# UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

Département des Laboratoires
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# Value of F-18-FDG PET/CT for determining malignant pleural effusion in patients with cancer

THESE

préparée sous la direction du Professeur John O. Prior

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

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par

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## Value of F-18-FDG PET/CT for determining malignant pleural effusion in patients with cancer

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**Résumé de thèse :**

**Thèse MD Igor LETOVANEC, sous la direction du Prof John O. Prior**

**Valeur du F-18-FDG PET/CT pour déterminer la nature maligne des épanchements chez les patients avec cancer** (*Value of F-18-FDG PET/CT for determining malignant pleural effusion in patients with cancer*)

Objectif : Les épanchements pleuraux sont fréquents chez les patients porteurs de cancer et déterminer s'ils sont de nature tumorale ou non relève d'une grande importance clinique, particulièrement pour le groupe des carcinomes pulmonaires NON à petites cellules (NSCLC). Le PET/CT s'est montré d'une grande utilité et est actuellement indiscutablement reconnu comme outils nécessaire dans la prise en charge et notamment la stadification et le suivi des cancers, et particulièrement des cancers pulmonaires. Sa capacité à pouvoir distinguer les épanchements pleuraux malins des épanchements pleuraux non tumoraux, « bénins » n'est pas précisément connue et n'a pas jusqu'à présent été investiguée de manière approfondie.

Matériel et méthodes : Nous avons examiné la captation du FDG (indice SUVmax) des épanchements pleuraux de 50 PET/CT réalisés chez 47 patients (29 hommes, 18 femmes, $60\pm16$ ans) avec épanchements pleuraux et cancer connu (24 NSCLC, 7 lymphomes, 5 cancer du sein, 4 GIST, 3 mésothéliomes, 2 cancer ORL, 2 tératomes malins, 1 carcinome colorectal, 1 carcinome oesophagien, 1 mélanome). Ces résultats ont été corrélés aux résultats des examens cytopathologiques réalisés après ponction de ces mêmes épanchements dans un intervalle médian de 21 jours (interquartile range –3 to 23). L'examen du liquide d'épanchement comportait la mesure du pH, la distribution relative des différents éléments cellulaires (macrophages, neutrophiles, éosinophiles, basophiles, lymphocytes, plasmocytes), la numération cellulaire et bien entendu présence de cellules tumorales.

Résultats : Parmis les épanchements, 17 étaient malins (34%) (6 NSCLC, 5 lymphomes, 2 cancers mammaires, 2 mésothéliomes, 2 tératomes malins).
Les SUV étaient plus élevés dans les épanchements malins que dans les épanchements bénins [3.7 (95%IC 1.8–5.6) vs. 1.7 g/ml (1.5–1.9), p = 0.001], avec une corrélation entre les épanchements malins et le SUV (coefficient de Spearman $\rho = 0.50$, p = 0.001). Il n'a pas été observé de corrélation entre aucun des autres paramètres cyptopathologiques ou radiologiques analysé (aire sous la courbe ROC $0.83 \pm 0.06$).
En utilisant un seuil du SUV de 2.2-mg/l, 12 examens PET/CT étaient interprétés comme positifs and 38 comme négatifs avec une sensibilité et une spécificité, valeur prédictive positive et négative de 53%, 91%, 75% and 79% respectivement. Concernant le groupe des NSCLC seulement (n = 24), aire sous la courbe ROC était de $0.95 \pm 0.04$. Sept examens étaient considérés comme positifs et 17 comme négatifs avec une sensibilité, une spécificité, valeur prédictive positive et négative de 83%, 89%, 71 et 94% respectivement.

Conclusion : Le PET/CT peut aider à différencier la nature bénigne ou maligne des épanchements avec une haute spécificité chez les patients avec tumeur connue, en particulier dans un contexte de carcinome NON à petites cellules.

# 18F-fluorodeoxyglucose PET/CT findings in pleural effusions of patients with known cancer
## A cytopathological correlation

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**Keywords**
Pleural effusion, tumour, PET/CT, FDG

**Summary**
Aim: Pleural effusion is common in cancer patients and to determine its malignant origin is of huge clinical significance. PET/CT with 18F-FDG is of diagnostic value in staging and follow-up, but its ability to differentiate between malignant and benign effusions is not precisely known. Patients, methods: We examined 50 PET/CT from 47 patients (29 men, 18 women, 60±16 years) with pleural effusion and known cancer (24 NSCLC, 7 lymphomas, 5 breasts, 4 GIST, 3 mesotheliomas, 2 head and neck, 2 malignant teratoma, 1 colorectal, 1 oesophageal, 1 melanoma) for FDG uptake in the effusions using $SUV_{max}$. This was correlated to cytopathology performed after a median of 21 days (interquartile range –3 to 23), which included pH, relative distribution (macrophages, neutrophils, eosinophils, basophils, lymphocytes, plasmocytes), and absolute cell count. Results: Malignant cells were found in 17 effusions (34%) (6 NSCLC, 5 lymphomas, 2 breasts, 2 mesotheliomas, 2 malignant teratomas). SUV in malignant effusions were higher than in benign ones [3.7 (95%CI 1.8–5.6) vs. 1.7 g/ml (1.5–1.9), p = 0.001], with a correlation between malignant effu-

