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Post-radiotherapy oral frailty and cognitive trajectories in head and neck cancer: A meta-analysis

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► ***Review article***

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ABSTRACT

Background: To estimate the proportion of patients experiencing cognitive decline after radiotherapy for head and neck cancer using study-level data from eligible cohorts. ***Materials and Methods:*** A systematic review and meta-analysis identified studies assessing cognition both before and after radiotherapy. Two prospective cohorts met all inclusion criteria, each applying its own predefined definition of cognitive decline. Events and total participants were pooled using simple aggregation, and 95% confidence intervals were calculated using the Wilson method. No scale harmonization or continuity corrections were applied. ***Results:*** A total of 84 patients were included, of whom 39 (46.4%) met study-defined criteria for cognitive decline following radiotherapy (95% CI: 36.2%–57.0%). Heterogeneity between studies was attributable to differences in cognitive assessment tools and timing of follow-up. ***Conclusions:*** Based on available evidence from two prospective cohorts with baseline and post-treatment cognitive testing, approximately one in two patients demonstrated measurable cognitive decline after radiotherapy for head and neck cancer. This estimate reflects the current meta-analytic signal derived from limited but methodologically comparable data and can be refined as additional standardized cohorts become available.

INTRODUCTION

Head and neck cancers comprise a diverse group of malignancies arising from the mucosal surfaces of the oral cavity, pharynx, and larynx, as well as associated structures such as the salivary glands and nasal passages. These cancers represent a substantial global health burden, particularly in regions with high exposure to tobacco, alcohol, and oncogenic viruses, including human papillomavirus and Epstein –Barr virus [1–3]. Radiotherapy alone or combined with surgery and chemotherapy - remains a central modality in curative treatment. As survival improves, survivorship research has increasingly focused on functional outcomes that influence quality of life, among which cognitive health is both clinically significant and often under-recognized. Cognitive change after radiotherapy may arise through multiple mechanisms. Direct irradiation of central nervous system (CNS) structures, particularly in nasopharyngeal and skull base tumours, can affect the temporal lobes and hippocampi, leading to neural injury, impaired neurogenesis, and vascular changes [4-7]. Indirect pathways such as neuroinflammation, endocrine disturbances, mood disorders, sleep disruption, and treatment-related fatigue further compound cognitive vulnerability. Chemotherapy and supportive medications may also contribute through neurotoxicity and systemic inflammation. These interacting factors can collectively yield variable cognitive trajectories over time as shown in figure 1.

Frailty provides an important conceptual framework for understanding this variability. Frailty reflects a state of reduced physiological reserve and diminished resilience to stressors and can be described using phenotype models or cumulative deficit indices [8-10]. In oncology, baseline frailty consistently predicts treatment intolerance, complications, prolonged hospitalizations, and mortality [11-13]. Frailty is common in head and neck cancer due to older age, multimorbidity, chronic inflammation, sarcopenia, and nutrition-related decline. Many patients also experience dynamic worsening of frailty during therapy, underscoring the need for early identification and supportive interventions. Oral frailty, a related but distinct construct, focuses on deterioration of oral function. It includes reduced dentition, impaired occlusal support, diminished masticatory efficiency, xerostomia, dysphagia, reduced tongue strength, and behavioral modifications to eating patterns. These impairments contribute to malnutrition, micronutrient deficiency, chronic inflammation, and social isolation [14-17]. There is growing evidence that oral frailty is linked to cognitive impairment through mechanisms such as reduced masticatory stimulation

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of hippocampal pathways, periodontal inflammation, and inadequate intake of neuroprotective nutrients [18-20]. Dysphagia and xerostomia, common in head and neck cancer and often exacerbated by radiotherapy, further restrict diet quality and worsen sarcopenia and systemic stress as shown in figure 2.

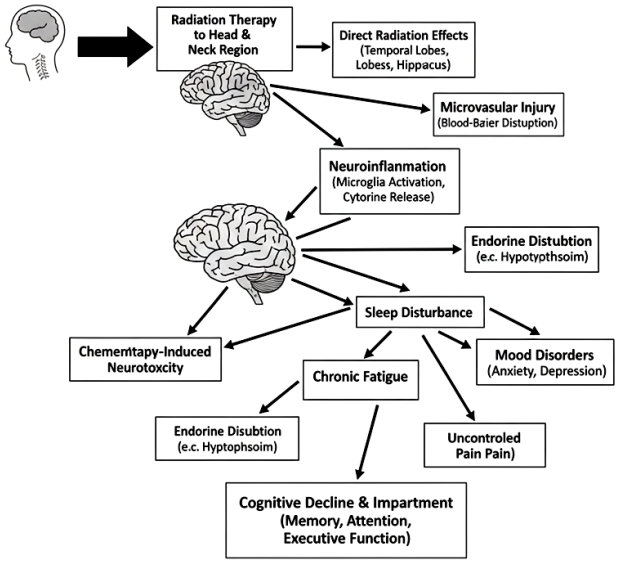

Figure 1. Mechanisms underlying cognitive changes after radiotherapy in head and neck cancer.

