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Research Article

Predictors of 1-Year Mortality in a Prospective Cohort of Elderly Patients With Cancer

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Background. Mortality prediction is crucial to select the optimal treatment in elderly cancer patients. Our objective was to identify cancer-related factors and Comprehensive Geriatric Assessment (CGA) findings associated with 1-year mortality in elderly inpatients and outpatients with cancer.
Methods. We prospectively included patients aged ≥70 years who had solid or hematologic malignancies and in whom the CGA was performed by geriatricians in two French teaching hospitals. We identified independent predictors of 1-year mortality after study inclusion, using multivariate Cox models stratified on inpatient/outpatient status. We built three multivariate Cox models, since strong correlations linked activities of daily living (ADL), Eastern Cooperative Oncology Group Performance Status (ECOG-PS), and timed get-up-and-go test (GUG) results; and since physicians' preferences for these three assessments vary. A sensitivity analysis was performed using multiple imputation.
Results. Of the 993 patients (mean age, 80.2 years; 51.2% men), 58.2% were outpatients and 46% had metastatic disease. Colorectal cancer was the most common malignancy (21.4%). Mortality rates after 6 and 12 months were 30.1% and 41.2%, respectively. In all models, tumor site and metastatic status ($p < .001$), age >80 years ($p < .05$), higher number of severe comorbidities ($p < .05$), and malnutrition ($p < .001$) were associated with death independently from impaired ECOG-PS ($p < .001$), ADL ($p < .001$), and GUG ($p < .001$). The adverse effect of metastatic status differed significantly across tumor sites, being greatest for breast and prostate cancer ($p < .001$). Multiple imputation produced similar results.
Conclusion. The predictors of 1-year mortality identified in our study may help physicians select the optimal cancer-treatment strategy in elderly patients.

Key Words: Elderly—Cancer—Mortality—Geriatric Assessment— Epidemiology.

In Europe and the United States, approximately 60% of cancers are diagnosed in patients aged 65 years and older, and 70% of cancer deaths occur in patients older than 65 years (1,2). Predicting outcomes, particularly mortality, is crucial to select the optimal treatment for elderly cancer patients but raises major challenges related to the heterogeneity of this population. Obstacles to optimal cancer treatment include the presence of comorbidities, disabilities, and geriatric syndromes. Comorbidities not only compete with cancer as a cause of death but also increase the risk of cancer- or treatment-related complications. A crucial step in everyday clinical practice is a comprehensive assessment of overall health status designed to identify those patients who require closer monitoring and specific treatment interventions, as well as to limit aggressive treatments in vulnerable patients at high risk for short-term death related to comorbidities, functional impairments, or frailty. The International Society of Geriatric Oncology (SIOG) and U.S. National Comprehensive Cancer Network (NCCN) (3,4) recommend a Comprehensive Geriatric Assessment (CGA) to detect multidomain health problems potentially associated with poorer outcomes, thereby improving cancer treatment selection (5–7). In addition, some of these problems may be reversible if appropriately managed (8). However, the CGA is time-consuming and the CGA components most closely associated with outcomes remain unclear. Identifying these components would benefit outcome prediction. Moreover, oncologists who cannot obtain a full CGA for their patients could use those individual components to guide treatment decisions. Only two studies assessed both cancer-related factors and CGA findings associated with early death (within 6 and 12 months) in elderly cancer patients, and their results are conflicting (9,10). In one study, only cancer-related factors independently predicted 1-year mortality (9); whereas, in the other, not only advanced tumor stage, but also malnutrition and impaired mobility independently predicted 6-month mortality (10).

We hypothesized that both cancer-related factors and CGA findings predicted 1-year mortality among elderly cancer patients. Our objective was to identify these predictors in a prospective study of elderly inpatients and outpatients with various cancer types.

Methods

Population

The ELCAPA (ELderly CAncer PAtient) survey is a prospective cohort study that included consecutive patients aged 70 years or older who had newly diagnosed solid or hematologic malignancies and were referred by oncologists, radiotherapists, surgeons, or other specialists to two geriatric oncology clinics in teaching hospitals in the Paris urban area, France. For the present study (ELCAPA06), we selected the 993 patients recruited between 2007 and 2012 whose follow-up data were available (Figure 1). The inclusion date was the date of the first geriatric oncology visit. Informed consent was obtained from all study patients prior to inclusion. The protocol was approved by the appropriate ethics committee (CPP Ile-de-France I, Paris, France).

