

## A Potential Role of <sup>68</sup>Ga-DOTATOC PET in Modifying Eligibility to Surgery in Patients with Recurrent Meningioma

Asma Bashir<sup>1</sup>, Morten Ziebell<sup>1</sup>, Kåre Fugleholm<sup>1</sup> and Ian Law<sup>2\*</sup>

<sup>1</sup>Department of Neurosurgery, Rigshospitalet, Faculty of Health and Medical Sciences, University of Copenhagen Blegdamsvej 9, 2100 Copenhagen, Denmark

<sup>2</sup>Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, Faculty of Health and Medical Sciences, University of Copenhagen Blegdamsvej 9, 2100 Copenhagen, Denmark

\*Corresponding author: Ian Law, Professor, PhD, DMSc., Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, Faculty of Health and Medical Sciences, University of Copenhagen Blegdamsvej 9, 2100 Copenhagen, Denmark, Tel: +45 3545 8513; Fax: +45 3545 3898; E-mail: [ilaw@pet.rh.dk](mailto:ilaw@pet.rh.dk)

Received date: Sep 16, 2015, Accepted date: Oct 09, 2015, Publication date: Oct 13, 2015

Copyright: © 2015 Bashir A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License; which permits unrestricted use; distribution; and reproduction in any medium; provided the original author and source are credited.

### Abstract

Patients with meningioma usually undergo surgery with curative intent, based on conventional imaging techniques such as computer tomography and magnetic resonance imaging. However, unidentified tumor lesions at the time of surgery can render the surgery non-curative. In the last decade, positron emission tomography (PET) with somatostatin receptor ligand DOTA-D-Phy<sup>1</sup>-Tyr<sup>3</sup>-octreotide labeled with gallium-68 (<sup>68</sup>Ga-DOTATOC) has increasingly become an important tool in the management of meningiomas compared to conventional imaging. However, its indications are not well defined. We present a case of a 60-year old woman who presented with a recurrence of an anaplastic meningioma in the right occipital region, 29 months after the primary excision of an initial diagnosed atypical meningioma. Despite two subsequent surgical excisions and two courses of stereotactic radiation treatment over a period of 42 months, the tumor continued to recur at different sites. A PET scan performed with the tracer <sup>68</sup>Ga-DOTATOC later revealed additionally small positive lesions, suggesting a meningioma composed of multiple foci. As meningioma recurrences, particularly with multiple foci, have a significant impact on determining treatment for the individual patient, a routine <sup>68</sup>Ga-DOTATOC PET could help avoid non-curative surgery by identifying patients with multifocal disease.

**Keywords:** Meningioma; <sup>68</sup>Ga-DOTATOC; MRI; Recurrent disease

### Abbreviations:

WHO: World Health Organization; CT: Computer Tomography; MRI: Magnetic Resonance Imaging; SSTR2: Somatostatin-Receptor Subtype 2; PET: Positron Emission Tomography; DOTATOC: DOTA-D-Phy<sup>1</sup>-Tyr<sup>3</sup>-octreotide; <sup>68</sup>Ga; Gallium-68; SRT: Stereotactic Radiotherapy; HRRT: High Resolution Research Tomograph

### Introduction

Meningiomas constitute the most common non-glial tumors, accounting for 27% of primary intracranial tumors in adults [1]. More than 90% are of benign histology (World Health Organization [WHO] grade I) with a low proliferation index and a slow growth, while the rest of them are either atypical (WHO grade II) or anaplastic (WHO grade III) with a high potential for recurrence and a lower median overall survival [1,2]. Patients with meningioma usually undergo surgery with curative intent, based on conventional contrast-enhanced imaging techniques such as computer tomography (CT) and magnetic resonance imaging (MRI). However, unidentified tumor lesions at the time of surgery can render the surgery non-curative, especially in cases with atypical and anaplastic meningiomas. Meningioma cells are well known to express a high level of several receptors. Among these, somatostatin-receptor subtype 2 (SSTR2) is the most abundant receptor, and offers the possibility of receptor-targeted imaging [3]. In the last decade, positron emission tomography (PET) with somatostatin receptor ligand DOTA-D-Phy<sup>1</sup>-Tyr<sup>3</sup>-octreotide labeled with gallium-68 (<sup>68</sup>Ga-DOTATOC) has increasingly become an

