ORIGINAL CONTRIBUTION

Cognitive Function of Patients With Nasopharyngeal Carcinoma With and Without Temporal Lobe Radionecrosis

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Background: Radiotherapy is the primary treatment for nasopharyngeal carcinoma, and temporal lobe necrosis is observed in about 7% of patients after radiotherapy. Although some studies reported that these patients demonstrated cognitive impairment after radiotherapy, it is still unclear if the cognitive deficits are related to the radiation exposure or the radiation-induced necrosis.

Objective: To compare the cognitive function of patients with and without temporal lobe necrosis after radiotherapy for nasopharyngeal carcinoma.

Methods: A comprehensive neuropsychological battery was administered to 53 patients with nasopharyngeal carcinoma who had completed their radiotherapy at least 1 year previously. As evidenced by magnetic resonance imaging, 31 patients developed necrosis after treatment. Thirty-one age- and education-matched individuals were recruited as normal control subjects.

Results: Whereas the performance of patients without temporal lobe necrosis was similar to that of normal control subjects, patients with temporal lobe necrosis demonstrated significant impairment on tests of verbal ($P<.001$) and visual memory (range, $P<.001$ to $P=.03$), language (range, $P<.001$ to $P=.01$), motor ability ($P=.02$), planning ($P=.02$), cognitive ability ($P=.007$), and abstract thinking (range, $P=.009$ to $P=.04$). However, the performance of patients with necrosis on tests of general intelligence (range, $P=.08$ to $P=.15$), attention (range, $P=.06$ to $P=.55$), and visual abilities (range, $P=.06$ to $P=.47$) was not significantly different from that of normal control subjects and patients without necrosis.

Conclusions: Radiotherapy for nasopharyngeal carcinoma seemed to have adverse but insignificant effects on the cognitive functions of the patients. However, for patients who developed temporal lobe necrosis after radiotherapy, memory, language, motor ability, and executive functions were significantly impaired, although their general intelligence remained relatively intact.

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WITH AN estimated incidence rate of 10 to 30 cases per 100 000 persons, nasopharyngeal carcinoma (NPC) is diagnosed in about 1000 people every year in Hong Kong, China. Although chemotherapy is sometimes used, radiotherapy remains the main treatment for NPC. Although the tumor receives the highest dosage of radiation, normal brain tissues along the pathway and brain structures in proximity to the nasopharynx are within the target volume. It is documented that the brainstem, upper cervical spinal cord, cranial and cervical sympathetic nerves, and inferomedial parts of the temporal lobe are exposed to radiation.[1-3]

Radiation is known to have deleterious effects on the cognitive functions. Studies on children with leukemia and intracranial tumors, such as medulloblastoma and cerebellar astrocytoma, indicate that cranial radiation is associated with adverse neuropsychological effects, such as decline in general intelligence,[4-10] fine motor speed,[10] and attention and cognitive flexibility.[11] Radiation-induced cognitive deficits are also reported in adults. Patients receiving radiation for intracranial tumors show marked impairment in problem solving and spatial memory,[12] whereas patients with small cell lung cancer are impaired in memory, attention, and information processing speed after radiation.[13,14] Deficits in cognitive functioning are also found in patients with NPC after radiotherapy. That is, patients with NPC who had normal cranial computed tomography (CT) after radiotherapy demonstrated poorer verbal memory, visual memory, social comprehension, and nonverbal reasoning, as well as lower IQ scores.[15]

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SUBJECTS AND METHODS

SUBJECTS

Fifty-three patients with NPC voluntarily participated in this study. They were recruited from the Neurology Clinic of Queen Elizabeth Hospital in Hong Kong. The clinic comprised approximately 270 patients who attended regular follow-up visits because of complications after radiotherapy. Between 1968 and 1997, these patients had received a complete course of radiotherapy within 6 to 7 weeks. Normal control subjects comprised 31 age- and education-matched subjects who reported no history of head injury, neurological diseases, or alcoholism.

