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Early View

Original article

PET/CT features of Extrapulmonary Tuberculosis at first clinical presentation - a cross-sectional observational ^{18}F-FDG imaging study across six countries

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Clean revision

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TITLE:

PET/CT features of Extrapulmonary Tuberculosis at first clinical presentation - a cross-sectional observational ^{18}F-FDG imaging study across six countries

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ABSTRACT

Background: A large proportion of the huge global burden of Extrapulmonary tuberculosis (EPTB) are treated empirically without accurate definition of disease sites, and extent of multi-organ disease involvement. Positron emission tomography (PET) imaging using ^{18}F-FDG in TB could be a useful imaging technique for localising disease sites and extent of disease.

Methods: We conducted a study of HIV-negative adult patients with a new clinical diagnosis of EPTB across 8 centres located in 6 countries: India, Pakistan, Thailand, South Africa, Serbia, and Bangladesh to assess the extent of disease and common sites involved at first presentation. ^{18}F-FDG PET/CT scans were performed within two weeks of presentation.

Findings: A total of 358 patients with EPTB (189 females; 169 males) were recruited over 45 months. Age range 18–83 years (females: median 30 years; males: median 38 years). 350/358 (98%) patients (183 female, 167 male) had positive scan. 118/350 (33.7%) had a single extrapulmonary site and 232/350 (66.3%) had more than one site (organ) affected. Lymph nodes, skeletal, pleura and brain were common sites. 100/358 (28%) of EPTB patients had ^{18}F-FDG PET/CT positive sites in the lung. 110 patients were ^{18}F-FDG PET/CT positive in more body sites than were noted clinically at first presentation and 160 patients had the same number of positive body sites.

Interpretation: ^{18}F-FDG PET/CT scan has potential for further elucidating the spectrum of disease, pathogenesis of EPTB, and monitoring the effects of treatment on active lesions over time, and requires longitudinal cohort studies, twinned with biopsy and molecular studies.

Role of Funding Source and Oversight: The International Atomic Energy Agency (IAEA) assisted in selection of recruitment centres with optimal ^{18}F-FDG PET/CT imaging facilities and provided support for ^{18}F-FDG PET/CT scans, consortium meetings, and centralised facilities for data storage.

Message: ^{18}F-FDG PET/CT can localise EPTB disease sites not clinically detected. It may serve a useful tool for research studies defining pathogenetic mechanisms an cure, relapse and recurrence.

INTRODUCTION

Background and Rationale:

Tuberculosis (TB) remains the leading infectious disease cause of death worldwide.[1] The annual global incidence of TB cases in 2017 was reported to be 10 million, of which an estimated 15% were extrapulmonary TB (EPTB). These figures may be an underestimate since EPTB is a neglected clinical problem worldwide[2–5] and the diagnosis of EPTB can easily be overlooked due to non-specific symptoms, chronic and cryptic protean clinical manifestations, low clinician awareness of the possibility of TB and lack of an accurate tool for detection of extrapulmonary disease sites.[4,5] Up to 45% of the global burden of EPTB remains undiagnosed and untreated.[1,6] Furthermore, definitions traditionally used for clinical presentations of TB have been generally classified by WHO as pulmonary TB (PTB) and extrapulmonary TB (EPTB). A large proportion of patients with EPTB are started on anti-TB treatment (ATT) empirically upon clinical suspicion, utilising current WHO management guidelines without an accurate definition of specific disease site(s) and extent of multi-organ involvement.

Positron emission tomography (PET) imaging using 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG) can provide functional information on sites with active inflammatory and immune cells which utilise glucose.[8] Acquiring ^{18}F-FDG PET and CT data together combines anatomical and functional information in one scan.[9] Preliminary studies of TB in macaques[10] and humans[11–14] using ^{18}F-FDG PET/CT as a research tool indicate it could have clinical applications as a imaging technique for localising disease sites.

Objectives:

We performed a cross sectional observational study under operational conditions in six countries to assess the potential clinical usefulness of 18F-FDG PET/CT in: a). localising disease site(s), b). defining the extent of disease and c). identifying common sites involved at first presentation.

METHODS:

Study Design: A multi-centre, cross-sectional observational study**.**

Setting and Study Centres: The study was conducted at eight centres approved by the International Atomic Energy Agency (IAEA) located in six countries: India (Delhi, Chandigarh, and Lucknow), Pakistan (Lahore), Thailand (Bangkok), South Africa (Pretoria), Serbia (Belgrade), and Bangladesh (Dhaka).

Ethics/IRB Approval: Study protocols were approved by the relevant local IRB/ethics committees.

