Int J Clin Oncol (2004) 9:51–58
DOI 10.1007/s10147-003-0362-4

ORIGINAL ARTICLE

**Niloy Ranjan Datta · Rajesh Pasricha · Sanjay Gambhir
Shambhu Nath Prasad · Rajendra Vishnu Phadke**

Comparative evaluation of ^{201}Tl SPECT and CT in the follow-up of irradiated brain tumors

Received: June 27, 2003 / Accepted: October 29, 2003

Abstract
Background. Radiation-induced changes in post-irradiated brain tumors may produce morphological alterations similar to those of tumor recurrence on computed tomography (CT). However, ^{201}Tl single-photon-emission computed tomography (SPECT), with its ability to image metabolic changes, may differentiate post-irradiated gliotic changes from metabolically active congregations of viable tumor cells. This study was carried out to compare these two imaging modalities for the follow-up evaluation of post-irradiated brain tumors.
Methods. Thirty-five patients with previously irradiated primary brain tumors were evaluated for this study. ^{201}Tl SPECT and CT were carried out during follow-up, which ranged from 3 to 125 months (median, 18 months). These findings were compared with the clinical outcome, as observed during the subsequent follow-up.
Results. Sensitivity, specificity, and the overall accuracy of ^{201}Tl SPECT were 82.7%, 83.3%, and 82.8%, compared to 58.6%, 66.6%, and 58.3%, respectively, for CT. Post-scan progression-free survival (PFS) was significantly different for those patients having positive and those having negative evidence of tumor recurrence based on the imaging studies during follow-up. However, PFS was better correlated with ^{201}Tl SPECT results than with the CT results. With ^{201}Tl-SPECT, median PFS was 4 months for those with positive reports, versus 33 months for those with negative reports ($P = 0.003$), compared to a corresponding median PFS of 3 months versus 14 months ($P = 0.025$), respectively, with CT. On multivariate analysis, age and ^{201}Tl SPECT were the only significant variables for predicting post-scan PFS.
Conclusion. ^{201}Tl SPECT, with its ability to be taken up by viable tumor tissues, is superior to CT for the follow-up evaluation of post-irradiated brain tumors.

Key words Brain tumors · Radiation therapy · Single-photon-emission computed tomography · Computed tomography · Thallium-201

Introduction

The follow-up of patients with brain tumors, after surgery or radiotherapy, is usually based on clinical examination, coupled with imaging studies comprising computed tomography (CT) or magnetic resonance imaging (MRI). Although the clinical signs and symptoms can provide reasonable clues to the clinician on the likelihood of disease progression or relapse, decisions are usually based on imaging studies. However, because radiation therapy forms an integral part of the adjuvant post-operative treatment in almost all patients with brain tumors, the interpretation of clinical and radiological findings could pose special problems, as changes evident on CT or MRI might be attributed not only to tumor progression but could also mimic radiation-induced secondary changes.[1–4]

Images obtained on CT are usually based on the anatomic alterations caused by the tumor in brain parenchyma, the ability of contrast material to pass through the breach in the blood-brain barrier (BBB), and the features of the vasculature of pre- and post-therapy tumor tissue. However, in post-irradiated brain parenchyma, the ensuing edema following radiotherapy could mask the presence of a nidus of active tumor cells, thereby causing uncertainties about disease status in a given patient during follow-up.[1,5]

Recently, with positron emission tomography (PET), it has been possible to explore the metabolic status of tissues

N.R. Datta (✉) · R. Pasricha · S.N. Prasad
Department of Radiotherapy, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Rae Barelli Road, Lucknow – 226014, India
Tel. +91-522-2668700/800/900, ext 2449; Fax +91-522-2668017, 2668973
e-mail: nrdatta@sgpgi.ac.in

S. Gambhir
Department of Nuclear Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

R.V. Phadke
Department of Radiodiagnosis, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

and tumor by monitoring glucose and amino-acid metabolism.[6,7] However, in view of the limited availability of PET, this investigative modality is not used as a routine in most centers, and, thus, decisions about the patient's disease status are usually based on routine radiological imaging studies with CT or MRI.

Radio-thallium (^{201}Tl), a monovalent cationic radioisotope, has biological properties similar to that of potassium, and follows the Na^+-K^+ pathway to cross the cell membrane.[4,8,9] The ^{201}Tl is taken up only by metabolically active and viable tumor cells. Like the contrast agents used in CT, ^{201}Tl uptake in the brain is also related to the breach in the BBB. However, in addition, uptake of ^{201}Tl is also related to other factors, such as tumor blood flow, extent of pathological vessel invasion, and, most significantly, the viable tumor cell fraction and its growth rate.[10]

^{201}Tl single-photon-emission computed tomography (SPECT) has been shown to distinguish between radiation-induced changes and residual/recurrent tumors with reasonable success.[11–16] Most of these studies demonstrated the utility of ^{201}Tl-SPECT either alone or with dual-isotope SPECT with ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) in the follow-up evaluation of primary brain tumors.[13–15] A comparative assessment of ^{201}Tl-SPECT with CT was reported by Lorberboym et al.[16] in high-grade gliomas following surgery, radiation, and/or chemotherapy during a mean follow-up period of 15 months. Because radiation-induced necrosis represents late radiation changes, studies with a longer duration of follow-up could further help to ascertain the predictive values of CT and ^{201}Tl-SPECT in post-irradiated brain tumors.

