

# Recurrent cerebral gliomas in MRI and Iodine-123-alpha-methyl-tyrosine SPECT: the use of digitally fused images

Piotr Grzelak<sup>1</sup>, Magdalena Górską-Chrzastek<sup>2</sup>,  
Witold Gajewicz<sup>1</sup>, Jacek Kuśmierk<sup>2</sup>, Krzysztof Tybor<sup>3</sup>,  
Ludomir Stefańczyk<sup>1</sup>

<sup>1</sup>Department of Radiology, Medical University, Łódź, Poland

<sup>2</sup>Department of Nuclear Medicine, Medical University, Łódź, Poland

<sup>3</sup>Department of Neurosurgery, Medical University, Łódź, Poland

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## Abstract

**BACKGROUND:** Early detection and site location of recurrent cerebral glioma helps design optimum therapeutic regimen, which contributes to prolonged survival time of the patients. However, diagnosing the neoplastic growth at the post-resection site is a difficult process. The diagnostic modality to provide the most extensive morphological data is dynamic MR tomography. On the other hand, the tumour-related metabolic changes can be best diagnosed using the PET and SPECT techniques of nuclear medicine that employ radiolabelled amino acid 131 I-alpha-methyl-tyrosine (IMT) as the tracer. Thus, for comprehensive diagnostics of brain tumours, it is most effective to combine both the modalities and evaluate the fused images. The aim of the present study was to verify the usefulness of the calculated algorithm for a digital fusion of RM/SPECT images for the assessment of post-resection site of cerebral gliomas.

**MATERIAL AND METHODS:** The findings of MR and SPECT imaging for 21 patients who had surgery for cerebral glioma were subject to assessment. Diagnosis was based on histopa-

thology results (8 cases of anaplastic astrocytoma and 13 cases of multiform glioblastoma). The site and size of the contrast enhancement areas from MR was compared with the hot focus location from SPECT.

**RESULTS:** The study confirmed the feasibility of digital fusion of images yielded by SPECT and MR. The fused images reflect the non-homogeneity of the post-resection site of cerebral gliomas. Contrast enhancement areas only partially overlapped with the hot foci which, furthermore, were found to be substantially smaller.

**CONCLUSIONS:** The consistency of tumour locations detected with MR and SPECT was higher for tumours of the anaplastic astrocytoma type than for multiform glioblastomas (higher polymorphism of pathological changes).

**Key words:** magnetic resonance, SPECT, fusion images, brain tumour

## Introduction

Although considerable progress has been made in the diagnosis and surgical and post-operative treatment of cerebral gliomas, the efficacy of the therapy often remains unsatisfying and the recurrent growth of these tumours is frequent. The routine treatment is surgical resection followed by radiotherapy (RTH) and chemotherapy (CHT) [1–3]. Early detection and location of the site of recurrent cerebral glioma helps design optimum therapeutic regimen, which contributes to a prolonged survival time of the patients [4]. However, it may sometimes be very difficult to diagnose the neoplastic growth at post-resection site and distinguish it from post-operative scars or radiation necrosis [5, 6]. The diagnostic modality to provide the most extensive morphological data is dynamic MR tomography. Despite the high spatial and tissue-specific resolution of MR images, they may yield inconclusive results in the diagnosis of recurrent tumours. The decisive criterion is thus the progressive development of the hot focus as detected in the follow-up examinations [7, 8]. On the other hand, the tumour-related metabolic changes can be best diagnosed using positron emission tomography (PET) and single photon emission computed tomography (SPECT) techniques of nuclear medicine

Correspondence to: Piotr Grzelak  
Department of Radiology, Medical University  
ul. Kopcińskiego 22, 90–153 Łódź, Poland  
Tel: (+48 42) 678 67 34; fax: (+48 42) 678 67 34  
e-mail: piotr.grzelak@insrad.am.lodz.pl

that employ radiopharmaceuticals (RP) as the tracer. Their increased uptake reflects an increased metabolic rate of amino acids or glucose [9, 10]. Iodine-labelled (123/131 I) alpha-methyl-tyrosine (123/131I-MT) is the only amino acid used for detection of recurrent gliomas in SPECT imaging [7]. In the diagnostics employing PET (a costly technique with limited availability) 11C-labelled amino acids are used while glucose analogue, 18F-fluorodeoxyglucose, owing to its high physiological uptake in cerebral cortex, is used mainly for tumour grading rather than its actual detection [9, 10].