Geriatric Assessment and Data Collection

For each patient, a geriatrician performed a CGA, collecting all variables listed in Table 1. The social environment was considered good if the patient had a primary caregiver, support at home, or a strong circle of friends and family capable of meeting the patient's needs at the time of the evaluation. Otherwise, the social environment was considered inappropriate. Functional status was considered abnormal if the activities of daily living (ADL) score was less than or equal to 5/6 (11) or the Eastern Cooperative Oncology Group performance status (ECOG-PS) was greater than or equal to 2 (12). Impaired mobility was defined as a timed get-up-and-go test (GUG) more than 20 seconds and/or a GUG score greater than or equal to 3/4 (13). As

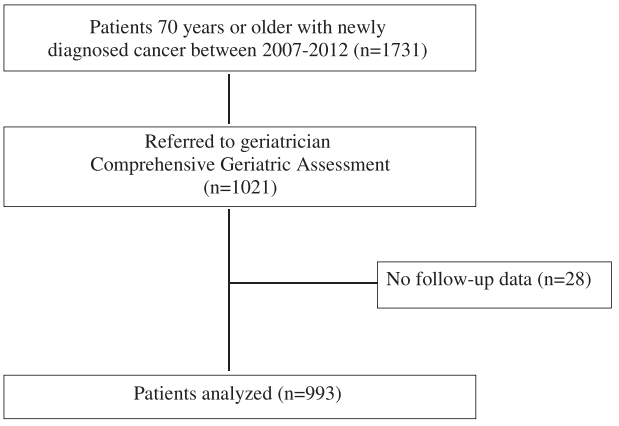

Figure 1. Flow diagram of participants.

recommended by the French National Authority for Health (14), malnutrition was defined as one or more of the following criteria: at least 10% weight loss in 6 months or 5% in 1 month and/or body mass index less than 21 kg/m^2 and/or Mini-Nutritional Assessment (MNA) score less than 17/30 (15) and/or serum albumin level less than 35 g/L. A Mini-Mental State Examination score (MMSE) less than 24/30 was considered abnormal (16). Depressive mood was defined as a Mini-Geriatric Depression Scale (mini-GDS) score greater than or equal to 1/4 (17) or presence of depressive symptoms based on the DSM-IV criteria (18). Comorbidities were a physician diagnosis of heart failure, coronary heart disease, cardiac arrhythmia, chronic obstructive pulmonary disease, hypertension more than or equal to 140/90 mm Hg, renal failure (creatinine clearance estimated by Cockcroft-Gault algorithm <60 mL/min or <30 mL/min for mild/moderate and severe renal failure, respectively), poststroke neurologic sequelae, diabetes mellitus, and urinary and/or fecal incontinence. The number of organ systems affected by grade 3–4 (severe) comorbidities was assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (19). Polypharmacy was defined as taking five or more drugs per day, including prescribed standing, prescribed as-needed, and over-the-counter medications (20). After the CGA, a multidisciplinary meeting was held to decide the cancer treatment strategy, which could consist in one or more of the following: chemotherapy, surgery, hormonal therapy, radiotherapy, and supportive care. We also assessed the following potential predictors of 1-year mortality: age, sex, tumor site, metastatic status (M0, no distant metastases; M1, distant metastases; Mx, metastatic status unknown; NA not applicable), planned treatment decision (palliative or curative), and planned treatment modalities (chemotherapy [yes/no], surgery [yes/no], hormonal therapy [yes/no], radiotherapy [yes/no], and supportive care [yes/no]), treatment change defined as a difference between the initially planned treatment proposed by the oncologists and the treatment finally selected during a multidisciplinary meeting (no change, treatment intensification by adding one or more modalities; treatment de-escalation by removing at least one modality, or replacement of specific cancer treatment by supportive care) (21). Tumor sites were classified as follows: colorectal, breast, prostate, upper gastrointestinal tract (stomach and esophagus) and liver, urinary system (bladder, upper urinary tract, and kidney), hematologic malignancies, and other tumors (including ovary, uterus, lung, head and neck, skin, thyroid, and unknown primary). Age was dichotomized using the median value (≤≤80 vs >80), which provided the best Akaike information criterion (AIC) value (22). Outpatient/inpatient status, year of inclusion, planned treatment decision, planned treatment modalities, and changes in planned treatment were considered potential confounders.

