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Thallium-201 SPECT in prognostic assessment of malignant gliomas treated with postoperative radiotherapy

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Objective: This study was designed to investigate the value of preoperative thallium-201 (^{201}Tl) SPECT as a predictor of outcome in malignant glioma. ***Methods:*** From January 1990 to September 2003, 109 patients with glioma were treated with postoperative radiotherapy. Of these, 36 patients with malignant gliomas who underwent preoperative ^{201}Tl-SPECT were included in this study (grade 3: n = 14, grade 4: n = 22). On early (10 minutes) and delayed (2 hours) images after 111 MBq ^{201}TlCl injection, we calculated radioactivity ratios of tumors to contralateral normal brain (T/N ratios) and retention indices (RIs). For early and delayed images, we compared outcome between a high T/N ratio group (T/N ratio equal or greater than the average) and a low T/N ratio group (T/N ratio less than the average). We also divided the patients into two groups on the basis of RI; a high RI group (RI equal or greater than the average) and a low RI group (RI less than the average), and similarly compared outcome between the two groups. ***Results:*** Median survival time was 12 months for both grade 3 and grade 4 tumors; however, two-year survival was 53% for grade 3 and 15% for grade 4. In both early and delayed images, outcome was significantly better for patients with low T/N ratios (early <4.71, delayed <3.96) than those with high T/N ratios (early: p = 0.030, delayed: p = 0.049). However, no significant survival difference was apparent between the low- (< −12.25) and high RI groups. In grade 3 glioma, patients with high T/N ratios demonstrated a tendency toward poorer outcome, although this trend was not significant (early: p = 0.079, delayed: p = 0.099). Overall outcome was poor for grade 4 glioma, and the difference in survival between low and high T/N ratio groups was not significant (early: p = 0.51, delayed: p = 0.53). However, long survival was seen only in patients with lower T/N ratios. ***Conclusions:*** Differences of ^{201}Tl uptake in malignant gliomas could predict outcome. ^{201}Tl-SPECT is potentially useful in the management of patients with malignant gliomas.

Key words: glioma, thallium-201, SPECT, radiotherapy, prognosis

INTRODUCTION

DESPITE RECENT PROGRESS in imaging and treatment, the overall survival of patients with malignant glioma has not improved.[1] Several prognostic factors are well known to influence survival in this condition; such as performance status, age, tumor grade and histology, tumor size, and extent of surgery.[2–4] Histological grade has been considered an important prognostic factor; however, there can be discrepancies between grade and prognosis. A reliable preoperative predictor of prognosis would therefore be useful in determining intensive treatment including radiotherapy and chemotherapy.

CT and MR imaging with contrast are excellent imaging techniques used at most centers to evaluate gliomas. These methods mainly assess morphologic abnormalities. Recently, some authors have reported prognostic assessment using perfusion MR or MR spectroscopy (MRS).[5,6] However, there may be difficulties in defining

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tumor extension and grade, or differentiating tumor recurrence from necrosis or scar in particular areas.[7,8]

Thallium-201 chloride (^{201}Tl) scintigraphy has been widely used to detect various tumors and to differentiate benign from malignant lesions in the lung and thyroid.[9,10] ^{201}Tl scintigraphy has been reported useful for differentiating low grade from high grade gliomas and for distinguishing residual or recurrent viable gliomas from post-therapeutic changes such as radiation necrosis.[4,11–19] However, the association between preoperative ^{201}Tl accumulation in malignant glioma and prognosis after postoperative radiotherapy has not been adequately investigated.

In the present study, we investigated whether preoperative ^{201}Tl-SPECT could predict prognosis in patients with malignant glioma.

