

## Research article

# Predictive factors for chemotherapy feasibility in elderly patients with solid tumor and colorectal cancer: Results of the GERCOR OLD prospective multicenter study

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## Abstract

**Purpose:** To identify geriatric predictors of first-line chemotherapy feasibility in elderly patients with solid tumors. **Patients and Methods:** This was a prospective multicenter study of patients aged 75 years and older with solid tumors. Ten geriatric parameters selected based on GERCOR expert opinion and published evidence were recorded: three-word recall test, orientation to date and place, simplified Instrumental Activities of Daily Living, fall risk assessment, prior hospitalization, polymedication, creatinine clearance, albumin, self-rated mood status, and the caregivers' presence. Treatment feasibility was defined as successful delivery of 3 months chemotherapy with at least two-third of a standard dose at the first treatment course. Tumor responses, survival, and safety were assessed. **Results:** Of 576 patients included in 49 centers between April 2008 and February 2012, 516 (89.6%) were eligible. Mean age was 81 years (range 75-96), 261 (50.6%) patients had colorectal cancer, 357 (69.2%) advanced disease, and 382 (74.0%) an Eastern Cooperative Oncology Group Performance Status of 0-1. Planned chemotherapy was feasible in 298 (57.7%) patients. Geriatric factors significantly associated with chemotherapy feasibility were hypoalbuminemia in all patients and in the colorectal cancer group (adjusted odds ratio [aOR] 2.6; CI 95%, 1.43-4.74 and 3.25; CI 95%, 1.40-7.54, respectively) and self-rated mood status in all patients (aOR 1.56; CI 95%, 0.95-0.56). Grade 3-4 toxicity was observed in 123 (23.8%) patients. **Conclusion:** Albuminemia and self-rated mood status were independent predictors for chemotherapy feasibility in elderly patients with solid tumors.

**Key words:** cancer, chemotherapy, predictive factors, feasibility, elderly

## Introduction

The majority of cancer incidence and mortality occurs in older adults. Indeed, approximately 50% of cancer diagnoses and 70% of cancer mortality occur in patients aged 65 and over [1]. Although specific data on the tolerability and efficacy of

treatment coming from clinical trials of elderly patients with solid tumors are scarce, these suggest an equivalent benefit from chemotherapy compared with younger patients, without any significant increase in toxic effects [2]. Nevertheless, older

patients in these trials are generally fit due to restrictive inclusion criteria thus represent a small percentage of all patients who enter into the study, and are not systematically evaluated for age-specific outcomes as these studies were most often designed for the general population [3]. As such, study results cannot be automatically extrapolated to elderly patients with cancer [4]. In fear of potential treatment-related toxicities older patients are less frequently treated than their younger counterparts, and they tend to receive less aggressive treatment or no treatment at all [5-7].

Comprehensive Geriatric Assessment (CGA) in geriatric oncology helps to evaluate several aspects of health status in elderly patients to generate the patient-tailored geriatric treatment plan. CGA components have shown their value in predicting and improving outcomes such as therapeutic decisions, chemotherapy-related toxicity, morbidity and mortality during cancer treatment [8-16]. However, well-conducted geriatric assessment is time consuming and clinically constraining in the oncology practice and requiring an extensive data collection. Several geriatric screening tools exist to identify frail and fit patients in order to establish a treatment plan best suited to their health status [17-26]. However, there is still a need for a better identification of geriatric predictive factors associated to chemotherapy feasibility and/or toxicity.

Two large prospective studies, the CARG and the CRASH, incorporated measures within CGA in order to identify independent risk factors for severe chemotherapy-related toxicity [10,11]. The CARG toxicity tool that was framed in a study of 500 patients with a mean age of 73 years estimated risk of severe chemotherapy toxicity ranging from 30% in the lowest-risk group to 83% in the highest-risk group. In a similar vein, the CRASH tool was evaluated in a study involving 518 patients with a mean age of 75 years. The estimated risk for hematologic grade  $\geq 4$  toxicity ranged from 7% in the lowest-risk group to 100% in the highest-risk group, while non-hematologic grade  $\geq 3$  toxicity ranged from 33% in the lowest-risk group to 93% in the highest-risk group. Although the predictive risk-stratification schemes reported by these studies are of great interest, these two scores still remain complex to use for oncologists according to the requirement of several clinical and biological parameters, not systematically collected in daily oncological practice.

The objective of this study was to identify predictors of chemotherapy feasibility in elderly patient with solid tumors using the 10-item geriatric GERCOR OLD scale.

## Patients and Methods

### Study design and patient population

The GERCOR OLD prospective multicenter study was conducted at 49 French centers (academic, public, and private). Patients diagnosed with solid tumor (whatever the tumor site and stage), aged  $\geq 75$ , and with no prior chemotherapy were eligible. Written informed consent was obtained from each patient prior to inclusion. This trial is registered with Clinical-

Trials.gov (NCT00664911).

### Objectives

The primary objective was to identify geriatric predictors of first-line chemotherapy feasibility in elderly patient with solid tumors using the 10-item geriatric GERCOR OLD scale. The treatment feasibility was assessed. A successful delivery of chemotherapy was defined as: 1) treatment duration of at least 3 months, 2) starting dose of at least two-third of a standard dose of regimen, and 3) a dose reduction of  $< 33\%$ . Secondary objectives were to evaluate safety, tumor response rates, and survival outcomes.

