Impact of Radionecrosis on Cognitive Dysfunction in Patients after Radiotherapy for Nasopharyngeal Carcinoma

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BACKGROUND. Cognitive dysfunction is common in patients who develop radionecrosis after receiving radiotherapy for nasopharyngeal carcinoma (NPC). However, the impact of the location and volume of radionecrosis on cognitive dysfunction remains unclear. The authors found a significant association between the severity of cognitive impairment and the volume of radionecrosis; in turn, the volume of radionecrosis was affected by patient age at time radiotherapy was completed.

METHODS. Fifty patients with NPC who received radiotherapy were evaluated by a battery of neuropsychologic tests of cognitive function. The brain lesion volume was quantified, and the lesion locations were identified by standardized brain templates. The results of the neuropsychologic tests were correlated with lesion volume. Gender, education, age at the completion of radiotherapy, brain volume, total dose, and fractional dose were evaluated as risk factors for lesion volume.

RESULTS. Lesion volume was correlated significantly with the severity of cognitive deficits. Larger left-hemisphere lesions were correlated with lower verbal memory (from $P < 0.001$ to $P = 0.008$) and language abilities (from $P = 0.001$ to $P = 0.018$), whereas larger right-hemisphere lesions were associated with worse visual memory (from $P = 0.009$ to $P = 0.039$). Finally, patients who received radiotherapy at a younger age had smaller lesion volumes ($P < 0.001$).

CONCLUSIONS. The volume and location of radionecrosis had an influential impact on the pattern of cognitive impairment found in patients with NPC, and patient age at the time radiotherapy was completed appeared to affect the volume of radionecrosis found after radiotherapy. ***Cancer*** **2003;97:2019–26.**

DOI 10.1002/cncr.11295

KEYWORDS: nasopharyngeal carcinoma, radionecrosis, neuropsychological function, radiotherapy.

Radiotherapy is the standard radical treatment for patients with nasopharyngeal carcinoma (NPC) and has produced excellent long-term results.[1–3] Radiotherapy is also an important treatment modality for patients with brain tumors, from radical, adjuvant, to palliative purposes, with definite survival benefits.[4] However, the treatment is not hazard free, and many patients encounter neurologic complications after radiation exposure. One possible sequel is the occurrence of radionecrosis,[5–8] which has been reported in many irradiated populations.[9–13] After 40–50 grays (Gy) of conventional, single, daily-fractionated radiation for brain tumors, the incidence rate of radiation brain injury at 5 years after treatment is about 5%.

Presented in part at the 29th Annual International Neuropsychological Society Conference, February 14–17, 2001, Chicago, Illinois.

Supported in part by a grant from the Research Grants Council of the Hong Kong Special Administrative Region (Project CUHK4110/99M).

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Received November 15, 2002; accepted December 20, 2002.

The rate increases substantially to 50% after a total dose of 60–70 Gy.[7,14,15]

Radionecrosis that develops after radiotherapy for NPC usually is found in the white matter.[16,17] In early, mild stages, the white matter changes are associated with edema, which may be related to endothelial cell loss.[6] This type of lesion may be focal or diffuse and extensive over the white matter. By using magnetic resonance imaging (MRI), this lesion usually is manifested as a finger-like, moderately uniform, high-intensity signal on T2-weighted images.[18] At later, chronic stages, radiation induces demyelination and fibrinoid changes in the blood vessels, which lead to parenchymal coagulative necrosis.[19,20] The necrosis usually is manifested focally in the form of cavities with central liquefaction and wall gliosis[21] and often is shown as a macroscopic high-intensity signal on T2-weighted MRI images.[18]

Cognitive impairment due to radionecrosis has been explored in several studies, and a decline in the cognitive function of patients with brain lesions due to radiation generally has been reported.[22–25] In our previous study,[22] we compared the cognitive profiles of patients with NPC after radiotherapy with and without moderate to macroscopic signal intensity indicating temporal lobe necrosis (TLN) on both hemispheres with the cognitive profiles of normal individuals. The results of that study indicated that patients with significant bilateral TLN generally manifested significant impairment in memory, language, motor performance, and executive function. In addition, mental deterioration was reported in patients who developed radiation-induced lesions after they received radiotherapy for intracranial tumors, and substantial mental impairment was more likely to occur in patients who had more severe radiation-induced lesions.[24,25]

