SPECT Studies of Brain Tumors with L-3-[^{123}I] Iodo-α-Methyl Tyrosine: Comparison with PET, ^{124}IMT and First Clinical Results

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L-3-[^{123}I]iodo-α-methyltyrosine (^{123}IMT) like tyrosine has been reported previously to have a high affinity for a transport system in the blood-brain-barrier (BBB). We examined the kinetic behavior of ^{124}IMT in brain and plasma in two patients with glioblastoma using dynamic positron emission tomography (PET). ^{124}IMT accumulated in brain and tumor tissue, reaching a maximum after 15 min, with a washout of 20% to 35% at 60 min postinjection. Animal experiments confirmed the accumulation of the intact tracer in murine brain, but there was no incorporation into proteins. SPECT studies with ^{123}IMT in patients with different types of brain tumors showed increased uptake in 26 of 32 tumors. Although nonspecific uptake in tumors must be considered, the accumulation of IMT in normal brain and in some tumors with intact BBB suggests a specific uptake of IMT. As transport is the main determinant of initial amino acid uptake, ^{123}IMT appears to be a suitable SPECT tracer of amino acid uptake although it is not incorporated into protein.

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The advent of positron emission tomography (PET) has made it possible to study the regional uptake and kinetics of carbon-11- (^{11}C) labeled amino acids in the human brain. L-[^{11}C]methionine proved to be particularly useful in the study of brain tumors. Some authors have reported larger tumor sizes on [^{11}C]methionine PET scans than on CT scans (*1,2*) and the relative uptake of [^{11}C]methionine correlated with the grade of malignancy (*3,4*). Also, preliminary data indicate that [^{11}C]methionine studies allow prediction of tumor response after the first cycle of chemotherapy (*4*). PET, however, is available only in a few research centers, and there is a strong demand for suitable radiotracers to conduct such studies in conventional nuclear medicine departments using single-photon emission computed tomography (SPECT). The radioiodinated amino acid analog L-3-[^{123}I]iodo-α-methyltyrosine (^{123}IMT) was used previously for scintigraphy of the pancreas and detection of melanomas (*5,6*). Recently, ^{123}IMT was proposed for brain SPECT and a large accumulation of tracer was reported in human brain tumors (*7*). A prerequisite for SPECT studies with rotating gamma camera systems is a constant tracer concentration during data acquisition. Fast changes in the uptake pattern or washout of tracer make SPECT studies impossible. Recent animal experiments suggest that IMT is a substrate of the carrier system of large neutral amino acids in the blood brain barrier (BBB), and that its uptake reflects amino acid transport (*8*). It remains unclear, however, whether the same is true for the human brain and whether the dynamics of the cerebral accumulation in man are suitable for SPECT studies. In this study, we have investigated the intracerebral kinetics of IMT with dynamic PET studies using ^{124}I-labeled IMT, to test the applicability of this tracer for SPECT studies. We have also performed further animal experiments to elucidate the metabolic fate of $^{123/124}$IMT in the brain. In addition, we present our first clinical results of brain SPECT studies with ^{123}IMT.

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MATERIALS AND METHODS

Synthesis and Metabolic Stability of L-3-[$^{123/124}$I] iodo-α-methyltyrosine

Synthesis of L-3-[$^{123/124}$I]iodo-α-methyltyrosine was performed by direct electrophilic iodination starting with no-carrier added (n.c.a.) ^{123}I or n.c.a. ^{124}I and 1 μg of carrier KI. The methods of labeling and of high-performance liquid chromatography (HPLC) for isolation and purification of the radiopharmaceutical were used as previously described (*5–7*). The specific activity was >25 TBq/mmol with a chemical purity of ≈99% and a radiochemical yield of ≈65% after sterile filtration of an isotonic solution. A synthesis with high-specific activity is recommended because of the possible pharmacologic and toxicologic effects of IMT (*9*).

