Neurocognitive Functioning of Patients with Sinonasal and Nasopharyngeal Cancers Treated With Multimodality Therapy

Dan Yaniv[1] Lindsay M. Niccolai[2] Jeffrey S. Wefel[2,3] Catherine M. Sullaway[2] Jack Phan[3] Clifton David Fuller[3] Kareem B. Haroun[4] Ehab Y. Hanna[1] Shirley Y. Su[1]

[1] Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States
[2] Department of Neuro-Oncology, Section of Neuropsychology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States
[3] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States
[4] Department of Otolaryngology, The University of Texas Medical Branch, Galveston, Texas, United States

Address for correspondence Shirley Y. Su, MBBS, MD, Anderson Cancer Center, Houston, TX, United States (e-mail: sysu@mdanderson.org).

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Abstract

Importance Few recent studies have examined neurocognitive functioning (NCF) in patients with sinonasal and nasopharyngeal cancers (NPCs) prior to and following multimodality therapy or the potential differences in NCF by disease variables such as disease site.

Objective The objective of this study is to determine rates of NCF impairments prior to and following multimodality therapy, declines in NCF following radiotherapy (RT), and possible differences in NCF by the disease site.

Design, Setting, and Participants We conducted a retrospective chart review of 39 patients with sinonasal and NPCs who underwent comprehensive neuropsychological evaluations. Twenty patients were evaluated prior to RT, of which eleven received follow-up evaluation after completion of RT. Nineteen patients were evaluated following various treatments without a pre-RT evaluation.

Main Outcomes and Measures Patients completed comprehensive neuropsychological evaluations. Decline from pre-RT to follow-up was defined on the basis of reliable change indices.

Results Thirty-nine patients completed comprehensive neuropsychological evaluations. For the entire cohort, the most frequently demonstrated impairments were in verbal memory (47%) and learning (43%), executive functioning (33%), and verbal fluency (22%). At post-RT follow-up, the most frequently observed declines were in verbal learning (46%) and memory (18%). Demographic and disease variables were not significantly associated with NCF at pre-RT or post-RT.

Conclusion and Relevance Patients with sinonasal and NPCs are at risk for NCF impairments in multiple areas at baseline and memory decline following RT. Future prospective studies are needed to investigate the impact of each treatment modality on NCF and specific risk factors for cognitive dysfunction.

Keywords
- executive functioning
- radiotherapy
- cognitive impairment
- chemotherapy

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Georg Thieme Verlag KG,
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Introduction

As advances in cancer treatments have extended survival, there has been a greater recognition of adverse effects of treatments that can negatively affect patients' functioning and quality of life. Neurocognitive functioning (NCF) has increasingly received attention as a significant problem in cancer survivors. While NCF has been extensively studied in some noncentral nervous system (non-CNS) cancer populations, such as breast cancer survivors, studies in head and neck cancer (HNC) of skull base origin are largely limited to older studies of nasopharyngeal cancer (NPC) from endemic populations in South East Asia.[1–6] Studies that evaluate the effects of modern multimodality treatments and advances in surgery, chemotherapy, and radiotherapy (RT) on NCF following multimodality treatment in sinonasal (SNC) and NPC are lacking.

Prior research demonstrate that patients with non-CNS cancers may have NCF impairment prior to receiving treatment.[7–10] Studies in HNC have shown NCF impairments prior to treatment in the areas of verbal learning and memory, verbal fluency, attention, processing speed, and executive functioning.[7,11–13] The etiology of NCF impairment in non-CNS cancer survivors is likely multifactorial with contributions from cancer-related mechanisms such as increased inflammation (e.g., cytokines) as well as treatment-related effects.[8] There may also be further exacerbations with psychological distress (e.g., depression and anxiety) and physical symptoms (e.g., fatigue[9]). HNC patients may have additional factors that increase their susceptibility to NCF impairments. They may come from more vulnerable socioeconomic backgrounds, have a higher frequency of alcohol and tobacco use, and have other subsequent medical comorbidities.[14]

