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Value of ^{123}I -IMT SPECT for diagnosis of recurrent non-astrocytic intracranial tumours

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Abstract The value of single-photon emission tomography (SPECT) using iodine-123-alpha-methyl-tyrosine (IMT) for the diagnosis of recurrent or residual gliomas is well established. In the current study we investigated whether IMT-SPECT could also be useful in the follow-up of brain metastases and other intracranial tumours of non-astrocytic origin. The study included 22 patients with suspected recurrent intracranial tumours of non-astrocytic origin (12 brain metastases, one supratentorial primitive neuroendocrine tumour (PNET), one rhabdoid tumour, two clivus chordomas, three ependymomas, two pituitary tumours, one anaplastic meningioma) who had previously been treated by surgery and/or radio/chemotherapy. SPECT results were correlated with clinical and MRI follow-up data. The study was true positive in 13 patients, true negative in five, false positive in one and false negative in three patients. Notably, all false negative findings were < 13 mm. The resulting sensitivity of the IMT-SPECT was 81%. We concluded that the IMT-SPECT is a promising complementary imaging tool for the detection of recurrences of non-astrocytic intracranial tumours and their distinguishing from treatment-induced changes. The limitation of the IMT-SPECT is its low sensitivity for the detection of small lesions.

Keywords Non-astrocytic brain tumours · $^3\text{-}^{123}\text{I}$ iodine- α -methyl-L-tyrosine · Single-photon emission tomography (SPECT)

Introduction

The major advantage of nuclear medicine methods in the diagnosis of brain tumours, compared with the standard imaging tools (CT, MRI), is their distinctly better ability to discriminate viable tumour from tissue alterations such as peritumoral oedema, postoperative scar and radiation necrosis [1–3]. This allows a more precise assessment of tumour extension and diagnosis of residual and recurrent tumours. In the past two decades development of radioactively labelled amino acids for positron-emission tomography (PET) and single-photon emission tomography (SPECT) have enabled the in-vivo determination of tumour proliferation. The value of SPECT using the radioactively labelled amino acid 3-[123I]iodo- α -methyl-L-tyrosine (IMT) for the diagnosis of brain tumours is well known [4–8]. Therefore, this method might play a role as an alternative to the less available PET. The majority of previous studies has focused on the usefulness of IMT-SPECT for the diagnosis of gliomas [6–8]; the investigations of non-astrocytic tumours have been reported only anecdotally [4]. Recently, Matheja et al. [9] addressed the feasibility of the IMT-SPECT for the detection of brain metastases and lymphomas and found a high IMT-uptake in most tumours. The aim of the presented retrospective study was to assess the potential value of IMT-SPECT in the follow-up of patients with pre-treated non-astrocytic intracranial tumours.

Materials and methods

Patients

Twenty-two patients with non-astrocytic intracranial tumours (12 brain metastases, one supratentorial primitive neuroendocrine tumour (PNET), one rhabdoid tumour, two clivus chordomas, three ependymomas, two pituitary tumours, one anaplastic meningioma) were part of a larger group of pre-treated consecutive patients who had been studied at our clinic with IMT-SPECT. The diagnoses had been previously verified by histology in all cases. All studied patients had previously been treated by surgery and/or radio/chemotherapy. A recurrent or residual tumour was suspected, based on MRI results (interval to IMT-SPECT < 2 weeks) in 19/22 patients. In three patients (nos. 6, 18 and 22) who presented with negative MR images (no progression of the known pre-treated lesion), a tumour relapse was supposed due to clinical aggravation.

Informed consent was obtained from all patients for the SPECT examinations. The study was approved by the local ethics committee at Charité and by the German Radioactive Protection Authorities.

SPECT imaging

The patients fasted overnight before undergoing the IMT-SPECT studies. In order to prevent possible uptake of free iodine, we blocked the thyroid with 400 mg sodium perchlorate 30 min prior to tracer application. Image acquisition was started 10 min after i.v. injection of 370 MBq 3-[123I]iodo- α -methyl-L-tyrosine. SPECT imaging was performed by a triple-head system (Multi-spect 3, Siemens Medical Systems). Images were acquired in step-and-shoot mode with 120 projection angles over 360° and an individually minimized radius of rotation. Matrix size was 128×128. The energy window (20%) was centred on 159 keV. Transversal, coronal and sagittal slices were reconstructed by filtered back projection with a Butterworth filter (cut-off frequency 0.38 Nyquist, order 6). First-order attenuation correction was applied by the method of Chang [10]. The reconstructed in-plane image resolution was 13 mm full width at half maximum (FWHM); the slice thickness was 3.5 mm.

