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Phenotyping older patients needing intensive treatment

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4 **FUNCTIONAL AND COGNITIVE IMPAIRMENT, SOCIAL FUNCTIONING, FRAILTY AND ADVERSE HEALTH OUTCOMES IN OLDER PATIENTS WITH ESOPHAGEAL CANCER, A SYSTEMATIC REVIEW**

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ABSTRACT

Background Older patients with esophageal cancer are at high risk of adverse health outcomes, but the association of geriatric assessment with adverse health outcomes in these patients has not been systematically evaluated. The aim of this systematic review was to study the association of functional and cognitive impairment, social environment and frailty with adverse health outcomes in patients diagnosed with esophageal cancer.

Methods We searched Pubmed, Embase, Web of Science and Cochrane Library for original studies reporting on associations of functional or cognitive impairment, social environment and frailty with adverse outcomes (mortality, functional or cognitive decline, adverse events during treatment, prolonged length of hospitalization (LOS) and health related quality of life (HRQoL)) after follow-up in patients with esophageal cancer.

Results Of 1.391 identified citations, nineteen articles were included that reported on 53 associations. The median sample size of the included studies was 110 interquartile range (IQR 91-359). Geriatric conditions were prevalent: between 14 and 67% of the included participants were functionally impaired, around 42% had depressive symptoms and between 5 and 23% did not have a partner. In nineteen of 53 (36%) associations functional or cognitive impairment or frailty were significant associated with adverse health outcomes, but the studies were small. In four out of six (67%) associations with the largest sample size ($n \geq 359$), functional impairment or social environment were significant associated with adverse health outcomes.

Conclusion Functional and cognitive impairment, depression and social isolation are prevalent in patients with esophageal cancer, and associate with adverse health outcomes. Geriatric measurements may guide decision-making and customize treatments, but more large studies are needed to explore the clinical usability.

INTRODUCTION

Esophageal cancer incidence strongly increases with age. In 2016 in the Netherlands there were 2545 newly diagnosed patients with esophageal cancer and in > 65% of these diagnoses the patient was 65 years of older [1]. Also the UK and the USA report similar numbers [2]. Esophageal cancer is associated with a poor prognosis, having an overall five-year survival ranging between 15 and 20% depending on the stage and treatment intention [3]. It is a challenge to select the older patients who are at high risk for adverse health outcomes, such as mortality, prolonged length of stay and reduced quality of life. This is mostly due to their varying levels of functional and cognitive capacity, mobility and frailty. However, it is unclear how geriatric impairments, such as functional and cognitive impairment or frailty, associate with adverse outcomes in patients diagnosed with esophageal cancer.

The optimal treatment for locally advanced esophageal cancer consists of preoperative concomitant chemoradiotherapy followed by surgical resection [4, 5] and the optimal treatment for early stage esophageal cancer is surgical or endoscopic resection [6]. In patients aged 70 years and older, esophagectomy has been associated with higher mortality and morbidity rates compared to patients younger than 70 years [7-10]. Often there is reluctance to have older patients undergo the general treatment modalities [11], because of their comorbidities, polypharmacy or poor physical functioning [12]. In other fields of medicine, recent research has shown that performing a geriatric assessment including the domains of functional or cognitive functioning, social functioning and frailty may guide decision making for older patients undergoing general surgery [13].

The aim of this systematic review was to study the association of functional and cognitive impairment, social environment and frailty prior to any treatment with adverse health outcomes (mortality, functional or cognitive decline, adverse events during treatment, prolonged length of hospitalization (LOS) and health related quality of life (HRQoL) after follow-up) in patients diagnosed with esophageal cancer.

METHODS

Search Strategy

We aimed to identify original longitudinal studies in patients with esophageal cancer with all disease stages, in which the association between a measurement of functional and cognitive impairment, social environment or frailty prior to any treatment initiation and adverse health outcome (mortality, functional or cognitive decline, adverse events during treatment, LOS and health related quality of life (HRQoL) after follow-up) after follow-up was examined.

One of the purposes of a geriatric assessment is to systematically explore different domains (functional status, cognitive status, social environment and frailty) as a reflection of patients' health [14, 15]. Therefore, using the geriatric assessment at baseline we determined functional capacity (including assessment of functional performance, mobility, and objectively measured physical capacity such as hand grip strength, gait speed or balance tests), cognitive capacity (including assessment of cognition, dementia diagnosis, and mood or depression), social environment (living situation, social support and marital status) and frailty (as measured using a frailty index or instrument such as Fried Frailty Phenotype or the Groningen Frailty Indicator). The geriatric assessment had to be done before treatment initiation. In this review articles describing patients treated with any of the available treatments are eligible (surgery, chemotherapy, (chemo)radiotherapy, palliative supportive care). We expect that a geriatric assessment mostly will be performed in older patients, though they might be relevant to younger patients as well. To decrease the risk of missing relevant articles we did not apply age limits in the search strategy. An esophageal tumor was defined as squamous cell carcinoma (SCC) or adenocarcinoma carcinoma (AC) of the esophageal wall or gastro-esophageal junction, all disease severity stages were included. Adverse health outcomes were defined as mortality, functional or cognitive decline, adverse events during treatment (e.g. delirium or side-effects), prolonged length of hospitalization (LOS) and health related quality of life (HRQoL) or global quality of life (QoL) after follow-up.

