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Original Research

^{11}C-Methionine PET/CT in Meningioma

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Positron emission tomography combined with computed tomography (PET/CT) is currently the standard imaging method in neuro-oncology for gliomas and metastatic lesions. There is much less experience with the use of PET/CT in meningioma, the most common primary tumor of the central nervous system, and there are some differences in how results are interpreted. The aim of the present work was to assess the potential for and features of the use of PET/CT to determine the degree of malignancy of meningioma, its prevalence, responses to radiotherapy, and diagnosis of relapse and/or post-radiation changes based on our own clinical experience and review of the literature. The study included 70 patients with 77 meningiomas who underwent ^{11}C-methionine PET/CT. Mean age at investigation was 57.4 years (range 19–86 years). The main parameter evaluated, the tumor/normal ratio (T/N) of ^{11}C-methionine (^{11}C-MET) in tumors, averaged 3.13 (1.00–10.66). Meningiomas had high ^{11}C-MET T/N, with values of >1.5 in 89.6% of cases. In histologically verified malignancy grade 1, 2, and 3 meningiomas (WHO scale), median T/N values were 4.06 [3.04; 4.57], 2.32 [2.12; 3.69], and 4.29 [2.60; 5.10] respectively, with no significant between-group differences. At the same time, non-growing or slowly growing histologically unverified meningiomas, i.e., incidentally discovered, had significantly lower ^{11}C-MET T/N than grade 1 and 3 meningiomas. There was no significant difference in T/N between irradiated meningiomas with controls for tumor growth (3.81 [2.97, 3.98]) and relapse (3.62 [2.60, 4.30]). Comparison of irradiated and non-irradiated grade 1, 2, and 3 meningiomas, as well as the combined group of grade 1–3 tumors, revealed no significant differences in ^{11}C-MET T/N. The use of PET/CT for meningiomas has a number of important characteristics. Meningiomas had high ^{11}C-MET T/N. Our data indicate that ^{11}C-MET PET/CT does not distinguish between meningiomas with different degrees of malignancy, i.e., WHO grades 1, 2, and 3. ^{11}C-MET T/N in meningiomas remains stably high or shows a slight decrease in cases with effective radiotherapy and long-term local control. Comparison of growing and non-growing meningiomas revealed no significant differences in ^{11}C-MET T/N between irradiated and non-irradiated tumors.

Keywords: meningioma, PET/CT, radiotracer, ^{11}C-methionine, degree of malignancy, continued tumor growth, radiotherapy, post-radiation changes.

Introduction. Positron emission tomography combined with computed tomography (PET/CT) is the current standard for evaluating neuro-oncology patients in a range of clinical situations [Verger et al., 2022]. PET/CT is a molecular imaging method, in contrast to the familiar methods of computed tomography and magnetic resonance imaging (CT and MRI), which are structure-based. PET/CT with amino acids, including ^{11}C-methionine (^{11}C-MET) and ^{18}F-fluorotyrosine (^{18}F-FET), is currently used routinely in the diagnosis of glial tumors of the brain. These radiotracers (RT) are used to assess the primary locations and grades of tumors [Verger et al., 2022]. Later in the treatment process, PET/CT allows differentiation of post-radiation changes from continued growth, assessment of tumor treatment responses, and determination of the metabolically active volume for delineation of radiotherapy targets. In addition, PET/CT can address all the same issues in cases of metastatic lesions of the central nervous system, yielding unique

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clinical information not always available using standard anatomical imaging methods.

These capabilities of the method generate the desire to use PET/CT for other nosological conditions, particularly for meningiomas, which are the most common primary intracranial tumors of the central nervous system and are actively treated with surgical and radiation methods [Rogers et al., 2015]. Treatment of meningiomas also consistently leads to questions which can potentially be resolved by PET/CT, such as non-invasive assessment of malignancy, clarification of the extent of the process, discrimination between therapeutic and tumor changes, confirmation of continued growth, etc.

However, the use of amino acid PET/CT in meningiomas has its own nuances and produces results differing from those of standard methods in the diagnosis of glial formations. The characteristics of the tissue structure of meningiomas have the result that, regardless of the degree of malignancy of the tumor, they have extremely high extents of vascularization, along with elevated levels of amino acid and fatty acid consumption. This explains the significant intensity of uptake of RT such as ^{11}C-MET and ^{18}F-FET, giving a high tumor/background ratio, which is referred to in the literature as the standardized uptake value (T/N). High T/N is seen equally in both malignant and the more common benign meningiomas [Slot et al., 2021].

