Assessment of Neurocognitive Impairment and Speech Functioning Before Head and Neck Cancer Treatment

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Key points

Question: Pre-treatment neurocognitive function in head and neck cancer patients is poorly studied and the relationship between neurocognitive and speech functioning is unknown.

Findings: In a cohort of 254 newly diagnosed head and neck patients, pre-treatment objective neurocognitive measures indicated 12 to 26% mild to moderate impairment and 5 to 15% moderate to severe impairment. Self-perceived neurocognitive functioning was significantly associated with speech function.

Meaning: Pre-treatment neurocognitive impairment is frequently present in head and neck cancer patients and low self-perceived neurocognitive and speech functioning may impact communicative participation and perceived quality of life.

Abstract

Importance. Head and neck cancer (HNC) and its treatment may negatively affect speech and neurocognitive functioning. However, the prevalence of neurocognitive impairment in HNC patients prior to treatment is poorly studied and the relationship between neurocognitive and speech functioning is unknown, which hampers good interpretability of the impact of HNC treatment on neurocognitive and speech function.

Objective. To document neurocognitive functioning in HNC patients prior to treatment and to investigate the relationship between neurocognitive and speech functioning.

Design, Setting, and Participants. Prospective cohort study of newly diagnosed HNC patients pre-treatment using a large sample collected in a nation-wide, multi-center setting (NET-QUBIC project).

Main Outcome and Measures: Objective neuropsychological measures of memory, fluency, and executive function, as well as patient-reported outcome measures (PROMs) on neurocognitive speech and functioning were collected before treatment.

Results. 254 HNC patients participated (182 men), with a mean age of 62 years. Response rate ranged from 82 to 85%. Objective neurocognitive measures indicated that 5-15% of patients presented with moderate to severe cognitive impairment. Mild to moderate impairment was found in 12-26% of patients. The most affected domains were memory and verbal fluency. 7% of the patients reported high levels of everyday neurocognitive failures and 43% reported speech problems. Objective neurocognitive function was not significantly related to patient-reported neurocognitive or speech functioning, but results from PROMs were significantly correlated.

Conclusions and relevance. The high prevalence of impaired speech functioning among HNC patients prior to treatment is in line with previous findings. A novel finding is that neurocognitive impairment is also highly prevalent, as objectively measured and as self-

perceived. Understanding the reason why HNC patients present with neurocognitive impairment prior to the start of treatment is important as this impairment may complicate patient-clinician interaction, impact treatment adherence, and treatment itself may (further) worsen cognitive functioning. Furthermore, low self-perceived neurocognitive and speech functioning before treatment may impact a patient's confidence in communicative participation and perceived quality of life. Disentangling the relations between objective and patient-reported neurocognitive and speech function is an important area for future research.

Keywords: communication; complications; neuropsychology; speech

Introduction

Being able to communicate is an important factor that predicts quality of life [1,2]. To communicate, speakers access information in long-term memory, employ executive function[3], and prepare and execute a speech-motor program [4,5]. Thus, neurocognitive function and speech-motor processes are inter-related in the production of speech. Speech and neurocognitive functioning are important domains of investigation in head and neck cancer (HNC) patients as HNC and its treatment may affect speech [6,7] as well as neurocognitive functions [8,9]. Research has indicated that neurocognitive and speech problems may already be present in HNC patients at baseline, that is, prior to treatment [10–13].

Speech problems at baseline have been detected using self-report questionnaires [11] as well as through objective assessments from recorded speech [10]. For example, 61% of the patients reported that they had speech problems at baseline, with more problems in cases of oral and oropharyngeal cancer relative to laryngeal/hypopharyngeal cancer [11]. Using objective measures from recorded speech, abnormal intelligibility, nasality, and articulation were found in 17-37% of the patients, with oral cavity tumor cases scoring more poorly than oropharyngeal tumor cases[10]. Both self-reported and objective measures of speech impairment correlated with patients' emotional distress or perceived quality of life[10,11].

Regarding neurocognitive functioning, much less is known. To date, only few studies have reported the prevalence of neurocognitive impairment (i.e., clinically relevant deficits as compared to an age- and education-adjusted normative sample), measured objectively prior to treatment in HNC patients[12–14]. These studies have found between 21-36% of neurocognitive impairment [12,14], using several neuropsychological tests, or about 55% using the Montreal Cognitive Assessment (MoCA) [13]. Besides impacting quality of life, a high prevalence of neurocognitive impairment in this population already before treatment may complicate the

patient-clinician interaction and impact treatment adherence [13]. These factors make a better characterization of pre-treatment neurocognitive impairment critical.

