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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

Linda Bras [a,1,*], Julius de Vries [a,1], Suzanne Festen [b], Roel J.H.M. Steenbakkers [c], Johannes A. Langendijk [c], Max J.H. Witjes [d], Bernard F.A.M. van der Laan [a], Geertruida H. de Bock [e], Gyorgy B. Halmos [a]

[a] Department of Otorhinolaryngology/Head and Neck Surgery, University of Groningen, University Medical Center Groningen, PO box 30.001, 9700 RB, Groningen, the Netherlands
[b] University Center for Geriatric Medicine, University Medical Center Groningen, PO box 30.001, 9700 RB, Groningen, the Netherlands
[c] Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, Groningen, PO box 30.001, 9700 RB, Groningen, the Netherlands
[d] Department of Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, PO box 30.001, 9700 RB, Groningen, the Netherlands
[e] Department of Epidemiology, University Medical Center Groningen, University of Groningen, PO box 30.001, 9700 RB, Groningen, the Netherlands

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ABSTRACT

Objectives: We aimed to evaluate the association between frailty screening and geriatric assessment (GA) on short term adverse events in patients treated for head and neck cancer (HNC) for the first time in a prospective study.
Materials and methods: Newly diagnosed HNC patients undergoing curative treatment were prospectively included in OncoLifeS, a data biobank. Prior to the start of treatment, frailty was assessed with a GA, Groningen Frailty Indicator (GFI) and Geriatric-8 (G8). The GA included comorbidity (Adult Comorbidity Evaluation – 27), nutritional status (Malnutrition Universal Screening Tool), functional status ((instrumental) Activities of Daily Living), mobility (Timed Up & Go), psychological (Geriatric Depression Scale 15) and cognitive (Mini Mental State Examination) measures. Clinically relevant postoperative complications (Clavien-Dindo $\geq$ grade 2) and acute radiation-induced toxicity (Common Terminology Criteria for Adverse Events version 4.0 $\geq$ grade 2) were defined as outcome measures. Univariable and multivariable logistic regression analyses were performed, yielding odds ratios (ORs) and 95% confidence intervals (95%CIs).
Results: Of the 369 included patients, 259 patients were eligible for analysis. Postoperative complications occurred in 41/148 (27.7%) patients and acute radiation-induced toxicity was present in 86/160 (53.7%) patients. Number of deficit domains of GA (OR = 1.71, 95%CI = 1.14–2.56), GFI (OR = 2.54, 95%CI = 1.02–6.31) and G8 (OR5.59, 95%CI = 2.14–14.60) were associated with postoperative complications, but not with radiation-induced toxicity.
Conclusion: Frailty and restrictions in geriatric domains were associated with postoperative complications, but not with radiation-induced acute toxicity in curatively treated HNC patients. The results of this prospective study further emphasizes the importance of geriatric evaluation, particularly before surgery.

Abbreviations: HNC, head and neck cancer; CGA, comprehensive geriatric assessment; GA, geriatric assessment; UMCG, University Medical Center of Groningen; ACE-27, Adult Comorbidity Evaluation-27; MUST, Malnutrition Universal Screening Tool; IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily Living; TUG, Timed Up & Go; GDS-15, Geriatric Depression Scale 15; MMSE, Mini Mental State Examination; G8, Geriatric 8; GFI, Groningen Frailty Indicator; CDC, Clavien-Dindo classification; CTCAE, Common Terminology Criteria for Adverse Events; OR, Odds ratio; 95%CI, 95% confidence intervals.

* Corresponding author at: PO box 30.001, HPC BB20, 9700 RB Groningen, the Netherlands.
E-mail address: l.bras@umcg.nl (L. Bras).
[1] these authors contributed equally to the study.

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Introduction

A challenging clinical problem for head and neck oncologists is the increase of the proportion of older patients [1]. This is a consequence of the ageing population in the Western world [2].

Ageing is a very heterogenic process, in which chronological age is a poor reflection of a patient's overall health condition [3]. Additionally, curative treatment regimens for head and neck cancer (HNC) are often multimodal and intensive, especially in advanced cases [4]. It is known that frail patients have a higher chance of adverse treatment outcome and loss of functioning [5]. This results in a complex treatment decision-making process for oncologists and their patients, in which ideally both undertreatment of fit older patients and overtreatment of frail younger patients should be avoided.

Frailty is a well-studied concept defined as those patients at risk of adverse outcomes after a stressful event due to a decrease in physiological reserves an homeostatic mechanisms [6]. The current gold standard in detecting frailty is a comprehensive geriatric assessment (CGA), a multidimensional, interdisciplinary diagnostic process usually performed by a geriatrician. A CGA focuses on physical health, functional status and psychosocial functioning in order to develop a tailored treatment plan to improve treatment outcomes in these vulnerable patients [7,8].