MATERIALS AND METHODS

Patients

From January 1990 to September 2003, 109 patients with glioma were treated with postoperative radiotherapy. Of these, 77 patients had been histologically diagnosed with malignant glioma (World Health Organization [WHO] grade 3 and grade 4). From this group, 36 patients (23 males, 13 females) who had all undergone ^{201}Tl-SPECT before surgery were included in this study. The other 41 patients did not undergo ^{201}Tl-SPECT before surgery because of their performance status, and/or their treatment schedules. Histological type was confirmed by examination of surgical specimens in all patients. All of them were malignant astrocytomas. Thirty-two tumors were located in supratentorial, 2 in cerebellum, and 2 in brain stem. Patient characteristics are shown in Table 1.

Table 1 Summary of patient characteristics

Histological grade		(n)
	grade 3	14
	grade 4	22
Gender		(n)
	male	23
	female	13
Age		(n)
	< 65 years	25
	≥ 65 years	11
	median	56 years
	range	12–76 years
KPS		(n)
	< 70	14
	≥ 70	22
Radiotherapy dose		(n)
	< 50 Gy	5
	50 Gy	22
	60 Gy	9
Follow-up*		(months)
	median	12
	range	0.8–103

KPS; Karnofsky performance status
* Duration from end of radiotherapy

All patients had undergone postoperative conventionally fractionated external-beam radiotherapy (EBRT) with or without chemotherapy. Thirty-three patients had received limited field EBRT (with margins around enhancing lesions in the order of 2 cm), and 3 patients had undergone EBRT with whole brain fields. Median radiation dose was 50 Gy (range, 27.5–60 Gy) in daily fractions of 2–2.5 Gy. Thirty-two patients had undergone combined EBRT and chemotherapy after surgery. Chemotherapy regimens were changed in 2000. From 1990 to 1999, 20 patients were treated with nimustine hydrochloride transcatheter arterial infusion. After 2000, 12 patients were treated with carboplatin and etoposide intravenous infusion.

Imaging

SPECT imaging was started at 10 minutes (early) and 2 hours (delayed) after 111 MBq of ^{201}Tl injection. SPECT imaging was performed using a four-head gamma camera (SPECT2000H-40, Hitachi Medical Corp., Tokyo, Japan) equipped with a low-energy, general-purpose collimator (until February 1999) and a three-head gamma camera (GCA9300-A, Toshiba Medical Corp., Tokyo, Japan) equipped with a low-energy, high-resolution collimator (from March 1999). Data were acquired with a 64 × 64 matrix, 20 seconds per projection for 64 projections in the four-head gamma camera, and with a 128 × 128 matrix, 75 seconds per projections for 45 projections (15 projections in each of three cameras) in the three-head gamma camera. Transaxial images were reconstructed by filtered back-projection with Ramp and Butterworth filters (cut-off 0.25/cm, order 10 in the four-head gamma camera, and cut-off 0.10/cm, order 8 in the three-head gamma camera). Attenuation correction was not performed.

Data Analysis

The axial slice with the highest count activity within the lesion identified on MR imaging or CT was chosen for quantitative analysis. A circular region of interest (ROI) was placed manually over the lesion on the slice showing greatest activity. The size of ROI was variably defined as surrounding the greatest activity area in the tumor. The contralateral ROI was drawn as a mirror image of the lesion ROI and manually moved in the area of presumably healthy brain. When the tumor was located in the midline area, the contralateral ROI was manually placed in the normal brain surrounding the tumor. Radioactivity ratios of tumors to contralateral normal brain (T/N ratios) were thus calculated; if accumulation of tracer in the tumor was not detected, the T/N ratio was defined as 1.

