Patients with head and neck cancer

Bras, Linda; Driessen, Daphne A. J. J. ; Vries, de, Julius; Festen, Suzanne; van der Laan, Bernard F.A.M.; van Leeuwen, Barbara L; de Bock, Gertruida H; Halmos, György B.

Published in:
European journal of cancer care

DOI:
10.1111/ecc.13170

Received: 19 March 2019 | Revised: 6 August 2019 | Accepted: 4 September 2019

DOI: 10.1111/ecc.13170

ORIGINAL ARTICLE

European Journal of Cancer Care WILEY

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

Linda Bras[1] | Daphne A. J. J. Driessen[2] | Julius de Vries[1] | Suzanne Festen[3] | Bernard F. A. M. van der Laan[1] | Barbara L. van Leeuwen[4] | Geertruida H. de Bock[5] | Gyorgy B. Halmos[1]

[1]Department of Otorhinolaryngology/Head and Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[2]Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands

[3]University Center for Geriatric Medicine, University Medical Center Groningen, Groningen, The Netherlands

[4]Department of Surgical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[5]Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence
Linda Bras, Department of Otorhinolaryngology/Head and Neck Surgery, University Medical Center Groningen, HPC BB20, Postbus 30001, 9700 RB Groningen, The Netherlands.
Email: l.bras@umcg.nl

Abstract

Objective: We aimed to compare frailty status between patients with head and neck cancer (HNC) and other solid malignancies.

Methods: Data collection was prospective, and the following were compared between cohorts at baseline: patient and tumour characteristics, Charlson Comorbidity Index (CCI), Groningen Frailty Indicator (GFI), Mini Mental State Examination (MMSE), Activities of Daily Living (ADLs), Instrumental ADLs (IADLs), Timed Up and Go (TUG) and Quality of Life (QoL). Univariate and multivariate logistic regression analyses were performed, and odds ratios (ORs) with their 95% confidence intervals (95% CIs) were estimated.

Results: In total, 242 patients with HNC and 180 with other oncology diagnoses were enrolled, of whom 32.6% and 21.8% were frail according to the GFI respectively. Comorbidity scores were not significantly different between the cohorts (7.4% vs. 13.1%; OR 0.54; 95% CI 0.28–1.02). In the univariate analysis, the GFI was significantly worse in the HNC cohort (OR 1.74; 95% CI 1.11–2.71). However, in the multivariate analysis, the MMSE, TUG and global QoL were significantly worse in the HNC cohort, with ORs of 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) respectively.

Conclusion: Patients with HNC appear to be frailer than patients with other solid malignancies despite comparable levels of comorbidity.

KEYWORDS

frail elderly, frailty, geriatric assessment, geriatric oncology, head and neck cancer, quality of life

1 | 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).

Linda Bras and Daphne A. J. J. Driessen contributed equally to the study.

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.

2 | MATERIAL AND METHODS

2.1 | 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.

2.2 | 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.

2.3 | 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).

2.4 | Frailty, geriatric assessment, 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,

TABLE 1 Patient and disease characteristics in the HNC and SO cohorts (*n* = 422; n [%])

Variables	HNC cohort (*n* = 242)	SO cohort (*n* = 180)	OR (95% CI)	*p*-value
Age (years)				.57
≤54	35 (14.5%)	33 (18.3%)	1	
55–74	158 (65.3%)	112 (62.2%)	1.33 (0.78–2.27)	.30
≥75	49 (20.2%)	35 (19.4%)	1.32 (0.69–2.51)	.40
Sex				
Female	66 (27.3%)	77 (42.8%)	1	
Male	176 (72.7%)	103 (57.2%)	1.99 (1.32–3.00)	**.001**
BMI				
<25	130 (53.9%)	59 (34.3%)	1	
≥25	111 (46.1%)	113 (65.7%)	0.45 (0.30–0.67)	**<.001**
Missing	1	8		
Relationship status				
In a relationship	153 (66.2%)	129 (72.9%)	1	
Single	78 (33.8%)	48 (27.1%)	1.37 (0.89–2.10)	.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)	.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)	.06
Missing	0	4		
Tumour 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)	.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)	.90
Missing	0	8		