The baseline neurocognitive and speech deficits observed in this population may have different and mutual etiologies. Cognitive deficits originate at the level of the central nervous system, but it remains unclear what their etiological mechanism is [12]. By contrast, motor-speech deficits are related to damage to the organs and muscles involved in speaking (e.g., speech problems are associated with tumor location [11]). However, speaking not only involves peripheral motor function including the vocal tract and speech organs, but also engages multiple cognitive processes, like long-term memory access [4,5] and executive function [3]. Importantly, being able to communicate is an important predictor of quality of life [1,2]. Given that both speech and neurocognitive functions may already be affected pre-treatment in HNC patients, examining these functions in one study sample provides valuable information about this population, as to date, no study has reported on neurocognitive and speech functioning pre-treatment in the same group of patients.

The present study focuses on neurocognitive functioning and speech pre-treatment, using prospective data from a large sample collected in a nation-wide, multi-center setting. Firstly, we document neurocognitive functioning, as measured objectively and subjectively in HNC patients prior to treatment. Secondly, we investigate demographic, behavioral, and disease-related features associated with low neurocognitive functioning in HNC patients. Finally, we characterize for the first time the relationship between neurocognitive and speech function in this population.

Materials and methods

Patients

The present study was part of a large, ongoing prospective cohort study investigating long-term quality of life in HNC patients and their caregivers (NET-QUBIC study; https://researchers.kubusproject.nl/general-information). For the present analyses, baseline data (collected prior to the start of treatment) was used from the first data release including 254 newly diagnosed HNC patients. Clinical and demographic characteristics, alcohol consumption and smoking status were collected via self-report questionnaires and medical records. The characteristics of this group of patients are presented in Table 1.

Patients were recruited from eight different hospitals in different regions in the Netherlands (VUmc Cancer Center Amsterdam, Radboudumc Nijmegen, UMCG Groningen, UMC Utrecht, Erasmus MC Rotterdam, Rijnstate Hospital Arnhem, Noordwest Ziekenhuisgroep Alkmaar, and Medisch Centrum Leeuwarden). Patients meeting the following inclusion criteria were invited to participate: 18 years of age or older, able to write, read, and speak Dutch fluently, newly-diagnosed with HNC (to increase homogeneity, restricted to oral, oropharynx, hypopharynx, larynx, and neck metastasis of unknown primary tumor with proven squamous cell histology; all stages), previously untreated and currently planned treatment with curative intent according to standard treatment guidelines, including surgery, radiotherapy and/or systemic antineoplastic therapy. Exclusion criteria were nasopharyngeal or skin malignancies (due to their low occurrence), malignancies of the salivary glands, lymphoma thyroid cancer, or severe psychiatric co-morbidities (e.g. schizophrenia, Korsakoff's syndrome, severe dementia). Comorbidity scores were defined according to the Adult Comorbidity Evaluation-27 (ACE-27)[15]. All participating patients signed a written consent. Ethical approval was obtained by the coordinating center (METc

VUmc 2013.301) and local approval was obtained for each individual center (see for a more detailed explanation about procedure and recruitment [16]).

Assessments

Assessments were conducted at the hospital and/or the patient's home by trained assessors. Cognitive assessment included the Trail Making Test (TMT; parts A and B), the Hopkins Verbal Learning Test (HVLT), and letter fluency (see[17] for a detailed description of these tests). Variables of interest in the present study were TMT-A (a measure of psychomotor speed), TMT- B (a measure of executive function and attentional control), letter fluency (a measure of verbal fluency, which depends both on linguistic, motor, and executive processes[18]), and delayed recall (a measure of verbal long-term memory) from the HVLT.

As patient-reported outcome measures, the Cognitive Failures Questionnaire (CFQ[19]) was used as a measure of self-perceived neurocognitive functioning. The CFQ is a questionnaire about failures in perception, attention, memory, and motor function (e.g., "Do you bump into people?", "Do you find you forget people's names?"). The Speech Handicap Index (SHI) questionnaire [20] was administered as a measure of self-perceived speech functioning, with questions about speech problems (e.g., "My speech makes it difficult for people to understand me", "The intelligibility is unpredictable"). The SHI is a valid and reliable speech-specific quality of life questionnaire that helps identify the nature and severity of the complaints that HNC patients have[20]. A total SHI score can be calculated, ranging from 0-120, with higher scores indicating more speech problems, and a cut-off point of 6 being able to identify patients with speech problems in daily life. Additionally, two subscales can be derived, reflecting psychosocial function and speech function.

