COMMENTARY

Evaluating novel radiation techniques for the treatment of cerebral metastases

A J CHALMERS

Brighton and Sussex Medical School, Genome Damage and Stability Centre, University of Sussex, Falmer BN1 9RQ, UK

Received 24 August 2009
Revised 1 September 2009
Accepted 2 September 2009

DOI: 10.1259/bjr/15790337

© 2010 The British Institute of
Radiology

Brain metastases are common [1] and their incidence appears to be increasing. The development of intracranial disease has a devastating impact on patients in terms of their prognosis, symptoms and quality of life, and therapeutic options are extremely limited. Traditionally, treatment has comprised high-dose steroids and whole brain radiotherapy (WBRT), but these are associated with significant risks of debilitating side effects [2] and the benefits are not always clear [1]. Attempts to improve outcomes by adding neurosurgical resection or stereotactic radiation therapy to WBRT have yielded benefits for a small subgroup of patients who are characterised by well-controlled systemic disease, good performance status and small numbers of intracerebral deposits [3]. Alongside these approaches, the policy of withholding or deferring WBRT by the aggressive use of localised treatments has been proposed. A lack of high-quality studies makes interpretation of the data difficult at present, but there is growing support for such a policy in selected patients, and large randomised studies are underway in Europe and North America (reviewed in [4]). However, many centres do not have access to stereotactic radiation therapy and many patients are ineligible for such treatment. Hence, there is an urgent need to identify alternative ways of delivering radiation therapy to improve outcomes and reduce toxicity.

Evaluating novel treatments for intracerebral malignancies is by no means straightforward. In particular, it is often difficult to differentiate between tumour progression and treatment-related toxicity. The symptoms, signs and radiological features of acute and late neurotoxicity overlap extensively with those of tumour progression. Performance status, quality of life and neurological status are potentially useful indices of clinical benefit or toxicity, but have been poorly reported

in the majority of studies. Many researchers have evaluated the ability of advanced imaging modalities to discriminate active tumour from radiation necrosis; of these modalities, magnetic resonance spectroscopy and positron emission tomography using amino acid tracers have shown the greatest promise, but are not widely available [5]. Functional MRI, particularly perfusion parameters, may prove to be of value but, at present, should be considered a research tool.

Against this background, it is informative to read two articles published in this edition describing novel techniques for delivering radiation therapy to brain metastases, both of which offer the potential for localised dose escalation to cerebral deposits in patients who are not suitable for conventional stereotactic treatment.

Sanghera et al [6] outline the development of a helical tomotherapy (HT) approach for delivering high-dose localised radiation to cerebral metastases in patients who had declined or did not tolerate stereotactic radiation delivered by a linear accelerator using a surgically positioned immobilisation frame. HT uses megavoltage CT imaging immediately before each treatment to achieve accurate patient positioning without the need for the frame; the manufacturers claim that the delivered dose is within 5% or 3 mm of the calculated dose. Accepting that immobilisation and imaging accuracy were likely to be inferior to that achieved by conventional stereotactic treatment, the authors added a 3 mm margin to the gross tumour volume (GTV). They compared the predicted dose–volume histograms for HT and linac-based stereotactic treatment of a representative lesion with a planning target volume (PTV) of 1.5 cm³, and confirmed that the volume of irradiated normal brain was indeed greater using HT. Volumes were outlined using MRI–CT fusion and the PTV was treated to 27 Gy in 5 fractions. Dose distribution was optimised to deliver 30 Gy (equivalent approximately to 60 Gy in 30 fractions in terms of late effects in normal brain) to as much of the GTV as possible, and to limit the dose received by critical normal tissues,

Address correspondence to: A J Chalmers, Brighton and Sussex Medical School, Genome Damage and Stability Centre, University of Sussex, Falmer BN1 9RQ, UK. E-mail: a.j.chalmers@sussex.ac.uk

including the eyes and the brain stem. Of note, "beam on" times per fraction varied between 7 and 11 min, which might exacerbate the impact of the inferior immobilisation associated with the HT technique. Five cases were presented, comprising a broad range of patient characteristics, including age, primary malignancy, performance status and previous radiation therapy. One or two sites per patient were treated, and the typical diameter of each deposit was ~10 mm, although this information was not provided for all cases. Details of clinical follow-up and imaging frequency and modality were not provided, but patients survived for between one-and-a-half months and more than 16 months, and two of nine metastases were stated to progress. The authors reported that no immediate or late radiation toxicity was observed.

In the second study, Edwards et al [7] describe the use of intensity-modulated radiation therapy (IMRT) for the treatment of 11 patients, each with no more than four brain metastases. No patient had previously received radiotherapy to the brain. The metastases were large, between 25 mm and 80 mm in diameter, and so patients were not considered to be eligible for stereotactic treatment. The aim of the treatment was to combine WBRT (30 Gy in 10 fractions) with simultaneous boosts to gross disease, such that tumour deposits received 40 Gy in 10 fractions (equivalent approximately to 60 Gy in 30 fractions for late brain effects). Again, treatment was delivered using a tomotherapy unit and a margin of 3 mm was added to the whole brain clinical target volume to allow for the quoted 3 mm set-up uncertainty. However, no margin was added to the GTVs of metastases because of concerns over the risk of neurotoxicity. Clinical follow-up included an assessment of neurological symptoms and signs, with MRI at one month and then at three to six months after treatment. All tumours were reported to have shown a response at one month. At a median follow-up of four months, seven patients were alive with no evidence of disease progression or recurrence. No acute or subacute complications were reported and no patient required prolonged steroid therapy.

