

Delayed leukoencephalopathy of non-small cell lung cancer patients with brain metastases underwent whole brain radiation therapy

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Abstract To explore the incidence, MR imaging findings, dynamic developing process of delayed leukoencephalopathy (DLE) in non-small cell lung cancer (NSCLC) patients with brain metastases patients who undergone whole brain radiation (WBRT) therapy, we retrospectively reviewed 48 NSCLC patients who underwent WBRT for brain metastases from January 2010 through June 2015 and had evaluable magnetic resonance imaging after treatment. The DLE were graded using a scale to evaluate T2-FLAIR (fluid attenuated image recovery) images: grade 1 = little or no white matter hyperintensity, grade 2 = limited periventricular hyperintensity and grade 3 = diffuse white matter hyperintensity. 48 NSCLC patients with brain metastases were enrolled. The median age of these patients was 55.7 years (range 33–75 years). The median follow-up was 12 months. The characteristic MR imaging of DLE in those patients was bilaterally diffuse white matter T2 hyperintensity around the periventricular areas without enhancement, sparing from U-fiber, callosum and gray matter structure. The incidence of DLE developed 6.25 % (3/48), 30.00 % (12/40), 48.39 % (15/31), 61.90 % (13/21), 85.71 % (6/7), 100 % (3/3) in those patients who were followed up for 3, 6, 9, 12, 24, 36 months, respectively. Through increased understanding of it, it may be possible to help clinicians develop further therapeutic strategies to maximize benefit while limiting

potential long term toxicities. These data supplement existing reports regarding the late effects of WBRT in NSCLC patients with brain metastasis.

Keywords Non-small cell lung cancer · Brain metastases · Whole brain radiation therapy · Delayed leukoencephalopathy · MRI

Introduction

Whole-brain radiation therapy (WBRT) is frequently used in the treatment of non-small cell lung cancer (NSCLC) patients to cure or palliate brain metastases. In the past, those patients with brain metastases had a short life expectancy, who did not survive long enough to suffer from late side effects of WBRT. However, with earlier cancer detection and advanced systemic treatments, the median survival has improved [1, 2]. Long-term survivors of NSCLC patients with brain metastases who have received WBRT are at risk for developing delayed leukoencephalopathy (DLE) which can result in dementia, cognitive dysfunction, urinary incontinence and mood [3].

A growing emphasis in cancer therapy has been on quality of life, not merely disease control, making DLE being a significant issue. DLE is related to white matter changes, which can be qualitatively shown on brain MRI images. Small cerebral vasculature and neuropil are damaged resulting in oligodendrocytic death and demyelination in white matter injury [4, 5].

DLE occurring in NSCLC patients with brain metastases patients who undergone WBRT hasn't been studied intensively. And recognition of DLE progression is critically important to any oncologist, here we explore the

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incidence, MR imaging findings, dynamic developing process of DEL in an attempt to better understand the treatment-associated leukoencephalopathy.

Methods

Patient selection

With Institutional Review Board approval, we retrospectively reviewed data from 220 consecutive NSCLC patients with brain metastases who underwent WBRT between January 2010 and June 2015. 48 NSCLC patients with brain metastases met the following criteria were enrolled: (a) histologically or cytologically proven NSCLC, with brain metastases identified by MRI. (b) had undergone WBRT once. (c) had evaluable imaging obtained every 3 month in the first year, and every 6 month after one year. (d) the first MR images showing no or less white matter hyperintensities. (e) had no neurosurgery history or prophylactic cranial irradiation (PCI). (f) free of any neurologic, psychiatric, or major systemic illnesses in the initial diagnosis.

WBRT

Cranial irradiation was given by lateral opposed fields to the whole brain delivered by Varian (6MV). Total dose used was 30 Gy in 10 fractions of 3 Gy in 2 weeks. No patient had repeat WBRT. No radiosensitizer was given during WBRT.

MR Imaging protocol

Brain MRI was performed on 1.5T or 3.0T scanner (Signa Excite HD GE Healthcare, Milwaukee, WI, USA). The parameters on 1.5T were as followed: image acquisition was performed with a fast spin-echo technique, including T2-weighted imaging, repetition time (TR)/echo time (TE) = 4300/102 ms; fluid attenuated inversion recovery (FLAIR) T2-weighted imaging, TR/TE = 8400/120 ms, inversion time = 2100 ms; T1WI contrast (axial), TR/TE = 500/12 ms. The parameters on 3.0T were as followed: image acquisition was performed with a spin-echo technique, including T2-weighted imaging, repetition time (TR)/echo time (TE) = 5100/130 ms; fluid attenuated inversion recovery (FLAIR) T2-weighted imaging, TR/TE = 9600/110 ms, inversion time = 2400 ms; T1WI, FLAIR, TR/TE = 2705/24 ms, inversion time = 860 ms; T1WI contrast (axial), TR/TE = 580/17 ms. Section thickness of all images was 5 mm and the interslice gap was 1 mm. All axial scans were parallel to the anteroposterior commissure (AC-PC) line. The gadopentetate dimeglumine was injected through ulnar vein with .1 mmol/kg.

