CORSO SUPERIORE SIFO IN FARMACIA CLINICA
Ed. 2015-2016 – II ANNO

Catania, 27 - 30 settembre 2016

I RADIOFARMACI

RUOLO DEL FARMACISTA IN MEDICINA NUCLEARE

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U.O.C. Medicina Nucleare
P.O. Nesima A.R.N.A.S. GARIBALDI

LA MEDICINA NUCLEARE

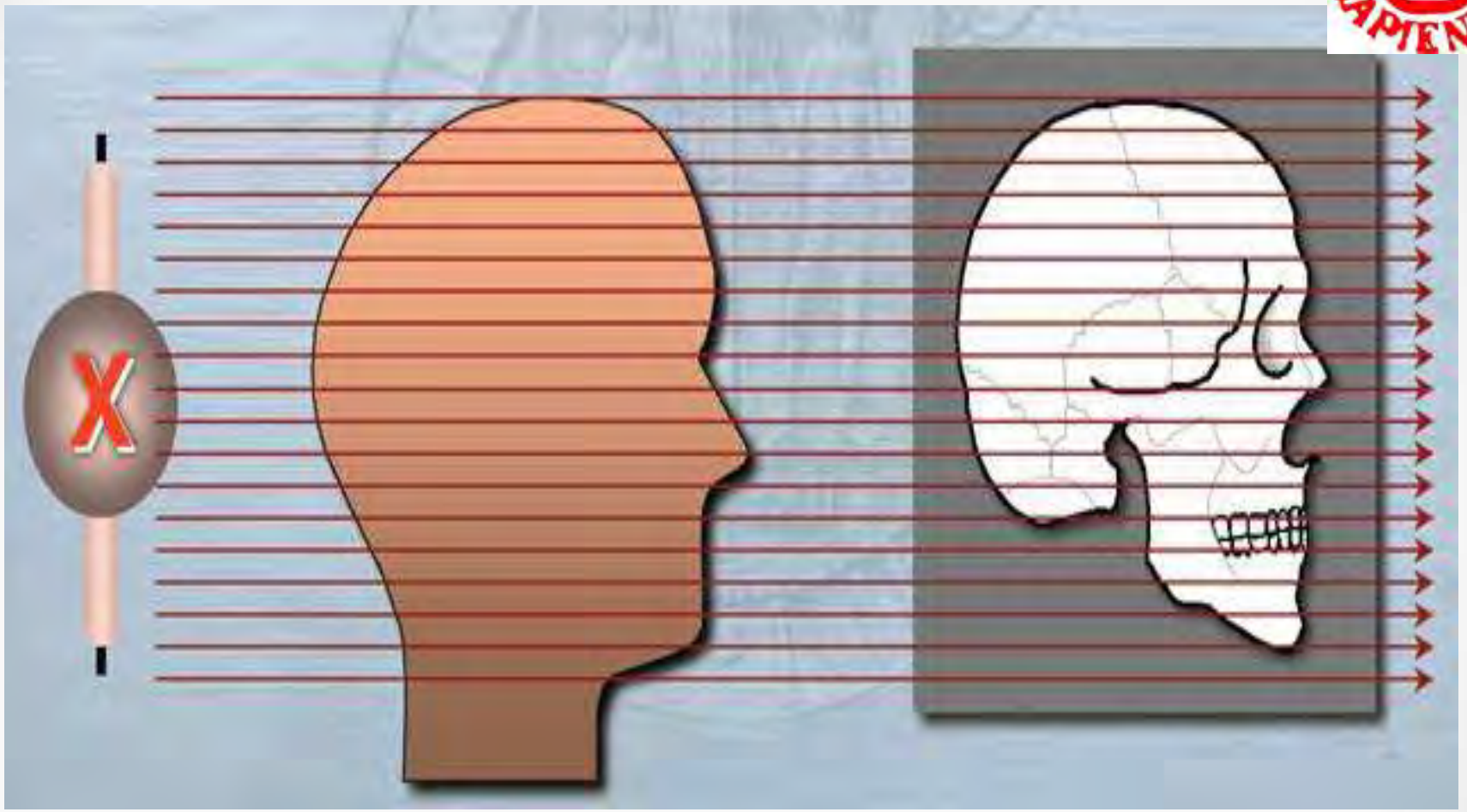
CHE COSA E'?

E' LA BRANCA SPECIALISTICA DELLA MEDICINA CHE SI AVVALE DELL'USO DI RADIONUCLIDI A SCOPO DIAGNOSTICO, TERAPEUTICO E DI RICERCA BIOMEDICA.

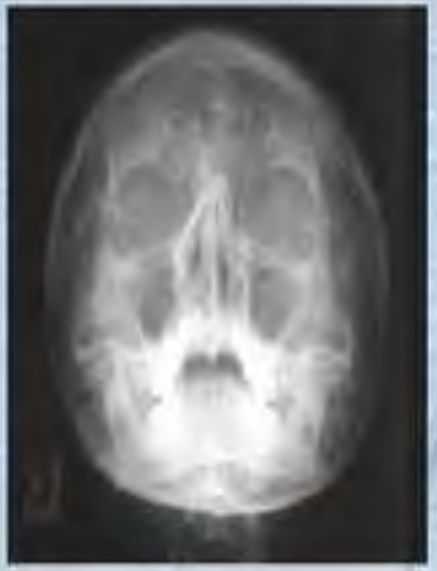
PERMETTE L'INDAGINE "IN VIVO" DEI PROCESSI BIOLOGICI, FISIOLOGICI E PATOLOGICI.

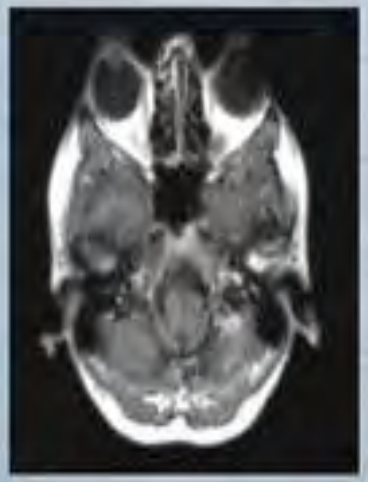
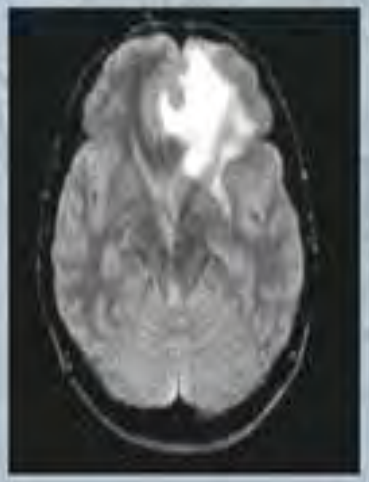
I RADIOISOTOPI, CONIUGATI A MOLECOLE O CELLULE CHE FUNGONO DA VETTORI E LI RENDONO "**INTELLIGENTI**", VENGONO INTRODOTTI NELL'ORGANISMO E PERMETTONO DI IDENTIFICARE ORGANI E TESSUTI SANI E MALATI E, IN ALCUNI CASI, DI IRRADIARE I TESSUTI PATOLOGICI

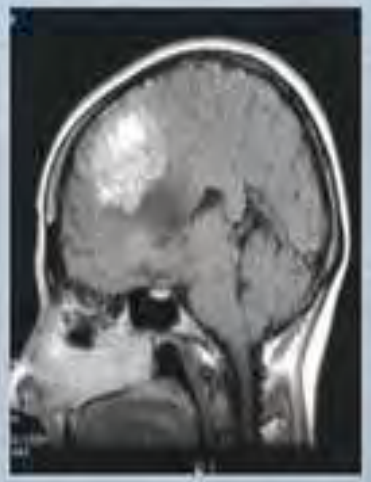
IMMAGINI RADIOLOGICHE



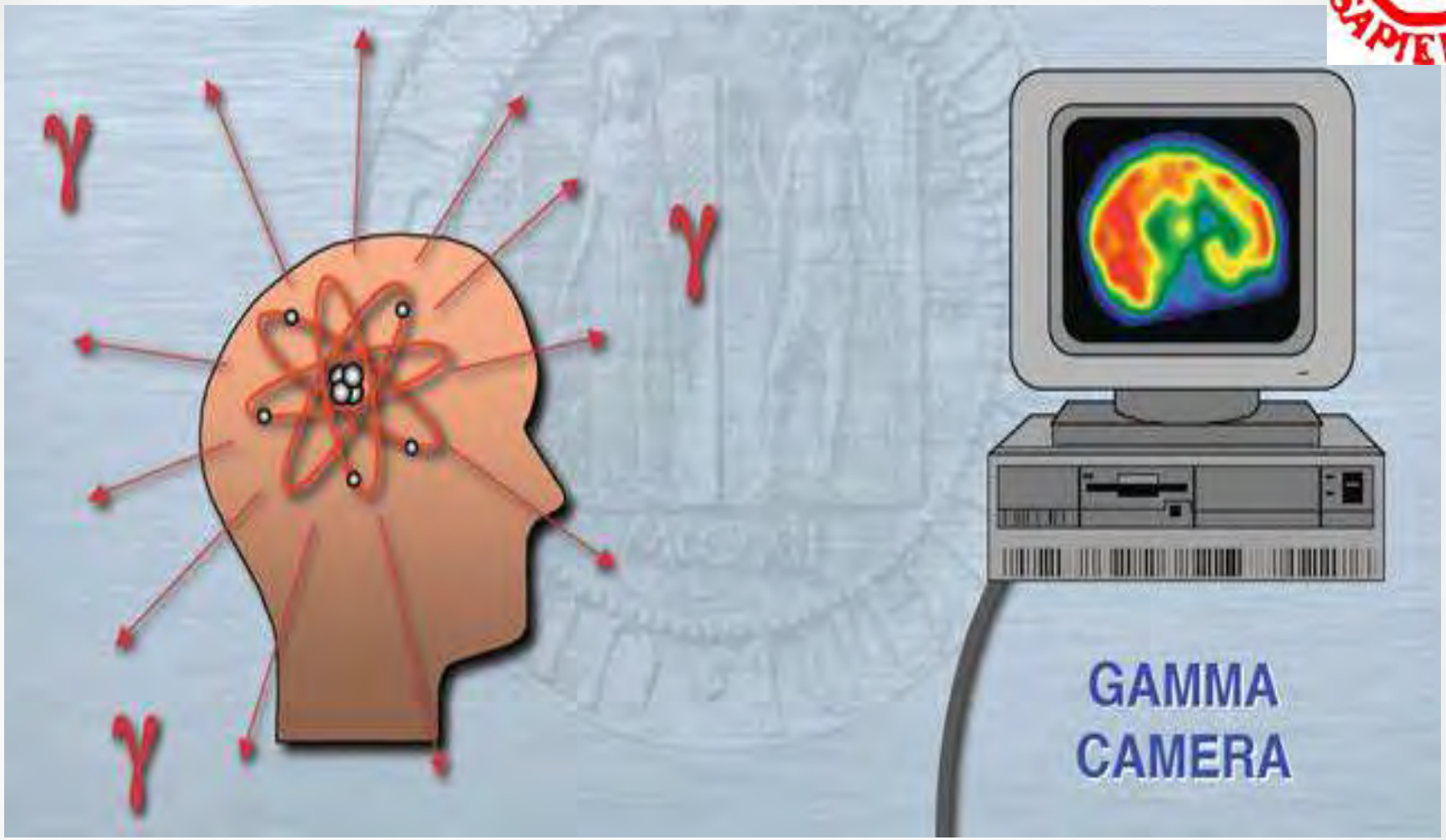
Il fascio di radiazioni X provenienti da un tubo radiogeno viene attenuato dai tessuti interposti da analizzare prima di raggiungere il sistema di rilevazione



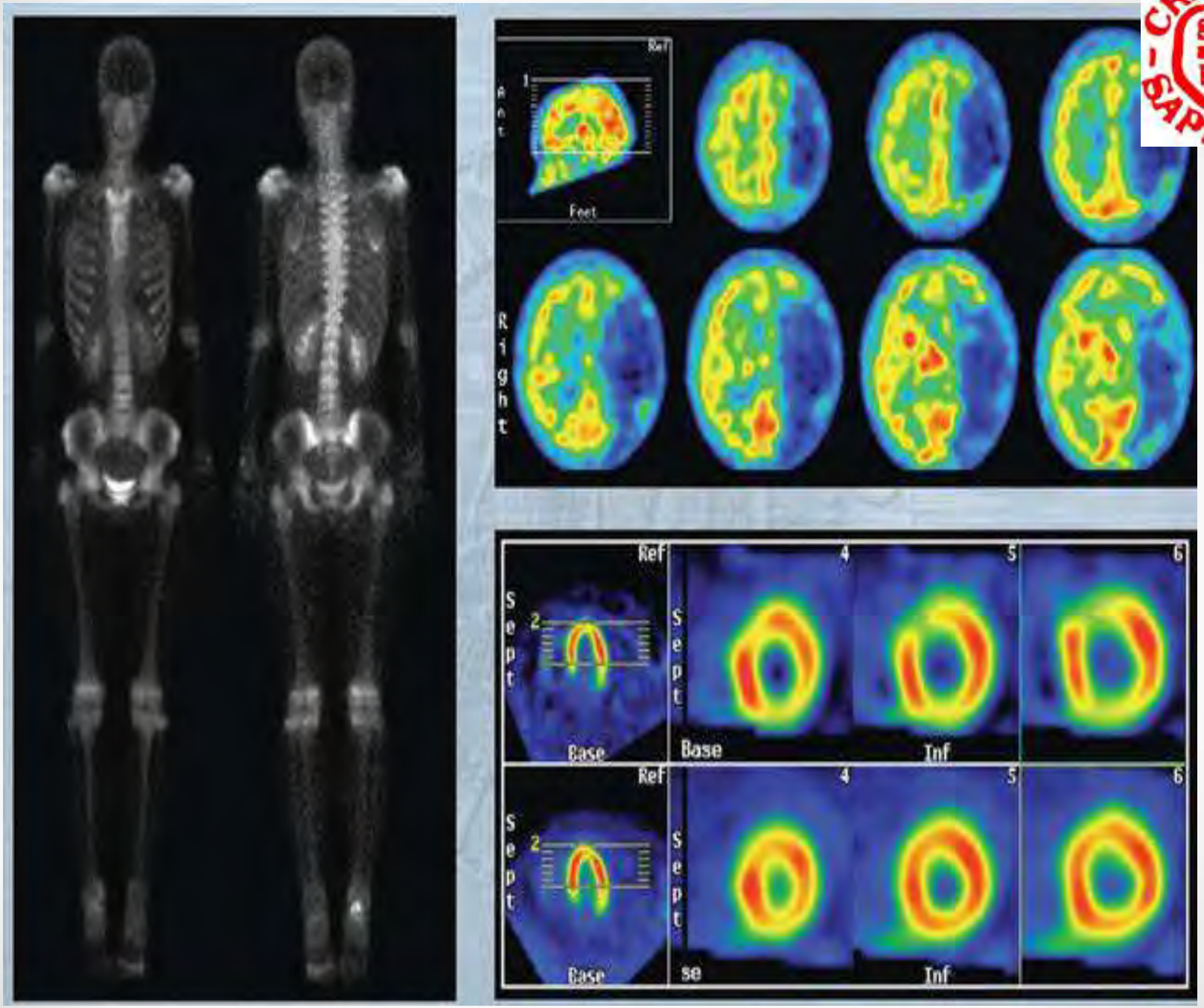


IMMAGINI MEDICO NUCLEARI



Si ottengono rilevando le radiazioni emesse dal radiofarmaco distribuito nell'organismo.

E' il paziente che emette le radiazioni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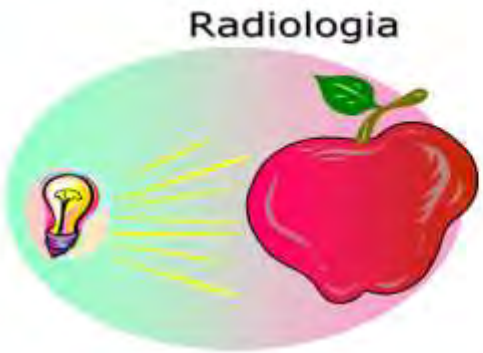
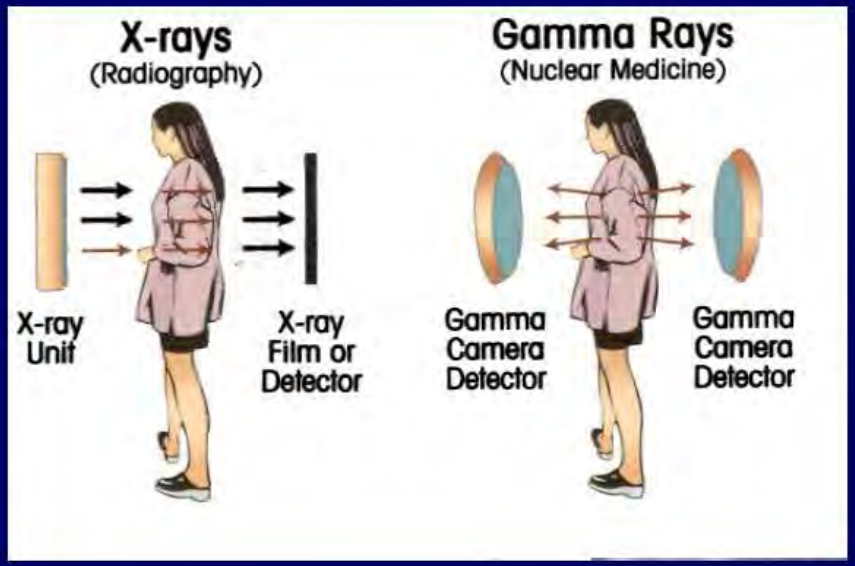
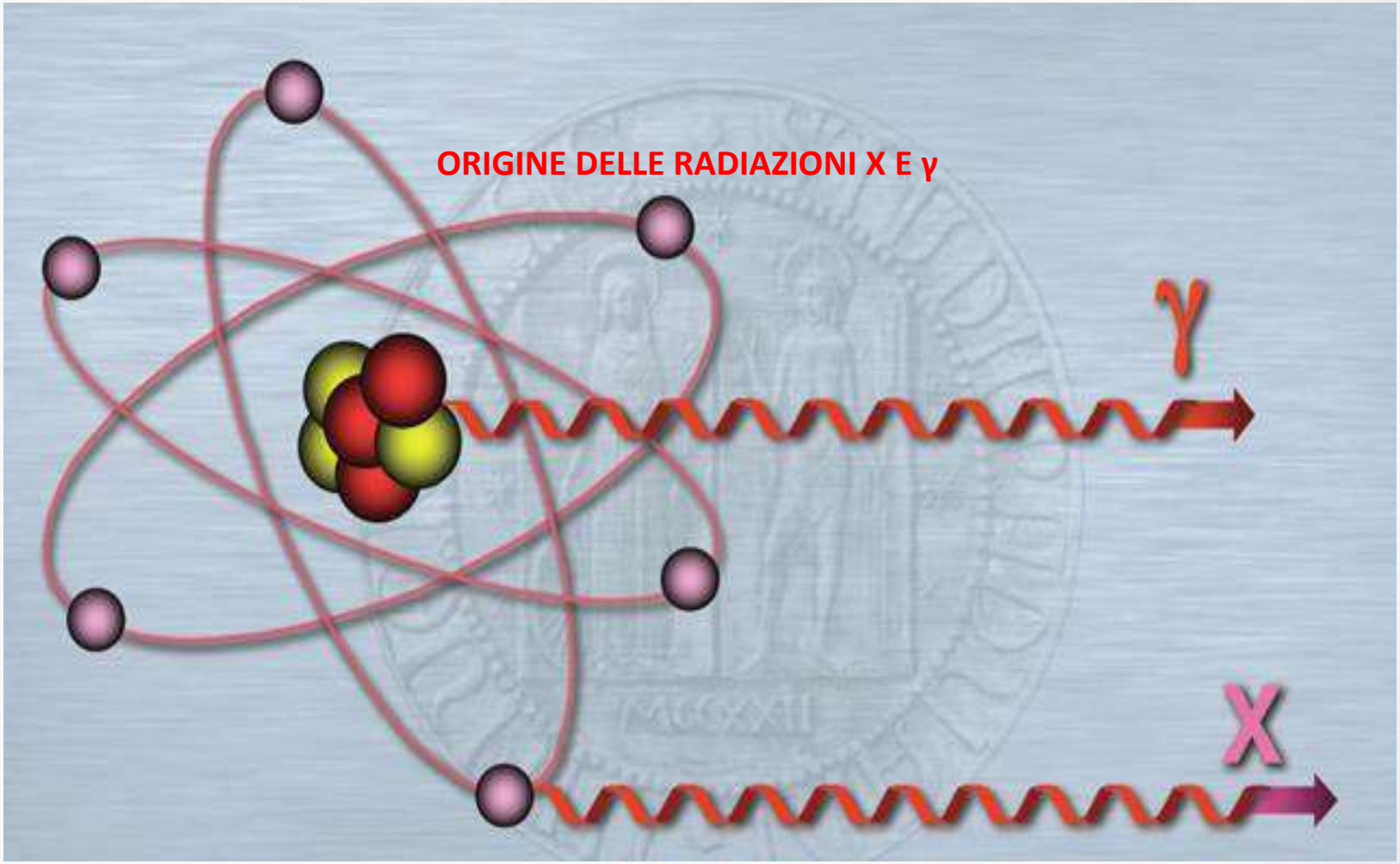


Nuclear Medicine Vs Radiography

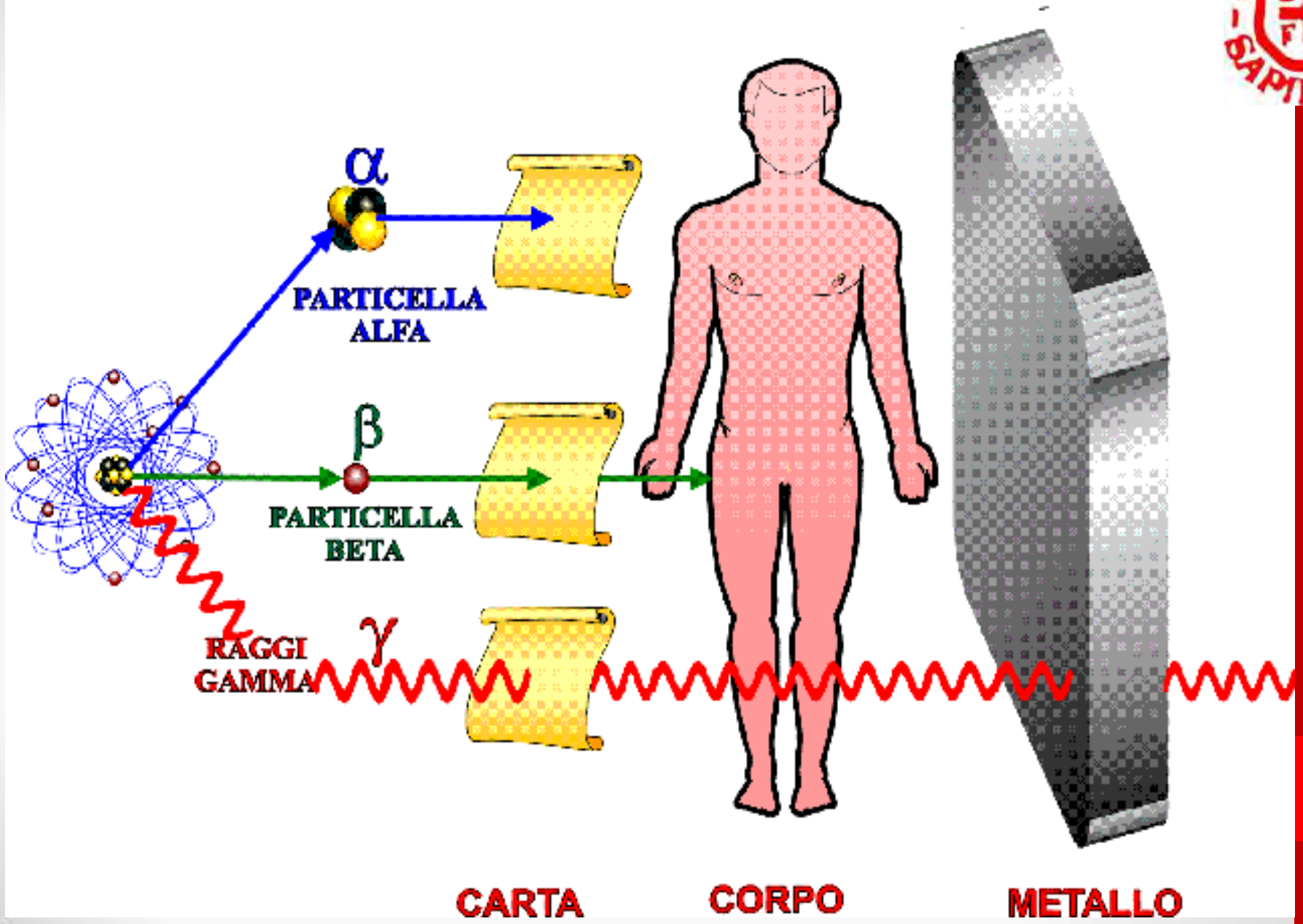


LA MEDICINA NUCLEARE E' ANCORA GRAVATA DA UN ALONE DI MISTERO E DI TIMORE LEGATO SOPRATTUTTO ALL'AGGETTIVO "NUCLEARE" CHE FA RIAFFIORARE ALLA MEMORIA OLOCAUSTICI BELLICI ED INCIDENTI NUCLEARI.



NON C'E' ALCUNA DIFFERENZA, A PARITA' DI ENERGIA, TRA GLI EFFETTI DI UNA RADIAZIONE "X" RADIOLOGICA ED UNA"γ"(gamma) MEDICO NUCLEARE

RADIAZIONI E LORO POTERE DI PENETRAZIONE



A COSA SERVE?

- **DOSAGGI DI LABORATORIO *"IN VITRO"***
- **IMAGING *"IN VIVO"* MEDIANTE LE SCINTIGRAFIE**
- **TERAPIA RADIOMETABOLICA**

LA MEDICINA NUCLEARE HA LA PECULIARIETA' DI EVIDENZIARE UN'ALTERAZIONE FUNZIONALE PRIMA CHE SIANO RICONOSCIBILI ALTERAZIONI ANATOMICHE

LE TECNICHE DI IMAGING MEDICO NUCLEARE NON SONO INVASIVE.

IL PAZIENTE SUBISCE AL MASSIMO UNA INIEZIONE ENDOVENOSA

I RADIOFARMACI USATI SONO ASSOLUTAMENTE SICURI E PRIVI DI REAZIONI AVVERSE

Single

Photon

Emission

***C*omputed**

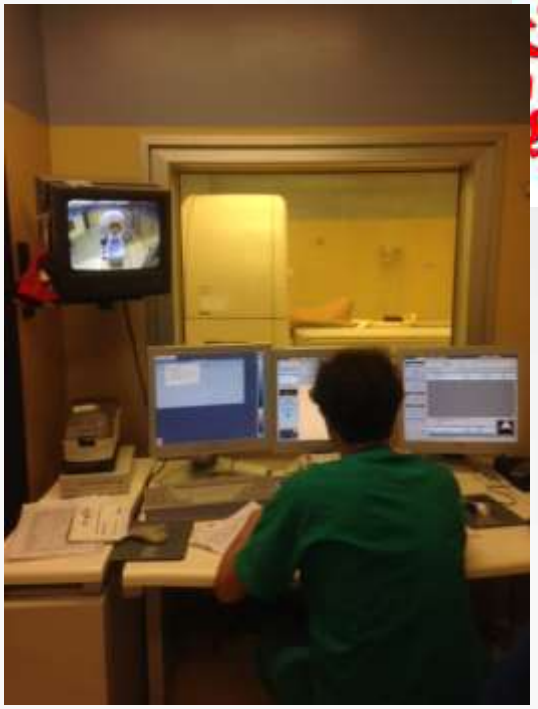
Tomography

Positron

Emission

Tomography


PHILIPS

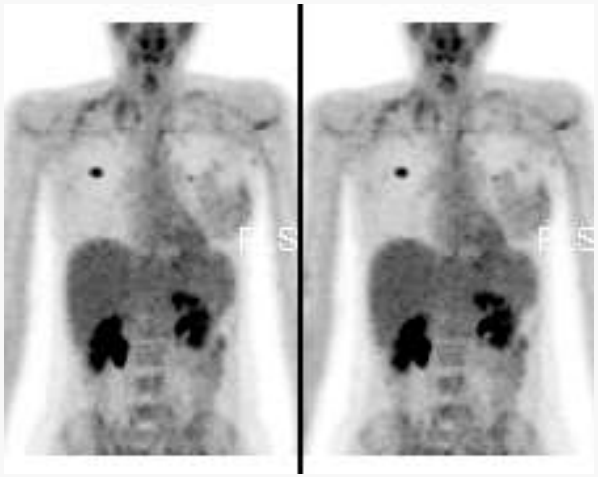


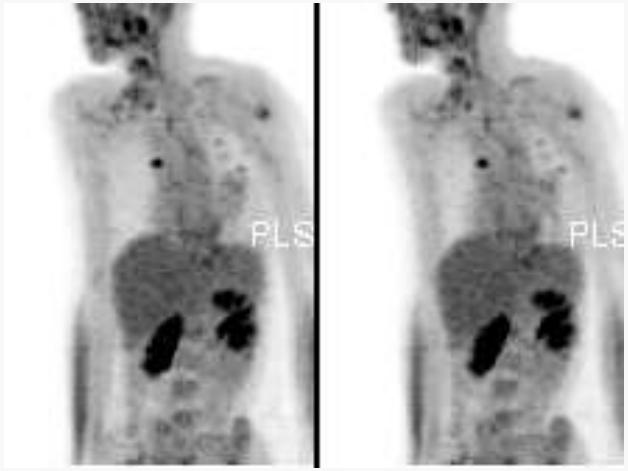
ARNAS GARIBALDI
CATANIA
AZIENDA OSPEDALIERA DI RILIEVO NAZIONALE E DI ALTA SPECIALIZZAZIONE

PET – quale imaging ?

Con la PET la rilevazione della distribuzione del tracciante all'interno dei distretti anatomici fornisce informazioni

metabolico-funzionali





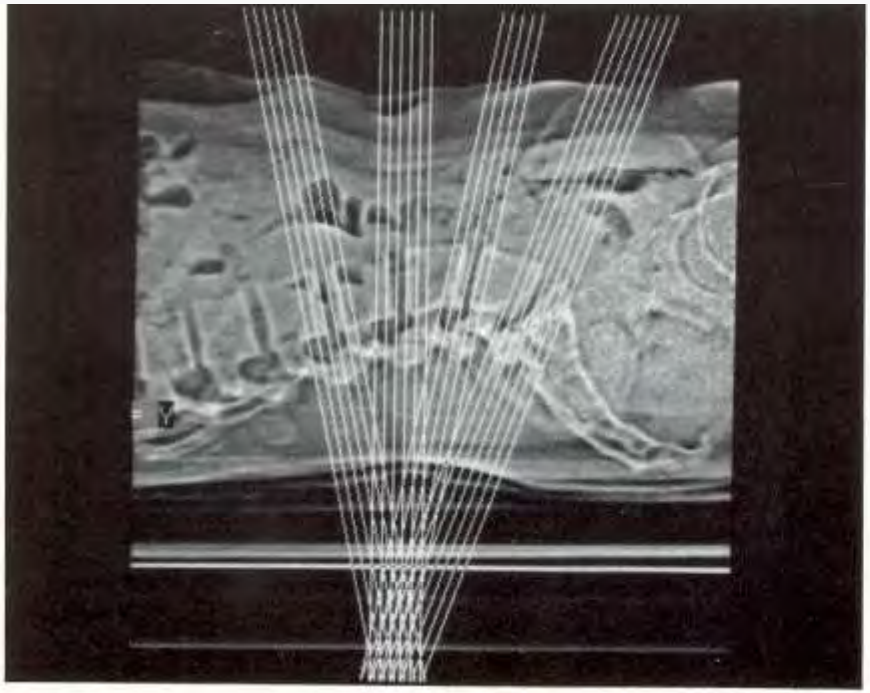
processi chimici e fisici

forniscono le informazioni

per rilevare l'immagine diagnostica

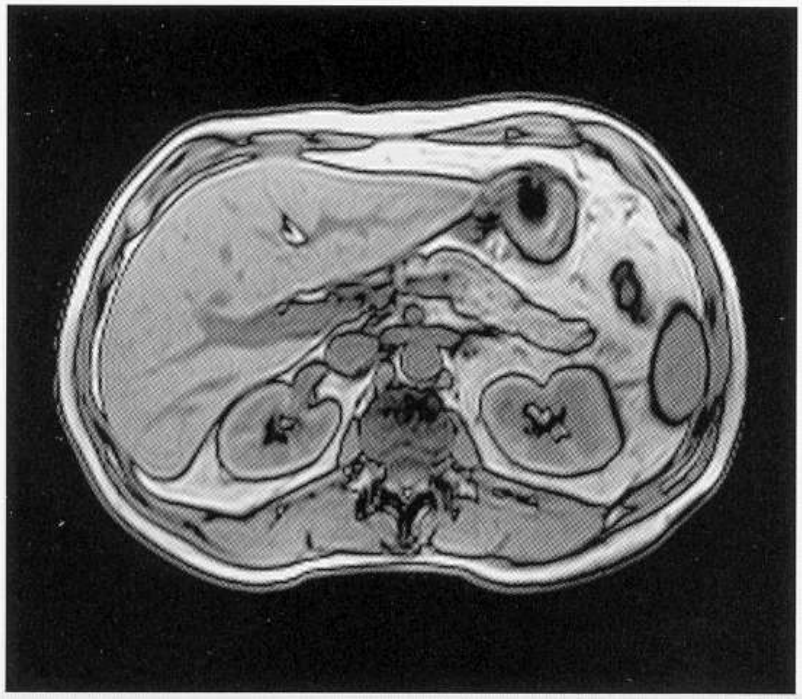
TAC – quale imaging ?

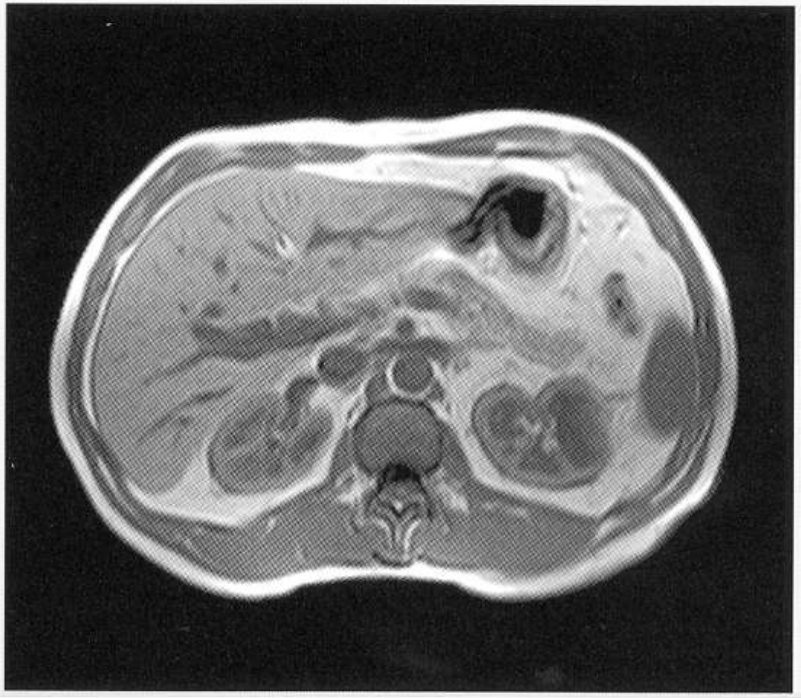
- ottimo imaging morfologico



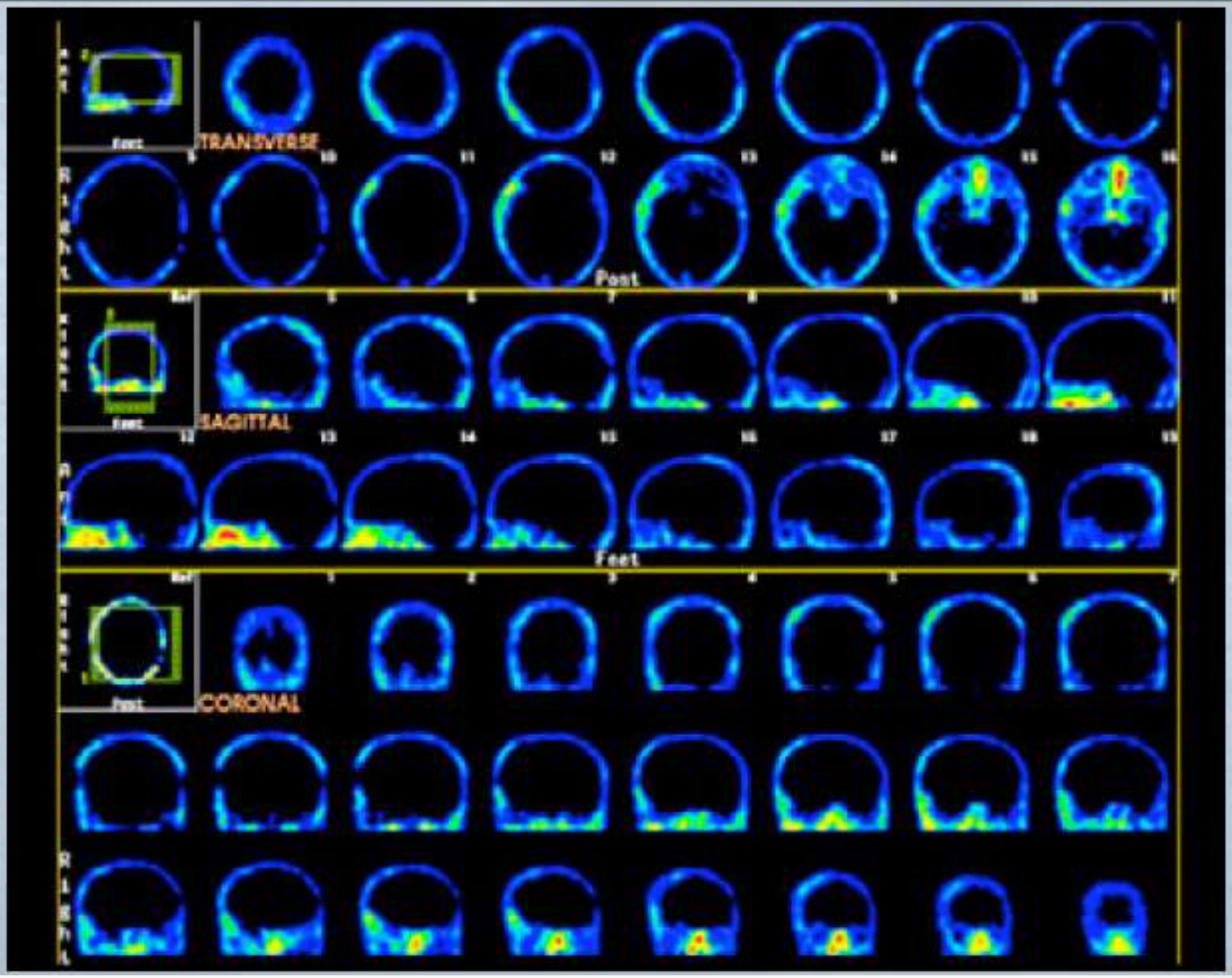
RMN – quale imaging ?

