The Usefulness of PET/CT In Detecting and Managing Cancers With Unknown Primary Site Depends on Histological Subtype

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Abstract

Introduction: We assessed the role of PET/CT in identifying and managing cancer of unknown primary site (CUP).

Methods: We reviewed 64 patients' PET/CT scans with CUP performed during 2012–2019.

Results: The median age was 65 years. Of 138-FDG-avid lesions, the mean SUVmax was10.6±6.0. Primary tumors (PT) were detected in 28(44%) patients. Detection was positive in only one(10%) patient with squamous cell carcinoma (SCC) histology, compared to 4/14(29%) with poorly differentiated carcinoma, 4/9(44%) with adenocarcinoma, 18/30(60%) of those for whom the origin could be presumed ($p= 0.034$ for SCC compared to other histologies). The mean age, mean SUVmax, and the distribution of organ involvement were similar between patients with and without discovered PTs, and also between patients with SCC and with the other histologies combined. However, those with SCC were less likely than the others to present with multi-lesion involvement, $p<0.001$. PET/CT interpretations apparently affected treatment of 8/28(29%) patients with PT detected and in none of the 35 whose PT was not discovered, $p<0.001$.

Conclusion: PET/CT detected PT in almost half of CUP. However, it did not appear beneficial in those with SCC histology. PET/CT showed limited overall value in guiding clinical management but benefited a subgroup with discovered PT.

Introduction

Cancer of unknown primary site (CUP) is a diverse group of cancers in which the anatomical site of origin remains occult despite detailed investigations. CUP accounts for 2–5% of cancers worldwide [1]. The American Cancer Society estimated that about 31,480 cases of CUP will be diagnosed in the United States in 2019, representing 2% of all cancer diagnoses [2]. The median age at presentation is 60–65 years and diagnosis is more common in men than women by a ratio of 3:2 [3]. CUP has a wide variety of clinical presentations and many histological types. Sensitivity to treatment tends to be low and median survival time is six to ten months [4]. Due to the difficulty of diagnosis and lengthy investigations, time from initial presentation to treatment is longer and pretreatment costs are higher in patients with CUP than in patients with a known primary site [5].

CT and conventional MRI enable the detection of only 22–36% of the primary sites of CUP [1, 6]. These low detection rates have been attributed to functional limitations of these imaging modalities. Both CT and MRI enable the detection of anatomical abnormalities and abnormal contrast enhancement; however, small and non-enhancing lesions in normal sized structures may be missed. In contrast, 18-fluorodeoxyglucose PET/CT (FDG-PET/CT) does not have these drawbacks as it leverages the increased glucose metabolism in many malignant cancers (Warburg effect) to detect abnormal uptake of the FDG[7]. While the use of FDG-PET/CT in the detection of primary tumors (PTs) in CUP has been

suggested for at least two decades [3, 8, 9], its roles in the diagnostic workup of patients with disseminated CUP remains inconclusive[10].

The primary purpose of this study was to assess the role of FDG-PET/CT in the identification of PTs, and therefore in the management of CUP in patients with negative conventional imaging. The secondary objectives were to evaluate the ability of PET/CT in discovering PTs according to their histological subtypes, and thus to evaluate its impact on clinical management.

Materials And Methods

Study design

We searched the Sheba Medical Center computerized database for FDG-PET/CT studies that included the term "Unknown Primary" in their reports (in the graph of “indication” for the referral) from April 2012 through February 2019. Medical history and tumor histopathologic analysis were included in clinical data. Imaging data were provided from the picture archive and communication system (PACS, Carestream Health 11.0, Rochester, NY) and clinical data from the computerized medical records at Sheba Medical Center.