In modern neuroradiology, an essential task is to collect information both on the morphology and metabolism of the pathological area. Thus, for comprehensive diagnosis of brain tumours, it is most effective to combine the imaging modalities under a single protocol and make an interpretation of the fused images [6, 7, 12, 13]. The aim of the present study was to verify the usefulness of the calculated algorithm for a digital fusion of MR/SPECT images for the assessment of post-resection site of cerebral gliomas.

## Material and methods

The findings of MR and SPECT imaging for 21 patients (12 males and 9 females, aged 22–58 years (mean 41 yr) with a history of surgical treatment for high-grade cerebral gliomas were subject to assessment. Diagnosis was based on histopathology of permanent sections. In eight cases (Group 1), anaplastic astrocytoma (WHO grade III) was found while the other 13 cases (Group 2) had multiform glioblastoma (WHO grade IV). Magnetic resonance and SPECT were performed between three and eighteen months after surgery. All the subjects were after surgical treatment and in the course of RTH and/or CHTH and they had recurrent tumour detected during the surgery, stereotactic biopsy or follow-up examinations.

The diagnostic procedure started with SPECT which was followed by MR imaging within seven days (mostly within the first 48 hours) after SPECT. Brain scintigraphy was performed 15 minutes after IV injection of 74–111 MBq 131I-MT, using a double-headed camera (Varicam, Elscint, Haifa, Israel) with high-energy collimators. The study protocol included precise positioning against the orthogonal plane; the transaxial plane was parallel to the bicallosal line. The patient's head was positioned so that the line connecting the cranial points and the apex of the auricles was at the right angle to the table. The images were evaluated visually; the result was positive if a hot focus indicating a recurrent tumour could be observed. Detailed diagnostic procedure was described by Górska-Chrząstek et al. [14].

Magnetic resonance was performed with SIEMENS Magnetom Vision Plus 1.5 T, with T1 and T2-dependent images before and after injection of Gd-DTPA contrast medium at a standard dose of 1 ml/kg b.w. Acquisition consisted of recording views on 256 × 256 pixel matrix in transverse, frontal and sagittal planes at 5 minutes after the injection. The thickness of the layer was 5 mm.

To construct the fused MR/SPECT images, a system developed at the Department of Radiology and Imaging Diagnostics, Medical University of Lodz, was applied. The background was 21 transverse cross-sections from MR and digital data from SPECT imaging [6, 12]. The data were transferred via fast internet connection and stored in DICOM format on a PACS server.

Scintigraphic images were re-processed because SPECT is characterized by a colour scale ranging from 124 to 171 units

which requires individual adjustment of the images. This was done with the use of HOTIRON graphic platform for mapping the intensity of contrast enhancement in the white-yellow-red scale, as the bedrock-type presentation, to select the areas with tracer intensity higher than the adopted level. Background subtraction was applied to eliminate voxels corresponding to RP uptake in intact tissues and retain only those representing hot foci. The cut-off level was determined based on RP uptake in the brain hemisphere ipsilateral to the focus, provided no focal proliferation was observed in the other hemisphere.

