Histological verification of positive positron emission tomography findings in the follow-up of patients with mediastinal lymphoma

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ABSTRACT

Background and Objectives

Follow-ups of patients with mediastinal lymphoma are not accurate if they rely on computed tomography (CT). Positron emission tomography (PET) has been suggested to be useful in several lymphoma settings, such as initial staging, evaluation of residual masses after therapy, and assessment of response early in the course of treatment. The aim of this retrospective study was to verify the reliability of positive PET scans of the mediastinum in following up patients wirh mediastinal lymphoma, using histological findings as a comparison.

Design and Methods

From January 2002 to July 2005, 151 patients with mediastinal lymphoma (57 with Hodgkin's disease [HD] and 94 with aggressive non-Hodgkin's lymphoma [NHL]) were followed-up after the end of front-line treatment. Patients with a positive PET scan of the mediastinum underwent CT scanning and surgical biopsy.

Results

In 30 (21 HD and 9 NHL) out of 151 patients (20%) a suspicion of lymphoma relapse was raised based on positive mediastinal PET scanning. Histology confirmed this suspicion in 17 (10 HD and 7 NHL) out of 30 patients (57%), whereas either benign (9 fibrosis, 3 sarcoid-like granulomatosis) or unrelated neoplastic conditions (1 thymoma) were demonstrated in the remaining 13 patients (43%). SUV_{max} was significantly higher among patients who had signs of relapse (17 true positive cases) than among those who stayed in remission (13 false positive cases), the median values being 5.95 (range, 3.5-26.9) and 2.90 (range, 1.4-3.3), respectively (p=0.01).

Interpretation and Conclusions

We suggest that a positive PET scan of the mediastinum of a patient being followed-up for a mediastinal lymphoma should not be considered sufficient for diagnostic purposes in view of its lack of discrimination. Histological confirmation can safely be carried out with various biopsy techniques, the choice of which should be made on the basis of the findings of the clinical and imaging studies of the individual case.

Key words: PET, biopsy, mediastinal lymphoma, follow-up, CT scan.

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In the last few years, fluorodeoxyglucose (FDG)-positron emission tomography (PET) has shown a number of potential advantages in refining and improving the management of Hodgkin's disease (HD) and aggressive non-Hodgkin's lymphoma (NHL). PET, a functional form of imaging based on the increased glucose metaobolism of tumor cells, plays a significant role in the initial staging,[1-4] in the evaluation of residual masses after therapy,[5-9] and in the monitoring of therapy response early in the course of treatment regimens.[10-15] In all these clinical settings, the accuracy of PET in monitoring the response to treatment has proven superior to that of conventional computed tomography (CT). Another important field of application is the medium- and long-term follow-up of HD and aggressive NHL with mediastinal involvement at diagnosis, after complete response has been achieved. The role of PET can be decisive in early identification of mediastinal relapse, as the reliability of CT in differentiating between fibrotic tissue and active tumor is inadequate.[10,16,17] In many centers, positive PET is among the main findings on which the decision to diagnose lymphoma relapse in the mediastinum rests, but no studies to date have verified the reliability of positive PET by comparing it with histological findings (the gold standard) in a consistent case series within this setting. The aim of the present retrospective study was to evaluate the specificity of PET in patients with suspected relapse of lymphoma, through comparison of positive PET with histological findings in a series of patients with suspected mediastinal relapse of either HD or NHL.

