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Clinical Study

Imaging changes after stereotactic radiosurgery of primary and secondary malignant brain tumors

Donald A. Ross[1], Howard M. Sandler[2], James M. Balter[2], James A. Hayman[2], Paul G. Archer[2] and Donna L. Auer[1,2]
[1]*Department of Surgery,* [2]*Section of Neurosurgery, Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan and Medford Neurological and Spine Clinic, Medford, OR, USA*

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Summary

After radiosurgery of malignant tumors, it can be difficult to discriminate between transient treatment effects, radiation necrosis, and tumor progression on post-treatment imaging. Misinterpretation of an enlarging lesion may lead to inappropriate treatment and contribute to disagreements about treatment efficacy. In an effort to clarify this problem, we reviewed our experience with interpreting post-radiosurgical imaging in patients with malignant primary and secondary brain tumors. We reviewed results of radiosurgery of 30 malignant gliomas and 35 metastatic brain tumors with minimum follow up of 1 year or until death. Of 30 gliomas, 73% were larger a mean of 13 weeks after radiosurgery. Of 35 metatstatic tumors, 22% were larger a mean of 10 weeks after radiosurgery. Eleven had ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) of enlarging lesions. Eight showed increased activity with respect to brain; three decreased activity. Of the eight, six predicted incorrectly based upon the patients' subsequent courses (all alive, mean follow up of 27 months), and two correctly, with the patients dying from the imaged lesions 8 and 13 months later. Of the three with FDG uptake less than brain, one patient was alive with 32 weeks of follow up, and two patients died from the imaged lesion 13 and 21 months later. Radiographic enlargement after radiosurgery is common, especially for gliomas. Physicians caring for these patients should be aware of this phenomenon and be cautious in interpreting post-treatment images. MRI appearance may be useful for metastases. FDG-PET seems unreliable. Further evaluation of Tl-201 and HMPAO SPECT or MRS is warranted.

Introduction

Stereotactic radiosurgery has become an accepted treatment option for cerebral metastatic tumors [1–7] and for recurrent gliomas [8–11]. After treatment, tumors may regress or remain stable, but frequently, the enhancing radiographic abnormality enlarges. Interpreting post-treatment images is difficult, and additional studies such as ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) [7], thallium or HMPAO SPECT [12–14], or biopsy [15] are often used to try to discriminate between transient treatment effects, radiation necrosis, and tumor progression. Even when patients are doing well clinically, biopsy may show persistent tumor at the radiosurgical site [15]. There is not universal agreement on the value of these studies and little literature on the management of patients whose radiographic abnormality enlarges after radiosurgery. Misinterpretation of an enlarging radiographic abnormality may contribute to disagreements about the efficacy of radiosurgery [16,17]. In an effort to clarify this problem, we review our experience with interpreting post-radiosurgical imaging in patients with malignant primary and secondary brain tumors.

Methods

We reviewed our results for radiosurgical treatment of all patients with malignant primary and secondary brain tumors over a period of 5 years since the inception of our radiosurgery program in March, 1995. Radiosurgery for gliomas was only offered in the setting of recurrence after primary therapy. Determination

of progression rather than radiation effect was made at a multidisciplinary tumor board attended by radiation oncologists, neuroradiologists, neuro-oncologists, and neurosurgeons. MRI and FDG-PET scans and occasional surgical biopsies were used to aid in this determination. Radiosurgery for metastases was offered for both primary treatment and for recurrences. Radiosurgical treatment was carried out using the Brown–Roberts–Wells stereotactic head frame (Radionics, Burlington, MA). All patients underwent stereotactic, thin slice (1.0 or 1.5 mm), contrast enhanced CT scans. Patients with very small tumors or poor lesion definition on CT underwent image fusion with MRI scans obtained prior to the day of treatment. Data was transferred into the treatment planning system (UMPLAN) [18,19] and the tumor was outlined on each CT slice. Treatment planning and quality assurance checking were carried out as previously described [20]. Patients not previously on an anticonvulsant were orally loaded with Dilantin. Patients already on an anticonvulsant had their serum levels checked and additional medication was given if the level was not in the high therapeutic range. All patients were given Dexamethasone 10 mg orally prior to treatment.

