Progetto CANOA

Negrar 2013

La PET ed il carcinoma mammario: quali indicazioni nella pratica clinica e quali prospettive per il futuro?

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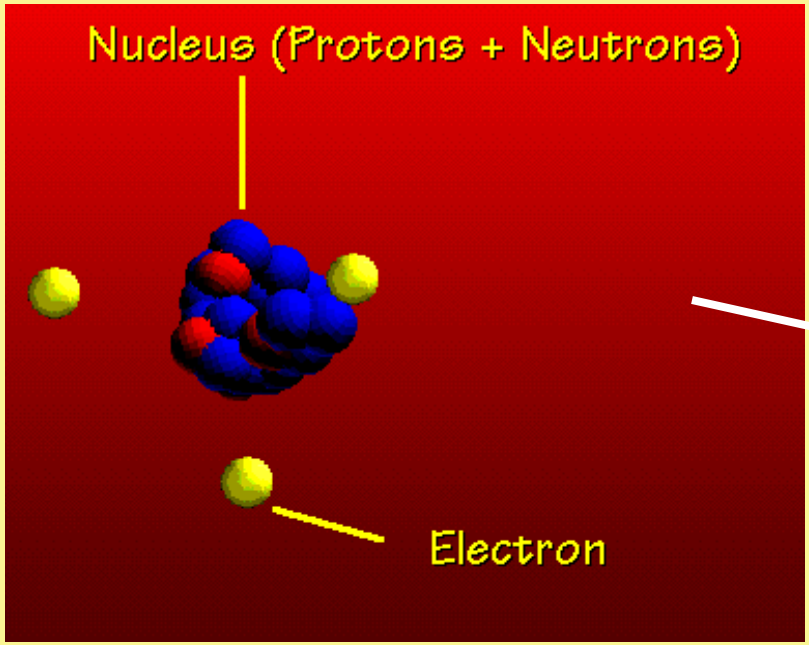
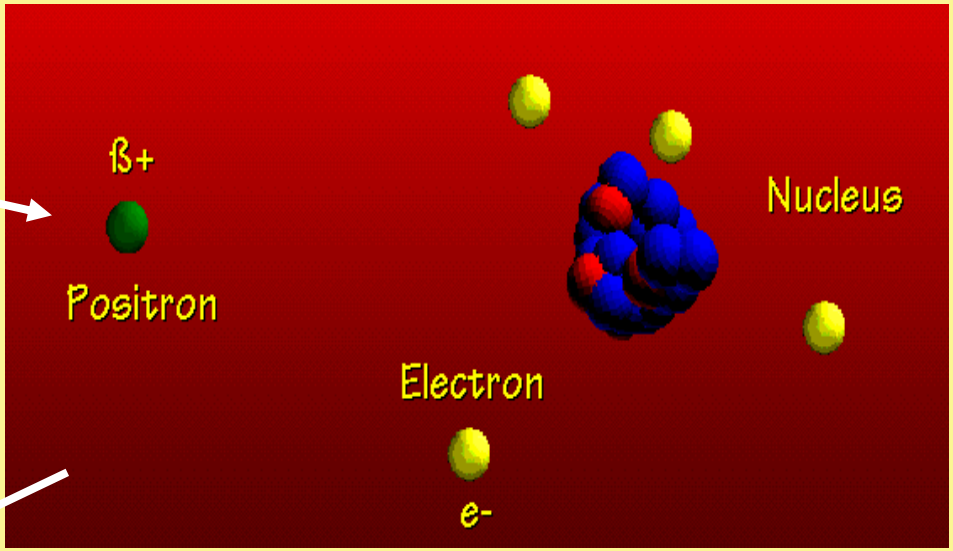
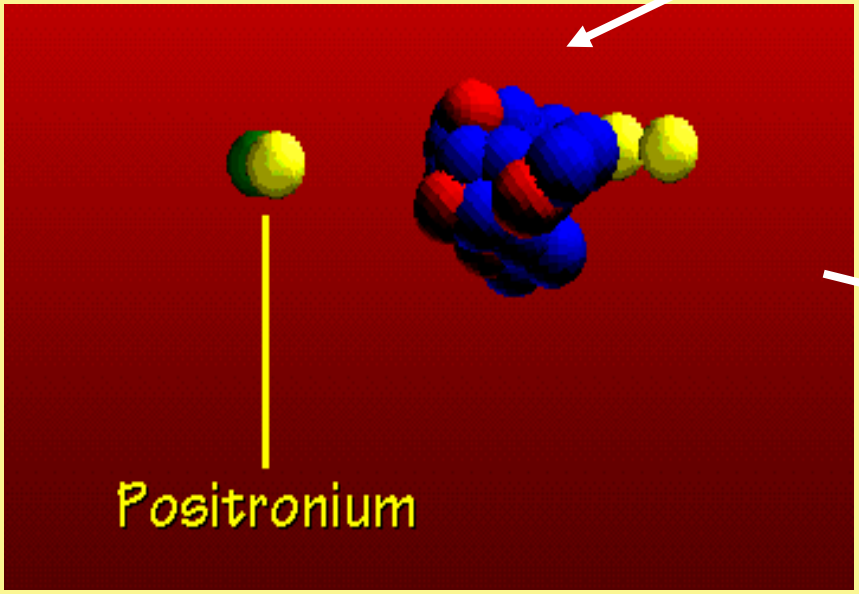
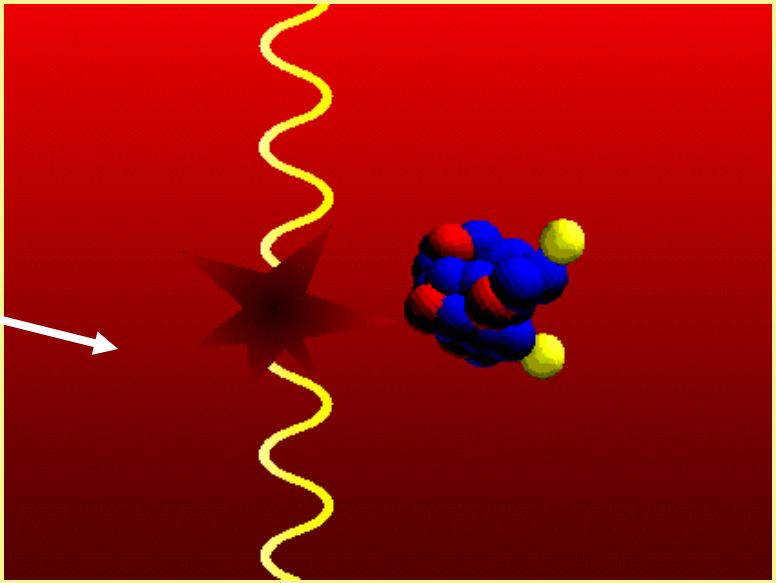
Annichilazione del positrone

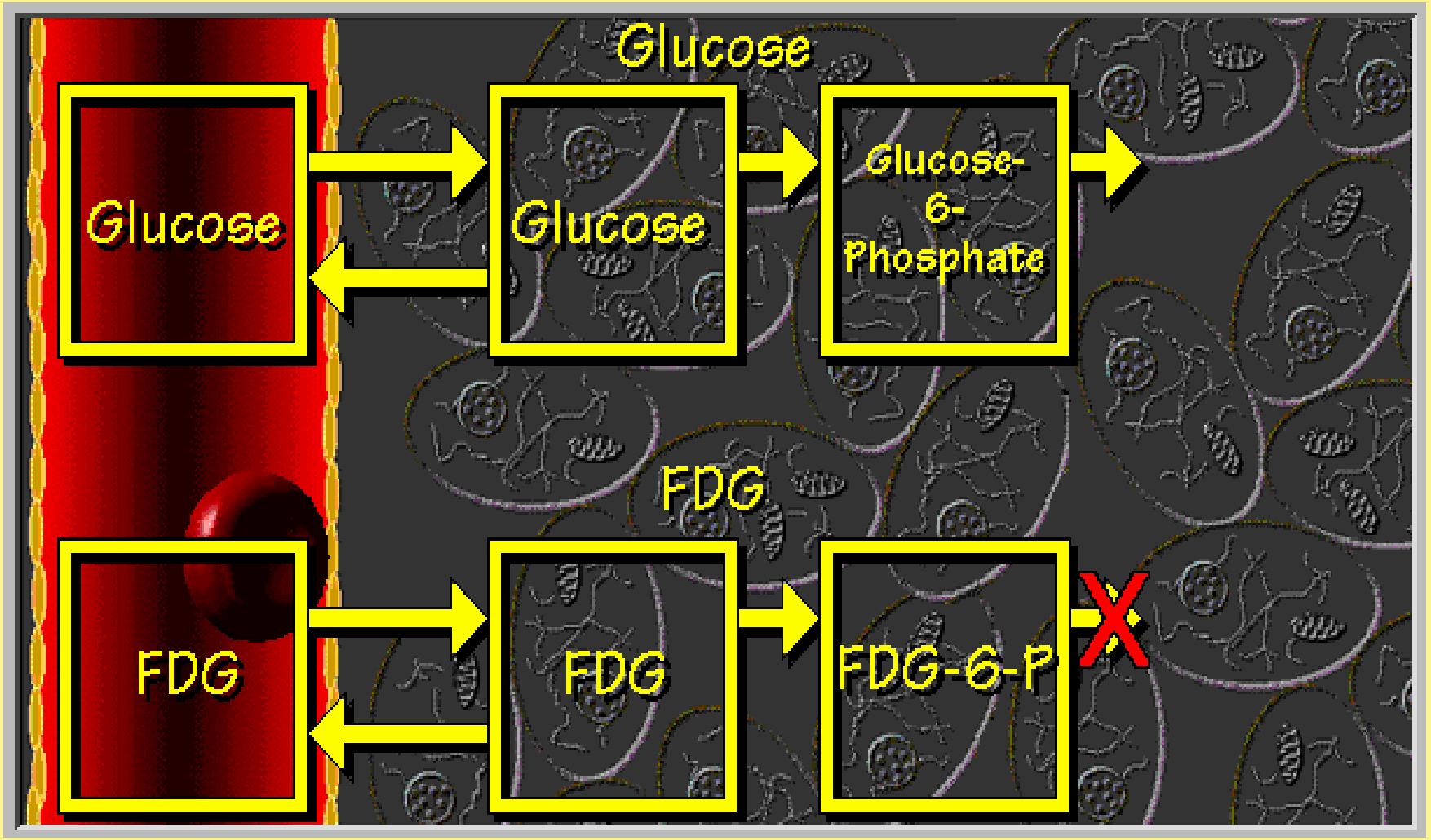




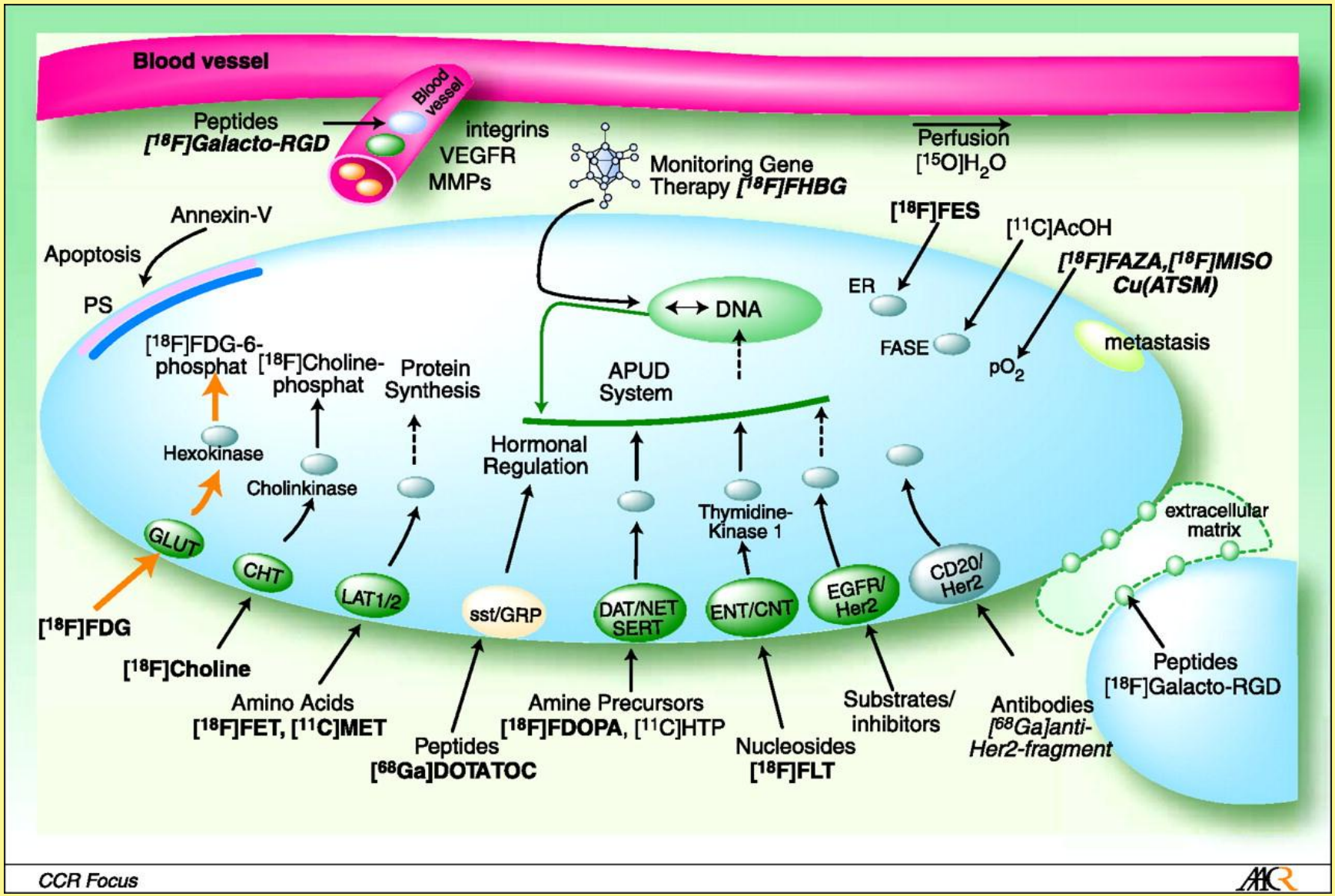




L’ FDG iniettato al paziente agisce come tracciante della glicolisi e si accumula maggiormente in sedi ove questa via metabolica è attivata in misura abnorme rispetto al consueto metabolismo aerobico, cosa che avviene in varie condizioni patologiche, come ad esempio nel contesto di tumori primitivi e di loro metastasi.



