Radiotherapy and Oncology 188 (2023) 109863

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review Article

Neurocognitive function following (chemo)radiotherapy for nasopharyngeal cancer and other head and neck cancers: A systematic review

Zsuzsanna Iyizoba-Ebozue [a], Robin Prestwich [a], Sarah Brown [b], Emma Hall [d], John Lilley [e], Matthew Lowe [f], David J Thomson [g,h], Finbar Slevin [a,c], Florien Boele [c,1], Louise Murray [a,c,*,1]

[a] Department of Clinical Oncology, Leeds Cancer Centre, Leeds, UK; [b] Leeds Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research; [c] Leeds Institute of Medical Research, University of Leeds, Leeds, UK; [d] The Institute of Cancer Research, London, UK; [e] Department of Radiotherapy Physics, Leeds Cancer Centre, Leeds, UK; [f] Department of Medical Physics and Engineering, The Christie NHS Foundation Trust, Manchester, UK; [g] Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK; [h] Manchester Academic Health Sciences Centre, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

ARTICLE INFO

Article history:
Received 8 May 2023
Received in revised form 13 August 2023
Accepted 16 August 2023
Available online 22 August 2023

Keywords:
Neurocognition
Head and neck cancer
Radiotherapy
Quality of life

ABSTRACT

When radiotherapy is used in the treatment of head and neck cancers, the brain commonly receives incidental doses of radiotherapy with potential for neurocognitive changes and subsequent impact on quality of life. This has not been widely investigated to date.

A systematic search of MEDLINE, EMBASE, Psycinfo Info and the Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases was conducted. Of 2077 records screened, 20 were eligible comprising 1308 patients. There were no randomised studies and 73.3% of included patients were from single center studies. IMRT was delivered in 72.6% of patients, and chemotherapy used in 61%. There was considerable heterogeneity in methods. Narrative synthesis was therefore carried out. Most studies demonstrated inferior neurocognitive outcomes when compared to control groups at 12 months and beyond radiotherapy. Commonly affected neurocognitive domains were memory and language which appeared related to radiation dose to hippocampus, temporal lobe, and cerebellum. Magnetic Resonance Imaging could be valuable in the detection of early microstructural and functional changes, which could be indicative of future neurocognitive changes. In studies investigating quality of life, the presence of neurocognitive impairment was associated with inferior quality of life outcomes.

(Chemo)radiotherapy for head and neck cancer appears to be associated with a risk of long-term neurocognitive impairment. Few studies were identified, with substantial variation in methodology, thus limiting conclusions. High quality large prospective head and neck cancer studies using standardised, sensitive, and reliable neurocognitive tests are needed.

Definitive radiotherapy (RT) +/- chemotherapy is a standard of care for the treatment of head and neck cancer (HNC) patients [1,2]. This is associated with potential for severe morbidity that can impact on long term quality of life[3–5]. Epidemiologic change, improved diagnostics and novel therapeutic modalities have translated to improved life expectancy[6,7]. With an increased focus on survivorship, achieving a balance between tumour control and toxicity prevention has become a key challenge[1,8,9]. Neurocognitive impairment can be a side effect of commonly used cancer treatments, including RT when dose is delivered to the brain [10–13], and chemotherapy [14]. Neurocognitive functioning is a performance outcome, and even subtle impairments may impact negatively on quality of life (QOL) and day to day functioning [15,16].

The radiation dose delivered to the brain tissue in patients with HNC is related to delivery technique, tumour site and consequently target volume. Achieving acceptable dosimetric coverage of target volumes adjacent to the skull base inevitably involves some dose deposition in nearby brain tissues. This is well documented in the treatment of nasopharynx cancer, for which temporal lobe necrosis is a recognised toxicity[17]. However, for other head and neck primary sites, treatment of retropharyngeal and/or retrostyloid lymph nodes is routinely required[18], extending target volumes towards the skull base. RT techniques also impact upon dose to adjacent brain structures. In the era of 2D or 3D conformal planning, this could involve high doses to nearby non-target brain

* Corresponding author at: Department of Clinical Oncology, Level 4, Bexley Wing, Leeds Cancer Centre, St. James's University Hospital, Beckett St., Leeds LS9 7TF, UK.
E-mail address: L.J.Murray@leeds.ac.uk (L. Murray).
[1] Both authors contributed equally to this work.

https://doi.org/10.1016/j.radonc.2023.109863
0167-8140/

tissue e.g temporal lobes in nasopharynx cancer. Intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) is now routinely used, which may deliver a low dose 'bath' to normal inferior regions of the brain[19] which has potential toxicity implications. For example, a phase 3 trial of IMRT versus conformal RT for parotid sparing for oropharynx cancer (PARSPORT trial) reported an increased fatigue in the IMRT arm with a potential relation to incidental dose to the brainstem[20].

It has been hypothesised that radiation doses delivered to central nervous system structures as part of curative-intent treatment for HNC could have a long term detrimental impact upon neurocognition in survivors[20,21].The impact of RT upon long term neurocognition and the importance of this as a survivorship issue remains uncertain. The study therefore aims to perform a systematic review and narrative synthesis regarding neurocognitive outcomes following definitive (chemo)RT in HNC survivors.

Methods

Objectives

This systematic review primarily aims to address the neurocognitive impact of RT with or without chemotherapy in the treatment of non-metastatic HNC. Secondarily, it aims to evaluate the impact of neurocognitive changes following such treatment on quality of life in HNC survivors.

PRISMA guidelines for systematic reviews[22] were used as a template for the methodology. A comprehensive systematic search strategy informed by an information specialist was used to query MEDLINE, EMBASE and Pyschinfo electronic databases from inception until September 2022 (additional search strategy information can be found in Supplementary Material). Review databases (Cochrane Systematic Review Register and PROSPERO) and trial registers were searched to identify any relevant on-going reviews and trials.

Selection criteria

The inclusion criteria for study selection were studies published in English, in full text and abstract form, reporting on neurocognition outcomes assessed using a screening tool or test battery or self-reported, following radical RT with or without chemotherapy in adult HNC patients. Studies that investigated potential associations between neurocognitive and MRI changes were also included. Studies within which the target population formed a subset of a wider sample (e.g., patients with multiple cancer types) were excluded. Studies that included paediatric patients (<18 years), case studies, review articles, conference abstracts, sample sizes of $\leq$ 20 patients (to mitigate limitations associated with very small sample sizes) and studies that examined palliative RT or adjuvant RT (to avoid the confounding effect of surgery) were excluded.

Data extraction

One reviewer (ZIE) conducted the database search and screened titles and abstracts. Two reviewers (ZIE and FS) independently reviewed full texts, with discordance between reviewers resolved following arbitration by a third reviewer (LM). The quality of each study was assessed using a quality appraisal tool for case series [23]. Extracted data including the following, first author and country in which the study took place, study type (prospective or retrospective), single/multi-centre status, study period/date of recruitment, number of patients, mean/median age, primary disease characteristics, primary treatment modalities, tools used to assess neurocognition and domains of cognition assessed, timing of neurocognitive assessment(s), structural changes on cross-sectional imaging, and quality of life measurements.

Synthesis

A narrative synthesis method was adopted to summarise, incorporate, and interpret the findings of included studies. This was considered appropriate given the significant heterogeneity in study methodology and outcome measures. The process of synthesis involved developing a preliminary synthesis, exploring relationships between included studies and assessing strength of the evidence, as guided by Popay et al[24].

Results

The systematic literature search identified 2077 unique records. After screening title and abstract, 77 full text articles were assessed, and 20 studies were included in the final analysis. A PRISMA flowchart of the systematic review is presented in Fig. 1.

The quality of the evidence varied per study, as reflected in the range of scores from the quality appraisal tool for case series studies (see Supplementary Material for summary of results). Therefore, findings should be interpreted with caution and study limitations should be considered.

Across the 20 included publications, a total of 1308 patients were included. 19/20 studies exclusively studied patients treated for nasopharyngeal cancer (NPC). Only one study included a heterogenous group of HNC patients but excluding NPC patients [25]. Sample sizes ranged from 22 to 146 patients and studies covered the period 1998–2021. IMRT (including VMAT) was used to treat 72.6% of patients and 61% received chemotherapy. Baseline patient and treatment characteristics are reported in Table 1. The impact of neurocognitive deficits on quality of life was evaluated in three studies.

A wide variety of tools were used for assessment of neurocognitive function: the Montreal Cognitive Assessment (MoCA; n = 12 studies)[26–37], Mini Mental State Exam (MMSE; n = 4) [17,32,38,39] and Wechsler Adult Intelligence Scale revised or edition III (WAIS- R/III; n = 4)[17,25,40,41]. In addition, four studies used multiple tools[17,32,38,40]. Two studies used self-reported measures of cognition as opposed to objective tests[26,42].

