Introduction to

Radiation Therapy

OMA Summer School
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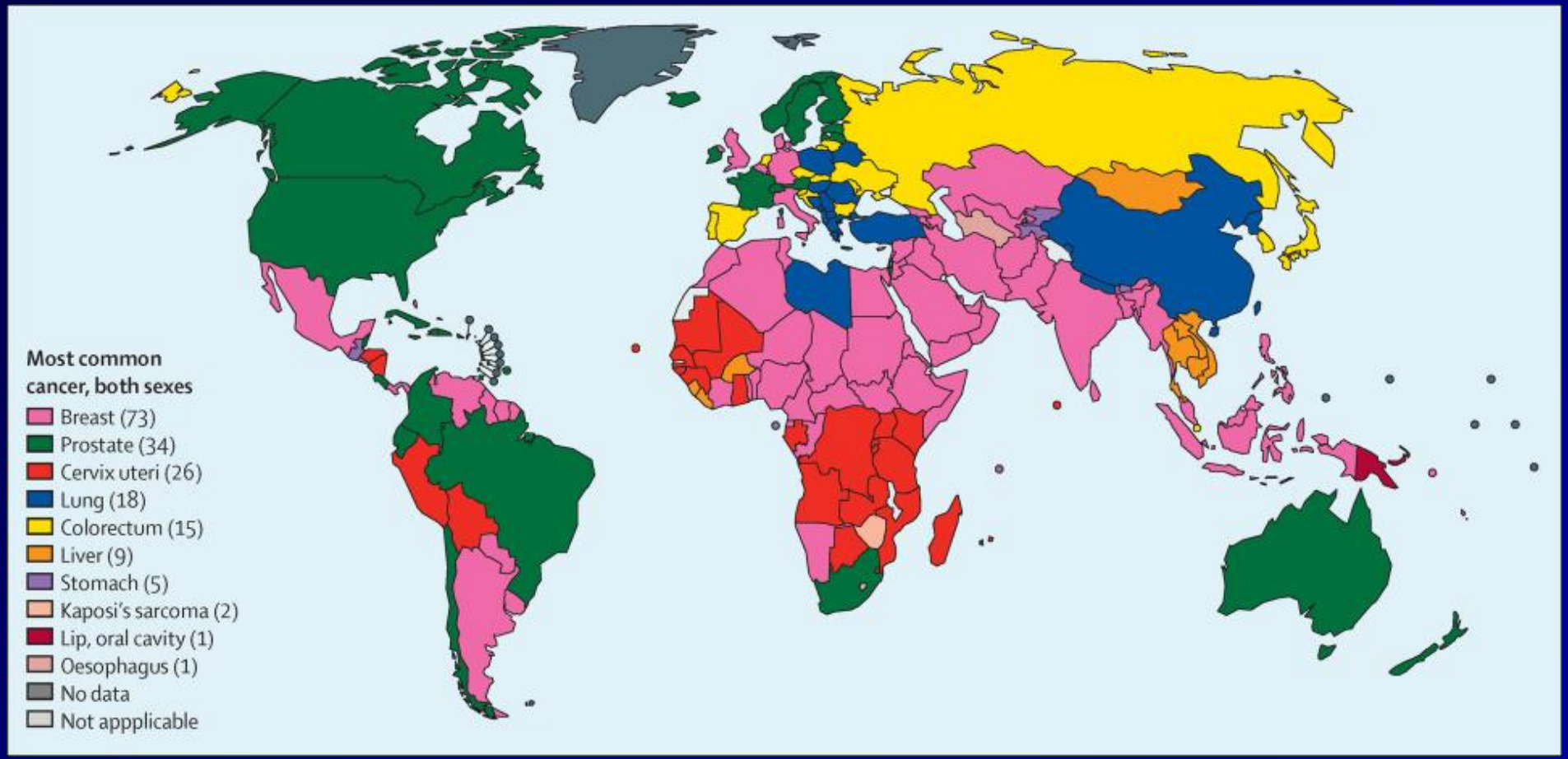
Most frequent cancer type



- 184 countries
- (n) number of countries in which that cancer is the most common
- Data from GLOBOCAN 2012, IARC (Lyon, France)

