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Health related quality of life in older patients with solid tumors and prognostic factors for decline

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ABSTRACT

Objectives: This study aims to investigate health-related quality of life (HRQOL) at baseline and at follow-up in older patients with cancer and to determine prognostic factors for HRQOL decline.
Methods: A prospective Belgian multicentre ($n = 22$) study was performed. Patients ≥70 years with a malignant tumor and abnormal G8 (≤14/17) screening tool were included. Patients underwent geriatric assessment (GA) and HRQOL evaluation with follow up at three months. Uni- and multivariate regression models were performed to determine factors associated ($p < .05$) with baseline HRQOL and HRQOL decline at follow-up.
Results: Results reflect data collected from 3673 patients. A multivariate analysis showed that younger patients, and those with poor Eastern Cooperative Oncology Group – Performance Status (ECOG-PS), specific tumor types (gastrointestinal, gynaecological and thorax) and higher stage had lower baseline HRQOL. In addition worse functional status and presence of pain, fatigue, depression and malnutrition were associated with lower baseline HRQOL.

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During treatment ($n = 2972$), improvement in HRQOL was observed in 1037 patients (35%) and a decline in 838 patients (28.2%). In multivariate analysis, stage and presence of baseline comorbidities, pain, fatigue or malnutrition were associated with HRQOL evolution.

Conclusion: Baseline HRQOL in older patients with cancer and an abnormal G8 depends on tumor and age related parameters. During follow-up, HRQOL improved in one third of patients, indicating that they may benefit from cancer treatment while one quarter demonstrated a HRQOL decline for which prognostic factors were identified.

1. Introduction

Health-related quality of life (HRQOL) is influenced both by the malignant disease and its treatment, and is thus an important parameter for physicians treating patients with cancer [1].

Evaluation of baseline and follow-up HRQOL provides knowledge of the effects of the disease and treatment on the patient's sense of well-being and may stimulate physician-patient communication, resulting in a better shared decision making [2–5]. In addition, baseline HRQOL may be prognostic for chemotherapy response and for survival [6–8].

HRQOL is an even more important endpoint for older patients with cancer [9,10]. Older patients with cancer often give preference to maintenance or improvement of HRQOL rather than an increase in survival [11,12]. As a consequence, older patients are less willing to accept severe toxicity and reduced HRQOL. In non-fit older patients with cancer this may complicate treatment decisions even more because HRQOL decreases with increased frailty [13].

Knowledge of baseline HRQOL and its evolution (i.e. improvement, maintenance, deterioration) during treatment as well as of factors influencing HRQOL is therefore essential for treatment decisions in (non-fit) older patients with cancer and may guide appropriate interventions and care. In addition, baseline HRQOL may be a possible stratification factor in studies specific to older patients with cancer in order to reduce imbalance between treatment arms.

For these reasons, the present study aims to investigate baseline and follow-up HRQOL in older patients with solid tumors and to identify prognostic clinical and geriatric characteristics for HRQOL decline.

2. Patients and Methods

2.1. Patient Population

A prospective, multicenter, observational cohort study with the main goal to investigate the adherence to geriatric recommendations based on a geriatric assessment (GA), was performed in 22 hospitals (eight academic, fourteen non-academic) in Belgium from November 2012 until February 2015 [14]. Patients 70 years and older with a solid tumor (including breast cancer, central nervous system tumors, carcinoma of unknown primary, digestive system tumors, gynaecologic tumors, head and neck tumors, musculoskeletal tumors, skin tumors, thorax tumors, and genitourinary tumors) or hematologic malignancy were included at the time a treatment decision (surgery, systemic therapy, radiotherapy, hormonal therapy, other therapy or a combination) had to be made. The study was approved by the ethical committee of all participating centers (B322201215495).

Here we present a substudy focusing on HRQOL at baseline and during follow-up in this large cohort. For this analysis, patients with hematologic tumors and ophthalmologic tumors were excluded as well as patients who were lost to follow up or deceased after three months.

