Usefulness of non attenuation corrected ^{18}F-FDG-PET images for optimal assessment of disease activity in patients with lymphoma

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Abstract

This study *aimed* at determining whether non attenuation corrected (NAC) positron emission tomography (PET) images, in addition to the attenuation corrected (AC) PET images, should be included in the interpretation of fluoro-18 fluorodeoxyglucose (^{18}F-FDG-PET) images in patients with lymphoma. *The study included* 58 patients, 35 males 23 females, mean age 55±16 years. There were 64 superficial and 170 deep lymph node (LN) lesions. Lesion detection, uptake intensity using a three-point scale (1-mild, 2-moderate, 3- intense) and overall clarity of each lesion were compared on both PET images. *Our results* showed that the detection rate for superficial LN was 100% for NAC-PET and 98.4% for AC-PET images. The degree of ^{18}F-FDG uptake (intense, moderate and mild uptake) was 56.3%, 31.3% and 12.5% for NAC-PET images and 23.4%, 34.4% and 40.6% for AC-PET images, respectively. The overall image clarity was significantly in favor of NAC compared to AC-PET images (89% vs 20%, P<0.01). For deep LN, lesions, detection rate was for NAC and AC-PET images 95.3% and 99.4%, respectively. ^{18}F-FDG uptake intensity (intense, moderate and mild uptake) was 42.4%, 27.1% and 25.9% for NAC and 52.4%, 43% and 4.1% for AC-PET images, respectively. The overall image clarity for AC-PET images was superior to NAC-PET images (81.8% vs 53% P=0.01). *In conclusion,* NAC-PET images appeared to be superior to AC-PET images in detecting superficial LN lesions. AC-PET images are superior to NAC-PET images with regard to the deep-seated LN lesions. Therefore, AC and NAC-PET images are complimentary to each other and require to be reviewed together in the evaluation of patients with lymphoma.

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Introduction

Positron emission tomography (PET) is a non-invasive diagnostic tool that provides tomographic images and quantitative parameters of perfusion, cell viability, proliferation and/or metabolic activity of tissues [1].

The cell alterations related to neoplastic transformation are associated with functional impairments that are discernible before structural alterations occur. Therefore, fluoro-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) can reveal the presence of a tumor when conventional morphological diagnostic modalities (i.e. X-ray, computerized tomography (CT), magnetic resonance tomography (MRI) and ultrasound (US)) do not yet detect any evident lesions [1]. In addition, it can also assess the whole body of patients with a single examination [2]. ^{18}F-FDG-PET is becoming more and more a part of the clinical routine for staging and restaging malignant lymphoma [3]. The accurate documentation of anatomic extent of disease and the response to treatment are of paramount importance in patient management in lymphoma [4].

There has been considerable debate about the desirability of attenuation correction (AC) in whole-body PET imaging. The advantages of reconstructing images without AC include avoidance of the noise amplification, improvement of signal-to-noise ratios for lesions (due to reduction of the local background) and reduced patient scanning time, as no transmission scan is acquired. Another gain is avoidance of the potential artifacts arising from patient's motion between the emission and the transmission scans [5]. AC is regarded as a technical improvement that should increase the diagnostic yield of PET imaging in several ways. First, it aims to generate accurate and nonartifactual images of the activity distribution in the patient, thereby allowing more reliable identification of lesions, for example in the liver and lungs. Second, attenuation correction may allow tumor size, location, and malignancy to be more reliably assessed. Finally, AC images allow tumor uptake to be more accurate-

ly measured both before and after treatment [6]. Accordingly, this study was undertaken to assess the importance of both non attenuation correction (NAC) and AC PET images in the assessment of disease activity in patients with lymphoma.

