TPM Vol. 32, No. S1, 2025
ISSN: 1972-6325
https://www.tpmap.org/

IMPACT OF CHEMORADIOTHERAPY ON COGNITIVE PERFORMANCE IN HEAD AND NECK CANCER PATIENTS COMPARED TO PRE-TREATMENT BASELINE: A PROSPECTIVE COHORT STUDY

DR. VARSHA RAGHU[1], DR. NIVEDA RAMACHANDRAN[2*], DR. RAADHIKA SHREE[3,] DR. K. RAMESH[4]

[1]JUNIOR RESIDENT, DEPARTMENT OF ENT, SAVEETHA MEDICAL COLLEGE, INDIA
[2]*ASSISTANT PROFESSOR, DEPARTMENT OF ENT, SAVEETHA MEDICAL COLLEGE, INDIA
[3]PROFESSOR, DEPARTMENT OF ENT, SAVEETHA MEDICAL COLLEGE, INDIA
[4]TUTOR, DEPARTMENT OF PROSTHODONTICS AND CROWN & BRIDGE, SREE BALAJI DENTAL COLLEGE & HOSPITAL, CHENNAI, INDIA

Abstract

Background:

Head and neck cancers (HNCs) are often managed with concurrent chemoradiotherapy (CTRT) in locally advanced stages. While CTRT improves locoregional control, its impact on neurocognitive function in HNC survivors remains underexplored. This study prospectively evaluates cognitive changes in patients undergoing CTRT, using validated screening tools over a 12-month follow-up period.

Methods:

A prospective cohort of 25 patients with biopsy-proven squamous cell carcinoma of the oropharynx, hypopharynx, larynx, or nasopharynx (Stage III–IVA, ECOG 0–2) was recruited. All received definitive CTRT with site-specific radiotherapy protocols and cisplatin-based chemotherapy. Cognitive function was assessed at baseline, and at 3, 6, and 12 months post-treatment using the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). Paired t-tests compared follow-up scores with baseline, with significance set at $p < 0.05$.

Results:

The mean baseline MoCA and MMSE scores were 26.76 ± 1.44 and 28.78 ± 0.87, respectively. Significant cognitive decline was observed at 3 months (MoCA: 23.96 ± 1.40, $p < 0.001$; MMSE: 27.03 ± 1.08, $p < 0.001$). Partial recovery occurred by 6 months and continued through 12 months, yet both scores remained significantly lower than baseline at final follow-up (MoCA: 25.30 ± 1.52, $p < 0.001$; MMSE: 27.78 ± 0.85, $p < 0.001$). The steepest decline occurred within the first 3 months after CTRT completion.

Conclusion:

CTRT in head and neck cancer patients is associated with measurable cognitive decline, most prominent in the early post-treatment phase, with incomplete recovery at 12 months. Routine cognitive screening in survivorship care may facilitate early detection and timely intervention.

Keywords:

Head and neck cancer, concurrent chemoradiotherapy, cognitive decline, Montreal Cognitive Assessment, Mini-Mental State Examination, cancer-related cognitive impairment, neurotoxicity, survivorship

INTRODUCTION

Head and neck cancers originate from diverse mucosal sites such as the oral cavity, pharynx, larynx, paranasal sinuses, and salivary glands. They represent approximately 4–5% of global cancer cases, with higher rates in regions like South-East Asia due to prevalent risk factors including tobacco, alcohol, betel quid, and HPV infection [1]. The standard of care for locally advanced, non-metastatic disease typically involves concurrent chemoradiotherapy (CTRT), particularly in oropharyngeal, hypopharyngeal, laryngeal, and adjuvantly treated

tumors[2]. Although CTRT enhances locoregional control, its long-term neurocognitive ramifications are understudied in head and neck cancer (HNC) survivors.

