Predictors of three-month mortality and severe chemotherapy-related adverse events in patients aged 70 years and older with metastatic nonsmall-cell lung cancer: a secondary analysis of ESOGIA-GFPC-GECP 08-02 Study

Sébastien Gendarme, Sonia Zebachi, Romain Corre, Laurent Greillier, Grégoire Justeau, Olivier Bylicki, Chantal Decroisette, Jean-Bernard Auliac, Florian Guisier, Margaux Geier, et al.

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

Sébastien Gendarme [1,2], Sonia Zebachi [1,3], Romain Corre [4], Laurent Greillier [5], Grégoire Justeau [6], Olivier Bylicki [7], Chantal Decroisette [8], Jean-Bernard Auliac [2], Florian Guisier [9,10], Margaux Geier [11], Charles Ricordel [12], Maxime Frelaut [13], Elena Paillaud [1,14], Christos Chouaïd [1,2], Florence Canouï-Poitrine [1,3]

Affiliations:

[1] Univ Paris Est Creteil, INSERM, IMRB (CEpiA Team), F-94010 Creteil, France

[2] Centre Hospitalier Intercommunal de Créteil, Service de Pneumologie, 40 avenue de Verdun, 94010 Créteil, France

[3] Assistance Publique-Hôpitaux de Paris, Hôpital Henri-Mondor, Service de Santé Publique et Unité de Recherche Clinique, 1 Rue Gustave Eiffel, 94010 Créteil, France.

[4] Centre Hospitalier Intercommunal de Cornouaille, Service de Pneumologie, 14 Av. Yves Thépot, 29000 Quimper, France

[5] Aix-Marseille Université, AP-HM, INSERM, CNRS, CRCM, Hôpital Nord, Service d'Oncologie Multidisciplinaire et Innovations Thérapeutiques, Marseille, France.

[6] CHU d'Angers, Service de Pneumologie, 4 Rue Larrey, 49100 Angers, France.

[7] HIA Sainte-Anne, Service de Pneumologie, 2, boulevard Saint-Anne, 83000 Toulon, France

[8] CH d'Annecy, Service de Pneumologie, 1, avenue de l'Hôpital, Metz-Tessy, 74374 Annecy, France

[9] Univ Rouen Normandie, LITIS Lab QuantIF team EA4108, CHU Rouen,

[10] Department of Pulmonology, Thoracic Oncology, and Respiratory Intensive Care & CIC-

CRB INSERM 1404 F 76000, Rouen, France

[11] CHU Morvan, Service de Pneumologie, 2, avenue Foch, 29200 Brest, France

[12] CHU Rennes, Service de Pneumologie, 2 Rue Henri le Guilloux, 35033 Rennes, France

[13] Gustave Roussy, Département d'Oncologie Médicale, 39 rue Camille-Desmoulins, 94805 Villejuif Cedex, France

[14] Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges-Pompidou, Service de Gériatrie, 20, rue Leblanc, 75908 Paris Cedex 15, France.

Corresponding author: S. Gendarme (sebastien.gendarme@u-pec.fr), Cepia Team (IMRB) 1 Rue Gustave Eiffel, 94010 Créteil Cedex

Abbreviations :

ADL, Activities of Daily living; ALB, albuminemia; CRAE, chemotherapy-related adverse event; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; GA, geriatric assessment; GPS, Glasgow Prognostic Score; TGUG, Test Get up and Go; IADL, Instrumental Activities of Daily Living; LDH, lactate dehydrogenase; MDRD, Modification of Diet in Renal Disease; MMSE, Mini-Mental State Examination; mNSCLC, metastatic non-small-cell lung cancers; OS, overall survival

ABSTRACT

Background : 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 and older (≥ 70y) with metastatic non-small-cell lung cancer (mNSCLC).

Material and Methods: This is a secondary analysis of the multicenter, randomized, phase III ESOGIA trial that compared, for patients ≥70y with mNSCLC, a treatment algorithm based on performance status and age to another algorithm based on geriatric assessment. To identify PGFs of 3-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-months 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 (a) HR: 5.71 [95% CI: 2.64–12.32]). For chemotherapy toxicity, Charlson Comorbidity Index ≥2 was independently associated with grade-3, -4 or- 5 CRAEs (aOR [95% CI]: 1.94 [1.06–3.56]).