Analyses

Although 254 patients met the inclusion and exclusion criteria, not all patients completed all of the neuropsychological tests or the self-report questionnaires (mainly due to

logistic reasons or patients' own withdraw from participation for that part, since patients could choose in which parts of the NET-QUBIC study they wanted to participate). Missing data for each individual test were identified and for each analysis, only completed cases at the analysis-specific level were included. For all results, we report the sample size on which each of the statistical tests were based.

Available normative data were used to convert the patients' scores of the neuropsychological tests into standardized T-scores (mean = 50, sd = 10), adjusted for age, sex, and education (patients for whom these were known were excluded; HVLT[21]; TMT[22]; verbal fluency, letters "B", "D", and "H", norms derived from own databases). The amount of patients performing >1SD and >2 SD below the age, sex and education adjusted norm was quantified. Neurocognitive impairment was classified as mild to moderate (T-scores 30-39, i.e., 1 to 2 SD below the normative mean), moderate to severe (T-scores ≤29, i.e. more than 2 SD below the normative mean), or unimpaired (T-scores > 39, i.e. less than 1 SD below the normative mean). For the CFQ, cut-off values were used to categorize the scores as very low (≤ 9), low (10-21), average (21-43), high (44-54), and very high(≥ 55)[23]. For the SHI, a previously established cut-off value of 6 was used[20]. The relationship between objectively measured and patient-reported neurocognitive function was assessed with the Spearman's rank correlation coefficient (as the assumptions of linearity and homoscedasticity, as indicated by a Breusch–Pagan test, were not met) for each neurocognitive test of interest separately at an alpha-level level of .05 (subsequently Holm-Bonferroni corrected) . 95% confidence intervals (CI) were computed via bootstrapping (1000 replicates). The relationship between patient-reported neurocognitive and speech function was also assessed in a similar fashion (for the SHI total score, and psychosocial and speech function subscales separately). Finally, a linear regression was used to assess the relative contribution of behavioral (i.e., alcohol consumption, continuous) and disease-related factors (i.e., tumor

stage, transformed into an ordinal variable from 1 to 4, corresponding to stages I, II, III, and IVA, IVB and IVC) as well as their interaction on neurocognitive functioning. For the objective measures, standardized T-scores were used (i.e., already corrected for age, sex, and education). For the patient-reported neurocognitive functioning, demographic variables (i.e., sex (women as the reference), age (continuous), education (transformed into an ordinal variable)) were also entered. All analyses were conducted in R, base library[24], and RVAideMemoire for computing 95% confidence intervals of Spearman's rank correlation coefficients. This study was pre-registered (see supplement for the pre-registration).

Results

The characteristics of the 254 participants are summarized in Table 1. Participants were predominantly men (72%) and the mean and median age was 62 years (range = 37 to 85, sd = 9.9), similar to other studies[9,12,13,25]. A majority of the participants had oropharyngeal cancer (35%) and stage IVa cancer (38%). Current alcohol consumption (total number of glasses beer, wine, and spirits per week) ranged between 0 and 140 (mean = 17; median = 12, sd = 19.9%).

When comparing the demographic and clinical variables between patients who completed all tests versus patients who did not complete one or more tests (shown in Table 1), no clinically meaningful differences were found for age (mean: 62.7 years vs 60.9 years, respectively), sex distribution , education level, tumor stage and location, literacy, or smoking status. The distribution of comorbidity scores did differ between the two groups: Those who completed all assessments had more often severe comorbidity scores or no comorbidity (severe:moderate:mild:none, respectively: 17.4:16.8:30.3:35.5%) relative to those who did not complete all tests (severe : moderate : mild : none, respectively: 13.4:17.1:48.8:20.7%). Twenty-eight patients did not complete the SHI and CFQ, but completed all objective

Table 1. Demographic and clinical characteristics of patients for the complete dataset (N = 254) and restricted to the set of patients who completed all patient-reported outcome measures and neurocognitive tests (N=162). Percentages are given in parentheses, rounded to one decimal point.

