Carcinoma Polmonare: fattori di rischio e diagnosi

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Timing di intervento dell'imaging medico nucleare nella neoplasia polmonare

- Management
- T-staging
- N-staging
- M-staging
- NPS
- PET for Interim Tumor Response Assessment
- Functional Imaging for Tumor Response
- MTV in Oncology

Lung Cancer

Staging Non-Small Cell Lung Cancer (NSCLC) by FDG-PET/CT is probably one of the main daily-practice indications encountered in a nuclear department.

Indeed, several non-invasive imaging modalities are available for staging NSCLC, but FDG-PET/CT utility and advantages have been clearly demonstrated long since.

The addition of FDG-PET/CT to the conventional staging assessment was reportedly shown to **change the management in 20%–30%** of patients with NSCLC, mostly by upstaging disease and, notably, by redefining unresectable a previously defined resectable disease by traditional radiological means.

Several recent studies, and in particular the **randomized multicenter study of Maziak (2009)**, reported that tumor staging with FDG-PET/CT immediately before surgery revealed more patients with mediastinal and distant metastatic disease than conventional imaging; disease was correctly upstaged in 23 of 167 FDG-PET/CT.

Likewise (2009) noticed that the use of FDG-PET/CT for preoperative staging of NSCLC reduced both the total number of thoracotomies and the number of futile thoracotomies but did not affect overall mortality .

Weng, E.; Tran, L.; Rege, S.; Safa, A.; Sadeghi, A.; Juillard, G.; Mark, R.; Santiago, S.; Brown, C.; Mandelkern, M. Accuracy and clinical impact of mediastinal lymph node staging with FDG-PET imaging in potentially resectable lung cancer. Am. J. Clin. Oncol. 2000, 23, 47–52.

Changlai, S.P.; Tsai, S.C.; Chou, M.C.; Ho, Y.J.; Kao, C.H. Whole body 18F-2-deoxyglucose positron emission tomography to restage non-small cell lung cancer. Oncol. Rep. 2001, 8, 337–339.

Taus, A.; Aguilo, R.; Curull, V.; Suarez-Pinera, M.; Rodriguez-Fuster, A.; Rodriguez de Dios, N.; Zuccarino, F.; Vollmer, I.; Sánchez-Font, A.; Belda-Sanchis, J.; et al. Impact of 18F-FDG PET/CT in the Treatment of Patients With Non-Small Cell Lung Cancer. Arch. Bronconeumol. 2014, 50, 99–104.

Maziak, D.E.; Darling, G.E.; Inculet, R.I.; Gulenchyn, K.Y.; Driedger, A.A.; Ung, Y.C.; Miller, J.D.; Gu, C.S.; Cline, K.J.; Evans, W.K.; et al. Positron emission tomography in staging e rly lung cancer: A randomized trial. Ann. Internal Med. 2009, 151, 221–228, W-48.

Fischer, B.; Lassen, U.; Mortensen, J.; Larsen, S.; Loft, A.; Bertelsen, A.; Ravn, J.; Clementsen, P.;
Høgholm, A.; Larsen, K.; et al. Preoperative staging of lung cancer with combined PET-CT. N. Engl. J. Med. 2009, 361, 32–39.

T Staging

FDG-ET/CT provides information on tumor staging according to TNM criteria. **The utility of FDG-PET/CT for determining T stage, and in particular T3 or T4 invasion, has not been definitely determined.**

The evaluation of tumor spread to the pleura by FDG-PET/CT is probably the main advantage compared to conventional imaging. Actually, pleural effusion is relatively frequent in patients with NSCLC, and may be malignant or benign, in particular in patients with postobstructive pneumonia.

The sensitivity and specificity of FDG-PET/CT in determining pleural invasion range from 70% to 95% and 64% to 94% respectively. The limitations of FDG-PET/CT for T staging are due to the anatomical localization and size measurement difficulties, microscopic disease underestimation, or absence of FDG uptake in case of low-metabolism tumors (bronchoalveolar cell carcinoma, carcinoid tumors).

Nevertheless, FDG-PET/CT turned out the most accurate tool for T staging assessment, with a correct T staging definition in 86% of patients, as compared to 68% with computed tomography (CT) alone(De Wever 2007, Imai 2014).

Imai, K.; Minamiya, Y.; Saito, H.; Motoyama, S.; Sato, Y.; Ito, A.; Yoshino, K.; Kudo, S.; Takashima, S.; Kawaharada, Y.; et al. Diagnostic imaging in the preoperative management of lung cancer. Surg. Today 2014, 44, doi:10.1007/s00595-013-0660-z. Cancers 2014, 6 1861
De Wever, W.; Ceyssens, S.; Mortelmans, L.; Stroobants, S.; Marchal, G.; Bogaert, J.; Verschakelen, J.A. Additional value of PET-CT in the staging of lung cancer: Comparison with CT alone, PET alone and visual correlation of PET and CT. Eur. Radiol. 2007, 17, 23–32.

T-staging e Bayes

coinvolgimento pleurico T dipendente

SE	0,7
SP	0,64
PREV	0,2
VPP	**0,327**
VPN	**0,105**

T3-T4

T1-T2

SE	0,95
SP	0,94
PREV	0,4
VPP	**0,913**
VPN	**0,034**

N Staging

Functional imaging with FDG-PET/CT proved to be superior to contrast-enhanced CT (CeCT) for N staging, in particular by adding metabolic information able to disclose morphologically undetectable nodal dissemination, ultimately **increasing specificity and positive predictive value of N staging (Chao, 2012)**.

For example, in a prospective study (106 patients with NSCLC), the sensitivity, specificity and accuracy was higher with FDG-PET/CT (respectively 85%, 84% and 84%) than with CeCT alone (respectively 70%, 69% and 69%).

However, the sensitivity of N staging by FDG-PET/CT remains disappointingly low (45%) and false negative cases have been reported, particularly for lymph nodes **size <10 mm (Se=32.4%) compared with lymph nodes >10 mm (Se = 85.3%)**. [Shim 2005].

Other limitations are the false-positive rates due to unspecific FDG uptake like inflammation or granulomatous disease (e.g., sarcoidosis), leading to a reduction in specificity.

Despite the above improvement in accuracy of N staging with FDG-PET/CT, surgical staging remains the standard, especially to detect occult mediastinal nodal invasion **[Li 2013 and Tandeberg 2013)**.

For these reasons, both endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) have been recommended as essential tools for tumor staging after FDG-PET/CT **(Adams 2009)**.

Chao, F.; Zhang, H. PET/CT in the staging of the non-small-cell lung cancer. J. Biomed. Biotechnol.2012, 2012, 783739.

Shim, S.S.; Lee, K.S.; Kim, B.T.; Chung, M.J.; Lee, E.J.; Han, J.; Choi, J.Y.; Kwon, O.J.;
Shim, Y.M.; Kim, S. Non-small cell lung cancer: Prospective comparison of integrated FDG PET/CT and CT alone for preoperative staging. Radiology 2005, 236, 1011–1019.

