Journal of Geriatric Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

journal homepage: www.elsevier.com/locate/jgo

Research Paper

Predictors of three-month mortality and severe chemotherapy-related adverse events in patients aged 70 years and older with metastatic non-small-cell lung cancer: A secondary analysis of ESOGIA-GFPC-GECP 08–02 study

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ARTICLE INFO

Keywords:
Frail dimension
Lung cancer
Geriatric assessment
Toxicity
Mortality

ABSTRACT

Introduction: Predictors for mortality and toxicity in older patients with cancer are mainly studied in cohorts with various cancers at different stages. This study aims to identify predictive geriatric factors (PGFs) for early death and severe chemotherapy related adverse events (CRAEs) in patients aged ≥70 years with metastatic non-small-cell lung cancer (mNSCLC).

Material and Methods: This is a secondary analysis of the multicenter, randomized, phase 3 ESOGIA trial that compared, for patients ≥70 years with mNSCLC, a treatment algorithm based on performance status and age to another algorithm based on geriatric assessment. To identify PGFs of three-month mortality and grade 3, 4, or 5 CRAEs, multivariate Cox models and logistic models, adjusted for treatment group and center, and stratified by randomization arm, were constructed.

Results: Among 494 included patients, 145 (29.4%) had died at three months and 344 (69.6%) had severe chemotherapy toxicity. For three-month mortality, multivariate analyses retained mobility (Test Get up and Go), instrumental activity of daily living (IADL) dependence and weight loss as PGFs. The combined effect of IADL ≤2/4 and weight loss ≥3 kg was strongly associated with three-month mortality (adjusted hazard ratio: 5.71 [95% confidence interval [CI]: 2.64–12.32]). For chemotherapy toxicity, Charlson Comorbidity Index ≥2 was independently associated with grade3, 4, or 5 CRAEs (adjusted odds ratio [95% CI]: 1.94 [1.06–3.56]).

Discussion: Mobility, IADL dependence, and weight loss were predictive of three-month mortality in a population aged ≥70 years treated for mNSCLC, while comorbidities were independently associated with severe chemotherapy toxicity.

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https://doi.org/10.1016/j.jgo.2023.101506
Received 22 November 2022; Received in revised form 27 March 2023; Accepted 21 April 2023

1. Introduction

The incidence of non-small-cell lung cancers (NSCLCs) in older patients is increasing in western countries, mainly due to an aging population. In Europe, almost half of patients with NSCLC were aged ≥70 years in 2020 [1]. Lung cancer diagnoses for this age group are often obtained late, at metastatic stage (mNSCLC). Despite recent progress made with targeted therapies and anti-programmed–death protein (PD)-1 or anti-PD1–ligand immunotherapy, chemotherapy retains an important role and the prognosis remains somber [2].

Although it is accepted that chronological age should not be a barrier to access systemic cancer treatments, it is necessary to evaluate the individual risks versus benefits of receiving cancer treatment for patients ≥70 years [3]. The under-representation of older patients in clinical trials, the broad heterogeneity of their comorbidities, dependence, and cognitive status make it difficult to devise therapeutic guidelines [4,5]. The inclusion limited to fit patients in pivotal therapeutic studies make it extremely difficult to extrapolate their findings to routinely manage older patients [6–8].

In this context, geriatric assessment (GA) is able to identify frailty parameters and comorbidities that could impact survival and the feasibility of oncological treatments. In that way, GA could prove useful to classify patients into frailty groups, and thereby optimize therapeutic strategies [9]. The phase 3 GFPC-GECP ESOGIA trial investigated a chemotherapy allocation strategy based on this geriatric classification in patients ≥70 years old with mNSCLC. This study randomized 494 patients, allotting them to one of two strategies to assign chemotherapy: (1) classical criteria based on Eastern Cooperative Oncology Group performance status (ECOG PS) and age or (2) an algorithm based on GA findings [10]. This study provided a geriatric characterization into three groups—fit, vulnerable, or frail—based on the GA conducted at inclusion for the entire population. Although the results were negative for the main outcome criterion, i.e., time to treatment failure and overall survival (OS), the chemotherapy related adverse events (CRAEs) and treatment failure frequencies were significantly lower in the GA arm than in the standard-strategy arm. These results were recently confirmed by two randomized trials [11,12]. The first, the GAP70+ trial, reported 20% fewer grade 3, 4, or 5 adverse events (AEs) in the GA-guided intervention arm in 718 patients with metastatic cancers; the second, the GAIN trial, demonstrated among 613 patients with metastatic cancers that a specific GA-driven intervention was able to lower grade 3 or 4 adverse events (AEs) by 10.1%.