On December 19th 2016, we searched four electronic bibliographic databases (PubMed, Embase, Web of Science and the Cochrane Library) using synonyms of esophageal cancer, combined with synonyms of the different domains of geriatric assessment. For the full Medline search, see Appendix A (available online).

Article selection

The eligibility of all studies identified by the search was independently evaluated by two authors Floor van Deudekom (FvD) and Henk Klop (HK). 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 the association between any of the geriatric measures at baseline and outcome after follow-up in patients with esophageal cancer in a longitudinal study design. In case of disagreement between the two authors (HK, FvD), consensus was reached after discussion with two other co-authors (MS and SM). In 1372 of the 1391 articles HK and FvD had consensus, making a 98% agreement overall. The reference list of the included publications was used for cross-referencing to ensure we identified all relevant articles.

Data extraction

Data extracted from each study included: publication data (author, year), study design and setting, patient characteristics (sample size, mean age, treatment modality), tumor type (SCC or AC) measurement of functional or cognitive impairment, social environment or frailty, follow up duration, outcome measures 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 endoscopic resection, surgery, surgery in combination with neoadjuvant chemoradiation, chemoradiation alone or treatment with no curative intent such as palliative chemotherapy or palliative radiotherapy or esophageal stent placement. Also, best supportive care was considered as a treatment modality. To assess the methodological quality and risk of bias of the included studies, we adapted the Newcastle-Ottawa scale [16] for the purpose of this review (Appendix B). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist, which is a checklist for evidence-based minimum set of items for reporting in systematic reviews [17], is available (online) see Appendix C.

Data presentation

Study characteristics are tabulated per individual study. Accumulated descriptive statistics of the selected studies are presented by calculating the proportion of studies reporting on measurements of functional or cognitive impairment, social environment or frailty, endpoints or treatment modalities. Combined sample size of the included studies is expressed as median and interquartile range (IQR). To get a complete overview we describe the total of significant associations with outcomes. All calculations are made with Statistical Package for the Social Sciences (SPSS) software version 23. In this review with an "association" is meant the relation between the geriatric determinant at baseline and the outcome after follow up. Main findings of the studies with respect to the association of measurement of functional or cognitive impairment, social environment or frailty with outcome are tabulated. If possible, a fully adjusted model controlling for possible confounders, including multiple known risk factors for poor outcome, such as comorbidity burden, was tabulated.

Supplementary analysis

Because of a low average sample size in the found articles, which can result in low power to detect statistical significance, we performed a supplementary analysis. In this analysis we analyzed the five studies with the largest sample size and describe the association of measurement of functional or cognitive impairment, social environment or frailty with the outcome of interest.

RESULTS

Search results and study selection

The database searches identified 1391 unique citations (Figure 1). After screening of title and abstract, 66 articles were considered potentially eligible. After full-text review, 47 were excluded; the remaining nineteen articles were included. Cross-referencing did not result in additional articles, so a total of nineteen articles were included in this review.