Data analysis

SPECT scans were automatically co-registered with individual MRI data by MPI Tool software (ATV, Kerpen, Germany) and analysed visually by two observers. The final interpretation of SPECT findings was based on consensus. For quantification, irregular regions of interest (ROIs) were placed around the suspicious lesion and an area of normal brain on the MR images and transferred onto the corresponding SPECT images. The tumour-to-brain ratios were calculated as the relationship of the maximal ¹²³I-IMT-uptake in the tumour to the mean uptake in the normal tissue [11].

The results of the study were analysed on a patient basis. With respect to the final diagnosis, the 22 patients were classified as having either recurrent tumour ($n = 16$) or treatment-related changes ($n = 6$). The final diagnoses were verified by prospective clinical follow-ups, including serial MRI control examinations. The MRI studies were analysed by a radiologist who manually delineated the contrast enhancement areas in the T1-weighted images and/or hyperintensity signal in the T2-weighted images. In the MRI, a recurrent tumour was diagnosed in the case of an increase in the contrast-enhanced or hyperintense area on the post-contrast media scans or T2-weighted MR images by more than 25% [12], or a development of new regions. In those patients who were diagnosed as having radiation-induced changes or post-surgical processes, no tumour relapse was registered in the follow-up of more than 6 months. For calculation of sensitivity, specificity and accuracy of IMT-SPECT for the detection of recurrent tumours, we first classified the findings as true positive, true negative, false positive or

false negative, based on the results of visual analysis of the scans. In addition, an optimal study-specific cut-off value for the ^{123}I -IMT uptake was estimated from receiver-operating characteristic (ROC) curves by the selection of those values that yielded the highest diagnostic accuracy. All statistical analyses were done with the software package SPSS v. 10 (SPSS, Chicago, Ill., USA).

Results

Twentytwo consecutive patients were included in the study. Patients' characteristics, pre-treatment data, and findings of the MRI and IMT-SPECT are detailed in Table 1. The optimal discrimination threshold value for ^{123}I -IMT-uptake, as defined by ROC analysis of SPECT quantification results, was determined as 1.43. When this cut-off was used, the scans were classified as negative or positive concordantly by both visual and quantitative analysis.

Abnormal tracer accumulations in the pre-treated tumour were found in 14/22 patients. In 13 of them, a recurrence was supported by the clinical follow-up and accordingly to the MR images, which were strongly suggestive of progressive tumour growth. In one patient with suspected recurrence of breast cancer metastasis (patient no. 10), the diagnosis could not be confirmed in the follow-up of 8 months (no enlargement of the enhancing lesion on the MR image, no clinical aggravation). This case was classified as false positive. In five out of eight patients with negative findings of the IMT-SPECT, no recurrent tumour was confirmed in the follow-up of 6–14 months. These cases were therefore judged to represent therapy-induced changes. The IMT-SPECT failed to detect a recurrent tumour in three patients. Notably, all of them had lesions < 13 mm. Two of these patients with false negative SPECT findings had brain metastases (patients no. 8 and 11), and one patient had an anaplastic ependymoma WHO grade III (patient no. 15).

Contribution of the findings of IMT SPECT and MRI

In three out of 19 patients who had presented with suspicious findings on MRI, the diagnosis of treatment-related changes was correctly estimated by IMT-SPECT (Table 2). In 12 further patients, IMT-SPECT confirmed a recurrent tumour. In two of these patients, a proliferating tumour was revealed in only one of two suspected lesions depicted by MRI (pat no. 2 and pat no. 21; Fig. 1); in two other patients, SPECT suggested a larger tumour extension than MRI had (patient no. 9; Fig. 2 and patient no. 16). In 4/19 patients with positive MRI, the IMT-SPECT was misleading (false negative in

three patients and false positive in one patient). IMT-SPECT was true negative in two out of three patients in whom the MRI revealed no progressive tumour. In another patient, the IMT-SPECT diagnosed a recurrence of an anaplastic meningioma before the tumour progression had been detected by MRI (patient no. 22).