High levels of somatostatin subtype 2 receptors (SSTR 2) make meningioma tissue highly sensitive to other, more specific RT based on somatostatin receptor ligands labeled with the isotope gallium-68 (^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC) [Filippi et al., 2022]. Among the major primary intracranial tumors, these receptors are found exclusively in meningiomas.

Methods. The study included 70 patients with 77 intracranial meningiomas who underwent ^{11}C-methionine PET/CT. Mean age at the time of investigation was 58.2 years (range 19.7–86.3 years). The ratio of men to women was 1 to 4.

In 21 cases, PET/CT was performed early in the evaluation as part of the diagnostic procedure before surgery or radiotherapy. In 14 patients, investigations were ordered to help differentiate between responses to radiation and continued tumor growth. In 35 cases, PET/CT was initially performed for other tumors (29 gliomas, three lymphomas, three metastatic lesions), meningioma being found as a concomitant disease.

All PET/CT studies were performed between 2011 and 2023. Most investigations (82.5%) were performed at the Burdenko National Medical Research Center for Neurosurgery.

Of the 77 meningiomas, 28 were verified histologically. Of these, 16 tumors were grade 1 malignancy on the WHO scale, seven were grade 2, and five were grade 3. A total of 49 meningiomas were not verified; these tumors were generally incidental findings and were characterized by slow or absent growth as demonstrated by MRI data over several (six or more) months. Clinical and radiological data (small size, clear outlines, round shape, absence of edema) indicated that these tumors could be classified as WHO grade 1. In the literature, tumors of this type are sometimes designated grade 0 [Kaul et al., 2014], as here.

Tumor locations were as follows: 26 (33.8%) were located convexitally, 16 (20.8%) were in the middle cranial fossa, 11 (14.3%) were parasagittal and in the posterior cranial fossa, eight (10.4%) were in the anterior cranial fossa, two (2.6%) each were in the tentorium and falx, and one (1.3%) was in the lateral ventricle.

Previous radiotherapy had been performed on 17 tumors (22.1%). The remaining 60 (77.9%) tumors had not previously been irradiated.

At the time of PET/CT investigations, 22 tumors displayed obvious growth over recent months, as indicated by MRI, along with the onset or aggravation of clinical manifestations. Nine of these formations had previously been irradiated. Pseudoprogression, i.e., temporary increases in tumors after radiotherapy, was excluded in these patients by acquisition of multiple images over time.

Forty-seven nonirradiated tumors were characterized by slow growth (minimal or insignificant changes in size over 1–3 years of follow-up) or stabilization at the time of PET/CT. Eight lesions were stable or shrinking after previous radiotherapy. Changes or the absence of changes were confirmed on the basis of sequences of MRI scans over periods of six months or more.

Statistical data analysis was run in the statistical programming language and environment R (version 3.6.1) in IDE RStudio (version 1.3.1093). The distributions of continuous and discrete quantitative variables in samples are presented as arithmetic means and standard deviations (M ± SD) for normally distributed random variables and medians and quartiles [Me [Q1; Q3]] for values with non-normal distributions. Categorical rates are presented as absolute numbers and percentages (n (%)). Compliance of samples with the normal distribution was determined using the Shapiro–Wilk test. The null hypothesis in statistical tests was rejected at a significance level of $p < 0.05$.

Results. The main assessment parameter, the index of RT accumulation in tumors, averaged 3.13 (1.00–10.66). Most meningiomas had high ^{11}C-MET T/N. T/N was >1.50 in 89.6% of cases and ≥2.00 in 70.1% of cases; just one case had T/N 1.00.

Median ^{11}C-MET accumulation indexes in meningiomas grades 0, 1, 2, and 3 were 2.24 [1.68; 2.99], 4.06 [3.04; 4.57], 2.32 [2.12; 3.69], and 4.29 [2.60; 5.10] respectively. We note that even histologically verified benign meningiomas WHO grade 1 often had a high RT T/N (Fig. 1). Pairwise comparison showed that the RT T/N of grade 0 meningiomas was significantly lower than those of grade 1 meningiomas ($p < 0.001$) and grade 3 meningiomas ($p = = 0.032$). T/N of histologically verified WHO grades 1, 2, and 3 meningiomas were not significantly different.

