Associazione Italiana di Radioterapia Oncologica

Azienda USL Valle d'Aosta-Vallée d'Aoste

L' imaging funzionale e la terapia radiometabolica nel carcinoma prostatico.

AZIENDA USL DELLA VALLE D' AOSTA – Ospedale "Umberto Parini"
Dipartimento di diagnostica per immagini e radiologia interventistica
S.C. MEDICINA NUCLEARE

Carlo Poti

AGENDA

- Imaging molecolare
- PET “basics”
- La PET con 18F-Colina nel carcinoma della prostata
- Imaging dell’osso: scintigrafia scheletrica con 99mTc-MDP e PET con 18F-NaF
- La palliazione del dolore osseo nelle metastasi scheletriche e radioterapia metabolica: 89 $SrCl_2$, 153Sm-EDTMP, 186 Re-HEDP, 223$RaCl_2$

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Imaging molecolare

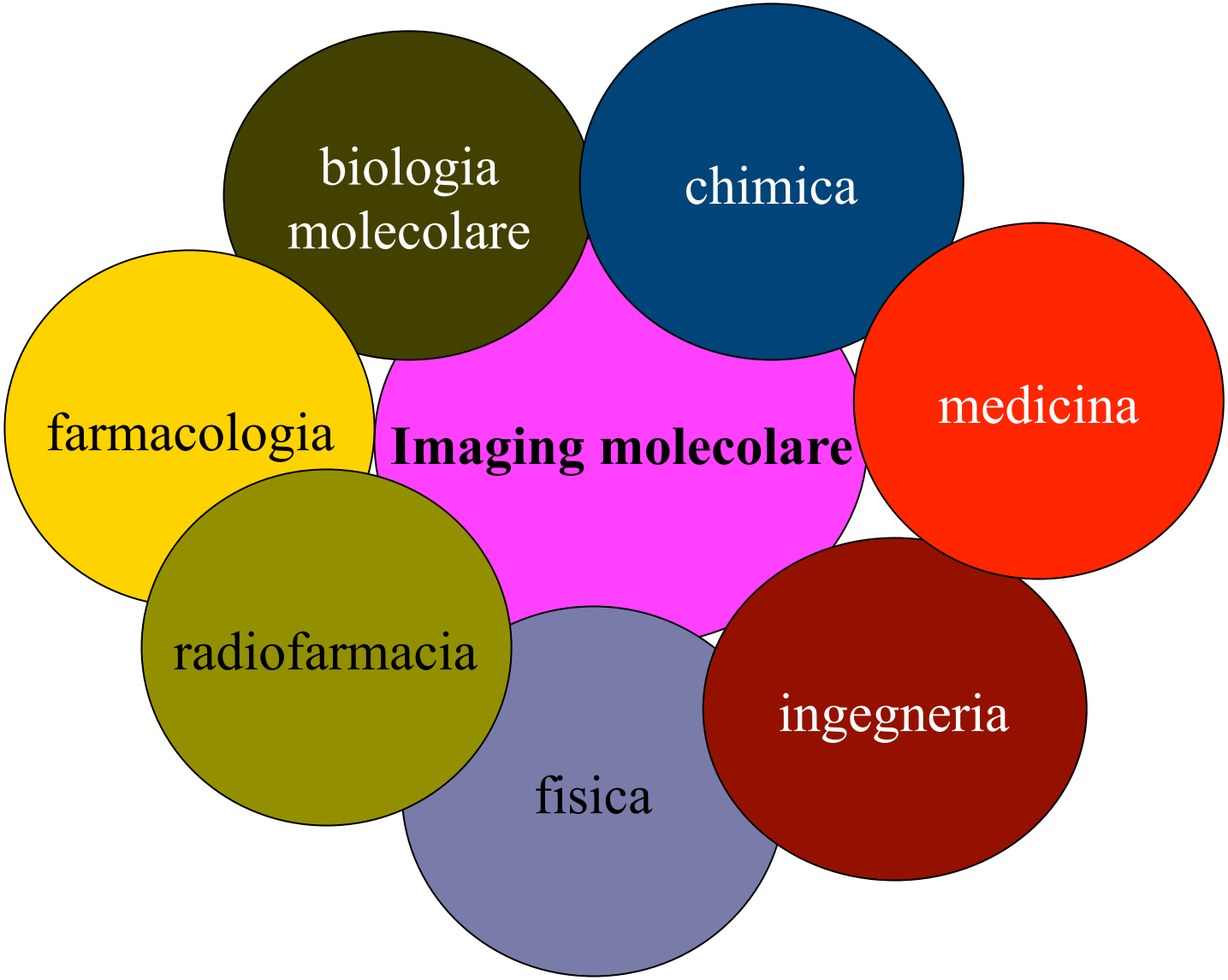
Distribuzione nello spazio e nel tempo di molecole o processi cellulari per lo sviluppo di applicazioni in campo diagnostico o terapeutico.

Thakur & Lentle, 2005

Rappresentazione visuale, caratterizzazione e quantificazione dei processi biologici che avvengono in un essere vivente a livello cellulare e sub-cellulare

In altre parole la misura "in vivo" e caratterizzazione di processi biologici a livello cellulare e molecolare.

Weissleder & Mahmood, 2001


biologia molecolare
chimica
farmacologia
Imaging molecolare
medicina
radiofarmacia
ingegneria
fisica

La prima applicazione pratica di un radiocomposto fu di György von Hevesy nel 1911.

Sospettò che il cibo che gli veniva proposto a pranzo fosse regolarmente ottenuto da avanzi dei giorni precedenti.

Per confermare il sospetto de Hevesy utilizzò una minuscola quantità di materiale radioattivo nel suo pranzo …..

Quando lo stesso cibo gli fu servito… ,"it was radioactive!"

La storia ha dimenticato la sua padrona di casa, ma George de Hevesy ottenne il premio Nobel nel 1943 e il riconoscimento "Atoms for Peace" nel 1959.

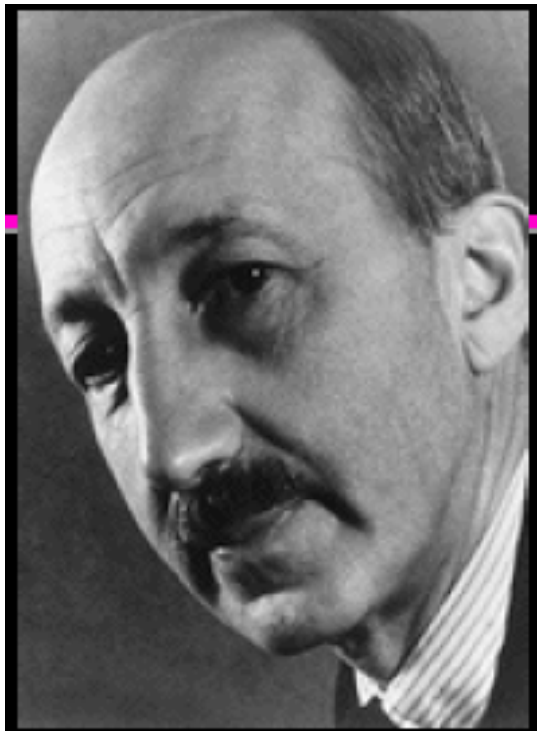
Concetto di "probe"

- 1924: Principio del radiotracciante

  La sostituzione di un atomo in una molecola con il suo analogo radioattivo (radioisotopo) non cambia significativamente il suo comportamento biologico

- Conseguenza:
- il movimento, la distribuzione e la concentrazione di una molecola può essere studiata con "modelli" matematici "compartimentali" e misurata con rivelatori per radiazioni

- Estensione del concetto in imaging molecolare
- Si utilizzano opportuni "*probes*" molecolari come *sorgente di contrasto* per l'immagine.
- Questi sono solitamente ottenuti a partire da un composto affine che interagisce con il *target* di interesse con l'aggiunta di una componente che produce un segnale.



•György von Hevesy (1885-1966)

Premio Nobel per la Chimica (1943)

"**per il suo lavoro nell'utilizzo di isotopi come traccianti nello studio dei processi chimici**"

Perché il “molecular imaging” è così imporante?

Imaging molecolare” per trovare la giusta “sonda molecolare” contro il giusto “target” per monitorare la specifica malattia.

“Biomarker”: trovare il farmaco giusto diretto contro il “target” appropriato per trattare la specifica malattia.

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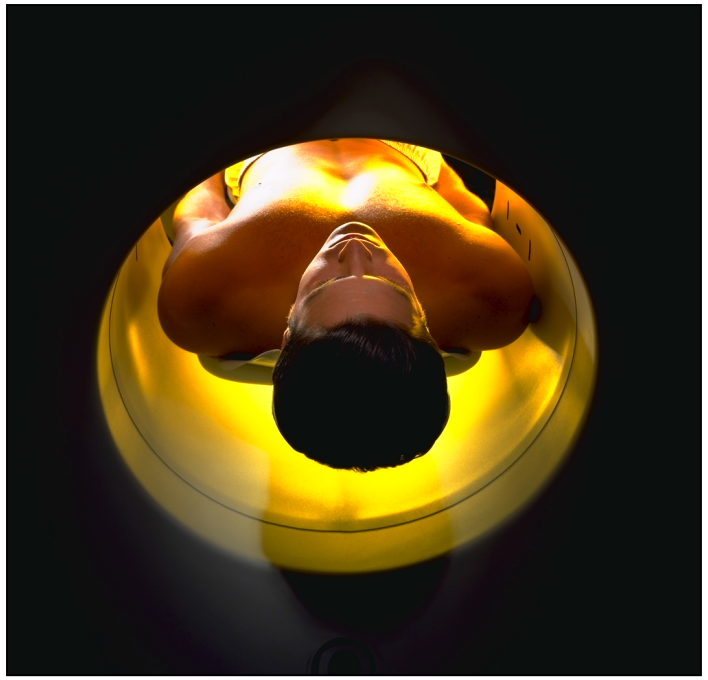
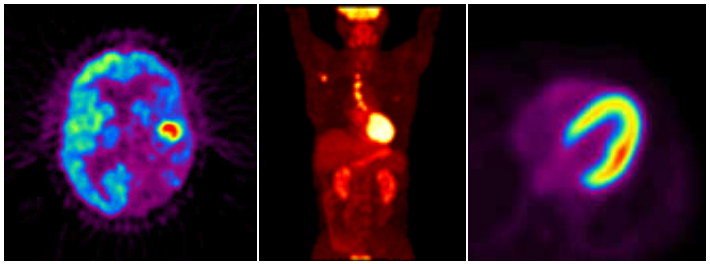
PET

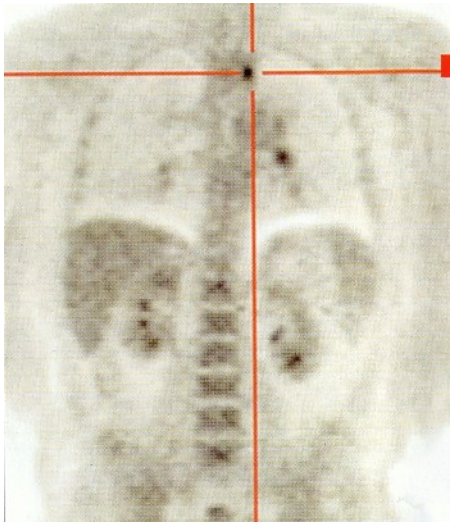
"Disease is a biological process and PET is a biological imaging technique that uses molecular probes."

Michael Phelps



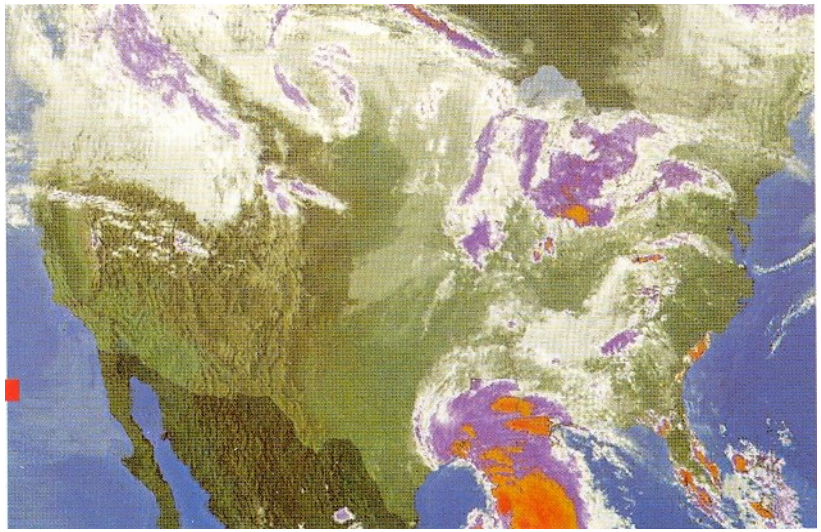


Imaging morfologico e funzionale



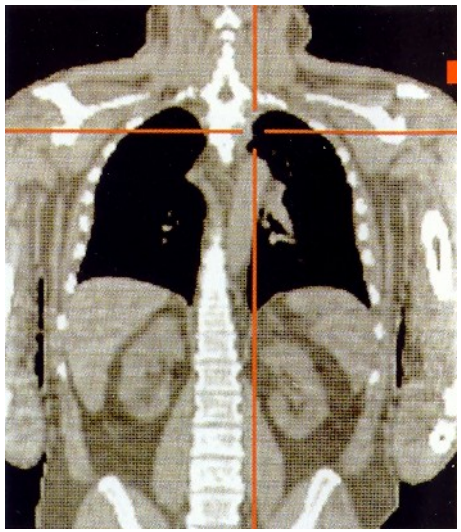
PET

Lo scan PET rivela aree di anormale attività, ma l'esatta localizzazione è sconosciuta



L'immagine dell'atmosfera presa da un satellite mostra le aree di intensa attività ma non le localizza in un preciso contesto geografico

CT



Un'immagine CT mostra precisamente l'anatomia del corpo ma non ne rivela la funzionalità chimica

La mappa mostra i confini degli stati ma non l'attività meteorologica

Positron Emission Tomography

La PET in estrema sintesi

Radiofarmaco marcato con nuclide emittente β⁺ somministrato al paziente

Emissione isotropa di β+ che localizza la distribuzione funzionale di radiofarmaco

β+ annichila nel tessuto ⇒ produzione di due fotoni di annichilazione quasi-opposti ($E_\gamma \geq 0.511$ MeV)

Fotoni di annichilazione rivelati in coincidenza elettronica

Ricostruzione della Linea di Volo (LOF) misurata⇒ imaging funzionale

Positron Radionuclides

Positron Source	Half-Life (minutes)	Maximum Energy
$^{11}C => ^{11}B$	20	960keV
$^{13}N => ^{13}C$	9	1.19 MeV
$^{15}O => ^{15}N$	2	1.72 MeV
$^{18}F => ^{18}O$	110	640 keV
$^{68}Ga => ^{68}Zn$	68	1.89 MeV
$^{82}Rb => ^{82}Kr$	1.3	3.35 MeV

Note: Mean photon energy for ^{18}F is 511 keV.

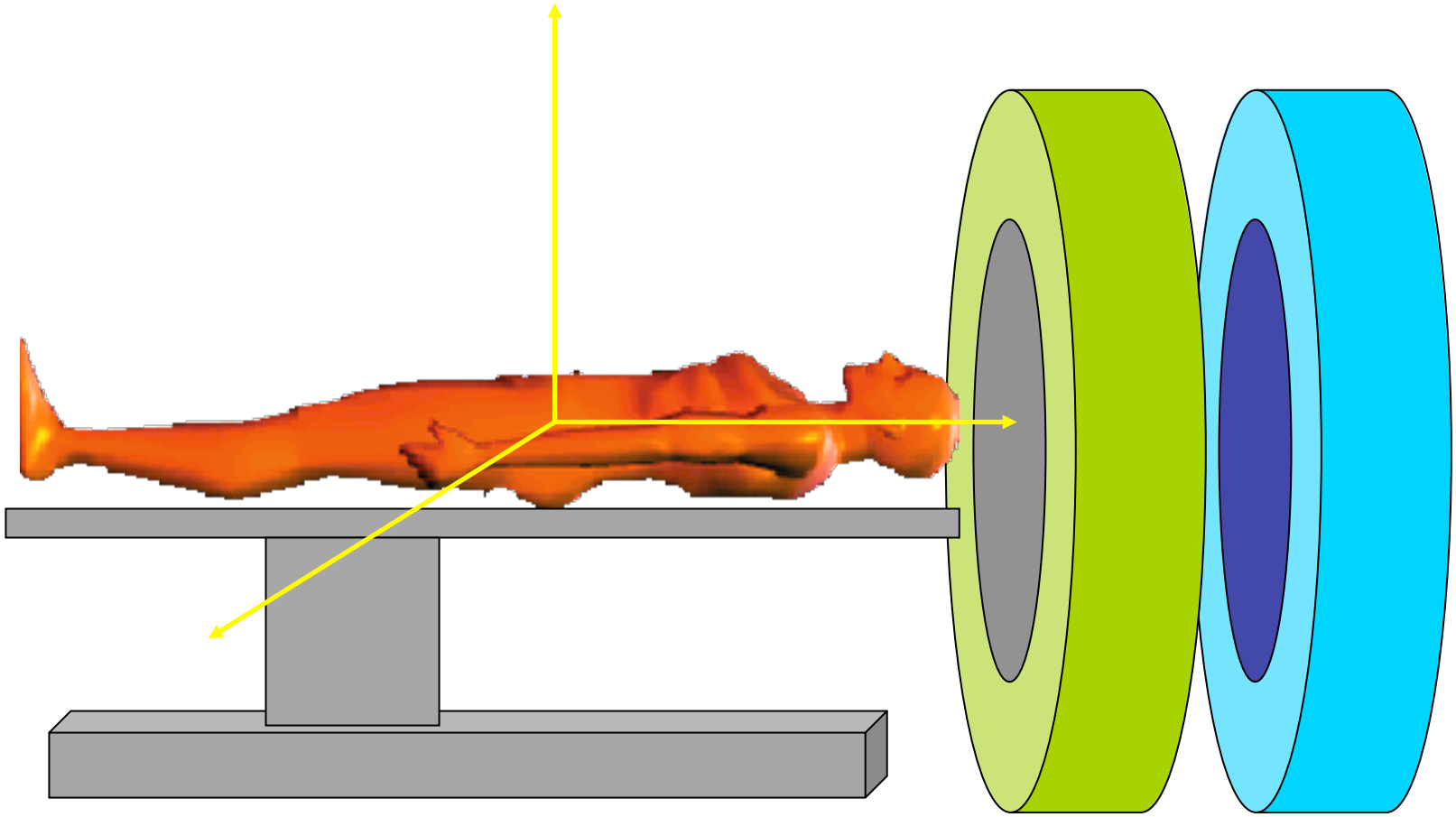
Perché il ^{18}Fluoro ?

- Molti nuclidi emittenti positroni sono prodotti con ciclotrone. Il 18F viene prodotto in quantità elevate e con relativa “facilità” in ciclotrone bombardando target di ^{18}O con protoni.

- Un nuclide PET ideale (e il radiofarmaco corrispondente) dovrebbe essere disponibile entro l’arco di tempo di un decadimento e il ^{18}Fluoro ha una half-life di poco meno di due ore, più che sufficiente per un trasporto “regionale”.

- “Flessibilità” radiochimica.

PET/CT



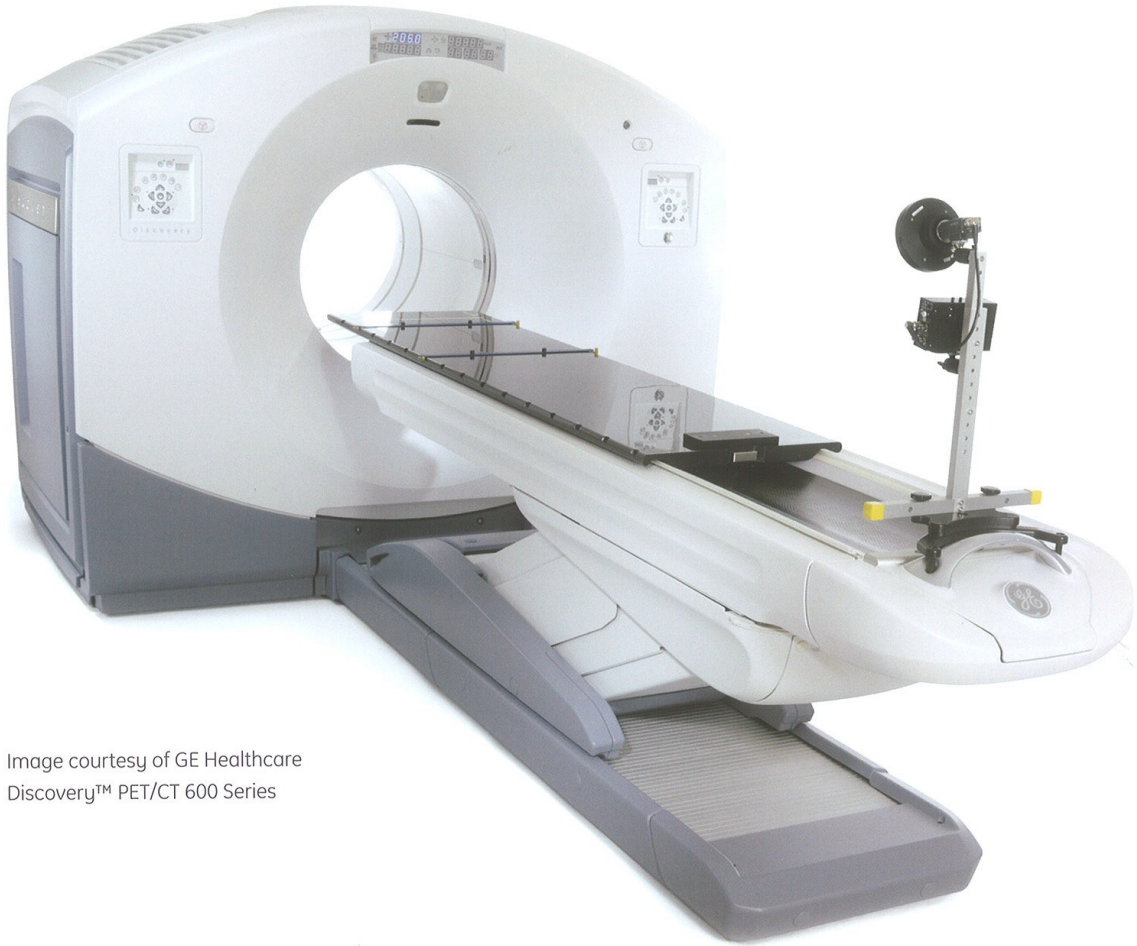
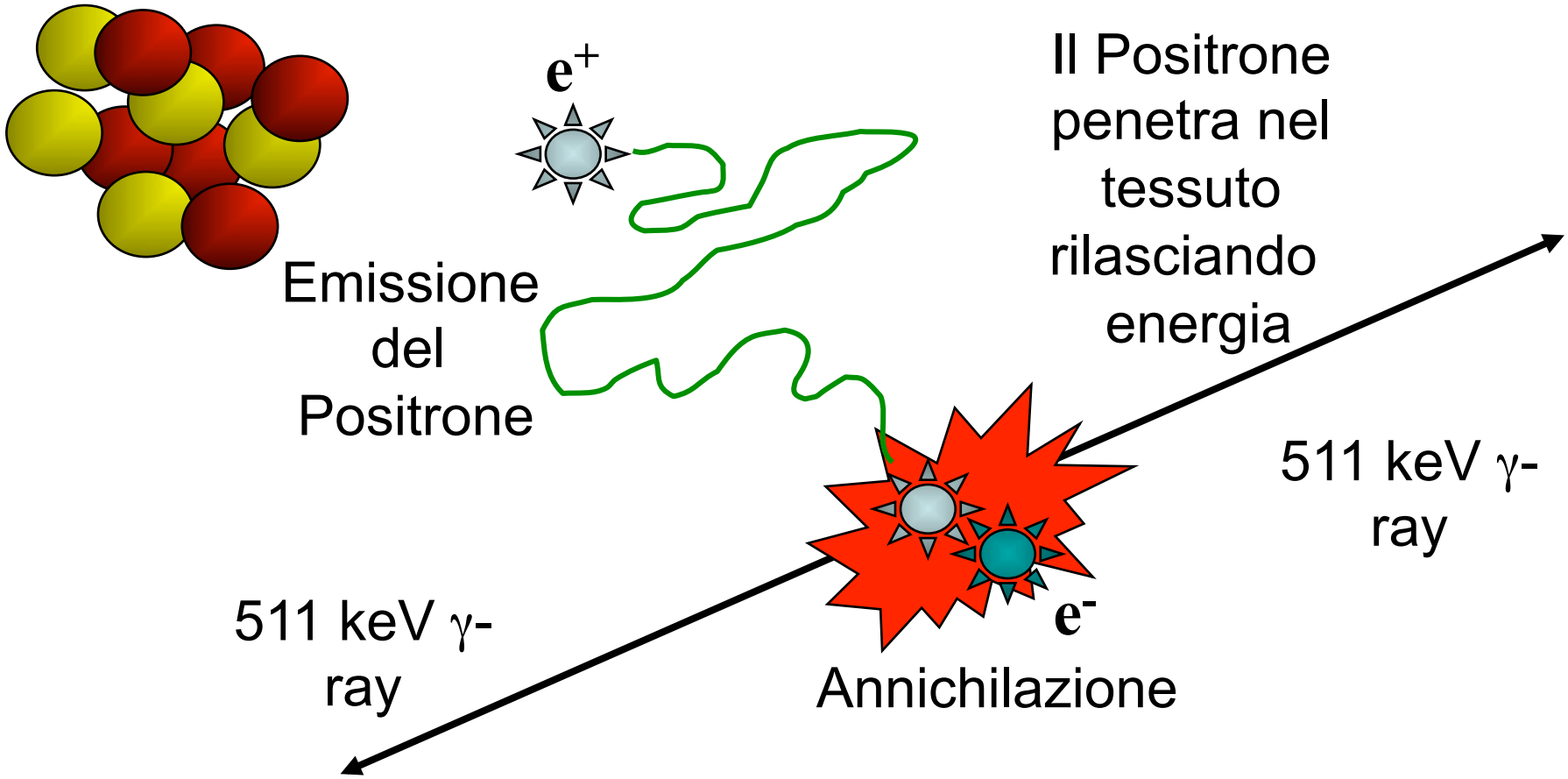
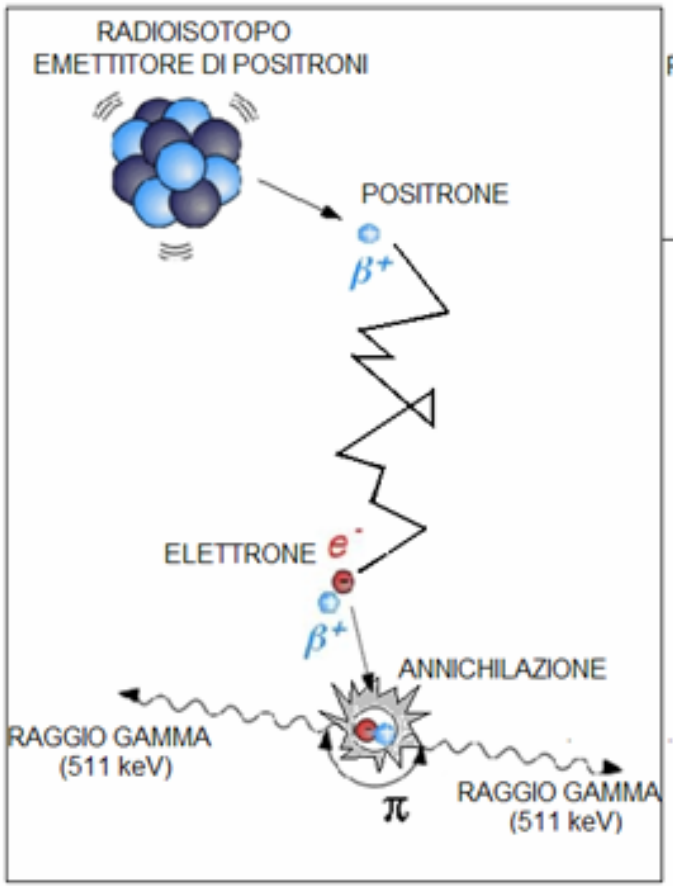