Discussion

In the follow-up of pre-treated intracranial neoplasms, imaging methods are targeted on early diagnosis of residual or recurrence and their differentiation from therapy-induced changes. Gadolinium (Gd)-enhanced MRI became a widely accepted standard diagnostic tool in neuro-oncology, having the advantage of high spatial and contrast resolution and allowing the investigation of a variety of tissue characteristics. However, the major drawback of MRI is a limited ability to distinguish between tumour relapse and treatment-related changes, because tissue alterations and scarring after therapy often impair the detection of residual or recurrent disease [13–15]. Nuclear medicine imaging provides information on tumour metabolism and has been shown to be highly valuable for diagnosis of recurrent brain tumours in addition to anatomical imaging. The value of PET, using a tracer of glucose metabolism, 2-[^{18}F] fluoro-2-deoxyglucose (FDG), in the diagnosis of recurrent high-grade brain tumours has been proven by many studies [16–18]. However, an important limitation of FDG-PET is a negative contrast between tumour tissue and normal brain in low-grade tumours owing, typically, a lower glucose metabolism the surrounding brain parenchyma [5, 19–21]. For the same reason, FDG-PET seems not to be useful for detection of cerebral metastases [22–24]. In this respect, amino acid tracers for PET and SPECT represent a more specific parameter of tumour metabolism and have been demonstrated—due to their ability to accumulate in the majority of low- and high-grade tumours—to be superior to FDG-PET for diagnosis of brain neoplasms [20, 25]. The most commonly used amino acid tracer for PET is ^{11}C -methionine (^{11}C -MET), which was reported by numerous studies to be highly valuable for detection of recurrences of high- and low-grade glioma as well as cerebral metastases and their differentiation from radiation necrosis and postoperative scar [3, 21, 26]. The radio-labelled synthetic amino acid suitable for SPECT imaging, (^{123}I -IMT), has been available since 1989. The value of IMT-SPECT for the diagnosis of recurrent brain tumours has been proven by several studies [6, 11] and has been shown to be comparable to PET using ^{11}C -methionine [27] as well as the newly introduced tracer ^{18}F -fluoroethyltyrosine [28]. Moreover, IMT-SPECT seems to be superior, for detection of recurrent gliomas, to another current diagnostic tool— ^1H -MR-spectroscopy [29].

Table 1 History and findings of IMT-SPECT and MRI (MTS metastasis(es), CA carcinoma, FL frontal lobe, PL parietal lobe, TL temporal lobe, OL occipital lobe, BG basal ganglia, Cer cerebellum, r left side, l right side, Rad radiation, Chemo chemotherapy, Res resection, n new, p progressive, CE contrast enhancement, HL T2-hyperintense lesion, P positive, N negative, RT recurrent or residual tumour, NP no tumour progress, st PNET supratentorial primitive neuroendocrine tumour, T/B tumour/brain ratio, Ventri ventricle)

