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Original Article

The normal variant ^{18}F FDG uptake in the lower thoracic spinal cord segments in cancer patients without CNS malignancy

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Abstract: Focal increased lower thoracic spinal cord ^{18}F FDG uptake is not infrequently observed as a normal physiological finding and may be confused for spinal cord metastases. This study was conducted to evaluate a possible correlation between the lower thoracic (T11-T12) spinal uptake and lower limb movements/ambulatory status of the patients as a surrogate. The primary endpoint was to identify the possible cause(s) of the normal variant focal increased thoracic spinal cord (T11-T12) ^{18}F FDG activity and correlate it with the lower limb movements/ambulatory status of the patients. This was a retrospective analysis of PET-CT scans of 200 patients with solid and hematological malignancies. The focal relatively increased ^{18}F FDG activity in the lower thoracic spinal cord correlated strongly with the ^{18}F FDG intensity of the liver, bowel, C3-C5 cervical cord activity, weight of the patient and injected dose of ^{18}F FDG. With regard to the primary endpoint, no significant correlation was found between the ambulatory status of patients in any of the groups and thoracic spine SUV_{max}. This could be further assessed by performing dual studies in the same patient with and without moderate to excessive leg motion. Identifying this variant focal increased ^{18}F FDG activity can minimize errors of misdiagnosis and unnecessary further investigation.

Keywords: ^{18}F FDG PET-CT, spinal cord, metastases, ambulatory status

Introduction

PET-CT scans are increasingly being used in the initial diagnosis and staging work-up and for follow-up post-therapy for a wide variety of cancer patients. Focal increased lower thoracic spinal cord ^{18}F FDG uptake is not infrequently observed as a normal physiological finding in some patients [1] and may be confused for spinal cord metastases (SCM), which constitute about 8-9% of all the central nervous system (CNS) metastases. Common primary tumors causing SCM include, lung cancer (50%), breast (11%), colorectal (3%), and kidney (10%), as well as melanomas (8%) and lymphomas (4%) amongst others [2, 3].

The physiological ^{18}F FDG uptake has been consistently visualized in the cervical spinal cord peaking at C4 level, and in the lower thoracic spinal cord peaking at the T11-T12 segments [1]. The cause of this uptake is indeterminate though various theories have been postulated. Some of them are: the uptake and inadequate clearance of FDG from the Artery of Adamkiewicz, the largest medullary segmental artery, which originates on the left side of the aorta between the T9-T11 vertebral segments [4] and the increased cross sectional area of the spinal cord in that location consistent with the cervical (C3-T1 vertebral bodies) and lumbar enlargements (T9-T12 vertebral bodies) of the spinal cord [1, 5-10].

We hypothesized a correlation between the lower thoracic (T11-T12) spinal uptake and lower limb movements since the lumbar enlargement gives rise to the nerves supplying

the lower limbs [5]. Since there were no records of measurable metrics of lower extremity activity level of the patients available, we anticipated that the ambulatory status of the patients would serve as a surrogate to the activity level of lower limbs on these groups of patients.

This study was conducted to evaluate the possible influence of lower limb activity on the lower thoracic cord FDG uptake, as defined by the patients ambulatory and performance status, as well as, better define the incidence of this normal variant FDG uptake while assessing possible related factors that may correlate to explain this phenomenon.

Methods and materials

We conducted a retrospective analysis of 345 consecutive patients who underwent ^{18}F FDG PET-CT study during a period of 5 months from July 2011 to November 2011. This study was approved by the Institutional Review Board of the University of Louisville School of Medicine review board (IRB). The patients were divided based on their initial diagnosis into two groups: solid malignancies (SM) that included melanomas, lung cancers, etc. and non-solid hematologic malignancies (HM), which included lymphomas and leukemia.

All sequential patients, in the age group of 18 years to 80 years, who underwent ^{18}F FDG PET-CT as a part of their routine care, were included until there were 100 patients in each group. Any repeat PET-CT studies on the same patient performed during the time of our study were not included. The exclusion criteria included patients' age less than 18 or greater than 80 years; patients with spinal cord/spine metastases; radiological evidence of spine pathology; history of spine surgery; or previous spine irradiation; and patients with extensive liver metastases (**Figure 1**).