The fused images were obtained on a PC Intel workstation operating on Linux. The core applications comprised MATLAB, a statistical and mathematical software package and Statistical Parametric Mapping (SPM), routinely used for the analysis of functional resonance magnetic imaging (fMRI) supplemented with graphic applications worked out for the purpose of this protocol (Pixel Technology). The key task was to construct 3D functional images of the brain in terms of transverse sections by employing a volumetric matrix which makes it possible to correct the size and location of voxels (Analyze format). Automatic spatial correction of voxels depicting a 3D brain image was made using an algorithm for maximization of statistical similarities (so-called mutual information — MI) [15–18]. By applying this technique, we could eliminate the use of external markers (capsules with trace amount of markers applied onto skin) that were administered in the preliminary phase of the study. This resulted in a shorter duration of the procedure and increased accuracy of image fusion (we resigned from manual correction of voxel placement, which increases the risk of error due to manipulation and is rather time-consuming — it takes about 40–60 minutes). The theoretical accuracy of fusions obtained via the automatic procedure is limited by the size of voxel matrix used for the acquisition of image data. The available diagnostic protocols for MR enable acquisition at voxel volume of 1 mm<sup>3</sup> (a matrix with a 5 mm layer is routinely used in diagnostic imaging). The accuracy of image fusion is limited by SPECT parameters where voxel volume amounts to 5–8 mm<sup>3</sup> and marks the theoretical resolution of a fused image.

The 3D reconstruction of MR and SPECT images, as well as fused images, allowed assessment of the size and location of areas with increased 131I-MT uptake and contrast enhancement at post-resection site. The location of hot foci in images obtained from all the three modalities was compared. Volumetric measurements of the affected areas were made using fragmentation algorithms that help to select voxels with the adopted intensity of MR signal or emission threshold of gamma-radiation.

For comparison of the two study groups, the Student *t*-test was applied for independent variables since the distribution of the parameters examined was found not to be significantly different from the normal distribution.

## Results

For all the images examined, the SPECT/MRI fusion technique made it possible to carry out spatial adjustment of image areas, while the graphic applications shortened the reconstruction time to 15–20 minutes. Elimination of voxel signals from intact tissue was found at the background cut-off level of 47–63% of the colour scale used (approx. 58%). In subtraction, this level is in concor-

**Table 1. The size and location of contrast enhancement area after Gd-DTPA injection in MRI, hot spots in SPECT (cm<sup>3</sup>) and overlapping area (fused MRI/SPECT) in the group with recurrent tumours**

Number	Histopathological findings (WHO grade)	VOI Gd-DTPA [cm <sup>3</sup> ]	VOI IMT [cm <sup>3</sup> ]	VOI Gd-DTPA/IMT [cm <sup>3</sup> ]	VOI Gd-DTPA/IMT
8	Anaplastic astrocytoma (III)	64	45	32	70%
		74	49	49	100%
		96	82	58	70%
		123	67	55	80%
		131	87	55	65%
		192	65	40	60%
		194	77	77	100%
		221	132	92	70%
13	Multiform glioblastoma (IV)	84	55	39	70%
		97	64	35	55%
		115	71	40	55%
		132	52	45	85%
		137	65	26	40%
		154	57	6	10%
		164	89	44	50%
		167	103	67	65%
		175	78	15	20%
		176	79	31	40%
		185	72	50	70%
		243	78	39	50%
		243	83	50	60%

VOI<sub>Gd-DTPA</sub> — volume [cm<sup>3</sup>] of contrast enhancement area (MRI) after Gd-DTPA injection; VOI<sub>IMT</sub> — volume [cm<sup>3</sup>] of hot focus (SPECT) calculated with background subtraction method; VOI<sub>Gd-DTPA/IMT</sub> — hot focus location within contrast enhancement area after Gd-DTPA injection (% of overlapping area); WHO — World Health Organization

dance with <sup>131</sup>I-MT kinetics data which point to a 1.5–2.5-fold increase in tracer uptake within the tumour [19–21].

In both the study groups, the size of the pathological area was similar. No statistically significant differences were found with respect to the size of the contrast enhancement areas in MRI or hot foci in SPECT — in all the cases, hot foci were smaller than the contrast enhancement areas. The mean volume of Gd-DTPA contrast enhancement area, calculated using volumetric segmentation algorithm amounted to 154 cm<sup>3</sup>, while that of hot focus came to 72 cm<sup>3</sup>; the difference was statistically significant (Table 1). The findings also revealed that whenever recurrent anaplastic astrocytoma was diagnosed, the IMT uptake area overlapped by 60–100% with the contrast enhancement area (Figure 1, Figure 2). For multiform glioblastomas, these two overlapped only by 10–85%, thus making the common area significantly smaller (Figure 3, Figure 4).

