VIA MEDICA

Nuclear Medicine Review 2004
Vol. 7, No. 2, pp. 135–141

ISSN 1506–9680

Original

Assessment of clinical usefulness of ^{131}I-alpha-methyl-tyrosine and fused SPECT/MRI imaging for diagnostics of recurrent cerebral gliomas

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[Received 12 XI 2004; Accepted 20 XI 2004]

Abstract

BACKGROUND: Early detection and diagnostic differentiation of neoplastic tissue from necrotic changes and scars following the treatment of cerebral gliomas is essential for determining further therapy and prognosis. The primary technique used for the diagnostics of recurrent neoplastic growth is the magnetic resonance imaging (MRI), which in some cases, however, does not allow one to identify the character of cerebral lesions. Recently, MRI has been supplemented with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) employing radiolabelled amino acids. e.g. tyrosine or methionine. The aim of the project was to assess the diagnostic potential of SPECT when iodine-131 alpha-methyl tyrosine (IMT), a Polish make of radiopharmaceutical (OBRI — POLATOM, Otwock-Świerk, Poland), was applied. The use of ^{131}I as a substitute for the more costly, imported iodine-123 has been justified in view of the nature and significance of the diagnostic problem on the one hand, and the possibility of 131-iodine application on a larger scale in CEE countries, on the other.
MATERIAL AND METHODS: MRI and SPECT were performed in 24 patients with a history of surgical treatment and radiotherapy of cerebral glioma (WHO grade II/IV). A SPECT was carried out 15 min after an i.v. injection of 74–111 MBq IMT. The tomograms were evaluated visually and in quantitative terms. The fused SPET/MR images were also analyzed. The obtained results were verified against histopathological findings, control MRI examinations and the clinical course of disease within 7–28 months of monitoring.
RESULTS: In 19 patients, an increased IMT uptake indicative of a recurrent tumour was found, and the presence of the tumour was confirmed. In five patients no hot spots were detected which would indicate the neoplastic growth and verification did not provide any evidence for relapse.
CONCLUSIONS: The examination employing iodine-131 IMT made it possible to confirm or exclude tumour recurrence in all the subjects, also in the cases when the CT/MR images were inconclusive. The MRI/SPECT fusion made it possible to more accurately identify the location of tumour recurrence as well as determine the area for spectroscopic MR analysis, for stereotactic biopsy and radiotherapy.
Key words: ^{131}I-alpha-methyl-tyrosine, glioma, MRI/SPECT image fusion

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Introduction

In the adult population, tumours within CNS are rather rare; they make up 9% of all cancer cases (they are more prevalent in children, at 20%). Gliomas make up 40% of CNS tumours, refer mainly to the male population, and their morbidity rate is estimated at 0.5–2/100,000 persons/year [1–3]. Combined treatment, including surgery, radiotherapy and chemiotherapy is usually

employed. Surgical resection of all, or almost all (more than 98%) of the tumour has a favourable prognostic value and results in a prolonged mean survival time. However, this treatment can be applied only when the size, site and clearcut morphological delineation of the tumour, based on CT/MR imaging, enable its complete excision. In malignant gliomas, total surgery is often impossible, and the treatment is supplemented with radiotherapy combined with chemiotherapy. In some cases, when the size of the tumour is less than 5 cm in diameter and the tumour is located far from large vessels and major neuroanatomic structures, brachytherapy can also be applied consisting of the administration of iodine, iridium or cesium [4] radioisotopes through the catheter directly to the tumour. A promising method also seems to be stereotactic surgery which consists of the precise dosing of ionizing radiation with a linear accelarator or gamma knife [4, 5] during surgery. Attempts have also been made at combining radiotherapy with hyperthermia. Conventional chemiotherapy with nitrosoammonia derivatives may only to a slight extent prolong the patient's life. Great expectations lie with the more and more commonly used complex chemotherapy in combination with intra-arterial or intra-tumour administration of agents passing through the blood-brain barrier as well as immunotherapy with interferon and the gene therapy [4–9].

Such aggressive treatment of the cerebral tissue results in numerous reactive changes such as scarring and radionecrotic foci within the brain and cerebrospinal meninges. The differentiation between these changes and the remainder or recurrence of the tumour is an important diagnostic problem. The non-invasive methods used to this end include computed tomography (CT) and magnetic resonance imaging (MRI). CT seems to be more effective when applied shortly after surgery to detect postoperative complications such as intracerebral bleeding and pathological liquid or air residues. Later, after surgery, to differentiate tumour remnants or recurrence from post-operative and post-radiation changes, a two-stage MRI examination, before and after injection of paramagnetic contrast medium, is usually performed (sometimes repeatedly) [10–15].