Atun R et al, Lancet Oncol 2016

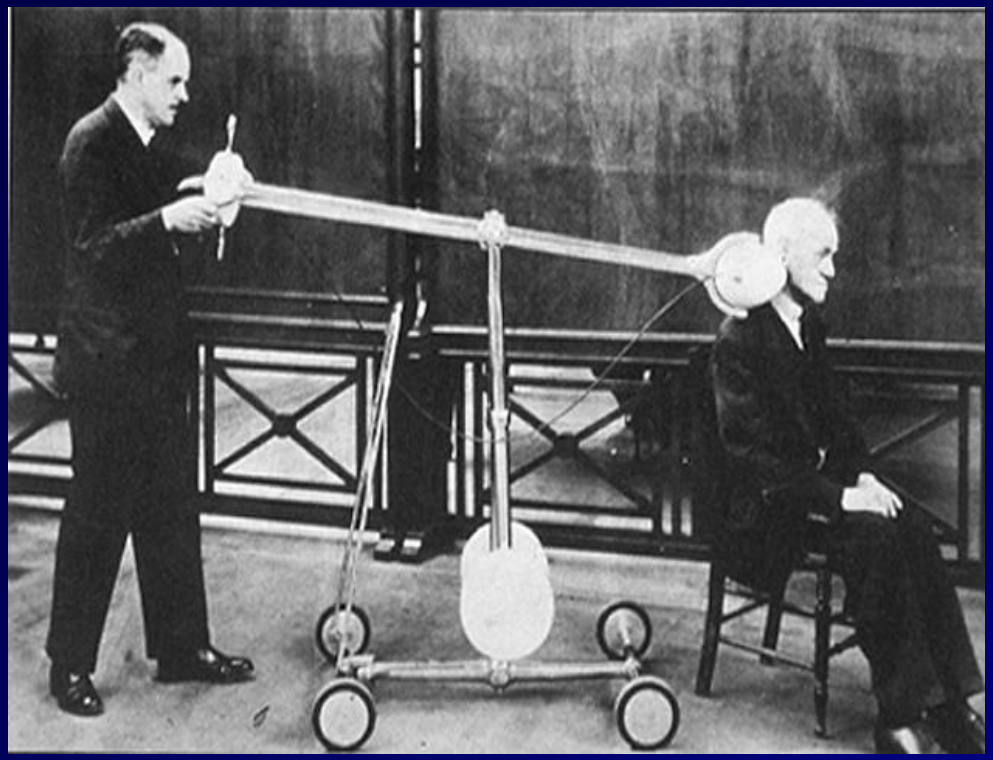
Need for RT. ESTRO-HERO estimation

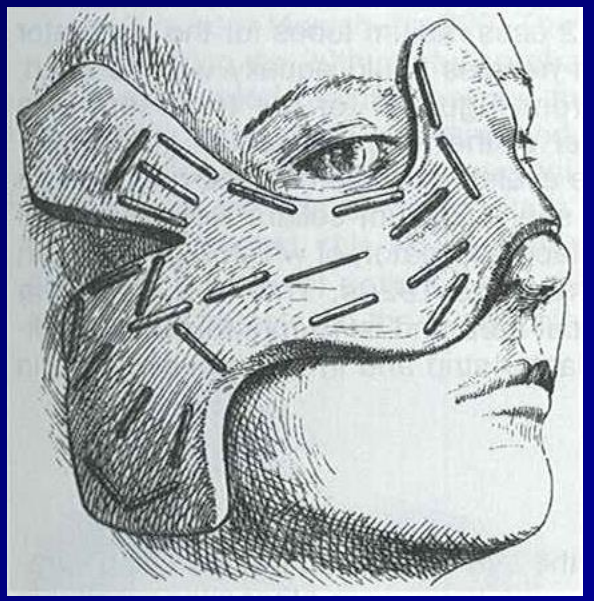
Country	First	Second	Third	Fourth	Fifth
Albania	Lung	Breast	Head&Neck	Brain	Stomach
Austria	Breast	Prostate	Lung	Head&Neck	Bladder
Belarus	Breast	Lung	Head&Neck	Prostate	Rectum
Belgium	Breast	Lung	Prostate	Bladder	Head&Neck
Bosnia Herzegovina	Lung	Breast	Head&Neck	Prostate	Rectum
Bulgaria	Breast	Lung	Rectum	Head&Neck	
Croatia	Lung	Breast	Prostate	Rectum	
Cyprus	Breast	Prostate	Lung	Bladder	
Czech Republic	Breast	Lung	Prostate	Rectum	
Denmark	Breast	Lung	Prostate	Rectum	
Estonia	Prostate	Breast	Lung	Rectum	
Finland	Breast	Prostate	Lung	Lymphoma	
France	Prostate	Breast	Lung	Head&Neck	
Germany	Breast	Prostate	Lung	Rectum	
Greece	Lung	Breast	Prostate	Bladder	
Hungary	Lung	Breast	Head&Neck	Rectum	
Iceland	Breast	Prostate	Lung	Rectum	
Ireland	Breast	Prostate	Lung	Lymphoma	
Italy	Breast	Lung	Prostate	Rectum	
Latvia	Breast	Lung	Prostate	Head&Neck	
Lithuania	Breast	Lung	Prostate	Head&Neck	
Luxembourg	Breast	Prostate	Lung	Rectum	
Macedonia	Lung	Breast	Prostate	Head&Neck	
Malta	Breast	Lung	Prostate	Bladder	
Moldova	Lung	Breast	Head&Neck	Rectum	
Montenegro	Lung	Breast	Prostate	Head&Neck	
Norway	Prostate	Breast	Lung	Rectum	
Poland	Lung	Breast	Prostate	Head&Neck	
Portugal	Breast	Prostate	Lung	Head&Neck	
Romania	Lung	Breast	Head&Neck	Prostate	
Russian Federation	Breast	Lung	Prostate	Head&Neck	
Serbia	Lung	Breast	Prostate	Head&Neck	Rectum
Slovakia	Breast	Lung	Prostate	Rectum	Head&Neck
Slovenia	Lung	Prostate	Breast	Rectum	Head&Neck
Spain	Lung	Breast	Prostate	Rectum	Head&Neck
Sweden	Prostate	Breast	Lung	Rectum	Lymphoma
Switzerland	Prostate	Breast	Lung	Lymphoma	Head&Neck
The Netherlands	Breast	Lung	Prostate	Rectum	Lymphoma
Ukraine	Breast	Lung	Head&Neck	Rectum	Prostate
United Kingdom	Breast	Lung	Prostate	Lymphoma	Rectum
Global	Breast	Lung	Prostate	Head&Neck	Rectum

Tumor site	RT courses 2012	Increase in number 2025	Increase in rate (%)
Breast	396,891	40,524	10.2
Lung	315,197	56,558	17.9
Prostate	243,669	59,493	24.4
Head&Neck	108,194	13,337	12.3
Rectum	99,493	18,314	18.4
Lymphoma	74,852	9871	13.3
Others	……	……	……

