PET using $^{11}$C-methionine in recognition of pseudoprogression in cerebral glioma after combined treatment

T.YU. SKVORTSOVA, Z.L. BRODSKAYA, A.F. GURCHIN

N.P. Bechtereva Institute of the Human Brain of Russian Academy of Sciences, St. Petersburg, Russia

The purpose of the study was to evaluate the value of PET using $^{11}$C-methionine (PET-Met) for distinction between true glioma progression and pseudoprogression (PsPr). 72 patients with treated cerebral glioma investigated by PET-Met were identified from prospective database. Entry criteria included new or progressive MR imaging enhancing lesions within first 6 months after irradiation and definite final diagnosis on the basis of the pathological study ($n=17$) or clinical-radiological follow-up on an average 16 months. PET examinations were assessed by visual inspection and calculating $^{11}$C-methionine uptake index (UI).

**Results.** Pseudoprogression was defined as early radiological progression with subsequent regress or stabilization, without salvage therapy. 42 patients were considered to exhibit PsPr and 30 patients had true glioma progression. In PsPr group PET scans were either negative ($n=6$) or slightly increased tracer uptake (UI range 1.2—2.0) was seen in the site of contrast-enhanced lesion. The UI was 1.48±0.39 (mean±SD). In comparison with pretreatment PET 15 patients showed decrease $^{11}$C-methionine uptake on an average by 26%. In recurrence group PET-Met showed abnormal high focal $^{11}$C-methionine uptake in the lesion. The UI was 2.54±0.84 (range 1.54—5.4). An UI threshold value of greater than 1.9 optimized differentiation between glioma progression and PsPr with sensitivity of 83.3% and specificity of 97.0%.

**Conclusion.** Metabolic characteristics of PsPr included negative tracer accumulation or slightly increased $^{11}$C-methionine uptake in the contrast-enhancing lesion with UI less than 1.9.

Keywords: PET, $^{11}$C-methionine, pseudoprogression, recurrent glioma.

The current standard of care for patients with malignant cerebral gliomas, primarily glioblastomas (GBs), includes the maximum possible amount of tumor resection followed by radiation therapy (RT) with the concomitant or adjuvant use of cytotoxic drugs, most commonly temozolomide (brand name temodal). During the period from 2000 to 2010, this approach increased 2-year survival of glioblastoma patients from 10 to 40% [13]. At the same time, it was found that the dynamic control, in the nearest months after RT completion, using magnetic resonance imaging (MRI) with the contrast enhancement (CE) technique may reveal neuroradiological signs of edema and contrast rising in the resected tumor bed. Approximately in half of these patients, contrast rising reflects true tumor progression. However, in the other half, CE eventually decreases or remains constant while continuing the same therapy, which indicates the transient nature of disorders [4]. This paradox, known as pseudoprogression, is often observed with addition of temodal during radiation regimen, but can develop after isolated RT or radiosurgery [5, 9, 16]. For the first time, the phenomenon of transient radiological changes was mentioned by W. Hoffman et al. in 1979 [12] and was more fully described in the publication by M. De Wit et al. in 2004 [10]. Studies in recent years, in the era of the new standard of glioblastoma treatment using temodal, have demonstrated that the frequency of pseudoprogression is 19—28.9% of the total number of patients [15, 20—22]. Usually, pseudoprogression occurs within the first 3 months after completion of treatment (60% of patients), but it can also develop in a period of several weeks up to 6 months after radiotherapy [8]. Pseudoprogression is a serious clinical problem that significantly complicates the diagnosis of continued growth of cerebral tumors and the tactics of patient treatment. Traditional neuroradiological methods do not allow differentiating between true tumor progression and pseudoprogression [23]. Currently, the most affordable and conventional method to differentiate between these states is dynamic MRI control. An analysis of serial MRI examinations documents the phenomenon of pseudoprogression in the case of reducing the contrast area or its disappearance. The use of functional techniques of MRI or positron emission tomography (PET) is promising, however, the assessment of their informative value in solving one of the key problems in monitoring of glioma treatment has just begun [14, 18].

The aim of this work was to develop metabolic criteria for pseudoprogression of brain gliomas using PET with $^{11}$C-methionine and to study the informative value of the method for differentiation between true glioma progression and pseudoprogression.

