Differentiating Radiation Effect From Tumor Progression After Stereotactic Radiosurgery: T1/T2 Matching

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Radiosurgery is a common approach for patients with brain tumors.[1-3] After stereotactic radiosurgery (SRS), the differentiation between tumor progression and radiation effects (RE) can be difficult using current clinical criteria supplemented by computed tomography (CT) or magnetic resonance (MR) imaging (MRI). This is one of the greatest challenges in radiosurgical practice and indeed in neuro-oncology. Metabolic imaging with single-photon emission computerized tomography (SPECT) or positron emission tomography (PET) also fails to provide reliable predictive information.[4-6]

We studied whether selected clinical and MRI criteria can reliably differentiate tumor progression from REs in patients who required resection of their brain mass. Differentiation between tumor progression and REs is a fundamental challenge that directly affects patient care.[7,8] Desquesada et al[9] recently reported that their novel radiographic feature, called the ''lesion quotient,'' which was the ratio of the nodule volume as seen on T2-weighted MR imaging to the total-enhancing area on T1-weighted MR imaging, was significantly associated with tumor recurrence or REs. We focused on the correlation of any nodular lesion margin (not the measured lesion volume) on T2-weighted MR imaging compared to T1-weighted enhanced imaging.

METHODS AND MATERIALS

Patient Population

From a series of > 3000 patients who had brain metastases radiosurgery, we studied 71 who required delayed surgical resection at our institution because of lesion enlargement and had serial MRI studies available for review. The series included 33 men and 38 women whose median age was 55 years (range, 24-81 years). Twenty-seven patients had other brain metastases (range, 2-6). Eight patients had undergone surgical resection before SRS. Five patients had undergone SRS more than once for the same lesion. Prior adjuvant management included whole-brain radiation therapy alone (n = 20), chemotherapy alone (n = 14), and both whole-brain radiation therapy and chemotherapy (n = 13) (Table 1).

The primary cancer histologies included non–small-cell lung cancer (n = 28, 39%), small-cell lung cancer (n = 3, 4%), melanoma (n = 16, 23%), breast cancer (n = 11, 15%), renal cell carcinoma (n = 5, 7%), gastrointestinal cancer (n = 7, 10%), and osteosarcoma (n = 1, 1%). Tumors were located in the frontal lobe (n = 34, 48%), parietal lobe (n = 7, 10%), temporal lobe (n = 10, 14%), occipital lobe (n = 9, 13%), and cerebellum (n = 9, 13%) (Table 1).

The median interval between the diagnosis of the primary site and the diagnosis of the brain metastases was 20.5 months (range, 0.5-196 months). The median interval between SRS and repeat SRS before the surgical resection was 8.5 months (range, 4.8-9.3 months) in the 6 patients who had repeat SRS before their resection. The median interval between SRS and resection was 6.9 months (range, 0.3-27.7 months).

Imaging Analysis

Two neurosurgeons blinded to the surgical pathology reviewed each MRI study. The terms ''T1/T2 match and mismatch'' are a categorical correlation of the margin of the enhancing lesion on T1-weighted enhanced MRIs with the margin of reduced intensity on T2-weighted images. T1/T2 match was defined as the border of a nodule or lesion wall on the T2-weighted MRIs matched with the border on the T1-weighted enhanced images (including a partially matched border on both images). T1/T2 mismatch was defined as follows: The enhancement on T1-weighted MR images did not match any corresponding and similar low-intensity mass on T2-weighted images.

Seven patients underwent PET with 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG-PET), and 3 patients underwent ^{201}Tl–single-photon emission computerized tomography (SPECT) before surgical resection after SRS. The median interval between PET or SPECT and surgical resection was 0.5 months (range, 0.1-1.9 months).