No/gender/age	Histology	Location	Pre-treatment interval (months)	Therapy-free interval (months)	MRI Lesion	Diameter (mm)	IMT-SPECT		Follow-up (months)	Diagnosis
							Visual interpretation	T/B max		
1/F/44F	MTS lung CA	r OL	Rad	12	pCE	14	P	2.56	17	RT
2/M/60	MTS lung CA	l OL, r Cer	Rad	13	pCE,HL l OL,r Cer	15	P r Cer, N l OL	1.48	21	RT
3/F/61	MTS lung CA	r BG, l Cer	Rad	6	pCE r BG	13	P r BG	1.68	20	RT
4/M/77	MTS lung CA	r OL	Res, Rad, Chemo	27	pCE	12	P	1.62	16	RT
5/M/32	MTS palate CA	r FL (x2)	Res, Chemo, Rad	7 ^a	pCE, HL	38	N	1.26	18	NP
6/F/60	MTS salivary gland CA	r FL	Rad, Chemo	11 ^a	NP	9	N	1.39	6	NP
7/F/50	MTS melanoma	r FL, r OL	Rad	8	pHL r FL	26	P r FL	1.48	17	RT
8/F/31	MTS melanoma	l PL	Rad, Chemo	5	pCE	7	N	1.32	14	RT
9/F/34	MTS breast CA	l PL	Res, Rad	3	pCE	17	P	1.90	13	RT
10/F/55	MTS breast CA	r PL, FL, TL, Cer	Rad, Chemo	9	pCE	17	P r PL	2.07	8	NP
11/F/54	MTS breast CA	l FL, l Cer, r TL	Res, Rad	12	pCE: l FL	9	N	1.28	2	RT ^b
12/M/66	MTS colonic CA	l Cer	Rad	4	pCE	40	P	1.61	5	RT
13/F/23	Rhabdoid tumour grade IV	r FL	Rad, Chemo	6	pCE	23	P	2.51	10	RT
14/M/28	Ependymoma grade II	Cer	Res, Rad	4	pCE	17	P	1.88	22	RT
15/F/32	Ependymoma grade III	Cer	2 x Res	4	pCE	12	N	1.10	19	RT
16/M/21	St PNET grade IV	r PL, TL	Res, Rad	3	pCE	13	P	1.83	22	RT
17/M/14	Clivus chordoma		Res, Rad	19	pHL	15	N	1.13	19	NP
18/M/64	Clivus chordoma		Res	9	NP	14	N	1.37	18	NP
19/M/21	Pituitary germ cell CA		Res, Rad, Chemo	7	pCE	18	P	1.51	17	RT
20/M/69	Pituitary CA		Res, Rad	96	pCE	10	N	1.35	6	NP
21/F/26	Ependymoma grade III	III Ventri	3 x Res, Rad, Chemo	48	pCE III Ventri, nrTL	20	P rTL, N III Ventri	1.57	6	RT
22/M/65	Anaplastic meningioma grade III	r PL	3 x Res, 2 x Rad	5	NP	11	P	1.58	5	RT
						Mean	17±9			

^aTime after radiation therapy, study was performed under chemotherapy

^bThe patient died after tumour progression 2 months after the study

Table 2 Contribution of the findings of IMT-SPECT and MRI in the 22 patients studied

<i>n</i> = 22	IMT-SPECT +	IMT-SPECT–
MRI +	13 (12 ^a)	6 (3 ^a)
MRI –	–	3 (1 ^a)

^aRecurrences were proven by follow-up

The available data on the usefulness of IMT-SPECT for detection of tumours other than glioma are sparse. The studies on small patient groups published so far suggest an ability of IMT to accumulate in some malignancies, including head and neck cancer, lung cancer and soft-tissue tumours [30–34]. However, the sensitivity of IMT-SPECT for detection of lymph node metastases was low, and, in cases of lung cancer, lesions smaller than 15 mm were not detectable [31, 32]. The sensitivity of IMT-SPECT for detection of soft-tissue tumours was comparable to those of FDG-PET [34]. Less encouraging results were published for melanomas and carcinoid tumours [35, 36]. It is, therefore, still unclear how far the favourable results of IMT-SPECT in the detection of recurrent astrocytomas are applicable to intracranial tumours of non-astrocytic origin. Most studies using IMT in the follow-up after treatment of brain tumours include only a limited number of non-astrocytic tumours [4].

In this retrospective study we analysed the ability of IMT-SPECT to identify recurrences of non-astrocytic intracranial tumours in a post-therapy patient population. In the current investigation, IMT-SPECT allowed a detection of 13/16 recurrent non-astrocytic tumours. The resulting sensitivity was 81%, which is lower than previously reported for gliomas by Samnick et al. [6] who found in a group of 66 histopathologically confirmed recurrences an overall sensitivity of 94%, but it is in accordance with findings of the smaller study of Kuwert et al. [7], in which a sensitivity of 78% was achieved in the 27 patients studied. Our results are also comparable to those reported for ¹¹C-MET-PET by Tsuyuguchi et al. [26]. In that study, ¹¹C-MET-PET allowed, in a group of 21 patients, the detection of recurrent cerebral metastases with a sensitivity of 78% and a specificity of 100%. In the study by Matheja et al. [9], IMT-SPECT was able to detect 91% of non-parenchymal brain tumours. However, due to the fact, that the majority of tumours (25/31) in that study had not been pre-treated previously, this finding cannot be directly compared with our data focusing on detection of recurrences. Another explanation for the lower sensitivity of IMT-SPECT in our study is the high proportion of small lesions (the middle lesion size was 17 ± 9 mm). The assessment of small lesions represents a significant limitation of SPECT because of the low spatial resolution of this technique [32]. Indeed, all three false negative