As a CGA is time consuming and not necessary for every patient, more simplified methods for geriatric evaluation, such as geriatric assessment (GA) or, even shorter, frailty screening tools, are proposed to select patients who need a CGA [8,9]. Using a frailty screening tool is the least time consuming option in performing a geriatric evaluation, but the sensitivity and specificity to detect vulnerable patients is poor [10]. As physical, functional and psychosocial problems are highly prevalent in the HNC population, it is likely that HNC patients could benefit from geriatric evaluation by using a CGA, GA or frailty screening tool [11]. It has already been shown that HNC patients are more frail compared to patients with other malignancies [12]. However, the value of a GA in the HNC population has not yet been thoroughly investigated [11,13]. Most of the published studies relay on retrospective data and suffer several disadvantages of a retrospective study, like missing data, inclusion bias, etc. Therefore, the goal of the present study was to determine the association between the outcomes of a GA and two frailty screeners and the incidence of postoperative complications and acute radiation-induced toxicity in a prospective cohort of curatively treated HNC patients.

Material and methods

Study design and ethical considerations

Data of newly diagnosed HNC patients were prospectively collected at the outpatient clinic of the Otorhinolaryngology, Head and Neck Surgery, and Oral and Maxillofacial Surgery departments at the University Medical Center of Groningen (UMCG). Patients were enrolled in OncoLifeS, an oncological data biobank, which has been approved by the Medical Ethical Committee of the UMCG and complies with the General Data Protection Regulation [14]. OncoLifeS is registered in the Dutch Trial Register, registration number: NL7839. Written informed consent was provided by all patients. The study protocol was approved by the scientific board of OncoLifeS. Data on radiation-induced toxicity was extracted from the prospective standardized follow-up program of the department of Radiation Oncology of the UMCG.

Study population

Between October 2014 and April 2016, all patients with a primary mucosal malignancy or a complex cutaneous malignancy (≥stage II) in the head and neck area were eligible for inclusion, regardless of age. Furthermore, patients with recurrent complex local and/or regional cutaneous malignancies and second (or more) primary complex mucosal malignancies treated with a curative intention were also included for the analyses. Patients with thyroid, hematological and recurrent mucosal malignancies of the head and neck area were excluded.

Data collection

Patient characteristics, such as age, gender, comorbidities, medications, intoxications, social status and living situation, were prospectively collected by a standardized questionnaire. Comorbidities were scored using the Adult Comorbidity Evaluation-27 (ACE-27) [15]. Use of ≥ 5 different medications was defined as polypharmacy.

A set of questionnaires and assessments was composed, which covered all domains required for a GA. The following domains were included in the GA: comorbidity (ACE-27), nutritional status (Malnutrition Universal Screening Tool (MUST)), functional status ((instrumental) Activities of Daily Living (IADL and ADL)), mobility (Timed Up & Go (TUG)), psychological status (Geriatric Depression Scale 15 (GDS-15)) and cognitive status (Mini Mental State Examination (MMSE)). A domain was considered deficient if at least one of the instruments regarding this domain showed restrictions. The Geriatric 8 (G8) and Groningen Frailty Indicator (GFI) were included as frailty screening tools. Cut off values were used, as validated in previous literature (Table 1) [16–24].

Questionnaires and assessments were partially completed in an interview during the first outpatient visit and partially filled in by patients at home and returned by mail.

Data on tumour localization, tumour stage, treatment modality and treatment intensity were obtained from the patients' medical chart. The seventh edition of the TNM Classification of Malignant Tumours from the Union for International Cancer Control was used for tumour staging [25]. Surgical treatment intensity was defined by length of surgery; major surgery was defined as 120 minutes or more [26]. Radiation treatment intensity was defined as major if the radiation field included regional lymph nodes in addition to the primary tumour.

Outcomes

Postoperative complications, occurring within 30 days after surgery,

Table 1
Overview of questionnaires and assessments used, with their cut-off values. *=not used in defining deficit domains.

