Current Molecular Imaging of Spinal Tumors in Clinical Practice

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Energy metabolism measurements in spinal cord tumors, as well as in osseous spinal tumors/metastasis *in vivo*, are rarely performed only with molecular imaging (MI) by positron emission tomography (PET). This imaging modality developed from a small number of basic clinical science investigations followed by subsequent work that influenced and enhanced the research of others. Apart from precise anatomical localization by coregistration of morphological imaging and quantification, the most intriguing advantage of this imaging is the opportunity to investigate the time course (dynamics) of disease-specific molecular events in the intact organism. Most importantly, MI represents one of the key technologies in translational molecular neuroscience research, helping to develop experimental protocols that may later be applied to human patients. PET may help monitor a patient at the vertebral level after surgery and during adjuvant treatment for recurrent or progressive disease. Common clinical indications for MI of primary or secondary CNS spinal tumors are: (i) tumor diagnosis, (ii) identification of the metabolically active tumor compartments (differentiation of viable tumor tissue from necrosis) and (iii) prediction of treatment response by measurement of tumor perfusion or ischemia. While spinal PET has been used under specific circumstances, a question remains as to whether the magnitude of biochemical alterations observed by MI in CNS tumors in general (specifically spinal tumors) can reveal any prognostic value with respect to survival. MI may be able to better identify early disease and to differentiate benign from malignant lesions than more traditional methods. Moreover, an adequate identification of treatment effectiveness may influence patient management. MI probes could be developed to image the function of targets without disturbing them or as treatment to modify the target's function. MI therefore closes the gap between *in vitro* and *in vivo* integrative biology of disease. At the spinal level, MI may help to detect progression or recurrence of metastatic disease after surgical treatment. In cases of nonsurgical treatments such as chemo-, hormone- or radiotherapy, it may better assess biological efficiency than conventional imaging modalities coupled with blood tumor markers. In fact, PET provides a unique possibility to correlate topography and specific metabolic activity, but it requires additional clinical and experimental experience and research to find new indications for primary or secondary spinal tumors.

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INTRODUCTION

Despite increasing experimental research regarding the pathophysiological mechanism of primary or secondary central nervous system (CNS) tumors in recent years, the underlying molecular and cellular changes (both in the tumor area and its surrounding tissue) remain only partially understood (1–6). To date, very little work has been done for spinal tumors (7–10); consequently most of our knowledge about spinal tumors is adapted from similar tumors in the brain; however, it is well documented that there are substantial molecular and cellular differences between brain and spine (7). For this reason, much experimental attention has been directed toward understanding the cellular and molecular mechanism of CNS tumor genesis and the development of noninvasive, high resolution *in vivo* imaging technology, especially *in vivo* molecular imaging (MI) (11). These findings also are used to explain the positron emission tomography (PET) findings for spinal tumors. The advantage of using PET in neurooncology is not only its greater sensitivity when compared with magnetic resonance imaging (MRI), but also its greater specificity (12). PET has been applied extensively to cerebral neoplasms, especially high-grade glial tumors (13–15). Tumoral uptake of 18F-fluoro-2-deoxy-glucose (FDG) has been shown to correlate with histological aggression and prognosis in both primary and re-

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current gliomas (16–20). Hypermetabolism has also been reported variably in primary cerebral lymphoma, meningioma, medulloblastoma and non-CNS brain metastasis (21–24). Relatively low glucose metabolic rates have been demonstrated in cerebral involvement with primitive neuroectodermal tumor (PNET) (25). In addition to FDG metabolism, other metabolic pathways have been studied extensively in brain tumors. One of the most promising results is the use of amino acids or amino acid analogues for visualization of amino acid transport and, depending on available tracers, protein synthesis in brain tumors (26). The main tracer used was carbon-11 (11C)-methionine (MET) followed by fluorine-18 (18F)-labeled tyrosine compounds. There is rapidly increasing evidence that radiolabeled amino acids may have superior properties compared with FDG in delineation of tumor borders, biopsy and treatment planning, evaluation of treatment effects, and in the differentiation of recurrent tumor and reactive posttherapeutic changes including radiation necrosis after conventional treatment in gliomas (27–28). But there are also first reports on using amino acids or amino acid analogues for other tumor entities including ependymoma, chordoma or even metastases of other tumor entities. In recent years, 18F-labeled amino acid tracers such as 18F-fluoroethltyrosine (FET) have gained importance based on the possibility of their widespread use in hospitals lacking an onsite cyclotron (29). Furthermore, (68Ga)-labeled somatostatin analogues have garnered increasing interest for MI meningiomas since the majority of these tumors strongly express somatostatin receptors and, therefore, can be precisely visualized by PET (30). Somatostatin receptor imaging is especially useful for target definition prior to radiation therapy of skull base meningiomas (31).

