteristics and geriatric assessment. From July 2008 to September 2016, 85 elderly patients with inoperable, locally advanced NSCLC were enrolled in the study. Mean follow-up was 24 months. Most patients (89%) were men and had a history of smoking (91%). Median age was 79.5 years (range 75–87), and a significant subset of participants (51%) was 80 years or older. The most common histological subtype was squamous cell carcinoma (55%), followed by adenocarcinoma (24%); a further 21% had an unspecified subtype (21%). Most patients ($n=66$, 78%) had good ECOG performance status (<2) at study entry.

Based on CGA, 31 (37%) participants were classified as fit, 41 (48%) as medium-fit, and 13 (15%) as unfit. A flowchart is presented in Figure 1. There were no statistically significant differences between these groups with regard to age, sex, smoking history, histology, or tumour stage (Table 1). Performance status was significantly correlated with CGA groups ($P<0.001$), with poorer scores ($\geqslant 2$) more common in medium-fit (19.5%) and unfit patients (77%) compared with fit patients (3%). We also observed a significant correlation between CGA groups and VES-13 scale ($P<0.001$). Interestingly, the VES-13 scale classified 23% of fit and 68% of medium-fit patients as vulnerable ($\geqslant 3$ score).

Univariate and multivariate analysis of OS. At the data cutoff point for this survival analysis, 65 out of 85 patients had died. At mean follow-up of 24 months, median OS was 17.7 months (95% confidence interval (CI): 14.9, 20.6). Regardless of the treatment received, the CGA categories were significantly associated with OS.

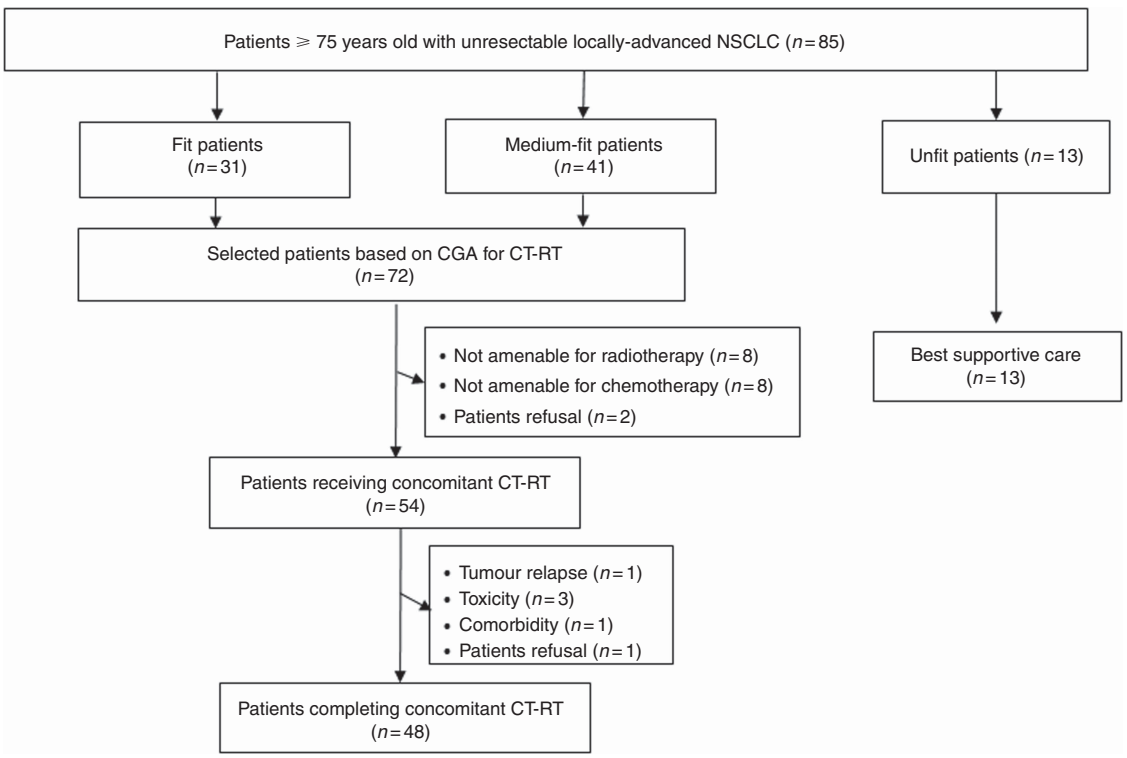

Figure 1. Study flowchart. CGA=comprehensive geriatric assessment; NSCLC=non-small-cell lung cancer.

