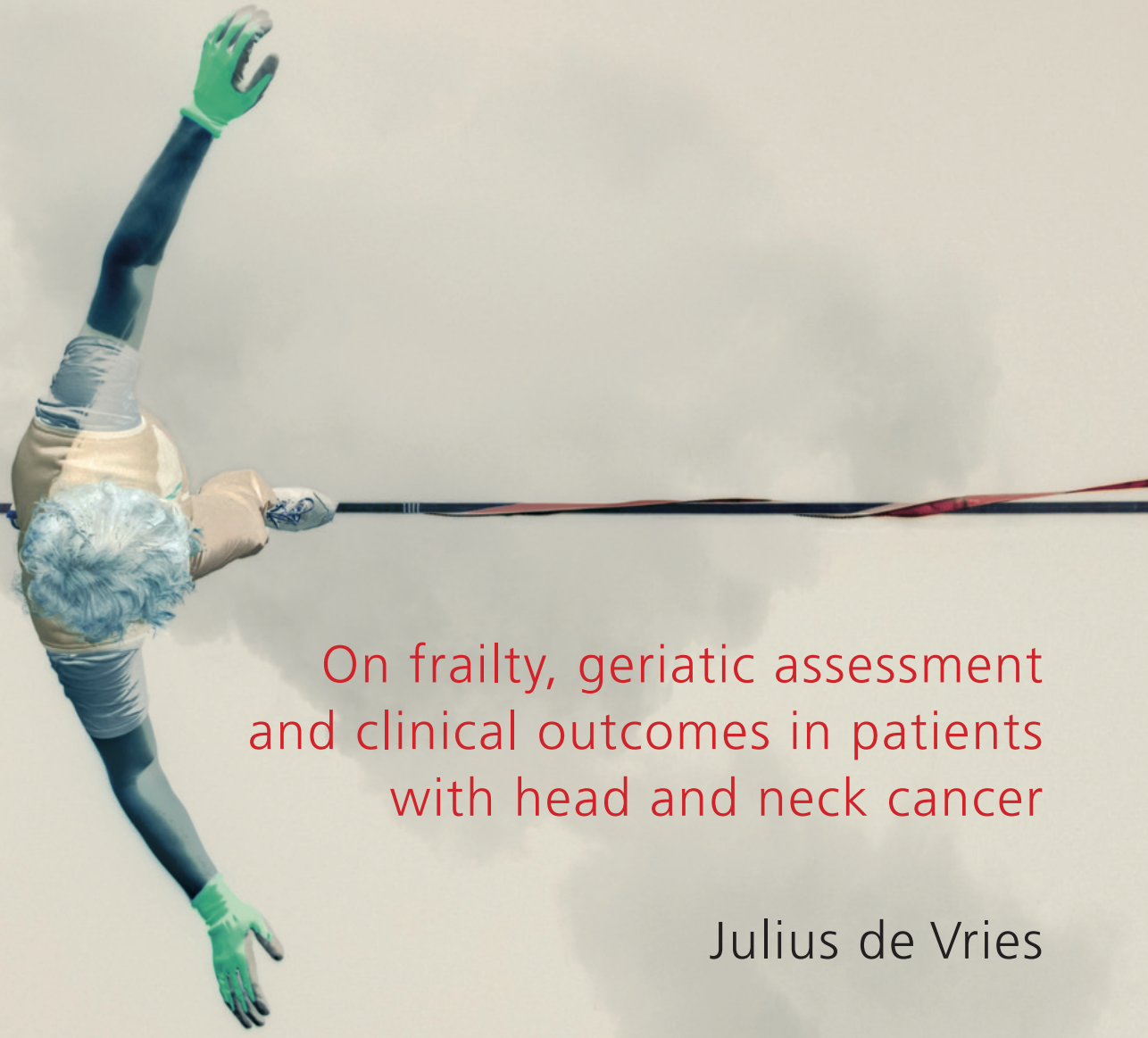

On frailty, geriatic assessment and clinical outcomes in patients with head and neck cancer

Julius de Vries

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Colophon

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chapter one

General introduction and outline of this thesis

Julius de Vries, MD

GENERAL INTRODUCTION

Head and neck cancer (HNC) accounts for approximately 900.000 new cases annually.[1] This comprises a group of cancers, mainly squamous cell carcinoma (HNSCC), arising from the oral, laryngeal, pharyngeal, nasal and paranasal mucosal epithelium, and other histopathological subtypes in the salivary glands. Other cancers often seen by head and neck oncologists may include complex or advanced stage melanoma and non-melanoma skin cancer, and cancer of the thyroid glands, although in the Netherlands the latter is treated by general surgical oncologists rather than by head and neck oncologists. Today already, and even more in the future, demographic and epidemiological changes are leading to an increase of older and potentially frail patients with HNC. This thesis focuses on the effects of geriatric deficiencies and frailty on clinical outcomes after treatment for cancers in the head and neck area. In this general introduction, the epidemiology, treatment and patient characteristics of patients with HNC, and frailty, screening and assessment, and the clinical problem will be addressed.

Epidemiology of head and neck cancer in an aging society

The incidence of cancer is rapidly increasing.[1] Worldwide, there are an estimated 19.3 million new cases annually (including non-melanoma skin cancer, excluding basal cell carcinoma).[1] This is projected to be 28.4 million in 2040.[1] Life expectancy is increasing and the proportion of elderly is dramatically on the rise.[2] Worldwide, the number of persons aged 65 or over is projected to more than double between 2019 and 2050 and the number of persons aged 80 or over is expected to triple within the same period of time.[3] In Europe and Northern America, where the population is already much older than in other parts of the world, the number of persons aged 65 or over is projected to increase from 200.4 million to 296.2 million people between 2019 and 2050, an increase of 48%.[3] For persons aged 80 or over, the projected change is even stronger, rising from 53.9 million to 109.1 million, an increase of 103%.[3] Because of these demographic transitions, the number of elderly with cancer is expected to increase as well.[4,5]

This is also the case with HNC in Europe. Incidence rates per 100.000 for all HNC anatomical sites combined are rising, within all ages categories.[6] Specifically, incidence rates of oropharyngeal cancer are on the rise, which is strongly associated with Human Papilloma Virus (HPV) infection, one of the etiological factors for oropharyngeal cancer.[7] Although, at first, HPV-positive oropharyngeal cancer seemed to be mainly present within in younger age categories, recent increase in the older age categories have been demonstrated as well.[8,9] Incidence rates for oral cavity and salivary gland cancers are steadily increasing, within all age categories.[6] Incidence rates of laryngeal, hypopharyngeal and nasopharyngeal cancer remain relatively stable, but may tend to be decreasing in women.[6] Possibly, this is a result of fewer people smoking. It should be taken into account that these are only incidence rates, and thus, with growth of the (older) population, the absolute number of new HNC cases will be even higher.

Treatment of head and neck cancer

At presentation, approximately 30 to 40% of patients with HNSCC have early-stage (stage I or II) disease, and more than 60% of patients advanced-stage (stage III or IV) disease.[10] Curative

treatment options for HNSCC include surgery, radiotherapy (RT) and chemotherapy (CT), but are often a combination of these modalities.[11] For oral cancers, the preferred primary treatment is surgery in operable cases, followed by adjuvant (chemo)radiotherapy ((C)RT), if indicated. For most pharyngeal cancers, due to their advanced stage, their inaccessible location, and risk of loss of function after surgery, the primary treatment of choice is generally (C)RT, although a small window of de-intensification is arising for early-stage oropharyngeal cancer using primary transoral robotic surgery as a single modality.[12] Also, there is a place for cetuximab as an alternative to CT such as cisplatin in the concurrent systemic treatment.[13] For laryngeal cancer in early-stage (T1a) transoral laser surgery is the choice of treatment, but for more advanced cases and the preferred primary treatment is (C)RT as well, as long as laryngeal function can be preserved, and may otherwise be extensive surgery followed by (C)RT, if indicated. In case of residual disease or recurrence, re-resection, re-irradiation or salvage surgery may be needed, however, in general, these cases have poor prognosis.[11] Altogether, with the exception of early-stage tumors that allow for local surgical control and patients undergoing definitive RT without concomitant CT, a large proportion of HNSCC patients require multimodal treatment. When treatment with curative intent is not possible, palliative treatment options for HNSCC may include RT, CT, or immunotherapy, in addition to supportive care.

Such a large proportion of older patients with advanced disease on the one hand and intensive multimodal treatments on the other hand brings up the question whether older patients are treated differently than their younger counterparts. And indeed, older patients are more likely to receive non-standard treatment, no treatment, limited surgery or no post-operative radiotherapy (PORT).[14] Also, older individuals with HNC receive more often palliative treatment, and less often multimodal treatment.[15] One of the clearest examples of treatment discrimination between older and younger HNSCC patients is the treatment with concomitant CT in addition to definitive RT. Since the large meta-analysis of CT in HNSCC patients (MACH-NC study) by Pignon et al. demonstrated the benefit of concomitant CT in patients aged 70 and younger but not in patients aged 71 and older,[16] guidelines recommend no concomitant CT above the age of 70. Regardless, the proportion of patients 71 and older was only 2%, the outcome measure overall survival could easily have been polluted by non-cancer deaths in this age category and only chronological age was used as a parameter. It seems that it is tempting to de-intensify treatments based on age. But when speaking of age, almost always there is referred to chronological age. Chronological age alone as an argument to withhold someone a treatment can be seen as ageism, which is referred to as discrimination based on someone's age. Ideally, a treatment plan should be based on the patients' biological age, and not on chronological age alone.

Clinical characteristics of patients with head and neck cancer

Patients with HNC make a complex patient population. More than half of the patients is older than 60 years and more than two-thirds of patients are male.[17] The difficulties begin with the etiological factors for HNSCC, such as alcohol and tobacco abuse, that are responsible for more than 75% of HNSCC.[18,19] Besides, at diagnosis, patients often still use tobacco and alcohol.[20] Such unhealthy lifestyle comes with comorbid conditions as well. In HNSCC patients, prevalence of comorbidities ranges from 36 to 89%, often includes multiple or severe comorbidities, occurring

mostly in the cardiovascular and pulmonary systems.[21] The prevalence of comorbidities before diagnosis is higher for patients with HNC than for other patients.[22] At diagnosis, highly prevalent comorbidities are hypertension, hyperlipidemia, chronic obstructive pulmonary disease (COPD), diabetes, anemia and cardiac disease.[23] Not only physical comorbidities, but also psychological and social issues are highly prevalent among patients with HNSCC. This includes depression, substance abuse, low educational level, poor social support and low socio-economic status.[24–26] The disease itself may seriously compromise the upper gastro-intestinal and upper respiratory tract. Presenting most often in advanced-stage, this may already lead to problems with nutritional intake and breathing. Sometimes, interventions, such as tracheostomy or tube feeding, are already needed before treatment to maintain life.[27] Also, with organs such as the larynx being affected, interpersonal interaction may be altered and lead to social isolation. Altogether, the stereotypical patient with HNSCC is older, male, smokes tobacco and drinks alcohol, has multiple comorbidities and psychosocial issues, and presents with advanced-stage and corresponding secondary health problems.

Patients with complex skin cancer in the head and neck area

A group of patients that is increasingly seen at the outpatient clinic of head and neck oncological surgeons, are patients with complex skin cancer in the head and neck area. Skin cancer is the most common type of cancer worldwide, with incidence rates rising quickly, and may sometimes even be referred to as the skin cancer epidemic.[1,28] As it mainly affects people aged 65 and older, this is probably related with the ageing population in general.[28] Within the head and neck area, most common histopathological types of skin cancer are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), malignant melanoma (MM) and Merkel cell carcinoma (MCC). For most skin cancers interference of a head and neck surgeon will not be needed, however for some cases of complex skin cancer this surely is required. Although there is no international definition on 'complex skin cancer', in The Netherlands patients with basal cell carcinoma in advanced-stage, squamous cell carcinoma stage III and higher, malignant melanoma, Merkel cell carcinoma, neck metastasis of any type skin cancer, involvement of external auditory canal or orbit of any type skin cancer, as well as less advanced cases in need of extensive surgery, are being referred to head and neck oncological surgeons, according to local guidelines.[29] Although novel treatment strategies are arising, mainly for malignant melanoma, surgery remains the cornerstone of treatment, which in case of complex skin cancer can be of extensive nature.

Biological age and frailty

Chronological age is an important predictor for health and survival.[30] Nevertheless, great diversity between individuals of the same age exists. The older the group of individuals, the greater the variance within can be. Ageing is a very heterogeneous process in which the ravages of time leave great diversity in health status between individuals. Some factors for this may already be present at birth, such as genetic factors. Other factors will be acquired during life, such as environmental factors. Although time underlies all events related to aging, it is too short-sighted to use chronological age alone as a marker for age, as individuals seem to age in different rates.[30] With ageing, the ability to withstand damage and stress declines. Thus, especially prior to intensive

treatments, it is important to be able to estimate treatment resilience. However, determining biological age is challenging. In an ideal world, a simple laboratory test for biomarkers of aging can be done to identify patients with a higher biological age. However, these biomarkers of biological age are still a utopia. From a more clinical perspective, biological age can be seen as a clinical diagnosis called frailty.[31] Frailty is defined as "a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse outcomes", and can be seen as an expression of aging.[31] An example is provided in Figure 1. A fit person may easily withstand a treatment (stressor) and regain independency soon, however, a frail person may have more difficulty recovering from the stressor and may not return to previous level of functioning. Although the term frailty had been coined in the 1970s already, two important conceptual models of frailty were described in 2001.[32] The phenotype model suggests that frailty is a syndrome of weight loss, exhaustion, low physical activity, slowness and weakness, known as the Fried criteria.[33] The deficit accumulation model advocates that frailty results from the accumulation of health-related deficits; the more health-related deficits are present, the frailer and the more risk of adverse outcomes.[34–37] Lifestyle factors that are exhibited frequently within the HNC population, are associated with higher frailty burden as well. Tobacco smoking is strongly associated with higher incidence and higher chances of development of frailty.[38,39] High alcohol consumption, although difficult to prove due to reverse causality and sick-quitter effects, predicted frailty as well.[40]

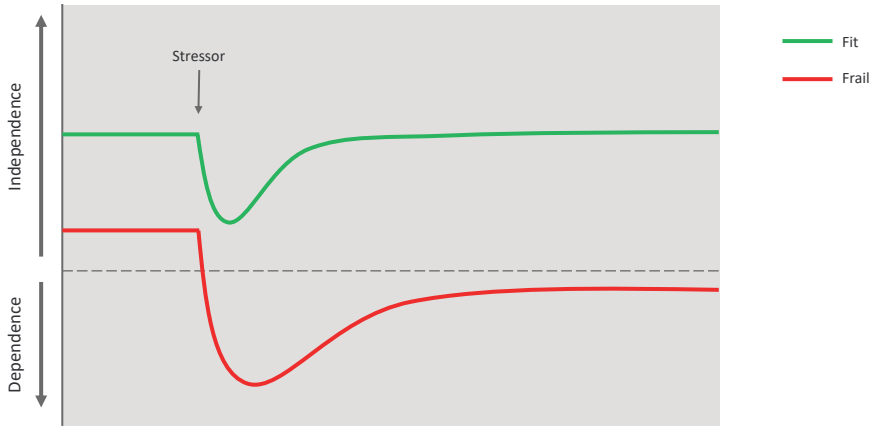

Figure 1 | Trajectories of dependency for fit and frail patients undergoing a stressor (e.g. surgery). Frail patients may have more difficulties of withstanding a stressor, difficulty recovering, and may not return to pre-treatment level of functioning. Adopted from Clegg et al., Lancet Volume 381, Issue 9868, 2–8 March 2013, Pages 752-762.

Screening and assessments to diagnose frailty

Frailty is poorly diagnosed by oncologists.[41] Therefore, doing a form of structural screening or assessment is necessary. The gold standard to diagnose frailty is a comprehensive geriatric assessment (CGA) by a geriatrician. A CGA can be defined as "a multi-dimensional, interdisciplinary,

diagnostic process to identify care needs, plan care, and improve outcomes of frail older people".[42] Typically, the physical, functional, psychological and socioenvironmental domains are incorporated within a CGA.[42] CGA can help professionals, patients and relatives in the decision making process, but may also reveal deficiencies that can be optimized ahead of treatment. An overview of items that may be included in a CGA is given in Figure 2. However, a CGA is time-consuming and health-care resources are limited. Referring all patients to a geriatrician would be infeasible and not needed. Frailty screening instruments have been developed to screen and select patients who could benefit from a CGA.[43] Examples of frailty screening instruments include the Fried frailty criteria, Geriatric 8 and Groningen Frailty Indicator.[44,45] In between a CGA and frailty screening there is the possibility of doing a geriatric assessment (GA) at the department of the treating oncologist. Such GA could be done by a oncology nurse and may include several items belonging to the physical, functional psychological and socioenvironmental domains.[46]

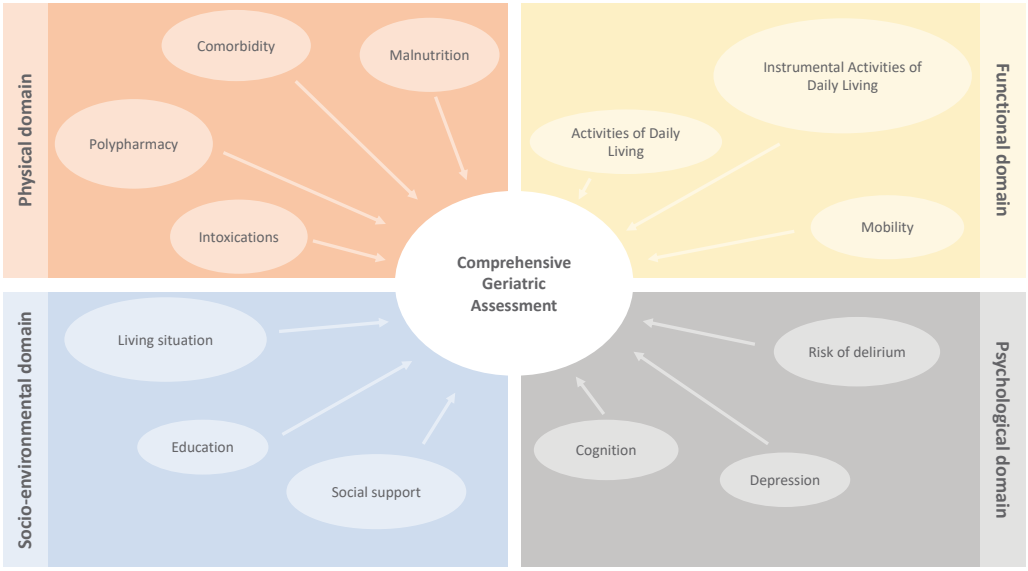

Figure 2 | Domains of a Comprehensive Geriatric Assessment and examples of items which may be evaluated in the domains.

Clinical problem

For head and neck oncologists, the contrast of the intensive multimodal treatments on the one hand and (biological) ageing on the other hand, results in difficulties regarding treatment decision making. When there is match between the chronological and biological age, there are usually no problems; for the young and fit a maximal curative treatment seems like the right choice, and for the old and frail it may be better to start a de-intensified or palliative treatment. However, when there is a mismatch between chronological and biological age, decisions may be more complex. For relatively fit older patients the risk of undertreatment is lurking. Undertreatment may give rise to suboptimal oncological treatment. The other way around, for relatively frail younger patients

the risk of overtreatment arises. Overtreatment may result in avoidable adverse outcomes. Ideally, under- and overtreatment should be prevented. Specifically for older patients, preservation of quality of life (QoL) is valued more important than life extension[47,48] Thus, how do we identify patients being at risk for adverse events, or decline in QoL?

OUTLINE OF THIS THESIS

The aim of this thesis was to investigate the frailty of patients with HNC, and to identify frailty screening instruments and items of GA that are associated with adverse events such as surgical complications and radiation-induced toxicity (RIT), and with decline of health-related quality of life (HRQoL). Starting October 2014, we have prospectively collected data on patient-, tumor- and treatment characteristics, outcomes of GA and frailty screening, and followed-up on HNC patients with respect to surgical complications, RIT and HRQoL.

Because we expected the HNC population to be particularly frail, in **Chapter 2**, we compare the population of patients with HNC to patients with other cancers that were seen in our (general) surgical oncology department, and compare their comorbidities, frailty status, and restrictions on items of a GA. In **Chapter 3**, we elaborate on the outcomes of GA and frailty screening and their association with surgical complications in a cohort of older patients with complex cutaneous malignancies, which are increasingly seen in older patients. In a general cohort of patients with HNC, we investigate frailty screening, geriatric assessment, and accumulation of geriatric deficits and compare the outcomes with both surgical and radiotherapeutical adverse events after curative treatment for HNC, in **Chapter 4**. In **Chapter 5**, we explore associations between the level of RIT during definitive or post-operative (C)RT and the frailty status of patients in more detail. We look into the association between outcomes of frailty screening and decline of QoL, functioning and level of symptom burden after treatment in **Chapter 6**. In **Chapter 7** we explore associations between deficits on GA, accumulation of deficits, and the deterioration of HRQoL up to two years after treatment for HNC. Last, in **Chapter 8**, we examine the risk of drop-out from follow-up of frail HNC patients, potentially resulting in underrepresentation of frail patients in clinical studies and consequent bias.

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chapter two

Patients with head and neck cancer: are they frailer than patients with other solid malignancies?

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ABSTRACT

Background
The aim of the study was to compare the frailty status, reflecting a patients biological age, of head and neck cancer (HNC) patients with patients with other solid malignancies.

Methods
Two prospectively collected cohorts including patient and tumor characteristics, Charlson Comorbidity Index (CCI), Groningen Frailty Indicator (GFI), Mini Mental State Examination (MMSE), (Instrumental) Activities of Daily Living (IADL and ADL), Timed-Up & Go (TUG) and Quality of Life (QoL) data were compared at baseline. Univariate and multivariate logistic regression analyses were performed to evaluate differences between the two cohorts. This way, odds ratios (ORs) and 95% confidence intervals (95%CIs) were estimated for membership of the HNC cohort.

Results
242 HNC patients and 180 other oncologic patients were included. 32.6% of the HNC patients were frail (GFI), compared to 21.8% of the other cohort. GFI (univariate OR 1.74 (95%CI 1.11-2.71)), MMSE, TUG and global QoL (multivariate OR, respectively 20.03 (95%CI 2.44-164.31), 11.56, (95%CI 1.86-71.68) and 0.98 (95%CI 0.97-1.00)) showed worse outcomes in the HNC cohort, while comorbidity scores were not significantly different (OR 0.54, (95%CI 0.28-1.02)).

Conclusion
HNC patients are more frail than patients with other solid malignancies while there were no significant differences in comorbidity.

INTRODUCTION

Population ageing is progressing at a rapid pace in the West, with increases in the proportion of people aged 65 years and older reflected in patients with head and neck cancer (HNC) (Netherlands Comprehensive Cancer Organisation (IKNL©) (2017). Defining the optimal treatment plan for each of these patients is challenging because of the need for intensive treatment in a population that tends to be considered unhealthy and vulnerable (Porceddu & Haddad, 2017).

Chronological age has been established as a highly relevant factor in clinical decision-making (Derks, de Leeuw, & Hordijk, 2005). Consequently, elderly HNC patients more often receive non-conventional or less intensive treatment than their younger peers, despite a lack of evidence for chronological age being a negative prognostic factor for adverse outcomes (Halmos et al., 2018; Teymoortash, Ferlito, & Halmos, 2016; van der Schroeff, Derks, Hordijk, & de Leeuw, 2007). Although comorbidity and age are often considered when making decisions, research in patients with laryngeal cancer has shown that age did not correlate with higher complication rates and that comorbidity in elderly was not associated with increased complication rates (T. T. A. Peters et al., 2011). Therefore, it might be reasonable to consider a patient's biological age rather than his or her chronological age and comorbidities when making treatment decisions.

Frailty is a well-studied concept that describes a biological state of increased susceptibility to adverse effects after exposure to a stressful event (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Porceddu & Haddad, 2017). The Comprehensive Geriatric Assessment (CGA) is the current gold standard for identifying frail patients through multidimensional evaluation of a patient's functional status, comorbidities, cognition, psychological state, social support, nutritional status and polypharmacy (Extermann & Hurria, 2007). However, the CGA is time-consuming, which has led to shorter frailty screening tools being developed. These tools can be used in a "two-step approach" to select eligible patients for a CGA. We considered that patients with HNC may have higher biological ages and greater frailty due to relatively unhealthy lifestyles compared with patients with other solid malignancies. This situation may then be further compounded by the higher risk of malnutrition due to dysphagia that results from tumour localisation in the upper aerodigestive tract (Derks et al., 2005; Noor et al., 2018). To date, this assumption has not been tested.

In the present study, we aimed to compare geriatric assessment data between patients with HNC and those with other solid malignancies in one study, using similar instruments. The present study builds on and develops existing knowledge, confirming previously held assumptions of frailty, thereby emphasising the importance of awareness of this state in patients with HNC. We anticipate that our findings will help to inform decisions about treatment and pre-treatment optimisation.

MATERIAL AND METHODS

Study design

We compared two cohorts in this observational study: an HNC cohort and a surgical oncology (SO) cohort. The data of each cohort were collected prospectively during the diagnostic process, before any decisions were made about treatment, and focused on patient characteristics, disease characteristics, frailty and quality of life (QoL).

The HNC cohort comprised a consecutive series of patients treated for primary squamous cell carcinomas of the oral cavity, oropharynx, hypopharynx, larynx, nasal cavity and paranasal sinuses at the University Medical Center Groningen (UMCG) between October 2014 and October 2017 who were registered in the OncoLifeS data-biobank. This data-biobank is managed by UMCG and includes details of oncology patients from several departments. We plan to publish results for this cohort in future research. The SO cohort was extracted from the database of the PICNIC B-HAPPY study and consisted of patients treated surgically at UMCG for a solid malignancy of the gynaecological tract, digestive tract, soft tissue or skin, breast, kidney or thyroid between August 2014 and December 2016 (Plas et al., 2017; Weerink et al., 2018). The primary aim of each original study was to identify predictive factors for treatment-related outcomes.

Ethical considerations

Data for patients with HNC were gathered as part of a major prospective study, and our institutional review board judged that the Dutch law on Research Involving Human Subjects (WMO) was not applicable and released a waiver. A separate proposal was placed for the current study to gain access to data stored in the OncoLifeS database, and approval was granted by the OncoLifeS Scientific Board. The PICNIC B-HAPPY study was approved by the central committee regarding human research (NL45602.042.14) and was registered on the Dutch Clinical Trial Database (NTR4564). All patients in each cohort provided written informed consent.

Patient and disease characteristics

The patient and disease characteristics available for each cohort are presented in Table 1. Intoxication data were not available for the SO cohort, so they are not provided. In both cohorts, tumours were staged according to the 7th edition of the TNM classification system of the American Joint Committee on Cancer and the Union for International Cancer Control (American Joint Committee on Cancer (AJCC) 2010). Tumour stage was dichotomized into early disease (stages I–II) and advanced disease (stage III–IV). Comorbidities were measured by the Charlson Comorbidity Index (CCI) in the SO cohort and by the Adult Comorbidity Evaluation (ACE)-27 in the HNC cohort. For the present study, the ACE-27 was manually converted into the CCI because all items embedded in the CCI are covered by the ACE-27 (Charlson, Pompei, Ales, & MacKenzie, 1987; van Leeuwen, Huisman, & Audisio, 2013; Nesic et al., 2012). A CCI score ≥ 3 defined patients with severe comorbidities (Boje et al., 2014).

Table 1 | Patient and disease characteristics of patients diagnosed with HNC compared to patients from surgical oncology (n=422; n(%)). Being member of the HNC cohort is defined as dependent variable. Abbreviations: HNC = head and neck cancer, OR = odds ratio, CI = confidence interval. BMI = body mass index, CCI = Charlson Comorbidity Index. Statistical test: univariate logistic regression analysis. Significant p-values are indicated in bold.

Variables	HNC (n=242)	Surgical oncology (n=180)	OR (95% CI)	p-value
Age (years)				0.57
≤54	35 (14.5%)	33 (18.3%)	1	
55-74	158 (65.3%)	112 (62.2%)	1.33 (0.78-2.27)	0.30
≥75	49 (20.2%)	35 (19.4%)	1.32 (0.69-2.51)	0.40
Sex				
Female	66 (27.3%)	77 (42.8%)	1	
Male	176 (72.7%)	103 (57.2%)	1.99 (1.32-3.00)	**0.001**
BMI				
<25	130 (53.9%)	59 (34.3%)	1	
≥25	111 (46.1%)	113 (65.7 %)	0.45 (0.30-0.67)	**<0.001**
Missing	1	8		
Relational status				
In a relationship	153 (66.2%)	129 (72.9%)	1	
Single	78 (33.8%)	48 (27.1%)	1.37 (0.89-2.10)	0.15
Missing	11	3		
Education				
Primary school	36 (17.1%)	24 (13.6%)	1	
Secondary and tertiary school	174 (82.9%)	153 (86.4%)	0.76 (0.43-1.33)	0.33
Missing	32	3		
CCI score				
<3	224 (92.6%)	153 (86.9%)	1	
≥3	18 (7.4%)	23 (13.1%)	0.54 (0.28-1.02)	0.06
Missing	0	4		
Tumor stage				
Early stage (I-II)	78 (32.2%)	53 (37.1%)	1	
Advanced stage (III-IV)	164 (67.8%)	90 (62.9%)	1.24 (0.80-1.91)	0.33
Missing	0	37		
Treatment intention				
Curative	220 (90.9%)	157 (91.3%)	1	
Palliative	22 (9.1%)	15 (8.7%)	1.05 (0.53-2.08)	0.90
Missing	0	8		

Frailty, geriatric assessment (GA) and QoL questionnaires and assessments

The frailty, geriatric assessment and QoL measures available in each cohort are presented in Table 2. The data set used the Groningen Frailty Indicator (GFI) as a screening tool for frailty (L. L. Peters, Boter, Buskens, & Slaets, 2012; Schuurmans, Steverink, Lindenberg, Frieswijk, & Slaets, 2004), the Mini-Mental State Examination (MMSE) as a measure for cognition (van der Cammen, van Harskamp, Stronks, Passchier, & Schudel, 1992), (Instrumental) Activities of Daily Living (Katz-ADL and Lawton-IADL) as scales of functional ability (Graf, 2009; Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963), the Timed Up and Go (TUG) for the assessment of mobility (Podsiadlo & Richardson, 1991) and the Quality of Life Questionnaire-Core Module (QLQ-C30) of the European Organization for Research and Treatment of Cancer (EORTC) for QoL (Aaronson et al., 1993).

Overviews of the questionnaires and their cut-off values are given in Table 3. According to a nationwide guideline of the Dutch safety programme, a cut-off value ≥ 2 was used for the Katz-ADL (VMSzorg, 2009). During implementation at UMCG, a seventh item regarding walking independently was added to the Katz-ADL scale. The item regarding financial handling was excluded from the Lawton-IADL scale. Only the global and functioning scales of the QLQ-C30 were used to compare QoL between the two cohorts. Scores for these scales range from 0 to 100 after applying linear transformation, as described by the EORTC, with higher scores indicating a high degree of functioning (Aaronson et al., 1993; Fayers et al., 2001; Pottel et al., 2014).

