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

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IMPORTANCE Head and neck cancer (HNC) and its treatment may negatively alter neurocognitive and speech functioning. However, the prevalence of neurocognitive impairment among patients with HNC before treatment is poorly studied, and the association between neurocognitive and speech functioning is unknown, which hampers good interpretability of the effect of HNC treatment on neurocognitive and speech function.

OBJECTIVES To document neurocognitive functioning in patients with HNC before treatment and to investigate the association between neurocognitive and speech functioning.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study of newly diagnosed patients with HNC before treatment using a large sample obtained in a nationwide, multicenter setting (Netherlands Quality of Life and Biomedical Cohort Study in Head and Neck Cancer [NET-QUBIC] project).

MAIN OUTCOME AND MEASURES Objective neuropsychological measures of delayed recall, letter fluency, and executive functioning, as well as patient-reported outcome measures on neurocognitive speech and functioning, were collected before treatment.

RESULTS In total, 254 patients with HNC participated (71.7% male), with a mean (SD) age of 62 (10) years. The response rate ranged from 81.9% (208 of 254) to 84.6% (215 of 254). Objective neurocognitive measures indicated that 4.7% (10 of 212) to 15.0% (32 of 214) of patients were initially seen with moderate to severe cognitive impairment. Mild to moderate impairment was found in 12.3% (26 of 212) to 26.2% (56 of 214) of patients. The most altered domains were delayed recall and letter fluency. Seven percent (15 of 208) of the patients reported high levels of everyday neurocognitive failure, and 42.6% (89 of 209) reported speech problems. Objective neurocognitive function was not significantly associated with patient-reported neurocognitive or speech functioning, but the results from patient-reported outcome measures were significantly correlated.

CONCLUSIONS AND RELEVANCE Results of this study demonstrate a high prevalence of impaired speech functioning among patients with HNC before treatment, which 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 patients with HNC are initially seen with neurocognitive impairment before the start of treatment is important because this impairment may complicate patient-clinician interaction and alter treatment adherence and because treatment itself may further worsen cognitive functioning. In addition, low self-perceived neurocognitive and speech functioning before treatment may decrease a patient's confidence in communicative participation and perceived quality of life. Disentangling the associations between objective and patient-reported neurocognitive and speech functions is an important area for future research.

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Supplemental content

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Being able to communicate is an important factor that predicts quality of life.[1,2] To communicate, speakers access information in long-term memory, use executive function,[3] and prepare and execute a motor speech program.[4,5] Therefore, neurocognitive function and motor speech processes are interrelated in the production of speech. Neurocognitive and speech functioning represent important domains of investigation in patients with head and neck cancer (HNC) because HNC and its treatment may alter speech[6,7] and neurocognitive functions.[8,9] Research has indicated that neurocognitive and speech problems may already be present in patients with HNC at baseline (ie, before treatment).[10-13]

Speech problems at baseline have been detected using self-report questionnaires[11] and through objective assessments from recorded speech.[10] For example, 61% of patients with HNC reported that they had speech problems at baseline, with greater difficulties in oral and oropharyngeal cancer relative to laryngeal and hypopharyngeal cancer.[11] Using objective measures from recorded speech, abnormal intelligibility, nasality, and articulation were found in 17% to 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, few studies[12-14] have reported the prevalence of neurocognitive impairment (ie, clinically relevant deficits compared with an age- and education-adjusted normative sample) as measured objectively before treatment among patients with HNC. These studies found between 21% and 36% neurocognitive impairment[12,14] using several neuropsychological tests, with about 55% using the Montreal Cognitive Assessment (MoCA).[13] Besides decreasing quality of life, a high prevalence of neurocognitive impairment among this population before treatment may complicate patient-clinician interaction and alter treatment adherence.[13] These factors emphasize that better characterization of pretreatment neurocognitive impairment is 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 their etiological mechanism remains unclear.[12] In contrast, motor speech deficits are associated with damage to the organs and muscles involved in speaking (eg, 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, such as long-term memory access[4,5] and executive function.[3] 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 before treatment in patients with HNC, examining these functions in one study sample provides valuable information about this population. To date, no study has reported on neurocognitive and speech functioning before treatment in the same group of patients.

The present study focused on neurocognitive functioning and speech before treatment using prospective data from a large sample collected in a nationwide, multicenter setting (Netherlands Quality of Life and Biomedical Cohort Study in Head and Neck Cancer [NET-QUBIC] project). First, we documented neurocognitive functioning as measured objectively and subjectively in patients with HNC before treatment. Second, we investigated demographic, behavioral, and disease-related features associated with low neurocognitive functioning in patients with HNC. Third, we characterized for the first time to date the association between neurocognitive and speech functioning in this population.

