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Potential of Positron Emission Tomography for Neurogenic Tumors and Spinal Disorders

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1. Introduction

Positron emission tomography (PET) is a three-dimensional nuclear medicine imaging technique that provides metabolic information about the body. This technique was first introduced by Kuhl et al. (Kuhl, Chamberlain et al. 1956). The basic principle of this system is to detect pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. The metabolic information as three-dimensional imaging is obtained from the positional information of the tracer, obtained by computer analysis of the gamma rays. The metabolic information obtained is considered a functional imaging technique, whereas computed tomography (CT) and magnetic resonance imaging (MRI) are regarded as morphologic imaging techniques. Moreover, the fusion of PET with CT (PET-CT) has further elevated the precision of functional imaging techniques. Clinical applications of PET have increased in the last decade and have proven to be vital in the evaluation and diagnosis of diseases. The broad scope, versatility and sensitivity of PET make it the most powerful molecular imaging technique currently available for clinical use.

2. Clinical use of PET

PET is currently employed for preliminary diagnosis, evaluation of therapy and to determine the aggressiveness of a disease. Its most common and beneficial use is in oncology. The therapeutic strategy used in oncology must be developed according to the stage of the malignancy. The importance of staging derives from the clinical finding that the prognosis of patients with localized malignant disease is generally much better than those with metastases throughout the body. PET is also used for assessment of a viable myocardium that may respond to reperfusion and for medically refractory epilepsy.

The measurement of glucose metabolic rate is one of the prime measures of physiology in the human body. Anaerobic glycolysis is an early indicator of malignant transformation of cells (Schlyer 2004). Whole-body PET imaging with ^{18}F-fluoro-2'-deoxy-D-glucose (^{18}FDG), enables the evaluation of glucose metabolism throughout the entire body in a single examination to improve the detection and staging of a cancer, selection of therapy, and assessment of therapeutic response. Clinical indications for ^{18}FDG-PET imaging are well

documented for many solid tumors in adults. Several studies have established that ^{18}FDG-PET techniques have higher specificity than CT (Czernin 2002).

This article focuses on the clinical use of PET in spine surgery. First, we describe the feasibility of using PET for obtaining a preliminary diagnosis, including peripheral benign nerve tumors. Second, the use of PET to assess the functional impairment of the spinal cord in patients with cervical myelopathy is described.

3. Feasibility of the use of PET for preliminary diagnosis

In clinical situations, spine surgeons often encounter patients demonstrating intractable pain or progressive neurologic deficits of unknown origin that cannot be detected by conventional imaging tools. We have had two cases for which PET provided helpful evidence in obtaining a definitive diagnosis.

3.1 Case report (intractable pain)

A 37-year old woman experienced severe sciatica after hitting her left buttock with great force on the edge of a bathtub. A physical examination demonstrated intense radiating pain from the left buttock to the lateral calf. There was weakness in the sciatic nerve innervated musculature. She was diagnosed with Piriformis syndrome by a local hospital. However, her symptoms remained unchanged after surgery to release the Piriformis. Conventional imaging of the sciatica, including plain radiographs, CT and MRI of the spine, showed no abnormal findings. ^{18}FDG-PET detected an abnormal lesion in the sciatic nerve in the posterior compartment of the patient's left thigh, indicating an intraneural tumor in the sciatic nerve. Subtotal resection was achieved and the histological evaluation of the specimen showed typical features of nodular fasciitis (Figure 1). After surgery, the patient was relieved of all symptoms with no evidence of recurrence at a recent two-year follow-up (Kakutani, Doita et al.).

3.2 Case report (Wegener's granulomatosis)

A 61-year old woman presented with progressive back pain, low-grade fever and gait disturbance. She was admitted to our hospital with paralysis of the left lower limb and bladder and rectal disturbances. A neurological examination revealed hyper-reflexia of the left patella and Achilles tendons, a positive Babinski's reflex, muscle weakness in the left lower extremities, foot drop and hypoesthesia below the T3 dermatome. The cranial nerve was not impaired. MRI of the thoracic spine revealed a diffuse space-occupying lesion at the anterior spinal cord in Th2-7. The lesion was hypointense on T1–weighted images and hyperintese on T2–weighted images. The lesion was enhanced after administration of contrast medium. ^{18}FDG-PET detected high uptake in the thoracic spine, bilateral upper lungs, and surrounding tissue of the abdominal aorta (Figure 2). Despite hospital admission and bed rest, the neurological deficit deteriorated, and the authors performed a laminectomy at Th1-T6 and posterior fusion with instrumentation at C7-Th7, including open biopsy. The histological examination of the surgical specimen showed fibrin deposition and granulation tissue formation with inflammatory infiltrate; no definitive diagnosis could be obtained from the surgery and biopsy. However, in addition to the abnormal ^{18}FDG-PET

