Workshop on Compton Sources for X/g Rays: Physics and Applications
Alghero (Porto Conte), Italy, September 7-12, 2008

Imaging in Radiotherapy

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What is Medical Imaging ?

Medical imaging refers to the techniques and processes used to create images of the human body (or parts thereof) for clinical purposes (medical procedures seeking to reveal, diagnose or examine disease) or medical science (including the study of normal anatomy and physiology).
As a discipline and in its widest sense, it is part of biological imaging and incorporates radiology (in the wider sense), radiological sciences, endoscopy, (medical) thermography, medical photography and microscopy (e.g. for human pathological investigations).

Wikipedia def. 28.08.08

And why not genes maps and proteins spectra ??

The role of Imaging in Radiotherapy & Oncology

•Stage definition and optimization of the strategy of the treatment

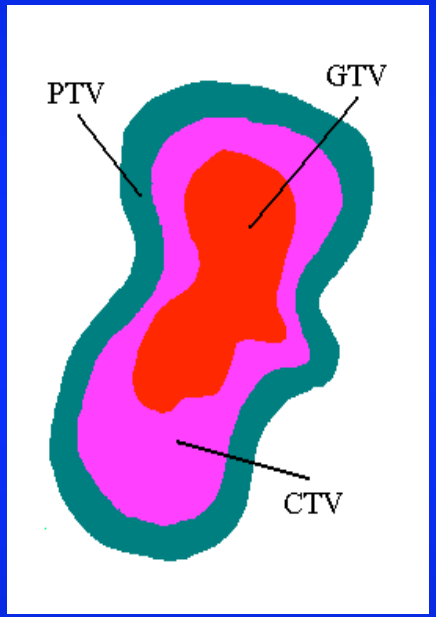
Volume's accurate definition [ICRU 50-62]
GTV="Gross Tumour Volume"
OAR="Organ at Risk"

Margins evaluation [ICRU 50-62, BIR 2003]
PTV="Planning Target Volume"
RV="Planning risk volume"

Evaluations of the predictive essays of the RT treatment outcome
Clinical evaluation of RT outcome after treatment (local control and OARs functionality)

Volume definition: GTV (Gross Tumour Volume)

- GTV: gross palpable / visible / demonstrable extent of malignant growth
- GTV (usually) contains the highest tumour cell density
- Its size and shape related to evaluation procedure / technique
- GTV is usually based on imaging: its definition may be based on all the complementary imaging information



GTV: optimal diagnostic tool for different sites

Site	Modality
Lung Mediastinal LN Apex	CT+IV PET NMR
Prostate	Transrectal US NMR
Bladder	CT
CNS residual/recurrence	NMR PET
Breast Recurrence	Mammografia US NMR

Carey, Estro Teaching Course 2002

LN= Linfonodi
CNS= Sistema Nervoso Centrale
IV= Mezzo di contrasto
PET=Tomografo ad emissione di positroni
US=Ultrasuoni
NMR=Risonanza Magnetica Nucleare

A minimal common language

Tab. I. Tabella 2 x 2 che esprime il risultato del test rispetto alla realtà. *Two way table. Test result and true situation.*

Risultato del test	Realtà		Totale
	Malato	Sano	
Positivo	a	b	a + b
Negativo	c	d	c + d
Totale	a + c	b + d	a + b + c + d

a = Vero positivo: il test è positivo e il soggetto è malato; b = Falso positivo: il test è positivo ma il soggetto è sano; c = Falso negativo: il test è negativo ma il soggetto è malato; d = Vero negativo: il test è negativo e il soggetto è sano.

Accuracy : $\frac{No.\,correct\ investigations}{total\ investigations} = \frac{a+d}{a+b+c+d}$

Specificity : capability to detect health : $\frac{d}{b+d}$

Sensitivity : capability to detect illness : $\frac{a}{a+c}$

Diagnostic modalities comparison

Methodology	Sensitivity	Spat. Res.	Time res.
CT	+++	< 1 mm	<1 sec
MRI	++++	< 1 mm	1 sec
PET	+++	3 – 4 mm	min
SPECT	++	8 – 12 mm	min
NIRF	+++	1 – 2 mm	msec
US	+++	< 1 mm	msec

Toward BTV ("biological target volume") ?

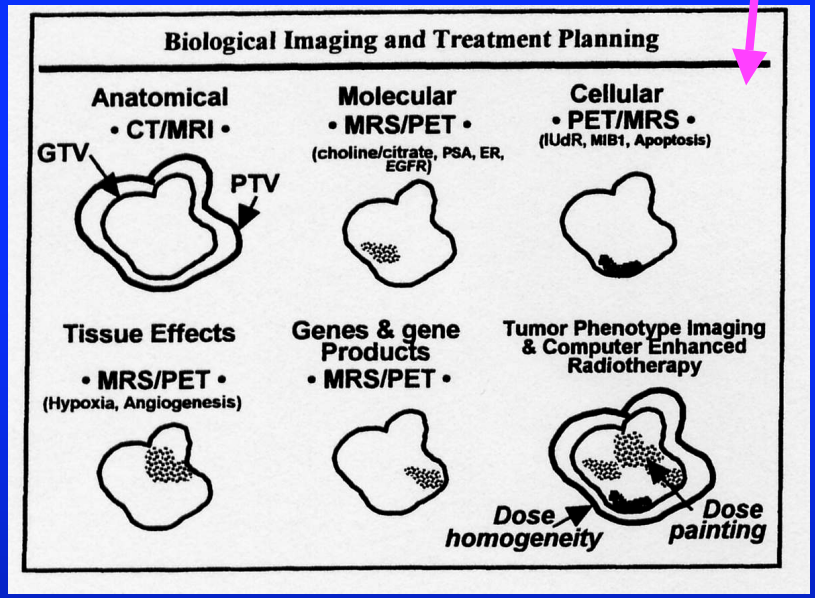
Barret A
Estro teaching course, 2002

Multimodal imaging potentiality to assess

functional, metabolic and molecular status

By means of
NMI ("Nuclear Magnetic Image")
functional
NMSI spettroscopica
PET ("Positron Emission Tomography")
using tumour biologically sensitive
tracers
to quantify

- Hypoxic component
- tumour angiogenesis
- Cell Repopulation during RT
- etc

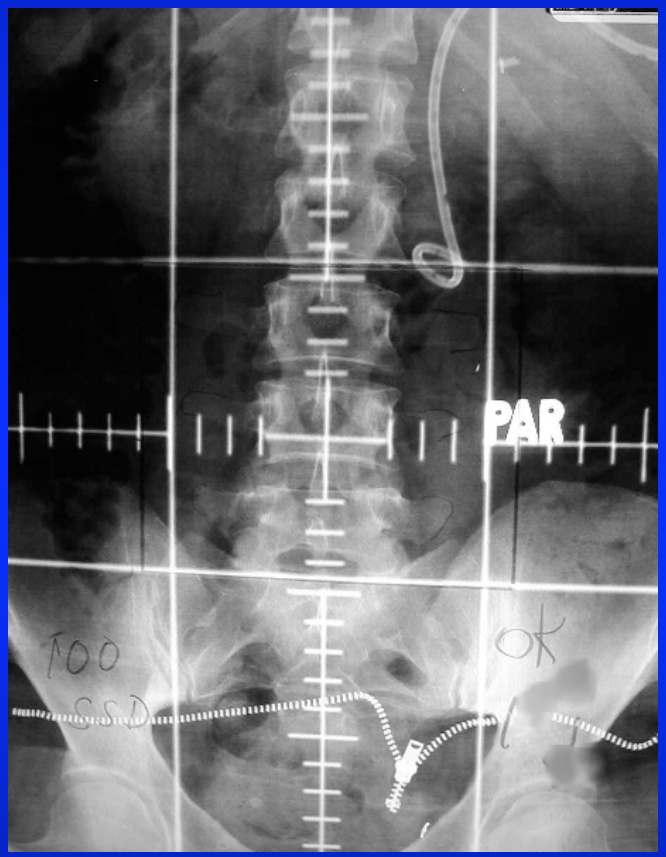


Technological development in RT

Years	RT Method	Treatment Volume delineation	set-up Verification
<1990	2D-RT	Rx	Rx
90's	3D-RT	CT	Rx , EPID
>2000	IMRT e IGRT	CT , PET , MR	EPID , kV-CT , MV-CT Optical Sys, US, etc

2D-RT

Calculations based on planar images and pts thickness measurements



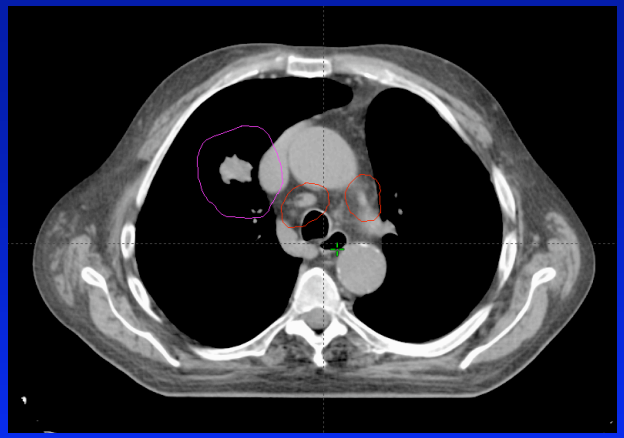
Limits

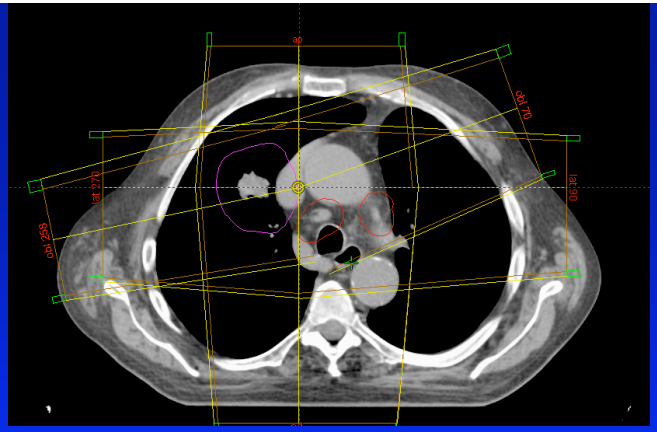
- inaccuracy of target def
- inaccuracy in the dose calcs
- inaccuracy in setup check

Consequences

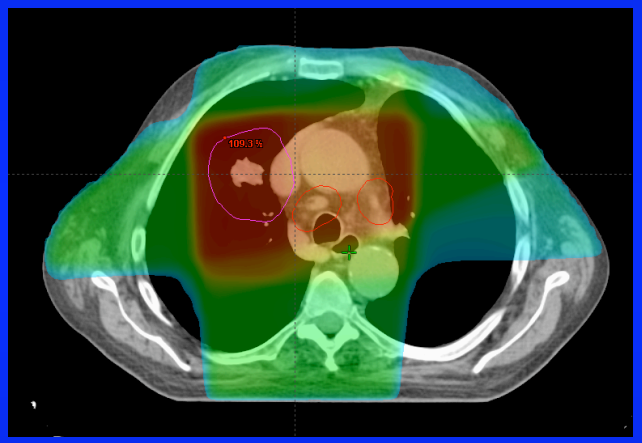
high toxicity of the treatments

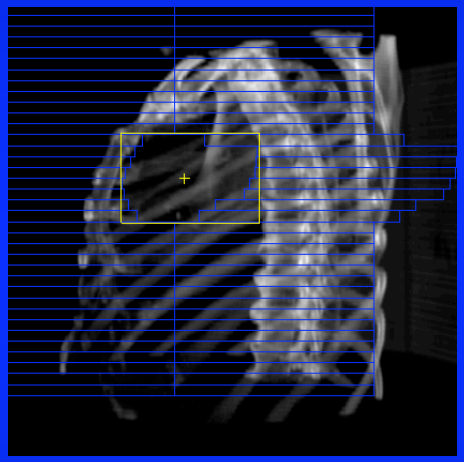
Poor clinical results





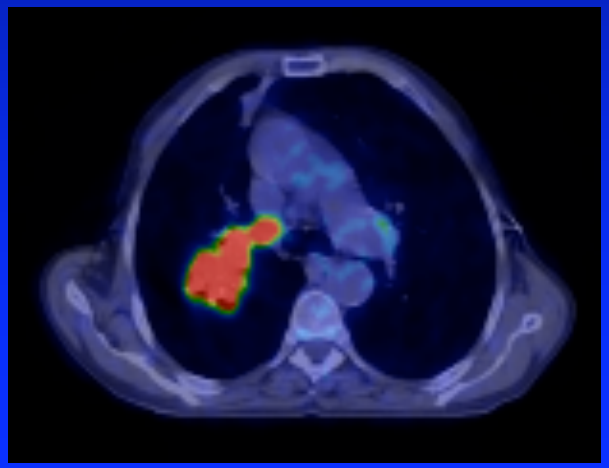
3D-RT

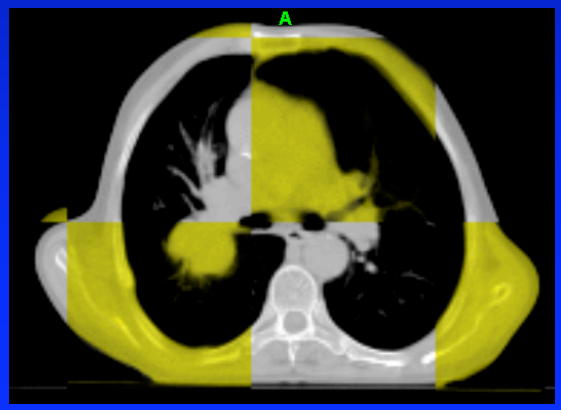




- **Improvement** in target definition (CT)
- **Better** Dose conformation
- **Dose Escalation** possibility (better local tumour control)
- set-up check **improvement(EPID)**
- **reduction** in toxicity