Bille, A.; Pelosi, E.; Skanjeti, A et al. Preoperative intrathoracic lymph node staging in patients with non-small-cell lung cancer: Accuracy of integrated positron emission tomography and computed tomography. Eur. J. Cardio-Thoracic Surg. 2009, 36, 440–445.

Li, S.; Zheng, Q.; Ma, Y.; et al. Implications of False Negative and False Positive Diagnosis in Lymph Node Staging of NSCLC by Means of (18)F-FDG PET/CT. PLoS One 2013, 8, e78552.

Tandberg, D.J.; Gee, N.G.; Chino, J.P. et al. Are discordant positron emission tomography and pathological assessments of the mediastinum in non-small cell lung cancer significant? J. Thoracic Cardiovasc. Surg. 2013, 146, 796–801.

Adams, K.; Shah, P.L.; Edmonds, L.; Lim, E. Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: Systematic review and meta-analysis. Thorax 2009, 64, 757–762.

N-staging e Bayes

coinvolgimento mediastinico N dipendente

SE	0,6
SP	0,95
PREV	0,2
VPP	**0,750**
VPN	**0,095**

Per N > 1 cm

Per N < 1 cm

SE	0,85
SP	0,9
PREV	0,6
VPP	**0,927**
VPN	**0,200**

M Staging

Long since, FDG-PET/CT proved very informative on metastatic spread in NSCLC, able to detect unsuspected distant metastases in up to **28% of patients**, and to impact in a relevant way the treatment plan in as many as 53% of cases.

FDG-PET/CT is for example useful for differentiating benign from malignant adrenal lesions, with a sensitivity and a specificity reported by Erasmus et al. of 100% and 80%–100% respectively, though in some cases a second imaging technique was needed.FDG-PET/CT is also accurate for detecting bone metastasis, with an even higher accuracy than Magnetic Resonance Imaging (MRI) and bone scintigraphy (BS) in some publications .

Eschmann, S.M.; Friedel, G.; Paulsen, F.; Budach, W.; Harer-Mouline, C.; Dohmen, B.M.; Bares, R. FDG PET for staging of advanced non-small cell lung cancer prior to neoadjuvant radio-chemotherapy. Eur. J. Nucl. Med. Mol. Imaging 2002, 29, 804–808.

Seltzer, M.A.; Yap, C.S.; Silverman, D.H.; Meta, J.; Schiepers, C.; Phelps, M.E.; Gambhir, SS.; Rao, J.; Valk, P.E.; Czernin, J. The impact of PET on the management of lung cancer: The referring physician‘s perspective. J. Nucl. Med. 2002, 43, 752–756.

Erasmus, J.J.; Patz, E.F., Jr.; McAdams, H.P.; Murray, J.G.; Herndon, J.; Coleman, R.E.Goodman, P.C. Evaluation of adrenal masses in patients with bronchogenic carcinoma using 18F-fluorodeoxyglucose positron emission tomography. AJR Am. J. Roentgenol. 1997, 168, 1357–1360.

Stone, W.Z.; Wymer, D.C.; Canales, B.K. Fluorodeoxyglucose-positron-emission tomography/computed tomography imaging for adrenal masses in patients with lung cancer: Review and diagnostic algorithm. J. Endourol. 2014, 28, 104–111.

DiPerna, C.A.; Wood, D.E. Surgical management of T3 and T4 lung cancer. Clin. Cancer Res.2005, 11, 5038s–5044s.

La Stadiazione Extramediastinica M

La PET-FDG ha dimostrato la capacità di identificare circa il 20% in più, rispetto alle altre metodiche, di pazienti metastatici extratoracici che si presentavano potenzialmente resecabili rispetto ad altri imaging

E' sempre un imaging Whole-Body

E' sempre Whole-Tissue
* con l'eccezione del tessuto cerebrale

Vesselle H, Turcotte E, Wiens L et al. Relationship between non-small cell lung cancer fluorodeoxyglucose uptake at positron emission tomography and surgical stage with relevance to patient prognosis. **Clin Cancer Res 2004; 10: 4709-16**

FDG-PET/CT in Solitary Pulmonary Nodule (SPN) (1)

Solitary Pulmonary Nodule (SPN) is one of the most frequent incidental findings (14.8% of asymptomatic patients), and could have both a benign or malignant origin. CeCT of high-resolution CT scan (HRCT) may give information on the morphologic characteristics of SPN (size, border, calcification, intra-nodular fat) and its size change, but this imaging modality has limits; 25%–39% of malignant nodules are inaccurately classified as benign. The gold standard for diagnosing SPN is pathology, with a tissue sample obtained either surgically or by biopsy.

FDG-PET/CT is a non-invasive diagnostic tool which gives metabolic evaluation of the SPN, and may reduce the numbers of unnecessary samples.

A qualitative and quantitative (SUV measurement) assessment of the SPN metabolic activity can be interpreted on FDG-PET/CT. The SUVMax was shown to be predictor of the neoplastic nature of the tissue: in a large (585 patients) prospective study, 496 patients with a median SUVMax of 8.5 (range, 0 to 36) had a malignant neoplasm, and 89 patients with a median SUV Max of 4.9 (range, 0 to 28) had a benign lesion ($p < 0.001$). False negative FDG-PET/CT findings were: broncho-alveolar carcinoma, carcinoid, and renal cell. False positives findings were related to fungal infections.

The threshold of SUVMax for distinguishing benign from malignant lesions is variable among the literature, and therefore lacks reproducibility. For example, Lowe et al. (2007) observed good performances of FDG-PET/CT with the most frequently SUVMax threshold used in the literature, which is 2.5 (overall sensitivity and specificity for detection of malignant nodules of 92% and 90%).

A same cut-off value has been used in other publications, like Hashimoto et al., who calculated a sensitivity of 100%, specificity of 63%, positive and negative predictive values of 62% and 100%, respectively. When an SUV of 1.59 was the cutoff for positive FDG-PET/CT results, the ROC analysis revealed a lower sensitivity (81%), but higher specificity (85%). In this study, the probability of malignancy in any visually evident lesion was about 60%. Other studies suggest a higher cut-off value (SUVMax > 3.5), or a visual interpretation by experienced physician .

FDG-PET/CT in Solitary Pulmonary Nodule (SPN) (2)

This variability among the different studies is probably explained by the fact that SUV may be affected by a large number of parameters, like equipment used, physic and biological factors.

In most studies, the sensitivity of FDG-PET/CT is higher than its specificity; FDG is a marker of glucose metabolism, and is not specific of neoplastic disease. Many benign abnormalities can produce false-positive findings on PET/CT, like granulomatosis, infection or inflammation.

Consequently, in endemic regions of infectious or granulomatous lung diseases, FDG-PET/CT has significant limits. To give an example, a study of 279 patients in south-central United States with high prevalence of histoplasmosis, the specificity of PET/CT was only of 40%. Another limit of FDG-PET/CT is its false-negatives rate encountered in case of small lesions (<1 cm, particularly <7 mm), low tumor metabolic activity like bronchioloalveolar carcinoma, or hyperglycemia.

