3-[123I]Iodo-α-methyl-L-tyrosine uptake in cerebral gliomas: relationship to histological grading and prognosis

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Abstract. 3-[123I]Iodo-α-methyl-L-tyrosine (IMT) is employed clinically as a tracer of amino acid transport in brain tumours using single-photon emission tomography (SPET). This study investigates the role of IMT SPET in the non-invasive histological grading and prognostic evaluation of cerebral gliomas. The files of patients investigated by IMT SPET in our clinic between 1988 and 1996 were evaluated retrospectively. Complete follow-up was available for 58 patients with cerebral gliomas investigated by IMT SPET shortly after tumour diagnosis. Seventeen patients had low-grade gliomas (WHO grade II), 14 had anaplastic gliomas (WHO grade III) and 27 had glioblastomas (WHO grade IV). Thirty-six cases were primary tumours and 22 cases, recurrences. Maximal and mean tumour-to-brain (T/B) ratios of IMT uptake at the first IMT SPET investigation were related to histological grading and survival time. Patients with low-grade gliomas showed significantly longer survival than patients with high-grade (grade III or IV) tumours. Gliomas without contrast enhancement on computed tomography or magnetic resonance imaging scans were associated with longer patient survival than tumours with contrast enhancement. The T/B ratios of IMT SPET showed no differences in relation to histological grading [WHO grade II: 1.73±0.59; WHO grade III: 1.74±0.38; WHO grade IV: 1.59±0.35, (mean±SD, T/B ratios of mean tumour uptake)]. The median survival time of patients with a high T/B ratio on IMT SPET was not significantly different from that of patients with a low T/B ratio (T/B ratio <1.6, 14.8 months; T/B ratio ≥1.6, 13.0 months). Thus, no evidence could be found for a relationship between IMT uptake in cerebral gliomas and either histological grading or survival time. Nevertheless, IMT SPET constitutes a useful method for the detection of primary and recurrent gliomas, determination of tumour extent and individual follow-up.

Keywords: Amino acids – 3-[123I]Iodo-α-methyl-L-tyrosine – Cerebral gliomas – Histological grading – Prognosis

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Introduction

Radiolabelled amino acids such as [methyl-11C]-L-methionine (MET), used in conjunction with positron emission tomography (PET), offer considerably improved diagnosis of cerebral gliomas as compared with conventional radiological methods [1, 2]. One advantage of using amino acids appears to be the visualization of the degree of intracerebral infiltration by gliomas [3, 4]. The introduction of the amino acid analogue 3-[123I]iodo-α-methyl-L-tyrosine (IMT) as a tracer for single-photon emission tomography (SPET) has enabled the widespread application of this technique [5, 6]. Although IMT is not incorporated into cerebral proteins [6, 7], this tracer shows similar results compared with the standard tracer MET [8, 9]. This phenomenon is explained by the fact that transport plays a dominant role in the increased accumulation of amino acids in cerebral gliomas [10, 11]. A number of clinical studies have indicated the potential of IMT SPET in the diagnostic evaluation of cerebral gliomas [12, 13, 14].

The role of IMT SPET in the determination of tumour grade in cerebral gliomas is a matter of controversy. While some authors have reported a high accuracy of IMT SPET for the differentiation of high-grade (grade III or IV) from low-grade gliomas [13, 15], others have not been able to confirm this observation [16, 17]. No data have so far been published concerning IMT uptake in gliomas and the survival time of patients. This retrospective study was performed with the specific purpose of assessing the prognostic value of IMT SPET in patients with cerebral gliomas.

Materials and methods

Patients. The files of patients investigated by IMT SPET in our clinic between 1988 and 1996 were evaluated retrospectively. Fifty-eight patients (38 male and 20 female patients; age range 23–78 years) with cerebral gliomas and available information on histological grading and survival time were included in the study. Survival time was measured from the time of first diagnosis of the primary tumour or the tumour recurrence. Histological evaluation was performed on tissue sections obtained by either stereotactic biopsy (16 patients) or open resection (42 patients). All tumours were histologically re-evaluated by two neuropathologists (G.R., J. F.) according to the recent World Health Organisation (WHO) Classification of Tumours of the Nervous System [18]. The histological re-evaluation was carried out blinded with respect to IMT SPET findings and patient survival.