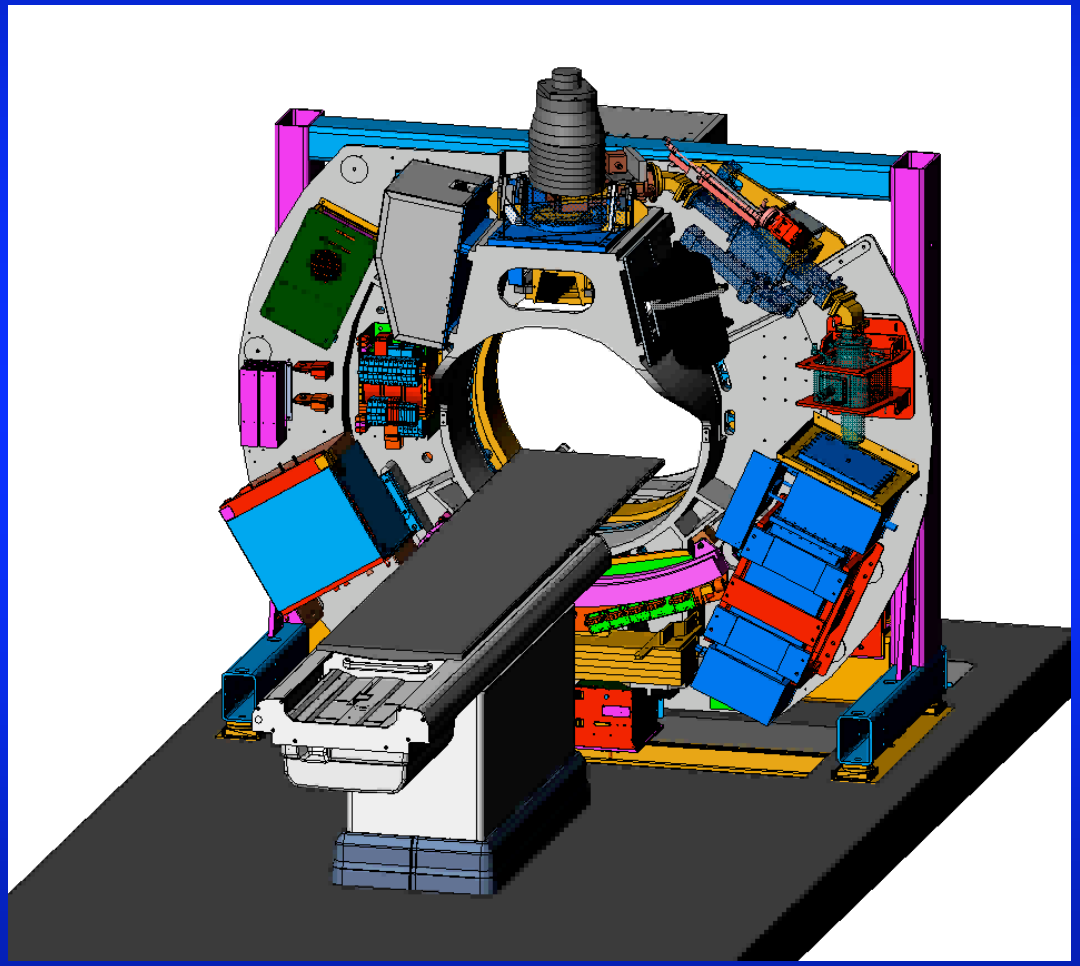
IMRT(Intensity Modulated Radiation Therapy)
IGRT (Image Guided Radiation Therapy)





- Further increase in geometrical target def (PET/CT ; NMR/CT; etc)
- Increased dose conformality on target(IMRT)
- better set up check (KV-CT, MV-CT, sistemi fluoroscopici, sistemi ottici, US, etc)
- Perspective for Hypofractionated regimens (up to 8 Gy x 4)
- Further toxicity reduction

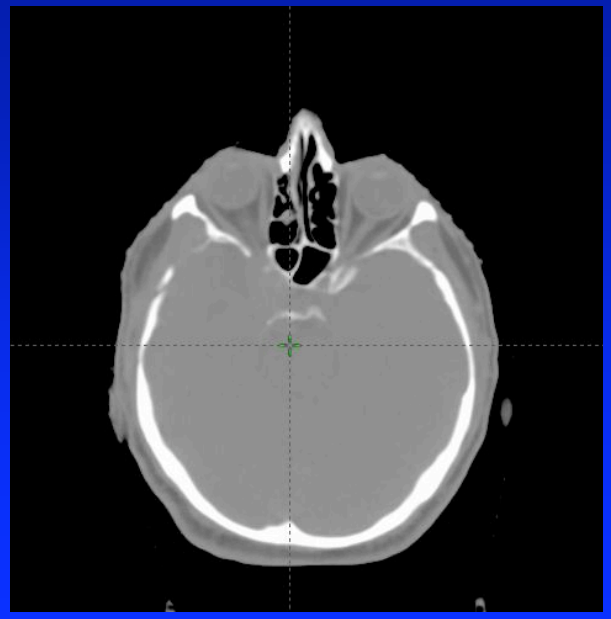
Tomotherapy : the last development of RT modality