In the present study, we attempted to evaluate the predictive value of CT and ^{201}Tl-SPECT by comparing the imaging findings with the clinical outcome in individual patients after the irradiation of brain tumors. The average follow-up period in the present study was 30 months (range, 3 to 125 months) and the progression-free survival after these scans were performed was used to compare the predictive values of the two investigative modalities.

Table 1. Patient demography (n = 35)

Characteristic	Distribution
Age (years)	42.9 ± 14.1[a]
Sex	
Male	25
Female	10
Histology	
Astrocytoma grade I	2
Astrocytoma grade II	2
Anaplastic astrocytoma	6
Glioblastoma multiforme	15
Oligodendroglioma	6
Lymphoma	2
Unknown	2
Surgery	
Complete resection	11
Partial resection	10
Decompression and biopsy	11
Biopsy alone	1
None	2
Radiotherapy	
Dose (Gy)	59.7 ± 3.1[a]
Fractions	32.4 ± 2.3[a]
Overall treatment time (days)	47.8 ± 8.5[a]
Chemotherapy	
Yes	28
No	7
Intervals	
Completion of RT and CT	441.7 ± 617.1 days
Completion of RT and ^{210}Tl-SPECT	459.9 ± 614.4 days
CT and last follow up	448.5 ± 572.1 days
^{210}Tl-SPECT and last follow up	430.3 ± 570.8 days

RT, radiotherapy; CT, computed tomography; SPECT, single-photon-emission computed tomography
[a] Mean ± SD

Subjects and methods

Patient population

Thirty-five patients with primary brain tumors who received postoperative radiotherapy during the period November 1990 to July 1998 and who, during the subsequent follow-up had undergone both CT and ^{201}Tl-SPECT (done with a short interval between the scans) were selected from the data base of patients with primary brain tumors. Their ages ranged from 7 to 64 years, and there was a male predominance (male/female, 2.5:1) (Table 1). Surgery consisted mostly of either complete or partial tumor resection. The majority of the patients had high-grade gliomas. Details of distribution of the patients are shown in Table 1.

Within 3 to 4 weeks of surgery, all patients received postoperative radiotherapy at doses ranging from 50.4 Gy to 72 Gy, at 1.8 Gy to 2 Gy per fraction, depending on the type of histology. After completion of the radiotherapy, most of the patients (28/35) received adjuvant treatment with single-agent lomustine (CCNU), or combination chemotherapy with CCNU, procarbazine, and vincristine. Two patients with brain-stem glioma did not receive any chemotherapy.

Imaging studies during follow-up

During the follow-up, both CT and ^{201}Tl-SPECT were done mostly as a routine evaluation in clinically stable patients (n = 30), while 5 patients were clinically symptomatic at the time of these investigations. Patients were considered for imaging studies as and when the concerned physician thought it appropriate, based on clinical evidence of neurological deterioration, or to reconfirm stable neurological status. This resulted in variable time intervals between the completion of radiotherapy and the ^{201}Tl SPECT/CT scans.

The intervals between completion of radiotherapy and CT scan ranged from 18 to 2787 days (median, 266 days), while the interval for ^{201}Tl-SPECT ranged from 12 to 2788 days (median, 282 days). The total follow-up period after surgery ranged from 3 to 125 months (median, 18 months), while the post-scan follow-up period ranged from 0 to 62 months (median, 7 months).

CT

Plain and contrast-enhanced CT was done in the axial plane, at an 8-mm slice thickness, on a spiral CT unit (PQ5000V, Picker, Clevland, OH, USA). The criteria used to label a case as positive for tumor recurrence on CT were: area of contrast enhancement within or around the suspected lesion and/or an increase in mass effect over and above that on the preoperative scan. For post-radiation effects, the CT appearances were nonspecific, and changes considered as radiation injury included homogenous decreased attenuation within the white matter.[5]

^{201}Tl-SPECT

SPECT was performed after the intravenous injection of 74.5–111 MBq ^{201}Tl as thallium chloride, and 64 images, at 40 s for each image in a 128 × 128-pixel matrix, were acquired 1 h later on a dual-head SPECT gamma camera (DSTXL; Sopha Medical Vision, BUC, France). Images were reconstructed in an 128 × 128-pixel matrix with metz filter at point spread function (psf) 5.5 full width half maximum (fwhm), order 8, and a uniform attenuation correction of 0.16/cm was applied. Tomographic images that best displayed the lesion in a slice thickness of 4.51 mm were chosen to visually classify the tumor region uptake and to classify the images into two groups – negative or positive, to indicate the absence or presence of viable tumor. In 64 images, ^{210}Tl uptake of tumor was evaluated by a qualitative method. The qualitative analysis was performed by the visual evaluation of tracer uptake. The degree of uptake was visually classified into two groups – negative or positive, thereby indicating the absence or presence of viable tumor. Before the commencement of the study, the ^{201}Tl uptake ratios of tumors were quantified in a separate group of 15 patients. The average ^{201}Tl index, described as the ratio of the count in the area of the lesion versus the count in the contralateral mirror image of the normal hemisphere, was estimated to find the cut-off point for the ^{201}Tl uptake ratio for tumor recurrence. A ratio of 1.2 and above was found to be specific for recurrence.