Different comparator groups have also been employed across the different studies: 11 studies compared irradiated patients to matched healthy controls at one or more time points and nine studies compared irradiated NPC patients with other NPC patients, including non-irradiated NPC patients (including within patient comparisons before and after RT) or irradiated NPC patients at different time points. In addition, one study[26] used 'cut-off' scores (score < 23 on the MoCA) to define neurocognitive impairment (range 13–30, mean 23.7, SD 3.4), without comparison to any other group.

Within these studies, 14 incorporated radiological imaging to categorise patients according to the presence or absence of structural (necrosis, bleeds, atrophy, dilatation) or functional (blood flow, nodal activity) brain changes following RT. These studies compared neurocognitive function between groups or referenced neurocognitive function to imaging changes. Multiple comparators were used in two studies[32,40].

Of the 20 studies, 11 performed longitudinal analysis, either using patients as their own controls and assessing within patient change over time (n = 4)[29,38,39,43] or in comparison to healthy controls at each time point (n = 7) [25,27,30,33,35–37].

Compared to a healthy population, five studies[25,30,35,40,41] observed inferior neurocognitive outcomes in irradiated NPC patients when assessed at least 12 months after RT (Table 2). In

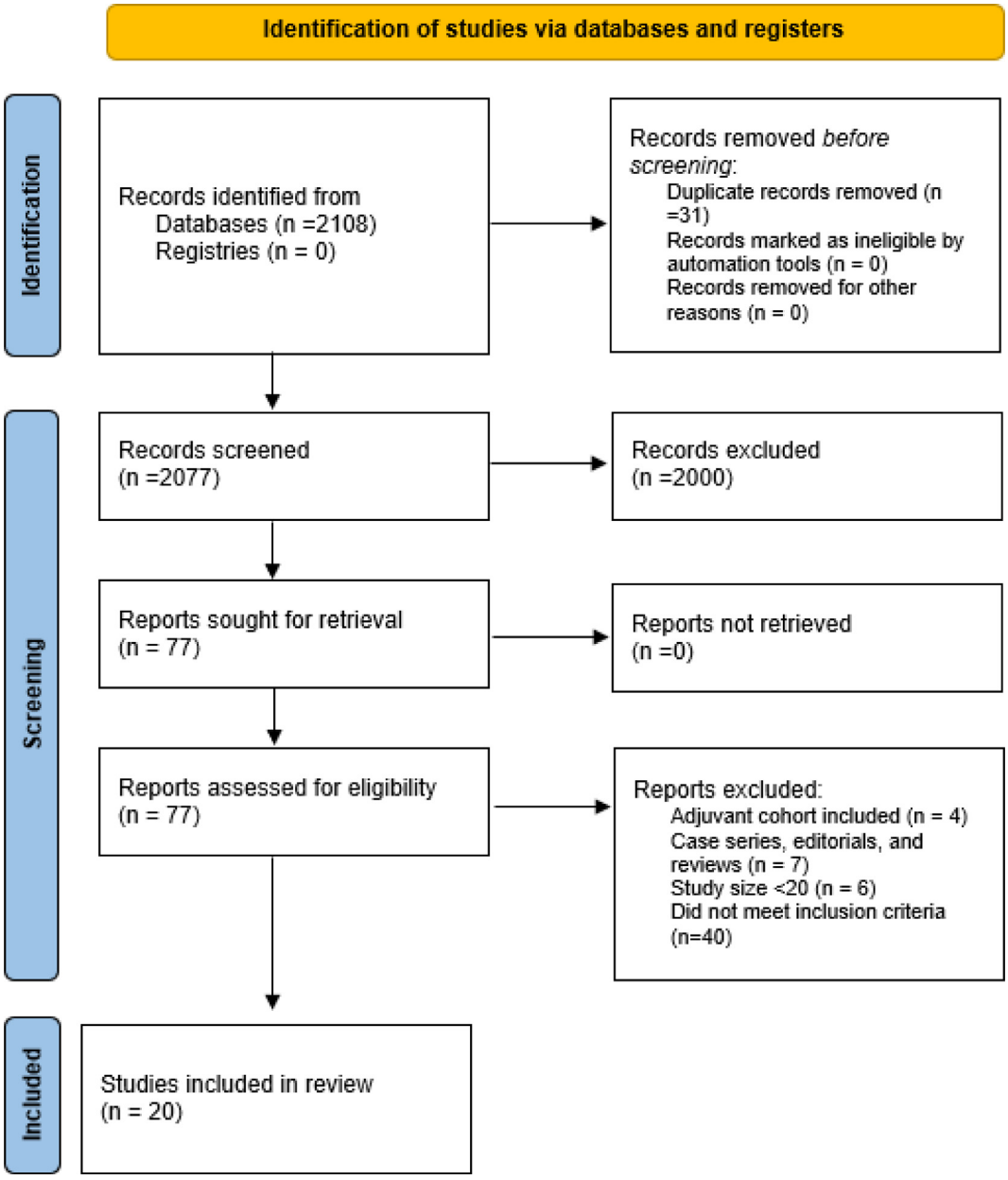

Fig. 1. PRISMA diagram showing the inclusion and exclusion of papers in the review.

one study, compared to healthy controls (matched for age and educational level), irradiated NPC patients demonstrated worse performance on most memory tests after a mean follow up of 28 months. [40] In the single non-NPC study, composite global function in irradiated patients (calculated using the mean score across domains in the test battery) progressively declined in the two years after definitive treatment with (chemo)RT compared to healthy controls (Cohen's d effect sizes; mean [and 95% CI] − 0.38 [−0.55 to − 0.22], −0.75 [−0.92 to − 0.58] and − 1.06 [−1.26 to − 0.86]) at 6, 12 and 24 months, respectively[25].

Nine studies (Table 3.) used non-irradiated NPC (yet to receive RT) patients as a potentially more comparative population to irradiated NPC patients than the general population. Hsia et al [38] and Wu et al[32], showed statistically significant differences between these groups in neurocognition assessed with screening tools. Inferior outcomes were observed in the irradiated groups, with statistically significant mean score differences on the Cognitive Abilities Screening Instrument (CASI; mean ± SD: 88.9 ± 8.19(non-irradiated) vs. 85.93 ± 8.02(irradiated), $p < 0.033$)[38], MoCA (27.2 ± 2.2 (non-irradiated) vs. 21.8 ± 5.3 (irradiated), $p < 0.001$) [32] and MMSE (28.9 ± 1.9 (non-irradiated) vs. 25.4 ± 4.6 (irradiated), $p < 0.001$)[32].

In total, 11 prospective studies including the one non-NPC study, evaluated longitudinal changes in neurocognition (i.e., within patient comparisons over time or in comparison to healthy controls at each time point). Ren et al[27] demonstrated alterations in cerebral functional based on functional MRI, 24 hours after RT compared to imaging pre-treatment, but no changes were observed in neurocognition over this time. Similarly, Mo et al[43] found no acute neurocognitive deficits following IMRT in a cohort in whom neurocognition was assessed one week before and after RT. In the subacute period (3–6 months post-RT), however, patients who displayed significant intracranial volume changes on imaging also manifested a rapid decline in neurocognitive function[30,33]. After the subacute period (6 months and beyond), Ma et al observed significant correlations between functional brain

Table 1
Patient characteristics.

Characteristics	n = 1308 (n/%)
Subsite	
Nasopharynx	1228 (93.9%)
Oropharynx	61 (4.7%)
Hypopharynx	5 (0.4%)
Laryngeal	7 (0.5%)
Nasal cavity	2 (0.1%)
Unknown primary	5 (0.4%)
Stage	
I/II	74 (5.7%)
III/IV	496 (37.9%)
Unreported	780 (56.4%)
Radiotherapy Technique	
IMRT (including VMAT)	950 (72.6%)
3D conformal planning (3DP)	239 (18.3%)
Tomotherapy	18 (1.4%)
Unreported	101 (7.7%)
Prescription dose to highest dose target (range)	66–80 Gy
Dose /fraction (range)	1.8–2.7 Gy
Use of chemotherapy	
Radiotherapy alone	94 (7.2%)
Concurrent chemoradiotherapy therapy (CRT)	636 (48.6%)
Neoadjuvant/adjuvant chemotherapy + CRT	162 (12.4%)
Unreported	416 (31.8%)
Timing of first neurocognitive assessment from treatment completion	
< 3 months or pre-treatment	193 (14.9%)
3–6 months	342 (26.1%)
> 6–12 months	139 (10.6%)
> 12 months	634 (48.4%)

connections on imaging and MoCA scores [34]. Most studies (n = 11) showed an increased rate of impaired neurocognitive functioning at 12 months and beyond definitive RT, with deficits increasing over time, including the non-NPC study, as detailed above [25,27,29,30,33–36,38,39,44]. The risk of deterioration in neurocognitive functioning was observed to extend into very long-term survivorship (>10 years) in one study[42].