sion and SUV (Spearman coefficient $\rho$ = 0.50, p = 0.001), but not with other cytopathological or radiological parameters (ROC area 0.83±0.06). Using a 2.2-mg/l SUV threshold, 12 PET/CT studies were positive and 38 negative with sensitivity, specificity, positive and negative predictive values of 53%, 91%, 75% and 79%, respectively. For NSCLC only (n = 24), ROC area was 0.95±0.04, 7 studies were positive and 17 negative with a sensitivity, specificity, positive and negative predictive values of 83%, 89%, 71 and 94%, respectively. Conclusion: PET/CT may help to differentiate the malignant or benign origin of a pleural effusion with a high specificity in patients with known cancer, in particular NSCLC.


**Schlüsselwörter**
Pleuraerguss, Tumor, PET/CT, FDG

**Zusammenfassung**
Ziel: Pleuraerguss ist ein häufiges Symptom, auch bei onkologischen Patienten, ohne dass es sich obligat um eine maligne Ätiologie handeln muss. Der Charakter des Ergusses und seine Pathogenese sind jedoch für weitere therapeutische Maßnahmen entscheidend. Die Wertigkeit der 18F-FDG-PET/CT für Staging und Nachsorge ist unbestritten, ob aber die PET zwischen ma-

lignem und benignem Erguss unterscheiden kann wurde noch wenig untersucht. Patienten und Methodik: Wir untersuchten 47 Tumor-Patienten (29 Männer, 18 Frauen, 60±16 Jahre) mit Pleuraergüssen [24 nicht-kleinzellige Lungenkarzinome (NSCLC), 7 Lymphome, 5 Mammakarzinome, 4 GIST, 3 Mesotheliome, 2 HNO-Karzinome, 2 maligne Teratome, 1 Kolon/Rektumkarzinom, 1 Ösophaguskarzinom, 1 Melanom] mit insgesamt 50 PET/CT. Die FDG-Konzentration in den Ergüssen wurde anhand Messungen des $SUV_{max}$ normalisiert auf das Körpergewicht geschätzt. Die Pleuraergüsse wurden alle punktiert, im Mittel 21 Tage (Interquartilbereich –6 bis +23 Tage) nach der PET-Untersuchung, und zytologisch untersucht, ebenso wurde die zelluläre Zusammensetzung (Makrophagen, Neutrophile, Eosinophile, Basophile, Lymphozyten, Plasmozyten) quantifiziert und der pH-Wert bestimmt. Ergebnis: Siebzehn Pleuraergüsse (34%) enthielten maligne Zellen (6 NSCLC, 5 Lymphome, 2 Mammakarzinome, 2 Mesotheliome, 2 maligne Teratome) und zeigten einen höheren $SUV_{max}$-Wert als Ergüsse ohne klare maligne Ursache [3,7 (95%CI 1,8–5,6) vs. 1,7 g/ml (1,5–1,9), p = 0,001]. Die malignen Pleuraergüsse korrelierten lediglich mit dem SUV (Spearman-Koeffizient $\rho$ = 0,50, p = 0,001), jedoch nicht mit zytologischen oder radiologischen Parametern (ROC-Area 0,83±0,06). Bei einer $SUV_{max}$-Schwelle von 2,2 mg/l, waren 12 PET/CT Untersuchungen positiv und 38 negativ, mit 53% Sensitivität, 91% Spezifität, was sich in einen 75% positiven und 79% negativen prädiktiven Wert übersetzt. Analysieren wir lediglich NSCLC (n = 24) wird eine ROC von 0,95±0,04 errechnet, 7 Unter-

suchungen waren positiv und 17 negativ, mit 83 % Sensitivität, 89 % Spezifität, und somit 71 % positivem und 94 % negativem prädiktivem Wert. Schlussfolgerung: Die PET/CT erlaubt mit hoher Spezifität zwischen malignen und benignen Pleuraergüssen zu unterscheiden, insbesondere bei NSCLC. Der negative prädiktive Wert von >90 % ist klinisch von Bedeutung.

Pleural effusion is defined as an accumulation of >15–20 ml of fluid in the pleural space (1). It is found in a wide range of clinical conditions (1), such as
- heart failure,
- inflammatory or infectious disease,
- cancer, or
- may be of renal or hepatic origin (1).

In patients over 50 years old, about 40 % of clinically significant effusions are due to malignancy, most commonly lung and breast cancer, lymphoma, mesothelioma, oesophageal or gastric cancer, ovarian carcinoma and germ cell tumours (1). In cancer patients, determining whether malignant cells are present in a pleural effusion is of great clinical significance, as it determines therapeutic attitude and prognosis.

> Malignant effusions are caused by local extension of lung cancer or by metastatic disease and usually represent an advanced stage.