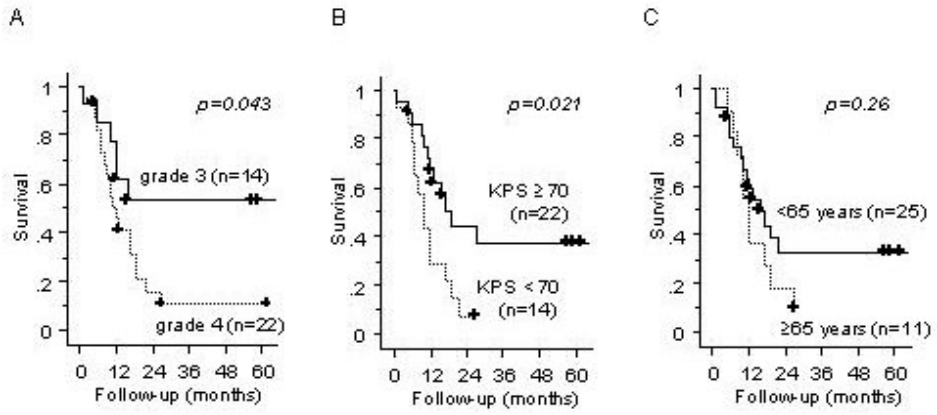

Fig. 1 Kaplan-Meier cumulative survival curves from the end of radiotherapy in all patients with malignant glioma according to histological grade (grade 3 vs. grade 4) (A), Karnofsky performance status (KPS, <70 vs. ≥70) (B), and age (<65 years vs. ≥65 years) (C). Differences between the survival curves were assessed by the log-rank test.

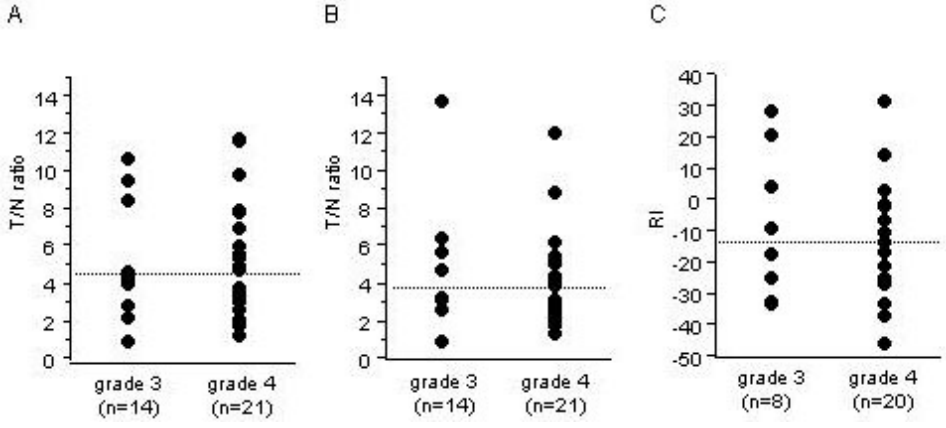

Fig. 2 Scattergrams of early T/N ratios (A), delayed T/N ratios (B), and retention indices (RIs) (C). Dashed lines represent mean values.

Patients were divided into two groups for early and for delayed images; those with low T/N ratios (less than the average T/N ratio) and those with high T/N ratios (equal or greater than the average T/N ratio). We compared outcome between these groups. Retention index (RI) was calculated as follows: RI = (delayed T/N – early T/N)/ early T/N × 100 (%). We also divided the patients into two groups with respect to RI, a low RI group (RI less than the average) and a high RI group (RI equal or greater than the average), and compared outcome between them. Of the patients with grade 4 glioma, early SPECT data were not available in one case due to patient movement, and delayed SPECT data were not available in another case because of the treatment schedule. As RI could not be calculated when no definite tumor accumulation of ^{201}Tl was appreciated and when early or delayed ^{201}Tl-SPECT data were unavailable, RI was calculated for 28 patients. We also investigated the relationship of outcome to the following clinical variables: histological grade (grade 3 or grade 4), gender (male or female), age (<65 years or ≥65 years), Karnofsky performance status (KPS) (<70 or ≥70), total irradiation dose (<50 Gy, 50 Gy, or 60 Gy), and concurrent chemotherapy (with or without).