Image courtesy of GE Healthcare
Discovery™ PET/CT 600 Series

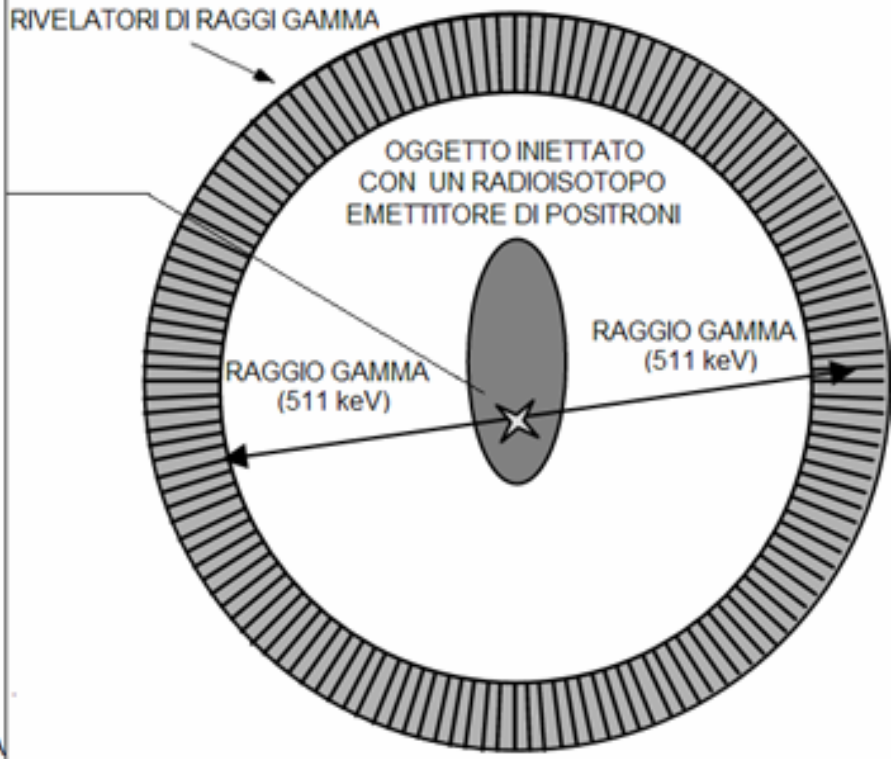
La Reazione di annichilazione



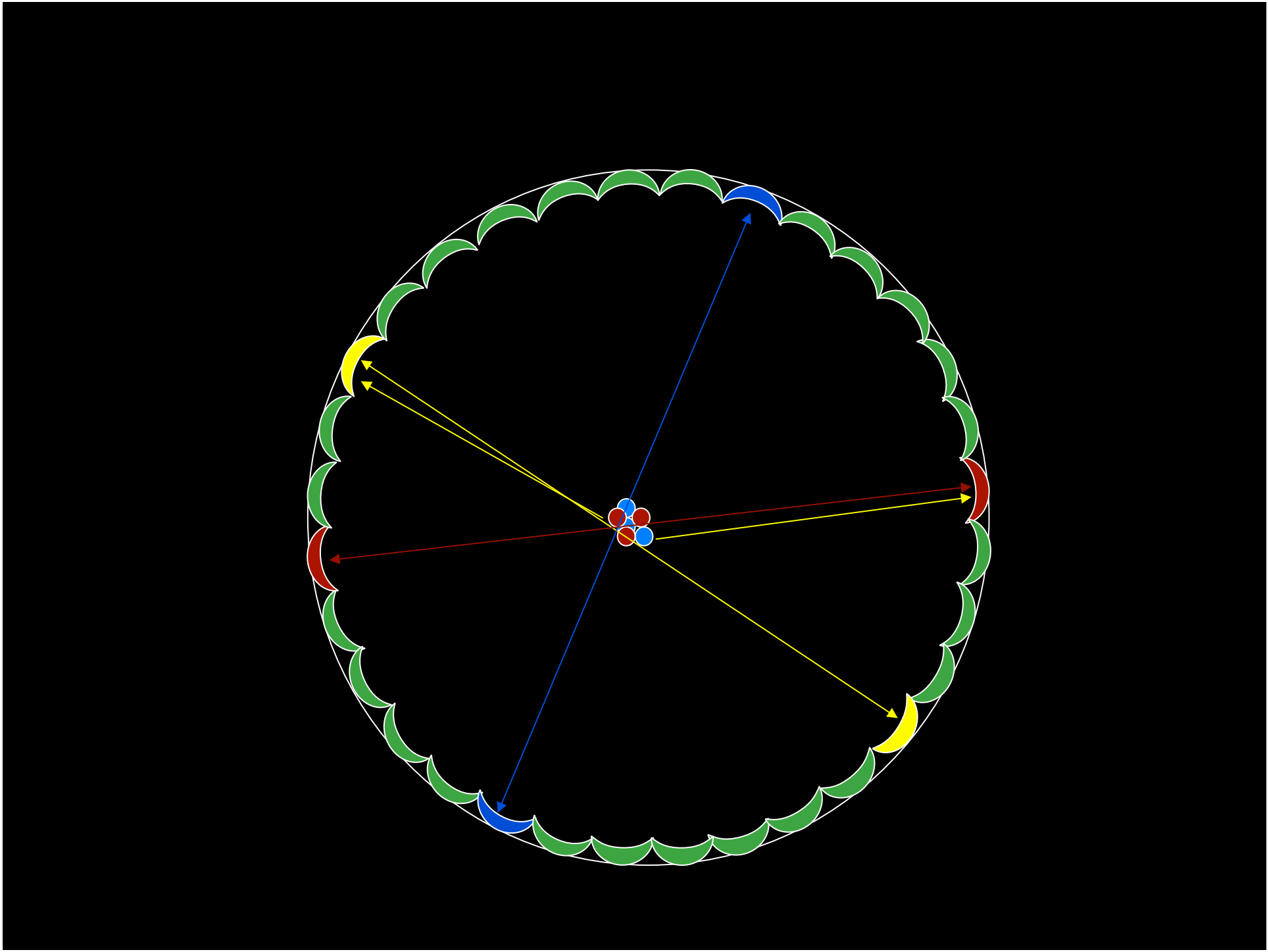
Principio della Tomografia a Emissione di Positroni (PET)



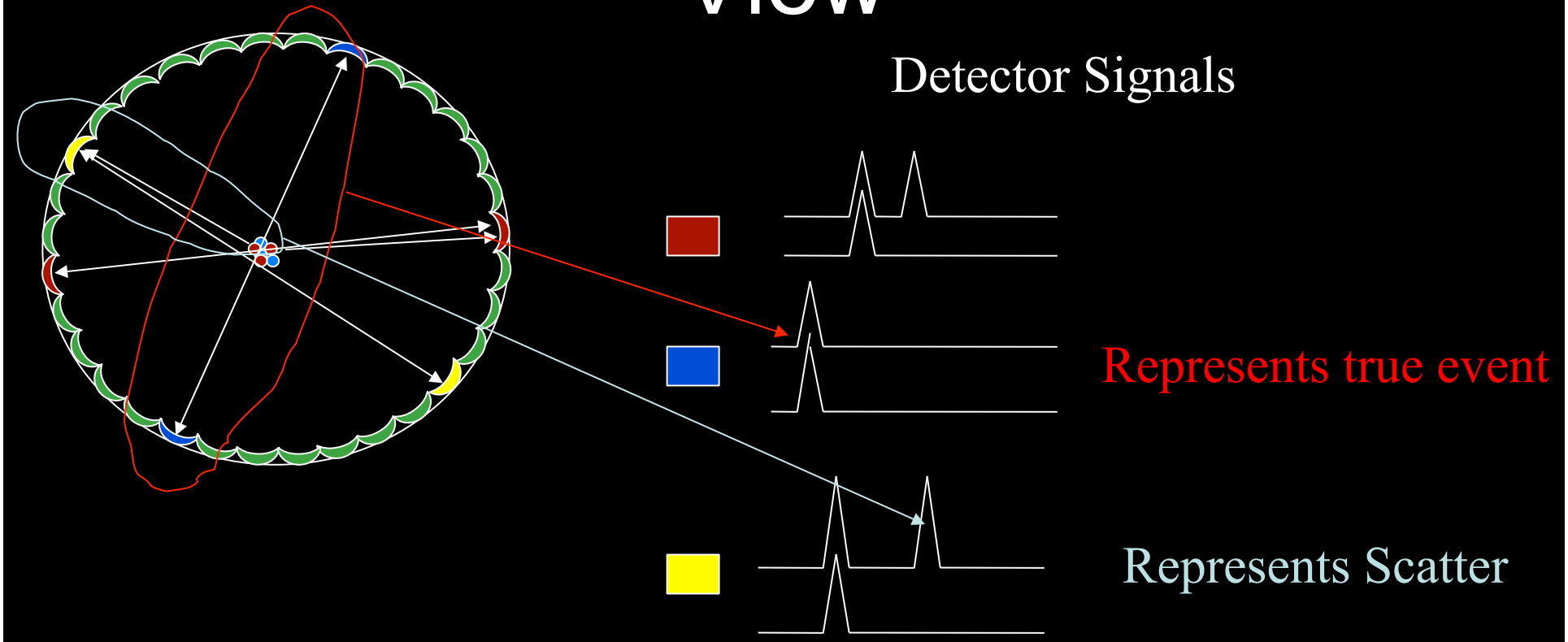
EMISSIONE DEL POSITRONE E ANNICHILAZIONE POSITRONE ELETTRONE



TOMOGRAFO PET



Coincidence Detection in Field of View

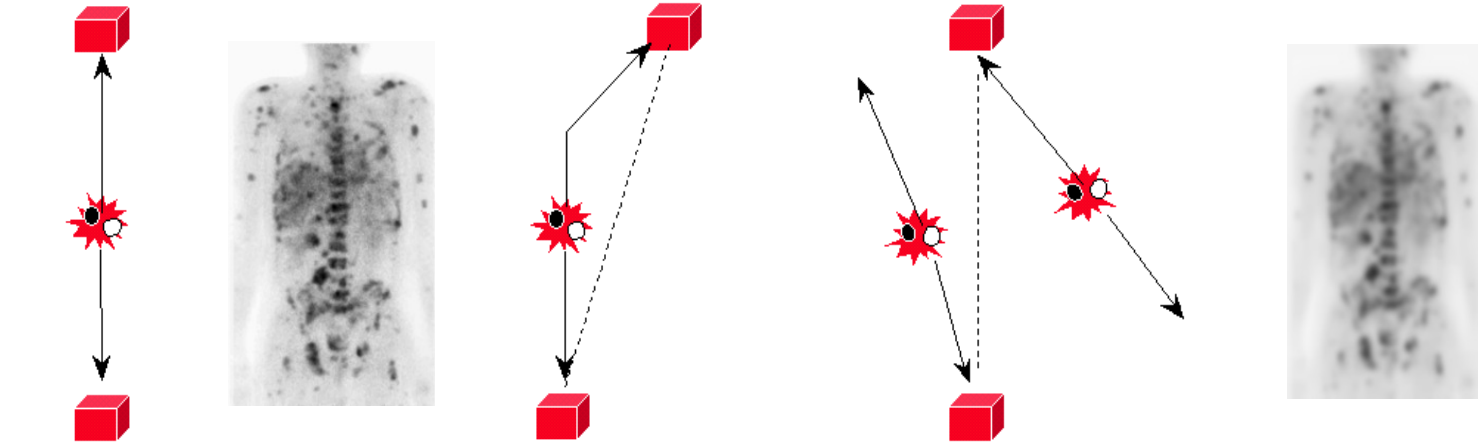


Coincident photon energies at each detector can be put into a matrix similar to the transmission data to construct an intensity-weighted image

*Minimum photon energy allowable for inclusion by detector is about 480 keV

Event Detection

3 Types of Coincidence Events



"Trues" "Scatter" "Randoms"

Valid Event

Invalid Events

(i.e. "background noise")

Overall spatial resolution around 4-5 mm

TRACERS for TUMOR CHARACTERIZATION

• Glucose metabolism	[^{18}F]FDG
• Membrane function	[^{11}C]Choline / [^{18}F]Choline
• Proliferation	[^{18}F]FLT
• Hypoxia	[^{18}F]FMISO
	[^{18}F]FAZA
	[^{64}Cu]ATSM
• Apoptosis	[^{18}F]Annexin V
• Angiogenesis	[^{18}F]NGR-peptide
• Neuroendocrine tumors	[^{68}Ga]DOTA

Perché il ^{18}F-FDG è il radiofarmaco PET più diffuso ?

- Meccanismo di captazione noto e comune a molte neoplasie (aumento GLUT, aumento del trasporto, aumento esochinasi, diminuzione glucosio-6-fosfatasi).

- Captazione relativamente elevata con favorevole rapporto tra tessuto neoplastico e tessuto sano.

- Costo limitato (specie se prodotto in sede)

- Diffusa disponibilità e possibile distribuzione regionale

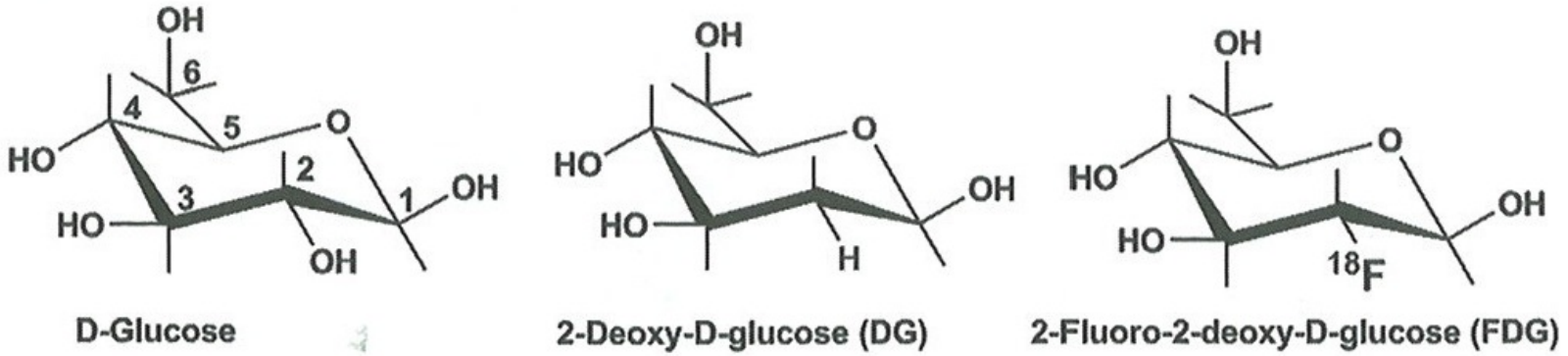
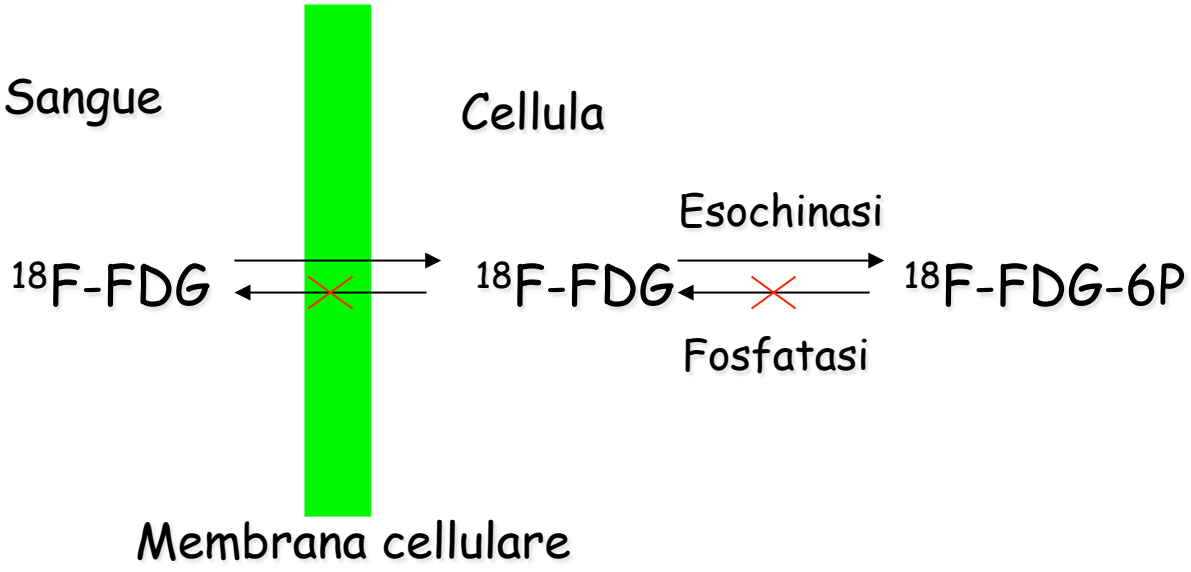
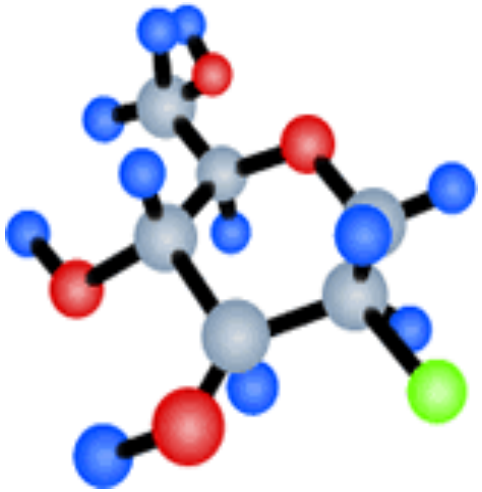


Figure 1 Glucose and its analogs; 2-deoxyglucose (DG) and fluorodeoxyglucose (FDG).

Come funziona ?

Il ^{18}F-FDG è un analogo del glucosio con un atomo di fluoro al posto del gruppo OH in posizione C_2. Iniettato, viene trasportato nelle cellule attraverso la membrana tramite 4 proteine "glucose transporters" (GLUT 1-4) e fosforilato a ^{18}F-FDG-6P (esochinasi) che non è substrato idoneo per i successivi enzimi della catena glicolitica e perciò non può essere ulteriormente metabolizzato.





PET FDG in oncologia

1.Il grado di attività metabolica e la entità dell'accumulo del FDG è correlato alla malignità del tumore

2.E' dimostrato che variazioni dell'attività metabolica precedono le variazioni morfo-dimensionali

3. I tumori hanno un metabolismo del glucosio aumentato

Quantification of PET Data

- On CT, each pixel in the field of view represents a Hounsefield unit (HU) of attenuation to x-ray transmission (water = 0 HU; bone ≈ 1000 HU).

- On a PET image, each pixel represents the number of coincident photons (> 480 keV) originating from FDG uptake at that position.

- SUV is a ratio to compare relative uptake in a Volume of Interest compared to expected background uptake.

$$SUV = \frac{Tissue\_Concentration(mCi/kg)}{Total\_Dose(mCi) \Big/ Patient\_Weight(kg)}$$

Standardized Uptake Value (SUV)

- Initial studies using SUV were done in studying pulmonary nodules led to a SUV of ≈ 3.0 as demarcation of benign from malignant pulmonary lesions.

- Higher SUV in pulmonary lesion is an independent predictor of poorer prognosis.
  - Ahuja V, Coleman RE, Herndon J, Patz EF Jr. *Cancer*. 1998 Sep 1;83(5): 918-24.

- It's a good practice to report the maximum SUV in the ROI.

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New Agents and Techniques for Imaging Prostate Cancer

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Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins Medical Institutions, Baltimore, Maryland

The successful management of prostate cancer requires early detection, appropriate risk assessment, and optimum treatment. An unmet goal of prostate cancer imaging is to differentiate indolent from aggressive tumors, as treatment may vary for different grades of the disease. Different modalities have been tested to diagnose, stage, and monitor prostate cancer during therapy. This review briefly describes the key clinical issues in prostate cancer imaging and therapy and summarizes the various new imaging modalities and agents in use and on the horizon.

Key Words: molecular imaging; MRI; PET; SPECT; radiopharmaceutical

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DOI: 10.2967/jnumed.109.061838

Prostate cancer (PCa) is the most common malignancy among men in the United States, with mortality superseded only by lung cancer, accounting for 10% of all cancer-related deaths in 2008 (*1*). PCa is currently characterized by its TNM stage, Gleason score, and prostate-specific antigen (PSA) serum level. PSA testing is the mainstay of detection and has reduced the rate of death from PCa. However, there remains growing concern regarding the potential risk of overdiagnosis and, consequently, overtreatment of potentially indolent disease. The rate of overdiagnosis of PCa, defined as diagnosis in men who would not have clinical symptoms during their lifetime, has been estimated to be as high as 50% (*2*). Urinary incontinence and erectile dysfunction are not uncommon after radical prostatectomy. Although PSA is a good marker for assessing response to therapy and detecting recurrence, PSA lacks the ability to differentiate low-grade from high-grade cancers. New biomarkers such as the recently described stage-dependent urinary marker sarcosine (*3*) may soon rival PSA for monitoring the presence and extent of disease.

Conventional imaging, which includes CT, MRI, and ultrasound, is currently used to detect organ-confined or metastatic disease for staging and determining prognosis. However, there is substantial room for improvement in the use of imaging for determining tumor grade and for identifying minimal, metastatic disease. At a recent workshop, the National Cancer Institute proposed intervention for PCa at 4 different levels (*4*). The roles of imaging in initial diagnosis, staging, disease recurrence after treatment, and assessment of response to therapy were discussed. Also discussed were the multiple new molecular imaging agents that are being tested and can be incorporated into the current paradigm of diagnosis, treatment, and rapid detection of recurrent disease. We will address new approaches to imaging PCa in the context of these 4 levels of intervention.

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INITIAL DIAGNOSIS

The current standard for diagnosis of PCa is sextant biopsy guided by transrectal ultrasound. PCa is the only malignancy for which the diagnosis is made from tissue obtained on a blind biopsy. That technique tends to underestimate the histologic grade. The heterogeneous nature and multifocality of the tumor renders a blind biopsy inadequate in assessing tumor grade. Up to 28% of clinically significant cancers have been reported to go undetected by the traditional sextant biopsy method (*5*). Imaging data, which are not susceptible to the sampling error that accompanies biopsy, can enhance biopsy by allowing for a more targeted approach.

T2-weighted MRI provides higher spatial and contrast resolution than does transrectal ultrasound and CT but lacks specificity (*6*). Magnetic resonance spectroscopy (MRS) provides a noninvasive method of detecting low-molecular-weight biomarkers within the cytosol and extracellular spaces of the prostate. MRS relies on the loss of a normal citrate peak from the peripheral zone and an increase in the choline peak, an indirect marker of cell death. The ratio of (choline + creatine)/citrate in PCa exceeds the mean ratio found in healthy prostate tissue. Pulsed field gradients are generally used for localization using volumes of interest and include point-resolved spectroscopy and stimulated echo acquisition mode, summarized in an excellent review by Mueller-Lisse and Scherr (*7*). Although the addition of MRS to MRI alone does not significantly improve the accuracy of PCa detection, together they are more accurate than biopsy in certain regions of the prostate, such as the apex (*8*). MRS combined with MRI may also supplement standard biopsy guided by endorectal ultrasound (*9*). Measurement of prostate tumor (choline + creatine)/citrate and tumor volume by MRS imaging correlates with Gleason score (*10*). In a small clinical trial, improved spatial and spectral resolution were achieved at 7 T, allowing for more sensitive detection of spermine, a metabolite having an inverse correlation with the presence of tumor cells (*11*).