The presence of malignant cells is determined by cytopathological examination of thoracocentesis obtained effusion fluid (18). Fourteen percent of patients with lung cancer have pleural effusion when diagnosis is first established (30). In the latest 7th edition of the AJCC TNM staging 2010 (8), malignant pleural effusion in lung cancer has been reclassified to a worse prognosis group, moving from T4 to M1 category, i. e. from stage IVA to IVB. Nevertheless, pleural effusions in cancer patients are not always malignant (8).

Hybrid imaging with positron emission tomography/computed tomography (PET/CT) has proved to be of high diagnostic value in staging and follow-up of patients with lung cancer (10, 11), as well as other tumours such as lymphoma, colorectal, breast and head and neck cancers, among others (24).

The uptake of 18F-fluorodeoxyglucose (FDG) during PET imaging, as measured by the maximum standardized uptake value reported for body weight ($SUV_{max}$) has been defined for solid tumours or masses and has a strong predictive value for determining their benign or malignant nature. Although PET/CT is becoming a standard procedure in cancer patient investigations, only a few studies have tried to evaluate pleural disease and effusions with PET or PET/CT (2, 6, 7, 9, 12, 16, 27). However, no study has presented a correlation between imaging and the cytopathological characteristics of the thoracocentesis liquid, which is important to understand the respective roles of inflammatory and malignant component of the effusion on SUV values. Indeed, it is known that the uptake of FDG is not specific of malignant cells, but can also be found in inflammatory cells such as lymphocytes, monocytes and macrophages (14, 17, 22). Thus, we aimed at determining the value of PET/CT in non-invasively predicting
- the malignant or benign nature of pleural effusion in cancer patients at initial staging or during follow-up, as well as
- the effect of the cytopathological characteristics on the FDG uptake.

## Patients, material, methods

### Patients

Data from the University Institute of Pathology and from the Nuclear Medicine Department of the Lausanne University Hospital were cross-matched for patients undergoing thoracocentesis with cytological examination of effusion fluid and PET/CT between June 2004 and December 2006. Only patients having both cytological evaluation of the fluid and imaging procedures within a 60-day interval were included in this study. The Institutional Review Board issued a waiver for patient informed consent for this retrospective study.

### Cytopathology

All pleural effusions were examined according to a standard protocol. When received, effusion fluid quantity was determined. The pH was measured when possible (delayed arrival of the fluid precluded this analyses in some cases) and cell numeration was performed. The pH was measured with a laboratory millivoltmeter PHM210 with a pHC3006–9 electrode (Radiometer Analytical, Villeurbanne, France).

Absolute cell count was assessed using a Neubauer haemocytometer chamber. After centrifugation at 2000 rpm for 10 minutes, six smears were made. Three were immediately fixed with Delaunay and Pap stained. The three others were air-dried from which two were stained with MGG (May-Gruenwald Giemsa). When cell concentration was low, additional cytospins were obtained. Cell distribution (macrophages, neutrophils, eosinophils, basophils, lymphocytes, plasma cells) and presence or absence of atypical or malignant cells was assessed. When needed, cellblocks were made, and standard immunostains (Calretinin, WT-1, BerEP4, B72.3, TTF-1, hormone receptors, lymphoid markers, etc.) were performed to determine the reactive or tumoural nature of the liquid as well as the origin of any atypical/tumour cells observed. All smears and immunostained slides were initially reviewed by a senior cytopathologist. Results of the routinely performed cytological examinations were collected and cytological slides were reviewed to complete any missing data.

### Imaging studies

#### PET/CT

Whole-body PET/CT was acquired 60 min after intravenous bolus injection of FDG (5 MBq/kg body weight). Patients were asked to refrain from eating ≥6 hours before PET and blood glucose at injection was <8.3 mmol/l (Discovery LS scanner, GE Healthcare, Milwaukee, Wisconsin). Attenuation correction was performed using a low-dose unenhanced CT (140 keV, 80 mA, slice thickness 5 mm).

#### Enhanced CT

All enhanced CT were performed for investigating increasing dyspnoea symptoms using the same pulmonary embolism protocol on an 8- or 16-detector CT scanner (GE Healthcare, Milwaukee, Wisconsin). Thirty seconds after intravenous (IV) iodinated contrast medium injection (80 ml at 3 ml/s, 300 mgI/ml, Accupaque®, Iohexol, GE Healthcare) data acquisition was performed (120 keV, 260mA, pitch 1.375, collimation 0.675, axial slice reconstruction 5 mm/5 mm for standard algorithm and 1.25 mm/1 mm for lung algorithm).

#### Imaging study analysis

PET/CT and enhanced CT, when available, were reviewed. On PET/CT, FDG uptake was measured using the maximum standardized uptake value corrected for body weight ($SUV_{max}$ in g/ml) in pleural effusions or in pleural lesions using a 1.2 cm circular region of interest and avoiding the thoracic wall and the lung parenchyma; in larger effusions, the region of interest was placed in the centre of the effusion. Pleural liquid quantity was estimated using a dichotomized scale (<500 ml,≥500 ml) based on the absence or presence of pleural effusion on more than half on the lung length [adapted from (29)]. Enhanced CT was used to determine presence of pleural lesions or serosal enhancement and their Hounsfield density (HU) was measured, as well as the one of the effusion fluid (15).

