ORIGINAL ARTICLES

Association between ^{18}F-FDG PET/CT and MRI appearance of spinal leptomeningeal disease before and after treatment at a tertiary referral center

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ABSTRACT

Objective: Leptomeningeal disease (LMD), the presence of metastasis in the subarachnoid space, has devastating implications if left untreated. The gold standard for LMD diagnosis is cytologic analysis of cerebrospinal fluid (CSF); MRI is also used to evaluate suspected LMD. The purpose of this study was to compare the appearance of LMD in the spinal canal on ^{18}F-FDG PET/CT imaging with the appearance of LMD on MRI and with CSF cytology.

Methods: In twenty-one patients with cytologically-proven spinal LMD, findings on ^{18}F-FDG PET/CT, MRI, and CSF cytology at diagnosis of LMD and after the initiation of treatment for LMD were retrospectively reviewed.

Results: At diagnosis of LMD, abnormal ^{18}F-FDG avidity was demonstrated in the spinal canal in six patients, and the anatomic distribution of ^{18}F-FDG activity corresponded to the sites of LMD on MRI. All six of these patients were then treated with intrathecal chemotherapy. Follow-up ^{18}F-FDG PET/CT and MRI were obtained in four of the six cases. In all four cases, normalization of ^{18}F-FDG activity in the spinal canal and reduction of enhancement on MRI corresponded to the cytologic response to treatment, as determined by CSF analysis.

Conclusion: ^{18}F-FDG avidity in the spinal canal greater than the normal contents of the canal can suggest spinal LMD. This abnormal avidity may be detected before the diagnosis of LMD has been established with MRI or CSF cytology. The spinal canal should be routinely evaluated on ^{18}F-FDG PET/CT in patients with suspected LMD so that appropriate treatment is initiated.

Key Words: Personalization, Recommendation of event attendance, Mapping categories of interest

1. INTRODUCTION

Leptomeningeal disease (LMD), the presence of metastatic cells in the subarachnoid space, often has devastating prognostic implications, even when aggressively treated. In patients with metastatic malignancies, LMD is diagnosed in approximately 5% of cases.[1] LMD is often undiagnosed or clinically silent.[1,2] At autopsy, in patients with metastases, the frequency of LMD is about 20%.[1,3] The median sur-

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vival after diagnosis of LMD is 4-6 weeks if the disease is not treated and 2-3 months if the disease is treated.[4]

The diagnostic sensitivity of cytologic analysis of cerebrospinal fluid (CSF) obtained by lumbar puncture in establishing a diagnosis of LMD is estimated to be 57%-100%[5] and depends on the volume of CSF and number of CSF samples obtained.[5] Currently, the imaging modality most frequently used to evaluate whether LMD is present is contrast-enhanced MRI, and the sensitivity ranges from 35% to 100%.[6,7] Although cytologic analysis of CSF is considered the gold standard for diagnosing LMD, MRI and CSF cytology are complementary, as MRI can show evidence of LMD when CSF cytology does not and vice versa.[8] To avoid delay in treatment, the diagnosis of LMD needs to be made as early as possible.

The use of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET/CT in staging cancer, especially hematologic malignancies, is becoming increasingly widespread. In evaluation of the spine the vertebrae are often the primary focus, as ^{18}F-FDG PET/CT is frequently performed to exclude osseous metastases. Many patients who could potentially have spinal LMD undergo ^{18}F-FDG PET/CT. Recent case reports have documented both intracranial and extracranial LMD on ^{18}F-FDG PET/CT.[9–14] To the best of our knowledge, however, no study to date has compared ^{18}F-FDG PET/CT, MRI, and CSF findings in patients with cytologically proven LMD. The purpose of this study was to compare spinal LMD on ^{18}F-FDG PET/CT and spinal LMD on MRI during the initial evaluation for LMD and after treatment of the LMD.