Despite the limited ability of ultrasound to delineate cancer, ultrasound has the advantage of low cost, wide availability, and speed over MR image–guided interventions. A recent study demonstrated the feasibility of prostate biopsy guided by fusion of transrectal ultrasound and MRI, with the entire procedure, including fusion, requiring about 10 min (*12*). Furthermore, with an ultrasound 3-dimensional (3D) navigation system, such as that developed by Bax et al. (*13*), needle guidance can be used for sampling small lesions. Tests of the accuracy of biopsy needle guidance in agar prostate phantoms showed a mean error of 1.8 mm in the 3D location of the biopsy core, with less than 5% error in volume estimation.

Imaging

I patienti con diagnosi di carcinoma della prostata rientrano in due categorie:

1. Chi ha una malattia accertata non ancora in trattamento per i quali un accurato **staging** rimane ancora “challenging”

2. Coloro che mostrano dopo terapia un rialzo del (PSA), per i quali targeted “**salvage**” **secondary therapies** possono essere determinanti per la prognosi a condizione che sia identificabile il sito della recidiva.

Imaging

- A rise in PSA value after radical prostatectomy or radiotherapy represents **biochemical recurrence**. In this clinical setting, although pathologic and clinical findings (e.g., PSA levels and kinetics) may be helpful, **imaging techniques are usually used to identify patients with local recurrence and those with distant metastases.**

- In patients with increasing PSA serum levels after radical prostatectomy, **ultrasonography- guided transrectal biopsy** is performed as the first procedure for evaluating local recurrence but is only 50% effective. The main limitations of this method are false-negative results due to tissue-sampling errors and painfulness as an invasive procedure.

- **MR imaging and CT are the most common modalities** currently used for the evaluation of LN metastases. The 2 modalities perform equally poorly, mainly because of the use of morphologic criteria.

Imaging

•In the last few decades, bone scintigraphy has been used for the evaluation of bone metastases, as the skeletal system is the most important single site of metastasis (85%–90% of prostate cancer patients).

•Despite its high sensitivity, it suffers from poor specificity, and further imaging modalities therefore are often required to characterize lesions with increased tracer uptake.

PET Imaging of Prostate Cancer Using Carbon-11-Choline

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Departments of Radiology and Urology, International Medical Center of Japan, Tokyo, Japan

Prostate cancer is difficult to visualize using current techniques. Recently, ^{31}P magnetic resonance spectroscopy has revealed that the tumor, in general, is characterized by an increased uptake of choline into the cell to meet increased synthesis of phosphatidylcholine, an important cell membrane phospholipid. We succeeded in using ^{11}C-choline to visualize prostate cancer and its local metastasis in PET. **Methods:** PET was performed on 10 prostate cancer patients from the level of pelvis to the lower abdomen. After transmission scanning, 370 MBq ^{11}C-choline were injected intravenously. The emission scan was performed 5–15 min postinjection. Finally, PET images were displayed so that each pixel was painted by a specified color representing the degree of the standardized uptake value (SUV). The ^{11}C-choline image was compared with the ^{18}F-fluorodeoxyglucose (FDG) image obtained from the same patient. **Results:** Imaging of prostate cancer and its local metastasis was difficult when ^{18}F-FDG was used because, within the pelvis, the areas of high uptake were concealed by the overwhelmingly abundant radioactivity in urine (in ureters and bladder). By contrast, it was easy when ^{11}C-choline was used because the urinary activity was negligible and tumor uptake was marked. The radioactivity concentration of ^{11}C-choline in prostate cancer and metastatic sites was at an SUV of more than three in most cases. The SUV of ^{18}F-FDG was considerably lower than that of ^{11}C-choline. **Conclusion:** Prostate cancer and its local metastasis were visualized clearly in PET using ^{11}C-choline.

Key Words: PET; carbon-11-choline; prostate cancer

J Nucl Med 1998; 39:990–995

Prostate cancer is a type of cancer in which it is difficult to determine the extent of its invasion and metastasis by current techniques. As a result, it also is difficult to estimate the outcome of surgery, radiotherapy, chemotherapy and hormonal therapy.

Despite the effectiveness of ^{18}F-fluorodeoxyglucose (FDG) PET in imaging various tumors, this technique is not appropriate for prostate cancer detection because the urinary excretion of ^{18}F-FDG is so large that it interferes with the imaging of tumors in the pelvis.

Recently, ^{31}P magnetic resonance spectroscopy (MRS) in vivo and in vitro has revealed an elevated level of phosphatidylcholine in tumors, which is the most abundant phospholipid in the cell membranes of all eukaryotic cells (*1–8*). It is thought that this elevation is the result of increased uptake of choline, a precursor of the biosynthesis of phosphatidylcholine (*9–14*).

We previously reported an application of ^{11}C-labeled choline for imaging brain tumors using PET (*15*). Since then, we successfully used this tracer to image many other types of tumors (*16*). Urinary excretion is negligible with ^{11}C-choline. Here we report the effectiveness of this tracer in PET imaging of prostate cancer in patients.

The tissue uptake of ^{11}C-choline is rapid after the intravenous injection, in accord with the rapid blood clearance (*15*). Once the radioactivity is absorbed into the tissue, the tissue uptake does not change for a long time with decay correction. It is practically constant from 5 to 40 min after injection in most organs. Because of these characteristics, the entire procedure of ^{11}C-choline PET in one patient takes 40 min.

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For correspondence or reprints contact: Toshihiko Hara, MD, Department of Radiology, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162, Japan.

MATERIALS AND METHODS

Patients

With our ethics committee's approval and the patients' informed consent, 10 patients who were admitted to the urology department of our hospital participated in this study. They had both ^{11}C-choline PET and ^{18}F-FDG PET studies before the beginning of treatment (two patients were reexamined after treatment, as discussed later). The PET studies were performed over 2 days before noon while patients were in the fasting state. Histological diagnosis was obtained on all patients before the PET study.

Radiopharmaceutical

Carbon-11-choline was prepared according to the method reported previously (*15*). Briefly, using a cyclotron to produce ^{11}C, and after reacting ^{11}C-methyl iodide with "neat" dimethylaminoethanol at 120°C for 5 min, the resulting product, ^{11}C-choline, was purified by evaporation of unreacted substrates followed by treatment of the remaining substance with cation-exchange resin (−COOH form), yielding an injection solution dissolved in saline. All synthetic and purification procedures were performed in an automated apparatus (Japan Steel Works, Muroran, Hokkaido, Japan).

Imaging Protocol

PET images were obtained using a PET camera (Headtome IV, 6-mm spatial resolution, Shimadzu, Kyoto, Japan) equipped with three rings to produce five slices at 13-mm intervals. For ^{11}C-choline, after acquiring transmission data, 370 MBq ^{11}C-choline were injected. Five minutes later, the emission scan was started. For ^{18}F-FDG, after acquiring transmission data followed by injection of 370 MBq ^{18}F-FDG, the patient was allowed to void. After placing the patient in the fixed bed position, the emission scan was started 40 min after injection. During transmission and emission scanning, the bed position was shifted six times upward from the level of pelvis to that of liver, with a total data acquisition time of 18 min. PET images were reconstructed after correcting the emission data by the transmission data. The horizontal images were displayed sequentially on a computer screen, where their slice levels were shown in a planar image made up from a whole set of the horizontal images (The planar image was helpful in determining the position of the prostate.) Finally, the horizontal images were displayed on the screen using a scale of the standardized uptake value (SUV). SUV is defined as:

$$\text{SUV} = \frac{\text{Regional radioactivity concentration}}{\text{Total injected dose/body weight}},$$

where the radioactivity concentration in a pixel (Bq/ml) was to be determined from an apparent pixel count (cps/pixel volume) and a

PET/CT – Colina

•Considering the mentioned limitations of the current imaging modalities, many recent investigations have assessed the value of **^{11}C- and ^{18}F-choline** PET/CT as a single noninvasive modality in the restaging of prostate cancer patients with biochemical recurrence after initial treatment.

•A sensitivity of between 43% and 95% was reported using choline PET/CT in the detection of malignant lesions in recurrent prostate cancer. Moreover, several studies have evaluated the influence of various clinical (e.g., **tumor stage, Gleason score, and ADT**) and laboratory findings (e.g., **PSA level, PSA velocity, and PSA doubling time**) on choline PET/CT in patients with rising PSA levels after initial treatment.

A Compartmental Model for Biokinetics and Dosimetry of ^{18}F-Choline in Prostate Cancer Patients

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PET with ^{18}F-choline (^{18}F-FCH) is used in the diagnosis of prostate cancer and its recurrences. In this work, biodistribution data from a recent study conducted at Skåne University Hospital Malmö were used for the development of a biokinetic and dosimetric model. **Methods:** The biodistribution of ^{18}F-FCH was followed for 10 patients using PET up to 4 h after administration. Activity concentrations in blood and urine samples were also determined. A compartmental model structure was developed, and values of the model parameters were obtained for each single patient and for a reference patient using a population kinetic approach. Radiation doses to the organs were determined using computational (voxel) phantoms for the determination of the S factors. **Results:** The model structure consists of a central exchange compartment (blood), 2 compartments each for the liver and kidneys, 1 for spleen, 1 for urinary bladder, and 1 generic compartment accounting for the remaining material. The model can successfully describe the individual patients' data. The parameters showing the greatest interindividual variations are the blood volume (the clearance process is rapid, and early blood data are not available for several patients) and the transfer out from liver (the physical half-life of ^{18}F is too short to follow this long-term process with the necessary accuracy). The organs receiving the highest doses are the kidneys (reference patient, 0.079 mGy/MBq; individual values, 0.033–0.105 mGy/MBq) and the liver (reference patient, 0.062 mGy/MBq; individual values, 0.036–0.082 mGy/MBq). The dose to the urinary bladder wall of the reference patient varies between 0.017 and 0.030 mGy/MBq, depending on the assumptions on bladder voiding. **Conclusion:** The model gives a satisfactory description of the biodistribution of ^{18}F-FCH and realistic estimates of the radiation dose received by the patients.

Key Words: ^{18}F-choline; PET; prostate carcinoma; biokinetics; dosimetry

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Choline uptake is increased in cancerous tissues because the high metabolic rates of tumor cells require choline for the synthesis of phospholipids. For example, choline kinase is overexpressed in prostate cancer cells (*1,2*), thus making choline a suitable indicator for early and differential diagnosis of prostate cancer.

PET with radiolabeled choline is therefore used for diagnosis of malignant and recurrent tumors and of metastases in prostate cancer patients (*3–7*). A correct evaluation of the patient dose and the optimization of the imaging protocols imply knowledge of the biodistribution and kinetics of the administered compounds. Recently, the biokinetics of ^{18}F-choline (^{18}F-FCH) in 4 prostate cancer patients were investigated in a study conducted in the frame of the European Collaborative project MADEIRA (Minimizing Activity and Dose with Enhanced Image quality by Radiopharmaceutical Administrations (*8–9*)). Six new patients have now been included in the study. In these investigations, biodistribution and excretion data were collected for up to 4 h after injection of the radiopharmaceutical. Previous human studies with ^{11}C- or ^{18}F-choline were limited up to 1 h after administration (*3–7,10*).

The aim of this work was to develop a compartmental model for ^{18}F-choline using the patients' data collected in the MADEIRA study. The study presented here represents 1 of the 2 different modeling approaches independently pursued within the project (*11*). Preliminary results on a smaller set of patients were presented at the 2010 meeting of the International Society for Optics and Photonics SPIE (*12*).

MATERIALS AND METHODS

Biokinetic Studies

Patient measurements were performed at the Department for Imaging and Functional Medicine of the Skåne University Hospital in Malmö according to the protocol approved by the Regional Ethical Vetting Board at Lund University. ^{18}F-FCH was synthesized using a TRACERlab MX module (GE Healthcare) and reagent kits (ABX GmbH) at the cyclotron facilities at

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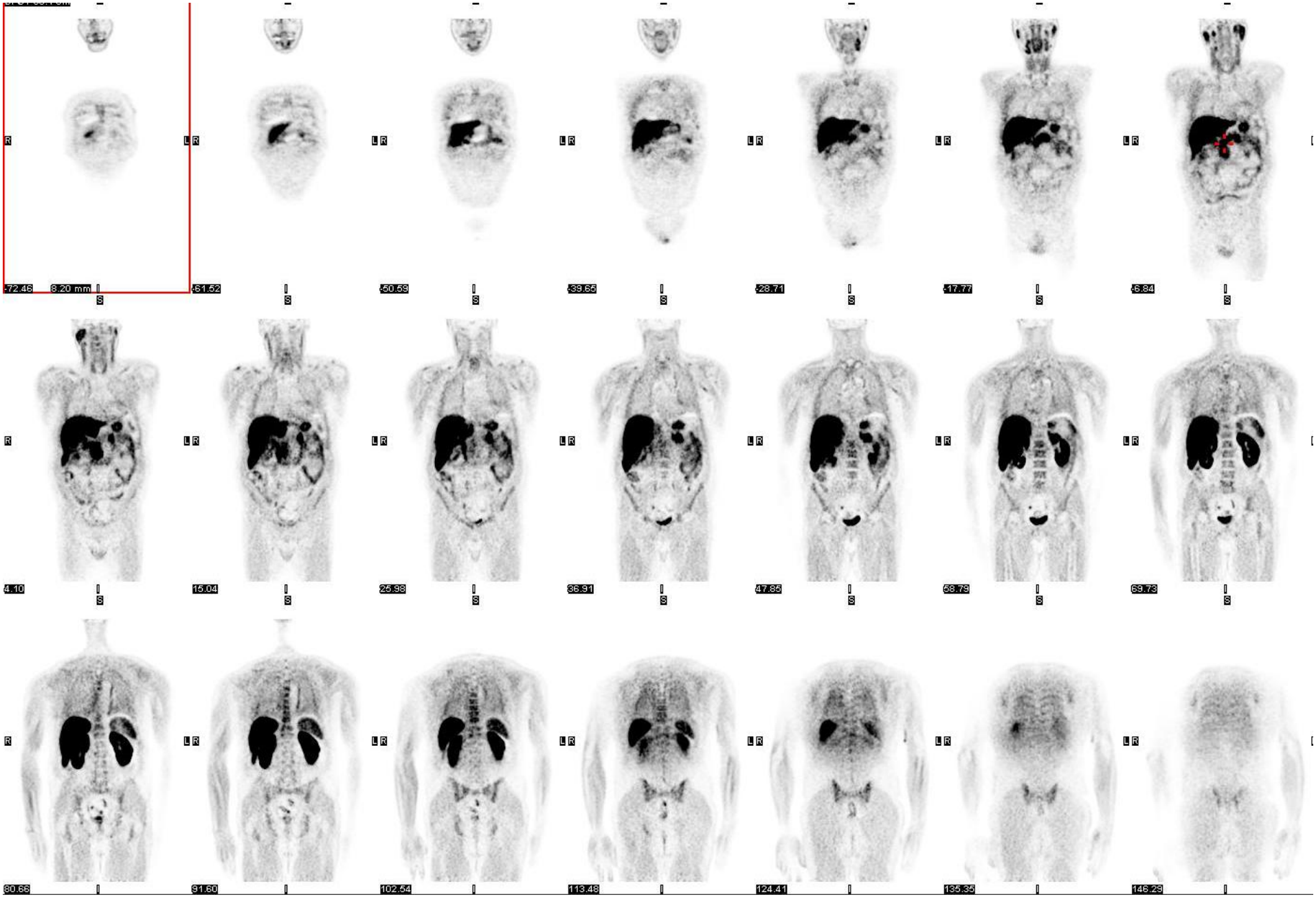
R
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36.91
47.85
58.79
69.73
80.66
91.60
102.54
113.48
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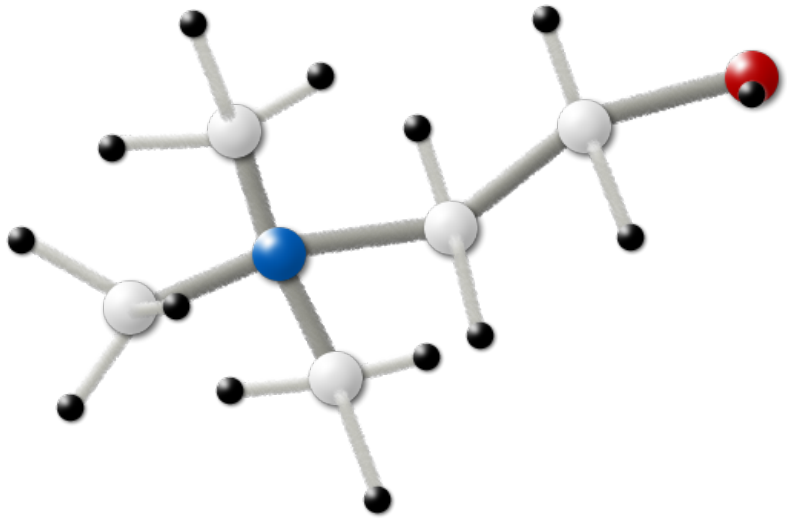
135.35
146.29

Modello “ Ball-and-stick” della **colina**, catione idrosolubile, nutriente essenziale.



Nitrogen (L’ atomo di azoto ha una carica positiva)

Oxygen

Carbon

Hydrogen

Choline is a quaternary ammonium salt with the chemical formula (CH3)3N+(CH2)2OHX−, where X− is a counter-ion such as chloride, hydroxide or tartrate. Choline chloride can form a low-melting deep eutectic solvent mixture with urea with unusual properties. **The** salicylate salt is used topically for pain relief of aphthous ulcers.

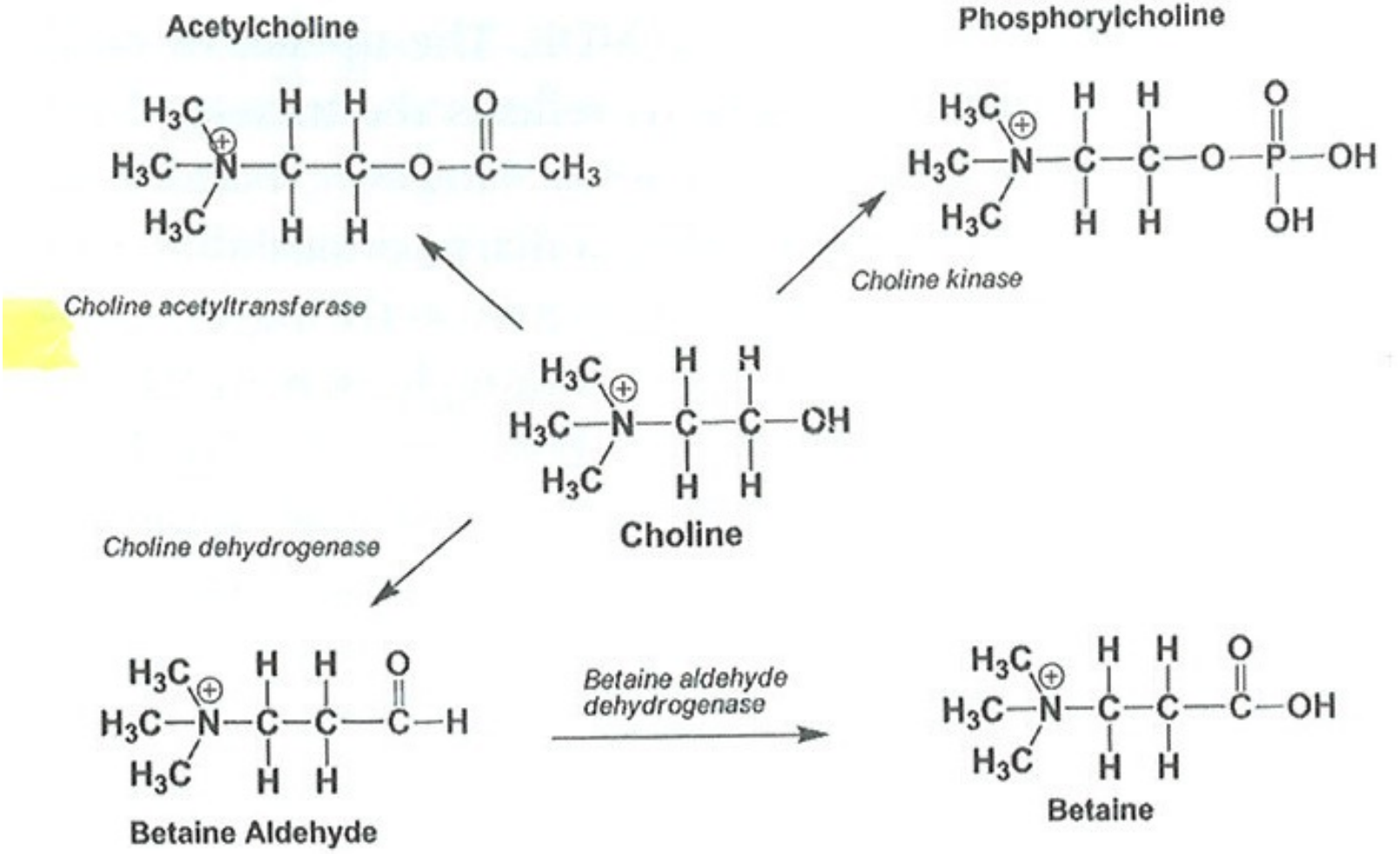
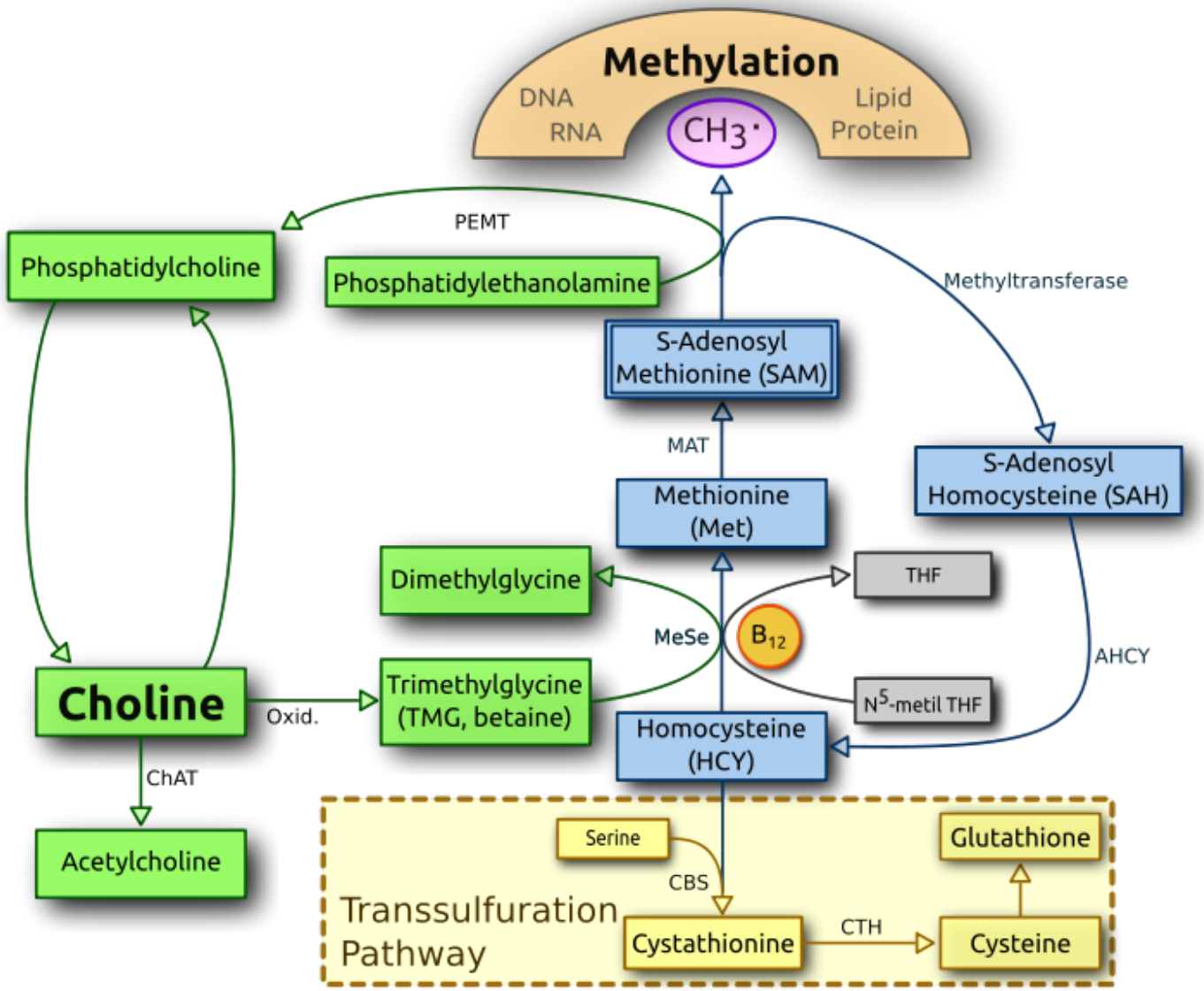


Figure 5 The cellular metabolism of choline: It is phosphorylated, acetylated, and oxidized. Phosphorylcholine is further converted to phophatidylcholine (lecithin), which is then incorporated into membrane synthesis.



Choline and its metabolites are needed for three main physiological purposes: structural integrity and signaling roles for cell membranes, cholinergic neurotransmission (acetylcholine synthesis), and a major source for methyl groups via its metabolite, trimethylglycine (betaine), which participates in the S-adenosylmethionine (SAMe) synthesis pathways.[

PET/CT – Colina

In sintesi:

•Il processo biochimico alla base dell'uso della Colina come tracciante PET è la **sintesi delle membrane**.

•Tutte le cellule usano **colina come precursore per la biosintesi di fosfolipidi**, componenti essenziali delle membrane cellulari.

•La colina entra nella cellula utilizzando **trasportatori specifici** di membrana

•All'interno della cellula la colina è fosforilata attraverso l'azione dell'enzima colina-chinasi (CK).

•La fosforil-colina è ulteriormente metabolizzata in fosfatidil-colina (**lecitina**), principale fosfolipide di membrana.

Le **cellule tumorali**, necessitano di quantitativi elevati di colina nei processi replicativi/proliferativi.

Riassumendo:PET/CT – Colina

•Gli analoghi della Colina (in particolare la FCH - 18F-fluoromethyldimethyl- 2-hydroxyethyl-ammonium) sono stati utilizzati come "oncological PET probes" in diversi tipi di tumore sulla base del presupposto di aumentata proliferazione cellulare.