important tool in diagnosing, treatment planning and follow-up of meningiomas due to a higher sensitivity in distinguishing meningiomas from normal intracranial structures and post-therapeutic conditions compared to conventional imaging [4-12]. However, its indications are not well defined.

Herein, we present a case of a female patient with a previously resected atypical meningioma, who underwent subsequent surgical excisions and radiation treatments for a recurrent anaplastic meningioma. A PET scan with the tracer <sup>68</sup>Ga-DOTATOC performed later revealed multiple meningiomas. The aim of this case report is to assist neurosurgeons in recommending and performing <sup>68</sup>Ga-DOTATOC PET as a standard imaging modality in cases with meningioma recurrence.

### Case Report

In 2011, a 60-year old woman presented with a small tumor recurrence in the occipital region on the right side, 29 months after surgical excision for an atypical meningioma (WHO grade II). At the time of excision, the patient had left-sided temporal visual field defect and gait disturbances. Since surgery, the patient was followed with serial MRI showing no evidence of tumor recurrence. The current MRI showed a contrast-enhancing mass, measuring 12 x 13 x 17 mm, in the right occipital region with close relation to the cerebellar tentorium. The patient had no additional new symptoms apart from those mentioned above. Because of the small size of tumor and no aggravation of the present symptoms, a conservative approach was chosen with another follow-up MRI six months later.

Surveillance MRI six months later demonstrated progression of the tumor, measuring now 23 x 27 mm, for which she underwent subsequent tumor resection three weeks later. Intra-operatively, the tumor was adherent to the cerebellar tentorium in several areas causing difficulty in gross tumor excision. Postoperative MRI showed only a minimal enhancement near the resection cavity. Histological examination revealed the characteristic appearance of an anaplastic meningioma (WHO grade III). The patient was then referred for adjuvant stereotactic radiotherapy (SRT) to the tumor bed (2 Gy x 30, 5 fractions per week).

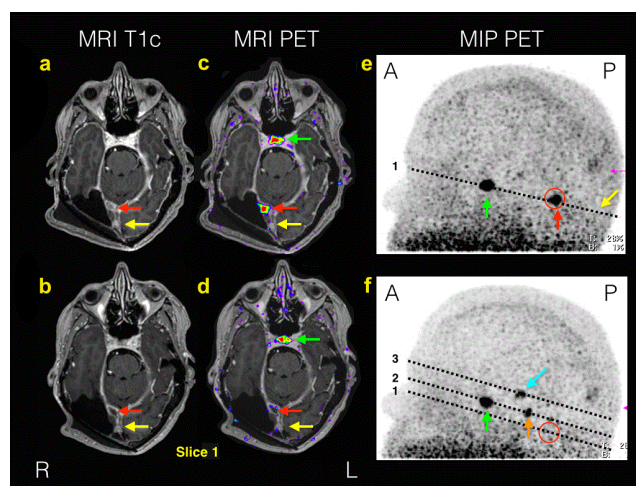
Follow-up MRIs every three months were stable until early 2013, when MRI revealed once again a renewed growth of the tumor in relation to the tentorium in the right occipital region measuring 7 x 7 x 9 mm, with progression over six months to 14 x 10 x 14 mm. In addition, another small meningioma was seen at the sinus confluence on the left side measuring 7 mm, which was not discovered on MRI six months earlier. The patient underwent another surgical resection of the tumor related to the tentorium. The surgery was complicated by venous bleeding thus only a small part of dura was removed than initially planned. Repeat SRT was not considered due to lack of tumor control from previously SRT.