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

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

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 are aged 70 years and older (≥70y) in 2020 [1]. As for the general population, 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 ≥70y [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 tricky 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 III 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: either classical criteria based on Eastern Cooperative Oncology Group performance status (ECOG PS) and age or 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 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, reporting 20% fewer grade-3, -4 or -5 adverse events (AEs) in the GA-guided intervention arm in 718 patients with metastatic cancers ; the latter, the GAIN trial, demonstrated among 613 patients with metastatic cancers that a specific GA-driven intervention was able to lower grade-3 or -4 AEs by 10.1%.

However, we still have little understanding of the geriatric parameters involved in limiting toxicity. Admittedly, 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, geriatric frailty parameters should be investigated in the specific setting of a population of patients ≥70y with advanced lung cancer. In the ESOGIA population, the common geriatric prognostic factors of death and chemotoxicity, 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 geriatric predictors for three-month mortality and severe chemotherapy related adverse events in patients ≥70y 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 III randomized GFPC-GECP ESOGIA trial enrolled between January 2010 and January 2013, 494 patients aged 70 years and older 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 $\leq$ 1 and $\leq$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 severe 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: *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) 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]; *cognitive status screening* (Folstein's Mini Mental Status Examination (MMSE) ≤23, cognitive impairment versus >23: no cognitive impairment) [20]; *comorbidities* (Charlson Comorbidity Index score ≥2 (moderate to frequent comorbidities) versus 0–1 (few or mild comorbidities) [21]; *depression* screening (Geriatric Depression Scale (GDS)-5 : 0–1 no risk; 2–3 moderate risk; 4–5 high risk) [22]; *mobility* (Test Get up and Go (TGUG) : normal versus abnormal) [23]; *continence* (yes or no); *fall* during last year (yes or no), and nutritional status (body mass index (BMI, kg/m²) <21; underweight, 21–24.99 normal; ≥25 overweight or obese); weight loss in the 6 past-months ≤3 versus ≥3 kg [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 women and <13 g/dL for men), 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]. 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 analysis 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 variables 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 (fourteen university hospitals, four 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].

227

228 *3.2. Overall survival*

229

230 Median OS was 5.4 [95% CI: 4.89–5.85] months, with three-month OS rate of 70.6%
231 [95% CI: 65.9% 74.8%]. Univariate analysis selected the following factors as being
232 significantly associated with higher three-month mortality : IADL score ≤ 2/4, MMSE ≤ 23,
233 GDS5 score 2–3, abnormal Test Get up and Go (TGUG), recent weight loss ≥3 kg and
234 Charlson Comorbidity Index ≥2 for geriatric parameters; and male sex, ECOG PS = 2,
235 anemia, ALB ≤ 30 g/L, a number of chemotherapy cycles < 4, elevated LDH and CRP
236 concentrations for non-geriatric parameters (**Table 2**).

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

249 The most performing and parsimonious multivariate Cox models for predicting three-
250 month mortality were driven by either IADL & weight loss (model OS-1) or TGUG (model
251 OS-2) or PS (model OS-3). These models have similar performance to predict three-month
252 mortality with 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 (≥ one during 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 III 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 and older (≥70y) treated for mNSCLC. The prognosis is even more dismal for patients combining several instrumental dependencies and weight loss equal to or greater than three kilograms 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 ≥70y, whose frequency has been estimated between 55% and 83% [11,12,29,30]. For patients ≥70y treated for cancer and who had undergone 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, respectively, 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. Although it remains difficult today to conclude on the prognostic role of dependence, it is accepted that a general health evaluation based on the ECOG PS or Karnofsky 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 II 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 3-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(s), 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 failed to achieve significance.

Even though comorbidities is not included in the CRASH and CARG score, comorbidity scores have already been reported to be associated to toxicities in older patients with various types of cancer [40] and with mNSCLC [41]. The predictive value of comorbidities for chemotoxicity might be stronger in real-life settings. Actually, 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 have reported a strong association between impaired IADL and grade 3-4 toxicity with an OR of 4.67 [IC 95% 1.42 - 15.32] [43]; and similar results were observed in ovarian cancer [44]. Recent falls, for their part, are included in the CARG score with a predictive value of OR = 2.47 [IC 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 geriatric patients are at greater risk of severe chemotherapy-associated toxicities, hospitalizations and treatment interruptions, independently 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 to predict 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].

4.4. 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, university centers but also 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 3-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.

Conflicts of interest and diclosures : All authors have no conflicts of interest and disclosures.

