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Remote assessment of cognition and quality of life following radiotherapy for nasopharyngeal carcinoma: deep-learning-based predictive models and MRI correlates

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Abstract

Purpose Irradiation of the brain regions from nasopharyngeal carcinoma (NPC) radiotherapy (RT) is frequently unavoidable, which may result in radiation-induced cognitive deficit. Using deep learning (DL), the study aims to develop prediction models in predicting compromised cognition in patients following NPC RT using remote assessments and determine their relation to the quality of life (QoL) and MRI changes.

Methods Seventy patients (20–76 aged) with MRI imaging (pre- and post-RT (6 months–1 year)) and complete cognitive assessments were recruited. Hippocampus, temporal lobes (TLs), and cerebellum were delineated and dosimetry parameters were extracted. Assessments were given post-RT via telephone (Telephone Interview Cognitive Status (TICS), Telephone Montreal Cognitive Assessment (T-MoCA), Telephone Mini Addenbrooke's Cognitive Examination (Tele-MACE), and QLQ-H&N 43). Regression and deep neural network (DNN) models were used to predict post-RT cognition using anatomical and treatment dose features.

Results Remote cognitive assessments were inter-correlated ($r > 0.9$). TLs showed significance in pre- and post-RT volume differences and cognitive deficits, that are correlated with RT-associated volume atrophy and dose distribution. Good classification accuracy based on DNN area under receiver operating curve (AUROC) for cognitive prediction (T-MoCA AUROC = 0.878, TICS AUROC = 0.89, Tele-MACE AUROC = 0.919).

Conclusion DL-based prediction models assessed using remote assessments can assist in predicting cognitive deficit following NPC RT. Comparable results of remote assessments in assessing cognition suggest its possibility in replacing standard assessments.

Implications for Cancer Survivors Application of prediction models in individual patient enables tailored interventions to be provided in managing cognitive changes following NPC RT.

Keywords Cognition · Nasopharyngeal carcinoma · Remote · Deep neural network · Radiotherapy

Introduction

Radiotherapy (RT) in combination with or without adjuvant chemotherapy is the primary treatment for patients with nasopharyngeal carcinoma (NPC) [1]. Nevertheless, neurological complications have been reported in patients following NPC irradiation that induces late cognitive deficits such as attention, short-term memory, language abilities, and executive function years after irradiation [2, 3]. As its serious complication could impact patient prognosis and quality of life (QoL), thus, it is essential to understand the effect of radiotherapy on brain pathophysiology.

The notion QoL has become increasingly paramount in patient treatment, given that RT could negatively impact on

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cognitive functioning and be deleterious to QoL [4]. Despite the advances in radiation treatment which improves patient life expectancy [5], maintaining health-related QoL and cognitive function following head and neck cancer RT are also imperative [6]. The affected regions are typically in the domains of attention, memory and executive functions [7] as well as numerous aspects of QoL including functional deficits such as speech, swallowing, hearing and breathing which are vital in daily functioning [6]. These changes are the underlying effect in the alteration of patients overall well-being.

In typical clinical practice, cognitive and QoL evaluations are performed with the physical presence of both patients and assessors. However, such methods are not feasible during pandemics or other limitations preventing face-to-face sessions. Therefore, validated remote telephone-based cognitive screening tools have been developed to cater for the needs in such circumstances, including Telephone Interview for Cognitive Status (TICS), Telephone Montreal Cognitive Assessment (T-MoCA), and Telephone-Mini Addenbrooke's Cognitive Examination (Tele-MACE). According to previous studies, removing visual components from the assessments still exhibits reasonable sensitivity and specificity in mild cognitive impairment (MCI) diagnoses [8–10]. Given its high accuracy and validity in assessing patients for MCI and dementia, [11, 12], implementation of the telephone-based cognitive screen is plausible and appears useful in clinical practice when in-person assessments are impossible. For QoL, European Organization for Research and Treatment of Cancer (EORTC) QLQ-H&N 43 is used to assess head and neck carcinoma patients [13] which evaluates the tumour effects, treatment symptoms, functions, and health-related QoL [14].

Studies have established the utility of quantitative volumetric magnetic resonance imaging (MRI) features to detect radiation-induced changes in normal-appearing brain tissue [15]. These changes were observed either specific to brain structures such as the hippocampus [16], cerebellum [17], temporal lobes (TLs) [18], or the white and grey matter structures [19, 20]. Several studies reported the correlation of brain volume loss to cognitive decline where the extent of radiation-induced brain injury varies depending on the duration of RT completion [18, 21]. Besides, radiotherapy-associated brain structural changes in NPC patients were also dose-dependent [18]; thus, reducing irradiation dose to vulnerable regions is important.