A year later, MRI showed a thickening of the falx and the tentorium suggesting *en plaque* meningioma, although a suspicion of an infiltration of the dura was raised as well (Figure 1a, yellow arrow). In addition, a small mass was seen located deeply in the resection cavity involving the medial edge of the tentorium measuring 9 x 11 mm (Figure 1a, red arrow). A PET scan with the tracer <sup>68</sup>Ga-DOTATOC was carried out, which did not show any evidence of tumor progression at the falx or tentorium, or *en plaque* meningioma (Figure 1c, yellow arrow), but confirmed the small mass located mesially to the resection cavity as seen on MRI (Figure 1c and 1e, red arrow). A repeat <sup>68</sup>Ga-DOTATOC-PET two months later revealed an additional mass of approximately 7 mm in diameter located lateral and inferior to the mass, which was not seen on latest MRI (not shown). Another three months later, MRI revealed growth of mass near the tentorial edge measuring now 10 x 16 mm, for which the patient underwent another SRT (18 Gy x 1). Three months after irradiation, MRI raised once again a suspicion of a continued progression of the tumor measuring now 14x18 mm (Figure 1b, red arrow). However, <sup>68</sup>Ga-DOTATOC PET could not confirm it, and findings were interpreted as reactive changes of irradiation rather than tumor progression (Figure 1d, red arrow; Figure 1f, empty red circle).

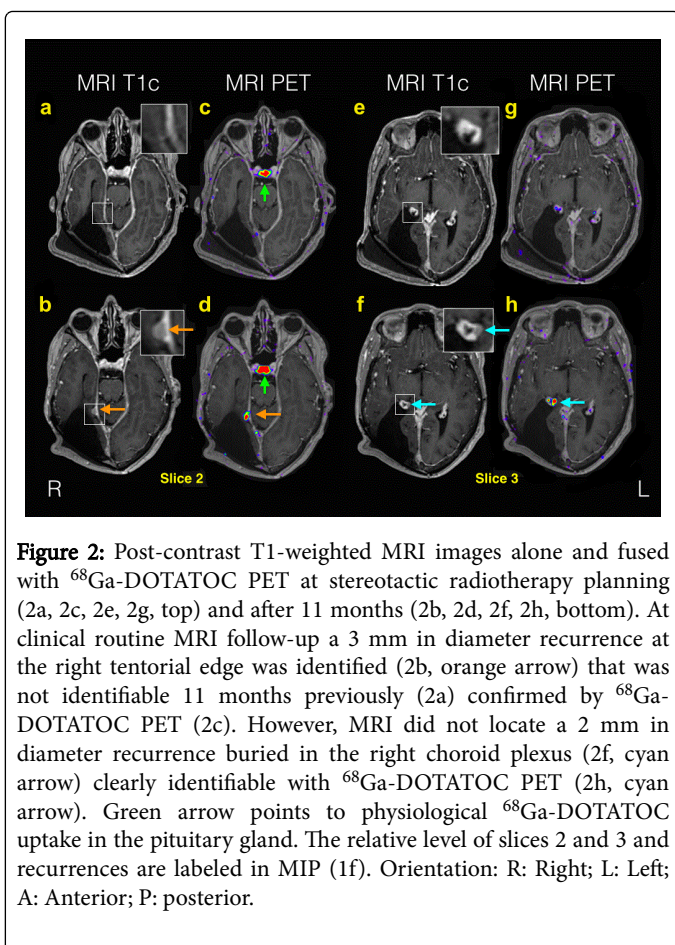
The tumor residual remained stable on MRI carried out in early 2015. However, a new mass suggesting a meningioma recurrence was observed at the anterior part of the tentorium measuring 5 x 7 x 6 mm (Figure 2b; Figure 1f, orange arrow) that was not detected on MRI 11 months previously (Figure 2a), confirmed by <sup>68</sup>Ga-DOTATOC PET (Figure 2c). <sup>68</sup>Ga-DOTATOC PET was carried out again, which revealed a high tracer-uptake in two new foci: one corresponding to the meningioma at the anterior part of the tentorial edge as detected on MRI (Figure 2d, orange arrow), and additional meningioma recurrence hidden in the contrast-enhanced choroid plexus on the right side (Figure 2h, cyan arrow) which was not identifiable on the latest MRI (Figure 2f) and neither on MRI nor <sup>68</sup>Ga-DOTATOC PET 11 months previously (Figure 2e and 2g). It was decided to repeat SRT with a single dose of 18 Gy.

