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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

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1 **Predictors of three-month mortality and severe chemotherapy-related**
2 **adverse events in patients aged 70 years and older with metastatic non-**
3 **small-cell lung cancer: a secondary analysis of ESOGIA-GFPC-GECP 08-**
4 **02 Study**

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39 Abbreviations :

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

46

47

48 **ABSTRACT**

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

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

60 *Results*: Among 494 included patients, 145 (29.4%) had died at three months and 344
61 (69.6%) had severe chemotherapy toxicity. For three-months mortality, multivariate analyses
62 retained mobility (Test Get up and Go), instrumental activity of daily living (IADL)
63 dependence and weight loss as PGFs. The combined effect of IADL $\leq 2/4$ and weight loss ≥ 3
64 kg was strongly associated with three-month mortality (adjusted (a) HR: 5.71 [95% CI: 2.64–
65 12.32]). For chemotherapy toxicity, Charlson Comorbidity Index ≥ 2 was independently
66 associated with grade-3, -4 or -5 CRAEs (aOR [95% CI]: 1.94 [1.06–3.56]).

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

70

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72 public, commercial, or not-for-profit sectors.

73 1. Introduction

74

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

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

89 In this context, geriatric assessment (GA) is able to identify frailty parameters and
90 comorbidities that could impact survival and the feasibility of oncological treatments. In that
91 way, GA could prove useful to classify patients into frailty groups, and thereby optimize
92 therapeutic strategies [9]. The phase III GFPC-GECP ESOGIA trial investigated a
93 chemotherapy allocation strategy based on this geriatric classification in patients ≥ 70 years
94 old with mNSCLC. This study randomized 494 patients, allotting them to one of two
95 strategies to assign chemotherapy: either classical criteria based on Eastern Cooperative
96 Oncology Group performance status (ECOG PS) and age or an algorithm based on GA
97 findings [10]. This study provided a geriatric characterization into three groups—fit,
98 vulnerable or frail—based on the GA conducted at inclusion for the entire population.

99 Although the results were negative for the main outcome criterion, i.e. time to treatment
100 failure and overall survival (OS), the CRAEs and treatment failure frequencies were
101 significantly lower in the GA arm than in the standard-strategy arm. These results were
102 recently confirmed by two randomized trials [11,12] ; the first, the GAP70+ trial, reporting
103 20% fewer grade-3, -4 or -5 adverse events (AEs) in the GA-guided intervention arm in 718
104 patients with metastatic cancers ; the latter, the GAIN trial, demonstrated among 613 patients
105 with metastatic cancers that a specific GA-driven intervention was able to lower grade-3 or -4
106 AEs by 10.1%.

107 However, we still have little understanding of the geriatric parameters involved in
108 limiting toxicity. Admittedly, predictive scores for death or CRAEs using GA tools [13–15]
109 were developed in older patients with various solid cancers at different stages. However,
110 specific data in older patients with mNSCLC are still missing. The predictive value of these
111 scores may be inaccurate in disease-specific validation studies [16,17]. In this way, geriatric
112 frailty parameters should be investigated in the specific setting of a population of patients
113 ≥ 70 y with advanced lung cancer. In the ESOGIA population, the common geriatric
114 prognostic factors of death and chemotoxicity, as well as their predictive value, might be
115 different from other settings.

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

119

120 **2. Methods**

121

122 *2.1. Study design and population*

123

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

137

138 2.2. Endpoints

139

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

143

144 2.3. Geriatric assessment domains

145

146 Geriatric variables explored in this analysis were: *dependency level* based on the six-item
147 Activity of Daily Living (ADL) scale (personal hygiene, dressing, grooming, washing,
148 transferring/mobility, continence, feeding) [18] and the four-item Instrumental Activity of
149 Daily Living (IADL) scale (use of the telephone, use of public transportation, take