Design and Methods

From January 2002 to July 2005, 151 patients with mediastinal lymphoma (i.e. mediastinal involvement at the time of diagnosis) (57 cases of HD and 94 cases of aggressive NHL) were followed-up after the end of front-line treatment (chemotherapy with/without radiotherapy). Table 1 summarizes their clinical characteristics at the time of diagnosis, including the histology of the aggressive NHL. All these patients were selected from the whole series of lymphoma patients treated over the same period, according to whether they achieved complete response (PET negativity) after front-line treatment. The treatment for patients with HD was ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) with or without local radiotherapy, whereas that for patients with aggressive NHL was CHOP (cyclophospamide, adriamycin, oncovin, prednisolone) plus rituximab or MACOP-B (methotrexate, adriamycin, cyclophosphamide, oncovin, prednisolone, bleomycin) with or without local radiotherapy. All patients were evaluated at diagnosis, during treatment and at the end-of -treatment restaging by CT and PET. All patients were notified of the investigational nature of this study; the study was approved by the institutional review board. The follow-up program for each patient included a PET scan every 6 months (starting from the PET at the time of final restaging after the end of treatment) for the first 2 years and then every 12 months for a further 3 years, and a physical examination with a hematologic and chemical survey every 3-4 months for the first 2 years and then every 6 months for the next 3 years. When the PET was positive, the patient underwent CT scanning for a global evaluation of the potential relapse condition. The median duration of response (until the presence of a positive PET scan potentially indicating a relapse) was 22 months (range 8-46 months). Thirty patients had a positive PET in the mediastinum area without any other PET positivity. Of these patients, 12 were males and 18 females; they were aged 14-67 years (median age 36 years). According to histology, 21 had HD and nine had aggressive NHL; 3/30 (10%) patients had concomitant appearance of systemic symptoms (one patient) or increased values of serum lactic dehydrogenase (LDH) (two patients). All these PET-positive patients underwent CT scanning and were assigned to four different subgroups according to the CT scan abnormalities: (i) hilar or anterior mediastinal masses with contrast enhancement (11 patients); (ii) hilar or anterior mediastinal areas of prevalent fibrosis with spots of contrast enhancement (8 patients); (iii) enlarged paratracheal or prevascular nodes (8 patients); (iv) substantially normal CT scan (presence of minimal spots of PET positivity) (3 patients). In groups 1, 2, and 3, CT contrast enhancement and PET positivity were in the same areas.

Table 1. Clinical characteristics of the 151 patients with mediastinal lymphoma.

	HD	*Aggressive NHL*
N. of patients	57	94
Age (years)		
Median	26	52
Range	16-42	28-65
Sex: male/female	30/27	54/40
Histology		
DLBCL		84
PMLBCL		10
Stage		
I-II	52	85
III-IV	5	9
Bulky disease in mediastinum	25	52

DLBCL: diffuse large B-cell lymphoma; PMLBCL: primary mediastinal large B-cell lymphoma.

Biopsy techniques

Percutaneous core needle biopsy under CT-guidance through a 15 G Menghini needle (Hepafix®, B Braun,

Melsunge, Germany) was employed in the case of bulky disease or in lesions ≥3cm close to the chest wall.[18,19] Video-mediastinoscopy (Richard Wolf GmbH, Knittlingen, Germany) was utilized for sampling paratracheal and hypocarinal pathologic nodes at imaging.[20,21] Pre-vascular mediastinoscopy was used to sample retrosternal lymph nodes or lesions in the absence of significant fibrosis.[21] *Extended* video-mediastinoscopy was proposed to sample prevascular lymph nodes and subaortic lymph nodes as an extension of conventional mediastinoscopy.[22] Anterior mediastinotomy was utilized for sampling tissue in the anterior mediastinum close to the chest wall or deep as the hilum.[23] Cervicotomy + manubriotomy (sternal split) was performed to gain access to retrosternal structures, mainy in the presence of fibrosis. It was considered elective for the radical removal of thymus and anterior mediastinal fatty and lymph node tissue.[23,24] Video-thoracoscopy (VATS) was used for lesions of the hilum and/or those close to the mediastinal pleura, mainly when fine surgical dissection was expected, or another morbid condition of the pleura and/or lung had to be treated.[23,25,26] Standard thoracotomy, which is the gold standard for major surgery of the lung and some mediastinal resections, was performed in cases for which a mini-invasive approach was considered inadequate. Frozen sections were always available to assess the nature of the tissue and eventually the quality of the sample.