Survival duration was measured from the end of radiotherapy. Cumulative survival rates were obtained using the Kaplan-Meier method and compared using the log-rank test, p values less than 0.05 were considered statistically significant. The interaction of each prognostic factor and its effect on survival was using the Cox proportional hazards model. Crude and adjusted rate ratios and their 95% CIs were calculated. Statistical analysis was performed with StatView for Windows version 5.0 (SAS Institute Inc., Cary, NC).

RESULTS

Significant differences were evident in outcome between the histological grades (Fig. 1). Median survival time was

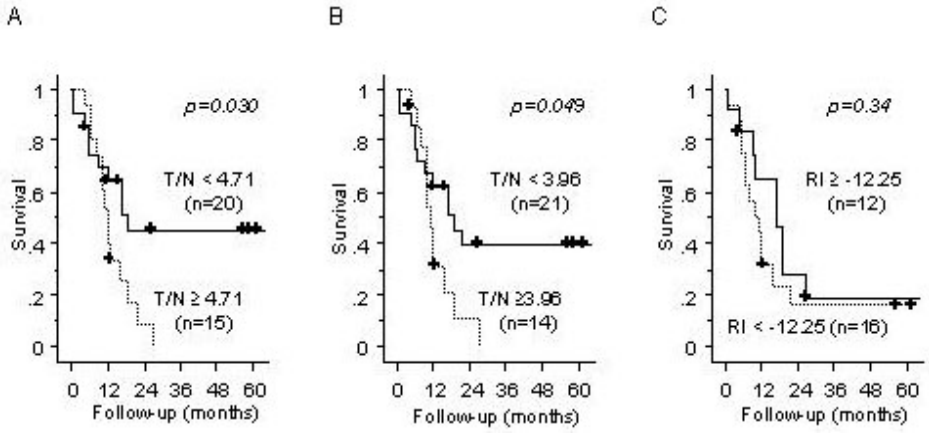

Fig. 3 Kaplan-Meier cumulative survival curves from the end of radiotherapy in all patients with malignant glioma, according to presence of low vs. high T/N ratios (early (A), delayed (B)), and RIs (C). Differences between the survival curves were assessed by the log-rank test.

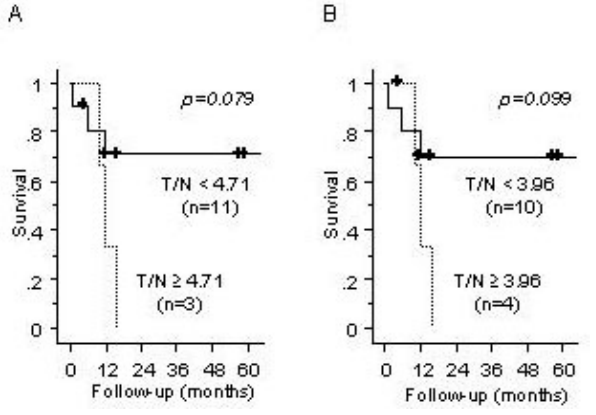

Fig. 4 Kaplan-Meier cumulative survival curves from the end of radiotherapy in patients with grade 3 glioma, according to presence of low vs. high T/N ratios (early (A), delayed (B)). Differences between the survival curves were assessed by the log-rank test.

12 months in both grades; however, two-year survival was 53% in grade 3 and 15% in grade 4. Neither gender (p = 0.71), age (p = 0.26), total irradiation dose (p = 0.16), nor concurrent chemotherapy (p = 0.084) affected survival; however, higher KPS was associated with longer survival than lower KPS (p = 0.021) (Fig. 1).

Mean T/N ratio was 4.71 in the early images and 3.96 in the delayed images. Both early and delayed T/N ratios exhibited wide variance, and substantial overlap of T/N ratio was found between grade 3 and grade 4. Mean RI was −12.25. Wide variance in RI was also evident (Fig. 2).