• Ad oggi, la maggior parte degli studi compiuti riguardano il tumore della prostata: **la PET/CT con Colina è utile nello studio delle recidive biochimiche di malattia e può giocare un ruolo nella stratificazione dei pazienti riguardo alle recidive locoregionali ed al coinvolgimento a distanza (linfonodale e scheletrico)**.

• L'esperienza iniziale con la PET/CT Colina in altri tipi di tumore è limitata ai **tumori cerebrali ed epatici primitivi**.

•Nel cervello, si osserva un elevato rapporto tra tumore e tessuto normale e grazie alla bassa captazione fisiologica nel tessuto cerebrale l'uptake della colina può essere utile nel differenziare gliomi ad alto grado, metastasi e lesioni benigne. Inoltre può essere utilizzato nella d.d. tra recidive e fibrosi post-RT.

•Nel fegato il rapporto di captazione è meno favorevole, ma sono in corso studi di validazione che potrebbero confermarne un utilizzo nell'epatocarcinoma, specie nel monitoraggio della terapia.

Summary of the literature of studies using 11C and 18F-Choline PET/CT in the evaluation of detecting untreated prostate cancer

Tracer	Authors	Years	*N*	PSA, median (range) (ng/mL)	Sen (%)	Spe (%)	Acc (%)	Modality
^{11}C-Cho	Farsad et al. [7]	2005	36	12.3 (2–70)	66	81	71	PET/CT
	Yamaguchi et al. [8]	2005	20	23.4 (4.3–93.9)	100	–	–	PET
					60	–	–	MRI (T2WI)
					65	–	–	MRS
	Martorana et al. [9]	2006	43	8.0 (2.5–70)	66	84	–	PET/CT
					61	97	–	TRUS
	Reske et al. [10]	2006	26	14.4 (2.8–64.3)	81	87	84	PET/CT
	Scher et al. [11]	2007	58	33.0 (2.4–266.0)	87	62	–	PET (25) and PET/CT (33)
	Testa et al. [12]	2007	26	13.9 (2.5–70)	55	86	67	PET/CT
					54	75	61	MRI (T2WI)
					81	67	76	MRS
	Giovacchini et al. [13]	2008	19	11.9 (0.2–33)	72	43	60	PET/CT
	Watanabe et al. [14]	2010	43	6.7 (2.5–335.3)	73	59	67	PET
					31	88	53	^{18}F-FDG PET
					88	88	88	MRI (T2WI + DCEI)
	Van den Bergh et al. [15]	2011	49	10.8 (1.5–70.9)	77	45	–	PET/CT
					34	95	70	MRI (T2WI)
^{18}F-FCho	Kwee et al. [20]	2005	17	7.4 (1.5–222.0)	93	48	–	PET
	Husarik et al. [21]	2008	43	11.6 (0.6–162)	98	–	–	PET/CT
	Kwee et al. [22]	2008	15	5.1 (3.5–13.8)	64	90	72	PET
	Igerc et al. [23]	2008	20	14.1 (5.8–70.8)	100	47	–	PET/CT

Cho choline, *FCho* fluorocholine, *N* number, *PSA* prostatic specific antigen, *Sen* sensitivity, *Spe* specificity, *Acc* accuracy, *MRI* magnetic resonance imaging, *T2WI* T2-weighted imaging, *MRS* magnetic resonance spectroscopy, *TRUS* transrectal ultrasound, *^{18}F-FDG* ^{18}F-fluorodeoxyglucose, *DCEI* dynamic contrast-enhanced imaging

Summary of the literature of studies using 11C and 18F-Choline PET/CT in the evaluation of pelvic lymph node staging in untreated prostate cancer

Tracer	Authors	Years	*N*	PSA, median (range) (ng/mL)	Sen (%)	Spe (%)	Analysis
^{11}C-Cho	Schiavina et al. [29]	2008	57	16.5 (0.6–70)	60	98	Patient-based
					41	99	Node-based
	Contractor et al. [30]	2011	28	44.3 (8.1–209)	78	82	Patient-based
					52	98	Node-based
	Budiharto et al. [31]	2011	36	14.6 (1.5–70.9)	19	95	Patient-based
					9	99	Node-based
^{18}F-FCho	Hacker et al. [32]	2006	20	27.1 (9.2–100)	10	80	Patient-based
	Husarik et al. [21]	2008	25	11.6 (0.6~162)	67	100	Patient-based
					20	100	Node-based
	Steuber et al. [33]	2010	20	12.6 (8.1–27)	0	100	Node-based
	Beheshti et al. [24]	2010	130	27 (0.25–462)	45	96	Patient-based
	Poulsen et al. [34]	2012	210	12 (1–108)	73	88	Patient-based
					56	94	Node-based

Cho choline, *FCho* fluorocholine, *N* number, *PSA* prostatic specific antigen, *Sen* sensitivity, *Spe* specificity

Summary of the literature of studies using 11C and 18F-Choline PET/CT in the evaluation of restaging prostate cancer

Tracer	Authors	Years	Site	*N* (therapy)	PSA, mean (range) (ng/mL)	Sen (%)	Spe (%)	Acc (%)
^{11}C-Cho	Rinnab et al. [41]	2007	LR, LNM, BM	50 (RP 40, brachy 7, RT 3)	2.42 (0.41–13.1)	95	40	84
	Scattoni et al. [35]	2007	LNM	25 (RP 25)	1.98 (0.23–23.1)	100	66	92
	Krause et al. [42]	2008	LR, LNM, BM	63 (RP 42, RT 21)	2.15 (0.2–39)	56	–	–
	Reske et al. [26]	2008	LR	46 (RP 46)	2.0 (0.3–12.1)	73	88	78
	Rinnab et al. [43]	2009	LR, LNM, BM	41 (RP 41)	2.1 (0.41–11.6)	93	36	78
	Richter et al. [45]	2010	LR, LNM, BM	73 (RP 49, RT 24)	2.9 (1.1–5.4)	61	–	–
	Giovacchini et al. [46]	2010	LR, LNM, BM	358 (RP 358)	1.27 (0.23–45)	85	93	89
	Breeuwsma et al. [47]	2010	LR, LNM, BM	80 (RT 80)	9.1 (0.6–54.7)	81	100	84
	Picchio et al. [38]	2012	BM	78 (RP 66, RT 12)	2.4 (0.2–500)	89	100	96
^{18}F-FCho	Schmid et al. [48]	2005	LR, LNM, BM	9 (RP 8, RT 1)	14.1 (0.7–46.3)	100	–	–
	Cimitan et al. [49]	2006	LR, LNM, BM	100 (RP 58, RT 21, AT 21)	(0.12–511.8)	98	100	–
	Heinisch et al. [50]	2006	LR, LNM, BM	17 (RP 15, RT 2)	(<5)	41	–	–
	Vees et al. [28]	2007	LR	10 (RP 10)	0.35 (0.11–0.73)	60	–	–
	Husarik et al. [21]	2008	LR, LNM, BM	68 (RP 47, RT 17)	10.81 (36–100)	86	–	–
	Beheshti et al. [40]	2009	BM	70 (pre 32, post 38)	39.7 (0.1–239)	79	97	84
	Schillaci et al. [51]	2012	LR, LNM, BM	49 (RP 49)	4.13 (0.09–15.51)	92	100	93
	Kwee et al. [52]	2012	LR, LNM, BM	50 (RP 28, RT 13, brachy 9)	5.2 (0.2–18.1)	62	–	–

Cho choline, *FCho* fluorocholine, *N* number, *PSA* prostatic specific antigen, *Sen* sensitivity, *Spe* specificity, *Acc* accuracy, *LR* local recurrence, *LNM* lymph node metastasis, *BM* bone metastasis, *RP* radical prostatectomy, *Brachy* brachytherapy, *RT* external-beam radiotherapy, *AT* androgen-deprivation therapy, *Pre* pre-therapy, *Post* post-therapy

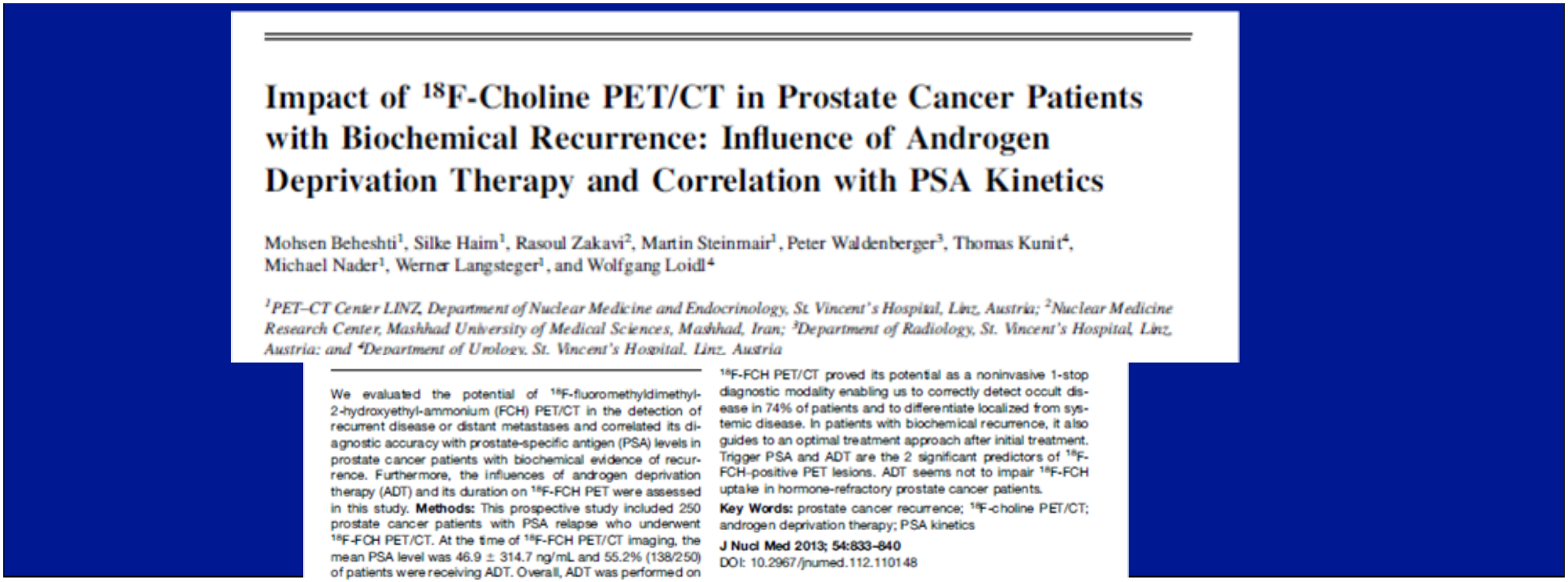
In sintesi:

•PET/CT with ^{18}F-fluorocholine, in patients presenting with recurrent biochemical prostate cancer, is a suitable single-step examination with the ability to exclude distant metastases when local salvage treatment is intended.

•^{18}F-choline PET/CT can also be used to detect (recurrent) local prostate cancer

•^{18}F-choline PET/CT have more **limited roles for the initial staging of prostate cancer** and for the detection of tiny lymph node metastases due to the low spatial resolution inherent to PET (4 mm).

•Overall, these modalities are most useful in patients with a high pre-test suspicion of metastatic disease.



Impact of ^{18}F-Choline PET/CT in Prostate Cancer Patients with Biochemical Recurrence: Influence of Androgen Deprivation Therapy and Correlation with PSA Kinetics

Mohsen Beheshti[1], Silke Haim[1], Rasoul Zakavi[2], Martin Steinmair[3], Peter Waldenberger[3], Thomas Kunit[4], Michael Nader[1], Werner Langsteger[3], and Wolfgang Loidl[4]

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We evaluated the potential of ^{18}F-fluoromethyldimethyl-2-hydroxyethyl-ammonium (FCH) PET/CT in the detection of recurrent disease or distant metastases and correlated its diagnostic accuracy with prostate-specific antigen (PSA) levels in prostate cancer patients with biochemical evidence of recurrence. Furthermore, the influences of androgen deprivation therapy (ADT) and its duration on ^{18}F-FCH PET were assessed in this study. **Methods:** This prospective study included 250 prostate cancer patients with PSA relapse who underwent ^{18}F-FCH PET/CT. At the time of ^{18}F-FCH PET/CT imaging, the mean PSA level was 46.9 ± 314.7 ng/mL and 55.2% (138/250) of patients were receiving ADT. Overall, ADT was performed on

^{18}F-FCH PET/CT proved its potential as a noninvasive 1-stop diagnostic modality enabling us to correctly detect occult disease in 74% of patients and to differentiate localized from systemic disease. In patients with biochemical recurrence, it also guides to an optimal treatment approach after initial treatment. Trigger PSA and ADT are the 2 significant predictors of ^{18}F-FCH-positive PET lesions. ADT seems not to impair ^{18}F-FCH uptake in hormone-refractory prostate cancer patients.

Key Words: prostate cancer recurrence; ^{18}F-choline PET/CT; androgen deprivation therapy; PSA kinetics

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DOI: 10.2967/jnumed.112.110148

It can also provide useful information even when there is a **low rising PSA level of 0.5 ng/mL** especially in intermediate- and high-risk patients.

•The **sensitivity** of 18F-FCH PET/CT was **directly related to the trigger PSA level**.

•However, there was no significant difference in 18F-FCH PET positivity between patients with a PSA doubling time of less than or equal to 10 mo and those with a doubling time of more than 10 mo

•The sensitivity of 18F-FCH PET/CT was significantly higher in patients with ongoing ADT than in those without ADT.
•Furthermore, ADT did not significantly impair 18F-FCH uptake in malignant lesions.

•The effect of radiotherapy and chemotherapy on 18F-FCH PET/CT findings seems to be negligible, and at least a 3-mo interval should be considered between completing these therapies and performing 18FFCH PET/CT.

PET/CT and radiotherapy in prostate cancer

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[4]*Department of Nuclear Medicine and Molecular Imaging University Medical Center Groningen, Groningen, The Netherlands*

Radiotherapy is one of the corner stone treatments for patients with prostate cancer. Especially for locally advanced tumors radiotherapy +/- adjuvant androgen deprivation treatment is standard of care. This brings up the need for accurate assessment of extra prostatic tumor growth and/or the presence of nodal metastases for selection of the optimal radiation dose and treatment volume. Morphological imaging like transrectal ultra sound, computed tomography (CT) and magnetic resonance imaging (MRI) are routinely used but are limited in their accuracy in detecting extra prostatic extension and nodal metastases. In this article we present a structured review of the literature on positron emission tomography (PET)/CT and radiotherapy in prostate cancer patients with emphasis on: 1) the pretreatment assessment of extra prostatic tumor extension, nodal and distant metastases; 2) the intraprostatic tumor characterization and radiotherapy treatment planning; and 3) treatment evaluation and the use of PET/CT in guidance of salvage treatment. PET/CT is not an appropriate imaging technique for accurate T-staging of prostate cancer prior to radiotherapy. Although macroscopic disease beyond the prostatic capsule and into the periprostatic fat or in seminal vesicle is often accurately detected, the microscopic extension of prostate cancer remains undetected. Choline PET/CT holds a great potential as a single step diagnostic procedure of lymph nodes and skeleton, which could facilitate radiotherapy treatment planning. At present the use of PET/CT for treatment planning in radiotherapy is still experimental. Choline PET based tumor delineation is not yet standardized and different segmentation-algorithms are under study. However, dose escalation using dose-painting is feasible with only limited increases of the doses to the bladder and rectum wall. PET/CT using either acetate or choline is able to detect recurrent prostate cancer after radiotherapy but stratification of patients for any local salvage treatment has not been addressed in the current literature.

KEY WORDS: Positron-emission tomography - Tomography, X-ray computed - Prostatic neoplasms – Radiotherapy.

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Radiotherapy is one of the corner stone treatments for patients with prostate cancer. In patients with an organ confined disease the current modalities of treatment like laparoscopic radical prostatectomy, external beam radiotherapy, brachytherapy, active surveillance and ablative techniques like cryoablation or high intensity focused ultrasound have to be considered on an individual basis. In cases of clinically detectable extra prostatic tumor growth (T3) and/or in cases of limited nodal metastases (N1) the combination of external beam radiotherapy plus adjuvant androgen deprivation therapy during 2-3 years has become the current standard of practice in many countries. So there is a persistent need for accurate assessment of extra prostatic tumor growth and/or the presence of nodal metastases for selec-

1–<2 ng/mL, 62% (5/8) for a PSA-value 2–<3 ng/mL and 73% (19/26) for PSA-levels ≥3 ng/mL. For the group of patients with a PSA-level <3 ng/ml, the mean detection rate was 47%.[45]

To evaluate the accuracy of [18F]FCH PET/CT for restaging of prostate cancer Husarik *et al.* evaluated 68 patients.[46] Only 14 patients received radiotherapy (6 received concomitant hormonal therapy). All these patient exhibited abnormal uptake of [18F] FCH. In another study reported local recurrence in 6/21 (29%) patients treated with radiotherapy with only 3/58 (5%) patients treated with surgery.[47] Bone and/or LN metastases recurred in 8/21(38%) patients treated with radiotherapy. Most of the negative PET/CT scans (78%) were observed in patients with a persistent rising PSA level after radical prostatectomy. Heinisch *et al.* studied 34 patients with prostate cancer who had undergone initial local therapy using [18F]Choline PET/CT during follow-up in case of demonstrable or rising PSA levels. This study aimed at the use in patients with low PSA levels. In eight of 17 examinations (47%) with PSA < 5 ng/mL, at least one [18F]Choline positive focus was detected. Follow up and additional imaging and or histology confirmed recurrent prostate cancer in 7/8 patients. In re-staging patients with prostate cancer, FCH PET/CT is able to yield true positive findings even at PSA < 5 ng/mL.

PET/CT using either acetate or choline is able to detect recurrent prostate cancer after radiotherapy. The clinical utility of PET/CT in stratification of patients for any local salvage treatment and its cost effectiveness has not been addressed in the current literature. These aspects have to be studied in relation to current clinical practice using PSA and PSA kinetics as threshold for salvage treatment.

Conclusions

PET/CT is not an appropriate imaging technique for accurate T-staging of prostate cancer prior to radiotherapy. Although macroscopic disease beyond the prostatic capsule and into the periprostatic fat or in seminal vesicle is often accurately detected, the microscopic extension of prostate cancer remains undetected. Choline PET/CT holds a great potential as a single step diagnostic procedure of lymph nodes and skeleton, which could facilitate radiotherapy treatment planning. At present the use of PET/CT for treatment planning in radiotherapy is still experimental. Choline-PET based tumor delineation is not yet standardized and different segmentation-algorithms are under study. However, dose escalation using dose-painting is feasible with only limited increases of the doses to the bladder and rectum wall. PET/CT using either acetate or choline is able to detect recurrent prostate cancer after radiotherapy but stratification of patients for any local salvage treatment has not been addressed in the current literature

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Clinical evidence on PET-CT for radiation therapy planning in prostate cancer

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Abstract

The present chapter is focused on the role of Positron Emission Tomography/Computed Tomography (PET/CT) and [11C]-labelled Choline ([11C]Choline) for the management of prostate cancer patients for radiation therapy planning.

Although still matter of debate, PET/CT with [11C]Choline is not routinely recommended for selecting patients for prostate cancer primary radiation treatment. However, due to its high accuracy in detecting and localizing recurrences when a biochemical failure occurs, [11C]Choline PET/CT may play a role in re-staging phase to distinguish patients with local versus distant relapse, thus influencing patient management (curative vs. palliative therapy).

Limited data are currently available on the role of [11C]Choline PET/CT in target volume selection and delineation. According to available literature, [11C]Choline PET/CT is not clinically recommendable to plan target volume both for primary prostate treatment and for local recurrence. Nevertheless, promising data suggested a potential role of [11C]Choline PET/CT as image guide tool for the irradiation of prostate cancer relapse. ■

Summary of available data on the use of PET-CT in radiotherapy planning in prostate cancer.

Tumour site / tracer	Patients selection	Target volume selection	Target volume delineation	Adaptive treatment	Patient outcome
Prostate/ 11C-Choline	Useful in re-staging phase to 1) exclude from local RT patients with distant metastases and 2) refer pts to appropriate therapeutic strategies.	No routine use yet in primary treatment Promising data in recurrence treatments, particularly for LN volume selection.	No routine use yet.	No routine use yet.	No data available yet.

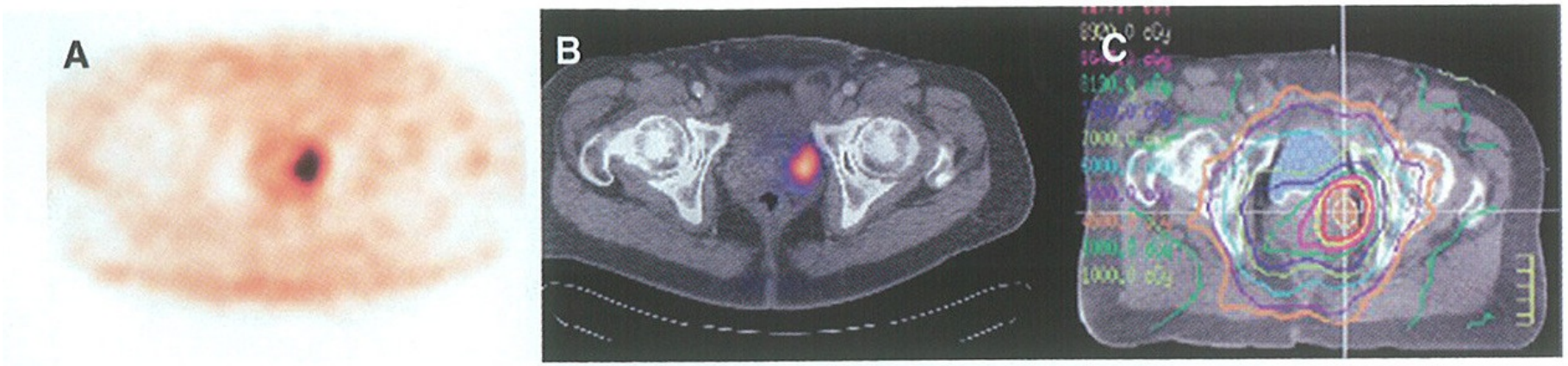
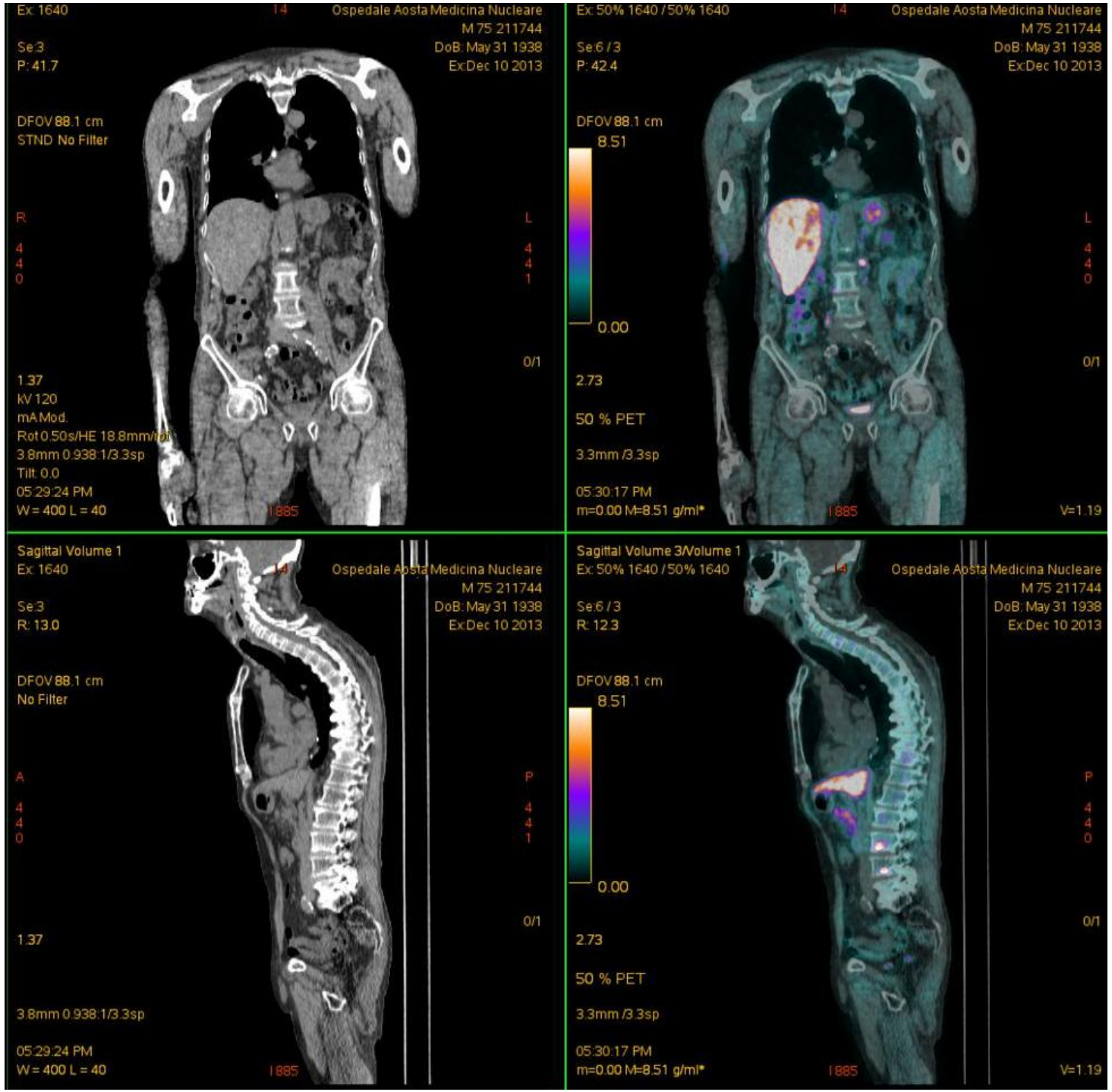