Note: Statistical test: univariate logistic regression analysis. Being member of the HNC cohort is defined as dependent variable.
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; HNC, head and neck cancer; OR, odds ratio; SO, surgical oncology.
Significant *p*-values are indicated in bold

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

TABLE 2 Frailty, geriatric assessment and QoL characteristics in the HNC and SO cohorts (*n* = 422; *n* (%), unless specified otherwise)

Variables	HNC cohort (*n* = 242)	SO cohort (*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)	**.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)	.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)	.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)	**<.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)	**.02**
Missing	15	16		
EORTC QLQ-C30[a]				
Global QoL scale	70.35 ± 20.31	75.62 ± 19.74	0.99 (0.98–1.00)	**.01**
Functioning scales				
Physical functioning	81.96 ± 20.76	85.10 ± 17.39	0.99 (0.98–1.00)	.15
Role functioning	83.80 ± 26.22	78.29 ± 26.65	1.01 (1.00–1.02)	**.02**
Emotional functioning	70.45 ± 23.75	79.95 ± 19.27	0.98 (0.97–0.99)	**<.001**
Cognitive functioning	90.70 ± 15.58	84.67 ± 19.12	1.02 (1.01–1.03)	**.001**
Social functioning	89.69 ± 17.68	85.71 ± 21.64	1.01 (1.00–1.02)	**.03**

Note: Statistical test: univariate logistic regression analysis. Being member of the HNC cohort is defined as dependent variable.

Abbreviations: ADL, Activities of Daily Living; CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-core module; GFI, Groningen Frailty Indicator; HNC, head and neck cancer; IADL, Instrumental Activities of Daily Living; MMSE: Mini-Mental State Examination; OR, odds ratio; SO, surgical oncology; TUG, Timed Up and Go.

Significant *p*-values are indicated in bold

[a]mean ± *SD*.

the EORTC, with higher scores indicating a high degree of functioning (Aaronson et al., 1993; Fayers et al., 2001; Pottel et al., 2014).

2.5 | 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

TABLE 3 Overview of questionnaires and assessments used, with their 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 and Go (TUG)	Mobility	0–∞ s	≥20 s: impaired mobility
EORTC QLQ-C30	Quality of life	0–100	n/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.

3 | RESULTS

3.1 | 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.

3.2 | Frailty, geriatric assessment and QoL 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.

3.3 | 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.

4 | 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

TABLE 4 Patient, disease, geriatric assessment and QoL characteristics of patients in the HNC and SO cohorts

Variables	OR (95% CI)	*p*-value
Sex		
Female	1	
Male	3.50 (2.00–6.12)	**<.001**
BMI		
<25	1	
≥25	0.37 (0.22–0.62)	**<.001**
MMSE		
Good cognitive functioning	1	
Restricted cognitive functioning	20.03 (2.44–164.31)	**.005**
TUG		
Good mobility	1	
Restricted mobility	11.56 (1.86–71.68)	**.009**
EORTC QLQ-C30		
Global QoL scale	0.98 (0.97–1.00)	**.04**
Functioning scales		
Physical functioning	0.98 (0.96–1.00)	.05
Role functioning	1.03 (1.01–1.04)	**.002**
Emotional functioning	0.96 (0.95–0.98)	**<.001**
Cognitive functioning	1.04 (1.02–1.06)	**<.001**
Social functioning	1.02 (1.00–1.04)	.06

Note: Statistical test: multivariate logistic regression analysis adjusted for age. Being member of the HNC cohort is defined as dependent variable.

Abbreviations: BMI, body mass index; CI, confidence interval; EORTC QLQ-C30; European Organization for Research and Treatment of Cancer QoL Questionnaire-core module; MMSE, Mini-Mental State Examination; OR, odds ratio; SO, surgical oncology; TUG, Timed Up and Go.

