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The association of frailty and outcomes of geriatric assessment with acute radiation-induced toxicity in patients with head and neck cancer

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ABSTRACT

Background and purpose: Geriatric impairments and frailty are highly prevalent in patients with head and neck cancer (HNC). This study investigated the association of frailty and outcomes of geriatric assessment (GA) with radiation-induced toxicity (RIT) in patients undergoing (chemo)radiotherapy ((C)RT) for HNC.

Materials and methods: Between October 2014 and April 2016, patients with HNC were prospectively included in OncoLifeS, an institutional data-biobank. Before treatment initiation, patients underwent GA and frailty screening (Groningen Frailty Indicator and Geriatric 8). The main outcome of this study was RIT (weight loss, mucositis, salivary gland inflammation, oral pain, sore throat, hoarseness, dry mouth, dysgeusia, dysphagia and general pain) according to the common terminology criteria of adverse events (CTCAE) version 4.0. Linear mixed models were performed, to analyse factors associated with increasing mean RIT over time during the treatment period.

Results: 160 patients were included. 114 (71.3%) were male and the mean age was 66.1 years. Age $\geq$ 65 ($\beta = 0.03$ (95 %CI = 0.01;0.05), $p = 0.01$), regional RT ($\beta = 0.05$(95 %CI = 0.02;0.09), $p = 0.004$), and concurrent chemotherapy ($\beta = 0.04$(95 %CI = 0.02;0.07), $p = 0.001$), were independent factors associated with increasing toxicity during the 7-week treatment period, adjusted for relevant covariates. None of the single items of GA, as well as the frailty screening instruments, were associated with increasing RIT.

Conclusion: In this study, frailty and GA were not associated with additional RIT during treatment. These results suggest that (C)RT is equally tolerated in frail and non-frail patients, with respect to acute RIT. RT could be a suitable alternative to surgery in selected frail patients.

Introduction

With the increasing incidence of cancer in an aging society, the proportion of older patients with head and neck cancer (HNC) is rising [1]. As ageing is associated with a decline in physiological functioning, chronological age is often considered in treatment decision making [2]. As a result, older patients often receive less intensive, and less multimodal treatment compared to younger patients [3]. Considering the patients biological age instead of chronological age, however, has been shown a better predictor of treatment tolerance in oncological surgery and medical oncology. Frailty, a clinical condition representing biological age, is defined as "a state of increased vulnerability to poor

Abbreviations: HNC, head and neck cancer; CGA, comprehensive geriatric assessment; GFI, Groningen Frailty Indicator; G8, Geriatric 8; RT, Radiotherapy; RIT, Radiation-induced toxicity; CRT, Chemoradiotherapy; UMCG, University Medical Center of Groningen; GA, Geriatric assessment; ACE-27, Adult Comorbidity Evaluation-27; MUST, Malnutrition Universal Screening Tool; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; TUG, Timed Up & Go; MMSE, Mini Mental State Examination; GDS-15, Geriatric Depression Scale 15; CTCAE, Common Terminology Criteria for Adverse Events.

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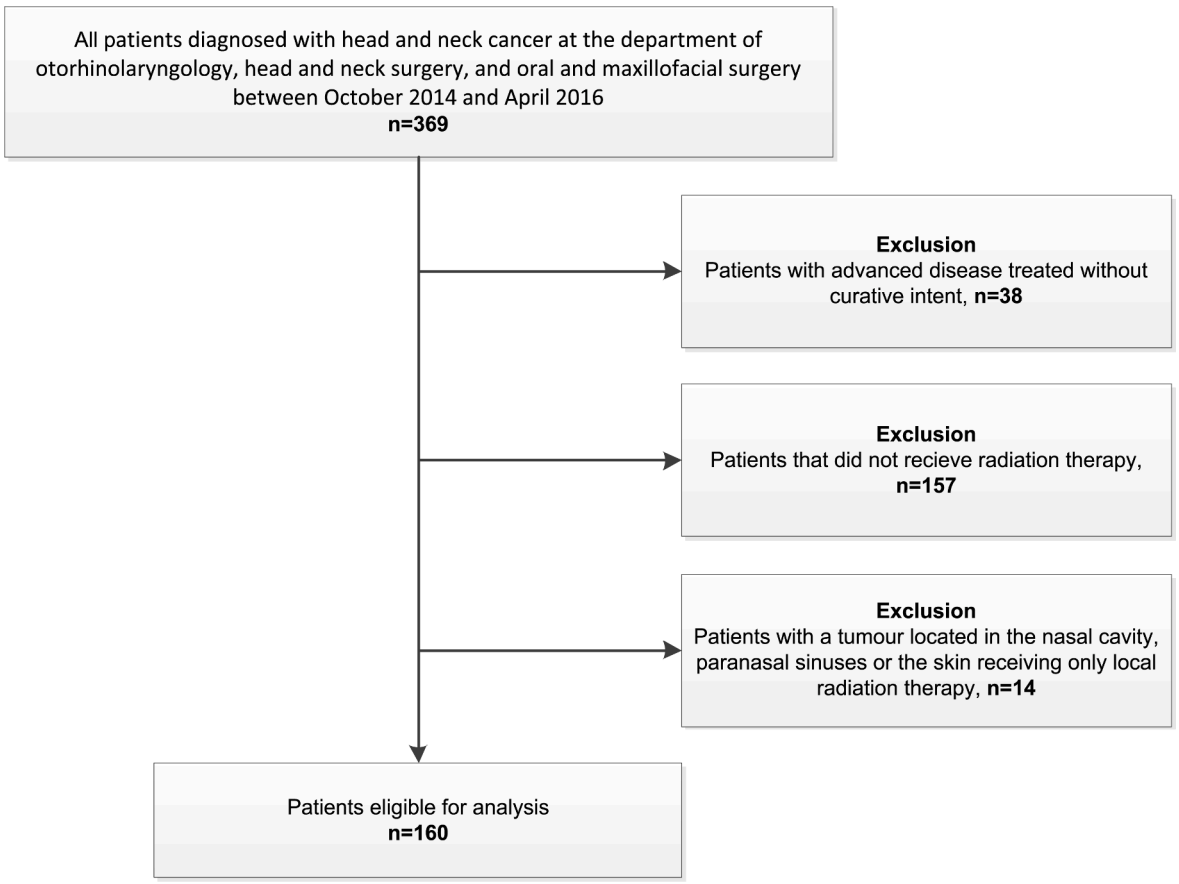

Figure 1. Flowchart diagram depicting the in- and exclusion of patients. Abbreviations: n = number of patients.

resolution of homeostasis following a stress, which increases the risk of adverse outcomes" [4]. Frailty can be identified by comprehensive geriatric assessment (CGA), which evaluates multiple domains of physiological functioning. However, the time-consuming nature of CGA has contributed to the development of shorter questionnaires, such as the Groningen Frailty Indicator (GFI) and Geriatric 8 (G8), which can be used in a two-step method to identify individuals that might benefit from a subsequent CGA [5–7].

HNC patients are often identified as being frail, as a result of their unhealthy lifestyle leading to increased comorbidity and psychosocial issues, and as a result of tumour-related factors such as malnutrition and loss of functioning [8]. This leads to a challenge for head and neck oncologists with respect to decision making in this particular population. Evidence in the field of frailty and HNC demonstrates that frailty is associated with surgical complications, decline in quality of life after treatment, and higher risk of discontinuation of (chemo)radiation therapy ((C)RT), a cornerstone in the treatment of HNC [9–11]. The latter can be the result of radiation-induced toxicity (RIT) reflected by side-effects of RT, including oral pain, and difficulting speaking, chewing, or swallowing [12]. Other studies, however, demonstrated that RT is often well tolerated in older patients [13,14].