Statistical analysis

To compare the two cohorts, patients were stratified by cohort in univariate logistic regression analyses. The diagnosis (being in the HNC cohort vs. being in the SO cohort) was considered the dependent variable, and the patient, disease, frailty and QoL characteristics were considered the independent variables. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated on this basis. Next, multivariate logistic regression analysis with backward selection was performed on the same basis to select independent predictors for being a member of the HNC cohort. All variables with a p-value < 0.20 by univariate analysis were entered in the model. Age was always included in the multivariable model to allow proper adjustment for this variable. To check for collinearity between the independent variables, we created a correlation table using Pearson's test, where any correlation > 0.80 was considered to indicate collinearity. Statistical analyses were performed using IBM SPSS version 23.0 (IBM Corp). Statistical significance was considered to be achieved if the p-value was < 0.05.

Table 2 | Frailty, CGA and QoL characteristics of patients diagnosed with HNC compared to patients from a surgical oncology cohort (n=422; n(%), unless specified otherwise). Being member of the HNC cohort is defined as dependent variable. †mean ± SD. Abbreviations: HNC = Head and Neck Cancer, OR = Odds Ratio, CI = Confidence Interval, GFI = Groningen Frailty Indicator, ADL = Activities of Daily Living, IADL = Instrumental Activities of Daily Living, MMSE: Mini Mental State Examination, TUG = Timed Up & Go, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core module Statistical test: univariate logistic regression analysis. Significant p-values are indicated in bold.

Variables	HNC (n=242)	Surgical oncology (n=180)	OR (95% CI)	p-value
GFI				
Non-frail	159 (67.4%)	140 (78.2%)	1	
Frail	77 (32.6%)	39 (21.8%)	1.74 (1.11-2.71)	**0.02**
Missing	6	2		
ADL				
Independent	223 (94.1%)	164 (94.8%)	1	
(Moderately) dependent	14 (5.9%)	9 (5.2%)	1.14 (0.48-2.71)	0.76
Missing	5	7		
IADL				
No restrictions	180 (74.4%)	141 (81.5%)	1	
Restrictions	62 (25.6%)	32 (18.5%)	1.52 (0.94-2.45)	0.09
Missing	0	7		
MMSE				
Good cognitive functioning	205 (85.4%)	176 (98.9%)	1	
Restricted cognitive functioning	35 (14.6%)	2 (1.1%)	15.02 (3.56-63.36)	**<0.001**
Missing	2	2		
TUG				
Good mobility	211 (93.0%)	162 (98.8%)	1	
Restricted mobility	16 (7.0%)	2 (1.2%)	6.14 (1.39-27.10)	**0.02**
Missing	15	16		
EORTC QLQ-C30†				
Global quality of life scale	70.35 ± 20.31	75.62 ± 19.74	0.99 (0.98-1.00)	**0.01**
Functioning scales				
Physical functioning	81.96 ± 20.76	85.10 ± 17.39	0.99 (0.98-1.00)	0.15
Role functioning	83.80 ± 26.22	78.29 ± 26.65	1.01 (1.00-1.02)	**0.02**
Emotional functioning	70.45 ± 23.75	79.95 ± 19.27	0.98 (0.97-0.99)	**<0.001**
Cognitive functioning	90.70 ± 15.58	84.67 ± 19.12	1.02 (1.01-1.03)	**0.001**
Social functioning	89.69 ± 17.68	85.71 ± 21.64	1.01 (1.00-1.02)	**0.03**

Table 3 | Overview of used questionnaires and assessments and its cut-off values.

Questionnaires/assessments	Goal	Range	Cut-off value
Charlson Comorbidity Index (CCI)	Comorbidity	n/a	≥3
Groningen Frailty Indicator (GFI)	Frailty screener	0-15	≥4: frail
Mini Mental State Examination (MMSE)	Cognition	0-30	≤24: impaired cognition
Katz Activities of Daily Living + 1 (ADL)	Functional scale	0-7	≥2: (moderately) dependent in ADL
Instrumental Activities of Daily Living (IADL)	Functional scale	0-7	≤6: restrictions in IADL
Timed Up & Go (TUG)	Mobility	0-∞ seconds	≥20 s: impaired mobility
EORTC QLQ-C30	Quality of life	0-100	n/a

RESULTS

Patient and disease characteristics

In total, 422 patients were included in the present study, with 242 (57.3%) and 180 (42.7%) in the HNC cohort and SO cohort respectively. Univariate analysis revealed that, compared with the SO cohort, the HNC cohort contained more male patients (72.7% vs. 57.2%; OR 1.99, 95% CI 1.32–3.00) fewer overweight patients (46.1% vs. 65.7%; OR 0.45, 95% CI 0.30–0.67) and fewer patients with high comorbidity scores (7.4% vs. 13.1%; OR 0.54, 95% CI 0.28–1.02; not significant). In the HNC cohort, 5.4% of the patients had a body mass index (BMI) <18.5 kg/m^2, whereas in the SO cohort, no patients were underweight. However, we observed no statistically significant differences in age, relationship status, education level, tumour stage or treatment intention between the two cohorts.

Frailty, GA and Quality of Life questionnaires

According to the GFI, 32.6% of the HNC cohort could be classified as "frail" compared with 21.8% in the SO cohort (OR 1.74, 95% CI 1.11–2.71). The HNC cohort also had more impairments on the IADL, MMSE and TUG. Notably, they had worse outcomes on the MMSE (14.6% vs. 1.1%) and TUG (7.0% vs. 1.2%), with respective ORs of 15.02 (95% CI 3.56–63.36) and 6.14 (95% CI 1.39–27.10). Patients in the HNC cohort generally scored lower on the global QoL scale, with a mean difference of 5 points compared with the SO cohort (OR 0.99, 95% CI 0.98–1.00). Patients with HNC also had a lower score on the emotional functioning scale, with a mean difference of 9 points compared with the other cohort (OR 0.98, 95% CI 0.97–0.99). The mean scores in role (OR 1.01, 95% CI 1.00–1.02), cognitive (OR 1.02, 95% CI 1.01–1.03) and social (OR 1.01, 95% CI 1.00–1.02) functioning were higher in the HNC cohort.

Multivariate analysis

A multivariate model was fitted that included age, sex, BMI, relationship status, CCI, GFI, IADL, MMSE, TUG and all QoL scales. The results of this analysis are summarised in Table 4. The HNC cohort again included more male patients (OR 3.50, 95% CI 2.00–6.12) and fewer overweight patients (OR 0.37, 95% CI 0.22–0.62). Also, the HNC cohort had worse scores than the SO cohort for the MMSE (OR 20.03, 95% CI 2.44–164.31) and TUG (OR 11.56, 95% CI 1.86–71.68), as well as for global QoL (OR 0.98, 95% CI 0.97–1.00) and emotional functioning (OR 0.96, 95% CI 0.95–0.98). By contrast, the HNC cohort had better role functioning (OR 1.03, 95% CI 1.01–1.04) and cognitive functioning (OR 1.04, 95% CI 1.02–1.06) scores according to the EORTC QLQ–C30. Collinearity was not identified between the variables in the multivariate model.

Table 4 | Patient, disease, CGA and QoL characteristics of patients diagnosed with HNC compared to patients from surgical oncology. Being member of the HNC cohort is defined as dependent variable. Abbreviations: OR = odds ratio, CI = confidence interval, BMI = body mass index, MMSE = mini mental state examination, TUG = timed up and go, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core module. Statistical test: multivariate logistic regression analysis adjusted for age. Significant p-values are indicated in bold.

Variables	OR (95% CI)	p-value
Sex		
Female	1	
Male	3.50 (2.00-6.12)	**<0.001**
BMI		
<25	1	
≥25	0.37 (0.22-0.62)	**<0.001**
MMSE		
Good cognitive functioning	1	
Restricted cognitive functioning	20.03 (2.44-164.31)	**0.005**
TUG		
Good mobility	1	
Restricted mobility	11.56 (1.86-71.68)	**0.009**
EORTC QLQ-C30		
Global quality of life scale	0.98 (0.97-1.00)	**0.04**
Functioning scales		
Physical functioning	0.98 (0.96-1.00)	0.05
Role functioning	1.03 (1.01-1.04)	**0.002**
Emotional functioning	0.96 (0.95-0.98)	**<0.001**
Cognitive functioning	1.04 (1.02-1.06)	**<0.001**
Social functioning	1.02 (1.00-1.04)	0.06

DISCUSSION

Despite a lack of direct evidence, it has often been stated that patients with HNC are frailer than their peers with other solid malignancies, mainly due to their comparatively less healthy lifestyles. In the present study, we used multiple validated instruments to compare a cohort of patients with HNC and a cohort of patients with other solid malignancies. To our knowledge, no study to date has directly compared the frailty status of an HNC cohort with another SO cohort within one study in one centre, using similar geriatric assessment tools. The key finding of this research was that the HNC cohort had a significantly higher level of frailty, as measured by the GFI, and significantly more cognitive (MMSE) and mobility (TUG) impairments. Moreover, despite comparable age and tumour stage between the cohorts, the HNC cohort had worse global QoL (EORTC QLQ-C30). These findings emphasise the importance of awareness of frailty in HNC services.

Given that tobacco and alcohol use are the main risk factors for developing HNC, we expected that the HNC cohort would have an increased number of comorbidities (Maasland, Brandt, Kremer, Goldbohm, & Schouten, 2014). The CCI score in our HNC cohort (CCI ≥ 3 in 7.4%) was comparable to that published in large Danish (CCI ≥ 3 in 10%) and Canadian (CCI ≥ 3 in 7%–11%) cohorts of patients with HNC (Boje et al., 2014; Habbous et al., 2014). In contrast with our expectations, we found non-significantly fewer comorbidities in the HNC cohort compared with the SO cohort.

Positive associations between comorbidity and frailty have also been made in the literature. Nieman et al. (2018) reported a significantly increased comorbidity rate in a frail HNC cohort (52.8%) compared with a non-frail cohort (37.1%), which supported earlier research (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004; Theou, Rockwood, Mitnitski, & Rockwood, 2012). They even described a synergistic interaction in their cohort between frailty and comorbidities, with an increased post-operative complication risk and longer hospitalisation in patients with both factors (Nieman et al., 2018). By contrast, Fried et al. (2004) reported that 31.3% of frail patients in their cohort had no comorbidities. These data suggest that frailty has a distinct role, independent of comorbidity, which is supported by the results of the present study.

Although the CGA is the current gold standard for measuring frailty, many screening instruments are available, albeit with varying degrees of success (Extermann & Hurria, 2007). For example, the predictive value of the GFI in oncology cohorts has been questioned in the literature. Hamaker et al. (2012) conducted a systematic review of the predictive value of several available instruments for demonstrating impairments at a CGA in elderly oncology patients. They found that all tested frailty screening tools had rather poor discriminative powers. For the GFI, the sensitivity and specificity were 39%–62% and 69%–86% respectively. However, we were principally interested in identifying differences in frailty data rather than in using its predictive power. Given that the GFI has high construct validity and internal consistency, it should still have served as a useful tool for comparison of frailty data between the two cohorts (Metzelthin et al., 2010; Steverink, Slaets, Schuurmans, & van Lis, 2001).

In the present study, the prevalence of frailty was 32.6% and 21.8% in the HNC cohort and SO cohort respectively. Although frailty was more common in the HNC cohort, as expected,

the prevalence in both cohorts was lower than previously described. In an HNC cohort (mucosal and cutaneous) of patients older than 65 years, we previously reported that 40% of patients were frail (Bras et al., 2015). Also, we found no difference in frailty between patients with HNC and those with skin cancer. In research by Plas et al. (2017), a comparable GFI frailty percentage of 35% was reported in a group of 219 patients aged 65 years and older who were treated surgically for solid malignancy. In another study, 24.6% of the 310 patients undergoing surgery for colorectal cancer aged ≥70 years were frail, though this may have been underestimated compared to our study, which used a higher GFI cut-off point of ≥5 (Reisinger et al., 2015). Given that frailty is related to age, a lower frailty level could reasonably be expected in the present cohorts because we did not discriminate by age in the inclusion process (Clegg et al., 2013). Another possible explanation is that there was selection bias in the SO cohort, which only included surgically treated patients. In this instance, it is possible that very frail patients were not considered suitable for surgical treatment and so were never referred.

Cognitive impairment is another factor associated with frailty, leading to the inclusion of cognitive tests in CGAs (Clegg et al., 2013; Fougere et al., 2017). Impaired pre-treatment cognitive status has been found to be correlated with adverse health outcomes in patients with HNC and other cancers (van Deudekom et al., 2017; Libert et al., 2016). Several studies have investigated the degree of cognitive decline after oncologic surgery; however, the impact of any change remains inconclusive because both decreases and increases in cognitive function have regularly been observed (Extermann & Hurria, 2007; Plas et al., 2017). Impaired MMSE has been reported at rates ranging from 11% to 29% in the elderly (both community-dwelling and with cancer), which is consistent with our findings in the HNC cohort (14.6%), but is substantially higher than in our SO cohort (1.1%) (Kenig, Olszewska, Zychiewicz, Barczynski, & Mitus-Kenig, 2015; Macuco et al., 2012; Plas et al., 2017). Again, selection bias was likely to have played a key role in this difference, with the inclusion of only surgically treated patients with other solid malignancies.

The TUG test is a simple, quick and reliable test for evaluating mobility, and it is both sensitive and specific for identifying frailty in the elderly (Podsiadlo & Richardson, 1991; Savva et al., 2013). Huisman et al. (2014) found the TUG to be prognostic of surgery-related complications in geriatric oncology. In their prospective study, of 263 patients aged > 70 years who were surgically treated for a solid tumour, 16.0% had restricted mobility according to the TUG. In other research, Kenig et al. (2015) found that 15% of their population also had restricted mobility. This is a greater proportion than found in either our SO cohort (1.2%) or our HNC cohort (7.0%), which we presume is because of the 10-year difference in median ages (76 years vs. 66 and 67 years).

Although significant differences were found in cognition and mobility between the two cohorts, the 95% CIs for the MMSE and the TUG are very wide in both the uni- and multivariate logistic regression analyses, due to the low number of patients with impaired cognition and restricted mobility in the SO cohort.

A significant association between frailty and QoL has been demonstrated in patients with cancer and particularly in patients with HNC (Geessink, Schoon, Goor, Olde Rikkert, & Melis, 2017; Kenig et al., 2015). In the current study, the EORTC QLQ-C30 was used to compare QoL status in each cohort. According to a method proposed by Osoba et al., the difference in the mean

global QoL score of 5.27 in favour of the SO cohort can be interpreted as minor (5–10 points) (Osoba, Rodrigues, Myles, Zee, & Pater, 1998). The same applies to the difference in emotional functioning that favoured the SO cohort and to the differences in cognitive and role functioning that favoured the HNC cohort. Of note, cognitive functioning was higher in the HNC cohort when using this subjective scale, whereas the MMSE revealed cognitive impairment. Conflicting results have previously been described when comparing these tools in patients with cancer, emphasising the importance of differentiating between objective and subjective measures in cognitive assessments (Cull et al., 1996; Klepstad et al., 2002; Mystakidou, Tsilika, Parpa, Galanos, & Vlahos, 2007).

The main strength of this study was that we applied several validated and internationally accepted tests to compare prospectively collected data about frailty in two relatively large cohorts of patients with cancer. However, the study results should be interpreted in the context of several limitations. For example, there was a need to merge the two different comorbidity scores, which may have led to inaccuracy in the analysis. Furthermore, the potential for selection bias in the SO cohort may have affected the results.

Unfortunately, we were also unable to compare data regarding smoking and alcohol consumption because relevant data were missing in the SO cohort. Recent literature indicates that current smokers have a greater than twofold increased risk of developing frailty compared with non-smokers and former smokers (Kojima, Iliffe, Jivraj, Liljas, & Walters, 2018). Interestingly, this association has not been found for alcohol consumption, which may in fact be protective (Kojima et al., 2019; Kojima, Liljas, Iliffe, Jivraj, & Walters, 2018). We cannot exclude the possibility that a higher number of current smokers in the HNC cohort, if present, could have explained their higher frailty statuses.

A final limitation of the study is the lack of data to allow comparison of nutritional statuses between the cohorts. BMI was the only available variable, and our results indicated that there were more underweight patients in the HNC cohort. Given that malnutrition is also associated with frailty, this finding may have contributed to the higher number of frail patients in the HNC cohort (Kurkcu, Meijer, Lonterman, Muller, & de van der Schueren, 2018). The lack of underweight patients in the SO cohort precluded statistical comparison of the BMI data.

CONCLUSION

Patients with HNC had more impairments on multiple geriatric assessment and QoL measures than patients with other solid malignancies (e.g. MMSE, TUG and global QoL and emotional functioning on the EORTC QLQ-C30). However, there were no statistically significant differences in comorbidity rates between cohorts. These findings confirm the previously held assertion that patients with HNC tend to be frailer than patients with other solid malignancies, emphasising the importance of proper geriatric assessments in HNC services.

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chapter three

Geriatric assessment of patients treated for cutaneous head and neck malignancies in a tertiary referral center: predictors of postoperative complications

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ABSTRACT

Introduction

As cutaneous head and neck malignancies are highly prevalent especially in older patients, the risk of surgical complications is substantial in this potentially vulnerable population. The objective of this study was to evaluate the value of geriatric assessment of this population with respect to postoperative complications.

Methods

Patients were prospectively included in OncoLifeS, a databiobank. Before surgery, patients underwent a geriatric assessment including multiple validated screening tools for frailty, comorbidity, polypharmacy, nutrition, functional status, social support, cognition and psychological status. Postoperatively, complications (Clavien-Dindo ≥ grade II) were registered. Uni- and multivariable logistic regression analyses were performed yielding odds ratios (ORs) and 95% confidence intervals (95%CIs).

Results

151 patients undergoing surgery for cutaneous head and neck malignancies were included in this study (mean age 78.9 years, 73.5% male). In a multivariable analysis, frailty measured by the Geriatric 8 (G8) (OR=6.34; 95%CI:1.73-23.25) was the strongest independent predictor of postoperative complications, among other predictors such as major treatment intensity (OR=2.73; 95%CI:1.19-6.26) and general anesthesia (OR=4.74; 95%CI:1.02-22.17), adjusted for age and sex.

Conclusion

Frailty, measured by G8, is the strongest predictor of postoperative complications in patients undergoing surgery for cutaneous head and neck malignancies in addition to treatment intensity and type of anesthesia. Geriatric screening on multiple domains is recommended for patients with cutaneous malignancies undergoing head and neck surgery is recommended, as this population includes old patients and frequently suffers postoperative complications.

INTRODUCTION

Skin cancer is the most common type of cancer worldwide.[1] In the United States, the incidence of non-melanoma skin cancer (NMSC) and cutaneous melanoma (CM) is estimated to be at least over 5.5 million annually.[2,3] The incidence of both NMSC and CM are dramatically on the rise,[4–6] with especially the proportion of older patients increasing.[7] This results from the expanding older population in general and also due to older patients' higher cumulative sun exposure. Possibly, associated diseases,[8,9] use of immunosuppressive medications,[10] or exposure to prior radiation therapy,[11] contribute to this as well.

Cutaneous malignancies of the head and neck occur more frequently[12,13] and are at higher risk for metastasis than other subsites.[14] The cornerstone of treatment in most of the cases is surgery, ranging from a straightforward local excision to extended resections with neck dissections and even complex reconstructive surgery. If radical surgery is beyond possibilities, because of expected functional or cosmetic impairments or foreseen complications in older patients, radiotherapy is an effective treatment modality both as primary therapy or as an adjuvant therapy.[15] With surgery remaining the primary choice of treatment, the risk of postoperative complications is substantial in this elderly and possibly vulnerable population, like previously described after head and neck oncological surgery.[16]

Comprehensive Geriatric Assessment (CGA) by a geriatrician or specialized nurse is the gold standard to expose vulnerabilities in older patients, which may be treated to prevent perioperative complications.[17] CGA focuses on multiple geriatric domains such as comorbidities, polypharmacy, nutritional status, functional status, social support and psychological status.[18] Because of its time consuming nature, screening tools such as the Groningen Frailty Indicator (GFI) and the Geriatric 8 (G8) have been developed to detect vulnerable patients who may benefit from a CGA.[19,20]

The role of geriatric screening is established in many oncological patient populations, but not in cutaneous malignancies, even though this population is relatively old. Therefore, in the present study, we evaluated the role of geriatric assessment and frailty screening with respect to postoperative complications in surgically treated patients for cutaneous head and neck malignancies in a tertiary center.

MATERIALS AND METHODS

Study design

The present cohort study included patients who were enrolled in OncoLifeS, a prospective oncological databiobank at the University Medical Center Groningen. Study protocol was approved by the OncoLifeS scientific board.

Study population

Between October 2014 and October 2018 all consecutive patients referred for a cutaneous malignancy to the Department of Otorhinolaryngology, Head and Neck Surgery were included,

regardless of age. Treatment strategies were according to national guidelines and discussed within the multidisciplinary head and neck tumor board and melanoma board, if applicable. If curative treatment was not possible or if patients received other primary treatment than surgery, patients were excluded from this study.

Data collection

Patient, tumor- and treatment characteristics were obtained from the electronic medical record and OncoLifeS database. Tumor stage was defined according to the seventh edition of the Union for International Cancer Control TNM Classification.[21] At the first day of consultation, patients underwent a geriatric assessment at the outpatient clinic of our department, including the following geriatric domains: comorbidities, polypharmacy, nutritional status, functional status, social support, cognition and psychological status. Comorbidities were graded using the Adult Comorbidity Evaluation (ACE-27) as none, mild, moderate or severe.[22] Polypharmacy was defined as the prescription of five or more medications on a daily basis.[23] Nutritional status was assessed using the Malnutrition Universal Screening Tool (MUST).[24] Functional status consisted of Activities of Daily Living (Katz-ADL), Instrumental Activities of Daily Living (IADL), Timed Up & Go (TUG) and history of falls.[25–27] Social support was based on patient reported questionnaires. Socioeconomic status (SES) scores are publicly available scores, based on income, employment rate and educational status of postal code areas.[28] Cognition was assessed by the Mini Mental State Examination (MMSE) and presence of risk factors for delirium.[29,30] Psychological status was scored using the Geriatric Depression Scale (GDS-15).[31] Furthermore, two frailty screening instruments were completed including the Groningen Frailty Indicator (GFI) and the Geriatric 8 (G8).[19,20] Postoperative complications occurring within 30 days after surgery were assessed from medical files using the Clavien-Dindo classification.[32]

Statistical analysis

Patient characteristics were presented as mean ± standard deviation, median (range) or value (percentage). Univariable logistic regression analyses were performed to identify factors associated with postoperative complications. Analyses yielded odds ratios (ORs) with 95% confidence intervals (95%CIs). For multivariable logistic regression analysis with step backward method, variables with $p<0.10$ were included. When collinearity was present between variables using Pearson and Spearman correlation coefficients, only clinically most relevant variables were selected. For variables eligible for multivariable analysis, missing values were imputed using multiple imputation. The multivariable model was fitted using a stepwise selection of predictors. All statistical analysis was performed with SPSS Statistics 23.0 software (IBM, Armonk, New York, United States of America). P-value <0.05 was considered statistically significant.

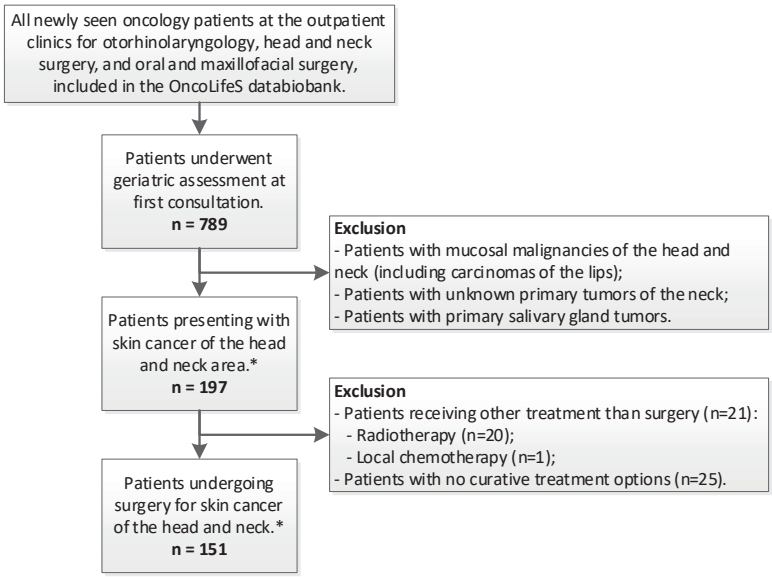

Figure 1 | Flowchart diagram representing the inclusion of patients into the final cohort of 151 patients who were surgically treated for cutaneous head and neck malignancies. * Cohorts showed no significant differences in age and sex throughout exclusion process.

RESULTS

Study selection

Between October 2014 and October 2018, 197 patients with cutaneous head and neck malignancies were included in the OncoLifeS databiobank. After exclusion of patients treated with other primary treatment modalities than surgery and patients with no curative treatment options, a total of 151 patients remained eligible for analysis (Figure 1). There were no significant age and sex differences after exclusion.

Patient characteristics

Patient characteristics are presented in Table 1. The mean age of the patients was 78.9 years, ranging from 46.6 to 96.7 years. In this tertiary referral center, less than half of patients were referred with a primary tumor (49.7%), and others with residual tumor after recent treatment (29.8%) or recurrent tumor (20.5%). Most frequent histopathological subtypes of malignancies were squamous cell carcinoma (SCC; 59.6%), basal cell carcinoma (BCC; 18.5%), cutaneous melanoma (CM; 11.3%) and Merkel cell carcinoma (MCC; 6.0%).

Variables	Value n=151
Age	
Mean ± SD, y	78.9 ± 9.0
Median (range), y	78.9 (46.6-96.7)
Categories	
< 70	27 (17.9%)
70-80	55 (36.4%)
80-90	53 (35.1%)
≥ 90 78.9	15 (10.6%)
Sex	
Male	111 (73.5%)
Female	40 (26.5%)
Reason for referral	
Primary tumor	75 (49.7%)
Residual tumor	45 (29.8%)
Recurrent tumor	31 (20.5%)
Primary tumor location	
Frontal	9 (6.0%)
Scalp	33 (21.9%)
Temporal	10 (6.6%)
Ear	56 (37.1%)
Cheek	9 (6.0%)
Peri-orbital	7 (4.6%)
Nose	21 (13.9%)
Peri-oral	3 (2.0%)
Neck	3 (2.0%)
Histopathology	
Basal cell carcinoma	28 (18.5%)
Squamous cell carcinoma	90 (59.6%)
Malignant melanoma	17 (11.3%)
Merkel cell carcinoma	9 (6.0%)
Other [a]	7 (4.6%)
Stage of disease	
Stage I	59 (39.1%)
Stage II	53 (35.1%)
Stage III	25 (16.6%)
Stage IV	14 (9.3%)
Immunocompromised [b]	
No	130 (86.1%)
Yes	21 (13.9%)

Table 1 | Characteristics of surgically treated patients with cutaneous malignancies of the head and neck area, seen in a tertiary referral head and neck oncology center. [a] Included malignancies were angiosarcoma, atypical fibroxanthoma, malignant adnexal tumor, pleomorphic dermal sarcoma, dermatofibrosarcoma protuberans and adenoid cystic carcinoma. [b] Immunosuppression included patients who have been using long-term immunosuppressive medication e.g. post transplantation, chronic lymphocytic leukemia, Non-Hodgkin's lymphoma, severe rheumatism and Crohn's disease.

Table 2 | Postoperative complications in patients undergoing surgery for cutaneous head and neck malignancies.

Clavien-Dindo	Value n=151
No complications	89 (58.9%)
Grade I	22 (14.6%)
Grade II	25 (16.6%)
Grade III	13 (8.6%)
Grave IV	2 (1.3%)
Grade V	0 (0.0%)

Univariable analysis of predictors for postoperative complications

Occurrence of postoperative complications is listed in Table 2. Forty patients (26.5%) experienced complications grade II and higher according to the Clavien-Dindo classification. Factors associated with postoperative complications are shown in Table 3. Age was not a significant predictor (OR 0.98; 95%CI 0.94-1.02). Tumor characteristics, such as advanced tumor stage (OR 6.53; 95%CI 1.86-22.99) and large tumor diameter (OR 3.89; 95%CI 1.12-13.51) significantly predicted postoperative complications. Treatment characteristics, including locoregional surgery (OR 4.38; 95%CI 1.98-9.68), major treatment intensity (OR 3.46; 95%CI 1.62-7.39) and general anesthesia (OR 7.70; 95%CI 1.75-33.81), were also significantly related to postoperative complications.

Among the individual domains of geriatric assessment, only polypharmacy (OR 2.36; 95%CI 1.11-5.07) predicted postoperative complications respectively significantly (Table 3). Comorbidities, or impairments in functional status, social support, cognitive status or psychological status alone were not significantly associated with postoperative complications. Of the frailty screeners, the G8 was a strong, significant predictor of complications (OR 5.83; 95%CI 1.68-20.26) and GFI was not (OR 1.43; 95%CI 0.63-3.26).

Independent predictors of postoperative complications

A multivariable model was fitted with eligible variables (Table 4). Within the multivariable model, adjusted for age and sex, major treatment intensity (OR 2.73; 95%CI 1.19-6.26), surgery under general anesthesia (OR 4.74; 95%CI 1.02-22.17) and frailty, measured by G8 (OR 6.34; 95%CI 1.73-23.25) were the most significant independent predictors of postoperative complications grade II and higher.

Table 3 | Patient-, tumor- and treatment characteristics and domains of geriatric assessment in a univariable logistic regression predicting postoperative complications grade II and higher. Abbreviations: CI=Confidence Interval, SD=Standard Deviation, 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 and Go, NL=Netherlands, MMSE=Mini Mental State Examination, GDS-15=Geriatric Depression Scale 15, G8=Geriatric 8, GFI=Groningen Frailty Indicator. [a] Immunosuppression included patients who have been using long-term immunosuppressive medication e.g. post transplantation, chronic lymphocytic leukemia, Non-Hodgkin's lymphoma, severe rheumatism and Crohn's disease. [b] Included malignancies were angiosarcoma, atypical fibroxanthoma, malignant adnexal tumor, pleomorphic dermal sarcoma, dermatofibrosarcoma protuberans and adenoid cystic carcinoma. [c] Defined as surgery > 120 minutes or three or more stages of Mohs micrographic surgery.