The increase in recurrent tumour growth measured in terms of the volume of tissue subject to Gd-DTPA contrast enhancement did not correspond to the proportion of increase in the size of hot focus area. In the case of larger-size tumours, the proportion: Gd-DTPA contrast enhancement/IMT uptake areas was higher.

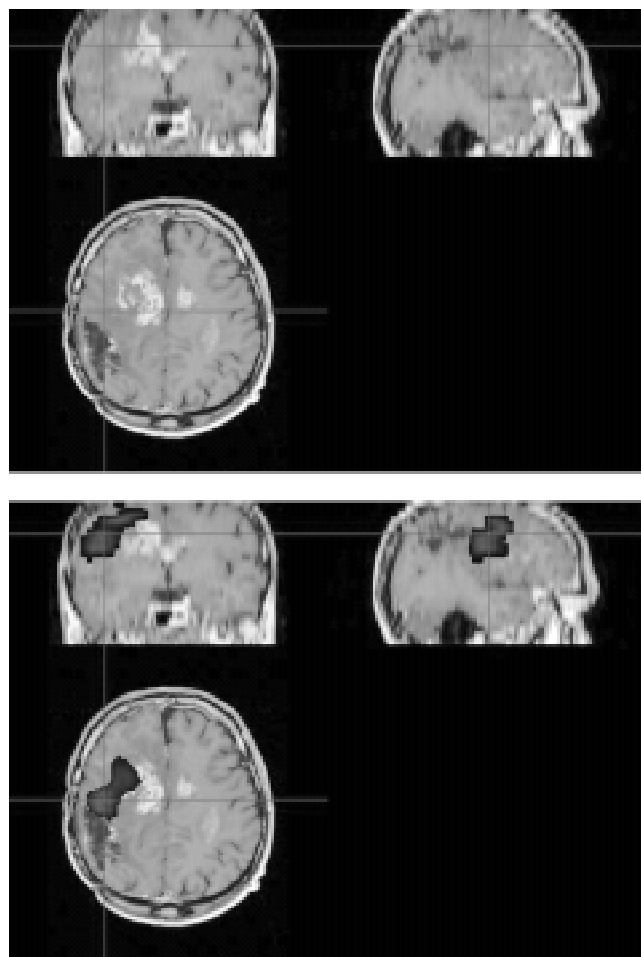
A statistically significant difference was found between the nominal value of the size of overlapping contrast enhancement and IMT uptake area in relation to the histological type of the tumour ( $p = 0.019$ ). A higher consistency in overlapping applied to anaplastic astrocytomas (Group 1). In the group diagnosed with multiform glioblastoma, in six cases the hot focus was located mostly out of the contrast enhancement area, and in four cases the RP uptake area covered the contrast enhancement area and

adjacent solid tissue which were not subject to enhancement but produced an altered MRI signal: low signal in T1-dependent and low signal in T2-dependent images (Figure 5). In two cases, the hot focus was located practically out of the contrast enhancement area (common area of less than 20%). In MR imaging, the site of hot focus corresponded to solid oedematous tissue, which was indicated by low signal in T1-dependent and high signal in T2-dependent images.