Cognitive impairment—sometimes referred to as cancer-related cognitive impairment (CRCI) or "chemo brain"—encompasses deficits in domains such as memory, attention, and executive processing, and can endure for months or even years post-treatment [3]. Importantly, radiotherapy targeting tumors near the skull base or temporal lobes may inflict direct neurological injury via vascular damage, demyelination, or hippocampal insult, particularly in nasopharyngeal carcinoma survivors [4]. Cisplatin, the common radiosensitizer in CTRT regimens, may potentiate neurotoxic effects through oxidative stress and neuroinflammation even with limited blood–brain barrier penetration [5].

Emerging evidence—including a systematic review by Iyizoba-Ebozue et al.—indicates that neurocognitive impairments post-CTRT are associated with dose to hippocampal and temporal regions, and may significantly impact quality of life [6]. Another prospective longitudinal study found that 38% of HNC patients exhibited persistent cognitive decline up to two years following radiotherapy or CTRT [7]. Early investigations—such as Bond et al.—observed that approximately 22% of patients showed decline in at least one cognitive domain by three months post-treatment[8].

Considering improved HNC survival rates, cognitive trajectories have become a pressing survivorship concern. This longitudinal cohort study employs the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) at baseline and at 3, 6, and 12 months post-CTRT to characterize cognitive changes and assist in targeted survivorship planning.

METHODOLOGY

Study Design

This was a prospective cohort study conducted in a tertiary care centre in India over a period of 12 months. A total of 25 patients with biopsy-proven squamous cell carcinoma of the oropharynx, hypopharynx, larynx, or nasopharynx were recruited.

Inclusion Criteria

- Age >18 years
- Biopsy-proven squamous cell carcinoma of head and neck sites (oral cavity, oropharynx, hypopharynx, larynx, nasopharynx)
- ECOG performance status 0–2
- Staging as per AJCC 8th edition
- Planned definitive or adjuvant CTRT
- No prior history of cognitive impairment or neurodegenerative disease

Exclusion Criteria

- History of other malignancies
- Prior chemotherapy or radiotherapy to the head and neck
- Pre-existing psychiatric illness
- Evidence of CNS metastasis or intracranial pathology
- Inability to complete cognitive assessments due to language or sensory deficits

Intervention

All patients underwent definitive CTRT as per institutional protocol:

Radiotherapy schedules (site-specific):

- **Oropharynx, Hypopharynx, Larynx:**
  - Definitive RT: 70 Gy in 35 fractions (2 Gy/fraction) over 7 weeks to the primary tumor and involved nodes
  - Elective nodal irradiation: 50–54 Gy to uninvolved nodal regions
- **Nasopharynx:**
  - Definitive RT: 70 Gy in 33–35 fractions (2–2.12 Gy/fraction) to primary and involved nodes
  - Elective nodal coverage: 50–54 Gy

Chemotherapy:

- Cisplatin: Either
  - 100 mg/m² intravenously every 3 weeks (Days 1, 22, 43)
  - or 40 mg/m² weekly during radiotherapy (as per clinician discretion and patient tolerance)

Outcome Measures

Cognitive function was assessed using:

- Montreal Cognitive Assessment (MoCA) — measures attention, memory, executive function, visuospatial ability, and language (score 0–30)
- Mini-Mental State Examination (MMSE) — assesses global cognition (score 0–30)

Assessments were conducted:

- Baseline: Within 1 week prior to CTRT initiation
- Follow-up: At 3 months, 6 months, and 12 months after completion of CTRT

Outcome Measures

Cognitive function was assessed using:

- **MoCA**: Evaluates multiple cognitive domains; score range 0–30
- **MMSE**: Widely used cognitive screening tool; score range 0–30

Assessments were conducted:

- **Baseline**: Within 1 week prior to CTRT initiation
- **Follow-up**: 3 months, 6 months, and 12 months post-CTRT completion

Statistical Analysis

Data were analyzed using SPSS v[version]. Continuous variables were expressed as mean ± standard deviation (SD). Paired t-test was used to compare baseline and follow-up scores. A p-value <0.05 was considered statistically significan

Results

A total of **25 patients** with biopsy-proven squamous cell carcinoma of the head and neck were enrolled and completed baseline and follow-up cognitive assessments. The **mean age** of the cohort was **55.7 ± 8.7 years**, with a **male predominance** (19 patients, 76%) compared to females (6 patients, 24%). The **primary tumor sites** included the oropharynx in 13 patients (52%), larynx in 8 patients (32%), hypopharynx in 3 patients (12%), and nasopharynx in 1 patient (4%).