Variables	Value (%) n=151	Univariable analysis Odds ratio (95% CI)	p-value
Patient characteristics			
Age			
Mean ± SD, y	78.9 ± 9.0	0.98 (0.94-1.02)	0.27
Median (range), y	78.9 (46.6-96.7)		
Sex			
Male	111 (73.5%)	1	
Female	40 (26.5%)	0.90 (0.39-2.06)	0.80
Immunocompromised [a]			
No	130 (86.1%)	1	
Yes	21 (13.9%)	1.89 (0.72-4.96)	0.20
Tumor characteristics			
Reason for referral			
Primary tumor	75 (49.7%)	1	0.71
Residual tumor	45 (29.8%)	0.95 (0.41-2.25)	0.91
Recurrent tumor	31 (20.5%)	1.40 (0.56-3.51)	0.47
Stage			
Stage I	59 (39.1%)	1	**< 0.05**
Stage II	53 (35.1%)	1.93 (0.78-4.78)	0.15
Stage III	25 (16.6%)	1.91 (0.63-5.76)	0.25
Stage IV	14 (9.3%)	**6.53 (1.86-22.99)**	**< 0.01**
Tumor diameter			
< 20 mm	72 (59.5%)	1	**< 0.05**
20-40 mm	36 (29.8%)	**2.57 (1.04-6.36)**	**< 0.05**
≥ 40mm 72	13 (10.7%)	**3.89 (1.12-13.51)**	**< 0.05**
Invasion depth			
Mean ± SD, mm	5.2 ± 3.3	1.13 (0.99-1.29)	
Median (range), mm	4.7 (0.3-19.5)		

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Table 3 | continued

Variables	Value (%) n=151	Univariable analysis Odds ratio (95% CI)	p-value
Histopathology			
Basal cell carcinoma	28 (18.5%)	1	0.23
Squamous cell carcinoma	90 (59.6%)	**3.96 (1.11-14.20)**	**< 0.05**
Malignant melanoma	17 (11.3%)	3.47 (0.71-16.99)	0.13
Merkel cell carcinoma	9 (6.0%)	1.04 (0.10-11.47)	0.97
Other [b]	7 (4.6%)	3.33 (0.44-25.39)	0.25
Treatment characteristics			
Primary treatment			
Local surgery	113 (74.8%)	1	
Locoregional surgery	38 (25.2%)	**4.38 (1.98-9.68)**	**< 0.01**
Treatment intensity [c]			
Minor	96 (63.6%)	1	
Major	55 (36.4%)	**3.46 (1.62-7.39)**	**< 0.01**
Anesthesia			
Local anesthesia	34 (22.5%)	1	
General anesthesia	117 (77.5%)	**7.70 (1.75-33.81)**	**< 0.01**
Reconstructive surgery			
No reconstructive surgery	45 (29.8%)	1	0.10
Intraoperative reconstruction	81 (53.6%)	1.07 (0.45-2.56)	0.88
Subsequent reconstructive surgery	25 (16.6%)	2.75 (0.96-7.92)	0.06
Intoxications			
Smoking			
Never or former	113 (86.3%)	1	
Current	18 (13.7%)	2.03 (0.72-5.74)	0.18
Drinking			
None or mild	117 (88.6%)	1	
Heavy (> 2/day)	15 (11.4%)	2.78 (0.93-8.35)	0.07
Comorbidities			
ACE-27			
None or mild	53 (35.1%)	1	
Moderate or severe	98 (64.9%)	1.61 (0.73-3.55)	0.24
Polypharmacy			
Medication count			
< 5 medications	95 (65.1%)	1	
≥ 5 medications	51 (34.9%)	**2.36 (1.11-5.07)**	**< 0.05**

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Table 3 | continued

Variables	Value (%) n=151	Univariable analysis Odds ratio (95% CI)	p-value
MUST			
Low risk	128 (92.1%)	1	
Medium to high risk	11 (7.9%)	3.46 (0.99-12.07)	0.05
Functional status			
ADL			
No restrictions (< 1)	114 (82.6%)	1	
Restrictions (≥ 1)	24 (17.4%)	1.69 (0.65-4.39)	0.28
IADL			
No restrictions (< 1)	100 (69.4%)	1	
Restrictions (≥ 1)	44 (30.6%)	1.07 (0.48-2.38)	0.87
TUG			
Mean ± SD, s	11.4 ± 6.7	1.04 (0.98-1.11)	0.19
Median (range), s	10 (5-70)		
History of falls			
No	124 (91.2%)	1	
Yes	12 (8.8%)	0.96 (0.24-3.76)	0.95
Social support			
Education			
Low level of education	60 (48.8%)	1	0.64
Middle level of education	38 (30.9%)	1.52 (0.61-3.76)	0.37
High level of education	25 (20.3%)	1.04 (0.35-3.10)	0.95
Marital status			
In a relationship	89 (67.9%)	1	0.69
Widow	32 (24.4%)	1.38 (0.60-3.37)	0.47
Single	10 (7.6%)	0.76 (0.15-3.86)	0.74
Social Economic Statusscore (SES)			
Below average (NL)	119 (79.3%)	1	
Above average (NL)	31 (20.7%)	0.99 (0.40-2.44)	0.98
Cognitive status			
MMSE			
Normal cognition (> 24)	108 (76.6%)	1	
Declined cognition (≤ 24)	33 (22.6%)	0.83 (0.34-2.05)	0.69
Risk of delirium			
No	113 (77.4%)	1	
Yes	26 (18.7%)	0.85 (0.35-2.08)	0.72

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Table 3 | continued

Variables	Value (%) n=151	Univariable analysis Odds ratio (95% CI)	p-value
Psychological status			
GDS-15			
No depression (< 6)	113 (81.3%)	1	
Depression (≥ 6)	26 (18.7%)	1.17 (0.45-3.09)	0.75
Frailty screeners			
G8			
Non-frail (> 14)	39 (26.7%)	1	
Frail (≤ 14)	107 (73.3%)	**5.83 (1.68-20.26)**	**< 0.01**
GFI			
Non-frail (< 4)	98 (70.5%)	1	
Frail (≥ 4)	41 (29.5%)	1.43 (0.63-3.26)	0.40

Table 4 | Multivariable logistic regression model predicting postoperative complications grade II and higher patients receiving in surgery for cutaneous head and neck malignancies. [a] Adjusted for age and sex. [b] Defined as surgery > 120 minutes or three or more stages of Mohs micrographic surgery.

Variables	←No complications Complications→	Multivariable model [a] Odds ratio (95% CI)	p-value
Treatment intensity [b]			
Minor		1	
Major		**2.73 (1.19-6.26)**	**<0.05**
Anesthesia			
Local anesthesia		1	
General anesthesia		**4.74 (1.02-22.17)**	**<0.05**
Frailty			
Non-frail (> 14)		1	
Frail (≤ 14)		**6.34 (1.73-23.25)**	**<0.01**

DISCUSSION

Patients with complex cutaneous head and neck malignancies are old and frequently experience postoperative complications. To our knowledge, this is the first study evaluating the value of geriatric assessment in a cohort of patients with cutaneous head and neck malignancies. Key findings show that frailty, measured by G8, is the strongest predictor of postoperative

complications. Furthermore, tumor features, such as tumor size and stage, and treatment related predictors, such as treatment intensity and type of anesthesia seem to be related to postoperative complications.

With a mean age of nearly 80 years, the population of patients with cutaneous head and neck malignancies being referred to our tertiary hospital was remarkably aged. However, age did not predict postoperative complications within this population. This corresponds with other dermatological cohorts with head and neck skin malignancies.[33–35] Pascual et al. showed that complications did not significantly differ between patients younger and older than 80 years, except for hemorrhagic complications.[36] This finding is in line with a large prospective cohort of Amici et al., showing more hemorrhagic complications in the elderly as well.[37] As significance disappears after correcting for use of anticoagulant medications, the higher amount of hemorrhagic complications is probably related to the increased use of anticoagulants with aging, and not to age itself. Just as age does not predict postoperative complications, it neither affects prognosis of patients with skin cancer.[38] Moreover, the majority of patients with a lower life expectancy, defined as age 85 years and older or a Charlson Comorbidity Index of 3 or higher, die of other causes than NMSC.[39] Whilst this does not apply directly to our cohort with much more complex cases, it does call the attention to the dilemma of "time to benefit", referring to a clinical prediction, estimating whether the patient will live long enough to benefit from the treatment.[37] It is suggested that a comprehensive approach towards treatment decisions should at least include consideration of comorbidity, functional status and anticipated life expectancy in this specific population.[40]

Complications after surgery of cutaneous head and neck malignancies performed by a dermatologist are usually rare. Percentages of the largest cohorts range between 3 and 6%.[37,41–43] With 26.5% of patients suffering postoperative complications in our cohort, these outcomes seem much worse. However, our cohort suffers from a negative bias; higher tumor stage, more complex locations, more often lymph node metastasis, and consequently more major surgeries under general anesthesia. Furthermore, referral to a tertiary center may include more residual or recurrent tumor, which was the case in more than half of the patients. Clinical research on tertiary cohorts of cutaneous head and neck malignancies are rarely reported; therefore comparison is difficult.

Our results show that tumor features such as histopathological type, tumor size and stage, and treatment characteristics, such as treatment intensity, adjuvant neck dissection and type of anesthesia, predict postoperative complications. Many of these variables are closely related to each other. After all, increased tumor size and more aggressive histopathological tumor type lead to more advanced stage, requiring extended surgery, possibly including neck dissection and general anesthesia. As a result, only the strongest predictors were included in multivariable analysis. Treatment intensity, defined as surgery time more than 120 minutes or 3 or more stages of Mohs micrographic surgery, and surgery under general anesthesia were found to be the most important predictors of postoperative complications. Length of surgery and neck dissection has been proven to predict postoperative complications in general head and neck oncological surgery as well.[16,44–46] Even in case of excision under local anesthesia, length of surgery predicts postoperative complications in skin cancer surgery. [37]

Frailty, measured by G8, was mostly associated with postoperative complications in this cohort. As far as we know, frailty has never been examined in a cohort undergoing surgery for cutaneous malignancies. Valdatta et al. investigated the FRAIL index in a cohort undergoing reconstructive surgery after NMSC excision.[47] A higher score on the FRAIL index was associated with more moderate to severe complications. Furthermore, Bras et al. included 45 patients with skin malignancies in their cohort of head and neck oncological patients.[45] The domain health problems of the GFI significantly predicted postoperative complications; however, subgroup analysis for patients with skin malignancies was not performed in that study. Interestingly, in our analysis, GFI showed no prognostic value. Comparing these studies is difficult, as there are large differences among frailty screening tools.[48] Domains that are covered by the G8 are nutritional status, polypharmacy, neuropsychological status and mobility. The G8 has been proven to be a useful tool in liver and colorectal surgery as a predictor of surgical complications.[49,50] However, the value of G8 remains questionable, as the majority of our patients scored frail on the G8 (73.3%). This is in line with Pottel et al. and Hamaker et al. evaluating the G8 and other screening tools.[48,51] They found that the G8 is very sensitive but not very specific with respect to its gold standard, a CGA. Referring all frail patients, based on G8 to a geriatrician for a CGA would be infeasible.

From all individual geriatric domains, polypharmacy and malnutrition were most significantly related with post-operative complications in our population. These domains are both well represented in the G8 as well. Polypharmacy is related to frailty and comorbidities, but also associated with outcome parameters such as postoperative complications, delirium, (chemo)radiation toxicity, increased hospital stay and mortality.[23] Across literature, however, polypharmacy lacks definition and cut-off values range largely, with ≥5 being the mostly used.[23] Whether certain specific medications such as anticoagulants were related to postoperative complications, just like in the study of Amici et al., was not possible to investigate using the current dataset.[37] Malnutrition is very common and undertreated in elderly.[52] Evaluation of the nutritional status is therefore important in preoperative screening. Higher risk of malnutrition using MUST is associated with postoperative complications, increased hospital stay and mortality.[53–55] Often, the body mass index (BMI) is used as an indicator for nutritional status, just as in MUST. However, normal values of 18.5-24.9 kg/mm^2 are based on mortality risk within a young and healthy population.[56] For older patients, a BMI <23 kg/mm^2 is already associated with increased mortality, and may therefore be a better cut-off value for underweight. The 7.9% of patients having risk of malnutrition measured by MUST in our cohort may be an underestimation of the real prevalence of malnutrition. Identification of such deficits is particularly important, as a geriatrician or a dietary consultant may be able to respectively manage polypharmacy or prevent malnutrition, lowering the risk of complications.

Based on our results, it seems that G8 is a very predictive screening tool. However, lack of specificity does not make it possible to adequately select vulnerable patients. Meanwhile, individual geriatric domains such as polypharmacy or malnutrition are too incomprehensive to point out patients at risk for surgical complications. The question arises what would then be an adequate screening strategy for elderly patients with cutaneous malignancies. As a recommendation, a two-step approach may bring a solution to this problem. The first step would be a short geriatric screening by a trained nurse, gathering information on all geriatric

domains including comorbidities, polypharmacy, nutritional status, functional status, social support, cognition and psychological status, using short screening instruments. Then, the patients' screening information is discussed within a multidisciplinary team for elderly patients, in which the nurse, a geriatrician, and head and neck surgeon are present. The geriatrician may then already advise on perioperative management, or indicate a CGA and start pre-treatment optimization (second step). In this way, all potentially vulnerable patients have been reviewed prior to treatment, efficiently with respect to limited capacity of geriatric health care.

A strength of this work is the broad range of validated geriatric instruments and screening tools that were used to assess patients at baseline. Besides, many patient, tumor and treatment characteristics were available to adjust for existing differences between patients. Furthermore, patients were prospectively included and the selection of the study population was done carefully with respect to changes through exclusion process.

Limitations of our study may include that it is a single center study in a tertiary care hospital. As a result, the cohort contains a high percentage of complex cases, regarding tumor and treatment characteristics. Furthermore, the population was heterogenic, also in terms of tumor characteristics, like histopathology. However, as we were primarily investigating patient-related factors, this seemed to be less relevant in our study. Lastly, most complications have only temporary effect on the patients' lives. Other outcome parameters, such as health related quality of life may be of more value to this specific population and should be studied.

CONCLUSION

Frailty, measured by G8, is the strongest factor associated with postoperative complications in patients undergoing surgery for cutaneous head and neck malignancies, besides treatment related predictors, such as treatment intensity and type of anesthesia. Geriatric screening on multiple domains is recommended in patients with cutaneous head and neck malignancies, as this population includes old patients and frequently suffers postoperative complications.

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chapter four

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

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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 ≥ grade 2) and acute radiation-induced toxicity (Common Terminology Criteria for Adverse Events version 4.0 ≥ 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.

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 head and neck cancer 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.

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	20, 23
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

Outcomes

Postoperative complications, occurring within 30 days after surgery, 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.

RESULTS

Study population

A total of 369 patients were included in this study. After exclusion of patients with recurrent disease, palliative treatment and incomplete data, 259 patients remained eligible for inclusion and analysis.(Figure 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.

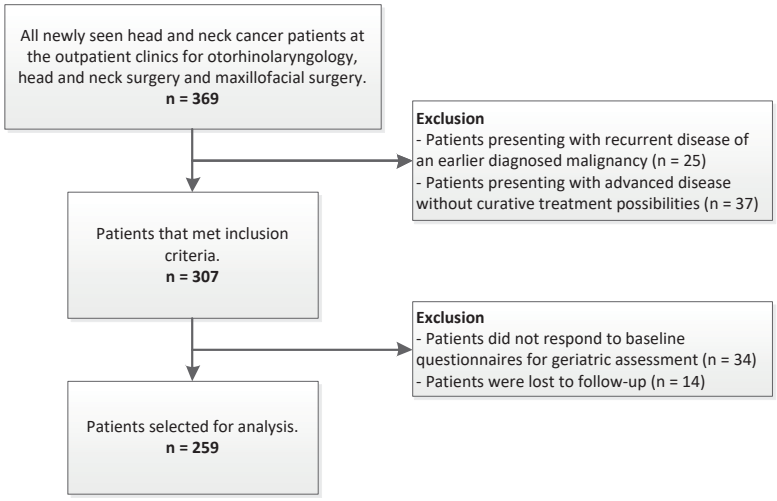

Figure 1 | Flowchart diagram representing the process of patient selection.

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%).

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

Variable	Non-response n = 34	Lost to follow-up n = 14	Cohort n=259
Age			
Mean ± SD (y)	69.4 ± 14.2	79.3 ± 8.9	67.4 ± 10.8
Sex			177 (68.3%)
Male	20 (58.8%)	10 (71.4%)	82 (31.7%)
Female	14 (41.2%)	4 (28.6%)	
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%)

Variables	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%)

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

Postoperative complications CDC ≥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)

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.

Variables	**Value (%)** n=148	**Univariable analysis** Odds ratio (95% CI)	p-value	**Multivariable analysis** 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 minutes)	41 (27.0%)	1		1	
Major (surgery ≥ 120 minutes)	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**

Continued on next page

Table 4 | continued

Variables	Value (%) n=148	Univariable analysis Odds ratio (95% CI)	p-value	Multivariable analysis Odds ratio (95% CI)	p-value
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%)	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**		

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.

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.

Variables	**Value (%)** n=160	**Univariable analysis** Odds ratio (95% CI)	p-value	**Multivariable [a] analysis** 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 (surgery < 120 minutes)	49 (30.6%)	1		1	
Major (surgery ≥ 120 minutes)	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		

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Table 5 | continued

Variables	Value (%) n=160	Univariable analysis Odds ratio (95% CI)	p-value	Multivariable [a] analysis Odds ratio (95% CI)	p-value
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%)	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%)	1.42 (0.44-4.53)	0.558		
ADL					
No restrictions (< 1)	146 (93.0%)	1			
Restrictions (≥ 1)	11 (7.0%)	0.69 (0.20-2.35)	0.551		

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.

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 (%) n=148**	**Unadjusted** Odds ratio (95% CI)	p-value	**Adjusted** [a] 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**	**1 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 (%) n=160**	**Unadjusted** Odds ratio (95% CI)	p-value	**Adjusted** [c] 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 (0.51-2.53)	0.397	1.22 (0.87-1.72)	0.241

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 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 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 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≥2) occurred in 27.7% and radiation induced toxicity (CTCAE≥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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SUPPLEMENTARY DATA

Clavien-Dindo Classification Grades	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regions are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside .
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention; not under general anesthesia or under general anesthesia.
IV	Life-threatening complication (including CNS complications) requiring IC/ICU-management; with single organ dysfunction (including dialysis) or multi organ dysfunction.
V	Death of a patient.

Appendix Table A.2 | Common Terminology Criteria for Adverse Events, version 4.0.

Common Terminology Criteria for Adverse Events, version 4.0					
	Grade				
Adverse event	I	II	III	IV	V
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-
Mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-

Continued on next page

Appendix Table A.2 | continued

Common Terminology Criteria for Adverse Events, version 4.0					
	Grade				
Adverse event	**I**	**II**	**III**	**IV**	**V**
General pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-
Salivary duct inflammation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/ oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-

chapter five

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 ≥65 (β=0.03(95%CI=0.01;0.05), p=0.01), regional RT (β=0.05(95%CI=0.02;0.09), *p*=0.004), and concurrent chemotherapy (β=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 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 HNC 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.

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 (Figure 1).

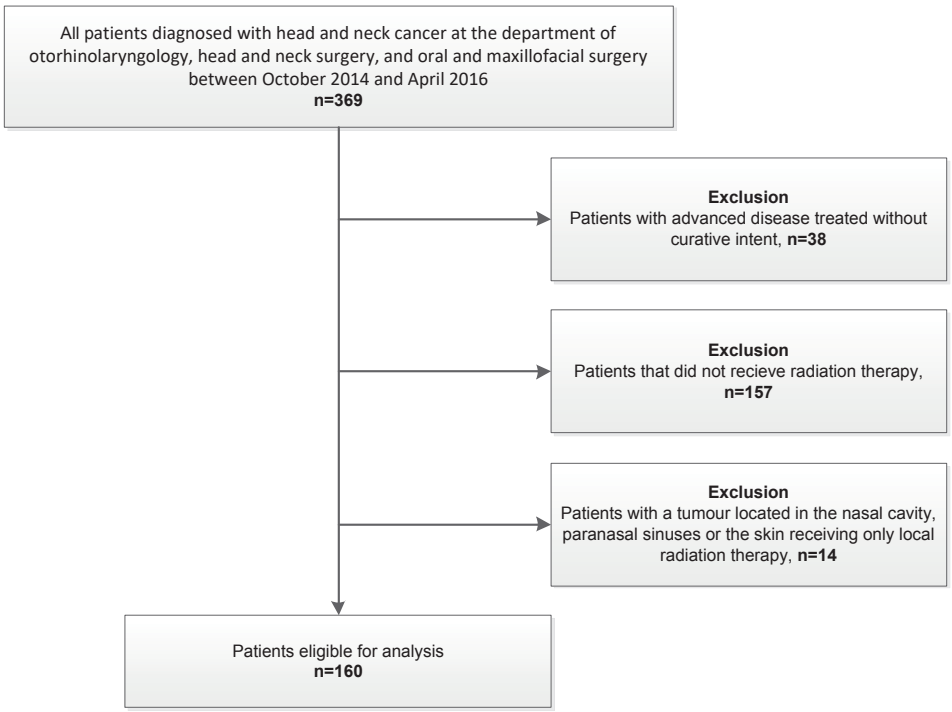

Figure 1 | Flowchart diagram depicting the in- and exclusion of patients. Abbreviations : n = number of patients

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 without excluding entire cases and limiting bias. The dependent variable was the mean CTCAE grade, and measures were repeated weekly from 0-7 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.

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

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%)

Continued on next page

Table 1 | continued

Patient-, tumour- and treatment characteristics		n (%)[a]
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%)

Continued on next page

Table 1 | continued

Patient-, tumour- and treatment characteristics		n (%)[a]
TUG	No restrictions (<13.5) Declined mobility (≥13.5)	143 (89.4%) 17 (10.6%)
ADL	No restrictions (<1) Restrictions (≥1)	145 (92.4%) 12 (7.6%)
IADL	No restrictions (<3) Restrictions (≥3)	138 (86.3%) 22 (13.8%)
MMSE	Normal cognitive function (>24) Declined cognitive function (≤24)	144 (90.0%) 16 (10.0%)
GDS-15	No depression (<6) Depression (≥6)	140 (89.7%) 16 (10.3%)
Living situation	Independent Assisted Nursing home	145 (91.2%) 13 (8.2%) 1 (0.6%)
Marital status	Single In a relationship	113 (70.2%) 47 (29.2%)
Frailty screening		
GFI	Non-frail Frail	108 (68.4%) 50 (31.6%)
G8	Non-frail Frail	72 (45.3%) 87 (54.7%

RESULTS

Patient characteristics

After exclusion, 160 patients remained eligible for analysis (Figure 1). Patient-, tumour- and treatment characteristics are presented in Table 1. The mean age of the ureatients 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 Figure 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(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.

Toxicity grades in frail patients, defined by either G8 or GFI, were not significantly different from those observed among non-frail patients, in both univariable and adjusted models (Table 4 and Figure 2).

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
Weight 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)

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. 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.

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		**0.01**
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		

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Table 3 | continued

Variable	Model parameters	Univariable models		Multivariable model	
		β (95% CI)	p-value	β (95% CI)	p-value
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**

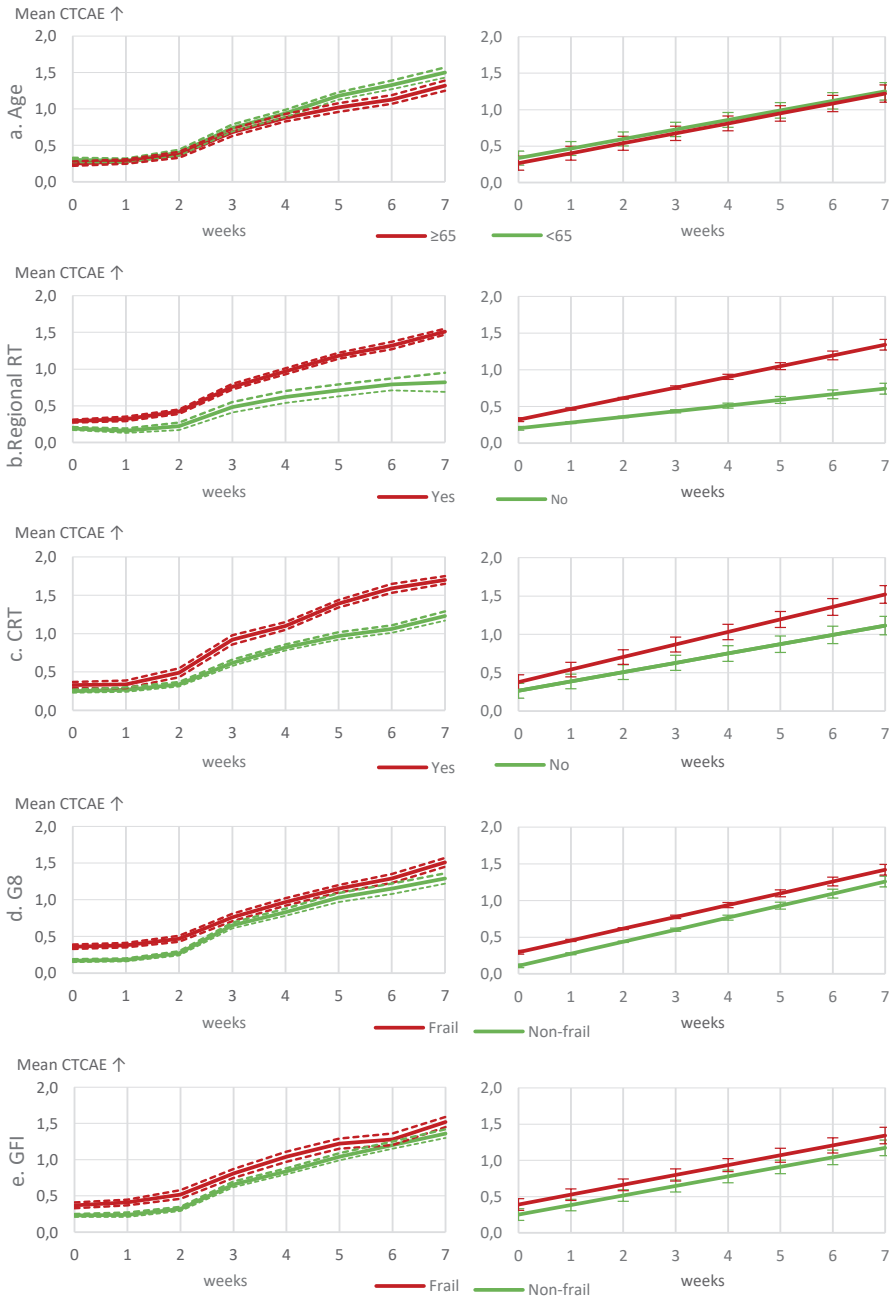

Figure 2 | Radiation-induced toxicity during treatment time points week 1-week 7. The left figures represent radiation-induced toxicity scores grouped by the binary outcome of age, regional RT, CRT, G8 and GFI. The right figures represent the predicted toxicity patterns for both groups. * significance 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.

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. 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.

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
Poly-pharmacy	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	0.00 (-0.02; 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

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Table 4 | continued

Variable	Model parameters	Univariable models		Adjusted models	
		β (95% CI)	p-value	β (95% CI)	p-value
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 (-0.01; 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	ref		ref	
	Declined cognitive	-0.02 (-0.15; 0.11)	0.79	-0.01 (-0.13; 0.12)	0.94
	Normal cognitive *time	ref		ref	
	Declined cognitive *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

Continued on next page

Table 4 | continued

Variable	Model parameters	Univariable models		Adjusted models	
		β (95% CI)	p-value	β (95% CI)	p-value
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; 0.52)	**0.001**
	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

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.

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SUPPLEMENTARY DATA

Supplementary table 1 | Transformation table for UMCG dysphagia scale to CTCAE dysphagia scale. Abbreviations: UMCG = University Medical Center Groningen. CTCAE = Common Terminology Criteria of Adverse Events. TPN = Total Parenteral Nutrition. AE = Adverse Event.

UMCG	CTCAE
Symptomatic but regular diet	1 Symptomatic, able to eat regular diet
Symptomatic and altered diet	2 Symptomatic and altered eating/swallowing
Liquids only Tube feeding dependent, oral intake possible Completely tube feeding dependent	3 Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated
	4 Life-threatening consequences; urgent intervention indicated.
	5 Death related to AE.

Supplementary table 2 | Data availability. Abbreviations: n = number of patients. CTCAE = Common Terminology Criteria of Adverse Events.

CTCAE scale	Number of patients								
	baseline	week 1	week 2	week 3	week 4	week 5	week 6	week 7	week 12
Weight loss		157	156	151	155	148	120		114
Sore throat	160	159	157	159	156	157	149	123	153
Hoarseness	156	151	148	150	149	149	140	123	144
Oral pain	160	159	157	159	156	156	149	123	153
Mucositis	159	159	157	159	156	156	140	123	153
General pain	159	158	157	159	156	157	149	123	151
Dysgeusia	160	159	147	159	156	157	148	123	153
Salivary duct inflammation	149	159	157	159	156	157	148	123	153
Xerostomia	160	159	157	159	156	157	147	123	153
Dysphagia	160	159	157	159	156	157	150	123	153
Total CTCAE	160	159	159	159	158	158	153	123	153

Frailty is associated with decline in health-related quality of life of patients treated for head and neck cancer

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chapter six

ABSTRACT

Objective

To determine the effect of frailty on Health Related Quality of Life (HRQoL) after treatment for Head and Neck Cancer (HNC).

Materials and methods

Patients were prospectively included in OncoLifeS, a data-biobank. Before treatment, patients underwent geriatric screening, including the Groningen Frailty Indicator (GFI) and Geriatric 8 (G8). Patients' HRQoL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) at three, six, twelve and twenty four months after treatment. Linear mixed models were used for statistical analysis. All models were adjusted for baseline HRQoL values, relevant confounders at baseline and yielded estimates (β), 95% confidence intervals and p-values.

Results

88 patients were included. The mean age was 68.4 years and 68.8% were male. During follow-up, 84 patients had tumor recurrence and 66 died. Response to EORTC-QLQ-C30 ranged from 77.3% to 87.8%. Frail patients, defined by GFI, had significantly worse Global Health Status/Quality of Life (GHS/QoL) (β=-8.70(-13.54;-3.86), p<0.001), physical functioning (β=-4.55(-8.70;-0.40), p<0.032), emotional functioning (β=-20.06(-25.65;-15.86), p<0.001), and social functioning (β=-8.44(-13.91;-2.98), p<0.003) three months after treatment compared to non-frail patients. Furthermore, frail patients had a significantly worse course of GHS/QoL (β=-7.47(-11.23;-3.70), p=0.001), physical functioning (β=-3.28(-6.26;-0.31), p=0.031) and role functioning (β=-7.27(-12.26;-2.28), p=0.005) over time, compared to non-frail patients. When frailty was determined by G8, frailty was significantly associated with worse GHS/QoL (β=-6.68(-11.00;-2.37), p=0.003) and emotional functioning (β=-5.08(-9.43;-0.73), p=0.022) three months after treatment.

Conclusion

Frail patients are at increased risk for decline in HRQoL, and further deterioration during follow-up after treatment for HNC.