findings, further examinations revealed elevated levels of MPO-ANCA of 66 U/ml (normal<10.0 U/ml) and we concluded that the epidural spinal tumor was a complication associated with Wegener's granulomatosis. The high uptake in the bilateral upper lungs and surrounding tissue of the abdominal aorta detected by ^{18}FDG-PET was the conclusive evidence for the definitive diagnosis of Wegener's granulomatosis (Kasagi, Saegusa et al.).

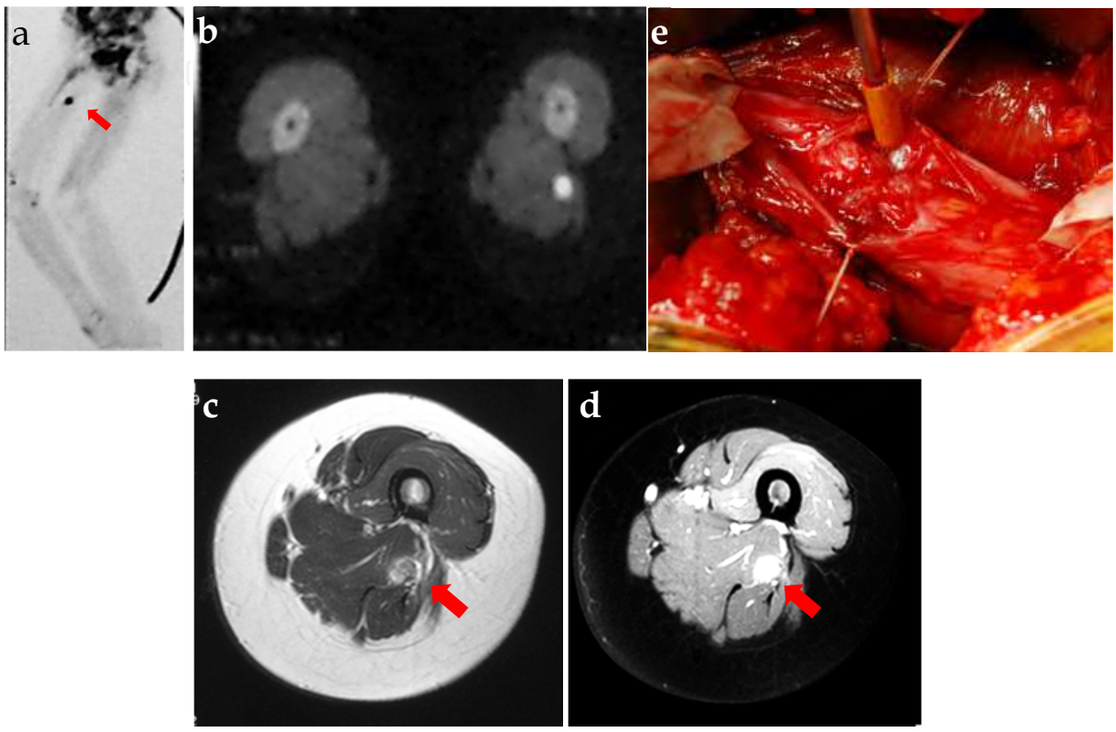

Fig. 1. Nodular fasciitis in the sciatic nerve detected by ^{18}FDG-PET (a,b). T2-weighted MRI (c) and Gd enhanced MRI (d) demonstrated the mass in the right hamstring. After fascicular dissection, the lesion under fascicular of sciatic nerve is disclosed entrapping the perineurium of sciatic nerve(e).