Key Points

Question What is pretreatment neurocognitive function in patients with head and neck cancer and what is the association between neurocognitive and speech functioning?

Findings In a cohort study of 254 newly diagnosed patients with head and neck cancer, pretreatment objective neurocognitive measures indicated 12.3% to 26.2% mild to moderate impairment and 4.7% to 15.0% moderate to severe impairment. Self-perceived neurocognitive functioning was significantly associated with speech function.

Meaning Results of this study suggest that pretreatment neurocognitive impairment is frequently present in patients with head and neck cancer, and low self-perceived neurocognitive and speech functioning may alter communicative participation and perceived quality of life.

Methods

Patients

This research was part of a large, ongoing prospective cohort study investigating long-term quality of life in patients with HNC and their caregivers (NET-QUBIC study [https://researchers.kubusproject.nl/general-information]). For the present analyses, baseline data (collected before the start of treatment) were used from the first data release, which included 254 newly diagnosed patients with HNC. 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 listed in the **Table**.

Patients were recruited from 8 hospitals in different regions in the Netherlands (Radboud University Medical Center, Nijmegen; Amsterdam UMC, Amsterdam; University Medical Center, Utrecht; University Medical Centre Groningen, Groningen; 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 or older; able to write, read, and speak Dutch fluently; newly diagnosed with HNC (to increase homogeneity, restricted to larynx, hypopharynx, oropharynx, oral cavity, and neck metastasis of unknown primary tumor with proven squamous cell histology [all stages]); and 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 cancers (due to their low occurrence), tumors of the salivary glands, lymphoma thyroid cancer, or severe psychiatric comorbidities (eg, schizophrenia, Korsakoff syndrome, and severe dementia). Comorbidity scores

Table. Demographic and Clinical Characteristics of Patients for the Complete Data Set and Restricted to the Set of Patients Who Completed All Patient-Reported Outcome Measures and Neurocognitive Tests

Variable	No. (%)	
	Complete Data Set (N = 254)	Completed All Tests (n = 162)
Sex distribution, No. (%)		
Men	182 (71.7)	116 (71.6)
Women	72 (28.3)	46 (28.4)
Education		
Primary (6 y)	13 (5.1)	7 (4.3)
Lower or preparatory vocational (9 y)	53 (20.9)	38 (23.5)
Intermediary general secondary (10 y)	33 (13.0)	25 (15.4)
Senior general secondary (11 y)	40 (15.7)	29 (17.9)
Higher general secondary (15 y)	23 (9.1)	19 (11.7)
Higher professional (16 y)	38 (15.0)	30 (18.5)
University (18 y)	16 (6.3)	14 (8.6)
Missing	38 (15.0)	0
Literacy		
Excellent (mother tongue)	173 (68.1)	134 (82.7)
Good	40 (15.7)	26 (16.0)
Average	4 (1.6)	2 (1.2)
Missing	37 (14.6)	0
Tumor stage		
I	57 (22.4)	42 (25.9)
II	39 (15.4)	23 (14.2)
III	51 (20.1)	31 (19.1)
IVA	96 (37.8)	62 (38.3)
IVB	10 (3.9)	4 (2.5)
IVC	1 (0.4)	0
Tumor site		
Larynx	66 (26.0)	40 (24.7)
Hypopharynx	23 (9.1)	14 (8.6)
Oropharynx	89 (35.0)	57 (35.2)
Oral cavity	72 (28.3)	47 (29.0)
Unknown	4 (1.6)	4 (2.5)
Comorbidity score		
Severe	38 (15.0)	27 (16.7)
Moderate	40 (15.7)	26 (16.0)
Mild	87 (34.3)	47 (29.0)
No comorbidity	72 (28.3)	55 (34.0)
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)

were defined according to the Adult Comorbidity Evaluation 27 (ACE-27).[15] All participating patients signed an informed consent. Ethical approval was obtained by the coordinating center (Medical Ethical Committee Vrije UMC), and local approval was obtained for each individual center (a more detailed explanation about the procedure and recruitment has been previously published[16]).