Figure 3 FCH-PET-guided radiotherapy. (A) The black area on this transaxial PET image corresponds to increased FCH uptake in a malignant tumor situated in the left lobe of the prostate gland. In an experimental treatment plan, this PET-defined biological target volume (BTV) will be prescribed a radiation dose of at least 90 Gy. (B) A "fused" PET/CT image is used to plan the radiation treatment. In this patient, the prostate volume was 62 mL and the BTV volume was 14 mL. (C) The experimental treatment plan is summarized by colored lines corresponding to prescribed iso-doses of radiation. Doses of 91 Gy and 76 Gy were prescribed to the BTV and prostate, respectively, without significantly increasing radiation exposure to un-involved organs (rectum and bladder).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R
L
1.37
kV 120
mA Mod.
Rot 0.50s/HE 18.8mm/ro
3.8mm 0.938:1/3.3sp
Tilt: 0.0
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I 885
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M 75 211744
DoB: May 31 1938
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Ex: 50% 1640 / 50% 1640
Se:6 / 3
P: 42.4
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8.51
0.00
2.73
50 % PET
3.3mm /3.3sp
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V=1.19
Sagittal Volume 1
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Se:3
R: 13.0
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No Filter
A
P
1.37
3.8mm 0.938:1/3.3sp
05:29:24 PM
W = 400 L = 40
Sagittal Volume 3/Volume 1
Ex: 50% 1640 / 50% 1640
Se:6 / 3
R: 12.3
DFOV 88.1 cm
8.51
0.00
2.73
50 % PET
3.3mm /3.3sp
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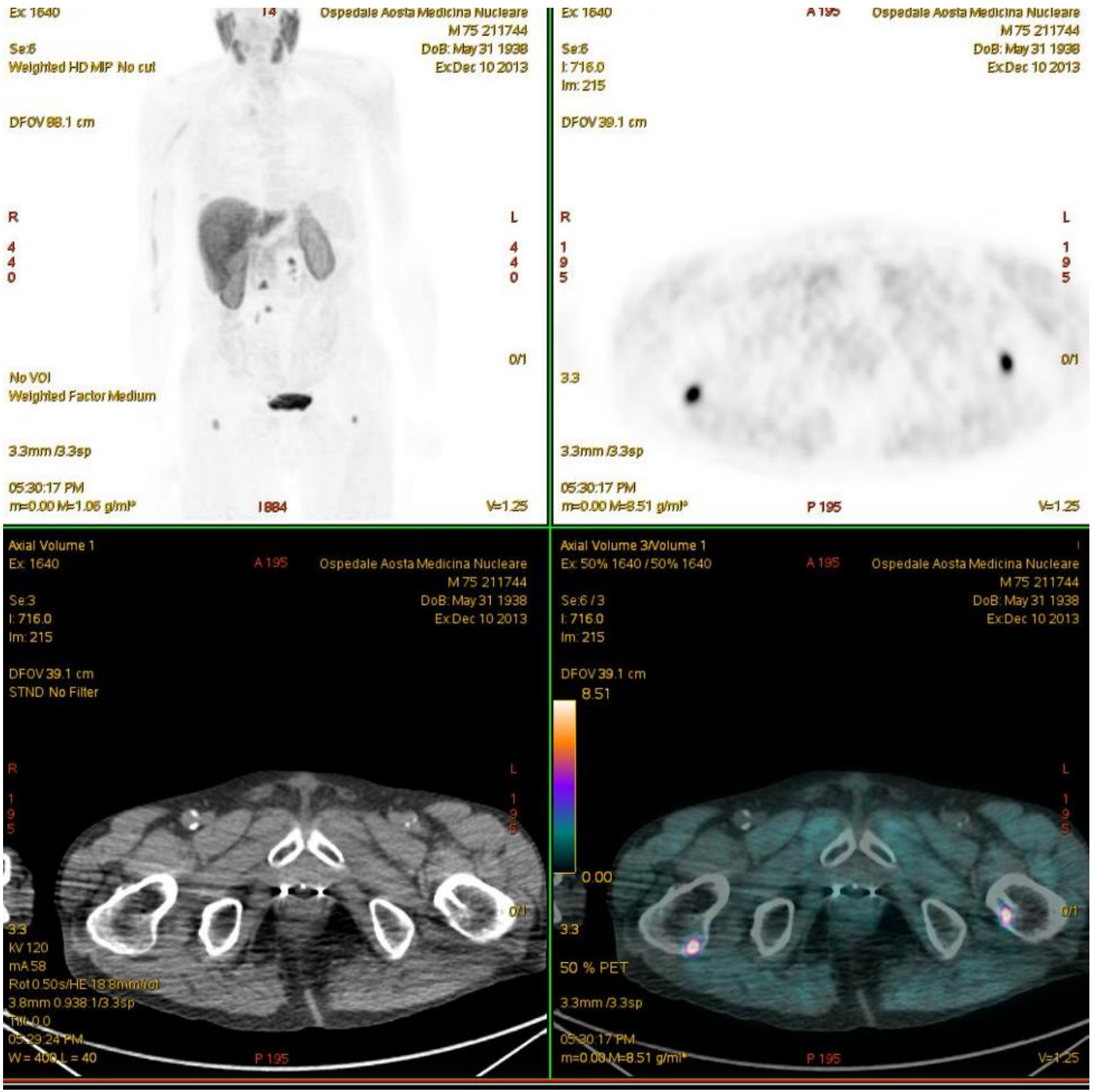
V=1.19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Ospedale Aosta Medicina Nucleare
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DoB: May 31 1938
Ex:Dec 10 2013
Se:6
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DFOV 88.1 cm
R
L
No VOI
Weighted Factor Medium
3.3mm /3.3sp
05:30:17 PM
I 884
V=1.25
Ex: 1640
A 195
Ospedale Aosta Medicina Nucleare
M 75 211744
DoB: May 31 1938
Ex:Dec 10 2013
Se:6
I: 716.0
Im: 215
DFOV 39.1 cm
R
L
3.3
3.3mm /3.3sp
05:30:17 PM
P 195
V=1.25
Axial Volume 1
Ex: 1640
A 195
Ospedale Aosta Medicina Nucleare
M 75 211744
DoB: May 31 1938
Ex:Dec 10 2013
Se:3
I: 716.0
Im: 215
DFOV 39.1 cm
STND No Filter
R
L
3.3
kV 120
mA 58
Rot 0.50s/HE 18.8mm/rot
3.8mm 0.938:1/3.3sp
Tilt: 0.0
05:29:24 PM
W = 400 L = 40
P 195
Axial Volume 3/Volume 1
Ex: 50% 1640 / 50% 1640
A 195
Ospedale Aosta Medicina Nucleare
M 75 211744
DoB: May 31 1938
Ex:Dec 10 2013
Se:6 / 3
I: 716.0
Im: 215
DFOV 39.1 cm
8.51
0.00
R
L
3.3
50 % PET
3.3mm /3.3sp
05:30:17 PM
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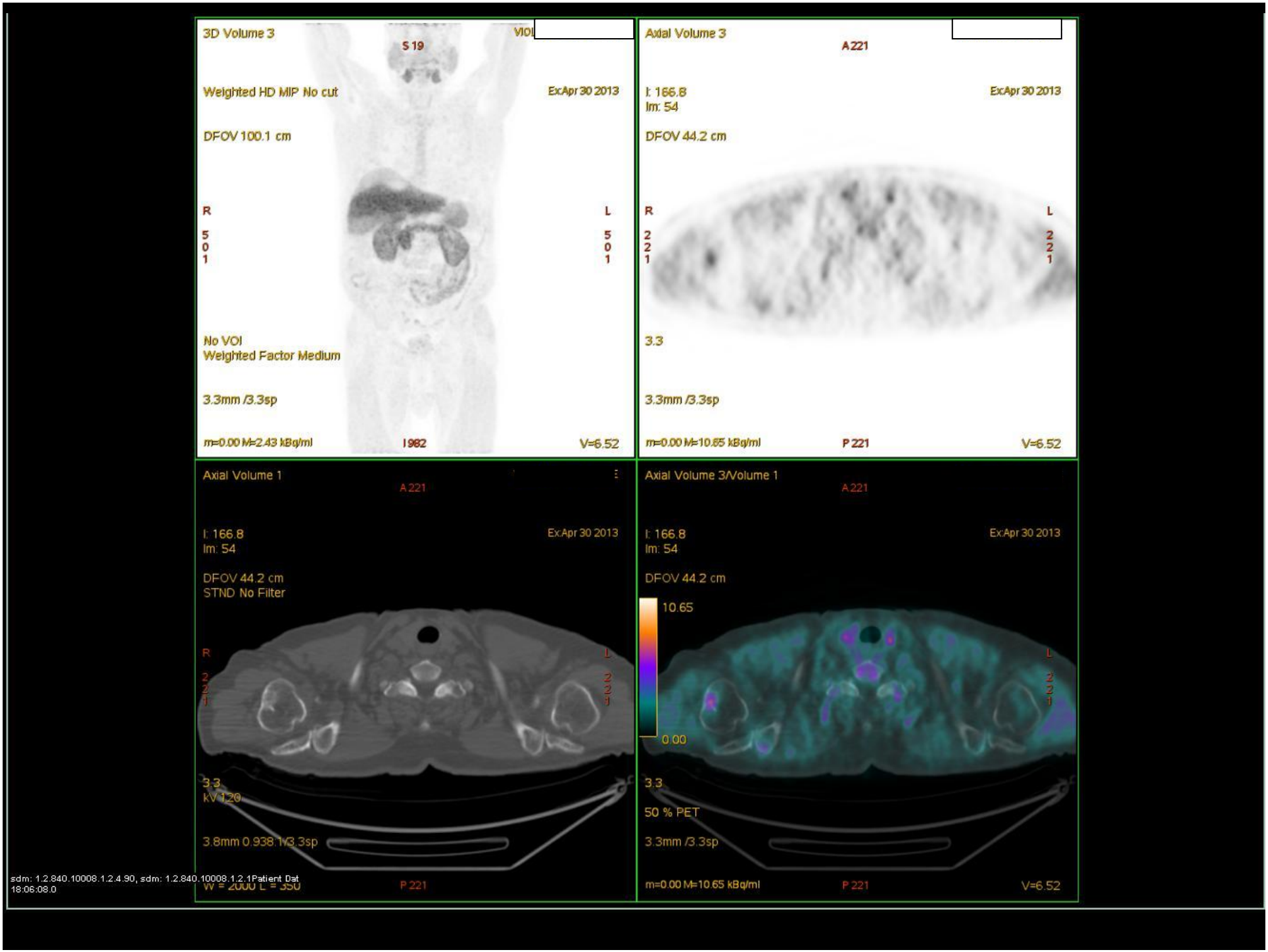
P 195
V=1.25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R
L
No VOI
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I 982
V=6.52
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A221
I: 166.8
Im: 54
ExcApr 30 2013
DFOV 44.2 cm
R
L
3.3
3.3mm /3.3sp
m=0.00 M=10.65 kBq/ml
P 221
V=6.52
Axial Volume 1
A 221
I: 166.8
Im: 54
Ex:Apr 30 2013
DFOV 44.2 cm
STND No Filter
3.3
kV 120
3.8mm 0.938 I/3.3sp
W = 2000 L = 350
P 221
Axial Volume 3/Volume 1
A 221
I: 166.8
Im: 54
Ex:Apr 30 2013
DFOV 44.2 cm
10.65
0.00
3.3
50 % PET
3.3mm /3.3sp
m=0.00 M=10.65 kBq/ml
P 221
V=6.52
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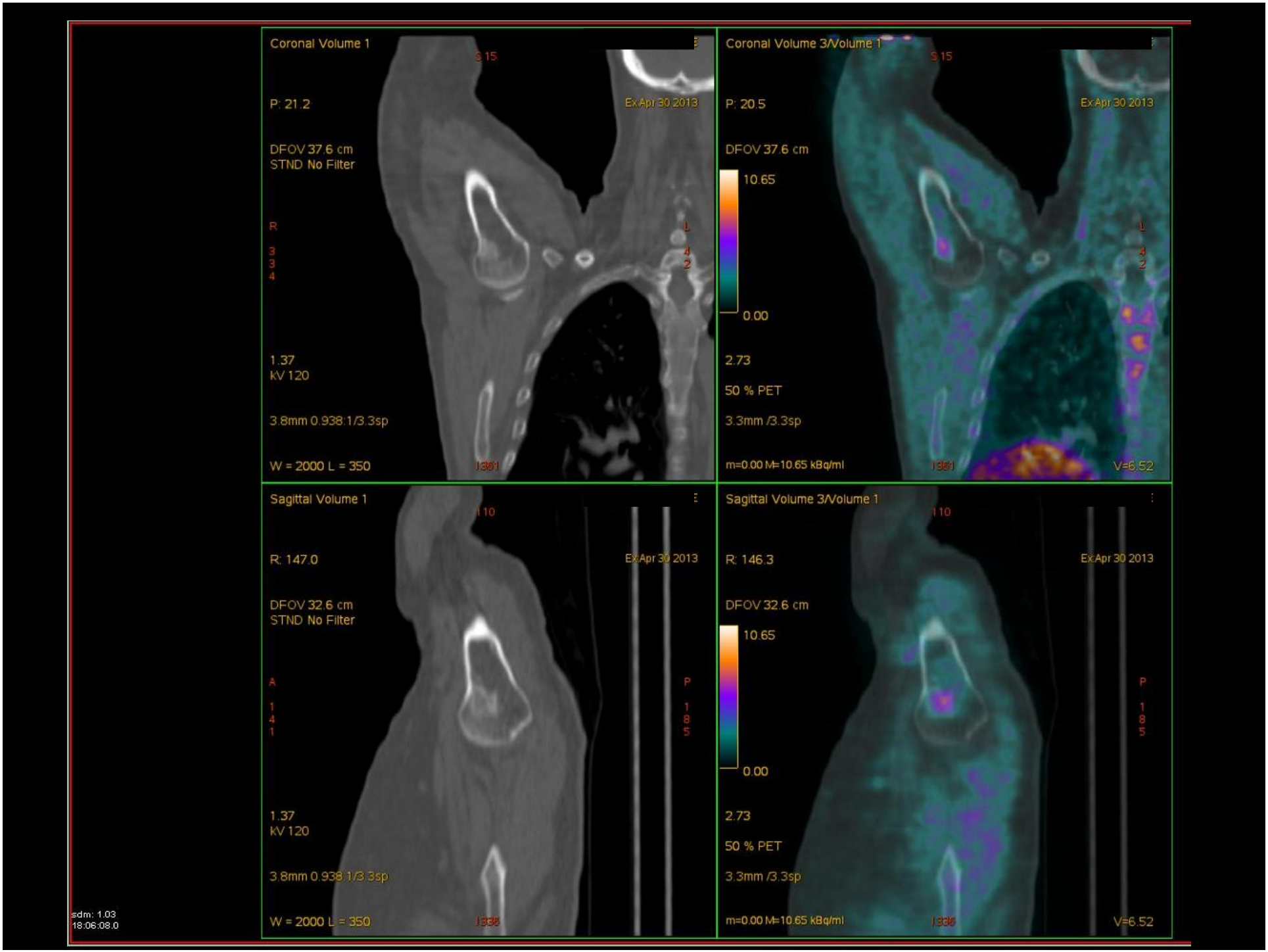
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S 15
P: 21.2
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R
L
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kV 120
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Coronal Volume 3/Volume 1
S 15
P: 20.5
Ex Apr 30 2013
DFOV 37.6 cm
10.65
0.00
2.73
50 % PET
3.3mm /3.3sp
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V=6.52
Sagittal Volume 1
I 10
R: 147.0
Ex Apr 30 2013
DFOV 32.6 cm
STND No Filter
A
P
1.37
kV 120
3.8mm 0.938:1/3.3sp
W = 2000 L = 350
Sagittal Volume 3/Volume 1
I 10
R: 146.3
Ex Apr 30 2013
DFOV 32.6 cm
10.65
0.00
2.73
50 % PET
3.3mm /3.3sp
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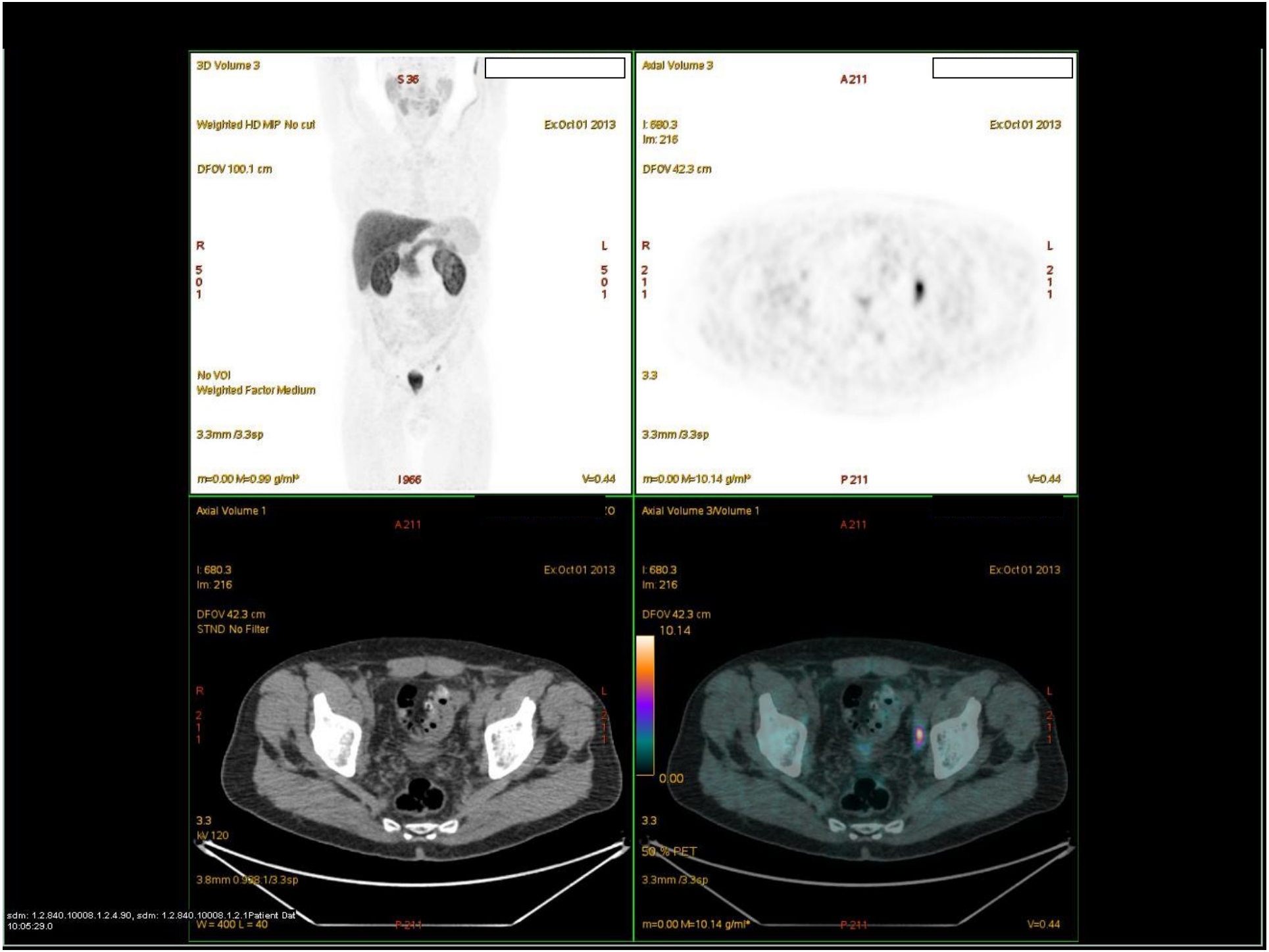
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R
L
No VOI
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I 966
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A 211
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DFOV 42.3 cm
R
L
3.3
3.3mm /3.3sp
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P 211
V=0.44
Axial Volume 1
A 211
I: 680.3
Im: 216
Ex Oct 01 2013
DFOV 42.3 cm
STND No Filter
R
L
3.3
kV 120
3.8mm 0.938:1/3.3sp
W = 400 L = 40
P 211
Axial Volume 3/Volume 1
A 211
I: 680.3
Im: 216
Ex Oct 01 2013
DFOV 42.3 cm
10.14
0.00
L
3.3
50 % PET
3.3mm /3.3sp
m=0.00 M=10.14 g/ml*
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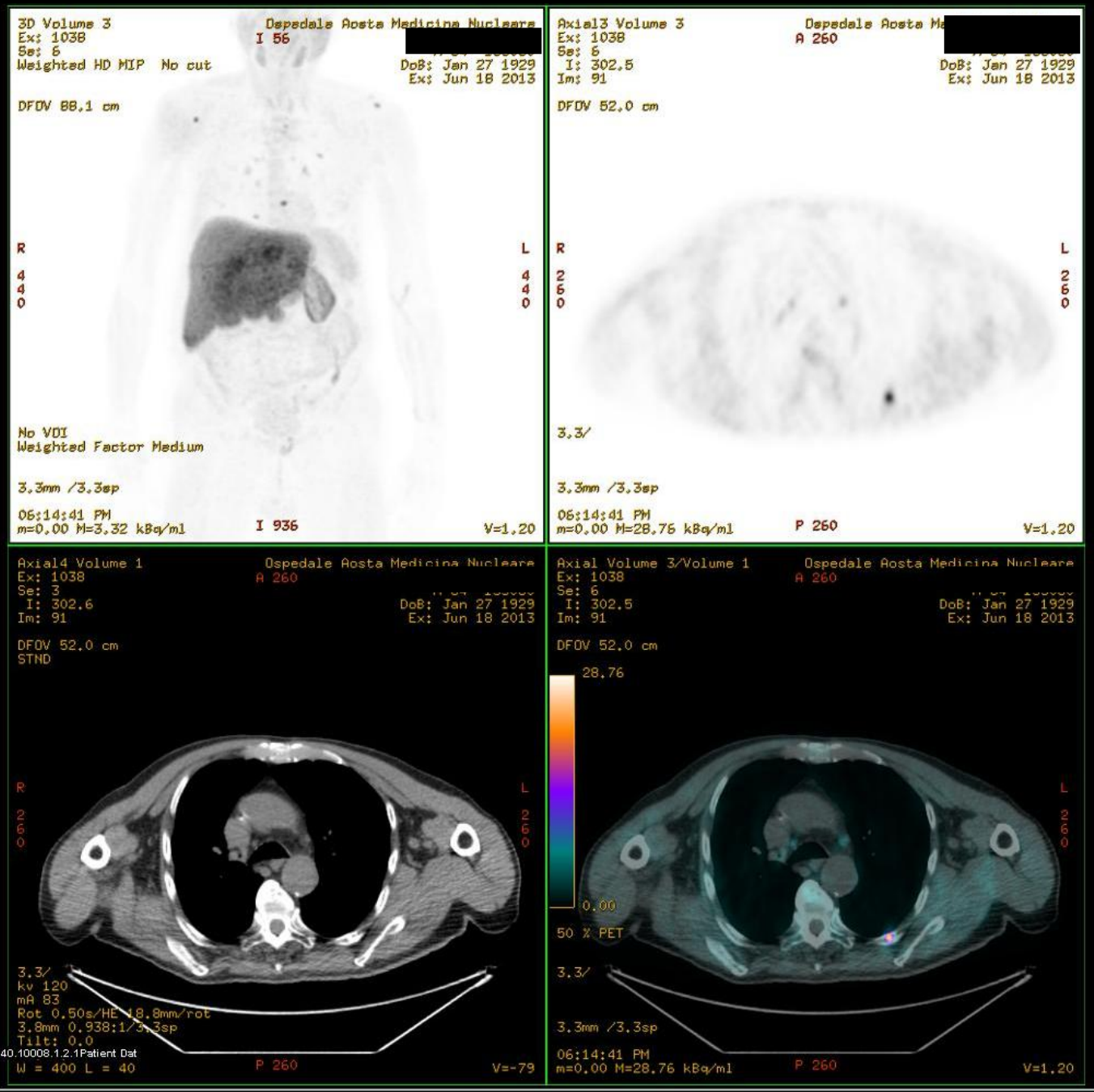
V=0.44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Ospedale Aosta Medicina Nucleare
I 56
DoB: Jan 27 1929
Ex: Jun 18 2013
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R
L
No VOI
Weighted Factor Medium
3.3mm /3.3sp
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I 936
V=1.20
Axial3 Volume 3
Ex: 1038
Se: 6
I: 302.5
Im: 91
Ospedale Aosta Ma
A 260
DoB: Jan 27 1929
Ex: Jun 18 2013
DFOV 52.0 cm
3.3/
3.3mm /3.3sp
06:14:41 PM
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P 260
V=1.20
Axial4 Volume 1
Ex: 1038
Se: 3
I: 302.6
Im: 91
Ospedale Aosta Medicina Nucleare
A 260
DoB: Jan 27 1929
Ex: Jun 18 2013
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STND
3.3/
kv 120
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Se: 6
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Im: 91
Ospedale Aosta Medicina Nucleare
A 260
DoB: Jan 27 1929
Ex: Jun 18 2013
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28.76
0.00
50 % PET
3.3/
3.3mm /3.3sp
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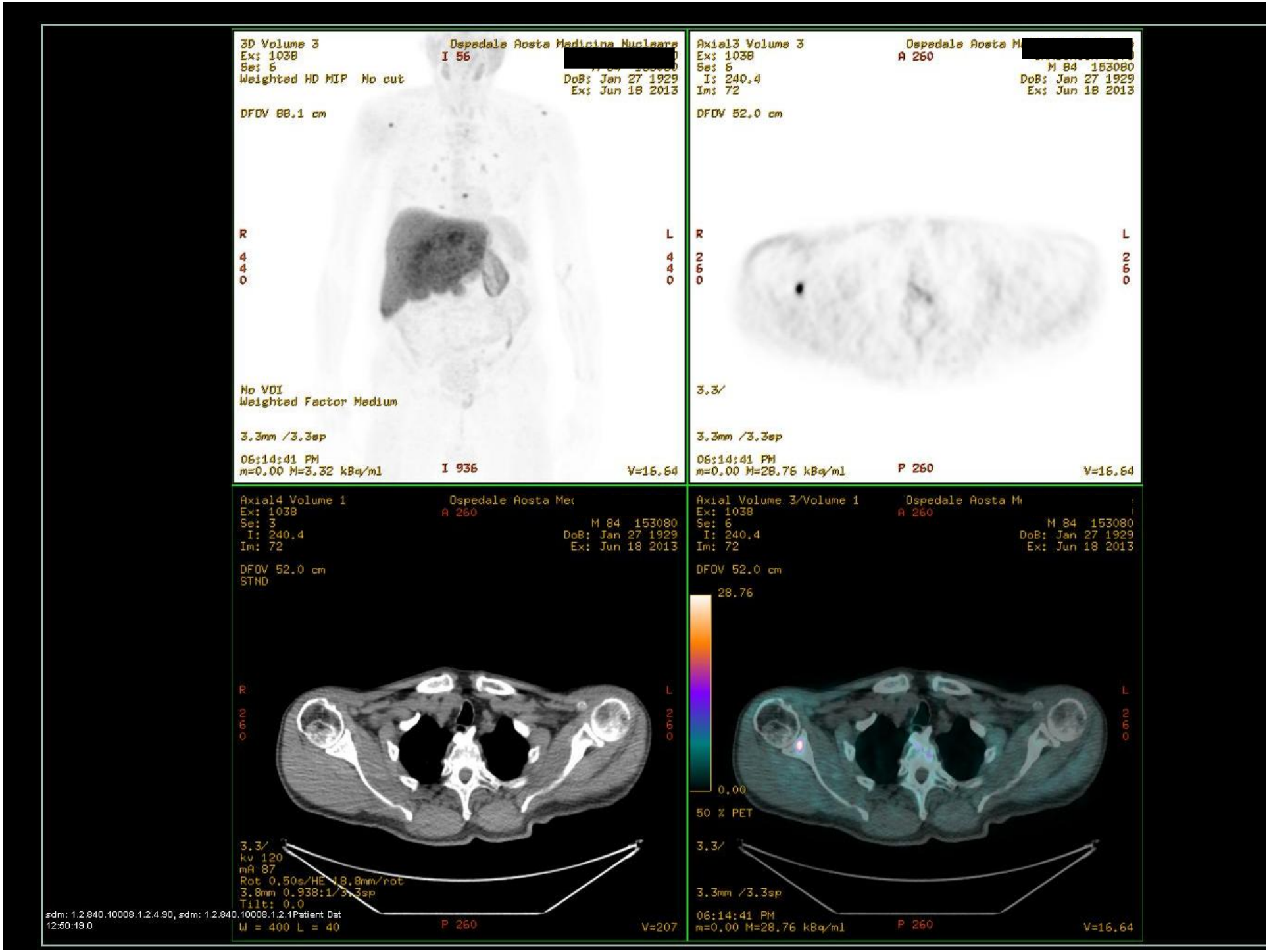
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Se: 5
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R
L
No VOI
Weighted Factor Medium
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Im: 72
A 260
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DoB: Jan 27 1929
Ex: Jun 18 2013
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3.3/
3.3mm /3.3sp
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P 260
V=16.64
Axial4 Volume 1
Ex: 1038
Se: 3
I: 240.4
Im: 72
A 260
M 84 153080
DoB: Jan 27 1929
Ex: Jun 18 2013
DFOV 52.0 cm
STND
3.3/
kv 120
mA 87
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3.8mm 0.938:1/3.3sp
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V=207
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I: 240.4
Im: 72
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M 84 153080
DoB: Jan 27 1929
Ex: Jun 18 2013
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28.76
0.00
50 % PET
3.3/
3.3mm /3.3sp
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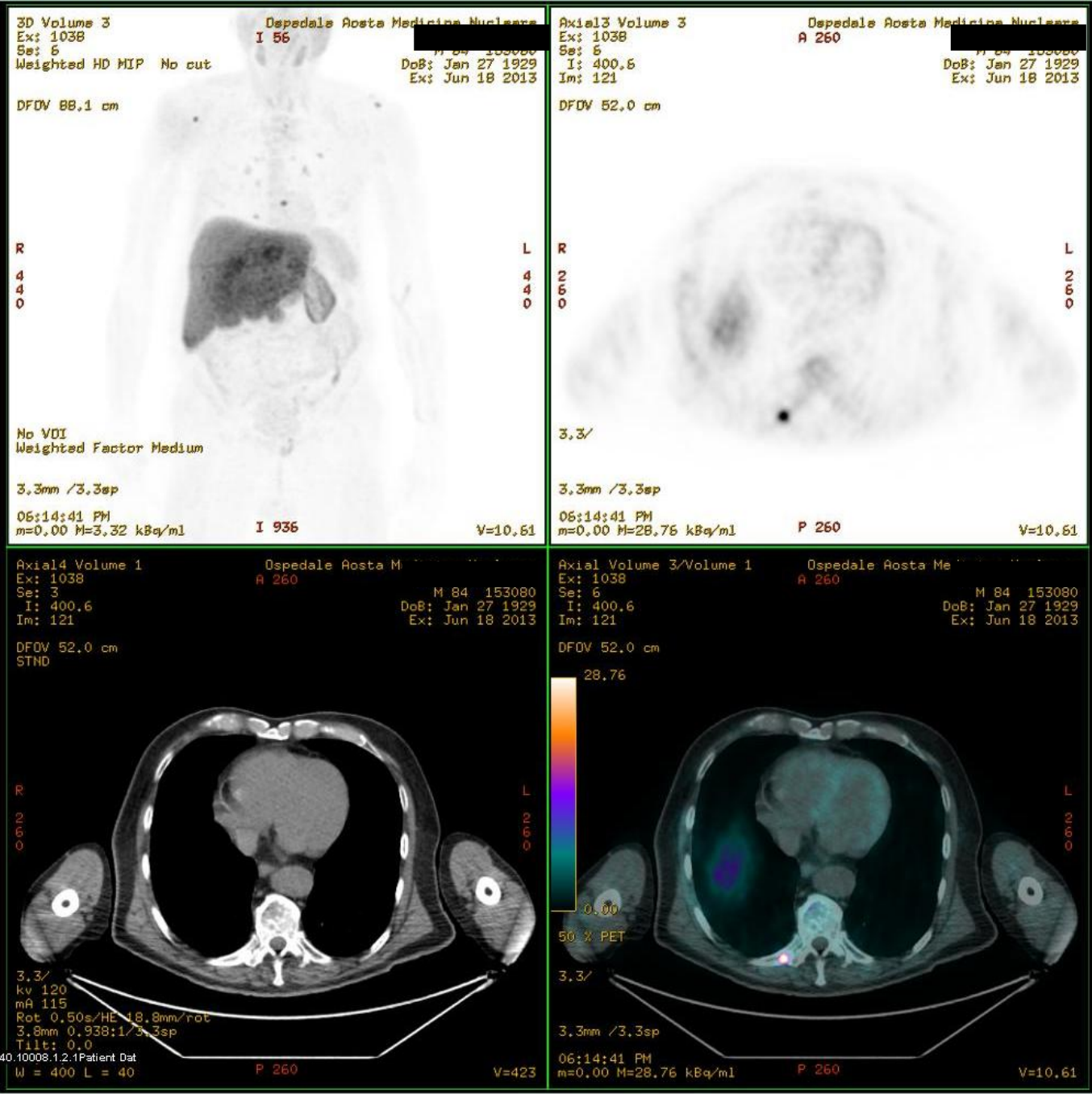
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R
L
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Ex: 1038
Se: 6
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Im: 121
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DoB: Jan 27 1929
Ex: Jun 18 2013
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3.3mm /3.3sp
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P 260
V=10.61
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Se: 3
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Im: 121
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STND
M 84 153080
3.3/
kv 120
mA 115
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0.00
50 % PET
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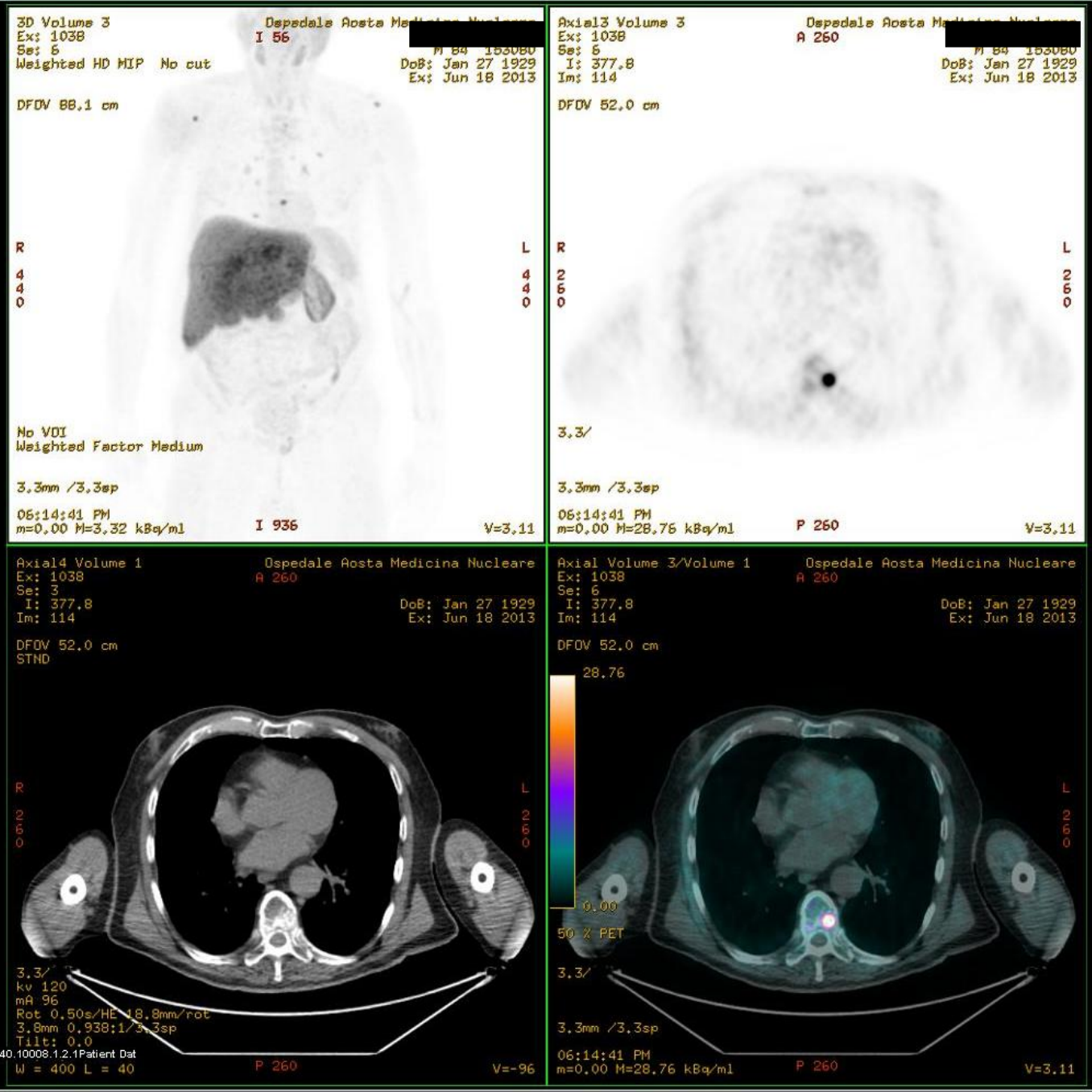