In this study, we aimed to build prediction models using multiple linear regression (MLR) and deep neural network (DNN) in predicting the possibility of compromise cognition in patients following NPC RT using remote or teleconsultation assessments in assessing cognitive status and QoL of NPC patients while evaluating their correlates to anatomical volume change and dosimetry parameters.

Materials and methods

Subjects

A total of 70 healthy controls (HC), randomly selected and 70 NPC patients who received RT treatment from 2015 to 2021, had two MRI sessions (pre- (before the initiation of RT) and post-RT (6 months to 1 year)) were identified from the National Cancer Institute database with staging from T1N0M0 to T4N2M0. Patients were planned for radiotherapy using three-dimensional (3D) conformal, intensity-modulated radiotherapy (IMRT) or Tomotherapy with a dose prescription of 69.96 Gy in 33 fractions or 70 Gy in 35 fractions. The inclusion criteria were NPC patients aged between 20 and 76 years, able to understand and communicate in Malay or English. Exclusion criteria were brain metastases, other brain abnormalities, neurological or psychiatric diseases, without RT and flow-up scan, claustrophobic, and contraindicated for MR imaging. Ethical approval was given by the Institutional Review Board (or Ethics Committee) of Malaysia Ministry of Health and patients provided their informed consent to participate in this study.

Remote neurocognition and quality of life (QoL) assessment tools

Remote neurocognition tools

The TICS is a brief, standardized test of cognitive functioning administered via phone with eleven test items. Each item's scores are summed to obtain the TICS total score, which provides a measure of global cognitive functioning and can be used to monitor changes in cognitive functioning over time. It takes less than 10 min to administer and score. The optimal cutoff score is ≤ 31 to separate subjects with MCI from normal cognition [22]. T-MoCA [23] assesses several cognitive domains which are used for the detection of MCI. The domains are memory, attention, language, abstraction, delayed recall, and orientation (to time and place). It contains a 22-point test and takes 10 min to administer. A score of 18 and higher are generally considered normal cognition. As for Tele-MACE, the cognitive screening test evaluates three main cognitive domains (orientation, memory, and language). It is an adaptation of Mini-Addrenbrooke's Cognitive Examination with the omission of visuospatial domain. The test denominators were reduced to 25 with a score of 19 and higher considered normal cognition. Remote neurocognitive assessments were given at a time frame of 3.8 (1–7) years following the completion of NPC RT which complements the study on cognitive deficit that often occurs

at the late-delayed phase (more than 6 months post-RT). While the assessments of healthy controls were done prior to NPC patients assessment.

Quality of Life (QoL) tools

The EORTC QLQ H&N43 has 43 items with six multi-item scales and thirteen single-item symptom subscales [14]. Each item is rated on a 4-point Likert scale and each subscale score ranges from 0 to 100 where higher scores indicate greater symptoms. It is used jointly with QLQ-C30 that consists 30 items with functional, symptom and global health status scales. The validated Malay and English version of the QLQ-C30 and QLQ-H&N43 were used [24]. All the tests and assessments were responded by patients without assistance. Clear and precise instructions and explanations were given to patients before conducting questionnaire.

Implementation of tests

All the tests were performed in the original form once by a single caller to avoid variability and the results from the remote assessments were analyzed blindly by the neuropsychologist. Data analyses were also done blindly, with neurocognitive tests performed prior to image delineation and dose-volume extraction.

Data collection and ROIs dose features

Information such as age, gender, education and staging; based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) were retrieved from the institutional database. Regions of interest (ROIs) were delineated and dose-related parameters of the hippocampus, left and right TLs, cerebellum, caudate nucleus (CN), corpus callosum (CC), amygdala, thalamus, optic chiasm (OC), spinal cord (SC), and brain stem (BS) were collected by a single trained radiation therapist. Regions selected are based on their proximity to the tumour within the treatment area, institution standard protocol and previous studies [25, 26]. Dose-volume histograms (DVH) features of each delineated structures were extracted, including the volumes, mean/maximum/minimum dose (Dmean/Dmax/Dmin), aV10 (absolute volume receiving more than 10 Gy), aV10-aV60 in aV10 increments, D10 (dose to 10% of volume), D10-D60 in D10 increments and each evaluated structure was assumed to be independent. These were done using Monaco 5.1 and TomoHD 5.1.1.6 treatment planning systems. Information extracted was used as predictive measures in prediction models.

