Clinical Oncology 33 (2021) e203–e210

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Impaired Geriatric 8 Score is Associated with Worse Survival after Radiotherapy in Older Patients with Cancer

J.G. Middelburg [*], R.A. Middelburg [†‡], M. van Zwienen [*], M.E. Mast [§], A. Bhawanie [¶], J.J. Jobsen [¶], T. Rozema [‖], H. Maas [**], E.D. Geijsen [††], A.H. van der Leest [‡‡], D.H.J.G. van den Bongard [§§], J. van Loon [¶¶], T. Budiharto [‖‖], M.J. Aarts [***], C.H.J. Terhaard [§§], H. Struikmans [§] On Behalf of the LPRO (Dutch National Organization for Radiotherapy in the Elderly)

[*] *Erasmus Medical Center, Radiotherapy, Rotterdam, the Netherlands*
[†] *Sanquin Research, Center for Clinical Transfusion Research, Leiden, the Netherlands*
[‡] *Leiden University Medical Center, Department of Clinical Epidemiology, Leiden, the Netherlands*
[§] *Haaglanden Medical Center, Department of Radiotherapy, The Hague, the Netherlands*
[¶] *Medisch Spectrum Twente, Radiation Oncology, Enschede, the Netherlands*
[‖] *Institute Verbeeten, Radiotherapy, Tilburg, the Netherlands*
[**] *Elisabeth-Tweesteden Hospital, Department of Geriatric Medicine, Tilburg, the Netherlands*
[††] *Academic Medical Center, Radiotherapy, Amsterdam, the Netherlands*
[‡‡] *University Medical Center Groningen, Radiotherapy, Groningen, the Netherlands*
[§§] *University Medical Centre Utrecht, Department of Radiotherapy, Utrecht, the Netherlands*
[¶¶] *Maastricht University Medical Center, GROW-School for Oncology and Developmental Biology, Department of Radiation Oncology (Maastro Clinic), Maastricht, the Netherlands*
[‖‖] *Catharina Ziekenhuis, Department of Radiotherapy, Eindhoven, the Netherlands*
[***] *Netherlands Comprehensive Cancer Organization IKNL, Netherlands Cancer Registry, Utrecht, the Netherlands*

Received 25 April 2020; received in revised form 11 August 2020; accepted 4 September 2020

Abstract

Aims: To investigate whether the Geriatric 8 (G8) score and the Timed Get Up and Go Test (TGUGT), together with clinical and demographic patient characteristics, are associated with survival and late toxicity after (chemo)radiation therapy, administered with curative intent in older patients with cancer.
Materials and methods: Four hundred and two patients aged ≥65 years (median age 72 years, range 65–96 years), diagnosed with either breast, non-small cell lung, prostate, head and neck, rectal or oesophageal cancer, and referred for curative (chemo)radiation therapy, took part in a multicentre prospective cohort study in eight radiotherapy centres in the Netherlands. The G8 and TGUGT scores were assessed before starting treatment. Other potential predictors and late toxicity were also recorded. Survival status and date of death, if applicable, were ascertained at the Dutch national death registry.
Results: After 2.5 years, the overall survival was 83%. Survival was 87% for patients with high G8 scores and 55% for patients with low G8 scores (Log-rank *P* value < 0.0001). Survival was 77% for patients with good TGUGT results and 50% for patients with poor TGUGT results (Log-rank *P* value < 0.001). In multivariable analysis, in addition to age and type of primary tumour, the association of the G8 score with overall survival remained, with a hazard ratio of 2.1 (95% confidence interval 1.2–3.8) for low versus high scores.
Conclusions: G8 was associated with overall survival in older patients with cancer irradiated with curative intent. This association was independent of the predictive value of age and primary tumour.

Key words: Cancer; elderly; G8; radiotherapy; survival; TGUGT

Author for correspondence: J.G. Middelburg, Erasmus Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. Tel.: +31-649656674.
E-mail address: j.g.middelburg@gmail.com (J.G. Middelburg).

https://doi.org/10.1016/j.clon.2020.09.002

Introduction

Radiotherapy treatment guidelines are preferably based on evidence obtained from the results of clinical trials. This could pose a problem for older patients with cancer, because they are underrepresented in clinical trials [1]. Half of patients with cancer are 70 years or older and the proportion of older patients among patients with cancer is still increasing [2]. Moreover, we know that older patients differ from younger patients because they experience comorbidities more often. Hence, they are at a higher risk of being frail. Frailty implies that even a minor stressor can have major negative implications on physical, psychological and social domains [3,4]. Frailty places patients at greater risk of adverse health outcomes. (Chemo)radiotherapy may lead to major stressors and could, therefore, be less suitable for frail, older patients with cancer. Frailty may have various dimensions and patients sensitive to one stressor may be less sensitive to another. Therefore, it remains unclear whether a general measure of frailty will accurately predict for outcomes after radiotherapy.

