Journal of Neuro-Oncology **21**: 171–176, 1994.

Clinical Study

Radiotherapy response of cerebral metastases quantified by serial MR imaging

Euphemia J. Zijlstra,[1] Martin J.B. Taphoorn,[2] Frederik Barkhof,[1] Frank G.C. Hoogenraad,[3] Jan J. Heimans[2] and Jacob Valk[1]
From the departments of [1] Diagnostic Radiology, [2] Neurology and [3] Biomedical Engineering, Free University Hospital, Amsterdam, the Netherlands

Key words: brain neoplasms, metastasis, MRI, quantification, radiotherapy

Summary

A patient with cerebral metastases, treated with radiotherapy, underwent serial gadolinium-enhanced MR imaging. The MR images were quantified using home developed software to evaluate the changes in volumes of tumor mass and edema after radiotherapy (mean precision of the quantification technique less than 5%). The decrease in tumor volume and edema observed after radiotherapy preceded clinical improvement. The presented technique can be used to accurately assess, more directly than using clinical scales, the effect of putative therapies.

Introduction

Cerebral metastases occur in about 15–20% of patients with malignant disease, especially in malignant melanoma, breast and lung cancer [1]. Early diagnosis and treatment of brain metastases, while only rarely curative, may relieve neurological symptoms and both enhance the patient's quality of life and prolong survival. Whole-brain radiotherapy in combination with steroids is the treatment most frequently applied [2].

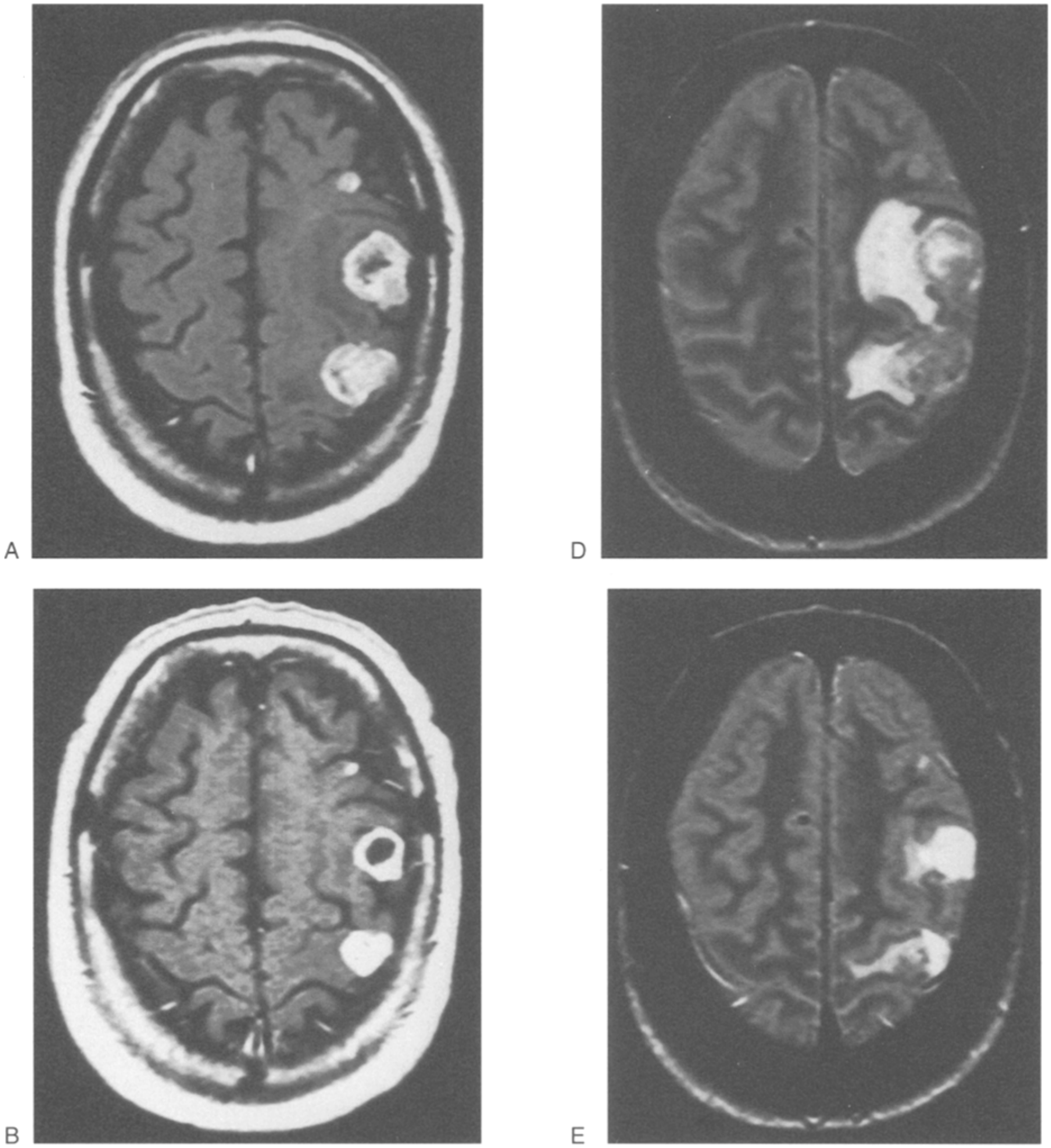
The effect of radiotherapy is usually evaluated by assessing survival time and symptom relief expressed in general performance status or function scales. While such indirect measurements have indicated that irradiation is of value in the treatment of brain metastases, more specific parameters for tumor response have rarely been reported [3].

