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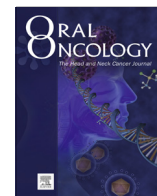
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Review

Functional and cognitive impairment, social environment, frailty and adverse health outcomes in older patients with head and neck cancer, a systematic review



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ABSTRACT

Objectives: Older head and neck cancer patients are at increased risk for adverse health outcomes, but little is known about which geriatric assessment associates with poor outcome. The aim is to study the association of functional or cognitive impairment, social environment and frailty with adverse health outcomes in patients with head and neck cancer.

Methods: Four libraries were searched for studies reporting on an association of functional or cognitive impairment, social environment and frailty with adverse outcomes in head and neck cancer patients.

Results: Of 4158 identified citations, 31 articles were included. The mean age was ≥ 60 years in twelve studies (39%). Geriatric conditions were prevalent: between 40 and 50% of the included participants were functional impaired, around 50% had depressive symptoms, and around 40% did not have a partner. Functional impairment was assessed in 18 studies, two studies reported on a cognitive test, eight studies examined mood and social status was depicted by 14 studies. None of the included studies addressed frailty or objectively measured physical capacity such as hand grip strength, gait speed or balance tests. In 64% of the reported associations, a decline in functional or cognitive impairment, mood or social environment was associated with adverse outcomes.

Conclusion: Functional and cognitive impairment, depressive symptoms and social isolation are highly prevalent in head and neck cancer patients and associate with high risk of adverse health outcomes. In the future, these measurements may guide decision-making and customize treatments, but more research is needed to further improve and firmly establish clinical usability.

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Introduction

With population ageing there will be an increasing number of older patients with cancer. This trend can also be observed in the patient population presenting with head and neck cancer. In the USA, it is estimated that between 2010 and 2030 the incidence of oral cavity and pharyngeal cancer in people aged 65 years and over

will approximately increase from 19,000 patients in 2010 to 31,000 patients in 2030. This would be an increase with more than 60% [1]. Older patients are very heterogenic with respect to functional capacity, cognitive functioning, mobility and frailty, therefore it remains challenging to identify older patients who are at highest risk for adverse health outcomes such as delirium, side-effects, prolonged length of hospital stay, reduced quality of life or mortality. Besides, head and neck cancer patients have a severe prognosis with an estimation of 50% after 5 years with large variations across tumor sites [2,3]. However, the prognostic value of functional capacity, cognitive functioning, mobility and frailty to assist clinical decision making in older head and neck cancer patients has not been systematically evaluated.

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Head and neck cancer patients have a high prevalence of previous excessive alcohol drinking and smoking [4–6] putting this group at high risk for deterioration in functional [7] and cognitive decline [6,8]. Previously identified risk predictors in older patients with head and neck cancer are the burden of comorbidities [9] and nutritional status [10,11]. A recent review concluded that there was strong evidence for a positive association of pre-treatment physical functioning with survival and change in global quality of life [12]. But, with regard to other HRQoL domains (emotional, cognitive and social functioning) there was insufficient evidence. In other fields of geriatric medicine the value of measures of functional capacity, cognitive functioning, the role of social environment and frailty [13–15], has been firmly established, but these have not been reviewed for older patients with head and neck cancer.

Therefore, the aim of this present systematic review is to study the association of functional or cognitive impairment, social environment and frailty with adverse health outcomes in patients with head and neck cancer.

Methods

Search strategy

We aimed to identify original longitudinal studies in head and neck cancer patients in which the association between a measurement of functional and cognitive impairment, social environment or frailty prior to treatment initiation and adverse health outcome after follow-up was examined. A head and neck tumor was defined as cancers in the sinonasal, nasopharyngeal, oral, oropharyngeal, hypopharyngeal, supraglottic, glottis, subglottic regions or laryngeal cancer. Since the etiologic, risk factors and treatment for skin tumors and thyroid cancer are different from mucosal tumors, skin tumors and thyroid cancers were not included in the search. As baseline measurement we assessed the presence of functional impairment (including assessment of functional performance, mobility, and objectively measured physical capacity such as hand grip strength, gait speed or balance tests), cognitive impairment (including assessment of cognition, dementia diagnosis, and mood or depression), social environment (living situation, social support and marital status) and frailty (the use of a frailty index or instrument such as Fried Frailty Phenotype or the Groningen Frailty Indicator). We assessed adverse health outcomes as mortality, functional or cognitive decline, adverse events during or after treatment (such as side-effects or delirium), prolonged length of hospital stay (LOS) and health related quality of life (HRQoL) of global quality of life (QoL) after follow-up.

On April 28th 2016, we searched four electronic bibliographic databases (PubMed, Embase, Web of Science and the Cochrane Library) using synonyms of head and neck cancer, combined with synonyms of the different domains of geriatric assessment. No limits in age were applied. For full Medline search, see Supplemental Material A.

Article selection

The eligibility of all studies identified by the search was independently evaluated by two of the authors (F.v.D. and A.S.). Of any article that seemed potentially relevant based on title and abstract, full text was retrieved and screened. Studies were included if the full text contained original data reporting on an association between any geriatric measure at baseline and outcome after follow-up in head and neck cancer patients in a longitudinal study design. In case of disagreement between the two authors (F.v.D., A.S.), consensus was reached after discussion with

two other co-authors (S.P.M., L.vd.V.). The reference list of the included publications was used for cross-referencing to ensure we identified all relevant articles.