Borras JM et al, Radiother Oncol 2016

Radium





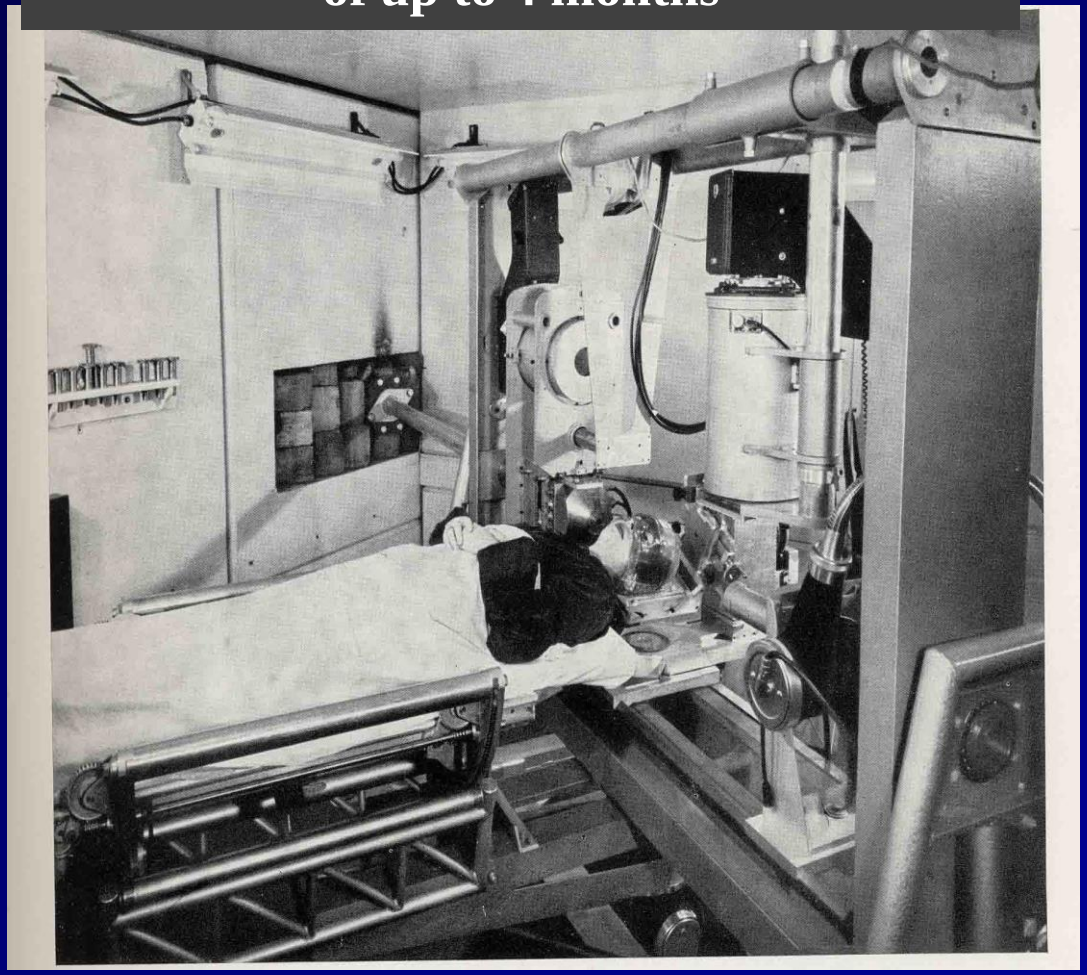
Paris schedule cervix uteri

Continous treatment for 120 hours
Uterine tube of 33.3 mg radium
Two vaginal cylindrical corks: 13.3 mg radium each

The Early 1920s

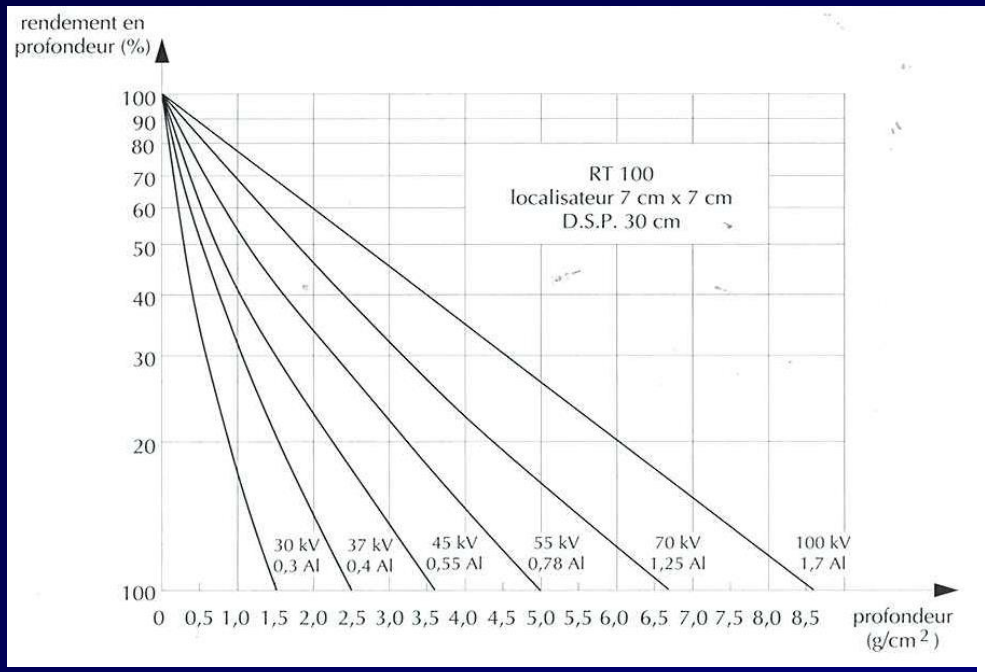
Coutard: daily fractions lasting 2-3 hours on regimen lasting 4-6 weeks

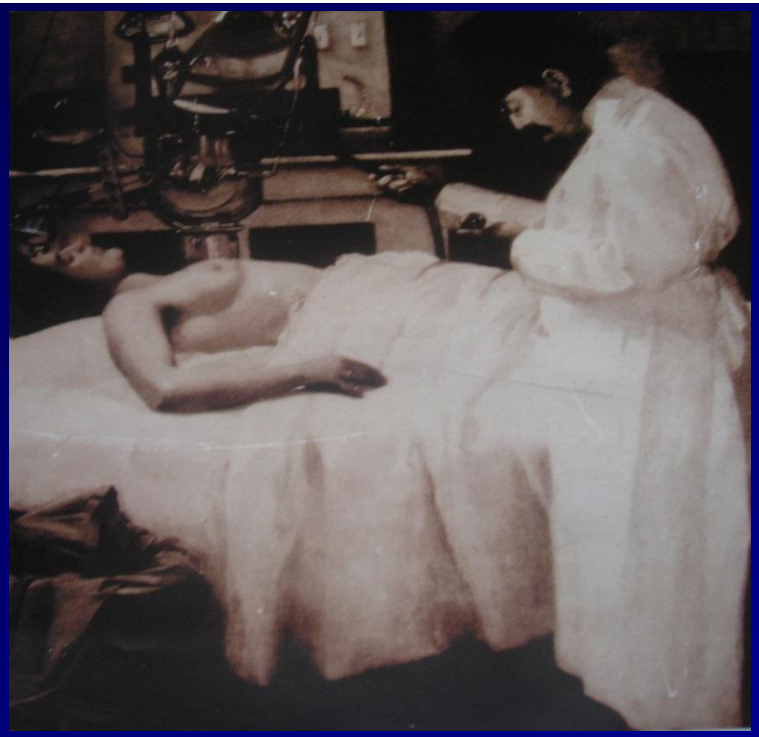
Baclesse: daily doses of 200R (1.8 Gy) given over 10 minutes using regimens of up to 4 months