Participants and Patient Eligibility Criteria: The selection of patients and the study referral pathway are outlined in **Tables 1 and Table 2.**

***Inclusion criteria*:** (1) ≥18 years of age; (2) negative HIV test; (3) patients with previous TB who had completed their treatment and been labelled as cured at least 6 months previously; (4) WHO criteria for EPTB7[7,14] with one of the following: a positive culture for *M. tuberculosis*, in any clinical specimen, a positive nucleic acid amplification culture GeneXpert MTB Rif/Assay (Cepheid, Sunnyvale, CA, USA) from any clinical specimen or a histopathological diagnosis of TB.

***Exclusion criteria*:** (1) Pregnant and lactating patients; (2) positive HIV test; (3) history of cancer or undergoing radiotherapy or chemotherapy; (4) receipt of anti-TB treatment at the time of presentation; (5) known multi-drug resistant TB (MDR TB); (6) blood glucose levels ≥11 mmol/l or ≥200 mg/dl); (7) use of systemic investigational drugs; 8) any social condition that the investigator believed would warrant exclusion.

Anti-TB Treatment (ATT): Newly diagnosed EPTB were started on WHO-recommended ATT regimens[15] of 6 months duration, except in patients with bone and CNS involvement, in whom they were continued for 9–12 months based on clinical response.

^{18}F-FDG PET/CT Scans and Procedure: ^{18}F-FDG PET/CT scans were performed according to international guidelines [9]. PET/CT scanners used were General Electric Discovery STE (BGO Detector) with 16 SLice CT Scanner at the Pakistan, India, Bangladesh and Thailand sites and Siemens mCTBiograph, 64-slice PET/CT at the Serbia and South Africa sites. The radiation dose for the ^{18}F-FDG PET/CT scan is approximately 12 millisieverts (mSv) -this level of radiation dose is considered safe.

Interpretation of ^{18}F-FDG PET/CT Scans: Scans were reported as positive or negative. A positive scan was defined as abnormally increased ^{18}F-FDG uptake in a lesion (with CT correlate) which is greater than surrounding background and not explained by normal physiological organ uptake. The increase in metabolic activity was quantified by measuring the standardised uptake values (SUV_{max}). Maximum standardised uptake values (SUV_{max}) are a relative measure of FDG metabolism:

$SUV = \frac{r}{(a'/w)}$ where r = radioactivity concentration (kBq/ml), a' = is the decay-corrected amount of radiolabelled FDG [kBq], and w = weight of patient [g]. A SUV_{max} of ≥2·5 was considered as ^{18}F-FDG PET positive. Scan reports were made available within 24 h to the referring study clinician.

Statistical Analysis Plan: Descriptive statistics were used to summarise patients' characteristics. For continuous variables, median and interquartile ranges were given, and for categorical variables, proportions falling into different categories were calculated. Statistical analysis was performed using Stata version 15 (SE 15 data version, StataCorp, 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

RESULTS:

Study Population:

Figure 1 depicts patient enrolment chart. A total of 358 patients with EPTB (189 females; 169 males) were recruited across the eight centres in six countries from April 2014 to December 2017. Age range was 18–83 years (females: 18–83 years, median 30 years, IQR [23, 48 years]; males: 18–81 years, median 38 years, IQR [27, 54 years]. The geographical origin of study patients is shown in **Figure 2**. Of the 189 female patients, 17 were from Africa, 158 from Asia (India, Pakistan, Bangladesh, and Thailand) and 14 from Serbia. Of the 169 male patients, 8 were from Africa, 152 from Asia, and 9 from Serbia. Clinical features at enrolment are shown in **Figure 3 and Table 3**. There was no difference in anatomical distribution patterns across geographical sites. No adverse effect was observed due to injection of ^{18}F-FDG, during scanning and on followup a week after. scanning.

Baseline Anatomical Distribution of ^{18}F-FDG PET/CT Positive EPTB Sites

Table 4 depicts the anatomical location of PET/CT positive sites and SUV_{max} values in all 358 patients. Of the 358 patients, 350 (98%; 183 female, 167 male) had a positive scan, of whom 118 (33·7%) had a single extrapulmonary site and 232 (66·3%) more than one site (organ). Lymph nodes, skeletal, pleura, and brain were common sites.

Clinical versus PET/CT findings: 110 patients were ^{18}F-FDG PET/CT positive at more body sites than had been noted clinically at first presentation. In 160 patients the suspected clinical site was confirmed as diagnosed clinically with no additional sites involved, while 80 showed fewer sites than had been suspected clinically. **Figure 4** shows an example of a positive ^{18}F-FDG PET/CT scan due to pericardial TB which was missed clinically.

EPTB with concomitant pulmonary TB: 100/358 (28%) EPTB patients had ^{18}F-FDG PET/CT positive sites in the lung. Pulmonary TB (PTB) was not suspected at enrolment in 28 of these. **Figure 5** shows an example of missed pulmonary disease in a patient initially diagnosed as having lymph node EPTB.