However, we still have little understanding of the older adult-specific parameters involved in limiting toxicity. Predictive scores for death or CRAEs using GA tools [13–15] were developed in older patients with various solid cancers at different stages, however, specific data in older patients with mNSCLC are still missing. The predictive value of these scores may be inaccurate in disease-specific validation studies [16,17]. In this way, frailty parameters should be investigated in the specific setting of a population of patients ≥70 years with advanced lung cancer. In the ESOGIA population, the common prognostic factors of death and chemotoxicity in older adults, as well as their predictive value, might be different from other settings.

The objective of this secondary analysis of the ESOGIA study was to determine predictors for three-month mortality and severe chemotherapy related adverse events in patients ≥70 years with mNSCLC.

2. Methods

2.1. Study Design and Population

This was an ancillary analysis of the ESOGIA trial data, whose methods and results were published previously [10]. Briefly, the phase 3 randomized GFPC-GECP ESOGIA trial conducted between January 2010 and January 2013 enrolled 494 patients aged ≥70 years with stage IV mNSCLC about to receive first-line therapy. Median follow-up was 4.5 months (range, 0 to 36.7 months), and the final cutoff date was March 2014. Two chemotherapy-attribution algorithms were compared. One, based on the usual criteria (ECOG PS and age), prescribed carboplatin-based doublet when PS ≤ 1 and age ≤ 75 years, docetaxel monotherapy when PS = 2 or age > 75 years; the other, based on GA results, administered carboplatin-based doublet for fit patients, docetaxel monotherapy for dependent patients, or best supportive care for frail patients. Data from the entire ESOGIA trial population that underwent GA at inclusion were analyzed. ESOGIA trial was approved by the Rennes Ethics Committee and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

2.2. Endpoints

The main outcome measure was three-month mortality. Secondary endpoint was grade 3, 4, or 5 CRAEs, as defined in the Common Terminology Criteria for Adverse Events version 4.

2.3. Geriatric Assessment Domains

Geriatric variables explored in this analysis were: (1) *Dependency level* based on the six-item Activity of Daily Living (ADL) scale (personal hygiene, dressing, grooming, washing, transferring/mobility, continence, feeding) [18] and the four-item Instrumental Activity of Daily Living (IADL) scale (use of the telephone, use of public transportation, take medications, manage finances). These were consistently classified in the ESOGIA trial [10] as follows: ADL = 6 (independence) or ADL ≤5 and IADL = 4 (independence) or IADL = 3 or IADL ≤2) [19]; (2) *cognitive status screening* using Folstein's Mini Mental Status Examination (MMSE) (≤23, cognitive impairment versus >23: no cognitive impairment) [20]; (3) *comorbidities* based on Charlson Comorbidity Index score (≥2, moderate to frequent comorbidities versus 0–1, few or mild comorbidities) [21]; (4) *depression screening* using Geriatric Depression Scale (GDS) (score is out of 5: 0–1 no risk, 2–3 moderate risk, 4–5 high risk) [22]; (5) *mobility* with the Test Get up and Go (TGUG), scored as normal versus abnormal [23]; (6) *continence* (yes or no); (7) *falls* during last year (yes or no), and (8) *nutritional status* measured by body mass index (BMI, kg/m^2) (<21; underweight, 21–24.99 normal; ≥25 overweight or obese) and weight loss in the past six months (≤3 kg [low-risk], versus ≥3 kg [high-risk]) [24,25].

2.4. Other Parameters

Non-geriatric variables were also considered for the models fitting: **demographics** (age and sex); **smoking status** (never, former, or active smokers); **functional status**: ECOG PS; **cancer-related**: treatment type (carboplatin-based doublet, monotherapy, i.e., docetaxel or best supportive care), and number of chemotherapy cycles; and **biological markers**: hemoglobin (anemia defined as <12 g/dL for females and < 13 g/dL for males), Modification of Diet in Renal Disease (MDRD) algorithm-estimated renal clearance (mL/min) (<30, renal failure; 30–60, moderate renal insufficiency; ≥60, normal renal function) [26], lactate dehydrogenase (LDH) (analyzed as a continuous variable), C-reactive protein (CRP; analyzed as a continuous variable) and albuminemia (ALB; <30 vs ≥30 g/dL) [27] were also measured. The latter two variables were also analyzed as the CRP/ALB ratio, and as a composite parameter according to the Glasgow Prognostic Score (GPS): 0 (CRP ≤ 10 mg/L and ALB ≥35 g/L) vs 1 (CRP ≤ 10 mg/L and ALB <35 g/L) vs 2 (CRP > 10 mg/L and ALB <35 g/L) [28].

