Focal 3D conformal high-dose hypofractionated radiotherapy for brain metastases

Antonin Levy[a], Philippe Saiag[b], Cyrus Chargari[c] and Avi Assouline[d]

The optimal management of patients with few brain metastases is complex. On one hand, stereotactic radiation therapy is a keystone of treatment but is only applicable to highly selected patients fulfilling specific criteria who have access to an adequate radiation unit. On the other, whole-brain radiation therapy may improve survival, but deleterious effects on neurocognitive functions are well known. It has, however, been reported that selected subgroups of patients may benefit from focal dose escalation to brain metastases to prolong survival and the time to intracranial disease progression. Here, we discuss a clinical case to consider the interest of a focal high-dose hypofractionated radiation delivered through a conventional linear accelerator on a large brain metastasis for a patient with metastatic melanoma excluded for stereotactic radiotherapy. *Melanoma Res* 22:406–409 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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[a]Department of Radiation Oncology, Gustave Roussy Institute, Paris XI University, Villejuif, [b]Department of General and Oncologic Dermatology, Versailles Saint Quentin en Yvelines University, APHP, Ambroise Paré Hospital, [c]Department of Radiation Oncology, Val de Grace Hospital, Paris and [d]Department of Radiation Oncology, Porte de Saint Cloud Clinical Center, Boulogne-Billancourt, France

Correspondence to Avi Assouline, MD, Department of Radiation Oncology, Porte de Saint Cloud Clinical Center, 30 Rue de Paris, 92100 Boulogne-Billancourt, France
Tel: +331 41 10 27 20; fax: +33 147 129 463; e-mail: avi.assouline@ccpsc.fr

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Background

Brain metastases are common in the natural history of malignant tumors, accounting for more than one-half of all intracranial tumors. Because of advances in the detection of small metastases by MRI and greater control of systemic disease by systemic therapies, the incidence of brain metastases is increasing [1,2]. Standard treatment includes neurosurgery (in case of solitary brain or symptomatic metastases or necessity of histopathological confirmation) and sterotactic radiation therapy (SRT) for patients with few brain metastases [3,4]. However, a limited number of patients are eligible for SRT, which is highly effective, but can be applied only when selective inclusion criteria are fulfilled: size less than 4 cm, fewer than four metastases, good general health status, and rather well-controlled systemic disease. Thus, of 25 000 new cases of brain metastases per year, only 1200 may benefit from SRT annually in France [5]. Although whole-brain radiation therapy (WBRT) may improve local control, it has been reported that neurocognitive impairment should also be considered [6]. Moreover, it has been reported that subgroups of patients may benefit from more aggressive local treatments of their intracranial disease. It is also suggested that the focal dose to the brain metastases should be increased to prolong survival and the time to intracranial disease progression [7,8]. In light of the controversy on aggressive treatment for brain metastases [9], we contribute to the debate on the value of a conformal (3D) focal high-dose hypofractionated radiation delivered to the metastatic site and we report a case of a patient who might have benefited from this alternative treatment.

Case presentation

A 40-year-old man was referred in September 2011 for brain metastases irradiation in the context of a stage IV melanoma. He had undergone a local surgery for his primitive melanoma located on his left knee in May 2010. A nodal recurrence in January 2011 was treated with surgery and adjuvant interferon α. Then, in April 2011, he received a BRAF inhibitor (tumor harboring the V600E mutation in the *BRAF* gene) for a systemic (brain and subdiaphragmatic lymph nodes) relapse. The patient later experienced important response of extracranial and cerebral metastases, but one brain metastasis later progressed, with intratumoral bleeding. Physical examination indicated a patient with an Eastern College Oncology Group (ECOG) performance status (PS) of 2, presence of confusion, a right hemiparesis, and a high intracranial pressure syndrome. A total body computed tomography showed a complete extracranial response. Brain MRI showed an increase in the number and the size of the multiple secondary brain lesions with a 5.5 cm left frontoparietal metastasis with a mass effect on the left temporal lobe and a subfalcine herniation. The patient was classified recursive partitioning analysis (RPA) class 3 and an intermediate score index for radiosurgery in brain metastases (SIR) group. Given the size of the lesion, stereotactic radiotherapy was collegially refused. Conformal focal hypofractionated palliative radiotherapy (40 Gy in eight fractions over 12 days) was then delivered on the brain frontoparietal metastasis. A conventional accelerator was used to deliver five fields of 6 MV photon. Dose constraints to the critical organs were based on the Quantitative Analysis of Normal Tissue Effects in the