### Data collection and geriatric assessment

All eligible patients completed a 10-item geriatric GERCOR OLD assessment scale at baseline. Ten items selected based on GERCOR expert opinion and published evidence [27-30] that included variables considered as good prognostic factors in geriatric patients with cancer were: cognitive function measures assessed by a three-word recall test and orientation to date and place; dependence and mobility measures estimated by Instrumental Activities Daily Living (IADL)-4-item and fall risk assessment; co-morbidities measures assessed by hospitalization in the year preceding study for causes other than cancer, and polymedication; renal function and nutritional status based on creatinine clearance and albumin level; and psychological and social environment items evaluated through depressed mood self-assessment and the caregivers' presence. Patient and treatment characteristics and chemotherapy administration status (feasible/unfeasible) were collected. Toxicity was assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3 [31].

### Statistical analyses

The chemotherapy feasibility was analyzed according to the geriatric GERCOR OLD scale and selected clinical parameters (age, sex, tumor location, tumor stage, and Eastern Cooperative Oncology Group Performance Status [ECOG PS]). The analysis population consisted of patients who received chemotherapy (mono/doublet, with/without targeted agent). Frequencies and percentages were calculated for categorical variables and mean  $\pm$  standard deviation (SD), median and range (minimum-maximum) for continuous variables. Continuous variables were analyzed by Student's t-test for normally distributed data and Wilcoxon test for skewed data. Categorical variables were compared by Chi-square test. Chi-square test and Fisher's exact test were used to compare grade  $\geq 3$  toxicity rate and chemotherapy feasibility.

Overall survival (OS) was calculated from the date of beginning chemotherapy to the date of death (from any cause). Progression-free survival (PFS) was defined as the time from the date of beginning chemotherapy to disease progression or death from any cause. Disease-free survival (DFS) was defined

as time from the date of beginning chemotherapy to the date of first recurrence (local or distant) or death from any cause whatever occurred first. Alive patients without progression (PFS) or relapse (DFS) were censored at the date of the latest news.

Adjusted odds ratios (aORs) and 95% CIs were estimated from univariate and multivariate models. If a relationship between an individual factor and treatment feasibility had a P-value  $\leq 0.20$ , the factor was entered into a subsequent multivariable analysis using a backwards-stepwise elimination. Discrimination and calibration were assessed using the receiver operator characteristic (ROC) curve and Hosmer-Lemeshow test, respectively [32,33]. Bootstrapping was used on the final model for internal validation.

OS, PFS, and DFS were analyzed by the Kaplan-Meier method and presented with hazard ratios (HRs) and corresponding 95% confidence interval (CI). Median follow-up was calculated using the reverse Kaplan-Meier method.

The data were analyzed using STATA software version 11 (STATA Corporation College Station TX, USA).

## Results

### Patient characteristics

Between April 14, 2008 and February 1, 2012, 576 patients were included in the study. The cut-off date for data collection was May 2, 2016. In total, 516 were eligible for feasibility analysis (Figure 1). The main tumor and patient characteristics are presented in Table 1. The median age of patients was 81 years (range 75-96). Most patients had advanced disease ( $n = 357$ , 69.2%) and ECOG PS of 0-1 ( $n = 382$ ; 74.0%). Half of patients ( $n = 261$ , 50.6%) had colorectal cancer (CRC), mainly advanced representing the largest group of patients within the whole population ( $n = 189$ , 36.6%).

Overall, 198 (38.4%) patients received mono-chemotherapy and 313 (60.6%) received doublet chemotherapy (Supplementary Table S1). Most common single-agent regimens were fluoropyrimidines ( $n = 84$ , 42.4%) and gemcitabine ( $n = 57$ , 28.8%). Oxaliplatin-based regimens (FOLFOX or XELOX;  $n = 153$ , 48.9%) were the most often used doublets (Supplementary Table S1).

Baseline geriatric characteristics of the whole and CRC populations are given in Table 2. The large majority of patients gave favorable answer in any of the cognitive function measures, had favorable baseline biological parameters (creatinine clearance  $>30$  mL/min and albumin  $>30$  g/L), was not depressed, and had a caregiver. However, 217 (42.0%) of patients were IADL-dependent, and 238 (46.1%) were hospitalized in the previous year. Overall, only 48 (9.3%) of patients endorsed no deficit on all of the 10 items.

### Chemotherapy feasibility

Treatment feasibility was observed in 298 (57.7%) and 161 (61.7%) patients in the whole and CRC population, respectively (Supplementary Table S1). Those patients represented the feasibility group. In the whole population, treatment was

considered unfeasible in 218 (42.2%) patients mainly due to death (22.9%), severe adverse events (20.6%), early tumor progression/relapse (13.3%), investigator decision (5.9%), patient's choice (2.2%), and lost to follow-up (1.3%). These patients represent the unfeasibility group.

### Predictive factors for chemotherapy feasibility

In the whole population, factors significantly associated with chemotherapy unfeasibility in the multivariate analysis were tumor location (non-colorectal versus colorectal;  $P = 0.005$ ), hypoalbuminemia ( $P = 0.001$ ), and self-rated mood status ( $P = 0.040$ ; Table 3).