Although previous studies have suggested that radionecrosis leads to impaired cognitive function, very little is known about the impact of volume and location of this lesion on the severity and pattern of cognitive deficits found in patients with NPC after they receive radiotherapy. Currently, our understanding about the correlation between the volume of brain lesions and the degree of cognitive deficits is drawn largely from lesions due to neurologic problems, such as multiple sclerosis (MS)[26,27] or genetic problems, like cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).[28] Although the neuropathologic changes from MS mainly involve axon demyelination,[29] it is believed that damage to the vascular system is the crucial etiologic mechanism for radiation-induced lesions.[30] Due to the difference in etiologic mechanisms and neuropathologic characteristics, results from MS studies may not be applicable to patients with NPC who develop brain lesions after exposure to radiation. Therefore, it may be of clinical significance to determine the impact of radiation-induced lesions on the severity of cognitive impairment found in patients with NPC.

The objective of the current study was to investigate the correlation between the degree and pattern of cognitive deficits in patients with NPC and the volume and location of the radionecrosis by studying a group of patients with NPC who developed cerebral lesions after radiotherapy. It was anticipated that larger radionecrosis lesions would be associated with poorer global cognitive functioning. Furthermore, because cognitive functions are mediated by specific brain regions, the association of the lesion and the cognitive deficit is location specific.[31] It is known that, after patients receive treatment for NPC, radionecrosis commonly is located in the temporal lobes.[32] Because the temporal lobes are responsible for memory and language,[31] it was anticipated that memory and language functions would be associated with lesion volume in these regions. The other functions, for instance, motor ability and executive function, which are mediated by the frontal lobe, would not be affected by lesions in the temporal lobes.

Because patients with NPC who receive radiotherapy eventually may develop neuropathologic changes, some studies have been conducted to identify the risk factors for the radionecrosis. The results show that the fractional dose,[5,33,34] the total dose,[11,33] and the brain volume under radiation[25,35,36] were significant factors in predicting the presence of lesions. In addition, the incidence of lesion is affected by the age of the patient at the time of radiation.[10,25] Although some factors are related to the likelihood of the occurrence of the radiation-induced lesions, it remains unknown whether these factors also may predict the volume of the lesion if it occurs. Furthermore, the effect of demographic characteristics, including education and gender, has not been explored to date. Therefore, the second objective of the current study was to explore whether these demographic and clinical characteristics may be possible predictors of lesion volume in patients with NPC who develop brain lesions after exposure to radiation.

MATERIALS AND METHODS

Patients

A total of 50 patients with NPC were recruited from the Neurology Clinic of Queen Elizabeth Hospital in Hong Kong on a voluntary basis. The clinic had long-term follow-up experience with more than 400 patients who developed different neurologic and/or endocrine

TABLE 1
Demographic and Clinical Characteristics

Variable	No. of patients (*n* = 50)	Mean ± SD	Range
Age (yrs)	—	55.74 ± 9.29	31–72
Age at the time of completion (yrs)	—	42.60 ± 9.91	24–69
Education level (yrs)	—	8.30 ± 3.69	0–18
Male:female ratio	38:12	—	—
Radiation treatment			
Total dosage (Gy)			
One course, lower dosage	12	50.20 ± 0.69	48.0–50.4
One course, higher dosage	28	60.10 ± 0.84	57.2–62.5
Two courses	8	112.14 ± 14.84	80.0–125.6
Dosage per fraction (Gy)			
Lower	36	2.44 ± 0.15	2.0–2.6
Higher	12	4.18 ± 0.58	4.0–4.2

SD: standard deviation.

complications after radiotherapy. Between 1968 and 1997, these patients had completed radiotherapy for their NPC within 6–7 weeks. Two fractionation schedules were employed.[33] Thirty-six patients were irradiated with a lower dose of 2.0–2.6 Gy per fraction 4–5 times weekly for 24 fractions, up to a total dose of 57.2–62.5 Gy. Due to recurrences, eight of those patients were treated further with a second course of radiotherapy. Twelve patients were treated with a higher fractional dose of 4.0–4.2 Gy per fraction twice per week for 12 fractions, up to a total dose of 48.0–50.4 Gy. Two patients received their radiotherapy in mainland China, and information about their radiation schedules was not available. The demographic and clinical characteristics of the patients studied are shown in Table 1.

Neuroimaging Measurement

All patients underwent MRI studies of their brain in Queen Elizabeth Hospital between 1993 and 1999 using 1.0 Tesla machine (Siemens, Erlangen, Germany), and the whole brain was covered by 20 images. The lesions manifested in the form of edema or cysts shown on the T2 MRI images (for example, see Fig. 1).