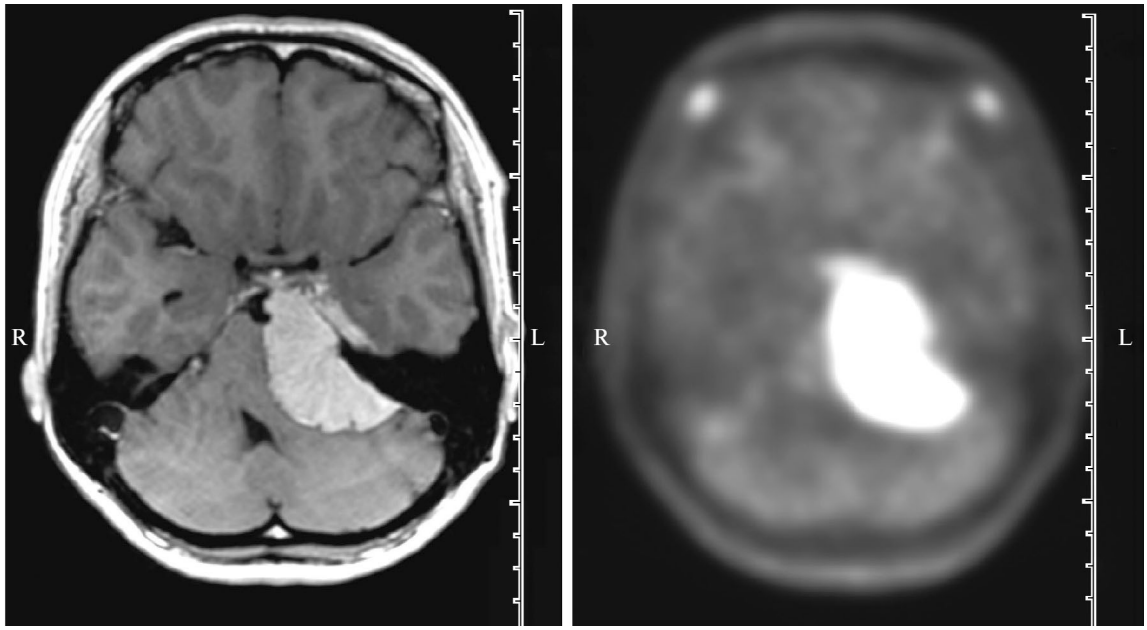

Fig. 1. WHO grade 1 petroclival meningioma on MRI (left) and ^{11}C-methionine PET/CT (right). PET/CT reveals a high level of RT accumulation: 5.5.

Comparison of ^{11}C-MET T/N of grade 1 meningiomas (4.06 [3.04; 4.57]) and grades 0 and 1 meningiomas (2.63 [1.81; 3.82]) with that of grade 2 and 3 meningiomas (3.11 [2.28; 4.49]) did not reveal any statistically significant difference. Comparison results did not change after exclusion of previously irradiated tumors from the comparison groups.

Comparison of ^{11}C-MET T/N was performed in three groups: actively growing clinically significant meningiomas, meningiomas stable after irradiation, and asymptomatic slowly growing or non-growing meningiomas. ^{11}C-MET T/N in the group of asymptomatic slowly growing or non-growing meningiomas was significantly lower (2.24 [1.70; 2.95]) than in the group of actively growing tumors (4.00 [2.39; 5.11]) ($p < 0.001$) and the group of meningiomas not growing after radiotherapy (3.81 [2.97; 3.98]) ($p = 0.018$). The groups consisting of clinically significant meningiomas with active growth and irradiated non-growing meningiomas were not significantly different from each other in terms of T/N. Median T/N values for these were 4.00 [2.39; 5.11] and 3.81 [2.97; 3.98] respectively. Exclusion of malignant grade 2 and 3 meningiomas from the groups under comparison did not alter these results.

There was no significant difference in T/N between irradiated meningiomas with controls for tumor growth (3.81 [2.97; 3.98]) and recurrent tumors (3.62 [2.60; 4.30]). There were also no differences in T/N between the groups of irradiated meningiomas grade 0 and 1 when comparing growing (4.00 [3.34; 4.31]) and non-growing (3.86 [2.70; 4.06]).