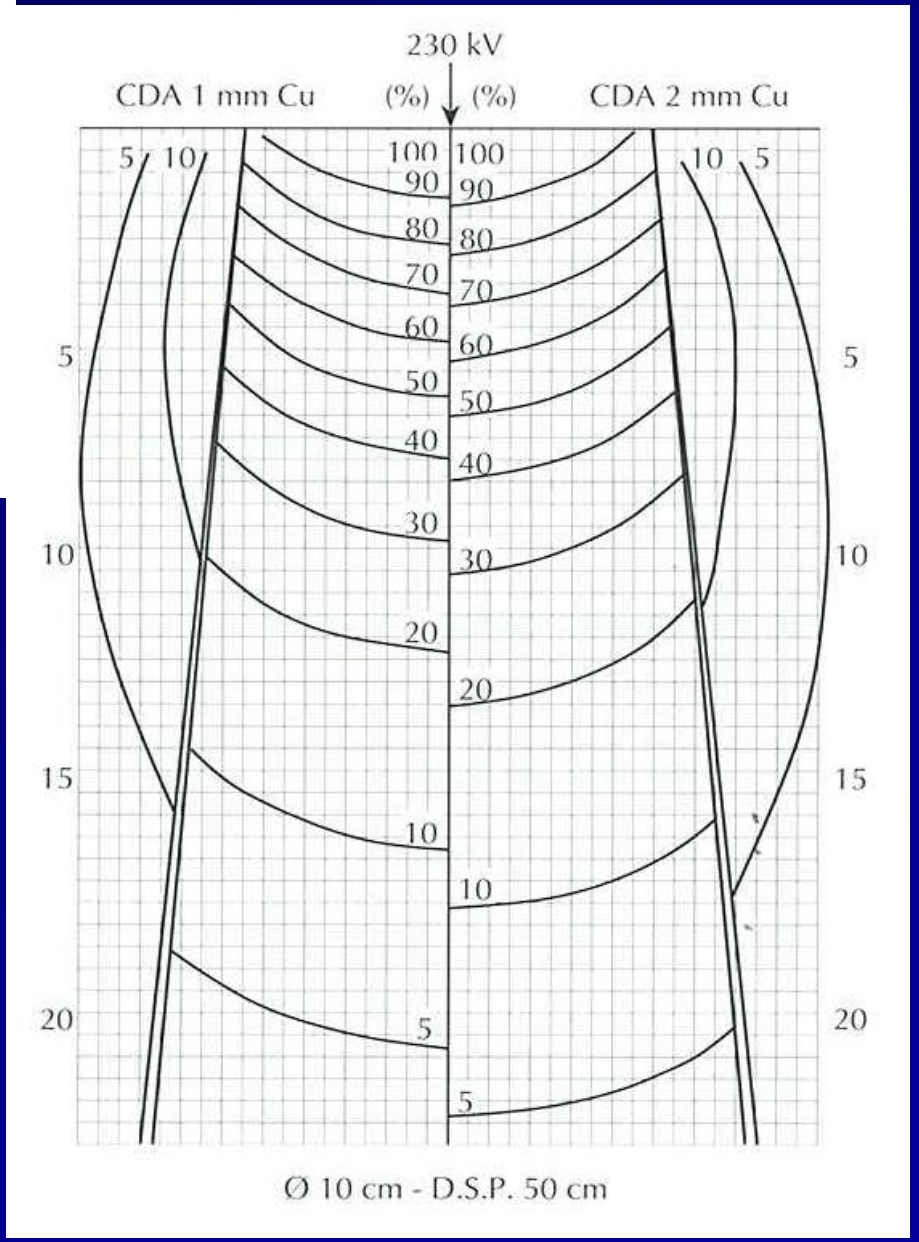


Once more reliable equipment became available, single fraction treatments were tried, with German speakers more in favour of massive single dose, **“Terapia Magna Sterilans”** and Francophones delivering **”Fractionated treatment”**