Selected targets and corresponding nuclear imaging probes already established for nuclear molecular imaging in the clinic or currently under assessment in clinical studies

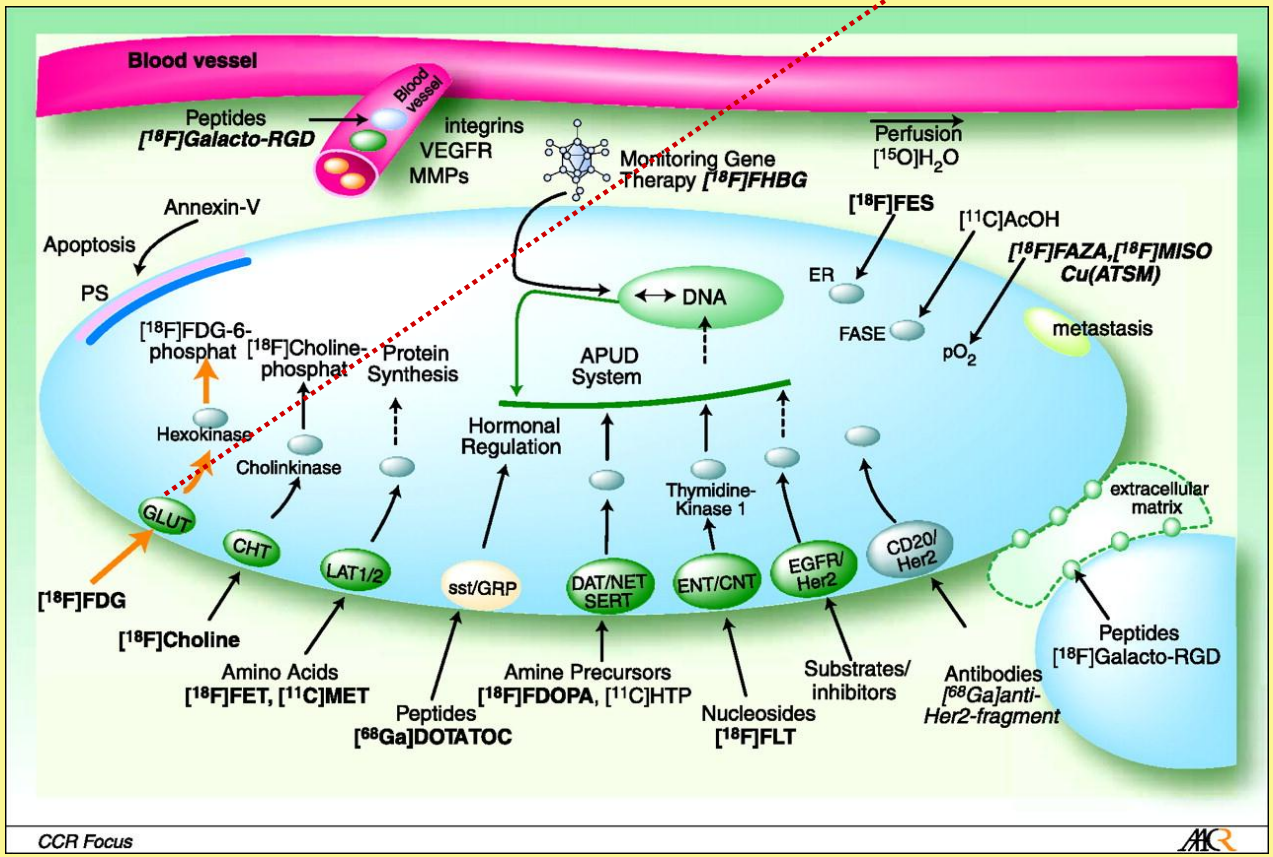


Wester H Clin Cancer Res 2007;13:3470-3481

Clinical Cancer Research

Selected targets and corresponding nuclear imaging probes already established for nuclear molecular imaging in the clinic or currently under assessment in clinical studies

E' veramente l'unica informazione oncologicamente rilevante?



Wester H Clin Cancer Res 2007;13:3470-3481

Clinical Cancer Research

Breast Cancer and Micad

Molecolar Imaging Contranst Agent Database

1: Human Studies: PET18F -> 16α-[18F]Fluoro-17β-estradiol

2: Background: PET64Cu -> HSDAVFTDNYTKLRKQ-NIe-AVKK-(3-OCH3,4-OH)-FLNSSV-GABA-L-(Dap-(BMA)2)-64Cu

3: Background: Multimodal64Cu, quantum dot (QD705) -> 64Cu-1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid-quantum dot-vascular endothelial growth factor

4: Background: PET64Cu -> 64Cu-DOTA hu4D5v8 (scFv-CH2-CH3)2

5: Human Studies: PET18F -> [18F]Fluorocholine

6: Background: PET64Cu -> 64Cu-N,N'-Bis(S-benzoyl-thioglycoloyl)diaminopropanoate-KRAS-PNA-d(Cys-Ser-Lys-Cys)

7: Human Studies: PET18F -> 3'-Deoxy-3'-[18F]fluorothymidine

8: Rodents: PET18F -> 16α-[18F]Fluoro-17β-estradiol -> Animal Studies

9: Background: SPECT99mTc -> 99mTc-N,N'-Bis(S-benzoyl-thioglycoloyl)diamidopropanoyl-KRAS-PNA-d(Cys-Ser-Lys-Cys)

10: Human Studies: PET18F -> [18F]Fluoro-2-deoxy-2-D-glucose

11: Rodents: PET64Cu -> 64Cu-1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid-interleukin-18-binding protein-Fc -> Animal Studies

12: Rodents: PET68Ga -> 68Ga-Trastuzumab F(ab') fragment -> Animal Studies

13: Background: PET11C -> l-[methyl-11C]Methionine

14: Background: SPECT99mTc -> 99mTc-glutamate peptide 3-aminoethyl estradiol

15: Background: PET18F -> 5-[(E)-2-(4-[18F]Fluorophenyl)ethenyl]-1,3-benzenediol

16: Background: PET89Zr -> 89Zr-Labeled trastuzumab, a humanized monoclonal antibody against epidermal growth factor receptor 2

17: Background: PET64Cu -> 64Cu-1,4,7-Triazacyclononane-1,4-diacetate-8-aminooctanoic acid-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH2

18: Background PET11C -> [O-11C-methyl]4-N-(3-Bromoanilino)-6,7-dimethoxyquinazoline

19: Background: PET11C -> (S)-6-[(4-Chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-[11C]methyl-1H-benzotriazole

20: Background: PET64Cu -> 64Cu-1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid-interleukin-18-binding protein-Fc

21: Rodents: PET64Cu -> 64Cu-DOTA hu4D5v8 (scFv-CH2-CH3)2 -> Animal Studies

22: Background: PET18F -> [18F]Fluoro-2-deoxy-2-D-glucose

23: Rodents: PET11C -> N-[N-[(S)-1,3-Dicarboxypropyl]carbamoyl]-S-[11C]methyl-L-cysteine -> Animal Studies

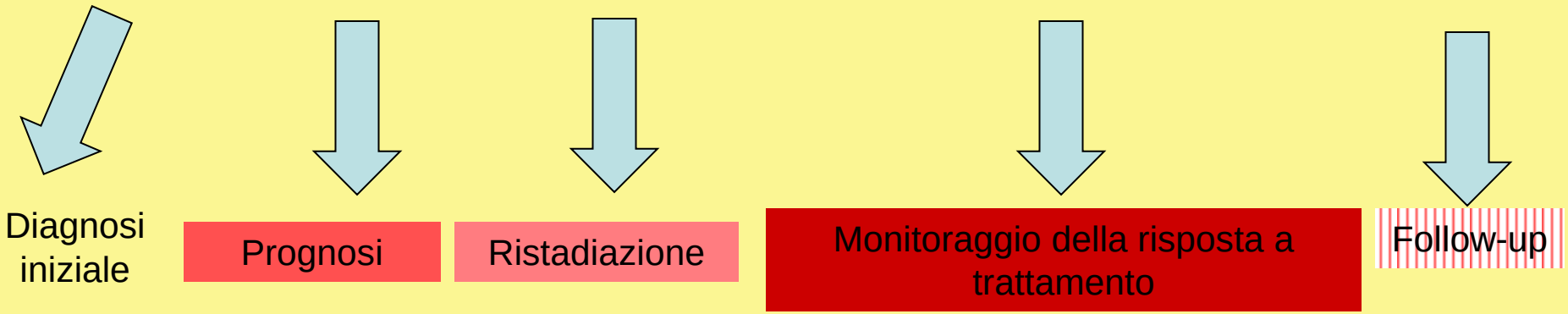
24: Rodent an humans: PET11C -> [11C]Choline -> Animal Studies

25: Human Studies: PET18F -> 1-(2'-Deoxy-2'-[18F]-fluoro-β-D-arabinofuranosyl)thymine

NB) Possibilità di utilizzo del Na-18F, per la ricerca di metastasi ossee o per studi MIXED con FDG.

CANOA

Fare la Pet?...Quando la PET?...Quale PET?



Nella caratterizzazione di lesioni mammarie cito-istologicamente non determinate

La PET-TC non trova significative applicazioni

Nella stadiazione delle stazioni linfatiche locoregionali

La PET-TC presenta un elevatissimo PPV > 90%

Tuttavia lo scarso PPN non permette di escludere lo studio del LS (nettamente più accurato)

Stadiazione

Breast 2012.

Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastases in newly diagnosed breast cancer.

Review sistematica 1995-2011

Obiettivi:

- **identificazione della prevalenza delle metastasi a distanza**
- **la misura dell'accuratezza dell'imaging di stadiazione nella identificazione delle metastasi a distanza asintomatiche**

Stadiazione

Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastases in newly diagnosed breast cancer.

22 studi selezionati

Totale di 14.824 pazienti

Età media di 53 aa

Prevalenza media di metastasi a distanza 7%

Correttamente verificato l'incremento della prevalenza con l'incremento del BC stage

Stadiazione

Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastases in newly diagnosed breast cancer.

Sensibilità e la specificità sono risultate rispettivamente:

imaging radiologico convenzionale 78% e 91%

scintigrafia ossea 98% e 93.5%

ecografia epatica 100% 96%

CT cest/abdomen 100% 93%

FDG PET 100% 96%

FDG PET/TC 100% 98%

Stadiazione

Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastases in newly diagnosed breast cancer.

I limiti della studio sono la relativa elevata prevalenza delle metastasi a distanza (7%, neoplasie di grandi dimensioni e frequente coinvolgimento linfatico ascellare) che spiega in parte le elevate performance della metodica (vedi specificità).

Diagnostica delle recidive

[18F]-Fluorodeoxyglucose positron emission tomography in patients with suspected recurrence of breast cancer.

Kamel EM, Wyss MT, Fehr MK, von Schulthess GK, Goerres GW.

Division of Nuclear Medicine, Department of Medical Radiology, University Hospital of Zurich, Raemistrasse 100, 8091 Zurich, Switzerland.

AIM: To evaluate the role of [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) in patients presenting with a suspicion of breast cancer relapse after primary treatment.

MATERIALS AND METHODS: Sixty consecutive female patients with clinical (n=35) or radiological (n=25) suspicion of breast cancer recurrence were evaluated by FDG-PET. Positive PET findings were further evaluated by histological examination or clinical and radiological follow-up. In 25 patients, the serum tumor marker (CA 15-3) status was compared to the PET results.

RESULTS: Disease relapse was proven in 40 patients. Additionally, in three patients a second cancer was diagnosed with (n=1), and without (n=2) concomitant disease relapse. PET missed local recurrence in three patients, and was false positive in another four. In patient-based analysis, the overall sensitivity, specificity, and accuracy were 89%, 84%, and 87%, and 100%, 97%, and 98% for locoregional recurrence and distant metastases, respectively. **FDG-PET was more sensitive than the serum tumor marker CA 15-3 in detecting relapsed breast cancer.**

CONCLUSION: FDG-PET is a valuable tool in the follow-up of patients with breast cancer.

J Cancer Res Clin Oncol. 2003 Mar;129(3):147-53. Epub 2003 Mar 12.

Diagnostica delle recidive

Follow-up of women with breast cancer: comparison between MRI and FDG PET.

Goerres GW, Michel SC, Fehr MK, Kaim AH, Steinert HC, Seifert B, von Schulthess GK, Kubik-Huch RA.
Division of Nuclear Medicine, University Hospital, Raemistrasse 100, 8091 Zurich, Switzerland. gerhard.goerres@dmr.usz.ch

The aim of this study was to compare MRI of the breast with (18)F-fluoro-deoxy-glucose (FDG) positron emission tomography (PET) in patients with suspected local or regional breast cancer recurrence or suspected contralateral breast cancer. Thirty-two patients (mean age 57.2 years, age range 32-76 years) with suspected loco-regional recurrence (n=19), chest wall recurrence (n=5), and suspected secondary tumor of the contralateral breast (n=8) underwent MRI of the breast and FDG PET of the whole body and breast region. Cytology/histology (n=17) or a clinical follow-up examination (n=15) with additional imaging served as the standard of reference. A McNemar test was performed to compare PET and MRI, and kappa was determined to quantify agreement of both methods. Sensitivity was 79 and 100%, specificity was 94 and 72%, and accuracy was 88 and 84% for MRI and PET, respectively. Additional metastases outside the field of view of MRI were found in PET in 5 patients.

In this study both imaging methods had comparable accuracy. The detection of distant metastases with whole-body PET imaging can influence patient management.

Eur Radiol. 2003 Jul;13(7):1635-44

20% di metastasi a distanza

Diagnostica delle recidive

[18F]FDG in recurrent breast cancer: diagnostic performances, clinical impact and relevance of induced changes in management.

Grahek D, Montravers F, Kerrou K, Aide N, Lotz JP, Talbot JN.
Service de Médecine Nucléaire et centre TEP AP-HP, Hôpital Tenon, Paris, France. dany.grahek@tnn.ap-hop-paris.fr

Prognosis and management of patients with recurrent breast cancer depend on the spread of the disease. The aim of this study was to evaluate the performance of fluorine-18 fluorodeoxyglucose gamma camera positron emission tomography (FDG-GPET) in detecting breast cancer recurrence, its clinical impact and the relevance of induced changes in management. Patients (n = **134**) with suspicion of recurrence either clinically or on conventional imaging **(suspected recurrence: SR**) or with an isolated increase in tumour marker levels **(occult recurrence: OR)** underwent FDG-GPET on a coincidence gamma camera. The reference standard for evaluation of accuracy, either histology (n = 26) or follow-up for 1 year (n = 49), was available in 75 (56%) patients. A questionnaire was sent to the referring clinician to evaluate the impact of FDG on management. Responses were obtained for 75 patients. Information regarding both approaches was available for 46 patients (46/134 = 34%). At the patient level, the sensitivity of FDG-GPET was 84%, significantly higher than the 63% sensitivity for conventional modalities, and the specificity was 78% versus 61%. The values for FDG-GPET were 81% and 86% respectively in the SR group and 90% and 73% respectively in the OR group, without any significant difference between these settings.

The rate of change in management was 44% overall, 43% in the SR group and 45% in the OR group. Within the two groups, intermodality (major) changes were more frequent than intramodality (minor) changes. In the 46 patients for whom both approaches were available, 93% of management modifications were relevant (validated by biopsy or clinical follow-up).

The results of this retrospective study show that FDG-GPET has an important role to play in patient management by confirming and evaluating the extent of recurrence or by localising occult recurrence.

Eur J Nucl Med Mol Imaging. 2004 Feb;31(2):179-88.

Effetto whole body

Ripresa di malattia o localizzazione secondaria

(Stato dell'arte)

J Cancer Res Clin Oncol. 2010 Jul;136(7):1007-22. Epub 2010 Jan 21.

FDG-PET and other imaging modalities for the evaluation of breast cancer recurrence and metastases: a meta-analysis.

Pan L, Han Y, Sun X, Liu J, Gang H. Chinese Academy of Sciences, 730000 Lanzhou, China.

Abstract

BACKGROUND AND PURPOSE: Breast carcinoma is the most common cancer in female patients with a propensity for recurrence and metastases. The accuracy of ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), scintimammography (SMM) and positron emission tomography (PET) in diagnosing the recurrent and/or breast cancer has never been systematically assessed, and present systematic review was aimed at this issue.

METHODS: MEDLINE and EMBASE were searched for articles dealt with detection of recurrent and/or metastatic breast cancer by US, CT, MRI, SMM or PET whether interpreted with or without the use of CT. Histopathologic analysis and/or close clinical and imaging follow-up for at least 6 months were used as golden reference. We extracted data to calculate sensitivity, specificity, summary receiver operating characteristic curves and area under the curve and to test for heterogeneity.

RESULT: In 42 included studies, US and MRI had highest pooled specificity (0.962 and 0.929, respectively); MRI and PET had highest pooled sensitivity (0.9500 and 0.9530, respectively). The AUC of US, CT, MRI, SMM and PET was 0.9251, 0.8596, 0.9718, 0.9386 and 0.9604, respectively. Results of pairwise comparison between each modality demonstrated that AUC of MRI and PET was higher than that of US or CT, $p < 0.05$. No statistical significance was found between MRI and PET. There was heterogeneity among studies and evidence of publication bias.

CONCLUSION: In conclusion, MRI seemed to be a more useful supplement to current surveillance techniques to assess patients with suspected recurrent and/or metastatic breast cancer. If MRI shows an indeterminate or benign lesion or MRI was not applicable, FDG-PET could be performed in addition.

J Cancer Res Clin Oncol. 2010 Jul;136(7):1007-22. Epub 2010 Jan 21.

In our meta-analysis, both MRI and PET had highest SE, which resulted in higher cancer detection rate. Regarding that PETs' high expense and modest whole-body radiation exposure, PET was not suited for screening purposes in breast cancer. Therefore, MRI should be the next diagnostic step in patients with an indeterminate or low probability of malignancy. Since that whole-body mets with MRI is impractical in most circumstances, PET had its own advantages in wholebody surveillance for mets. When MRI shows an indeterminate or benign lesion or MRI was not applicable (e.g., pacemaker), FDG-PET could be performed in addition. Furthermore, a lesion that was indeterminate or benign on MRI and negative on PET indicated a very low probability of malignancy. In conclusion, MRI seemed to be a more useful supplement to current surveillance techniques to assess patients with suspected recurrent and/or metastatic breast cancer.