Regarding **disease stage**, 13 patients (52%) presented with Stage III disease, and 12 patients (48%) had Stage IVA disease. **ECOG performance status** at baseline was 0 in 6 patients (24%), 1 in 10 patients (40%), and 2 in 9 patients (36%).

Table 1 summarizes the demographic and clinical characteristics.

Variable	Value
Age (years)	55+/- 8
Sex (Male/Female)	19/6
Primary site	Oropharynx – 13, Larynx – 8. Hypopharynx – 3,Nasopharynx - 1
ECOG performance status	1 : 10 (52%) , 2: 9 (34%), 0:6(24%)

Table 1: Demographic and Clinical Characteristics of Study Population

Cognitive Performance Changes

At **baseline**, the mean MoCA score was **26.76 ± 1.44**, and the mean MMSE score was **28.78 ± 0.87**.

- **MoCA scores** showed a significant decline at all follow-up points:
  - **3 months post-CTRT**: 23.96 ± 1.40 (**p < 0.001**)
  - **6 months post-CTRT**: 24.18 ± 1.59 (**p < 0.001**)
  - **12 months post-CTRT**: 25.30 ± 1.52 (**p < 0.001**)
    The largest decline was observed at 3 months (mean difference: –2.80, 95% CI: –3.06 to –2.53), with partial recovery by 12 months, though scores remained significantly lower than baseline.
- **MMSE scores** also declined significantly:
  - **3 months**: 27.03 ± 1.08 (**p < 0.001**)
  - **6 months**: 27.20 ± 0.99 (**p < 0.001**)
  - **12 months**: 27.78 ± 0.85 (**p < 0.001**)
    The mean difference at 3 months was –1.74 (95% CI: –1.96 to –1.53).

Patterns of Decline

The trajectory of cognitive decline was similar for both assessment tools:

- **Sharpest decline** within the first 3 months after completion of CTRT
- **Partial recovery** at 6 months
- **Further improvement** by 12 months, but not returning to pre-treatment baseline levels

Measure	Baseline Mean ± SD	Follow-up Mean ± SD	Mean Diff	p-value
MoCA: 3m vs Base	26.76 ± 1.44	23.96 ± 1.40	-2.80	<0.001
MoCA: 6m vs Base	26.76 ± 1.44	24.18 ± 1.59	-2.58	<0.001
MoCA: 12m vs Base	26.76 ± 1.44	25.30 ± 1.52	-1.46	<0.001
MMSE: 3m vs Base	28.78 ± 0.87	27.03 ± 1.08	-1.74	<0.001
MMSE: 6m vs Base	28.78 ± 0.87	27.20 ± 0.99	-1.58	<0.001
MMSE: 12m vs Base	28.78 ± 0.87	27.78 ± 0.85	-1.00	<0.001

Table 2: Cognitive Scores at Baseline and Follow-up

DISCUSSION

In this longitudinal cohort, we observed significant cognitive decline following CTRT in patients with head and neck malignancies, as evidenced by declines in MoCA and MMSE scores. The nadir occurred at three months post-treatment, after which partial recovery ensued—but values remained statistically below baseline. This acute-to-subacute pattern mirrors findings in other populations such as nasopharyngeal carcinoma survivors, where early cognitive impairments persisted for months and were associated with temporal lobe radiation exposure [9].

Our results are in alignment with Iyizoba-Ebozue et al., who identified long-term neurocognitive deficits correlated with radiation dose to hippocampal and temporal structures [10]. Similarly, the longitudinal study by Zer et al. reported that over one-third of HNC survivors displayed neurocognitive deficits up to two years post-treatment.Bond et al. documented post-treatment domain-specific declines in a smaller cohort, reinforcing our observations. These data collectively suggest that CTRT confers a measurable cognitive cost in HNC survivors.