However, in some cases, this diagnostic is insufficient to make a definite diagnosis. Then, MRI is supplemented with a spectroscopic analysis of proton or phosphoric spectra of different metabolites and their ratios. This analysis concerns the volume of interest, the precise selection of which is fundamental for confirming the diagnosis of cancer [16, 17].

In cases which are difficult to diagnose, the radioisotope diagnostics: single-photon emission topography (SPECT) and positron emission topography (PET), are of great value as are MRI auxiliary examinations.

For detecting glioma recurrence, the radiopharmaceuticals are used; their accumulation reflecting an increased metabolism of amino acids or glucose in the tumour. In the PET technique, which is costly and still not often available, the essential compounds are radiocarbon-labelled (^{11}C) amino acids: methionine, tyrosine and leucine, which have a low uptake in the healthy cerebral tissue. Owing to the physiologically high level of glucose consumption in the gray matter, glucose analogue, ^{18}F-fluoro-deoxy-D-glucose (FDG) is used for the assessment of malignancy diagnosed using other methods rather than for tumour detection [18–20].

Iodine-labelled (usually ^{123}I) alpha-methyl-tyrosine is a radiopharmaceutical used in the SPECT examinations which are more easily available than the PET technique. In the diagnostics of recurrent brain tumours, a more and more frequently applied method is a combination of data elicited from imaging of the morphological changes (CT, MRI) and of the dysfunction, e.g. modified metabolism, due to a given pathology (PET, SPET) [21–24].

This project was undertaken to assess the usefulness of ^{131}I-alpha-methyl-tyrosine, a radiopharmaceutical of Polish origin (POLATOM-OBRI, Otwock-Świerk, Poland) for the diagnostics of recurrent gliomas as well as to evaluate the clinical usefulness of fused SPET-MRI images.

Material and methods

The subjects were 24 patients (14 males and 10 females), aged 22–53 (mean 43) who received treatment for cerebral gliomas (WHO grade II/IV). All patients underwent surgery (five had it performed twice); seven subjects had an external radiotherapy; four had brachytherapy and another four, chemotherapy. The decision whether or not a given patient should be classified for MRI and SPECT employing ^{131}I-alpha-methyl-tyrosine was made by a neurosurgeon after consulting a radiologist and nuclear medicine specialist.

MRI examinations were made using 1.5 T SIEMENS Magneton Vision Plus (Siemens, Erlangen, Germany), using a T1 and T2-dependent time, before and after injection of Gd-DTPA contrast medium (using a head coil). The study protocol included precise positioning against the orthogonal plane; the transaxial plane was parallel to bicallosal line. Five days before scintigraphy and five days after the examination, the subjects were administered a Lugol solution at the dose of 20 drops, three times a day for a temporary thyroid blockage. A brain scintigraphy was performed 15 min. after an i.v. injection of 74–111 MBq ^{131}I-alpha-methyl-tyrosine. A double-headed camera (Varicam, Elscint, Haifa, Israel) with high-energy collimators was used for SPECT imaging. The patient's head was positioned in the same way as during the MRI examination.

Acquisition consisted in recording 90 views, of 40 s each, within the full angle of rotation, in the 64×64 matrix (which corresponds to 8.8×8.8 mm^2 pixel). A transaxial reconstruction was made using filtered back-projection (Hanning filter, 0.32, Nyquist). The images were evaluated visually, the result was positive if a hot focus, indicating a recurrent tumour, could be observed. A semiquantitative uptake analysis was carried out. Uptake indices were calculated as the relative ratio of maximal tumour uptake to average uptake in the reference region.

To locate the sites with increased lesional IMT uptake in the brain structures, the data from MRI and SPECT diagnostics were fused applying a 3D overlaying technique with the statistical Mutual Information algorithm, using a software package for MRI functional examinations [22–24].

SPECT results were verified based on the:

— histopathology in patients who had a stereotactic biopsy or underwent re-operation;
— monitoring of the further course of the disease: the intensification of clinical symptoms; the progression of changes in control MRI or MRS examinations, the patient's death, or no signs of disease progression, both clinically and in control MRI and MRS examinations (observation period: 7–24 months).