Treatment was carried out on a Racetrack Microtron accelerator (Scanditronix MM50) (Uppsalla, Sweden) using a computer control system developed at the University of Michigan [18]. The isocenter was first localized with an orthogonal laser system and a commercial laser target localization frame (Radionics, Burlington, MA) and then confirmed with source to surface distances and orthogonal radiographs which were compared with digitally reconstructed radiographs generated by the treatment planning system. Treatment took approximately 30 min, after which patients were discharged to home. Anticonvulsants were discontinued unless the patient was on such medication prior to treatment or had a history of seizures. Steroids doses were adjusted according to clinical response and radiographic data with an effort to use the lowest dose at which the patients' symptoms and side effects were minimized. Patients underwent regular post-treatment imaging, either by the referring oncologist or by the Radiosurgery Program if they so desired.

Results

Over the last 5 years, 33 patients have been treated for recurrent high grade glioma (10 glioblastomas, 9 grade III astrocytomas, 2 anaplastic ependymomas, 10 anaplastic oligoastrocytomas, and 2 malignant gangliogliomas) and 58 metastatic tumors have been treated in 52 patients. For the purposes of this study, only patients with one year of follow up or who have died were included. Imaging responses were grouped into the following categories based upon subsequent imaging:

1. Target lesion disappeared
2. Target lesion regressed
3. Target lesion stable
4. Target lesion larger

Thirty patients with gliomas had adequate follow up (median 24 months). On imaging obtained a mean of 13 weeks after radiosurgery, 5 (17%) had regressed, 3 (10%) were stable, and 22 (73%) were larger. Of the 22 patients whose lesions enlarged, seven underwent reoperation, five received only steroids, seven received chemotherapy, one received additional fractionated radiation and chemotherapy, and two died with no additional treatment. Pathology reports on the operated patients showed recurrent high grade glioma in four cases, pure radiation necrosis in two cases, and mixed tumor and necrosis in one case.

Thirty-five patients with 37 metastatic tumors had adequate follow up (median 25 months). On imaging obtained a mean of 10 weeks after radiosurgery, 1 (2.9%) lesion had disappeared, 18 (49%) had regressed, 10 (27%) were stable, and 8 (22%) were larger. Of the eight lesions which enlarged, two were treated with steroids only, three received chemotherapy, one underwent reoperation, and two died with no additional therapy. The pathology report on the one reoperated patient showed mainly radiation necrosis, but contained islands of adenocarcinoma cells. The patient's esophageal carcinoma subsequently recurred in the scalp incision and he succumbed to his disease.

Eleven patients had FDG-PET scans as part of their evaluation after enlarging lesions were detected. It was our hypothesis that FDG uptake higher than that of brain would indicate the presence of active tumor and indicate that tumor progression was likely. Eight studies showed increased metabolic activity with respect to normal brain, and three showed decreased activity. Of the eight studies read as increased activity, six were thought to be incorrect based upon the patients' subsequent courses (all alive with a mean follow up of 27 months and without progression of the lesion imaged), and two were correct with the patients dying from the imaged lesions 8 and 13 months later. Of the three studies showing decreased activity, one was

correct with the patient alive but with only 8 weeks of follow up, and two were incorrect with patients dying from the imaged lesion 13 and 21 months later.

Five patients had ^{201}thallium single photon emission computed tomography (SPECT) as part of their evaluation after enlarging lesions were detected. Three studies showed uptake of the tracer, and two showed no uptake. Of three positive tests for tracer uptake, all three patients died of the imaged lesion a mean of 9 months later. Of two negative tests, one was correct with the patient alive and well 20 months later, and one was incorrect with the patient dying from the imaged lesion 13 months later.

Examples of imaging responses are given for patients with persistent or enlarging lesions.

Target lesion regressed

T.W., a 50-year-old man, presented with headaches and ataxia. CT revealed a right thalamic mass and hydrocephalus. He underwent stereotactic biopsy and ventriculoperitoneal shunting. Pathology revealed non-small-cell lung cancer. He underwent fractionated whole brain irradiation to 30 Gy and underwent chemotherapy with carboplatin and Taxol. Six months later, his symptoms recurred and CT and MRI revealed a recurrence of his thalamic mass. He was treated with radiosurgery, receiving 15 Gy to the 82% isodose surface of a 10.9 cc target. Subsequent imaging 5 months later showed marked diminution in the size of the enhancing mass, but persisting perilesional edema. He continued to require steroids for the remainder of his life, and succumbed to systemic disease 9 months after radiosurgery (Figure 1).