Questionnaires/assessments	Abbreviation	Domain	Range	Cut-off value	Literature reference
Groningen Frailty Indicator	GFI	Frailty screener	0–15	≥4	[16]
Geriatric-8	G8	Frailty screener	0–17	≤14	[21]
Mini Mental State Examination	MMSE	Cognition	0–30	≤24	[17]
Geriatric Depression Scale 15	GDS-15	Psychological	0–15	≥6	[22]
Delirium Risk*	n/a	Psychological	0–5	≥1	[39]
Malnutrition Universal Screening Tool	MUST	Nutritional status	0–6	≥1: intermediate risk≥2: high risk	[23]
Timed Up and Go	TUG	Mobility	0-∞	≥13.5 s	[20,24]
Fall risk*	n/a	Mobility	0–1	1	[39]
Lawton Instrumental Activities of Daily Living	IADL	Functional	0–7	≥1	[18]
Katz Activities of Daily Living	ADL	Functional	0–7	≤6	[19]

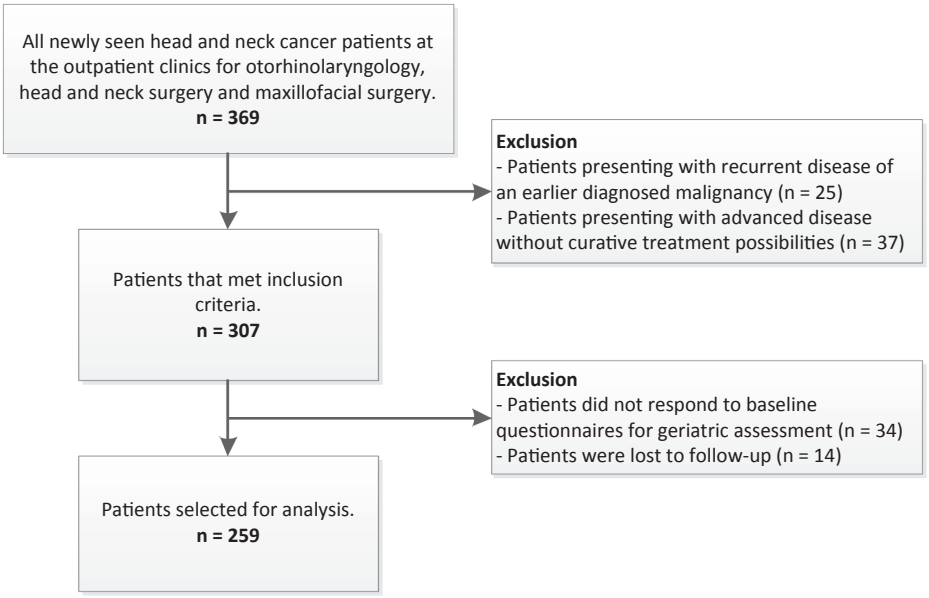

Fig. 1. Flowchart diagram representing the process of patient selection.

were scored using the Clavien-Dindo classification (CDC) (Appendix Table A.1) [27] For analysis, clinically relevant postoperative complications were defined as a CDC-score ≥ 2.

The Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0) were used to classify acute physician-rated radiation-induced toxicity. Items included weight loss, sore throat, oral pain, mucositis, general pain, dysgeusia, salivary duct inflammation, dry mouth and hoarseness (Appendix Table A.2) [28]. These scores were collected 12 weeks after the start of the therapy, at one time point and not as a cumulative score. If a patient scored grade ≥ 2 on one of the items of the CTCAE, it was classified as clinically relevant acute radiation-induced toxicity. Patients treated with primary (chemo)radiation, as well as patients treated with postoperative (chemo)radiation were analyzed as one cohort for the acute radiation-induced toxicity.

Cut-off values for both adverse event scales are chosen, based on clinical relevance.

Statistical analysis

To identify factors associated with postoperative complications and acute radiation-induced toxicity, univariable logistic regression analyses were performed, providing odds ratios (ORs), 95% confidence intervals (95%CIs) and p-values. Subsequently, multivariable logistic regression analyses with stepwise backward and forward selection were performed, including all potential confounders for the defined outcome measures. Also, separate univariable and multivariable logistic regression analyses were performed with GFI, G8 and the number of deficient geriatric domains to determine their association with both postoperative complications and radiation-induced toxicity. For this last-mentioned variable, the number of deficient domains, the tools of the GA were clustered in domains, as shown in Table 1. One domain was considered deficient if at least one test was abnormal. The association between the sum of deficient domains and adverse events were then analyzed. Pearson and Spearman correlation coefficients were calculated to check for collinearity. If collinearity was present, only the most relevant variable, based on expert knowledge, was included in the model. SPSS Statistics 23.0 software (IBM, Armonk, New York, United States of America) was used for the statistical analyses. A p-value < 0.05 was defined as statistically significant.

Table 2
Patient characteristics. (n(%), unless specified otherwise).