Table 1. Clinicopathological characteristics and geriatric features according to the CGA risk groups

	Fit, $n=31$	Medium-fit, $n=41$	Unfit, $n=13$	All, $n=85$	*P*-value
Age (years)					
Median	79.7	79.0	80.5	79.5	0.290[a]
⩾80, *n* (%)	17 (55)	18 (45)	8 (61.5)	43 (51)	0.454[b]
Sex, *n* (%)					
Men	26 (84)	39 (95)	11 (85)	76 (89)	
Women	5 (16)	2 (5)	2 (15)	9 (11)	0.255[b]
Smoking history, *n* (%)					
Current	4 (13)	9 (22)	3 (23)	16 (19)	
Former	22 (71)	30 (73)	9 (69)	61 (72)	
Never	5 (16)	2 (5)	1 (8)	8 (9)	0.499[b]
Histology, *n* (%)					
Squamous cell	11 (35.5)	26 (63.5)	10 (77)	47 (55)	
Adenocarcinoma	11 (35.5)	7 (17)	2 (15)	20 (24)	
Unspecified	9 (29)	8 (19.5)	1 (8)	18 (21)	0.065[b]
Stage, *n* (%)					
IIA	1 (3)	2 (5)	0 (0)	3 (4)	
IIB	3 (10)	4 (10)	1 (8)	8 (9)	
IIIA	20 (64)	23 (56)	6 (46)	48 (58)	
IIIB	7 (23)	12 (29)	6 (46)	25 (29)	0.806[b]
ECOG-PS, *n* (%)					
0–1	30 (97)	33 (80.5)	3 (23)	66 (78)	
⩾2	1 (3)	8 (19.5)	10 (77)	19 (22)	**<0.001**[b]
Geriatric assessment variables					
Physical function, *n* (%)					
ADL – Barthel					
⩾ 90	31 (100)	41 (100)	4 (31)	76 (89)	**<0.001**[b]
<90	0 (0)	0 (0)	9 (69)	9 (11)	
IADL – Lawton					
⩾5	31 (100)	0 (0)	3 (23)	34 (40)	
<5	0 (0)	41 (100)	10 (77)	51 (60)	**<0.001**[b]
Cognitive function, *n* (%)					
Pfeiffer					
<2	31 (100)	41 (100)	10 (77)	82 (96.5)	**<0.001**[b]
⩾2	0 (0)	0 (0)	3 (23)	3 (3.5)	
Mood assessment, *n* (%)					
Yesavage					
<1	30 (97)	38 (93)	12 (92)	80 (94)	0.732[b]
⩾1	1 (3)	3 (7)	1 (8)	5 (6)	
Comorbidity, *n* (%)					
CIRS-G					
Total score (median)	4	6	11	6	**<0.001**[a]
Severity score (median)	1.5	1.6	2.2	1.7	**<0.001**[a]
Polypharmacy, *n* (%)					
⩽5	19 (61)	9 (22)	0 (0)	28 (33)	
>5	12 (39)	32 (78)	13 (100)	57 (67)	**<0.001**[b]
Geriatric syndromes, *n* (%)					
0	31 (100)	41 (100)	9 (69)	81 (95)	
⩾1	0 (0)	0 (0)	4 (31)	4 (5)	**<0.001**[b]
Social support, *n* (%)					
Yes	31 (100)	36 (88)	11 (85)	78 (92)	
No	0(0)	5(12)	2 (15)	7 (8)	0.105[b]
Weight loss, *n* (%)					
<5%	26 (84)	29 (71)	9 (69)	64 (75)	
>5%	5 (16)	12 (29)	4 (31)	21 (25)	0.379[b]
VES-13 scale, *n* (%)					
<3	24 (77)	13 (32)	0 (0)	37 (43.5)	
⩾3	7 (23)	28 (68)	13 (100)	48 (56.5)	**<0.001**[b]

Abbreviations: ADL = Barthel Activities of Daily Living; ANOVA = analysis of variance; CGA = comprehensive geriatric assessment; CIRS-G = Cumulative Illness Ratio Scale for Geriatrics; ECOG-PS = Eastern Cooperative Oncology Group performance status; IADL = Lawton Index of Instrumental Activities of Daily Living; VES-13 = Vulnerable Elders Survey. Values in bold are statistically significant.