In addition to baseline NCF impairments, research has also investigated treatment effects on NCF in HNC and NPC. Prior studies have consistently reported that incidental radiation-induced brain injury to the vasculature and nerve fibers in the temporal lobe and hippocampus[15–17] may result in memory decline and other cognitive problems.[2–6,15] Whereas these cognitive deficits may be subtle, many domains of cognition—attention, memory, visuospatial functioning, information processing speed, executive functioning, and reaction time—can be affected.[5,18] In patients treated for SNC, a prior publication from our institution reported memory impairment in 80% of patients treated with 3D RT up to 60cGy and one-third manifested difficulty with visual-motor speed, frontal lobe executive functions, and fine motor coordination. The pattern of test findings was consistent with radiation injury to subcortical white matter, and NCFs were related to the total dose of radiation delivered but not to the volume of brain irradiated, side of radiation boost, or chemotherapy treatment.[18] Similarly, a previous cross-sectional survey of 122 skull base survivors post-RT from our group showed that 44% of the patients had either frank impairment or ambiguous cognitive status changes and that mild-to-moderate patient-reported cognitive changes were experienced by the majority of those surveyed; however, these cases lacked pretherapy baseline examination.[19]

The majority of studies evaluating the effects of treatment in NPC and HNC are older works that explored single-modality RT effects on NCF using 3D radiotherapyext. Patients with NPC and SNC treated in the modern era receive multimodality therapies, including combinations of endonasal surgery, induction chemotherapy, and/or concurrent chemoradiation with intensity-modulated radiation therapy and proton beam RT. Treatment with chemoradiation may result in impairments in NCF due to neurotoxicities associated with both chemotherapy and RT.[20] Cytotoxic drugs frequently used in NPC and SNC (i.e., cisplatin and 5-fluorouracil) are associated with direct neurotoxicity.[21,22] Direct tumor invasion and RT may disrupt the functioning of the blood–brain barrier, further potentiating the neurotoxic effects of chemotherapy in patients with NPC and SNC.[23] Exposure to chemoradiation in HNC patients may increase the risk of NCF impairment, especially in memory, than in those treated with RT alone,[11,20,24] and these NCF impairments may persist even 2 years following treatments.[25]

Although fewer studies have evaluated NCF in HNC patients as compared with other cancer populations, the limited number of previous studies suggested that HNC patients may have NCF impairments prior to and following treatments. Pretreatment NCF data in patients with SNC and NPC is lacking despite the proximity of the tumors to the CNS and a significant proportion of patients have direct CNS invasion at presentation. Even within the broader HNC literature, there are several limitations of the prior research. These studies often utilized brief cognitive screeners rather than comprehensive neuropsychological evaluations that more thoroughly measure NCF, included only pre- or post-treatment data, and/or contained small sample sizes.[19] To the best of our knowledge, prior studies have not evaluated the potential different impacts of disease sites on NCF in NPC and SNC patients, as some disease sites may receive more incidental radiation to the brain than others. Due to anatomical relationships, irradiation of the nasal cavity and nasopharynx may lead to greater incidental irradiation to the temporal lobe[15] rather than more inferior sites such as the maxilla.

To address some of these limitations, the present study examined NCF in patients with sinonasal and NPCs who presented for comprehensive neuropsychological evaluation prior to and following multimodality treatment. First, we determined the rates of NCF impairments prior to and following multimodality treatment. Second, we investigated the potential declines in NCF following treatment with RT. Third, we examined the possible differences in NCF by disease site and other disease variables.