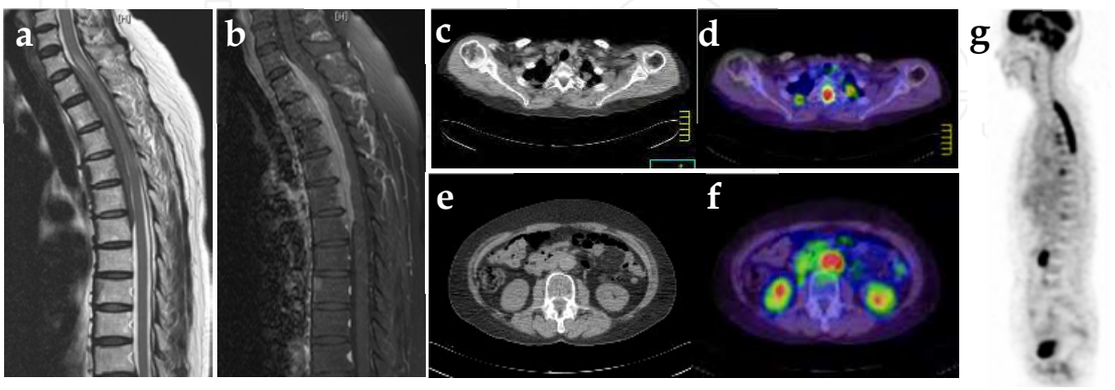

Fig. 2. MRI showing a diffuse space-occupying lesion at the anterior spinal cord: T2-weighted MRI (a); Gd-enhanced (b). Axial CT (c,e); axial PET/CT fusion (d,f) and sagittal PET image (g) demonstrating FDG uptake in the abdominal aorta and bilateral upper lungs.

Although these two case reports represent very rare cases, ^{18}FDG-PET provided helpful diagnostic clues for obtaining the definitive diagnosis. While meticulous physical examinations and the symptoms themselves are usually enough to aid identification of the correct pathomechanism, spine surgeons often encounter patients whose cases are difficult to diagnose using conventional imaging tools, such as MRI and CT. In our cases, the differential diagnosis was intramedullary tumor, extraspinal neurogenic tumor, especially in the pelvis, or inflammatory lesion of the central nervous system (CNS), including the neurosarcoidosis and human T-lymphotropic virus type I-associated myelopathy (HTLV-1 myelopathy). Conventional imaging tools, MRI, CT and scintigraphy, revealed pathological changes consistent with these diagnoses; however MRI without enhancement with gadolinium did not indicate the abnormal findings expected in intramedullary tumor or inflammatory lesion of the CNS. Furthermore, almost all neurogenic tumors are negative with tumor scintigraphy by ^{67}Ga-citrate, ^{201}TICI and Tc-99m. In contrast, PET, providing metabolic information as three-dimensional imaging, can reveal neurogenic tumors in the whole body and CNS inflammatory lesions (Zhuang, Yu et al. 2005). FDG-PET is not only important for detecting malignant tumors, but also has potential for evaluation of a variety of inflammatory and infectious disorders (Zhuang, Yu et al. 2005). Because ^{18}FDG, the most common radiopharmaceutical for PET in oncology, is not tumor-specific, ^{18}FDG-PET cannot differentiate between malignancies and inflammatory processes, a disadvantage for oncological diagnoses. This property is, however, an advantage for screening spinal and neurogenic disorders.

3.3 Tumors and inflammation

Significant tracer accumulation can also occur in viral, bacterial and fungal infections, or in other forms of inflammatory tissue. FDG accumulation in inflammatory tissue may cause false positives during cancer screening. Other PET tracers considered to be proliferation markers may allow improved differential diagnosis of tumor and inflammation. Proliferation activity can be measured by lipid precursors, amino acids, nucleosides and receptor ligands. Only labeled nucleosides incorporated into DNA are true proliferation markers, while amino acid transport, membrane metabolism, enzyme activity and receptor expression can serve as surrogate markers of cellular proliferation based on the tissue kinetics. Established imaging targets for oncology are: (i) glucose transport (^{18}FDG); (ii) choline kinase activity (^{11}choline); (iii) amino acid transport (^{11}C-methionine); and (iv) activity of thymidine kinase 1 (^{18}FLT). Radiolabeled choline, amino acids and nucleosides have been reported to show greater tumor-specificity than ^{18}FDG, both in experimental animals and in humans (van Waarde and Elsinga 2008), although the specificity of any tracer is not absolute. FDG, choline and C-methionine are accumulated in such inflammatory process as bacterial and sterile infections. Although proliferation activity is a key factor of malignancy, cell division can also occur in benign tumors and inflammation processes. Consequently the tumor specificity of PET will never achieve 100%.

Sahlmann et al. reported that the dual time point ^{18}FDG uptake, which was measured at 30 and 90 minutes after injection, showed different pattern between chronic bacterial osteomyelitis and malignant bone tumor. In osteomyelitis, the standard uptake value (SUV) between 30 and 90 minutes post-injection remained stable or decreased, while, in contrast, in malignant bone tumor, the SUV between 30 and 90 minutes post-injection increased

(Sahlmann, Siefker et al. 2004). Moreover, high-grade sarcomas were found to reach peak activity concentration approximately 4 hours after injection of FDG, while benign tumors reached maximum within 30 minutes (Lodge, Lucas et al. 1999). Thus, the dynamic dual time point ^{18}FDG-PET provides is a characteristic pattern in chronic osteomyelitis, similar to inflammatory processes in other locations, differentiating it from malignant tumors. However, clarification of the difference between inflammatory lesions and benign tumors, which have similar uptake patterns, is yet to be accomplished.