In both early and delayed images, patients with low T/N ratios had a significantly better outcome than those with high T/N ratios (early: p = 0.030, delayed: p = 0.049, Fig. 3). For example, using early T/N ratios, two-year survival rate was 45% in the low T/N group but only 8.3% in the high T/N group. No significant difference in survival was

Table 2 Summary of 3 patients with grade 3 glioma showing high T/N ratios on both early and delayed ^{201}Tl-SPECT images

	Patient 1	Patient 2	Patient 3
Histological grade	3	3	3
Gender	male	male	male
Age (years)	68	71	12
KPS	60	60	90
Early T/N ratio	10.72	9.54	8.49
Delayed T/N ratio	13.79	6.51	5.72
Retention index (%)	28.64	−31.76	−32.63
Radiation dose (Gy)	50	50	50
Prognosis (months)*	10	12	16

KPS; Karnofsly performance status
* Duration from end of radiotherapy

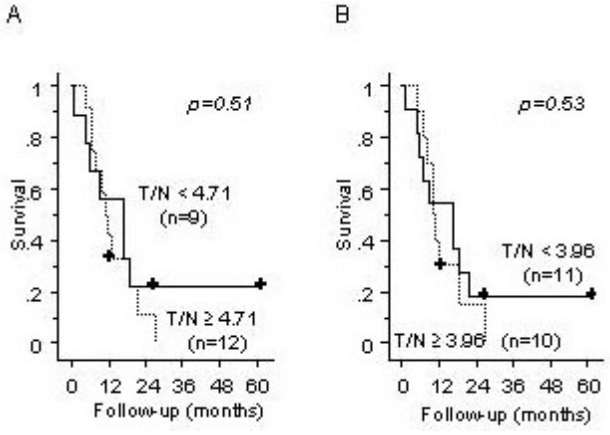

Fig. 5 Kaplan-Meier cumulative survival curves from the end of radiotherapy in patients with grade 4 glioma, according to presence of low vs. high T/N ratios (early (A), delayed (B)). Differences between the survival curves were assessed by the log-rank test.

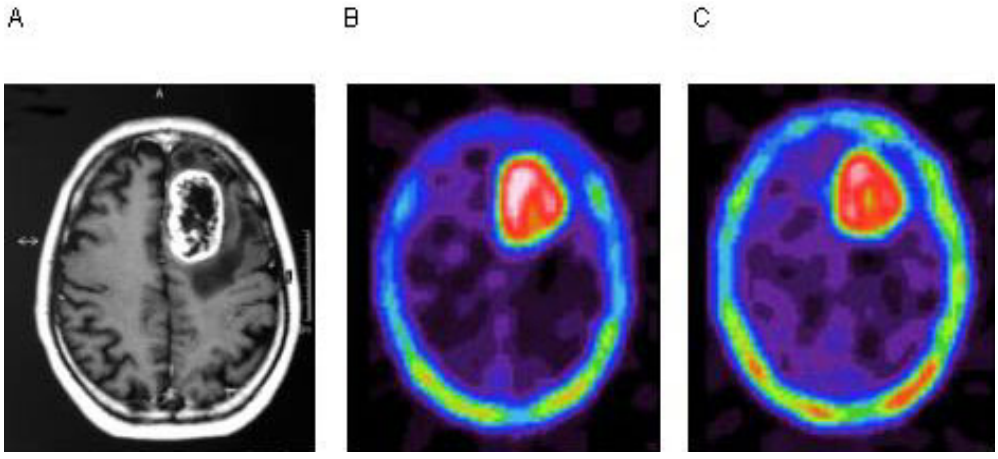

Fig. 6 A 56-year-old man with glioblastoma (grade 4) in the left frontal lobe. MR image before therapy shows a ring-like well-enhanced lesion on gadolinium contrast-enhanced T1-weighted image (Gd-T1WI) (A). Intense tumor uptake with high T/N ratios (early: 9.88, delayed: 6.25) was seen on both the early (B) and the delayed (C) ^{201}Tl-SPECT images. Total tumor resection and postoperative external beam irradiation (total 50 Gy) were performed, but this patient died of related disease 10 months after radiotherapy.