The technical aspects of the study were invalid standardized uptake value (SUV) of liver; time from injection of ^{18}F FDG to start of scan less than 55 minutes or greater than 85 minutes (average=60 minutes); large infiltration of radioactive material at the injection site; dose of ^{18}F FDG injected less than 9 mCi or greater than 16 mCi. Further, patients with any inflammatory bowel disease like Crohn's, inflammatory enterocolitis, Gastro-Intestinal Stromal Tumors (GIST) and Gut-Associated Lymphoid Tissue (GALT) tumors with disease present in the region of interest, were also excluded from the study.

Patients with a history of resected colon cancer were not excluded. With the application of the above criteria a total of 145 patients were excluded. The ambulatory status of the study population was then determined based on review of the medical records and when available, the appearance of the patients and questioning during the time of PET-CT scan. The data on the performance status of the patients were based on the Karnofsky Performance Status (KPS) (0-100%) and ECOG (Eastern Co-operative Group) (0-5) scales and was available for most patients [11-13].

The primary endpoint of this study was to identify the possible cause(s) of the so called normal variant focal increased thoracic spinal cord (T11-T12) ^{18}F FDG activity and correlate it with the lower limb activity/ambulatory status of the patients or any other clinically detectable factors. Statistical analyses were then performed to evaluate factors thought to be predictive of increased spinal cord FDG uptake. R2, Pearson's coefficient was used to calculate the correlation between the different SUV values.

Whole-body ^{18}F FDG PET-CT image acquisition technique

PET-CT studies were performed using a dedicated combined Biograph LSO PET/CT scanner (Siemens Molecular Imaging, Hoffman Estates, IL, USA) with the patient in the supine position. Images were acquired after a 6-hour fast, and within 55-85 minutes after intravenous injection of ^{18}F FDG (9.2-16.0 mCi or 340.4-592.0 MBq) with an intended maximum dose of 15 mCi or 555 MBq. All patients were required to have had a blood sugar level of less than or equal to 200 mg/dl before ^{18}F FDG injection. A water based oral contrast agent (500-800 ml) was used for bowel marking within the ^{18}F FDG uptake phase.

First, CT scan data was acquired in the supine position and in a caudo-cranial direction, using six 4 mm detectors, a pitch of 1.4 and 5 mm thick slices (collimation was 6x3.0 mm). CT exposure factors were 110 kVp and reference mAs of 95±10% (CAREDose 4D on). A whole-