The area of the lesion on each slice was measured from the horizontal scan by a well-trained technician who was blind to the cognitive performance of the patients. The boundaries of the lesions in the brain were outlined by a combination of thresholding and automatic outlining techniques provided by the IMAGE computer software program (version 1.61; National Institutes of Health, Bethesda, MD). The numbers of pixels identified within the lesion were calibrated spatially into an area measured in terms of cm^2. By multiplying the slice thickness (in cm), the volume of the lesion was calculated. The total brain lesion was either the sum of lesion volume in both hemispheres if the lesions were bilateral or the lesion volume in a specific hemisphere if the lesion was unilateral.

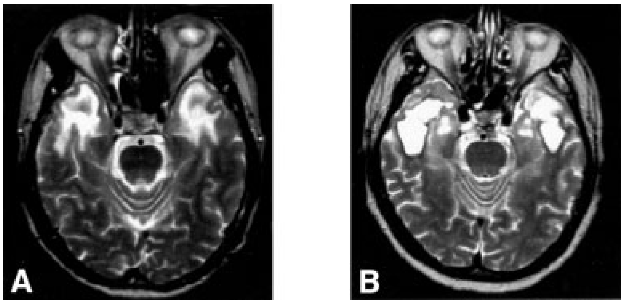

FIGURE 1. Radiation-induced lesions shown on magnetic resonance images. (A) T2-weighted horizontal image from a patient with nasopharyngeal carcinoma showing finger-like edema in the bilateral temporal lobes (B) T2-weighted horizontal image showing cysts in the bilateral temporal lobes.

To identify the location of each lesion more precisely, the templates developed by Talairach and Tournoux[37] were used to determine the coverage of the lesion in the brain. The horizontal MR images of the patients were overlapped by the templates with the horizontal degree close to the images. The templates were enlarged or compressed to cover the whole brain as much as possible. The exact location of the lesion was then read from the corresponding landmarks on the templates.

Neuropsychologic Assessment

Neuropsychologic tests were administered individually to each patient at least 1 year after radiotherapy by a trained examiner who was blind to the patients' neuropathologic changes. Written, informed consent was obtained from all patients.

A Cantonese version of the Mini-Mental Status Examination (CMMSE)[38] was used to determine global cognitive performance. The Hong Kong List Learning Test (HKLLT)[39] and a Story Recall Test were employed as measures of verbal memory. The Visual Reproduction subtest of the Wechsler Memory Scale-revised (WMS-R VR)[40] was used to assess visual memory.

Expressive language ability was assessed by the Chinese version of the Category Fluency Test,[41] a short form of the Boston Naming Test[42] in which the patients were required to name 30 pictured objects selected from the full version. Complex motor speed was assessed with the Grooved Pegboard Test,[43] and executive function was evaluated with the Copy Trial of the

Rey-Osterrieth Complex Figure Test,[44] the Color Trail Test Trial 2,[45] and the Five-Point Test.[46]

Statistical Analysis

Initial analysis showed that the lesion volume had a positively skewed distribution (skewness value, 2.424), and the distribution was not normal ($P < 0.0001$). Therefore, the data were transformed by taking the raw score of lesion volume into its cubic root form to obtain a relatively normal distribution.

To explore the association between lesion volume and specific cognitive functions, analysis of the correlation between the cubic root of the lesion volume in the left and right hemispheres and the raw scores of cognitive measures on memory, language, motor ability, and executive function was performed. However, because cognitive measures also were correlated with age and education, the correlation coefficient was calculated by performing the correlation controlling for age and education using SPSS software (version 10.0.7; SPSS Inc., Chicago, IL).

We used a linear multiple regression model to test whether demographic and clinical characteristics could predict brain lesion volume. We selected the cubic root of lesion volume as a dependent variable, and the predictors identified were dose per fraction, total dose, total brain volume under radiation, age at the time of finishing radiotherapy, education, and gender. Based on the fractionation schedules,[33] the dose per fraction was grouped into two categories: 1) lower doses between 2.0 Gy and 2.6 Gy and 2) higher doses between 4.0 Gy and 4.2 Gy. The total dose was subdivided into three categories, including 1) one course with a lower total dose between 48.0 Gy and 50.4 Gy, 2) one course with a higher dose between 57.2 Gy and 62.5 Gy, and 3) two courses with a dose > 80.0 Gy that was applied to the patients who received a second course of radiotherapy. These two variables and gender were entered into the model as nominal data, whereas total brain volume under radiation, age at the time of finishing radiotherapy, and education were entered as continuous variables. A stepwise regression procedure was used by adding the predictors with the greatest increase in R^2 with P to enter ≤ 0.05 and removing the predictor with the smallest decrease in R^2 with P to remove ≥ 0.10.