Table 1. The subject's personal characteristics and diagnostic data

No.	Gender	Age (yrs)	Histopathological diagnosis WHO classification	MRI results	SPECT results Qualitative evaluation	SPECT results tumour/ /background ratio	SPECT results verification Relapse (+) No relapse (–) (Obs. time: months)
1	M	39	Astrocytoma fibryllarae II/III	(+/–)	(–)	0.84	Clin. obs. (–) (7)
2	M	40	Astrocytoma fibryllarae II/III	(+/–)	(–)	0.91	Clin. obs. (–) (24)
3	F	41	Glioblastoma multiforme (III)	(+)	(+)	1.40	Clin. obs. (+) †
4	F	34	Astrocytoma anaplasticum (IV)	(+)	(+)	1.50	Clin. obs. (+) †
5	M	53	Glioblastoma multiforme (IV)	(+)	(+)	1.70	Clin. obs. (+) †
6	M	30	Glioblastoma multiforme (IV)	(+)	(+)	1.23	Clin. obs. (+)
7	M	51	Astrocytoma anaplasticum (III)	(+)	(+)	2.45	Hist-pat (Astrocytoma)
8	M	44	Oligoastrocytoma (III)	(+)	(+)	2.05	Hist-pat (Astrocytoma)
9	M	42	Oligodendroglioma anaplasticum (III)	(+/–)	(+)	1.58	Hist-pat (Oligodendroglioma)
10	F	31	Glioblastoma multiforme (IV)	(+)	(+)	1.47	Clin. obs. (+) †
11	F	25	Glioblastoma multiforme (IV)	(+/–)	(+)	1.43	Clin. obs. (+) †
12	M	52	Glioblastoma multiforme (IV)	(+/–)	(+)	1.55	Clin. obs. (+) †
13	F		Glioblastoma multiforme (IV)	(+/–)	(+)	1.54	Clin. obs. (+) †
14	F	42	Astrocytoma fibrillare (II)	(+/–)	(–)	0.90	Clin. obs. (–) (17)
15	F	43	Glioblastoma multiforme (IV)	(+/–)	(+)	2.02	Clin. obs. (+)
16	F	43	Glioblastoma multiforme (IV)	(+)	(+)	1.85	Clin. obs. (+) †
17	M	49	Glioblastoma multiforme (IV)	(+/–)	(+)	1.85	Clin. obs. (+)
18	F	51	Glioblastoma multiforme (IV)	(+)	(+)	2.40	Clin. obs. (+) †
19	M	51	Glioblastoma multiforme (IV)	(+)	(+)	1.22	Clin. obs. (+)
20	M	29	Astrocytoma anaplasticum (III)	(+)	(+)	1.43	Clin. obs. (+)
21	M	41	Astrocytoma anaplasticum (III)	(+/–)	(–)	0.95	Clin. obs. (–) (12)
22	M	28	Astrocytoma fibrillare (II)	(+/–)	(–)	0.58	Clin. obs. (–) (12)
23	F	26	Oligoastrocytoma (II)	(+/–)	(+)	1.25	Clin. obs. (+)
24	M	37	Astrocytoma anaplasticum (III)	(+)	(+)	1.68	Hist-pat (Astrocytoma)

MRI and SPECT findings: (+) positive; (–) negative; (+/–) inconclusive. MRI/SPECT verification: (+) recurrent tumour-histopathological assessment in patients after stereotactic biopsy or re-operation, or intensification of clinical symptoms, progression of changes in MRI, MRS examinations, or the patient's death; (–) no recurrent tumour — negative diagnostic results, no clinical signs of recurrence; † deceased

Results

The data on histopathological findings after surgery and tumour resection as well as MRI and SPECT results and their verification are summarised in Table 1.

MRI results were as follows:

— in 12 patients, MRI revealed a polymorphic focus, subject to contrast enhancement indicating a residual tumour or recurrent tumour;
— in another 12 patients, the MRI results did not allow one to diagnose a recurrent tumour due to post-operative and post-radiation changes.