ottimo imaging morfologico

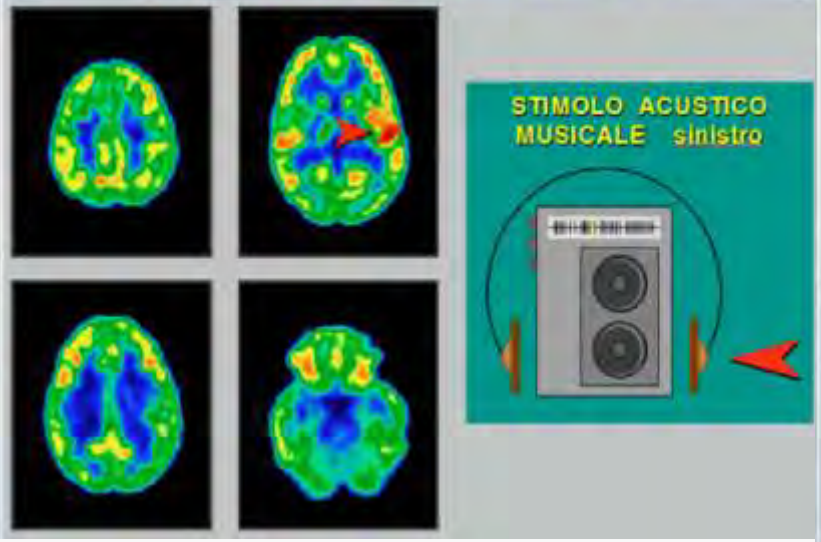




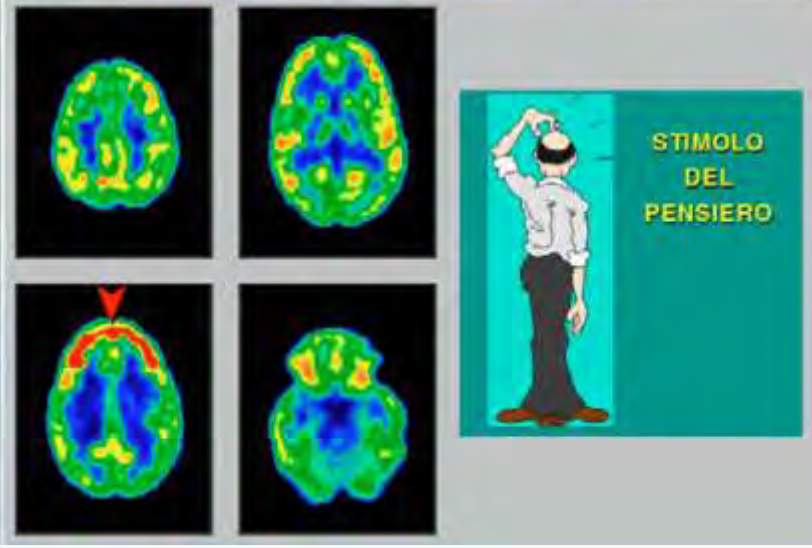
TRAUMA 48h - Brain Death



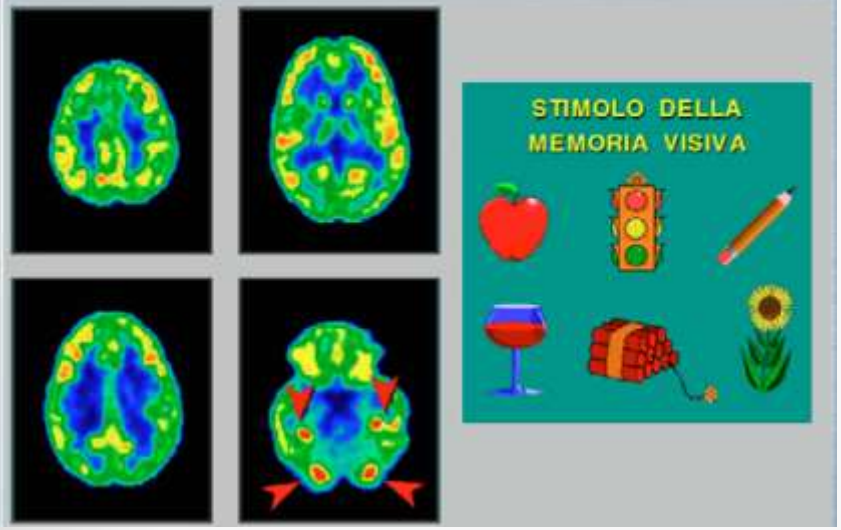
PET CEREBRALE con ^{18}FDG



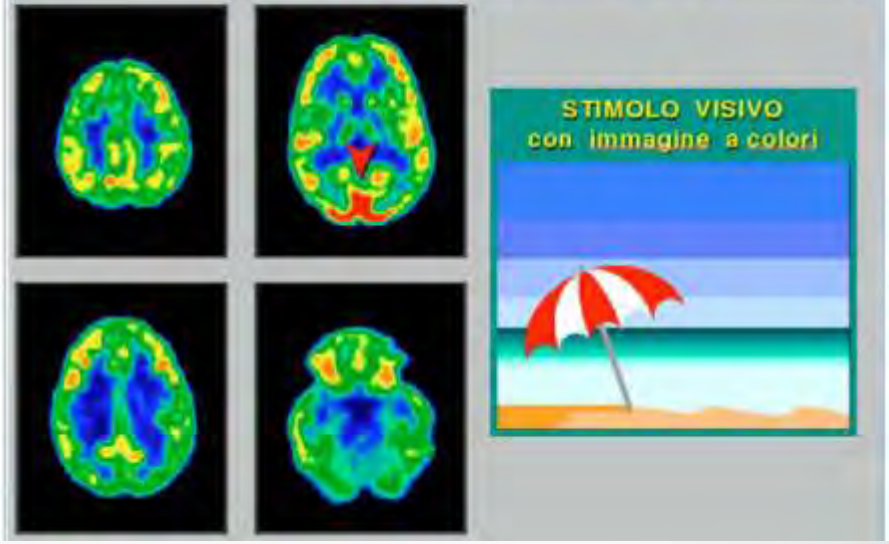
PET CEREBRALE con ^{18}FDG



PET CEREBRALE con ^{18}FDG



PET CEREBRALE con ^{18}FDG

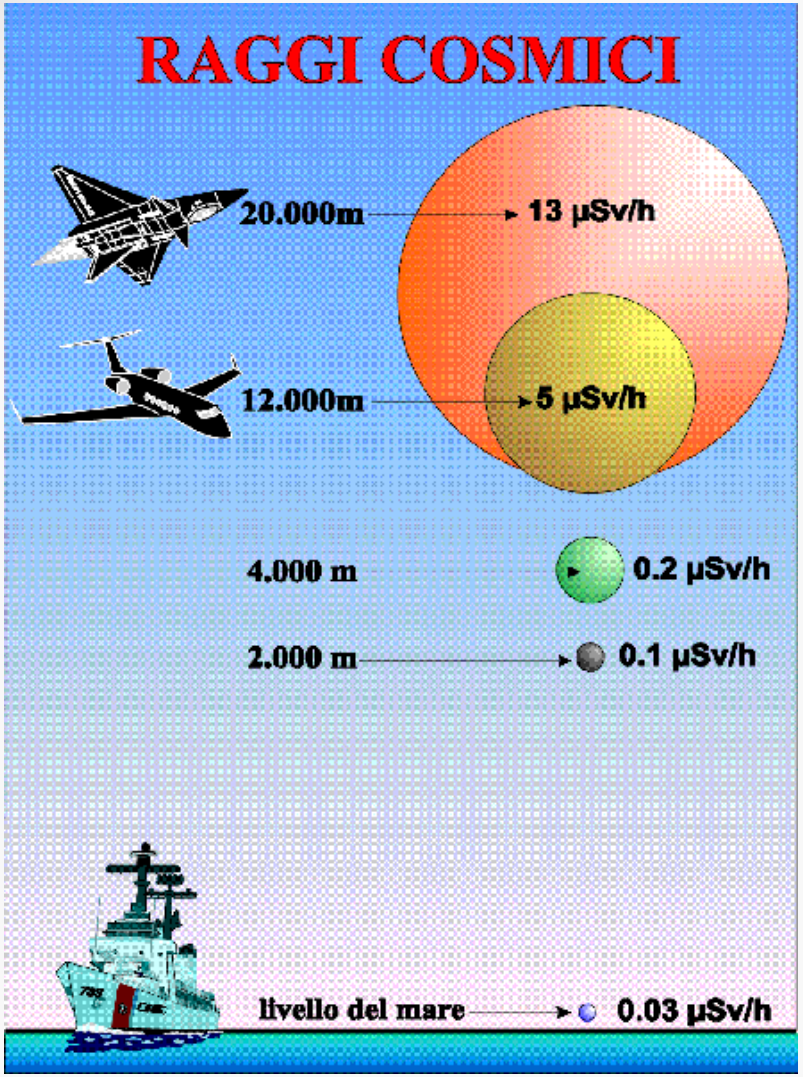


FA MALE ?

SICURAMENTE NO!

LE TECNICHE DI IMAGING MEDICO NUCLEARE NON SONO INVASIVE. IL PAZIENTE SUBISCE AL MASSIMO UNA INIEZIONE ENDOVENOSA

I RADIOFARMACI USATI SONO ASSOLUTAMENTE SICURI E PRIVI DI REAZIONI AVVERSE



LA RADIOATTIVITA' E' NORMALMENTE PRESENTE NELL'AMBIENTE

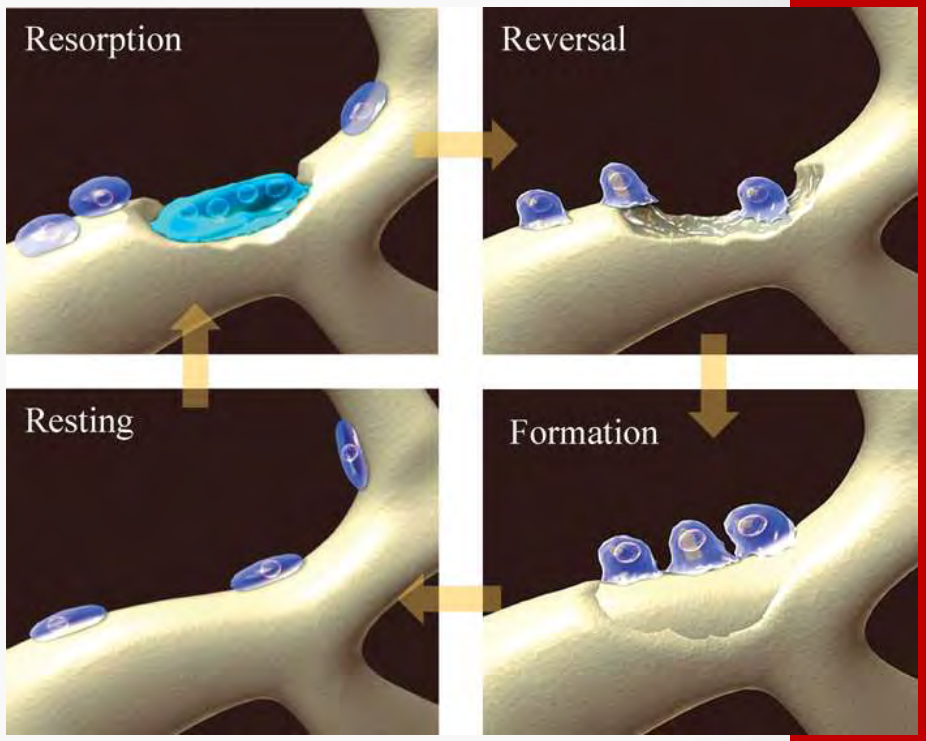
BASTI PENSARE ALLE RADIAZIONI COSMICHE O A QUELLE PRODOTTE DALLE ROCCE , ASSORBITE DURANTE VIAGGI INTERCONTINENTALI IN AEREO O DURANTE TERAPIE TERMALI.

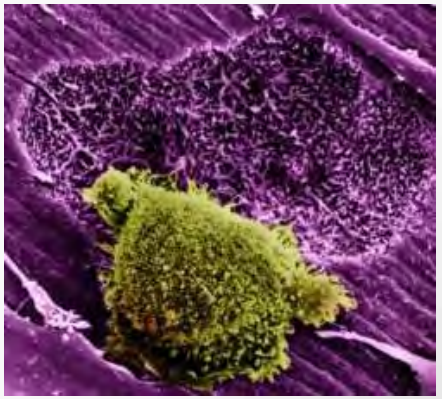
Radiofarmaci per l'apparato osteoarticolare

Biologia dell'osso

L'osso è sempre in uno stato attivo di rimodellamento(costruzione/distruzione)

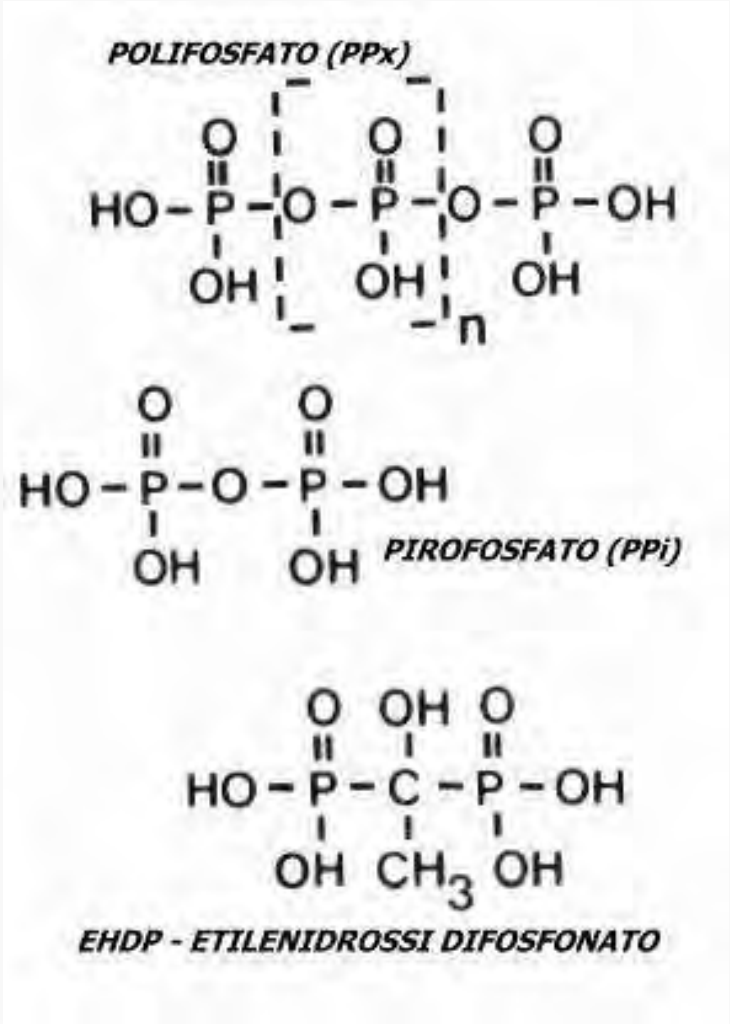
- **Riassorbimento**: gli osteoclasti stimolati erodono l'osso creando una cavità.
- **Inversione**: la superfice ossea è preparata per gli osteoblasti che iniziano a formare osso.
- **Formazione**: Gli osteoblasti sostituiscono l'osso riassorbito e riempiono le cavità con osso nuovo.
- **Riposo**: la superfice dell'osso riposa sino al nuovo ciclo di riassorbimento.

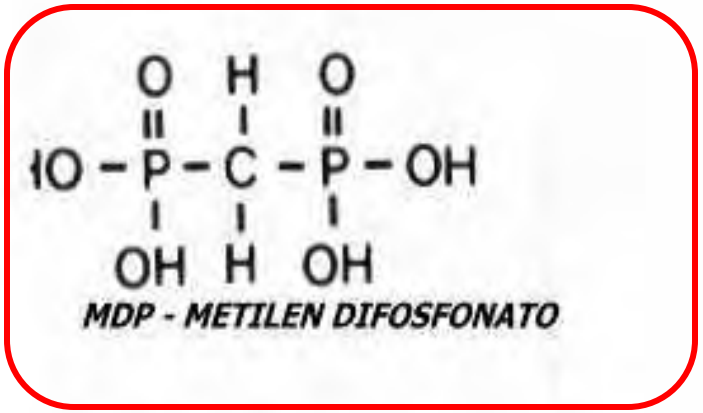


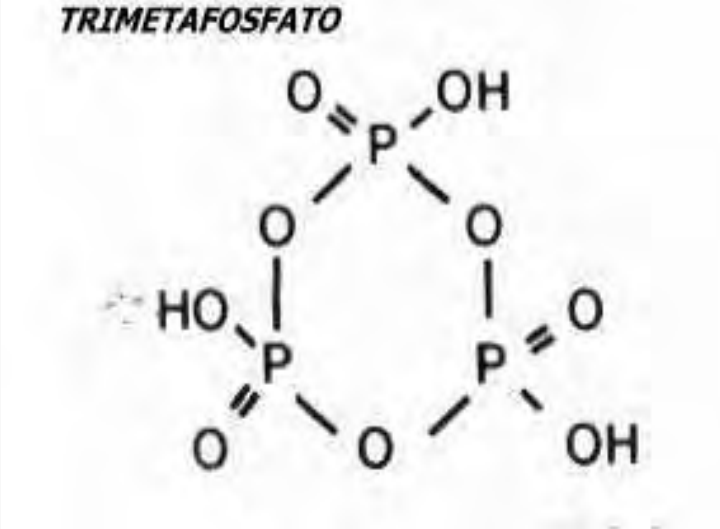


Adattato da Novert's Pharmaceuticals

Bone Radiopharmaceuticals







Scintigrafia Total Body

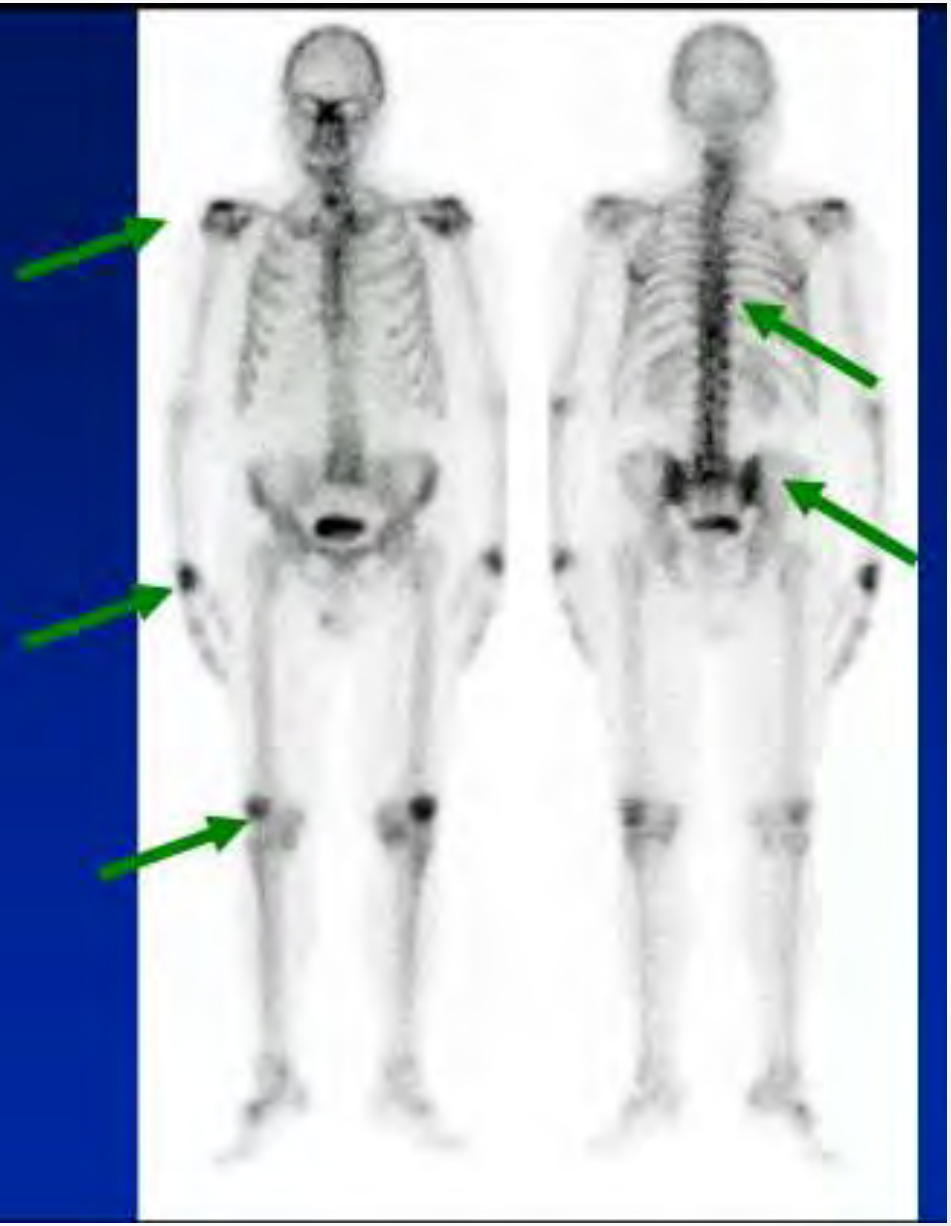
Scintigrafia Normale :

Scheletro assiale ed appendicolare, simmetria, presenza di attività nei tessuti molli, reni con minima attività, vescica, tiroide, contaminazione.

Radiofarmaci per scintigrafia ossea

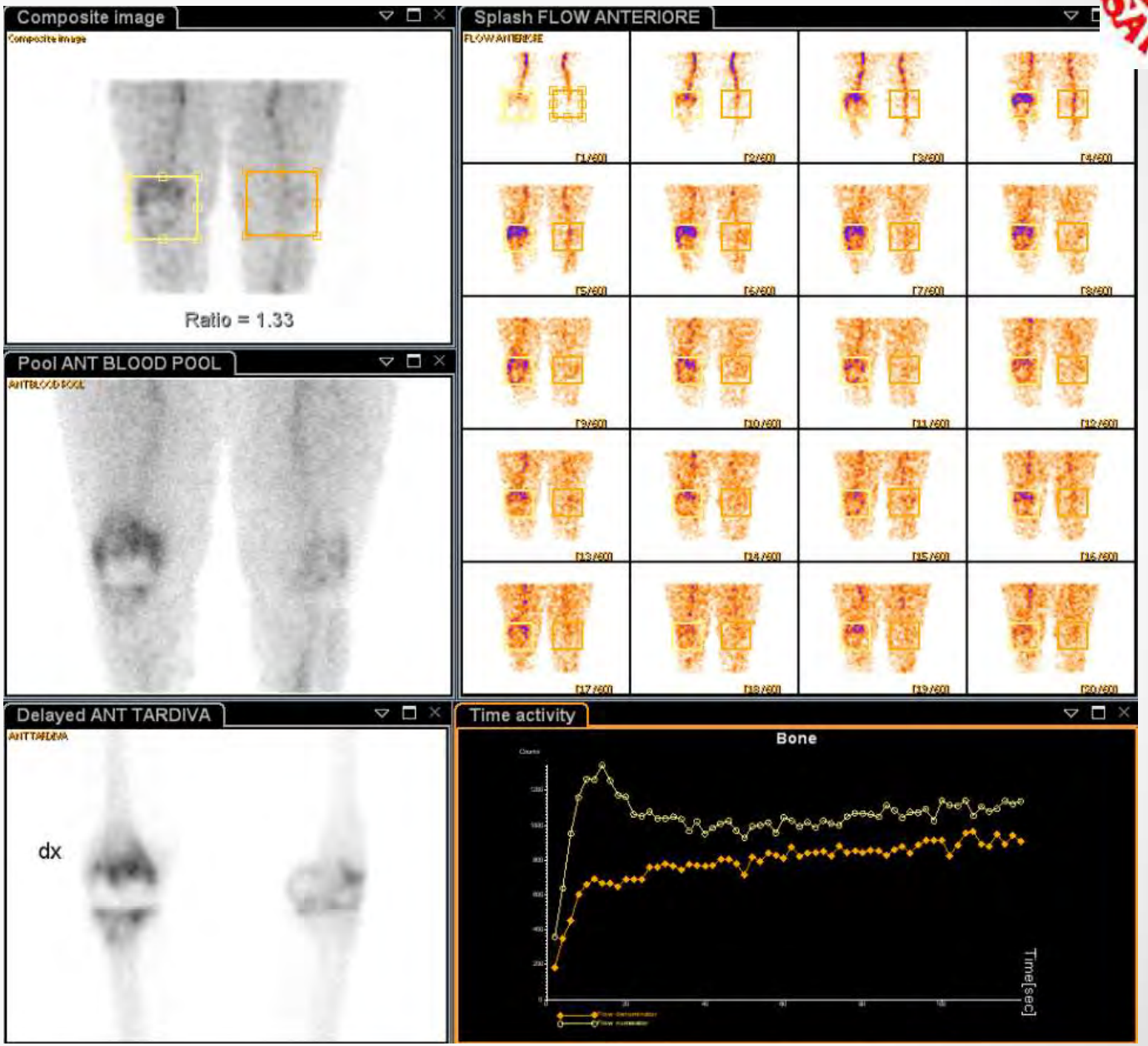
- I difosfonati marcati con tecnezio-99m sono i radiofarmaci di scelta per la scintigrafia ossea
- Diffondono passivamente negli spazi extra-vascolari ed extracellulari e si depositano intorno alla matrice ossea
- La quota di radiofarmaco che non viene legata, viene eliminata dal plasma per escrezione renale
- Le immagini tardive mostrano il legame del tracciante alla matrice ossea, visualizzando l'intero apparato scheletrico
- L'esame viene eseguito 2-3 ore dopo l'iniezione per ottenere un elevato rapporto osso/fondo, che garantisce una buona qualità dell'immagine
- Maggiore è il flusso ematico e l'attività metabolica di una particolare regione ossea, maggiore sarà la concentrazione del tracciante

Artrosi



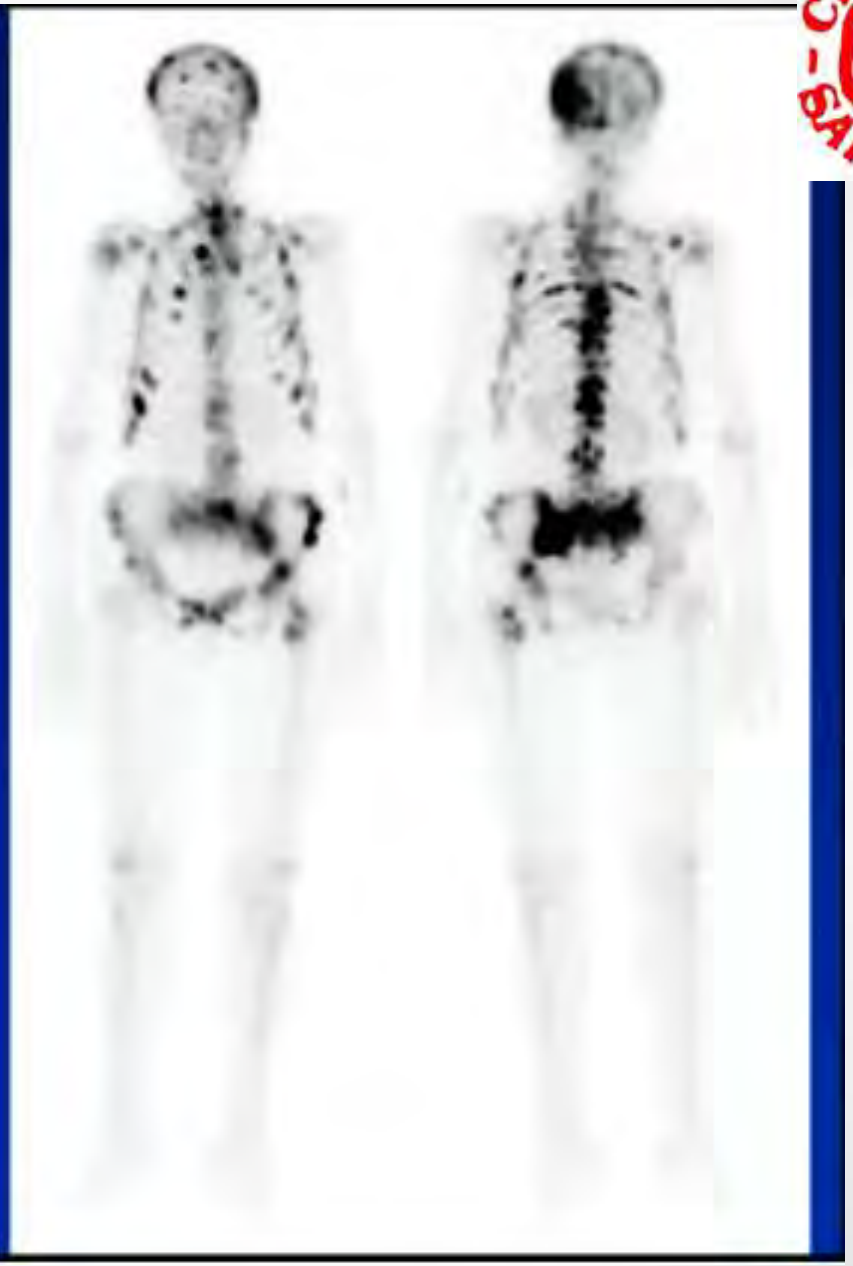
Crollo vertebrale di n.d.d.

SCINTIGRAFIA TRIFASICA

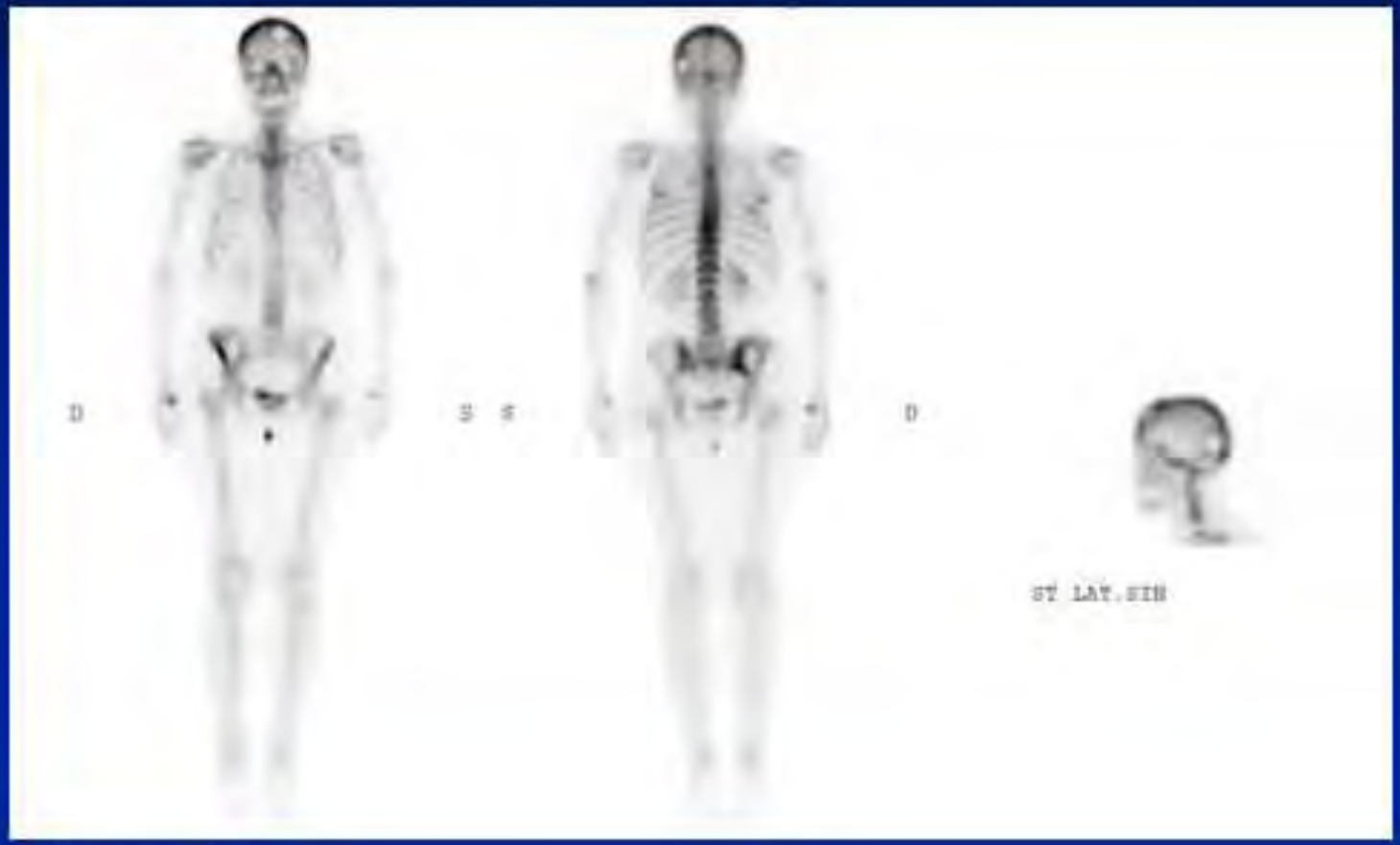


Metastasi ossee

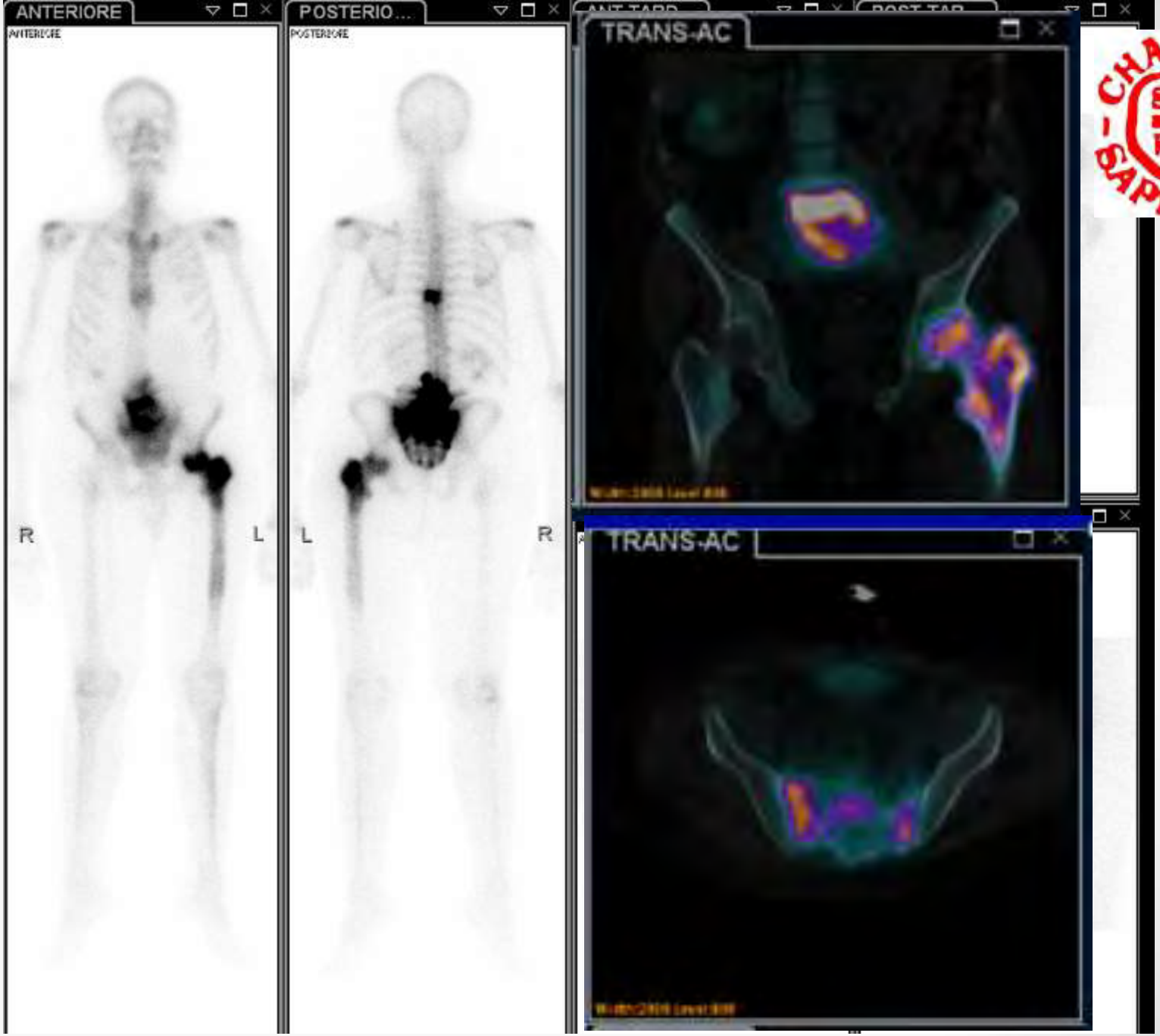
- Carcinoma gastrico



Lesioni metastatiche “fredde”

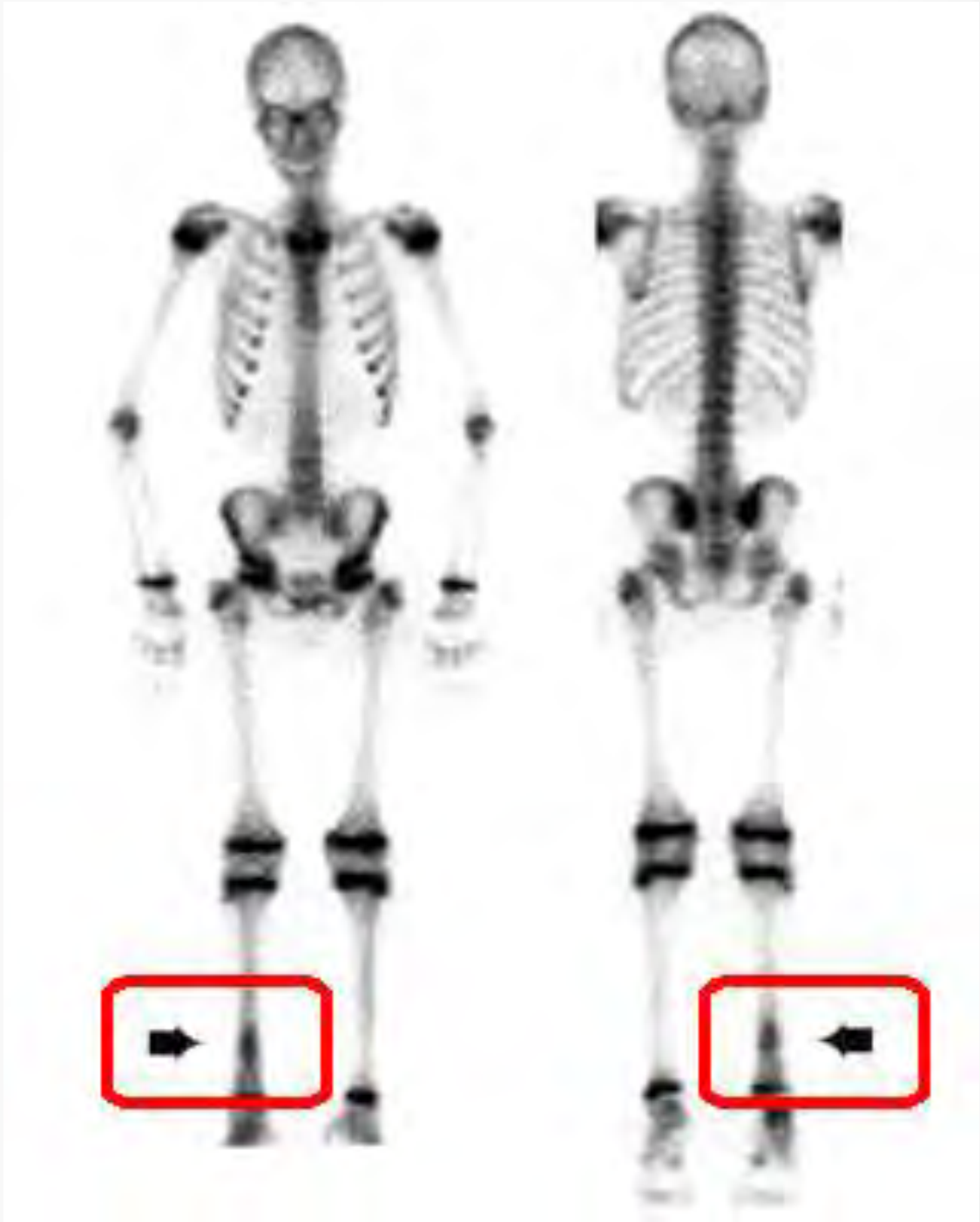


K mammella

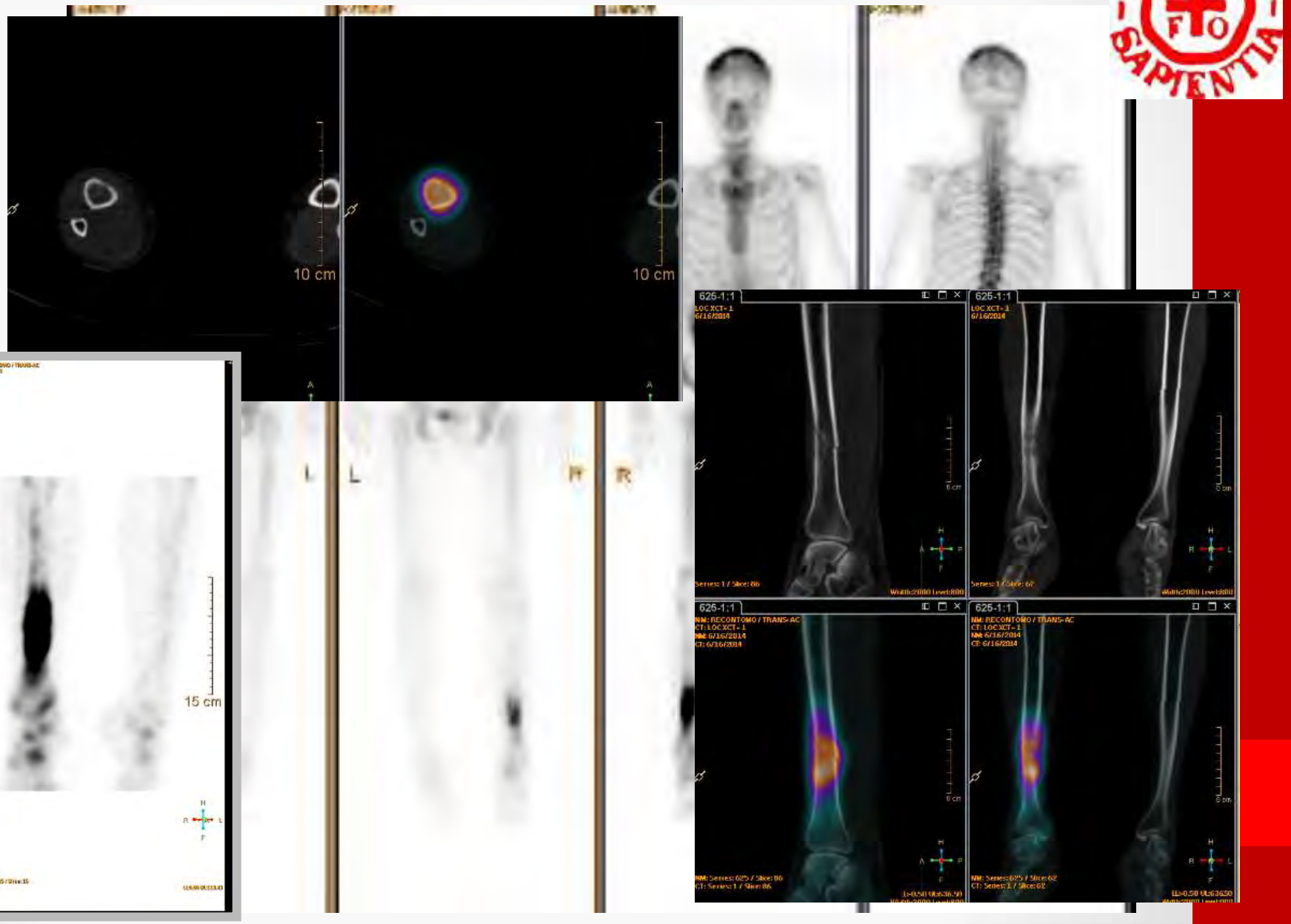


Paget

Fratture costali



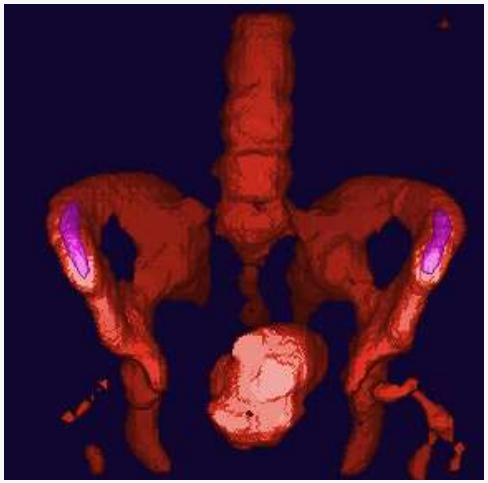
“Hot lesion”