Measuring tumor volume and edema might be a more direct and objective way to evaluate the effect of (radio)therapy [4]. Visualization and monitoring of cerebral metastases have improved considerably with the advent of computed tomography (CT) [5]. Few investigators have used CT to qualitatively evaluate changes in size, contrast enhancement and surrounding edema as indicators of tumor response [6, 7].

Magnetic resonance (MR) imaging is superior to CT in the detection of cerebral metastases [8]. As the contrast resolution of MR is superior to CT, this technique provides a unique possibility to quantitatively evaluate the response of metastases to radiotherapy. We performed serial MR imaging in a patient with brain metastases treated with radiotherapy and compared volumes of tumor and cerebral edema with clinical scores.

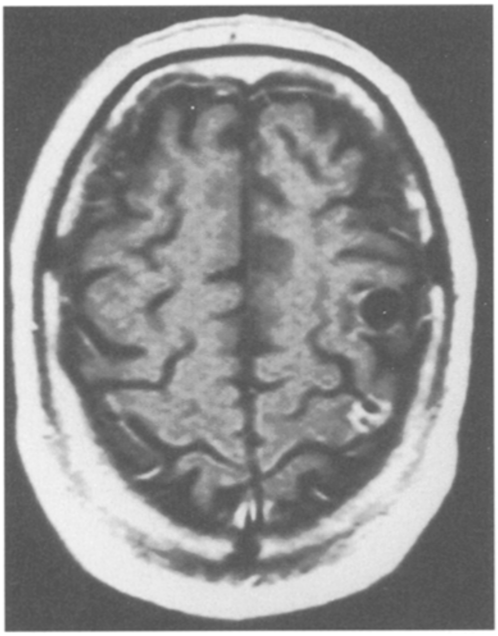
Patient and methods

A 60 year old man, who had previously been in good health, began to complain of hoarseness. Squamous cell laryngeal carcinoma was diagnosed at laryngoscopy. In addition, chest radiography showed masses



in the upper lobes of both right and left lung. Needle biopsy of these lesions revealed an undifferentiated large cell bronchial carcinoma. Screening for distant metastases demonstrated two contrast-enhancing metastases in the left cerebral hemisphere on MR. Neurological examination at that time was normal.