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TABLE 1. Patient Characteristics[a]

Characteristics	n
Sex	
Male	33
Female	38
Median age (range), y	54.8 (24.4-80.9)
Prior WBRT alone	20
Prior chemotherapy alone	14
Prior WBRT and chemotherapy	13
No prior WBRT and chemotherapy	24
Surgical removal before SRS	
Total removal	7
Partial removal	1
Tumor location	
Frontal	34
Parietal	7
Temporal	10
Occipital	9
Basal ganglia	2
Cerebellum	9
Primary cancer	
LK (NSCLC)	28
LK (SCLC)	3
Melanoma	16
Breast	11
Kidney	5
Gastrointestinal tract	7
Sarcoma	1

[a]LK, lung cancer; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

Radiosurgery Technique

Our radiosurgical technique has been described in detail in previous reports.[10,11] In brief, patients underwent application of an imaging-compatible stereotactic head frame under local anesthesia supplemented by intravenous sedation. High-resolution MRI was then performed. Patients underwent either a sagittal scout MRI or a 3-dimensional localizer sequence that included axial, coronal, and sagittal images. The tumor was then imaged with contrast-enhanced volume acquisition images, occasionally supplemented with fat suppression technique. T2-weighted MRIs using fast spin echo technique also were acquired to assess the infiltrative tumor volume and to define the size of peritumoral edema. The target volume included enhanced tumor regions. In all patients, the SRS dose was prescribed to the entire tumor volume.

The median tumor volume at the time of the prior SRS was 7.1 cm^3 (range, 0.5-25.5 cm^3) (Table 2). A median of 4 isocenters (range, 1-12) were used for dose planning. The median prescription dose delivered to the tumor margin was 17.0 Gy (range, 12-20 Gy). The maximum dose varied from 24 to 40 Gy (median, 33.0 Gy). SRS was performed with a model U, B, C, or 4-C Leksell Gamma Knife (Elekta Inc, Atlanta, GA).

TABLE 2. Tumor Characteristics at the Time of Stereotactic Radiosurgery and Surgical Resection[a]

Variables	At SRS, median (range)	At Surgical Resection, median (range)
Tumor volume, cm^3	7.1 (0.5-25.5)	13.5 (1.3-81.2)
Tumor size, mm	22.6 (4.0-52.0)	30.0 (12-120)
Maximum axial edema, mm	35.0 (4.0-98.6)	52.0 (16.0-134)

[a]SRS, stereotactic radiosurgery.

Surgical Indications

Patients were evaluated clinically and by MRI at intervals of 1 to 3 months after SRS. Surgical resection after SRS was performed because of clinical deterioration associated with progressive lesion enlargement and mass effect unresponsive to corticosteroids. The goal of surgery was to obtain histopathological confirmation of the mass and to achieve gross-total resection of the lesion. The follow-up MRIs were compared with the radiosurgery images, and tumor dimensions were measured in the axial, sagittal, and coronal planes. The edema size was measured by the largest dimension at the time of SRS and surgical removal after SRS.

The median follow-up time after initial cancer diagnosis, after SRS, and after surgical resection was 43.4 months (range, 7.1-226 months), 13.2 months (range, 0.7-115 months), and 7.5 months (range, 0.03-105 months), respectively.

Statistical Analysis

We conducted our statistical analyses using the Mann-Whitney *U* test and Kaplan-Meier curves using the log-rank test to assess factors that might influence the length between SRS and surgical resection. For univariate analysis of the factors that might influence the rate of tumor recurrence, we used the Kruskal-Wallis test and Fisher exact test with $P < .05$ set as significant. This retrospective study was approved by the University of Pittsburgh Institutional Review Board.

RESULTS

Overall Survival

At the time of assessment, 12 patients (17%) were alive and 59 patients (83%) had died at a median of 40 months after the initial diagnosis of their primary cancer (range, 8.6-208 months). As a group, the patients survived a median of 13.2 months (range, 0.7-115 months) after radiosurgery before they underwent surgical resection. They survived a median of 7.5 months after surgical resection (range, 0.03-105 months).

The cause of death in the majority of patients (63%) was systemic disease progression. However, 22 patients (37%) died of brain tumor progression. This included 16 patients who died of tumor progression despite SRS and surgical resection. Six patients died of progression of other brain metastases. At a median of 6 months (range, 4.2-12.2 months), these 6 patients developed new brain metastases after SRS.

Response to SRS

The median Karnofsky performance status was 90, and the median recursive partitioning score (RPA) was 2 (range, 1-2) at the time of SRS. The median tumor volume at the time of SRS was 7.1 cm^3 (range, 0.5-25.5 cm^3). The median edema maximum dimension at the time of SRS was 3.5 cm (range, 0.4-9.9 cm). The reasons for surgical resection after SRS included neurological deterioration (n = 52), imaging-defined tumor progression without new neurological symptoms (n = 4), intractable seizures (n = 5), headache unresponsive to medical management (n = 5), and declining level of consciousness (n = 5).