For the present study, quantification of ratios was not done, and cases were considered as positive if the ^{201}Tl uptake was significantly and clearly more than that in the noninvolved contralateral region of the brain. This was done deliberately to provide the same scale of qualitative interpretation of the images as is the practice with the CT scan images.

Neither the nuclear medicine physician nor the radiologist was informed of the clinical status of patients at the time of the imaging studies, to avoid any bias in interpretation of their findings. Thus, these CT or ^{201}Tl-SPECT reports were based only on the interpretation of the imaging findings.

Histopathological confirmation at relapse

Patients were regularly reviewed, and a detailed neurological examination was carried out at each examination. Patients suspected of relapse underwent CT and/or ^{201}Tl-SPECT and these findings were reviewed by the neurosurgeons before they decided on the possibility of re-exploration.

Histopathological confirmation at the time of relapse was obtained in three patients. In all other cases, either the patient was not willing to undergo any surgery (due to financial constraints, deteriorating neurological condition, or associated comorbid conditions) or definite neurosurgical intervention was contraindicated because of the extent and size of the suspected recurrent lesion.

Statistical analysis

The intervals between the completion of radiotherapy and CT or ^{201}Tl-SPECT scans were estimated. The post-scan progression-free survival was computed from the day of either the CT scan or the ^{201}Tl-SPECT scan carried out in the post-irradiated period to the date of the last follow-up. Univariate analysis of various categories of positive and negative scans for each CT and ^{201}Tl-SPECT was done by the Kaplan Meier method.[17] Cox's proportional hazard model, using the stepwise forward Wald method, was used for multivariate analysis to detect significant independent predictors for various post-scan progression-free survival outcomes.[18]

Statistical analysis was carried out using SPSS version 9.0 for Windows (SPSS, Chicago, IL, USA).

Results

Patient demography

The detailed demographic profiles of the 35 patients are shown in Table 1. Median age was 45 years, with 22 patients below 50 years and the remaining 13 aged 50 years or more. Except for 2 patients with brain-stem gliomas, all patients had histological confirmation of their malignancy. In the remaining 33 patients, gliomas constituted the majority of cases (31/33). Surgery (either complete or partial resection) or decompressive procedures were performed in the majority of the patients.

Imaging studies versus clinical condition at follow-up

The median intervals between the end of radiotherapy and the performance of ^{201}Tl SPECT and CT scans were 282 days and 266 days, respectively, and the paired-sample *t*-test for differences in means between these two variables was nonsignificant ($P = 0.089$). The interval between ^{201}Tl SPECT/CT scans and the last follow-up depended on the survival of each individual patient. Thus, the mean ± SD for post-^{201}Tl SPECT survival was 430.1 ± 570.8 days, while for CT, it was 448.5 ± 572.1 days (paired sample *t*-test; $P = 0.089$).

In 30 patients, scans were done when the patients were neurologically stable, while in the remaining 5 patients, scans were done when they were symptomatic and had signs

of neurological deterioration. Fifteen of these 30 stable patients were reported to have positive evidence of recurrence on CT, while there was positive evidence in 20 of these 30 patients on ^{201}Tl-SPECT. In the remaining 5 symptomatic patients, CT was positive in 4, while all these 5 patients had positive reports on ^{201}Tl-SPECT.

The median intervals between CT or ^{201}Tl-SPECT scans and the last follow-up were 155 days (range, 0 to 1940 days) and 135 days (range, 0 to 1872 days) respectively. Thus, the results of the scans carried out during follow-up were evaluated in terms of patient status at the time of the last follow-up, when a total of 29 patients were symptomatic and had shown signs of worsening neurological status, while only 6 patients continued to be stable. CT scans done earlier had correctly predicted tumor recurrence for 17 patients, while 24 of the ^{201}Tl-SPECT results had correctly predicted tumor recurrence in these 29 patients. In the 6 patients who continued to be stable, CT findings were negative in 4, while ^{201}Tl-SPECT findings were negative in 5 patients. Thus, the overall accuracy with respect to the patient's condition at longterm follow-up was 58.3% with CT and 82.8% with ^{201}Tl-SPECT. The sensitivity, specificity, and positive and negative predictive values were comparatively much better with ^{201}Tl-SPECT than with CT (Table 2).

Histopathological confirmation

Histopathological confirmation of tumor relapse was carried out in three patients. In all three, there was evidence of tumor recurrence. In two patients, the histopathology was the same as that at the initial surgery, while in the other patient, the tumor had progressed to glioblastoma multiforme from the initial grade-I astrocytoma. In all three patients, ^{201}Tl-SPECT was positive, while in two patients, CT was reported as negative for any signs of tumor recurrence. In the first patient, the time intervals between CT scan, ^{201}Tl-SPECT, and surgery were 40 and 42 days, respectively, while in the second patient, the corresponding time intervals were 63 and 60 days, respectively. In the third patient, the CT scan was negative, while ^{201}Tl-SPECT was positive. However, the patient became neurologically symptomatic only 34 months after the ^{201}Tl-SPECT report; he was then reoperated and found to have a recurrent tumor. The time intervals between CT scan, ^{201}Tl-SPECT, and surgery in this patient were 1001 and 980 days, respectively.

