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R B Schwartz, P A Carvalho, E Alexander, 3rd, J S Loeffler, R Folkerth and B L Holman

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Radiation Necrosis vs High-Grade Recurrent Glioma: Differentiation by Using Dual-Isotope SPECT with ^{201}Tl and $^{99\text{m}}\text{Tc}$ -HMPAO

Richard B. Schwartz¹
 Paulo A. Carvalho¹
 Eben Alexander III²
 Jay S. Loeffler³
 Rebecca Folkerth⁴
 B. Leonard Holman¹

Conventional imaging techniques are often unreliable in distinguishing between radiation necrosis and recurrent glioma in patients who are symptomatic after high-dose radiotherapy. We performed dual-isotope single-photon emission computed tomography (SPECT) with the use of thallium-201 (^{201}Tl) and the perfusion agent $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime (HMPAO) to aid in this differentiation in 15 patients with glioma prior to biopsy. We found that dual-isotope SPECT scanning correlated with the pathologic findings in 14 of the 15 cases. All patients with high ^{201}Tl uptake in their treated tumor beds had local tumor recurrence, and all patients with low ^{201}Tl uptake showed only radiation changes without evidence of solid tumor. In patients with an intermediate level of ^{201}Tl concentration in their tumor bed, $^{99\text{m}}\text{Tc}$ -HMPAO uptake differentiated those patients with active tumor from those without; three of four patients with preserved or increased perfusion had pathologic evidence of solid tumor, whereas none of the four patients with decreased perfusion to the tumor bed had evidence of local recurrence.

We believe that dual-isotope SPECT with ^{201}Tl and $^{99\text{m}}\text{Tc}$ -HMPAO may be useful in differentiating sites of likely tumor growth from nonspecific radiation changes in patients treated for malignant glioma.

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¹ Department of Radiology, Harvard Medical School and the Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115. Address reprint requests to R. B. Schwartz.

² Department of Neurosurgery, Harvard Medical School and the Brigham and Women's Hospital, Boston, MA 02115.

³ Department of Radiation Therapy, Harvard Medical School and the Brigham and Women's Hospital, Boston, MA 02115.

⁴ Department of Neuropathology, Harvard Medical School and the Brigham and Women's Hospital, Boston, MA 02115.

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In the months following radiation therapy for high-grade gliomas, patients often have clinical deterioration due to either radiation necrosis or recurrent tumor progression in the treatment field [1-3]. The distinction between these entities would be helpful in designing and implementing further treatment. However, tumor and radiation necrosis can appear identical on CT and MR examinations [4-6]. The preoperative identification and localization of sites of likely tumor recurrence would be of great importance in avoiding sampling errors during biopsy that can limit the accuracy of diagnosis [1, 7]. Positron emission tomography (PET) has been shown to be effective in differentiating glioma from radiation necrosis [6, 8-10]. However, PET technology is very expensive and available in only a few centers.

Thallium-201 (^{201}Tl), a potassium analogue, has been used to localize and characterize gliomas with both planar and single-photon emission computed tomography (SPECT) imaging [11-14]. However, uncertainty may arise in cases of treated glioma, in which modest thallium uptake can represent either recurrent tumor or radiation change. We predicted that imaging with a perfusion agent such as $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime (HMPAO) would add additional information that would assist in making this distinction.

We performed high-resolution dual-isotope SPECT imaging with ^{201}Tl and $^{99\text{m}}\text{Tc}$ -HMPAO in 15 patients with high-grade gliomas who developed progressively worsening symptoms after radiation therapy. These images were correlated with CT scans in order to provide stereotaxic three-dimensional coordinates for biopsies. The biopsy results were compared with the findings on SPECT in each case.

Subjects and Methods

Subjects

Fifteen consecutive patients 9–65 years old (mean, 43 years) were evaluated for suspected recurrent high-grade glioma from August 1989 through January 1990. Each patient had been initially diagnosed with high-grade astrocytoma, and the tumor had been debulked surgically. Fourteen subsequently were treated with 5940 cGy of external-beam radiation. Of these patients, nine received additional brachytherapy with iodine-125 radiation implants, and two received stereotaxic photon-beam radiosurgery to the tumor. One patient received two sets of implants (iodine-125 and iridium-193) without prior external-beam therapy (see Table 1).