Lesion progression was identified at a median of 5 months (range, 0.3-24.6 months) after SRS. The median interval between SRS and surgical resection was 7 months (range, 0.3-28 months). The median time between tumor progression and surgical resection was 1 month (maximum, 14 months).

The median Karnofsky performance status was 80 and recursive partitioning score was 2 at the time of surgical resection. The median tumor volume at the time of the surgical resection was 13.5 cm^3 (range, 1.3-81.2 cm^3). The median maximum edema dimension at the time of surgical resection was 5.2 cm (range, 1.6-13.4 cm) (Table 2).

Correlation of Pre-resection MRI and Pathology

At pathology, 34 lesions had recurrent cancer without REs, 25 had residual cancer and REs, and 12 had only REs but no residual tumor. Illustrative cases are shown in the Figure. We found that a distinct lesion margin on T2- and a contrast-enhanced margin on T1-weighted images (a finding we have called T1/T2 match) was highly correlated with tumor progression ($P < .0001$). T1/T2 match was associated with 31 lesions with recurrent cancer without necrosis, 23 with mixed cancer and necrotic tissue, and 2 that had all necrosis without cancer. When the lesion border on T2-weighted MRIs ($P < .0001$) did not correspond to the contrast-enhanced T1 lesion volume (T1/T2 mismatch), the pathology was associated with higher rate of necrosis ($P < .0001$) (Table 3). T2/T1 mismatch was associated with 10 lesions that had all necrosis without cancer, 2 with mixed cancer and necrotic tissue, and 3 with recurrent cancer without necrosis. Lack of any defined lesion shape on the T2-weighted MRI included 10 with necrosis without cancer, 3 with mixed recurrent cancer and necrotic tissue, and 2 with recurrent cancer without necrosis. On the other hand, the appearance of peripheral rim enhancement $\geq$ 1 cm thick on T1-weighted images, a solid lesion, or a cystic lesion was not correlated one way or another with the finding of necrosis. The sensitivity of the T1/T2 mismatch in identifying necrosis was 83.3% and the specificity was 91.2%. On the other hand, the sensitivity of T1/T2 match in identifying tumor recurrence was 93.9% and the specificity was 76.9%.

Correlation of Pre-resection PET or SPECT and Pathology

Five of 7 patients who underwent FDG-PET imaging demonstrated increased tracer uptake in the irradiated tumor area, and 2 patients demonstrated reduced uptake (Table 4). On pathological review, 4 of 5 patients with increased uptake in FDG-PET had mixed tumor and necrotic tissue, and 1 patient had all tumor. Two patients with reduced uptake in FDG-PET had either all tumor or mixed tumor and necrotic tissue. Hypo-uptake on FDG-PET was not significantly associated with identifying REs ($P = .67$). Thus, FDG-PET showed a sensitivity of 71.4%.

All 3 patients who underwent SPECT before surgical resection demonstrated increased uptake in the irradiated tumor area. At pathology, 1 patient demonstrated all tumors, 1 demonstrated mixed tumor and necrosis, and 1 demonstrated all necrosis.

DISCUSSION

Clinicians are challenged to interpret brain imaging after prior irradiation. REs after aggressive radiation and/or radiosurgical management for malignant brain tumors are increasingly likely as patient experience grows.[12] REs can arise months to years after irradiation and can lead to headache, seizures, focal neurological deficits, and symptoms from increased intracranial pressure. REs are usually treated with corticosteroids, but some cases need surgical resection as a result of neurological deterioration or steroid dependency.

Dequesada et al[9] reported that a novel radiographic feature called the lesion quotient, the ratio of the nodule seen on T2 imaging (maximum cross-sectional area) to the total-enhancing area on T1 imaging, had high predictive value, sensitivity, and specificity for identifying the presence of radiation necrosis alone. In their series, the sensitivity of the lesion quotient in identifying recurrent tumor only was 100% and the specificity was 32%. The sensitivity of the lesion quotient in identifying REs only was 80% and the specificity was 96%. Whether this concept, which necessitates multiple measurements, will prove practical for clinicians to use remains to be seen. Our method involves only a visual assessment of the lesion margin. We do not propose a mathematical formula because we think this method requires the use of software-based measurements and is less likely to be widely adopted. We aimed to create an even simpler approach, based only on appearance, that was predictive of