Seventeen patients had low-grade gliomas (WHO grade II), 14 suffered from anaplastic gliomas (WHO grade III) and 27 were diagnosed with glioblastoma (WHO grade IV). Thirty-six cases were primary tumours and 22 cases, tumour recurrences. Quantitative data on the expression of the tumour proliferation antigen Ki-67 were determined for a subset of 25 tumours. Further details of the patients and the histological diagnoses are summarized in Table 1. Permission for the diagnostic application of IMT in patients with brain tumours was obtained from federal authorities. All subjects had given written informed consent for the IMT SPET investigation.

SPET. IMT was prepared as previously described with a specific activity of >170 TBq/mmol (>4,500 Ci/mmol) [19]. Thirty minutes prior to the SPET study, the patients received 900 mg sodium perchlorate to block possible uptake of free radioiodide by the thyroid. SPET acquisitions with a duration of 35 min were started 10–15 min after intravenous injection of 370–550 MBq IMT. Patients admitted between 1988 and April 1991 (n=22) were investigated with a single-head SPET system (Philips Diagnost Tomo-Gamma camera, Shelton, Conn.). A 30° slant hole collimator and a special head holder were used to allow a minimum radius of rotation so that a resolution of 14 mm full-width at half-maximum was achieved. Patients admitted after April 1991 (n=36) were investigated with a triple-head SPET system (TRIONIX, Ohio) equipped with ultra-high-resolution fan-beam collimators. All SPET data were reconstructed by filtered back-projection using a Butterworth filter (0.35 high cut, 3.0 roll-off) and corrected for attenuation according to Chang (first order μ=0.1) using a contour-finding procedure for each slice. No scatter correction was performed. Data with the single-head SPET system and the triple-head SPET system were comparable with respect to tumour-to-brain (T/B) ratios as tested with a brain phantom using [^{123}I]NaI as the radiation source.

Data analysis. The SPET data were evaluated by regions of interest (ROIs) placed on the tumour and an area of normal brain according to corresponding computed tomography (CT) or magnetic resonance imaging (MRI) scans, which were performed within a few days before or after the SPET studies. The tumour uptake was quantified in terms of the T/B using the average count rate per pixel in each region.

For the patient data acquired with the triple-head SPET system (n=36), a program for tumour delineation and calculation of mean and maximal tumour uptake was used which takes into account the mean background activity and is thus optimized for the problem of tumour definition in IMT SPET [20]. The program includes all slices containing a tumour in the calculation of T/B ratios.

The computer program could not be applied to the patient data acquired with the single-head SPET system (n=22) because the software was not compatible with the older computer system (PDP 11, DEC). Therefore, the data of these patients are based on the manual analysis carried out by an experienced physician, and only mean T/B ratios are available for these patients. It has been shown, however, that the determination of mean tumour values by an experienced observer does not differ significantly from the data produced with the computer program [20].

Statistical analysis. Values are expressed as mean±standard deviation. Statistical methods used were t test for group comparisons, and the Mann-Whitney rank sum test when the normality or equal variance test failed. For the evaluation of survival time and prognosis, the study group was divided into a subgroup that had values or ratios lower than the median and a subgroup that had values or ratios equal to or higher than the median [21]. Comparison of survival between the two subgroups was performed using the Kaplan-Meier life-table method [22] and the log-rank test. Probability values less than 0.05 were considered significant.