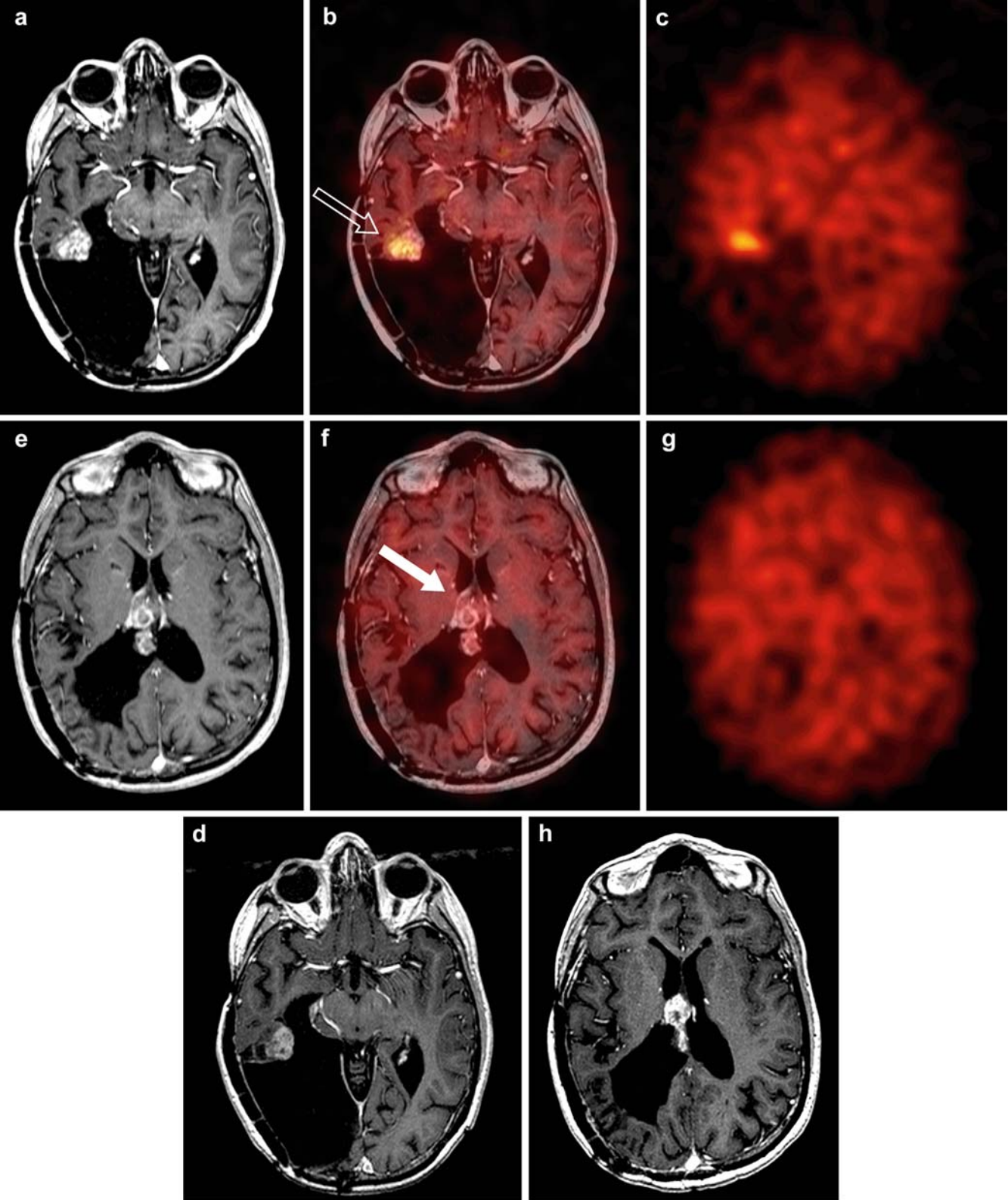
Fig. 1 A 26-year-old female patient presented 4 years after surgery and radiochemotherapy with an ependymoma grade III (patient no. 21). The T1-weighted MR image (a, e) shows a suspicious enhancing lesion in the region of the known tumour, as well as the development of a new enhancing lesion ventral to the resection defect. SPECT (c) and fused image (b) demonstrate a high ¹²³I-MT uptake in the new tumour lesion (empty arrow), but show no tracer accumulation in the pre-treated tumour (e, f, g) (solid arrow). Based on these findings, the IMT-accumulating lesion was treated by stereotactic radiation therapy. Control MRI 6 months later showed no change in the IMT non-accumulating lesion (h) and a size reduction of the irradiated tumour (d)