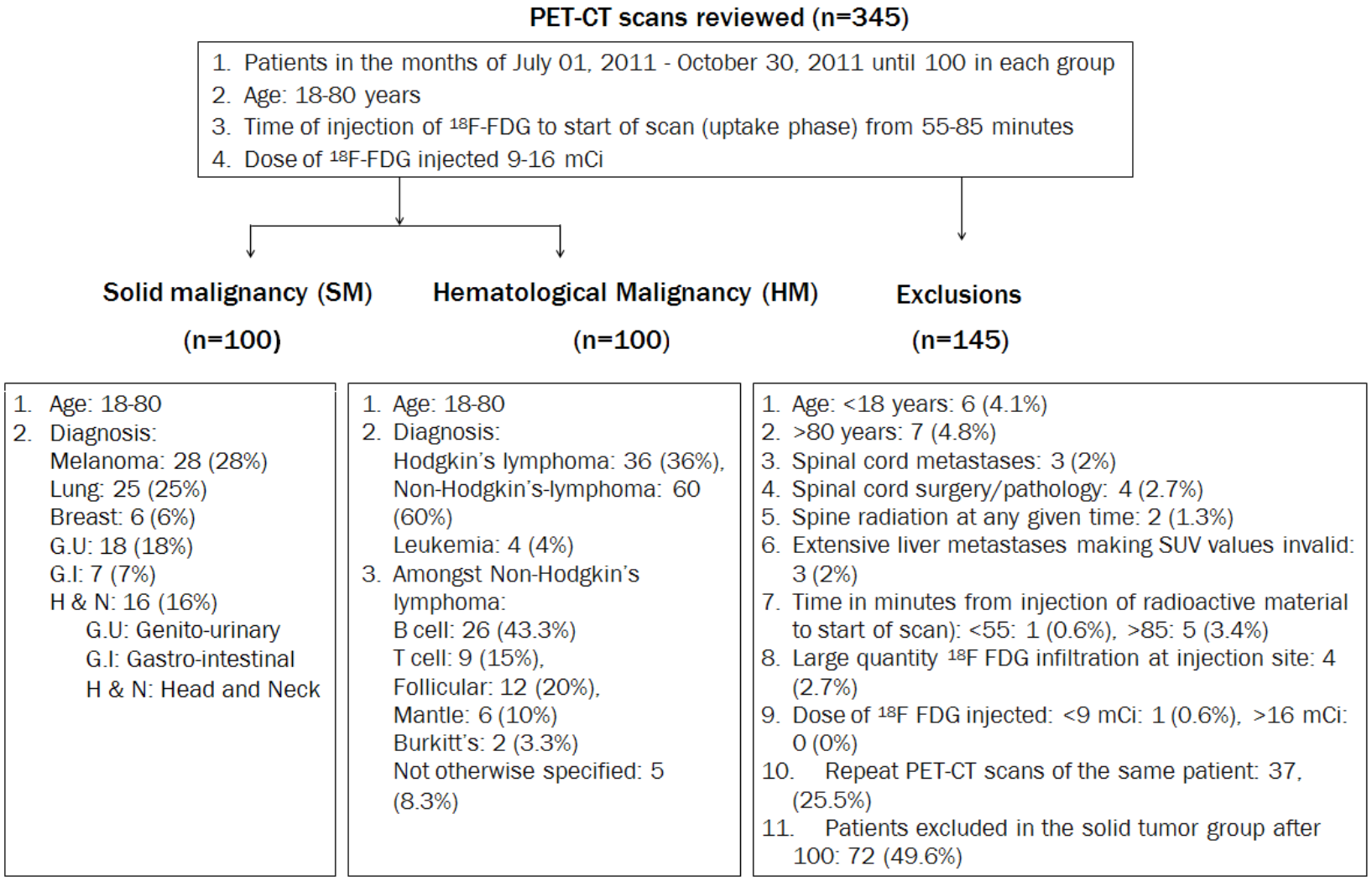

Figure 1. Flow-Chart of the study.

Table 1. Patient Characteristics. The summary of all the variables analyzed including the race, sex, ambulatory status, treatment status, thoracic spinal cord uptake, and presence of contrast in bowel

Variables		SM* (%)	HM* (%)	SM+HM (N, %)
Sex	Male	52	66	118 (59)
	Female	48	34	82 (41)
Race	Caucasian	89	89	178 (89)
	African-American	9	8	17 (8.5)
	Other	2	3	5 (2.5)
Ambulatory Status	Ambulatory	77	83	160 (80)
	Bed-ridden	23	17	40 (20)
Primary Malignancy	Melanoma	28	HL 36	
	Lung	25	NHL 60	
	Breast	6	Leukemia 4	
	Genito-urinary	18		
	Gastro-intestinal	7		
	Head & Neck cancer	16		
Chemotherapy	Receiving	37	78	115 (57)
	None	63	22	85 (42.5)
Chemotherapy Phase	Initial/baseline scan	40	18	58 (29)
	Receiving	14	18	32 (16)
	End of treatment	46	64	110 (55)
Radiation Therapy	Receiving	28	30	58 (29)
	None	72	70	142 (71)
Diabetes Mellitus	Present	10	8	18 (9)
	Absent	90	92	182 (91)
Thoracic Spine Uptake	Apparent	20	25	45 (22.5)
	None	77	73	150 (75)
	Partially seen	3	2	5 (2.5)
Contrast In Bowel	Present	28	25	53 (26.5)
	Absent	45	55	100 (50)
	Partially present	27	20	47 (23.5)

*SM: solid malignancy; HM: hematologic malignancy.

body (mid skull to mid-thigh) PET scan was acquired in 3-D mode with 3.5, 4.5, or 5.5 minutes per bed position, depending on the body weight, over the identical body area that was covered with CT. PET images were reconstructed using CT data for attenuation correction and using ordered-subsets expectation maximization, with 4 iterations and 8 subsets.

SUV measurements

An experienced nuclear medicine physician (ACC) reviewed all the ^{18}F FDG PET images and determined the maximum and average standardized uptake value (SUV_{max}; SUV_{avg}) for all patients in the liver and the bowel in the right lower quadrant (ascending colon), C3-C5, and T11-T12 regions.

