European Journal of Plastic Surgery (2026) 49:1
https://doi.org/10.1007/s00238-025-02385-4

REVIEW

Association between deep cervical lymph node dissection and dementia incidence in patients with head and neck cancer: a systematic review

Mahad Omar[1] · Ceyhan Yazicioglu[2] · Stuart Winter[1] · Henk Peter Giele[1]

Received: 13 August 2025 / Accepted: 12 December 2025

Abstract

Background Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by the accumulation of amyloid-β plaques and hyperphosphorylated tau tangles in the central nervous system (CNS). It is the most common form of dementia and presents spectrum of clinical symptoms, including memory loss, increasing confusion, personality changes, and progressive deterioration in language, spatial awareness, abstract reasoning, and but cognitive impairment is the hallmark. The purpose of this systematic review was to: (a) evaluate the current evidence of cognitive impairment in adult patients following head and neck cancer (HNC) surgical management; (b) assess whether an association exists between cognitive decline and surgical treatment in HNC patients; and (c) identify gaps in the literature for future research directions and clinical practice.

Methods We performed a systematic search of the PubMed, Embase, Google Scholar, and Medline databases to identify English-language publications (January 2001 to January 2025) that investigated cognitive impairment in adult patients with head and neck cancer (HNC). Study quality was assessed using the Newcastle–Ottawa Scale (NOS). The search and reporting processes adhered to the PRISMA 2020 guidelines for systematic reviews. Studies evaluating clinical cognitive outcomes in HNC patients using validated cognitive assessment tools were included. The primary outcomes of interest were measurement of cognition and quality of life following HNC treatment.

Results Twenty-three studies met the eligibility criteria, a total of 28,054 patients with HNC. The majority of studies evaluated cognitive impairment as part of quality-of-life outcomes. Three studies specifically reported an increased incidence of dementia following HNC surgery. Two studies assessed postoperative cognitive decline reported an incidence of cognitive deterioration ranging from 7% to 40%. Three studies investigated postoperative quality-of-life scores reported an incidence of severe cognitive dysfunction of 37%. Two large studies identified a significant association between the neck dissection and cognitive decline. One study reported a dementia incidence of 0.7 per 100 patient-years, with a cumulative incidence of 10.34% over 8.6 years (95% CI; $p=0.028$). Bilateral supraomohyoid neck dissection (SOHND) and modified radical neck dissection (MRND**)** demonstrated significant cognitive decline (CI 95%, $p=0.016$).

Conclusions HNC management is known to be associated with reduced quality of life; however, the relationship between neck dissection and cognitive impairment remains under-researched. Further high-quality studies are needed to explore the potential association between deep cervical lymph node dissection **(**dCLND**)** and the development of neurodegenerative conditions, including AD. Investigating cognitive outcomes across different types of neck dissection is essential to identify underlying mechanisms and to clarify whether surgical disruption of cervical lymphatic pathways contributes to postoperative or long-term neurocognitive decline and guide future clinical practice.

Level of Evidence: Not gradable.

Keywords Cervical lymph node clearance · Lymph node dissection · Head and neck cancer · Postoperative cognitive function · Quality of life · Dementia and alzheimer's disease

Extended author information available on the last page of the article

Published online: 05 January 2026

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by the accumulation of amyloid-β plaques and hyperphosphorylated tau tangles in the central nervous system (CNS) [1]. It is the most common form of dementia and presents spectrum of clinical symptoms, including memory loss, increasing confusion, personality changes, and progressive deterioration in language, spatial awareness, abstract reasoning, and but cognitive impairment is the hallmark. These symptoms affect interpersonal relationships, occupational functioning, and independent living, ultimately resulting in a substantial economic burden on affected individuals, their families, and society [1, 2].

Recent discoveries has demonstrated brain parenchyma metabolic pathways of the cerebrospinal fluid (CSF), interstitial fluid (ISF), glymphatic, and meningeal lymphatic vessels (MLVs) drains into peripheral deep cervical lymphatic vasculature [3–7]. The meningeal lymphatic vessels accompany the vasculature of the CNS and exits the base of the skull draining into the cervical lymphatic system [8, 9]. Animal study ligating deep cervical lymphatic vessel demonstrated aggravate AD-like clinical symptoms and increased accumulation of neuropathology in mice [10]. Patients with AD have increased levels of these β-amyloid and tau proteins in the deep cervical lymph nodes [11]. Evidence suggests a role for the obstruction and dysfunction of the brain parenchyma lymphatic metabolic pathways draining into the deep cervical lymphatic system leading to the onset of AD and that manipulation of these pathways for example by lymphovenous bypasses (LVA) may enhance lymphatic drainage and protein clearance thereby improving symptoms of dementia and neurodegenerative diseases [12–14].

If the hypothesis that obstruction of brain parenchymal lymphatic drainage into the deep cervical lymphatic is the underlying the neurodegenerations: dCLND particularly bilaterally should be associated with an increased incidence of dementia. HNC patients would provide a valuable clinical cohort study. Therefore, we conducted a systematic review to examine the existing literature on HNC patients undergone surgical resection and neck dissection, with the aim of determining whether these procedures are associated with an increased incidence of dementia.

Materials and methods

Search strategies

This systematic review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (Registration CRD420250653203**).** The methodology followed the PRISMA 2020 guidelines for systematic reviews [15]. A comprehensive search strategy was developed using predefined keywords and applied across PubMed, Medline, Embase, Web of Science, and Google Scholar, covering publications from January 2001 to January 2025. This timeframe was selected in recognition of the limited studies investigating cognitive impairment following HNC management particularly involving dCLND to ensure all relevant studies were included.