RESULTS

MRI Measures

The measures of lesion volume in the two hemispheres are displayed in Table 2. The volume of the total white matter lesion in the 50 patients ranged from 0.21 cm^3 to 157.67cm^3. Among 50 patients, 36 patients developed bilateral cerebral lesions, but there was no statistical difference in the mean lesion volume between two hemispheres (left, 18.26 cm^3; right, 14.13 cm^3; $t = 1.57$; degrees of freedom [df] = 35; nonsignificant). The other 14 patients had unilateral lesions after radiotherapy: 8 of those patients had lesions in the left hemisphere, and the other 6 patients had lesions in the right hemisphere.

TABLE 2
Brain and Lesion Volume

Volume	Mean ± SD (cm^3)	Range (cm^3)
Total brain	1396.14 ± 142.07	1166.84–1814.18
Total lesion	25.77 ± 30.60	0.21–157.67
Left lesion	16.59 ± 21.17	0.21–100.61
Right lesion	13.30 ± 12.76	0.73–57.06

SD: standard deviation.

Regarding the locations of the lesions, most were found in the temporal lobes (left, 86%; right, 91%). Other locations included the amygdala (left, 52%; right, 58%), the fusiform gyrus (left, 43%; right, 42%), the parahippocampal gyrus (left, 41%; right, 42%), and the hippocampus (left, 41%; right, 35%).

Correlation between Total Lesion Volume and Global Cognitive Performance

A correlation was established between the total lesion volume and the measure of global cognitive function, as determined with the CMMSE. The mean score for the CMMSE was 26.96 (standard deviation, ± 3.86). The results showed that there was a significant, negative correlation between the total white matter lesion volume and global cognitive performance (correlation coefficient [r] = -0.54; $P < 0.001$), with patients who had larger lesion volume showing worse global cognitive performance.

Correlation between Left Lesion Volume and Cognitive Functions

Table 3 shows the correlations and 95% confidence intervals between the left lesion volume and the results of neuropsychologic tests. There was a strong negative correlation between left lesion volume and verbal memory, as assessed by the Immediate-Recall Trial and the 30-Minute Delayed Recall Trial of the HKLLT ($P < 0.001$) and the Story Recall Test (range, from $P = 0.004$ to $P = 0.008$). Regarding the language function, significant correlation was found between the left lesion volume and the Category Fluency Test ($P = 0.018$) and Boston Naming Test ($P = 0.001$). Therefore, larger left lesion volume was associated with worse verbal memory and language function. Left

TABLE 3
Scores of Neuropsychologic Tests, Their Correlation, and 95% Confidence Intervals with Lesion Volume

		Left lesion volume			Right volume lesion		
Test	Mean ± SD	*r*	95% CI	*P* value	*r*	95% CI	*P* value
Verbal memory							
HKLLT[a]							
Immediate	18.67 ± 7.35	− 0.724	− 0.84, − 0.55	< 0.001	− 0.140	− 0.40, 0.15	0.44
30-minute delay	4.48 ± 3.56	− 0.567	− 0.73, − 0.34	< 0.001	− 0.200	− 0.46, 0.09	0.27
Story-Recall Test[a]							
Immediate	18.72 ± 9.08	− 0.473	− 0.67, − 0.22	0.004	− 0.114	− 0.38, 0.18	0.53
30-minute delay	11.70 ± 9.71	− 0.433	− 0.63, − 0.17	0.008	− 0.221	− 0.47, 0.07	0.22
Visual memory							
WMS-R VR[a]							
Immediate	27.98 ± 7.83	− 0.303	− 0.54, − 0.02	0.06	− 0.336	− 0.57, − 0.07	0.039
30-minute delay	19.80 ± 11.87	− 0.254	− 0.50, 0.03	0.12	− 0.426	− 0.63, − 0.17	0.009
Language							
Category Fluency[a]	23.45 ± 6.11	− 0.398	− 0.61, − 0.13	0.018	0.231	− 0.48, 0.06	0.20
Boston Naming[a]	20.43 ± 5.33	− 0.511	− 0.69, − 0.27	0.001	− 0.151	− 0.41, 0.14	0.40
Motor ability							
Grooved Pegboard Test[b]							
Right hand	98.33 ± 58.91	0.115	− 0.39, 0.17	0.47	0.140	− 0.40, 0.14	0.40
Left hand	96.71 ± 32.68	0.116	− 0.39, 0.17	0.48	0.111	− 0.38, 0.18	0.50
Executive function							
Rey-O[a]	25.84 ± 4.40	− 0.167	− 0.43, 0.12	0.31	− 0.178	− 0.44, 0.11	0.29
Color Trial 2[b]	145.15 ± 73.37	0.549	0.32, 0.72	< 0.001	− 0.234	− 0.48, 0.06	0.19
Five Point Test[a]	3.27 ± 4.81	− 0.009	− 0.29, 0.27	0.96	− 0.025	− 0.31, 0.25	0.88

