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# Thallium-201 Brain Tumor Imaging: A Comparative Study with Pathologic Correlation

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In patients with gliomas who were stable or improving, we noted a disparity between clinical status and computed tomography (CT) brain scan results. To elucidate this finding, 29 patients were sequentially scanned with 2.0 mCi of  $^{201}\text{Tl}$  (5–30 min), 20 mCi [ $^{99\text{m}}\text{Tc}$ ]glucoptate (GH) (3–4 hr) and 7–10 mCi  $^{67}\text{Ga}$  (48–72 hr). A total of 198 images were obtained. A set of three scans at a midpoint in follow up was selected for analysis. Seven patients who died had neuropathologic data available; brain sections were reconstructed to match radionuclide views without knowledge of image results. In the seven patients with autopsy data,  $^{201}\text{Tl}$  offered the most accurate correlation with viable tumor. Gallium-67 gave similar results in patients not receiving steroids. Technetium-99m GH scans could not allow differentiation between tumor, necrosis, and edema. Similarly, the CT scan could not routinely differentiate between fibrotic, nonfibrotic, necrotic, and neoplastic tissue. In the 22 patients without autopsy data,  $^{201}\text{Tl}$  scans commonly showed smaller and more focal abnormal uptake when compared with [ $^{99\text{m}}\text{Tc}$ ]GH and  $^{67}\text{Ga}$  scans.

Thallium-201 scans more accurately reflect viable tumor burden than other radionuclide studies of primary brain tumors, are minimally affected by concomitant steroid administration, can be performed immediately following tracer administration, and complement the anatomic data obtained from CT scans.

J Nucl Med 28:47–52, 1987

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**A** major difficulty in chemotherapy trials for the treatment of malignant gliomas has been the evaluation of tumor response; since the clinical expression of brain tumors depends upon the anatomic location, the patient can commonly harbor a silent recurrence. In a group of such patients, we noted a disparity between computerized tomographic (CT) brain scans and patient performance scores such that patients were either stable or demonstrated improved clinical status in the face of an unchanged intracerebral mass lesion as defined by CT scan.

In an effort to further elucidate this disparity, we sequentially imaged such patients using thallium-201 as thallos chloride ( $^{201}\text{Tl}$ ), technetium-99m glucoptate ([ $^{99\text{m}}\text{Tc}$ ]GH) and gallium-67 citrate ( $^{67}\text{Ga}$ ). Upon expiration, a subset of these patients underwent postmortem examination of the brain. This report compares the

results of radionuclide scanning and in some cases CT scans and histopathology.

## MATERIALS AND METHODS

### Patients

Over an 18-mo interval, 29 patients with grades 3 and 4 malignant gliomas (21 males and 8 females, median age 39 yr, range 16–59 yr) were evaluated by 198 sequential radionuclide scans. These patients had been referred to our institute for intensive chemotherapy followed by autologous bone marrow transplantation (1). Of the 29 patients, 19 had received prior brain irradiation, seven prior chemotherapy, and at the time of imaging, 15 were receiving oral steroid therapy.

## IMAGING

### Radionuclide Imaging

*Thallium-201 imaging.* Patients were administered 2 mCi of  $^{201}\text{Tl}$  intravenously and positioned for that single view which best depicted the greatest extent of tumor (usually a lateral projection) beneath a 37 photomultiplier tube, low-

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Received Oct. 12, 1985; revision accepted June 18, 1986.

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energy mobile, small field-of-view Anger camera fitted with a converging collimator. The camera was peaked on  $^{201}\text{Tl}$  with a 20% window centered over the 68–80 keV x-rays. Imaging began within 5 min of injection and 300,000 count scintiphotos (1,500 to 3,000 sec) were obtained.

**Technetium-99m GH imaging.** At the completion of  $^{201}\text{Tl}$  imaging, patients were administered 20 mCi of [ $^{99\text{m}}\text{Tc}$ ]GH intravenously and returned for a comparative image 3–4 hr later. Patients were positioned so as to produce a scintiphoto identical in orientation to that obtained with  $^{201}\text{Tl}$ . The same gamma camera and collimation were used and 300,000 count images were collected using a 20% window centered over the 140 keV photopeak.

