Roles and Limitations of FDG-PET in Pediatric Non-Hodgkin Lymphoma

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Abbreviated title: FDG-PET for pediatric NHL

No financial disclosure. No conflict of interest

Abstract

Purpose of the Report:

The usefulness of FDG-PET in pediatric Hodgkin lymphoma (p-HL) has been well demonstrated; however, pediatric non-Hodgkin lymphoma (p-NHL) has distinct characteristics from p-HL and adult NHL. We assessed roles of FDG-PET in p-NHL.

Materials and Methods:

Nineteen patients with p-NHL underwent 80 scans. Scans for staging (Group A, n=6) and response assessment (Group B, n=42) were compared with conventional imaging modalities (CIM). Scans within Group B for end-chemotherapy assessment (subgroup B+, n=11) and for post-therapeutic surveillance (Group C, n=32) were analyzed for diagnostic performance.

Results:

In Group A, PET and CIM demonstrated comparable. In Group B, PET diagnoses were concordant with CIM in 21 and discordant in 11. Of the discordant cases, PET suggested remnant lesions in 5 cases while CIM suggested in 6. PET modified therapeutic strategy in 4 cases by detecting new extra-nodal lesions. In subgroup B+, sensitivity, specificity, and accuracy for predicting relapse were 50%, 71%, and 64%, respectively. In Group C, sensitivity, specificity, and accuracy were 100%, 87%, and 88%, respectively, but positive predictive value was 33%.

Conclusions:

The role of FDG-PET in p-NHL may be limited, unlike with p-HL or adult NHL. Nevertheless, FDG-PET may serve complementarily in detecting unexpected lesions that can emerge in p-NHL.

Keywords

F-18 FDG; PET; pediatrics; lymphoma; Non-Hodgkin

Introduction

Lymphoma is a common malignant disease in children, and has a different presentation from lymphoma in adults, especially in non-Hodgkin lymphoma (NHL). The majority of children with NHL have high-grade tumors. The presentation of pediatric NHL (p-NHL) is also different from that of pediatric Hodgkin lymphoma (p-HL). The tendency toward extra-nodal involvement is common in p-NHL but uncommon in p-HL.[1] Overall survival rate is higher than 90% in p-HL and approximately 70% in p-NHL; however, prognosis is generally poor with relapsed disease in p-NHL, especially in cases with initial intensive multi-agent chemotherapy.[2]

The utility of F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) or PET/computed tomography (CT) using for children with lymphoma has yet to be sufficiently discussed, as compared to the extensive studies that have proven the considerable utility of FDG-PET in adult lymphoma.[3] Recently, several articles have indicated the value of FDG-PET or PET/CT for pediatric lymphoma, and reported that disease staging and clinical management could be modified in 10–27% of cases.[4-8] However, in most published studies the number of patients with p-HL was larger than that of patients with p-NHL. Indeed, p-NHL represents approximately 60% of pediatric lymphomas with p-HL representing the remainder in the United States. Furthermore, p-HL is much rarer in Asian populations.[9] Therefore, the patient population studied was not entirely representative of the overall incidence of p-HL and p-NHL. The European Network of Paediatric Hodgkin's Lymphoma consists of over 100 treatment centers throughout the

European Union, and large-scale multicenter prospective studies about p-HL are underway.[10] In contrast, there are still only a few studies that discuss the role of FDG-PET in p-NHL.[11] Shankar et al. stated in their review article that unlike the validated or estimated utility in p-HL, the role of FDG-PET may be limited in p-NHL and its utility for response assessment has not been settled.[12] Thus, it is considered preferable that the role of FDG-PET in p-NHL should be discussed separately from p-HL because of their different clinical manifestations and prognoses. Therefore, we evaluated the performance of FDG-PET in p-NHL for initial staging, response assessment during chemotherapy, and surveillance for relapse.

Materials and Methods

Patients and study design

Between February 2000 and June 2010, 19 patients (4 females and 15 males) under 20 years of age (range, 2–18, median age at the time of initial study, 10) who had histologically-confirmed NHL underwent a total of 80 FDG-PET (or PET/CT) examinations at our institute. The histological tumor subtypes were Burkitt lymphoma in 6 patients, DLBCL in 5 patients, lymphoblastic lymphoma in 5 patients, ALCL in 2 patients, and Natural Killer/T cell lymphoma in one patient. The stage of disease was evaluated according to the Murphy classification.[13] Patients' profiles including their treatment protocol and their outcome are given in Table 1. All studies involved daily clinical diagnostic checkups, and written informed consent was obtained from all patients along

with their parents as requested by our ethics committee. The examinations were divided into one of the following three groups, according to the purpose of the PET scan (Fig. 1).

Group A: PET examinations for initial staging were assigned to this group. It included scans acquired after excision biopsy as long as they took place prior to the commencement of chemotherapy. This group comprised 6 studies in 6 patients. The contribution to staging was assessed through a comparison with conventional imaging modalities (CIM) such as ultrasound sonography, CT, or magnetic resonance imaging (MRI).

Group B: PET examinations during or at the completion of chemotherapy were assigned to this group and included scans acquired after any number of cycles of chemotherapy. Examinations acquired during or after salvage therapy were also included. This group comprised 42 studies in 12 patients. Concordance or discordance in comparison with CIM and the influence on treatment plans were surveyed.

We defined a further subgroup, termed "subgroup B+", which consisted only of examinations for response assessment at the time of completion of remission-induction chemotherapy, excluding scans during or after salvage therapy. Subgroup B+ comprised 11 studies in 11 patients. In this subgroup, PET scans were acquired 6–46 days (average 19 days) after completion of the scheduled chemotherapy regimen. Diagnostic performance at predicting relapse was estimated by calculating the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

Group C: This group included PET scans acquired for follow-up surveillance for recurrence after the achievement of complete remission and comprised 32 studies in 13 patients. Diagnostic performance at detecting relapse was estimated.