Neurocognitive performance is typically conceptualised in terms of functional domains and these domains are not independent of each other [45]. For language function, Hua et al[41] found performance of post-RT patients comparable to normal controls and patients awaiting RT in mean scores across the 3 groups evaluated by token test (42.02 ± 2.36 (post-RT patients) vs 42.29 ± 1.72 (healthy controls) vs 41.48 ± 3.09 (pre-RT patients), p = 0.46), visual naming subtest (54.74 ± 5.76 (post-RT) vs 54.86 ± 5.4 (healthy controls) vs 54.0 ± 4.99 (pre-RT), p = 0.81) and semantic association (36.47 ± 9.69 (post-RT) vs 37.96 ± 7.91 (healthy controls) vs 37.48 ± 8.86(pre-RT), p = 0.80.This differs from the other studies that examined language: Lam et al[40] reported lower scores in patient groups than control group in WAIS-R tests of verbal intelligence (p=<0.05 on digit span, difference in recall from the third trial onward p=<0.05).This finding was attributed to possible underlying semantic memory deficits[40]. Wu et al[32] also found significant reduction in language subdomain mean scores on the MoCA (2.9 ± 0.3 (patients without radionecrosis) vs 2.3 ± 1.0 (patients with radionecrosis), p=<0.001) and MMSE (8.8 ± 0.5 vs 8.3 ± 1.2, p=<0.001) compared to patients without cerebral radionecrosis on imaging.

Impaired performance in memory in irradiated patients was reported in all studies that assessed neurocognitive domains. Hua et al[41] also found episodic memory test performance of normal controls and non-irradiated NPC patients was superior to irradiated NPC patients, reaching statistical significance in the Word Sequence Learning [correct (healthy controls: 58.89 ± 5.2 vs pre-RT patients: 51.14 ± 8.68 vs post-RT patients: 48.67 ± 9.38, respectively, p = 0.03] and recall[4.0 ± 1.41 vs 3.11 ± 1.71 vs 2.96 ± 1.76, respectively, p = 0.02]) and figure memory subtest of the WMS-R (7.23 ± 1.44 vs 6.93 ± 1.21 vs 6.33 ± 1.59, respectively = 0.05) [41]. Lam et al[40] evaluated working memory by using the digit and visual span tests and episodic memory with the Rey auditory and visual learning tests. Patients with temporal lobe injury had lower scores on forward visual span compared to healthy controls (one-way ANOVA, F3.39, df 2.67, p=<0.05). On the Rey auditory test differences in recall became significant from the third trial onward in patients with and without temporal lobe injury compared to healthy controls (one-way ANOVA, p=<0.05) and on the Rey visual learning test, again, patients with and without temporal lobe injury performed worse (one-way ANOVA, p=<0.05)). Deficits after RT were considered related to retrieval problems rather than encoding strategies[40]. In addition, over time, verbal memory was better preserved than visual memory[40].

Zer et al[25] converted neurocognitive test scores to age-corrected *z* scores (patient deficit defined as −1.64 SD.) and found comparable degrees of decline across all domains at 6 months post-RT compared to healthy controls, but at 24 months more patients demonstrated declines in specific domains, including verbal memory (Cohen's effect $d = -0.16$; 95%CI − 0.33 to 0.02; $d = -0.38$; 95%CI − 0.64 to − 0.12; and $d = -0.53$; 95%CI − 0.74 to − 0.32, measured at 6, 12 and 24 months, respectively).

Attention and processing speed have also been shown to be impacted post-RT in HNC patients compared to healthy controls and HNC patients without radiation related structural changes on MRI. Zer et al. [25] reported a decline in these domains over time (measured at 6, 12 and 24 months): intellectual capacity (Cohen's $d = -0.46$; 95%CI − 0.64 to − 0.30; $d = -0.51$; 95%CI − 0.72 to − 0.30; and $d = -0.70$; 95%CI − 0.92 to − 0.49 respectively), concentration (Cohen's $d = -0.19$; 95%CI, −0.37 to 0.00; $d = -0.38$; 95%CI − 0.55 to − 0.21; and $d = -0.54$; 95%CI − 0.71 to − 0.37, respectively) and executive function (Cohen's $d = -0.14$; 95% CI − 0.27 to − 0.00; $d = -0.34$; 95%CI − 0.52 to − 0.16; and $d = -0.43$; 95%CI − 0.64 to − 0.22, respectively) post RT. Attention was significantly worse compared to control group based on mean MOCA scores (5.0 ± 1.2 vs 5.7 ± 0.5, p=<0.001) and MMSE(3.6 ± 1.7 vs 4.3 ± 1.0, p = 0.002) in the study by Wu et al[32].

In three studies that examined patients treated for NPC, neuroimaging was used to identify groups for comparison of neurocognitive function (e.g., those with and without structural brain changes) and in seven studies neuroimaging was used to detect significant and progressive RT-associated structural brain changes following RT for NPC.

Lv et al[33] demonstrated a time-dependent pattern of atrophy in the hippocampus and cerebellar subfields with elevated volume losses associated with rapid decline in neurocognitive function on the MoCA over 6 months(left hippocampus: r = 0.01, $p = 0.017$, right hippocampus: r = 0.013, $p = 0.002$). Longitudinal dilation of the ventricles was also found to correlate with longitudinal reduction of neurocognition (β coefficient= − 4.63, p = 0007). An increased number of cerebral microbleeds, defined as haemorrhagic microvascular lesions or microangiopathy affecting the function of the neurovascular unit was shown to result in neurocognitive dysfunction as defined by scores < 26 on MoCA (odds ratio 1.03, CI 1.01–1.04; p = 0.003)[28]. Selective and time-dependent white matter atrophy in the right inferior temporal gyrus was correlated with progressive neurocognitive impairment demonstrated by decreasing MoCA scores (r = 0.53, p=<0.001)[35]. In a prospective study by Liu et al[39] of 86 patients with temporal lobe necrosis with a median follow-up of 32 months, only 26 patients (30%) showed obvious neurocognitive dysfunction as quantified by MMSE scores (≤26). In all patients who displayed

Table 2
Studies with 'healthy' individuals as comparators (n = 11).

Study (Type of study)	N receiving intervention (radiotherapy)	H &N subsite	Radiotherapy Technique	Comparator group	MRI	Follow-up interval / time to neurocognitive assessment (and imaging if relevant)	Tool to assess cognition	Neurocognitive function (NCF) outcome
Hua et al, 1998 [41] National Taiwan University Hospital (retrospective)	27	NPC	3-DP	35 age and education matched healthy controls	Not reported	Median 1.7 years (range 7 days to 9 years)	WAIS- R	Neuropsychological impairments ($p < 0.05$) in auditory attention / concentration, recent memory, immediate and delayed verbal recall and immediate visual recall, higher-order visuospatial abilities, and bimanual dexterity following RT
Cheung et al, 2000 [17] Queen Elizabeth Hospital Hong Kong (retrospective)	53	NPC	3-DP	31 age and education matched healthy controls	31/53 had Temporal lobe necrosis (TLN) on MRI	Unreported	Cantonese-MMSE WAIS-R	NCF of patients without TLN similar to controls. Patients with TLN had memory and other NCF impairments; verbal (p=<0.001) and visual memory (range p=<0.001 to $P = 0.03$), language (range, p=<0.001 to p = 0.01), motor ability (p = 0.02), planning (p = 0.02), cognitive ability (p = 0.007), and abstract thinking (range p = 0.009 to p = 0.04).
Lam et al, 2003 [40] Prince of Wales Hospital Hong Kong (retrospective)	60	40 NPC patients with CT or MRI evidence of temporal lobe injury	3-DP	20 NPC patients without temporal lobe injury and 19 healthy controls matched for age and educational level.	Cohort of 40 with CT or MRI evidence of temporal lobe injury and 20 without imaging evidence of TLI	Mean interval from RT of 5.5 years (TLI) and 5.0 years (no TLI). Followed up for 28 months (range 11––42 months)	Chinese WAIS-R Rey auditory test Visual learning test	Both patient groups performed significantly worse on most memory tests compared to healthy controls. No significant difference between patient groups with or without temporal lobe injury
Shen et al, 2016 [28] Sun Yat-Sen University, Guangzhou (retrospective)	106	NPC	IMRT (35.8%)	66 patients with other diseases, no RT or brain pathology matched for age and education.	At least 1 cerebral microbleeds (CMB) was found in 98.7% in the radionecrosis (RN) group, in 42.9% in the non-RN group, and in 21.2% in the control group.	5.3–6.5yrs	MoCA	Number of temporal cerebral microbleeds independently associated with increased likelihood of cognitive dysfunction in patients with RN. (OR 1.03; CI 1.01–1.04; p = 0.003) CMBs occurred most frequently (76.4%) in temporal lobes, followed by cerebellum (23.7%), basal ganglia (15.8%), occipital lobe (10.5%), brain stem (9.2%), and frontal lobe (3.9%)
Guo et al, 2018 [36] Guangzhou Medical University (prospective)	63	NPC	IMRT	20 age and education matched healthy controls	Longitudinal MRI to monitor structural brain changes.	6 months MoCA and MRI carried out at baseline (before RT), 3 and 6 months after RT	MoCA	Longitudinal dilation of the ventricles correlated with longitudinal reduction of neurocognition in NPC patients (β coefficient= − 4.63, p = 0007). Significant time-dependent decreases in volumes of total grey matter, & bilateral temporal lobes
Zer et al, 2018 [25] Princess Margaret, Toronto (prospective)	80	Hypopharynx (5) Oropharynx (61) Laryngeal (7) Nasal Cavity (2) Unknown Primary (5)	IMRT	40 age matched healthy control	Unreported	24 months Neurocognitive assessments done at 4 time points: baseline (within 2 weeks prior to start of treatment), end of treatment (6 months after baseline), 12 and 24 months after baseline	WAIS-III	Significant differences in some domains (attention, verbal memory, executive function) in HNC patients, with deficits increasing over 2 years. Significantly Increased rate of impaired global neurocognitive functioning among patients (38%) at 24 months compared with controls (0%)
Ren et al, 2019 [27] National Can-	22	NPC	IMRT	20 age, gender and education matched healthy control	Longitudinal functional MRI	1 day before to 1 day after RT	MoCA and functional MRI	Cerebral functional alterations occur immediately after RT. No significant changes in MoCA in patients