In clinical practice we need to find ways to distinguish older patients with cancer who will respond to radiotherapy from those who will not, as frail older patients may not fully recover from radiotherapy-induced toxicity. This is especially relevant in radiotherapy given with curative intent, where we tend to accept more acute toxicity. This acute toxicity will immediately reduce quality of life, which is only acceptable if patients will fully recover and have a sufficiently long life expectancy. For frail patients, neither might be true. Therefore, it is very important to identify frail patients before the start of radiotherapy with curative intent. Unfortunately, little is known about the presence (or absence) of frailty in radiotherapy in general and frailty testing before radiotherapy with curative intent in particular. A standard clinical assessment will provide only a very limited and subjective insight into the frailty status of the patient. Currently, it is this standard clinical assessment that is used to guide treatment decisions. There are a number of frailty tests available. We decided to use the following two frailty screening tests in our study.

The first is Geriatric 8 (G8). G8 is a short screening tool developed to identify frail patients who can benefit from a full geriatric assessment [5]. It has also been validated in older patients with cancer [6,7]. It consists of eight questions and takes about 5 min to complete [8]. Patients with a total score of 14 or less are considered frail and a full geriatric assessment is recommended [9].

However, apart from its proven value to identify patients who will benefit from a full geriatric assessment, G8 itself may also have a directly relevant predictive value for patient outcomes after radiotherapy with curative intent. Even in patients in whom a full geriatric assessment may not yet be indicated, G8 might still predict poor outcomes. In a previous study, multivariable analysis showed that patients with cancer with a low G8 score had a significantly shorter overall survival [10]. However, previous studies did not specifically focus on older patients irradiated with curative intent. In the heterogenous population of those studies, a low G8 score could be a more general marker for a poor prognosis (i.e. patients receiving radiotherapy with palliative intent) [10]. Patients treated with curative intent have a relatively favourable prognosis. In this more homogenous population, distinguishing those with a slightly less favourable prognosis is exceptionally challenging.

The second frailty screening test we used is the Timed Get Up and Go Test (TGUGT). It is a physical performance test to quantify mobility as a measure of frailty [11]. A poor TGUGT score was associated with increased 1-year mortality in patients with cancer [12]. Furthermore, gait speed, another physical performance measure, predicts early death, disability, falls and hospitalisations in older patients with cancer [13].

We have previously reported that G8 was univariably associated with acute toxicity, in older patients with six different types of cancer, irradiated with curative intent. However, in multivariable analyses, neither G8 nor the TGUGT was associated with acute toxicity or non-compliance [14].

Here we report the results of 2.5 years of follow-up for this cohort of older patients with cancer irradiated with curative intent, to investigate whether G8, TGUGT and clinical and demographic patient characteristics were associated with serious late (radiotherapy-related) toxicity and overall survival.

Materials and Methods

Patients

Consecutive patients aged $\geq$65 years, diagnosed with either breast cancer, non-small cell lung cancer (NSCLC; except those treated with stereotactic radiotherapy), prostate cancer, head or neck cancer, rectal cancer or oesophageal cancer, who were referred for radiotherapy with curative treatment (primary radiotherapy, postoperative radiotherapy or chemoradiotherapy), and had not undergone prior radiotherapy, were prospectively recruited from April 2015 until the end of October 2015, in eight radiotherapy centres in the Netherlands. G8 and TGUGT scores were assessed before the start of radiotherapy and G8 was reassessed after 2 years of follow-up. The test results did not influence treatment decisions. All radiotherapy with curative intent was carried out as it was planned before performing G8 and the TGUGT. The test results were used for research purposes only, to assess potential relevance for clinical decision making in the future, but not during this study.

The study protocol was approved by the appropriate institutional review boards (Breda, Rotterdam and METC Zuid West Holland). These review boards waived the need for written informed consent, because routinely collected data were used.

