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EDITORIAL

Fifty shades of meningioma: challenges and perspectives of different PET molecular probes

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Most meningiomas are classified as primitive grade I brain tumors, following the World Health Organization (WHO), and represent approximately 30% of all intracranial tumors, which are particularly frequent in the elderly. Atypical or anaplastic meningiomas, classified as grade II and III, represent a minority, likely associated with neurological symptoms. These tumors need aggressive treatment and the conundrum for clinicians and surgeons is whether treating these patients with surgery and/or radiotherapy. Furthermore, the possibility of metastatic extra-cranial spread must be taken into account [1] and in the further course of the disease the possibility of local relapse [2] which represents a challenge to nuclear medicine physicians and radiologists. In routine clinical practice, meningiomas may represent diagnostic pitfalls occurring during single photon emission computed tomography (SPECT) or positron emission tomography (PET) scans, performed for somatic tumors. Several papers describe the possibility of incidental uptake of various radiopharmaceuticals applied for the diagnostics of meningiomas. The development of hybrid imaging, especially PET/CT scanners, allowed to easily recognize meningiomas as hyperdense areas with calcifications, following CT diagnostic criteria. Despite this improvement of specificity, the report of such brain lesions still represents a diagnostic dilemma, in terms of differential diagnosis with metastatic lesions from somatic tumors or other malignant primary brain tumors. The ideal radiopharmaceutical in nuclear medicine should accumulate in the specific target tissue only. Nevertheless, increased uptake of ^{18}F/^{11}C-choline has been observed in meningiomas of patients who were examined during staging or restaging of prostate cancer [3, 4]. Recently, similar findings have also been reported for ^{64}Cu/^{68}Ga labeled prostate-specific membrane antigen (PSMA) [5–7], demonstrating a limited specificity of these tracers for prostate cancer. Moreover, meningiomas have been reported as avid of several other PET radiopharmaceuticals, such as L-3,4-dihydroxy-6-[18F]fluorophenylalanine (^{18}F-DOPA) [8], ^{18}F-NaF [9, 10], ^{18}F-fluroethylthyrosine (^{18}F-FET) [11] and ^{68}Ga-DOTA-DPhe1,Tyr3-octreotate (^{68}GaDOTATATE) [12, 13].

The molecular mechanisms leading to increased uptake of these tracers in meningiomas remain to be elucidated. Being a lesion with a conspicuous calcific component, the uptake of ^{18}F-NaF is most likely to be related to the deposition of hydroxyapatite crystals in the intralesional calcifications. The moderate rise of lipogenesis associated with the increased production of cellular walls and the higher rate of protein synthesis could induce the uptake of radiolabeled choline and that of amino acid tracers, such as ^{11}C-methionine [14], ^{18}F-FET [11] and ^{18}F-DOPA [8]. The ^{64}Cu/^{68}Ga PSMA uptake in meningioma could be due to the neo-vasculature of the tumor tissue [7]. Anyway, the molecular causes of the uptake of several PET radiopharmaceuticals still need to be addressed. Furthermore, the higher proliferative activity as shown by the direct relationship between Ki67 expression and tumor grade [15], could lead to greater metabolic activity of meningiomas.

Generally, the very low background radioactivity of radiolabeled choline and amino acid tracers facilitates the recognition of cerebral neoplastic processes. This feature represents a major advantage for the application of these radiopharmaceuticals in neuro-oncology but their lack of specificity remains a challenge. Co-registration with

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Magnetic Resonance Imaging (MRI) or the use of hybrid PET/MRI scanners can increase diagnostic accuracy by depicting specific structural or functional changes with higher accuracy than CT [16].

The use of radiolabeled somatostatin analogues for the diagnosis of meningiomas has developed from incidental findings during whole body scans performed in patients with neuroendocrine tumors [12]. A recent study reported that ^{68}Ga-DOTATATE uptake in grade I and II meningiomas as expressed by the maximum Standardized Uptake Value (SUVmax) is a reliable predictor of tumor growth rate and that trans-osseous expansion corresponds to highest ^{68}Ga-DOTATATE binding [13]. On this topic, also ^{11}C-methionine has been described as useful radiotracer in the evaluation of the long-term effect of proton beam treatment. The ^{11}C-methionine uptake decreases during the time indicating good response to therapy. In patients with meningioma remnant, ^{11}C-methionine uptake ratio is recorded prior to the volume increase on MRI [14].

Based on these observations different groups of researchers are investigating novel applications of ^{18}F-FET PET/CT to provide additional information for the non-invasive grading of meningiomas and, possibly, for the discrimination of tumors in critical areas of the skull base, as in the sphenoidal sinus, pituitary gland and tentorium [11].

Therefore, standing to these forewords, the following statements can be made.

The discovery of intracranial ^{18}F/^{11}C-choline uptake during whole body PET/CT scans of patients with prostate cancer may indicate the presence of meningioma, which, however, presents an uncommon diagnostic pitfall [17], occurring in 1% of prostate cancer patients [4]. Nevertheless, it is recommendable to include the entire skull into the standard whole body imaging acquisition protocol, to avoid misdiagnosing. This is particularly important during anti-androgenic therapy which can influence tumor growth of meningiomas and lead to neurological symptoms as a consequence of regional mass effects [4]. The same applies to the application of ^{64}Cu/^{68}Ga-PSMA in patients with prostate cancer which can occasionally show tracer uptake in meningiomas [5, 6].

Second, it is important to consider a meningioma during diagnostic assessment of cerebral gliomas and metastases with radiolabeled amino acids, owing to the high rate of meningiomas in the elderly and the limited specificity of amino acid tracers. This possibility needs to be taken into account even in the follow-up of patients after surgery and/or radiotherapy of gliomas or metastases. Nevertheless, correlative imaging with MRI usually allows to recognize meningiomas. Histological sample remains the corner stone when it is needed to achieve a secure diagnosis.

Finally, the detection of meningiomas as "*tracer avid lesions*" could represent a challenge for nuclear medicine in case of previously unknown lesions as well as in assessing their evolution. Beyond the incidental report of meningiomas with amino acid tracers, (^{18}F/^{11}C) radiolabeled choline and ^{18}F-NaF during whole body scans for somatic tumors, we must state that these cited radiopharmaceuticals seem to play a limited role in the clinical management of these lesions. On the other hand, preliminary data seem to support the usefulness of ^{18}F-FET in predicting the lesions tumor grade even if the optimal tracer for the differential diagnosis between benign and malignant meningiomas still needs to be addressed. Anyway, ^{11}C-methionine has been texted as valid marker of tumor growth and response to therapy [14].

In parallel, ^{68}Ga-DOTATATE uptake has been demonstrated to be reliable predictor of tumor growth [18]. This feature is enlarging PET applications with radiolabeled somatostatin analogues to imaging meningiomas for non-invasively characterizing primitive brain lesions, by means of PET/CT and PET/MRI [19]. PET with somatostatin analogues can help to evaluate the response to radio-guided surgery techniques [20]. Thus, for the best of our knowledge, ^{68}Ga-DOTATATE can be the best radiopharmaceutical in this clinical setting, also due to its added value as preliminary imaging tracer prior to consider ^{90}Y-DOTATOC as a valid theranostic agent for recurrent and malignant meningiomas [21].

In conclusion, the recent developments in PET imaging of meningiomas represent an interesting example of how new diagnostic and therapeutic applications can develop out of diagnostic pitfalls.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Ethical approval This study does not contain any study performed on humans and animals.

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