Several studies have reported on acute and chronic RIT and the results are controversial about the effect of age on treatment-related toxicities [15–17]. Whether RIT is worse in frail patients, has never been investigated, to our knowledge. The aim of the current study was to investigate the association of outcomes of frailty screening and geriatric assessment with RIT during (C)RT in patients with HNC.

Materials and methods

Study design

This prospective observational study was carried out at the outpatient clinics of the department of Otorhinolaryngology, Head and Neck surgery, Oral- and Maxillofacial Surgery, and Radiation Oncology at the University Medical Center Groningen (UMCG), Groningen, The Netherlands. The study made use of larger hospital based oncological data-biobank (OncoLifeS) and was approved by the OncoLifeS scientific committee. OncoLifeS has been approved by the medical ethical committee of the UMCG and is registered in the Dutch Trial Register (registration number NL7839) [18]. To confirm participation in OncoLifeS, all patients provided written informed consent.

All patients underwent a geriatric assessment (GA) and frailty screening at baseline (before treatment) and were followed during treatment and until 12 weeks after onset of treatment with respect to RIT.

Treatment

Treatment planning was discussed at the multidisciplinary head and neck tumour board of the UMCG. Treatment was applied according to national and international guidelines using intensity-modulated radiotherapy with or without concurrent chemotherapy. The intention of GA and frailty screening were purely observational; however, attention for geriatric impairments and frailty may unconsciously have led to more referrals to a geriatrician.

Table 1
Patient- tumour- and treatment characteristics, and outcomes of geriatric assessment and frailty screening tools.

Patient-, tumour- and treatment characteristics		n (%)[a]
Age (mean ± SD)		66.1 (10.1)
	<65	74 (46.3%)
	≥65	86 (53.8%)
Gender	Male	114 (71.3%)
	Female	46 (28.7%)
Stage	Early (I-II)	37 (23.4%)
	Advanced (III-IV)	121 (76.6%)
Location	Oropharynx	53 (33.1%)
	Larynx	46 (28.7%)
	Oral Cavity	33 (20.6%)
	Skin	9 (5.6%)
	Hypopharynx	8 (5%)
	Salivary glands	4 (2.5%)
	Nasopharynx	4 (2.5%)
	Unknown primary	3 (1.9%)
Histopathology	SCC	148 (92.5%)
	Other	12 (7.5%)
Smoking status	Never	20 (12.6%)
	Former	61 (38.4%)
	Current	78 (49.1%)
Drinking status	Never	29 (18.5%)
	Former	27 (17.2%)
	Mild/moderate	63 (40.1%)
	Heavy	38 (24.2%)
BMI	Low (<18.5)	7 (4.4%)
	Middle (≤18.5 and < 25)	73 (45.9%)
	High (≥25)	79 (49.7%)
Treatment modality	Primary (C)RT	110 (68.8%)
	Post-operative (C)RT	50 (31.2%)
Local RT	Yes	153 (95.6%)
	No	7 (4.4%)
Primary radiation dose (Gy)	Mean +- SD	67.2 (5.6)
	Median (range)	70 (28–70)
Regional RT	No regional RT	30 (18.8%)
	Unilateral	24 (15.0%)
	Bilateral	106 (66.3%)
Regional radiation dose (Gy)	Mean +- SD	66.9 (5.0)
	Median (range)	70 (48–70)
Concurrent chemotherapy	Yes	47 (29.4%)
	No	113 (70.6%)
Geriatric Assessment		
ACE-27	None	34 (21.3%)
	Mild	60 (37.5%)
	Moderate	42 (26.3%)
	Severe	24 (15.0%)
MUST	Low risk (=0)	110 (71.4%)
	Medium risk (=1)	19 (12.3%)
	High risk (≥2)	25 (16.2%)
Polypharmacy	<5 medications	108 (67.5%)
	≥5 medications	52 (32.5%)
TUG	No restrictions (<13.5)	143 (89.4%)
	Declined mobility (≥13.5)	17 (10.6%)
ADL	No restrictions (<1)	145 (92.4%)
	Restrictions (≥1)	12 (7.6%)
IADL	No restrictions (<3)	138 (86.3%)
	Restrictions (≥3)	22 (13.8%)
MMSE	Normal cognitive function (>24)	144 (90.0%)
	Declined cognitive function (≤24)	16 (10.0%)
GDS-15	No depression (<6)	140 (89.7%)
	Depression (≥6)	16 (10.3%)
Living situation	Independent	145 (91.2%)
	Assisted	13 (8.2%)
	Nursing home	1 (0.6%)
Marital status	Single	113 (70.2%)
	In a relationship	47 (29.2%)
Frailty screening		
GFI	Non-frail	108 (68.4%)
	Frail	50 (31.6%)
G8	Non-frail	72 (45.3%)
	Frail	87 (54.7%)

Abbreviations: [a] unless otherwise specified. SCC = Squamous Cell Carcinoma, (C)RT = (Chemo) Radiation therapy, Gy = Gray, BMI = Body Mass Index, ACE-27 = Adult Comorbidity Evaluation 27. MUST = Malnutrition Universal Screening Tool. TUG = Timed Up and Go. ADL = Activities of Daily Living. IADL = instrumental activities of daily living. MMSE = Mini Mental State examination. GSD-15 = Geriatric Depression Scale 15, GFI = Groningen Frailty Indicator, G8 = Geriatric 8.

Study population

Patients diagnosed with a primary mucosal, salivary gland or a complex cutaneous malignancy (i.e., squamous cell carcinoma stage II or higher, giant basal cell carcinoma, melanoma, Merkel cell carcinoma or neck metastasis of any of the before mentioned tumours) in the head and neck area between October 2014 and April 2016 were eligible for inclusion, regardless of age. The cohort included patients requiring primary or post-operative (C)RT of the head and neck area. Patients treated with palliative intention or exclusively by surgery were excluded from this study. In addition, patients that solely received local irradiation of early stage tumours located at the nasal cavity, paranasal sinuses and the skin were also excluded (Fig. 1).

Geriatric assessment and frailty screening

Comorbidities were assessed using the 27-item Adult Comorbidity Evaluation (ACE-27) [19]. To screen for nutritional risk, the Malnutrition Universal Screening Tool (MUST) was used [20]. Polypharmacy was defined by the use of five or more medications [21]. Functional status was evaluated by scoring self-maintaining activities of daily living (ADL) and instrumental activities of daily living (IADL). Mobility was evaluated with the Timed Up & Go (TUG) [22–24]. Mini-Mental State Examination (MMSE) was applied for cognition and depression defined by the Geriatric Depression Scale (GDS-15) [25,26]. Living situation and marital status were used to assess socio-environmental status of the patients, as part of a standardized questionnaire.

Furthermore, two frailty screening tools, including the G8 and the GFI were completed [6,7].

Questionnaires were completed during an interview with an investigator or nurse together with the patient at the first visit at the outpatient clinic or completed later and returned by mail.

Outcome measures

Data on RIT was obtained from the database of the standardized follow-up program (SFP) of the department of Radiation Oncology at the UMCG. RIT was graded by a radiation oncologist using the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v 4.0) [27]. Toxicity levels were assessed at baseline and graded each week during the 6-to-7-week treatment period and at 12 weeks after onset of treatment.

