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Longitudinal brain structural alterations in patients with nasopharyngeal carcinoma early after radiotherapy

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ABSTRACT

Background and purpose: To investigate effects of radiotherapy on normal brain tissue using in vivo neuroimaging in patients with nasopharyngeal carcinoma (NPC).

Methods and materials: We used longitudinal MRI to monitor structural brain changes during standard radiotherapy in patients newly diagnosed with NPC. We assessed volumetric measures in 63 patients at 2–3 time points before and after radiotherapy, with 20 NPC-free participants as normal controls. Images were processed using validated software (FreeSurfer). Automated results were inspected visually for accuracy. We examined changes in volume of the whole brain, gray matter, white matter, and ventricles, as well as in cerebral volumes partitioned into temporal, frontal, parietal, and occipital lobes. A linear mixed model was used to evaluate longitudinal changes in these measurements. Statistical significance was evaluated at $p < 0.05$, which was corrected for multiple comparisons.

Results: Volumes of the gray matter, and bilateral temporal lobes decreased in a time-dependent manner, whereas ventricle volume showed a time-dependent increase after radiotherapy. No volume changes were detected in NPC patients before radiotherapy when compared normal controls. No volume changes were detected in the subcohort of patients after completion of induction chemotherapy but prior to initiation of radiotherapy. Changes of bilateral temporal lobe volume correlated with irradiation dose in this region. Expansion of the ventricles correlated with a reduction in cognition assessment.

Conclusions: We detected significant and progressive radiotherapy-associated structural changes in the brains of patients with NPC who were treated with standard radiotherapy, especially in the bilateral temporal lobe in which the effect was dose-dependent. Expansion of the ventricles can serve as an imaging marker for treatment-related reduction in cognitive function. Future studies with longer follow-ups are needed to evaluate morphometric changes long-term after radiotherapy.

1. Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors affecting the population in southern China, especially in Guangdong Province (Chan, 2010; Cao et al., 2011). Radiation therapy (RT) with or without adjuvant chemotherapy is the primary treatment modality for patients with NPC (Xu et al., 2017; Wei and Kwong, 2010). The radiation field for NPC encompasses areas adjacent to the primary tumor including the base of skull, which places normal brain tissue, especially the temporal lobe, at risk of injury. After RT, patients often experience cognitive impairment (Hsiao et al., 2010; Kiang et al., 2016; Tang et al., 2012), which may be mediated by injury to the brain, especially regions within the irradiation target. However, brain injury related to irradiation is poorly understood and has no effective prevention or long-term treatment. Current knowledge of irradiation-related brain injury in NPC patients after RT has been derived primarily from studies of animal models or patients with brain tumors (Balentova and Adamkov, 2015; Chapman et al., 2016; Edelstein et al., 2017).

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However, radiation fields and radiation dosing schemes are quite different between NPC patients and patients with brain tumors or non-central nerve system tumors with prophylactic cranial irradiation. Thus, brain alterations after irradiation may differ between NPC patients and patients with brain tumors. Identification of an accurate and sensitive biomarker of brain injury and neurotoxicity after RT in NPC patients is necessary to develop treatment strategies that may prevent or minimize brain injury.

Ideally, these biomarkers should be obtained during standard treatment planning and follow-up evaluation and correlate with clinical outcome measures of cognitive function. However, to the best our knowledge, no longitudinal studies have explored brain alterations and correlations with irradiation dose or cognitive changes in NPC patients after RT. Our previous cross-sectional studies found that normal-appearing gray matter volume (Lv et al., 2014), bilateral temporal white matter microstructure (Wang et al., 2012) as well as metabolite (Xiong et al., 2013) underwent diverse damaged following RT based on the duration of completion of RT. Moreover, we found that regional gray matter volume loss in the left superior temporal gyrus, left middle temporal gyrus, and right fusiform gyrus negatively correlated with the mean dose to the ipsilateral temporal lobe, which indicated that irradiation-related injury is dose-dependent (Lv et al., 2014). In another cross-sectional study comparing 3 NPC groups with different durations of completion for RT, Wang and colleagues found that gray and white matter mean kurtosis values were significantly higher at 1 week after RT, but significantly lower at 6 months and 1 year after RT; mean diffusivity values were significantly lower at 1 week after RT, but returned to normal by 6 months and 1 year after RT (Wang et al., 2016). These studies suggest that irradiation causes brain injury in NPC patients after RT, and the extent of injury varies depending on the duration of completion of RT. However, cross-sectional studies can be influenced by between-subject variance and possible cohort effects (Schaie, 2005) as well as an inability to detect intra-individual alterations. Thus, a cross-sectional comparison is not sufficient to assess the effects of RT on the brain. Longitudinal studies are needed to elucidate these effects.