[a]ANOVA *P*-value.

[b]χ^2 *P*-value.

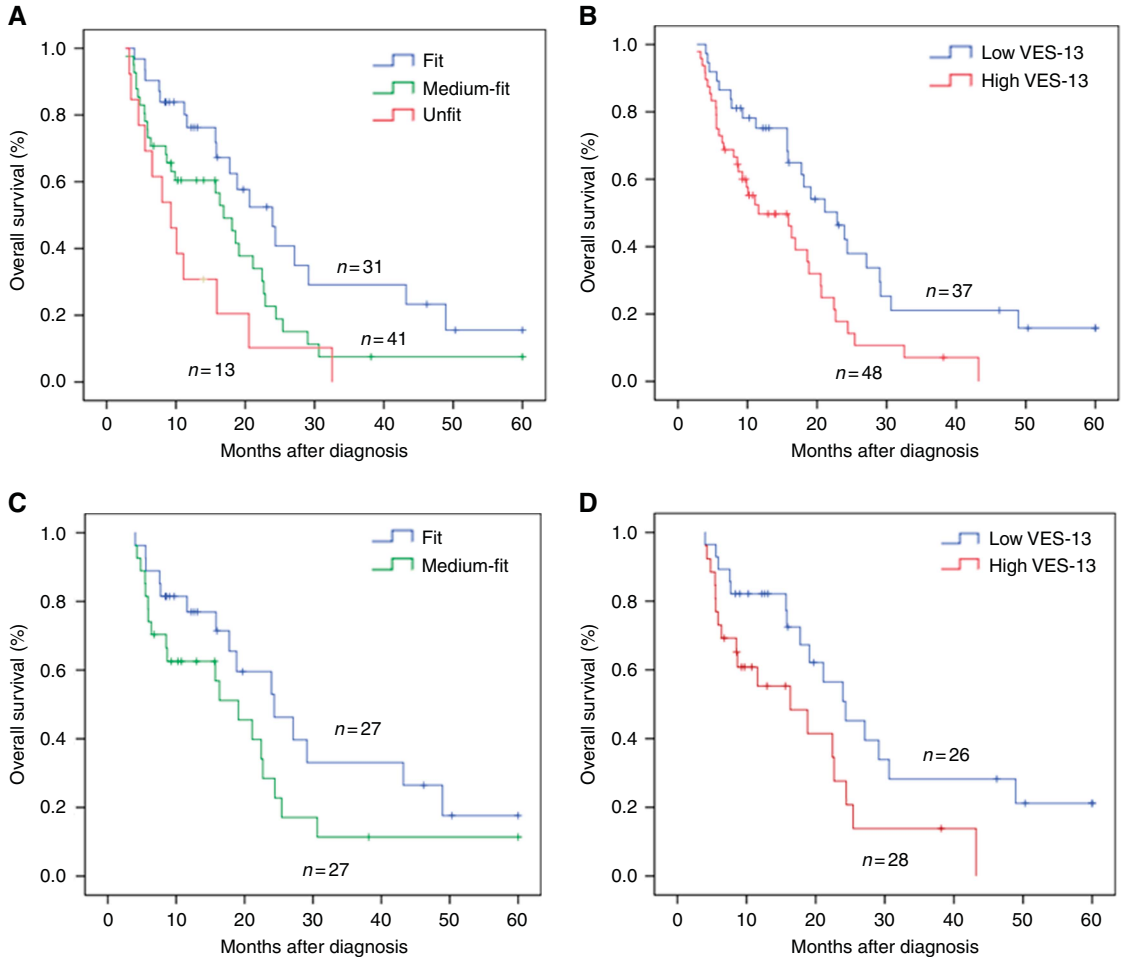

Figure 2. Kaplan–Meier plots of OS that include the whole cohort of patients ($n=85$) classified according to CGA (**A**) and VES-13 (**B**), and the subset of patients treated with chemoradiotherapy ($n=54$) classified by CGA (**C**) and VES-13 (**D**). CGA = comprehensive geriatric assessment; OS = overall survival; VES-13 = Vulnerable Elders Survey.