Assessments

Assessments were conducted at the hospital and/or the patient's home by trained assessors. Cognitive assessment included the Trail Making Test[17] (TMT) parts A and B, the Hopkins Verbal Learning Test[18] (HVLT), and letter fluency (a detailed description of these tests has been previously published[19]). 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), delayed recall (a measure of verbal long-term memory) from the HVLT, and letter fluency (a measure of verbal fluency that depends on linguistic, motor, and executive processes[20]).

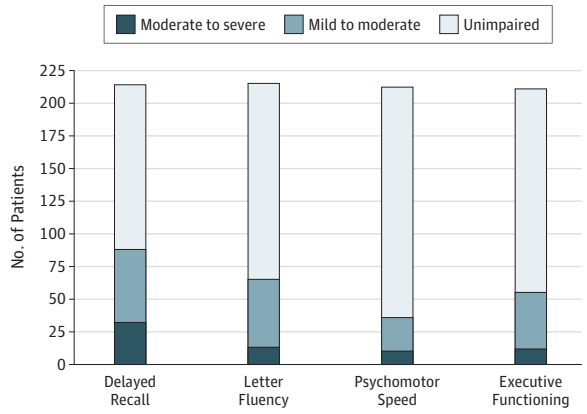
As patient-reported outcome measures, the Cognitive Failures Questionnaire[21] (CFQ) was used as a measure of self-perceived neurocognitive functioning. The CFQ is a questionnaire about failures in perception, attention, memory, and motor function (eg, "Do you bump into people?" and "Do you find you forget people's names?"). The Speech Handicap Index[22] (SHI) questionnaire was administered as a measure of self-perceived speech functioning, with questions about speech problems (eg, "My speech makes it difficult for people to understand me" and "The intelligibility is unpredictable"). The SHI is a valid, reliable speech-specific quality-of-life questionnaire that helps identify the nature and severity of the problems experienced by patients with HNC.[22] A total SHI can be calculated ranging from 0 to 120, with higher scores indicating more speech problems and with a cutoff value of 6 being able to identify patients with speech problems in daily life. In addition, 2 subscales can be derived that reflect psychosocial function and speech function.

Statistical Analysis

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 the patients' own withdrawal from participation for that part because 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 was based.

Available normative data were used to convert the patients' results on the neuropsychological tests into standardized T scores (mean [SD], 50 [10]), adjusted for age, sex, and education (HVLT[18]; TMT[17]; and verbal fluency, letters *B*, *D*, and *H*, norms derived from own databases). Patients for whom demographic information was unknown were excluded. The proportions of patients performing more than 1 SD and more than 2 SDs below the age-, sex-, and education-adjusted norm were quantified. Neurocognitive impairment was classified as mild to moderate (T score, 30-39 [ie, 1-2 SDs below the normative mean]), moderate to severe (T score, ≤29 [ie, >2 SDs below the normative mean]), or unimpaired (T score, >39 [ie, <1 SD below the normative mean]). For the CFQ, cutoff values were used to categorize the scores as very low (≤9), low (10-20), average (21-43), high (44-54), or very high (≥55).[23] For the SHI, a previously established cutoff value of 6 was used.[22] The association between objectively measured and patient-reported neurocognitive function was assessed with the Spearman rank correlation coefficient (because the assumptions of linearity and homoscedasticity as indicated by a Breusch-

Figure 1. Rate of Neurocognitive Impairment



Patients scoring in the moderate to severe, mild to moderate, and unimpaired range for delayed recall (from the Hopkins Verbal Learning Test), letter fluency and psychomotor speed (from the Trail Making Test Part A), and executive functioning (from the Trail Making Test Part B).

Pagan test were not met) for each neurocognitive test of interest separately. The 95% CIs were computed via bootstrapping (1000 replicates). The association between patient-reported neurocognitive and speech functions was also assessed in a similar fashion (for the total SHI, psychosocial and speech function subscales separately). Finally, a linear regression was used to assess the relative contribution of behavioral (ie, alcohol consumption [continuous]) and disease-related factors (ie, 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 with neurocognitive functioning. For objective measures, standardized T scores were used (ie, already corrected for age, sex, and education). For patient-reported neurocognitive functioning, demographic variables (ie, age [continuous], sex [women as the reference], and education [transformed into an ordinal variable]) were also entered. All analyses were conducted in R (The R Foundation),[24] R base library, and RVAideMemoire (CRAN [cran.r-project.org]) for computing 95% CIs of Spearman rank correlation coefficients. This study was preregistered, and the preregistration is available in Supplement 1.

