Original Research Article

Neurocognitive Function after (Chemo)-Radiotherapy for Head and Neck Cancer – Prevalent Study

Haripriya K[1], Sivagnanam Balaji[2*], G. Selavalakshmi[3], Vasanth Christopher[4]

[1]MD RT Lecturer, Department of Radiation Oncology, Cancer Institute, Adyar, Chennai, Tamil Nadu, India
[2]Senior Assistant Professor, Department of Radiation Oncology, Madras Medical College, Tamil Nadu, India
[3]Professor, Cancer Institute, Adyar, Chennai, Tamil Nadu, India
[4]Assistant Professor, Department of Radiation Oncology, Cancer Institute, Adyar, Chennai, Tamil Nadu, India
[*]Corresponding author email: **sriramchristopher@gmail.com**

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Abstract

Background: The head and neck malignancy is fourth most common cancer seen worldwide and causes a trend of incidence is increasing, and occur in part due to the epidemic of infection seen in high- risk strains of the human papilloma virus.
Aim: To assess and understand impact of chemo/radiotherapy in head neck cancer on Neurocognitive function, and to consider what measures can be taken to minimize treatment-related neurotoxicity.
Materials and methods: Neurocognitive function had been assessed with NIMHANS Neuropsychological battery. Patients who received chemoradiation in head and neck cancers had been studied in two groups, one as study arm and other as control arm. Study had been done exclusively for IMRT planning technique. Study Arm contained patients who received dose to hippocampal region, e.g. in nasopharynx, hypopharynx, oropharynx, hard palate, supraglottic larynx. The control arm was the patients who didn't receive dose to hippocampal region.
Results: On assessment for each individual based on the study group and control group, study group showed variation in cognition when compared to control group. Nearly on comparison cognition impairment was about 63% in study group whereas there was no much variation in control group.

Conclusion: This study had suggested that there is impairment in cognition of those patients, receiving radiation in IMRT technique.

Key words

Neurocognitive Function, Chemotherapy, Radiotherapy, Head and neck cancer.

Introduction

The head and neck malignancy is fourth most common cancer seen worldwide and causes a trend of incidence is increasing, and occur in part due to the epidemic of infection seen in high- risk strains of the human papilloma virus. The changing trend of incidence of HNC seen in the last thirty years in Western countries that has resulted in more cohort of younger patients presenting early with potentially treatable disease. They tend to cause changes have occurred mainly along the same time as major technological advancement in the delivery of radical treatment for HNC, that have the potential to improve the patient outcomes early [1].

In two-thirds of patients seen in HNC usually present with locally advanced stage without evidence of distant metastases and are amenable to treat with multimodality locoregional therapy. A multimodality combination of surgery, radiotherapy and chemotherapy is useful attempt to eradicate disease while trying to preserving organ function.

Radiotherapy plays a pivotal role in the management of the HNC and most people with HNC will receive radiotherapy treatment along with or without induction regimen chemotherapy or concomitant chemotherapy.

The disability and morbidity associated with radiotherapy to the head and neck are due to the irradiation of along with the normal tissues and organs surrounding the target tumor volume. As primary tumor and associated cervical lymph node metastases, often try to lie in close proximity to the brain and other neural structures, a portion of the volume of these vital organs inevitably lies along in the path of radiation beams used to deliver radiotherapy [2].

A typical radical radiotherapy plan for HNC inevitably used to delivers some radiation dose to the vital CNS and particularly to the following brain regions: basal frontal lobes, temporal lobes, olfactory bulbs, pituitary, hypothalamus, cerebellum and brainstem and Depends on the site of the primary tumor, radical radiotherapy for HNC may expose these vital brain structures to radiation doses close to their tolerances.

The CNS radiotherapy tolerance doses which are used to constrain intensity-modulated radiotherapy (IMRT) planning related to the risk of necrosis of tissue rather than to any lesser, but nevertheless still potentially clinically significant, types of tissue injury. In particular, existing CNS radiotherapy tolerance doses do not address the risk of radiotherapy-induced impairment of neurocognitive function (NCF), which must be a long recognized and potentially debilitating sequel to brain irradiation [3].