2.5. Statistical Analyses

Standard descriptive analyses were used. Continuous variables are expressed as mean (standard deviation, SD) or median (interquartile range, IQR) and categorical variables as number (%). Three-month OS from the date of randomization was estimated using the Kaplan–Meier

method.

Geriatric factors associated with three-month mortality were identified using Cox proportional hazards models, systematically adjusted for treatment group and center, and included randomization arm as a strata. We add a "strata" option to the Cox model to assume that the baseline hazard can be group specific due to the design; but the coefficients are the same. For all endpoints, the variables with $p < 0.20$ in univariate analyses were further examined in multivariate analyses. Correlations between each GA variables were tested in bivariate models using Cramer's test to perform distinct models if correlations were high ($\rho > 0.3$). Multivariate Cox models were constructed with manual step-by-step adjustment considering the number of chemotherapy cycles variable as a confounding factor. Indeed, the number of chemotherapy cycles had an effect on mortality and toxicity and may be related to both geriatric factors and outcomes. Because the number of chemotherapy cycles cannot be considered a baseline characteristic, it was considered a time-varying covariate, obtained by splitting each observation into time intervals, with each interval corresponding to a chemotherapy cycle (0–4 cycles). Interactions between each geriatric variable were examined and interaction coefficient terms were tested manually in the multivariate model. Separate models were run to account for correlated variables and to estimate each geriatric domain's prognostic effect. Backward variable elimination according to the Akaike information criterion (AIC) identified the most accurate and parsimonious model. Association strengths are reported as hazard ratio (HR) [95% confidence interval (CI)]. The proportional hazards assumption was assessed statistically using the Schoenfeld residuals test. Imputation was used to correct for missing laboratory values (e.g., ALB, CRP, LDH, hemoglobin level) using the predictive mean-matching method (function pmm in Stata software) in multivariate analyses. Overall fit of the models was assessed with the Brier score, calibration was assessed with the calibration slope and discrimination capability with Harrell's C statistic.

The same method was applied for predicting severe (grade 3, 4, or 5) CRAEs using logistic-regression models, adjusted for treatment group, center, and included randomization arm as a strata, and results are reported as odds ratio (OR) [95% CI].

All tests were two-sided, and $p < 0.05$ was considered significant. Analyses were computed using STATA software version 15.0 (StataCorp, College Station, TX) and R Studio Desktop (version 1.4.1106).

3. Results

3.1. Patients

Between January 2010 and January 2013, 45 French and Spanish centers (14 university hospitals, 4 cancer centers, and 27 community hospitals) enrolled 494 patients (median age 77 years; 74.2% male; 79.6% former or current smokers; 18.9% with ECOG PS = 2) (Table 1). All patients underwent GA, 14.4% exhibited ADL dependence (ADL ≤ 5), 28.6% had IADL dependence (IADL ≤3), 15.4% had cognitive disorders risk (MMSE ≤23), 15.6% were at risk of depression (GDS5 ≥ 2), 23.9% had major comorbidities (Charlson Comorbidity Index ≥2) and 20.3% malnutrition (BMI < 21 kg/m2). Platinum-based doublet (carboplatin-pemetrexed and carboplatin–gemcitabine for 30.0% and 10.1%, respectively), docetaxel monotherapy and only best supportive care, respectively, were assigned to 40.1%, 48.5% and 11.4%. Median follow-up was 4.5 (range: 0–36.7) months. The median number of chemotherapy cycles was 4 [IQR 1–4].

3.2. Overall Survival

Median OS was 5.4 [95% CI: 4.89–5.85] months, with three-month OS rate of 70.6% [95% CI: 65.9% 74.8%]. Univariate analysis selected the following factors as being significantly associated with higher three-month mortality: IADL score ≤ 2/4, MMSE ≤23, GDS5 score 2–3, abnormal Test Get up and Go (TGUG), recent weight loss ≥3 kg and Charlson Comorbidity Index ≥2 for geriatric parameters; and male sex, ECOG PS = 2, anemia, ALB ≤30 g/L, a number of chemotherapy cycles <4, elevated LDH and CRP concentrations for non-geriatric parameters (Table 2).

Table 1
Baseline characteristics of the 494 ESOGIA-trial participants.