Data Collection and Assessments

The data were prospectively recorded through an online clinical report form on a website of the Netherlands Comprehensive Cancer Organization (IKNL). Recorded variables were: age at inclusion, type of primary tumour, gender, comorbidities (presence or absence of diabetes mellitus, chronic obstructive pulmonary disease, hypertension, previous cancer and other comorbidities), the European Cooperative Oncology Group (ECOG)/World Health Organization (WHO) performance score [15], number of medications, perspective (i.e. patient's motivation for treatment: 0 not motivated to 10 highly motivated), pathological TN status (clinical TN status if pathological status was not available), specification of radiotherapy regimen (primary local, primary locoregional, postoperative local, postoperative locoregional, primary chemoradiotherapy, radiotherapy followed by surgery, chemoradiotherapy followed by surgery and unknown), compliance with the treatment (radiotherapy or chemoradiotherapy as planned, interruption or adjustment of the radiotherapy, interruption or adjustment of the chemotherapy, radiotherapy not completed, chemotherapy not completed, chemoradiotherapy not completed and unknown; all forms of non-compliance were aggregated into one variable in the final analyses) and the level of acute toxicity according to a modification of the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (none; grade 1: mild; grade 2: moderate; grade 3: severe or medically significant; grade 4: life-threatening consequences; grade 5: death related to adverse event, or death not related to adverse event, or unknown) [16]. The results of the TGUGT and the G8 score were recorded before the radiotherapy treatment started. All assessments and recording of variables were carried out by either radiation oncologists or (clinical or research) nurses. After 2 years of follow-up, occurrence of late ($\geq$3 months after last fraction) toxicity (according to CTCAE V4.0) was assessed and the G8 score was repeated, by telephone or during a visit to the out-patient clinic. TGUGT was not carried out during follow-up. Unlike G8 and toxicity, TGUGT could not be scored by telephone and therefore offered an insurmountable logistical challenge if patients were non-compliant for follow-up visits. Survival status and date of death, if applicable, were ascertained at the Dutch national death registry, which has a coverage of over 99%.

Timed Get Up and Go Test

TGUGT is a physical performance test to quantify mobility, as a measure of frailty. For assessing the TGUGT, patients had to stand up from an armchair and walk for 3 m, turn without touching the wall, walk back and sit down [11]. The time needed to do so was recorded. TGUGT was coded missing for patients in a wheelchair, as wheelchair dependence was unrelated to frailty.

The instruction was to walk at their normal speed. Patients were asked to practice two times. The test was repeated three times. The average of these three scores was used. The TGUGT is interpreted as follows: $\leq$10 s: normal; 11–20 s: frail; $>$20 s: needs further evaluation. For the current study, all frail patients (with a score of 11–20 s or with a score of $>$20 s) were aggregated into one group: TGUGT $>$10 s.

Geriatric 8

G8 is a geriatric screening tool that was originally designed to select older patients with cancer who could benefit from a geriatric assessment [5].

G8 consists of the seven questions from the Mini Nutritional Assessment and age. The questions from the Mini Nutritional Assessment are about food intake, weight loss, mobility, psychological status, body mass index, number of medications and self-perception of health. G8 provides a numerical score with a maximum score of 17 (no impairment) and a minimum of 0 (heavily impaired). A score $\leq$14 is considered a marker for frailty [5].

Statistical Analyses

Descriptive statistics were reported. The unadjusted association of baseline G8 scores with late toxicity grade $\geq$3 was analysed using the Fisher exact test. These results were reported as risk differences with corresponding 95% confidence intervals and *P* values. To show unadjusted differences in overall survival between different subgroups, life table techniques were applied to construct Kaplan–Meier failure time graphs. G8 scores before and after treatment were compared using a paired *t*-test, as the before–after difference was assumed to be sampled from an approximately normal distribution.

Furthermore, the association of survival and late toxicity grade $\geq$3 with baseline variables was assessed using Cox proportional hazards univariable and multivariable regression models. Covariates for multivariable regression were selected by an automatic backward stepping procedure with a selection criterion of $P = 0.05$. The results of the Cox regression were reported as hazard ratios with corresponding 95% confidence intervals and *P* values. *P* values $\leq$ 0.05 were considered statistically significant. All statistical analyses were conducted using SPSS version 23 software (IBM SPSS Statistics for Windows. Armonk, NY, USA: IBM Corp. 2018).

Results

Population

As previously described, between April and October 2015, 402 patients were included in the study [14]. Baseline characteristics are shown in Table 1. The median age was 72 years (mean 73; range: 65–96 years); 14% were older than 80 years. Follow-up for G8 score and late toxicity was carried out after a median of 25 months (interquartile range

Table 1
Baseline characteristics

		n	
Gender	Male	208	48.3%
	Female	194	51.7%
Age	Years; mean (range)		73 (65–96)
	65–75	271	67.6%
	75–85	114	28.4%
	>85	16	4.0%
World Health Organization performance score	0	225	56.3%
	1	143	35.8%
	2	31	7.8%
	3	1	0.2%
Primary tumour	Breast cancer	141	35.2%
	Prostate cancer	73	18.2%
	Rectal cancer	70	17.5%
	Non-small cell lung cancer	53	13.2%
	Head and neck cancer	32	8.0%
	Oesophageal cancer	29	7.2%
	Unknown	3	0.7%
Radiotherapy	Primary local radiotherapy	118	29.6%
	Postoperative local radiotherapy	91	22.9%
	Primary radiotherapy/chemotherapy	47	11.8%
	Radiotherapy/chemotherapy followed by surgery	39	9.8%
	Radiotherapy followed by surgery	38	9.3%
	Postoperative locoregional radiotherapy	36	9.0%
	Primary locoregional radiotherapy	29	7.3%
	Unknown	1	0.3%

Note: due to rounding, percentages do not always add up to 100; and due to missing values, numbers do not always add up to 402.

