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Radiation-induced abnormal cortical thickness in patients with nasopharyngeal carcinoma after radiotherapy

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A B S T R A C T

Conventional MRI studies showed that radiation-induced brain necrosis in patients with nasopharyngeal carcinoma (NPC) in years after radiotherapy (RT) could involve brain gray matter (GM) and impair brain function. However, it is still unclear the radiation-induced brain morphological changes in NPC patients with normal-appearing GM in the early period after RT. In this study, we acquired high-resolution brain structural MRI data from three groups of patients, 22 before radiotherapy (pre-RT) NPC patients with newly diagnosed but not yet medically treated, 22 NPC patients in the early-delayed stage after radiotherapy (post-RT-ED), and 20 NPC patients in the late-delayed stage after radiotherapy (post-RT-LD), and then analyzed the radiation-induced cortical thickness alteration in NPC patients after RT. Using a vertex-wise surface-based morphometry (SBM) approach, we detected significantly decreased cortical thickness in the precentral gyrus (PreCG) in the post-RT-ED group compared to the pre-RT group. And the post-RT-LD group showed significantly increased cortical thickness in widespread brain regions, including the bilateral inferior parietal, left isthmus of the cingulate, left bank of the superior temporal sulcus and left lateral occipital regions, compared to the pre-RT group, and in the bilateral PreCG compared to the post-RT-ED group. Similar analysis with ROI-wise SBM method also found the consistent results. These results indicated that radiation-induced brain injury mainly occurred in the post-RT-LD group and the cortical thickness alterations after RT were dynamic in different periods. Our findings may reflect the pathogenesis of radiation-induced brain injury in NPC patients with normal-appearing GM and an early intervention is necessary for protecting GM during RT.

1. Introduction

Radiation-induced brain injury, including structural and functional deficits, is a severe complication for patients with nasopharyngeal carcinoma (NPC) after radiotherapy (RT) (Zeng, et al., 2015). Based on the onset time of RT, three phases of the pathophysiological reaction to irradiation in normal brain tissue can be classified, acute reaction period (few days to few weeks), early delayed radiation period (1–6 months), and late delayed radiation period (6 months to few years) (Lell, 2015). Previous studies mainly focused on the radiation-induced functional deficits and structural necrosis (irreversible and progressive) in NPC patients in the late-delayed period after RT (Hsiao, et al., 2010; Shen, et al., 2015). However, most NPC patients after RT exhibited little change in their brain tissue according to the routine conventional MRI examination (Wang, et al., 2012), but they had the potential to suffer the radiation-induced cognitive impairment in future (Hsiao, et al., 2010). Thus, it is necessary to evaluate early radiation-induced injury (potentially reversible) in the NPC patients with normal-appearing brain tissue and

Abbreviations: NPC, nasopharyngeal carcinoma; RT, radiotherapy; GM, gray matter; pre-RT, before radiotherapy; post-RT-ED, in the early-delayed stage after radiotherapy; post-RT-LD, in the late-delayed stage after radiotherapy; SBM, surface-based morphometry; CMBs, cerebral microbleeds; WM, white matter; VBM, voxel-based morphometry; AJCC, American Joint Committee on Cancer; 2D-CRT, conventional two-dimensional radiotherapy; IMRT, intensity-modulated radiation therapy; KPS, Karnofsky performance status scale; FWHM, full width at half maximum; ANOVA, analysis of variance; GLM, general linear model; FDR, false discovery rate; CT, cortical thickness; RA, relative alteration; PreCG, precentral gyrus; bSTS, bank of the superior temporal sulcus; ICC, isthmus of the cingulate cortex; LOC, lateral occipital cortex; IPC, inferior parietal cortex; PoCG, postcentral gyrus; cMFC, caudal middle frontal cortex; STC, superior temporal cortex; MTC, middle temporal cortex; PreCUN, precuneus; DMN, default mode network.