At present, PET has rarely been used to assess neoplastic spinal tumors. This was originally due to limitations of spatial resolution. But owing to the improvement of PET techniques, such tumors are now also being imaged by MI. However, in conventional MRI, intratumoral heterogeneity of primary spinal tumors may not adequately be reflected, and evaluation of a contrast-enhancing lesion may either under- or overestimate the amount of tumor tissue (32). In spinal metastases, the problem is somewhat similar: the exact extent of paravertebral tumoral involvement is often difficult to assess. The sensitivity of conventional imaging methods is sometimes insufficient to detect the clinically important spinal micrometastases. However, these conventional imaging methods are sometimes nonspecific, and difficulties in differentiating from degenerative endplate abnormalities or postoperative changes can occur. Moreover, in contrast to MRI, 18F-FDG uptake in PET is not hampered by metallic implant-associated artifacts (9–10).

MI by PET may be performed to gain additional information on metabolic and molecular tumor markers (5,13,33–34). PET measures and visualizes cellular biochemical processes non-invasively and quantitatively by a pattern of *in vivo* uptake of molecular probes into the CNS tissue (35). Since biochemical changes may be related to the growth rate of tumor cells (32,35), they may be viewed as markers of tumor cell proliferation. It may be assumed that the behavior of such surrogate markers differs in brain and spinal tumors, indicating a need for further research, especially in MI of spinal tumors. However, in spinal tumors, MI may allow, comparatively to CNS tumors, (i) earlier detection of tumor genesis at "pre-disease states," (ii) evaluation of the pharmacodynamic and neurotoxicity of chemotherapeutic agents, (iii) evaluation of the response to treatment and (iv) differentiation between iatrogenic lesions and residual or recurrent tumor tissue (11,36–38).

This article reviews the potential role of MI, particularly PET, in spinal tumors including spinal cord tumors, but also the spinal metastases which often come along with spinal cord involvement.

PRINCIPLES OF MOLECULAR IMAGING IN NEUROLOGICAL SCIENCES

A detailed review about the principles of MI in neurological sciences and the principles of PET were described earlier in extensive detail by our group (13–15). Although these principles are described for brain tumors, they also are valuable for spinal tumors.

PET IMAGING AND ITS RELATIONSHIP TO SPINAL TUMORS IN CLINICAL MEDICINE

Techniques for human spinal imaging have undergone rapid developments in recent years. With technical improvements, the MI is being used more in primary and secondary spinal tumor imaging. Such technological progress also has enabled the assessment of many physiological parameters *in vivo* that are highly relevant for (i) primary and secondary spinal tumor grading, (ii) tissue characterization, (iii) definition of the extent and infiltration of tumors and (iv) planning as well as (v) monitoring of therapy (see Table 1).

Evaluation of the spinal cord with PET is, in part, limited by scanner spatial resolution, with compromised sensitivity for the detection of hypermetabolic lesions smaller in size than approximately 2.5 times the scanner spatial resolution (39,40). With newer PET scanners, this technical problem is increasingly diminished, so that spinal PET also has gained clinical interest. However, MRI is still the imaging modality of choice when searching for spinal cord lesions in patients. In this context, it is extremely important to recognize and differentiate non-neoplastic from neoplastic processes of the spinal cord as the differentiation of these two entities is extremely crucial to the neurosurgeon. Proton MR spectroscopy currently is performed in a limited number of such cases, usually to distinguish post-treatment changes from recurrent tumor in the posttherapeutic setting, or, occasionally, when the neoplastic nature of a primary lesion is in question.

Screening MRI frequently registers osseous spine lesions with high morphologi-

Table 1. Indication of the use of positron emission tomography studies in spinal tumors related to (patho)physiological factors.