Characteristic	Value
Age (years) (n = 493)	77 [74–80]
Male sex (n = 493)	366 (74.2)
Smoker status (n = 368)	
Never-smokers	75 (20.4)
Former smokers	60 (16.3)
Current smokers	233 (63.3)
Treatment (n = 493)	
Docetaxel monotherapy	239 (48.5)
Best supportive care	56 (11.4)
Carboplatin doublet	198 (40.2)
Carbo-gemcitabine	50 (10.1)
Carbo-pemetrexed	148 (30.0)
ECOG PS (n = 493)	
0–1	400 (81.1)
2	93 (18.9)
Activities of Daily Living score (n = 493)	
6	422 (85.6)
<6	71 (14.4)
Instrumental Activities of Daily Living score (n = 493)	
4	352 (71.4)
3	90 (18.3)
≤2	51 (10.3)
Mini-Mental State Examination score (≤23) (n = 493)	76 (15.4)
Geriatric Depression Scale 5 score (n = 492)	
0–1	416 (84.4)
2–3	61 (12.4)
4–5	15 (3.0)
Continence (n = 493)	469 (95,1)
Fall during last year (n =,493)	74 (15.0)
TGUG (n = 490)	
Normal	358 (73.1)
Abnormal	132 (26.9)
Recent weight loss (> 3 kg) (n = 484)	270 (55.8)
Body mass index kg/m^2 (n = 493)	
21–24.99	195 (39.6)
<21	100 (20.3)
≥25	198 (40.2)
Charlson Comorbidity Index score (n = 493)	
0–1	375 (76.1)
≥2	118 (23.9)
Albuminemia (≤30 g/L) (n = 348)	93 (26.7)

Values are expressed as number (%) or median [IQR].
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status; TGUG, Test Get Up and Go.

After backward stepwise regression analysis (according to the AIC), MMSE ($p = 0.597$) and GDS5 ($p = 0.838$) for three-month mortality were removed while all other factors included in the multivariate Cox regression turned out to be essential. We found a strong correlation between IADL and TGUG ($\rho = 0.51$), IADL, and ECOG PS ($\rho = 0.44$) as well as anemia and CRP ($\rho = 0.45$) (**eTable 1**). Given the collinearity among these variables, predictors were fitted in separate multivariable models. Multivariate analyses retained the following variables as independent factors associated with three-month mortality: IADL dependence (IADL ≤2/4), abnormal TGUG mobility, weight loss ≥3 kg for geriatric parameters, and male sex, functional status (ECOG PS = 2), anemia, CRP/ALB ratio, and LDH for non-geriatric parameters. An interaction was found between recent weight loss and several IADL dependencies (IADL ≤2). When these two factors were present, the risk of death at three months was much greater (HR 5.71 [95% CI 2.64–12.32]; $p < 0.001$; Fig. 1).

The most performing and parsimonious multivariate Cox models for predicting three-month mortality were driven by either IADL and weight loss (model OS-1), TGUG (model OS-2), or PS (model OS-3). These models have similar performance predicting three-month mortality with

Table 2
Factors associated with 3-month mortality: univariate analysis.