^{18}F-FDG PET/CT negative scans: 8/358 patients showed low-grade uptake below the positive cut-off (SUV_{max} <2·5) and were classified as scan negative. In two patients, there was diffuse leptomeningeal disease (SUV_{max} 1·8 and 2·1 respectively), and one of the two had a ring-enhancing lesion in the left temporal region. Four had lesions in the spine and hips (SUV_{max} 1·7–2·1), and two had abdominal TB, with low-grade metabolism noted in ascitic fluid, thickened omentum and mediastinal lymph nodes (SUV_{max} less than 2·5).

DISCUSSION:

This study is the largest cross-sectional observational cohort PET-CT study from six countries of HIV-negative adult patients with a diagnosis of EPTB. ^{18}F-FDG PET/CT scans have been performed at first clinical presentation. The data obtained further inform the current dialogue and debate on the clinical usefulness of PET/CT as an imaging tool for defining extent of disease and aiding management. There are several notable findings from our study:

First, ^{18}F-FDG PET/CT scan detected EPTB sites in 98% of EPTB cases enrolled.

Second, more extrapulmonary active sites were detected compared with the number suspected clinically at first diagnosis of EPTB. This study reaffirms the spatial and temporal heterogeneity of TB lesions that has been previously demonstrated in smaller single centre studies.

Third, pulmonary involvement was more frequently found than was considered at first clinical presentation. Our study detected more pulmonary sites than were suspected at first admission, thereby raising again the vexed issue of definitions traditionally used for clinical presentations of TB. These have been generally classified by WHO as PTB and EPTB,[7] the former being assumed to be more common. A patient with both PTB and EPTB is classified by WHO as a case of mixed PTB and not EPTB, while intrathoracic TB lymphadenitis or pleural effusion constitutes a case of EPTB. EPTB specifically refers to TB involving organs other than the lungs, such as pleura, lymph nodes, gastrointestinal tract, urogenital tract, bones and joints, liver, spleen, meninges, and brain (examples from our study are shown in Figures 4,5,6 and 7). Global estimates of the incidence, prevalence, and treatment outcomes of EPTB are inaccurate and WHO[1] acknowledges that there is a large undiagnosed burden of EPTB, and current estimated data are unreliable, due to current definitions of EPTB and PTB.

Our study focussed on HIV-negative patients in the first instance to exclude confounding factors of co-morbidities and co-infections. However, in difficult-to-treat clinical situations such as EPTB in HIV patients, detection of extrapulmonary lesions may be particularly useful since these could be due to various infectious or non-infectious complications of HIV/AIDS. In these individuals obtaining tissue or fluid for analysis from cryptic sites may not always be possible. Detection of active inflammatory sites by ^{18}F-FDG PET/CT offers opportunities for identifying disease sites and obtaining tissue biopsies for microbiological, molecular investigations and for understanding EPTB pathogenesis. In animal TB model studies an increase in ^{18}F-FDG activity, reflected as SUV_{max} values, was found to be proportional to the number of *M. tuberculosis* bacilli in caseating granulomas.[19] However PET/CT findings only reflect inflammatory activity and do not identify the underlying specific microbial or other causes.

Our study was observational and there are several limitations to the acquisition and interpretation of our data. PET/CT technology has been in use for more than a decade for scanning cancer patients, albeit only in large tertiary centres. ^{18}F-FDG PET/CT scans by design detect glucose metabolism and therefore are not specific for the detection of TB lesions and cannot differentiate between TB infection, co-infection and tumours.[24] Detection of brain tuberculomas and meningeal involvement is difficult since, as our data show, the normal brain grey matter shows relatively high uptake due to cerebral cortical metabolic activity. Furthermore, if the lesions are small ($\leq$1 cm), they will very likely be missed due to partial volume effects. Larger and metabolically more active lesions are easily detected. Interpretation of PET/CT of kidneys and urinary bladder is limited since these organs contribute to physiological ^{18}F-FDG tracer excretion and the intensity of uptake is sufficiently high to mask small lesions. ^{18}F-FDG PET/CT therefore has low sensitivity in detecting small EPTB lesions in the kidney and urinary bladder, and conventional imaging should be used to identify lesions when urological TB is suspected. An important area where the role of ^{18}F-FDG PET/CT requires evaluation is childhood TB. Diagnosis and management of EPTB in this age group remains challenging, and further work is needed to address this. Currently, most cases of childhood TB are missed, while in diagnosed cases empirical treatment is instituted. Obtaining non-invasive clinical samples in children is difficult and microbiological diagnosis of childhood EPTB requires tissue biopsy; even then microbiological confirmation is achieved in only a small proportion of treated cases. ^{18}F-FDG PET/CT is now being assessed for the detection of TB lesions and assessment of disease activity in children.[25]