2. METHODS

Our Institutional Review Board approved this study and waived the requirement for informed consent. Data acquisition was performed in compliance with all applicable Health Insurance Portability and Accountability Act regulations. We searched the Neurosurgery database at our institution to identify all patients with cytologically proven LMD who underwent MRI of the spine during the period from 2007 through 2010. This search returned 157 patients. Within this group, we searched for patients who also underwent ^{18}F-FDG PET/CT, which returned 26 patients. We then excluded patients whose MRI, PET/CT, and CSF collection documenting LMD were not performed within 6 weeks of each other (n = 5), which left 21 patients in our study. The patients' demographic data, clinical data, and findings on both MRI and ^{18}F-FDG PET/CT performed before and after treatment of LMD were retrospectively reviewed. On the basis of the qualitative imaging assessment by two readers, a neuroradiology fellow and neuroradiology attending with over 10 years' experience, leptomeningeal enhancement in the spinal canal on MRI was recorded as diffuse filling of the spinal canal, thin linear, thick linear, or nodular enhancement. The maximum standardized uptake value (SUV) of ^{18}F-FDG PET/CT avidity in the spinal canal was recorded. The overall hypermetabolic disease burden on ^{18}F-FDG PET/CT was quantified as high (extensive nodal or extranodal disease), mid (mild extranodal disease), or low (absent or nodal disease confined to 1 side of the diaphragm). For the CSF samples, the white blood cell count (normal range 0-5/μL), glucose level (normal range 40-70 mg/dL), and protein level (normal range 15-55 mg/dL) were recorded both at diagnosis of LMD and after treatment of LMD.

The MRI examinations were performed using the following parameters: sagittal T1-weighted sequence (TR, 400-650 ms; TE, 9-19 ms), sagittal fast spin echo (FSE) T2-weighted (TR, 3,000-6,100 ms; TE, 90-110 ms), axial T1-weighted pre-gadolinium (TR, 350-850 ms; TE, 9-14 ms), axial T1-weighted post-gadolinium (TR, 400-750 ms; TE, 9-19 ms), and sagittal T1-weighted post-gadolinium (TR, 400-800 ms; TE, 9-18 ms). Axial images were acquired at a section thickness of 4-5 mm with a section gap of 1 mm, and sagittal images were acquired at a slice thickness of 5-8 mm with a section gap of 1-2 mm. Intravenous gadolinium (Omniscan, GE Medical Systems, Milwaukee, WI) was administered in all cases.

^{18}F-FDG PET/CT scans were performed on a dedicated PET/CT system (Discovery ST, Discovery STe, or Discovery RX; GE Medical Systems). Scans were acquired from the orbits through the mid-thighs and performed 60-90 minutes after intravenous administration of ^{18}F-FDG. PET studies were acquired in either 2-dimensional or 3-dimensional acquisition mode at 3-5 minutes per bed position (depending on the patient's body mass index).

3. RESULTS

Twenty-one patients met the criteria for inclusion in this study: 11 men and 10 women ranging from 29 years to 78 years old (mean $\pm$ standard deviation: 55 $\pm$ 12 years). Primary malignancies, cancer treatment at diagnosis of LMD, and imaging findings at diagnosis of LMD are summarized in Table 1.The disease status of the primary malignancy at the time of diagnosis of LMD was new in six patients, recurrent in 12 patients, and recurrent, but refractory to treatment in 3 patients. ^{18}F-FDG PET/CT was performed between 36 days before and 14 days after the initial MRI (3 $\pm$ 12 days before) and between 30 days before and 7 days after the initial CSF collection (7 $\pm$ 12 days before).The patients were undergoing various combinations of the following treatments when their LMD was diagnosed by CSF analysis: systemic chemotherapy (n = 14), steroids (n = 9), intrathecal chemotherapy (n =

4), stem cell transplant (n = 1), and radiation therapy (n = 1). Table 1).
All 21 patients had evidence of LMD on the initial MRI (see

Table 1. Primary cancer status, prior treatments, and imaging findings at diagnosis of LMD