Methods

Participants

A retrospective chart review was performed of the University of Texas MD Anderson Cancer Center Neuropsychology database and the Department of Head and Neck Surgery databases from 2005 to 2019 to identify patients with

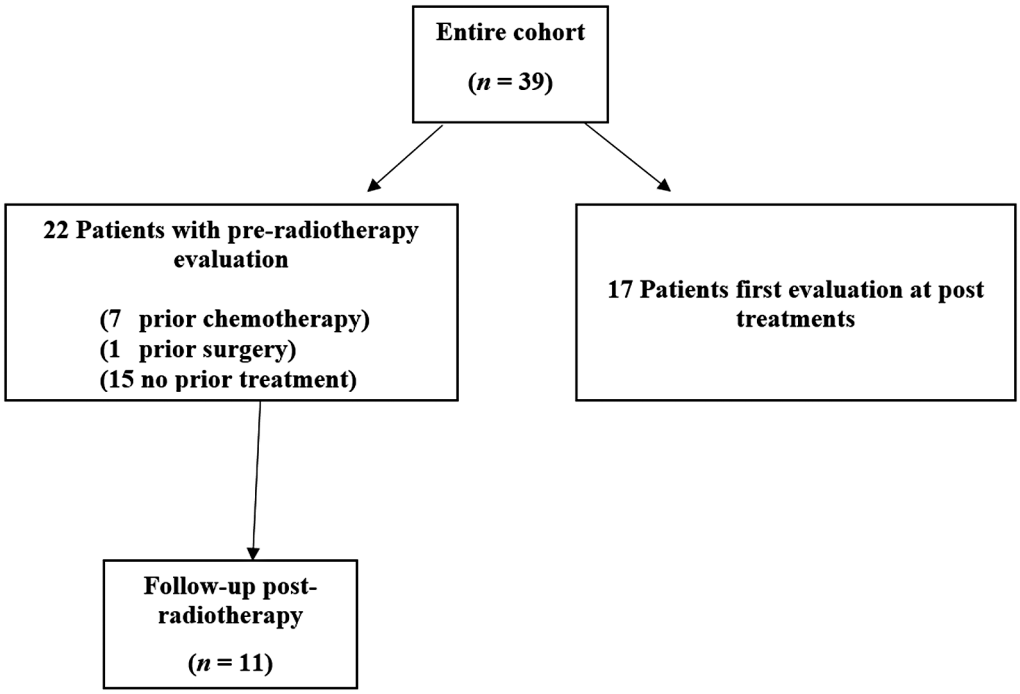

Fig. 1 Flow chart of sample.

sinonasal and NPCs. Thirty-nine patients with sinonasal and NPCs underwent comprehensive neuropsychological evaluations at some point during their care. Twenty-two patients were evaluated prior to RT. Of this cohort, 15 patients had no prior treatment, 7 patients received or were receiving chemotherapy, and 1 patient had undergone surgery. The majority of the patients who completed evaluations as a baseline prior to RT were part of an induction chemotherapy interventional trial and not prompted by symptoms. Eleven of the twenty-two patients evaluated prior to RT completed follow-up evaluations after RT, again driven by investigational protocols, not symptoms. Nineteen patients were evaluated following various treatments without a pretreatment evaluation. These patients were sent for neurocognitive evaluation due to symptoms (10 patients were referred for memory difficulties, 2 patients had problems with concentration, 2 patients had general cognitive decline, 3 patients were referred for baseline evaluation with no specific symptoms, and 2 patients were referred for lethargy). See the flow chart describing the sample presented in ►**Fig. 1**.

Measures

Patients completed comprehensive neuropsychological evaluations prior to RT and/or follow-up. Neuropsychological measures were administered in a standardized manner by a neuropsychologist or a trained neuropsychology staff member (i.e., psychometrist, neuropsychology extern, or neuropsychology fellow) supervised by a neuropsychologist. The neuropsychological evaluations utilized a flexible battery performed for clinical purposes. Therefore, the number of patients administered a specific NCF measure varied by instrument. ►**Table 1** lists the NCF measures that are routinely administered by domain with abbreviations defined. NCF testing consisted of measures of each cognitive domain including attention, learning and memory, processing speed, executive functioning, language, and visuospatial skills.