Variable	Levels	N = 254 (%)	N = 162
Sex distribution	Men:women	182:72 (71.7:28.3%)	116:46 (71.6:28.4%)
Education	Primary education (6 y)	13 (5.1%)	7 (4.3%)
	Lower or preparatory vocational education (9 y)	53 (20.9%)	38 (23.5%)
	Intermediary general secondary education (10 y)	33 (13%)	25 (15.4%)
	Senior general secondary education (16 y)	40 (15.7%)	29 (17.9%)
	Higher general secondary education (15 y)	23 (9.1%)	19 (11.7%)
	Higher professional education (16 y)	38 (15%)	30 (18.5%)
	University (18 y)	16 (6.3%)	14 (8.6%)
	Missing	38 (15%)	0
Literacy	Excellent (mother tongue)	173 (68.1%)	134 (82.7%)
	Good	40 (15.7%)	26 (16%)
	Average	4 (1.6%)	2 (1.2%)
	Missing	37 (14.6%)	0
Tumor stage	Stage I	57 (22.4%)	42 (25.9%)
	Stage II	39 (15.4%)	23 (14.2%)
	Stage III	51 (20.1%)	31 (19.1%)
	Stage IVA	96 (37.8%)	62 (38.3)
	Stage IVB	10 (3.9%)	4 (2.5%)
	Stage IVC	1 (0.4%)	0
Tumor site	Hypopharynx	23 (9.1%)	14 (8.6%)
	Larynx	66 (26%)	40 (24.7%)
	Oral cavity	72 (28.3%)	47 (29%)
	Oropharynx	89 (35%)	57 (35.2%)
	Unknown	4 (1.6%)	4 (2.5%)
Comorbidity score	Severe	38 (15%)	27 (16.7%)
	Moderate	40 (15.7%)	26 (16%)
	Mild	87 (34.3%)	47 (29%)
	None	72 (28.3%)	55 (34%)
	Missing	17 (6.7%)	7 (4.3%)
Smoking status	Never	24 (9.4%)	16 (9.9%)
	Current	67 (26.4%)	49 (30.2%)
	Former	118 (46.5%)	90 (55.6%)
	Missing	45 (17.7%)	7 (4.3%)

Note: y = years

neurocognitive tests. No differences were found in scores between the two groups for any test (all 95% CIs overlap with zero). Thirty-two patients did not complete any of the objective

neurocognitive tests, but completed both SHI and CFQ. No differences were found in the scores between the two groups (all 95% CIs overlap with zero).

Moderate to severe impairments were found in 15% of the patients in delayed recall (N = 214), 6% in letter fluency (N = 215), 5% in psychomotor speed (TMT-A, N = 212), and 6% in executive functioning (TMT-B, N = 211). Mild to moderate impairments were found in 26% of the patients in delayed recall, 24% in letter fluency, 12% in psychomotor speed, and 20% in executive functioning, as shown in Figure 1.

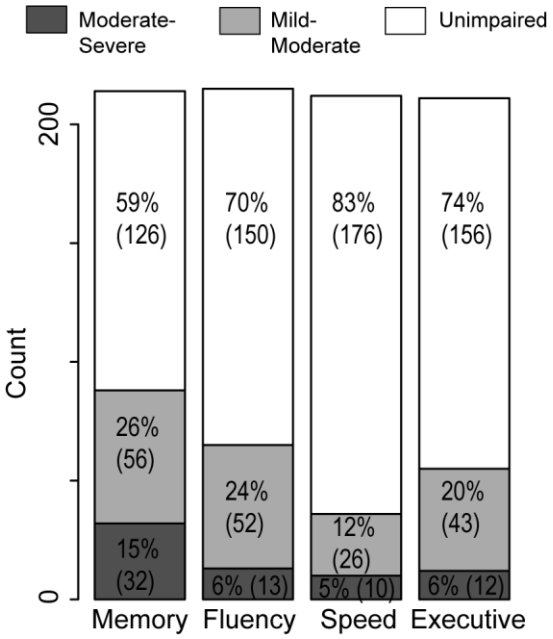

Figure 1. Rate of neurocognitive impairment. Amount and proportion of patients scoring in the unimpaired (white), mild to moderately impaired (light grey), and moderately to severely impaired (dark grey) range for delayed recall of the Hopkins Verbal Learning Test ("Memory"), verbal fluency, psychomotor speed ("Speed"), calculated from the Trial Making Test – part A, and executive function, calculated from the Trial Making Test – part B.