Target lesion stable

K.G., a 51-year-old woman, was diagnosed with non-small-cell lung cancer and treated with chemotherapy, radiation, and resection. A year later, deteriorating handwriting lead to the diagnosis of three presumed metastases in the right cerebellum. She underwent fractionated whole brain radiation therapy to 30 Gy with a focal boost to 39 Gy. Nine months later, two of the three lesions were found to be enlarging and she was referred for radiosurgery. All three lesions were treated with two isocenters, delivering 15 Gy to the 82% isodose line of a 3.6 cc target and 15 Gy to the 82% isodose line of a 0.19 cc target. Fifteen months later, the lesions were still present, but had not enlarged since treatment. She died of systemic disease 17 months after radiosurgery.

Target lesion larger

M.N., a 52-year-old woman, was diagnosed with breast cancer 4 years earlier and had undergone lumpectomy,

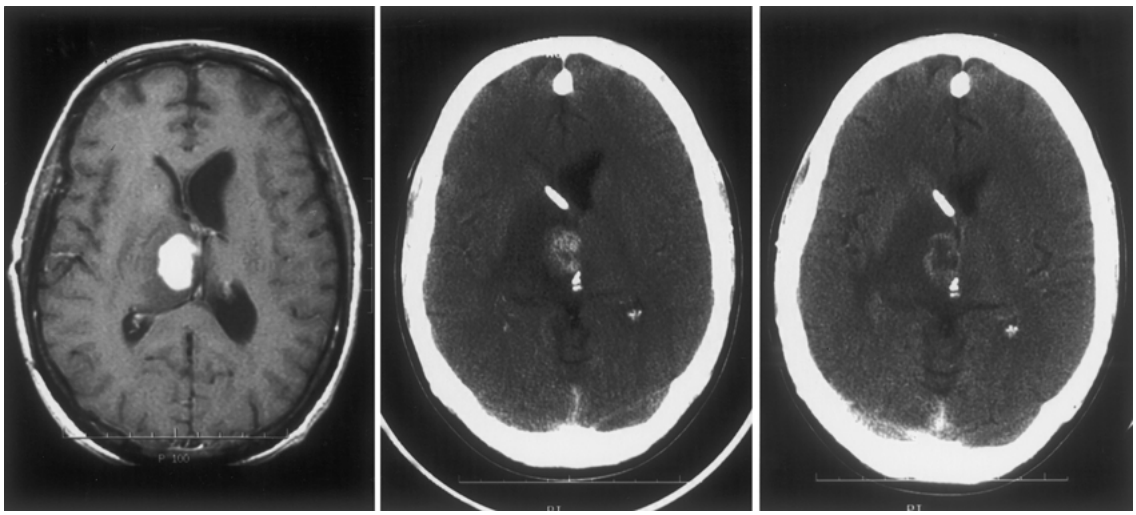

Figure 1. Metastatic large cell lung carcinoma. Gadolinium enhanced T1 weighted axial MRI from day of treatment (left), and contrasted enhanced axial CT scans from 2 (center) and 5 (right) months after radiosurgery for a recurrent metastatic large cell lung cancer, treated with 15 Gy to the 82% isodose surface of a 10.9 cc mass. The lesion has regressed in size and lost its central enhancement, but has not disappeared.

radiation, and chemotherapy. Three years later, she developed a left frontal metastasis which was resected elsewhere. She then underwent fractionated whole brain radiation to 30 Gy with a 10 Gy boost to the resection site. One year later, two asymptomatic right parietal and occipital tumors were detected and she was referred for radiosurgery. She received 18 Gy to the 87% isodose line of a 6.48 cc target and 18 Gy to the 81% isodose line of a 3.99 cc target. An MRI 2 months later showed both lesions to be larger, and was interpreted by the radiologist as showing progression. A thallium 201 SPECT scan was obtained by the referring oncologist 4 months after radiosurgery and was interpreted as showing significant uptake in both of the tumors. The patient was treated with steroids, but became progressively debilitated and expired 6 months after radiosurgery. No autopsy was performed.