Data extraction and quality assessment

Items extracted from each study included: publication data (author, year), study design and setting, patient characteristics (sample size, mean age, treatment modality), tumor type and tumor site measurement of functional or cognitive impairment, social environment or frailty, follow up duration, outcome measure and results of the association functional and cognitive impairment, social environment and frailty with adverse health outcome. Treatment modality can include therapy with a curative intent such as surgery, radiation therapy, chemoradiation (or as a combination) or with no curative intent such as chemotherapy, and also no treatment with palliative intent was taken into account as a treatment modality. To assess the methodological quality and risk of bias of the included studies, we adapted the Newcastle-Ottawa scale [16] to the purpose of this review (Supplemental Material B). In case of disagreement between the two authors (F.v.D., A.S.) with regards to data extraction or quality assessment, consensus was reached after discussion with the other two co-authors (S.P.M., L.vd.V.).

Data presentation

Study characteristics are tabulated per individual study. Accumulated descriptives of the selected studies are presented by calculating the proportion of studies reporting on measurement of functional or cognitive impairment, social environment or frailty, endpoints or treatment modalities. Sample size aggregate of the included studies is expressed as median- and interquartile range (IQR), calculated with SPSS software version 20. Main findings with respect to the association of measurement of functional or cognitive impairment, social environment or frailty with outcome are tabulated. In case the hazard ratios (HR), odds ratios (OR) and relative risk (RR) are at least adjusted for age in the multivariate analysis this is mentioned as aHR, aOR and aRR. If studies are adjusted for other factors than age, this is reported in the abbreviations.

Results

Search results and study selection

The database searches identified 4158 unique citations (Fig. 1). After the initial screening of title and abstract, 106 articles were considered potentially eligible. After full-text review, another 76 were excluded; the remaining 30 articles were included. Cross referencing yielded one additional relevant article, which resulted in a total of 31 studies that were included in the present review.

Study characteristics

Table 1 shows an overview of the study characteristics of the 31 included studies. The median sample size of all 31 studies included was 306 (IQR 124–600) and the mean age was over 60 years in twelve studies (39%). Twenty-one studies (68%) were conducted in Europe, the United States or Canada. Most studies consisted of head and neck cancer patients with various cancer types and locations combined, six studies included patients with a specific kind of tumor, five studies had specific inclusion criteria such as stage III/IV or (locally) advanced cancer and six studies included only one treatment modality. Only three studies focused exclusively on older patients and included age ≥ 70 years in their study population [17–19]. Several studies used specific exclusion criteria: four