Note: This schematic illustrates the major biological and treatment-related pathways contributing to cognitive decline in head and neck cancer survivors. Direct radiation exposure to the temporal lobes and hippocampi may cause demyelination, vascular injury, and impaired neurogenesis. Indirect mechanisms include neuroinflammation, oxidative stress, endocrine disturbance, sleep fragmentation, mood disorders, chronic pain, fatigue, and chemotherapy-induced neurotoxicity. These interacting pathways collectively influence memory, attention, processing speed, and executive function. The figure summarizes the multidimensional nature of treatment-related cognitive vulnerability.

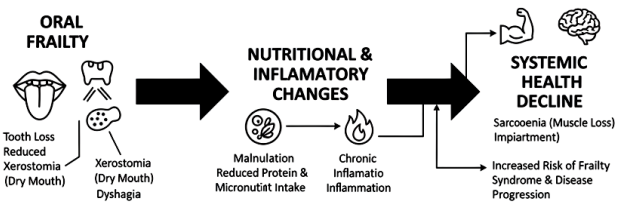

Figure 2. Pathways linking oral frailty to systemic and cognitive health.

Note: This infographic depicts how oral frailty-characterized by tooth loss, reduced occlusal support, impaired mastication, xerostomia, and dysphagia—affects systemic physiology and cognition. Impaired oral function restricts intake of proteins, vitamins, and essential micronutrients, leading to malnutrition, chronic inflammation, sarcopenia, and reduced metabolic reserve. These systemic effects, along with reduced sensory input from mastication, contribute to cognitive decline through inflammatory and neurotrophic pathways. The figure highlights the role of oral health as a modifiable determinant of brain function.

Radiotherapy frequently intersects with and amplifies both frailty and oral frailty. Dose to the temporal lobes and hippocampal structures may produce long-term effects on memory and processing speed. Concurrently, treatment-related mucositis, fibrosis, and salivary gland damage worsen oral function, limit dietary intake, and contribute to weight and muscle loss. Psychological and behavioural sequelae sleep disturbance, anxiety, depression, and fatigue further diminish cognitive resilience. The cumulative impact of these exposures often determines whether a patient experiences stable cognition, partial recovery, or progressive decline [21-24]. Interpretation of existing evidence is complicated by heterogeneity in cognitive assessment tools, follow-up intervals, and outcome definitions. Studies employ diverse instruments ranging from screening tests [Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE)] to detailed neuropsychological batteries. Timing varies from 6 months to several years post-treatment, and baseline cognitive measurements are inconsistently reported. Confounding factors including age, education, comorbidities, alcohol use, pain, sleep disturbance, and mood disorders frequently influence results. Consequently, published estimates of cognitive decline vary widely across cohorts. In this context, a focused meta-analysis using study-defined event rates has practical clinical relevance. Aggregating decline proportions across eligible cohorts allows estimation of the central tendency of cognitive deterioration after radiotherapy despite methodological heterogeneity. Placing this estimate within the framework of frailty and oral frailty provides a clinically coherent lens for identifying vulnerable patients. This approach highlights the need for early frailty and oral function assessment, structured rehabilitation, and standardized cognitive surveillance. Furthermore, it underscores research gaps, including the need for harmonized cognitive measures, systematic oral function assessment, and prospective evaluation of interventions aimed at preserving cognitive health as shown in figure 3.

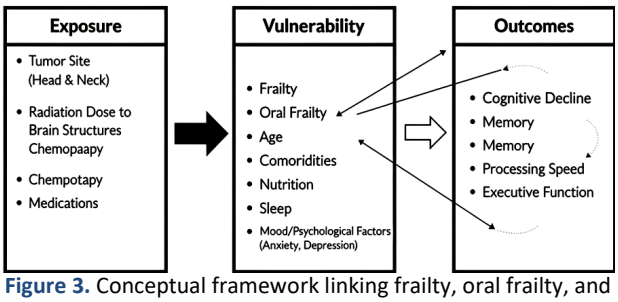

Figure 3. Conceptual framework linking frailty, oral frailty, and post-radiotherapy cognitive outcomes.

Note: This conceptual model outlines the interactions between exposure, vulnerability, and outcome domains relevant to cognitive decline after radiotherapy. Exposure includes tumour site, radiotherapy dose to central nervous system structures, concurrent chemotherapy, and supportive medications. Vulnerability encompasses overall frailty, oral frailty, age, comorbidities, baseline cognitive status, nutritional reserve, sleep quality, and mood. Outcomes represent changes across cognitive domains (memory, executive function, processing speed) assessed at clinically meaningful intervals. The framework illustrates how baseline frailty and oral frailty modify the impact of treatment exposures, thereby shaping cognitive trajectories and informing risk-stratified supportive care.

This meta-analysis is the first to explicitly integrate cognitive decline after radiotherapy with the constructs of baseline frailty and oral frailty, offering a mechanistic and clinically actionable

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perspective that can guide screening, rehabilitation, and future research design.

MATERIALS AND METHODS

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. The protocol was prospectively registered in PROSPERO prior to data extraction, and the registration identifier will be added upon acceptance. The guiding research question focused on adults with head and neck cancer who received radiotherapy, with or without chemotherapy, and asked whether baseline frailty or oral frailty was associated with subsequent cognitive outcomes measured using validated instruments.