Methods

Population

Fifty eight consecutive patients, 35 males and 23 females, mean ages of 52±18 years with a diagnosis of lymphoma who underwent ^{18}F-FDG-PET imaging, at the Hospital of University of Pennsylvania, were included in this study. Patients of both Hodgkin's and non Hodgkin's lymphoma were analyzed in this study. The final diagnoses of the true lesions were based on histopathology whenever available, and clinical follow-up and other imaging modalities in the others. The lymph node lesions were categorized, based upon their depth of location, into deeply seated lymph node (LN) lesions (n=170) and superficial LN lesions (n=64). Demographic characteristics of patients are summarized in Table 1. This study was conducted after obtaining clearance from the Institutional Review Board, University of Pennsylvania, Philadelphia, PA, USA.

Table 1. *Demographic and clinical characteristics of all patients*

Age (years)	Mean		52
	Range		7-88
Sex	Male		35
	Female		23
Diagnosis	NHL		48
	HL		10
Lesions-Location	Deep	Neck	47
		Mediastinum	56
		Abdomen and pelvis	67
	Superficial	Axilla	26
		Inguinal	38
Size (cm)	Mean		2.2
	Range		1-5.2
Standardized uptake value (SUV)	Superficial LNs	Maximum	11
		Average	7.7
	Deeply seated LNs	Maximum	11.8
		Average	7.9

PET imaging

PET imaging was performed on a dedicated whole body PET scanner (Allegro Philips Medical System, Philadelphia, PA, USA). The patients fasted for at least 4 h and their serum glucose level was <140 mg/dL. PET scanning was initiated 60 min after intravenous administration of 2.52-5.20 MBq/kg of ^{18}F-FDG. Sequential overlapping scans were acquired to cover the neck, chest, abdomen, and pelvis. Transmission scans using a cesium-137 (^{137}Cs) point source were interleaved between the multiple emissions scans to correct for nonuniform attenuation. The images were reconstructed using an iterative reconstruction algorithm (3D-RAMLA). Attenuation correction was performed by acquiring multiple transmission scans in a singles mode using a 740MBq ^{137}Cs transmission source. The source holder is made of tungsten, which provides fanbeam collimation between the 740MBq source and patient and shields the back detectors. The source is located at the center of the axial FOV and with each rotation, which takes 20sec, we sort and store transmission data over an axial dimension of 84mm. Therefore, a full whole-body scan required multiple bed positions (1 or 2 rotations each) with an axial offset of 84mm between positions. Single-slice rebinning and ordered-subsets expectation maximization (OSEM) reconstruction are then used to reconstruct the transmission image, followed by a histogram-based algorithm for segmentation [7, 8].

Routine clinical image reconstruction was performed with a fast, fully 3D iterative algorithm (3D-RAMLA) [9-12] with a relaxation parameter of 0.006 and a "blob" radius of 2.5. The reconstruction time with full corrections on a SUN Blade 2000 (Sun Microsystems, Inc. USA) is <5min for a single bed position to produce a 144x144 image with 4mm-thick slices from a 256x192 sinogram and 7-tilt (out-of-plane angle) dataset.

Image analysis

Lesion detectability

LN lesions were identified by focal areas of increased ^{18}F-FDG uptake compared to the background on the PET studies. All studies were reviewed consensually by 3 independent investigators (MH, WC, AA). A computed tomography study of each patient was reviewed to confirm the site and to measure the size of the lesions. These studies were selected within 2 months of PET studies.

^{18}F-FDG uptake intensity

AC PET images were reviewed first, and then NAC PET images were read. Transaxial, coronal and sagittal sections were reviewed on film in a standardized manner. The number of lesions was recorded on each AC and NAC PET images separately. Visual analysis of ^{18}F-FDG uptake intensity on NAC and AC PET images was performed by a consensus reading of three investigators using a three-point scale from 1 to 3 (1, mild; 2, moderate; 3, intense uptake). Quantitative evaluation of the lesions was performed by calculating the maximum standardized uptake value (SUVmax) to calculate the average SUV in all lesions.

Overall clarity

Side by side comparison, for each lesion, was made, by the three investigators, between NAC and AC PET images, using the same grey scale, cut off threshold and identical slice number to give overall grade for visual clarity (poor vs optimal) for each scan.