PET or PET/CT scanning

The administered dose of FDG was determined in accordance with the revised European Association of Nuclear Medicine (EANM) pediatric dosage card after 2008.[14] Earlier than the publication date administered activity concentrations were approximately 6 MBq/kg (0.16mCi/kg) for 2-dimensional (2D) mode acquisition and approximately 3 MBq/kg (0.08mCi/kg) for 3-dimensional (3D) mode acquisitions. Patients received intravenous administration of FDG after fasting for at least 4 hours, and whole-body PET images were acquired approximately 50 minutes later.

Eighteen studies were performed using a combined 3D PET/CT scanner (Discovery ST Elite, GE Healthcare, Waukesha, WI), which integrates a bismuth germinate crystal PET system with a 16-slice multi-detector-row CT. Fifty-seven studies were performed using a 2D PET scanner (Advance, GE Healthcare, Waukesha, WI), and the remaining 5 studies were performed using a 3D PET scanner (C-PET plus, ADAC, Philadelphia, PA). The extent of image acquisition was usually from skull to upper thighs. Entire legs and arms were included when involvement was suspected. The need for sedation during acquisition was assessed by experienced pediatric physicians, and undertaken with the agreement of the parents.

Standard of reference

In the staging of lymphoma, clinical staging as a standard of reference was determined using all imaging modalities, tissue diagnosis, bone marrow biopsy, and cerebrospinal fluid cytology.

For the chemotherapy response assessment and recurrence surveillance cases, all patients underwent regular follow-up for at least 6 months with the exception of those who died of progressive disease within their follow-up period. The diagnoses of relapse after remission required confirmation by biopsy and histological examination. However, when tumors did not show remission in spite of chemotherapy, tumor enlargement at subsequent images was regarded as an evidence of tumor relapse. When there were no abnormal image findings suggesting relapse during their follow-up period, they were considered to be no evidence of recurrent disease. Spontaneous disappearance of FDG uptake at subsequent scan was also considered benign reactive change.

Interpretation and data analysis

Interpretation of FDG-PET (or PET/CT) images was performed by consensus of at least two experienced nuclear medicine physicians, together with all available clinical information such as patients' history, physical examination, chemotherapy protocol, and prior imaging data. Interpretation criteria were determined according to those provided in the consensus guidelines of the Imaging Subcommittee of the International Harmonization Project in Lymphoma.[15] In addition to the consensual criteria, we considered homogeneously increased thymus uptake with bi-lobed or inverted-"V" shape as an

exclusion of positive findings, since such uptake is ordinarily observed physiologically or as thymic rebound after chemotherapy in children and adolescents. Interpretation of CIM images was performed by experienced radiologists, together with all available clinical information. Interpretations were based on morphological abnormalities and changes.

Results

Group A

The results of initial staging are given in Table 2. FDG-PET did not contribute to up- or down-staging. As summarized in Table 3, PET staging results were comparable with those by CIM in all studies.

In two cases, FDG-PET did not result in an accurate staging. Although these cases were both diagnosed as stage III by FDG-PET and CIM, the final determined stage was IV as a result of positive bone marrow biopsy in one case and positive cerebrospinal fluid cytology in the other. In the case of bone marrow involvement (No. 5), FDG-PET showed diffuse moderate uptake in bone marrow, which was read as equivocal since it was difficult to distinguish tumor involvement from physiological hypermetabolic bone marrow.

Group B

The judgments about the achievement of remission were concordant with the findings obtained by CIM in 21 studies and discordant in 11 studies. In the remaining 10 studies, CIM findings were not available. Among the 21 concordant cases, both methods suspected

residual tumor in 11 cases, and suggested the achievement of remission in 10 cases. Among the 11 discordant studies, PET alone suspected residual tumor in 5 cases, and in the other 6 cases, PET suggested the achievement of complete remission despite CIM results that showed a residual lesion (Fig. 2). It was difficult to determine which was predominant, but PET results contributed toward the alteration of treatment strategy in 4 cases, as listed in Table 4; PET detected additional bone involvement after chemotherapy that resulted in additional radiotherapy in 2 cases; PET showed recurrent bone and neural involvement that led to the withdrawal of standard therapy in the other 2 cases (Fig. 3). As shown in Table 4, two of these four cases were confirmed by biopsy or cytology. The remaining two cases (No. 3 each) were not, because she had already experienced recurrence repeatedly by that time. Tumor biopsies just after FDG-PET were not held except the abovementioned two additional lesions, which also made it difficult to consider which modality was predominant in this group.

Subgroup B+

All 11 patients (No. 1-4, 8-14) also underwent CT or MRI as an end-of-chemotherapy assessment. FDG-PET showed abnormal uptake in four patients. Of these, one patient (No. 2), whose PET finding indicated residual abdominal tumor, turned out to be positive by cerebrospinal fluid cytology and to have sciatic nerve involvement afterward. Another patient (No. 13) was found to have new bone involvement in her distal femur despite the disappearance of the primary abdominal tumor. Both of their diseases deteriorated thereafter. In the remaining two patients (No. 3, 12), FDG-PET showed residual uptake in

the primary tumor, however the tumor remained in remission until the end of their follow-up period. For patient No. 12, who had a submandibular mass at the beginning of therapy, CT at the end of therapy showed a nonspecific lymph node, indicating that the CIM result was true-negative and the PET result was false-positive.

FDG-PET showed no significant abnormal uptake in 7 patients. Of these, 5 patients (No. 4, 8, 10, 11, 14) maintained remission without relapse. For patient No. 11, the CT scan showed a small residual tumor in the anterior mediastinum, suggesting that CIM showed a false-positive and PET showed a true-negative result. The remaining 2 patients relapsed afterward in spite of PET-negative results. In one patient (No. 9), who had lymphoma of thymus, FDG-PET at the end of chemotherapy showed only physiological uptake in the thymus, but focal intense uptake superimposed on physiological thymic uptake was observed 8 months later and the lesion was resected and proven to be in relapse (Fig.4). This patient was also found to have bone marrow involvement, and died as a consequence of the disease 17 months after the end-therapy assessment scan. In the other patient (No. 1), who had CNS involvement, tumor relapse was discovered in the testis 23 months after the scan.