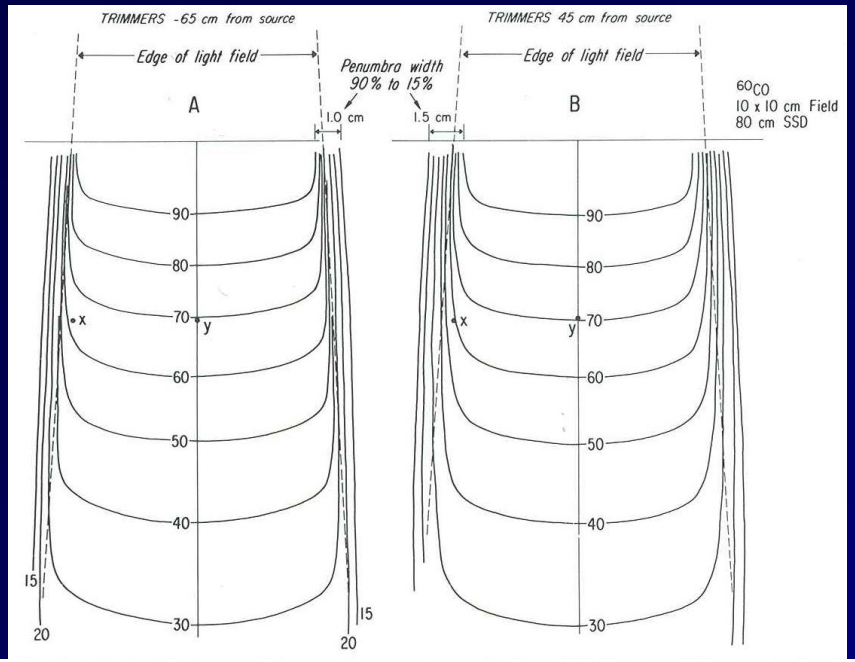
Orthovoltage

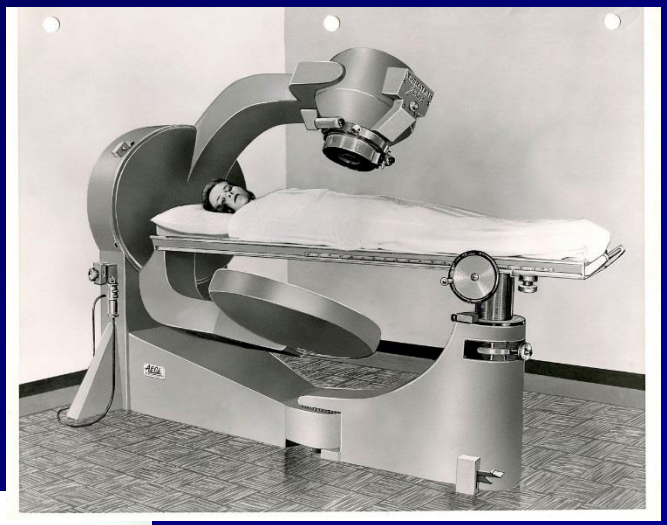


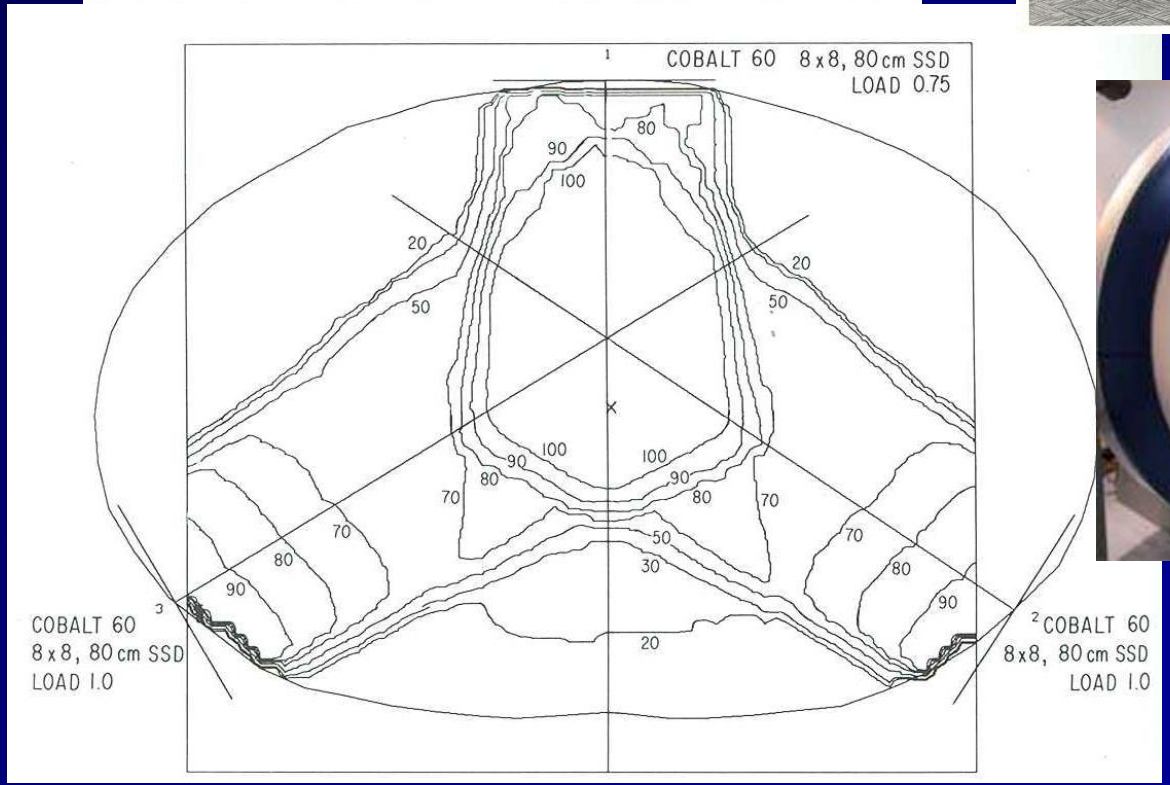




Megavoltage

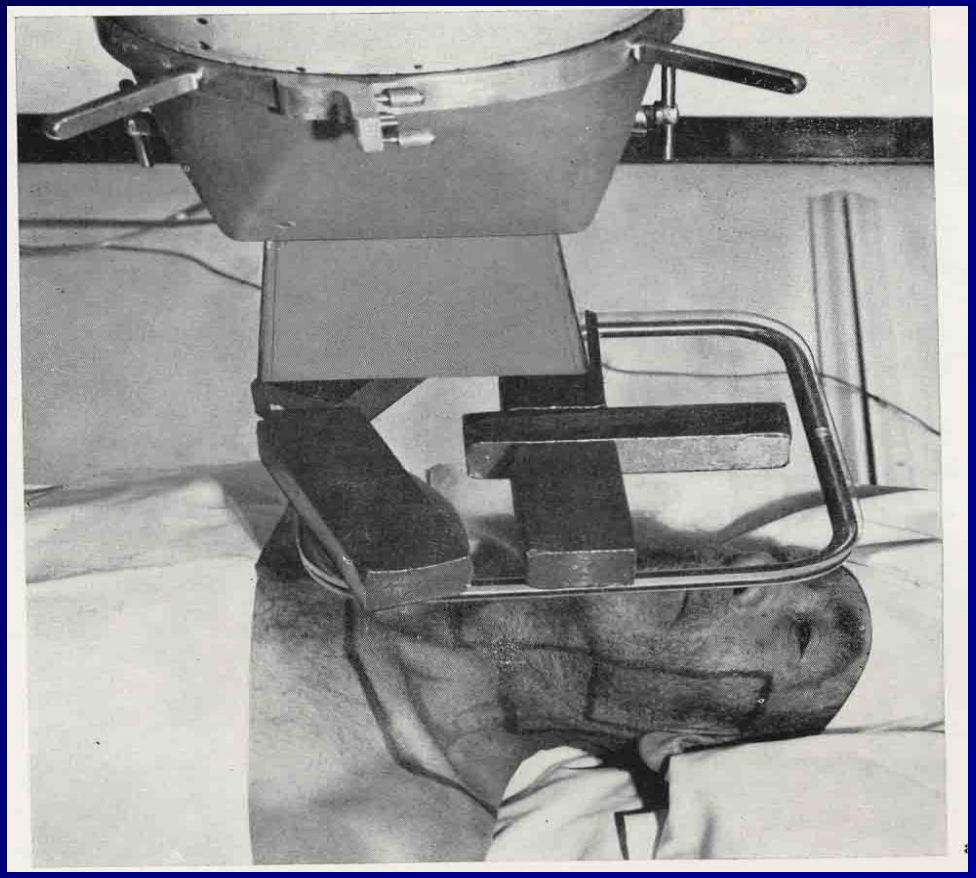






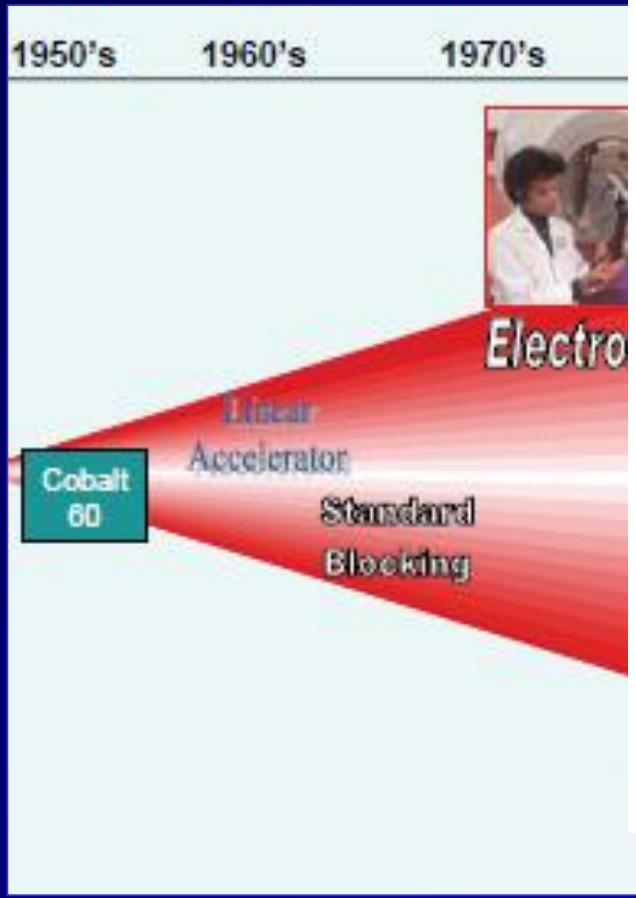
G Fletcher since1948

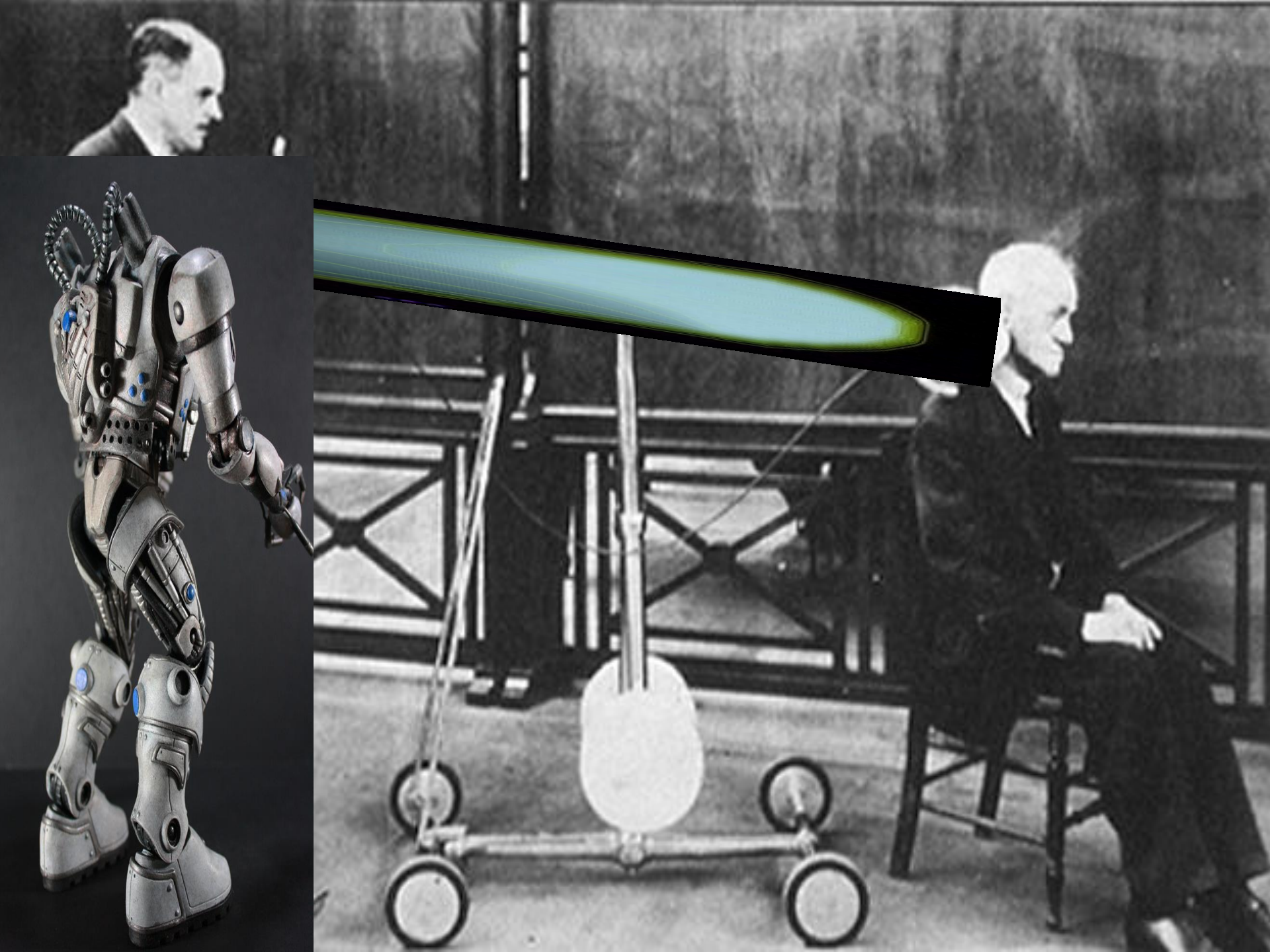
As a results of his influence and teaching there is a belief amongst radiation oncologists in the USA that to treat using fewer than 30 fractions is inherently dangerous



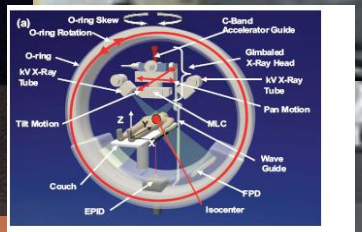
Coincidentally, owing to reimbursement practices in the USA, regimen using fewer than 30 fractions are also less lucrative