SD: standard deviation; *r*: correlation coefficient; 95% CI: 95% confidence interval; HKLLT: Hong Kong List Learning Test; WMS-R VR: Visual Reproduction subtest of the Wechsler Memory Scale-Revised; Rey-O: Rey–Osterrieth Complex Figure Test.

[a] Raw score.

[b] Time in seconds to complete test.

lesion volume was not correlated with visual memory, motor function, or executive function, suggesting that lesions in the left hemisphere are not associated with cognitive function mediated by the right temporal lobe and the frontal lobe.

Correlation between Right Lesion Volume and Cognitive Functions

Consistent with our hypothesis, a significant negative correlation was found between the right lesion volume and visual memory, as determined by the Immediate-Recall Trial (P = 0.039) and the 30-Minute Delayed Recall Trial (P = 0.009) of the WMS-R VR (Table 3). There was no significant correlation between right lesion volume and verbal memory, language function, motor function, or executive function. Therefore, larger right lesion volume was associated only with worse visual memory but not with functions that are mediated by the left temporal lobe and the frontal lobe.

Effects of Demographic and Clinical Characteristics on Lesion Volume

Two variables were retained in the final regression model that predicted the lesion volume ($F_{2,35}$ = 16.05; P = 0.000; R^2 = 0.478). The strongest predictor was the age at which patients completed radiotherapy ($F_{1,36}$ = 17.67; P = 0.000; R^2 = 0.329) (Fig. 2). This variable may explain ≈ 33% of the variance in the cubic root of the total brain lesion volume. The second predictor retained in the model was the variable of retreat radiation, with a total dose $>$ 80 Gy (F change = 10.00; P = 0.003; R^2 change = 0.149), resulting in an R^2 increase of ≈ 15%. Further analysis showed no interaction between these two independent variables, suggesting that the lesion volume in patients who underwent a second course of radiotherapy generally was larger compared with the lesion volume in patients who underwent only one course of treatment, regardless of their age at completion. Other variables, including gender, education, fractional dose, and total brain volume, were excluded from the model.

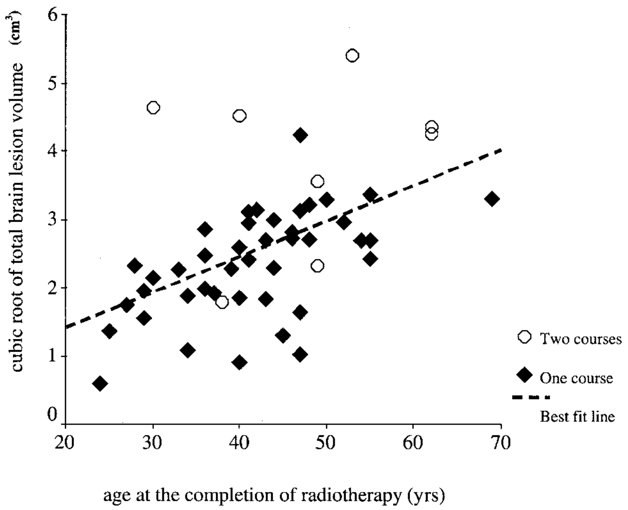

FIGURE 2. Scatterplot of total brain lesion volume versus age at the completion of radiotherapy.