Figure 2 summaries the patients' self-reported cognitive functioning (based on N = 208) and speech (based on N = 209), overall and by tumor site. For the CFQ, 7% of the patients reported experiencing above-average failures, whereas 43% of the patients scored in the impaired range for self-perceived speech problems (i.e., above the cut-off of 6 points on the SHI total score[20].

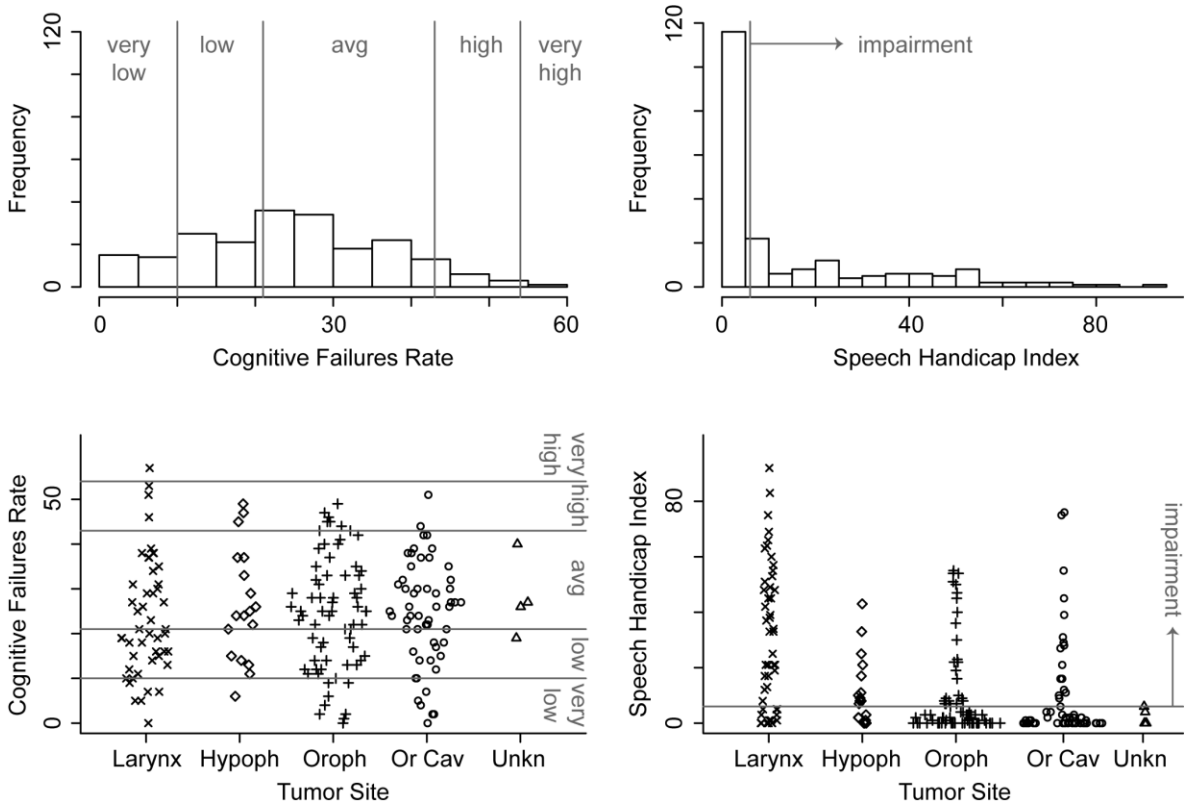

Figure 2. Patient-reported neurocognitive and speech functioning. Histograms of the neurocognitive function (upper left) and speech handicap (upper right) and distribution of neurocognitive functioning (lower left) and speech handicap (lower right) scores per tumor site. Higher values indicate more impairment. Upper panels. The vertical lines indicate the cut-off values (for neurocognitive functioning, categories are indicated on top). Lower panels. The horizontal lines indicate the cut-off values (for neurocognitive functioning, categories are indicated to the right). Each data point represents one participant. Avg = average; Hypoph = hypopharynx; Oroph = oropharynx; Or Cav = oral cavity; Unkn = Unknown.

