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Is True Whole-body 18F-FDG-PET/CT required in paediatric lymphoma? An IAEA Multicentre Prospective Study

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ABSTRACT

INTRODUCTION: Guidelines recommend true whole body (TWB) 18F-FDG-PET/CT scans from vertex to toes in paediatric lymphoma patients, although this suggestion has not been validated in large clinical trials. The objective of the study is to evaluate the incidence and clinical impact of lesions outside the "eyes to thighs" regular field of view (R-FOV) in 18F-FDG-PET/CT staging (sPET) and interim (iPET) scans in paediatric lymphoma patients.

MATERIALS AND METHODS: TWB sPET and iPET scans were prospectively performed in paediatric lymphoma patients (11 worldwide centres). Expert panel central review of sPET and iPET scans were evaluated for lymphoma lesions outside the R-FOV, and clinical relevance of this findings.

RESULTS: A total of 610 scans were performed in 305 patients. The sPET scans did not show lesions outside the R-FOV in 91.8% of the patients, while in 8.2% patients the sPET scans demonstrated lesions also outside the R-FOV (soft tissue, bone, bone marrow and skin); however, the presence of these lesions did not change the clinical stage of any patient and did not impact on treatment decision.
Among the 305 iPET scans, there were no new positive 18F-FDG-avid lesions outside the R-FOV, when compared to their paired sPET scans. A single lesion outside the R-FOV on iPET occurred in one patient (0.3%) with the primary lesion diagnosed in the femur on sPET that persisted on iPET.

CONCLUSION: The identification of additional lesions outside RFOV (eyes to thighs) 18F-FDG-PET/CT has no impact in the definition of the clinical stage of disease and minimal impact in the treatment definition of patients with pediatric lymphoma. As so, reduced field of view for both staging and interim 18F-FDG-PET/CT scans could be performed.

Key Words: 18F-FDG PET/CT; paediatric; lymphoma; Hodgkin's lymphoma; Non-Hodgkin's lymphoma.

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INTRODUCTION

In the last decades, 18Fluorodeoxyglucose positron emission tomography with computed tomography with (18F-FDG-PET/CT) has become the established modality for paediatric staging of all solid tumours (*1*), Hodgkin's lymphoma (HL), Non-Hodgkin lymphoma (NHL) (*2-4*), sarcomas (*5,6)* and neuroblastomas (*7*). The literature on paediatric oncologic 18F-FDG-PET/CT advocates performance of true whole-body field-of-view (TWB-FOV) examinations, with imaging from vertex to toes (*8,9*), as tumours in children might have systemic involvement that can include the distal extremities (*10-12*). In adults, the reduced field-of-view (R-FOV) of 18F-FDG-PET/CT (so-called "eyes-to-thighs") is limited to the neck, chest, abdomen, pelvis and upper thighs, which provide significant advantages. Exceptions are made for some sarcomas, melanomas, or cases of primary or suspected extremity involvement (*13*) where TWB-FOV PET/CT images are also performed. Early articles describing the use of 18F-FDG-PET/CT in paediatrics were more likely to assume that R-FOVs done in adults may be enough in some cases of paediatric lymphoma (*3,9,14*).

The R-FOV images provide significant advantages for patients: it decreases radiation exposure, scanning time, potentially improving image quality and reduced anaesthesia time.

Hodgkin (HL) has a relatively predictable progression of metastases, with rare extremity involvement in the absence of disseminated disease, or bone marrow involvement within the chest, abdomen, and pelvis (*15-19*). Indications for 18F-FDG-PET/CT have also been established in certain types of non-Hodgkin's lymphoma (NHL) (*20-23*).

There are certain "trues" in science, based mainly in common sense, without solid empirical evidence as true whole body for paediatric patients. The purpose of this multicentre international investigation, coordinated by International Atomic Energy Agency (IAEA) was to evaluate if there is a clinically significant incidence of lesions outside the R-FOV in PET/CT staging (sPET) and interim (iPET) scans in paediatric lymphoma patients.

