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The use of ^{1}H-magnetic resonance spectroscopy in studying radiation-induced injury of the brain in elderly and young patients with nasopharyngeal carcinoma

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► ***Original article***

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ABSTRACT

Background: This study aims to investigate the metabolic characteristics of radiotherapy-induced temporal lobe injury in elderly patients with nasopharyngeal carcinoma using ^{1}H-magnetic resonance spectroscopy (MRS). ***Materials and Methods***: Data were collected from 21 elderly patients and 33 young patients before and during therapy with different radiation dosages (20, 40, and 60 Gy). The Student's t-test was used to compare the 1H -MRS-based N-acetyl aspartate /Creatine (NAA/Cr), Choline/Creatine (Cho/ Cr), and NAA/Cho ratios in the temporal lobes. ***Results:*** Statistically significant differences in the NAA/Cr and NAA/Cho ratios was found between the two groups ($P < 0.05$) at 20, 40, and 60 Gy. The Cho/Cr ratios (20/40/60 Gy) were 1.82 ± 0.16/1.61 ± 0.29/1.37 ± 0.13 and 1.77 ± 0.19/1.48 ± 0.17/1.06 ± 0.14 in the elderly and young patients, respectively. We found significant differences between the two groups at the dosages of 40 and 60 Gy ($P<0.05$). The decrease in the NAA/Cr and NAA/Cho ratios in the elderly group was significantly higher than that in the young patients with dosages of 20, 40, and 60 Gy. The decrease in the Cho/Cr ratio in the elderly group (2.15%/11.29%/12.90%) was significantly lower than that in the young patients (3.30%/15.93%/17.58%). ***Conclusion:*** Under the same radiotherapy pattern and radiation dosage, the injury to the neurons in the temporal lobes was significantly greater in elderly patients than that in young patients. The intervention conducted in elderly patients at a dosage of 20 Gy might help minimize the injury to the neurons.

Keywords: *Nasopharyngeal carcinoma, radiotherapy, radiation injuries, magnetic resonance spectroscopy.*

INTRODUCTION

Nasopharyngeal carcinoma (NC) is the most common head and neck tumor in southern China, and radiotherapy is the preferred method to treat NC [1]. Radiotherapy is normally accompanied by radiation-induced brain injuries in important sites such as the temporal lobe and brain stem, more commonly in the anterior part of both the temporal lobes. Therefore, the clinical outcome of radiotherapy as well as the quality of life of the patients who survive might be affected [1, 2]. Effective monitoring and prevention of radiation-induced brain injuries has been a popular focus of national and international research [3-6]. NC was more commonly found in middle-aged and young individuals, although some proportion of the elderly population also develops it. Given the differences in the brain metabolism between elderly and middle-aged/young individuals, the degrees and mechanisms of radiation-induced

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brain injuries in the different age-groups are not entirely the same [7, 8]. Therefore, studying the characteristics of radiation-induced brain injuries among patients with NC that belong to different age-groups is necessary. Although a few studies have investigated radiation-induced brain injuries in elderly people [9-11], our study applied magnetic resonance spectroscopy (MRS) to compare the characteristics of radiation-induced brain injuries between young and elderly patients who underwent radiotherapy in the same period of time. We aimed to provide objective evidence for the effective monitoring and timely prevention of radiation-induced brain injuries in elderly individuals.

MATERIALS AND METHODS

Clinical data

The inclusion criteria for the elderly patient group were: 1) age ≥ 60 years, and 2) diagnosis of NC for the first time as confirmed by the imaging examination and focal biopsy in the Hainan Provincial People's Hospital from July 2006 to December 2012; the exclusion criteria were: 1) combined lesions such as brain white matter lesions, brain atrophy, cerebrovascular diseases, brain tumors, etc.; 2) diagnosis of diabetes mellitus, hyperthyroidism, hypothyroidism, or other endocrine and immune diseases; 3) any obvious abnormality on conventional MR images before radiotherapy using Varian Trilogy Accelerator (Varian Medical Systems Ins., Palo Alto, CA). In total, 21 patients met these criteria (males, 16; females, 5; mean age, 66 ± 4 years). The inclusion criteria for the young patient group were: 1) age ≤ 45 years, and 2) a confirmed diagnosis of NC for the first time; the exclusion criteria were: 1) evidence of cerebrovascular and other intracranial organic brain diseases on routine craniocerebral MR imaging before the radiotherapy; 2) history of diseases in the heart, liver, kidney, and other vital organs; 3) metabolic and immune diseases confirmed by physical examination and laboratory tests. In total, 33 cases met these criteria (males, 21; females, 12; mean age, 37 ± 8 years). This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of People's Hospital of Hainan Provincial People's Hospital. Written informed consent was obtained from all participants.