In the CRC population, hypoalbuminemia was the only factor significantly associated with chemotherapy unfeasibility in the multivariate analysis ( $P = 0.0027$ ; Table 3). Other variables were not significant.

### Treatment tolerance

Adverse events for the whole and CRC populations are shown in Supplementary Table S2. In total, 104 (104/516, 24.0%) patients in the whole population experienced at least one grade 3 toxicity. Grade 3-5 decreased neutrophil counts were reported in 8.9% ( $n = 46$ ) of patients. There was slightly more patients with grade 3-5 toxicities in the feasibility group ( $P = 0.144$ ) than in the unfeasibility groups ( $P = 0.095$ ; Supplementary Table S3).

In the CRC population, 60 (60/261, 23.0%) patients experienced at least one grade 3 toxicity. Grade 3-5 decreased neutrophil counts were reported in 4.4% ( $n = 23$ ) of patients. There were more patients with grade 3-5 toxicities in the feasibility group ( $P = 0.144$ ) than in the unfeasibility group ( $P = 0.095$ ; Supplementary Table A3). The occurrence of toxic effects according to chemotherapy treatment in the CRC population is reported in Supplementary Table S4. Overall, toxicities were regarded as mild (grade 1-2). CRC patients treated with oxaliplatin-based chemotherapy experienced a greater number of adverse events compared with those treated with other regimens.

### Tumor response

In all patients with advanced disease (357/516, 69.2%), the tumor response rate (complete and partial) was 30.8%, stable disease was 42.6%, and disease progression was 22.7% after 3 months of treatment (Supplementary Table S1). In the metastatic CRC population ( $n = 189$ ), the tumor response rate (complete and partial) was 30.2%, stable disease was 43.9%, and disease progression was 16.9% after 3 months of treatment (Supplementary Table S1).

### Survival according to chemotherapy feasibility

In the whole population, the 1-year OS rate was 66.6% (Supplementary Table S5). The median OS was 18.6 months (95% CI, 16.7-22.6) in the feasibility group and 8.4 months in the unfeasibility group (95% CI, 5.8-13.0; Figure 2A and