Nella totalità dei lavori vengono confrontate performance RM "regionali" con PET whole body estrapolando da queste il dato regionale, metodo alquanto discutibile

J Cancer Res Clin Oncol. 2010 Jul;136(7):1007-22. Epub 2010 Jan 21.

PET–CT is a full-ring-detector clinical PET scanner combined with a multi-detector row helical CT scanner, which allows contemporaneous and co-registered acquisition of both PET and CT images (Fueger et al. 2005). In a retrospective review of 75 patients with suspected breast cancer, Tatsumi et al. (2006) compared performance of PET and PET/CT. PET/CT resulted in improved diagnostic confidence compared with PET in 60% of patients and in 55% of regions. Another two publications (Radan et al. 2006; Pecking et al. 2001) drew similar results; the use of PET/CT technology indicated only a marginal improvement in diagnostic accuracy, reporting SE, SP and accuracy rates of 90, 71, 83%, and 94, 84, 99%, respectively. Most importantly, several studies demonstrated that FDG-PET/CT had an impact on the management of 51–69% of patients (Radan et al. 2006; Eubank et al. 2004).

Il 70% della letteratura utilizzata è basata su studi PET e non PET/CT

È il dato di gran lunga più importante che non trova analoga performance in RM

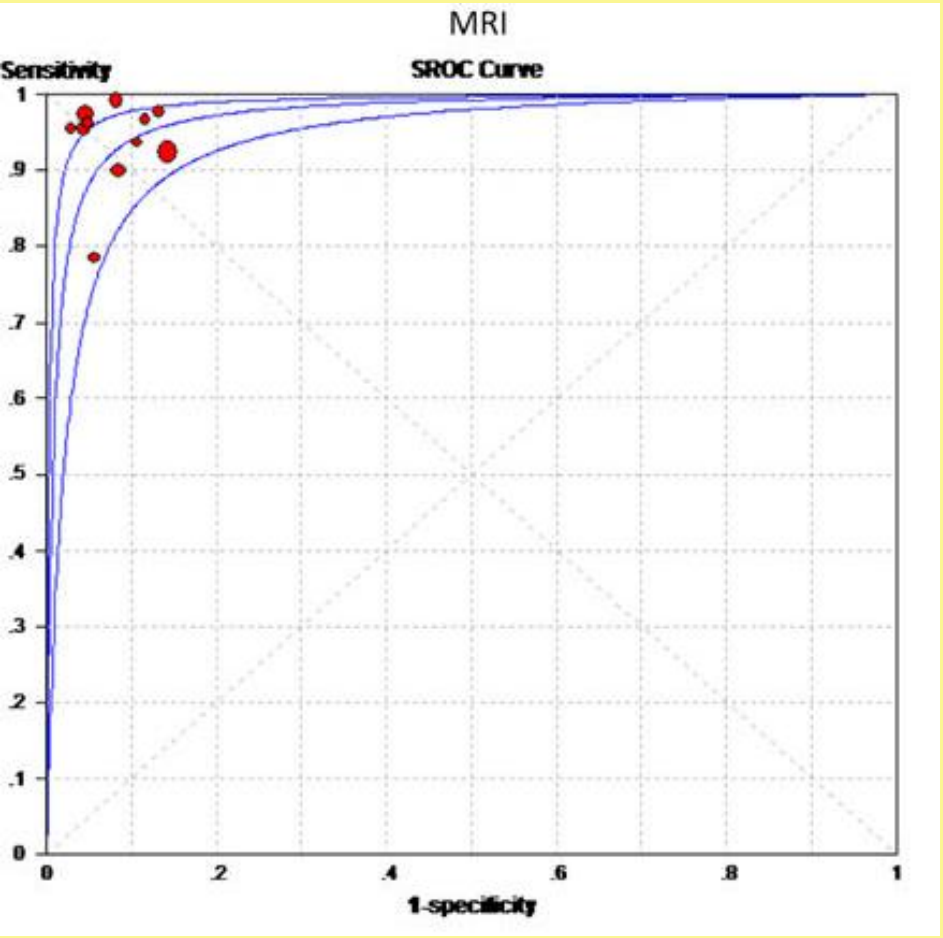
Perché quindi queste conclusioni con queste premesse?

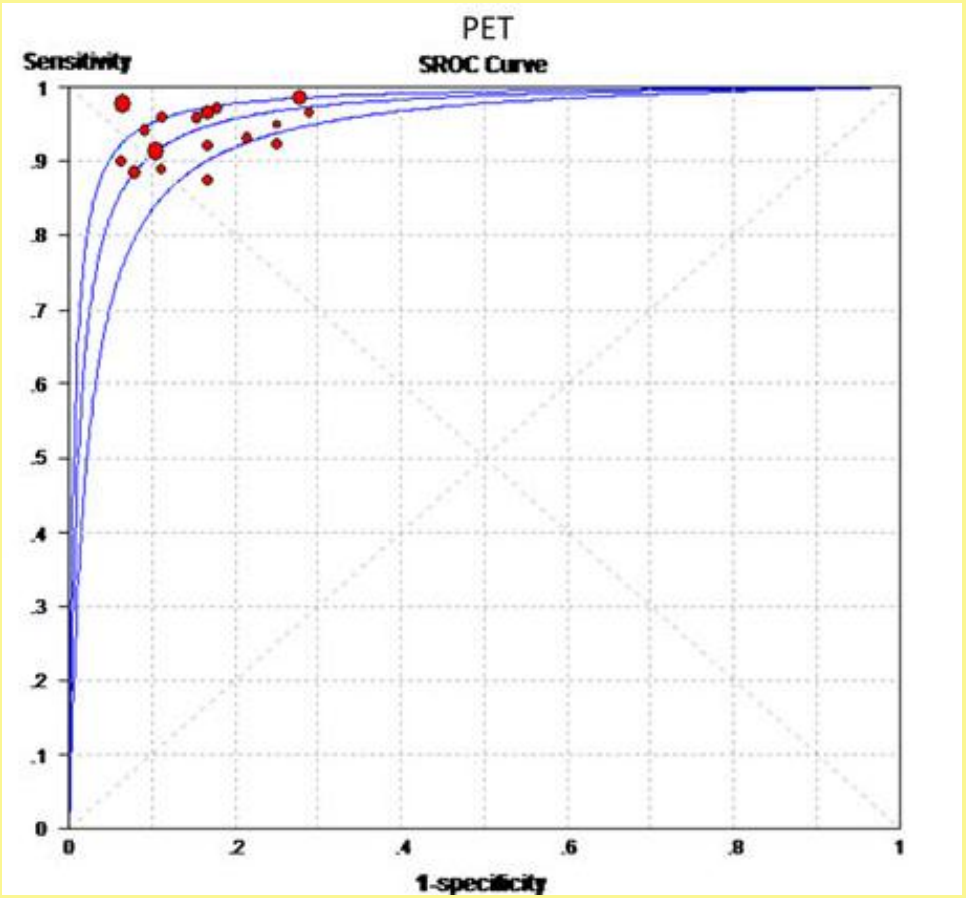
Summary estimates of sensitivity, specificity, and diagnostic odds ratio (DOR) for US, CT, MRI, SPECT and PET

Modality	Sensitivity (%)	Specificity (%)	Diagnostic OR
US	0.85 (0.80–0.89)	0.96 (0.95–0.97)	40.92 (18.2–91.5)
CT	0.84 (0.81–0.88)	0.75 (0.69–0.8)	13.62 (4.8–37.9)
MRI	**0.95 (0.92–0.97)**	**0.92 (0.90–0.95)**	**131.7 (70.9–244.8)**
SMM	0.90 (0.85–0.93)	0.79 (0.71–0.86)	29.4 (14.8 –58.1)
PET	**0.95 (0.93–0.96)**	**0.86 (0.82–0.89)**	**106.8 (68.1–167.7)**

J Cancer Res Clin Oncol. 2010 Jul;136(7):1007-22. Epub 2010 Jan 21.

Perché queste conclusioni con queste premesse?





J Cancer Res Clin Oncol. 2010 Jul;136(7):1007-22. Epub 2010 Jan 21.

Response to Therapy in Breast Cancer

Norbert Avril1, Stefanie Sassen2, and Rebecca Roylance3
1Department of Nuclear Medicine, Barts and The London School of Medicine, Queen Mary, University of London, London, United Kingdom; 2Department of Pathology, Technische Universit ¨ at Munchen, Munich, Germany; and 3Centre for Molecular Oncology and Imaging, Institute of Cancer, Barts and the London School of Medicine and Dentistry, London, United Kingdom

Increasing numbers of patients with newly diagnosed breast cancer receive primary systemic therapy followed by surgery.

Histopathology provides an accurate assessment of treatment efficacy on the basis of the extent of residual tumor and regressive changes within tumor tissue. However, only approximately 20% of breast cancer patients achieve a pathologic complete response, a fact that necessitates methods for monitoring therapeutic effectiveness early during therapy. 18F-FDG PET and 18F-FDG PET/CT provide essential information regarding a response to primary chemotherapy. Patients with low tumor metabolic activity on pretreatment 18F-FDG PET are not likely to achieve a histopathologic response. The degree of changes in 18F-FDG uptake after the initiation of therapy is correlated with the histopathologic response after the completion of therapy.

Thus, tumor metabolic changes assessed early during therapy predict therapeutic effectiveness in individual patients. Early identification of ineffective therapy also might be helpful in patients with metastatic breast cancer because many palliative treatment options are available. Changes in metabolic activity generally occur earlier than changes in tumor size, which is the current standard for the assessment of a response.

Although treatment stratification based on a metabolic response is an exciting potential application of PET, specific PET response assessment criteria still need to be developed and validated on the basis of patient outcomes before changes in treatment regimens can be implemented. There is increasing clinical evidence for metastatic breast cancer and other tumors that 18F-FDG PET/CT is the most accurate imaging procedure for assessment of the response at the end of treatment when both CT information and tumor metabolic activity are considered. Importantly, in the setting of primary chemotherapy, neither PET/CT nor conventional imaging procedures can assess the extent of residual breast cancer as accurately as histopathology.

Observation of changes in tumor blood flow or tumor cell proliferation is an additional encouraging approach for predicting a response. Ultimately, the prediction of therapeutic effectiveness by PET and PET/CT could help to individualize treatment and to avoid ineffective chemotherapies, with their associated toxicities.

Misura di risposta a terapia

Early 18F-2-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography May Identify a Subset of Patients With Estrogen Receptor-Positive Breast Cancer Who Will Not Respond Optimally to Preoperative Chemotherapy

Andrea A. Martoni; Claudio Zamagni; Sara Quercia; Marta Rosati; Nicoletta Cacciari; Alessandra Bernardi; Alessandra Musto; Stefano Fanti; Donatella Santini; and Mario Taffurelli. Cancer 2010;116:805–13. VC 2010

A pathologic complete response (pCR) and minimal residual disease (pMRD) after preoperative chemotherapy (PCT) for early stage or locally advanced breast cancer (BC) correlates with a good prognosis. METHODS: Patients who received from 6 to 8 cycles of PCT for BC were monitored by 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET), and the maximal standardized uptake value (SUVmax) was calculated at baseline, after 2 cycles, after 4 cycles, and at the end of PCT. SUVmax percentage changes (D-SUV) were compared with the pathologic response rate. Patients who had a pCR or pMRD in the tumor and an absence of cancer cells in ipsilateral axillary lymph nodes were defined as having obtained an optimal pathologic response (pR), whereas all the other conditions were classified as a pathologic nonresponse (pNR).

RESULTS: Of 34 patients, 7 (21%) achieved a pR (3 patients had a pCR, and 4 patients had pMRD). After the second cycle, the D-SUV threshold with optimal negative predictive value to predict a pR was 50%. Twenty-six patients (76%) had a D-SUV >50%, including all 7 patients who had a pR and 19 patients who had a pNR. Conversely, all 8 patients who had a D-SUV 50% had a pNR. All 8 of those patients had estrogen recepetor-positive tumors.

CONCLUSIONS: Early evaluation of metabolic response by 18F-FDG-PET during PCT was able to identify 30% of patients, all with estrogen receptor-positive tumors, who would not obtain pR after completion of chemotherapy program.

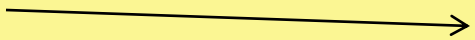
Breast Cancer. 2010 Jul 9.

Early metabolic response to neoadjuvant letrozole, measured by FDG PET/CT, is correlated with a decrease in the Ki67 labeling index in patients with hormone receptor-positive primary breast cancer: a pilot study.

Ueda S, Tsuda H, Saeki T, Omata J, Osaki A, Shigekawa T, Ishida J, Tamura K, Abe Y, Moriya T, Yamamoto J.

Department of Surgery, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama, 359-8513, Japan, syueda2000@yahoo.co.jp.

CONCLUSION: Cell-cycle response monitored by the Ki67 labeling index correlates with metabolic response monitored by tumor SUV(max). Monitoring of tumor SUV(max) using FDG PET/CT may be feasible to predict cell-cycle response to neoadjuvant endocrine therapy of primary breast cancer.



Il tassello mancante è l'identificazione di uno specifico parametro PERCIST di giudizio che dovrebbe essere ritagliato specificatamente sulla neoplasia e sul trattamento

Association between [18F]fluorodeoxyglucose uptake and prognostic parameters in breast cancer

A. Gil-Rendo1, F.Martˊınez-Regueira1, G. Zornoza1, M. J. Garcˊıa-Velloso2, C. Beorlegui1 and
N. Rodriguez-Spiteri1. Departments of 1Surgery and 2Nuclear Medicine, Clinica Universitaria of Navarra, C/PIıo XII 36, 31008 Pamplona, Navarra, Spain

This study analysed the correlation between [18F]fluorodeoxyglucose (FDG) uptake assessed by positron emission tomography (PET) in breast tumours, and histopathological and inmunohistochemical prognostic factors.

Methods: FDG–PET was performed before surgery in **275** women with primary breast cancer. The standarized uptake value (SUV) was compared with histopathological findings after surgery.

Results: A positive relationship was found between the SUV and tumour size (r = 0·46, P < 0·001), axillary lymph node status (P < 0·001), histological type (P < 0·001), histological grade (P < 0·001), oestrogen receptor status (P < 0·001), p53 (P < 0·001) and Ki-67 (P < 0·001) expression. Multivariable linear regression showed that tumour size, histological grade, Ki-67 expression, oestrogen receptor status and histological type were significantly related to the SUV.

Conclusion: The SUV is a preoperative and non-invasive metabolic factor that relates to some prognostic factors in breast cancer.

British Journal of Surgery 2009; **96**: 166–170

Stato dell'arte Timidina

Methods. 2009 Jun;48(2):205-15. Epub 2009 Mar 24.

Molecular imaging of proliferation in vivo: positron emission tomography with [18F]fluorothymidine.

Buck AK, Herrmann K, Shen C, Dechow T, Schwaiger M, Wester HJ.

Nuklearmedizinische Klinik und Poliklinik, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, D-81675 Munich, Germany. andreas.buck@tum.de

Abstract

Deregulated cell cycle progression is a hallmark of cancer. Accordingly, a major part of therapeutic drugs has been designed to inhibit cell proliferation and tumor growth. Metabolic imaging with positron emission tomography (PET) and the glucose analog 2'-[(18)F]fluoro-2'-deoxyglucose (FDG) has been demonstrated to sensitively detect malignant tumors and to identify responding tumors early in the course of anticancer treatment. However, tumoral uptake of FDG reflects proliferation only in part and is associated with false positive findings due to unspecific tracer retention in inflammatory processes. Most recent advances in cancer treatment have come from the development of disease specific, molecular agents, many of which induce cell cycle arrest (cytostatic effect) instead of tumor cell death (cytotoxic effect).

Thus, evaluating alterations in DNA metabolism may reflect response to treatment better than alterations in glucose utilization. PET with the thymidine analog 3'-deoxy-3'-[(18)F]fluorothymidine (FLT) enables non-invasive imaging and quantification of the proliferation fraction of tumors. Furthermore, FLT has been suggested as surrogate marker for assessment of response to treatment, especially when targeted drugs are utilized.

This article reports on metabolic pathways of radionucleosides in proliferating cells. Methods for in vivo assessment of the proliferative activity in preclinical and clinical studies are described with a focus on early monitoring response to therapy.

Stato dell'arte Timidina

J Natl Cancer Inst. **2007 Jan 17;99(2):167-70.**

Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer.