Results

The general characteristics of the patient group were comparable to those reported in the literature [23]. Patients with WHO grade II gliomas showed a longer median survival time than patients with WHO grade III or IV gliomas (34.6 months, n=17 vs 10.6 months, n=41, P<0.01). Patients aged 50 years or older showed a shorter median survival time than patients younger than 50 years, especially in the group with high-grade gliomas (8.1 months, n=17, vs 16.5 months, n=24, P<0.03). Patients with a Ki-67 index <5% showed a tendency towards a longer median survival time than patients with a Ki-67 index >5% (33.2 months, n=11 vs 18.8 months, n=14, P=0.06). Patients without contrast enhancement on CT or MRI scans showed significantly longer survival than patients with contrast enhancement (32.2 months, n=9 vs 10.6 months, n=23; median, P=0.05). There were no significant differences in survival time with respect to tumour localization, extent of surgical resection or gender.

Table 1. Patient details, histological diagnoses, T/B ratios and survival times

Pat. no.	Age (yrs)	Gender	Histological-diagnosis	Primary/ recurrent tumour	T/B (mean)	T/B (max)	Survival time (months)
1	66	M	GBM IV	PT	1.59	1.93	14.8
2	36	M	AO III	PT	1.92	–	55.6
3	60	M	GBM IV	PT	1.42	1.70	15.0
4	23	F	GBM IV	RT	1.64	2.15	8.1
5	65	F	GBM IV	PT	1.40	–	1.4
6	38	M	GS IV	PT	1.52	1.98	3.0
7	46	M	AA III	PT	1.41	1.81	32.9
8	48	M	GBM IV	PT	1.39	1.92	3.5
9	51	M	AOA III	RT	1.60	2.76	29.6
10	56	M	GBM IV	RT	1.80	–	7.9
11	60	F	AA III	PT	1.60	–	2.3
12	56	M	AOA III	RT	1.93	2.93	5.0
13	28	F	A II	PT	2.29	4.75	38.2
14	38	M	GBM IV	RT	1.98	3.15	0.6
15	35	F	AO III	RT	2.32	3.25	36.6
16	49	M	AO III	RT	1.59	2.72	28.9
17	50	M	GS IV	RT	1.54	2.08	4.5
18	71	F	GBM IV	PT	1.00	–	4.4
19	68	M	GBM IV	PT	1.00	–	5.3
20	65	F	GBM IV	RT	1.61	2.42	22.2
21	70	F	GBM IV	RT	1.10	1.73	7.7
22	50	M	A II	PT	1.00	–	54.8
23	54	M	GBM IV	PT	1.40	–	5.6
24	47	F	GBM IV	RT	1.10	–	17.4
25	57	M	GBM IV	RT	1.86	2.97	5.9
26	64	M	GBM IV	PT	1.58	2.41	10.6
27	37	M	GBM IV	RT	1.82	3.04	12.0
28	47	M	OA II	PT	1.43	2.09	35.5
29	42	F	A II	PT	1.80	3.05	48.5
30	56	M	A II	PT	1.52	2.41	42.1
31	53	M	A II	PT	1.83	2.80	34.6
32	56	F	AA III	PT	1.72	3.35	15.8
33	38	F	AA III	PT	1.39	1.72	32.2
34	44	M	A II	PT	0.99	–	0.1
35	43	M	A II	PT	2.07	3.18	51.3
36	50	M	AO III	PT	2.00	–	18.4
37	54	F	A II	PT	1.77	3.15	29.8
38	78	M	GBM IV	PT	1.00	–	2.3
39	50	M	A II	PT	1.52	2.46	1.5
40	56	M	GBM IV	PT	1.90	–	0.6
41	62	M	A II	PT	1.78	2.93	60.5
42	24	M	GBM IV	PT	1.50	1.98	18.7
43	32	F	A II	RT	1.49	1.95	32.3
44	42	F	A II	PT	1.00	–	7.4
45	25	M	AA III	RT	0.99	–	14.9
46	55	F	GBM IV	PT	2.50	–	0.8
47	48	M	AO III	PT	1.60	–	0.1
48	33	F	GBM IV	RT	1.00	–	12.8
49	40	M	GBM IV	PT	1.84	3.44	9.4
50	59	F	A II	RT	2.11	4.05	13.0
51	53	M	A II	RT	1.80	–	1.7
52	56	M	GBM IV	PT	1.70	–	2.2
53	49	M	A II	PT	3.50	–	1.5
54	56	F	AO III	RT	2.44	3.56	19.9
55	32	M	AA III	RT	1.89	–	14.1
56	51	M	GBM IV	PT	1.55	2.56	15.6
57	60	M	GBM IV	RT	1.53	2.50	16.1
58	49	F	A II	RT	1.57	2.08	44.9

