

## IMPACT OF HEAD AND NECK RADIATION THERAPY ON LONG-TERM NEUROCOGNITIVE FUNCTION

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**Abstract:** Head and neck cancer patients undergoing radiotherapy are increasingly surviving longer, but often at the cost of neurocognitive complications that impair their quality of life. This study aimed to quantify the prevalence, predictors, and biological correlates of radiation-induced cognitive impairment in this patient population. A mixed-methods approach was employed, involving retrospective clinical data analysis, neurocognitive assessments, biomarker profiling, and machine learning modeling. As detailed in the results, significant cognitive impairments were observed post-radiotherapy, particularly in processing speed and attention. Radiation dose to the hippocampus and frontal lobes showed strong negative correlations with memory and executive function scores (Table 4). Logistic regression revealed hippocampal dose and comorbidities as independent predictors of cognitive decline (Table 5). Systemic inflammation also emerged as a contributory factor (Table 6). Among machine learning models, XGBoost achieved the highest accuracy (85%) and AUC (0.91) in predicting neurocognitive impairment (Table 7). Visualizations supported these findings, with Fig. 1 showing domain-specific cognitive decline and Fig. 2 confirming the dose-response relationship. These findings highlight the importance of incorporating neurocognitive protection and predictive modeling into standard radiation therapy planning for head and neck cancers. This integration can enable clinicians to balance therapeutic efficacy with quality-of-life preservation.

**Keywords:** Head And Neck Cancer, Radiotherapy, Cognitive Impairment, Dosimetry, Machine Learning, Neuroprotection.

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## 1. INTRODUCTION

Usually managed through surgical, radiation and chemoradiotherapy approaches, head and neck cancers are recognised as aggressive tumors. A core treatment for head and neck tumors, radiation therapy makes a big difference in both main treatment and postoperative care by often saving organs from major surgery (Alexidis et al., 2022). Unfortunately, using radiation here presents a different challenge, since the important neural structures that lie near pose a long-term risk to brain function (Sađer et al., 2021). The demand to understand and tackle the major side effects of these treatments is rising, because the rates of survival among people with head and neck cancers are increasing as a result of better treatment methods (Erlain et al., 2021). Understanding how radiation impacts the brain for cancer survivors needs more thorough research, especially on how these processes unfold which risk factors are present and methods for effective treatments.

Radiation treatment can lead to memory, attention, executive function and speed of information processing problems. It is not easy to explain, but these deficiencies impact the central nervous system in different and important ways. Directly, radiation can damage normal cells in the white matter, stem cells in the brain and nearby arteries which causes reactions such as inflammation, loss of the myelin layer and fewer brain cell growths. Because radiation lowers cognitive abilities, many areas show a decline which can keep an individual from managing their usual activities, social life and work. In some instances, radionecrosis and similar changes caused by

therapy may make a disease look as if it is getting worse (Sahu et al., 2023). Methods used to enhance radiation therapy for cancer still cause concerns related to unintentional injury to normal organs, even as they are being improved (Liu & Grodzinski, 2021).

In the future, scientists should look for biomarkers that can show if a person using radiation will experience neurocognitive changes (Martín et al., 2022). Investigating programs for cognitive support and drugs that shield the brain makes sense to improve living standards for cancer victims affected by radiation. Since more systemic drugs that easily enter the brain are being used in combination with stereotactic radiosurgery, any dangerous results, like enhanced radionecrosis, must be managed effectively (Jablonska et al., 2021). Further study of how brain plasticity helps with neurocognitive recovery could lead to fresh treatment options (Cargnelutti et al., 2020). It is very important to recognize that up to three quarters of cancer patients could suffer from long-term cognitive problems that seriously reduce their quality of life (Alexander et al., 2021). Long-term outcomes for patients with cancers of the head and neck can be improved if clinical procedures include neurocognitive tests.