Variable	Non-response n = 34	Lost to follow-up n = 14	Value n = 259
Age			
Mean ± SD (y)	69.4 ± 14.2	79.3 ± 8.9	67.4 ± 10.8
Sex			
Male	20 (58.8%)	10 (71.4%)	177 (68.3%)
Female	14 (41.2%)	4 (28.6%)	82 (31.7%)
Stage			
Stage I	9 (28.1%)	5 (38.5%)	60 (24.2%)
Stage II	11 (34.4%)	4 (30.8%)	55 (22.2%)
Stage III	3 (9.4%)	1 (7.7%)	35 (14.1%)
Stage IV	9 (28.1%)	3 (23.1%)	98 (39.5%)
Location			
Oral cavity	7 (21.2%)	1 (7.1%)	69 (26.6%)
Oropharynx	4 (12.1%)	3 (21.4%)	50 (19.3%)
Hypopharynx	0 (0.0%)	0 (0.0%)	8 (3.1%)
Larynx	13 (39.4%)	2 (14.3%)	65 (25.1%)
Nasal cavity and paranasal sinus	1 (3.0%)	1 (7.1%)	13 (5.0%)
Nasopharynx	0 (0.0%)	0 (0.0%)	4 (1.5%)
Salivary glands	0 (0.0%)	0 (0.0%)	5 (1.9%)
Skin	8 (24.2%)	6 (42.9%)	39 (15.1%)
Unknown primary tumour	0 (0.0%)	1 (7.1%)	6 (2.3%)
Histopathology			
Squamous cell carcinoma	29 (87.9%)	12 (85.7%)	223 (86.4%)
Other	4 (12.1%)	2 (14.3%)	36 (13.6%)
Treatment modality			
Surgical	21 (61.8%)	2 (14.3%)	148 (57.1%)
Surgery only	18 (52.9%)	0 (0.0%)	94 (36.3%)
Adjuvant (chemo) radiotherapy	3 (8.8%)	2 (14.3%)	54 (20.8%)
Primary radiotherapy	9 (26.5%)	11 (78.6%)	69 (26.6%)
Chemoradiation	2 (5.9%)	1 (7.1%)	42 (16.2%)

Results

Study population

A total of 369 patients were included in this study. After exclusion of

Table 3
Outcome measures: postoperative complications and acute radiation induced toxicity. (n(%)).

Variable	Value
	n = 259
Clavien-Dindo classification	
None	81 (54.7%)
Grade I	26 (17.6%)
Grade II	23 (15.5%)
Grade III	13 (8.8%)
Grade IV	4 (2.7%)
Grade V	1 (0.7%)
Total	148 (100%)
Radiation-induced toxicity (CTCAE v4.0)	
None	15 (9.4%)
Grade I	59 (36.9%)
Grade II	76 (47.5%)
Grade III	9 (5.6%)
Grade IV	1 (0.6%)
Grade V	0 (0.0%)
Total	160 (100.0%)

patients with recurrent disease, palliative treatment and incomplete data, 259 patients remained eligible for inclusion and analysis (Fig. 1). Patients who did not return questionnaires (n = 34) showed more restrictions in cognition (MMSE), functionality (IADL) and mobility (TUG), and were more frail (G8), than patients who did return questionnaires, based on available data from first outpatient visit.

Patient, tumour and treatment characteristics are presented in Table 2. More than two-thirds of the patients were male (n = 177, 68.3%) and the mean age was 67.4 years. More than half of the patients presented with advanced stage (n = 133, 53.6% stage III/IV). Oral cavity (n = 69, 26.6%) and larynx (n = 65, 25.1%) were the most affected tumour sites, followed by oropharynx (n = 50, 19.3%) and skin (n = 39, 15.1%). Histopathological diagnosis was predominantly squamous cell carcinoma (n = 223, 86.4%). Surgical treatment was performed in 148 patients (57.1%), of which 54 patients (20.8%) underwent postoperative (chemo)radiation. Primary (chemo)radiation was given in 111 patients (42.9%).

Postoperative complications CDC $\geq$ 2 occurred in 41 (27.7%) surgically treated patients. One patient died during the first 30 days after surgery. Acute radiation-induced toxicity was present in 86 (53.7%) patients who underwent primary or postoperative (chemo)radiation (Table 3).

Postoperative complications

Advanced tumour stage (OR = 3.67, 95%CI = 1.66–8.08), major treatment intensity (OR = 3.35, 95%CI = 1.21–9.30), history of smoking (OR = 4.22, 95%CI = 1.20–14.79) and moderate or severe comorbidities (OR = 2.66, 95%CI = 1.25–5.63) were associated with postoperative complications in the univariable analysis (Table 4). Regarding the items of the GA, intermediate risk of malnutrition (OR = 4.64, 95%CI = 1.41–15.28), TUG time (OR = 1.10, 95%CI = 1.01–1.20) and restrictions in ADL (OR = 2.73, 95%CI = 1.02–7.31) were associated with postoperative complications in univariable analysis.