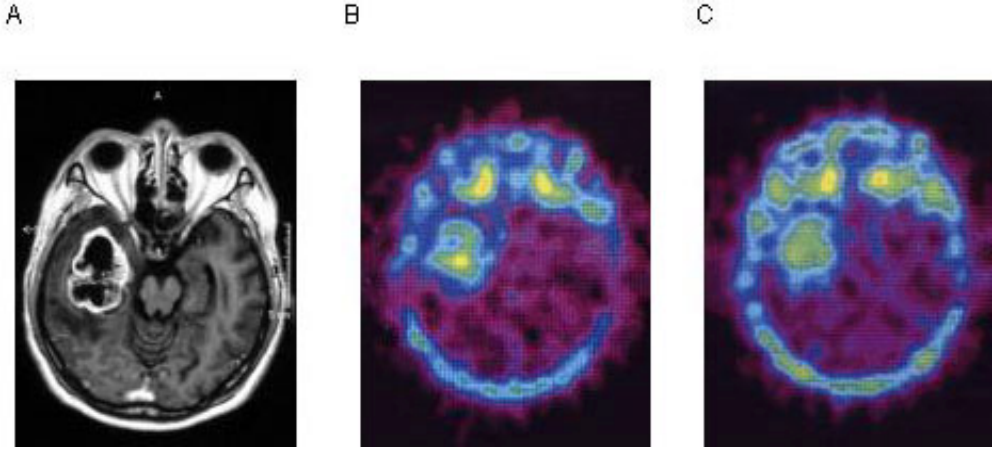

Fig. 7 A 64-year-old man with glioblastoma (grade 4) in the right temporal lobe (Table 3; Patient 2). MR image before therapy shows a ring-like well-enhanced lesion on gadolinium contrast-enhanced T1-weighted image (Gd-T1WI) (A). Tumor uptake was seen on both the early (B) and the delayed (C) ^{201}Tl-SPECT images, but the T/N ratios of 3.87 and 2.93 fell within the low T/N ratio group. Subtotal tumor resection and postoperative external beam irradiation (total 50 Gy) were performed, and this patient remains alive at 62 months after radiotherapy.

evident between the low-RI group and high-RI group ($p = 0.34$).

Although the difference was not significant (early: $p = 0.079$, delayed: $p = 0.099$) in patients with grade 3 glioma, patients with high T/N ratios had a tendency toward poorer prognosis (Fig. 4). Two-year survival rates in patients with low T/N ratios were 71% for the early images and 70% for the delayed images, while all patients with high T/N ratios died within 16 months (Table 2).

In patients with grade 4 glioma, overall prognosis was poor, and no significant difference was evident between the high- and low-T/N groups (early: $p = 0.51$, delayed: $p = 0.53$) (Fig. 5). However, in both early and delayed images, long survival was only seen in patients with lower T/N ratios (Table 3). There are representative cases in Figure 6 and Figure 7. These two patients with grade 4 glioma showed a similar enhanced pattern on gadolinium contrast-enhanced T1-weighted MR images; however, one (Fig. 6) died 10 months after radiotherapy and his preoperative ^{201}Tl-SPECT showed high T/N ratios, while the other (Table 3; Patient 2, Fig. 7) remains alive at 62 months after radiotherapy and his preoperative ^{201}Tl-SPECT showed low T/N ratios.