## PET imaging

A dedicated brain High Resolution Research Tomograph (HRRT) PET scanner (CTI/Siemens, Knoxville, USA) [13,14] with an axial field of view of 25 cm, and a near isotropic resolution of 2 mm was used for scanning. Initially a 6 min transmission scan with a rotating <sup>137</sup>Cs single-photon point source was performed for attenuation correction. Forty-five minutes after injection of 100 MBq <sup>68</sup>Ga-DOTATOC a single 20 min PET frame was recorded. The images were reconstructed using a 3D-ordered subset expectation maximization algorithm with correction for the measured point spread function (3D-OSEM-PSF) [15]. Each image consisted of 207 image planes in a 256 x 256 matrix with an isotropic voxel size of 1.22 x 1.22 x 1.22 mm<sup>3</sup>. All images were corrected for randoms, scatter, attenuation [16], decay and dead time, and filtered with a 3-D Gaussian 2 mm filter. For co-registration to an anatomical reference, a post-contrast T1-weighted (MPRAGE) MRI (1 x 1 x 1 mm TR=1900 ms, TE 2.32 ms, TI =900 ms) from a Siemens Verio 3-Tesla MR scanner was obtained.



**Figure 1:** Post-contrast T1-weighted MRI images alone (1a-b, left) and fused with <sup>68</sup>Ga-DOTATOC PET (1c-d, middle) and maximum image projections (MIP) (1e-f, right) at stereotactic radiotherapy planning (1a, 1c, 1e, top) and after 11 months (1b, 1d, 1f, bottom). The MIP shows all activity in the head in the sagittal plane. The broken lines in the MIP show the relative locations of slices 1-3 and colored arrows the lesions in Figures 1 and 2. The MIP (1e) shows the position of slice 1 with only 2 active foci, the recurrent tumor (red arrow and circle) and physiological <sup>68</sup>Ga-DOTATOC uptake in the pituitary gland (green arrow), respectively. Initial MRI (1a) indicated a 5 mm in diameter regional tumor recurrence (red arrow) that was confirmed with <sup>68</sup>Ga-DOTATOC PET (1c). <sup>68</sup>Ga-DOTATOC PET was used for radiotherapy planning and MRI and PET 11 month later (1b and 1d) showed structural and functional response on MIP (1f, empty red circle). Initially a larger *en plaque* meningioma was suspected on MRI (1a, yellow arrow) but this could not be confirmed on PET (1c) indicating reactive changes and the area was not included in the therapy field. This area was structurally and functionally stationary on follow-up. Orientation: R: Right; L: Left; A: Anterior; P: posterior.



**Figure 2:** Post-contrast T1-weighted MRI images alone and fused with  $^{68}\text{Ga}$ -DOTATOC PET at stereotactic radiotherapy planning (2a, 2c, 2e, 2g, top) and after 11 months (2b, 2d, 2f, 2h, bottom). At clinical routine MRI follow-up a 3 mm in diameter recurrence at the right tentorial edge was identified (2b, orange arrow) that was not identifiable 11 months previously (2a) confirmed by  $^{68}\text{Ga}$ -DOTATOC PET (2c). However, MRI did not locate a 2 mm in diameter recurrence buried in the right choroid plexus (2f, cyan arrow) clearly identifiable with  $^{68}\text{Ga}$ -DOTATOC PET (2h, cyan arrow). Green arrow points to physiological  $^{68}\text{Ga}$ -DOTATOC uptake in the pituitary gland. The relative level of slices 2 and 3 and recurrences are labeled in MIP (1f). Orientation: R: Right; L: Left; A: Anterior; P: posterior.