Dowsett M, Smith IE, Ebbs SR, Dixon JM, Skene A, A'Hern R, Salter J, Detre S, Hills M, Walsh G; IMPACT Trialists Group.

Academic Department of Biochemistry, 4th Floor, Wallace Wing, The Royal Marsden Hospital, Fulham Road, London SW3 6 JJ, UK. mitch.dowsett@icr.ac.uk

Comment in:

J Natl Cancer Inst. 2007 Jul 4;99(13):1053; author reply 1053-4.

Abstract

Tumor expression of the proliferation antigen Ki67 is widely used to assess the prognosis of cancer patients. A change in the expression of Ki67 after short-term exposure of patients to therapeutic agents is frequently used as a pharmacodynamic marker of efficacy, particularly among breast cancer patients before undergoing surgery. To determine the clinical significance of the level of tumor cell proliferation during endocrine therapy for breast cancer, we measured the expression of Ki67 in tumor biopsy samples taken before and after 2 weeks of presurgical treatment with anastrozole or tamoxifen or the combination of anastrozole plus tamoxifen in 158 patients with hormone receptor-positive primary disease. In a multivariable analysis, we found that higher Ki67 expression after 2 weeks of endocrine therapy was statistically significantly associated with lower recurrence-free survival (P = .004) whereas higher Ki67 expression at baseline was not. Larger baseline tumor size and lower estrogen receptor level after 2 weeks of treatment were also statistically significantly associated with poorer recurrence-free survival (P < .001 and P = .04, respectively).

Our data indicate that measurements of tumor Ki67 level after short-term endocrine treatment may improve the prediction of recurrence-free survival by integrating the prognostic value of Ki67 level at baseline with changes in Ki67 level that are associated with treatment benefit.

Stato dell'arte Timidina

Semin Nucl Med. 2007 Nov;37(6):429-39.

FLT: measuring tumor cell proliferation in vivo with positron emission tomography and 3'-deoxy-3'-[18F]fluorothymidine.

Salskov A, Tammisetti VS, Grierson J, Vesselle H.

Division of Nuclear Medicine, Department of Radiology, University of Washington, Seattle, WA 98195, USA.

Erratum in:

Semin Nucl Med. 2008 Mar;38(2):148.

Abstract

Positron emission tomography (PET) using the radiotracer 3'-deoxy-3'-[(18)F]fluorothymidine (FLT) can image cellular proliferation in human cancers in vivo. FLT uptake has been shown to correlate with pathology-based proliferation measurements, including the Ki-67 score, in a variety of human cancers. Unlike pathology-based measurements, imaging-based methods, including FLT-PET, are noninvasive, easily repeatable, and less prone to sampling errors. FLT-PET may therefore be a useful tool for assessing tumor aggressiveness, predicting outcome, planning therapy, or monitoring response to treatment.

Three recent clinical studies have reported that FLT-PET can accurately predict response very early after the initiation of chemotherapy. Especially with the advent of cytostatic chemotherapy agents, methods of biologically assessing a tumor's response will take on increasing importance, since changes in tumor size will not always be expected. To date, most studies of FLT-PET have focused on validating it as a means of quantifying cellular proliferation and testing its ability to accurately stage cancer.

In some settings, FLT-PET has shown greater specificity for cancer than (18)F-fluorodeoxyglucose (FDG)-PET, which can show false-positive uptake in areas of infection or inflammation. However, because of FLT's lower overall uptake and higher background activity in liver and bone marrow, FLT-PET should not be considered a potential replacement for staging by FLT-PET.

Instead, FLT-PET should be considered a powerful addition to FDG-PET, providing additional diagnostic specificity and important biological information that could be useful in predicting prognosis, planning treatment, and monitoring response.

Future opportunità)

Breast. 2009 Oct;18 Suppl 3:S66-73.

Molecular imaging of breast cancer.

Traccianti per Ipossia:
F-MISO (Farmacopea 1/2014), FAZA, 64Cu ATSM
Misure di risposte a terapie
Stratificazione prognostica,
Valutazione pre-radioterapica

Molecular imaging of breast cancer can potentially be used for breast cancer screening, staging, restaging, response evaluation and guiding therapies. Techniques for molecular breast cancer imaging include magnetic resonance imaging (MRI), optical imaging, and radionuclide imaging with positron emission tomography (PET) or single photon emission computed tomography (SPECT). This review focuses on PET and SPECT imaging which can provide sensitive serial non invasive information of tumor characteristics. Most clinical data are gathered on the visualization of general processes such as glucose metabolism with the PET-tracer [(18)F]fluorodeoxyglucose (FDG) and DNA synthesis with [18F]fluoro-L-thymidine (FLT).

Increasingly more breast cancer specific targets are imaged such as the estrogen receptor (ER), growth factors and growth factor receptors. Imaging of the ER with the PET tracer 16-alpha-[(18)F]fluoro-17-beta-estradiol (FES) has shown a good correlation between FES tumor uptake and ER density.

(111)In-trastuzumab SPECT to image the human epidermal growth factor receptor 2 (HER2) showed that in most patients with metastatic HER2 overexpressing disease more lesions were detected than with conventional staging procedures.

The PET tracer (89)Zr-trastuzumab showed excellent, quantifiable, and specific tumor uptake.

(111)In-bevacizumab for SPECT and (89)Zr-bevacizumab for PET-imaging have been developed for vascular endothelial growth factor (VEGF) imaging as an angiogenic marker. Lastly, tracers for the receptors EGFR, IGF-1R, PDGF-betaR and the ligand TGFbeta are under development. Although molecular imaging of breast cancer is still not commonly used in daily clinical practice, its application portfolio is expanding rapidly.

Bayes (1763)

- Il teorema fissa la regola dell'inferenza statistica, processo necessario per ricavare conclusioni valide da valori osservati. I valori si riferiscono a variabili causali e quindi il procedimento si identifica con un'induzione statistica
- P(B/A)= p(B)*p(A/B)/p(A)
- Il Teorema di Bayes contiene come variabili l'informazione a priori ed i dati sperimentali, cioè l'informazione condizionata insieme all'ipotesi da verificare.
- Secondo il teorema di Bayes la probabilità a posteriori si trova moltiplicando la probabilità a priori per un fattore numerico determinato dai dati sperimentali e dal modello.

Stadiazione neoplasia mammaria

Stadio	Tis	N0	M0
Stadio I	T1*	N0	M0
Stadio IIA	T0 T1* T2	N1 N1 N0	M0 M0 M0
Stadio IIB	T2 T3	N1 N0	M0 M0
Stadio IIIA	T0 T1* T2 T3	N2 N2 N2 N1, N2	M0 M0 M0 M0
Stadio IIIB	T4	N1, N2, N3	M0
Stadio IIIC	Ogni T	N3	M0
Stadio IV	Ogni T	Ogni N	M1

Quale sarà la prevalenza di M1 in queste classi?, è una classificazione che tiene conto di modelli di stadiazione non PET e soprattutto non PET-TC

*T1 comprende T1mic.

Classificazione istologica neoplasia mammaria

- **Duttale**
  - Intraduttale (in situ).
  - Invasive con prevalente componente intraduttale
  - Invasivo, NOS.
  - Comedo.
  - Inflammatorio.
  - Midollare con infiltrati linfocitari.
  - Mucinoso (colloide).
  - Papillare.
  - Scirro.
  - Tubulare.
  - Altri

- **Lobulare**
  - In situ.
  - Invasivo con componente in situ predominante.
  - Invasivo

- **Capezzolo**
  - Malattia di Paget, NOS.
  - Malattia di Paget con carcinoma intraduttale.
  - Malattia di Paget con carcinoma duttale infiltrante.

- **altri**
  - Carcinoma indifferenziato.

Come influiranno le caratteristiche istologiche e di biologia molecolare sulla prevalenza M1 in PET-TC?

Modelli

A = markers in aumento

B = sospetto ad imaging eco e rx convenzionale

C = clinica

Ricerca di metastasi? Stadio?
Prevalenza di M1 per stadio I, II, III

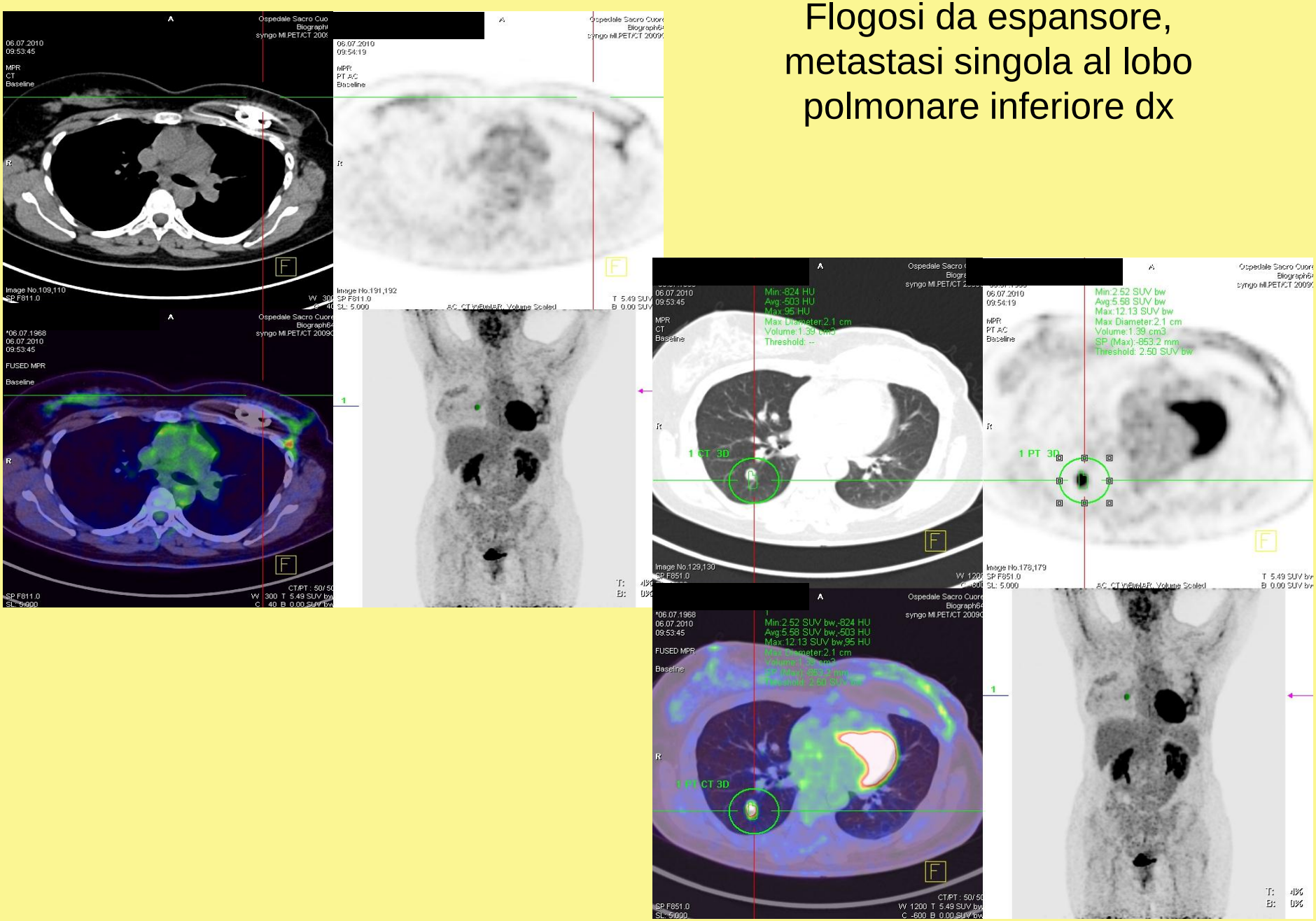
SE	?
SP	?
PREV	?
VPP	**#VALORE!**
VPN	**#VALORE!**

Caso di prevalenza 10% (pazienti ad alto rischio di ricaduta circa 40% nei primi 5 anni)

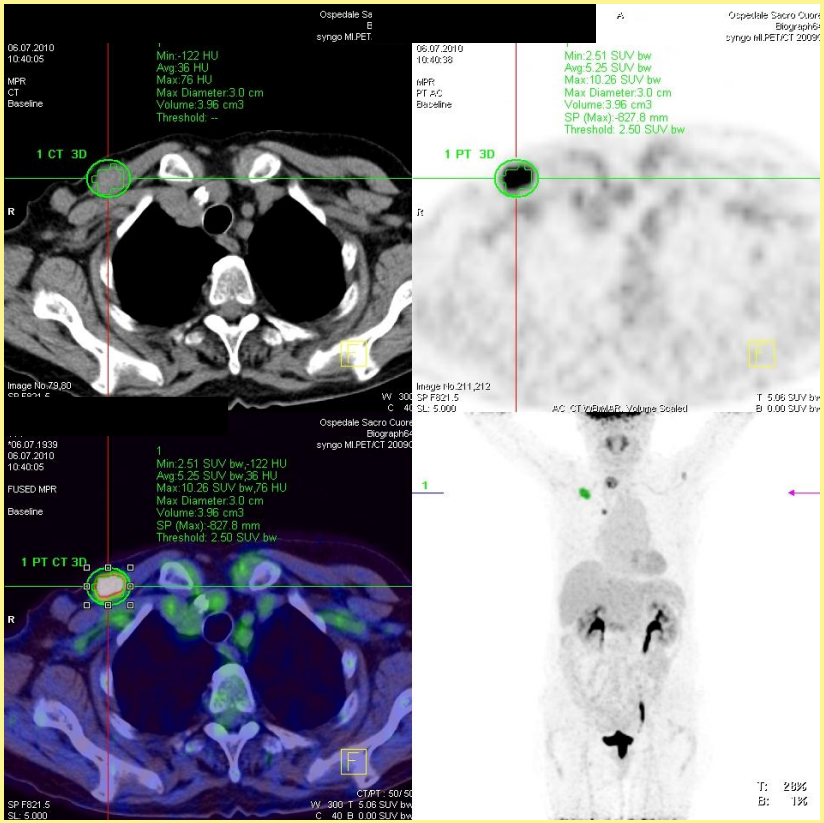
Le performance considerate sono quella della review sistematica 2012 Breast.