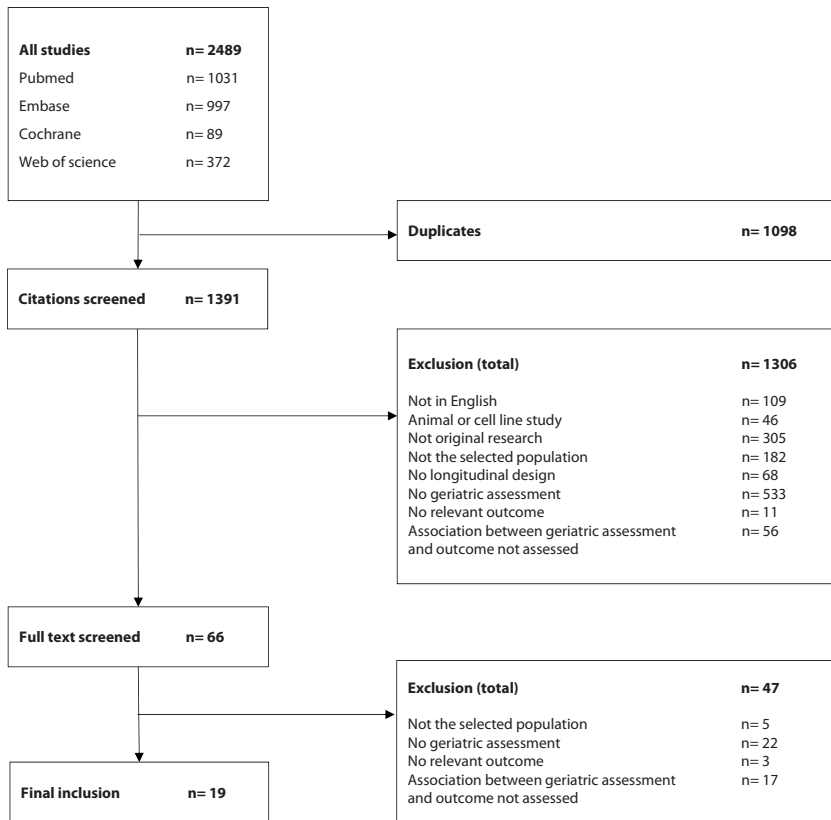


Fig 1. Flowchart

Study characteristics

Table 1 shows an overview of the study characteristics of the nineteen included studies. Eighteen out of nineteen studies (95%) were published after the year 2000. The median sample size of the included studies was one hundred ten (interquartile range (IQR) 91-359). Ten out of nineteen studies (53%) were conducted in the United States or Europe. Out of the nineteen studies, thirteen studies (68%) included adenocarcinoma and squamous cell carcinoma; six studies (32%) included patients with only one of those two types. Four studies had specific selection criteria such as (locally) advanced cancer, ability to complete self-report questionnaires and seven studies included only one treatment modality. Only two studies (11%) focused on older patients and included exclusively patients aged 70 years and older in their study population.

Association of measures for functional status, cognitive or social functioning with adverse health outcomes

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 nineteen studies reported on a total of 53 associations between various determinants with adverse outcomes: 25 out of 53 associations (47%) assessed functional impairment, ten out of 53 associations (19%) were reporting on cognitive function, two out of 53 associations (4%) examined depressive symptoms, social status was studied in eleven out of 53% associations (21%) and physical capacity was studied in five out of 53 associations (9%) (Figure 2). Objectively measured physical capacity, such as hand grip strength or the six-minute walking test was examined in five associations (9%). None of the studies used an instrument to measure frailty as a determinant of adverse health outcomes.

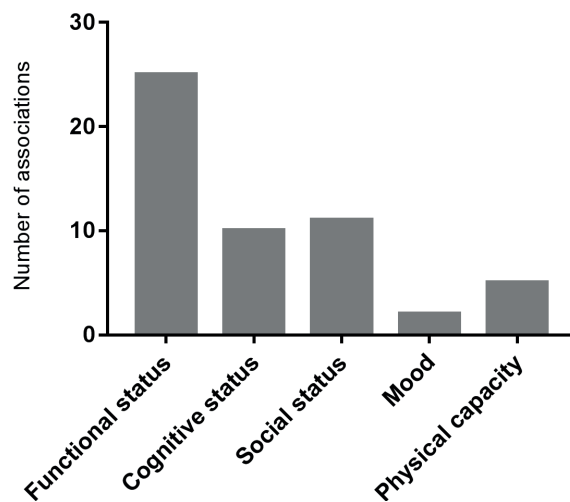


Fig. 2 Graphic representation of the number of associations described per geriatric domain

Table 1. Characteristics of included articles

Publication characteristics		Study population			Clinical characteristics		
Author	Year	Country	Number of patients	Age, yr (mean)	Patient selection	Tumor characteristics	Treatment modality
Bergquist <i>et al.</i> ^[24]	2007	Sweden	94	67	Patients with newly diagnosed cancer. Exclusion: declined participation, unable to complete the questionnaires, expected survival < 1 month	AC and SCC	Any
Bergquist <i>et al.</i> ^[18]	2008	Sweden	96	74	Patients with incurable cancer Exclusion: withdrawn consent, previous esophagectomy or concomitant malignancy, expected survival < 1 month	AC, SCC and 2% other	P (stent, brachytherapy, anti-reflux valve)
Blazeby <i>et al.</i> ^[19]	2001	UK	89	70 [§]	Exclusion: no obtained QOL data	AC and SCC	S, C, RTx, P or intubation
Brusselsaers <i>et al.</i> ^[30]	2014	Sweden	606	NA	Exclusion: no marital status available	AC and SCC	S
Chang <i>et al.</i> ^[33]	2014	Taiwan	99 [†]	55.5	Exclusion: patient unable to self-report, inoperable tumor	AC and SCC	S with or without CRTx
Chang <i>et al.</i> ^[20]	2016	Taiwan	67 [†]	56 [§]	Exclusion: mortality < 6 months, circumferential margin tumor R1 or R2	AC and SCC	S
Dandara <i>et al.</i> ^[32]	2015	South Africa	1868	60 [§]	All patients with carcinoma of the esophagus	AC and SCC	Any
Egmond <i>et al.</i> ^[23]	2016	Netherlands	94	63.8	All esophageal patients with cancer scheduled for esophagectomy. Exclusion: severe cognitive impairment, functional or nutritional impairments.	All tumor types	CRTx and S
Fakhrian <i>et al.</i> ^[61]	2012	Germany	163	62	Patients with stages T1-T4, N0-1, cM0 Exclusion: cM1, adjuvant or salvage radiation treatment, exclusive intraluminal brachytherapy (IBT)	SCC	CRTx
Fang <i>et al.</i> ^[21]	2004	Taiwan	110	NA	Newly diagnosed patients Exclusion: no Stage T1-T4N0-N1M0-M1 a preoperative or postoperative RT, a radiation dose < 50 Gy, treatment with brachytherapy, had tumor recurrence or synchronous malignancies, or were unable to complete the questionnaire.	SCC	RTx