RIT included physician rated weight loss, mucositis, salivary gland inflammation, oral pain, sore throat, hoarseness, dry mouth, dysgeusia, dysphagia and general pain of the head and neck area. Based on a previous study, the UMCG scale for assessing dysphagia was converted into the CTCAE scale for dysphagia [28] (Supplements Table 2). A mean CTCAE grade for all toxicities combined was calculated at each time point, capturing changes in toxicity over time very well.

Statistical analysis

Statistical analysis was performed using SPSS statistics 23.0 software (IBM, Armonk, New York, United States of America). Descriptive statistics regarding patient- tumour- and treatment- characteristics, GA, and frailty screening were presented as mean ± standard deviation (SD) or value (percentage).

For the analysis of repeated measures of mean CTCAE grades, linear mixed-effect models (LMMs) were employed. As an advantage, this method allows for missing data points in a large longitudinal dataset

Table 2
Heatmap depicting the mean (±SD) radiation-induced toxicity scores according to the CTCAE v 4.0 per week. Radiation-induced toxicity was scored on different time points. Week 0 = baseline, week 1–7, and week 12. Cut-off points for colors: 0.00 – 0.49 = green, 0.50 – 0.99 = yellow,. 1.00 – 1.49 = orange, > 1.50 = red. SD = Standard Deviation. CTCAE = Common Terminology Criteria for Adverse Events.

Toxicity	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 12
Weighth loss		0.01 (0.08)	0.01 (0.08)	0.03 (0.18)	0.08 (0.18)	0.15 (0.36)	0.22 (0.43)		0.22 (0.43)
Pain throat	0.32 (0.62)	0.30 (0.60)	0.29 (0.71)	0.62 (0.71)	0.87 (0.81)	0.97 (0.83)	1.11 (0.86)	1.15 (0.80)	0.39 (0.64)
Hoarseness	0.47 (0.79)	0.46 (0.88)	0.45 (0.83)	0.53 (0.90)	0.66 (1.00)	0.82 (1.10)	0.87 (1.05)	0.81 (0.99)	0.40 (0.74)
Oral pain	0.16 (0.47)	0.15 (0.48)	0.22 (0.55)	0.45 (0.73)	0.51 (0.78)	0.73 (0.88)	0.77 (0.89)	0.81 (0.86)	0.29 (0.60)
Mucositis	0.00 (0.00)	0.01 (0.08)	0.20 (0.52)	0.75 (0.91)	1.06 (1.07)	1.45 (1.20)	1.57 (1.22)	1.74 (1.15)	0.59 (0.82)
General pain	0.45 (0.74)	0.44 (0.71)	0.52 (0.90)	1.03 (0.82)	1.19 (0.81)	1.27 (0.79)	1.55 (0.75)	1.51 (0.78)	0.64 (0.81)
Dysgeusia	0.16 (0.43)	0.18 (0.46)	0.36 (0.63)	0.77 (0.81)	1.17 (0.89)	1.35 (0.83)	1.45 (0.82)	1.54 (0.74)	1.04 (0.76)
Sticky saliva	0.23 (0.48)	0.23 (0.50)	0.43 (0.59)	0.69 (0.68)	0.92 (0.71)	1.08 (0.72)	1.25 (0.75)	1.44 (0.74)	0.85 (0.71)
Xerostomia	0.20 (0.40)	0.23 (0.42)	0.47 (0.59)	0.78 (0.67)	1.04 (0.71)	1.26 (0.71)	1.34 (0.73)	1.47 (0.79)	0.96 (0.77)
Dysphagia	0.48 (0.82)	0.88 (1.10)	0.92 (1.14)	1.35 (1.11)	1.66 (1.05)	1.86 (1.07)	2.02 (1.02)	2.14 (1.08)	1.45 (1.24)
Total CTCAE	0.27 (0.26)	0.29 (0.29)	0.38 (0.36)	0.71 (0.41)	0.91 (0.46)	1.09 (0.50)	1.22 (0.54)	1.41 (0.52)	0.70 (0.47)

without excluding entire cases and limiting bias. The dependent variable was the mean CTCAE grade, and measures were repeated weekly from 0 to 7 weeks. The 12-weeks measurement point was omitted for the LMMs. The intercept, time and factors to investigate were added as fixed effects. For random effects, an intercept was included. The estimation method was maximum likelihood. As RIT gradually increases during (C)RT, only linear time was added to the models.

First, all factors to investigate were individually put in a simple model with the parameters intercept, time, factor (main effects), factor*time (interaction term) (Table 3 and Table 4, left column). Second, a multivariable model was made from patient- tumour- and treatment characteristics relevant for RIT (Table 3, right column). Third, simple models evaluating items of GA and frailty screening were adjusted for patient- tumour- and treatment characteristics that were significantly associated with RIT (Table 4, right column).

All models provided estimates (β), 95% confidence intervals (95 % CI), and p-values. For interpretation, the main effects (factor) refer to the difference in mean CTCAE grade at baseline, ahead of treatment, and the interaction term (factor*time) refers to the newly arising difference between factor + and factor- patients per week. Significance was set at a p-value of < 0.05. Mean predicted values and standard error of predicted values were saved for graphs and shown per category in figures.

Results

Patient characteristics

After exclusion, 160 patients remained eligible for analysis (Fig. 1). Patient-, tumour- and treatment characteristics are presented in Table 1. The mean age of the patients was 66.1 years and patients were predominantly male (n = 114, 71.3%). Patients were most frequently diagnosed with squamous cell carcinoma (SCC, n = 148, 92.5%), advanced disease (stage III-IV, n = 121, 76.6%) and oropharyngeal (n = 53, 33.1%), laryngeal (n = 46, 28.7%) or oral cancer (n = 33, 20.6%). Most patients received primary (C)RT (n = 110, 68.8%) and 50 patients (31.2%) post-operative (C)RT. A total of 47 patients (29.4%) received concurrent systemic treatment.

Outcome measures

Mean completeness for outcomes measures was 94.0% and data availability is demonstrated in Supplementary table 2. One patient dropped out of treatment at the fifth week of RT.

In general, RIT increased during treatment with peaks around week 6 and 7. Twelve weeks after the start of treatment, most side-effects of RT resolved (Table 2).

Patient characteristics and RIT

Univariable models showed that, female gender (β(95 %CI) = 0.09 (0.005;0.18), p = 0.04), advanced stage (β(95 %CI) = 0.014(0.05;0.24), p = 0.002), current smoking (β(95 %CI) = 0.14(0.07;0.21), $p < 0.001$), regional RT (β(95 %CI) = 0.11(0.01;0.21), p = 0.03) and concurrent chemotherapy (β(95 %CI) = 0.12(0.03;0.20), p = 0.008) were associated with higher toxicity grades at baseline (Table 3, left column). More importantly, advanced stage (β(95 %CI) = 0.05(0.03;0.07), $p < 0.001$), regional RT (β(95 %CI) = 0.07(0.05;0.09), $p < 0.001$) and concurrent chemotherapy (β(95 %CI) = 0.04(0.02;0.06), $p < 0.001$) were associated with more toxicity during treatment (interaction terms with time in models).