Factor	HR[a]	95% CI	p
Age, per 1-year increase	0.99	0.95–1.04	0.793
Age, years			
70–74	1.00 (ref)	–	0.325
75–79	0.74	0.46–1.18	
≥80	0.71	0.44–1.15	
Male vs female sex	2.39	1.47–1.57	<0.001
Smoker status			
Never-smokers	1.00 (ref)	–	0.235
Former smokers	1.26	0.58–2.73	
Current smokers	1.63	0.90–2.95	
Treatment			
Carboplatin-based doublet	1.00 (ref)	–	<0.001
Docetaxel monotherapy	2.70	1.70–4.27	
Best supportive care	6.81	3.84–12.08	
No. of chemotherapy cycles			
4	1.00 (ref)	–	<0.001
3	58.31	12.18–279.09	
2	151.15	35.65–640.91	
1	593.08	137.77–2553.01	
0	229.86	44.02–1200.42	
Growth factors: yes vs no (n = 315)	0.8	0.46–1.39	0.436
ECOG PS			
0	1.00 (ref)	–	<0.001
1	3.15	1.72–5.77	
2	6.85	3.50–13.42	
Activities of Daily Living score			
6	1.00 (ref)	–	0.375
<6	1.24	0.77–1.99	
Instrumental Activities of Daily Living score			
4	1.00 (ref)	–	<0.001
3	1.86	1.18–2.94	
≤2	4.28	2.60–7.04	
Continence, no vs yes	1.09	0.56–2.09	0.805
TGUG: abnormal vs normal	1.61	1.08–2.39	0.019
Fall during last year, yes vs no	1.12	0.70–1.80	0.642
Mini-Mental State Examination score: ≤23 vs >23	2.34	1.50–3.64	<0.001
Geriatric Depression Scale 5 score			
0–1	1.00 (ref)	–	0.033
2–3	1.71	1.08–2.72	
4–5	1.98	0.91–4.26	
Body mass index, kg/m^2			
21–24.99	1.00 (ref)	–	0.235
<21	1.24	0.79–1.94	
≥5	0.84	0.55–1.26	
Recent weight loss (≥3 vs <3 kg)	2.66	1.75–4.04	<0.001
Charlson Comorbidity Index: ≥2 vs 0–1	1.86	1.27–2.74	0.002
Renal function: ≥60 mL/min (n = 459)	1.00 (ref)	–	0.502
30–60	1.18	0.73–1.89	
<30	4.28	0.97–18.85	
Albuminemia: ≤30 vs >30 g/L (n = 348)	2.94	1.88–4.62	<0.001
C-reactive protein per 1 SD increase[b] (n = 309)	1.72	1.48–2.00	<0.001
Hemoglobin (g/dL) (n = 476)	0.98	0.91–1.06	0.614
Anemia[c]: yes vs no (n = 476)	2.39	1.60–3.57	<0.001
Lactate dehydrogenase, per 1 SD increase[d] (n = 323)	1.3	0.96–4.08	0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; TGUG, Test Get up and Go.

[a] All Cox models were adjusted for treatment,center, and included randomization arm as a strata.

[b] C-reactive protein: SD = 48.9.

[c] Anemia: <12 g/dL for women and < 13 g/dL for men.

[d] Lactate dehydrogenase: SD = 364.

respective Harrell's C Statistic and Brier scores of 0.874 [95% CI: 0.840–0.895] and 0.0114 for the model OS-1, 0.845 [95% CI: 0.803–0.872] and 0.0140 for the model OS-2 and 0.862 [95% CI: 0.826–0.884] and 0.0139 for the model OS-3 (Table 3). The predicting multivariate Cox models with albumin, CRP, and LDH used instead of anemia (correlated variables) are shown in **eTable 2.** Calibration slopes indicate an underestimation of three-month mortality risk for middle range (25–50%) and overestimation of three-month mortality risk for high range (50%–100%) (**eFigure 1**).

3.3. Toxicities

Univariate analyses identified the following factors as being significantly associated with the risk of grade 3, 4, or 5 CRAEs: IADL score ≤ 3, Charlson Comorbidity Index ≥2, the number of chemotherapy cycles <4, fall during the preceding year, and elevated CRP (**eTable 3**).

After imputation of missing values and backward stepwise regression analysis, two parsimonious logistic models were constructed (Table 4). In both, severe comorbidities (CCI ≥2) were significantly and independently associated with the risk of grade 3, 4, or 5 CREAs (aOR [95% CI], respectively, 1.94 [95% CI: 1.06–3.56] in the model T1 and 1.88 [95% CI: 1.03–3.44] in the model T2). IADL dependence (IADL score ≤ 3) and falls (≥1during the previous year) were also included in the best performing models but were not significantly associated with severe CREAs (aOR [95% CI]), respectively, 1.79 [95% CI: 0.99–3.24]; p = 0.053] and 2.09 [95% CI: 0.93–4.70]; p = 0.076) (Table 4).

AUROC-assessed discrimination of the model T1 was 0.631 [95% CI: 0.56–0.67], with a Brier score of 0.1902. The model T2 achieved AUROC discrimination of 0.642 [95% CI: 0.58–0.68], with a Brier score of 0.1905 (Table 4).

4. Discussion

4.1. Geriatric Predictive Factors of Three-Month Mortality

This secondary analysis of ESOGIA phase 3 clinical trial found several GA factors, i.e., IADL dependence, nutritional status (weight loss >3 kg), and mobility (TGUG), to be associated with greater risk of three-month mortality in patients aged ≥70 years treated for mNSCLC. The prognosis is even more dismal for patients combining several instrumental dependencies and weight loss equal to or >3 kg during the last six months. To our knowledge, our study is the first to find that the interaction between recent weight loss and dependence is a major predictive factor in older patients with mNSCLC. The combination of these two factors might be a more important predictor of OS than PS in this population.