Radiotherapy program and MRS examination

The MRS examination was conducted at specific time points. The joint field comprising the face and neck was used for the radiotherapy; the irradiating sites included the nasopharynx and neck, as well as the bilateral temporal lobes, and the conventional fractionation method was applied (dose: 2 Gy/d, 5 times/week). The examinations included conventional brain MR scanning before and after the radiotherapy, as well as MRS examination before the radiotherapy and when the dose reached 20, 40, and 60 Gy.

The MR scanning was performed on a GE Signa Twinspeed / Excite II 1.5 T MR scanner. The conventional scanning protocol included axial T1-weighted imaging (TR, 400 ms; TE, 15 ms), T2-weighted imaging (TR, 4000 ms; TE, 120 ms), and fluid-attenuated inversion recovery sequence (FLAIR) T2-weighted imaging (TR, 6000 ms; TE, 120 ms; TI, 2000 ms). The T2-weighted FLAIR sequence was used as the positioning image for the spectral acquisition (figure 1), and the multi-voxel acquisition (TR, 1000 ms; TE, 144 ms) was performed with the point-resolution method (PRESS).

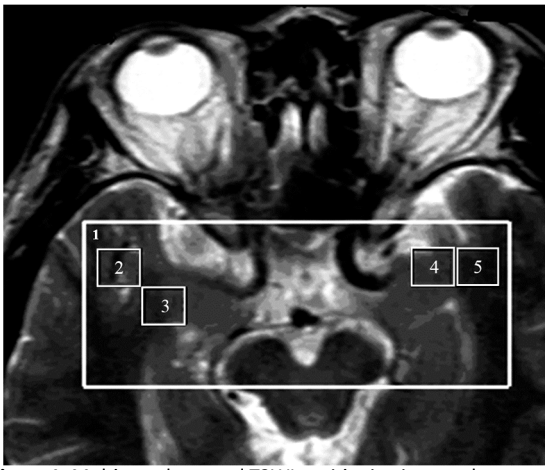

Figure 1. Multi-voxel spectral T2WI positioning image, the spectral scanning region covered the anterior part of temporal lobes, and two small voxels that had the highest SNR in the bilateral temporal lobes were selected for analysis.

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The spectral scanning range was focused on the anterior part of the bilateral temporal lobes with 6 saturated zones set around them. The full width at half maximum (FWHM) was set to ~6-12 mm, with the water suppression (WS) set as >98% for the auto acquisition, and automatic shimming was also performed.

Spectral analysis

The spectral data were transmitted to the ADW 4.0 workstation, and the post-processing analysis was performed using the Functool 2 software (GE Medical Systems, Milwaukee, WI, USA). Since the radiation-induced brain injuries mainly occurred in the white matter of the anterior temporal lobe and the white matter was more sensitive to radiation than gray matter [12], the bilateral temporal lobes were included within the spectral scanning range. Two small voxels (size, 30 ± 5 mm^2) that had the highest SNR and an ideal spectral curve for the analysis were selected. The concentrations of the main metabolites, N-acetyl aspartate (NAA), creatine (Cr), and choline (Cho), as well as their relative average values (NAA/Cr, Cho/Cr, and Cho/NAA) were calculated, and the changes in the trends of these values during the treatment were analyzed.

Statistical analysis

The SPSS 12.0 software package was used for the statistical analyses. The spectral data were expressed as mean ± SD. The independent sample t-test was used to compare the NAA/Cr, Cho/Cho, and NAA/Cho ratios between the two groups at the different dosages. Results with *P* values less than 0.05 were considered statistically significant.

RESULTS

In total, 54 patients were recruited in the study including both the elderly (n = 21) and the young (n = 33) patients. None of the patients were exposed to any artificial intervention, such as hormones, neurotrophic drugs, and vasodilators, from the beginning of radiotherapy until the total radiation dose reached 60 Gy. Conventional MR scanning at the end of the radiotherapy provided no evidence of abnormal signs such as obvious cerebral edema. No related clinical symptoms, such as intracranial hypertension and nerve injury, were observed in the patients.