(*continued on next page*)

Table 2 (*continued*)

Study (Type of study)	N receiving intervention (radiotherapy)	H &N subsite	Radiotherapy Technique	Comparator group	MRI	Follow-up interval / time to neurocognitive assessment (and imaging if relevant)	Tool to assess cognition	Neurocognitive function (NCF) outcome
cer Hospital Beijing (prospective)								before and after RT compared to healthy controls.
Lv et al, 2019 [33] Sun Yat-sen University Cancer Center, China (prospective)	58	NPC	IMRT (91.4%) Tomotherapy (8.6%)	20 comparable normal controls	MRI evidence of volume reduction in the hippocampal and subfield region	Longitudinally followed up; prior to RT, 3 and 6 months after RT	MoCA	High volume losses in the hippocampus and subfields (specific regions in cerebellum) significantly associated with a rapid decline in neurocognitive function. Left hippocampus: Pearson's correlation coefficient for volume loss and MoCA score (r) = 0.01, p = 0.017, Right hippocampus: r = 0.013, p = 0.002, Hippocampal Left Subfield r = 0.061p = 0.018, L Granular Cell Layer r = 0.102p = 0.011, R Granular Cell layer r = 0.158p = 0.022, Right Molecular layer r = 0.285p = 0.002
Qui et al, 2021 [30] Guangzhou Medical University (prospective)	146	NPC	Unreported	19 comparable normal control	Longitudinal changes in white matter on MRI	1 year Imaging and neurocognitive assessment at 4 time points; Pre-RT and follow-up scans within 1–3 months, 6 months and 9–12 months after RT.	MoCA	RT-associated progressive diffusion reduction in the left CAB correlated with longitudinal atrophy of the ipsilateral hippocampus (β coefficient = 1.15, P = 0.033) and progressive cognitive impairment in NPC patients post-RT (β coefficient 5.49, p = 0.048).
Lin et al, 2021 [35] Guangzhou Medical University (prospective)	120	NPC	IMRT (91.7%) Tomotherapy (8.3%)	20 normal controls	MRI evidence of white matter volume alterations	12 months Followed up at 4 time points, baseline (pre-RT), within 3 months post-RT, 6 months post-RT and 9–12 months post-RT	MoCA	Selective and time-dependent white matter atrophy of the right inferior temporal gyrus correlated with cognitive decline over time (r = 0.53, p < 0.001).
Fu et al, 2022[37] Sun Yat-sen University Cancer Center (prospective)	36	NPC	IMRT (91.7%) Tomotherapy (8.3%)	15 age, gender and education matched normal controls	Longitudinal changes of brain network seen after RT	12 months Followed up at baseline, within 3 months and 12 months post RT	MoCA	Altered nodal efficiency seen in bilateral frontal, temporal lobes and the right insula displayed a "decrease-increase/recovery" pattern over time. Relationship between network measures and MoCA scores was not established No within subject or between subject group significant differences in MoCA scores

Nasopharyngeal Cancer (NPC), Wechsler Adult Intelligence Scale -third edition (WAIS-III), Montreal Cognitive Assessment (MoCA), Temporal Lobe Necrosis (TLN), Mini Mental State Exam (MMSE), Neurocognitive function (NCF), Wechsler Adult Intelligence Scale -Revised (WAIS-R), Cerebral Micro Bleeds (CMB), Wechsler Adult Intelligence Scale (WAIS-III), Cingulate Angular Bundle (CAB), Radiotherapy (RT), Intensity modulated radiotherapy (IMRT), 3D conformal planning (3-DP). p value documented where reported.

Table 3
Studies using non-irradiated comparators (including within patient comparisons), irradiated patients at different time points and cut-off scores (n = 9).

Study (Type of study)	N = receiving intervention (radiotherapy)	H &N subsite	Radiotherapy technique	Comparator group	MRI	Follow-up interval / time to neurocognitive assessment (and imaging if relevant)	Tool to assess cognition	Neurocognitive function (NCF) outcome
Hsia et al, 2010 [38] Kaohsiung Hospital, Taiwan (prospective)	30	NPC	IMRT	Pre-treatment baseline NCF (i.e., within patient comparison)	No temporal lobe necrosis on follow-up CT or MRI	Mean 18 months (range 12–26 months) Neurocognitive tests at 1 day before RT and at least 12 months after RT	CASI (combination of MMSE & Hasegawa Dementia rating scale)	23/30 (76.7%) had significantly lower post-RT NCF scores compared with pre-RT NCF scores (difference in mean score on CASI 85.93 ± 8.02 vs 88.9 ± 8.19 5, p = 0.033)
Tang et al, 2012 [31] Memorial Hospital and Cancer Center Sun Yat-sen, China (retrospective)	46	46 NPC patients with MRI evidence of radiation injury	3-DP	46 Irradiated NPC patients without radiation injury on imaging	Cohort of 46 with MRI evidence of radiation injury and 46 without imaging evidence of radiation injury	Median 6 years (range 1–19 years)	MoCA	Radiation injury was significantly associated with cognitive impairment (MoCA score < 26). Score in MoCA of patients with radiation injury was significantly lower than that of patients without radiation injury (mean score and SD 21.32 ± 2.45vs. 25.98 ± 1.73, p < 0.001) Chemotherapy was a risk factor for cognitive dysfunction. Cognitive impairment was a significant predictor of worse global QOL (β-coefficient = 1.575, p = 0.047)
Mo et al, 2014 [43] Cancer Hospital Guangxi, China (prospective)	51	NPC	IMRT	Pre-treatment baseline NCF (i.e., within patient comparison)	MRI pre and post RT, findings unreported	1-week post-RT; compared to baseline testing	Das–Naglieri cognitive assessment system	Cognitive assessment pre-RT similar to immediate post-RT results. No acute cognitive deficits seen.
Wu et al, 2014 [32] First Affiliated Hospital Sun Yat-Sen and Cancer Center Guangzhou China (retrospective)	80	NPC	IMRT	36 newly diagnosed (non-irradiated) NPC patients.	Cerebral Necrosis (CRN) on MRI in 40 patients, no CRN in 40 patients	No– CRN cohort 3.8 ± 2.6yrs CRN cohort 4.3 ± 2.9yrs	MMSE MoCA (Beijing version) ADL	CRN patients generally manifest cognitive and psychological impairment compared to patients without CRN and pre radiotherapy Thirty (75%) of the RT + CRN patients were deemed cognitively impaired by the MoCA compared with 9 (22.5%) by the MMSE (χ 2 = 22.064; p < 0.001)
Ma et al, 2017[34] Guangzhou University Hospital (retrospective)	59	NPC	IMRT	24 NPC patients pre-RT matched for age, gender, education, and clinical stage	Functional MRI	Range 6–87 months	MoCA	Altered cerebellar–cerebral functional connectivity was observed in irradiated patients, and two connections significantly correlated to MoCA score, functional connectivity between the right cerebellar lobule VIIb and right fusiform gyrus (r= − 0.34, p = 0.008), and between the left cerebellar lobule VIII and right crus I (r = − 0.30, p = 0.021).
Qui et al, 2018 [29] Sun Yat-sen University Cancer Center (prospective)	39	NPC	IMRT	Pre-treatment baseline NCF (i.e., within patient comparison)	Longitudinal structural and functional MRI changes	3 months MoCA and functional imaging at baseline (pre-RT) and 3 months after RT	MoCA	Intra-network and the inter-network functional connectivity significantly reduced 3 months post-RT in NPC patients. General cognitive function significantly declined post-RT (means score difference on MoCA 24 [at 3 months post RT] vs 25.2[pre-RT], p < 0.05)
Kiang et al, 2016 [42] University of California (retrospective)	44	NPC	IMRT	4 cohorts based on the duration since the end of radiotherapy. (<2.5 years, >2.5–6 years, 6–10 years and > 10 years post-radiotherapy)	Unreported	Median 5 years (range 5 months-16 years)	FACT-Cog	All QoL measures were low during the initial recovery period (≤2.5 years) and were significantly higher by 6 years post-IMRT. At > 10 years post-IMRT, lower scores were observed in NPC-specific and cognitive QoL domains.