Significant *p*-values are indicated in bold

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 postoperative 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.

5 | 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.

CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

ORCID

Linda Bras https://orcid.org/0000-0003-4315-5662
Bernard F. A. M. Laan https://orcid.org/0000-0002-5016-2871
Barbara L. Leeuwen https://orcid.org/0000-0002-6745-4424
Geertruida H. Bock https://orcid.org/0000-0003-3104-4471
Gyorgy B. Halmos https://orcid.org/0000-0003-2460-2260

REFERENCES

Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., … Takeda, F. (1993). The european organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute*, *85*(5), 365–376. https://doi.org/10.1093/jnci/85.5.365

American Joint Committee on Cancer (AJCC) (2010). *What is cancer staging?*. Retrieved from https://cancerstaging.org/references-tools/Pages/What-is-Cancer-Staging.aspx. Accessed 30/11, 2017.

Bøje, C. R., Dalton, S. O., Primdahl, H., Kristensen, C. A., Andersen, E., Johansen, J., … Overgaard, J. (2014). Evaluation of comorbidity in 9388 head and neck cancer patients: A national cohort study from the DAHANCA database. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology*, *110*(1), 91–97. https://doi.org/10.1016/j.radonc.2013.11.009

Bras, L., Peters, T., Wedman, J., Plaat, B., Witjes, M., van Leeuwen, B. L., … Halmos, G. B. (2015). Predictive value of the groningen frailty indicator for treatment outcomes in elderly patients after head and neck, or skin cancer surgery in a retrospective cohort. *Clinical Otolaryngology: Official Journal of ENT-UK; Official Journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery*, *40*(5), 474–482. https://doi.org/10.1111/coa.12409

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases*, *40*(5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8

Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people. *Lancet (London, England)*, *381*(9868), 752–762. https://doi.org/10.1016/S0140-6736(12)62167-9

Cull, A., Hay, C., Love, S. B., Mackie, M., Smets, E., & Stewart, M. (1996). What do cancer patients mean when they complain of concentration and memory problems? *British Journal of Cancer*, *74*(10), 1674–1679. https://doi.org/10.1038/bjc.1996.608

Derks, W., de Leeuw, R. J., & Hordijk, G. J. (2005). Elderly patients with head and neck cancer: The influence of comorbidity on choice of therapy, complication rate, and survival. *Current Opinion in Otolaryngology & Head and Neck Surgery*, *13*(2), 92–96. 00020840-200504000-00004

Extermann, M., & Hurria, A. (2007). Comprehensive geriatric assessment for older patients with cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *25*(14), 1824–1831.

Fayers, P. M., Aaronson, N. K., Bjordal, K., Groenvold, M., Curran, D., Bottomley A., … on behalf of the EORTC Quality of Life Group (2001). *The EORTC QLQ-C30 scoring manual* (3rd edition). Brussels: European organisation for research and treatment of cancer.

Fougere, B., Daumas, M., Lilamand, M., Sourdet, S., Delrieu, J., Vellas, B., & Abellan van Kan, G. (2017). Association between frailty and cognitive impairment: Cross-sectional data from toulouse frailty day hospital. *Journal of the American Medical Directors Association*, *18*(11), 990.e1–990.e5. S1525-8610(17)30367-5

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *59*(3), 255–263. https://doi.org/10.1093/gerona/59.3.M255

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

Graf, C. (2009). The lawton instrumental activities of daily living (IADL) scale. *Medsurg Nursing: Official Journal of the Academy of Medical-Surgical Nurses*, *18*(5), 315–316.