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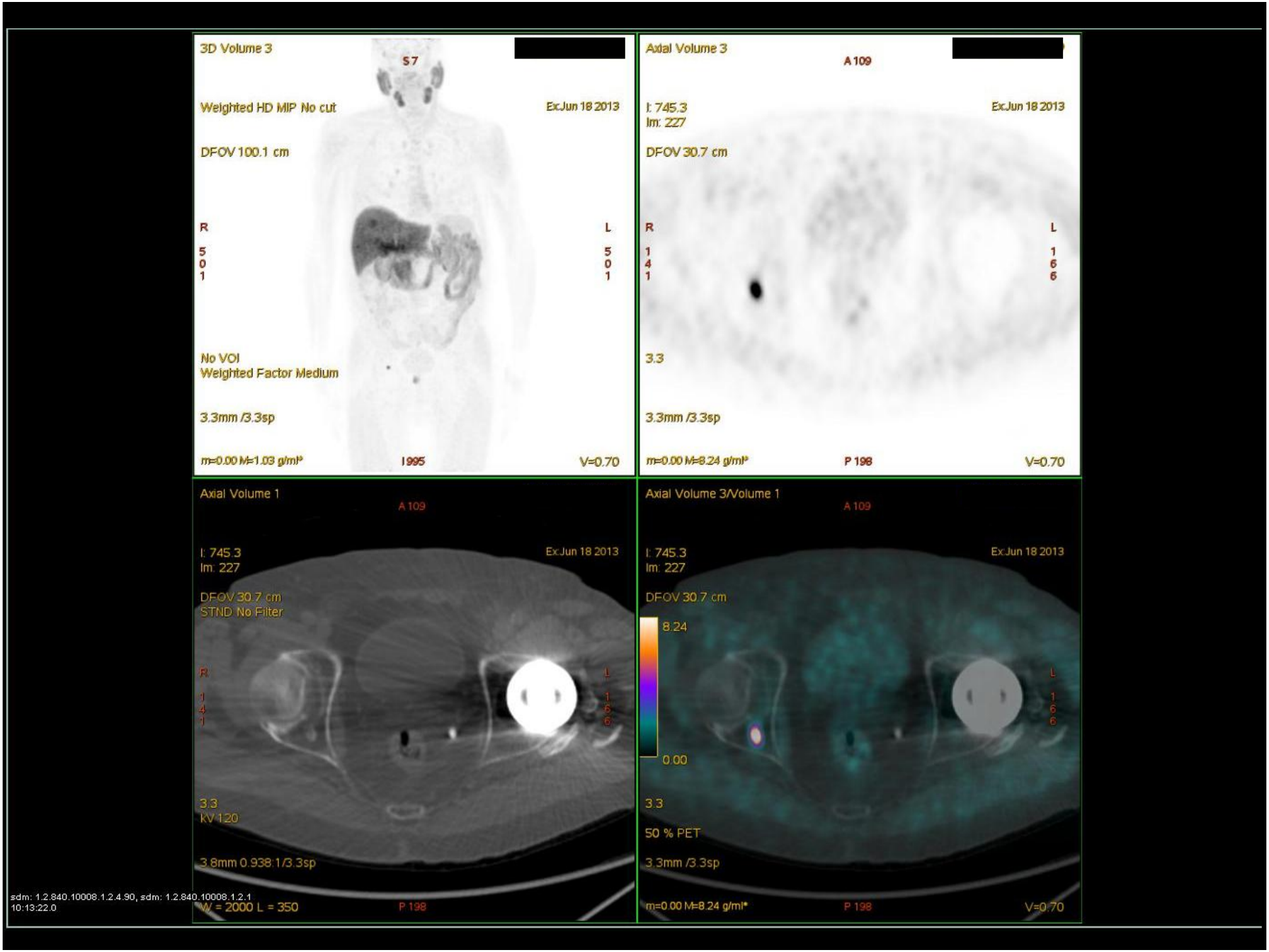
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R
L
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5 0 1
No VOI
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I 995
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[redacted]
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Im: 227
Ex:Jun 18 2013
DFOV 30.7 cm
R
L
1 4 1
1 6 6
3.3
3.3mm /3.3sp
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P 198
V=0.70
Axial Volume 1
A 109
I: 745.3
Im: 227
Ex:Jun 18 2013
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STND No Filter
R
L
1 4 1
1 6 6
3.3
kV 120
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W = 2000 L = 350
P 198
Axial Volume 3/Volume 1
A 109
I: 745.3
Im: 227
Ex:Jun 18 2013
DFOV 30.7 cm
8.24
0.00
L
1 6 6
3.3
50 % PET
3.3mm /3.3sp
m=0.00 M=8.24 g/ml*
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V=0.70
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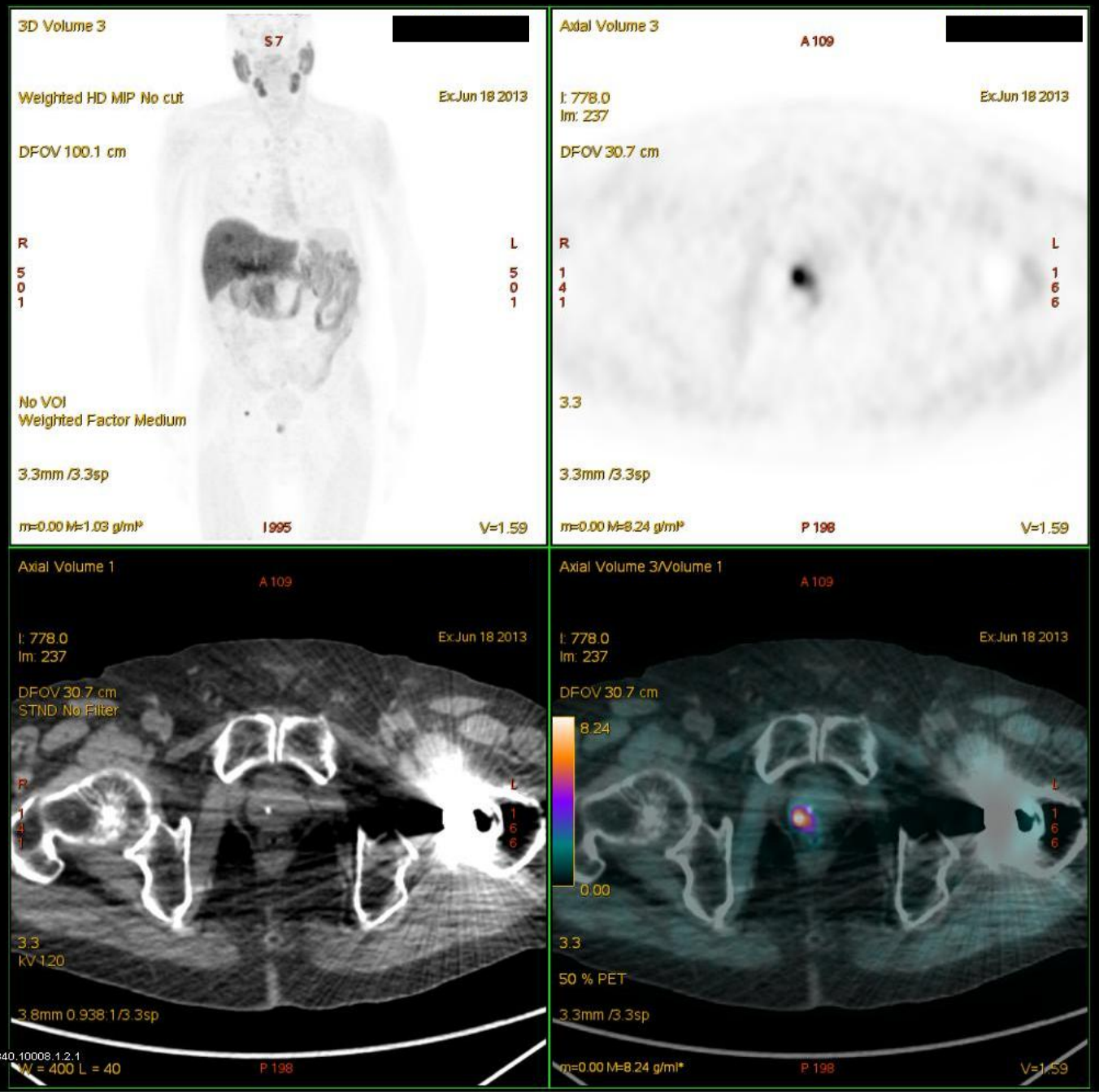
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R
L
5
0
1
5
0
1
No VOI
Weighted Factor Medium
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V=1.59
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I: 778.0
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DFOV 30.7 cm
R
L
1
4
1
1
6
6
3.3
3.3mm /3.3sp
m=0.00 M=8.24 g/ml³
P 198
V=1.59
Axial Volume 1
A 109
I: 778.0
Im: 237
Ex:Jun 18 2013
DFOV 30.7 cm
STND No Filter
R
L
1
4
1
1
6
6
3.3
kV 120
3.8mm 0.938:1/3.3sp
W = 400 L = 40
P 198
Axial Volume 3/Volume 1
A 109
I: 778.0
Im: 237
Ex:Jun 18 2013
DFOV 30.7 cm
8.24
0.00
L
1
6
6
3.3
50 % PET
3.3mm /3.3sp
m=0.00 M=8.24 g/ml³
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V=1.59
sdm: 1.2.840.10008.1.2.4.90, sdm: 1.2.840.10008.1.2.1
10:13:22.0

PET/CT – …oltre la Colina

Novel Tracers and Their Development for the Imaging of Metastatic Prostate Cancer*

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There are presently no accurate methods of imaging prostate cancer metastases to bone. An unprecedented number of novel imaging agents, based on the biology of the disease, are now available for testing. We reviewed contemporary molecular imaging modalities that have been tested in humans with metastatic prostate cancer, with consideration of the studies' adherence to current prostate cancer clinical trial designs. Articles from the years 2002 to 2008 on PET using ^{18}F-FDG, ^{11}C-choline, ^{18}F-choline, ^{18}F-flouride, ^{11}C-acetate, ^{11}C-methionine, and ^{18}F-fluoro-5α-dihydrotestosterone in patients with metastatic prostate cancer were reviewed. Although these studies are encouraging, most focus on the rising population with prostate-specific antigen, and many involve small numbers of patients and do not adhere to consensus criteria for clinical trial designs in prostate cancer. Hence, although many promising agents are available for testing, such studies would benefit from closer collaboration between those in the fields of medical oncology and nuclear medicine.

Key Words: prostate cancer; positron emission tomography; ^{18}F-fluorodeoxyglucose; ^{11}C-choline; ^{18}F-fluorocholine; ^{11}C-acetate; ^{11}C-methionine; ^{18}F-fluoro-5α-dihydrotestosterone

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In the past several decades, understanding of the molecular biology of prostate cancer has expanded, particularly related to growth despite androgen-reducing agents and the transformation from a tumor cell dependent on prostate stroma to one that participates in bone metabolism (*1,2*). The identification of biologic targets not only has led to the introduction of novel therapies for prostate cancer but also has opened up new possibilities for imaging the disease. These biologic targets can be used to characterize underlying molecular biology of the tumor at a lesional level, assess the pharmacodynamics of targeted therapy, and assess clinical responses.

Such new imaging modalities are sorely needed for prostate cancer patients, particularly those with metastatic disease. Between 80% and 90% of prostate cancer patients with metastatic disease have involvement of the axial skeleton (*3–6*). Although contemporary data show an increasing proportion of soft-tissue lesions in prostate cancer patients with metastatic disease (*4,5*), bone metastases still continue to represent the predominant manifestation for most patients and the primary cause of morbidity and mortality. However, bone metastases are considered nonmeasurable by the Response Evaluation Criteria in Solid Tumors. The lack of accurate imaging modalities to directly, reproducibly, and effectively delineate bone metastases limits the clinical management of prostate cancer patients and the advancement of new therapies.

It is difficult to introduce and test any new agent in prostate cancer—whether it is a therapeutic drug or a novel tracer—because there is no gold standard imaging modality that can establish whether a drug is having an effect on the cancer, whether a tracer is actually detecting disease, or whether there has been a change in disease. As a result, designing clinical trials for prostate cancer is uniquely challenging (*7,8*). In addition to the difficulty of imaging prostate cancer, the disease itself has a heterogeneous clinical course, as do its patients, who face significant noncancer-related morbidities as well.

Faced with these challenges, the field has adopted a clinical-states framework for organizing the natural history of disease (Fig. 1). The model highlights the objectives of the intervention rather than the treatment itself. In addition, unlike traditional staging schema based on primary tumor characteristics, nodal status, and metastatic involvement at diagnosis, the model is not fixed but describes the entire disease course.

Leaders in prostate cancer clinical trials have developed state-specific consensus criteria for clinical trials, from eligibility criteria to outcome measures (*9–11*). These

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*NOTE: FOR CE CREDIT, YOU CAN ACCESS THIS ACTIVITY THROUGH THE SNM WEB SITE (http://www.snm.org/ce_online) THROUGH DECEMBER 2009.
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^{11}C-Acetate PET/CT Before Radical Prostatectomy: Nodal Staging and Treatment Failure Prediction

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Despite early detection programs, many patients with prostate cancer present with intermediate- or high-risk disease. We prospectively investigated whether ^{11}C-acetate PET/CT predicts lymph node (LN) metastasis and treatment failure in men for whom radical prostatectomy is planned. **Methods:** 107 men with intermediate- or high-risk localized prostate cancer and negative conventional imaging findings underwent PET/CT with ^{11}C-acetate. Five underwent LN staging only, and 102 underwent LN staging and prostatectomy. PET/CT findings were correlated with pathologic nodal status. Treatment-failure–free survival was estimated by the Kaplan–Meier method. The ability of PET/CT to predict outcomes was evaluated by multivariate Cox proportional hazards analysis. **Results:** PET/CT was positive for pelvic LN or distant metastasis in 36 of 107 patients (33.6%). LN metastasis was present histopathologically in 25 (23.4%). The sensitivity, specificity, and positive and negative predictive values of PET/CT for detecting LN metastasis were 68.0%, 78.1%, 48.6%, and 88.9%, respectively. Treatment failed in 64 patients: 25 with metastasis, 17 with a persistent postprostatectomy prostate-specific antigen level greater than 0.20 ng/mL, and 22 with biochemical recurrence (prostate-specific antigen level > 0.20 ng/mL after nadir) during follow-up for a median of 44.0 mo. Treatment-failure–free survival was worse in PET-positive than in PET-negative patients ($P < 0.0001$) and in those with false-positive than in those with true-negative scan results ($P < 0.01$), suggesting that PET may have demonstrated nodal disease not removed surgically or identified pathologically. PET positivity independently predicted failure in preoperative (hazard ratio, 3.26; $P < 0.0001$) and postoperative (hazard ratio, 3.07; $P = 0.0001$) multivariate models. **Conclusion:** In patients planned for or completing prostatectomy, ^{11}C-acetate PET/CT detects LN metastasis not identified by conventional imaging and independently predicts treatment-failure–free survival.