Morphological changes

Before the radiotherapy, the NAA peak was the highest peak in both the groups, followed by the Cho peak. The difference between the heights of the two peaks was smaller in the elderly patient group compared to the young patient group (figure 2A, 2B). During the course of radiotherapy, both the groups showed a decrease in the NAA and Cho peak heights compared to the peak height before radiotherapy.

The ratios of the three main metabolites

When the total dose of radiation reached 20 Gy, the NAA/Cr, Cho/Cr, and NAA/Cho ratios all decreased, and there was no significant difference between groups (figure 2C, D); when the total dose reached 40 and 60 Gy, however, the ratios further decreased and the between-groups comparison revealed significant differences (table 1). 2) The decreased NAA/Cr ratios in the elderly patients were 6.70%, 14.43%, and 24.23% at doses of 20, 40, and 60 Gy, respectively. These decreases were significantly greater in magnitude than those observed in the young patients group (4.25%, 5.19%, and 7.08%). The reduced Cho/Cr (2.15%, 11.29%, and 12.90%) percentages in the elderly patients were lesser than those in the young patients (3.30%, 15.93%, and 17.58%) (figure 2E, F). On the other hand, the reduced NAA/Cho percentages in the elderly patients (8.59%, 5.47%, and 21.09%) were greater than those in the young patients (2.56%, 10.26%, and 16.67%).

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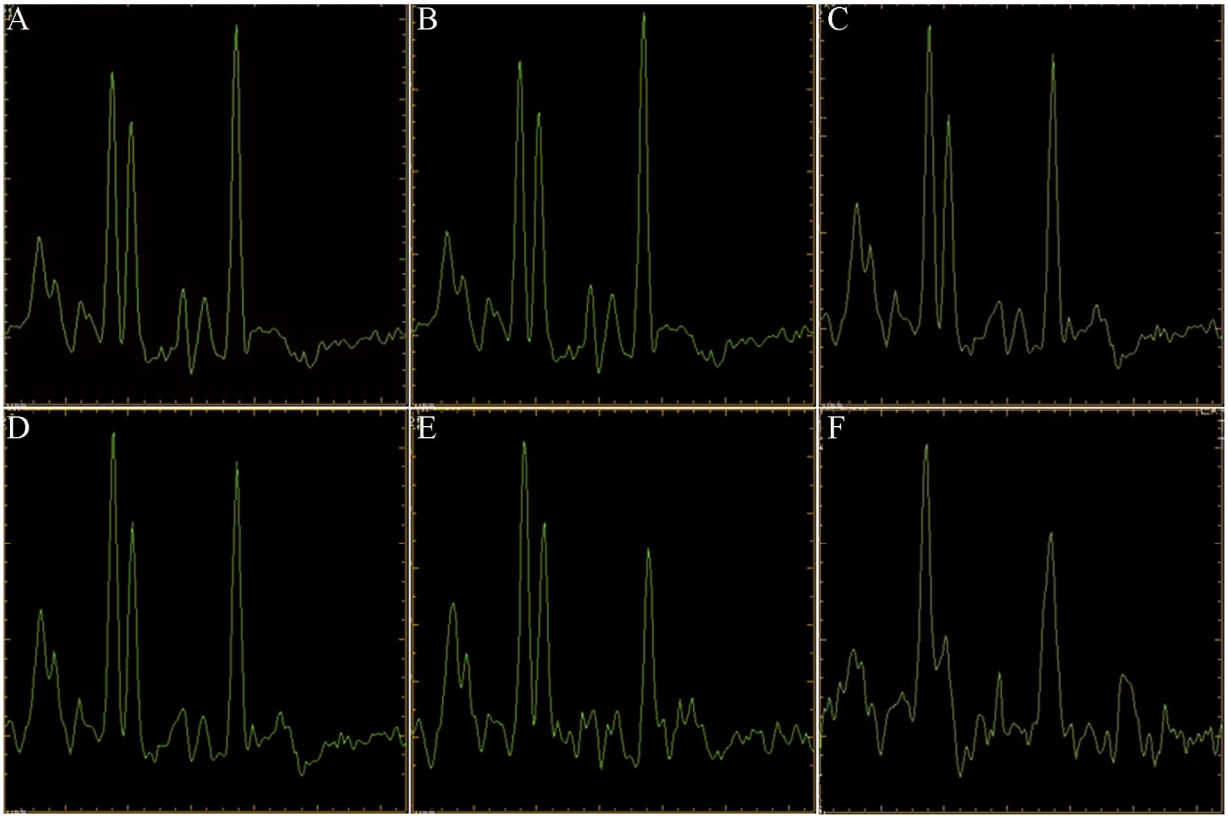