Table 1. Characteristics of included articles (continued)

Publication characteristics			Study population		Clinical characteristics		
Author	Year	Country	Number of patients	Age, yr (mean)	Patient selection	Tumor characteristics	Treatment modality
Ghadimi <i>et al.</i> ^[81]	2012	Iran	359	55.23	No selection criteria available	All tumor types	Any
Healy <i>et al.</i> ^[22]	2008	Ireland	185	61.6	Patients offered surgery or multimodal treatment with clinical stage T1-3 N0-1 M0	AC and SCC	CRTx with or without additional S
Kawashima <i>et al.</i> ^[25]	1998	Japan	362	72.5	Patients treated with Definitive Radiotherapy (DRT) Exclusion: No description of survival	SCC, AC and 1.7% other	RTx without S
Kim <i>et al.</i> ^[62]	2008	Korea	180	64.5	3 RCTs; patients locally advanced, but resectable cancer	SCC	CRTx with or without additional S
Mak <i>et al.</i> ^[63]	2010	USA	34	79.55	Aged ≥ 75 ; full-dose chemoradiation (> 45 Gy) with at least ≥ 1 cycle of concurrent chemo	AC, SCC and poorly differentiated (5.9%)	CRTx with or without additional S
Murphy <i>et al.</i> ^[26]	2013	USA	191	60.5	Patients with locally advanced cancer Exclusion: synchronous primary cancers, cancer of cervical or proximal esophagus, emergency, redo and salvage esophagectomies.	AC	CRTx and S
Raymond <i>et al.</i> ^[27]	2016	USA	4321	63.3	Patient with esophageal cancer needing surgery. Exclusion: benign disease, missing clinical stage and tumor histology	AC and SCC	S
Tatematsu <i>et al.</i> ^[20]	2013	Japan	51	65.0	Patients with esophageal cancer Exclusion: gait disturbances requiring assistive devices	SCC	S
Yamamoto <i>et al.</i> ^[28]	2016	Japan	91	78.4	Patients aged ≥ 75 with esophageal cancer Exclusion: two-stage surgery, no SCC	SCC	S

* abbreviations C=chemotherapy, CRTx= chemoradiation, RTx= radiotherapy, S= surgery, P= palliative, SCC= squamous cell carcinoma, AC= Adenocarcinoma, NA= not available

† Studies are used in the same cohort

§ Median

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

Authors	No. of patients	Geriatric measure and patients measured method	Outcome	Association
Bergquist <i>et al.</i> ^[24]	94	Functional status by KPS Depression by HADS	Anxiety and Depression, Overall Survival	No significant change in the HADS total score over time was found in patients with a different KPS. No correlations were found between any of the HADS scores at inclusion and survival. [*]
Bergquist <i>et al.</i> ^[18]	96	Functional status by KPS Functional, cognitive and social status by EORTC QLQ-C30.	Overall Survival	Functional (HR 0.91, p=0.02) and cognitive scales (HR 0.92, 0.03) were significantly associated with survival. Cognitive functioning was not (HR0.93, p=0.161). Social scale showed trend with survival (HR 0.93, p=0.05). KPS was significantly associated with survival (HR 0.98, 0.002). [‡]
Blazebly <i>et al.</i> ^[19]	89	Functional, cognitive and social status by EORTC QLQ-C30.	Overall Survival	Higher functional (HR 0.88, p=0.002) and social scores (HR 0.91, p=0.028) were associated with lower likelihood of death. After adjusting for associations between the score, only functional scale was significantly associated with survival (HR 0.88, p = 0.002).
Brusselslaers <i>et al.</i> ^[30]	606	Social status by marital status	Overall 5-year survival	Marital status was not significant associated with overall survival in any of the regression models (HRs ranging from 0.79 – 1.02).
Chang <i>et al.</i> ^[33]	99 [†]	Functional status by ECOG (0 vs. 1-4)	QOL via EORTC QLQ-C30	Functional status at baseline showed no significant association with any of the QOL scales 1 and 6 months after surgery (difference in score -4.4 compared to baseline, p>0.05).
Chang <i>et al.</i> ^[20]	67 [†]	Functional, cognitive and social status by EORTC QLQ-C30	Survival after 6 months post-surgery	Functional, cognitive and social status at baseline were not significantly associated with survival after 6 months postoperatively (HR's 0.989-0.999, p>0.05). [‡]
Dandara <i>et al.</i> ^[22]	1868	Functional status by ECOG	Overall Survival	Patients with ECOG ≤ 2 had statistically improved survival over those with ECOG 3-4.
Egmond <i>et al.</i> ^[23]	94	Functional status by LAPAQ. Physical status by IMS and HGS, EORTC QLQ-C30	Postoperative complications (< 30 days or during hospital stay)	Functional and physical status [*] were not associated with postoperative complications (ORs 0.99-1.00, p>0.05). EORTC QLQ-C30 domains were not associated with postoperative complications (OR 1.02, p=0.22). [‡]
Fakhrian <i>et al.</i> ^[61]	163	Functional status by ECOG	Overall Survival	Higher functional status at baseline was significantly associated with better OS in multivariate analysis (HR 0.50, p=0.005). [†]