Author contributions : Sebastien Gendarme for Conceptualization, Methodology, Validation,

Formal analysis, Writing - Original Draft, Visualization ; Sonia Zebachi for Methodology, Software, Formal analysis, Data Curation, Visualization ; Romain Corre for Investigation, Resources, Writing - Review & Editing; Laurent Greillier for Investigation, Resources ; Grégoire Justeau for Investigation, Resources ; Olivier Bylicki for Investigation, Resources ; Chantal Decroisette for Investigation, Resources ; Jean Bernard Auliac for Investigation, Resources ; Florian Guisier for Investigation, Resources ; Margaux Geier for Investigation, Resources ; Charles Ricordel for Investigation, Resources ; Maxime Frelaut for Writing - Review & Editing ; Elena Paillaud for Writing - Review & Editing ; Christos Chouaid for Conceptualization, Formal analysis, Investigation, Resources, Project administration ; Florence Canoui-Poitrine for Conceptualization, Methodology, Validation, Formal analysis, Supervision

References

[1] Source: ECIS - European Cancer Information System From https://ecis.jrc.ec.europa.eu, accessed on 28/07/2022 © European Union, 2023 n.d.

[2] Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv192–237. https://doi.org/10.1093/annonc/mdy275.

[3] Pallis AG, Gridelli C, Wedding U, Faivre-Finn C, Veronesi G, Jaklitsch M, et al. Management of elderly patients with NSCLC; updated expert's opinion paper: EORTC Elderly Task Force, Lung Cancer Group and International Society for Geriatric Oncology. Ann Oncol 2014;25:1270–83. https://doi.org/10.1093/annonc/mdu022.

[4] Extermann M. Basic assessment of the older cancer patient. Curr Treat Options Oncol 2011;12:276–85. https://doi.org/10.1007/s11864-011-0161-5.

[5] Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol 2004;22:4626–31. https://doi.org/10.1200/JCO.2004.02.175.

[6] Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078–92. https://doi.org/10.1056/NEJMoa1801005.

[7] Mok TSK, Wu Y-L, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819–30. https://doi.org/10.1016/S0140-6736(18)32409-7.

[8] Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123–35. https://doi.org/10.1056/NEJMoa1504627.

[9] Ferrat E, Paillaud E, Caillet P, Laurent M, Tournigand C, Lagrange J-L, et al. Performance of Four Frailty Classifications in Older Patients With Cancer: Prospective Elderly Cancer Patients Cohort Study. J Clin Oncol 2017;35:766–77. https://doi.org/10.1200/JCO.2016.69.3143.

[10] Corre R, Greillier L, Le Caër H, Audigier-Valette C, Baize N, Bérard H, et al. Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study. J Clin Oncol 2016;34:1476–83. https://doi.org/10.1200/JCO.2015.63.5839.

[11] Mohile SG, Mohamed MR, Xu H, Culakova E, Loh KP, Magnuson A, et al. Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. Lancet 2021;398:1894–904. https://doi.org/10.1016/S0140-6736(21)01789-X.

[12] Li D, Sun C-L, Kim H, Soto-Perez-de-Celis E, Chung V, Koczywas M, et al. Geriatric Assessment-Driven Intervention (GAIN) on Chemotherapy-Related Toxic Effects in Older Adults With Cancer: A Randomized Clinical Trial. JAMA Oncol 2021;7:e214158. https://doi.org/10.1001/jamaoncol.2021.4158.

[13] Boulahssass R, Gonfrier S, Ferrero J-M, Sanchez M, Mari V, Moranne O, et al. Predicting early death in older adults with cancer. Eur J Cancer 2018;100:65–74. https://doi.org/10.1016/j.ejca.2018.04.013.

[14] Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer 2012;118:3377–86. https://doi.org/10.1002/cncr.26646.