23–28). Survival was assessed after a median follow-up period of 28 months (interquartile range 26–29).

Geriatric 8 and Timed Get Up and Go Test Results Before and after Treatment

According to G8, 44% of the patients were considered frail (i.e. G8 $\leq$ 14) before treatment. Re-measurement of G8 showed stable scores. The mean G8 before treatment was 14.6 and after treatment it was 14.2. The mean difference was −0.40 ($P = 0.0056$) (95% confidence interval −0.67 to −0.12). According to the TGUGT, 19% of the patients were frail (i.e. TGUGT >10 s) before treatment.

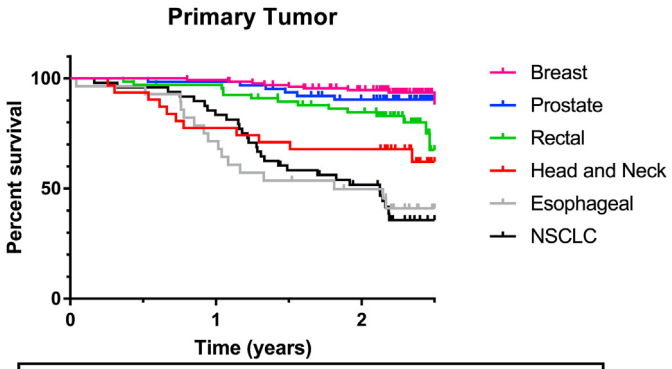
Geriatric 8 and Timed Get Up and Go Test Results and Survival

The cumulative incidence of death after 2.5 years was 27.5% ($n = 87$). Of these 87 patients, 32 died of disease progression, five of treatment complications, five of co-morbidity and 45 of other or unknown causes. Survival after 2.5 years of follow-up for patients aged 65–74 years was 84% and for patients aged 75 years and older was 49% (Log-rank P value < 0.0001). Overall survival after 2.5 years was 87% for patients with high G8 scores and 55% for patients with low G8 scores (Log-rank P value < 0.0001). Survival was 77% for patients with good TGUGT results and 50% for patients with poor TGUGT results (Log-rank P value < 0.001).

The overall survival after 2.5 years of follow-up was the highest for patients with breast cancer (90%), followed by prostate (88%), rectal (68%), head and neck (62%), oesophageal cancer (41%) and NSCLC (36%) (Figure 1).

Classifying patients according to their G8 scores, the 2.5-year overall survival was 78% for low scores and 95% for high scores in patients with breast cancer (Log-rank P value $= 0.15$); 77% for low scores and 95% for high scores in patients with prostate cancer (Log-rank P value $= 0.022$); 39% for low scores and 97% for high scores for patients with rectal cancer (Log-rank P value < 0.0001); 52% for low scores and 78% for high scores for patients with head and neck cancer (Log-rank P value $= 0.30$); 41% for low scores and 44% for high scores for patients with oesophageal cancer (Log-rank P value $= 0.75$); 36% for low scores and 32% for high scores for patients with NSCLC (Log-rank P value $= 0.29$). Overall survival according to primary tumour is depicted in Figure 1, according to G8 and TGUGT in Figure 2 and according to both primary tumour and G8 in Figure 3.

According to the results of univariable analyses, variables with statistically significant associations with worse survival were: age (75–85 years and >85 years, both compared with those aged 65–75 years), gender (male), type of primary tumour (oesophageal, NSCLC, head and neck and rectal cancer, compared with breast cancer), chemoradiotherapy, G8, TGUGT, number of medications (>3), WHO performance score (>0), acute toxicity (grade $\geq$3 compared with grade 0) and non-compliance (with any part of the prescribed treatment) (Table 2).



	Numbers remaining at risk					
Time (years)	0	0.5	1	1.5	2	2.5
Breast	133	132	132	127	116	17
NSCLC	48	46	40	27	22	4
Prostate	63	62	62	58	51	15
Head and Neck	31	29	24	22	21	5
Rectal	67	65	64	57	52	6
Esophageal	28	27	20	15	12	2

Fig 1. Kaplan–Meier survival graph according to type of primary tumour. Lines indicate survival. Markers indicate censoring.