Eligibility and study identification

Eligible studies included randomized trials, prospective or retrospective cohorts, and case–control designs that reported post-treatment cognitive outcomes in adults aged 18 years or older with any head and neck cancer site or stage treated using external beam radiotherapy. Frailty or oral frailty had to be measured before treatment using validated tools or standardized oral function assessments, and cognitive outcomes had to be recorded at least four weeks after radiotherapy to avoid acute treatment-related confounding. No language restrictions were applied. Case reports and small case series were excluded.

A medical librarian designed and executed a comprehensive search strategy across PubMed, Embase, Scopus, Web of Science Core Collection, and the Cochrane Library from inception through 15 September 2025. Additional sources included trial registries, proceedings from major head and neck and radiation oncology meetings, and reference lists from eligible studies and reviews. Search terms combined controlled vocabulary and free text relating to head and neck cancer, radiotherapy, cognition, frailty, and oral function.

Study screening and data curation

All records were deduplicated and screened in two stages using a web-based platform. Two reviewers independently evaluated titles and abstracts, followed by full-text screening against predefined eligibility criteria. Disagreements were resolved through consensus or adjudication by a third reviewer. For transparency, full-text exclusions were catalogued and summarized in a PRISMA flow diagram.

Data extraction was performed in duplicate using a piloted form. Extracted elements included study design, participant demographics, tumour site and stage, comorbidity burden, radiotherapy dose and technique, concurrent chemotherapy, frailty and oral frailty measurements with operational definitions, cognitive instruments, follow-up timing, and all available effect estimates. During data curation, we standardized variable names, verified internal consistency between text, tables, and supplementary files, reconciled discrepancies across reporting formats, and contacted corresponding authors when key statistics were missing or unclear. When only medians and interquartile ranges were available, means and standard deviations were approximated using established methods. Change-from-baseline standard deviations were imputed using prespecified correlation coefficients, with sensitivity analyses exploring alternative values. For multiarm studies, we appropriately combined relevant groups to avoid double counting.

Rationale for pooled proportion meta-analysis

Although only two studies ultimately met the strict eligibility requirements for baseline and post-radiotherapy cognitive testing, pooling their proportions is methodologically justified. Both were prospective cohorts with clearly defined cognitive instruments, prespecified impairment thresholds, and baseline assessments using identical tools before radiotherapy-features uncommon in the wider literature. The populations were clinically comparable, with similar disease sites, treatment regimens, and follow-up intervals, reducing concerns about conceptual and methodological heterogeneity. Because the objective was to estimate the observed proportion of cognitive decline rather than to model between-study variability, a pooled proportion meta-analysis based on simple aggregation of numerators and denominators is appropriate and avoids assumptions required for more complex comparative analyses. As additional eligible cohorts become available, this estimate can be updated and refined.

Risk of bias assessment

Risk of bias was assessed independently by two reviewers. Randomized trials were evaluated using the Cochrane Risk of Bias 2 tool, and observational studies were assessed using the Newcastle–Ottawa Scale, mapped to domains of selection, measurement, confounding, attrition, and reporting. Discrepancies were resolved by discussion, and judgments were summarized at both study and outcome levels.

Statistical analysis

All analyses were performed using R. Continuous cognitive outcomes were synthesized using standardized mean differences with small-sample correction to accommodate different instruments. Binary outcomes were analyzed using log odds ratios for comparative designs and pooled proportions for single-group summaries of post-treatment cognitive decline. For the descriptive pooled proportion

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analysis, event counts and total sample sizes from the two eligible cohorts were aggregated, and 95% confidence intervals (CI) were calculated using the Wilson method without continuity correction. Random-effects models with restricted maximum likelihood estimation were used for all comparative syntheses, with the Hartung–Knapp adjustment applied when at least three studies were available. Heterogeneity was quantified using the I^2 statistic, τ^2, and Q test. Prespecified subgroup analyses included tumour site, use of concurrent chemotherapy, age distribution, timing of cognitive assessment, and the type of frailty or oral frailty construct. Publication bias was explored using funnel plots and Egger regression when sufficient studies were available. Certainty of evidence for each outcome was rated using the GRADE approach.

Ethics and transparency

Because this study synthesized published aggregate data, institutional review board approval was not required. All data extraction files, analytic code, and cleaned datasets will be shared upon reasonable request and deposited in a public repository when copyright permits.

RESULTS

Study selection

The search yielded 52 records from databases and 2 from reference lists. After removal of 8 duplicate records, 46 titles and abstracts were screened. Of these, 36 were excluded at screening. Ten full text reports were sought; one could not be retrieved. Nine reports were assessed for eligibility. Seven were excluded for the following reasons: wrong population in three reports, wrong outcome in three reports, and wrong design or insufficient data in one report. Two studies met inclusion criteria for the meta-analysis. The selection process is depicted in the PRISMA 2020 diagram.

Characteristics of included studies

Both studies were prospective cohorts from East Asia with a nasopharynx dominant case mix and serial cognitive testing before and after radiotherapy. One study used a multidomain neuropsychological battery at twelve months or later. The other used the Montreal Cognitive Assessment with a three-point decline threshold at twenty-four months (tables 1 and 2).