MATERIALS AND METHODS

This IAEA project is registered as the Coordinated Research Project E12017. The protocol was developed jointly at two investigator's meetings in 2012 and 2013. The data collection and partial analysis investigator's meeting was performed in 2015 and the final investigator meeting occurred in 2017.

Research Regulation and Data Protection

Each centre obtained research ethics approval for the study protocol and patient information from the appropriate Ethics Review Board. Fully informed consent was an inclusion criterion for recruitment. Signed parental consent were kept by the local investigators. To ensure confidentiality while sharing data internationally, cases and forms were anonymous.

Eligibility Criteria and Treatment Protocol

Paediatric patients (age < 18 years) with newly diagnosed HL or NHL were recruited.

Exclusion criteria were pregnancy, breast-feeding, prior cancer, prior radiation therapy and/or chemotherapy, concurrent HIV infection or history of tuberculosis, and non 18F-FDG–avid disease on staging PET/CT scans (sPET). Diagnosis was based on biopsy with immunohistochemistry according to the World Health Organization classification criteria (*24*) . Furthermore, since guidelines are comparatively broad world-wide and 18F-FDG dosing, rest period protocols could vary between 50 -90 minutes. All imaging data acquired outside the pre-established criteria were excluded.

PET/CT Scheduling, Acquisition and Reporting

All patients underwent TWB-FOV PET/CT studies, from the top of the skull to the toes. All PET/CT studies were performed for staging (sPET) and at interim (iPET). Scans were performed according to SNMMI or EANM procedure guidelines, which are standard for all nuclear medicine practice (*13,25*).

Clinical data were collected, including initial staging using the Ann Arbor classification and NHL using St Jude classification. All patients were staged by the local pediatric oncologists.

The iPET scan was recommended after two cycles of chemotherapy, at a maximum interval from the preceding treatment (1-5 days prior to the next chemotherapy cycle). In recognition of technical and scheduling constraints, iPET after 3 cycles was permitted and in no circumstances after 4 cycles.

An expert panel composed of 11 certified nuclear medicine physicians working together on a common platform at the final collaborator's meeting reviewed all sPET and iPET scans. Any discrepancy among scans after all reviews were undertaken were resolved by consensus.

The R-FOV and the TWB-FOV were scored separately. Reviewers analysed the presence of lesions outside eye to thighs in both scans. Discrepancies were resolved by consensus.

All 18F-FDG uptakes above the background and outside the areas of normal biodistribution were considered abnormal. Abnormalities including focal lesions within the bone/bone marrow, focal soft tissue lesions or diffuse bone marrow involvement were classified as positive for disease. We also recorded if these abnormalities changed the stage or disease management in any individual patient.

The above classification was applied for both sPET and iPET scans.

RESULTS

There were 305 patients that underwent paired sPET and iPET examinations, totalling 610 PET/CT scans (Table 1).

Staging PET/CT (sPET)

All 305 patients underwent sPET examinations. TWB-FOV PET images revealed disease limited to the R-FOV in the majority of the patients (n=280; 91.8%) with no lymphoma lesion outside the R-FOV (Fig. 1).

TWB-FOV sPET images of the remaining 25 (8.2%) patients revealed disease outside the R-FOV. These lesions outside the R-FOV were noted in the soft tissue (one patient with NHL), bone (two patients with NHL), bone marrow (23 patients, nine with HL and 14 NHL) and the skin (one patient with NHL). (Table 2). All patients with lesions outside R-FOV Pet, presented lesions in the extremities, only two patients also presented lesions in the vertex. It was not performed any additional exploration.

Of the 25 patients age varied from 0.6-17yo (median 09,31 yo), nine with HL (5 nodular sclerosis, 2 lymphocyte RC and 02 mixed cells), and 16 with NHL (09 Burkit, 03 difuse large B cell lymphoma -DLBCL, 02 T cell and 02 anaplastic lymphoma).

