Long-term survival in a patient with extensive-stage small cell lung cancer treated with multiple courses of salvage stereotactic radiation after whole brain radiotherapy: A case report

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Abstract. Intracranial recurrence following initial cranial irradiation for extensive-stage small cell lung cancer (ES-SCLC) can often be a treatment dilemma given the aggressive nature of the disease, the overall poor prognosis and concerns regarding re-treatment toxicity. The present report describes the case of a 62-year-old man diagnosed with ES-SCLC and synchronous brain metastases who initially underwent whole brain radiotherapy, chemotherapy and consolidative thoracic radiotherapy. The patient was found to have a solitary intracranial recurrence at both 3.5 and 6 years after his diagnosis. On both occasions, the patient received salvage stereotactic radiation, 30 Gy in 5 fractions, and continues to remain functionally independent. Overall, the present case demonstrates that with the appropriate patient selection, aggressive local salvage of recurrent intracranial ES-SCLC with stereotactic radiation can yield excellent and durable clinical outcomes.

Introduction

Small cell lung cancer (SCLC) is a poorly differentiated pulmonary neuroendocrine carcinoma that is characterized by its rapid doubling time, high growth fraction, early development of widespread metastases, and high sensitivity to initial chemotherapy and radiotherapy (1). Approximately two-thirds of patients present with extensive stage disease (ES-SCLC), which has been classically defined as tumour or nodal volume that cannot be safely encompassed within a single radiation field. Even with treatment, ES-SCLC has a poor prognosis with a median survival of 8 to 13 months and a 5-year survival of 3% relative to the overall population (2-4).

Brain metastases, in particular, are found in 20% of patients at the time of diagnosis (5,6). Notably, whole brain radiotherapy (WBRT) has historically been preferred over stereotactic approaches in SCLC due to the frequent occurrence of multiple metastases and high likelihood of occult disease, as demonstrated by often rapid and diffuse central nervous system (CNS) progression (7). Despite its radiosensitivity, intracranial recurrence after cranial irradiation can occur in up to 30% of patients, and this risk increases with prolonged survival (8-10). In the literature, the rates of intracranial recurrence are reported primarily after prophylactic cranial irradiation (PCI) and usually occur between 4 and 27 months post-PCI (6,10-13).

Treatment decisions for intracranial recurrence are often complex and should account for a variety of factors including volume of disease, extent of extracranial disease, symptom burden, previous therapy, performance status, and patient preference (10). For patients previously treated with WBRT, stereotactic approaches including stereotactic radiosurgery are often advantageous in providing local control while reducing the volume of brain re-irradiated and thus overall toxicity. In this article, we present a case of a patient with ES-SCLC experiencing long-term survival following initial WBRT and subsequent salvage stereotactic radiation for multiple intracranial recurrences.

Case report

A 62-year-old man with a 40-pack-year smoking history presented to the Emergency Department in 2015 with acute-on-chronic dyspnea and a 5-week history of right-sided sensory changes in both the upper and lower extremities. Physical exam findings confirmed right-sided focal neurological deficits but preserved cranial nerve and cerebellar function. His Eastern Cooperative Oncology Group (ECOG) performance status score was 1.

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Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ES, extensive-stage; PCI, prophylactic cranial irradiation; SCLC, small cell lung cancer; WBRT, whole brain radiotherapy

Key words: ES-SCLC, WBRT, intracranial recurrence, stereotactic radiation

MRI of the head revealed 7 intracranial metastases within the left cerebral hemisphere, the largest of which measured 2 cm in diameter and was located in the left postcentral gyrus (Fig. 1A). Staging investigations demonstrated an 8.1 cm mass in the right apex of the lung with involvement of the chest wall and mediastinum, with no further distant metastases. Pathology from a CT-guided core biopsy of the lung mass revealed small cell carcinoma with positive immunohistochemical staining for synaptophysin, thyroid transcription factor 1, and cytokeratin AE1/AE3, with a perinuclear dot staining pattern. The malignant cells were negative for p63 and cytokeratin 5/6. Therefore, the patient was diagnosed with ES-SCLC.

