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The Role of Thallium-201 Uptake and Retention in Intracranial Tumors After Radiotherapy

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This study prospectively assessed the diagnostic accuracy and prognostic value of ^{201}Tl uptake and retention in primary and metastatic intracranial tumors treated by conventional radiotherapy and/or radiosurgery. **Methods:** An initial ^{201}Tl study (early and delayed images), was obtained in 60 postsurgical patients, 6–12 wk after radiotherapy or radiosurgery. Repeat imaging was performed as clinically warranted. Tumor-to-background count ratios and a retention index (RI) were calculated for all lesions. **Results:** Abnormally increased ^{201}Tl uptake was observed in 40 of 60 patients. In all patients with positive results, the diagnosis of residual tumor was confirmed at biopsy or by clinical follow-up. In 20 of 60 patients, no abnormal ^{201}Tl uptake was observed, despite findings on CT and/or MRI scans that were suspicious for tumor. Ten of the negative ^{201}Tl studies were confirmed as true-negatives by the clinical course and by resolution of CT/MRI abnormalities. The remaining 10 negative SPECT studies ultimately proved to be false-negatives: six of these patients had lesions <1 cm in maximum diameter; one patient had a large metastatic choriocarcinoma; and three patients had low-grade astrocytomas >2 cm in minimum diameter. Tumor-to-background ratio of ^{201}Tl uptake did not distinguish between tumor type, or predict clinical outcome. The RI of ^{201}Tl was significantly higher for metastatic melanoma than for other tumor metastases. It demonstrated reasonably good correlation with clinical outcome: 6/7 patients with eventual tumor regression showed a decrease in RI on follow-up examination, and 4/5 patients with eventual tumor progression had an increase in RI. **Conclusion:** Thallium-201 brain SPECT appears to be a useful noninvasive imaging technique in patients irradiated for intracranial tumors. Thallium-201 scintigraphy has very high specificity (100% in this cohort) for detecting viable residual tumor. False-negative findings may occur. Quantitative analysis of ^{201}Tl uptake has limited diagnostic and prognostic significance, but changes in ^{201}Tl retention after radiation therapy seems to have prognostic value.

Key Words: thallium-201; intracranial tumors; radiation therapy; retention index

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Experience of past decades has established that radiation therapy is an effective adjunct to surgery in the treatment of intracranial tumors (*1,2*). More recently, stereotactically guided radiotherapy (radiosurgery) has been used alone and in combination with surgery for aggressive treatment of a variety of adult and pediatric intracranial malignancies, primary and metastatic (*3,4*). Radiosurgery and conventional radiation therapy may induce severe parenchymal changes that are clinically indistinguishable from changes induced by tumor growth (*5–8*).

CT and MRI are sensitive but not specific in evaluating tumor response to radiation therapy (*9*). Although even very small lesions are detected by these imaging modalities, any single postradiation abnormality on MRI or CT may be viable tumor or may represent radiation-induced necrosis or gliosis. Since these alternatives cannot be differentiated by clinical criteria, tissue biopsy has often been necessary for definitive evaluation (*10*).

Because ^{201}Tl, a potassium analog, is taken up by viable tumor cells but not by necrotic tissue or nonproliferating glial cells (*11*), brain imaging with this radionuclide has been introduced as a noninvasive method of improving the specificity of CT and MRI. Several reports have shown that if brain SPECT is performed after ^{201}Tl administration, the radiotracer localizes in tumor with a clinically useful target-to-background ratio, apparently in proportion to the rate of neoplasm cell growth (*9,11,12*). Furthermore, the ^{201}Tl retention has been reported to be a reliable quantitative parameter for predicting tumor type and grade (*13,14*).

This prospective study evaluates the diagnostic accuracy and prognostic value of ^{201}Tl brain SPECT for irradiated primary and metastatic intracranial tumors in a large cohort of patients. Scintigraphic images were evaluated visually and analyzed quantitatively. Long-term follow-up is available for all patients.