#### Statistical analysis

Cytopathological examination of pleural effusion fluid after thoracocentesis is considered the most accurate procedure to determine the benign or malignant nature of an effusion, and was considered as the so-called gold standard in our study (8).

The ability of SUV to determine the presence of malignant cells in pleural effusion was evaluated using receiver operating characteristics (ROC) curves and computing sensitivity, specificity, negative (NPV) and positive predictive value (PPV) as compared to the gold standard (cytopathology) (23). The effect of other cytopathological parameters, especially inflammatory cells, as well as pleural liquid quantity, CT density and contrast enhancement was examined. Significance was considered for p < 0.05.

## Results

In total, 50 18F-FDG PET/CT studies and cytological analysis of the thoracocentesis were performed in 47 patients with known cancer. There were 29 men and 18 women with a mean age of 60 ± 16 years, who were investigated for
- non-small cell lung cancer (NSCLC) (n = 24, 48 %),
- lymphoma (n = 7, 14 %),
- breast cancer (n = 5, 10 %),
- GIST (n = 4, 8 %),
- mesothelioma (n = 3, 6 %),
- head and neck cancer (n = 2, 4 %),
- malignant teratoma (n = 2, 2 %),
- colorectal carcinoma (n = 1, 2 %),
- oesophageal carcinoma (n = 1, 2 %) and
- melanoma (n = 1, 2 %).

Thoracocentesis was performed within a median interval of 21 days (interquartile range –6 to 23 days) after PET/CT imaging; in a few examinations (n = 18), it was performed before the PET/CT.

### Cytological examinations

Out of the 50 cytological analyses,
- 33 (66 %) were benign and
- 17 (34 %) were malignant.

Of the latter, 6 (35 %) were positive for NSCLC, 5 (29 %) for lymphomas, 2 (12 %) breast cancer, 2 (12 %) for mesothelioma and 2 (12 %) for malignant teratoma. De-

Tab. 1
Results of 50 thoracocentesis liquid samples, grouped according to the final diagnosis of benign versus malignant effusions

| results | variable mean ± SD (range) | | effusion | | p |
|---|---|---|---|---|---|
| | | | benign (n = 33) | malignant (n = 17) | |
| cytopathology | thoracocentesis volume (ml) | | 227±353 (2–1400) | 296±443 (5–1880) | 0.18 |
| | absolute cell count (10⁹/l)* | | 1.2±1.1 (0.075–4.3) | 3.3±4.9 (0.20–15.2) | 0.21 |
| | effusion pH | | 7.6±0.3 (7.3–8.3) | 7.5±0.3 (7.0–7.8) | 0.32 |
| | relative distribution (%) | macrophages | 20±23 (0–82) | 14±11 (0–34) | 0.96 |
| | | neutrophils | 22±26 (0.5–89) | 12±22 (0–85) | 0.21 |
| | | eosinophils | 1.9±4.1 (0–20.5) | 2.4±5.1 (0–19) | 0.94 |
| | | basophils | 0.02±0.09 (0–0.5) | 0 (0–0) | 0.47 |
| | | lymphocytes | 50±28 (2–97) | 57±32 (3–99) | 0.59 |
| | | plasmocytes | 0.36±1.1 (0–6) | 0.53±1.7 (0–7) | 0.70 |
| | | others | 0.16±1.0 (0–6) | 2.6±10 (0–42) | 0.23 |
| PET/CT, enhanced CT | SUV (g/ml) | | 1.7±0.6 (0.6–3.9) | 3.7±3.8 (1.3–16) | 0.001 |
| | effusion quantity (ml) estimate (%) | 0–500 | 18/33 (55 %) | 6/17 (35 %) | 0.24 |
| | | ≥ 500 | 15/33 (45 %) | 11/17 (65 %) | |
| | CT density (HU)# | effusion | 9±6 (-8–20) | 11±3 (5–15) | 0.41 |
| | | parietal | 18±8 (7–40) | 18±3 (14–21) | 0.44 |