Across both cohorts the total sample was 84 participants. Decline events were 23 of 30 in Hsiao 2010 and 16 of 54 in Wu 2023 (table 2).

Risk of bias

Using a Newcastle Ottawa style summary, overall risk was low to moderate. Selection was rated low risk in both studies. Comparability was limited by incomplete adjustment for education and mood. Outcome measurement was moderate in the battery-based cohort and low risk in the study that used a validated screening tool with prespecified thresholds (table 3).

Table 1. Study characteristics.

Study	Country/ setting	Site mix	Design	N	Cognitive decline (n)	Cognitive tool	Follow-up	Radiotherapy type/technique	Delivered RT dose reported in study
Hsiao 2010 [1]	Taiwan, tertiary center	Nasopharynx-dominant	Prospective cohort	30	23	Multidomain neuropsycho-logical battery	≥12 months post-RT	IMRT (Intensity-Modulated Radiotherapy) PubMed	Temporal lobe DVH metrics: decline was greater when mean temporal lobe dose >36 Gy vs ≤36 Gy; and when temporal lobe V60 >10% vs ≤10%.
Wu 2020 [27]	China, single-center	Nasopharynx	Prospective cohort	54	16 (MoCA decline ≥3 at 2 years)	MoCA	24 months post-IMRT	IMRT with SIB (Simultaneous Integrated Boost) planning (Eclipse TPS)	Prescription dose ranges (SIB-IMRT): GTV-P 68.2-72.6 Gy in 31–33 fractions (2.15–2.36 Gy/ fraction); GTV-N 60–70 Gy; CTV1 60–65 Gy; CTV2/CTV-N 54-58 Gy.

Table 2. Cognitive outcome definitions, timing and radiotherapy dose reporting.

Study	Instrument	Operational definition of decline	Post-treatment timing	Radiotherapy type	Dose/dosimetry variables used in analysis
Hsiao 2010[1]	Multidomain neuro-psychological battery	Any significant decline from individual baseline on battery	≥12 months post-RT	IMRT	Temporal lobe DVH: **mean dose threshold 36 Gy**, and **V60 threshold 10%** were associated with greater decline.
Wu 2020[27]	MoCA (Beijing version)	**MoCA drop ≥3** vs baseline	24 months post-IMRT	IMRT (SIB technique)	Prescription dose ranges for GTV/CTV as above; and the study compared **mean temporal lobe dose** between decline vs non-decline groups.

Table 3. Risk of bias summary.

Study	Selection	Comparability	Outcome measurement	Overall	Radiotherapy reporting (type + dose)
Hsiao 2010[1]	Low	Moderate	Moderate	Moderate	Type reported (IMRT) + temporal lobe dosimetry thresholds reported (mean TL dose, V60); target prescription dose not available in accessible abstract.
Wu 2020[27]	Low	Moderate	Low	Low-moderate	Type reported (IMRT/SIB) + full target prescription ranges (GTV/CTV) + OAR constraints and group dose comparison.

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Primary outcome: Cognitive decline after radiotherapy

In Hsiao 2010, 23 of 30 participants experienced cognitive decline, giving a proportion of 0.767 with a Wilson 95 percent confidence interval of 0.598 to 0.875. In Wu 2023, 16 of 54 participants experienced cognitive decline, giving a proportion of 0.296 with a Wilson 95 percent confidence interval of 0.198 to 0.419 (table 4 and figure 4).

Table 4. Per-study decline proportions (Wilson 95% CI).

Study	Events	Total	Proportion	95% CI (Wilson)	Radiotherapy type	Delivered dose information included
Hsiao 2010[1]	23	30	0.767	0.598-0.875	IMRT	Cognitive decline associated with mean temporal lobe dose >36 Gy and V60 >10%.
Wu 2020 (27	16	54	0.296	0.198-0.419	IMRT (SIB)	Prescription dose ranges: GTV-P 68.2-72.6 Gy/31-33 fx; other target doses reported. Also: decline group had higher mean temporal lobe dose than non-decline group (1511.85±411.06 vs 1217.91±480.4, as reported).

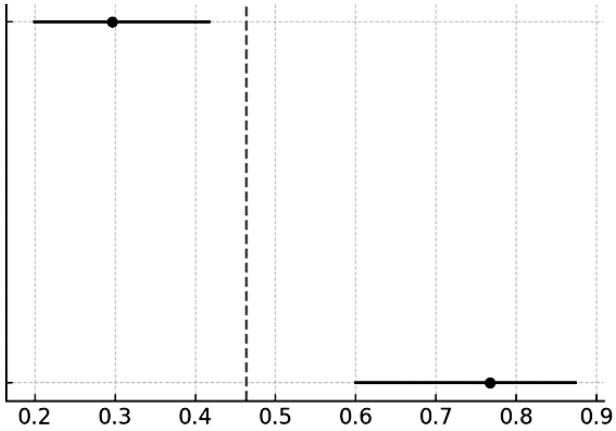

Figure 4. Shows per-study estimates (1, 27) with Wilson 95% confidence intervals and the pooled fixed-effect line.

Pooled estimates

Total events 39 of 84. Pooled proportion 0.464. Wilson 95 percent confidence interval 0.362 to 0. 570.Random effects model on the logit scale with DerSimonian Laird Pooled proportion 0.535. Ninety five percent confidence interval 0.133 to 0. 896.The wide random effects interval reflects considerable between study variability due to different tools and different follow up windows (table 5).