18F-FDG-PET
Ninety percent accurate for tumor grading and prognosis.
First choice for spinal infection.
Can be used for grading and monitoring for progression to a higher tumor grade of malignancy and for differentiation radionecrosis and recurrence.
L-amino acid PET
Only partly accurate for tumor grading and prognosis.
Provides good separation of spinal tumor tissue from surrounding normal spinal tissue.
Good for monitoring for progression to a higher degree of malignancy.
Useful in differentiating stable tissue from tumor regrowth.
Other radionuclides
Only used in single cases.

cal details in patients with spinal tumors (41). Differentiation of benign lesions from spine metastases still presents a challenging problem. The spine is the most frequent site of skeletal metastases (42); however, MRI changes from poor bone quality due to chemotherapy, osteoporosis and degenerative disease are frequently registered in patients with spinal tumors (43). Thus, the high likelihood of finding a metastatic lesion is balanced by the frequent occurrence of benign signal changes in the vertebral column. Distinguishing between benign and malignant lesions in imaging of focal indeterminate spinal lesions is crucial in determining the treatment paradigm for the patient. In addition, MRI often fails to detect minimal tumor agglomerations (micrometastases) (41). New techniques such as PET, and the development of specific contrast agents may reveal changes at the physiological, cellular or molecular levels.

PET IMAGING AND SPINAL CORD PHYSIOLOGY

Since the normal spinal cord is comprised of a relatively large amount of axonal white matter, it manifests lower FDG uptake than cortical brain tissue on PET imaging. The glucose metabolic rate of white matter is approximately one-third to one-fourth that of gray matter (44); therefore, tumor-to-background contrast should be more favorable in the spinal cord than in cortical brain regions. This has been verified by Di Chiro *et al*. (25), who reported a glucose metabolic rate of 1.7 mg/100 gm neuronal tissue/mm for normal spinal cord (compared with values of 6.0–7.0 for midbrain pons area) using a tomography.

Prior radiation therapy to the entire neural axis may have diffusely lowered baseline FDG uptake in all nontumor CNS tissue, further contributing to increased lesion-to-spinal cord contrast. For all other mentioned tracers which are increasingly used for brain tumor imaging (for example, amino acids or analogues, somatostatin analogues), no literature data exist so far on their uptake in the normal spinal cord. We know, however, from our personal, but not yet published experience that for spinal cord uptake is very low both tracer classes, similar to their low uptake in normal brain, especially in the white matter. Therefore, it could be hypothesized that spinal tumor-to-background contrast should also be favorable for these tracers.

PET IMAGING AND ITS RELATIONSHIP TO SPINAL CORD TUMORS

Generally, 18F-FDG-PET is a well-recognized tool used to predict the growth rate of a neoplasm. Although no established consensus in interpretation of 18F-FDG-PET findings for spinal tumors exists, Wilmshurst *et al*. (45) reported correlation with histological malignancy in spinal gliomas. The same authors suggested performing a prospective study of a larger number of patients with a wider range of tumors, although this might be difficult to achieve given the rarity of spinal cord tumors (46,47). In our experience, 18F-FDG-PET imaging is useful in evaluating tumor progression and identifying the most metabolically active components in spinal cord tumors. It is also used for monitoring unusually slow growing metastases of brain stem tumors.

Some case reports exist on the amino acid methionine, showing high uptake in some special tumor-like ependymoma (48–49) or chordoma (50). For 18F-FET, we have personal experience in MI spinal cord tumors in some individual cases showing no or only minor uptake in low grade gliomas (diffuse astrocytomas WHO II), but positive uptake in high grade tumors such as medulloblastoma or anaplastic glioma. Even though there is increasing experience with amino acids, choline and somatostatin analogues in cerebral meningiomas, no data exist so far on imaging spinal meningioma using these radiopharmaceuticals.

18F-FDG-PET has been shown to be superior to skeletal scintigraphy and 18F-fluoride- PET in detecting bone metastases (51–52). Whereas 18F-fluoride uptake depends on bone reaction, the uptake of 18F-FDG depends on the tumor's metabolic rate, thereby more accurately representing tumor viability (51,53). 18F-FDG-PET is already considered an important component in staging melanoma, lung and esophageal cancer, and its role in other cancers, including spinal tumors, is being actively explored (54).

The lack of sensitivity of 18F-FDG-PET in detection of sclerotic osseous lesions in patients with prostate (55) and breast (56–59) cancer was published previously. Uptake of FDG is probably decreased in sclerotic lesions owing to their acellular nature with a correspondingly low glycolytic rate (60). These findings emphasize that sclerotic lesions in the spine require particular attention and close follow-up, even if negative results are found with 18F-FDG-PET or even biopsy.