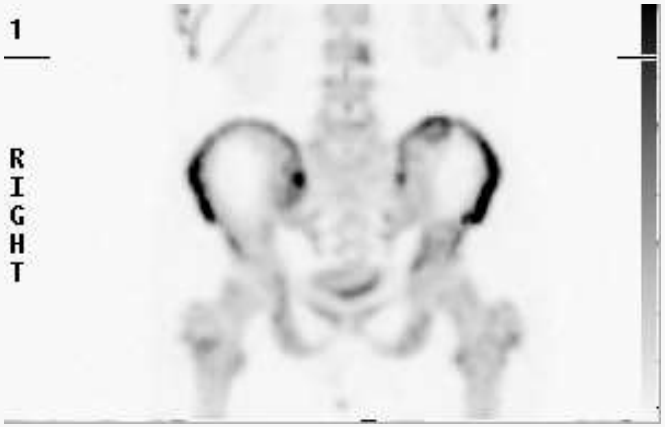
SPET

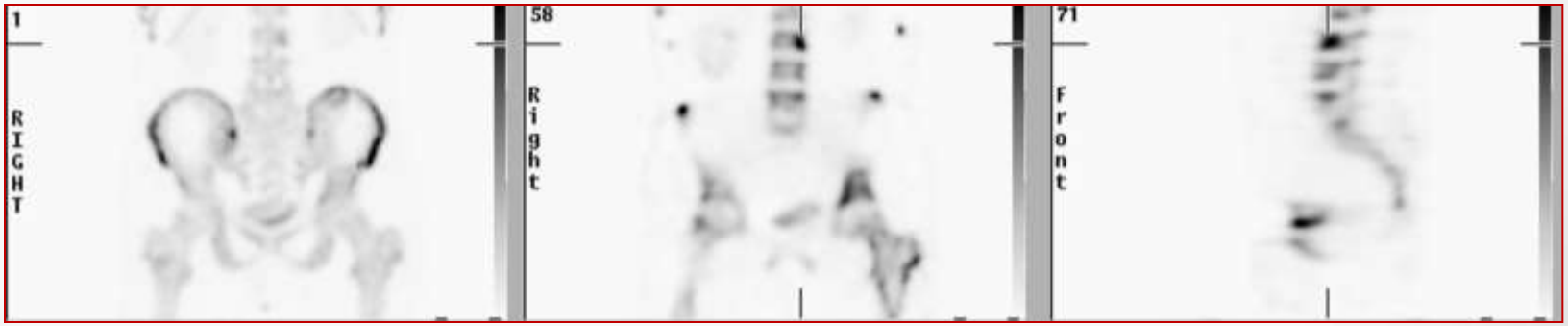
Aumenta la Sensibilità ed il dettaglio anatomico

I. 3D



II. tomographic slices



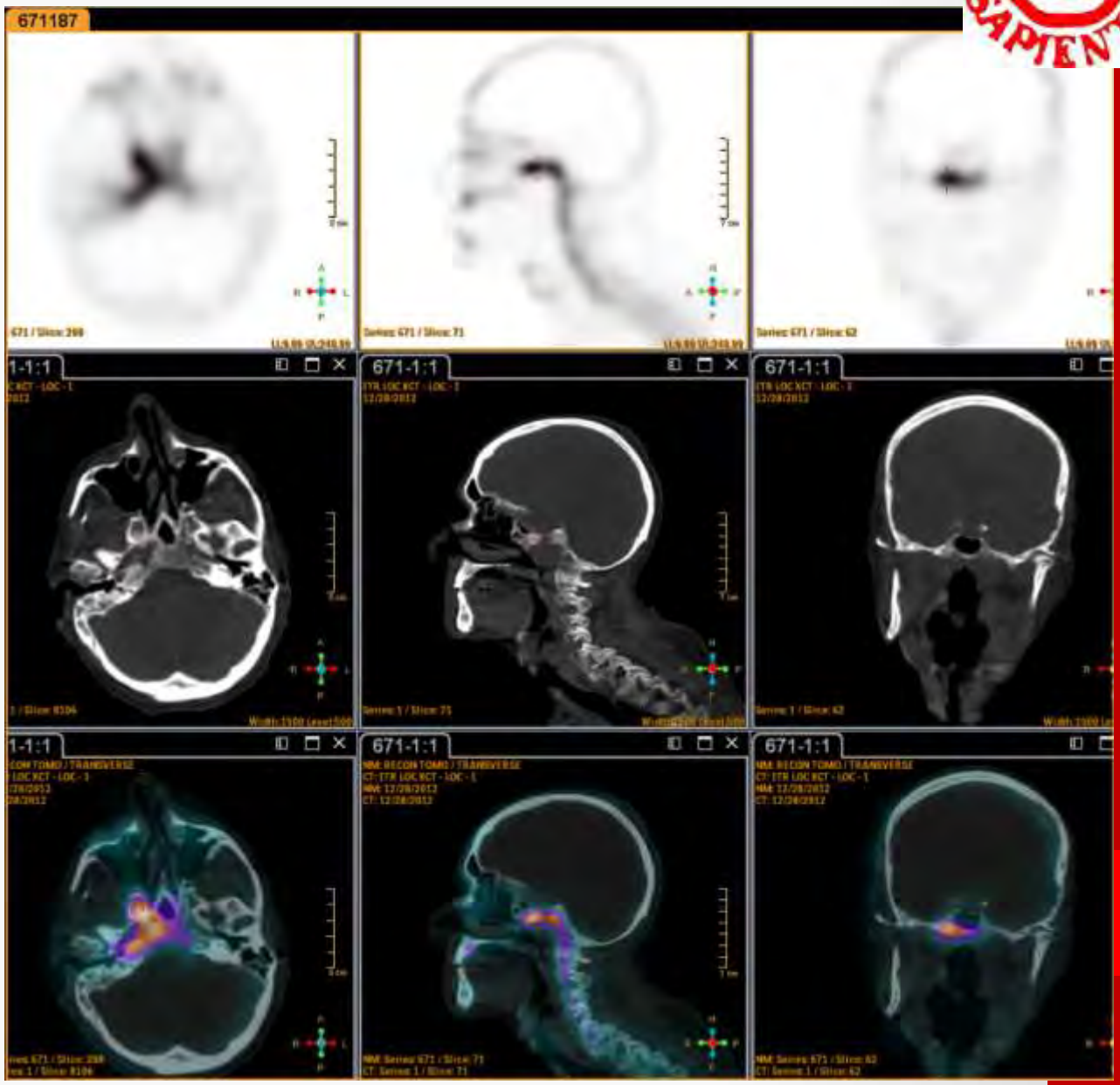


SPECT/CT - Ossee

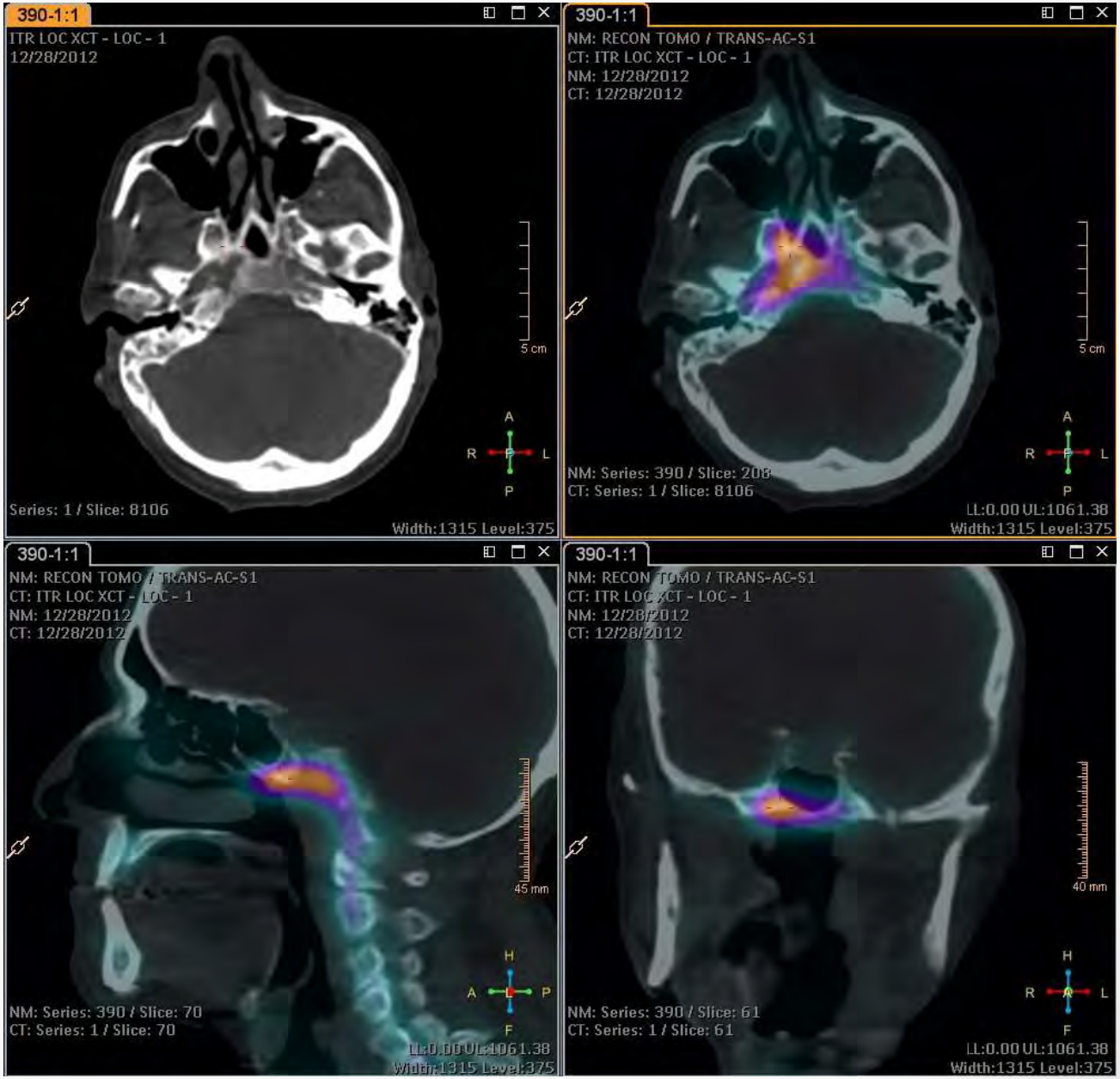
SPECT/CT – S.Sudek

SPECT/CT - Otorino

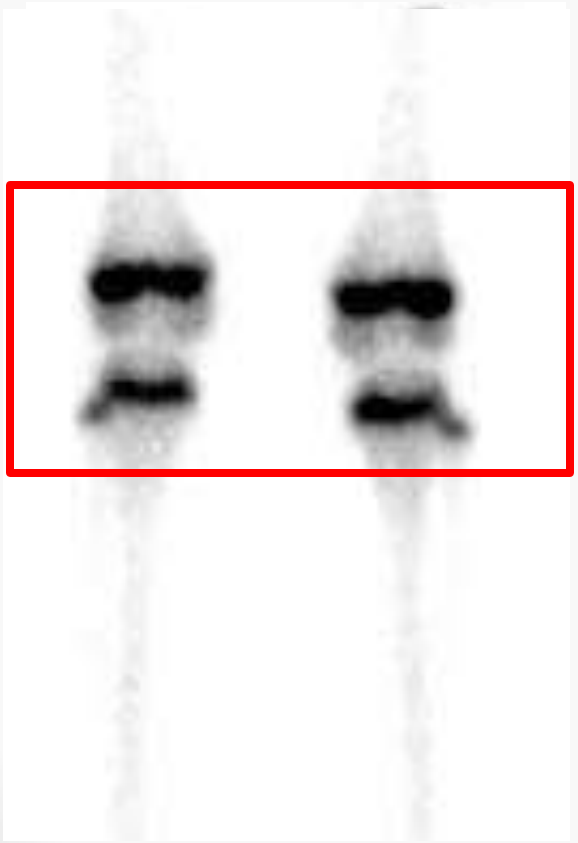
Otite maligna

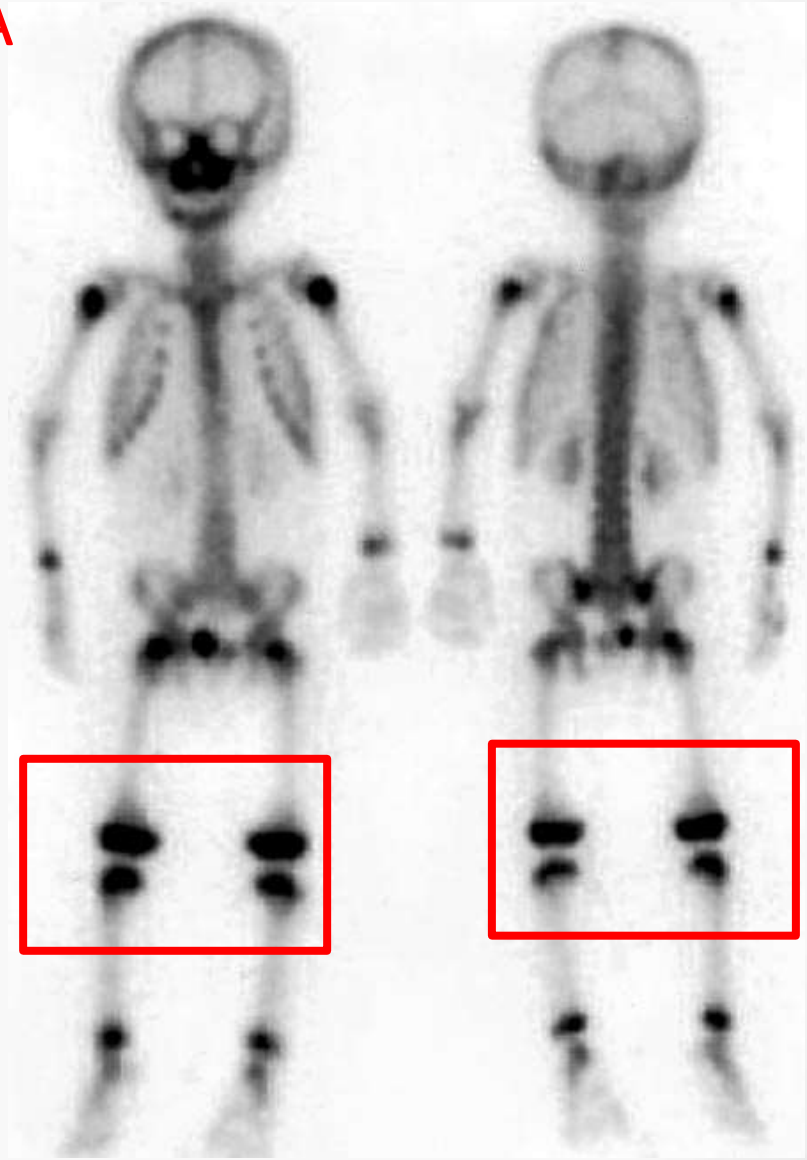


SPECT/CT - Otorino



SCINTIGRAFIA OSSEA PEDIATRICA



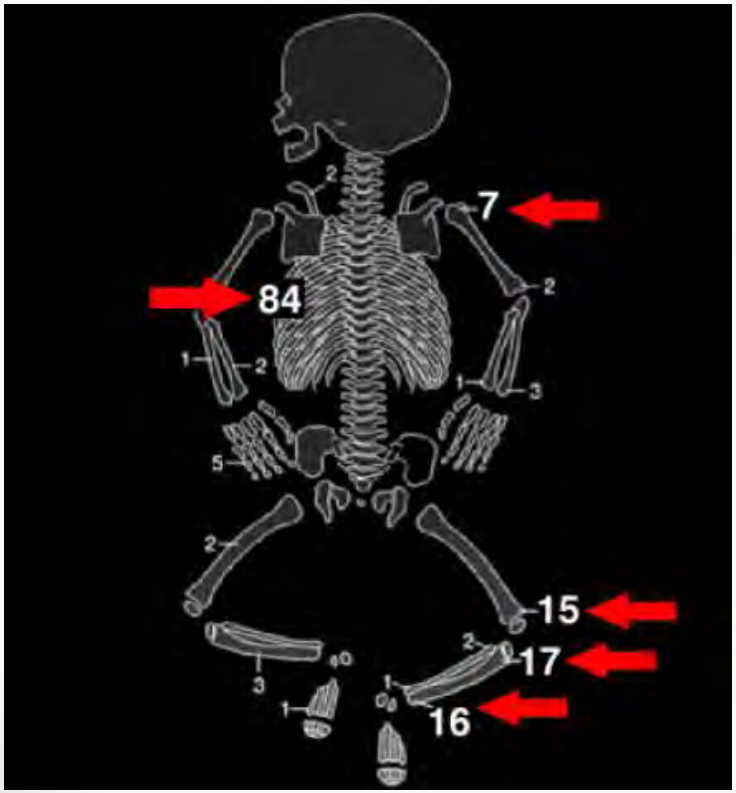


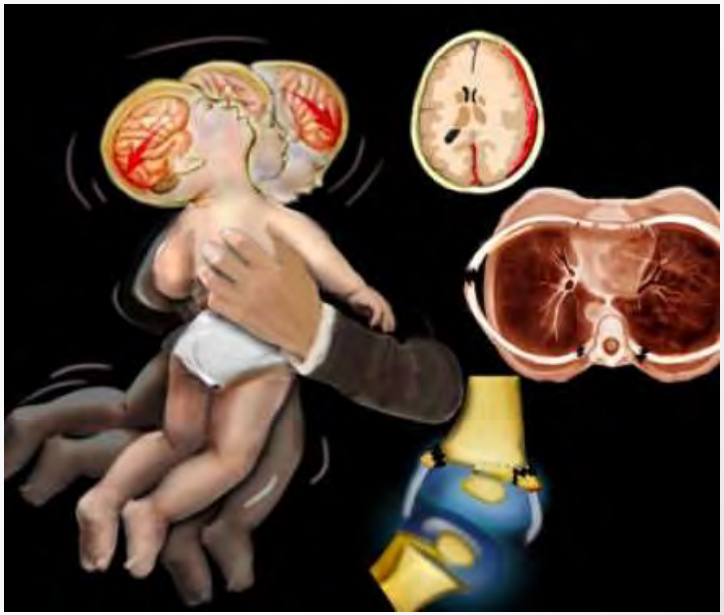
AMERICAN ACADEMY OF PEDIATRICS

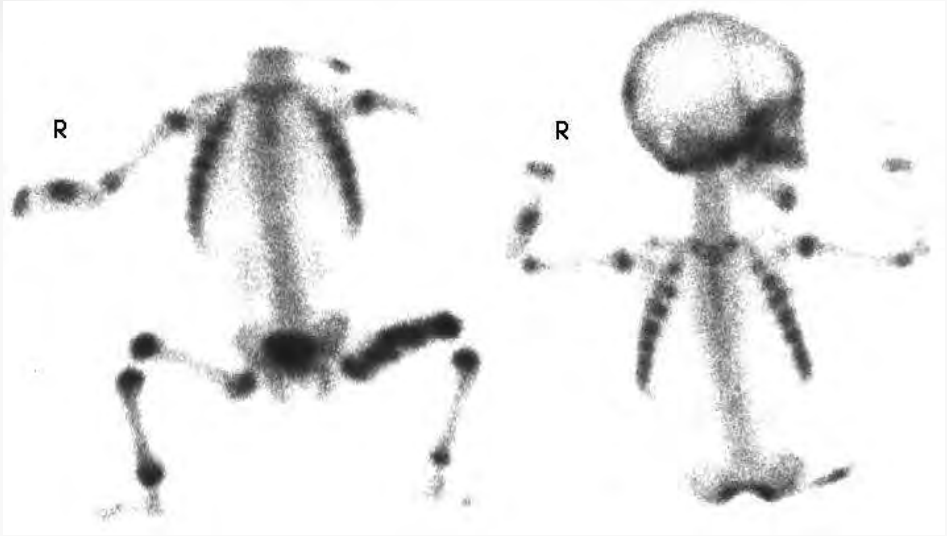
Diagnostic Imaging of Child Abuse

Fractures *High Specificity for Child Abuse*

Bucket handle or Corner fractures
Ribs (especially posterior)
Acromion
Spinous processes
Sternum
Occipital impression fractures



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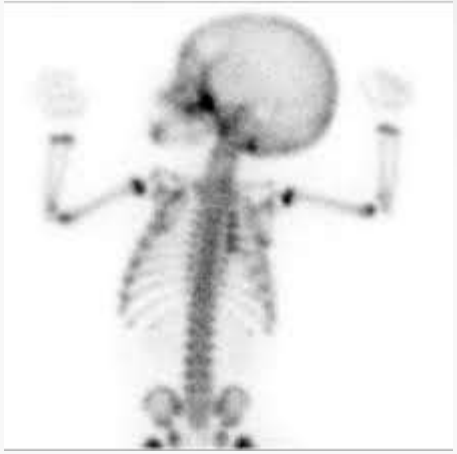
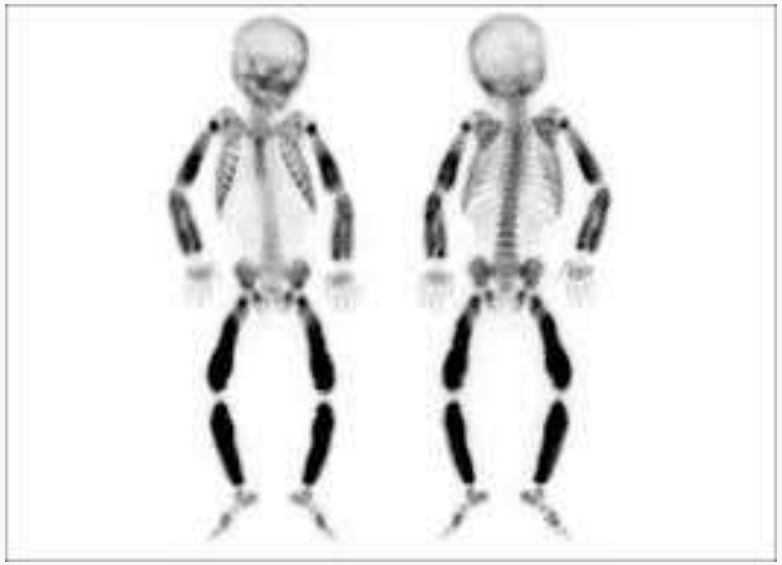
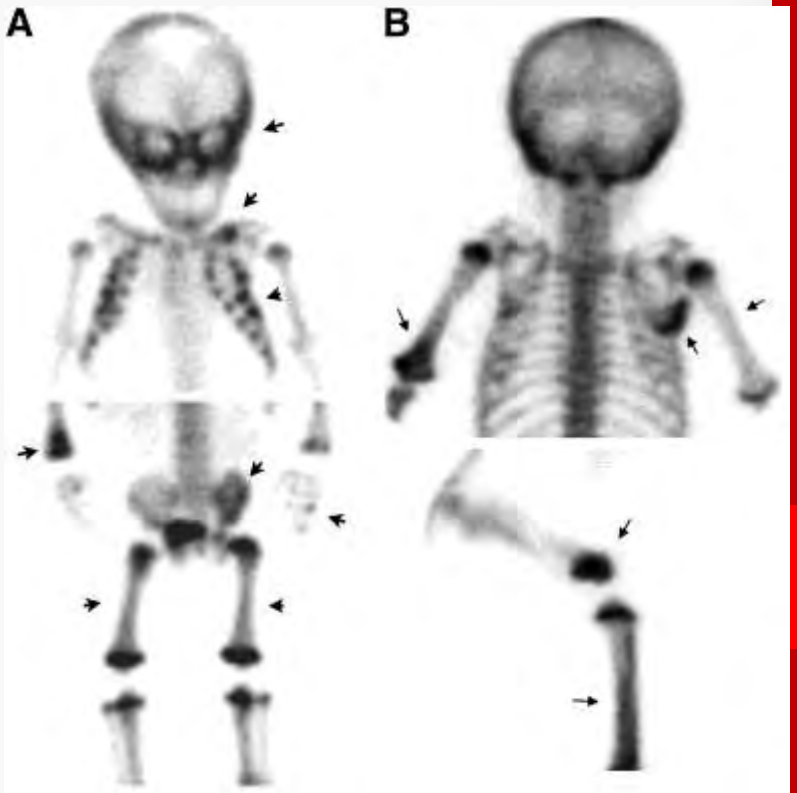
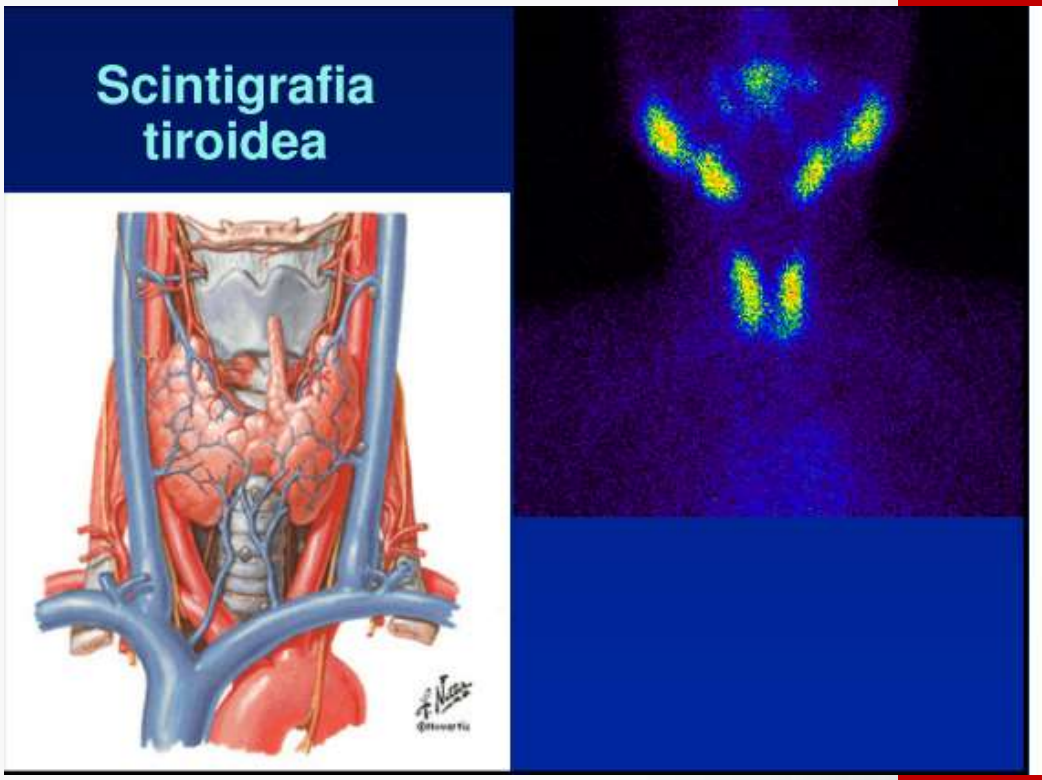
R






A
B

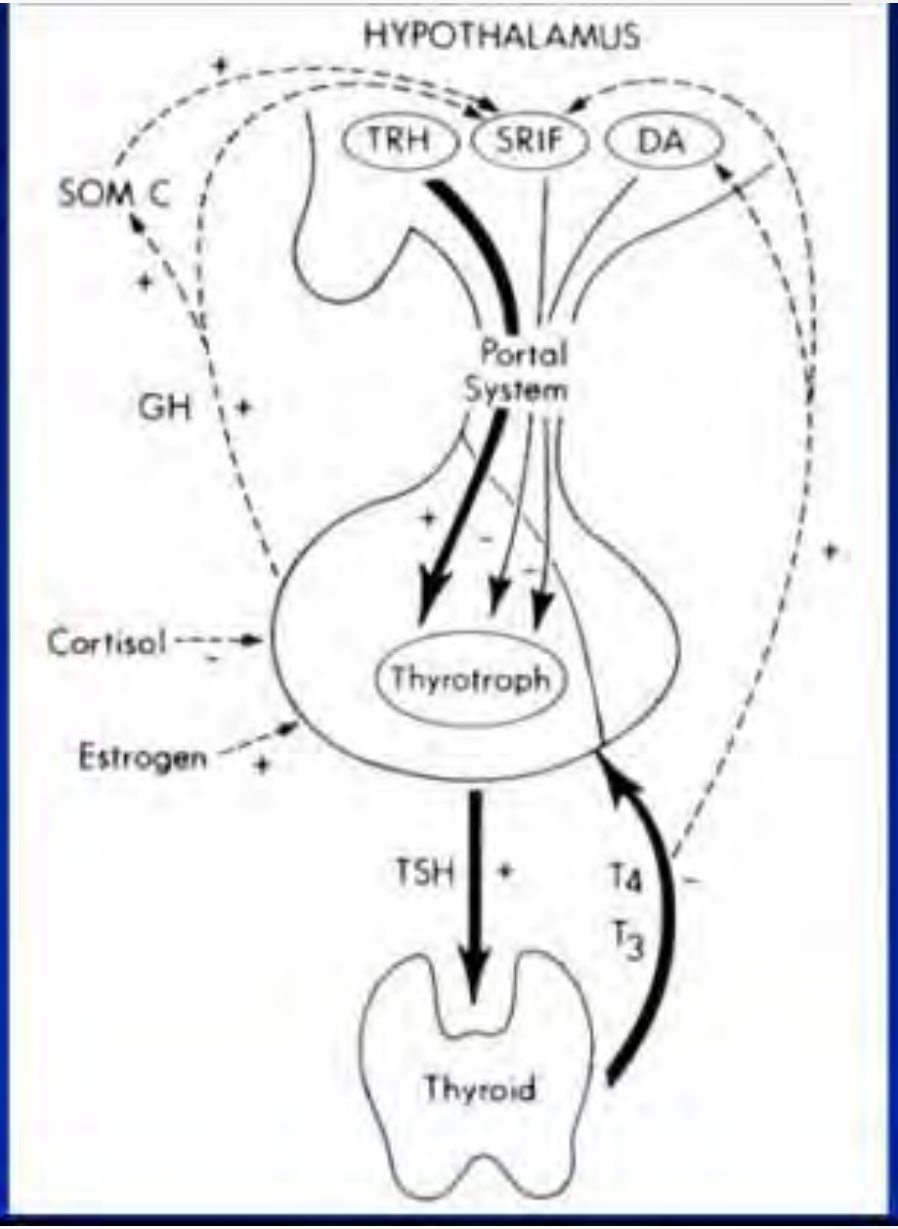
Radiofarmaci per scintigrafia tiroidea

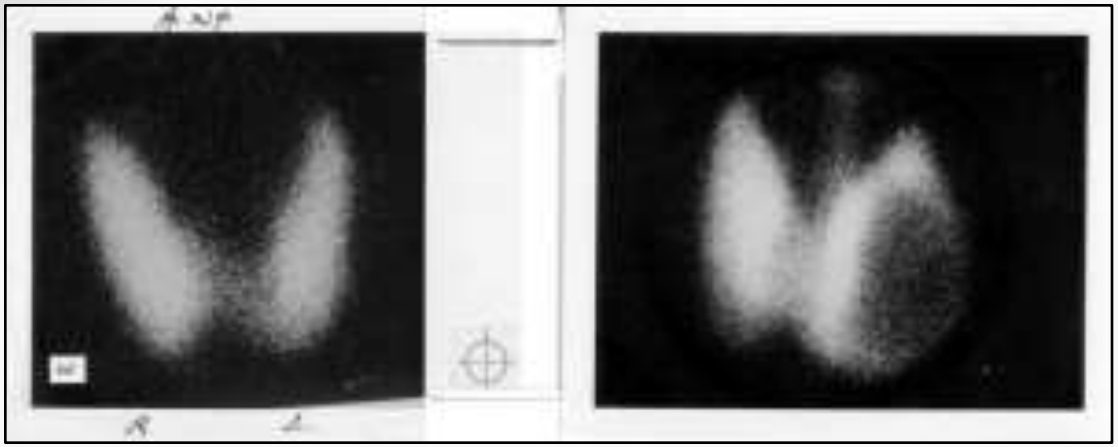


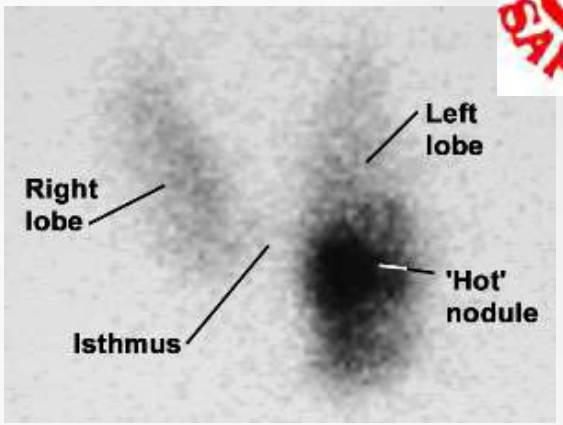
Radioisotopi per lo studio della tiroide

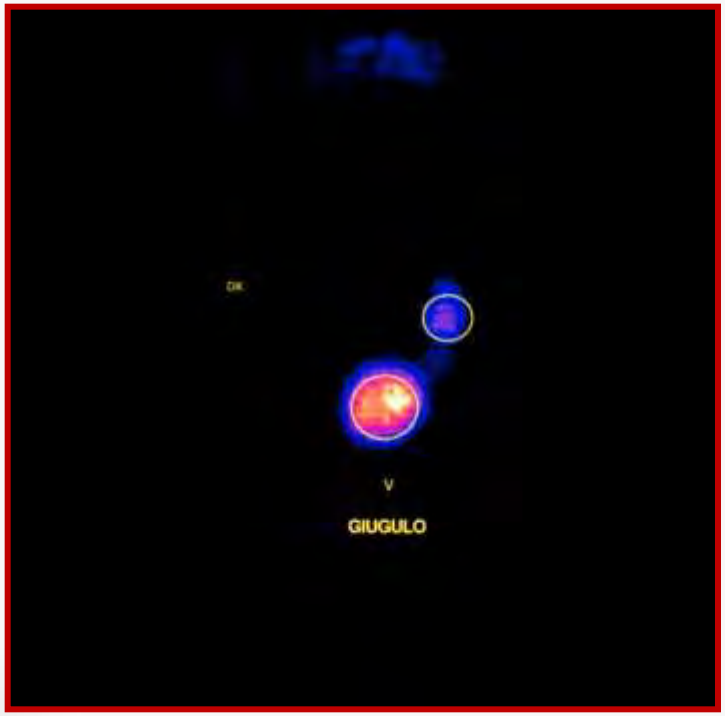
	Emivita	KeV	MBq	Caratteristiche
Tc-99m	6 h	140	100	Facilmente disponibile Poco costoso Bassa dose al paziente
I-131	8 g	364	1.4	Relativamente alta dose
I-123	13 h	159	3.7 – 18.5	Proprietà fisiche favorevoli Costo elevato Difficilmente disponibile

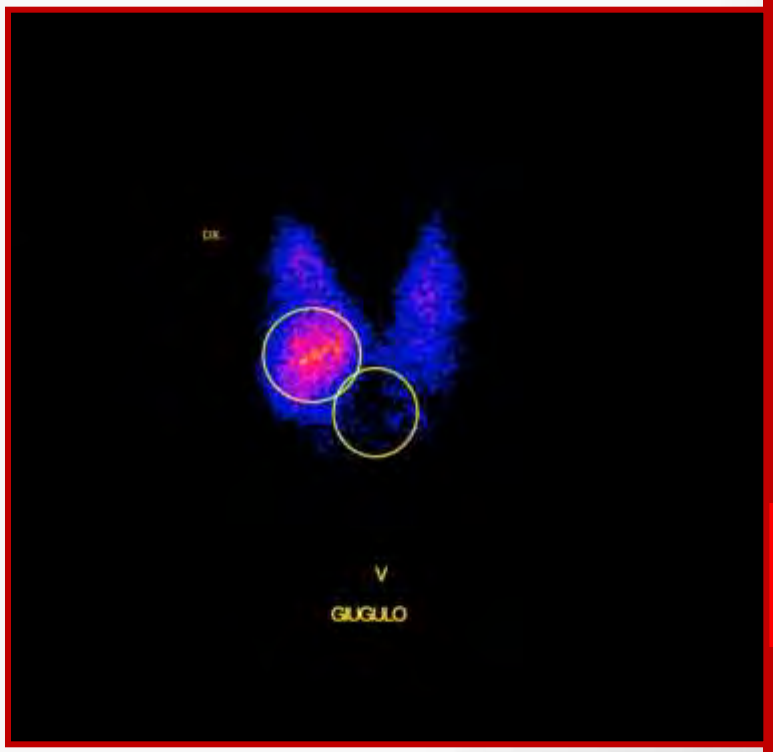
Asse ipotalamo-ipofisi-tiroide



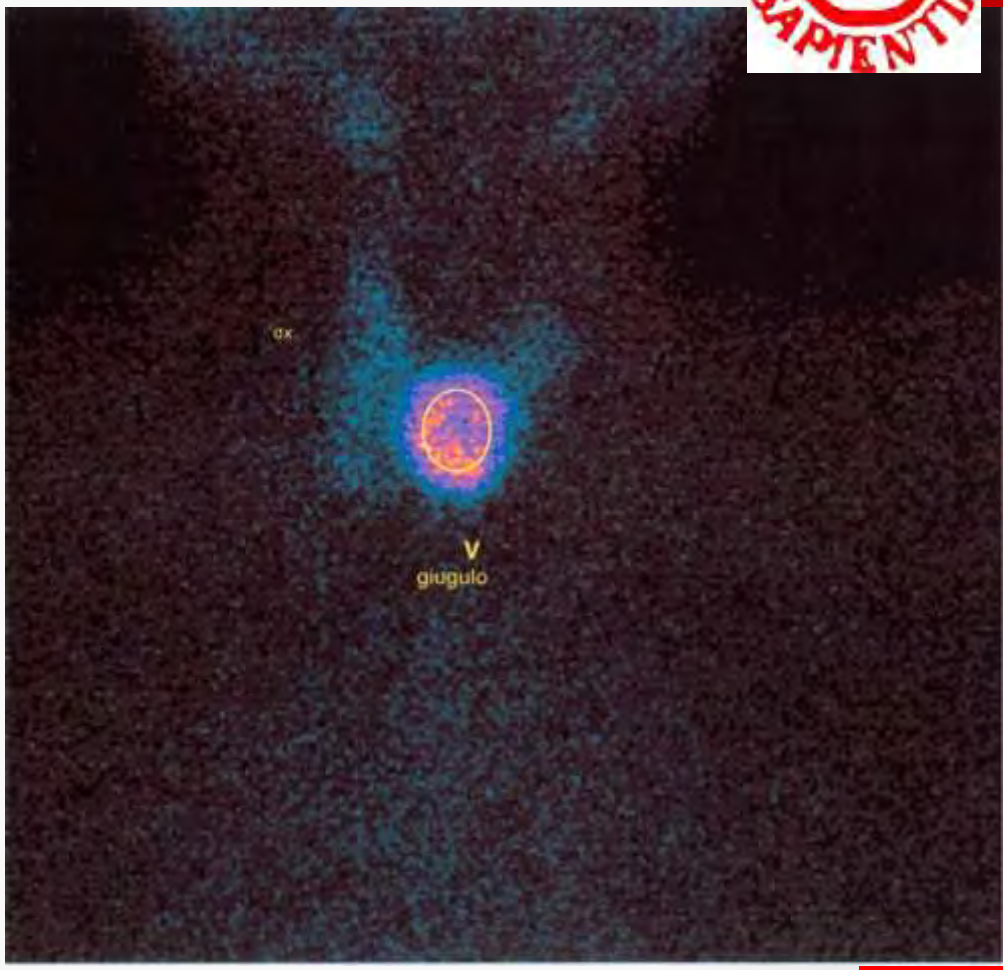



Left
lobe
Right
lobe
'Hot'
nodule
Isthmus

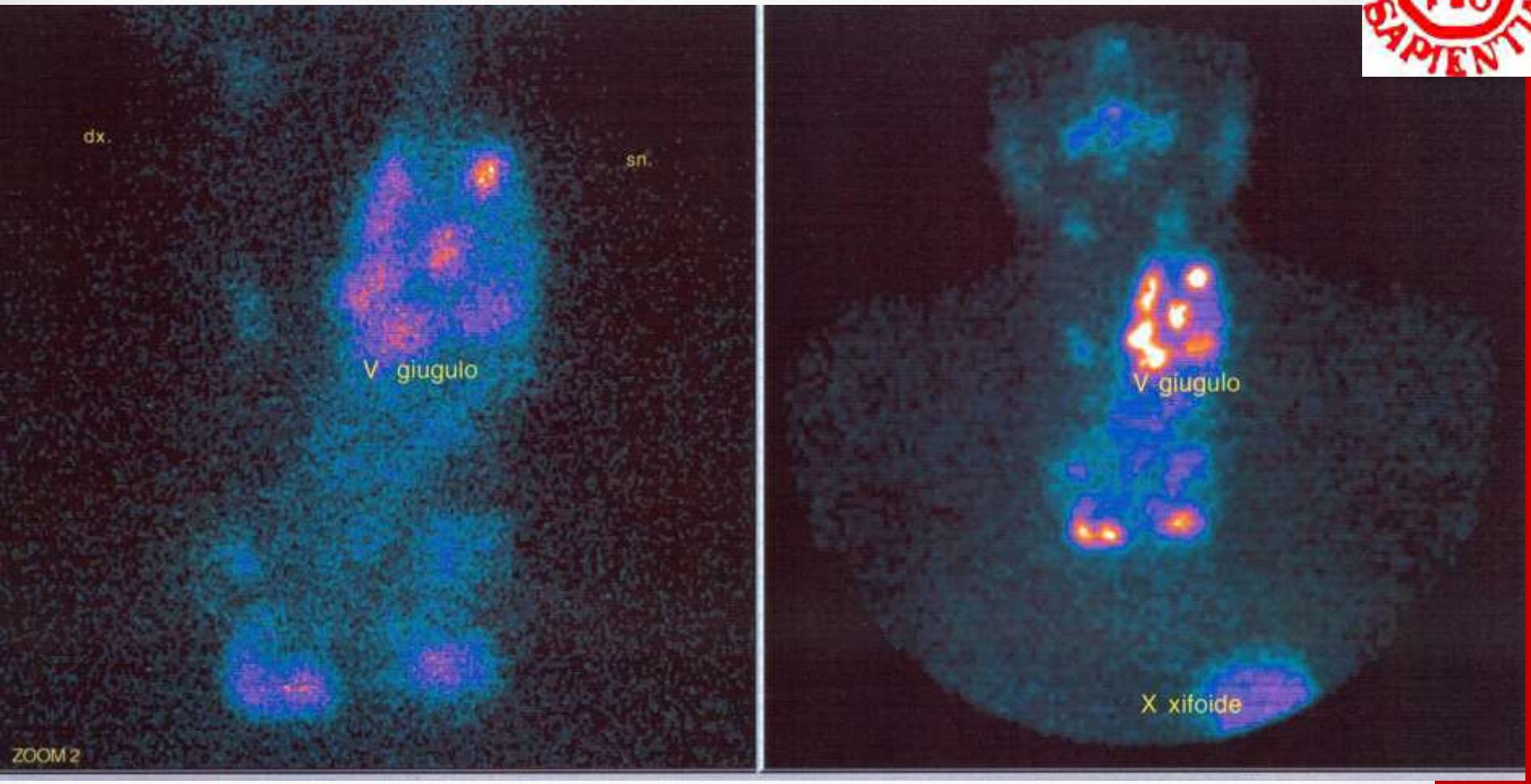

DX
V
GIUGULO


DX
V
GIUGULO

Adenoma Tiroideo lobo sn a "capacità inibente"