In order to investigate the metabolic behavior of IMT in the brain, 0.75–1.5 MBq ^{123}IMT dissolved in 50–100 μl of 0.9% NaCl were injected via the tail vein into NMRI mice

(30 g body weight). Four animals were killed 40 min postinjection, and the brains were removed within 20 sec and frozen in liquid nitrogen. Samples of brain were weighed; their total radioactivity measured and homogenized. In some experiments, proteins were precipitated by addition of trichloroacetic acid (TCA), and the proteins were sedimented by centrifugation. The radioactivity in the pellet and supernatant was determined. The supernatant was further analyzed using HPLC for identifying unchanged ^{123}IMT and measuring its radioactivity. The protein precipitates were further separated according to their molecular weights by a discontinuous gel-electrophoresis method as recently applied for L-2-[^{18}F]fluorotyrosine (^{18}FDG) (*10*).

Tests of metabolic stability of the radioiodinated α-methyltyrosine in human blood were performed by HPLC in three patients. Blood was sampled up to two hours, heparinized, centrifuged, and aliquots of plasma were analysed for intact tracer and free radioactive iodide at different time intervals.

PET Studies

Dynamic PET studies with ^{124}IMT (^{124}I: 25% β^+ decay, maximum β^+ energy 2.1 MeV, half-life 5.15 days) were performed in two patients with glioblastoma (Patients 1 and 2 in Table 1). The tumors were inoperable because of their unfavorable location. Histopathology of the tumors was procured by stereotactic biopsy. At the time of the PET studies, both patients had been pretreated with radiotherapy (60 Gy) and several cycles of intraarterial chemotherapy using the nitrosourea ACNU. The first patients showed tumor progression in spite of these therapeutic efforts. The second patient exhibited tumor recurrence after 12 mo of remission. Informed consent to the studies was given by the patients. On each of the three days preceding the PET study, the patients received 900 mg sodium-perchlorate to block possible uptake of free ^{124}I by the thyroid. After i.v. injection of 5 mCi (185 MBq) ^{124}IMT, dynamic PET studies were implemented for 60 min in Patient 1 and for 90 min in Patient 2. The gantry of the PET scanner was positioned parallel to the orbitomeatal line. The PET studies were performed using a PET scanner (Scanditronix PC-4096-15WB), which provides 15 brain slices simultaneously with an optimum spatial resolution of 5 mm FWHM. Sixteen samples of "arterialized" venous blood were taken, and the activity of the whole blood as well as plasma were measured in a cross-calibrated well counter. The plasma input function was corrected for the non-IMT radioactivity after HPLC analysis.

Within one week before or after the ^{124}IMT-PET, a SPECT study with ^{123}IMT, a PET study with 2-[^{18}F]fluoro-deoxyglucose, as well as studies with transmission computed tomography (CT) were done.

TABLE 1
Patient Data and Results of ^{123}IMT-SPECT in 32 Patients with Brain Tumors

Patient no.	Age	Sex	Histopathology	Therapy before ^{123}IMT-SPECT			Tumor/ Cerebellum ratio
				Surg.	Rad.	Chemo.	
1	24	m	Glioblastoma	n	y	y	1.20
2	47	m	Glioblastoma	n	y	y	2.26
3	75	m	Glioblastoma	y	y	y	1.53
4	48	m	Glioma III-IV	y	y	y	1.64
5	65	f	Glioblastoma	n	n	n	1.21
6	65	f	Neurinoma	n	n	n	1.04
7	47	f	Glioblastoma	y	y	y	1.01
8	55	m	Astrocytoma III	n	n	n	1.32
9	50	f	Glioblastoma	n	n	n	2.37
10	54	f	Glioblastoma	n	n	n	1.39
11	38	f	Glioblastoma	y	y	y	1.26
12	63	f	Metastasis	n	n	n	1.89
13	45	f	Neurinoma	n	n	n	2.29
14	59	f	Glioblastoma	y	y	y	1.14
15	69	f	Glioblastoma	n	n	n	1.20
16	63	m	Astrocytoma III	n	n	n	2.54
17	71	f	Glioblastoma	n	n	n	1.18
18	47	f	Astrocytoma II	n	n	n	0.94
19	60	m	Glioblastoma	n	n	n	1.31
20	45	f	Glioma III	n	n	n	1.25
21	56	m	Glioblastoma	n	n	n	2.02
22	77	m	Glioblastoma	n	n	n	1.60
23	57	m	Glioblastoma	n	n	n	1.40
24	53	m	Astrocytoma III	y	n	n	1.40
25	48	m	Oligodendroglioma II-III	n	n	n	1.66
26	47	m	Carcinoma	n	n	n	0.65
27	54	m	Metastasis	n	n	n	1.45
28	43	m	Mixed glioma II	n	n	n	1.59
29	56	m	Astrocytoma IV	y	y	n	1.75
30	55	f	Glioblastoma	n	n	n	2.45
31	18	m	Glioma II	n	n	n	1.00
32	50	m	Glioma II	n	n	n	1.00