All patients had deteriorating symptoms between 1 and 14 months after radiation therapy and had abnormal CT and MR scans. Each patient had a dual-isotope SPECT scan 1 day before biopsy and resection.

Imaging Protocol

On the day before the scheduled biopsy, brain SPECT was performed with the ASPECT brain imager [15]. Three cobalt-57 markers (5 μ Ci [185 kBq]) were placed over three constant scalp positions to assist in positioning and to ascertain patient motion between SPECT studies. After IV injection of 3 mCi (111 MBq) of ^{201}Tl -chloride, the subjects were positioned in the ASPECT brain imaging system. Data were acquired by using a pulse-height analyzer window centered at the 74- to 80-keV photopeak. After acquisition was completed, and without moving the patient, $^{99\text{m}}\text{Tc}$ -HMPAO (15–20 mCi [555–740 MBq]) was injected IV. Two pulse-height analyzer windows were used, one set at 140 ± 14 keV and one set to acquire scatter information from 112 to 126 keV. The reconstructed slices were displayed as a set of 16 images (5.0-mm slice thickness) and with a resolution of 8.2 mm at the center of the image [12]. Coronal, sagittal, and rotating three-dimensional displays were calculated for these slices.

CT images were obtained by using a Siemens Somatom unit (Siemens Medical Systems, Iselin, NJ) on the morning of the scheduled biopsy. A Brown-Roberts-Wells head frame (Radionics, Inc., Burlington, MA) was placed on the patient before the CT scan, and scans were obtained after the injection of 100 ml of IV contrast material. The scan plan was the same as for the SPECT scans, parallel to the orbitomeatal line. Sequential 8-mm-thick scans were obtained.

Data Analysis

The ^{201}Tl and $^{99\text{m}}\text{Tc}$ -HMPAO transaxial image sets from each study were assessed visually for abnormal regional tracer uptake. Maximal ^{201}Tl uptake was judged to be moderate or low relative to the maximal scalp uptake in the contralateral hemisphere, according to a ^{201}Tl lesion-to-scalp ratio (low = <1.0 , moderate = 1.0 – 2.0 , high = >2.0). A region of interest was drawn around the region of maximal ^{201}Tl tracer uptake, then transferred to the corresponding image on the $^{99\text{m}}\text{Tc}$ -HMPAO data set by using a specialized computer graphic system. Local perfusion was judged to be increased, similar, or decreased relative to perfusion in that region in the contralateral hemisphere after accounting for the effects of local distortion due to the lesion. The position of the site of maximal ^{201}Tl uptake was then localized on the corresponding CT image, which in turn was used intraoperatively to direct the biopsy or resection. The Brown-Roberts-Wells head frame system provided stereotaxic coordinates for biopsy.

Pathologic Analysis

Tissue samples obtained by stereotaxic biopsy and en bloc resection were oriented, and their locations were recorded by the neurosurgeon at the time of the operation. Tissues were fixed in 10% formalin and routinely paraffin-embedded, cut, and stained with hematoxylin and eosin. To avoid bias in interpretation, histologic evaluation by the neuropathologist was made without knowledge of the results of preoperative imaging studies. Analysis of excised and biopsied tissues was carried out with particular attention to the presence and growth pattern of abnormal astrocytes. The spatial distribution of these cells, when present, was recorded as representing either solid tumor or isolated atypical astrocytes, according to the concept of tumor growth proposed by Daumas-Duport et al. [16, 17].

The specimen obtained from the irradiated field was considered to have mass tumor if nests of densely packed abnormal astrocytes replaced normal parenchyma (Fig. 1D); these tumor cells were considered likely to have proliferative capabilities, and were interpreted as indicative of recurrent tumor growth. Sparse dysplastic astrocytes, infiltrating but not replacing brain tissue, were considered to represent primarily irradiated tumor cells (Fig. 2D); the proliferative capacity of cells at these sites was considered indeterminate.