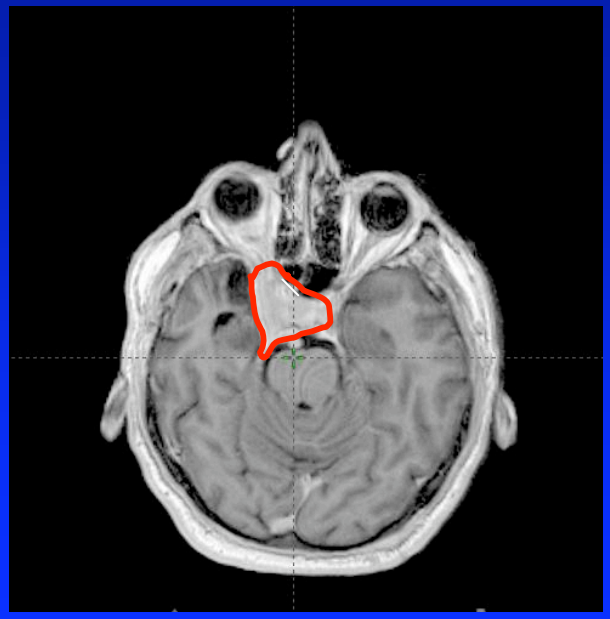


Diagnostic imaging comparison and fusion - integration

Part 1 : MR & CT

CT

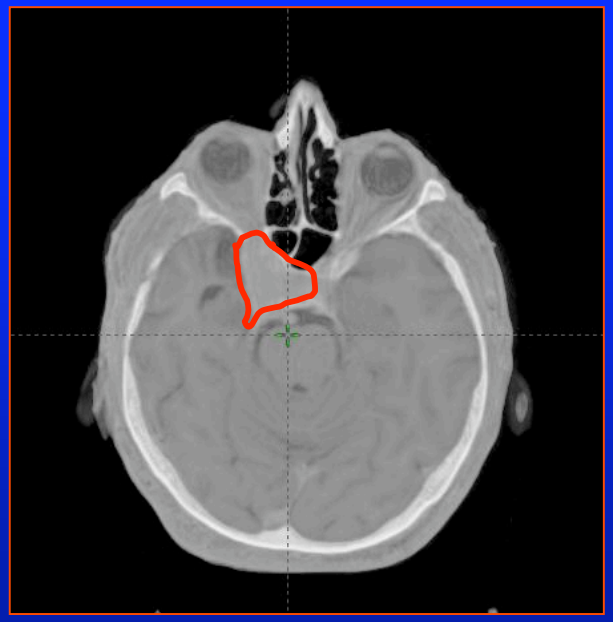


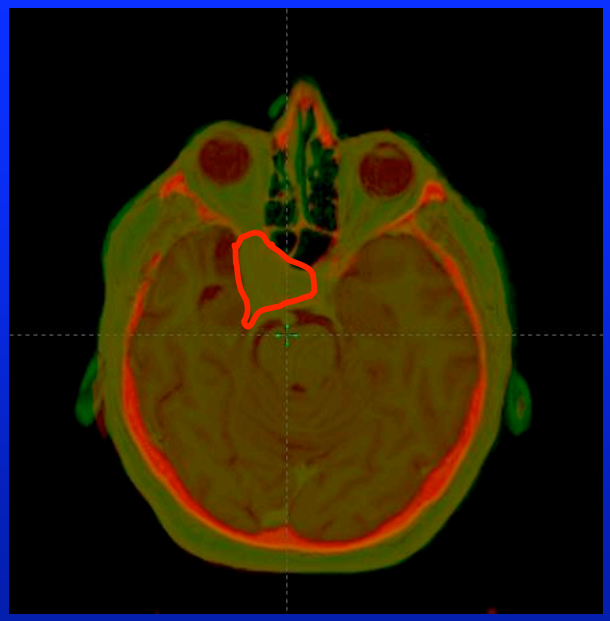


MR

CT

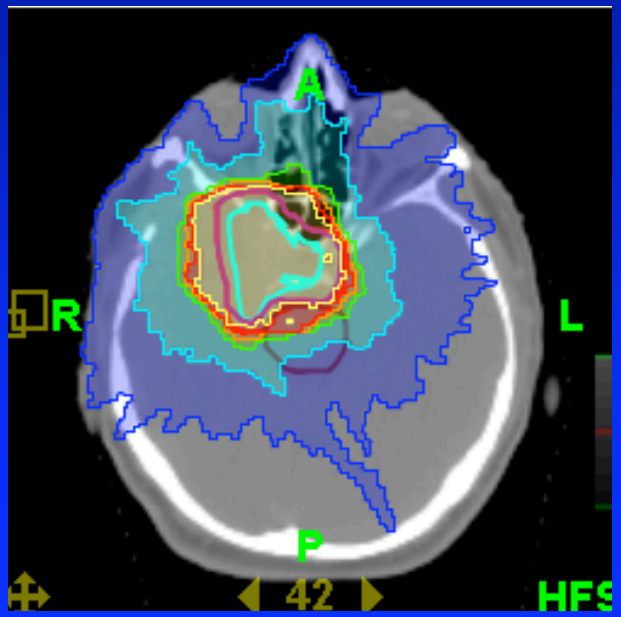
RM

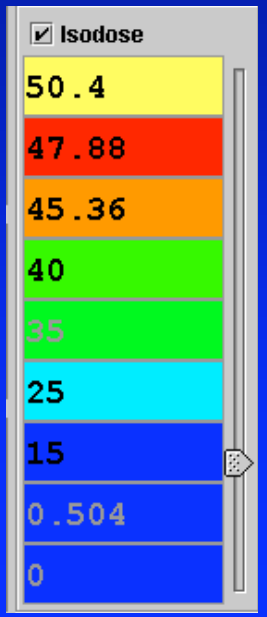


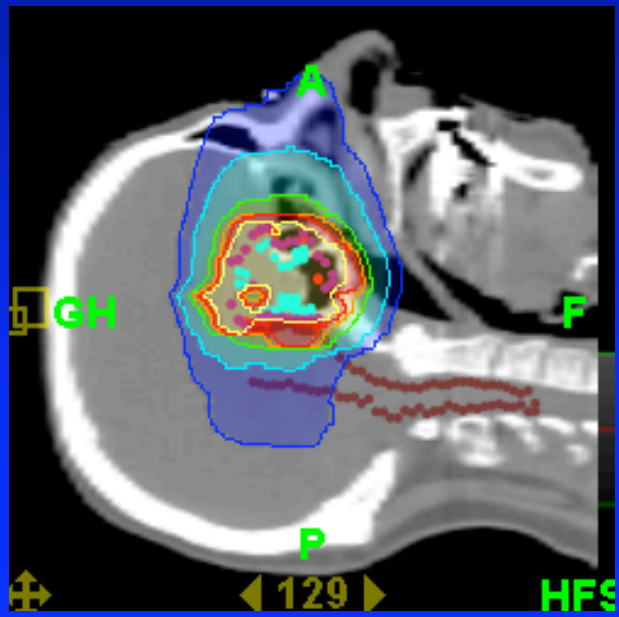


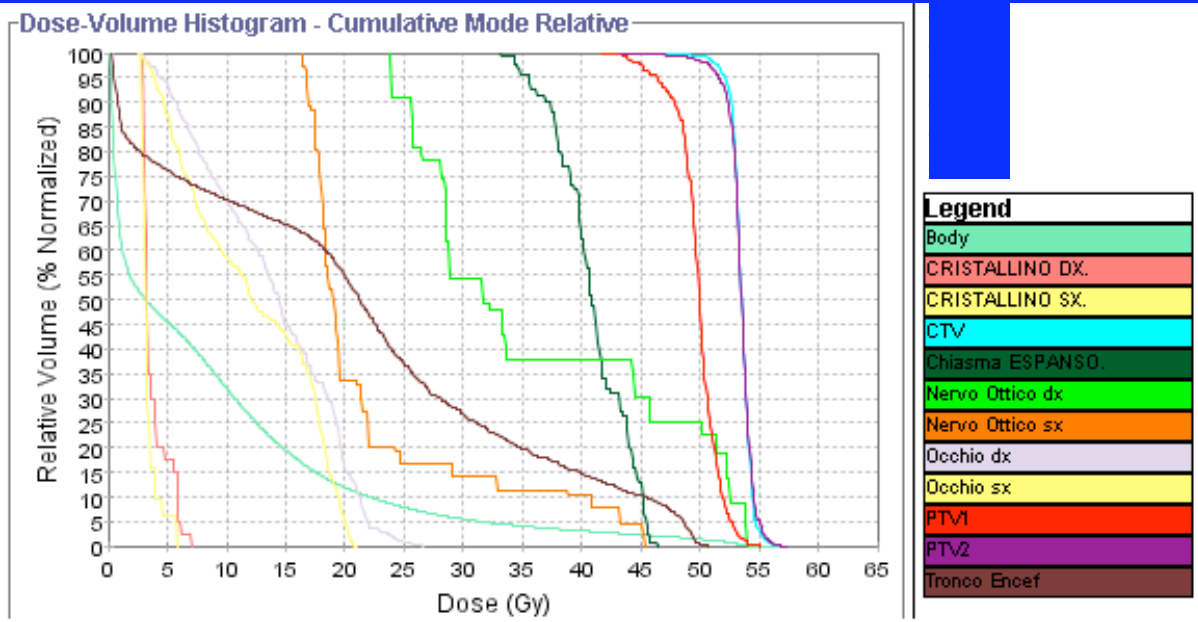
CT

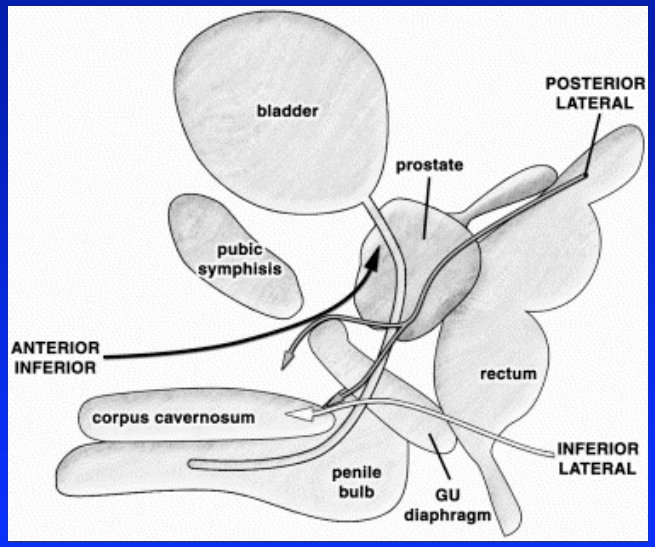
RM

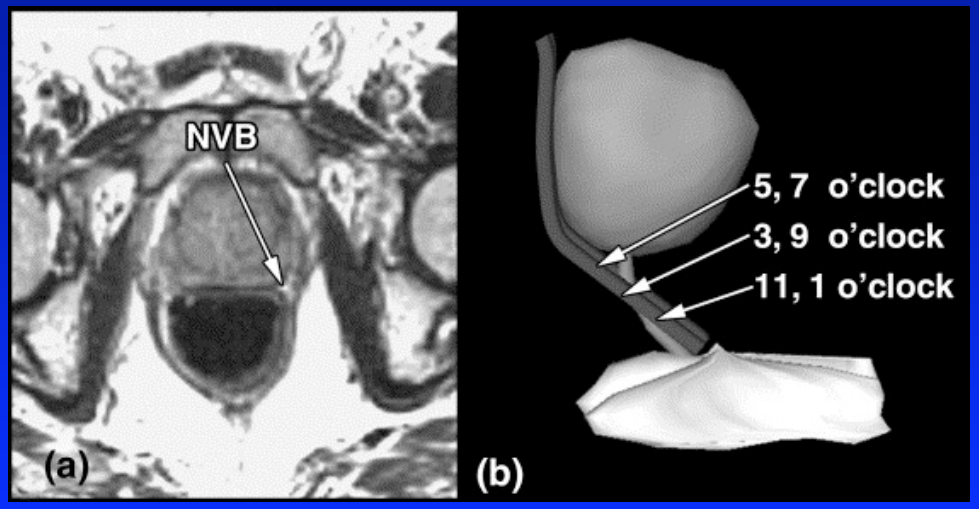

A
R
L
P
42
HFS

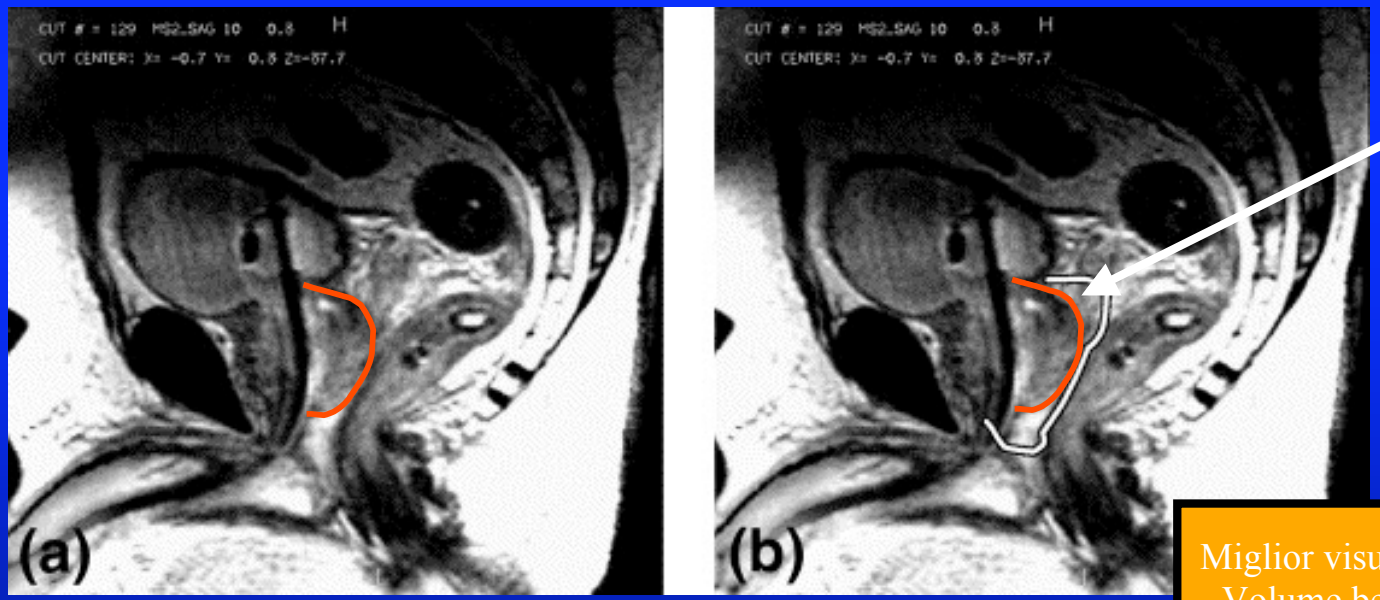

Isodose
50.4
47.88
45.36
40
35
25
15
0.504
0


A
GH
P
P
129
HFS


Dose-Volume Histogram - Cumulative Mode Relative
Relative Volume (% Normalized)
Dose (Gy)
Legend
Body
CRISTALLINO DX.
CRISTALLINO SX.
CTV
Chiasma ESPANSO.
Nervo Ottico dx
Nervo Ottico sx
Occhio dx
Occhio sx
PTV1
PTV2
Tronco Encef







Differenza tra prostata definita su MRI (rosso) e CT (bianco)

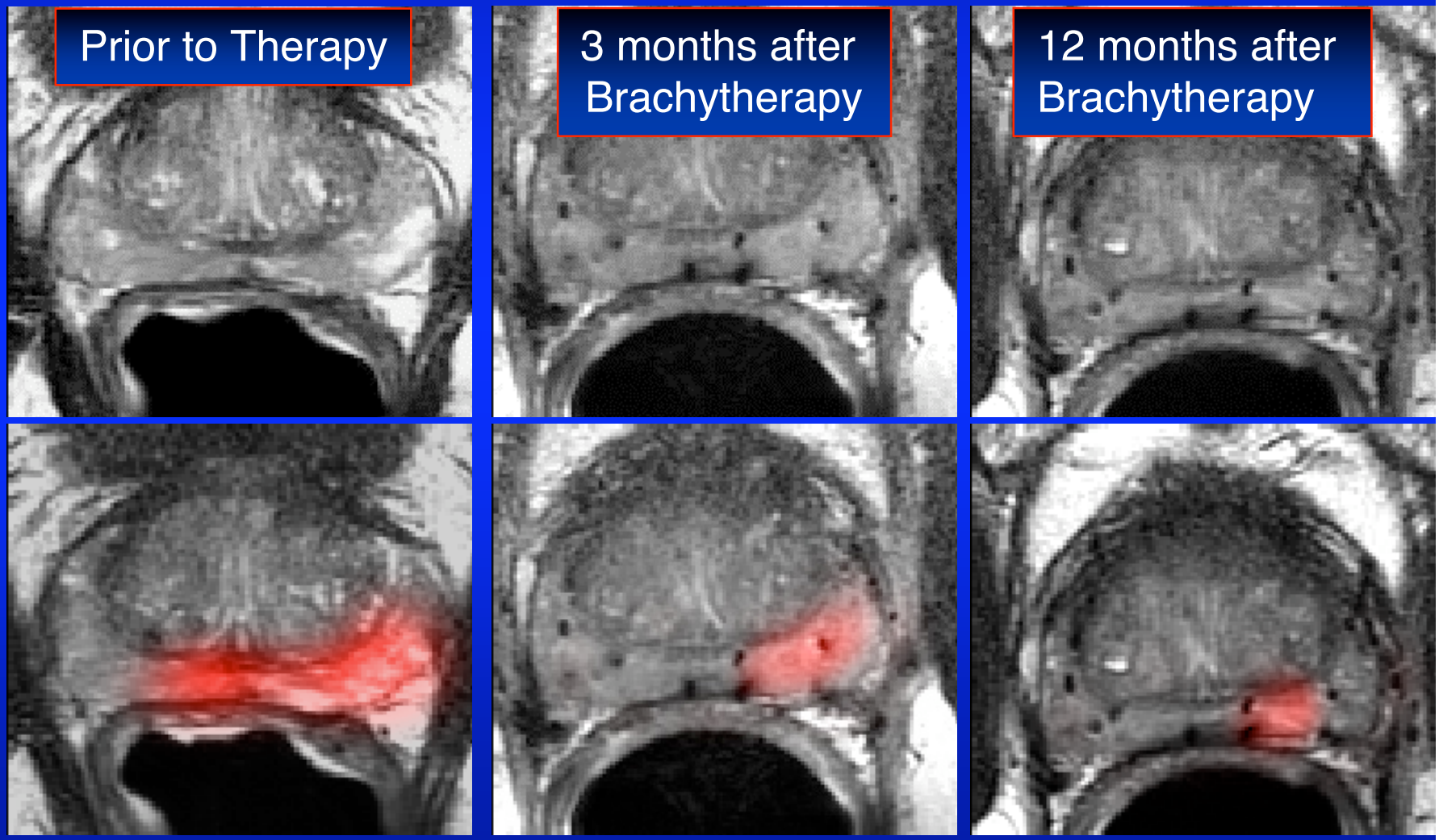
Miglior visualizzazione:
- Volume bersaglio (riduzione ~20%)
- Interfaccia verso retto
- OAR di piccole dimensioni