In the context of numerous symptomatic brain metastases, palliative WBRT was delivered to a total dose of 20 Gy in 5 fractions. The patient then completed 6 cycles of palliative chemotherapy with cisplatin and etoposide. He endorsed overall improvement in his symptoms and functional abilities with treatment. Subsequent imaging showed interval reduction in the size of the right lung mass with no evidence of brain metastases on CT head (Fig. 1B). The patient then completed consolidative thoracic radiotherapy to a total dose of 30 Gy in 10 fractions. Regular follow-up imaging over the next 40 months revealed no evidence of disease progression in the thorax or CNS.

In mid-2019, approximately 3 years post-treatment, the patient began to notice a persistent, left-sided headache accompanied by short-term memory deficits. Physical examination demonstrated left-sided cerebellar dysfunction with nystagmus and clumsiness on heel-to-toe walking. Restaging investigations identified a new solitary mass measuring 3.6 cm with a broad dural base overlying the lateral left temporal and occipital lobe (Fig. 2A). No other evidence of intrathoracic or intraabdominal disease was appreciated. Neurosurgery was consulted but did not recommend surgical resection given the high risk of morbidity, particularly Wernicke's aphasia. The patient thus underwent stereotactic radiation to the solitary brain metastasis, 30 Gy in 5 fractions (Table SI). Follow-up MRI imaging demonstrated positive response to treatment with a gradual decrease in the size of the mass. However, there was also subsequent evidence of evolving radiation necrosis in the treated area, associated with mild memory loss and word-finding difficulties (Fig. 2B). As these symptoms were overall quite minor and improved spontaneously with time, no specific treatments for radionecrosis were implemented.

In late 2021, almost 6 years from his initial diagnosis, the patient began to experience episodes of transient aphasia. Repeat imaging of the head revealed a new enhancing mass in the right parietooccipital lobe measuring 1.1 cm in diameter, with no evidence of residual metastasis in the left hemisphere (Fig. 3). Further staging investigations did not identify any extracranial disease progression. Notably, the previous area of radionecrosis remained stable over time and the patient continued to deny any significant neurologic symptoms that would necessitate intervention. He went on to receive a second course of stereotactic radiotherapy, 30 Gy in 5 fractions, and will be monitored for treatment response. At the present time, the patient is functionally independent, ambulatory, and continues to participate within his local community by teaching firearm safety. His ECOG performance status remains unchanged. The timeline of the present case is shown in Fig. 4.

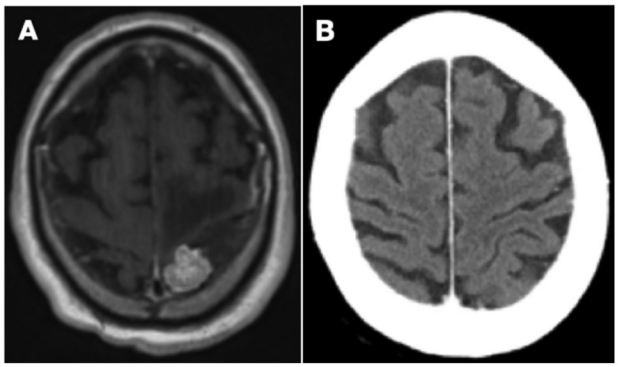

Figure 1. (A) Axial T1-weighted MRI of the head with contrast showing an enhancing mass in the superior medial aspect of the left postcentral gyrus. (B) Axial CT of the head with contrast showing no evidence of intracranial metastases following completion of whole brain radiotherapy and 6 cycles of chemotherapy.

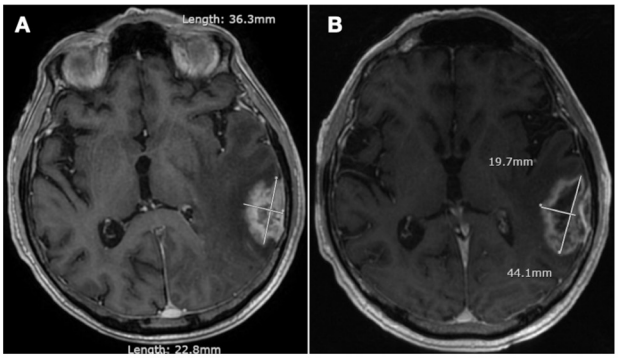

Figure 2. (A) Axial T1-weighted MRI of the head with contrast showing a large mass with a broad dural base overlying the lateral left temporal and occipital lobe. (B) Axial T1-weighted MRI of the head with contrast showing an area of heterogenous enhancement within the left temporal lobe representing radionecrosis 8 months after completion of stereotactic radiation.