Habbous, S., Harland, L. T. G., La Delfa, A., Fadhel, E., Xu, W., Liu, F.-F., … Liu, G. (2014). Comorbidity and prognosis in head and neck cancers: Differences by subsite, stage, and human papillomavirus status. *Head & Neck*, *36*(6), 802–810. https://doi.org/10.1002/hed.23360

Halmos, G. B., Bras, L., Siesling, S., van der Laan, B. F. A. M., Langendijk, J. A., & van Dijk, B. A. C. (2018). Age-specific incidence and treatment patterns of head and neck cancer in the netherlands-A cohort study. *Clinical Otolaryngology: Official Journal of ENT-UK; Official Journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery*, *43*(1), 317–324. https://doi.org/10.1111/coa.12991

Hamaker, M. E., Jonker, J. M., de Rooij, S. E., Vos, A. G., Smorenburg, C. H., & van Munster, B. C. (2012). Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: A systematic review. *The Lancet. Oncology*, *13*(10), e437–e444. https://doi.org/10.1016/S1470-2045(12)70259-0

Huisman, M. G., van Leeuwen, B. L., Ugolini, G., Montroni, I., Spiliotis, J., Stabilini, C., … Audisio, R. A. (2014). "Timed up & go": A screening tool for predicting 30-day morbidity in onco-geriatric surgical patients? *A Multicenter Cohort Study. Plos One*, *9*(1), e86863. https://doi.org/10.1371/journal.pone.0086863

Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., & Jaffe, M. W. (1963). Studies of illness in the aged: The index of ADL: A standardized measure of biological and psychosocial function. *JAMA*, *185*(12), 179–186. https://doi.org/10.1093/geront/9.3_Part_1.179

Kenig, J., Olszewska, U., Zychiewicz, B., Barczynski, M., & Mitus-Kenig, M. (2015). Cumulative deficit model of geriatric assessment to predict the postoperative outcomes of older patients with solid abdominal cancer. *Journal of Geriatric Oncology*, *6*(5), 370–379. https://doi.org/10.1016/j.jgo.2015.03.004

Klepstad, P., Hilton, P., Moen, J., Fougner, B., Borchgrevink, P. C., & Kaasa, S. (2002). Self-reports are not related to objective assessments of cognitive function and sedation in patients with cancer pain admitted to a palliative care unit. *Palliative Medicine*, *16*(6), 513–519. https://doi.org/10.1191/0269216302pm587oa

Kojima, G., Iliffe, S., Jivraj, S., Liljas, A., & Walters, K. (2018). Does current smoking predict future frailty? the english longitudinal study of ageing. *Age and Ageing*, *47*(1), 126–131. https://doi.org/10.1093/ageing/afx136

Kojima, G., Jivraj, S., Iliffe, S., Falcaro, M., Liljas, A., & Walters, K. (2019). Alcohol consumption and risk of incident frailty: The english longitudinal study of aging. *Journal of the American Medical Directors Association*, *20*(6), 725–729. S1525-8610(18)30584-X

Kojima, G., Liljas, A., Iliffe, S., Jivraj, S., & Walters, K. (2018). A systematic review and meta-analysis of prospective associations between alcohol consumption and incident frailty. *Age and Ageing*, *47*(1), 26–34. https://doi.org/10.1093/ageing/afx086

Kurkcu, M., Meijer, R. I., Lonterman, S., Muller, M., & de van der Schueren, M. (2018). The association between nutritional status and frailty characteristics among geriatric outpatients. *Clinical Nutrition ESPEN*, *23*, 112–116. S2405-4577(17)30241-3

Libert, Y., Dubruille, S., Borghgraef, C., Etienne, A.-M., Merckaert, I., Paesmans, M., … Razavi, D. (2016). Vulnerabilities in older patients when cancer treatment is initiated: Does a cognitive impairment impact the two-year survival? *PLoS ONE*, *11*(8), e0159734. https://doi.org/10.1371/journal.pone.0159734

Maasland, D. H., van den Brandt, P. A., Kremer, B., Goldbohm, R. A., & Schouten, L. J. (2014). Alcohol consumption, cigarette smoking and the risk of subtypes of head-neck cancer: Results from the netherlands cohort study. *BMC Cancer*, *14*, 187–2407-14-187. https://doi.org/10.1186/1471-2407-14-187