NCF test scores were standardized using published normative data,[26–33] all of which were normed by patient age, as well as gender, race, and level of education as appropriate. NCF test scores were converted into z-scores ($M = 0$, $SD = 1$). Performance on a particular NCF measure at or below a z-score of -1.5 was considered impaired.

Statistical Analysis

Rates of NCF impairment ($z \leq -1.5$) on standardized NCF tests were calculated for the initial and follow-up evaluations. The association between NCF impairment and demographic and disease variables was tested with point-biserial correlations for dichotomous variables and Pearson's *r* correlation for continuous variables for dichotomous variables and point-biserial correlations for continuous variables. The decline from initial evaluation to follow-up was defined on the basis of reliable change indices (RCI). The association between RCI decline on NCF variables and demographic and disease variables was tested with chi-square analyses for dichotomous variables and point-biserial correlations for continuous variables.

Results

Patient Characteristics

Demographic and disease characteristics are presented in ►**Tables 2** and **3**, respectively. Demographic variables

Table 1 Measures of neurocognitive functioning by domain

Test	Abbreviation	Norms
Attention		
WAIS-III and IV digit span	Digit span	Wechsler, 1997 and 2008[32,33]
Learning and memory		
HVLT-R total recall	HVLT-R TR	Benedict et al 1998[27]
HVLT-R delayed recall	HVLT-R DR	Benedict et al 1998[27]
HVLT-R recognition	HVLT-R Rec	Benedict et al 1998[27]
BVMT-R total recall	BVMT-R TR	Benedict et al 1997[26]
BVMT-R delayed recall	BVMT-R DR	Benedict et al 1997[26]
BVMT-R recognition	BVMT-R Rec	Benedict et al 1997[26]
Processing speed		
WAIS-IV coding	Coding	Wechsler, 2008[32]
Trail making test part A	TMT-A	Tombaugh, 2004[31]
Executive functioning		
Trail making test part B	TMT-B	Tombaugh, 2004[31]
WAIS-IV similarities	Similarities	Wechsler, 2008[32]
Language		
Boston naming test	BNT	Heaton et al 2004[29]
MAE controlled word association	COWA	Ruff et al 1996[30]
Visuospatial		
WAIS-IV block design	Block design	Wechsler, 2008[32]

Abbreviations: BVMT-R, Brief Visuospatial Memory Test - Revised; HVLT-R, Hopkins Verbal Learning Test – Revised; MAE, Multilingual Aphasia Examination; WAIS-IV, Wechsler Adult Intelligence Scale - Fourth Edition.
Note: Norms refer to normative comparison groups.

(i.e., age, education, gender, race, and self-reported history of smoking) were not significantly associated with NCF at the initial or follow-up evaluations. Disease variables (i.e., disease site, presence of intracranial invasion, and recurrence) were not significantly associated with NCF at the initial or follow-up evaluations. Of note, only one participant had a self-reported remote history of alcohol misuse, so alcohol use was not examined in the statistical analyses.

Table 2 Demographic characteristics

	Total $n = 39$ (%)
Age	
Mean (SD)	60.0 (14.8)
Range	22–87
Gender, *n* (%) male	27 (69)
Race, *n* (%) white	25 (62)
Education, years	
Mean (SD)	13.8 (3.2)
Range	9–20
Disease site, *n* (%)	
Nasal cavity	11 (28)
Ethmoid sinus	9 (23)
Maxillary sinus	12 (30)
Nasopharynx	7 (18)
History of smoking, *n* (%)	29 (74)

Abbreviation: SD, standard deviation.

In the group evaluated post-RT, the mean time from RT to neurocognitive evaluation was 944 days (range 14–5,017 days, interquartile range: 183 days).

