Attualità e progressi nel trattamento multimodale del Tumore Prostatico

Aosta
16 dicembre 2017

Carlo Poti – S.C. Medicina Nucleare

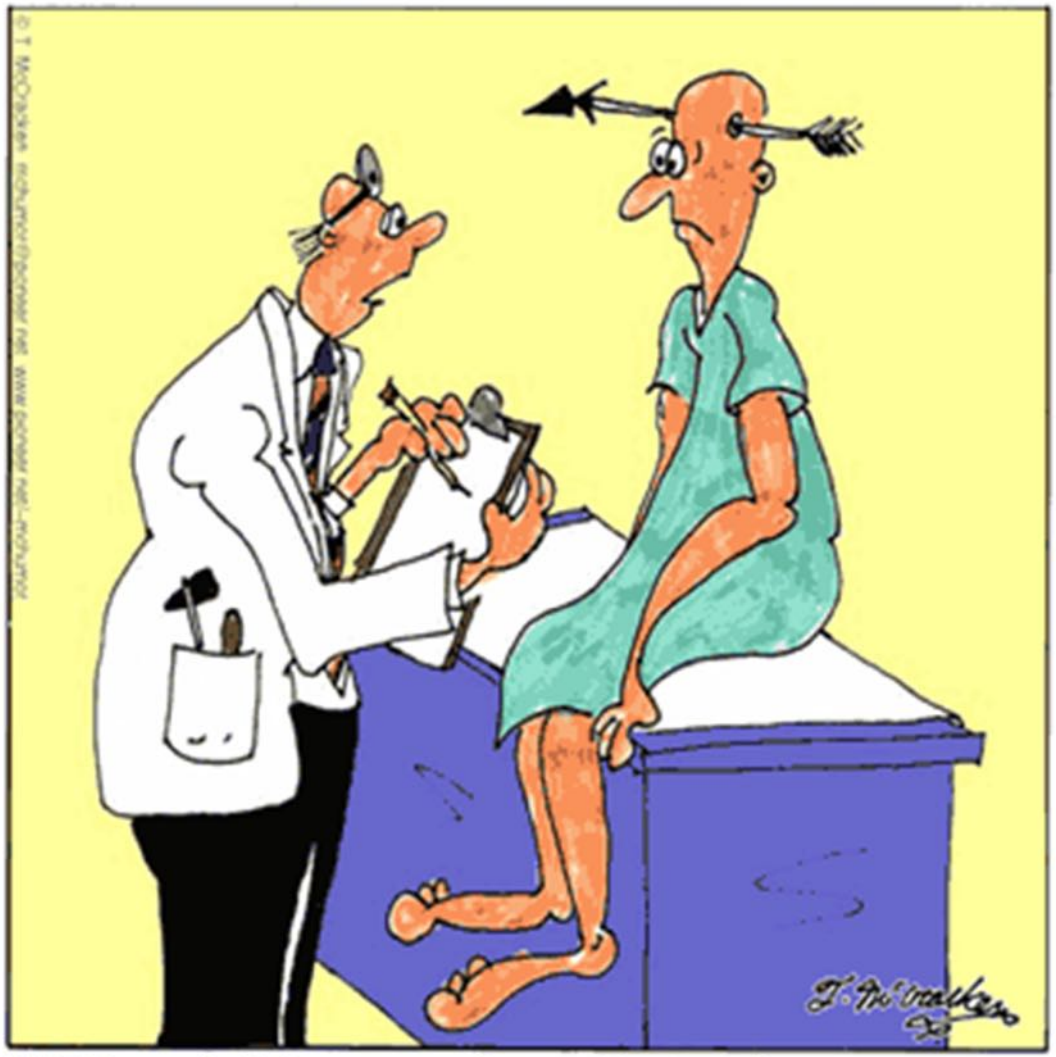
Imaging molecolare: nuovi traccianti e implicazioni cliniche

Disclosures

Responsabile scientifico studio multicentrico «CALIPSO» con il contributo di Bayer International (in corso)

«Treatment of Metastatic prostate cancer castration resistant (mCRPC) with 223RaCl2: response evaluation with a novel tracer 68Ga PSMA PET molecular imaging (CALIPSO).

McHUMOR by T. McCracken



"Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests."

Imaging molecolare

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

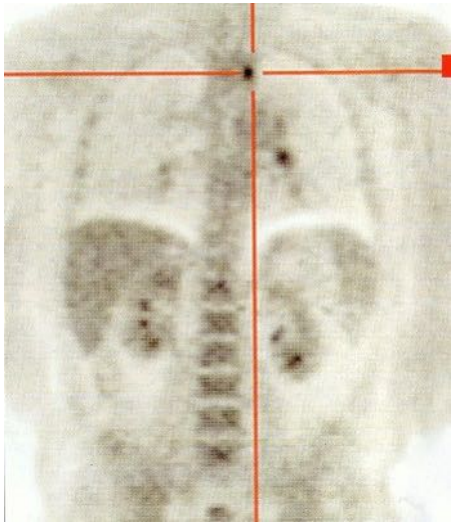
Thakur & Lentle, 2005

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.

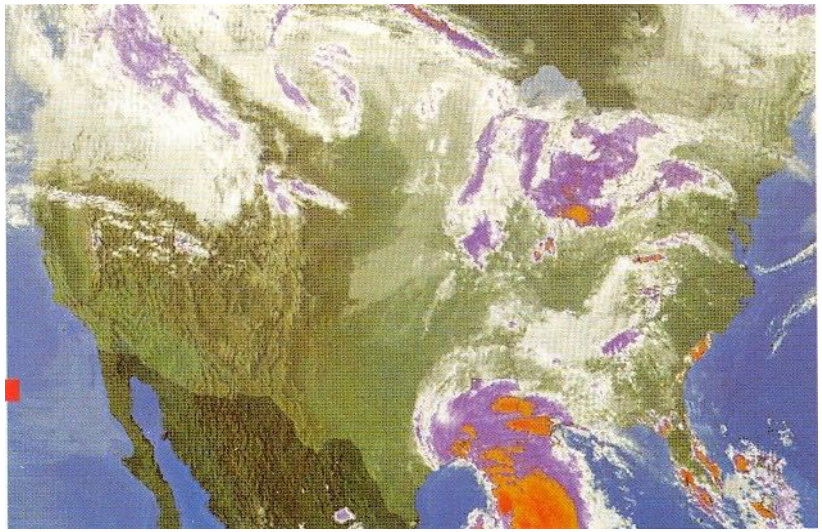
Weissleder & Mahmood, 2001

Imaging morfologico e funzionale



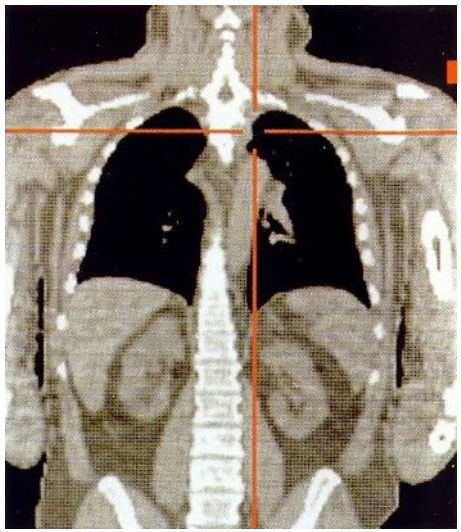
PET

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

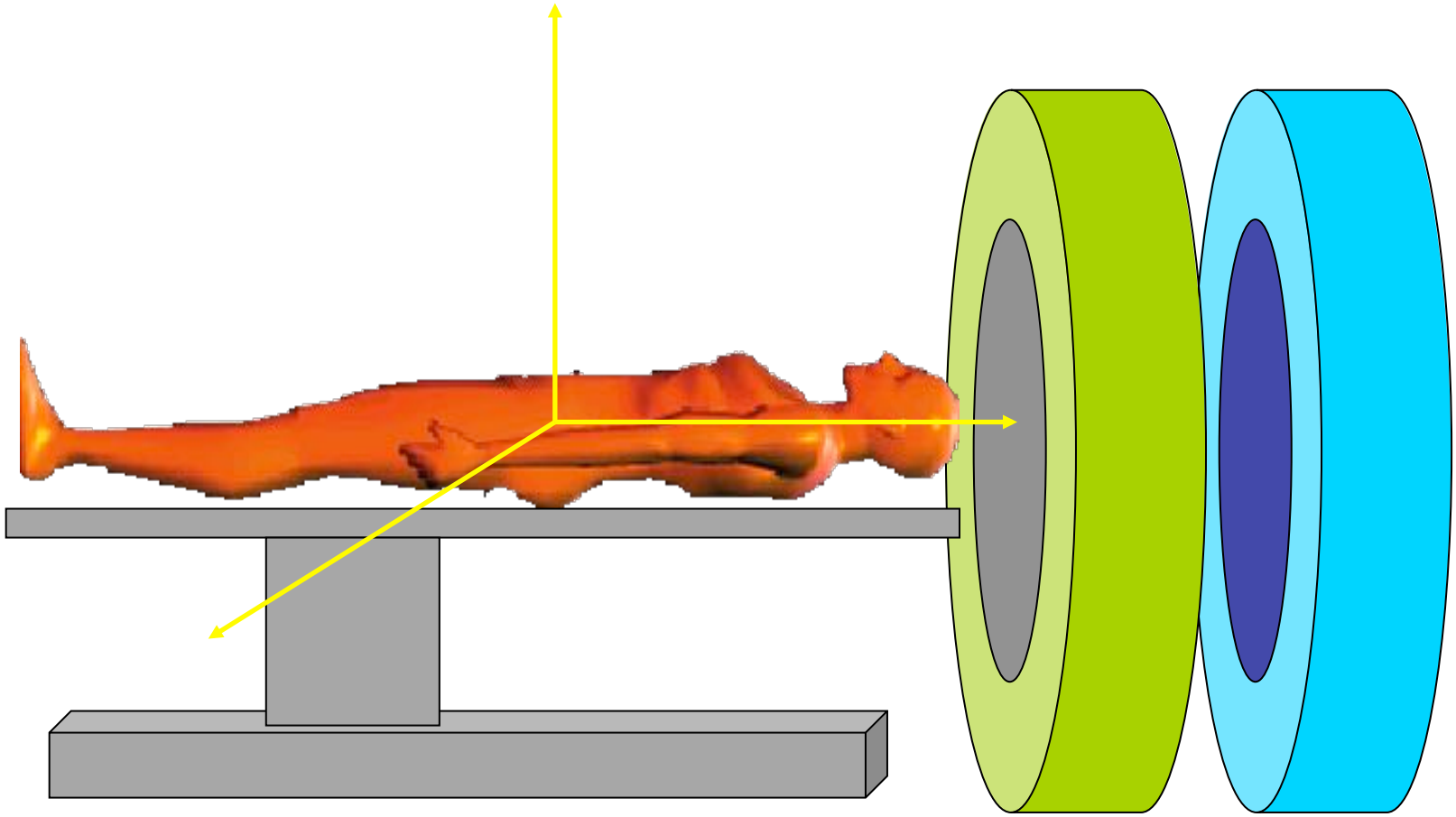
CT



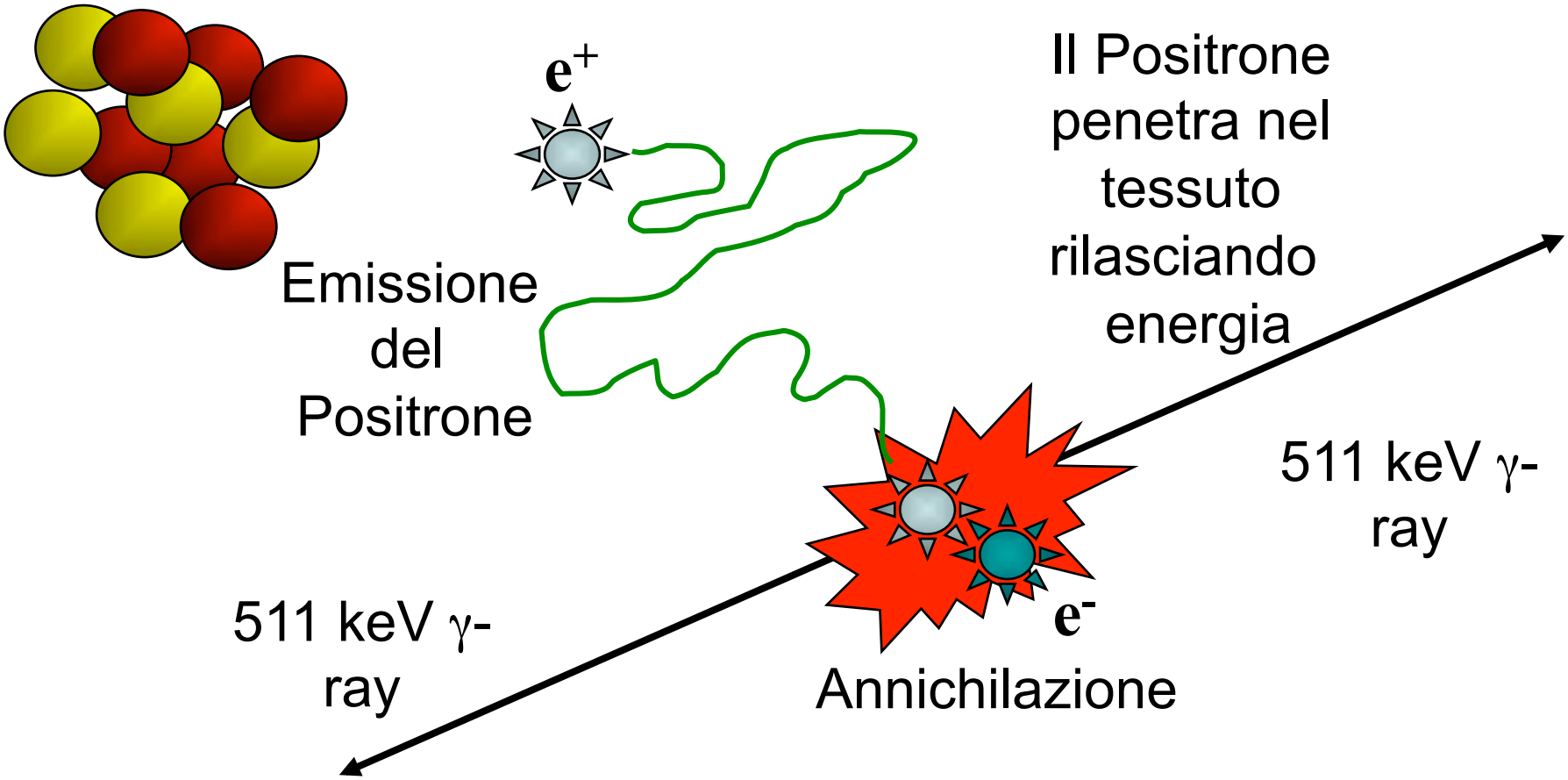
Un'immagine CT mostra precisamente l'anatomia del corpo ma non ne rivela la funzionalità chimica

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

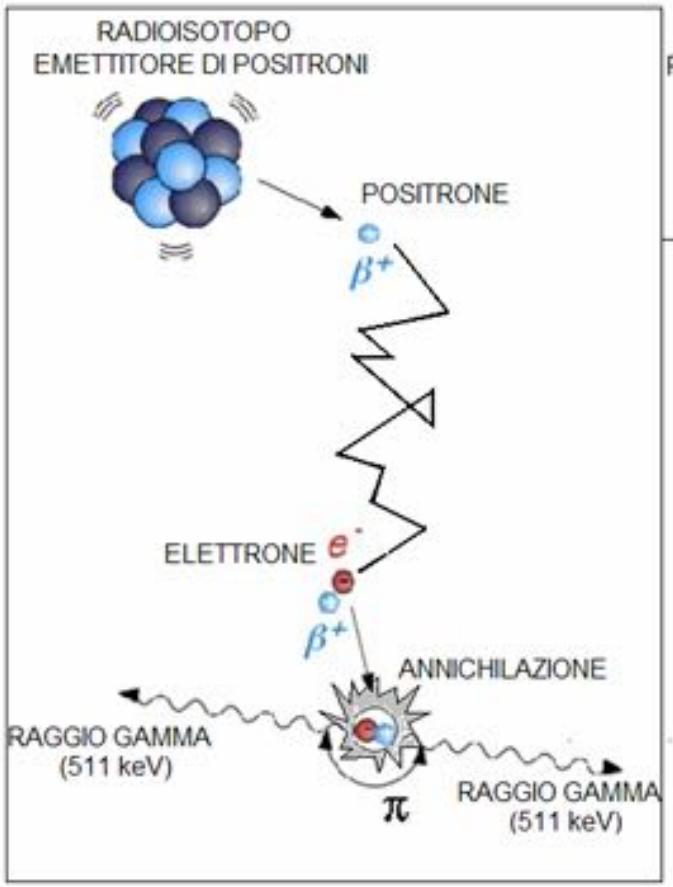
PET/CT



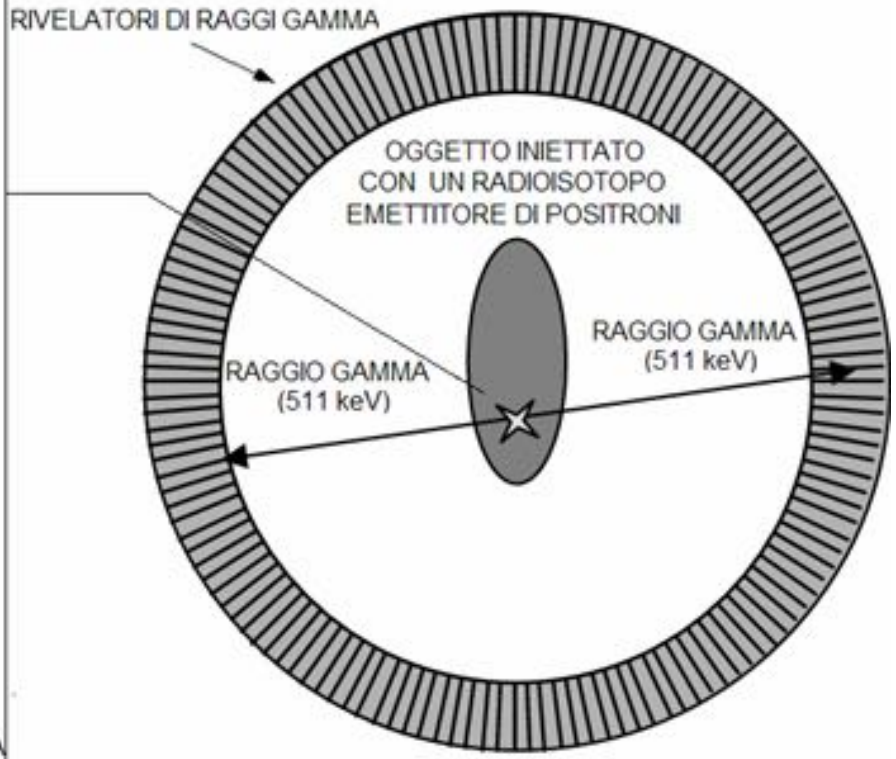
La Reazione di annichilazione



Principio della Tomografia a Emissione di Positroni (PET)



EMISSIONE DEL POSITRONE E
ANNICHILAZIONE POSITRONE ELETTRONE



TOMOGRAFO PET

Positron Emission Tomography

La PET in estrema sintesi

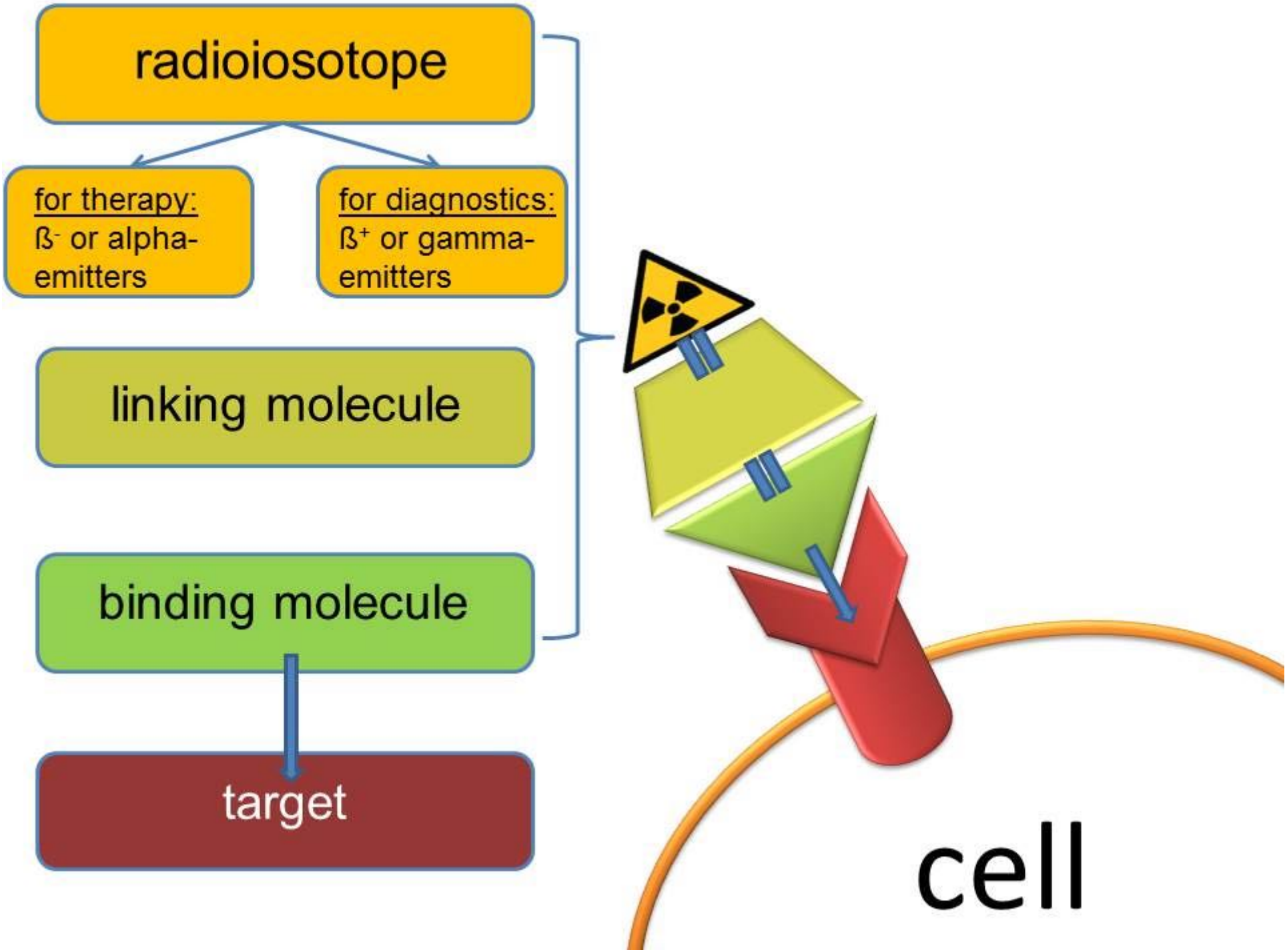
Radiofarmaco marcato con nuclide emittente β^+ somministrato al paziente