Thus, all the 4 cases that experienced relapse were confirmed by either histology or cytology in this subgroup. As summarized in Table 5, the sensitivity, specificity, PPV, NPV, and accuracy of FDG-PET for predicting relapse were 50%, 71%, 50%, 71%, and 64%, respectively. CIM showed the same diagnostic performance, although the individual results were not entirely identical.

Group C

Among 32 studies performed, two (6.3%) indicated a relapse, both of which were confirmed histologically (No. 1, 9). PET identified the relapsed lesions in both cases, and there were no cases PET failed to detect a relapse. There were 4 false-positive results; the lesion was resected and proved to be lymphadenitis in one case, and no further accumulation was observed in subsequent studies of the remaining three cases. The other 26 studies showed no abnormal uptake and to date no relapse has occurred. Moderate uptake was seen in an area corresponding to the thymus in several studies, but these incidences were regarded as physiological. Taken together, the sensitivity, specificity, PPV, NPV, and accuracy for relapse were 100%, 87%, 33%, 100%, and 88%, respectively, as summarized in Table 6.

Discussion

FDG-PET is acknowledged as being superior to other imaging modalities for the evaluation of malignant lymphoma. However, in the present study for p-NHL, the performance of FDG-PET was not as satisfactory as was expected based on prior experiences reported in the literature.

In the present study, when used for initial staging, FDG-PET demonstrated no contribution to up- or down-staging compared with CIM. This may be because all patients except one with primary cutaneous lymphoma were in stage III or worse. In p-NHL, unlike p-HL or adult NHL, most patients present at the hospital in an advanced stage and tend to

have extensive disease.[2] CIM are usually sufficient to detect such lesions. Depas et al. examined the initial staging of 19 pediatric patients (14 with p-HL and 5 with p-NHL) and observed discordance from conventional methods in three patients, none of whom had p-NHL.[6] Amthauer et al. studied the initial staging of six p-NHL patients, and reported the detection of additional nodal lesions in half of the patients, but resulting in the up-staging of only one patient.[11] In addition, Murphy stage IV is described as the presence of bone marrow and/or CNS involvement.[13] In the present study, FDG-PET did not result in correct up-staging of two cases because of undetected microscopic bone marrow and cerebrospinal involvement. Therefore, in p-NHL, our preliminary data suggest that the clinical role of FDG-PET for initial staging is limited; furthermore, it appears difficult to justify the omission of bone marrow biopsy and cerebrospinal fluid cytology even when PET shows negative results. Nevertheless, FDG-PET may be helpful for correct up-staging, for example, when massive extra-nodal bone marrow or CNS involvement is also present, as such cases were encountered in the present study for the scans acquired during chemotherapy.

When FDG-PET was acquired during or at the end of chemotherapy, several results were obtained that were discordant from CIM, contrary to the findings with the initial staging group, in the present study. As for the cases where PET alone indicated negative, the discordance was thought to be influenced by the fact that FDG uptake mainly reflected biological activity dependent upon glucose metabolism while CIM simply represented morphological changes. These changes were not synchronous. Decreased FDG uptake often occurs soon after the initiation of chemotherapy and precedes tumor volume reduction.

Many studies have demonstrated that FDG-PET acquired in the early cycles of chemotherapy is superior to CT in predicting the effects of therapy.[16] However, Terasawa et al. meta-analyzed the prognostic accuracy for interim response assessment and concluded that it was a reliable test for HL but remained unproven for NHL.[17] Therefore, we caution against concluding that the disappearance of FDG uptake represents tumor cell disappearance and a desirable outcome in p-NHL. As for the cases where PET alone indicated positive, the discordance was presumed to be because of several reasons. First, tumor necrosis and inflammation after chemotherapy may be causes of "false" positive uptake, although no case was confirmed histopathologically. Riad et al. noted that such phenomenon frequently occurred in Burkitt lymphoma, based upon their surgically validated experiences.[18] Second, unexpected relapses were identified as a new "true" positive uptake in several cases. It is important to note that more than 90% of p-NHL cases have high-grade tumor and aggressive behavior.[2] Patients with chemotherapy-resistant lymphoma tend towards rapid progressive relapse.[19] FDG-PET would be an effective modality for detecting such lesions. We presume that the discordant positive uptake arising from these reasons may be one of the distinct FDG-PET imaging characteristics of p-NHL when compared to p-HL.

The results of FDG-PET for end-of-therapy response assessment in p-NHL may not be considered favorable. From the results, the likelihood ratio was calculated as 1.75. By contrast, in p-HL, Furth et al. examined 40 patients and they reported that the sensitivity, specificity, PPV, NPV, and accuracy of the end-therapy response assessment were 100%, 78%, 25%, 100%, and 79%, respectively, with the likelihood ratio of 4.5.[10] They concluded

that in response assessment of p-HL patients, those with a negative PET result would have an excellent prognosis, while those with a positive result would have an increased risk for relapse. As compared with their results for p-HL, the present study of p-NHL showed a lower likelihood ratio. The sensitivity and NPV were lower in our population. Relapse of disease occurred even in the PET-negative cases. Mody et al. studied 26 patients with p-NHL for end-of-therapy response assessment and reported that among four patients with a negative PET result, there were two patients who relapsed within 12 months.[20] The present data suggest that the role of FDG-PET for end-of-therapy response assessment may be limited, and negative PET results may not necessarily imply a favorable outcome in p-NHL, unlike those in p-HL where several studies have demonstrated the utility of such a finding. The International Harmonization Project provided updated guidelines on the use of PET and stated that it was essential for the post-treatment assessment of DLBCL and HL; however, in pediatric cases, NHL could have different characteristics and distinct histological subtypes from NHL in adults.[3]

For routine surveillance after complete remission, FDG-PET is currently not recommended.[3] In p-HL, Levine et al. and Meany et al. found that PET was sensitive but not specific for post-treatment evaluation with a strong NPV (100%) but poor PPV (11–18%).[21, 22] In the present study for surveillance of p-NHL, we also found a low PPV (33%). Several benign conditions such as post-therapeutic inflammation or physiological activities are liable to cause false-positive results in pediatric patients. FDG accumulation into rebound thymic hyperplasia is common among children and adolescents. The accumulation into activated brown adipose tissue can often be observed unless the room temperature is

moderately warmed. Conversely, in the present study PET was of value in identifying relapse in two patients, and showed excellent sensitivity. Therefore, although the role of FDG-PET for surveillance in asymptomatic people remains unsettled, we believe it may provide beneficial information if there are clinical signs of relapse.