SPECT results were as follows:

— in 12 patients with signs of recurrent tumour in MRI, the SPECT revealed a focus of increased IMT uptake (Figure 1) (tumour/ /background — 1.22–2.45). Six of them had a rapid progression of glioma resulting in death. Two patients were subject to re-operation; and tumour recurrence was confirmed by histopathology. In four patients, the progression of the brain tumour was confirmed clinically and in control examinations;
— in seven patients with inconclusive MRI findings, a SPECT revealed a focus of increased IMT uptake (tumour/background ratio 1.23––2.40): one patient out of this group underwent re-operation, one had a stereotactic biopsy, two patients presented clinical signs of tumour progression, and three patients died from brain tumours;
— in another five patients with inconclusive MRI results, SPECT displayed no foci of an increased IMT uptake (Figure 2) (tumour/background ratio 0.84–0.95), which was regarded as a negative finding that did not provide grounds for diagnosing a recurrent brain tumour. The clinical condition of these patients remains good (they have been monitored for 7–24 months) and the control MRI/MRS examinations do not reveal any signs of tumour progression.

Fused SPECT-MRI results:

For all the 24 patients, their fused SPECT and MR images were evaluated. In 19 patients with recurrent tumours, the areas showing an increased IMT uptake partially overlapped with contrast enhancement areas from MRI, including seven patients with inconclusive findings with the sites interpreted as being suspected of glioma proliferation (Figure 3). In the five cases with negative SPECT results, in the fused images, the most suspected site within the post-resection area did not reveal an increased IMT uptake.

Discussion

Contemporary diagnostic imaging offers methods that make it possible to display both changes in tissue morphology (CT, MRI) and a modified metabolism (SPECT, PET, MRS). The advancement in diagnostic technologies over the last several years en-

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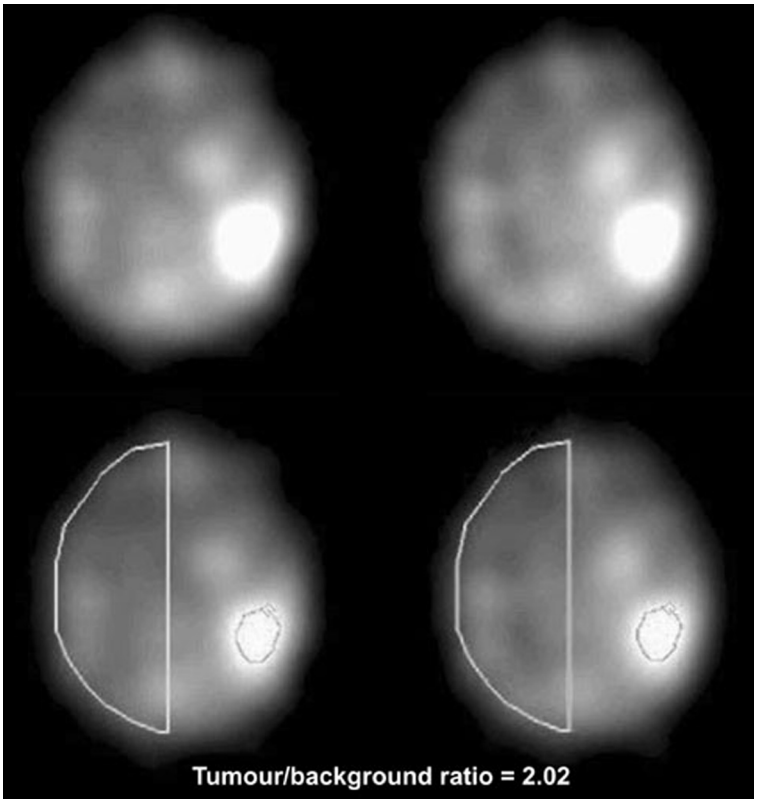

Figure 1. Scintigraphic images from SPECT using ^{131}I-alpha-methyl-tyrosine in a patient with suspected recurrent cerebral glioma. The images show the focus of increased IMT uptake in the right occipital lobe area. ROIS for calculating uptake indices: tumour and symmetrical semisphere for background.