## Discussion

In recent years, a number of retrospective and prospective studies have compared the performance of  $^{68}\text{Ga}$ -DOTATOC PET scan with conventional imaging modalities in pre-therapeutic assessment of patients with meningioma. The results of these studies suggest that  $^{68}\text{Ga}$ -DOTATOC PET has a greater diagnostic and delineated accuracy, and its use is recommended in addition to other imaging modalities for targeting the volume definition prior to radiotherapy [4-12]. Henze et al. [4] were the first to show the utility of  $^{68}\text{Ga}$ -DOTATOC PET in meningioma in a small population of three patients with a total of eight meningiomas. They found that  $^{68}\text{Ga}$ -DOTATOC PET was able to detect all lesions, including the smallest ones measuring only 7-8 mm in diameter, and offered a very high tumor-to-background ratio. Afshar-Oromieh et al. [5] evaluated  $^{68}\text{Ga}$ -DOTATOC in 134 patients with meningiomas. They detected a total of 190 meningiomas by using  $^{68}\text{Ga}$ -DOTATOC PET, whereas MRI detected only 171, as MRI was unable to detect very small tumors (~7 mm in diameter), tumors adjacent to the falx cerebri or located at the skull base, or tumors obscured by imaging artefacts. Miker-Zebal et al. [6] investigated another dimension of  $^{68}\text{Ga}$ -DOTATOC PET, which included precise tumor volume delineation for planning of radiotherapy in meningioma. In a pilot study, the authors reported that  $^{68}\text{Ga}$ -DOTATOC PET delivered additional information with regards to the extent of tumor, and led to a significant modification in fractionated SRT field planning in about two third of the 26 patients with meningiomas compared to treatment planning based on

stereotactic MRI or CT alone. Similar results have also been reported by other studies [7-11].

$^{18}\text{F}$ -2-fluoro-2-deoxy-D-glucose ( $^{18}\text{F}$ -FDG) is widely used PET tracer for imaging various malignant tumors and one of the first PET tracers used in the study of meningiomas [17,18], although conflicting results are reported in the literature [19-21].  $^{18}\text{F}$ -FDG has shown particular difficulty in characterizing and delineating meningiomas due to similar basal glucose metabolic rate of normal brain tissue. Cremerius et al. [19] demonstrated high sensitivity (89%) and specificity (88%) of  $^{18}\text{F}$ -FDG PET for detection of atypical and malignant meningiomas (WHO grades II and III) and recurrent tumors, compared to meningioma WHO grade I. In contrast, Lee et al. [21] reported that the sensitivity of  $^{18}\text{F}$ -FDG PET in detecting high-grade meningiomas was low, but  $^{18}\text{F}$ -FDG uptake correlated significantly with the proliferative potential of the tumor. The authors suggested that the clinical role of  $^{18}\text{F}$ -FDG PET could rather be to predict tumor recurrence and prognosticate patient survival than to detect high-grade meningiomas. There are no studies comparing  $^{18}\text{F}$ -FDG with  $^{68}\text{Ga}$ -DOTATOC directly. However, as the uptake of  $^{68}\text{Ga}$ -DOTATOC in the normal brain tissue is negligible,  $^{68}\text{Ga}$ -DOTATOC allows a better delineation of brain tumor contours [4-12], and therefore is preferable for evaluating both primary and recurrent meningiomas.

