Journal of Geriatric Oncology 8 (2017) 176–184

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Functional status decline in older patients with breast and colorectal cancer after cancer treatment: A prospective cohort study

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ARTICLE INFO

Article history:
Received 22 September 2016
Received in revised form 17 December 2016
Accepted 18 January 2017
Available online 31 January 2017

Keywords:
Colorectal cancer
Breast cancer
Chemotherapy
Older patients
Elderly
Activities of daily living
Instrumental activities of daily living
Functional status

ABSTRACT

Objectives: The aim of the present study was to disentangle the impact of age and that of cancer diagnosis and treatment on functional status (FS) decline in older patients with cancer.
Materials and Methods: Patients with breast and colorectal cancer aged 50–69 years and aged ≥ 70 years who had undergone surgery, and older patients without cancer aged ≥ 70 years were included. FS was assessed at baseline and after 12 months follow-up, using the Katz index for activities of daily living (ADL) and the Lawton scale for instrumental activities of daily living (IADL). FS decline was defined as ≥ 1 point decrease on the ADL or IADL scale from baseline to 12 months follow-up.
Results: In total, 179 older patients with cancer (≥ 70 years), 341 younger patients with cancer (50–69 years) and 317 older patients without cancer (≥ 70 years) were included. FS decline was found in 43.6%, 24.6% and 28.1% of the groups, respectively. FS decline was significantly worse in older compared to younger patients with cancer receiving no chemotherapy (44.5% versus 17.6%, $p < 0.001$), but not for those who did receive chemotherapy (39.4% versus 30.8%, $p = 0.33$). Among the patients with cancer, FS decline was significantly associated with older age (OR 2.63), female sex (OR 3.72), colorectal cancer (OR 2.81), polypharmacy (OR 2.10) and, inversely, with baseline ADL dependency (OR 0.44).
Conclusion: Cancer treatment, and older age are important predictors of FS decline. The relation of baseline ADL dependency and chemotherapy with FS decline suggest that the fittest of the older patients with cancer were selected for chemotherapy.

1. Introduction

Cancer mainly affects the older population [1]. In Europe, over 364,000 and 342,000 patients a year are diagnosed with breast and colorectal cancer, respectively [1]. At the time of diagnosis, 40% of patients with breast cancer and 60% of patients with colorectal cancer are aged ≥ 70 years [2]. With the aging of the population, the number of older patients with cancer is expected to rise further in the coming decades [2].

Evidence for the optimal treatment of patients with cancer is largely limited to younger patients or selected older patients with good overall health, while other older patients, especially those with poor performance status and comorbid conditions, have been underrepresented in clinical trials [3,4]. The International Society of Geriatric Oncology (SIOG) has reported that clinical trials often use endpoints inappropriate for older patients with cancer [5]. The most frequently investigated endpoints are still progression-free survival (PFS) and overall survival (OS) [3,4,6], while older patients often prefer preservation of independency as the most relevant endpoint [7,8]. Hence, additional endpoints besides PFS and OS, like maintaining an independent functional status (FS), should be investigated in older patients in order to choose the appropriate treatment for an older patient with cancer [7]. Previous

Abbreviations: FS, functional status; PFS, progression-free survival; OS, overall survival; ADL, Activities of daily living; IADL, Instrumental activities of daily living; KLIMOP, study (Cancer in Limburg Older Patients).

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http://dx.doi.org/10.1016/j.jgo.2017.01.003
1879-4068/

studies have shown a positive association between functional independency, quality of life and survival, emphasizing the importance of studying FS in older patients with cancer [9,10]. FS declines with age and after cancer treatment. As a result, older patients with cancer are at higher risk of FS decline than older patients without cancer [11].

The aim of the present study was therefore to examine the impact of age and that of cancer diagnosis and treatment on FS decline in older patients with cancer.

2. Methods

2.1. Patients

Patients were selected from participants of the KLIMOP study (Cancer in Limburg Older Patients), a longitudinal cohort study that included older patients with cancer (aged ≥70 years), younger patients with cancer (aged 50–69 years), and participants without a previous diagnosis of cancer (aged ≥70 years) [12].

Participants were recruited between June 2010 and August 2014. Younger and older patients with cancer were recruited through nine academic and non-academic hospitals in Belgium and in the Netherlands. The participants without cancer were recruited through family practices from the same region as the patients with cancer. The general practitioners asked all eligible patients to participate until 20 patients per general practitioner agreed to participate.

The inclusion criteria were a new diagnosis of cancer (i.e. lung, prostate, gastrointestinal, or breast cancer), an estimated life expectancy of more than six months, and no previous diagnosis of cancer except for non-melanoma tumors of the skin. The exclusion criteria were inability to speak Dutch and a formal diagnosis of dementia.

In the present analysis, we included patients with breast and colorectal cancer who had undergone surgery, and all participants without a previous diagnosis of cancer. We excluded participants with other cancer types in order to pursue a more homogeneous study population. Patients who died, were lost to follow-up, or had missing functional status measurements at baseline or after 12 months of follow-up were excluded from the analysis.

The medical research ethics committees of KU Leuven, UZ Leuven (S52097-ML6279) and the Maastricht University Medical Center (NL414.068.10) approved the KLIMOP study. Written informed consent was obtained from all participants.