**Gallium-67 imaging.** Following the [ $^{99\text{m}}\text{Tc}$ ]GH scan, patients were administered between 7 and 10 mCi of  $^{67}\text{Ga}$  citrate intravenously and returned at 48 to 72 hr later for imaging of the brain. They were positioned under a large field-of-view, 37 photomultiplier tube Anger camera fitted with a medium-energy collimator. Three 20% windows were centered over the 93, 184, and 300 keV photopeaks. Again, 300,000 count images were collected in the same position as were those performed with  $^{201}\text{Tl}$  and [ $^{99\text{m}}\text{Tc}$ ]GH.

#### Computed Tomographic Imaging

CT scan data were analyzed for the seven individuals who experienced and underwent neuropathologic evaluation; scans were performed on an EMI Scanner, Model #1005 second generation instrument. CT scans were obtained within one to 20 days of the  $^{67}\text{Ga}$  brain scan. Of the seven patients, five were administered contrast agent to enhance definition of neoplastic tissue. No correlation was made between CT and radionuclide data in the 22 patients in whom no postmortem information was available.

#### Image Evaluation

Patients were imaged either (a) at a point in time coincident with a disparity between CT scan data and performance scores (20 patients undergoing either one or two, sequential radionuclide studies) or (b) over an extended period of clinical follow-up (nine patients receiving between three and six sequential radionuclide studies). For all patients, the set of three radionuclide scans selected for critical evaluation was acquired at approximately the midpoint of clinical followup.

#### Image Interpretation

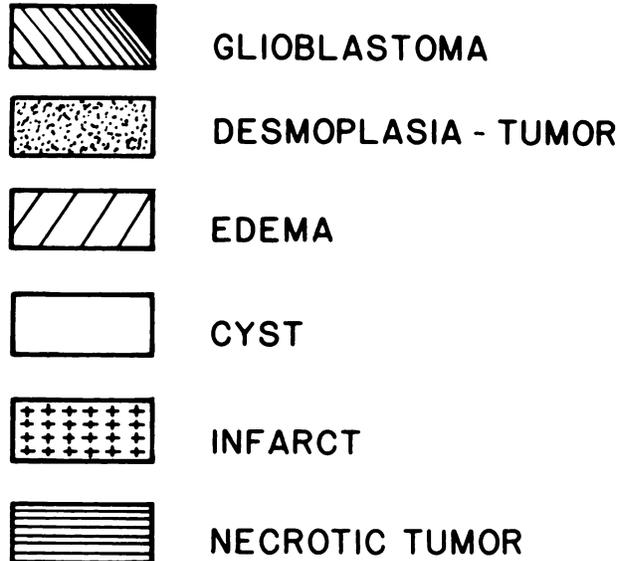
Abnormalities on the sequential  $^{201}\text{Tl}$ , [ $^{99\text{m}}\text{Tc}$ ]GH, and  $^{67}\text{Ga}$  images in 22 patients were graded with respect to lesion size, configuration, and intensity (using calvarial uptake as the reference). Very large and intense focal uptake was equated with 4+ decreasing through 1+ which represented small and less intense foci of tracer accumulation. In images showing no abnormal tracer accumulation, scans were graded as 0.

#### POSTMORTEM STUDIES

##### Brain Sectioning

The brains of the seven patients in whom postmortem examinations were performed were initially sectioned in the transverse plane to correlate with CT scan presentations. The three-dimensional information obtained from these sections was then reconstructed in the plane of the scintigraphic images

#### KEY



**FIGURE 1**  
Key for histopathologic brain sections.

**TABLE 1**  
Relative<sup>T</sup> Tracer Uptake Seen in 22 Malignant Glioma Patients Imaged with  $^{201}\text{Tl}$ , [ $^{99\text{m}}\text{Tc}$ ]GH, and  $^{67}\text{Ga}$