Of the 53 patients, 31 showed positive findings on MR imaging, with moderate to gross hypointensity in T1-weighted images and moderate to gross hyperintensity in T2-weighted images on both hemispheres, which indicated the presence of vasogenic edema or cysts. **Figure 1** illustrates an example of the T2-weighted MR images of a patient with bilateral TLN. The remaining 22 patients did not exhibit signs referable to the temporal lobe, resulting in negative findings on MR imaging.

There was no significant difference in terms of age ($F_{2,81}$=1.78; *P*=.18) and level of education ($F_{2,81}$=0.22; *P*=.81) among the 2 patient groups and the normal control subjects. In addition, no significant difference was found between patients with and without TLN in the mean total dosage (t_{46}=−0.29; *P*=.77) and dosage per fraction (t_{46}=0.43; *P*=.67) (**Table 1**).

NEUROPSYCHOLOGICAL ASSESSMENT

The neuropsychological tests were administered individually to each subject. The battery was delivered in 2 sessions within a month. Written informed consent was obtained from all subjects.

A Chinese version of the Wechsler Adult Intelligence Scale–Revised (WAIS-R)[30] was used to obtain the verbal, performance, and full-scale IQ scores. A Cantonese version of the Mini-Mental State Examination[31] was also used to determine global cognitive level and to screen out demented subjects.

Attention was assessed by the Color Trail Test Part I[32] and the digit symbol and digit span subtests of the WAIS-R.

The Hong Kong List Learning Test (HKLLT)[33] was used as a test of memory. It is a word-list test in which the subjects listened to a list of 16 two-character Chinese words 3 times. The subjects recalled as many words as possible immediately after each presentation and after 10-minute and 30-minute delays. A 32-item list for recognition consisting of words from the original list and 16 distracter items was read to the subjects after the 30-minute delay recall.

An adapted Chinese version of the logical memory subtest of the Wechsler Memory Scale–Revised (WMS-R)[34] was used. Apart from the regular administration, an adapted version of a recognition task[35] of 20 questions with 5 options related to 2 stories was developed locally.

The Brief Visual Memory Test–Revised (BVMT-R)[36] and the visual reproduction subtest of the WMS-R[34] were used to assess visual memory.

Expressive language ability was assessed by the Verbal Fluency Test, in which 4 categories (animals, vehicles, furniture, and fruits and vegetables) were used, and a short form of the Boston Naming Test,[37] in which the subjects were required to name 30 pictured objects selected from the full version. Verbal comprehension was evaluated by the information and comprehension subtests of the WAIS-R.

Visual ability was assessed by the copy trial of the visual reproduction subtest of WMS-R and block design subtest of the WAIS-R. A short form of the Facial Recognition Test[38] was used to evaluate facial recognition ability. The Grooved Pegboard Test[39] was used to assess visual motor coordination.

Planning and organization were evaluated by copy trial of the Rey-Osterrieth Complex Figure Test. Verbal concept formation was assessed by the similarities subtest of the WAIS-R, and the Concept Thinking and Common Knowledge Tests. In the Concept Thinking Test, subjects were asked to choose the correct meaning of 10 Chinese proverbs from 4 choices. The Common Knowledge Test consists of questions on 8 real-life situations, and the subjects were asked to choose the correct answer from 4 choices. The Color Trail Test Part II[26] was used to assess cognitive flexibility. The presence of perseveration was evaluated by the Five-Point Test.[40]

STATISTICAL ANALYSIS

Raw scores between the 3 groups were compared by analysis of variance (ANOVA), followed by Student-Newman-Keuls test with significance level of .05. Repeated-measures ANOVAs (group × trial) were conducted for analysis of data on memory tests.