^{11}C-MET T/N in irradiated and non-irradiated meningiomas were compared. Grade 0 meningiomas were excluded from the analysis, as, according to previously presented data, these tumors had a significantly lower T/N and were generally incidental findings and were mainly under dynamic observation. Comparison of irradiated and non-irradiated grades 1, 2, 3, meningiomas and the combined grades 1–3 tumors group did not reveal any significant differences. Median T/N values of irradiated grades 1, 2, 3 and grades 1–3 meningiomas were 3.81 [3.00; 4.23], 3.62 [2.97, 3.69], 2.60 [2.60; 3.85], and 3.66 [2.60; 4.13] respectively, compared with 4.75 [3.10; 5.99], 2.12 [2.03; 2.95], 6.19 [5.24; 7.14], and 4.34 [2.21; 5.50] respectively in non-irradiated tumors.

Discussion. Published data show that PET/CT for meningiomas is generally performed with a variety of RT.

The most common tracer for PET imaging in oncology is ^{18}F-fluorodeoxyglucose (^{18}F-FDG), though this is used infrequently in neuroimaging because of its high level of physiological uptake in the cerebral cortex. In the case of meningiomas, which are mostly benign, slow-growing tumors with low energy metabolism, it is used even less frequently because of low image contrast [Slot et al., 2021; Hua et al., 2019; Lee et al., 2009].

Given that almost 100% of meningiomas show elevated expression of somatostatin receptors and that these receptors are extremely specific for meningiomas, recent years have seen active employment of the following ligands for PET/CT: ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC [Filippi et al., 2022]. These RT provide high sensitivity and contrast due to the lack of accumulation in tissues surrounding meningiomas (with the exception of the pituitary gland, which shows high physiological uptake) and can also be used to make differential diagnoses [Kowalski et al., 2021; Filippi et al., 2022]. However, PET/CT data should be evaluated in conjunction with other studies, as somatostatin receptor expression and activity can sometimes be detected by specific PET/CT in metastases (for example, breast cancer, etc.),

foci of granulomatous inflammation, pituitary adenomas and adenocarcinomas, gliomas, esthesioneuroblastomas, and fibrous dysplasia [Afshar-Oromieh et al., 2012; Palmisciano et al., 2022]. Increased accumulation of amino acids or their analogs, such as ^{11}C-MET and ^{18}F-FET, is known to occur in slowly growing benign glial tumors [Astner et al., 2008]. Amino acid PET/CT has higher background contrast than ^{18}F-FDG [Mitamura et al., 2018; Arita et al., 2012]. RT based on somatostatin receptor ligands and amino acids (^{11}C-MET and ^{18}F-FET) are currently the most widely used for evaluation of meningiomas on PET/CT, these latter being used more commonly.

PET/CT for meningiomas usually has multiple objectives, and the RT used here have different potentials and capabilities for fulfilling these. PET/CT with somatostatin receptor ligands, and also with amino acids, produce high contrast between meningiomas and surrounding tissues [Filippi et al., 2022; Mitamura et al., 2018]. This method may be more informative than MRI and CT in detecting meningiomas [Rachinger et al., 2015; Kowalski et al., 2021].

A study of 134 patients reported by Afshar-Oromieh et al. [2012] identified 190 meningiomas using ^{68}Ga-DOTATOC PET/CT and only 171 meningiomas using contrast-enhanced MRI. The authors concluded that ^{68}Ga-DOTATOC PET/CT had greater sensitivity than MRI, especially for falx and skull base formations and tumors obscured by calcification and artifacts.

One current area of application of PET/CT for meningiomas is that of defining targets for radiotherapy, as standard imaging methods (CT and MRI) have limitations in terms of assessing the extent of tumors in the sinuses, skull base, and orbit.

Grosu et al. [2006] found discrepancies in meningioma volumes by more than 20% in three out of 10 cases when outlining was performed by different specialists. Use of ^{11}C-MET PET/CT reduced variability in target detection and accelerated the process. After addition of PET, the correlation between volumes increased from 0.855 to 0.988. Astner et al. [2008] found that use of ^{11}C-MET PET to define targets in most cases (29 out of 32) allowed addition of small tumor fragments (1.6 ± 1.7 cm^3) not visible on MRI or CT [Astner et al., 2008]. On average, this increase was by $9.4\% \pm 10.7\%$ in terms of volume.