The patient was treated with radiotherapy for both laryngeal carcinoma (62.5 Gy in 25 fractions) and lungcarcinoma (42 Gy in 14 fractions). He did well until 18 months later when be began to complain of headache and experienced partial epileptic seizures of the right hand. Apart from clumsiness of the right hand, no abnormalities were found on neurological examinations. MR imaging revealed an increase both in number and size of brain metas-



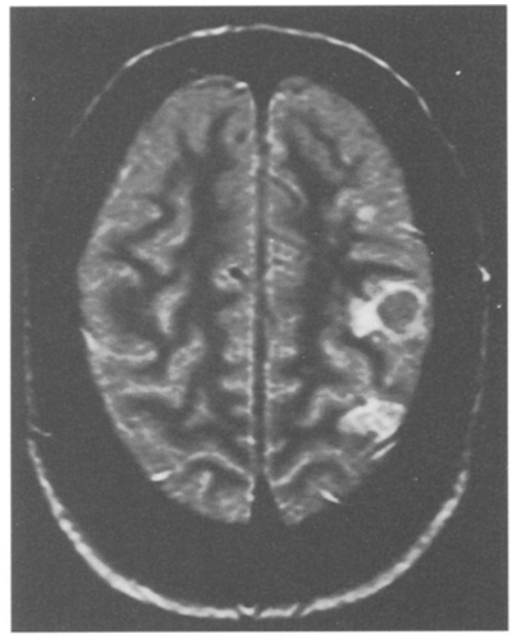


Fig. 1. Axial MR images through a selected level of the brain, showing 3 metastases before radiotherapy (RT) and the response after radiotherapy. (a–c) short TR images, (d–f) long TR images: (a, d) before RT, (b, e) 4 weeks after RT, (c, f) 15 weeks after RT. After 4 weeks a marked decrease of edema and enhancing tumor mass is seen. Only at 15 weeks tumor mass has nearly disappeared and substantial necrosis has developed.

tases and an increase in surrounding edema. He was treated with whole brain radiotherapy (25 Gy in 5 fractions), oral steroids (dexamethasone 16 mg/day, tapered off in three weeks) and valproic acid. Soon after initiation of therapy symptoms disappeared. At the moment, two years later, he is still in reasonably good condition: he only feels more tired than before and has slight disturbances of memory and concentration. The Karnofsky Performance Status is 70 (maximal 100) [9]. During the course of his illness, his neurological status was evaluated using a neurological status deficit scale ranging from 1 (no neurological deficit) to 5 (consious respons not possible or terminal). Before radiotherapy his score was 3, whereas after 18 weeks it had decreased to 1.

MR images were obtained before radiotherapy and at 0, 1, 2, 4, 8, 15, 24, 42 and 58 weeks after radiotherapy. MR imaging was performed at 0.6 T (Technicare, Solon, Ohio). Axial spin-echo images with an in-plane resolution of 1.3 × 1.0 mm and a slice thickness of 5 mm (1.25 mm gap) were planned from a sagittal scout view, with the Z-center aligned with the caudal border of the splenium of the corpus callosum to reassure identical slicing at follow-up.

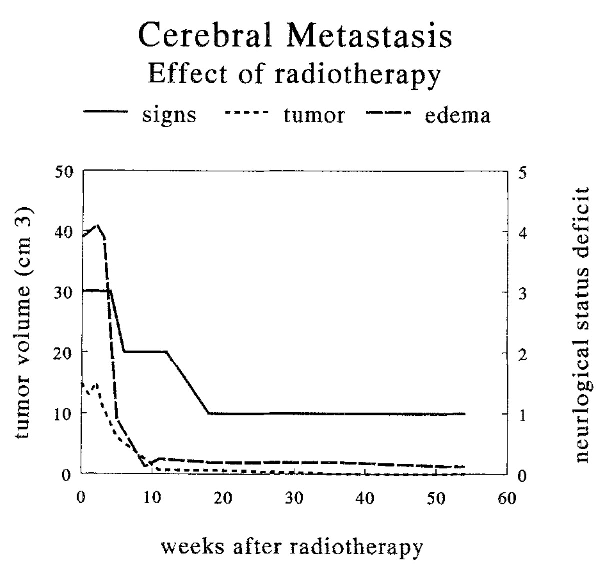


Fig. 2. Comparison of changes in total volumes of tumor and edema (left y-axis) of brain metastases with clinical score (right y-axis) after radiotherapy (time in weeks). Continuous line: neurological score (score 1 represents absence of neurological deficit).