3.4 Benign and malignant neurogenic tumors

The cause of nerve pain and neurological deficit is often considered to be extradural tumors, including such neurogenic tumors as schwannoma, neurofibroma, perineurioma, intraneural ganglion and malignant peripheral nerve sheath tumor (MPNST), as well as such intradural tumors as schwannoma, meningioma and ependynoma, etc (Figure 3,4). Generally detection of these benign neurogenic tumors by tumor scintigraphy using ^{67}Ga-citrate, ^{201}TICI or Tc-99m is difficult, as is detection of meningioma except for MPNST.

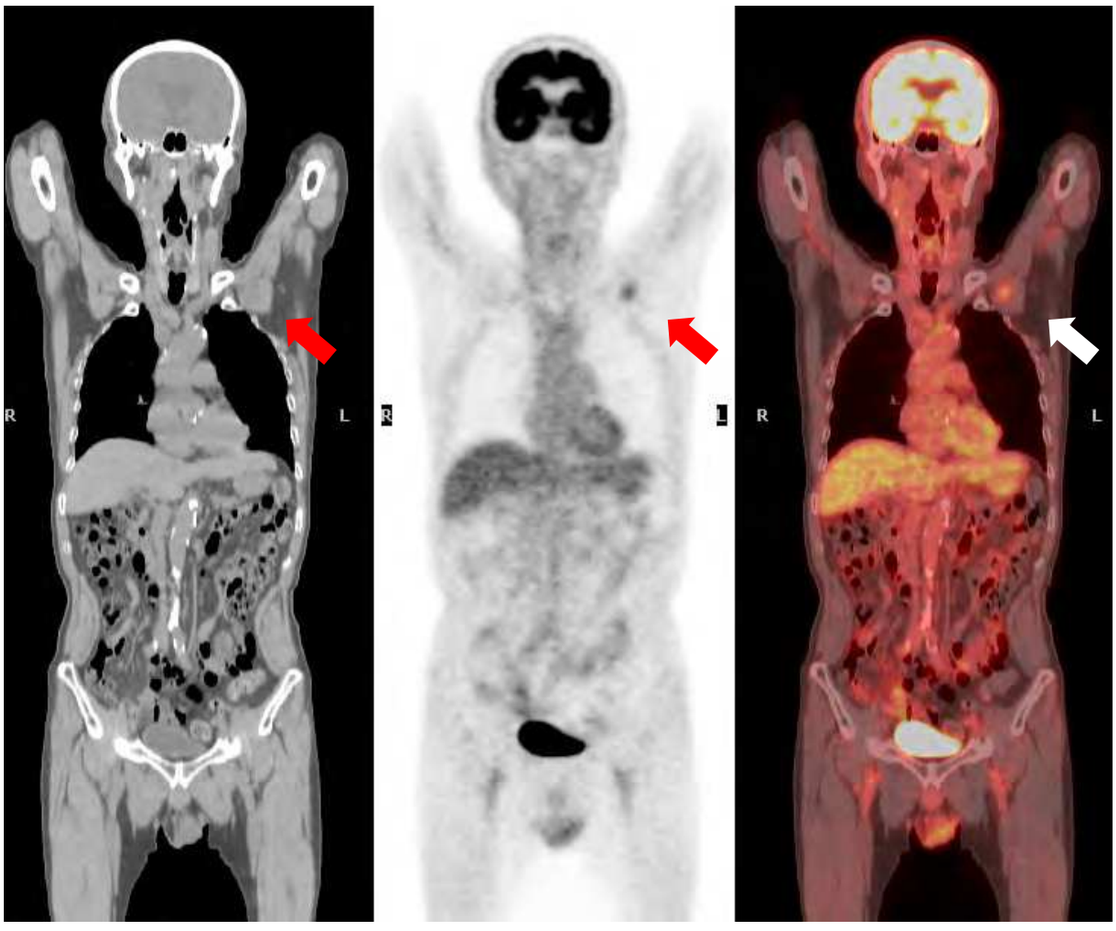

Fig. 3. CT, FDG and PET/CT images showing accidental detection of schwannoma in the left brachial plexus.