MR Imaging evaluation

DLE were scored according to Monaco et al. [6]: grade 1, little or no white matter hyperintensity; grade 2, limited periventricular hyperintensity; and grade 3, diffuse white matter hyperintensity. All images were reviewed independently by two neuroradiologists, who had more than 10-year work experience in neuroradiology. They were blinded to the patients' clinical findings and history. All discrepancies were rechecked and consensus was achieved by discussion.

Figure 1 shows representative MRIs.

Statistical analysis

Descriptive statistics such as mean with standard deviation and median with range were used for continuous data. The cumulative incidence was calculated using the Kaplan–Meier method. Categorical data were compared using χ^2 test. Normally distributed continuous data were compared using appropriate *t* test (SPSS 13.0). A *P* value of .05 was considered statistically significant.

Results

Patient characteristics

48 NSCLC patients with brain metastases were enrolled, with 22 men and 26 females. The median age of the patients was 55.7 years (range 33–75 years, SD 10.6). The median follow-up was 12 months. At diagnosis, the median Karnofsky Performance Score (KPS) was 90 (range 70–100). Symptoms developed a median of 6 months (range 3–12 months) after WBRT. 34 patients (70.8 %) presented with headache, 20 (41.7 %) with cognitive dysfunction, 11 (22.9 %) with motor deficits and 2 (4.2 %) with confusion. The mean number of brain metastases lesions was 5.8 (SD 3.4) at diagnosis. After WBRT, 29 (60.4 %) patients had a favorable effect of brain metastases.

MR imaging of delayed leukoencephalopathy

DLE showed low signal intensity on T1-weighted imaging and high signal on T2-weighted imaging around the periventricular areas, reflecting the increase in water content and loss of myelin. It became sporadic patchy T2-FLAIR hyperintensities in the semiovale areas at the beginning, and developed progressively bilaterally diffuse white matter T2-FLAIR hyperintensities over months, with irregular border, sparing from U-fibra, corpus callosum and gray matter (Fig. 2). No enhancements or any mass effects

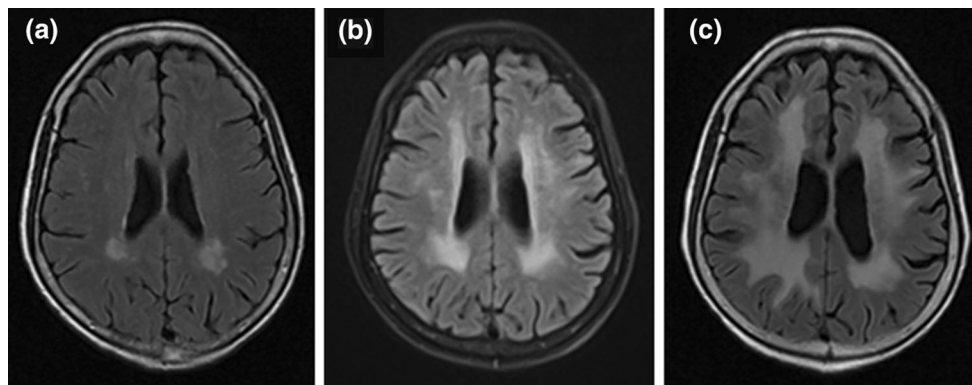


Fig. 1 T2-FLAIR imaging **a** grade 1, **b** grade 2 and **c** grade 3 white matter changes