The study inclusion criterion was an unknown PT according to the clinical referral letter at the performance of the PET/CT scan, with or without known tumor histology. This included patients who, subsequent to the PET/CT scan, received results of a histology in which the origin could be presumed (for example, melanoma and pancreatic tumors). Patients without any available histological data were not included in the study. For this research, tumors were divided into five broad categories based on their histology: poorly differentiated carcinoma, adenocarcinoma, squamous cell carcinoma (SCC), neuroendocrine carcinoma and tumors where the origin can be presumed. Metastatic spread was characterized by both the organ/ site of the tumor and by the number of FDG-avid lesions. Additionally, metastatic spread was classified as oligo-lesion (up to two lesions) or multi-lesion spread (more than two lesions).

Image assessment

An experienced physician with two specializations (nuclear medicine and radiology) reviewed all the cases of the study. The intensity of FDG uptake in the lesions was calculated by standardized uptake values max (SUVmax) by manually generating a region of interest over the pathological lesion.

The protocol of the PET CT scans was similar to those described in previously reported studies [11, 12].

We assessed the impact of PT detection by PET/CT on clinical management by examining treatment decisions that were made by a referring physician or by a tumor board and, that were influenced by the identification or non- identification of PT. The performance of additional diagnostic procedures after a PET/CT study was not considered a change in management.

Statistical analysis

Data are demonstrated as medians with ranges or as means with standard deviations (SD(for continuous variables, and as percentages for categorical parameters. Correlations between subgroups were analyzed using the T-test for continuous variables, and the Chi-Square Test and Fisher's Exact Test for categorial variables. The SPSS version 25.0 (SPSS, IBM, USA) was used. A P value of less than 0.05 was considered statistically significant

Ethics

The institutional review board of Sheba Medical Center approved our single-institution study, and informed consent was waived due to the retrospective nature of the study. All methods were performed in accordance with the relevant guidelines and regulations of Sheba Medical Center.

Results

Of 33,679 FDG-PET/CT scans performed during the study period, 64 FDG-PET/CT included the term “Unknown Primary”. Demographic and clinical characteristics of the population are presented in Table 1. The study cohort comprised 36 males (56%); the median age was 65 years (range: 18–87 years). The patients had a total number of 138 FDG–avid lesion sites, with a mean SUVmax of 10.58 (range: 2.2–27.8). The most common sites of FDG uptake were the lymph nodes: 39/138 (28.3%), bones: 24 (17.4%), liver: 17 (12.3%), lungs: 17 (12.3%), and brain: 6 (4.3%). The remaining 35 sites (25.4%) included regions of the head and neck, the uro-gynecological system, esophagus, peritoneum, skin, colon, thyroid and muscles. The median number of sites/organs involved was 2 (range: 1–5), as follows: 20 patients (31.3%) had a finding in one site, 26 (40.6%) had findings in 2 sites, 11 (17.2%) in 3 sites, 5 (7.8%) in 4 sites, and 2 (3.1%) had findings in more than 5 sites.

Table 1
Demographic, clinical and radiographic characteristics of the study cohort

	Patients (n = 64)
Sex	36 (56.3%)
Male	28 (43.7%)
Female	
Median age	65 (range 18–87)
Total FDG-avid lesions	138
Mean SUVmax	10.58 (SD 6)
FDG uptake sites	39 (28.3%)
Lymph nodes	24 (17.4%)
Bones	17 (12.3%)
Liver	17 (12.3%)
Lungs	6 (4.3%)
Brain	7 (10%)
Head/Neck	35 (25.4%)
Other [a]	
Number of uptake organ/sites	20 (31.3%)
1	26 (40.6%)
2	11 (17.2%)
3	5 (7.8%)
4	2 (3.1%)
5<	

[a] 'Other' includes the uro-gynecological system, esophagus, peritoneum, skin, colon, thyroid and muscles

[b] Number of patients with management data is 63, one patient with squamous cell carcinoma and an undetected primary site was lost to follow-up