Results

The characteristics of 254 newly diagnosed patients with HNC are summarized in the Table. Participants were predominantly male (182 patients [71.7%]), and the mean (SD) and median age was 62 (10) years (range, 37-85 years), similar to other studies.[9,12,13,25] Most of the participants had stage IVA cancer (37.8% [96 of 254]) and oropharyngeal cancer (35.0% [89 of 254]). Current alcohol consumption (total number of glasses of beer, wine, and spirits per week) ranged from 0 to 140 (mean [SD], 17 [20]; median, 12). The response rate ranged from 81.9% (208 of 254) to 84.6% (215 of 254).

When comparing the demographic and clinical variables between patients who completed all tests vs patients who did not complete 1 or more tests (summarized in the Table), no clinically meaningful differences were found for age (mean, 62.7 vs 60.9 years, respectively), sex distribution, education, literacy, tumor stage and tumor site, or smoking status. The distribution of comorbidity scores did differ between the 2 groups. Those who completed all assessments more often had severe comorbidity scores or no comorbidity (17.4% severe, 16.8% moderate, 30.3% mild, and 35.5% none) relative to those who did not complete all tests (13.4% severe, 17.1% moderate, 48.8% mild, and 20.7% none). Twenty-eight patients did not complete the CFQ and the SHI, but they completed all objective neurocognitive tests. No differences were found in the scores between the 2 groups for any test (all 95% CIs overlap with zero). Thirty-two patients did not complete any of the objective neurocognitive tests, but they completed both the CFQ and the SHI. No differences were found in the scores between the 2 groups (all 95% CIs overlap with zero).

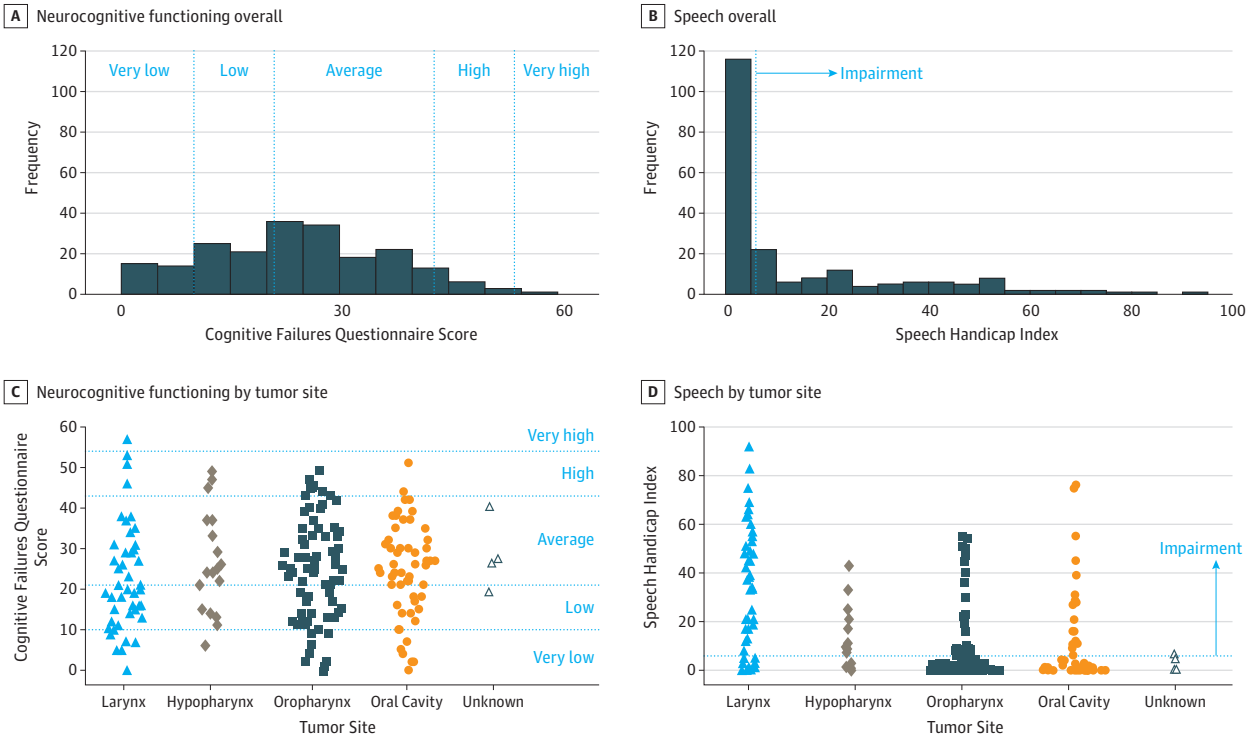
As shown in **Figure 1**, moderate to severe impairment was found in 15.0% (32 of 214) of the patients in delayed recall, 6.0% (13 of 215) in letter fluency, 4.7% (10 of 212) in psychomotor speed (TMT-A), and 5.7% (12 of 211) in executive functioning (TMT-B). Mild to moderate impairment was found in 26.2% (56 of 214) of the patients in delayed recall, 24.2% (52 of 215) in letter fluency, 12.3% (26 of 212) in psychomotor speed, and 20.4% (43 of 211) in executive functioning.