*#available in a subset of patients (effusions *n = 30, #n = 24); SUV: standardized uptake value
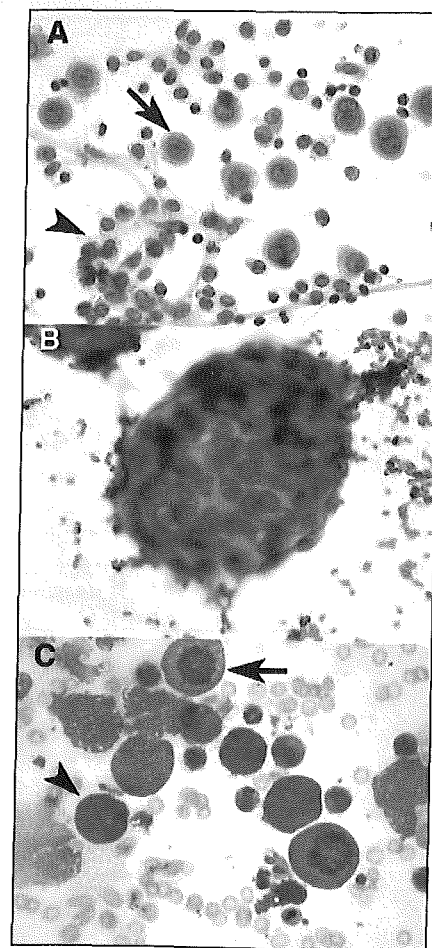
Fig. 1  Cytological examinations
A) reactive effusion with reactive mesothelial cells (→) in an inflammatory background (arrowhead) (PAP stain, ×400)
B) malignant effusion with lung adenocarcinoma cells in aggregates presenting voluminous and vacuolated cytoplasm (PAP stain, ×400)
C) lymphoma with malignant lymphoid cells in mitosis (→) and atypical lymphocytes with deeply basophilic cytoplasm (arrowhead) (MGG stain, ×600).

tailed cytological characteristics of the benign and malignant effusions are summarized in ▶Table 1. Except for the presence of atypical cells, there were no significant differences among benign or malignant effusions. Some of the cytological findings are illustrated for benign (▶Fig. 1A) and malignant thoracocentesis liquid samples (▶Fig. 1B and 1C).

### PET-CT and enhanced CT findings

The PET/CT and enhanced CT are presented in ▶Table 1. There was a significantly higher SUV in malignant effusions as compared to benign effusions (▶Tab. 2, ▶Fig. 2). All other imaging characteristics were not significantly different between benign and malignant pleural effusions, notably the pleural effusion volume estimate, or the CT Hounsfield density of the effusion or parietal region. All enhanced CT (n = 24) were performed because of sudden respiratory symptoms onset, to exclude pulmonary embolism. Three of the enhanced CT showed parietal pleural lesion with enhancement with a mean CT density of 56 (47–65) HU and a mean SUV uptake of 4.3 (2.2–8.6) g/ml; two of these, were diagnosed with malignant effusion.

As illustration, ▶Figure 2 shows examples of PET/CT images for patients with a positive (▶Fig. 2A) and negative (▶Fig. 2B) cytopathological examination for malignant cells in the effusion.

### Predictive value of PET/CT imaging

The association of cytopathological and imaging characteristics with the final diagnosis of malignant pleural effusion is presented in ▶Table 2. There was no significant correlation between any cytopathological parameters, except for a strong association of presence of malignant cells with SUV (Spearman $\rho$ = 0.50, p < 0.001) and a trend for decreased neutrophils being associated with malignant cells. Inversely, we also found no significant association of PET/CT SUV with any other cytopathological parameters or CT HU density of the effusion or of the parietal part (▶Tab. 2). When analysed separately for the subgroup of patients with NSCLC, these associations remained, with a much stronger correlation between SUV and the presence of malignant cells (Spearman $\rho$ = 0.66, p < 0.0001). For the subgroup of patients with cancer other than NSCLC, the correlation between SUV and the presence of malignant cells remained, although it was weaker (Spearman $\rho$ = 0.41, p = 0.041).

We also performed a ROC analysis to predict the malignant nature of the pleural effusion using SUV as the only independent predictor (▶Fig. 3). The area under the curve (AUC) was 0.81±0.07 (▶Fig. 3A). Using a threshold of ≥2.2 g/ml led to 9 true positive, 30 true negative, 3 false positive and 8 false negative examinations. This allowed obtaining a
- sensitivity of 53% (95%CI 28–77%),
- specificity of 91% (76–98%),
- positive predictive value of 75% (43–95%),
- negative predictive value of 79% (63–90%).

The corresponding odds ratio was 6.9 (1.9–41) on logistic regression (p = 0.005). Nearly half of our population were patients with non-small cell lung cancer (n = 24). We examined the performance of PET/CT SUV to determine the presence of malignant cells in this population. Thus, for NSCLC, the AUC was excellent with 0.94±0.05 (▶Fig. 3B). Using the same threshold ≥2.2 g/ml resulted in 5 true positive, 16 true negative, 2 false positive and 1 false negative examinations. This led to a
- sensitivity of 83% (95%CI 36–99%),
- specificity of 89% (65–99%),
- positive predictive value of 71% (29–96%),
- negative predictive value of 94% (71–99%).

The corresponding odds ratio was 16 (1.7–151) on logistic regression (p = 0.016). Finally, we tested separately the group of patients with cancers other than NSCLC and found a lower AUC of 0.74±0.10, which led to a
- sensitivity of 36% (11–69%),
- specificity of 93% (68–99%),
- positive predictive value of 80% (28–99%),
- negative predictive value of 67% (43–85%).