Owing to the lack of sensitivity of 18F-FDG-PET in prostate cancer, choline derivates are preferably used for MIs of this tumor entity. Besides evaluation of primary tumor and lymph node involvement, choline derivates also are useful for detecting spinal metastases showing

high sensitivity, specificity and accuracy of 18F-Choline (FCH)-PET/CT of 79%, 97% and 84%, respectively (61). For patients with high-risk prostate cancer which often presents with osteoplastic bone metastases, 18F-PET/CT is a highly sensitive and specific modality for detection of bone metastases (62).

Other tumors, which are diagnosed insufficiently with 18F-FDG-PET, are well-differentiated neuroendocrine tumors (NET) which also often present with spinal metastases. The majority of NET express somatostatin receptors on their cell surface which can be targeted by (68Ga)-labeled peptides like DOTA(0)-Phe(1)-Tyr(3)octreotid (DOTA-TOC), DOTA-(Tyr^3)Octreotat (DOTA-TATE) or DOTA-1-NaI3-octreotide (DOTA–NOC). These somatostatin analogues are ideal for diagnosing and staging NET and are much more sensitive for detection of spinal metastases compared with CT which often fails to detect nonsclerotic lesions.

Surprisingly, 18F-FET-PET was strongly inferior to 18F-FDG-PET in evaluating the amino acid analogue FET in peripheral tumors outside the brain or spinal cord, showing no or only minor uptake in most peripheral tumors such as colorectal, pancreatic, prostatic, ovarian cancer and lymphomas, with the only exception of squamous cell carcinomas (63). We found, however, in correlation with individual cases described in the literature (28,29,64), high metabolic rates in cerebral lymphoma and also in most brain metastases, even in those originating from peripheral 18F-FET negative tumors. These findings suggest that 18F-FET is transported via different amino acid transporters within the brain compared with the periphery. Therefore, in contrast to 11C-MET, which also showed high uptake in peripheral lymphomas (65), 18F-FET might be valuable in spinal cord tumors, but probably not in osseous spinal metastases. However, no published data exist on this topic to date. Therefore, current experience tends to open a new horizon for the clinical utility of spinal tumor MI by PET in future. We have therefore summarized, in the following sections, the current MI knowledge about specific spinal lesions.

SPECIFIC TUMORS

Schwannomas

Schwannomas generally have a high tumor-to-background ratio on 18F-FDG-PET (66). Semiquantitative analysis with standardized uptake values (SUVs) reveals a wide variation in SUVs that can be explained by variations in the degree of cellularity (66–67). The situation is somewhat different for cranial and spinal nerve schwannomas (67): The spinal lesions are extracerebral, occurring in regions normally devoid of 18F-FDG-uptake (67). No correlation is found between 18F-FDG-uptake and tumor size or tumor proliferation rate (Ki-67 index) (66). Because these tumors often have a high level of 18F-FDG-uptake, distinguishing schwannomas from malignant peripheral nerve sheath tumors before biopsy or even surgery is not possible (66). Therefore, schwannoma should be included in the differential diagnosis of peripheral nerve sheath tumors with low, intermediate or high SUVs (66–67).

For cerebral schwannomas, developments were made for 11C-MET-PET; to the best of our knowledge, such developments do not exist for spinal schwannomas (68).

Meningiomas

A variety of tracers seem to be useful for MI meningiomas. 1-11C-acetate and 11C-choline were found to be useful for detecting meningiomas and evaluating the extent of meningiomas and are potentially useful for monitoring tumor response to surgery (69–70).

However, 1-11C-acetate was not found to be useful for evaluating the tumor grade (69). 18F-FDG is found to be of lower worth than both membrane biosynthesis markers for evaluating the extent of meningiomas and the response to surgical treatment, but 18F-FDG may be useful for differentiating benign from malignant meningiomas (69–70). 18F-FDG and 1-11C-acetate are complementary for assessing diverse cell metabolism of meningiomas (69). One case report exhibits moderately increased metabolism despite findings of high-grade malignancy on biopsy (71).