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Key Words: prostatic cancer; PET; acetate; cancer staging; lymphatic metastasis
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Although many patients in the United States with newly diagnosed prostate cancer have low-risk disease, 40%–50% have intermediate- or high-risk localized disease (*1,2*). Up to 20% of these patients have metastatic disease, usually in lymph nodes (LNs). Identification of LN involvement is important for treatment planning (*3,4*). These patients typically undergo CT or MR imaging. However, neither is sensitive for detecting nodal metastasis unless the nodes are enlarged (*4*). In a recent meta-analysis, the sensitivity of CT and MR imaging was 39%–42% for detecting pelvic LNs (*5*). MR imaging with ultrasmall superparamagnetic iron oxide contrast material (which is not available in the United States) and diffusion-weighted MR imaging appear to have improved sensitivity (*6*), but experience is still limited.

Because of the unreliability of imaging, nomograms based on clinical parameters, such as prostate-specific antigen (PSA), T stage, and Gleason score, are used to estimate the risk of nodal metastasis (*3,7,8*) and may justify omission of lymphadenectomy in patients with an estimated risk of less than 5% since there is an 8%–20% complication rate for lymphadenectomy (*9,10*). This approach is not ideal, however, as in some cases the disease will be under-staged.

PET allows for detection of characteristic biochemical attributes of malignant cells and is not dependent on size criteria alone. PET with ^{18}F-FDG effectively stages many cancers but has limited utility for initial staging of prostate cancer because urinary excretion may obscure nodal uptake; additionally, most prostate cancers have low rates of glucose metabolism, and ^{18}F-FDG uptake is similar in prostate cancer, benign prostatic enlargement, and inflammation (*11,12*).

Biodistribution, Tumor Detection, and Radiation Dosimetry of ^{18}F-DCFBC, a Low-Molecular-Weight Inhibitor of Prostate-Specific Membrane Antigen, in Patients with Metastatic Prostate Cancer

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Prostate-specific membrane antigen (PSMA) is a type II integral membrane protein expressed on the surface of prostate cancer (PCa) cells, particularly in androgen-independent, advanced, and metastatic disease. Previously, we demonstrated that *N*-[*N*-[(*S*)-1,3-dicarboxypropyl]carbamoyl]-4-^{18}F-fluorobenzyl-L-cysteine (^{18}F-DCFBC) could image an experimental model of PSMA-positive PCa using PET. Here, we describe the initial clinical experience and radiation dosimetry of ^{18}F-DCFBC in men with metastatic PCa. **Methods:** Five patients with radiologic evidence of metastatic PCa were studied after the intravenous administration of 370 MBq (10 mCi) of ^{18}F-DCFBC. Serial PET was performed until 2 h after administration. Time–activity curves were generated for selected normal tissues and metastatic foci. Radiation dose estimates were calculated using OLINDA/EXM 1.1. **Results:** Most vascular organs demonstrated a slow decrease in radioactivity concentration over time consistent with clearance from the blood pool, with primarily urinary radiotracer excretion. Thirty-two PET-positive suspected metastatic sites were identified, with 21 concordant on both PET and conventional imaging for abnormal findings compatible with metastatic disease. Of the 11 PET-positive sites not identified on conventional imaging, most were within the bone and could be considered suggestive for the detection of early bone metastases, although further validation is needed. The highest mean absorbed dose per unit administered radioactivity (μGy/MBq) was in the bladder wall (32.4), and the resultant effective dose was 19.9 ± 1.34 μSv/MBq (mean ± SD). **Conclusion:** Although further studies are needed for validation, our findings demonstrate the potential of ^{18}F-DCFBC as a new positron-emitting imaging agent for the detection of metastatic PCa. This study also provides dose estimates for ^{18}F-DCFBC that are comparable to those of other PET radiopharmaceuticals such as ^{18}F-FDG.

Key Words: prostate-specific membrane antigen; prostate cancer; ^{18}F; urea; PET/CT

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DOI: 10.2967/jnumed.112.104661

Prostate cancer (PCa) is the most commonly diagnosed cancer and the second leading cause of cancer death among men in the United States (*1*). The early detection and improved local therapies for primary PCa have greatly improved survival. However, most patients will still experience relapse and require continued surveillance and ongoing therapy (*2*). In addition to hormonal therapy and antitubulin-based chemotherapy, several promising new targets and therapeutic agents have recently been approved for patients with castrate-resistant PCa (*3*). These recent advances suggest that accurate detection and characterization of disease by molecular imaging will have an increasing impact on clinical management and patient-specific therapeutic optimization.

The prostate-specific membrane antigen (PSMA) is a promising, well-characterized biomarker of PCa and is associated with tumor aggressiveness. Histologic studies have associated high PSMA expression with metastasis (*4*), androgen independence (*5*), and progression (*6*). Previous attempts to image PSMA by SPECT using the agent ^{111}In-capromab pendetide (ProstaScint™; EUSA Pharma), approved by the Food and Drug Administration, demonstrated poor performance due to several factors, including the inherent limitations of intact antibody-mediated imaging (poor tumor penetration and slow blood-pool clearance),

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Imaging osseo

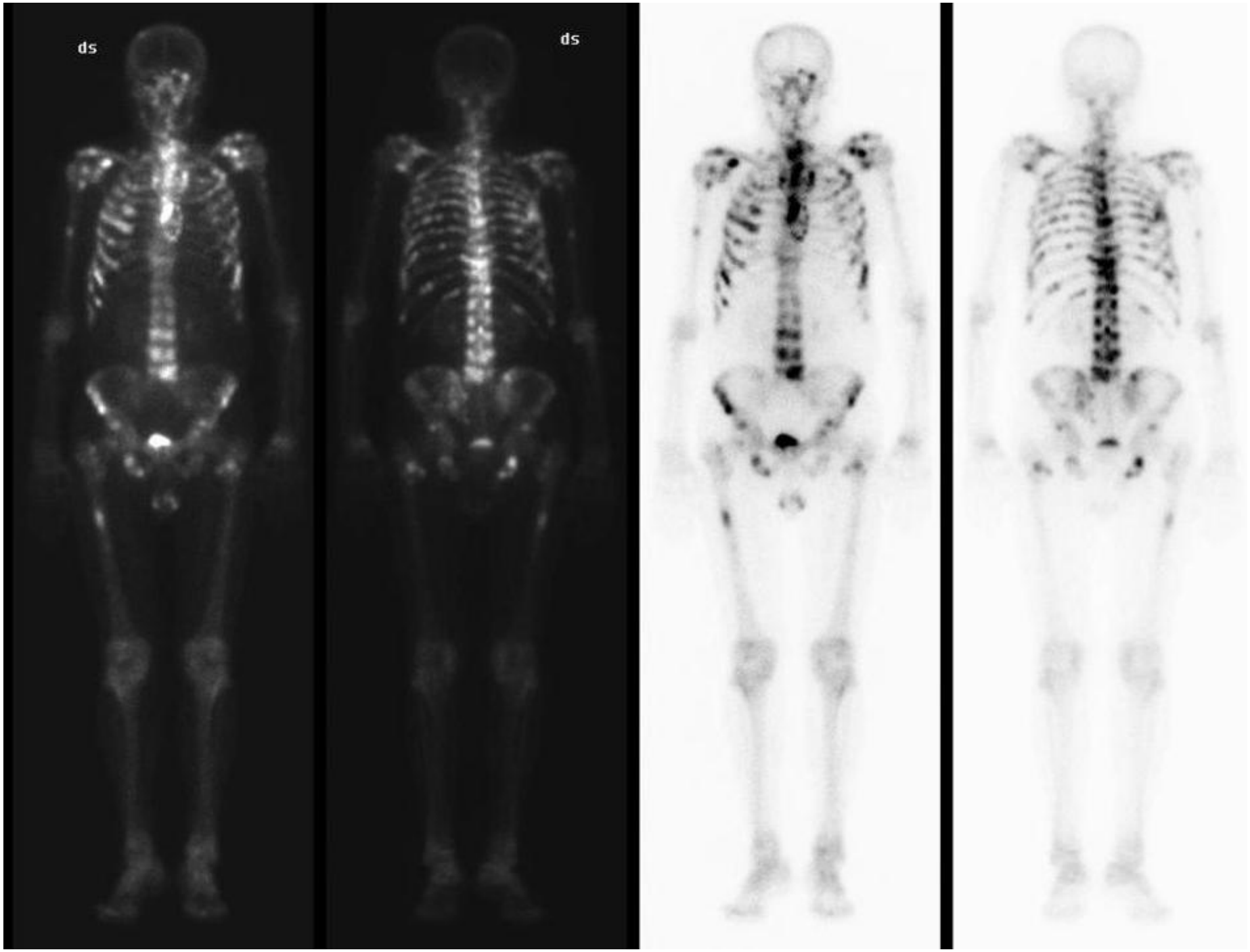
•Patienti con “low-risk prostate cancer” hanno una bassa probabilità di avere metastasi ossee.

• Il “bone scan” (BS) è indicato principalmente per patienti con tumori “high-risk”, aumentati livelli sierici di fosfatasi alcalina, dolori ossei e/o lesioni ossee di riscontro con altre metodiche non univocamente interpretabili.

•Il 90% dei patienti che muoiono di tumore della prostata sono portatori di MTS scheletriche.

Imaging osseo

- La dimostrazione precoce o l'esclusione di MTS scheletriche è fondamentale nel "clinical management" di patienti con "high-risk prostate cancer"
  - In pazienti di nuova diagnosi con malattia localizzata senza MTS è possibile un trattamento radicale locale con intento curativo
  - In pazienti con metastasi sarà indicato un tempestivo avvio della deprivazione androgenica e la terapia medica evitando terapie radicali non necessarie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Imaging osseo

- The primary goal of scintigraphic assessment in patients with high-risk prostate cancer is to detect, as early as possible, the presence of bone metastases

- Exclusion of bone metastases by negative bone scan is another goal, particularly when nonspecific equivocal bony lesions have been detected on CT

Imaging osseo

Imaging of bone metastases in prostate cancer: an update

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Assessing bone metastases is often beyond the scope of plain - film radiography, and nuclear imaging in particular with bone scintigraphy has proved the mainstay for detection of bony disease for over 40 years. Bone scanning with 99mTechnetium – labeled diphosphonates relies on the detection of pathological osteoblastic response elicited from malignant cells. This technique offers the advantage of whole body examination, low cost, availability and high sensitivity. However, it suffers from relative low specificity. The addition of single-photon emission computed tomography (SPECT) to bone scintigraphy has markedly improved the diagnostic benefit. Although the accuracy of SPECT is significantly higher than that of planar scintigraphy, there is still room for improvement of anatomic localization and morphological characterization, a limitation that has currently been mainly overcome with the upcoming of combined SPECT-CT (computed tomography).
Positron emission tomography (PET), a modality with higher spatial resolution than that of SPECT can be particularly helpful in detecting small lesions. Moreover, PET imaging using various specific radiotracers has the advantage of detecting malignant disease in both bone and soft tissues. It is highly sensitive mainly in detecting early bone marrow as well as for diagnosing lytic bony metastases and can be also reliably used to monitor therapy response. In this review, we present the current role of SPECT and PET in the imaging of skeletal metastases from prostate cancer.

KEY WORDS: Skeleton - Neoplasm metastasis - Tomography, emission-computed, single-photon - Positron-emission tomography - Prostatic neoplasms.

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Bone metastases have been reported in about 350000 patients in the United States each year.[1-3] The skeletal system is the third most common site of metastases after the lungs and liver, and 80% of all reported metastatic bone diseases is in patients with breast and prostate cancer. This review assesses the role of SPECT and PET in the imaging of skeletal metastases from prostate cancer.

Bone scintigraphy

Early diagnosis of metastatic bone disease in prostate cancer is crucial for selecting appropriate therapy, to assess the patient's prognosis, and to determine the efficacy of bone specific treatments that may reduce future bone associated morbidity. Bone pain, pathologic fracture, hypercalcemia and spinal cord compression are the common complications of bone metastases which affect the quality of life in these patients.

Therefore, early detection of metastatic disease may prevent the complications and improve the quality of

Imaging osseo

Although only a few studies compare 18F NaF with 99m Tc-99m MDP for the diagnosis of bone metastases, 18F NaF PET seems to be more sensitive than conventional bone scanning [86] showing a higher contrast between normal and abnormal tissue and with the potential for the detection of additional lesions especially in the spine.[37, 50, 86-91]

18F NaF diffuses through the capillaries into the extracellular fluid followed by a slow exchange of hydroxyl ions in the hydroxylapatit, thus indicating the rate of bone turnover.[91] 18F NaF offers substantially higher sensitivity and resolution than that of Tc-labelled tracers due to its higher bony extraction as well as faster blood excretion.[91]

In a prospective comparative study, Even-Sapir *et al.*[30] assessed 44 high risk prostate cancer patients for distant metastases using planar bone scintigraphy, bone SPECT, 18F NaF PET and PET-CT. The sensitivity and specificity for detection of bone metastases was 70% and 57% for planar bone scintigraphy, 92% and 82% for bone SPECT, 100% and 62% for PET and 100% and 100% for PET – CT, respectively. 18F NaF

^{18}F-Fluoride Positron Emission Tomography and Positron Emission Tomography/Computed Tomography

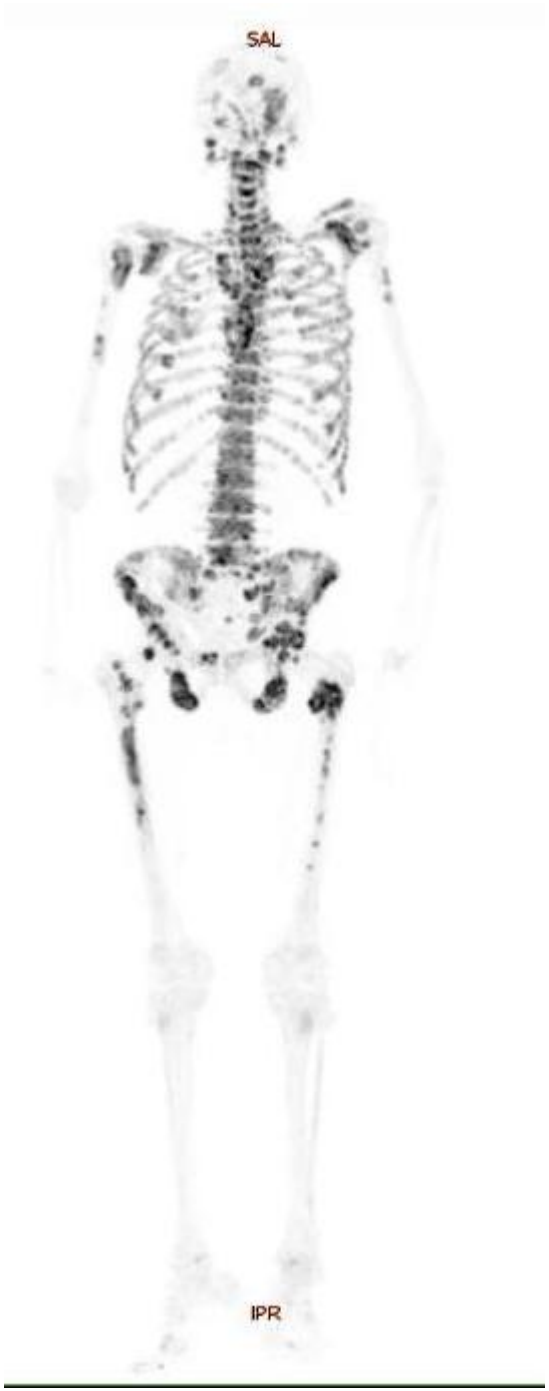
Einat Even-Sapir, MD, PhD,* Eyal Mishani, PhD,† Gideon Flusser, MD,‡ and Ur Metser, MD*

^{18}F-Fluoride is a positron-emitting bone-seeking agent, the uptake of which reflects blood flow and remodeling of bone. Assessment of ^{18}F-fluoride kinetics using quantitative positron emission tomography (PET) methods allows the regional characterization of lesions of metabolic bone diseases and the monitoring of their response to therapy. It also enables the assessment of bone viability and discrimination of uneventful and impaired healing processes of fractures, bone grafts and osteonecrosis. Taking advantage of the favorable pharmacokinetic properties of the tracer combined with the high performance of PET technology, static ^{18}F-fluoride PET is a highly sensitive imaging modality for detection of benign and malignant osseous abnormalities. Although ^{18}F-fluoride uptake mechanism corresponds to osteoblastic activity, it is also sensitive for detection of lytic and early marrow-based metastases, by identifying their accompanying reactive osteoblastic changes, even when minimal. The instant fusion of increased ^{18}F-fluoride uptake with morphological data of computed tomography (CT) using hybrid PET/CT systems improves the specificity of ^{18}F-fluoride PET in cancer patients by accurately differentiating between benign and malignant sites of uptake. The results of a few recent publications suggest that ^{18}F-fluoride PET/CT is a valuable modality in the diagnosis of pathological osseous conditions in patients also referred for nononcologic indications. ^{18}F-fluoride PET and PET/CT are, however, not widely used in clinical practice. The limited availability of ^{18}F-fluoride and of PET and PET/CT systems is a major factor. At present, there are not enough data on the cost-effectiveness of ^{18}F-fluoride PET/CT. However, it has been stated by some experts that ^{18}F-fluoride PET/CT is expected to replace ^{99m}Tc-MDP bone scintigraphy in the future.
Semin Nucl Med 37:462-469

- 18F-Fluoride is characterized by a 2-fold higher bone uptake than 99mTc-MDP, a faster blood clearance, and a better target-to-background ratio

- 18F-Fluoride was reported to be highly sensitive for detecting bone metastases in oncologic patients.

- 18F-Fluoride PET has been reported to be more sensitive for detection of metastases than 99mTc-methylene diphosphonate (99mTc-MDP) BS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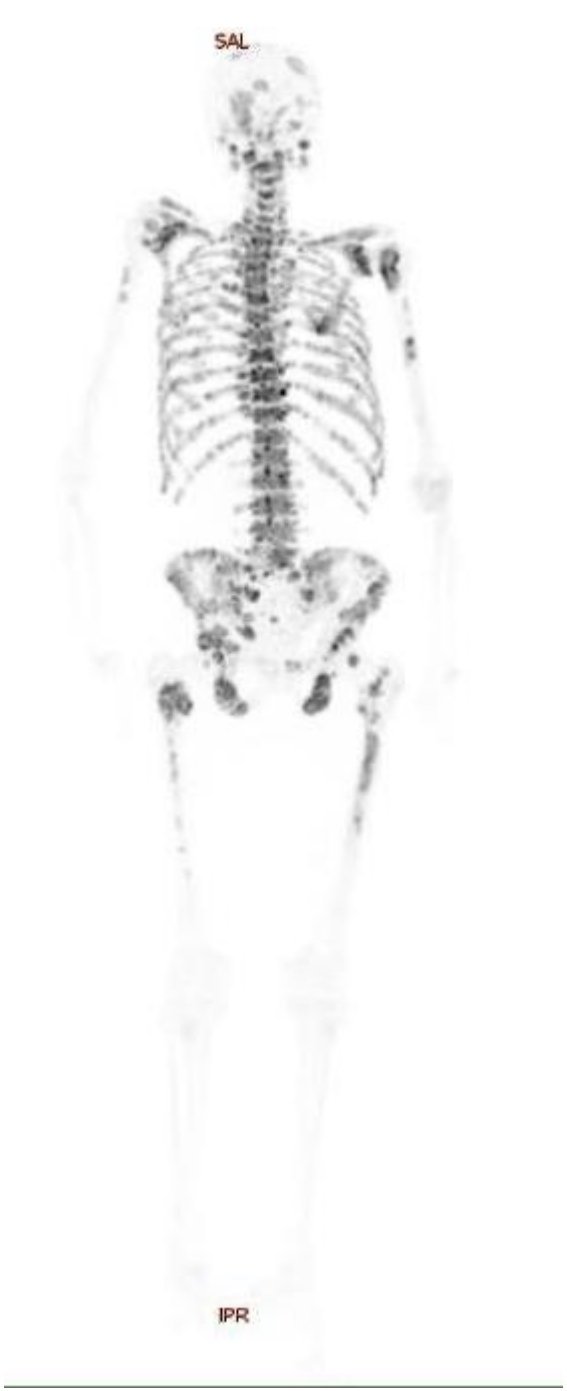
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In sintesi:

- ^{18}F-Fluoride PET/CT is a highly sensitive and specific modality for detection of bone metastases in patients with high-risk prostate cancer

- ^{18}F-Fluoride PET/CT is more sensitive and specific than planar and SPECT BS.

- This added value of ^{18}F-Fluoride PET/CT may beneficially impact the clinical management of patients with high- risk prostate cancer.

^{18}NaF PET/CT

Whether ^{18}F-Fluoride PET/CT should be introduced as a routine imaging approach of metastatic bone survey in cancer patients with high-risk for bone metastases, a meticulous cost-effective analysis is required.

PET-CT was significantly more sensitive and specific than bone scintigraphy (P<0.001) and more specific than PET alone (P<0.001). They concluded that 18F NaF PET-CT is a highly sensitive and specific imaging modality for the detection of bone metastases in high risk prostate cancer patients.

In a recent prospective study, Iagaru *et al.*[92] examined 52 patients with proven malignancy referred for the evaluation of bone metastases. The authors reported superior image quality and diagnostic accuracy of 18F NaF PET-CT for the evaluation of the extent of skeletal disease over 99mTc MDP scintigraphy and FDG PET-CT. At the same time, FDG PET was able to detect extraskeletal disease that could significantly change disease management. They concluded that a combination of FDG PET-CT and 18F NaF PET-CT may be recommended for cancer detection.

Another recent comparative study by our own group [93] attempts to determine the potential of 18F NaF PET-CT and FCH PET-CT for detecting bone metastases in 38 prostate cancer patients. In a lesion-based analysis, the sensitivity and specificity of PET-CT in detection of bone metastasis was 81% and 93% by 18F NaF PET-CT and 74% and 99% by FCH PET-CT, respectively. In a patient-based analysis, there was good agreement between FCH and 18F NaF PET-CT (kappa =0.76). 18F NaF PET-CT demonstrated higher sensitivity than FCH PET-CT in the detection of bone metastases, however, it was not statistically significant.

FCH PET-CT has proved to be a more specific method than 18F NaF PET-CT. Furthermore it has the potential for initial assessment of high risk prostate cancer patients, in particular for the early detection of bone marrow metastases. However, in patients with FCH negative suspicious sclerotic lesions, a second bone seeking agent (*e.g.* 18F NaF) should be performed.

We also noted that hormone therapy may be associated with increasing bone mineralization and sclerosis in malignant lesions and that due to such a response to therapy, 18F NaF PET could also be negative in highly dense sclerotic lesions.

We also predict that 18F NaF PET-CT will replace conventional bone imaging with Tc-99m labelled diphosphonates within the next few years.[37, 50, 94]

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La palliazione del dolore osseo nelle metastasi scheletriche
Trattamento sistemico metabolico con radiofarmaci

•Il dolore osseo nelle MTS scheletriche rappresenta la causa più comune di dolore cronico nei pazienti oncologici.

•Circa il 65% dei pazienti affetti da tumore della prostata potranno presentare metastasi scheletriche sintomatiche.

•Riduce significativamente la qualità di vita ed è causa di importanti comorbidità (ipercalcemia, fratture patologiche, compressioni midollari, etc.)

•Il trattamento è spesso complesso e necessita ovviamente di un approccio multidisciplinare che, di solito, include analgesici, terapie ormonali, bifosfonati, irradiazione a fasci esterni e terapia radiometabolica.

La palliazione del dolore osseo nelle metastasi scheletriche
Trattamento sistemico metabolico con radiofarmaci

•La terapia radiometabolica, per la sua efficacia e il profilo di sicurezza, rappresenta una valida opzione per la palliazione del dolore da metastasi nel caso di metastasi diffuse.

•Consiste nella somministrazione per via sistemica di radiofarmaci con affinità elettiva per il tessuto osseo ma concentrazione selettiva prevalente nelle metastasi scheletriche.

•Il vantaggio principale è rappresentato dalla possibilità di avere come bersaglio in maniera rapida, selettiva e contemporanea tutti i siti ossei metastatici coinvolti.

La palliazione del dolore osseo nelle metastasi scheletriche
Trattamento sistemico metabolico con radiofarmaci

La terapia sistemica delle metastasi ossee con radionuclidi è efficace nel somministrare alte dosi a lesioni ossee diffuse, limitando la dose ai tessuti sani.

A questo scopo vengono utilizzati radionuclidi beta/alfa-emettitori, per la ridotta capacità di penetrazione (alto LET) delle particelle beta e alfa ed il rilascio locale di energia. Queste proprietà sono presenti in misura ancora maggiore nel caso di radionuclidi che emettano particelle alfa.

I principali radiofarmaci per la terapia sintomatica delle metastasi scheletriche sono:

- ^{89}Stronzio cloruro (Metastron)
- ^{186}Renio HEDP – etidronam (Re-Bone)
- ^{153}Samario EDTMP – lexidronam (Quadramet)
- ^{223} $RaCl_2$ (Alpharadin)

- Sono in corso valutazioni sull'effetto tumoricida ottenibile con radiofarmaci alfa-emittenti ($^{223}RaCl_2$– Alpharadin) con riduzione di estensione delle localizzazioni e conseguente indicazione terapeutica in stadi precoci di metastatizzazione, in aggiunta all'indicazione primaria di effetto palliativo del dolore.

La palliazione del dolore osseo nelle metastasi scheletriche
Trattamento sistemico metabolico con radiofarmaci

La terapia radiometabolica induce un effetto antalgico nel 75-85% dei casi, con una risposta completa (totale abbandono degli analgesici e recupero della funzionalità) del 30-50%. La durata mediana della risposta varia da 11 a 29 settimane.