### Discussion

Malignant effusion in patients with known cancer is of clinical significance and usually represents advanced disease stage. PET/CT is a tool frequently used to help staging in oncologic patients. We showed that

- the uptake of FDG was significantly elevated in patients with malignant pleural effusion,
- SUV was the only variable showing an association with the malignant nature of the thoracocentesis fluid on uni- and multivariate analyses.

No other imaging or cytological parameters were associated with malignant cells, even HU density on enhanced CT. Using a threshold of 2.2 g/ml allowed to accurately classifying 81% of effusions with a high specificity of 91%, with a poor sensitivity of 53%, however. When considering only patients with NSCLC, the same 2.2-mg/dl SUV threshold allowed to correctly classify 94% of effusions, with a good specificity of 89% and an excellent negative predictive value. This high negative predictive value is of huge clinical value, as the latest AJCC TNM staging for NSCLC would put a patient with malignant pleural effusion in the worst-prognosis M1 group. The performances for the subgroup of patients with cancer types other than NSCLC were poorer, but a significant association existed only between SUV and the presence of malignant cells.

In the literature, only two studies using PET/CT were reported so far for investigating pleural effusions (2, 16). Both studies reported higher sensitivity of determining the presence of malignant effusion in patients with NSCLC, but were methodologically different by reporting the highest FDG uptake in the pleural region (93 and 88%, respectively). In our study, only three patients showed parietal lesions out of the 33 patients with positive parietal effusion, leaving the sensitivity of this criterion under 10% in the study presented here. Only the study by Kim et al. did measure the SUV in the pleural effusion itself and determined a much lower sensitivity of 29% with a very high specificity of 100% and an accuracy of 0.61 when using a threshold of SUV > 1.56 for malignancy on PET/CT (16). This was not suited to help differentiating the malignant or benign origin of pleural effusion, however.

In the other study, Alkhawaldeh et al. did not measure the effusion SUV but only the pleural SUV. Yet, they found that dual-time acquisition was useful and could increase
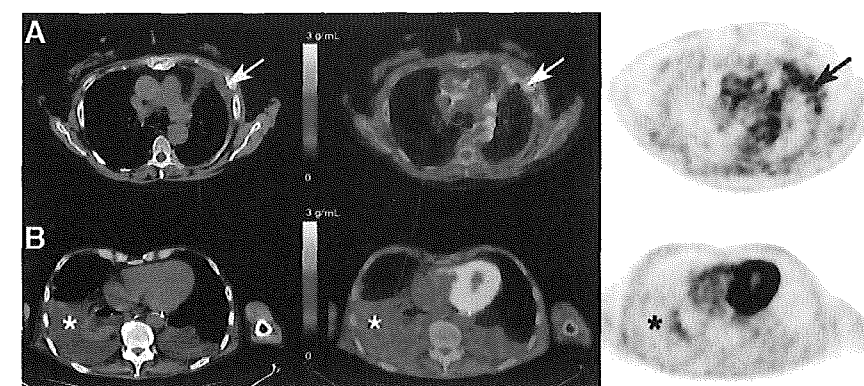


Fig. 2  CT, PET/CT fusion and PET images
A) woman (69 years) with pulmonary adenocarcinoma showing a 3.5-g/ml-SUV pleural effusion with malignant cells (→)
B) man (69 years) with oesophageal adenocarcinoma and a 1.2-g/ml-SUV pleural effusion containing only macrophages and no malignant cells (*)

Tab. 2  Univariate association of cytological and imaging parameters with diagnosis of malignant effusion and standardized value uptake (SUV)

| variable (n = 50) | | Spearman correlation | | | |
|---|---|---|---|---|---|
| | | malignant cells | p | SUV | p |
| thoracocentesis volume | | 0.18 | 0.21 | 0.08 | 0.57 |
| absolute cell count* | | 0.26 | 0.16 | 0.04 | 0.82 |
| effusion pH | | −0.23 | 0.33 | −0.01 | 0.96 |
| relative distribution (%) | macrophages | −0.01 | 0.97 | 0.10 | 0.47 |
| | neutrophils | −0.25 | 0.09 | −0.25 | 0.08 |
| | eosinophils | −0.01 | 0.94 | 0.08 | 0.58 |
| | basophils | −0.10 | 0.48 | −0.05 | 0.71 |
| | lymphocytes | 0.08 | 0.60 | 0.02 | 0.86 |
| | plasmocytes | 0.05 | 0.71 | 0.02 | 0.91 |
| | others | 0.17 | 0.23 | 0.08 | 0.56 |
| absolute cell count (10⁹/l)* | macrophages | 0.13 | 0.47 | 0.02 | 0.92 |
| | neutrophils | −0.17 | 0.34 | −0.18 | 0.34 |
| | eosinophils | −0.01 | 0.98 | −0.06 | 0.74 |
| | basophils | −0.13 | 0.49 | 0.12 | 0.53 |
| | lymphocytes | 0.16 | 0.39 | 0.03 | 0.88 |
| | plasmocytes | 0.19 | 0.29 | −0.10 | 0.61 |
| | others | 0.25 | 0.18 | 0.09 | 0.65 |
| standardized uptake value | | 0.50 | <0.001 | 1.00 | — |
| effusion quantity estimate | | 0.18 | 0.20 | 0.16 | 0.28 |
| CT density† | effusion | 0.17 | 0.42 | 0.10 | 0.61 |
| | parietal | 0.16 | 0.46 | −0.14 | 0.50 |