(*continued on next page*)

Table 3 (*continued*)

Study (Type of study)	N = receiving intervention (radiotherapy)	H &N subsite	Radiotherapy technique	Comparator group	MRI	Follow-up interval / time to neurocognitive assessment (and imaging if relevant)	Tool to assess cognition	Neurocognitive function (NCF) outcome
Liu et al, 2020 [39] Fudan University Shanghai Cancer Center, China (prospective)	86	NPC	IMRT	Longitudinal monitoring of cognition and size of necrotic mass every 3 months (i.e., within patient comparison)	Entire cohort had MRI evidence of temporal lobe necrosis	32 months (26–50 months) Once necrosis diagnosed neurocognition and size of the necrotic evaluated every 3 months	MMSE	26 patients with temporal lobe necrosis (30%) demonstrated obvious cognitive impairment (MMSE scores $\leq$ 26) over time.
McDowell et al, 2019 [26] Princess Margaret, Toronto (retrospective)	102	NPC	IMRT	Comparing objective and subjective assessments post-RT	TLN was identified in 22 patients (22%).	Median follow-up of 7.5 years	MoCA Self-reported memory MDASI-HN	Impaired MoCA scores (cut-off < 23, mean 23.7, SD 3.4,) observed in 32%. Moderate to high rates of neurocognitive impairment on patient and family assessment Clinically significant impairment in executive function Lower QoL correlated with higher neurobehavioral symptoms (total, r = − 0.62, p < 0.001; apathy, r = − 0.65, p < 0.001; disinhibition, r =- 0.51, p < 0.001; executive dysfunction, r =- 0.51, p < 0.001).

Montreal Cognitive Assessment (MoCA), Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog), Nasopharyngeal Cancer (NPC), Radiotherapy (RT), Intensity Modulated Radiotherapy (IMRT), Quality of life (QoL), MD Anderson Symptom Inventory for head and neck cancer (MDASI-HN), Mini Mental State Exam (MMSE), Cognitive Abilities Screening Instrument (CASI), Neurocognitive Function (NCF,) Activities of Daily Living (ADL Temporal

neurocognitive impairment, necrotic masses larger than 3.5 cm in maximum diameter were observed on MRI[39].

Neurocognitive deficits have also been observed in morphologically normal appearing brains of NPC patients after RT. Ren et al [27] used the amplitude of the low-frequency fluctuations (ALFF) in blood oxygen level-dependent signal and functional connectivity (FC) to characterise cerebral functional changes. Statistically significant reductions were observed in ALFF (p < 0.05) and FC (P < 0.001) in multiple cerebellar–cerebral regions[27]. This was not associated with significant changes in the MoCA as expected, perhaps given the very short interval of 24 hours between RT and imaging. Functional neuroimaging data also showed altered nodal efficiency distributed in the bilateral frontal and temporal lobes as well as the right insular region[37].

In one study, altered cerebellar–cerebral functional connectivity significantly correlated to attention scores on the MoCA (functional connectivity between the left cerebellar lobule VIII and right cerebellar crus I and MoCA r = − 0.32, p = 0.001), left cerebellar lobule VIII and right medial frontal gyrus and MoCA r = − 0.27, p = 0.040), and the right cerebellar lobule VIIb and right fusiform and MoCA r = − 0.41, p = 0.002))[34].

Guo et al[36] focused on areas of the brain that showed significant radiation-induced changes over time after RT (IMRT delivering a dose of 68–70 Gy in 30–33 fractions at 2.12–2.33 Gy/fraction) and the MoCA, and found changes in bilateral temporal lobe volume after RT correlated with mean irradiation dose to the corresponding temporal lobe (left temporal β coefficient = − 4.75, p = 0.0064 and right temporal lobe β coefficient = -8.13, p=<0.001)... Lv et al[33] also highlighted significant negative correlations between volume changes of the left hippocampus and the mean dose to the left hippocampus (β coefficient= − 0.112, p = 0.021) in a cohort treated mainly with IMRT, with elevated volume losses associated with neurocognitive decline as evaluated by the MoCA (left hippocampus: β coefficient = 0.01, p = 0.017, right hippocampus: β coefficient = 0.013, p = 0.002). Following IMRT, McDowell et al[26] using Frontal Systems Behaviour Scale (FrSBe) tool reported greater declines in apathy (β coefficient = 0.236, p = 0.027), and executive dysfunction (r = 0.267, p = 0.007) corelated with combined dose to both temporal lobes (V75Gy).

Survivors of HNC are at risk of detriment in QoL, even if treated with highly conformal techniques such as IMRT. Kiang et al[42] analysed neurocognitive QoL in patients treated for NPC (n = 44) at different time points (<2.5 years, >2.5–6 years, 6–10 years and > 10 years post-RT), using the FACT-Cog questionnaire which allocated summary scores (out of 132) based on perceived cognitive abilities, perceived cognitive impairments, impact on quality of life, and comments from others[42]. FACT-Cog mean scores were low (with a lower number corresponding to worse overall QoL) during the initial recovery period $\leq$ 2.5 years (88.1 ± 22.9) and at > 10 years post-RT (88.9 ± 22.9) with statistical difference reported (p = 0.02 on post hoc Newman-Keuls pairwise comparisons). There were also significant differences in mean scores at the different time points in the subscales of perceived cognitive abilities (15.8 ± 5.3 (<2.5 years) vs 23.0 ± 4.9 (>2.5–6 years) vs 20.8 ± 6.2 (6-10yrs) vs 18.2 ± 3. (>10yrs), p = 0.01) and perceived cognitive impairments (50.8 ± 14.1 (<2.5 years) vs 62.3 ± 10.0 (<2.5–6 years) vs 56.7 ± 10.4 (6–10 years) vs 47.8 ± 15.8 (>10 years) respectively, p = 0.04) [42].

In a cohort of NPC patients (n = 46) with median follow up of 6 years, Tang et al[31], demonstrated patients with radiation injury had significantly impaired cognition using the MoCA compared to control (mean score and SD in group with radiation injury: 21.32 ± 2.45 vs control group: 25.98 ± 1.73; p < 0.001). Exhibiting negative emotions with the MoCA score was a significant predictor of QoL measured on regression analysis (β coefficient = 21.050, p=<0.001).There was a significant difference between patient and

control groups in QoL score (using the World Health Organization Quality of Life Brief Version (WHOQOL-BREF) a 26-item instrument with higher scores reflecting better QOL) in domains of physical health (16.50 ± 11.05 (patient) vs. 35.02 ± 10.43 (control), p < 0.001), psychological health (17.70 ± 10.33 vs 39.48 ± 12.00), and social relationship (48.00 ± 18.65 and 67.15 ± 19.70, p = 0.001)[31]. In contrast, McDowell et al [26] in an NPC cohort (n = 102) reported that poor performance on the MoCA (cut off score < 23 indicating impairment; mean 23.7 ± 3.4; 32% in the impaired range) was associated with a non-significant trend in reporting lower QoL (FACT-H&N, linear regression estimate 0.02, 95% CI:0–0.05, p = 0.072) and lower QoL was instead found to be strongly correlated with higher neurobehavioral symptoms (total, r = -0.62, p < 0.001; apathy, r = -0.65, p < 0.001; disinhibition, r = -0.51, p < 0.001; executive dysfunction, r = -0.51, p < 0.001)[26].

Discussion

In the current systematic review, we aimed to evaluate neurocognitive outcomes of HNC survivors treated with (chemo)RT.

There is a limited number of studies exploring neurocognitive outcomes in HNC and considerable heterogeneity exists amongst included studies in terms of RT technique and timing and methods of neurocognitive assessment. However, many of the studies (n = 15) demonstrate inferior neurocognitive outcomes in irradiated HNC patients compared to controls. The vast majority of studies focused on neurocognitive outcomes in patients with NPC. Due to anatomical location of NPC and the increased extent of skull base irradiation required, NPC patients can be considered a high risk group amongst HNC patients for neurocognitive toxicity, with proximity of tumours in this region to crucial brain components such as the temporal lobes, brainstem and the hippocampi [17,38,42]. This could either be due to higher doses adjacent to target structures (or in more distant brain tissue with non-IMRT delivery techniques) or due to the lower dose 'bath' to inferior areas of brain tissue with IMRT. However, the impact of irradiation of the posterior fossa, which commonly receives lower doses of radiation is also potentially important[46]. In the single study with a mixed cohort of non-NPC HNC patients, of which 76% of patients had oropharyngeal cancers, impaired neurocognitive function was reported from 6 months compared to control[25]. Similar results have also been observed in other series (not meeting inclusion criteria of this review) that include non-NPC patients [47–50].