2.2. Demographic, Functional, and Clinical Characteristics

Demographic characteristics were collected within three months after cancer diagnosis and included age (years), gender, living situation (living together or alone), and educational level (age when leaving school). Functional characteristics included activities of daily living, using the Katz scale (ADL, cut-off for dependency ≥1) [13]; instrumental activity of daily living, using the Lawton scale (IADL, cut-off for dependency ≥1) [14]; cognitive function, using the mini mental state examination (MMSE, cut-off for cognitive impairment ≤23) [15]; depressive symptoms, using the geriatric depression scale-15 (GDS-15, cut-off for depressive symptoms ≥5) [16]; nutritional status, using body mass index (BMI, cut-offs for low BMI < 20, normal BMI 20–30, and high BMI > 30) [17]; number of daily medications being used (cut-off for polypharmacy ≥5) [18,19]; comorbidity, using the diseases listed in the charlson comorbidity index (CCI) [20]; fatigue, using a visual analogue scale (VAS, cut-off for fatigue ≥4) [21,22]; and social support (available or not available). Clinical tumor characteristics were obtained from the medical charts and included cancer type (breast cancer, colorectal cancer), stage (stage I to II, stage III to IV) and cancer treatment (surgery, radiotherapy, hormone therapy, and chemotherapy).

2.3. Functional Status (FS) Decline

FS decline was defined as ≥1 point decrease on the Katz ADL scale [13] or the Lawton IADL scale [14] between baseline and 12 months follow-up. The Katz ADL scale contains six items (bathing, dressing, toileting, transferring, continence, and feeding). All items were scored as 0 (dependent) or 1 (independent). The Katz ADL score ranges from 0 (unable to perform any activity) to 6 (able to perform all activities) and ADL dependency was defined as being unable to perform one or more activities [13]. The Lawton IADL scale contains five items for men and eight items for women, namely using a telephone, shopping, preparing a meal, cleaning the house, preparing things in the house, doing the laundry, moving around outside the home, taking medications, and handling financial matters. All items were scored as 0 (dependent, able to perform activity with some help or not able to perform activity without help) or 1 (independent, able to perform activity). The Lawton IADL scale ranges from 0 (unable to perform any activity) to 5 and 8 for men and women, respectively (able to perform all activities). IADL dependency was defined as needing help or being unable to perform one or more activities [14].

2.4. Statistical Analysis

The primary endpoint of this analysis was the impact of age on FS decline in patients with cancer aged 50–69 years compared with patients with cancer aged ≥70 years. The secondary endpoint was the impact of cancer diagnosis and treatment on FS decline in patients with cancer and control patients without cancer aged ≥70 years. Demographic, clinical, and functional characteristics were described and compared using the chi-square test and Mann–Whitney, where appropriate.

Logistic regression analysis was performed with a non-step model in order to use the best model for FS decline (with a = 0.20). Variables included in the analysis (coded as 0 or 1, unless otherwise specified) were age (50–69 years vs. ≥ 70 years), gender (male, female), cancer diagnosis (breast cancer, colorectal cancer), cancer stage (stage I or II, stage III or IV), chemotherapy (yes vs. no), baseline ADL (independent vs. dependent), baseline IADL (independent vs. dependent), polypharmacy (4 or less vs. higher scores), MMSE (24 or more vs. lower scores), GDS (4 or less vs. higher scores), body mass index (1 = 20–30; 2 = < 20; 3 = > 30), fatigue (3 or less vs. higher scores), living alone, and presence of caregiver. The collinearity of the models was analyzed with the variance inflation factor (VIF) in a regression model. In this model we did not detect collinearity for FS decline (VIF < 2.8). Comorbidity was not included in the model because it is clinically related to polypharmacy. The same predictors, except for cancer stage and treatment, were included in a logistic regression analysis for patients with cancer and control patients without cancer aged ≥70 years. The model calibration was assessed using the Hosmer and Lemeshow's goodness-of-fit test, and the discrimination of the model was based on the area under the receiver operating curve (AUC).

Sensitivity analyses to assess the influence of missing values for FS decline were performed, making a worst and best case scenario by merging all missing values as either a normal or an abnormal score.

Unadjusted and adjusted Odd Ratios (ORs) with 95% confidence intervals (CI) were calculated. We used SPSS (Statistical Package for the Social Sciences) version 21.0 for all analyses.

3. Results

Among the 1490 patients included in the KLIMOP study, 1217 had been diagnosed with breast or colorectal cancer or were older patients without cancer (Fig. 1). After 12 months, 22 of the patients (1.8%) had died, 63 (5.2%) had missing ADL and IADL data, and 295 (24.2%) were lost to follow-up.