McLaughlin 2005

Diagnostic imaging comparison and fusion - integration

Part 2 :NMR & NMRS

MRI/MRSI - Improved Planning and Assessment of Brachytherapy



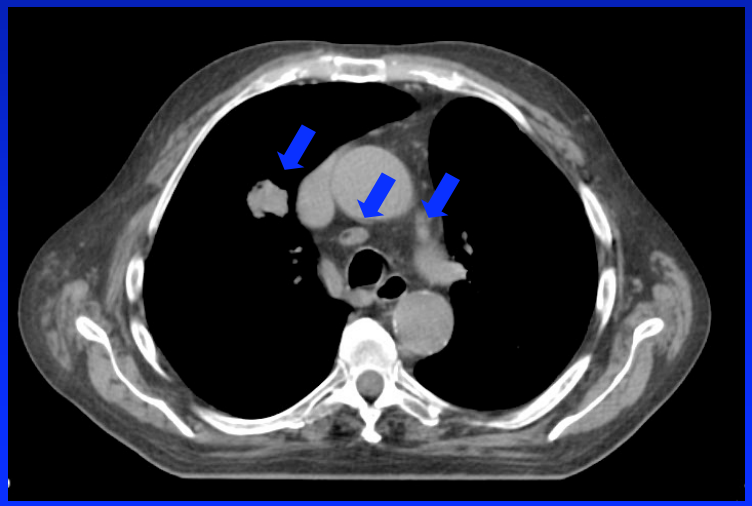
Diagnostic imaging comparison and fusion - integration

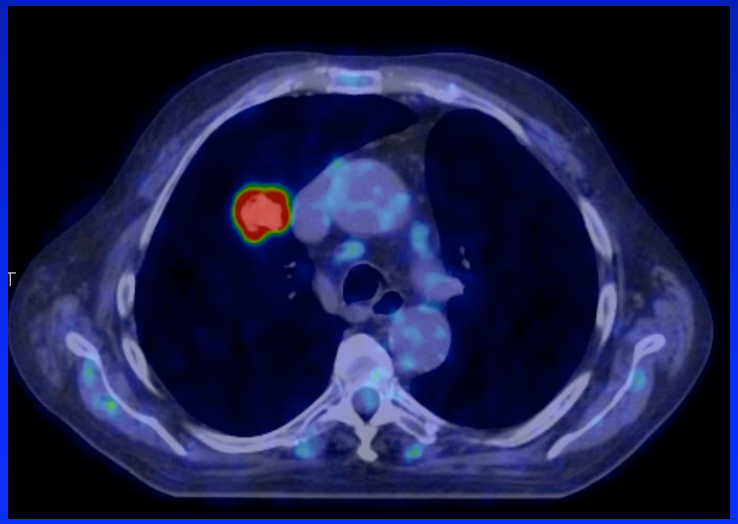
Part 3: PET, CT PET, 4D CT PET

Comparison between CT and FDG-PET for nodal staging (Gregoire V et al. , R&O, 2004)

Site	Sensitivity (%)		Specificity (%)	
	CT	FDG-PET	CT	FDG-PET
NSCLC	45	80-90	85	85-100
LYMPH.	81	86-89	41	96-100
ESOF. CA	11-87	30-78	28-99	86-98
H&N CA.	36-86	50-96	56-100	88-100

PET/TC: BTV outline





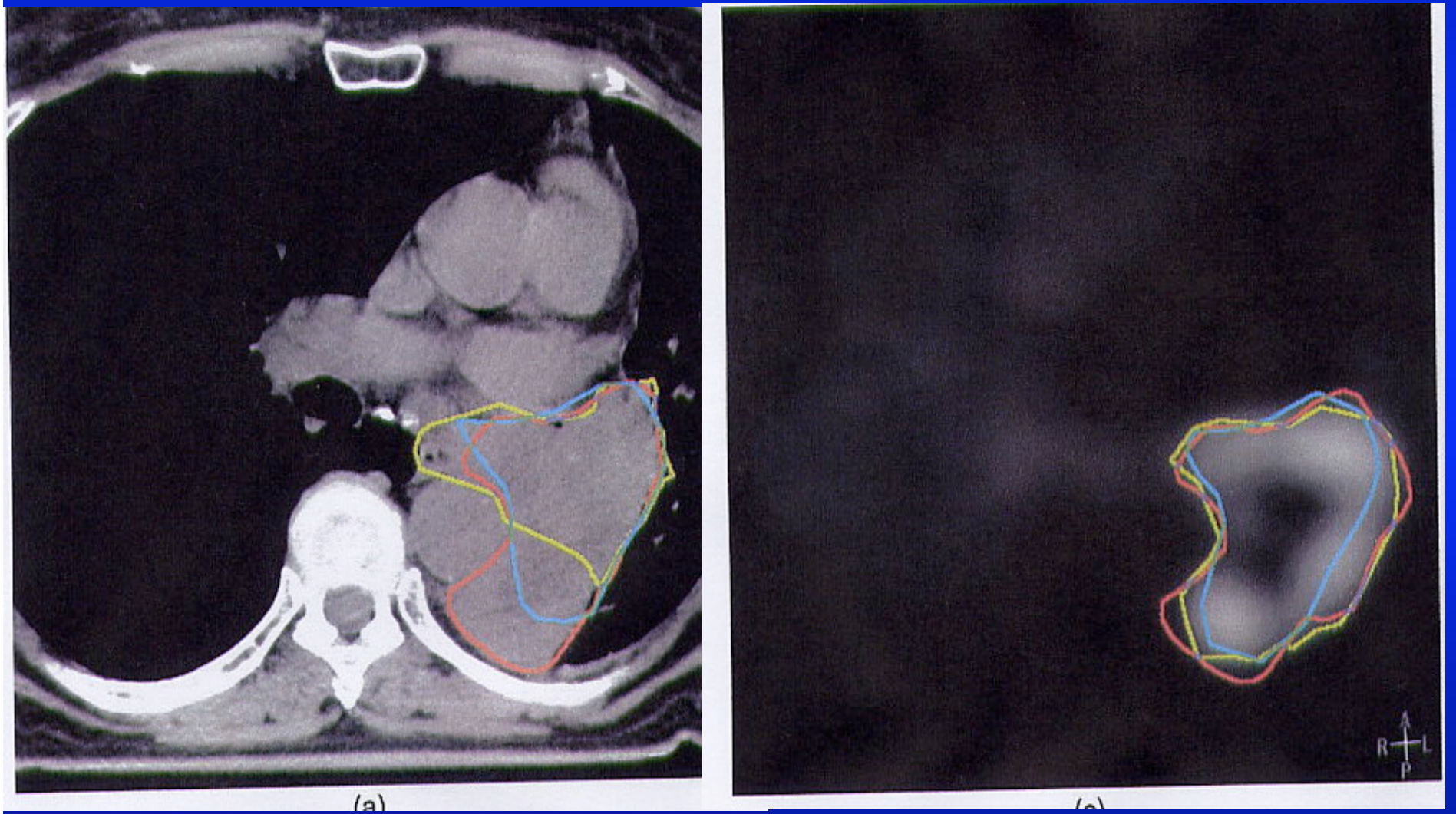
IMRT

IMRT

Caldwell IJROBP 2001 [Lung Tumours]

GTV_CT

GTV_CTPET

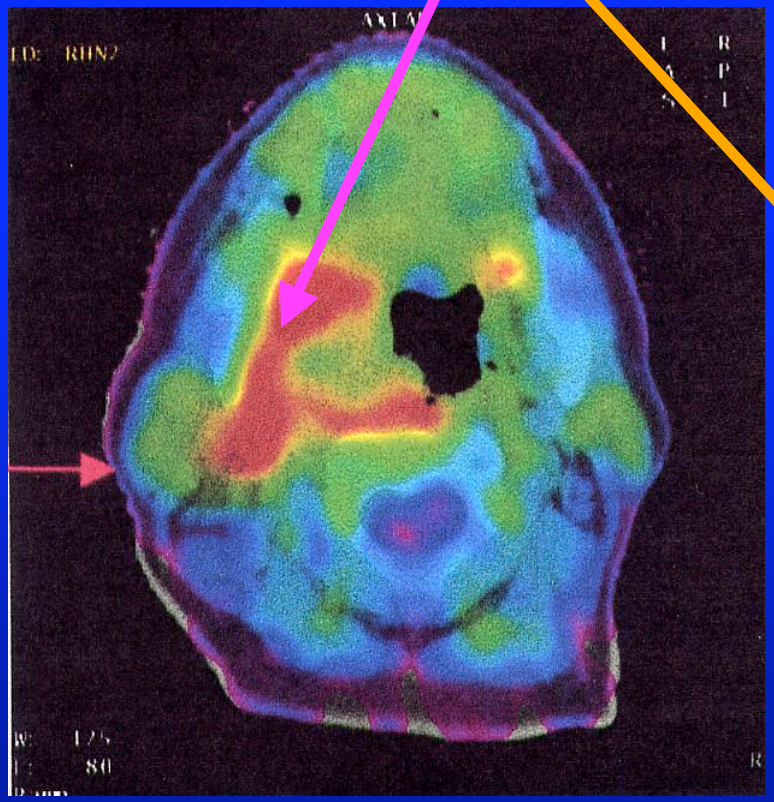


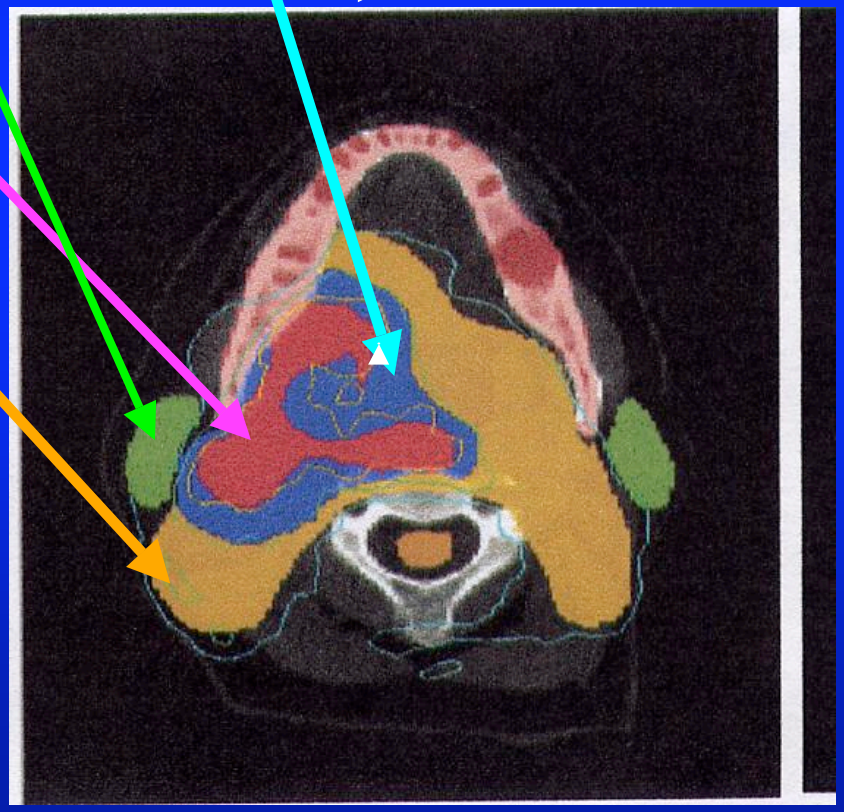
PET/CT: Oncological tracers other than FDG