Accurate microbiological diagnosis of EPTB is hindered by the difficulty in obtaining clinical samples from relatively inaccessible sites. Sentinel autopsy studies from Africa have shown a significant undiagnosed burden of EPTB and PTB in adults and children antemortem.[26-29] Clinico-pathological discrepancies have been identified in identifying the underlying cause(s) cause of death in adults with many missed cases of TB.[28] A recent autopsy study from Mozambique[29] of 223 deaths (57 maternal deaths, 112 adults and 54 children) showed that *Mycobacterium tuberculosis* DNA can be identified using molecular methods despite absence of TB lesions on histology. In a study of 150 individuals suspected of having cancer, biopsy of pulmonary nodules localised by PET/CT identified ten cases of active TB, with nine having a maximum SUV above the threshold of 2·5.[16] There is a need for accurate imaging to localise sites of disease activity which can be targeted to obtain clinical samples for microbiological and pathological analyses.

Currently there are several ongoing studies on the application of PET/CT and other modalities for insight into pathogenesis.[30] These include studies on spectrum of latent Tb infection, subclinical

disease and paucibacillary disease. Studies of EPTB patients with sequential serial scans during the course of treatment may provide further information on the usefulness of PET-CT in predicting or monitoring response to therapy, defining cure, and detecting relapse.[30]

The current challenge for TB-specific PET/CT is the development of new *M. tuberculosis*-specific tracers targeting high-density surface epitopes, gene targets, or metabolic pathways. A recent study developed a multidrug treatment model in rabbits with experimentally induced TB meningitis and performed serial dynamic ^{11}C-rifampin PET over 6 weeks, demonstrating that rifampicin penetration into infected brain lesions is limited and spatially heterogeneous and decreases rapidly as early as 2 weeks into treatment.[23] These data demonstrate the proof of concept of ^{18}F-FDG PET/CT as a clinically translatable imaging tool for measurement of intralesional antimicrobial distribution in infected tissues that might be useful in establishing individualised treatment regimens.

Translation of ^{18}F-FDG PET/CT into a diagnostic tool for resource-poor countries will remain a vexed issue and challenging. The technology is relatively expensive compared with some conventional imaging modalities. Innovation will be needed to reduce the cost and complexity if it is to be used as a tool in patients with high-risk or confirmed EPTB. It is likely that PET/CT will be useful in Western countries with a low TB incidence and in tertiary care facilities in high TB endemic areas and research facilities. The limited availability of PET/CT and limited facilities for production of isotope and high cost (around US$ 800-1000 per scan) make the use of PET/CT in developing countries, unlikely in the near future. Thus, PET/CT currently will remain a research tool for TB and will not have any significant impact on the day to day management of the majority of patients in high TB endemic countries.

CONCLUSIONS:

^{18}F-FDG PET/CT shows promise as a useful imaging technique for detecting the extent of EPTB disease and detects more extrapulmonary and pulmonary active sites compared with the number suspected clinically at first diagnosis of EPTB. The potential of ^{18}F-FDG PET/CT in further elucidating the spectrum of disease, the pathogenesis of EPTB, and monitoring the effects of treatment on active lesions over time, including in HIV-infected, paediatric, and MDR-TB patients, requires longitudinal cohort studies of those with microbiologically confirmed and clinically suspected cases, twinned with biopsy and molecular studies over longer periods.

AUTHOR ROLES:

Jamshed Bomanji, Thomas NB Pascual, and Alimuddin Zumla developed the concept and initiated discussions which led to the formation of the consortium. All authors developed and helped finalise the study protocols. Rajnish Sharma, Bhagwant Rai Mittal, Sanjay Gambhir, Ahmad Qureshy, Shamim Momtaz Ferdousi Begum, Mike Sathekge, Mariza Vorster, Dragana Sobic Saranovic, and Pawana Pusuwan led the study sites. Sobhan Vinjamuri conducted quality assessment of imaging data. Olga Morozova collated the CRFs. Vera Mann performed the data analyses. Jamshed Bomanji led the imaging studies, and with Alimuddin Zumla, Diana Paez, and Thomas NB Pascual developed the first and subsequent drafts of the manuscript. All authors contributed to data interpretation and writing of the manuscript.

CONFLICTS OF INTEREST: All authors declare no conflicts of interest.

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KEY POINTS:

QUESTION:

What is the clinical usefulness of ^{18}F-FDG PET/CT scan, an imaging tool, for localising active disease sites, determining extent of disease in adult HIV-negative patients with Extrapulmonary TB (EPTB)?.

PERTINENT FINDINGS:

First, ^{18}F-FDG PET/CT scan detects EPTB sites in 98% of EPTB cases enrolled.

Second, more extrapulmonary active sites were detected compared with the number suspected clinically at first diagnosis of EPTB.