INTRODUCTION

With the incidence of cancer and specifically the proportion of elderly with cancer rising, oncologists may increasingly encounter the geriatric syndrome of frailty.[1] Frailty results from the heterogenic process of aging, leaving great diversity in populations with respect to physical, functional, psychological and social status, and is defined as 'a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse outcomes'.[2] Often, chronological age is not very representative of a patient's biological age. One of the populations that is thought to be very frail are patients with Head and Neck Cancer (HNC). In this population, functional and cognitive impairment, depressive symptoms and social isolation have shown to be highly prevalent.[3] The burden of frailty in HNC patients is higher than in patients with other solid malignancies.[4] Probably, general symptoms secondary to tumor extension and location, such as weight loss and malnutrition, contribute to this.[5] Additionally, patient related factors such as lifelong tobacco and alcohol abuse, which are etiological factors for HNC, increase frailty status as well.[6,7]

For head and neck oncologists, this leads to a challenging clinical problem. On the one hand, intensive, often multimodal, treatment is indicated; on the other hand, patients may be vulnerable with multiple comorbidities, polypharmacy, functional and psychosocial restrictions. This makes decision making challenging. Ideally, by determining the biological age (i.e. frailty), undertreatment of fit elderly and overtreatment of frail young patients should be prevented. The gold standard to assess frailty is a Comprehensive Geriatric Assessment (CGA) by a geriatrician.[8] Because of its time consuming nature, burden for the patient and limited health care capacity, screening tools have been developed to select patients that need CGA.[9]

In HNC, frailty has already been associated with increased frequency and severity of postoperative complications, prolonged length of hospital stay, increased readmission rates and worse overall survival.[10] Although these outcome measures are all clinically relevant, they do not represent the perspective of the patient. Older patients have different priorities regarding treatment outcome than their younger counterparts; e.g. Health Related Quality of Life (HRQoL) may be considered more important than survival in decision making.[11–13]

Long-term HRQoL as reported by patients is increasingly considered a valuable outcome measure for cancer treatment. Previous studies showed that frailty is associated with worse HRQoL in other oncological cohorts.[14–17] However, this has never been investigated specifically in HNC patients. A more accurate prediction of patient-rated HRQoL may be of help in decision making and management of expectations. In the present prospective study, we investigated how frailty affects HRQoL shorty after treatment for HNC, and how frailty affects the course of HRQoL during long-term follow-up after treatment.

MATERIAL AND METHODS

Study design

The present study is a prospective observational cohort study with two years of follow-up. All patients were enrolled in OncoLifeS, a prospective oncological data-biobank at the University Medical Center Groningen (UMCG).[18] OncoLifeS has been approved by the local Medical Ethical Committee and the study protocol was approved by the OncoLifeS scientific board.

Study population

Between October 2014 and May 2016, all consecutive patients referred to the UMCG with a mucosal, salivary gland or complex cutaneous malignancy (giant basal cell carcinoma, squamous cell carcinoma stage II or higher, melanoma, Merkel cell carcinoma and neck metastasis of any cutaneous malignancy, requiring major surgery and/or radiotherapy) of the head and neck were asked to participate in OncoLifeS and were included after obtaining written informed consent (Figure 1). Patients were seen at the outpatient clinics of the department of Otorhinolaryngology, Head and Neck Surgery, and the department of Oral and Maxillofacial Surgery. Patients were treated according to (inter)national guidelines and discussed within our multidisciplinary head and neck tumor board. Exclusion criteria were palliative treatment, non-standard treatment (e.g. in the scope of other clinical trials) and missing baseline data on HRQoL (Figure 1). As the burden of frailty is expected to be relatively high in young HNC patients as well, age was not an exclusion criterion in our study, in contrast to other studies investigating frailty. Tumor recurrence or death led to exclusion from the analyses from that time point onwards (Figure 1).

Data collection

Patients' age, sex, tumor site, histopathology, cancer stage, primary treatment and comorbidities were registered at baseline. Staging was done according to the seventh edition of the Union for International Cancer Control (UICC) TNM classification of malignant tumors.[19] Comorbidities were graded using the Adult Comorbidity Evaluation (ACE-27) as none, mild, moderate or severe.[20] As part of a geriatric screening at our outpatient clinic, within the scope of OncoLifeS, frailty status of patients was assessed using two validated frailty screening instruments. The Groningen Frailty Indicator (GFI), a fifteen-item questionnaire, was completed by patients either at the outpatient clinic or at home and returned by mail. Patients with a GFI score greater than or equal to four were considered frail.[21] The Geriatric 8 (G8), an eight-item scoring instrument, was completed by one of the investigators or a nurse together with the patient at the outpatient clinic. Patients with a G8 score lower than or equal to fourteen were considered as frail.[22] Although the intention of the study was purely observational, advancing insights of patients' frailty status might have unconsciously led to referral to a geriatrician.

As our primary measure of follow-up, patients were asked to report HRQoL using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) before treatment and at three, six, twelve and twenty four months after treatment.[23] Global health status, functional scales, symptom scales and summary score were calculated according to the EORTC-QLQ-C30 scoring manuals.[24,25]

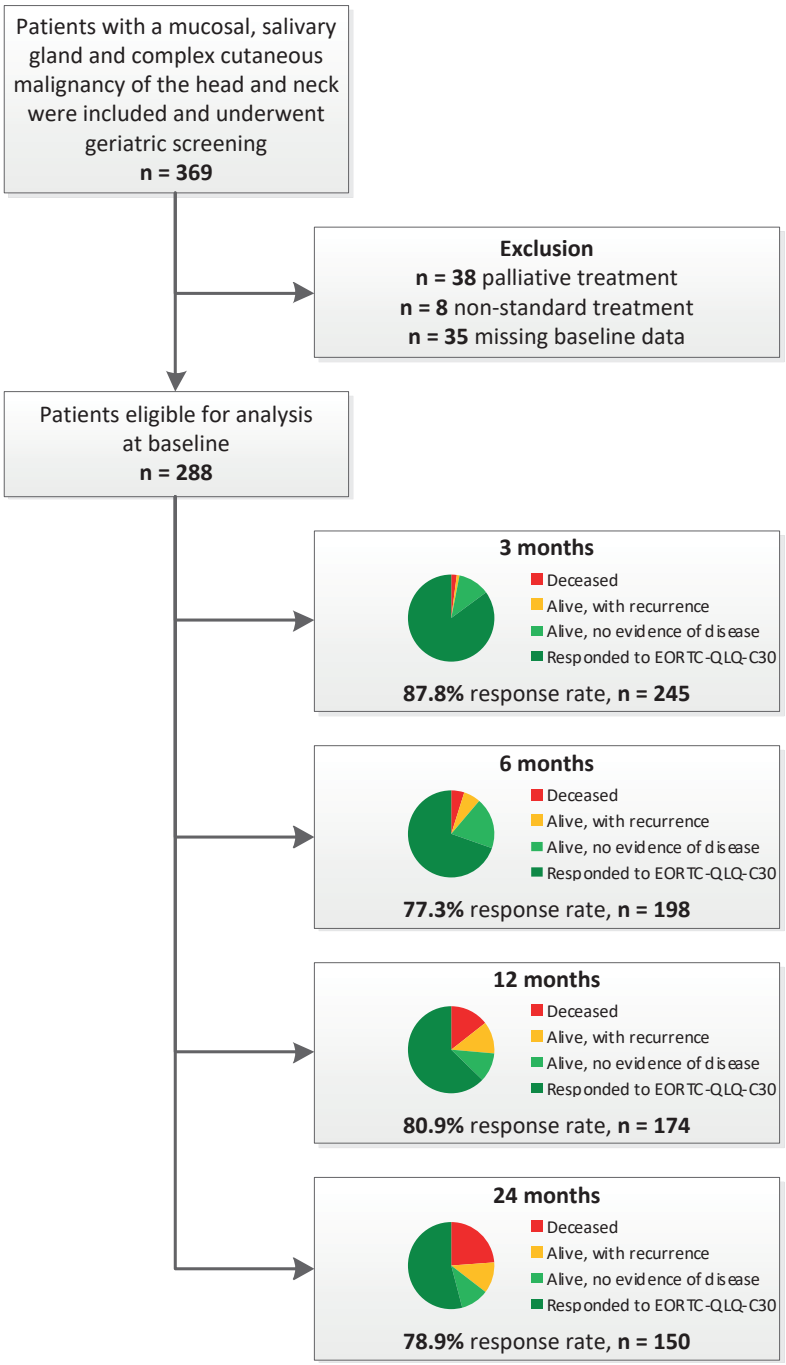

Figure 1 | Flowchart diagram with the in- and exclusion of patients and follow-up statistics of the analyzed cohort.

Statistical analysis

All statistical procedures were performed with SPSS Statistics 23.0 software (IBM, Armonk, New York, United States of America). Descriptive statistics were presented as mean ± standard deviation (SD), median (interquartile range) or frequency (percentage). Differences between groups were analyzed with T-test for normally distributed continuous data and χ^2 test or Fisher's exact test for categorical data.

We employed Linear Mixed-effect Models (LMMs) for the analyses of repeated continuous measures, i.e. the EORTC-QLQ-C30 scales. LMMs are a superior method for analyzing large longitudinal datasets as they allow missing data points without discarding entire cases. An online available methods paper was used as a reference.[26] Typically, HRQoL decreases steeply during treatment, and then slowly tends to get better over time (Figure 2a).[27] Due to this irregular shape of trajectory, we only performed analysis on the three to twenty-four month interval, treating it as being linear (Figure 2b). Leaving out polynomial terms makes interpreting coefficients possible and thus allows for assessing clinical relevance rather than a p-value.

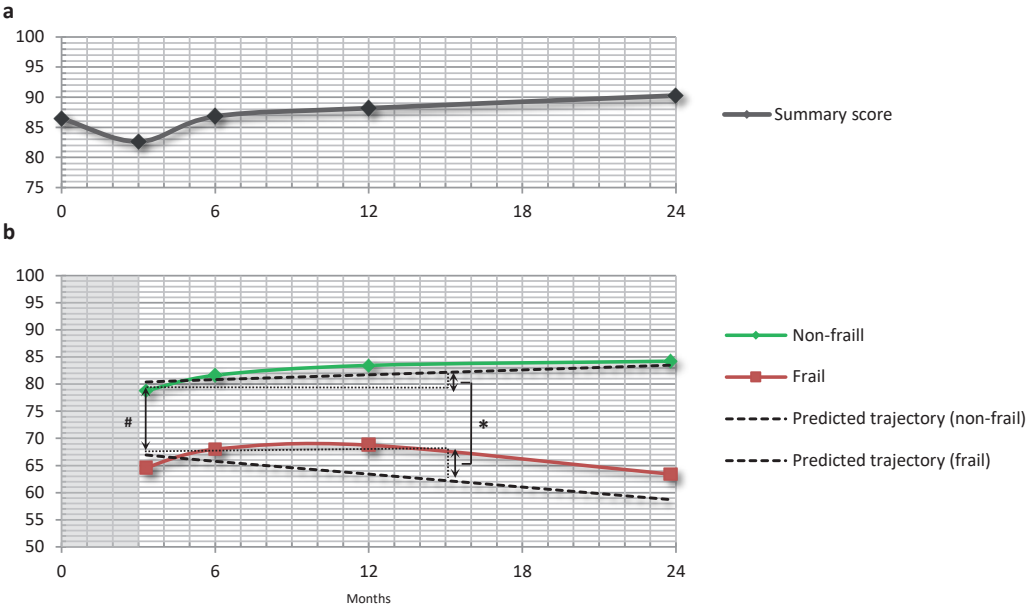

Figure 2 | Quality of life during and after treatment for head and neck cancer. **a**) Mean summary EORTC-QLQ-C30 score: a typical shape of quality of life trajectory. **b**) Example of Global health status/QoL trajectory for the interpretation of linear mixed model analysis. Green (non-frail patients) and red (frail patients) lines indicate means. Dashed lines indicate predicted trajectory by the linear mixed model. # Refers to the difference in quality of life at 3 months after treatment (*frail* estimate in the models). * Refers to the different course of quality of life trajectories for frail and non-frail patients with respect to 1 year (*frail**time estimate in the models).

For the analyses, covariance type was set to unstructured. Fixed effects included the intercept and at least the variables time, frailty and frailty*time. Coefficients for frailty refer to the difference in HRQoL for frail and non-frail patients at three months after treatment. Coefficients for the interaction term frailty*time refer to the effect of frailty on change of HRQoL over time (per year). Coefficients yielded 95% confidence intervals (CIs) and p-values. All models were adjusted for baseline differences between frail and non-frail patients, by adding the baseline score of dependent EORTC-QLQ-C30 scale to the model. Furthermore, all models were adjusted for age, sex, cancer stage, treatment modality and comorbidity as well as their interaction with time (coefficients not shown in table). For random effects an intercept was included for between subject differences and covariance type was unstructured. Estimation method was set to Maximum Likelihood (ML) and predicted values and standard error of predicted values were saved for graphs. Between models, model fit was compared using likelihood ratio testing.

RESULTS

Patient characteristics

In this study, 288 patients were included. Follow-up and drop-out statistics are shown in Figure 1. During follow-up, 84 patients developed recurrent disease and 66 patients died. Response rates for EORTC-QLQ-C30 remained stable throughout follow-up, averaging around 80%.

Patient characteristics are presented in Table 1. The mean age was 68.4 years and approximately two-thirds of patients were male. Most patients had mucosal cancer (79.5%), followed by skin malignancy (18.8%) and malignant salivary gland tumor (1.7%). Most patients (86.1%) had squamous cell carcinoma. The most common primary mucosal sites were oral cavity (25.7%), larynx (22.9%) and oropharynx (18.1%). Patients underwent either primary surgery (56.6%), radiotherapy (28.8%) or chemoradiation (14.6%), or a combination of those. According to the GFI, 29.3% of patients were frail, while using the G8, 54.7% were considered frail. Tumor site, histopathology, stage and treatment type did not differ between frail and non-frail patients; however, frail patients (both by GFI and G8) had significantly higher age and more severe comorbidity (Table 1).

Frailty is associated with decline in quality of life

Mean EORTC-QLQ-C30 scores at baseline and during follow-up are provided in Supplementary table 1 and 2. Frailty, measured by GFI was associated with significantly worse Global Health Status/Quality of Life (GHS/QoL) at three months after treatment (β=-8.70(-13.54;-3.86), p<0.001), but also with a further decline of GHS/QoL during two years after treatment (β=-7.47(-11.23;-3.70), p<0.001), in models adjusted for baseline and relevant covariates (Table 2 and Figure 3a). Frailty measured by G8 was associated with worse GHS/QoL at three months after treatment (β=-6.68 (-11.00;-2.37), p=0.003) as well, but not with a worse course over time (Table 2 and Figure 3g).

Table 1 | Patient characteristics of the included cohort (n=288). Values given as *n(%)* unless otherwise specified. *P-values* given for [a] t-test [b] χ^2 test or [c] Fisher's exact test. ACE-27 = Adult Comorbidity Evaluation 27.

Patient characteristics	**Groningen Frailty Indicator**			**Geriatric 8**			**Total (n=288)**
Baseline	Non-frail (n=203)	Frail (n=84)	p-value	Non-frail (n=126)	Frail (n=152)	p-value	
Age							
Mean ± SD	67.2 ± 10.6	71.4 ± 11.2	**0.003**[a]	65.8 ± 9.6	70.4 ± 11.7	**0.001**[a]	68.4 ± 10.9
Median (Iqr)	67.2 (59.6-75.4)	69.1 (62.5-80.7)			69.2 (62.4-79.4)		68.2 (60.6-76.7)
Sex							
Male	142 (70.0)	55 (65.5)	0.457[b]	95 (75.4)	96 (63.2)	**0.028**[b]	198 (68.8)
Female	61 (30.0)	29 (34.5)		31 (24.6)	56 (36.8)		90 (31.3)
Reason for referral							
Primary tumor	190 (93.6)	78 (92.9)	0.819[b]	117 (92.9)	143 (94.1)	0.680[b]	269 (93.4)
Recurrent tumor	13 (6.4)	6 (7.1)		9 (7.1)	9 (5.9)		19 (6.6)
Tumor site							
Oral cavity	52 (25.6)	22 (26.2)	0.377[c]	30 (23.8)	41 (27.0)	0.327[c]	74 (25.7)
Nasal cavity and paranasal sinus	13 (6.4)	2 (2.4)		8 (6.3)	7 (4.6)		16 (5.6)
Nasopharynx	4 (2.0)	0 (0.0)		3 (2.4)	1 (0.7)		4 (1.4)
Oropharynx	36 (17.7)	16 (19.0)		24 (19.0)	28 (18.4)		52 (18.1)
Hypopharynx	5 (2.5)	4 (4.8)		2 (1.6)	7 (4.6)		9 (3.1)
Larynx	44 (21.7)	22 (26.2)		36 (28.6)	29 (19.1)		66 (22.9)
Salivary glands	3 (1.5)	2 (2.4)		1 (0.8)	4 (2.6)		5 (1.7)
Skin	38 (18.7)	16 (19.0)		19 (15.1)	32 (21.1)		54 (18.8)
Unknown primary tumor	8 (3.9)	0 (0.0)		3 (2.4)	3 (2.0)		8 (2.8)
Histopathology							
Squamous Cell Carcinoma	172 (84.7)	76 (90.5)	0.196[b]	110 (87.3)	129 (84.9)	0.561[b]	248 (86.1)
Other	31 (15.3)	8 (9.5)		16 (12.7)	23 (15.1)		40 (13.9)

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Table 1 | continued

Patient characteristics	Groningen Frailty Indicator			Geriatric 8			Total (n=288)
Baseline	Non-frail (n=203)	Frail (n=84)	p-value	Non-frail (n=126)	Frail (n=152)	p-value	
Stage							
I	51 (25.8)	20 (23.8)	0.987[b]	36 (28.6)	31 (21.1)	0.368[b]	71 (24.7)
II	40 (20.2)	18 (21.4)		27 (21.4)	28 (19.0)		58 (20.1)
III	28 (14.1)	12 (14.3)		15 (11.9)	24 (16.3)		40 (13.9)
IV	79 (39.9)	34 (40.5)		48 (38.1)	64 (43.5)		114 (39.6)
Primary treatment							
Surgery	117 (57.7)	45 (53.6)	0.455[b]	70 (55.6)	86 (56.6)	0.498[b]	163 (56.6)
Postoperative radiotherapy	42 (20.7)	18 (21.4)		22 (17.5)	38 (25.0)		61 (21.2)
Postoperative chemoradiation	4 (2.0)	1 (1.2)		3 (2.4)	2 (1.3)		5 (1.7)
Radiotherapy	53 (26.1)	30 (35.7)		35 (27.8)	45 (29.6)		83 (28.8)
Chemoradiation	33 (16.3)	9 (10.7)		21 (16.7)	21 (13.8)		42 (14.6)
ACE-27							
No comorbidity	55 (27.1)	7 (8.3)	**0.000**[b]	37 (29.4)	24 (15.8)	**0.000**[b]	62 (21.5)
Mild comorbidity	71 (35.0)	31 (36.9)		52 (41.3)	47 (30.9)		102 (35.4)
Moderate comorbidity	54 (26.6)	21 (25.0)		25 (19.8)	45 (29.6)		76 (26.4)
Severe comorbidity	23 (11.3)	25 (29.8)		12 (9.5)	36 (23.7)		48 (16.7)

Frailty is associated with decline in functioning

Frail patients, according to GFI, had worse physical (β=-4.55(-8.70;-0.40), p=0.032), emotional (β=-10.92(-16.06;-5.79), p<0.001) and social functioning (β=-8.44 (-13.91;-2.98), p=0.003) at three months after treatment than their non-frail counterparts, adjusted for baseline and covariates (Table 2 and Figure 3b,d,f). Moreover, these patients showed a significant further decline of physical (β=-3.28(-6.26;-0.31), p=0.031) and role functioning (β=-7.27(-12.26;-2.28), p=0.005) over time, compared to non-frail patients (Table 2 and Figure 3b,c). When frailty was measured by G8, only emotional functioning (β=-5.02(-9.43;-0.73), p=0.022) was different between frail and non-frail patients at three months after treatment (Table 2 and Figure 3j).

Table 2 | Results of linear mixed model analysis. Frailty measured by Groningen Frailty Indicator and Geriatric 8 alters quality of life after treatment. *Frail* refers to the difference in score of frail patients with respect to non-frail patients at 3 months. *Frail*Time* refers to the interaction of frailty and time, indicating the amount of change in Quality of Life over time (with respect to 1 year) for frail compared to non-frail patients. [a] All models were adjusted for baseline differences in corresponding EORTC-QLQ-C30 scale, and age, sex, stage, treatment modality and comorbidity and their interaction with time.

EORTC-QLQ-C30 3 to 24 months after treatment		**Groningen Frailty Indicator[a]**				**Geriatric 8[a]**			
		Estimate (β)	95% CI		p-value	Estimate (β)	95% CI		p-value
Summary score	Frail	-6.12	-9.57	-2.67	**< 0.001**	-2.87	-5.84	0.10	0.058
	Frail*Time	-1.70	-4.28	0.88	0.191	-0.74	-2.65	1.18	0.448
Global health status/QoL	Frail	-8.70	-13.54	-3.86	**< 0.001**	-6.68	-11.00	-2.37	**0.003**
	Frail*Time	-7.47	-11.23	-3.70	**< 0.001**	-2.39	-5.55	0.77	0.138
Functional scales									
Physical functioning	Frail	-4.55	-8.70	-0.40	**0.032**	-1.85	-5.43	1.74	0.311
	Frail*Time	-3.28	-6.26	-0.31	**0.031**	-1.36	-3.76	1.03	0.262
Role functioning	Frail	-5.70	-12.42	1.02	0.096	-5.31	-11.22	0.59	0.078
	Frail*Time	-7.27	-12.26	-2.28	**0.005**	-2.57	-6.49	1.36	0.198
Emotional functioning	Frail	-10.92	-16.06	-5.79	**<0.001**	-5.08	-9.43	-0.73	**0.022**
	Frail*Time	2.07	-2.45	6.60	0.367	0.41	-3.05	3.86	0.817
Cognitive functioning	Frail	-3.88	-8.13	0.37	0.074	-2.59	-6.38	1.20	0.180
	Frail*Time	-0.89	-4.31	2.54	0.610	-0.44	-3.29	2.41	0.761
Social functioning	Frail	-8.44	-13.91	-2.98	**0.003**	-2.78	-7.51	1.95	0.248
	Frail*Time	-2.73	-6.77	1.30	0.183	-2.68	-6.02	0.65	0.114
Symptom scales									
Fatigue	Frail	8.25	2.15	14.36	**0.008**	4.58	-0.90	10.07	0.101
	Frail*Time	3.59	-0.74	7.92	0.104	1.26	-2.23	4.75	0.475
Nausea and vomiting	Frail	1.46	-1.55	4.47	0.340	0.34	-2.42	3.10	0.809
	Frail*Time	2.87	0.66	5.09	**0.011**	2.13	-0.23	4.49	0.077
Pain	Frail	10.09	5.05	15.13	**<0.001**	4.57	-0.11	9.26	0.056
	Frail*Time	3.31	-1.53	8.15	0.178	0.03	-3.97	4.03	0.988
Dyspnoea	Frail	8.53	3.21	13.85	**0.002**	5.02	0.14	9.90	**0.044**
	Frail*Time	0.14	-4.01	4.30	0.946	0.49	-2.86	3.84	0.773
Insomnia	Frail	8.07	1.35	14.79	**0.019**	4.13	-1.76	10.03	0.169
	Frail*Time	-3.45	-8.91	2.01	0.214	-0.37	-4.87	4.12	0.871
Appetite loss	Frail	14.23	7.65	20.81	**<0.001**	7.21	1.03	13.39	**0.022**
	Frail*Time	-2.99	-8.29	2.31	0.267	-1.12	-5.61	3.37	0.623
Constipation	Frail	3.25	-1.26	7.77	0.157	0.01	-4.07	4.09	0.996
	Frail*Time	-0.25	-3.90	3.39	0.891	-0.53	-3.64	2.57	0.736
Diarrhoea	Frail	4.58	1.16	8.01	**0.009**	3.40	0.27	6.54	**0.033**
	Frail*Time	0.67	-3.13	4.46	0.730	0.08	-3.05	3.21	0.959
Financial difficulties	Frail	7.36	2.80	11.93	**0.002**	3.72	-0.47	7.91	0.082
	Frail*Time	0.89	-3.08	4.85	0.660	1.68	-1.62	4.98	0.315

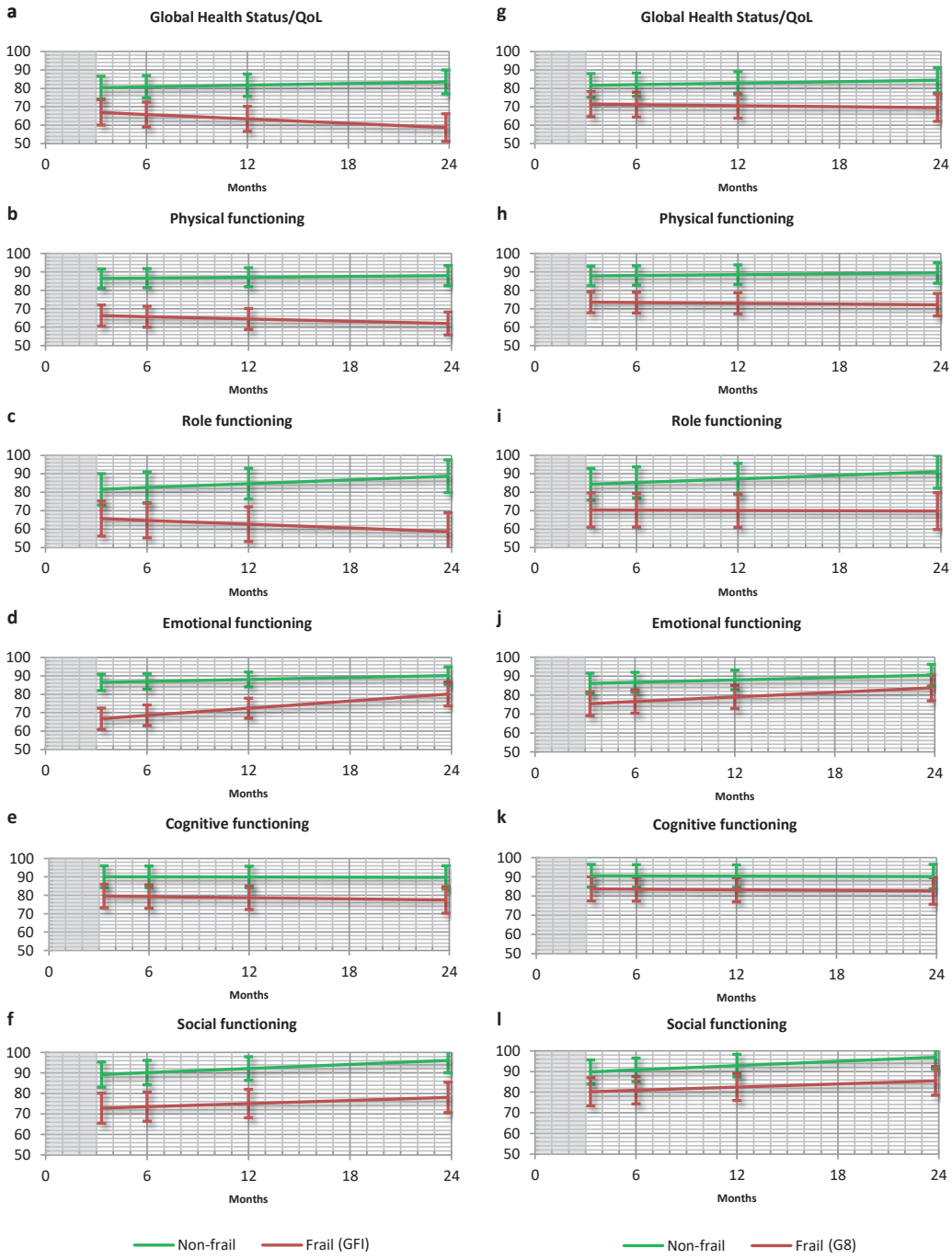

Figure 3 | Predicted values and standard error of predicted values by linear mixed models for EORTC-QLQ-C30 scales. **a-f** = frailty defined by Groningen Frailty Indicator. **g-l** = frailty defined by Geriatric 8.

Frailty is associated with increased symptom burden

Frail patients, measured by GFI, showed more fatigue (β=8.25(2.15;14.36), p=0.008), pain (β=10.09(5.05;15.13),p<0.001),dyspnea(β=8.53(3.21;13.85),p=0.002),insomnia(β=8.07(1.35;14.79), p=0.019), appetite loss (β=14.23(-7.65;20.81), p<0.001), diarrhea (β=4.58(1.16;8.01), p=0.009), and financial difficulties (β=7.36(2.80;11.93), p=0.002) than non-frail patients in models adjusted for baseline and relevant covariates, at three months after treatment (Table 2). Additionally, prolonged complaints of nausea and vomiting were seen in frail patients (β=2.87(0.66;5.09), p=0.011). Frailty, measured by the G8, was associated with more dyspnea (β=5.02(0.14;9.90), p=0.044), appetite loss (β=7.21(1.03;13.39), p=0.022), and diarrhea (β=3.40(0.27;6.54), p=0.033) at three months after treatment (Table 2).

DISCUSSION

To our knowledge, this is the first study examining the association between frailty and changes in HRQoL after treatment in HNC patients. Key findings include that frailty, identified by two different frailty screening tools, was associated with a decline in QoL, different functioning domains, and increased symptom burden after treatment for HNC, independently of other relevant factors. Moreover, frailty at baseline was also associated with further deterioration of QoL and functioning during two years of follow-up. These findings emphasize the importance of implementing frailty screening in treatment counseling and decision making.

As we expected, frail patients showed worse GHS/QoL after treatment than non-frail patients, regardless of their baseline score, and age, sex, cancer stage, treatment modality and comorbidity. This was not only the case at three months after treatment, but their trajectory increasingly diverged from non-frail patients during the two years of follow-up. This effect was most pronounced when frailty was measured by using the GFI and may roughly be interpreted in two ways: either the frail patients' GHS/QoL trajectory deteriorates over time compared to non-frail patients, or recovery for frail patients is not as good as for non-frail patients. Plotted trajectories (Figure 3a) reveal that this is a combination of both deterioration and worse recovery, however, this should be interpreted for each EORTC-QLQ-C30 scale independently.

Although only a minor difference (8.70 points) on the GHS/QoL scale between frail and non-frail patients was found at three months after treatment (Table 2, frail term), adding the increase per year (7.47 points, Table 2, frail*time term) resulted in a major cumulative difference (21.77 points) two years after treatment, which was adjusted for confounding factors. This is seen in plotted trajectories as well (Figure 3a). According to classification of Osoba et al. (5-10 points difference should be interpreted as 'little' change, 10-20 points as 'moderate' change and >20 as ' very much' change), the relative decrease in GHS/QoL is clinically highly relevant.[28] These findings could have a major impact on decision making: being aware of poorer outcomes for frail patients may and should be taken into account during shared decision making.

Comparing our results with published literature, a similar analysis was recently performed by Kirkhus et al. in a heterogeneous oncological cohort.[17] Frailty, assessed using a modified geriatric assessment, was associated with worse GHS/QoL but not with further decline over time

during twelve months follow-up.[17] However, this study did not adjust for baseline differences between frail and non-frail patients, which have been shown to be significant at baseline already.[29] This may explain the larger estimates than in our present study. Other studies that have addressed frailty with respect to GHS/QoL did not find significant differences in the breast cancer and colorectal cancer population.[15,16] Only one study included a small proportion of HNC patients (4.3%) and found within a frail population (based on G8) that several factors such as stage, pain, fatigue, nutrition and comorbidity were associated with decline in GHS/QoL.[30] Though, the study population was very heterogeneous, analyses were unadjusted for different treatment modalities and lacked long-term follow-up.