	Patients (n = 64)
Tumor histology	30 (46.9%)
Origin can be presumed	14 (21.9%)
Poorly differentiated carcinoma	10 (15.6%)
Squamous cell carcinoma	9 (14%)
Adenocarcinoma	1 (1.6%)
Neuroendocrine carcinoma	
Primary Lesion detected by FDG-PET/CT	28 (43.7%)
Detected	36 (56.3%)
Undetected	
Patient management before FDG-PET/CT scan [b]	31 (48%)
Specific chemotherapy	4 (6%)
Empiric chemotherapy	6 (9%)
Palliative radiation	5 (8%)
Surgery	6 (9%)
Chemo-radiation	11 (17%)
No medical treatment	
[a] 'Other' includes the uro-gynecological system, esophagus, peritoneum, skin, colon, thyroid and muscles	
[b] Number of patients with management data is 63, one patient with squamous cell carcinoma and an undetected primary site was lost to follow-up	

Additionally, most patients had a multi-lesion metastatic spread disease, 47/64 (73%).

Tumor histologies included: 30 (46.9%) tumors where the origin could be presumed, 14 (21.9%) poorly differentiated carcinomas, 10 (15.6 %) SCC, 9 (14 %) adenocarcinomas and 1 (1.6%) neuroendocrine carcinoma.

Primary tumors (PT) discovered by PET/CT

PET/CT discovered the PT in 28 patients (43.7%); while in the remaining 36 (56.3%), the PTs were not located. Table 2 presents the characteristics of the two groups. There were no statistically significant differences in mean patient age) 61.2 vs. 61.9, p = 0.72), mean SUVmax of the lesions (10.3 vs 10.76, p =

0.08) and the mean number of organs/sites involved by FDG –avid lesions (2.4 vs. 1.8, p = 0.47) between patients with and without an identified PT (p = 0.72, p = 0.08 and p = 0.47, respectively).

Table 2
Characteristics of patients with cancer of unknown primary site according to FDG-PET/CT detection of the primary site

	Tumor detection by FDG-PET/CT		P value
	Detected (n = 28)	Undetected (n = 36)	
Mean age	61.2 (SD +-13.6)	61.9 (SD +-14.7)	0.72
Mean SUVmax	10.3 (SD +-5.0)	10.76 (SD +-6.8)	0.08
Mean number of sites involved	2.4 (SD +-1.0)	1.8 (SD +-1.0)	0.47
Histology of the primary tumors:	18/30 (60%)		
-origin could be presumed,	4/9 (44%)		
- adenocarcinomas,	4/14 (29%)		
-poorly differentiated carcinomas,	1/10 (10%)		
-squamous cell carcinoma	1/1 (100%)		
-neuroendocrine carcinoma			
FDG-PET/CT effects on management [b]	8 (29%)	0	< 0.001
Changed	20 (71%)	35 (100%)	
Unchanged			

[a] Number of patients with management data is 63, one patient with squamous cell carcinoma and an undetected primary site was lost to follow-up

The histologies of the PTs identified by PET/CT included 18/30 (60%) tumors where the origin could be presumed, 4/9 (44%) adenocarcinomas, 4/14 (29%) poorly differentiated carcinomas, 1/10 (10%) SCC and the sole (100%) neuroendocrine carcinoma .

FDG-PET/CT detection of PTs was significantly worse for the 10 patients with SCC than for the other 54 patients with other combined pathologies: 1/10 (10%) vs. 27/54 (50%) (p = 0.03). Therefore, we decided to examine in more depth the subgroup of patients with SCC pathology and to compare their characteristics to the combined subgroup of patients with pathologies other than SCC (Table 3). FDG-avid lesion detection at various anatomic organ /locations was similar between patients with SCC and those with the other histologies combined, and also between patients with and without discovered PTs.