Patient	Cancer type	Status of cancer at diagnosis of LMD	Cancer treatment being received at diagnosis of LMD	Steroid treatment being received at diagnosis of LMD	Systemic disease burden on ^{18}F-FDG PET/CT	Spinal LMD on ^{18}F-FDG PET/CT (SUV)	LMD enhancement on MRI
1	Anaplastic large cell lymphoma	New	Chemo, ITC	No	Low	-	Thin linear
2	Mantle cell lymphoma	Recurrent	Chemo	No	High	7.4	Diffuse
3	Low-grade B-cell lymphoma	New	None	No	Low	-	Thin linear
4	Diffuse large B-cell lymphoma	Recurrent	Chemo	No	Low	10.8	Thick linear
5	Large cell lymphoma	New	ITC	No	Low	-	Thin linear
6	Diffuse large B-cell lymphoma	Recurrent	Chemo	No	Low	-	Thick linear
7	Diffuse large B-cell lymphoma and HIV	New	Chemo and ITC	Yes	High	4.8	Diffuse
8	Breast cancer	Refractory	Chemo	No	High	-	Thick linear
9	Breast cancer	Recurrent	Chemo	Yes	Low	-	Nodular
10	Mantle cell lymphoma	Recurrent	Chemo	Yes	Low	-	Thick linear
11	Adenocarcinoma (unknown primary tumor)	Refractory	Chemo	No	Low	-	Nodular
12	Non-Hodgkin lymphoma	Recurrent	Chemo	No	Low	11.1	Thick linear
13	Lung cancer (non-small cell)	Recurrent	Chemo	Yes	Low	-	Thin linear
14	Follicular lymphoma	Recurrent	Chemo + ITC + XRT	No	Intermediate	4.8	Diffuse
15	Mantle cell lymphoma	Recurrent	Chemo	Yes	Low	-	Nodular
16	Melanoma	Recurrent	None	No	Low	-	Thin linear
17	Multiple myeloma	Recurrent	SCT	Yes	Low	-	Thin linear
18	Malignant hematolymphoid neoplasm	New	None	Yes	Intermediate	-	Thin linear
19	T-cell lymphoma	Recurrent	Chemo	Yes	Intermediate	-	Nodular
20	Waldenström macroglobulinemia	Recurrent	None	Yes	Low	-	Diffuse
21	Waldenström macroglobulinemia	New	None	No	High	2.8	Diffuse

Note. Chemo=systemic chemotherapy, ITC=intrathecal chemotherapy, SCT=stem cell transplant, XRT=radiation therapy.

3.1 Initial evaluation

On the initial ^{18}F-FDG PET/CT, abnormal ^{18}F-FDG avidity was demonstrated in the spinal canal in six patients (four men and two women, 29-69 years old [52 ± 13 years]) (see Figure 1, A-C). The maximum SUV in these six patients ranged from 2.8 to 11.1 (7 ± 3.4). The ^{18}F-FDG PET/CT studies in these six patients were obtained for restaging (n = 5) or initial staging (n = 1). In these six patients, ^{18}F-FDG PET/CT was performed from 36 days before to 14 days after initial MRI (3 ± 11 days before) and from 29 days before to 7 days after initial CSF analysis (7 ± 12 days before). In these six patients, the primary malignancies were lymphoma (n = 5) and Waldenström macroglobulinemia (n = 1). The neurologic symptoms in these patients at the time of ^{18}F-FDG PET/CT were cauda equina syndrome (n = 2), headache (n = 1), lower-extremity weakness (n = 1), and ptosis (n = 1); one patient had no neurologic symptoms.