Macuco, C. R., Batistoni, S. S., Lopes, A., Cachioni, M., da Silva Falcao, D. V., Neri, A. L., & Yassuda, M. S. (2012). Mini-mental state examination performance in frail, pre-frail, and non-frail community dwelling older adults in ermelino matarazzo, sao paulo, brazil. *International*

Psychogeriatrics, *24*(11), 1725–1731. https://doi.org/10.1017/S1041610212000907

Metzelthin, S. F., Daniels, R., van Rossum, E., de Witte, L., van den Heuvel, W. J., & Kempen, G. I. (2010). The psychometric properties of three self-report screening instruments for identifying frail older people in the community. *BMC Public Health*, *10*, 176–2458-10-176. https://doi.org/10.1186/1471-2458-10-176

Mystakidou, K., Tsilika, E., Parpa, E., Galanos, A., & Vlahos, L. (2007). Brief cognitive assessment of cancer patients: Evaluation of the mini-mental state examination (MMSE) psychometric properties. *Psycho-Oncology*, *16*(4), 352–357. https://doi.org/10.1002/pon.1090

Nesic, V. S., Petrovic, Z. M., Sipetic, S. B., Jesic, S. D., Soldatovic, I. A., & Kastratovic, D. A. (2012). Comparison of the adult comorbidity evaluation 27 and the charlson comorbidity indices in patients with laryngeal squamous cell carcinoma. *The Journal of Laryngology and Otology*, *126*(5), 516–524. https://doi.org/10.1017/S0022215112000254

Netherlands Comprehensive Cancer Organisation (IKNL©) (2017). *The netherlands cancer registry*. Retrieved from http://www.cijfersoverkanker.nl/.

Nieman, C. L., Pitman, K. T., Tufaro, A. P., Eisele, D. W., Frick, K. D., & Gourin, C. G. (2018). The effect of frailty on short-term outcomes after head and neck cancer surgery. *The Laryngoscope*, *128*(1), 102–110. https://doi.org/10.1002/lary.26735

Noor, A., Gibb, C., Boase, S., Hodge, J. C., Krishnan, S., & Foreman, A. (2018). Frailty in geriatric head and neck cancer: A contemporary review. *The Laryngoscope*, *128*(12), E416–E424. https://doi.org/10.1002/lary.27339

Osoba, D., Rodrigues, G., Myles, J., Zee, B., & Pater, J. (1998). Interpreting the significance of changes in health-related quality-of-life scores. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *16*(1), 139–144. https://doi.org/10.1200/JCO.1998.16.1.139

Peters, L. L., Boter, H., Buskens, E., & Slaets, J. P. (2012). Measurement properties of the groningen frailty indicator in home-dwelling and institutionalized elderly people. *Journal of the American Medical Directors Association*, *13*(6), 546–551. https://doi.org/10.1016/j.jamda.2012.04.007

Peters, T. T. A., van der Laan, B. F. A. M., Plaat, B. E. C., Wedman, J., Langendijk, J. A., & Halmos, G. B. (2011). The impact of comorbidity on treatment-related side effects in older patients with laryngeal cancer. *Oral Oncology*, *47*(1), 56–61. https://doi.org/10.1016/j.oraloncology.2010.10.016

Plas, M., Rotteveel, E., Izaks, G. J., Spikman, J. M., van der Wal-Huisman, H., van Etten, B., … van Leeuwen, B. L. (2017). Cognitive decline after major oncological surgery in the elderly. *European Journal of Cancer*, *8049*(17), 394–402. https://doi.org/10.1016/j.ejca.2017.09.024

Podsiadlo, D., & Richardson, S. (1991). The timed "up & go": A test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society*, *39*(2), 142–148.