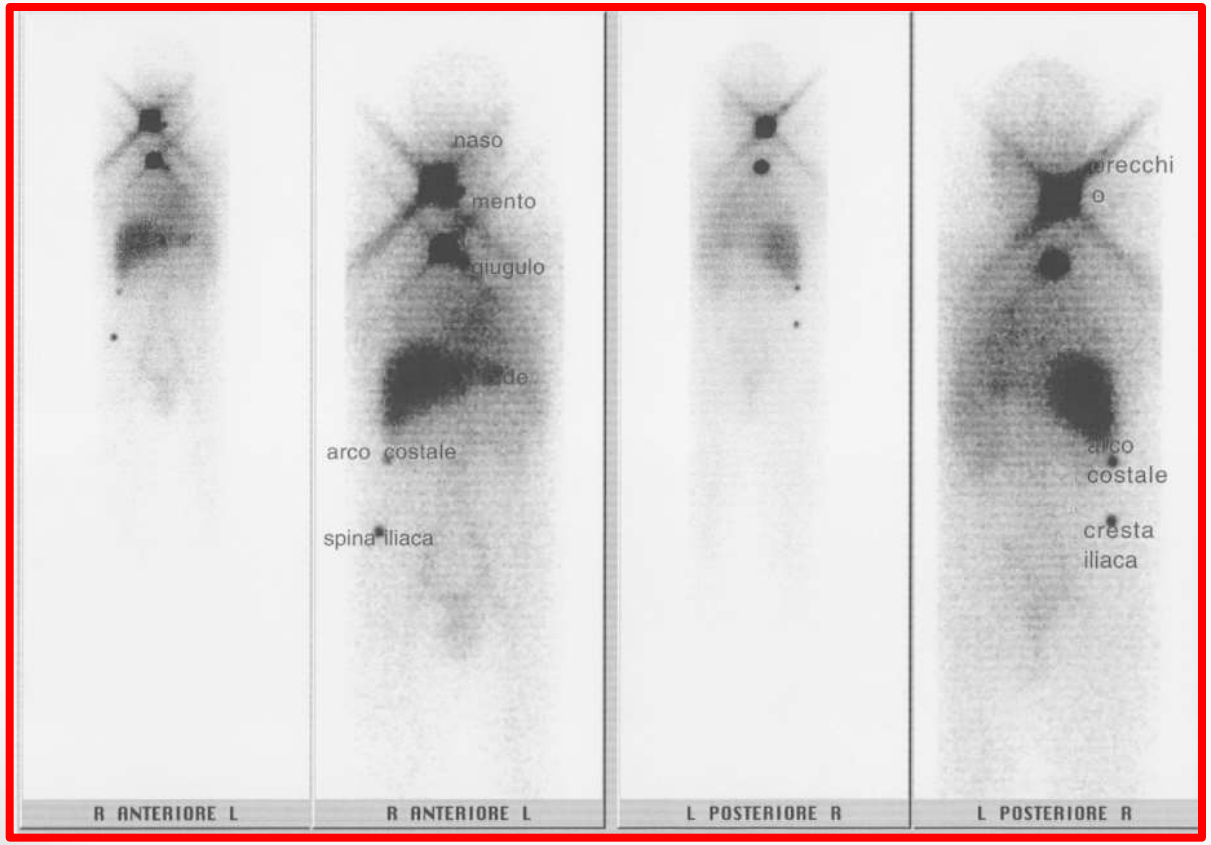


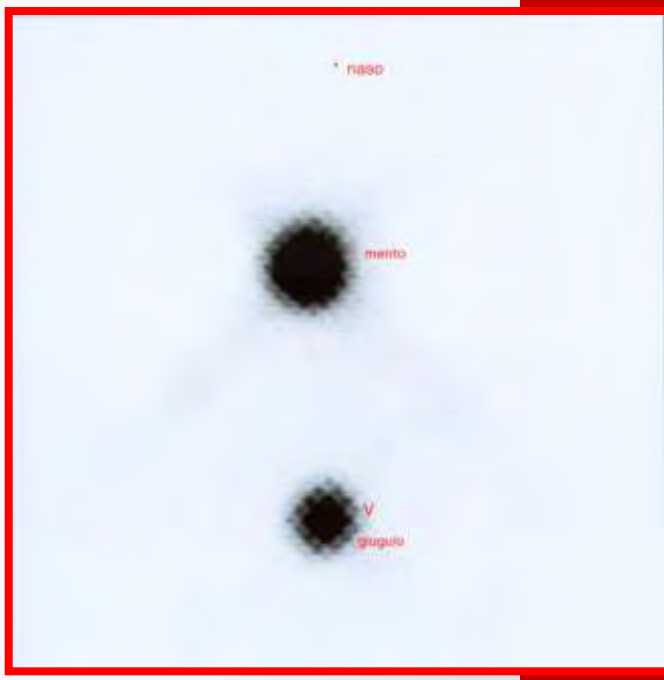
Adenoma Tiroideo con necrosi colliquativa



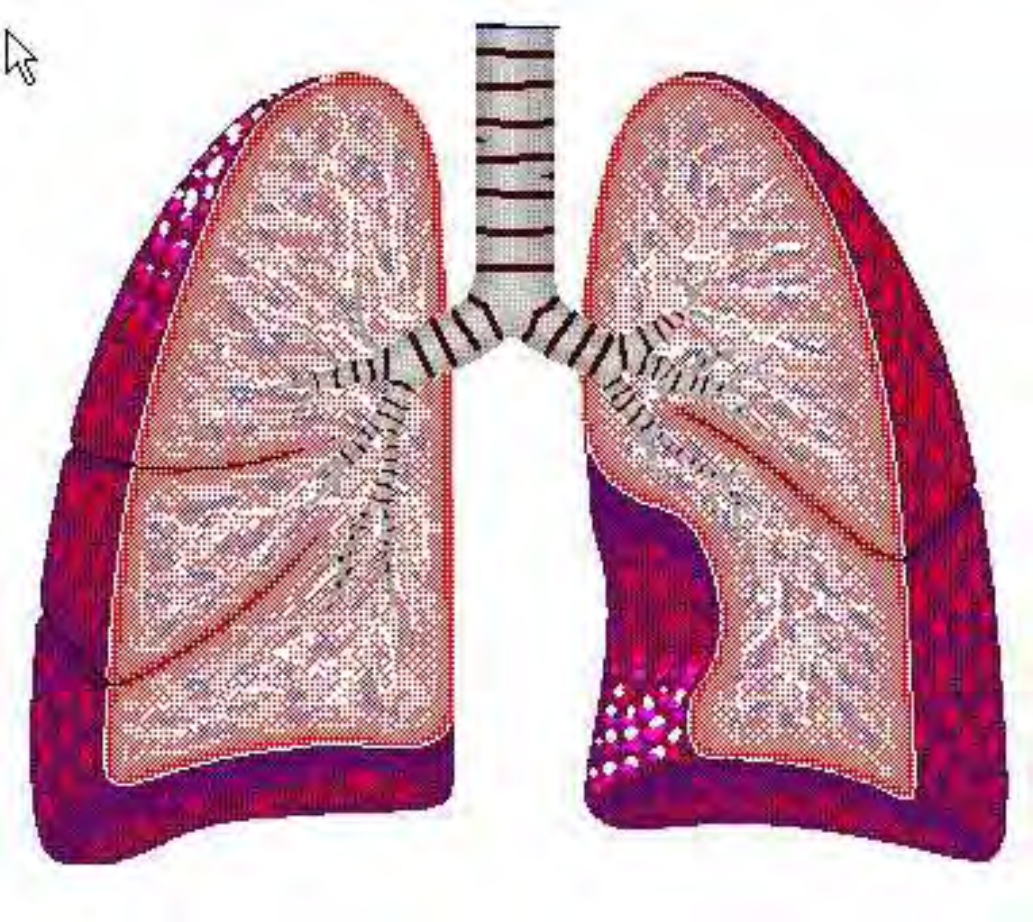
Voluminoso gozzo intratoracico

Scintigrafia TB 7 gg dopo dose terapeutica 3.7 GBq 131Iodio K TIROIDE





Radiofarmaci per lo studio dei polmoni



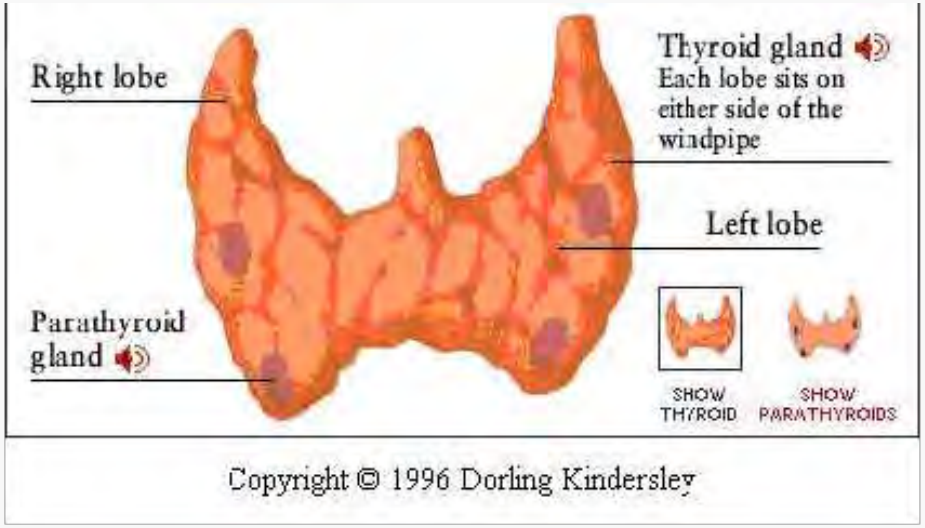
Macroaggregati di albumina (MAA)

- **Preparati per denaturazione al calore di albumina umana e coniugati con 99mTc.**
- **Dimensioni: il 90% tra 5-90 µm, la maggior parte tra 10-40 µm.**

SCINTIGRAFIA POLMONARE

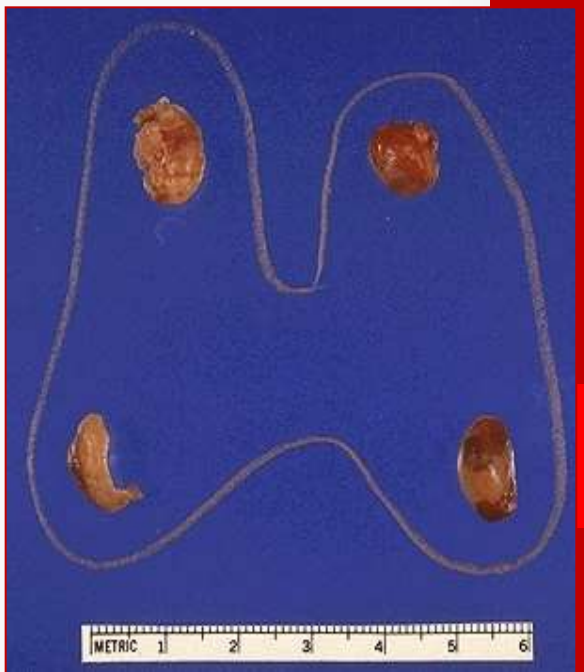
Valutazione funzionale preoperatoria

Radiofarmaci per paratiroidi



4 ghiandole (2 superiori e 2 inferiori) situate nel collo dietro la tiroide ma spesso in sede ectopica:

- Intratimiche
- Mediastiniche
- Intratiroidee



Favorisce (indirettamente Vit D) l'assorbimento intestinale di calcio

PTH

Favorisce il riassorbimento tubulare di calcio

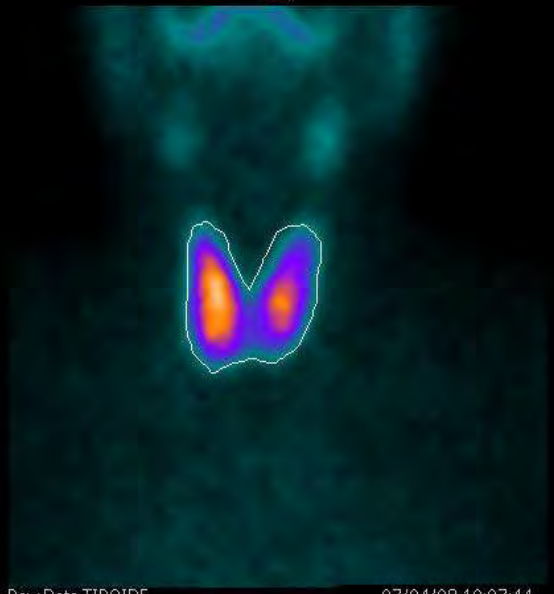
- riassorbimento minerale e spostamento di calcio nel sangue

- rimodellamento osseo: osteite fibrosa

RICCERI GRAZIA 1548-08 PARATIROID July 24, 2008

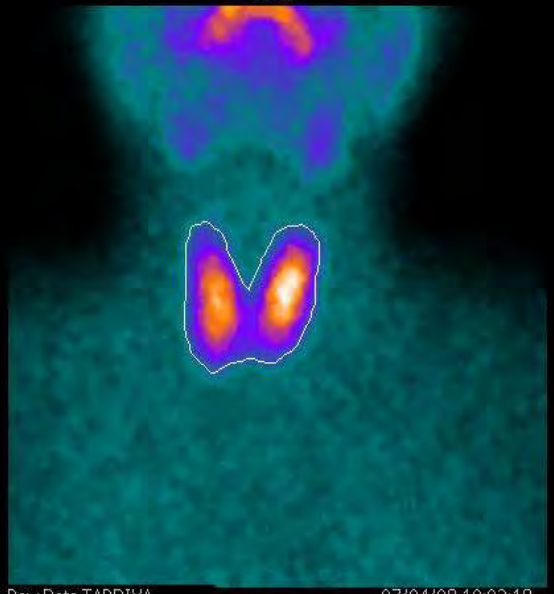
NOT FOR DIAGNOSTIC PURPOSES

Early



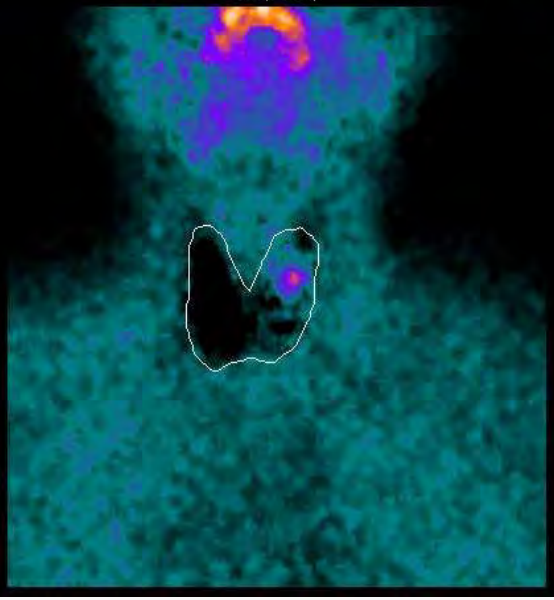
Raw Data TIROIDE 07/24/08 10:27:44

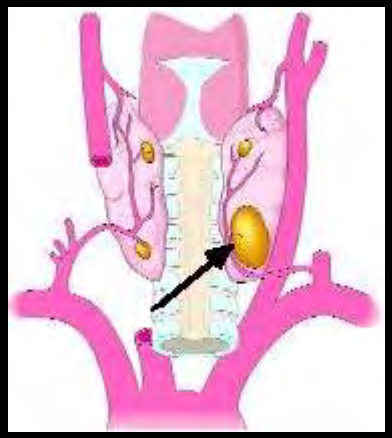
Delay



Raw Data TARDIVA 07/24/08 12:23:18

Delay - Early

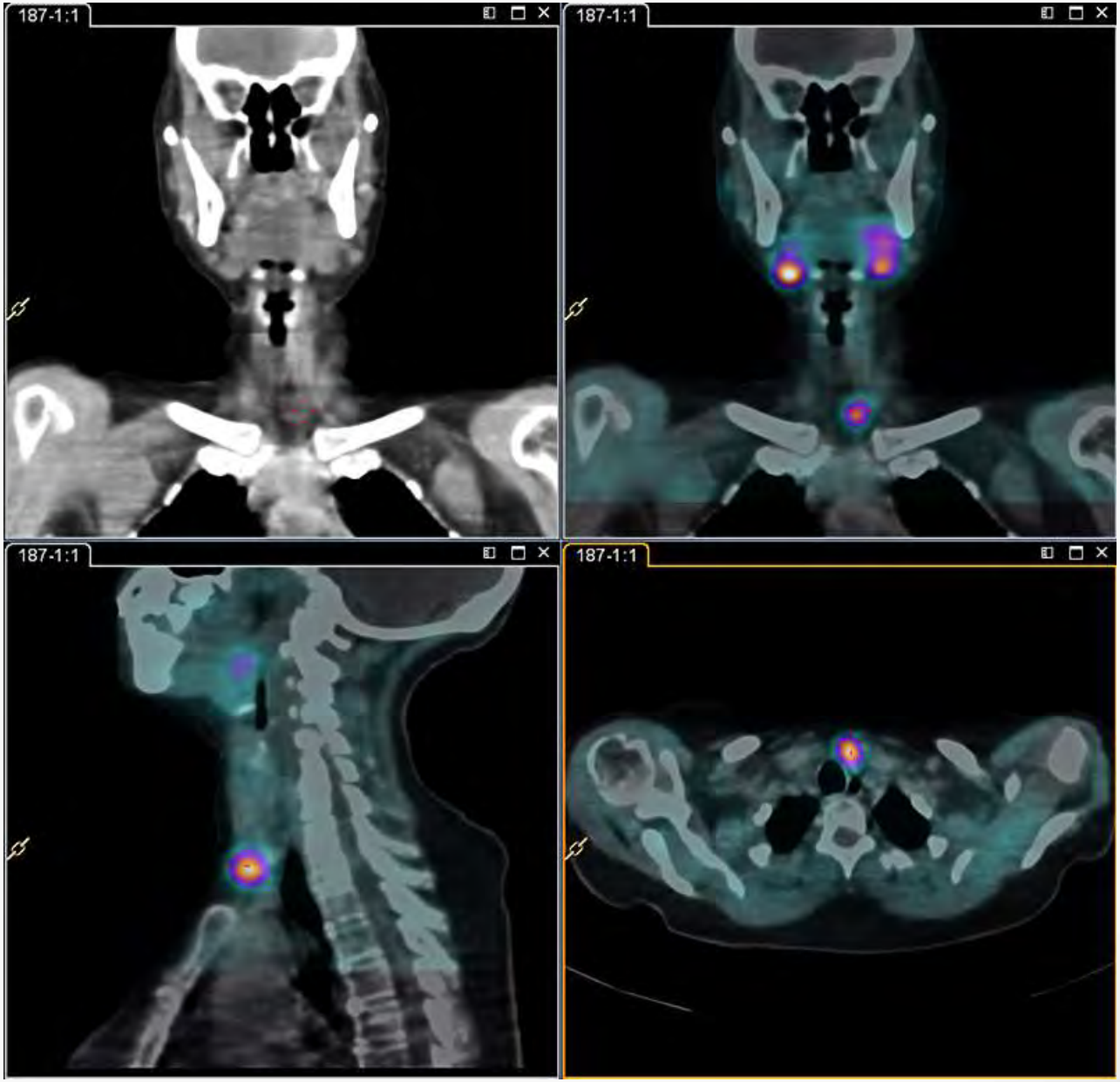




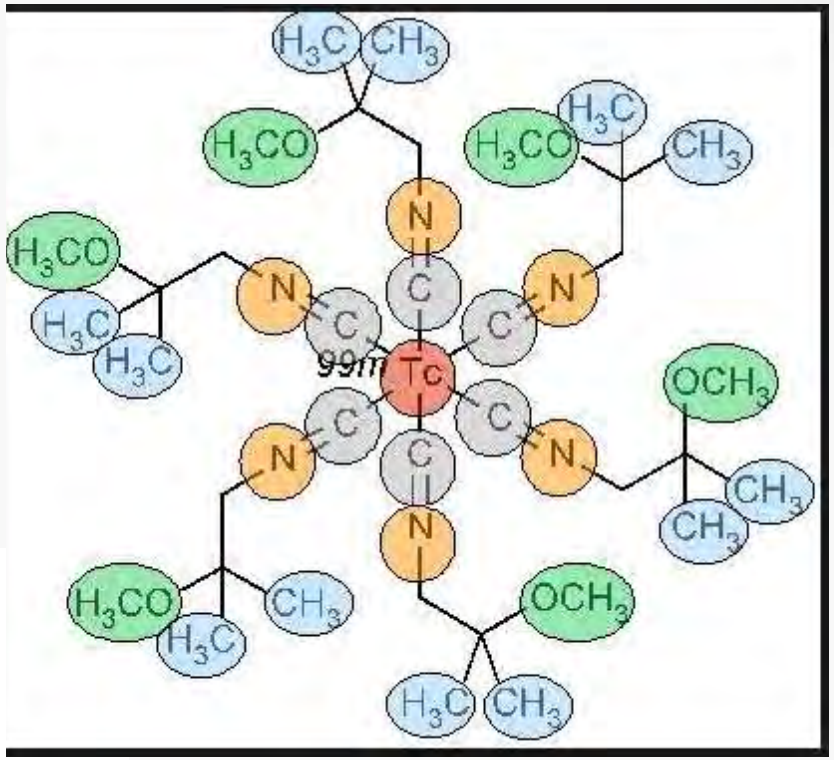
Counts in early ROI = 45403.

Counts in late ROI = 69592.

SPECT/CT - Paratiroidi



Sestamibi



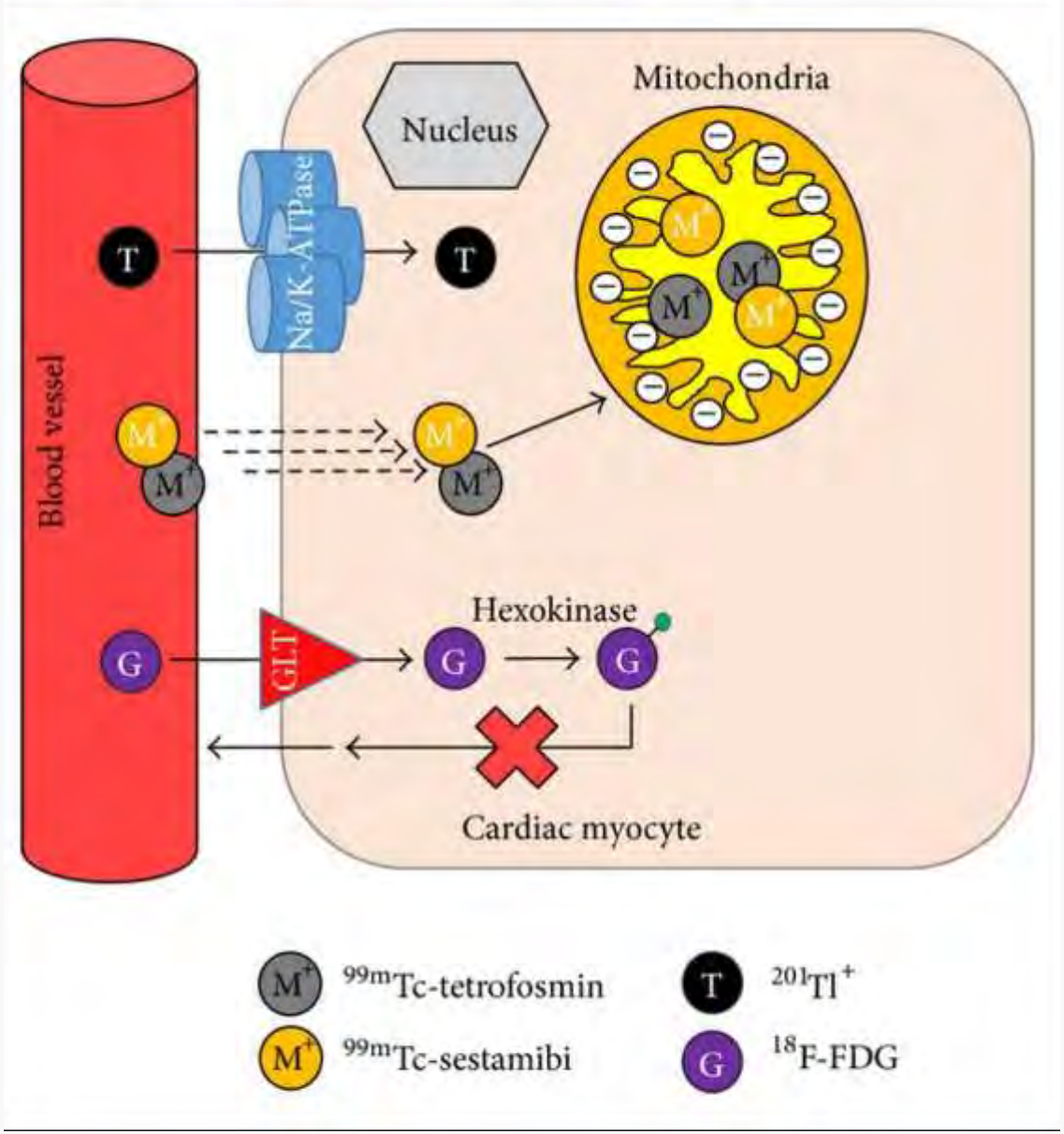
Cardiolite ®

^{99m}Tc-Sestamibi

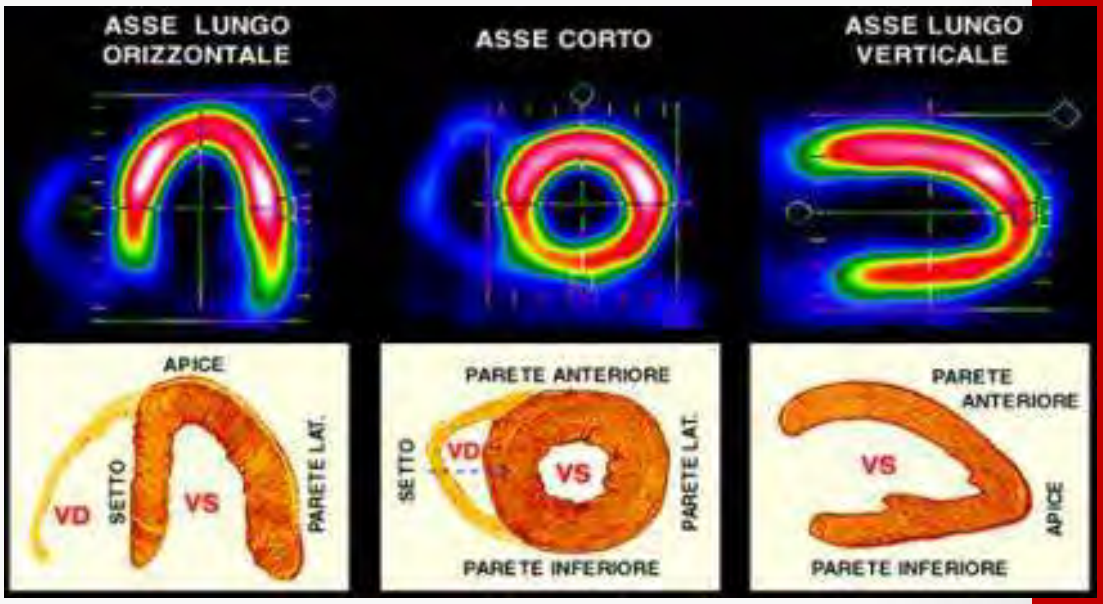
Protocollo di marcatura:

- **1-3 ml di pertecnetato sodico**
- **Agitare fino a completa dissoluzione**
- **10 min a 100 ° C**
- **Raffreddare**
- **Stabile 10h**

$[^{99m}TcO_4]Na$

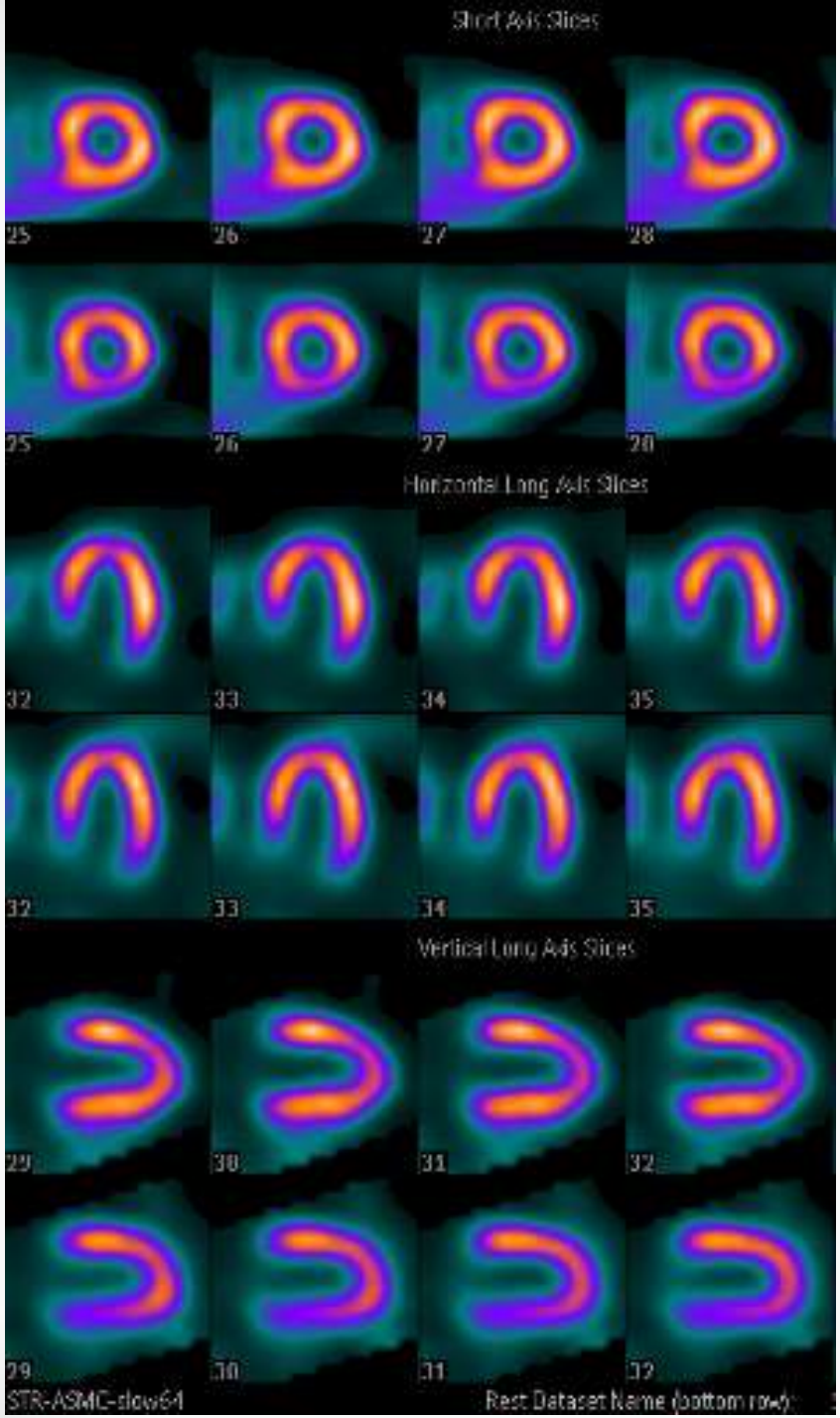

Mitochondria
Nucleus
Na/K-ATPase
T
T
Blood vessel
M+
M+
M+
M+
M+
M+
Hexokinase
G
GLT
G
G
Cardiac myocyte
M+ 99mTc-tetrofosmin
M+ 99mTc-sestamibi
T 201Tl+
G 18F-FDG

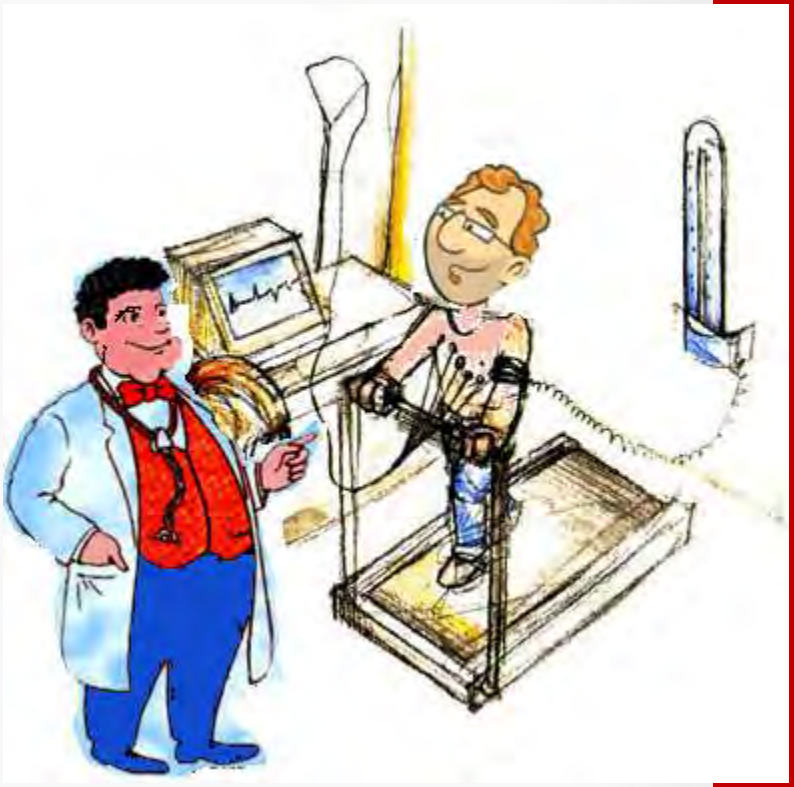
Radiofarmaci per il cuore

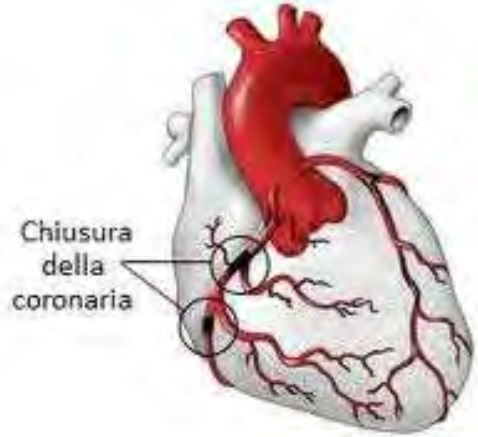



Apice
Setto
Parete laterale
Parete anteriore
Setto
Parete laterale
Normale
Parete inferiore

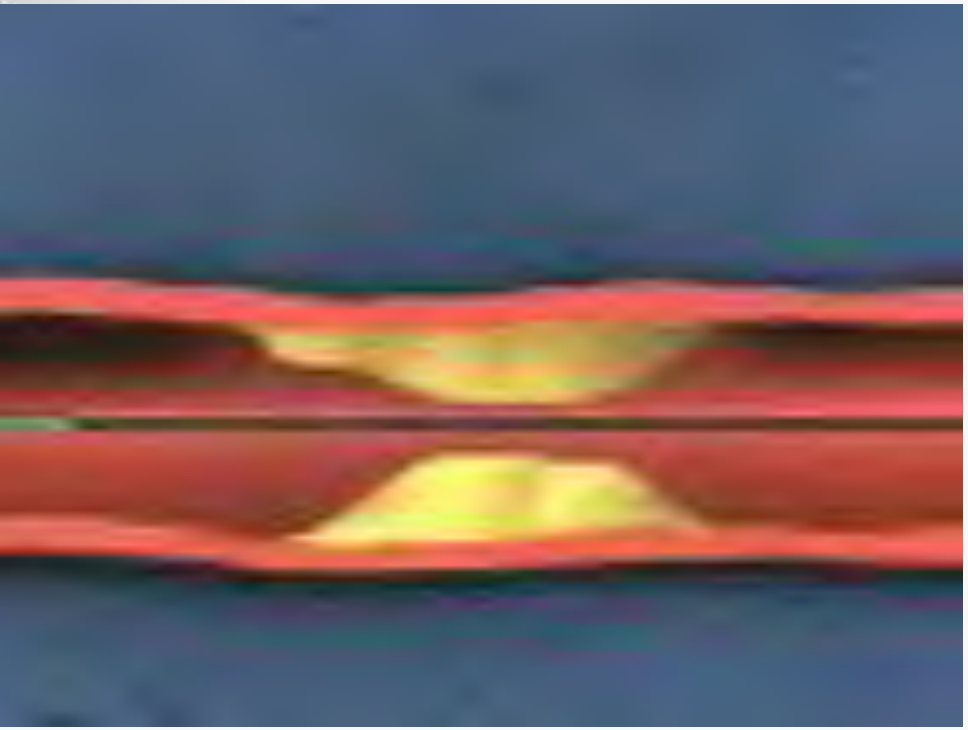

Apice
Setto
Parete laterale
Parete anteriore
Setto
Parete laterale
Positiva
Parete inferiore

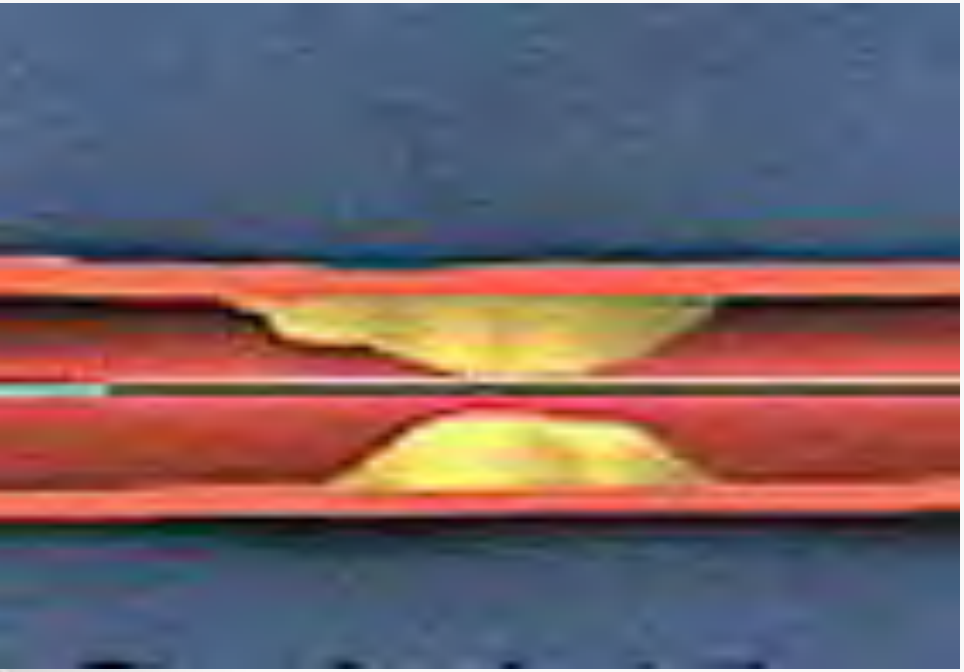

Short Axis Slices
25
26
27
28
25
26
27
28
Horizontal Long Axis Slices
32
33
34
35
32
33
34
35
Vertical Long Axis Slices
29
30
31
32
29
30
31
32
STR-ASMC-slow64
Rest Dataset Name (bottom row)