MATERIALS AND METHODS

Patients

From November 1993 to November 1995, 60 consecutive patients with pathologically defined primary and metastatic intra-

TABLE 1
Histologic Diagnoses of Intracranial Tumors

Primary Intracranial Tumors	n = 33
Glioblastoma multiforme	n = 10
Oligodendroglioma	n = 3
Low-grade astrocytoma	n = 1
Pituitary adenoma	n = 12
Medulloblastoma	n = 1
Primitive neuroectodermal tumor	n = 1
Acoustic neuroma	n = 1
Lymphoma	n = 1
Meningioma	n = 3
Metastatic tumors	n = 27
Renal	n = 2
Melanoma	n = 6
Lung	n = 13
Breast	n = 4
Esophagus	n = 1
Multiple myeloma	n = 1

cranial tumors (Table 1) were referred for postoperative adjunctive radiation therapy or radiosurgery. All patients (32 women, 28 men; mean age 52 yr; age range 15–77 yr) entered a study protocol approved by the institutional review board, a protocol which includes ^{201}Tl SPECT in addition to CT and MRI examinations. Separate informed consent was obtained prior to each SPECT study. For all patients, an initial ^{201}Tl scan was performed 6–12 wk after radiation therapy or radiosurgery. Scans were repeated at suitable intervals, as dictated by clinical course and tumor response to therapy. Ninety-four sets of thallium studies were performed.

Brain Scintigraphy

Each examination consisted of an initial scan and a delayed scan—performed 10 min and 3 hr, respectively, after intravenous administration of 4 mCi (148 MBq) ^{201}Tl. SPECT images were obtained using a 16% symmetric window centered at 71 keV. Sixty-four projections of 40 sec each were acquired using a low-energy, high-resolution, parallel-hole collimator on a dual-head gamma camera. The images were prefiltered using a Butterworth filter (cutoff frequency = 0.15 cycles/cm; power factor = 5). Transaxial, coronal, and sagittal slices (thickness = 1 pixel = 3.5 mm) were reconstructed and displayed on a 128 × 128 matrix.

Image Interpretation

All SPECT studies were interpreted by an experienced nuclear medicine physician using contemporaneous CT/MRI images for anatomic correlation. A study was interpreted as consistent with viable tumor if radiotracer uptake in the region of the CT/MRI abnormality was greater than the uptake in the corresponding contralateral area.

Quantification

The transaxial image in which the lesion showed the greatest activity was selected, and a region of interest (ROI) was traced around the lesion. An ROI of similar size and shape was drawn on the opposite side in a corresponding location. Special care was taken to exclude areas where high radiotracer activity is normal, such as the scalp and the base of the brain. For each image set, early and delayed, an uptake ratio was calculated

$$\frac{\text{average counts/pixel in the lesion ROI}}{\text{average counts/pixel in the normal ROI}}.$$

A retention index was also calculated (*13*):

$$\frac{\text{delayed uptake ratio}}{\text{early uptake ratio}}.$$

TABLE 2
Thallium-201 Scintigraphy after Radiation Therapy

	Abnormal ^{201}Tl scan	Normal ^{201}Tl scan
True-positives	40	
False-positives	0	
True-negatives		10
False-negatives		10*
Total	40	20

*Six patients had lesions <1 cm in maximum diameter.

Statistical Analysis

The ANOVA F-test and multiple comparison tests (including Duncan's multiple range test, Newman-Keuls test, and Tukey's studentized range test) were used to determine whether the early uptake ratio and retention index (RI) could distinguish any group of patients with a specific tumor histology from other groups of patients with other tumor histologies. A Fisher's exact test was used to evaluate the change in early uptake ratio and RI in patients who had serial scans.

RESULTS

Scintigraphic Findings

Focally increased ^{201}Tl uptake was observed in 40 patients (Table 2). In all patients with a positive ^{201}Tl scan, the diagnosis of viable tumor was confirmed by histopathology (12 patients) or inferred from rapid reduction in lesion size (28 patients) after additional therapy. (Post-RT changes would not be expected to diminish rapidly when more radiation is delivered.) These 40 true-positive ^{201}Tl studies detected lesions with a minimum size of 1 cm on contemporaneous CT or MRI scans (median size 2.3 cm; size range 1.2–7.7 cm). No false-positive ^{201}Tl finding was observed.