In this series, as usual, the least invasive biopsy technique was selected on the basis of imaging. When a procedure was considered unsatisfactory or risky, the least invasive enlargement or more aggressive technique was applied. All interventions were performed by the same team (*MB, MA, SFP*).

PET scans

PET scans for restaging were was performed 1 month after the end of chemotherapy and 3 months after completion of radiotherapy.

To optimize FDG uptake in normal and neoplastic tissue, patients were asked to fast for at least 6 h before undergoing the PET examination; no patient had a history of diabetes. FDG was produced in our radiopharmacy using standard synthesis techniques. Each patient was injected i.v. with about 6 MBq/kg of FDG; the PET scanning was carried out 70-90 min after injection of the tracer. Before PET scanning, patients were encouraged to void in order to minimize radioactivity in the bladder. FDG-PET scans were carried out using a dedicated tomograph (Advance NX, General Electrics Medical Systems, Milwakee, USA). Emission scans were acquired for 4 min at every table positron; 2-min transmission scans were also recorded in all patients. In all, about six bed positions were required for each patient, with a total scanning time of about 40 min. Images were reconstructed by segmented attenuation correction. PET images were evaluated by visual inspection and semi-quantitative analysis performed by three experienced readers. Standardized uptake values (SUV) were, in all cases, available to readers at the moment of reporting. Nonetheless PET scans were not categorized on the basis of a threshold SUV value, but by taking into account all available data, and in particular the site and degree of FDG accumulation.[27] Areas of focal increased uptake were interpreted as suspicious of lymphoma unless they were at sites of known accumulation, including the kidney and bladder, gastrointestinal tract; skeletal areas showing symmetrical joint uptake (especially within the shoulder) were considered as due to arthritis.

PET evaluations were scored as negative or positive.[28] Negative scans were defined as those showing no focal uptake that could be evidence of disease; positive scans were defined as those showing increased uptake possibly indicative of malignant disease. Thus for the purposes of the present study uncertain findings and findings suggestive of minimal residual disease were also considered as positive. Also, when areas of abnormal FDG uptake were identified, the intensity of FDG uptake was quantified by calculating the SUV. For the calculation of SUV, circular regions of interest (≥70 pixels) were drawn on transaxial images around the areas with increased FDG uptake; the highest SUV measured was the one used (SUV_{max}).

Histological preparations

All specimens were formalin-fixed and paraffin-embedded, after which 3-mm thick sections were cut and stained with hematoxylin and eosin (H&E). Additional sections were obtained for histochemical study and immunophenotypic analysis, which were performed according to the avidin-biotin peroxidase complex method and by applying a panel of antibodies including the key-markers listed in the WHO classification.[29] All histological examination were performed sequentially by two histopathologists (*AC and SP*).

Statistical methods

Data from the two groups were compared using the χ^2 test for categorical data (SUV_{max} data).[30,31]

Results

Twenty-seven (91%) patients had concurrent CT and PET positive results, while only three patients proved PET-positive and CT-negative. In all these three patients, the histopathological findings (based on a sternal split in two patients and VATS in the other one) were positive for lymphoma relapse (two HD and one aggressive NHL). Figure 1 shows the positive PET (1A) and the negative CT (1B) scan of a patient who had a histolpathological diagnosis of HD. Thirty patients underwent 33 procedures: 2 core needle biop-