Malnutrition of patients with cancer is an already well-established predictive factor of OS, including for patients ≥70 years, whose frequency has been estimated between 55% and 83% [11,12,29,30]. For patients ≥70 years treated for cancer who underwent GA, nutritional status was significantly associated with change in chemotherapy strategy [31], completeness of the treatment regimen, and OS [32].

Concerning the degree of autonomy (ADL or IADL), literature findings are contradictory, predictive of OS in some studies [33] but not others [13], even if the multivariate analysis included the same adjustment dataset as ours [29,30]. In a retrospective Japanese study on 4837 older NSCLC patients [34], among all GA variables, the strongest contribution to the OS-predictive model was provided by ADL. The association was even stronger as the ADL dependence increased with HRs [95% CI] at 1.54 [1.37–1.73], 2.48 [2.19–2.83] or 3.21 [2.80–3.68] for mild, moderate, or severe dependence, respectively. Although it remains difficult to conclude on the prognostic role of dependence, it is accepted that a general health evaluation based on the ECOG PS or Karnofsky

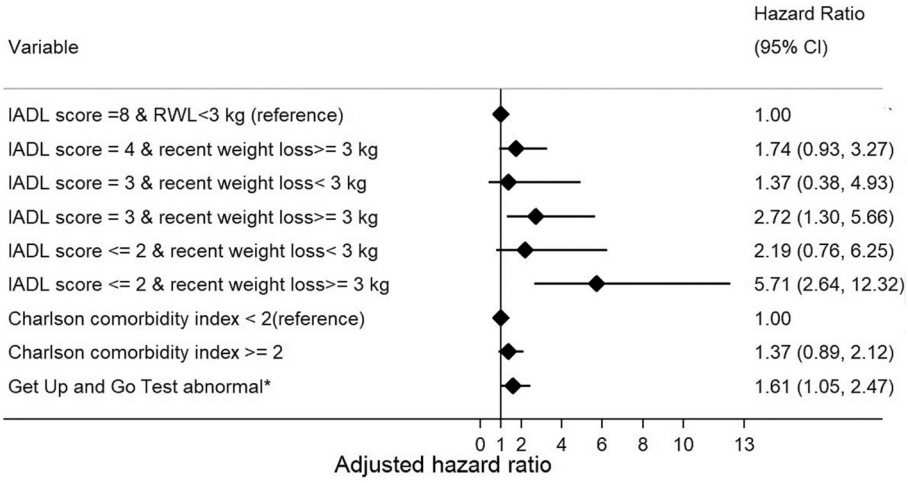

Fig. 1. Forest plot of the HR [95% CI] for geriatric predictors of 3-months mortality.
Note: * The hazard ratio of TGUG is derived from the OS-2 multivariate model because of the correlation of TGUG with IADL.
Abbreviations: kg, kilograms; CI, confidence interval; IADL, Instrumental Activities of Daily Living;
Caption: HR were calculated from parsimonious Cox proportional hazards models accounting correlated variables adjusted for treatment, center and number of chemotherapy cycles, and included randomization arm as a strata.

Table 3
Multivariate Cox analysis for the prediction of 3-months mortality (models with anemia)

Variables	Model OS-1 (with IADL)[a]			Model OS-2 (with TGUG)[a]			Model OS-3 (with PS)[a]		
	aHR	**95% CI**	**p**	**aHR**	**95% CI**	**p**	**aHR**	**95% CI**	**p**
Female sex (ref)	2.03	1.13–3.67	0.018	2.31	1.25–4.28	0.008	2.25	1.24–4.09	0.008
ECOG PS									
0 (ref)	–	–	–	–	–	–	1.00	–	–
1	–	–	–	–	–	–	1.90	1.00–3.63	0.051
≥2	–	–	–	–	–	–	3.07	1.51–6.26	0.002
Normal GUGT (ref)	–	–	–	1.61	1.05–2.47	0.028	–	–	–
IADL = 4 & RWL <3 kg (ref)	1.00	–	–	–	–	–	–	–	–
IADL = 4 & RWL ≥3 kg	1.74	0.93–3.27	0.085	–	–	–	–	–	–
IADL = 3 & RWL <3 kg	1.37	0.38–4.93	0.627	–	–	–	–	–	–
IADL = 3 & RWL ≥3 kg	2.72	1.30–5.66	0.008	–	–	–	–	–	–
IADL ≤2 & RWL <3 kg	2.19	0.76–6.25	0.144	–	–	–	–	–	–
IADL ≤2 & RWL ≥3 kg	5.71	2.65–12.30	< 0.001	–	–	–	–	–	–
RWL ≥3 kg vs <3 kg	–	–	–	2.06	1.26–3.37	0.004	1.89	1.17–3.07	0.009
CCI ≥2 vs 0–1	1.37	0.89–2.12	0.154	1.36	0.88–2.11	0.164	1.28	0.83–1.98	0.260
Anemia[b] (yes vs no), $n = 496$	1.89	1.18–3.04	0.008	2.01	1.26–3.19	0.003	1.98	1.25–3.15	0.004
No. of chemotherapy cycles (continuous–tdv)	0.28	0.23–0.35	<0.001	0.26	0.21–0.32	<0.001	0.28	0.23–0.35	<0.001
Harrell'C statistic		0.874			0.862			0.875	
Bootstrapped[1] Harrell'C statistic		0.874 [0.840–0.895]			0.845 [0.803–0.872]			0.862 [0.826–0.884]	
Brier Score		0.0114 [0.0076–0.0151]			0.0140 [0.0096–0.00184]			0.0139 [0.0095–0.0182]	