In a multivariable model, female gender (β(95 %CI) = 0.10 (0.01;0.18), p = 0.02), and advanced stage (β(95 %CI) = 0.16 (0.03;0.29), p = 0.02) were independent factors associated with elevated toxicity grades at baseline (Table 3, right column). Moreover, age ≥ 65 (β(95 %CI) = 0.03(0.01;0.05), p = 0.01), regional RT (β(95 % CI) = 0.05(0.02;0.09), p = 0.004), and concurrent chemotherapy (β(95 %CI) = 0.04(0.02;0.07), p = 0.001), were independent factors associated with additional toxicity during the 7-week treatment period (interaction terms, Table 3 and Fig. 2).

GA and RIT

In models adjusted for age, gender, stage, treatment modality, regional RT and concurrent chemotherapy, medium to high nutritional risk defined by MUST (β(95 %CI) = 0.19(0.11;0.27), $p < 0.001$), restricted mobility defined by TUG (β(95 %CI) = 0.15(0.03;0.28), p = 0.02), restrictions in IADL (β(95 %CI) = 0.11(-0.0001;0.22), p = 0.05) and depression defined by GDS-15 (β(95 %CI) = 0.14(0.02;0.27), $p = 0.03$) were associated with elevated baseline toxicity (Table 4, right column).

None of the GA items were associated with additional RIT over time during the 7-week treatment period in both univariable and multivariable models (Table 4).

Frailty and RIT

Univariable analysis revealed that frailty according to GFI (β(95 % CI) = 0.14(0.06;0.52), p = 0.001) as well as G8 (β(95 %CI) = 0.18

Table 3

Associations between patient-, tumour- and treatment characteristics and CTCAE score by Linear Mixed Models. Left column: univariable linear mixed models with mean CTCAE score as the dependent variable. Right column: a multivariable linear mixed model derived from all variables in the left column through a step backward selection procedure. Beta coefficients of main effects refer to the difference in CTCAE at baseline. Beta coefficients of interaction terms refer to the different slope in CTCAE score over time with respect to one week.

Variable	Model parameters	Univariable models		Multivariable model	
		β (95% CI)	p-value	β (95% CI)	p-value
Age	Intercept	0.20 (0.14; 0.26)	**<0.001**	0.37 (0.23; 0.51)	**<0.001**
	Time	0.16 (0.14; 0.17)	**<0.001**	0.20 (0.17; 0.23)	**<0.001**
	Age < 65	ref		ref	
	Age ≥ 65	−0.04 (−0.12; 0.05)	0.39	−0.04 (−0.12; 0.05)	0.41
	Age < 65 * time	ref		ref	
	Age ≥ 65 * time	−0.01 (−0.03; 0.01)	0.48	0.03 (0.01; 0.05)	**0.01**
Gender	Intercept	0.36 (0.28; 0.43)	**<0.001**		
	Time	0.14 (0.12; 0.16)	**<0.001**		
	Male	ref		ref	
	Female	0.09 (0.01; 0.18)	**0.04**	0.10 (0.01; 0.18)	**0.02**
	Male*time	ref		ref	
	Female*time	0.01 (−0.01; 0.04)	0.23	0.02 (0.00; 0.04)	0.11
Stage	Intercept	0.32 (0.28; 0.37)	**<0.001**		
	Time	0.14 (0.13; 0.15)	**<0.001**		
	Early (I-II)	ref		ref	
	Advanced (III-IV)	0.14 (0.05; 0.24)	**0.002**	0.16 (0.03; 0.29)	**0.02**
	Early (I-II)*time	ref		ref	
	Advanced (III-IV)*time	0.05 (0.03; 0.07)	**<0.001**	0.005 (−0.03; 0.04)	0.77
Histopathology	Intercept	0.23 (0.09; 0.42)	**0.002**		
	Time	0.13 (0.09; 0.17)	**<0.001**		
	SCC	ref			
	Other	−0.06 (−0.21; 0.09)	0.42		
	SCC*time	ref			
	Other*time	0.00 (−0.04; 0.04)	0.98		
Current smoking	Intercept	0.36 (0.32; 0.42)	**<0.001**		
	Time	0.13 (0.11; 0.14)	**<0.001**		
	No	ref			
	Yes	0.14 (0.07; 0.21)	**<0.001**		
	No*time	ref			
	Yes*time	−0.01 (−0.03; 0.01)	0.36		
Current drinking	Intercept	0.26 (0.21; 0.31)	**<0.001**		
	Time	0.13 (0.12; 0.14)	**<0.001**		
	No	ref			
	Yes	−0.07 (−0.15; 0.01)	0.11		
	No*time	ref			
	Yes*time	0.01 (−0.01; 0.03)	0.44		
BMI	Intercept	0.15 (0.03; 0.27)	**0.03**		
	Time	0.17 (0.16; 0.19)	**<0.001**		
	Low	0.26 (−0.15; 0.67)	0.14		
	Middle	0.07 (−0.10; 0.24)	0.30		
	High	ref			
	Low*time	−0.02 (−0.07; 0.03)	0.45		
	Middle *time	−0.01 (−0.03; 0.01)	0.47		
	High *time	ref			
Treatment modality	Intercept	0.25 (018; 0.33)	**<0.001**		
	Time	0.14 (0.12; 0.16)	**<0.001**		
	PRT	ref		ref	
	PORT	−0.05 (−0.14; 0.03)	0.24	−0.07 (−0.15; 0.02)	0.14
	Time*PRT	ref		ref	
	Time*PORT	0.00 (−0.02; 0.02)	0.98	0.00 (−0.02; 0.02)	0.76
Regional RT	Intercept	0.31 (0.27; 0.36)	**<0.001**		
	Time	0.14 (0.13; 0.15)	**<0.001**		
	No	ref		ref	
	Yes	0.11 (0.01; 0.21)	**0.03**	−0.02 (−0.16; 0.12)	0.78
	No*time	ref		ref	
	Yes*time	0.07 (0.05; 0.09)	**<0.001**	0.05 (0.02; 0.09)	**0.004**
Concurrent chemotherapy	Intercept	0.39 (0.31; 0.46)	**<0.001**		
	Time	0.17 (0.15; 0.18)	**<0.001**		
	No	ref		ref	
	Yes	0.12 (0.03; 0.20)	**0.01**	0.04 (−0.06; 0.14)	0.45
	No*time	ref		ref	
	Yes*time	0.04 (0.02; 0.06)	**<0.001**	0.04 (0.02; 0.07)	**0.001**

Abbreviations: β = Estimate, CI = Confidence Interval, ACE-27 = Comorbidity Evaluation 27, MUST = Malnutrition Universal Screening Tool, TUG = Timed Up and Go, ADL = Activities of Daily Living, IADL = instrumental activities of daily living, MMSE = Mini Mental State Examination, GSD-15 = Geriatric Depression Scale 15, G8 = Geriatric 8, GFI = Groningen Frailty Indicator, CTCAE = Common Terminology Criteria for Adverse Events.

Table 4

Associations between outcomes of geriatric assessment and CTCAE score by Linear Mixed Models. Left column: univariable linear mixed models with mean CTCAE score as the dependent variable. Right column: linear mixed models investigating the same parameter, adjusted for: age, gender, stage, treatment modality, regional radiotherapy and concurrent chemotherapy (variables from multivariable model, Table 3 right column). Beta coefficients of main effects refer to the difference in CTCAE at baseline. Beta coefficients of interaction terms refer to the different slope in CTCAE score over time with respect to one week.