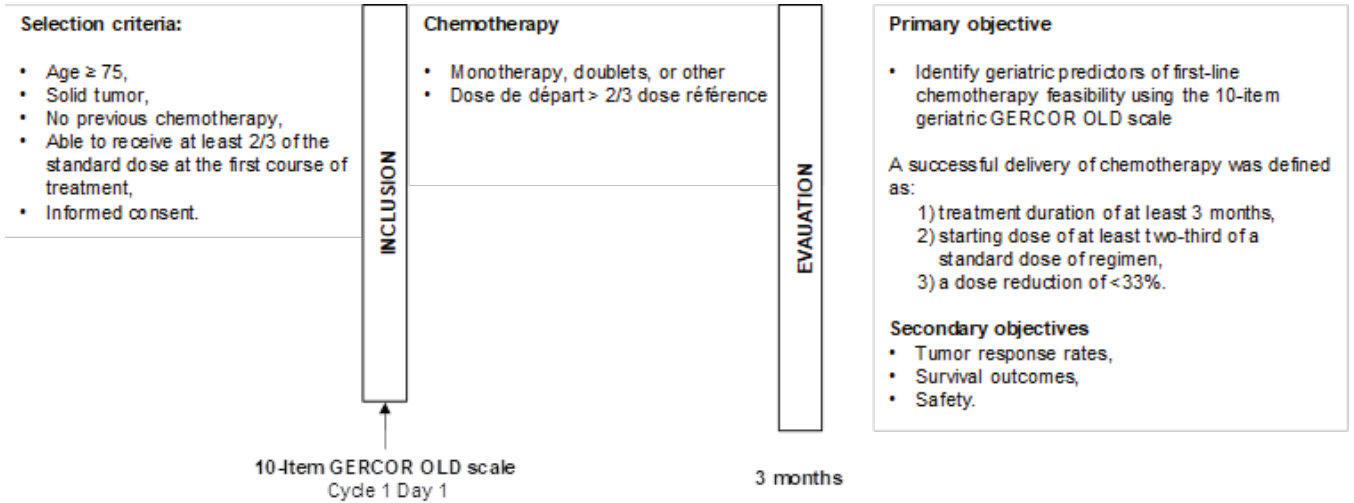


Figure 1. Study flow-chart

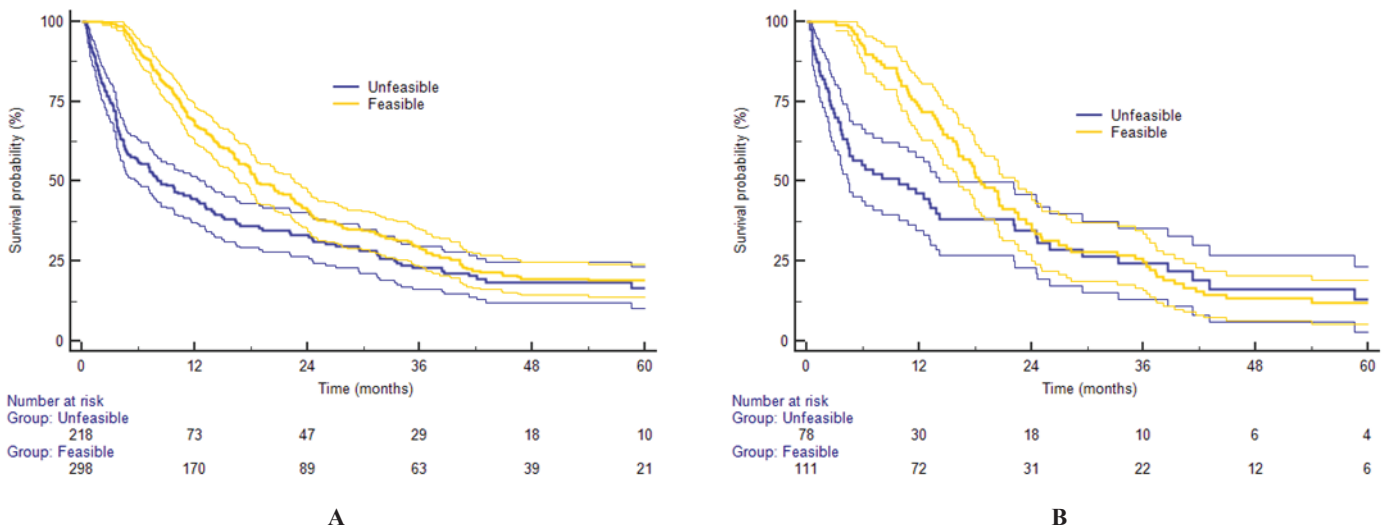


Figure 2. Overall survival according to treatment feasibility in the whole (A) and metastatic colorectal (B) populations

Table 1. Patients and tumor characteristics

	Population						
	All No. (%)	Colorectal cancer No. (%)	Pancreatic cancer No. (%)	Lung cancer No. (%)	Breast cancer No. (%)	Ovarian cancer No. (%)	Other No. (%)
N	516 (100)	261 (50.6)	55 (10.6)	38 (7.4)	35 (6.8)	34 (6.6)	93 (18.0)
Age (years range)	81 (75-96)	81 (75-96)	80 (75-90)	79 (75-89)	80 (75-90)	80 (75-88)	
Sex							
Male	251 (48.6)	143 (54.8)	28 (50.9)	25 (65.8)	2 (5.7)	0	93 (18.0)
Female	265 (51.3)	118 (45.2)	27 (49.1)	13 (34.2)	33 (94.3)	34 (100)	93 (18.0)
Stage							
Early	159 (30.8)	71 (27.2)	22 (40.0)	14 (36.8)	11 (31.4)	4 (11.8)	37 (39.8)
Advanced	357 (69.2)	189 (72.4)	33 (60.0)	23 (60.5)	24 (68.6)	30 (88.2)	58 (62.4)
Unknown	0	1 (0.4)	0	1 (2.6)	0	0	2 (2.1)
ECOG PS							
0	145 (28.1)	74 (28.3)	13 (23.6)	12 (31.5)	11 (31.4)	8 (23.5)	27 (29.0)
1	237 (46.9)	126 (48.3)	26 (47.3)	17 (44.7)	10 (28.6)	17 (50.0)	41 (44.1)
$\geq$ 2	75 (14.5)	35 (13.4)	11 (20.0)	5 (13.1)	6 (17.1)	3 (8.8)	15 (16.1)
Unknown	59 (11.4)	26 (10.0)	5 (9.1)	4 (11.5)	8 (22.8)	6 (17.6)	10 (10.7)

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status



**Table 2.** Patient geriatric characteristics in the whole and colorectal cancer populations

			All (N = 516)	Colorectal cancer population (N = 261)
Dimension		Measure Item	No. (%)	No. (%)
Cognitive function	1 <sup>I</sup>	Orientation to date and place No error At least one error Missing	443 (85.9) 68 (13.2) 5 (0.9)	227 (86.9) 32 (12.3) 2 (0.77)
	2 <sup>II</sup>	Three-word recall test No error At least one error Missing	382 (74.0) 125 (24.2) 9 (1.7)	186 (71.3) 70 (26.8) 5 (1.9)
Dependence and fall risk	3 <sup>I</sup>	IADL score Independence Partial dependence Missing	443 (85.9) 68 (13.2) 4 (0.8)	227 (86.9) 32 (12.3) 2 (0.8)
	4 <sup>I</sup>	Fall risk test Successful Unsuccessful Missing	346 (67.1) 156 (30.2) 14 (2.7)	183 (70.1) 74 (28.3) 4 (1.5)
Co-morbidity	5 <sup>II</sup>	Hospitalization during the previous year No Yes Missing	270 (52.3) 238 (46.1) 8 (1.6)	134 (51.3) 125 (47.9) 2 (0.8)
	6 <sup>II</sup>	Polymedication > 5 Successful Unsuccessful Missing	318 (61.6) 190 (36.8) 8 (1.6)	166 (63.6) 93 (35.6) 2 (0.8)
Co-morbidity	7 <sup>II</sup>	Creatinine clearance >30 ml/min No Yes Missing	498 (96.5) 12 (2.3) 6 (1.2)	251 (96.1) 7 (2.7) 3 (1.1)
	8 <sup>II</sup>	Albumin > 30 g/L Yes No Missing	379 (73.4) 88 (17.1) 49 (9.5)	199 (76.2) 45 (17.4) 17 (6.5)
Co-morbidity	9 <sup>II</sup>	Depressed mood self-assessment No Yes Missing	356 (69.0) 153 (29.7) 7 (1.4)	181 (69.3) 76 (29.1) 4 (1.5)
	10 <sup>I</sup>	Caregivers presence Yes No Missing	473 (91.7) 37 (7.2) 6 (1.2)	241 (92.3) 16 (6.1) 4 (1.5)

Abbreviations: IADL: score Instrumental Activities of Daily Living score; I<sup>I</sup>“Geriatric dimensions” subgroup

Supplementary Table S5).