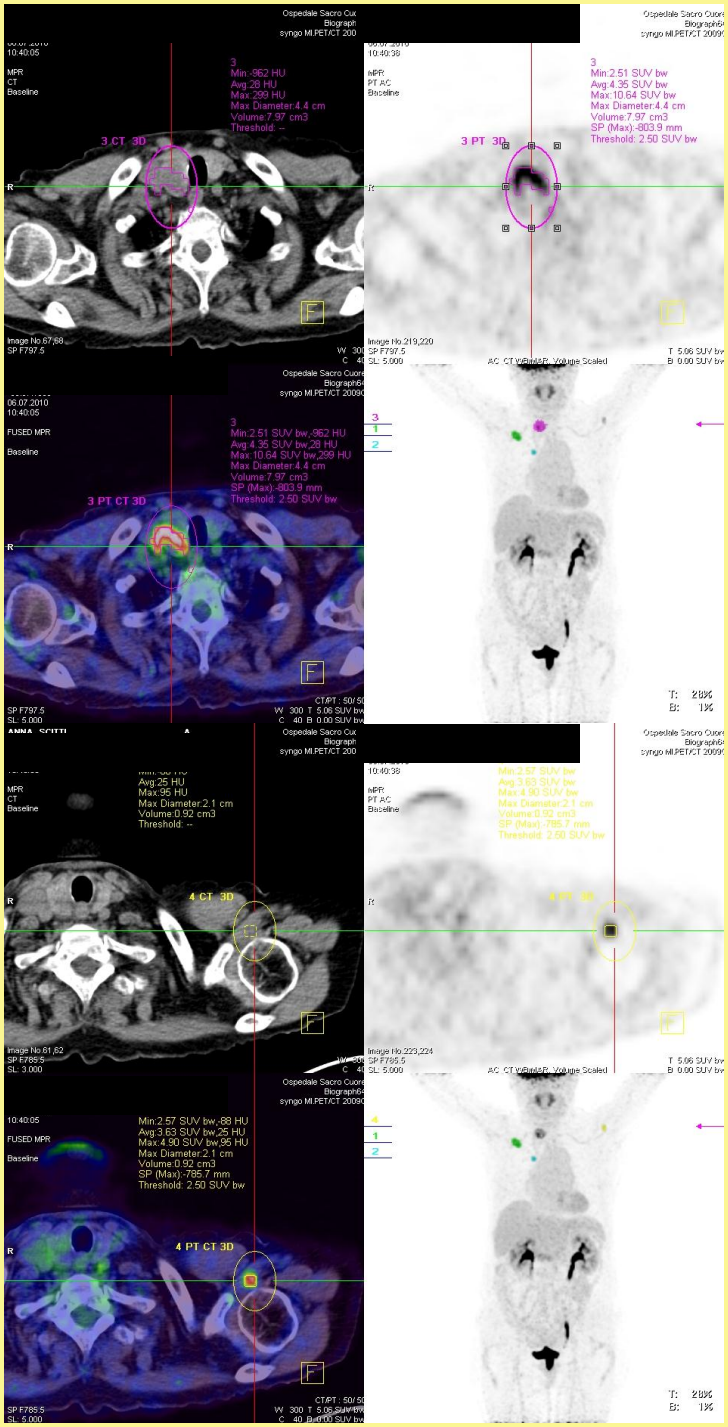
SE	1
SP	0,96
PREV	0,1
VPP	**0,735**
VPN	**0,000**

Flogosi da espansore, metastasi singola al lobo polmonare inferiore dx



Ripresa di malattia su muscolo pettorale dx, metastasi tiroidea, stiramento muscolare