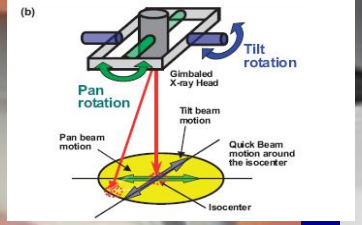
Since ‘60 Evolution Radiation





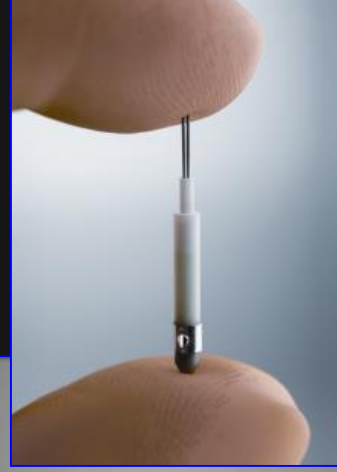
High Tecnology & IGRT

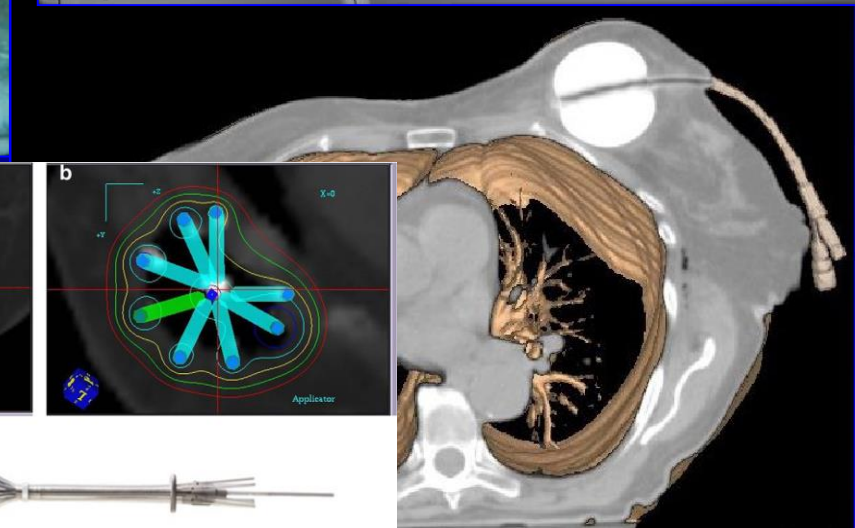




IEO
Arc Advanced Radiotherapy Center

High Tecnology & BRT





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Improved Dose distribution

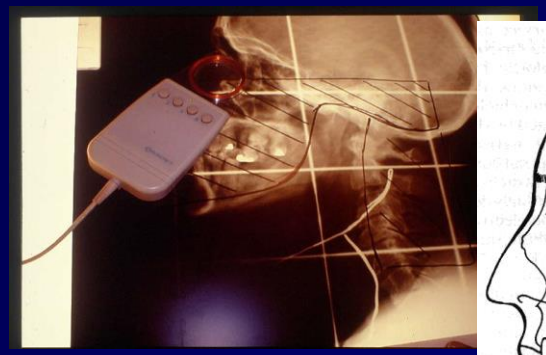
Technology

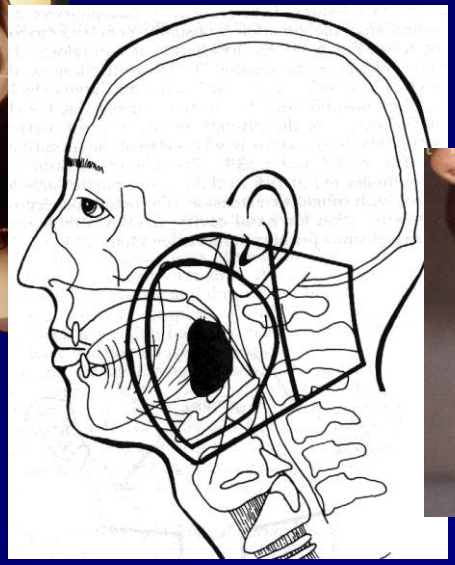
Smaller volume + Higher dose =

Inverse Square Law

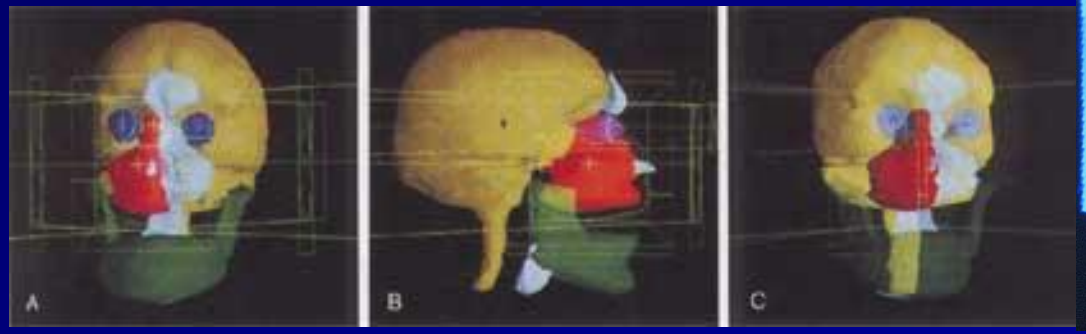
- Shorter treatment
- > LC & Survival
- < Toxicity