Image acquisition

Siemens Magnetom Verio 3 Tesla (3 T) MRI machine was used to scan pre- and post-RT brain images on each patient. Patients laid supine on MRI couch and 8-channel RF head coil was used. The standardised protocol includes pre- and post-contrast 3-dimensional (3D) volumetric T1-weighted multi-echo magnetisation-prepared rapid-acquisition gradient echo (MPRAGE) and 3D T2-weighted fluid-attenuation inversion recovery (FLAIR) images. MR images parameters applied were TR = 1900 ms, TE = 2.52 ms, T1 = 900 ms, flip angle = 9°, voxel size = $1.0 \times 1.0 \times 1.0$ mm^3, with no interslice gap. During scanning, subjects were instructed to remain calm and keep their eyes closed. The scans took approximately 45 min.

Statistical analysis

Pearson's correlation analysis was performed to assess the correlation between the remote cognitive assessments and remote assessments to QoL. Additional correlation analyses were performed to measure the association between clinical factors (age, gender, education and post-RT volumes) and cognitive assessments. Independent *t* tests and chi-square tests were used to analyze demographic differences between NPC patients and HC at baseline for continuous variables (age, cognitive, and QoL) and categorical variables (gender and education). To assess the volumetric changes following RT, paired *t* tests and Wilcoxon signed-rank tests were used. $P < 0.05$ was considered statistically significant.

Multiple linear regression (MLR) analysis was done to determine the risk factors for radiotherapy-related cognitive deficits, with brain volume changes, DVH factors, education and overall stage as the contributing factors using the backward stepwise method. Hold-out sample cross-validation was done to test the model's performance. Estimation of R^2 index, which is the amount of the variation in the dependent variable explained or predicted by the independent features was done for all the neurocognitive tests and all the assumptions of regression modeling were tested. To test for multicollinearity, we estimated the variance inflation factors (VIF) for each model (< 10) [27] and tolerance indices (> 0.1) [28].

Deep neural network (DNN)

DNN was performed by SPSS with two hidden layers using hyperbolic tangent as the activation function and softmax in the output layer for rescaling the dependent variables in predictors associated with the incidence of cognitive deficit. The dataset was randomly divided into a train set (70%) and a test set (30%) using hold-out cross-validation. We estimated the specificity, sensitivity, area under the receiver

operating curve (AUROC), Variable Importance Index and the proportion of accurately classified groups for the DNN. Normalised Importance Index (NII) ranges between 0.00 and 100% showing the weightage of each independent variable in predicting the cognitive groups (deficit and normal cognitive groups). Higher indices of the variable exhibit a more substantial influence in predicting cognitive groups.

Results

Demographic tests

There were no significant differences in age, gender, and education between NPC patients to HC recruited in the study (Table 1).

Remote assessments

Significant differences were shown ($p < 0.001$) in all remote assessments of HC to NPC patients (Table 1). The remote cognitive assessments of NPC patientswere significantly inter-correlated but negatively correlated to QoL (Table 2). Additionally, age was negatively correlated (TICS, $r = -0.387$; T-MoCA, $r = -0.36$; Tele-MACE, $r = -0.366$, all $p < 0.001$) with neurocognitive assessments but not significant with QoL. Years of education was positively correlated with the neurocognitive assessments (TICS, $r = 0.759$, T-MoCA, $r = 0.693$; Tele-MACE, $r = 0.711$, all $p < 0.001$) and negatively correlated to QoL ($r = -0.457$, $p < 0.001$).

Cerebral volume

Cerebral volumes in NPC patients' post-RT decreased significantly in the delineated ROI (Table 3). Significant differences were shown in the mean and standard deviation (SD) value between pre- and post-RT volumes. Both left (difference, $\Delta = 6.89 \pm 2.1$) and right ($\Delta = 7.12 \pm 2.18$) TLs and cerebellum ($\Delta = 2.52 \pm 1.15$) showed the most changes significantly ($p < 0.001$), given their large area and proximity to irradiated volume.

Table 1 Descriptive data

Variable	Mean ± SD		*p*-value
	RT + NPC ($n = 70$)	HC ($n = 70$)	
Gender, M/F	49/21	42/28	0.749~
Age, years	52.76 ± 12.73 (20–76)	49.13 ± 11.03 (20–65)	0.074*
Education, level	11.83 ± 1.77	13.23 ± 0.77	0.314~
Overall Stage	3.37 ± 0.75		
TICS	30.31 ± 11.51	44.94 ± 4.23	0.001*
T-MoCA	13.99 ± 5.30	18.99 ± 1.47	0.001*
Tele-MACE	15.21 ± 4.93	20.90 ± 2.05	0.001*
QoL	52.56 ± 17.31	36.51 ± 6.42	0.001*