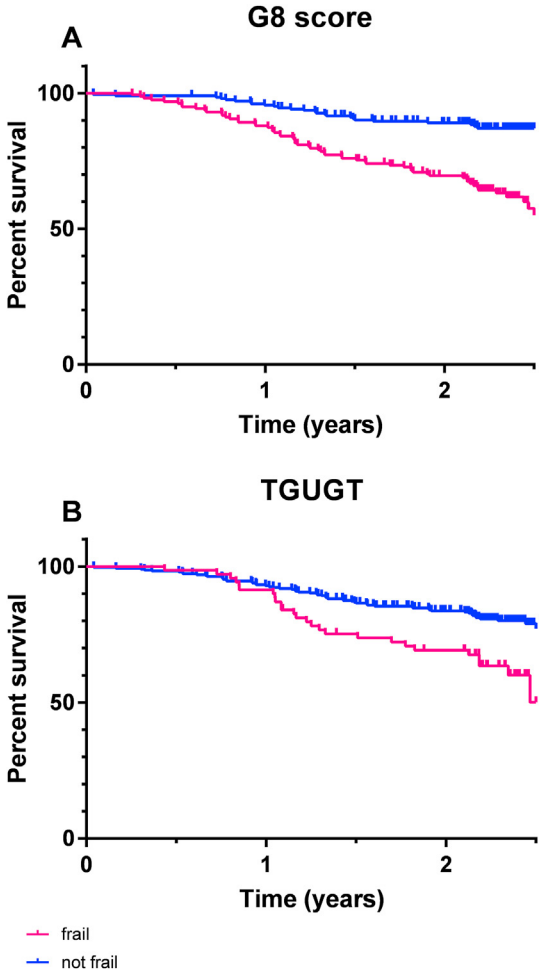


Fig 2. Kaplan–Meier survival graphs according to frailty as determined by Geriatric 8 (G8) and the Timed Get Up and Go Test (TGUGT). Lines indicate survival. Markers indicate censoring.

After multivariable selection, only the type of primary tumour (oesophageal, NSCLC, head and neck and rectal cancer, compared with breast cancer), age (75–85 years and >85 years, both compared with those aged 65–75 years) and G8 remained statistically significantly associated with a worse survival probability (Table 2).

Late Toxicity

Late toxicity scores were available for 276 patients. Toxicity scores were unknown for 87 patients who died before the measurement moment and, therefore, did not have late toxicity recorded, and for 39 patients who were lost to follow-up for the assessment of late toxicity. In patients for whom late toxicity scores were available, in 51% ($n = 142$) no radiotherapy-related toxicity was observed. Grade 1 toxicity was observed in 29% ($n = 81$), grade 2 toxicity in 16% ($n = 43$), grade 3 toxicity in 1.4% ($n = 4$), grade 4 toxicity in 0.4% ($n = 1$) and grade 5 toxicity in 1.8% ($n = 5$). Eighty-two patients died of causes unrelated to radiotherapy.

Geriatric 8 and Timed Get Up and Go Test Results and Late Toxicity

Three of the 169 patients (1.8%) who had a high score on G8 developed late toxicity grade ≥3 compared with four of the 96 patients (4.2%) who had a low score on G8. The difference was 2.4% (95% confidence interval −2.1 to 6.9%; $P = 0.24$).

Seven of the 228 patients (3.1%) who had good results on the TGUGT developed late toxicity grade ≥3 compared with two of the 43 patients (4.7%) who had poor results on the TGUGT. The difference was 1.6% (95% confidence interval −5.1 to 8.37%; $P = 0.60$).

Discussion

In older patients with cancer irradiated with curative intent, low G8 scores predicted for decreased overall survival. In multivariable analyses, low G8 score, age of the patient and type of primary tumour remained statistically significantly associated with survival. This association of the G8 score, with mortality, appeared to vary between the different types of primary tumour. The G8 score was an especially strong predictor for mortality in rectal and prostate cancers, although group sizes did not allow a test for statistical interaction to be reliably carried out. Therefore, these differences should be considered hypothesis generating. In multivariable analyses, TGUGT did not statistically significantly predict for decreased survival. Neither the G8 score nor the TGUGT were statistically significantly associated with late toxicity of grade 3 or higher in any type of cancer. However, this study was underpowered for conclusions about late toxicity, due to the remarkably low incidence of late toxicity. Larger studies are therefore needed to investigate predictors of late radiation-induced toxicity. Re-measurement of G8