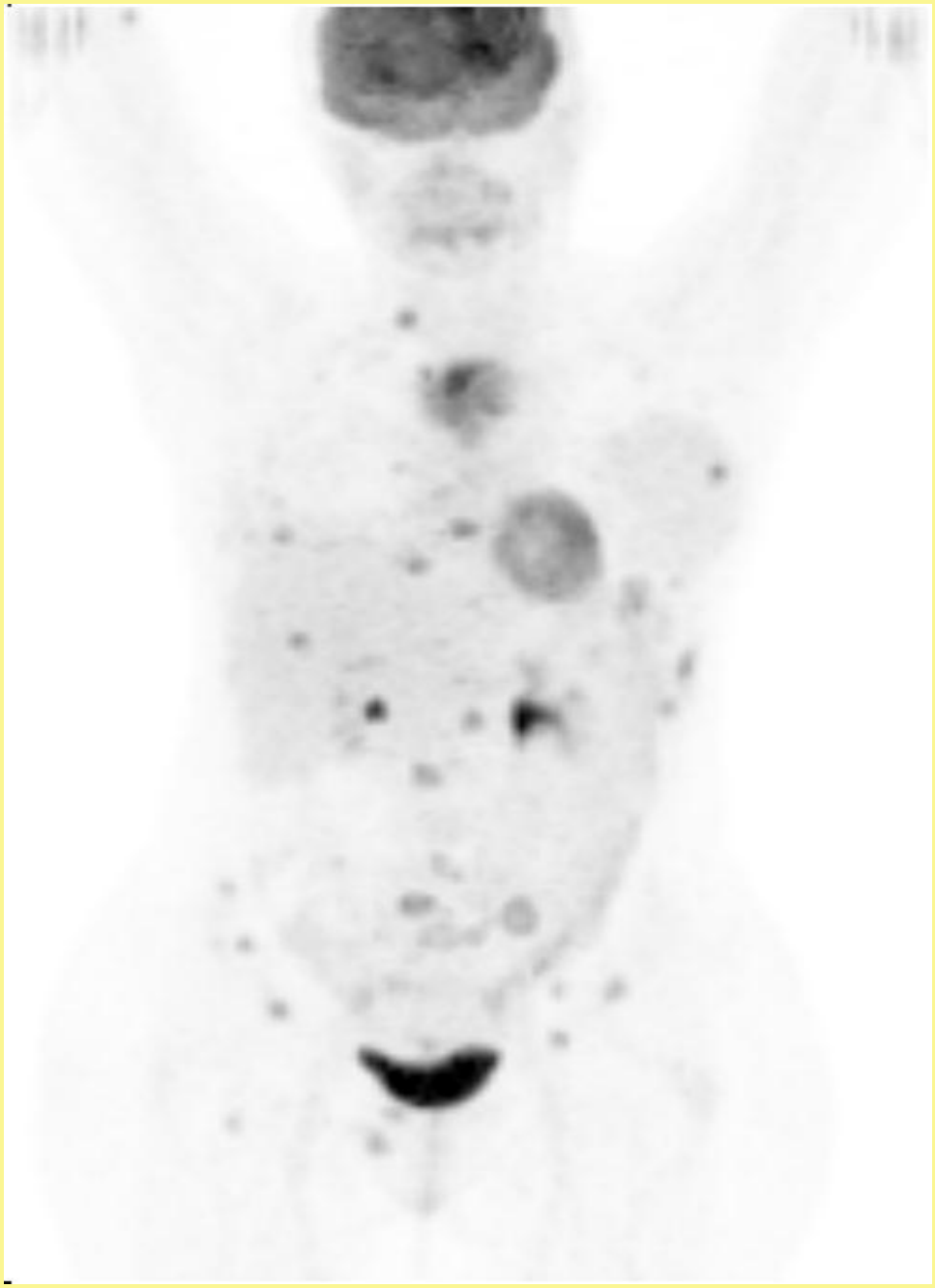




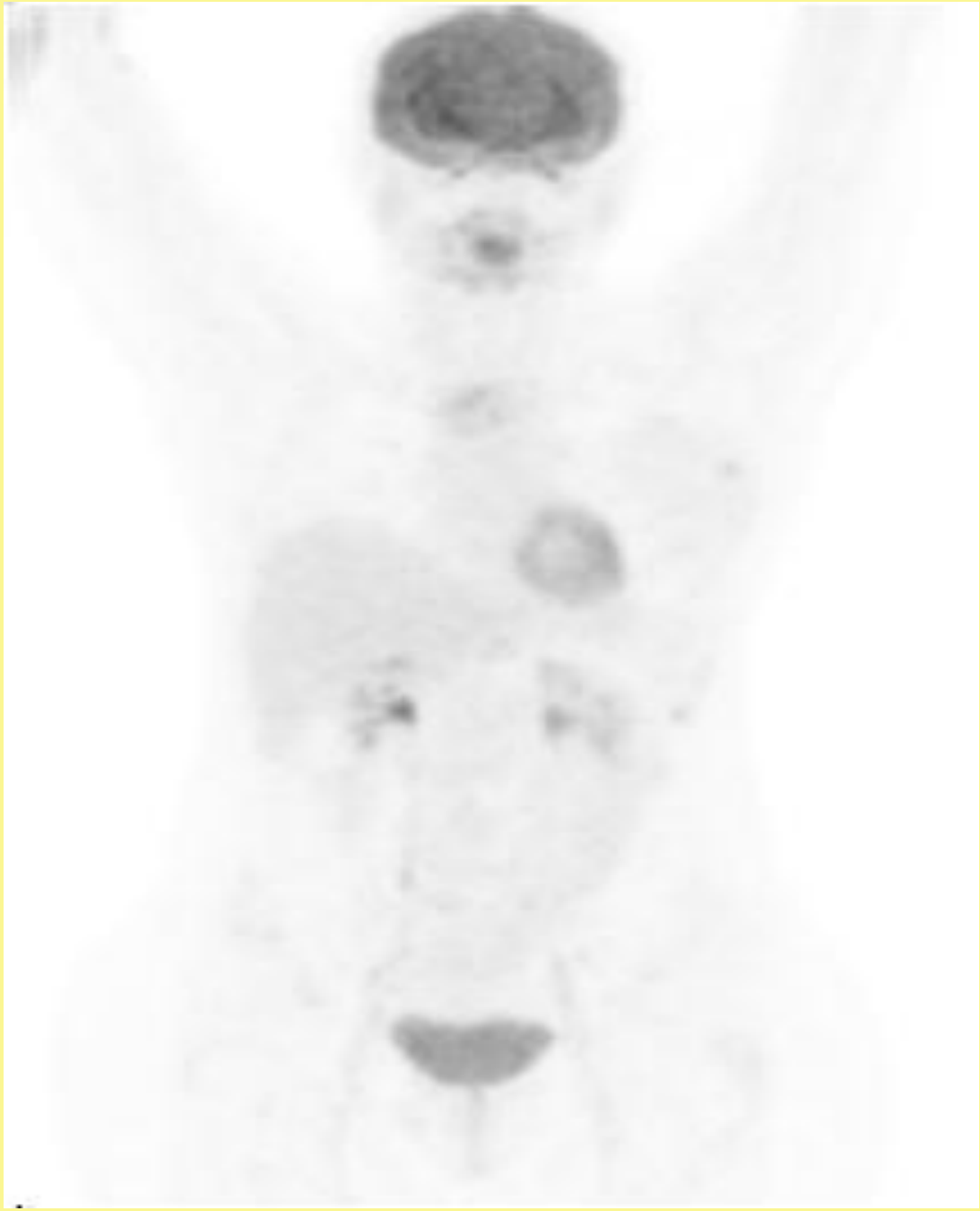
Studio pre-terapia

Recettori estrog. e prog +

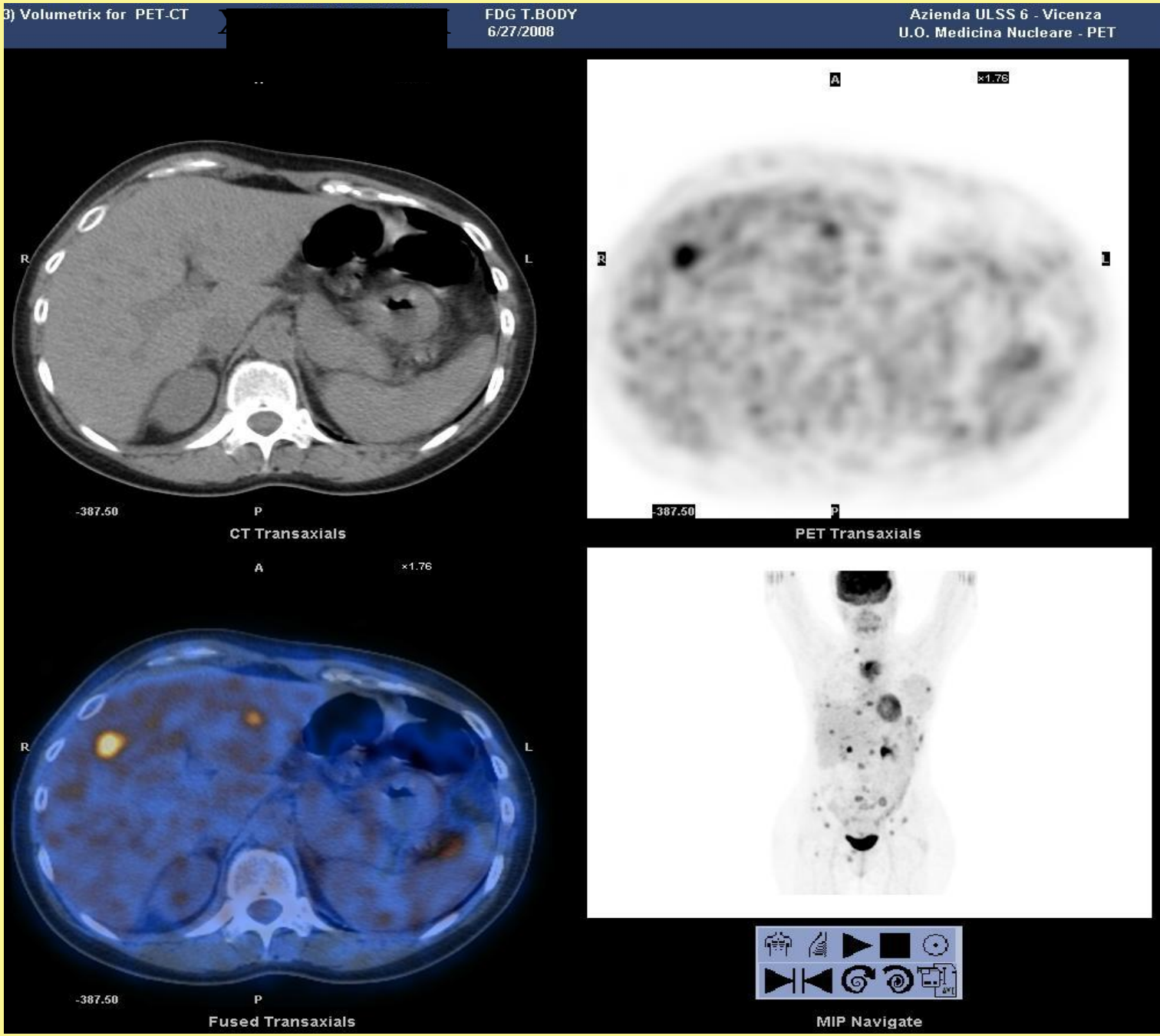
HER2-



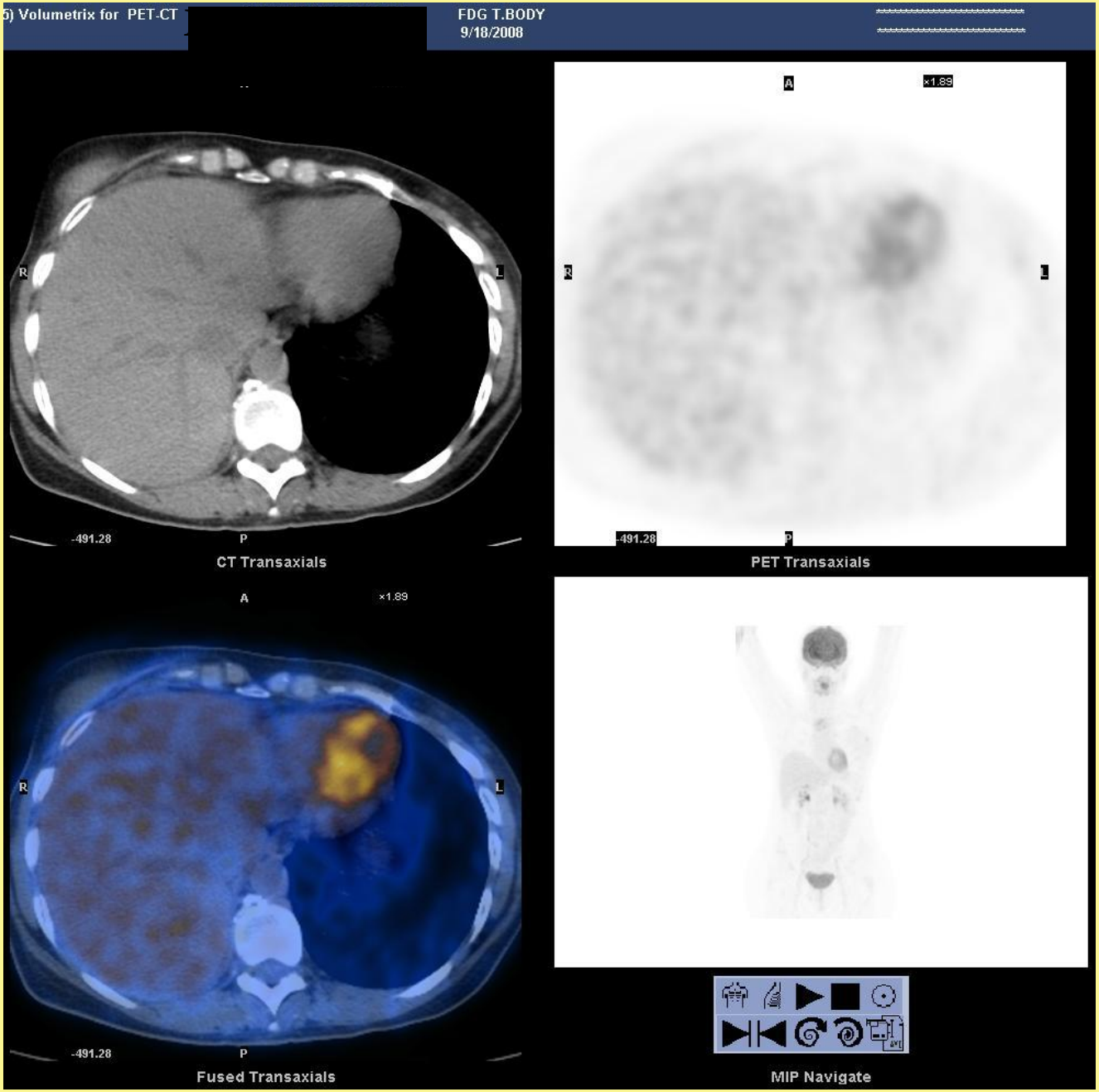
Studio post-terapia



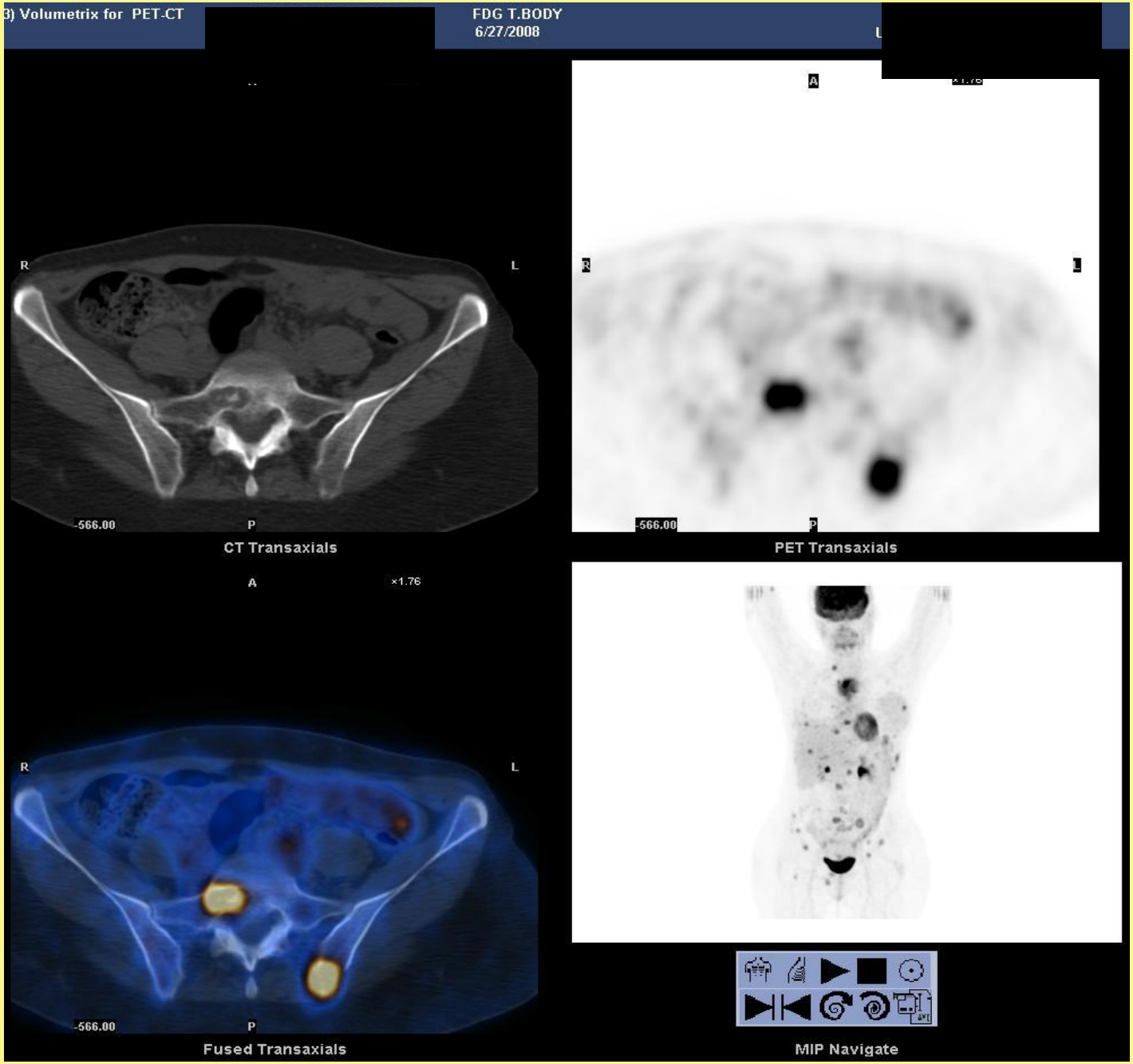
Fegato pre-terapia



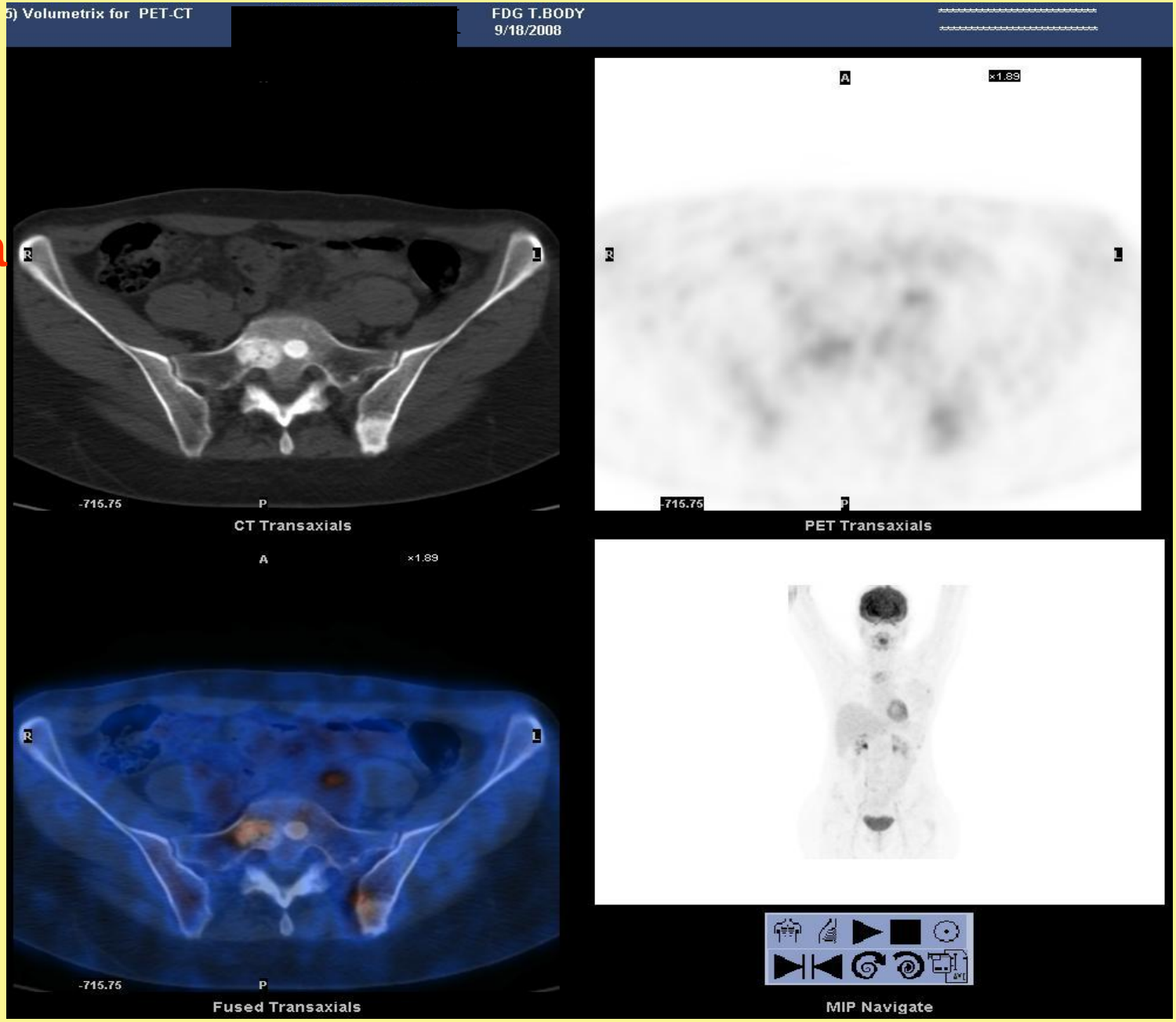
Fegato post-terapia



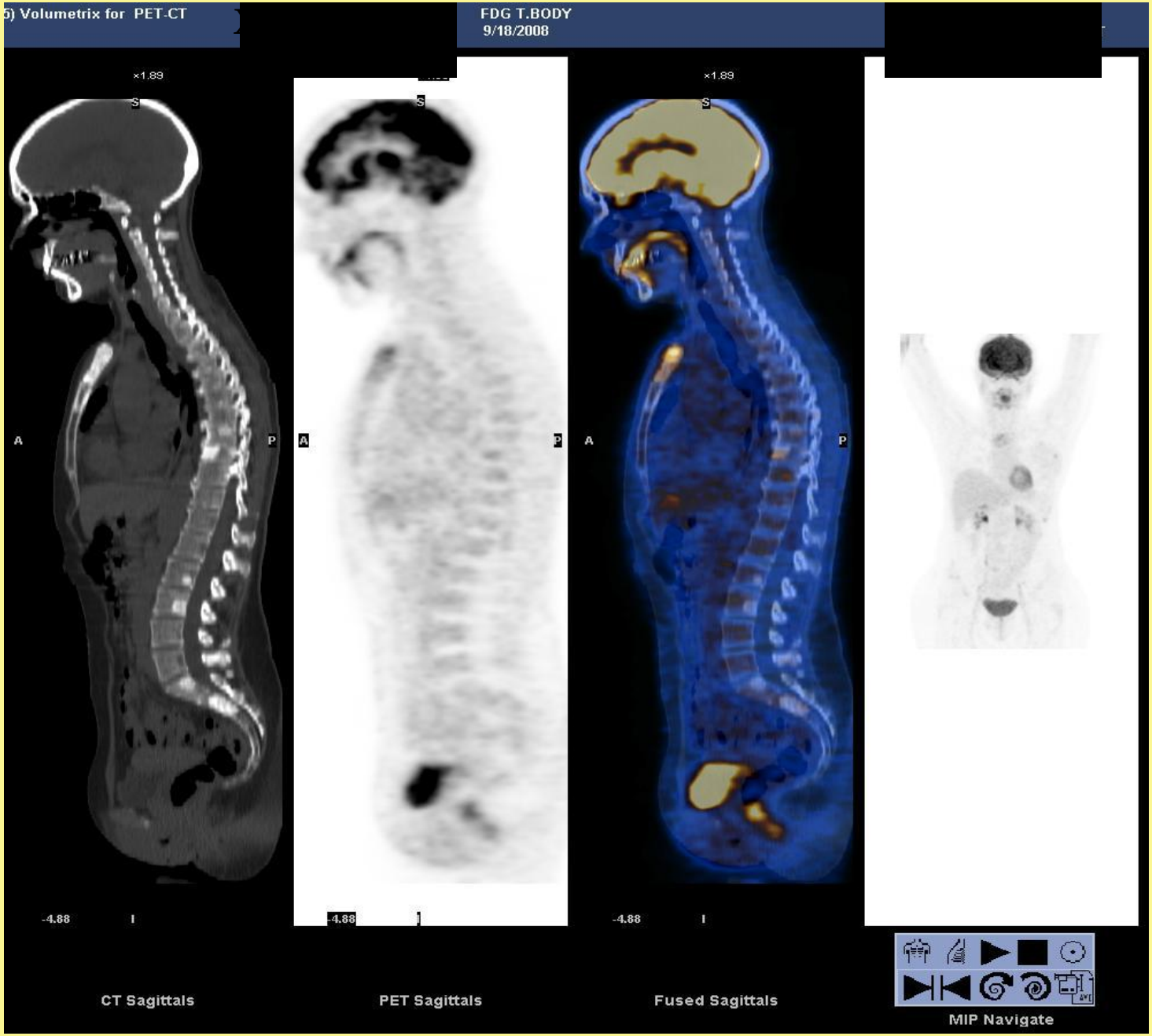
Osso
pre-terapia

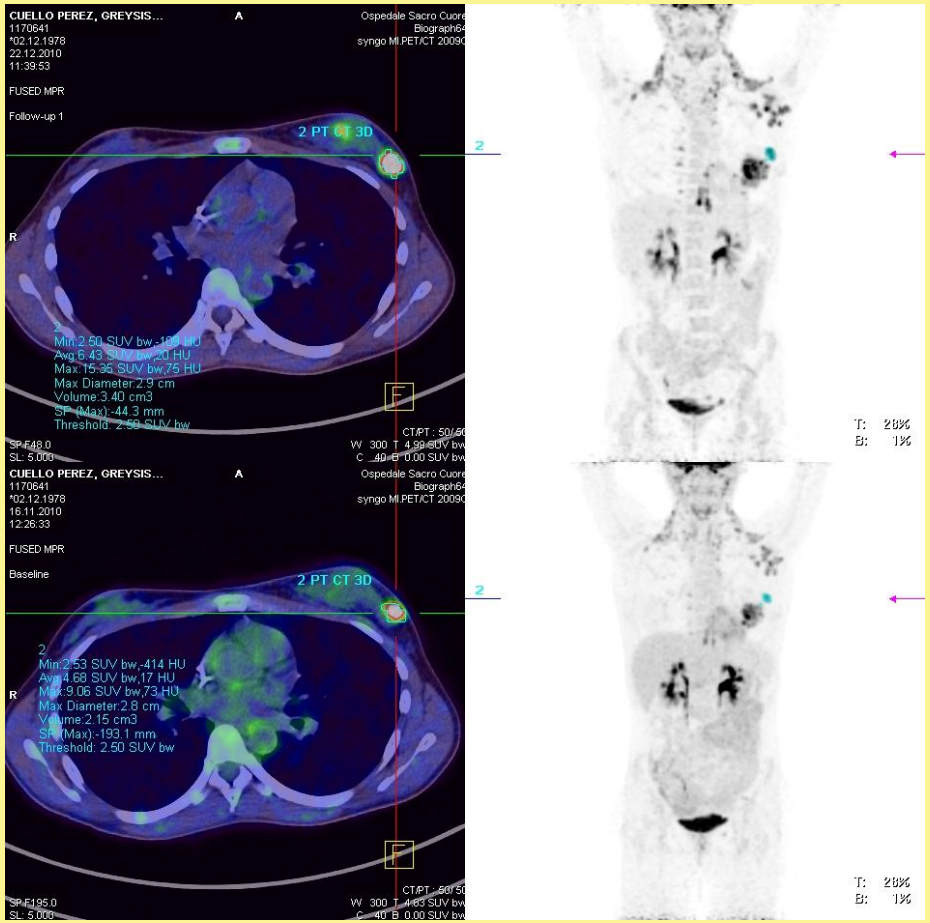


Osso post-terapia risposta incompleta



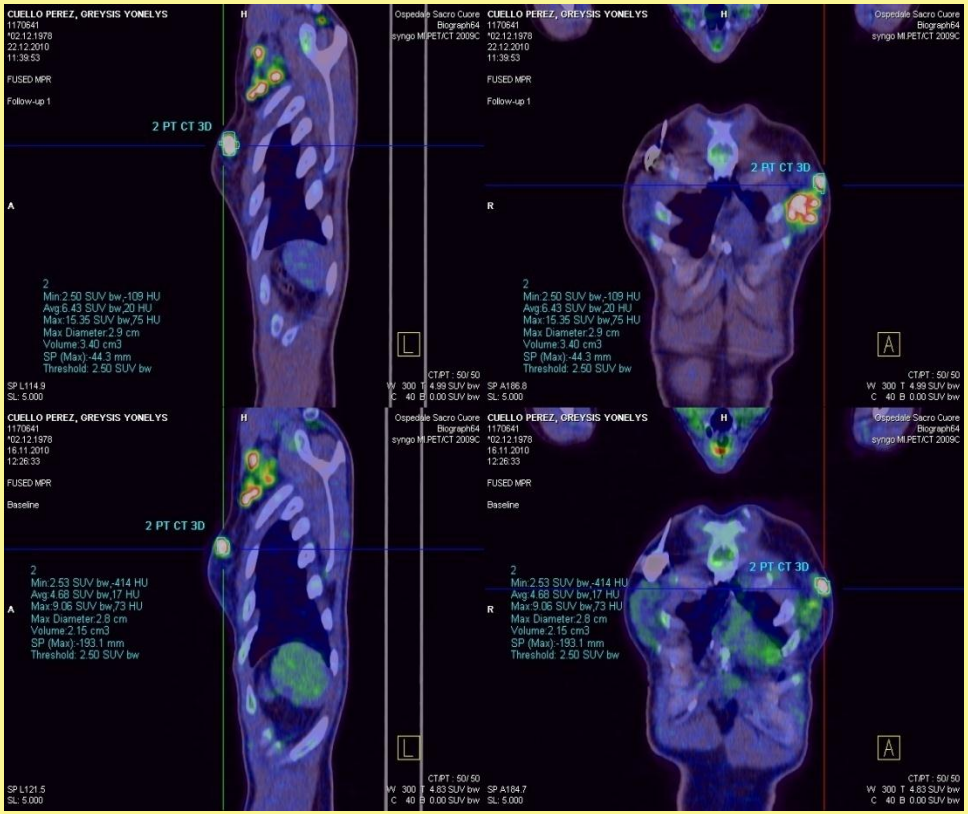
Osso post-terapia risposta quasi completa