Variable	Model parameters	Univariable models		Adjusted models	
		β (95% CI)	p-value	β (95% CI)	p-value
ACE-27	Intercept	0.21 (0.04; 0.38)	**0.03**	0.40 (0.25; 0.55)	**<0.001**
	Time	0.16 (0.13; 0.20)	**0.002**	0.20 (0.16; 0.23)	**<0.001**
	Non/mild	ref		ref	
	Moderate/severe	0.03 (−0.22; 0.29)	0.58	0.05 (−0.03; 0.13)	0.22
	Non/mild*time	ref		ref	
	Moderate/severe*time	0.01 (−0.04; 0.02)	0.48	−0.004 (−0.02; 0.01)	0.65
MUST	Intercept	0.44 (0.37; 0.51)	**<0.001**	0.46 (0.32; 0.61)	**<0.001**
	Time	0.13 (0.11; 0.15)	**<0.001**	0.19 (0.16; 0.23)	**<0.001**
	Low risk	ref		ref	
	Medium-High risk	0.21 (0.13; 0.30)	**<0.001**	0.19 (0.11; 0.27)	**<0.001**
	Low risk*time	ref		ref	
	Medium-High risk*time	0.00 (−0.02; 0.03)	0.85	−0.01 (−0.04; 0.01)	0.19
Polypharmacy	Intercept	0.28 (0.21; 0.35)	**<0.001**	0.38 (0.22; 0.54)	<0.001
	Time	0.13 (0.11; 0.15)	**<0.001**	0.20 (0.17; 0.24)	<0.001
	No polypharmacy	ref		ref	
	Polypharmacy	−0.02 (−0.10; 0.07)	0.66	0.01 (−0.08; 0.10)	0.81
	No polypharmacy *time	ref		ref	
	Polypharmacy*time	−0.01 (−0.03; 0.02)	0.67	0.00 (−0.02; 0.02)	0.69
TUG	Intercept	0.31 (0.16 – 0.46)	**<0.001**	0.49 (0.32 – 65)	**<0.001**
	Time	0.18 (0.15 – 0.21)	**<0.001**	0.21 (0.17 – 0.25)	**<0.001**
	No restrictions	ref		ref	
	Restrictions	0.13 (−0.02 – 0.29)	0.10	0.15 (0.03 – 0.28)	**0.02**
	No restrictions*time	ref		ref	
	Restrictions*time	0.01 (−0.02 – 0.04)	0.53	0.01 (−0.02 – 0.04)	0.60
ADL	Intercept	0.28 (0.14; 0.43)	**<0.001**	0.29 (−19361.32; 19361.89)	0.87
	Time	0.10 (0.06; 0.14)	**<0.001**	0.21 (−4220.61; 4221.04)	0.82
	No restrictions	ref		ref	
	Restrictions	−0.01 (−0.16; 0.14)	0.92	0.02 (−15341.39; 15341.44)	0.95
	No restrictions*time	ref		ref	
	Restrictions*time	−0.03 (−0.07; 0.01)	0.12	−0.02 (−2606.47; 2606.42)	0.90
IADL	Intercept	0.38 (0.27; 0.49)	**<0.001**	0.45 (0.29; 0.61)	**<0.001**
	Time	0.13 (0.10; 0.16)	**<0.001**	0.20 (0.16; 0.24)	**<0.001**
	No restrictions	ref		ref	
	Restrictions	0.11 (−0.01; 0.22)	0.07	0.11 (0.00; 0.22)	0.05
	No restrictions*time	ref		ref	
	Restrictions*time	0.00 (−0.03; 0.03)	0.89	0.00 (−0.03; 0.03)	0.95
MMSE	Intercept	0.27 (0.15; 0.40)	**<0.001**	0.36 (0.18; 0.55)	**<0.001**
	Time	0.13 (0.10; 0.16)	**<0.001**	0.21 (0.17; 0.26)	**<0.001**
	Normal cognitive function	ref		ref	
	Declined cognitive function	−0.02 (−0.15; 0.11)	0.79	−0.01 (−0.13; 0.12)	0.94
	Normal cognitive function*time	ref		ref	
	Declined cognitive function*time	0.00 (−0.03; 0.03)	0.98	0.01 (−0.02; 0.04)	0.43
GSD-15	Intercept	0.35 (0.19; 0.51)	**<0.001**	0.50 (0.32; 0.69)	**<0.001**
	Time	0.17 (0.12; 0.21)	**<0.001**	0.22 (0.18; 0.26)	**<0.001**
	No depression	ref		ref	
	Depression	0.16 (−0.01; 0.33)	0.06	0.14 (0.02; 0.27)	**0.03**
	No depression*time	ref		ref	
	Depression*time	0.00 (−0.04; 0.05)	0.83	0.02 (−0.01; 0.05)	0.18
Living situation	Intercept	0.33 (0.20; 0.46)	**<0.001**	0.43 (0.24; 0.61)	**<0.001**
	Time	0.14 (0.11; 0.17)	**<0.001**	0.22 (0.17; 0.26)	**<0.001**
	Independent	ref		ref	
	Dependent/nursery	0.04 (−0.10; 0.18)	0.53	0.09 (−0.05; 0.22)	0.20
	Independent*time	ref		ref	
	Dependent/nursery*time	0.01 (−0.02; 0.05)	0.53	0.02 (−0.01; 0.05)	0.23
Marital status	Intercept	0.36 (0.29; 0.43)	**<0.001**	0.30 (−7.12; 7.73)	0.31
	Time	0.14 (0.12; 0.16)	**<0.001**	0.25 (−0.07; 0.56)	0.06
	Relationship	ref		ref	
	Single	0.09 (0.01; 0.18)	**0.03**	0.08 (−3.77; 3.92)	0.47
	Relationship*time	ref		ref	
	Single*time	0.02 (−0.01; 0.04)	0.15	0.01 (−0.15; 0.18)	0.46
GFI	Intercept	0.38 (0.31; 0.45)	**<0.001**	0.46 (0.31; 0.60)	**<0.001**
	Time	0.13 (0.12; 0.15)	**<0.001**	0.20 (0.17; 0.24)	**<0.001**
	Non frail	ref		ref	
	Frail	0.14 (0.06; 0.52)	**0.001**	0.14 (0.06; 0.22)	**0.001**

(*continued on next page*)

Table 4 (*continued*)

Variable	Model parameters	Univariable models		Adjusted models	
		β (95% CI)	p-value	β (95% CI)	p-value
	Non frail*time	ref		ref	
	Frail*time	0.01 (−0.01; 0.03)	0.45	0.003 (−0.02; 0.02)	0.74
G8	Intercept	0.36 (0.31; 0.41)	**<0.001**	0.28 (−26.51; 27.06)	0.37
	Time	0.13 (0.12; 0.15)	**<0.001**	0.23 (−3.14; 3.61)	0.18
	Non frail	ref		ref	
	Frail	0.18 (0.10; 0.25)	**<0.001**	0.19 (−18.77; 19.15)	0.35
	Non frail*time	ref		ref	
	Frail*time	0.01 (−0.01; 0.03)	0.47	−0.01 (2.16; 2.13)	0.55

Abbreviations: ACE-27 = Comorbidity Evaluation 27, MUST = Malnutrition Universal Screening Tool, TUG = Timed Up and Go, ADL = Activities of Daily Living, IADL = instrumental activities of daily living, MMSE = Mini Mental State Examination, GSD-15 = Geriatric Depression Scale 15, G8 = Geriatric 8, GFI = Groningen Frailty Indicator, CTCAE = Common Terminology Criteria for Adverse Events.