The following search terms, combined with Boolean operators guidelines [16], were applied: ("head and neck cancer" OR "malignant head and neck tumour" OR "larynx" OR "pharynx" OR "oral cavity cancer" OR "sinus" OR "salivary gland tumour" OR "nasal cavity" OR "intraoral cancer" OR "tonsil") AND ("quality of life" OR "QOL" OR "cognitive decline" OR "neurodegenerative impairment" OR "dementia" OR "Alzheimer's disease" OR "neurodegenerative decline")AND ("cervical lymph nodes" OR "cervical lymphadenectomy"). Additional searches were performed using variations of these terms, including "cognitive impairment post head and neck dissection" and related combinations. The reference lists of all included studies were also screened to identify further relevant publications.

Eligibility criteria

Studies were included in this systematic review if they assessed cognitive outcomes in patients with HNC who underwent surgical treatment. Eligible studies were required to report cognitive outcomes using standardised or validated assessment tools, such as the EORTC QLQ-C30, MMSE and MoCA, or to evaluate cognitive function as part of a quality-of-life assessment. Studies published between January 2001 and January 2025 with a defined follow-up period were included.

Exclusion criteria were

Studies were excluded if they: Involved patients with pre-existing neurodegenerative conditions, such as AD; included patients who underwent surgery for non-cancerous head and neck lesions; involved participants younger than 18 years; or did not use validated questionnaires or standardised tools to assess cognitive impairment.

Risk of bias and quality assessments

Two independent researchers assessed the quality of the included studies using the NOS which consists of nine standardised, predefined criteria [17]. The appraisal domains included: [1] clarity of selection methods [2],

representativeness of the study population [3], definition and appropriateness of the control group [4], comparability of groups, and [5] adequacy of exposure or outcome assessment. For each criterion that was clearly fulfilled, one point was awarded. Studies that did not meet a criterion either due to insufficient methodological description or because the criterion was not mentioned were assigned zero points. The final NOS score for each study reflected the sum of fulfilled criteria. 45 articles were assessed using NOS and 23 met the quality criteria. The quality assessment of those met criteria were 2 article selections, control group and exposure scored 8, followed studies ranged 5 to 7, 21 studies scored ≥5 points moderate quality, 7–9 high quality. Studies scored 3 and below were excluded (Table 1).

Literature search results

A total of 45,578 publications were identified through searches of the five databases. After removing 19,730 duplicates, 25,848 records remained for screening. Title and abstract screening yielded 74 potentially relevant studies, of which 23 met inclusion criteria following full-text assessment and were subjected to critical appraisal. Figure 1 presents the PRISMA flow diagram outlining the selection process and the number of publications meeting the inclusion criteria. The findings from the 23 included studies are summarised in Table 2.

Study characteristics

The 23 included studies, published between 2001 and 2024, comprised a combined total of 28,054 participants. These studies were conducted across Europe ($n=12$), North America ($n=7$), and Asia ($n=4$). Study designs included prospective, retrospective, and longitudinal cohort studies ($n=19$), randomised controlled trials ($n=2$), and retrospective observational studies ($n=2$). Sample sizes ranged from 17 to 20,135 participants, with reported ages between 36 and 90 years (mean age>55). Patients received a range of multimodality treatments, including surgical resections, neck dissections, reconstructive free-flap procedures, and combinations of surgery, radiotherapy, and chemotherapy. All included studies assessed cognitive outcomes as part of postoperative quality-of-life evaluations, with follow-up durations of up to 12 months. Additionally, nine studies examined cognitive impairment and quality-of-life outcomes over 5–10 years, while eight studies followed participants for 12 months to 3 years.

Data extraction

One researcher (M.O.) conducted the database searches and performed the initial screening of titles and abstracts. A second researcher (C.Y.) independently reviewed the full-text articles. Any disagreements between the two reviewers were resolved through discussion with a third reviewer (H.G.), who provided consensus. Quality of each included study was assessed using the **(**NOS). Data extraction included: authors, year of publication, study design, sample size and participant demographics, cognitive outcomes, used tools to cognition. Assessments of cognitive impairment with specific domains were evaluated, and all relevant outcomes was extracted from each study (Table 2).

Synthesis

A narrative synthesis approach was used to summarise and interpret the findings of the included studies, with particular on AD cognitive domains: complex attention, executive function, learning and memory, language, perceptual–motor skills, and social cognition. The synthesis process involved identifying studies and evaluating the strength, consistency, and robustness of the evidence. This approach followed established methodological guidance [18].

Results

The systematic literature search identified 19,730 potential publications. After screening titles and abstracts, 40 full-text articles were retrieved for detailed assessment, and 23 studies met the inclusion criteria for the final analysis. The PRISMA flowchart outlining the study selection process is presented in Fig. 1. The quality of evidence across the included studies was evaluated using established appraisal tools, with scoring ranges for retrospective and cross-sectional designs. The findings of this systematic review should be interpreted with caution, and the methodological limitations of the included studies should be taken into account when considering the cognitive outcomes.

A total of 28,054 patients were included across the 23 studies in this systematic review, all of which exclusively examined individuals with HNC cognitive outcome. Two studies (826/28,054; 3.0**%**) specifically investigated the association between cognitive impairment and dCLND. The remaining 21 studies assessed cognitive outcomes as part of broader quality-of-life evaluations following surgical and adjuvant treatments. One study focused explicitly on cognitive outcomes across different types of neck dissection, comparing bilateral, unilateral, and no dissection. Follow-up durations across all studies ranged from 1 to 15 years. Sample sizes varied from 17 to 576 cohort, and publications spanned 2001 to 2025. Baseline patient characteristics are summarised in Table 1. All 21 studies evaluated quality-of-life and neurocognitive outcomes in HNC patients.