findings in our study were smaller than 13 mm, whereas in the study by Matheja et al. [9], the smallest lesion was 14 mm in diameter. Therefore, a high reliability of IMT-SPECT is given only in patients with suspect findings in MRI of > 13 mm. PET imaging that uses amino acid markers ¹¹C-MET or ¹⁸F-FET might be more reliable for the determination of small lesions.

Non-parenchymal brain tumours, especially cerebral metastases, are often presented as multiple lesions. In the case of pre-treated tumours, the correct characterization of the viability of the different lesions is mandatory for the selection of an appropriate treatment (tumour resection, radiosurgery, conformal or whole-brain radiation therapy). In two patients in our study, IMT-SPECT detected a viable tumour in only one of two lesions, which were assessed as suspicious by MRI (see Fig. 1). Thus, IMT-SPECT may be helpful for definition of the treatment strategy in the case of multiple lesions. The fact that a high IMT uptake was found outside of tumour borders, defined by MRI in two out of 16 patients with recurrent tumours, indicate the potential usefulness of IMT-SPECT in the definition of target volume for the radiation therapy in non-astrocytic tumours [37]. The value of nuclear medicine imaging with amino acid tracers for planning of radiation therapy of gliomas has already been estimated by previous investigations [38, 39].

Limitations of the study

Some limitations of the present study should be noted. Owing to the low proportion of patients with therapy-related changes (six out of 22), no reliable estimation of the specificity of IMT-SPECT was possible. In the current study, as also in many previous investigations of the value of PET or SPECT in the follow-up of brain tumours [7, 40, 41], the classification of lesions in recurrences and therapy-induced changes was based on the clinical and MRI follow-up after SPECT imaging and not on biopsy. The MRI criteria used for the tumour growth are possibly imperfect because they may be not applicable to the different tumour types. Although a lack of pathological verification of clinical diagnoses repre-