In univariate analysis, significant differences were seen

Table 3 Summary of 2 patients with grade 4 glioma showing low T/N ratios on both early and delayed ^{201}Tl-SPECT images

	Patient 1	Patient 2
Histological grade	4	4
Gender	female	male
Age (years)	76	64
KPS	60	70
Early T/N ratio	2.13	3.87
Delayed T/N ratio	2.11	2.93
Retention index (%)	–0.94	–24.29
Radiation dose (Gy)	50	50
Outcome (months)*	27†	62†

KPS; Karnofsky performance status
* Duration from end of radiotherapy
† Alive

Table 4 Multivariate analysis of prognostic factors

		Rate ratio	95% CI	p Value
KPS	< 70	1.7	0.7–4.0	0.24
	≥ 70	1.0		
Histological grade	grade 3	0.6	0.2–1.7	0.33
	grade 4	1.0		
Early T/N ratio	High	1.7	0.7–4.2	0.25
	Low	1.0		

KPS; Karnofsky performance status

in KPS, histological grade, and T/N ratios, whereas multivariate analysis showed no significant difference (Table 4).

DISCUSSION

Several large trials have analyzed a wide range of prognostic factors in patients with malignant glioma, and these trials have consistently shown that age, performance status, mental status, tumor grade and histology, and extent of surgical resection are the most significant prognostic factors influencing survival.[3] Jeremic et al. reported that age, KPS, size, and extent of surgery were independent prognosticators of survival/progression-free survival.[2] The present study showed that while KPS was a statistically significant prognostic factor of survival, age was not (Fig. 1).

One of the important prognostic factors identified is tumor histological grade. However, discrepancies are often experienced in this regard. While the present study demonstrated histological grade to be a statistically significant prognostic factor, some patients with grade 3 glioma exhibited a poor outcome, while some patients with grade 4 tumors survived for a relatively long period.

^{201}Tl scintigraphy has been widely used to detect various tumors. ^{201}Tl SPECT has been reported to be a non-invasive tool not only for the detection of glioma but also for the prediction of both tumor type and histological grade.[11] However, while many previous ^{201}Tl SPECT studies have been directed at evaluating the therapeutic effect or detecting tumor recurrence,[11–16] the literature contains few reports regarding the usefulness of preoperative ^{201}Tl SPECT in evaluating post therapeutic prognosis.[17–20]

Previously, Oriuchi et al. reported a positive correlation between ^{201}Tl uptake and proliferation activity estimated by bromodeoxyuridine (BUdR) labeling and suggested that ^{201}Tl could potentially be an effective medium for characterizing tumor proliferation.[17] They also reported that mean ^{201}Tl index and BUdR-labeling index were significantly associated with patient death. However, they did not investigate the correlation between ^{201}Tl uptake and survival. Higa et al. reported that ^{201}Tl-SPECT results were correlated with histological grade and were correlated most closely with outcome, identifying a group at high risk of dying from the disease.[18] Their study investigated the correlation between ^{201}Tl uptake and survival; however they assessed the degree of ^{201}Tl uptake by visual grading. In addition, because Higa et al.'s study included low grade gliomas, it would appear inadequate for assessing differences in prognosis for malignant glioma. Kosuda et al. reported that the lesion/normal (L/N) ratio was very useful in predicting survival of patients with grade 3 glioma or a solitary cerebral metastasis, when evidence of a mass lesion persisted after the initial combined modality treatment. On the other hand, the L/N ratio did not predict survival of grade 4 glioma patients in whom a mass lesion was apparent after the initial combined modality treatment.[19] In our preoperative ^{201}Tl-SPECT study, patients with low T/N ratios demonstrated a significantly better outcome than those with high T/N ratios. In grade 3 glioma, patients with high T/N ratios exhibited a poorer outcome than those with low T/N ratios. In grade 4 glioma, although overall outcome was poor, long survival was only seen in patients with low T/N ratios.