Post-scan progression-free survival

Of the 35 patients, 31 had shown evidence of disease progression during their follow-up, as indicated by worsening of neurological symptoms, periodic CT/MRI, or ^{201}Tl-SPECT. Patients with a positive report of tumor recurrence on CT had a median progression-free survival of 3 months, compared to 14 months in those with a negative report (P = 0.025; Fig. 1). For ^{201}Tl-SPECT, patients with positive uptake had a median progression-free survival of 4 months, compared to 33 months in those with negative ^{201}Tl uptake (P = 0.003; Fig. 2). Thus, of the 31 patients who eventually had disease progression, 19 patients were reported to be positive for tumor recurrence on CT, and 25 were positive on ^{201}Tl-SPECT. On the other hand, of the 16 patients reported to be negative on CT, 12 had disease progression, while disease progression was evident in 6 of the 10 patients reported to be negative on ^{201}Tl-SPECT.

To determine the impact of various patient demographic parameters, such as age, sex, tumor grade, histology, radiotherapy dose parameters, chemotherapy, interval between surgery and the start of postoperative radiotherapy and the ^{201}Tl SPECT and CT reports, the variables were analyzed in a multivariate Cox's regression model, with post-scan progression-free survival as the dependent variable. As is evident from Table 3, age and the ^{201}Tl SPECT report were the only parameters that were found to be the significant variables to predict post-scan progression-free survival. Patients younger than 50 years had a median survival of 12 months, compared to 3 months for those beyond 50 years (P = 0.016). Of the four patients who had no evidence of any disease progression, 3 were younger than 50 years. Similarly,

Table 2. Clinical outcome versus CT and ^{201}Tl-SPECT reports, determined both at the time of the scan and at last follow-up, and their predictive values

Clinical status	CT			^{201}Tl-SPECT		
	Positive	Negative	Prediction	Positive	Negative	Prediction
At the time of scan						
Stable	15	15		20	10	
Symptomatic	4	1		5	–	
Total	19	16		25	10	
At the last follow-up						
Stable	2	17		1	5	
Progression	4	12		24	5	
Total	6	29		25	10	
Predictive value (based on last follow-up)						
Sensitivity			58.6%			82.7%
Specificity			66.6%			83.3%
Overall accuracy			58.3%			82.8%
Positive predictive value			85.0%			96.0%
Negative predictive value			33.3%			50.0%

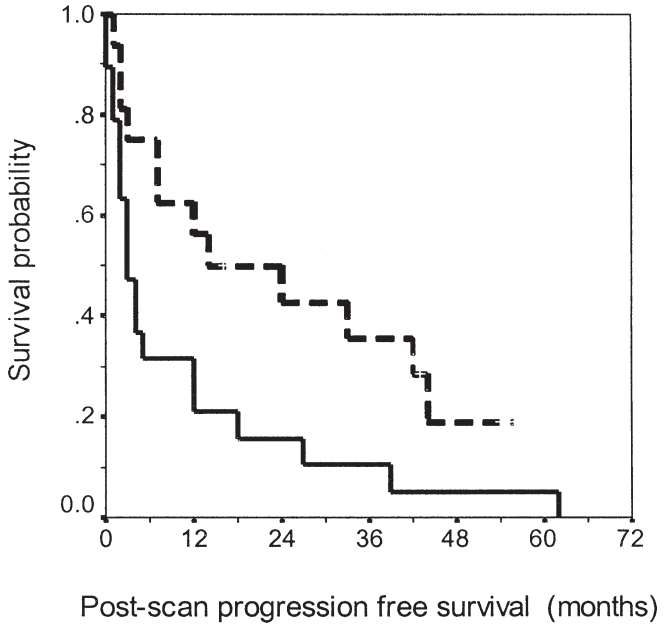

Fig. 1. Post-scan progression-free survival for patients reported to be positive or negative on computed tomography (CT) scan. Median survivals for patients reported to be positive (*continuous line*) or negative (*broken line*) were 3 months and 14 months, respectively ($P = 0.025$)

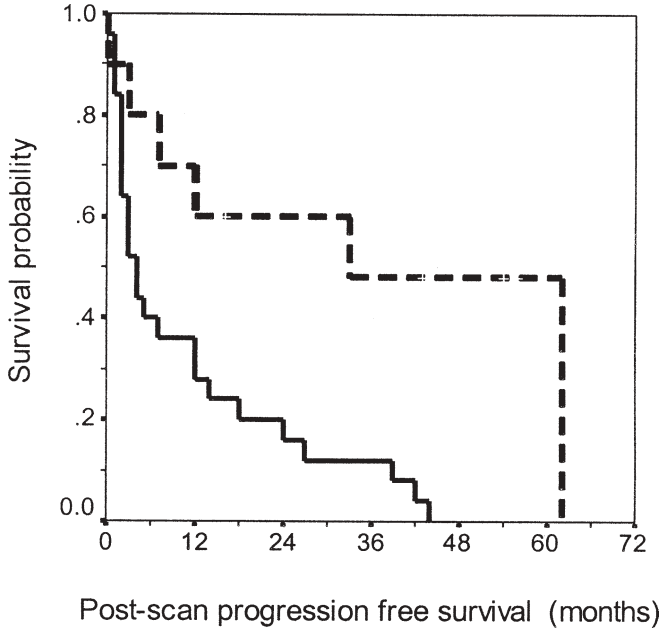

Fig. 2. Post-scan progression-free survival for patients reported to be positive or negative on ^{201}Tl single-photon-emission CT (SPECT). Median survivals for patients reported to be positive (*continuous line*) or negative (*broken line*) were 4 months and 33 months, respectively ($P = 0.003$)

as stated above, the median post-scan progression-free survival was 4 months in those with positive ^{201}Tl SPECT uptake, compared to 33 months in those in whom ^{201}Tl was not detected ($P = 0.003$; Fig. 2).