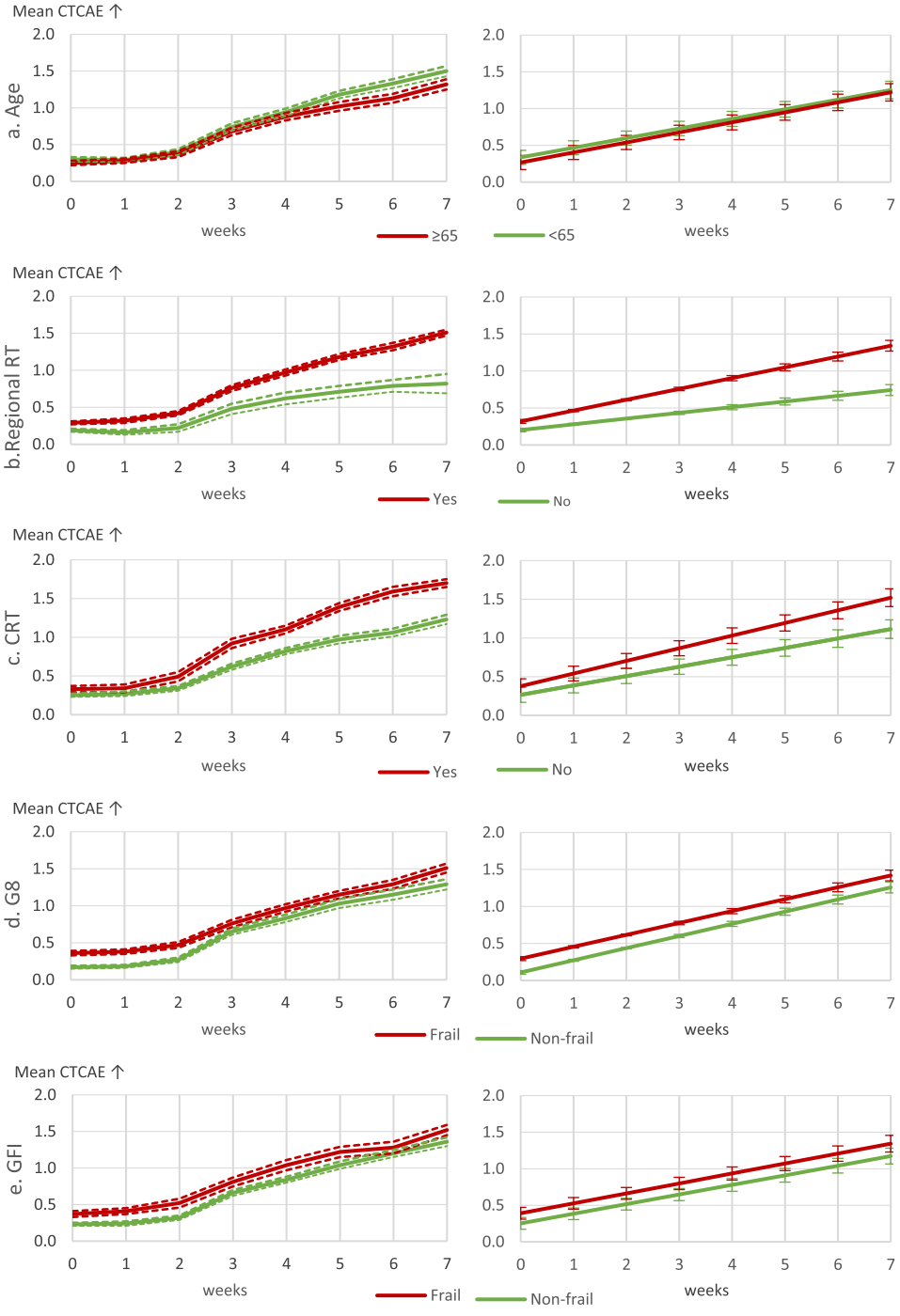

Figure 2. Radiation-induced toxicity during treatment time points week 1-week 7. The left figures represent radiation-induced toxicity scores grouped by the binary outcome of age, regional RT, CRT, G8 and GFI. The right figures represent the predicted toxicity patterns for both groups. * significance regarding the interaction term (predictor*time) ($p < 0.05$). Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, RT = Radiotherapy, CRT = Chemoradiation, G8 = Geriatric 8, GFI = Groningen Frailty Indicator.

(0.10;0.25), $p < 0.001$), was independently associated with elevated baseline toxicity. After adjusting for age, gender, stage, treatment modality, regional RT, and concurrent chemotherapy, GFI remained independently associated (β(95 %CI) = 0.14(0.06;0.22), $p < 0.001$), but G8 did not demonstrate to be independently associated with elevated baseline toxicity.

The course of RIT in frail patients, defined by either G8 or GFI, was not significantly different from RIT observed among non-frail patients, in both univariable and adjusted models (Table 4 and Fig. 2).

Discussion

To our knowledge, this is the first study that captures measures of frailty in relation to acute RIT during primary and post-operative RT. The main finding is that the different components of GA, as well as clinical frailty defined by two frailty screening tools, were not associated with additional RIT during treatment. However, age, concurrent chemotherapy, and regional RT did show significant association with elevated toxicity during RT.

Frail patients are expected to have worse toxicity outcomes compared to non-frail patients. However, in our cohort, frailty was not associated with higher RIT. The literature is controversial on this issue. Our findings are in line with a previous study on patients with HNC, which showed that neither frailty status, nor any of the items of GA are associated with RT related adverse events 12 weeks after the start of treatment [11]. Accumulation of deficits on GA and frailty screeners, however, were independently associated with post-operative complications in patients undergoing major surgery. These differences are possibly caused by the different intensity of the two treatment modalities. Surgery results in a large amount of stress in just a short time interval, however, the stress resulting from RT is more spread out over several weeks. In contrast to our findings, a prospective observational study in cancer patients reported that patients with a vulnerable status were less likely to complete RT [9]. This study only considered patients aged 75 years and older, with approximately half of the patients treated without curative intent, which may have affected outcomes. Just like frailty screening, none of the individual GA items were associated with an additional increase in RIT during RT. This finding is quite surprising, as items of GA often associate with other treatment related adverse events in oncological patients [29,30]. Recently, a prospective observational study in patients with HNC found that severe acute toxicities occurred more often in patients with moderate to severe comorbidities as defined by the ACE-27 [31]. The different outcomes may be explained by the fact that these studies mainly considered systemic toxicities, in contrast to the current study, which mainly investigated local adverse events related to RT.

Due to the impact of RIT on nutritional intake, previous findings identified risk of malnutrition as an important risk factor for developing serious adverse events during RT [32]. In contrast, risk of malnutrition defined by the MUST was not associated with additional toxicity during treatment in our study. Probably, standard screening for malnutrition embedded in the care-pathway and subsequent dietary intervention prevented further development of severe toxicities. Other components of GA, including impaired IADL and depression, as well as frailty defined by GFI, were associated with elevated toxicity at baseline. Baseline toxicity data may reflect decreased health related quality of life as well as the worse self-perceived quality of life of frail patients [33]. Therefore, frail patients may experience a higher symptom burden before the start of treatment compared to non-frail patients. Moreover, before the start of RT, RIT-like complaints can already be present caused by the tumour itself, such as hoarseness of the voice, a sore throat, and difficulty eating [34], which may alter baseline toxicity data. This is supported by the finding that patients who presented themselves with advanced tumour stage showed higher baseline toxicity grades in comparison to patients presented with early tumour stage. Even though items of geriatric assessment were not associated with additional toxicity, older age (≥65) was associated with increased RIT during treatment. This is supported by previous literature, demonstrating that older patients with HNC suffered more frequently from moderate to severe acute toxicities and required gastrostomy tube placement more often compared to their younger counterparts [16,17]. Furthermore, treatment characteristics, including concurrent chemotherapy and regional RT were also associated with toxicity in our patient cohort. Indeed, both chemotherapy and a higher radiation dose administered to the neck area have been previously identified as risk factors contributing to development of RIT [12,35,36].