SPECT Studies

Iodine-123-IMT SPECT studies were performed on 32 patients with brain tumors. Information on the status of pretreatment at the time of the first SPECT study is given in Table 1. Twenty-three patients had malignant gliomas (grade III and IV), four patients benign gliomas (grade II), two patients neurinomas, two patients metastases, and one patient an intracerebral carcinoma. Because competition between ^{123}IMT and other neutral amino acids at the BBB was expected, most patients were fasted for at least 8–9 hr prior to the SPECT study to guarantee maximal tracer uptake.

The SPECT studies were started 15 min after i.v. injection of 5–10 mCi (185–370 MBq) ^{123}IMT. Sixty-four images of 35 sec each were acquired using a Philips diagnostic Tomo-Gamma-Camera (Shelton, CT) with a 30-degree slant-hole collimator (360° rotation). The 30-degree slant-hole collimator and a special head holder were used to allow a minimum radius of rotation so that a resolution of ~14 mm FWHM was achieved (*11*). The first and the last projection images were evaluated by a region of interest over the brain to measure the changes in the count rate during the acquisition. Orbitomeatal parallel slices were reconstructed by ramp-filtered backprojection. The tumor uptake was quantified in terms of the tumor/cerebellum ratio (T/C) using the average count rate per pixel in each region.

In five patients, conjugate ventral and dorsal whole-body scans were performed after the SPECT study. In another five patients, urine was collected after tracer injection. Cerebral tracer uptake was determined on the basis of the whole-body scans with a similar method as used for pharmacokinetic measurements of thallium-201 (*12*).

RESULTS

Metabolism of L-3-[^{123}I]Iodo-α-methyltyrosine

At 40 min postinjection of ^{123}IMT, the mice brain had taken up 0.8% ± 0.1% of the injected radioactivity of wet-weight of tissue. The radioactivity in brain precipitated by TCA varied form 4% to 18% (n = 8). Upon redissolving in an alkaline solution and subsequent discontinuous SDS gel-electrophoresis, all radioactivity could be eluted as a monomolecular mass fraction as show in Figure 1, confirming our expectation that there is no incorporation of IMT into protein. Furthermore, HPLC analysis shows that 40 min after injection, more than 95% of the radioactivity in brain is still present as intact IMT (n = 4), i.e., no metabolite of IMT is formed in brain or taken up from plasma. Analysis of the patient's plasma exhibits a linear decrease of radioactivity in the form of administered tracer to ~30% of total plasma activity 90 min postinjection. Free radioactive iodide in plasma increases slowly from 0.5% at 4 min to 4% of total plasma activity at 90 min postinjection.

PET Studies

The kinetics of tracer in the cerebral cortex, tumor, and plasma during the PET studies of Patients 1 and 2 are shown in Figures 2 and 3. In both patients, ^{124}IMT accumulated in brain and tumors, reaching a maximum after 15 min, which was followed by a tracer washout of 20%–35% at 60 min postinjection (Table 2). The tumor/cortex ratio remained constant between 15 and 60 min after injection in Patient 1 but showed a slight decrease of 9.4% in Patient 2.