R.L., a 56-year-old man, had undergone a nephrectomy for renal cell carcinoma 2 years earlier. Because of pulmonary metastases, he was under consideration for immunotherapy. A screening head CT disclosed a left frontal polar asymptomatic presumed metastasis and he was referred for radiosurgery. He received 21 Gy to the 83% isodose surface of a 1.0 cc target. After some consideration, he then underwent fractionated whole brain radiotherapy to a total dose of 37.5 Gy delivered in 2.5 Gy fractions. Five months later, he was referred emergently to neurosurgery for consideration of resection because a follow up MRI showed a massive increase in the enhancing abnormality. An FDG-PET scan was obtained which was read as showing increased uptake consistent with recurrent/persistent tumor. It was the opinion of the radiosurgery team that this was not likely to be the case, and no further therapy was recommended other than steroids for symptomatic relief. Another MRI 2 months later, showed a marked decrease in the enhancement. The patient remains asymptomatic 20 months after treatment (Figure 2).

M.R., a 21-year-old woman, experienced her first seizure. MRI showed a large right frontal intra-axial mass without contrast enhancement. The lesion was entirely resected at an awake craniotomy, with complete resection confirmed by a post-operative MRI. Pathology was a Grade III ganglioglioma. She received fractionated radiation therapy to 45 Gy with a boost to 75.6 Gy. Six weeks later, MRI showed a new contrast enhancing nodule in the wall of the resection cavity and radiosurgery was recommended. She received 17 Gy to the 84% isodose surface of a 5.7 cc target. One month later, the mass had increased in size on CT and the patient had developed a hemiparesis. An FDG-PET scan was obtained and showed a focal area of increased uptake corresponding to the contrast enhancing region and interpreted as tumor progression. PCV chemotherapy was begun. Five months after radiosurgery the scan continued to worsen, so chemotherapy was changed to carboplatin and VP-16. One year after radiosurgery, the enhancement had diminished markedly. Twenty-three months later, there is no contrast enhancement on her MRI scan (Figure 3).

G.J., a 51-year-old man, was diagnosed with a left frontal Grade III oligoastrocytoma 8 years previously. After radical resection, he received 59.4 Gy

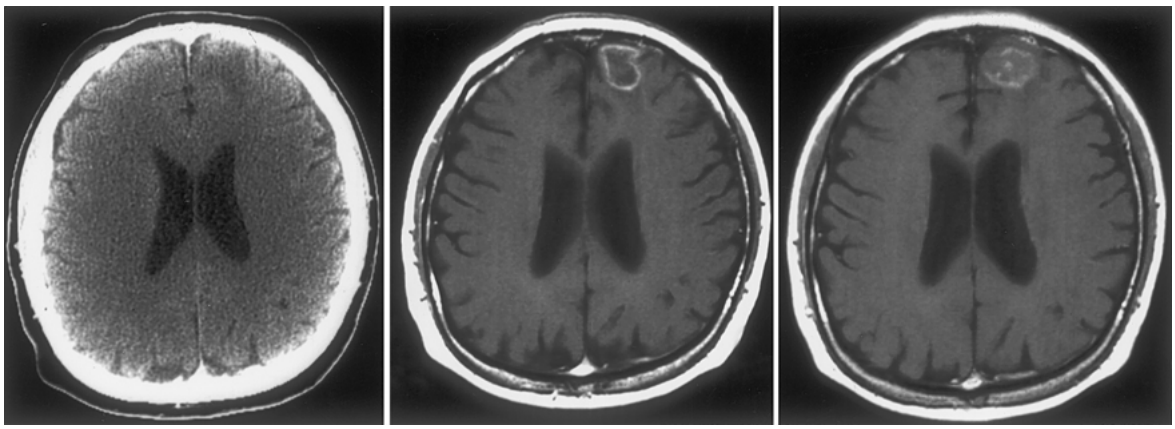

Figure 2. Metastatic renal cell carcinoma. Axial contrast enhanced CT scan from day of radiosurgery (left), and axial, T1 weighted, gadolinium enhanced MRI from 8 months (center) and 11 months (right) after radiosurgery. The patient received 21 Gy to the 83% isodose surface of a 1.0 cc tumor. The radiographic abnormality has increased in size, but shows ring enhancement only.