Temporal lobe necrosis (TLN) is one of the major neurological complications after radiotherapy for NPC[2,3,16]; the incidence rate is about 7.3%, with a median latent interval of 6.7 years.[17] With the use of CT or magnetic resonance (MR) imaging, 2 distinctive manifestations of the necrosis are observed. In the early stage, TLN is manifested as fingerlike hypodense shadows that are associated with reactive white-matter edema. In some cases, these finger signs develop into cysts, which are shown as roundish hypodense shadows on CT and MR imaging.[1,18,19]

It is well known that damage to the medial part of the temporal lobe results in amnesia,[20-23] with a specific memory impairment profile. First, the memory impairment of patients with temporal lobe amnesia (TLA) is non–material specific in that patients show impairment in recalling both verbal and nonverbal materials.[23-27] Second, patients with TLA demonstrate a rapid rate of forgetting, ie, they lose the newly learned information relatively quickly.[28] Third, given that the memory impairment of patients with TLA is caused by an encoding problem, cues for retrieval such as recognition do not seem to facilitate their performance.[23,26] One purpose of the present study was to examine whether patients with temporal lobe necrosis manifest the memory profile of TLA.

Cognitive impairment associated with radionecrosis in patients with NPC and its relevance to amnesia have been explored in 2 studies, but their findings are somewhat inconsistent. In one study,[18] 11 patients with ei-

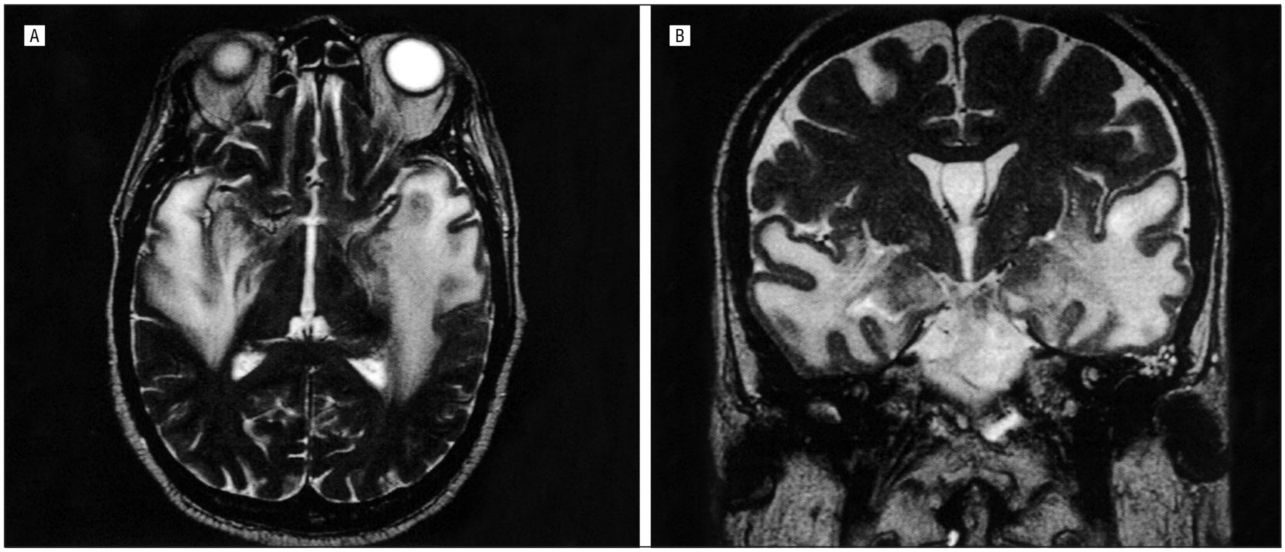

Figure 1. *A, Bilateral temporal lobe necrosis shown by magnetic resonance imaging. T2-weighted horizontal image of patient with nasopharyngeal carcinoma showing fingerlike edema on both sides of the temporal lobe. B, T2-weighted coronal magnetic resonance image of the same patient showing bilateral temporal lobe necrosis.*

Table 1. Demographic Information for Normal Control Subjects, Patients Without TLN, and Patients With TLN*