• Membrane function	[^{11}C]Choline
• Hypoxia	[18F]FAZA [64Cu]ATSM
• Amino acids metabolism	[^{18}F]FET / [^{11}C]MET
• Proliferation	[^{18}F]FLT [^{18}F]FMISO
• Apoptosis	[^{18}F]Annexin V
• Angiogenesis	[^{18}F]RGD peptide

IMRT: GTVs, CTV prescribed doses

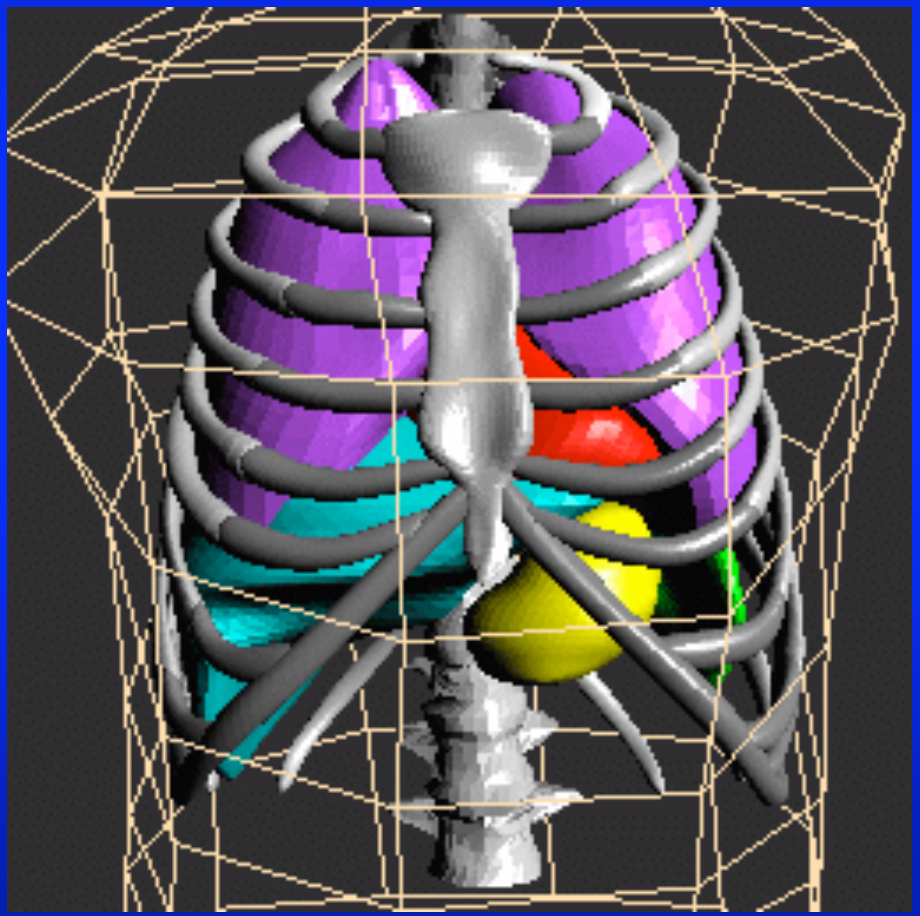
- Plan :
  - 80 Gy, 35 f hGTV
  - 70 Gy, 35 f GTV
  - 60 Gy, 35 f CTV
  - Parotid glands V30< 50%





ORGAN MOTION

Polmoni, fegato, pancreas e gli altri organi addominali possono muoversi di diversi centimetri a seguito della respirazione



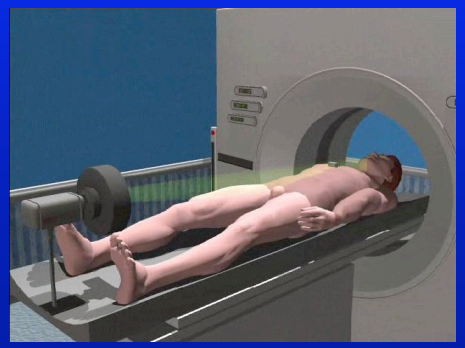
NCAT phantom: Johns Hopkins Center

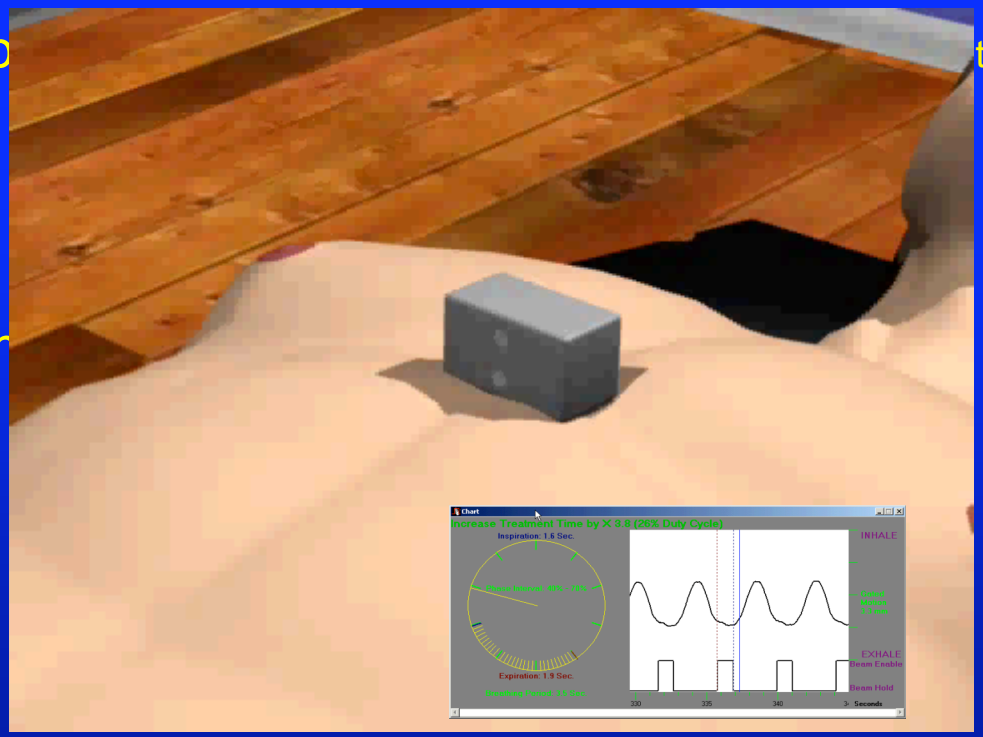
1° Solution 4D PET/CT
Respiratory Gating Acquisition
Gating Irradiation Techniques

- Integrated PET/CT system
  (Discovery-STE: General Electric Medical Systems : PET BGO Block Detector, MSCT 16slices)

- Standard RTP pallet (Flat table)
- Immobilization devices (personal b t
Technologies, Nevada-USA)

- Respiratory monitoring system :
  RPM (Real Time Position Manager



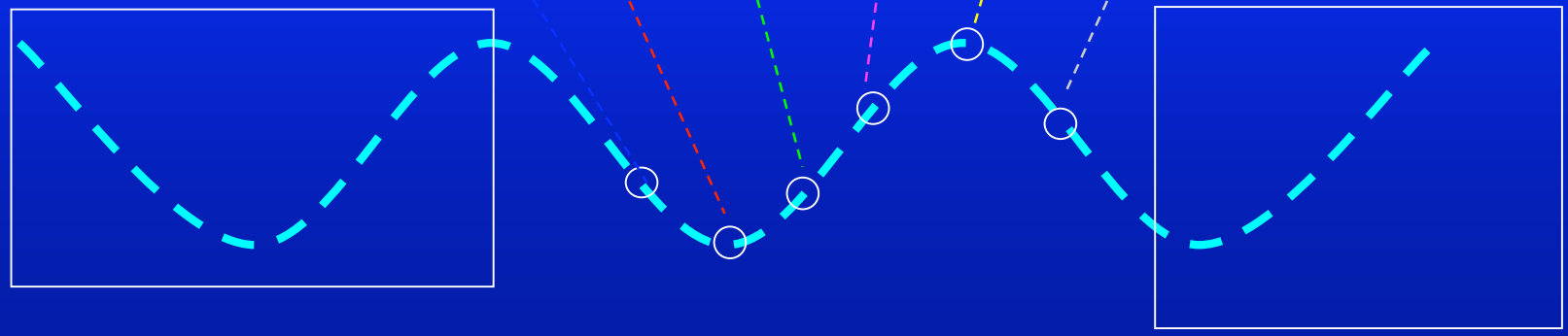


4D PET/CT
Respiratory Gating : Data Processing

- 4D CT images → Six CT phases
- The six CT Phases are then used for Attenuation Correction in the reconstruction of the corresponding PET phases