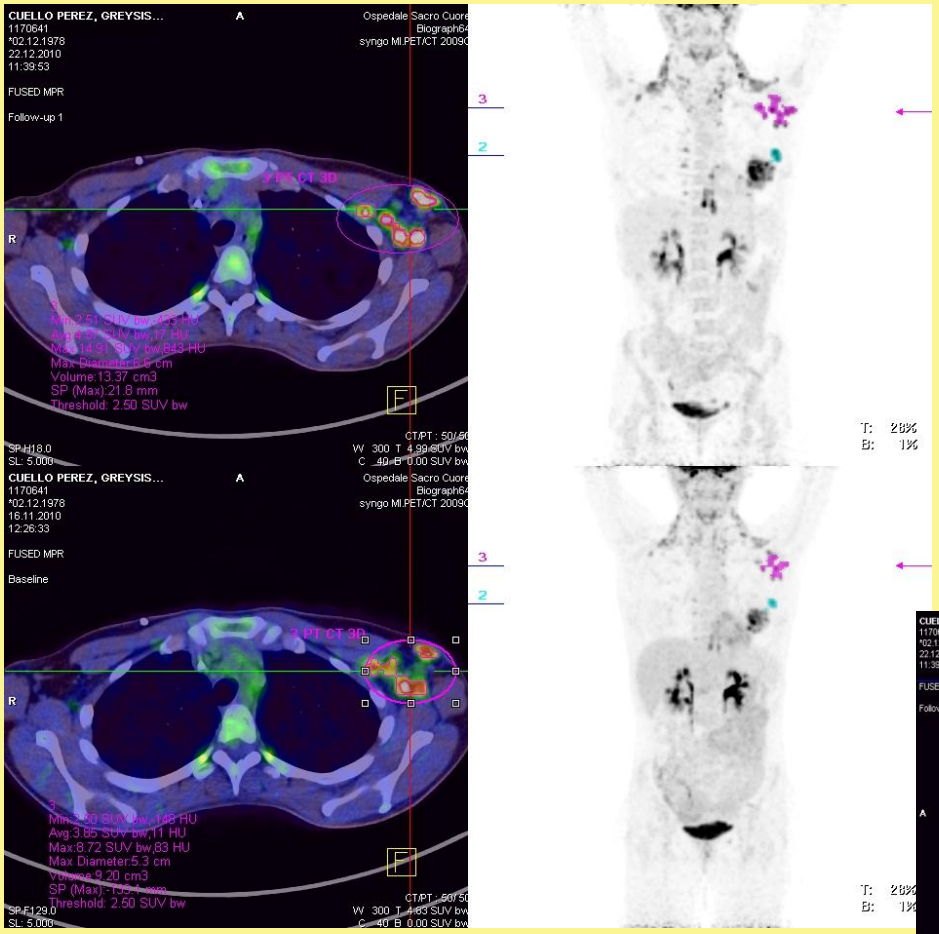




E-, P-, Her2+

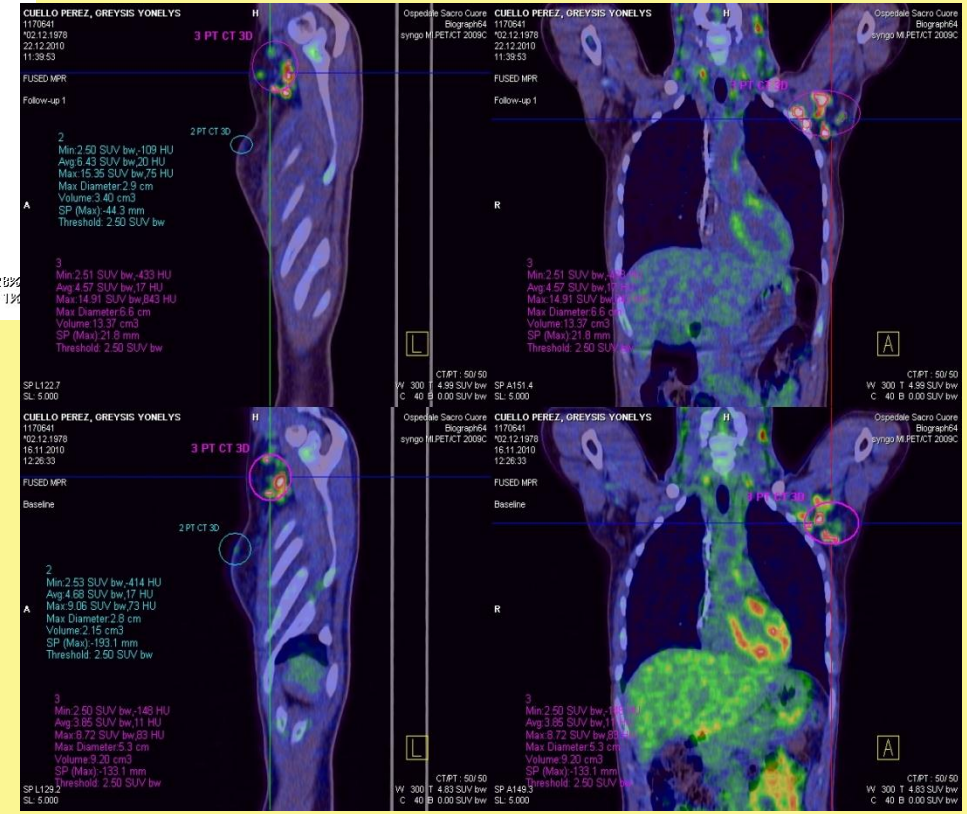
Progressione in corso di terapia neoadiuvante





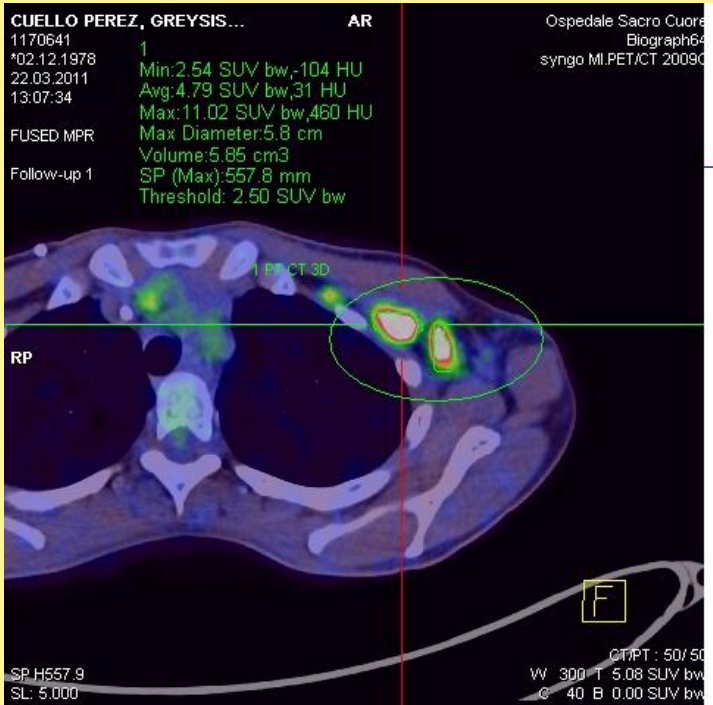
E-, P-, Her2+

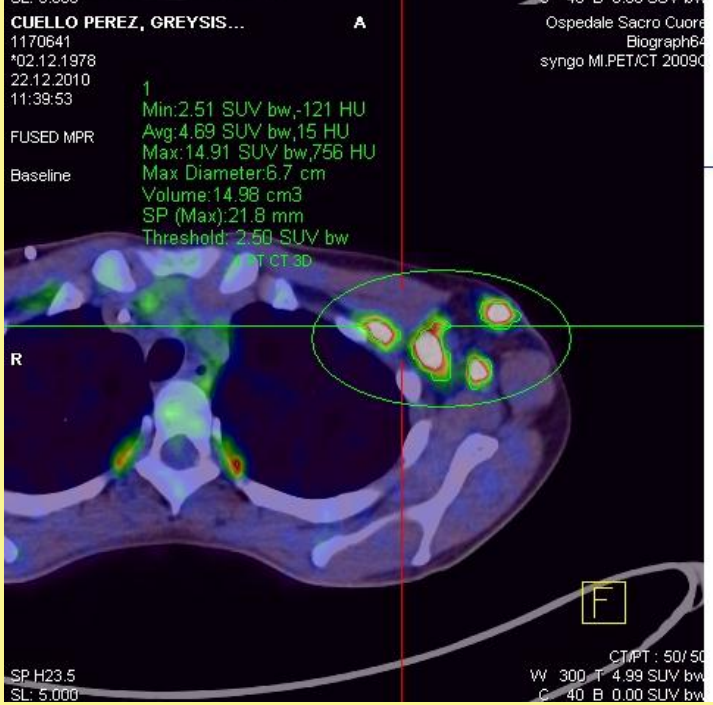
Progressione in corso di terapia neoadiuvante