Our results suggest several features that distinguish p-NHL from p-HL and from lymphoma in adults. Therefore, we believe the role of FDG PET should also differ. Several drawbacks due to the more aggressive behaviors of p-NHL may reduce the utility of PET for disease staging and response assessment. Several benign conditions that are characteristic in children could also hinder the diagnostic performance of PET. The role of FDG-PET in staging for determining more appropriate therapeutic strategy may be somewhat different between p-HL and p-NHL.[12] In p-HL, more detailed and accurate information regarding the spread of involved lesions is required to plan the delivery of radiotherapy, and FDG-PET often provides information resulting in correct up-staging.[23] Conversely, in p-NHL where treatment is typically risk-adapted intensive chemotherapy without radiotherapy, the precise localization of every site of small bulk disease is not always necessary to achieve high cure rates.[24] Moreover, for stage IV patients already diagnosed by bone marrow biopsy or cerebrospinal fluid cytology, FDG-PET can no longer contribute to either up-staging or the alteration of treatment strategy. For response assessment or surveillance of relapse, we believe the difference of biological behavior, especially the difference of the aggressiveness between p-HL and p-NHL, would explain our suggestion that FDG might have a more limited role for p-NHL than for p-HL. As Kasamon et al. have mentioned, lymphomas are usually not diagnosed until they reach a

size of 10^{10}-10^{11} cells and the limit of resolution of FDG-PET for the detection of lymphoma generally is a size of approximately 10^{8}-10^{9} cells. FDG-PET can only measure the first 2-3 log units of tumor cell killing, depending on the initial size of tumor.[25] In short, a negative PET result does not indicate total eradication of disease. Most of p-NHL would have higher aggressiveness than p-HL, and we presume that in p-NHL even a small amount of tumor cells below the level of the detectability of PET would overcome anti-tumor immunity. However, we emphasize the ability of PET to identify unexpected lesions, which may occur more frequently in p-NHL, even during therapy. The use of PET could be quite effective in some lesions, such as involvement of peripheral nerves or focal bone marrow involvement that cannot be easily identified by other imaging modalities.

There exists a trade-off between repeated PET scans, especially PET/CT scans, and lifetime risk of cancer incidence attributable to increasing radiation dose. Many pediatric patients with malignancy tend to undergo repeated scans. Therefore, the reasonable use of the scans is required to avoid unnecessary radiation exposure. Modifying imaging protocols so as to minimize injected FDG activity and CT dose according to patients' size is required.

The present study has several limitations. It was not prospective and thus our population might contain a bias. Also, the size of the study population was not large. The follow-up periods varied among the patients and the protocols used for image acquisition and injected dose were not unified because PET studies were performed with three different scanners.

In conclusion, FDG-PET for p-NHL can sometimes contribute to the determination of more appropriate therapeutic strategies by identifying unexpected lesions; however, its clinical role may not be as promising when compared with the developing consensus about

p-HL. Clinicians should make every effort to perform PET/CT scanning properly so as to reasonably reduce the lifetime risk of secondary cancers in pediatric patients. Because p-NHL has considerably distinct clinical characteristics from p-HL, prospective investigations regarding p-NHL cases might be needed to establish the optimal role of FDG-PET.

Conflict of interest: None

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Fig. 1 Patients' grouping

Fig. 2 Concordance and discordance between CIM and PET judgments about the achievement of remission in Group B

Fig. 3 A 3-year-old boy (No. 2) with Burkitt lymphoma with peripheral nerve involvement. The cerebrospinal cytology was positive at the initial staging. At the end of chemotherapy, he complained of a nocturnal crural pain. FDG-PET showed lymphoma involvement in the sciatic nerves (straight arrows) in addition to a known abdominal tumor (wavy arrow). He was scheduled to undergo surgical resection of the remnant abdominal tumor if the chemotherapy was effective, but it was cancelled as a result of progressive disease (A: Maximum intensity projection image, B: fused PET/CT image)

Fig. 4 An 11-year-old boy (No. 9) with T-lymphoblastic lymphoma of thymus. He was regarded as having achieved complete response. The scan for response assessment (A) only showed physiological thymic uptake. However, eight months later, he underwent FDG-PET again for surveillance (B) and was found to have relapse in the thymus. Focal intense uptake superimposed on the physiological uptake (arrow) was identified. The tumor was resected and relapse was confirmed

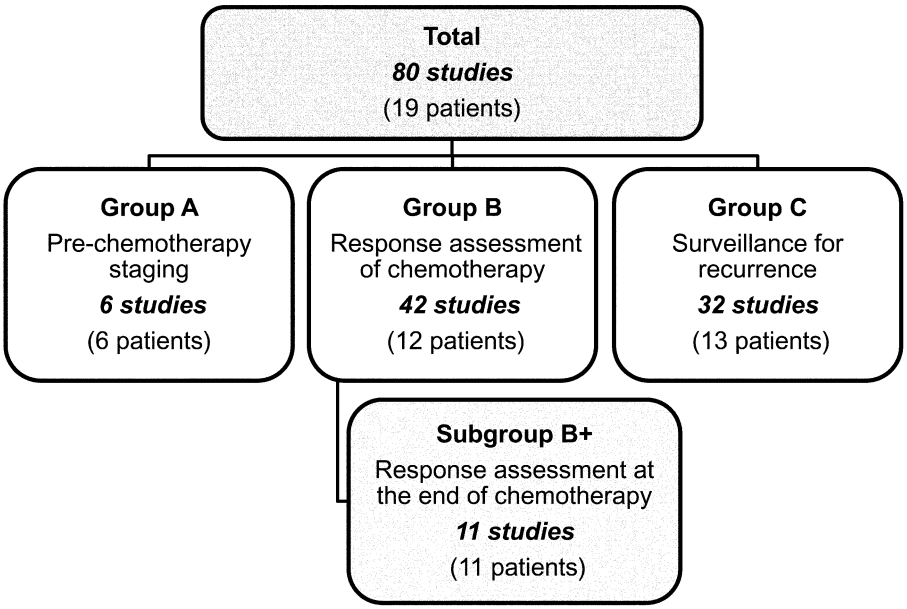
Total
80 studies
(19 patients)
Group A
Pre-chemotherapy staging
6 studies
(6 patients)
Group B
Response assessment of chemotherapy
42 studies
(12 patients)
Group C
Surveillance for recurrence
32 studies
(13 patients)
Subgroup B+
Response assessment at the end of chemotherapy
11 studies
(11 patients)