Variable	Normal Control Subjects (n = 31)	Patients Without TLN (n = 22)	Patients With TLN (n = 31)
Age, y	52.8 ± 12.0	52.0 ± 10.9	57.0 ± 9.4
Sex, No. M/F	19:12	13:9	25:6
Level of education, y	8.8 ± 4.7	9.5 ± 4.5	8.7 ± 4.5
Radiation treatment			
Total dosage, Gy	NA	58.1 ± 4.5	58.4 ± 4.5
Dosage per fraction, Gy	NA	2.8 ± 0.7	2.7 ± 0.7

**TLN indicates temporal lobe necrosis; NA, not applicable. All variables except sex are expressed as mean ± SD.*

ther unilateral or bilateral TLN identified by CT were examined. Only some of them demonstrated impaired memory, poor general knowledge, and social comprehension and showed deficits in the functions predominantly mediated by the frontal lobe, such as abstract thinking, problem solving, and verbal reasoning. In fact, 4 patients did not manifest amnesia, whereas 5 patients did not have cognitive dysfunction. A different cognitive profile related to radionecrosis was reported in a case study of a 34-year-old patient with bilateral temporal lobe lesions outside the hippocampus and memory-related limbic system as evidenced by MR imaging.[29] That patient demonstrated selective memory impairment on verbal but not visual materials, and there was no evidence of significant frontal lobe dysfunction, as assessed by the F, A, and S portions of the Word Fluency Test and by the Wisconsin Card-Sorting Test.

Thus, it remains to be determined whether radionecrosis resulting from radiotherapy causes other cognitive deficits in addition to memory impairment. Hence, another purpose of the present study was to examine the cognitive profile of patients with NPC after radiotherapy. In addition to general intelligence, memory, and executive function, we evaluated attention, language, visual perception, and construction and motor performances, which were not evaluated by previous studies.

Given that both radiation and radionecrosis are found to have deleterious effects on the cognitive functions of patients after radiotherapy for NPC, the present study also examined the neuropsychological sequelae after radiation on groups of patients with and without bilateral TLN identified by MR imaging. The goal was to examine the effects of radiation and radionecrosis on patients' cognitive functions.

RESULTS

COGNITIVE DEFICITS

Memory

The learning ability of the subjects was measured by their performance on the immediate recall trials on the HKLLT, logical memory and visual reproduction subtests of the WMS-R, and BVMT-R. The first 2 tests are verbal learning tests, while the latter 2 are visual learning ones. The percentages of possible total material recalled by the subjects on the 4 tests are presented in **Figure 2**, A. A repeated-measure ANOVA disclosed a significant group effect ($F_{2,77}=18.06$; $P<.001$), and the post hoc *t* tests showed that the patients with TLN performed significantly worse than the patients without TLN and the normal control subjects across the 4 memory tests. In addition, the interaction effect was not significant ($F_{6,231}=0.95$; $P=.46$), suggesting that the learning deficit of the patients with TLN is not material specific. Although the patients without TLN obtained lower scores than the normal control subjects, there was no significant difference between them.

The rate of forgetting was evaluated by comparing the total number of recalls on the last learning trial with that of the delayed recall trials of the HKLLT, logical

