Pulsed Reduced Dose-rate Radiotherapy as Re-irradiation for Brain Metastasis in a Patient with Lung Squamous-celled Carcinoma

Guang-Hui Li1,∗, Yong Liu2, Jin-Liang Tang3, Dong Zhang4, Pu Zhou1, Ding-Qiang Yang1 and Chuan-Kun Ma1

1Institute for Cancer Research in People’s Liberation Army, Xinqiao Hospital, Third Military Medical University, Chongqing, 2Department of Neurology, Xinqiao Hospital, Third Military Medical University, Chongqing, 3Department of Pathology, Xinqiao Hospital, Third Military Medical University, Chongqing and 4Department of Radiology, Xinqiao Hospital, Third Military Medical University, Chongqing, China

∗For reprints and all correspondence: Guang-Hui Li, Institute for Cancer Research in People’s Liberation Army, Xinqiao Hospital, Third Military Medical University, Chongqing 400037, China. E-mail: liguanghui_2000@yahoo.com.cn

Received March 21, 2012; accepted May 15, 2012

The recurrence and progression of brain metastases after brain irradiation are a major cause of mortality and morbidity in patients with cancer. The risk of radiation-induced neurotoxicity and efficacy probably leads oncologists to not consider re-irradiation. We report the case of a 48-year-old Asian male diagnosed with squamous cell lung cancer and multiple brain metastases initially treated with 40 Gy whole-brain radiotherapy and 20 Gy partial brain boost. Fourteen grey stereotactic radiosurgery as salvage for brain metastases in the left occipital lobe was performed after initial irradiation. The recurrence of brain metastases in the left occipital lobe was demonstrated on magnetic resonance imaging at 9 months after initial radiotherapy. He received the second course of 28 Gy stereotactic radiosurgery for the recurrent brain metastases in the left occipital lobe. The third relapse of brain metastases was demonstrated by a magnetic resonance imaging scan at 7 months after the second radiotherapy. The third course of radiotherapy was performed because he refused to undergo surgical resection of the recurrent brain metastases. The third course of irradiation used a pulsed reduced dose-rate radiotherapy technique. It was delivered in a series of 0.2 Gy pulses separated by 3-min intervals. The recurrent brain metastases were treated with a dose of 60 Gy using 30 daily fractions of 2 Gy. Despite the brain metastases receiving 162 Gy irradiation, this patient had no apparent acute or late neurologic toxicities and showed clinical improvement. This is the first report of the pulsed reduced dose-rate radiotherapy technique being used as the third course of radiotherapy for recurrent brain metastases.

Key words: CNS-RadOncol – palliative care – radiation oncology

INTRODUCTION

It is estimated that 20–40% of patients with systemic cancer will develop metastases. The incidence of metastatic tumour to the central nervous system is about 10 times that of primary brain tumours (1). Lung cancer is the most common malignancy in the world. Brain metastases are the most common features in patients with non-small-cell lung cancer (NSCLC) and represent a major cause of mortality and morbidity. The management of brain metastases in patients has improved over time with the developments in technology and a better knowledge of brain metastases (2). But the prognosis of brain metastases continues to remain poor in patients with NSCLC.

Therapeutic modalities of brain metastases include whole-brain radiotherapy (WBRT), surgery, stereotactic radiosurgery (SRS) and chemotherapy (3). The mainstay of treatment
for multiple brain metastases is WBRT. However, the relapse of brain metastases in patients with NSCLC has consistently been the most frequently observed manifestations. Surgery and/or SRS often have been used for limited number recurrent brain metastases in patient with NSCLC. Chemotherapy may offer some palliative benefit to multiple brain metastases, but it does not show significantly prolonged survival. However, the treatment with re-irradiation of recurrent brain lesions after initial radiotherapy increases the risk of increased late neurotoxicity and radionecrosis of the brain.

A novel technique of re-irradiation, pulsed reduced dose-rate radiotherapy (PRDR), was developed for local failure of the tumour after radiotherapy. It delivers a series of 0.2 Gy pulses separated by 3 min intervals. It caused a high local control rate and good tolerance in patients with local recurrence of glioblastoma (4,5). Therefore, PRDR as the fourth times radiotherapy for the recurrent brain metastases was performed in a patient with NSCLC.

CASE REPORT

A 48-year-old Asian male was admitted to our hospital with complaints of cough and haemoptysis in October 2008. A mass in the left inferior lung and multiple enlarged mediastinal lymph nodes were detected on thoracic computerized tomography (CT). A biopsy of the mass in the left lung was performed. The pathological specimens were diagnosed as a poorly differentiated squamous carcinoma. After a magnetic resonance imaging (MRI) scan of the brain, bone scan and ultrasound examination of abdomen, the cancer of this patient was assigned to stage T2N3M0 according to the TNM Staging Criterion (AJCC2002) (6). Then, six cycles of chemotherapy and three-dimensional conformal radiotherapy (3D-CRT) of the tumour of the left inferior lung and mediastinal lymph nodes was performed from December 2008 to May 2009. The chemotherapy regimen consisted of docetaxel 75 mg/m² on Day 1 and cisplatin 75 mg/m² on Day 1 every 21 days. The prescribed dose of 3D-CRT is 60 Gy in 2 Gy fractions. Tumour response evaluation was stable disease (SD) according to Response Evaluation Criteria in Solid Tumors (RECIST).