Abbreviations: aHR, Adjusted Hazard Ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GUGT, Get up and Go Test; HR: hazard ratio; IADL, Instrumental Activities of Daily Living; RWL: recent weight loss; CCI: Charlson Comorbidity Index; tdv, time-dependent variable.
[a] All Cox models were adjusted for treatment and center, and included randomization arm as a strata.
[b] Anemia: <12 g/dL for women and < 13 g/dL for men.
[1] bias-corrected bootstrap estimates.

Table 4
Multivariate analysis of clinical factors associated with grade 3, 4, or 5 (versus 0, 1, or 2) chemotherapy-induced toxicities in 437 patients given such therapy.

	Model T1			Model T2		
Variables	OR[a]	95% CI	p	OR[a]	95% CI	p
IADL score ≤ 3 vs 4	1.79	0.99–3.24	0.053	–	–	–
Charlson Comorbidity Index score, ≥2 vs 0–1	1.94	1.06–3.56	0.033	1.88	1.03–3.44	0.04
Falls during last year, yes vs no	–	–	–	2.09	0.93–4.70	0.076
No. of chemotherapy cycles, 4 vs <4	0.55	0.35–0.88	0.012	0.54	0.34–0.85	0.008
AUROC	**0.631 [0.56–0.67]**			**0.642 [0.58–0.68]**		
Brier Score	0.1905			0.1902		
Hosmer–Lemershow goodness-of-fit	$p = 0.90$			$p = 0.45$		

Abbreviations: AUROC, area under the receiver operating characteristics curve; CI, confidence interval; IADL, Instrumental Activities of Daily Living; OR, odds ratio.
[a] All logistic-regression models were adjusted for treatment and center, and stratified by randomization arm.

index underestimates the extent of functional limitations in older patients [35].

Our results also indicated that mobility was a factor associated with three-month mortality. These findings are consistent with an analysis of 348 patients treated for cancer (all sites combined) that found a significant TGUG–OS association (HR 2.55 [95% CI: 1.32–4.94]) [29].

However, an analysis limited to mNSCLC patients [30], pooling the data from two randomized phase 2 studies, failed to find an association between the different GA domains and OS, albeit mobility trended towards significance with HR at 0.25 [95% CI: 0.06–1.01] ($p = 0.06$). Mobility impairment is a major quality of life factor, also associated with PS and depressive symptoms, which should be carefully considered among older adults with cancer [36].

The predictive role of comorbidities on survival in oncology has been extensively reported [29,30,34,37]. For example, *Le Caer* found an HR of 1.46 [95% CI: 1.07–1.99] ($p = 0.02$) [30] for mNSCLC patients. Our analysis did not find that association, probably because three-month mortality for mNSCLC patients is mainly linked to oncologic prognosis. Comorbidities would rather have an impact at intermediate term, with, in particular, a higher risk of competitive mortality, greater treatment-associated toxicity or suboptimal treatment, especially in the context of renal insufficiency [38,39].

Although GA-directed treatment allocation strategy wasn't associated with improved OS for patients with cancer [10], it provided a personalized evaluation that, along with other factors usually considered in oncology, could potentially help guide treatment choice, dose adaptation, or both supportive and geriatric care interventions.