Materials and methods

Patients who received chemoradiation in head and neck cancers had been studied in two groups, one as study arm and other as control arm. Study had been done exclusively for IMRT planning technique. Study arm contained patients who received dose to hippocampal region, e.g. in nasopharynx, hypopharynx, oropharynx, hard palate, supraglottic larynx. The control arm was the patients who didn't receive dose to hippocampal region, e.g. tongue, cheek, floor of mouth, larynx. NIMHANS neuropsychological battery had been used to assess the performance for each individual.

Inclusion criteria:
Disease characteristics:

- Histological proven head and neck cancers of any histology (squamous cell carcinoma, adenocarcinoma and neuroendocrine carcinoma).
- Locally advanced head and neck cancers of TNM stage I- IVA were included.

Patient characteristics:

- Age 20-60 years
- Both sexes
- Stage I - IV A- Radical treatment
- Site- Oral cavity, orophraynx, nasopharynx, hypopharynx, larynx.
- Educational status – 6th and above.
- Performance status - ECOG 0,1 and 2
- No metastatic disease

Exclusion criteria:

Disease characteristics:

- Disease with metastatic spread to distant organs.
- Recurrent disease either after radiation or surgery is also excluded.
- Brain tumors.

Patient characteristics:

- No psychiatric or addictive disorders or other conditions that would preclude the patient from meeting the study requirements.
- Educational status – below 6th standard.
- Patients presenting with previous history of other malignancies, who received high dose chemotherapy or radiation are also excluded.
- Palliative treatment.

Results

Neurocognitive function had been assessed in two groups, each group 11 patients had studied completely based on NIMHANS neuropsychological battery. Assessment had been made before the start of treatment and another assessment had been made after completion of chemoradiation approximately after 6 weeks from end of treatment. On assessment for each individual based on the study group and control group, study group showed variation in cognition when compared to control group. Nearly on comparison cognition impairment was about 63% in study group whereas there was no much variation in control group. Dose to hippocampus varies for each site depending on the site and extension of the disease status and theses patients received >= 11 Gy.

In this randomized prospective study assessment of neurocognitive is performed by comparing with the 40 patients who was treated with IMRT (with Cisplatin based Chemotherapy) during the same period. Study arm contained patients who received dose to hippocampal region, e.g. in nasopharynx, hypopharynx, oropharynx, supraglottic larynx. The control arm was the patients who didn't receive dose to hippocampal region, e.g. tongue, cheek, floor of mouth, larynx. NIMHANS neuropsychological battery had been used to assess the performance for each individual.

40 Patients those who met both the inclusion and exclusion criteria, as mentioned above, were allowed for this study after obtaining their written informed consent. Each patient had been assessed with NIMHANS neuropsychological battery before the start of treatment and 2 months after the end of treatment. Each test was explained clearly in detail before the start process and based on timing basis the results were calculated. Here the hippocampus had been contoured and dose receiving to hippocampal were have been studied and analyzed. The results were analysed as per **Table – 1 to 5**.

Discussion

The neuropsychological tests used in our study have taken from the "NIMHANS neuropsychological battery". The battery system consists of 21 different neuropsychological subtests. It was originally developed by different authors and was standardized in the Indian population by "Rao, Subbakrishna, and Gopukumar "(2004) [1]. The battery are extensively used in research methodology on neuropsychological performances of a wide

variety of groups involving the normal individuals and clinical populations, and hence has proven validity and applicability [1].

The different areas of functions covered in the test battery are: "attention and concentration; motor speed; executive functions such as planning ability, category fluency, phonemic fluency, working memory, set shifting and response inhibition, verbal learning and memory; visual learning and memory; expressive and receptive speech; visuo- constructive ability; and focal signs" [2].

Table – 1: Details of patients included in the study arm (arm-a): hippocampus not spared.

Site	Hypo- pharynx	Oro- pharynx	Supra glottis larynx	Naso- pharynx
No. Patients	6	6	4	4
STAGE	II -IVA	II-IVA	II-IVA	III-IV
RT DOSE	60Gy	60-66Gy	66Gy	66Gy
HIPPPO	12.77Gy	12.89Gy	13.49Gy	14.25Gy

Table – 2: Details of patients included in the control arm (arm-b): hippocampus spared.