Some authors have proposed dual-time point FDG-PET/CT imaging, using the change in SUV between early and delayed scans to help differentiate benign from malignant lesion. However, even if dual time point FDG-PET/CT appears to be more specific than single time point FDG-PET/CT (73% vs. 59% respectively), the results of a recent meta-analysis indicate that dual time point FDG-PET/CT and single time point FDG-PET/CT have similar accuracy in the differential diagnosis of pulmonary nodules (Area Under Curve—AUC): 0.8244 vs. 0.8220). Despite of the limits of this imaging modality,

NPS-staging e Bayes
caratterizzazione

Fattori che incremento i falsi positivi

Gruppi ad alta prevalenza di malattie infiammatoria

Fattori che incrementano i falsi negativi

Caratteristiche radiologiche che depongono per istologie diverse dal NSCLC

Scarso controllo glicemico

Dimensioni inferiori agli 8 mm

NPS-staging e Bayes

caratterizzazione

SE	0,85
SP	0,9
PREV	0,2
VPP	**0,680**
VPN	**0,040**

NPS > 7mm e < 1 cm

NPS > 1 cm

SE	0,85
SP	0,9
PREV	0,4
VPP	**0,850**
VPN	**0,100**

NPS-staging e Bayes
caratterizzazione

In generale:

In pazienti con nodulazioni piccole (< 1 cm) ad elevata attività metabolica il PPP tende a crescere esponenzialmente in funzione di determinanti geometrici (effetto volume parziale)

Per lesioni di dimensioni maggiori (> 1 cm) PET negative il PPN della metodiche non sembra così alto da poter esentare la caratterizzazione cito-istologica.

Tecniche come la Dual point, Gated-PET o Breath Hold possono incrementare l'accuratezza diagnostica

Le caratteristiche radiologiche delle nodulazioni possono indirizzare verso altro imaging funzionale fin dall'inizio:

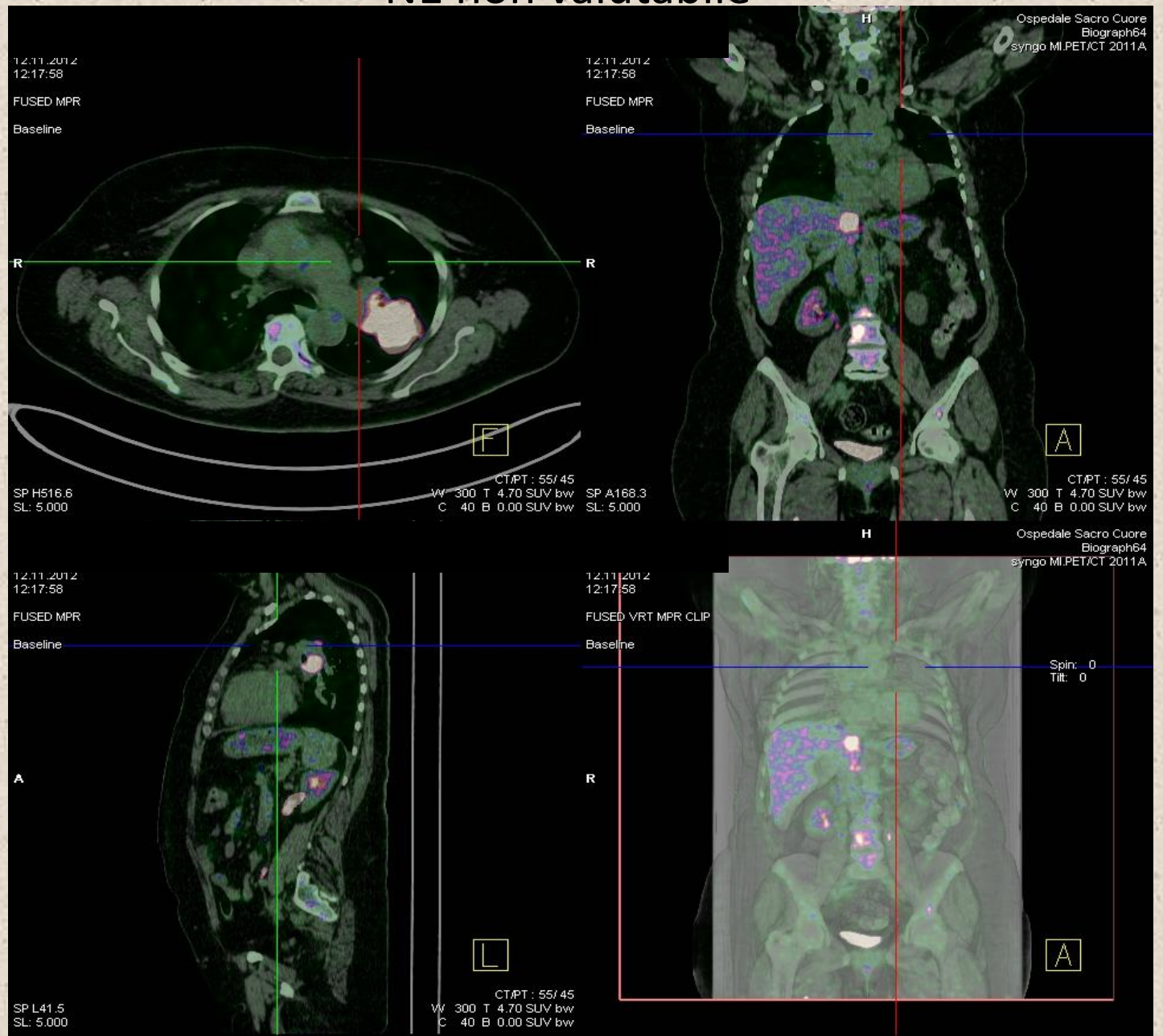
Ga68-Dotatoc per sospetto neuroendocrino
18F-Colina per sospetto bronchiolo-alveolare

- PET for Interim Tumor Response Assessment
  - Sicuro campo in sviluppo (per l'impatto economico) dove il limite principale è l'identificare parametri oggettivi (no il SUV) di risposta a terapia, (Entropia?)