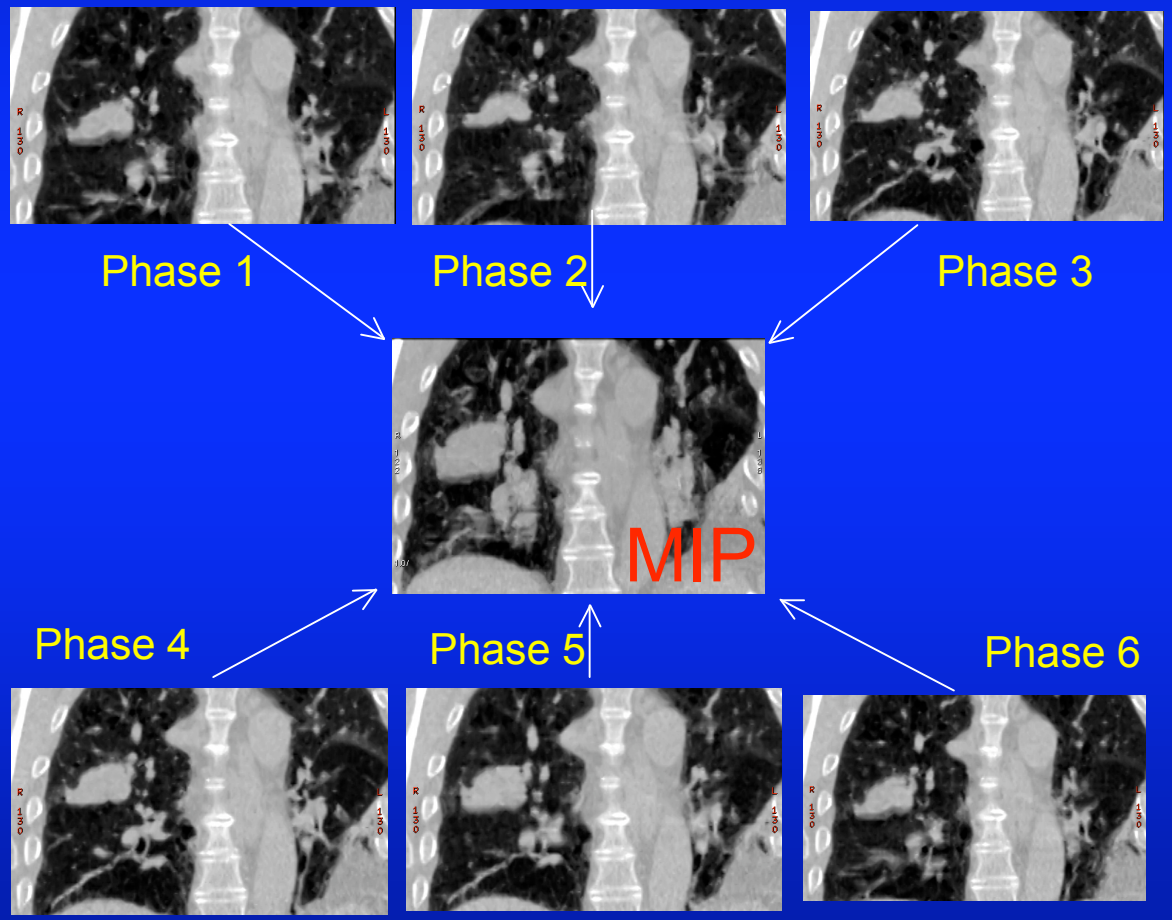
Six CT phases

Six PET phases

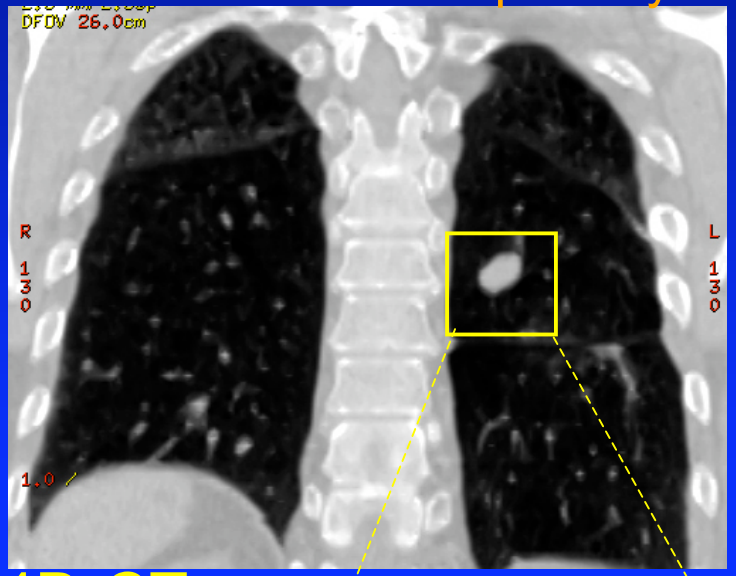


4D PET/CT
Respiratory Gating: Data Processing

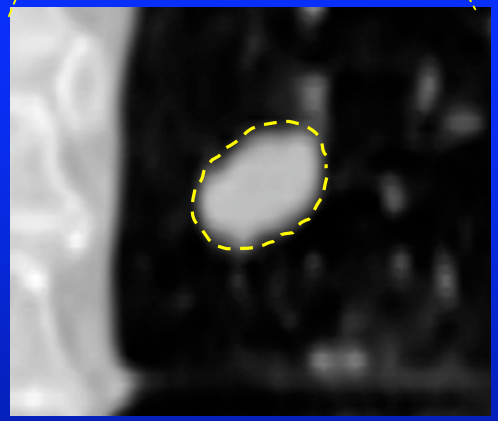
The six CT Phases are also processed (only for lung study) to generate a new serie of images MIP (Maximum Intensity Pixel).



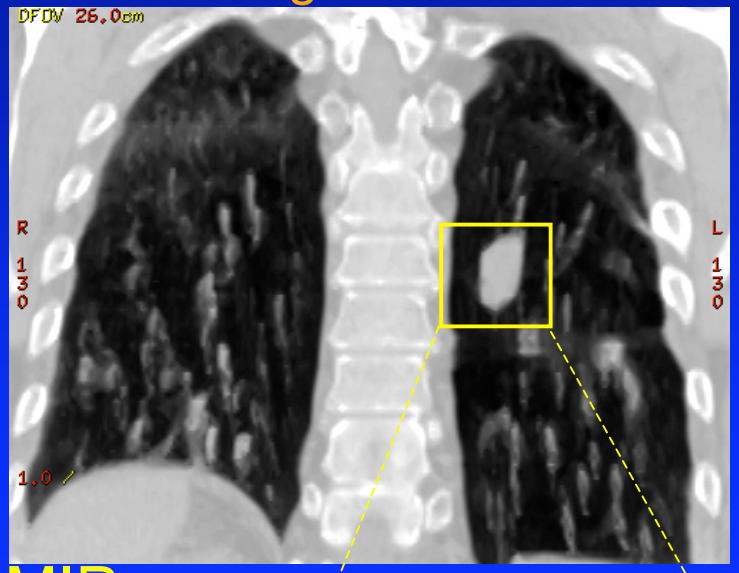
4D PET/CT
Respiratory Gating: Data Processing



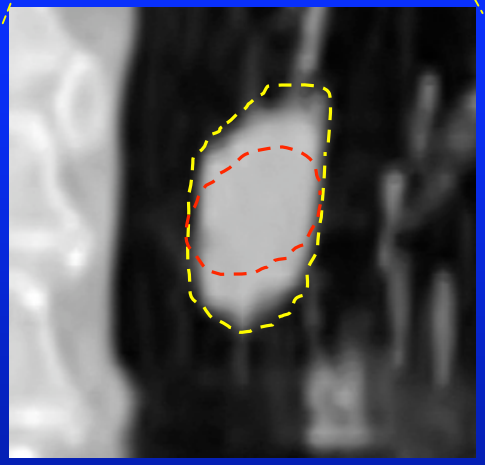
4D-CT Phase



GTV on a 4D-CT Phase

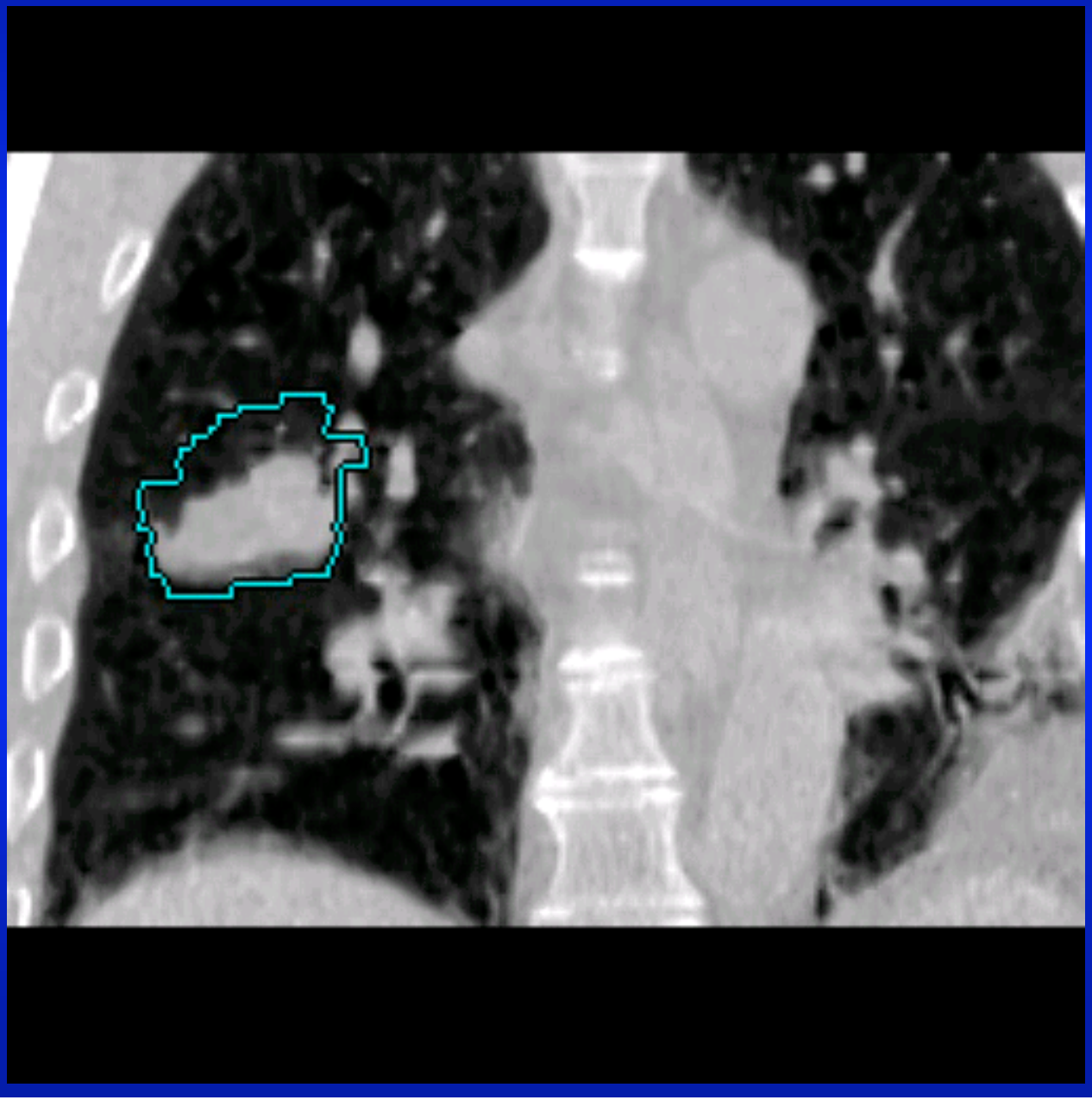


MIP image

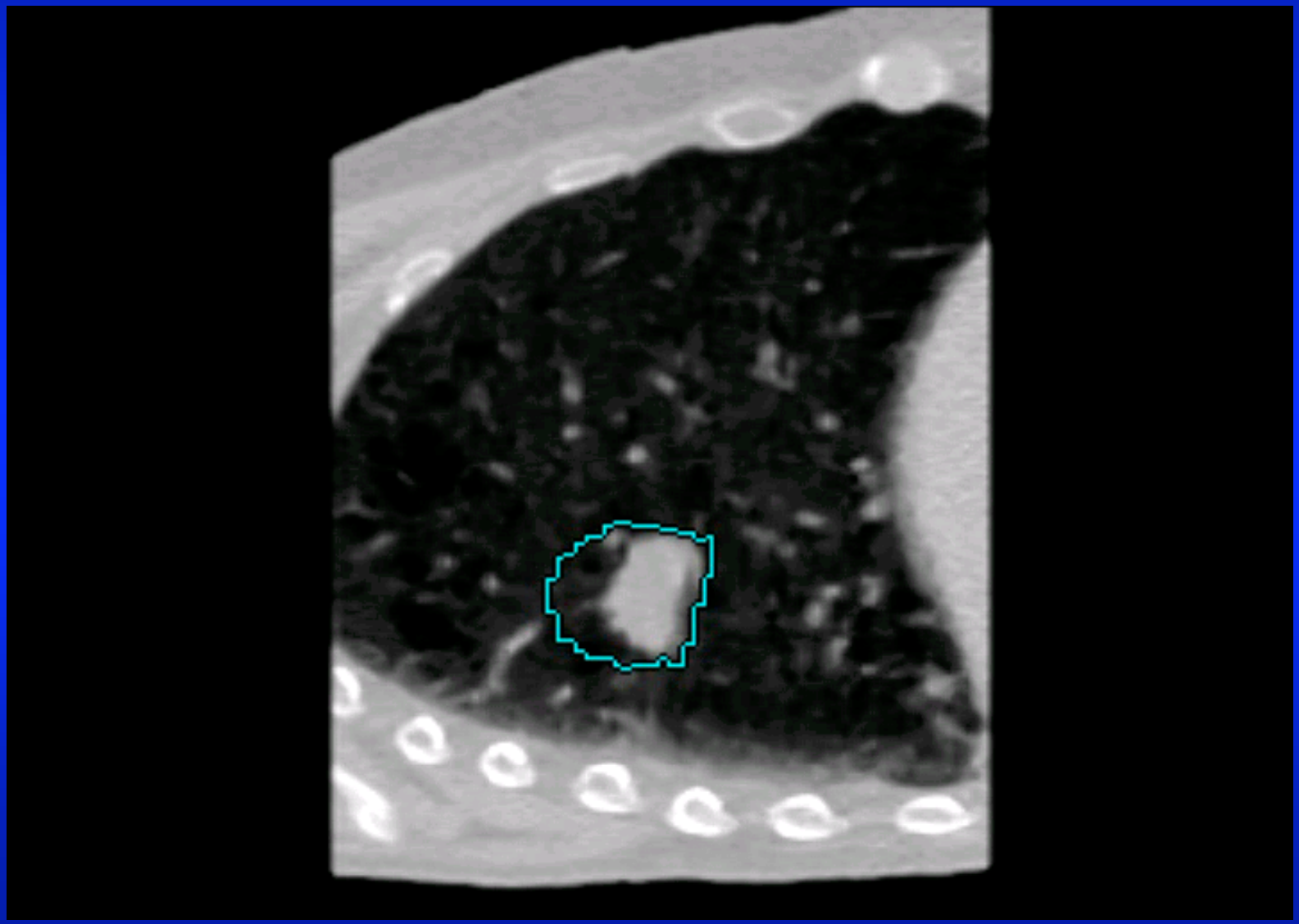


"ITV" on a MIP image

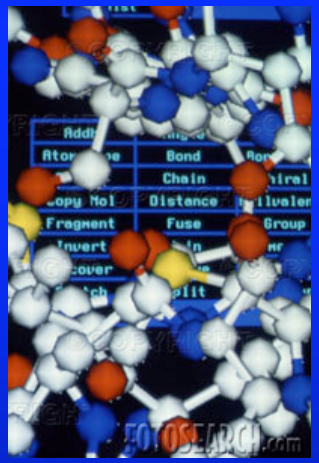
4D TC - CONTORNAMENTO



4D TC - CONTORNAMENTO



Molecular Imaging



Molecular Imaging

What do we mean as Molecular Imaging ?