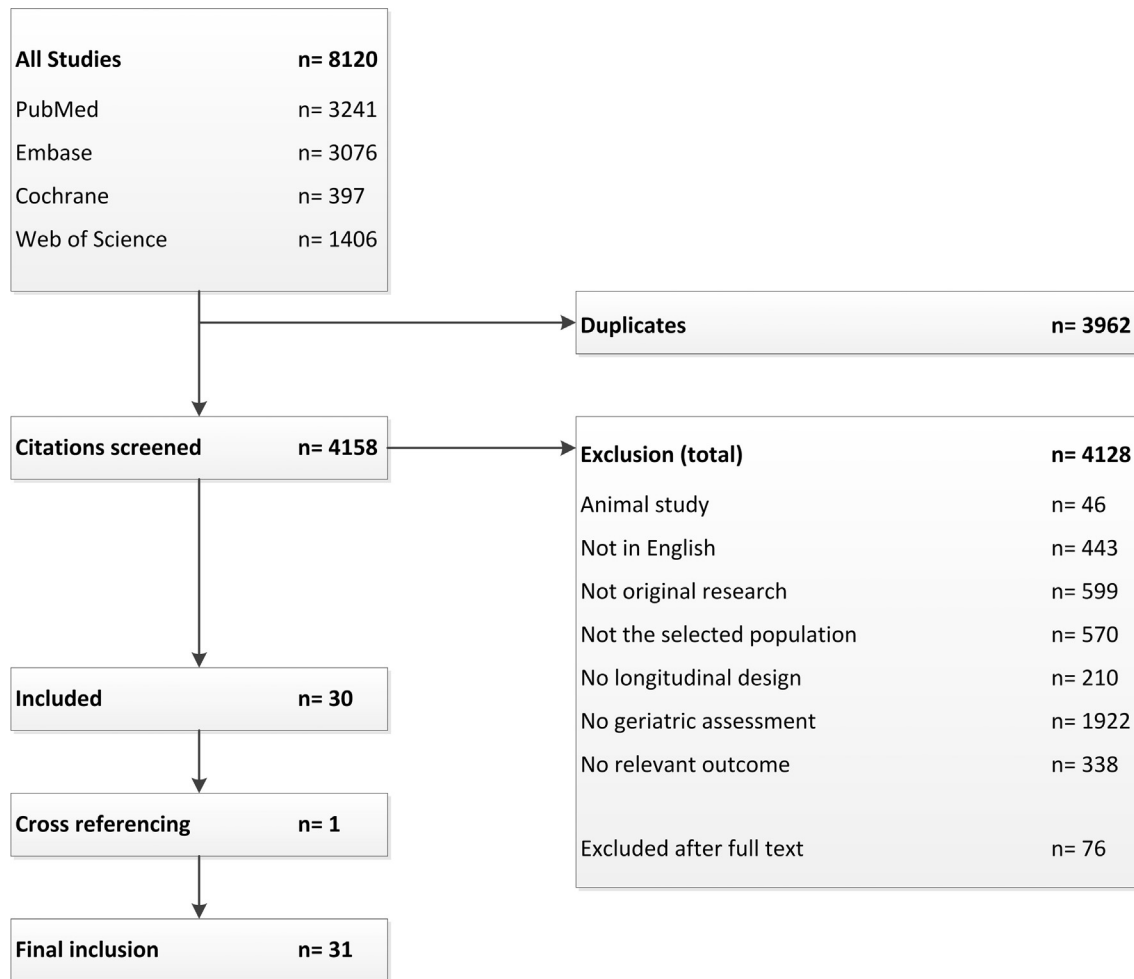


Fig. 1. Flowchart.

excluded patients with cognitive impairment, five excluded specific cut off for age, such as excluding aged over 70, 75 or 80 years, some functional impairment (n = 3) or patients with no curative intent (n = 8).

Table 2 shows an overview of the associations of measures of functional or cognitive impairment, social environment and frailty with adverse health outcomes after follow up. The thirty-one studies reported on a total of 45 associations. Functional impairment was assessed in 18 studies, there were two studies reporting on a cognitive test, eight studies examined depressive symptoms and social status was studied in 14 studies. None of the studies addressed frailty or objectively measured physical capacity (such as hand grip strength, gait speed or balance tests). Survival (overall, total or disease specific survival) was the main outcome of interest in 21 studies (68%), the remaining studies assessed quality of life (global or health related, 19%), side effects (7%), the development of post-treatment delirium (7%) or prolonged length of stay in the hospital (7%). No studies were found reporting on cognitive or functional decline after treatment for head and neck cancer. Of the 45 reported associations, twenty-nine times (64%) a decline in functional or cognitive performance, mood or social environment was associated with an increased risk of one of the adverse outcomes (Fig. 2).

Functional impairment

Functional performance was assessed in 18 studies, mostly using the Eastern Cooperative Oncology Group Scale (ECOG-scale,

6 studies) [19–24], or the Karnofsky Performance Score (KPS, 8 studies) [17,18,25–30]. Functional impairment was prevalent in most studies. For instance, the largest study of Siddiqui et al., included 1093 patients and 517 (47%) had a KPS between 60 and 80, indicating patients were not able to work or need some help with daily care. Functional impairment was associated with increased risk of adverse outcomes in 12 out of 18 studies (67%). Functional performance was found to be associated with (overall) survival in 9 out of 12 studies (75%) [18,20,21,23,25,27,29–31]. Siddiqui et al. and found that KPS (90–100 vs 60–80) was an independent prognostic factor for overall survival (aHR 1.51 (95% CI 1.27–1.79)).

Cognitive impairment

There were only two articles that reported on the association between cognitive status and adverse health outcome. Shah et al. reported a prevalence of cognitive impairment of 5%, defining pre-existing cognitive impairment as any history or physical findings of stroke, transient ischemic attack or dementia [32]. The outcome measured was the development of a postoperative delirium, and 11 out of 39 patients with cognitive impairment developed a postoperative delirium (28%). Pre-existing cognitive impairment was significant correlated with a postoperative delirium (aHR 3.83 (95% CI 1.70–8.63)). Weed et al. measured cognitive function using the Folstein Mini-Mental State questionnaire (MMS) [34]. In this study 24 out of 138 patients (17%) developed a postoperative delirium, and these 24 patients had a mean MMS-score of 26.3

Table 1
Characteristics of included studies.