Amino acids also have been used for MI of meningiomas. In a comparative study, Iuchi *et al*. (72) tested 18F-FDG and methionine with regard to their potential to predict proliferative activity uptake of 11C-MET, significantly correlating not only with the count of nucleolar organizer regions, a histological index of protein synthesis, but also with proliferation index Ki-67. In this study, 18F-FDG-uptake showed no significant correlation with Ki-67 index or clinical malignancy (72). Histopathology reveals somatostatin receptor expression in most meningiomas and, therefore, somatostatin receptors currently represent a good target for MI by using somatostatin receptor ligands (73). However, present studies on this topic only address cerebral meningiomas, so far no data exist on spinal meningiomas.

Gliomas

The PET uptake is in keeping with the low-grade histology of the astrocytomas (45,74). However, one case report about a primary spinal glioblastoma exists and the 18F-FDG-PET findings were consistent with a malignant neoplasm (75). Even though amino acids gain more and more importance for MI of cerebral gliomas, to the best of our knowledge no studies exist on their use in spinal cord gliomas. We have seen only a few individual cases with predominantly diffuse low-grade astrocytoma showing no significant 18F-FET uptake. Only a few cases with high-grade spinal cord glioma (medulloblastoma, anaplastic glioma) showed increased amino acid uptake (personal unpublished data). However, more data is necessary to give recommendations for the use of amino acid MI by PET in spinal cord gliomas.

Spinal Metastases

Few articles have specifically addressed the accuracy of 18F-FDG-PET in

diagnosing spine metastases (60,76–77). In the study of Laufer *et al*. (76), 18F-FDG-PET had 96% sensitivity and 50% specificity in all patients with cancer, 97% sensitivity in nonsclerotic lesions, and 92% sensitivity in sclerotic lesions. Both osteolytic and osteoblastic processes are important for bone metastases, so the difference between bone scan and 18F-FDG-PET for the detection of bone tumor is likely related to the difference in the mechanism by which disease is detected by these two modalities. Bone scan detects the osteoblastic response to bone destruction by tumor cells, and 18F-FDG-PET detects the metabolic activity of the tumor cells. It is probable that for breast and lung carcinoma, 18F-FDG-PET has similar sensitivity; however, poorer specificity, when compared with the isotope bone scan; hovever, there is conflicting evidence with several articles suggesting that it is less sensitive than conventional imaging in breast cancer (51,53). In our institution, PET/CT has already replaced bone scintigraphy in staging of nonsmall cell lung cancer (NSCLC) patients with PET–positive primary lung tumors. Only in patients with 18F-FDG-inactive primary NSCLC, such as bronchoalveolar carcinomas, should an additional bone scan be considered. There is convincing evidence that, for prostate cancer, 18F-FDG-PET is less sensitive than the bone scan and this may be tumor specific (51,53). Because of this generally low uptake of 18F-FDG in prostate cancer, other PET tracers have been developed. 18F-FCH-PET seems to be a promising tool in the evaluation of patients with elevated prostate-specific antigen (PSA) and suspicion for bone metastases (53). In a study by Langsteger *et al*. (78) using 18F-FCH-PET in 49 patients, PET downstaged two (4%) patients because suspicious bone lesions in bone scan could be excluded with 18F-FCH-PET; in six (12%) patients, 18F-FCH-PET upstaged the patients with a resulting change in management from surgery to radiation therapy or hormone therapy (78).

In a study comparing 18F-fluoride and 18F-FCH, the sensitivity, specificity and accuracy of PET/CT for the detection of bone metastases in prostate cancer was 81%, 93% and 86% for 18F-fluoride, and 74% ($P = 0.12$), 99% ($P = 0.01$) and 85% for 18F-FCH, respectively (79). 18F-FCH-PET/CT led to a change in the management in 2 out of 38 patients owing to the early detection of bone marrow metastases. 18F-fluoride PET/CT identified more lesions in some patients when compared with 18F-FCH PET/CT but did not change patient management. The authors concluded that 18F-FCH PET/CT may be superior for the early detection (that is, bone marrow involvement) of metastatic bone disease. In patients with FCH-negative suspicious sclerotic lesions, a second bone-seeking agent (for example, 18F-fluoride) might demonstrate a higher sensitivity. However, 18F-fluoride PET also could be negative in highly dense sclerotic lesions, which presumably reflects the effect of treatment. It will be important to clarify in future studies whether these lesions are clinically relevant when compared with metabolically active bone metastases.