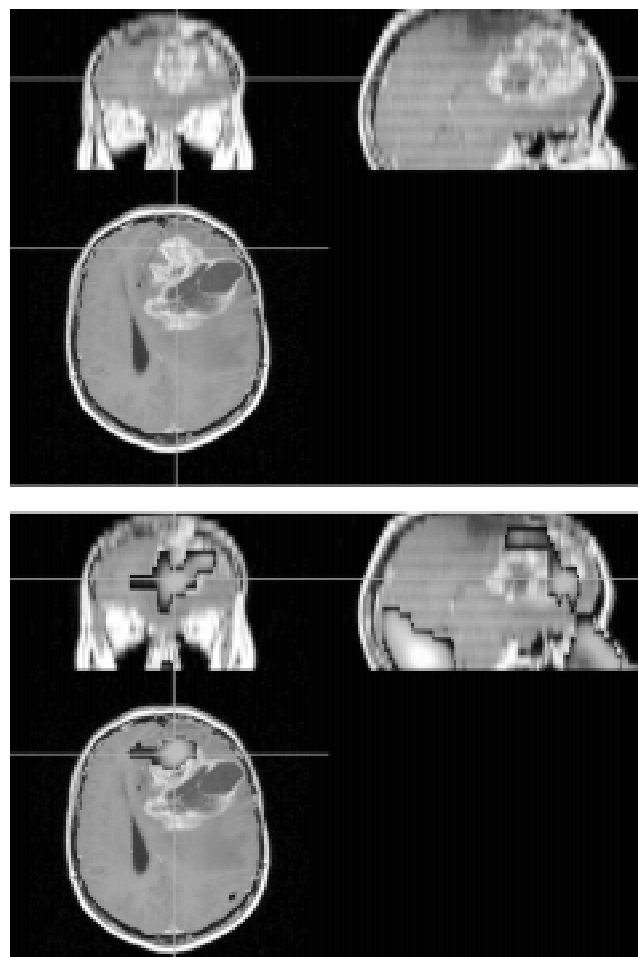
## Discussion

The post-resection site of cerebral gliomas is characterised by a high level of polymorphism in imaging diagnostics. The site morphology as revealed by CT or MRI is a consequence of multiple processes and their effects: lesions, post-resection scars and possibly tissue proliferation. The most prevalent pathologies include cystoid lesions filled with cerebrospinal fluid, gliomatous scars, post-radiation changes developing about six months after RTH and inflammatory effects. The radiological image can be imitative of a recurrent tumour since the site is subject to contrast enhancement [22]. The presence of oedematous changes hinders the diagnostics of multiform glioblastomas.

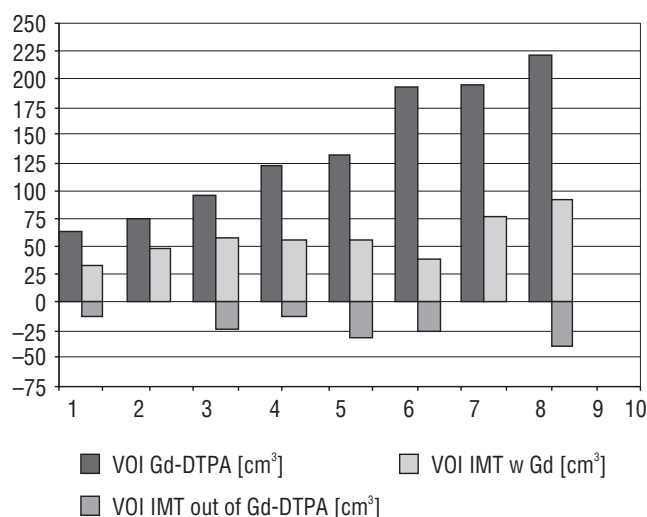
Radio-iodine-labelled IMT has been used as a tracer in the diagnostics of recurrent brain tumours since 1989. It is thought to be a marker of increased aminoacid demand by atypical cells. The ratio between IMT uptake in normal brain tissue and pathological glia proliferation is high and it enables the diagnosis of recurrent tumour making use of SPECT alone. Scintigraphy with



**Figure 1.** Fused MR/SPECT image of recurrent anaplastic astrocytoma in left frontal lobe: solid changes prevailing; contrast enhancement area (MRI) and hot focus (SPECT) clearly visible (hot focus smaller, completely within contrast enhancement area).



**Figure 3.** Fused MR/SPECT image of multiform glioblastoma in right frontal lobe: a change with non-homogenous morphology; contrast enhancement area (MR) and hot focus (SPECT) clearly visible (hot focus smaller, partially overlapping with contrast enhancement area).