Table 3. Multivariate analysis for variables predicting post-scan progression-free survival (Cox's proportional hazard model)

Variable	β	SE	*P* value
Age	0.031	0.016	0.047
^{201}Tl-SPECT	−1.320	0.509	0.010

SE, standard error

Discussion

The follow-up of irradiated brain tumors poses a special problem for clinicians, because of the gray zone in the interpretation of images obtained by conventional forms of imaging (i.e., CT and MRI) to distinguish between radiation-induced changes (gliosis) and tumor recurrence.[1,5,19] Coupled with this, it is usually not feasible to obtain histopathological confirmation in most of these patients. Clinical signs and symptoms of tumor recurrence cannot be reliably distinguished from post-therapy edema and necrosis by CT. The lack of specificity of CT occurs because contrast enhancement depends primarily on the breakdown of the BBB, and one of the important criteria for recurrence on CT is the presence of abnormal contrast enhancement. Many of these lesions show minimal contrast enhancement. Furthermore, in some cases, peripheral contrast enhancement can also be seen around radiation-induced gliotic changes. MRI delineates the tumor more clearly, but it may be difficult to distinguish persistent/recurrent tumor from edema and necrosis. Moreover, corticosteriods, which are freely used in the management of brain tumors, may decrease the area of contrast enhancement and may cause considerable difficulty in the interpretation of treatment results.

A direct estimation of tumor activity could be carried out if the metabolic activity of tumor cells could be evaluated to differentiate viable and necrotic tumor from edematous or gliotic brain, especially following surgery or radiotherapy. This activity could possibly be ascertained by using functional imaging such as PET, SPECT, and magnetic resonance spectroscopy (MRS). Functional data obtained from these imagings could be of additional value to determine tumor blood flow, rate of tumor growth, oxygenation, pH, along with selective amino acid, nucleic acid, and carbohydrate metabolism.[11,19] In glial tumor cells, increased glucose and amino-acid uptake measured by PET has been reported to accurately identify tumor recurrence from post-treatment changes. However, its routine use is limited due to its prohibitive cost and limited availability.

Although the precise mechanism of ^{201}Tl uptake into tumor cells is unknown, the possibilities involved could include disruption of the BBB, cellular metabolic activity, and Na^+-K^+-ATPase activity.[15,20] The latter two activities could permit a distinction to be made between viable tumor cells and radionecrotic areas in post-irradiated brain tumors. On CT or MRI, the regions of viable tumor have been considered to be those areas which are enhanced after intravenous contrast administration. These areas, in reality,

would represent areas with a breach in the BBB and, thus, could have necrotic tissue, or viable tumor cells, or both. However with ^{201}Tl-SPECT, the presence of a breach in the BBB alone will not necessarily increase the uptake of ^{201}Tl, as non-neoplastic lesions associated with BBB breakdown, such as radionecrosis or resolving hematomas, will have little or no ^{201}Tl uptake.[3]

Based on the above assumptions, a number of workers have demonstrated the utility of ^{201}Tl-SPECT for the differential diagnosis of ring-enhancing brain lesions i.e., differentiating between gliomas and abscesses,[10] for assessing viable glioma tumor cells after surgery,[21] for preoperative grading of gliomas,[22] and for correlation with tumor cell kinetics and proliferative index.[23]

^{201}Tl-SPECT has also been used for differentiating between active tumor and post-radiation necrosis. Carvalho et al.[12] assessed the ability of ^{201}Tl-SPECT and ^{99m}Tc HMPAO SPECT to distinguish tumor recurrence from radiation-induced changes. Recurrence was confirmed in 12 of their 13 patients, with ^{201}Tl tumor/scalp ratios of 3.5 or greater and with ^{99m}Tc HMPAO tumor/cerebellum ratios of 0.51 or more. Schwartz et al.[13] observed a similar relation, in terms of survival, using dual-isotope SPECT with ^{201}Tl and ^{99m}Tc HMPAO. One-year survival was 6.7% if ^{201}Tl tumor/scalp ratios were 3.5 or greater and ^{99m}Tc HMPAO tumor/cerebellum ratios were 0.51 or more, compared to 83% with ^{201}Tl tumor/scalp ratios of less than 2 and ^{99m}Tc HMPAO tumor/cerebellum ratios less than 0.5.

Vertosick et al.[14] quantified ^{201}Tl tumor/myocardium ratios in post-irradiated glioblastoma multiforme patients and reported that a ratio of less than 0.3 favoured a longer average survival, of 13 months, compared to 4 months in those with ratios of more than 0.3. Kline et al.[15] reported that ^{201}Tl tumor/scalp ratios greater than 2 had a positive predictive value for tumor recurrence of 92%, while the negative predictive value for tumor recurrence was 83% for ratios less than 0.5. They observed that the sensitivity and specificity for ^{201}Tl SPECT were 95% and 60%, respectively, in post-irradiated patients.