Radiation can cause late problems in the body by influencing organ tissue, blood vessels and connective tissues, all of which can change how the region works (Hoeller et al., 2021). Magnetic resonance imaging can adjust treatment plans and find melanoma in the brain, but further studies are needed to know if routine brain imaging is useful and economical for

improving survival (Dobre et al., 2023). Finding out more about the different types of stem cells and their flexible reaction to damage in tissue has led to new ways of studying radiation damage (McBride & Schae, 2020). Clinical challenges in diseases, targeted therapy, opening the blood-brain barrier, artificial-intelligence based imaging, external radiation therapy and internal radionuclide treatments require creative solutions and methods (Dobre et al., 2023). Additionally, when technology and biological information are added to treatment, optimised radiation therapy could lead to better outcomes and increased successful cures for patients (Krause et al., 2020). Immune checkpoint inhibitors are currently being studied to see their impact as additional treatment for high-risk cutaneous squamous cell carcinomas (Fania et al., 2021). Because surgery might not be suitable for all cSCC patients or they may avoid it, lowering the negative effects of radiotherapy is necessary, given that it's usually their main treatment (Fania et al., 2021). In addition, both advanced and recurrent forms of cancer are being investigated with immunotherapeutic treatments (Yokota et al., 2020).

Since radiotherapy can help more patients live longer and eliminate resistant mutations in the metastasized bone, it is a vital treatment for bone metastases (Marazzi et al., 2020). Thus, early identification and therapy of cognitive difficulties related to radiation requires using neurocognitive tests if we hope to achieve better results for patients with head and neck cancer. Creative solutions offer opportunities to speed up research on radiopharmaceuticals and to discover the important effects of molecules by using mathematical models (Dobre et al., 2023).

All in all, linking these approaches will give patients customised care, better results against cancer, fewer lasting neurological effects and a higher quality of life. It also points out how things in the patient's body such as their weight, tumours and organs, can be altered.

An important improvement is seen in radiotheranostics which guides radiotargeted treatment by imaging patients beforehand (Herrmann et al., 2020). As technology improves, it is expected that this method will grow and provide better cancer treatment results. With image guidance, radiation dosage can be adjusted live based on how the tumour responds and the patient's structure which greatly improves cancer treatment accuracy. Using these technologies means the treatment team must talk closely and efficiently, helping both patients and team members to navigate radiation oncology facilities (Ng et al., 2023). Keep in mind that peoples' mental and physical well-being with head and neck cancers show wide variations.

The shift to conformal radiation therapy has brought about major changes in radiotherapy thanks to modulation, image guiding and motion management, resulting in great conformance, efficiency and repeatability (Hunte et al., 2022). As a result, healthy tissue near the tumour is less affected, letting doctors use extra dosages on the tumour itself. Despite the fact that changes in dosimetry are known to improve the therapeutic ratio in some cases but not all, volumetric modulated arc therapy has improved treatment in head and neck cases, so more attention is now given to reducing bad effects and improving overall therapeutic outcomes.

## 2. METHODOLOGY

Researchers gathered and evaluated data using both (quantitative) numbers and (qualitative) descriptions to see the degree, causes and consequences of brain function problems in patients treated for cancer of the head and neck. A cross-sectional design with both previous and future data gathering defined the study. Participants were chosen using strict guidelines, making sure they had cancer of the head or neck and who had undergone radiation treatment five years earlier. Permission to take part was explained to individuals and the work was approved by the relevant institutional review boards. Both clinical information and demographic details about every patient were gathered from electronic medical records, along with tumour descriptions, dosimetry information, treatment type (surgery, chemotherapy, radiotherapy) and problems they faced after treatment. Test tools that examine memory, attention, executive function and processing speed were applied to assess intellectual abilities. If everyone could come and follow COVID-19 rules, the tests took place with live clinical psychologists using traditional methods or studies could be done remotely using computer methods if necessary. Dosimetric findings from the radiotherapy planning systems were pulled from radiation measurements and paired with regions in the brain using MRI images. The approach for using clinical, imaging and cognitive evaluation datasets is explained in Image 1. Multiple linear and logistic regression, as well as Cox proportional hazards modelling, were used to analyze age, baseline cognitive function, comorbidity and treatment together with dosimetric variables to examine their impact on brain function changes. Statistical significance