M, Male; F, female; A II, astrocytoma WHO grade II; AA III, anaplastic astrocytoma WHO grade III; AO III, anaplastic oligodendroglioma WHO grade III; OA II, oligoastrocytoma WHO grade II; AOA III, anaplastic oligoastrocytoma WHO grade III; GBM IV, glioblastoma multiforme WHO grade IV; GS IV, gliosarcoma WHO grade IV; PT, primary tumour; RT, recurrent tumour; T/B, tumour/brain ratio; –, data not available

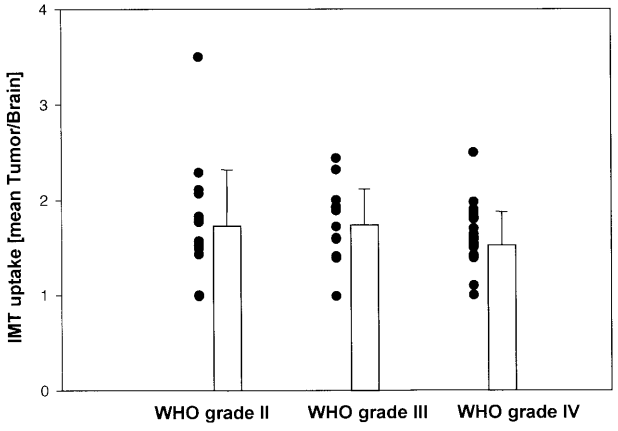

Fig. 1. Tumour/brain ratios of IMT uptake (mean tumour uptake) in relation to histological grading. There is no significant difference in IMT uptake in the different tumour grades

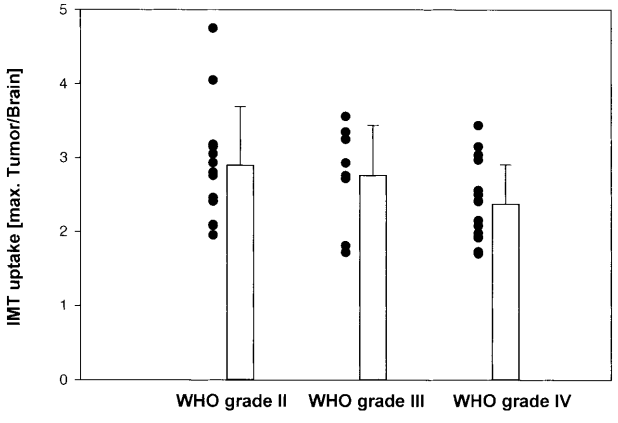

Fig. 2. Tumour/brain ratios of IMT uptake (maximal tumour uptake) in relation to histological grading. Again, there is no significant difference in IMT uptake in the different tumour grades

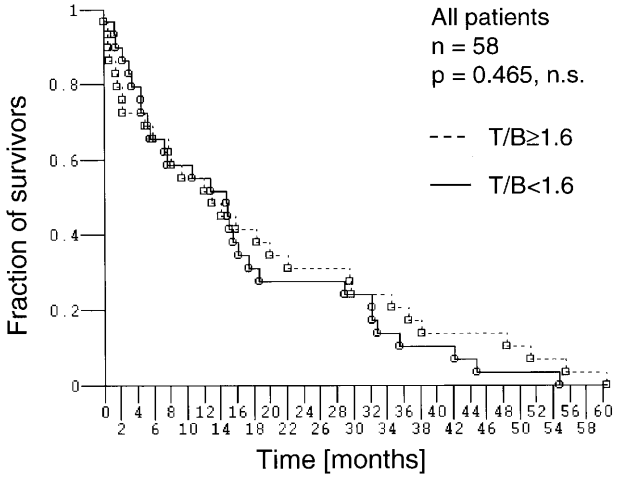

Fig. 3. Kaplan-Meier plots of survival time of all glioma patients. Patients are classified into two groups with T/B ratios of IMT uptake (mean tumour uptake) above and below the median (1.6). There is no significant difference in survival time between the two groups