Publication		Patients		Study population		
Author	Publication year	Number of patients	Age, yr (mean)	Tumor characteristics	Exclusion criteria	Treatment modality*
Aarstad [39]	2005	79	59.9	SCC (maxilla, oral cavity, pharynx and larynx)	Not able to answer questions, aged >80, KPS <75, female	NA
Barber [38]	2015	71	59.7	Mucosal squamous cell carcinoma, salivary gland tumors and skin cancer	Pre-existing psychiatric history, not able to read or complete questionnaires, not able to give consent, not willing to complete follow-up	S, C
Borggreven ¹ [46]	2007	80	58	Advanced SCC of the oral cavity or oropharynx	>75 year, cognitive impairment, not speaking Dutch	S with or without RTx
Epstein [48]	2005	573	62.4	Oropharyngeal cancer	No exclusion criteria available	NA
Fang [25]	2004	102	52.6 ^e	Stage III or IV head and neck cancer of the oral cavity, oropharynx, hypopharynx or larynx	Recurrent malignancies, synchronous malignancies, not able to complete QOL questionnaire	RTx with or without C
Gerude [17]	2014	67	78 ^e	SCC of upper aerodigestive tract	≤74 year, unable to walk, unable to answer questions due to hearing, cognitive or speech deficits, impossibility anthropometric measurements	S
de Graeff [26]	2001	208	60	SCC of the oral cavity, oropharynx, hypopharynx or larynx	≥80 year, recurrent malignancies, synchronous malignancies, cognitive impairment, not speaking Dutch, no curative intent	S, RTx or combination
Hall [20]	2009	856	46.3 ^a	SCC of the hypopharynx	No exclusion criteria available	S, RTx, C or combination
Hammerlid [35]	2001	232	61	Primary head and neck cancer (larynx, oral cavity, pharyngeal and other)	Not able to answer question due to cognitive impairment, mental disturbance or severe disease	S, RTx, CRTx or combination
Howren [36]	2010	306	60	Upper aerodigestive tract carcinoma (oral cavity, pharynx, larynx or other)	No exclusion criteria available	S, RTx or combination
Howren [47]	2013	364	59.6	Upper aerodigestive tract carcinoma (oral cavity, pharynx, larynx or other)	No exclusion criteria available	S, RTx or combination
Hsieh [21]	2011	151	NA	SCC of the head and neck (oral, oropharynx, hypopharynx and larynx)	Nasopharyngeal cancer, medical conditions associated with leucocytosis and thrombocytosis, anaemia, metastatic cancer, non-head and neck SCC	NA
Karvonen [40]	2008	495	58.4	Head and neck cancer of the upper aerodigestive tract	Pregnancy, <18 years, not speaking English, recurrent tumor	S, RTx, C or combination
Kim [41]	2015	241	61 [§]	SCC of the oral cavity, oropharynx, larynx or hypopharynx	No curative intent, distant metastasis, recurrent tumor, aged <18 or >80 years	S, RTx, C or combination
Konski [‡] [27]	2003	1073	NA	Locally advanced SCC (oral cavity, oropharynx, hypopharynx and supraglottic) of head and neck	No exclusion criteria available	RTx
Lotfi [28]	2008	258	57.7	Head and neck malignant neoplasm (mouth/lip/submandibular gland, oropharynx, larynx, hypopharynx)	No curative intent	S
Mell [22]	2010	479	56.2	Stage III-IV carcinoma (oropharynx, larynx, hypopharynx, oral cavity, nasopharynx and other) of the head and neck	No exclusion criteria available	CRTx, C or S
Oskam ¹ [42]	2010	80	58	Advanced SCC of the oral cavity or oropharynx	≥75 year, serious cognitive impairment, not speaking Dutch	S with or without RTx
Osthus [45]	2013	106	61	SCC (laryngeal, oral cavity or oropharyngeal) of the head and neck	≥78 year, cognitive impairment, no curative intent	S, C, or RTx
Pedruzzi [31]	2008	361	57	Primary SCC of the oropharynx	Distant metastasis	RTx with or without C
Ronis [37]	2008	316	58.6	SSC (oral cavity, pharynx, larynx, oropharynx and nasopharynx)	Pregnancy, <18 years, not speaking English or mentally unstable	S, C, or RTx
Sadat [29]	2012	169	NA	SCC (oral cavity, oropharynx, hypopharynx, and larynx) of the head and neck	Operable SCC	RTx or CRTx
Sanabria [18]	2007	310	76	Head and neck cancer (larynx, oral cavity, oropharynx and hypopharynx)	<70 year, no curative intent, distant metastasis, recurrent disease, surgery for thyroid cancer, skin cancer or melanoma, orbit tumors	S, RTx or combination
Shah [32]	2012	774	63	SCC of the head and neck	No exclusion criteria available	S
Siddiqui [‡] [30]	2008	1093	NA	Several different cancers in two cohort-studies	No exclusion criteria available	RTx, C, S
Sze [19]	2012	990	74 [§]	Nasopharyngeal carcinoma	Palliative treatment, disseminated disease	RTx with or without C

Table 1 (continued)

Publication		Patients		Study population		
Author	Publication year	Number of patients	Age, yr (mean)	Tumor characteristics	Exclusion criteria	Treatment modality [*]
Tarsitano [43]	2012	124	60	SSC of the oral cavity	Recurrent disease, palliative treatment	S with or without RTx
Urba [23]	2012	704	57.7	SCC (hypopharynx, larynx, oral cavity or oropharynx) head and neck cancer	Performance score \geq 3, abnormal liver/kidney function, <18 year, recurrent or metastatic cancer	C
Wang [24]	2015	600	62.3	Primary SCC of the oral cavity, oropharynx, larynx or hypopharynx	No SCC, unknown primary, treatment with palliative intent	S, RTx, C or combination
Weed [34]	1995	138	64	All kinds of head and neck cancer needing major surgery	No exclusion criteria available	S
Wong [44]	2006	1010	51.7	Oral cancer (lip, mouth floor, tongue, gingiva, buccal mucosa, palate, retromolar trigone, palatine tonsil, tongue base, and posterior pharyngeal wall)	No pathological rapport, treated at other institute, no complete therapeutic protocol, inadequate chart records	S with or without RTx, C, CRTx

^{*} Abbreviations: C = chemotherapy, CRTx = chemoradiation, RTx = radiotherapy, S = surgery, SCC = squamous cell carcinoma, NA = not available.