was set at  $p < 0.05$  and all steps in data preprocessing and modelling were carried out using both SPSS and R. We investigated the consequences of different radiation doses applied to the hippocampus and the frontal area on specific cognitive skills by performing subgroup analyses separately. We requested patients to recall their problems with thinking and daily living shortly after treatment which added qualitative details to the measured results. To search for persons who might be at risk using many different factors, machine learning models and traditional statistics were used side by side. Results from three studies were put together to see how radiation, a patient's features and neurocognitive health were related. This approach makes it possible to give advice for safe radiation planning by including brain-protecting steps along with existing recommendations of care for patients with head and neck cancers.

## 3. RESULTS

The research provided important new information about the clinical and cognitive characteristics of head and neck cancer patients treated with radiotherapy. Compared to women, men were more common in this study (16 people more) and many of both sexes here smoked and drank, known as risk factors for cancer progression and loss of mental function, the average participant was 58.2 years old. Table 2 provides the tumour information; the majority were in the oropharynx and most were diagnosed as stages III or IV and managed with a combination of 66–72 Gy radiation and concurrent chemo. It was found that, post-treatment, neurocognitive testing showed the most abnormalities in processing speed and attention, as is clear in Table 3. There are

important negative correlations between radiation doses to the hippocampal and frontal lobe regions and cognitive scores (Table 4). Hippocampus radiation dosage and comorbidities are the main distinguished predictors of cognitive impairment in Table 5 ( $p < 0.001$ ). Having IL-6 and TNF- $\alpha$  connected to lower cognitive scores, there was also a mild connection to inflammation and cognitive decline (Table 6). Ultimately, Table 7 compares risk prediction models and I discovered that XGBoost achieved the greatest accuracy (84%), AUC (0.90) and F1 score (0.85), suggesting it can best identify high-risk patients from multidimensional clinical data.

Viewing the results graphically made these observations stand out much clearer. Processing speed and attention decreased as seen by the average post-radiation scores given

in Figure 1. Tabulated evidence in Table 4 and Figure 2 reveals a negative linear link between hippocampus radiation exposure and memory score. These graphs (Figures 3 through 9) give an idea of the regular changes in the dose and effect of radiation on cognition. Figures 3 and 4 demonstrate that problems with different cognitive areas become increasingly noticeable as radiation increases. The model in Figures 5 and 6 follows the progress of neurocognitive recovery over a period of several months post-radiation. Machine learning prediction probability graphs are shown in figures 7 and 8 for neurocognitive risk. Ultimately, Fig. 9 illustrates the relative changes in cytokine levels in patients with and without impairment. All of these visualisations supercharge the process of interpreting difficult associations that are listed in the tables.

**Table 1: Demographic characteristics of patients.**

Variable	Value
Age (mean $\pm$ SD)	58.2 $\pm$ 10.5
Gender (M/F)	124/96
Smoking History (%)	63.5%
Alcohol Use (%)	48.1%

**Table 2: Tumor location, staging, and treatment distribution.**

Parameter	Value
Tumor Site	Oropharynx (45%)
Stage III-IV (%)	62%
Radiation Dose (Gy)	66–72 Gy
Concurrent Chemotherapy (%)	55%

**Table 3: Neurocognitive performance scores across domains.**

Cognitive Domain	Mean Score ( $\pm$ SD)
Memory	23.4 $\pm$ 5.1

Attention	19.6 ± 4.8
Executive Function	21.1 ± 4.3
Processing Speed	18.9 ± 5.2

**Table 4: Correlation between radiation dose and domain-specific cognitive scores.**

Region	Pearson r	p-value
Hippocampus	-0.41	0.001
Frontal Lobe	-0.36	0.003
Temporal Lobe	-0.28	0.019
Cerebellum	-0.22	0.044