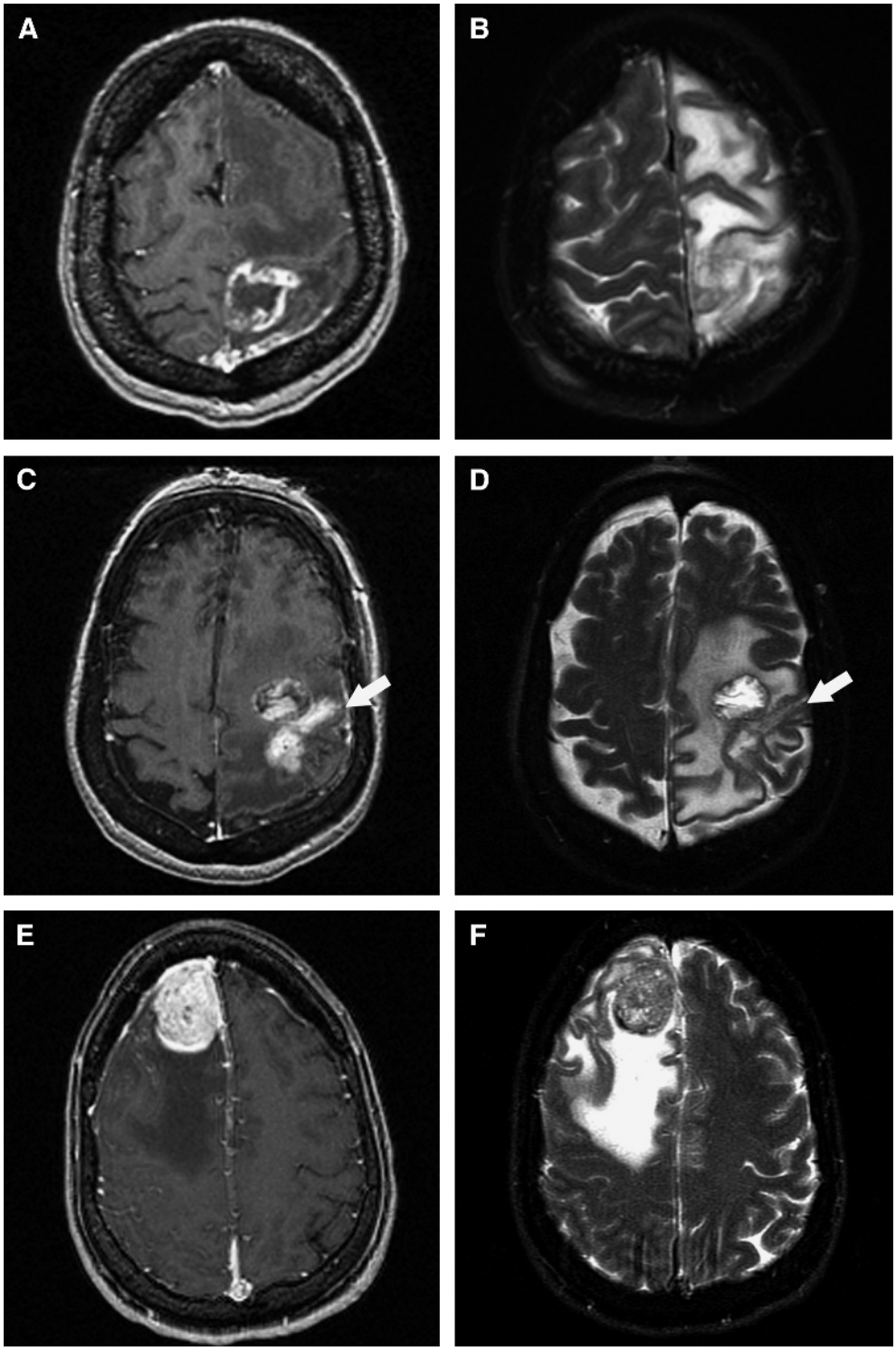

FIGURE. Top, Axial paired magnetic resonance images (MRIs) of non–small-cell lung cancer demonstrate a poor correspondence between the T1-weighted contrast-enhanced MRI (A) and the lesion defined by the T2-weighted image (B), indicating a T1/T2 mismatch. Postoperative histopathology showed necrosis and no residual tumor. Middle, Axial paired MRIs of breast cancer demonstrating correlation between the T1-contrast enhanced image (C) and a region with a distinct border seen on the T2-weighted image (small arrow) (D). An indistinct region on T2 is identified by the arrow. Imaging shows both a T1/T2 match and a T1/T2 mismatch. Histopathology revealed mixed tumor and necrosis. Bottom, Axial paired MRIs of melanoma demonstrating a clear margin on the contrast enhancement on the T1-weighted image (E) and the margin on the T2-weighted image (F) (T2/T1 match). Histopathology revealed cancer.