Note: ~Chi-square, *Independent t-test

Table 3 Cerebral volume differences pre- and post-radiotherapy (RT) of NPC

	Pre-RT (mean ± SD)	Post-RT (mean ± SD)	*p* value
Hippocampus	3.28 ± 1.8	3.08 ± 1.69	< 0.001*
Right temporal lobe	73.63 ± 13.25	66.51 ± 11.29	< 0.001*
Left temporal lobe	71.22 ± 12.35	64.33 ± 10.47	< 0.001*
Cerebellum	49.81 ± 12.67	47.29 ± 11.53	< 0.001*
Corpus callosum	3.95 ± 1.67	3.82 ± 1.62	< 0.001*
Amygdala	3.06 ± 1.26	2.96 ± 1.21	< 0.001*
Caudate nucleus	2.16 ± 1.11	2.04 ± 1.02	< 0.002*
Thalamus	7.33 ± 2.12	6.96 ± 2.2	< 0.001~
Spinal cord	21.24 ± 9.6	20.75 ± 9.36	< 0.001*
Brain stem	25.83 ± 4.05	24.28 ± 3.8	< 0.001*
Optic chiasm	0.61 ± 0.28	0.58 ± 0.27	< 0.001*

Note: *Paired *t*-test, ~Wilcoxon-signed rank

Table 2 Correlation of TICS, T-MoCA, Tele-MACE, and QoL

Correlations					
		TICS	T-MoCA	Tele-MACE	QOL
TICS	Pearson correlation	1	0.920	0.913	−0.626
	Sig. (2-tailed)		< 0.001	< 0.001	< 0.001
T-MoCA	Pearson correlation	0.920	1	0.978	−0.614
	Sig. (2-tailed)	< 0.001		< 0.001	< 0.001
Tele-MACE	Pearson correlation	0.913	0.978	1	−0.652
	Sig. (2-tailed)	< 0.001	< 0.001		< 0.001
QoL	Pearson correlation	−0.626	−0.614	−0.652	1
	Sig. (2-tailed)	< 0.001	< 0.001	< 0.001	

Correlation between volume changes and neurocognitive tests

Volume changes in hippocampus and SC were significantly correlated to TICS (hippocampus: $r = 0.265$, $p = 0.027$; SC: $r = 0.288$, $p = 0.016$), T-MoCA (hippocampus $r = 0.303$, $p = 0.011$; SC: $r = 0.250$, $p = 0.037$) and Tele-MACE (hippocampus $r = 0.238$, $p = 0.047$; SC $r = 0.239$, $p = 0.045$). No significant correlation between cerebral volumes and neurocognitive assessments was shown in other ROI regions.

Dose and volume-related cognition-response in irradiated patients

T-MoCA

The post-RT volume of delineated brain regions and DVH factor values were fitted into multiple linear regression (MLR) to explain cognitive score. For T-MoCA, the overall model explains 79.4% ($R^2 = 0.794$) variation of the cognitive score and is significantly useful in explaining the T-MoCA score, F (19,50) = 10.115, $p < 0.001$. With a one-unit increase in the post-RT volume, the T-MoCA score increases by 1.584 in the hippocampus, $t(50) = 4.906$, $p < 0.001$, 0.08 in the left temporal lobe (LT TL), t(50) = 2.371, $p = 0.025$ and 6.002 in the OC, $t(50) = 3.443$, $p = 0.001$. In addition, with a one-unit increase in dose to the region examined, the cognitive score decreases by − 0.012 in the SC Dmin, $t(50) = -3.726$, $p < 0.001$, − 0.004 in the OC Dmin, $t(50) = -4.825$, $p < 0.001$, − 0.005 in the BS Dmin, $t(50) = -3.193$, $p = 0.002$, − 0.003 in the hippocampus Dmean, $t(50) = -6.118$, $p < 0.001$, − 0.003 in the right temporal lobe (RT TL) Dmean, $t(50) = -3.591$, $p = 0.001$, − 0.001 in the RT TL Dmax, $t(50) = -3.633$, $p = 0.001$, − 0.003 in the OC Dmax, $t(50) = -2.792$, $p = 0.007$ and − 0.002 in the SC Dmax, $t(50) = -2.186$, $p = 0.034$. Besides that, the T-MoCA score also increases by 3.674 ($t(50) = 6.269$, $p < 0.001$) with one unit increase in the education years and decreases by − 0.735 with one unit increase in age ($t(50) = -2.131$, $p = 0.038$) and by − 1.387 with one unit increase in staging ($t(50) = -2.076$, $p = 0.043$).