A multivariable model was fitted using eligible variables. Age (OR = 1.05, 95%CI = 1.01–1.10), major treatment intensity (OR = 5.75, 95% CI = 1.67–19.85), history of smoking (OR = 7.36, 95%CI = 1.71–31.74), moderate to severe comorbidities (OR = 2.43, 95%CI = 1.01–5.82) and intermediate risk of malnutrition (OR = 5.45, 95%CI = 1.43–20.74) were independently associated with the occurrence of postoperative complications.

Acute radiation-induced toxicity

Advanced tumour stage (OR = 4.28, 95%CI = 2.03–9.04), major treatment intensity (OR = 6.17, 95%CI = 2.88–13.20), concomitant chemoradiation (OR = 3.55, 95%CI = 1.67–7.53) and level of education were associated with acute radiation-induced toxicity in univariable analysis (Table 5).

A multivariable model was fitted using eligible variables. Major treatment intensity (OR = 5.18, 95%CI = 2.29–1.74) and concomitant chemoradiation (OR = 2.95, 95%CI = 1.17–7.45) were independently associated with acute radiation-induced toxicity, adjusted for age.

Comparing GFI, G8 and GA and its association with adverse treatment outcomes

Frailty on GFI and G8, and the number of deficit domains on GA were all associated with postoperative complications in both unadjusted and adjusted models (Table 6). G8-frailty (OR = 5.59, 95%CI = 2.14–14.60) had a stronger association with postoperative complications than GFI-frailty (OR2.54, 95%CI = 1.02–6.31). An increase in the number of deficit domains on GA resulted in a 1.71 (95%CI = 1.14–2.56) times higher risk of developing postoperative complications.

Radiation-induced toxicity was not associated with GFI, G8 and the number of deficit domains on GA in both unadjusted and adjusted models.

Discussion

To our knowledge, this is the first prospective study investigating the association between GA and frailty screeners, and short term adverse treatment outcomes in a cohort of HNC patients, regardless of treatment modality. The analyses reveal that both GA and frailty screeners are independently associated with postoperative complications in HNC patients, but not with acute radiation-induced toxicity. Focusing on independent instruments of the GA, more advanced comorbidities and an intermediate malnutrition risk are found to be associated with a higher risk of postoperative complications, besides more advanced age, major treatment intensity and (history of) smoking. Analyzing the GA domains as separate entities, each additional restricted domain causes a nearly twofold increase risk of postoperative complications.

These findings confirm the results of a previous study, proposing a preoperative head and neck surgery risk index combining data about comorbidities, functional and nutritional domains with patient characteristics and treatment intensity, as a predictor for postoperative adverse events [29]. Some other studies also found frailty and major treatment intensity to be associated with an increased risk for postoperative complications in HNC patients [30,31]. A recent review has confirmed that frailty objectively can predict outcome after surgical treatment of oral and oropharyngeal cancer and suggests routine preoperative frailty screening [32]. Since a GA, which is a prospective method by definition, is able to detect as yet unknown (health) problems in patients, it is likely that the retrospective study design of the three aforementioned studies leads to underreporting of restrictions in the investigated domains of life [29–31,33]. Besides this current study, no other prospective studies investigating GA in relation to postoperative complications in HNC patients are currently available [34].

Regarding treatment outcomes after (chemo)radiation in relation to frailty and GA only limited data is available. Like our findings, VanderWalde et al. concluded in a study with both HNC and lung cancer patients that concomitant chemoradiation is associated with poor treatment tolerance due to treatment related toxicity, while restrictions in IADL are not related with poor treatment tolerance [35]. We can only speculate why a GA is associated with adverse treatment outcomes in surgically treated patients, but not in patients undergoing radiation treatment. Probably, the gradual increase in complaints during the course of the radiation treatment is better tolerated in frail patients than

Table 4
Univariable and multivariable logistic regression analyses with surgical complications as the dependent variable, yielding odds ratios, 95% confidence intervals and p-values (significant values are highlighted with bold letter type). Abbreviations: BMI = Body Mass Index, ACE-27 = Adult Comorbidity Evaluation 27, MMSE = Mini Mental State Examination, GDS-15 = Geriatric Depression Scale 15, MUST = Malnutrition Universal Screening Tool, TUG = Timed Up and Go, IADL = Instrumental Activities of Daily Living, ADL = Activities of Daily Living.