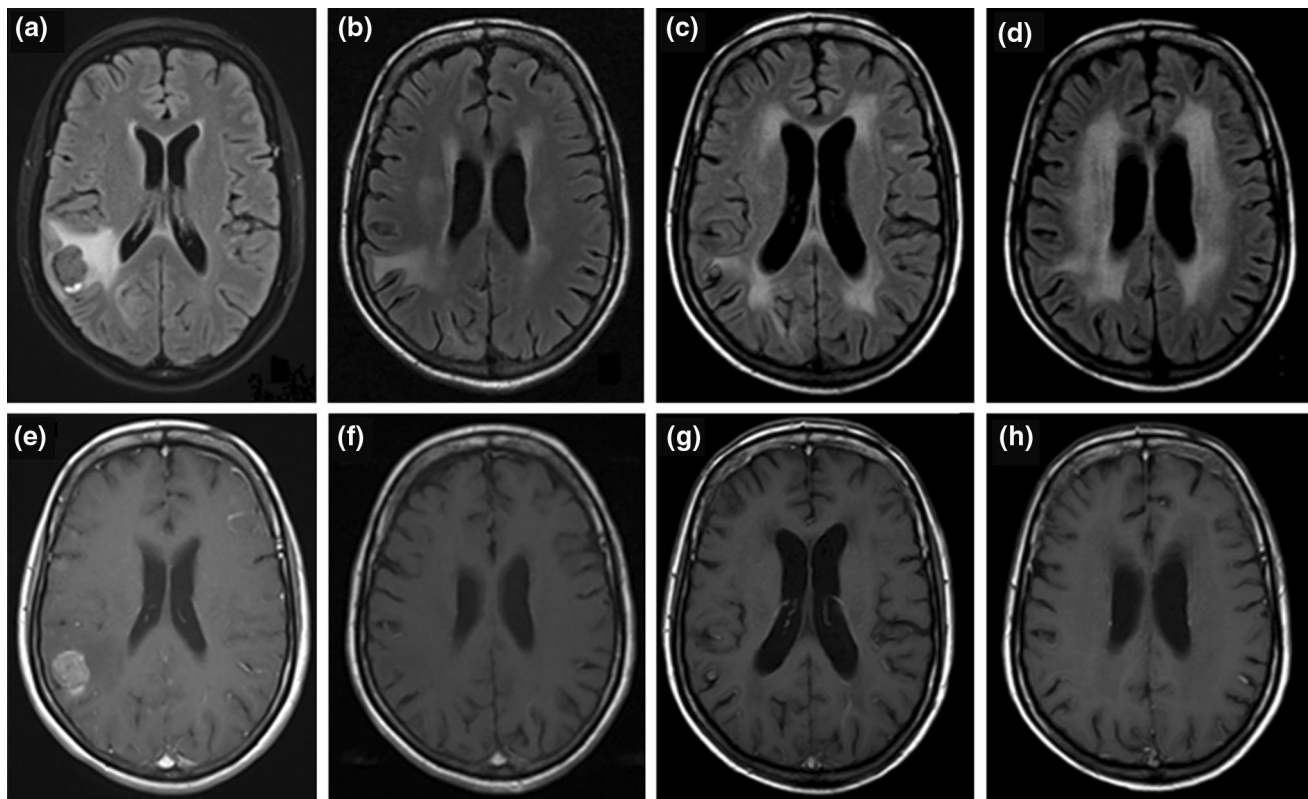


Fig. 2 A 51-year-old woman with brain metastases from NSCLC underwent whole-brain radiation therapy (WBRT). **a–d** T2-FLAIR images show patchy white matter changes in the periventricular areas

were found. It revealed as well cortical-subcortical atrophy, with variable degrees of ventriculoectasis.

Incidence of delayed leukoencephalopathy

Among 48 patients, 24 patients (50 %) developed treatment-related DLE a median of 6 months after WBRT (range 3–9 months). The patients had similar initial white matter grades, which both are \leq grade 1. Among 24 patients, male/female was 10/14 and the median age was 59. The incidence of DLE developed 6.25 % (3/48), 30.00 % (12/40), 48.39 %

and develop to diffuse white matter changes over months. **e–h** No enhancements of those white matter changes were found

(15/31), 61.90 % (13/21), 85.71 % (6/7), 100 % (3/3) in these patients who were followed up for 3, 6, 9, 12, 24, 36 months, respectively (Fig. 3).

Discussion

WBRT has been advised as the primary treatment for metastatic brain cancer, as it can reduce metastatic tumor recurrence [2, 7]. We found high incidence of treatment-related delayed leukoencephalopathy (\geq grade 2) that have

