ORIGINAL RESEARCH

Effect of radiotherapy on cognitive functioning in nasopharyngeal carcinoma

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Abstract

Background: Radiotherapy is used in the treatment of nasopharyngeal carcinoma (NPC). The temporal lobes are at risk because they lie directly in the path of radiation beams; hence the effect of radiotherapy on cognitive functioning is a major concern.

Aims: To investigate the effect of radiotherapy on cognitive functioning in nasophyingeal carcinoma patients.

Materials & methods: A battery of neuropsychological tests consisting of attention, memory & learning and visuospatial functions was done on 20 patients before and after radiation therapy. Also computerized tomography (CT) was done in all cases. The results showed significant impairment in attention (p=0.0001), verbal fluency (p=0.05), visuospatial functions (p=0.005), and learning & memory.

Conclusions: Radiotherapy for nasopharyngeal carcinoma shows significant decline on cognitive functioning.

Keywords: nasopharyngeal; carcinoma; radiotherapy; cognitive deficits; memory; attention; visuospatial

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Introduction

Radiotherapy is considered to be effective with malignant tumors of the brain, scalp and surrounding structures (paranasal sinuses, nasopharynx, parotid glands, eye, orbit and lymph nodes of the cervical region) but there are several potential hazards. Some, like acute reaction and transient demyelination, are temporary [1], some like calcification of the basal ganglia and cerebral atrophy [2] are permanent but give rise to few symptoms; others like tumors and late cerebral radionecrosis, are serious and potentially fatal.

The risk of neuropsychological impairment in adults who undergo cerebral radiotherapy (RT) is well recognized but its incidence is unknown [3]. Reports

range from no change [4] to progressive dementia in up to 30-42% of patients [5]. The potential neurotoxicity of radiotherapy is of particular importance for low-grade gliomas because over one half of these patients are alive and free of progression, 5 years after diagnosis and also the management of these tumors is still controversial.

When radiation therapy is used in the treatment of NPC, the temporal lobes are at risk because they lie directly in the path of the radiation beams. Damage to the temporal lobes, particularly the medial aspects, is associated with memory loss. It follows therefore that radiation therapy for nasopharyngeal carcinoma has the attendant risk of memory loss as an enduring side effect. For instance, Parkin and Hunkin reported that memory disorder arising from late temporal lobe necrosis in a case of nasopharyngeal carcinoma, after radiotherapy treatment [6]. Also Woo et al in a study of 11 patients, who were given radiotherapy for nasopharyngeal carcinoma, found memory disturbance [7].

Lee et al. studied sixteen patients who had a NPC who were treated with radiation therapy [8]. The irradiated group was significantly poorer in overall IQ, non-verbal memory recall, and reported a substantially greater number of memory related complaints. Kuan-Yin Hsiao et al. prospective study evaluated effect of modulated radiotherapy on neurocognitive functions in nasopharyngeal carcinoma patients and found significant decline on memory, language, and fluency [9].

To summarize this review, it can be said that reports of radiotherapy induced cognitive impairment varies from 0 to 86% in published series [10]. Reports of neurological and psychological complications of central nervous system (CNS) radiotherapy have been inconsistent and range from no change to acute but reversible cognitive decline to progressive dementia [11].

Method

Sample

Twenty patients with nasopharyngeal carcinoma were studied in the out patient clinic of the department of radiotherapy. They were recruited into the study if they satisfied the following criteria: 1) Age between 20-50years, 2) Staging at initial diagnosis being stage I, II or III, 3) Patients with head and neck carcinoma, who are to receive a dose of 28 fractions / 6500 rad once daily for 5 days a week for 5½ weeks and without other modality of treatment, 4) A minimum education of 5th standard.

All patients were evaluated by an oncologist and clinical psychologist. They were diagnosed by according to TNM classification. All subjects received a standard neurological examination and a cranial computed tomography (CT) to identify any area of radiation necrosis or any evidence of intracranial lesion. Patients with history of psychosis, head injury, epilepsy, mental retardation, substance use and other neurological disorders were excluded from the study. Informed consent was obtained from all subjects. All the patients were assessed before single course radiotherapy and after radiotherapy on the battery of neuropsychological tests.

Neuropsychological assessment

All patients were assessed on a battery of neuropsychological tests before and after radiation by a clinical psychologist. Neuropsychological battery consisted of tests of attention: Trail making test – Part B (TMT), digit span test [12], digit symbol substitution test. Tests of memory: Rey complex figure test a test of non verbal memory recall where subjects were asked to copy a geometric figure and then to reproduce it after 30 min. Logical memory test [13] involved an immediate and a 30 min delayed recall of short prose passage. The score is obtained by the number of segment of story correctly recalled. Benton visual retention test [14] of 10 geometric figures where patients were immediately asked to reproduce score is one for each correct reproduction. Other executive tests like test of Verbal fluency involving category test of round and wooden things in one minute each. Series completion test [15] which assess concept formation ability. Block design test was also done to know patients visuospatial abilities. Rating scales used were Hamilton anxiety and depression scale (HADS).