Table 1 Patient characteristics

Subsite		*n* = 28,054		
Total pharyngolaryngectomy		1780 (6.34%)		
Nasopharynx		1900 (6.77%)		
Oropharynx		9373 (33.40%)		
Hypopharynx		5730 (20.42%)		
Laryngeal		7130 (25.41%)		
Nasal cavity		1890 (6.73%)		
Scalp		4509(16.07%)		
Unknow		8,845(31.523%)		
Author and year	Study (n)	Assessment tool	Cognitive outcomes	
Karri et al. 2011	17	QLQ-C30 scores	Mean score 83.3	Timing of cognitive
Segna et al. 2018	30	Mental Health Composite Score (MCS)	Mean with SD 44.7 (9.5)	
Momeni et al. 2013	60	EORTC QLQ-C30	Significant P 0.04	
Lahtinen et al. 2018	29	EORTC-C30	Mean score 91.7 (11.2), $P = 0.981$	
Klug et al. 2002	181	(QLQ 30 and QLQ H&N 35)	Mean score 80	
Airoldi et al. 2011	36	RTOG-EORTC	Mean 30.87 SD 12.31, $p < 0.05$	
Nemade et al. 2024	25	EORTC QLQ 30 & HN3	Mean = 80	
Bejenaru et al. 2022	89	EORTC QLQ-30and QLQ-H&N35		Mean 58.3 poor outcome
Chaukar et al. 2009	212	EORTC QLQC-30	Mean 89.8 $P = 0.256$	
Abendstein et al. 2005	357	EORTC QLQ-H&N35	Mean 84, $p = 0.05$ between 1 to 5 year after surgery	
van der Schroe et al. 2006	117	EORTC QLQ-C30	Mean 87, after 5 years	
Schiefke et al. 2008	49	EORTC QLQ-H&N35	Mean 74.3 SD (626.5), $p = 0.192$	
Kovács et al. 2015	135	EORTC QLQ-C30	mean 85.9, SD(19.7), $p = 0.020$	
Rogers, et al. 2008	73	Functional Assessment of Cancer Treatment Cognitive (FACT-Cog)	Bil (mean 22.8, 10.8; $p = 0.006$)	
Hammerlid et al. 2001	357	EORTC QLQ-C30 and QLQ-H&N35	Mean 84, $p = 0.5$	
Regier et al. 2009	48	Montreal Cognitive Assessment (MoCA	40% of patient scored impaired range while only 13% of controls scored in the impaired range. Sample $P < 0.001$	
Hwan et al. 2023	576 HNC vs. 2304 None HNC	MMSE	AD incidence 14.92 in HNC vs. 9.77 in control, CI 95%, $p < 0.001$.	
Chao et al. 2024	234	MMSE	CLND SND, MRND	Demonstrate association between CLND and dementia incidence 0.7 per 100 patient-years, with a cumulative incidence of 10.34% over 8.6 years
Timing of cognitive assessments from the post treatment				
5–10 year *n* = 2,143 (9.45%)				
1–4 year 21,279 (90.90%)				

A number of validated tools were used to assess clinical cognitive function across the included studies. The most commonly used instrument was the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core Module (QLQ-C30), which was employed in 17 studies. Additional objective cognitive assessments included the Montreal Cognitive Assessment (MoCA; $n = 2$) and the Mini-Mental State Examination (MMSE; $n = 1$). One study utilised the Katz-15 Index of Independence, which evaluates Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL), to identify cognitive decline. Three studies relied primarily on self-reported measures of cognitive function, rather than objective clinical assessments.