Numerosi fattori condizionano la riposta antalgica, quali il tipo di radiofarmaco utilizzato, l'aspettativa di vita, il perfomance status e il numero e le caratteristiche delle metastasi ossee presenti.

I radiofarmaci sono controindicati in pazienti con funzione midollare seriamente compromessa e vanno utilizzati con cautela in pazienti con < 60.000 PLT e < 2.400 WBC.

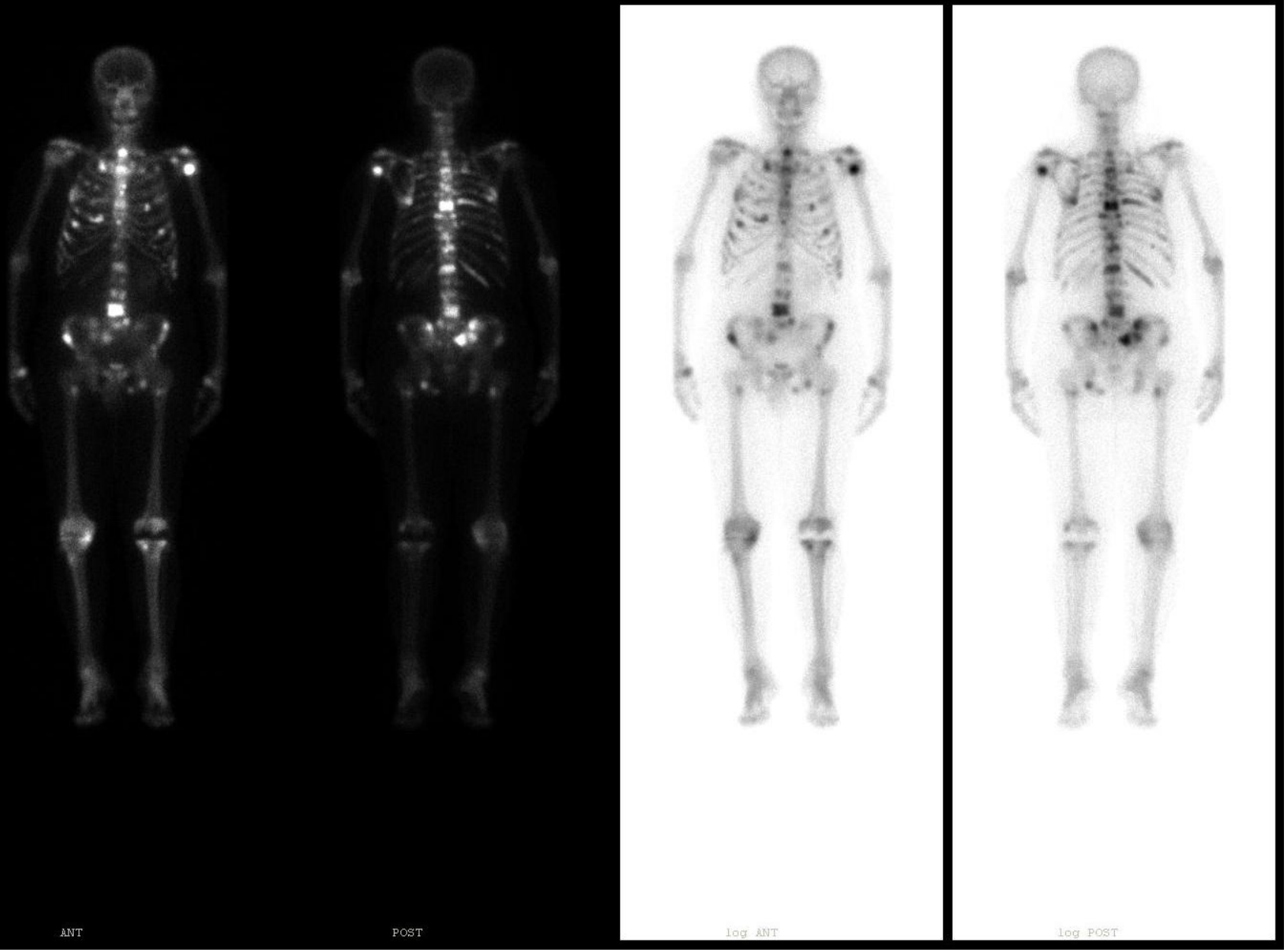
I trattamenti sono controindicati in gravidanza/allattamento, se c'è ipersensibilità ai componenti, in caso di compressione midollare, in presenza di grave insufficienza renale o di marcata riduzione della riserva midollare e quando l'aspettativa di vita è inferiore a 1 mese.

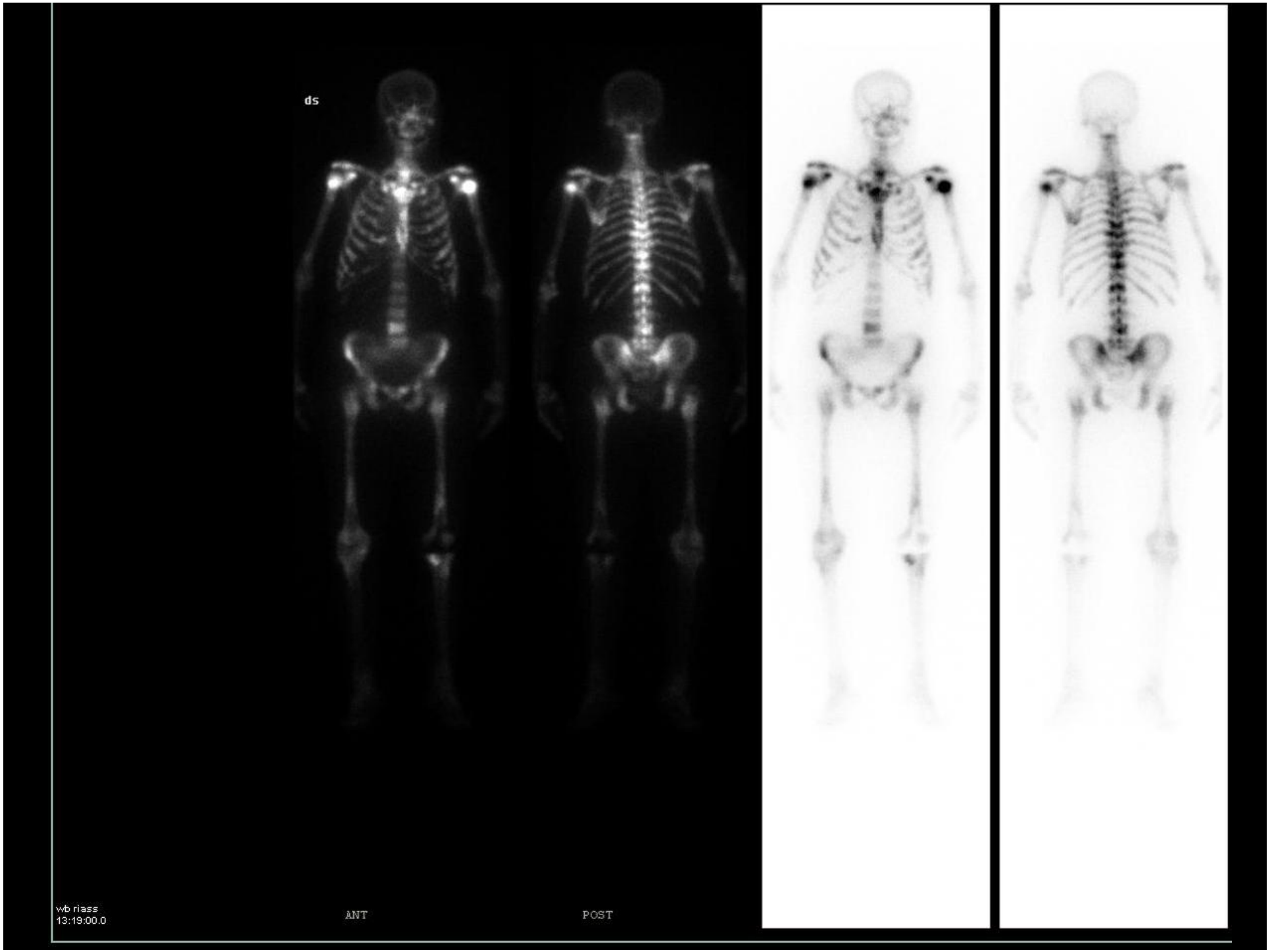
Patient Id: 173084

Ospedale Regionale VDA

Date & Time: 12/27/2012

Manufacturer Model: INFINIA

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La palliazione del dolore osseo nelle metastasi scheletriche
$223RaCl_2$ (Alpharadin)

•Il $^{223}RaCl_2$ (Alpharadin), come elemento alcalino-terroso, è considerato un agente *bone-seeking*, in particolare un *volume-seeker*, per la proprietà di essere rapidamente assorbito nelle regioni ossee dove esiste un'attiva mineralizzazione, specie nel caso delle lesioni ossee metastatiche osteocondensanti.

•E' un alfa-emittente, perciò il principale vantaggio terapeutico è rappresentato dall'elevato LET (il LET medio della radiazione emessa dall'Ittrio 90 è pari a 0.2 KeV/ µm mentre quello della particella alfa emessa dall'Attinio 211 è 97 KeV/ µm.

•Di conseguenza il range medio in tessuto è di 3960 µm per la particella beta e 70 µm per quella alfa.

•Facilmente deducibili i vantaggi dal punto di vista radiobiologico con citotossicità molto più alta nelle lesioni e più selettiva per il risparmio dei tessuti non target.

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- E' un alfa-emittente con un tempo di dimezzamento fisico di 11.43 giorni

- La somministrazione prevede un' attività di 50 kBq/kg

- La biocinetica del radiofarmaco contenente 223Ra è particolarmente favorevole, "…poiché svolge una azione localizzata di inibizione della crescita delle micro-metastasi attraverso un danno selettivo alle cellule tumorali."(P.J. Cheetham, 2012).

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•L'escrezione avviene principalmente per **via gastrointestinale**, a causa del sangue circolante, per secrezione attraverso la mucosa gastro-intestinale.
•Rispetto alla escrezione urinaria il rapporto è stimato circa 30:1.

•L'escrezione per via gastrointestinale avviene **nelle prime 48 ore** dalla somministrazione, con un'entità stimata attorno al 25% dell'attività somministrata, ed il 3% per via urinaria. Il radiofarmaco nella forma $223RaCl_2$ in soluzione acquosa viene somministrato per via endovenosa.

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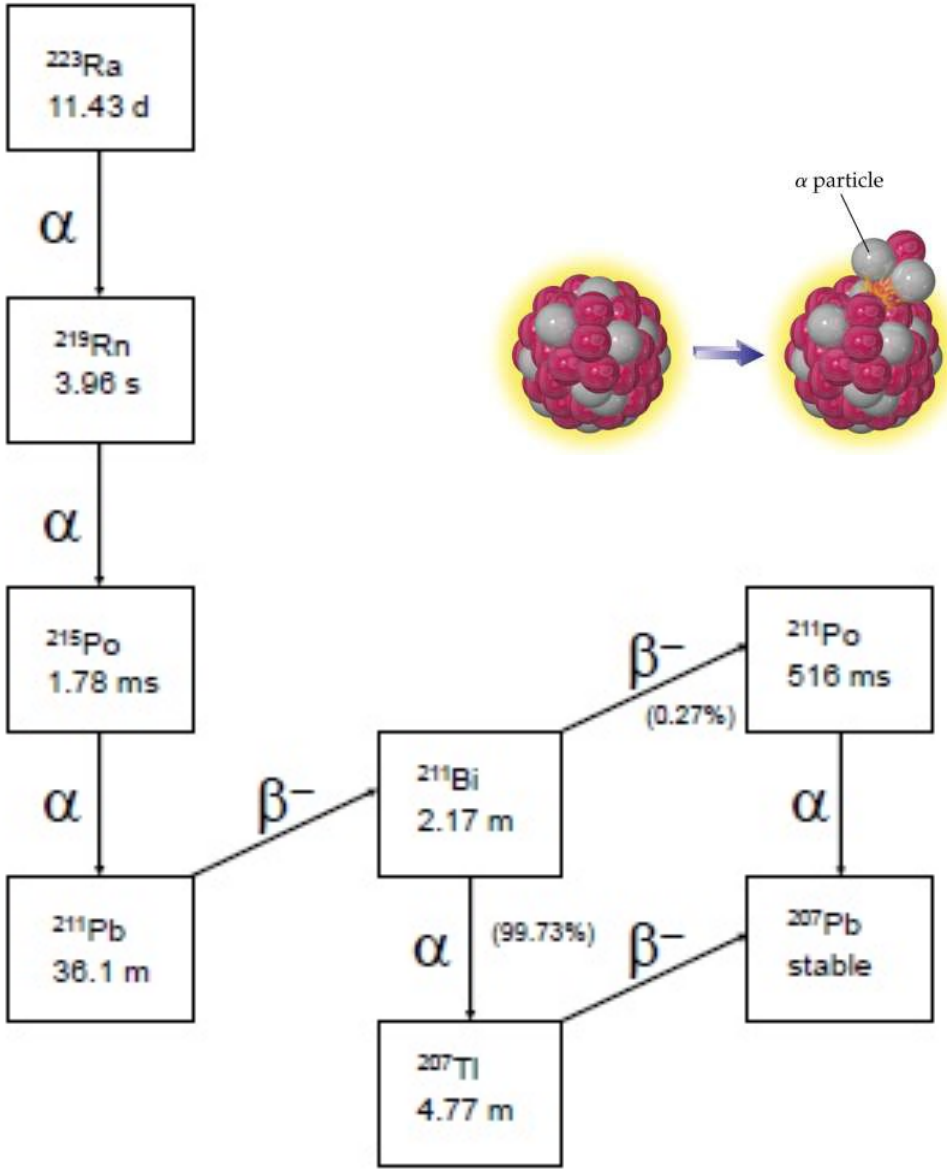
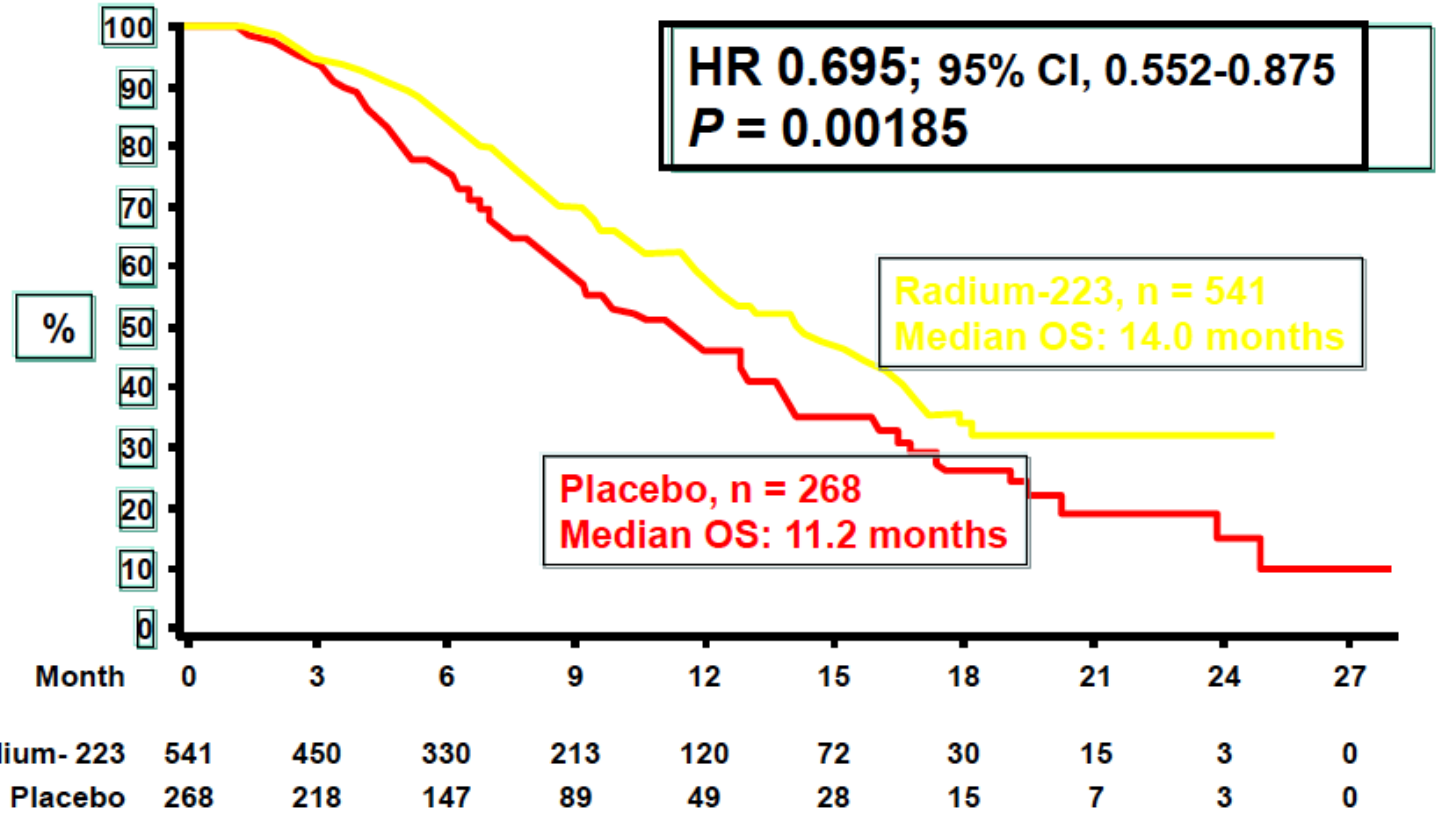
tempo di dimezzamento fisico (giorni)	11.43
tempo per riduzione a 10^{-4} della attività iniziale (mesi)	5
principale tipo di radiazione emessa	alfa (93.5%), beta (3.5%), X e γ (2%)
range nel tessuto (µm)	63 (30-70)
energia *media* delle particelle alfa (MeV)	5.67 (D.R.Fisher, 1989)
LET (keV/ µm)	90 (5.67 MeV/63 µm)
energia dei fotoni emessi (keV)	269 ÷ 402
rateo di dose a 1 metro (µGy m^2 h^{-1} MBq^{-1})	0.02 (D.S. Smith, 2012)
dose a 1 cm (µGy h^{-1} MBq^{-1})	200
dose a 10 cm	2

Il ^{223}Ra decade con emissione di 4 particelle alfa, secondo il seguente schema di decadimento



ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design

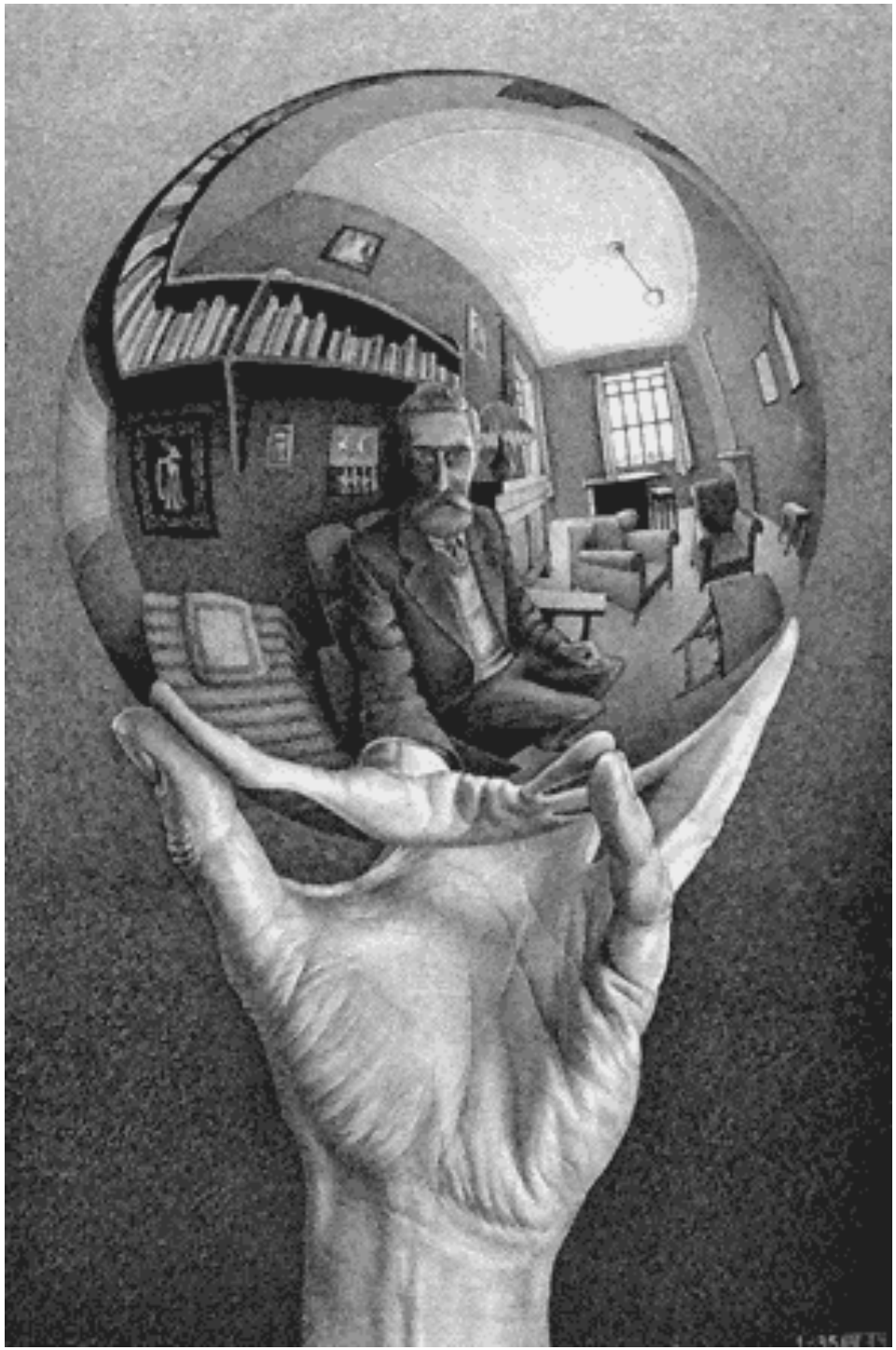
ALSYMPCA Ra-223 Overall Survival

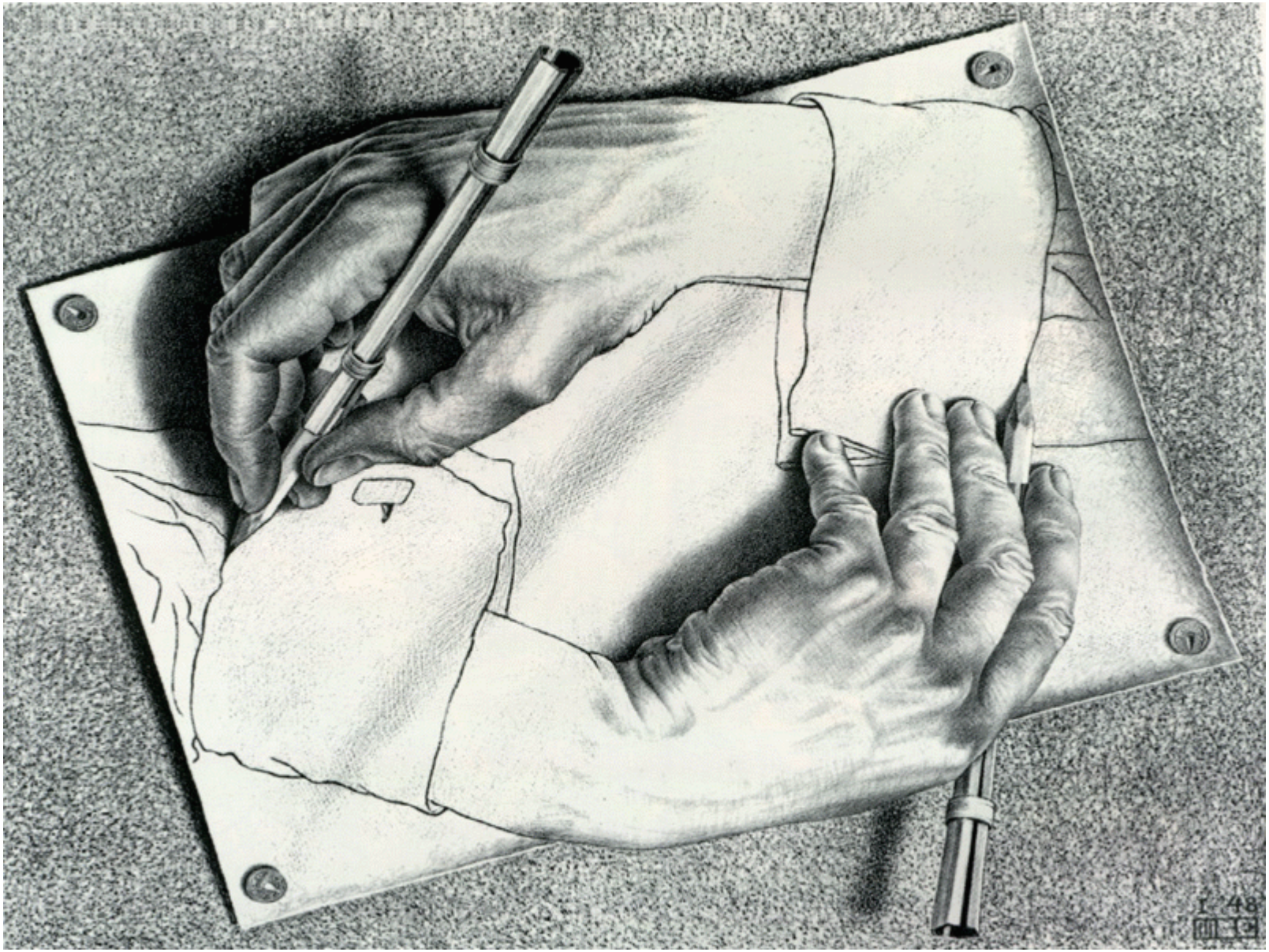


PATIENTS

- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Postdocetaxel or unfit for docetaxel

Planned follow-up is 3 years

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