Reasons for not participating at 12 months follow-up were personal problems (e.g. loss of a spouse), health problems (e.g. cancer

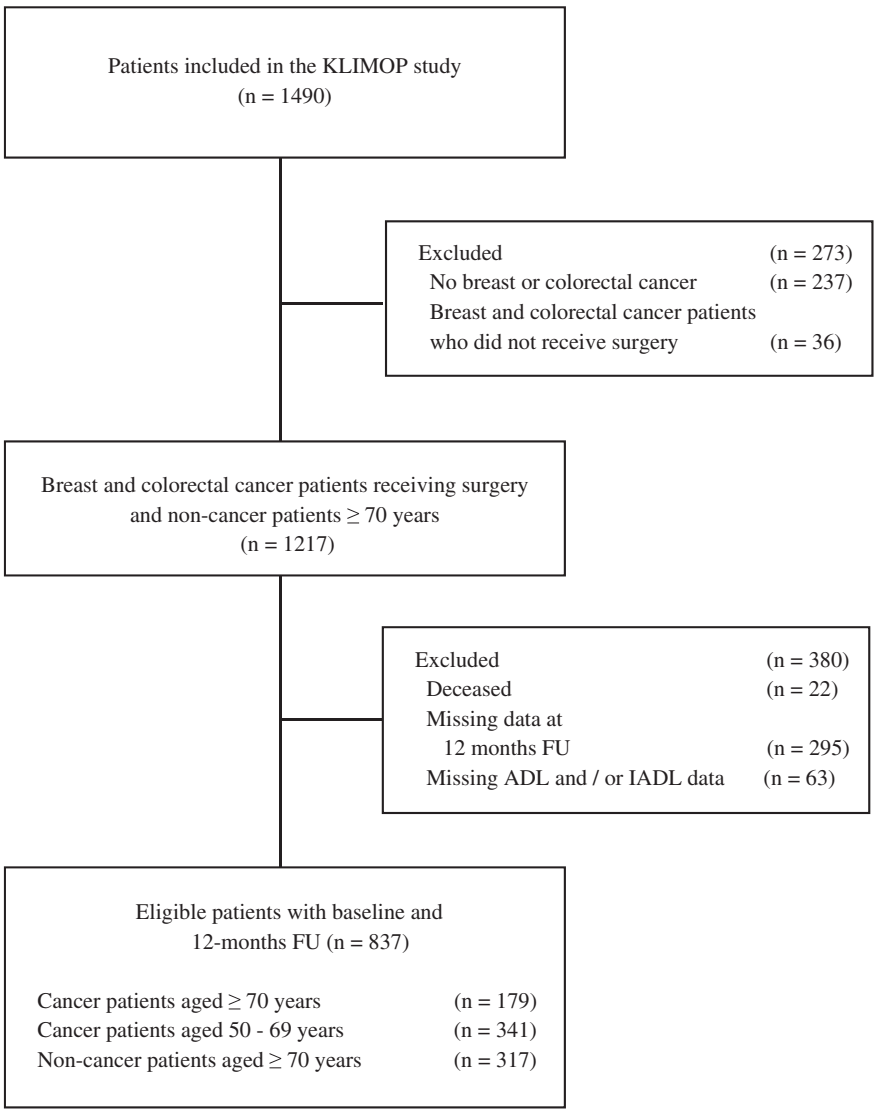

Fig. 1. Flowchart for patients included in the KLIMOP study ADL, activities of daily living; IADL, instrumental activities of daily living.

recurrence), or other (e.g. too busy). Hence, the analysis included 837 patients: 179 older patients with cancer, 341 younger patients with cancer and 317 older patients without cancer. Compared to the older patients with cancer available for analysis, those with missing data or those lost to follow-up were more likely to be male (26.4% vs. 15.6%), more likely to have colorectal cancer (50.0% vs. 20.7%), and less likely to have stage I or II disease (59.1% vs. 73.2%). Younger patients with cancer with missing data or lost to follow-up were more likely to have colorectal cancer than those available for analysis (28.7% vs. 22.9%).

3.1. Baseline Characteristics

Baseline characteristics are described in Table 1.

Compared to younger patients, older patients with cancer were less likely to be treated with chemotherapy (18.4% vs. 53.4%, $p < 0.01$), more likely to be ADL- (50.3% vs. 28.4%, $p < 0.001$) and IADL-dependent (33.0% vs. 23.2%, $p < 0.03$), more likely to have polypharmacy (26.8% vs. 14.7%, $p < 0.01$), more likely to have impaired cognition (10.1% vs. 2.6%, $p < 0.01$), more likely to be living alone (33.0% vs. 14.7%, $p < 0.001$), and more likely to have left school at a younger age (22.9% vs. 9.4%, $p < 0.001$). On the other hand, younger patients with cancer were more likely to report depressive symptoms than older patients with cancer (12.3% vs. 6.1%, $p < 0.03$) at baseline.

Compared to older patients without cancer, older patients with cancer were more likely to be female (84.4% vs. 61.5%, $p < 0.00$), less likely to have polypharmacy (26.8% vs. 48.6%, $p < 0.001$), more likely to be ADL-dependent (50.3% vs. 37.2%, $p < 0.03$), and more likely to receive social support (65.4.5% versus 48.9%, $p < 0.001$).

3.2. Impact of Age, Cancer Diagnosis, and Treatment

In the group of older patients with cancer, 78 patients (43.6%) declined in FS, against 84 (24.6%) in the group of younger patients with cancer, and 89 (28.1%) in the group of older patients without cancer. Thirty-three (18.4%) of the 179 older patients with cancer available for analysis received chemotherapy, compared to 182 (53.4%) of the 341 younger patients with cancer. FS decline was significantly worse for older compared to younger patients with cancer receiving no chemotherapy (44.5% versus 17.6%, $p < 0.001$), but not for those who did receive chemotherapy (39.4% versus 30.8%, $p = 0.33$) (Fig. 2).