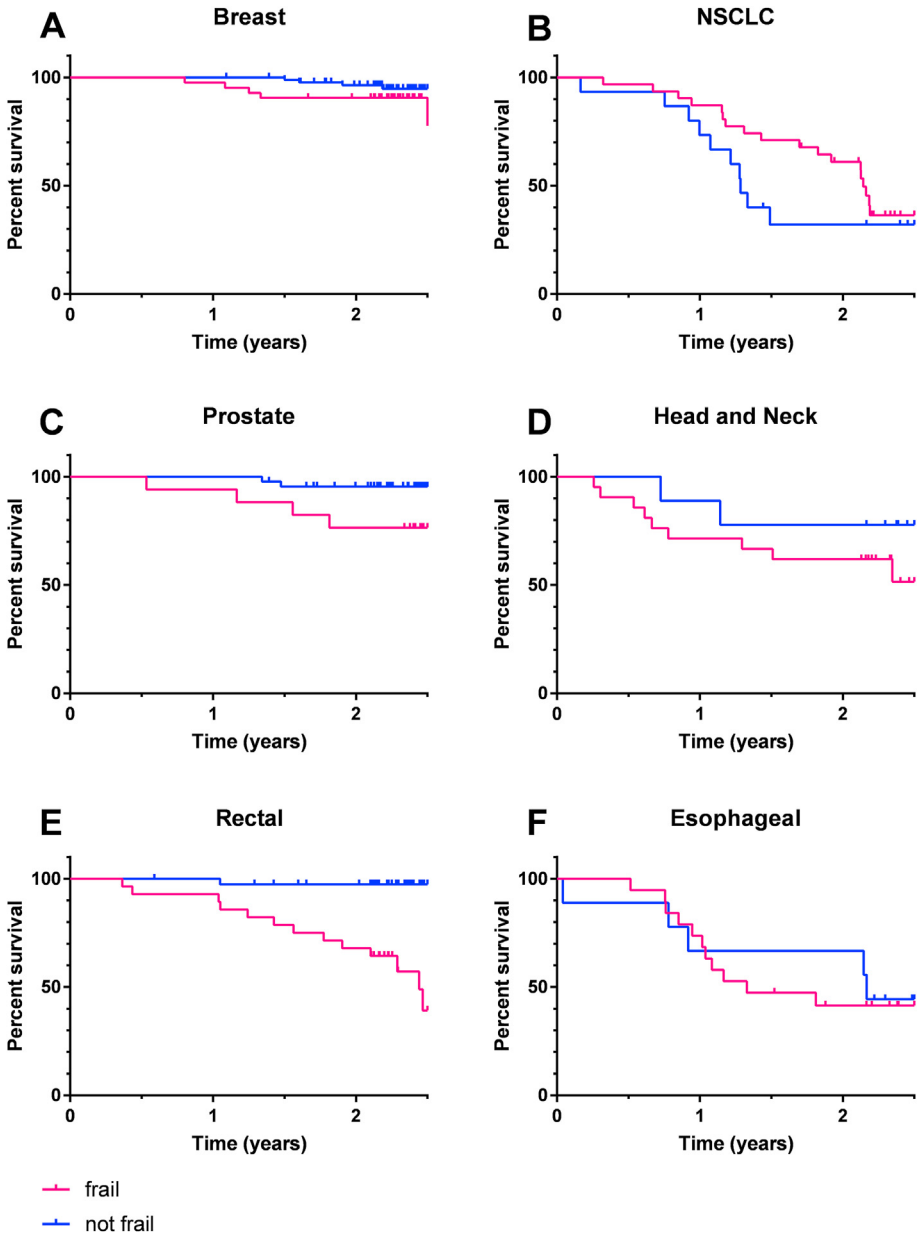


Fig 3. Kaplan–Meier survival graphs according to frailty as measured by Geriatric 8 (G8), stratified by type of primary tumour. Lines indicate survival. Markers indicate censoring.

showed a small statistically significant decline in G8 scores, but this difference was not of a clinically relevant magnitude.

In univariable analyses, the ECOG/WHO performance score seemed like a strong predictor. However, it did not remain statistically significantly associated with decreased survival in multivariable analyses. This was due to the fact that only very few patients had a poor performance score. The predictive value of a poor performance was therefore very high only for these few patients. However, most patients received a 0 score for the performance score, whereas many of these were actually frail according to G8. Therefore, for the total patient group, the added value of the performance score was extremely limited compared with G8. We also noted a substantial difference in the percentage of patients considered frail, according to either G8 or TGUGT. This was probably due to the fact that the TGUGT measures only physical frailty, whereas G8 is multidimensional. This observation therefore underscores the need for a multidimensional assessment to fully appreciate frailty.