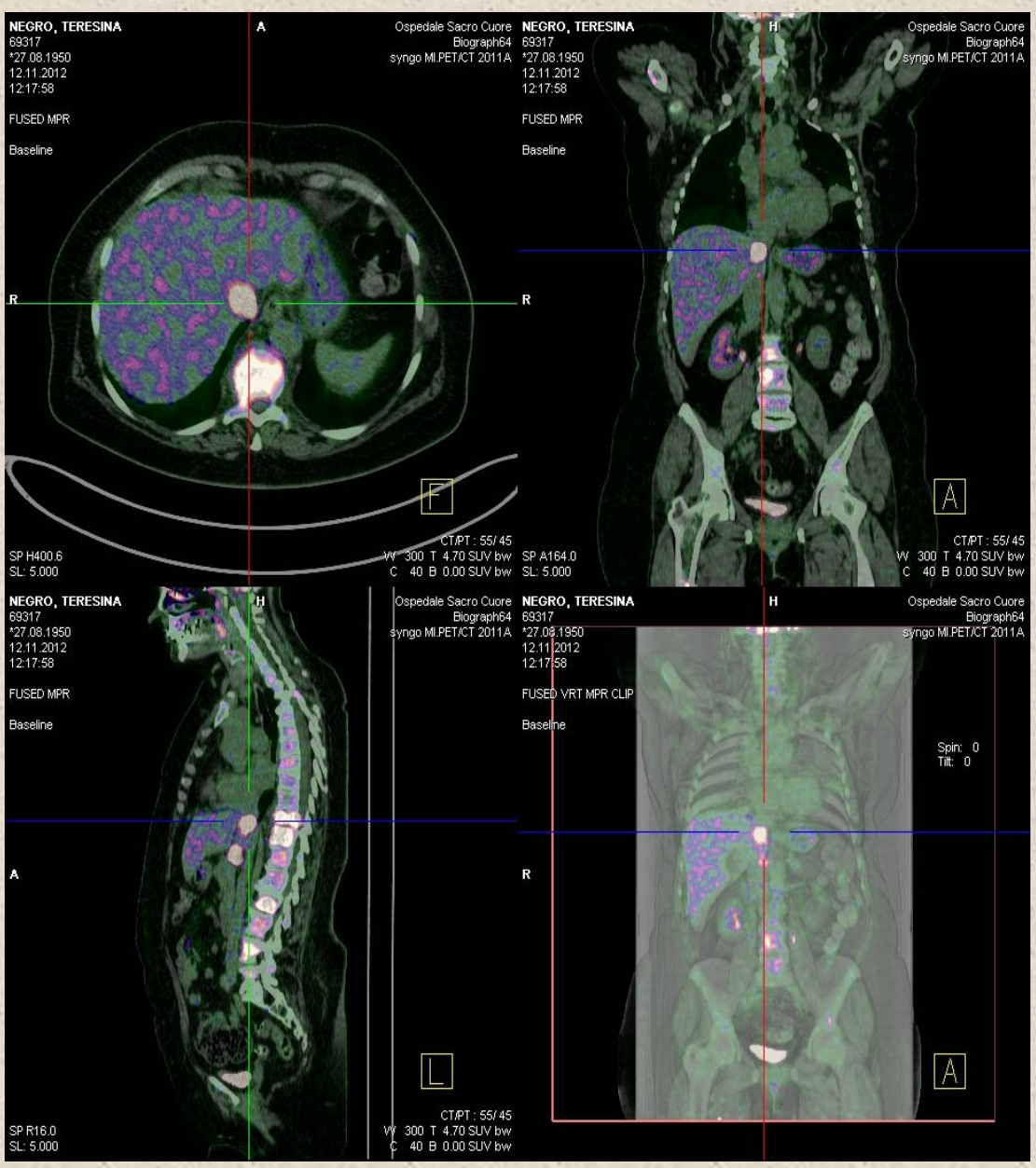
- Functional Imaging for Tumor Response
  - Caratterizzazione biologica della risposta in relazione a diverse caratteristiche metaboliche studiabili (trasportatore del glucosio GLUT, attività timidina kinasi)

- MTV in Oncology
  - Volume di malattia che stiamo trattando, caratterizzato e misurato metabolicamente, appare parametro interessante; ad oggi già utilizzato nei piani radioterapici

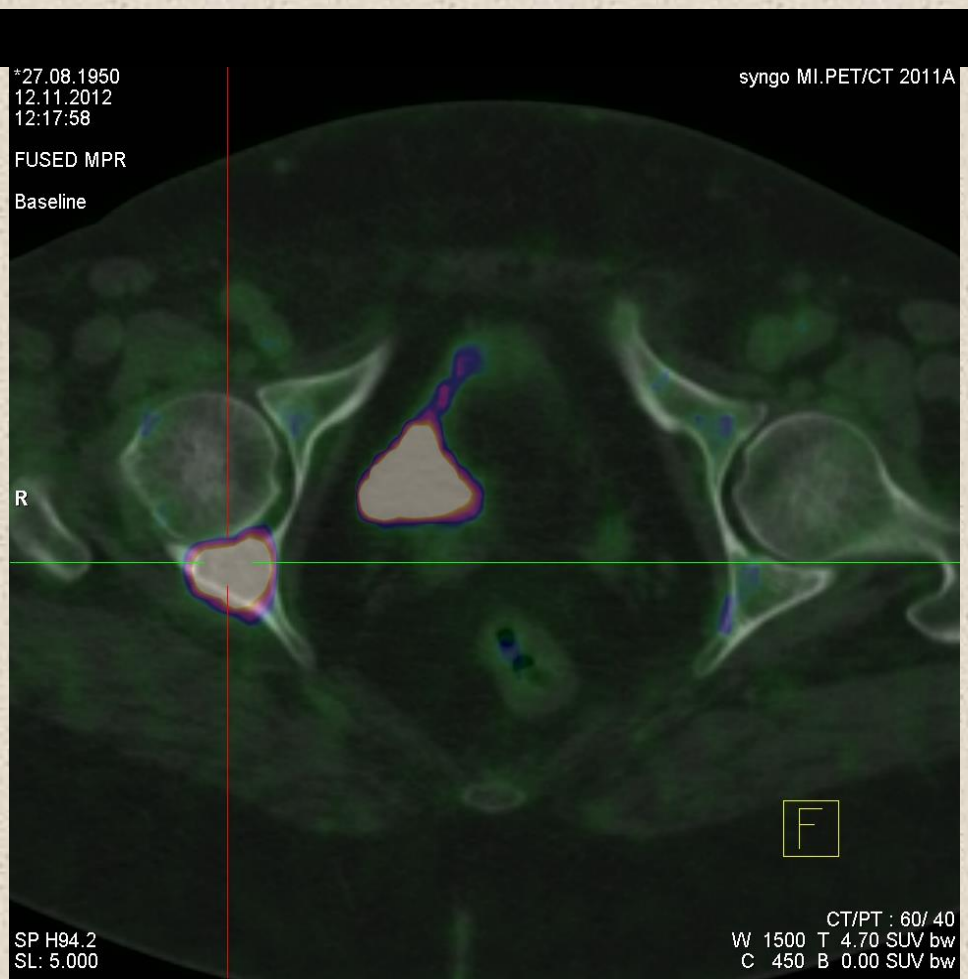
Neoplasia di 4 cm ha elevatissimo metabolismo con N2 ed N3 negativi, N1 non valutabile