Patient no.	$^{201}\text{Tl}$	[ $^{99\text{m}}\text{Tc}$ ]GH	$^{67}\text{Ga}$
1	+++ <sup>†</sup>	+++	+ <sup>‡</sup>
2	0	+++	0 <sup>¶</sup>
3	++	++++ <sup>§</sup>	+
4	++++ <sup>†</sup>	+++	+
5	++	+++	+
6	0	+++	0
7	+	++	+
8	+++	+++	+++
9	++	++++	+++
10	++	++++	++
11	+++	+++	+++
12	+++	+++	+++
13	++	+++	++
14	+++	+++	+++
15	+	++	++
16	+++	++	+
17	+++	+++	+++
18	0	++	0
19	0	+	0
20	+++	+++	+++
21	+++	++	0
22	++++	+++	+

<sup>T</sup> = Lesion intensity relative to calvarial intensity.

<sup>†</sup> Receiving steroid therapy.

<sup>‡</sup> Medium size lesion, moderate uptake.

<sup>§</sup> Large lesion, intense uptake.

<sup>¶</sup> Very large lesion, intense uptake.

<sup>††</sup> Small lesion, minimal uptake.

<sup>¶¶</sup> No abnormal uptake.

(usually the lateral projection). These reconstructions were performed (J.H.M.) without knowledge of either radionuclide or CT scan results. Pathologic sections defined the anatomic location of tumor, as well as areas of desmoplasia, edema, cyst formation, infarction, and necrosis (Fig. 1).