Pre-clinical and clinical evidence support several possible mechanisms behind radiation related neurocognitive decline. These complex mechanisms include (i) reduced neurogenesis in the hippocampus and altered neural stem cell differentiation, (ii) chronic inflammation/abnormal relationship between neural stem cells and microvasculature; (iii) altered neuron morphology leading to impaired synaptic function; and (iii) vascular insufficiency with ischemia-induced excitotoxicity, as observed in vascular dementia[51–55]. The pathophysiological reaction of normal brain tissue to irradiation has been classified according to symptom onset into; acute (a few days to a few weeks), early delayed/subacute (1–6 months) and a late delayed reaction period (more than 6 months to a few years) after RT[37,56]. Much of the evidence suggests the risk of neurocognitive dysfunction is a late effect occurring at 12 months or more after irradiation.

The most reported affected neurocognitive domain in the studies included in this review was memory, especially episodic memory (memory of everyday events that can be explicitly conjured). This is in keeping with findings from the earliest study exploring neurocognitive outcomes in HNC by Lee et al, which reported impaired retrieval from long term memory and non-verbal recall [57].The critical regions in the developed brain for neurogenesis are thought to be the sub granular zone (SGZ) of the hippocampus and the subventricular zone (SVZ) of the lateral ventricles[58]. Memory impairment is therefore thought likely to be mediated by damage to the hippocampus following RT [59,60]. The impact on language is less certain, but the deficits in verbal intelligence reported in one of the studies included here was ascribed to impaired semantic memory [40]. Semantic memory is memory necessary for the use of language and, like episodic memory, semantic memory also depends critically on the hippocampus [61]. In a small study that investigated brain region-specific delivered dose and impairment in specific neurocognitive domains, the cerebellar lobes of the brain were identified as likely to receive clinically significant radiation doses in HNC[62]. One study, included in this review, indicated that post-RT cerebral microbleeds might underlie neurocognitive deficits, and these occurred most frequently in the temporal lobes, followed closely by the cerebellum[28]. The posterior lobe of the cerebellum is vital to cognition with lesions in this area leading to deficits in executive function, visual spatial processing, linguistic skills, and regulation of affect[63,64]. The domains of attention and processing speed have also been shown to be impacted in post-RT HNC patients [25,32] and impaired connectivity between the cerebellar vermis and hippocampus has been found to be significantly correlated with attention score, assessed using the MoCA[65]. In a study in patients with sinonasal cancers, a positive correlation was found between executive dysfunction (measured on Stroop Colour Word test) and higher doses to the left hippocampus and left temporal lobe (r = 0.7; p=<0.01)[49]. Despite these observations, during HNC RT planning, the hippocampus and cerebellum are not routinely outlined or regarded as organs at risk [66].

While specific brain sub-structures were highlighted as potentially important in this review in terms of neuro-cognition, no specific dose-volume thresholds were generated. Gondi et al[67] demonstrated a dose–response relationship between the hippocampus and cognition, reporting D40% of the bilateral hippocampi greater than 7.3 Gy to be associated with long-term neurocognitive impairment(in patients irradiated for benign or low-grade adult brain tumours).The evidence supporting a specific safe dose threshold to the majority of CNS sub-structures relevant for radiation induced neurocognitive toxicity is limited and there is need for future development of NTCP models. The ROC-oN study (REC reference: 22/WM/0207, IRAS project ID: 315880), a cross sectional study evaluating quality of life and neurocognitive impairment following radiotherapy in patients with oropharyngeal cancer includes an exploratory analysis of dose to base of brain structures on neurocognitive function and is relatively unique given its focus on head and neck cancer (as opposed to brain tumour) patients.

The effect of radiation on the brain likely involves morphologic and functional aspects and so neuroimaging could help identify treatment-associated brain changes underling neurocognitive impairment following RT. Radiation-induced temporal lobe necrosis in NPC, which was more common prior to the routine use of IMRT[68], was found to be associated with impaired memory and learning, especially when the area of necrosis was greater than 3.5 cm in maximum diameter[17,39]. However ventricular dilatation, volume loss and microbleeds identified on MRI, have also been identified as independent predictors of impaired cognition [28]. More recently, functional MRI (fMRI) has been used to explore brain functional connectivity. One study detected significantly altered connections between the left cerebellar lobule VIII and right medial frontal gyrus, the left cerebellar lobule VIII, and right crus I, and the right cerebellar lobule VIIb and right fusiform gyrus [34]. In another, reduction in functional connectivity was demonstrated in multiple cerebellar–cerebral regions: cerebellum, para hippocampus, hippocampus, fusiform gyrus, inferior frontal gyrus,

inferior occipital gyrus, precuneus, and cingulate cortex[27]. This altered functional connectivity might account for attention dysfunction, memory impairment, and executive deficits[27,34]. These studies could help to explain the neurocognitive deficits that may be observed in patients with morphologically normal-appearing brains.

Several studies have explored the relationship between neurocognitive impairment and QOL in patients with primary and secondary brain tumours[69–72] However little work has been performed in this area in HNC patients. Although Lv et al[33] identified that atrophy in the hippocampus and cerebellar subfields on MRI correlated with decline in neurocognitive function, in one small study, reduction in hippocampal volume was not found to be related to lower QoL[73]. No correlation was found between neurocognitive decline and QoL by McDowell et al[26] in patients with NPC or by Sharma et al in patients with sinonasal cancers[49]. In contrast, Tang et al[31] and Kiang et al [42] concluded that impaired neurocognitive function was associated with lower QoL scores. It is pertinent to consider that moderate-severe neurocognitive decline might not be always reflected in deterioration of general QoL and even the presence of mild neurocognitive decline might significantly impact on QoL. The impact of neurocognition on QoL is influenced by timing of assessment (in relation to treatment) and patient expectations[74].

The present systematic review identified significant variation in assessment of neurocognition. The MoCA was the most frequently used assessment tool but was also used in different ways, including the use of a cut-off of 26 to indicate mild neurocognitive impairment or by comparing scores across groups.However the MoCA, is a brief cognitive screening tool which is generally not considered to be highly sensitive[75]. Similarly, the MMSE screening tool used in some studies is not efficacious in detecting subtle neurocognitive decline[76]. The International Cognition and Cancer Task Force (ICCTF) founded is focused on understanding cancer-therapy related neurocognitive dysfunction[77]. The ICCTF recommend an objective test-battery that measures several domains and that includes the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and the Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination[78]. Future prospective studies should strive to assess neurocognition using such an objective test battery.

This systematic review has specific limitations and heterogeneity of studies and methodologies precludes meta-analysis of results. Although the analysis points towards neurocognitive impairment as a late toxicity, since the literature is almost exclusively based on NPC, it is uncertain if this applies to non-NPC, although the one prospective non-NOC HNC study suggests this may be the case[25] The cause of neurocognitive impairment is also unclear: effect of chemotherapy, nutritional changes as a sequel of head and neck treatment and age etc could all impact. The impact of chemotherapy on neurocognitive outcomes was evaluated in only two of the included studies with conflicting results. Tang et al[31] reported chemotherapy as a risk factor for neurocognitive dysfunction while Zer et al found[25] neurocognition to be unaffected by chemotherapy on exploratory analysis. The impact of chemotherapy on neurocognition in this population should form an area for further work.

In addition, with regards to the impact of RT, there is uncertainty if neurocognitive impairment is attributable to the high dose to adjacent brain or low dose bath. Furthermore, older conformal RT techniques produced different dose distribution to IMRT, and it was not possible to ascertain the impact of each technique in this analysis. In addition, there is limited information on the clinical significance of reported results within studies. Finally, due to inclusion criteria, some studies with important findings could also have been excluded: studies published after the last search date were not included.

Nevertheless, the present systematic review provides an extensive review of the literature and identifies neurocognitive impairment following HNC RT as a problem. Specific domains of cognition appear to be particularly impacted and highlights regions of interest in the brain, which could be future targets for radiation sparing strategies. In addition, this review demonstrates the value of MRI as a non-invasive tool, which can detect microstructural and functional changes that may be indicative of neurocognitive changes. It also identifies the need for appropriately sensitive neurocognitive testing to be included within prospective studies and the need to consider the impact of RT in non-NPC HNC patients. Neurocognition was assessed in most studies using the MoCA which might be insufficient in this cohort. Minimal work has been done in evaluating the contribution of minimal or moderate radiation dose to specific regions of the brain on long-term neurocognitive effects.

High quality large prospective studies that use standardised, sensitive, and reliable neurocognitive tests in different HNC subsites are clearly needed. Also, a deeper understanding of radiation dose-volume effects, correlating incidence, and severity of neurocognitive impairment to specific volumes of normal brain irradiated is crucial in guiding future RT treatment planning and dose sparing protocols.

Funding

ZIE is a Clinical Research Fellow supported by a Cancer Research UK Award (Leeds-Manchester Stella Erdheim Clinical PhD Fellowship – Grant Reference Number 95653122/95653121).

LM is an Associate Professor funded by Yorkshire Cancer Research (award number L389LM).