Figure 2 summarizes the patients' self-reported cognitive functioning (n = 208) and speech (n = 209) overall and by tumor site. For the CFQ, 7.2% (15 of 208) of the patients reported experiencing above-average failure; for the total SHI, 42.6% (89 of 209) of the patients scored in the impaired range for self-perceived speech problems (ie, above the cutoff value of 6).

Patient-reported and objective neurocognitive functioning was not associated with any variable (demographic, behavioral, or disease related): the models' adjusted R^2 values were −0.006 for the CFQ, 0.025 for the SHI, −0.016 for delayed recall, −0.018 for letter fluency, 0.026 for psychomotor speed, and −0.003 for executive functioning). Furthermore, no significant associations were found in regression models with additional variables of literacy, tumor site, comorbidity score, and smoking status: the models' adjusted R^2 values were −0.035 for the CFQ, 0.116 for the SHI, −0.052 for delayed recall, 0.034 for letter fluency, 0.068 for psychomotor speed, and −0.051 for executive functioning). The results of these models are summarized in eTables 1, 2, 3, and 4 in Supplement 2.

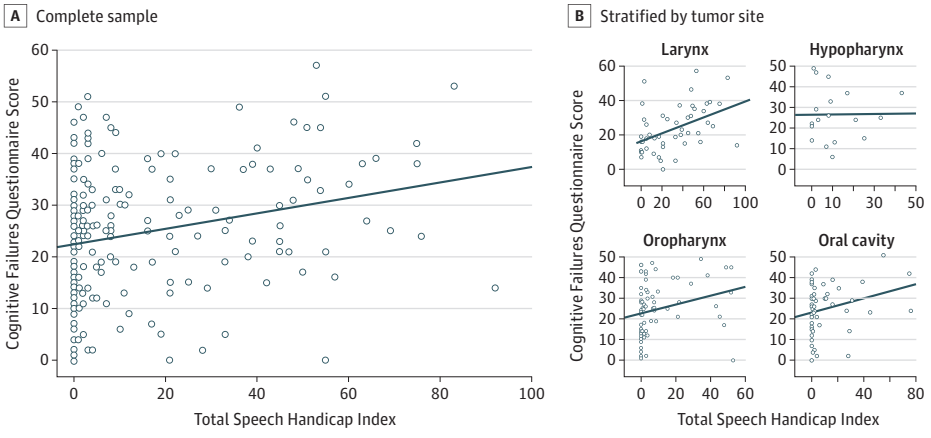
Objective and patient-reported neurocognitive measures did not correlate significantly (all Spearman rank correlation coefficients were between −0.026 and 0.155, and 95% CIs overlapped with zero except for TMT-A [95% CI, 0.009-0.289]). Objective neurocognitive measures did not correlate significantly with patient-reported speech outcome (all Spearman rank correlation coefficients were between 0.124 and 0.172, and 95% CIs overlapped with zero except for TMT-B [95% CI, 0.018-0.321]). Patient-reported neurocognitive functioning was significantly correlated with speech functioning (total SHI), with a small effect size (ρ = 0.266; 95% CI, 0.126-0.400) (n = 195), as shown in **Figure 3** (also by tumor site). When the analyses were restricted to the group that completed all tests (n = 162), the exact same association was observed (ρ = 0.266). The SHI

Figure 2. Patient-Reported Neurocognitive and Speech Functioning



A-D, Patient self-reported cognitive functioning and speech overall and by tumor site. Higher values indicate more impairment. A and B, The vertical blue lines indicate the cutoff values. C and D, The horizontal blue lines indicate the cutoff values. Each data point represents 1 participant.