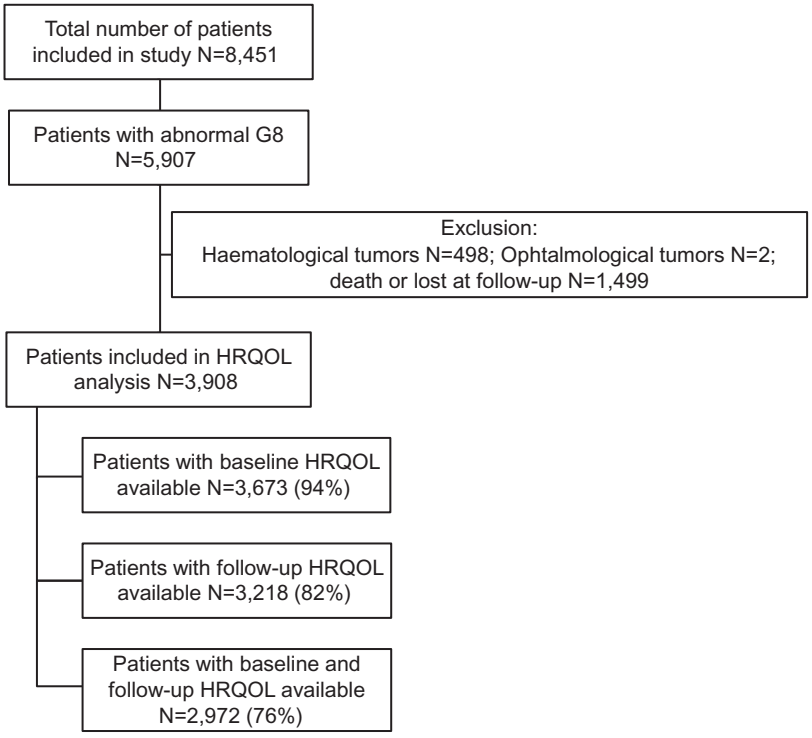

Fig. 1. Patient Flow Chart. Legend: N = Number of patients; HRQOL = Health Related Quality of Life.

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2.2. Baseline Assessment

At baseline, all patients were screened using the G8 screening tool [15,16].

In the present analysis only patients with an abnormal G8 screening (score ≤ 14/17) were included, since patients with a normal G8 were not referred for baseline GA or HRQOL assessment.

Table 1
Patient characteristics and results of geriatric assessments for the patients with baseline quality of life available ($N = 3673$) and for the patients with baseline and follow-up quality of life available ($N = 2972$).

		Patients with baseline QoL available N = 3673	Patients with baseline and follow-up QoL available N = 2972
Patient characteristics	Categories	N (%)	N (%)
Age	Median	80	79
	Standard deviation	5.84	5.76
Gender	Female	2099 (57.2)	1681 (56.6)
	Male	1574 (42.9)	1291 (43.4)
Living situation	Home with partner	1799 (49)	1515 (51)
	Home with family member	241 (6.6)	196 (6.6)
	Home alone	1345 (36.6)	1056 (35.5)
	Assisted Living Community apartment	85 (2.3)	65 (2.2)
	Institution (e.g. nursing home)	163 (4.4)	107 (3.6)
	Other	40 (1.1)	33 (1.1)
Tumor	Digestive system	1286 (35)	1063 (35.8)
	Breast	804 (21.9)	661 (22.2)
	Genitourinary system	351 (9.6)	281 (9.5)
	Thorax	353 (9.6)	289 (9.7)
	Gynaecologic	302 (8.2)	236 (7.9)
	Head and Neck	167 (4.6)	128 (4.3)
	Skin	74 (2)	57 (1.9)
	CNS	33 (0.9)	25 (0.8)
	Musculoskeletal	31 (0.8)	22 (0.7)
	CUP	28 (0.8)	20 (0.7)
	Prostate	244 (6.6)	190 (6.4)
Time of inclusion	New diagnosis	2945 (80.2)	2385 (80.3)
	Progression/relapse	728 (19.8)	587 (19.8)
Stage	Stage I	479 (13)	390 (13.1)
	Stage II	778 (21.2)	645 (21.7)
	Stage III	900 (34.5)	729 (24.5)
	Stage IV	1223 (33.3)	993 (33.4)
	Missing	293 (9)	215 (7.2)
ECOG-PS	0–1	2126 (57.9)	1803 (60.7)
	≥2	1547 (42.1)	1169 (39.3)
Chemotherapy	No	2977 (81.05)	2384 (80.22)
	Yes	696 (18.95)	588 (19,78)
Age-related parameters	Operationalization	N(%)	N (%)
Functional status:	Independent: score = 6	1625 (44.2)	1388 (46.7)
ADL (6–24)	Dependent: score ≥ 7	2048 (55.8)	1584 (53.3)
Functional status:	Independent: score 5(male) or 8(female)	1290 (35.1)	1095 (36.8)
IADL (0–5 male/0–8 female)	Dependent: score < 5 or 8	2371 (64.6)	1868 (62.9)
	Missing	12 (0.3)	9 (0.3)
Falls	No falls	2366 (64.4)	1965 (66.1)
	Presence of falls (≥1)	1301 (35.4)	1003 (33.8
	Missing	6 (0.2)	4 (0.1)
Pain (VAS 0–10)	No pain (0/10)	1812 (49.3)	1455 (49)
	Presence of pain (≥1/10)	1850 (50.4)	1003 (50.8)
	Missing	11 (0.3)	4 (0.1)
Fatigue (VAS 0–10)	No fatigue (0/10)	940 (25.6)	774 (26)
	Presence of fatigue (≥1/10)	2701 (73.5)	2177 (73.3)
	Missing	32 (0.9)	8 (0.3)
Cognition:	Normal cognition: score ≥ 24	2735 (74.5)	2288 (77)
MMSE (0−30)	Cognitive impairment: score < 24	654 (17.8)	471 (15.9)
	Missing	284 (7.7)	213 (7.2)
Depression:	Not at risk for depression: score < 5	2319 (63.1)	1921 (64.6)
GDS (0–15)	At risk for depression: score ≥ 5	1207 (32.9)	950 (32)
	Missing	147 (4)	101 (3.4)
Nutrition:	Normal nutritional status: score ≥ 12	769 (20.9)	650 (21.9)
MNA-SF (0–14)	Risk for malnutrition <12	2907 (79.2)	2322 (79.1)
	Missing	3 (0.1)	0 (0)
Comorbidity:	No comorbidity: score 0	1007 (27.4)	825 (27.8)
CCI (0–37)	Presence of comorbidity: score ≥ 1	2640 (71.9)	2134 (71.8)
	Missing	26 (0.7)	13 (0.4)
Polypharmacy	Number 0–4	1413 (38.5)	1141 (38.4)
	Number ≥ 5	2210 (60.2)	1796 (60.4)
	Missing	50 (1.4)	35 (1.2)