Table 1
Baseline characteristics of cancer patients aged 50–69 years, cancer patients aged ≥70 years, and non-cancer patients aged ≥70 years.

	Cancer patients aged 50–69 years (n = 341) n (%)	p value †	Cancer patients aged ≥70 years (n = 179) n (%)	p value ‡	Non-cancer patients aged ≥70 years (n = 317) n (%)
Median age, years (range)	60.0 (50–69)	< 0.001	75.0 (70–93)	< 0.001	77.0 (70–97)
Gender					
Male	53 (15.5)	0.98	28 (15.6)	< 0.001	122 (38.5)
Female	288 (84.5)		151 (84.4)		195 (61.5)
Cancer diagnosis					
Breast	263 (77.1)	0.66	135 (75.4)		-
Colorectal	78 (22.9)		44 (24.6)		
Stage					
I - II	247 (72.4)	0.06	131 (73.2)		-
III - IV	83 (24.3)		28 (15.6)		
Unknown	11 (3.2)		20 (11.2)		
Chemotherapy					
No	159 (46.6)	< 0.001	146 (81.6)		-
Yes	182 (53.4)		33 (18.4)		
Katz ADL (0–6)					
Independent (6)	244 (71.6)	< 0.00	89 (49.7)	< 0.03	199 (62.8)
Dependent (≤ 5)	97 (28.4)		90 (50.3)		118 (37.2)
Lawton IADL (0–5/8)					
Independent (5 / 8)	247 (72.4)	< 0.03	118 (65.9)	0.55	200 (63.1)
Dependent (≤ 4 / ≤ 7)	79 (23.2)		59 (33.0)		113 (35.6)
Missing	15 (4.4)		2 (1.1)		4 (1.3)
Comorbidity (CCI)					
0			111 (62.0)		165 (36.1)
1	251 (73.6)	< 0.001	42 (23.5)	< 0.001	110 (24.1)
≥ 2	65 (19.1)		25 (14.0)		120 (26.3)
Missing	25 (7.3)		1 (0.6)		62 (13.6)
Polypharmacy					
No (≤ 4)	291 (85.3)	< 0.01	131 (73.2)	< 0.001	163 (51.4)
Yes (≥ 5)	50 (14.7)		48 (26.8)		154 (48.6)
Cognition (MMSE, 0–30)					
Normal (≥ 24)	272 (79.8)	< 0.01	139 (77.7)	0.13	294 (92.7)
Impaired (≤ 23)	9 (2.6)		18 (10.1)		23 (7.3)
Missing	60 (17.6)		22 (12.3)		0 (0)
Depressive symptoms (GDS)					
None (≤ 4)	278 (81.5)	< 0.03	152 (84.9)	0.19	277 (87.4)
Mild or severe (≥ 5)	42 (12.3)		11 (6.1)		32 (10.1)
Missing	21 (6.2)		16 (8.9)		8 (2.5)
Body mass index (BMI)					
Normal (20–30)	251 (73.6)	0.73	134 (74.9)	0.92	246 (77.6)
Low (< 20)	22 (6.5)		9 (5.0)		14 (4.4)
High (> 30)	66 (19.4)		31 (17.3)		55 (17.4)
Missing	2 (0.6)		5 (2.8)		2 (0.6)
Fatigue (0–10)					
No (≤ 3)	142 (44.8)	0.94	56 (31.3)	0.75	142 (44.8)
Yes (≥ 4)	187 (54.9)		75 (41.9)		174 (54.9)
Missing	12 (3.5)		48 (26.8)		1 (0.3)
Living situation					
Alone	50 (14.7)	< 0.001	59 (33.0)	0.23	100 (31.0)
Living together	287 (84.2)		111 (62.0)		209 (65.9)
Institutionalized	0 (0.0)		7 (3.9)		5 (1.6)
Missing	4 (1.2)		2 (1.1)		3 (0.9)
Social support					
Not available	63 (18.4)	0.69	24 (13.4)	< 0.001	157 (49.5)
Available	266 (78.0)		117 (65.4)		155 (48.9)
Missing	12 (2.3)		38 (21.2)		5 (1.6)
Age at leaving school					
≤ 14 years	32 (9.4)	< 0.001	41 (22.9)	0.46	85 (26.8)
15–18 years	155 (45.5)		90 (50.3)		143 (45.1)
≥ 19 years	143 (41.9)		42 (23.5)		84 (26.8)
Missing	11 (3.2)		6 (3.4)		4 (1.3)

ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, mini mental state examination; GDS-15, geriatric depression scale-15; CCI, charlson comorbidity index.
† p values refer to the comparison of the cancer patients aged ≥70 years with the cancer patients aged 50–69 years;
‡ p values refer to the comparison of the cancer patients aged ≥70 years with the non-cancer patients aged ≥70 years.