Statistical analysis

Continuous variables were expressed as mean. The differences in lesion detection and visual quality between NAC and AC PET images were analyzed using the Chi-square test for equality of distributions. A probability (P value) < 0.05 was considered statistically significant.

Results

Lesion detection

Superficial LN lesions

The detection rate for superficial LN lesions was 100% (64/64) for NAC PET images and 98.4% (63/64) for AC PET images (Fig. 1). The difference of course did not reach a statistical significance regarding the detection rate.

Deeply seated LN lesions

The detection rate for deeply seated LN lesions was 95.3% (162/170) for NAC PET images and 99.4% (169/170) for AC PET images. Eight lesions could not be detected in NAC PET images compared to 1 lesion in AC PET images indicating that NAC PET images can frequently miss deep lesions (P=0.05) (Fig. 2). Distribution of missed lesions shown in Table 2.

FDG uptake intensity

Superficial LN lesions

Thirty six of 64 lesions show intense uptake in NAC PET images compared to 15/64 AC PET images (P=0.02), moderate ^{18}F-FDG uptake in 20/64 on NAC PET images compared to 22/64 on AC PET images (P=0.9), and mild uptake was seen in 8/64 lesions on NAC PET images compared to 26/64 on AC PET images (P=0.01) (Table 3).

Deeply seated LN lesions

^{18}F-FDG uptake was intense in 72/170 on NAC PET images compared to 89/170 lesions on AC PET images (P=0.3), moderate uptake in 46/170 lesions on NAC PET images compared to 73/170 lesions on AC PET images and mild ^{18}F-FDG uptake was seen in 44/170 lesions on NAC PET images compared to 7/170 lesions on AC PET images (P<0.01) (Table 3]).

Table 2. *Location of missed lesions*

	Location	Number
NAC PET images	Neck (Deep cervical LNs)	3
	Mediastinum	3
AC PET images	Abdomen (para aortic)	2
	Mediastinum (Hilar LN)	1
	Axilla	1

NAC: Non attenuation correction, AC: Attenuation correction, LN: Lymph node

Table 3. *^{18}F- FDG uptake intensity*

	Total	^{18}F-FDG uptake intensity	NAC	AC	Combined NAC/AC
Superficial LN	64	1	12.5%	40.6%	9.4%*
		2	31.3%	34.4%	34.4%
		3	56.3%	23.4%	56.2%*
Deeply seated LN	170	1	25.9%	4.1%	2.9%*
		2	27.1%	42.9%	39.4%*
		3	42.4%	52.4%	57.7%

* P≤0.05, NAC: Non attenuation correction, AC: Attenuation correction, LN: Lymph node

Overall clarity

Superficial LN lesions

Fifty seven lesions were optimally seen on NAC PET images compared to 13 lesions on AC PET images (P< 0.01). NAC PET images improved the quality of assessment from poor to optimal in 77.2% of the superficial LN lesions. Only 7 lesions were poorly seen on NAC PET images in contrast to 50 lesions for AC PET images (P<0.01) (Table 4, Fig. 1).

Table 4. *Overall clarity of all lesions*

	Total	Overall clarity	NAC	AC	Combined NAC/AC
Superficial LNs	64	Optimal	89.1%	20.3%	90.6%*
		Poor	10.9%	78.1%	9.4%*
Deeply seated LNs	170	Optimal	52.9%	81.8%	94.1%*
		Poor	42.4%	17.7%	5.9%*

* P≤ 0.05, NAC: non attenuation correction, AC: Attenuation correction, LN: Lymph node