Statistical analysis: Descriptive statistics and Wilcoxon matched-pairs signed-ranks test was done. A 2-tailed P-value of less than 0.05 was considered as significant on standard Statistical Package for Social Sciences (SPSS).

Results

20 head and neck carcinoma cases were studied, out

of them 11 were diagnosed as oral cavity carcinoma, 3 pharyngeal carcinoma and 6 laryngeal carcinoma in accordance with TNM classificatory system diagnosed by an oncologist. The majority of cases were oral cavity carcinoma. All the patients were in either IInd or IIIrd stages of carcinoma. The mean age of the patients in this sample was 52.1 years (± 7.28). Demographic data of all patients were married, majority were male patients and hindus. Most of the patients were having primary & secondary educational levels and working (Table 1).

Table 1: Demographic details.

Demographic Data	*No of Patients*	*Percentage (%)*
Oral cavity carcinoma	11	55
Pharyngeal carcinoma	3	15
Laryngeal carcinoma	6	30
Male	17	85
Female	3	15
Primary education	10	50
Secondary education	9	45
Graduate	1	5
Non professional	5	25
Farmer	6	30
Housewife	3	15
Family craft	3	15
Retired	2	10
Others	1	5

On the hospital anxiety and depression scale, there was no significant difference in the scores on the anxiety and depression subscales pre and post radiation (Table 2). On all tests of attention i.e. digit span test both digit forward and backward, digit symbol substitution test and trial making test - total time taken and the number of errors committed all scores shows a decline in performance after radiation indicating attentional deficits in patients (Table 3).

On verbal fluency test for wooden and round things, there was a significant difference in scores pre and post radiation. On series completion test which is a test of concept formation also shows significant difference pre and post radiation in both total time taken (P= 0.0015) and total score (P= 0.0004) (Table 4). On visuospatial functions i.e. block design test showed that the difference in scores was significant. There was no significant difference on complex figure copying test indicating that there are no deficits on visuomotor functions (Table 5). On verbal learning and memory test, though there was no significant difference pre and post radiation on Trial I, there was significant difference pre and post radiation on Trials II, III and IV. On Benton visual retention test as well as complex figure test, Trials I to IV, there was a significant difference in the median scores pre and post radiation indicating a decline in verbal & visual learning and memory after radiation all P<0.05 as shown in Table 6.

Summarizing the results it can be said that the mean age of the sample was 52.1 years, majority of them

Table 2: Anxiety and Depression Scores on HADS.

Variable	*Pre-radiation*		*Post-radiation*		*Wilcoxon test Z value*	*P value*
	Median	*Range*	*Median*	*Range*		
Anxiety	7.5	0-14	7	0-11	-0.470	0.637
Depression	8	0-16	6	0-9	-1.17	0.239

Table 3: Measures of Attention.

Variable	*Pre-radiation*		*Post-radiation*		*Wilcoxon test Z Value*	*P Value*
	Median	*Range*	*Median*	*Range*		
Digit span forward	5	4-6	4	3-5	-2.52	0.011 *
Digit span reversed	4	3-5	3	3-4	-2.13	0.033 *
Digit symbol substitution test	24	15-40	15	10-27	-3.88	0.0001*
Trial making test-time taken	414	207-525	482.5	325-625	-3.88	0.0001*
Trial making test- errors	4.5	0-8	8	4-9	-3.91	0.0001*

Table 4: Test of verbal fluency and concept formation.

Variable	*Pre-radiation*		*Post-radiation*		*Wilcoxon test Z value*	*P value*
	Median	*Range*	*Median*	*Range*		
Verbal fluency-wooden things	8	4-11	6	3-10	-3.45	0.0005*
Verbal fluency- round things	6	2-11	4	2-8	-3.29	0.001*
Series completion test- total time taken	462.5	159-192	585	230-1090	-3.17	0.0015 *
Series completion test –total score	7	2-8	4.5	1-8	-3.52	0.0004 *

Table 5: Test of visuospatial and visuomotor function.

Variable	*Pre-radiation*		*Post-radiation*		*Wilcoxon test Z value*	*P value*
	Median	*Range*	*Median*	*Range*		
Block design test	20	12-32	16	12-24	-3.5	0.0005*
Copy figure test	21	20-21	20	20-21	-1.12	0.262

Table 6: Tests of learning and memory.

Variable	*Pre-radiation*		*Post-radiation*		*Wilcoxon test Z value*	*P value*
	Median	*Range*	*Median*	*Range*		
Verbal Learning & memory test – Trial I	8	5-12	6.5	5-11	-1.72	0.0840
Verbal Learning & memory test – Trial II	10	5-15	8.5	5-13	-2.17	0.029*
Verbal Learning & memory test – Trial III	14	6-17	10	6-14	-3.10	0.001*
Verbal Learning & memory test – Trial IV	9	6-14	7	4-12	-3.33	0.0009 *
Visual learning & memory test- Trial I	8.75	6-16.5	7	5-11	-2.36	0.017*
Visual learning & memory test-Trial II	11	5-13	9	7-15	-2.39	0.016*
Visual learning & memory test-Trial III	13.5	8-20	10	7-17	-3.24	0.001*
Visual learning & memory test-Trail IV	10	5-20	7	4-17	-3.13	0.0017*
Benton visual retention test	6	3-9	4	2-7	-3.80	0.0001*

being male, having oral carcinoma and Hindu by religion, as well as married, literate and employed. On the neuropsychological battery except on the test of visuomotor functioning, there was significant decline in performance after radiotherapy on test of attention, verbal fluency, concept formation and verbal & visual learning and memory.