After pathologic analysis was performed, the data were correlated with the spatial information recorded intraoperatively for each specimen.

Results

In each of 15 patients, CT showed large intraparenchymal mass lesions of predominantly low attenuation internally and with peripheral enhancement and a marked amount of surrounding edema. SPECT scanning, however, provided more specific information that correlated with pathologic and clinical findings. The results are summarized in Table 1.

High ^{201}Tl Uptake

In four patients, foci of high ^{201}Tl accumulation were observed on SPECT images; in two of these patients, the $^{99\text{m}}\text{Tc}$ -HMPAO uptake in these areas was greater than that in normal brain (Fig. 1), and in two patients the $^{99\text{m}}\text{Tc}$ -HMPAO uptake was equal to that in normal brain. In all cases, solid tumor was identified, and each has died of locally recurrent tumor.

Moderate ^{201}Tl Uptake

In eight patients, SPECT images displayed a maximal regional ^{201}Tl uptake of moderate intensity. This group can be subdivided on the basis of perfusion characteristics; in four patients, $^{99\text{m}}\text{Tc}$ -HMPAO perfusion in this region of maximal thallium uptake was increased or similar to that in normal brain, and in four patients, perfusion in the area was decreased relative to normal brain. In the first subgroup, three patients had pathologic evidence of focal solid tumor; at present, one is alive with local tumor recurrence and the other two have died of the disease.

One patient with increased uptake of $^{99\text{m}}\text{Tc}$ -HMPAO and all four patients with decreased perfusion to the area of moderate thallium uptake demonstrated only reactive pathologic

TABLE 1: Summary of Findings in the Differentiation of Radiation Necrosis from High-Grade Recurrent Glioma with Dual-Isotope Single-Photon Emission CT

Uptake/ Case No.	Age (yr)	Radiation Therapy	Interval to Biopsy (months)	Biopsy Results	Interval to Follow-up (months)	Current Status
High ²⁰¹Tl; increased ^{99m}Tc-HMPAO						
1	53	External beam; implants	3	Extensive solid tumor	2	Died of locally recurrent tumor
2	45	External beam	12	Extensive solid tumor	7	Died of locally recurrent tumor
High ²⁰¹Tl; similar ^{99m}Tc-HMPAO						
3	37	External beam	2	Focal solid tumor	2	Died of locally recurrent tumor
4	41	External beam	1	Focal solid tumor	12	Died of locally recurrent tumor
Moderate ²⁰¹Tl; increased ^{99m}Tc-HMPAO						
5	50	External beam; implants	14	Focal solid tumor	16	Alive with local recurrence
6	30	External beam; implants	1	Reactive changes	13	No local tumor recurrence
Moderate ²⁰¹Tl; similar ^{99m}Tc-HMPAO						
7	63	External beam; radiosurgery	7	Focal solid tumor	7	Died of locally recurrent tumor
8	56	External beam; implants	2	Focal solid tumor	2	Died of locally recurrent tumor
Moderate ²⁰¹Tl; decreased ^{99m}Tc-HMPAO						
9	46	External beam	11	Reactive changes	16	Distant new tumor focus
10	55	External beam; implants	7	Reactive changes	6	Died of pneumonia; inactive tumor
11	26	External beam; implants	11	Reactive changes	7	Died with meningeal seeding
12	9	External beam; implants	12	Reactive changes	7	No local tumor recurrence
Low ²⁰¹Tl; decreased ^{99m}Tc-HMPAO						
13	65	External beam; implants	8	Reactive changes	15	No local tumor recurrence
14	34	No external beam; implants ×2	5	Reactive changes	10	Died of distant new tumor focus
15	33	External beam; radiosurgery	13	Reactive changes	13	No local tumor recurrence

changes (gliosis and sparse dysplastic astrocytes), but with no evidence of solid tumor. In this group, two patients are alive and well, one has since died of pneumonia with no evidence of active intracranial tumor, one has developed a distant tumor focus in the opposite hemisphere, and one has died with scalp and meningeal infiltration presumably secondary to seeding from the original craniotomy; this patient was free of intraparenchymal tumor.