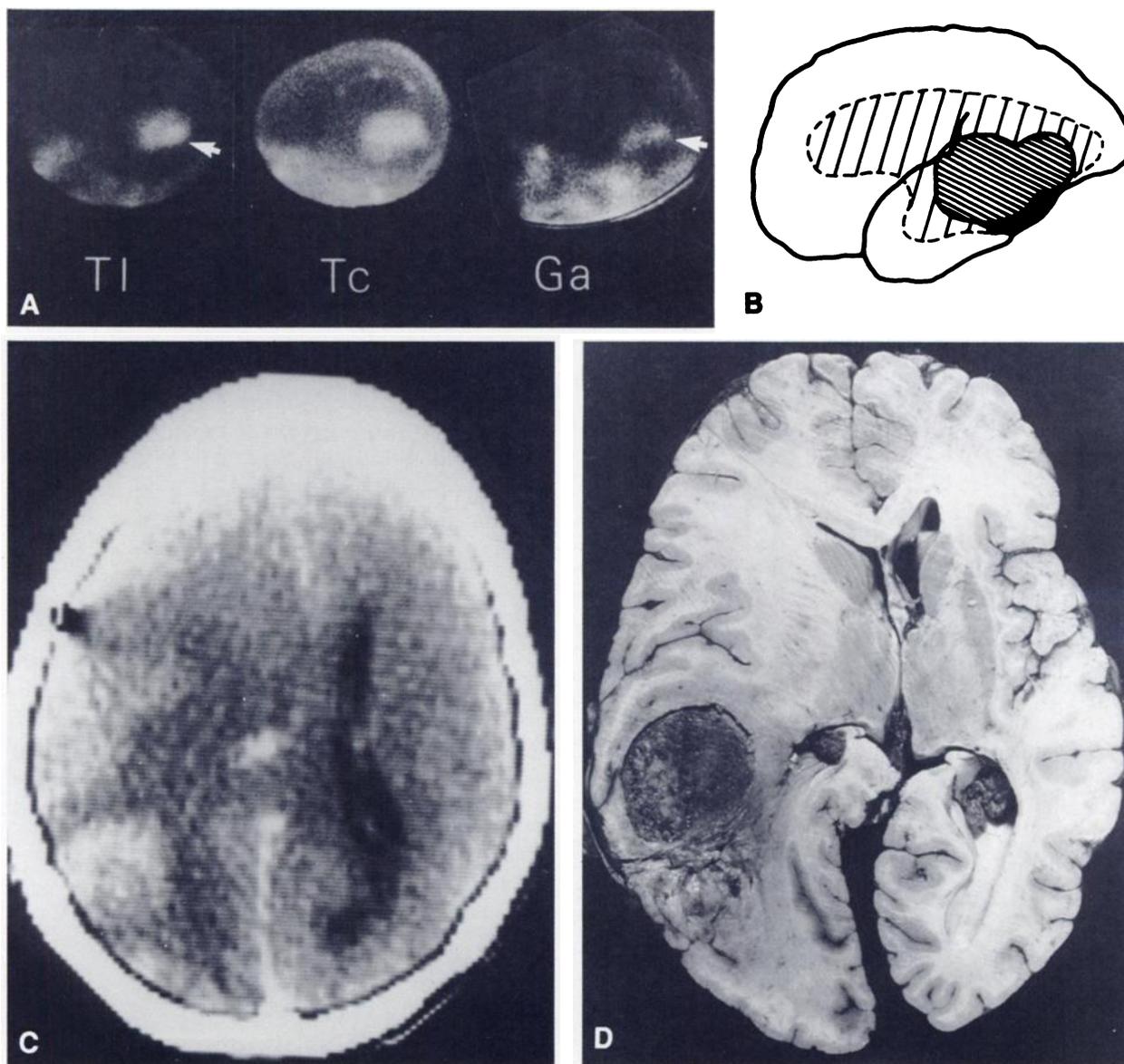
#### IMAGE CORRELATIONS

Radionuclide and CT scans were graded as 3+ = excellent correlation, 2+ = good correlation, 1+ = fair correlation, and 0 = no correlation with the histopathologic data.

## RESULTS

### Thallium-201 Scan Dynamics

There was rapid uptake of  $^{201}\text{Tl}$  within tumor deposits. Imaging, which commenced immediately following tracer administration, resulted in scintiphotos which were similar to those obtained on 3–4 hr  $^{99\text{m}}\text{Tc}$ ]GH or 2–3 day  $^{67}\text{Ga}$  studies. Thallium-201 accumulation within the neoplastic foci persisted for the duration of



**FIGURE 2**

A: Left lateral  $^{201}\text{Tl}$ ,  $^{99\text{m}}\text{Tc}$ ]GH, and  $^{67}\text{Ga}$  brain images. Thallium-201 and  $^{67}\text{Ga}$  images are similar showing smaller lesion than is seen with  $^{99\text{m}}\text{Tc}$ ]GH. Craniotomy scar is seen on  $^{99\text{m}}\text{Tc}$ ]GH image. An additional discrete abnormal focus inferiorly (arrows) not seen on  $^{99\text{m}}\text{Tc}$ ]GH image. B: Histopathologic reconstruction of brain seen in Figure 2A. Thallium-201 depicted tumor only, whereas  $^{99\text{m}}\text{Tc}$ ]GH did not define inferior region of greatest tumor burden but did delineate region of edema. C: A representative CT slice showing contrast enhancement in a region of brain anterior to tumor which is involved exclusively by regional edema and not neoplasia. D: A gross pathologic section at the same level as the CT scan seen in Figure 2C showing tumor mass with diffuse extension posteriorly and edematous changes anteriorly.

**TABLE 2**  
Correlation of Radionuclide and CT Scan Results  
with Pathology

Patient no.	$^{201}\text{Tl}$	$^{99\text{m}}\text{Tc}$ ]GH	$^{67}\text{Ga}$	Interval <sup>†</sup>	CT
23	+++ <sup>‡</sup>	++ <sup>§</sup>	+ <sup>¶</sup>	18	++ <sup>††</sup>
24	+++	++	++	23	+++
25	+++	++	++/+++	23	+
26	+++	++	++	17	+
27	+++	0 <sup>**</sup>	0	44	+
28	+++	++	+++	13	+++
29	+++	+++	+	13	+ <sup>††</sup>

<sup>‡</sup> Receiving steroid therapy.

<sup>†</sup> Interval in days between last RN scan and postmortem exam.

<sup>‡</sup> Excellent correlation with pathology.

<sup>§</sup> Good correlation with pathology.

<sup>¶</sup> Fair correlation with pathology.

<sup>\*\*</sup> No correlation with pathology.

<sup>††</sup> No intravenous contrast administered.

the time of imaging with no apparent change in the target-to-background ratios.