FB is an Associate Professor supported by Yorkshire Cancer Research (L389FB).

The authors would also like to acknowledge Cancer Research UK funding for the Leeds Radiotherapy Research Centre of Excellence (RadNet; C19942/A28832).

CRediT authorship contribution statement

Zsuzsanna Iyizoba-Ebozue: Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Robin Prestwich:** Conceptualization, Methodology. **Sarah Brown:** Methodology. **Emma Hall:** Methodology. **John Liley:** Methodology. **Matt Lowe:** Methodology. **David Thomson:** Methodology. **Finbar Slevin:** Methodology, Formal analysis. **Florien Boele:** Conceptualization, Methodology, Formal analysis, Supervision. **Louise Murray:** Conceptualization, Methodology, Formal analysis, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109863.

References

[1] Rosenberg AA-O, Vokes EE. Optimizing Treatment De-Escalation in Head and Neck Cancer: Current and Future Perspectives.

[2] Cramer JD, Burtness B, Le QT, Ferris RL. The changing therapeutic landscape of head and neck cancer. Nat Rev Clin Oncol 2019;16:669–83.
[3] Høxbroe Michaelsen S, Grønhøj C, Høxbroe Michaelsen J, Friborg J, von Buchwald C. Quality of life in survivors of oropharyngeal cancer: A systematic review and meta-analysis of 1366 patients. Eur J Cancer 2017;78:91–102.
[4] Al-Mamgani A, van Rooij P, Verduijn GM, Mehilal R, Kerrebijn JD, Levendag PC. The impact of treatment modality and radiation technique on outcomes and toxicity of patients with locally advanced oropharyngeal cancer. Laryngoscope 2013;123:386–93.
[5] Nguyen-Tan PF, Zhang Q, Ang KK, Weber RS, Rosenthal DI, Soulieres D, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. J Clin Oncol 2014;32:3858–66.
[6] Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.
[7] Pruijssen JT, Wenmakers A, Kessels RPC, Piai V, Meijer FJA, Pegge SAH, et al. Long-term cognitive, psychosocial, and neurovascular complications of unilateral head and neck irradiation in young to middle-aged adults. BMC Cancer 2022;22:244.
[8] Mirghani H, Blanchard P. Treatment de-escalation for HPV-driven oropharyngeal cancer: Where do we stand? Clin Transl Radiat Oncol 2018;8:4–11.
[9] Mehanna H, Rischin D, Wong SJ, Gregoire V, Ferris R, Waldron J, et al. De-escalation after DE-ESCALATE and RTOG 1016: A head and neck cancer InterGroup framework for future de-escalation studies. J Clin Oncol 2020;38:2552–7.
[10] McDonald AM, Murdaugh DL, Milner D, Cardan RA, Bhatia S. Brain dosimetry from locally advanced head and neck cancer radiotherapy: implications for neurocognitive outcomes research. Acta Oncol (Stockholm, Sweden) 2018;57:1589–92.
[11] Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: A review. Front Oncol 2012;2:73.
[12] Cramer CK, McKee N, Case LD, Chan MD, Cummings TL, Lesser GJ, et al. Mild cognitive impairment in long-term brain tumor survivors following brain irradiation. J Neurooncol 2019;141:235–44.
[13] Lawrie TA, Gillespie D, Dowswell T, Evans J, Erridge S, Vale L, et al. Long-term neurocognitive and other side effects of radiotherapy, with or without chemotherapy, for glioma. Cochrane Database Syst Rev 2019;8:CD013047.
[14] Janelsins MC, Heckler CE, Peppone LJ, Kamen C, Mustian KM, Mohile SG, et al. Cognitive complaints in survivors of breast cancer after chemotherapy compared with age-matched controls: An analysis from a nationwide, multicenter, prospective longitudinal study. J Clin Oncol 2017;35:506–14.
[15] Boele FW, Zant M, Heine ECE, Aaronson NK, Taphoorn MJB, Reijneveld JC, et al. The association between cognitive functioning and health-related quality of life in low-grade glioma patients. Neuro-Oncol Pract 2014;1:40–6.
[16] Giovagnoli AR, Boiardi A. Cognitive impairment and quality of life in long-term survivors of malignant brain tumors. Ital J Neurol Sci 1994;15:481–8.
[17] Cheung M, Chan AS, Law SC, Chan JH, Tse VK. Cognitive function of patients with nasopharyngeal carcinoma with and without temporal lobe radionecrosis. Arch Neurol 2000;57:1347–52.
[18] Biau J, Lapeyre M, Troussier I, Budach W, Giralt J, Grau C, et al. Selection of lymph node target volumes for definitive head and neck radiation therapy: a 2019 Update.
[19] Dunlop A, Welsh L, McQuaid D, Dean J, Gulliford S, Hansen V, et al. Brain-sparing methods for IMRT of head and neck cancer. PloS one. 2015;10: e0120141-e.
[20] Gulliford SL, Miah AB, Brennan S, McQuaid D, Clark CH, Partridge M, et al. Dosimetric explanations of fatigue in head and neck radiotherapy: an analysis from the PARSPORT Phase III trial. Radiother Oncol : J Eur Soc Therap Radiol Oncol 2012;104:205–12.
[21] Sharma MB, Jensen K, Urbak SF, Funding M, Johansen J, Bechtold D, et al. A multidimensional cohort study of late toxicity after intensity modulated radiotherapy for sinonasal cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2020;151:58-65.
[22] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021;10:89.
[23] Moga C, Guo B, Schopflocher D, Harstall C. Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique. 2012.
[24] Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme Version. 2006;1:b92.
[25] Zer A, Pond GR, Razak ARA, Tirona K, Gan HK, Chen EX, et al. Association of neurocognitive deficits with radiotherapy or chemoradiotherapy for patients with head and neck cancer. JAMA Otolaryngol– Head & Neck Surg 2018;144:71–9.
[26] McDowell LJ, Ringash J, Xu W, Chan B, Lu L, Waldron J, et al. A cross sectional study in cognitive and neurobehavioral impairment in long-term nasopharyngeal cancer survivors treated with intensity-modulated radiotherapy. Radiother Oncol : J Eur Soc Therap Radiol Oncol 2019;131:179–85.
[27] Ren W-T, Li Y-X, Wang K, Gao L, Yi J-L, Huang X-D, et al. Cerebral functional abnormalities in patients with nasopharyngeal carcinoma after radiotherapy: an observational magnetic resonance resting-state study. Chin Med J (Engl) 2019;132:1563–71.
[28] Shen Q, Lin F, Rong X, Yang W, Li Y, Cai Z, et al. Temporal cerebral microbleeds are associated with radiation necrosis and cognitive dysfunction in patients treated for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2016;94:1113–20.
[29] Qiu Y, Guo Z, Han L, Yang Y, Li J, Liu S, et al. Network-level dysconnectivity in patients with nasopharyngeal carcinoma (NPC) early post-radiotherapy: longitudinal resting state fMRI study. Brain Imaging Behav 2018;12:1279–89.
[30] Qiu Y, Guo Z, Lin X, Li J, Li Z, Han L, et al. Standard radiotherapy for patients with nasopharyngeal carcinoma results in progressive tract-specific brain white matter alterations: A one-year follow-up via diffusion tensor imaging. Radiother Oncol : J Eur Soc Therap Radiol Oncol 2021;159:255–64.
[31] Tang Y, Luo D, Rong X, Shi X, Peng Y. Psychological disorders, cognitive dysfunction and quality of life in nasopharyngeal carcinoma patients with radiation-induced brain injury. PLoS One 2012;7:e36529.
[32] Wu X, Gu M, Zhou G, Xu X, Wu M, Huang H. Cognitive and neuropsychiatric impairment in cerebral radionecrosis patients after radiotherapy of nasopharyngeal carcinoma. BMC Neurol 2014;14:10.
[33] Lv X, He H, Yang Y, Han L, Guo Z, Chen H, et al. Radiation-induced hippocampal atrophy in patients with nasopharyngeal carcinoma early after radiotherapy: a longitudinal MR-based hippocampal subfield analysis. Brain Imaging Behav 2019;13:1160–71.
[34] Ma Q, Zeng L-L, Qin J, Luo Z, Su J, Wu D, et al. Radiation-induced cerebellar-cerebral functional connectivity alterations in nasopharyngeal carcinoma patients. Neuroreport 2017;28:705–11.
[35] Lin X, Tang L, Li M, Wang M, Guo Z, Lv X, et al. Irradiation-related longitudinal white matter atrophy underlies cognitive impairment in patients with nasopharyngeal carcinoma. Brain Imaging Behav 2021;15:2426–35.
[36] Guo Z, Han L, Yang Y, He H, Li J, Chen H, et al. Longitudinal brain structural alterations in patients with nasopharyngeal carcinoma early after radiotherapy. NeuroImage Clin 2018;19:252–9.
[37] Fu G, Xie Y, Pan J, Qiu Y, He H, Li Z, et al. Longitudinal study of irradiation-induced brain functional network alterations in patients with nasopharyngeal carcinoma. Radiother Oncol : J Eur Soc Therap Radiol Oncol 2022;173:277–84.
[38] Hsiao K-Y, Yeh S-A, Chang C-C, Tsai P-C, Wu J-M, Gau J-S. Cognitive function before and after intensity-modulated radiation therapy in patients with nasopharyngeal carcinoma: a prospective study. Int J Radiat Oncol Biol Phys 2010;77:722–6.
[39] Liu P, Niu X, Ou D, Qiu J, Lou P, Xue L, et al. Dynamic changes in cognitive function in patients with radiation-induced temporal lobe necrosis after IMRT for nasopharyngeal cancer. Front Oncol 2020;10:450.
[40] Lam LCW, Leung SF, Chan YL. Progress of memory function after radiation therapy in patients with nasopharyngeal carcinoma. J Neuropsychiatry Clin Neurosci 2003;15:90–7.
[41] Hua M-S, Chen S-T, Tang L-M, Leung W-M. Neuropsychological function in patients with nasopharyngeal carcinoma after radiotherapy. J Clin Exp Neuropsychol 1998;20:684–93.
[42] Kiang A, Weinberg VK, Cheung KHN, Shugard E, Chen J, Quivey JM, et al. Long-term disease-specific and cognitive quality of life after intensity-modulated radiation therapy: a cross-sectional survey of nasopharyngeal carcinoma survivors. Radiat Oncol (London, England) 2016;11:127.
[43] Mo Y-L, Li L, Qin L, Zhu X-D, Qu S, Liang X, et al. Cognitive function, mood, and sleep quality in patients treated with intensity-modulated radiation therapy for nasopharyngeal cancer: a prospective study. Psychooncology 2014;23:1185–91.
[44] Franco P, Numico G, Migliaccio F, Catuzzo P, Cante D, Ceroni P, et al. Head and neck region consolidation radiotherapy and prophylactic cranial irradiation with hippocampal avoidance delivered with helical tomotherapy after induction chemotherapy for non-sinonasal neuroendocrine carcinoma of the upper airways. Radiat Oncol (London, England) 2012;7:21.
[45] Harvey PD. Domains of cognition and their assessment Dialogues Clin Neurosci. 2019;21:227-37.
[46] Merchant TE, Sharma S, Xiong X, Wu S, Conklin H. Effect of cerebellum radiation dosimetry on cognitive outcomes in children with infratentorial ependymoma. Int J Radiat Oncol Biol Phys 2014;90:547–53.
[47] Abdul Razak AR, Siu LL, Chan A, Pond GR, Tirona KM, Chen EX, et al. Neurocognitive function (NCF) in patients (pts) treated with chemo/bio-radiotherapy (C/B-RT) for head and neck cancers (HNC). J Clin Oncol 2011;29:5522 -.
[48] Gan HK, Bernstein LJ, Brown J, Ringash J, Vakilha M, Wang L, et al. Neurocognitive outcomes of head and neck chemoradiotherapy: A pilot study. J Clin Oncol 2009;27:6068.
[49] Sharma MB, Jensen K, Amidi A, Eskildsen SF, Johansen J, Grau C. Late toxicity in the brain after radiotherapy for sinonasal cancer: Neurocognitive functioning, MRI of the brain and quality of life. Clin Transl Radiat Oncol 2020;25:52–60.
[50] Meyers CA, Geara F Fau - Wong PF, Wong Pf Fau - Morrison WH, Morrison WH. Neurocognitive effects of therapeutic irradiation for base of skull tumors.
[51] Wilke C, Grosshans D, Duman J, Brown P, Li J. Radiation-induced cognitive toxicity: pathophysiology and interventions to reduce toxicity in adults. Neuro Oncol 2018;20:597–607.
[52] Lyubimova N, Hopewell J. Experimental evidence to support the hypothesis that damage to vascular endothelium plays the primary role in the development of late radiation-induced CNS injury. Br J Radiol 2004;77:488–92.