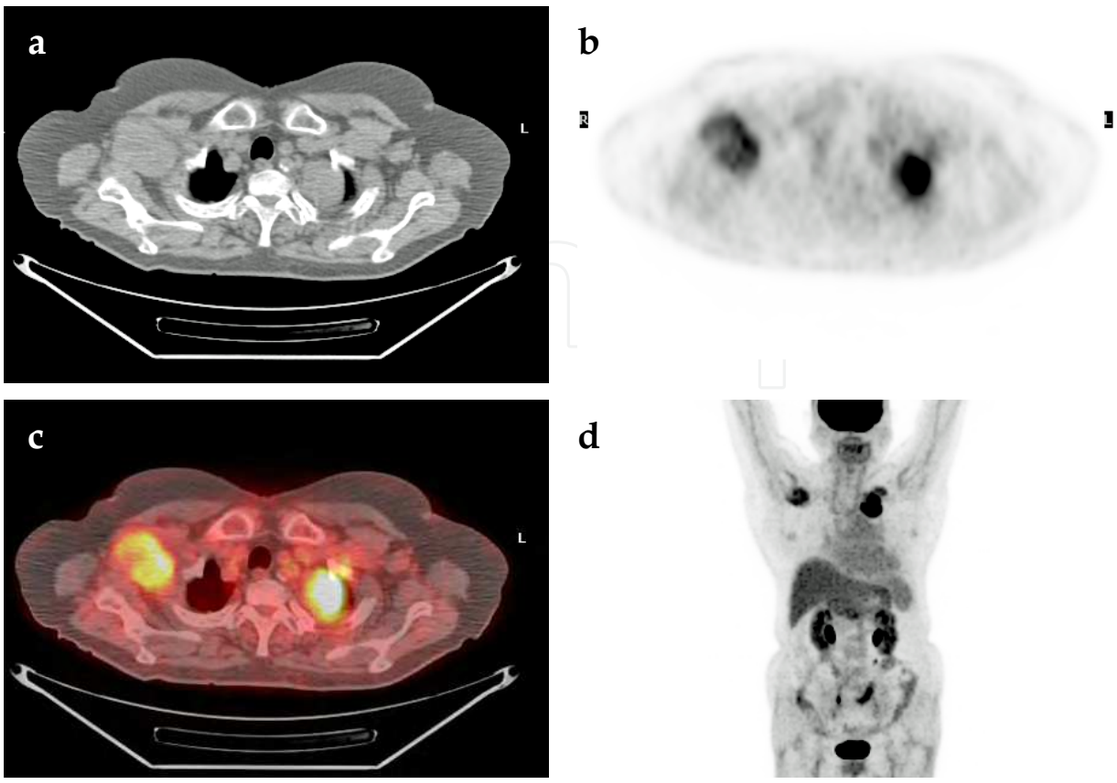

Fig. 4. Malignant peripheral nerve sheath tumor (MPNST) located in the right brachial plexus and the left upper lung demonstrated by axial CT (a), axial PET (b), axial PET/CT fusion (c) and coronal PET (d).

In contrast, ^{18}FDG-PET reveals benign neurogenic tumors and menigiomas in the whole body (Ahmed, Watanabe et al. 2001);(Lippitz, Cremerius et al. 1996; Antoch, Egelhof et al. 2002; Beaulieu, Rubin et al. 2004; Ghodsian, Obrzut et al. 2005; Hamada, Ueda et al. 2005; Halac, Cnaral et al. 2008). Studies have investigated the tumor growth characteristics of schwannoma and meningioma by PET. Ahmed et al. retrospectively reviewed schwannoma of the extremities in 22 patients. They found that ^{18}FDG-PET and ^{18}FMT-PET, in which ^{18}F-fluoro-α-methyl tyrosine (^{18}FMT) is an amino acid tracer to monitor protein metabolism, detected schwannoma in all cases, and reflected proliferation activity of the schwannoma. The authors suggested that ^{18}FMT-PET is more reliable for differentiation between benign schwannoma and malignancy than ^{18}FDG-PET (Ahmed, Watanabe et al. 2001). Kubota et al. studied the feasibility of differentiating benign and malignant schwannomas by dual time point ^{18}FDG-PET, comparing uptake 1 hour post-injection to 2 hours post-injection. Most malignant schwannomas showed greater increase at 2 hours post-injection than at 1 hour post–injection, while most normal tissue showed lower ^{18}FDG uptake at 1 hour than at 2 hours (Kubota, Itoh et al. 2001). In addition, from analysis of the SUV of ^{18}FDG on 55 patients with benign and malignant tumors involving the musculoskeletal system, the cut-off point, 1.9, was calculated and the sensitivity of ^{18}FDG -PET for correctly diagnosing malignancy was 100%, with a specificity of 76.9% and an overall accuracy of 83.0%(Watanabe, Shinozaki et al. 2000). Thus, dual time point PET and the cut-off value of

SUV can furnish useful diagnostic information for differentiating benign and malignant schwannomas.