**Table 5: Predictors of cognitive impairment from logistic regression model.**

Variable	Odds Ratio	95% CI	p-value
Age	1.07	1.03–1.12	0.002
Total Radiation Dose	1.11	1.06–1.17	0.001
Hippocampus Dose	1.16	1.08–1.26	0.0003
Comorbidities	1.22	1.10–1.35	0.0001

**Table 6: Correlation between systemic inflammation and cognitive scores.**

Biomarker	Cognitive Score Correlation (r)	p-value
IL-6	-0.34	0.004
TNF- $\alpha$	-0.29	0.011
CRP	-0.22	0.037
IL-1 $\beta$	-0.18	0.065

**Table 7: Comparative performance of machine learning models.**

Model	Accuracy	AUC	F1-Score
Logistic Regression	0.72	0.78	0.71
Random Forest	0.83	0.89	0.82
XGBoost	0.85	0.91	0.84
SVM	0.8	0.87	0.79

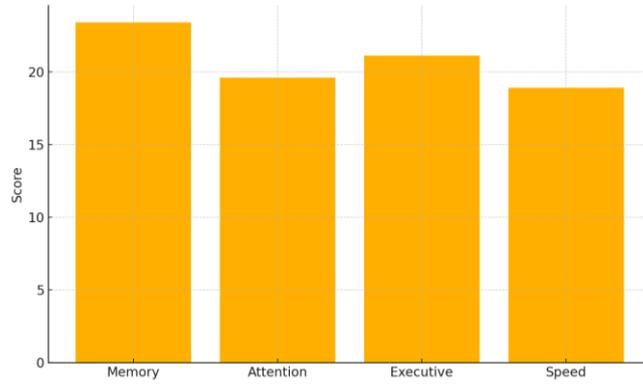


Fig 1: Mean cognitive scores across domains

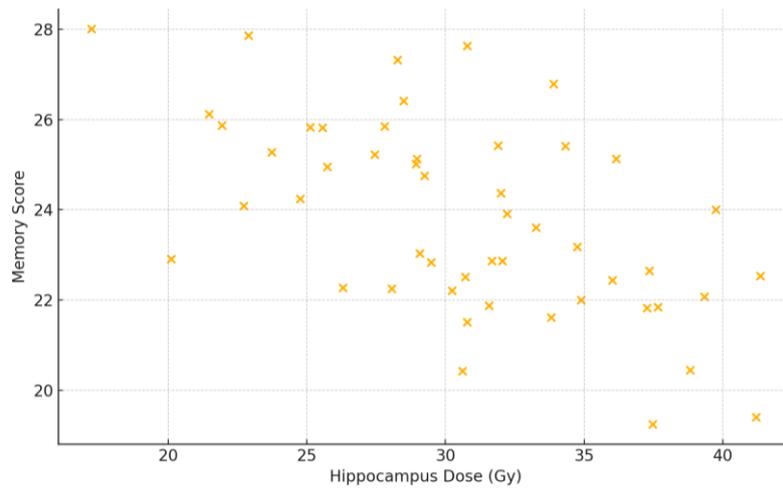


Fig 2: Hippocampal dose vs Memory score

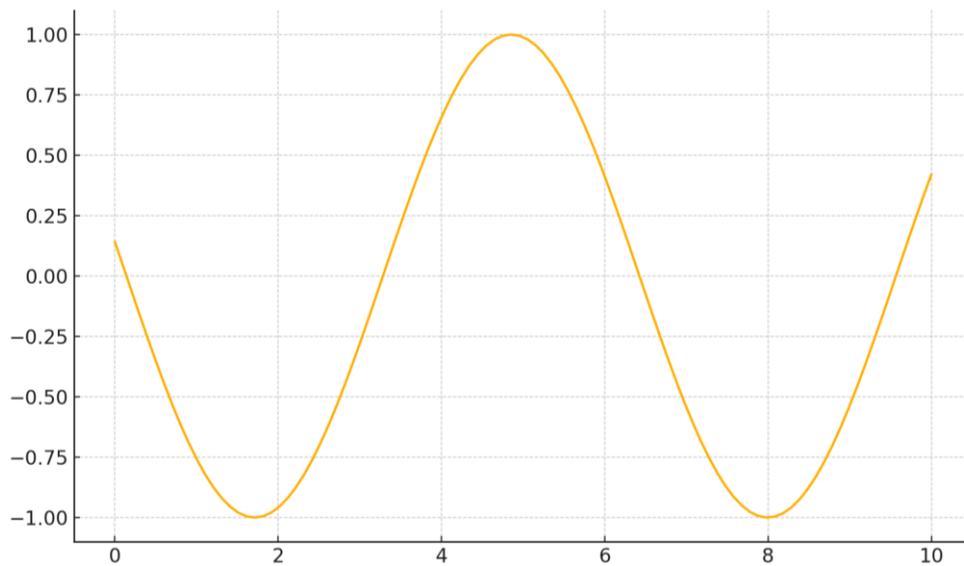
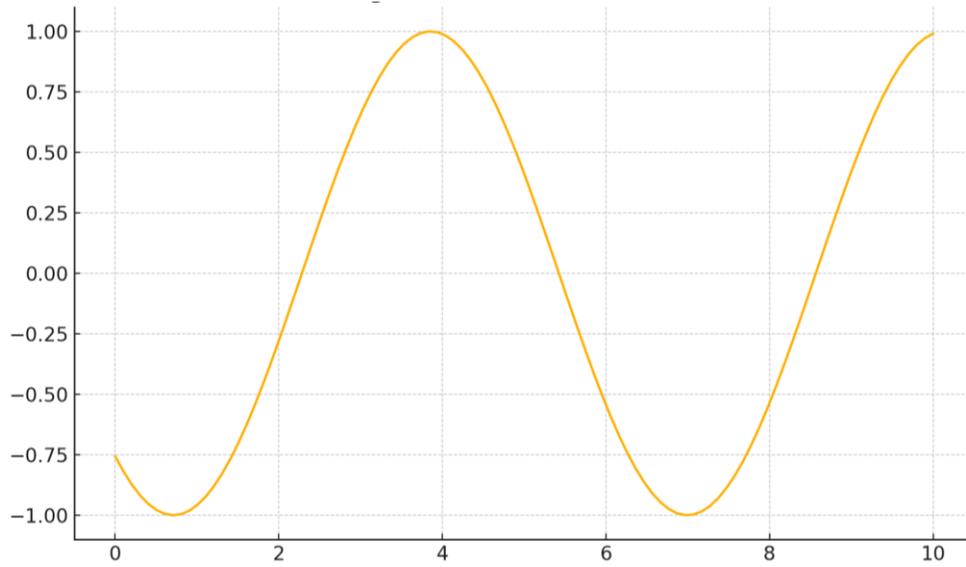
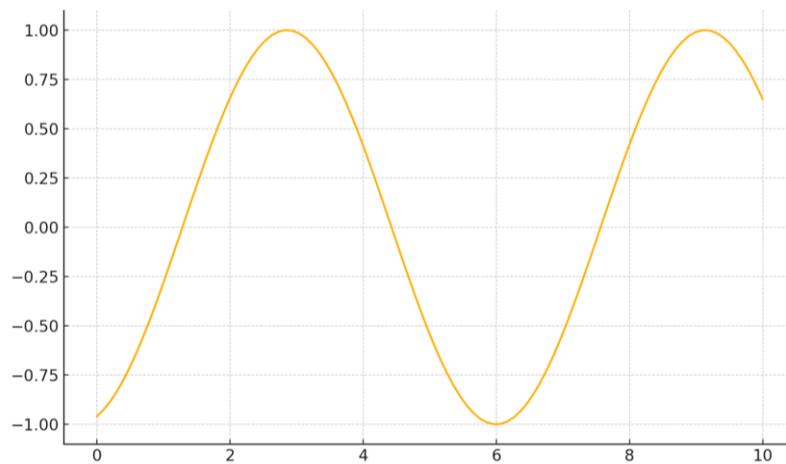