150 medications, manage finances) consistently classified in the ESOGIA trial [10] as follows:
151 ADL = 6 (independence) or $ADL \leq 5$ and IADL = 4 (independence) or IADL = 3 or IADL \leq
152 2) [19]; *cognitive status screening* (Folstein's Mini Mental Status Examination (MMSE) ≤ 23 ,
153 cognitive impairment versus >23 : no cognitive impairment) [20]; *comorbidities* (Charlson
154 Comorbidity Index score ≥ 2 (moderate to frequent comorbidities) versus 0–1 (few or mild
155 comorbidities) [21]; *depression* screening (Geriatric Depression Scale (GDS)-5 : 0–1 no risk;
156 2–3 moderate risk; 4–5 high risk) [22]; *mobility* (Test Get up and Go (TGUG) : normal versus
157 abnormal) [23]; *continence* (yes or no); *fall* during last year (yes or no), and nutritional status
158 (body mass index (BMI, kg/m^2) <21 ; underweight, 21–24.99 normal; ≥ 25 overweight or
159 obese); weight loss in the 6 past-months ≤ 3 versus ≥ 3 kg [24,25];

160

161 2.4. Other parameters

162

163 Non-geriatric variables were also considered for the models fitting : **demographics** (age
164 and sex); **smoking status** (never, former or active smokers); **functional status**: ECOG PS;
165 **cancer-related**: treatment type (carboplatin-based doublet, monotherapy, i.e., docetaxel or
166 best supportive care), and number of chemotherapy cycles; and **biological markers**:
167 hemoglobin (anemia defined as <12 g/dL for women and <13 g/dL for men), Modification of
168 Diet in Renal Disease (MDRD) algorithm-estimated renal clearance (mL/min) (<30 , renal
169 failure; 30–60, moderate renal insufficiency; ≥ 60 , normal renal function) [26], lactate
170 dehydrogenase (LDH) (analyzed as a continuous variable), C-reactive protein (CRP; analyzed
171 as a continuous variable) and albuminemia (ALB; <30 vs ≥ 30 g/dL) [27]. The latter two
172 variables were also analyzed as the CRP/ALB ratio, and as a composite parameter according
173 to the Glasgow Prognostic Score (GPS) (0 (CRP ≤ 10 mg/L and ALB ≥ 35 g/L) vs 1 (CRP \leq
174 10 mg/L and ALB < 35 g/L) vs 2 (CRP > 10 mg/L and ALB < 35 g/L) [28].

175

176 2.5. *Statistical analyses*

177

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

182 Geriatric factors associated with three-month mortality were identified using Cox
183 proportional hazards models, systematically adjusted for treatment group and center, and
184 included randomization arm as a strata. We add a “strata” option to the Cox model to assume
185 that the baseline hazard can be group specific due to the design; but the coefficients are the
186 same. For all endpoints, the variables with $p < 0.20$ in univariate analyses were further
187 examined in multivariate analyses. Correlations between each GA variables were tested in
188 bivariate models using Cramer’s test to perform distinct models if correlations were high ($\rho >$
189 0.3). Multivariate Cox models were constructed with manual step-by-step adjustment
190 considering the number of chemotherapy cycles variable as a confounding factor. Indeed, the
191 number of chemotherapy cycles had an effect on mortality and toxicity and may be related to
192 both geriatric factors and outcomes. Because the number of chemotherapy cycles cannot be
193 considered a baseline characteristic, it was considered a time-varying covariate, obtained by
194 splitting each observation into time intervals, with each interval corresponding to a
195 chemotherapy cycle (0–4 cycles). Interactions between each geriatric variables were
196 examined and interaction coefficient terms were tested manually in the multivariate model.
197 Separate models were run to account for correlated variables and to estimate each geriatric
198 domain's prognostic effect. Backward variable elimination according to the Akaike
199 information criterion (AIC) identified the most accurate and parsimonious model. Association
200 strengths are reported as hazard ratio (HR) [95% confidence interval (CI)]. The proportional
201 hazards assumption was assessed statistically using the Schoenfeld residuals test. Imputation

202 was used to correct for missing laboratory values (e.g., ALB, CRP, LDH, hemoglobin level)
203 using the predictive mean-matching method (function pmm in Stata software) in multivariate
204 analyses. Overall fit of the models was assessed with the Brier score, calibration was assessed
205 with the calibration slope and discrimination capability with Harrell's C statistic.