4.2. Geriatric Predictors of Severe Chemotherapy Related-Adverse Events

As previously noted [40], we found that the Charlson Comorbidity Index was associated with more CRAEs in a population treated for mNSCLC and whose management considered geriatric frailty. However, IADL dependence and mobility were not significantly associated with CRAEs in this population.

Even though comorbidities are not included in the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) and the Cancer and Aging Research Group (CARG) score, comorbidity scores have already been reported to be associated to toxicities in older patients with various types of cancer, [40] including mNSCLC [41]. The predictive value of comorbidities for chemotoxicity might be stronger in real-life settings. A recent study in a real-life cohort developed a predictive score for toxicity which included cancer type, performance status, comorbidities, body mass index, and CHEMOTOX score, and found an AUC of 0.78 [17].

Autonomy impairment is not predictive for chemotoxicity in the CARG score [15] but is a predictor of hematologic toxicity in the CRASH score [14] and an important predictor for toxicity in The Vulnerable Elders Survey (VES-13) [42]. The predictive value of dependence also appears to vary by cancer site. Unlike our findings, a prospective trial in 123 older patients with previously untreated metastatic colorectal cancer reported a strong association between impaired IADL and grade 3–4 toxicity with an OR of 4.67 [CI 95% 1.42–15.32] [43]; and similar results were observed in ovarian cancer [44]. Recent falls are included in the CARG score, with a predictive value of OR = 2.47 [CI 95% 1.43–4.27] but not in the CRASH score, illustrating the difficulties of replicating results in studies with a highly heterogeneous population.

More broadly, it is accepted that frail older adults are at greater risk of severe chemotherapy-associated toxicities, hospitalizations, and treatment interruptions, independent of chronologic age and ECOG PS [37,45,46]. Unfortunately, even for our analysis of a sample of patients with the same stage and tumor location, the identification of geriatric factors associated with toxicity remained poor, which clearly highlights the difficulties of predicting toxicity in older subjects. Other indicators, like resting energy expenditure or low lean mass, are being examined to better evaluated the risk of CRAEs in this population [47,48].

4.3. Study Limitations

The results of this analysis must be interpreted taking certain limitations into account. As with any clinical trial, the ESOGIA trial proceeded to a selection of the study population, but in a pragmatic way, with few exclusion criteria (ECOG PS > 2, severe concurrent disorders, symptomatic brain metastases, and bronchoalveolar, neuroendocrine, or composite cancer histology) and from a large number of participating centers, both university centers and general hospitals. To support this, the enrolled patients had a median OS of 5.4 months and almost 70% of the subjects were classified as vulnerable or fragile after the GA. Another limitation is that the GA was done by the oncologist treating the patient—not by a specialized geriatric oncology team, which could be a source of measurement bias. However, the clinicians participating in the ESOGIA trial were trained to conduct GA. Extrapolation to clinical practice is restricted by the time required for the GA and the accessibility to geriatric expertise. A screening score, like G8, could better identify patients who would benefit the most from a GA [29,49]. Finally, the agents used in thoracic oncology to treat metastatic disease have considerably evolved over the past few years, particularly with immunotherapy alone or combined with chemotherapy, leading to different toxicity spectra [50,51] that were not analyzed herein.

In conclusion, the combined effect of dependence, weight loss, and mobility were the main geriatric factors associated with three-month mortality of patients >70 years with mNSCLC whose management was decided after GA. Concerning chemotherapy toxicity, it will be necessary to seek out other factors to evaluate the CRAE risk, a major outcome determinant in this population. For personalized prediction, it would be necessary to optimize the calibration of the models.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

Sébastien Gendarme: Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft, Visualization. **Sonia Zebachi:** Methodology, Software, Formal analysis, Data curation, Visualization. **Romain Corre:** Investigation, Resources, Writing – review & editing. **Laurent Greillier:** Investigation, Resources. **Grégoire Justeau:** Investigation, Resources. **Olivier Bylicki:** Investigation, Resources. **Chantal Decroisette:** Investigation, Resources. **Jean-Bernard Auliac:** Investigation, Resources. **Florian Guisier:** Investigation, Resources. **Margaux Geier:** Investigation, Resources. **Charles Ricordel:** Investigation, Resources. **Maxime Frelaut:** Writing – review & editing. **Elena Paillaud:** Writing – review & editing. **Christos Chouaïd:** Conceptualization, Formal analysis, Investigation, Resources, Project administration. **Florence Canouï-Poitrine:** Conceptualization, Methodology, Validation, Formal analysis, Supervision.

Declaration of Competing Interest

All authors have no conflicts of interest and disclosures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2023.101506.

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