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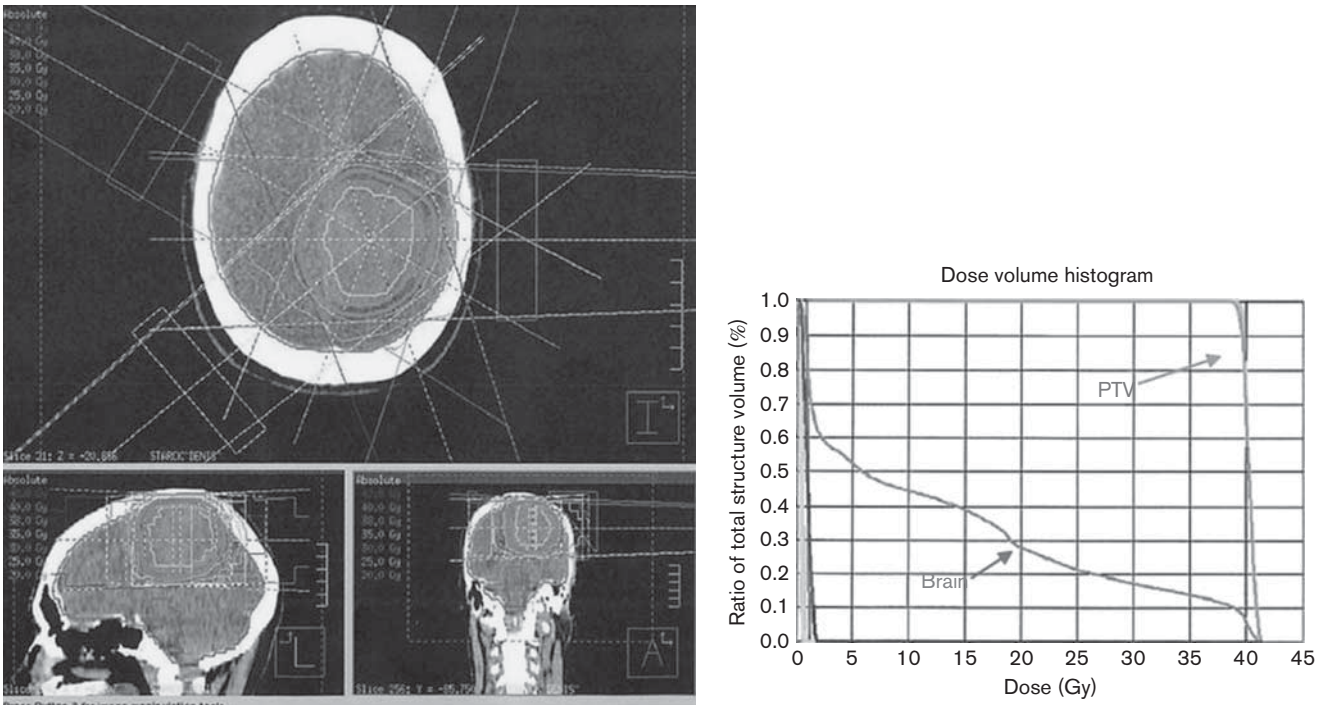
Fig. 1



Dose distribution in frontoparietal brain metastasis in conformal external radiotherapy: axial, sagittal, coronal views, and dose volume histogram using a five-field technique. PTV, planned target volume.

Clinic recommendations [10] (Fig. 1). Treatment was well tolerated and there were no acute toxicities. Clinical improvement could be assessed at the end of treatment, with a PS of 1, absence of confusion, but persistence of the right hemiparesis. Brain MRI performed 4 months after the completion of radiotherapy indicated a local control on the parietal metastasis with a central necrosis (3.5 vs. 5.5 cm initially; Fig. 2), but a progression of the subtentorial brain metastases. Hypofractionated conformal radiation (30 Gy in six fractions) was then provided on the cerebellum only. The patient died because of cerebellum progression 6 months after the completion of the first radiation course.