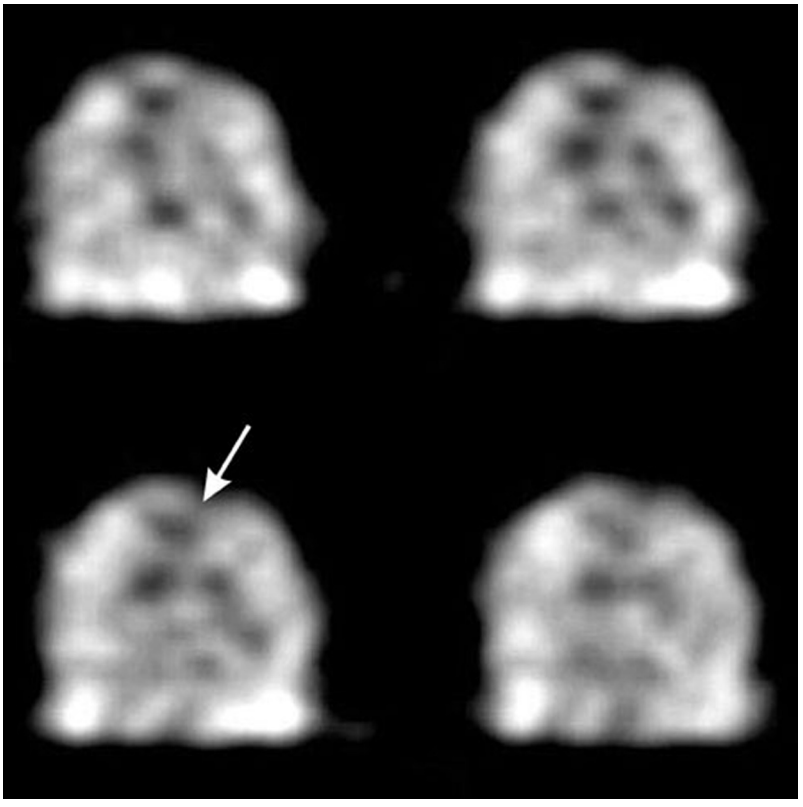

Figure 2. Scintigraphic images from SPECT using ^{131}I-alpha-methyl-tyrosine in a patient with suspected recurrent cerebral glioma. The image does not display the focus of increased IMT uptake, the decreased uptake area coincides with the post-resection site (arrow).

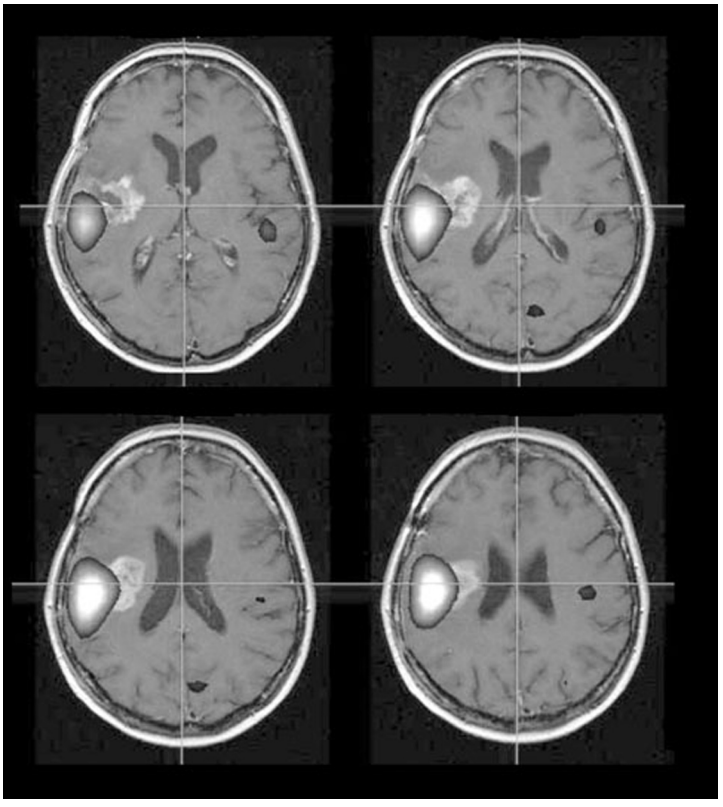

Figure 3. Fused SPECT-MR image from a patient with recurrent cerebral glioma. The focus of the highest IMT uptake is located within the solid structures of the tumour.

ables one to make a complex interpretation of data of an anatomic and functional character. In highly developed countries, the combined diagnostic imaging PET/CT or SPECT/CT (still unavailable in Poland) is a routine practice; however, no combination with MRI is possible. As already reported, MRI exhibits a higher sensitivity than CT in the diagnostics of brain tumours. Therefore, developing the technique that would yield the fusion of MR and SPECT images [21–25] has become an issue of vital importance.