Table 3
Characteristics of patients with cancer of unknown primary site according to tumor histology: squamous cell carcinoma versus other tumor histologies

	Tumor histology		P value
	Squamous cell carcinoma (n = 10)	Other (n = 54)	
Mean age	61.7 (SD +-13.5)	61.6 (SD +-14.4)	0.85
Mean SUVmax	11.3 (SD +-7.4)	10.4 (SD +-5.8)	0.38
Mean number of sites involved	1.5 (SD +-0.5)	2.2 (SD +-1.0)	0.09
Primary Lesion detected by FDG-PET/CT	1 (10%)	27 (50%)	0.03
Detected	9 (90%)	27 (50%)	
Undetected			
Number of lesions	8 (80%)	9 (17%)	< 0.001
2 or less	2 (20%)	45 (83%)	
Above 2			
FDG uptake sites	7		
Lymph nodes	0		
Bones	0		
Liver	0		
Lungs	0		
Brain	2		
Head and neck	2		
Other [a]			

[a] 'Other' includes the uro-gynecological system, esophagus, peritoneum, skin, colon, thyroid and muscles

[b] Number of patients with management data is 63, one patient with squamous cell carcinoma and an undetected primary site was lost to follow-up

	Tumor histology		P value
FDG-PET/CT effects on management [b]	1 (11.1%)	7 (13%)	1.0
Changed	8 (88.9%)	47 (87%)	
Unchanged			

[a] 'Other' includes the uro-gynecological system, esophagus, peritoneum, skin, colon, thyroid and muscles

[b] Number of patients with management data is 63, one patient with squamous cell carcinoma and an undetected primary site was lost to follow-up

Moreover, statistically significant differences were not observed between patients with SCC and those with other combined pathologies, in mean age (61.7 vs 61.6, p = 0.85), mean SUVmax of FDG -avid lesions (11.3 vs 10.4, p = 0.38) and the mean number of involved organs/sites (1.5 vs 2.2, p = 0.09). However, the proportion of patients with SCC who had multi-lesion spread was substantially lower than for the rest of the cohort: 2/10 (25%) vs. 45/54 (83%) (p < 0.001). Figure 1,2,3

FDG-PET/CT and treatment management

Clinical data about treatment were available for 63 patients; of them, 31 (48%) received specific chemotherapy, 4 (6%) empiric chemotherapy and 6 (9%) palliative radiation; 5 (8%) underwent surgery and 6 (9%) chemo-radiation. Eleven (17%) did not receive medical treatment. One patient with SCC histology and whose PT was not detected by PET/CT was lost to follow up.

The PET/CT findings did not appear to affect the clinical management of 55 (87%) of the 63 patients with available data. Treatment was apparently affected in 8/28 (29%) patients with a PT detected by PET/CT: seven received chemotherapy that was specific to the diagnosis, and one patient received palliative radiotherapy.

Treatment was obviously not affected by the PET/CT scan in any of the 35 for whom the PT was not detected (p < 0.001, Table 2). Therefore, considering the entire cohort, PET/CT findings seem to have changed clinical management in 8/63 (13%) patients. Despite the much lower detection rates among patients with SCC, the effect of PET/CT findings on clinical management did not appear to differ between these patients and those with the other combined pathologies: 1/9 (11%) vs. 7/54 (13%) (p = 1.0, Table 3).

Discussion

More than one decade ago, a multidisciplinary expert panel of oncologists, radiologists, and nuclear physicians recommended the use of FDG PET in the diagnosis of patients with CUP [13]. Despite the common use of this imaging technique in this context, data are sparse regarding the characteristics of

CUP for which PET/CT is most and least effective. Interestingly, in the current study of patients with CUP and negative conventional imaging, PET/CT detected the PT in only 1 (10%) of the patients with SCC compared to 50% of those with other combined pathologies. Nonetheless, the apparent effects of the PET/CT findings on clinical management were similar between these two groups: 11% vs. 13%. Thus, surprisingly, the greater detection of PTs in pathologies other than SCC compared to SCC did not have clinical implications.