Table 2. Multivariate Cox regression analysis of OS for all patients ($n=85$) based on CGA and VES-13 categories

	HR (95% CI)	*P*-value
Age, continuous	0.94 (0.86, 1.02)	0.128
Sex (men *vs* women)	1.72 (0.60, 4.92)	0.308
Histology (SCC *vs* non-SCC)	1.55 (0.87, 2.75)	0.135
Stage (III *vs* II)	1.14 (0.47, 2.72)	0.777
Weight loss (≥5 *vs* <5%)	1.25 (0.63, 2.46)	0.525
CGA group (fit *vs* medium-fit)	1.98 (1.06, 3.71)	**0.033**
CGA group (fit *vs* unfit)	3.81 (1.53, 9.45)	**0.004**
VES-13		
Age, continuous	0.96 (0.88, 1.04)	0.128
Sex (men *vs* women)	1.92 (0.69, 5.38)	0.308
Histology (SCC *vs* non-SCC)	1.52 (0.87, 3.58)	0.144
Stage (III *vs* II)	1.46 (0.59, 3.58)	0.403
Weight loss (≥5% *vs* <5%)	1.57 (0.84, 2.92)	0.157
VES-13 (≥3 *vs* <3)	2.30 (1.28, 4.15)	**0.005**

Note: For dichotomous variables, HR indicates the risk for the first variable. Abbreviations: CGA = comprehensive geriatric assessment; CI = confidence interval; HR = hazard ratio; OS = overall survival; SCC = squamous cell carcinoma; VES-13 = Vulnerable Elders Survey. Values in bold are statistically significant.

Median OS was significantly shorter for unfit and medium-fit patients (9.3 and 16.9 months, respectively) compared with fit patients (23.9 months, log-rank $P=0.01$; Figure 2A). The respective 2- and 5-year OS rates were 47% and 15% in fit, 23% and 8% in medium-fit, and 10% and 0% in unfit participants.

Participants with a VES-13 score indicating vulnerability (≥3) also had significantly shorter median OS (11.6 months, 95% CI: 4.3, 18.9) than non-vulnerable patients (22.9 months, 95% CI: 16.1, 29.6; log-rank $P=0.007$; Figure 2B).

In the univariate Cox regression analysis, performance status, geriatric classification, and VES-13 were prognostic factors for OS (Supplementary Table S4). In the multivariate Cox regression analysis adjusted for age, sex, histology, tumour stage, and weight loss, and compared to fit participants, OS was worse for medium-fit (hazard ratio (HR) 1.98, 95% CI: 1.06, 3.71) and unfit groups (HR = 3.81, 95% CI: 1.53, 9.45, Table 2). In the multivariate Cox regression adjusted for the same covariates, vulnerability was also significantly associated with worse OS (HR = 2.30, 95% CI: 1.28, 4.15, $P=0.005$, Table 2).

Survival results in patients treated with cCRT. All patients classified as unfit ($n=13$) received best supportive care, which included palliative thoracic radiotherapy in four cases. Out of 72 fit and medium-fit patients initially considered candidates for cCRT, only 54 patients (75%) were actually treated (Figure 1). The reasons for not administering cCRT were: non-suitable for radiotherapy (tumour extension or poor respiratory function) ($n=8$), specific contraindication to chemotherapy ($n=8$), and patient's decision ($n=2$).