In 20 patients, the ^{201}Tl scan did not demonstrate residual tumor, despite CT and/or MRI findings suspicious for tumor (Table 2). In 10 of these patients, the ^{201}Tl scans were eventually validated as true-negatives by the clinical course and by resolution of CT/MRI findings. For the remaining 10 patients, the ^{201}Tl studies ultimately proved to be false-negative. These 10 patients harbored viable tumor: six had metastases smaller than 1 cm in maximal dimension, one had a large choriocarcinoma metastasis that was resected immediately, and three had biopsy-confirmed, low-grade astrocytomas larger than 2 cm in smallest dimension.

Quantification

Figure 1 illustrates the early uptake ratio (EUR) and RI of ^{201}Tl in the 40 true-positive thallium SPECT examinations. There was no consistent correlation across groups between the EUR and the RI. That is, some tumors exhibited significant uptake of ^{201}Tl but relatively poor retention of it, whereas other tumors with relatively low radiotracer uptake retained activity avidly. No significant difference was found in the mean EUR of different tumor types. However, the ANOVA F-test showed a significant difference for the RI between the groups ($p = 0.05$). The multiple comparison test confirmed a significant difference between the mean RI of melanoma and the mean RI of other metastases.

Twelve patients diagnosed with residual tumor were re-irradiated. Of these, seven had a favorable outcome, as determined by clinical improvement and by reduction in tumor size on CT and/or MRI. Tumors continued to grow in the remaining five patients, despite repeat radiation. Figure 2 depicts the EUR and RI of the radiation-responsive lesions (right), and the EUR

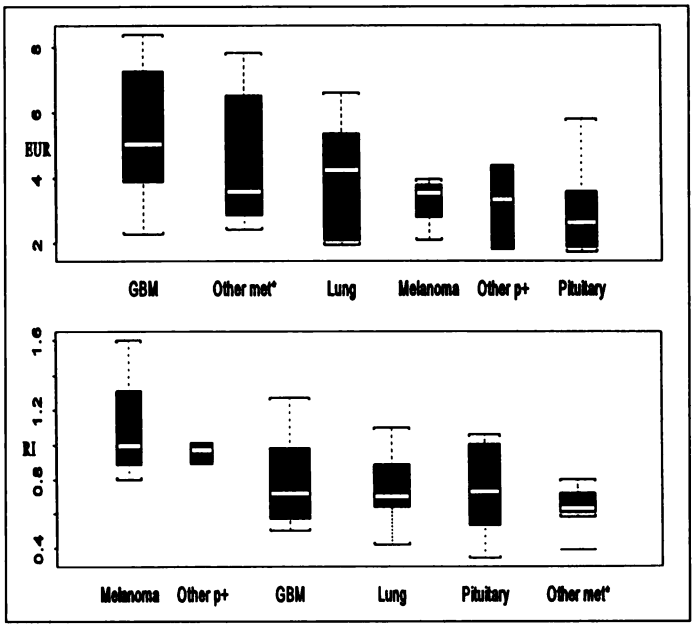

FIGURE 1. EUR and RI of ^{201}Tl in patients with intracranial tumors using boxplots: The line inside the box represents the median. Extreme values are highlighted. Relative box width represents the difference in sample size.

and RI of the radiation-resistant cases (left). In neither subgroup does EUR disclose a consistent trend. In both subgroups, however, RI is shown to parallel clinical tumor burden: A decrease in RI predicted a decrease in tumor burden, and an increase in RI predicted an increase in tumor burden. Based on the Fisher's exact test, these RI data are significant ($p = 0.04$) when a one-tailed test is utilized but are only moderately significant when a two-tailed test is applied ($p = 0.07$).

DISCUSSION

Refinements in surgical techniques, more sophisticated chemotherapeutic regimens and advances in radiotherapy have combined to improve the prognosis of patients with primary and metastatic intracranial tumors. However, the incidence of intracranial tumor recurrence at a previously treated site remains high (*15–16*).