Rates of grade $\geq$3 late toxicity in our study were low (3.6%) and there was no significant difference between the patients scoring high or low on either G8 or the TGUGT. Our results seem to suggest that radiotherapy could be administered safely in the studied population of older (>65 years) patients with cancer treated with radiotherapy with curative intent. However, late toxicity was not assessed in

Table 2
Univariable and multivariable analyses of associations with overall survival

		Univariable (confidence interval)		*P*	Multivariable (confidence interval)		*P*
Frail	G8 (≤14)	3.5	(2.2–5.5)	<0.001	2.1 (1.2–3.8)		0.0086
	TGUGT (>10 s)	2.2	(1.4–3.4)	0.0011			
Age (years)	65–75	Reference		<0.001	Reference		<0.001
	75–85	2.7	(1.7–4.2)	<0.0001	2.4	(1.4–4.0)	<0.0001
	>85	5.8	(2.9–11.3)	0.0033	3.9	(1.7–9.0)	0.0012
Medications	>3	1.9	(1.2–2.9)	0.0057			
Chemotherapy		3.1	(2.0–4.7)	0.0029			
Perspective	<10	0.96	(0.62–1.5)	0.85			
Primary tumour	Breast	Reference		<0.0001	Reference		<0.0001
	Non-small cell lung cancer	12.5	(5.9–26)	<0.0001	9.2	(4.0–21)	<0.0001
	Prostate	1.4	(0.49–3.9)	0.55	1.4	(0.45–4.2)	0.58
	Head and neck	6.4	(2.7–16)	<0.0001	2.7	(0.97–7.5)	0.058
	Rectal	3.4	(1.5–7.8)	0.0044	2.8	(1.2–6.8)	0.025
	Oesophageal	13.0	(5.7–29)	<0.0001	10.4	(4.3–25)	<0.001
World Health Organization performance score	>0	4.0	(2.5–6.3)	<0.0001			
Acute toxicity	Grade 0	Reference		<0.001			
	Grade 1 and 2	2.0	(0.85–4.6)	0.11			
	Grade ≥ 3	4.3	(1.8–10.7)	0.0015			
Non-compliance		2.8	(1.4–5.3)	0.0025			
Previous cancer		1.4	(0.80–2.5)	0.23			
Gender	Male	0.52	(0.33–0.80)	0.003			

G8, Geriatric 8; TGUGT, Timed Get Up and Go Test.

patients who died during follow-up. It can therefore not be ruled out that these patients experienced late toxicity before dying. Furthermore, all patients in this study were already selected for radiotherapy with curative intent. It can, therefore, also not be ruled out that a broader selection of older patients with cancer would experience more late toxicity.

We observed that a low score on G8 remained statistically significantly associated with survival after multivariable analysis. Previous studies have shown that a low score on G8 was associated with worse survival [8,10,17,18]. However, those studies included different treatment strategies, including both palliative and curative intent. Patients treated with palliative intent are more likely to be frail. Therefore, in this heterogeneous population low G8 scores could in part measure worse disease status and associated poor prognosis. In contrast, our study included only older patients with cancer receiving (chemo)radiotherapy with curative intent. This group has a relatively good prognosis and is much more homogenous than the groups included in those previous studies. Therefore, prediction of poor performance is even more challenging. Yet, G8 also predicted survival in this selected population, showing for the first time the value of this screening tool in older patients with cancer with relatively favourable prognosis treated with radiotherapy with curative intent. It is noteworthy that, even in this selected population of relatively fitter patients, still almost half the patients were frail according to G8. This observation clearly illustrates the ability of G8 to identify frail patients much more sensitively than, for example, the performance score.

A potential limitation of our study could be that we included patients with six different types of tumour. Therefore, the numbers of patients per individual tumour type are more limited than they would have been in a similar sized study focusing on a single type of tumour. However, in spite of this potential limitation, we were still able to clearly show differences in the predictive value of G8 for mortality, between the various tumour types. Furthermore, by including these six different tumour types, we also included treatment heterogeneity, which could have diluted associations. However, we still observed strong associations and by including the six most common types of tumour eligible for radiotherapy in older patients, we also provide a comprehensive picture of the population of older patients with cancer. A more selected and homogenous population would have been less informative for the broader range of patients seen in daily clinical practice. Another strength is the completeness of the data. Our mortality data were over 99% complete due to a mandatory national registration system in the Netherlands. The degree of completeness of the follow-up for late toxicity scores was also very high, with complete data for 90% of the patients still alive at the time of follow-up.

A limitation inherent to this type of study, but not specific to our study, is the potential for overfitting of the model to the particularities of the study population. This overfitting can limit external validity, which is why models like these should always be validated and calibrated in an independent population. However, our final model included only three variables. For all of these it is biologically plausible that they are indeed predictive of

mortality. Therefore, the risk for overfitting is probably very limited.

In conclusion, G8 is an easy to use scoring tool that provides good prediction of mortality in addition to the predictive value of the age of the patient and the type of primary tumour. The predictive value of G8 does seem to vary between types of tumour.

Therefore, the G8 score, in the future, may contribute to the individualisation of treatment decisions for older patients with cancer, especially by adding this assessment in the group of patients who are now treated with curative intent, based on only the tumour characteristics, age and general clinical assessment. The results of G8 could then be used to have a better-informed discussion with the patient about the probability of treatment success or failure. However, the results of this study need to be confirmed. Furthermore, more precise estimates of differences between different type of tumour need to be obtained in larger international studies.