Porceddu, S. V., & Haddad, R. I. (2017). Management of elderly patients with locoregionally confined head and neck cancer. *The Lancet. Oncology*, *18*(5), e274–e283. S1470-2045(17)30229-2

Pottel, L., Lycke, M., Boterberg, T., Pottel, H., Goethals, L., Duprez, F., … Debruyne, P. R. (2014). Serial comprehensive geriatric assessment in elderly head and neck cancer patients undergoing curative radiotherapy identifies evolution of multidimensional health problems and is indicative of quality of life. *European Journal of Cancer Care*, *23*(3), 401–412. https://doi.org/10.1111/ecc.12179

Reisinger, K. W., van Vugt, J. L. A., Tegels, J. J. W., Snijders, C., Hulsewé, K. W. E., Hoofwijk, A. G. M., … Poeze, M. (2015). Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Annals of Surgery*, *261*(2), 345–352. https://doi.org/10.1097/SLA.0000000000000628

Savva, G. M., Donoghue, O. A., Horgan, F., O'Regan, C., Cronin, H., & Kenny, R. A. (2013). Using timed up-and-go to identify frail members of the older population. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *68*(4), 441–446. https://doi.org/10.1093/gerona/gls190

Schuurmans, H., Steverink, N., Lindenberg, S., Frieswijk, N., & Slaets, J. P. (2004). Old or Frail: What Tells Us More? *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *59*(9), M962–M965.

Steverink, N., Slaets, J., Schuurmans, H., & van Lis, M. (2001). Measuring frailty: Developing and testing the GFI (groningen frailty indicator). *Gerontologist*, *41*, 236–237.

Teymoortash, A., Ferlito, A., & Halmos, G. B. (2016). Treatment in elderly patients with head and neck cancer: A challenging dilemma. *Hno*, *64*(4), 217–220. https://doi.org/10.1007/s00106-016-0138-6

Theou, O., Rockwood, M. R., Mitnitski, A., & Rockwood, K. (2012). Disability and co-morbidity in relation to frailty: How much do they overlap? *Archives of Gerontology and Geriatrics*, *55*(2), e1–8. https://doi.org/10.1016/j.archger.2012.03.001

van der Cammen, T., van Harskamp, F., Stronks, D., Passchier, J., & Schudel, W. (1992). Value of the mini-mental state examination and informants' data for the detection of dementia in geriatric outpatients. *Psychological Reports*, *71*(3 pt 1), 1003–1009. https://doi.org/10.2466/pr0.1992.71.3.1003

van der Schroeff, M. P., Derks, W., Hordijk, G. J., & de Leeuw, R. J. (2007). The effect of age on survival and quality of life in elderly head and neck cancer patients: a long-term prospective study. *European Archives of Oto-Rhino-Laryngology*, *264*(4), 415–422. https://doi.org/10.1007/s00405-006-0203-y

van Deudekom, F. J., Schimberg, A. S., Kallenberg, M. H., Slingerland, M., van der Velden, L. A., & Mooijaart, S. P. (2017). Functional and cognitive impairment, social environment, frailty and adverse health outcomes in older patients with head and neck cancer, a systematic review. *Oral Oncology*, *64*, 27–36. S1368-8375(16)30219-6

van Leeuwen, B. L., Huisman, M. G., & Audisio, R. A. (2013). Surgery in older cancer patients - recent results and new techniques: Worth the investment? *Interdisciplinary Topics in Gerontology*, *38*, 124–131. https://doi.org/10.1159/000343582

VMSzorg,, (2009). *Praktijkgids kwetsbare ouderen*. Retrieved from https://www.vmszorg.nl/wp-content/uploads/2017/11/web_2009.0104_praktijkgids_kwetsbare_ouderen.pdf.

Weerink, L. B. M., van Leeuwen, B. L., Gernaat, S. A. M., Absalom, A. R., Huisman, M. G., van der Wal- Huisman, H., … de Bock, G. H. (2018). Vitamin status and the development of postoperative cognitive decline in elderly surgical oncologic patients. *Annals of Surgical Oncology*, *25*(1), 231–238. https://doi.org/10.1245/s10434-017-6118-6

How to cite this article: Bras L, Driessen DAJJ, de Vries J, et al. Patients with head and neck cancer: Are they frailer than patients with other solid malignancies? *Eur J Cancer Care*. 2019;00:e13170. https://doi.org/10.1111/ecc.13170