One of the main strengths of this study is that the study used prospectively gathered data, and therefore, does not suffer from disadvantages of retrospective studies. Additionally, this study used well-known validated geriatric screening tools, RIT were physician-rated with the commonly used CTCAE, and data were relatively complete. This, combined with the use of a robust statistical analysis allowing for missing data without excluding entire cases, and adjusting for relevant covariates, results in a lower risk of bias.

There were some limitations of the current study, including the relatively heterogeneity of the cohort in terms of patient, tumour and treatment characteristics. Different treatment modalities were incorporated in this study, including primary RT and post-operative RT, sometimes in combination with chemotherapy. Secondly, patients that revealed to be more vulnerable were possibly more likely to be referred to a geriatrician compared to patients that were less vulnerable, and standard care measures such as dietary consulting or gastrostomy tube placement may have blurred outcomes. Last, this study did not consider late RIT, although evidence demonstrates that late RIT, defined by toxicities occurring > 90 days after initiation of RT, can have a significant impact on quality of life [37,38]. Worse quality of life is associated with frailty and deficits on geriatric assessment as well[10,39], thus it seems important to investigate whether quality of life may be affected through the mechanism of late RIT or worse resolution of acute RIT.

Using the mean CTCAE grade as an outcome measure for RIT can be debated. The mean CTCAE grade has often been utilized in studies on adverse events, and is especially useful for the general interpretation of multiple CTCAE scales together and comparison between time points [40–43]. Mean CTCAE grades steadily followed the expected trend as it increase until the last week of RT, and decreased afterwards and, as a positive control, were associated with well-known predictors of RIT such as larger radiation fields and concomitant chemotherapy.

Future research can provide more insights in the development of late toxicities. The results of this study suggest that RT seems to be relatively well tolerated in frail patients during treatment. The findings of this study are important to consider in treatment decision-making, since treatment related toxicity can impact the ability to cope with the disease and treatment of the disease. Currently, the decision between primary (C)RT and surgery is mainly based on oncological outcome. As frailty is strongly associated with severe post-operative complications, but not with acute toxicity as is demonstrated in our study, this suggests that possibly, in selected cases, primary (C)RT may be preferred over surgery with respect to acute adverse events. Future research needs to investigate whether this is the case for long-term toxicity as well, and which patients specifically benefit from (C)RT more than from surgery.

Conclusions

This study demonstrated that components of a GA, as well as frailty, defined by two frailty screening tools, were not associated with more RIT during treatment. These results suggest that, with respect to short-term adverse events, RT may be a suitable alternative to surgery in selected cases of frail patients with a considerable risk of post-operative complications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper: [Johannes A. Langendijk declared receiving grants from the European Union and Dutch Cancer Society, receiving consulting fees and honorarium from IBA, paid to UMCG Research BV, receiving research grants from IBA, RaySearch, Elekta, Mirada and Siemens, serving in the monitoring or advisory board of UMCN, IBA and RaySearch, and serving as chair of the NVRO. The other authors reported no disclosures.].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2022.105933.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424. https://doi.org/10.3322/caac.21492.

[2] Derks W, de Leeuw RJ, Hordijk GJ. Elderly patients with head and neck cancer: the influence of comorbidity on choice of therapy, complication rate, and survival. Curr Opinion Otolaryngol Head Neck Surg 2005;13(2):92–6. https://doi.org/10.1097/01.moo.0000156169.63204.39.

[3] Halmos GB, Bras L, Siesling S, van der Laan BFAM, Langendijk JA, van Dijk BAC. Age-specific incidence and treatment patterns of head and neck cancer in the Netherlands—A cohort study. Clin Otolaryngol 2018;43(1):317–24. https://doi.org/10.1111/coa.12991.

[4] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381(9868):752–62. https://doi.org/10.1016/S0140-6736(12)62167-9.

[5] Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. Lancet Oncol Oct. 2012;13(10):e437–44. https://doi.org/10.1016/S1470-2045(12)70259-0.

[6] Bellera CA, Rainfray M, Mathoulin-Pélissier 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):2166–72. https://doi.org/10.1093/annonc/mdr587.

[7] Steverink N, Slaets JPJ, Schuurmans H, van Lis M. Measuring frailty: Developing and testing the GFI (Groningen frailty indicator). Gerontologist 2001;41:236–7.

[8] Bras L, Driessen DAJJ, Vries J, Festen S, Laan BFAM, Leeuwen BL, et al. Patients with head and neck cancer: Are they frailer than patients with other solid malignancies? Eur J Cancer Care 2020;29(1). https://doi.org/10.1111/ecc.13170.

[9] Spyropoulou D, Pallis AG, Leotsinidis M, Kardamakis D. Completion of radiotherapy is associated with the Vulnerable Elders Survey-13 score in elderly patients with cancer. J Geriatric Oncol 2014;5(1):20–5. https://doi.org/10.1016/j.jgo.2013.08.002.

[10] de Vries J, Bras L, Sidorenkov G, Festen S, Steenbakkers RJHM, Langendijk JA, et al. Frailty is associated with decline in health-related quality of life of patients treated for head and neck cancer. Oral Oncol 2020;111:105020. https://doi.org/10.1016/j.oraloncology.2020.105020.

[11] Bras L, et al. Frailty and restrictions in geriatric domains are associated with surgical complications but not with radiation-induced acute toxicity in head and neck cancer patients : A prospective study. Oral Oncol 2021;118(April):105329. https://doi.org/10.1016/j.oraloncology.2021.105329.

[12] Chambers MS, Garden AS, Kies MS, Martin JW. Radiation-induced xerostomia in patients with head and neck cancer: Pathogenesis, impact on quality of life, and management. Head Neck 2004;26(9):796–807. https://doi.org/10.1002/hed.20045.

[13] VanderWalde NA, Deal AM, Comitz E, Stravers L, Muss H, Reeve BB, et al. Geriatric assessment as a predictor of tolerance, quality of life, and outcomes in older patients with head and neck cancers and lung cancers receiving radiation therapy. Int J Radiat Oncol Biol Phys 2017;98(4):850–7. https://doi.org/10.1016/j.ijrobp.2016.11.048.

[14] Benhmida S, Sun R, Gherga E, Hammoud Y, Rouvier J, Mauvais O, et al. Split-course hypofractionated radiotherapy for aged and frail patients with head and neck cancers. A retrospective study of 75 cases. Cancer/Radiotherapie 2020;24(8):812–9.

[15] Müller von der Grün J, Martin D, Stöver T, Ghanaati S, Rödel C, Balermpas P. Chemoradiotherapy as definitive treatment for elderly patients with head and neck cancer. Biomed Res Int 2018;2018:1–9. https://doi.org/10.1155/2018/3508795.

