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Original Article

Characterisation of Lesions after Stereotactic Radiosurgery for Brain Metastases: Impact of Delayed Contrast Magnetic Resonance Imaging

S. Wagner [*†], H. Gufler [‡], G. Eichner [§], H. Lanfermann [†¶]

[*] *Department of Neuroradiology, Friedrich-Schiller-University Jena, Jena, Germany*
[†] *Institute of Neuroradiology, Johann-Wolfgang-Goethe University Frankfurt, Frankfurt am Main, Germany*
[‡] *Department of Diagnostic Radiology, Martin-Luther-University Halle-Wittenberg, Halle/Saale, Germany*
[§] *Mathematical Institute, Justus-Liebig-University Giessen, Giessen, Germany*
[¶] *Institute of Diagnostic and Interventional Neuroradiology, Hannover Medical School, Hannover, Germany*

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Abstract

Aims: To investigate if brain metastases and radiation injuries after stereotactic radiosurgery (SRS) have different signal intensity (SI) time courses up to 55 min after contrast agent application and if delayed contrast magnetic resonance imaging (MRI) contributes to improve diagnostic accuracy.
Materials and methods: Thirty-four consecutive patients treated with SRS for cerebral metastases were prospectively enrolled in the study. T1-weighted images were acquired on a 3-Tesla MR unit at three time points, at 2 (TP1), 15 (TP2) and 55 (TP3) min after administering contrast agent. A simultaneous, matched-pairs approach was used for region of interest analysis of the entire contrast-enhancing lesion (SI-e), the centre (SI-c), the border of the lesion (SI-b) and the adjacent non-contrast-enhancing tissue (SI-p). SIs of brain metastases and radiation injuries after SRS were compared using a two-level, linear, mixed-effects regression model.
Results: In total, 41 lesions were analysed: 16 metastases and 25 radiation injuries. The SI time course of SI-e, SI-c and SI-b proved to be significantly different for both entities ($P < 0.001$) from TP2 to TP3. The SI of 39/41 lesions increased from TP1 to TP2 for the three parameters. Radiation injuries showed a further signal increase at least for SI-c from TP2 to TP3, whereas for all the three parameters SI decreased in all metastases.
Conclusion: Brain metastases and radiation injuries after SRS have a characteristic and statistically significantly different SI time course on sequential gadolinium enhancement MRI when late MR studies are included.

Key words: Brain metastases; delayed contrast MRI; gadolinium-DTPA; MRI; radionecrosis; stereotactic radiosurgery

Introduction

Brain metastases affect 20–40% of patients with systemic cancer [1]. Prognosis varies according to primary tumour type, age, performance status, number of brain metastases and extracranial disease status [2]. Stereotactic radiosurgery (SRS) is an established treatment option for brain metastases in addition to surgery, whole brain radiation therapy, chemotherapy and combinations of these treatments. The evidence that SRS improves patient-relevant outcomes is for patients with up to three brain metastases, good performance status and controlled extracranial disease [2]. The goals of each treatment or combinations of treatments are better local tumour control, improved quality of life and prolonged survival [1–6]. After radiation treatment, follow-up magnetic resonance imaging (MRI) can depict lesions of the brain with a high sensitivity, but it has limitations in distinguishing radiation injuries from a malignancy [7–9]. Clinically, this differentiation has significant implications for patient care and outcome and is mandatory for adequately adjusting therapeutic strategies as early as possible. Although most patients with radiation injuries stabilise or improve with symptomatic treatments, those patients with local or distant tumour recurrences require specific therapy [10].

Author for correspondence: S. Wagner, Department of Neuroradiology, Friedrich-Schiller-University Jena, Erlanger Allee 101, 07747 Jena, Germany. Tel: +49-3641-9324768; Fax: +49-3641-9324762.
E-mail address: sabine-m-wagner@gmx.de (S. Wagner).

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Many studies have been carried out in an attempt to non-invasively distinguish benign from malignant lesions after SRS, but it remains a diagnostic challenge on standard anatomical MRI as the radiographic appearance of these two entities shows many of the same features. More sophisticated MR techniques and positron emission tomography have also been evaluated for this purpose [11–15]. Although lower apparent diffusion coefficient values have been found in benign as compared with malignant lesions with diffusion-weighted MRI, tumour recurrence could not be reliably distinguished from radiation necrosis [12]. Using dynamic susceptibility-weighted contrast-enhanced perfusion MRI, a cut-off relative cerebral blood volume ratio greater than 2.1 yielded a sensitivity and specificity for identifying malignancy at 100 and 95.2%, respectively [13]. A relative cerebral blood volume ratio below 1.35 was observed exclusively in radiation injuries [14], leaving much overlap in benign and malignant lesions. Lizarraga *et al.* [15] reported that delayed radiation injury (i.e. radiation necrosis) could be distinguished from progressive brain metastasis with a sensitivity of 81.3% and a specificity of 84.3% using 6-18F-fluoro-L-dopa.