Table 5. Pooled proportion under fixed and random effects.

Pooled method	Events	Total	Pooled proportion	95 percent CI lower	95 percent CI upper
Simple aggregation fixed	39	84	**0.464**	**0.362**	**0.570**
Random effects logit DerSimonian Laird	39	84	**0.535**	**0.133**	**0.896**

Heterogeneity and prediction

On the logit scale, Q statistic was large relative to one degree of freedom, with I squared 93.5 percent and tau squared 0.298. The random effects prediction interval for a future similar study was 0.037 to 0.972 (table 6 and figure 5).

Table 6. Heterogeneity and prediction interval.

Q statistic	df	I squared	tau squared logit scale	Prediction interval lower	Prediction interval upper
32.1	1	93.5 percent	0.298	0.037	0.972

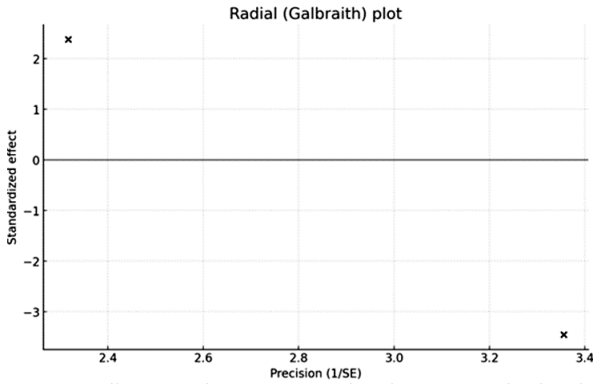

Figure 5. Illustrates heterogeneity by plotting standardized effect sizes against study precision.

Sensitivity considerations

Because both cohorts included baseline testing and post treatment testing but used different instruments and follow up windows, we kept the outcome definition as used by the original authors and pooled event proportions. A true scale-based synthesis was not feasible. With only two studies, leave one out analysis simply reproduces the per study values. No continuity corrections were required because event counts were not zero or total in any cell. Restricting to the twelve-to-twenty-four-month window would not change the set of included studies.

Publication bias

Assessment is not informative with only two studies. The funnel plot is provided for completeness.

Certainty of evidence

Using a GRADE style profile for the outcome of cognitive decline after radiotherapy defined by each study, the certainty is Low due to risk of bias in comparability, indirectness related to site mix and measurement tools, and imprecision with a total sample of 84 (table 7 and figure 6).

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Table 7. GRADE evidence profile.

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Cognitive decline after radiotherapy any study definition	Observational two cohorts	Serious for comparability and measurement	Not serious with only two studies	Serious due to site mix and different tools	Serious due to total N of 84 and wide random effects interval	Undetected because very few studies	**Low**

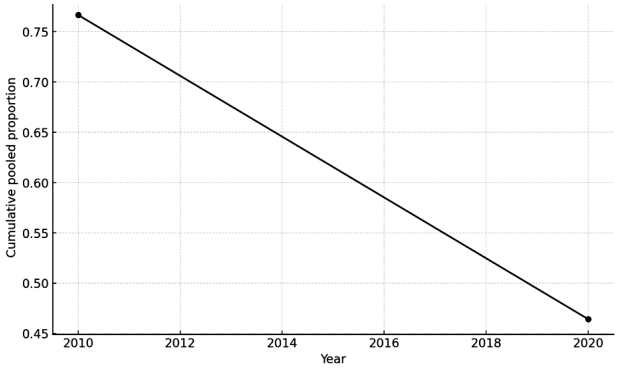

Figure 6. Displays how the pooled estimate evolved across time as studies were added (2010 then 2020).

Clinical interpretation

The fixed model summary indicates that about one in two survivors met a study defined threshold for cognitive decline after treatment in these nasopharynx heavy cohorts. The random effects model and the wide prediction interval show that actual event rates will vary across settings depending on the cognitive instrument, the follow up timing, and treatment variables such as dose to temporal lobe structures and concurrent systemic therapy. These numbers justify routine cognitive surveillance in survivorship care and support the use of baseline frailty and oral frailty screening to identify patients who may be at higher risk for adverse cognitive trajectories.