Variable	Value	Univariable analysis		Multivariable analysis	
	n = 148	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age					
Mean ± SD (y)	69.3 ± 11.1	1.03 (0.99–1.06)	0.118	**1.05 (1.01–1.10)**	**0.023**
Sex					
Male	95 (64.2%)	1			
Female	53 (35.8%)	0.57 (0.26–1.25)	0.161		
Stage					
Early stage (I-II)	78 (52.7%)	1			
Advanced stage (III-IV)	65 (43.9%)	**3.67 (1.66–8.08)**	**0.001**		
Treatment intensity					
Minor (surgery < 120 min)	41 (27.0%)	1		1	
Major (surgery ≥ 120 min)	107 (73.0%)	**3.35 (1.21–9.30)**	**0.016**	**5.75 (1.67–19.85)**	**0.006**
BMI					
< 18.5	4 (2.8%)	1	0.833		
≥ 18.5 and < 25	57 (40.1%)	1.07 (0.10–11.11)	0.954		
≥ 25	81 (57.0%)	1.34 (0.13–13.52)	0.804		
History of smoking					
No	30 (20.5%)	1		1	
Yes	116 (79.5%)	**4.22 (1.20–14.79)**	**0.025**	**7.36 (1.71–31.74)**	**0.007**
History of drinking					
No	37 (27.8%)	1			
Yes	96 (72.2%)	1.06 (0.45–2.48)	0.899		
Education					
Low level of education	64 (44.8%)	1	0.560		
Middle level of education	50 (35.0%)	1.54 (0.67–3.52)	0.309		
High level of education	29 (20.3%)	1.04 (0.37–2.91)	0.941		
Marital status					
Single	30 (20.4%)	1			
In a relationship	117 (79.6%)	0.49 (0.21–1.15)	0.101		
ACE-27					
None or mild	76 (51.4%)	1		1	
Moderate or severe	72 (48.6%)	**2.66 (1.25–5.63)**	**0.011**	**2.43 (1.01–5.82)**	**0.047**
Polypharmacy					
< 5 medications	92 (62.6%)	1			
≥ 5 medications	55 (37.4%)	1.46 (0.70–3.04)	0.313		
MMSE					
Normal cognitive function (>24)	129 (88.4%)	1			
Declined cognitive function (≤24)	17 (11.6%)	1.47 (0.50–4.26)	0.483		
GDS-15					
No depression (<6)	134 (92.4%)	1			
Depression (≥6)	11 (7.6%)	2.36 (0.68–8.21)	0.178		
History of delirium					
No	143 (97.3%)	1			
Yes	4 (2.7%)	2.67 (0.36–19.59)	0.335		
MUST					
Low risk (=0)	117 (83.6%)	1	**0.034**	1	**0.042**
Intermediate risk (=1)	13 (9.3%)	**4.64 (1.41–15.28)**	**0.012**	**5.45 (1.43–20.74)**	**0.013**
High risk (≥2)	10 (7.1%)10 (7.1%)	0.73 (0.15–3.61)	0.694	0.92 (0.16–5.37)	0.924
TUG					
Mean ± SD (s)	9.8 ± 4.7	**1.10 (1.01–1.20)**	**0.029**		
History of falls					
No	127 (88.8%)	1			
Yes	16 (11.2%)	0.81 (0.25–2.68)	0.731		
IADL					
No restrictions (<3)	129 (87.8%)	1			
Restrictions (≥3)	18 (12.2%)	1.78 (0.64–4.96)	0.271		
ADL					
No restrictions (<1)	129 (87.2%)	1			
Restrictions (≥1)	19 (12.8%)	**2.73 (1.02–7.31)**	**0.046**		

the major stressor at once during surgery. Surgery is an event which results in acute physical stress. On the other hand, curative radiation therapy is a treatment which is usually spread over 6 or 7 weeks. The longer treatment period allows compensation. As frailty refers to a decrease in physiological reserves and homeostatic mechanisms after a stressful event increases, one can speculate that the length and intensity of the stress is an important factor. If the stressful event is very intensive at one time point, like a surgery, the patient may run out of its physiological reserves easier. In contrast, if the stressful event is long lasting and less intensive at one time point, like radiation therapy, the patient has more time to compensate.

A punctual assessment, 12 weeks after the start of radiation therapy, was used as a measure for acute radiation induced toxicity. At this time point it is expected that patients recovered from the peak of radiation-induced toxicity occurring after six to seven weeks. A high CTCAE score at 12 weeks indicates a slow recovery after completing the

Table 5
Univariable and multivariable logistic regression analyses with radiation-induced toxicity as the dependent variable, yielding odds ratios, 95% confidence intervals and p-values (significant values are highlighted with bold letter type). [a] = Adjusted for age. Abbreviations: BMI = Body Mass Index, ACE-27 = Adult Comorbidity Evaluation 27, MMSE = Mini Mental State Examination, GDS-15 = Geriatric Depression Scale 15, MUST = Malnutrition Universal Screening Tool, TUG = Timed Up and Go, IADL = Instrumental Activities of Daily Living, ADL = Activities of Daily Living.