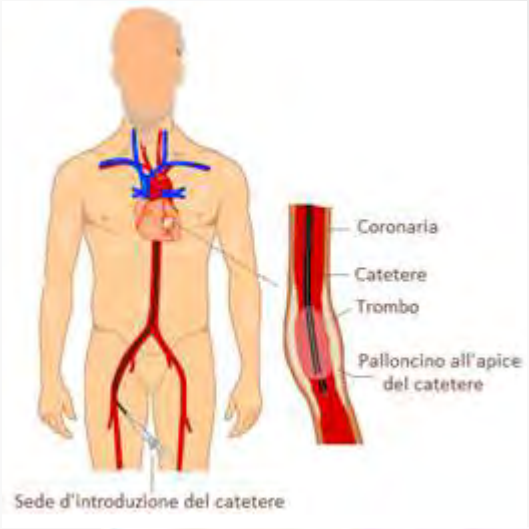


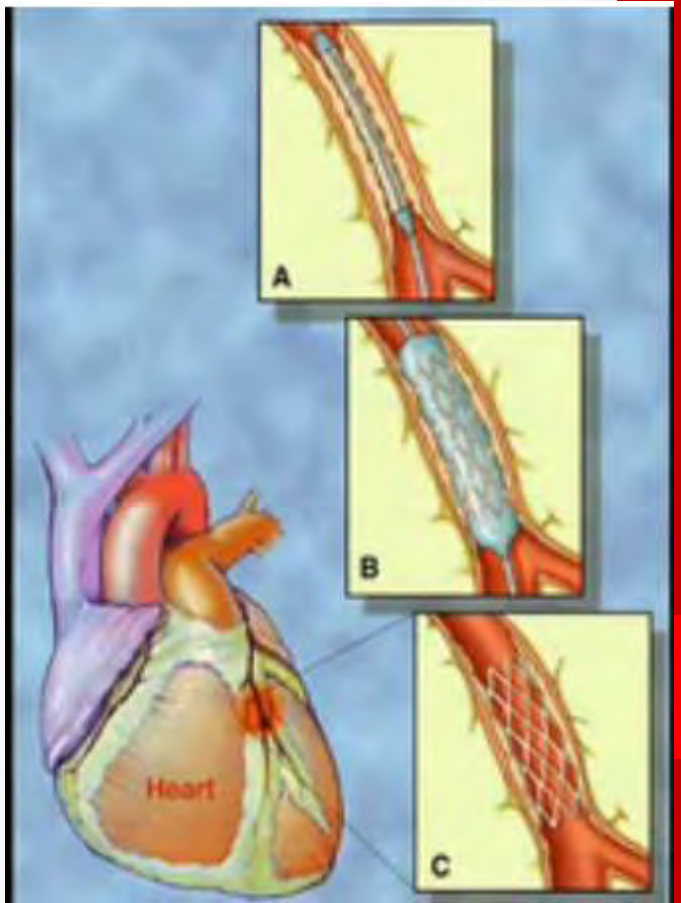

Chiusura
della
coronaria

SFORZO
RIPOSO
AREA
IPOCAPTANTE
SCOMPARE
PERSISTE
SI RIDUCE
ISCHEMIA
NECROSI
NECROSI con
ISCHEMIA



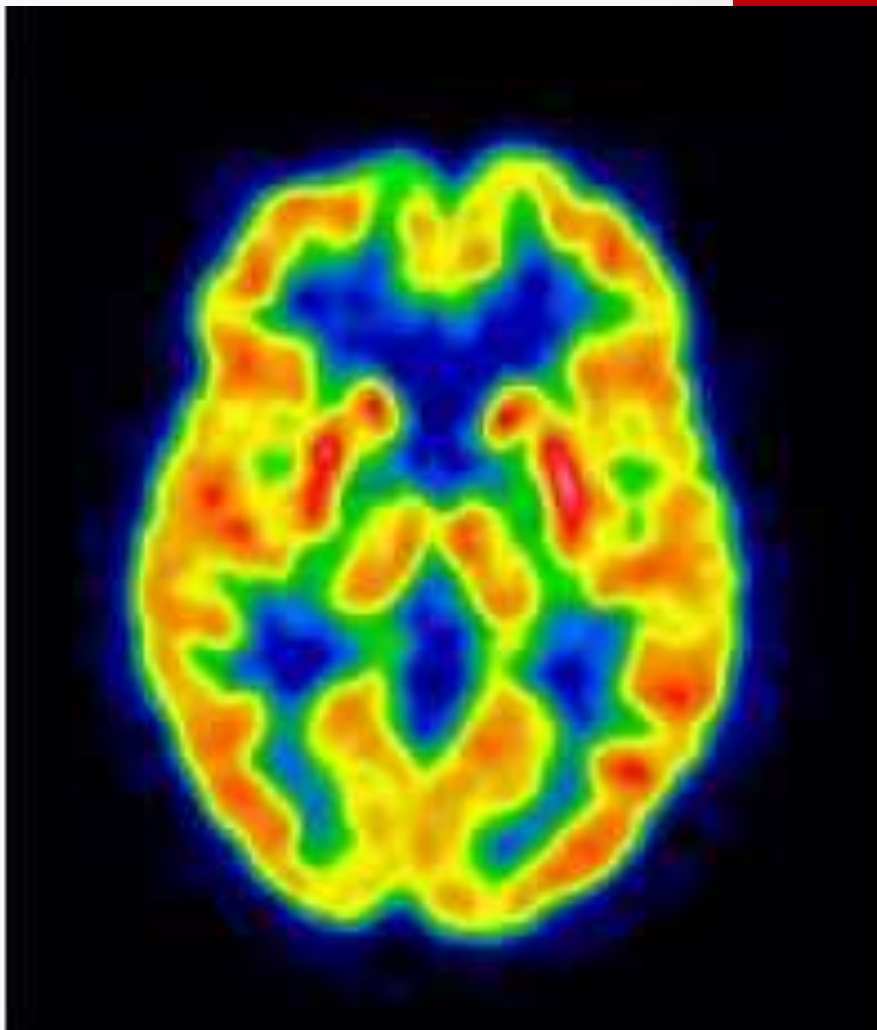


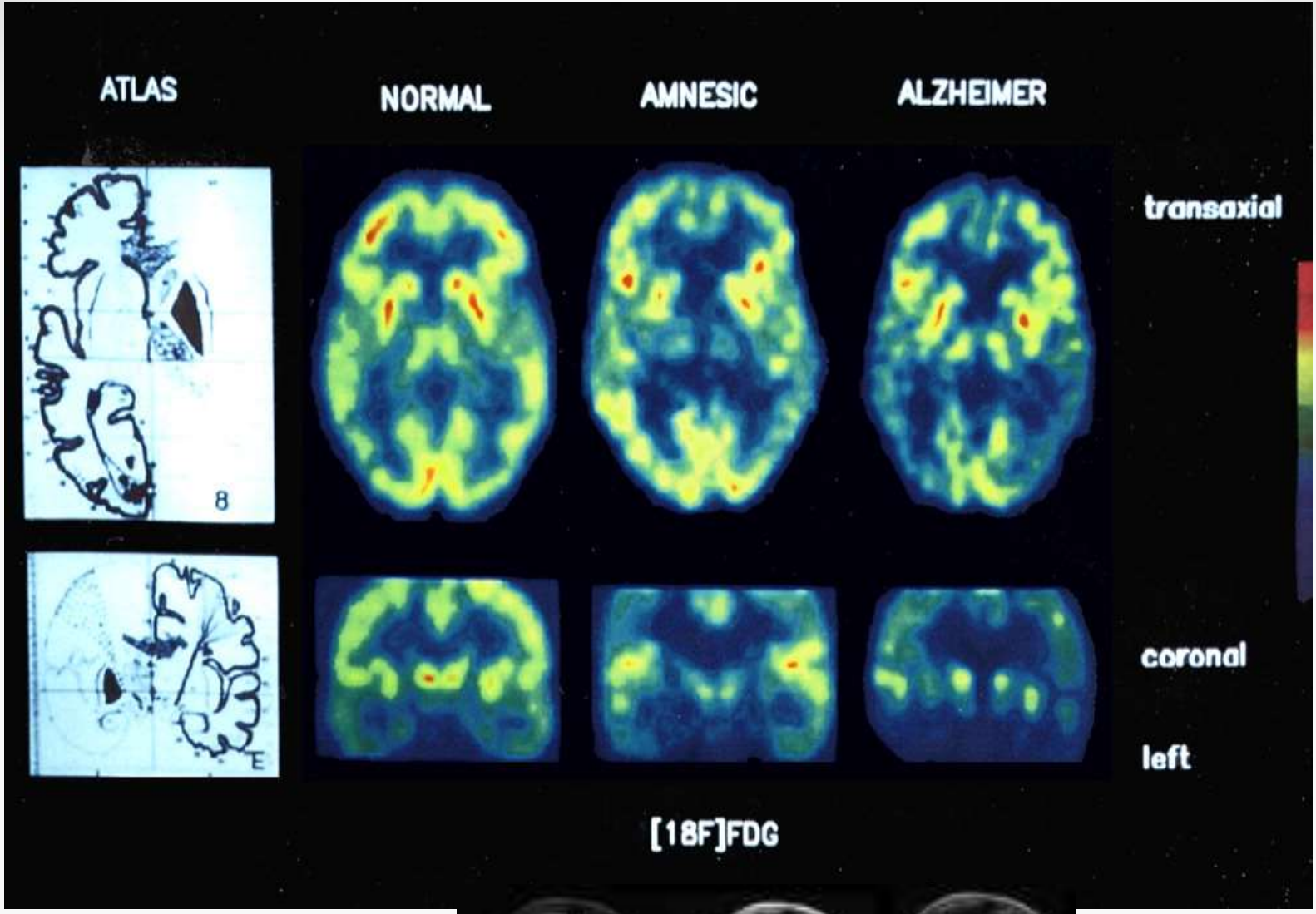

Coronaria
Catetere
Trombo
Palloncino all'apice del catetere
Sede d'introduzione del catetere

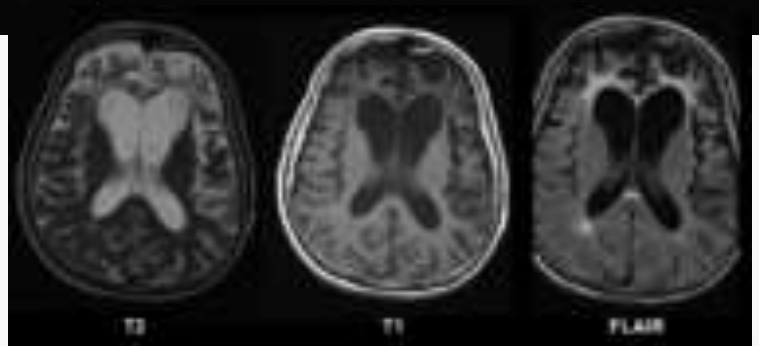

A
B
C
Heart

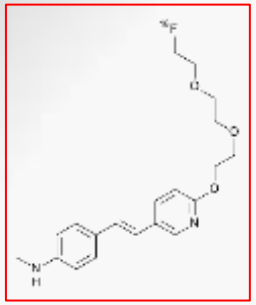

Prima
Dopo

Radiofarmaci per lo studio del sistema nervoso centrale



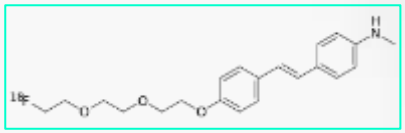

ATLAS
NORMAL
AMNESIC
ALZHEIMER
transaxial
coronal
left
[18F]FDG

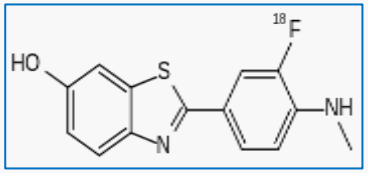


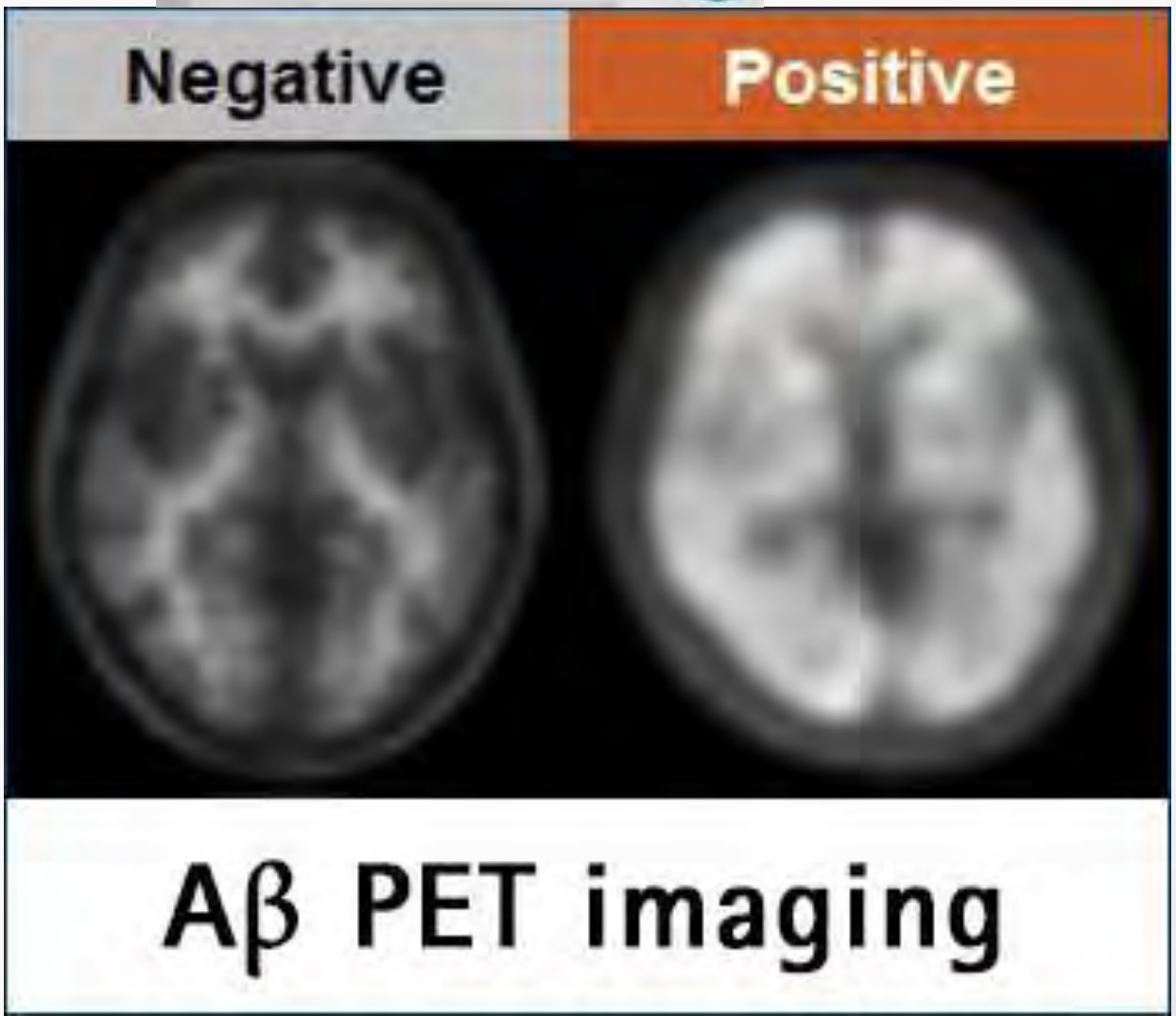


Radiofarmaci ^{18}F per l'imaging della β-amiloide

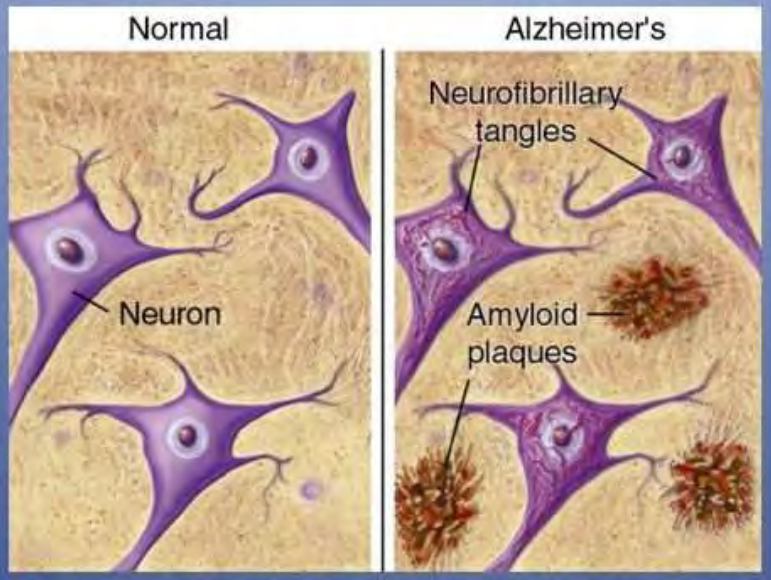
- (18)F]3'-F-PiB (Flutemetamol)
- (18)F-AV-45 (Florbetapir)
- (18)F-AV-1 (Florbetaben)
- ^{18}F-AZD4694

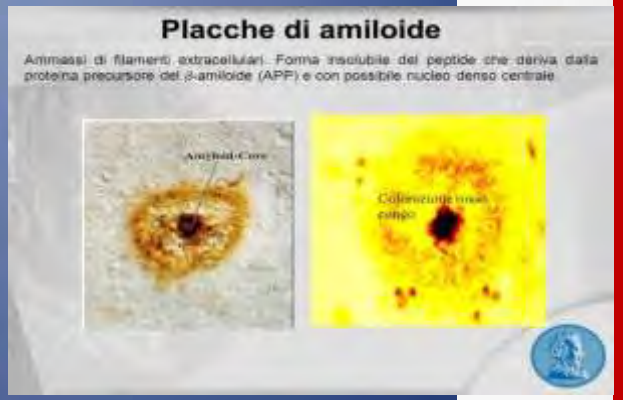






LA MALATTIA DI ALZHEIMER





Dal punto di vista neuropatologico, i cervelli dei pazienti colpiti da Alzheimer sono caratterizzati da placche costituite dall'accumulo di proteina beta-amiloide e dalla formazione di grovigli (ammassi neurofibrillari della proteina tau).

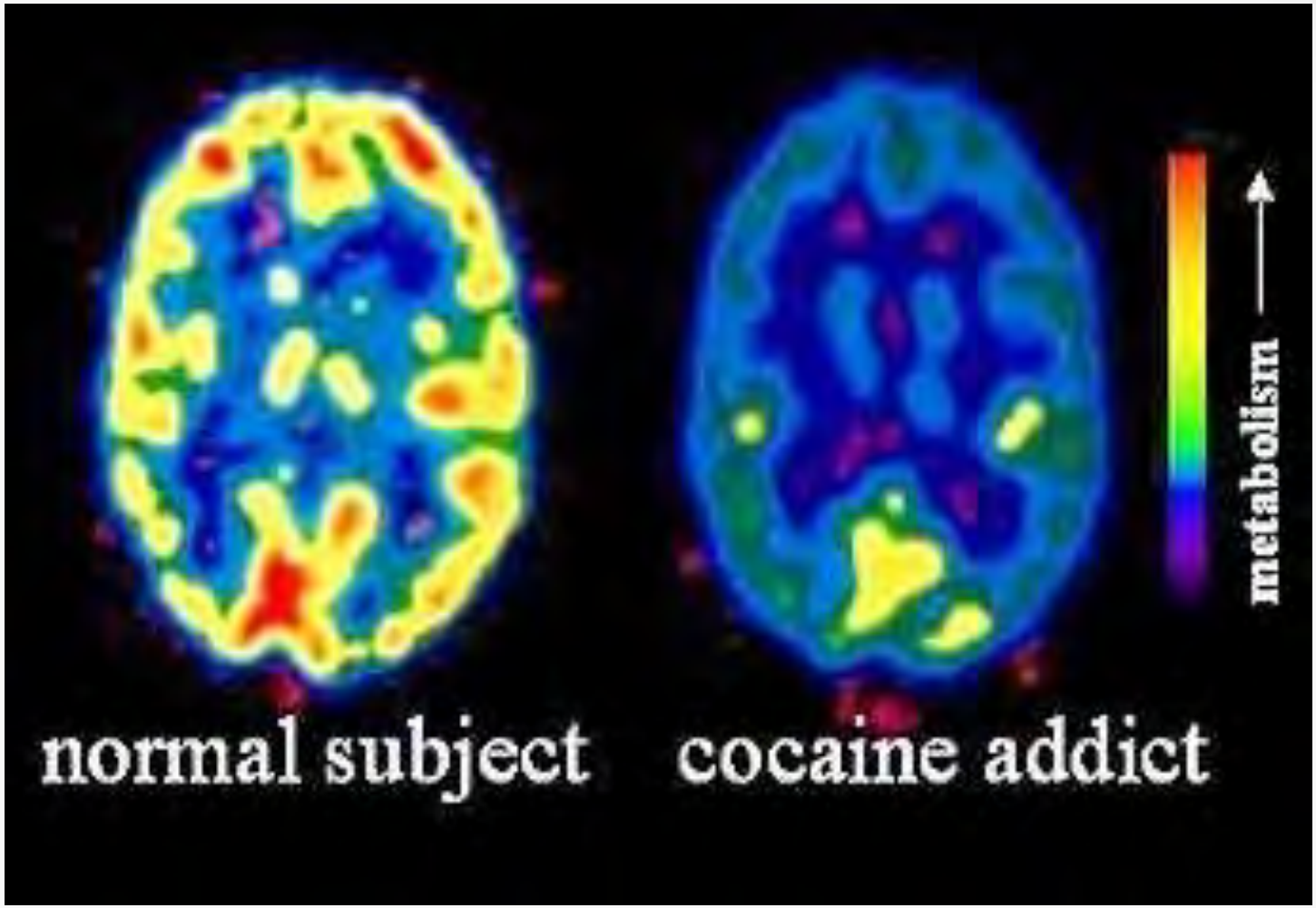

metabolism
normal subject
cocaine addict

Fig. 3

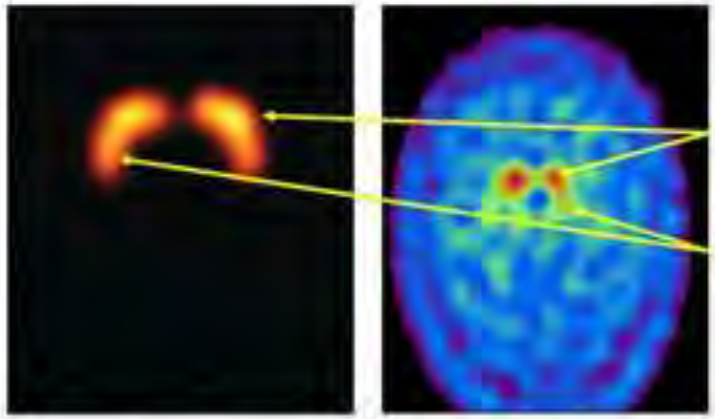
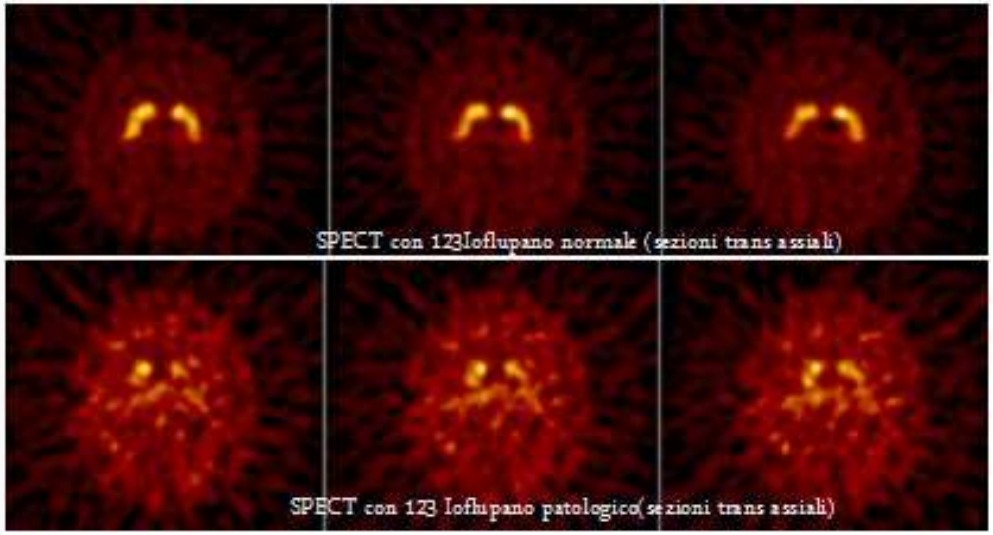
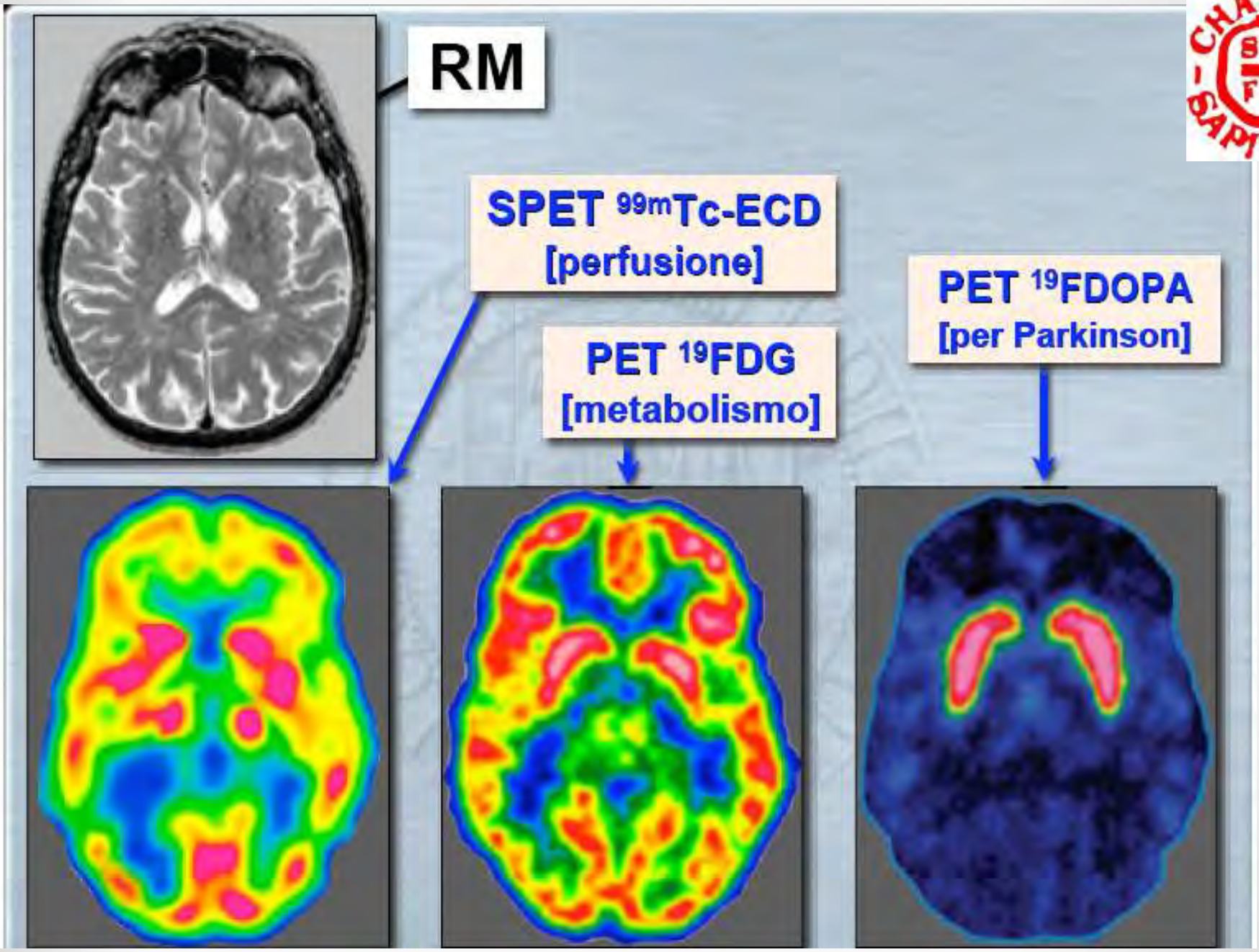
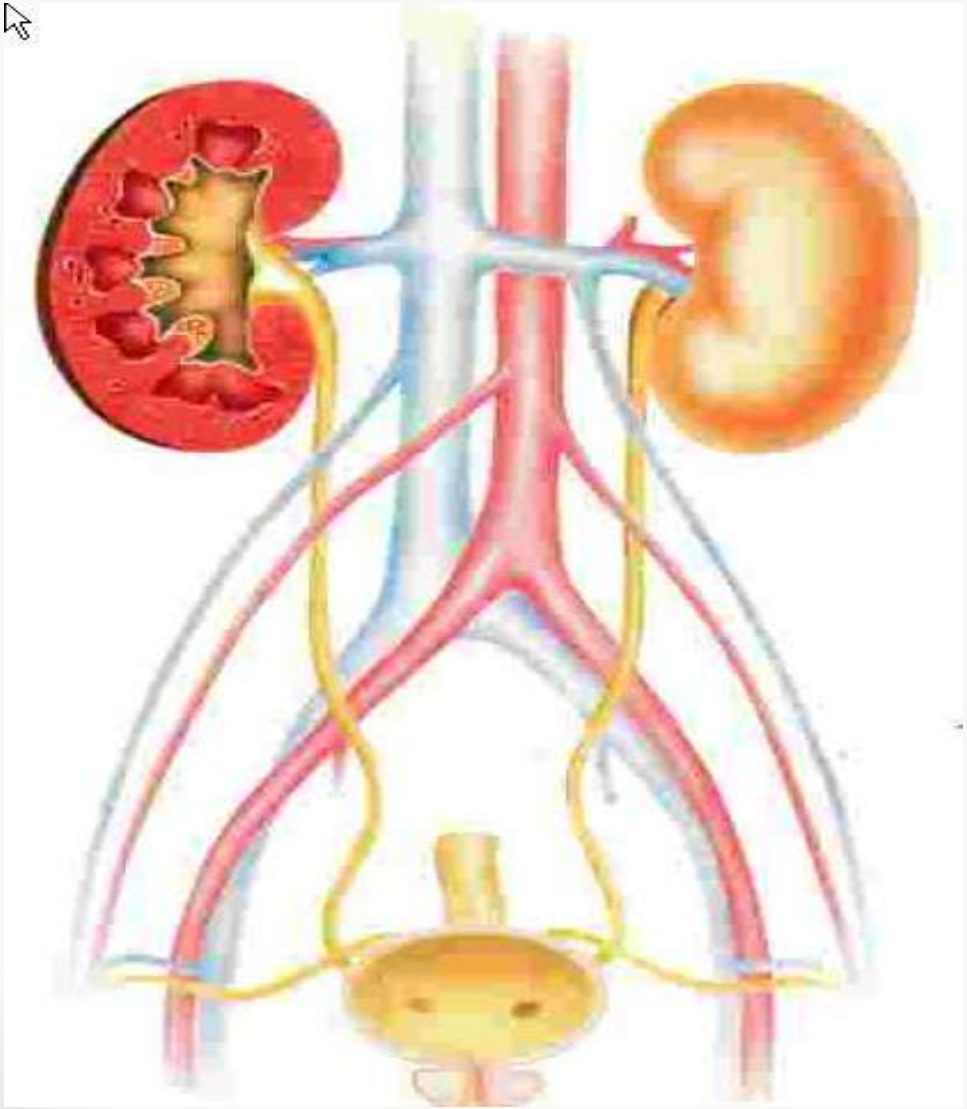

Caudate nucleus
Putamen
NORMAL
PARKINSON'S DISEASE

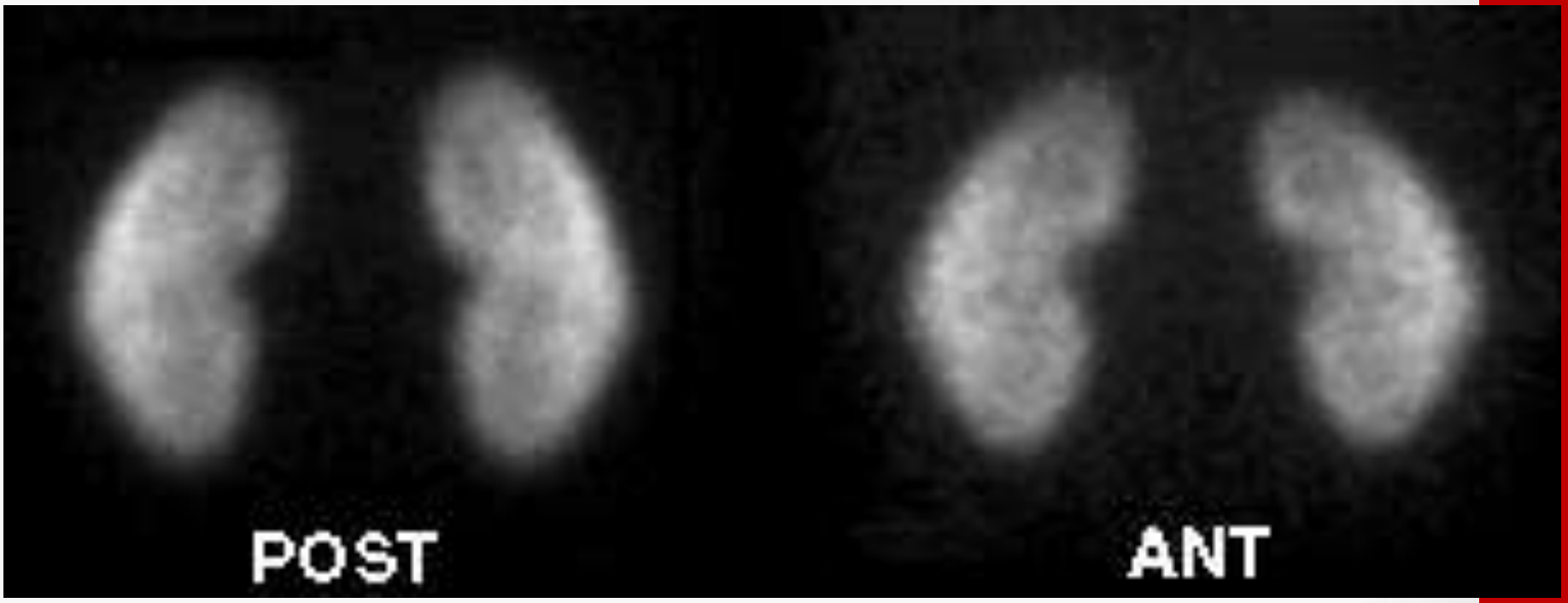
Fig. 4

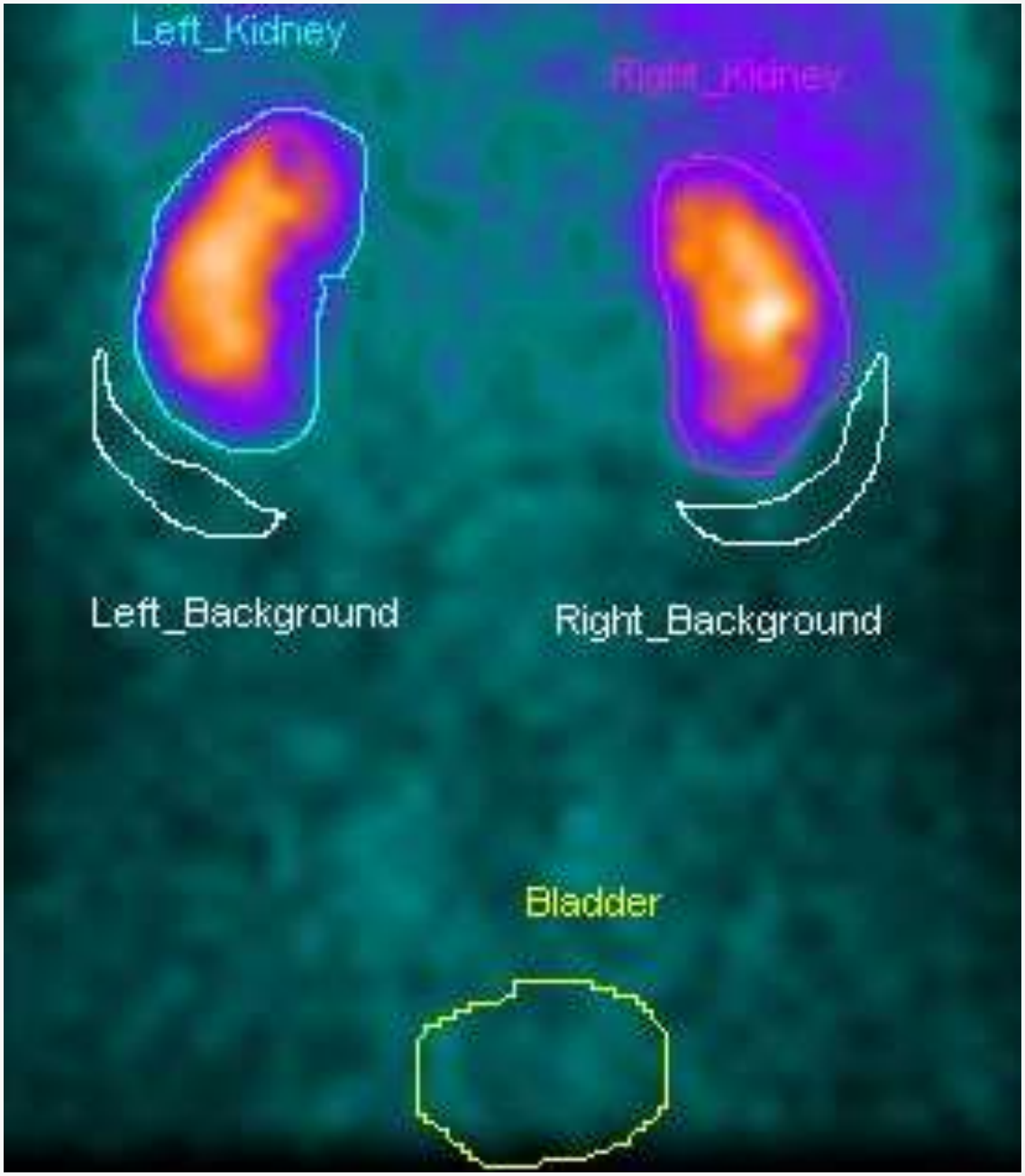

SPECT con 123Ioflupano normale (sezioni trans assiali)
SPECT con 123 Ioflupano patologico(sezioni trans assiali)

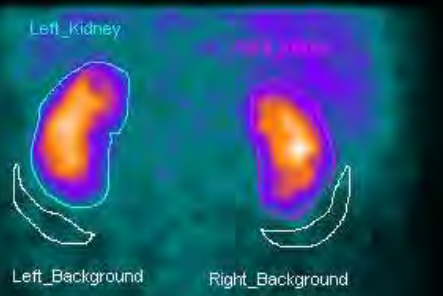

RM
SPET 99mTc-ECD
[perfusione]
PET 19FDG
[metabolismo]
PET 19FDOPA
[per Parkinson]

Radiofarmaci per l'apparato urinario




POST
ANT


Left_Kidney
Right_Kidney
Left_Background
Right_Background
Bladder



01/27/04
RENAL SCAN
renal_results
P2Reframe
28

Bladder Image

No Post-void Image

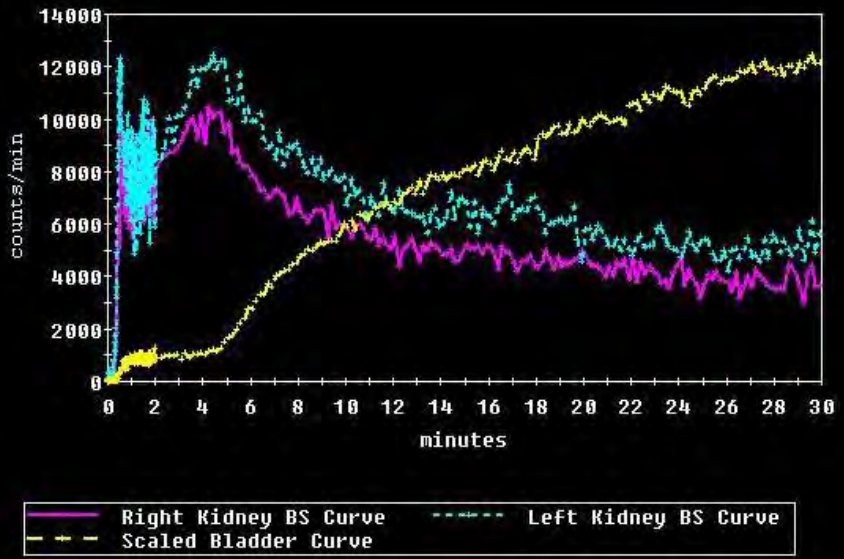
01/27/04
RENAL SCAN
renal_results
FuncSum1