*†available in a subset of patients (effusions *n = 30, †n = 24)

the diagnostic accuracy (2). Whether this would hold true in pleural effusion SUV remain to be verified. Other studies using PET only investigated the value of pleural activity to define the malignant nature of

effusions (7, 9, 12, 25, 27) also showing high sensitivities (88–100%) and good specificities (67–94%).

Only Toaff et al. investigated the uptake in the pleural effusion of patient with

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extra-pleural primary malignancies using a 1.7-g/ml SUV threshold to find a sensitivity of 43% with a 70% specificity and an accuracy of 55% (27). Interestingly, they report on an already proposed criteria (28) based on a higher FDG uptake than lung on non-attenuation corrected PET images being associated with a high probability of malignant effusion. In summary, we found higher sensitivity, specificity and accuracy in determining pleural malignancy in our study than the two previously published studies on effusion FDG uptake (16, 27).

> The uniqueness of our study was to correlate cytopathological parameters with the effusion FDG uptake represented by the effusion SUV.

We found no significant correlation with the presence of inflammatory cells, even though such association could be supposed from the FDG uptake mechanism, which accumulates in activated inflammatory cells particularly neutrophils, activated lymphocytes and macrophages (14, 17, 22). Thus, in pleural effusion, only the presence of malignant cells was associated with increased FDG uptake in contrary to what can be observed in many situations where FDG is known to be increased by inflammatory processes (19). Moreover, the lower SUV threshold in pleural effusion than in solid tumours might be explained by a lower tumour cell charge and that FDG penetrates pleural cavity by exudation/transudation and not by perfusion.

The clinical management of pleural effusions in cancer patients prompts for the determination of the malignant or benign origin. Indeed, benign effusions are treated according to the primary cause, while in malignant effusions symptoms relief can be obtained with pleurodesis or may respond to chemotherapy in case of lymphoma, small cell lung carcinoma or germ cell tumours. PET/CT may be used

- for excluding the presence of malignant cells in patients with known cancers when
  - thoracocentesis is not feasible, i.e. when there is less than 10-mm of pleural effusion on ultrasonography (18) or
  - patients are in poor condition, keeping in mind that the negative predictive value is 79%, which may still be clinically relevant.
- to identify patients with previously undetected malignant effusion with for instance negative thoracocentesis, whom should be referred for thoracoscopy.

Specifically, in NSCLC, the presence of malignant effusion is associated with a poor prognosis and limited survival of 2–6 months (30). Including information on performance status may be of high clinical relevance. Indeed, determining whether a pleural effusion in a NSCLC patient with poor performance index is of malignant origin or not may not be necessary (30). On the contrary, identifying a subset of patients with better survival may be of critical importance (30). Thus, due to its high negative predictive value (94% in our study), PET/CT may help to select patients with satisfactory performance index and a likely better prognosis in whom thoracoscopy could be avoided.

> Patients with satisfactory performance index, negative cytology and positive PET/CT in pleural effusion could be referred for thoracoscopic evaluation of the pleural effusion before being referred to surgery to exclude a false negative result of the thoracocentesis.

The exact place of PET/CT in the management of patients with cancer presenting pleural effusion would need to be determined in a prospective study to see where it can be adequately implemented in the clinical management (21). As mentioned, further studies would be needed:

- on patients with pleural effusion and cancers other than NSCLC; and
- on whether using a different or modified protocol for investigating pleural effusion with PET/CT would be of interest to appreciate the role of exudation on pleural effusion SUV values.

## Limitations

Our study was retrospective, but the nuclear medicine physicians and radiologists were blinded to the cytopathology results. Moreover, in a few examinations (n = 18), thoracocentesis was performed before the PET/CT and may have induced an inflammatory response that may theoretically increase the FDG uptake in the pleural effusion. However, there was no significant difference in SUV in benign pleural effusion when thoracocentesis was performed before PET/CT imaging as compared to the group where thoracocentesis was performed thereafter (1.5±0.5, n = 10 vs. 1.8±0.6, n=23; p = 0.17). Also, the time interval of 60 days between the PET/CT and thoracocentesis might be seen as a limitation, but similar differences in SUV between malignant and benign effusions were observed when this interval was limited to 30 days (3.9±4.0, n = 15 vs. 1.7±0.7, n = 21; p=0.019), as well as nearly identical Spearman ranks correlation between the presence of malignant cells and SUV (ρ = 0.52, n = 36; p = 0.0012).