An important contributor to patients' HRQoL is the level of functioning. Physical functioning has been demonstrated to be worse in older patients after treatment for HNC.[31] In our study, after adjusting for age, frailty was associated with worse physical functioning both shortly after treatment as well as with further deterioration during follow-up. Literature data on this issue is heterogeneous[15–17,32], but most importantly, not investigated in HNC. Differences between cohort characteristics and research methodology may largely explain differences.

Role functioning is often overlooked in literature and rarely investigated as a primary outcome measure with respect to frailty. In our study, frailty (GFI) was strongly associated with decline in role functioning over time. When reviewing the EORTC-QLQ-C30 questions involved in role functioning 'Were you limited in doing either your work or other daily activities?' and '*Were you limited in pursuing your hobbies or other leisure time activities?*', these seem important matters for QoL.

Emotional functioning was significantly worse for frail (GFI and G8) patients three months after treatment. Since frailty is a multidimensional geriatric syndrome including a significant psychological domain as well, this was to be expected: patients with premorbid psychological issues have a higher risk of developing psychological problems during and after treatment.[33] Improvement of emotional functioning after treatment occurred in both frail and non-frail patients (Figure 3d,j), despite the known high prevalence of fear of recurrence, depression and even high suicide risk in the HNC population in other studies.[34–36]

Cognitive functioning was not significantly affected by treatment or by frailty during follow-up in our study. Another study investigating HNC patients treated with radiotherapy, however, did show significant decline of cognitive function within seven years after treatment.[37] Probably, their objective assessment of cognitive function is much more sensitive to cognitive alterations than the patient-reported cognitive functioning scale, employed in our study. These results should therefore be interpreted with care.[38]

Social functioning is specifically at risk in HNC treatment due to the diseases' relation with the organs for communication.[39,40] We found frail (GFI) patients to have worse social functioning than non-frail patients shortly after treatment, but both groups gradually improved in the following years, similar to data in literature.[41]

Clearly, large differences exist between screening tools such as GFI and G8. This leads to the question: which are the most important domains of a geriatric screening with respect to changes in QoL? G8 is known as a very physically oriented screening tool with more than half of the questions related to nutrition, weight loss and comorbidities.[9] G8 is strongly associated with

surgical complications as well as survival in oncological cohorts, but the relation with HRQoL has rarely been investigated.[42] In our study, G8 showed a weaker association with HRQoL than GFI. The GFI covers larger functional and psychosocial domains of frailty[9] which are, apparently, superior in long-term patient reported outcomes. Some studies have already investigated separate domains of geriatric screening in relation to QoL in more heterogeneous oncological cohorts: one found comorbidity and nutrition to be associated with decline in QoL after three months and another showed associations of malnutrition,[30] depression and impaired mobility with decline in QoL after six months.[43]

It has been difficult to show the objective benefit of implementing a geriatric screening in standard oncological healthcare with outcomes such as adverse events, QoL or survival.[44,45] Though, it has been shown that treatment recommendations are significantly different when an onco-geriatric multidisciplinary team is involved in decision making.[12] This does not necessarily mean that we should stop treating frail patients. After all, frail patients do not regret the decision that was made more than non-frail patients,[46] but identification of vulnerabilities may open doors to pre-treatment optimization or a more patient-tailored treatment plan. Prehabilitation studies are currently being carried out, also in the field of HNC.

The main strengths of this study include the prospective inclusion of a relatively large cohort, the use of well-known validated questionnaires to address frailty and HRQoL, and a notable two years of follow-up. Solid statistical analysis was performed handling missing data well and therefore limiting bias, and also controlling for baseline differences and confounders. Some limitations may be the relative heterogeneity of the cohort, which includes mucosal, salivary gland and cutaneous tumors, and possibly underrepresentation of the frailest patients. Inclusion of frail patients remains difficult due to refusal to participate, inability (being overburdened) to undergo geriatric screening or non-responses to questionnaires.[47]

CONCLUSION

Frailty is significantly associated with decline in QoL and functioning after treatment for HNC and even further deterioration in the long-term. Screening for frailty is highly recommended in the HNC population, as it may have implications for decision making or pre-treatment optimization.

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Supplementary table 1 | Mean and standard deviation of EORTC-QLQ-C30 scales at baseline to 24 months after treatment for frail and non-frail patients defined by Groningen Frailty Indicator.

EORTC-QLQ-C30	Baseline				3 months				6 months				12 months				24 months			
	Non-frail		Frail		Non-frail		Frail		Non-frail		Frail		Non-frail		Frail		Non-frail		Frail	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
n(%)	203 (70.7)		203 (70.7)		180 (73.8)		64 (26.2)		143 (77.7)		44 (22.3)		137 (79.2)		36 (20.8)		121 (81.2)		28 (18.8)	
Summary score	90.75	9.26	75.93	15.26	86.36	12.21	71.98	15.57	89.25	9.72	78.10	13.28	91.70	8.88	74.36	17.12	92.79	7.60	78.41	15.33
Global health status/QoL	77.29	18.07	59.34	21.71	78.75	18.11	64.58	19.30	81.63	14.20	67.99	23.08	83.45	15.09	68.75	21.95	84.24	13.61	63.39	22.94
Functional scales																				
Physical functioning	88.23	15.44	66.13	23.34	84.87	17.52	64.39	22.24	88.64	13.12	71.40	24.08	88.35	15.90	69.63	23.87	88.92	14.06	68.10	25.03
Role functioning	91.79	18.35	70.63	31.86	79.00	26.77	64.32	31.27	83.44	22.34	67.80	31.62	87.59	22.69	64.81	30.02	90.36	19.81	66.67	28.33
Emotional functioning	94.58	11.03	82.54	20.36	90.32	14.00	79.43	24.80	89.54	16.32	84.47	19.15	90.51	15.10	74.54	26.87	90.08	15.00	78.57	26.39
Cognitive functioning	78.53	19.64	58.07	24.64	86.33	16.03	65.06	24.88	86.35	16.59	72.47	24.83	90.39	14.39	75.08	23.31	90.69	14.90	80.46	20.79
Social functioning	93.51	12.86	79.37	23.94	87.83	19.29	72.14	30.44	90.63	17.40	78.03	24.84	93.55	13.44	76.39	27.13	96.53	9.39	79.76	28.09
Symptom scales																				
Fatigue	14.40	18.99	36.24	25.30	29.62	23.30	44.79	27.88	22.08	21.55	38.01	25.39	16.30	17.67	41.05	25.59	12.99	15.14	33.33	25.48
Nausea and vomiting	2.30	8.63	6.55	16.37	7.21	17.88	12.76	19.86	3.05	10.01	3.41	8.49	2.31	8.62	10.65	21.88	1.24	4.39	9.52	17.23
Pain	12.97	22.40.	26.98	28.21	14.34	20.58	27.86	29.10	10.57	16.64	21.97	24.32	7.79	14.44	28.70	27.78	5.37	12.95	22.02	28.71
Dyspnoea	10.07	21.37	25.40	33.78	11.99	21.11	29.17	32.80	10.89	19.05	23.26	28.67	10.46	17.50	30.56	34.16	10.19	20.11	25.00	26.64
Insomnia	14.29	23.65	31.75.	34.67	13.78	23.36	32.81	33.33	12.28	20.90	22.73	31.15	12.65	22.91	30.56	32.24	10.19	20.57	17.28	25.10
Apetite loss	5.91	15.49	23.29	33.63	16.29	26.66	37.10	32.00	8.55	18.60	28.79	33.40	4.66	15.80	19.05	25.93	3.31	12.48	18.52	26.69
Constipation	3.12	12.24	10.71	22.65	8.99	18.93	15.10	26.51	4.79	12.34	9.85	18.44	3.65	12.58	14.81	26.96	3.58	12.02	7.14	18.94
Diarrhoea	4.29	13.44	9.92	22.42	4.87	15.08	13.54	23.55	2.61	11.80	6.06	13.01	2.68	12.17	11.11	17.82	3.31	10.89	11.90	26.00
Financial difficulties	6.80	18.95	10.44	19.43	9.23	23.22	19.58	27.85	7.68	20.11	21.21	28.84	7.54	19.38	14.81	23.16	4.44	16.13	14.29	26.34

Supplementary table 2 | Mean and standard deviation of EORTC-QLQ-C30 scales at baseline to 24 months after treatment for frail and non-frail patients defined by Geriatric 8.

EORTC-QLQ-C30	Baseline				3 months				6 months				12 months				24 months			
	Non-frail		Frail		Non-frail		Frail		Non-frail		Frail		Non-frail		Frail		Non-frail		Frail	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
n(%)	126 (45.3)		152 (54.7)		120 (50.2)		119 (49.8)		101 (52.6)		91 (47.4)		93 (55.0)		76 (45.0)		88 (60.3)		58 (39.7)	
Summary score	93.13	6.46	80.77	14.84	87.09	12.47	77.78	15.30	90.31	8.50	82.56	13.13	92.20	8.95	83.25	15.51	93.17	6.57	85.42	14.35
Global health status/QoL	79.10	17.28	65.37	21.75	79.10	16.94	70.80	21.15	83.58	12.05	72.80	20.56	83.24	15.76	76.97	19.33	84.87	12.49	73.28	21.95
Functional scales																				
Physical functioning	91.56	13.47	73.87	22.21	85.71	17.19	73.01	22.35	90.28	11.65	78.26	21.14	88.60	16.05	78.99	21.90	89.62	13.26	78.05	22.89
Role functioning	94.97	14.03	77.41	29.43	81.50	26.04	68.50	29.94	85.48	22.44	73.81	27.57	91.40	17.13	73.68	30.22	91.10	17.50	77.59	29.04
Emotional functioning	94.71	11.67	88.16	17.33	90.76	13.50	83.75	21.42	90.26	17.04	86.26	19.96	89.78	16.31	83.55	22.19	90.91	14.93	83.33	21.85
Cognitive functioning	78.64	19.10	66.61	24.82	85.45	16.71	75.68	23.64	87.16	15.28	78.08	22.71	89.16	15.63	84.58	19.87	91.09	13.85	84.82	19.79
Social functioning	94.71	11.67	85.09	21.03	88.98	14.46	79.27	26.75	91.42	16.09	84.07	22.62	93.91	13.41	85.31	22.27	96.93	8.25	87.64	22.63
Symptom scales																				
Fatigue	8.82	13.65	30.12	24.92	27.12	24.07	40.10	23.64	19.25	19.49	33.15	25.34	15.41	17.26	28.61	24.57	11.55	15.58	24.52	21.90
Nausea and vomiting	1.46	5.97	5.26	14.66	8.19	19.34	9.52	18.10	2.64	10.20	3.85	9.32	2.51	9.18	5.70	16.45	1.14	4.23	5.46	13.02
Pain	8.07	15.88	24.89	28.84	13.17	19.15	22.41	26.96	9.24	14.81	17.58	22.27	8.78	16.59	16.45	22.85	6.06	13.65	12.64	23.22
Dyspnoea	6.88	14.80	20.53	31.71	10.56	19.80	22.51	29.63	10.56	16.95	17.78	26.54	10.04	17.57	20.61	28.27	10.61	19.28	17.24	25.93
Insomnia	12.70	21.85	25.66	32.20	13.45	23.09	24.09	30.66	11.22	20.15	18.15	26.89	10.75	20.36	22.37	29.51	9.47	20.18	14.62	23.58
Apetite loss	1.85	8.75	18.76	29.21	14.08	26.06	29.91	31.07	8.33	17.33	19.05	29.46	3.62	15.20	12.89	22.52	2.65	9.07	11.70	23.98
Constipation	1.59	7.13	8.33	20.75	9.04	19.81	12.32	22.91	5.61	13.39	6.59	15.09	4.66	16.73	7.89	17.95	3.79	11.78	5.17	16.28
Diarrhoea	2.93	10.38	8.33	20.39	5.08	14.86	9.24	20.78	1.98	11.37	5.49	13.39	1.79	11.38	7.46	15.96	3.03	9.64	8.05	21.00
Financial difficulties	8.80	20.37	6.89	16.96	10.45	23.75	13.11	25.13	8.33	19.17	12.82	25.22	6.81	16.71	10.96	22.04	4.98	15.69	8.62	22.99

Association of deficits identified by geriatric assessment with deterioration of health-related quality of life in patients treated for head and neck cancer

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chapter seven

ABSTRACT

Importance

Accumulation of geriatric deficits, leading to an increased frailty state, makes patients susceptible for decline in health-related quality of life (HRQOL) after treatment for head and neck cancer (HNC).

Objective

To assess the association of single and accumulated geriatric deficits with HRQOL decline in patients after treatment for HNC.

Design, Setting, and Participants

Between October 2014 and May 2016, patients at a tertiary referral center were included in the Oncological Life Study (OncoLifeS), a prospective data biobank, and followed up for 2 years. A consecutive series of 369 patients with HNC underwent geriatric assessment at baseline; a cohort of 283 patients remained eligible for analysis, and after 2 years, 189 patients remained in the study. Analysis was performed between March and November 2020.

Interventions or Exposures

Geriatric assessment included scoring of the Adult Comorbidity Evaluation 27, polypharmacy, Malnutrition Universal Screening Tool, Activities of Daily Living, Instrumental Activities of Daily Living (IADL), Timed Up & Go, Mini-Mental State Examination, 15-item Geriatric Depression Scale, marital status, and living situation.

Main Outcomes and Measures

The primary outcome measure was the Global Health Status/Quality of Life (GHS/QOL) scale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Differences between patients were evaluated using linear mixed models at 3 months after treatment (main effects, β [95% CI]) and declining course per year during follow-up (interaction × time, β [95% CI]), adjusted for baseline GHS/QOL scores, and age, sex, stage, and treatment modality.

Results

Among the 283 patients eligible for analysis, the mean (SD) age was 68.3 (10.9) years, and 193 (68.2%) were male. Severe comorbidity (β = −7.00 [−12.43 to 1.56]), risk of malnutrition (β = −6.18 [−11.55 to −0.81]), and IADL restrictions (β = −10.48 [−16.39 to −4.57]) were associated with increased GHS/QOL decline at 3 months after treatment. Severe comorbidity (β = −4.90 [−9.70 to −0.10]), IADL restrictions (β = −5.36 [−10.50 to −0.22]), restricted mobility (β = −6.78 [−12.81 to −0.75]), signs of depression (β = −7.08 [−13.10 to −1.06]), and living with assistance or in a nursing home (β = −8.74 [−15.75 to −1.73]) were associated with further GHS/QOL decline during follow-up. Accumulation of domains with geriatric deficits was a major significant factor for GHS/QOL decline at 3 months after treatment (per deficient domain β = −3.17 [−5.04 to −1.30]) and deterioration during follow-up (per domain per year β = −2.74 [−4.28 to −1.20]).

Conclusions and Relevance

In this prospective cohort study, geriatric deficits were significantly associated with HRQOL decline after treatment for HNC. Therefore, geriatric assessment may aid decision-making, indicate interventions, and reduce loss of HRQOL.

Trial Registration

trialregister.nl Identifier: NL7839

INTRODUCTION

The presence of geriatric deficits is abundant in patients with head and neck cancer (HNC).[1] Accumulation of these deficits is associated with frailty, defined as "a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse outcomes."[2(p752)] It is believed that the HNC population is particularly prone to frailty,[3] not only because of the aging population in general and therewith increasing proportion of older patients with cancer,[4] but also because of the etiological factors for HNC, such as tobacco and alcohol abuse that may accelerate the process of aging,[5,6] and tumor-related factors leading to impairments. This results in a heterogenic population burdened by geriatric deficits, which are often poorly recognized by oncologists.[7]

The underestimation of frailty may result in substantial risks for patients with HNC, like overtreatment and undertreatment. Frailty has extensively been associated with adverse treatment outcomes, such as surgical complications, increased length of hospital stay, and worse overall survival.[8,9] Recently, it has been shown that frailty may be associated with decline in short- and long-term Health-Related Quality of Life (HRQOL) as well.[10,11] Yet specifically older patients find it more important to maintain adequate HRQOL rather than to target life extension or survival.[12-14]

Ideally, all patients would be subjected to a comprehensive geriatric assessment (CGA) by a geriatrician, which is defined as "a multi-dimensional, interdisciplinary, diagnostic process to identify care needs, plan care, and improve outcomes of frail older people."[15(p474)] However, owing to limited health care capacity and increasing numbers of patients, referring all patients to a geriatrician would be infeasible. Short frailty screening tools have been developed to select patients who may benefit from a CGA; however, they seem to lack specificity and predictive value.[16] In between, a geriatric assessment (GA) at the department of the treating (head and neck) oncologist may offer a solution. Such a GA can be relatively short and led by a nurse, include various validated tests[17] for relevant geriatric domains (physical, functional, psychological, socioenvironmental),[15] and can be followed by interdisciplinary consultation with a geriatrician to indicate care needs.

In the present study, we aimed to identify which specific geriatric deficits exposed by a GA are associated with deterioration of HRQOL in patients treated for HNC. Furthermore, we were interested in the association between accumulation of domains with geriatric deficits and deterioration of HRQOL over time.

METHODS

Study Design

The present study is a prospective observational study. Starting October 2014, all consecutively seen patients with HNC at the departments of Otorhinolaryngology–Head and Neck Surgery and Oral and Maxillofacial Surgery were asked to participate in the Oncological Life Study (OncoLifeS). OncoLifeS is a hospital-based oncological data biobank approved by the Medical Ethical

Committee at the University Medical Center Groningen (UMCG) in Groningen, the Netherlands.[18] Patients were enrolled after providing written informed consent. OncoLifeS is registered in the Netherlands Trial Register (trialregister.nl identifier: NL7839).

All patients diagnosed with any mucosal, salivary gland, and complex cutaneous malignant neoplasm of the head and neck area between October 2014 and May 2016 were included. Complex cutaneous malignant neoplasm was defined as either giant basal cell carcinoma, squamous cell carcinoma stage II or higher, melanoma, Merkel cell carcinoma, or neck metastasis of any cutaneous malignant neoplasm. Patients were excluded when palliative treatment or a nonstandard treatment regimen was carried out, or if baseline HRQOL was missing as a reference for further deterioration. Also, when tumor recurrence or death occurred during follow-up, patients were excluded from that moment onward.

At baseline, all patients underwent a GA, performed by one of the researchers or a dedicated nurse. The intention of the GA was purely observational, and treating oncologists were blinded to GA results at the time of patient presentation and treatment determination. However, unconsciously, increasing attention for frailty by nurses and physicians could have led to increased referral to a geriatrician, and this was not withheld from patients. Patients were treated according to (inter)national guidelines and discussed within a multidisciplinary head and neck tumor board. At baseline and during follow-up at 3, 6, 12, and 24 months after treatment, questionnaires for HRQOL were collected.

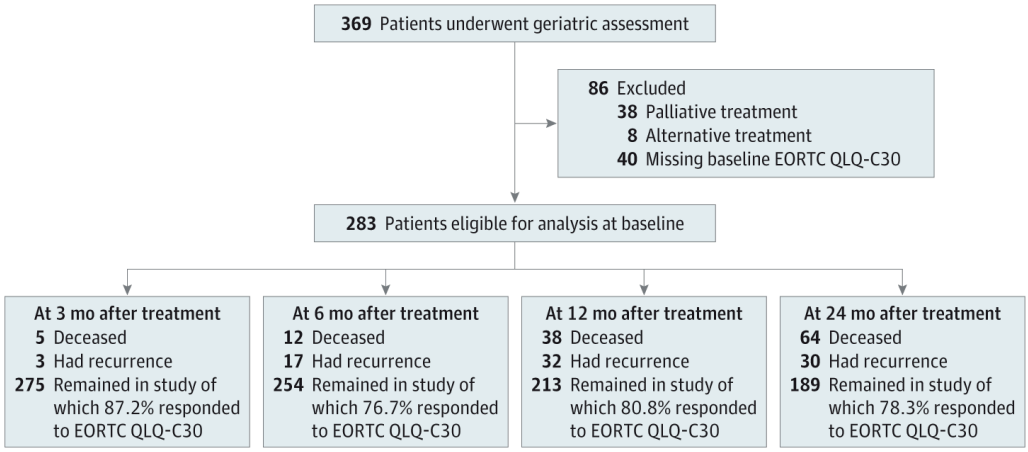

Figure 1 | Flowchart of Inclusion and Follow-up of Study Patients. EORTC QLQ-C30 indicates European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

Patient, Tumor, and Treatment Characteristics

Patient, tumor, and treatment characteristics were extracted from the OncoLifeS data biobank. The Union for International Cancer Control's TNM Classification of Malignant Tumors (Seventh Edition)19 was used for staging of tumors.

Geriatric Assessment

The domain of physical health consisted of grading of comorbidity into none, mild, moderate, or severe using the Adult Comorbidity Evaluation 27 (ACE-27),[20] identifying polypharmacy by medication count with 5 or more medications as a commonly used cutoff value,[21] and screening for the risk of malnutrition with the Malnutrition Universal Screening Tool (MUST).[22] Functional status was evaluated by administration of patients' Activities of Daily Living (ADL)[23] and Instrumental Activities of Daily Living (IADL)[24] and performing the Timed Up & Go (TUG) test[25]; 13.5 seconds was used as a cutoff value for restricted mobility.[26] Psychological health was assessed using the Mini-Mental State Examination (MMSE) with respect to cognitive function[27,28] and the 15-item Geriatric Depression Scale (GDS-15) for mood disorders.[29] The socioenvironmental factors, marital status, (single vs in a relationship) and living situation (at home vs assisted or nursing home) were registered with a standardized questionnaire.

When a domain (either physical, functional, psychological, socioenvironmental) had 1 or more impairments on the GA items belonging to the corresponding domain, this was considered as a "domain with deficits." The accumulation of domains with geriatric deficits refers to the sum of domains with geriatric deficits.

HRQOL

Patient-reported HRQOL using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was collected either by mail or at the outpatient clinic.[30] The Global Health Status/Quality of Life (GHS/QOL) scale was used as the primary outcome measure and was calculated according to the EORTC QLQ-C30 Scoring Manual.[31] Scores for the GHS/QOL scale range from 0 to 100. Higher score indicates better GHS/QOL.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 23.0 software (IBM). For descriptive statistics, continuous variables are presented as mean (SD) or median (IQR), and categorical variables are presented as frequency (percentage).

Linear mixed models were used to analyze repeated GHS/QOL measurements and associated factors. Linear mixed models permit missing data without eliminating entire cases, therewith maintaining statistical power and limiting bias, which is ideal in large longitudinal data sets. Procedures were carried out according to methods developed by Shek and Ma[32] and in a similar fashion as in the study by de Vries et al.[10] The EORTC QLQ-C30 GHS/QOL score at 3, 6, 12, and 24 months was defined as the dependent variable, and the baseline GHS/QOL score was incorporated as an adjusting factor. The covariance type was set to unstructured. Fixed effects for each model that investigated "parameter" included time, parameter, parameter × time, and adjusting variables. Estimates (β coefficients) for parameter refer to the main effects, the difference in GHS/QOL between parameter(+) and parameter(–) patients at 3 months after treatment, and estimates for the interaction term parameter × time refer to the different slope in GHS/QOL between parameter(+) and parameter(–) patients with respect to 1 year. Thus, the β coefficient of parameter should be interpreted as the newly developed difference in GHS/

QOL between patient categories at 3 months after treatment. Furthermore, the β coefficient of parameter × time should be interpreted as the increasing or decreasing difference in GHS/QOL between patient categories over time, and specifically refers to the increasing or decreasing difference per year. Estimates (β) are presented with 95% CIs and P values and were considered statistically significant if $P < .05$. All models were adjusted for age, sex, stage, treatment modality, and baseline differences in GHS/QOL by adding the corresponding variables and the baseline score as fixed effects to the model. For random effects, the intercept was included and covariance type was set to identity. The estimation method was set to maximum likelihood. If needed, model fit between models was compared using maximum likelihood ratio testing. Predicted values and SE of predicted values were saved for graphs. As a sensitivity analysis, estimates were compared between total study population and patients with complete follow-up.

RESULTS

Study Population

Between October 2014 and May 2016, 369 patients with suspicion of malignant neoplasm underwent GA. After exclusion, 283 patients remained eligible for analysis. Dropout owing to tumor recurrence or death during follow-up and questionnaire response rates are presented along with the exclusion process in Figure 1.

Patient characteristics at baseline are summarized in Table 1. The mean (SD) age was 68.3 (10.9) years and 193 (68.2%) were male. Included tumor sites were oral cavity (73 [25.7%]), nasal cavity and paranasal sinus (15 [5.3%]), nasopharynx (4 [1.4%]), oropharynx (52 [18.4%]), hypopharynx (9 [3.2%]), larynx (66 [23.3%]), salivary glands (5 [1.8%]), complex skin cancer (52 [18.4%]) and unknown primary tumor of the neck (7 [2.5%]). Most cancers were squamous cell carcinoma (244 [86.1%]), presenting in advanced stage (stage III-IV, 152 [54.7%]), and were treated by either primary surgery (158 [55.8%]), whether or not followed by postoperative (chemo) radiation, or primary (chemo)radiation (125 [44.2%]). Mean GHS/QOL by stage and treatment categories are shown in eTable 1 in the Supplement. Results of GA are included in Table 1.

Association Between Geriatric Deficits and Deterioration of QOL

Mean GHS/QOL discriminated by deficits on GA is shown in eTable 2 in the Supplement and in Figure 2 (top row of graphs in each panel). Results of linear mixed models are presented in Table 2 with predicted values of these models in Figure 2 (second row of graphs in each panel).

Within the physical domain, patients with severe comorbidities showed significantly worse GHS/QOL at 3 months after treatment (β = −7.00; 95% CI, −12.43 to −1.56) and further deterioration over time (β = −4.90; 95% CI, −9.70 to −0.10; Figure 2A). Polypharmacy was not associated with changes in GHS/QOL (Figure 2A). Patients at risk for malnutrition had worse GHS/QOL at 3 months after treatment (β = −6.18; 95% CI, −11.55 to −0.81), which did not significantly deteriorate further over time (Figure 2A).

Variables	Value, n(%) [a]
Age	
Mean ± SD, y	68.3 (± 10.9)
Median (range), y	68.2 (60.5-76.5)
Sex	
Male	193 (68.2)
Female	90 (31.8)
Reason for referral	
Primary tumor	266 (94.0)
Recurrent tumor	17 (6.0)
Tumor site	
Oral cavity	73 (25.7)
Nasal cavity and paranasal sinus	15 (5.3)
Nasopharynx	4 (1.4)
Oropharynx	52 (18.4)
Hypopharynx	9 (3.2)
Larynx	66 (23.3)
Salivary glands	5 (1.8)
Skin	52 (18.4)
Unknown primary tumor	7 (2.5)
Histopathology	
Squamous cell carcinoma	244 (86.1)
Other	39 (13.9)
Stage	
I	70 (25.2)
II	56 (20.1)
III	40 (14.4)
IV	112 (40.3)
Primary treatment	
Surgery	158 (55.8)
Postoperative radiotherapy	54 (19.1)
Postoperative chemoradiation	3 (1.1)
Radiotherapy	83 (29.3)
Chemoradiation	42 (14.8)

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Table 1 | Patient characteristics and geriatric assessment of the cohort included at baseline. a Values presented as n (%) unless otherwise specified. SD = Standard Deviation. IQR = Inter Quartile Range; 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.

Table 1 | continued

	Variables	Value, n(%) [a]
PHYSICAL	**Comorbidity (ACE-27)**	
	None	62 (21.9)
	Mild	99 (35.0)
	Moderate	74 (26.1)
	Severe	48 (17.0)
	Polypharmacy	
	< 5 medications	187 (66.1)
	≥ 5 medications	96 (33.9)
	Malnutrition (MUST)	
	No risk of malnutrition (< 1)	208 (78.8)
	Medium to high risk of malnutrition (≥ 1)	56 (21.2)
FUNCTIONAL	**ADL**	
	Independent (< 1)	252 (89.7)
	Dependent (≥ 1)	29(10.3)
	IADL	
	No restrictions (< 1)	234 (82.7)
	Restrictions (≥ 1)	49 (17.3)
	TUG	
	Normal mobility (< 13.5s)	237 (87.5)
	Restricted mobility (≥ 13.5s)	34 (12.5)
PSYCHOLOGICAL	**Cognition (MMSE)**	
	No cognitive deficits (> 24)	249 (88.3)
	Cognitive deficits (≤ 24)	33 (11.7)
	Depression (GDS-15)	
	No signs of depression (< 6)	256 (91.1)
	Signs of depression (≥ 6)	25 (8.9)
SOCIO-ENVIRONMENTAL	**Marital status**	
	In a relationship	212 (75.2)
	Single	70 (24.8)
	Living situation	
	Independent	248 (88.3)
	Assisted or nursing home	33 (11.7)

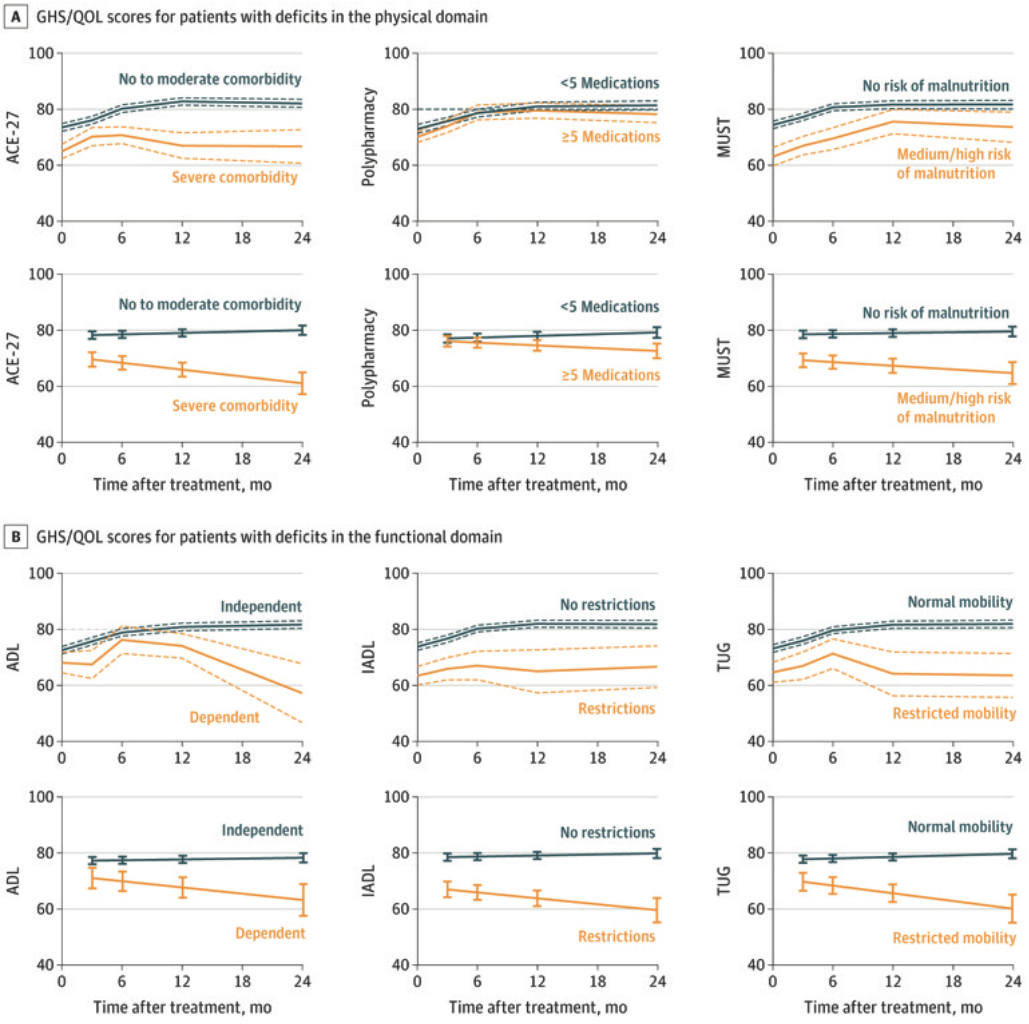

Figure 2 | Deterioration of Global Health Status/Quality of Life (GHS/QOL) Over Time for Patients With Geriatric Deficits. The y-axes refer to the GHS/QOL score on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. The x-axes refer to time in months, in which 0 refers to the pretreatment score. Figures in the first rows contain mean (solid lines) and SE (dashed lines) of the mean grouped by the binary outcome of the aforementioned geriatric assessment. Figures in the second rows contain predicted trajectories by the linear mixed effects models with corresponding SE (error bars) for the same geriatric assessment (estimates shown in Table 2). ACE-27 indicates Adult Comorbidity Evaluation 27; ADL, Activities of Daily Living; GDS-15, 15-item Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; MUST, Malnutrition Universal Screening Tool; TUG, Timed Up & Go.