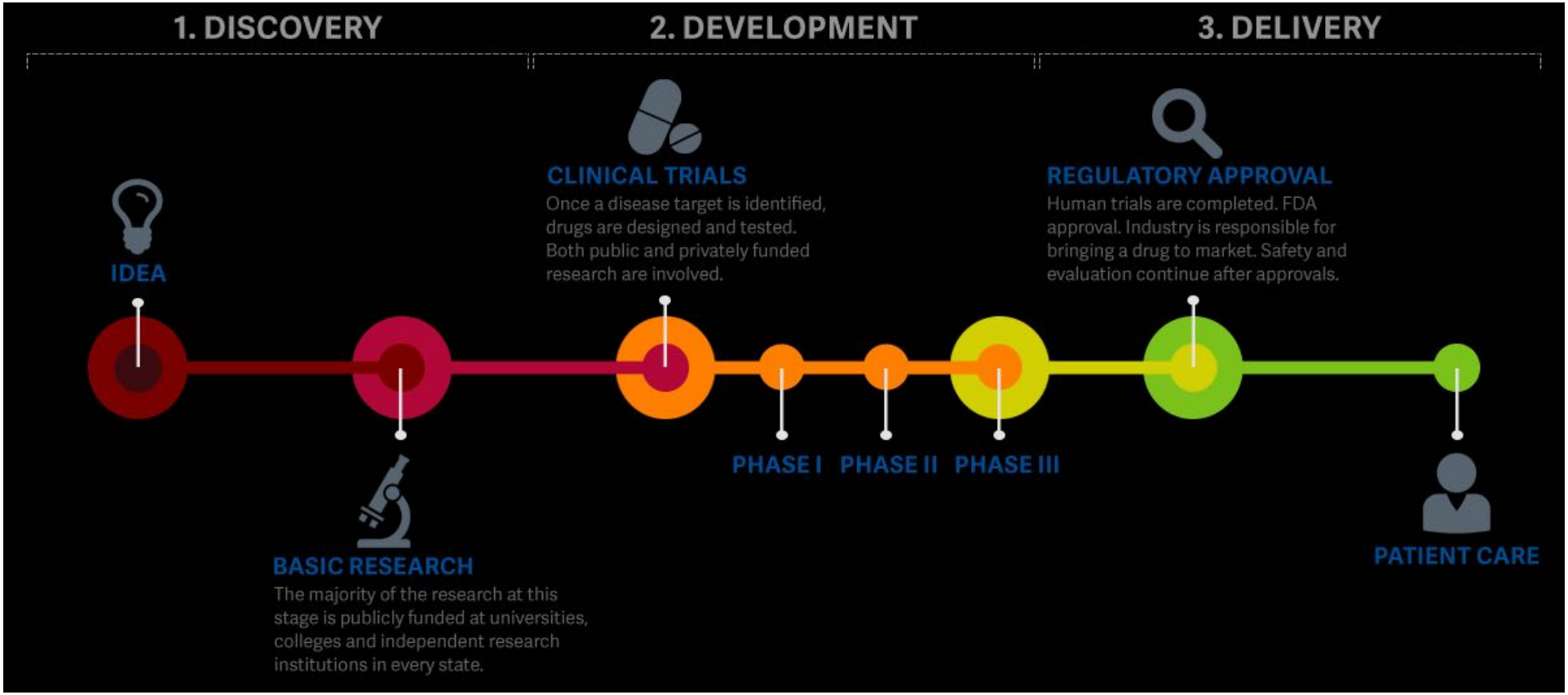
Emissione isotropa di β+ che localizza la distribuzione funzionale di radiofarmaco

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


radioiosotope
for therapy:
ß- or alpha-emitters
for diagnostics:
ß+ or gamma-emitters
linking molecule
binding molecule
target
cell


1. DISCOVERY
2. DEVELOPMENT
3. DELIVERY
IDEA
BASIC RESEARCH
The majority of the research at this stage is publicly funded at universities, colleges and independent research institutions in every state.
CLINICAL TRIALS
Once a disease target is identified, drugs are designed and tested. Both public and privately funded research are involved.
PHASE I
PHASE II
PHASE III
REGULATORY APPROVAL
Human trials are completed. FDA approval. Industry is responsible for bringing a drug to market. Safety and evaluation continue after approvals.
PATIENT CARE

PET Imaging of Prostate Cancer Using Carbon-11-Choline

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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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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

Tracer	Radionuclide	Synthesis	Mechanism / Target	Number of not yet recruiting, recruiting, active, invited, or completed clinical trials using the tracer for PCa on clinicaltrials.gov (as of 07/17)
PSMA				
DCFPyL	18F	Cyclotron	PSMA	17
HBED-CC-PSMA (PSMA-11)	68Ga	Generator	PSMA	15
J591	89Zr	Cyclotron	PSMA (ImmunoPET)	4
IAB2M	89Zr	Cyclotron	PSMA (immunoPET)	2
P16-093	68Ga	Generator	PSMA	1
Lipid metabolism				
Choline, Fluorocholine, Ethylcholine, Fluoroethylcholine	18F/11C	Cyclotron	Membrane turnover	35
Acetate	11C	Cyclotron	Lipid synthesis	9
Nutrient Transport				
FDG	18F	Cyclotron	Glucose transport	25
Fluciclovine (FACBC, axumin)	18F	Cyclotron	Amino Acid Transport	13
MeAIB	11C	Cyclotron	Amino Acid Transport	1
Methionine	11C	Cyclotron	Amino Acid Transport	1
Sarcosine	11C	Cyclotron	Amino Acid Transport	1
GRPR Targeting				
RM2	68Ga	Generator	Gastrin Releasing Peptide Receptor (GRPR) antagonist	4
MJ9	68Ga	Generator	Gastrin Releasing Peptide Receptor (GRPR) antagonist	1
RM26	68Ga	Generator	Gastrin Releasing Peptide Receptor (GRPR) antagonist	1
MATBBN	18F	Cyclotron	Gastrin Releasing Peptide Receptor (GRPR) antagonist	1
BBN-RGD	68Ga	Generator	Gastrin Releasing Peptide Receptor (GRPR) and avB3 integrin	1
Hypoxia				
FMISO	18F	Cyclotron	Hypoxia	1
HX4	18F	Cyclotron	Hypoxia	1
FAZA	18F	Cyclotron	Hypoxia	1
Bone Targeting				
NaF	18F	Cyclotron	Osteoblast activity	14
P15-041	68Ga	Generator	Bone	1
DNA Synthesis				
FMAU	18F	Cyclotron	DNA synthesis	3
FLT	18F	Cyclotron	DNA synthesis	4
Miscellaneous				
FDHT, FMDHT	18F	Cyclotron	Androgen Receptor	4
AE105	68Ga/64Cu	Generator/Cyclotron	Urokinase Plasminogen Activator Receptor (uPAR)	3
TP3805	64Cu	Cyclotron	VPAC1	2
Gallium citrate	68Ga	Generator	Multiple mechanisms	1
MSTP2109A	89Zr	Cyclotron	STEAP1 (immunoPET)	1

Joseph Ippolito, M.D., Ph.D., ver 07/24/2017

New Agents and Techniques for Imaging Prostate Cancer

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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

Patients with a diagnosis of prostate cancer fall into two categories

1. those who have **untreated** pathologically confirmed disease for whom accurate **staging** remains a challenge

2. those with a rising prostate-specific antigen (PSA) after treatment, for whom targeted "**salvage" secondary therapies** might be life-saving if the site(s) of recurrence can be defined.

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.

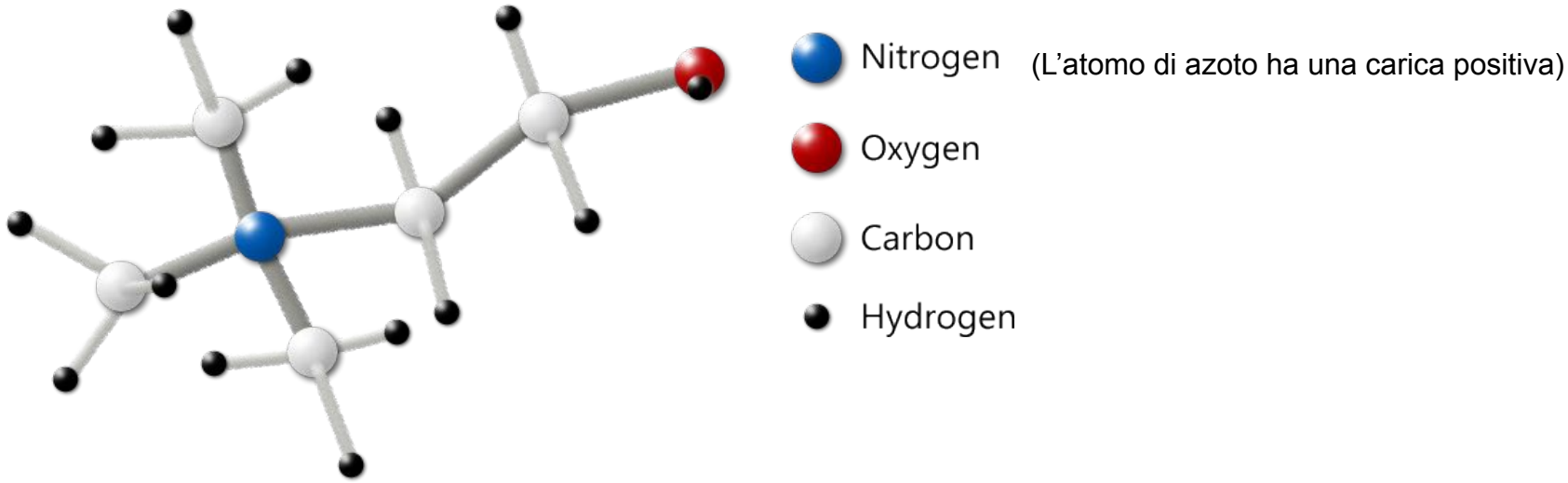
• La maggior parte degli studi compiuti riguardano il tumore della prostata: **la PET/CT con Colina è utile nello studio delle recidive biochimiche di malattia e può giocare un ruolo nella stratificazione dei pazienti riguardo alle recidive locoregionali ed al coinvolgimento linfonodale e scheletrico**.

• 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.

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



(L’atomo di azoto ha una carica positiva)

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.

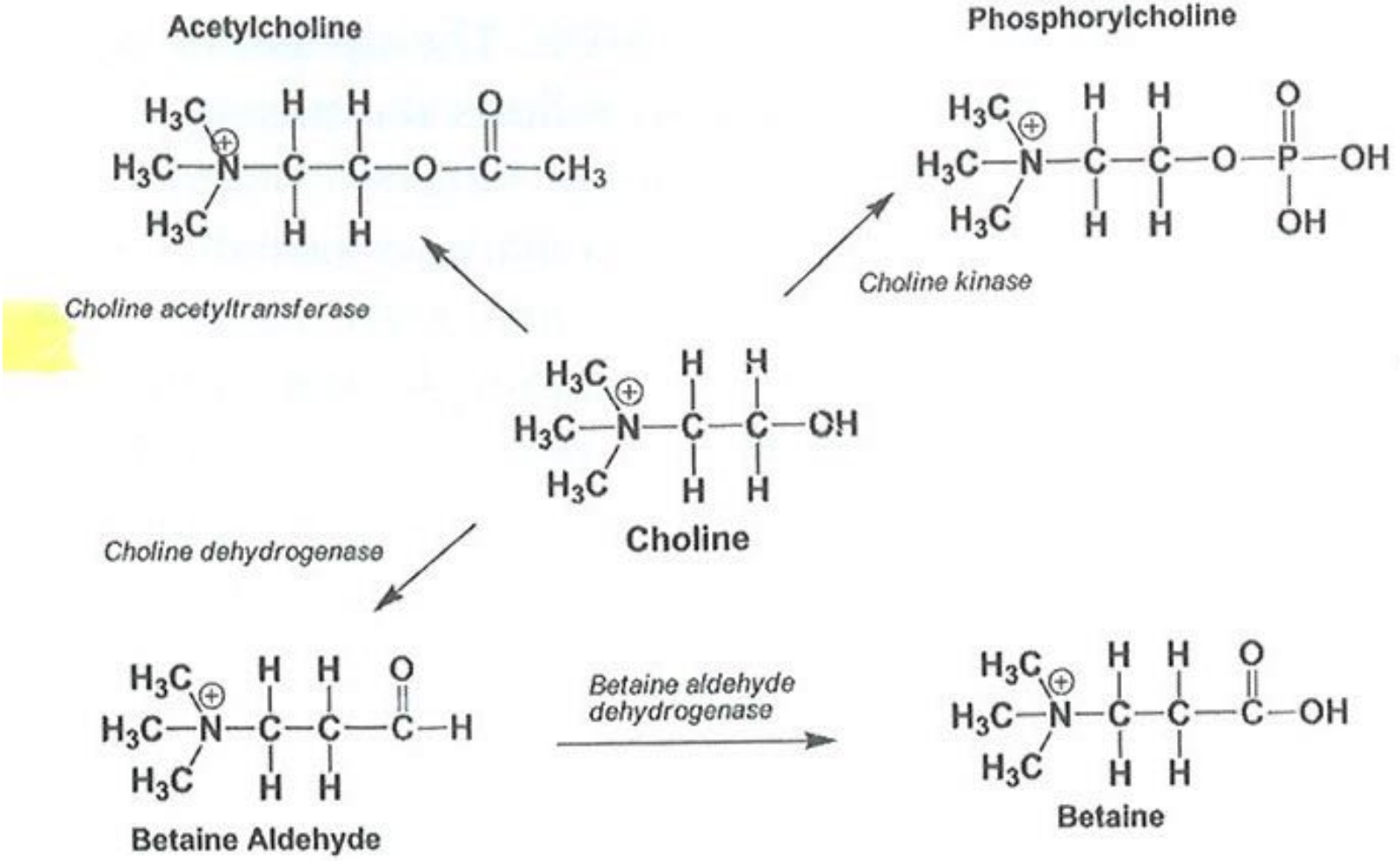
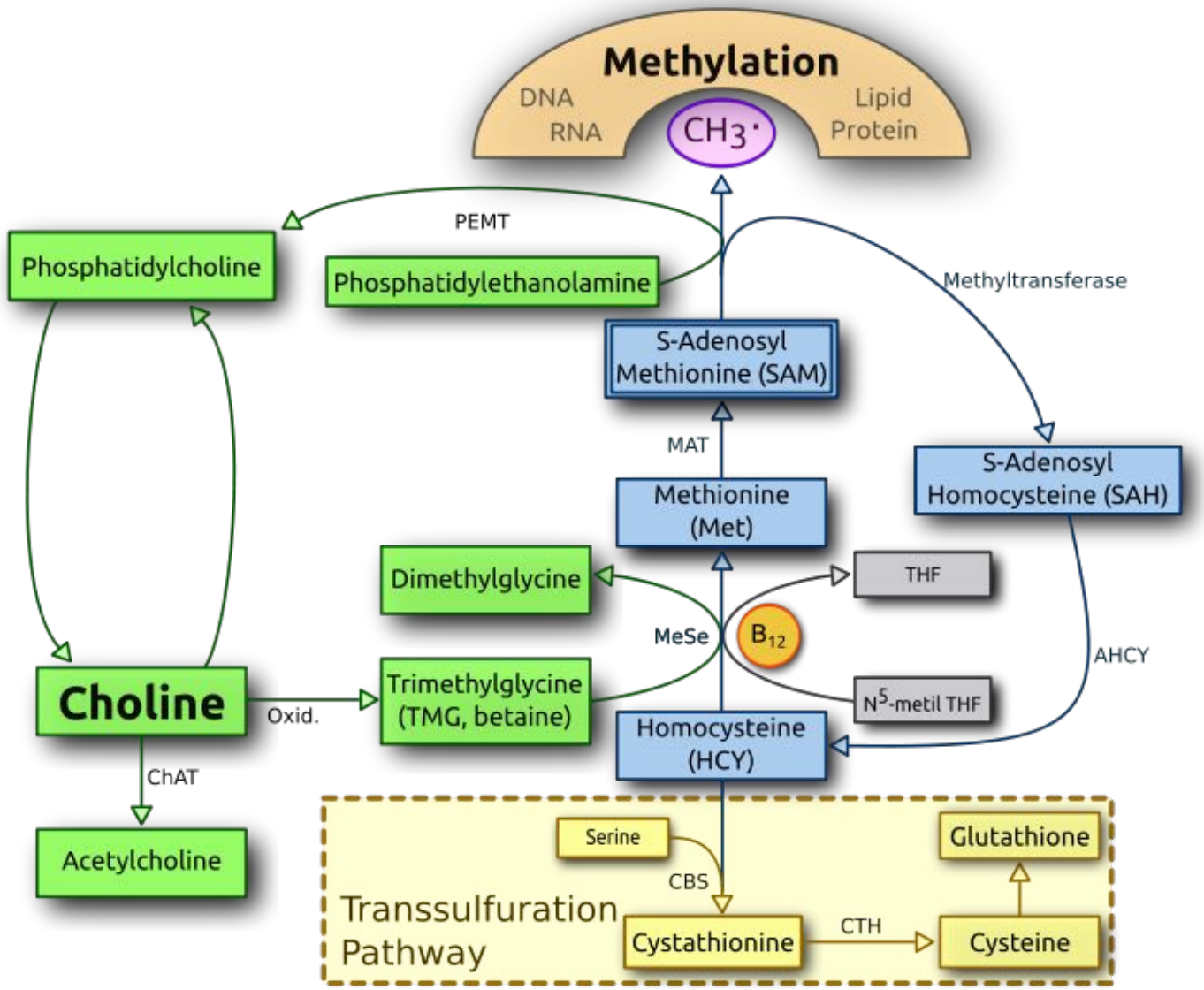


Figure 5 The cellular metabolism of choline: It is phosphorylated, acetylated, and oxidized. Phosphorylcholine is further converted to phophatidylcholine (lecithin), which is then incorporated into membrane synthesis.



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.

PET/CT – Colina

•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.

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

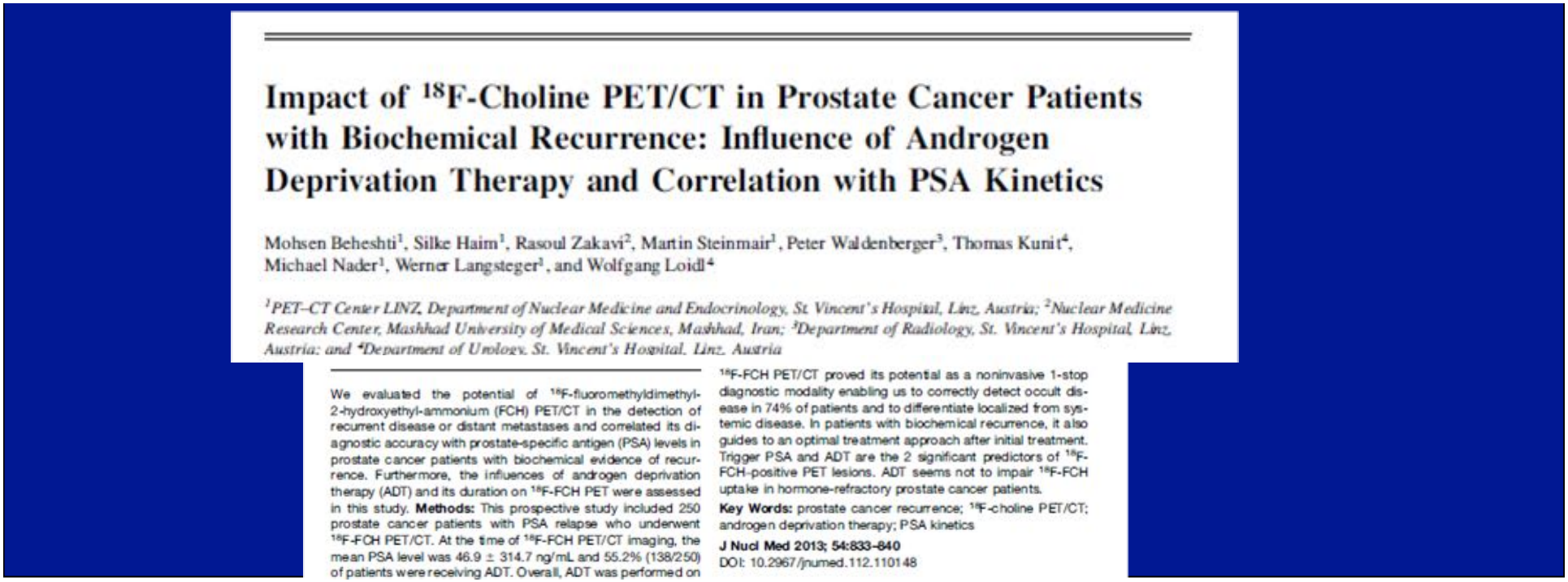
Tracer	Authors	Years	*N*	PSA, median (range) (ng/mL)	Sen (%)	Spe (%)	Analysis
^{11}C-Cho	Schiavina et al. [29]	2008	57	16.5 (0.6–70)	60	98	Patient-based
					41	99	Node-based
	Contractor et al. [30]	2011	28	44.3 (8.1–209)	78	82	Patient-based
					52	98	Node-based
	Budiharto et al. [31]	2011	36	14.6 (1.5–70.9)	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



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

•18F-FCH PET/CT proved its potential as a **noninvasive 1-stop shop diagnostic modality** to correctly differentiate localized from systemic disease and to guide to the optimal treatment approach in prostate cancer patients with biochemical recurrence.

•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 – …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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^{68}Ga-Labeled Inhibitors of Prostate-Specific Membrane antigen (PSMA) for Imaging Prostate Cancer

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Abstract

Gallium-68 is a generator-produced radionuclide for positron emission tomography (PET) that is being increasingly used for radiolabeling of tumor-targeting peptides. Compounds [^{68}Ga]**3** and [^{68}Ga]**6** are high-affinity, urea-based inhibitors of the prostate-specific membrane antigen (PSMA) that were synthesized in decay-uncorrected yields ranging from 60 – 70% and radiochemical purities of more than 99%. Compound [^{68}Ga]**3** demonstrated 3.78 ± 0.90 percent injected dose per gram of tissue (%ID/g) within PSMA+ PIP tumor at 30 min post-injection, while [^{68}Ga]**6** showed a two hour PSMA+ PIP tumor uptake value of 3.29 ± 0.77%ID/g. Target (PSMA+ PIP) to non-target (PSMA− flu) ratios were 4.6 and 18.3, respectively, at those time points. Both compounds delineated tumor clearly by small animal PET. The urea series of imaging agents for PSMA can be radiolabeled with ^{68}Ga, a cyclotron-free isotope useful for clinical PET studies, with maintenance of target specificity.