#### Radionuclide Images

There was a disparity between the relative uptake noted on  $^{201}\text{Tl}$  scans when compared with those performed with either  $^{99\text{m}}\text{Tc}$ ]GH or  $^{67}\text{Ga}$  (Table 1). Lesions depicted with  $^{201}\text{Tl}$  tended to be smaller and less intense (18 out of 22) than those seen with  $^{99\text{m}}\text{Tc}$ ]GH, but larger and more intense than those defined by  $^{67}\text{Ga}$  (18 out of 22) (Figs. 2A and B).

When  $^{99\text{m}}\text{Tc}$ ]GH images were compared with those obtained with  $^{67}\text{Ga}$ , the former showed equal or greater size and intensity in 22 of 22 instances.

#### Image and Pathology Correlation

When radionuclide and CT scans were correlated with pathologic brain sections, closest agreement was noted between the  $^{201}\text{Tl}$  images and persistent tumor. Technetium-99m GH,  $^{67}\text{Ga}$ , and CT scans inconsis-

tently defined the precise amount and location of active neoplastic tissue present (Table 2, Figs. 2C and D, 3A and B, 4A and B).

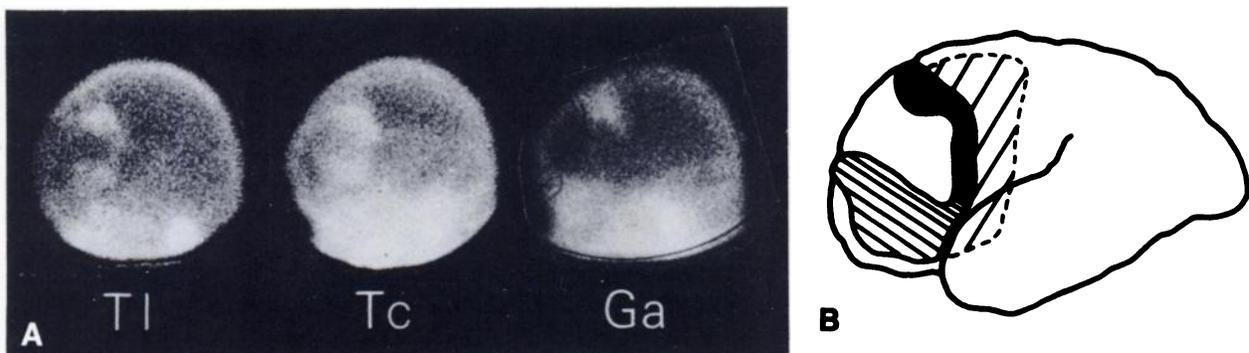
#### DISCUSSION

In the absence of therapy, patients with highly malignant gliomas have been shown to survive from 2 to 4 mo from time of diagnosis. This time can be extended with the administration of combined modality therapy (2). Unfortunately, the damage incurred by the central nervous system as a result of initial tumor destruction which is then compounded by surgical intervention and/or radiation therapy is usually permanent. In the presence of these changes, the current method of evaluating intracerebral alterations, the CT scan, may not always accurately reflect the status of tumor burden.

Observations in our patient population revealed a subset of individuals who demonstrate a clinical response but no significant response in the CT scan data. Use of radionuclides presented an opportunity for a physiologic estimate of intracerebral events.