Low ²⁰¹Tl Uptake

All three patients with low intracranial ²⁰¹Tl accumulation had decreased ^{99m}Tc-HMPAO uptake in these regions, and biopsy showed only reactive changes with no solid tumor (Fig. 2). Two patients are well without evidence of recurrence; one has died of distant new tumor focus.

Discussion

Thallium is a potassium analogue with a high affinity for sodium- and potassium-activated adenosine triphosphatase (NaK ATPase) and a slow washout from cells [18–20]. The precise mechanism for thallium uptake is unknown, although it appears that the thallium ion requires a disrupted blood-brain barrier to gain entry into the neuropil, and once available to the tissue, is taken up by cells in proportion to their metabolic activity [11, 20]. Uptake appears to be dependent on the NaK ATPase [20] as well as cotransport systems and facilitated diffusion [18, 19]. In previous small clinical studies, the relative accumulation of thallium correlated generally with the malignant grade of untreated tumors [13] and with the presence of residual tumor in treated patients [12]. Accordingly, in our series of glioma patients who were imaged after high-dose radiotherapy, we found that regions of intense

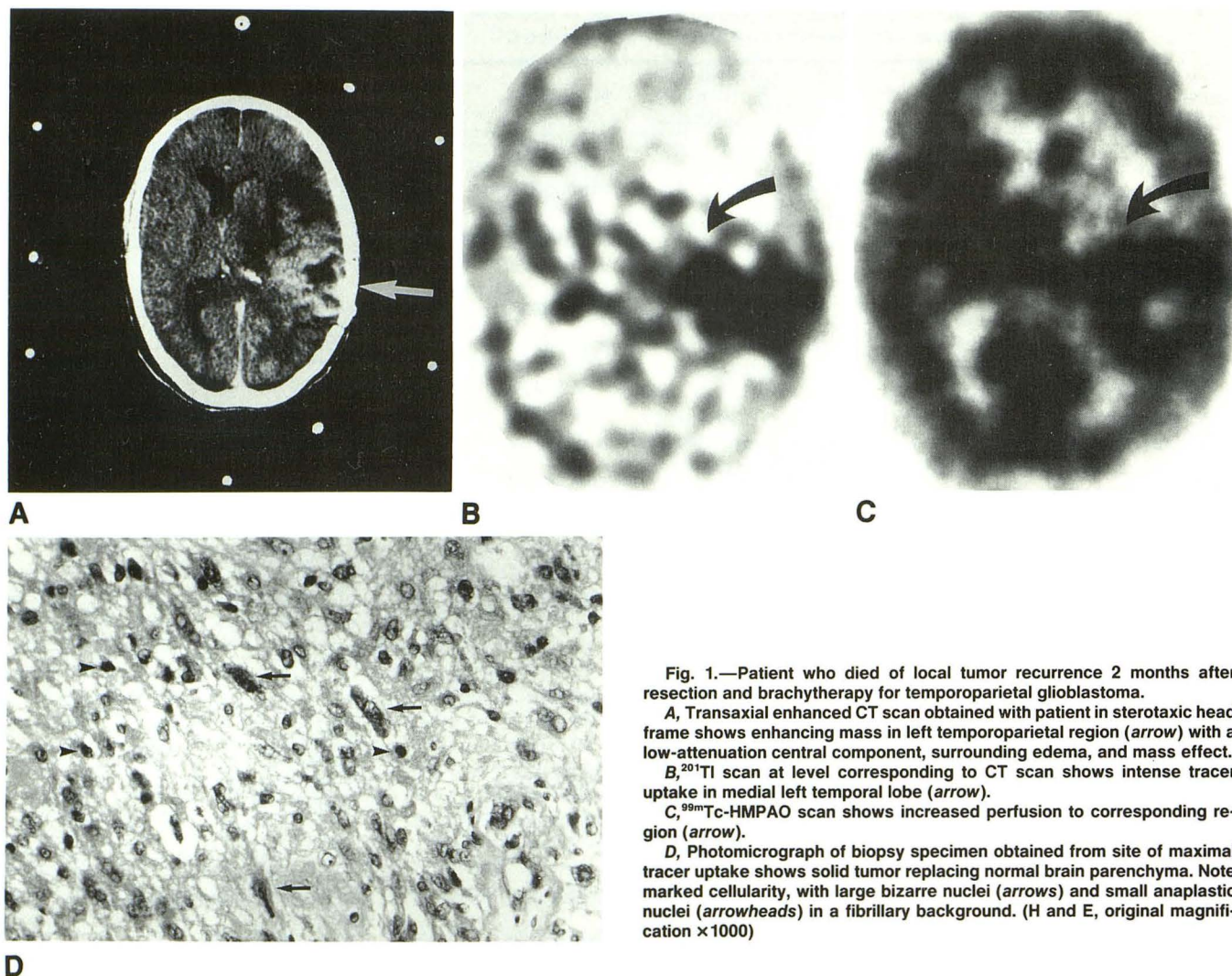


Fig. 1.—Patient who died of local tumor recurrence 2 months after resection and brachytherapy for temporoparietal glioblastoma.

A, Transaxial enhanced CT scan obtained with patient in stereotaxic head frame shows enhancing mass in left temporoparietal region (arrow) with a low-attenuation central component, surrounding edema, and mass effect.

B, ^{201}Tl scan at level corresponding to CT scan shows intense tracer uptake in medial left temporal lobe (arrow).

C, $^{99\text{m}}\text{Tc}$ -HMPAO scan shows increased perfusion to corresponding region (arrow).

D, Photomicrograph of biopsy specimen obtained from site of maximal tracer uptake shows solid tumor replacing normal brain parenchyma. Note marked cellularity, with large bizarre nuclei (arrows) and small anaplastic nuclei (arrowheads) in a fibrillary background. (H and E, original magnification $\times 1000$)