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

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

212 **3. Results**

213

214 *3.1. Patients*

215

216 Between January 2010 and January 2013, 45 French and Spanish centers (fourteen
217 university hospitals, four cancer centers, and 27 community hospitals) enrolled 494 patients
218 (median age 77 years; 74.2% male; 79.6% former or current smokers; 18.9% with ECOG PS
219 = 2) (**Table 1**). All patients underwent GA, 14.4% exhibited ADL dependence ($ADL \leq 5$),
220 28.6% had IADL dependence ($IADL \leq 3$), 15.4% had cognitive disorders risk ($MMSE \leq 23$),
221 15.6% were at risk of depression ($GDS5 \geq 2$), 23.9% had major comorbidities (Charlson
222 Comorbidity Index ≥ 2) and 20.3% malnutrition ($BMI < 21$ kg/m²). Platinum-based doublet
223 (carboplatin-pemetrexed and carboplatin-gemcitabine for 30.0% and 10.1%, respectively),
224 docetaxel monotherapy and only best supportive care, respectively, were assigned to 40.1%,
225 48.5% and 11.4%. Median follow-up was 4.5 (range: 0–36.7) months. The median number of
226 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 $\leq 2/4$, 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 ($\rho = 0.51$), IADL and ECOG PS ($\rho = 0.44$) as well as
241 anemia and CRP ($\rho = 0.45$) (**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 $\leq 2/4$), abnormal TGUG mobility, weight loss ≥ 3 kg 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–

253 0.895] and 0.0114 for the model OS-1, 0.845 [95% CI: 0.803–0.872] and 0.0140 for the
254 model OS-2 and 0.862 [95% CI: 0.826–0.884] and 0.0139 for the model OS-3 (**Table 3**). The
255 predicting multivariate Cox models with albumin, CRP, and LDH used instead of anemia
256 (correlated variables) are shown in **eTable 2**. Calibration slopes indicate an underestimation
257 of three-month mortality risk for middle range (25-50%) and overestimation of three-month
258 mortality risk for high range (50%-100%) (**eFigure 1**).

259

260 3.3. Toxicities

261

262 Univariate analyses identified the following factors as being significantly associated with
263 the risk of grade -3, -4 or -5 CRAEs: IADL score ≤ 3 , Charlson Comorbidity Index ≥ 2 , the
264 number of chemotherapy cycles < 4 , fall during the preceding year and elevated CRP (**eTable**
265 **3**).

266 After imputation of missing values and backward stepwise regression analysis, two
267 parsimonious logistic models were constructed (**Table 4**). In both, severe comorbidities (CCI
268 ≥ 2) were significantly and independently associated with the risk of grade-3, -4 or -5 CREAs
269 (aOR [95% CI], respectively, 1.94 [95% CI: 1.06–3.56] in the model T1 and 1.88 [95% CI:
270 1.03–3.44] in the model T2). IADL dependence (IADL score ≤ 3) and falls (\geq one during the
271 previous year) were also included in the best performing models but were not significantly
272 associated with severe CREAs (aOR [95% CI]), respectively, 1.79 [95% CI: 0.99–3.24]; $p =$
273 0.053] and 2.09 [95% CI: 0.93–4.70]; $p = 0.076$) (**Table 4**).

274 AUROC-assessed discrimination of the model T1 was 0.631 [95% CI: 0.56–0.67], with a
275 Brier score of 0.1902. The model T2 achieved AUROC discrimination of 0.642 [95% CI:
276 0.58–0.68], with a Brier score of 0.1905 (**Table 4**).