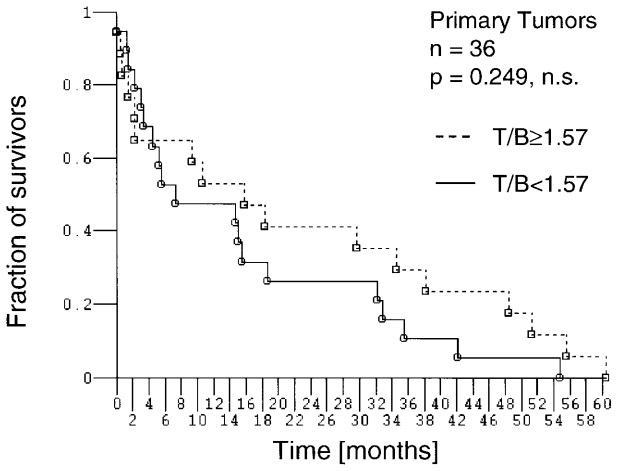

Fig. 4. Kaplan-Meier plots of survival time of glioma patients (only primary tumours). Patients are classified into two groups, according to whether the T/B ratio of IMT uptake (mean tumour uptake) was above or below the median (1.57). There is no significant difference in survival time between the two groups

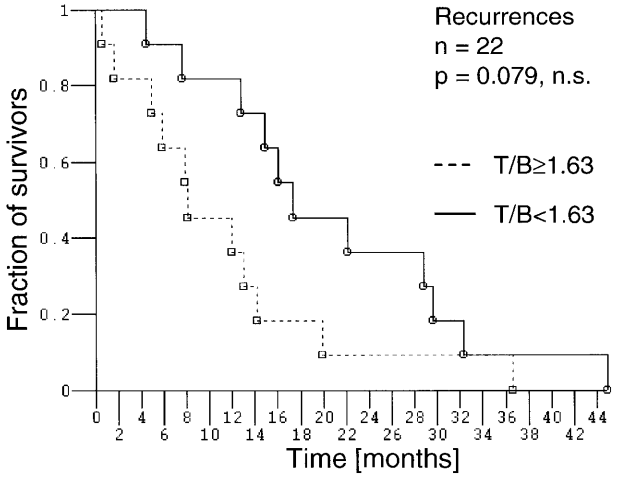

Fig. 5. Kaplan-Meier plots of survival time of patients with recurrent gliomas. Patients are separated into two groups according to whether the T/B ratio of IMT uptake (mean tumour uptake) was above or below the median (1.63). There is a tendency for longer survival among patients with lower a IMT uptake

The T/B ratios of IMT SPET (mean tumour uptake) showed no significant differences in relation to histological grading, as shown in Fig. 1 [WHO grade II: 1.73±0.59, *n*=17; WHO grade III: 1.74±0.38, *n*=14; WHO grade IV: 1.59±0.35, *n*=27 (mean±SD, NS)]. Results were similar when the T/B ratios of maximal tumour uptake were analysed [WHO grade II: 2.91±0.83, *n*=12; WHO grade III: 2.76±0.68, *n*=8; WHO grade IV: 2.37±0.54, *n*=16(mean±SD, NS)] as depicted in Fig. 2.