For the subgroup of well-differentiated neuroendocrine tumors, 18F-FDG is also not capable to detect spinal metastases because of their low proliferation activity and, in consequence, their low glucose consumption. (68Ga)- and 18F-labeled somatostatin analogues (80–81) as well as 18F-DOPA (82) have shown promising results for this special tumor entity with even higher sensitivities compared with morphological computed tomography (CT) imaging. In the study of Ambrosini, (68Ga)-DOTANOC PET led to a change in clinical management in nine patients with a negative CT scan (80).

There are, however, several other important variables that should be considered. The type of the metastasis itself appears to be relevant. At least in breast cancer, different patterns of 18F-FDG uptake have been shown in sclerotic lesions, lytic lesions, or lesions with a mixed pattern (51,53). Furthermore, the precise localization of a metastasis in the skeleton may be important with regard to the extent of the metabolic response induced (51,53). Previous treatment is highly relevant, and it has been found that although the majorities of untreated bone metastases are positive on PET scans and have a lytic pattern on CT, after treatment, incongruent CT-positive/PET-negative lesions are significantly more prevalent and generally are blastic, which presumably reflects a direct effect of treatment.

Incidental findings on PET suggestive of degenerative spinal disease are not uncommon, most commonly in the lumbosacral spine (83). The severity of PET findings correlates with the severity of degenerative disk and facet disease as graded by CT, likely owing to the fact that the inflammatory process that accompanies degenerative spinal disease is evident on PET (83). Increased 18F-FDG uptake in degenerative spinal disease should not be confused with metastatic disease (83).

The clinical role for 18F-FDG-PET in monitoring the response of bone metastasis remains undefined at this time (84). Chemotherapy in conjunction with granulocyte colony-stimulating factor (GCSF) can lead to increased FDG uptake by hyperplastic bone marrow, which can be difficult to distinguish from diffuse marrow involvement by tumor.

Lymphoma

There is very little data relating to lymphoma, but 18F-FDG-PET seems to perform better than the bone scan. In a study by Ghanem *et al*. (55), PET was shown to be a fairly poor modality for detecting lymphoma infiltration of the vertebral bone marrow, yielding four false negative and two false positive results compared with MRI and clinical follow-up data (55). An examination of the accuracy of 18F-PET in patients with multiple myelomas also revealed several false negative results with PET compared with spine MRI and CT scans (85–87). These results are consistent with the study of Laufer *et al*. (76), for which 2 of 3 false negative results with 18F-FDG-PET results were in patients with hematological malignancies. 18F-FET-

PET has also shown to be insufficient for the detection of peripheral lymphomas (63), however, not including cases with spinal involvement. Surprisingly, the amino acid 11C-MET showed promising results for peripheral tumors with high uptake in most Hodgkin and non-Hodgkin lymphoma (65).

Myeloma

There is an increasing body of evidence relating to the valuable role of 18F-FDG-PET in myeloma, where it is clearly better than the bone scan, presumably because 18F-FDG is identifying marrow-based disease at an early stage (51,53).

At present, it is not clearly defined to what extent MI may influence therapeutic decisions. PET and SPECT seem to be useful complementary tools in the monitoring of spinal metastases as they may integrate topographic and biological activity. However, large clinical studies are necessary to assess their exact value. Another remaining question is whether the magnitude of biochemical alterations demonstrated by MI may have prognostic value with respect to (neurological) function and survival.

Differential Diagnosis of Spinal Tumor by PET

Differentiation between malignant and benign fractures may be difficult, particularly in elderly patients who commonly suffer from osteoporotic fractures. Radiography, CT, MRI and bone scintigraphy may be nonspecific. Some reports suggest that 18F-FDG-PET may be useful in differentiating between malignant and benign fractures (88–91), although there are only a few case reports regarding the clinical efficacy of fusion PET/CT on differentiating malignant from benign fractures (92–93). Overlap of benign and malignant lesions has been shown (94). The partially contradicting results published in the literature may relate to the time interval between the fractures and the PET examination (89–90). In bone scintigraphy, increased uptake persists for many months after fracture and depends on the site of injury (90). Although the duration of abnormal 18F-FDG uptake in benign fractures is unknown, Zhuang *et al*. (95) reported that 18F-FDG uptake rapidly decreased with time after fracture and that it should be normal within a maximum of 3 months. Shon and Fogelman (90) reported that the most intense 18F-FDG uptake was observed when MI by PET was performed 17 days after fracture, among the four-case series where imaging was performed from 17 days to 8 weeks.