thallium uptake (i.e., greater than twice the scalp uptake) suggested active tumor. However, moderate thallium uptake was a relatively nonspecific finding, and could be shown either by tissues of low metabolic activity without a blood-brain barrier, such as the scalp and choroid plexus, or in areas of blood-brain barrier breakdown associated with reactive changes, as is present in hematomas, infarcts, and abscesses [13]. Specifically, in patients treated with radiotherapy for high-grade gliomas, regions of moderate thallium uptake can either reflect the presence of small foci of active recurrent tumor or represent reactive changes due to radiation damage without the presence of active tumor. We found that correlation with perfusion imaging was helpful in distinguishing between these two possibilities.

The brain perfusion agent $^{99\text{m}}\text{Tc}$ -HMPAO is a lipophilic compound that crosses the blood-brain barrier, becomes readily absorbed into cell membranes, and is retained in tissue [21, 22]. Regional uptake of HMPAO is proportionate to the flow of blood to a given brain area [23, 24], and since high-grade tumors have increased metabolic rates and possess abnormal vasculature favoring radiotracer delivery [25], areas

of intense $^{99\text{m}}\text{Tc}$ -HMPAO in this patient population suggest tumor. Radiation necrosis, however, characteristically is poorly perfused and thus is associated with low $^{99\text{m}}\text{Tc}$ -HMPAO uptake.

The SPECT findings in our series are in good agreement with the histopathologic data and clinical follow-up of the 15 patients. In seven of the eight patients whose scans showed regions of moderate to intense ^{201}Tl uptake that were well perfused with $^{99\text{m}}\text{Tc}$ -HMPAO, solid foci of recurrent tumor were found in biopsy specimens, and six of these patients since have died of local recurrence. However, none of the seven patients whose scans showed only moderate to low ^{201}Tl uptake with decreased perfusion had evidence of solid tumor. Their biopsies showed only sparse tumor cells infiltrating brain tissue.