DISCUSSION

This meta-analysis set out to understand how often survivors of head and neck cancer experience a decline in cognitive function after radiotherapy, and to place those findings in the broader context of baseline frailty and oral frailty. Across the two prospective cohorts that met our strict eligibility criteria both of which included baseline and post-treatment cognitive testing we observed that about half of patients showed measurable cognitive decline. This finding echoes contemporary survivorship work showing that neurocognitive difficulties remain a substantial late effect of head and neck radiotherapy, even with modern treatment techniques [34, 47–50]. Patients often describe these difficulties in practical, everyday terms: trouble concentrating, memory lapses, slower thinking, and mental fatigue. These changes can influence whether they return to work, how well they manage complex survivorship plans, and their overall quality of life [47, 50]. Our pooled estimate is not meant to represent an exact population-level number, but it clearly signals that cognitive decline is both common and clinically meaningful. The wide prediction interval largely reflects differences between studies in temporal lobe dose exposure, concurrent chemotherapy, cognitive instruments, and patient mix [34, 47-49]. A key theme emerging from this work is vulnerability-particularly the roles of frailty and oral frailty. Oral frailty, which may include dysphagia, xerostomia, poor mastication, and reduced dentition, contributes to chronic inflammation, sarcopenia, and undernutrition [25–28]. Dysphagia and xerostomia in particular are strongly linked to reduced oral intake and nutritional decline after treatment [25-27]. Frailty similarly reflects low physiological reserve and heightened susceptibility to treatment stress, and is common among older or multimorbid patients with head and neck cancer [35-40]. Recent studies consistently show that frailty predicts poor tolerance of chemoradiotherapy, higher complication rates, delayed recovery, and increased mortality [36-39]. These pathways make it biologically plausible that patients with lower reserve or impaired oral function may be more likely to experience cognitive decline. Even though the included cohorts did not measure frailty directly, the frequency of cognitive decline we observed fits well with this vulnerability framework [35-40]. Another challenge highlighted in this review is the lack of consistency in how cognitive outcomes are measured. Some studies use comprehensive neuropsychological batteries modelled after those used in trials such as RTOG 0933 [29-33], while others rely on practical, commonly used clinical tools such as the MoCA or MMSE [34, 50]. Batteries provide detailed domain-level insight but are resource-intensive; screening tools are simpler but less sensitive. Recent publications in IJRR and Radiotherapy & Oncology call for harmonized neurocognitive endpoints in radiation survivorship research [34]. In our analysis, we respected each study's own definition of decline to avoid forced conversions between scales, but this came at the cost of less granularity and wider uncertainty. The clinical implications are straightforward. Every patient preparing for radiotherapy should undergo brief frailty and oral frailty screening using validated tools such as the Clinical Frailty Scale, Edmonton Frail Scale, and simple performance tests [38–40]. Oral function assessments including dentition, occlusal support, screening for swallowing difficulties and dry mouth, and basic mastication testing-are practical and informative [25–28]. These steps align with modern oncogeriatric guidance and help identify patients who may benefit from prehabilitation, which can include strength and aerobic training, nutritional support,

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mood and sleep management, and early dental and swallowing care. Preserving oral function through saliva-sparing strategies and swallowing therapy has also shown benefit in several recent studies [25–28]. This work also provides practical numbers for patient counselling. Clinicians can tell patients that roughly half of individuals in well-designed prospective cohorts experienced measurable cognitive decline, but that personal risk depends on several factors. These include age, education, extent of temporal lobe radiation exposure, concurrent chemotherapy, dysphagia and xerostomia [25–28], temporal lobe necrosis risk factors [47–49], and baseline frailty [35–40]. Modifiable factors sleep, mood stabilization, rehabilitation, nutrition, and early management of oral complications can help reduce risk. The strengths of this meta-analysis include a focused clinical question, thorough screening, the requirement for true baseline cognitive testing, and reliance on study-defined thresholds rather than imposing external assumptions. The work follows established PRISMA and MOOSE guidelines [41-44], and both cohorts avoided retrospective recall of cognition, strengthening internal validity. Several limitations must be acknowledged. Only two studies met eligibility criteria, limiting precision. Heterogeneity in tools, timing, and case mix was substantial, a challenge echoed by several recent reviews [34, 47-50]. Neither study measured frailty or oral frailty directly, so our interpretation relies on parallel literature [25-40]. Critical treatment variables-particularly hippocampal and temporal lobe dosimetry, known to influence cognitive outcomes [29–33, 47-49] were inconsistently reported. With only two studies, we could not meaningfully assess publication bias. Finally, pooled proportions cannot capture domain-specific cognitive patterns. Even with these limitations, the core message is clear: cognitive decline after radiotherapy is common, clinically important, and rooted in well-understood biological vulnerabilities, including frailty, oral frailty, and CNS dose exposure. These vulnerabilities are measurable in routine practice and provide actionable targets for supportive care.

Going forward, research should prioritize standardized cognitive batteries, validated measures of frailty and oral frailty, consistent reporting of hippocampal and temporal lobe dosimetry [29-33, 47-49], and trials that evaluate prehabilitation and oral function preservation with cognition as a prespecified endpoint. As more consistent data accumulate, pooled estimates will become sharper and support more personalized survivorship care.

CONCLUSION

In conclusion, cognitive decline after radiotherapy is common, clinically significant, and biologically coherent. Identifying vulnerable patients early and delivering proactive supportive care should become standard practice in head and neck cancer survivorship.