**Material and Methods**

A prospective analysis of the results of PET with $^{11}$C-methionine was performed in 72 patients (35 males and 37 females) aged from 3 to 68 years (36±19 years) with brain gliomas after combined therapy of the primary tumor (54 patients) or its continued growth (18 patients). The inclusion criteria were signs of the early development of radiological progression in the primary tumor bed in the form of the emergence or increase of CE during a MRI examination in the period from 1 to 6 months after RT completion. The first PET examination in 23 patients was performed before treatment. In the remaining 49 cases, it was performed, if continued tumor growth was suspected. The final diagnosis was based on the...
results of a histopathological examination after repeated ope-
ration (n=16) or autopsy (n=1) as well as the results of follow-
up, including MRI and PET. The mean follow-up period after
detection of the radiological progression of glioma was 16±10
months (from 1 to 44 months). A total of 225 PET examina-
tions were performed.

PET examinations were performed on a Scanditronix PC
2048 positron emission scanner (Sweden) designed to scan the
head. The scanner enables simultaneous acquisition of 15
axial slices with the interslice distance of 6.5 mm. The spatial
resolution of the camera was 6.5 mm. The studies were con-
ducted in the dynamic or static scanning mode. The correction
of emission data for the heterogeneity of medium permeabili-
ty to gamma ray was performed using software. Some patients
were examined on Philips Gemini TF positron emission and
computed tomography (PET-CT) scanners with the PET scan-
er spatial resolution of 5 mm.

A radiopharmaceutical drug (RPD), L-(methyl-\(^{11}\)C)-
methionine (\(^{11}\)C-methionine) was synthesized in the radio-
chemical laboratory of this Institute by methylation with
L-homocysteine thiolactone and isolation of the final product
by solid phase extraction [1].

An image analysis was performed on a workstation using
software developed specially for the scanner. Resulting PET
images were visually evaluated as positive or negative based on
the \(^{11}\)C-methionine accumulation level in accordance with the
location of a positive contrast lesion on MRI scans as well as
in other brain structures. The level of RPD accumulation ex-
ceeding that of the unaffected brain portions was considered
positive (elevated). A semi-quantitative analysis was to deter-
dine the uptake index (UI) for \(^{11}\)C-methionine that was cal-
dulated by dividing the RPD concentration in the region of
interest by the activity value in the contralateral cortex.

A statistical analysis included descriptive statistics for all
variables: the calculation of group mean values, standard de-
viation, and median. Conventional indicators of the method
informative value were calculated according to standard for-
mulas. To evaluate the statistical significance of quantitative
indicator differences between the selected groups, the non-
parametric Mann-Whitney test was used. The level of \(p<0.05\)
was considered as significant.

**Results**

The mean term for emergence of signs of the radiological
progression on MRI scans after RT completion was 3.7±1.8
months (median of 4 months). Based on the final diagnosis,
patients were divided into two groups: the changes were con-
sidered as pseudoprogression in 42 patients, and true progres-
sion of glioma was diagnosed in 30 patients.

Pseudoprogression is defined as an early radiological pro-
gression in the area of the primary tumor localization, usually
followed by regress or stabilization of the changes based on the
results of follow-up for at least 6 months. In 39 patients, the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>pseudoprogression</th>
<th>continued growth of glioma</th>
</tr>
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<tbody>
<tr>
<td>Histostructure of glioma, abs.:</td>
<td></td>
<td></td>
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<tr>
<td>benign glioma</td>
<td>11</td>
<td>6</td>
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<tr>
<td>An. ASC/ODG/ependymoma</td>
<td>10/1/3</td>
<td>2/1/0</td>
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<tr>
<td>glioblastoma</td>
<td>15</td>
<td>19</td>
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<tr>
<td>unverified glioma</td>
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<td>2</td>
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<tr>
<td>Previous treatment, abs. (%)</td>
<td></td>
<td></td>
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<tr>
<td>RT and CT</td>
<td>9 (21.4)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>RT and temodal</td>
<td>21 (50.0)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>RT</td>
<td>6 (14.3)</td>
<td>6 (20.0)</td>
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<tr>
<td>RS</td>
<td>6 (14.3)</td>
<td>6 (20.0)</td>
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<tr>
<td>CE localization, abs. (%)</td>
<td></td>
<td></td>
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<tr>
<td>near postoperative cyst</td>
<td>18 (42.9)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>tumor mass</td>
<td>24 (57.1)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>multifocal pattern</td>
<td>0</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>(^{11})C-methionine UI (mean ± standard deviation)</td>
<td>1.48±0.39</td>
<td>2.54±0.84</td>
</tr>
<tr>
<td>Observation, months (mean ± standard deviation)</td>
<td>19.5±10.2</td>
<td>8.4±5.5</td>
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<td>diagnosis verification, abs.:</td>
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<td>Outcome, abs.:</td>
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<tr>
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<tr>
<td>death</td>
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</table>