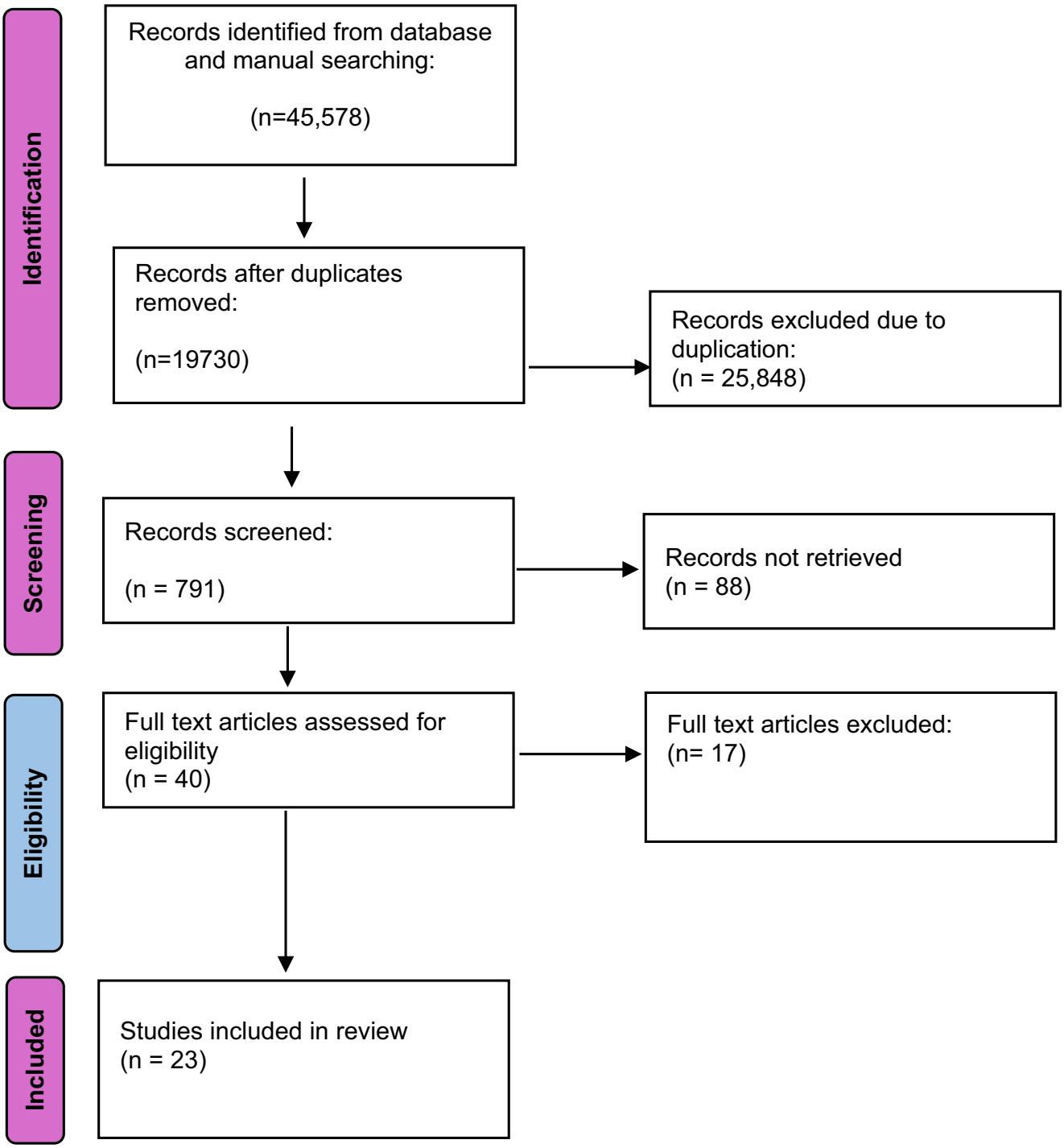

Fig. 1 Flow chart illustrating the search and selection of studies and exclusions articles

Across the included studies, 11 incorporated a controlled group. One multicentre investigation from Swedish and Norwegian compared 340 patients with 352 controls of similar demographic and pathological characteristics who had undergone surgery and irradiation [19].

Regier and colleagues evaluated a study cohort and a control group using the MoCA to quantify cognitive function, demonstrating significantly greater impairment in patients with HNC ($p < 0.001$). Cognitive function was assessed at two follow-up time points: 6 months and 18 months post-treatment [20].

Two studies specifically examined the type of neck dissection as a risk factor for cognitive impairment. Rogers and colleagues analysed differences bilateral, unilateral, and no

Table 2 Illustrating the association between of cognitive impairments and HNC neck dissection

Author	Type of study	*N*	Mean Age	F/U	Measurements	Cognitive Functioning	Treatment
Diagnosis of dementia							
Chao et al., 2024	R case note study 2007–2023	251 HNC compared to population prevalence	60–90 years	(mean) 8.6 years, range 1–15 years	Calculated incidence rate of dementia	9 patients developed dementia at mean 50 months (8.6years) post op range 14–104 months. incident rate 10.34% or 0.7/100 pt years compared to population prevalence of 8%. Bilateral ND greater risk than unilateral or selective ND.	Neck dissection various levels and sides + in some RT
Lee et al., 2023	R	576 HNC compared to 2304 controls	NA	HNC pts from 2003-5 followed up in database until 2013	Dementia Incidence rate reported	Database study comparing HNC cohort vs. case matched controls 4:1 ratio. AD incidence rate 14.92 HNcancer vs. 9.77 non-cancer group ($p<0.001$)	Treatment not specified.
Chen et al., 2015	R	20,135 HNC (8724 had surgery alone, compared to 7118 multimodal therapy vs. 4293 chemoradiotherapy only)	Age > 65	HNC pts from 2002–2010 Followed until 2012	Dementia Incidence rate reported	Surgery vs. surgery and chemo vs. chemo radiotherapy 1.44 vs. 1.04 vs. 1.98 Dementia incidence per 1000 risk but no population controls so can't tell if this is different from normal.	Type of surgery not specifiedNeck dissection /RT/CHEM/Comb
Detailed cognitive assessment							
Regier 2019	case control	88 and 88 (Only 40% of participants had HNC incl oesophageal and gastric)	66 (41–88 years)	At 6 and 18 months	MOCA	Cognitive impairment 48% at 6/12 and 40% at 18/12 compared to 13% controls	Only 40% of participants had HNC/gastric or oesphageal cancer, rest were colorectal cancer.
Bruijnen 2021	R	68	> 70	1 year	MMSE pre-op TICS post-op	No change in cognitive state	Surgery but only 33% had CLND
QOL studies							

Table 2 (continued)

Author	Type of study	*N*	Mean Age	F/U	Measurements	Cognitive Functioning	Treatment
Schiefke et al., 2009	R	49 compared 24 supraomohyoid neck dissection and 25 sentinel node biopsy	63 (32–89)	1–5 years post op (26.8 ± 17.3months)	EORTC QLQ-C30, EORTC QLQ-HN35, HADS, PA-F-KF	Selective ND:74.3(± 26.5) vs. Sentinel ND: 84.7 (± 17.6) no difference in cognitive scores between neck dissection or sentinel node biospsy.	Neck dissection sentinel node versus selective node
Hammerlid et al., 2001	L	232 of which 133 completed the last questionnaire at 3 years	61	3yrs	EORTC QLQ-C30, QLQ-H&N35,HAD	Pre treatment score: 85, 1 year score 83, 3 year score 87 No change in cognitive function from diagnosis or at 1 and 3 years.	39% had surgery but not specified, 90% had radiotherapy
Rogers L et al., 2008	Cs	58	60.4 ± 13.1	18+/-27 months post treatment but 55% less than 12 months	GCF, FACT-COG	significant difference in cognitive decline between no ND vs. bilateral ND $p = 0.006$, and unilateral ND vs. bilateral ND $p = 0.022$, but no difference between no ND and unilateral ND not significant difference between no ND vs. unilateral ND	Neck dissection 47% with 20% bilateral RT 90% Chemo48%
Kovacs 2015	CS	135	61(25–88)	Mean 6 years (1.3–16.6 yrs)	EORTC QLQ C30 compared to EORTC reference control population	Reduced cognitive function score of 81 compared with control 86 but not correlated to treatment types or extent of CLND.	Multi-modal treatment CLND bilateral in 47% unilateral in 37%
Schliephake 2002	P	83 of which 45 completed the 12 month assessment	59 (39-88years)	Pre-op, 12 mths	EORTC QLQ C30	No change in cognitive function pre-op 87 to post op 84.8 at 12 months	All had surgery and CLND of different levels
Van der Schroeff 2006		57 completed the cognitive functioning component	45–70 years	3–6 years	EORTC QLQ C30,	No change in cognitive function between baseline and 3–6 year follow up.	Surgery in 44/57 but number who had CLND is unspecified.