Our overall rate of tumor detection was 44%, which is within the range of 10% – 75% [3, 9, 14–16] reported in other studies. While CUP is a relatively common clinical entity, presentations and histologies are diverse. Notably, there is no consensus as to whether CUP is simply a group of metastatic tumors with an undetected source or a distinct entity with its own characteristics and behavior [17–19]. Most researchers currently believe that CUP is a heterogenous collection of metastatic tumors [20]. Accordingly, treatment strategies have shifted from empiric cytotoxic therapies to identifying the PT and targeting therapy at the tumor type [21]. Importantly, detecting PT sites and additional metastases improves disease staging; this helps define prognosis and can better guide surgical intervention with curative intent[15]. Indeed, several studies have shown longer survival times in CUP patients in whom a PT was detected [22, 23].

Sixteen percent of the patients in the current cohort were with SCC. This compares to 5% of patients with CUP reported in the literature[24], but differs substantially from the extremely high rate of 57% that has been reported [9]. Differences between studies may be due at least in part to the lack of a standardized definition of CUP, including the clinical workup and imaging tests required for the diagnosis [3, 25], and the resultant heterogeneity in selection criteria between studies. Of our 10 patients with SCC, 7 (70%) had FDG-PET/CT uptake in the head and neck. Similarly, head and neck cancers have been reported to represent 75% of CUP cases with SCC histology[6]. In one of 7 (14.3%) of our SCC patients with head and neck findings, the PT was detected and in none of three SCC patients without head and neck findings. This compares with the detection by PET/CT of the PT in 25% of patients with head /neck metastases from a PT that was not detected by other modalities [26]. Notably, despite our relatively high proportion of patients with SCC, the age and sex distributions are comparable to those reported in other studies of PET/CT in CUP [3]. Further, patients' age, SUVmax of the lesions, and the site distribution of FDG-avid lesions were similar between patients whose PT was and was not detected by FDG-PET/CT; and also between patients with SCC and those with all other combined pathologies. Thus, the distributions of age, involved organ/site, and FDG avidity do not explain the low detection of PTs among our patients with SCC compared to those with all other pathologies.

Interestingly, our patients with SCC tumors were significantly more likely to present with oligo-lesion metastatic spread disease involvement than were patients with the all other combined pathologies. We speculate that this finding is due to lower metastatic rates in SCC or to poor FDG-PET/CT uptake in small SCC metastases, or to a combination of the two. SCC has been shown to have a lower ratio of metastases per PT than adenocarcinoma [27], while FDG-PET/CT uptake in SCC has been shown to be directly correlated to tumor size and lower in metastatic tumors than in PTs [28].

FDG-PET/CT detections of primary sites were attributed to a change in treatment in 29% of our patients with a newly detected PT. However, considering the entire cohort, including patients for whom the PT was not detected, FDG-PET/CT apparently affected clinical management in only 13%; this is on the lower end of the range of 10–58% (mean 35%) that was reported in a review of 10 studies [15]. That review found that patients with a planned curative treatment for cancers such as breast, ovary and prostate most benefited from the PET scan; thus, differences between studies in the types of cancers may explain the large variability in detection rates [15].

While the impact of FDG-PET/CT on clinical management may be limited to a subgroup of patients with discovered PT, this imaging technique may have additional benefits for patients with CUP. This may explain some disparities between studies in the interpretation of the usefulness of PET/CT for clinical decisions. Reinert at al. [9] reported a PT detection rate in only 23% of patients with CUP, but changes in treatment management in twice the number of patients [9]. FDG-PET/CT has been recommended for accurate staging, monitoring of the treatment response in CUP patients undergoing active therapy and for their further follow-up, and also as an alternative to contrast CT in patients with severe iodine dye allergy [10]. Moreover, the use of FDG-PEFT/CT in place of conventional imaging may lead to earlier diagnosis of the PT and may facilitate earlier targeted therapy [15].