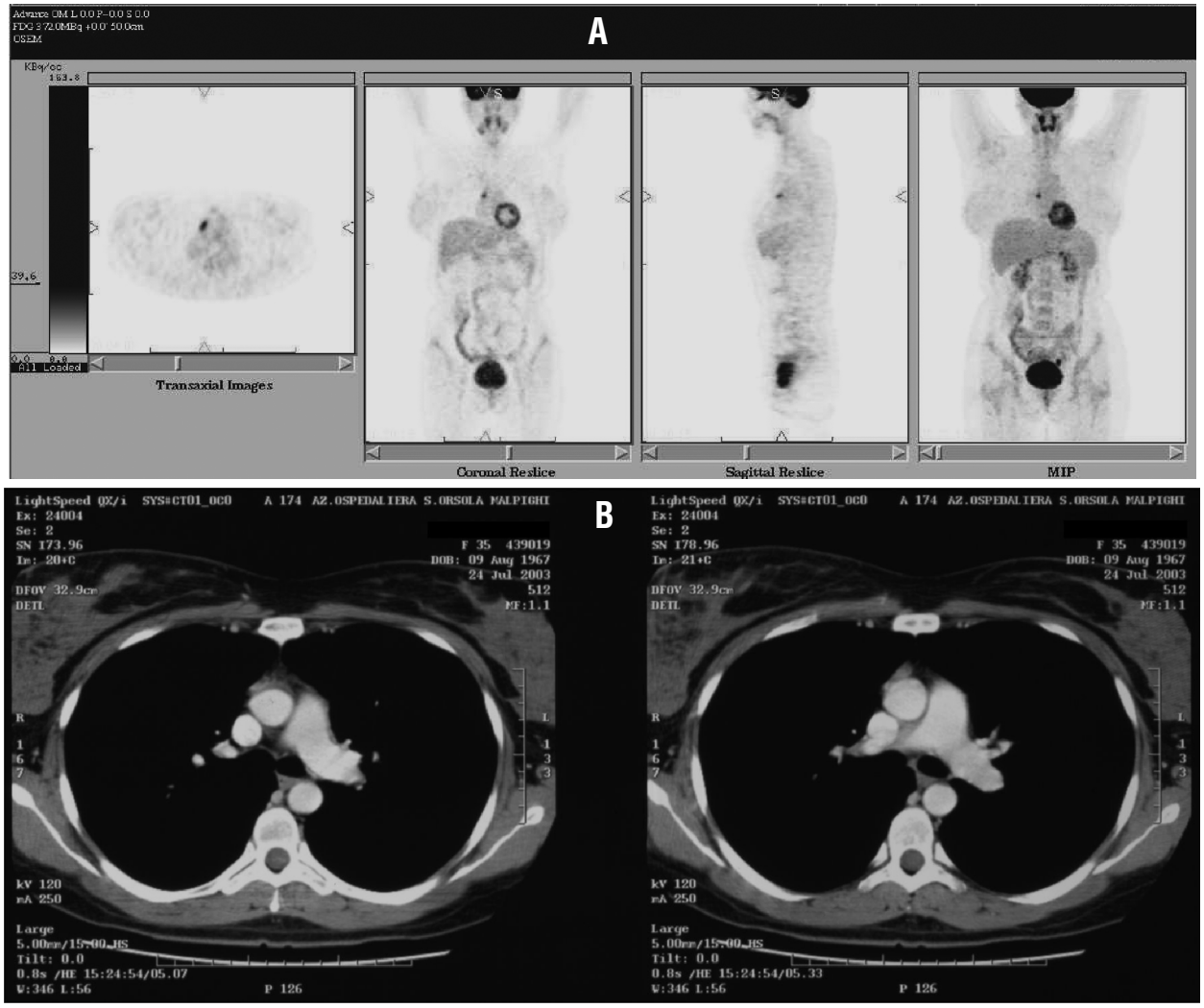

Figure 1. FDG PET showing an area of increased uptake in the mediastinum (A). The corresponding CT (after 7 days) was reported as negative for active disease (B).

sies, 8 video-mediastinoscopies (3 extended, 1 prevascular), 2 mediastinotomies, 7 sternal splits, 12 VATS, 2 thoracotomies (1 radical segmentectomy and 1 incisional biopsy).