Figure 2. The spectrum change map of the young and elderly groups before and the process of radiotherapy. A, B: MRS images before the radiotherapy: male, aged 62 years old, the NAA peak was the first highest peak, slightly higher than the Cho peak, and the difference between these 2 peaks' heights was small, the NAA/Cho ratio was 1.246 (figure 2A); male, aged 43 years old, the NAA peak was higher than the Cho peak, and the difference between these 2 peaks' heights was bigger, the NAA/Cho ratio was 1.524 (Figure 2B). C, D: MRS images when the radiation dose reached 20Gy, both the NAA and Cho peaks of the two groups were decreased, while the declined degrees were not obvious. Male, aged 61 years old, the height of the NAA peak was lower than the Cho peak (figure 2C); female, aged 38 years old, the height of the NAA peak was slightly lower than the Cho peak (figure 2D). E, F: MRS images at the end of the radiation, namely the dose reached 60Gy: Figure 2E, male, aged 64 years old, the NAA peak was significantly reduced than that before the radiotherapy, the Cho peak was also reduced, and the ratio of NAA/Cho was 1.031; Figure 2F, male, 41 years old, both the NAA and Cho peaks were reduced than those before the radiotherapy, and the ratio of NAA/Cho was1.330.

Table 1. Comparison of the ratios of 3 main metabolites between the 2 groups at different radiation doses ($\bar{x}\pm s$)

Group	N	NAA/Cr				Cho/Cr				NAA/Cho			
		Before radio-therapy	20Gy	40Gy	60Gy	Before radio-therapy	20Gy	40Gy	60Gy	Pre-radio-therapy	20Gy	40Gy	60Gy
Elderly	21	1.94±0.15	1.81±0.14	1.53±0.16	1.06±0.08	1.86±0.20	1.82±0.16	1.61±0.29	1.37±0.13	1.28±0.13	1.17±0.15	1.10±0.08	0.83±0.05
Youth	33	2.12±0.25	2.03±0.16	1.92±0.21	1.77±0.18	1.82±0.24	1.77±0.19	1.48±0.17	1.06±0.14	1.56±0.14	1.52±0.13	1.36±0.15	1.10±0.17
T value		1.417	8.386	9.113	13.729	1.070	0.455	5.230	9.322	5.023	5.862	2.560	9.754
P value		>0.05	<0.05	<0.05	<0.01	>0.05	>0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.01

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DISCUSSION

Radiotherapy is the preferred treatment for nasopharyngeal carcinoma despite the associated risk of damaging the surrounding tissues [2]. The efficacy of radiotherapy is positively correlated with radiation doses, although the increased doses would also increase the damage towards the normal brain tissues. Radiation-induced brain injury was the main factor that limited the dose of radiotherapy. The exact mechanism of radiation-induced brain injuries is unclear; it is thought that the radiation [13] would directly damage the glial cells, leading to the demyelination, softening, and necrosis of white matter. The fibration of middle or small arterial walls can cause stenosis or occlusion inside the lumen, thereby leading to cerebral ischemia in the related brain regions. Moreover, the radioactive ionizing radiation contains oxidative free radicals, which can cause membrane lipid injuries and autoimmune reactions. When the radiation acts on normal brain tissues, it can cause a series of physiological and biochemical reactions, leading to various degrees of metabolic and functional damage. The extent of brain damage is not only related to the radiation dose, but also to another important factor, namely the patient's age.