In our study, ^{131}I-labelled alpha-methyl-tyrosine of Polish origin was used, which made it possible to largely reduce the cost of the examination. The application of this radiopharmaceutical at an activity level as high as 100 MBq has been considered fully justified in view of the significance of the diagnostic problem per se; in addition, this method is essential in making decisions with respect to the therapy and prognosis in patients with brain tumour, a severe disease with a very high mortality rate.

Iodine-labelled alpha-methyl-tyrosine has been used for brain tumour diagnostics since 1989 [26]. This ligand is an L-tyrosine analogue, it readily passes through the blood-brain barrier, is accumulated in the brain tissue but not metabolized in its cells (not incorporated in the proteins) since the (bound) iodine molecule changes the molecule size and makes it undetectable for transporting RNA (tRNA). The tumour's metabolism is generally increased compared to the rate of metabolic processes in unaffected tissue, or that with necrotic changes. This is reflected in an increased IMT uptake in the tumour, what allows a differential diagnosis to be made [27–29].

In the present study, scintigraphy using 131 IMT, not only helped to confirm glioma recurrence detected in control MR examination but also to precisely locate the part of the tumour where the tissue exhibits an increased IMT uptake and hence the highest metabolic activity. In all the cases of recurrent tumour, the areas with increased IMT uptake were smaller than the contrast enhancement sites in MR images. Also the sites interpreted as questionable were characterised by an increased IMT uptake.

It seems that distinguishing within the tumour an area with the highest metabolic rate makes it possible to precisely locate the optimum site for:

— further MRS analysis (in three patients the spectral pattern for the highest IMT activity area indicates the presence of neoplastic tissue;
— stereotactic biopsy (the material appropriate for histopathological assessment was obtained only from one patient);
— planning target radiotherapy. As reported by other authors [30, 31], an increased uptake of the tracer may indicate the presence of cells that may need higher radiation doses (biological target volume) than other areas of the tumour.

In 12 patients treated for cerebral glioma, MRI yielded inconclusive results: in the post-resection site, regressive changes such as post-radiation necrosis and liquid residues, prevailed. In seven of these patients, a SPET with alpha-methyl-tyrosine revealed the increased uptake of the tracer, which was interpreted as evidence of a tumour recurrence. The fusion of SPECT-MR images made it possible to precisely locate the focus of the increased IMT uptake in the structures of the non-homogenous post-resection site. For

five patients, SPECT did not display any sites with an increased IMT uptake (negative result). Repeated check-ups, non-invasive diagnostics (MRI and MRS) as well as the clinical examinations in these patients do not show any signs of tumour progression (observation period: 8–27 months).

When ^{131}I-labelled alpha-methyl-tyrosine was used as a radiopharmaceutical the quality of SPECT images obtained was found to be slightly lower than when the imaging employed 123-iodine, which is due to the physical properties of the 131-isotope. However, it was adequate for the visual assessment and proper interpretation of the findings. Moreover, the fusion of the SPET image with the morphological picture provided by MR, enabled one to locate with highly accurate precision, the site within brain structure that showed the highest IMT activity. This may be useful for determining the site for biopsy, spectroscopy or the installation of a catheter with a radiation source for radiotherapy.

The visual assessment of scintigraphic images was supplemented with a semi-quantitative assessment of the tumour/background uptake ratio. The obtained values fall within the range of (1.22–2.45) and are similar to those reported by other authors who applied IMT labelled with 123-iodine [32, 33].

The application of 131-iodine may contribute to a more common use of alpha-methyl-tyrosine that could replace the more costly radiopharmaceuticals labeled with 123-iodine.

The effective doses of ionizing radiation in i.v. injections of ^{131}I-alpha-methyl-tyrosine were estimated based on the available dosimetric data for ^{123}I-alpha-methyl-tyrosine as published by Schmidt et al [34]. Their calculations were made with the use of ICRP-recommended methodology [35, 36]. The effective dose as calculated per activity unit of 123-iodine was 0.0073 mSv/MBq.

In our study, ^{131}I-alpha-methyl-tyrosine was not subject to significant accumulation in the body organs, except for the tumour tissue, and was quickly eliminated in urine. According to IRCP Publication no. 80, it can be shown that for iodine-labelled compounds with similar properties, the effective dose per activity unit of 131-iodine is several to ten times higher than that for 123-iodine.