Correlation of the PET with the CT scan determined that the areas of intense focal uptake in the bowel were not related to any inflammatory or neoplastic process. Region of interest of the spine primarily lay in the region of thoracic vertebral segments T-11 and T-12 and cervical vertebral segments C3-C5. The CT vertebral body level was used as the guide for marking the ROI in the spinal cord. The ROIs for spinal cord measurements were manually drawn around the focal ^{18}F FDG uptake area by referring to CT images in corresponding sections. The SUVs of the predetermined areas and spinal cord regions were calculated as SUV=activity concentration (kBq [μCi]/mL)/(injected dose [MBq (mCi)]/body weight [kg]). To minimize the partial-volume effects we used the SUV_{max} [14]. The SUV_{max} is defined as the SUV of a 1-pixel region of interest corresponding to the maximum value in the ROI; thus, SUV_{max} represents the value least affected by the partial-volume effect. The SUV average is defined as the SUV of a 1-pixel region of interest corresponding to the average value in the ROI.

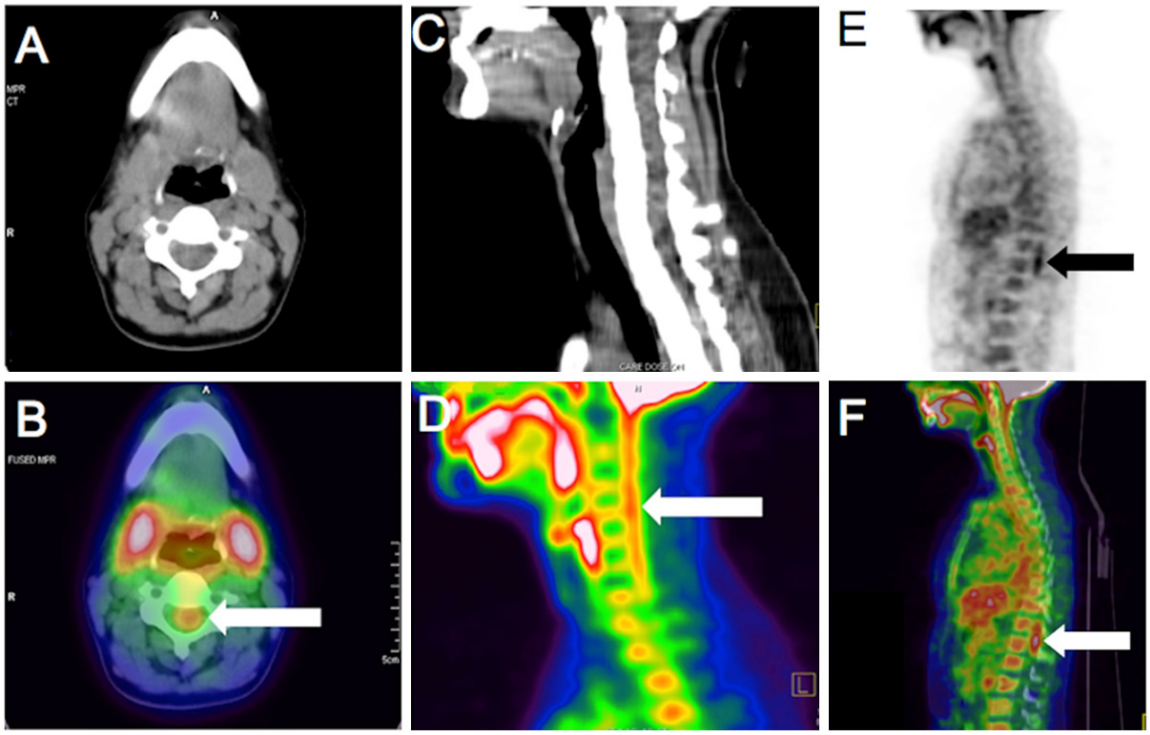

Figure 2. A 33 year-old physically active female with ovarian cancer treated with surgery and chemotherapy underwent a repeat ^{18}F FDG PET-CT scan after 83 minutes of ^{18}F FDG injection as part of her follow up work-up. The Liver SUV_{max} was 2.7 and Liver SUV_{avg} 2.1. Her C-spine $SUV_{max/avg}$ were 3.0/2.6, T11-T12 spine $SUV_{max/avg}$ were 3.5/2.9 PET-CT scan did not reveal any signs of malignancy. The enhanced ^{18}F FDG activity along the cervical spinal cord is seen as depicted by arrow in fused transverse PET-CT image (B), and in sagittal view (D). Corresponding CT images are depicted in Figure 2A and 2C. The focal increased ^{18}F FDG activity in T11-T12 segment thoracic spinal cord is depicted by the arrow in a sagittal PET image (E), and in a fused sagittal PET-CT image (F), which was classified as a normal variant in this asymptomatic patient.