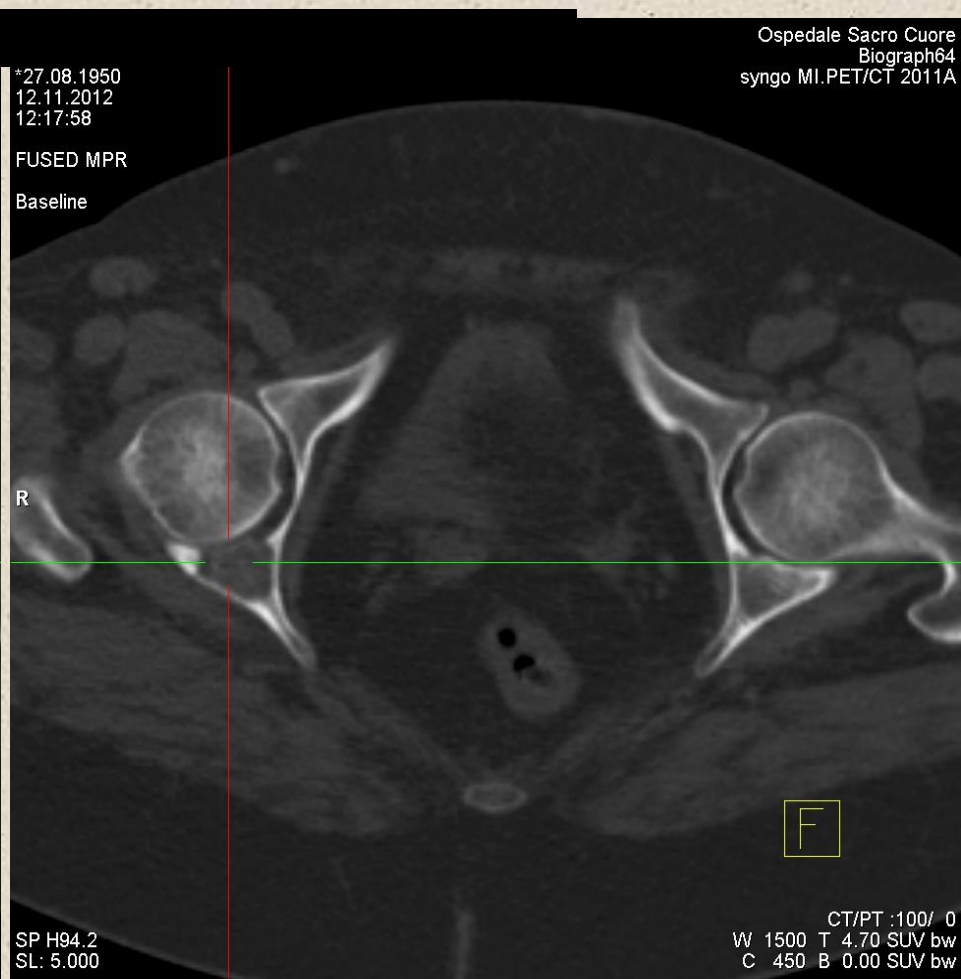


Neoplasia di 4 cm ha elevatissimo metabolismo con N2 ed N3 negativi, N1 non valutabile



Meta ossee visibili/visibili