Table 1. Patient Characteristics and Baseline Variables Associated With Overall 1-y Mortality by Univariate Analysis

Variables	Patients (*N* = 993)	Survivors (*N* = 614)	Nonsurvivors (*N* = 379)	Unadjusted†	*p* Value‡
	N (%)*	*N* (%)*	*N* (%)*	HR (95% CI)	
General characteristics					
Year of patient inclusion					
2007	98 (9.9)	49 (8.0)	49 (50.0)	1.00 (referent)	.158
2008	146 (14.7)	88 (14.3)	58 (15.3)	0.88 (0.60–1.28)	
2009	219 (22.1)	126 (20.5)	93 (24.5)	0.90 (0.63–1.27)	
2010	165 (16.6)	111 (18.1)	54 (14.2)	0.62 (0.42–0.92)	
2011	181 (18.2)	117 (19.1)	64 (16.9)	0.78 (0.54–1.13)	
2012	184 (18.5)	123 (20.0)	61 (16.1)	0.73 (0.50–1.07)	
Age, y					
Mean (*SD*)	80.2 (5.6)				
>80	446 (44.9)	251 (40.9)	195 (51.5)	1.44 (1.18–1.77)	<.001
Male gender	509 (51.2)	290 (47.2)	218 (57.5)	1.39 (1.14–1.71)	.001
Tumor site					
Colorectal	213 (21.4)	143 (23.3)	70 (18.5)	1.00 (referent)	<.001
Upper gastrointestinal tract/liver	174 (17.5)	70 (11.4)	104 (27.4)	2.64 (1.95–3.58)	
Breast	169 (17.0)	144 (23.5)	25 (6.6)	0.41 (0.26–0.64)	
Prostate	109 (11.0)	83 (13.5)	26 (6.9)	0.72 (0.46–1.12)	
Other urologic malignancies	139 (14.0)	85 (13.8)	54 (14.2)	1.30 (0.91–1.85)	
Hematologic malignancies	83 (8.4)	48 (7.8)	35 (9.2)	1.49 (0.99–2.23)	
Other	106 (10.7)	41 (6.7)	65 (17.2)	2.78 (1.98–3.89)	
Metastatic status (*n* = 921)					
M0	414 (45.0)	323 (57.7)	91 (25.2)	1.00 (referent)	<.001
M1	414 (45.0)	186 (33.2)	228 (63.2)	3.48 (2.73–4.44)	
Mx	10 (1.0)	3 (0.5)	7 (1.9)	6.14 (2.84–13.25)	
NA	83 (9.0)	48 (8.6)	35 (9.7)	2.38 (1.61–3.52)	
Inpatient status	415 (41.8)	170 (27.7)	245 (64.6)	3.83 (3.10–4.73)	<.001
Palliative treatment decision (*n* = 884)	472 (54.4)	196 (36.7)	276 (78.9)	5.08 (3.93–6.58)	<.001
Changes in planned treatment (*n* = 926)					
No change	796 (86.0)	518 (89.9)	278 (79.4)	1.00 (referent)	<.001
De-escalation	116 (12.5)	48 (8.3)	68 (19.4)	2.16 (1.65–2.81)	
Intensification	14 (1.5)	10 (1.8)	4 (1.2)	0.78 (0.29–2.09)	
Planned cancer treatment modalities					
Surgery (*n* = 868)	278 (32.0)	229 (43.0)	49 (14.6)	0.27 (0.20–0.37)	<.001
Chemotherapy (*n* = 854)	352 (41.2)	223 (42.6)	129 (39.1)	0.82 (0.66–1.03)	.085
Hormonal therapy (*n* = 880)	146 (16.6)	127 (23.7)	19 (5.5)	0.23 (0.14–0.36)	<.001
Radiotherapy (*n* = 858)	210 (24.5)	165 (31.5)	45 (13.5)	0.38 (0.28–0.53)	<.001
Supportive care (*n* = 859)	228 (26.5)	75 (14.2)	153 (46.1)	3.97 (3.19–4.93)	<.001
Social					
Lives alone (*n* = 989)	374 (37.8)	234 (38.2)	140 (37.1)	0.96 (0.78–1.18)	.688
Inadequate social support§ (*n* = 989)	203 (20.5)	114 (18.6)	89 (23.7)	1.30 (1.02–1.65)	.032
Nursing home resident (*n* = 990)	69 (7.0)	46 (7.5)	23 (6.1)	0.88 (0.58–1.34)	.543
Function/mobility					
GUG ≥ 3 and/or >20 s (*n* = 985)	448 (45.5)	191 (31.4)	257 (68.4)	3.81 (3.06–4.74)	<.001
ECOG-PS (*n* = 991)					
0–1	488 (49.2)	393 (64.0)	95 (25.2)	1.00 (referent)	<.001
2	168 (17.0)	104 (16.9)	64 (17.0)	2.27 (1.65–3.12)	
3–4	335 (33.8)	117 (19.1)	218 (57.8)	6.12 (4.80–7.81)	
ADL score ≤ 5/6 (*n* = 913)	314 (34.4)	124 (21.8)	190 (55.1))	3.84 (3.10–4.75)	<.001
Malnutrition‖	538 (54.4)	242 (39.5)	296 (78.7)	4.55 (3.55–5.83)	<.001
Emotional and cognitive function					
MMSE score < 24 (*n* = 909)	235 (25.9)	121 (21.0)	114 (34.2)	2.02 (1.61–2.53)	<.001
Mini-GDS score ≥ 1 (*n* = 878)	303 (34.5)	153 (27.3)	150 (47.3)	2.10 (1.68–2.62)	<.001
Depression, DSM-IV criteria (*n* = 964)	278 (28.8)	129 (21.4)	149 (41.3)	2.20 (1.78–2.71)	<.001
Comorbidities/polypharmacy					
Heart failure (*n* = 985)	123 (12.5)	57 (9.3)	66 (17.6)	1.98 (1.52–2.59)	<.001
Coronary artery disease (*n* = 991)	215 (21.7)	124 (20.2)	91 (24.1)	1.16 (0.92–1.47)	.205
Cardiac arrhythmia (*n* = 989)	299 (30.1)	163 (26.5)	136 (35.9)	1.46 (1.18–1.80)	<.001
Hypertension ≥ 140/90 mm Hg (*n* = 988)	650 (65.8)	400 (65.2)	250 (66.7)	1.06 (0.85–1.31)	.620
Diabetes mellitus (*n* = 988)	221 (22.4)	130 (21.2)	91 (24.3)	1.17 (0.92–1.48)	.190