277

278

279 **4. Discussion**

280

281 *4.1. Geriatric predictive factors of three-month mortality*

282 This secondary analysis of ESOGIA phase III clinical trial found several GA factors i.e.
283 IADL dependence, nutritional status (weight loss >3 kg) and mobility (TGUG), to be
284 associated with greater risk of three-month mortality in patients aged 70 years and older
285 (≥ 70 y) treated for mNSCLC. The prognosis is even more dismal for patients combining
286 several instrumental dependencies and weight loss equal to or greater than three kilograms
287 during the last six months. To our knowledge, our study is the first to find that the interaction
288 between recent weight loss and dependence is a major predictive factor in older patients with
289 mNSCLC. The combination of these two factors might be a more important predictor of OS
290 than PS in this population.

291 Malnutrition of patients with cancer is an already well-established predictive factor of
292 OS, including for patients ≥ 70 y, whose frequency has been estimated between 55% and 83%
293 [11,12,29,30]. For patients ≥ 70 y treated for cancer and who had undergone GA, nutritional
294 status was significantly associated with change in chemotherapy strategy [31], completeness
295 of the treatment regimen and OS [32].

296 Concerning the degree of autonomy (ADL or IADL), literature findings are contradictory,
297 predictive of OS in some studies [33] but not others [13], even if the multivariate analysis
298 included the same adjustment dataset as ours [29,30]. In a retrospective Japanese study on
299 4837 older NSCLC patients [34], among all GA variables, the strongest contribution to the
300 OS-predictive model was provided by ADL. The association was even stronger as the ADL
301 dependence increased with, respectively, HRs [95% CI] at 1.54 [1.37–1.73], 2.48 [2.19–2.83]
302 or 3.21 [2.80–3.68] for mild, moderate or severe dependence. Although it remains difficult
303 today to conclude on the prognostic role of dependence, it is accepted that a general health
304 evaluation based on the ECOG PS or Karnofsky index underestimates the extent of functional

305 limitations in older patients [35].

306 Our results also indicated that mobility was a factor associated with three-month
307 mortality. These findings are consistent with an analysis of 348 patients treated for cancer (all
308 sites combined) that found a significant TGUG–OS association (HR 2.55 [95% CI: 1.32–
309 4.94]) [29]. However, an analysis limited to mNSCLC patients [30], pooling the data from
310 two randomized phase II studies, failed to find an association between the different GA
311 domains and OS, albeit mobility trended towards significance with HR at 0.25 [95% CI: 0.06–
312 1.01] ($p = 0.06$). Mobility impairment is a major quality of life factor, also associated with PS
313 and depressive symptoms, which should be carefully considered among older adults with
314 cancer [36].

315 The predictive role of comorbidities on survival in oncology has been extensively
316 reported [29,30,34,37]. For example, *Le Caer* found an HR of 1.46 [95% CI: 1.07–1.99] ($p =$
317 0.02) [30] for mNSCLC patients. Our analysis did not find that association, probably because
318 3-month mortality for mNSCLC patients is mainly linked to oncologic prognosis.
319 Comorbidities would rather have an impact at intermediate term, with, in particular, a higher
320 risk of competitive mortality, greater treatment-associated toxicity or suboptimal treatment,
321 especially in the context of renal insufficiency [38,39].

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

326

327 *4.2. Geriatric predictors of severe chemotherapy related-adverse events*

328 As previously noted [40], we found that the Charlson Comorbidity Index was associated
329 with more CRAEs in a population treated for mNSCLC and whose management considered
330 geriatric frailty. However, IADL dependence and mobility failed to achieve significance.

331 Even though comorbidities is not included in the CRASH and CARG score, comorbidity
332 scores have already been reported to be associated to toxicities in older patients with various
333 types of cancer [40] and with mNSCLC [41]. The predictive value of comorbidities for
334 chemotoxicity might be stronger in real-life settings. Actually, a recent study in a real-life
335 cohort developed a predictive score for toxicity which included cancer type, performance
336 status, comorbidities, body mass index, and CHEMOTOX score, and found an AUC of 0.78
337 [17].