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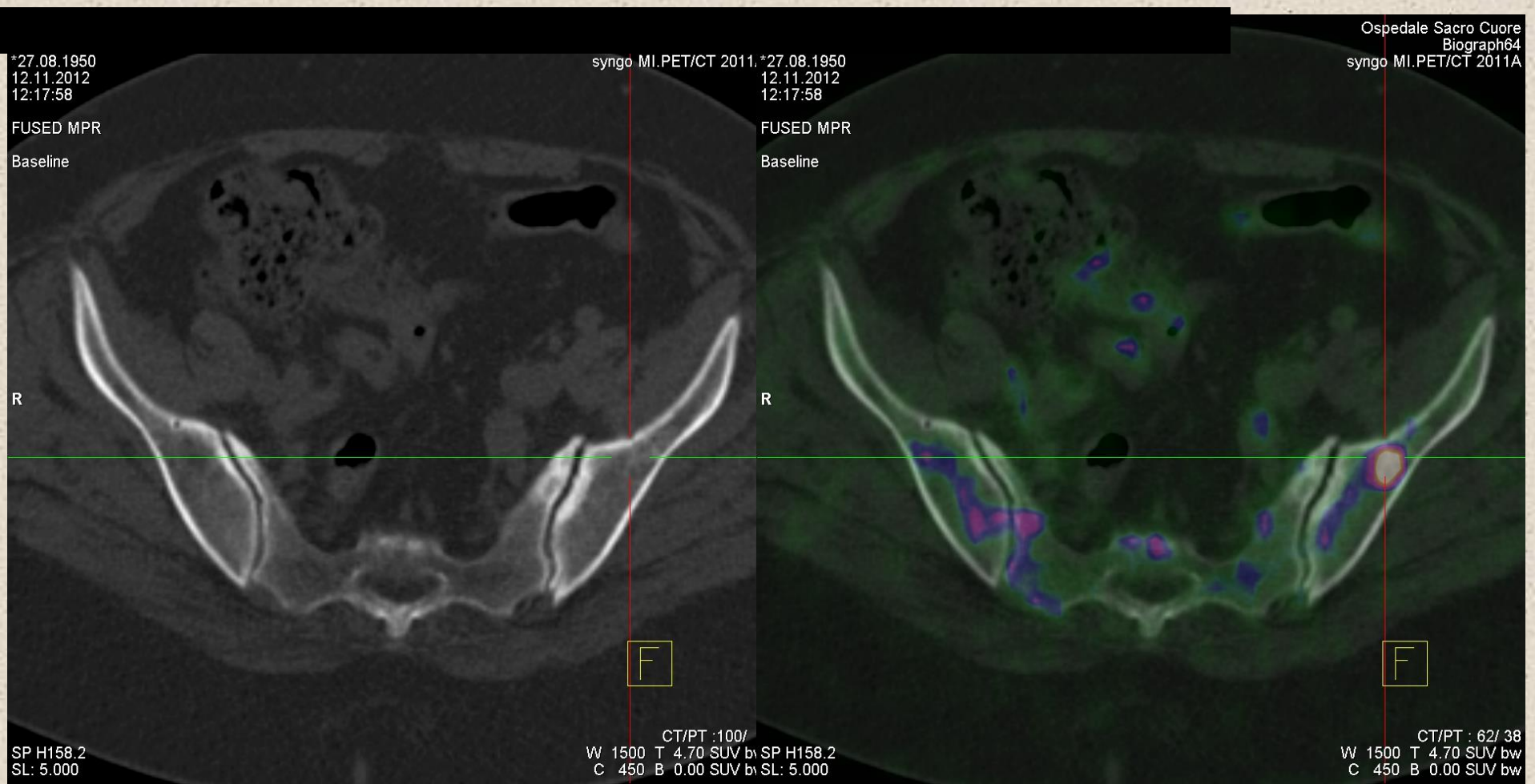
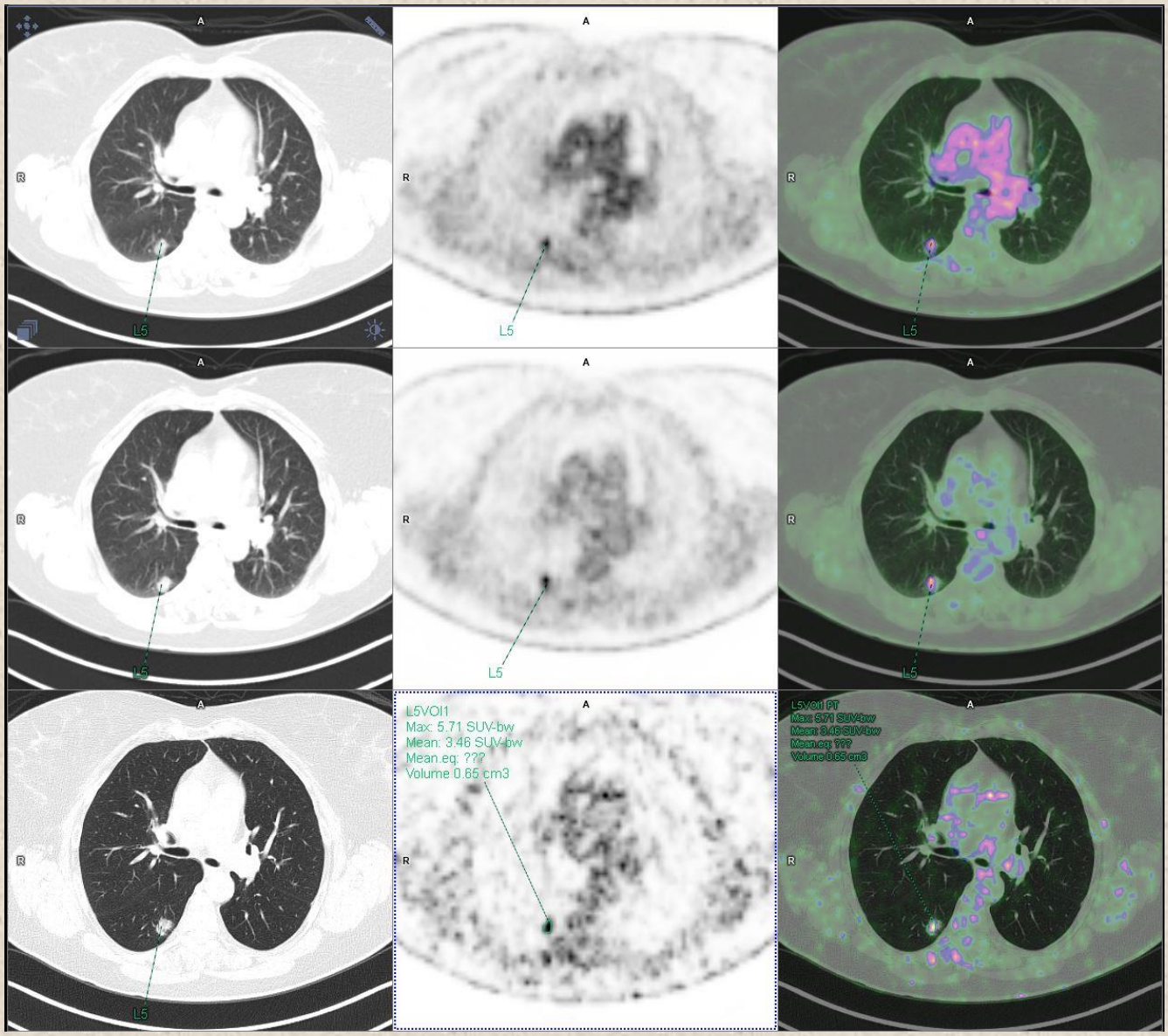