Table 2 shows the results of the logistic regression analysis for FS decline for all patients with cancer, to assess the impact of aging. The characteristics associated with FS decline in the multivariate analysis were age > 70 years (odds ratio [OR] 2.63; 95% confidence interval [CI] 1.63–4.23), female sex (OR 3.72; 95% CI 1.59–8.71), colorectal cancer (OR 2.81; 95% CI 1.33–5.91), polypharmacy (OR 2.10; 95% CI 1.25–3.54), and, inversely, ADL dependency (OR 0.44; 95% CI 0.27–0.70). IADL decline was not predicted by colorectal cancer (OR

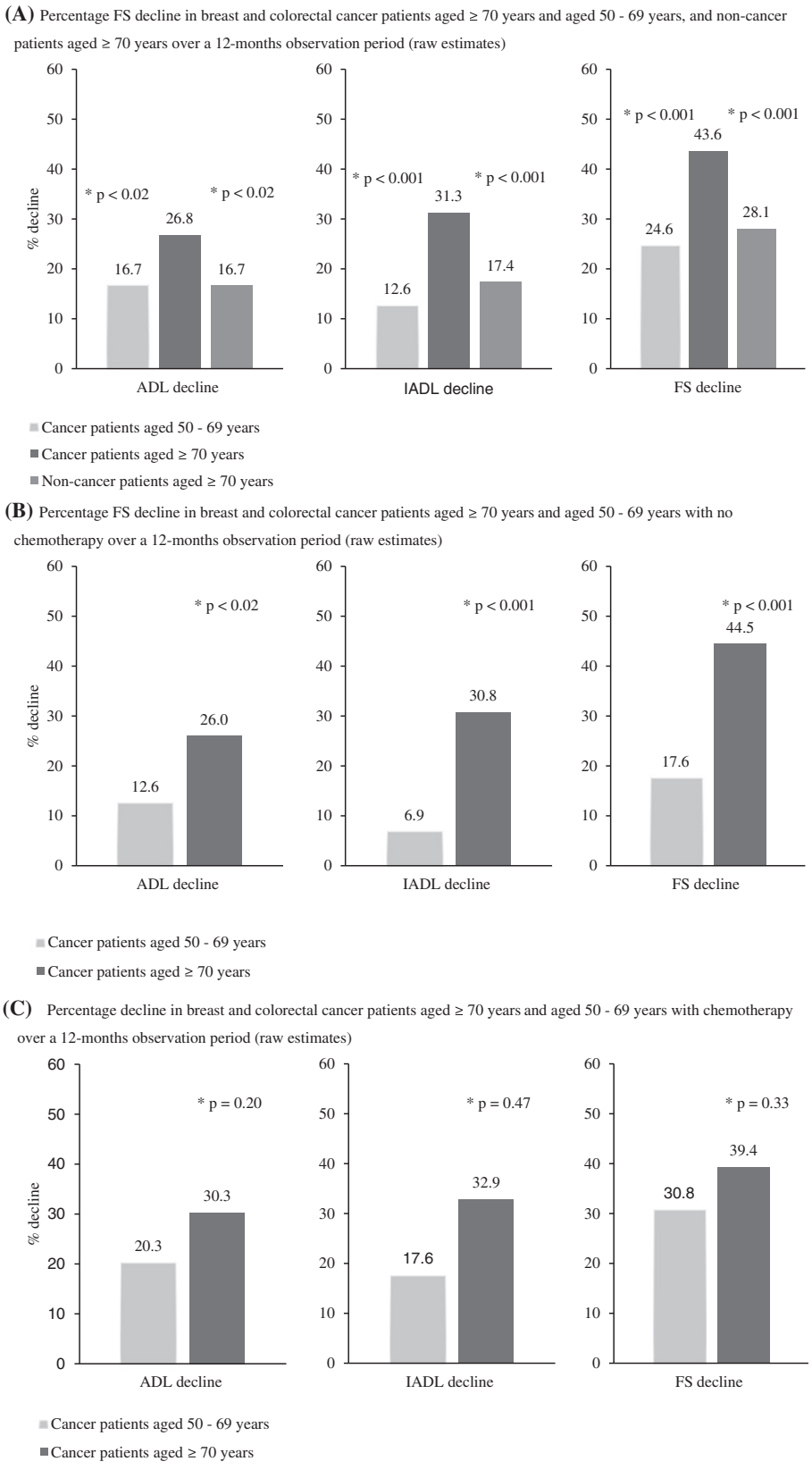

Fig. 2. Percentage ADL decline, IADL decline, and functional status (FS) decline over a 12-months observation period.

1.58; 95% CI 0.68–3.66) or ADL dependency (OR 1.37; 95% CI 0.83 0 2.27). Similar predictors were found for ADL decline.

Table 3 presents the results of the logistic regression analysis for all older patients, assessing the impact of cancer. In the multivariate model, the risk of FS decline was higher in patients aged ≥80 years (OR 2,90: 95% CI 1.77–4.76), after cancer treatment (OR 1.77; 95% CI 1.19–2.63), polypharmacy (OR 2.36; 95% CI 1.47–3.82), and fatigue at baseline (OR 2.05; 95% CI

Table 2
Logistic regression analysis for ADL decline, IADL decline, and functional status (FS) decline in older and younger cancer patients over a 12-month observation period.