DISCUSSION

To our knowledge, this is the first study to explore the impact of radionecrosis on the severity of cognitive impairment found in patients with NPC after radiotherapy. The results demonstrated a significant association between the volume of radionecrosis and the level of cognitive impairment after radiotherapy in the 50 patients evaluated. The total brain lesion was proportional to the severity of general cognitive impairment; that is, the larger the lesion volume, the more severe the cognitive impairment. This finding is consistent with the previous reports on patients with brain lesions due to genetic or neurologic etiologies, such as MS[26,27] and CADASIL.[28] Whereas the etiology of MS is associated mainly with demyelination of the axon, radiation-induced lesions primarily affect the vascular system. Although the neuropathologic changes in patients with MS differ from the changes found in patients with radiation-induced lesions, the extent of the associated lesions are correlated strongly with the level of cognitive impairment. Therefore, regardless of the underlying etiologic mechanism, it seems that, the greater the extent of brain lesion, the more severe the cognitive impairment suffered by the patient will be. This finding may be important in analyzing the risk-benefit trade-off during treatment for neurologic disorders, because the treatment may lead to brain damage that may affect the cognitive function. For instance, radiotherapy is a treatment of choice for patients with NPC and for patients with various types of central nervous system tumors, but it can induce necrosis. Therefore, radiotherapy may or may not improve the cognitive function of patients, and their prognosis will depend on the extent of brain damage induced by radiotherapy.

Whereas our previous study[22] included patients who had NPC with moderate to macroscopic, bilateral TLN, patients with lesion volumes as small as 0.21 cm^3 and patients with unilateral lesions also were included in the current study to determine the association between lesion volume, location, and cognitive functions. Consistent with the notion of localization of brain function, our study showed a strong association between the location of radionecrosis and the types of cognitive impairment. It is well understood that language abilities, including fluency and naming, are mediated by the left hemisphere.[32] Our findings suggest that the volume of the lesion in the left hemisphere was associated strongly with language abilities. A double-dissociation phenomenon also was observed between lesion volume and memory abilities. The verbal memory is mediated by the left hemisphere, whereas the visual memory is processed primarily by the right hemisphere.[32] Larger lesion volume in the left hemisphere was associated with worse verbal memory. A similar association was observed with the visual memory, in which the severity of a patient's visual memory impairment was determined by the right lesion volume. Because the severity of cognitive impairment is associated consistently with the location of the radiation-induced lesion, it may be essential to spare the relatively more specialized and essential brain region whenever possible, such as the Broca area, from exposure to radiation during treatment.

Although previous studies found that fractional dose, total dose, and total brain volume under radiation predicted the occurrence of radionecrosis, the current study failed to support these variables as possible factors correlated with lesion volume in patients with NPC. One possibility may be that different factors affect the occurrence and the extent of the lesion. At the same time, the possibility that our sample size may not have been representative or large enough cannot be ruled out. In the current study, 50 patients were included, most of whom received a total dosage of 50–60 Gy to treat their NPC. Only 8 patients who received a second course of radiotherapy had total dosages > 80 Gy. It is known that total dosages as high as 80 Gy[25] or as low as 30 Gy[47] may be delivered to treat tumors of other etiologies. Therefore, the insignificant result may be explained by our small sample size and the relatively narrow range of the total dose. In fact, our result showed that the retreated patients who received additional doses of radiation during their second course of radiotherapy seemed to have larger lesion volumes (mean ± standard deviation, $71.64 \text{ cm}^3 \pm 49.72 \text{ cm}^3$). In addition, a further correlation analysis suggested that there was a positive trend between the lesion volume and total dose among the 8 patients who received a second course of radiotherapy ($r = 0.75$; df = 8; $P = 0.032$). Therefore, the effect of total dose on the lesion volume cannot be ruled out at this point. In view of the limited number of patients used to examine this factor with the volume of radiation-induced lesion, more studies are recommended before a conclusion can be reached.

Within our sample, it was found that patient age at the time radiotherapy completion was one possible predictor for the volume of radionecrosis. The smallest total brain lesion was 0.21 cm^3, which was observed in a patient who completed radiotherapy at age 24 years, whereas the largest total brain lesion (157.67 cm^3) was observed in a patient who finished treatment at age 53 years. Therefore, smaller brain lesions were found in patients who received radiotherapy at a younger age, compared with the size of lesions in patients who completed radiotherapy at an older age. The lesion volume may vary nearly 750-fold due to differences in patient age as great as 30 years at the time radiotherapy is completed. Although this implication is very significant for patients and medical professionals during treatment planning, more research should be carried out to determine whether the current results may be replicated in other patient populations with radiation-induced white matter lesions. Furthermore, it should be remembered that the volume of the radiation-induced lesion may change over time. Longitudinal studies that keep track of lesion volume in patients over time will be required to provide further verification of this finding.