Using the mean uptake of the tumour ROI, the median survival time of the subgroup of patients with T/B ratios equal to or higher than the median was not significantly different from that of the subgroup of patients

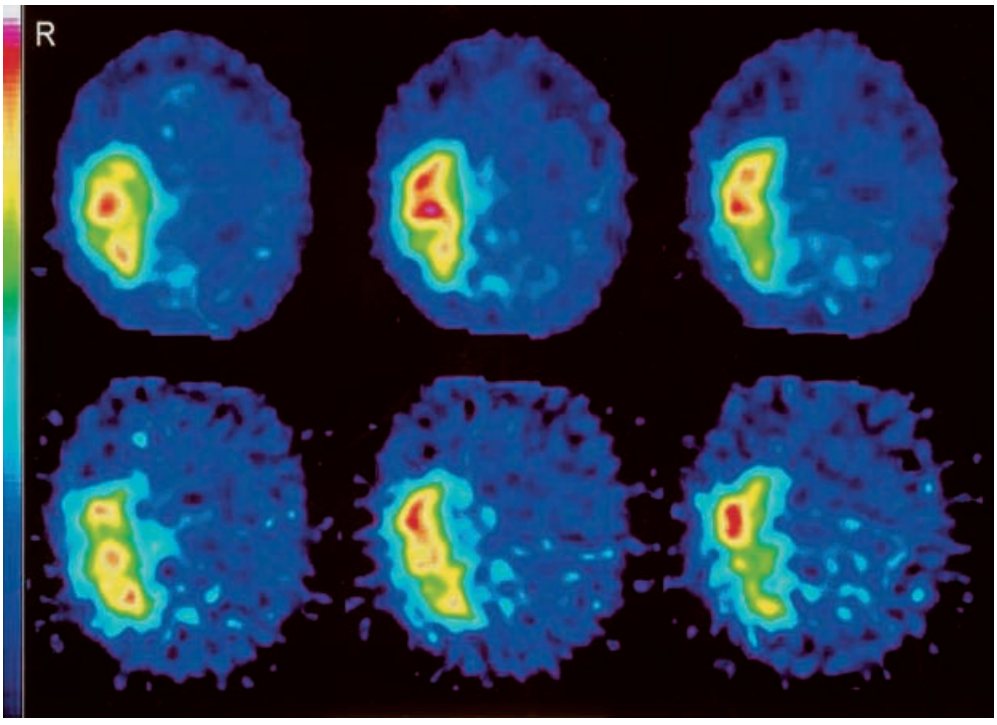

Fig. 6. SPET scans of a patient (no. 35) with an astrocytoma of WHO grade II with high IMT uptake and a favourable outcome. At the time of diagnosis (*upper row*), the tumour in the right temporal lobe exhibited a maximal T/B ratio of 3.18. The tumour was resected and the patient presented with a tumour recurrence 25 months later (*lower row*). Again, IMT uptake was high. The patient received additional radiotherapy and died 51 months after diagnosis of the primary tumour

with T/B ratios lower than the median (T/B <1.6, *n*=29, 14.8 months; T/B ratios ≥1.6, *n*=29, 13.0 months, *P*=0.465, NS, Fig. 3). The separate analysis of primary tumours (T/B <1.57, *n*=19, 7.4 months; T/B ratios ≥1.57, *n*=17, 15.8 months; *P*=0.249, NS, Fig. 4) also yielded no significant relationship between T/B ratios and survival time. For recurrent tumours there was a tendency towards longer survival among patients with T/B ratios lower than the median (T/B <1.63, *n*=11, 17.3 months; T/B ratios ≥1.63, *n*=11, 8.1 months; *P*=0.079, NS, Fig. 5). Using T/B ratios of maximal tumour uptake (peak values), which could only be obtained for the patients investigated after April 1991, the same relationship between IMT uptake and survival time was observed (data not shown).

Figure 6 demonstrates IMT SPET scans of a patient with an astrocytoma grade II in the right temporal lobe. Both the primary tumour and the tumour recurrence exhibited high IMT uptake. The patient had a favourable outcome, with a survival time of 51 months.