Table 2 (continued)

Author	Type of study	*N*	Mean Age	F/U	Measurements	Cognitive Functioning	Treatment
Abendstein 2005	P	357 (167 at 5 years)	61 (18–86 years)	5 years	EORTC QLQ C30	Baseline score 88 and unchanged at 1 or 5 years No difference between younger or older patients	69/167 had surgery unspecified
Chauker 2009	CS	212	50 (16–80)years	Minimum 1 year, max unknown	EORTC QLQ C30	29 had "poor cognitive functioning" but no difference in treatment modality (surgery 93.9 vs. 83.3 radiotherapy)	Surgery alone in 66, surgery and radiotherapy in 14
Benjenaru 2022	P	89	58	3 years	EORTC QLQ C30	Cognitive functioning improved between admission (score 50) and 3 year follow up (score 100) except for oral cancer patients who had pre-op score of 75 and dropped to 32 post-op.	Unsure exactly but 61 had laryngectomy, 13 oral cancers with floor of mouth and mandibular reconstruction
Nemade 2024	R	25	43 (27–74)	Min 5 years	EORTC QLQ C30	No comparison made with pre-op but cognitive functioning scores said to be 98+/-5 comparable to reference EORTC scores.	All post total glossectomy and bilateral functional neck dissection
Airoldi	R	36	60.5 (31–79)	63 (24–96 months)	EORTC QLQ C30	Cognitive functioning score reported as 30.87 SD12.31 (reference score is 83 so this represents poor cognitive functioning) but the narrative reports this as good scores so there may be an error in the linear transformation in the raw scores.	All oral cancer reconstructed with free radial forearm flap and radiotherapy
Klug 2002	R	67	56 +/- 9.5years	Min 3 years max 11 yrs	EORTC QLQ C30	CF score = 82 SD19	Chemoradiotherapy and surgery including neck dissection and free flap

Table 2 (continued)

Author	Type of study	*N*	Mean Age	F/U	Measurements	Cognitive Functioning	Treatment
Borggreven 2007	P	80 of which 44 completed the 12 months follow up	58 (23–74)	12mths	EORTC QLQ C30	Baseline CF score 85.6, no change to 12 months score at 87.9	Surgery, chemoradiotherapy and flap reconstruction. no data on CLND
Lahtinen 2018	R	53	62.9 +/-9.7	Mean 114 weeks SD50.9, min 12 months	EORTC QLQ C30	Mean CF score of 91 at follow up.	Surgery and free flap reconstruction, 81% had CLND
Momeni 2012	R	21	57.9 (24–87)	24 (18–48 mths)	EORTC QLQ C30	CF score 100 (IQR 83–100), they found those pts who suffered a complication had lower CF scores of 75 (58–100)	Surgery and free flap reconstruction and radiotherapy, no data on CLND
Pierre 2013	R	80	85% less than 70 yrs	5.5 years (1.1–11)	EORTC QLQ C30	CF score 86.3	Surgery and free flap reconstruction and radiotherapy, no data on CLND
Segna 2013	P	30	65.5 (23–87)yrs	12 mths	SF36	No change in MSE component of SF36 between pre- and post-op.	Surgery and free flap and CLND but no data on level or type.
Karri 2011	R	17	49(35–69) yrs	6-72mths	EORTC QLQ C30	CF score 83.3 SD19.5 but interestingly 5.9% (one patient) scored less than 33.3	Pharyngolaryngectomy and radical neck dissection

ACE-III Addenbrooke's, *Chem* Chemotherapy, *CS* cross-sectional, *GCF* global cognitive function, *ND* neck dissection, *P* prospective, *R* Retrospective, *RT* radiotherapy, *SNB* Sentinel lymph node, *SD* dissection, *SU* surgery, *POCD* Postoperative cognitive dysfunction, *non-POCD* No postoperative cognitive dysfunction, *MMSE* Mini-mental state examination, *TICS* telephone interview for cognitive state, *MOCA* Montreal cognitive assessment

neck dissections, reporting that bilateral neck dissection was associated with a statistically significant decline in cognitive function ($p = 0.006$). However, this study did not stratify this finding by specific neck dissection subtypes [21]. study by Choa and colleagues compared subtypes of cervical lymph node dissections, reporting a dementia incidence rate of 0.7 per 100 patient-years and a cumulative incidence of 10.34% over 8.6 years. Deep cervical lymph node dissections were significantly associated with dementia ($p = 0.028$). A higher-risk groups included patients undergone bilateral supraomohyoid neck dissection (SOHND) / modified radical neck dissection (MRND), as well as those who had unilateral MRND plus any neck dissection type on the contralateral side of MRND or SOHND ($p = 0.016$). This study and others also highlighted there are association between the higher incident of dementia and neck dissection zone IV and V [3, 22]. Indicating that this zone may plays critical role in draining brain parenchyma lymphatic pathways into this neck zone [3]. It has been observed that animal studies the lymphatic system mainly directs flow from the CNS to deep cervical lymph nodes zone IV and V [23, 24]. This was further fortified a large controlled group of HNC study cohort demonstrating the incidence of AD was 14.92 in HNC patients and 9.77 in non-cancer patients [25].

In total, 13 prospective studies including one evaluating longitudinal changes of cognitive impairment comparing controlled group of none HNC patients. 9 studies were conducted as retrospective studies and one study as control multi centred trial. There was study reporting no CNS imaging as integral part of cognitive decline diagnosis.