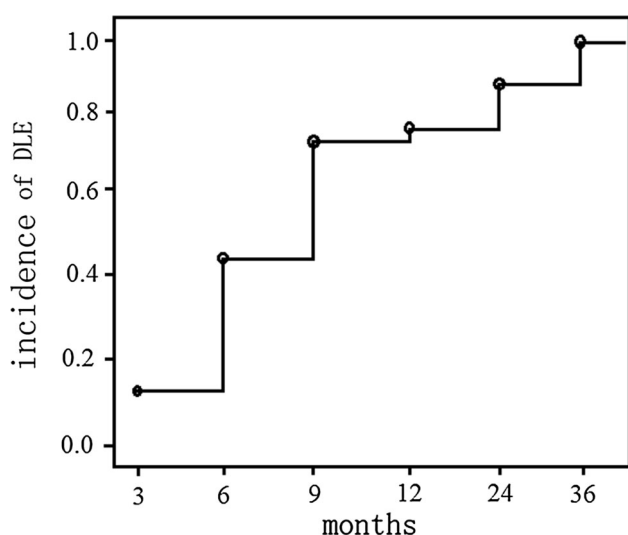


Fig. 3 Incidence of DLE

correlated with white matter changes in those NSCLC patients with brain metastases. The incidence of DLE developed 6.25 % (3/48), 30.00 % (12/40), 48.39 % (15/31), 61.90 % (13/21), 85.71 % (6/7), 100 % (3/3) in these patients who were followed up for 3, 6, 9, 12, 24, 36 months, respectively, which were varied in other studies. Ebi et al. found that the incidence were 34.4 % (11/32), 42.9 % (6/14), 66.7 % (2/3), and 100 % (2/2) of the patients with brain metastases who were followed up for 6, 12, 24, and 36 months, respectively [8]. Stokes et al. found that the incidence were 25.7, 31.4, 50.1 and 69.5 % in breast cancer brain metastases patients who received WBRT plus SRS for 6, 9, 12 and 15 month, respectively [9]. Fujii et al. detected it in 83 % of long-term survivors treated with WBRT for brain metastases, but not before 6 months [10]. Steven et al. declared that diffuse white matter changes can also occur in normal aging people, but it had a more slower progress [11]. Among the possible reasons for the high incidence of our study might be the generally older age of NSCLC patients with brain metastases after WBRT, which was similar with Ebi et al.

The complications of radiation-leukoencephalopathy are usually divided into acute effects that can occur during the course of radiation therapy, early-delayed effects that appear 2–4 months after radiation therapy, and late effects that can develop >90 days after the initiation of radiation therapy, which have been reviewed in detail in previous publications [12, 13]. We found that, the DLE of NSCLC patients with brain metastases developed a median of 6 months (range 3–9 months) after WBRT. Patients typically exhibit memory problems, motor disorders, urinary incontinence and personality changes, which impact their quality of life. To improve its efficacy, several randomized trials attempted to modify WBRT via different

fractionation schedules or the use of radiation sensitizers but failed [14–16]. Some radioprotectants like memantine are being explored [17].

Among 48 patients who underwent WBRT, 24 patients developed DLE compared with a normal pretreatment MR. At the first 3 months after WBRT, there were near-normal MR images. At the median month of 6, MRI revealed various degrees of cerebral atrophy and diffuse white matter T2-FLAIR hyperintensity sparing of the U-fiber and gray matter, which developed spot, patchy white matter T2-FLAIR hyperintensity around the periventricular areas at the beginning and progressed to diffuse white matter changes over months or years. The cerebral atrophy and ventricular dilatation are more likely secondary to the white matter process. The pathophysiological mechanisms include damage to oligodendrocytes, thereby creating axonal demyelination and disruption of vascular endothelial cells, contributing to coagulative necrosis, vessel thickening, and focal mineralization [18, 19]. DLE was a progressive development over time since it occurred, which was a classic time-dependent course. It was irreversible and treatment with steroids had modest benefit.

A growing emphasis have been linked to neurocognitive dysfunction and white matter changes in brain metastases patients after WBRT. Correal et al. systematically reviewed studies and found that comparisons between patients treated with combined modality therapy versus chemotherapy alone indicated greater cognitive impairments in patients who also had WBRT [20]. In a secondary analysis of a randomized trial revealed that WBRT had nonnegligible effect on neurocognitive function despite of metastatic tumor recurrence [21]. And Chang et al. also demonstrated that patients treated with stereotactic radiosurgery (SRS) plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone [22]. White matter changes have been associated with cognitive dysfunction, in addition, impaired hippocampal neurogenesis after WBRT was also related to neurocognitive functions decline. Therefore, hippocampal-avoidance whole brain radiation therapy (HA-WBRT) as an innovative approach has been investigated [23]. Gondi et al. reported the results from the phase III RTOG 0933 trial of HA-WBRT might mitigate the neurocognitive effects of WBRT [24]. And two cooperative group trials such as NRG (National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, and Gynecologic Oncology Group) CC (Cancer Control) 003 and NRG-CC001 to elucidate the effects of HA-WBRT will be performed.

Our study had several limitations. It was retrospective and lacked pathologies. Long-term survivors of NSCLC patients with brain metastases remain the minority.

Prolongation of survival for our patients was not analyzed, as the main object of our study was to demonstrate the incidence and MR imaging of DLE in a different cancer history. And we lacked of association between white matter abnormalities and cognitive and motor performance. Despite these limitations, the results in our study suggested the high incidence of DLE in NSCLC patients after WBRT was true. This work added to mounting evidence demonstrating the delayed effects of WBRT in those brain metastatic patients. Through increased understanding of it, it may be possible to develop further therapeutic strategies to maximize benefit while limiting potential long term toxicities.

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Compliance with ethical standards

Conflict of interest None.

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