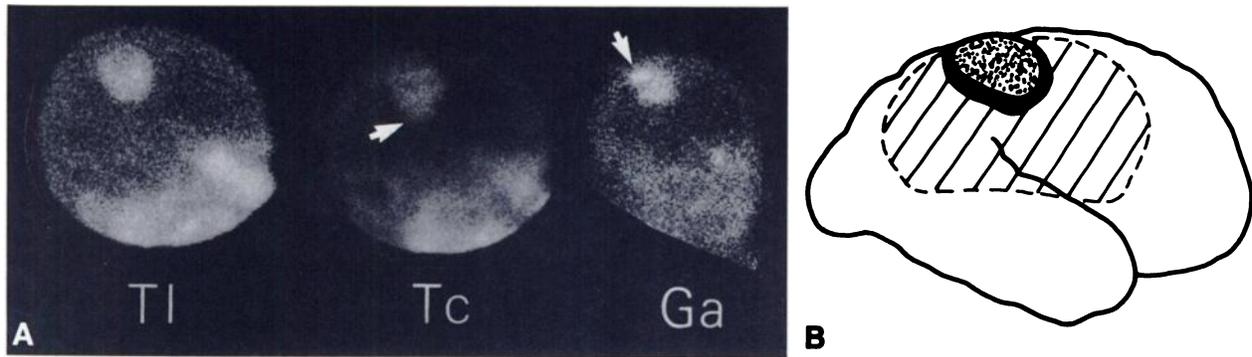
Thallium-201 has been utilized in the study of a variety of tumors (3-7) with a pattern of tissue distribution similar to that seen with potassium. A number of possible explanations exist to explain tumor uptake (8-10). Tumor sequestration of  $^{201}\text{Tl}$  is certainly a function of blood flow and tissue viability; this is the basis for its use in myocardial scintigraphy and must also govern tumor uptake to a major extent.

Alterations in the blood brain barrier although relevant, are probably not the exclusive explanation for abnormal  $^{201}\text{Tl}$  uptake in malignant gliomas. Indeed, our results show that patients can simultaneously manifest an absence of  $^{201}\text{Tl}$  accumulation within a "brain tumor" in the face of a positive  $^{99\text{m}}\text{Tc}$ ]GH scan; it would be unreasonable to expect that  $^{201}\text{Tl}$ , as a small ionic substance, is unable to cross an altered blood



**FIGURE 3**

A: Left lateral  $^{201}\text{Tl}$ ,  $^{99\text{m}}\text{Tc}$ ]GH, and  $^{67}\text{Ga}$  brain images. Note  $^{99\text{m}}\text{Tc}$ ]GH image (center) suggests larger lesion than that seen with  $^{201}\text{Tl}$ . Gallium-67 image (right) shows abnormal uptake only in most superior aspect of tumor. B: Histopathologic reconstruction of brain seen in Figure 3A. Note closest correlation of tumor burden with  $^{201}\text{Tl}$  scan. Extensive area of edema posterior to tumor seen only on  $^{99\text{m}}\text{Tc}$ ]GH scan.



**FIGURE 4**

Right lateral  $^{201}\text{Tl}$ , [ $^{99\text{m}}\text{Tc}$ ]GH, and  $^{67}\text{Ga}$  brain images. Note central decrease in  $^{201}\text{Tl}$  uptake which correlates with region of desmoplasia (Figure 4B). Technetium-99m GH scan shows additional abnormal uptake inferiorly (arrow) in area of edema depicted on Figure 5B. Gallium-67, with intense focal uptake superiorly (arrow), shows poorest correlation with region of active tumor. B: Histopathologic reconstruction of brain seen in Figure 4A.

brain barrier while [ $^{99\text{m}}\text{Tc}$ ]GH and  $^{67}\text{Ga}$  bound to transferrin, both larger in size, are able to do so.

Abnormal uptake may also be related to the presence of a functioning ATP cell membrane pump. It may be that when therapy is effective, and tumor cells are destroyed, the membrane pump of that tumor cell becomes nonfunctional. Thus, following the administration of  $^{201}\text{Tl}$ , there can be no active transport of this tracer into the treated tumor focus. On the other hand, presence of viable, dividing tumor cells, with intact cell membrane pump mechanisms, will allow for avid  $^{201}\text{Tl}$  accumulation.

Although CT scanning is accepted as the standard whereby intracerebral tumor can be monitored as a function of therapy, in our study we noted that in four of seven instances, this diagnostic modality was unable to precisely define neoplastic status (Table 2, Figs. 2C and D). When compared to histopathologic sections, the CT scan could not differentiate central necrosis from viable tumor, showed fibrotic tissue enhancing with contrast to a greater degree than nonfibrotic tissue, and did not accurately define the degree of intracerebral edema present. In addition, the CT scan findings did not always correlate well with patient performance status, due in part to the relationship between anatomic lesion location and secondary clinical manifestations.