^{201}Tl uptake may be related to a combination of factors including regional cerebral blood flow, blood brain barrier permeability, and cellular uptake that may involve transmembrane transport into viable tumor cells.[16,22] Some authors have commented that ^{201}Tl-SPECT delayed images and RI are useful in differentiating benign thyroid tumors and thoracic lesions from malignancy.[9,10] With regard to brain tumors, studies have demonstrated these indices to be useful,[21,22] but only in distinguishing low-grade from high-grade tumors. ^{201}Tl-SPECT delayed images and RI have not been shown to be valuable in distinguishing grade 3 from grade 4 glioma or in prediction of survival of malignant glioma. The present study investigated delayed ^{201}Tl-SPECT images; however, we could not demonstrate any superiority of delayed over early imaging. Hence, RI was not a significant predictor of survival in malignant glioma. Indeed many studies of ^{201}Tl-SPECT in malignant glioma mentioned only early

images.[4,12,14,15,17–20]

In the present study, overall outcome of patients with grade 4 glioma was poor; however, long survival was seen only in patients with low T/N ratio. Hence, ^{201}Tl-SPECT might reflect outcome better than histological grade. This might be explained by the fact that although resected specimens contained few aggressively malignant elements, pathologists classified tumors as grade 4. Accordingly, tumor accumulation of ^{201}Tl (in other words, T/N ratio in this study) appears to be averaged (reduced) when the proportion of tissue with higher uptake is small.

On the other hand, in grade 3 glioma, a clear trend was evident; patients with high T/N ratios exhibited a poorer outcome than those with low T/N ratios. The heterogeneous nature of glioma might lead to high histological sampling variation, thereby reducing the reliability of histological diagnosis.[20] For example, a patient with high T/N ratio (Table 2; Patient 1) was histologically diagnosed as having grade 3 glioma, but his post-therapeutic survival was poor. Postoperative MR imaging showed residual tumor at the site of a hot spot seen on preoperative ^{201}Tl-SPECT. It seems likely that the residual mass contained more malignant cells than the rest of the tumor, and hence grade might have been underestimated. We did not investigate the correlation between residual tumor and the site of hot spots on ^{201}Tl-SPECT in other individual cases. However, this might enable us to reduce discrepancies between histological grade and prognosis by recommending that the neurosurgeon performs biopsy as close as possible to the hot spot on ^{201}Tl-SPECT. Moreover, presence of residual tumor at the site of a hot spot on preoperative ^{201}Tl-SPECT, might justify increasing the focal dose of postoperative radiotherapy using stereotactic radiosurgery or intensity-modulated radiation therapy.[23,24]

Patients with high T/N ratios exhibited a poorer outcome than those with low T/N ratios in grade 3, but there was no significant difference in this study. Additionally, multivariate analysis could not show any independent prognostic factor. The smaller number of patients may be one of the limitations and have influenced the results. However, this study indicates that ^{201}Tl uptake in malignant glioma could predict outcome. Further investigation is needed.

Recently, perfusion MR, MR spectroscopy, and ^{11}C-methionine PET have been reported as prognostic markers in patients with gliomas.[5,6,25] Kim et al. reported that ^{11}C-methionine PET was an independent significant prognostic factor and ^{11}C-methionine uptake was correlated with cellular proliferation.[25] However, this study investigated about gliomas including low grade. About perfusion MR, Lev et al. reported that gadolinium-based relative cerebral blood volume (rCBV) maps could be a marker of high-grade glioma, and degree of normalized CBV elevation was a stronger predictor of both tumor grade and survival than was degree of enhancement.[5] In addition, Tarnawski et al. reported about MRS that the strongest prognostic factor was lactate/*N*-acetyl aspartate (NAA) ratio in postoperative patients with malignant gliomas.[6] Comparative studies of these modalities and ^{201}Tl-SPECT would be recommended.

CONCLUSION

In the present study, patients with low T/N ratios exhibited significantly better prognosis than those with high T/N ratios. In grade 3 glioma, patients with high T/N ratios exhibited a poorer outcome than those with low T/N ratios. In grade 4 glioma, long survival was only seen in patients with lower T/N ratios. These results indicate that ^{201}Tl uptake in malignant glioma could predict prognosis. Hence, ^{201}Tl-SPECT could potentially be useful in the management of malignant glioma.

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