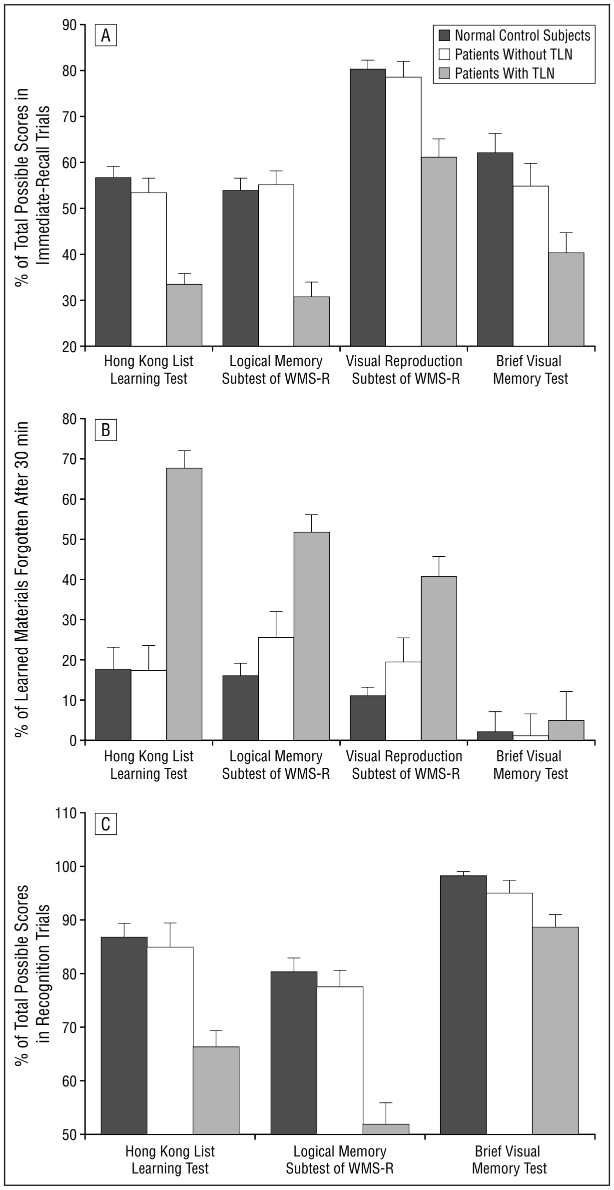

Figure 2. *Performance on tests of memory in terms of learning verbal and nonverbal materials (A), the rate of forgetting after 30 minutes (B), and the ability to recognize newly learned materials (C). Patients with temporal lobe necrosis (TLN), when compared with normal control subjects and patients without TLN, demonstrated impaired performance. WMS-R indicates Wechsler Memory Scale–Revised.*

memory and visual reproduction subtests of the WMS-R, and BVMT-R. Figure 2, B, shows that the patients with TLN lost significantly more information after 30 minutes than the patients without TLN and the normal control subjects ($F_{2,75}$=28.49; $P<.001$). The difference was greatest on the HKLLT but was nonsignificant on the BVMT-R. No significant difference between the patients without TLN and the normal control subjects was found.

A repeated-measure ANOVA on the subjects' performance on the recognition trials of the HKLLT, WMS-R logical memory, and BVMT-R disclosed a significant group effect ($F_{2,77}$=24.16; $P<.001$) and an interaction effect ($F_{4,154}$=4.74; P=.001). Figure 2, C, demonstrates that the patients with TLN recognized a significantly smaller percentage of total possible items than the patients without TLN and the normal control subjects, while the patients without TLN did not differ significantly from the normal control subjects ($F_{2,81}$=11.73; $P<.001$). A similar group difference was obtained on the logical memory subtest of the WMS-R ($F_{2,78}$=23.29; $P<.001$) and the BVMT-R ($F_{2,80}$=6.27; P=.003).

Overall, the patients with TLN demonstrated non–material-specific impairment of learning and memory and a rapid rate of forgetting. Given that their performances on the recognition and recall trials were consistent, the memory impairment of patients with TLN is most likely attributed to an encoding rather than a retrieval problem.

Table 2. Scores on Language, Motor Speed, and Executive Function*

Variables	Normal Control Subjects	Patients Without TLN	Patients With TLN
Language			
Boston Naming	25.3 ± 3.7	23.0 ± 4.3	19.5 ± 5.2†
Verbal Fluency	68.5 ± 15.0	60.8 ± 11.2	49.1 ± 15.3†
Information	17.7 ± 6.2	16.8 ± 5.6	12.2 ± 4.9†
Comprehension	18.1 ± 4.9	17.1 ± 4.5	14.4 ± 5.5‡
Motor			
Pegboard (right)	71.2 ± 12.6	77.8 ± 14.6	82.1 ± 17.3‡
Pegboard (left)	78.5 ± 10.3	84.7 ± 20.7	94.5 ± 30.8‡
Executive Function			
Rey-Osterrieth (copy)	27.2 ± 3.8	27.9 ± 4.1	24.9 ± 4.3§
Concept Thinking	7.1 ± 2.6	7.1 ± 2.3	5.0 ± 3.4†
Common Knowledge	7.7 ± 0.5	7.3 ± 1.2	7.1 ± 1.0‡
Color Trail 2	103.4 ± 39.7	111.9 ± 48.1	142.2 ± 56.1†
Similarities	15.5 ± 5.7	13.8 ± 6.2	10.9 ± 6.4‡

All values are reported as mean ± SD. No statistical difference was found between the patients without temporal lobe necrosis (TLN) and the normal control subjects.