Figure 3. Association Between Self-perceived Neurocognitive and Speech Functioning



A-B, Lines of fit are derived by fitting an ordinary least squares model to the data. A, Among 195 patients (ρ = 0.266, unstandardized β = 0.149). B, Larynx (n = 48, ρ = 0.489, unstandardized β = 0.231), hypopharynx (n = 18, ρ = 0.018, unstandardized β = 0.012), oropharynx (n = 70, ρ = 0.379, unstandardized β = 0.205), and oral cavity (n = 55, ρ = 0.225, unstandardized β = 0.168).

subscales were also significantly correlated with patient-reported neurocognitive functioning (ρ = 0.245; 95% CI, 0.110-0.374 for psychosocial function and ρ = 0.250; 95% CI, 0.116-0.390 for speech function). However, with both SHI subscales as variables in a regression model of patient-reported neurocognitive functioning, only the psychosocial function subscale was significant (psychosocial unstandardized β = 0.409, t = 2.262; speech unstandardized β = −0.025, t = −0.194; adjusted R^2 = 0.064).

Discussion

Using prospective data from a large sample collected nationwide, the present study documented the prevalence of neurocognitive and speech impairment before treatment among patients newly diagnosed as having HNC. Moreover, we report for the first time to our knowledge an association 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 failure was observed in a small subgroup of the patients.

The prevalence of neurocognitive impairment we report herein is similar to or slightly higher than that previously reported using comparable neuropsychological tests,[12,14] with additional similarity in age, sex, and education between the samples. However, the sample size is more than 3 times larger in our study, and our data were collected in a multicenter setting. Furthermore, the prevalence we report is lower than that previously reported using the MoCA,[13] with which more than half of the patients were found to have mild cognitive impairment. However, the MoCA has both a lower sensitivity and a lower specificity than the neuropsychological tests we used.[26,27] In addition, the MoCA has limited adjustment for education level.[27] These 2 factors could explain the discrepancy between our results and the findings based on that assessment.

The rates of severe to moderate impairment we observed (4.7%-15.0%) are higher than what can be expected in the healthy population (in which by definition 2.3% of the population performs ≥2 SDs below the normative mean). Therefore, there is a substantial subgroup of patients with HNC who are seen with moderate to severe cognitive impairment already at baseline, which could not be explained by demographic variables, such as age, sex, and education, or by alcohol consumption or disease stage (as well as literacy, tumor site, comorbidity score, and smoking status as summarized in eTables 1, 2, 3, and 4 in Supplement 2). Understanding the reason why this subgroup is seen with neurocognitive impairment before the start of treatment is important because treatments may trigger cerebrovascular disease[28] and consequently influence 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 alter both cognitive functioning and the pathology itself.[12] For example, Bond et al[12] found an association between smoking and alcohol abuse on the one hand and between smoking and global neurocognitive deficit on the other hand. However, the association with alcohol abuse was not significant at the level of the individual neurocognitive measures. In our sample, performance on 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 after treatment, enabling comparison across different treatment types, may also help elucidate this question because surgery alone is expected to have a smaller influence on the central nervous system than chemotherapy or radiotherapy.

Limitations

Our study has some limitations. We did not include objective measures of speech functioning, but they are necessary for further understanding what alters a patient's communicative participation. In addition, we did not have performance validity measures that would enhance the interpretation of the neuropsychological tests (eg, in helping exclude the possibility that low performance on 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.

Conclusions

Understanding impairment in neurocognitive functioning at baseline, as well as in relation to speech function, is important not only in itself (eg, for patient counseling and education and for treatment decision making) but also for understanding treatment-related changes. Previous research examining the decline in neurocognitive function due to cancer therapy has been criticized for a lack of baseline data.[29] Our study is the first to date to systematically examine the association between patient-reported neurocognitive functioning and patient-reported speech functioning already at baseline. We found an association, albeit weak, between the patient-reported outcomes of neurocognitive functioning and speech functioning. This association was especially prominent among the patients with laryngeal cancer in our sample. This group does not show notably high rates of patient-reported cognitive failure, 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 influences. Furthermore, it is possible that individuals who experience more neurocognitive failure also have more communication difficulty. This interpretation is further supported by the finding herein that the psychosocial function subscale of the SHI better explains the variance in patient-reported neurocognitive functioning than does the speech function subscale of the SHI. Overall, the data suggest that patient-reported neurocognitive and speech functioning do dissociate but may interact at the level of daily life situations, shaping the patients' perception of their functioning. This association merits further investigation because it may hold important clues to understanding patient-clinician interaction as well as the patients' perceived communicative participation and quality of life.[30]

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Author Contributions: Dr Piai had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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