In contrast, because meningioma cells have high uptake levels for 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic-acid-D-Phe1-Tyr3-oc treotide (^{68}Ga-DUTATOC), a new PET radiotracer with high specific binding to somatostatin receptors, ^{68}Ga-DUTATOC can be used to image the meningioma (Henze, Schuhmacher et al. 2001). Lipptiz et al. investigated the correlation of ^{18}FDG-uptake with the histopathology, cellularity and proliferation rate of intrancanial meningioma. They found significant differences between ^{18}FDG-uptake in World Health Organization (WHO) grade I vs. grades II and III, low vs. high cellularity and Ki-67 index < 2% vs. > 2% intracranial meningomas (Lippitz, Cremerius et al. 1996). These results indicate that a portion of a tumor can be imaged using this specific tracer and dynamic dual time point examination and show that PET is useful not only for screening but also as a noninvasive predictor of tumor growth characteristics of schwannoma and meningioma.

3.5 Inflammatory lesion of spinal cord

When clinical manifestations are more severe than imaging indicates an inflammatory lesion of the spinal cord should be considered in the differential diagnosis. Inflammatory diseases of the spinal cord, such as neurosarcoidosis and HTLV-1 myelopathy, present a wide spectrum of clinical and radiological manifestations, making them difficult to diagnose. Bolat et al. explored the usefulness of PET in the diagnosis of neurosarcoidosis (Bolat, Berding et al. 2009). In addition, Umehara et al. found ^{18}FDG-PET to be helpful for diagnosing HTLV-1 myelopathy (Umehara, Hagiwara et al. 2008). Radu et al. measured experimental autoimmune encephalomyelitis by ^{18}FDG-PET; their results highlighted the potential use of serial ^{18}FDG-PET for monitoring neuroinflammation in encephalomyelitis. They also suggested that similar approaches could be applied to the diagnosis and evaluation of other autoimmune and inflammatory disorders in animal models and humans (Radu, Shu et al. 2007).

4. Prediction of surgical outcomes in cervical sclerotic myelopathy

Conventional morphological imaging with CT and MRI can visualize precisely the location and pathological cause of stenosis and compression; however the severity of morphological stenosis does not necessarily correlate with either the actual functional deficits or the clinical course of the condition. Therefore, alternative diagnostic methods to morphological imaging are needed to better reflect the functional impairment of the cervical cord.

To accurately predict prognosis and neurological improvement after neurosurgical decompression, it is essential to be able to assess spinal cord function in patients with cervical compression myelopathy. Most conventional evaluations focus on morphologic and pathologic changes to the compressed cord, which can be identified on MRI. MRI is a valuable tool because it visualizes not only the magnitude of the spinal cord compression, but also intramedullary signal intensity. Several investigators have reported a correlation between morphologic and pathologic changes on MRI and neurologic status, with most studies suggesting that preoperative MRI findings could be used to predict surgical outcome and prognosis (Okada, Ikata et al. 1993; Wada, Yonenobu et al. 1999; Singh, Crockard et al. 2001; Alafifi, Kern et al. 2007).

The spinal cord is considered to have viscoelastic properties that allow it to return to its original configuration following decompression, leading to recovery of physiologic function of sensorimotor pathways. However, spinal cord atrophy is associated with significantly reduced extensibility and the atrophic spinal cord in patients with profound paresis fails to regain its original configuration after decompression. It has been reported that patients who show early postoperative expansion of the spinal cord tend to have favorable neurologic improvements (Baba, Maezawa et al. 1997). The restoration of the transverse area and sagittal diameter of the spinal cord also correlates with better neurologic improvement (Fukushima, Ikata et al. 1991; Yone, Sakou et al. 1992). An important issue is the significance of changes in MRI intramedullary signal intensity. Increased capillary permeability with subsequent stromal edema and venous congestion can be visualized on T2-weighted MRI. Although it is unclear whether intramedullary signal intensity of the spinal cord on a T2-weighted MRI can be used to predict neurologic recovery following decompression, a number of investigators have suggested that high-signal intensity on T2-weighted MRI is a marker for poor neurologic prognosis (Ramanauskas, Wilner et al. 1989; Mehalic, Pezzuti et al. 1990); (Takahashi, Yamashita et al. 1989).