histology. We found that a match between a distinct T2 margin and a distinct lesion border on contrast-enhanced T1-weighted images was highly correlated with tumor ($P < .0001$). In contrast, an indistinct T2 lesion that failed to correlate with the T1 contrast volume was significantly associated with detection of necrosis ($P < .0001$). The sensitivity of the T1/T2 mismatch in identifying necrosis was 83.3% and the specificity was 91.2%. On the other hand, the sensitivity of T1/T2 match in identifying tumor recurrence was 93.9% and the specificity was 76.9%. Dequesada et al[9] also reported that traditional radiographic

TABLE 3. Relationship Between Histopathology Findings and Magnetic Resonance Imaging Features[a]

		Imaging		
Histopathology	Patients, n	T1/T2 Match, n	T1/T2 Mismatch, n	*P*
Recurrent tumor (no RE)	34	31	3	< .0001 (vs RE)
Tumor plus REs	25	23	2	< .0001 (vs RE)
REs only	12	2	10	N/A

[a]RE, radiation effect.

features, including arteriovenous shunting, gyriform distribution, pattern of enhancement, edema, and cyst formation, also had low sensitivity.

SRS is now used as first-line care for patients with small and multiple brain metastases. Repeat SRS remains an option for progression of smaller tumors. However, a resection may be indicated for large recurrent tumors and those with raised intracranial pressure or symptomatic mass effect not quickly responding to corticosteroids. All patients had lesions that showed contrast enhancement. When the contrast-enhanced rim on T1-weighted image was associated with a distinct border on T2, the pathology was usually recurrent tumor. In these patients, the T2 margin ''mismatched'' the contrast-enhanced T1 margin. When the lesion appeared indistinct on T2, the histology usually showed necrosis. In these patients, there was a T1/T2 mismatch. Such findings may argue for longer continued medical therapy if symptoms of mass effect are not disabling. In addition to corticosteroids, selected patients may benefit from a combination of vitamin E and pentoxifylline or bevacizumab. These agents have been associated with imaging-defined repair of adverse REs.[13,14]

A biopsy or surgical removal is the most definitive way to distinguish REs from tumor progression. The sensitivity and specificity of biopsy are > 95%.[15,16] The decision to continue with medical management, to perform stereotactic biopsy or resection, is first based on imaging appearance.[17,18] In general, conventional diagnostic imaging using CT or MRI has failed to distinguish REs from tumor progression. Both REs and tumor may have a contrast-enhancing mass and perilesional cerebral edema.[19-21]

TABLE 4. Relationship Between Histopathology Findings and Fluoro-2-Deoxy-D-Glucose–Positron Emission Tomography Features[a]

		Imaging		
Histopathology	Patients, n	T1/T2 Match, n	T1/T2 Mismatch, n	*P*
Recurrent tumor (no REs)	1	1	0	.67 (vs RE)
Tumor plus REs	4	4	0	.13 (vs RE)
REs only	2	0	2	NA

[a]RE, radiation effect.

PET, SPECT, and magnetic resonance spectroscopy are additional imaging studies to assist in the determination of REs versus tumor. Limitations of these tools include lack of routine use and inconsistency of reimbursement by third-party payers. Griffeth et al[22] detected only 68% of metastases using FDG-PET, whereas Thompson et al[23] identified 80% of primary glial neoplasms with a volume of contrast enhancement > 10 cm^3 but only 25% when the volume of enhancement was < 6 cm^3. Chao et al[24] reported that FDG-PET showed a sensitivity of 65% and a specificity of 80% in 32 patients with brain metastases after SRS with regard to distinguishing tumor recurrence and necrosis. When FDG-PET and MRI were coregistered in a subgroup of 12 patients, FDG-PET had a sensitivity of 86% and a specificity of 80%. In our series, selected patients in the patient series also underwent FDG-PET imaging, but no correlation with histology was found ($P = .677$).

Disclosure

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