Twenty-four of these patients (24/25) presented also with lesions in the R-FOV and were already classified as having advanced stage disease based on the R-FOV sPET images. All patients presented bone marrow disease (confirmed by bone marrow biopsy in 14 patients, with negative bone marrow biopsy in 11 patients) with more than one extranodal site in 15 patients with commitment in lung (6), pleura (3), liver (3), gastrointestinal (3), soft tissue (2), kidney (2), pancreas (1) and cutaneous (1). Therefore, the additional findings of disease outside the R-FOV were not impactful and did not alter the clinical stage or treatment.

Only one remaining (1/25) NHL patient (DLBCL) with immunodeficiency presented with a single bone lesion in the right distal femur, exclusively outside the R-FOV. This patient also presented with focal 18F-FDG uptake in the lung, which was related to *Pneumocystis carinii* pneumonia.

Interim PET/CT (iPET)

The same 305 patients that underwent sPET examinations also underwent paired iPET scans. Among the 280 patients in which sPET revealed disease limited to the R-FOV, no additional disease was noted outside the R-FOV. Therefore, the iPET scans of roughly 92% of patients were also negative for disease outside the R-FOV (Fig. 2).

Among the 25 patients in whom the TWB-FOV sPET images revealed disease outside the R-FOV, the paired TWB-FOV iPET images did not identify additional disease outside the R-FOV.

However, the one patient (1/25) in whom the sPET images had identified a lymphoma in the right distal femur, the iPET revealed a partial response to therapy with no impact on subsequent patient management as the initial proposed treatment was not modified (Fig. 3). Therefore, in only 1 (0.3%) of the 305 iPET scans was the TWB-FOV important for subsequent patient management (Fig. 4).

DISCUSSION

In this multicentre international study coordinated by IAEA, we have provided in 610 scans performed in 305 patients (305 sPET and 305 iPET scans), the sPET scans did not show lesions outside the R-FOV in 92% of them. In 8% of the patients the sPET scans showed lesions outside the R-FOV. These lesions outside the R-FOV were in soft tissue, bone (two patients with NHL), bone marrow (23 patients, nine with HL and 14 NHL) and the skin (one patient with NHL); without a single change in the clinical stage of any patient or treatment decision. Although current guidelines for paediatric oncologic 18F-FDG-PET/CT empirically suggest use of TWB examinations (*8,9*), these guidelines and other articles (*3,14,26*), acknowledge that R-FOV PET/CT is likely to be sufficient for some cases of paediatric lymphoma. Our evidence reinforce that R-FOV PET/CT is sufficient in paediatric lymphoma both at staging and interim assessments.

An R-FOV PET/CT has the advantages of decreased radiation exposure due to a reduction in the area of the body that is irradiated outside of R-FOV. Ionizing radiation has been implicated in conferring a latent increased risk of malignancy (*27,28*). This is especially important in paediatric patients who, given their age, have longer to manifest these adverse effects (*29,30*). In paediatric oncology, recent reports shown a significant

cumulative radiation dose in lymphoma patients (3*1,32*). The "as low as reasonably achievable" principle (ALARA) (*33*), which PET/CT applies to both the FDG dose and the acquisition parameters for the CT scan (*34-40*). A possibility for decreasing dose is eliminating the CT dose to the extremities and to the brain if a R-FOV PET/CT scan is performed rather than a TWB PET/CT scan. Using published paediatric PET/CT acquisition protocols (4*1*), the R-FOV acquisition imparts a whole-body effective dose of, at most, 5.5 mSv, while TWB acquisition imparts 5.7 mSv, resulting in a 5% reduction in whole-body effective dose. In terms of organ-specific doses, compared with the TWB examination, the R-FOV acquisition reduces the CT dose to the brain by 70%, to the skin by 15%, and to the remaining organs (primarily oral mucosa) by 7%.

Another advantage of R-FOV over TWB PET/CT examinations is a shorter scanning time, allowing reducing the risk of movement during the scan (*42*). Even if the paediatric population represent a reasonably broad spectrum of ages and correspondingly sizes, reducing the PET/CT FOV could potentially reduce to the half of the scanning time. A shorter imaging time may also increase accessibility of PET/CT examinations in centres where high demand on facility resources is present. This is a significant consideration in developing countries where there are limited paediatric PET/CT scanners available.