A lymphoma relapse was diagnosed in 17/30 (57 %) patients (ten with HD and seven with aggressive NHL). All three patients who had concomitant systemic symptoms and increased values of serum LDH proved to have a lymphoma relapse (one with HD and two with aggressive NHL, respectively). Table 2 reports the clinical characteristics of these relapsing patients. In the remaining cases, biopsy revealed: fibrosis in nine patients, sarcoid-like lymph node granulomatosis in three patients, and stage I thymoma in one patient. Table 3 summarizes the different diagnoses obtained by the different surgical techniques in the four imaging subgroups. There was no evidence of any correlation among the size of residual mass, positive PET and relapse. All diagnoses of fibrosis were made on very large specimens. No deaths or severe complications occurred. Only two mild complications were reported:

Table 2. Clinical characteristics of the 17 patients with lymphoma relapse.

	HD	*Aggressive NHL*
N. of patients	10	7
Age (years)		
Median	25	50
Range	18-38	31-59
Sex: male/female	6/4	3 / 4
Histology		
DLBCL		5
PMLBCL		2
Stage		
I-II	10	7
Bulky disease in mediastinum	5	4

DLBCL: diffuse large B-cell lymphoma; PMLBCL: primary mediastinal large B-cell lymphoma.

Table 3. The different diagnoses obtained using various surgical techniques in the four imaging subgroups.

Imaging subgroup	*N. of pts. (30)*	*Procedure*	*N. (33)*	*Relapse (17)*	*Fibrosis (9)*	*Other (4)*	*Non-diagnostic (3)*
Hilar or anterior mediastinal masses with contrast enhancement	11	Core biopsy	2	1			1
		Mediastinotomy	1	1			
		VATS	9	7	1	1 thymoma	
		Sternal split	3		2	1 sarcoid	
Hilar or anterior mediastinal areas of fibrosis with spots of contrast enhancement	8	Mediastinotomy	1	1			
		VATS	2		2		
		Thoracotomy	2	1	1		
Enlarged paratracheal or prevascular nodes	8	V-mediastinoscopy	4	1	2	1 sarcoid	
		Prevascular V-mediastinoscopy	1		1		
		Extended V-mediastinoscopy	3		1 sarcoid	2*	
Sternal split	2	2*					
Substantially normal CT (minimal spots of pathological PET)	3	Sternal split	2	2			
		VATS	1	1			

**Enlargement from extended mediastinoscopy to sternal split in the course of the same procedure.*

one pneumothorax complicating a non-diagnostic needle biopsy was treated in the course of a diagnostic VATS; one prolonged air leak following a thoracotomic segmentectomy required a 9-day drainage.

Concerning the 13 patients whose biopsy revealed benign or unrelated neoplastic conditions, no further PET follow-up has yet shown any new positivity although one case (fibrosis as diagnosed by previous biopsy) was found to have permanent minimal residual uptake at PET scanning and a lower SUV than at the time of the biopsy. The SUV_{max} was significantly higher among patients who presented signs of relapse (17 true positive cases) than among those who stayed in remission (13 false positive cases): median 5.95 (range 3.5-26.9) versus median 2.90 (range 1.4-3.3), respectively (p=0.01).

Discussion

Many patients with mediastinal lymphoma prove to have local residual masses after completing induction therapy, but less than 20% of them eventually relapse. Detection of potential relapse during follow-up is, therefore, of major clinical importance. Before the introduction of PET for clinical evaluation of lymphoma patients, no available method could predict the course of the disease since CT findings do not reliably differentiate active lymphoma from necrosis and/or fibrosis. Magnetic resonance imaging (MRI) has been shown to have low sensitivity and is, therefore, not useful for lymphoma assessment[32,33] while although 67-gallium scintigraphy is a valid metabolic imaging technique for detecting active tumor tissue, it has drawbacks such as low spatial resolution and difficulty in identifying active abdominal masses.[34,35] In recent years, a series of reports have shown that PET is the most helpful non-invasive metabolic imaging technique for patients with either HD or aggressive NHL. It has been suggested that PET can distinguish between active lymphoma and fibrosis,[16] and that it has important prognostic value in initial staging, in evaluation after treatment, in the early response to primary treatment and in the pre-autotransplant setting.[13,14]

