Neurocognitive impairment after intensity-modulated radiotherapy in patients with nasopharyngeal cancer: association with radiation dose and retinal vascular characteristics (abridged secondary publication)

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KEY MESSAGES

1. Neurocognitive impairment is prevalent among nasopharyngeal carcinoma survivors who underwent definitive intensity-modulated radiotherapy.
2. Significant impairments were observed in multiple neurocognitive domains including verbal memory, executive function, processing speed, motor dexterity, and language ability.
3. Radiation doses to the whole brain, hippocampus, and temporal lobe were associated with neurocognitive impairment.
4. Retinal image analysis may be useful to detect neurocognitive impairment.

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Introduction

Treatment outcomes for nasopharyngeal carcinoma (NPC) have significantly improved in recent decades.[1] Although intensity-modulated radiotherapy (IMRT) for NPC has greatly enhanced tumour target conformity, a large volume of brain tissue is inevitably exposed to radiation. Previous studies investigating neurocognitive impairment in IMRT-treated patients with NPC were limited by small sample sizes, the use of simple cognitive screening tools, and short follow-up intervals.[2] The pattern and severity of this late complication remain unclear, as does the clinical-dosimetric relationship.

Radiation microangiopathy and the disruption of neurovascular relationships are two major mechanisms of radiation-associated cognitive dysfunction. Retinal characteristics are associated with white matter hyperintensity on magnetic resonance imaging, which is a hallmark of radiation brain injury.[3] Advances in automated machine learning–based analytic algorithms have greatly improved the efficiency and reproducibility of retinal image analysis for detecting various neurological diseases.

This cross-sectional study aimed to determine the prevalence and pattern of neurocognitive impairment in post-IMRT NPC survivors using a comprehensive battery of multidomain neurocognitive assessments. Additionally, associations between radiation dose-volume parameters in brain substructures and retinal characteristics were also investigated.

Methods

Patients with NPC who remained in disease remission for at least 1 year after definitive IMRT were included. All radiotherapy plans were developed using a simultaneous integrated boost technique whereby high-risk clinical target volumes received 66 to 70 Gy and low-risk volumes received 54 to 60 Gy, both delivered in 33 fractions.

Participants were evaluated using the Montreal Cognitive Assessment-Hong Kong and the Depression Anxiety Stress Scale. Subsequently, neurocognitive functions across eight domains were assessed using the Wechsler Adult Intelligence Scale-IV for intellectual capacity, Wechsler Adult Intelligence Scale-IV Digit Span for attention span, Wechsler Memory Scale-III for visual-spatial span, Wechsler Memory Scale-III Visual Reproduction Span for visual memory, Auditory Verbal Learning Test for verbal memory, Trail Making Test for processing speed, Stroop Test for executive function, Grooved Pegboard Test for motor dexterity, and Verbal Fluency Test for language ability. Raw scores were normalised to participant age and educational level, expressed as percentiles or Z-scores. Neurocognitive performance was categorised as follows: normal (≥25th percentile or Z-score ≥ -0.67), low average (9th-24th percentile or Z-score -1.33 to

-0.68), borderline impairment (3rd-8th percentile or Z-score -2.00 to -1.34), impairment (1st-2nd percentile or Z-score -2.50 to -2.01), and profound impairment (<1st percentile or Z-score < -2.50).

The IMRT plans for all participants were retrieved. The whole brain and various substructures (eg, frontal lobe, parietal lobe, temporal lobe, occipital lobe, hippocampus, pituitary gland, hypothalamus, thalamus, and cerebellum) were delineated on simulation computed tomography images in accordance with standardised atlases. Radiation dose-volume parameters were collected for each brain sub-structure; these included maximum dose, minimum dose, mean dose, median dose, and volume-based metrics.

Retinal images of both eyes were captured. Vascular features such as retinal vessel measurements, arteriole-venous nicking, arteriole occlusion, haemorrhages, exudates, tortuosity, bifurcation coefficients, branch asymmetries, and bifurcation angles were evaluated using a machine learning–based algorithm. This automated approach incorporated fractal analysis, high-order spectra analysis, and statistical texture analyses.

Mean age-normalised and education level–normalised percentiles and Z-scores from the neurocognitive assessments were compared with the 50th percentile and a Z-score of 0 using one-sample *t*-tests. Associations between neurocognitive outcomes and radiation doses to brain substructures were determined using multivariable logistic regression. Model generation was restricted to neurocognitive domains with a sufficient number of impaired cases for robust analysis.

Results

In total, 190 NPC survivors were enrolled between 15 December 2020 and 8 July 2022 (Table 1). The median interval from IMRT completion to neurocognitive assessment was 7.0 (range, 1.0-13.6) years. The mean Montreal Cognitive Assessment score was 23.6; 48 (25.3%) participants were classified as cognitively impaired according to age- and education-level-adjusted cut-offs. Additionally, 4.7%, 18.5%, and 4.2% of participants exhibited severe or very severe depression, anxiety, or stress, respectively.