Conflict of Interest

J.G. Middelburg and R.A. Middelburg are married.

Acknowledgments

The authors would like to thank all the participating physicians and data managers for including patients and recording data, and all participating patients for their cooperation.

References

[1] Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004;22(22):4626–4631. https://doi.org/10.1200/JCO.2004.02.175.

[2] IKNL. Kankerzorg in beeld: de oudere patient (2016). Available at:https://shop.iknl.nl/shop/kankerzorg-in-beeld-de-oudere-pati%C3%ABnt-(2016)/123187; 2018.

[3] Bras L, Peters TT, Wedman J, Plaat BE, Witjes MJ, van Leeuwen BL, *et al*. Predictive value of the Groningen Frailty Indicator for treatment outcomes in elderly patients after head and neck, or skin cancer surgery in a retrospective cohort. *Clin Otolaryngol* 2015;40(5):474–482. https://doi.org/10.1111/coa.12409.

[4] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013;381(9868):752–762. https://doi.org/10.1016/S0140-6736(12)62167-9.

[5] Bellera CA, Rainfray M, Mathoulin-Pelissier S, Mertens C, Delva F, Fonck M, *et al*. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol* 2012;23(8):2166–2172. https://doi.org/10.1093/annonc/mdr587.

[6] Russo C, Giannotti C, Signori A, Cea M, Murialdo R, Ballestrero A, *et al*. Predictive values of two frailty screening tools in older patients with solid cancer: a comparison of SAOP2 and G8. *Oncotarget* 2018;9(80):35056–35068.

[7] Deluche E, Leobon S, Lamarche F, Tubiana-Mathieu N. First validation of the G-8 geriatric screening tool in older patients with glioblastoma. *J Geriatr Oncol* 2019;10(1):159–163.

[8] Soubeyran P, Bellera C, Goyard J, Heitz D, Cure H, Rousselot H, *et al*. Screening for vulnerability in older cancer patients: the ONCODAGE Prospective Multicenter Cohort Study. *PLoS One* 2014;9(12):e115060. https://doi.org/10.1371/journal.pone.0115060. eCollection 2014.

[9] Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, *et al*. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014;32(24):2595–2603.

[10] Martinez-Tapia C, Paillaud E, Liuu E, Tournigand C, Ibrahim R, Fossey-Diaz V, *et al*. Prognostic value of the G8 and modified-G8 screening tools for multidimensional health problems in older patients with cancer. *Eur J Cancer* 2017;83:211–219. https://doi.org/10.1016/j.ejca.2017.06.027.

[11] Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39(2):142–148.

[12] Ferrat E, Paillaud E, Laurent M, Le Thuaut A, Caillet P, Tournigand C, *et al*. Predictors of 1-year mortality in a prospective cohort of elderly patients with cancer. *J Gerontol A Biol Sci Med Sci* 2015;70(9):1148–1155. https://doi.org/10.1093/gerona/glv025.

[13] Pamoukdjian F, Paillaud E, Zelek L, Laurent M, Levy V, Landre T, *et al*. Measurement of gait speed in older adults to identify complications associated with frailty: a systematic review. *J Geriatr Oncol* 2015;6(6):484–496. https://doi.org/10.1016/j.jgo.2015.08.006.

[14] Middelburg JG, Mast ME, de Kroon M, Jobsen JJ, Rozema T, Maas H, *et al*. Timed Get Up and Go Test and Geriatric 8 scores and the association with (chemo-)radiation therapy noncompliance and acute toxicity in elderly cancer patients. *Int J Radiat Oncol Biol Phys* 2017;98(4):843–849. https://doi.org/10.1016/j.ijrobp.2017.01.211.

[15] ECOG-ACRIN. ECOG performance status 2018. Available at: https://ecog-acrin.org/resources/ecog-performance-status.

[16] SERVICES USDOHAH. *Common Terminology Criteria for Adverse Events (CTCAE)*. Version 4.0 2010. Available at:, https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

[17] Kenis C, Decoster L, Van Puyvelde K, De Greve J, Conings G, Milisen K, *et al*. Performance of two geriatric screening tools in older patients with cancer. *J Clin Oncol* 2014;32(1):19–26. https://doi.org/10.1200/JCO.2013.51.1345.

[18] Schulkes KJG, Souwer ETD, van Elden LJR, Codrington H, van der Sar-van der Brugge S, Lammers JJ, *et al*. Prognostic value of Geriatric 8 and identification of seniors at risk for hospitalized patients screening tools for patients with lung cancer. *Clin Lung Cancer* 2017;18(6):660–666. https://doi.org/10.1016/j.cllc.2017.02.006. e1.