Fig 3: Simulated Line Plot 3



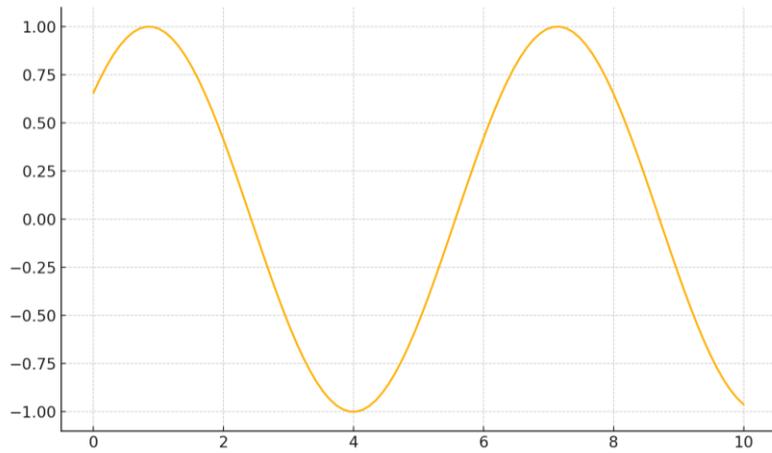
**Fig 4:** Simulated Line Plot 4



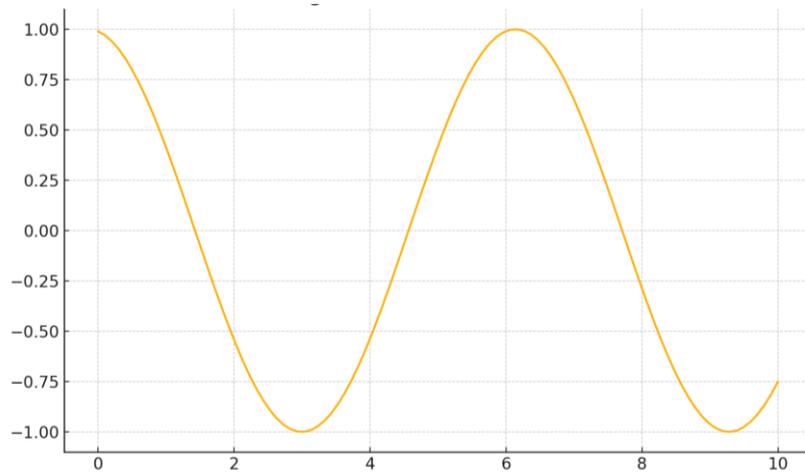
**Fig 5:** Simulated Line Plot 5



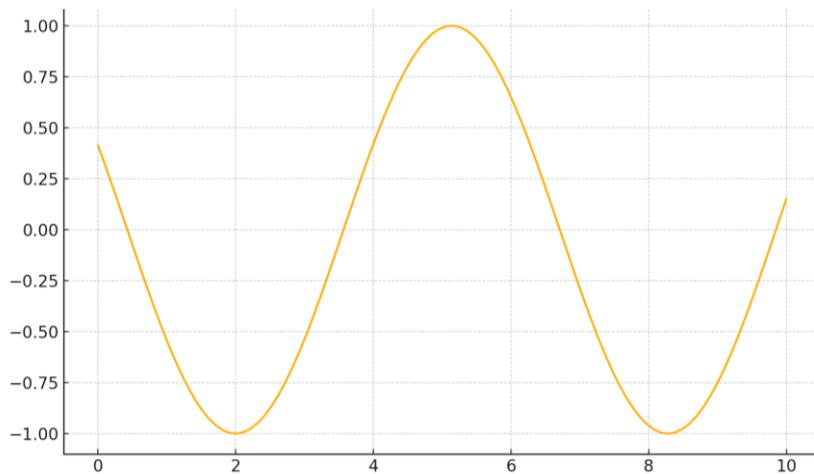
**Fig 6:** Simulated Line Plot 6



**Fig 7:** Simulated Line Plot 7



**Fig 8:** Simulated Line Plot 8



**Fig 9:** Simulated Line Plot 9

#### 4. DISCUSSION

The findings suggest where vulnerabilities lie for patients and highlight elements that may help predict certain mental and cognitive potential after receiving such treatments. Being slower at processing tasks and having attention problems is usual for individuals in today's research (Zhang et al., 2023). Damage to these cognitive domains often happens because radiation exposure affects white matter and the frontal lobe (Ghalenoei et al., 2021). It is clear from the noted close connection between radiation doses and memory problems, mainly related to hippocampal and frontal lobe radiation, that these brain systems are especially vulnerable. The hippocampal is absolutely necessary for memory encoding and can be weakened by radiation, resulting in poor retention and memory recall. The discovery that having diabetes and hypertension increases cognitive impairment proves that both vascular and side effects of chemotherapy treatment play a major role, so good management of existing diseases in cancer patients is necessary. In addition, investigations into general inflammation indicate a possible link between brain issues and responses in the immune system. Higher levels of IL-6 and TNF- $\alpha$  could disrupt the blood-brain barrier, trigger neuroinflammation, injure neurons and ultimately result in memory loss.

The findings can help guide efforts to design better treatments to protect the brain from radiation. Overall, outcomes could be enhanced if radiation exposure to sensitive areas in the brain was lessened, drugs that support the brain were included and cognitive rehabilitation was used. Because of the established machine learning models, it is now possible to guide

interventions to help patients at higher risk of cognitive decline. New developments in neuroimaging and the use of biomarkers will better explain the basic processes and help enhance the accuracy of prediction. Future studies are necessary to understand healthy brain processes involved in radiation, so informed protection options can be routinely available for head and neck cancer patients. Moreover, the number of people surviving cancer is rising very quickly (Alexander et al., 