The process of visualization of the localization in space and time of the molecular cellular processes

Therefore it gives a map of the current molecular processes

Tool for diagnosis and monitoring of the disease

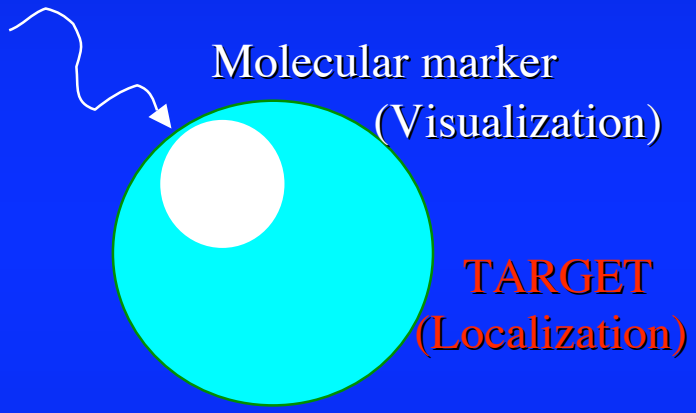
Molecular imaging tools

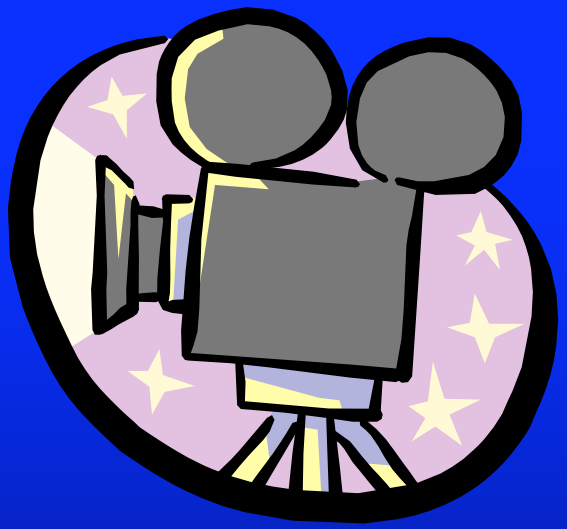
- Radiotracers IMAGING
- RM IMAGING
- optical IMAGING
- Ultrasound IMAGING

Molecular Imaging Agents : requirements

- safe
- not influencing the molecular process under observation
- selective in the quantity necessary to be detected (specificity)
- on site for a time long enaught to be detected

How it works



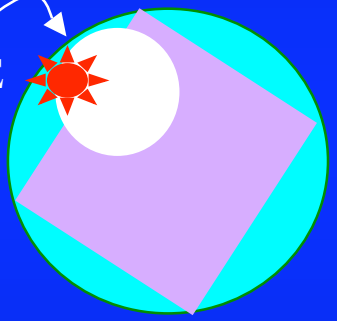


Method of visualization

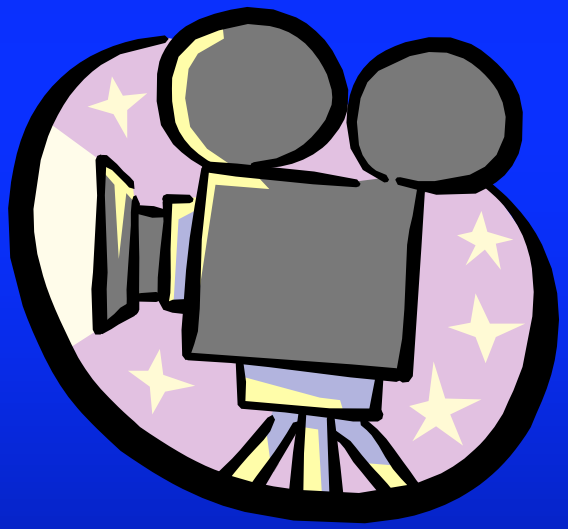
Molecular Imaging by radiotracers

Molecular Agent = radiotracer

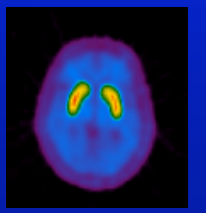
[^{11}C] RACLOPRIDE

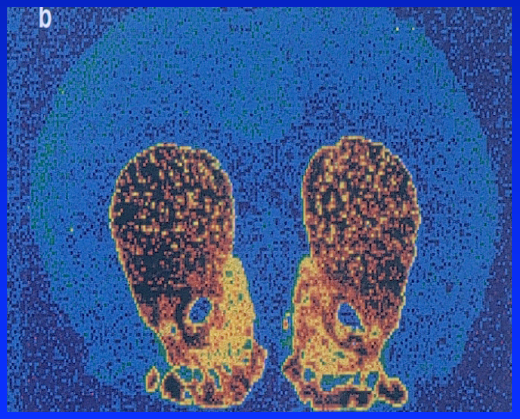


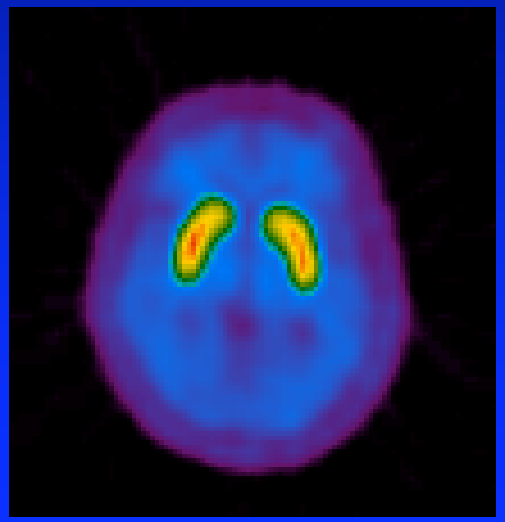
TARGET = molecule rapresentative of the pathologic process



TOMOGRAFIA AD EMISSIONE DI POSITRONI (PET)







ISTOPATOLOGIA EX-VIVO

COLORANTE

MICROSCOPIO

ISTOPATOLOGIA IN-VIVO

AGENTE RADIOATTIVO

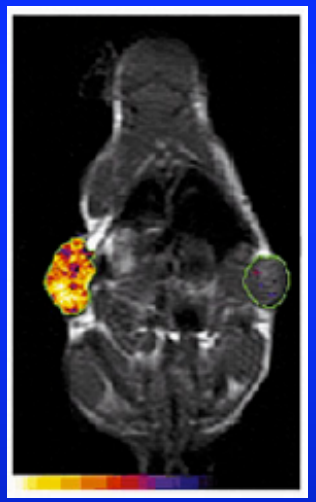
TOMOGRAFIA AD EMISSIONE
DI POSITRONI (PET)

NON-INVASIVA

Molecular Imaging by NMR

Agents: Paramagnetic or super paramagnetic (iron oxides nanocompounds) molecules changing the relaxation times of the neighboring nuclei

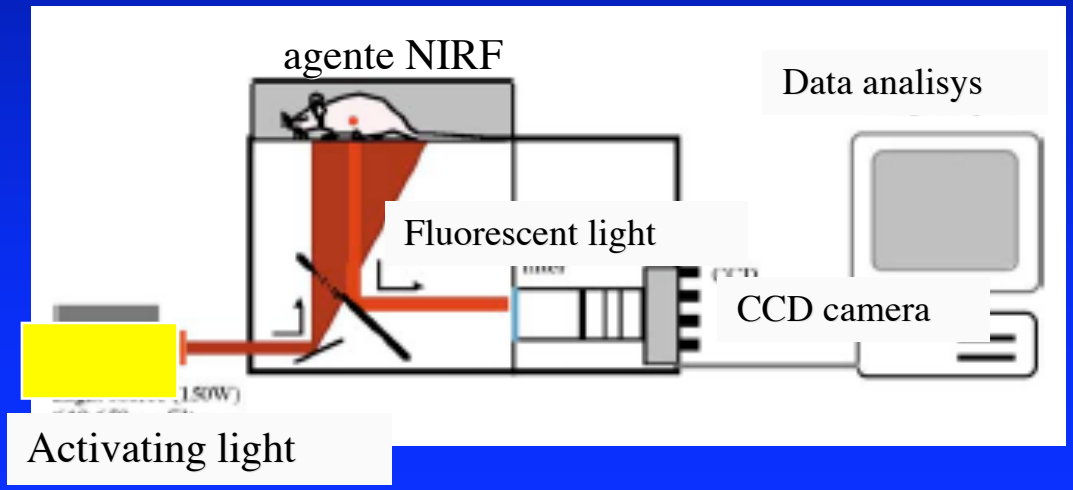
Target : Oncology (angiogenesis e apoptosis monitoring)



Weissleder et al, 2000, nature Med 6:351-4

T1 + T2 (colorata). Transferrina legata con MION.

Optical Imaging (NIRF) : small depth



Depth in tissues up to 7 mm

Clinical uses (work in progress)

- Skin cancer, breast , colonscopy, small animals, margin evaluation during surgery

NIRF Agents:

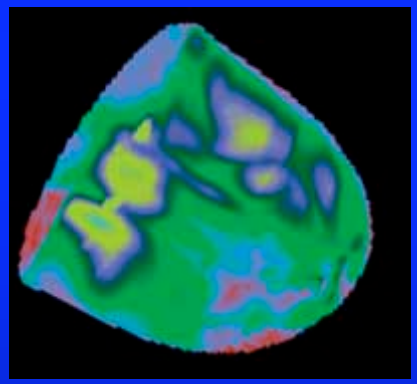
fluorescent molecules (eg. indocyanine green)
protein fluorescence gene (GFP)
Fluorescent particles (linked to specific sites in vivo)

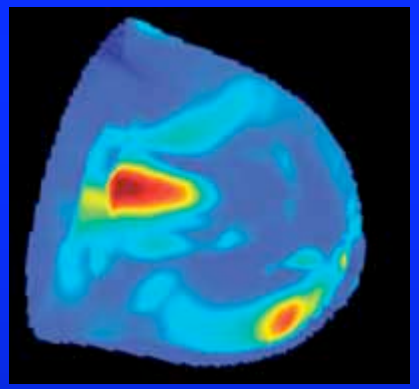
Optical Imaging (NIRF) : great depth (few centimeters)

Optical Imaging at depth greater than 1 cm becomes possible by intercorrelation among spectra of water, oxigenated hemoglobin (HbO) and reduced hemoglobin (Hb)

The principle of the method is based on the capability to recognize the angiogenesys , the preliminary visible factor related to the new breast cancers.

Infact tumour can't proliferate without an adeguate blood vessels network beyond the radius of 1 – 2 mm.