Footnote. An. — anaplastic; ASC — astrocytoma; ODC — oligodendrogliaoma; RT — radiation therapy; CT — chemotherapy; RS — radiosurgery.
previously selected chemotherapy or surveillance was continued. In 3 patients, bevacizumab was additionally used for treatment.

Upon true tumor progression, patients had unsatisfactory outcome with the neurological deficit progression as well as radiological and metabolic disorders with the spread of lesions into the adjacent portions of the brain or histologically confirmed tumor growth. The main characteristics of the groups are summarized in the Table.

In the group of patients with pseudoprogression, the PET results were negative in 6 patients (Fig. 1). In the remaining 36, moderately increased uptake of 11C-methionine in the area of positive contrast cerebral lesion was observed. UI was within 1.2—2.0 often in combination with an ametabolic region, caused by necrosis, coinciding in the localization with the contrast region on a MRI scan. In 12 patients who were examined before treatment and during the radiological progression, a reduction in the level of 11C-methionine tumor uptake occurred by 26%, on average, with a possible decrease in the lesion size due to the lack of RPD accumulation in the area of radiation injury (Fig. 2). A histopathological examination after re-operation in 6 patients demonstrated a combination of radiation pathomorphism and individual glioma cells.

Follow-up results. According to the PET data, 38 patients were observed with regress or stabilization of positive contrast anomalies on the MRI scan and the metabolic activity in the region of interest in the first 6 months of follow-up. Despite the fact that the early RT effect is usually transient in nature, 4 patients had augmentation of radiation injury in the form of CE progression with the development of large radiation necrosis or the emergence of new lesions of postcontrast enhancement of the MRI signal. 12 patients developed local (n=8) or distant (n=4) continued glioma growth in 18 months, on average, (range of 13 to 44 months) after the first PET.

30 patients were diagnosed with true progression of the tumor in the form of a large lesion of high 11C-methionine uptake that coincided in the location with the contrast area on the MRI scan (Figs. 3, 4). 11C-methionine UI ranged from 1.54 to 5.4 and was statistically significantly different from that in pseudoprogression (Fig. 5). Upon comparison with the PET pattern obtained prior to treatment or in the immediate postoperative period (n=11), the emergence of a new site of high RPD uptake, when the previous PET pattern after total glioma resection was negative (n=2), or an increase in size of the high RPD accumulation site, often with a simultaneous UI increase, was detected.

Fig. 1. Pseudoprogression of glioblastoma.
After total resection of glioblastoma and 4 months after chemoradiotherapy, the contrast area near the wall of a postsurgical cyst of the right temporal lobe appeared on the MRI scan (a). Upon PET with 11C-methionine, negative methionine uptake eliminated progression of glioma (b). 24 months later, a significant reduction in the contrast area on the MRI scan was observed (c) with a stable negative PET pattern (d).
As it follows from the results, the metabolic characteristic of pseudoprogresion includes negative or moderately increased uptake of $^{11}$C-methionine with UI of less than 1.9 in accordance with the location of a positive contrast lesion in the MRI scan. The threshold UI value of more than 1.9 enabled differentiation between continued tumor growth and its pseudoprogresion with the sensitivity of 83.5% and the specificity of 97.0%.