[†] Both studies used the same cohort.

[‡] Studies conducted partly on same trial, Siddiqui et al. used partly the same patients (n = 689) as Konski et al.

[§] Median.

[¶] by approach, calculated from data.

[34]. In this small sample size, there was no association reported of cognitive status measured by the Folstein Mini-Mental State questionnaire with the development of postoperative delirium.

Eight studies examined depression by using five different types of inventories using different scales. The study of Ronis et al., assessed depression by using the GDS-SF and 156 of 316 patients (49%) had significant depressive symptoms at baseline, and about the same prevalence was found in other studies. Five out of eight studies (62.5%) found a significant association of depression with an increased risk of one of the adverse health outcomes. In four studies assessing depressive symptoms was found that depressive symptoms at baseline were associated with lower global/health related quality of life after follow-up [35–38]. Depressive symptoms at baseline were a significant predictor of a negative change in HRQoL one year after diagnosis (adjusted for age $p \leq 0.05$, no estimation reported). The association of mood/depression and survival as outcome is inconsistent. One study [39] found that depression, measured by Beck Depression Inventory (BDI), at baseline predicts overall survival (aHR 1.13; $p = 0.03$) and disease specific survival (aHR 1.19; $p < 0.001$). On the other hand Karvonen-Gutierrez et al. measured depression by the Geriatric Depression Scale Short Form (GDS-SF) and found that this was no significant prognostic factor for overall survival (HR 1.30 (95% CI 0.98–1.73)) [40] and also Kim et al. found that pre-treatment depression was not significant predictive for three-year overall survival (aHR 1.52 (95% CI 0.82–281)) [41].

Social environment

Fourteen studies examined social environment and this was mostly assessed by marital status (34%) and living situation (10%), one study used Social Provision Scale (SPS). Around 35% of the participants did not have a (married) partner. Ten out of fourteen studies (71%) found an association of social environment with one of the outcomes. Six studies found that marital status (not married or not having a partner) was associated with a worse overall survival [26,30,40,42–44] and two studies did not find an association [25,45]. The quality of life after 3, 6 or 12 months was lower in patients who did not have a partner compared to patients who did have a partner [46,47]. There was only one study assessing the living situation with overall survival, this study found that patients living dependently had a higher risk for a reduced overall

survival (aRR 2.33, $p \leq 0.001$) and disease specific survival (aRR2.16, $p \leq 0.001$) [48].

Quality assessment

The overall study quality assessed by the modified Newcastle-Ottawa scale was moderate (Table 3). Overall there were some concerns regarding the validity of the selection, the determination of outcome or reporting of the duration of follow up. The greatest concern with a majority of the studies was the representativeness of the study population, as 14 studies (48%) examined the association between a geriatric measure at baseline with outcome in a selected population in which only one kind of tumor, one kind of treatment modality or treatment intent was used. Furthermore, in several studies a risk of selection bias persisted because of various reasons: excluding older patients, cognitive impaired patients or with a restriction on the functional performance [17,26,27,30,35,37,39,41,42,45,46].

Discussion

In the present systematic review, we identified 31 articles reporting on the association of functional or cognitive impairment, social environment or frailty with adverse outcomes in patients with head- and neck cancer. There were three main findings: first, the decline in functional performance, depressive symptoms and decline in social environment were prevalent. Second, the majority of the studies reported a statistically significant association of impairment in functional and cognitive performance, mood or social environment with a higher risk of adverse outcome. Third, cognitive function was only assessed in two studies and frailty and objectively measured physical capacity, were not assessed at all in patients with head and neck cancer.

Impairment in functional performance, depression and social environment were highly prevalent, which emphasizes that the head and neck cancer patients are a very vulnerable patient group. Possibly, the observed associations in the present review are underestimated due to the relatively young population in the studies compared to the average population in the clinic, with only twelve studies (39%) reaching a mean age of 60 years and older.

Table 2
Association of functional and cognitive impairment, social environment and frailty with adverse health outcomes.