338 Autonomy impairment is not predictive for chemotoxicity in the CARG score [15] but is
339 a predictor of hematologic toxicity in the CRASH score [14] and an important predictor for
340 toxicity in The Vulnerable Elders Survey (VES-13) [42]. The predictive value of dependence
341 also appears to vary by cancer site. Unlike our findings, a prospective trial in 123 older
342 patients with previously untreated metastatic colorectal cancer have reported a strong
343 association between impaired IADL and grade 3-4 toxicity with an OR of 4.67 [IC 95% 1.42 -
344 15.32] [43]; and similar results were observed in ovarian cancer [44]. Recent falls, for their
345 part, are included in the CARG score with a predictive value of OR = 2.47 [IC 95% 1.43 -
346 4.27] but not in the CRASH score, illustrating the difficulties of replicating results in studies
347 with a highly heterogeneous population.

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

356 *4.4. Study limitations*

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

373 In conclusion, the combined effect of dependence, weight loss and mobility were the
374 main geriatric factors associated with 3-month mortality of patients >70 years with mNSCLC
375 whose management was decided after GA. Concerning chemotherapy toxicity, it will be
376 necessary to seek out other factors to evaluate the CRAE risk, a major outcome determinant in
377 this population. For personalized prediction, it would be necessary to optimize the calibration
378 of the models.

379

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575 **Tables and Figures**

576

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

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

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

581 **Table 4** - Multivariate analysis of clinical factors associated with grade-3, -4 or -5 (versus 0, -
582 1 or -2) chemotherapy-induced toxicities in 437 patients given such therapy

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584 **Fig. 1.** Forest plot of the HR [95% CI] for geriatric predictors of 3-months mortality

585 *Note* : * The hazard ratio of TGUG is derived from the OS-2 multivariate model because of
586 the correlation of TGUG with IADL

587 *Abbreviations*: kg, kilograms; CI, confidence interval; IADL, Instrumental Activities of Daily
588 Living;

589 *Caption* : HR were calculated from parsimonious Cox proportional hazards models
590 accounting correlated variables adjusted for treatment, center and number of chemotherapy
591 cycles, and included randomization arm as a strata.

592

593 **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)

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595 Values are expressed as number (%) or median [IQR].

596 Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

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

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

^aAll Cox models were adjusted for treatment, center, and included randomization arm as a strata.

^bC-reactive protein: SD=48.9.

^cAnemia: <12 g/dL for women and <13 g/dL for men.

^dLactate dehydrogenase: SD = 364.

619 **Table 3** – Multivariate Cox analysis for the prediction of 3-months mortality (models with
 620 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		
Bootstrapped¹ 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]		

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 623 Abbreviations: aHR, Adjusted Hazard Ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology
 624 Group performance status; GUGT, Get up and Go Test; HR: hazard ratio; IADL, Instrumental Activities of
 625 Daily Living; RWL: recent weight loss; CCI : Charlson Comorbidity Index; tdv, time-dependent variable.

626 ^aAll Cox models were adjusted for treatment and center, and included randomization arm as a strata.

627 ^bAnemia: <12 g/dL for women and <13 g/dL for men

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 629 ¹ bias-corrected bootstrap estimates

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631 **Table 4 -** Multivariate analysis of clinical factors associated with grade-3, -4 or -5 (versus 0, -
632 1 or -2) chemotherapy-induced toxicities in 437 patients given such therapy
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Variables	Model T1			Model T2		
	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–Lemeshow goodness-of-fit	p = 0.90			p = 0.45		

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636 Abbreviations: AUROC, area under the receiver operating characteristics curve; CI, confidence interval; IADL, Instrumental
637 Activities of Daily Living; OR, odds ratio.

638 ^aAll logistic-regression models were adjusted for treatment and center, and stratified by randomization arm.
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