The present case report demonstrates a great impact of  $^{68}\text{Ga}$ -DOTATOC PET in the management of recurrent meningioma. The diagnosis of tumor recurrence might be challenging, as the findings are often uncertain or equivocal on conventional MRI. In the present case report,  $^{68}\text{Ga}$ -DOTATOC PET identified all meningiomas with very high tumor-to-background ratios including small foci, which were not always detected by MRI. In addition,  $^{68}\text{Ga}$ -DOTATOC PET was able to confirm and refute the suspicious lesions of recurrence as seen on MRI. It also showed to be valuable in distinguishing tumor remnant or recurrent meningioma from post-therapeutic changes, which is in line with the published literature [11]. The high  $^{68}\text{Ga}$ -DOTATOC uptake in meningioma cells therefore highlights its clinical relevance, and not only it has a potential impact on the treatment of patients with meningioma by finding previously undiagnosed recurrences but also on detecting multiple meningiomas in patients already diagnosed with seemingly localized meningioma recurrence.

Surgical excision usually is the preferred treatment modality in management of meningiomas, but is not always feasible [12,22,23]. Unidentified sites of meningiomas at the time of surgery could cause subsequent clinical relapse or render the surgery non-curative, as reported in the present case report. Identification of meningiomas with unexpected foci, particularly multiple foci, by  $^{68}\text{Ga}$ -DOTATOC PET might be helpful in selection of patients for surgery by identifying those who will not benefit from surgery, thus avoiding non-curative and potentially morbid surgery. At last,  $^{68}\text{Ga}$ -DOTATOC PET also opens up the possibility of preoperative evaluation of meningiomas [6-10], and could modify the surgical strategy and increase the accuracy of surgical resection, particularly in meningiomas with features associated with growth [24].

## Conclusion

The present case report suggests that  $^{68}\text{Ga}$ -DOTATOC PET offers complementary information in patients with uncertain and equivocal results on MRI, and is particularly accurate in distinguishing benign post-therapeutic scar from tumor remnant or recurrence. As

meningioma recurrence, particularly with multiple foci, have a significant impact on individual patient management, a routine <sup>68</sup>Ga-DOTATOC PET could be useful in determining and modifying the treatment planning and follow-up, all of which are of potential clinical benefits to patients.