Dotted line: volume of enhancing tumor mass.

Dashed line: volume of surrounding edema.

Table 1. Total volumes of metastases and edema before and after radiotherapy

Total volume Assessment	Tumor		Edema	
	1	2	1	2
before RT (a)	14.92	14.65	38.94	40.58
directly after RT	12.59	12.77	38.95	40.38
1 week after RT	14.78	15.16	40.77	40.74
2 weeks after RT	10.38	10.97	37.03	38.64
4 weeks after RT	5.36	5.53	9.31	8.76
8 weeks after RT	3.25	3.38	0.53	0.27
15 weeks after RT	0.70	0.91	2.44	2.58
24 weeks after RT	0.38	0.29	1.82	2.13
42 weeks after RT	0.09	0.09	2.24	1.85
58 weeks after RT	0.16	0.14	1.36	1.24

volumes in cm^3.
(a) RT: radiotherapy.

Short TR images [580/20/4](TR/TE/excitations) and long TR images [2750/60,120/2] were obtained before contrast. Short TR sequences were repeated after IV injection of 0.2 mmol/kg gadolinium-DTPA (Schering AG, Berlin).

Imaging analysis was performed on a Sparc-2 workstation (Sun, Palo Alto, CA) using home developed software. Two techniques were used to define regions of interest. The first technique is the seed-growing method: a seed-point is positioned in a part of the lesion with typical signal intensity. Then the boundary of the defined region is grown towards interactively set threshold intensities. The second technique was performed when seed growing was hampered by insufficiently defined borders, and consisted of manual tracing including a possibility to make adjustments. Volumes were calculated by multiplying the outlined surfaces with interslice distance (6.25 mm). The contrast enhanced short TR images were used to assess tumor volume (area of enhancement) and the volume of necrotic tissue (non-enhancing tissue central in the metastasis). In primary brain tumors malignant cells have been found outside the area of enhancement [10]. In metastatic disease, however, such a radiological-pathological dissociation has not been reported, to our knowledge. Volume of edema was calculated by subtracting the volume of tumor and necrosis from the volume of tumor, necrosis and edema as assessed on the long TR images (total area of high signal intensity). All measurements were performed by one single observer, and repeated in a second session. Precision of the quantification technique was assessed by evaluating the intra-observer variation.

Results

Eight metastases with a total tumor volume of 14.79 cm^3 and a total volume of 39.76 cm^3 edema were present before treatment. Serial MR images clearly depict the changes after radiotherapy (Fig. 1). The short TR images show that after one week gadolinium enhancement becomes irregular and that necrosis develops centrally after 2 weeks. The long TR images show that the amount of surrounding vasogenic edema starts to decrease after 4 weeks and has more or less resolved after 15 weeks. On the last scan (after 58 weeks) new areas of hyperintense signal developed on the long TR images, which were not contingent with the residual metastatic disease, with ill-defined borders. As the pattern did not represent the pattern of vasogenic edema it was considered to be radiation encephalopathy [11].

The volumetric changes of the lesions are represented in Table 1. The total volumetric changes and their relation to clinical changes can be appreciated more accurately using the quantitative measurements (Fig. 2). The decrease of edema is most marked during week 3 to 5 after treatment, whereas tumor volume decreases more gradually over a period of 11 weeks. The initial increase in edema could be ascribed to termination of steroid intake, which temporarily suppresses the formation of vasogenic edema [12]. The changes in tumor volume and edema precede clinical improvement as can be seen from Fig. 2.