Keywords

gallium; molecular imaging; positron emission tomography; prostate-specific membrane antigen; radiopharmaceutical

Introduction

Prostate cancer is the most commonly diagnosed malignancy and the second leading cause of cancer-related death in men in the United States.[1] In 2009, approximately 192,000 men were diagnosed with prostate cancer with 27,000 succumbing to the disease. The integral membrane protein prostate-specific membrane antigen (PSMA) is becoming increasingly recognized as a viable target for imaging and therapy of prostate and other forms of cancer.[2, 3]

Because of its similarity to Fe(III), Ga(III) complexes are emerging as an interesting alternative to Pt-based anticancer agents.[4–6] From a diagnostic standpoint, positron-emitting versions of Ga(III) can be used for tumor imaging.[7–9] Recently, the application of ^{68}Ga-labeled peptides has attracted considerable interest for cancer imaging because of the physical characteristics of ^{68}Ga.[10] ^{68}Ga is available from an in-house ^{68}Ge/^{68}Ga generator

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Supporting Information Available
Additional figures demonstrating the HPLC traces for [^{68}Ga]**3** and [^{68}Ga]**6** as well as the high-resolution mass spectra for these compounds are provided. Also provided is a figure containing a PET blocking study for [^{68}Ga]**3**. These materials are available free of charge *via* the Internet at http://pubs.acs.org.

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PET Imaging in Prostate Cancer: Focus on Prostate-Specific Membrane Antigen

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Abstract

Prostate cancer (PCa) is the second leading cause of cancer-related death in American men. Positron emission tomography/computed tomography (PET/CT) with emerging radiopharmaceuticals promises accurate staging of primary disease, restaging of recurrent disease, detection of metastatic lesions and, ultimately, for predicting the aggressiveness of disease. Prostate-specific membrane antigen (PSMA) is a well-characterized imaging biomarker of PCa. Because PSMA levels are directly related to androgen independence, metastasis and progression, PSMA could prove an important target for the development of new radiopharmaceuticals for PET. Preclinical data for new PSMA-based radiotracers are discussed and include new ^{89}Zr- and ^{64}Cu-labeled anti-PSMA antibodies and antibody fragments, ^{64}Cu-labeled aptamers, and ^{11}C-, ^{18}F-, ^{68}Ga-, ^{64}Cu-, and ^{86}Y-labeled low molecular weight inhibitors of PSMA. Several of these agents, namely ^{68}Ga-HBED-CC conjugate **15**, ^{18}F-DCFBC **8**, and BAY1075553 are particularly promising, each having detected sites of PCa in initial clinical studies. These early clinical results suggest that PET/CT using PSMA-targeted agents, especially with compounds of low molecular weight, will make valuable contributions to the management of PCa.

Keywords

DCFBC; molecular imaging; positron emission tomography; PSMA; radiopharmaceutical

INTRODUCTION

Broadly defined, molecular imaging is the non-invasive detection and measurement of cellular and molecular processes in whole living beings using a variety of modalities including positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance (MR), computed tomography (CT), ultrasound,

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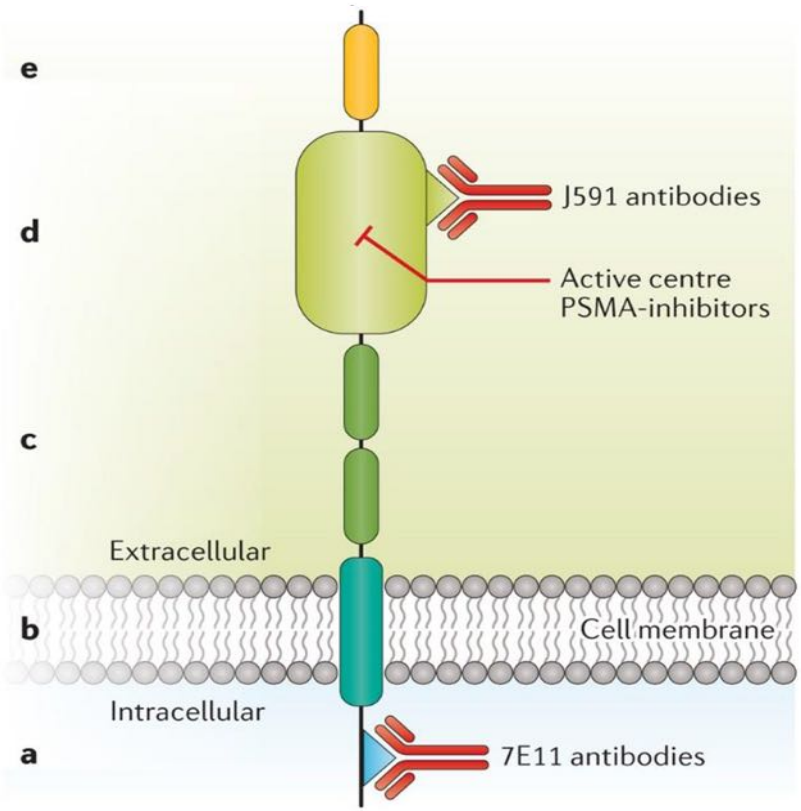
CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

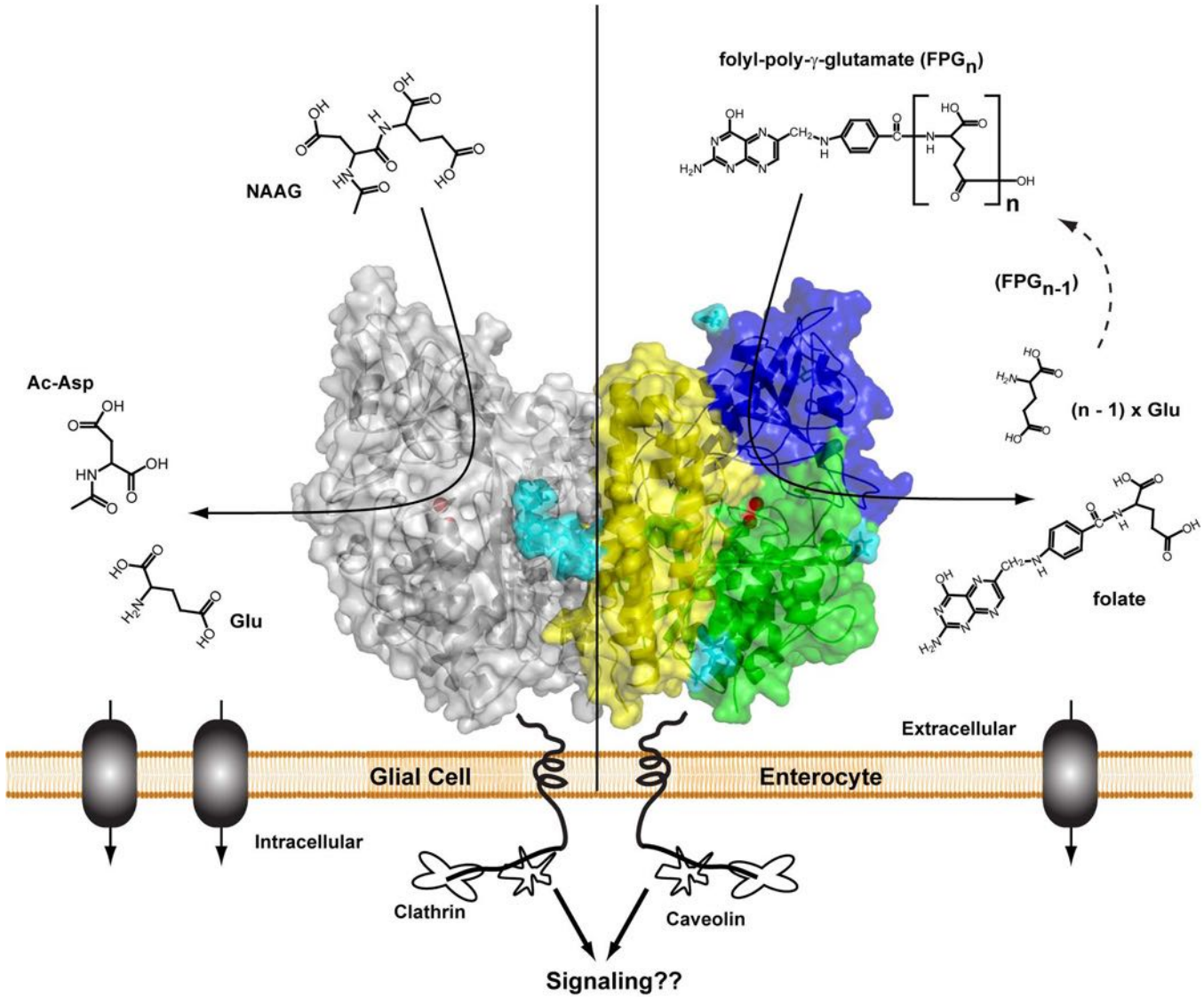
DISCLOSURE

"Part of information included in this article has been previously published in "[Current Medicinal Chemistry VOLUME: 19 ISSUE: 9 DOI: 10.2174/092986712 799462 612 <http://dx.doi.org/10.2174/092986712799462612>]" [http://www.eurekaselect.com/76655/article <http://www.eurekaselect.com/76655/article>]".



Nature Reviews | Urology

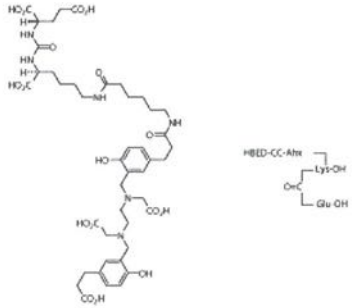
Figure 1 | **The structure of prostate-specific membrane antigen (PSMA), its binding sites for PSMA ligands and the most frequently used antibodies. a** | The short intracellular domain containing a binding site that can be targeted with 7E11 antibodies. **b** | The hydrophobic transmembrane region. The extracellular part of PSMA consists of section **c** | that contains two domains of unknown function and proline-rich and glycine-rich regions as linkers, **d** | that is the large catalytic domain, which contains a binding site for J591 antibodies as well as the active substrate recognition site that is being targeting by PSMA inhibitors and **e** | the final domain of unknown function to which a helical dimerization domain is localized.


NERVOUS SYSTEM
SMALL INTESTINE
folyl-poly-γ-glutamate (FPG$_n$)
NAAG
(FPG$_{n-1}$)
(n - 1) x Glu
Ac-Asp
Glu
folate
Extracellular
Glial Cell
Enterocyte
Intracellular
Clathrin
Caveolin
Signaling??

Catalogue Number	Product	Order number / Unit

9921 DKFZ-PSMA-11 (GMP)

Please inquire for customized filling and bulk quantities.



Precursor for [^{68}Ga]DKFZ-GaPSMA-11
PSMA: prostate-specific membrane antigen

Manufactured according to GMP requirements for APIs
for use in clinical trials (ICH Q7 chapter 19)

Molar Mass: 947.0 (net peptide)

$C_{44}H_{62}N_6O_{17}$

[1366302-52-4]

Colourless to off-white solid packaged in dark glass screw cap vials.

Purity: ≥ 95 %

Certificates:
CoA; MS; HPLC

Chemical Name:
For chemical information please refer to product number 9920.

Synonymes:
Please refer to product number 9220.

Literature:
For literature references please refer to product number 9220.

date of product catalogue issue: 04 October 2013

Eur J Nucl Med Mol Imaging (2014) 41:11–20
DOI 10.1007/s00259-013-2525-5

ORIGINAL ARTICLE

Comparison of PET imaging with a ^{68}Ga-labelled PSMA ligand and ^{18}F-choline-based PET/CT for the diagnosis of recurrent prostate cancer

Ali Afshar-Oromieh · Christian M. Zechmann · Anna Malcher · Matthias Eder · Michael Eisenhut · Heinz G. Linhart · Tim Holland-Letz · Boris A. Hadaschik · Frederik L. Giesel · Jürgen Debus · Uwe Haberkorn

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Abstract
Purpose Positron emission tomography (PET) with choline tracers has found widespread use for the diagnosis of prostate cancer (PC). However, choline metabolism is not increased in a considerable number of cases, whereas prostate-specific membrane antigen (PSMA) is overexpressed in most PCs. Therefore, a ^{68}Ga-labelled PSMA ligand could be superior to choline tracers by obtaining a high contrast. The aim of this study was to compare such a novel tracer with standard choline-based PET/CT.

Methods Thirty-seven patients with biochemical relapse of PC [mean prostate-specific antigen (PSA) 11.1±24.1 ng/ml, range 0.01–116] were retrospectively analysed after ^{18}F-fluoromethylcholine and ^{68}Ga-PSMA PET/CT within a time window of 30 days. Radiotracer uptake that was visually considered as PC was semi-quantitatively analysed by measuring the maximum standardized uptake values (SUV_{max}) of the scans acquired 1 h after injection of ^{68}Ga-PSMA complex solution (median 132 MBq, range 59–263 MBq) and ^{18}F-fluoromethylcholine (median 237 MBq, range 114–374 MBq),

A related editorial can be found at doi:10.1007/s00259-013-2573-x.

Electronic supplementary material The online version of this article (doi:10.1007/s00259-013-2525-5) contains supplementary material, which is available to authorized users.

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ORIGINAL ARTICLE

The diagnostic value of PET/CT imaging with the ^{68}Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer

Ali Afshar-Oromieh · Eleni Avtzi · Frederik L. Giesel · Tim Holland-Letz · Heinz G. Linhart · Matthias Eder · Michael Eisenhut · Silvan Boxler · Boris A. Hadaschik · Clemens Kratochwil · Wilko Weichert · Klaus Kopka · Jürgen Debus · Uwe Haberkorn

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Abstract
Purpose Since the introduction of positron emission tomography (PET) imaging with ^{68}Ga-PSMA-HBED-CC (=^{68}Ga-DKFZ-PSMA-11), this method has been regarded as a significant step forward in the diagnosis of recurrent prostate cancer (PCa). However, published data exist for small patient cohorts only. The aim of this evaluation was to analyse the diagnostic value of ^{68}Ga-PSMA-ligand PET/CT in a large cohort and the influence of several possibly interacting variables.
Methods We performed a retrospective analysis in 319 patients who underwent ^{68}Ga-PSMA-ligand PET/CT from 2011 to 2014. Potential influences of several factors such as prostate-specific antigen (PSA) level and doubling time (DT), Gleason score (GSC), androgen deprivation therapy

Electronic supplementary material The online version of this article (doi:10.1007/s00259-014-2949-6) contains supplementary material, which is available to authorized users.

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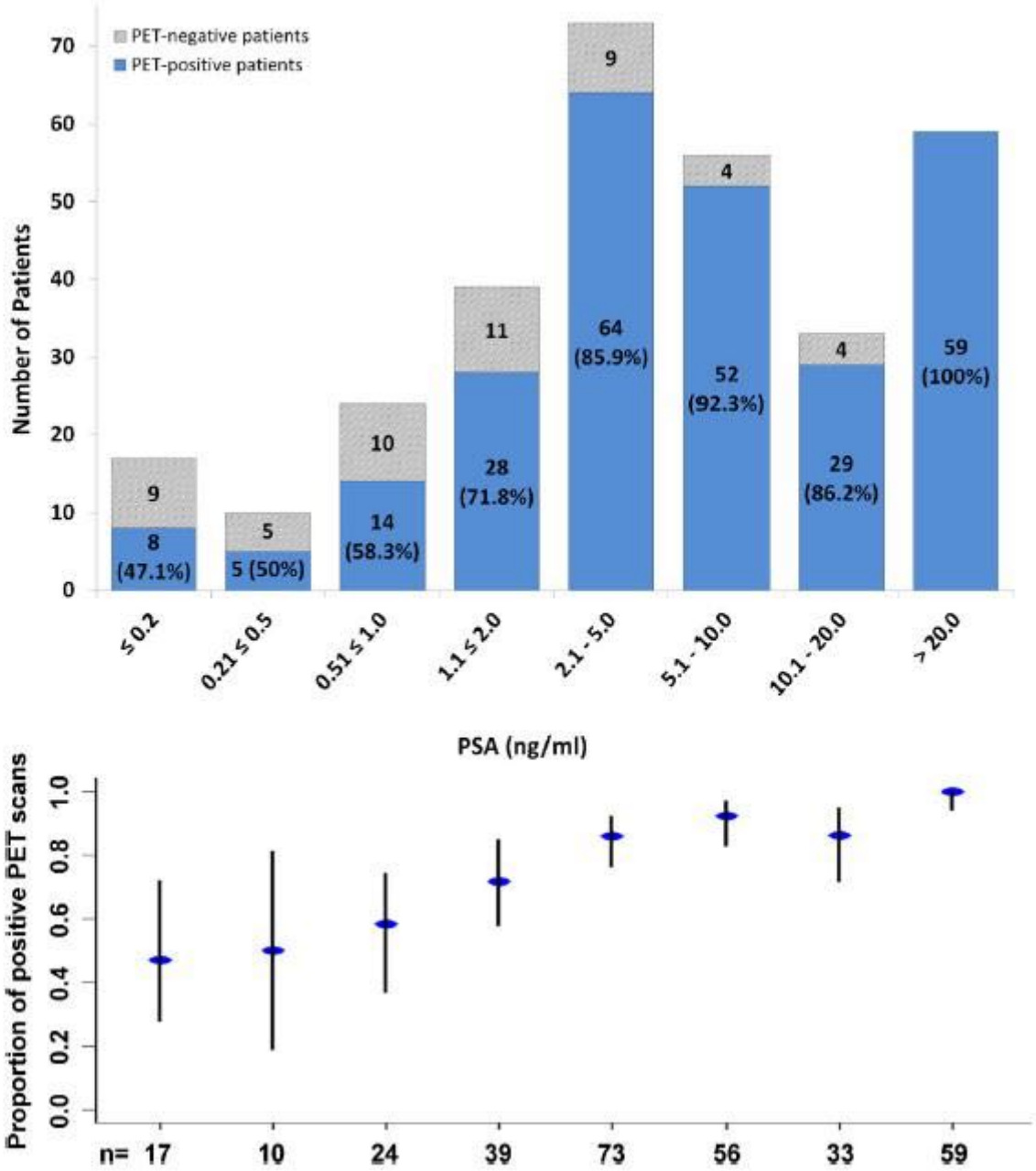

Fig. 3 Probability of a pathological ^{68}Ga-PSMA-ligand PET/CT as histogram (*above*) and plot of the rates of pathological PET/CTs with confidence intervals (*below*) depending on PSA levels in 311 patients. *Blue columns* include the number of pathological PET/CTs and their rate in %

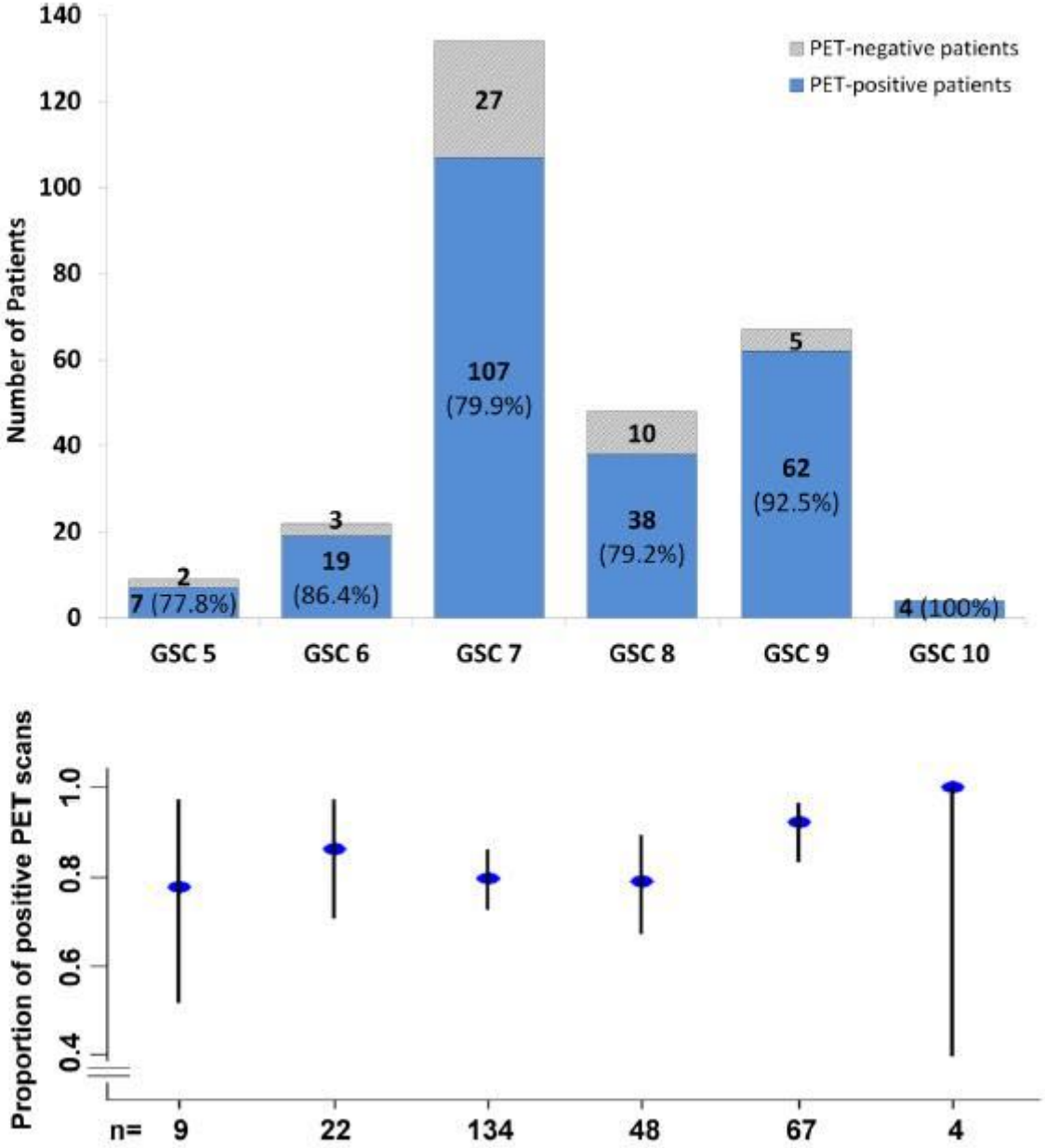

Fig. 4 Probability of a pathological ^{68}Ga-PSMA-ligand PET/CT as histogram (*above*) and plot of the rates of pathological PET/CTs with confidence intervals (*below*) depending on GSC in 284 patients. *Blue columns* include the number of pathological PET/CTs and their rate in %

Evaluation of Hybrid ^{68}Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy

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The expression of prostate-specific membrane antigen (PSMA) is increased in prostate cancer. Recently, ^{68}Ga-PSMA (Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga(HBED-CC)]) was developed as a PSMA ligand. The aim of this study was to investigate the detection rate of ^{68}Ga-PSMA PET/CT in patients with biochemical recurrence after radical prostatectomy. **Methods:** Two hundred forty-eight of 393 patients were evaluable for a retrospective analysis. Median prostate-specific antigen (PSA) level was 1.99 ng/mL (range, 0.2–59.4 ng/mL). All patients underwent contrast-enhanced PET/CT after injection of 155 ± 27 MBq of ^{68}Ga-PSMA ligand. The detection rates were correlated with PSA level and PSA kinetics. The influence of antihormonal treatment, primary Gleason score, and contribution of PET and morphologic imaging to the final diagnosis were assessed. **Results:** Two hundred twenty-two (89.5%) patients showed pathologic findings in ^{68}Ga-PSMA ligand PET/CT. The detection rates were 96.8%, 93.0%, 72.7%, and 57.9% for PSA levels of ≥2, 1 to <2, 0.5 to <1, and 0.2 to <0.5 ng/mL, respectively. Whereas detection rates increased with a higher PSA velocity (81.8%, 82.4%, 92.1%, and 100% in <1, 1 to <2, 2 to <5, and ≥5 ng/mL/y, respectively), no significant association could be found for PSA doubling time (82.7%, 96.2%, and 90.7% in >6, 4–6, and <4 mo, respectively). ^{68}Ga-PSMA ligand PET (as compared with CT) exclusively provided pathologic findings in 81 (32.7%) patients. In 61 (24.6%) patients, it exclusively identified additional involved regions. In higher Gleason score (≤7 vs. ≥8), detection efficacy was significantly increased (P = 0.0190). No significant difference in detection efficacy was present regarding antiandrogen therapy (P = 0.0783). **Conclusion:** Hybrid ^{68}Ga-PSMA ligand PET/CT shows substantially higher detection rates than reported for other imaging modalities. Most importantly, it reveals a high number of positive findings in the clinically important range of low PSA values (<0.5 ng/mL), which in many cases can substantially influence the further clinical management.