Initial Neurocognitive Functioning

►**Table 4** shows NCF scores at the first neuropsychological evaluation for patients that were evaluated before receiving any treatment group ($n = 15$) and the entire cohort ($n = 39$). These measurements are presented for descriptive purposes since not all the cohort has a pre-RT and post-RT measurement and are. Percentages are based upon the total number of instances of an administered measure, which varies slightly depending on the battery of tests tailored for some patients. In patients evaluated prior to undergoing any type of treatment, the most frequently demonstrated impairments were in verbal memory retrieval (46%), verbal learning (46%), and set-shifting (46%). When examining NCF in the entire cohort, the most frequently demonstrated impairments were in verbal memory retrieval (47%), learning (43%), and consolidation (25%) on the Hopkins Verbal Learning Test (HVLT-R) and 33% had impairment in set-shifting (i.e., Trail Making Test), which is a key aspect of executive functioning. Other NCF impairments were observed in visual

Table 3 Disease characteristics

	Total $n = 39$ (%)
Pathology	
Squamous cell carcinoma	18 (46)
Nasopharyngeal carcinoma	7 (18)
Sinonasal undifferentiated carcinoma	5 (13)
Olfactory neuroblastoma	3 (7)
Mucosal Melanoma	2 (5)
Sarcoma	2 (5)
Neuroendocrine carcinoma	1 (3)
Adenocarcinoma	1 (3)
Primary disease at presentation	39 (100)
Intracranial invasion	10 (26)
Stage III/IV	32 (82)
Overall treatment	
Induction chemotherapy + (C)RT	17 (44)
Induction chemotherapy + (C)RT + surgery	3 (7)
Induction chemotherapy + surgery + (C)RT	4 (10)
Induction chemotherapy + surgery	2 (5)
Surgery + (C)RT	8 (21)
Surgery	1 (3)
Radiotherapy	3 (7)
Chemoradiotherapy	1 (3)

Abbreviation: (C)RT, radiotherapy or chemoradiotherapy.

learning (25%) and visual memory retrieval (29%) on the Brief Visuospatial Memory Test-Revised, naming (29%) on the Boston Naming Test , and verbal fluency (22%) on Controlled Word Association.

Evaluating Neurocognitive Changes from Pre- to Post-Radiotherapy

For the 22 patients who were evaluated longitudinally with both pre- and post-RT evaluations, differences in scores were examined using RCI. ►**Table 5** shows the post-RT performances that had significantly declined, improved, or remained relatively stable as compared with the pre-RT evaluation. At post-RT follow-up, some of the most frequently observed declines were in verbal learning (46%) and memory retrieval (18%) on the HVLT-R. Other performances were generally stable, and a few patients experienced improvements in areas of NCF post-RT. Demographic and disease variables were not significantly related to decline; however, this may be due to a small sample size. When examining patients who experienced a decline in verbal learning and/or memory retrieval at the post-RT evaluation, there was not a statistically significant association with NCF impairment on these measures at pre-RT initial evaluation.

Discussion

The present study shows that many patients with sinonasal and NPCs exhibit impairments in multiple areas of NCF prior to and following multimodality therapy. We found that demographic variables, disease site, presence of intracranial invasion and/or recurrence, and a self-reported history of

Table 4 First neurocognitive functioning for never treated patients and the entire cohort

Neurocognitive Measure	Never treated M (SD)	Never treated *n* (% impaired)	Cohort M (SD)	Cohort *n* (% impaired)
Digit span	−0.11 (1.2)	0/15 (0%)	−0.4 (1.5)	1/38 (3%)
HVLT-R TR	−1.0 (1.4)	7/15 (46%)	−1.2 (1.2)	16/37 (43%)
HVLT-R DR	−0.89 (1.2)	7/15 (46%)	−1.1 (1.2)	17/36 (47%)
HVLT-R Rec	−0.5 (1.02)	3/14 (21%)	−1.0 (1.7)	9/36 (25%)
BVMT-R TR	−0.6 (1.3)	1/3 (33%)	−0.8 (1.3)	5/17 (29%)
BVMT-R DR	−0.43 (0.97)	1/3 (33%)	−0.4 (1.2)	4/17 (24%)
BVMT-R Rec	−0.81 (0.7)	0/3 (0%)	−0.5 (0.6)	0/16 (0%)
Coding	−0.17 (0.9)	1/14 (7%)	−0.3 (0.9)	2/36 (6%)
TMT-A	0.22 (1.37)	1/14 (7%)	−0.1 (1.3)	4/36 (11%)
TMT-B	−1.0 (2.39)	7/15 (46%)	−0.8 (1.8)	12/36 (33%)
Similarities	0.0 (0.72)	0/4 (0%)	−0.2 (0.9)	3/21 (14%)
BNT	−0.83 (1.4)	1/3 (33%)	−0.4 (1.5)	5/17 (29%)
COWA	−0.46 (1.59)	4/11 (27%)	−0.6 (1.3)	8/37 (22%)
Block design	−0.25 (0.41)	0/4 (0%)	−0.2 (1.1)	2/22 (9%)