Table 1. *Continued*

Variables	Patients (*N* = 993)	Survivors (*N* = 614)	Nonsurvivors (*N* = 379)	Unadjusted†	*p* Value‡
	N (%)*	*N* (%)*	*N* (%)*	HR (95% CI)	
Chronic obstructive pulmonary disease (*n* = 984)	66 (6.7)	29 (4.7)	37 (9.9)	1.90 (1.35–2.67)	<.001
Renal dysfunction (Cockcroft, mL/min) (*n* = 864)					
Absent	320 (37.0)	219 (41.1)	101 (30.5)	1.00 (referent)	.001
Mild-moderate (clearance < 60 mL/min)	459 (53.1)	270 (50.7)	189 (57.1)	1.37 (1.07–1.74)	
Severe (clearance < 30 mL/min)	85 (9.8)	44 (8.3)	41 (12.4)	1.94 (1.33–2.76)	
Poststroke neurologic sequelae (*n* = 988)	33 (3.3)	19 (3.1)	14 (3.7)	1.38 (0.81–2.36)	.232
Urinary and/or fecal incontinence (*n* = 988)	230 (23.3)	118 (19.3)	112 (29.9)	1.77 (1.42–2.21)	<.001
Number of severe comorbidities (grade 3–4, CIRS-G) (*n* = 940)					
Median (IQR)	1 (0–2)	0 (0–1)	1 (0–3)	1.47 (1.38–1.57)	<.001
Polypharmacy (≥5 drugs/d) (*n* = 957)	648 (67.7)	372 (61.8)	276 (77.8)	1.94 (1.51–2.50)	<.001

Notes: ADL = activities of daily living; CIRS-G = Cumulative Illness Rating Scale for Geriatrics; ECOG-PS = Eastern Cooperative Oncology Group performance status; GUG = timed get-up-and-go test; HR = hazard ratio; IQR = interquartile range; M0 = absence of distant metastases; M1 = presence of distant metastases; Mini-GDS = Mini-Geriatric Depression Scale; MMSE = Mini-Mental State Evaluation; Mx = metastatic status unknown; NA = not applicable.

*Data are number (%) for qualitative variables and mean (*SD*) or median (range) for quantitative variables.

†Unadjusted HRs obtained using univariate Cox models.

‡Logrank test for categorical variables and Wald test for quantitative variables.

§Absence of a primary caregiver or of adequate support at home or of a strong network of family and friends able to meet the needs of the patient at the time of the evaluation.

‖One or more of the following criteria: at least 10% weight loss in 6 months or 5% in 1 month and/or body mass index <21 kg/m^2 and/or Mini-Nutritional Assessment score <17/30 and/or serum albumin <35 g/L.

Outcome

The primary outcome was overall 1-year mortality following the CGA. Vital status was determined from the medical records or public records office.