Study by Roger and colleagues converted cognitive score into Mann-Whitney's U-test evaluating association between bilateral neck dissection, unilateral and none neck dissection sub groups. This study found there were significant global cognitive difference function in 3 comparative analyses bilateral neck dissection (mean ranks5 22.8, 10.8; $p = 0.006$) and unilateral and bilateral neck dissection (mean

ranks = 15.5, 8.5; $p = 0.022$). There was no significant difference between none and unilateral neck dissection cognitive outcome [21]. This findings in keeping with similar study which found that the highest risks of dementia incidence were patients with bilateral neck dissections [22].

post-treatment radiotherapy in HNC patients is associated with measurable cognitive impairment, converting test score age adjusted z score (patient deficit define 1.64 SD) demonstrated significant decline of all of domain decline in 6 months compare to control group. Further analysis in 24 months revealed greater decline of global cognitive domain including attention and 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, analysed at 6, 12 and 24 period, respectively [26]. Post radiotherapy in HNC patient demonstrate attention was significantly reduced compare to control healthy group 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, $p = 0.002$) [27].

Discussion

In this systematic review, we aimed to investigated cognitive outcomes in HNC patients post-surgical and adjuvant treatments. There are very few studies investigating cognitive outcomes in HNC surgical resection and considerable heterogeneity exist amongst included research in terms of surgical techniques and timing of cognitive evaluations. However, majority of these studies ($n = 20$) evaluating cognitive outcomes demonstrated worse outcomes compare control groups. The majority of the studies investigated cognitive outcomes as part of quality of life in HNC patient post-surgical treatment. Three studies specifically analysed the affected of neck dissection demonstrating cognitive decline. Emerging evidence suggests that brain parenchymal metabolic waste is cleared through pathways that drain into the deep cervical lymph nodes, and that obstruction of these pathways either due to surgical resection or radiation-induced damage may contribute to the accumulation of β-amyloid and other neurotoxic metabolites [22, 33]. However, cognitive decline is a complex and may also explained including malignant proximity to critical parts of the brainstem, temporal and hippocampi which radiotherapy can affected in this region [28–30]. Chemoradiotherapy can lead to neurotoxicity to the brain tissues that disrupting cognitions. However, study comparing healthy controlled group with none radiated patients with oropharyngeal cancer demonstrated 75% cognitive decline [26]. Similar cognitive outcomes have also demonstrated in other research investigating none irritated HNC studies [31–33].

Preclinical animal studies provide important evidence regarding brain waste-clearance pathways by comparing normal rodents with transgenic or knockout models of AD, which consistently demonstrate accumulation of β-amyloid (Aβ) and hyperphosphorylated tau. Wang and colleagues surgically ligated the deep cervical lymphatic vessels in rodents and compared them with controls group. Behavioural cognitive assessment using the open-field and Y-maze tests showed that mice with dcLN ligation exhibited significant cognitive impairment ($p = 0.0401$). further Immunohistological analysis demonstrated exacerbated Aβ burden and increased phosphorylated tau accumulation within the hippocampus and temporal lobes of ligated animals [10].

Petal and colleagues investigated cerebral lymphatic clearance pathways using radiological imaging and plasma biomarkers to track labelled tau proteins in wild-type and transgenic mice lacking functional CNS lymphatic vessels. This study showed that tau and other neurotoxic waste products drained through the deep cervical lymphatic system, and mice lacking CNS lymphatic function retained substantially greater quantities of tau compared with controls [34].

It has been shown radiotherapy reduces stem-cell differentiation in the hippocampus, leading to chronic neuroinflammation, and microvascular insufficiency, which can result ischemic neurotoxicity [33, 35]. Clinically, cognitive decline can be stratified into: acute, occurring within days to weeks; subacute, occurring up to 6 months; and delayed onset, emerging after 6 months to several years [30, 36].

This systematic review investigated cognitive as part of the HNC neck dissection and explored the relationship in neurocognitions decline. The most reported affected cognitive domain was memory specifically episodic memory. This is in keeping with previously research investigating cognitive outcomes in HNC which reported impaired long term memory recall [37]. Key cerebral regions involved in memory and executive function including the inferior occipital gyrus, precuneus, and cingulate cortex play central roles in neurogenesis and higher-order cognitive processing. Disruption of the dynamic connectivity within these networks may occur following radiation therapy or dCLND [22, 38]. These mechanisms may help explain why some patients exhibit cognitive impairment despite having normal-appearing cerebral parenchyma on conventional imaging.

This systematic review identified significant gap in assessing cognitive outcomes in HNC patients and role of the management as contributor factor as mechanisms that may lead to neurocognitive deficit. The EORTC QLQ-C30 was the most common tool in assessing cognitive decline in this study. The EORTC QLQ-C30 consistent 30 items questionnaire scoring from 0 to 100 including cognitive impairments, emotional wellbeing and overalls of quality-of-life

for cancer patient. This was scored and converted into statistical analysis to demonstrate the association between cognitive decline in HNC patients (Table 1). Several studies used MoCA and MMSE to assess neurocognitive impairments. However, MoCA and MMSE screening tools are generally consider not highly sensitive [39, 40].

More sensitive tools for assessing cognition have been recommended by the International Cognition and Cancer Task Force (ICCTF), which focuses on advancing understanding of cancer therapy–associated neurocognitive dysfunction [40]. The ICCTF endorses an objective, standardised test that evaluates multiple cognitive domains, including the Hopkins Verbal Learning Test Revised (HVLT-R) and the Controlled Oral Word Association (COWA) subtest of the Multilingual Aphasia Examination [41]. Future studies should incorporate these more sensitive, validated instruments to objectively assess cognitive impairment in HNC patients.

There are several limitations to this systematic review, including substantial heterogeneity in study designs, methodologies, and cognitive assessment tools. A limited number of studies specifically investigated the association between dCLND and cognitive impairment. The pathophysiology underlying neurocognitive decline in HNC patients is likely multifactorial, and future research must adequately control for potential confounding factors to determine whether a direct association exists between dCLND and cognitive outcomes. Cognitive impairment in this population may arise from a combination of chemoradiotherapy, surgical interventions, and the extent of neck dissection, making causal attribution challenging.