[53] Miyatake S-I, Nonoguchi N, Furuse M, Yoritsune E, Miyata T, Kawabata S, et al. Pathophysiology, diagnosis, and treatment of radiation necrosis in the brain. Neurol Med Chir (Tokyo) 2015;55:50–9.
[54] Turnquist C, Harris BT, Harris CC. Radiation-induced brain injury: current concepts and therapeutic strategies targeting neuroinflammation. Neuro-Oncol Adv 2020;2:vdaa057.
[55] Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. Nat Rev Neurol 2017;13:52–64.
[56] Voon NS, Lau FN, Zakaria R, Md Rani SA, Ismail F, Manan HA, et al. MRI-based brain structural changes following radiotherapy of Nasopharyngeal Carcinoma: A systematic review. Cancer/Radiothér 2021;25:62–71.
[57] Lee PW, Hung Bk Fau - Woo EK, Woo Ek Fau - Tai PT, Tai Pt Fau - Choi DT, Choi DT. Effects of radiation therapy on neuropsychological functioning in patients with nasopharyngeal carcinoma.
[58] Gonzalez-Perez O. Neural stem cells in the adult human brain. Biol Biomed Rep 2012;2:59–69.
[59] Bird CM, Burgess N. The hippocampus and memory: insights from spatial processing. Nat Rev Neurosci 2008;9:182–94.
[60] Seibert TM, Karunamuni R, Bartsch H, Kaifi S, Krishnan AP, Dalia Y, et al. Radiation dose-dependent hippocampal atrophy detected with longitudinal volumetric magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2017;97:263–9.
[61] Duff MC, Covington NV, Hilverman C, Cohen NJ. Semantic memory and the hippocampus: Revisiting, reaffirming, and extending the reach of their critical relationship. Front Hum Neurosci 2020;13:471.
[62] McDowell L, Corry J, Ringash J, Rischin D. Quality of life, toxicity and unmet needs in nasopharyngeal cancer survivors. Front Oncol 2020;10:930.
[63] Schmahmann JD. The cerebellum and cognition.
[64] Eekers DBP, in 't Ven L, Deprez S, Jacobi L, Roelofs E, Hoeben A, et al. The posterior cerebellum, a new organ at risk? Clinical and Translational Radiation Oncology. 2018;8:22-6.
[65] Ma Q, Wu D Fau - Zeng L-L, Zeng Ll Fau - Shen H, Shen H Fau - Hu D, Hu D Fau - Qiu S, Qiu S. Radiation-induced functional connectivity alterations in nasopharyngeal carcinoma patients with radiotherapy.
[66] Brouwer CL, Steenbakkers RJHM, Bourhis J, Budach W, Grau C, Grégoire V, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother Oncol 2015;117:83–90.
[67] Gondi V, Hermann BP, Mehta MP, Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int J Radiat Oncol Biol Phys 2012;83:e487–93.
[68] Zhou G-Q, Yu X-L, Chen M, Guo R, Lei Y, Sun Y, et al. Radiation-induced temporal lobe injury for nasopharyngeal carcinoma: a comparison of intensity-modulated radiotherapy and conventional two-dimensional radiotherapy. PLoS One 2013;8:e67488.
[69] Liu R, Page M, Solheim K, Fox S, Chang SM. Quality of life in adults with brain tumors: Current knowledge and future directions. Neuro Oncol 2009;11:330–9.
[70] Steinbach JP, Blaicher H-P, Herrlinger U, Wick W, Nägele T, Meyermann R, et al. Surviving glioblastoma for more than 5 years: The patient's perspective. Neurology 2006;66:239–42.
[71] Gustafsson M, Edvardsson T, Ahlström G. The relationship between function, quality of life and coping in patients with low-grade gliomas. Support Care Cancer 2006;14:1205–12.
[72] Sun A, Bae K, Gore EM, Movsas B, Wong SJ, Meyers CA, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. J Clin Oncol 2011;29:279–86.
[73] Olsson E, Eckerström C, Berg G, Borga M, Ekholm S, Johannsson G, et al. Hippocampal volumes in patients exposed to low-dose radiation to the basal brain. A case–control study in long-term survivors from cancer in the head and neck region. Radiat Oncol 2012;7:202..
[74] Karimi AM, Gairola M, Ahlawat P, Tandon S, Pal M, Sachdeva N, et al. Health-related quality of life assessment for head-and-neck cancer patients during and at 3 months after radiotherapy - A prospective, analytical questionnaire-based study. Natl J Maxillofac Surg 2019;10:134–40.
[75] Ribeiro M, Durand T, Roussel M, Feuvret L, Jacob J, Psimaras D, et al. Sensitivity of the Montreal Cognitive Assessment in screening for cognitive impairment in patients with newly diagnosed high-grade glioma. J Neurooncol 2020;148:335–42.
[76] Pan FF, Huang L, Chen KL, Zhao QH, Guo QH. A comparative study on the validations of three cognitive screening tests in identifying subtle cognitive decline.
[77] Vardy J, Wefel JS, Ahles T, Tannock IF, Schagen SB. Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop. Ann Oncol 2008;19:623–9.
[78] Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol 2011;12:703–8.