Third, pulmonary involvement was more frequently found than was considered at first clinical presentation.

IMPLICATIONS FOR PATIENT CARE

^{18}F-FDG PET/CT shows promise as a useful imaging technique for defining the extent of EPTB disease, and aiding diagnosis at first presentation.

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LEGENDS TO FIGURES

Figure 1: Patients demographics and number of active lesions on PET-CT scan

Figure 2: Study population: Geographical distribution and gender

Figure 3: Clinical features at first enrolment

Figure 4: ^{18}F-FDG PET/CT scan showing disease involvement of the pericardium missed at presentation.
Pericardial activity is demonstrated (large blue arrow), as are lymph node stations above and below the diaphragm (small blue arrows). Normal metabolic activity is noted in the liver (open arrow, blue) and excreted activity is observed in the kidneys (open arrow, red) and urinary bladder (arrowhead, red).

Figure 5: ^{18}F-FDG PET/CT scan showing nodal EPTB and unexpected pulmonary tuberculosis.
Whole-body projection is shown.
The yellow arrows indicate, from top to bottom, ^{18}F-FDG uptake in the bilateral cervical nodes, axillary nodes, subcarinal nodes, and retroperitoneal nodes. Small white arrows indicate pulmonary TB.

Figure 6:
^{18}F-FDG PET/CT scan showing nodal, bone and muscle involvement from EPTB.
(A) Whole body projections of ^{18}F-fluorodeoxyglucose (FDG) PET/CT scan shown with corresponding (B) transaxial fused slices (PET and CT) at areas of interest
(A) ^{18}F-FDG PET- revealing intense ^{8}F-FDG avidity in the L1-L2 vertebrae (blue arrow), with bilateral psoas abscess (B) (red arrows) and few mediastinal and cervical lymph nodes (small black arrows).

Figure 7: ^{18}F-FDG PET/CT scan showing nodal and acetabular EPTB.
Whole body projections from ^{18}F-fluorodeoxyglucose (FDG) PET scans are shown.
Panel A, shows (large black arrows indicate^{18}F-FDG uptake in mediastinal nodes; small black arrows, indicate uptake in right iliac nodes;
Panel B, red arrow, indicates involvement of right posterior acetabular bone -shown in axial section).

LEGENDS TO TABLES

Table 1: **Clinical guide used to assist in the diagnosis of extrapulmonary tuberculosis (EPTB)**
(Modified from WHO EPTB management guidelines -ref 7)

Table 2: Clinical Selection Criteria and Referral Pathway Algorithm:

Table 3: Clinical and Laboratory Characteristics of 358 Patients at Enrolment.

Table 4: Baseline first PET/CT scan: Positive ^{18}F-FDG PET/CT extrapulmonary disease sites in 358 patients.

Figure 1:

Patients demographics and number of active lesions o PET-CT scan.

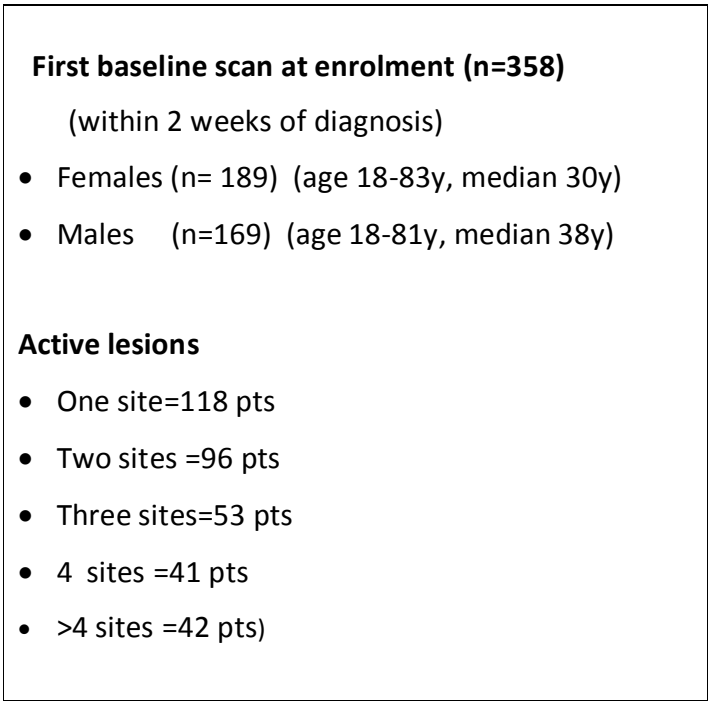
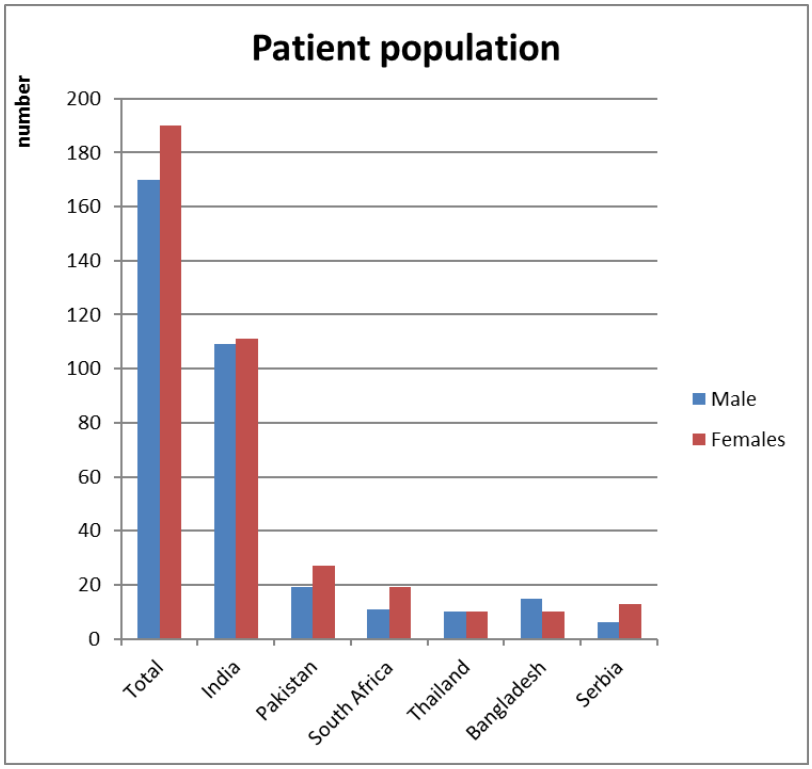