Site	Tongue	Buccal mucosa	Lip	Gingivum
No. Patients	8	6	3	3
STAGE	II -IVA	II-IVA	III-IVA	III-IV
RT DOSE	60-66Gy	60-66Gy	60Gy	60Gy
HIPPPO	1O.63Gy	10.26Gy	8.76Gy	9.67Gy

Table – 3: Details of target volume and organ at risk.

Site	Hippocampus not spared	Hippocampus spared
Target volume	Primary and nodal regions.	Primary and nodal regions.
Total dose	60-66Gy	60-66Gy
Organ at risk	Spinal cord, Parotids, Brainstem.	Spinal cord, Parotids, Brainstem.

From this neuropsychological test battery, the following eight tests were used in the present investigation. In the study 16 subsets of test are used. Each test are been explained in detail to the patient before they perform the tasks and mostly seen associated only with memory function. The different test include verbal, for speed, attention, visual, concept formation. These tests are performed at start of treatment and 6 weeks after end of treatment [3].

Different subsets of tests used for assessing:

1. Test of speed- Digital Symbol Substitution Test.
2. Test of attention –
   a. Color Trails Test
   b. Digit Vigilance Test
   c. Triads Test
3. Test of executive function-
   a. COWA Test
   b. Animal names Test
   c. Design Fluency Test
   d. N Black test
   e. Tower of London
   f. Wisconsin Card Sorting Test g. Stroop Test
4. Test of Comprehension –
   a. Token Test
5. Tests of Learning and Memory –
   a. Auditory Verbal Learning Test
   b. Logical Memory Test
   c. Complex Figure Test
   d. Design Learning Test

Conclusion

This study had suggested that there is impairment in cognition of those patients, receiving radiation in IMRT technique. Dose to hippocampus region plays an important factor in determining the

memory function of an individual. Sparing of hippocampal region is necessary and need to be considered as organ at risk for each individual.

References

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Table – 4: Hippocampus not spared.

Tests		HIPPOCAMPUS NOT - SPARED			
		Pre		Post	
		Score	Percentile	Score	Percentile
Digit Symbol Substitution Test		534	15-18	604	8
Color Trails Test	1	58	88-91	127	9-12
	2	158	72	294	7-9
Digit Vigilance Test	1	979	13-15	1114	7-9
	2	4	95	97	<2
Triads Test	1	12	53	10	47
	2	10		10	
COWA Test		5.66	30-40	NA	NA
Animal Names Test		8	10 TO 15	NA	NA
Design Fluency Test	1	5	70	8	60-70
	2	2	5	2	5
N Back Tests	1	5	40	6	25
	2	3	20	6	10
Tower of London Test	1	2	100	2	100
	2	3	100	3	100
	3	2	26.34	3	66-100
	4	0	0	2	65
Wisconsin Card Sorting Test		12	20	4	40 -75
Stroop Test		163	46-49	NA	NA
Token Test		34	40-50	32	40
Logical Memory Test		8	25-30	2	5
Complex Figure Test	C	29	30-35	6	30-35
	IR	18	25-30	3	7
	DR	17	40	1	3
Design Learning Test		26	80-85	10	50

Table – 5: Hippocampus spared.

Tests		HIPPOCAMPUS SPARED			
		Pre		Post	
		Score	Percentile	Score	Percentile
Digit Symbol Substitution Test		512	21-24	489	32
Color Trails Test	1	161	12-Oct	102	37
	2	288	15	233	32
Digit Vigilance Test	1	NA	NA	NA	NA
	2	NA	NA	NA	NA
Triads Test	1	14	81	11	11
	2	12		9	
COWA Test		NA	NA	NA	NA
Animal Names Test		NA	NA	NA	NA
Design Fluency Test	1	10	40	10	40
	2	8	25-40	6	15
N Back Tests	1	7	25-30	9	80-95
	2	6	20-50	9	85-90
Tower of London Test	1	2	100	2	100
	2	4	85	2	100
	3	4	100	4	100
	4	7	52.57	12	8
Wisconsin Card Sorting Test		3	15	5	2
Stroop Test		NA	NA	NA	NA
Token Test		34	60-70	36	90-95
Logical Memory Test		7	20	4	10
Complex Figure Test	C	29	30-35	32	95
	IR	18	25-30	15	20
	DR	17	40	12	10
Design Learning Test		18	95	19	95