The present PET-based follow-up analysis suggests that the specificity of PET in patients with suspected mediastinal relapse of lymphoma after front-line treatment is not optimal and that histological confirmation should be obtained whenever possible in order to choose the correct and reliabe therapeutic approach. In the present series mediastinal relapse of lymphoma, suspected from PET scanning results, was actually not confirmed by histology in 13 out of 30 patients (43%). It should be emphasized that we used PET positivity criteria designed to maximize sensitivity for the detection of relapse. Thus all non-negative PET findings were regarded as suspicious of viable tumor, which meant including patients with minimal residual disease in the PET-positive group. HD patients with minimal PET findings have already been reported to have a good prognosis.[36] The reported prognostic value of interim FDG-PET after two or three cycles of chemotherapy in HD[36] and our study support the hypothesis that such cases may be considered similar to patients in complete remission.

Compared to other studies, we found a relatively lower specificity for FDG PET. There are two main reasons for this difference: a) criteria used to score PET as

positive (as just described) and b) criteria for including patients in the studies. With regards to the population studied, we excluded from further evaluation patients with PET findings at additional sites apart from the mediastinum. The extent of PET positivity is clearly related to the likelihood of relapse, so that the exclusion of such cases probably led to a decrease in the true positive rate of our PET findings.

Our study also suggests that reliable histological confirmation can be obtained in this setting with low morbidity, provided that the timing and the type of biopsy technique is chosen appropriately, taking into account the clinical and imaging findings of the individual patient. We employed several different surgical techniques ranging from the least invasive technique of needle biopsy to radical removal of tissue through extensive sampling. In detail, in this series, 24 biopsy procedures were mini-invasive, and seven were performed through a sternal split, which can be considered a mini-invasive technique in view of the minimal trauma, pain and hospital stay. It should be noted that even *difficult* biopsies, such as those performed in the presence of mediastinal fibrosis, which is constantly present in these patients, can be carried out in the large majority of cases through a mini-invasive approach. Only two biopsies were performed following a thoracotomy: in one case we performed radical resection of a fibrotic mass, and in another de-bulking was attempted but not carried as it would have required full-scale pneumonectomy, which was deemed excessive.

All nine diagnoses of fibrosis were made on very large specimens from patients who had substantial excision of pathologic tissues. The minimal amount and site of tissue to be sampled in order to yield a diagnosis of fibrosis is still an open issue: in this series frozen sections were used in seven cases to assess the nature of the tissue and, in some cases, the quality of the sample; when these were found not to indicate relapse, extensive sampling of presumed *fibrotic tissue* was carried out. Following diagnosis of thymoma, radical removal of a 5-cm mass was subsequently performed through an open chest procedure.

The occurrence of sarcoidosis and sarcoid-like reactions has already been reported in patients with both HD and NHL, these being secondary reactions to tumor antigens and/or immunological aberrations triggered by chemotherapeutic agents as the likely pathogenetic events.[38,39]

In no case was repeat surgery necessary: the two extended mediastinoscopies in which the sampling was deemed unsatisfactory were easily enlarged through a sternal split in the course of the same anesthesia.

In conclusion, the present study suggests that positive PET in the mediastinum of a patient being followed-up for a mediastinal lymphoma (hence after front-line treatment) should not be considered sufficient for final diagnostic purposes. Histological confirmation can be safely obtained by various biopsy techniques, the choice of which should be made on the basis of the clinical and imaging study findings of the individual case.

Authors' Contributions

PLZ and MB contributed to the design, conduction and analysis of the study and wrote the paper; MT, RT, SF, VS, MA, PC, GM, GD, LA, EM, MF, CP, AC, AB, RC and SP performed the research and collected data; SP and MB critically reviewed the manuscript.

Conflict of Interest

The authors reported no potential conflicts of interest.

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