Incremento del SUV nell'imaging in Breath Hold

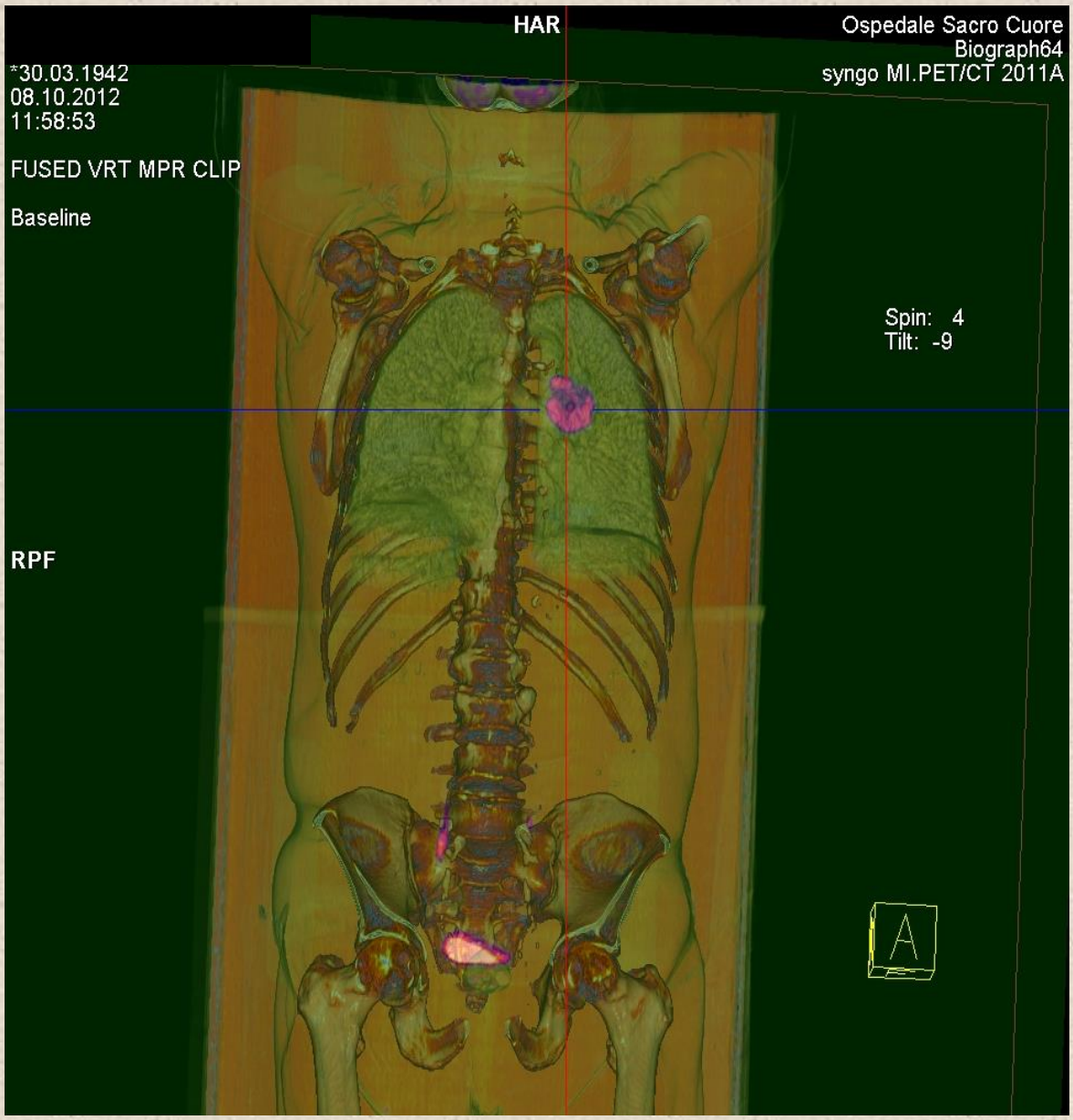


Scansione a 60 min
SUV 2.2

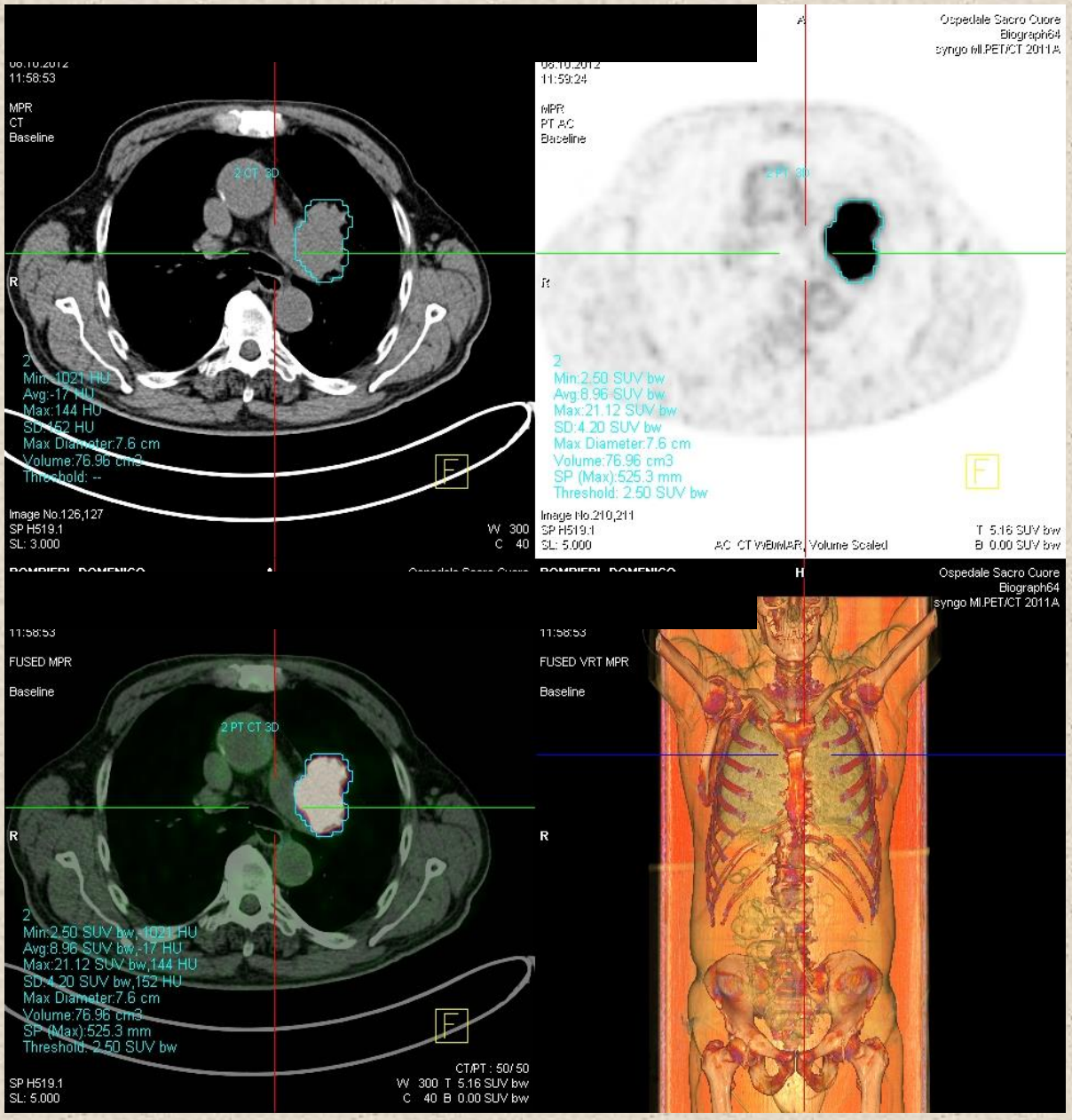
Scansione a 120 min
SUV 2.3

Scansione in 30 sec
SUV 3.5 (+50%)