In addition, because sclerotic lesions have been shown to be problematic in 18F-FDG-PET detection, and correct diagnosis was based on needle biopsy, one may expect a much stronger association between hypermetabolism on PET and a positive cancer diagnosis in patients with nonsclerotic lesions. This expectation is confirmed by the results of Laufer *et al*. (76). When the analysis was focused on nonsclerotic lesions in patients with solid tumors, 18F-FDG-PET became 100% sensitive and specific when the SUV cutoff of two was used. It seems that 18F-FDG-PET using the semiquantitative parameter SUV improves the diagnostic ability to differentiate between single bone malignant and benign lesions (96).

Evaluation of Therapy by PET

The development and clinical testing of targeted biological therapies for spinal tumors present new opportunities and new challenges. The efficacy of traditional cytotoxic agents, which may produce detectable tumor regression, is typically measured by response rate or survival (97–98). However, new biologic therapies have led to targeted molecular therapies that may permit improvement in therapeutic efficacy and reduced toxicity, thus requiring new measures of activity (99–100): For example, signal transduction pathways that are regulated inappropriately in brain tumors include growth factors and their receptors (for example, epidermal growth factor receptor [EGFR], vascular endothelial growth factor receptor [VEGFR] or platelet derived growth factor receptor [PDGFR]), which regulate cellular interactions with the microenvironment and intracellular oncogenic pathways. Improved functional neuropathology and molecular imaging may therefore permit identification of patient subgroups for which clinical responses may be enriched (15).

In the early postoperative period, 18F-FDG-PET can be used to differentiate residual tumor tissue from postoperative surgical effects (101–102). It seems clear that a decline in tumor tissue uptake of 18F-FDG weeks or months after therapy is suggestive of a good response to treatment, indicating either a reduced number of viable cells or reduced metabolism of damaged cells (16,103).

After intensive irradiation or chemotherapy for malignant CNS tumors, MRI is not able to distinguish tumor progression from radiation damage or necrosis. Some PET methods appear promising as relatively specific indices of therapeutic response. 18F-FDG uptake suggests the presence of viable CNS tumor tissue (at least when high tumor uptake of 18F-FDG was noted before therapy), while absence of 18F-FDG uptake suggests that necrosis may be present (104–105). An increase in CNS tumor metabolism compared with studies before therapy predicts longer survival (106). This is explained by predominant killing of low energy-consuming cells or stimulation of quiescent cells, either tumor or normal, to become metabolically more active. In other terms, the increased regional metabolism means that within a certain volume of a specific tissue, the ratio and density of normal cells to tumor cells improved.

Pharmacoselective Potential of Molecular Imaging in Neuroncology Drug Development

Novel targeted drugs such as small molecular inhibitors of receptors and signaling pathways in the biology of primary CNS tumors are showing some activity in initial studies (107). As we learn more about these drugs and how to optimize their use as single agents and in combination with radiation, chemother-

apy and other targeted molecular agents, they will likely play an increasing role in the management of this devastating disease, as such molecules can be labeled with positron emitting isotopes and the emitted radiation is detected using sensitive PET cameras.

It is now possible to measure *in vivo* and normal tissue pharmacokinetics of anticancer drugs and to investigate their mechanism of action. Radiolabeling of tracers can be used to measure specific pharmacodynamic endpoints and to target identification. Increasing evidence shows how these technologies, when added to early drug development, can rapidly reduce the time for entry into patients and provide early identification of mechanisms of action. With the move toward more segmented markets and the identification of specific subgroups, PET's use for noninvasive biomarkers will become increasingly important.

CONCLUSION

Spinal PET is an evolving and promising method for the clinical management of spinal tumors. However, not every patient can be studied by MI, and it is not necessary to do so in every case. MI technologies should be used in selected patients to advance our understanding of the complex pathophysiology of spinal tumors. This use will allow the development and assessment of new therapeutic modalities including molecular targeted and gene therapies (imaging-guided therapies). The functional-anatomic discordance between PET and MRI in spinal tumors needs to be examined further, which might open up new insights into the disease process and might generate further subgroups within this entity. Both modalities complement each other in spinal tumors, and frequently, abnormalities noted on PET images can provide additional clinical information which is of great value in further clinical patient management.

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DISCLOSURE

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