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Key Words: PSMA ligand; PET/CT; hybrid imaging; prostate cancer; biochemical recurrence

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In biochemical recurrence after radical prostatectomy (RP), an increase of the prostate-specific antigen (PSA) level precedes a clinically detectable recurrence by months to years (*1*). However, it cannot differentiate between local, regional, or systemic disease with the necessary precision that is essential for further disease management (*2*). Furthermore, PSA kinetics such as PSA velocity (PSAvel) and PSA doubling time (PSAdt) play an important role, with high PSA kinetics facilitating disease detection (*3*).

Morphologic imaging methods exhibit considerable limitations: sensitivity ranges between 25% and 54% for the detection of local recurrence by transrectal ultrasound or CT and is moderately improved using functional MR imaging techniques (*2,4*). The sensitivity for detection of lymph node metastases of CT or MR imaging is reported to be 30%–80% (*5*). Ultra-small particles of iron oxides proved to be effective; however, they have not been approved by regulatory authorities so far (*6*).

Various targets have been addressed by molecular imaging to improve the detection of recurrent prostate cancer (PC). For PET imaging, mainly ^{11}C- and ^{11}F-labeled choline derivates have been used in the past (*7–9*). However, especially in patients with PSA values below 3 ng/mL, the detection rate is only 40%–60% (*3,4,7*). Recently, a new molecular probe targeting, for example, the gastrin-releasing peptide receptor or the prostate-specific membrane antigen (PSMA), has been developed (*10–12*). PSMA is a membrane-bound enzyme with significantly elevated expression in PC cells in comparison to benign prostatic tissue (*13*). The localization of the catalytic site of PSMA in the extracellular domain allows the development of small specific inhibitors that are internalized after ligand binding (*14*). Older agents targeting the intracellular domain of PSMA showed disappointing results due to low image contrast, low sensitivity, or high background signal (*15*). The recent development

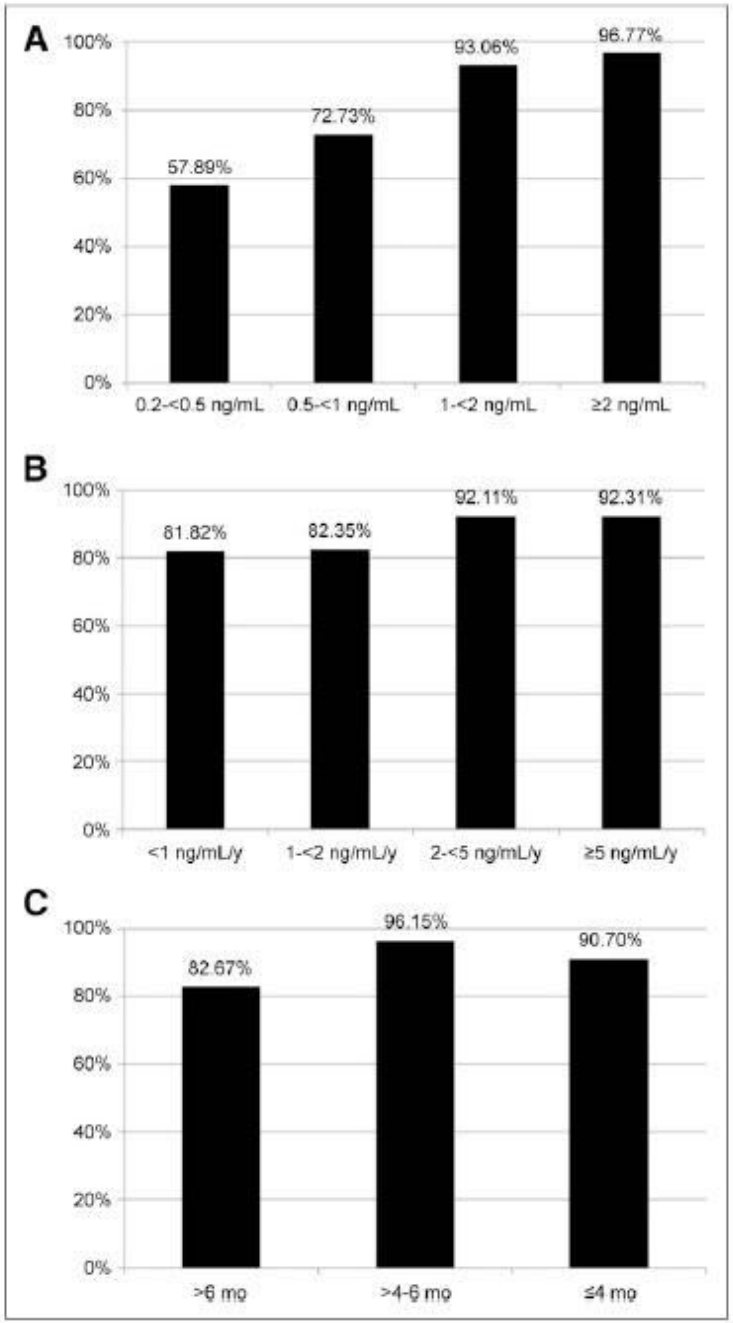

FIGURE 2. Detection rate of ^{68}Ga-PSMA ligand PET/CT in relation PSA level (A), PSAvel (B), and PSAdt (C).

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-017-3670-z

GUIDELINES

^{68}Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0

Wolfgang P. Fendler[1,2] · Matthias Eiber[1,3] · Mohsen Beheshti[4] · Jamshed Bomanji[5] · Francesco Ceci[6] · Steven Cho[7] · Frederik Giesel[8] · Uwe Haberkorn[8] · Thomas A. Hope[9] · Klaus Kopka[10] · Bernd J. Krause[11] · Felix M. Mottaghy[12,13] · Heiko Schöder[14] · John Sunderland[15] · Simon Wan[5] · Hans-Jürgen Wester[16] · Stefano Fanti[6] · Ken Herrmann[1,17]

Abstract The aim of this guideline is to provide standards for the recommendation, performance, interpretation and reporting of ^{68}Ga-PSMA PET/CT for prostate cancer imaging. These recommendations will help to improve accuracy, precision, and repeatability of ^{68}Ga-PSMA PET/CT for prostate cancer essentially needed for implementation of this modality in science and routine clinical practice.

Keywords PSMA · PET · Prostate cancer · Staging · Restaging · Guideline

Wolfgang P. Fendler and Matthias Eiber contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s00259-017-3670-z) contains supplementary material, which is available to authorized users.

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PSMA PET nella recente letteratura

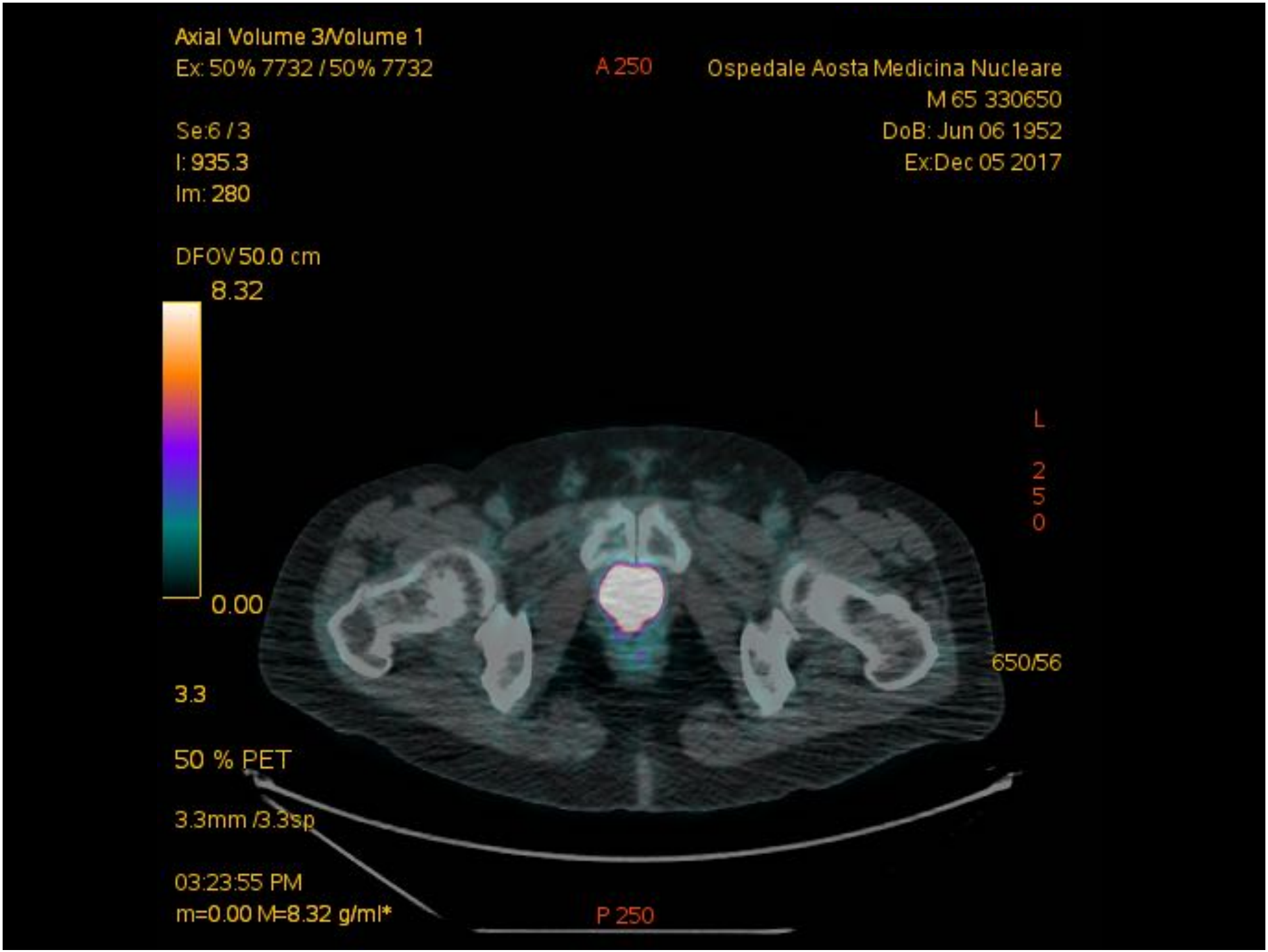
«PSMA PET PROSTATE»

Pubmed search «PSMA PET»: 562 risultati

Nel corso del 2017 risultano pubblicati 299 lavori (full papers e review)

QUESITO DIAGNOSTICO: recidiva biochimica di malattia PSA 1,42 ng/mL.

<u>In anamnesi</u>: 05/2014 prostatectomia radicale laparoscopica extraperitoneale Gleason score 6 (3+3), pT2c R0.
Confronto con PET colina del 21/06/17 e scintigrafia ossea del 18/07/17.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I: 935.3
Im: 280
DFOV 50.0 cm
8.32
0.00
L
2
5
0
650/56
3.3
50 % PET
3.3mm /3.3sp
03:23:55 PM
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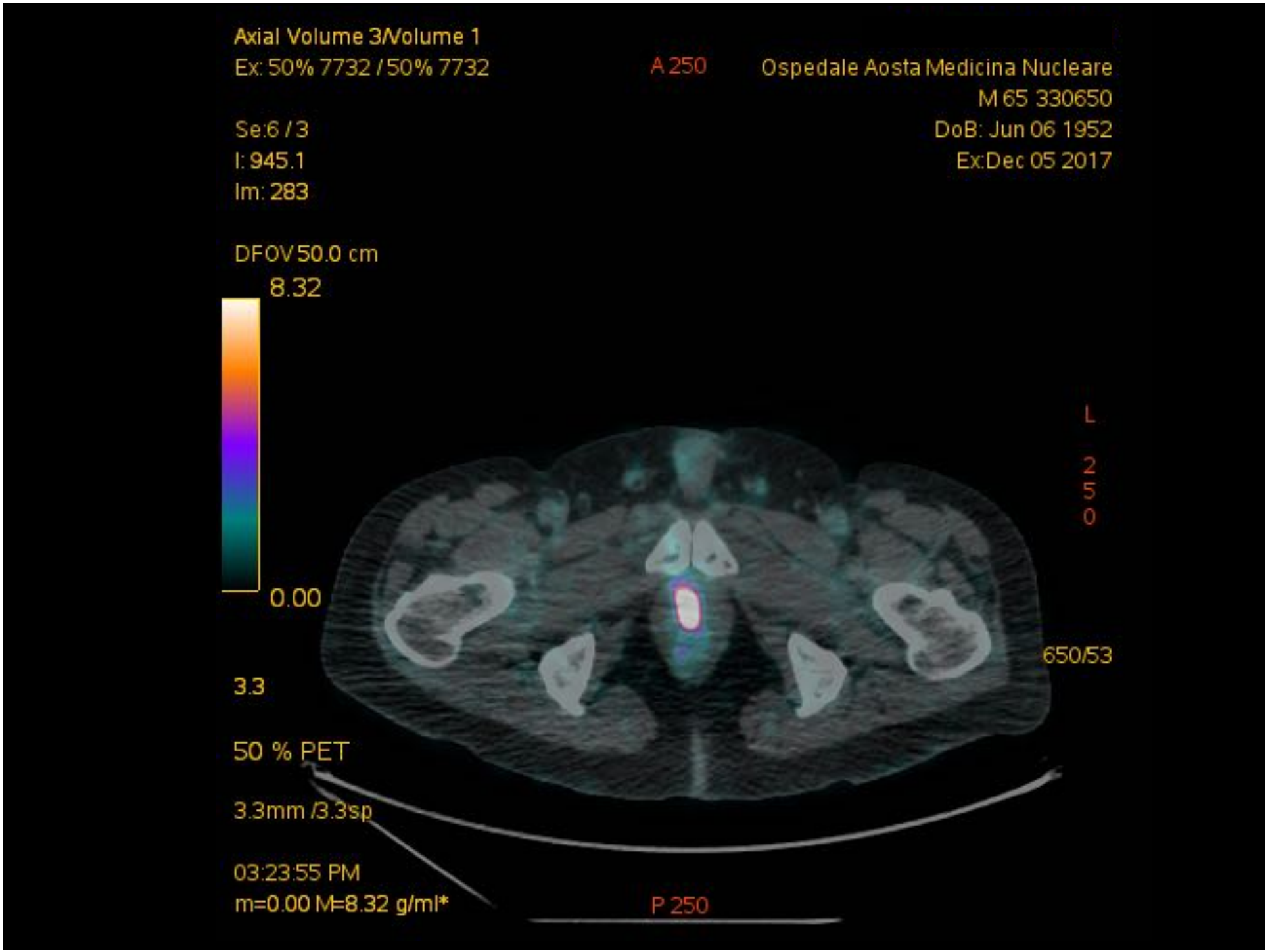
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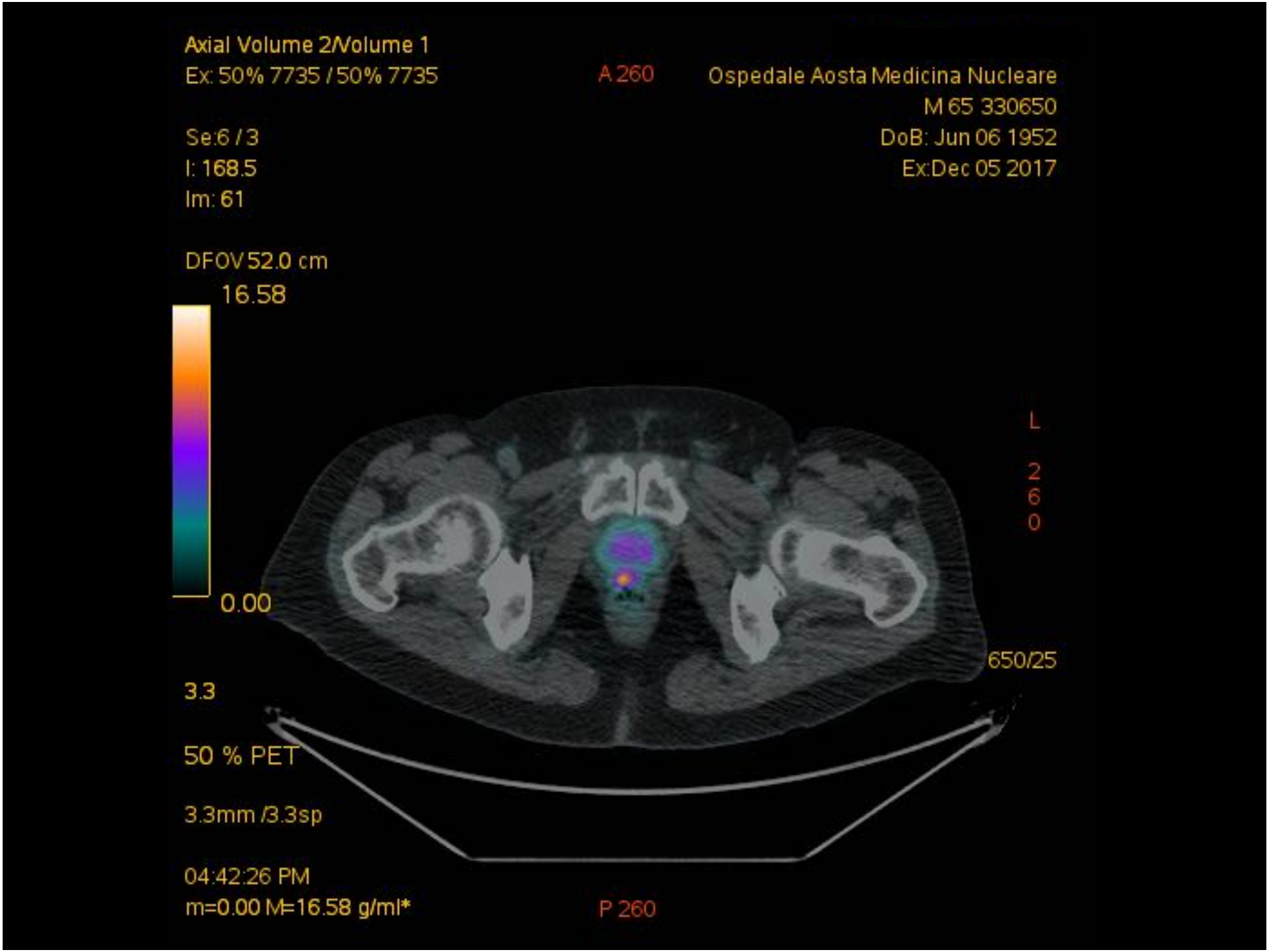
0.00
L
2
5
0
650/53
3.3
50 % PET
3.3mm /3.3sp
03:23:55 PM
m=0.00 M=8.32 g/ml*
P 250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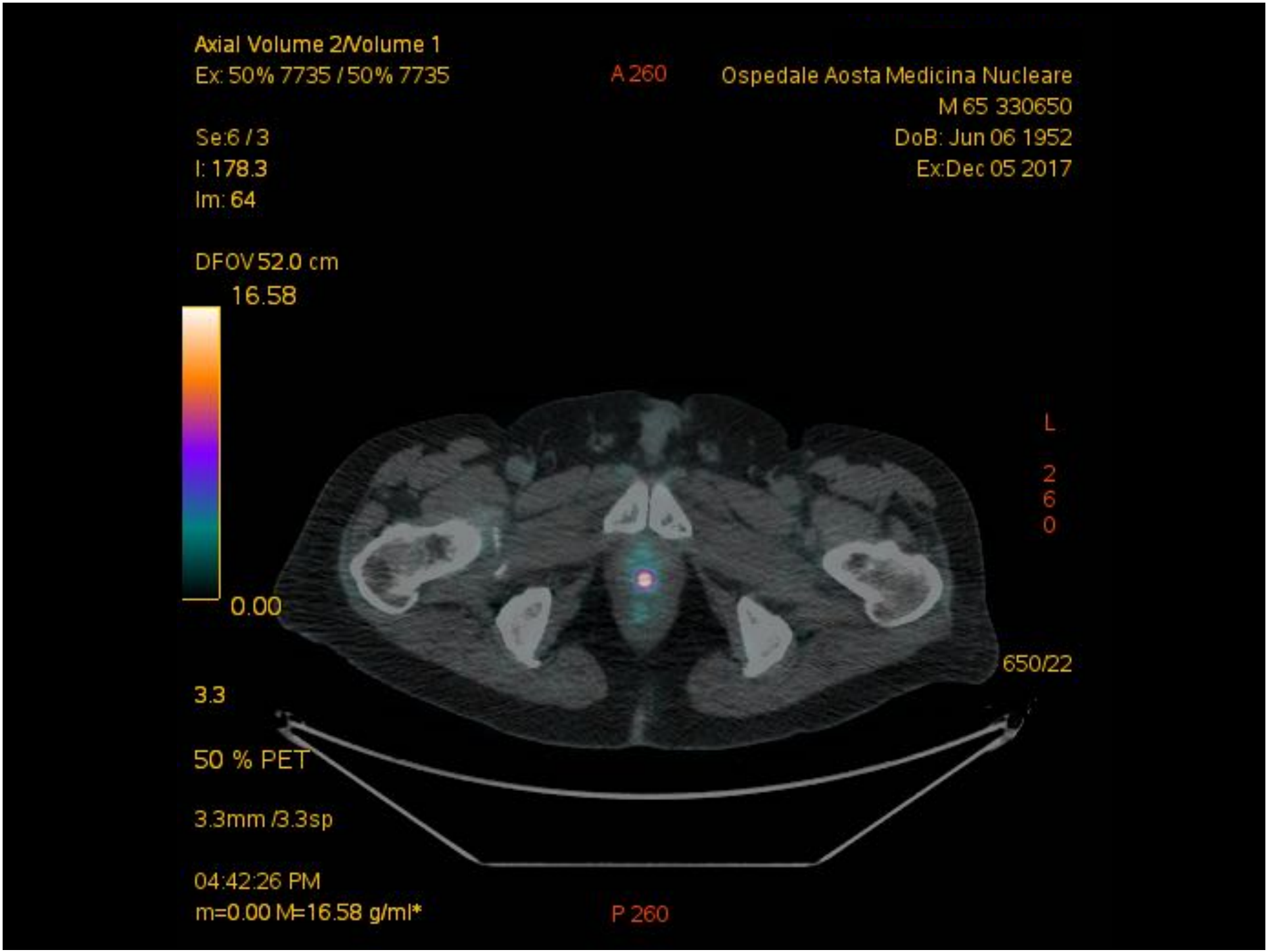
Ex:Dec 05 2017
Se:6 / 3
I: 168.5
Im: 61
DFOV 52.0 cm
16.58
0.00
L
2
6
0
650/25
3.3
50 % PET
3.3mm /3.3sp
04:42:26 PM
m=0.00 M=16.58 g/ml*
P 260