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

Authors	No. of patients	Geriatric measure and measured patients method	Outcome	Association
Fang <i>et al.</i> ^[21]	110	Functional, cognitive and social status by EORTC QLQ-C30. Functional status by KPS	Survival	In univariate analysis, physical functioning (HR 0.9789, p=0.0007), social functioning (HR 0.9883, p=0.02) and KPS <80 (p=0.02) were associated with survival and cognitive functioning was not associated (HR 0.9986, p=0.83). Functional status by EORTC QLQ-C30 was the only significant association in multivariate analysis (RR 0.98, p=0.0002).
Ghadimi <i>et al.</i> ^[31]	359	Social function by marital status	Overall Survival	Marital status was not a prognostic factor for survival in any of the models (HR/RR range 1.06-1.23, p>0.05).
Healy <i>et al.</i> ^[22]	185	Functional, cognitive and social status by EORTC QLQ-C30.	Postoperative morbidity, in-hospital mortality, early recurrence and 1-year survival	None of the EORTC QLQ-C30 scales (physical, cognitive and social) associated significantly with the different outcomes in univariate (p>0.05) or multivariate analysis (ORs 1.0 p-values > 0.05)
Kawashima <i>et al.</i> ^[25]	362	Functional status by KPS	Overall Survival	Patients with a KPS \geq 80 (HR 1.56, p=0.0009) had a significantly better overall survival. The overall survival rate of octogenarians was significantly affected by KPS (p=0.009), while the KPS did not affect the survival of younger patients (p=0.958).
Kim <i>et al.</i> ^[62]	180	Functional status by ECOG	Overall Survival	In univariate analysis, a good functional status (score 0 or 1) was associated with higher survival, both in the entire study population (HR 2.37, p=0.001) and in patients that had esophagectomy (HR 2.64, p=0.001).
Mak <i>et al.</i> ^[63]	34	Functional status by ECOG	Toxicity and OS	Functional status was not statistically associated with either survival or risk of grade 3 toxicity.
Murphy <i>et al.</i> ^[66]	191	Functional status by Zubrod performance score	Prolonged length of stay (LOS)	Decreased functional status (0 vs \geq 1) was associated (β =-0.1514, p=0.021) with increased LOS (10 v 11 days, p=.024).
Raymond <i>et al.</i> ^[27]	4321	Functional status by Zubrod score	Postoperative mortality and morbidity (< 30 days)	Functional impairment, indicated by a Zubrod score > 1 vs 0, was significantly associated with morbidity (OR 1.89, p<0.001) and mortality (OR 3.31, p<0.001).

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

Authors	No. of patients	Geriatric measure and measured patients method	Outcome	Association
Tatematsu <i>et al.</i> ^[26]	51	Physical status by knee-extensor muscle strength, 6-minute walking distance and IPAQ (METs [*] h/wk)	Postoperative complications	Only low level physical status measured by IPAQ was significantly associated with postoperative complications in multivariate analysis (OR 28.3, p=0.02 (95%CI 3.5-227.7)).
Yamamoto <i>et al.</i> ^[28]	91	Functional status by Barthel index and IADL Cognitive status measured by MMSE, Depression by GDS15.	Postoperative delirium	Functional status was not associated with postoperative delirium (p>0.05). Cognitive status (OR 1.4, p<0.0001) and depression (OR 1.3, p=0.004) were associated with postoperative delirium.

* abbreviations: ECOG= The Eastern Cooperative Oncology Group; EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; GDS15= Geriatric Depression Scale 15; HADS= Hospital Anxiety and Depression Scale; HGS= handgrip strength; HR=Hazard ratio; IADL= Instrumental Activities of Daily Living; IMS= inspiratory muscle strength; IPAQ= International Physical Activity Questionnaire, KPS= Karnofsky Performance Status; LPAQ= LASA physical activity questionnaire; MMSE= the Mini-Mental State Examination; OR=Odds Ratio, , RR=Relative Risk.