For the patients with metastatic disease (n = 357), the median OS was 13.9 months (95% CI, 11.5-16.7) and the median PFS was 5.6 months (95% CI, 4.7-6.7). In the feasibility group the median OS and PFS were 18.0 and 7.2 months, while

in the unfeasibility group the median OS and PFS were 5.8 and 2.8 months (Supplementary Table S5).

In the metastatic CRC population, the median OS was 16.3 months (95% CI, 13.9-20.4); 18.6 months in the feasibility group and 9.9 months in the unfeasibility group (Figure 2B and Supplementary Table S5). The median PFS was 7.4 in the feasibility group versus 3.4 months in the unfeasibility group (Supplementary Figure S1 and Table S5).

## Discussion

Our study showed that first-line chemotherapy was feasible in 57.7% of elderly patients with solid tumors. Albumin and self-rated mood status were the two predictive factors that were independently associated with treatment feasibility. Grade 3-4 adverse events were observed in only 23.8% of all patients. In this study the response rates were 30.8% and 30.2% in all and metastatic CRC patients, respectively. The median OS was longer in the feasibility group than in the unfeasibility group for all (18.6 versus 8.4 months) and CRC patients (18.6 versus 9.9 months).

Chemotherapy feasibility rate in our study was in line with previous reports of older patients with different cancers [7,14,34-40]. However, the chemotherapy feasibility definition differs between our and other studies. Treatment in this study was defined as a successful delivery of at least two-third of a standard dose of regimen at the first treatment course of the planned 3-month chemotherapy, while this definition in other reports included various measures such as the completion of planned number of cycles (from 4 to 12), dosage reduction, treatment interruptions, and grade 3-4 toxicity in other studies [7,8,14,35,36]. Moreover, unlike in other studies, the evaluation parameters were not the decisive factor in the choice of a chemotherapy treatment [11,14,35].

The baseline clinical and geriatric characteristics of our population (ECOG PS, IADL, hospitalization in the previous years, and polymedication) are similar to those observed in other geriatric evaluation studies of elderly patients using different scales and tools [14,35].

Our multivariate analysis showed that albumin was associated with chemotherapy feasibility. Serum albumin is an indicator of nutritional status and related to chronic inflammation [41-43]. During cancer-induced inflammatory response, albumin may reflect its severity, the patient's general condition, and consequently the patient's ability to tolerate chemotherapy.

Albumin has been described as an independent prognostic factor of response and survival, morbidity and mortality, toxicity, or early termination of chemotherapy in various tumors [13,14,35,44-57]. The value of albuminemia for chemotherapy feasibility and survival prediction that emerges from our analysis in addition to those described underlines the clinical importance of this multi-potent factor. Moreover, self-rated mood status in our study was associated with chemotherapy unfeasibility in all patients and not with chemotherapy-induced severe toxicity, early functional decline during chemotherapy, or

Table 3. Factors associated with chemotherapy feasibility in the whole and colorectal cancer populations

	Univariate analysis						Multivariate analysis					
	Whole population (n = 516)			Colorectal population (n = 261)			Whole population (n = 516)			Colorectal population (n = 261)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age, year (median)												
≤ 80	1			1								
> 80	1.18	0.83-1.68	0.353	1.16	0.60-2.26	0.671						
Sex												
Male	1			1								
Female	0.98	0.69-1.39	0.917	1.05	0.63-1.73	0.859						
Tumor location												
Colorectal	1						1			1		
Digestive	1.86	1.12-3.07					1.55	1.12-3.07		1.55		
Gynecologic	0.82	0.48-1.41					0.84	0.48-1.41		0.84		
Genitourinary	0.79	0.35-1.78					0.74	0.35-1.78		0.74		
Lung	2.61	1.40-4.88	0.003				3.08	1.40-4.88	0.005	3.08		
Stage												
Early	1			1			1			1		
Advanced	1.46	0.97-2.19	0.072	1.60	0.85-3.03	0.148	1.45			1.45		
Stage												
≤1	1			1			1			1		
>1	1.61	0.98-2.66	0.059	2.08	1.00-4.33	0.049	1.34			1.492	0.72-3.08	0.129
<b>GERCOR OLD scale items</b>												
Orientation to date and place												
At least one error	1			1								
No error	0.94	0.56-1.59	0.832	0.95	0.44-2.05	0.903						
Three-word recall test												
At least one error	1			1								
No error	1.46	0.97-2.20	0.073	0.87	0.49-1.55	0.643						
Dependence and Mobility												
IADL												
Independence	1			1								
Partial dependence	1.13	0.79-1.62	0.485	1.25	0.75-2.08	0.392						
Fall risk assessment												
Successful	1			1								
Unsuccessful	1.43	0.97-2.09	0.068	1.57	0.90-2.70	0.116						
Comorbidity												
Hospitalization in the prior year												
Yes	1			1								
No	1.12	0.79-1.60	0.520	1.87	0.52-1.44	0.587						
Polymedication > 5												
Yes	1			1								
No	1.48	1.03-2.13	0.034	1.61	0.69-1.95	0.575						
Creatinine clearance > 30 ml/min												
Yes	1			1								
No	1.39	0.44-4.45	0.058	1.99	0.26-5.54	0.816						
Albumin > 30 g/L												
Yes	1			1			1			1		
No	2.31	1.44-3.71	0.001	2.40	1.24-4.65	0.009	2.36	1.44-3.86	0.001	2.31	1.10-4.86	0.003
Self-rated mood status												
Yes	1			1								
No	1.61	1.10-2.36	0.014	1.69	0.98-2.92	0.058						