Legend: ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale; MNA-SF: Mini Nutritional Assessment- Screening Form; CCI: Charlson Comorbidity Index;

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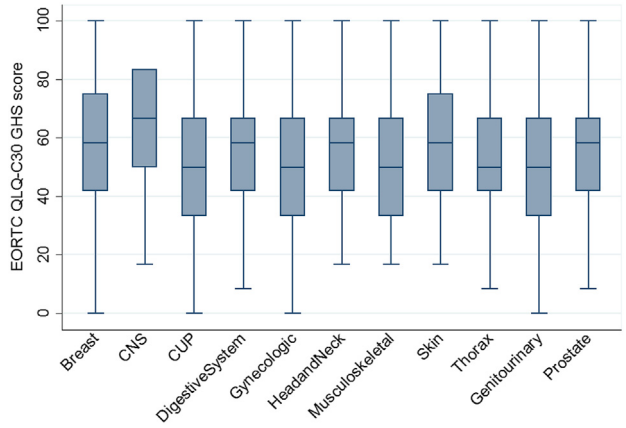

Fig. 2. Boxplots showing the baseline median, interquartile range (25–75 percentiles) and minimum and maximum of the EORTC QLQ-C30 GHS score by tumor type. Legend: EORTC QLQ-C30 GHS = Eoropean Organization of Research and Treatment of Cancer Quality of Life Questionnaire-C30 Global Health Score; CNS = Central Nervous System; CUP: Carcinoma of Unknown Primary.

All included patients underwent a baseline GA, as previously described [14,17]. This GA included following geriatric domains: functional status by activities of daily living (ADL) [18] (independent score 6 versus dependent score ≥ 7) and instrumental activities of daily living (iADL) [19] (independent score 5/5 in males and 8/8 in females versus dependent score < 5 in males and < 8 in females), the presence of falls in the past year (no falls versus at least one fall), the presence of pain and fatigue using a visual analogue score (VAS) (no pains versus presence of pain VAS ≥1/10 and nog fatigue versus presence of fatigue VAS ≥1/10), cognition by mini mental state examination (MMSE) [20] (normal cognition score ≥ 24/30 versus cognitive decline score < 24/30), mental status using the geriatric depression scale (GDS-15) [21] (no risk for depression score < 5/15 versus risk for depression score ≥ 5/15), nutritional status using the mini nutritional assessment – short form (MNA-SF) [22–24] (no risk for malnutrition score ≥ 12/14 versus risk for malnutrition score < 12/14), comorbidities using the Charlson Comorbidity index [25] (no comorbidities versus comorbidities score ≥ 1/37) and polypharmacy by the number of drugs taken the week before inclusion (number of drugs <5 versus ≥5) [26].