To investigate whether there was a systemic bias between the first and second assessment, we compared the temporal observations of the first and second assessment for each individual metastasis. We found no systemic bias between both assessments using Wilcoxon's signed rank test (2-tailed, all p-values > 0.05). The average of the assessments was used to characterize the precision of the separate assessments. The estimate of precision of our technique was based on the summarized volumes per timepoint (total volume of edema and tumor per scan). With the average of the two assessments as the gold standard the variation of the total volumes of *edema* was less than 8% for smaller (≤ 12.5 cm^3) and less than 2% for larger (≥ 37.5 m^3) volumes, (mean 4.4%). For total volumes of *tumor* the variation was less than 13% for smaller (≤ 5 cm^3) and less than 8% for larger (≥ 7.5 cm^3) volumes (mean 3.2%).

Discussion

The patient presented here is an exceptional case in whom multiple brain metastases were diagnosed that caused no clinical symptoms or signs until 18 months later and subsequently showed an extremely good response to radiotherapy. For that reason this patient was well suited to undergo serial MR analysis.

Although the beneficial clinical effect of radiation therapy is well established, not much is known about morphological and functional characteristics of tumor and edema after treatment. This is largely due to the fact that most studies used clinical scoring scales to evaluate the effect of radiotherapy, as more direct methods of evaluation were not available. With the advent of MR imaging, a tool has become available that is safe and combines optimal tissue contrast with a high sensitivity.

Apart from treatment with whole-brain radiotherapy focal brain radiotherapy, (stereotactical radiosurgery), neurosurgery and chemotherapy are of value for selected patients with brain metastases. To evaluate the effectiveness of both radiation therapy and these newer treatment modalities, quantified MR image analysis may serve as a useful endpoint of tumor response and can be used in addition to survival time, symptom relief scales and quality of life measures.

We have quantified the changes of cerebral metastases after treatment with radiotherapy using MR image analysis. The precision (intra-observer variation) of this technique is acceptable. This method allows the separate assessment of vital tumor volume and edema, which could be of value in the evaluation of putative treatments.

References

1. Posner JB: Brain metastases: A clinician's view. In: Weiss L, Gilbert H, Posner JB (eds). Brain metastasis. Hall, Boston, 1980, pp 2–29
2. Coia LR, Aaronson N, Linggood R, Loeffler J, Priestman TJ: A report of the consensus workshop panel on the treatment of brain metastases. Int J Radiat Oncol Biol Phys 23: 223–227, 1992
3. Coia LR: The role of radiation therapy in the treatment of brain metastases. Int J Radiat Oncol Biol Phys 23: 229–238, 1992
4. Steen-Banasik van der E, Hermans J, Tjho-Heslinga R, Caspers R, Leer JW: The objective response of brain metastases on radiotherapy. Acta Oncol 31: 777–780, 1992
5. Bentson JR, Steckel RJ, Kagan AR: Diagnostic imaging in clinical cancer management: Brain metastases. Invest Radiol 23: 335–341, 1988
6. Brown SB, Brant-Zawadzki M, Eifel P, Coleman CN, Enzmann OR: CT of radiated solid tumor metastases to the brain. Neuroradiology 23: 127–131, 1982
7. Kretzschmar K, Schicketanz KH: Measurements of the volume and density of intracerebral tumors by CT following therapy. Neuroradiology 23: 175–184, 1982
8. Castel JC, Caillé JM: Imaging of irradiated brain tumours: value of magnetic imaging. J Neuroradiol 16: 81–132, 1989
9. Karnovsky DA, Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer. In MacLeod CM (ed). Evaluation of chemotherapeutic agents. Colombia University Press, New York, 1949, pp 191–205

10. Kelly PJ, Daumas-Duport C, Kispert DB *et al.*: Imaging-based stereotaxic serial biopsies in untreated intracranial glial neoplasms. J Neurosurg 66: 865–874, 1987
11. Valk PE, Dillon WP: Radiation injury of the brain. AJNR 12: 45–62, 1991
12. Müller W, Kretzschmar K, Schicketanz K-H: CT-analyses of cerebral tumors under steroid therapy. Neuroradiology 26: 293–298, 1984

Address for offprints: F. Barkhof, Diagnostic Radiology, Free University Hospital, P.O. Box 7057, NL-1007 MB Amsterdam, The Netherlands