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then provide neuroimaging biomarkers to facilitate clinical diagnose, treatment, and prevention.

Several underlying pathophysiological mechanisms have been described as cerebral microbleeds (CMBs), white matter (WM) and gray matter (GM) lesions in NPC patients after RT (Chan, et al., 1999; Chen, et al., 2015; Shen, et al., 2015). And CMBs in the temporal lobe is believed associating with increased likelihood of cognitive dysfunctions in NPC patients after RT (Shen, et al., 2015). Previous studies have found WM alterations in the temporal lobe in the earlier period after RT, including metabolic changes (Xiong, et al., 2013), and abnormalities of water diffusion (Chen, et al., 2015). Actually, brain abnormalities after RT may be multifocal and dispersed throughout GM within the treatment fields (Peterson, et al., 1995), especially in the temporal lobe (Chan, et al., 1999). Studies indicated that radiation-induced GM necrosis are often found in years after the completion of RT and are predominant hyper-intense on the conventional MRI (Chan, et al., 1999; Peterson, et al., 1995). To date, it is still unclear the radiation-induced brain morphological changes in normal-appearing GM in NPC patients in the early period after RT. Thus, objective methods are needed to characterize it thoroughly.

Both voxel-based morphometry (VBM) and surface-based morphometry (SBM) analyses were widely used to examine the morphological GM changes in various diseases, such as leukemia (Tamnes, et al., 2015), breast cancer (de Ruiter, et al., 2012), and glioma (Karunamuni, et al., 2016). With VBM analysis, Lv, et al. (2014) examined the radiation-induced changes in normal-appearing GM for NPC patients and found GM volume deficits in the temporal lobe in patients after RT. However, the VBM approach has some limitations. The smoothing step, registration, and templates used in the VBM analysis might influence the accuracy of the results (Li, et al., 2014). On the other hand, the VBM analysis potentially confounded several parameters, including cortical thickness, cortical surface area, and cortical folding (Grant, et al., 2015). Therefore, the alternative approach of SBM analysis has been developed, which facilitates highly sensitive characterization of cortical thickness, and provides more sensitive measurements of GM compared to the GM volume measure used with VBM analysis (Li, et al., 2014; Pereira, et al., 2012).

In practice, both vertex-wise and ROI-wise SBM approaches are widely used to assess the abnormalities of cortical thickness in various brain diseases (Blanc, et al., 2015; Jednoróg, et al., 2012). For example, the vertex-wise SBM approach been used to characterize patterns of GM changes in Alzheimer's disease (Blanc, et al., 2015), Parkinson's disease (Biundo, et al., 2015), and Depressive disorder (Qiu, et al., 2014), while the ROI-wise SBM approach has been used to depict brain morphometry involving socioeconomic status on children's brain structures (Jednoróg, et al., 2012), childhood maltreatment on brain structures (Kelly, et al., 2013), and brain structures of individuals with high familial risk of mood disorders (Papmeyer, et al., 2015). However, as far as we know, no studies have reported radiation-induced cortical thickness abnormalities in the normal-appearing GM for NPC patients with SBM approach.

The present study aims to noninvasively measure the radiation-induced changes of cortical thickness in the normal-appearing GM in NPC patients before and in different periods after RT using both vertex- and ROI-wise SBM approaches. NPC is sensitive to the radiation and the bilateral temporal lobes in these patients receive high doses of radiation because the temporal lobes are near to the tumor (Chan, et al., 1999; Lell, 2015). Thus, these patients have the potential for development of radiation-induced damage to the temporal lobes. Previous studies (Khong, et al., 2006; Moretti, et al., 2005) reported that NPC patients who received RT showed profound alterations of frontal functions, such as attention focusing, executive functions, and analogical judgment. And functional impairment in vision was common found in NPC patients who received RT (Chen, et al., 2005; Fang, et al., 2002; Wang, et al., 2012). Considering the findings of these studies, we hypothesized that cortical thickness would be altered in some areas of the brain in NPC patients after RT, especially in the temporal, frontal and occipital regions.