Axial Volume 2/Volume 1
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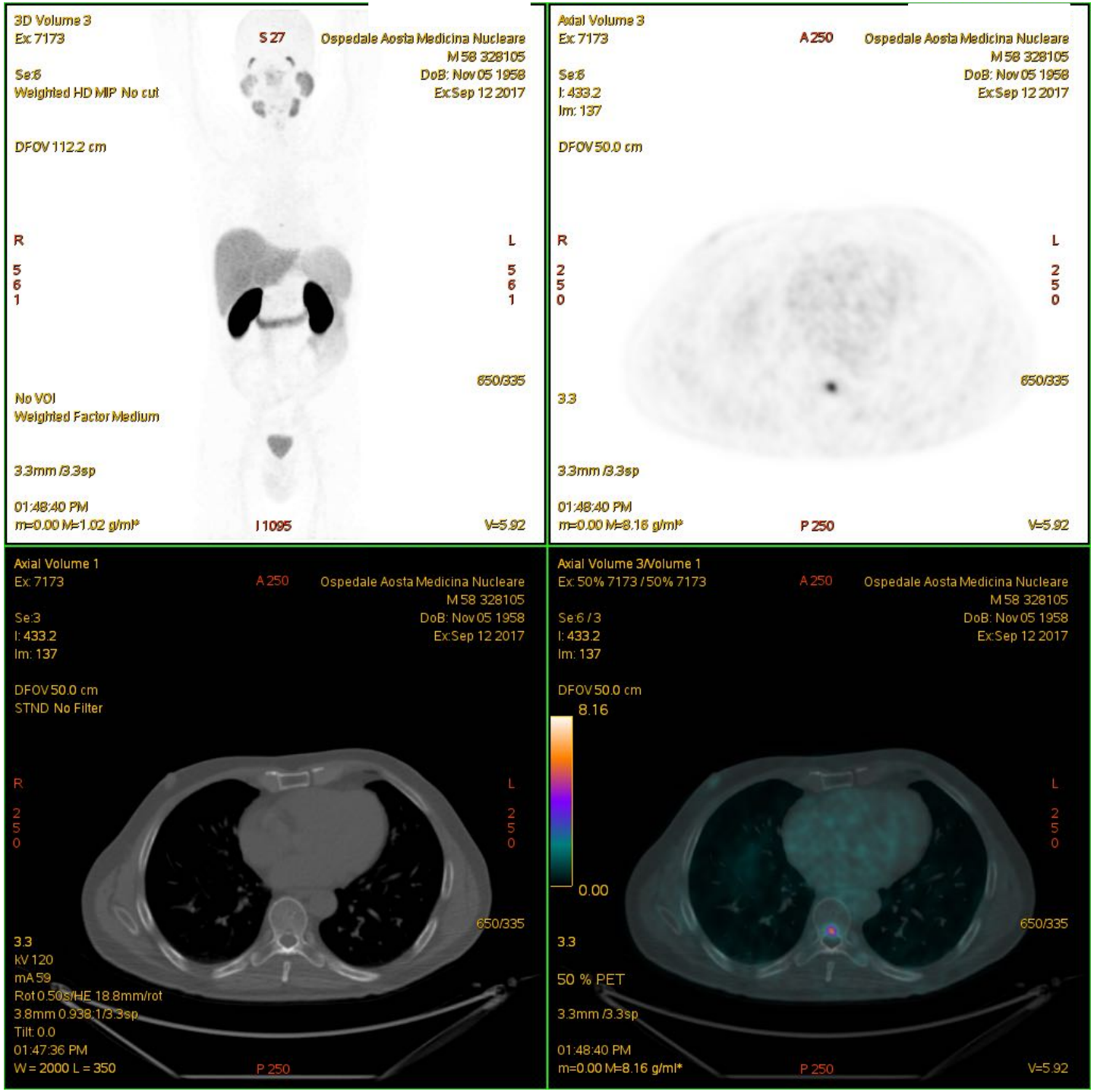
Ospedale Aosta Medicina Nucleare
M 65 330650
DoB: Jun 06 1952
Ex:Dec 05 2017
Se:6 / 3
I: 178.3
Im: 64
DFOV 52.0 cm
16.58
0.00
L
2
6
0
650/22
3.3
50 % PET
3.3mm /3.3sp
04:42:26 PM
m=0.00 M=16.58 g/ml*
P 260

QUESITO DIAGNOSTICO: ricerca di localizzazioni ripetitive in paziente con recidiva biochimica di malattia.

In anamnesi: nel 2011 prostatectomia radicale+LAD+N.S. a dx - adenocarcinoma prostatico pT3a N0 - GS 7 (4+3) margini negativi + RT adiuvante. Il 27/05/2016 esegue PET con 18F-Colina per recidiva biochimica (PSA 0.6 ng/ml) con sospetto di recidiva in loggia prostatica, non confermato alla RM del 15/09/2016.
A gennaio 2017 terapia con estramustina per un mese con azzeramento del PSA e successivo nuovo rialzo del PSA (attuale 0,25 ng/ml). Confronto con PET 64Cu-PSMA del 06/12/2016 (negativa).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S 27
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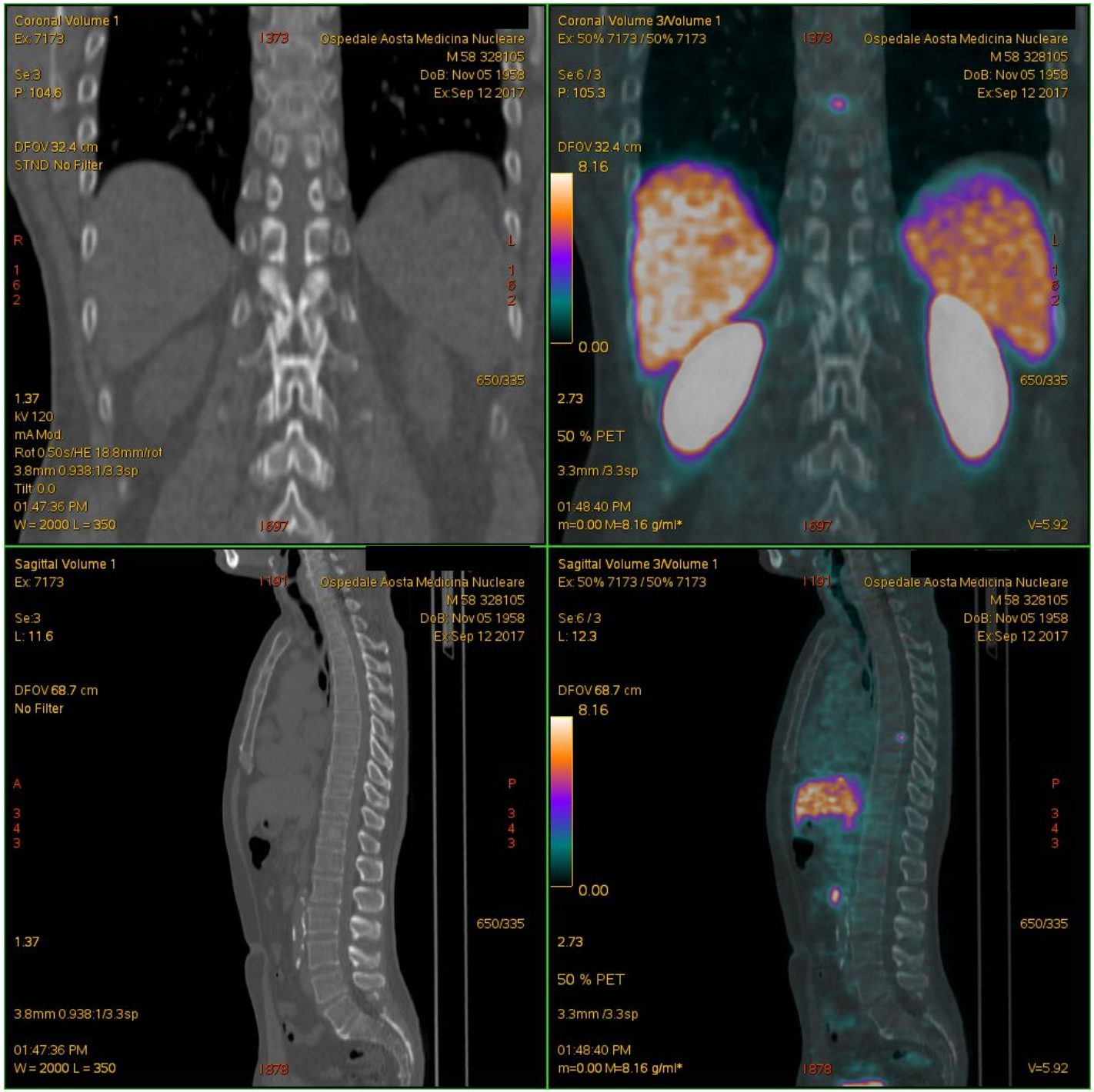
Ex:Sep 12 2017
Se:8
Weighted HD MIP No cut
DFOV 112.2 cm
R
L
5
6
1
650/335
No VOI
Weighted Factor Medium
3.3mm /3.3sp
01:48:40 PM
m=0.00 M=1.02 g/ml*
I 1095
V=5.92
Axial Volume 3
Ex: 7173
A 250
Ospedale Aosta Medicina Nucleare
M 58 328105
DoB: Nov 05 1958
Ex:Sep 12 2017
Se:8
I: 433.2
Im: 137
DFOV 50.0 cm
R
L
2
5
0
650/335
3.3
3.3mm /3.3sp
01:48:40 PM
m=0.00 M=8.16 g/ml*
P 250
V=5.92
Axial Volume 1
Ex: 7173
A 250
Ospedale Aosta Medicina Nucleare
M 58 328105
DoB: Nov 05 1958
Ex:Sep 12 2017
Se:3
I: 433.2
Im: 137
DFOV 50.0 cm
STND No Filter
R
L
2
5
0
650/335
3.3
kV 120
mA 59
Rot 0.50s/HE 18.8mm/rot
3.8mm 0.938:1/3.3sp
Tilt: 0.0
01:47:36 PM
W = 2000 L = 350
P 250
Axial Volume 3/Volume 1
Ex: 50% 7173 / 50% 7173
A 250
Ospedale Aosta Medicina Nucleare
M 58 328105
DoB: Nov 05 1958
Ex:Sep 12 2017
Se:6 / 3
I: 433.2
Im: 137
DFOV 50.0 cm
8.16
0.00
R
L
2
5
0
650/335
3.3
50 % PET
3.3mm /3.3sp
01:48:40 PM
m=0.00 M=8.16 g/ml*
P 250
V=5.92


Coronal Volume 1
Ex: 7173
I373
Ospedale Aosta Medicina Nucleare
M 58 328105
DoB: Nov 05 1958
Ex:Sep 12 2017
Se:3
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DFOV 32.4 cm
STND No Filter
R
L
650/335
1.37
kV 120
mA Mod.
Rot 0.50s/HE 18.8mm/rot
3.8mm 0.938:1/3.3sp
Tilt: 0.0
01:47:36 PM
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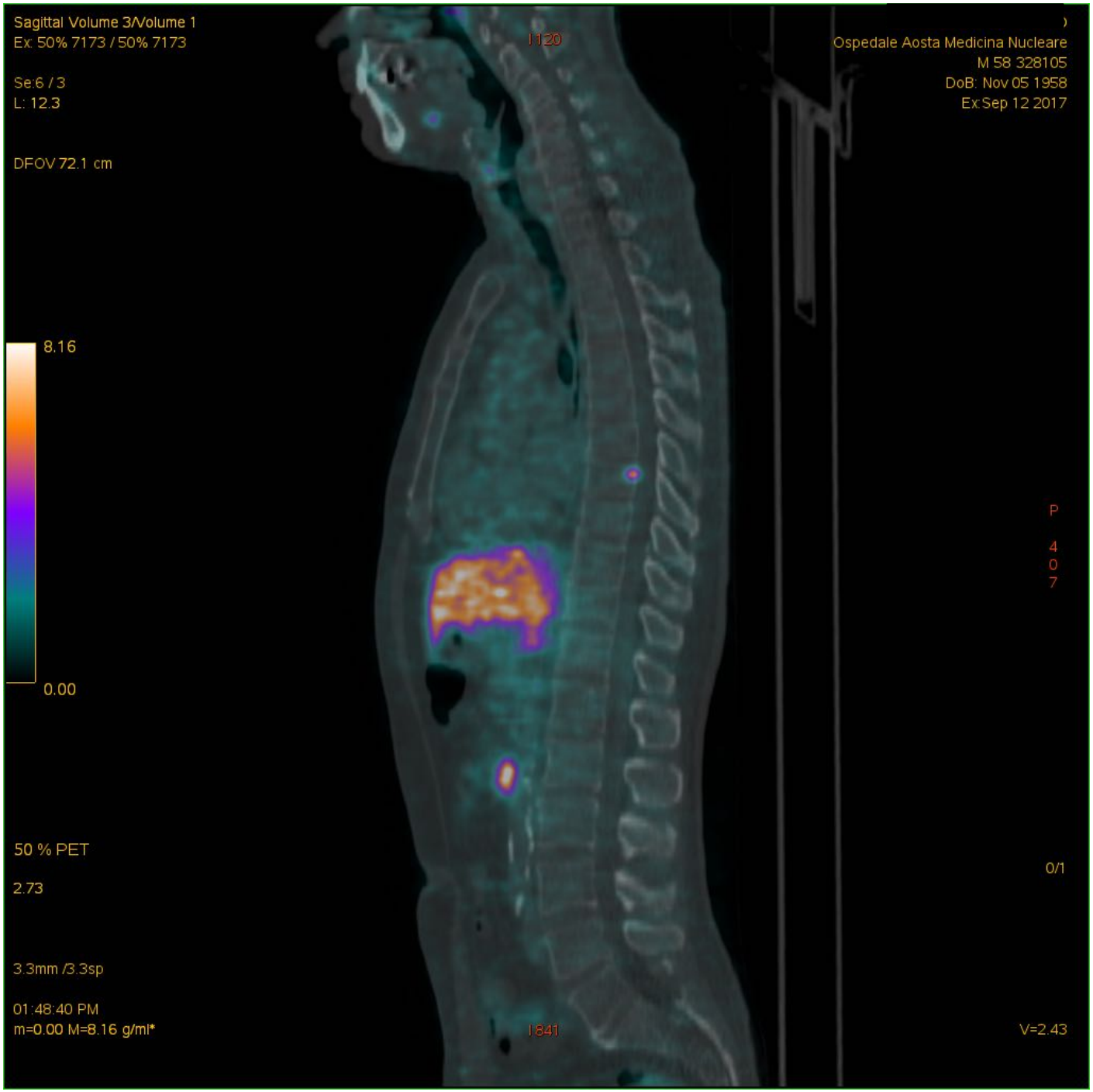
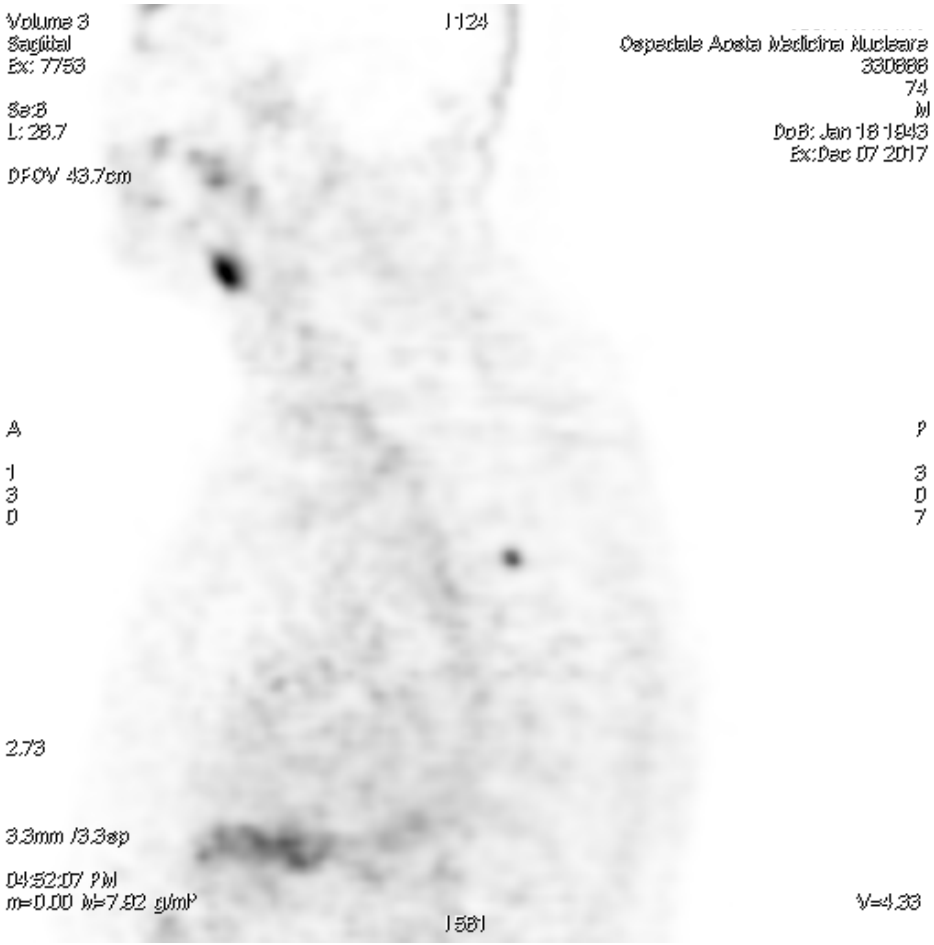
I697
Coronal Volume 3/Volume 1
Ex: 50% 7173 / 50% 7173
Se:6 / 3
P: 105.3
DFOV 32.4 cm
8.16
0.00
650/335
2.73
50 % PET
3.3mm /3.3sp
01:48:40 PM
m=0.00 M=8.16 g/ml*
V=5.92
Sagittal Volume 1
Ex: 7173
I191
Ospedale Aosta Medicina Nucleare
M 58 328105
DoB: Nov 05 1958
Ex:Sep 12 2017
Se:3
L: 11.6
DFOV 68.7 cm
No Filter
A
P
650/335
1.37
3.8mm 0.938:1/3.3sp
01:47:36 PM
W = 2000 L = 350
I878
Sagittal Volume 3/Volume 1
Ex: 50% 7173 / 50% 7173
Se:6 / 3
L: 12.3
DFOV 68.7 cm
8.16
0.00
650/335
2.73
50 % PET
3.3mm /3.3sp
01:48:40 PM
m=0.00 M=8.16 g/ml*
V=5.92


Sagittal Volume 3/Volume 1
Ex: 50% 7173 / 50% 7173
Se:6 / 3
L: 12.3
DFOV 72.1 cm
I 120
Ospedale Aosta Medicina Nucleare
M 58 328105
DoB: Nov 05 1958
Ex:Sep 12 2017
8.16
0.00
P
4
0
7
50 % PET
2.73
0/1
3.3mm /3.3sp
01:48:40 PM
m=0.00 M=8.16 g/ml*
I 841
V=2.43

QUESITO DIAGNOSTICO:
progressione biochimica di malattia (24/11/17 PSA 0.26 ng/ml) in corso di terapia con Enantone.