Abbreviations: BNT, Boston Naming Test; BVMT-R, Brief Visuospatial Memory Test - Revised; COWA, Controlled Word Association; HVLT-R, Hopkins Verbal Learning Test - Revised; M, mean; Pt, Patient; RT, radiotherapy; SD, standard deviation; TMT, Trail Making Test.
Note: Means are represented as *z*-scores. The total number is represented by the number of instances of a given measure, and clinical test batteries somewhat varied by patient.

Table 5 Reliable change from pre- to post-radiotherapy evaluations

Neurocognitive measure	Declined *n* (%)	Stable *n* (%)	Improved *n* (%)
Digit span	1/10 (10%)	8/10 (80%)	1/10 (10%)
HVLT-R TR	5/11 (46%)	3/11 (27%)	3/11 (27%)
HVLT-R DR	2/11 (18%)	7/11 (64%)	2/11 (18%)
HVLT-R Rec	1/11 (9%)	7/11 (64%)	3/11 (27%)
BVMT-R TR	2/2 (100%)	0/2 (0%)	0/2 (0%)
BVMT-R DR	0/2 (0%)	2/2 (100%)	0/2 (0%)
BVMT-R Rec	0/2 (0%)	2/2 (100%)	0/2 (0%)
Coding	0/11 (0%)	10/11 (91%)	1/11 (9%)
TMT-A	0/11 (0%)	10/11 (91%)	1/11 (9%)
TMT-B	1/11 (9%)	8/11 (73%)	2/11 (18%)
Similarities	0/3 (0%)	3/3 (100%)	0/3 (0%)
BNT	0/3 (0%)	2/3 (67%)	1/3 (33%)
COWA	0/11 (0%)	11/11 (100%)	0/11 (0%)
Block design	0/3 (0%)	2/3 (67%)	1/3 (33%)

Abbreviations: BNT, Boston Naming Test; BVMT-R, Brief Visuospatial Memory Test - Revised; COWA, Controlled Word Association; HVLT-R, Hopkins Verbal Learning Test - Revised; TMT, Trail Making Test.

smoking were not significantly associated with NCF impairment at the initial or follow-up post-RT evaluations. This work builds on and extends prior prospective assessment by our group of post-therapy patient-reported/telephone interview for cognitive assessment of skull base tumors[19] by utilizing more rigorous neurocognitive assessment tools and capturing both baseline and post-therapy function and provides further clarity regarding the degree, kinetics, and characteristics of cognitive injury in this rare cancer population.

When patients were evaluated prior to any therapy, the most frequently observed impairments were in verbal memory retrieval (46%), verbal learning (46%) and executive functioning (46%). Other studies have also previously noted NCF impairments prior to receiving RT in HNC patients.[11,34] We present data for patients never treated with any modality in ►**Table 4**. Interestingly, demographic, disease variables (i.e., disease site, and the presence of intracranial invasion and/or recurrence), and a history of smoking were not significantly associated with NCF.