Statistical Analysis

Categorical variables are described as numbers and percentages and quantitative variables as mean (*SD*) or median (interquartile range) according to their distribution. Overall survival was defined as the time from evaluation to death within 1 year or to last follow-up for censored patients. Overall survival was estimated using the Kaplan–Meier method, and survival curves were compared using the logrank test for categorical variables and Wald test based on a univariate Cox model for quantitative variables. Cox proportional hazards regression was performed to estimate unadjusted hazard ratios (HRs) and their 95% confidence intervals (95% CIs). Variables associated with *p* values less than .20 by univariate analysis were selected for multivariate analysis. Confounders and interactions were assessed in bivariate models. Log-linearity for quantitative variables was tested. To avoid introducing strongly correlated variables into multivariate Cox models, we assessed correlations using Cramer's *V* for categorical variables and the nonparametric Spearman's rank correlation (Rho) for quantitative variables; values greater than 0.50 were taken to indicate strong correlations (23,24). The choice of the most relevant variables relied on clinical relevance, the missing data rate (<15%) to avoid potential section bias, and the AIC. The proportional hazards (PH) assumption was tested using Schoenfeld residual plots and tests (25). We used stratified Cox models to deal with time-dependent variables (ie, inpatient/outpatient status). Model discrimination was assessed using Harrell's C-index with bootstrapped 95% CIs (26). Model goodness-of-fit was assessed using the GrØnnesby and BØrgan calibration test (27) (good fit if $p > .20$) and Cox-Snell residuals (28). We considered that the model associated with the lowest AIC value had the best fit. These analyses were conducted after excluding patients with missing data.

Sensitivity Analysis

We estimated missing values for the covariates independently associated with 1-year mortality in the final model using the multiple-multivariate-imputations-by-chained-equations procedure in STATA, with the missing-at-random assumption. All predictors in the multivariate models and outcome were used to impute missing values, and 20 imputed datasets were created. Logistic regression for binary and ordinal variables, multinomial logistic regression for categorical variables with *k* greater than 2 classes, and predictive mean matching for quantitative variables were performed to impute missing values (29). Similarly, we performed a second sensitivity analysis including the treatment modalities using multiple imputation as the total missing value rate for all treatment modalities was more than 15%.

Subgroup Analyses

We performed subgroup analyses of potential associations linking functional measures (GUG, ADL score, and ECOG-PS) to 1-year mortality according to age, gender, metastatic status (M0 vs M1/Mx), planned treatment decision, and ECOG-PS (<3 vs ≥3). We also performed an analysis confined to patients with ECOG-PS less than 3, to assess the potential added value of the GUG and ADL score in this population.

All tests were two-sided, and *p* values less than or equal to .05 were considered significant. Analyses were performed using STATA software version 12.0 (StataCorp, College Station, TX).

Results

Study Population

Table 1 reports the main patient characteristics. Mortality rates after 6 and 12 months were 30.1% (27.3–33.1) and 41.2% (38.0–44.5), respectively. At 6 and 12 months, information on vital status was unavailable for 84 (8.5%) and 160 (16.1%) patients, respectively, who were born abroad or for whom the place of birth was not recorded or the public records office failed to provide information.

Table 2. Multivariable Cox Regression Analyses Identify Factors Predicting 1-y Mortality

	Model 1 With GUG (*N* = 821)		Model 2 With ECOG-PS (*N* = 827)		Model 3 With ADL (*N* = 767)	
	Adjusted HR[†] (95% CI)	*p*[‡]	Adjusted HR[†] (95% CI)[‡]	*p*	Adjusted HR[†] (95% CI)	*p*[‡]
Tumor site and metastatic status						
Colorectal M0	1.00 (referent)	<.001	1.00 (referent)	<.001	1.00 (referent)	<.001
Colorectal M1/Mx	2.16 (1.27–3.68)		2.07 (1.21–3.52)		2.01 (1.15–3.51)	
Upper gastrointestinal tract/liver M0	2.36 (1.30–4.27)		2.32 (1.28–4.20)		1.99 (1.07–3.71)	
Upper gastrointestinal tract/liver M1/Mx	6.89 (4.12–11.53)		6.32 (3.78–10.57)		5.42 (3.15–9.31)	
Breast or prostate M0	0.16 (0.05–0.56)		0.14 (0.04–0.47)		0.14 (0.04–0.49)	
Breast M1/Mx	2.46 (1.31–4.63)		2.06 (1.10–3.87)		2.16 (1.12–4.13)	
Prostate M1/Mx	3.21 (1.70–6.09)		2.73 (1.44–5.19)		2.78 (1.43–5.39)	
Other urologic malignancies M0	3.35 (1.74–6.48)		3.19 (1.66–6.15)		2.69 (1.38–5.24)	
Other urologic malignancies M1/Mx	3.81 (2.11–6.87)		3.69 (2.06–6.62)		3.62 (1.94–6.75)	
Hematologic malignancies*	2.45 (1.37–4.39)		2.00 (1.12–3.57)		1.95 (1.07–3.57)	
Other malignancies M0/M1/Mx	4.54 (2.65–7.80)		4.02 (2.35–6.88)		3.86 (2.21–6.76)	
Age > 80 y	1.27 (1.01–1.60)	.040	1.32 (1.05–1.66)	.018	1.31 (1.03–1.66)	.028
GUG ≥ 3 and/or >20 s	2.39 (1.84–3.10)	<.001	—		—	
ADL score ≤ 5/6	—		—		1.73 (1.31–3.00)	<.001
ECOG-PS	—				—	
0–1			1.00 (referent)	<.001		
2			1.57 (1.10–2.44)			
3–4			3.33 (2.42–4.58)			
Number of severe comorbidities (grade 3–4, CIRS-G)[§]	1.14 (1.04–1.24)	.005	1.11 (1.02–1.22)	.021	1.14 (1.04–1.25)	.007
Malnutrition	2.11 (1.57–2.83)	<.001	1.81 (1.34–2.45)	<.001	2.13 (1.57–2.89)	<.001