Caregivers' presence												
Yes	1			1			1			1		
No	0.62	0.30-1.28	0.196	0.53	0.17-1.71	0.292	1.55	1.02-2.35	0.040	1.68	0.90-3.16	0.106

Abbreviations: OR: odds ratios; ECOG PS: Eastern Cooperative Oncology Group performance status; IADL: Instrumental Activities of Daily Living. Note: Harrell's C index=0.7711; Area under the curve (AUC): 0.724 (95% CI, 0.67-0.77); Hosmer and Lemeshow P value: P = 0.548

decreased survival like in other studies [8,36]. It should be noted that IADL impairment, was not independent predictor of chemotherapy feasibility in our study, nevertheless it has been seen in a large proportion of patients (42%). In other studies of older patients, IADL was shown to be strongly related to poor health-related quality of life, hospitalization, morbidity, and mortality.

Only 23.8% of patients in our study had grade 3-4 toxicity unlike in other studies, which found an incidence of adverse events a twice higher [7,10,11,35,58-60]. A large CRC population treated with less toxic chemotherapy and limited number of patients with an ECOG PS  $\geq 2$  in our series (16% versus 28-47% in other studies) might account for this observation. Patients who were capable to tolerate and complete planned chemotherapy (the feasibility group) had more grade 3-4 toxicity than other patients because they received more chemotherapy overall.

Our survival results show that older patients are likely to demonstrate similar clinical benefits as younger patients if receiving optimal therapy. This observation is in agreement with subgroup analyses from pooled first-line clinical studies of patients with metastatic CRC [37,61,62].

The treatment efficacy results in terms of OS and PFS in the feasible group observed in our study are similar to these from randomized phase II and phase III of metastatic CRC patients more than 75 years old treated with doublet or single-agent first-line chemotherapy with the median OS ranging between 11.3 and 21.7 months and the median PFS between 5.1 and 10.4 months [37,58-60,63,64].

The strength of our study is that it represents one of the largest prospective multicenter studies focusing on treatment feasibility in chemotherapy-naïve elderly (a median age of 81 years old) patients with solid tumors. However, the study has some limitations. We cannot exclude results bias. The GERCOR OLD geriatric scale has limitation in terms of its pragmatism and over simplicity that could lead to non-significant results. Another limitation is population heterogeneity in terms of tumor location, however with CRC being the most frequent (37%). In addition, the majority of patients included in our study were judged fit (ECOG PS 0-1; 74%) by their oncologist for receiving first-line chemotherapy. Although IADL was not significantly related to chemotherapy feasibility in our analysis, it was found impaired in 42% of patients. In a study by Owusu et al., ECOG PS demonstrated excellent discriminatory abilities for identifying IADL disability and cognitive impairments [65]. These observations probably reflect limitation of ECOG PS measure for chemotherapy feasibility assessment in an elderly-specific population. This variable alone is insufficient for assessment in an elderly-specific population. There-

fore, we hypothesized that ECOG PS can be associated with albumin and self-related mood status in order to increase to better prognostic performance.

In conclusion, our study showed that albumin and self-rated mood status are independent chemotherapy feasibility factors of chemotherapy feasibility suggesting that these parameters should be systematically included in the geriatric assessment of patients with cancer. Based on these results and the published phase III AVEX study data [58], a phase III COLAGE trial to determine the feasibility of two therapeutic strategies using a depression-albumin-ECOG-PS-based scale is planned.