Study		Geriatric measure and measured method	Outcome	Association
Author	No. of patients			
Aarstad [39]	79	Depression measured by (BDI)	Total and disease specific survival, quality of life	Depression at baseline associated with worse overall survival (aHR 1.13 per increase in depression level $p = 0.03$) and disease specific survival (aHR 1.19; $p < 0.001$) No correlation between depression at diagnosis and QOL at follow-up (in subset of $n = 27$)
Barber [38]	71	Depression measured by Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR)	FACT-NH-score, LOS, overall survival	Moderate-Severe depressive symptoms (QIDS-SR score 11–27) is a significant predictor of worse postoperative FACT-HN scores (aRR 5.66, $p = 0.03$), and a prolonged length of stay ($p = 0.02$) in comparison to normal-mild depressive symptoms. The overall survival was significantly worse in the moderate-severe group
Borggrevén† [46]	80	Social environment depicted by marital status	Global quality of life	Not having a partner was significant associated with lower global QOL after six months (no estimate reported; $p = 0.017$), but not after 12 months (no estimate or p -value reported)
Epstein [48]	573	Social environment depicted by living situation	Overall and disease free survival	Living in a long-term care facility associate with a significantly reduced overall (aRR 2.33 $p \leq 0.001$) and disease specific survival (aRR 2.16, $p < 0.001$) when compared to independently-living
Fang [25]	102	Social environment depicted by marital status Functional capacity measured by KPS	Survival	Marital status is no predictor for overall survival ($p = 0.095$). KPS (< 80 vs ≥ 80) was an independent prognostic factor for survival (HR#2.03 (95% CI 1.27–3.24))
Gerude [17]	67	Functional capacity measured by ADL (Katz), IADL (Lawton-Brody) and KPS	Postoperative complications, (LOS)	IADL dependence (score ≥ 18) was significantly associated with postoperative complications (RR 2.19 (95% CI 1.21–3.94), $p = 0.005$) and a prolonged length of stay (RR 1.97 (95% CI 1.07–3.61) $p = 0.02$) There was no association of ADL or the KPS with postoperative complications or a prolonged length of stay
de Graeff [26]	208	Social environment depicted by marital status. Functional capacity measured by KPS. Depression measured by CES-D.	Survival, time to event (=progression or death)	Marital status (unmarried) was significantly related to survival (RR 1.82 (95% CI 1.03–3.23)), compared to married status. CES-D and KPS were both no prognostic factor for survival or time to event
Hall [20]	856	Functional capacity measured by the ECOG-scale	Overall and disease specific survival	ECOG-score was an independent predictor for overall (aHR 1.24 (95% CI 1.12–1.38)) and disease specific survival (aHR 1.26 (95% CI 1.10–1.43))
Hammerlid [35]	232	Depression measured by HADS	Global quality of life	Depression at diagnosis was an independent predictor for global QOL after 3 years (adjusted for age, $p \leq 0.05$, no estimate reported)
Howren [36]	306	Depression measured by BDI	Health related quality of life	Depressive symptoms at time of diagnosis, negatively affect HRQOL over time
Howren [47]	364	Social environment measured by the (SPS)	Global and head and neck specific HRQOL	Greater perceived support present at diagnosis significantly predicted more favourable global and head and neck cancer specific HRQOL (on subdomains speech, eating, aesthetics, social disruption) at 3 and 12 months, adjusted for age
Hsieh [21]	151	Functional capacity measured by the ECOG-scale	Overall survival	ECOG performance status (0–1 vs ≥ 2) had a significant adverse impact on survival (aRR 5.203 (95% CI 2.257–11.993))
Karvonen [40]	495	Depression measured by the GDS-SF Social environment depicted by marital status	Survival	Depressive symptoms were no prognostic factor for survival (HR 1.30 (95% CI 0.98–1.73)). Marital status (married) was significantly associated with survival (aHR 0.62 (95% CI 0.47–0.83))
Kim [41]	241	Depression measured by de BDI-II, a revised form of the BDI	Overall survival	Pretreatment depression was not significantly predictive for 3-year overall survival (aHR 1.52 (95% CI 0.82–2.81))
Konski‡ [27]	1073	Functional capacity measured by KPS	Overall survival	KPS (90–100 vs 60–80) was an independent prognostic factor for overall survival (HR 1.90 $p \leq 0.0001$)
Lotfi [28]	258	Functional capacity measured by KPS	Surgical-site infection	There was no association with the risk of surgical-site infection and the KPS ($p = 0.489$)
Mell [22]	479	Functional capacity measured by ECOG-scale	Competing mortality	Univariate analysis ECOG performance status (1–2) was significantly associated with mortality (HR 1.57 (95% CI 1.05–2.36)). Multivariate analysis showed no association
Oskam† [42]	80	Social environment depicted by marital status	Overall and disease specific survival	Marital status (partner vs no partner) was predictive for disease specific survival (aRR 3.10 (95% CI 1.36–7.06)) and overall survival (no estimate reported)
Osthus [45]	106	Social environment depicted by marital status	Overall survival	Marital status (married vs other) was no prognostic factor for survival (aHR 0.68 (95% CI 0.34–1.35))
Pedruzzi [31]	361	Functional capacity measured by Zubrod-scale	Death	Zubrod-scale scores of 2 and 3 were independent prognostic factors risk of death (aHR 1.49 (95% CI 1.1–2.0) and aHR 1.94 (95% CI 1.2–3.3))
Ronis [37]	316	Depression measured by GDS-SF Social environment depicted by marital status	Health related quality of life with SF-36 and HnQoL	Depressive symptoms at baseline is a significant predictor of change HRQOL one year after diagnosis, across various domains of SF-36 and HnQoL ($p \leq 0.05$), adjusted for age Marital status is not a predictive factor

Table 2 (continued)