†*Patients with TLN were significantly different from normal control subjects and patients without TLN (P<.01).*

‡*Patients with TLN were significantly different from normal control subjects (P<.05).*

§*Patients with TLN were significantly different from normal control subjects and patients without TLN (P<.05).*

Language

Table 2 shows that the patients with TLN scored significantly lower than the patients without TLN and the normal control subjects on the Boston Naming Test ($F_{2,80}$=13.04; $P<.001$), Verbal Fluency Test ($F_{2,76}$=13.60; $P<.001$), and information subtest ($F_{2,77}$=7.74; $P<.001$). On the comprehension subtest, the performance of the patients with TLN was significantly different from that of the normal control subjects ($F_{2,80}$=4.55; P=.01). There was no significant difference between the patients without TLN and the normal control subjects.

Motor Performance

The patients with TLN were significantly slower than the normal control subjects on fine motor speed for both right ($F_{2,77}$=4.06; $P<$=.02) and left ($F_{2,77}$=3.91; P=.02) hands. The motor speed of the patients without TLN was not different from that of the normal control subjects (Table 2).

Executive Function

The patients with TLN scored significantly lower than the patients without TLN and the normal control subjects on the copy trial of the Rey-Osterrieth Complex Figure Test ($F_{2,81}$=4.23; P=.02), Concept Thinking Test ($F_{2,79}$=5.00; P=.009), Common Knowledge Test ($F_{2,80}$=3.44; P=.04), and Color Trail Test Part II ($F_{2,79}$=5.29; P=.007). Group difference was also significant on the similarities subtest ($F_{2,80}$=4.31; P=.02), with the patients with TLN obtaining significantly lower scores than the normal control subjects (Table 2). The patients without TLN and the normal control subjects did not differ significantly.

RELATIVELY INTACT COGNITIVE ABILITIES

Performance of the patients with and without TLN on tests assessing general intelligence (the Mini-Mental State Examination and full-scale, verbal, and performance IQs), attention (the digit span and digit symbol subtests of the WAIS-R and the Color Trail Test Part I), visual abilities (the visual reproduction subtest copy trial, block design subtest, and Facial Recognition Test), and perseverative tendency (the Five-Point Test) was comparable with that of the normal control subjects (**Table 3**).

Table 3. Performance on General Intelligence, Attention, Visual Perception and Construction, and Perseveration Tests*

Variable	Normal Control Subjects	Patients Without TLN	Patients With TLN
General intelligence			
Full-scale IQ	95.2 ± 11.1	92.6 ± 12.8	89.5 ± 10.3
Verbal IQ	94.6 ± 13.7	95.0 ± 12.3	89.1 ± 9.7
Performance	94.1 ± 18.3	90.9 ± 14.6	90.7 ± 13.1
MMSE	28.4 ± 1.9	27.8 ± 2.1	27.2 ± 2.2
Attention			
Digit Span	17.2 ± 4.5	18.3 ± 4.6	16.9 ± 4.6
Digit Symbol	43.6 ± 14.6	41.1 ± 16.1	34.2 ± 16.6
Color Trail I	54.8 ± 16.2	59.2 ± 32.2	63.8 ± 25.7
Visual Abilities			
Visual reproduction (copy)	36.5 ± 3.5	36.6 ± 3.1	35.0 ± 3.6
Block design	24.7 ± 10.1	24.5 ± 8.7	21.9 ± 10.2
Facial recognition	45.2 ± 4.1	44.1 ± 5.8	42.2 ± 5.0
Perseveration			
Five-Point	2.9 ± 3.5	3.0 ± 5.2	4.5 ± 7.3