2-3 Minute Summed Image

Patient Information

Height (cm)	2
Weight (kg)	100.0
Age (years)	42.0
Isotope	----
Dose Injected (MBq)	185.00
Transplant	NO
No Lasix	

Background Subtracted Kidney Curves

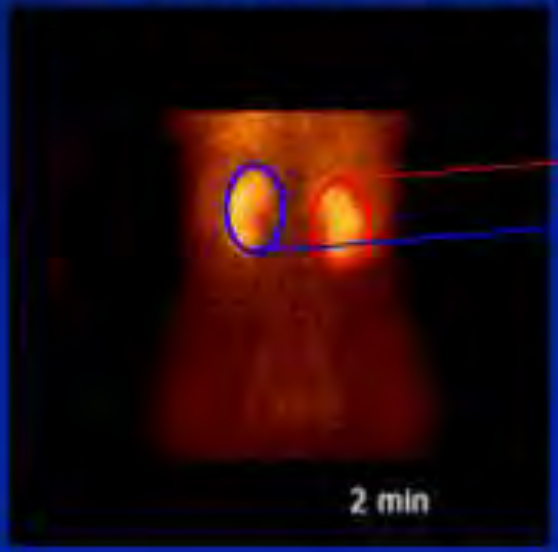


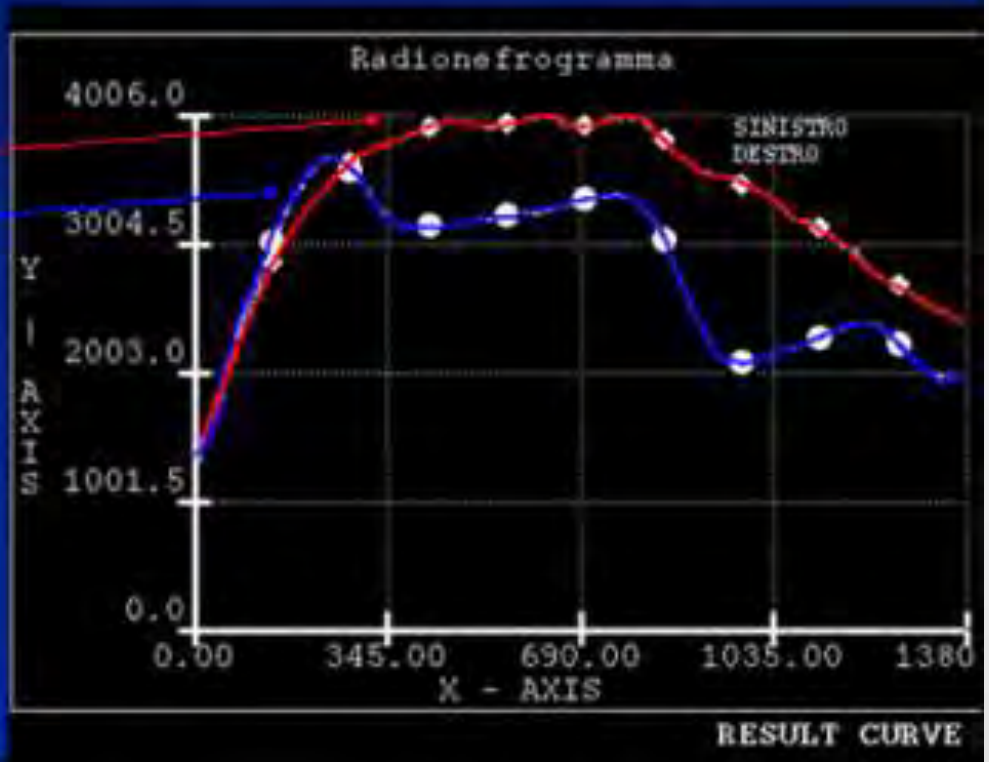
Function Results

	Left	Right
Uptake (%) (2-3 min)	51.7	48.3
TTP (min)	4.42	4.25
Peak Count Rate (counts/min)	12460.3	10436.7
T 1/2 from peak (min)	15.22	10.86
Left Kidney : Bladder peak ratio		0.37

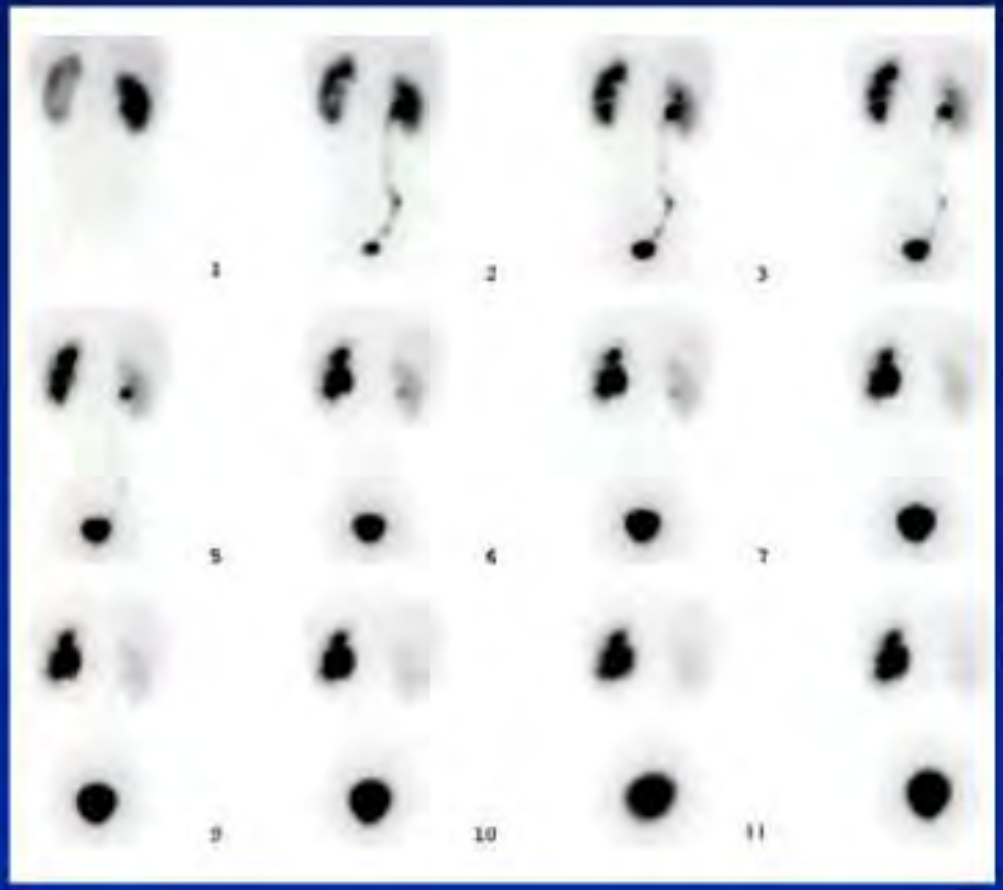
Radionefrogramma

- E' la rappresentazione grafica del transito di tracciante attraverso ciascun rene
  - Fase angiografica
  - Tempo di picco
  - Fase di eliminazione





Stenosi del giunto pielo-ureterale sin.



SCINTIGRAFIA CON LEUCOCITI MARCATI O CON Ab-monoclonali Antigranulociti

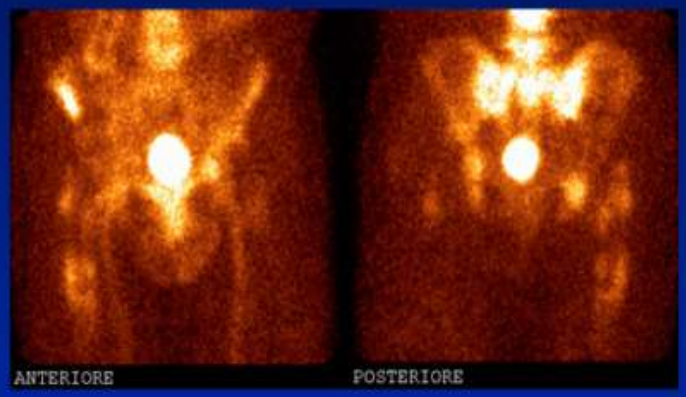
STUDIO DEI PROCESSI SETTICI/INFIAMMATORI

Fig. 2A

Fig. 2B

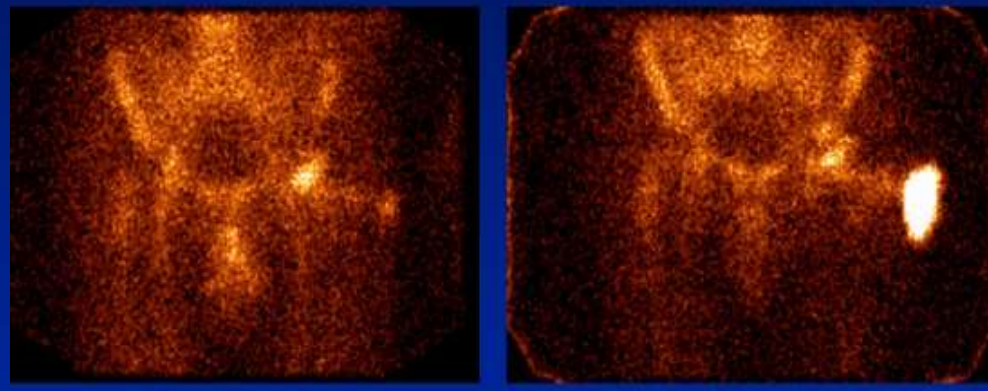
Fig. 2C

Protesi di anca infetta (^{99m}Tc-HMPAO)



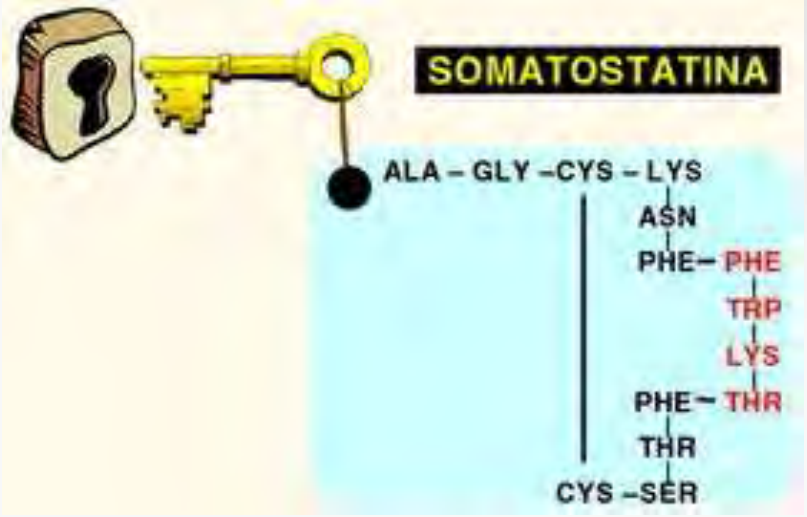
Scintigrafia ^{99m}Tc-HMPAO-leucociti autologhi marcati, per sospetta infezione di artroprotesi coxo-femorale destra completa

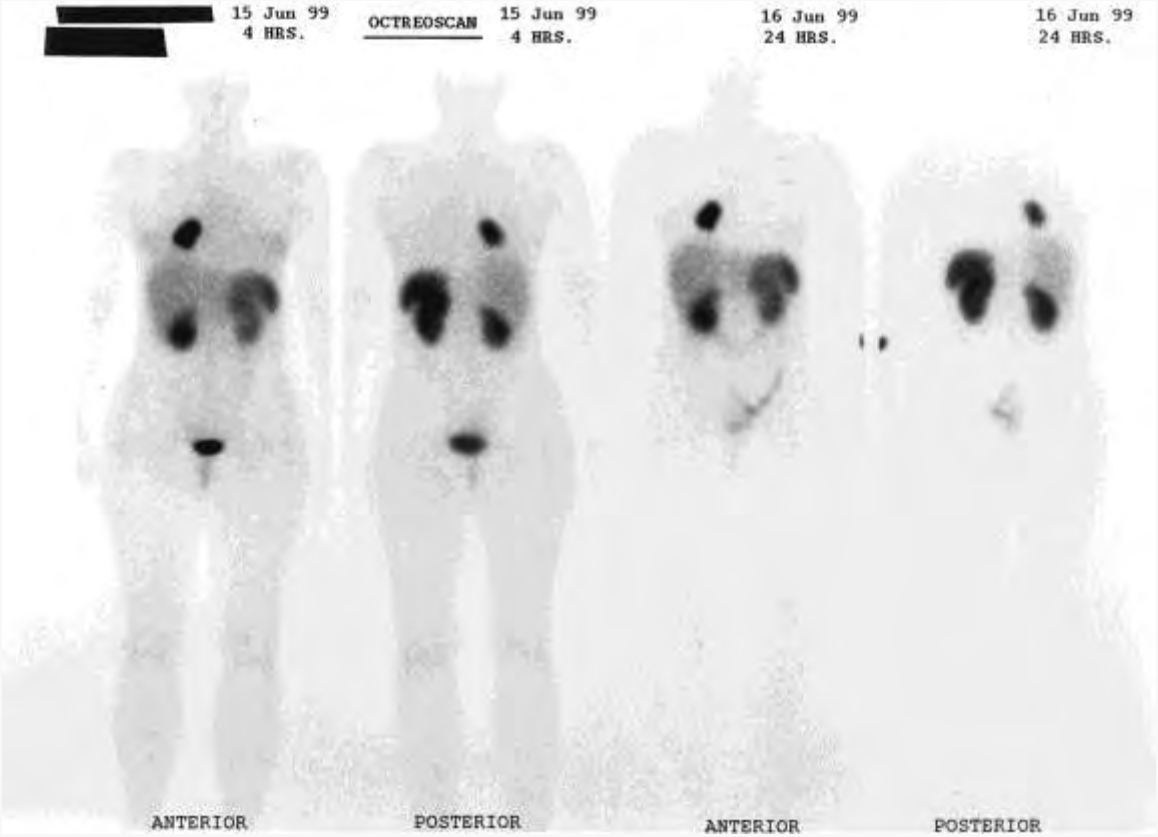
Protesi di anca infetta (^{111}In-oxinato)



Scintgrafia ossea con ^{111}In-oxinato leucociti autologhi marcati in infezione di artroprotesi con fistola cutanea


OctreoScan


SOMATOSTATINA
ALA – GLY –CYS – LYS
ASN
PHE– PHE
TRP
LYS
PHE– THR
THR
CYS –SER


15 Jun 99
4 HRS.
OCTREOSCAN
15 Jun 99
4 HRS.
16 Jun 99
24 HRS.
16 Jun 99
24 HRS.
ANTERIOR
POSTERIOR
ANTERIOR
POSTERIOR

LINFONODO SENTINELLA

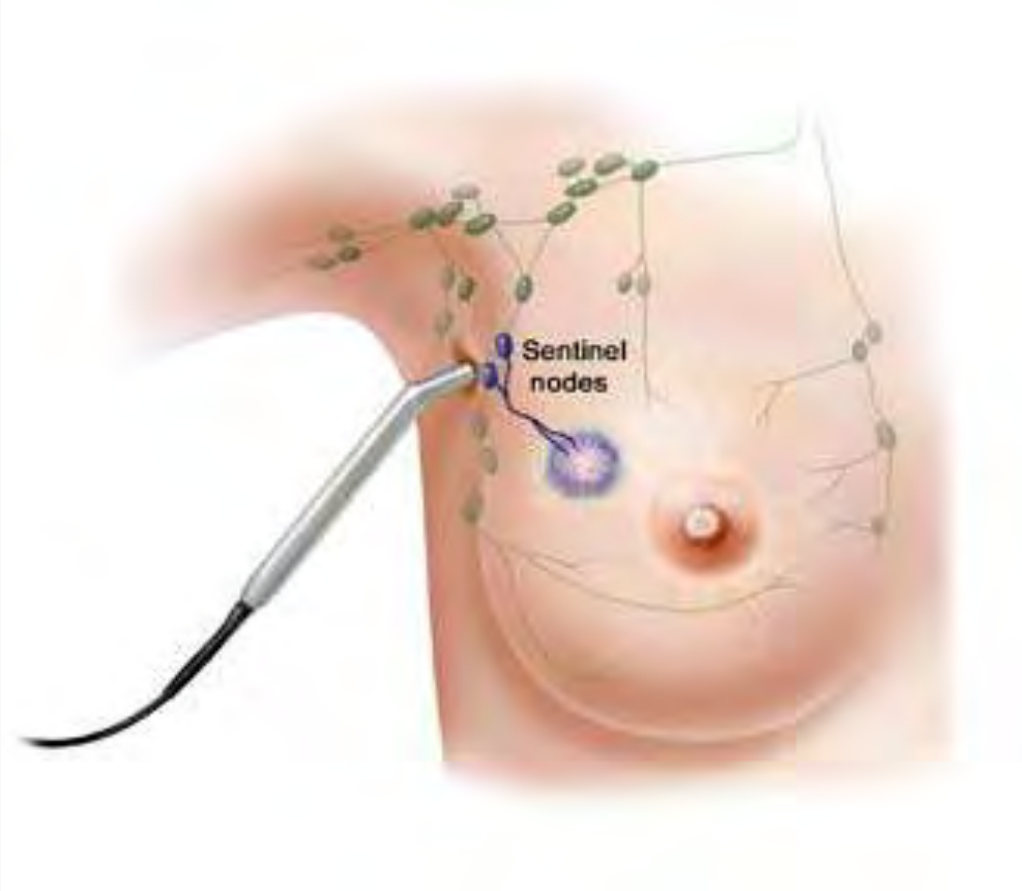
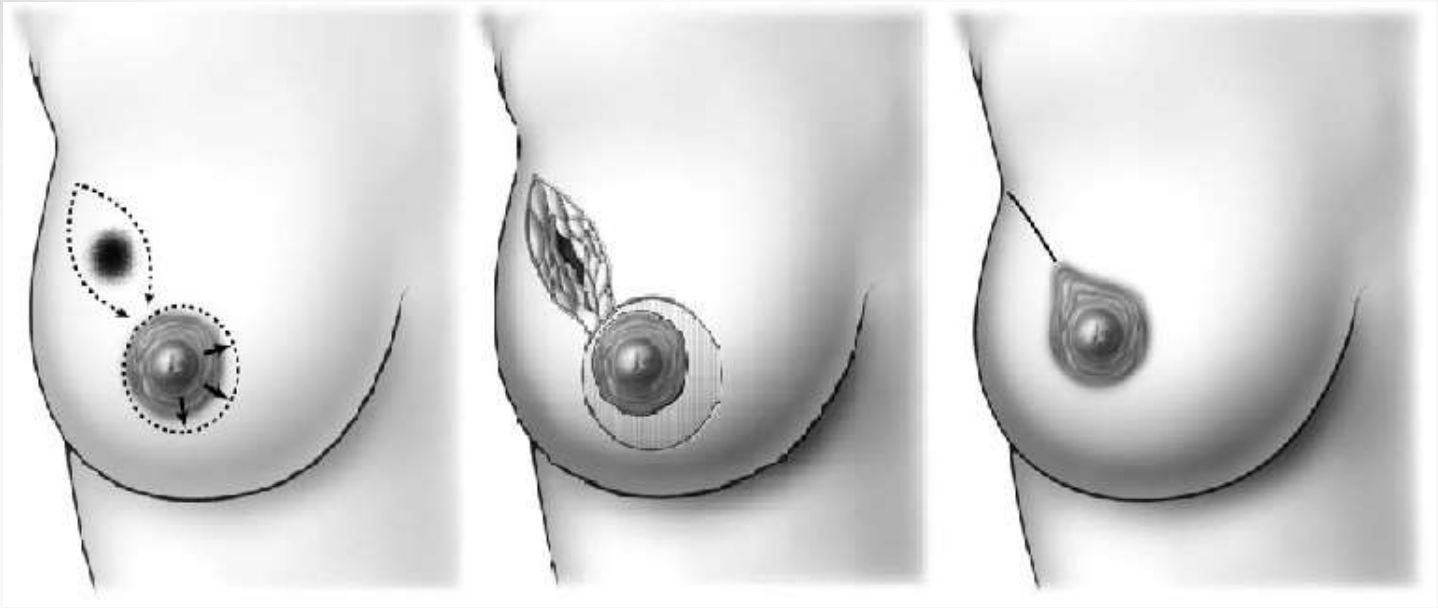
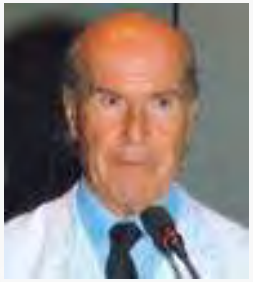
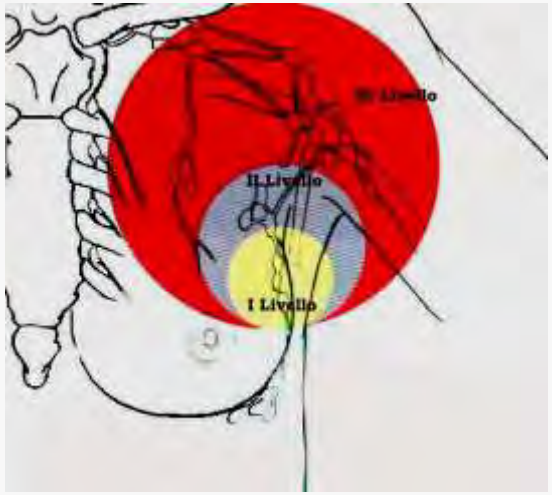


Figura 1 – Linfedema del braccio destro (dominante)

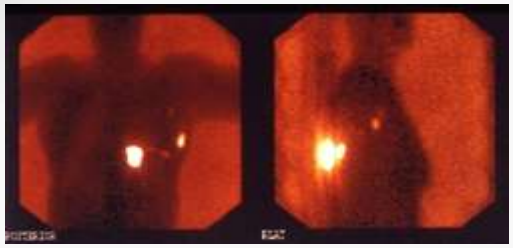






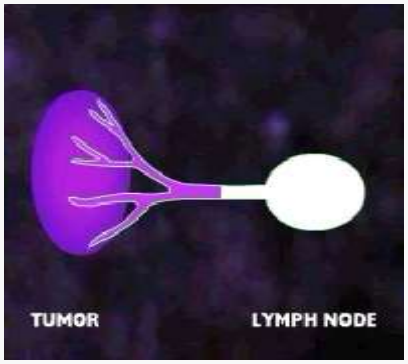
La dissezione ascellare di per se non migliora la prognosi, ma è importante come elemento di stadiazione

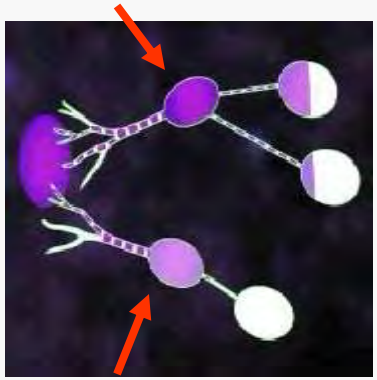
La biopsia radioguidata del Linfonodo SENTINELLA rappresenta attualmente lo standard nella terapia del carcinoma mammario di dimensioni limitate.

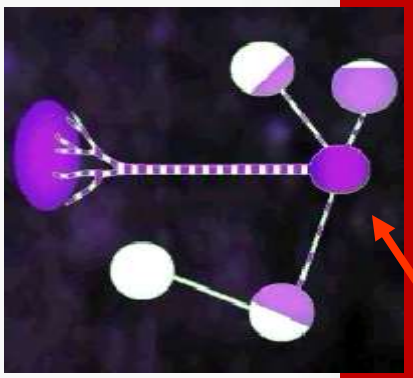


Linfoscintigrafia

Definizione di LINFONODO SENTINELLA



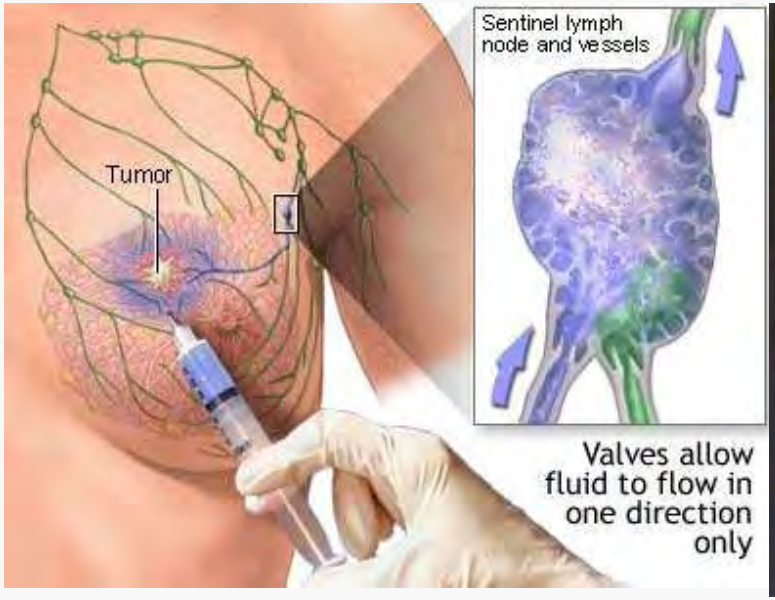




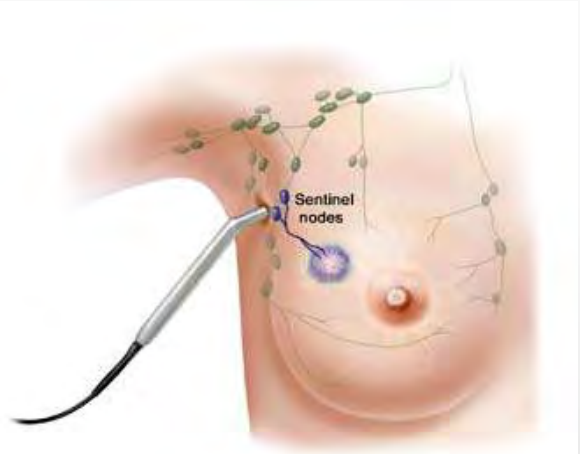
- Il Linfonodo Sentinella è quello che drena dal tumore primitivo con un canale linfatico diretto ed è pertanto il primo ad essere coinvolto dallo spreading linfatico tumorale

- Possono esservi più di un Linfonodo Sentinella

Biopsia del linfonodo sentinella

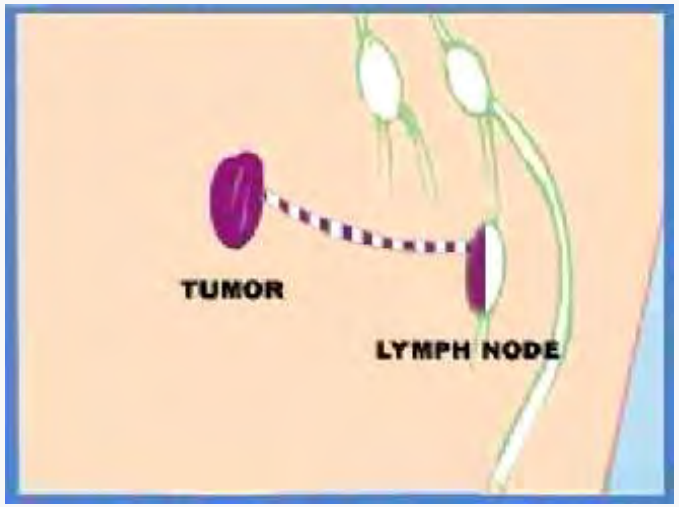


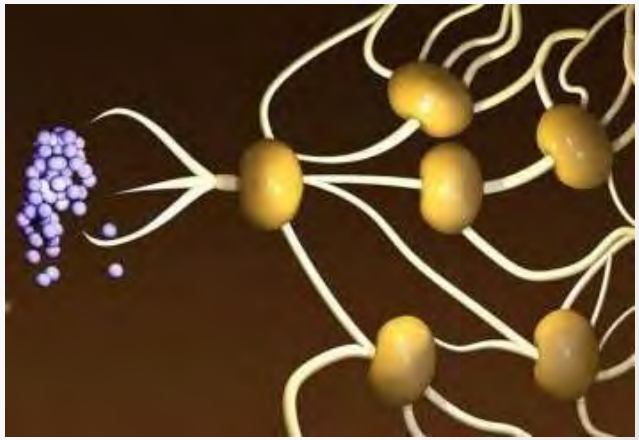
"Il primo possibile sito di metastasi dall'area di drenaggio linfatico della lesione primaria[1]"

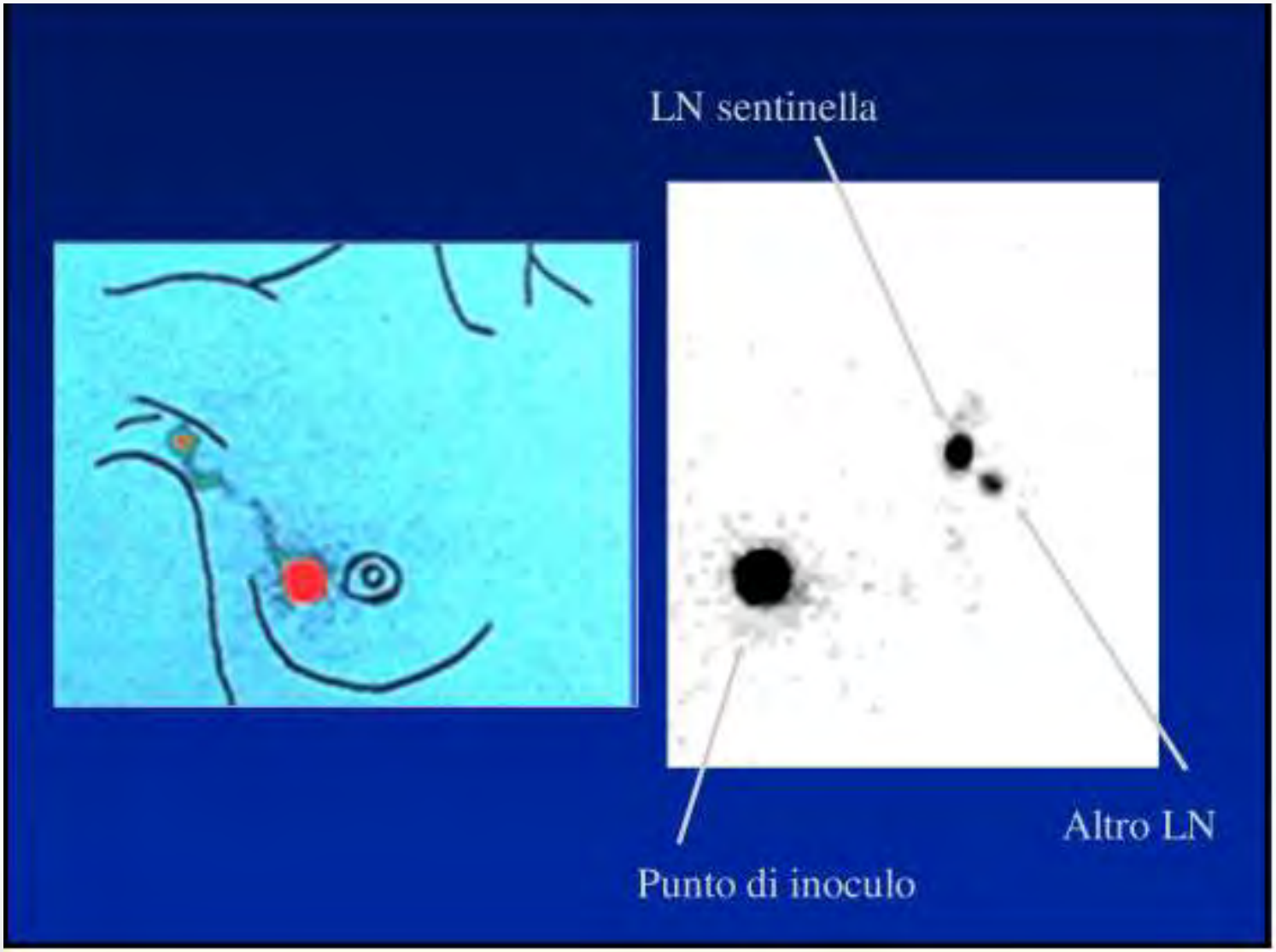


- Il coinvolgimento “tumorale” del linfonodo sentinella predici la diffusione metastatica del tumore agli altri linfonodi del bacino linfatico: tutti i linfonodi del bacino linfatico sono “sani” se il Linfonodo sentinella è “sano”.

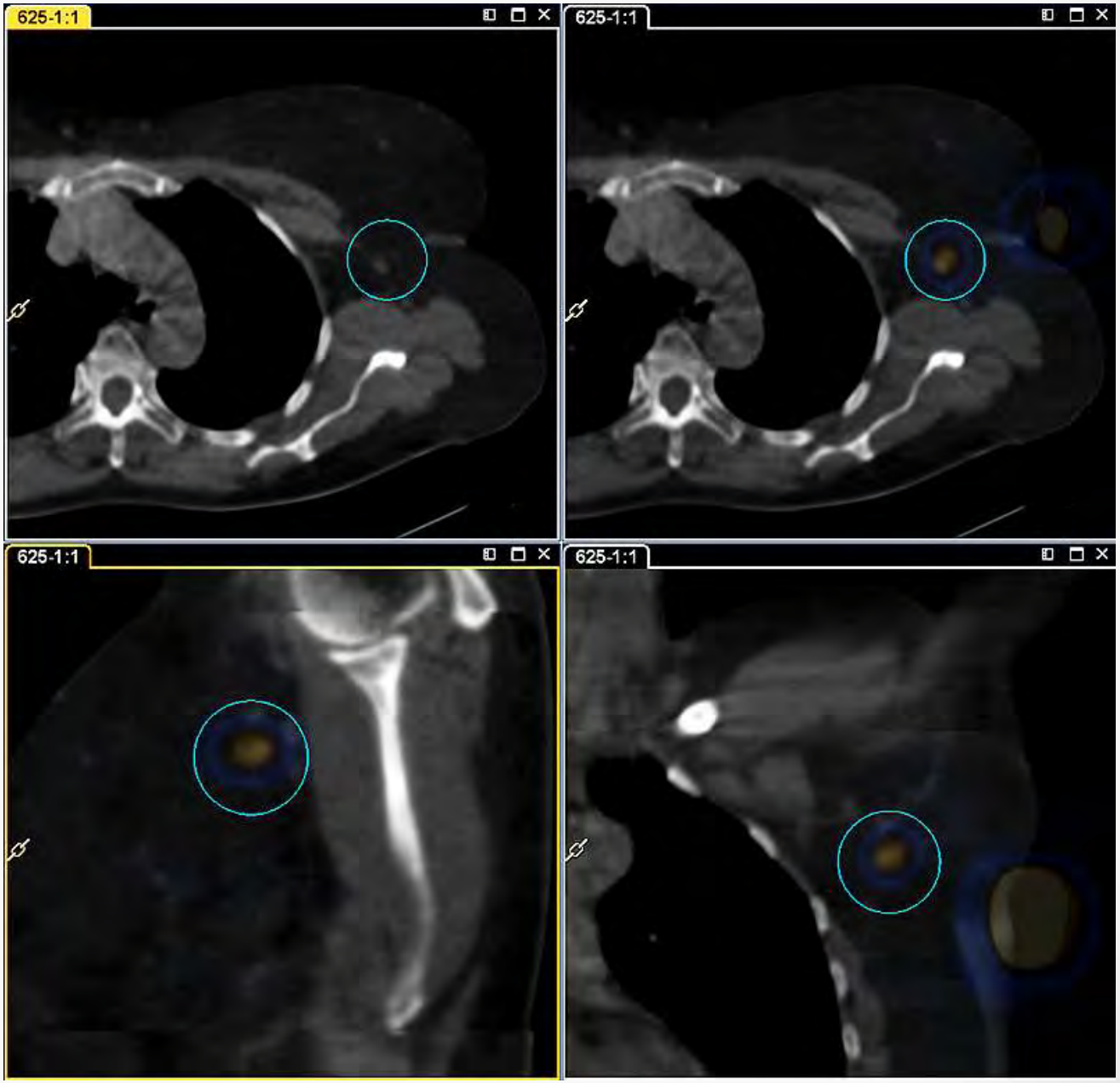
La Biopsia e l’esame istologico del Linfonodo Sentinella permettono di evitare la dissezione ascellare senza rinunciare all’informazione sullo stato dei linfonodi ascellari.

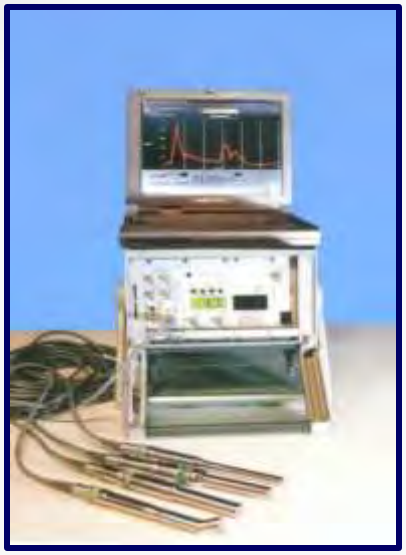





LN sentinella
Altro LN
Punto di inoculo

SPECT/CT – Studio Linfonodo Sentinella






224
20

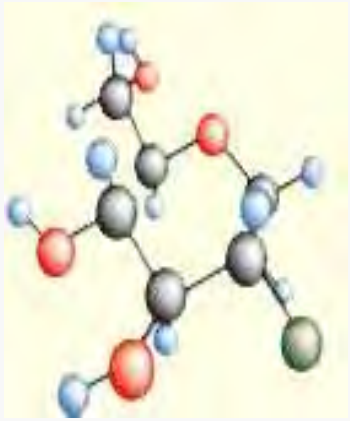

3018
NODE SEEKER 900


2002

Tecnica

- Impiego della sonda
  - Durante l'intervento chirurgico si utilizza una sonda per rilevare la radiazione gamma. La sonda viene passata molto lentamente e perpendicolare ai linfonodi del cavo ascellare per valutare il punto di maggiore emissione del segnale

PET :Tomografia ad Emissione di Positroni

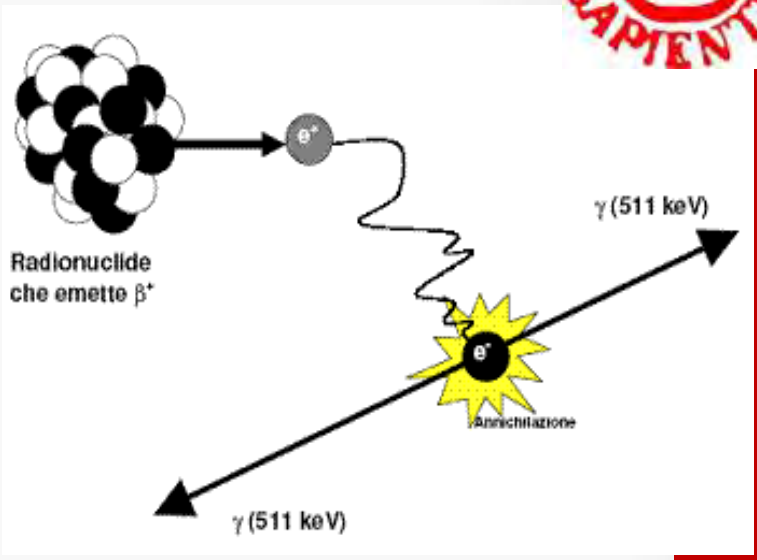


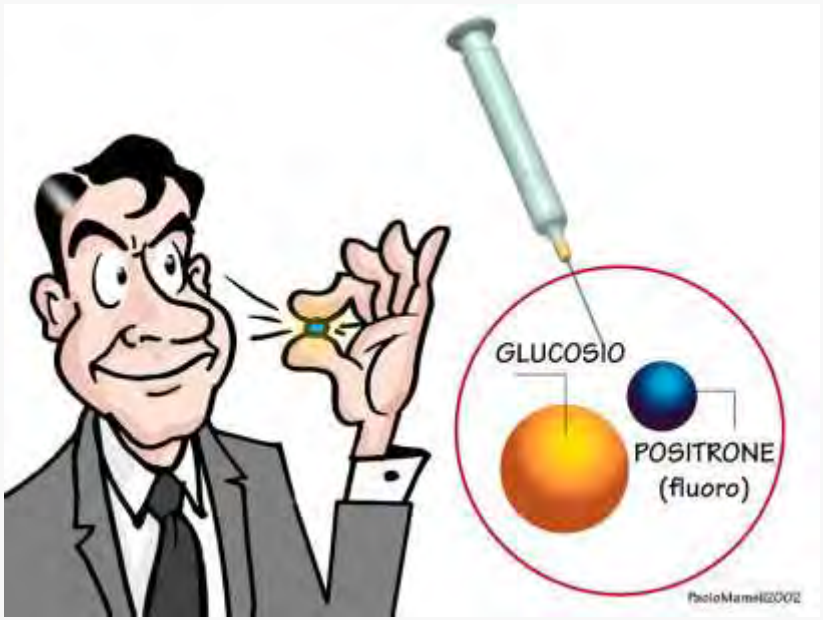
metodica non invasiva
di imaging funzionale

basata sull'impiego di traccianti radioattivi
che, inglobati in specifici complessi molecolari,
vengono somministrati al paziente in esame

PET?