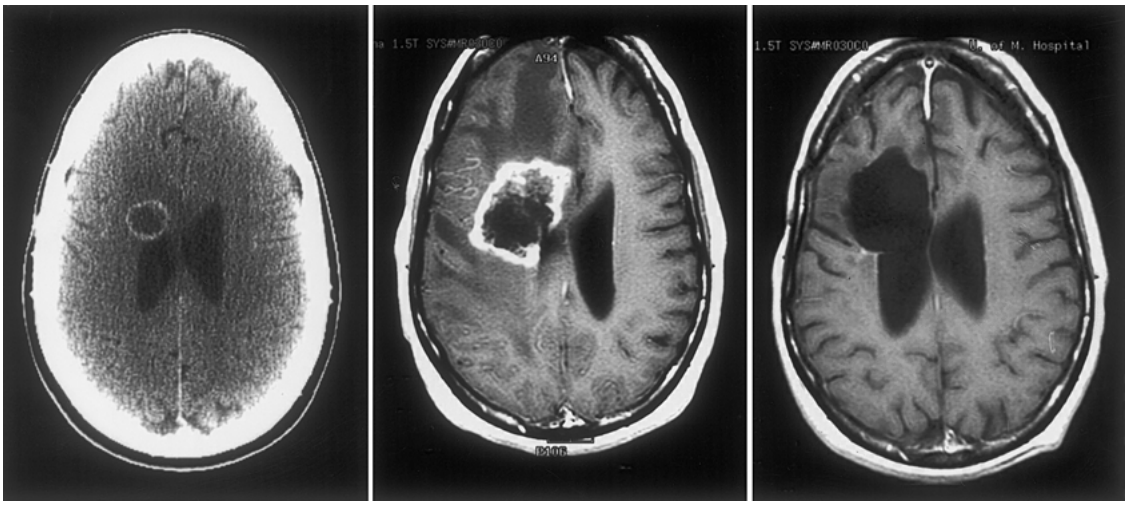

Figure 3. Recurrent high grade ganglioglioma after fractionated radiation. Axial, contrast enhanced CT on the day of treatment (left), and axial, T1 weighted, gadolinium enhanced MRI from 5 months (center) and 23 months (right) after radiosurgery. The patient received 17 Gy to the 84% isodose surface of a 5.7 cc mass.

of fractionated radiation. Serial imaging showed no residual tumor until 5 years after surgery, at which time a new area of contrast enhancement was detected and radiosurgery was recommended. He received 18 Gy to the 80% isodose surface of the 4.9 cc target. For the next 15 months, the radiographic lesion enlarged steadily, but the patient was asymptomatic. No additional therapy was recommended. The lesion then began to decrease in size. Three years after treatment, the lesion was no longer visible on CT.

Discussion

Although radiosurgical treatment of malignant primary and secondary brain tumors has become quite common, very little has been written about the interpretation of post-treatment imaging studies. Many comprehensive reports do not mention interpretation of post-treatment imaging except in relation to radiation necrosis [7,11]. Some reports consider radiographic enlargement an indication of treatment failure [16].

In a multi-institutional report of outcome of 122 patients after radiosurgery for single brain metastasis, results were reported at a median follow up of 123 weeks as 25% complete response, 34% partial response, 36% no response, and 6% progression [2]. No mention is made in this report of enlargement of the target lesion not thought to be due to tumor progression. The 6% rate of target enlargement is quite different from our experience, but is reported at much longer mean follow up, after much of the transient enlargement secondary to treatment effect would have resolved. Engenhart et al. [21] reported on 102 treated metastases in 69 patients, noting complete response in 20%, partial response in 35%, stable disease in 40%, and progression in 5%. One patient underwent craniotomy for what proved to be radiation necrosis, but no mention is made of how progression was determined. Increased perilesional edema and clinical worsening was noted in 10%. The University of Pittsburgh group reported that 10.8% of 229 metastases were seen to grow on subsequent imaging [3]. This report acknowledges that some of the patients classified as recurrences may have had radiation necrosis, but no patient had histologic confirmation. A later report from the same institution noted that 5 of 78 metastases (6.5%) were seen to enlarge on subsequent imaging [22]. Loeffler et al. [5] noted that metastatic adenocarcinomas decreased in size rapidly after treatment, but did not often regress completely. Other tumor types regressed very little after treatment and, at one year post-treatment, most patients had smaller ring-enhancing lesions with some persisting perilesional edema. They noted that it was important not to overreact to the presence of a persisting radiographic abnormality. Mehta et al. [6] reported that of 10 metastatic tumors which progressed after radiosurgery, three occurred after no initial response to treatment and three occurred after partial responses. Adler et al. [23] also noted that in 9% of their cases,

Table 1. Fraction of metastatic tumors enlarging on subsequent imaging

Reference	Patients/tumors	Progression (%)
Flickinger et al. [3]	157/229	10.8
Auchter et al. [2]	122/122	6
Engenhart et al. [21]	69/102	5
Mehta et al. [10]	40/58	18.5
Ross	35/37	22

after an initial decrease in the size of the enhancing abnormality, the lesion then enlarged. Biopsy of two such lesions showed only necrosis. They concluded that 'an assessment of local treatment failure, which is based solely on an increase in contrast enhancement observed on imaging studies, is difficult.' Results are summarized in Table 1.