We acknowledge several limitations to this retrospective study. Our database search relied on proper documentation of the disease in the FDG-PET/CT reports and could therefore present an incomplete sample of patients from our institution. The proportion of patients with SCC was higher than in other studies of CUP, yet the proportion of these patients with head and neck tumors was similar. We did not have data regarding the workups that patients underwent according to their clinical presentations. Larger studies of patients with various pathologies and tumor sites are needed to better define the role of PET/CT in CUP and to identify the CUP subtypes whose management is most influenced by FDG-PET/CT results.

Abbreviations And Acronyms

PET- Positron emission tomography

CT- Computed tomography

FDG- Fluorodeoxyglucose

SUV- Standardized uptake values

MRI- Magnetic resonance imaging

Declarations

Data availability

All data developed for and used in this study is available upon request of the authors.

Author contributions

E.N. and T.D. designed the study, A.Z. provided statistical advice for this manuscript**,** E.N. and T.D. gathered the imaging data, T.D. interpreted the data, I.B. designed the work and revised the article, U.A., L.B., A.Z., D.U., I.B., and T.D. wrote the main manuscript. T.D. prepared the Figures and approved the submitted version.

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Competing interests

The authors declare no competing interests.

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Figures

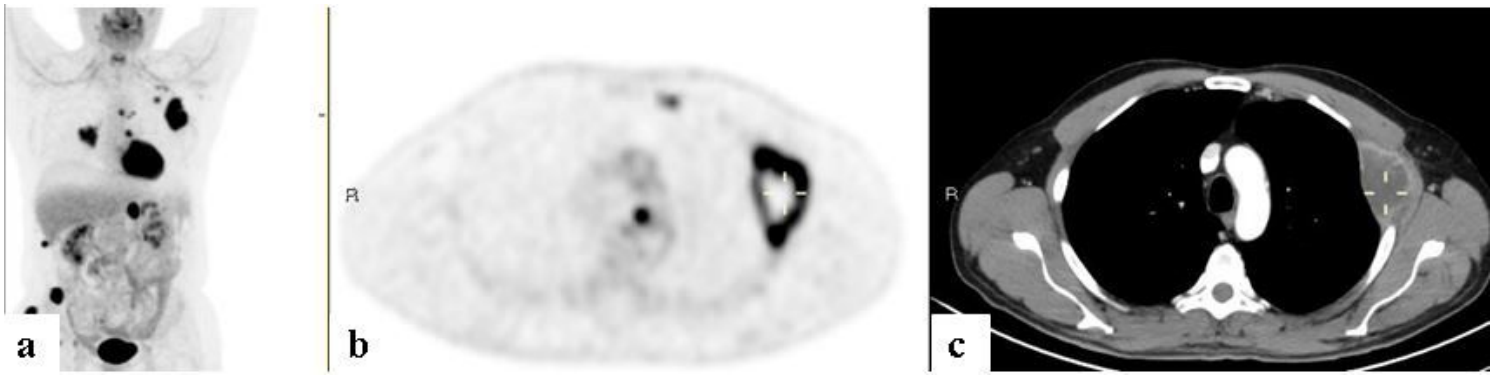

Figure 1

FDG-PET/CT: maximum intensity projection (MIP), (a) representative PET (b) and CT (c) axial slices. A 65 - year-old woman with a biopsy proven squamous cell carcinoma from a pelvic mass (A. b). Left obturator FDG avid enlarged lymph nodes (curser).