**Disclaimers:** All authors declare no conflict of interest.

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#### References

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER Cancer Statistics Review (CSR) 1975-2011. Available at: [http://seer.cancer.gov/csr/1975\\_2011/](http://seer.cancer.gov/csr/1975_2011/) Accessed November 2014.
2. Popescu RA, Norman A, Ross PJ, et al. Adjuvant or palliative chemotherapy for colorectal cancer in patients 70 years or older. *J Clin Oncol.* 1999; 17:2412-8.
3. 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.
4. Scott IA, Guyatt GH. Cautionary tales in the interpretation of clinical studies involving older persons. *Arch Intern Med.* 2010; 170:587-95.
5. Barthelemy P, Heitz D, Mathelin C, et al. Adjuvant chemotherapy in elderly patients with early breast cancer. Impact of age and comprehensive geriatric assessment on tumor board proposals. *Crit Rev Oncol Hematol.* 2011; 79:196-204.
6. Sanoff HK, Carpenter WR, Sturmer T, et al. Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *J Clin Oncol.* 2012; 30:2624-34.
7. Laurent M, Paillaud E, Tournigand C, et al. Assessment of solid cancer treatment feasibility in older patients: a prospective cohort study. *Oncologist.* 2014; 19:275-82.
8. Freyer G, Geay JF, Touzet S, 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.
9. Repetto L, Fratino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for

- Geriatric Oncology Study. *J Clin Oncol.* 2002; 20:494-502.
10. Extermann M, Boler I, Reich RR, 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.
  11. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol.* 2011; 29:3457-65.
  12. Soubeyran P, Fonck M, Blanc-Bisson 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.
  13. Hoppe S, Rainfray M, Fonck M, et al. Functional decline in older patients with cancer receiving first-line chemotherapy. *J Clin Oncol.* 2013; 31:3877-82.
  14. Falandry C, Weber B, Savoye AM, et al. Development of a geriatric vulnerability score in elderly patients with advanced ovarian cancer treated with first-line carboplatin: a GINECO prospective trial. *Ann Oncol.* 2013; 24:2808-13.
  15. Caillet P, Canoui-Poitaine F, Vouriot J, et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. *J Clin Oncol.* 2011; 29:3636-42.
  16. Kenis C, Bron D, Libert Y, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. *Ann Oncol.* 2013; 24:1306-12.
  17. Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. *J Am Geriatr Soc.* 2001; 49:1691-9.
  18. Soubeyran P, Bellera C, Goyard J, et al. Screening for vulnerability in older cancer patients: the ONCODAGE Prospective Multicenter Cohort Study. *PLoS One.* 2014; 9:e115060.
  19. Hoogendijk EO, van der Horst HE, Deeg DJ, et al. The identification of frail older adults in primary care: comparing the accuracy of five simple instruments. *Age Ageing.* 2013; 42:262-5.
  20. Hamaker ME, Jonker JM, de Rooij SE, et al. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol.* 2012; 13:e437-44.
  21. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* 2005; 173:489-95.
  22. Apostolo J, Cooke R, Bobrowicz-Campos E, et al. Predicting risk and outcomes for frail older adults: an umbrella review of frailty screening tools. *JBHI Database System Rev Implement Rep.* 2017; 15:1154-1208.
  23. Bellera CA, Rainfray M, Mathoulin-Pelissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol.* 2012; 23:2166-72.
  24. Martinez-Tapia C, Paillaud E, Liuu E, 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; 83:211-219.
  25. Luciani A, Ascione G, Bertuzzi C, et al. Detecting disabilities in older patients with cancer: comparison between comprehensive geriatric assessment and vulnerable elders survey-13. *J Clin Oncol.* 2010; 28:2046-50.
  26. Decoster L, Van Puyvelde K, Mohile S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations dagger. *Ann Oncol.* 2015; 26:288-300.
  27. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol.* 2014; 32:2595-603.
  28. Pallis AG, Wedding U, Lacombe D, et al. Questionnaires and instruments for a multidimensional assessment of the older cancer patient: what clinicians need to know? *Eur J Cancer.* 2010; 46:1019-25.
  29. Puts MT, Santos B, Hardt J, et al. An update on a systematic review of the use of geriatric assessment for older adults in oncology. *Ann Oncol.* 2014; 25:307-15.
  30. Puts MT, Hardt J, Monette J, et al. Use of geriatric assessment for older adults in the oncology setting: a systematic review. *J Natl Cancer Inst.* 2012; 104:1133-63, 2012
  31. Institute NC. National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE).2006.v 3.0.
  32. Metz CE: Basic principles of ROC analysis. *Semin Nucl Med.* 1978; 8:283-298.
  33. Hosmer DW, Lemeshow S: Applied Logistic Regression. New York, John Wiley, 1989.
  34. Fairfield KM, Murray K, Lucas FL, et al. Completion of adjuvant chemotherapy and use of health services for older women with epithelial ovarian cancer. *J Clin Oncol.* 2011; 29:3921-6.
  35. Aparicio T, Jouve JL, Teillet L, 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.
  36. Biesma B, Wymenga AN, Vincent A, et al. Quality of life, geriatric assessment and survival in elderly patients with non-small-cell lung cancer treated with carboplatin-gemcitabine or carboplatin-paclitaxel: NVALT-3 a phase III study. *Ann Oncol.* 2011; 22:1520-7.
  37. Folprecht G, Seymour MT, Saltz L, et al. Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: combined analysis of 2,691 patients in randomized controlled trials. *J Clin Oncol.* 2008; 26:1443-51.
  38. Dobie SA, Baldwin LM, Dominitz JA, et al. Completion of therapy by Medicare patients with stage III colon cancer. *J Natl Cancer Inst.* 2006; 98:610-9.
  39. Hilpert F, du Bois A, Greimel ER, et al. Feasibility, toxicity and quality of life of first-line chemotherapy with platinum/paclitaxel in elderly patients aged  $\geq 70$  years with advanced ovarian cancer--a study by the AGO OVAR Germany. *Ann Oncol.* 2007; 18:282-7.
  40. Kozuki T, Nogami N, Kitajima H, et al. Feasibility study of first-line chemotherapy using Pemetrexed and Bevacizumab for advanced or recurrent nonsquamous non-small cell lung cancer in elderly patients: TORG1015. *BMC Cancer.* 2016; 16:306.
  41. Don BR, Kaysen G: Serum albumin: relationship to inflammation and nutrition. *Semin Dial.* 2004; 17:432-7.
  42. Arroyo V, Garcia-Martinez R, Salvatella X: Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol.* 2014; 61:396-407.
  43. Artigas A, Wernerman J, Arroyo V, et al. Role of albumin in diseases associated with severe systemic inflammation: Pathophysiologic and clinical evidence in sepsis and in decompensated cirrhosis. *J Crit Care.* 2016; 33:62-70.
  44. Ikeda S, Yoshioka H, Ikeo S, et al. Serum albumin level as a potential marker for deciding chemotherapy or best supportive care in elderly, advanced non-small cell lung cancer patients with poor performance status. *BMC Cancer.* 2017; 17:797.
  45. Arrieta O, Michel Ortega RM, Villanueva-Rodriguez G, et al. Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. *BMC Cancer.* 2010; 10:50.
  46. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. *J Clin Epidemiol.* 1997; 50:693-703.
  47. Hannan JL, Radwany SM, Albanese T. In-hospital mortality in patients older than 60 years with very low albumin levels. *J Pain Symptom Manage.* 2012; 43:631-7.
  48. Heys SD, Walker LG, Deehan DJ, et al. Serum albumin: a prognostic indicator in patients with colorectal cancer. *J R Coll Surg Edinb.* 1998; 43:163-8.
  49. Onate-Ocana LF, Aiello-Crocifoglio V, Gallardo-Rincon D, et al. Serum albumin as a significant prognostic factor for patients with gastric carcinoma