TICS

A different set of regression modeling was shown in TICS with the overall model of 77.1% ($R^2 = 0.771$, F (18,51) = 9.545, $p < 0.001$). Significant changes were observed in the post-RT volume of the hippocampus ($t(51) = 4.57$, $p = 0.001$), the LT TL ($t(51) = 3.858$, $p < 0.001$), the OC ($t(51) = 4.013$, $p < 0.001$) and the CN ($t(51) = -4.617$, $p = 0.002$), treatment dose in the RT TL Dmean and Dmax ($t(51) = -4.116$, $p < 0.001$; $t(51) = -4.271$, $p < 0.001$) and the Dmin of the OC ($t(51) = -4.436$, $p = 0.001$), the SC ($t(51) = -3.489$, $p = 0.001$), the cerebellum ($t(51) = -2.517$, $p = 0.015$) and the CN ($t(51) = 2.598$, $p = 0.012$) and the Dmean of the hippocampus (t(51) = − 4.529, $p < 0.001$). Significant changes was also observed in education years (t(51) = 8.282, $p < 0.001$) and gender ($t(51) = -2.536$, $p < 0.014$).

Tele-MACE

The overall model of Tele-M ACE explains 78.4% ($R^2 = 0.784$) of the cognitive score and is statistically significant (F (19,50) = 9.547, $p < 0.001$). Significant changes were also shown in post-RT volume; hippocampus ($t(50) = 4.001$, $p < 0.001$), LT TL ($t(50) = 3.157$, $p = 0.003$), CN ($t(50) = -2.024$, $p = 0.048$), OC ($t(50 = 3.561$, $p = 0.001$), treatment dose Dmin; BS ($t(50) = -2.823$, $p = 0.007$), SC ($t(50) = -2.654$, $p = 0.011$), CN ($t(50) = 3.627$, $p = 0.001$), cerebellum ($t(50) = -4.45$, $p < 0.001$), OC (t(50) = − 4.48, $p < 0.001$), Dmax; RT TL ($t(50) = -3.591$, $p = 0.001$), SC ($t(50) = -2.608$, $p = 0.012$), OC ($t(50) = -2.182$, $p = 0.034$), Dmean; RT TL (t(50) = − 3.904, $p < 0.001$), hippocampus ($t(50) = -5.51$, $p < 0.001$), education years ($t(50) = 5.947$, $p < 0.001$), and age ($t(50) = -2.848$, $p = 0.006$).

DNN

DNN layers and weight indices

The neural network diagrams of T-MoCA, Tele-MACE and TICS comprised of 4 factors, 28 to 36 input variables, 11 neurons in the first hidden layer and 8 neurons in the second hidden layer, and 2 output levels (deficit and normal cognitive scores). The input variables comprised of post-RT volumes, stage, education years, gender, age, and DVH factors with cognitive-related dosimetric predictors selected in MLR.

Weight indices of the input and output variables for the networks is shown in Supplementary 1 [a–c]. The DNN weight statistics have intra-variable variation, unlike the β coefficients of the regression models. An example, the weights of LT_TL_P (left temporal lobe post-RT volume) across eleven neurons in the hidden layer, notated as H(1:1–1), is 0.026, 0.064, − 0.063, − 0.049, 1.71, − 0.184, − 0.154, − 0.03, − 0.354, − 0.384, and 0.15 in Tele-MACE network indicating high degree of nonlinearity between variables and cognitive classification. The relatively high intra-variable variance was also noted in other input variables across T-MoCA and TICS networks. By contrast, intra-variable variance is low in BS_D40 (0.184, 0.738, − 0.045, 0.35, 0.19, 0.017, 0.366, − 0.37, 0.534, 0.23, and 0.211) indicating some degree of linearity in the TICS network. Similarly, the weights of connection between the hidden and output layers have a relatively large range, indicating high nonlinearity. For

example in neuron H(2:3) with cognitive deficit item, group 0 and normal cognitive item, group 1 (Tele-MACE group 0 = −0.962, group 1 = 1.232; T-MoCA group 0 = −0.265, group 1 = 0.344; TICS group 0 = −0.408, group 1 = 0.2). Supplementary tables also present the bias statistics for both hidden and output layers, which bias helps the network to learn the underlying data patterns more effectively. In this case, all network bias coefficients exhibited some degree of variation.

Sensitivity and specificity

Overall, the networks had reasonably high accuracy, evidenced by the percentage of incorrect classifications in the testing and training stages (Table 4). The specificity of both testing and training subsamples is significantly high in most of the networks but moderate in the sensitivity statistics. The area under the ROC (AUROC) in the testing and training subsamples curve is between 0.8 and 0.9, which is considered good [29].