[16] Haehl E, Rühle A, David H, Kalckreuth T, Sprave T, Stoian R, et al. Radiotherapy for geriatric head-and-neck cancer patients: what is the value of standard treatment in the elderly? Radiation Oncol 2020;15(1). https://doi.org/10.1186/s13014-020-1481-z.

[17] Maggiore RJ, Curran EK, Witt ME, Haraf DJ, Vokes EE, Cohen EEW. Survival and selected outcomes of older adults with locally advanced head/neck cancer treated with chemoradiation therapy. J Geriatric Oncol 2013;4(4):327–33. https://doi.org/10.1016/j.jgo.2013.05.003.

[18] Sidorenkov G, Nagel J, Meijer C, Duker JJ, Groen HJM, Halmos GB, et al. The OncoLifeS data-biobank for oncology: a comprehensive repository of clinical data, biological samples, and the patient's perspective. J Translational Med 2019;17(1). https://doi.org/10.1186/s12967-019-2122-x.

[19] Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL. Prognostic importance of comorbidity in a hospital-based cancer registry. J Am Med Assoc May 2004;291(20):2441–7. https://doi.org/10.1001/jama.291.20.2441.

[20] Boléo-Tomé C, Monteiro-Grillo I, Camilo M, Ravasco P. Validation of the Malnutrition Universal Screening Tool (MUST) in cancer. Br J Nutr 2012;108(2):343–8. https://doi.org/10.1017/S000711451100571X.

[21] Sharma M, Loh KP, Nightingale G, Mohile SG, Holmes HM. Polypharmacy and potentially inappropriate medication use in geriatric oncology. J Geriatric Oncol Sep. 2016;7(5):346–53. https://doi.org/10.1016/j.jgo.2016.07.010.

[22] Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Biological and. JAMA 1963;185(12):914–9.

[23] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9(3 Part 1):179–86.

[24] Podsiadlo D, Richardson S. The Timed 'Up & Go': A Test of Basic Functional Mobility for Frail Elderly Persons. J Am Geriatr Soc Feb. 1991;39(2):142–8. https://doi.org/10.1111/j.1532-5415.1991.tb01616.x.

[25] van der Cammen TJ, van Harskamp F, Stronks DL, Passchier J, Schudel WJ. Value of the Mini-Mental State Examination and informants' data for the detection of dementia in geriatric outpatients. Psychol Rep 1992;71(3 Pt 1):1003–9. https://doi.org/10.2466/pr0.1992.71.3.1003.

[26] Sheikh J, Yesavage J. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clin Gerontol 1986;5(1–2):165–73. https://doi.org/10.1300/j018v05n01_09.

[27] National Cancer Institute, "Common Terminology Criteria for Adverse Events (CTCAE) version 4.0," 2009. Accessed: Feb. 01, 2021. [Online]. Available: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf.

[28] van Rijn-Dekker MI, van den Bosch L, van den Hoek JGM, Bijl HP, van Aken ESM, van der Hoorn A, et al. Impact of sarcopenia on survival and late toxicity in head and neck cancer patients treated with radiotherapy. Radiother Oncol 2020;147:103–10.

[29] Hamaker ME, Seynaeve C, Wymenga ANM, van Tinteren H, Nortier JWR, Maartense E, et al. Baseline comprehensive geriatric assessment is associated with toxicity and survival in elderly metastatic breast cancer patients receiving single-agent chemotherapy: Results from the OMEGA study of the Dutch Breast Cancer Trialists' Group. Breast 2014;23(1):81–7. https://doi.org/10.1016/j.breast.2013.11.004.

[30] Ørum M, Gregersen M, Jensen K, Meldgaard P, Damsgaard EMS. Frailty status but not age predicts complications in elderly cancer patients: a follow-up study. Acta Oncol 2018;57(11):1458–66. https://doi.org/10.1080/0284186X.2018.1489144.

[31] Monteiro AR, Garcia AR, Pereira TC, Macedo F, Soares RF, Pereira K, et al. ACE-27 as a prognostic tool of severe acute toxicities in patients with head and neck cancer treated with chemoradiotherapy: a real-world, prospective, observational study. Support Care Cancer 2021;29(4):1863–71. https://doi.org/10.1007/s00520-020-05679-4.

[32] Hopanci Bicakli D, Ozkaya Akagunduz O, Meseri Dalak R, Esassolak M, Uslu R, Uyar M. The effects of compliance with nutritional counselling on body composition parameters in head and neck cancer patients under radiotherapy. J Nutrit Metab 2017;2017:1–7. https://doi.org/10.1155/2017/8631945.

[33] Geessink N, Schoon Y, van Goor H, Olde Rikkert M, Melis R, Marengoni A. Frailty and quality of life among older people with and without a cancer diagnosis: Findings from TOPICS-MDS. PLoS ONE 2017;12(12):e0189648. https://doi.org/10.1371/journal.pone.0189648.

[34] Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet 2008;371(9625):1695–709.

[35] Chen SC, Lai YH, Huang BS, Lin CY, Fan KH, Chang JTC. Changes and predictors of radiation-induced oral mucositis in patients with oral cavity cancer during active treatment. Eur J Oncol Nursing 2015;19(3):214–9. https://doi.org/10.1016/j.ejon.2014.12.001.

[36] Lee SW, Kang KW, Wu HG. Prospective investigation and literature review of tolerance dose on salivary glands using quantitative salivary gland scintigraphy in the intensity-modulated radiotherapy era. Head Neck 2016;38(S1):1755. https://doi.org/10.1002/HED.

[37] Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol 2008;26(22):3770–6. https://doi.org/10.1200/JCO.2007.14.6647.

[38] Baudelet M, Van den Steen L, Tomassen P, Bonte K, Deron P, Huvenne W, et al. Very late xerostomia, dysphagia, and neck fibrosis after head and neck radiotherapy. Head Neck 2019;41(10):3594–603. https://doi.org/10.1002/hed.25880.

[39] de Vries J, Bras L, Sidorenkov G, Festen S, Steenbakkers RJHM, Langendijk JA, et al. Association of Deficits Identified by Geriatric Assessment with Deterioration of Health-Related Quality of Life in Patients Treated for Head and Neck Cancer.

JAMA Otolaryngol - Head Neck Surg 2021;147(12):1089. https://doi.org/10.1001/jamaoto.2021.2837.

[40] Fristrup N, Donskov F. Folic Acid Reduces Mucositis in Metastatic Renal Cell Carcinoma Patients: a Retrospective Study. Clin Genitourinary Cancer Aug. 2019; 17(4):254–9. https://doi.org/10.1016/J.CLGC.2019.03.023.

[41] Wu J, Freites-Martinez A, Hellmann MD, Rosenberg JE, Motzer RJ, Chapman PB, et al. Treatment outcomes of cutaneous adverse events to immune checkpoint inhibitors. JCO 2018;36(15_suppl):e22093. https://doi.org/10.1200/JCO.2018.36.15_SUPPL.E22093.

[42] Honma O, et al. Verification of the usefulness of an assessment and risk control sheet that promotes management of cancer drug therapy. Front Pharmacol Feb. 2022;13:264. https://doi.org/10.3389/FPHAR.2022.744916/BIBTEX.

[43] Thanarajasingam G, Minasian LM, Baron F, Cavalli F, De Claro RA, Dueck AC, et al. Beyond maximum grade: modernising the assessment and reporting of adverse events in haematological malignancies. Lancet Haematol 2018;5(11):e563–98.