The fact that thoracocentesis was used and results were not verified by thoracoscopic biopsy might be seen as a limitation. Indeed, the diagnostic yield of thoracocentesis with traditional cytology has been commonly described to be around 65% in the literature as compared to thoracoscopy-obtained or imaged-guided biopsy (13), although in our series less than 10% of the patient had pleural lesions suitable for an imaged-guided biopsy. The true value of thoracocentesis remains controversial, with values ranging from 62–90% (3) or 40–87% with a mean of 60% (20) in the consensus of the American and British Thoracic Societies. However, it is probably underestimated, as many additional cytopathology techniques can be added to pleural fluid examination, such as

- tumoural marker detection (carcino-embryonic antigen, carbohydrate antigen 15–3, cancer antigen 125),
- genetic analysis (DNA methylation, gene expression testing, aneuploidy detection, comparative genomic hybridization analysis) and
- immunologic and molecular cytogenetic testing for lymphoma (13, 30).

The addition of these special studies or different smear techniques, as performed in our study, can improve the rate of yield of thoracocentesis above 80% (5, 26). Therefore, the state-of-the-art augmented cytopathology techniques employed in our study cannot be considered as a limitation as compared to thoracoscopic biopsy.

Finally, it should be mentioned that the reported sensitivities and specificities are relatively independent on the prevalence of malignant pleural effusions in the observed population (4) and would be applicable to other centres, in contrary to positive and negative predictive values, which would more strongly depend on the prevalence of malignant pleural effusions in the observed population (34% in our population).

## Conclusion

Pleural effusion SUV was a significant and independent predictor of the presence of malignant cells in patients with known cancers with a high specificity, compared to common cytopathological parameters.

> PET/CT pleural FDG effusion uptake had a good specificity and high negative predictive value especially in patients with NSCLC. This allows clinicians to anticipate thoracocentesis results or to identify the subpopulation requiring thoracoscopic biopsy (in case of positive PET/CT with negative thoracocentesis findings).

This would be of clinical importance in patients with NSCLC, as malignant effusion would contraindicate surgery. Larger prospective studies are warranted to confirm our findings, preferably in a multi-centre trial.

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### Conflict of interest
The authors declare, that they have no conflict of interest.

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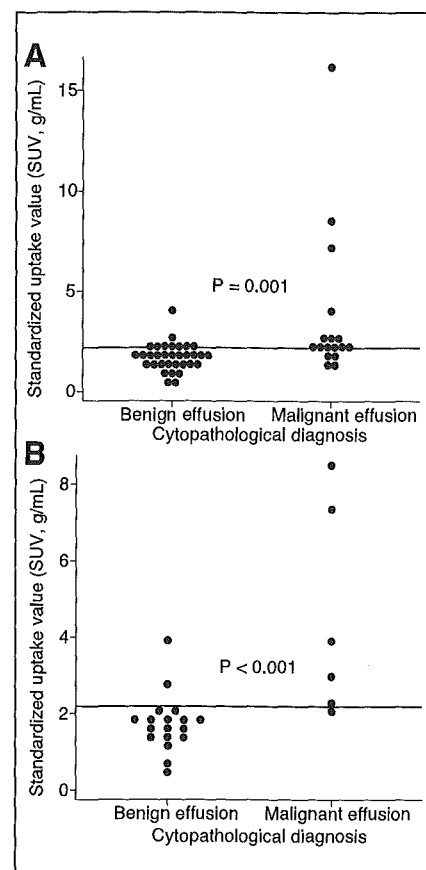
Fig. 3 SUV of patients with
A) benign (n = 33) versus malignant effusions (n = 17)
B) non-small cell lung carcinoma with benign (n = 18) versus malignant effusions (n = 6)
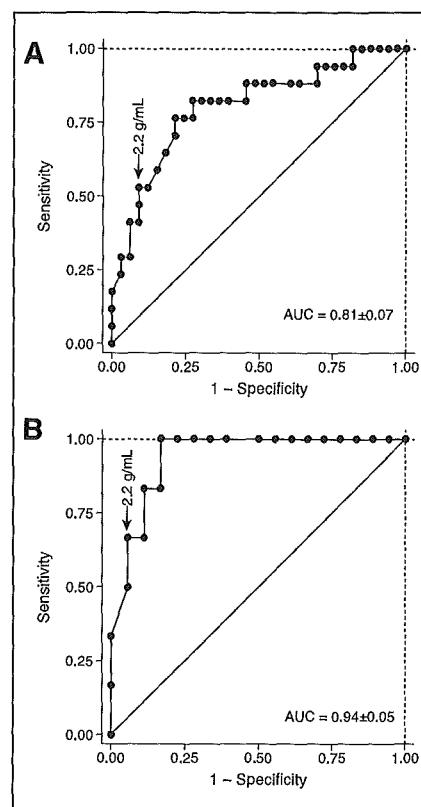


Fig. 4 ROC analysis (sensitivity versus 1 – specificity = false positive rate) of thoracocenteses
A) all patients (n = 50)
B) patients with non-small cell lung carcinoma (n = 24)

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