REFERENCES

1. Lee AW, Law SC, Foo W, et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976–1985: overall survival and patterns of failure. *Int J Radiat Oncol Biol Phys.* 1992;23:261–270.
2. Teo P, Tsao SY, Shiu W, et al. A clinical study of 407 cases of nasopharyngeal carcinoma in Hong Kong. *Int J Radiat Oncol Biol Phys.* 1989;17:515–530.
3. Sham JS, Choy D. Prognostic factor of nasopharyngeal carcinoma: a review of 759 patients. *Br J Radiol.* 1990;63:51–58.
4. Loeffler JS. Central nervous system tumors. In: Wang CC, editor. Clinical radiation oncology: indications, techniques, and results (2nd edition). New York: Wiley-Liss, 2000:583–604.
5. Schultheiss TE, Kun LE, Ang KK, et al. Radiation response of the central nervous system. *Int J Radiat Oncol Biol Phys.* 1995;31:1093–1112.
6. Hopewell JW. Radiation injury to the central nervous system. *Med Pediatr Oncol.* 1998;30(Suppl 1):1–9.
7. Philips TL. Early and late effects of radiation on normal tissues. In: Gutin PH, Leibel SA, Sheline GE, editors. Radiation injury to the nervous system. New York: Raven Press, 1991:37–55.
8. Muller RP. Radiation-induced injury of the central nervous system. In: Dunst J, Sauer R, editors. Late sequelae in oncology. Berlin: Springer-Verlag, 1995:23–27.
9. Packer RJ, Zimmerman RA, Kaplan AM, et al. Early cystic/necrotic changes after hyperfractionated radiation therapy in children with brain stem gliomas: data from the Children's Centre Group. *Cancer.* 1993;71:2666–2674.
10. Russo C, Fischbein N, Grant E, et al. Late radiation injury following hyperfractionated craniospinal radiotherapy for primitive neuroectodermal tumor. *Int J Radiat Oncol Biol Phys.* 1999;44:85–90.
11. Marks JE, Baglan RJ, Prasad SC, et al. Cerebral radionecrosis: incidence and risk in relation to dose, time, fractionation and volume. *Int J Radiat Oncol Biol Phys.* 1981;7:243–252.
12. Bleyer WA, Griffin TW. White matter necrosis, mineralizing microangiopathy, and intellectual abilities in survivors of children leukemia. In: Gilbert HA, Kagan AR, editors. Radiation damage to the nervous system: a delayed therapeutic hazard. New York: Raven Press, 1980:155–174.
13. Lee AWM. Complication of radiation therapy. In: van Hasselt CA, Gibb AG, editors. Nasopharyngeal carcinoma (2nd edition). Hong Kong: The Chinese University Press, 1999: 255–275.
14. Sheline GE, Wara WM, Smith V. Therapeutic irradiation and brain injury. *Int J Radiat Oncol Biol Phys.* 1980;6:1215–1228.
15. Emami B, Lyman J, Brown A. Tolerance of normal tissues to therapeutic irradiation. *Int J Radiat Oncol Biol Phys.* 1991; 21:109–122.
16. Burger PC, Bokyo OB. The pathology of central nervous system radiation injury. In: Gutin PH, Leibel SA, Sheline GE, editors. Radiation injury to the nervous system. New York: Raven Press, 1991:191–208.
17. Shaw EG, Bourland JD, Marshall MG. Cancers of the central nervous system. In: Khan FM, Potish RA, editors. Treatment planning in radiation oncology. Baltimore: Williams & Wilkins, 1998:491–543.
18. Lee AW, Cheng LO, Ng SH, et al. Magnetic resonance imaging in the clinical diagnosis of late temporal lobe necrosis following radiotherapy for nasopharyngeal carcinoma. *Clin Radiol.* 1990;42:24–31.
19. Rubinstein LJ. Tumors of the central nervous system. Washington, DC: Armed Forces Institute of Pathology, 1970.
20. Caverness WF. Experimental observation: delayed necrosis in normal monkey brain. In: Gilbert HA, Kagan AR, editors. Radiation damage to the nervous system: a delayed therapeutic hazard. New York: Raven Press, 1980:1–38.
21. Lee AWM, Ng SH, Ho JHC, et al. Clinical diagnosis of late temporal lobe necrosis following radiation therapy for nasopharyngeal carcinoma. *Cancer.* 1988;61:1535–1542.
22. Cheung M, Chan AS, Law SC, et al. Cognitive function of patients with nasopharyngeal carcinoma with and without temporal lobe radionecrosis. *Arch Neurol.* 2000;57:1347–1352.
23. Parkin AL, Hunkin NM. Memory loss following radiotherapy for nasal pharyngeal carcinoma—an unusual presentation of amnesia. *Br J Clin Psychol.* 1991;30:349–357.
24. Nishimura R, Takahashi M, Morishita S, et al. MR imaging of late radiation brain injury. *Radiat Med.* 1992;10:101–108.
25. Constine LS, Konsku A, Ekholm S, et al. Adverse effects of brain irradiation correlated with MR and CT imaging. *Int J Radiat Oncol Biol Phys.* 1988;15:319–330.
26. Rovaris M, Filippi M, Falautano M, et al. Relation between MR abnormalities and patterns of cognitive impairment in multiple sclerosis. *Neurology.* 1998;50:1601–1608.