CT and MRI are invaluable in their ability to detect intracranial tumor initially, in that they establish lesion size and location with great accuracy. However, CT and MRI do not provide reliable information about tumor metabolism or viability in the short term, just after treatment implementation (*17*). Furthermore, CT and MRI often cannot distinguish between recurrent tumor and post-treatment necrosis or post-treatment gliosis in the intermediate term. More accurate, early evaluation of treated tumors is of great importance because proof of ineffective treatment would dictate further therapy and, ultimately, patient prognosis would improve.

PET with [^{18}F]fluorodeoxyglucose (FDG) is used to evaluate treated intracranial neoplasms, and studies have indicated a role for PET in discriminating recurrent tumor from post-treatment changes (*17–20*). PET with FDG is still not specific enough, however, because FDG uptake may occur in inflammatory tissue, in abscesses, in scar tissue, and in seizure foci (*21–22*). Our study and others have confirmed that ^{201}Tl SPECT can be a clinically useful, noninvasive complement to CT and MRI. A positive SPECT examination indicates a very high likelihood of residual tumor—100% in our cohort. Patients in our study who had negative ^{201}Tl SPECT studies but who ultimately proved to harbor residual tumor fall into two general groups. The first group consists of patients with tumors smaller than 1 cm, the acknowledged size threshold for lesion detection by SPECT. The second group consists of patients whose tumors were larger than 1 cm but were not thallium-avid, either because the

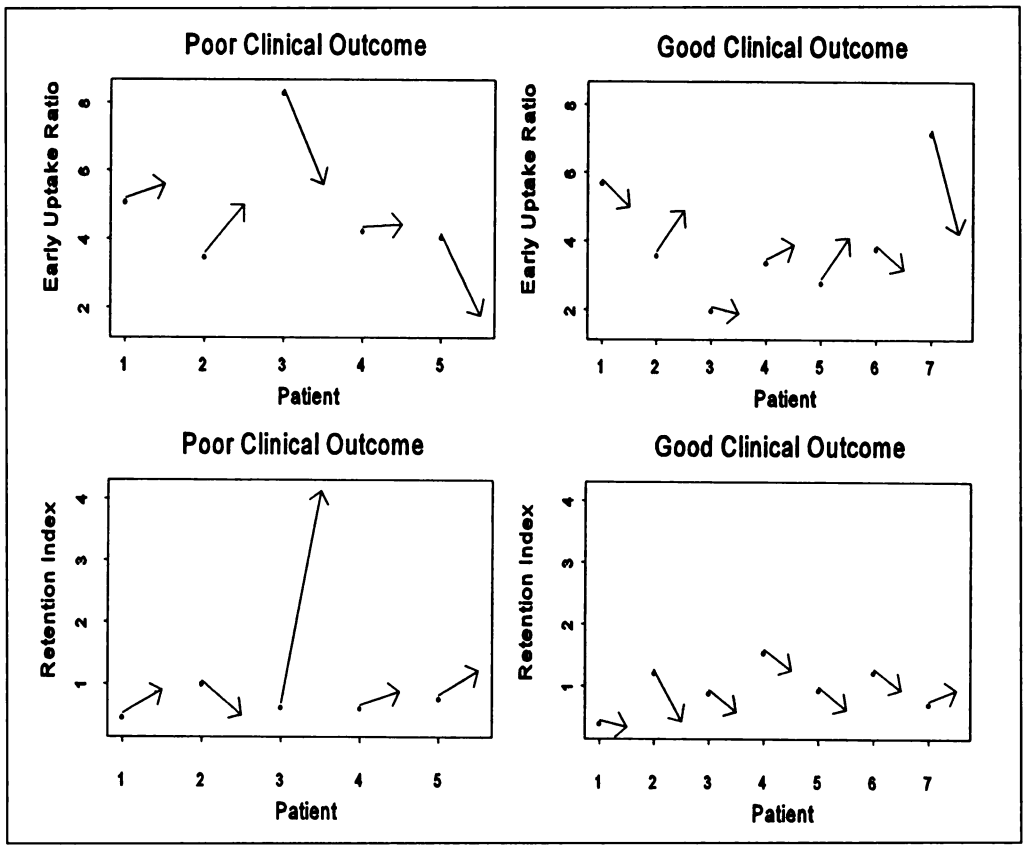

FIGURE 2. EUR (top) and RI (bottom) before and after therapy in five patients who had progression of disease with poor clinical outcome (left) and seven patients who had a favorable clinical outcome (right).

blood-brain barrier was sufficiently intact or because individual tumor metabolism did not compel radiotracer uptake into the lesion.