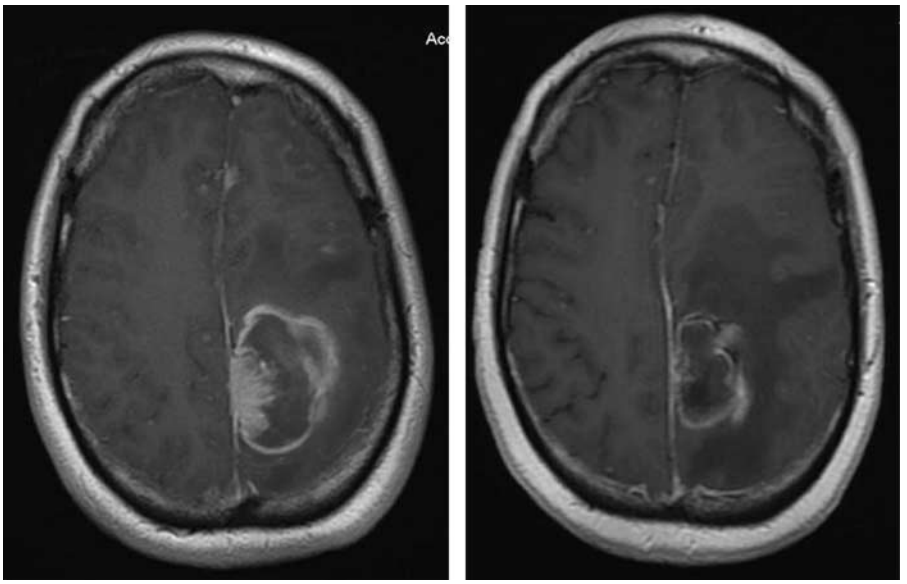
Discussion

Standard treatment includes neurosurgery and stereotactic radiation therapy for patients with few brain metastases and a controlled extracranial disease [3,4]. However, some patients may not have access to radiosurgery and some of them do not fulfill the inclusion criteria for such treatments because of the size of secondary lesions or prognostic factors. Knowledge of prognostic factors for patients with brain metastases is crucial for appropriate therapeutic strategies. The most widely used prognostic scores are the RPA and the SIR, which individualize prognostic groups according to the age, PS, systemic disease status, size, and number of brain lesions [11,12]. In fact, our patient did not undergo stereotactic surgery because of the size of his supratentorial lesion and because he was classified as RPA class 3/intermediate SIR group.

Nevertheless, although it remains debated, it is suggested that some patients may benefit from a focal hypofractionated boost delivered through a conventional accelerator. We have previously reported our experience of a retrospective series of 250 patients who had a median overall survival of 4.0 months when treated without radiation boost, vs. 8.9 months after receiving a 3D conformal radiation boost ($P = 0.0024$) on brain metastasis. However, this applied to a selected subgroup of patients younger than 65 years of age and with a limited number of intracranial lesions [7,8]. It is also sustained by radiobiology because brain metastases from radioresistant tumors (sarcoma, melanoma, and renal cell carcinoma) yield a low α/β value and may then require higher than standard fraction sizes to achieve effective cytotoxicity [13]. However, Hoskin *et al.* [9] have reported on 164 patients with single brain metastasis, and no difference in survival was found in the majority of patients on high-dose treatment, even in the absence of metastatic disease elsewhere.

WBRT is the standard for patients with multiple brain metastases and lead, in most patients, to symptomatic improvement and good local control. However, the results of WBRT may be suboptimal in terms of both efficacy and toxicity. In fact, in a study on 1137 melanoma patients

Fig. 2



Comparison of initial and postradiotherapy brain MRI (axial plane injected T1-weighted sequences): local control of the parietofrontal metastasis (3.5 cm at 4 months vs. 5.5 cm initially).

with cerebral metastases, the median survival was 3.4 months for the WBRT arm ($n = 234$) compared with 2.1 months for patients who did not receive radiation ($n = 210$) [14]. Moreover, WBRT is often provided after stereotactic radiotherapy in patients with brain metastases because of a variety of tumor types, but our patient did not receive WBRT. Indeed, the adjunctive use of WBRT after a local treatment is currently questioned by the oncologic community. Definitely, whether WBRT leads to an overall increase in survival or alters cognitive function is less clear. In the EORTC 22952-26001 phase III study, Kocher and colleagues randomized 359 patients treated by surgery or radiosurgery and to receive adjuvant WBRT or observation. Although WBRT reduced the 2-year relapse rate, the overall survival and the duration of functional independence were similar in both arms [15].

Anyway, in the era of ballistic optimization, a new radiation technique combined with image-guidance technology may also represent a possible intended-focal treatment alternative to stereotactic radiotherapy. Indeed, highly conformational radiation allows efficient target coverage and sparing of critical organs. A series of 120 patients were treated with a simultaneous integrated boost to individual intracranial lesions with arc-based image-guided radiotherapy. After a median follow-up of 5 months, Rodrigues *et al.* [16] reported a median overall survival of 5.9 months and the median time for intracranial radiological failure was not reached. The value of helical tomotherapy is also being evaluated currently. In a phase I study on 48 patients, the delivery of a simultaneous in-field boost of 60 Gy in 10 fractions with WBRT was achieved without dose-limiting central nervous system toxicity. Moreover, on 32 evaluable patients at 3 months after the completion of treatment, 2, 16, and 6 patients showed a complete response, partial response, and stable disease, respectively. A multi-institutional phase II trial is ongoing to assess helical tomotherapy as a noninvasive alternative to radiosurgery [17].

New imaging modalities may also provide us with the opportunity to reduce the side effects mentioned even with 3D conformal or SRT techniques. In fact, new MRI modalities may now include functional, perfusion, and diffusion tensor imaging. By reflecting the blood flow, functional and perfusion MRI may allow a better resolution of the tumor versus the surrounding edema at the tumor borders and can permit determination of the hypervascularity in brain tumors, respectively [18,19]. Finally, the diffusion-weighted imaging technique now includes diffusion tensor imaging, which provides microstructural mapping of abnormal brain tissues and tractography, which yields a 3D image of the fiber tracts [20,21]. By better defining normal and pathologic brain anatomy, these techniques may allow a refinement of radiotherapeutic treatment planning.

Conclusion

Although radiosurgery remains the standard procedure for patients with few brain metastases, an aggressive focal conformal treatment is also desirable for a selected subgroup of patients. Conventional linear accelerator or arc-therapy/tomotherapy may probably be an alternative for patients who may not have access to stereotactic

radiotherapy. Randomized trials are required to carefully investigate this issue and confirm the potential role of a focal conformal high-dose hypofractionated radiation.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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