Importantly, although none of these latter patients have manifested a local recurrence, three subsequently developed distant intracranial foci of tumor. These findings support the premise that dense clusters of tumor cells in a specimen indicate recurrent tumor, but scattered tumor cells in the irradiated field may have limited proliferative capacity; how-

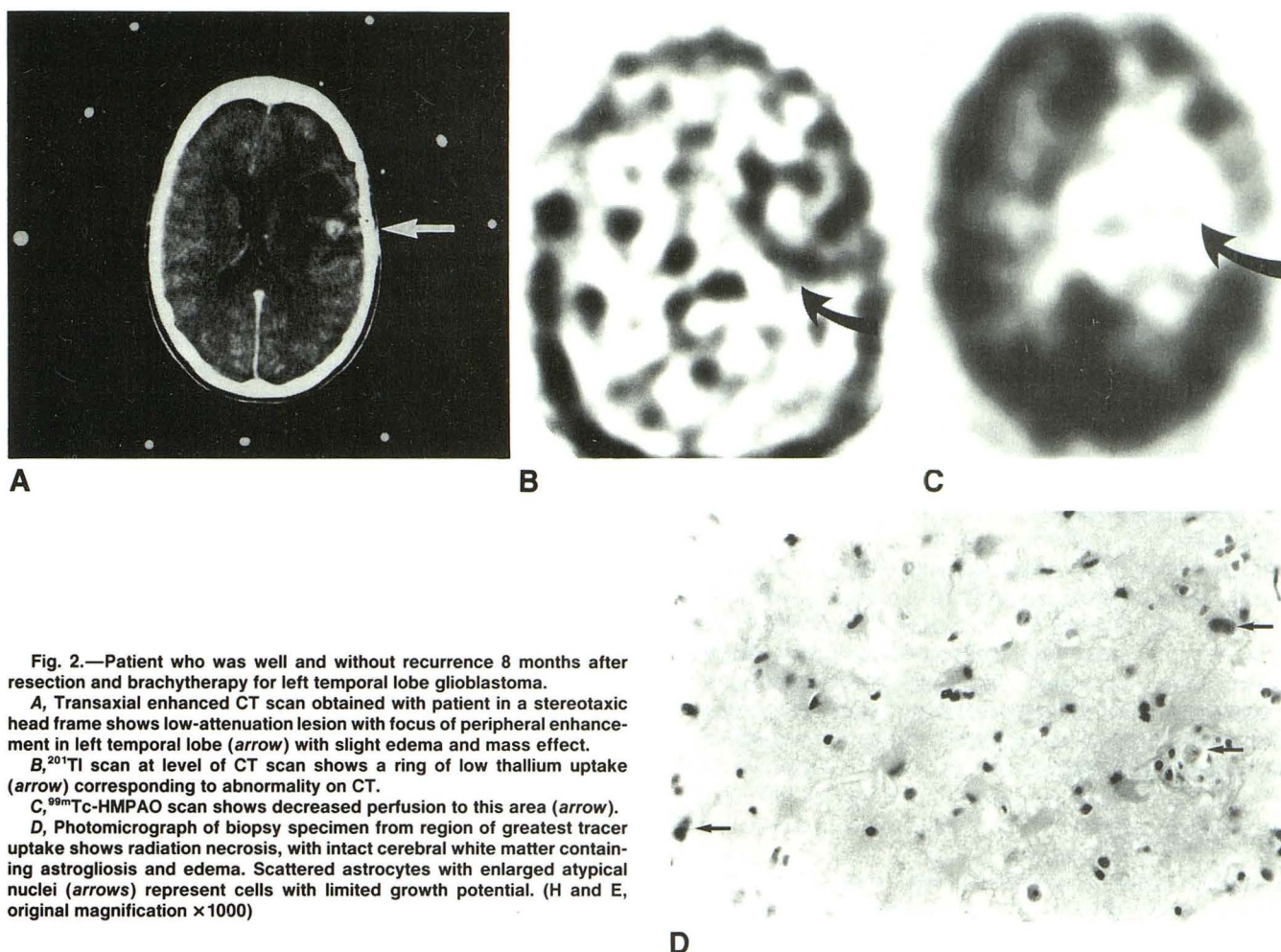


Fig. 2.—Patient who was well and without recurrence 8 months after resection and brachytherapy for left temporal lobe glioblastoma.