Dose escalation by stereotactic boost after WBRT has been shown to improve disease control [8], but many patients are not eligible for, or do not have access to, such treatment. Although the availability of HT is limited at present, an increasing number of centres are equipped to deliver IMRT. Together, the studies presented here represent pragmatic methods of escalating radiation dose. The important questions to be considered are: (i) whether the new treatments are associated with acceptable toxicity and (ii) whether they improve outcomes.

In the evaluation of pharmacological treatments, it is well established that early-phase clinical studies cannot, and should not, attempt to assess the relative efficacy of a novel approach. Such studies are non-randomised and involve small numbers of patients with diverse characteristics. These limitations apply equally to radiotherapeutic interventions. Hence, the two pilot studies presented here should be appraised in terms of how reliably they evaluate the safety and toxicity of the proposed treatment. As outlined earlier, identifying and measuring radiation toxicity in this patient group is not straightforward, but an objective and consistent

assessment of adverse effects must be included in the study design if the results are to be of scientific and clinical value.

Given the poor prognosis associated with the diagnosis of brain metastases and the lack of robust imaging techniques to differentiate between tumour progression and toxic effects, there is a strong argument for the use of functional outcome measures in studies involving this patient group. Parameters such as time to deterioration of Karnofsky Performance Status (KPS) and time to neurological deterioration have generated useful data in a number of studies (e.g. [8, 9]), and may reflect the overall balance between efficacy and toxicity more accurately than radiological parameters. Simple grading scales for neurotoxicity have been developed by the Radiation Therapy Oncology Group [8] and global neurological function can now be assessed using a five-point scale [10]. Accurate documentation of steroid dosage can also provide a useful surrogate marker of overall status [11]. These evaluations can be included in a protocol alongside routine imaging while maintaining an achievable study design. It is also important that the mode and frequency of clinical assessment be defined in advance to avoid potential bias. Quantitative quality of life measurements are not appropriate for small early-phase clinical studies but should be a feature of larger clinical trials in this disease setting.

In summary, the assessment of novel radiation techniques for brain metastases should be carried out alongside meaningful clinical assessment of the patients. Although definitive differentiation between tumour progression and radiation toxicity remains problematic, standard clinical and radiological assessments can be used to generate useful data regarding the overall risks and benefits of new techniques. Such assessment is particularly important in techniques involving re-irradiation and dose escalation, where clinical benefit remains unproven and the risk of adverse events is high.

References

1. Tsao MN, Lloyd N, Wong R, Chow E, Rakovitch E, Laperriere N. Whole brain radiotherapy for the treatment of multiple brain metastases. *Cochrane Database Syst Rev* 2006;3:CD003869.
2. Shibamoto Y, Baba F, Oda K, Hayashi S, Kokubo M, Ishihara S, et al. Incidence of brain atrophy and decline in mini-mental state examination score after whole-brain radiotherapy in patients with brain metastases: a prospective study. *Int J Radiat Oncol Biol Phys* 2008;72:1168–73.
3. Mehta MP, Tsao MN, Whelan TJ, Morris DE, Hayman JA, Flickinger JC, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys* 2005;63:37–46.
4. Vallow LA. Stereotactic radiosurgery alone to treat brain metastases. *Nat Rev Clin Oncol* 2009;6:377–8.
5. Waldman AD, Jackson A, Price SJ, Clark CA, Booth JC, Auer DP, et al. Quantitative imaging biomarkers in neuro-oncology. *Nat Rev Clin Oncol* 2009;6:445–54.
6. Sanghera P, Lightstone AW, Hyde DE, Davey P. Fractionated helical tomotherapy as an alternative to radiosurgery in patients unwilling to undergo additional radiosurgery for recurrent brain metastases. *Br J Radiol* 2010; 83, e25–e30.
7. Edwards AA, Keggins E, Plowman PN. The developing role for intensity-modulated radiation therapy (IMRT) in the

- non-surgical treatment of brain metastases. *Br J Radiol* 2010; 83, 133–136.
8. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004;363: 1665–72.
  9. Giese A, Kucinski T, Knopp U, Goldbrunner R, Hamel W, Mehdorn HM, et al. Pattern of recurrence following local chemotherapy with biodegradable carmustine (BCNU) implants in patients with glioblastoma. *J Neurooncol* 2004;66:351–60.
  10. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* 2000;47:291–8.
  11. Nieder C, Astner ST, Mehta MP, Grosu AL, Molls M. Improvement, clinical course, and quality of life after palliative radiotherapy for recurrent glioblastoma. *Am J Clin Oncol* 2008;31:300–5.