Study		Geriatric measure and measured method	Outcome	Association
Author	No. of patients			
Sadat [29]	169	Functional capacity measured by KPS and ECOG-scale	Overall survival	KPS (≤ 70), and ECOG (≥ 2) were an independent prognostic factor for overall survival (aHR 1.51 (95% CI 0.97–2.35))
Sanabria [18]	310	Functional capacity measured by KPS	Overall and cancer specific survival	KPS (≤ 80) was an independent prognostic factor for overall and cancer specific survival (aHR 2.0 (95% CI 1.40–2.87) and aHR 2.28 (95% CI 1.43–3.64))
Shah [32]	774	Functional capacity measured by Specific Activity Scale (SAS) Social environment depicted by living situation Cognitive impairment as any history or physical findings of a stroke, TIA or dementia	Delirium yes/no	There was no significant correlation with SAS (HR 2.43 (95% CI 0.78–7.63)) or living situation (HR 1.18 (95% CI 0.69–2.01)) and the development of postoperative delirium Cognitive impairment was significantly correlated with a postoperative delirium (aHR 3.83 (95% CI 1.70–8.63))
Siddiqui [‡] [30]	1093	Functional capacity measured by KPS Social environment depicted by marital status	Overall survival	KPS (60–80 vs 90–100, with aHR 1.507 (95% CI 1.268–1.791)) and marital status (with or without partner with aHR 1.235 (95% CI 1.218–1.747)) were independent prognostic factor for overall survival
Sze [19]	990	Functional capacity measured by ECOG-scale	Overall and cancer specific survival	ECOG performance status (2–3 vs 0–1) was not a prognostic factor for overall (aHR 1.01 (95% CI 0.55–1.84)) or cancer specific survival (aHR 0.85 (95% CI 0.28–2.54))
Tarsitano [43]	124	Social environment depicted by marital status	Overall survival	Having a partner was predictive for survival (no estimate or p-value reported)
Urba[23]	704	Functional capacity measured by ECOG-scale	Overall survival and progression free survival	ECOG performance status (0–1 vs 2) had a significant effect on overall survival (aHR 0.56 (95% CI 0.42–0.75)) and progression free survival (aHR 0.71 (0.53–0.93))
Wang [24]	600	Functional capacity measured by ECOG-scale	Overall and cancer specific survival	ECOG performance status was associated with borderline statistical significance (aHR 2.89 (95% CI 1.00–8.35)) with overall survival but not with cancer specific survival (aHR 0.86 (95% CI 0.11–6.48))
Weed [34]	138	Cognitive status measured by MMS-questionnaire Functional capacity measured by SAS Social environment depicted by living situation	Delirium yes/no	Patient living alone developed significantly more frequent a postoperative delirium (no estimate reported, $p = 0.005$). Cognitive status and functional capacity had no effect
Wong [44]	1010	Social environment depicted by marital status	Overall survival	Marital status (married vs unmarried) had a significant difference in overall survival (aRR 1.528, $p = 0.008$)

aHR, aRR, aOR = this are the adjusted values at least for age.

[†] Both studies used the same cohort.

[‡] Studies conducted partly on same trial, Siddiqui et al. used partly the same patients ($n = 689$) as Konski et al.

[#] Multivariate model contained: AJCC stage (IV vs III), N-status (N2-3 vs N0-1), KPS (< 80 vs ≥ 80).

[†] Multivariate model contained: race, educational level, TN-classification, KPS, site. Stratified by treatment.

According to the Surveillance, Epidemiology, and End Results database, approximately 47% of all patients diagnosed with head and neck cancer (HNC) in the U.S. between 1973 and 2013 were 65 years and older [49]. It is not surprising that we find limited number of older patients in these studies. A review in 2012 showed that only 7% of all randomized clinical trials are specially designed for older adults [50]. It is also known over various fields in medicine that older patients are underrepresented in clinical studies as a result of excluding individuals over a certain age or with a high burden of morbidities [50,51]. As a consequence, subjects enrolled in clinical trials, even those in the oldest cohort, often do not represent older patients in the general population [52,53]. Based on the results of the studies included in our review, we cannot determine which individual patient would experience adverse health outcomes and therefore the external validity of the individual studies is limited. The limited external validity is caused by the heterogeneous population, investigating a wide range of head and neck cancer types and treatment modalities and regimes, inclusion criteria, number of included patients, used geriatric assessment, age groups and outcome measurements.

Despite the heterogeneity of the studies and the low numbers of studies studying older patients it is the majority of included studies reported a significant association of functional impairment and social environment and some on cognitive impairment with

adverse outcomes. These associations also have been shown in other oncology patients [54–56] and in community dwelling older people [14,57]. In general oncology, geriatric assessments are frequently used to guide treatment decision-making. General oncologists often assess functional capacity by assigning KPS and ECOG-score, and both assessments are independent prognostic factors for outcomes [58,59]. In (oncological) surgery cognitive impairment is a well-known risk factor for postoperative complications such as delirium and mortality [60–62]. In two recent meta-analyses depression diagnosis and higher levels of depressive symptoms in patients with different kind of cancers predicted elevated mortality [63,64]. Social isolation has been linked to an increased risk of mortality in geriatric and oncology literature [65,66]. This could be explained by the intensive treatment program for (head and neck) cancer, the chance of success of the intensive treatment is highest when there is a good social support. Although we cannot rule out publication bias with negative associations not being published, our findings are in line with the literature describing associations of impairments with adverse outcome. Most of the studies identified in the present systematic review, found an association with social status, depicted by marital status, and a worse overall survival.