The CT, ^{18}FDG-PET, ^{124}IMT-PET, and ^{123}IMT-SPECT scans for Patient 2 are shown in Figure 4. The tumor exhibited contrast enhancement in the CT scan and an increased ^{18}FDG uptake. The area of increased tracer uptake in the PET scan using ^{124}IMT was larger than the size of the tumor in the CT and in the ^{18}FDG-PET scan. The ^{123}IMT-SPECT study yielded nearly the same result as the ^{124}IMT-PET study. The delineation of the tumor, however, was less sharp because of the poorer resolution of the SPECT scan.

SPECT Studies

Compared to the cerebellum, 26 of 32 tumors showed an increased ^{123}IMT uptake. The values of the T/C ratio for all patients are shown in Table 1. Three of the grade II gliomas showed the same ^{123}IMT uptake as the surrounding brain and could not be identified on the SPECT scans. The intracerebral carcinoma exhibited decreased ^{123}IMT uptake compared to the surrounding brain. No significant differences in the degree of ^{123}IMT uptake between grade IV gliomas (1.55 ± 0.45, n = 18),

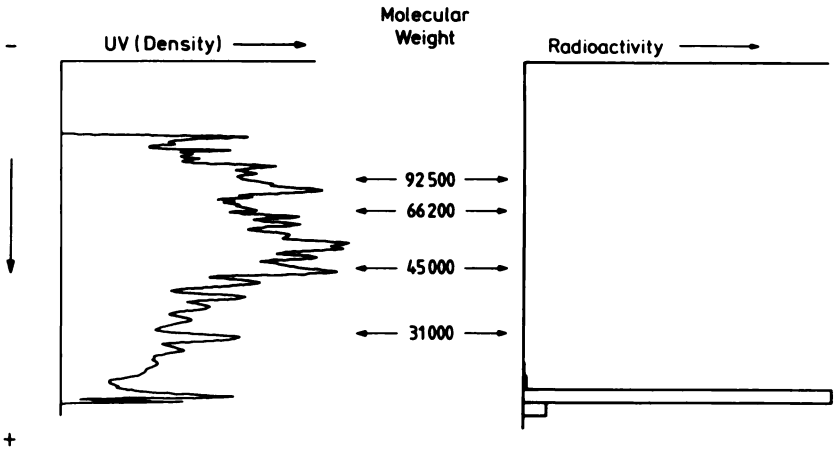

FIGURE 1
UV-absorbance and radioactivity distribution after molecular mass separation of cerebral proteins containing ^{123}IMT by discontinuous SDS gel-electrophoresis. Most of the radioactivity was contained in an apparently monomolecular fraction, indicating no incorporation into protein.

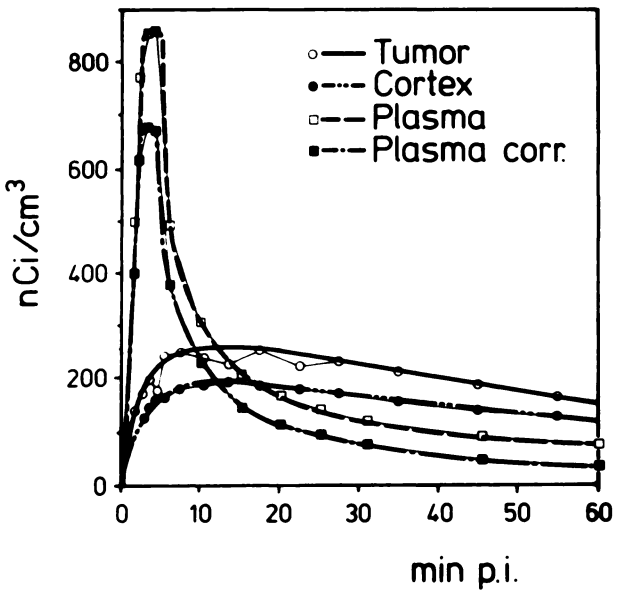

FIGURE 2
Kinetics of ^{124}IMT radioactivity in the tumor, in the cerebral cortex and in the plasma during the ^{124}IMT PET studies. The plasma input function is corrected for intact tracer.