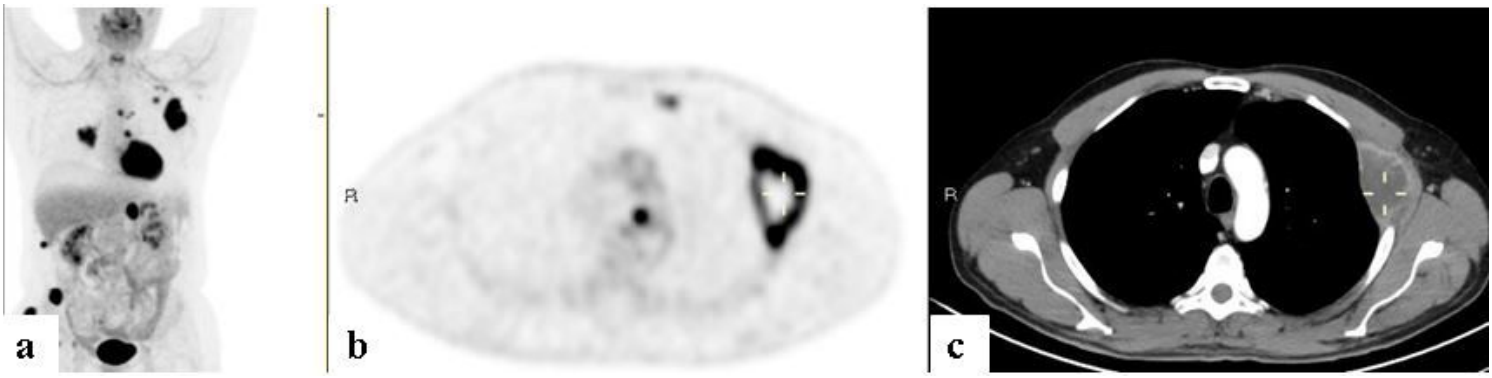

Figure 2

FDG-PET/CT: maximum intensity projection (MIP), (a) representative PET (b) and CT (c) axial slices. A 49 - year-old man with a biopsy-proven poorly-differentiated adenocarcinoma from a chest wall mass (A. b). Multiple sites of FDG avid lesions in the bones and in the left adrenal.

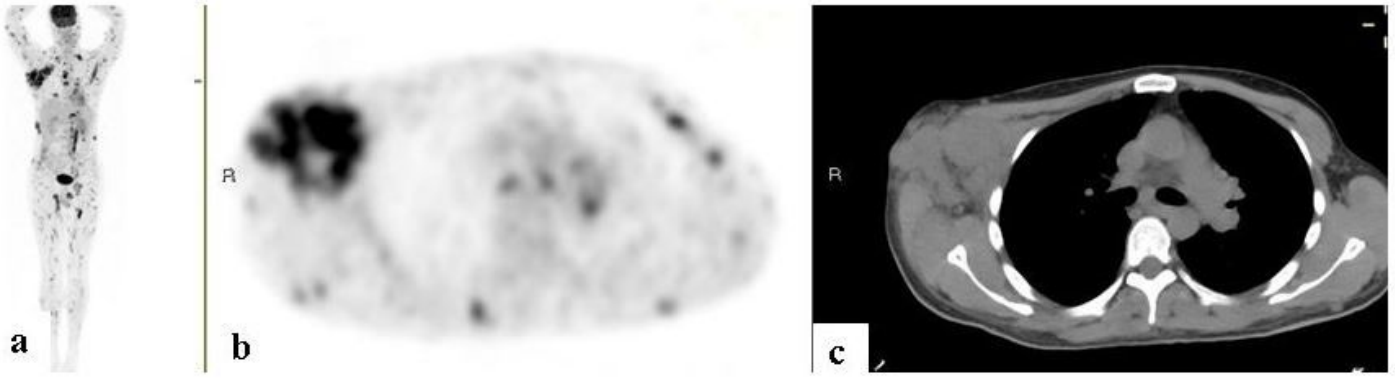

Figure 3

FDG-PET/CT: maximum intensity projection (MIP), (a) representative PET (b) and CT (c).axial slices A 35 - year-old man with melanoma diagnosed by a biopsy taken from the right axillary lymph nodes (A. b). Large lymph nodes in the right axilla and multiple FDG-avid soft tissue lesions.