Results

Patient baseline characteristics closely matched between the two groups (**Table 1**). The median age of the patients was 54 years (56 years in the SM and 47 years in the HM groups). Of the 200 patients studied, 160 patients were 'ambulatory', defined as patients able to do all activities of daily living. There were 40 patients confined to a bed or wheelchair, 'bedridden patients'. Of the 200 PET-CT scans analyzed, 45 patients had focal intense ^{18}F FDG thoracic spine activity. In the remaining 155 patients ^{18}F FDG thoracic spine activity was faint. **Figure 2** shows spinal cord uptake in a patient with ovarian cancer.

Based on the hypothesis and primary endpoint, no statistically significant correlation was found between the ambulatory status of patients in any of the groups and T11-T12 SUV_{max}. Statistically significant correlation was found between the T11-T12 SUV_{max} and bowel SUV_{max} in combined (p=0.0121), SM (p=0.0326) and HM groups (p=0.0478). Bowel SUV_{avg} also had a positive correlation with T11-T12 SUV_{avg} in both SM (p=0.0339) and HM group (p=0.0174). We also found a significant relationship between the contrast present in the bowel and T11-T12 SUV_{avg} in the combined patient group (p=0.0004) and SM group (p=0.0309) but it failed to achieve significance in the HM group (p=0.53). Spearman coefficient correlation analyses between the liver, C3-C5, T11-T12 and bowel SUV_{max} are shown in **Table 2**.

The relationship between T11-T12 SUV_{max} and dose of the radioactive tracer was significant in the combined patient population (p<0.0001) and the SM group (p<0.0001), but not in the HM group (p<0.0631). The dose of the radioactive tracer is dependent on the weight of the patient, which follows the same trend but is also significant in the HM patients (p<0.001).

Table 2. Spearman correlation coefficients for SUV_{max} of liver, bowel, thoracic and cervical spinal cord. This shows significant correlation between the T11-T12 SUV_{max} and the bowel SUV_{max}

		LIVER SUV_{max}			T11-T12 SUV_{max}			C3-C5 SUV_{max}			BOWEL SUV_{max}		
		T	L	T+L	T	L	T+L	T	L	T+L	T	L	T+L
LIVER SUV_{max}	Corr	1.000	1.000	1.000	0.590	0.523	0.557	0.433	0.423	0.429	0.295	0.232	0.260
	P-val				<0.001	<0.001	<0.001	<.001	<0.001	<0.001	0.003	0.020	<0.001
T11-T12 SPINE SUV_{max}	Corr	0.590	0.523	0.557	1.000	1.000	1.000	0.578	0.565	0.575	0.271	0.192	0.227
	P-val	<0.001	<0.001	<0.001				<0.001	<0.001	<0.001	0.006	0.056	0.001
C3-C5 SPINE SUV_{max}	Corr	0.433	0.423	0.429	0.578	0.565	0.575	1.000	1.000	1.000	0.233	0.255	0.220
	P-val	<.001	<0.001	<0.001	<0.001	<0.001	<0.001				0.020	0.010	0.002
BOWEL SUV_{max}	Corr	0.295	0.232	0.260	0.271	0.192	0.227	0.233	0.255	0.220	1.000	1.000	1.000
	P-val	0.003	0.020	<0.001	0.006	0.056	0.001	0.020	0.010	0.002			
N		100		200	100		200	100		200	100		200

Table 3. Summary Statistics for Continuous Variables, shown as Mean values and standard deviation of all variables