Discussion

According to many studies on NPC patients after radiation showed inconsistent results on the cognitive effects ranging from no deficits to significant deficits. The present study findings suggest significant impairment on attention, verbal fluency, visuospatial abilities and ability to acquire and recall after radiation therapy. In terms of anatomical correlations, the neuropsychological deficits were extensive and were not confined to functions of memory mediated by the temporal lobes. This may be due to vascular changes resulting to radiation injury which may not be confined to area of the radiation beams. As the majority of our patients had normal CT scans and had no correlation between cognitive functions and radiological abnormalities. However, it can be pointed out that CT may not detect subtle changes which neuropsychological tests can detect.

Effects of radiation on cognitive dysfunction was initially described in children with leukemia and various studies in adults of mild cases as a result of RadioNeurosis and also may be transient and probably related to radiation somnolence syndrome which can begin after the end of radiotherapy [16]. Perhaps another reason was that deficits were often not detected due to the limited opportunity that patients were tested on neuropsychological tests on cognitive functions.

Since some studies have indicated the presence of anxiety and depression in cancer patients and as these variables may influence cognitive performance the study sample was administered the hospital anxiety and depression scale (HADS) pre and post radiation [17]. On the HADS, the results indicated that there was no significant difference in the anxiety and depression subscale scores pre and post radiation. Also it may be noted that the mean scores on the anxiety subscale pre and post radiation were 7.4 and 7.1 respectively and the mean scores on the depression subscale pre and post radiation were 7 and 6.5 respectively. In accordance with the results of present study Armstrong et al. also found no significant difference in anxiety and depression scores pre and post CNS radiation [18].

The study shows significant decline in tests of attention, verbal fluency and concept formation, visuopatial and verbal memory functions after radiation these finding are in concordance with studies of Hochberg et al. [19] Twijnstra et al. [20] Parkin & Hunkin [6], Armstrong et al. [18] and Van Oosterhout et al. [21] found no disturbances on attentional skills subsequent to radiation therapy. These cognitive deficits are consistent with the pathologic change after radiation. Since the inferomedial region of both temporal lobes receives the highest dosage of radiation during radiotherapy, this area is believed to be the most susceptible to decline after radiotherapy. During the course of treatment, 1 anterior facial and 2 lateral parallel opposed wedged fields of photon beams are usually delivered to the tumor [22]. Therefore, the lateral part of temporal lobe is also along the radiation pathway causing disturbances in cognitive functions.

Overall, performance on neuropsychological test battery declined after radiation compared to baseline. As there was a significant decline in attention, ideational fluency, abstraction, visuospatial functions and learning and memory, it can be said that there was a global deterioration in cognitive functioning after radiation. Poorer performance was seen in tests assessing frontal (digit span test, trial making test, ideational fluency test, series completion test) temporal (verbal learning and memory test, benton visual retention test, complex figure test) and parietal (block design test) lobe functions, indicating a global decline in cognitive functioning. Hence, the results of the study validate the hypothesis that there will be a significant difference in cognitive functioning pre and post radiation. However, it should be noted that the global cognitive decline is not severe, but low grade, and only long term follow-up and periodic neuropsychological assessment will show whether the decline is reversible are not.

According to Asai et al. the elderly appear to be more susceptible to radiation induced atrophy and ultimately dementia [23]. Among the mechanisms proposed to account for the effects of radiation the most widely accepted hypothesis is one of vascular injury, which suggests that, the bulk of the injury from radiation therapy occurs to small and medium sized blood vessels of the brain. Laukkanen et al. report older age and modest educational level of their study sample has preexisting factors that may have contributed to the cognitive decline seen in their patients, following radiation [24]. In the present study, the older age of the sample by rendering it more vulnerable to the effects of radiation, coupled with the modest educational level, may have been factors along with radiotherapy, which could have contributed to the cognitive decline.

Limitations

1) The findings of the study can only be regarded as tentative because the sample size is small, 2) The mean ages of the sample was 52.1 years and as older people are more vulnerable to the effects of radiation, this may have influenced the findings, 3) The lack of normal control group (patients who do not have primaries and secondary head & neck carcinoma) for comparing pre radiation baseline scores was a drawback. Because the sample was predominantly male (85%) the question of generalisability of these findings to females could not be answered adequately. If an equal number of women were included, comparisons have been possible.

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Conflict of interest

The authors declare no conflict of interest.

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