In addition a HRQOL evaluation was performed using the European Organization for Research and Treatment Quality of Life Questionnaire core 30 (EORTC QLQ-C30) Global Health Status Scale (GHS). For the present study, the two general questions 29 and 30 were selected: "How would you rate your overall health during the past week?" and "How would you rate your overall quality of life during the past week?". Patients answer these two questions by means of seven-point Likert scales and the two scores are combined to define the GHS. The GHS score is linearly transformed to a 0–100 score to facilitate statistical interpretation. A higher HRQOL is reported by a higher GHS score. The GHS scale is one of the most frequently used QLQ-C30 subscales and administration of this instrument has been used as the primary endpoint in various trials [27,28].

Classical patient characteristics such as age and gender as well as oncologic parameters such as Eastern Cooperative Oncology Group - Performance Status (ECOG-PS), tumor characteristics (type and stage), and treatment details (surgery / systemic therapy/ radiotherapy / hormonal therapy / other therapy/ combination) were recorded.

3. Follow-Up Evaluation

Three months (+/− two weeks) after the baseline assessment, HRQOL was reassessed using the same questions.

3.1. Statistical Analysis

Unadjusted median scores and interquartiles (25th and 75th percentiles) of the baseline HRQOL score were plotted by tumor group.

To assess statistically the association between baseline HRQOL score and different patient, tumor and geriatric characteristics, uni- and multivariate normal regression models were applied. The final multivariate model was achieved in two steps. First, at univariate level, the association between baseline HRQOL and patient, tumor and geriatric characteristics was assessed for each patient. With regards to treatment, patients receiving chemotherapy alone were compared to patients not receiving chemotherapy treatment or receiving a combination of treatments. Those variables statistically significantly at univariate level ($p \leq .05$) were included in the final multivariate model. Results were reported with the least mean square difference (ß), its 95% confidence interval (CI) and the p-value. A HRQOL difference of ten points or more between different subgroups was considered clinical significant [27].

HRQOL change was defined as the difference between follow-up and baseline HRQOL score and categorized in three groups; HRQOL decline (<−10), HRQOL improvement (>10) and no HRQOL change over time (≥ − 10 and ≤ 10). Osoba et al. defined a threshold of ten points to categorize patients as clinically improved or deteriorated on any of the EORTC HRQOL scales [29]. A dummy variable was created to categorize patients that reported a HRQOL decline versus those patients that did not report a HRQOL decline; i.e. improvement and no change.

To assess statistically the association between HRQOL decline versus no HRQOL decline (improvement and no change) and patient, tumor and geriatric characteristics, uni- and multivariate logistic regression models were applied. The final multivariate model was achieved in two steps. First, at univariate model, HRQOL decline versus no decline was assessed for each patient characteristic separately. Those variables statistically significant at univariate level ($p \leq .05$) were included in the final multivariate model. Results were reported with the odds ratio (OR), its 95% confidence interval (CI) and the p-value. OR determine whether a particular exposure is a risk factor for an outcome (i.e. QOL decline or not) [30]. If an OR = 1 then exposure does not affect odds of outcome; OR > 1 then exposure associated with higher odds of outcome; OR < 1 then exposure associated with lower odds of outcome. The level of significance was set at $p = .05$.

For the regression modeling, missing patient values were imputed using chained equations (MICE) [31]. This method is based on fully conditional specification (FCS) where each incomplete variable is imputed by a separate model. All analysis were performed with Stata.

4. Results

4.1. Patient and Tumor Characteristics

The patient flow is presented in Fig. 1

Of the 8451 patients included in this study, 5907 had an abnormal G8 (≤14/17). For the present HRQOL analysis we excluded patients with a hematologic malignancy ($n = 498$), patients with ophthalmologic tumors ($n = 2$) and patients who were deceased or lost to follow-up after three months ($n = 1499$).

Of the remaining 3908 patients baseline HRQOL was available for 3673 patients (94%) and both baseline and follow-up HRQOL were available for 2972 (76%).

Patient characteristics and GA results are presented in Table 1

4.2. Baseline HRQOL

At baseline, the highest median HRQOL was observed in malignant tumors of the skin. The skin tumors ($n = 57$) were stage IV in approximately 33% ($n = 19$) and consisted of 36 melanoma (63%), 20 basal cell carcinoma (35%) and one Merkel cell carcinoma (2%). The lowest in

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tumors of the thorax, the musculoskeletal system, the genitourinary system, the gynaecological system and carcinomas of unknown primary (CUP). Median HRQOL and interquartile range (25–75 percentiles) as well as minimum and maximum by tumor type are presented in Fig. 2.

Table 2 presents the results of a uni- and multivariate analysis assessing the statistical significant correlation between baseline HRQOL and patient, tumor and geriatric characteristics.