- ma. *Ann Surg Oncol*. 2007; 14:381-9;
50. Seve P, Ray-Coquard I, Trillet-Lenoir V, et al. Low serum albumin levels and liver metastasis are powerful prognostic markers for survival in patients with carcinomas of unknown primary site. *Cancer*. 2006; 107:2698-705.
  51. Espinosa E, Feliu J, Zamora P, et al. Serum albumin and other prognostic factors related to response and survival in patients with advanced non-small cell lung cancer. *Lung Cancer*. 1995; 12:67-76.
  52. Lis CG, Grutsch JF, Vashi PG, et al. Is serum albumin an independent predictor of survival in patients with breast cancer? *JPEN J Parenter Enteral Nutr*. 2003; 27:10-5.
  53. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. *Nutr J*. 2010; 9:69.
  54. Lahr CJ, Soong SJ, Cloud G, et al. A multifactorial analysis of prognostic factors in patients with liver metastases from colorectal carcinoma. *J Clin Oncol*. 1983; 1:720-6.
  55. Cengiz O, Kocer B, Surmeli S, et al. Are pretreatment serum albumin and cholesterol levels prognostic tools in patients with colorectal carcinoma? *Med Sci Monit*. 2006; 12:CR240-7.
  56. Siddiqui A, Heinzerling J, Livingston EH, et al. Predictors of early mortality in veteran patients with pancreatic cancer. *Am J Surg*. 2007; 194:362-6.
  57. Boonpipattanapong T, Chewatanakornkul S. Preoperative carcinoembryonic antigen and albumin in predicting survival in patients with colon and rectal carcinomas. *J Clin Gastroenterol*. 2006; 40:592-5.
  58. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2013; 14:1077-1085.
  59. Aparicio T, Bouche O, Taieb J, et al. Bevacizumab+chemotherapy versus chemotherapy alone in elderly patients with untreated metastatic colorectal cancer: a randomized phase II trial-PRODIGE 20 study results. *Ann Oncol*. 2018; 29:133-138.
  60. Venderbosch S, Doornebal J, Teerenstra S, et al. Outcome of first line systemic treatment in elderly compared to younger patients with metastatic colorectal cancer: a retrospective analysis of the CAIRO and CAIRO2 studies of the Dutch Colorectal Cancer Group (DCCG). *Acta Oncol*. 2012; 51:831-9.
  61. Folprecht G, Cunningham D, Ross P, et al. Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials. *Ann Oncol*. 2004; 15:1330-8.
  62. Goldberg RM, Tabah-Fisch I, Bleiberg H, et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J Clin Oncol*. 2006; 24:4085-91.
  63. Aparicio T, Lavau-Denes S, Phelip JM, et al. Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001-02). *Ann Oncol*. 2016; 27:121-7.
  64. Price TJ, Zannino D, Wilson K, et al. Bevacizumab is equally effective and no more toxic in elderly patients with advanced colorectal cancer: a subgroup analysis from the AGITG MAX trial: an international randomised controlled trial of Capecitabine, Bevacizumab and Mitomycin C. *Ann Oncol*. 2012; 23:1531-6.
  65. Owusu C, Koroukian SM, Schluchter M, et al. Screening older cancer patients for a Comprehensive Geriatric Assessment: A comparison of three instruments. *J Geriatr Oncol*. 2011; 2:121-129.

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