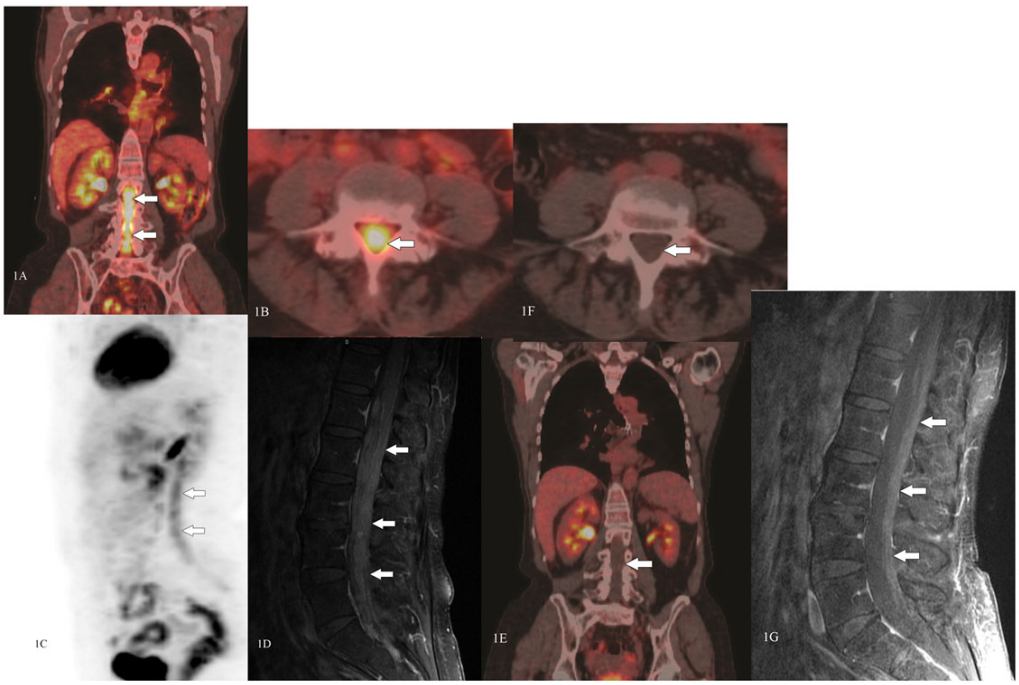

Figure 1. A 68-year-old-woman with diffuse large B-cell lymphoma (patient 4): A, B and C, Coronal (A), axial (B), and three-dimensional (C) ^{18}F-FDG PET/CT shows abnormal ^{18}F-FDG avidity in the spinal canal (arrows). D, Sagittal T1-weighted post contrast MRI demonstrates abnormal enhancement (diffuse filling within the spinal canal) consistent with LMD. E and F, Coronal (E) and axial (F) ^{18}F-FDG PET/CT demonstrate resolution of abnormally ^{18}F-FDG–avid disease in the spinal canal after treatment. G, Sagittal T1-weighted post contrast MRI shows decreasing enhancement of the spinal canal after treatment.

The patterns of leptomeningeal enhancement on the initial MRI in these six patients were thick linear (n = 3) and diffuse filling (n = 3). In all six cases, the anatomical distribution of abnormal ^{18}F-FDG avidity in the spinal canal corresponded to the extent of abnormal leptomeningeal enhancement on MRI (see Figure 1D). In the 15 patients without abnormal ^{18}F-FDG avidity in the spinal canal, a lack of LMD on MRI was present. All six patients with abnormal ^{18}F-FDG avidity in the spinal canal were treated with intrathecal chemotherapy after placement of an Ommaya reservoir.

Also during the initial evaluation for LMD, CSF analysis was performed in all 21 patients in this series: the 15 patients without and the six patients with abnormal ^{18}F-FDG avidity in the spinal canal. The CSF laboratory values in the 15 patients without abnormal ^{18}F-FDG avidity in the spinal canal were as follows: white blood cell count, 202 ± 325 cells/μl (mean ± *SD*); glucose level, 41 ± 14 mg/dl; and protein level, 197 ± 234 mg/dl. For the six patients with abnormal ^{18}F-FDG avidity in the spinal canal, the CSF values were as follows: white blood cell count, 3,985 ± 4,701 cells/μl; glucose level, 37 ± 12 mg/dl; and protein level, 1,158 ± 1,679 mg/dl.