Fig. 1

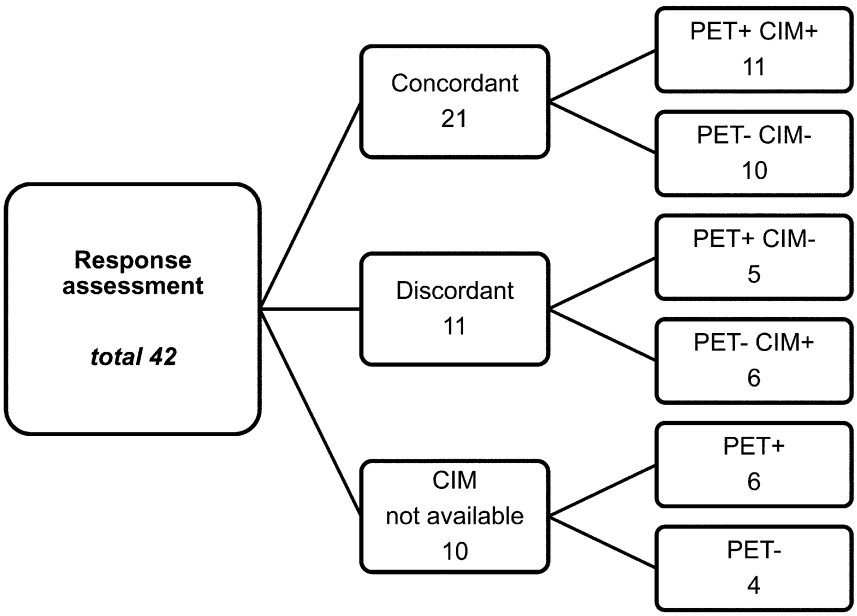
Response assessment
total 42
Concordant 21
Discordant 11
CIM not available 10
PET+ CIM+ 11
PET- CIM- 10
PET+ CIM- 5
PET- CIM+ 6
PET+ 6
PET- 4