For our patient population, when CT/MRI suggested that the tumor had been refractory to treatment and when abnormal ^{201}Tl uptake was shown at the site in question, additional radiotherapy was delivered. If CT/MRI demonstrated a substantial lesion (>1 cm) and the ^{201}Tl scan was negative, lesional biopsy was recommended. When CT/MRI demonstrated a lesion smaller than 1 cm in the face of a negative ^{201}Tl scan, close clinical and imaging follow-up were advocated.

Previous investigators have compared the early target-to-background ratio with the late (1–3-hr) target-to-background ratio, and they have reported that the resultant RI of ^{201}Tl is accurate in detecting viable tumor after chemotherapy and radiotherapy (*14,23*). Relatively high ^{201}Tl uptake may occur in nonmalignant, hypervascular tumors such as meningioma (*11,13*). Some researchers have shown a good correlation between RI and tumor histology (*14*), whereas other investigators have been unable to distinguish between primary and metastatic tumors using ^{201}Tl SPECT (*23*).

Our large series of intracranial tumors, of diverse histological types, uses ^{201}Tl indices for long-term evaluation following routine radiation therapy and/or radiosurgery. Data for gliomas of various histologic grades, other primary intracranial tumors, pituitary adenomas and metastases were analyzed. The RI did not distinguish between tumor types in general, although the RI in our few cases of metastatic melanoma was significantly higher than the RI of other intracranial metastases.

VX-2 tumors in rabbits receiving variable doses of radiation have shown diminution in ^{201}Tl uptake and concomitant decrease in bromodeoxyuridine uptake (*24*). Those data suggest that reduced ^{201}Tl localization after irradiation follows from suppression of tumor cell growth. Our human study does not confirm these findings. We found no consistent change in ^{201}Tl uptake after re-irradiation, either in tumors showing subsequent regression or in tumors eventually shown to have failed treatment. A different animal experiment (*25*) documented progressive ^{201}Tl uptake in tumors from the time of radiation delivery. Tumors in our human population did not demonstrate this behavior either. Some tumors in our study did evince an early increase and a subsequent decrease in ^{201}Tl uptake after radiation therapy. Analogous increase and then decrease in FDG uptake have been described on PET scans of humans following intracranial radiosurgery (*17*).

Uptake of ^{201}Tl after irradiation of animals and humans is variable because radiation-induced change in and around any single irradiated lesion is determined by a host of factors, including tumor cell response to radiation, alteration in local capillary permeability and the degree of inflammation incited in the surround (*13,24,26*). The balance of such factors determine ^{201}Tl uptake after radiation therapy, and this balance is difficult to predict.

It would seem that if uptake is not easily predicted in the postradiation state, quantification of uptake would have no clinical utility. Our data suggest, however, that determination of RI is useful. There is a suggestion that ^{201}Tl retention decreases in tumors that ultimately regress. Thallium-201 retention increases in tumors not responding to radiation therapy. Thus, a change in ^{201}Tl retention appears to carry prognostic value. Delayed SPECT is an integral part of the evaluation of treated intracranial tumors since it is necessary to calculate RI.

Relative ratios are somewhat inaccurate as absolute quantification of uptake in ^{201}Tl SPECT is not possible at this time. Each of our lesions, however, served as its own control both before and after treatment. A limitation of this study is the lack of proof of tumor response to radiotherapy. Long-term follow-up of our patients validates our interpretation of radiation response.

CONCLUSION

Thallium-201 brain SPECT provides clinically useful information about treated intracranial tumors. Quantification of the early uptake of ^{201}Tl has limited prognostic value, but the change in ^{201}Tl retention following radiation therapy appears to have prognostic relevance.

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