† Studies performed in the same cohort

‡ Univariate analysis

γ Details of multivariate model not available in the original article

Survival (overall, total or disease specific survival) was the main outcome of interest in 26 out of 53 associations (49%). From the remaining associations seventeen assessed side effects (32%), QoL or HRQoL was assessed by one association (2%), four assessed the development of post-treatment delirium (7.5%), one assessed depressive symptoms (2%), three assessed early recurrence (5.5%) and one assessed LOS (2%). No studies reported on cognitive or functional decline after treatment for esophageal cancer.

In nineteen out of 53 associations (36%) in all included studies and in four out of six (67%) of the studies with the largest sample size, functional, cognitive or social functional impairment was statistically significantly associated with a higher risk of adverse health outcomes.

Functional impairment and physical impairment

Nine of the associations reporting on overall functional performance used the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 [18-23], four used the Karnofsky Performance Score (KPS) [18, 21, 24, 25], six used the Eastern Cooperative Oncology Group (ECOG) score, three used the Zubrod performance score [26, 27] and two used Barthel index and Instrumental Activities of Daily Living (IADL) [28]. Functional impairment was prevalent in most of the studies with rates between 14-67%. For example, one of the largest studies of Kawashima *et al.* included 362 patients and 158 (43.6%) had a $KPS \leq 70$, which indicates that patients are unable to carry on active work or require assistance. Functional impairment was found to be associated with increased risk for any adverse outcome in twelve of the 25 associations (47%). Kawashima *et al.* reported that a higher KPS (≥ 80 versus ≤ 70) was associated with a higher overall survival in patients treated with definitive radiotherapy (RR 1.56 $p = 0.0009$). If the data were stratified for age, the overall survival rate of 31 octogenarians (stage I/II) was significantly higher with increasing KPS ($p = 0.009$), while it did not associate with increasing survival in the 63 younger patients ($p = 0.958$) [25].

Two associations used inspiratory muscle strength and handgrip strength [23], while the other three used knee-extensor muscle strength, six-minute walking distance and International Physical Activity Questionnaire (IPAQ) [29]. Physical impairment was associated with higher risk adverse outcomes in one out of the five reported associations (20%). The study by Tatematsu *et al.*, included 51 participants and assessed the association between physical impairment and postoperative complications showing that physical impairment was statistically significantly associated with postoperative complications in multivariate analysis (odds ratio (OR) 28.3 95% confidence interval (CI) 3.5-227.7) [29].

Cognitive impairment and depressive symptoms

Cognitive status was measured with the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) cognitive scale, which contains one self-report question on cognitive performance, in nine out of the ten associations [18-23]. Cognitive status was found to be associated with increased risk for any adverse outcome in two out of ten associations (20%). The prevalence of cognitive impairment was not reported. Only one study by Yamamoto *et al.* used an objective assessment to measure cognition, the Mini-Mental State Examination (MMSE). In this study 24 of the 91 individuals developed postoperative delirium and these patients had a lower mean MMSE score of 23 compared to 27 in patients without delirium, indicating a lower cognitive status. In this study, a one point decrease in MMSE score associated with a 40% increased risk of delirium (odds ratio (OR) 1.4 (95% CI 1.2-1.6)) [28].

Depressive symptoms were measured with the Hospital Anxiety and Depression Scale (HADS) [24] and the Geriatric Depression Scale fifteen (GDS15) [28]. One study reported a prevalence of 42% patients having depressive symptoms. Depressive symptoms were associated with an increased risk for adverse outcomes in one out of two associations (50%). The study that assessed the association between depression and postoperative delirium used the GDS15. This study showed that for the 24 patients who developed a delirium, the mean score was 4.92 compared to a mean score of 2.45 for patients without delirium. A one point increase in GDS15 score, indicating a higher chance of depression, was associated with a 30% increased risk for delirium (odds ratio (OR) 1.3 (95% CI 1.1-1.6)) [28]. The other study used the HADS questionnaire in 94 participants to assess if depressive symptoms and anxiety at baseline were associated with survival, reporting no significant correlations between any of the HADS scores at baseline and survival [24].

Social functioning

Social impairment was mostly measured with the EORTC QLQ-C30 social scale, in nine of the eleven associations [18-23]. Between 5% and 23% of the included participants were single and 30% lived alone. Social impairment was found to be associated with increased risk for any adverse outcome in three of the eleven associations (27%). A study by Brusselaers *et al.* assessed the association between social functioning, depicted by marital status and overall five-year mortality in 606 participants. Of these patients, 334 were married and 272 had a different marital status (e.g. unmarried or remarried). Marital status was not significantly associated with five-year mortality [30].

Supplementary Analysis

To test the robustness of our finding that 36% of the associations reported a significant association of functional, cognitive or social functional impairment with a higher risk of adverse health outcomes, we performed a supplementary analysis.