3.2 Follow-up

Follow-up ^{18}F-FDG PET/CT and MRI were performed in four of the six cases with initial ^{18}F-FDG PET/CT showing LMD. In these four patients, the interval between the ini-

tial ^{18}F-FDG PET/CT and the follow-up ^{18}F-FDG PET/CT ranged from 1 to 19 months (10 ± 9 months), and the interval between the initial MRI and the follow-up MRI ranged from 5 to 16 months (8 ± 7 months). In all four cases, the follow-up ^{18}F-FDG PET/CT demonstrated normalization of spinal ^{18}F-FDG activity (see Figure 1E, 1F), and the follow-up MRI demonstrated reduction in enhancement in the spinal canal (see Figure 1G). Between 5 days before and 3 months after (1 ± 2 months after) the follow-up ^{18}F-FDG PET/CT was acquired, all four of these patients also had negative CSF cytologic results.

After intrathecal chemotherapy for LMD, CSF analysis was performed in 20 of the 21 patients in the series: 14 patients who lacked abnormal ^{18}F-FDG avidity and the six patients who had abnormal ^{18}F-FDG avidity in the spinal canal during their initial evaluation for LMD. The CSF analysis was performed between 5 days and 8 months after (90 ± 70 days after) the initiation of intrathecal chemotherapy in the 14 patients without initial abnormal ^{18}F-FDG avidity and between 9 days and 22 months after (10 ± 9 months after) the initiation of therapy intrathecal chemotherapy in the six patients with initial abnormal ^{18}F-FDG avidity. The CSF laboratory values in 14 patients without abnormal ^{18}F-FDG avidity were as follows: white blood cell count, 0.4 ± 1.1 cells/μl; glucose level, 66 ± 28 mg/dl; and protein level, 44 ± 33 mg/dl. For the 6 patients with initial abnormal ^{18}F-FDG avidity, the CSF values were as follows: white blood cell count, 1.2 ± 2.4 cells/μl; glucose level, 66 ± 16 mg/dl; and protein level, 34 ± 36 mg/dl.

Nineteen of the 21 patients had died of their cancer at last follow-up. The patients survived a median of 6 ± 7 months (1 month to 25 months) after the LMD was detected by CSF cytology. Two patients (patients #3 and #20), both of whom did not have abnormal ^{18}F-FDG avidity in the spinal canal were still alive at last follow-up and had survived a median of 5.1 ± 0.3 years (4.8-7.0 years).

4. DISCUSSION

Our results suggest that ^{18}F-FDG PET/CT can demonstrate LMD in the spinal canal. In cases in which LMD was detected on ^{18}F-FDG PET/CT, the anatomic extent of abnormal ^{18}F-FDG avidity on PET/CT corresponded to the LMD burden and anatomic distribution seen on MRI. All six patients with positive ^{18}F-FDG PET/CT results demonstrated thick linear enhancement or diffuse filling of the spinal canal on the corresponding MRI examinations, whereas none of the patients

with nodular or thin MRI enhancement had positive findings on ^{18}F-FDG PET/CT. There does not, however, appear to be a threshold qualitative LMD burden on MRI that corresponds to abnormal ^{18}F-FDG avidity, as several cases with thick linear enhancement or diffuse filling on MRI did not show abnormal ^{18}F-FDG avidity.

Multiple factors may explain the observed low sensitivity of ^{18}F-FDG PET/CT for detecting LMD in the spinal canal. Low-grade or indolent lymphomas have been reported to be less FDG avid than high-grade or aggressive types.[15] Higher-grade follicular lymphoma, non-Hodgkin lymphoma, and large B-cell lymphoma have been reported to demonstrate higher ^{18}F-FDG metabolism, usually three times as great as that of lower-grade follicular lymphoma, marginal zone lymphoma, and small cell lymphoma.[15] In our study, the 4 of 6 patients with ^{18}F-FDG avid LMD in the spinal canal had diffuse large B-cell lymphoma (n = 2), non-Hodgkin lymphoma and follicular lymphoma (see Table 1). Chemotherapy and steroid therapy also have been shown to lower the efficacy of ^{18}F-FDG PET/CT in detecting malignancy and may lead to false-negative results.[16] In our study, 15 patients had ^{18}F-FDG PET/CT findings negative for spinal LMD; nine of these 15 patients had low-volume disease on their initial MRI, eight received steroids, and 10 were undergoing systemic or intrathecal chemotherapy when their LMD was diagnosed by cytology. Other possible explanations for the presence or lack of abnormal ^{18}F-FDG avidity in the spinal canal include prior treatment and degree of disease burden (see Table 2).