For those patients assessed pre- and post-RT, the most frequently observed declines were in verbal learning and memory retrieval. Several other studies in HNC demonstrated memory decline following RT.[3–6,15,18,20] Incidental radiation to the temporal lobes is a proposed mechanism of memory decline[24] in patients with and even without radiation necrosis.[1,5] Higher RT doses to the temporal lobes may also be associated with a higher frequency of post-RT NCF impairment.[20,24] In addition to the temporal lobe, there may also be injury to the hippocampus, a key anatomical structure for memory and an area of adult neurogenesis.[24] Impaired hippocampal neurogenesis may also play a role in radiation-induced memory decline.[35] Radiation appears to induce microglial inflammation and increased proinflammatory cytokines that can inhibit neuronal differentiation of stem cells. Potential strategies to limit and/or ameliorate NCF impairment secondary to RT have been investigated in patients with brain metastases, such as hippocampal avoidance radiation techniques, cognitive rehabilitation, and neuro-protectants.[36–39] Further exploration of these methods is needed in patients with HNC receiving RT. Assessing patients before RT and having sufficient follow-up before retesting are of course of paramount importance.

The strengths and limitations of the present study should be acknowledged. This study examined NCF using a comprehensive neuropsychological evaluation to thoroughly assess aspects of NCF in this cohort, whereas our prior studies in HNC only utilized brief cognitive screeners. To our knowledge, this study was the first to examine disease sites in sinonasal and NPCs to determine differential impact on NCF following RT in recent years. The retrospective nature of this study has several limitations. Patients participated in neuropsychological evaluations at various time points while receiving multimodality therapy. Therefore, it may be difficult to determine the specific effects on NCF of a particular treatment, such as chemotherapy, in isolation. In addition, the small sample size of our post-RT group who also had pre-RT baseline testing made it difficult to detect any significant associations between NCF declines, demographic and disease variables. We present 15 patients that did not receive any type of therapy before going through evaluations for the first time. In addition to these 15 patients, we also had 7 more patients that had some sort of therapy before first evaluation, but not RT, bringing the total number of patients evaluated before RT to 22. It is important to note that while the patients who had evaluations before RT were asymptomatic and their testing reflects a baseline ($n = 22$), the patients who were referred to testing after treatment were already

symptomatic ($n = 17$). As such, our study serves as a descriptive report of patterns of neurocognitive impairments prior to and after RT. Future prospective studies with larger samples with longer periods of follow-up may better examine longitudinal impacts on NCF at each stage of treatment.

Conclusion

We examined neurocognitive functioning in patients with sinonasal and NPCs prior to and following RT. A large percentage of patients exhibited impaired NCF prior to any therapy. NCF impairment was not significantly associated with demographic or disease variables. When examining the patients who were evaluated longitudinally at both pre- and post-RT time points, the most frequent declines were in verbal learning and memory. Larger prospective, longitudinal studies that include baseline and long-term posttreatment assessments may better determine the effects of particular treatments on NCF in this at-risk population with NPC and SNC. Impaired NCF may negatively impact the patients' abilities to understand and adhere to the treatment demands associated with multimodality therapy, and patients may require increased support. Future research may identify risk factors for NCF decline and inform the development of prevention strategies and interventions to mitigate the effects of NCF impairment in patients with sinonasal and NPCs.

Conflict of Interest

C.D.F. received/receives funding and salary support during the period of study execution from: the National Institutes of Health (NIH) NIBIB Research Education Programs for Residents and Clinical Fellows Grant (R25EB025787–01); NIDCR Academic Industrial Partnership Grant (R01DE028290); NCI Parent Research Project Grant (R01CA258827) NCI Early Phase Clinical Trials in Imaging and Image-Guided Interventions Program (1R01CA218148); an NIH/NCI Cancer Center Support Grant (CCSG) Pilot Research Program Award from the UT MD Anderson CCSG Radiation Oncology and Cancer Imaging Program (P30CA016672); and an NSF Division of Civil, Mechanical, and Manufacturing Innovation (CMMI) grant (NSF 1933369).

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