Patient-reported and objective neurocognitive functioning were not predicted by any variable, be it demographic, behavioral, or disease-related (models' adjusted R^2, CFQ = -.006, SHI = .025, memory = -.016, fluency = -.018, psychomotor speed = .026, executive function = -.003). Furthermore, no significant effects were found in regression models with additional predictors (comorbidity, literacy, smoking status, and tumor site, models' adjusted R^2, CFQ = -.035, SHI = .116, memory = -.052, fluency = .034, psychomotor speed = .068, executive function = -.051). The results of these models are reported in the supplement.

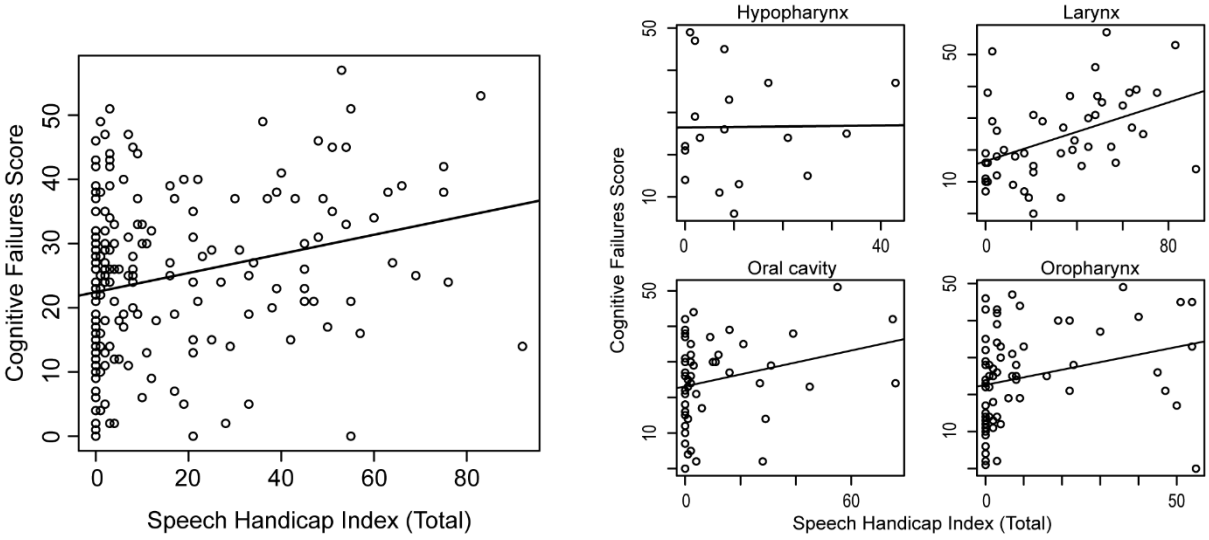

Figure 3. Relationship between self-perceived neurocognitive and speech functioning. Lines of fit are derived by fitting an ordinary least-squares model to the data. Left. Complete sample (N = 195, *rho* = .266, unstandardized beta coefficient = .149). Right. Stratified by tumor site. Hypopharynx: N = 18, *rho* = .018, unstandardized beta coefficient = .012; Larynx: N = 48, *rho* = .489, unstandardized beta coefficient = .231; Oral cavity: N = 55, *rho* = .225, unstandardized beta coefficient = .168; Oropharynx: N = 70, *rho* = .379, unstandardized beta coefficient = .205.

Objective and patient-reported neurocognitive measures did not correlate significantly (all Spearman coefficients were between -.026 and .155 and 95% CIs overlapped with zero, except for TMT-A [.009, .289]. Objective neurocognitive measures did not correlate significantly with patient-reported speech outcome (all Spearman coefficients were between -.124 and .172 and 95% CIs overlapped with zero, except for TMT-B [.018, .321]). Patient-reported neurocognitive functioning was significantly correlated with speech functioning (total SHI score) with a small effect size, *rho* = .266, 95% CI [.126, .4] (N = 195), as shown in Figure 3 (also by tumor site). When the analyses were restricted to the group who completed all tests (*N* = 162), the exact same relationship was observed (*rho* = .266). The SHI subscales were also significantly correlated with patient-reported neurocognitive functioning: psychosocial function, *rho* = .245, 95% CI [.110, .374]; speech function, *rho* = .250, 95% CI [.116, .39]. However, with both SHI subscales as predictors in a regression model of patient-reported neurocognitive functioning, only the psychosocial subscale was

significant (psychosocial: unstandardized beta = .409, t = 2.262; speech: unstandardized beta = -.025, t < 1; adjusted R^2 = .064).