Notes: ADL = activities of daily living; CIRS-G = Cumulative Illness Rating Scale for Geriatrics; ECOG-PS = Eastern Cooperative Oncology Group performance status; GUG = timed get-up-and-go test; HR = hazard ratio; M0 = absence of distant metastases; M1 = presence of distant metastases; Mx = metastatic status unknown.

*Metastatic status not applicable.

[†]All Cox models were stratified by outpatient/inpatient status at the time of evaluation and adjusted for year of patient inclusion and changes in planned cancer treatment.

[‡]*p* of heterogeneity for nonordinal variables and *p* of trend for ordinal variables.

[§]Per additional comorbidity.

Variables Associated With Overall 1-Year Mortality

Tumor site was significantly associated with mortality: compared to colorectal cancer (reference category), breast cancer was associated with significantly lower 1-year mortality and upper gastrointestinal tract/liver cancer and other malignancies with significantly higher 1-year mortality (Table 1). A significant interaction was found between tumor site and metastatic status ($p < .001$): the adverse effect of having metastatic disease differed across tumor sites, being highest in breast and prostate malignancies. As the univariate analysis stratified by metastatic status (M0 vs M1) yielded similar findings in both groups (Supplementary Table 1), we performed analyses based on a composite variable including tumor site and metastatic status, with nonmetastatic colorectal cancer as the reference category. Because patients with nonmetastatic prostate or breast cancer had few events and similar HR values, we pooled these two groups. For the "other cancer" site, we pooled nonmetastatic and metastatic cancers, as well as Mx and M1 cancers, because the numbers of patients were small and HRs (95% CIs) closely similar.

Multivariate Models

Because we found strong correlations linking ADL, ECOG-PS, and GUG (all Cramer's $V > .55$), and because the choice among these three markers varies with physician preference, we built three separate multivariate Cox models, one for each marker. As treatment decision correlated strongly with metastatic status and ECOG-PS (all Cramer's $V > .50$), and supportive care correlated strongly with chemotherapy (Cramer's $V = .51$), neither was considered for the multivariate analyses. Independent predictors of 1-year mortality, namely tumor site, metastatic status, functional impairment, mobility impairment, higher number of severe comorbidities, older than 80 years, and malnutrition, were similar across the three models (Table 2). Gender, social support, depression, cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, renal dysfunction, polypharmacy, and incontinence were not significant predictors by multivariate analysis.

All three models had good discrimination (Harrell's c-index: GUG model, 0.77 [95% CI: 0.74–0.79]; ECOG-PS model, 0.78 [0.75–0.80]; and ADL model, 0.76 [0.73–0.78]) and good calibration ($p > .20$ for all models). The ECOG-PS model had the best fit (lowest AIC and best calibration).

Sensitivity Analyses

Multiple imputation analyses with or without the addition of treatment modalities produced closely similar results (Supplementary Tables 2 and 3.)

Subgroup Analyses

Analyses of associations between functional measures and 1-year mortality stratified by age, gender, metastatic status (M0 vs M1/Mx), planned treatment decision, and ECOG-PS (<3 vs ≥3)