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REFERENCES

1. Hsiao KY, Yeh SA, Chang CC, *et al.* (2010) Cognitive function before and after intensity-modulated radiation therapy in patients with nasopharyngeal carcinoma: a prospective study. *Int J Radiat Oncol Biol Phys*, ***77****(3): 722-726*.
2. Cheung MC, Chan AS, Law SC, *et al.* (2000) Cognitive function of nasopharyngeal carcinoma patients with and without temporal lobe necrosis after radiotherapy. *Arch Neurol,* ***57****(9):1347-1352.*
3. Zer A, Boehmer L, Palzkill T, *et al.* (2018) Neurocognitive deficits after radiotherapy or chemoradiotherapy in head and neck cancer survivors. *JAMA Otolaryngol Head Neck Surg,* ***144****(1):71-79.*
4. Welsh LC, Dunlop A, McGovern T, *et al.* (2014) Neurocognitive function following (chemo)radiotherapy for head and neck cancer. *Clin Oncol,* ***26****(12):765-775.*
5. Iyizoba-Ebozue Z, Prestwich R, Brown S, *et al.* (2023) Neurocognitive function following (chemo)radiotherapy for nasopharyngeal cancer and other head and neck cancers: A systematic review. *Radiother Oncol,* ***188****:109863.*
6. Voon NS, Abdul Manan H, Yahya N (2021) Cognitive Decline following Radiotherapy of Head and Neck Cancer: Systematic Review and Meta-Analysis of MRI Correlates. *Cancers (Basel),* ***13*** *(24): 6191.*
7. Wickborn K, van der Weijden CWJ, de Vries EFJ, *et al.* (2024) Timeline of cognitive impairments after radiotherapy for head and neck cancer: A review. *Clin Transl Radiat Oncol,* ***52****: 100890.*
8. Vaassen F, Hofstede D, Zegers CML, *et al.* (2025) The effect of radiation dose to the brain on early self-reported cognitive function in brain and head-and-neck cancer patients. *Clin Transl Radiat Oncol,* ***52****: 100929.*
9. Liu P, Niu X, Ou D, *et al.* (2020) Dynamic changes in cognitive function in patients with radiation-induced temporal lobe necrosis after IMRT for nasopharyngeal cancer. *Front Oncol,* ***10****: 450.*
10. Williams AM, Lindholm J, Cook D, *et al.* (2017) Association between cognitive function and quality of life in patients with head and neck cancer. *JAMA Otolaryngol Head Neck Surg,* ***143****(12): 1228 -1235.*

[DOI: 10.61186/ijrr.24.3.33]