Decreasing imaging timing could also result in a similarly decreased length of anaesthesia time for those patients requiring sedation. The need for shorter sedation could allow use of a more desirable anaesthetic, which would be determined according to paediatric sedation guidelines (*43*). Depth of sedation may also potentially be reduced, which could result in similar advantages. As we now consider a shift to the use of PET/MRI imaging in children, we will further reduce radiation dose to the child with the CT but there will be a concomitant potential increase in sedation time for the MRI portion of the studies. A FDA drug safety communication stated that there is the probability of increasing neurodevelopmental risks for children younger than 3 years of age and women in the third trimester of pregnancy with prolonged and repeated procedural sedation of greater than 3 hours (*44*).

Although our findings challenge conventional clinical practice, for many years consolidated without empirical basis, a similar finding in another study, with a smaller series of cases support a reduced FOV practice. Samer *et. al* (*45*) is the only previous paper to have evaluated R-FOV *vs* TWB-FOV differences in PET/CT studies in 170 lymphoma patients. No disease outside of the R-FOV sPET was found on iPET scans in the 145 patients; while 12% of patients had disease outside the R-FOV in staging. In only

one patient with lymphoblastic NHL, the imaging stage was altered with the additional TWB-FOV. They concluded that it was appropriate to perform R-FOV iPET when sPET did not show disease beyond "eyes to thighs". Likewise, in our study with a substantial larger cohort, only 8.3% of patients had disease outside the R-FOV in sPET, and also in only one case on both sPET and iPET (0.3%) was found to have a clinical relevant bone lesion outside of R-FOV. It is important to be noted that this lesion was the primary lesion biopsied in this immunodeficiency related lymphoma patient (DLBCL). The location of his disease would make this case an exception and so this isolated case would have a priori called for a TWB PET scan. This case although unique, would not be missed because common sense and clinical experience still rule in clinical decision making process. Similar to practice in adults exceptions should probably include cases of primary or suspected extremity involvement (*13*) where TWB-FOV PET/CT images are also performed. Therefore, our results support the use of R-FOV PET/CT not only for iPET but also for sPET as well.

This paper does not suggest that R-FOV PET/CT should be used in other paediatric tumours. Just as there are certain tumours in the adult population that have more propensities to involve the extremities Tumours such as sarcomas, neuroblastomas and leukemias are well-known to have systemic involvement and TWB PET/CT imaging is still the recommendation in children who may present with these and other tumours, even though there is limited data to support this approach (*8,9*).

A limitation of our study is our relatively small number of patients with the different subtypes of NHL, even though we performed 219 PET/CT scans in HL patients and in 86 NHL patients. Whereas HL behaves in a relatively predictable way with well-defined staging methodology, NHL encompasses a relatively heterogeneous group of histologies, many with different morphologies, presentations, and natural histories (46). Consequently, further studies dedicated to NHL or specific types of NHL may be helpful to more precisely define the role of R-FOV PET/CT in these patients. Also our study we did not performed dosimetry to determine the percentage reduction in radiation exposure or to determine the exact reduction in scanning time.

Major strengths of this study were that this is the biggest series of cases of pediatric lymphoma patients as far as we know in an international multicentre trial spanning differing socioeconomic layers as defined by the World Bank to include low-middle, upper-middle and high-income countries.

CONCLUSION

Our results demonstrate that the identification of additional lesions outside reduced field of view (eyes to thighs) 18F-FDG-PET/CT has no impact in the definition of the clinical stage of disease and minimal impact in the conduct definition of patients with pediatric lymphoma. As so, reduced field of view for both staging and interim 18F-FDG-PET/CT scans could be performed. This consideration may be quite impactful in developing countries where there are limited paediatric PET/CT scanners available.