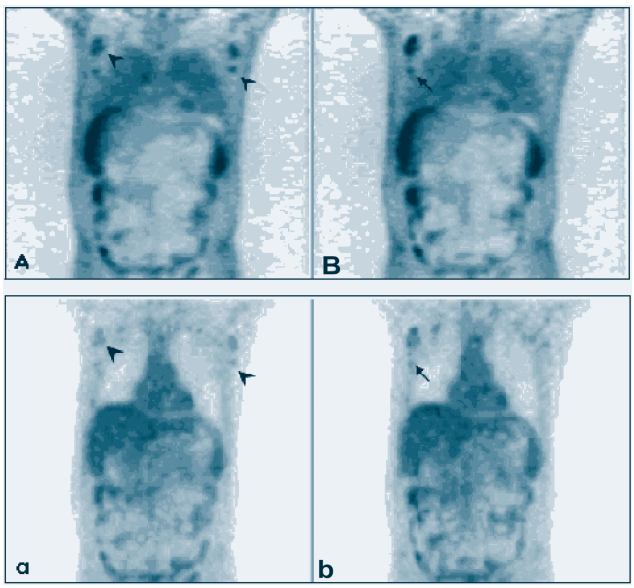

Figure 1. Coronal PET images, NAC PET images(A) and AC PET images (a). One superficial LN lesion in the axilla which is seen on NAC PET images cannot be appreciated on AC PET images (black arrow). Another two LN with poor overall clarity on AC PET images as compared to NAC PET images (arrow head).

Deeply seated LN lesions

Among 170 deeply seated LN lesions, 90 lesions were optimally seen on NAC PET images compared to 139 lesions on AC PET images (P= 0.01). AC improved the quality from poor to optimal in 27% deep LN lesions.

The percentage of discrepancy of the optimal performance on NAC PET images between superficial and deep LN lesions was 40.5%, while on AC PET images was 75.2%. Seventy two lesions were poorly demonstrated on NAC PET images compared to 30 lesions on AC PET images (P= 0.01) (Table 4, Fig. 2).

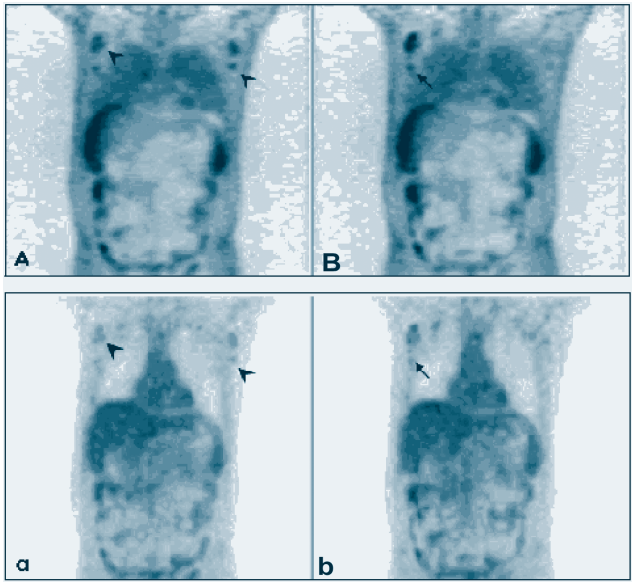

Figure 2. Coronal PET images, NAC PET images (A, B) and AC PET images (a, b). Two mediastinal LN cannot be appreciated on NAC PET images but seen on AC PET images (black arrow). Another one LN with poor overall clarity on AC PET images and is better seen on NAC PET images (arrow head).

Discussion

^{18}F-FDG-PET is a powerful modality for demonstrating malignant nodal involvement in patients with lymphoma and is now considered standard of care in the management of this malignancy. This has been demonstrated in a number of prospective studies [13-16]. The most important goal of whole-body PET is to obtain information about the extent of the disease activity and tumor staging, as precise staging is an important prerequisite for selecting adequate treatment. ^{18}F-FDG-PET can demonstrate lesions with maximum contrast for focal tracer uptake, which is desirable and may provide the highest sensitivity. NAC PET images are characterized by "hot skin" and the appearance of the lungs with high tracer uptake and the appearance of low tracer concentrations in the mediastinum [13]. In contrast, on AC PET images the relative uptake of ^{18}F-FDG in the lungs and the nearby soft tissue is correctly recovered [5].