Discussion

Despite wide recognition of the pseudoprogresion phenomenon, this term is not clearly defined, and a pathological substrate of pseudoprogresion is not completely unique. The published data, including pathological and radiological correlations, are extremely scarce. M. Chamberlain et al. [7], using a histological examination of surgical specimens of 7 patients, characterized pseudoprogresion as treatment-induced necrosis without signs of the tumor tissue. Given the fact of the frequent development of radiation effects in glioblastomas with methylation of the promoter region of the MGMT gene (O6-methylguanine-DNA methyltransferase), necrosis can be caused by highly effective chemoradiotherapy [3]. The development mechanism of this effect was proposed by A. Chakvarti et al. [6] who found that temodal enhances the glioblastoma response to radiation in the presence of methylation of the MGMT gene promoter by damaging the DNA double helix, which is a critical factor of cell death under the influence of irradiation. Monitoring of neutron capture RT with boron compounds (BNRT) revealed large necroses and individual viable cells with a low proliferative activity in tissue samples of 5 operated patients suspected for early progression of malignant glioma that allowed the authors of [17] to consider pseudoprogresion as radiation-induced intratumoral necrosis developing in the subacute phase after BNRT. The pathomorphological picture after combined treatment of glioma is known to include a combination of radiation pathomorphism of the tissue and residual/progressive tumor [19]. In the presence of tumor tissue, the precise delineation of the residual tumor and its progression is the key factor to make a decision on further treat-
**Fig. 3. Continued growth of anaplastic oligodendroglioma.**

MRI scan 3 months after radiosurgery for recurrent glioma of the right parietal lobe. A contrast enhancement in the intervention region was detected (a). High $^11$C-methionine uptake (UI=2.44), on PET (b) and combined PET/CT (d) scans, coinciding in the localization with a postcontrast increase in the MRI signal documents the true progression of glioma confirmed during reoperation.

**Fig. 4. Continued growth of glioblastoma of the right temporal lobe.**

MRI scan 6 months after RT with concomitant use of temodal. A new ring-contrast focus appeared in the surgery region (a, b — arrow). During PET, a focus of high $^11$C-methionine uptake (UI=2.0) was detected that coincided with EC, which indicates continued growth of glioblastomas (c, d — dotted arrows) verified by surgery.
ment. It is assumed that the pathological changes in pseudoprogression include elements of radiation-induced necrosis and viable tumor cells with a lower cell density and proliferative activity in comparison with a primary tumor prior to treatment [11]. This hypothesis includes two interacting pathological processes leading to pseudoprogression: transient vascular lesion and antiproliferative effect of tumor treatment. The concept of pseudoprogression is terminologically close to well-known early radiation damage of the brain, and the current concept suggests using the term “pseudoprogression” instead of early radiation damage [4].

From a practical point of view, the emergence or expansion of the contrast area in the irradiated tumor bed arouses reasonable suspicion of its progression, and determination of the origin of this phenomenon becomes the main task. Evaluation of the treated tumor metabolic status can provide substantial assistance in interpretation of the negative dynamics of the radiological picture. The use of PET with 11C-methionine upon suspicion of continued tumor growth is based on pathophysiological differences between the actively growing tumor tissue and brain responses to therapy: increased transport and metabolism of the amino acid in the proliferating tumor and, conversely, a low level of metabolism in treatment-induced brain lesions [2]. As our results demonstrated, which are consistent with the pathomorphological data, two main types of pseudoprogression are possible. After total glioma removal, the development of CE on the post-contrast MRI scan in the nearest months after RT in combination with a negative PET pattern can be considered as an isolated subacute brain’s response to chemoradiotherapy. However, in cases of incomplete glioma removal or conservative treatment of the tumor, radiation injury develops within or near the tumor residue, i.e. a combination of radiation pathomorphism and survived glioma cells occurs. In these cases, the PET examination in the region of interest detects a moderately elevated level of RPD accumulation, often in combination with an ametabolic focus caused by the development of radiation-induced necrosis. A more accurate estimation of the glioma metabolism is possible upon follow-up by comparison with baseline, prior to the start of therapy. The oncostatic and oncolytic effect of effective therapy, along with the development of therapeutic pathomorphism, causes a decrease in the metabolic glioma activity, and the divergence arises between the progression of structural pathology and regress of its metabolic characteristic. A typical combination of the increased permeability of the blood-brain barrier, which is reflected in the CE phenomenon on the post-contrast MRI scan, and the lack of high metabolism during a PET examination indicate the development of the subacute radiation reaction.

**Conclusion**

Therefore, there is currently an urgent need to select additional neuroimaging techniques that would identify glioma pseudoprogression, because incorrect interpretation of the origin of early radiological progression may lead to unnecessary and potentially dangerous surgery or undue abandonment of highly effective therapy in almost half of patients with a progressive structural lesion. In this aspect, PET with 11C-methionine is a promising biomarker for differentiating between true progression of cerebral glioma and pseudoprogression. A low metabolic tumor activity and its reduction upon the dynamic PET control allow excluding continued tumor growth and interpreting the CE development of as the radiation effect.