Variable	Value	Univariable analysis		Multivariable analysis [a]	
	n = 160	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age					
Mean ± SD (y)	65.8 ± 10.4	0.99 (0.96–1.02)	0.574		
Sex					
Male	115 (71.9%)	1			
Female	45 (28.1%)	0.76 (0.38–1.52)	0.441		
Stage					
Early stage (I-II)	45 (28.1%)	1			
Advanced stage (III-IV)	115 (71.9%)	**4.28 (2.03–9.04)**	**< 0.001**		
Treatment intensity					
Minor (local radiotherapy)	49 (30.6%)	1		1	
Major (locoregional radiotherapy)	111 (69.4%)	**6.17 (2.88–13.20)**	**< 0.001**	**5.18 (2.29–11.74)**	**< 0.001**
Concomitant chemotherapy					
No	113 (70.6%)	1		1	
Yes	47 (29.4%)	**3.55 (1.67–7.53)**	**0.001**	**2.95 (1.17–7.45)**	**0.022**
BMI					
< 18.5	8 (5.0%)	1	0.759		
≥ 18.5 and < 25	71 (44.7%)	0.62 (0.14–2.78)	0.530		
≥ 25	80 (50.3%)	0.73 (0.16–3.28)	0.685		
History of smoking					
No	21 (13.2%)	1			
Yes	138 (86.8%)	1.31 (0.52–3.28)	0.565		
History of drinking					
No	23 (15.5%)	1			
Yes	125 (84.5%)	1.30 (0.53–3.17)	0.562		
Education					
Low level of education	67 (44.4%)	1	**0.039**		
Middle level of education	50 (33.2%)	0.59 (0.28–1.23)	0.158		
High level of education	34 (22.5%)	1.95 (0.80–4.70)	0.139		
Marital status					
Single	44 (27.7%)	1			
In a relationship	115 (72.3%)	0.86 (0.43–1.73)	0.669		
ACE-27					
None or mild	95 (59.4%)95 (59.4%)	1			
Moderate or severe	65 (40.6%)	1.12 (0.59–2.11)	0.732		
Polypharmacy					
< 5 medications	108 (67.5%)	1			
≥ 5 medications	52 (32.5%)	0.71 (0.37–1.39)	0.319		
MMSE					
Normal cognitive function (>24)	147 (91.9%)	1			
Declined cognitive function (≤24)	13 (8.1%)	2.05 (0.60–6.94)	0.251		
GDS-15					
No depression (<6)	141 (88.1%)	1			
Depression (≥6)	16 (10.2%)	1.10 (0.39–0.312)	0.858		
History of delirium					
No	152 (95.6%)	1			
Yes	7 (4.4%)	0.64 (0.14–2.96)	0.568		
MUST					
Low risk (=0)	114 (72.6%)	1	0.710		
Intermediate risk (=1)	18 (11.5%)18 (11.5%)	0.67 (0.25–1.82)	0.434		
High risk (≥2)	25 (15.9%)	1.07 (0.45–2.55)	0.883		
TUG					
Mean ± SD (s)	9.5 ± 4.1	1.04 (0.96–1.11)	0.378		
History of falls					
No	140 (89.2%)	1			
Yes	17 (10.8%)	3.16 (0.98–10.16)	0.054		
IADL					
No restrictions (<3)	147 (91.9%)	1			
Restrictions (≥3)	13 (8.1%)13 (8.1%)	1.42 (0.44–4.53)	0.558		
Katz-ADL					
No restrictions (<1)	146 (93.0%)	1			
Restrictions (≥1)	11 (7.0%)	0.69 (0.20–2.35)	0.551		

radiation treatment [36]. Although nine items of the CTCAE were included to evaluate radiation-induced toxicity in this study, these items only scored locoregional complaints and not systemic problems (e.g. fatigue, infections, laboratory toxicities). Unfortunately, these items are not available for all patients in our cohort.

A geriatric evaluation, in the form of a GA or CGA, has potential in detecting previously unidentified but manageable problems. This geriatric evaluation might lead to better outcomes, by improving treatment tolerance and adjusting oncologic treatment plans in the elderly cancer population [9,33,37,38].

Conflicting results are available on the role of a geriatric evaluation with tailored interventions and its effect in short term treatment

Table 6
Univariable and multivariable logistic regression models for frailty screening as a predictor of postoperative complications and radiation induced toxicity (dependent variables), yielding odds ratios, 95% confidence intervals and p-values (significant values are highlighted with bold letter type). [a] = Adjusted for age, sex, stage, treatment intensity, and history of smoking. [b] Domains are clustered in comorbidity, nutrition, functional, mobility, psychological and cognitive, corresponding tools for the specific domains are listed in Table 1. [c] = Adjusted for age, sex, stage, treatment intensity and chemotherapy.