The adult human brain accounts for approximately 2% of total body weight, yet consumes 20% of the body's oxygen, 25% of glucose, and receives 20–25% of cardiac output [42]. Disruption or dysfunction of the brain's metabolic drainage pathways, including the glymphatic, meningeal lymphatic, and deep cervical lymphatic systems, may contribute to cognitive decline by impairing clearance of metabolic waste products. This area of research warrants further investigation to determine whether alterations in these pathways are associated with postoperative or long-term neurocognitive impairment. Multicentre, high-quality, large-scale prospective studies employing standardised, sensitive, and reliable cognitive assessments are urgently needed.

Future research should also aim to better understand the dynamic interaction between CNS CSF pathways including ISF, glymphatic, MLVs and deep cervical lymphatic systems. Integrating biomarkers, advanced imaging, and rigorous cognitive testing may provide a more comprehensive understanding of mechanisms involving cognitive decline. Moreover, subgroup analyses of different neck dissection types are essential to explore whether specific neck dissection and extensive surgical resection such as total pharyngolaryngectomy are associated with cognitive outcomes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00238-025-02385-4.

Author contributions All authors contributed to the conception and design of the systematic review. Literature search, study selection, data extraction, and quality assessment were conducted by Mahad Omar, Ceyhan Yazicioglu and Henk Giele. Data synthesis and analysis were performed by Mahad Hared Omar, Ceyhan Yazicioglu and Henk Giele . The first draft of the manuscript was written by Mahad Hared Omar, Ceyhan Yazicioglu, and Henk Peter Giele, and all authors critically revised the manuscript for important intellectual content. Mahad Hared Omar, Ceyhan Yazicioglu, Stuart Winter, and Henk Peter Giele read and approved the final manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval (IRB/Committee) Not applicable. No ethical approval was required for this systematic review.

Consent to participate Not applicable. No human participants were enrolled in this systematic review.

Human ethics and consent to participate Not applicable, as no human participants were directly involved.

Clinical trial registration Not applicable.

Competing interests The authors declare no competing interests.

References

1. Takahashi RH, Nagao T, Gouras GK (2017) Plaque formation and the intraneuronal accumulation of β-amyloid in alzheimer's disease. Pathol Int 67(4):185–193
2. Kamatham PT, Shukla R, Khatri DK, Vora LK (2024) Pathogenesis, diagnostics, and therapeutics for alzheimer's disease:

breaking the memory barrier. Ageing Res Rev 101. Elsevier Ireland Ltd
3. Hong JP, Chen WF, Nguyen DH, Xie Q (2025) A proposed role for lymphatic supermicrosurgery in the management of alzheimer's disease: a primer for reconstructive microsurgeons. Arch Plast Surg 52(02):096–103
4. Shetty AK, Zanirati G (2020) The interstitial system of the brain in health and disease. Aging Disease 11(1):200
5. Bacyinski A, Xu M, Wang W, Hu J (2017) The paravascular pathway for brain waste clearance: current understanding, significance and controversy. Front Neuroanat 11:101
6. Bakker EN, Bacskai BJ, Arbel-Ornath M, Aldea R, Bedussi B, Morris AW, Weller RO, Carare RO (2016) Lymphatic clearance of the brain: perivascular, paravascular and significance for neurodegenerative diseases. Cell Mol Neurobiol 36(2):181–194
7. Cserr HF, Harling-Berg CJ, Knopf PM (1992) Drainage of brain extracellular fluid into blood and deep cervical lymph and its immunological significance. Brain Pathol 2(4):269–276
8. Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E et al (2015) Clearance systems in the brain—implications for alzheimer disease. Nat Rev Neurol 11(8):457–470
9. Jaffe RJ, Dave RS, Byrareddy SN (2019) Meningeal lymphatics in aging and alzheimer's disease. Ann Transl Med 7(S1):S2–S2
10. Wang L, Zhang Y, Zhao Y, Marshall C, Wu T, Xiao M (2019) Deep cervical lymph node ligation aggravates AD-like pathology of APP/PS1 mice. Brain Pathol 29(2):176–192
11. Nauen DW, Troncoso JC (2022) Amyloid-beta is present in human lymph nodes and greatly enriched in those of the cervical region. Alzheimer's Dement 18(2):205–210 Guo X,
12. Zhang G, Peng Q, Huang L, Zhang Z, Zhang Z (2023) Emerging roles of meningeal lymphatic vessels in alzheimer's disease. J Alzheimer's Disease 94:355–366
13. Li X, Zhang C, Fang Y, Xin M, Shi J, Zhang Z et al (2024) Promising outcomes 5 weeks after a surgical cervical shunting procedure to unclog cerebral lymphatic systems in a patient with alzheimer's disease, vol 37. BMJ Publishing Group, General Psychiatry
14. Yang G, Yang G, Wang F, Chu Q (2025) Deep cervical lymphovenous bypass for parkinson's disease: a hypothesis. Med Hypotheses 195:111559
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372
16. Lee JH, Kin WY, Kim MH, Lee YJ. On the evaluation of Boolean operators in the extended Boolean retrieval framework. In Proceedings of the 16th annual international ACM SIGIR conference on Research and development in information retrieval 1993 Jul 1. pp 291–297
17. Cook DA, Reed DA (2015) Appraising the quality of medical education research methods: the medical education research study quality instrument and the Newcastle–Ottawa scale-education. Acad Med 90(8):1067–1076
18. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, Britten N, Roen K, Duffy S (2006) Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC. Methods Programme Version 1(1):b92
19. Hammerlid E, Taft C (2001) Health-related quality of life in long-term head and neck cancer survivors: a comparison with general population norms. Br J Cancer 84(2):149–156
20. Regier NG, Naik AD, Mulligan EA, Nasreddine ZS, Driver JA, Sada YHF et al (2019) Cancer-related cognitive impairment and associated factors in a sample of older male oral-digestive cancer survivors. Psychooncology 28(7):1551–1558
21. Rogers LQ, Courneya KS, Robbins KT, Rao K, Malone J, Seiz A et al (2008) Factors associated with fatigue, sleep, and cognitive function among patients with head and neck cancer. Head Neck 30(10):1310–1317
22. Chao S, Kuan C, Huang C, Lin Y, Huang H, Hsieh J et al (2024) Association between cervical lymph node dissection and dementia: a retrospective analysis. J Plast Reconstr Aesthetic Surg 99:584–591
23. Ahn JH, Cho H, Kim JH, Kim SH, Ham JS, Park I, Suh SH, Hong SP, Song JH, Hong YK, Jeong Y (2019) Meningeal lymphatic vessels at the skull base drain cerebrospinal fluid. Nature 572(7767):62–66
24. Ma Q, Ineichen BV, Detmar M, Proulx ST (2017) Outflow of cerebrospinal fluid is predominantly through lymphatic vessels and is reduced in aged mice. Nat Commun 8(1):1434
25. Lee IH, Yu H, Ha SS, Yang HG, Kim DK (2023) Increased risk of alzheimer's disease in patients with head and neck cancer. Cancers 15(23):5516
26. Zer A, Pond GR, Razak AR, Tirona K, Gan HK, Chen EX, O'Sullivan B, Waldron J, Goldstein DP, Weinreb I, Hope AJ (2018) Association of neurocognitive deficits with radiotherapy or chemoradiotherapy for patients with head and neck cancer. JAMA otolaryngology–head Neck Surg 144(1):71–79
27. Wu X, Gu M, Zhou G, Xu X, Wu M, Huang H (2014) Cognitive and neuropsychiatric impairment in cerebral radionecrosis patients after radiotherapy of nasopharyngeal carcinoma. BMC Neurol 14(1):10
28. Cheung MC, Chan AS, Law SC, Chan JH, Tse VK (2000) Cognitive function of patients with nasopharyngeal carcinoma with and without Temporal lobe radionecrosis. Arch Neurol 57(9):1347–1352
29. Hsiao KY, Yeh SA, Chang CC, Tsai PC, Wu JM, Gau JS (2010) Cognitive function before and after intensity-modulated radiation therapy in patients with nasopharyngeal carcinoma: a prospective study. Int J Radiation Oncology* Biology* Phys 77(3):722–726
30. Kiang A, Weinberg VK, Cheung KH, Shugard E, Chen J, Quivey JM, Yom SS (2016) Long-term disease-specific and cognitive quality of life after intensity-modulated radiation therapy: a cross-sectional survey of nasopharyngeal carcinoma survivors. Radiat Oncol 11(1):127
31. Abdul Razak AR, Siu LL, Chan A, Pond GR, Tirona KM, Chen EX, Hope AJ, Ringash J, O'Sullivan B, Waldron JN, Chan K (2011) Neurocognitive function (NCF) in patients (pts) treated with chemo/bio-radiotherapy (C/B-RT) for head and neck cancers (HNC). J Clin Oncol 29(15suppl):5522
32. Gan HK, Bernstein LJ, Brown J, Ringash J, Vakilha M, Wang L, O'Sullivan B, Waldron J, Chen EX, Siu LL (2009) Neurocognitive outcomes of head and neck chemoradiotherapy: A pilot study. J Clin Oncol 27(15suppl):6068
33. Wilke C, Grosshans D, Duman J, Brown P, Li J (2018) Radiation-induced cognitive toxicity: pathophysiology and interventions to reduce toxicity in adults. Neurooncology 20(5):597–607
34. Patel TK, Habimana-Griffin L, Gao X, Xu B, Achilefu S, Alitalo K, McKee CA, Sheehan PW, Musiek ES, Xiong C, Coble D (2019) Dural lymphatics regulate clearance of extracellular Tau from the CNS. Mol Neurodegeneration 14(1):11
35. Meyers CA, Geara F, Wong PF, Morrison WH (2000) Neurocognitive effects of therapeutic irradiation for base of skull tumors. Int J Radiation Oncology* Biology* Phys 46(1):51–55
36. Fu G, Xie Y, Pan J, Qiu Y, He H, Li Z, Li J, Feng Y, Lv X (2022) Longitudinal study of irradiation-induced brain functional network alterations in patients with nasopharyngeal carcinoma. Radiother Oncol 173:277–284
37. Lee PW, Hung BK, Woo EK, Tai PT, Choi DT (1989) Effects of radiation therapy on neuropsychological functioning in patients with nasopharyngeal carcinoma. J Neurol Neurosurg Psychiatry 52(4):488–492

38. Qiu Y, Guo Z, Han L, Yang Y, Li J, Liu S, Lv X (2018) Network-level dysconnectivity in patients with nasopharyngeal carcinoma (NPC) early post-radiotherapy: longitudinal resting state fMRI study. Brain Imaging Behav 12(5):1279–1289
39. Ribeiro M, Durand T, Roussel M, Feuvret L, Jacob J, Psimaras D, Noel G, Keller A, Bompaire F, Hoang-Xuan K, Bernier MO (2020) Sensitivity of the Montreal cognitive assessment in screening for cognitive impairment in patients with newly diagnosed high-grade glioma. J Neurooncol 148(2):335–342
40. Vardy J, Wefel JS, Ahles T, Tannock IF, Schagen SB (2008) Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop. Ann Oncol 19(4):623–629
41. Wefel JS, Vardy J, Ahles T, Schagen SB (2011) International cognition and cancer task force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol 12(7):703–708
42. Watts ME, Pocock R, Claudianos C (2018) Brain energy and oxygen metabolism: emerging role in normal function and disease. Front Mol Neurosci 11:216

Authors and Affiliations

Mahad Omar[1] · Ceyhan Yazicioglu[2] · Stuart Winter[1] · Henk Peter Giele[1]

✉ Mahad Omar
mahad.omar@stx.ox.ac.uk

✉ Ceyhan Yazicioglu
c_yazicioglu@yahoo.com

[1] University of Oxford, Oxford, UK

[2] King's College London, London, UK