NAA is a recognized neuronal marker, with its peak located at 2.02 ppm in the spectrum. Both the number of neurons and the metabolic changes in them could lead to changes in the NAA/Cr ratio; the reduced ratio indicates neuronal loss and/or a metabolic disorder [14]. Our results showed that the NAA/Cr ratios of the bilateral temporal lobes in both the groups showed a decreasing trend during the entire process of radiation; although this trend was not significant at 20 Gy, the trends in the elderly patient group at 40 and 60 Gy were significantly different from those in the young patient group. We believe that the low cumulative dose in the initial stages of radiotherapy causes lesser radiation-induced damage in the neuronal mitochondria, thereby impacting the energy metabolism and resulting in decreased NAA/Cr values. However, when the doses reached 40 and 60 Gy, the decrease in the NAA/Cr ratio in the elderly group was greater than that observed in the young patient group. With the increase of cumulative radiation doses, the metabolic function of neuronal mitochondria was further compromised and the degree of injury increased. The cell membranes and DNA of a small number of neurons may exhibit ionizing radiation-induced apoptosis, and neurons of the different age groups might have different tolerances towards the radiation. The number of apoptotic neurons in the elderly group was more than the young patient group, and the unit voxel content was relatively lower. There are a few reports of MR spectral measurements in the normal temporal lobes, which have recognized the higher level of NAA in the gray matter [11, 15, 16], and the lower level of NAA in the white matter. The small voxels selected in this study mainly contained the white matter of the temporal lobe. The NAA/Cr ratio decreased faster when the dose reached 20 Gy, in line with the results reported by Armstrong *et al.* [7]. The progressive decrease in the NAA/Cr ratio in the elderly group was greater than that in the young patient group. Thus, under the same radiation pattern and dosage conditions, radiation-induced injuries in the neurons in the elderly patients were greater than those seen in young patients with NC.

Choline (Cho) levels reflect the total choline content, including phosphorylcholine, phosphatidylcholine, and phosphoglycerolcholine, which are associated with phospholipid metabolism and myelination of the cell membrane. The choline content of glial cells is significantly higher than that of neurons. Thus, it is likely that the changes in Cho content mainly reflect the metabolic and functional changes in glial cells [17]. In this study, the Cho/Cr ratio before radiotherapy in the elderly group was slightly higher than that in the young patient group. A higher Cho/Cr ratio indicates more active proliferation of glial cells and an increased membrane metabolic rate, most likely because when glial cells receive the irradiation, the mitochondrial energy metabolism decreases, thereby reducing cell activity. Although both the groups showed a decrease in the ratio during the

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course of radiotherapy, the decreased percentage in the elderly group was smaller than that in the young patient group, which might be because some glial cells might exhibit a relatively more active reactive hyperplasia of the cell membrane when exposed to the radiation. However, it was also reported that the Cho/Cr ratio increased shortly after the beginning of radiotherapy following a glioma surgery [18]; this inconsistency can be explained by different radiation patterns and intensities used in the two protocols, and the differences in the degrees and mechanisms of glial cell injury. Some researchers believe that with a large dose of radiation, the increase in the Cho/Cr ratio is correlated with the increase in water-soluble phosphorylcholine content in response to cell membrane damage-induced tissue necrosis [19]. Others believe that using a lower radiation dose might be easier to effect the reactive proliferation of glial cell membrane; our results support this view [20, 21]. Furthermore, considering that the metabolic changes in cerebral substances during the course of radiotherapy might cause a fluctuation in the Cr content, thereby impacting the NAA/Cr and Cho/Cr ratios; we also measured and compared the NAA/Cr value and found that the trends of change in the NAA/Cho and NAA/Cr ratios were close, consistent with the results of Law *et al*. [12] and Butzen *et al*. [22]. Haga *et al*. [11] divided the brain spectral data of healthy adults into the young group (<60 years old) data and the elderly group (≥60 years old) data for their meta-analysis, and found a large difference in the metabolic levels of brain substances between the two groups. The brain substance metabolism in elderly patients with NC might be intervened by more potential physical factors. Thus, we selected the elderly patients who had no obvious physical diseases for the comparison with the young group (<45 years old). This reduced the potential confounds related to the differences in basic metabolism and diseases.

However, our study also had certain inevitable flaws; for example, the MR images of the temporal lobe could be disturbed by multiple factors such as the skull, sphenoid sinus, and cerebrospinal fluid. Thus, we needed to adjust the scanning range and saturation band several times in order to meet the collection requirements. It was, therefore, difficult to ensure the identical position of the same patient's voxels selected for the analysis during each examination. In addition, expressing the ratios of brain metabolites using the relative quantification method might affect their accuracy to some extent. The above bias might be reduced through increasing the sample size, selecting smaller voxels for the average, and optimizing the statistical methods.

In conclusion, we investigated the MR spectra of the temporal lobe in the elderly and young patients with NC that were administrated radiotherapy during the same period. Our results suggest that under the same radiotherapy pattern and radiation dose, the neuronal injuries in the elderly patients were greater than those in the young patients, although the damage to glial cells was relatively small. Therefore, we believe that it would helpful to administer the radiotherapy in the elderly patients at a dose of 20 Gy in order to alleviate neuronal injuries and improve the treatment outcomes as well as the quality of life of the patients [23].

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***Conflicts of interest*:** *Declared none.*

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