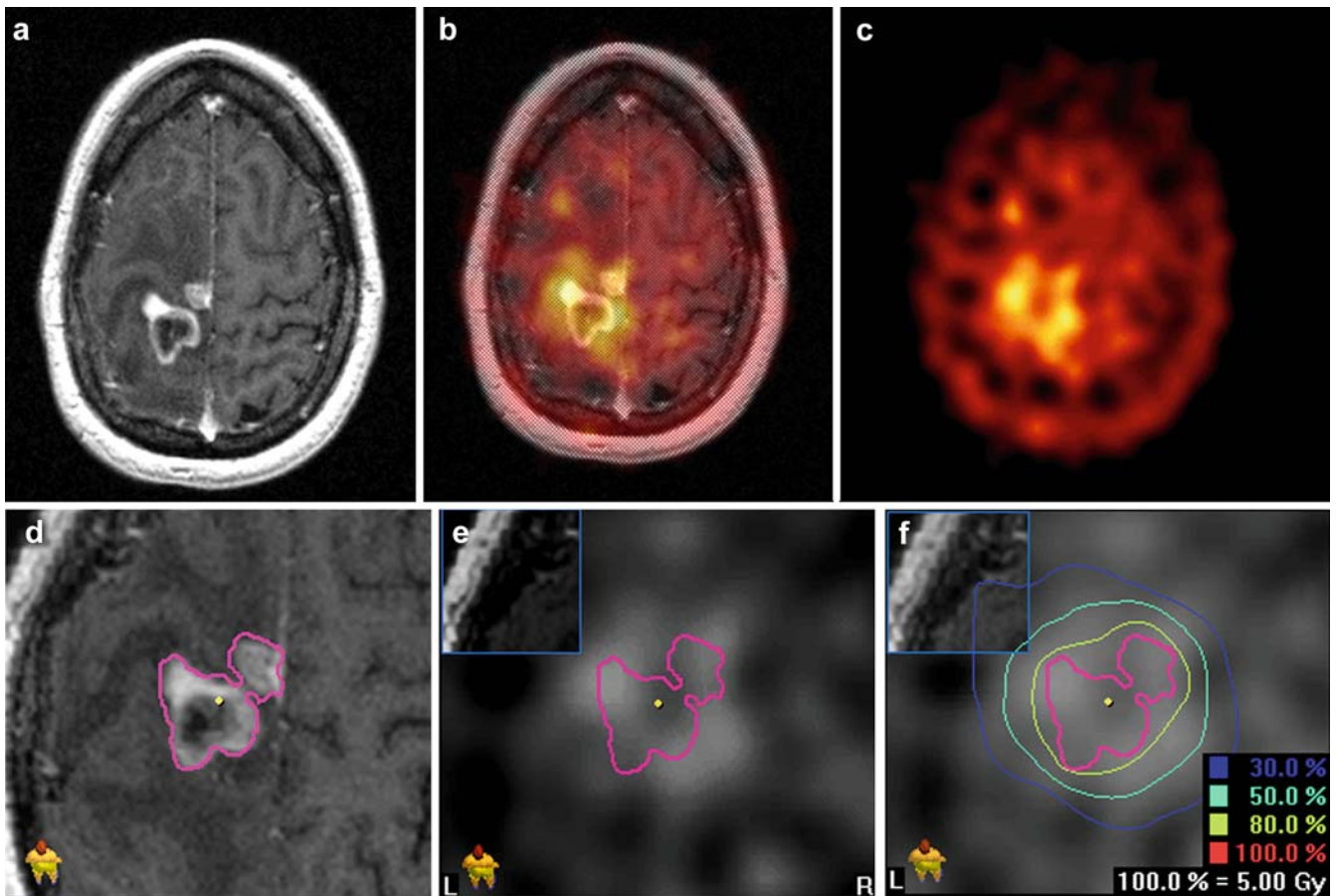


Fig. 2 A 34-year-old female patient with a metastasis of a breast cancer presented 5 months after radiation therapy (patient no. 9). The T1-weighted MR image (a) depicted a progressive, ring-like enhancement with a nodular component, suspicious of recurrence. IMT-SPECT (c) shows a high amino acid accumulation in the lesion and suggests a larger tumour extension than the MR image does (fused image, b). If the planning target volume (PTV > 80% of isodose) is defined on the basis of MRI alone (d), significant parts of proliferating tumour are still outside of the PTV (e, f, Brain SCAN 5.1, Brain Lab AG, Heimstetten, Germany)

sents a theoretical limitation of the current study, the biopsy cannot be regarded as “gold standard” for the detection of tumour recurrences. Firstly, gliomas are not homogeneous, particularly after surgery and irradiation, and even if the stereotactically guided biopsy is used as a reference, an error rate of approximately 10% should be taken in consideration [15]. Secondly, in the case of pre-treated tumours, the presence of tumour cells in a biopsy specimen is not a reliable proof of tumour progression, since these cells may be unable to proliferate after therapy [42]. Our group of patients was inhomogeneous and included those with some rare tumour entities; for that, the feasibility of SPECT/PET amino acid imaging has not been systematically investigated, so far. In the present study, focusing on the role of IMT-SPECT in the follow-up of tumours, the pre-therapeutic IMT up-

take was not assessed. Therefore, it cannot be excluded that some negative IMT-SPECT findings may reflect an inability of particular tumours to accumulate radio-labelled amine acids. Results of our study might, therefore, not apply to a different sample with other tumour types. Further investigations involving larger cohort of patients with particular tumour entities and higher proportion of therapy-induced changes are, therefore, required to assess the diagnostic accuracy of IMT-SPECT and to answer the question of how much of an impact will the use of IMT-SPECT have on the management of patients with non-astrocytic tumours dependent on the particular histology.

Conclusion

Our results indicate that IMT-SPECT may be a potentially useful complementary imaging tool for the differentiation of recurrences from postoperative scar/radiation necrosis in patients with pre-treated brain metastases and other non-astrocytic intracranial tumours. The restriction of SPECT is a limited spatial resolution, leading to false negative results in lesions < 13 mm.

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