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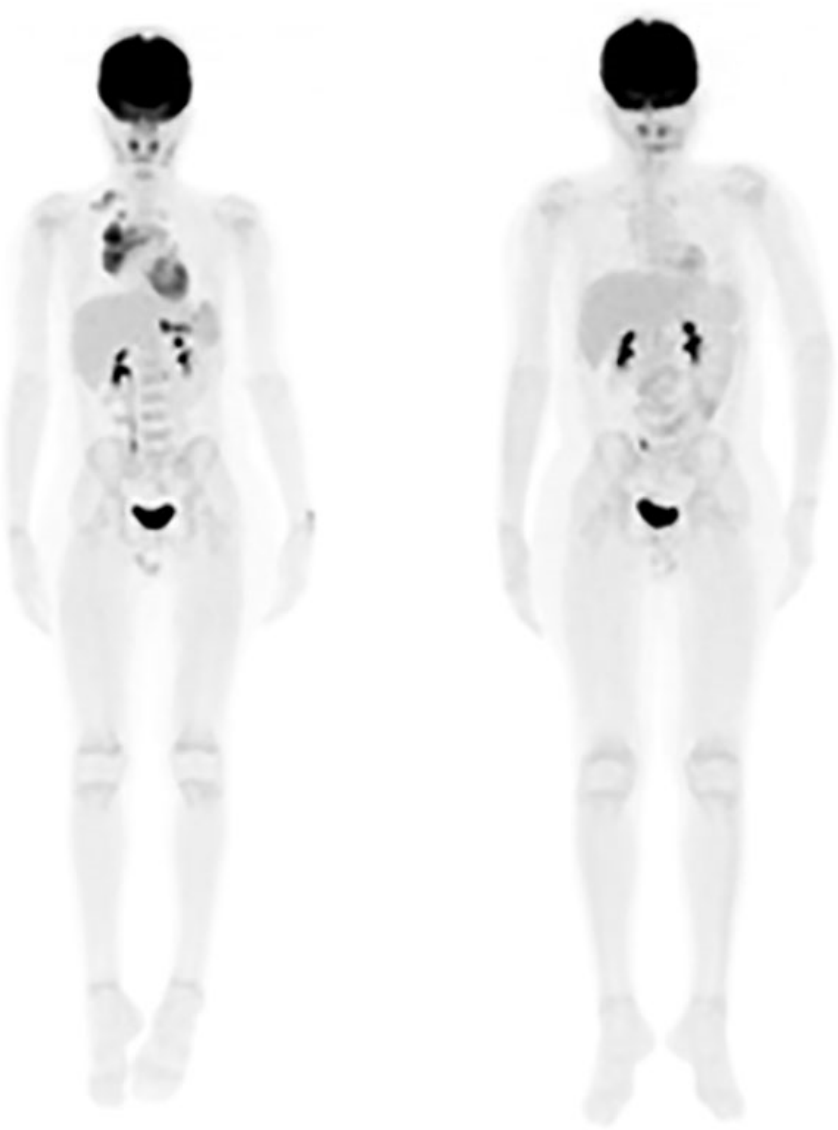

Figure 1. A 12-year-old male patient was diagnosed with clinical stage 2 NHL and submitted to staging (sPET) and interim (iPET) PET/CT studies. The sPET (left image) shows no lymphoma lesions outside the regular field of view (R-FOV). The iPET (right image) performed after two cycles of chemotherapy showed a complete metabolic response (Lugano Classification score 1). He was disease free at 12 months of follow-up.