In the univariate analysis, statistical significant associations ($p < .05$) were observed between baseline HRQOL and different baseline patient and tumor characteristics such as age, ECOG-PS, tumor type, time of inclusion (new diagnosis versus progression/relapse), stage and planned chemotherapy treatment, Moreover, all geriatric characteristics except comorbidity were significantly associated with baseline HRQOL.

In the multivariate analysis assessing the baseline correlation, increasing age was associated with a higher HRQOL ($p < .001$). Patients with a bad ECOG-PS (≥2) had a significantly worse HRQOL compared to patients with a good ECOG-PS (0 or 1) ($p < .001$). Patients with gastrointestinal tumors, gynaecological tumors and tumors of the thorax had significantly lower HRQOL compared to older patients with breast cancer (p-values 0.030; 0.017 and 0.017 respectively). In addition patients with higher stage had worse baseline HRQOL when compared to patients with stage I ($p = .004$, 0.042 and 0.004 for stage II, III and IV respectively). Finally a significantly lower HRQOL was observed in

Table 2
Uni- and multivariate analysis to investigate the association between patient characteristics and geriatric domains and baseline quality of life.

Variables	Categories	Number of patients	Univariate analysis			Multivariate analysis		
		N (%)	β	CI	p-value	β	CI	p-value
Patient and tumor characteristics								
Age		2972 (100)	0.34	0.22;0.46	*<0.001*	0.31	0.18;0.44	*<0.001*
Gender	Female	1681 (56.6)						
	Male	1291 (43.4)	0.29	−0.17;0.76	0.696			
Living Situation	Home with partner	1516 (51.0)						
	Home with family member	196 (6.6)	−0.57	−3.53;2.39	0.705			
	Home alone	1055 (35.5)	−0.50	−2.06;1.06	0.529			
	Service flat	65 (2.2)	1.82	−2.89;6.65	0.456			
	Institution	108 (3.7)	1.86	−5.37;1.63	0.295			
	Other	32 (1.1)	1.88	−5.09;8.86	0.596			
ECOG-PS	0–1	1803 (60.7)						
	≥2	1169 (39.3)	−5.39	−6.01;-4.79	*<0.001*	−4.49	−5.29;-3.69	*<0.001*
Tumor type	Breast	660 (22.2)						
	CNS	24 (0.8)	1.13	−7.77;10.05	0.802	7.80	−0.21;15.81	0.056
	CUP	21 (0.7)	−8.69	−18.61;1.23	0.086	−7.75	−16.62;1.12	0.087
	Digestive system	1064 (35.8)	−1.91	−4.08;0.25	0.083	−2.64	−4.68;-0.60	0.011
	Gynaecologic	235 (7.9)	−4.32	−7.65;-1.01	0.011	−4.31	−7.29;-1.32	0.005
	Head and neck	128 (4.3)	−1.27	−5.49;2.94	0.554	−0.58	−4.35;3.19	0.764
	Musculoskeletal	24 (0.8)	−8.23	−17.71;1.24	0.089	−5.61	−14.03;2.82	0.192
	Skin	56 (1.9)	1.50	−4.53;7.54	0.625	0.83	−4.53;6.20	0.760
	Thorax	288 (9.7)	−4.48	−7.56;-1.39	0.004	−4.03	−6.89;-1.15	0.006
	Genitourinary	282 (9.5)	−2.25	−5.36;0.86	0.156	−2.05	−4.82;0.73	0.149
	Prostate	190 (6.4)	−2.15	−5.75;1.44	0.241	−1.66	−4.99;1.66	0.327
Time of inclusion	New diagnosis	2385 (80.3)						
	Progression/relapse	587 (19.7)	−3.37	−5.17;-1.59	*<0.001*	0.51	−1.54;2.58	0.625
Stage	Stage I	422 (14.2)						
	Stage II	692 (23.3)	−3.43	−5.94;-0.92	*0.007*	−3.11	−5.60;-0.63	**0.014**
	Stage III	786 (26.5)	−3.12	−5.51;-0.71	*0.011*	−1.55	−4.02;0.91	0.217
	Stage IV	1072 (36.1)	−7.22	−9.54;-4.09	*<0.001*	−3.32	−5.89;-0.76	**0.001**
Chemotherapy	No	2384 (80.2)						
	Yes	588 (19.2)	−3.99	−5.82;-2.16	*<0.001*	−1.38	−3.44;0.66	0.185
Age related parameters								
Funtional status: ADL	Independent	1388 (46.7)						
	Dependent	1584 (53.3)	−6.38	−7.80;-4.95	*<0.001*	0.23	−1.43;1.94	0.782
Functional status:	Independent	1094 (36.8)						
IADL	Dependent	1878 (63.2)	−7.71	−9.19;-6.23	*<0.001*	−2.20	−3.89;−0.50	*0.011*
Falls	No falls	1967 (66.2)						
	Presence of falls	1005 (33.8)	−3.74	−5.23;-2.25	*<0.001*	−0.92	−2.48;0.65	0.249
Pain: VAS	No pain	1459 (49.1)						
	Presence of pain	1513 (50.9)	−9.56	−10.96;-8.16	*<0.001*	−5.35	−6.84;−3.85	*<0.001*
Fatigue: VAS	No fatigue	*782 (26.3)*						
	Presence of fatigue	*2190 (73.7)*	***−12.76***	−14.35;-11.17	*<0.001*	−7.54	−9.24;-5.84	*<0.001*
Cognition: MMSE	Normal cognition	1988 (66.9)						
	Cognitive decline	984 (33.1)	−2.86	−4.71;-1.03	*0.002*	1.04	−1.01;3.08	0.321
Depression: GDS	Not at risk for depression	1988 (66.9)						
	At risk for depression	984 (33.1)	***−13.16***	−14.63;-11.70	*<0.001*	−8.04	−9.66;-6.41	*<0.001*
Nutrition: MNA-SF	Normal nutritional status	651 (21.9)						
	Risk for malnutrition	2321 (78.1)	***−10.19***	−11.92;-8.46	*<0.001*	−4.93	−6.73;0.69	*<0.001*
Comorbidity: CCI	No comorbidity	829 (27.9)						
	Presence of comorbidity	2143 (72.1)	1.09	−0.50;2.69	0.177			
Polypharmacy	Number 0–4	1156 (38.9)						
	Number ≥ 5	1816 (61.1)	−3.63	−5.09;-2.15	*<0.001*	−0.83	−3.44;0.66	0.284