The mechanisms behind these deficits likely involve radiation-induced microvascular changes, hippocampal damage, and neuroinflammation, particularly in contexts involving temporal or skull base irradiation [11]. Additionally, cisplatin may contribute centrally through oxidative stress pathways. Systemic sequelae including fatigue, emotional distress, and nutritional deficits—common in HNC populations—may further compound cognitive vulnerability.

Clinically, diminished cognition can adversely affect functional independence, communication, and return-to-work outcomes, especially in HNC survivors already managing speech and swallowing impairments. Yet, cognitive dysfunction often remains under-detected in standard follow-ups. Screening tools like MoCA and MMSE are brief and could facilitate early identification. Interventions—including cognitive rehabilitation, psychosocial support, and consideration of radiotherapy techniques that spare critical neural structures—may mitigate long-term impairment.

Strengths of this study include its prospective design, repeated standardized assessments, and focus on a homogeneous CTRT cohort. Nonetheless, limitations include the relatively small sample size, single-centre scope, lack of a non-CTRT comparison arm, and limited psychometric depth of MoCA and MMSE. Follow-up duration of only 12 months may also preclude detection of late-delayed cognitive decline.

Future research should pursue larger, multicentre, long-term studies that integrate advanced neuroimaging, biomarkers of inflammation, and neuropsychological batteries. Randomized trials exploring hippocampal-sparing radiotherapy, pharmacological neuroprotection, and structured cognitive healthcare pathways are warranted to preserve neurocognitive outcomes in this growing survivor population.

CONCLUSION

In this prospective cohort of head and neck cancer patients undergoing concurrent chemoradiotherapy, significant cognitive decline was observed within the first 3 months post-treatment, with only partial recovery at 12 months. These findings underscore the importance of incorporating cognitive function assessment into routine oncology follow-up. Early recognition and intervention may help mitigate long-term neurocognitive morbidity and improve quality of survivorship. Larger studies are warranted to confirm these findings and explore preventive strategies.

REFERENCES

1. Voon NS, Rieken S, Schirmer M. Systematic Review of MRI Correlates of Cognitive Decline after Radiotherapy in Head and Neck Cancer. *J Clin Med*. 2021
2. Iyizoba-Ebozue Z, et al. Systematic Review: Neurocognitive Function following (Chemo)Radiotherapy in Head and Neck Cancers. *Radiother Oncol*. 2023;188:109863.
3. Zer A, et al. Longitudinal Neurocognitive Outcomes in Head and Neck Cancer Patients After Radiotherapy. *JAMA Otolaryngol Head Neck Surg*. 2018;144
4. Bond SM, et al. Neurocognitive Function in Patients with Head and Neck Cancer Undergoing Chemoradiation. *Support Care Cancer*. 2016;24(10):4433–4442.
5. Cheung MW, et al. Cognitive Function in Nasopharyngeal Carcinoma Post-Radiotherapy. *JAMA Neurol*. 2000;
6. Welsh LC, et al. Cognitive Function After Radiotherapy or Chemoradiotherapy for Head and Neck Cancer: A Review. *Clin Oncol*. 2011;
7. Wikipedia contributors. Radiation-induced cognitive decline. *Wikipedia*. 2024.
8. Wikipedia contributors. Post-chemotherapy cognitive impairment. *Wikipedia*. 2025.
9. McDowell LJ, et al. Cognitive Impairment in Long-term Nasopharyngeal Cancer Survivors. *Toxicology & Applied Pharmacology*. 2019;
10. Gan HK, et al. Cognitive Functioning After Radiotherapy or Chemoradiotherapy for H&N Cancer. *Int J Radiat Oncol Biol Phys*. 2011;81(1):126–134.
11. Schagen SB, et al. Chemotherapy-related cognitive impairment: mechanisms and management. *Ann Oncol*. 2019;30(12):1915–1924.