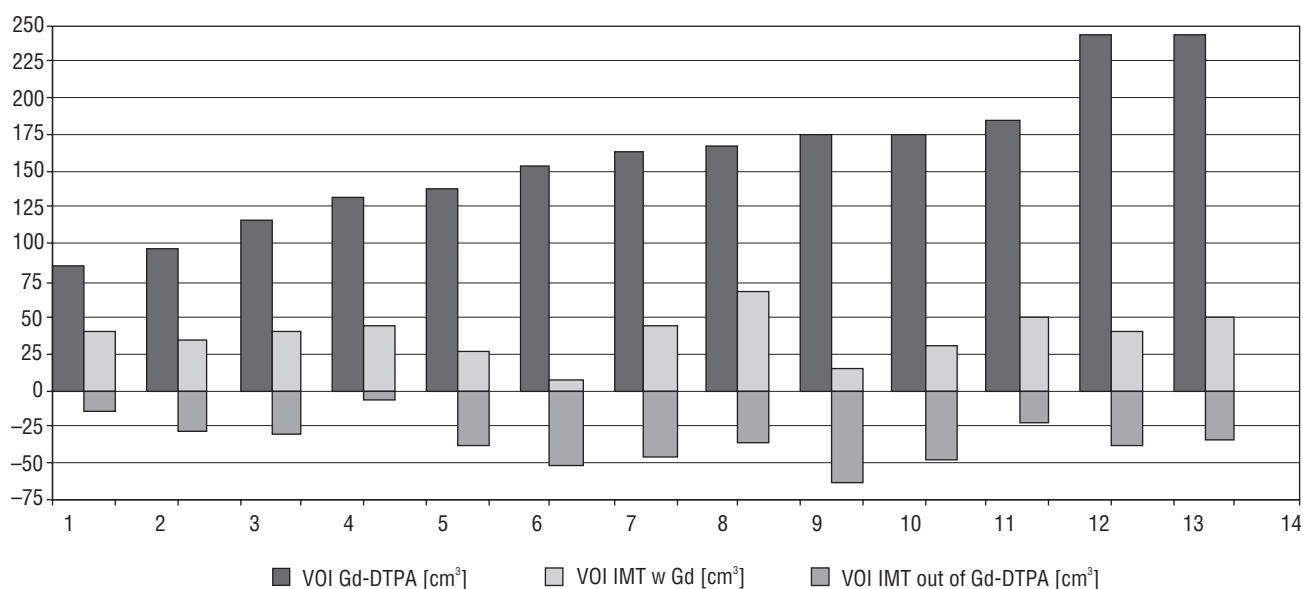


**Figure 2.** Volumes of contrast enhancement area (MRI), hot focus (SPECT) and overlapping area (fused MRI/SPECT) in the group with recurrent anaplastic astrocytoma.

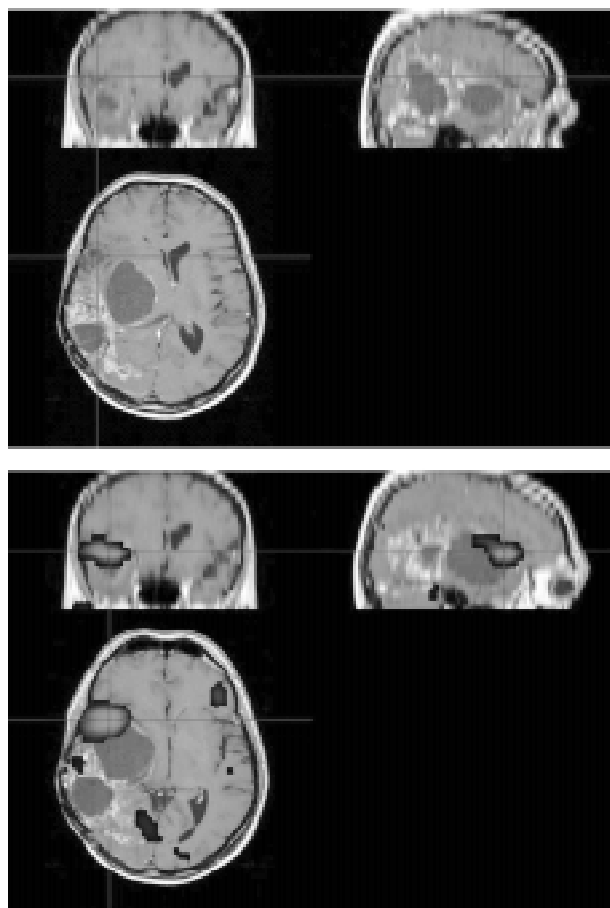
$^{131}\text{I}$ -labelled RPs is limited by a relatively low spatial resolution which impairs the accuracy of locating the pathological changes [5].