Discussion

The role of radiolabelled amino acids in the determination of tumour grade and prognosis in patients with cerebral gliomas is controversial. During the use of IMT SPET in the clinical management of glioma patients for more than a decade, we observed a number of patients who exhibited high tumour uptake of IMT and had an excellent clinical course with constantly high IMT uptake values.

In this retrospective follow-up study we analysed the role of IMT uptake as an indicator of the histological grading of gliomas and prognosis. We did not find any evidence for a relationship of IMT uptake in gliomas with histological grading. In addition, IMT uptake did not correlate with postoperative survival time. Only in patients with recurrent gliomas was a tendency towards longer survival with lower IMT uptake observed. The results were the same regardless of whether maximal or mean tumour uptake values were considered. A separate analysis excluding oligodendrogliomas led to the same results (data not shown).

It remains unclear why our data concerning IMT uptake and tumour grading are at variance with other publications [13, 15]. The characteristics of our patient group were comparable to those of other groups reported in the literature [23]. It can be assumed that our patient group constitutes a representative sample of the population of patients with diffuse cerebral gliomas. In order to exclude variations in the histological classification between 1989 and 1996, the histological specimens of all tumours were re-evaluated according to the current WHO classification of nervous system tumours [18]. Our results are in line with two previous studies that also did not detect a clear correlation of tumour grades with IMT SPET findings [16, 17]. These studies found fluorine-18 fluorodeoxyglucose PET to be more reliable for this purpose.

Recently, a preliminary report demonstrated significantly longer survival times in patients without IMT uptake after resection of primary brain tumours than in patients with residual IMT uptake [24]. However, these da-

ta probably reflect the known influence of total tumour resection on the prognosis of patients with cerebral gliomas, rather than supporting the predictive value of IMT uptake for individual prognosis. Thus, this particular study confirms the potential of IMT SPET for the identification of residual tumour tissue.

Studies that have used MET PET in patients with cerebral gliomas have reported a higher degree of MET accumulation in high-grade gliomas than in low-grade gliomas, although the differentiation of high-grade from low-grade gliomas appears not to be superior to that achieved when using FDG PET [1, 25, 26, 27]. A recent report demonstrated significantly longer survival times for glioma patients with a T/B ratio of MET uptake <2.1 than for those with a T/B ratio of MET uptake >2.1 [28].

In contrast to these results, PET studies using tyrosine derivatives have demonstrated a poor relationship between tracer uptake in brain tumours and histological grading. No significant correlation between tumour grading and the influx rate of 2-[^{18}F]fluoro-L-tyrosine was found in 15 patients with various brain tumours [11]. Similarly, L-[1-^{11}C]tyrosine PET revealed no correlation between the protein synthesis rate and the histological grade or proliferative activity of human brain tumours [29, 30].

It may be speculated that differences in the transport and in the physiological behaviour of MET as compared with tyrosine derivatives may account for the observed clinical differences. However, in vitro studies have demonstrated that the transport mechanisms of IMT and MET in human glioma cells are similar [31, 32]. Comparative clinical studies of MET PET versus IMT SPET and *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine PET have shown a significant correlation between the T/B ratios in glioma patients [8, 33]. IMT, however, exhibited lower T/B ratios than MET [8, 9], which may contribute to less pronounced differentiation of high-grade from low-grade gliomas as compared with that achieved using MET PET.

Given the controversial results obtained with radiolabelled amino acids for tumour grading and prognosis, we recommend that SPET or PET data on amino acid uptake in individual patients be handled with caution. However, the clinical relevance of IMT SPET for the diagnostic evaluation of gliomas is not substantially restricted by the results of our study. IMT SPET remains a very useful method to identify glioma tissue and tumour recurrence [12, 14, 34]. It can provide additional information on tumour extent (as compared to CT or MRI), and therefore is of relevance for therapy planning [35, 36] as well as for the follow-up of individual patients [37]. For the determination of grading and prognosis, FDG PET and thallium-201 SPET appear to be more useful than IMT SPET.

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