IMAGING High Frequency US (20 -100 MHz)

US Agents

- microsphere filled with gas (1-10 μm) *(Different density and elasticity respect neighbor molecules)*
- Lipids, Proteins and Polymers

Effects

Selective high intensity echoes

Features

High sensitivity also for low agents concentration

IMAGING High Frequency US

Clinical targets

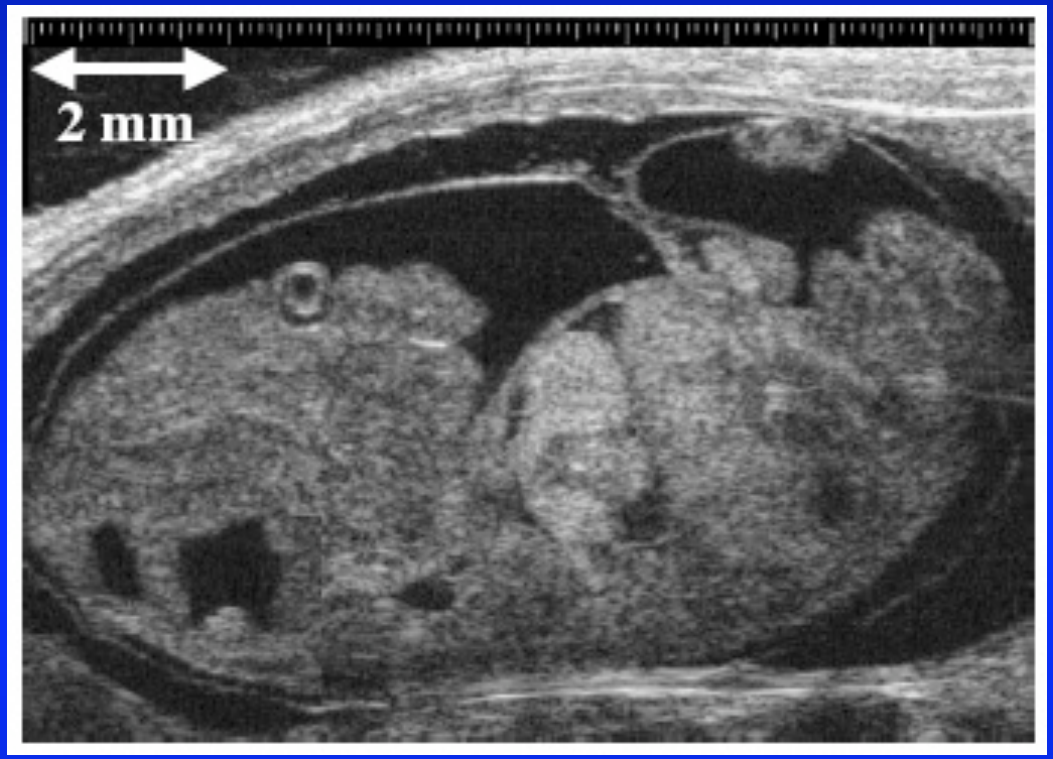
-animals
-Vascular Inflammations (arteriosclerosys) (microsfere non escono dai vasi sanguigni), vascular diseas, blood cells
-Hepatic oncology (microspheres entered in healty cells)
-High detail Phoetus observations

US Agents in progress

Chemically modified microspheres to be attached to agents linkable to specific biomolecules (for ex.: by means of receptors)

Nanoparticles coupled with overexpressed antigen antibodies

IMAGING High Frequency US

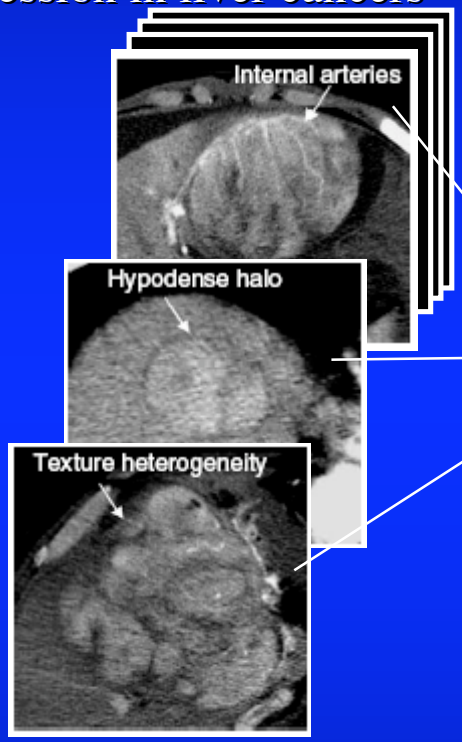


Foster et al. 2002 Ultrasound Med biol 28: 1165-72

Immagine US (40Mhz) di un feto di ratto (13 giorni)

The Fusion

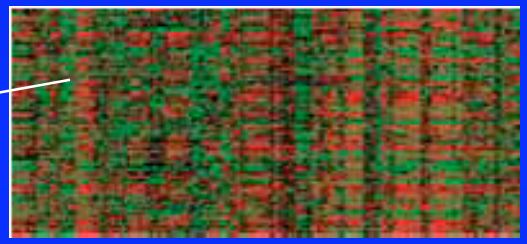
A correlation exists between images traits of CT scans and gene expression in liver cancers



138 “tratti” CT

Combinazioni, relazioni logiche

AND OR

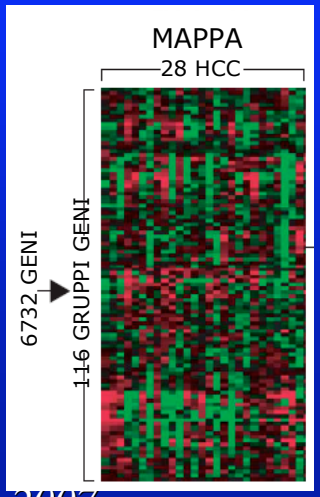


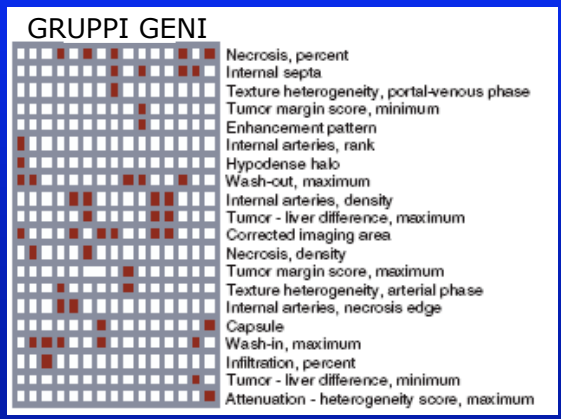
6732 geni

Cell proliferation

Liver function,

prognostic factors





Ogni gruppo di gene associato con combinazioni di tratti

RISULTATI

28 tratti informativi HCC

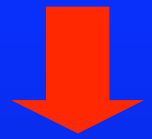
116 gruppi di geni con variazioni coerenti

Segal E. et al, Nature Biotecnology, June 2007

Diagnostic (Imaging) for RT : the future

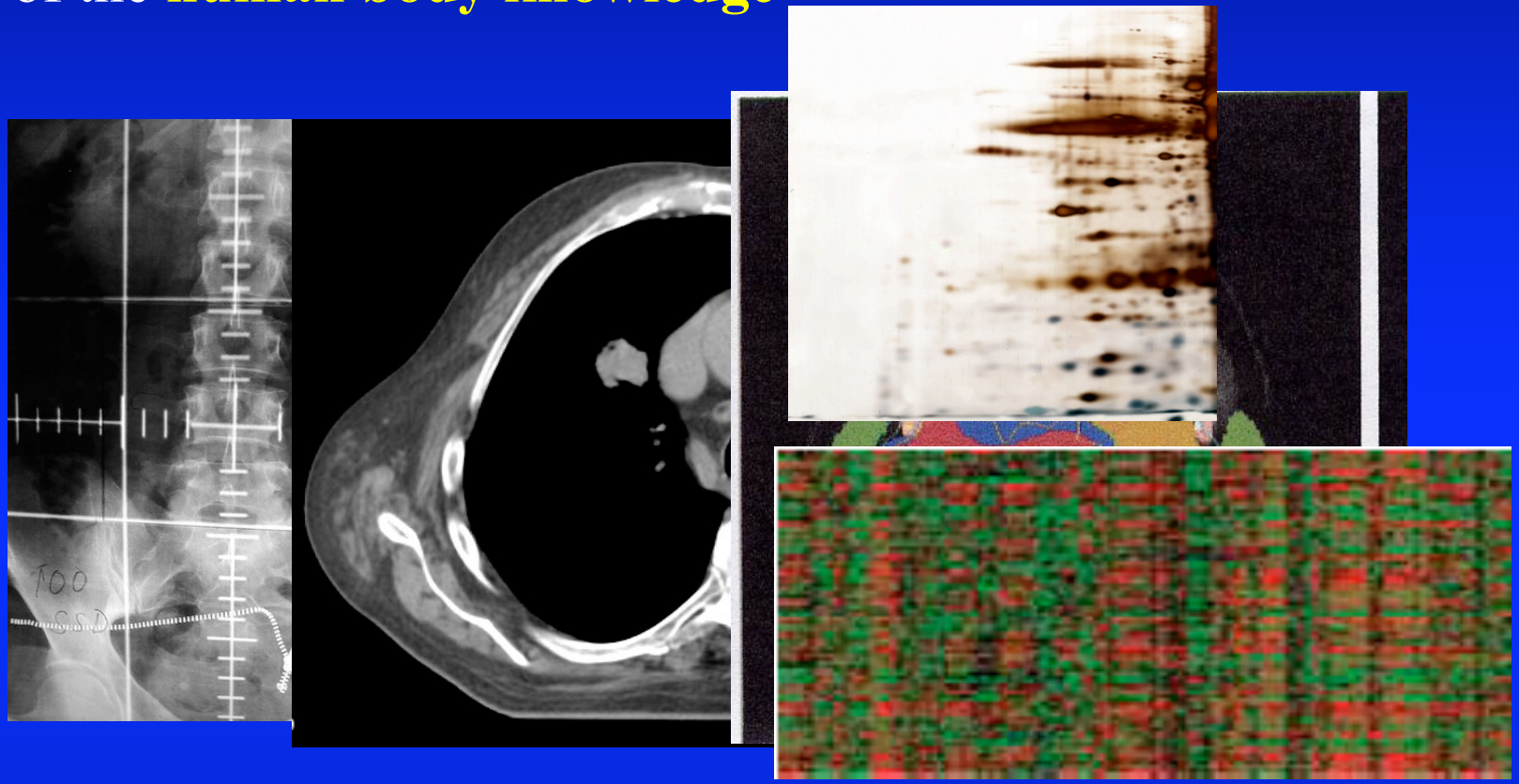
Genetic profile and proteins informations for every pts

Ethiology, prognosis, tumour response to therapy



Individually Personalized terapy periodically monitored

The **concept of image** is in progress following the evolution of the **human body knowledge**



the increased amount and quality of information obtained by different imaging methods improves the clinical benefits of the therapy.

Imaging in RT

We shall acquire a lot of different methods to obtain diagnostic information of a tumour.

Many of these will be derived by gene maps, proteins distribution and so on; but **radiotherapy** will always need the most accurate definition of the localization and geometrical information of the tumour and its spread.

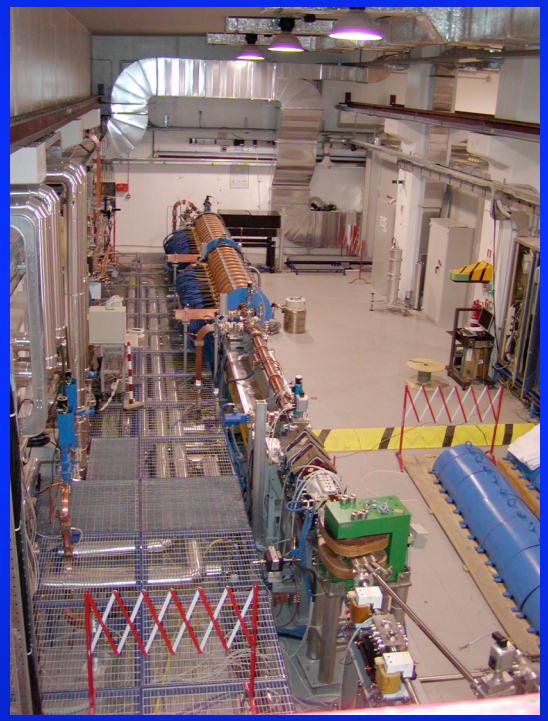
X Rays Imaging representing anatomical details, as well as Tissues density matrix, will remain the basic reference for every present and future Radiotherapy plan.

What do we expect from diagnostic imaging improvements (Monocromatic X rays ?)

In a simple and syntetic sentence we can say:

"We expect an increase in the ability of the diagnostic tools in the detection of the tumours , that is, discover the tumour at the earliest stage" (to increase the survival)

Today we can detect tumour size of 1 cc with a body effective dose of 10 mSv. The goal would be to increase the detectability of 2- 3 order of magnitude (10^9 to 10^6 cells) decreasing the dose to 1 mSv.



The best things, as humans probably are, need the best images

Thanks for your attention