PET/TC

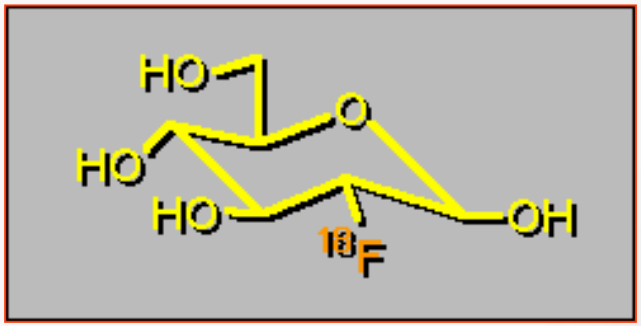

Radionuclide
che emette β+
γ (511 keV)
Annichilazione
γ (511 keV)


GLUCOSIO
POSITRONE
(fluoro)

Isotopi β + emittenti PET

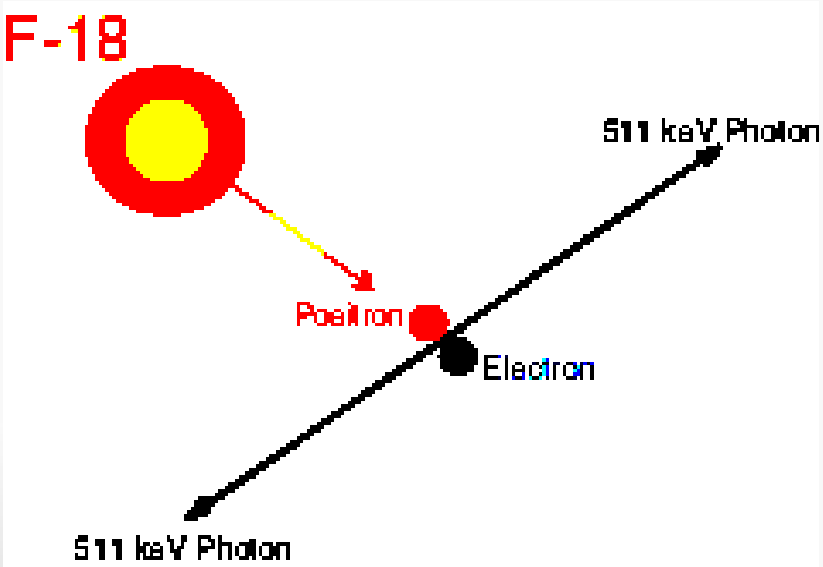
Isotopo β+	T ½ (minuti)
^{11}C	20,3
^{13}N	10,0
^{15}O	1,8
^{18}F	109,0
^{68}Ga	68,3
^{75}Br	102,0
^{77}Kr	72,0
^{82}Rb	1,3

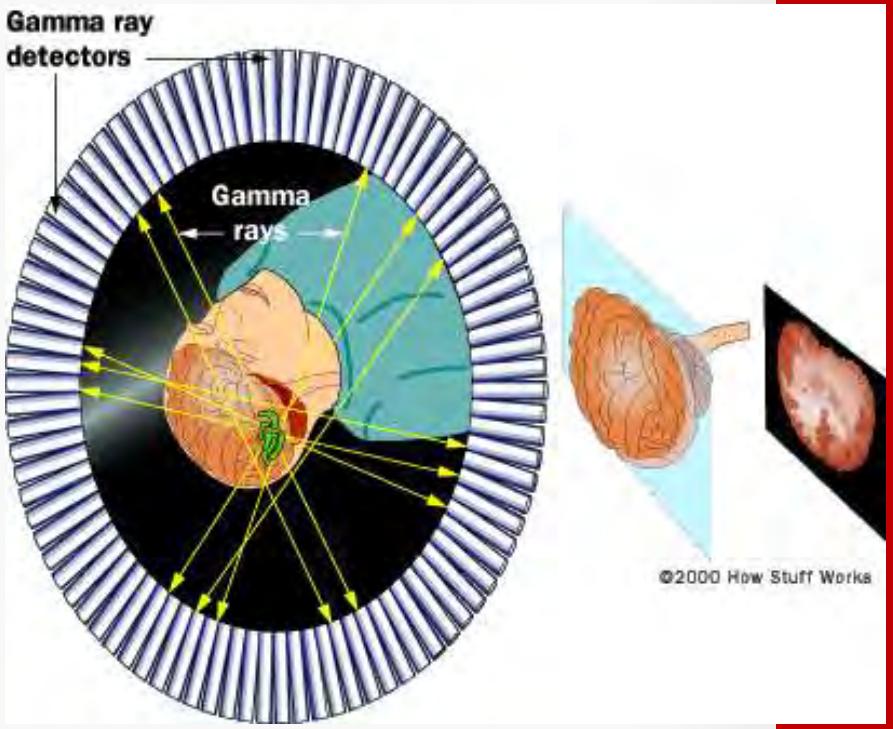
^{18}F-Fluorodesossiglucosio (FDG)

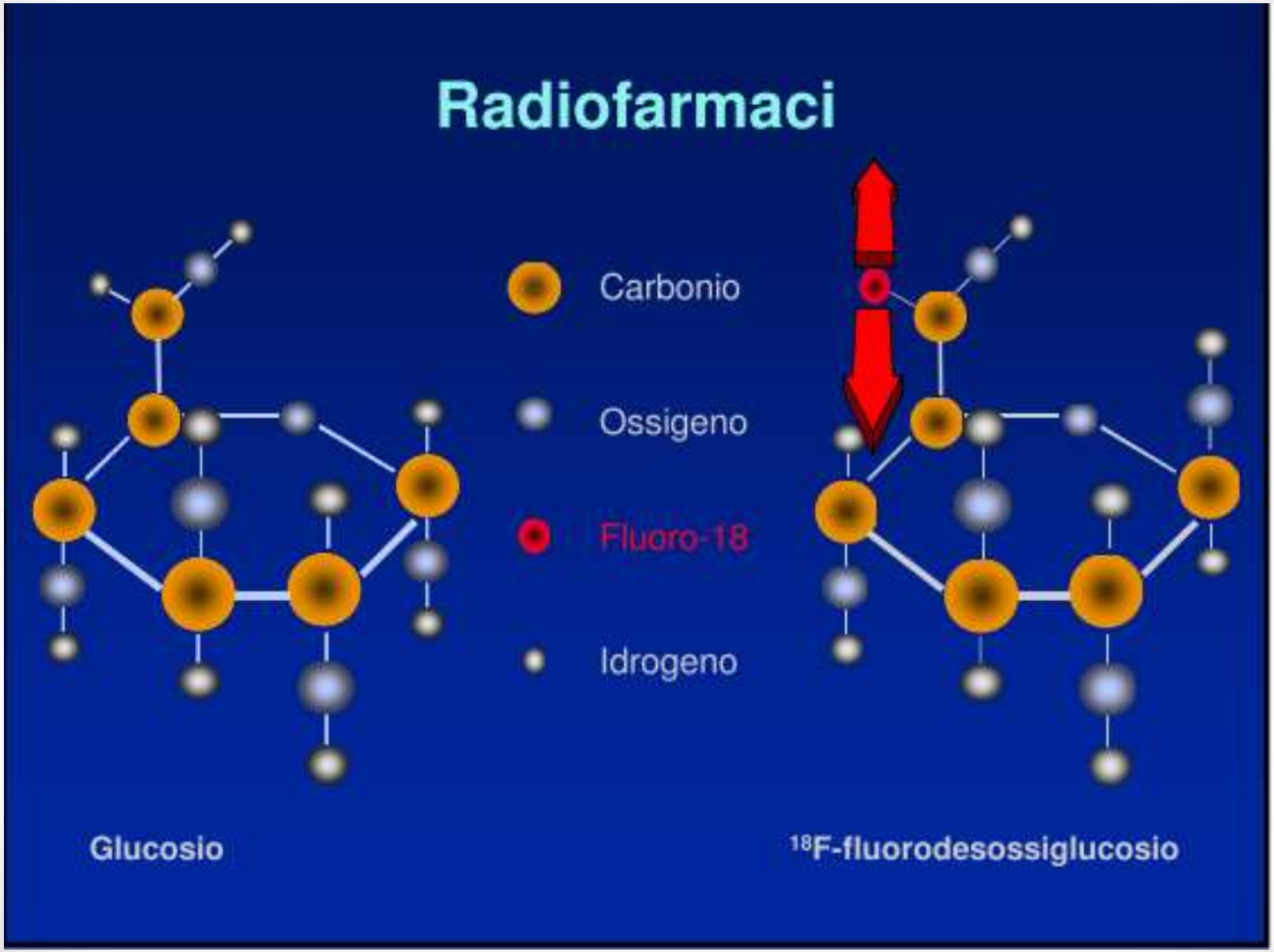


Gli isotopi PET sono emettitori di positroni (e^+)

$e^+ + e^- \rightarrow 2\gamma$

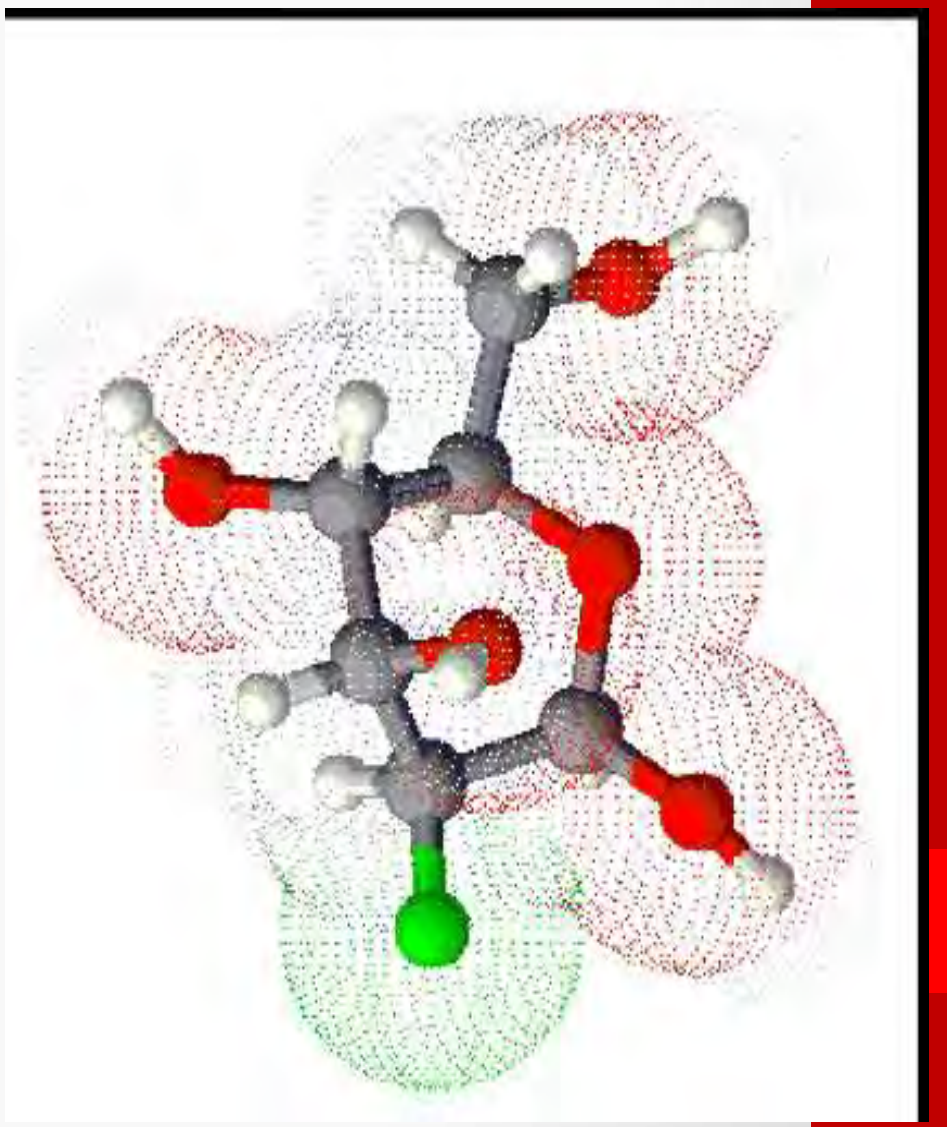


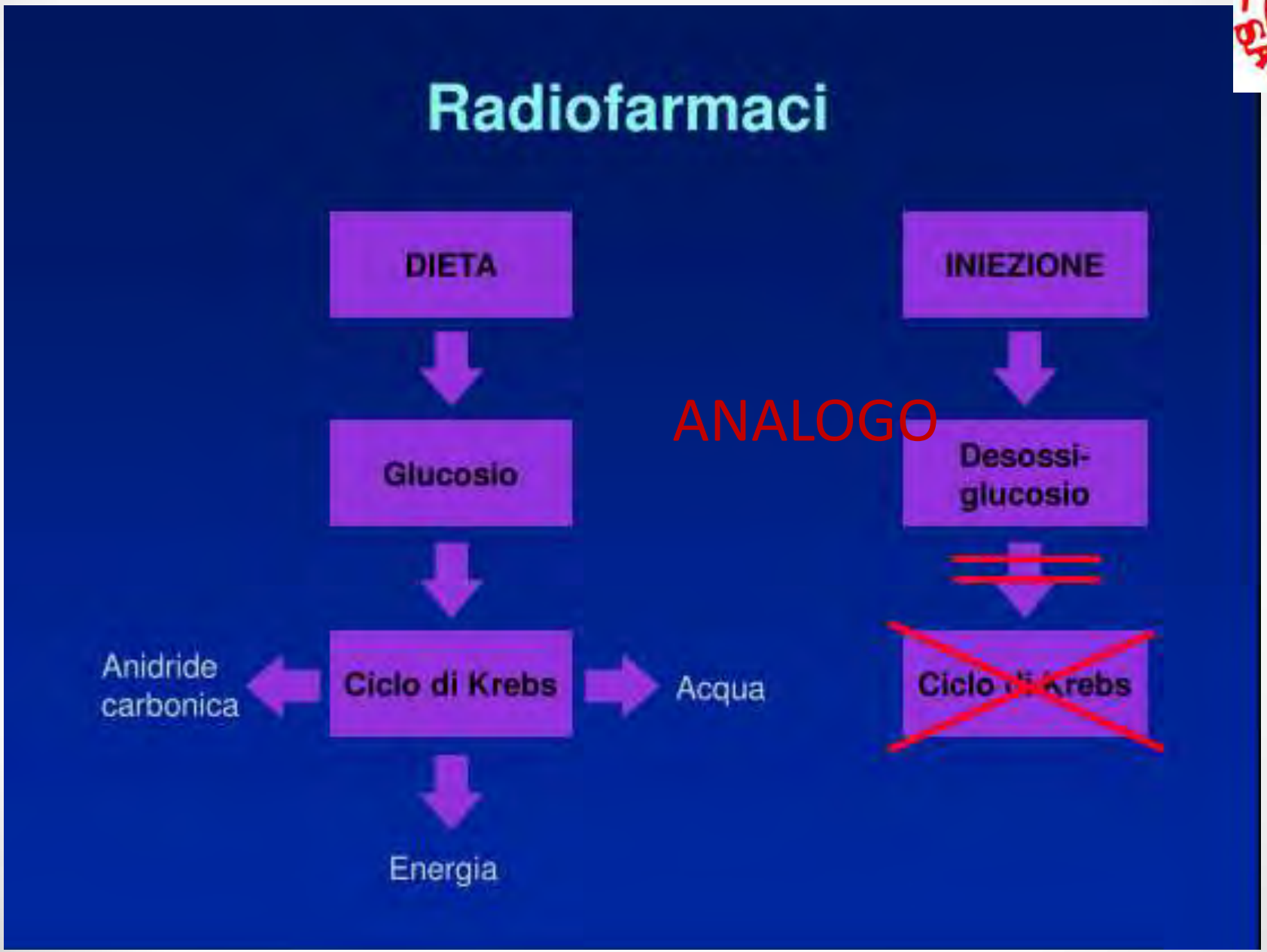



Radiofarmaci
Carbonio
Ossigeno
Fluoro-18
Idrogeno
Glucosio
18F-fluorodesossiglucosio

[18F]-FDG Il radiofarmaco principe

- Il radiofarmaco più utilizzato in Medicina Nucleare PET (95% degli esami è il 18F-FDG)
- Il 18F-FDG è un analogo del glucosio a cui è stato sostituito un gruppo ossidrile (- OH) con il fluoro radioattivo
- E’ un tracciante del metabolismo glucidico.




Radiofarmaci
DIETA
Glucosio
Ciclo di Krebs
Anidride carbonica
Acqua
Energia
INIEZIONE
Desossi-glucosio
Ciclo di Krebs
ANALOGO


"cellule colonizzatrici"
PaoloMarmeli2002


GLUCOSIO!!
PaoloMarmeli2002


PaoloMarmeli2002

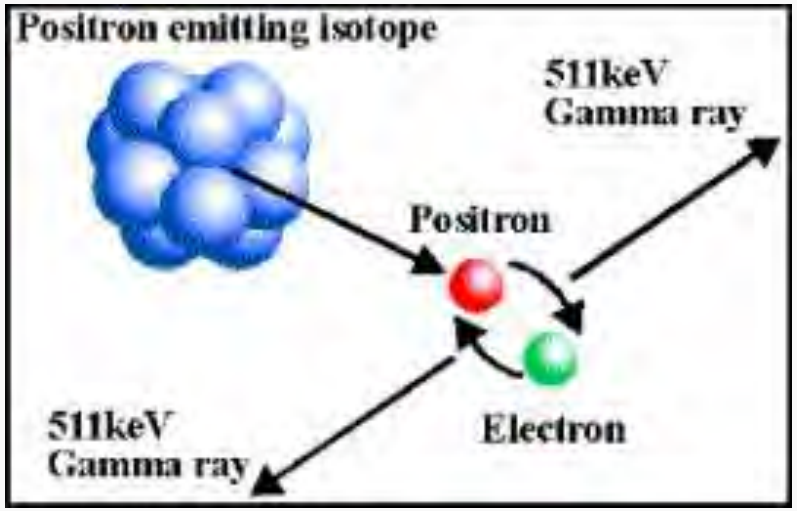
L’accumulo di FDG nel tumore

E’ STRETTAMENTE CORRELATO

- **al numero di cellule vitali ed**

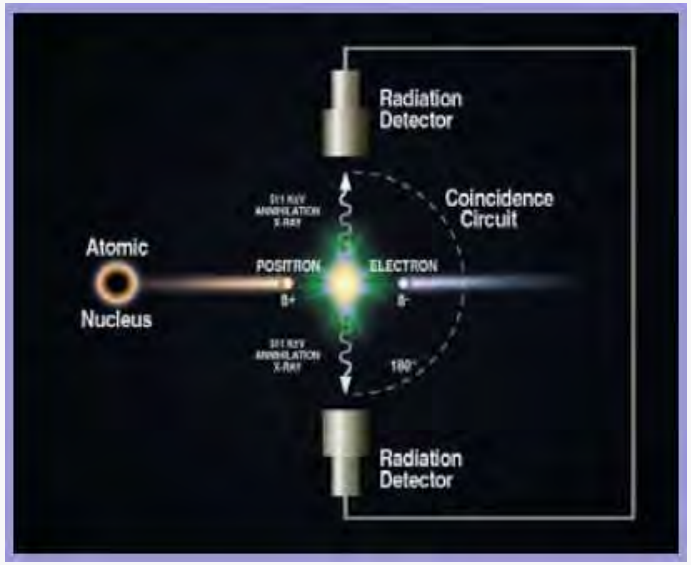
all’attività metabolica

L' FDG iniettato al paziente si comporta come il glucosio e si accumula maggiormente in sedi ove la glicolisi è attivata in misura abnorme rispetto al consueto metabolismo aerobico, cosa che avviene in varie condizioni patologiche, come ad esempio nel contesto di **tumori primitivi e di loro metastasi.**



Una serie di rivelatori disposti a corona intorno al paziente, è in grado di registrare questi impatti catturando i fotoni opposti emessi durante le annichilazioni e trasformandoli in segnali elettrici.

- Un calcolatore riceve queste informazioni e calcola la posizione dell'impatto. Con questi dati ricostruisce poi delle immagini in due o tre dimensioni della zona analizzata
- I raggi gamma, di energia pari a 0.511 MeV, essendo in grado di fuoriuscire dal corpo del paziente, possono essere facilmente rivelati.



Il Metabolismo dei glucidi

- I glucidi vengono metabolizzati dalle cellule (cioè convertiti in energia) attraverso una serie di reazioni chimiche cicliche. La Glicolisi, Il ciclo di Krebs, La catena di trasporto degli elettroni

- Queste reazioni avvengono all'interno di ogni cellula del nostro corpo ma in alcuni tessuti (o per ragioni fisiologiche o a causa di malattia) la richiesta di energia è molto maggiore.

- **Cervello Cuore Tessuti Neoplastici**

- In queste cellule il fabbisogno e consumo di zuccheri risulta maggiorato rispetto alla norma

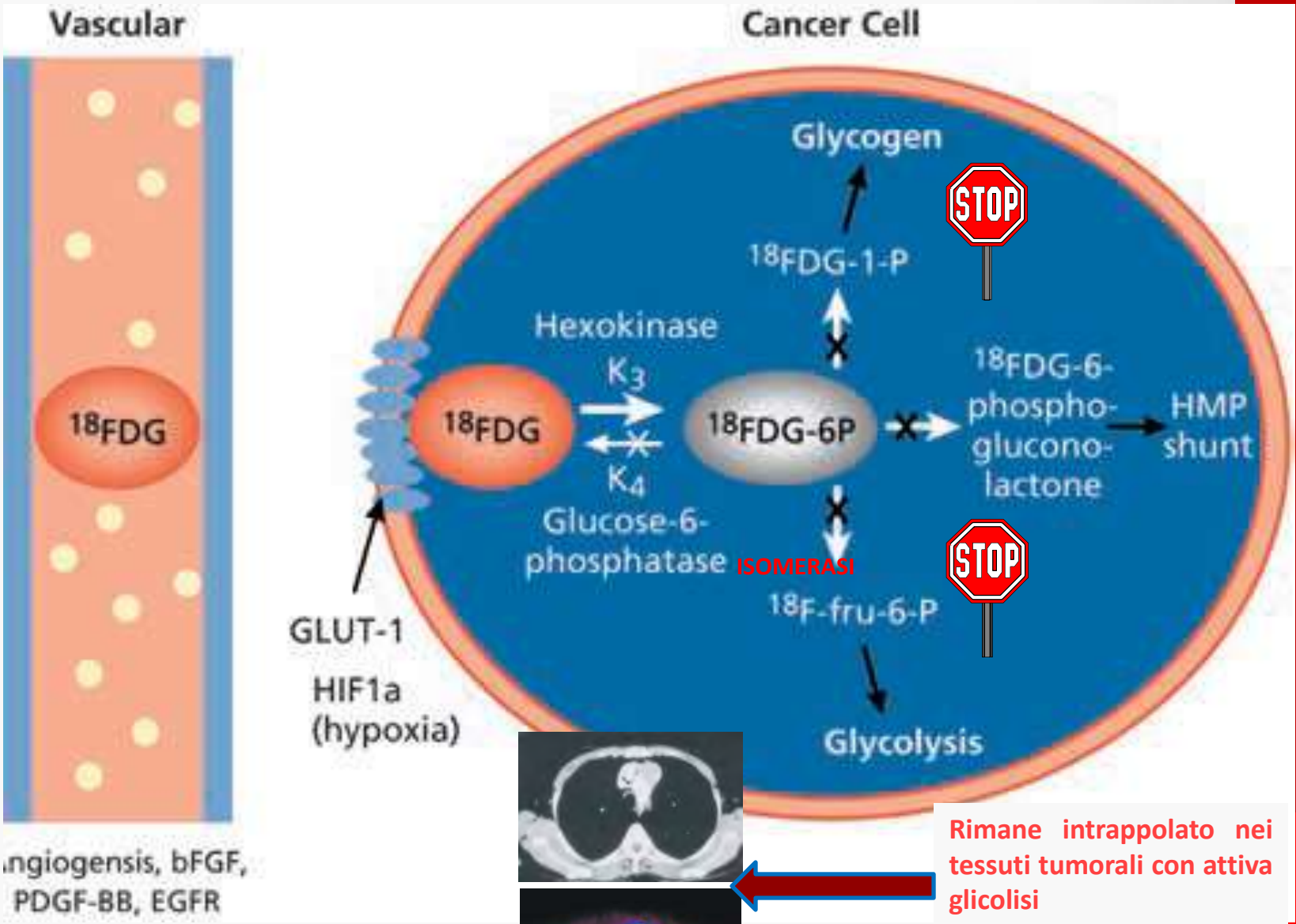
Il Metabolismo dei glucidi: Glucosio e FDG a confronto

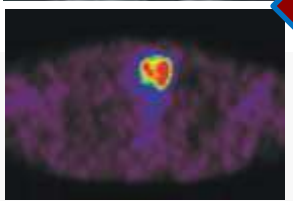
- **L’ FDG segue il metabolismo dei glucidi, inizia la glicolisi ma non è riconosciuto dal secondo enzima del ciclo (isomerasi) e rimane bloccato nelle cellule.**

- **In particolare le cellule neoplastiche hanno una intensa attività glicolitica e quindi accumulano maggiori quantità di farmaco.**

"Metabolic trapping" del FDG

Analogo del Glucosio





Rimane intrappolato nei tessuti tumorali con attiva glicolisi

Imaging metabolico ed oncologia

Le cellule tumorali presentano caratteristiche alterazioni a livello genetico, a cui corrispondono modificazioni del comportamento metabolico

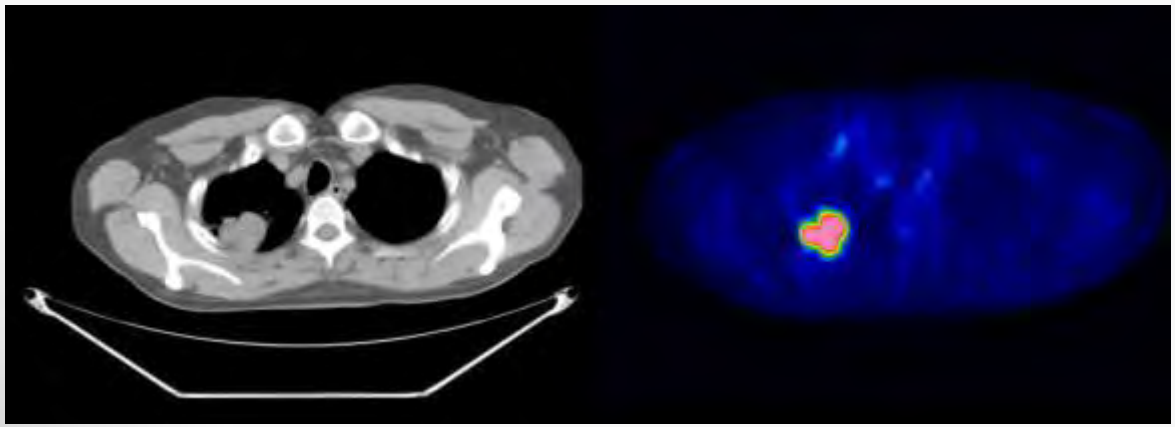
L'accumulo di FDG nel tumore

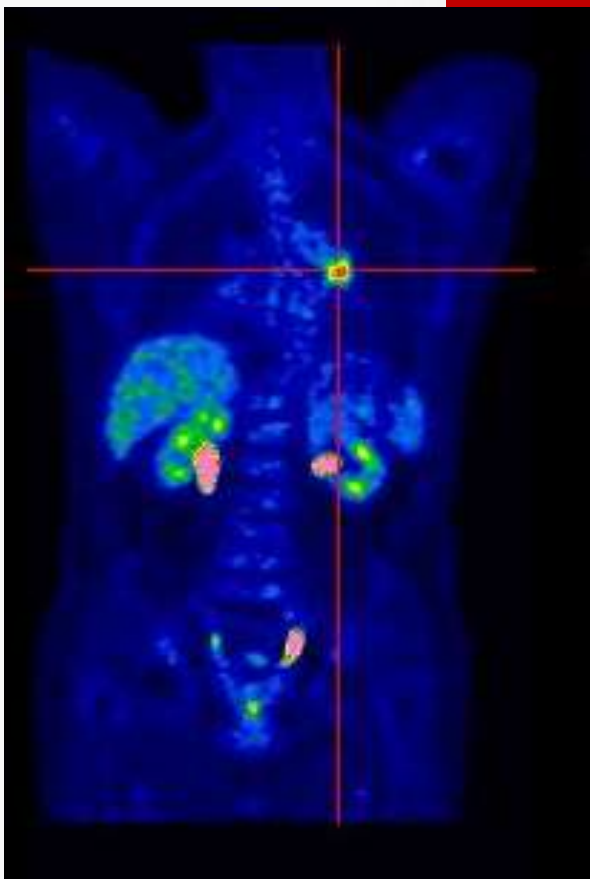
E' STRETTAMENTE CORRELATO

al numero di

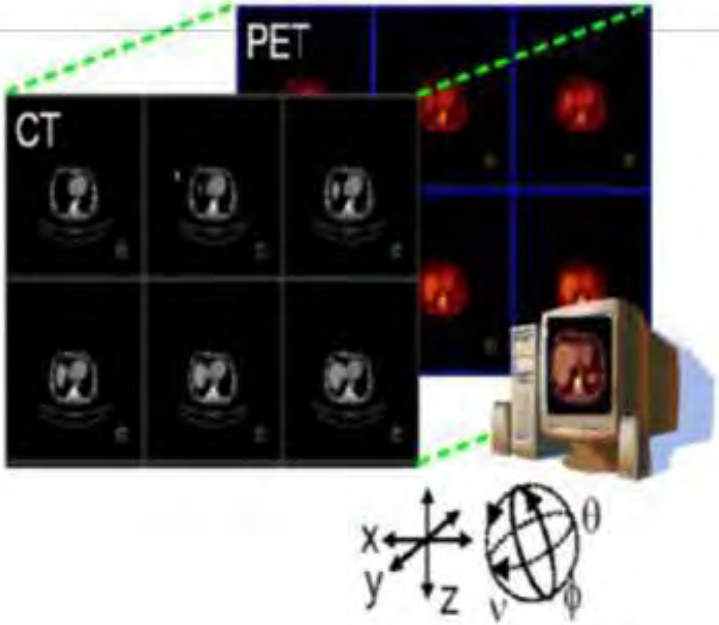
cellule vitali ed all'incemento dell'attività

metabolica glicolitica tumorale



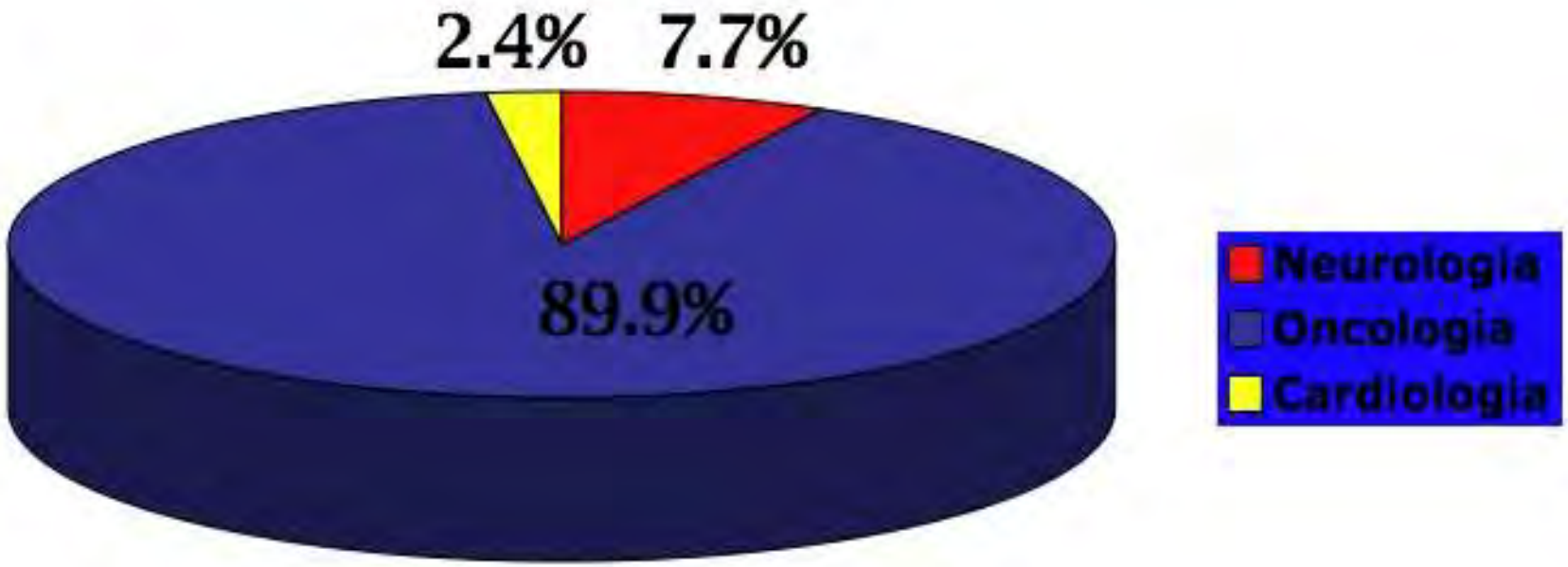



CT
PET

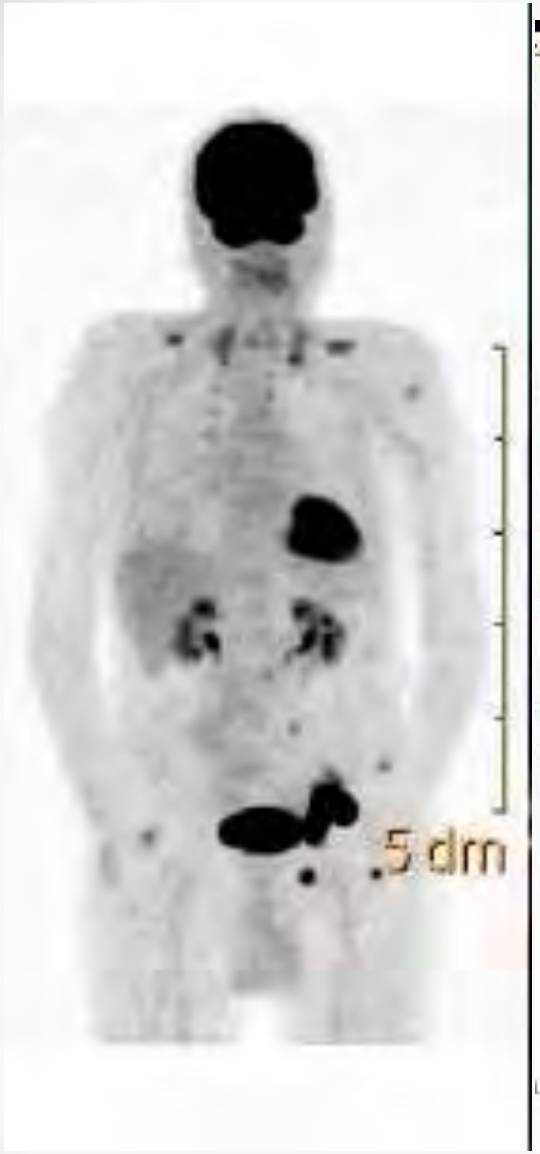

PET
CT
x
y
z
θ
φ


PET/CT

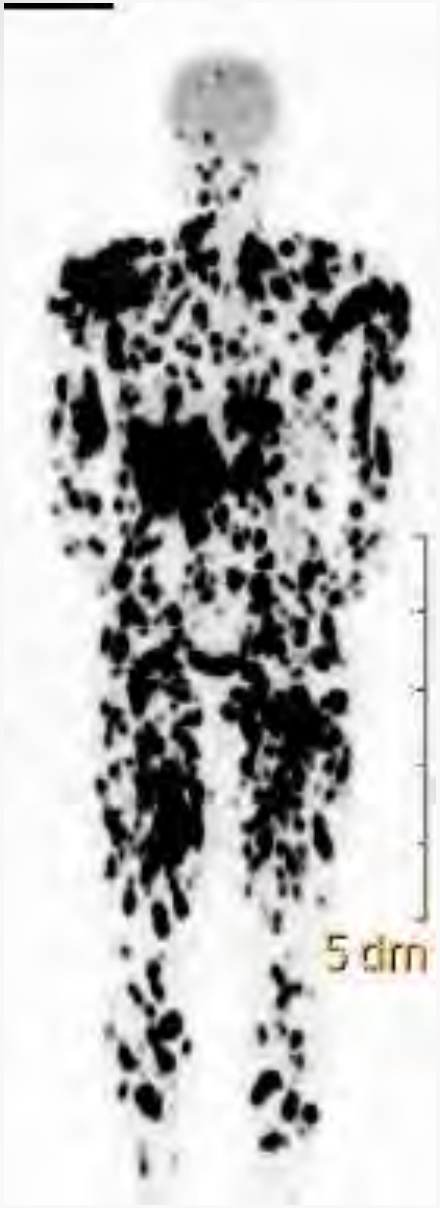
Applicazioni cliniche della FDG-PET



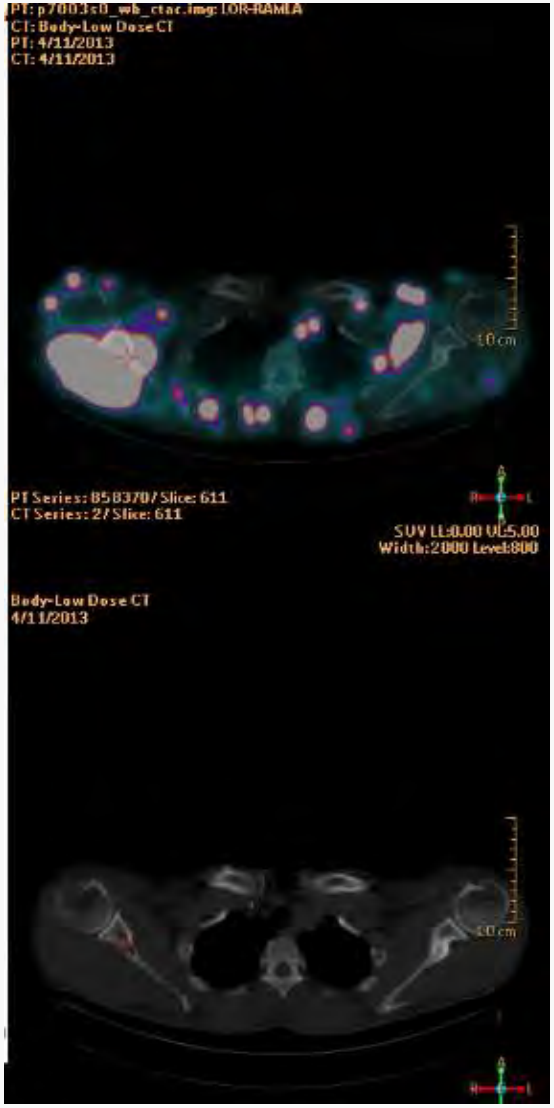
esami PET in Italia

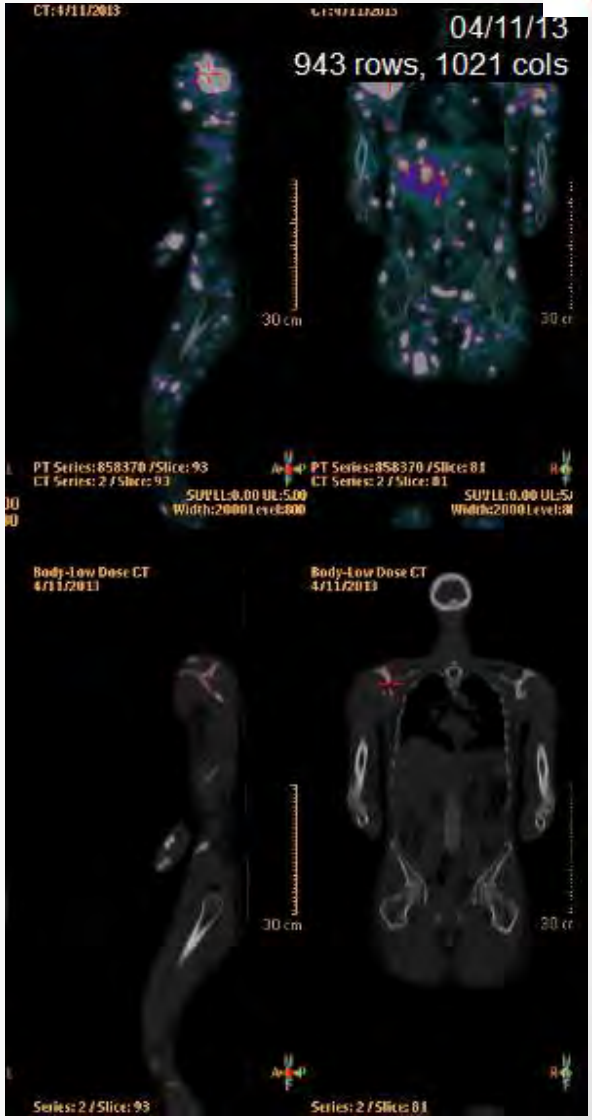


^{18}F-Fluorodesossiglucosio (FDG)



^{18}F-Fluorodesossiglucosio (FDG)





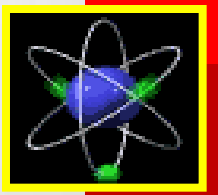
Pz. 48 aa K mammella

Standardized Uptake Value (SUV)

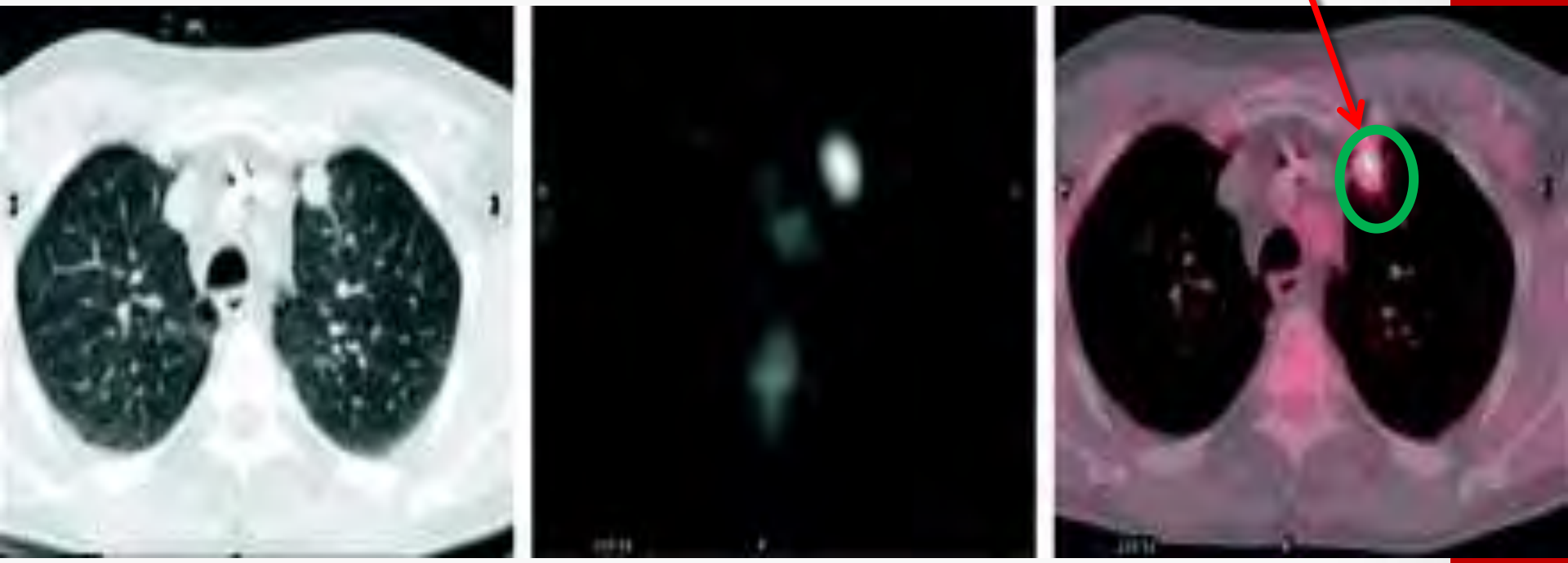
- Parametro semiquantitativo che normalizza la quantità di FDG in una ROI in rapporto all'attività iniettata ed al peso del paziente, corretta per il decadimento

$$SUV = \frac{\text{Attività ROI (mCi/ml)}}{\text{Dose iniettata (mCi)/ Peso pz. (gr)}}$$

- **Può orientare la diagnosi differenziale tra una lesione benigna ed una neoplastica.**
- **Utile per valutare la risposta al trattamento.**



SUV 6.7



PET/TC

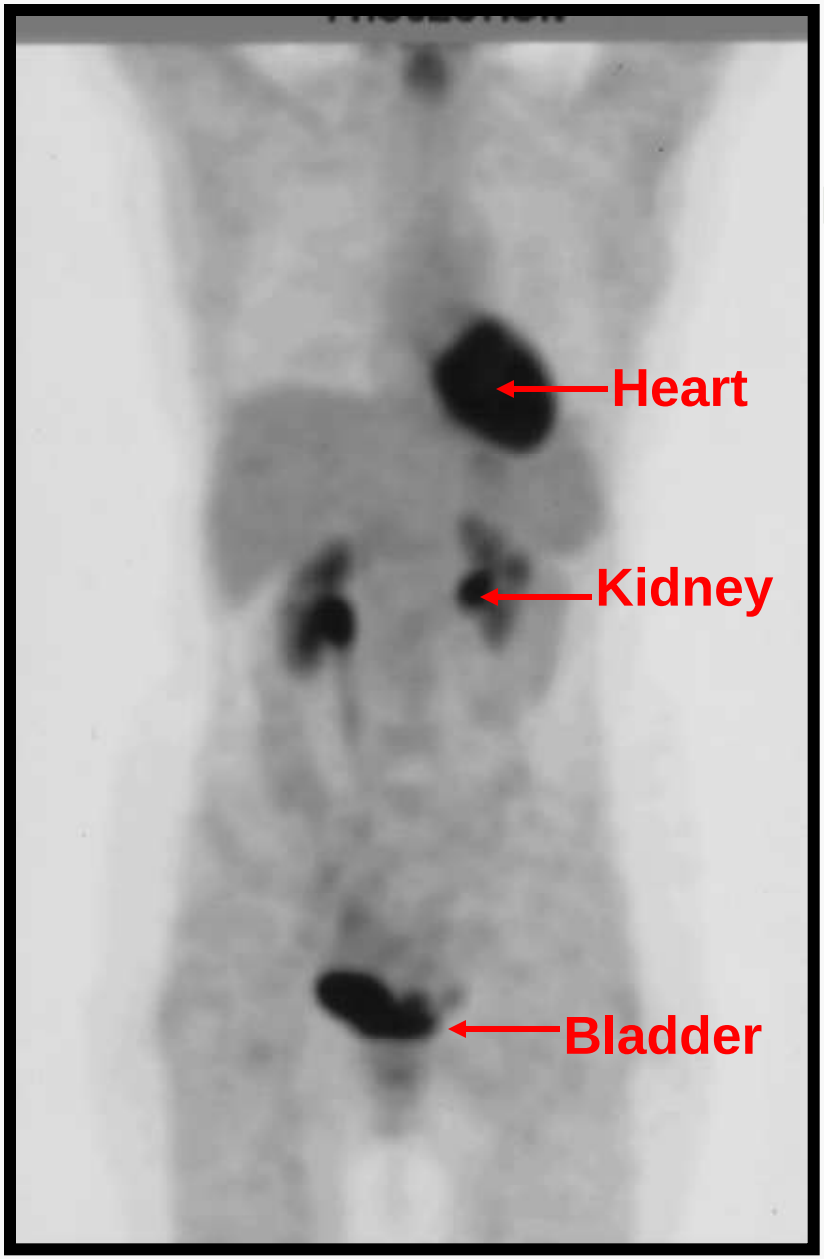
PET Scans Have Limited Use in Some Situations

Normal retention in:

- **brain**
- **heart**
- **bowel**
- **kidneys**
- **bladder**

Infection can show increased FDG uptake.