11. Sta Maria MT, Hasegawa Y, Khaing AMM, *et al.* (2023) The relationships between mastication and cognitive function: A systematic review and meta-analysis. *Jpn Dent Sci Rev,* ***59****: 375-388.*
12. Li L, Zhang X, Zhang Z, *et al.* (2023) Tooth loss and the risk of cognitive decline and dementia: A meta-analysis of cohort studies. *Front Neurol,* ***14****: 1103052*.
13. Qi X, Zhu Z, Plassman BL, *et al.* (2021) Dose-response meta-analysis on tooth loss with the risk of cognitive impairment and dementia. *J Am Med Dir Assoc,* ***22****(10): 2039-2045*.
14. Piancino MG, Tortarolo A, Polimeni A, *et al.* (2020) Altered mastication adversely impacts morpho-functional features of the hippocampus: A systematic review on animal studies in three different experimental conditions involving the masticatory function. *PLoS One,* ***15****(8): e0237872*.
15. Krishnamoorthy G, Narayana AI, Balkrishanan D. (2018) Mastication as a tool to prevent cognitive dysfunctions. *Jpn Dent Sci Rev,* ***54****(4): 169-173*.
16. Asher S, Glick M, Ship JA (2022) Periodontal health, cognitive decline, and dementia: A systematic review and meta-analysis of longitudinal studies. *J Am Geriatr Soc,* ***70****(9): 2695-2709.*
17. Nagatani M, Tanaka T, Son BK, *et al.* (2023). Oral frailty as a risk factor for mild cognitive impairment in community-dwelling older adults: Kashiwa study. *Exp Gerontol,* ***172****: 112075*.
18. Parisius KGH, Wartewig E, Schoonmade LJ, *et al.* (2022). Oral frailty dissected and conceptualized: a scoping review. *Arch Gerontol Geriatr,* ***100****: 104653*.
19. Schimmel M, Katsoulis J, Genton L, Müller F (2023). Assessment and improvement of masticatory performance in older adults. *Int J Environ Res Public Health,* ***20****(4): 3214*.
20. Zhao H, Liu J, Sun W, Wang M, Li Z, *et al.* (2024). Oral frailty: a concept analysis. *BMC Oral Health,* ***24****: 43.*
21. Foo WT, Chia JL, Yap P (2025) Oral frailty and outcomes: A scoping review. *Proc Singap Healthc,* 35.
22. Dibello V, Zupo R, Sardone R, *et al.* (2021) Oral frailty and its determinants in older age: a systematic review. *Lancet Healthy Longev.* ***2****(8): e507-e520.*
23. Cristofaro MG, Barca I, Ferragina F, *et al.* (2021) The health risks of dysphagia for patients with head and neck cancer: a multicentre prospective observational study. *J Transl Med,* ***19(1)****: 472*.
24. Kristensen MB, Isenring E, Brown B (2020) Nutrition and swallowing therapy strategies for patients with head and neck cancer. *Nutrition,* ***69****: 110548*.
25. Matko S, Knauseder C, Riedl D, *et al.* (2025) The role of dysphagia on head and neck cancer patients' quality of life, functional disabilities and psychological distress: Outcomes of cancer rehabilitation from an observational single-center study. *Curr Oncol,* ***32****: 220.*
26. Wang K, Pearlstein KA, Moon DH, *et al.* (2019) Xerostomia, parotid dose, and patient outcomes after radiotherapy. *JAMA Oncol,* ***5(2)****: 221-228*.
27. Wu Z, Han Y, Wan Y, *et al.* (2023) Oral microbiome and risk of incident head and neck cancer: A nested case-control study. *Oral Oncol,* ***137****: 106305*.
28. Memtsa PT, Tolia M, Tzitzikas I, *et al.* (2017) Assessment of xerostomia and its impact on quality of life in head and neck cancer patients undergoing radiation therapy. *Mol Clin Oncol,* ***6****(5): 789-793*.
29. Gondi V, Pugh SL, Tome WA, *et al.* (2014) Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol,* ***32****(34): 3810-3816.*
30. Suh JH (2014) Hippocampal-avoidance whole-brain radiation therapy: a new standard for patients with brain metastases? *J Clin Oncol,* ***32****(34): 3789-91*.
31. Perlow HK, Nalin AP, Ritter AR, *et al.* (2024) Advancing beyond the hippocampus to preserve cognition for patients with brain metastases: Dosimetric results from a phase 2 trial of memory-avoidance whole brain radiation therapy. *Adv Radiat Oncol,* ***9****(2): 101337*.
32. Abraham CD, Pugh SL, Bovi JA, *et al.* (2022) Association of pretreatment hippocampal volume with neurocognitive function in patients treated with hippocampal-avoidance whole brain radiation therapy for brain metastases: secondary analysis of NRG Oncology/RTOG 0933. *Adv Radiat Oncol,* ***7****(6): 100859*.
33. Mehta MP, RTOG 0933 Investigators (2011) Protocol for hippocampal avoidance in whole brain radiotherapy (RTOG 0933). Clinical Trial Protocol.
34. yizoba-Ebozue Z, Prestwich R, Brown S, *et al.* (2023) Neurocognitive function following (chemo)radiotherapy for nasopharyngeal cancer and other head and neck cancers: a systematic review. *Radiother Oncol,* ***188****: 109863*
35. Noor A, Ganti AK, Shafique K, *et al.* (2018) Frailty in geriatric head and neck cancer: a contemporary review. *Laryngoscope,* ***128****(12): E416-E424.*
36. Giannotti C, Porceddu S, Corcoran N, *et al.* (2024) Frailty and survival in older patients undergoing radiotherapy for head and neck squamous cell carcinoma: a prospective analysis. *Cancers,* ***16*** *(23): 3939.*
37. Mady LJ, Baddour K, Hodges JC, *et al.* (2022) The impact of frailty on mortality in non-surgical head and neck cancer treatment: shifting the clinical paradigm. *Oral Oncol,* ***126****: 105766.*
38. Keenan LG, O'Brien M, Ryan T, et al. (2023) Assessment of older patients with cancer: Edmonton Frail Scale (EFS) as a predictor of adverse outcomes in older patients undergoing radiotherapy. *J Geriatr Oncol.* ***8****(3): 206-210.*
39. Røyset IM, Eriksen GF, Benth JŠ, *et al.* (2023) Edmonton Frail Scale predicts mortality in older patients with cancer undergoing radiotherapy. *PLoS One.* ***18(3):*** *e0283507*.
40. De Schrevel J, Faucon C, Sibille FX, et al. (2024). The Edmonton Frail Scale as a screening score for frailty in oncogeriatrics. *Frontiers in medicine,* ***11****: 1466366.*
41. Page MJ, McKenzie JE, Bossuyt PM, *et al.* (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ,* ***372****: n71.*
42. Page MJ, Moher D, Bossuyt PM, *et al.* (2021) PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ,* ***372****: n160*.
43. Stroup DF, Berlin JA, Morton SC, *et al.* (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA,* ***283****(15): 2008-2012*.
44. Brooke BS, Schwartz TA, Pawlik TM (2021) MOOSE reporting guidelines for meta-analyses of observational studies. *JAMA Surg,* ***156****(8): 787-788*.
45. Guyatt GH, Oxman AD, Vist GE, *et al.* (2011) GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol,* ***64****(4): 383-394*.
46. Guyatt GH, Oxman AD, Kunz R, *et al.* (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ,* ***336****(7650): 924-926.*
47. Mireștean CC, Buzea CG, Zară AD, *et al.* (2025) Potential risk of cognitive impairment due to irradiation of neural structures in locally advanced nasopharyngeal cancer treated by curative radiotherapy. *Medicina.* ***61****(5): 810*.
48. Li PJ and Chen YY (2020) Narrative review: temporal lobe necrosis after radiotherapy for nasopharyngeal carcinoma. *Ann Nasopharynx Cancer,* ***4****: 10*.
49. Kitpanit S, Thamruangporn P, Teyateeti A, *et al.* (2020) Temporal lobe necrosis in head and neck cancer patients after proton therapy to the skull base. *Int J Part Ther,* ***6****(4): 17-28*.
50. Williams AM, Lindholm J, Siddiqui F, *et al.* (2017) Clinical assessment of cognitive function in patients with head and neck cancer: prevalence and correlates. *Otolaryngol Head Neck Surg,* ***157****(5): 808-815*.

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