**REFERENCES**

Pseudoprogression and pseudoresponse: challenges in the assessment of post-treatment glioma.


Commentary

It should be recognized that the present study is devoted to the actual research topic set out in the title as well as to the most modern and understudied approaches to solving problems set in the study: positron emission tomography (PET) of the brain using radiolabeled methionine.

In general, the presented data are important and allow one to clarify the situation, where clinicians and neuroradiologists cannot answer the question whether it is radiation-induced necrosis or tumor progression. And yet, there are a number of important questions to the authors (debatable questions that, in our opinion, are very significant, especially within the framework of the presented topic of “pseudoprogression of glioma”).

First, pseudoprogression of glioma is a concept formulated upon the analysis of results of a study by Stupp et al. [1] on the use of temozolomide chemotherapy and radiotherapy in patients with glioblastoma. According to the concept developed in the world, the issue is an increase in the contrasted volume of necrosis in malignant glioma patients during the postirradiation period. J Neurosurg 1979; 50: 5: 624—628.

Immediate post-radiotherapy changes in malignant glioma can mimic tumor progression. The tentative threshold radiopharmaceutical uptake index of 1.9 is also important data. The possibility of using brain PET with contrast and PET with methionine is not completely clear, which patients and why were decided to be operated on repeatedly, and which patients and why were decided not to be operated on.

In the light of the two above comments, it is, first, not pseudoprogression, but an early radiation reaction, and, second, it is not completely clear how this specificity of this threshold value was proved and how much it is reasonable. We are well aware, based on clinical collaboration with the authors, that when they examine patients who are under our surveillance that the uptake index of 1.6 or even 1.5 means tumor growth rather than progression. Is it really only in 3% of patients? Or we are wrong, and this specificity is related only to the early radiation reactions (according to the authors, to pseudoprogression), but not to all cases of radiation reactions?

Second, the algorithm of clinical decisions on the basis of an examination using MRI with contrast and PET with methionine is not completely clear, which patients and why were decided to be operated on repeatedly, and which patients and why were decided not to be operated on.

In the light of the two above comments, it is, first, not pseudoprogression, but an early radiation reaction, and, second, it is not completely clear how this specificity of this threshold value was proved and how much it is reasonable. We are well aware, based on clinical collaboration with the authors, that when they examine patients who are under our surveillance that the uptake index of 1.6 or even 1.5 means tumor growth rather than progression. Is it really only in 3% of patients? Or we are wrong, and this specificity is related only to the early radiation reactions (according to the authors, to pseudoprogression), but not to all cases of radiation reactions?

So, without retracting the indirect discussion with the authors, we will formulate the main things, in which we agree with, and in which we do not fully agree with the authors. The possibility of using brain PET with methionine provides us with very important, and often key, information about the “tissue events” in the area of the tumor that was subjected to surgery, radiation therapy, or chemotherapy. It should be taken into account before determining the indications for re-intervention. The tentative threshold radiopharmaceutical uptake index of 1.9 is also important data.
However, it would be incorrect to use the term “pseudoprogression” for all cases of contrasting in the area of interest in different (albeit more or less early, up to 6 months) periods after radiotherapy. This term is considered in connection with just-performed radiation (or chemoradiation) therapy; in the other periods, to our opinion, the term “radiation reaction” is more appropriate, while the terminological question of its time (early, middle, or late) should be addressed to experts of radiation therapy of gliomas. There are more questions about the threshold value. I am afraid that it is a too large threshold value, i.e., I believe that 1.9 and higher mean almost certainly progression, but what the situation is with 1.7—1.8 values? Is it really only 3% of patients in whom progression was observed? We think that, giving credit to brain PET with amino acids, it is necessary to develop a more comprehensive algorithm for evaluation of the event of progression/radiation injury with allowance for both neuroimaging and clinical parameters. For instance, within another large study (published later then this paper was submitted to our editorial board), AVA-Glio [2], researchers proposed a clinical and neuroimaging algorithm (without PET, so it can be improved) for determining pseudoprogression. Probably, this experience should be used as a starting point in developing an algorithm based on the data of PET with met-hionine.

In conclusion, I would like to thank the authors for the very important and complex topic, for their presented data and an interesting discussion with the scientific literature. The article, undoubtedly, is of considerable scientific and methodological interest for specialists who are engaged in neuro-oncology.

REFERENCES


G.L. Kobyakov (Moscow, Russia)