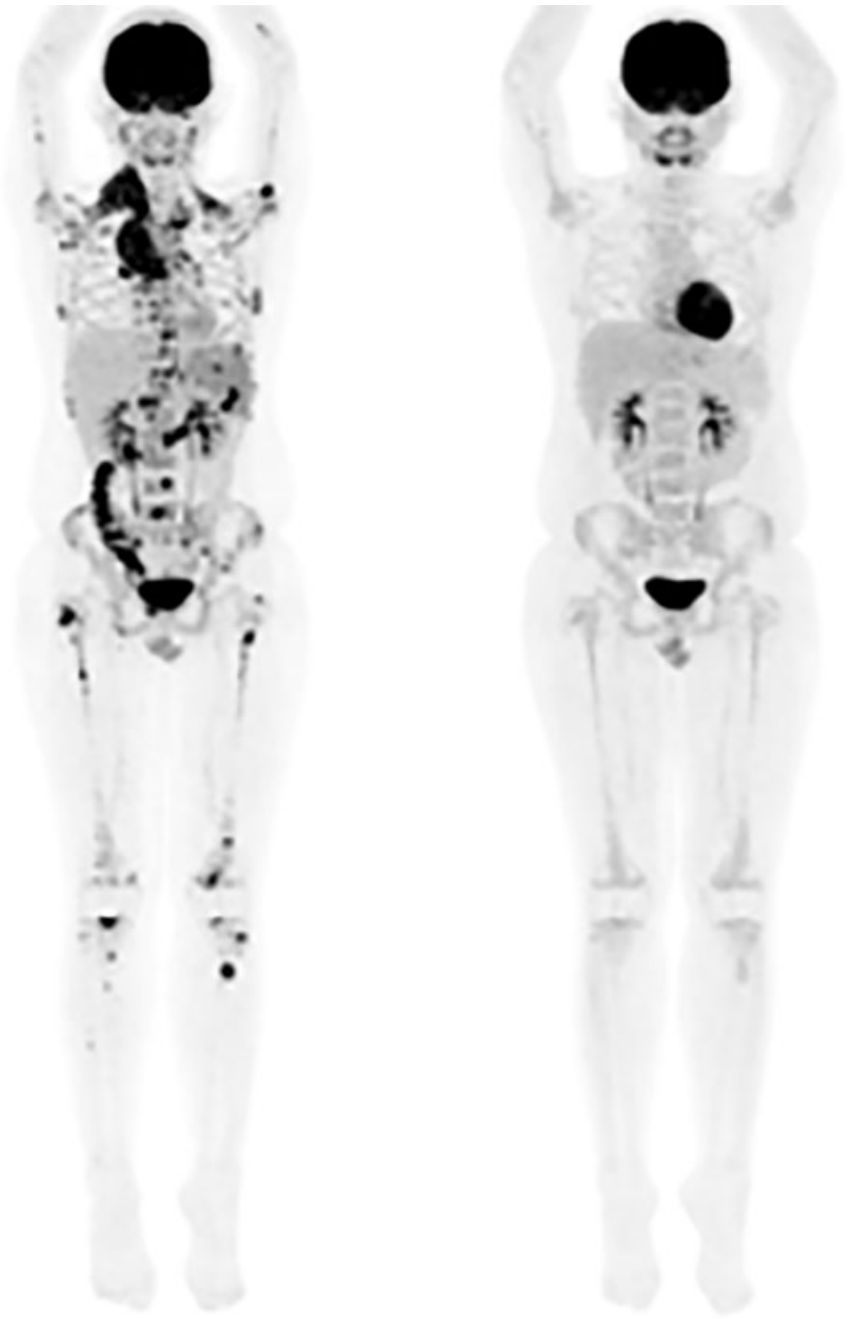

Figure 2. A 15-year-old male patient was diagnosed with clinical stage 4 HL. In addition to the bone marrow lesions identified within the R-FOV, the sPET (left image) shows lesions outside the R-FOV, including bone marrow lesions in both humeri, femur and tibiae. The iPET (right image) performed after two cycles of chemotherapy showed a complete metabolic response (Lugano Classification score 1). The patient is still disease-free at 33 months of follow-up.

Figure 3. A 7-month-old male patient was diagnosed with clinical stage 4 NHL, sPET (left image) shows 18F-FDG-avid lesions in the lungs and the right distal femur. Further investigation revealed an infectious process due to *Pneumocystis carinii* in the lungs (the 18F-FDG uptake in the left elbow is the site of injection). The iPET (right image) performed after two cycles of chemotherapy showed partial response in the lymphoma in the right distal femur (Lugano Classification score 4). At the end of treatment there was a complete response and the patient was still alive after 38 months of follow up.