Legend: β: least mean square difference; CI: confidence Interval; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; VAS: Visual Analogue Score: MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale; MNA-SF: Mini Nutritional Assessment- Screening Form; CCI: Charlson Comorbidity Index;
Values in italique indicate statistical significant p-value.
Values in bold italique indicate clinical significant difference in quality of life.

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patients with a dependency on IADL ($p = .006$), with presence of pain ($p < .001$), fatigue ($p < .001$) or depression (<0.001) and with malnutrition ($p < .001$). However, no clinical significant differences (>10 points) were observed for any of the tumor or age related parameters.

4.3. HRQOL at Follow-Up

At follow-up, HRQOL improved with ≥10 points in 1037/2972 patients (35%) with a mean improvement of 29.75 (CI 28.9; 30.6). HRQOL declined with ≥10 points in 838/2972 patients (28,2%) with a mean decline of 29.4 (CI -30.4;-28.4). Patients with tumors of the central nervous system (CNS) experienced most frequently a decline in HRQOL (40%). A HRQOL improvement was observed most frequently for older patients with musculoskeletal tumors (45.5%) and carcinoma of unknown primary (45%). HRQOL change per tumor type is listed in Appendix A.

Table 3 describes the uni- and multivariate analysis to determine which patient, tumor and geriatric characteristics are prognostic for HRQOL decline.

In the multivariate analysis, the odds of experiencing a HRQOL deterioration was higher for those patients who were diagnosed with stage III carcinoma patients (28%: $p = .025$) compared to those patients who were diagnosed with stage I carcinoma at baseline. The odds of experiencing a HRQOL deterioration during treatment was lower for those patients who reported pain (22%; $p = .016$), fatigue (38%: $p = .001$), malnutrition (22%: $p = .044$) at baseline compared to those

Table 3
Uni- and multi variate analysis to determine prognostic socio-demographic, clinical and geriatric factors for quality of life decline as defined by the EORTC QLQ-C30 Global Health Scale.