	ADL decline				IADL decline				Functional status decline			
	OR_1	(95% CI)	OR_2	(95% CI)	OR_1	(95% CI)	OR_2	(95% CI)	OR_1	(95% CI)	OR_2	(95% CI)
Age												
50–69 years	1.00		1.00		1.00		1.00		1.00		1.00	
≥70 years	**3.83**	**(1.86–7.89)**	**2.16**	**(1.28–3.83)**	**2.99**	**(1.90–4.71)**	**2.96**	**(1.70–5.14)**	**2.36**	**(1.61–3.47)**	**2.63**	**(1.63–4.23)**
Gender												
Male	1.00		1.00		1.00		1.00		1.00		1.00	
Female	0.95	(0.53–1.69)	**3.35**	**(1.28–8.76)**	1.10	(0.59–2.07)	**2.14**	**(0.83–5.57)**	1.25	(0.74–2.13)	**3.72**	**(1.59–8.71)**
Cancer diagnosis												
Breast	1.00		1.00		1.00		1.00		1.00		1.00	
Colorectal	1.89	(1.18–3.02)	**4.16**	**(1.77–9.79)**	1.22	(0.74–2.03)	1.58	(0.68–3.66)	1.34	(0.87–2.05)	**2.81**	**(1.33–5.91)**
Stage												
I–II	1.00		1.00		1.00		1.00		1.00		1.00	
III–IV	1.74	(1.06–2.83)	1.29	(0.64–2.58)	1.56	(0.92–2.62)	1.41	(0.71–2.78)	1.52	(0.98–2.37)	1.25	(0.70–2.23)
Chemotherapy												
No	1.00		1.00		1.00		1.00		1.00		1.00	
Yes	1.19	(0.78–1.84)	1.24	(0.67–2.31)	0.94	(0.60–1.48)	1.69	(0.90–3.18)	1.08	(0.74–1.57)	1.46	(0.88–2.42)
Katz ADL (0–6)												
Independent	1.00				1.00		1.00		1.00		1.00	
Dependent	**0.30**	**(0.18–0.52)**	**0.16**	**(0.08–0.31)**	**1.87**	**(1.20–2.91)**	1.37	(0.83–2.27)	0.72	(0.49–1.07)	**0.44**	**(0.27–0.70)**
Lawton IADL (0–5/8)												
Independent (5/8)	1.00				1.00		1.00		1.00		1.00	
Dependent (≤4/≤7)	1.69	(1.07–2.69)	1.64	(0.93–2.88)	0.92	(0.56–1.51)	0.64	(0.36–1.13)	1.12	(0.73–1.69)	0.95	(0.59–1.52)
Polypharmacy												
No (≤4)	1.00		–		1.00		1.00		1.00		1.00	
Yes (≥5)	**1.79**	**(1.08–2.96)**	**2.07**	**(1.12–3.85)**	**1.90**	**(1.14–3.17)**	**1.93**	**(1.09–3.42)**	**1.79**	**(1.14–2.82)**	**2.10**	**(1.25–3.54)**
Cognition (MMSE, 0–30)												
Normal (≥24)	1.00				1.00				1.00			
Impaired (≤23)	0.87	(0.32–2.37)			1.02	(0.40–2.62)			1.01	(0.44–2.31)		
Depressive symptoms (GDS)												
None (≤4)	1.00				1.00				1.00			
Mild or severe (≥5)	0.59	(0.26–1.36)			0.73	(0.33–1.60)			0.71	(0.31–1.37)		
Body mass index (BMI)												
Normal (20–30)	1.00		1.00		1.00				1.00			
Low (<20)	0.67	(0.23–1.97)	0.52	(0.11–2.42)	1.07	(0.60–1.90)			0.67	(0.42–1.07)		
High (>30)	**1.83**	**(1.10–3.04)**	**2.23**	**(1.25–3.97)**	1.18	(0.41–3.33)			0.66	(0.28–1.60)		
Fatigue (0–10)												
No (≤3)	1.00				1.00				1.00			
Yes (≥4)	1.21	(0.75–1.84)			1.36	(0.81–2.28)			1.12	(0.74–1.69)		
Living situation												
Alone	1.00				1.00				1.00			
Living together, institutionalized	0.75	(0.45–1.24)			1.14	(0.66–1.97)			1.05	(0.67–1.67)		
Social support												
Not available	1.00				1.00				1.00			
Available	0.93	(0.52–1.67)			0.97	(0.53–1.78)			0.88	(0.53–1.47)		
Hosmer en Lemeshow test			14.25	(p = 0.08)			12.97	(p = 0.11)			10.26	(p = 0.17)
Area under the curve			0.76	(0.71–0.81)			0.69	(0.62–0.75)			0.68	(0.63–0.73)

OR1, univariate analysis; OR2, multivariate analysis.
Significant OR's are indicated in bold.
ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination; GDS-15, Geriatric Depression Scale-15.

1.26–3.34). Similar predictors were found for ADL and IADL decline.

3.3. Sensitivity Analysis

Results changed slightly when adjusting the missing values as either a best or worst case scenario. Gender was not a significant factor when adjusting the missing values as best case scenario in all older patients, while cancer treatment was not a significant factor when adjusting the missing values as best case scenario in patients with cancer. Other results did not change (Additional Table S1, and S2).