In anamnesi:
prostatectomia radicale nel 2009 (pT3a GS 4+3) + successiva RT su loggia; nel 2011 linfadenectomia radicale retroperitoneale; 2015 RT su recidiva linfonodale presacrale. A gennaio 2017 inizia terapia con enantone per nuova recidiva biochimica.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Sagittal
Ex: 7753
I 124
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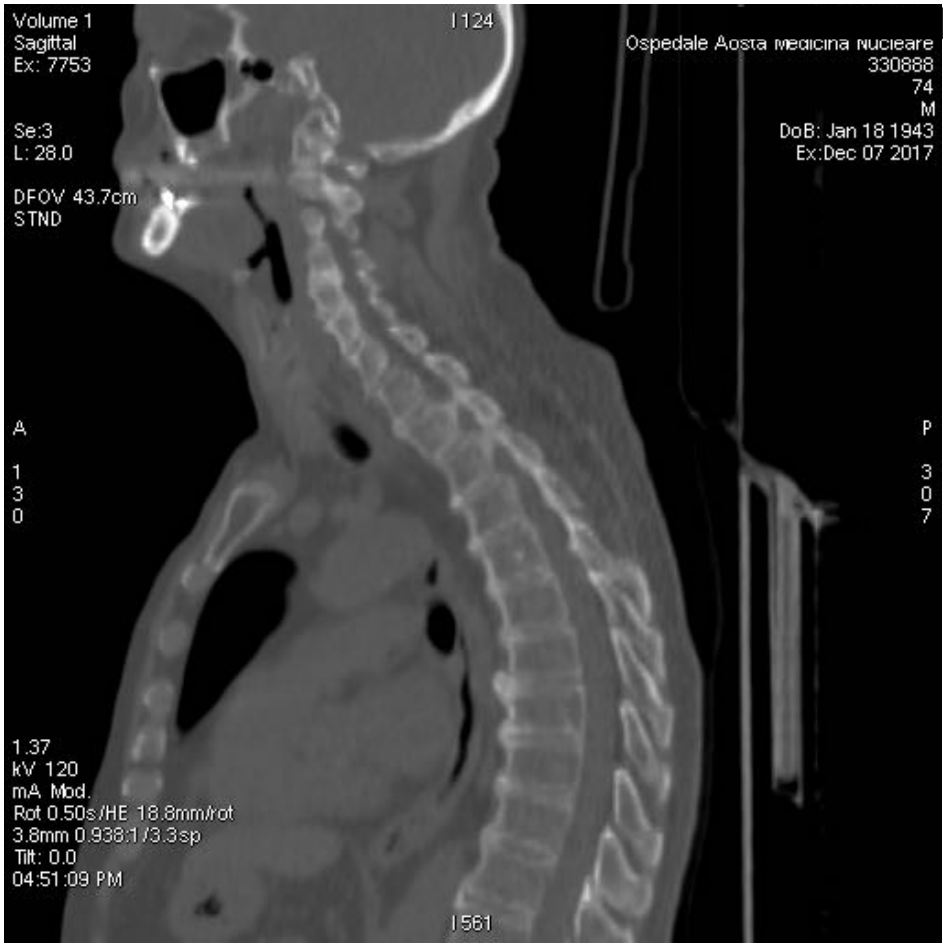
L: 28.7
DFOV 43.7cm
A
P
1
3
0
3
0
7
2.73
3.3mm /3.3sp
04:52:07 PM
m=0.00 M=7.92 g/ml²
V=4.33
I 561
Ospedale Aosta Medicina Nucleare
330888
74
M
DoB: Jan 18 1943
Ex:Dec 07 2017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DFOV 43.7cm
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P
1
3
0
3
0
7
1.37
kV 120
mA Mod.
Rot 0.50s/HE 18.8mm/rot
3.8mm 0.938:1/3.3sp
Tilt: 0.0
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I 561
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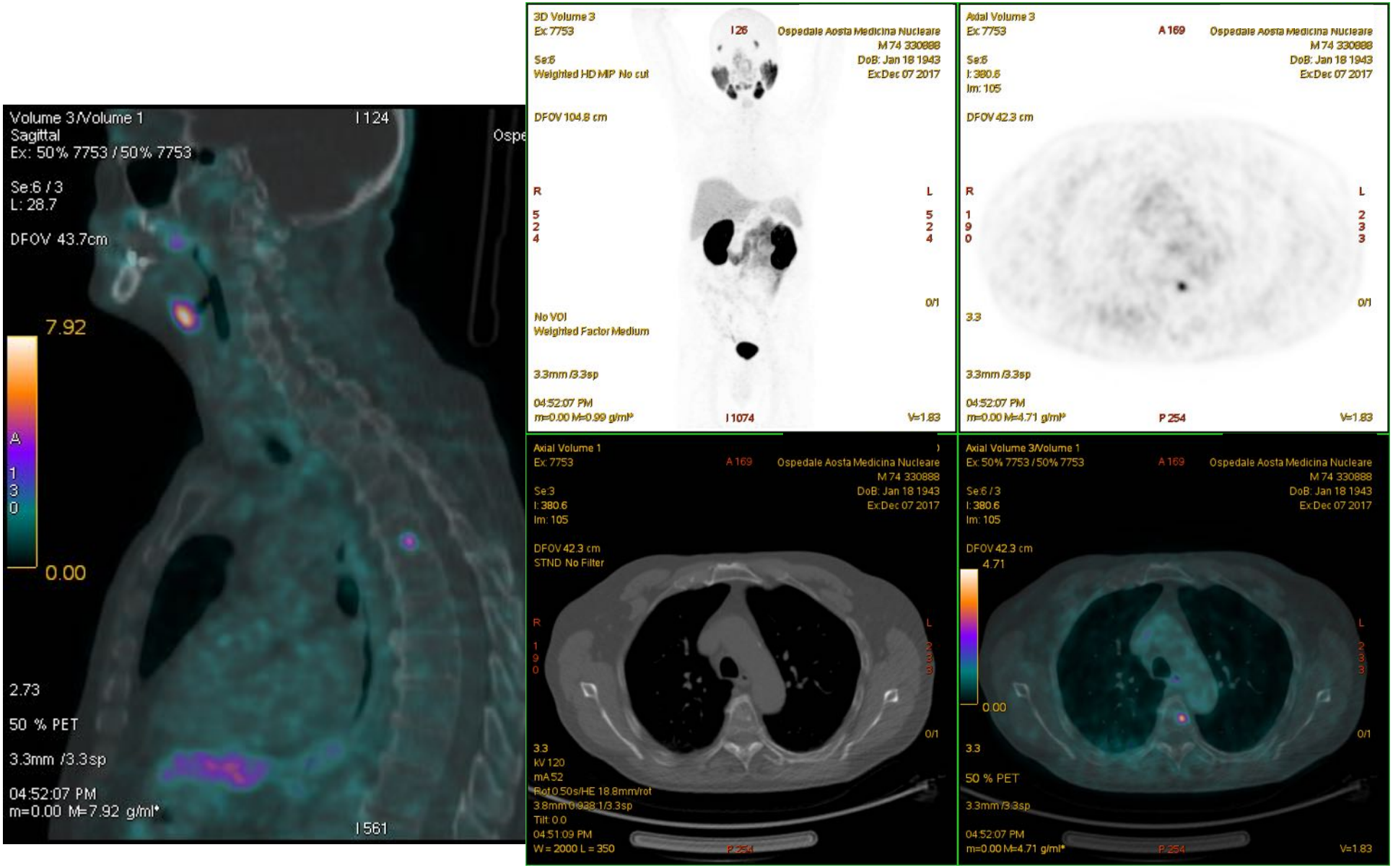
330888
74
M
DoB: Jan 18 1943
Ex:Dec 07 2017


Volume 3/Volume 1
I 124
Sagittal
Ex: 50% 7753 / 50% 7753
Se:6 / 3
L: 28.7
DFOV 43.7cm
7.92
A
1
3
0
0.00
2.73
50 % PET
3.3mm /3.3sp
04:52:07 PM
m=0.00 M=7.92 g/ml*
I 561
3D Volume 3
Ex: 7753
I 26
Ospedale Aosta Medicina Nucleare
M 74 330888
Se:6
DoB: Jan 18 1943
Weighted HD MIP No cut
Ex:Dec 07 2017
DFOV 104.8 cm
R
L
5
2
4
0/1
No VOI
Weighted Factor Medium
3.3mm /3.3sp
04:52:07 PM
m=0.00 M=0.99 g/ml*
I 1074
V=1.83
Axial Volume 3
Ex: 7753
A 169
Ospedale Aosta Medicina Nucleare
M 74 330888
Se:6
DoB: Jan 18 1943
I: 380.6
Ex:Dec 07 2017
Im: 105
DFOV 42.3 cm
R
L
1
9
0
2
3
3
0/1
3.3
3.3mm /3.3sp
04:52:07 PM
m=0.00 M=4.71 g/ml*
P 254
V=1.83
Axial Volume 1
Ex: 7753
A 169
Ospedale Aosta Medicina Nucleare
M 74 330888
Se:3
DoB: Jan 18 1943
I: 380.6
Ex:Dec 07 2017
Im: 105
DFOV 42.3 cm
STND No Filter
R
L
1
9
0
2
3
3
0/1
3.3
kV 120
mA 52
Rot 0.50s/HE 18.8mm/rot
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M 74 330888
Se:6 / 3
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Ex:Dec 07 2017
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DFOV 42.3 cm
4.71
0.00
L
2
3
3
0/1
3.3
50 % PET
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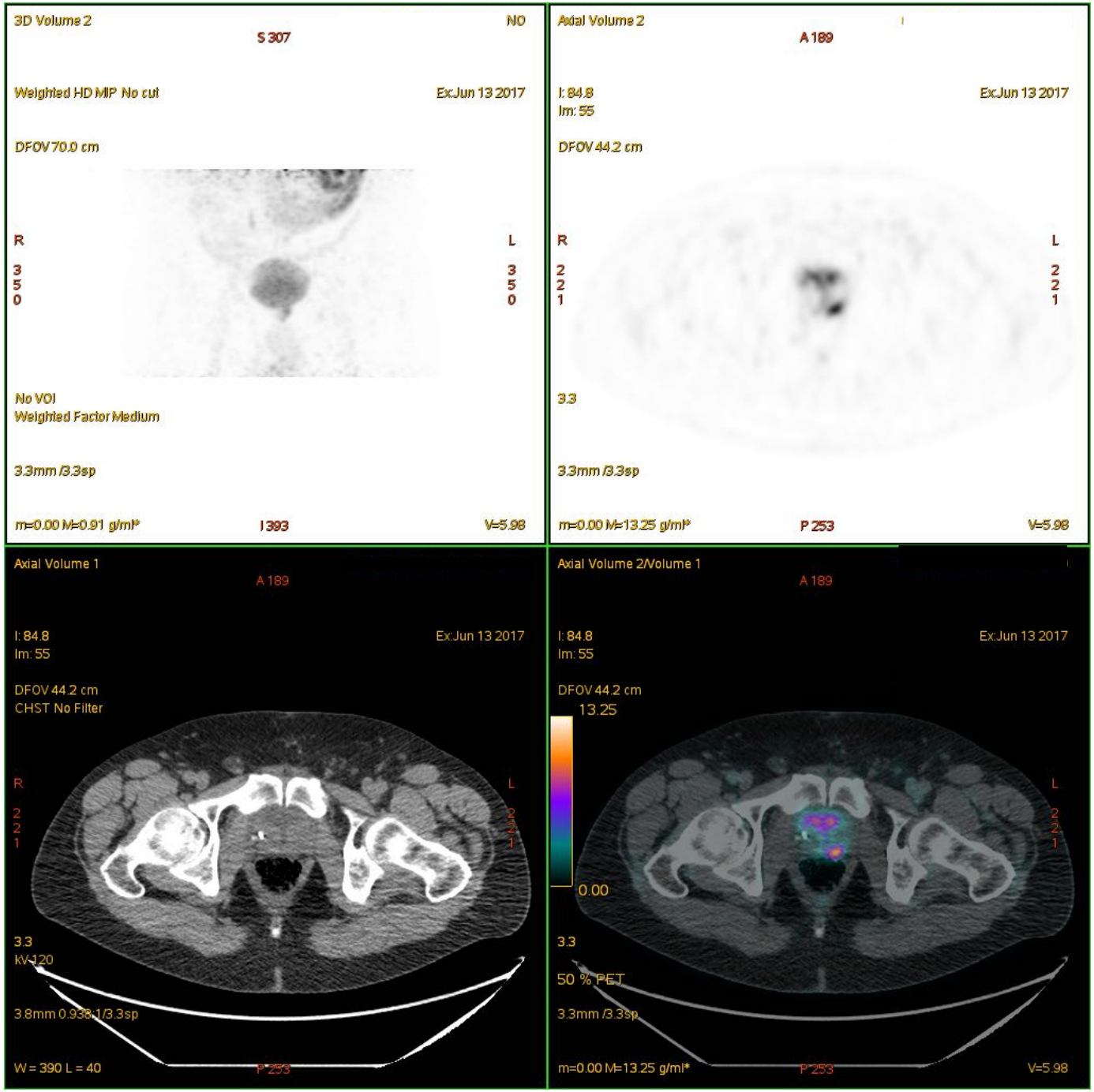
P 254
V=1.83

QUESITO DIAGNOSTICO:
marzo2015 prostatectomia radicale retropubica, nerve sparing e neck sparing+linfadenenctomia iliaca ed otturatoria - GS:3+3 - pT2cN0.

Ristadiazione per incremento dei valori del PSA (ultimo di giugno 2017 : 0.26 ng/ml).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R
L
3
5
0
3
5
0
No VOI
Weighted Factor Medium
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I 393
V=5.98
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I: 84.8
Im: 55
Ex:Jun 13 2017
DFOV 44.2 cm
R
L
2
2
1
2
2
1
3.3
3.3mm /3.3sp
m=0.00 M=13.25 g/ml*
P 253
V=5.98
Axial Volume 1
A 189
I: 84.8
Im: 55
Ex:Jun 13 2017
DFOV 44.2 cm
CHST No Filter
R
L
2
2
1
2
2
1
3.3
kV 120
3.8mm 0.938:1/3.3sp
W = 390 L = 40
P 253
Axial Volume 2/Volume 1
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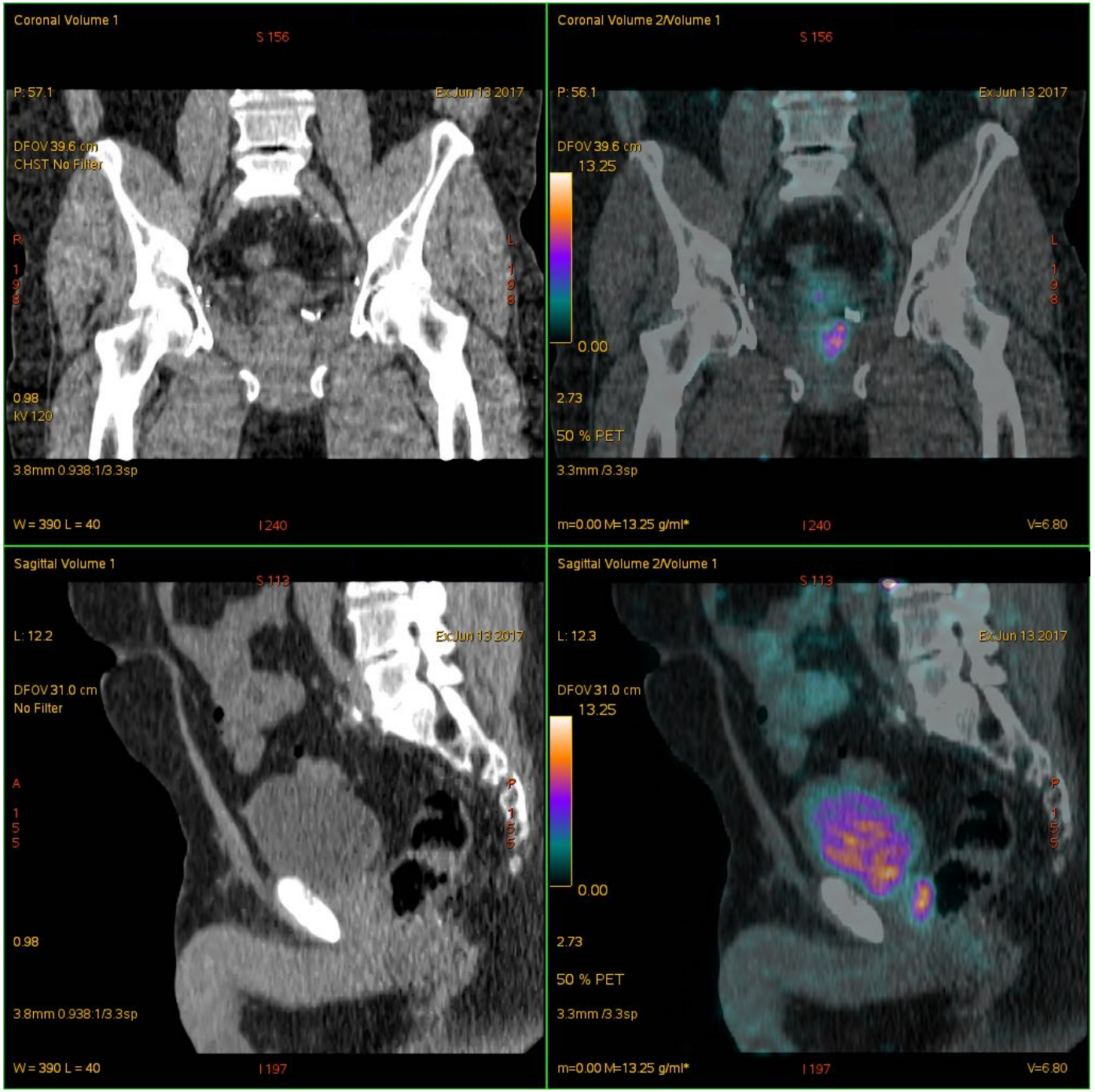
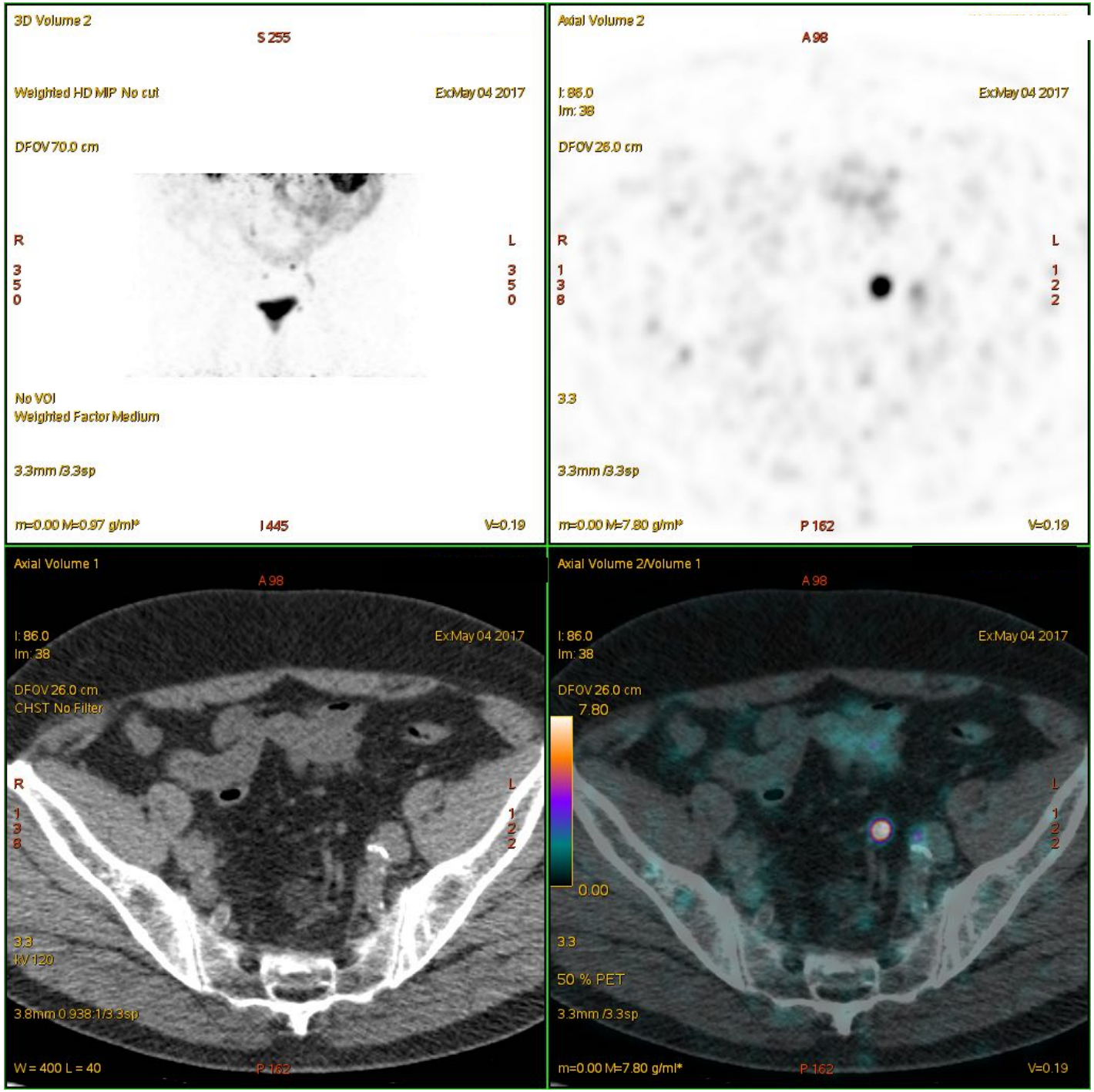
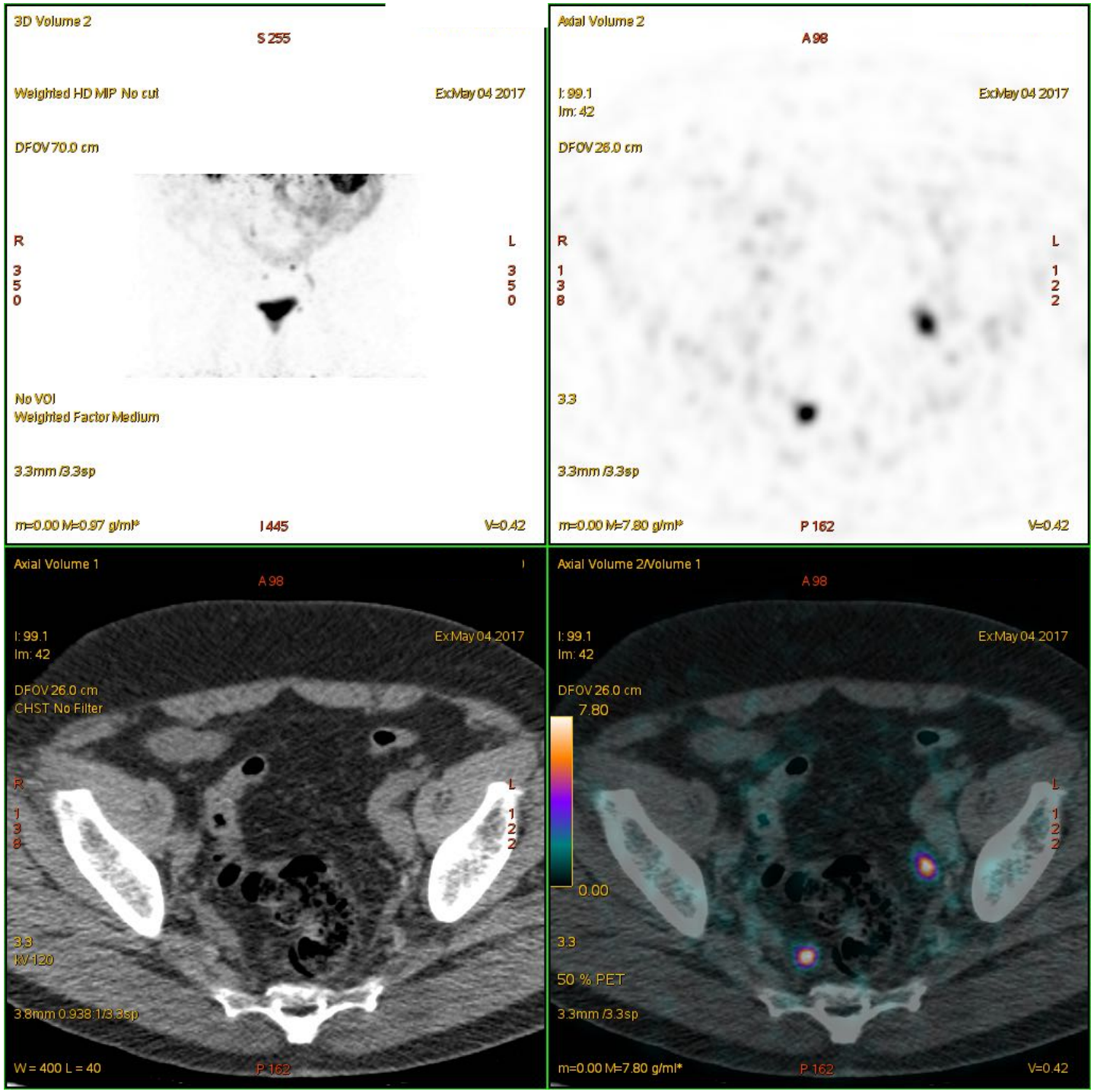
I: 84.8
Im: 55
Ex:Jun 13 2017
DFOV 44.2 cm
13.25
0.00
R
L
2
2
1
2
2
1
3.3
50 % PET
3.3mm /3.3sp
m=0.00 M=13.25 g/ml*
P 253
V=5.98