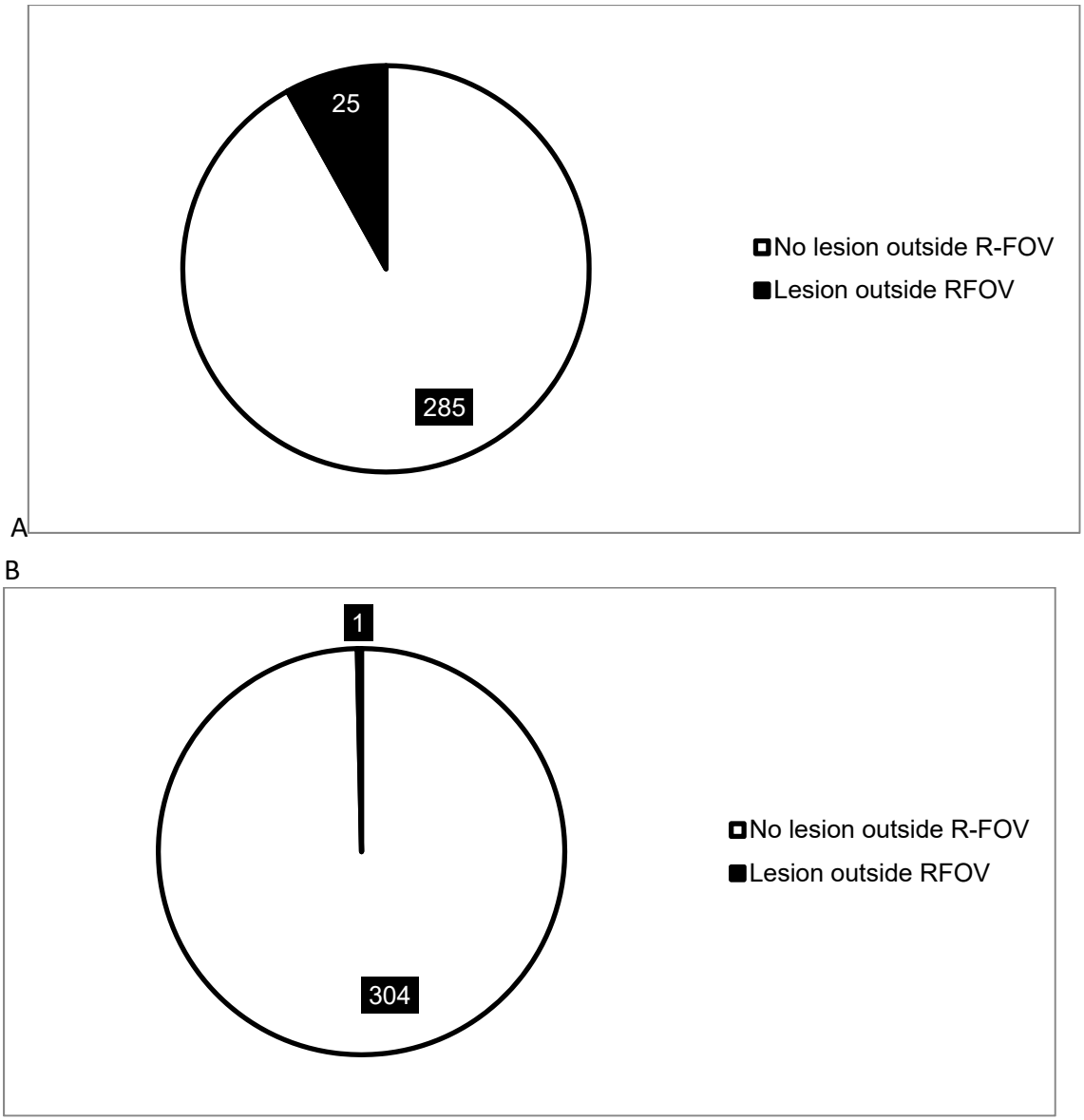

Figure 4: Results of the presence of lesions inside and outside the R-FOV on sPET (A) and iPET(B).