So far, however, none of these techniques, individually or in combination, has been found to be a reliable tool to non-invasively distinguish benign from malignant lesions.

Contrast enhancement of the brain parenchyma on conventional MRI is a consequence of disruption or lack of a blood–brain barrier with exchange of contrast medium between different compartments. These exchanges are known to be time dependent [16] and in other fields, such as cardiac imaging, so-called late gadolinium enhancement studies [17] are already established for making differential diagnoses. MR signal changes caused by contrast agent extravasation are determined by several factors, including tissue perfusion and capillary permeability [18]. As the histopathology of radionecrosis and malignancy differ, analysis of MR signal changes over time may be able to provide additional valuable pathophysiological information.

The aim of our study was to determine if radiation injuries and metastases have significantly different signal intensity (SI) time courses up to 55 min after contrast agent application and, second, if delayed contrast MRI contributes to improve diagnostic accuracy.

Materials and Methods

Patients

The study was approved by the local ethics committee. All participants gave their informed consent. Thirty-four consecutive patients were prospectively enrolled. They had been treated with SRS for cerebral metastases. For SRS a gamma knife was used with multiple isocentres for a highly conformal dose distribution. The definition of the prescription dose was the dose that covered around 95% of the tumour volume as defined on the stereotactic MRI. Depending on the size of the target volume, the dose was 20–25 Gy for small to medium brain metastases and 15–18 Gy for large metastases. Some of the participants of this study were part of an earlier analysis with a different aspect.

Inclusion criteria for the study were presence of a contrast-enhancing lesion at the site of a previously SRS-treated metastasis or a newly diagnosed lesion on routine follow-up MRI examinations, which were carried out every 3–6 months after SRS treatment. Exclusion criteria were claustrophobia, gadolinium allergy, impaired renal function and contraindications for 3-Tesla MRI due to ferromagnetic foreign materials.

Magnetic Resonance Imaging

MRI was carried out on a 3-Tesla scanner (Magnetom Allegra, Siemens Medical Systems, Erlangen, Germany) using a transmit/receive quadrature four-channel head coil. The same imaging protocol was used in all patients and was standardised for timing and sequence order: a three-dimensional high-resolution T1-weighted gradient-echo sequence (repetition time 2500 ms, echo time 4.38 ms, matrix size 256 × 192, section thickness 1 mm, field of view 24 × 24 mm) was carried out 2 min after intravenous administration of 0.1 mmol/kg bodyweight of gadolinium-Diethylenetriaminepentaacetic acid (DTPA) with an additional saline flush of 30 ml. This was defined as time point 1 (TP1). T1-weighted spin echo (SE) sequences (repetition time 600 ms, echo time 9.1 ms, slice thickness 3 mm, field of view 24 × 24 mm) were added at 15 (TP2) and 55 min (TP3), respectively, after administering the contrast agent. Axial slice orientation was preferred. In order to minimise artefacts, three lesions in the posterior fossa and in the brain stem were acquired in coronal orientation.

Data Processing and Quantitative Analysis

For post-processing and offline analysis, the data sets were transferred to a workstation equipped with the software tool Xrayline™ Workstation 2.0. For quantitative analysis, a polygonal region of interest was drawn, covering the entire contrast-enhancing lesion (SI-e), the lesion border (SI-b), the centre of the lesion (SI-c) (Figs 1, 2), as well as in the surrounding brain parenchyma (SI-p) adjacent to the lesion. The mean value of each SIs measurement was used. Care was taken to draw regions of interest on precisely corresponding positions for all images acquired at the three different time points.

Final Diagnosis and Follow-up of Patients

To establish the final diagnosis, it was mandatory to know the medical history, the number of SRS radiation courses and the number of treated metastases with reproducible location on previous MRIs. Local control was defined as a complete or a partial response. The first post-SRS scan was used as the baseline. Thereafter, the assessment of therapy response was based on the lowest measured diameter throughout the follow-up. The maximal

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