The average sample size in the articles is relatively low resulting in low power to detect statistical significance, which may explain the low number of reported significant associations. To test this hypothesis, we analyzed the five studies with the largest sample size [25, 27, 30-32]. This resulted in six associations, with a minimal sample size of 359 patients. Three assessed functional status and two investigated social status, while in all associations survival was the main outcome. In four out of six (67%) associations a significant association of functional, cognitive or social functional impairment with a higher risk of adverse health outcomes was reported (Figure 3).

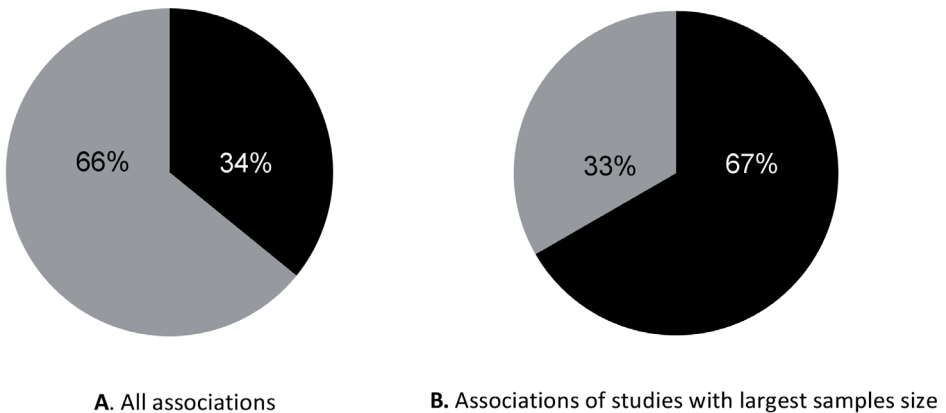


Fig. 3 Visual representation of significant associations in different selections.

Legend: Black: significant. Grey: not significant.

Quality assessment

The overall study quality assessed by the modified Newcastle-Ottawa scale was moderate (Table 3). Overall the biggest concern was the representativeness of the study populations. In six out of the nineteen studies (31.6%), the association between a geriatric measure and outcome was examined in a preselected population with specific tumor characteristics (e.g. only locally advanced) or only one treatment modality was used. Furthermore, several studies had specific selection criteria, such as excluding patients who were cognitively impaired [21, 24, 33] or with an impaired physical status at baseline [29], which may increase the risk on selection bias. Finally, only in ten out of nineteen (53%) studies the interpretation of the results were reliable because the confounders and the way there was controlled for these confounders were reported.

Table 3. Quality assessment of the included studies

Publication	Selection		Results		Outcome		
	Publication year	Representativeness of the exposed cohort	Ascertainment of exposure (geriatric measure)	The reliability of interpretation of the results by reporting the confounders	Assessment of outcome	Sufficient duration of follow-up	Adequacy of follow-up
Bergquist ^[24]	2007	+	+	?	+	+	+
Bergquist ^[18]	2008	+/-	+	-	+	+	?
Blazeby ^[19]	2001	+	+	+	+	+	+
Bruselaers ^[30]	2014	+	+	+	+	+	?
Chang ^[33]	2014	+	+	?	+	+	?
Chang ^[20]	2016	+/-	+	-	+	+	?
Dandara ^[32]	2015	+	+	+	+	+	+
Egmond ^[23]	2016	+	+	-	+	+	?
Fang ^[21]	2004	+/-	+	+	+	+	?
Fakhrian ^[61]	2012	+/-	+	?	+	+	?
Ghadimi ^[31]	2012	+	+	+	+	+	?
Healy ^[22]	2008	+/-	+	+	+	?	?
Kawashima ^[25]	1998	+/-	+/-	?	+	+	?
Kim ^[62]	2008	+/-	+	-	+	+	?
Mak ^[63]	2010	+/-	+	?	+	+	?
Murphy ^[26]	2013	+/-	+	+	+	+	?
Raymond ^[27]	2016	+/-	+/-	+	+	+/-	?
Tatematsu ^[28]	2013	+/-	+	+	+	+	?
Yamamoto ^[28]	2016	+/-	+	+	+	+/-	?

DISCUSSION

In the present systematic review, there were four main findings. First, geriatric impairments such as functional impairment, social isolation and depressive symptoms were prevalent. Second, we identified nineteen articles reporting on 53 associations of functional or cognitive impairment or social environment with adverse outcomes in patients with esophageal cancer. Third, one-third of all studies, and 67% of the studies with the largest sample size, reported a significant association of functional, cognitive or social impairment with increased risk for adverse health outcomes. Fourth, objectively measured functional and cognitive function were only assessed in one study, while frailty was not assessed at all in patients with esophageal cancer.