4. Discussion

The aim of this study was to analyze the impact of age, cancer diagnosis, and treatment on FS decline in patients with cancer. In our study population, we found that FS decline was common among older patients with cancer. Almost half of the older patients with cancer reported FS decline, compared to a quarter of the younger patients with cancer. Important predictors of FS decline were cancer diagnosis and, within the patient group with cancer, higher age, female sex, colorectal cancer, and polypharmacy.

An unexpected finding in our study was that ADL dependency at baseline was a protective factor for FS decline in patients with cancer. This is in contrast with previous studies, where baseline functional dependency was a risk factor for FS decline [23]. It seems likely that part of this ADL dependency at baseline was caused by tumor-related complaints, which could have improved after specific antitumor treatment was provided or with supportive care measures such as radiotherapy for painful bone metastases or use of painkillers. Unfortunately, this data was not collected in our study. Another explanation might be a ceiling effect where ADL dependent patients are less likely to decline any further in FS.

We noted FS decline in 39.4% of the older patients with cancer who did receive chemotherapy, against 44.5% of the older patients with cancer who did not receive chemotherapy. The opposite effect was seen in younger patients with cancer, with FS decline in 17.6% of the patients who did not receive chemotherapy compared to 30.8% of patients with chemotherapy. Apparently, the older patients with cancer were

Table 3
Logistic regression analysis for ADL decline, IADL decline, and functional status (FS) decline in older cancer and older non-cancer patients over a 12-month observation period.

	ADL decline				IADL decline				Functional status decline			
	OR1	(95% CI)	OR2	(95% CI)	OR1	(95% CI)	OR2	(95% CI)	OR1	(95% CI)	OR2	(95% CI)
Age												
70–79 years	1.00		1.00		1.00		1.00		1.00		1.00	
≥80 years	**2.08**	**(1.33–3.26)**	**2.96**	**(1.67–5.25)**	**2.96**	**(1.91–4.59)**	**2.87**	**(1.63–5.05)**	**2.57**	**(1.75–3.78)**	**2.90**	**1.77–4.76)**
Gender												
Male	1.00		1.00		1.00		1.00		1.00		1.00	
Female	**2.29**	**(1.32–3.98)**	0.81	(0.45–1.45)	1.35	(0.84–2.18)	0.92	(0.52–1.62)	**1.93**	**(1.25–2.98)**	1.58	(0.95–2.64)
Cancer treatment												
No	1.00		1.00		1.00		1.00		1.00		**1.00**	
Yes	**1.85**	**(1.19–2.89)**	**2.59**	**(1.43–4.71)**	**2.13**	**(1.38–3.28)**	**2.42**	**(1.37–4.29)**	**1.98**	**(1.35–2.90)**	**1.77**	**(1.19–2.63)**
Katz ADL (0–6)												
Independent	1.00		1.00		1.00		1.00		1.00		1.00	
Dependent	**0.62**	**(0.39–0.99)**	1.52	(0.86–2.66)	**2.32**	**(1.51–3.57)**	1.55	(0.89–2.68)	1.16	(0.80–1.69)	0.67	(0.40–1.12)
Lawton IADL (0–5/8)												
Independent (5/8)	1.00		1.00		1.00		1.00		1.00		1.00	
Dependent (≤4/≤7)	**1.91**	**(1.22–2.99)**	0.60	(0.33–1.12)	1.13	(0.72–1.75)	0.61	(0.34–1.11)	1.25	(0.85–1.85)	0.82	(0.49–1.39)
Polypharmacy												
No (≤4)	1.00		1.00		1.00		1.00		**1.00**		**1.00**	
Yes (≥5)	**1.78**	**(1.15–2.78)**	**2.46**	**(1.42–4.25)**	**2.18**	**(1.42–3.35)**	**2.46**	**(1.42–4.25)**	**1.95**	**(1.35–2.85)**	**2.36**	**(1.47–3.82)**
Cognition (MMSE, 0–30)												
Normal (≥24)	1.00		1.00		1.00				1.00		1.00	
Impaired (≤23)	1.65	(0.79–3.43)	0.86	(0.35–2.12)	1.58	(0.77–3.25)			1.85	(0.97–3.52)	1.24	(0.57–2.72)
Depressive symptoms (GDS)												
None (≤4)	1.00				1.00				1.00			
Mild or severe (≥5)	1.11	(0.51–2.41)			1.80	(0.91–3.58)			1.22	(0.64–2.34)		
Body mass index (BMI)												
Normal (20–30)	1.00				1.00				1.00		1.00	
Low (<20)	0.56	(0.33–0.98)			0.80	(0.48–1.40)			0.63	(0.39–1.01)	1.41	(0.49–4.02)
High (>30)	0.47	(0.13–1.75)			1.76	(0.60–5.13)			0.89	(0.35–2.29)	1.65	(0.93–2.93)
Fatigue (0–10)												
No (≤3)	1.00		1.00		1.00		1.00		1.00		**1.00**	
Yes (≥4)	**2.30**	**(1.37–3.86)**	**2.42**	**(1.35–4.32)**	**2.52**	**(1.50–4.22)**	**2.29**	**(1.31–4.02)**	**2.21**	**(1.45–3.39)**	**2.05**	**(1.26–3.34)**
Living situation												
Alone	1.00				1.00				1.00			
Living together, institutionalized	0.99	(0.62–1.59)			1.39	(0.87–2.24)			0.94	(0.64–1.40)		
Social support												
Not available	1.00				1.00				1.00			
Available	1.19	(0.74–1.91)			1.27	(0.79–2.04)			1.30	(0.87–1.96)		
Hosmer en Lemeshow test			6.95	(p = 0.54)			5.74	(p = 0.68)			13.20	(p = 0.10)
Area under the curve			0.74	(0.69–0.80)			0.74	(0.69–0.80)			0.72	(0.67–0.78)

