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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

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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.

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.

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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   ≥70y 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 ≥70y 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 $\leq$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

6

150 medications, manage finances) consistently classified in the ESOGIA trial [10] as follows:

151 ADL = 6 (independence) or ADL ≤ 5 and IADL = 4 (independence) or IADL = 3 or IADL ≤

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/m²) <21; underweight, 21–24.99 normal; ≥25 overweight or

159 obese); weight loss in the 6 past-months ≤3 versus ≥3 kg [24,25];

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161 *2.4. Other parameters*

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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 ≤

174 10 mg/L and ALB < 35 g/L) vs 2 (CRP > 10 mg/L and ALB < 35 g/L) [28].

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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 ≤ 5),

220 28.6% had IADL dependence (IADL ≤ 3) , 15.4% had cognitive disorders risk (MMSE ≤ 23),

221 15.6% were at risk of depression (GDS5 ≥ 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].

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3.2. Overall survival

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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**).

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 ≥ 3kg 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; **Figure 1**).

The most performing and parsimonious multivariate Cox models for predicting three-month mortality were driven by either IADL & weight loss (model OS-1) or TGUG (model OS-2) or PS (model OS-3). These models have similar performance to predict three-month mortality with respective Harrell's C Statistic and Brier scores of 0.874 [95% CI: 0.840–

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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

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.

13

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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381

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

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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

583

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)

594
595   Values are expressed as number (%) or median [IQR].
596   Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

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]		

621
622
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 [a]All Cox models were adjusted for treatment and center, and included randomization arm as a strata.
627 [b]Anemia: <12 g/dL for women and <13 g/dL for men
628
629 [1] bias-corrected bootstrap estimates
630

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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634

	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		

635
636 Abbreviations: AUROC, area under the receiver operating characteristics curve; CI, confidence interval; IADL, Instrumental
637 Activities of Daily Living; OR, odds ratio.
638 [a]All logistic-regression models were adjusted for treatment and center, and stratified by randomization arm.
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