Patients treated with cCRT ($n=54$) achieved a median OS of 21.1 months (95% CI: 16.2, 26.0). Most participants (89%)

Table 3. Moderate and severe toxicity in patients treated with concurrent chemoradiotherapy according to the CGA groups ($n=54$)

	Fit ($n=27$)		Medium-fit ($n=27$)		Total ($n=54$)	
Toxicity	**G3–4, *n* (%)**	**G5, *n* (%)**	**G3–4, *n* (%)**	**G5, *n* (%)**	**G3–4, *n* (%)**	**G5, *n* (%)**
Neutropenia	7 (26)	0 (0)	4 (15)	0 (0)	11 (20)	0 (0)
Febrile neutropenia	2 (7.5)	0 (0)	2 (7.5)	0 (0)	4 (7.5)	0 (0)
Anaemia	0 (0)	0 (0)	2 (7.5)	0 (0)	2 (4)	0 (0)
Thrombocytopenia	1 (4)	0 (0)	2 (7.5)	0 (0)	3 (6)	0 (0)
Fatigue	2 (7.5)	0 (0)	4 (15)	0 (0)	6 (11)	0 (0)
Diarrhoea	1 (4)	0 (0)	0(0)	0 (0)	1(2)	0 (0)
Oesophagitis	0 (0)	0 (0)	1(2)	0 (0)	1(2)	0 (0)
Respiratory infection	2 (7.5)	0 (0)	7 (26)	2 (7.5)	7 (13)	2 (7.5)
Radiation pneumonitis	2 (7.5)	0 (0)	5 (18.5)	2 (7.5)	7 (13)	2 (7.5)

Abbreviation: CGA = comprehensive geriatric assessment.

completed the planned treatment, and there were no differences in compliance between CGA groups. The reasons for not completing the planned cCRT were treatment-related toxicity ($n=3$), cancer progression ($n=1$), patient's decision ($n=1$), or aggravation of comorbidities ($n=1$).

The chemotherapy schedules used most often were carboplatin 2.5 AUCs (area under the plasma drug concentration–time curve) plus vinorelbine 15 mg m^{-2} on days 1, 8, 22, and 29 and weekly carboplatin 2 AUCs plus paclitaxel 45 mg m^{-2} (Supplementary Table S3).

Analysis did not show any statistically significant differences in median OS between fit and medium-fit patients treated with cCRT (24.3 and 19.1 months, respectively, log-rank $P=0.096$; Figure 2C). Non-vulnerable patients (according to VES-13) receiving cCRT had significantly longer median OS (24.3 months, 95% CI: 16.6, 32.1) than vulnerable patients (16.3 months, 95% CI: 4.7, 27.9, log-rank $P=0.027$; Figure 2D). Interestingly, in the multivariate Cox regression adjusted for age, sex, histology, tumour stage, and weight loss, vulnerable patients (VES-13 score $\geqslant 3$) had significantly shorter median OS (HR 2.90, 95% CI: 1.30, 6.45, $P=0.009$).

Association between CGA and toxicity. Among the 54 patients receiving cCRT, medium-fit patients experienced a higher rate of grade 3–4 adverse events (59%) than fit patients (37%), but these differences were not statistically significant ($P=0.173$). Vulnerable patients as defined by VES-13 had a significantly higher rate of grade 3–4 adverse events (65%) than non-vulnerable patients (32%, $P=0.028$). We did not observe differences in grade 3–4 haematologic toxicity between fit and medium-fit patients or between vulnerable and non-vulnerable patients. Four (3.8%) fit and no medium-fit patients experienced grade 3–4 haematologic toxicity ($P=0.31$), while eight (24%) fit and three (10%) medium-fit patients experienced grade 3–4 non-haematologic toxicity ($P=0.09$).

The most common grade 3–4 adverse events were neutropenia (20%), febrile neutropenia (7.5%), asthaenia/fatigue (11%), respiratory infection (13%), and radiation pneumonitis (13%). All treatment-related deaths occurred in the medium-fit group: two due to radiation pneumonitis and two due to respiratory infection. Toxicity according to geriatric group is summarised in Table 3.