	SM (N=100)		HM (N=100)		SM+HM (N=200)	
VARIABLES	Mean	SD	Mean	SD	Mean	SD
AGE (yrs.)	56.21	10.80	46.58	15.54	51.40	14.19
WEIGHT (lbs.)	176.95	53.38	198.07	53.96	188.01	54.48
TIME (mins)	65.84	7.27	66.85	8.00	66.35	7.64
DOSE (mCi)	11.87	1.92	12.36	1.75	12.11	1.85
BOWEL SIZE (cms)	13.83	3.28	12.36	3.45	13.10	3.44
LIVER SUV_{max}	3.06	0.80	3.11	0.68	3.09	0.74
LIVER SUV_{avg}	2.47	0.58	2.50	0.50	2.48	0.54
T11-T12 SPINE SUV_{max}	2.47	0.65	2.58	0.62	2.53	0.63
T11-T12SPINE SUV_{avg}	1.93	0.50	2.01	0.51	1.97	0.50
C3-C5 SPINE SUV_{max}	2.17	0.62	2.24	0.52	2.20	0.57
C3-C5 SPINE SUV_{avg}	1.79	0.53	1.85	0.46	1.82	0.49
BOWEL SUV_{max}	4.56	3.10	3.60	1.42	4.08	2.46
BOWEL SUV_{avg}	2.77	2.00	2.14	1.00	2.45	1.61

The liver SUV_{max} strongly correlated with the T11-T12 activity in all patient populations. Race of the patients was also in significant correlation with the T11-T12 SUV_{avg} (p=0.0235), with Caucasians having a higher incidence.

The mean liver SUV_{max} and liver SUV_{avg} were 3.0 and 2.4 in this study (3.0/2.5 in SM and 3.1/2.5 in HM). The mean SUV_{max} and SUV_{avg} of T11-T12 segments were 2.5/1.9 in SM and 2.6/2.0 in HM. The SUV_{max} and SUV_{avg} of the bowel were 4.6/2.8 in SM and 3.6/2.1 in HM (**Table 3**). Univariate linear regression model statistics showed statistically significant correlation between the T11-T12 SUV_{max} and weight of the patient, liver SUV_{max} and C3-C5 SUV_{max} of both SM and HM groups (p<0.0001) (**Table 4**).

Discussion

Though the usefulness of ^{18}F FDG in the management and treatment planning of spinal cord metastases has been reported, a normal variant physiologic ^{18}F FDG uptake in the spinal cord segments, when prominent and not recognized as a normal variant, could be a common cause of misdiagnosis [15, 16]. The physiology of glucose metabolism in the spinal cord provides insight into various pathologies including inflammatory and neoplastic conditions [17, 18]. Pre-clinical studies in rat models demonstrated differential metabolic uptake at the spinal cord levels secondary to acute and chronic pain [19]. Rapid nerve stimulation from inflammatory conditions such as chronic knee pain from monoarthritis also demonstrated foci of hypermetabolism [20].

Physiologic ^{18}F FDG uptake is most visible in the cervical (C3-C5) and lower thoracic (T11-T12) segments as determined by study of glucose metabolism in the spinal cord using ^{18}F FDG in children and oxygen metabolism through functional Magnetic Resonance Imaging (fMRI)

Table 4. Univariable Linear Regression Model (Solid Tumors/Hematological malignancy: T11-T12 SUV$_{max}$). The thoracic spinal cord SUV$_{max}$ is significantly correlated with the weight of the patient, dose of radioactive tracer injected, liver and cervical cord SUV$_{max}$

		SM			HM			SM+HM		
Predictor		Estimate	*p*-value		Estimate	*p*-value		Estimate	*p*-value	
Weight		0.006	<0.001	0.282	0.005	<0.001	0.178	0.005	<0.001	0.233
Dose		0.167	<0.001	0.244	0.066	0.063	0.035	0.123	<0.001	0.128
Liver SUV$_{max}$		0.486	<0.001	0.360	0.481	<0.001	0.279	0.486	<0.001	0.322
C3-C5 Spine SUV$_{max}$		0.545	<0.001	0.269	0.681	<0.001	0.324	0.604	<0.001	0.294
Bowel SUV$_{max}$		0.045	0.033	0.046	0.086	0.048	0.039	0.046	0.012	0.031
Ambulatory Status				0.003			0.002			0.003
	Ambulatory	0.089	0.566		0.066	0.692		0.088	0.433	
	Bed-ridden	0			0			0		

in the cervical spinal cord [1, 21-25]. The cause of this increased uptake is postulated to be the increased cross sectional area from the cervical enlargement, between third cervical and first thoracic vertebrae and lumbar enlargement between the ninth and twelfth thoracic vertebrae along with the origin of upper and lower extremity motor and sensory neurons from these segments [5-7, 21, 26]. Various post-mortem, CT and MRI studies have established the increased cross sectional area in the cervical and lumbar enlargements [9, 10, 15, 17, 27, 28]. Another theory postulated is the increased amount of metabolic activity of the gray matter present in the spinal cord [19, 29].