Kessel et al. [2020] evaluated the impact of PET/CT on the outcome of radiotherapy for meningiomas. The study included 332 patients with 339 meningiomas. In 203 cases, PET/CT was used when planning radiotherapy (^{68}Ga-DOTA (104), ^{18}F-FET (26), and ^{11}C-MET (73)). With a median follow-up of 5.6 years, significant increases in overall and disease-free survival of patients with benign meningiomas was demonstrated when PET/CT was added to the planning process. This effect was not found in patients with malignant meningiomas.

Similar data on the informativeness of PET/CT were obtained in studies with somatostatin receptor ligands [Perlow et al., 2022; Kriwanek et al., 2022; Kowalski et al., 2021; Acker et al., 2019]. Similar studies with ^{68}Ga-DOTATATE demonstrated the ability of PET to exclude postoperative and post-radiation changes from the volume of radiation [Rachinger et al., 2015; Ivanidze et al., 2019].

In the present study, only one meningioma had an T/N of 1.00 and was not discriminated from the brain tissue background. Most meningiomas had high ^{11}C-MET T/N, such that tumors stood out from surrounding tissues. T/N was greater than 1.50 in 89.6% of cases and 2.00 or more in 70.1% of cases. ^{11}C-MET PET/CT can therefore be used both for the detection of meningiomas and for precise determination of target contours during radiotherapy.

PET/CT is of great importance in neurooncology for non-invasive assessment of the degree of malignancy of glial tumors. By analogy, attempts have been made to use PET/CT for the non-invasive determination of this parameter in meningiomas.

Most studies on the capabilities of ^{18}F-FDG PET/CT have demonstrated the ability of the technique to distinguish between benign (WHO grade 1) and malignant (WHO grades 2–3) meningiomas. A number of sources indicate that the threshold T/N in this case is 1–1.3 [Lee et al., 2009; Cremerius et al., 1997; Hua et al., 2019]. At the same time, studies using ^{11}C-MET and ^{68}Ga-DOTATATE have demonstrated that this method is unable to distinguish between benign and malignant meningiomas, as is traditionally done to discriminate diffuse glial tumors [Arita et al., 2012; Rachinger et al., 2015].

In 2021, Slot et al. presented a systematic review and meta-analysis on the grading of meningiomas using PET/CT [Slot et al., 2021]. This work included 22 studies of 432 patients, most using ^{18}F-FDG. The combined data showed that mean ^{18}F-FDG T/N in grades 2–3 meningiomas was greater than in grade 1 meningiomas by 0.42 (0.12–0.73), while mean ^{18}F-FDG SUV was greater by 2.51 (1.36–3.66). The authors also recalculated data for ^{18}F-FET, ^{11}C-MET, and other RT and found no relationship with the degree of malignancy of the tumor, noting the small number of such studies.

The present study found no significant difference in ^{11}C-MET T/N between histologically verified meningiomas of grades 1, 2, and 3, with medians of 4.06 [3.04; 4.57], 2.32 [2.12; 3.69], and 4.29 [2.60; 5.10] respectively. High levels of accumulation in meningiomas of WHO grade 1 malignancy should be noted, demonstrating the inability of ^{11}C-MET PET to provide adequate assessment of the degree of malignancy of these tumors. A significantly lower T/N was obtained in the group of grade 0 meningiomas, which consisted of small non-growing or slowly growing histologically unverified meningiomas, often incidental findings. Tumors of this type appear to have a lower level of amino acid metabolism than grade 1–3 meningiomas, whose growth produces clinical manifestations ultimately requiring surgical treatment. This group of grade 0 meningiomas was in fact a group of “asymptomatic slowly growing or

non-growing meningiomas" in which ^{11}C-MET T/N was significantly lower (2.24 [1.70, 2.95]) than in the group of "actively growing clinically significant meningiomas" (4.00 [2.39; 5.11]) and the group of "stable meningiomas after irradiation" (3.81 [2.97; 3.98]). The data obtained here may indicate metabolic and possibly clinical heterogeneity of benign meningiomas, which requires additional research.