Figure 2:

Study population: Geographical distribution and gender



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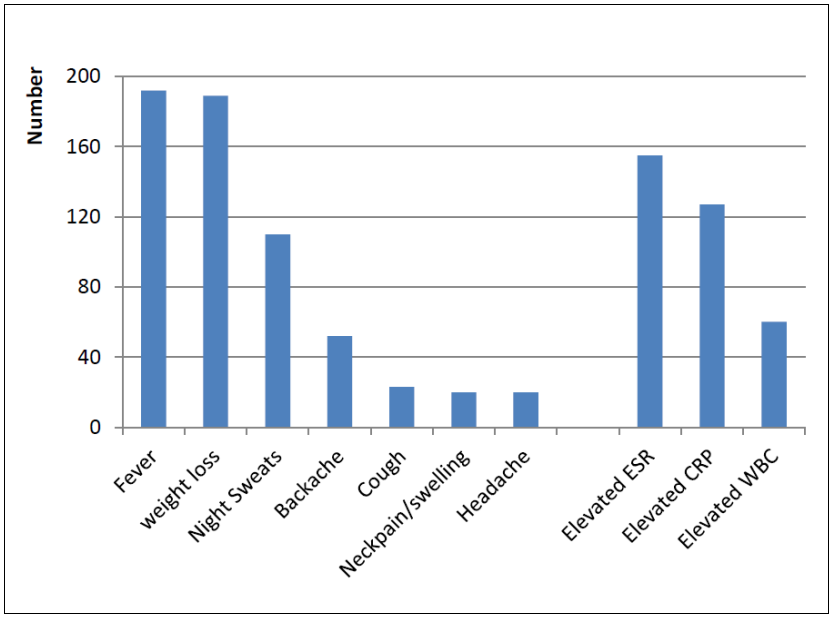
Clinical Features at first enrolment