OR1, univariate analysis; OR2, multivariate analysis.
Significant ORs are indicated in bold.
ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination; GDS-15, Geriatric Depression Scale-15.

correctly selected for chemotherapy, and more intensive chemotherapy may have been given to the younger patients with cancer.

Ronning et al. [24] investigated the impact of surgery in 84 older patients with colorectal cancer, and found that ADL and IADL decline were present in 31% and 69% of the patients, respectively. However, conflicting results have been reported regarding the impact of chemotherapy on FS decline, with studies reporting either a negative effect or no effect on FS [9,25–28]. Differences between these studies might be explained by the small sample sizes, different measures of FS decline, and different follow-up periods, hampering comparisons. In the present analysis, we defined FS decline as ≥1 point decrease on the Katz ADL or Lawton IADL scale between baseline and 12 months FU, while most studies only use ADL decline. Further, patients were defined as IADL dependent when they were not able to perform an activity with (some) help. While this cut-off point was also used in previous studies [29], a different cut-off point for decrease in FS could be more sensitive.

Also, a shorter follow-up period could have been chosen. However, we believe that the time frame of 12 months was appropriate because FS decline is known to occur most frequently in the first year after diagnosis [11]. Moreover, one year after diagnosis and treatment, a certain degree of recovery has often occurred and the measurement of FS at this time point will more reliably represent the FS. This was also demonstrated in the study by Petrick et al. [11], which found that most FS decline occurred in the first year after cancer diagnosis. Our study also demonstrated that the older patients with cancer without chemotherapy were more often ADL dependent at baseline compared to the older patients with cancer with chemotherapy. It is therefore possible that there was a selection of healthier older patients for chemotherapy. The observation that older patients with comorbid conditions or a poor performance status are less likely to receive chemotherapy has also been reported in previous studies [30].

In our study, we also analyzed the impact of cancer diagnosis among older patients with cancer compared to control patients without cancer in the same age group, and found that cancer treatment was an important predictor of FS decline. Petrick et al. [11] also described the impact of cancer on FS decline in a large prospective cohort of patients with cancer and healthy controls. They concluded that FS decline was more profound in patients with cancer than in healthy controls. In their study, they observed that most patients with cancer experienced FS decline in the first year after cancer diagnosis, and continued to decline after one year. Besides cancer and age, important predictors of FS decline found by Petrick et al. were educational level, comorbidity, obesity, smoking, and lack of health insurance. Previous studies of FS decline in older patients with cancer found that comorbidity [11], depressive symptoms [25], IADL dependency [25], and obesity [11] were associated with FS decline. This could not be confirmed in the present study. It should be noted that lack of health insurance is non-existent in the Netherlands and was therefore not included in our analyses. Consistent

with previous studies [11,23,24], we found that age was an important predictor of FS decline in patients with cancer.

The main strengths of our study include its longitudinal design, respectable sample size, and the analysis of three different patient groups, enabling us to compare FS decline in older patients with cancer with that in younger patients with cancer and that in older patients with cancer with that in older patients without cancer. This study also has several limitations. After 12 months of follow-up, data were incomplete for 31% of patients, although this is comparable with other longitudinal cohort studies that included older patients with cancer [31]. The older and younger patients with cancer not available for analysis were more likely to have colorectal cancer than those available for analysis. This may have caused an underestimation of FS decline in our study population, because patients with colorectal cancer who were evaluable showed a higher risk of FS decline compared to patients with breast cancer [11]. Another limitation was the timing of our baseline interview. For practical reasons we included patients within a time frame of 0 to 3 months after diagnosis. In fact, some of the patients had already started treatment at the time of the baseline interview, and this could have affected their baseline health and FS. Another limitation is the lack of multiple time points to evaluate functional status, and the exclusion of non-surgical patients.

In conclusion, FS decline is common among older patients with cancer. Important overall predictors of FS decline are age and cancer diagnosis. The high percentage of FS decline in older patients with cancer underlines the need for more studies to investigate the impact of cancer treatment on FS decline in this specific group. Maintaining FS could play an important role in improving survival and quality of life and in developing a personalized treatment plan for the older patients with cancer.

Disclosures and Conflict of Interest Statements

The authors have no conflicts to report.

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Acknowledgements

The KLIMOP study was supported by the European Union / Interreg IV Grensregio Vlaanderen - Nederland (IVA-VLANED-3.46) and the Vlaamse Liga tegen Kanker (Flemish League against Cancer) (10482). The authors had complete authority over design, execution, analysis, and interpretation of the study.

We wish to thank all the participants of the KLIMOP study for their contributions. Finally, we wish to thank the research group of the KLIMOP study, the nurses and physicians for their support and advice.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jgo.2017.01.003.

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