Table 4. Univariate logistic regression analysis to predict grade 3–4 toxicity in patients treated with concurrent chemoradiotherapy ($n=54$)

Variable	OR (95% CI)	*P*-value
Age, continuous	0.92 (0.76, 1.12)	0.409
Sex (men *vs* women)	4.35 (0.45, 41.8)	0.203
Histology (SCC *vs* non-SCC)	1.08 (0.37, 3.19)	0.884
Smoking status (smoker *vs* never smoker)	4.35 (0.45, 41.8)	0.203
Stage (III *vs* II)	1.90 (0.41, 8.94)	0.414
Weight loss (≥ 5 *vs* $<5\%$)	1.33 (0.27, 6.63)	0.725
ECOG-PS (≥ 2 vs <2)	1.04 (0.14, 7.99)	0.969
VES-13 score (≥ 3 *vs* <3)	3.99 (1.28, 12.37)	**0.017**
CGA group (medium-fit *vs* fit)	2.72 (0.89, 8.26)	0.078

Note: For dichotomous variables, the OR indicates the risk for the first variable. Abbreviations: CGA = comprehensive geriatric assessment; CI = confidence interval; ECOG-PS = Eastern Cooperative Oncology Group performance status; OR = odds ratio; SCC = squamous cell carcinoma; VES-13 = Vulnerable Elders Survey. Values in bold are statistically significant.

Logistic regression was performed to assess the ability of distinct variables to predict grade 3–4 toxicity. While CGA-defined groups were not predictive of this outcome, vulnerable patients as defined by VES-13 were at significantly higher risk of grade 3–4 toxicity (odds ratio (OR) 3.99, 95% CI: 1.28, 12.37, $P=0.017$; Table 4).

DISCUSSION

This prospective study, carried out in the clinical practice setting, included a cohort of 85 consecutive participants aged 75 years or older with inoperable, locally advanced NSCLC who were evaluated by CGA. To our knowledge, this is the first prospective study assessing the value of CGA for selecting patients for cCRT therapy in this specific elderly population, for whom treatment decisions are particularly challenging. Indeed, a significant proportion of participants were octogenarians.

At present, treatment decisions are based on clinical assessment, age, and performance status. Patients of advanced age, with poor performance status, weight loss, or comorbidities are considered 'poor-risk' patients and have generally been excluded from clinical trials evaluating cCRT (Cardenal *et al*, 2015). However, CGA detects geriatric impairments even in patients with good performance status (Jolly *et al*, 2015). A recent systematic review on CGA for lung cancer patients found that CGA could detect multiple geriatric impairments that are generally missed by other measures such as ECOG performance status (Schulkes *et al*, 2016), and some of these can be reversed through subsequent geriatric-based interventions (Kalsi *et al*, 2015). In our study, 3% of fit and 19.5% of medium-fit patients had a performance status score of 2 or more and would be considered as 'poor-risk' and excluded from cCRT.

Most previous studies addressing the relevance of CGA in lung cancer were conducted in patients with advanced disease or with distinct tumour stages (Maione *et al*, 2005; Corre *et al*, 2016; Gajra *et al*, 2016; Karampeazis *et al*, 2017). Recently, the Elderly Selection on Geriatric Index Assessment study compared a standard strategy of treatment allocation (carboplatin-based doublet or single agent on the basis of performance status and age) *vs* an experimental CGA-based allocation to the same chemotherapies or best supportive care in elderly patients with advanced NSCLC (Corre *et al*, 2016). Although that study failed to show an improvement in failure-free survival and OS in patients in the CGA-guided arm, these patients showed better tolerance to chemotherapy and lower

treatment failure due to toxicity, and nearly one-quarter of them were spared chemotherapy without compromising survival for the whole group.

A recent individual patient data meta-analysis of 16 trials ($n=3600$) assessing cCRT in unresectable stage III NSCLC included 832 (23%) elderly participants ($\geqslant 70$ years old); elderly patients had a shorter OS than their younger counterparts (17.0 *vs* 20.7 months, $P<0.01$) (Stinchcombe *et al*, 2017). The JCOG0301 randomised phase III clinical trial, performed specifically in patients aged 70 years or older with stage III NSCLC, showed better outcomes for cCRT *vs* RT alone in a group of participants who had not undergone geriatric characterisation (Atagi *et al*, 2012). An ongoing phase II study assessing CGA in the inoperable, locally advanced NSCLC setting (RACCOSSA, GFPC 08-06) is evaluating tolerance to cCRT (cisplatin plus vinorelbine concurrently with thoracic radiotherapy) in participants aged 70 years or older and considered fit by geriatric assessment (Locher *et al*, 2011).