In total, 182 participants completed all domain-specific neurocognitive assessments. Of these participants, 79.4% demonstrated impairment in at least one neurocognitive domain. Compared with normative population references, participants showed significant impairments across multiple neurocognitive domains (Fig). Regarding visual memory, participants performed worse in delayed recall (mean percentile difference= -4.15, P=0.027), image copying (mean percentile difference= -4.47, P=0.009), and retention of graphical memory (mean percentile difference= -9.27, P<0.001). Significant impairments were also observed in short-term (mean Z-score= -0.56, P<0.001) and long-term (mean Z-score= -0.70, P<0.001) retention of verbal memory. Regarding executive function, significant impairments were detected in the ability to inhibit cognitive interference (mean Z-score= -1.90, P<0.001). Regarding processing speed, reaction times to complete the basic (mean Z-score= -1.04, P<0.001) and advanced (mean Z-score= -0.38, P<0.001) coloured trails were prolonged. Regarding motor dexterity, participants required longer time to complete the grooved pegboard test with both the dominant (mean Z-score= -0.97, P<0.001) and non-dominant (mean Z-score= -0.93, P<0.001) hands. Participants also demonstrated impaired language ability (mean Z-score= -0.29, P=0.001). No significant impairments in intellectual quotient or attention span were observed.

Radiation doses to brain substructures were extracted from the IMRT plans of 145 participants. The average mean dose to the whole brain was 11.87 Gy. Among the four cerebral lobes, the temporal lobe received the highest average mean dose of 19.82 Gy, followed by the occipital, parietal, and frontal lobes, which had average mean doses of 14.42 Gy, 4.68 Gy, and 2.74 Gy, respectively. The average mean and maximum doses to the hippocampus were 25.82 Gy and 50.03 Gy, respectively.

Domain-specific neurocognitive impairments were associated with radiation dose-volume parameters in multiple brain substructures. The radiation dose to the whole brain was positively associated with impairments in executive function (odds ratio [OR]=1.120, 95% confidence interval [CI]=1.032-1.215, P=0.007) and motor dexterity of the dominant hand (OR=1.003, 95% CI=1.001-1.006, P=0.018). The maximum dose to the hippocampus was associated with worse short-term (OR=1.001, 95% CI=1.000-1.002, P=0.019) and long-term (OR=1.001, 95% CI=1.000-1.001, P=0.080) retention of verbal memory. The maximum dose to the temporal lobe was associated with impaired processing speed (OR=1.003, 95% CI=1.000-1.006, P=0.047).

In logistic regression models built using clinical and radiation dosimetric data, the area under the curve was 0.664 to 0.864. In models built using retinal characteristics, the area under the curve significantly improved to 0.949 to 0.997 (Table 2); sensitivities were >80% across neurocognitive domains and negative emotions (except for motor dexterity based on dominant-hand reaction time), and corresponding specificities were >90%.

Discussion

We found that >80% of NPC survivors exhibited impairment in at least one neurocognitive domain. The impairments predominantly affected verbal memory, executive function, processing speed, motor dexterity, and language ability, but general

TABLE 1. Characteristics of participants (n=190)

Characteristic	Value*
Age, y	55.5±9.5
Sex	
Male	140 (73.7)
Female	50 (26.3)
Employment status	
Unemployed	31 (16.3)
Employed	112 (59.0)
Retired	47 (24.7)
Education level	
Primary or below	24 (12.6)
Secondary	146 (76.9)
Tertiary or above	20 (10.5)
Smoking	
No	162 (85.3)
Yes	28 (14.7)
Alcohol consumption	
No	159 (83.7)
Yes	30 (15.8)
Unknown	1 (0.5)
Medical comorbidity	
Diabetes mellitus	13 (6.8)
Hypertension	52 (27.4)
Hyperlipidaemia	14 (7.4)
Stroke	2 (1.1)
Others	18 (9.5)
Histology	
Undifferentiated carcinoma	178 (93.7)
Non-keratinising squamous cell carcinoma	8 (4.2)
Keratinising squamous cell carcinoma	4 (2.1)
T-stage	
T1	32 (16.8)
T2	19 (10.0)
T3	116 (61.1)
T4	23 (12.1)
N-stage	
N0	6 (3.2)
N1	38 (20.0)
N2	129 (67.9)
N3	17 (8.9)
American Joint Committee on Cancer stage (8th Edition)	
I	4 (2.1)
II	17 (8.9)
III	130 (68.5)
IVA	39 (20.5)
Chemotherapy	
None	24 (12.6)
Concurrent	108 (56.9)
Concurrent + adjuvant	32 (16.8)
Induction + concurrent	24 (12.6)
Other chemotherapy combinations	2 (1.1)
Montreal Cognitive Assessment-Hong Kong score	23.6±3.7
Impairment using cut-off of <23	62 (32.6)
Impairment using age-/education level–adjusted cut-offs	48 (25.3)
Depression Anxiety Stress Scale	
Depression	
Normal	138 (72.7)
Mild	23 (12.1)
Moderate	20 (10.5)
Severe	5 (2.6)
Extremely severe	4 (2.1)
Anxiety	
Normal	80 (42.1)
Mild	19 (10.0)
Moderate	56 (29.5)
Severe	21 (11.1)
Extremely severe	14 (7.3)
Stress	
Normal	157 (82.6)
Mild	14 (7.4)
Moderate	11 (5.8)
Severe	5 (2.6)
Extremely severe	3 (1.6)

* Data are presented as mean ± standard deviation or No. (%) of participants

intelligence and attention span were relatively unaffected. Considering the relatively young bimodal age distribution of NPC incidence, which peaks at approximately 30 and 55 years, this high prevalence of post-radiation cognitive dysfunction has substantial implications for quality of life, daily activities, social interactions, and work rehabilitation among long-term survivors.