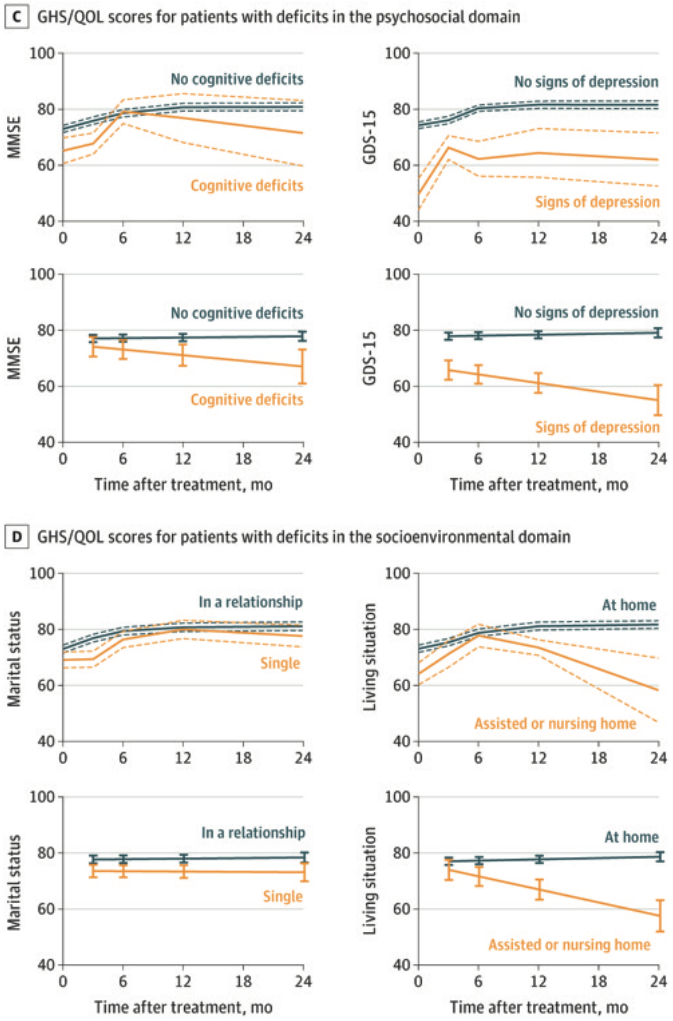
C GHS/QOL scores for patients with deficits in the psychosocial domain
MMSE
No cognitive deficits
Cognitive deficits
GDS-15
No signs of depression
Signs of depression
Time after treatment, mo
D GHS/QOL scores for patients with deficits in the socioenvironmental domain
Marital status
In a relationship
Single
Living situation
At home
Assisted or nursing home
Time after treatment, mo

Table 2 | Linear mixed model analysis of associations between geriatric assessment and Global Health Status/QoL trajectory. Estimates (beta coefficients) for normal model parameters refer to the main effects and can be interpreted as the novel difference in Global Health Status/QoL after treatment at the three months follow-up interval between parameter categories. Estimates (beta coefficients) for model parameters*time refer to the interaction term with time and can thus be interpreted as the increasing or decreasing difference in Global Health Status/QoL between parameter categories over time with respect to one year. A domain with deficits was defined as a geriatric domain (either physical, functional, psychological or socio-environmental) with at least one impairment on the items of geriatric assessment belonging to the corresponding domain. P-values are shown in bold when significant at $p < 0.05$. [a] All models were adjusted for baseline Global Health Status/QoL scores, and age, sex, stage and treatment modality. CI = Confidence Interval; 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 Score.

	Model parameters [a]	Estimate (β)	95% CI		p-value
Physical	ACE-27 (none to moderate)	ref			
	ACE-27 (severe)	-7.00	-12.43	-1.56	**0.01**
	ACE-27*time (none to moderate)	ref			
	ACE-27*time (severe)	-4.90	-9.70	-0.10	**0.05**
	Polypharmacy (< 5medications)	ref			
	Polypharmacy (≥ 5 medications)	-0.82	-5.19	3.55	0.71
	Polypharmacy*time (< 5medications)	ref			
	Polypharmacy*time (≥ 5 medications)	-2.76	-6.01	0.48	0.10
	MUST (no risk of malnutrition)	ref			
	MUST (medium to high risk of malnutrition)	-6.18	-11.55	-0.81	**0.02**
	MUST*time (no risk of malnutrition)	ref			
	MUST*time (medium to high risk of malnutrition)	-3.83	-8.47	0.81	0.10
Functional	ADL (independent)	ref			
	ADL (dependent)	-7.17	-14.91	0.57	0.07
	ADL*time (independent)	ref			
	ADL*time (dependent)	-5.32	-11.89	1.24	0.11
	IADL (no restrictions)	ref			
	IADL (restrictions)	-10.48	-16.39	-4.57	**0.001**
	IADL*time (no restrictions)	ref			
	IADL*time (restrictions)	-5.36	-10.50	-0.22	**0.04**
	TUG (normal mobility)	ref			
	TUG (restricted mobility)	-6.09	-12.78	0.60	0.07
	TUG*time (normal mobility)	ref			
	TUG*time (restricted mobility)	-6.78	-12.81	-0.75	**0.03**

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Table 2 | continued

	Model parameters [a]	Estimate (β)	95% CI		p-value
Psychological	MMSE (no cognitive deficits)	ref			
	MMSE (cognitive deficits)	-0.13	-7.35	7.08	0.97
	MMSE*time (no cognitive deficits)	ref			
	MMSE*time (cognitive deficits)	-6.14	-13.43	1.13	0.10
	GDS-15 (no signs of depression)	ref			
	GDS-15 (signs of depression)	-4.22	-11.33	2.91	0.25
	GDS-15*time (no signs of depression)	ref			
	GDS-15*time (signs of depression)	-7.08	-13.10	-1.06	**0.02**
Socio-environmental	Marital status (in relationship)	ref			
	Marital status (single)	-3.17	-7.77	1.42	0.18
	Marital status*time (in relationship)	ref			
	Marital status*time (status)	-0.98	-4.74	2.78	0.61
	Living situation (at home)	ref			
	Living situation (assisted or nursing home)	-2.62	-10.55	5.30	0.52
	Living situation*time (at home)	ref			
	Living situation*time (assisted or nursing home)	-8.74	-15.75	-1.73	**0.02**
Deficit accumulation	# domains with deficits	-3.17	-5.04	-1.30	**0.001**
	# domains with deficits *time	-2.74	-4.28	-1.20	**0.001**
	< 3 domains with deficits	ref			
	≥ 3 domains with deficits	-9.62	-15.35	-3.88	**0.001**
	< 3 domains with deficits *time	ref			
	≥ 3 domains with deficits *time	-14.81	-20.40	-9.22	**< 0.001**

On the functional domain, dependency on ADL was not significantly associated with worse GHS/QOL after treatment (Figure 2B). However, restrictions in IADL were significantly associated with worse GHS/QOL at 3 months after treatment (β = −10.48; 95% CI, −16.39 to −4.57) and with further decline in GHS/QOL (β = −5.36; 95% CI, −10.50 to −0.22; Figure 2B). Furthermore, although restricted mobility did not show significant decay in GHS/QOL at 3 months after treatment, it was significantly associated with deterioration of GHS/QOL over time (β = −6.78; 95% CI, −12.81 to −0.75; Figure 2B).

With respect to psychological domain, cognitive decline was not associated with worse GHS/QOL after treatment (Figure 2C). Signs of depression, however, were significantly associated with decay over time (β = −7.08; 95% CI, −13.10 to −1.06; Figure 2C).

On the socioenvironmental domain, marital status was not associated with GHS/QOL trajectories (Figure 2D), but living situation of the patient did show deteriorating trajectories for those in need for assistance at home or living in a nursing home (β = −8.74; 95% CI, −15.75 to −1.73; Figure 2D).

Association Between Accumulated Domains With Geriatric Deficits and Deterioration of QOL

As a continuous factor, accumulation of domains with geriatric deficits resulted in a 3.17-point worse GHS/QOL score per domain with deficits at 3 months after treatment (β = −3.17; 95% CI, −5.04 to −1.30), and in a 2.74-point worse GHS/QOL score per additional domain with deficits per year (β = −2.74; 95% CI, −4.28 to −1.20; Table 2 and Figure 3A). Dichotomously, having more than 3 domains with deficits was associated with worse GHS/QOL after 3 months (β = −9.62; 95% CI, −15.35 to −3.88) and with further decline over time for each year (β = −14.81; 95% CI, −20.81 to −9.22; Table 2 and Figure 3B).

Sensitivity Analysis

Loss to follow-up was higher in patients with geriatric deficits (eTable 2 in the Supplement). Comparison of estimates between the total study population and patients having complete follow-up revealed mostly minor and few major changes in estimates (eTable 3 in the Supplement).

DISCUSSION

In this prospective observational study, to our knowledge for the first time, the association of both individual geriatric deficits and accumulated domains with geriatric deficits with deterioration of HRQOL was evaluated during 2 years of follow-up after treatment for HNC. Within all geriatric domains (physical, functional, psychological, socioenvironmental), deficits were significantly associated with short- and long-term deterioration of HRQOL. The accumulation of deficits in geriatric domains was a very significant factor associated with deterioration of both short- and long-term HRQOL. These findings underscore the importance of multidomain GA of patients facing treatment for HNC.

The deficit accumulation model as an approach to describe frailty is well investigated in the field of geriatrics[33-37] and describes frailty as "a multidimensional risk state that can be measured by the quantity rather than by the nature of health problems."[36(p67)] Its multidimensional character makes it especially suitable for patients with HNC, as this population is burdened by such health problems.[1,3] In this study, we have simplified this deficit accumulation model by dividing the GA items into the physical, functional, psychological, and socioenvironmental domains and when at least 1 of the corresponding GA items was impaired considered it as a domain with deficits. In a similar fashion, earlier work has shown that the accumulation of domains with deficits may be associated with a nearly 2-fold increase in risk for severe postoperative complications.[38]

In the present study, the most significant factor associated with deterioration of HRQOL after treatment for HNC was the accumulation of domains with geriatric deficits. The β coefficients can be interpreted as follows. For each additional domain with deficits, the GHS/QOL score was estimated to be worse (decrease of 3.17 points/domain, the β coefficient referring to the main effects) after 3 months already compared with patients without domains with deficits. Additionally, during 2 years of follow-up, GHS/QOL was estimated to decline further per additional domain with deficits per year (decrease of 2.74 points/domain/y, the β coefficient referring to the interaction term with time), compared with patients without geriatric deficits.

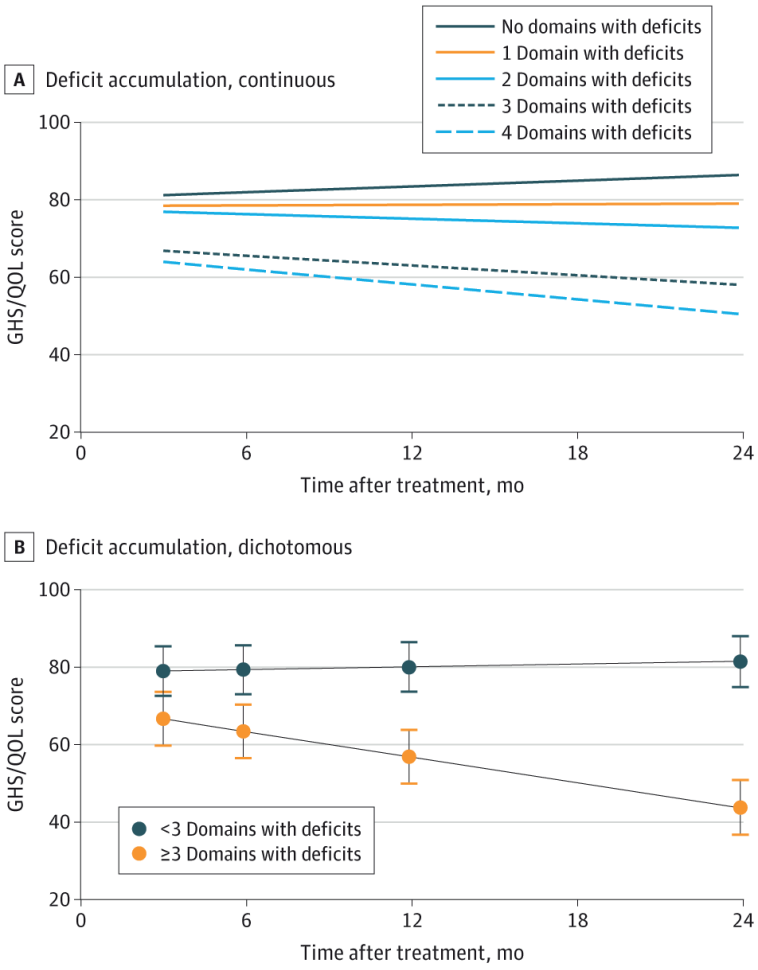

Figure 3 | Predicted Global Health Status/Quality of Life (GHS/QOL) Trajectory for Patients With Accumulation of Domains With Deficits. The y-axes refer to the predicted GHS/QOL score on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 by linear mixed effect models (Table 2). The x-axes refer to time in months after treatment. A domain with deficits was defined as a geriatric domain (either physical, functional, psychological, or socioenvironmental) with at least 1 impairment on the items of geriatric assessment belonging to the corresponding domain. A, Increase in domains with deficits leads to increase in deterioration of GHS/QOL after treatment (continuous model). B, Using 3 or more domains with deficits as a cutoff shows the strongest deterioration of GHS/QOL.

These may sound like irrelevant differences on the 0 to 100 GHS/QOL scale; however, cumulatively after 2 years, this led to much larger decline (decrease of 7.96 points after 2 years) for patients with only 1 domain with deficits. Patients with HNC often have deficits in multiple domains. For

instance, for a patient with severe comorbidities, signs of depression and living in social isolation (3 domains with deficits), decline may be devastating (decrease of 23.90 points after 2 years) compared with patients without geriatric deficits. Such declines on the EORTC QLQ-C30 GHS/QOL scale are regarded as a clinically highly significant deterioration by studies investigating patient-based, anchor-based, and distribution-based minimally important differences, which range from 5 to 15 points.[39-41]

In recent literature, it was already demonstrated that frailty, defined by short frailty screening instruments, is associated with decline in HRQOL after treatment for HNC.[10] Another recent article by Thomas et al[11] shows similar trends of HRQOL for frail HNC patients during twelve months of follow-up, and addresses that the frailty status itself may change over time as well. With approximately 30% to 70% of patients with HNC being frail according to such screening instruments and the fact that these tests lack specificity, however, this would be a suboptimal strategy to identify and treat frail patients.16 Therefore, multidomain assessment may identify deficits more specifically and reveal leads for pretreatment optimization.

Within the physical domain, estimates for patients with severe comorbidity indicate clinically important deterioration of HRQOL compared with patients with none to mild comorbidity. This is consistent with most earlier findings in HNC,[42-44] but the literature is controversial on this, as 1 study showed equal HNC-specific QOL,[45] and another study showed a converging HRQOL trend between comorbid and noncomorbid patients.[46] Most studies, however, had less extensive follow-up and smaller sample size and did not evaluate the deteriorating trend of HRQOL with such detail. The difference in HRQOL between comorbid and noncomorbid patients may be explained by the fact that patients with comorbidities have increased risk of surgical complications, prolonged hospital stay, and readmission.[47,48] Polypharmacy has not been investigated in HNC with respect to HRQOL before, but was significantly associated with physical QOL after treatment in a general oncology cohort.[49] In the present study, there was a decreasing trend over time, but the estimate was neither significant nor clinically relevant. For malnutrition, being one of the best investigated physical conditions in HNC, estimates can be interpreted as clinically significant HRQOL decline, consistent with results from other studies.[50-52]

Level of functioning is implicitly associated with HRQOL. In the present study, ADL dependency demonstrated a statistically insignificant but clinically relevant deteriorating trend. Probably, the low number of patients with ADL restrictions affects this finding. Other studies in HNC used ADL as an outcome measure rather than as a factor.[53,54] Though, in a general oncology population, ADL was significantly associated with baseline and posttreatment HRQOL; however, deterioration after treatment was not investigated.[55] Instrumental Activities of Daily Living investigates more complex tasks, which makes it more sensitive to functional restrictions than ADL but also sensitive to cognitive decline.[56] The diverging HRQOL trajectories for patients with and without IADL restrictions can be interpreted as clinically highly relevant. In contrast to results of the present study, earlier findings showing less decline for patients with impaired IADL during treatment and a stable course after treatment.[57] Probably, the different time window (8 weeks vs 2 years) explains these different outcomes. The TUG encompasses a short, easy-to-administer mobility test in which the patient is asked to get up, walk 3 meters, turn around, walk back, and sit down. It is strongly associated with increased risk of surgical complications.[58] Our finding that

patients with limited mobility deteriorate over time has not been shown before in patients with HNC but seems clinically important given the size of the estimates. Another study investigating GA with respect to HRQOL in a heterogeneous oncology population showed similar findings.[55]

From the psychological domain, cognitive decline was not a statistically significant factor for HRQOL, although the estimate reveals a clinically relevant negative trend. Possibly, loss to follow-up of these patients and therewith underrepresentation leads to bias. Cognition has been shown to be associated with pretreatment HRQOL in patients with HNC[59,60]; however, the literature lacks longitudinal studies. Depression rates in our cohort were similar to earlier findings in patients with HNC.[61] The association of depression with HRQOL decline has already thoroughly been investigated and is in line with the significant and clinically important difference that was found in our study.[62]

In the social domain, marital status was not associated with decline in HRQOL, but living situation was a strong statistically and clinically significant factor. There is no consensus in the literature. Some studies found social support to be associated with better HRQOL,[63,64] but others did not.[65,66] Different definitions of variables, lack of use of validated tools, and lack of longitudinal HRQOL studies may explain differences.

Proving the benefits of GA has been difficult with respect to study designs and ethical considerations. However, the yields of GA are too large to ignore and do lead to altered treatment recommendations.[67] This does not mean that treatment should be downgraded for frail patients. Accordingly, frail patients also did not regret the treatment decision that was made more than nonfrail patients.[68] However, loss of HRQOL might have been prevented by providing a more tailored treatment. Potential interventions can include pretreatment referral to a geriatrician, optimization of comorbidities, management of polypharmacy, nutritional support, and professional psychosocial support. Prehabilitation studies and routine clinical care pathways are under investigation, also in HNC.[69]

Based on these data, we strongly recommend a broad screening of all geriatric domains and involving a geriatrician with the screening. Currently, in our department, all presenting patients undergo a broad geriatric screening by a nurse that consists of compact screening tools but includes all geriatric domains. The results of this screening are subsequently discussed with a geriatrician in a multidisciplinary team and a CGA and paramedic consultation can be indicated, or other recommendations can be given. Forthcoming information from the CGA or consultation can be incorporated in the multidisciplinary head and neck tumor board where the final treatment proposal is made, to be discussed with the patient.

Strengths and Limitations

Strengths of this study were the prospective inclusion and long-term follow-up of a relatively large cohort, use of a large set of validated GA tools, and strong statistical analysis, allowing identification of longitudinal trends, adequate missing data handling, and consideration of baseline differences and confounders. A limitation may be the underrepresentation of very frail patients at the moment of inclusion and also during follow-up, because of higher loss to follow-up, leading to potential bias (ie, underestimation of the observed differences).[70] Estimates that

change when comparing the cohort with a complete follow-up cohort can be explained by reduction of sample size and specifically the disproportionate reduction of patients with deficits. This may therefore introduce more bias (underestimation) and underscores the importance of using linear mixed models for maximizing use of data points that would otherwise be missed. Factors that may have blurred outcomes can be the unconscious additional attention for frailty by oncologists and knowledge of GA outcomes by nurses, potentially leading to increased geriatric consultation, and measures that were taken by the Dutch national Safety Management System (Veiligheidsmanagementsysteem) on vulnerable older adults admitted to the hospital. Hospitalized vulnerable older adults were, as a standard of care in the Netherlands, referred to a physiotherapist or dietary consultant and benefited by fall prevention and delirium screening when this was indicated by screening. Furthermore, limitations were the relative heterogeneity of the cohort and absence of data on human papillomavirus status, which may influence HRQOL decline as well.[71]

CONCLUSIONS

In this prospective cohort study, geriatric deficits and especially the accumulation of domains with deficits were associated with HRQOL deterioration after treatment for HNC. Incorporating GA in the workup of patients with HNC can aid decision-making, indicate interventions, and hopefully reduce loss of HRQOL.

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eTable 1 | Mean Global Health Status/Quality of Life by stage and treatment categories. n = number of available data.

		Baseline		3 months		6 months		12 months		24 months	
		n	mean	n	mean	n	mean	n	mean	n	mean
Stage	Stage I	70	74.05	61	76.91	51	79.08	52	77.24	48	77.78
	Stage II	56	76.19	48	78.13	39	77.78	37	81.53	30	81.67
	StageIII	40	75.00	35	81.90	30	81.11	27	83.64	24	82.29
	StageIV	112	67.34	95	69.82	74	78.04	56	81.25	45	82.59
Treatment	Surgery	158	72.68	137	76.28	109	79.05	102	79.74	92	79.08
	Postoperative radiotherapy	54	71.45	46	72.28	39	79.70	31	85.22	28	79.46
	Postoperative chemoradiation	3	69.44	3	63.89	3	77.78	1	91.67	1	91.67
	Radiotherapy	83	71.89	66	75.51	54	78.40	43	82.75	35	81.90
	Chemoradiation	42	39.84	40	70.42	34	77.94	29	79.89	22	83.71
Total	Total	283	72.03	243	75.10	197	78.68	174	80.51	149	80.43

eTable 2 | Mean Global Health Status/Quality of Life by individual geriatric tests. n = number of available data; 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 Score.

		Baseline		3 months		6 months		12 months		24 months	
		n	mean	n	mean	n	mean	n	mean	n	mean
Physical	ACE-27										
	None to moderate	235	73.48	203	76.07	166	80.17	149	82.77	133	82.08
	Severe	48	64.93	40	70.21	31	70.70	25	67.00	16	66.67
	Polypharmacy										
	< 5 medications	187	72.99	158	75.69	137	78.59	117	80.98	103	81.39
	≥ 5 medications	96	70.14	85	74.02	60	78.69	57	79.53	46	78.26
	MUST										
	No risk of malnutrition (< 1)	208	74.44	180	77.31	147	80.73	133	81.70	121	81.68
	Medium to high risk of malnutrition (≥ 1)	56	63.10	48	67.01	35	69.52	27	75.62	18	73.61
Functional	ADL										
	Independent (< 1)	252	72.59	221	75.79	183	78.92	164	80.89	141	81.74
	Dependent (≥ 1)	29	67.10	20	67.50	13	76.28	10	74.17	8	57.29
	IADL										
	No restrictions (< 1)	234	73.82	208	76.64	174	80.22	159	81.97	135	81.85
	Restrictions (≥ 1)	49	63.44	35	65.95	23	67.03	15	65.00	14	66.67
	TUG										
	Normal mobility (< 13.5s)	237	74.13	209	76.00	176	79.64	157	81.63	136	81.92
	Restricted mobility (≥ 13.5s)	34	64.71	25	67.00	18	71.30	13	64.10	8	63.54
Psycho-logical	MMSE										
	No cognitive deficits (> 24)	249	72.96	218	75.92	182	78.62	164	80.74	141	80.85
	Cognitive deficits (≤ 24)	33	65.15	24	67.71	14	79.19	9	76.85	7	71.43
	GDS-15										
	No signs of depression (< 6)	256	74.28	219	76.14	178	80.43	163	81.60	140	81.61
	Signs of depression (≥ 6)	25	49.67	23	66.30	19	62.28	11	64.39	9	62.04
Socio-environ-mental	Marital status										
	In a relationship	212	73.00	183	76.87	152	79.33	136	80.70	119	81.09
	Single	70	69.05	59	69.35	44	76.33	37	79.95	29	77.59
	Living situation										
	Independent	248	73.08	219	75.38	183	78.78	161	81.11	139	81.71
	Assisted or nursing home	33	64.14	22	71.21	12	77.78	11	73.48	8	58.33
Total	Total	283	72.03	243	75.10	197	78.68	174	80.51	149	80.43

eTable 3 | Complete-response analysis comparing estimates between complete responses (all outcome measurements present [n=124]) vs. total study population (n=283). Estimates for normal model parameters refer to the main effects (difference in Global Health Status/QoL after treatment at the three months follow-up interval). Estimates for model parameters *time refer to the interaction term with time (thus, the effect on the course of Global Health Status/QoL over time with respect to one year). A domain with deficits was defined as a geriatric domain (either physical, functional, psychological or socio-environmental) with at least one impairment on the items of geriatric assessment belonging to the corresponding domain. Grey shaded estimates changed by more than 5 points. n = number of available data; 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 Score.

		Total study population n=283, 763 measurements)			Complete cases (n=124, 496 measurements)		
	Model parameters [a]	Estimate (β)	95% CI		Estimate (β)	95% CI	
Physical	ACE-27 (none to moderate)	ref			ref		
	ACE-27 (severe)	-7.00	-12.43	-1.56	-4.93	-12.82	2.95
	ACE-27*time (none to moderate)	ref			ref		
	ACE-27*time (severe)	-4.90	-9.70	-0.10	-2.04	-7.72	3.63
	Polypharmacy (< 5medications)	ref			ref		
	Polypharmacy (≥ 5 medications)	-0.82	-5.19	3.55	1.57	-3.57	6.72
	Polypharmacy*time (< 5medications)	ref			ref		
	Polypharmacy*time (≥ 5 medications)	-2.76	-6.01	0.48	-2.72	-6.37	0.93
	MUST (no risk of malnutrition)	ref			ref		
	MUST (medium to high risk of malnutrition)	-6.18	-11.55	-0.81	10.80	-8.02	6.43
	MUST*time (no risk of malnutrition)	ref			ref		
	MUST*time (medium to high risk of malnutrition)	-3.83	-8.47	0.81	-5.06	-10.38	0.21
Functional	ADL (independent)	ref			ref		
	ADL (dependent)	-7.17	-14.91	0.57	-11.92	-22.15	-1.69
	ADL*time (independent)	ref			ref		
	ADL*time (dependent)	-5.32	-11.89	1.24	1.53	-6.06	9.14
	IADL (no restrictions)	ref			ref		
	IADL (restrictions)	-10.48	-16.39	-4.57	-11.85	-22.43	-1.27
	IADL*time (no restrictions)	ref			ref		
	IADL*time (restrictions)	-5.36	-10.50	-0.22	2.54	-5.05	10.13
	TUG (normal mobility)	ref			ref		
	TUG (restricted mobility)	-6.09	-12.78	0.60	-6.70	-18.21	4.81
	TUG*time (normal mobility)	ref			ref		
	TUG*time (restricted mobility)	-6.78	-12.81	-0.75	-4.98	-13.30	3.33

Continued on next page

eTable 3 | continued

	Model parameters [a]	Total study population n=283, 763 measurements) Estimate (β)	95% CI		Complete cases (n=124, 496 measurements) Estimate (β)	95% CI	
Psychological	MMSE (no cognitive deficits)	ref			ref		
	MMSE (cognitive deficits)	-0.13	-7.35	7.08	9.06	-2.26	20.38
	MMSE*time (no cognitive deficits)	ref			ref		
	MMSE*time (cognitive deficits)	-6.14	-13.43	1.13	-8.06	-16.26	0.15
	GDS-15 (no signs of depression)	ref			ref		
	GDS-15 (signs of depression)	-4.22	-11.33	2.91	-3.88	-13.63	5.88
	GDS-15*time (no signs of depression)	ref			ref		
	GDS-15*time (signs of depression)	-7.08	-13.10	-1.06	-5.22	-11.80	1.37
Socio-environmental	Marital status (in relationship)	ref			ref		
	Marital status (single)	-3.17	-7.77	1.42	2.85	-2.88	8.59
	Marital status*time (in relationship)	ref			ref		
	Marital status*time (status)	-0.98	-4.74	2.78	-0.85	-5.04	3.34
	Living situation (at home)	ref			ref		
	Living situation (assisted or nursing home)	-2.62	-10.55	5.30	-3.01	-18.80	12.77
	Living situation*time (at home)	ref			ref		
	Living situation*time (assisted or nursing home)	-8.74	-15.75	-1.73	1.21	-9.49	11.91
Accumulation, continuous	# domains with deficits	-3.17	-5.04	-1.30	-0.55	-3.20	2.11
	# domains with deficits *time	-2.74	-4.28	-1.20	-1.79	-3.66	0.09
Accumulation, dichotomous	< 3 domains with deficits	ref			ref		
	≥ 3 domains with deficits	-9.62	-15.35	-3.88	-8.52	-19.89	2.85
	< 3 domains with deficits *time	ref			ref		
	≥ 3 domains with deficits *time	-14.81	-20.40	-9.22	-10.24	18.33	-2.14

Head and neck cancer patients with geriatric deficits are more often non-responders and lost from follow-up in quality of life studies

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chapter eight

ABSTRACT

Objectives

To identify associations between frailty and non-response to follow-up questionnaires, in a longitudinal head and neck cancer (HNC) study with patient reported outcome measures (PROMs).

Materials and methods

Patients referred with HNC were included in OncoLifeS, a prospective data-biobank, underwent Geriatric Assessment (GA) and frailty screening ahead of treatment, and were followed-up at 3, 6, 12 and 24 months after treatment using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Head and Neck 35. Statistical analysis for factors associated with non-response was done using Generalized Linear Mixed Models.