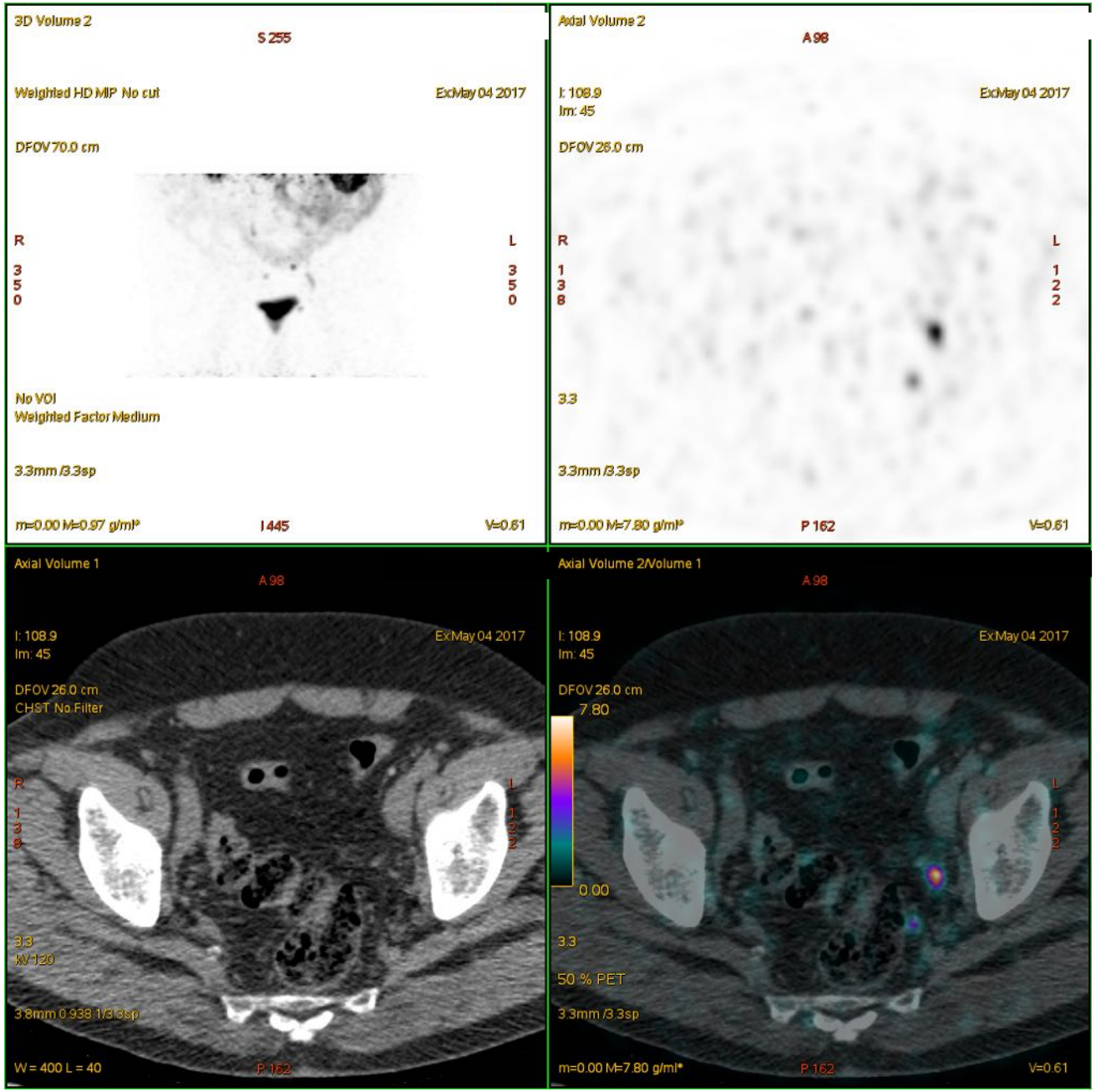

Coronal Volume 1
S 156
P: 57.1
Ex Jun 13 2017
DFOV 39.6 cm
CHST No Filter
R
L
0.98
kV 120
3.8mm 0.938:1/3.3sp
W = 390 L = 40
I 240
Coronal Volume 2/Volume 1
S 156
P: 56.1
Ex Jun 13 2017
DFOV 39.6 cm
13.25
0.00
2.73
50 % PET
3.3mm /3.3sp
m=0.00 M=13.25 g/ml*
I 240
V=6.80
Sagittal Volume 1
S 113
L: 12.2
Ex Jun 13 2017
DFOV 31.0 cm
No Filter
A
P
0.98
3.8mm 0.938:1/3.3sp
W = 390 L = 40
I 197
Sagittal Volume 2/Volume 1
S 113
L: 12.3
Ex Jun 13 2017
DFOV 31.0 cm
13.25
0.00
2.73
50 % PET
3.3mm /3.3sp
m=0.00 M=13.25 g/ml*
I 197
V=6.80

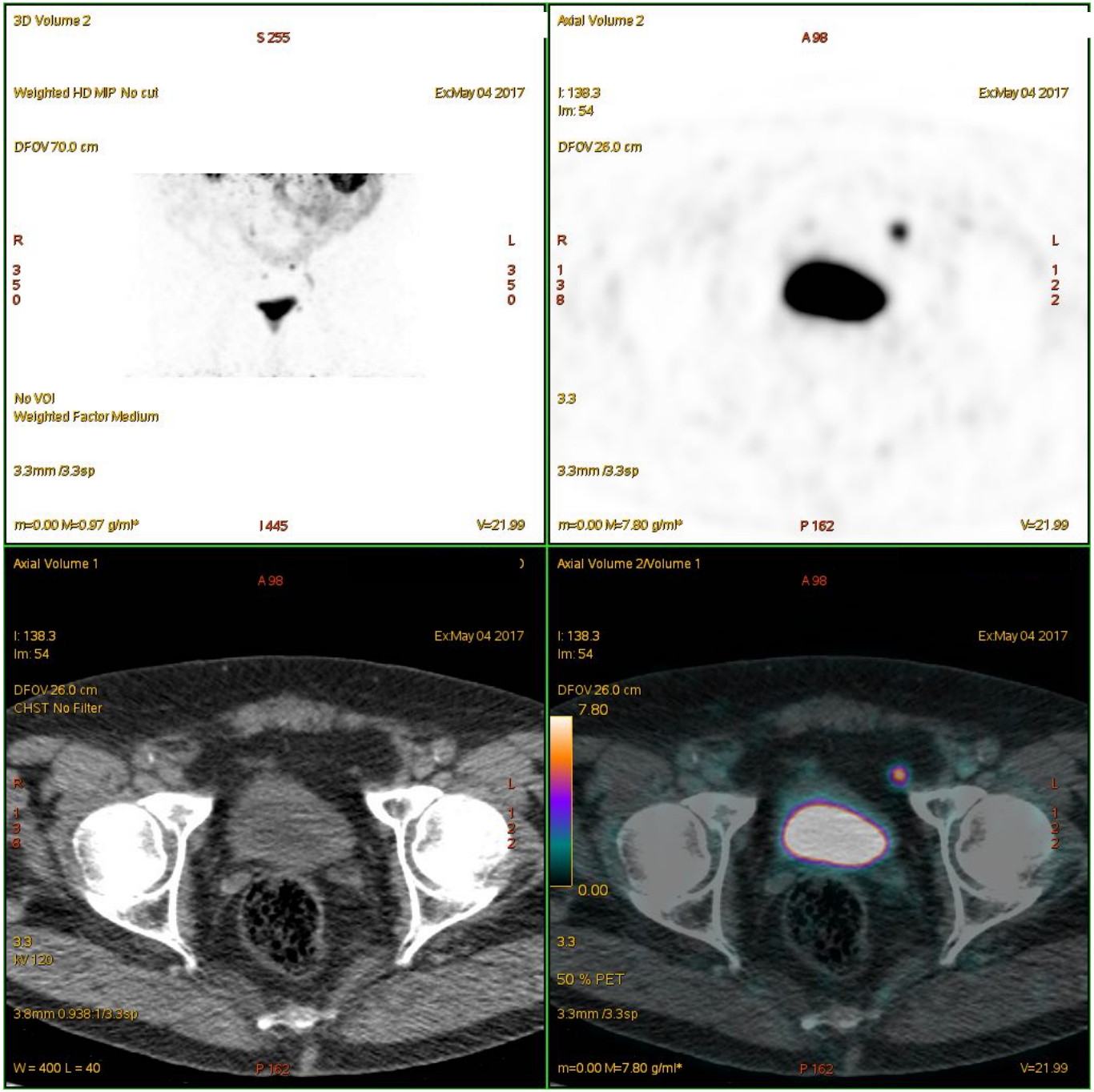
QUESITO DIAGNOSTICO:
ripresa biochimica di malattia (PSA 0.43 ng/ml del 21/04/17).

In anamnesi: marzo 2012 prostatectomia radicale e linfoadenectomia estesa per adenocarcinoma GS 8 (4+4) pT3aN0 R1; RT adiuvante terminata nel novembre nel 2012.


3D Volume 2
S 255
Weighted HD MIP No cut
ExMay 04 2017
DFOV 70.0 cm
R
L
3
5
0
3
5
0
No VOI
Weighted Factor Medium
3.3mm /3.3sp
m=0.00 M=0.97 g/ml*
I 445
V=0.19
Axial Volume 2
A 98
I: 86.0
Im: 38
ExMay 04 2017
DFOV 26.0 cm
R
L
1
3
8
1
2
2
3.3
3.3mm /3.3sp
m=0.00 M=7.80 g/ml*
P 162
V=0.19
Axial Volume 1
A 98
I: 86.0
Im: 38
ExMay 04 2017
DFOV 26.0 cm
CHST No Filter
R
L
1
3
8
1
2
2
3.3
kV 120
3.8mm 0.938:1/3.3sp
W = 400 L = 40
P 162
Axial Volume 2/Volume 1
A 98
I: 86.0
Im: 38
ExMay 04 2017
DFOV 26.0 cm
7.80
0.00
L
1
2
2
3.3
50 % PET
3.3mm /3.3sp
m=0.00 M=7.80 g/ml*
P 162
V=0.19


3D Volume 2
S 255
Weighted HD MIP No cut
ExMay 04 2017
DFOV 70.0 cm
R
L
3
5
0
3
5
0
No VOI
Weighted Factor Medium
3.3mm /3.3sp
m=0.00 M=0.97 g/ml*
I 445
V=0.42
Axial Volume 2
A 98
I: 99.1
Im: 42
ExMay 04 2017
DFOV 26.0 cm
R
L
1
3
8
1
2
2
3.3
3.3mm /3.3sp
m=0.00 M=7.80 g/ml*
P 162
V=0.42
Axial Volume 1
A 98
I: 99.1
Im: 42
ExMay 04 2017
DFOV 26.0 cm
CHST No Filter
R
L
1
3
8
1
2
2
3.3
kV 120
3.8mm 0.938:1/3.3sp
W = 400 L = 40
P 162
Axial Volume 2/Volume 1
A 98
I: 99.1
Im: 42
ExMay 04 2017
DFOV 26.0 cm
7.80
0.00
L
1
2
2
3.3
50 % PET
3.3mm /3.3sp
m=0.00 M=7.80 g/ml*
P 162
V=0.42


3D Volume 2
S 255
Weighted HD MIP No cut
ExMay 04 2017
DFOV 70.0 cm
R
L
3
5
0
3
5
0
No VOI
Weighted Factor Medium
3.3mm /3.3sp
m=0.00 M=0.97 g/ml*
I 445
V=0.61
Axial Volume 2
A 98
I: 108.9
Im: 45
ExMay 04 2017
DFOV 26.0 cm
R
L
1
3
8
1
2
2
3.3
3.3mm /3.3sp
m=0.00 M=7.80 g/ml*
P 162
V=0.61
Axial Volume 1
A 98
I: 108.9
Im: 45
ExMay 04 2017
DFOV 26.0 cm
CHST No Filter
R
L
1
3
8
1
2
2
3.3
kV 120
3.8mm 0.938:1/3.3sp
W = 400 L = 40
P 162
Axial Volume 2/Volume 1
A 98
I: 108.9
Im: 45
ExMay 04 2017
DFOV 26.0 cm
7.80
0.00
L
1
2
2
3.3
50 % PET
3.3mm /3.3sp
m=0.00 M=7.80 g/ml*
P 162
V=0.61


3D Volume 2
S 255
Weighted HD MIP No cut
ExMay 04 2017
DFOV 70.0 cm
R
L
No VOI
Weighted Factor Medium
3.3mm /3.3sp
m=0.00 M=0.97 g/ml*
I 445
V=21.99
Axial Volume 2
A 98
I: 138.3
Im: 54
ExMay 04 2017
DFOV 26.0 cm
R
L
3.3
3.3mm /3.3sp
m=0.00 M=7.80 g/ml*
P 162
V=21.99
Axial Volume 1
A 98
I: 138.3
Im: 54
ExMay 04 2017
DFOV 26.0 cm
CHST No Filter
R
L
3.3
kV 120
3.8mm 0.938:1/3.3sp
W = 400 L = 40
P 162
Axial Volume 2/Volume 1
A 98
I: 138.3
Im: 54
ExMay 04 2017
DFOV 26.0 cm
7.80
0.00
L
3.3
50 % PET
3.3mm /3.3sp
m=0.00 M=7.80 g/ml*
P 162
V=21.99

Journal of Nuclear Medicine & Radiation Therapy

Gupta et al., J Nucl Med Radiat Ther 2017, 8:5
DOI: 10.4172/2155-9619.1000342

Abstract

Prostate cancer (PCa) has a unique tropism to bone. Indeed, bone is the most frequent site of distant metastasis and cause of morbidity due to skeletal complications. 99mTc-Methylene diphosphonate (MDP) bone scintigraphy/scan (BS) is the current standard imaging due to increase adsorption of the tracer at osteoblastic sites. However, it has limited specificity due to false positives in degenerative changes, benign causes and false negatives in bone marrow metastasis and lytic lesions. Another drawback of BS is flare response. Prostate Specific Membrane Antigen (PSMA) has been the most studies target in prostate cancer imaging in recent time due to 100-1000 time over-expression in cancer cells. 68Ga-PSMA-11, a small molecule with PSMA enzyme inhibition activity has been found promising in recurrence and lymph-node staging. In our experience of 97 staging prostate cancer patients, PSMA PET-CT showed 57.41% with pure sclerotic metastasis. Mixed (33.33%), marrow (7.14%) and lytic (2.3%) types of lesions constitute the rest and thus BS alone in these patients may leads to underestimation of bony disease burden. PSMA has not been found positive in degenerative changes however its role in response to anti-androgen needs caution due to know synergistic effect on PSMA expression. We concluded, PSMA PET-CT would have better sensitivity and specificity due to unique distinction for detecting non-sclerotic metastases. We presumed if PSMA has been performed for staging workup then there is limited role of BS except in clinical trial patient. Overall PSMA PET may become one-stop-shop for PCa workup.

the incidence is less than the western world, it is showing a rising trend now. Indeed in many metro-cities like Delhi it has become the runners up with age-adjusted incidence of $10.9/10^5$ person-years [2]. A large number of patients diagnosed with early stage PCa got cured with definitive local therapy i.e. Radical prostatectomy or Radiotherapy, however many will develop metastatic disease. PCa has a unique exquisite tropism to spread in bone [3]. Haematogenous spread in red bone marrow of axial and proximal appendicular skeleton leads to development of bone metastases (BMs). BMs are the most frequent and main distant metastatic site in about 80% of PCs patients and is therefore one of the most important determinants of treatment and outcome [4,5]. Skeletal complications known as 'skeletal-related events (SREs)' accounts for most of the PCa's morbidity and mortality [6]. Bone marrow replacement by PCa cells leads to anaemia while involvement of cortical bone can lead to pain, fractures, and spinal cord compression. Once bone metastasis is diagnosed, local definitive treatment goes out of the picture and the intent of treatment become palliative. Hence timely diagnosis of bone metastasis is important for correct treatment planning and prevention of SREs.

Bone scintigraphy/scan (BS) with 99mTc-Methylene diphosphonate (MDP) is the most favoured investigation for detecting BMs. This is [8]. Therefore, most guidelines suggest BS to be performed in patients with high risk PCa or those presenting with bone symptoms [9-11].

BS has been associated with number of limitations as well. It is a well-known fact that BM begins in bone marrow, hence it is predicted that BS will not able to detect bone marrow lesions or early lesion with insufficient osteoblastic activity. In addition it is a non-specific tracer and many a times it is hard to differentiate between degenerative bone disease and BMs hence frequently requiring additional imaging modality for characterization [12]. With modern hybrid imaging SPECT-CT (Single Photon Emission Computed Tomography-Computed Tomography), MDP BS has largely addressed this issue of low specificity and able to correctly characterized planner imaging equivocal lesions. It has been reported that the number of equivocal lesions dropped from 61 to 8% with addition of SPECT-CT [13]. Flare response is another known fact in BS [14]. Post treatment increase in tracer activity or new lesion is tricky in interpretation. Whether this is due to reparative response or due to disease progression is a matter of concern. Nonetheless this phenomenon has been assumed as response by most physicians and presumed to have better outcome.

^{68}Ga-PSMA-11 PET as a Gatekeeper for the Treatment of Metastatic Prostate Cancer with ^{223}Ra: Proof of Concept

Hojjat Ahmadzadehfar*[1], Kambiz Azgomi*[1], Stefan Hauser[2], Xiao Wei[1], Anna Yordanova[1], Florian C. Gaertner[1], Stefan Kürpig[1], Holger Strunk[3], and Markus Essler[1]

[1]Department of Nuclear Medicine, University Hospital Bonn, Bonn, Germany; [2]Department of Urology, University Hospital Bonn, Bonn, Germany; and [3]Department of Diagnostic Radiology, University Hospital Bonn, Bonn, Germany

We retrospectively evaluated the utility of ^{68}Ga-PSMA-11 PET for planning $^{223}RaCl_2$ therapy of patients with metastatic prostate cancer and its impact on the therapeutic response as determined by prostate-specific antigen (PSA) and alkaline phosphatase (ALP), as well as the correlation of PSA changes with the results of prostate-specific membrane antigen (PSMA) PET follow-up scans. **Methods:** Sixty-three patients with a median age of 73 y who underwent 307 cycles of therapy with $^{223}RaCl_2$ were analyzed. In 31 patients, bone scanning and radiologic imaging were performed for pretherapeutic imaging (group 1). In 32 patients, bone scanning and PSMA PET were performed before therapy (group 2). Patients with small lymph node metastases and local recurrence were not excluded from treatment, consistent with current guidelines. PSA and ALP were measured before each treatment cycle and 4 wk after the final cycle. Thirteen patients from group 2, who underwent a second PSMA PET scan as a follow-up, were evaluated to determine the significance of PSA changes as a follow-up marker. **Results:** In group 1, 4 patients (12.9%) showed a PSA decline, of whom 2 patients and 1 patient showed a PSA decline of more than 30% and more than 50%, respectively. In contrast, in group 2, 14 patients (43.8%) showed a PSA decline, of whom 10 and 8 patients showed a decline of more than 30% and more than 50%, respectively ($P = 0.007$). Thirty-seven patients had a high ALP level (19 from group 1 and 18 from group 2). Twelve (63.2%) and 16 (88.9%) patients in groups 1 and 2, respectively, showed an ALP decline. This difference was not significant; however, 7 (36%) and 13 (72.2%) patients in groups 1 and 2, respectively, showed an ALP decline of more than 30% ($P = 0.04$). Considering any ALP decline as a response, no patient with increasing ALP showed a PSA response ($P = 0.036$). There was a significant correlation between the PSA changes and the therapeutic response according to follow-up PSMA PET. **Conclusion:** When PSMA PET is used as the gatekeeper in addition to bone scanning, radionuclide therapy with ^{223}Ra may be more effective and have more success regarding changes in the PSA. An increase in PSA during therapy cycles occurs because of disease progression.

Key Words: ^{223}Ra; radionuclide therapy; PSMA; PET; bone scan; prostate cancer; bone metastases

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DOI: 10.2967/jnumed.116.178533

Although different β-emitters, such as ^{153}Sm, ^{188}Re, and ^{82}Sr (*1*), have been used for many years for the treatment of bone metastases of prostate cancer (PC), ^{223}Ra-dichloride (^{223}Ra; Xofigo) is the first α-emitting radiopharmaceutical agent approved for the treatment of patients with symptomatic bone metastases without visceral metastases that has been shown to improve overall survival. It has also been shown to delay skeletal-related events (*2–5*) and is recommended by international guidelines (*6–8*). Prostate-specific antigen (PSA) is the most important PC-related biomarker for the evaluation of therapeutic response in many studies (*9–11*); however, during therapy cycles with ^{223}Ra, several patients show a continuous PSA increase, which may be interpreted as therapy-induced. Thus, regarding therapy for bone metastases using ^{223}Ra, the Prostate Cancer Working Group recommends basing the decision to discontinue treatment on clinical symptomatology and therapeutic tolerability as well as on radiographic progression, not solely on PSA kinetics (*12*). Therefore, it is recommended that patients receive all 6 cycles of ^{223}Ra, which is the recommended treatment course to achieve an overall survival benefit (*13,14*). Bone scintigraphy should precede radionuclide therapy with ^{223}Ra for the evaluation of eligible candidates. The existence of any visceral metastasis is a contraindication for ^{223}Ra therapy. Bone marrow involvement should also be a contraindication, which cannot be diagnosed using bone scanning or CT. Presently, at least in central Europe, ^{68}Ga-PSMA-11 PET (PSMA PET; PSMA is prostate-specific membrane antigen) is increasingly performed for PC, with a high diagnostic sensitivity and specificity (*15–19*). PSMA PET should also precede radioligand therapy with ^{177}Lu-PSMA (*20*). In our recently published study, we showed a significant correlation between PSA changes and the degree and number of PSMA-expressing lesions in patients treated by ^{177}Lu-PSMA (*21*), which confirms the value of PSA as a follow-up marker. Compared with PSA, alkaline phosphatase (ALP) may be a better biomarker to evaluate treatment response (*3,5,13*); however, as a marker, it is only useful in patients with high ALP levels. ALP also has prognostic potential in metastatic PC treated with ^{223}Ra (*3*). For the planning of therapy with ^{223}Ra, to rule out visceral metastases as well as bone marrow involvement, we recommend PSMA PET in addition to bone scintigraphy; however, this cannot be performed routinely in our department because of reimbursement issues. In this study, we retrospectively evaluated the utility of PSMA PET for therapy planning and its influence on the therapeutic response measured by PSA and ALP. We also evaluated the significance of PSA changes in correlation with the results of PSMA PET, acquired as a follow-up scan.