In our experience, this has been even more challenging with malignant gliomas. Mehta et al. [10] reported on 31 patients with glioblastomas undergoing radiosurgery as part of initial therapy. Progression was classified as within the high dose radiosurgical region, within 2 cm of the border of the high dose region, or greater than 2 cm from the tumor margin. They noted 'the delineation of progression, recurrence, and necrosis in glioblastoma is not possible to make with absolute clarity in each case.' Eighty-four percent of the patients progressed on clinical grounds, and 83% of 24 evaluable patients were thought to have progressed based on serial imaging, including MRI, MRS, PET, and SPECT. Of these 24 patients, no failures were within the high dose region, 19 were peripheral failures, four were distant, and one was both peripheral and distant. Four of these 31 patients were ultimately determined to have necrosis based upon PET and/or SPECT in one patient and biopsies in two, for a false positive rate of 13%. All three of these were thought to have progressed radiographically, indicating 'the potential pitfalls in relying on a radiographic diagnosis of progression.' Shrieve et al. [11] noted that among 14 patients undergoing reoperation after radiosurgery for recurrent glioblastoma, pathological examination showed both necrosis and tumor cells in all cases, and that there was no correlation between the findings at surgery and the eventual outcome. Likewise, the Pittsburgh group reported that 12% of glioblastoma patients and 23% of anaplastic astrocytoma patients required reoperation after radiosurgery, with the indication for surgery described as an increase in tumor volume and regional mass effect [9]. The pathology reports on these patients showed a mixture of viable tumor and necrosis in almost all cases, but these authors noted 'it is difficult to know the significance of each histologic finding on the clinical and imaging progression observed.'

Additional radiologic studies, such as FDG-PET and thallium 201 and/or HMPAO SPECT [12–14], have been reported to be of use in discriminating between tumor progression and radiation effect. Thompson et al. [24] studied 15 patients with surgical histological confirmation of diagnosis and reported that FDG-PET was only 43% sensitive in distinguishing recurrent tumor from radiation effect, and was least accurate when the lesion volume was under 6 cc. Schwartz et al. [14] have reported that the combination of low thallium and low HMPAO uptake is associated with benign radiation changes at surgery; whereas, increased uptake of either agent or both was associated with recurrent/persistent tumor at biopsy and a poor prognosis. However, false positive FDG-PET and Tl-210 SPECT have been reported with biopsy proven radiation necrosis [25]. Our own experience underlines the need for care in interpreting these studies as well. In particular, FDG-PET was falsely positive in six of eight cases and falsely negative in two of three cases, and may not be useful in this setting for predicting progression of the tumor. Increased FDG uptake might indicate that more closely spaced surveillance imaging or biopsy is necessary, but we do not recommend that it be used as the sole indicator for additional treatment. Thallium SPECT was more reliable in our institution, but not universally so. MR spectroscopy may prove useful in this setting [26].

The pattern of contrast enhancement may be useful in the case of metastatic tumors. Whereas the tumors themselves tend to have discrete borders with adjacent brain on enhanced MRI, radiation effect is more likely to produce a fuzzy, indiscrete pattern of enhancement suggestive of breakdown of the blood–brain barrier adjacent to the target (see Figure 3).

In conclusion, radiographic worsening after radiosurgery for malignant primary and secondary brain tumors is quite common. Neurosurgeons, radiation oncologists, and neuro-oncologists caring for patients undergoing radiosurgery should be aware of this phenomenon and be cautious in interpreting post-treatment images. FDG-PET and Tl-201 or HMPAO SPECT may be helpful, but are not always reliable in discriminating necrosis from recurrent tumor. Further evaluation of the combination of Tl-201 and HMPAO SPECT and MRS in predicting outcome is warranted.

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Address for offprints: Donald A. Ross, Medford Neurological Clinic, 2900 State Street, Medford, OR 97504, USA; Tel.: 541-779-1672; Fax: 541-779-0986; E-mail: drdoom867@yahoo.com