The hypothesis was that the excess lower extremity motor function of the patients may play an important role in focal increased ^{18}F FDG activity, in T11-12 spinal cord areas. Since the degree and extend of lower extremity activity on patients were not available, we used presumed surrogates and grouped patients as 'ambulatory' and 'bedridden' based on their recorded Karnofsky Performance Status (KPS) and Eastern Co-operative Group (ECOG) scales. However, such grouping failed to show statistically significant difference between either group's T11-12 spine ^{18}F FDG activities. This may in part be due to the lack of a clear difference between levels of lower extremity motor activity between the two groups since the studied patient population is composed of cancer patients, and understandably with levels of relatively limited physical activity.

We did find a significant correlation between ^{18}F FDG bowel and the T11-12 activity. The injected dose of ^{18}F FDG and the weight of the patient also show a statistically significant correlation ($p<0.0001$). We did not directly compare upper extremity movements to C-spine uptake due to lack of a standard comparison scale.

In a study by Amin et al, no significant correlations were found between the ^{18}F FDG cord activity expressed as SUV$_{max}$ in all areas of the spinal cord and age, sex, BMI and mobility status [15]. These are consistent with the findings of our analyses. Nakamoto et al evaluating the normal ^{18}F-FDG distribution pattern in the head and neck also showed no significant correlation of FDG uptake in the cervical spinal cord with the age of patients and blood glucose level [30].

In our study, there was statistically significant correlation with the oral contrast agent present in the bowel and ^{18}F FDG thoracic spine SUV$_{avg}$ activity.

The limitations of this study include its retrospective nature and the fact that PET-CT studies included were only for the evaluation of cancer patients, who have relatively limited levels of physical activities. Our ability to identify, correctly those patients with excess lower extremity activities were lacking or imprecise due to lack of adequate information on patients' pre-procedural physical activities and/or their level of physical capacities (lack of Performance Based Physical Capacities Evaluation).

Thus, in the lack of evaluation of physical capability, patients were sub grouped into bed-ridden/non-ambulatory versus 'ambulatory' without being able to differentiate them into highly active, exercising, or mobile but sedentary. Considering that all the patients were suffering from cancer, it is likely that their "ambulatory" status was limited or modest, to say in the least.

Also, this grouping obviously has limited ability to predict the actual lower extremity movement in individual patients at the time of the PET scan; that would require direct observation in a prospective fashion to achieve a greater degree of accuracy. Also, dual studies in the same patient with and without leg motion may provide valuable insights and help further clarify this issue. The data on the performance status of the patients based on KPS and ECOG scales was not available for all patients, but when available was used as a suitable surrogate for ambulatory status. Data was also not available to calculate the BMR (Basal Metabolic Rate) of the patients as height of all patients was not recorded. Hence, our analysis was based primarily on the weight of the patients.

Despite these limitations, we were able to evaluate various patient factors (age, weight, sex, race and diagnosis of diabetes) contributing to the normal variant ^{18}F FDG metabolic activity of the T11-12 spinal cord area. We also found that diagnosis of the patient (solid vs. hematologic malignancies) and the use of chemotherapy does not influence this focal spinal cord FDG activity.

Conclusion

The focal ^{18}F FDG activity in the lower thoracic spinal cord represents a normal physiologic entity, which should be noted in the routine interpretation of PET-CT studies. It must not be confused to represent spinal cord abnormality or metastases. This finding is correlated strongly with the liver, bowel, cervical cord ^{18}F FDG uptake, weight of the patient and injected dose of ^{18}F FDG and does not depend on a diagnosis of solid vs. non-solid malignancies. Although no statistical significance in this study could be demonstrated, there might still be a correlation between limb movements and the physiological FDG uptake in the lower T-spine, which warrants further evaluation by dual studies performed in the same patient with and without leg motion. Identifying this variant can minimize errors of misdiagnosis and unnecessary further investigation.

Disclosure of conflict of interest

No conflicts of interest.

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