2. Material and methods

2.1. Subjects

We recruited 64 patients (51 M/13 F, aged 22–63 years old, 46.06 ± 8.69 years old, Han Chinese population) who were diagnosed with nonkeratinizing undifferentiated NPC from the Sun Yat-sen University Cancer Center, Guangzhou, China. All patients were diagnosed on the basis of histopathology. The clinical stages of NPC were classified according to American Joint Committee (AJCC) on cancer staging system (7th edition) (Edge and Compton, 2010), and the TNM (T = Tumor, N = Nodes, and M = Metastasis) stage for all of the patients were ranged from T1N0M0 to T4N2M0. Each patient underwent a detailed pre-treatment evaluation, including physical examination, nasopharyngeal fiberoptic endoscopy, MRI scan of the nasopharynx and neck, chest radiography, abdominal sonography, and whole body bone scan. We divided the 64 patients into 2 subgroups according to the time before and after completion of RT. Among the patients, 22 were before radiotherapy (pre-RT) patients with staging from T1N0M0 to T4N2M0, while the remaining 42 were after radiotherapy (post-RT) patients with staging from T1N0M0 to T4N2M0. The duration period between the receiving RT and MRI scanning was in range of 1–18 months.

Based on the onset time of symptom, the typical brain response to RT has been divided into three periods, the acute reaction period (few days to few weeks), early delayed radiation period (1–6 months), and late delayed radiation period (6 months to few years) (Duan, et al., 2016; Moretti, et al., 2005; New, 2001). To explore the effect of RT on brain structure in different periods, we sub-classified all of the 42 post-RT patients in the present study into two groups. One group, the post-RT-ED group, included 22 patients in the early-delayed stage after RT who had undergone 1–6 months RT prior to the MRI scanning. And the other group, the post-RT-LD group, included 20 patients in the late-delayed stage after RT who had undergone 7–18 months RT prior to the MRI scanning. Fig. 1 illustrates the procedures for selecting NPC patients in this study.

The protocol for nasopharynx and neck RT included the conventional two-dimensional radiotherapy (2D-CRT) and intensity-modulated radiation therapy (IMRT). The description of the 2D-CRT and IMRT techniques used in the present study can be found in previous studies (Lai, et al., 2011; Sun, et al., 2013; Xia, et al., 2000). In the 2D-CRT treatment, patients were immobilized in the supine position with a mask and treated with two lateral opposing faciocervical portals to irradiate the nasopharynx and the upper neck in one volume, followed by application of the shrinking-field technique to limit irradiation of the spinal cord. An anterior cervical field was used to treat the neck with a laryngeal block. The accumulated radiation doses were 66–76 Gy with 2 Gy per fraction applied to the primary tumor for each patient. In the IMRT treatment, immobilization for IMRT was the same as that used for 2D-CRT, and the primary tumor and the upper neck above the caudal edge of the cricoid cartilage were treated with IMRT. Then inverse IMRT planning was performed using the Corvus system (version 3.0, Peacock, Nomos, Deer Park, IL, USA). Meanwhile, a MIMiC multileaf collimator (Nomos, Sewickley, PA, USA) was used for planning and treatment. The total dose of radiotherapy was 58–70 Gy, divided into 30–33 fractions. Moreover, for the patients with stage I to IIa disease, no chemotherapy was required according to the guidelines (defined by the 6th edition of the UICC/AJCC staging system for NPC). However, it was recommended to provide concurrent chemoradiotherapy for stage IIb, and concurrent chemoradiotherapy with/without neoadjuvant/adjuvant chemotherapy for stages III to IVa–b. Overall, 1 patient in the post-RT-ED group and 1 patient in the post-RT-LD group received only RT. The remaining patients were treated with concurrent chemoradiotherapy, with cisplatin and 5-FU and/or 1–3 courses of neoadjuvant/