As the study group of patients with cerebral glioma were administered ^{131}I-alpha-methyl-tyrosine with an activity of 74 to 111 MBq, the effective dose was estimated as ranging between 5–8 mSv, i.e. a dose typical for nuclear medicine examinations. For the calculation of the effective dose, an upper limit was determined for nuclide related increase in a dose of IMT labelled with 131-iodine, as compared to that labelled with 123-iodine. It should be mentioned that the patients were given an blocking treatment to prevent even a trace-level accumulation of 131-iodine in the thyroid.

The effective doses and the related risk of potential cancer induction are relatively small when compared to the side-effects of radio- and chemotherapy of gliomas. Thus, the risk pertaining to a scintigraphic examination should be considered in the context of the diagnosed neoplastic disease and the significant decrease in the life expectancy of the patient.

Conclusions

SPECT examinations with the use of ^{131}I-labelled alpha-methyl-tyrosine made it possible to obtain 100% diagnostic effectiveness in confirming or excluding the presence of neoplastic growth in the suspected site whenever MRI findings were inconclusive.

The fusion of SPECT-MR images makes it possible to precisely locate the site of tumour recurrence as well as the site for MRS, stereotactic biopsy and radiotherapy

The scintigraphic images obtained from SPECT after the administration of ^{131}I-alpha-methyl-tyrosine are clear enough and enable proper interpretation for the diagnosis to be made.

The usefulness of ^{131}I-alpha-methyl-tyrosine is so good that it can be considered as a substitute for IMT labelled with ^{123}-iodine.

References

1. Jaskólski DJ, Papierz W, Rieske P, Biernat W, Liberski P. Tumours of the central nervous system In the light of the WHO 2000 classification. Aktualności Neurologiczne 2001; 2: 200–235.
2. Waker AE, Robins M, Weinfeld FD. Epidemiology of brain tumors: the national survey of intracranial neoplasms. Neurology 1985; 35: 219––226.
3. Annegers JF, Schoenberg BS, Okazaki H, Kurland LT. Epidemiologic study of primary intracranial neoplasms. Arch Neurolol 1981; 38: 217––219.
4. Loeffler JS, Alexander E III, Wen PY. Results of stereotactic brachytherapy used in the initial management of patients with glioblastoma. J Natl Cancer Inst 1990; 82: 1918–1921.
5. Shenouda G, Souhami L, Podgorsak EB. Radiosurgery and accelerated radiotherapy for patients with glioblastoma. Can J Neurol Sci 1997; 24: 110–115.
6. Lacroix M, Abi-Said D, Fourney DR. A multivariate analysis of 416 patients with glioblasoma multiforme: prognosis, extent of resection and survival. J Neurosurgery 2001; 95: 190–198.
7. Keles GE, Lamborn KR, Berger MS. Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome. J Neurosurgery 2001; 95: 735–745.
8. Fine HA, Dear KB, Loeffler JS. Meta-analysis of radiation therapy with and without adjuvant chemiotherapy for malignant gliomas in adults. Cancer 1993; 71: 2585–2597.
9. Harsh GR IV, Levin VA, Gutin PH. Reoperation for recurrent glioblastoma and anaplastic astrocytoma. Neurosurgery 1987; 21: 615–621.
10. Ryterski J, Pytlewski A, Bogusławska R, Skrzyński S, Twarkowski P. MR imaging of postoperative changes in the brain. Rez Magn Med 1998; 6: 17–22.
11. Elster A, DiPersio D. Cranial postoperative site: assessment with contrast-enhanced MR imaging. Radiology 1990; 174: 93–98.
12. Henegar M, Moran C, Silbergeld D. Early postoperative magnetic resonance imaging following nonneoplastic cortical resection. J Neurosurg 1996; 84: 174–179.
13. Jeffries B, Kishore P, Singh et al. Contrast Enhancement in the postoperative brain. Radiology 1981; 139: 409–413.