The central nerve system, brain and spinal cord, is known to mainly utilize glucose for basic metabolism. ^{18}FDG-PET can reflect spinal cord neural cell activity by visualization and measurement of glucose utilization. In myelopathy patients, ^{18}FDG-PET uptake and glucose utilization rate in the cervical spinal cord is variable. Metabolic evaluation of space-occupying and spinal cord-compressing spinal cord abnormalities with ^{18}FDG-PET has been used successfully for more than 25 years, especially for neoplastic disease (Nguyen, Sayed et al. 2008) (Francken, Hong et al. 2005); (Di Chiro, Oldfield et al. 1983; Meltzer, Townsend et al. 1998; Wilmshurst, Barrington et al. 2000; Poggi, Patronas et al. 2001). In all these space-occupying and spinal cord-compressing lesions, ^{18}FDG-PET was used to differentiate between benign and malignant abnormalities or to monitor the biological activity of a condition. Consequently, ^{18}FDG-PET should be considered a contemporary advanced technology for further assessment of chronically damaged spinal cords in patients with cervical myelopathy.

SUV is a potentially suitable parameter for assessment of neurologic status in clinical practice. Kamoto et al. reported that the normal value of metabolic rate of glucose utilization in the cervical spinal cord in healthy Japanese subjects was 1.93 ± 0.23 (Kamoto, Sadato et al. 1998). Although several investigators have reported ^{18}FDG uptake levels in cervical compressive myelopathy, the relationship between metabolic activity and severity of neurologic dysfunction is controversial.

Baba et al. utilized mouse animal models and observed that during the early stages of cord compression, neuropeptide activity in neurons and glial cells was increased by external pressure, thus stimulating glucose utilization by the spinal cord. Chronic compression, however, leads to atrophy and necrosis of anterior grey horn cells, and the loss of glucose-consuming neurons leads to decreased ^{18}FDG uptake of the spinal cord (Baba, Uchida et al. 1999). Uchida et al. reported that patients with mild to moderate myelopathy have a significantly higher SUV, while those with marked and profound tetraparaesis have significantly lower values (Uchida, Kobayashi et al. 2004). Uchida et al. also analyzed the SUV during neurologic improvement of cervical myelopathy, and found that more improved patients had significantly higher preoperative SUV compared to patients with less

improvement (Uchida, Nakajima et al. 2009). Interestingly, classification by preoperative SUV did not differ significantly from classification by the intramedullary signal intensity of the spinal cord on MRI. It is possible that the absolute level of the SUV is not decisive for assessment of the metabolic status of the cervical cord. Floeth et al. studied homogenous myelopathy patients with monosegemental chronic degenerative stenosis using ^{18}FDG-PET, and found that patients with chronic compressive myelopathy had normal glucose utilization just above the level of the stenosis but significantly decreased ^{18}FDG uptake below the level of cord compression (Floeth, Stoffels et al.2010). They noted that these results are compatible with those of Baba et al. (Baba, Uchida et al. 1999).