## References

1. Lee JH (2009) Meningiomas diagnosis, treatment, and outcome. Springer-Verlag London Limited.
2. Dansk Neuro-Onkologisk Gruppe (2010) Retningslinjer for Meningeom.
3. Dutour A, Kumar U, Panetta R, Ouafik L, Fina F, et al. (1998) Expression of somatostatin receptor subtypes in human brain tumors. *Int J Cancer* 76: 620-627.
4. Henze M, Schuhmacher J, Hipp P, Kowalski J, Becker DW, et al. (2001) PET imaging of somatostatin receptors using [<sup>68</sup>Ga]DOTA-D-Phe1-Tyr3-octreotide: first results in patients with meningiomas. *J Nucl Med* 42: 1053-1056.
5. Afshar-Oromieh A, Giesel FL, Linhart HG, Haberkorn U, Haufe S, et al. (2012) Detection of cranial meningiomas: comparison of <sup>68</sup>Ga-DOTATOC PET/CT and contrast-enhanced MRI. *Eur J Nucl Med Mol Imaging* 39: 1409-1415.
6. Milker-Zabel S, Bois AZ, Henze M, Huber P, Schulz-Ertner D, et al. (2006) Improved target volume definition for fractionated stereotactic radiotherapy in patients with intracranial meningiomas by correlation of CT, MRI and [<sup>68</sup>Ga]-DOTATOC-PET. *Int. J. Radiation Oncology Biol. Phys* 65: 222-227.
7. Gehler B, Paulsen F, Oksüz MO, Hauser TK, Eschmann SM, et al. (2009) [<sup>68</sup>Ga]-DOTATOC-PET/CT for meningioma IMRT treatment planning. *Radiat Oncol* 4: 56.
8. Nyuyki F, Plotkin M, Graf R, Michel R, Steffen I, et al. (2010) Potential impact of (<sup>68</sup>Ga)-DOTATOC PET/CT on stereotactic radiotherapy planning of meningiomas. *Eur J Nucl Med Mol Imaging* 37: 310-318.
9. Thorwarth D, Henke G, Müller AC, Reimold M, Beyer T, et al. (2011) Simultaneous <sup>68</sup>Ga-DOTATOC-PET/MRI for IMRT treatment planning for meningioma: first experience. *Int J Radiat Oncol Biol Phys* 81: 277-283.
10. Graf R, Plotkin M, Steffen IG, Wurm R, Wust P, et al. (2012) Magnetic resonance imaging, computed tomography, and <sup>68</sup>Ga-DOTATOC positron emission tomography for imaging skull base meningiomas with infracranial extension treated with stereotactic radiotherapy--a case series. *Head Face Med* 8: 1.
11. Combs SE, Weizel T, Habermehl D, Rieken S, Dittmar J-O, et al. (2013) Prospective evaluation of early treatment outcome in patients with meningiomas treated with particle therapy based on target volume definition with MRI and <sup>68</sup>Ga-DOTATOC-PET. *Acta Oncologica* 52: 514-520.
12. MacCarty CS, Piepgras DG, Ebersold MJ (1982) Meningeal tumors of the brain. (2nd edn). Neurological Surgery. Philadelphia: WB Saunders 5: 2936-2966.
13. Wienhard K, Schmand M, Casey ME, Baker K, Bao J, et al. (2002) The ECAT HRRT: performance and first clinical application of the new high resolution research tomograph. *IEEE Trans Nucl Sci* 49: 104-110.
14. de Jong HW, van Velden FH, Kloet RW, Buijs FL, Boellaard R, et al. (2007) Performance evaluation of the ECAT HRRT: an LSO-LYSO double layer high resolution, high sensitivity scanner. *Phys Med Biol* 52: 1505-1526.
15. Keller SH, Svarer C, Sibomana M (2013) Attenuation correction for the HRRT PET-scanner using transmission scatter correction and total variation regularization. *IEEE Trans Med Imaging* 32: 1611-1621.
16. Sureau FC, Reader AJ, Comtat C, Leroy C, Ribeiro MJ, et al. (2008) Impact of image-space resolution modeling for studies with the high-resolution research tomograph. *J Nucl Med* 49: 1000-1008.
17. Di Chiro G (1987) Positron emission tomography using [<sup>18</sup>F] fluorodeoxyglucose in brain tumors. A powerful diagnostic and prognostic tool. *Invest Radiol* 22: 360-371.
18. [No authors listed] (1991) Assessment: positron emission tomography. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 41: 163-167.
19. Cremerius U, Bares R, Weis J, Sabri O, Mull M, et al. (1997) Fasting improves discrimination of grade 1 and atypical or malignant meningioma in FDG-PET. *J Nucl Med* 38: 26-30.
20. Park YS, Jeon BC, Oh HS, Lee SM, Chun BK, et al. (2006) FDG PET/CT assessment of the biological behavior of meningiomas. *J Korean Neurosurg Soc* 40: 428-433.
21. Lee JW, Kang KW, Park SH, Lee SM, Paeng JC, et al. (2009) 18F-FDG PET in the assessment of tumor grade and prediction of tumor recurrence in intracranial meningioma. *Eur J Nucl Med Mol Imaging* 36: 1574-1582.
22. Maxwell RE, Chou SN (1982) Preoperative evaluation and management of meningiomas. *Operative Neurosurgical Techniques. Indications, Methods, and Results.* New York: Grune & Stratton 1: 481-489.
23. Ojemann RG (1980) Meningiomas of the basal parapatituary region: technical considerations. *Clin Neurosurg* 27: 233-262.
24. Pirotte BJM, Levivier M, Goldman S, Massager N, Wikler D, et al. (2009) Positron emission tomography-guided volumetric resection of supratentorial high-grade gliomas: a survival analysis in 66 consecutive patients. *Neurosurgery* 64: 471-481.