A, Transaxial enhanced CT scan obtained with patient in a stereotaxic head frame shows low-attenuation lesion with focus of peripheral enhancement in left temporal lobe (arrow) with slight edema and mass effect.

B, ^{201}Tl scan at level of CT scan shows a ring of low thallium uptake (arrow) corresponding to abnormality on CT.

C, $^{99\text{m}}\text{Tc}$ -HMPAO scan shows decreased perfusion to this area (arrow).

D, Photomicrograph of biopsy specimen from region of greatest tracer uptake shows radiation necrosis, with intact cerebral white matter containing astroglia and edema. Scattered astrocytes with enlarged atypical nuclei (arrows) represent cells with limited growth potential. (H and E, original magnification $\times 1000$)

ever, such cells outside the field of treatment may possess an aggressive growth potential [1, 17]. Thus, a relatively benign appearance on SPECT of areas outside the radiation field does not rule out the presence of cells that may eventually develop into a mass of solid tumor. Indeed, this represents a common mode of failure in patients receiving local high-dose radiotherapy [3].

In the present series, no cases were false negative. However, one case represented a false-positive result; this patient showed moderate uptake of ^{201}Tl that was associated with increased perfusion, but no solid tumor was evident in the biopsy specimen and the patient has had no recurrence. Although the precise cause for the discrepancy in this case is unclear, aberrantly increased perfusion may occur transiently to an area of irradiated tissue if autoregulatory properties are disturbed and the blood-brain barrier is disrupted [26]. Alternatively, contamination of the $^{99\text{m}}\text{Tc}$ -HMPAO preparation with free pertechnetate could also produce false-positive results by diffusing passively to metabolically quiescent areas. Further experience in a larger series may determine if this represents a significant source of error.

As this is a preliminary study, there are certain limitations to the conclusions that can be drawn from our data. First, the

number of patients in various clinical subgroups is too small to provide meaningful statistics concerning treatment protocols, SPECT findings, or pathologic results. Second, we have not collected a sufficient number of normal examinations and cases of nonneoplastic brain abnormalities to establish the specificity and sensitivity of our SPECT technique. And most importantly, the protocol followed in this study was associated with inherent constraints in the ability to correlate precisely the foci of radioisotope activity with the location of the surgical specimens. Regions of interest drawn around suspicious foci on the SPECT scans were manually transcribed onto the corresponding CT images, and these data then were translated into stereotaxic coordinates for biopsy and resection; a loss of spatial resolution could have occurred during any step in this procedure. In the next phase of our study, which is currently underway, SPECT images are being superimposed onto CT or MR scans by use of an interactive computer algorithm so that stereotaxic biopsy sites can be chosen directly on the basis of radiotracer uptake. This procedure should ensure an accurate registration of SPECT and biopsy data necessary to further define and classify various ^{201}Tl and $^{99\text{m}}\text{Tc}$ -HMPAO uptake patterns and their histopathologic correlates.

Finally, we are in the process of evaluating various techniques for the quantification of radiotracer values. Comparisons of SPECT data among subjects must be based on relative ratios of regional uptake to uptake within an internal reference structure. Thus, we expressed local perfusion data as a ratio to the uptake in an equivalent area in the opposite hemisphere, but other valid approaches we are investigating include comparison with a functionally stable area such as the cerebellar cortex or with whole-brain uptake values. For thallium data, we chose to use the contralateral scalp as our internal thallium reference, since scalp activity was well defined in all cases and could be assessed easily and reproducibly; moreover, we found that using the contralateral normal brain as a thallium reference [13, 14] yielded highly variable data in our initial group of patients. Nevertheless, we are currently attempting to determine in a larger patient population whether the scalp or the contralateral parenchyma provides the more reliable reference for quantitative analysis of thallium uptake data.

In conclusion, our experience suggests that dual-tracer SPECT scanning may prove to be a valuable resource in detecting sites of likely tumor recurrence in patients who remain symptomatic after radiation therapy, and in directing the surgeon to these areas for biopsy. We believe that this technique warrants further assessment as a potentially important tool in the management of patients undergoing therapy for high-grade gliomas.

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