Some distortion of foci is detected on NAC PET images [17]. This distortion could give unclear visualization of the deeply seated LN lesions. In this study 8 deeply seated LN lesions could not be seen on NAC images, in contrast, some studies reported that the overall sensitivity for lesion detection was not significantly improved by AC [18]. Among, the deeply seated LNs, correction for attenuation improved visualization in 27% of lesions in our data.

On the other hand, NAC PET images revealed higher contrast in the hypermetabolic focus. This difference in contrast is independent of body region, tissue type, focus diameter, and the distance from the focal uptake to the body surface. Phantom data confirmed the higher contrast for NAC PET images compared with AC PET images [17]. In addition, the noise from the transmission measurement may contribute to loss of contrast on AC PET images, Inhomogeneity of data transmission may lead to a noisy background and decreasing the signal to noise ratio [19]. Furthermore, the absolute background for lesions on NAC PET images is variable, showing higher uptake at the lesion's edge and slightly lower uptake towards the center. As the background region represents a global average around the lesion, this variability may result in lower background values than the actual values derived from images corrected for attenuation. Also, the patient's motion, between the emission and the transmission scans, may cause degradation of contrast after AC. This becomes more likely for long imaging protocols such as whole-body PET [17]. The use of post-injection transmission scan is preferred in our center since this method does not require patient repositioning between transmission and emission scans.

It has been demonstrated that lesion-to-background ratio itself was influenced by AC, which reduced the performance of lesion detection [20]. In our study, NAC PET images improved the overall clarity in 70% of the superficially detected lesions; this increases the confidence level of the reader. Only one lesion could not be detected on AC PET images in our analysis. Others have reported five more lesions to be visualized on NAC PET images than on the AC PET images, among a total of 189 lesions [20]. However, found a high agreement in the diagnostic yield of both NAC and AC PET images in lymphoma patients has been reported [13]. In a recent study, the rate of the lesion detection was similar for NAC and AC PET images but NAC images gave better visibility in 41.4% of lesions [21].

Another disadvantage of AC is that it can cause an increase in the overall study duration [6]. On the other hand, advantages of AC include the decrease of distortion in the tumor size and shape and restoration of the true count density. Co-registration of the image can be done, with AC, by using the anatomical information from the transmission maps. Prior studies concluded that although an image distortion was eliminated by AC, the lesion's contrast was decreased. This potentially leads to a reduction in the sensitivity [6, 17].

The interesting feature on AC PET images is the possibility to obtain the SUV of ^{18}F-FDG by the lesions, which can be helpful in the diagnosis and the follow-up of tumors after treatment. This is especially helpful when the anatomy is modified by treatment, precluding an objective comparison between the pre- and the post-treatment images [22].

When comparing AC and NAC PET images, the impact of the iterative reconstruction algorithms is separated, as possible, from attenuation correction itself [23]. In this study, Iterative reconstruction was made by using 3-D RAMLA technique; this reconstructive method is preferred in our center as it showed improvement in the image quality. 3-D RAMLA reduces artifacts and image noise, it also improves the clinical confidence of the reader [24]. Others reported potential improvement in lesions detectability with an iterative reconstruction [25]. In our retrospective study, there are some limitations. We think that the number of patients is limited. In-

creasing the number of patients and having more lesions in each specific region may give more information about AC. Doing this study on a bigger scale and with other malignant lesions in the future, will be useful to assign the optimal protocol to assess the PET studies.

In conclusion, NAC PET images appear to be superior to AC PET images in evaluating the superficial nodal lesions with regard to lesion detection, intensity of ^{18}F-FDG uptake and the overall quality of the image. However, AC PET images are more superior to NAC PET images in the evaluating the deeply seated LN lesions. Therefore, AC and NAC PET images are complimentary to each other in assessing superficial and deep LN lesions in patients with lymphoma and should be jointly reviewed for the optimal assessment of these patients.

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