Lorberboym et al.[16] compared the utility of ^{201}Tl-SPECT versus CT scan in 34 post-irradiated patients, the majority of whom had glioblastoma multiforme. On initial workup, ^{201}Tl-SPECT demonstrated disease in 23 of the 34 patients, while CT was able to document this in 20 of the 23 patients who had positive ^{201}Tl uptake. Follow-up with ^{201}Tl-SPECT suggested disease progression in 9 of 11 patients, while progression was evident in only 3 patients on CT during a mean follow-up period of 15 months.

In the present study, we tried to address the issue of the utility of ^{201}Tl-SPECT by carrying out a comparative assessment with CT in patients with a considerably long follow-up after postoperative radiotherapy, extending to a maximum of 125 months. There was no attempt to quantify ^{201}Tl-SPECT in ratios as has been done by previous studies. This was to provide homogeneity in the reporting of CT and ^{201}Tl-SPECT, because the interpretation of CT is based solely on visual inspection of images. Thus, to provide a similar scale of interpretation, the reporting of the findings for both imaging modalities was based on visual interpretation. Moreover, in spite of the better resolution of CT compared to ^{201}Tl SPECT, the predictive value of ^{201}Tl SPECT was observed to be superior to that of CT irrespective of the tumor size. Similar results have been shown by Lorberboym et al.[16]

Histological documentation of either a tumor recurrence or radiation-induced changes remains, undoubtedly, the gold standard. Of the seven patients who had positive ^{201}Tl-SPECT uptake but were reported to be negative on CT, three underwent reexploration. In all three patients, the recurrence was confirmed histopathologically. However, in the clinical setting, although every effort is made to explore the possibility of re-exploration, it may not always be possible to subject patients to reoperation and biopsy, as, often, patients may refuse to give their consent to be subjected to further surgery when they are made aware of the limited benefit, due to the associated surgical morbidity and mortality of reexploration. All seven patients noted above had already been subjected to postoperative radiotherapy and chemotherapy, and, hence, even an incomplete resection may not have provided a significant change in the clinical outcome. Added to this is the cost, which, when it has to be borne by the patient, adds a another factor to the decision-making process for reexploration. In some cases, the neurosurgeon may feel that reexploration would be of no benefit in view of the site, size, and the extent of lesion.

The predictive value of ^{201}Tl-SPECT, in terms of sensitivity, specificity, and overall accuracy, was estimated to be 82.7%, 83.3%, and 82.8%, compared to 58.6%, 66.6%, and 58.3%, respectively, for CT. The post-scan progression-free survival also was better predicted by ^{201}Tl-SPECT (Figs. 1 and 2). The cumulative hazard for disease progression in patients with positive uptake on ^{201}Tl-SPECT was 3.22, compared to 2.94 with CT. In contrast, the cumulative hazard for disease progression was 1.66 for patients reported to be negative on CT (Fig. 3) and 0.73 for those who were negative on ^{201}Tl-SPECT (Fig. 4). This further emphasizes that ^{201}Tl-SPECT is a better and an earlier predictor of events than CT during the follow-up of irradiated brain tumor.

A comparative study of SPECT with technetium-99m sestamibi [hexakis (2-me-thoxyisobutylisonitrile) technetium] and CT was done by Maffioli et al.[2] in post-irradiated brain tumors. SPECT images were analyzed only qualitatively, and no quantitative ratios were estimated. Histopathological proof was available in 8 of the 105 patients studied, and the results of CT and SPECT were scored on the basis of the clinical course of the disease over a period of 6 months. Sensitivity, specificity, overall accuracy, and positive and negative predictive values for SPECT were 88%, 91%, 88%, 98%, and 63%, while these values for CT were 98%, 67%, 92%, 93%, and 86%, respectively. In patients in the present study, the median follow-up after surgery was 18 months (range, 3 to 125 months) and the median post-scan follow-up was 7 months (range, 0 to 62 months); we consider this period to be reasonable to assess whether the clinical deterioration could be attributed to tumor recurrence. The above predictive values are similar to those we obtained for ^{201}Tl-SPECT in the present study, and similar to those reported by other authors.[15,24]

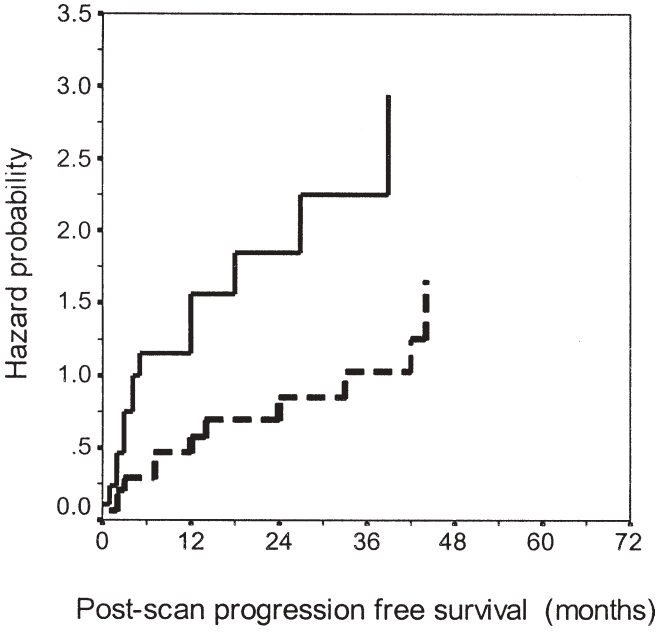

Fig. 3. Hazard plots for post-scan progression-free survival for patients reported to be positive (*continuous line*) or negative (*broken line*) on computed tomography (CT) scan