Variables	Categories	Number of patients	Univariate analysis			Multivariate analysis		
		N (%)	OR	CI	*p*-value	OR	CI	p-value
Patient characteristics								
Age		2972 (100)	1.01	0.99;1.02	0.558			
Gender	Female	1681 (56.6)	reference		0.994			
	Male	1291 (43.4)	1.01	0.83;1.14				
Living Situation	Home with partner	1516 (51.0)	reference					
	Home with family member	196 (6.6)	1.04	0.69;1.31	0.814			
	Home alone	1055 (35.5)	1.04	0.85;1.19	0.681			
	Service flat	65 (2.2)	1.04	0.48;1.43	0.901			
	Institution	108 (3.7)	1.18	0.81;1.43	0.306			
	Other	32 (1.1)	0.46	0.26;1.35	0.309			
ECOG-PS	0–1	1803 (60.7)	reference		0.445			
	≥2	1169 (39.3)	0.94	0.26;1.09				
Tumor type	Breast	660 (22.2)	reference	0.26;1.37				
	CNS	24 (0.8)	0.61	0.53;4.88	0.229			
	CUP	21 (0.7)	1.61	0.85;1.32	0.398			
	Digestive system	1064 (35.8)	1.06	0.84;1.66	0.596			
	Gynaecologic	235 (7.9)	1.18	0.44;1.26	0.329			
	Head and neck	128 (4.3)	0.65	0.61;5.43	0.162			
	Musculoskeletal	24 (0.8)	1.81	0.48;1.56	0.286			
	Skin	56 (1.9)	0.87	0.73;1.34	0.651			
	Thorax	288 (9.7)	0.98	0.73;1.34	0.920			
	Genitourinary	282 (9.5)	0.99	0.89;1.89	0.980			
	Prostate	190 (6.4)	1.29		0.170			
Time of inclusion	New diagnosis	2385 (80.3)	reference					
	Progression/relapse	587 (19.7)	0.93	0.70;1.12	0.462			
Stage	Stage I	422 (14.2)	reference			reference		
	Stage II	692 (23.3)	1.12	0.84;1.33	0.369	1.11	0.82;1.32	0.453
	Stage III	786 (26.5)	1.29	1.07;1.45	*0.013*	1.28	1.04;1.45	*0.025*
	Stage IV	1072 (36.1)	1.18	0.94;1.37	0.126	1.18	0.89;1.38	0.212
Chemotherapy	No	2384 (80.2)	reference					
	Yes	588 (19.2)	0.97	0.75;1.15	0.750			
Geriatric domains								
Functional status: ADL	Independent	1388 (46.7)	reference					
	Dependent	1584 (53.3)	0.96	0.78;1.10	0.608			
Functional status:	Independent	1094 (36.8)	reference					
IADL	Dependent	1878 (63.2)	0.98	0.81;1.14	0.833			
Falls	No falls	1967 (66.2)	reference					
	Presence of falls	1005 (33.8)	1.16	0.99;1.29	0.054			
Pain: VAS	No pain	1459 (49.1)	reference			reference		
	Presence of pain	1513 (50.9)	0.69	0.46;0.88	*0.001*	0.78	0.57;0.96	*0.016*
Fatigue: VAS	No fatigue	782 (26.3)	reference			reference		
	Presence of fatigue	2190 (73.7)	0.55	0.27;0.78	*<0.001*	0.62	0.35;0.84	*0.001*
Cognition: MMSE	Normal cognition	1988 (66.9)	reference					
	Cognitive decline	984 (33.1)	1.17	0.99;1.32	0.062			
Depression: GDS	Not at risk for depression	1988 (66.9)	reference					
	At risk for depression	984 (33.1)	0.84	0.63;1.02	0.086			
Nutrition: MNA-SF	Normal nutritional status	651 (21.9)	reference			reference		
	Risk for malnutrition	2321 (78.1)	0.78	0.54;0.98	*0.029*	0.78	0.54;0.99	*0.044*
Comorbidity: CCI	No comorbidity	829 (27.9)	reference			reference		
	Presence of comorbidity	2143 (72.1)	1.17	1.03;1.31	*0.024*	1.17	1.01;1.30	*0.043*
Polypharmacy	Number 0–4	1156 (38.9)	reference					
	Number ≥ 5	1816 (61.1)	0.96	0.79;1.12	0.643			

Legend: OR: Odds Ratio; CI: confidence Interval; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; VAS: Visual Analogue Score: MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale; MNA-SF: Mini Nutritional Assessment- Screening Form; CCI: Charlson Comorbidity Index;
Values in italique indicate statistical significant p-value.

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patients who reported no pain, no fatigue or malnutrition at baseline. The odds of experiencing a HRQOL deterioration during treatment was higher for those patients who reported at baseline presence of comorbidity (17%; $p = .043$) compared to those patients who did not experience comorbidities at baseline.

5. Discussion

This Belgian prospective study is, to our knowledge, the largest to investigate HRQOL in older patients with solid tumors, who have an abnormal G8 screening tool.

In a multivariate analysis of this study, baseline HRQOL was influenced by patient characteristics such as age and ECOG-PS, tumor characteristics such as type and stage and age related characteristics such as functional status, pain, fatigue, mental status and nutritional status. The findings of our study confirm previous findings in smaller studies where performance status, tumor type, functional status, pain, fatigue and depression were prognostic for baseline HRQOL [32–38]. The association between nutritional status and HRQOL has also been reported in the general older population and in a non small cell lung cancer population [39,40]. Interestingly, in our large study.