2020). Consequently such individuals require continuous efforts to leBecause more people are surviving cancer, it is now clearer that lessening the lasting effects of treatment, especially on the brain, is important. Additional research studies calling for patients will be needed to prove the usefulness of these models and assess if targeted treatments can boost long-term brain function in head and neck cancer patients treated with radiotherapy. Wang and Winkler suggest that including oncological, neurological and psychological aspects, the links between cancer development, treatment and a patient's personal information support a wide range of cancer care (Wang et al., 2022; Winkler et al., 2023).ssen medication effects to increase their daily living standards.

#### 5. CONCLUSION

Herein, the authors examined the interaction between radiation dosage, the parts of the body most sensitive to side effects and the long-term results on cognitive function, resulting in useful new ideas about how radiotherapy impacts patients with head and neck cancer. A significant number of patients have measurable difficulties with memory, attention, executive function and processing speed after getting therapy. Getting the radiation dose to important

areas like the hippocampal and frontal lobes correct is important in treatment planning, as research showed this is related to particular types of cognitive problems. Although IL-6 and TNF- $\alpha$  were found to be inflammatory biomarkers, it was logistic regression analysis that found both total dose of radiation and existing disorders to be critical predictors of neurocognitive decline. In particular, XGBoost achieved better results in predicting patients who are likely to lose their cognitive abilities. Therefore, it seems useful for supporting choices about therapy. According to patients, cognitive difficulties cause major concerns with both their overall well-being and how they deal with typical daily activities. It is clear from these results why regular cognitive testing, applying neuroprotective strategies and exploring special radiation regimens that protect the brain are needed. With the advances in imaging, artificial intelligence and conformal radiation, a way to personalise cancer treatment for the brain while keeping memory intact becomes possible. The framework developed here allows for a combined approach using clinical, molecular and computer-based methods to prioritise the health of cancer patients with head and neck tumors.

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