27. Sperling RA, Guttmann CRG, Hohol MJ, et al. Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: a longitudinal study. *Arch Neurol.* 2001;58:115–121.
28. Dichgans M, Filippi M, Bruning R, et al. Quantitative MRI in CADASIL: correlation with disability and cognitive performance. *Neurology.* 1999;52:1361–1367.
29. Adams RD, Victor M, Ropper AH. Principles of neurology. New York: McGraw-Hill, 1997.
30. Chan YL, Yeung DKW, Leung S, et al. Proton magnetic resonance spectroscopy of late delayed radiation-induced injury of the brain. *J Magn Reson Imaging.* 1998;10:130–137.
31. Lezak MD. Neuropsychological assessment. New York: Oxford University Press, 1995.
32. Chan YL, Leung SF, King, AD, et al. Late radiation injury to the temporal lobe: morphologic evaluation at MR imaging. *Radiology.* 1999;213:800–807.
33. Lee AWM, Foo W, Chappell, R, et al. Effect of time, dose, and fractionation on temporal lobe necrosis following radiotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 1998;40:35–42.
34. Marks JE, Wong J. The risk of cerebral radionecrosis in relation to dose, time, and fractionation: a follow-up study. *Progr Exp Tumor Res.* 1985;29:210–218.
35. Leung SF, Kreel L, Tsao SY. Aysmptomatic temporal lobe injury after radiotherapy for nasopharyngeal carcinoma: Incidence and determinants. *Br J Radiol.* 1992;65:710–714.
36. Sham J, Choy D, Kwong PWK, et al. Radiotherapy for nasopharyngeal carcinoma: shielding the pituitary may improve therapeutic radio. *Int J Radiat Oncol Biol Phys.* 1994;29:699–704.
37. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. New York: Thieme Medical Publishers, 1988.
38. Chiu HFK, Lee HC, Chung WS, et al. Reliability and validity of the Cantonese version of Mini-Mental State Examination—a preliminary study. *J Hong Kong Coll Psychiatrists.* 1994;4(Suppl 2):25–28.
39. Chan AS, Kwok IC. Hong Kong List Learning Test. Hong Kong: Department of Psychology, The Chinese University of Hong Kong, 1999.
40. Wechsler D. Wechsler Memory Scale-revised. San Antonio: The Psychological Corporation, 1987.
41. Chan AS, Poon MW. Performance of 7- to 95-year-old individuals in a Chinese version of the category fluency test. *J Int Neuropsychol Soc.* 1999;5:525–533.
42. Kaplan E, Goodglass H, Weintraub S. Boston Naming Test. Philadelphia: Lea & Febiger, 1983.
43. Matthews CG, Klove H. Instruction manual for the Adult Neuropsychology Test Battery. Madison: University of Wisconsin Medical School, 1964.
44. Osterrieth PA. Le test de copie d'une figure complexe [The test of copying a complex test]. *Arch Psychol.* 1944;30:286–356.
45. Maj M, D'Elia L, Satz P, et al. Evaluation of two new neuropsychological tests designed to minimize cultural bias in the assessment of HIV-1 seropositive persons: a WHO study. *Arch Clin Neuropsychol.* 1993:8;123–135.
46. Regard M, Strauss E, Knapp P. Children's production on verbal and non-verbal fluency tasks. *Percept Motor Skills.* 1982;55:859–844.
47. Packer RJ, Zimmerman RS, Bilaniuk LT. Magnetic resonance imaging in the evaluation of treatment related central nervous system damage. *Cancer.* 1986;58:635–640.