Results

289 patients were eligible for analysis. Mean age was 68.4 years and 68.5% were male. Restrictions in Activities of Daily Living (OR 4.46(2.04-9.78)) and Instrumental Activities of Daily Living (OR 4.33(2.27-8.24)), impaired mobility on Timed Up & Go test (OR 3.95(1.85-8.45)), cognitive decline (OR 4.85(2.28-10.35)) and assisted living (OR 5.54(2.63-11.67)) were significantly associated with non-response. Frailty screening, with Geriatric 8 and Groningen Frailty Indicator, was also associated with non-response (OR respectively 2.64(1.51-4.59) and 2.52(1.44-4.44)). All findings remained significant when adjusted for other factors that were significantly associated with non-response, such as higher age, longer study duration and subsequent death.

Conclusion

Frail HNC patients respond significantly worse to follow-up PROMs. The drop-out and underrepresentation of frail patients in studies may lead to attrition bias, and as a result underestimating the effect sizes of associations. This is of importance when handling and interpreting such data.

INTRODUCTION

The global incidence of cancer is rapidly increasing, specifically among older populations.[1] Older patients, however, are strongly underrepresented in clinical trials in all fields of medicine.[2] This is the case for large cancer trials, which are important for the establishment of international guidelines, as well.[3–5] Barriers for trial inclusion can be raised by the system, by care-providers, but also by patients themselves.[6]

Besides the evident difficulty of including older patients in clinical studies, retaining older patients in clinical studies may be difficult as well, and lead to higher non-response and study dropout.[7,8] This may be referred to as 'attrition'. Especially with the growing use of patient reported outcome measures (PROM's), the risk of non-response is lurking, and this may be even more the case in the older and frail population.[9] PROM's, however, such as questionnaires for quality of life (QoL), are increasingly being recognized as important outcome measures, besides recurrence or survival alone. Specifically for older patients this may be the case, as they may prioritize outcomes such as QoL over length of life, for example.[10]

Yet, the occurrence of non-response and study dropout for older and frail patients relative to their younger and fit counterparts is important to know. Systematic loss of patients from specific study groups may lead to attrition bias.[11] Consequences of this may be under- or overestimating outcomes, misinterpretation of the results and poor generalizability.

The age of patients with head and neck cancer averages around 65 and the burden of geriatric deficits and therewith frailty is large in this population, compared to patients with other solid malignancies.[12] The risk of introducing bias into studies may therefore be high. In our previous studies we encountered that frail patients were more difficult to include because of their poor response to baseline questionnaires.[13] Therefore, the goal of the current study was to investigate whether frail patients exhibit more non-response than non-frail patients to follow-up questionnaires and whether specific items of a routinely performed geriatric assessment (GA) are associated with non-response.

MATERIALS AND METHODS

Study design

This study covers a retrospective analysis of prospectively collected data from the longitudinal observational Oncological Life Study (OncoLifeS), a large hospital-based oncological data-biobank at the University Medical Center Groningen (UMCG), Groningen, The Netherlands.[14] OncoLifeS is approved by the Institutional Review board of the UMCG this study was approved by the scientific committee of OncoLifeS. In OncoLifeS patients are included after providing written informed consent. Between October 2014 and May 2015, all patients referred with (suspicion of) primary or recurrent cancer in the head and neck area (mucosal, salivary gland and cutaneous) were consecutively included. Patients were seen at the outpatient clinic of the departments of Otorhinolaryngology, Head and Neck Surgery, Oral and Maxillofacial Surgery and Radiation Oncology. Patients underwent a GA, including frailty screening, at baseline, before treatment.

Patients were excluded from the analysis when initially palliative or nonstandard treatment was conducted or when patients did not return the baseline questionnaires. Also, data of patients was excluded when recurrence or death occurred during follow-up, from that moment onward. Patients were followed-up during two years after treatment using QoL questionnaires (see Follow-up).

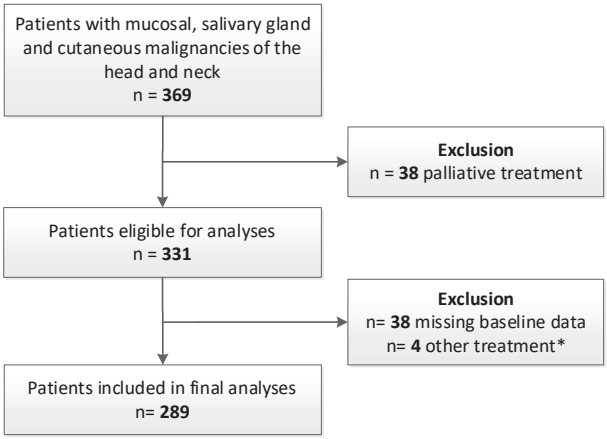

Figure 1 | Flowchart of study inclusion. * = experimental or unknown treatment. n = number

Patient, tumour and treatment characteristics

Patient, tumour and treatment characteristics were withdrawn from the OncoLifeS data-biobank. Disease was staged according to the seventh edition of the Union for International Cancer Control's TNM Classification.[15]

Baseline assessments

Before treatment patients underwent GA, including a frailty screening and assessment of the somatic, functional, psychological and socio-environmental domains. Somatic assessments included scoring of the 27-item Adult Comorbidity Evaluation (ACE-27), polypharmacy (5 or more medications) and the Malnutrition Universal Screening Tool (MUST).[18–20] Functional assessments were Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL) and the Timed Up & Go (TUG) with a cut-off at 13.5s.[21–24] The Mini Mental State Examination (MMSE) and the 15-item Geriatric Depression Scale (GDS-15) were used for the psychological assessments.[25–27] Marital status, living situation and educational level assessed for the socio-environmental domain and were registered as part of a standardized questionnaire. Frailty screening consisted of the Groningen Frailty Indicator (GFI) and Geriatric 8 (G8) questionnaires.[16,17]

Follow-up

Patients were followed-up using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Head and Neck 35 (EORTC-QLQ-HN35) at 3, 6, 12 and 24 months after treatment. Follow-up was conducted by sending and returning questionnaires by mail (dept. of Otorhinolaryngology, Head and Neck Surgery, dept. of Oral and Maxillofacial Surgery) or by filling out questionnaires at the outpatient clinic (dept. of Radiation Oncology). This difference between methods was incorporated as a variable in the dataset.

Outcome

Non-response was defined as both complete QoL questionnaires missing in the dataset. This was recalculated to a binary outcome (yes/no) for each of the follow-up moments (3, 6, 12 and 24 months) after treatment initiation, regardless of the previous outcomes, and until recurrence or death occurred.

Statistical analysis

All statistical procedures were performed with SPSS Statistics 28 (IBM). Descriptive statistics are presented as n (%) unless specified otherwise. Generalized Linear Mixed Models (GLMM) were used to calculate odds ratios of the association between frailty and non-response for any data point in the follow up. As an advantage, this allows for using all data points before exclusion due to death or recurrence and thus reducing risk of bias. Patients with upcoming (but not yet diagnosed) recurrence or death may have worse response; therefore, 'subsequent recurrence' and 'subsequent death' tested as variables as well. For all models, non-response was the target variable in a binary logistic fashion. For fixed effects an intercept and the predictor variable were included. For random effects an intercept was included and covariance type was set to unstructured. At first, GLMMs were carried out for patient characteristics, both univariate and in a multivariable model. Second, frailty screening instruments and GA items were evaluated in a GLMM, both in an unadjusted model and then in a model adjusted for all relevant patient characteristics.

RESULTS

During the study period, 369 patients with mucosal, salivary gland and cutaneous malignancies in the head and neck area were included in OncoLifeS. After exclusion of patients receiving palliative or non-standard treatment and patients not responding to baseline questionnaires, 289 patients remained in the study for analysis (Figure 1). The mean age was 68.4 years and 68.5% were male. 54.5% of patients had advanced stage disease. Recurrence, death and response to follow-up questionnaires are shown in Figure 2. From all patient and study characteristics, age (OR 3.21(1.80-5.72)), time (per year OR 1.47(1.10-1.97)) and subsequent death (OR 2.84(1.62-4.99)) were significantly associated with non-response to follow-up questionnaires, in univariate GLLMs (Table 1). All remained significant in the multivariable model (Table 1).

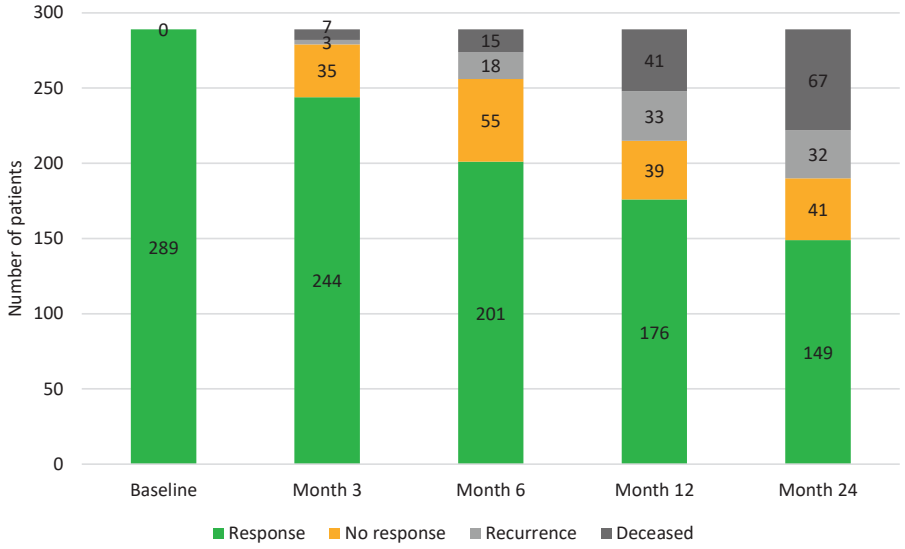

Figure 2 | Response and non-response to questionnaires, recurrence and death among patients.

Regarding GA items, restrictions in ADL (OR 4.46(2.04-9.78)), IADL (OR 4.33(2.27-8.24)), impaired mobility on the TUG (OR 3.95(1.85-8.45)), signs of cognitive decline on the MMSE (OR 4.85(2.28-10.35)), assisted living or living in a nursing home (OR 5.54(2.63-11.67)) were significantly associated with non-response to questionnaires in univariate GLLMs (Table 2).This remained the case after adjusting for patient and study characteristics, that showed significance in the univariate model, such as age, time and subsequent death (Table 2).

Frailty screening by both G8 and GFI, was significantly associated with non-response (OR respectively 2.64 (1.51-4.59) and 2.52 (1.44-4.44)), even after adjusting for the abovementioned factors (Table 2).

DISCUSSION

In this longitudinal observational study, we investigated whether frail patients exhibit more non-response to follow-up questionnaires than non-frail patients and whether specific items of a routinely performed GA are associated with this. Main findings were that frailty screening tools were associated with worse response to follow-up questionnaires. . Besides, impaired ADL and IADL, restricted mobility, cognitive decline and dependent living situation were specifically associated with poorer response to follow-up questionnaires. These associations were independent of other significant factors, such as age, duration of the study and subsequent death during the study. To our knowledge, this is the first study demonstrating the association between geriatric factors and response to PROMs in patients with HNC. These results are important for the interpretation of all studies dealing with PROMS, because of the increasing proportion of older and frail patients.

Table 1 | Patient characteristics and generalized linear mixed models for non-response. Generalized linear mixed models (binary logistic) showing odds ratios for non-response to follow-up questionnaires within the period of 24 months. Patients were excluded upward from recurrence or death. Values presented in n(%) unless otherwise specified. OR = odds ratio; CI = confidence interval; ORL-HNS = otorhinolaryngology, head and neck surgery; RT = radiotherapy.

Patient characteristics	Value	Univariate models		Multivariable model	
		OR (95%CI)	p-value	OR (95%CI)	p-value
Age					
≤65 year	113 (39.1)	ref		ref	
>65 year	176 (60.9)	**3.21 (1.80 – 5.72)**	**< 0.001**	**2.91 (1.61 – 5.28)**	**< 0.001**
Sex					
Male	198 (68.5)	ref			
Female	91 (31.5)	0.74 (0.41 – 1.31)	0.30		
Stage					
I-II	129 (45.4)	ref			
III-IV	155 (54.6)	0.36 (0.46 – 1.33)	0.36		
Primary treatment					
Surgery	163 (56.4)	ref			
Radiotherapy	84 (29.1)	0.51 (0.22 – 1.19)	0.12		
Chemotherapy	42 (14.5)	1.33 (0.74 – 2.40)	0.35		
Follow-up					
By mail	97 (33.5)	ref			
At outpatient clinic	192 (66.4)	0.86 (0.50 – 1.49)	0.59		
Time					
Per year		**1.47 (1.10 – 1.97)**	**0.009**	**1.70 (1.25 – 2.32)**	**0.001**
Subsequent recurrence					
No		ref			
Yes		1.64 (0.90 – 3.01)	0.11		
Subsequent death					
No		ref			
Yes		**2.84 (1.62 – 4.99)**	**<0.001**	**3.13 (1.72 – 5.73)**	**< 0.001**

In our study, higher age was significantly associated with non-response during follow-up. This is in line with some earlier studies,[8,28–30] however, other studies found no significant differences.[9,31–33] Comparison is difficult, given the different cancer types (and therewith age groups) and study methodologies which may explain the divergent outcomes.

Table 2 | Geriatric assessment, frailty screening and generalized linear mixed models for non-response. Generalized linear mixed models (binary logistic) showing odds ratios for non-response to follow-up questionnaires within the period of 24 months. Patients were excluded upward from recurrence or death. Values presented in n(%) unless otherwise specified. *models were adjusted for age, time and subsequent death (items of the multivariable model in the right column of Table 1). OR = odds ratio; CI = confidence interval; 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 and Go; MMSE = Mini Mental State Examination; GDS-15 = Geriatric Depression Scale- 15; G8 = Geriatric 8; GFI = Groningen Frailty Indicator.

Geriatric assessment	**Value**	**Univariate models**		**Adjusted models***	
		OR (95%CI)	p-value	OR (95%CI)	p-value
ACE-27					
None to mild (<2)	164 (56.7)	ref		ref	
Moderate to severe (≥2)	125 (43.3)	1.21 (0.71 – 2.07)	0.48	0.82 (0.47 – 1.46)	0.51
Polypharmacy					
# medications (<5)	188 (65.3)	ref		ref	
# medications (≥5)	100 (34.7)	1.04 (0.59 – 1.82)	0.90	0.70 (0.39 – 1.28)	0.25
MUST					
No malnutrition (0)	211 (78.1)	ref		ref	
Risk of malnutrition (≥1)	59 (21.9)	1.16 (0.59 – 2.31)	0.67	1.33 (-.64 – 2.77)	0.44
ADL					
No restrictions (0)	257 (88.9)	ref		ref	
Restrictions (≥1)	29 (10.1)	**4.46 (2.04 – 9.78)**	**< 0.001**	**3.16 (1.39 – 7.19)**	**0.006**
IADL					
No restrictions (0)	239 (83.0)	ref		ref	
Restrictions (≥1)	49 (17.0)	**4.33 (2.27 – 8.24)**	**< 0.001**	**3.11 (1.57 – 6.16)**	**0.001**
TUG					
<13.5 seconds	242 (87.7)	ref		ref	
≥13.5 seconds	34 (12.3)	**3.95 (1.85 – 8.45)**	**< 0.001**	**2.60 (1.16 – 5.83)**	**0.02**
MMSE					
Normal cognition (>24)	153 (88.2)	ref		ref	
Cognitive decline (≤24)	34 (11.8)	**4.85 (2.28 – 10.35)**	**< 0.001**	**3.57 (1.60 – 7.93)**	**0.002**
GDS-15					
No depression (<6)	261 (91.3)	ref		ref	
Signs of depression (≥6)	72 (25.0)	0.84 (0.31 – 2.25)	0.73	0.68 (0.23 – 2.00)	0.48

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Table 2 | continued

Geriatric assessment	Value	Univariate models OR (95%CI)	p-value	Adjusted models* OR (95%CI)	p-value
Marital status					
In a relationship	216 (75.0)	ref		ref	
Single	72 (25.0)	1.56 (0.86 – 2.83)	0.14	1.42 (0.76 – 2.66)	0.28
Living situation					
Independent	253 (88.2)	ref		ref	
Requires help/ nursing home	34 (11.8)	**5.54 (2.63 – 11.67)**	**< 0.001**	**3.83 (1.73 – 8.45)**	**0.001**
Educational level					
Lower education	119 (43.3)	ref		ref	
Middle or higher education	156 (56.7)	0.92 (0.63 – 1.59)	0.77	1.10 (0.63 – 1.94)	0.74
Frailty screening					
G8					
Non-frail (>14)	126 (45.2)	ref		ref	
Frail (≤14)	153 (54.8)	**2.64 (1.51 – 4.59)**	**0.001**	**2.02 (1.12 – 2.66)**	**0.02**
GFI					
Non-frail (<4)	203 (70.5)	ref		ref	
Frail (≥4)	85 (29.5)	**2.52 (1.44 – 4.44)**	**0.001**	**2.02 (1.11 – 3.68)**	**0.02**

A recent study, however, did investigate study retention and attrition in a longitudinal study of HNC patients in the Netherlands, collecting PROMs, fieldwork data and biobank materials up to two years.[34] In this study age was not associated with attrition, unlike other factors such as higher tumour stage, poorer physical performance and worse comorbidity score. The latter, comorbidity, was in line with other studies,[28,30,32] however, not with our study which identified no significant differences in response between patients with none to mild and moderate to severe comorbidities. A reason for this may be the fact that other studies often assign patients with recurrent disease and even deceased patients to the attrition or non-response group as well. In this way, there is a risk of predicting death or recurrence rather than non-response due to other (geriatric) factors. In our study, we have excluded patients with recurrence or death from the analyses, from the moment that recurrence or death occurred. This gives superior understanding underlying non-response mechanisms.

Other items of GA or frailty screening with respect to non-response, drop-out or attrition have rarely been investigated and not at all in the unique population of HNC. In other studies, the

most valuable data available is originating from the PROMs themselves that patients were asked to fill out, but then used at baseline as a predictor for drop-out. Among some different studies in other cohorts, poor functional status, symptom burden, depressive symptoms, cognitive failure, psychosocial symptoms, lower socioeconomic status, low educational level, and poor baseline QoL were associated with attrition.[9,29,31–33] It must be noted that study methodology differed greatly between studies, and none of the studies specifically aimed HNC. Besides, one may question the ability of a QoL questionnaire subscale to diagnose e.g. 'cognitive failure', often based on just a few questions, compared to specifically developed screening tools such as MMSE in the case of cognition. In our current study, where we have employed well-known and frequently used instruments for GA (and not subscales of the PROMs), we have seen consistent associations of restricted ADL and IADL, poor mobility, cognitive decline and dependent living situation with non-response.

Frailty screening tools, such as the G8 and GFI, were significantly associated with increased non-response as well, which was also expected given the share of functional, cognitive and psychosocial items in the screening tools. This is in line with another study, in which frailty was significantly associated with drop-out from a cohort study.[35]

Attrition is common in longitudinal studies, especially with the use of PROMs. When data is missing (completely) at random, this usually does not lead to bias. However, when attrition rates are distinct for different study groups, e.g. in this case when comparing frail to non-frail patients, this may introduce attrition bias.[36] Data may be not missing at random anymore, as for instance frail patients systematically respond worse to the questionnaires and may have different outcomes as well. In such studies, such as in studies evaluating QoL outcomes between frail and non-frail patients,[37,38] the observed differences may be an underestimation of the real difference. Although ideally this should be prevented ahead of time by creating a strategy to take care of frail patients at risk for dropping-out (e.g. alternative study visits, using patients peer support, supportive telephone contacts),[39] it is important to know how to handle and interpret these data. According to experts, mixed-models remain the best choice for the analysis of repeated measures and longitudinal data.[36]

Strengths of this study include the prospective inclusion of patients, the large range of validated screening instruments, the ability to adjust for relevant covariates such as subsequent death or recurrence and study characteristics, and the maximum use of data points by using mixed-models and therewith limiting bias as much as possible. Limitations of this study may be the different collection methods of PROMs between departments (which was adjusted for), the absence of information why patients dropped out, the relatively small and heterogeneous study cohort, which included both mucosal as cutaneous malignancies. Besides, by excluding patient not responding to baseline questionnaires, some form of bias may already be present from the beginning.

CONCLUSION

Frailty, measured by deficiencies on GA, such as impaired ADL and IADL, restricted mobility, cognitive decline and dependent living situation, or by frailty screening instruments (G8 and GFI), is significantly associated with worse response to follow-up PROMs. This is of importance when handling and interpreting data on older or frail HNC patients, as with the resulting attrition bias the observed effects may be an underestimation of the real differences.

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General discussion and future perspectives

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chapter nine

GENERAL DISCUSSION

The aim of this thesis was to determine the frailty of patients with head and neck cancer (HNC) , and to explore the association of frailty and deficits on geriatric assessment (GA) with relevant clinical outcome measures, such as surgical complications, radiation-induced toxicity (RIT) and health-related quality of life (HRQoL). We investigated this in data from a large prospective observational study at the University Medical Center Groningen, The Netherlands. An introduction to the subject of frailty and GA in the particular population of patients with HNC is provided in **Chapter 1**. In **Chapter 2**, we demonstrated that patients with HNC are a frail population compared to patients with other types of solid cancer, based on the outcomes of frailty screening and GA. We showed that frailty and (cumulative) deficits on GA are associated with an increased risk of severe surgical complications in both a population of patients with complex skin cancer in the head and neck area, and a general cohort of patients with HNC undergoing surgery, in **Chapter 3** and **4**, respectively. In contrary, we found that frailty and outcomes of GA are not associated with an increase in RIT after and during definitive or post-operative (chemo)radiotherapy ((C)RT), as illustrated in **Chapter 4** and **5**. This is very likely due to the nature of the different modalities, as surgery is a large stressor at a certain moment and stress of (C)RT is spread out over a duration of weeks. In **Chapter 6** we have demonstrated that frail patients exhibit stronger decline of HRQoL and functioning, and experience higher symptom burden after treatment for HNC than non-frail patients, and in **Chapter 7** we presented the deterioration of HRQoL after treatment for HNC, along with the accumulation of geriatric deficits. Last, we enlightened that there is a risk of attrition bias in studies including frail patients, due to the inequal losses of data during follow-up, in **Chapter 8**. Main findings are summarized in Table 1. Altogether, these finding are important for treatment counseling, decision making, treatment planning and future research.

Frailty of patients with head and neck cancer

It has often been suggested that patients with HNC are relatively frail, because of their unhealthy lifestyle, resulting comorbidities and symptoms secondary to tumor location and extension. In **Chapter 2** we have demonstrated, that this is indeed the case by comparing a cohort of patients with HNC with a cohort of patients with other solid cancer seen on a surgical oncology outpatient clinic. The main findings of this study were that patients with HNC were more often frail, had more cognitive restrictions, had poorer mobility, and exhibited worse global QoL, physical and emotional functioning on the EORTC-QLQ-C30 compared to patients with other types of cancer (Table 1). Comorbidity scores did not significantly differ between cohorts. Invariably, comorbidity is an item of frailty screening and GA and, in general, frail patients will have more comorbidities, in HNC as well.[1] However, frailty is not equal to comorbidities: with nutritional, functional, psychological and socioenvironmental domains adding to frailty as well, the increased frailty status with equal comorbidities can be explained. Besides, care seeking behavior may be different for patients with HNC patients compared to patients with other cancers, resulting in less comorbid diagnoses.[2]

Unfortunately, in our study, no GA for malnutrition was available for comparison between cohorts. Specifically in HNC patients, the proportion of patients with malnutrition is raised due to the tumor location in the upper gastrointestinal tract, and often coexists with frailty.[3,4] Besides,

malnutrition is described as a cornerstone of frailty.3 BMI was the only available proxy measure, and was significantly lower in patients with HNC compared to the other group.
Furthermore, there was no data on tobacco and alcohol abuse in our study. Therefore it cannot be stated with certainty that the higher ratio of frailty is due to the mechanism of intoxications. However, recent studies have added to this and found that tobacco smoking but not alcohol use is a causative agent of frailty.[5]

There are no other studies directly comparing the frailty status of patients with HNC to other populations. Frailty rates in HNC populations may differ strongly across screening and assessment methods and across populations.[6–8] The rate of frailty in HNC patients in our study (33%) was slightly lower than has been shown in other studies employing the Groningen Frailty Indicator (GFI, 40-52%).[9,10] However, cohort characteristics vary widely here as well. For example, one study included patients with complex skin cancer besides patients with laryngeal cancer.9 Furthermore, another study only included patients above the age of 70.[10] Studies performing a Comprehensive Geriatric Assessment (CGA), the gold standard, in HNC populations found rates of 52-72% of patients being frail, however, only selected patients 65 or 70 years and older.[7,11–13] This makes comparison between cohorts difficult. More recent studies in HNC have shown that the proportion of frailty in younger patients with HNC is significant as well, and that also in this category frailty is associated with poorer treatment outcomes.[14,15] Although many oncology services will screen or assess only 'older' patients above the age of 65 or 70, we propose that for patients with HNC this should also be done at younger age as well, due to their relatively high biological age.

One of the epidemiological transitions to keep in mind is the increase in patients with HPV-positive HNC. Although this population contains both younger and older patients nowadays,[16,17] they could be less frail due to the different etiology of the disease, which is in these cases not tobacco and alcohol abuse. However, the separation between HNC related to HPV on the one hand and to lifestyle on the other hand is not distinct. For example, patients using tobacco with HPV-positive HNC seem to have higher risk of recurrence and worse survival as well.[18,19] Besides, complaints secondary to tumor location and extension, such as malnutrition, may still be present, leading to additional or even comparable frailty in the population with HPV-positive HNC as well.

Previous studies on geriatric screening and treatment-related outcomes

Ahead of the publications presented in this thesis, previous studies focusing on clinical outcome measures had already shown that older patients are, but should not be treated differently than their younger counterparts based on their chronological age.[20] Chronological age alone was not associated with an increase in severe surgical complications, recurrence or disease specific survival in several HNC subpopulations.[21–25] The interest in comorbidity grew and the first work on identifying associations between pre-operative frailty status and treatment-related outcomes in HNC dates from 2015, by Bras et al.[9] In the following years several studies showed a relation between frailty and clinical outcome measures, however, with retrospective study designs, high risk of bias, and lacking data on dropouts, their level of evidence is low.[26] The latter, data of patients who could not be included or were lost during follow-up, seems important as these are often the frailest patients (**Chapter 4** and **8**). A review from 2020 on frailty in HNC by Fu et al. denotes only retrospective studies until then and calls for further research and specifically prospective studies.[26]

In this thesis, we prospectively analyzed the associations between a pre-treatment frailty screening and broad GA on the one hand, and relevant clinical outcome measures, such as adverse events (surgical complications and RIT), HRQoL, functioning and survival on the other hand, reducing the risk of bias. Given the quantity of data that this combination of variables and outcomes would generate, collaboration with a large epidemiological hospital-based data-biobank the 'Oncological Life Study' (OncoLifeS) was started.[27] All new patients with cancer are asked to participate in OncoLifeS, also at several other oncological departments. After inclusion, patient data, including different assessments and questionnaires, and biomaterials, including blood, tissue samples, and other material, are collected and stored in a biobank. Such a data-biobank provides an adequate infrastructure for data collection, handling, storage and access, adherence to high legal and ethical standards, and provides opportunities for many kinds of research.[27]

Frailty and adverse events

In a prospective study, we demonstrated the associations between frailty and restrictions in geriatric domains with adverse events such as surgical complications and RIT in patients undergoing curative treatment for HNC (**Chapter 4**). From the items of GA, moderate to severe comorbidities and an intermediate risk of malnutrition were, along with higher age, major surgery and a history of smoking, independently associated with higher risk of surgical complications Clavien-Dindo grade II and higher. Additionally, significant univariable factors associated with a higher risk of surgical complications were limited mobility and restrictions in Activities of Daily Living (ADL). With respect to RIT at three months after onset of treatment, only major treatment intensity and concomitant CT were independently associated with higher RIT, and none of the items of GA were. Moreover, frailty, diagnosed with frailty screening tools such as the Geriatric 8 (G8) and GFI, and the number of domains of GA with restrictions, were all strongly associated with surgical complications, but not with RIT (Table 1).

Around the same period, another prospective study by Goldstein et al. was published focusing merely on complications after surgery and using the Fried's Frailty Index, in which frailty was a significant factor for medical complications and severe surgical complications, independent of age and comorbidity, but not for overall complications.[28] Later, more prospective studies would investigate frailty as a predictor of surgical complications and draw the comparable conclusions,[13,29] including a recent study doing an actual CGA and finding frailty to be a significant factor for surgical complications, operation time and estimated blood loss as well.[13]

From this work it became clear that it is not just one specific item, such as comorbidity, depression, or restrictions in activities of daily living, that is associated with an increased risk of surgical complications, but that it is rather the coexistence of multiple deficits that leads to an increased susceptibility. This is in line with the deficit accumulation theory for frailty proposed by Rockwood et al.[30–32] However, discarding all individual items and employing only a frailty screening instrument would not be specific enough (it may select more than 50% of cases to be frail) andwould not contain enough information about the actual underlying deficits. Besides, when a specific deficit is found this should ideally lead to a succeeding pre-treatment optimization orintervention (prehabilitation) as well. An ideal geriatric evaluation should therefore contain at least a short assessment for every geriatric domain.

Table 1 | Summary of main findings in this thesis. * = in unviariable analysis; ** = for the interaction term with time; OR = Odds Ratio; MMSE = Mini Mental State Examination; TUG = Timed Up & Go; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GFI = Groningen Frailty Indicator; HNC = Head and Neck Cancer; G8 = Geriatric 8; CTCAE = Common Terminology Criteria for Adverse Events; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living.
at three to twenty-four months after treatment were associated with frailty screened by GFI.