grade III gliomas (1.63 ± 0.53, n = 5), and grade II gliomas (1.12 ± 0.28) could be identified in this group of patients. The mean decrease of count rate over the brain during the SPECT studies (15–60 min postinjection) was 34.2% ± 7.1%.

The total uptake in brain of $^{123/124}$IMT, as determined by whole-body scans (n = 5) and PET studies (n = 2), ranged from 2% to 6% of injected dose at 60 min postinjection. The urinary excretion of $^{123/124}$IMT at 60 min postinjection ranged from 40% to 70% of injected

TABLE 2
Tracer Washout and Changes of the Tumor/Cortex Ratio in the ^{124}IMT-PET Studies Between 15 min and 60 min Postinjection

	Patient 1	Patient 2
^{124}IMT washout		
Tumor	35.5%	26.7%
Cortex	35.0%	18.8%
Tumor/Cortex ratio		
15 min p.i.	1.31	2.34
60 min p.i.	1.30	2.11

dose (n = 5). Whole-body scans showed an almost equal distribution of ^{123}IMT throughout the body with a large accumulation only in the bladder. Using the MIRD Report No. 5 (*13*) and assuming the same kinetics for $^{123/124}$IMT as for sodium iodide in a hypothyroid state, the radiation dose to the whole body was estimated at 0.1 mSv/MBq, (0.36 rad/mCi) for ^{124}IMT and 0.007 mSv/MBq (0.025 rad/mCi) for ^{123}IMT.

DISCUSSION

Recent animal experiments have shown that L-3-iodo-α-methyltyrosine is a substrate of the transport system of large neutral amino acids at the BBB (*8*). This study investigated the fate of IMT in the brain. Our experiments with mice show that the tracer does, indeed, accumulate in brain tissue in sufficient amounts for tomographic studies. Iodine-123-IMT exhibits a four-fold higher uptake than that of the nonmethylated 3-iodotyrosine (*14*). The ^{124}IMT-PET studies demonstrate that IMT also crosses the human BBB and is rapidly taken up by the normal brain tissue. Because IMT is a molecule that cannot easily cross lipid mem-

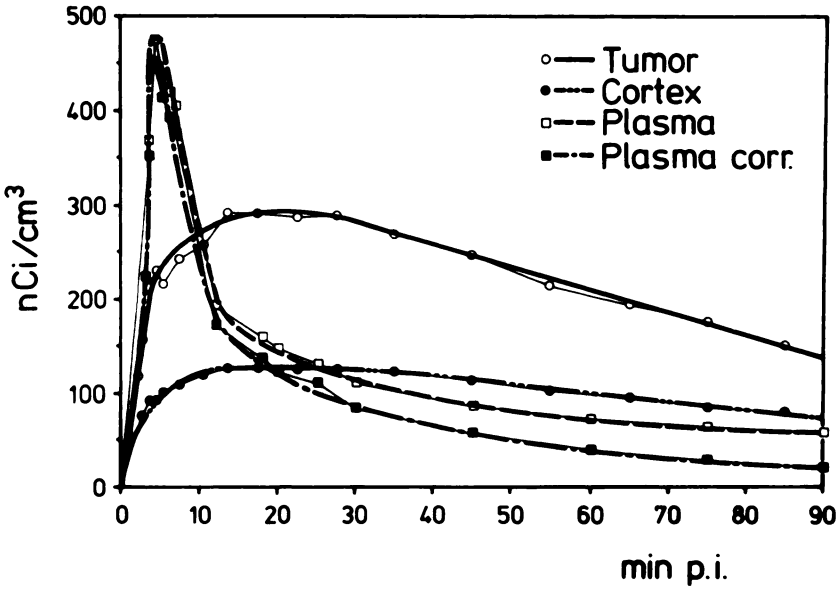

FIGURE 3
Kinetics of tracer activity in cerebral cortex, tumor and plasma during ^{124}IMT PET studies.