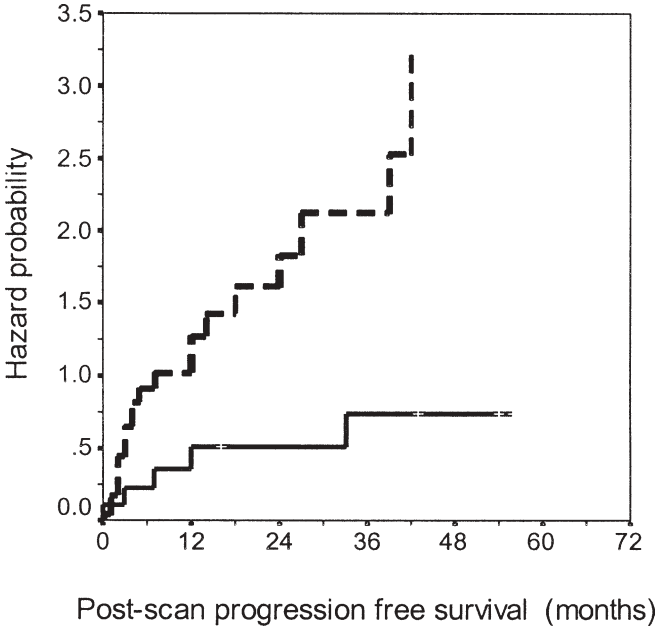

Fig. 4. Hazard plots for post-scan progression-free survival for patients reported to be positive (*broken line*) or negative (*continuous line*) on ^{201}Tl-SPECT

Table 4. Clinical outcome at last follow-up versus CT and ^{201}Tl-SPECT reports, and the respective predictive values based on the time interval (less than 180 days or 180 days and beyond) between the completion of radiotherapy and the imaging study

Clinical outcome	CT scan				^{201}Tl-SPECT			
(at last follow-up)	+ve	−ve	*P* value	Predictive value	+ve	−ve	*P* value	Predictive value
A. Interval between completion of radiotherapy and imaging study less than 180 days (n = 8)								
Stable	1	0	0.408[a]		1	0	0.686[a]	
Progression	4	3			6	1		
Total	5	3			7	1		
Median PFS (months)	3	3	0.896[b]		3	3	0.561[b]	
Sensitivity (%)				57.1				85.7
Specificity (%)				0				0
Overall accuracy (%)				50				75
Positive predictive value (%)				80				85.7
Negative predictive value (%)				0				0
B. Interval between completion of radiotherapy and imaging study at 180 days or more (n = 27)								
Stable	1	4	0.114[a]		0	5	<0.001[a]	
Progression	13	9			18	4		
Total	14	13			18	0		
Median PFS (months)	4	33	0.036[b]		5	62	0.006[b]	
Sensitivity (%)				59.1				81.8
Specificity (%)				80				100
Overall accuracy (%)				62.9				85.1
Positive predictive value (%)				92.8				100
Negative predictive value (%)				30.7				55.5

PFS, progression-free survival
[a] χ^2
[b] Log rank

The interval between the end of radiation and the time of performing CT or ^{201}Tl-SPECT could be important and could have a bearing on the predictive value. Because the late effects of radiation in the brain are usually considered to start around 6 months after radiation, the data were segregated into two time intervals – scans done within 6 months and those done beyond 6 months. Of the 35 patients, 8 patients had scans within 6 months, while in the remaining 27, imaging studies were carried out more than 6 months after radiation. Even though the number of patients in each of these subgroups was limited, it is apparent, from Table 4, that, within 6 months, the predictive values and the endpoints estimated for the two imaging modalities were quite similar. However, as the post-radiotherapy scan inter-

val went beyond 6 months, the predictive values of ^{201}Tl-SPECT became better than those of the CT scan. Even the post-scan progression-free survivals were better represented by a negative ^{201}Tl-SPECT report than by a negative CT report. This shows that ^{201}Tl-SPECT could be of much greater use than CT to differentiate tumor recurrence from late radiation effects in the brain as the post-radiotherapy follow-up period increases.

MRI, which is the imaging modality of choice in brain tumors, has diagnostic problems similar to those with CT in differentiating tumor recurrence from radiation necrosis. This has been reported recently in a comparative study between CT, MRI, and ^{201}Tl-SPECT, carried out to assess treatment response in 20 patients with high-grade gliomas by Vallejos et al.[24] The study reconfirmed the efficacy of ^{201}Tl-SPECT in 89% of the patients; this was much better than that of CT or MRI.

Thus, until functional imaging with PET or MRS becomes routine in the follow-up evaluation of post-irradiated brain tumors, ^{201}Tl-SPECT could serve as an important investigative modality for predicting the progression-free survival. It has a better diagnostic and predictive accuracy than CT and appears to be a valuable independent predictor of PFS. Because of its inherently lower spatial resolution compared to CT, it might be difficult to consider ^{201}Tl-SPECT as a definitive diagnostic tool for radiation-induced changes or tumor recurrence, especially in small and early post-irradiated brain tumors. However, it could certainly be considered as a complement to CT scanning in these patients, especially with the currently available co-registration software. The uptake of ^{201}Tl does not, perhaps, have the same implications as PET, which helps to monitor cell metabolism. However, ^{201}Tl is actively taken up through the cell membrane following the Na^+-K^+ pathway, and uptake would be possible only if the cell is viable. ^{201}Tl SPECT, thus, gives some evidence of cell viability and, indirectly, evidence of cell metabolism. One may therefore consider ^{201}Tl SPECT as a "poor man's option for PET." The use of ^{201}Tl-SPECT would help in the consideration of early definitive therapy to take care of the nidus of viable residual tumor even before the patient becomes symptomatic, and before the tumor proliferates to dimensions which may not be amenable to any definite interventions.