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*Contributed equally to this work.
Published online Sep. 22, 2016.

Treatment Outcomes from ^{68}Ga-PSMA PET/CT–Informed Salvage Radiation Treatment in Men with Rising PSA After Radical Prostatectomy: Prognostic Value of a Negative PSMA PET

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[1]Department of Diagnostic Imaging, St. Vincent's Public Hospital, Sydney, Australia; [2]The Garvan Institute of Medical Research/The Kinghorn Cancer Centre, Sydney, Australia; [3]University of New South Wales (UNSW), Sydney, New South Wales, Australia; [4]Australian Prostate Cancer Research Centre, New South Wales, Australia; [5]Department Radiation Oncology, RNSH, Sydney, Australia; and [6]Genesis Cancer Care, Sydney, Australia

See an invited perspective on this article on page 1969.

^{68}Ga-PSMA (prostate-specific membrane antigen) PET/CT is increasingly used in men with prostate-specific antigen (PSA) failure after radical prostatectomy (RP) to triage those who will benefit from salvage radiation treatment (SRT). This study examines the value of PSMA-informed SRT in improving treatment outcomes in the context of biochemical failure after RP. **Methods:** We analyzed men with rising PSA after RP with PSA readings between 0.05 and 1.0 ng/mL, considered eligible for SRT at the time of PSMA. For each patient, clinical and pathologic features as well as scan results, including site of PSMA-positive disease, number of lesions, and a certainty score, were documented. Subsequent management, including SRT, and most recent PSA were recorded using medical records. Treatment response was defined as both PSA ≤ 0.1 ng/mL and >50% reduction in PSA. Multivariate logistic regression analysis was performed for association of clinical variables and treatment response to SRT. **Results:** One hundred sixty-four men were included. PSMA was positive in 62% (n = 102/164): 38 of 102 in the prostatic fossa, 41 of 102 in pelvic nodes, and 23 of 102 distantly. Twenty-four patients received androgen-deprivation therapy (ADT) and were excluded for outcomes analysis. In total, 99 of 146 received SRT with a median follow-up after radiation treatment of 10.5 mo (interquartile range, 6–14 mo). Overall treatment response after SRT was 72% (n = 71/99). Forty-five percent (n = 27/60) of patients with a negative PSMA underwent SRT whereas 55% (33/60) did not. In men with a negative PSMA who received SRT, 85% (n = 23/27) demonstrated a treatment response, compared with a further PSA increase in 65% (22/34) in those not treated. In 36 of 99 patients with disease confined to the prostate fossa on PSMA, 81% (n = 29/36) responded to SRT. In total, 26 of 99 men had nodal disease on PSMA, of whom 61% (n = 16/26) had treatment response after SRT. On multivariate logistic regression analysis, PSMA and serum PSA significantly correlated with treatment response, whereas pT stage, Gleason score, and surgical margin status did not. **Conclusion:** PSMA PET is independently predictive of treatment response to SRT and stratifies men into a high treatment response to SRT (negative or fossa-confined PSMA) versus men with poor response to SRT (nodes or distant-disease PSMA). In particular, a negative PSMA PET result predicts a high response to salvage fossa radiotherapy.

Key Words: prostate specific membrane antigen; PSMA; PET/CT; treatment outcome; biochemical failure; post radical prostatectomy

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Radical prostatectomy (RP) is the most widely used treatment for men with localized prostate cancer (PC). After surgery, patients are monitored with serial prostate-specific antigen (PSA) measurements. Approximately 20%–50% of pT2–3, node-negative PC patients treated with RP will experience biochemical recurrence, particularly those with poorly differentiated disease and positive surgical margins. Salvage radiation treatment (SRT) to the prostatic fossa (or fossa + pelvic nodes in higher risk patients) is the only potentially curative treatment option for patients with biochemical failure after RP. The 5-y progression-free survival rate in patients undergoing salvage radiation treatment (RT) is 56%, varying from 71% in men with pre-RT PSA level of less than 0.01–0.2 ng/mL, down to 18% in men with a PSA greater than 1.5 ng/mL undergoing SRT without androgen-deprivation therapy (ADT) (*1–4*). This indicates that men with low-volume recurrent PC benefit the most from SRT; and that there are a significant number of patients who do not show a lasting PSA response after salvage. Because SRT is only clinically useful in patients with local disease (disease confined to the fossa), and because SRT is related to significant disadvantages in treatment-related quality of life, patients with tumor spread outside the prostatic fossa should ideally be excluded when selecting patients for prostatic fossa–only SRT. Postoperative conventional imaging techniques such as transrectal ultrasound, MRI, CT, and bone scanning are neither sensitive nor specific enough to detect

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E-mail: emmetthruby@gmail.com
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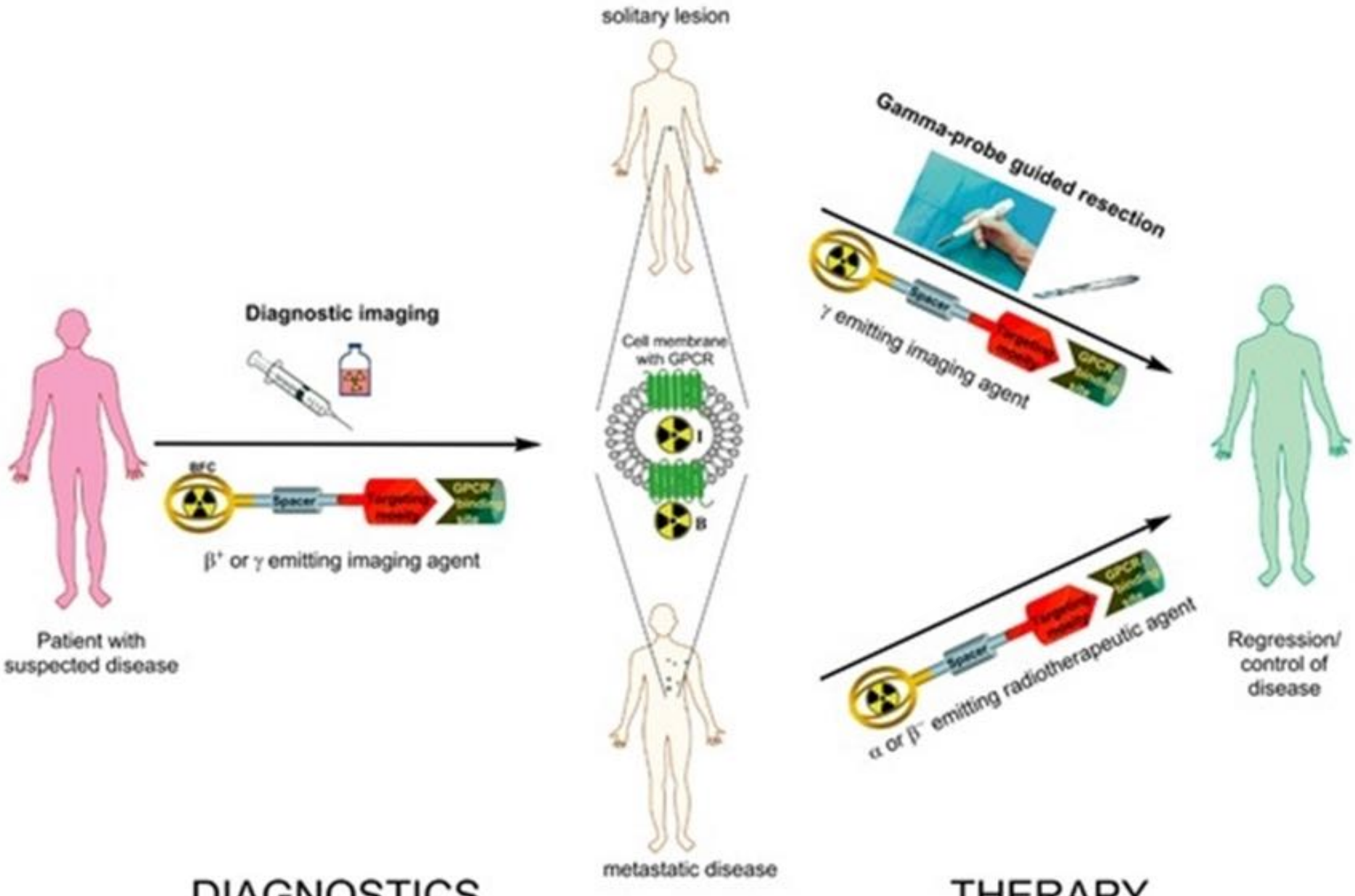
SUMMARY

- PSMA SCANNING IS THE NEWEST TOOL IN DIAGNOSING AND TREATING PROSTATE CANCER
- POTENTIAL DIAGNOSTIC USE AT ALL STAGES OF DISEASE
- CHANGING OUR APPROACH TO PROSTATE CA AT ALL TREATMENT DECISION POINTS
- WITH RADIOTHERANOSTICS IS A NEW TOOL TO TREAT RESIDUAL/RECURRENT AND METASTATIC DISEASE IN A PERSONALIZED PLAN



Theranostic

^{177}Lu-Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy

Richard P. Baum*[1], Harshad R. Kulkarni*[1], Christiane Schuchardt[1], Aviral Singh[1], Martina Wirtz[2], Stefan Wiessalla[1], Margret Schottelius[2], Dirk Mueller[1], Ingo Klette[1], and Hans-Jürgen Wester[2]

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The objective of this study was to analyze the safety and efficacy of the ^{177}Lu-labeled DOTAGA-based prostate-specific membrane antigen (PSMA) ligand ^{177}Lu-DOTAGA-(I-y)fk(Sub-KuE) (^{177}Lu-PSMA) in patients with metastatic castration-resistant prostate cancer (mCRPC). **Methods:** Fifty-six mCRPC patients underwent PSMA radioligand therapy (RLT) with ^{177}Lu-PSMA. ^{68}Ga-PSMA-*(N,N'*-bis-[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-*N,N'*-diacetic acid) (^{68}Ga-PSMA) PET/CT was used for patient selection and follow-up after PSMA RLT. Hematologic status, renal function, and serum prostate-specific antigen levels were documented before and after therapy. Dosimetry was performed in 30 patients. **Results:** ^{177}Lu-PSMA demonstrated high absorbed tumor doses (median, 3.3 mGy/MBq) compared with the levels in normal organs. Parotid glands received higher doses (1.3 mGy/MBq) than kidneys (0.8 mGy/MBq). All patients tolerated the therapy without any acute adverse effects. Except for mild reversible xerostomia in 2 patients, no long-term side effects were observed. There was a small but statistically significant reduction in erythrocyte and leukocyte counts; only the reduction in erythrocyte counts decreased slightly below the reference range. No thrombocytopenia occurred. The severity of pain was significantly reduced in 2 of 6 patients (33.3%). A decrease in prostate-specific antigen levels was noted in 45 of 56 patients (80.4%). Of 25 patients monitored for at least 6 mo after 2 or more PSMA RLT cycles, a molecular response evaluation (^{68}Ga-PSMA PET/CT) revealed partial remission in 14, stable disease in 2, and progressive disease in 9 patients. Contrast-enhanced CT revealed partial remission in 5, stable disease in 13, and progressive disease in 7 patients. The median progression-free survival was 13.7 mo, and the median overall survival was not reached during follow-up for 28 mo. **Conclusion:** PSMA RLT with ^{177}Lu-PSMA is feasible, safe, and effective in end-stage progressive mCRPC with appropriate selection and follow-up of patients by ^{68}Ga-PSMA PET/CT through application of the concept of theranostics.

Key Words: PSMA; radioligand therapy; theranostics

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E-mail: richard.baum@zentralklinik.de
*Contributed equally to this work.
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Metastatic castration-resistant prostate cancer (mCRPC) has a poor prognosis, with an estimated 27,540 prostate cancer deaths in the United States in 2015 (*1*). The novel agents abiraterone and enzalutamide provide limited survival benefits of 3.9 and 4.8 mo, respectively (*2,3*). Overall survival has been reported to improve by 3.6 mo with ^{223}Ra-chloride, but it is indicated for patients with skeletal metastases only (*4*). Immunotherapy with sipuleucel-T confers a survival benefit of a few months but has no impact on the time to progression and is associated with immunologic adverse events (*5*).

Prostate-specific membrane antigen (PSMA) is a glutamate carboxypeptidase II overexpressed in prostate cancer (*6*). In 2002, Pomper et al. performed the first in vivo study with a urea-based compound targeting PSMA for diagnosis (*6*). Their high-affinity, urea-based inhibitor of PSMA maintained target specificity after radiolabeling with ^{68}Ga (*7*). ^{68}Ga-labeled PSMA inhibitors with *N,N'*-bis-[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-*N,N'*-diacetic acid as a chelator (^{68}Ga-PSMA) have been successfully used for the imaging of prostate cancer, with high sensitivity and specificity (*8,9*). These small molecules penetrate solid tumors and, compared with whole antibodies, have the advantage of rapid clearance from blood. Radioimmunotherapy with PSMA antibody ^{177}Lu-DOTA-J591 was limited by myelosuppression and nonhematologic toxicity, with a maximum tolerated activity per cycle of 2,450 MBq/m^2 (*10*). Zechmann et al. performed endoradiotherapy of mCRPC using a PSMA small molecule labeled with ^{131}I (*11*). The ^{68}Ga-, ^{111}In-, or ^{177}Lu-labeled diagnostic or therapeutic PSMA ligand (DOTAGA-(I-y)fk(Sub-KuE), also called PSMA-I&T, for "imaging and therapy") possesses a unique potential for the management of advanced prostate cancer (*12–14*). PSMA radioligand therapy (RLT) with PSMA-I&T could achieve high tumor-to-background ratios of mean absorbed doses (*13,15*).

We analyzed the safety and efficacy of the ^{177}Lu-labeled DOTAGA-based PSMA ligand ^{177}Lu-DOTAGA-(I-y)fk(Sub-KuE) (^{177}Lu-PSMA) in a larger cohort of patients with mCRPC. The endpoints of our analysis, which was performed in correlation with kinetics and dosimetry, were safety, objective response, progression-free survival, and overall survival.

MATERIALS AND METHODS

Patient Characteristics

Fifty-six patients who had progressive mCRPC (median age, 72 y; median Gleason score, 8) and rising prostate-specific antigen (PSA)

German Multicenter Study Investigating ^{177}Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients

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^{177}Lu-labeled PSMA-617 is a promising new therapeutic agent for radioligand therapy (RLT) of patients with metastatic castration-resistant prostate cancer (mCRPC). Initiated by the German Society of Nuclear Medicine, a retrospective multicenter data analysis was started in 2015 to evaluate efficacy and safety of ^{177}Lu-PSMA-617 in a large cohort of patients. **Methods:** One hundred forty-five patients (median age, 73 y; range, 43–88 y) with mCRPC were treated with ^{177}Lu-PSMA-617 in 12 therapy centers between February 2014 and July 2015 with 1–4 therapy cycles and an activity range of 2–8 GBq per cycle. Toxicity was categorized by the common toxicity criteria for adverse events (version 4.0) on the basis of serial blood tests and the attending physician's report. The primary endpoint for efficacy was biochemical response as defined by a prostate-specific antigen decline ≥ 50% from baseline to at least 2 wk after the start of RLT. **Results:** A total of 248 therapy cycles were performed in 145 patients. Data for biochemical response in 99 patients as well as data for physician-reported and laboratory-based toxicity in 145 and 121 patients, respectively, were available. The median follow-up was 16 wk (range, 2–30 wk). Nineteen patients died during the observation period. Grade 3–4 hematotoxicity occurred in 18 patients: 10%, 4%, and 3% of the patients experienced anemia, thrombocytopenia, and leukopenia, respectively. Xerostomia occurred in 8%. The overall biochemical response rate was 45% after all therapy cycles, whereas 40% of patients already responded after a single cycle. Elevated alkaline phosphatase and the presence of visceral metastases were negative predictors and the total number of therapy cycles positive predictors of biochemical response. **Conclusion:** The present retrospective multicenter study of ^{177}Lu-PSMA-617 RLT demonstrates favorable safety and high efficacy exceeding those of other third-line systemic therapies in mCRPC patients. Future phase II/III studies are warranted to elucidate the survival benefit of this new therapy in patients with mCRPC.

Key Words: prostate cancer; PSMA-617; mCRPC; radioligand therapy

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According to the American Cancer Society, prostate cancer is the most common cancer and second most frequent cause of cancer-related death in men in the United States (*1*). The 5-y survival rate of locally advanced prostate cancer is nearly 100%; however, the rate is significantly lower in the case of metastatic disease (31%) (*2*). Therefore, developing new strategies for diagnosis, imaging, and treatment of metastatic prostate cancer is of major importance.

Prostate-specific membrane antigen (PSMA) is overexpressed in prostate cancer and even more so with increasing de-differentiation or castration-resistant disease (*3*). Radiolabeled ligands targeting PSMA have recently been the subject of numerous studies showing high sensitivity and contrast in detecting recurrent prostate cancer and its metastases with remarkable detection rates (*4–7*). Recent studies have also shown a high sensitivity of PSMA-targeted imaging in determining the local extent of disease before radical prostatectomy (*8–10*). The high PSMA expression in prostate cancer metastases makes it also a promising approach to develop new tracers for targeted radionuclide therapies.

Benešová et al. introduced a high-affinity PSMA ligand (PSMA-617) that can be labeled with ^{68}Ga or ^{177}Lu and demonstrates superior tumor-to-background uptake (*11*). Since 2015, several studies reported promising results for response rates and a favorable safety profile after radioligand therapy (RLT) with ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (mCRPC) (*12–16*). In a single-center study of 28 patients, a slight improvement

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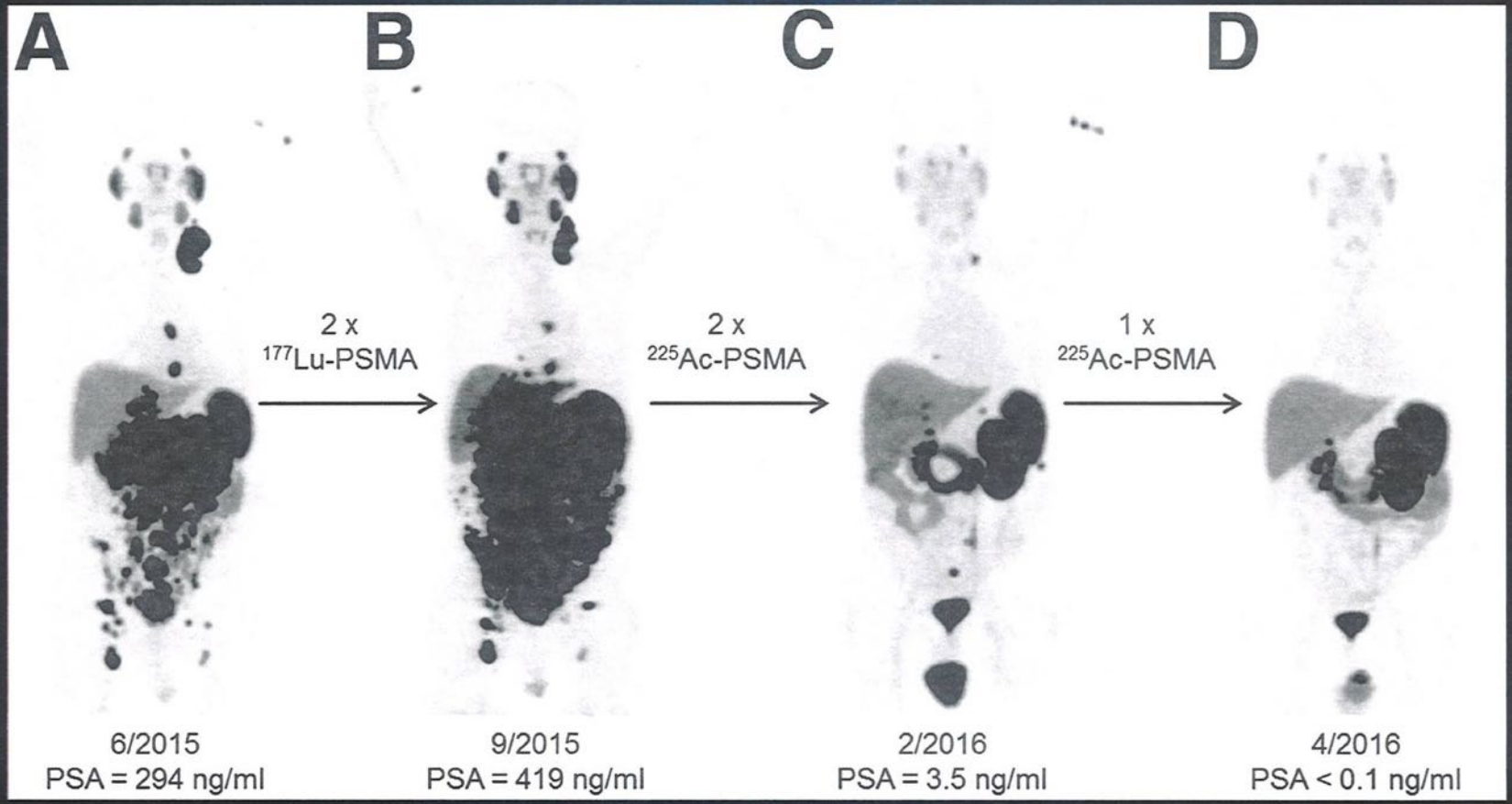

68Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting 177Lu-PSMA-617 presented progression (B). Clemens Kratochwil et al. J Nucl Med 2016;57:1941-1944

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