Massa ilare polmonare N0

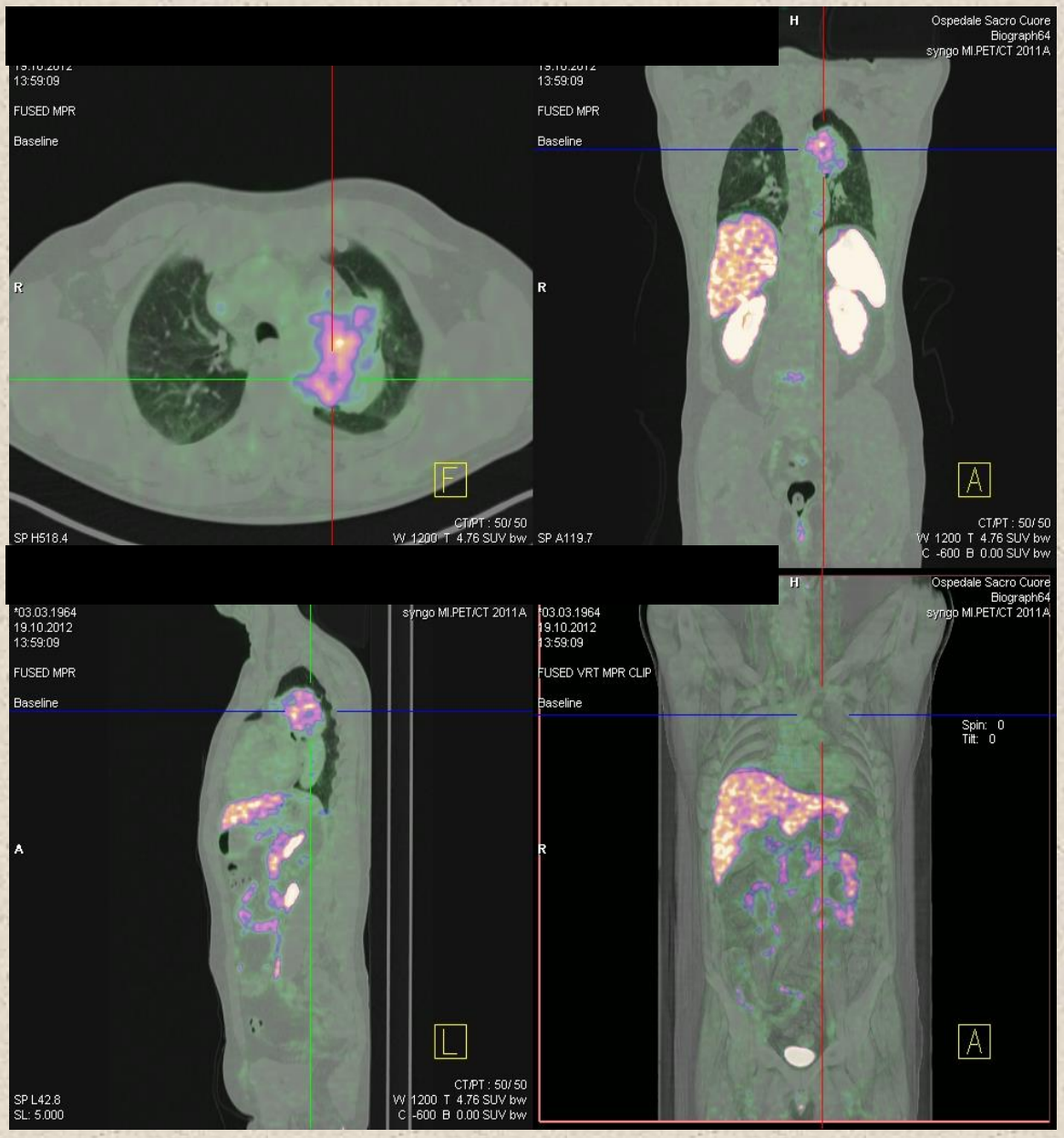


Massa ilare polmonare N0

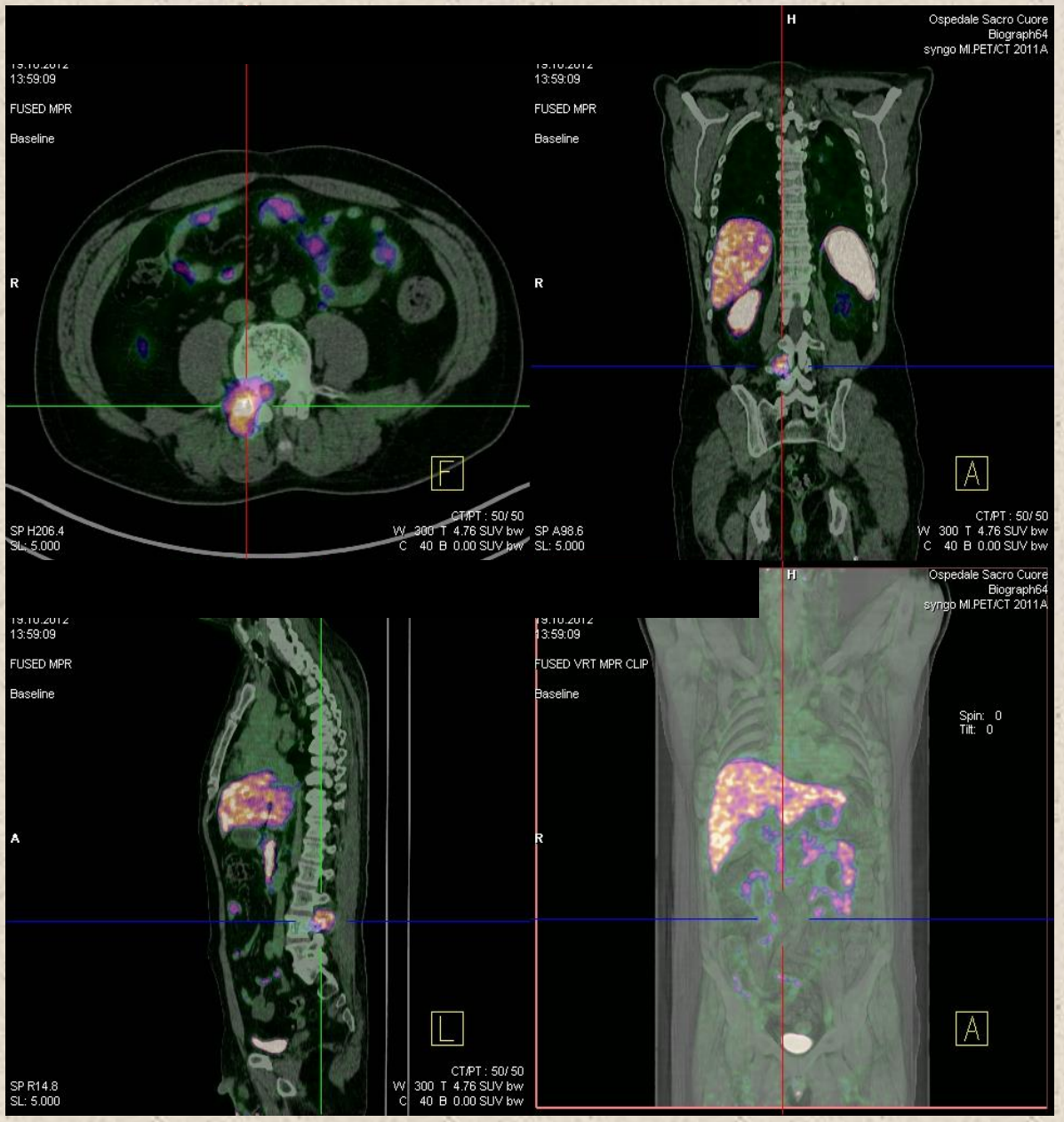


Neuroendocrino polmone

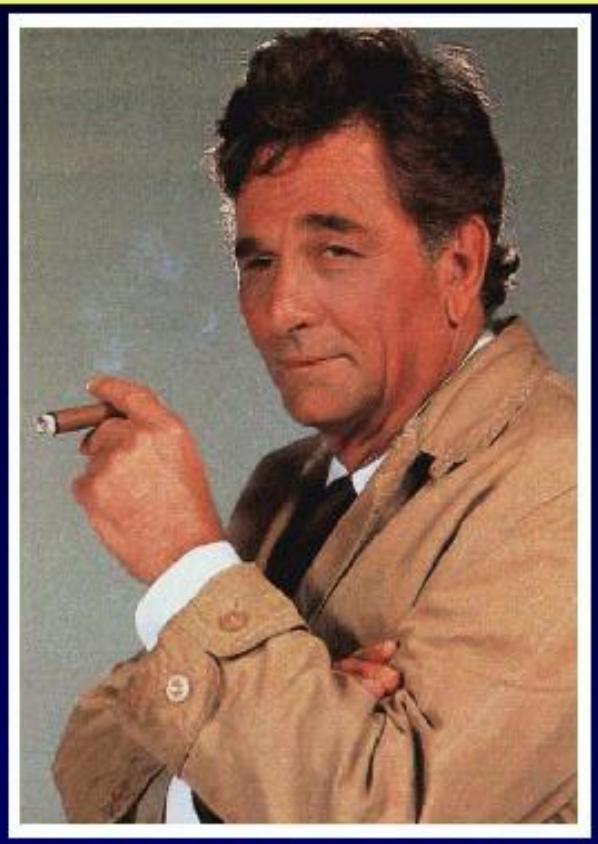
Neuroendocrino polmone



Neuroendocrino polmone



Decidere in condizioni di incertezza



Prendere in considerazione dati dissonanti e interpretarli correttamente è spesso la chiave che apre le porte alla diagnosi (cfr Tenente Colombo)