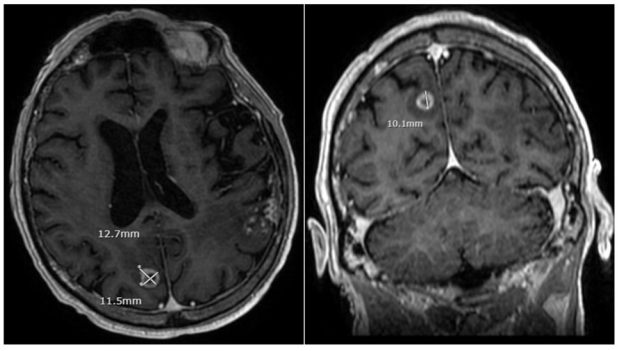

Figure 3. Axial and coronal T1-weighted MRI of the head with contrast showing an ovoid enhancing mass in the subcortical white matter of the right parietooccipital lobe.

Discussion

Following initial WBRT in ES-SCLC, repeat WBRT has been a conventional consideration for intracranial recurrence given the high likelihood of occult disease. However, the life expectancy for such patients is already quite poor, and even with salvage WBRT, median survival ranges from

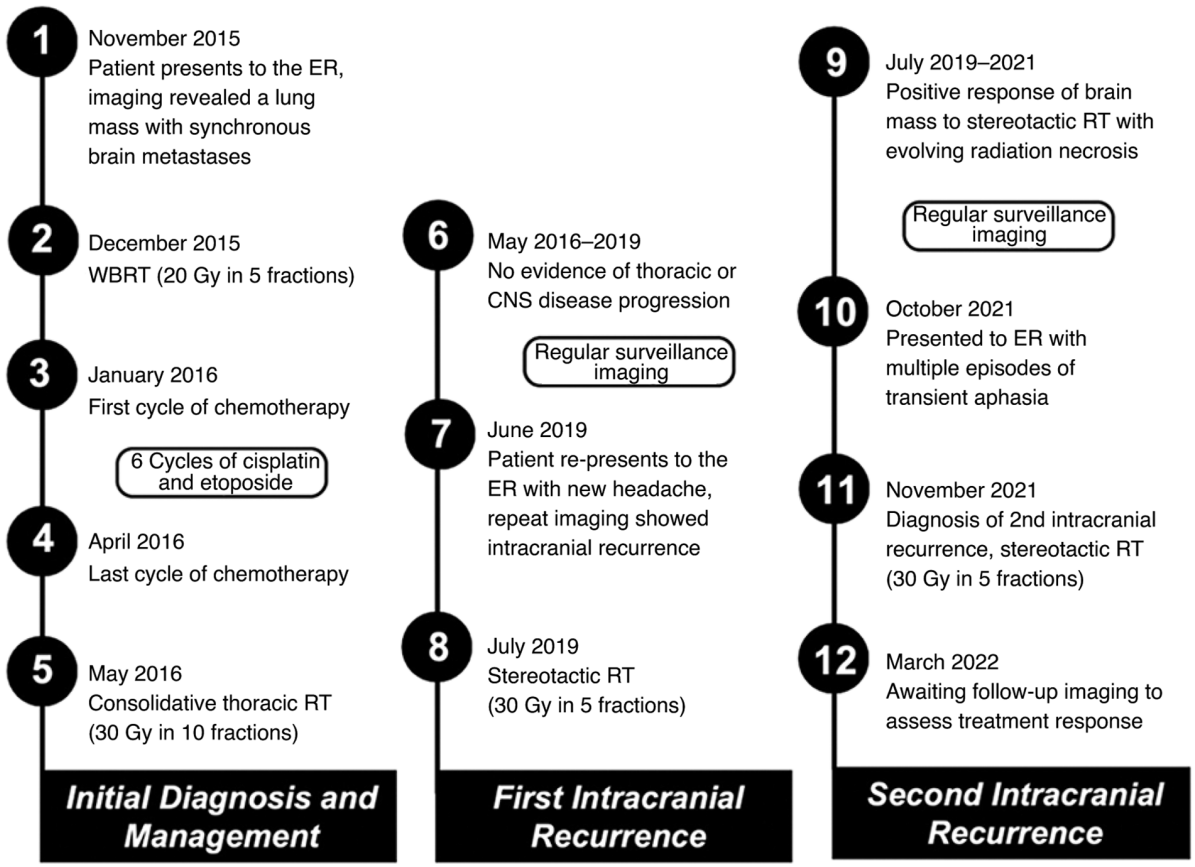

Figure 4. Timeline depicting the events surrounding the initial diagnosis and management of the patient, and the subsequent identification and treatment of two intracranial recurrences over the course of 6 years. CNS, central nervous system; ER, emergency room; RT, radiotherapy; WBRT, whole brain radiotherapy.