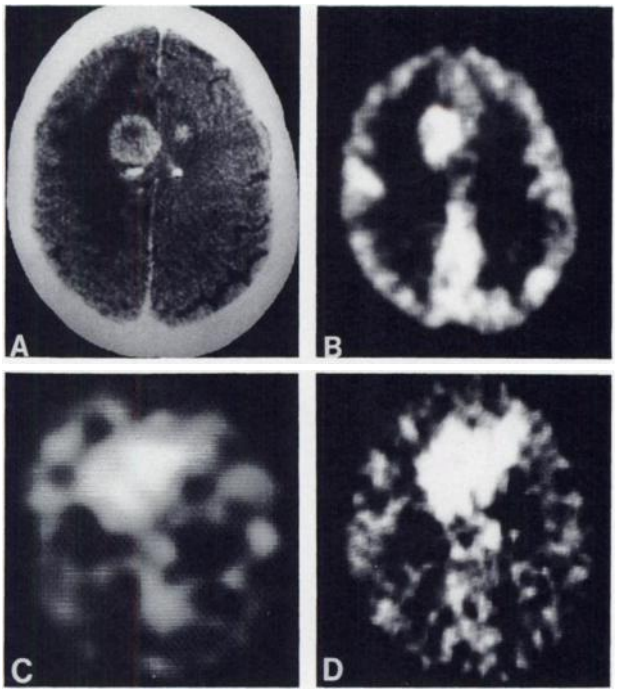

FIGURE 4
Contrast enhanced CT scan (A), ^{18}FDG-PET scan (B), ^{123}IMT-SPECT scan (C), and ^{124}IMT-PET scan (D) of Patient 2. The tumor size appears larger on the ^{124}IMT-PET scan than on the CT scan and on the ^{18}FDG-PET scan. This finding resembles that in brain tumor studies with ^{11}C-L-methionine, where a similar relationship prevailed and in which the area of the visualized tumor is correlated exactly with the anatomic tumor size (*1*). The ^{123}IMT-SPECT scan gives nearly the same result as the ^{124}IMT-PET scan.

branes, this result suggests that a carrier-mediated transport system exists. Based upon the experiments of Kaway et al. (*8*), this is probably a transport system involving the carrier enzyme for large neutral amino acids. Since the analysis of human plasma after administration of $^{123/124}$IMT indicates that a certain extent of metabolic degradation takes place, one may question whether the radioactivity in the brain is due to metabolites of IMT. The animal experiments, however, demonstrate that metabolites do not cross the BBB. All radioactivity within the brain of mice is present in the form of intact ^{123}IMT.

Furthermore, our animal experiments demonstrate that 4%–18% of $^{123/124}$IMT in the brain is precipitable with TCA as a protein pellet. SDS gel-electrophoresis showed that the radioactive material was not incorporated into protein. Indeed, a utilization of IMT for protein synthesis could not be expected because no specific transfer-RNA exists for such an iodinated an methylated analog of tyrosine.

The fact that IMT is not incorporated into the proteins does not exclude the clinical utility of this tracer. PET studies of low-grade astrocytomas using [^{11}C]-L-methionine have shown that transport of amino acids into the tumors adapts to the regional metabolic demand (*15*). Therefore, the initial uptake of IMT, which appears to be related to amino acid transport, may be an indicator of the metabolic demand by the tissue. The published data on [^{11}C]-L-methionine uptake in brain tumors are based mainly on the initial, transport-related uptake and not on protein incorporation. The latter is a relatively slow process (*3*).