Our study contributes to the preexisting literature of multiple case reports describing abnormal ^{18}F-FDG avidity on PET/CT corresponding to LMD.[9–14] However, to the best of our knowledge, this is this first series to compare spinal LMD on ^{18}F-FDG PET/CT with its MRI appearance and cytologic CSF results and to evaluate changes after intrathecal chemotherapy through an Ommaya reservoir on follow-up studies. Unlike a retrospective review of neurolymphomatosis with neurologic manifestations of LMD, in which 91% of patients showed abnormal ^{18}F-FDG avidity in the central or peripheral nervous system, our study demonstrates an overall lower sensitivity of 29% (LMD was detected in six of 21 cases).[17] The lower sensitivity in our study could be attributed to our focusing exclusively on spinal LMD and the fact that the patients we included were undergoing treatment at the time of their initial assessment for LMD. Additionally, our study only included patients with leptomeningeal disease confirmed by cytology. Since MRI can show evidence of LMD when CSF cytology does not and vice versa, it is conceivable that ^{18}F-FDG PET/CT could demonstrate evidence of LMD in patients with negative MRI and/or cytology. Future studies, possibly involving multiple centers could include patients receiving ^{18}F-FDG PET/CT and MRI

before the initiation of therapy and compare the results of those imaging studies with the disease burden in the CSF shown by cytologic analysis.

For the diagnosis of LMD, a lumbar puncture demonstrating malignant cells and/or the presence of LMD on contrast-enhanced MRI is required.[18] In 50% of patients with LMD, the cytologic results are positive. When LMD is not detected on MRI, CSF cytologic results are positive in only 30% of patients with LMD.[19] In our study, all 21 of the patients had positive CSF cytology as this was part of the inclusion criteria. Future studies could be expanded to include patients with LMD diagnoses by CSF cytology, MRI or clinical findings.

In patients with LMD, white blood cell counts and protein levels in the CSF are often elevated, and glucose levels are often reduced.[20,21] In our study, all the patients in our cohort had CSF findings similar to those of patients with LMD in the literature, with elevated white blood cell counts and protein levels and decreased glucose levels. In the six patients with abnormal ^{18}F-FDG avidity in the spinal canal, white blood cell counts and protein levels were markedLy higher than in the 15 patients without abnormal ^{18}F-FDG avidity in the spinal canal on initial evaluation for LMD, possibly because of a greater disease burden in the patients with abnormal ^{18}F-FDG avidity. The glucose levels were fairly similar between the patients with and without abnormal ^{18}F-FDG avidity. On follow-up CSF evaluation, after the initiation of treatment, the white blood cell counts and protein levels decreased, and the previously reduced glucose levels increased indicating that the treatment reduced LMD.

Table 2. Possible explanations for absence or presence of LMD on PET/CT

Patient	Spinal LMD on PET	Possible explanation
1	No	Low disease burden, thin linear enhancement on MRI, recent intrathecal chemotherapy
2*	Yes	Finished chemotherapy 3 months before PET/CT , diffuse disease on lumbar MRI
3	No	Low disease burden, low-grade lymphoma
4*	Yes	Diffuse large B-cell lymphoma, thick linear enhancement on MRI
5	No	Recent intrathecal chemotherapy, thin linear enhancement on MRI
6	No	Chemotherapy 1 month before PET/CT
7*	Yes	Diffuse large B-cell lymphoma, diffuse enhancement on lumbar MRI, limited therapy
8	No	Long course of chemotherapy
9	No	Low disease burden , recent chemotherapy
10	No	Low disease burden , recent chemotherapy
11	No	Low disease burden, long course of chemotherapy
12*	Yes	Non-Hodgkin lymphoma, thickened nerve root enhancement on lumbar MRI
13	No	Low disease burden, on steroids
14*	Yes	Diffuse disease on lumbar MRI, last treatment 8 months prior
15	No	Steroids, finished chemotherapy 2 weeks before PET/CT
16	No	Low disease burden
17	No	Low disease burden, steroid taper
18	No	Intermediate disease burden, steroids
19	No	Intermediate disease burden, chemotherapy, steroids
20	No	Steroids
21*	Yes	Diffuse enhancement on lumbar MRI