HRQOL increased with increasing age, which can be explained by some of the oldest patients reporting an extremely good HRQOL. The phenomenon of older patients reporting very good HRQOL has been observed previously in a non-cancer population [41] and could be explained by adaptation which leads to a change of the personal goals and standards [42]. Additionally our study could not confirm the relationship between comorbidity and baseline HRQOL which was reported previously in two smaller studies [35,36]. This may be explained by the fact that the Charlson Comorbidity Index is a very objective measure of comorbidity and that subjective assessments of comorbidity by means of self-reported disease burden have been shown to correlate more strongly with HRQOL [43].

At three months follow-up, our study observed a clinical improvement (>10) in HRQOL in one third of older patients with cancer, which was consistent with the observations of Puts et al. at 12 months follow-up [44]. In addition Ronning et al. observed significant improvement in HRQOL at three months after surgery for colorectal cancer, also in the subgroup of frail patients according to GA [45]. We can therefore conclude that a substantial proportion of older patients with cancer demonstrate an improvement in HRQOL during cancer treatment. This is an important observation both for treating physicians and for older patients with cancer when discussing treatment options. Even if the survival benefit is low for certain older patients, an improvement in HRQOL can be considered as a reason to propose a certain treatment modality.

On the other hand, one quarter of older patients with cancer demonstrate a decline in HRQOL during cancer treatment in our study and in the studies of Puts et al. and Esbensen et al. [44,46] In order to identify patients at risk for such a HRQOL decline it is important to identify prognostic factors.

In the study by Puts et al., none of the sociodemographic, health or functional status variables were associated with decline in QOL during the first year after diagnosis [44]. In our study patients experiencing pain, fatigue or malnutrition at baseline demonstrated a significant lower risk of HRQOL decline in multivariate analysis. This is certainly reassuring since these patients have a lower baseline HRQOL. A possible explanation for this observation, may be that treatment of the cancer may have resulted in an improvement or resolution of these complaints. Ebensen et al. identified functional status by means of 'contact with district nurse at baseline' and 'need more help in daily living at baseline and mental status by means of 'low level at hope' as prognostic for HRQOL decline at six months [45]. In our larger study, functional status by means of ADL and IADL and mental status by means of GDS-15 were not prognostic for HRQOL decline at three months.

Finally, our study demonstrated that patient comorbidities at baseline had a higher risk of HRQOL decline than patients with no comorbidities, although there was no significant difference at baseline between these two groups. This observation indicates that patients with comorbidities should be followed with extreme caution during follow-up.

Our study has several limitations. First of all we included only patients with an abnormal G8, which is not a perfect screening tool (sensitivity 65–92%) to identify unfit patients according to CGA [16]. On the other hand, this may also be considered a strength of our study, since we focus on those patients that are potentially at the highest risk of HRQOL decline. In addition the G8 on itself has shown to be predictive for HRQOL-adjusted survival in older patients with head and neck cancer [47]. Secondly, we excluded patients with hematologic malignancies because they were considered as a different entity. In addition we excluded patients who had died or were lost to follow-up at three months. These may have been some of the frailest patients, but on the other hand a life expectancy of three months is often regarded necessary to consider treatment for cancer. Thirdly, the population in this study is heterogeneous, but this may also be a strength since our results are applicable to a large population of older patients with cancer. Finally the follow-up of three months is relatively short. We therefore do not have information of the evolution of HRQOL at the long term, which may reflect the recuperation of older patients after for example an adjuvant treatment. On the other hand, this short follow-up may also be considered as a strength since it shows that anticancer treatment may very quickly improve HRQOL in a substantial number of patients.

In conclusion, the results of this large Belgian study demonstrate that baseline HRQOL is influenced by different tumor, patient and geriatric characteristics and may therefore be an interesting stratification factor for further studies in older patients with cancer. An important subset of older patients with cancer and an abnormal G8 screening result reported an improvement of HRQOL at follow-up. Since this is an important end point for older patients with cancer, treatment decisions should not be based on age or the presence of an abnormal screening tool. We also identified the presence of comorbidities as a prognostic factor for HRQOL decline at follow-up. Therefore, we encourage integrating conversations about comorbidities in the treatment discussion with these patients.

Author Contribution List

Conception and design: LDC, CQ, CK, HW
Data collection: all authors
Analysis and interpretation of data: LDC, CQ, CK
Manuscript writing: LDC
Approval of final manuscript: all authors

Conflict of Interest Statement

The authors declare no conflict of interest

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2019.03.018.

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