14. Sato N, Bronen R, Sze G et al. Postoperative changes in the brain: MR imaging findings in patients without neoplasms. Radiology 1997; 204: 939–846.
15. Spetzger U, Thorn A, Glisbach J. Immediate postoperative CT contrast enhancement following susgery of cerebral tumoral lesions. J Com Assist Tomogr 1998; 22: 120–125.
16. Bruhn H, Frahm J, Gyngell M et al. Noninvasive differentiation of tumors with use of localized H1MR spectroscopy in vivo: Initial experience in patients with cerebral tumors. Radiology 1989; 172: 541––548.
17. Fulham MJ, Bizzi A, Dietz MJ et al. Mapping of brain tumor metabolites with proton MR spectroscopic imaging: clinical relevance. Radiology 1992; 185: 675–686.
18. Mateja P, Schober O. 123I-IMT SPET: introducing another research tool into clinical neuro-oncology? Eur J Nucl Med 2001; 28: 1–4.
19. Di Chiro G. Positron emission tomography using [18F] fluorodeoxyglucose in brain tumours; a powerful diagnostic and prognostic tool. Invest Radiol 1986; 22: 360–371.
20. Langen KJ, Pauleit D, Coenen H. 3-(123I)iodo-alfa-methyl-L-tyrosine: uptake mechanism and clinical applications. Nucl Med and Biol 2002; 29: 625–631.
21. Stokking R, Zuiderveld KJ, Holleke E et al. Normal fusion for three-dimensional integrated visualization of SPECT and Magnetic Resonance brain images. J Nucl Med 1997; 38: 624–629.
22. Nariari T, Senda M, Ishii K et al. Three- dimensional imaging of cortical structure function and glioma for tumor resection. J Nucl Med 1997; 38: 1563–1568.
23. Stokking R, van Isselt JW, van Rijk PP et al. Integrated visualisation of functional and anatomic brain data; a validation study. J Nuclear Med 1999; 40: 311–316.
24. Zuchora Z, Makarewicz R. Fuzje obrazów — zastosowanie w onkologii — teraźniejszość i perspektywy. Probl Med Nukl 2002; 16: 25.
25. Gajewicz W, Grzelak P, Rotkiewicz A et al. Przydatność obrazów fuzyjnych RM i SPECT do planowania protonowej spektroskopii RM (1HMRS) w diagnostyce nowotworów mózgu — doniesienie wstępne. Twój Magazyn Medyczny Ultrasonografia i Radiologia 2004; 447–453.
26. Biersack H-J, Coenen HH, Stocklin G et al. Imaging of brain tumors with L-3-(123I)iod-methyl tyrosine and SPECT. J Nucl Med 1989; 30: 110–112.
27. Riemann B, Stogbauer F, Kopka K et al. Kinetics of 3-[^{123}I]iodo-L--alpha-methyltyrosine transport in rat C6 glioma cells. Eur J Nucl Med 1999; 26: 1274–1278.
28. Weckesser M, Griesmeier M, Schmidt D et al. Iodine-123 alfa-methyl tyrosine single-photonemission tomography of cerebral gliomas: standardized evaluation of tumour uptake and extent. Eur J of Nucl Med 1998; 25: 150–156.
29. Kuwert T, Woesler B, Morgenroth C et al. Diagnosis of recurrent glioma with SPECT and iodine-123-alfa-methyl tyrosine. J Nucl Med 1998; 39: 23–27.
30. Kuwert T, Probst-Cousin S, Woesler B et al. Iodine-123-alfa-methyl tyrosine in gliomas: correlation with cellular denstity and proliferative activity. J Nucl Med 1997; 38: 1551–1555.
31. Saier MH Jr, Daniels GA, Boerner P, Lin J. Neutral amino acids transport system in animal cells; potential targets of oncogene action and regulators of cellular growth. J Membr Biol 1988; 104: 1–20.
32. Kuwert T, Morgenroth C, Woesler B et al. Uptake of iodine-123-alpha-methyl tyrosine by gliomas and non-neoplastic brain lesions. Eur J Nucl Med 1996; 23: 1345–1353.
33. Riemann B, Papke K, Kuwert T et al. Noninvasive grading of untreated gliomas; a comparative study of MR imaging and 3-(iodine 123)-L--alpha-methyltyrosine SPECT. Radiology 2002; 225: 567–574.
34. Schmidt D, LangenK-J, Herzog H et al. Whole-body kinetics and dosimetry of L-3(123I)iodo-alfa-methyltyrosine. Eur J Nucl Med 1997; 24: 1162–1166.
35. Radiation Dose to Patients from Radiopharmaceuticals ICRP Publ. No 53; Annals of the ICRP: Vol. 18, No. 1–4, 1987.
36. Radiation Dose to Patients from Radiopharmaceuticals (Addendum to ICRP 53 and 72) ICRP Publ. No 80; Annals of the ICRP; Vol. 28, No. 3, 1998.