[15] Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29:3457–65. https://doi.org/10.1200/JCO.2011.34.7625.
[16] Chan W-L, Ma T, Cheung K-L, Choi H, Wong J, Lam K-O, et al. The predictive value of G8 and the Cancer and aging research group chemotherapy toxicity tool in treatment-related toxicity in older Chinese patients with cancer. J Geriatr Oncol 2021;12:557–62. https://doi.org/10.1016/j.jgo.2020.10.013.
[17] Maxime Frelaut PC, Stephane Culine, Elena Paillaud, Christophe Tournigand, Florence Canoui-Poitrine. External validation of two predictive scores of chemotherapy toxicities among older patients with solid cancer, from ELCAPA prospective cohort. ASCO annual meeting: J Clin Oncol 38: 2020 (suppl; abstr 12050); 2020 n.d.
[18] Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963;185:914–9. https://doi.org/10.1001/jama.1963.03060120024016.
[19] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–86.
[20] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98. https://doi.org/10.1016/0022-3956(75)90026-6.
[21] Extermann M. Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol 2000;35:181–200. https://doi.org/10.1016/s1040-8428(00)00090-1.
[22] Clément JP, Nassif RF, Léger JM, Marchan F. [Development and contribution to the validation of a brief French version of the Yesavage Geriatric Depression Scale]. Encephale 1997;23:91–9.
[23] Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39:142–8. https://doi.org/10.1111/j.1532-5415.1991.tb01616.x.
[24] Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol 2012;23:2166–72. https://doi.org/10.1093/annonc/mdr587.
[25] Komai S, Watanabe Y, Fujiwara Y, Kim H, Edahiro A, Kawai H, et al. Association between the nutritional status and the severity of sarcopenia among community-dwelling elderly Japanese people. Nihon Ronen Igakkai Zasshi 2016;53:387–95. https://doi.org/10.3143/geriatrics.53.387.
[26] Vervoort G, Willems HL, Wetzels JFM. Assessment of glomerular filtration rate in healthy subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation. Nephrol Dial Transplant 2002;17:1909–13. https://doi.org/10.1093/ndt/17.11.1909.
[27] Haute Autorité de Santé HAS. Diagnosis of malnutrition in people aged 70 and over. Saint-Denis La Plaine: 2021.
[28] McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev 2013;39:534–40. https://doi.org/10.1016/j.ctrv.2012.08.003.
[29] Soubeyran P, Fonck M, Blanc-Bisson C, Blanc J-F, Ceccaldi J, Mertens C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. J Clin Oncol 2012;30:1829–34. https://doi.org/10.1200/JCO.2011.35.7442.
[30] Le Caer H, Borget I, Corre R, Locher C, Raynaud C, Decroisette C, et al. Prognostic role of a comprehensive geriatric assessment on the management of elderly patients with advanced non-small cell lung cancer (NSCLC): a pooled analysis of two prospective phase II trials by the GFPC Group. J Thorac Dis 2017;9:3747–54. https://doi.org/10.21037/jtd.2017.09.51.

[31] Sourdet S, Brechemier D, Steinmeyer Z, Gerard S, Balardy L. Impact of the comprehensive geriatric assessment on treatment decision in geriatric oncology. BMC Cancer 2020;20:384. https://doi.org/10.1186/s12885-020-06878-2.
[32] Schulkes KJG, Hamaker ME, van den Bos F, van Elden LJR. Relevance of a Geriatric Assessment for Elderly Patients With Lung Cancer-A Systematic Review. Clin Lung Cancer 2016;17:341-349.e3. https://doi.org/10.1016/j.cllc.2016.05.007.
[33] Maestu I, Muñoz J, Gómez-Aldaraví L, Esquerdo G, Yubero A, Torregrosa MD, et al. Assessment of functional status, symptoms and comorbidity in elderly patients with advanced non-small-cell lung cancer (NSCLC) treated with gemcitabine and vinorelbine. Clin Transl Oncol 2007;9:99–105. https://doi.org/10.1007/s12094-007-0019-2.
[34] Morishima T, Sato A, Nakata K, Miyashiro I. Geriatric assessment domains to predict overall survival in older cancer patients: An analysis of functional status, comorbidities, and nutritional status as prognostic factors. Cancer Med 2020;9:5839–50. https://doi.org/10.1002/cam4.3205.
[35] Couderc A-L, Boulahssass R, Nouguerède E, Gobin N, Guérin O, Villani P, et al. Functional status in a geriatric oncology setting: A review. J Geriatr Oncol 2019;10:884–94. https://doi.org/10.1016/j.jgo.2019.02.004.
[36] Presley CJ, Arrato NA, Janse S, Shields PG, Carbone DP, Wong ML, et al. Functional Disability Among Older Versus Younger Adults With Advanced Non-Small-Cell Lung Cancer. JCO Oncol Pract 2021;17:e848–58. https://doi.org/10.1200/OP.20.01004.
[37] Hamaker ME, Vos AG, Smorenburg CH, de Rooij SE, van Munster BC. The value of geriatric assessments in predicting treatment tolerance and all-cause mortality in older patients with cancer. Oncologist 2012;17:1439–49. https://doi.org/10.1634/theoncologist.2012-0186.
[38] Read WL, Tierney RM, Page NC, Costas I, Govindan R, Spitznagel ELJ, et al. Differential prognostic impact of comorbidity. J Clin Oncol 2004;22:3099–103. https://doi.org/10.1200/JCO.2004.08.040.
[39] Wang S, Wong ML, Hamilton N, Davoren JB, Jahan TM, Walter LC. Impact of age and comorbidity on non-small-cell lung cancer treatment in older veterans. J Clin Oncol 2012;30:1447–55. https://doi.org/10.1200/JCO.2011.39.5269.
[40] Wildes TM, Ruwe AP, Fournier C, Gao F, Carson KR, Piccirillo JF, et al. Geriatric assessment is associated with completion of chemotherapy, toxicity, and survival in older adults with cancer. J Geriatr Oncol 2013;4:227–34. https://doi.org/10.1016/j.jgo.2013.02.002.
[41] Aregui A, Pluvy J, Sanchez M, Israel T, Esnault H, Guyard A, et al. Measuring Walking Speed Failed to Predict Early Death and Toxicity in Elderly Patients with Metastatic Non-Small-Cell Lung Cancer (NSCLC) Selected for Undergoing First-Line Systemic Treatment: An Observational Exploratory Study. Cancers (Basel) 2022;14:1344. https://doi.org/10.3390/cancers14051344.
[42] Luciani A, Biganzoli L, Colloca G, Falci C, Castagneto B, Floriani I, et al. Estimating the risk of chemotherapy toxicity in older patients with cancer: The role of the Vulnerable Elders Survey-13 (VES-13). J Geriatr Oncol 2015;6:272–9. https://doi.org/10.1016/j.jgo.2015.02.005.
[43] Aparicio T, Jouve J-L, Teillet L, Gargot D, Subtil F, Le Brun-Ly V, et al. Geriatric factors predict chemotherapy feasibility: ancillary results of FFCD 2001-02 phase III study in first-line chemotherapy for metastatic colorectal cancer in elderly patients. J Clin Oncol 2013;31:1464–70. https://doi.org/10.1200/JCO.2012.42.9894.
[44] Freyer G, Geay J-F, Touzet S, Provencal J, Weber B, Jacquin J-P, et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients

with advanced ovarian carcinoma: a GINECO study. Ann Oncol 2005;16:1795–800. https://doi.org/10.1093/annonc/mdi368.
[45] Ruiz J, Miller AA, Tooze JA, Crane S, Petty WJ, Gajra A, et al. Frailty assessment predicts toxicity during first cycle chemotherapy for advanced lung cancer regardless of chronologic age. J Geriatr Oncol 2019;10:48–54. https://doi.org/10.1016/j.jgo.2018.06.007.
[46] Baitar A, Van Fraeyenhove F, Vandebroek A, De Droogh E, Galdermans D, Mebis J, et al. Geriatric screening results and the association with severe treatment toxicity after the first cycle of (radio)chemotherapy. J Geriatr Oncol 2014;5:179–84. https://doi.org/10.1016/j.jgo.2013.12.004.
[47] Boudou-Rouquette P, de Moura A, Martinez-Tapia C, Serrano AG, Chahwakilian A, Jouinot A, et al. Energy expenditure profiles and the risk of early limiting toxicity in older patients with cancer: The ELCAPA-25 prospective cohort survey. Clin Nutr 2022;41:1073–82. https://doi.org/10.1016/j.clnu.2022.02.016.
[48] Steinmeyer Z, Gérard S, Filleron T, Lozano S, Brechemier D, Abellan Van Kan G, et al. Low lean mass and chemotherapy toxicity risk in the elderly: the Fraction study protocol. BMC Cancer 2019;19:1153. https://doi.org/10.1186/s12885-019-6377-7.
[49] Martinez-Tapia C, Paillaud E, Liuu E, Tournigand C, Ibrahim R, Fossey-Diaz V, et al. Prognostic value of the G8 and modified-G8 screening tools for multidimensional health problems in older patients with cancer. Eur J Cancer 2017;83:211–9. https://doi.org/10.1016/j.ejca.2017.06.027.
[50] Gomes F, Lorigan P, Woolley S, Foden P, Burns K, Yorke J, et al. A prospective cohort study on the safety of checkpoint inhibitors in older cancer patients - the ELDERS study. ESMO Open 2021;6:100042. https://doi.org/10.1016/j.esmoop.2020.100042.
[51] Welaya K, Loh KP, Messing S, Szuba E, Magnuson A, Mohile SG, et al. Geriatric assessment and treatment outcomes in older adults with cancer receiving immune checkpoint inhibitors. J Geriatr Oncol 2020;11:523–8. https://doi.org/10.1016/j.jgo.2019.05.021.

Tables and Figures

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

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

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

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

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 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 (> 3kg) (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.

597

598 **Table 2 -** Factors associated with 3-month mortality: univariate analysis
599

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.

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

Variables	Model OS-1 (with IADL)			Model OS-2 (with TGUG)			Model OS-3 (with PS)		
	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 (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.