Note. *LMD demonstrated on PET/CT.

Our study demonstrates that the evaluation of ^{18}F-FDG avidity within the spinal canal should be part of radiologists' primary search pattern. In our study, ^{18}F-FDG PET/CT, was performed a mean 3 days before MRI. Therefore, close attention to the spinal canal is recommended as interpreters of ^{18}F-FDG PET/CT can potentially be the first to diagnose spinal LMD. However, while evaluating the contents of the spinal canal on ^{18}F-FDG PET/CT, radiologists should be aware of the normal variations of the spinal canal to avoid mistaking physiologic ^{18}F-FDG avidity of the spinal cord for abnormal avidity associated with LMD. The normal spinal cord ^{18}F-FDG activity generally decreases in a craniocaudal

direction and then peaks again at the level of T11/T12 near the conus medullaris.[22] Normally, there is no significant ^{18}F-FDG avidity of the nerve roots along the cauda equina. In a series of patients with non–central nervous system malignancies, the mean SUVmax values were 2.3, 1.0, and 2.1 at the cervical, thoracic, and lower thoracic (T11/T12) levels of the spinal cord, respectively.[23] The spinal cord also can show an absence of ^{18}F-FDG avidity. Physiologic ^{18}F-FDG avidity also may vary over the course of serial patient examinations and is reported to be more frequently detected in the winter and colder months.[24]

Although spinal cord ^{18}F-FDG activity is more commonly detected in neoplastic myelopathy it can also be seen in inflammatory myelopathies.[25] Abnormal ^{18}F-FDG avidity corresponding to dural or intramedullary metastases also has been described in the literature.[26] However, ^{18}F-FDG PET/CT is limited in its spatial resolution, and it can be difficult to discriminate leptomeningeal pathology from dural or intramedullary pathology using ^{18}F-FDG PET/CT.

The limitations of our study include its relatively small sample size and the limitations inherent to its retrospective nature. Also, many of the patients in our study did not demonstrate neurologic symptoms related to spinal LMD, and previously reported sensitivities of various diagnostic tests for detecting LMD were determined in patients presenting with neurologic manifestations of LMD. Therefore, the sensitivity of ^{18}F-FDG PET/CT for spinal LMD may be greater in patients with ongoing neurologic symptoms.

5. Conclusion

^{18}F-FDG avidity in the spinal canal that exceeds that of the normal contents of the canal can suggest spinal LMD. This abnormal avidity may be detected before the diagnosis of LMD has been established on MRI or CSF cytologic analysis. The spinal canal should be routinely evaluated by ^{18}F-FDG PET/CT for evidence of abnormal ^{18}F-FDG avidity as an early indication of LMD, which, when detected, necessitates further evaluation with MRI and possibly CSF cytologic analysis to avoid a delay of appropriate treatment for LMD, including intrathecal chemotherapy. The resolution of abnormal ^{18}F-FDG avidity in the spinal canal after intrathecal chemotherapy may parallel that of MRI enhancement and seems to be associated with treatment response. The type and grade of the primary cancer, the degree of enhancement on spinal MRI, and recent treatment with steroids or chemotherapy should be considered when one is interpreting ^{18}F-FDG PET/CT to determine the presence of spinal LMD.

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Conflicts of Interest Disclosure

The author declares that there is no conflict of interest statement.

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