In the nineteen articles we identified, functional, physical and cognitive impairment, depressive symptoms and impairment in social environment were prevalent, this confirms that patients with esophageal cancer are vulnerable. Major risk factors, especially for squamous cell carcinoma, include alcohol consumption and tobacco use. Both factors were also associated for deterioration in functional and cognitive decline as well [34, 35]. Possibly, the reported prevalence in the different studies could be explained by the relatively young included study population, this review reports only two studies who exclusively included patients aged 70 years and older in their study population.

Based on the incidence of esophageal cancer in the general population [36] and based on experience with other reviews in head and neck patients with cancer [37] and patients with end-stage renal disease [38], we had expected to find more articles. The mean age in the included population in this systematic review was above 60 years in only eight of the nineteen studies (42%), while the median age of patients with esophageal cancer is 68 years and 56% of the patients are aged 70 over at time of diagnosis [12]. It is a known phenomenon that clinical trials include limited numbers of older patients. This underrepresentation can be explained by the exclusion of older adults because of age, comorbidities and polypharmacy [39] and this is also known from drug trials [40], cardiology trials [41, 42] and oncology trials [43]. The consequence of this underrepresentation is that it is unknown if the results can be applied to the individual patient in the outpatient department and therefore the external validity is limited. The large heterogeneity in inclusion criteria, treatment modalities, geriatric assessment and outcome measures, hampers drawing definitive conclusions for individual patients.

In this review, more than one-third of the reported associations found a significant association of functional, cognitive or social impairment with increased risk for adverse health outcomes. In general oncology, oncologists often assess functional capacity by

assigning KPS and ECOG-score, to guide treatment decision-making. Both assessments are independent prognostic factors for survival [44-46]. Also, IADL has been identified as a significant prognostic factor for survival in lung cancer [44] and in patients with cancer undergoing surgery [47, 48]. In this review, one study objectively assessed cognitive status and found an association with postoperative delirium [28]. This is in line with previous research that reported impaired cognitive status to be associated with adverse outcomes in patients undergoing thoracic surgery [49] and older patients [50]. In this review, social assessment by marital status, assessed in one study, was not associated with survival. In a recent systematic review in patients with head and neck cancer, social status depicted by marital status was associated with adverse health outcomes such as overall survival [37]. In general, the number of associations between functional, cognitive or social impairment with increased risk for adverse health outcomes was higher in other patients with cancer [37, 51]. One possible explanation may be the lack of statistical power of the included studies, as the median sample size was low (< 100 patients). This hypothesis is supported by our finding that 67% of the associations in the articles with the highest sample size, associations of functional impairment or social environment with adverse health outcomes, did reach statistical significance. On the other hand, the number of significant associations may inversely be affected by publication bias, as negative associations in multivariate analyses may not have been reported in some of the studies. Overall, we conclude that in older patients with esophageal cancer impairments on functional, cognitive or social environment in 67% of the reported associations there was an increased risk of adverse outcomes.

Objectively measured functional and cognitive status were assessed in only one study [28]. The predictive value of a geriatric assessment, which extensively examines functional, physical, cognitive and social performance, has been established in other patients with cancer [44, 52, 53], but was not reported for patients with esophageal cancer. An often used concept 'frailty' has not been studied in patients with esophageal cancer. This is surprisingly since frailty is extensively described in other oncological fields [54-56]. Frailty also has been associated with increased risk of mortality, treatment complications and treatment completion in older patients with cancer [57, 58]. However, in older patients with esophageal cancer evidence of physical capacity and frailty and its associations with adverse health outcomes is lacking.

A limitation of the present review is that we did not perform a meta-analysis. Due to the heterogeneity of the included studies with respect to the low number of included patients, geriatric measures that were used, outcome measures and the reported association measure (HR, OR and RR) and often the absence of an estimate of the effect, a summary statistic would be hard to interpret. A cumulative statistic of associations

would only provide information to the reader about whether an overall association exists in a statistical way. Clinical usefulness of such a summary statistic would be minimal as it is unclear what determinant associates with what outcome and whether or not there is confounding or bias. Strengths of this review include the systematic search we performed, assessing all potential relevant associations of functional and cognitive impairment, social environment and frailty with adverse health outcomes in patients with esophageal cancer. Furthermore, quality assessment of the studies was performed to identify potential factors that may impede external validity.

Given the high prevalence of geriatric impairments described in this review it is likely that systematic geriatric screening and a multidisciplinary approach could be of added value in the treatment of older patients with esophageal cancer. Patients who are at high risk for adverse outcomes can be identified and preventive measures, for example to prevent for a delirium or functional decline, could be taken. This benefit is already described in different patient populations [59, 60]. Furthermore, we advise that future observational studies should report their outcomes in such a way that a meta-analysis is possible.

Conclusion

Functional and cognitive impairment, depression and social isolation are prevalent in patients with esophageal cancer, and associate with adverse health outcomes. Geriatric measurements may guide decision-making and customize treatments, but more large studies are needed to explore the clinical usability.

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