Normalised Importance Index (NII)

Table 5 presents the 10 most important independent variables for each network which influenced cognitive grouping to deficit and normal cognition. Hippocampus, BS, SC, and cerebellum dose and volume parameters had the most influence on all the cognitive assessments (Tele-MACE, T-MoCA, and TICS) as indicated by its NII. Spinal cord_Dmin played major importance in the prediction output of all the networks (T-MoCA 92.6%, TICS 90%, Tele-MACE 71.2%). Only Tele-MACE reported the left TL (76.6) and the right TL (74.1) dosimetry as the top important variables in prediction output. Emphasis was given more on SC parameters in the T-MoCA and hippocampus parameters in the TICS cognitive assessments in estimating the prediction output. Additionally, age also showed the importance in the prediction output given the NII more than 50% (TICS 54.8%, Tele-MACE 51.7%) but not in gender (Tele-MACE 34.2%, T-MoCA 31%, TICS 7.6%). The NII of the remainder of the input variables gradually decreases but never reaches zero suggesting each variable made a significant contribution to the test group's cognitive. Overall, the DNN modeling yielded different Importance Indices with good sensitivity and specificity and outperformed the linear regression models of Tele-MACE, T-MoCA, and TICS.

Discussion

Demographic factors such as gender, age, and education were matched-sample between HC to NPC RT treated patients showed that patients have worse cognitive function than HC following RT. A significant decrease in post-RT

Table 4 Classification accuracy, specificity, and sensitivity estimated by the DNN model

		Percentage of incorrect predictions	Specificity	Sensitivity	AUC-ROC
T-MoCA	Testing	26.1%	79.4%	73.9%	0.878
	Training	21.7%	83.3%	82.3%	
Tele-MACE	Testing	12.0%	94.7%	66.7%	0.919
	Training	11.8%	91.7%	88.2%	
TICS	Testing	23.1%	80.0%	74.1%	0.890
	Training	16.7%	83.3%	85.7%	

Table 5 The DNN-estimated importance of independent variables in classifying cognitive group in Tele-MACE, T-MoCA, and TICS

	Tele-MACE	Importance	T-MoCA	Importance	TICS	Importance
1	Brain stem_D_{30}	100	Spinal cord_V_{60}	100	Hippocampus_D_{30}	100
2	Thalamus_V_{10}	84.6	Optic chiasm post-volume	99.1	Hippocampus_V_{60}	95.9
3	Left temporal lobe_D_{60}	76.6	Brain stem_$D_{\min}$	98.7	Spinal cord_D_{min}	90
4	Right temporal lobe_$D_{\max}$	74.1	Amygdala_D_{20}	92.8	Brain stem_D_{min}	83.1
5	Cerebellum_D_{30}	72	Spinal cord_$D_{\min}$	92.6	Thalamus_V_{20}	79.5
6	Cerebellum_$D_{\min}$	71.8	Spinal cord_V_{20}	80.6	Hippocampus post-volume	76.6
7	Spinal cord_$D_{\min}$	71.2	Spinal cord_D_{20}	74.1	Cerebellum_D_{50}	67.1
8	Hippocampus_V_{60}	70.4	Hippocampus_$D_{\min}$	71.8	Caudate nucleus post-volume	62.8
9	Spinal cord_$D_{\max}$	69.8	Spinal cord_$D_{\max}$	68.7	Hippocampus_D_{10}	60
10	Cerebellum_V_{20}	67.8	Hippocampus_D_{60}	67.9	Spinal cord_V_{60}	59.1

brain structure volumes relative to pre-RT was shown in all the delineated ROI and both hippocampus and SC were also significantly correlated to cognition. Moreover, cognitive changes were also shown in the irradiated ROI regions of NPC patients. This suggests the impact of radiation on human cognition that arises and slowly worsen in patients after RT completion with the diminishing brain volume. In addition, cognition was also correlated to the patient's age and education, which implies that both factors could affect the patient's perception and understanding of the neurocognitive assessments. The study presented a moderate negative correlation between cognitive outcomes to QoL, which proposes that reducing the cancer burden or being cancer-free outweighs the effect of cognitive deficit.

Nonetheless, it is important to recognize that cognitive deficit is multifactorial, as deficit may be caused by the tumour itself, number of interventions, assessment time after treatment, functional deficit, preexisting cognitive abnormalities, and other adjuvant treatments [30–32]. Thus, it is not possible to precisely designate cognitive dysfunction to an isolated factor. According to Piai et al. [33], moderate to severe cognitive impairment is already shown at baseline of head and neck cancer patients when compared with healthy controls. The deficit was evident in the domains of delayed recall, letter fluency, psychomotor speed and executive function [33]. Furthermore, cognitive deficit was also associated with RT [19] and the extent or injury varies depending on the duration of RT completion [18, 34, 35] with the memory and executive function domains being the most affected [36, 37]. In some studies, cognitive deficit was more pronounced in patients receiving 2 Gy fraction doses [38–40]. Besides that, cerebral volume atrophy is also dose-dependent. This is validated by prior studies [18, 19, 34, 41]. According to Seibert et al. [42], radiation dose-dependent atrophy was observed in the hippocampus 1-year post-RT compared to baseline with a higher radiation dose (30 Gy) induced earlier and severe histological changes than a lower radiation dose (25 Gy) [18]. Dose-dependent atrophy is also shown in the bilateral TLs and cerebellum, suggesting that radiation-induced changes may not be confined to the target area but also to other encephalic regions [3, 43]. Significant radiation dose-dependent volume loss is also determined in other cerebral structures with a loss of 0.16 to 1.37%/Gy in the amygdala [44], thalamus, putamen, and globus pallidus [16].