Chapter	Main findings	OR / β	Effect size 95% CI	Outcome measure
2	Patients with: - cognitive restrictions (MMSE), - restricted mobility (TUG), - worse QoL (EORTC-QLQ-C30), - worse physical functioning (EORTC-QLQ-C30), - worse emotional functioning (EORTC-QLQ-C30), - and being frail (GFI)*, were more often patients with HNC than other malignancy.	 OR OR OR OR OR OR	 20.03 (2.44-164.31) 11.56 (1.86-71.68) 0.98 (0.97-1.00) 0.98 (0.96-1.00) 0.96 (0.95-0.98) 1.74 (1.11-2.71)	Being a patient with HNC
3	Patients with complex skin cancer: - undergoing major surgery (>120min), - general anaesthesia, - and being frail (G8), had a higher risk of surgical complications.	 OR OR OR	 2.73 (1.19-6.26) 4.74 (1.02-22.17) 6.34 (1.73-23.25)	Surgical complications Clavien-Dindo grade ≥ II
4	In patients with HNC undergoing surgery: - frailty diagnosed by GFI, - frailty diagnosed by G8, - and the number of deficient geriatric domains, was associated with surgical complications. In patients with HNC undergoing radiotherapy: - frailty diagnosed by GFI, - frailty diagnosed by G8, - and the number of deficient geriatric domains, were not associated with toxicity.	 OR OR OR OR OR OR	 2.54 (1.02-6.31) 5.59 (2.14-14.60) 1.71 (1.14-2.56) 1.13 (0.51-2.53) 0.72 (0.35-1.50) 1.22 (0.87-1.72)	Surgical complications Clavien-Dindo grade ≥ II CTCAE grade ≥ 2 at 12 weeks after start of treatment
5	In patients with HNC undergoing radiotherapy: - frailty diagnosed by GFI, - frailty diagnosed by G8, were not associated with increased toxicity over time, unlike: - regional extend of radiation field - concurrent chemotherapy - and age (>65).	 β** β** β** β** β**	 0.003 (-0.02;0.02) -0.01 (-2.16;2.13) 0.05 (0.02;0.09) 0.04 (0.02;0.07) 0.03 (0.01;0.05)	CTCAE grade during weeks 1-7 after start of treatment

Continued on next page

Table 1 | continued

Chapter	Main findings	OR / β	Effect size 95% CI	Outcome measure
6	In patients with HNC undergoing curative treatment:			
	- global health status / QoL,	β	-8.70 (-13.54;-3.86)	EORTC-QLQ-C30 at 3 to 24 months after treatment
	- physical functioning,	β	-4.55 (-8.70;-0.40)	
	- role functioning,	β**	-7.27 (-12.26;-2.28)	
	- emotional functioning,	β	-10.92 (-16.06;-5.79)	
	- social functioning,	β	-8.44 (-13.91;-2.98)	
	- fatigue,	β	8.25 (2.15-14.36)	
	- pain,	β	10.09 (5.05-15.13)	
	- and dyspnoea	β	8.53 (3.21;13.85)	
	at three to twenty-four months after treatment were associated with frailty screened by GFI.			
7	In patients with HNC undergoing curative treatment:			
	- the number of domains with geriatric deficits	β	-3.17 (-5.04;-1.30)	EORTC-QLQ-C30 at 3 to 24 months after treatment
	- and ≥ 3 domains with deficits	β	-2.74 (-4.28;-1.20)	
	were associated with decline of QoL three months after treatment, and			
	- the number of domains with geriatric deficits	β**	-9.62 (-15.35;-3.88)	
	- and ≥ 3 domains with deficits were associated with further deterioration of QoL during two years, besides individual assessments within all domains.	β**	-14.81 (-20.40;-9.22)	
8	In HNC patients included in a prospective observational study:			
	- restrictions in ADL,	OR	3.16 (1.39-7.19)	Non-response to follow-up EORTC-QLQ
	- restrictions in IADL,	OR	3.11 (1.57-6.16)	
	- poor mobility (TUG),	OR	2.60 (1.16-5.83)	
	- signs of cognitive decline,	OR	3.57 (1.60-7.93)	
	- and dependent living situation	OR	3.83 (1.73-8.45)	
	were associated with worse response to follow-up measurements, as well as patients being			
	- frail diagnosed by GFI,	OR	2.02 (1.12-2.66)	
	- And frail diagnosed by G8.	OR	2.02 (1.11-3.68)	

RIT during or after treatment with (C)RT is an important adverse event as well, as high toxicity may lead to the need for interventions such as tracheostomy, gastrostomy, need for medication or presentation at the emergency department,[33] and poorer QoL.[34] In **Chapter 4** we showed that RIT was not elevated at three months after onset of definitive or post-operative (C)RT for frail patients. Moreover, in **Chapter 5**, we have demonstrated, in patients with HNC undergoing either definitive or post-operative (C)RT, that, besides well-known treatment related factors such

as larger irradiation fields and concomitant CT, outcomes of GA were not associated with higher RIT during treatment. This may be the result of the different intensity of the treatments. The stress of (C)RT is usually spread out over 35 fractions and few infusions, whereas the stress of surgery consists of a large amount of stress in only a short period of time. This difference may prevent frail patients to deteriorate during (C)RT compared to surgery, although there is no evidence to support this theory.

Possibly, in selected cases, primary (C)RT can be a good alternative to primary surgery, when aiming to reduce adverse events within the first months. Though, from an oncological and functional perspective this needs to be possible as well, which is not always the case. For example, for advanced stage laryngeal or hypopharyngeal cancer, primary surgery, i.e. removal of the larynx and partial pharynx, would be needed anyway when laryngeal function cannot be preserved anymore.

The studies shown in **Chapter 4** and **5** found no association between frailty and RIT in HNC. A comparable study found that frailty, defined by a broad GA, was associated with poorer treatment tolerance, a higher percentage of hospitalization, and a higher incidence of treatment-related adverse events.[14] This cohort of 502 patients included both head and neck and esophageal cancer, only patients younger than 65, and all undergoing concurrent CT. The measures for adverse events focused on laboratory tests, rather than local consequences of the therapy. Studies in other oncological populations are contradictory as well, but also use very different measurements for toxicity.[35,36] Altogether, the differences in methodology may explain the contradictive results. More research would be needed to draw firmer conclusions, and should especially include long-term toxicity as well, as these sequalae may influence QoL even more.[37]

Frailty and health-related quality of life

HRQoL, being a patient-reported outcome measure, is probably considered one of most important outcome measures today. Specifically in older patients, QoL is prioritized as the main treatment goal, rather than life extension.[38] In **Chapter 6**, we investigated whether frailty, defined by frailty screening instruments such as the G8 and GFI, was associated with changes in HRQoL over time during two years of follow-up (Table 1). We demonstrated that QoL for frail patients, based on GFI, decreases shortly after treatment already, and declines even further during the two years of follow-up compared to non-frail patients. Also, we found that frail patients exhibited stronger declines with respect to level of physical-, role-, emotional- and social functioning, compared to non-frail patients. Moreover, symptom burden was higher in frail patients, compared to non-frail patients.

This study was the first investigating frailty and long-term QoL after treatment for HNC prospectively. Later, however, few other studies added to this field. Thomas et al. found that frail patients had comparable QoL, functioning and symptom trajectories during 12 months after surgery, (C)RT or a combination of both.[39] Moreover, they found that the frailty status itself, measured by Fried's Frailty Index, was changing over time as well (frail patients became less frail at 12 months after treatment). This dynamic perspective of frailty was later confirmed by Farrugia et al. in patients undergoing (C)RT only, however, they found that patients were more frail directly at

the end of (C)RT than before.[40] Obviously, the timing of measurement underlies this dissimilarity. Nonetheless, for decision making and treatment prognostication, the changing state of frailty would be irrelevant, as this has to be done at the moment ahead of treatment. However, we must remember that the higher frailty status may partially be because of the disease itself or treatment-related functional decline.

From our own results and from literature, it is obvious that there are large differences between frailty screening tools.[6] For example, in **Chapter 5**, the GFI was strongly associated with decline in QoL, but the G8 was not. The G8, however, in **Chapter 3** and **4**, showed stronger associations with an increased risk of surgical complications. Probably, this is caused by the included geriatric conditions in the instruments, which are very physically and nutritionally oriented for the G8, but more functionally and psychosocially focused in the GFI.[6] Besides, nowadays, there is an explosive increase in the number of frailty screening instruments. Some identify 75% of patients as frail, and others 7.5%, they are lacking specificity and/or sensitivity, and are validated in divergent cohorts, often only with patients older than 65, 70 or even 75 years.[41] Altogether, the approach of using only a frailty screening instrument for the HNC population seemed too unspecific, lacking information about the underlying deficits, and, besides, referring all potentially frail patients to the geriatrician would be infeasible due to capacity limitations.

In **Chapter 7** we have explored the outcomes of a broad GA and compared the outcomes of the assessments with long-term QoL after treatment. We found that deficits within all domains (physical, functional, psychological, socioenvironmental) were associated with poorer QoL outcomes after treatment (Table 1). Moreover, the accumulation of domains with deficits was strongly associated with deterioration of QoL, with specifically more than two domains with deficits being a cut-off for severe deterioration.

Although, some other studies had shown relations between few of the individual assessments and QoL, as described in **Chapter 7**, no other work has been done with such broad GA and deficit accumulation and comparing this with QoL outcomes in the long-term. Just as in **Chapter 4**, the results of this study support the deficit accumulation theory.[30–32] With visualizing how all domains add to frailty, it seems to be helpful to intervene on these domains. Knowing which domains contain deficits, may give leads for pre-treatment optimization of comorbidity and concurrent (poly)pharmaceutical management, nutritional status, functional needs or psychological support.

The quantitative decline of QoL is important to know with respect to treatment counseling. It raises the question whether patients, knowing their chances of declining QoL and functioning, would make the same decision about the treatment. It seems that frail patients did not regret their decision more often than other patients.[42] Also, it is known that health care preferences, such as life extension or maintaining QoL, may change over time as well. With increasing age and decline in certain health domains, additional decline in these domains would be more easily accepted.[43] Thus, a patient's own estimation of what they would accept in the future might not always be what they truly find acceptable in the end.

The comparisons in **Chapter 6** and **7** obviously show significant differences in QoL trajectories between frail and non-frail patients. Whether this is the result of the disease and its

treatment, or whether it is the natural course of QoL for frail patients regardless of the cancer treatment, remains an unanswered question, as there was no control group in our studies. However, a study by Kojima et al. did investigate natural QoL trajectory in patients aged 65 and older and found indeed that higher frailty score was associated with negative change in the QoL score during life (-2.95 per 2,5 years on a 165 points Older People's Quality of Life Questionnaire 35 (OPQOL-35) scale).[44] Comparing this with the -14.81 per 1 year on the 100 points EORTC-QLQ-C30 scale from our study in **Chapter 7**, it is likely that this decline is not just the result of naturally different QoL courses, but must be related to a deteriorating event such as the cancer treatment.

Complex skin cancer in the head and neck area

Patients with complex skin cancer in the head and neck area are expected to be seen more frequently at head and neck oncological services, because of the increasing incidence mainly driven by ageing, sun-exposure and possibly climate change as well.[45,46] The gold standard for the treatment of older patients with skin cancers remains surgery, however, RT can be considered a good alternative.[47] From **Chapter 3** it can be deducted that this group of patients is frail in a different way. They are not frail because of their unhealthy lifestyle and thus relatively high biological age, but more because of their actual age (which averaged around 79 years in our cohort), comorbid conditions and functional restrictions.

In many cases of older and vulnerable patients with a limited life expectancy, radical surgery for skin cancer is considered as overtreatment, because patients will most likely die of other causes before symptomatic recurrence occurs.[48,49] This paradigm is referred to as the 'time to benefit'.[47] However, the estimated life expectancy and time until symptomatic recurrence can be difficult. In some patients recurrent or residual tumor may progress. These are the complex cases, together with the other cases by the Dutch definition of complex and advanced skin cancer as described in **Chapter 1**. In such a cohort, undergoing surgery for complex or advanced head and neck skin cancer, we have evaluated surgical complications after performing frailty screening and GA, as described in **Chapter 3**. Although the cohort was heterogenic in terms of the extension of the surgical treatment, from ear or nose amputation to local excision with parotidectomy and neck dissection, the results were clear: frailty (diagnosed by the G8) was strongly associated with an increased risk of surgical complications, aside from other factors such as duration of the surgery and type of anesthesia (Table 1). Unfortunately, comparison with literature is difficult due to the absence of an international definition for this group of patients. In a cohort with both skin cancer and other HNC, Bras et al. found a significant association of surgical complications with health problems on the GFI as well.[9] Moreover, studies have shown that more complications are present in patients undergoing reconstructive surgery for defects after skin cancer excision.[50,51] On the other hand, a study investigating local excision of skin cancers, found no association between frailty and complications.[52] A comprehensive review recognized that literature data is indeed sparse on older and frail patients with complex skin cancer in the head and neck area, and suggested that a one-size-fits-all approach is not sufficient, but that tumor characteristics, life expectancy, frailty and comorbidities have to be evaluated ahead of treatment, to assist with decision making.[53]

Risk of bias for studies investigating frail patients

As a result of the prospective study design of the presented studies in this thesis, new insights were obtained regarding the excluded patients. For example, in the study presented in **Chapter 4**, it seemed that especially the very frail patients were difficult to include as they often did not complete the baseline assessments. Awareness of this potential inclusion bias is very important, as it may result in an underestimation of the real burden of frailty and may therefore lead to bias in the results.

In **Chapter 8**, we investigated the effect of frailty and geriatric deficits on response to follow-up questionnaires. We found, that frailty in general (diagnosed with a frailty screening instrument), and specifically impaired activities of daily living and instrumental activities of daily living, restricted mobility, cognitive decline and dependent living situation, were associated with poorer response to follow-up questionnaires. Although one earlier study found results pointing in the same direction in a non-oncological population, this had not been investigated before in oncological or specifically HNC studies.[54]

Attrition, the loss of study subjects from the study population, is common in longitudinal studies.[55] Studies employing Patient Reported Outcome Measures (PROMs) may be even more susceptible to this. Randomly missing data should usually not lead to bias. However, when data from a particular study group is disproportionately missing, this may lead to attrition bias. In the case of investigation of a group of frail patients, this may lead to an underestimation of the effect size of frailty. Besides, in general, the underrepresentation of frail patients makes study result less generalizable. This is important to take into consideration when analyzing and interpreting study results, and planning of novel studies.

Organization of geriatric evaluation in head and neck cancer care pathway

With ageing of the world population, rising cancer incidence, increasing numbers of older patients with cancer and specifically with HNC,[56–61] referring all of our patients to a geriatrician for an optimal pre-treatment work-up is impossible. The often proposed two-step approach, screening for frailty using frailty screening instrument(s) and referring possibly frail patients to the geriatrician, would be infeasible as well due to the high percentage of HNC patients that score frail on such instruments. Besides, the patient selection is then very dependent on the type of screening tool that is used, and the prognostic value of these frailty screening instruments is questionable.[6] Therefore, a more extensive geriatric multidomain screening is preferably performed already at the outpatient clinic of the head and neck oncology service, and embedded in the routine care-pathway. Implementation of a geriatric evaluation in the care-pathway can be challenging however, due to workforce limitations, time, logistics, training, finance and practical concerns.[62]

Based on literature and the studies currently presented, requirements for setting up a GA at the outpatient clinic may be as follows. The GA should be initiated regardless of age, as HNC patients may be frail at younger age already (**Chapter 2**), and regardless of the oncologists' clinical judgement, since a GA is superior in identifying frailty.[63] The geriatric evaluation should include assessments for all geriatric domains, and not only a general frailty screening tool, as all individual domains add to the frailty state (**Chapter 4** and **7**), may give rise to optimization

strategies, and general frailty screening instruments lack prognostic value.[6] Ideally, the GA should only take a short amount of time, for the continuation of the care-pathway, and, preferably, the GA and possibly needed subsequent consultation of a geriatrician are performed parallel to the other diagnostics, so that relevant outcomes can be incorporated in decision making.

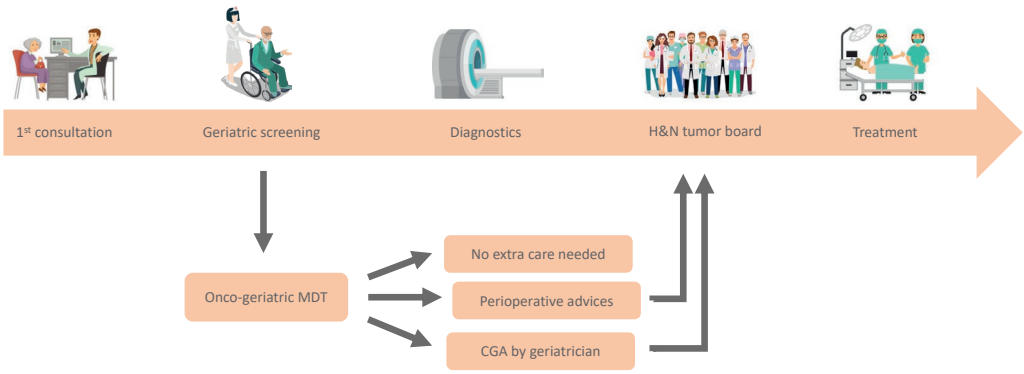

Figure 1 | Care pathway for potentially frail patients with head and neck cancer. MDT = multidisciplinary team, H&N = head and neck, CGA = Comprehensive Geriatric Assessment.

Today, at our outpatient clinic of Otorhinolaryngology, Head and Neck surgery, in the University Medical Center Groningen, we aim to assess all patients referred with a malignancy in the head and neck area, regardless of their age, and regardless of the judgement of the counseling ENT-surgeon. An overview is provided in Figure 1. The GA takes place at the same day as the appointment with the ENT-surgeon, and is carried out by a trained oncology nurse. The assessment consists of multiple short screening tools for all geriatric domains (somatic, psychological, functional, social), as well as history taking by the oncology nurse, and takes around 30 minutes. At the end of the day, all new cases are discussed in an onco-geriatric multidisciplinary team (MDT). Here, the oncology nurse is in the lead and presents cases to the geriatrician. An ENT-surgeon, oral- and maxillofacial surgeon, dermatologist and radiation oncologist are present as well, to answer questions regarding the expected treatment regimens, if needed. Outcomes of the onco-geriatric MDT can be, for example, that no further interference of a geriatrician is needed, peri-operative or other advices can be given, paramedical consultation can be initiated, or a referral to the geriatrician can be indicated. In such geriatric consultation, health outcome priorities can be inventoried to assist with decision making.[64] This is essential, as maintaining independence is often prioritized over life extension, although the latter is the focus of most cancer treatments.[65] This is performed parallel to the other diagnostics, so that all outcomes can be discussed in the Multidisciplinary Head and Neck Tumor Board, to formulate a treatment proposal.

FUTURE PERSPECTIVES

The largest present knowledge gap in this field is the actual benefit of a standard geriatric evaluation in the HNC care-pathway. A geriatric evaluation could improve outcomes in two possible ways: by guiding interventions before treatment and by modifying treatment decisions.

Looking at interventions before treatment, for older patients admitted to the hospital for any reason, undergoing a CGA improves the patients' survival chances and posttreatment independence.[66] Although it seems plausible that this may be the case for oncology or specifically HNC patients as well, the level of evidence is low. Only one randomized controlled trial investigating this in HNC has been carried out and found no differences in death, weight loss and decline of ADL for patients who underwent GA driven interventions versus patients undergoing the standard of care.[67] More research has been done in general oncology, however, the results are divergent. Some trials found positive effects of GA driven interventions in patients undergoing CT, with respect to toxicity.[68,69] Other trials did not find benefit of GA driven interventions in patients undergoing RT or surgery, such as toxicity and surgical comlications.[70,71] The differences can be attributed to many things such as heterogeneity of the cohorts, interventions, timing and outcome measures. Many trials for which protocols have appeared, have yet to be published. A protocol for a Cochrane review investigating the CGA guided treatment versus usual care for older patients with cancer is still to be concluded as well.[72]

Regarding the influence on oncological decision making, it has been demonstrated that geriatric evaluation affects treatment plans, and may improve treatment tolerance and completion.[73] Also, treatment modifications were not associated with excess mortality but were associated with shorter hospital stay and fewer complications, in retrospective analysis.[74] For the future, however, to support the current strategies, which take a lot of effort by patients, care-givers and logistics, we will need to prove the benefits of both GA driven interventions and GA directed decision making in large randomized clinical trials.

From a clinical point of view, besides the obvious need of building a standard and robust geriatric care trajectory, the most important aspect would be the incorporation the outcomes of a GA within the decision-making process. First, this applies to the decision-making in the Head and Neck Tumor Board about the possible treatment regimens. The outcomes of GA should be brought up here to assist with deciding between e.g. extensive surgery, less extensive surgery if applicable, RT, or even palliative therapies. Just as it has been proposed before to include comorbidity in the staging system for HNC, it may be helpful to include a measure of frailty or performance in the staging process, and therewith not only staging the disease, but also the condition of the patient.[75] Second, it will become more important to employ the outcomes of GA with the final decision-making in the consultation room with the patient, where the patient preferences should be taken into account as well, to decide on the treatment strategy together. This complies with the current 'Samen beslissen' (Deciding together) campaign in The Netherlands.[76]

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appendices

SUMMARY (NL)

De incidentie van kanker is de afgelopen decennia aanzienlijk toegenomen. Daarnaast stijgen zowel de algemene levensverwachting als het aantal ouderen in de bevolking. Vanwege deze demografische verschuivingen wordt verwacht dat het aantal ouderen met kanker in de toekomst sterk zal toenemen. Dit geldt ook voor patiënten met hoofd-hals kanker. Dit betreffen meestal plaveiselcelcarcinomen uitgaande van de mucosale bekleding van de mondholte, larynx, (oro-, hypo- en naso-) farynx, en neus- en neusbijholte. Ook kunnen andere histopathologische subtypen voorkomen, zoals bij maligniteiten die uitgaan van de speekselklieren. De incidentie van hoofd-hals kanker neemt toe in alle leeftijdsgroepen. Vooral de incidentiecijfers van het orofarynxcarcinoom zijn gestegen, hetgeen sterk geassocieerd is met een infectie door het humaan papillomavirus (HPV). Hoewel het HPV-positieve orofarynxcarcinoom aanvankelijk vooral voorkwam bij jongere patiënten, is er recentelijk ook een toename waargenomen in oudere leeftijdsgroepen.

Bij de eerste presentatie bevindt de ziekte zich bij 30 tot 40% van de patiënten met hoofd-hals kanker in een vroeg stadium (stadium I of II) en bij meer dan 60% in een gevorderd stadium (stadium III of IV). Een curatieve behandeling van deze gevorderde tumoren kan bestaan uit chirurgie, eventueel gevolgd door postoperatieve (chemo)radiotherapie, of primaire (chemo) radiotherapie, waarna in sommige gevallen nog salvage chirurgie nodig is. In veel gevallen is een combinatie van behandelmodaliteiten vereist. Voor dergelijke intensieve behandelingen wordt regelmatig de leeftijd van de patiënt in overweging genomen bij de besluitvorming, waarbij helaas vaak de chronologische leeftijd in plaats van de biologische leeftijd wordt gehanteerd.

Juist van de populatie van patiënten met hoofd-hals kanker wordt aangenomen dat deze een relatief hoge biologische leeftijd heeft. Meer dan de helft van de patiënten is ouder dan 60 jaar en ongeveer twee-derde is mannelijk. Vaak betreft het patiënten die roken en alcohol gebruiken of dit in het verleden veel hebben gedaan. Dit gaat gepaard met gebruikelijke comorbiditeiten en psychosociale problemen. Invasie van de ziekte in de bovenste lucht- en voedselweg kan bovendien leiden tot cachexie en dyspnoe, met noodzaak tot spoedinterventies al voorafgaande aan de oncologische behandeling.

Veroudering is een zeer heterogeen proces. De tand des tijds veroorzaakt grote gezondheidsverschillen tussen individuen, afhankelijk van aangeboren-, verworven- of omgevingsfactoren. Chronologische leeftijd alleen is dus onvoldoende: de biologische leeftijd lijkt veel belangrijker te zijn, vooral voorafgaand aan een intensief behandeltraject. Vanuit een klinisch perspectief kan een (te) hoge biologische leeftijd worden beschouwd als kwetsbaarheid ('frailty'). Dit wordt gedefinieerd als een staat van verhoogde kwetsbaarheid waarbij men niet goed kan herstellen van een stressor, hetgeen het risico op ongunstige uitkomsten verhoogt. Frailty wordt slecht herkend door oncologen. De gouden standaard voor het diagnosticeren van frailty is een uitgebreide geriatrische beoordeling (Comprehensive Geriatric Assessment, CGA) door een geriater, waarbij alle geriatrische domeinen zoals het fysieke, functionele, psychologische en sociale domein worden onderzocht. Om patiënten te selecteren die voor een dergelijke klinische geriatrische beoordeling in aanmerking komen, zijn screeningtools ontwikkeld. Als tussenvorm bestaat nog de geriatrische beoordeling (Geriatric Assessment, GA), bijvoorbeeld uitgevoerd door de oncologieverpleegkundige.

Een andere patiëntenpopulatie die steeds vaker wordt gezien door hoofd-hals oncologen zijn patiënten met complexe huidmaligniteiten in het hoofd-halsgebied, zoals gigantische basaalcelcarcinomen, plaveiselcelcarcinomen stadium III of hoger, maligne melanomen en Merkelcelcarcinomen. De incidentie van huidmaligniteiten neemt epidemisch toe en deze zijn sterk geassocieerd met oudere leeftijd. Vaak worden deze tumoren veroorzaakt door blootstelling aan ultraviolette straling en de cumulatieve schade daarvan door de jaren heen. Uitgebreide chirurgie kan noodzakelijk zijn als hoeksteen van de behandeling.

Met enerzijds intensieve behandeltrajecten en anderzijds een kwetsbare patiëntenpopulatie, kan dit uitdagingen in de besluitvorming opleveren. Dit is vooral het geval als de biologische leeftijd niet correleert met de chronologische leeftijd. Onderbehandeling kan leiden tot suboptimale oncologische uitkomsten, en overbehandeling tot vermijdbare complicaties, terwijl juist bij de oudere populatie de kwaliteit van leven een hoog gewaardeerde uitkomstmaat is. Het doel van dit proefschrift was om associaties tussen frailty, GA en klinische uitkomstmaten aan te tonen in observationele prospectief verkregen data.

Om te beginnen vergeleken we in **Hoofdstuk 2** de populatie van patiënten met hoofd-hals kanker met een cohort van patiënten met andere solide tumoren. Hoewel er geen significante verschillen in leeftijd, stadium en comorbiditeit waren, werden de patiënten met hoofd-hals kanker vaker geclassificeerd als frail volgens de Groningen Frailty Indicator (GFI). Bovendien hadden zij onafhankelijk van elkaar meer cognitieve problemen, een slechtere mobiliteit en een lagere kwaliteit van leven en functioneren.

We onderzochten in een cohort van patiënten met complexe huidmaligniteiten welke onderdelen van een GA en frailty screening geassocieerd waren met het optreden van chirurgische complicaties, in **Hoofdstuk 3**. In dit cohort, met een gemiddelde leeftijd van bijna 80 jaar, waren een langere operatieduur, het gebruik van algehele anesthesie en classificatie als frail volgens de Geriatric 8 (G8) geassocieerd met het optreden van chirurgische complicaties.

In **Hoofdstuk 4** vergeleken we de uitkomsten van frailty screening en GA met chirurgische complicaties en radiotoxiciteit bij chirurgisch en/of radiotherapeutisch behandelde patiënten met hoofd-hals kanker. Frailty, op basis van een screeningsinstrument of het aantal geriatrische domeinen met gebreken, was sterk gerelateerd aan klinisch relevante chirurgische complicaties, maar niet aan ernstigere radiotoxiciteit 12 weken na de start van de behandeling.

Aangezien acute radiotoxiciteit waarschijnlijk eerder optreedt, onderzochten we in **Hoofdstuk 5**, in een cohort van patiënten met hoofd-halskanker die primaire of postoperatieve radiotherapie ondergingen, al dan niet gecombineerd met chemotherapie, de radiotoxiciteit gedurende de behandeling in relatie tot frailty. Ook hier waren onderdelen van een GA en frailty screening niet geassocieerd met toenemende radiotoxiciteit, in tegenstelling tot gebruikelijke factoren zoals stadium, regionale radiotherapie en concomitante chemotherapie.

We richtten ons op de kwaliteit van leven, het functioneren en de symptomen na behandeling voor hoofd-halskanker, tot twee jaar na de behandeling, in **Hoofdstuk 6**. Voor patiënten die met een screening als frail werden geïdentificeerd met de GFI, nam de kwaliteit van leven direct na de behandeling en op lange termijn af, evenals het fysieke, rol-, emotionele en sociale functioneren. Symptomen waren juist meer aanwezig bij deze patiënten.

In **Hoofdstuk 7** vergeleken we de onderdelen van een GA en de optelsom van meerdere afwijkende geriatrische domeinen met achteruitgang van kwaliteit van leven tot twee jaar na de behandeling. Hieruit kwam naar voren dat binnen alle geriatrische domeinen (fysiek, functioneel, psychologisch en sociaal) afwijkende onderdelen van een GA geassocieerd zijn met achteruitgang van kwaliteit van leven na de behandeling. De sterkste associatie was echter met de optelsom van het aantal domeinen waarin er gebreken zijn. Des te meer domeinen met gebreken er zijn, des te slechter de kwaliteit van leven lijkt te worden. Dit gold vooral voor drie of meer domeinen.

Tot slot vroegen we ons af of er een verhoogd risico op bias zou zijn bij kwaliteit van leven onderzoek naar kwetsbare patiënten, omdat mogelijk de respons op vragenlijsten minder zou kunnen zijn. Uit de resultaten in **Hoofdstuk 8** bleek dat patiënten met beperkingen in functioneren, mobiliteit, cognitie en woonsituatie minder vaak de vragenlijsten invulden dan andere patiënten. Bovendien gold dit ook voor patiënten die bij een screening met GFI en G8 als frail werden geclassificeerd.

Samenvattend lijkt de populatie van patiënten met hoofd-hals kanker bijzondere aandacht te verdienen ten aanzien van het screenen op frailty, omdat dit relatief veel voorkomt. Frailty is bovendien geassocieerd met meer klinisch relevante chirurgische complicaties na chirurgie voor hoofd-hals kanker en complexe huidmaligniteiten, maar niet met ernstigere radiotoxiciteit tijdens of na (postoperatieve) radiotherapie. Kwetsbare patiënten hebben een hoger risico op een lagere kwaliteit van leven, een lager niveau van functioneren en meer symptomen na de behandeling. Daarbij geldt dat hoe meer geriatrische gebreken er zijn, des te lager de te verwachten kwaliteit van leven zal zijn. Aangezien deze groep kwetsbare patiënten minder geneigd is vragenlijsten in te vullen, kan er bias optreden en kunnen deze resultaten een onderschatting zijn van de daadwerkelijke verschillen.

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ABOUT THE AUTHOR

Julius de Vries was born on May 5th 1991 in the city of Groningen, The Netherlands. He was raised in a creative family together with his younger brother Lucas. After completing his pre-university education at the Praedinius Gymnasium in 2009, Julius embarked on an around-the-world journey in 2010. Following his return, he decided to study Medicine and enrolled at the University of Groningen. During his early days as a medical student, Julius demonstrated his interest in Otorhinolaryngology, Head and Neck Surgery, undertaking various projects in the field. In pursuit of academic and sociocultural adventure, in 2014, he moved to Philadelphia, Pennsylvania, United States of America, to undertake a research clerkship at the University of Pennsylvania. This experience culminated in his master's thesis entitled 'Contralaterally triggered functional electrical stimulation: restoration of symmetrical whisker movements in a rodent model of facial paralysis'. Upon his return to Groningen, Julius commenced his clinical rotations, and met Simone during this period. In 2016, he relocated to Zwolle, The Netherlands, to continue his rotations at the Isala Klinieken. It was during this period that he made the decision to pursue a career in Otorhinolaryngology, Head and Neck Surgery, setting the course of his professional trajectory. In 2017, Julius started working as a resident and PhD candidate at the University Medical Center Groningen, Groningen, The Netherlands. His formal training in Otorhinolaryngology, Head and Neck Surgery, began in 2019. After completing both academic and non-academic internships, and undertaking another great journey across the Asian continent, Julius is currently finalizing his residency alongside this doctoral research titled 'On frailty, geriatric assessment and clinical outcomes in patients with head and cancer'. He will start working as an ENT-surgeon in the Isala Klinieken, Zwolle, in 2025. For now, Julius and Simone reside in Groningen.