We observed a significant association between CGA groups and clinical outcome, as fit and medium-fit patients had longer median OS than unfit patients. This survival outcome cannot be entirely attributed to the expected beneficial effect of cCRT; rather, this difference is likely related to the poorer health profile of unfit patients compared with fit and medium-fit patients. Besides, as our study is non-comparative, the interaction between treatment and CGA categories in terms of prognosis cannot be assessed.

On the other hand, the survival results in the selected group of fit and medium-fit patients who did receive cCRT (median OS 21.1 months, 95% CI: 16.2, 26.0) were in the range of those reported for younger patients in clinical trials (Santana-Davila *et al*, 2015; Steuer *et al*, 2016). Atagi *et al* (2012) reported that cCRT resulted in a median OS slightly higher than ours (22.4 months, 95% CI: 16.5, 33.6), but inclusion was restricted to participants of Asian ethnicity with good performance status (96% of patients had an ECOG score of 0–1). A recent systematic review of sequential or concurrent CRT *vs* radiotherapy alone in elderly patients with stage III NSCLC concluded that fit patients showed good tolerance to cCRT, which was associated with a 34% reduction in the hazard ratio for death (Dawe *et al*, 2016).

Toxicity is a special concern in elderly patients because of its greater potential impact on functionality and quality of life compared to the general population. Our safety data provides support for using cCRT in older adults. In our sample, the rate of grade 3–4 toxicities associated with cCRT was consistent with the range of values reported in other elderly specific studies (Atagi *et al*, 2012; Dawe *et al*, 2016). The proportion of participants completing the planned treatment in our selected sample was 78%, and although we do not have a benchmark for this parameter in routine clinical practice, it is higher than that reported by Stinchcombe *et al* (2017) in elderly patients participating in phase II–III trials (47%).

Comprehensive geriatric assessment has not been universally adopted as a standard of care because it is time-consuming and resource-intensive for busy oncological practices (Decoster *et al*, 2015). VES-13 requires less time and professional intervention, and can also be self-administered. The capability of the VES-13 screening tool for predicting prognosis and toxicity in this clinical setting is a remarkable finding of our research. In our study, vulnerable participants (VES-13 $\geqslant 3$) had significantly shorter median OS and a higher risk of grade 3–4 toxicity, as previously reported in patients older than 75 years with several tumours (Luciani *et al*, 2015). The ability of the VES-13 scale to capture physical functioning might explain its capacity to detect vulnerability in lung cancer patients for whom functional status has a significant weight. Although screening tools appear to simplify the geriatric assessment, they skip processes covered by CGA that are relevant for decision-making, such as diagnosing impairments, defining patient priorities, setting the pretreatment baseline, and implementing interventions (Hamaker *et al*, 2017). For this reason these tools cannot replace CGA (Decoster *et al*, 2015).

Major strengths of our study are its prospective design; the performance of a standardised CGA on all patients diagnosed with locally advanced NSCLC, without any previous selection; and the concurrent CRT approach used, as opposed to other currently accepted treatment strategies for these patients, such as sequential CRT, definitive radiotherapy alone, or chemotherapy alone.

Our study has some limitations. It is a pilot exploratory study carried out at a single institution with a limited sample size, and our frailty assessments did not include any physical performance measure shown to have predictive ability (Guralnik *et al*, 1995). It is a nonrandomised study with a predetermined treatment strategy, so it was not designed to demonstrate whether patients would benefit from treatment regimens adapted to frailty profile. The ongoing ELDAPT clinical trial (NCT02284308) compares concurrent and sequential CRT in elderly patients with stage III NSCLC who have been assessed by CGA.

In conclusion, the present study demonstrates that CGA can identify elderly patients with inoperable, locally advanced NSCLC suitable for cCRT, with encouraging survival and toxicity outcomes. We observed a high capability of VES-13 for assessing prognosis and predicting toxicity, but these results need to be validated in a larger cohort. We hope this work will promote research in elderly patients who are candidates for multimodal treatment, correcting the existing misperceptions of poor outcomes based on outdated empirical treatment eligibility criteria. Large, multicentre studies in the field are a priority.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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