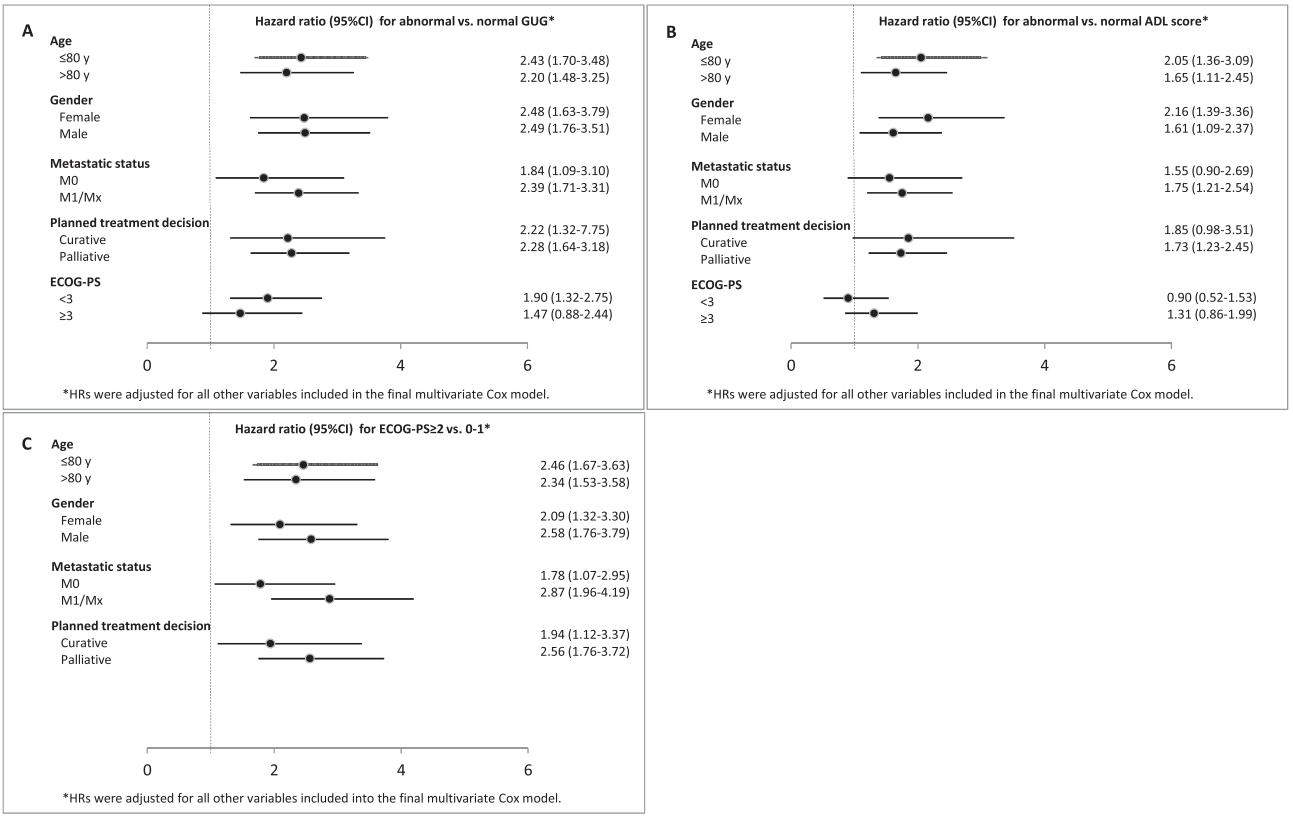

Figure 2. Associations between functional measures (**A** = GUG, **B** = ADL, and **C** = ECOG-PS) and death in prespecified subgroups. ADL = activities of daily living; ECOG-PS = Eastern Cooperative Oncology Group performance status; GUG = timed get-up-and-go test.

produced closely similar findings (Figure 2). When we confined the analysis to patients with ECOG-PS less than 3, abnormal GUG was associated with early death (HR: 1.90 [1.32–2.75]; p = .001), whereas abnormal ADL score was not (HR: 0.90 [0.52–1.53]). When focusing only on patients with ECOG-PS less than 3, including the GUG produced slightly better discrimination (C = 0.77 [0.73–0.81]) compared to the same model without the GUG (C = 0.76 [0.72–0.80]); however, including ADL did not improve discrimination (C = 0.77 [0.73–0.80] with ADL and C = 0.77 [0.73–0.80] without ADL).

Discussion

In our large cohort of elderly inpatients and outpatients with various tumor sites, both cancer-related factors and CGA findings were independently associated with overall 1-year mortality. Cancer-related predictors were tumor site and metastatic status. Predictors identified by the CGA were older than 80 years, functional impairment (ECOG-PS or ADL), mobility impairment (GUG), higher number of severe comorbidities, and malnutrition. The adverse effect of metastatic status was greatest for breast and prostate cancers.