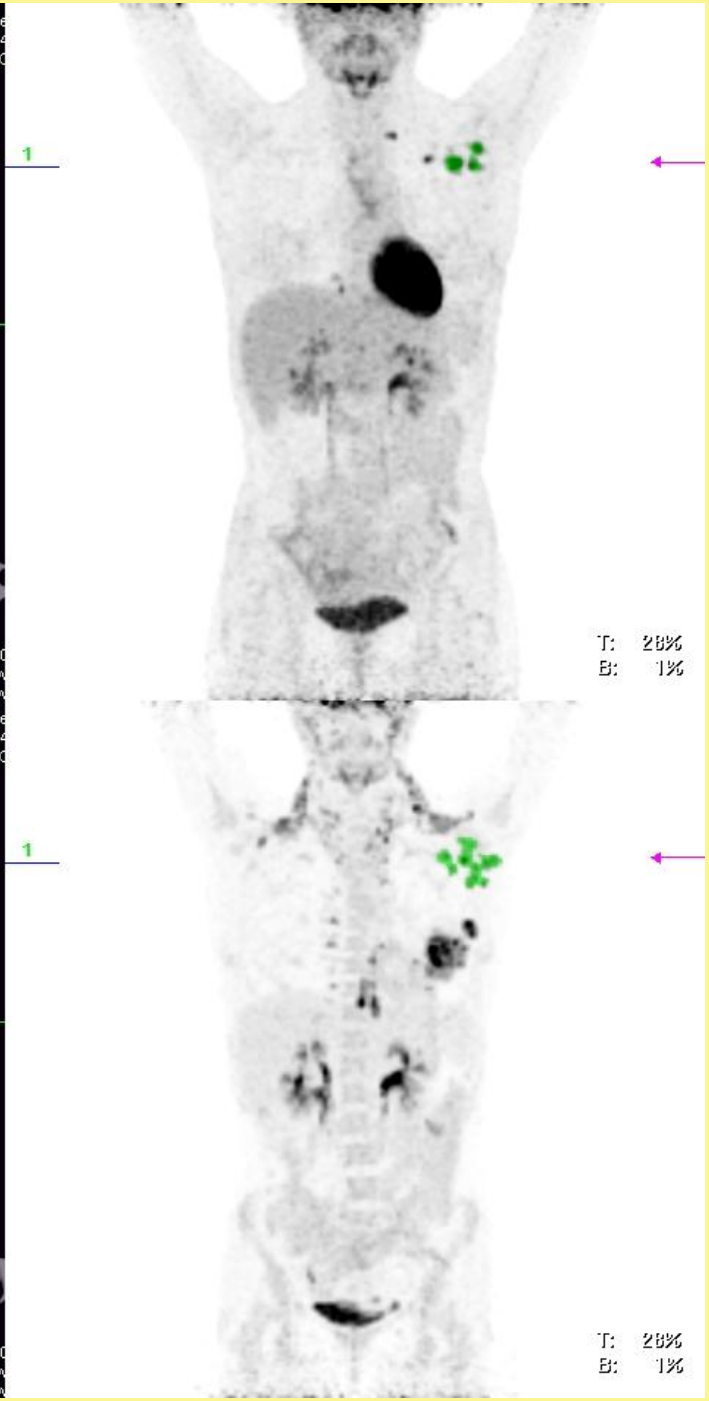


E-, P-, Her2+

Progressione in corso di terapia

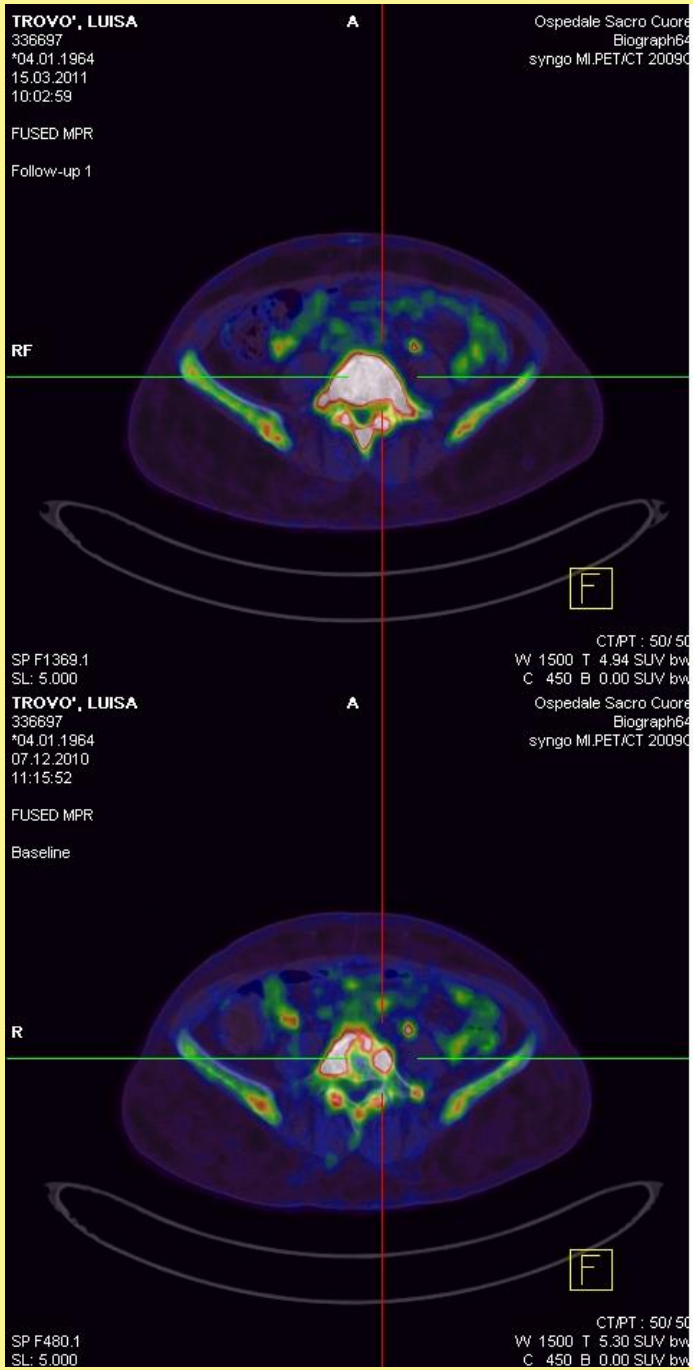


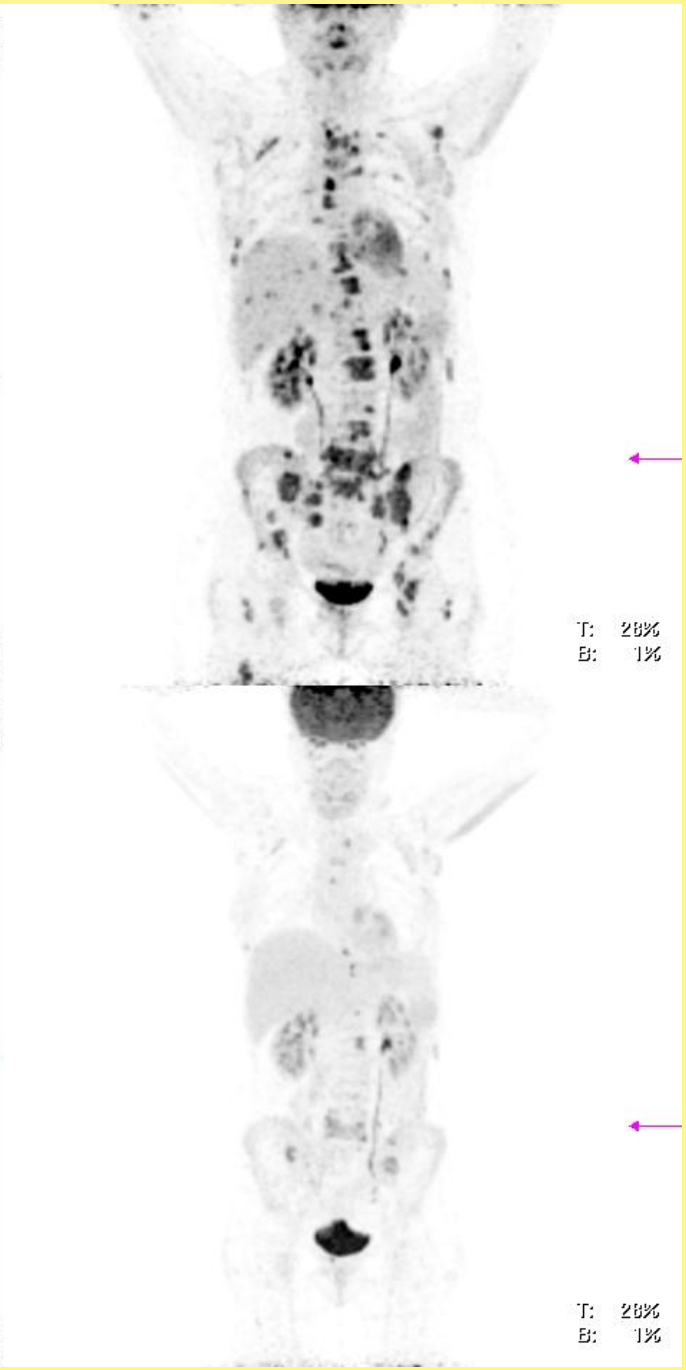




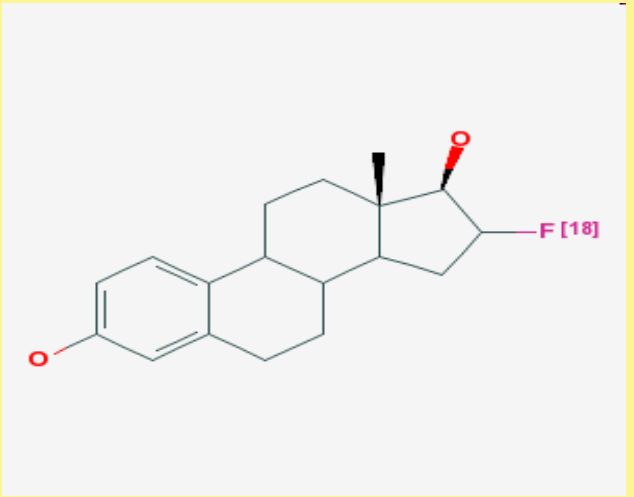
E+, P+, Her2-

Progressione in corso di terapia





Chemical name:16α-[18F]Fluoro-17β-estradiol

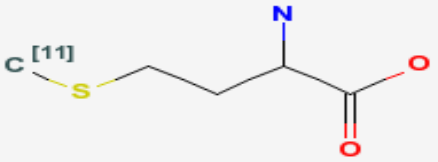


Abbreviated name:[18F]FES **Synonym:**16-Fluoroestradiol, fluoroestradiol
Target: Estrogen receptor; **Target category:** Receptor
Method of detection:PET. **Source of signal:**18F
Activation: No**Studies:***Litterature: In vitro,* Rodents, Humans

Recently, automated synthesis procedure has been developed for clinical large-scale production of [18F]FES in good yields (15-35%) with high radiochemical purity (>99%) (8).

Human Studies
Thirteen patients with primary breast lesions were studied with [18F]FES PET (14). PET images demonstrated uptake of the tracer at sites of primary tumors and in several axillary lymph node metastases, as well as in one distant metastatic lesion. There was an excellent correlation between uptake within the primary tumor measured on the PET images and the tumor ER concentration measured by *in vitro* receptor binding assays after excision (r = 0.96). In a study with 15 breast cancer patients (15), [18F]FES was cleared from the blood and metabolized in 20 min with only 20% of intact [18F]FES, most of which was bound to plasma proteins. Liver uptake of [18F]FES was rapid, and [18F]FES metabolites appeared in the blood as early as 5 min. The major, labeled metabolites in the blood and urine were sulfate and glucuronidate conjugates of [18F]FES, as measured by HPLC.
Human dosimetry of [18F]FES was determined from blood samples and PET images in 49 patients after intravenous injection of [18F]FES (16).The effective dose equivalent was 0.022 mSv/MBq (80 mrem/mCi). The organ that received the highest dose was the liver (0.13 mGy/MBq (470 mrad/mCi)), followed by the gallbladder (0.10 mGy/MBq (380 mrad/mCi)) and the urinary bladder (0.05 mGy/MBq (190 mrad/mCi)). Uptake of [18F]FES in a series of patients with primary breast lesions and recurrent/metastatic breast tumors was compared with *in vitro* ER content and tumor uptake of [18F]FDG (17). There was no correlation between tumor ER status and [18F]FDG uptake or between tumor [18F]FES and [18F]FDG uptake in these patients. However, the [18F]FES PET assessments were in agreement with the *in vitro* ER binding assays. Anti-estrogen therapy decreased [18F]FES uptake in patients with ER-positive lesions (18), and patients with high initial uptake of [18F]FES were more likely to respond favorably to hormonal therapy (19). Peterson et al. (20) studied seventeen patients with primary or metastatic breast cancer with dynamic [18F]FES PET. For each tumor, partial-volume-corrected standardized uptake values (SUVs) of [18F]FES uptake were compared with ER expression measured by 3 different ER scoring methods: qualitative scoring, the Allred score , and a computerized immunohistochemistry (IHC) index. There was excellent agreement (r = 0.99) between observers using IHC as well as the different methods of measuring ER content (P < 0.001) with the best correlation being between the IHC index and [18F]FES SUVs.
Tumor imaging with [18F]FES PET is useful in the determination of ER status and prognosis of therapy in breast cancer patients.
NIH Support CA25836, CA42045, CA48286, CA72064, CA72964, DK15556, HL13851, RR17229

Chemical name:L-[methyl-11C]Methionine [11C]METSynonym:2-Amino-4-[11C]methylsulfanyl-butanoic acid, l-[S-methyl11C]methionine



Agent Category: Amino acid, **Target:**L-type amino acid transporter system and Na+-dependent system B0,

Target Category: Neutral amino acid uptake and protein synthesis,

Method of detection: PET, **Source of signal:** 11C, **Activation:** No

Studies: *In vitro,* Rodents,Other non-primate mammals, Non-human primates,Humans

Human Studies

[PubMed]

Seventeen patients with suspected astrocytomas (9 of grade II and 8 of grade III) were studied by PET with FDG and [11C]MET (10). In all patients, PET images of [11C]MET and FDG provided higher tumor/white matter ratios than tumor/corresponding contralateral region ratios and tumor/mean cortical uptake ratios. In grade II patients, FDG did not exhibit a significant increase in tumor uptake, whereas [11C]MET was a good tumor predictor with ratios of about 1.50 ± 0.48. In grade III patients, both FDG and [11C]MET exhibited higher uptake ratios than for grade II, with [11C]MET(ratios of 2.50 ± 0.85) being better than FDG, possibly suggesting enhanced protein synthesis.

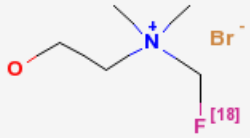
[11C]MET PET studies were performed the first 8 to 24 h after the onset of neurological symptoms and at the follow-up study 14 days after the ischemic attack (16). Increased [11C]MET uptake was found significantly in patchy areas in the immediate vicinity of infarction as well as in distant areas within the same hemisphere. In those areas, regional cerebral blood flow and oxygen extraction fraction were highly variable, and the regional cerebral metabolic rate of oxygen was preserved or slightly reduced. It was postulated that there were alterations of amino acid transport or protein synthesis in the brain tissue because of either blood-brain barrier disruption or post-ischemic hyper-perfusion.

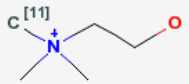
Human dosimetry of [11C]MET was estimated in five normal volunteers (17). The average injected dose was 558 MBq (15.08 mCi). The organs that received the highest absorbed doses were found to be the bladder wall (0.027 mGy/MBq or 100 mrad/mCi), the pancreas (0.019 mGy/MBq or 70 mrad/mCi), the liver (0.018 mGy/MBq or 66 mrad/mCi), and the kidneys (0.011 mGy/MBq or 41 mrad/mCi). The effective dose was calculated as 0.0053 mSv/MBq (20 mrem/mCi) for a 70-kg-standard man.

For many years, [11C]MET was used for brain imaging of gliomas, astrocytomas, oligodendrogliomas, and other malignant brain tumors [PubMed]. [11C]MET PET is useful to evaluate low-grade brain tumors and their responses to treatment (18). However, about 20% of low-grade brain tumors were not detectable, and some infarcts, hematomas, and inflammatory tissues may show high uptake (3). [11C]MET is proved to be a reliable and highly accurate imaging PET tracer for localizing parathyroid adenomas in patients in whom conventional imaging techniques have failed (19).

Chemical name:[18F]Fluorocholine

Abbreviated name:[18F]FCH, FCHSynonym:[18F]Fluoromethyl-dimethyl hydroxyethylammonium





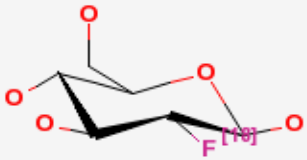
Target: Choline kinase
Target Category: Phosphorylation and incorporation into phospholipids of cell membranes
Method of detection:PET
Source of signal:18F, **Activation:**No, **Studies:***In vitro,* Rodents, Humans

Human Studies

FCH was cleared from blood in the first 5 min after administration in humans. The radioactivity in the liver increased rapidly in the first 10 min and then gradually thereafter. The FCH PET scan of 12 normal human subjects showed the highest uptake in the kidneys, liver, and spleen. Human dosimetry was estimated based on murine and human biodistribution data. The kidneys received the highest dose of radioactivity, followed by the bladder, liver, and spleen (10). The effective dose equivalent of administration of 4.07 MBq/kg (0.11 mCi/kg) is about 0.03 mSv/MBq (0.1 rad/mCi).
PET imaging studies of cancer patients showed the feasibility of FCH uptake in prostate cancer, breast cancer, and brain tumors. Osseous, soft tissue and lymph node metastases were also detected by FCH uptake foci (5, 6). Two recent prostate cancer studies with 36 patients showed that malignant tumors, recurrent tumors and lymph node metastases could be localized with FCH PET scans (11, 12). However, Schmid et al. (12) noted in their study that differentiation of benign hyperplasia from malignant prostate lesions was not possible with FCH PET.

Chemical name:[18F]Fluoro-2-deoxy-2-D-glucose

Abbreviated name:[18F]FDG, FDG**Synonym:**[18F]Fluorodeoxyglucose



Target: Glucose transporters and hexokinases
Target Category: Uptake and phosphorylation
Method of detection:PET, **Source of signal:**18F, **Activation:**No

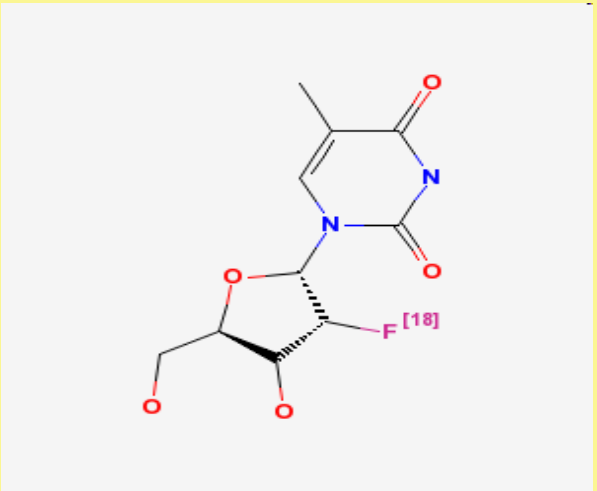
Studies:*In vitro,* Rodents, Other non-primate mammals, Non-human primates, Humans

Human Studies

In 1976, the first images of [18F]FDG metabolism in humans were obtained and showed high uptake in the bladder, heart, and brain (5, 32). Regional kinetic constants and rCMRglc in normal human subjects were determined by [18F]FDG PET (33-36). Human dosimetry was estimated from absorbed dose in organs after intravenous administration of [18F]FDG using whole-body PET scans in six normal volunteers (37). The bladder received the highest dose of radioactivity, followed by the spleen, heart, and brain. Mejia et al. (38) estimated the effective dose equivalent to be 0.024 mSv/MBq (81 mrem/mCi). [18F]FDG PET imaging techniques are widely used in clinical applications. In central nervous system disorders, the clinical applications are in Alzheimer's disease, dementia, epilepsy, brain trauma, Huntington disease, cerebrovascular disorders, brain tumors, schizophrenia, and mood disorders (39, 40). In oncology, the clinical applications are in diagnosis, treatment monitoring, and tumor staging and have been used in non-small cell lung cancer, colorectal carcinoma, malignant melanoma, Hodgkin and non-Hodgkin lymphoma, esophageal carcinoma, head and neck cancer, breast cancer, and thyroid carcinoma (9, 41). In cardiovascular disorders, the clinical applications are in myocardial viability and atherosclerosis (42). In infectious and inflammatory diseases, the clinical applications are in orthopedic infections, osteomyelitis, ileitis, sarcoidosis, rheumatologic disease, and vasculitis (42).

Chemical name:1-(2’-Deoxy-2’-[18F]fluoro-β-D-arabinofuranosyl)thymine

Abbreviated name:[18F]FMAUSynonym:2’-Deoxy-2’-[18F]fluoro-5-methyl-1-β-D-arabinofuranosyluracil; 1-(2’-deoxy-2’-[18F]fluoro-β-D-arabinofuranosyl)-5 methyluracil



Target:DNA,**Target Category:**Incorporation into DNA

Method of detection: Positron emission tomography (PET)

Source of signal:18F**Activation:**No

Studies: *In vitro,* Rodents, Non-primate non-rodent mammals, Humans

Human Studies

A pilot study was conducted to evaluate [18F]FMAU for DNA synthesis in tumors and to determine its biodistribution in cancer patients (10). The radiopharmaceutical was used to image patients (*n* = 14) with either prostate, brain, colorectal, lung, or breast cancer. Dynamic PET images were obtained 60 min after the administration of [18F]FMAU, and metabolite clearance was also determined with HPLC in the blood and urine. The normal bone marrow was reported to have a mean standardized uptake value (SUV) of 0.7, and the tumor SUVs were 2.19, 1.28, 2.21, and 2.27–4.42 for lesions in the breast, brain, lungs, and prostate. High SUVs were observed in the liver (SUV 10.07–20.88) and the kidneys (SUV 7.18–15.66), probably because of metabolism and excretion in these organs. Compared to these organs, the bladder had a low mean SUV of 2.03. The investigators reported that 95% of the activity was cleared from blood circulation within 10 min, and 70% of the activity in the urine was intact [18F]FMAU at 60 min after administration (10).

Tehrani et al. investigated the uptake of [18F]FMAU in patients with brain (*n* = 4) and prostate (*n* = 6) cancers to determine the easiest approach for image acquisition and analysis (11). The investigators obtained 60-minute dynamic images and determined the mean and maximum SUVs for the tumors. The mean tumor SUVs obtained between 5 and 11 min were reported to correlate with the values obtained between 30 and 60 min (r2 = 0.92; *P* < 0.0001), and the maximum SUVs also showed a similar correlation. The investigators cautioned that, although this radiopharmaceutical was suitable to obtain usable images of the brain and prostate tumors at 11 min after administration of [18F]FMAU, the study was performed with a small number of patients which means that it would be necessary to perform this study in a larger patient population with a wide range of tumors to generalize this procedure.