Moreover, damage to cerebral volume after RT also correlates to cognitive function. This was observed between the dilation of the ventricles that correlates with grey matter loss [45] and cognitive impairment [18, 46]. Furthermore, bilateral hippocampal doses greater than 7.3 Gy was also associated with long-term cognitive deficit [47]. As radiation induces inflammation and microvascular damage thereby altering the hippocampal neurogenesis, this is thought to contribute to a deficit in memory function following RT [48, 49]. Increased radiation dose to the bilateral TLs and cerebellum were also significantly correlated to worsen memory performance, executive ability and motor coordination [3, 21, 50]. Due to their proximity to the radiation field of NPC RT, both the TL and cerebellum are susceptible to radiation damage, with the TL being associated with the default mode network (DMN), which is highly sensitive to radiation [21, 51]. In addition, cerebellar atrophy was also correlated to oral and written processing speed and depended significantly on the mean dose, time after radiotherapy, and patient age [52–54]. Delayed neurological complications of cranial nerve palsies, cervical myelopathy and temporal lobe necrosis (TLN) may also occur from NPC RT [55]. Having said that, changes in the central nervous system (CNS) that disseminate with time could form irreversible structural abnormalities that could cause permanent cognitive disability [39, 56]. Since dose-volume parameters are highly correlated to developing TLN [57, 58], it may cause cognitive deficit and severely affect a patient's quality of life (QoL) [59]. Therefore, this suggests that the tumour and radiation could influence cognitive functioning.

Consequently, radiation-induced brain injury can occur as early as a few days or weeks after RT, which has time continuity and does not halt even with the termination of radiation. The pathophysiological changes fluctuate within the three phases (acute (few days to weeks), early-delayed (1 month to 6 months) often with reversible injuries, and late-delayed (more than 6 months to few years) after RT) with severe functional deficits that is usually permanent, irreversible and progressive [15, 60]. In this study, focus is on late-delayed reactions, as cognitive deficit is usually observed during this period. Besides, this is to limit confounding factors underlying the acute and early delayed injury likely due to edema with an increase in nerve cell or stromal size [61]. Notably, during the late-delayed phase, patients tend to experience deficits in memory, spatial relations, visual motor processing, quantitative skills and attention, including somnolence syndromes [48, 62]. Interestingly, in the present study, a negative correlation was observed between the neurocognitive tests and QoL. This suggests that patients might have good resilience by alleviating emotional distress and thus might not have a decrease in their QoL as they were better at coping with cancer [63, 64]. The better resilience and acceptance could be due to the patients' ages (52.76 ± 12.73 years), as previous studies had shown that patients aged more than 50 years showed a drop in physical domain rather than social domain [37] and emotional domain [65, 66]. However, given that patients were taken from a government institution where only very minimal medical fees are required, thus, the financial burden was not a factor, contrary to studies suggesting financial difficulty is a factor in affecting QoL [64, 67].

Due to the recent COVID-19 pandemic with movement restrictions and in-person constraints, neuropsychological assessments were done remotely, thus the absence of standard assessments. Regardless, validation of the teleconsultation assessment was done in previous studies [8–10]. Besides, evidence concerning the feasibility and utility of telephone-based psychological and health assessments were also shown in brain tumour [68], hematologic malignancies [69] and head and neck cancer patients [70]. This is the first-ever study that uses remote neurocognitive assessments in monitoring NPC patients' cognitive functions following RT and correlating them with morphological changes and dose-volume parameters. From the study, all the regression models showed a relatively strong effect size ($R.^2 > 0.7$) [71] which results were similar to conventional neurocognitive assessments in post-RT patients [3, 17, 20]. This suggests that the implementation of remote cognitive assessments could perhaps be comparable to standard cognitive assessments, therefore, the possibility of replacing or use as an alternative during situation that preclude from standard implementation. Furthermore, comparison between standard and tele-consultation assessment had been performed in previous studies [10, 72, 73] and showed that tele-consultation assessments were able to independently distinguish MCI from normal cognition with high sensitivity and specificity in predicting and assessing dementia and MCI even with removal of visual items from the assessment scale [9]. Therefore, implementation of remote neurocognitive assessments is feasible in clinical settings.Two methods were implemented in constructing the predictive models of the study, MLR and MLP-DNN, with each method contributing 3 neurocognitive endpoints (TICS, T-MoCA and Tele-MACE).