Numerous studies have addressed assessment of responses of meningiomas to radiotherapy. MRI examination can show lack of change in tumor size after irradiation and can sometimes show signs of "pseudoprogression." The use of PET/CT may provide additional clinical information in these cases [Jung et al., 2022].

A study by Jeltema et al. compared ^{11}C-MET PET/CT data acquired before radiotherapy and at follow-up (median 84 months) in 20 patients with meningiomas [Jeltema et al., 2021]. These researchers noted a high level of RT accumulation in meningiomas not progressing as indicated by MRI. T/N was in the range 2.16–3.17. Among several parameters, irradiation was followed by a significant decrease only in median peak T/N, from 2.57 to 2.20.

Gudjonsson et al. evaluated changes in ^{11}C-MET PET/CT over 36 months after proton irradiation of meningiomas in 19 patients [Gudjonsson et al., 2000]. In 15 cases, WHO grade 1 meningioma was confirmed histologically. T/N was 1.35–5.1 before radiotherapy and 1.13–4.62 after 36 months. The mean reduction in T/N was by 0.71. T/N decreased over time in 15 of 19 cases, while four cases showed increases without obvious tumor progression on MRI scans. Ryttlefors et al. [2016] reported follow-up of these patients for up to 10 years with repeat ^{11}C-MET PET/CT scans. Continued growth was detected in 2 patients during this period, this being preceded by increases in ^{11}C-MET T/N two and three years before MRI-demonstrated tumor progression.

Similar results were obtained using somatostatin receptor ligands in a small series: most of the patients showed slight decreases in activity, while a minority showed stabilization or increases in parameters on MRI monitoring of tumor growth [Lütgendorf-Caucig et al., 2023; Kowalski et al., 2021]. However, comparison of ^{68}Ga-DOTATATE SUV in irradiated and non-irradiated meningiomas did not identify any statistically significant differences [Campos Neto et al., 2022].

Our work also found no significant difference in ^{11}C-MET T/N between irradiated and non-irradiated meningiomas. Thus, T/N of actively growing clinically significant meningiomas (4.00 [2.39; 5.11]) was no different from T/N of stable irradiated meningiomas (3.81 [2.97; 3.98]). There were no differences in the level of ^{11}C-MET activity in irradiated meningiomas with monitoring of tumor growth (median IR = 3.81 [2.97, 3.98]) and with relapse (median IR = 3.62 [2.60, 4.30]). Comparison of grades 1, 2, 3 irradiated and non-irradiated meningiomas and the combined group of grade 1–3 tumors yielded no significant differences in ^{11}C-MET T/N.

Thus, single PET/CT studies with a variety of RT do not lead to any conclusions regarding the efficacy of radiotherapy and do not confirm relapse; however, dynamic PET/CT with assessment of the level of RT metabolism may be indicated for solving these problems.

Conclusions. Use of PET/CT in meningioma has a number of features, though direct extrapolation of experience in the diagnosis of glial tumors on PET/CT can lead to diagnostic errors.

The main RT used today are a group of amino acids (^{18}F-FET and ^{11}C-MET) and somatostatin receptor ligands, which have similar diagnostic capabilities (^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC). PET/CT with these RT demonstrates high levels of metabolic and receptor activity in meningiomas with different degrees of malignancy, which, on the one hand, makes it impossible to differentiate malignant tumors from benign tumors, but on the other hand contributes to more detailed visualization and reliable assessment of tumor volume in comparison with standard MRI. In this context, the use of PET/CT is indicated for identification of meningiomas in locations which are difficult for MRI visualization (base of the skull, venous sinuses) and for delineating the target when planning radiotherapy.

It should be noted that a single PET/CT scan may not be informative for the purpose of diagnosing continued growth of meningioma after previous radiotherapy. Repeat studies over time can confirm relapse by detecting increases in amino acid accumulation activity or increases in the level of somatostatin receptors. This technique requires additional clinical studies. In addition, PET/CT is of demonstrated value in the differential diagnosis of tumor tissue and post-radiation changes.

Thus, PET/CT can solve a number of problems in the diagnosis and treatment of meningiomas. Knowledge of the capabilities of various RT and the correct identification of indications for investigations provide the basis for obtaining clinically significant results.

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