Multiple promising geriatric assessments, such as various frailty indices and objectively measured physical capacity were not

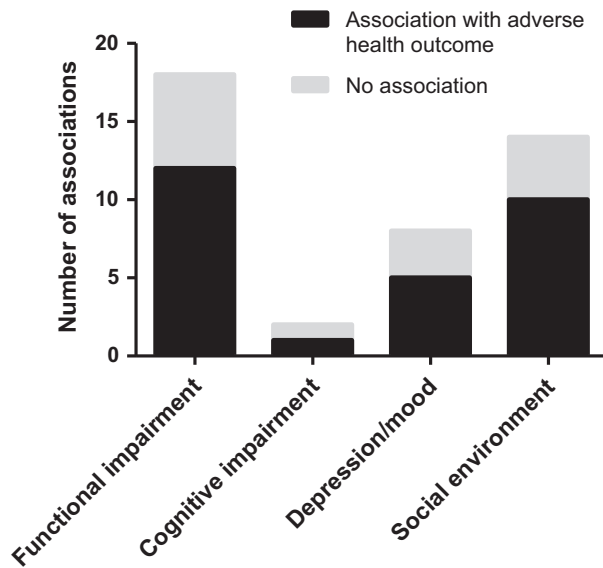


Fig. 2. Graphic representation of association of functional or cognitive impairment and social environment with adverse health outcomes in patients with head and neck cancer. No studies reported the association between frailty and adverse health outcomes.

assessed in patients with head and neck cancer. Objective geriatric measurements, such as gait speed, handgrip strength or Timed Up to GO Test (TUGT) can be useful geriatric screenings tools for the physician to risk stratify patients. Several studies examining the relation between physical capacity and outcomes as mortality or disability, found an association both in general and in oncological

patient populations [67–70]. Frailty is associated with adverse health outcomes in surgical patients [61] as well in community dwelling older adults [14]. In addition, in a recent review in older cancer patients, frailty is associated with an increased risk of chemotherapy intolerance, postoperative complications and mortality [71]. In conclusion, both objective geriatric measurements and frailty are predictive of poor outcomes in general oncology, (oncologic) surgical patients, as well as community dwelling older adults. However, in older head and neck cancer patients evidence of physical capacity and frailty and its associations with adverse health outcomes is lacking.

A limitation of our study was that, due to heterogeneity among the included studies, especially with respect to the geriatric measure that was used, the reported measure of association (HR, OR, and relative risk), outcome measures, and covariate adjustments, made it impossible to compare outcomes of studies in a meta-analysis or to make a proper sub group analysis. Secondly, interpretation of the results may be hampered by possible publication bias, as negative associations in multivariate analyses may not have been reported in the studies. Strengths of this review include the systematic search we performed in several databases, assessing all potential relevant associations of functional and cognitive impairment, social environment and frailty with adverse health outcomes in head and neck cancer patients. Furthermore, quality assessment of the studies was undertaken to identify potential factors hampering external validity.

Our findings implicate that apart from specialists in head and neck oncology (such as head and neck surgeons and oncologists) the older head and neck cancer patient could benefit from an even more multidisciplinary approach. This could be implemented for instance by including a geriatrician in the multidisciplinary team in both the pre- and post-operative phase.

Table 3
Quality assessment.

Publication		Selection		Outcome		
First author	Publication year	Representativeness of the exposed cohort	Ascertainment of exposure (geriatric measure)	Assessment of outcome	Sufficient duration of follow-up	Adequacy of follow-up
Aarstad	2005	–	+	+	+	?
Barber	2015	+	+	+	+/-	+
Borggreven	2007	+/-	+	+	+	–
Epstein	2005	–	+	+	+	?
Fang	2004	+/-	+	+	?	?
Gerude	2011	–	+	+	+	+
de Graeff	2001	+/-	+	+	+	?
Hall	2009	+/-	+	+	+	+
Hammerlid	2001	+	+	+	+	–
Howren	2010	+	+	+	+	+
Howren	2013	+	+	+	+	+
Hsieh	2011	–	+	+	+	?
Karvonen	2008	+	+	+	+	?
Kim	2015	+	+	+	+/-	+
Konski	2003	+/-	+	+	?	?
Lotfi	2008	+	+	+	+	+
Mell	2010	+/-	+	+	+	?
Oskam	2010	+/-	+	+	+	?
Osthus	2013	+	+	+	+	+
Pedruzzi	2008	+/-	+	+	+	?
Ronis	2008	+	+	+	+	+
Sadat	2012	–	+	+	+	?
Sanabria	2007	+	+	+	+	?
Shah	2012	+/-	+	+	?	?
Siddiqui	2008	+/-	+	+	+	?
Sze	2012	+/-	+	+	+	?
Tarsitano	2012	–	+	+	+	?
Urba	2012	+/-	+	+	+/-	+
Wang	2014	+	+	+	+	?
Weed	1995	+/-	+	+	?	?
Wong	2006	+/-	+	+	+	?

Conclusion

Functional and cognitive impairment, depressive symptoms and social isolation are highly prevalent in head and neck cancer patients and associate with high risk of adverse health outcomes. In the future, these measurements may guide decision-making and customize treatments, but more research is needed to further improve and firmly establish clinical usability.

Conflict of interest

None declared.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.oraloncology.2016.11.013>.

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