The lower overall 1-year mortality rate in our study (41.2%) compared to previous reports (64%–68%) may be partly ascribable to our large number of patients with breast or prostate cancer (28.0%) (9,30). In the Eurocare study, the 1-year relative survival rate was higher in elderly patients with cancer at either of these sites compared to other sites (31). In the two previous studies focusing on early death (within 6 and 12 months), metastatic status or advanced disease was independently associated with death, in keeping with our results, although neither study reported an interaction between tumor site and metastatic status (9,10). In addition, we found a significant association between older age and 1-year mortality that was not identified in the two previous studies (9,10), perhaps because their patient populations were younger (75 and 77 years, respectively, vs 80 years in our study). Furthermore, studies focusing on longer term survival in elderly cancer patients showed an independent association between older age and death (32–34).A consensus is lacking about the age cutoff that best predicts mortality in elderly cancer patients, and we consequently used the median value (80 years). Although patients 85 years and older had a high prevalence of frailty, dependence, and geriatric syndromes in earlier studies (35), the median age of 80 years was the best cutoff for predicting 1-year mortality in our study. The independent association between early death and mobility impairment (GUG) has been reported previously (10). In contrast, neither of the two above-mentioned studies found an association between early death and functional status (ADL or ECOG-PS) (9,10). One study in patients with colorectal cancer and a mean age of 73.5 years assessed changes in functional status and health care service utilization over the pretreatment to posttreatment period and found that ADL was independently associated with 6-month mortality (36). In several other studies, functional impairment assessed using the ADL (37–39) or ECOG-PS (38,40,41) was associated with death in elderly cancer patients, in keeping with our findings. Our study supports the GUG as a relevant predictor of 1-year mortality in patients whose function is globally preserved (ECOG-PS < 3). Instrumental ADLs were not considered, as the 37% missing data rate carried a risk of inducing selection bias. Although an independent association between a higher number of severe comorbidities and death has been reported (32,42,43), the two studies of early death found no significant effect of the number of severe comorbidities according to the CIRS-G or

Charlson score (9,10). Cancer treatment may worsen comorbidities, thereby hastening death. The NCCN has therefore recommended that effects of comorbidities on life expectancy be evaluated before treatment initiation (4). No single comorbidity was independently associated with 1-year mortality in our study. In keeping with our results, several studies in cancer patients documented a major independent prognostic effect of malnutrition as assessed by the MNA, weight loss, or serum albumin (10,37,41,44,45). To our knowledge, we provide the first evidence that malnutrition defined as percent weight loss in the past 6 months or 1 month and/or body mass index and/or MNA and/or serum albumin independently predicts 1-year mortality in elderly inpatients and outpatients with cancer.

The diversity of our patient population reflects everyday practice and strengthens the external validity of our results. Other strong points of our study are the use of validated scales to assess the CGA domains, in compliance with current international guidelines; this also supports the applicability of our results to other healthcare institutions. We took confounders into account and adjusted all models for year of cohort inclusion to avoid potential bias due to changes in cancer management over time. We also adjusted for planned treatment modalities in a sensitivity analysis and for CGA-based changes in planned treatment modalities, to factor in potential effects of treatment intensity on survival. Indeed, we previously reported that after the CGA, the initial cancer treatment plan was modified for 78 (20.8%) of 375 patients, usually to decrease treatment intensity (21). Another study found that the geriatric oncology consultation led to a modification of the cancer treatment plan in more than one third of cases (46).

The similar results of the sensitivity analyses support the robustness of our findings. Finally, we chose to build three different models, because strong correlations linked the functional markers (ie, ADL, ECOG-PS, and GUG), and since physicians' preferences for these three assessments vary. Potential limitations of our study are that treatments were not included among potential confounders in the complete-case analysis, because of the high missing data rate, and that we assumed the best available treatments were used in all patients and produced the same relative benefits across all risk groups. However, a sensitivity analysis including treatment modalities after multiple imputation yielded closely similar findings. Data about causes of death were not available. Therefore, we could not investigate if the same factors both predicted cancer-specific death and death from other causes. The inclusion of patients with various tumor sites and stages increases the general applicability of our results, but the numbers of patients with each tumor site are too small for subgroup analyses. The inclusion of elderly cancer patients referred by physicians for a geriatric evaluation may have introduced selection bias.

Conclusion

Both cancer-related factors (tumor site and metastatic status, especially in breast and prostate cancer) and CGA findings (functional and mobility impairments, malnutrition, and number of severe comorbidities) as well as age older than 80 years independently predicted 1-year mortality in elderly inpatients and outpatients with various cancer types. Several CGA findings that may interfere with cancer treatments may be amenable to improvement (eg, malnutrition, functional status, and certain comorbidities). Physicians involved in managing elderly cancer patients should primarily assess function, nutrition, and comorbidities. Several randomized trials assessing the impact of the CGA on outcomes such as mortality, quality of life, and chemo-toxicity in elderly cancer patients are ongoing (http://www.clinicaltrials.gov/ct2/show/record/NCT01749995?term=Comprehensive+Geriatric+Assessment+AND+Cancer&rank=1). Finally, we are conducting a randomized trial to assess the impact of the CGA combined with a geriatric intervention program on treatment decision making and on patient function, nutritional status, quality of life, and overall survival in a population of elderly patients with head and neck cancer (clinical trials.gov NCT02025062).

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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