Fig. 2

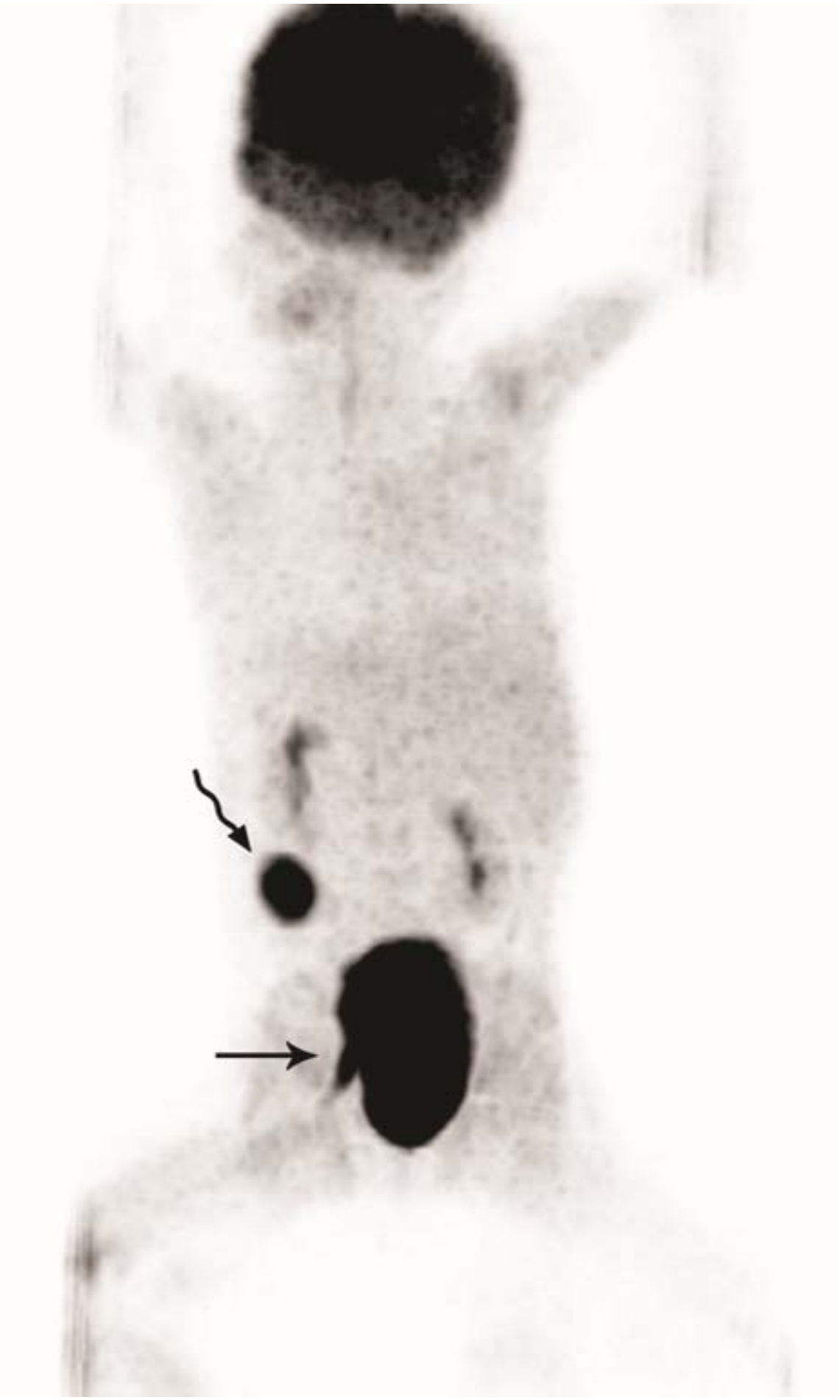

Fig. 3A

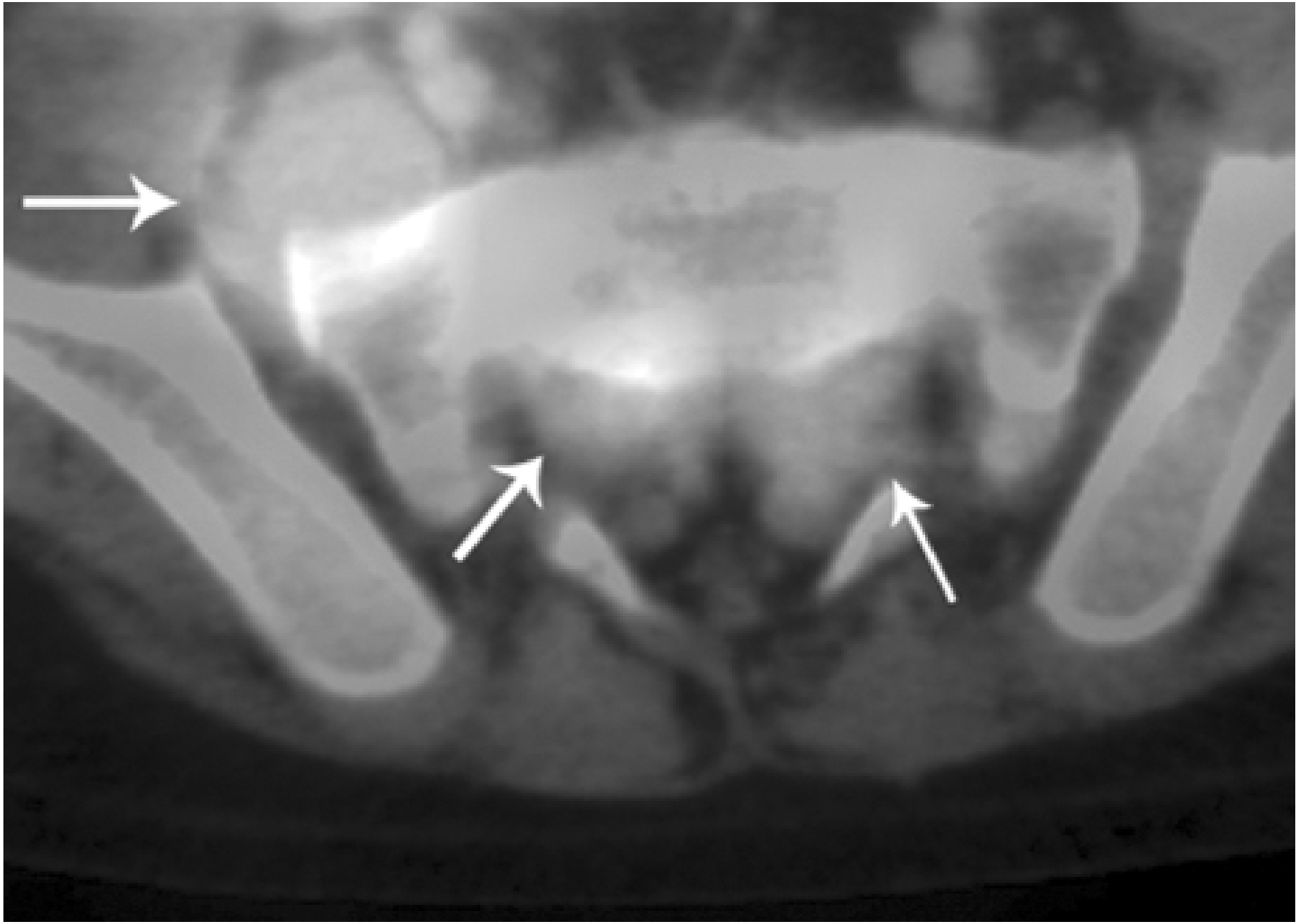

Fig. 3B

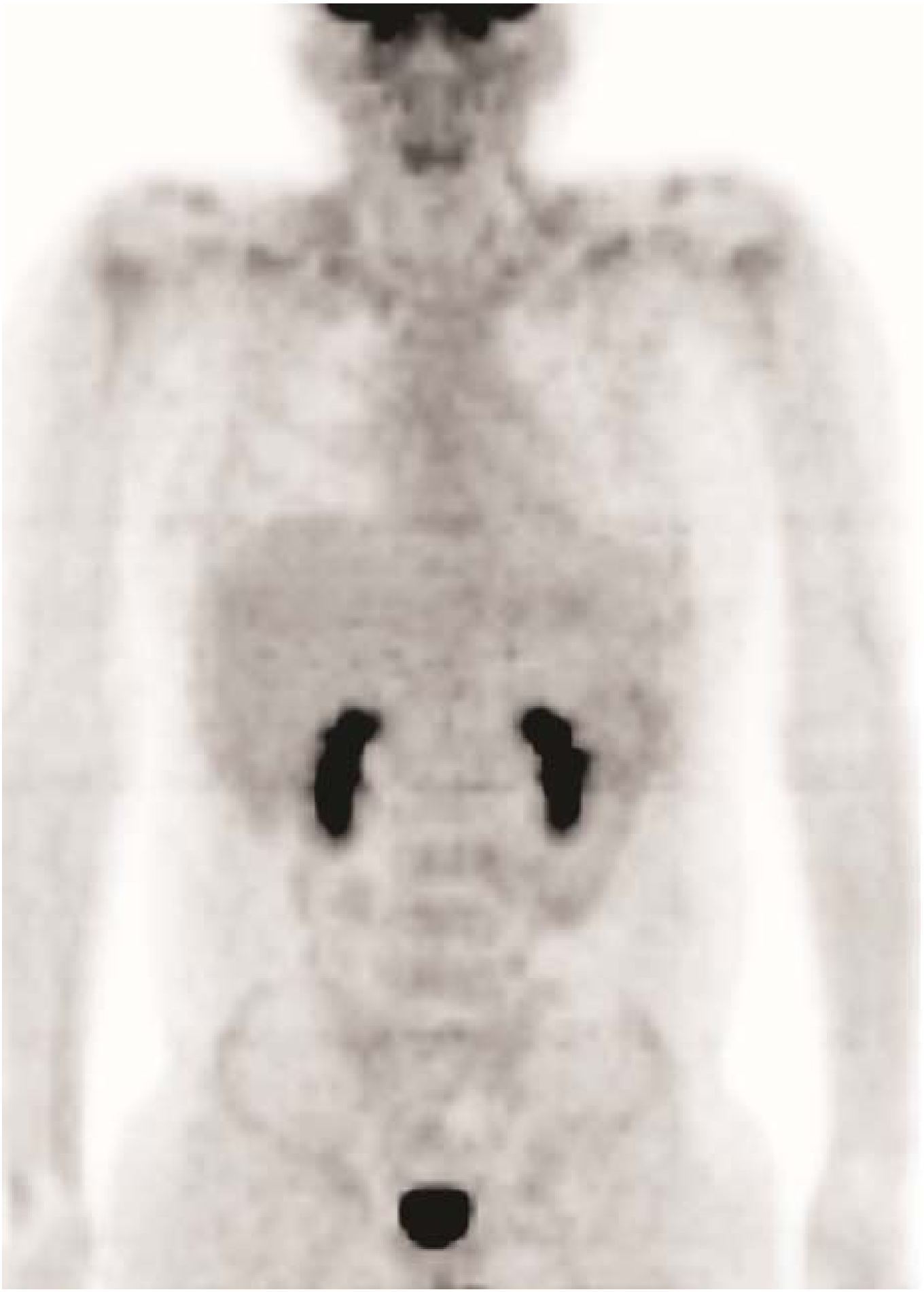

Fig. 4A

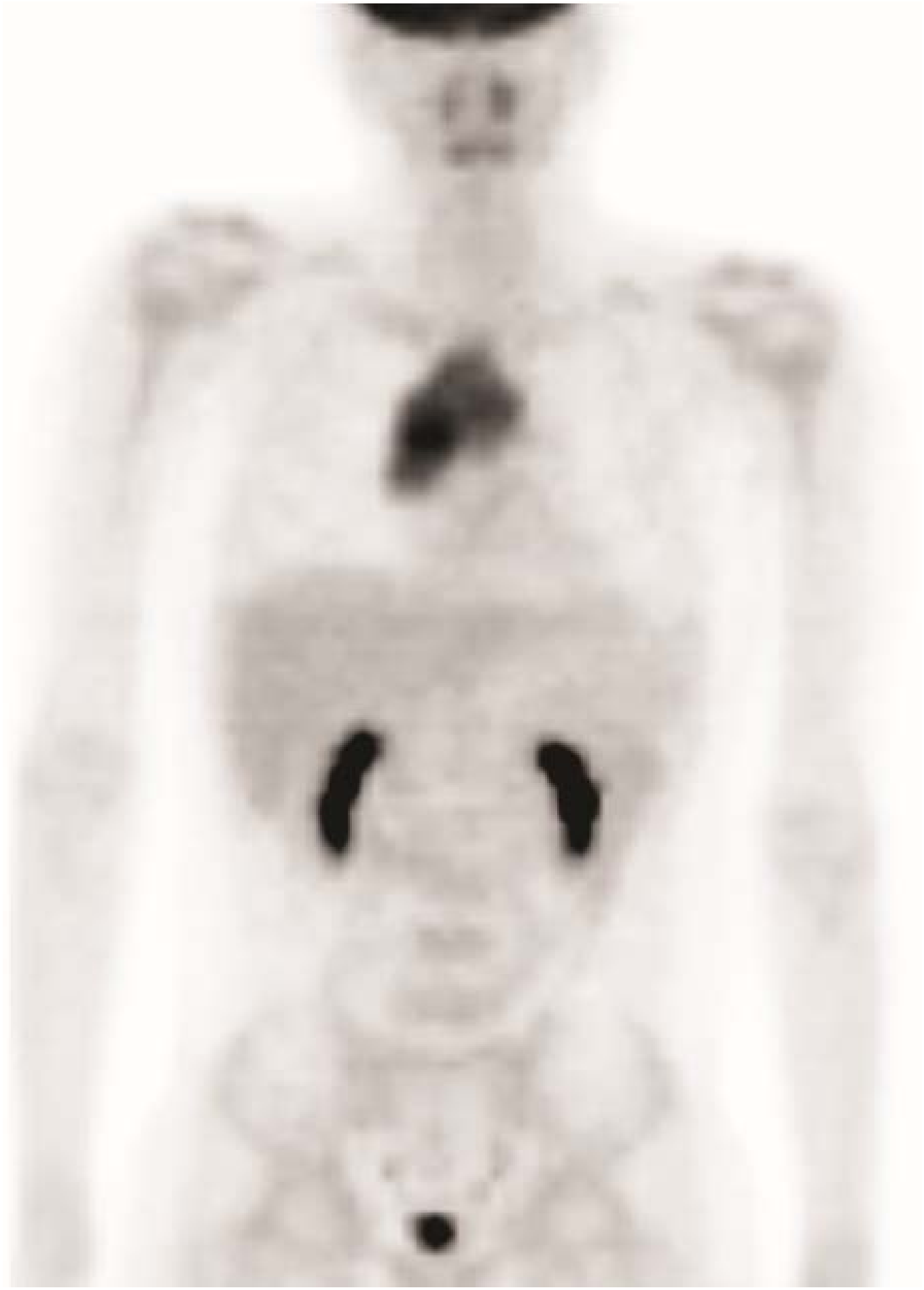

Fig. 4B

Table 1 Patient profile

Pt. #	Age at the initial exam	Sex	Histological subtype	Stage	Aim of PET exams	Number of exams	Outcome
1	6	M	Lymphoblastic	IV	A	1	Relapse after
					B	2	CR
					C	1	
2	2	M	Burkitt	IV*	A	1	Relapse and
					B	6	death
3	14	M	ALCL	II	A	1	CR
					B	2	
					C	2	
4	10	M	DLBCL	III	A	1	CR
					B	3	
					C	1	
5	9	M	Lymphoblastic	IV	A	1	CR
6	5	M	Lymphoblastic	IV	A	1	CR
7	3	M	Burkitt	IV	B	1	CR
8	18	M	NK-T	II	B	3	CR
					C	1	
9	11	M	Lymphoblastic	III→IV†	B	2	Relapse and
					C	1	death after CR
10	5	M	Burkitt	IV	B	1	CR
11	8	F	ALCL	IV	B	1	CR
					C	3	