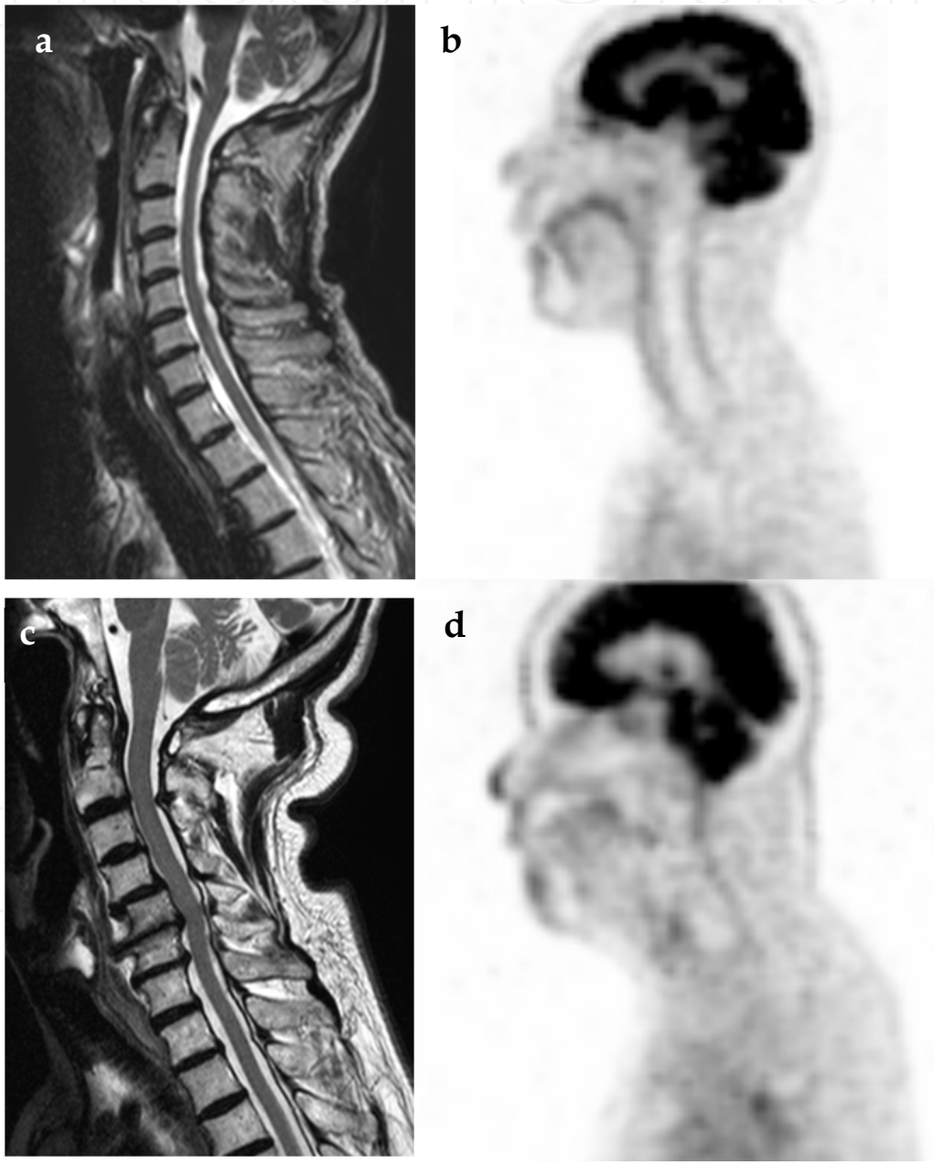

Fig. 5. MRI (a) and PET (b) showing homogenous FDG uptake in a patient with a normal cord, and MRI (c) and PET (d) illustrating reduced FDG uptake at the compression level in a patient with mild myelopathy.

^{18}FDG-PET can reflect the glucose utilization of the spinal cord in spinal disorder patients (Figure 5). It can be an important predictor for prognosis and neurological improvement after neurosurgical decompression. However, ^{18}FDG uptake is affected by the range of stenosis, whether it is bi- or multisegmental stenosis, and duration and severity of symptoms. Further studies in a larger series of patients with chronic and clinically stable myelopathy, and in patients with an acute and rapidly progressing myelopathy are needed.

5. Conclusion

^{18}FDG-PET is important not only for detecting malignant tumors but also for its potential use in the evaluation of a variety of inflammatory and infectious disorders (Zhuang, Yu et al. 2005). For oncology, there is the limitation that ^{18}FDG-PET cannot differentiate between malignant and inflammatory processes. However, this limitation would be considered an advantage when screening for spinal anomalies and benign neurogenic tumors. Therefore, despite the high cost and relative scarcity of PET scanners at institutions, the role of PET in screening for and assessment of benign neurogenic tumors and compressive myelopathies is expected to increase.

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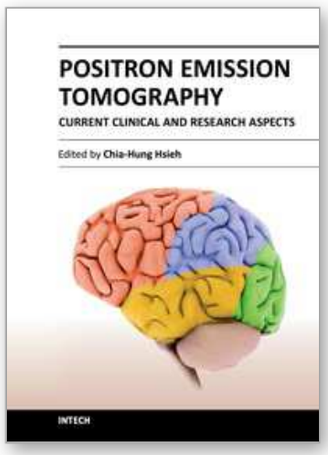

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This book's stated purpose is to provide a discussion of the technical basis and clinical applications of positron emission tomography (PET), as well as their recent progress in nuclear medicine. It also summarizes current literature about research and clinical science in PET. The book is divided into two broad sections: basic science and clinical science. The basic science section examines PET imaging processing, kinetic modeling, free software, and radiopharmaceuticals. The clinical science section demonstrates various clinical applications and diagnoses. The text is intended not only for scientists, but also for all clinicians seeking recent information regarding PET.

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