In brain tumors, the accumulation of IMT may be caused by nonspecific concentration of IMT due to the disruption of the BBB. Some findings, however indicate that tumor uptake is, at least in part, specific. The uptake of IMT in the tumors, for example in Patient 2 (Fig. 3), is much higher and faster than would be expected from a tracer that simply reflects a breakdown of the BBB and, in time, reaches an equilibrium between circulating blood and tumor tissue. Furthermore, tracers which indicate a breakdown of the BBB result in a continuous increase of the tumor/brain ratio in time, whereas IMT shows a nearly constant tumor/brain ratio, which is in agreement with a previous study (*7*). Moreover, there is increased IMT uptake in a grade II glioma where, according to the contrast-enhanced CT scan, the BBB is intact (Patient 28). In addition, in Patient 2 (Fig. 4) the tumor size is larger on the ^{124}IMT-PET scan than the area of contrast enhancement on the CT scan. These data indicate that a disruption of the BBB is not a prerequisite for increased uptake of IMT and that IMT uptake differs from the uptake of tracers which demonstrate a breakdown of the BBB only. Nevertheless, some nonspecific concentration of IMT in brain tumors cannot be excluded by our study.

The kinetics of uptake by brain of ^{124}IMT in the PET studies are different from previous data which report a rapid uptake of ^{123}IMT in the brain within one minute after injection followed by a plateau phase (*7*). These data, however, were obtained with a planar gamma camera. Therefore, the influence of the blood in the overlaying scalp, which plays an important role during the first 15 min postinjection, may have masked the slower accumulation of ^{123}IMT in the brain tissue. From the tracer kinetics in the PET study, it is evident that the optimal time for the SPECT acquisition is within 15–60 min postinjection. Before that time there is insufficient accumulation of tracer in the brain and the activity in the blood influences significantly the first projection images of a SPECT study.

In the patients studied with ^{124}IMT and PET, the tracer washout between 15 and 60 min postinjection ranged from ≈20% to ≈35% for the cerebral cortex and tumors (Table 2). This indicates similar washout kinetics for normal and malignant tissue. The tumor/cortex ratios of Patients 1 and 2 showed only minimal changes between 15 and 60 min postinjection. Similar results

were reported using early and late ^{123}IMT SPECT scans in tumor patients (*7*). The mean cerebral washout of ^{123}IMT determined from the planar projection images of all SPECT studies at 15 min and 60 min postinjection was 34.2% ± 7.1%, which is tolerable for SPECT studies in our opinion. In Figure 4, it can be seen that the ^{123}IMT-SPECT scan is similar to the corresponding ^{124}IMT-PET scan and no major artifacts are created by the tracer washout of ≈20% in this patient.

Because the uptake of amino acids by the brain is generally relatively low, SPECT studies suffer from rather low count densities, which hampers evaluation of the scans. The quality of the ^{123}IMT scans improved by using a long scanning time (45 min) and by increasing the tracer dose from 5 to 10 mCi. The latter appears acceptable because of the rapid urinary elimination of ^{123}IMT.

The increased ^{123}IMT uptake in nearly all brain tumors studied is in agreement with preliminary observations (*7*). Although there was a tendency for grade II gliomas to present with a lower uptake (1.12 ± 0.28, n = 4) as compared with grade III gliomas (1.63 ± 0.53, n=5) and grade IV gliomas (1.55 ± 0.45, n=18), the differences were not statistically significant. The number of grade II gliomas in this study, however, is still too small to be conclusive.

In summary, it appears that the uptake of $^{123/124}$IMT reflects amino acid transport. Although IMT is not incorporated into the proteins, it may be a useful tracer since the main determinant of initial amino acid uptake is transport. Since the washout is slow, ^{123}IMT appears to be a useful tracer for SPECT studies. In brain tumors, some nonspecific uptake of IMT due to the disruption of the BBB must be considered. However, the rapid uptake, the constant tumor/brain ratio and the accumulation of IMT in tumor areas with intact BBB suggests a specific uptake in brain tumors. Further studies are needed to investigate the clinical potential of the tracer.

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