From the regression models, demographic factors and dose-volume parameters were the variables in the prediction models. All three regression models included education as a predictive variable predicting neurocognitive function deficit. Besides, age was also associated with compromised cognition in the regression models. The findings were similar to previous studies that suggested higher age and lower education negatively affect cognitive results [74, 75], which were associated to language and motor dexterity (age at RT and education years), executive function and speed (age at RT), verbal and working memories (education years) domains [76]. Moreover, higher age, lower educational level, initiation of radiotherapy and years since diagnosis were predictors for long-term health-related QoL or neurocognitive deficit in NPC patients [77–79]. From the regression models, apart from education and age, lower hippocampus, LT TL, and OC volumes, higher Dmean in the hippocampus and higher Dmean and Dmax in the RT TL were predictors for neurocognitive deficits. Nevertheless, not all variables were independently related to the measured outcomes, such as gender and overall staging. This is in line with previous studies [75, 80] that stated gender was not associated with cognitive function and not a significant determinant of QoL for head and neck cancer patients [65, 66]. It is possible that the severity of other conditions masked the potential impact of gender on cognition. Clinical variables such as tumour grade, type and lesion volume were not significantly correlated to cognitive function, but correlation to cognition was found in RT type; thus, tumor characteristics may likely have less of an impact on cognitive functioning than radiation treatment and its side effects [7, 81]

In radiation oncology, DNN can be divided according to the primary purpose, such as image fusion, image segmentation, prognosis and outcome prediction. Application of DNN predictions in predicting the toxicity following RT were shown in several studies, for example, xerostomia in head and neck RT [82], radiation pneumonitis in thoracic RT [83] and late genitourinary system toxicity in prostate cancer [84], where the neural networks showed good prediction results. Besides, DNN was also applied in predicting tumour recurrence in non-small-cell lung cancer (NSCLC) that demonstrated a better-performed prediction model compared to the conventional model, with an AUROC of 0.842 [85] and dose-distribution in breast cancer patients with doses predicted by the neural networks were superior to conventional knowledge-based planning [86]. From the study, the DNN analysis showed that dosimetric features could substantially contribute to differentiating cognitive groups of patients following NPC RT with high accuracy. The application of artificial neural networks is also superior to conventional methods such as discriminant and regression analyses [83, 87, 88] provided its significantly high precision [89]; thus, its expansion in radiation oncology.

It is acknowledged that this study has several limitations. First, the cross-sectional design limits the interpretation of the study results as the absence of baseline cognitive assessments. Second, the relatively low number of patients accrued in this study may be a deterrent in concluding the study outcome, limiting the ability of the DNN models and measured outcomes. Even so, good prediction models were generated from the study. Even with small data sets, deep neural nets can achieve superior classification accuracy without overfitting [90]. Third, the causative factor of the impaired cognitive function is ambiguous as we cannot clearly distinguish it from the chemotherapy or RT although chemotherapy did not instigate volumetric brain changes [18]. Nonetheless, the synergy between chemotherapy and RT may have affected the results in the present study; thus, a future study segregating chemotherapy and RT should be conducted to elucidate such effects. Fourth, as cognitive assessments were done remotely, administration procedures might be affected by poor line connection, difficult for patients with hearing impairment and loss of visual cues, and those with poor communication skills and shorter attention spans [8, 10]. Despite the intrinsic limitations, remote assessments can potentially increase sample

size by reaching a broad range of populations, minimizing costs, reducing selection bias and conducting longitudinal follow-ups [8, 91]. Nevertheless, test-retest and parallel-test reliabilities of the assessments should be evaluated in future studies [8]. Finally, the discrepancies in DVH generated from multimodal treatment planning systems could overestimate the structure volumes and parameters. Regardless, dose distributions were almost identical, and no significant dose differences were observed [92].

Radiation-induced brain impairments in NPC patients following RT is dose-dependent and volume-dependent, suggesting the possibility of early biomarkers in cognitive deficit. Given the streamlined approach and comparable result of remote neurocognitive assessments, monitoring a patient's cognitive status could be easily integrated into current primary care settings and probably to even replace standard assessments. The prediction models can be used to identify individual patients with the possibility of suffering from cognitive deficits following NPC RT, thus, enabling tailored interventions and supportive care services to be provided in managing cognitive changes following NPC RT.

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Data availability The data presented in this article are available in the main article or supplementary materials.

Declarations

Ethics approval and consent to participate The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Malaysia Ministry of Health (NMRR-19–2456-49608 (IIR), 14 July 2020).

Consent for publication Informed consent was obtained from all subjects involved in the study.

Competing interests The authors declare that they have no competing interests.

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