2 to 5 months (14-16). Furthermore, re-irradiation of the whole brain raises concerns regarding cumulative tissue toxicity impacting cognition and quality of life (17).

In contrast, stereotactic treatments deliver high dose and precisely targeted radiation to attain local control while limiting dose to surrounding normal structures (18). It has become increasingly popular in the treatment of limited intracranial disease for non-small cell histologies, although the literature supporting its use in SCLC is sparse. Retrospective studies, however, suggest local control rates upwards of 70% and minimal toxicity even after prior WBRT. Yet, median overall survival remains poor, ranging from 3 to 14 months following salvage stereotactic radiotherapy (8,18-25). Furthermore, despite the decent local control rates, distant brain failure occurs in the majority of patients. In these instances, further retreatment with stereotactic radiation is often feasible and represents an additional advantage of stereotactic approaches over repeat WBRT.

One of the largest retrospective studies investigating outcomes of re-irradiation for intracranial recurrence in the setting of SCLC comes from the MD Anderson Cancer Center (9). Salvage stereotactic radiation was associated with a significant overall survival benefit at 6 months compared to salvage WBRT (58 vs. 21%; P<0.001), although this is likely confounded by selection bias (9). On multivariate analysis, poor performance status and uncontrolled extracranial disease were associated with worse overall survival. Other important prognostic factors include the receipt of chemotherapy prior to intracranial recurrence, tumour volume, and time between initial WBRT and salvage therapy (9,18,21,23). The patient presented in this case report had many positive prognostic factors, highlighting the importance of not only control of systemic disease, but also aggressive management of intracranial recurrence in maximizing CNS control, overall survival, and quality of life (10,23).

While salvage stereotactic radiation can reduce the cumulative radiation dose to the entire brain compared to repeat WBRT, stereotactic approaches do still carry a risk of neurologic morbidity from radiation necrosis (10,26). The patient presented here was no exception. Radionecrosis rates following salvage stereotactic radiation after previous WBRT or PCI range from 0 to 12.5% and can lead to adverse symptoms such as hemiparesis, imbalance, aphasia, and loss of vision (21,23,25,27). However, fractionated stereotactic regimens can reduce the risk of radionecrosis particularly for larger brain metastases (28). For neuroendocrine tumours that are inherently radiosensitive, using a lower stereotactic dose may further minimize late effects while still providing reasonable disease control. The specific dose and fractionation used in this case report, 30 Gy in 5 fractions, was selected with this in mind, and is in fact one of several standard regimens for intact brain metastases at the institution where this patient was treated. Ultimately, optimizing radiation dose and fractionation is necessary to balance local control with treatment-related toxicity, though more data is still required to better understand the long-term effects of stereotactic radiation.

In conclusion, we present a case of a patient with ES-SCLC who has survived over 6 years following initial WBRT and multiple courses of salvage stereotactic radiation for separate intracranial recurrences. This case challenges commonly held notions that intracranial recurrence in SCLC is always diffuse and associated with simultaneous systemic disease progression or clinical deterioration. Amongst patients with isolated intracranial recurrence, it is important to identify appropriate candidates for salvage stereotactic radiation in order to maintain quality of life, expand re-treatment options, and ultimately prolong survival.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AV acquired and collected patient data, performed the literature review and data interpretation, and drafted the manuscript. BA conceived and designed the present study, revised the manuscript, and was responsible for the treatment of the patient. TT contributed to the conceptualization of the case report and manuscript drafting, and provided critical revisions on the intellectual content. AV, BA and TT confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was provided by the patient for publication of the case report in all formats, including publication of all clinical details and diagnostic images.

Competing interests

The authors declare that they have no competing interests.

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