References

1. Byrne TN (1990) Imaging in gliomas. Semin Oncol 21:162–171
2. Maffioli L, Gasparini M, Chiti A, et al. (1996) Clinical role of technetium-99m sestamibi single-photon emission tomography in evaluating pretreated patients with brain tumours. Eur J Nucl Med 23:308–311
3. Sun D, Liu Q, Liu W, et al. (2000) Clinical application of 201 Tl SPECT imaging of brain tumours. J Nucl Med 41:5–10
4. Cipri S, Mannino R, Ruggieri R, et al. (2001) Clinical evaluation of thallium-201 single photon emission tomography in equivocal neuroradiological supratentorial lesions. J Neurosurg Sci 45:75–82
5. Madison MT, Hall WA, Latchaw RE, et al. (1994) Radiologic diagnosis, staging, and follow-up of adult central nervous system primary malignant glioma. Radiol Clin North Am 32:183–196
6. Sonoda Y, Kumabe T, Takahashi T, et al. (1998) Clinical usefulness of 11C-MET PET and 201-Tl SPECT for differentiation of recurrent gliomas from radiation necrosis. Neurol Med Chir (Tokyo) 38:342–347
7. Tralins KS, Douglas JG, Stelzer KJ, et al. (2002) Volumetric analysis of 18 F-FDG PET in glioblastoma multiforme: prognostic information and possible role in definition of target volumes in radiation dose escalation. J Nucl Med 43:1667–1673
8. Prat-Acin R, Diaz-Vicente J, Banzo J, et al. (1996) Use of SPECT with 201-Tl in the evaluation of brain tumours. Rev Neurol 24:909–913
9. Britten JS, Blamk M (1968) Thallium activation of the (Na^+-K^+) activation ATPase of rabbit kidney. Biochim Biophys Acta 159:160–166
10. Källén K, Heiling M, Anderson A-M, et al. (1997) Evaluation of malignancy in ring enhancing brain lesions on CT by thallium-201 SPECT. J Neurol Neurosurg Psychiatry 63:569–574
11. Benard F, Romsa J, Hustinx R (2003) Imaging gliomas with positron emission tomography and single photon emission computed tomography. Semin Nucl Med 33:148–162
12. Carvalho PA, Schwartz, RB, Alexander E (1992) Detection of recurrent gliomas with quantitative thallium-201/technitium 99m HMPAO single photon emission computerized tomography. J Neurosurg 77:565–570
13. Schwartz RB, Holman L, Polak JF, et al. (1998) Dual-isotope single photon emission computerized tomography scanning in patients with glioblastoma multiforme: association with patient survival and histopathological characteristics of tumor after high-dose radiotherapy. J Neurosurg 89:60–68
14. Vertosick FT, Selker RG, Grossman SJ, et al. (1994) Correlation of thallium-201 single photon emission computed tomography and survival after treatment failure in patients with glioblastoma multiforme. Neurosurgery 34:396–401
15. Kline JL, Noto RB, Glantz M (1996) Single-photon emission CT in the evaluation of recurrent brain tumor in patients treated with gamma knife radiosurgery or conventional radiation therapy. AJNR Am J Neuroradiol 17:1681–1686
16. Lorberboym M, Baram J, Feibel M, et al. (1995) A prospective evaluation of thallium-201 single photon emission computerized tomography for brain tumor burden. Int J Radiat Oncol Biol Phys 32:249–254
17. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481
18. Cox DR (1972) Regression models and life tables. J R Stat Soc B 34:187–220
19. Thomas DGT, Kitchen ND (1995) Functional and metabolic imaging of brain tumors. In: Kaye AH, Laws ER Jr (eds) Brain tumors. Churchill Livingstone, Edinburgh, pp 247–262
20. Schwartz R, Carvalho P, Alexander E III, et al. (1993) Radiation necrosis versus high grade recurrent glioma: differentiation by using dual isotope SPECT with ^{210}Tl and ^{99m}Tc-HMPAO. AJNR Am J Neuroradiol 12:1187–1192
21. Källén K, Geijer B, Andersson AM, et al. (1999) Assessment of glioma by estimating ^{210}Tl SPECT tumor uptake volume. Nucl Med Commun 20:837–844
22. Källén K, Heiling M, Andersson AM, et al. (1996) Preoperative grading of glioma malignancy with thallium-201 single–photon emission CT: comparison with conventional CT. AJNR Am J Neuroradiol 17:925–932
23. Oriuchi N, Tamura M, Shibazaki T, et al. (1993) Clinical evaluation of thallium-201 SPECT in supratentorial gliomas: relationship to histological grade, prognosis and proliferative activities. J Nucl Med 34:2085–2089
24. Vallejos V, Balana C, Fraile M, et al. (2002) Use of 201 Tl SPECT imaging to assess the response to therapy in patients with high grade gliomas. J Neurooncol 59:81–90