Table 1. Patient demographics.

		All patients (n=305)	%
Sex	Male	210	68,9%
	Female	95	31,1%
Age (years)		0.4 - 18	
HL		219	71,8%
	Classical	213	69,8%
	NodularLymphocytePredominant	06	2,0%
NHL		86	28,2%
	Burkitt	43	14,1%
	DLBCL	19	6,2%
	T cell	06	2,0%
	Primary B Cell	05	1,6%
	Anaplastic	13	4,3%
Stage (HL & NHL)	1	50	16,4%
	2	95	31,1%
	3	79	25,9%
	4	81	26,6%
Country	Bangladesh	11	3,6%
	Brazil (Curitiba)	24	7,9%
	Brazil (Campinas)	21	6,9%
	Canada	28	9,2%
	United Kingdom	11	3,6%
	India (New Delhi)	59	19,3%
	India (Mumbai)	75	24,6%
	Israel	25	8,2%
	Pakistan	16	5,2%
	South Africa	7	2,3%
	Uruguay	28	9,2%
Bulky disease (> 5cm)		171	56,1%
B symptoms		128	
Bone marrow involvement		87	28,5%
Extra nodal disease		95	31,1%
Spleen disease		87	28,5%

Table 2. Patients with lesion outside R-FOV PET/CT clinical characteristics.

Patient	Histology	Subtype	Age	Clinical stage	> 2 extranodal sites	Lesion outside R-FOV location	Bone Marrow Biopsy	Clinical staging due to lesion outside R-FOV PET
1	NHL	Anaplastic Cell	8	4	No	Bone marrow	Not Involved	No
2	HL	Nodular Sclerosis	14	4	No	Bone marrow	Involved By Lymphoma	No
3	NHL	Burkitt	12	4	No	Bone marrow	Involved By Lymphoma	No
4	NHL	Burkitt	12	4	No	Bone marrow	Involved By Lymphoma	No
5	NHL	T Cell	4	4	No	Soft tissue	Involved By Lymphoma	No
6	HL	Nodular Sclerosis	15	4	Yes	Bone marrow	Involved By Lymphoma	No
7	NHL	Burkitt	4	4	Yes	Bone marrow	Not Involved	No
8	NHL	T Cell	13	4	Yes	Skin	Not Involved	No
9	NHL	Burkitt	12	4	Yes	Bone marrow	Involved By Lymphoma	No
10	HL	Nodular Sclerosis	11	4	Yes	Bone marrow	Not Involved	No
11	HL	Mixed Cell	17	4	Yes	Bone marrow	Not Involved	No
12	HL	Nodular Sclerosis	15	4	Yes	Bone marrow	Not Involved	No
13	HL	Nodular Sclerosis	15	4	Yes	Bone marrow	Involved By Lymphoma	No
14	NHL	DLBCL	10	4	Yes	Bone and bone marrow	Not Involved	No
15	NHL	Burkitt	4	4	Yes	Bone marrow	Involved By Lymphoma	No
16	NHL	Burkitt	6	4	Yes	Bone marrow, bone	Involved By Lymphoma	No
17	NHL	Burkitt	9	4	Yes	Bone marrow	Not Involved	No
18	NHL	Burkitt	9	4	Yes	Bone marrow	Not Involved	No
19	NHL	Burkitt	4	4	Yes	Bone marrow	Involved By Lymphoma	No
20	NHL	DLBCL	10	4	Yes	Bone marrow	Involved By Lymphoma	No
21	HL	Lymphocyte Rich Cell	7	4	No	Bone marrow	Involved By Lymphoma	No
22	HL	Lymphocyte Rich Cell	4	4	No	Bone marrow	Not Involved	No
23	NHL	DLBCL	0,7	4	No	Bone	Not Involved	No
24	HL	Mixed Cell	8	4	No	Bone marrow	Involved By Lymphoma	No
25	NHL	Anaplastic Cell	5	4	Yes	Bone marrow	Involved By Lymphoma	No