The patient experienced headache, dizziness and visual extinction in June 2009. Enhancing brain MRI showed multiple metastases in brain tissue and the largest metastases bed in the left occipital lobe (Fig. 1). He was treated with a WBRT dose of 40 Gy/20 F/4 W with a fractionated dose of 2 Gy and a boost dose of 20 Gy/10 F/2 W for the metastases of the left occipital lobe. His headache and dizziness were completely resolved and visual extinction lightened after radiotherapy. Brain enhancing MRI demonstrated that the brain metastases disappeared, except for one in the left occipital lobe in August 2009 (Fig. 2). Then, the patient was treated with SRS as salvage and the prescribed dose of 14 Gy/4 F/8 day delivered to the metastases in the left occipital lobe. The neurological symptoms had complete resolution. Subsequently, he had a follow-up every 3 months.

The patient did well until June 2010, when he had a serious headache. An enhancing recurrence in the left occipital lobe was demonstrated on a brain MR (Fig. 3). Evaluation of the left lung cancer and mediastinal lymph nodes was SD and no new metastases were found on radiologic examination and physical examination. He refused to undergo surgical resection of the recurrent brain metastases and received the second SRS and nimustine (ACNU) chemotherapy. The prescribed dose of SRS was 28 Gy/8 F/2.5 W. His headache was relieved after the second SRS treatment and the recurrent brain metastases showed partial remission.
on brain enhancing MRI (Fig. 4). Chemotherapy (ACNU 2 mg/kg/dose/once 4–6 weeks) was terminated until December 2010 because of grade IV myelosuppression.

The patient complained of vomiting, dizziness and serious headache in February 2011. Subsequent brain MRI showed diminished enhancing metastases of the left occipital lobe enlarged and with necrosis in the centre (Fig. 5). The left lung cancer and mediastinal lymph nodes remained stable on thoracic CT images and no other metastases were found on radiologic examination and physical examination. Since he refused to receive surgical resection again and he was not eligible for clinical trial, the patient was treated with three-dimensional conformal PRDR for the recurrent brain metastases. It was carried out by delivering 6 MV-X rays in a series of 0.2 Gy pulses separated by 3-min intervals. A total of 60 Gy was delivered using 30 daily fractions of 2.0 Gy. The treatment of this patient was completed on 23 March 2011. The patient had resolution of headache, vomiting and dizziness after the PRDR treatment.

The patient was followed up every 3 months. However, he refuses to undergo any examination by diagnostic imaging, blood and biochemistry except for physical examination. The patient lives entirely self-dependently and complains occasionally of bloody phlegm and episodes of headache for several seconds. The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment Beijing Version (MoCA-Beijing) were used to assess brain global cognitive function. The Instrumental Activities of Daily Living (IADL) was used to assess independence in activities of daily living and depressive symptoms (7,8). Evaluation of his capability and intelligence was performed on the last follow-up using MMSE, IADL and MoCA-Beijing on 6 December 2011. His score of MMSE was 24adj and his IADL was categorized into 28 as independent. The MoCA-Beijing score of the

Figure 3. The recurrent brain metastases in the left occipital lobe were shown on axial and sagittal MRI with gadolinium contrast 9 months after WBRT and stereotactic radiosurgery (SRS) as salvage.

Figure 4. Axial and sagittal T1-weighted MRI with gadolinium contrast obtained 1 month after the second SRS treatment. The recurrent brain metastases were in partial remission.
The results of IADL, MMSE and MoCA-Beijing indicated that he had independent ability for daily living and distinct cognitive function.

**DISCUSSION**

Brain metastases, particularly for patients with multiple lesions, have an overall poor prognosis. Radiotherapy is the main treatment option for brain metastases. However, no studies provide evidence to identify which adjuvant therapies are beneficial in the setting of recurrent/progressive brain metastases after initial radiotherapy. Treatment of recurrent brain metastases after initial radiotherapy should be individualized based on a patient’s functional status, previous treatment and type of primary cancer, state of primary cancer and recurrent or progressing metastatic brain tumour and so on. SRS of re-irradiation and surgical resection are major palliative therapeutic modalities.

The tolerance dose for the brain to a single course of radiotherapy is 50–60 Gy in 2 Gy daily fractions. Clinicians are reluctant to perform re-irradiation of the brain, because of the risk of severe side effects. Re-irradiation of brain metastases by radiosurgery or brachytherapy has been reported. Evidence shows that most patients had no relevant radiation-induced toxicity after a second course of WBRT or SRS (9). However, no studies provide experience of a third course of radiotherapy for the second relapse of brain metastases and radiation-induced toxicity.

PRDR, a novel re-irradiation technique, delivers a series of 0.2 Gy pulses separated by 3 min intervals and obtains an apparent dose rate of 0.0667 Gy/min. It may increase radiosensitivity of tumour cells and provides a fixed time interval to improve sublethal damage repair of normal tissue (10,11). Studies by Howard demonstrated that PRDR is a well tolerated and safe re-irradiation approach to treat the recurrent glioma with a palliative benefit (12). The patient received the third course of radiotherapy using PRDR and the dose distribution of PRDR was shown in Fig. 6. The total dose of metastases in the left occipital lobe was 162 Gy. The result of the evaluation of capability and intelligence showed that the patient had no serious radiation-induced neurotoxicity.

**CONCLUSION**

PRDR as a re-irradiation technique for the recurrence or the second relapse of a larger volume of brain metastases may
be a promising treatment option for carefully selected patients, but prospective studies are needed to delineate its efficacy and toxicity.

PATIENT CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

Authors’ roles

G-H.L. is an attending physician and radiation oncologist of this patient and drafted this manuscript. Y.L., D.Z. and J-L.T. took part in the diagnosis and evaluation of capability and intelligence for this patient. P.Z., D-Q.Y. and C-K.M. attended to the treatment of this patient. All authors read and approved the final manuscript.

Conflict of interest statement

None declared.

References