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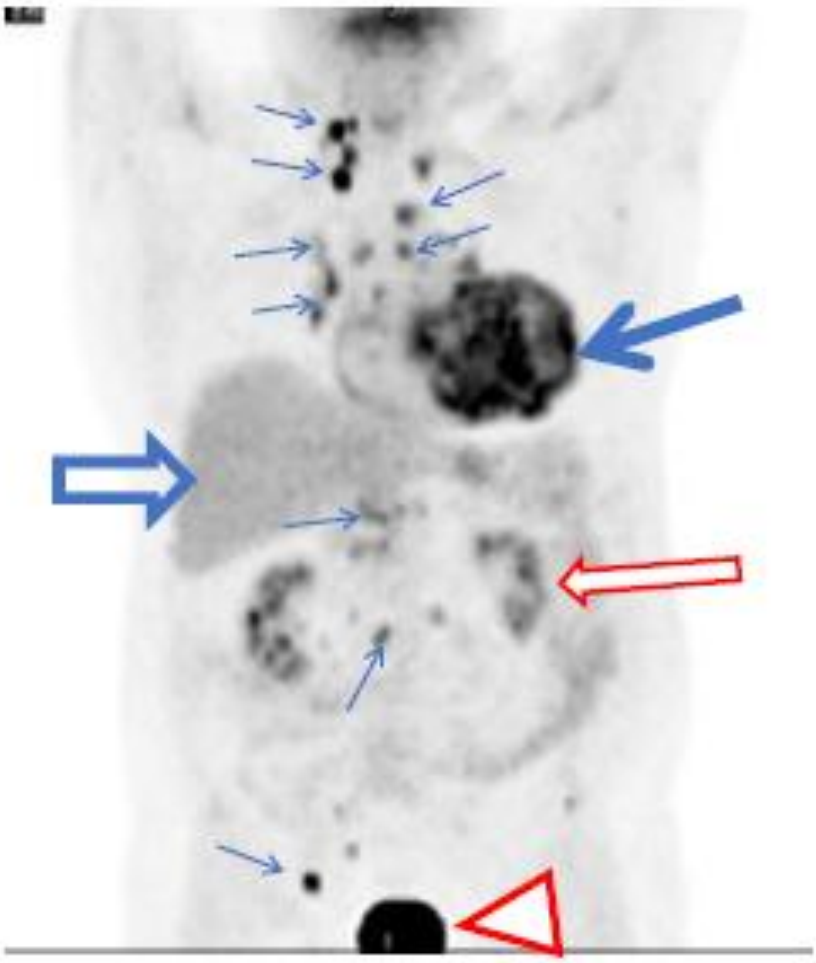

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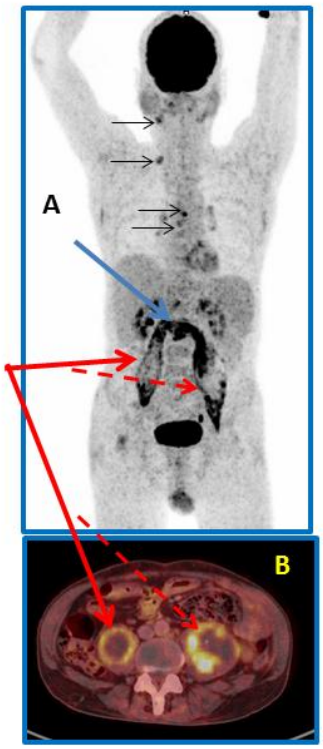

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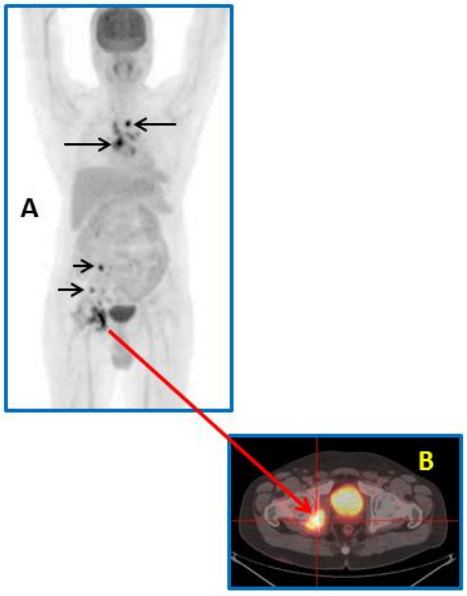

Figure 7

Table 1:

Clinical guide used to assist in the diagnosis of extrapulmonary tuberculosis (EPTB) (Modified from WHO EPTB management guidelines ref 7)

Suspect EPTB in patients with:

- Cough for 2 weeks or more
- Unintentional weight loss with
  - Night sweats and
  - Temperature >37.5 °c or feels feverish
- Breathlessness (pleural and pericardial effusion effusion)
- Swellings in neck or armpit or abdomen
- Chronic headache, vomiting or altered mental state or meningeal signs
- Symptoms of recurrent urinary tract infections but not responsive to antibiotics
- Chest X-ray or CT
  - Miliary or diffuse shadowing
  - Large heart (especially if symmetrical and rounded)
  - Pleural effusion
  - Enlarged lymph nodes inside the

Determine Clinical Features:

- Lymph nodes swelling in the neck or armpits (if present with other types of EPTB it may provide clue/sample to confirm the diagnosis)

(Possible tuberculosis lymphadenitis)

- Signs of fluid in the chest
  - absent breath sounds
  - reduced chest wall movement
  - dull to percussion

(Possible tuberculosis pleural effusion)

Signs of fluid around the heart

- heart sounds distant
- swollen legs and/or abdomen
- neck and hand veins distended with arm held above the shoulder

(Possible tuberculosis pericarditis)

Signs of meningitis

- neck stiffness
- confusion
- abnormal eye movements

(Possible tuberculosis meningitis)

Table 2:

Clinical Selection Criteria and Referral Pathway algorithm:

1. Patient presenting/referred to Respiratory/TB clinic with chronic cough of more than 2 weeks, weight loss, night sweats, fever, SOB, headache, altered mental state, pain in bone/joint, and a lump or mass. History of close TB contact, clinician's clinical suspicion of EPTB for any other reason.
2. EPTB suspected by local Chest Physicians.
3. Clinical assessment, chest radiography, Tuberculin skin test, HIV test, cultures, GeneXpert MTB Rif/assay on clinical samples, and other investigations as clinically indicated to confirm presence of *Mycobacterium Tuberculosis*
4. Except for suspected TB meningitis, no treatment initiated before ^{18}F-FDG PET/CT scan.
5. Consent obtained.
6. Patients with high likelihood of EPTB on clinical grounds and confirmed -ve HIV status, referred to Nuclear Medicine Imaging Department for ^{18}F-FDG PET/CT scan

7. **^{18}F-FDG PET/CT scan** performed as soon as possible after referral (immediately for TB meningitis suspects or those critically ill)
6. Scans reported locally and sent to referrer/TB clinic within 24hrs
7. Results of other Investigations available
8. CRF completed after results.
9. Anti-TB treatment initiated
10. CRF and Images loaded centrally to IAEA database (Austria)

Table 3:

Clinical and Laboratory Characteristics of 358 Patients at Enrolment

Gender and Age	**All Participants (n = 358)**
Males	169 (47%)
Females	189 (53%)
Median age (range) - years	33 (18-83)
History of previous tuberculosis (stopped TB treatment 6 months previously)	28 (7.8%)
Investigations	
Positive Sputum culture for *M. tuberculosis*	28 (7.8%)
EPTB specimen *M. tuberculosis* culture positive (eg ascites, CSF, pleural, synovial fluid)	75 (20.9%)
M. tuberculosis biopsy positive	180 (50.2%)
Elevated white cell count- no./total no (%)	60 (16.8%)
Elevated ESR- no./total no (%)	155 (43.3%)
Elevated CRP- no./total no (%)	126 (35.2%)
Positive ^{18}F-FDG PET/CT scan	350/358 (97.8%)

Table 4:
Baseline first PET/CT scan: Positive ^{18}F-FDG PET/CT extrapulmonary disease sites in 358 patients

Anatomical site	PET/CT positive		SUV_{max}		
	Number of patients	%	Range	Mean	Median
Brain	34	9·5%	4–19	10	10
Cardiac	2	0·6%	3·2–13·8	8·5	8·5
Pleura	34	9·5%	2·6–17·7	7·1	6·7
Muscles*	10	2.8%	2·8–15·9	7·4	6·7
Liver	7	2·0%	3·8–23·3	12·4	13·1
Spleen	11	3·1%	2·7–20·1	5·2	3·5
Gastrointestinal tract	8	2·2%	3·4–17·4	4·8	9·3
Urogenital tract	7	2·0%	2·6–16·9	9·7	10
Bone	151	42·2%	2·5–32·8	9·5	8·1
Lymph nodes	225	62·8%	2·8–32·3	10·7	9·9
Cervical	108	30·2%	2·6–22·3	8.2	7.2
Supraclavicular	69	19·3%	3·1–24·4	8·4	6·9
Axillary	51	14·2%	2·5–20	7·1	5·8
Mediastinal	152	42·4%	2·5–21·2	6·9	5·9
Hilar	70	19·6%	2·7–23	6·3	5·3
Retrocrural	9	2·5%	2·7–15·7	6·4	5·3
Retroperitoneal/mesenteric	55	15·4%	3–16·1	7·0	6·4
Pelvic	28	7·8%	2·5–21·5	6·9	6·4
Inguino-femoral	18	5·0%	2·5–11·5	5·7	5·0
Other sites**	21	5·9%	2·5–32	7·5	5·7

* Iliopsoas 4 patients, pectoral muscle 1 patient, posterior intercostal 1 patient, gluteal 2 patients, thigh 1 patient, obturator internus 1 patient

** Paravertebral mass/collection 12 patients (SUV_{max} 2·5–9·8), adrenals 3 patients (SUV_{max} 3·9–6·5), joint effusions 3 patients (SUV_{max} 12·9–32), endometrium/ovary 2 patients (SUV_{max} 4·1–7·1), focal bone marrow lesion 1 patient (SUV_{max} 5·2)

Note: Some patients had more than one organ involved
SUV = Standardised uptake values. Maximum standardised uptake values (SUV_{max}) are a relative measure of FDG metabolism.

$$SUV = \frac{r}{(a'/w)}$$

r = radioactivity concentration (kBq/ml)
a' = is the decay-corrected amount of radiolabelled FDG (kBq)
w = weight of patients (g)