**TLN indicates temporal lobe necrosis; MMSE, Mini-Mental State Examination. All values are reported as mean ± SD. No significant difference between groups was noted by analysis of variance.*

COMMENT

Patients with NPC who have developed TLN after radiotherapy, when compared with age- and education-matched normal control subjects, manifested significant impairment in learning and memory. This finding is consistent with results of previous neuropsychological studies in patients with NPC.[15,18,29] Although previous studies seemed to suggest that memory impairment is a common cognitive deficit associated with radionecrosis in this group of patients, little is known about the nature of their memory impairment. The present findings suggest that their memory impairment profile is similar to that of TLA. That is, memory impairment of patients with TLN was non–material specific in that both verbal and nonverbal memory were adversely affected. In addition, the patients manifested a rapid rate of forgetting newly learned information, and both free recall and recognition abilities were similarly impaired. Thus, the memory profile of patients with TLN is similar to that of patients who have medial temporal lobe damage.[20-28]

While it remains controversial whether other cognitive deficits besides memory are associated with the radionecrosis after radiation for NPC,[18,29] our findings suggest that more diffuse damage in language, motor performance, planning, and abstract and flexible thinking also occurs if patients develop necrosis after radiotherapy for NPC.

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.[41] Therefore, the lateral part of the temporal lobe is also along the radiation pathway. Radionecrosis was additionally detected in some cases in the frontal lobe and basal ganglia by MR imaging.

It is known that, whereas memory is mediated by the medial temporal lobe area,[21-23] language function is primarily mediated by the left lateral temporal region. Thus, the observed memory and language impairment in patients with NPC with TLN is consistent with the pathologic change of their temporal regions. Our findings of impaired planning and organization and abstract and flexible thinking as a consequence of radionecrosis reflects frontal lobe dysfunction, whereas significant motor slowness is suggestive of basal ganglia involvement. In addition, as the parietal and occipital lobes are relatively spared after radiation, visual abilities that are mediated by these cortical regions are also relatively intact in these patients.

We also included patients without TLN in this study. The performance of these patients tended to be poorer than that of normal control subjects, but the difference did not reach statistical significance. Their cognitive functioning was considered to be comparable to that of the normal control subjects. These findings were inconsistent with those reported by Lee and colleagues,[15] in which patients with NPC and normal CT results had lower IQs, impaired verbal memory, visual memory, social comprehension, and nonverbal reasoning than patients waiting for radiotherapy. One possible reason for the discrepancy may be the different imaging technique used in the 2 studies. That is, CT scans are regarded as being less sensitive than MR images in detecting postirradiation change and radiological abnormality in the brain.[42] Therefore, some of the patients who demonstrated normal CT scans in the study by Lee and colleagues may indeed have had TLN.

Unlike previous research on children with leukemia and brain tumors that showed decline in their general intelligence after radiation,[4-10] the present study suggested relatively intact general intelligence after radiotherapy for NPC. One reason for the difference may be the diffuse effects of whole-brain radiation that is conventionally used in treating leukemia and brain tumors in children as opposed to distinct sequelae induced by the localized radiation targeting NPC used in our study. In fact, whole-brain radiation is associated with a decline in children's IQ, whereas no significant change in IQ is noted after localized radiation.[43] In addition, chemotherapy is usually included in the treatment protocol for children but not for patients with NPC. It is still questionable whether the decline in general intelligence found in children after cranial radiation is really caused by radiotherapy or by the combined effects of radiotherapy and chemotherapy.

CONCLUSIONS

Exposure to radiation because of radiotherapy for NPC seems to have some adverse but insignificant effects on cognitive function. However, if patients develop TLN after radiotherapy, their memory, language, motor ability, and executive functions are significantly impaired. Thus, further studies to identify factors to predict the development of necrosis after radiotherapy in patients with NPC will be clinically valuable.

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