As a result of MR/SPECT image fusion, it was possible to distinguish  $^{131}\text{I}$ -MT uptake areas suspected of depicting recurrent tumour from contrast enhancement areas which also covered the retrograde changes [23, 24]. In all cases, the hot foci were smaller in size than the contrast enhancement areas. The necessity for precise location of the site of increased  $^{131}\text{I}$ -MT uptake is an implication of the studies employing PET/CT diagnostics.

Some authors postulate the presence of biological target volume (BTV) (Ling's hypothesis) and increased tracer uptake may indicate a cell fraction which needs a higher radiation dose during radiotherapy [3, 25]. Within the BTV area, the increased cellular vitality is related to their higher capacity for anaerobic processes [19]. It is worth noting that in the case of highly malignant multiform glioblastomas, increased  $^{131}\text{I}$ -MT uptake takes place also at the sites interpreted by MRI to be of doubtful character, at the border of the focus that is not contrast-enhanced. Probably, malignant infiltration proceeds at the site of  $^{131}\text{I}$ -MT uptake within the oedematous area but is not marked by contrast enhancement



**Figure 4.** Volumes of contrast enhancement area (MRI), hot focus (SPECT) and overlapping area (fused MRI/SPECT) in the group with recurrent multi-form glioblastoma.



**Figure 5.** Fused MR/SPECT image of multiform glioblastoma in right temporal lobe: cystoid change; contrast enhancement area (MR) and hot focus (SPECT) clearly visible (hot focus mainly in the peripheral areas of post-resection site, slightly overlapping with contrast enhancement area).

due to impaired perfusion processes. Recurrent growth of multi-form glioblastomas is characterised by a higher image polymorphism (a larger number of cystoid lesions) while the image of recurrent anaplastic astrocytomas depicts a more solid tissue.

The digital fusion of images obtained via imaging techniques based on different modes of acquisition offers more versatile diagnostics allowing a more comprehensive interpretation of results. The fused images provide complementary data on the morphology and metabolism of the affected tissue. In medical applications, this kind of imaging diagnostics is subject to dynamic growth when based mostly on PET/CT data. Yet, the procedure is costly and consequently rather infrequent even in highly developed countries. Recently, some systems have been developed for the combined acquisition of data from SPECT and CT. However, in brain tumour diagnostics, CT is inferior in morphological quality to MRI. While fused PET/CT and SPECT/CT images can be obtained via integrated diagnostic systems, the simultaneous acquisition of MR and SPECT images is impossible due to the mutual interference of these diagnostic instruments.

The technique described presently makes it possible to construct and interpret images acquired by different modes that can come even from distant laboratories and provides a functional interface for diagnostic systems from different locations. The versatility of the method and its relatively low cost justify introducing it to clinical practice on a large scale. Moreover, the method does not require additional instrument installations. If the positioning principles are observed, no extra acquisitions are necessary.

## Conclusions

1. It is possible to obtain fused images based on different imaging modalities (SPECT, MRI), provided a relevant data acquisition protocol is used.

2. Fused images depict a non-homogenous morphology of the post-resection sites of cerebral gliomas.
3. In MRI, contrast enhancement areas are larger than 131I-MT uptake areas in SPECT and these two are only partially overlapping.
4. For anaplastic astrocytoma, the compliance of pathological area location in MRI and SPECT is higher than for multiform glioblastomas.

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