In this study, we evaluated longitudinally brain structural alterations related to RT in NPC patients treated with intensity modulated radiotherapy (IMRT) and accounted for potential confounders such as chemotherapy, and age. Based on prior cross-sectional studies in NPC patients after RT (Lv et al., 2014; Wang et al., 2012; Xiong et al., 2013; Wang et al., 2016) and longitudinal studies of patients with brain tumors or non-central nerve system tumors who were treated with prophylactic cranial irradiation (Simo et al., 2016; Prust et al., 2015), we hypothesized the following: (a) Brain structural alterations can accurately detect and monitor RT-induced neurotoxicity in vivo and can be used as a biomarker for noninvasive evaluation of RT-induced brain injury; (b) Longitudinal changes in brain structure, especially in the temporal lobe, are dose dependent; (c) Longitudinal changes in brain structure are time dependent; (d) Longitudinal brain structural changes may underlie cognitive impairment.

2. Materials and methods

2.1. Standard protocol approvals, registrations, and patient consent

Data were obtained through a prospective clinical study of patients with NPC conducted at our institution (ChiCTR-OOB-15006982), which had been registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn/showproj.aspx?proj=11752). The local institutional review board approved this protocol. All participants provided written informed consent.

2.2. Patients

From December 2014 to November 2017, 83 subjects (with 168 scans) participated in this study. There were 20 NPC-free normal controls (13 male/7 female, 26–58 years old, mean age of 41.0 ± 10.0 years) and 63 patients (43 male/20 female, 21–62 years old, mean age of 39.7 ± 9.3 years) with newly diagnosed, histology-proven, non-keratinizing, undifferentiated NPC. Each patient underwent a detailed pretreatment evaluation, which included a physical examination, nasopharyngeal fiber optic endoscopy, chest radiography, MRI scan of the nasopharynx and brain, abdominal sonography, and whole body bone scan. The clinical stages of NPC were classified according to the American Joint Committee (AJCC) on Cancer staging system (7th edition).

Inclusion criteria for all participants were:

1. Age > 18 years but < 65 years.
2. Baseline Montreal Cognitive Assessment (MoCA) scores equal to or > 26.
3. No intracranial invasion, no distant metastases, no brain tumors, no alcoholism, no substance dependence, no neurological or psychiatric diseases, no prior substantial head trauma, no diabetes, no viral hepatitis, no positive human immunodeficiency virus status, no other major medical illness, not left-handed, and no contraindications for MRI scanning.

For the NPC patients, one more criteria are needed:

4. Must have at least 2 MRI scans: 1 before treatment and 1 at 3 or 6 months after treatment.

Exclusion criteria were:

1. Previous RT of the brain.
2. Contraindications for RT or MR imaging.
3. Other malignant disease that impacted prognosis of the patient and/or was likely to require treatment that would interfere with the study therapy.

2.3. Treatment

All patients were treated with the IMRT technique, which has been described previously (Cao et al., 2011; Xu et al., 2017; Lv et al., 2014; Qiu et al., 2017). Inverse planning was performed on the Corvus System (Peacock; Nomos, Deer Park, IL) using the simultaneous integrated boost technique. Target volumes were delineated slice-by-slice on treatment planning CT scans using an individualized delineation protocol that complies with International Commission on Radiation Units and Measurements reports 62 and 83. The prescribed radiation dose was as follows: a total dose of 68–70 Gy in 30–33 fractions at 2.12–2.33 Gy/fraction to the planning target volume (PTV) of the GTV-P, 60–70 Gy to the nodal gross tumor volume PTV (GTV-N), 60–64 Gy to the PTV of CTV-1 (high-risk regions), and 54–58 Gy to the PTV of CTV-2 (low-risk regions and neck nodal regions). All patients were treated with 1 fraction daily over 5 days per week. The dose-volume statistics for temporal lobes were calculated. Organs at risk were also outlined for dose constraint evaluation. Dose-volume statistics for the temporal lobes are listed in Table 1.

Table 1
Temporal irradiation dose for the 62 NPC patients. Abbreviation: NPC, Nasopharyngeal Carcinoma; N, Number.

Dose information	Dose (Gy)
Temporal.L dose (max)	68.6 (6.6)
Temporal.L dose (min)	2.0 (1.0)
Temporal.L dose (mean)	18.6 (5.8)
Temporal.R dose (max)	69.2 (6.8)
Temporal.R dose (min)	2.0 (1.0)
Temporal.R dose (mean)	18.7 (6.0)