Thallium-201 accumulation within intracerebral tumor foci appeared immediately, showed good target-to-background ratios and persisted throughout the imaging period (up to 1 hr). Ancrì et al. (11,12) showed that because of low blood background levels in the brain, cerebral lesions were particularly well defined with  $^{201}\text{Tl}$  and easy to distinguish from normal anatomic structures such as the base of the skull and large venous sinuses. This was our experience as well.

Interestingly, a number of our patients showed a marked discordance in the degree of abnormal  $^{67}\text{Ga}$  uptake when compared to  $^{201}\text{Tl}$  and [ $^{99\text{m}}\text{Tc}$ ]GH scan results. Waxman et al. (13) reported that steroid therapy

was capable of causing this finding; indeed, the majority of our patients who demonstrated this scan disparity were receiving steroids. That abnormal  $^{201}\text{Tl}$  uptake does not appear to be affected by concomitant steroid administration carries important clinical implications for following the effects of therapy.

In conclusion, results of our study indicate that  $^{201}\text{Tl}$  scans in brain tumor patients, compared to those performed with [ $^{99\text{m}}\text{Tc}$ ]GH and  $^{67}\text{Ga}$ , give the most precise estimate of intracerebral tumor burden, the examinations can be performed immediately following injection of tracer and accumulation appears to parallel the clinical status of the patient. Thus  $^{201}\text{Tl}$  brain scans may offer the most accurate assessment of response to therapy.

#### ACKNOWLEDGMENTS

The authors thank Deborah Hanson for the art work, John Buckley for photography, and Diane Brennan and Arlene Haury for their help in preparing the manuscript.

#### REFERENCES

1. Hochberg FH, Parker LM, Takvorian T, et al. High-dose BCNU with autologous bone marrow rescue for recurrent glioblastoma multiforme. *J Neurosurg* 1981; 54:455-460.
2. Walker MD, Green SB, Byar DP, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Engl J Med* 1980; 303:1323-1329.
3. Salvatore M, Carratu L, Porta E. Thallium-201 as a positive indicator for lung neoplasms: preliminary experiments. *Radiology* 1976; 121:487-488.
4. Tonami N, Hisada K. Clinical experience of tumor imaging with  $^{201}\text{Tl}$ -chloride. *Clin Nucl Med* 1977; 2:75-81.
5. Fukuchi M, Tachibana K, Kuwata K, et al. Thallium-201 imaging in thyroid carcinoma—appearance of a lymph node metastasis. *J Nucl Med* 1978; 19:195-196.

6. Cox PH, Belfer AJ, van der Pompe WB. Thallium-201 chloride uptake in tumors, a possible complication in heart scintigraphy. *Br J Radiol* 1976; 49:767-768.
7. Senja O, Miyakawa M, Shirota H, et al. Comparison of Tl-201 chloride and Ga-67 citrate scintigraphy in the diagnosis of thyroid tumor: concise communication. *J Nucl Med* 1982; 23:225-228.
8. Atkins HL, Budinger TF, Lebowitz E, et al. Thallium-201 for medical use. Part 3: Human distribution and physical imaging properties. *J Nucl Med* 1977; 18:133-140.
9. L'Abbate A, Biagini A, Michelassi C, et al. Myocardial kinetics of thallium and potassium in man. *Circulation* 1979; 60: 776-785.
10. Carlin RD, Jan K. Mechanism of thallium extraction in pump perfused canine hearts. *J Nucl Med* 1985; 26:165-169.
11. Ancrì D, Basset JY, Lonchamp MF, et al. Diagnosis of cerebral lesions by thallium 201. *Radiology* 1978; 128:417-422.
12. Ancrì DA, Basset JY. Diagnosis of cerebral metastases by thallium 201. *Br J Radiol* 1980; 53:443-453.
13. Waxman AD, Beldon JR, Richli W, et al. Steroid-induced suppression of gallium uptake in tumors of the central nervous system: concise communication. *J Nucl Med* 1978; 19:480-482.