We observed greater deficits in long-term memory retention than in short-term recall for verbal memory. This may be related to the uneven distribution of radiation doses within the brain. The temporal lobe, responsible for memory consolidation and retention, received a high average mean dose of 19.82 Gy because of its proximity to the primary NPC site. In contrast, short-term working memory is primarily governed by the prefrontal cortex in the frontal lobe, which received a relatively low scattered radiation dose of 2.74 Gy. Consistent with this hypothesis, our exploratory dosimetric analyses revealed positive associations

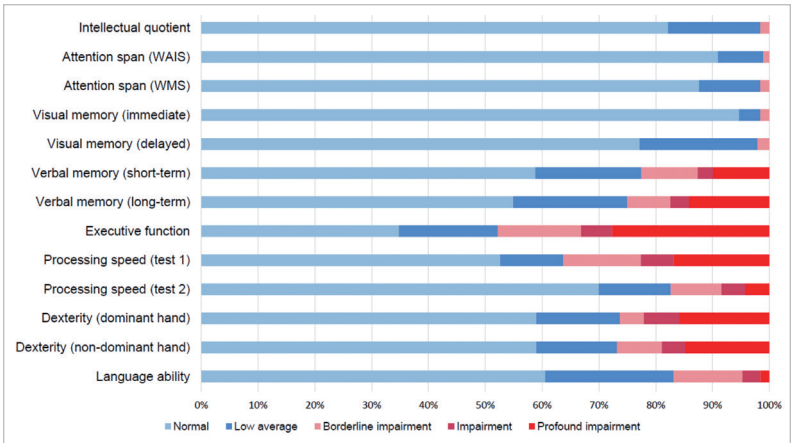

FIG. Patterns and severities of neurocognitive impairment across different domains
Abbreviations: WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale

TABLE 2. Area under the receiver operating characteristic curve in two prediction models

Neurocognitive assessments	No. of participants	Area under the curve	
		Model built using clinical and radiation dosimetric parameters	Model built using retinal image analysis features
Montreal Cognitive Assessment-Hong Kong for global cognitive screening	138	0.694	0.997
Verbal memory			
Short-term retention	131	0.864	0.986
Long-term retention	133	0.654	0.977
Word recognition	132	0.715	0.995
Stroop Test for executive function	136	0.708	0.954
Processing speed			
Colour Trail Test (basic)	138	0.664	0.965
Colour Trail Test (advanced)	138	0.849	0.993
Motor dexterity			
Dominant-hand reaction time	138	0.759	0.949
Non-dominant-hand reaction time	138	0.697	0.985

between the maximum doses to the temporal lobe and hippocampus, suggesting that lower radiation doses to these structures could reduce long-term memory impairments. Careful consideration of the hippocampus during radiotherapy planning may be beneficial. Small pilot studies have demonstrated the dosimetric feasibility of hippocampal-sparing IMRT for NPC without compromising tumour target coverage.[4] Nonetheless, prospective studies are needed to quantify the cognitive benefits of this approach.

Our study highlights the clinical value of incorporating automated retinal image analysis into survivorship care for patients with NPC. Retinal vascular characteristics may serve as indicators for susceptibility to neurological injury from radiation exposure. The machine learning–based image analysis system can detect retinal features specific to radiation damage, which can serve as markers of potential radiation-induced injury to the central nervous system. Currently, there are no established guidelines regarding appropriate screening methods for radiation-associated cognitive decline in NPC survivors. Automated retinal image analysis offers a rapid, efficient, objective, and non-invasive tool to identify high-risk patients for neurocognitive assessment. This approach may be particularly valuable in underserved areas with limited access to neuropsychological specialists.

Conclusions

Neurocognitive impairment is prevalent among NPC survivors after definitive IMRT, affecting multiple cognitive domains including verbal memory, executive function, processing speed, motor dexterity, and language ability. Automated retinal image analysis may be useful to detect post-radiation neurocognitive impairment.

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Disclosure

The results of this research have been previously published in:

1. Chow JCH, Lee J, Lai MMP, et al. Multi-domain neurocognitive impairment following definitive intensity-modulated radiotherapy for nasopharyngeal cancer: a cross-sectional study. Radiother Oncol 2024;193:110143.
2. Chow JCH, Ho JCS, Cheung KM, et al. Neurological complications of modern radiotherapy for head and neck cancer. Radiother Oncol 2024;194:110200.

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