12	18	M	Burkitt	I	B	1	CR
					C	3	
13	14	F	Burkitt	III→IV†	B	16	Relapse
14	3	F	DLBCL	IV	B	4	CR
					C	5	
15	18	F	DLBCL	I	C	1	CR
16	15	M	Lymphoblastic	I	C	1	CR
17	18	M	Burkitt	II	C	2	CR
18	17	M	DLBCL	IV	C	5	CR
19	8	M	DLBCL	II	C	6	CR

Abbreviations: Pt. #, Patient number; PET, positron emission tomography; M, male; F, female; ALCL, anaplastic large cell lymphoma; DLBCL, diffuse large B-cell lymphoma; NK-T, Natural killer-T cell; N.A., not available; CR, complete remission.

* Although the clinical stage was considered stage III by PET, cerebrospinal fluid cytology turned out to be positive.

†Although the initial staging was stage III, bone marrow involvement occurred as a relapse after therapy and so was classified as stage IV at re-staging.

Table 2 Summary of stages and findings in CIM and PET, and final diagnoses in Group A

Pt. #	Histology	CIM	PET	Final diagnoses
1	Lymphoblastic	Stage IV: No residual lesion after excision of CNS tumor with skull involvement	Stage IV: the same as CIM	Stage IV: CNS involvement (surgically proven)
2	Burkitt	Stage III: Extensive and unresectable intra-abdominal mass, abdominal lymph nodes swelling, and ascites	Stage III: Extensive primary intra-abdominal mass and abdominal lymph nodes with intense uptake	Stage IV: Positive cerebrospinal fluid cytology
3	ALCL	Stage II: Multiple subcutaneous nodules in legs	Stage II: Multiple subcutaneous nodules with high uptake in legs	Stage II: Greater numbers of small papules visually identified in legs and back (biopsy-proven)
4	DLBCL	Stage III: Multiple intra-abdominal extra-nodal masses, internal thoracic nodes swelling, and pleural effusion	Stage III: Multiple abdominal masses, some of which existed along the peritoneum. Internal thoracic nodes and subcarinal nodes also showed high uptake	Stage III: DLBCL was proved by internal thoracic node biopsy, but stage was determined by radiological findings (Not all lesions biopsied).
5	Lymphoblastic	Stage III: Huge anterior mediastinal mass with invasion to thyroid, pericardium, and lung	Stage III: Huge anterior mediastinal mass with intense uptake. Diffuse moderate bone marrow uptake as an inconclusive finding	Stage IV: Positive bone marrow biopsy
6	Lymphoblastic	Stage IV: Huge destructive bone tumor of scapula	Stage IV: Intense uptake into scapular tumor	Stage IV: (Biopsy-proven)

Abbreviations: CIM, conventional imaging modalities; CNS, central nerve system

Table 3 Comparison of CIM staging vs. PET staging vs. reference standard in Group A

(n=6)	CIM diagnosis	PET diagnosis	Final diagnosis
Stage I	0	0	0
II	1	1	1
III	3	3	1
IV	2*	2*	4

* One patient with CNS involvement was diagnosed by excision, as their disease stage was already known as stage IV before undergoing PET and CT scanning.

Table 4 Summary of cases in Group B in which FDG-PET influenced the treatment plan

Pt.#	Status	CIM findings	PET findings	Influence on treatment plan
2	End-CTx response assessment	+: The abdominal tumor grew despite chemotherapy.	+: Sciatic nerve involvement was identified in addition to the known abdominal lesion.	Withdrawal of the standard chemotherapy / Cancellation of the planned surgical resection of the remnant abdominal tumor. (The involvement was confirmed by cerebrospinal fluid cytology.)
13	Salvage CTx response assessment for relapse of the distal femur	-: No residual lesion was identified on CT.	+: Relapse of scapula was identified.	Withdrawal of the standard chemotherapy / Only rituximab was continued as palliative therapy. (The involvement was confirmed by biopsy.)
13	Salvage CTx response assessment for relapse of scapula	-: No residual lesion was identified on CT.	+: Re-relapse of scapula after remission was identified.	RTx for scapula / Cancellation of the planned bone marrow transplantation. (No histological confirmation)
13	Salvage CTx & RTx response assessment	Not performed	+: Relapse of ilium was identified, while the	RTx for the ilium. (No histological confirmation)

	for relapse of scapula	uptake in the scapula disappeared.

Abbreviations: CTx, chemotherapy; RTx, radiotherapy; +, positive results; -, negative results.

Table 5 Diagnostic performances at completion of remission-induction chemotherapy for predicting relapse (Subgroup B+)

(n=11)	CIM		PET	
	Positive	Negative	Positive	Negative
No. of relapse	2	2	2	2
No. of remission	2	5	2	5
Sensitivity	50%		50%	
Specificity	71%		71%	
PPV	50%		50%	
NPV	71%		71%	
Accuracy	64%		64%	

Abbreviations: PPV, Positive predictive value; NPV, Negative predictive value.

The two results were not identical. In one case, CIM showed false-positive but PET showed true-negative. In another one case, CIM showed true-negative but PET showed false-positive.

Table 6 Diagnostic performance of PET for detection of relapse after achievement of complete remission (Group C)

(n=32)		PET	
		Positive	Negative
Final diagnosis	No. of relapsed cases	2	0
	No. of non-relapsed cases	4	26
Sensitivity		100%	
Specificity		87%	
PPV		33%	
NPV		100%	
Accuracy		88%	