A physician needs to interpret PET in the context of all the clinical information

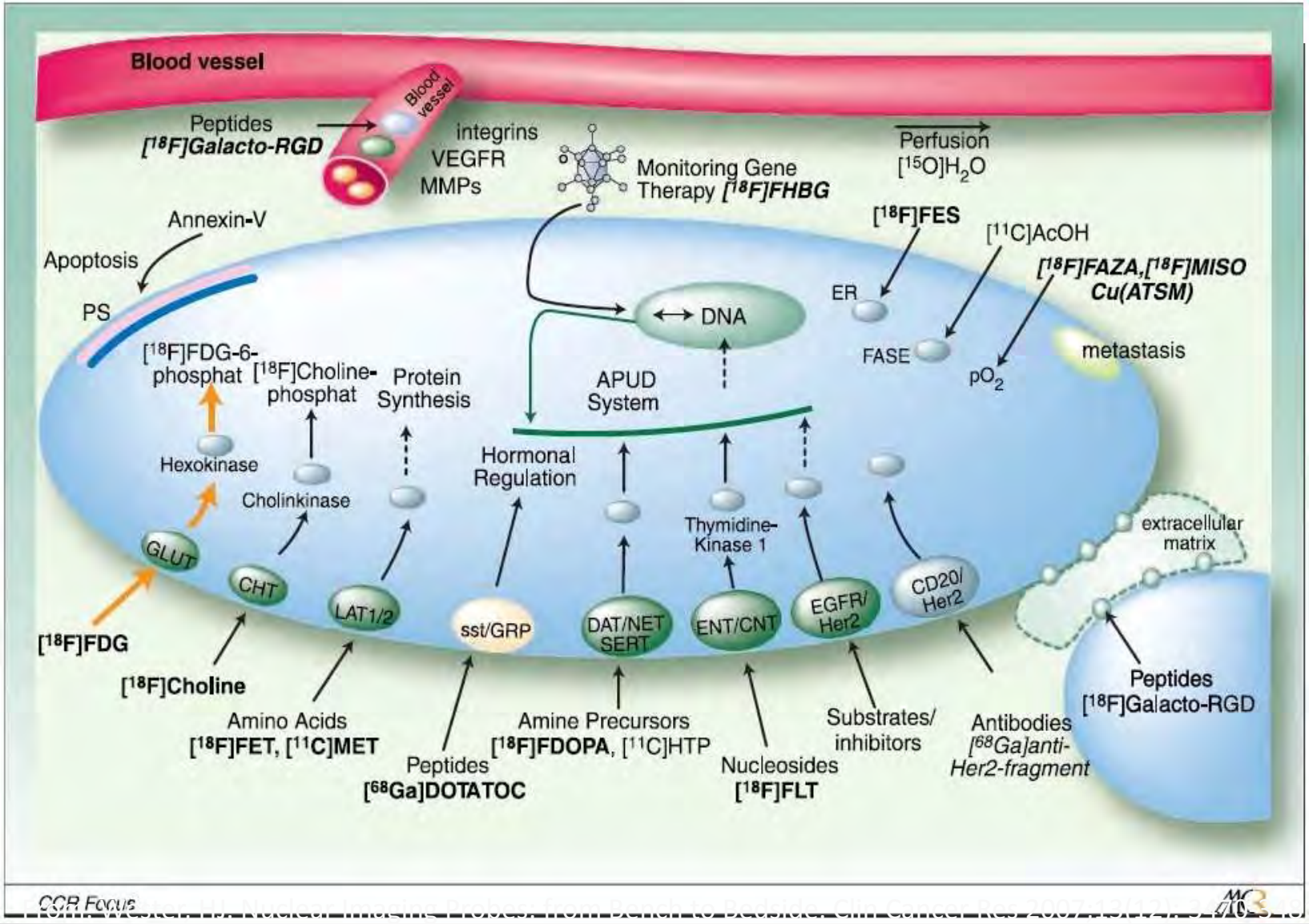


NORMAL FDG-PET

NORMAL FDG UPTAKE IN THE HEART, KIDNEYS, BLADDER


CLOSE TO HOME
JOHN MCPHERSON
Why PET?
© 1994 John McPherson Dist. by Universal Press Syndicate
McPHERSON
12-19
"Good news! The exploratory surgery turned up negative!"

Radiotracers of interest in oncology



Medicina Nucleare

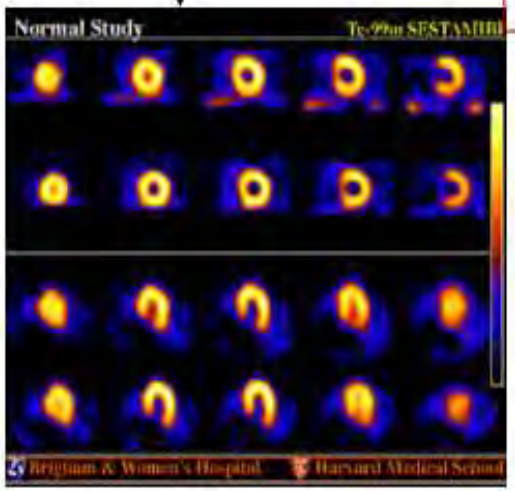
Diagnosi

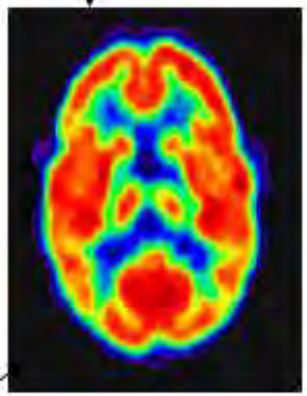
Terapia

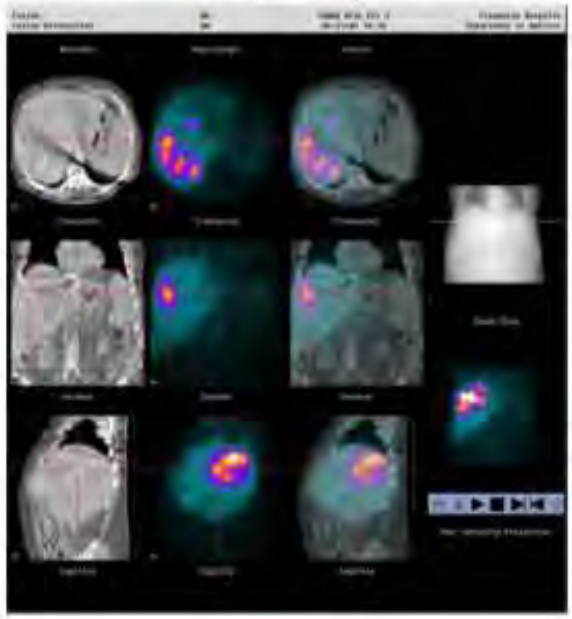
SPET
Tomografia ad emissione di fotone singolo
^{99m}**Tc**-MIBI

PET
Tomografia ad emissione di positroni
^{18}**F**-[FDG]

^{188}**Re**-Lipiodol
(componente γ)

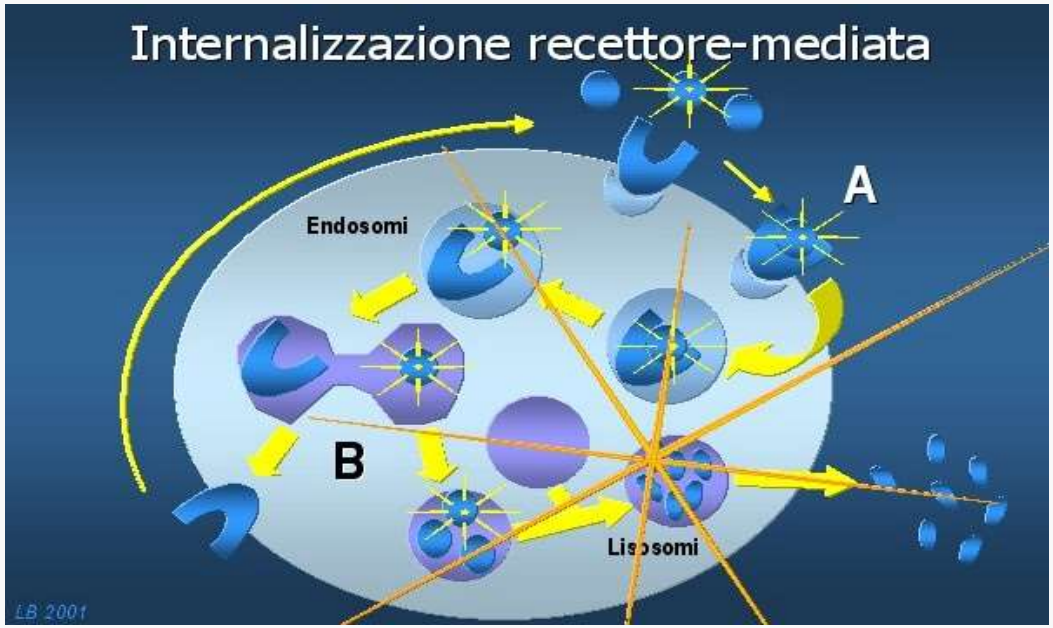


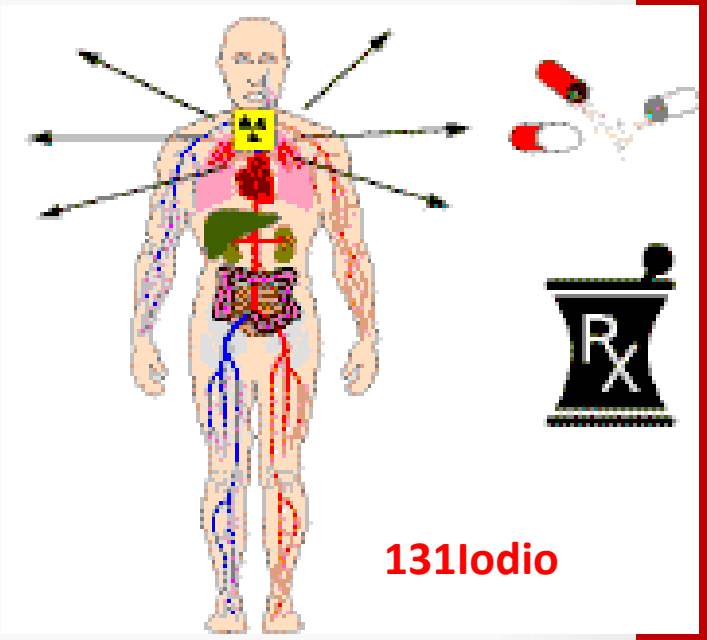


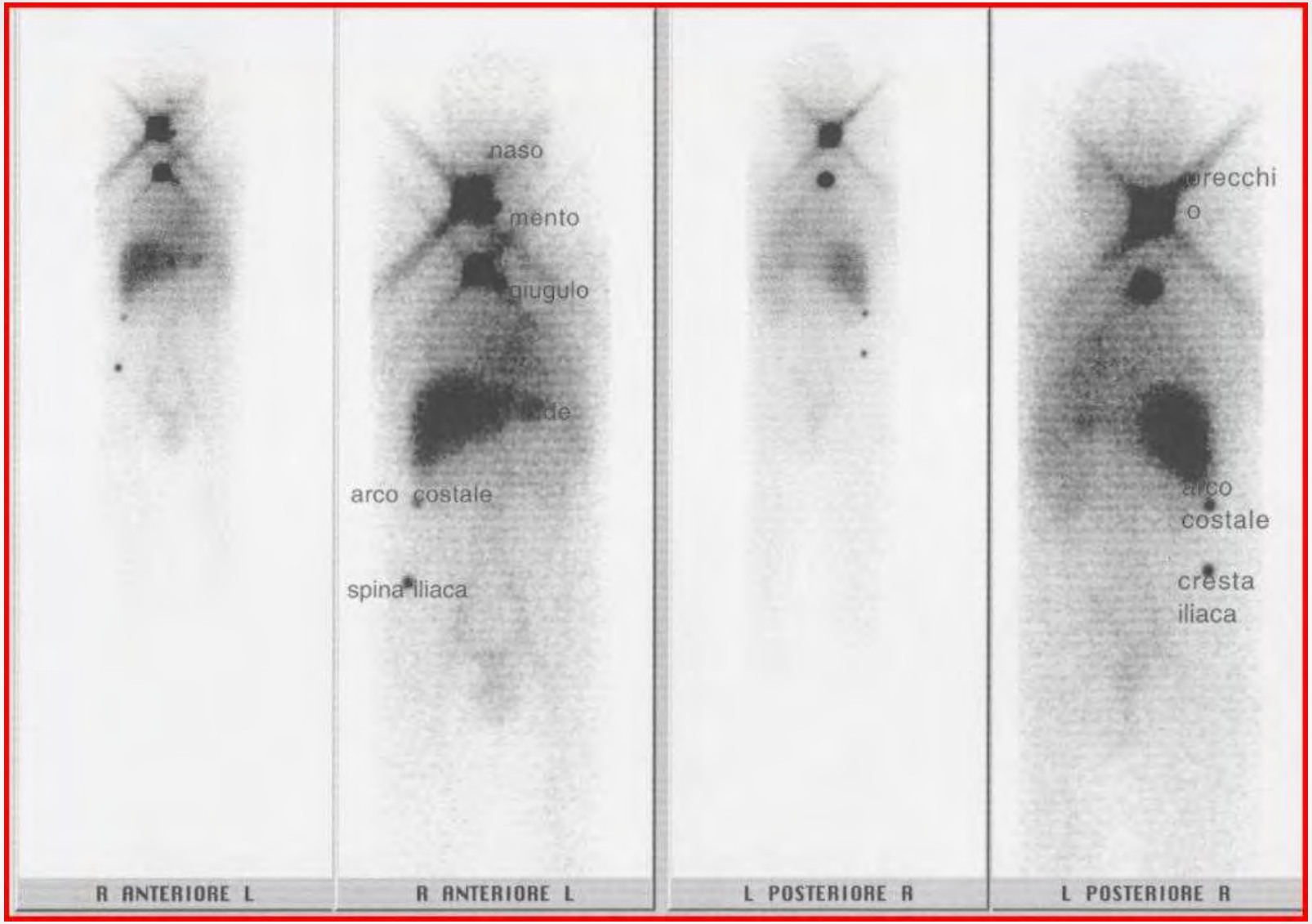


Scintigrafia

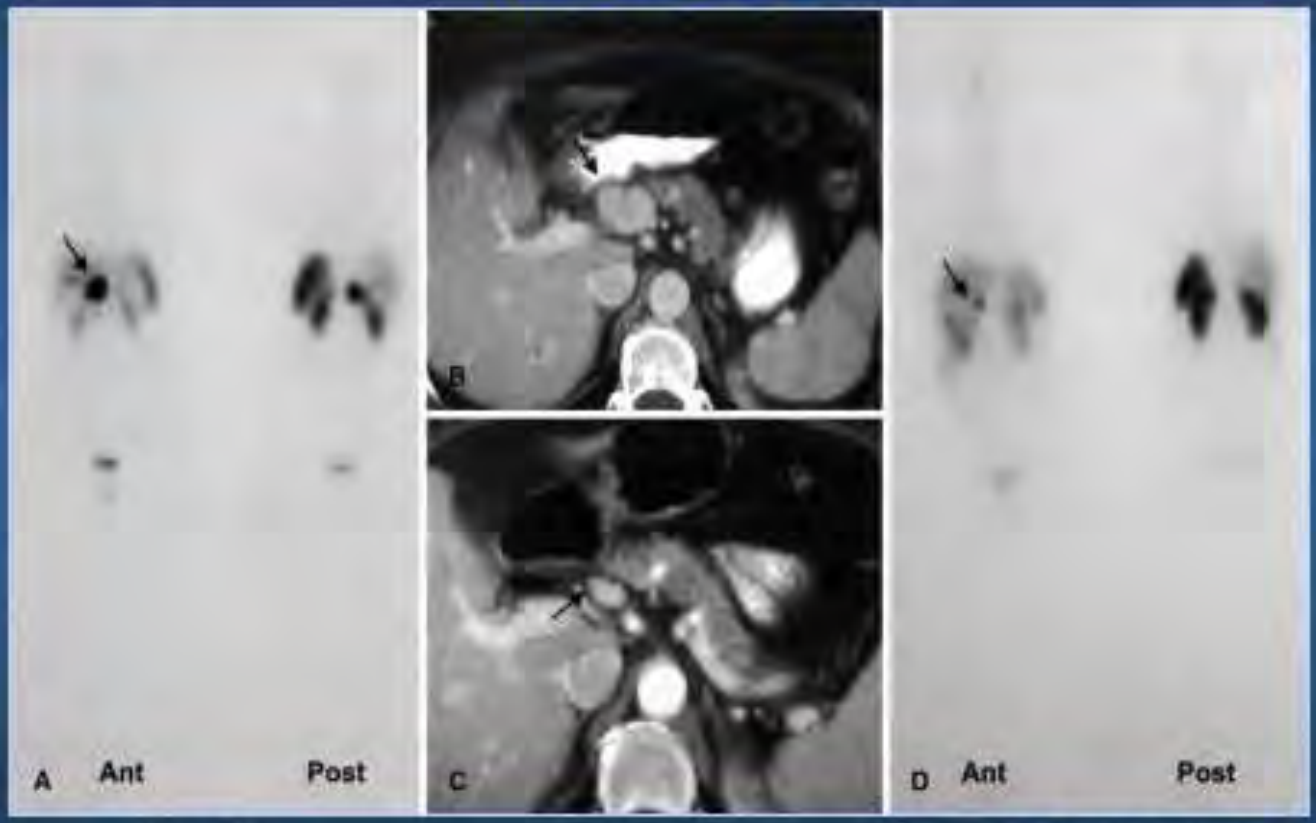
TERAPIA RADIOMETABLICA






naso
mento
giugulo
arco costale
spina iliaca
orecchi
o
arco
costale
cresta
iliaca
R ANTERIORE L
R ANTERIORE L
L POSTERIORE R
L POSTERIORE R

Carcinoma endocrino della testa del pancreas



basale

dopo ^{90}Y-DOTATOC

Paganelli, Eur J Nucl Med 2001

TERAPIA RADIOMETABOLICA DELLE METASTASI OSSEE

Confronti tra radiofarmaci Efficacia terapeutica

radiofarmaco	risultati		durata	inizio	mielotossicità
	totale miglioramenti	scomparsa del dolore			
89-Sr cloruro	70-75%	20-25%	3-6 mesi	< 2 settim.	moderata
186-Re-HEDP	65-75%	18-20%	2-3 mesi	1-2 settim.	lieve
153-Sm-EDTMP	65-75%	30%	2-3 mesi	1-2 settim.	lieve

Science For A Better Life

Medical Use of Radium-223 Chloride

Advisory Committee on the Medical Uses of Isotopes

- **Product name** Radium-223 chloride solution for injection
- **Interim Tradename** Alpharadin
- **Chemical name** Radium-223 chloride ($^{223}RaCl_2$)
- **Proposed Indication** Treatment of castration resistant (hormone refractory) prostate cancer patients with bone metastases

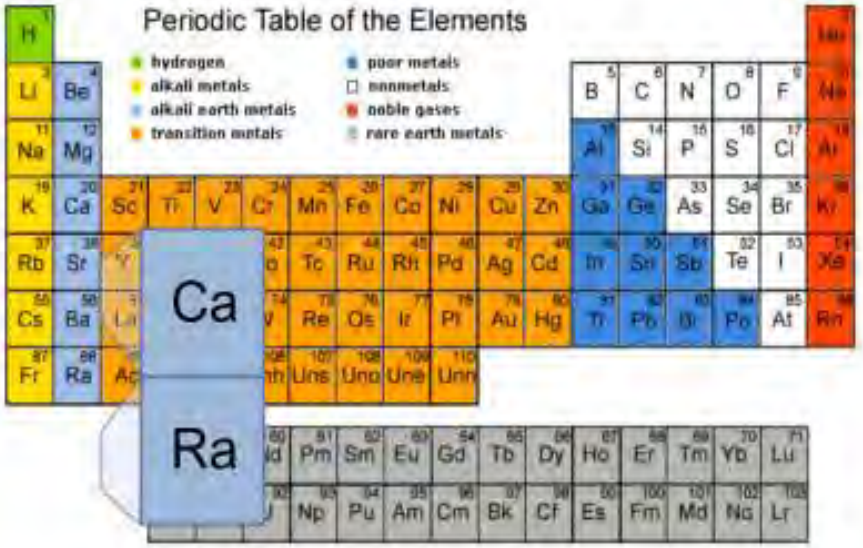
FDA-Approved Bone-Targeting Radionuclides for the Treatment of Bone Metastases

FDA Approval	Bone Agent	Indication
March 2013[1]	Radium-223	Treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease
March 1997[2]	Samarium-153 lexidronam	Relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan
June 1993[3]	Strontium-89	Relief of bone pain in patients with painful skeletal metastases

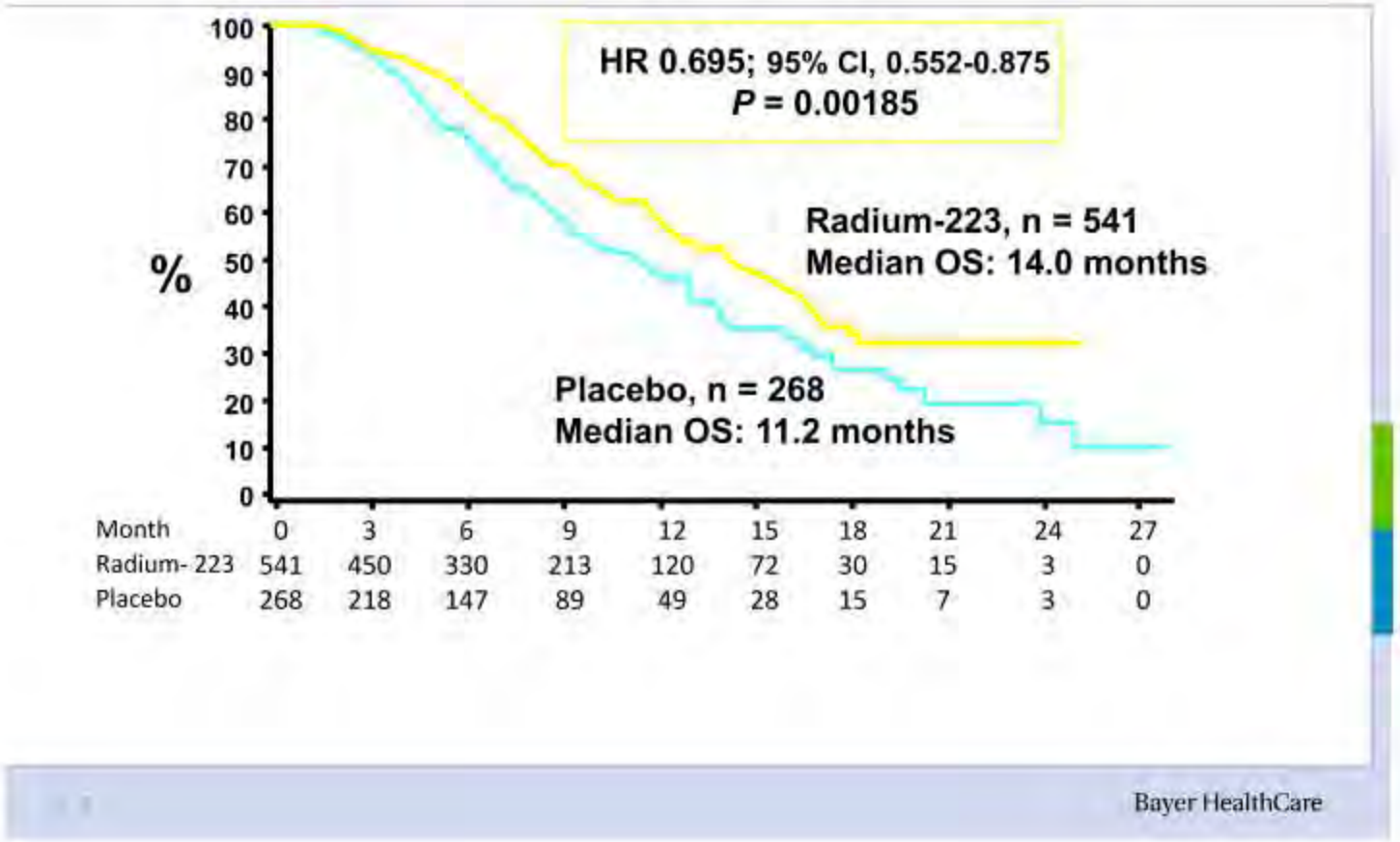
net [package insert]. Princeton, ights, IL: Medi-Physics, Inc.; 1998.

Radium-223 Targets Bone Metastases

- Radium-223 acts as a calcium mimetic
- Naturally targets new bone growth in and around bone metastases



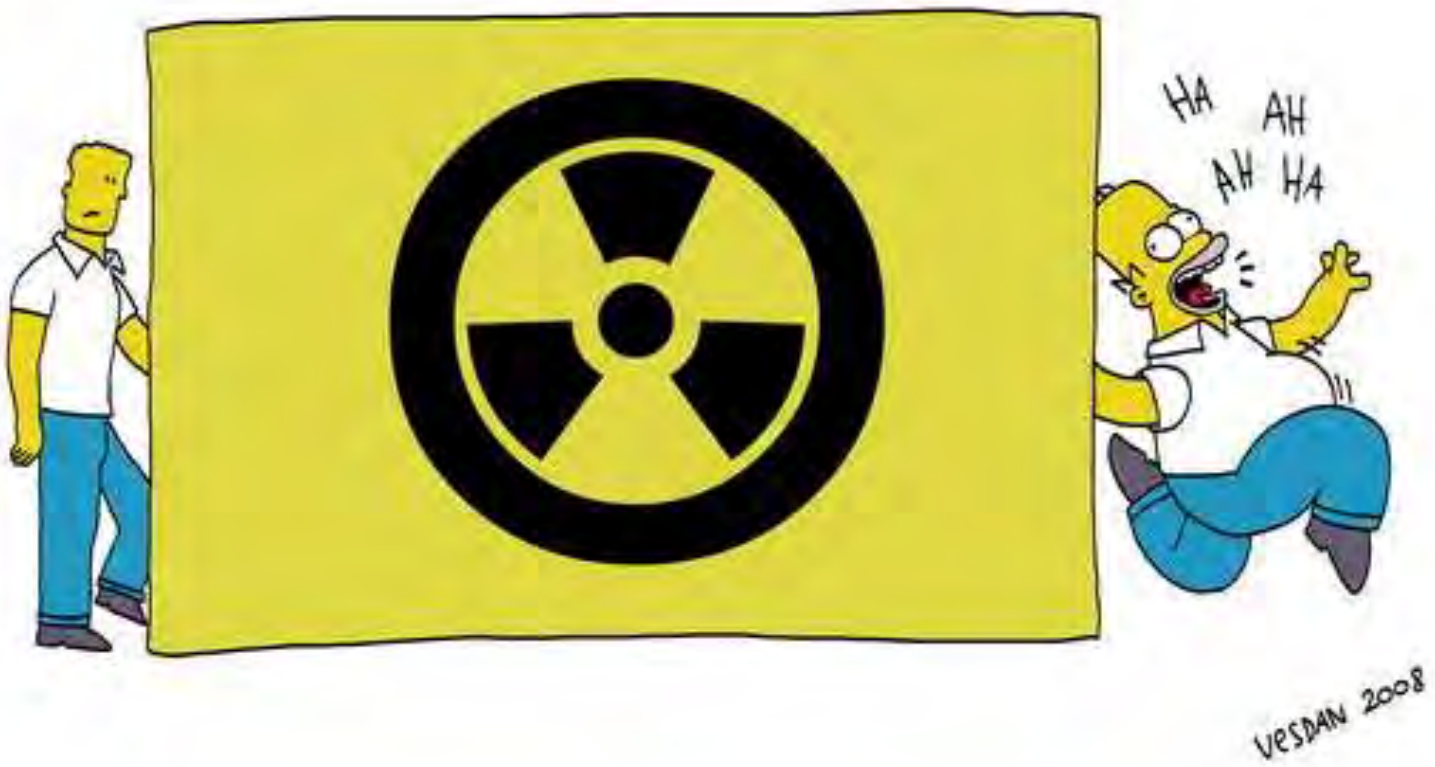
ALSYMPCA Overall Survival

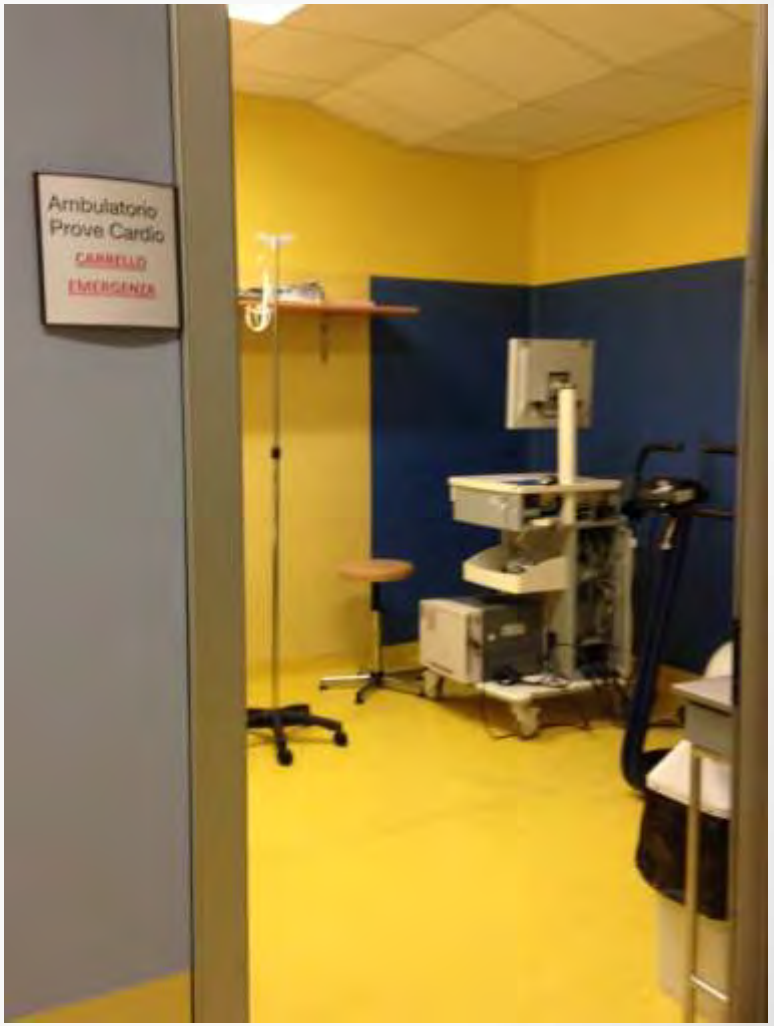


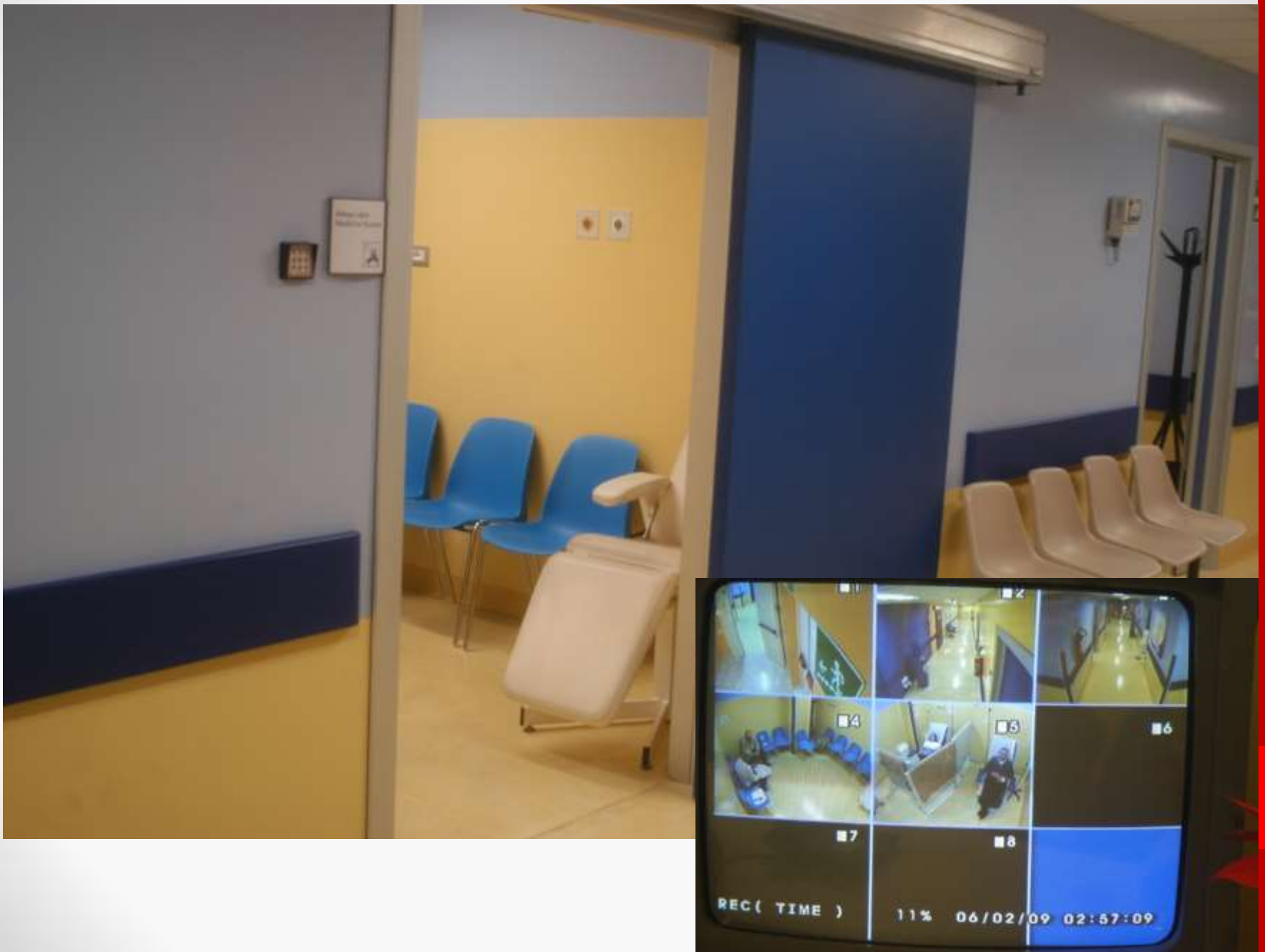
CHARITAS - SAPIENTIA -

DANKSCHEEN
SPASIBO
SNACHALJUYA
HUMIN
CHULTU
YAQHANYELAY
TASHAKKUR ATU
TINGKI
BÏYAN
SHUKRIA
THANK
GRACIAS
NADEEJA
MAITEKA
SUKSAMA
EKHMET
SPASIBO
DENKADJA
MENACHALJUYA
ARIGATO
SHUKURIA
HERASTANIY
GAIJITHO
TAVTAPUCH
MEDAHAGSE
GOZAIMASHITA
EFCHARISTO
AGUYJE
FAKAAUE
KOMAPSUMNIDA
MAAKE
GRAZIE
MEHRBANI
PALDIES
YOU
SINOMO
MIMMONCHAR
JUSPAXAR
BOLZÏN
MERCI

….. PIU’ TARDI…..
VISITA AL REPARTO


NUCLEARE: COSA CI ASPETTERÀ...
HA AH
AH HA
VESDAN 2008


Ambulatorio
Prove Cardio
CARRELLO
EMERGENZA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