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Differentiation between intra-axial metastatic tumor progression and radiation injury following fractionated radiation therapy or stereotactic radiosurgery using MR spectroscopy, perfusion MR imaging or volume progression modeling☆,☆☆,★

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Abstract

Objective: To determine the accuracy of magnetic resonance spectroscopy (MRS), perfusion MR imaging (MRP), or volume modeling in distinguishing tumor progression from radiation injury following radiotherapy for brain metastasis.
Methods: Twenty-six patients with 33 intra-axial metastatic lesions who underwent MRS (n=41) with or without MRP (n=32) after cranial irradiation were retrospectively studied. The final diagnosis was based on histopathology (n=4) or magnetic resonance imaging (MRI) follow-up with clinical correlation (n=29). Cho/Cr (choline/creatinine), Cho/NAA (choline/*N*-acetylaspartate), Cho/nCho (choline/contralateral normal brain choline) ratios were retrospectively calculated for the multi-voxel MRS. Relative cerebral blood volume (rCBV), relative peak height (rPH) and percentage of signal-intensity recovery (PSR) were also retrospectively derived for the MRPs. Tumor volumes were determined using manual segmentation method and analyzed using different volume progression modeling. Different ratios or models were tested and plotted on the receiver operating characteristic curve (ROC), with their performances quantified as area under the ROC curve (AUC). MRI follow-up time was calculated from the date of initial radiotherapy until the last MRI or the last MRI before surgical diagnosis.
Results: Median MRI follow-up was 16 months (range: 2–33). Thirty percent of lesions (n=10) were determined to be radiation injury; 70% (n=23) were determined to be tumor progression. For the MRS, Cho/nCho had the best performance (AUC of 0.612), and Cho/nCho >1.2 had 33% sensitivity and 100% specificity in predicting tumor progression. For the MRP, rCBV had the best performance (AUC of 0.802), and rCBV >2 had 56% sensitivity and 100% specificity. The best volume model was percent increase (AUC of 0.891); 65% tumor volume increase had 100% sensitivity and 80% specificity.
Conclusion: Cho/nCho of MRS, rCBV of MRP, and percent increase of MRI volume modeling provide the best discrimination of intra-axial metastatic tumor progression from radiation injury for their respective modalities. Cho/nCho and rCBV appear to have high specificities but low sensitivities. In contrast, percent volume increase of 65% can be a highly sensitive and moderately specific predictor for tumor progression after radiotherapy. Future incorporation of 65% volume increase as a pretest selection criterion may compensate for the low sensitivities of MRS and MRP.

Keywords: Radiation necrosis; Radiation injury; Magnetic resonance spectroscopy; Perfusion magnetic resonance imaging; Volume modeling; Brain metastasis; radiosurgery

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1. Introduction

Radiation injury, a delayed complication or reaction after cranial radiotherapy (RT), is often indistinguishable from tumor progression on magnetic resonance imaging (MRI) [1]. The incidence of radiation injury after standard fractionated external beam radiation therapy of 72 Gy is estimated to be 5% [2]. The incidence after stereotactic radiosurgery (SRS) is reported to be 5–20%, depending on the dose, volume and location of irradiation [3,4]. Non-invasive imaging methods, such as magnetic resonance spectroscopy (MRS) and perfusion-weighted MRI (MRP), have been used to distinguish radiation injury from tumor progression. Although there have been some promising retrospective reports [5–7], the accuracy and true value of MRS and MRP to guide clinical decision making have not been widely accepted [8]. Furthermore, the majority of those studies derived their data from primary gliomas, so the diagnostic utility of MRS and MRP for other brain tumors, including brain metastases, after RT remains less clear.

In this study, we retrospectively analyzed different diagnostic criteria of MRS and MRP to examine their predictive values in differentiating tumor progression from radiation injury after RT for brain metastasis. The secondary goal of the study was to investigate if conventional MRI volume progression modeling could be used to distinguish tumor progression from radiation injury.

2. Methods

2.1. Patient population

From December 2006 to June 2009, 29 patients with previously irradiated brain metastases underwent MRS±MRP to evaluate suspicious but indeterminate lesions at William Beaumont Hospital (WBH). MRS and MRP were ordered at physician discretion to distinguish tumor progression from radiation injury. Three patients had limited follow-up to establish a diagnosis and were excluded. The remaining 26 patients had 33 lesions evaluated by MRS±MRP, which comprised the study group. Our routine follow-up included MRI every 3–6 months. This study was reviewed and granted approval by the WBH Human Investigation Committee.

2.2. Radiation therapy

RT consisted of stereotactic radiosurgery (SRS, n=20), whole brain radiation therapy (WBRT, n=6), or a combination of both (WBRT+SRS, n=7). SRS was performed with a Leksell Gamma Knife Model 4C radiosurgery unit (Elekta Instruments, Atlanta, GA). WBRT was performed with linear accelerators (Elekta Instruments, Atlanta, GA). To allow comparison between different RT modalities, the cumulative biological effective dose (BED) was calculated using the linear quadratic model: $BED=nd[1+d/(\alpha/\beta)]$, with d=fraction dose [Gy], n=number of fractions, α/β=tissue repair capacity of brain=2 Gy. The BED was calculated for the normal brain tissue instead of tumor, because the end point of interest was radiation injury. Examples of WBRT and SRS fractionation schedules used and their corresponding BED values are listed in Table 1.

2.3. Indication for salvage treatment

The decision for salvage brain surgery after RT was based on both clinical and radiological criteria. Patients with symptomatic neurological deficits attributable to progressive lesions in the setting of stable systemic disease and good performance status typically underwent surgical resection. If patient declined surgery, salvage SRS was considered based on the location of the lesion, the previous RT dose and the time interval elapsed since the prior RT.

2.4. MRS and MRP protocol

First pass MRS and MRP were performed on a 1.5-T Siemens Sonata scanner (Siemens medical Solutions, Melvern, PA) equipped with a 4-channel head-coil. The region of interest (ROI) for MRS was determined by using post-gadolinium T1-weighted imaging in three planes. The multi-voxel MRS was performed via a measurement protocol employing Point Resolved Spectroscopy (PRESS) with a 2D-slab localized around the ROI, and with Hamming weighted signal averaging. PRESS is a multi-echo, single-shot spectroscopy. The pulse sequence scheme uses 90°-180°-180° slice selective pulses. The 90° radio frequency pulse rotates the spins in the yx-plane, followed by the first 180° pulse (spin rotation in the xz-plane) and the second 180° pulse (spin rotation in the xy-plane), which gives the signal. Due to the long echo times, species with longer relaxation times are better visualized [9,10]. In patients where the tumor location was close to ventricles or near the edges of brain, single-voxel MRS was often used. The interpulse timing was optimized with the shape of the resonance of the strongly coupled *N*-acetylaspartate (NAA) system and the echo time was set to 135 ms. A partial water signal suppression was achieved with outer volume saturation slabs and frequency selective RF pulses. A total of 512 phase encode steps were used with a scan time of 7 min 12 s. Prior to performing measurement, magnetic field shimming was performed automatically by a standard shim procedure and was further improved manually focused on

Table 1
Example BEDs for normal brain injury in selected fractionated radiation therapy and stereotactic radiosurgery schedules

	RT types					
	WBRT	SRS	SRS	SRS	WBRT+SRS	
d (Gy)	3	15	18	21	3	18
n	10	1	1	1	10	1
BED (Gy)	75	128	180	242	255	