Postoperative complications	Value	Unadjusted		Adjusted [a]	
	n = 148	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
GFI					
Non-frail (<4)	108 (74.0%)	1		1	
Frail (≥4)	38 (26.0%)	**2.83 (1.29–6.21)**	**0.009**	**2.54 (1.02–6.31)**	**0.045**
G8					
Non-frail (>14)	73 (49.7%)	1		1	
Frail (≤14)	74 (50.3%)	**4.54 (2.02–10.22)**	**< 0.001**	**5.59 (2.14–14.60)**	**< 0.001**
Number of deficient domains on GA[b]					
Continuous	N/A	**1.90 (1.34–2.69)**	**< 0.001**	**1.71 (1.14–2.56)**	**0.009**
Radiation-induced toxicity	Value	Unadjusted		Adjusted [c]	
	n = 160	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
GFI					
Non-frail (<4)	114 (71.3%)	1		1	
Frail (≥4)	43 (26.9%)	1.43 (0.70–2.91)	0.330	1.13 (0.51–2.53)	0.764
G8					
Non-frail (>14)	88 (55.0%)	1		1	
Frail (≤14)	72 (45.0%)	1.03 (0.55–1.93)	0.924	0.72 (0.35–1.50)	0.376
Number of deficient domains on GA[b]					
Continuous	N/A	1.13 (0.85–1.52)	0.397	1.22 (0.87–1.72)	0.241

outcomes in the elderly cancer population. A recent systematic review on this topic, merely including controlled studies on patients with various cancer types and treatment modalities, showed less adverse events in patients who underwent a geriatric evaluation in five out of nine included studies; however, no significant effect was seen in the four other studies [33]. It is likely that the above-mentioned potential benefits of a GA also apply to patients with HNC, and should be the foundation for future research on this topic.

A major strength of our study is the prospective collection of GA data, covering all the domains as required in a geriatric evaluation, by using multiple validated instruments. Some elements of the GA are linked to standardized interventions in the Dutch safety management system, implemented as standard care in our hospital [39]. For instance, interventions for delirium prevention were advised for patients at risk of delirium. Another example is malnutrition; patients with intermediate malnutrition risk received nutritional advices from a nurse and patients with high malnutrition risk were referred to a dietitian. The different degree of intervention may explain that intermediate malnutrition risk patients show a stronger association with postoperative complications than patients with a high malnutrition risk. It is likely that these interventions influenced the incidence of adverse events. Though, postoperative complications (CDC $\geq$ 2) occurred in 27.7% and radiation induced toxicity (CTCAE $\geq$ 2) in 50.6% of the patients in the current cohort, and are comparable with earlier reported percentages [26,36]. Another limitation of the present study is the possible underrepresentation of the frailest patients, since particularly these patients tend to not return questionnaires, and were therefore excluded due to incomplete baseline data. Last, but not least, the heterogeneity of tumour types and primary sites of the included patients can be regarded as a limitation. However, the present study aimed to evaluate the effect of GA on treatment related adverse events, like surgical complications and (chemo)radiation induced acute toxicity. These adverse events are more related to the treatment procedure rather than the histological features; however, tumour localization may affect the type and severity of treatment-related adverse events. By defining the treatment intensity and including this adjusting variable in the multivariable analyses, a distinction is made between treatment procedures with major and minor impact. A powered study with a more homogeneous patient population would require a multicenter setting, which seems to be very challenging, as such a detailed GA was already very demanding in one center, taking huge efforts of doctors and nurses.

Chronological age often does not correlate with biological age, specifically for patients with HNC. There is evidence, that HNC patients are frailer than patients with other solid malignancies [12]; therefore, these patients should undergo frailty screening. The results of the present study further emphasize the importance of assessing geriatric status (i.e. biological age), regardless of chronological age.

Based on the results of this study we recommend all healthcare professionals in head and neck oncology to perform geriatric evaluation in all newly diagnosed HNC patients, regardless of age. Besides the potential for optimizing the pretreatment condition of patients and tailoring treatment plans, it is strongly associated with short term outcomes. From our experience, collaboration with a geriatrician is very helpful for interpreting screening results and considering treatment options, especially in patients with multi-domain problems.

Conclusions

This study presents the value of pre-treatment frailty screening and GA in head and neck oncology in a prospective study, for the first time. Frailty and restrictions in geriatric domains are associated with postoperative complications in surgically treated HNC patients. In contrast, acute radiation-induced toxicity is not associated with the outcomes of a geriatric evaluation. Routine screening of newly diagnosed HNC patients, including an evaluation of all geriatric domains, is highly recommended, especially in patients eligible for surgical treatment.

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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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2021.105329.

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