Discussion

Using prospective data from a large sample collected nation-wide, the present study documented the prevalence of neurocognitive and speech impairment pre-treatment in patients newly diagnosed with head and neck cancer. Moreover, we reported for the first time the relationship between patient-reported neurocognitive and speech functioning and objectively measured neurocognitive functioning.

Regarding speech, almost half of the patients reported self-perceived speech in the impaired range. This prevalence is similar to what has been previously reported[11]. Self-perceived neurocognitive failures were observed in a small subgroup of the patients.

The prevalence of neurocognitive impairment we report is similar or slightly higher than previously reported using similar neuropsychological tests[12,14], despite the similarity in age, sex, and education level between the samples. However, the sample size is more than three times larger in our study and our data were collected in a multi-center setting. The prevalence we report is, however, lower than previously reported using the MoCA[13], with which more than half of the patients were found to have mild cognitive impairment. However, it should be noted that the MoCA has both a lower sensitivity and a lower specificity than the neuropsychological tests we employed [26,27]. Additionally, it has limited adjustment for education level [28]. These two factors could explain the discrepancy between our results and the findings based on that assessment.

The rates of severe to moderate impairment we observed (5-15%) are higher than what can be expected in the normal population (in which, by definition, 2.3% of the population performs 2 or more SDs below the normative mean). Thus, there is a substantial

subgroup of patients who present with moderate to severe cognitive impairment already at baseline, which could not be explained by demographic variables such as age, sex, and education, nor by alcohol consumption or disease stage (and also comorbidities, smoking, literacy, and tumor site, as reported in the supplement). Understanding the reason why this subgroup present with neurocognitive impairment prior to the start of treatment is important as treatments may trigger cerebrovascular disease [29] and, consequently, affect neurocognitive function. As mentioned previously, it remains an open question whether the neurocognitive impairment is caused by biological processes triggered by the cancer and/or by risk factors that impact both cognitive functioning and the pathology itself [12]. For example, Bond et al. found an association between smoking and alcohol misuse on the one hand, and global neurocognitive deficit on the other hand. The association with alcohol misuse was, however, not significant at the level of the individual neurocognitive measures. In our sample, the performance in the neuropsychological measures could not be explained by alcohol consumption. Additional large-scale studies focusing on this question are needed. Longitudinal studies on neurocognitive changes following treatment, enabling the comparison across different treatment types, may also help elucidate this question as surgery alone is expected to have a much smaller impact on the central nervous system than (chemo-)radiation.

Our study has a number of limitations. We did not include objective measures of speech functioning, but they are necessary for further understanding what impacts a patient's communicative participation. In addition, we did not have performance validity measures that would enhance the interpretation of the neuropsychological tests, for example, in helping to exclude the possibility that low performance in the neuropsychological tests was not due to a lack of effort put forth by the individuals when performing the tests. Our study also lacks

specific control data, making it more difficult to interpret the results in light of risk factors for neurocognitive decline.

Understanding impairments in neurocognitive functioning at baseline, also in relation to speech function, is not only important in itself (e.g., for patient counselling and education, and for treatment decision-making) but also for understanding treatment-related changes. Previous studies examining the decline of neurocognitive function due to cancer therapy have been criticized for the lack of baseline data [30]. Our study is the first to examine systematically the relationship between (patient-reported) neurocognitive and patient-reported speech functioning already at baseline. Interestingly, we found a relationship, albeit weak, between patient-reported outcomes, i.e., neurocognitive and speech functioning. This relationship was especially prominent in the group with laryngeal cancer in our sample. This group does not show notably high rates of patient-reported cognitive failures, but the rate of patient-reported speech impairment had a larger spread and generally higher values. An important question for future research is whether this group is particularly vulnerable to treatment effects. It is possible that individuals who experience more neurocognitive failures may also experience more communication difficulties. This interpretation is further supported by the finding that the psychosocial functioning subscale of the SHI measure better explains the variance in patient-reported neurocognitive functioning than the speech subscale of the SHI does. Overall, the data suggest that patient-reported speech and neurocognitive functioning do dissociate, but may interact at the level of daily life situations, shaping the patients' perception of their functioning. This relationship merits further investigation as it may hold important clues to understanding patient-doctor interactions, and the patients' perceived communicative participation and quality of life [31].

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