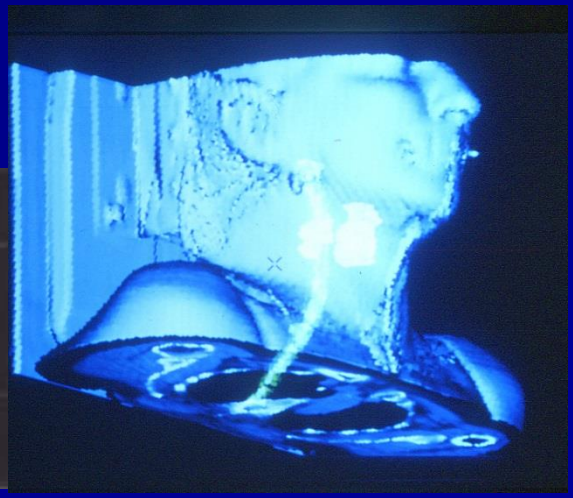
From 2-D



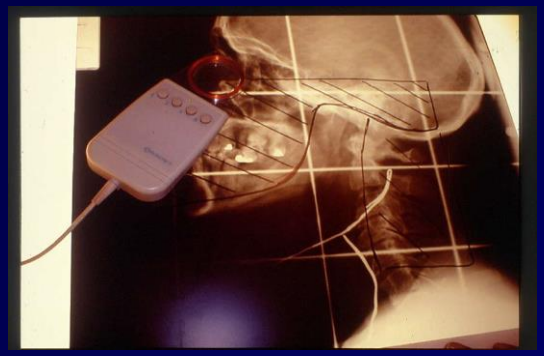


To 3-D

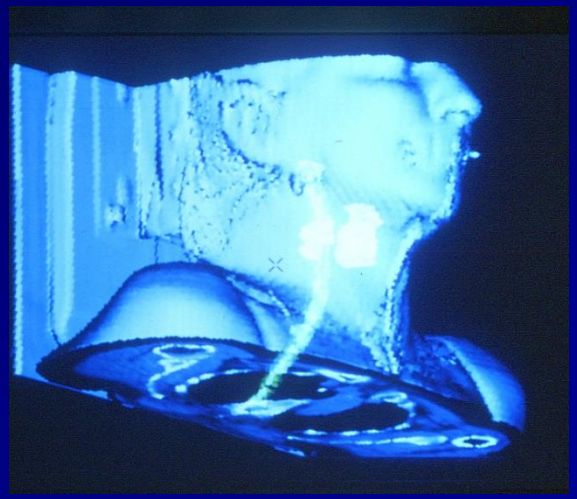




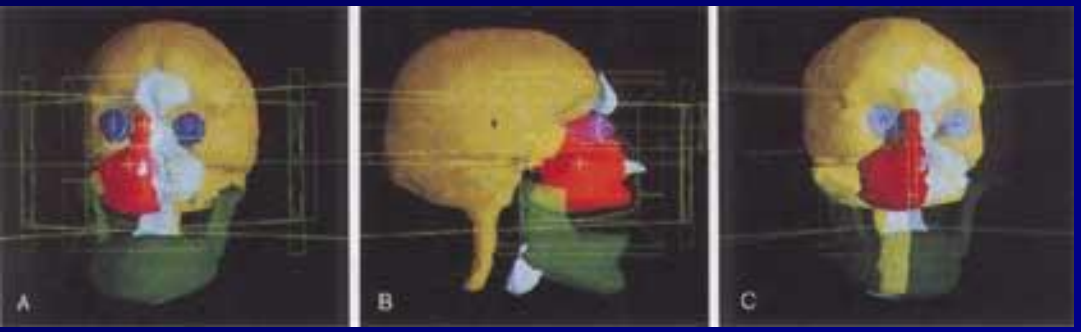
Emerging technologies in RT



RT 2-D



RT 3-D



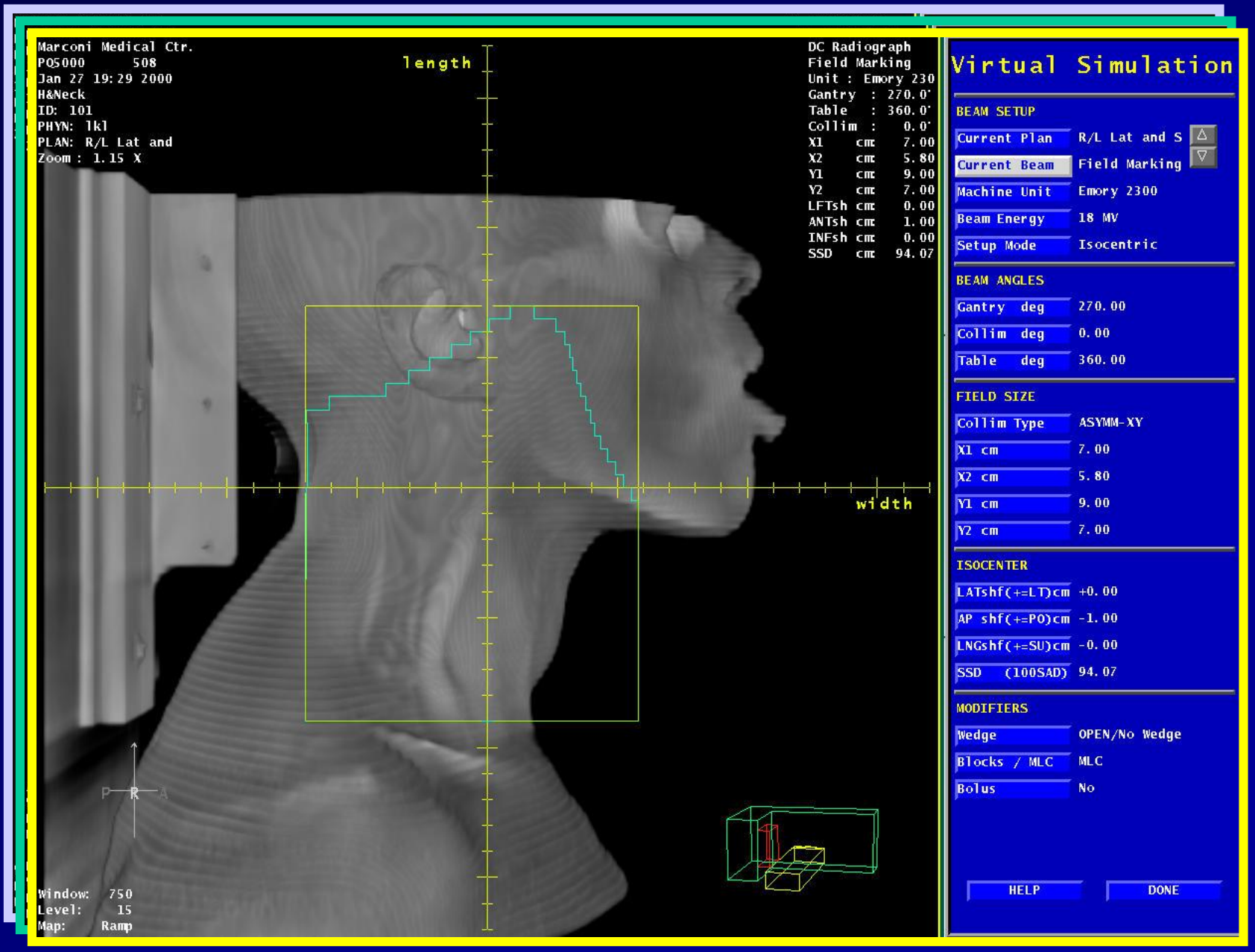
Inverse Planning ...
Biological Target Volume

IMRT

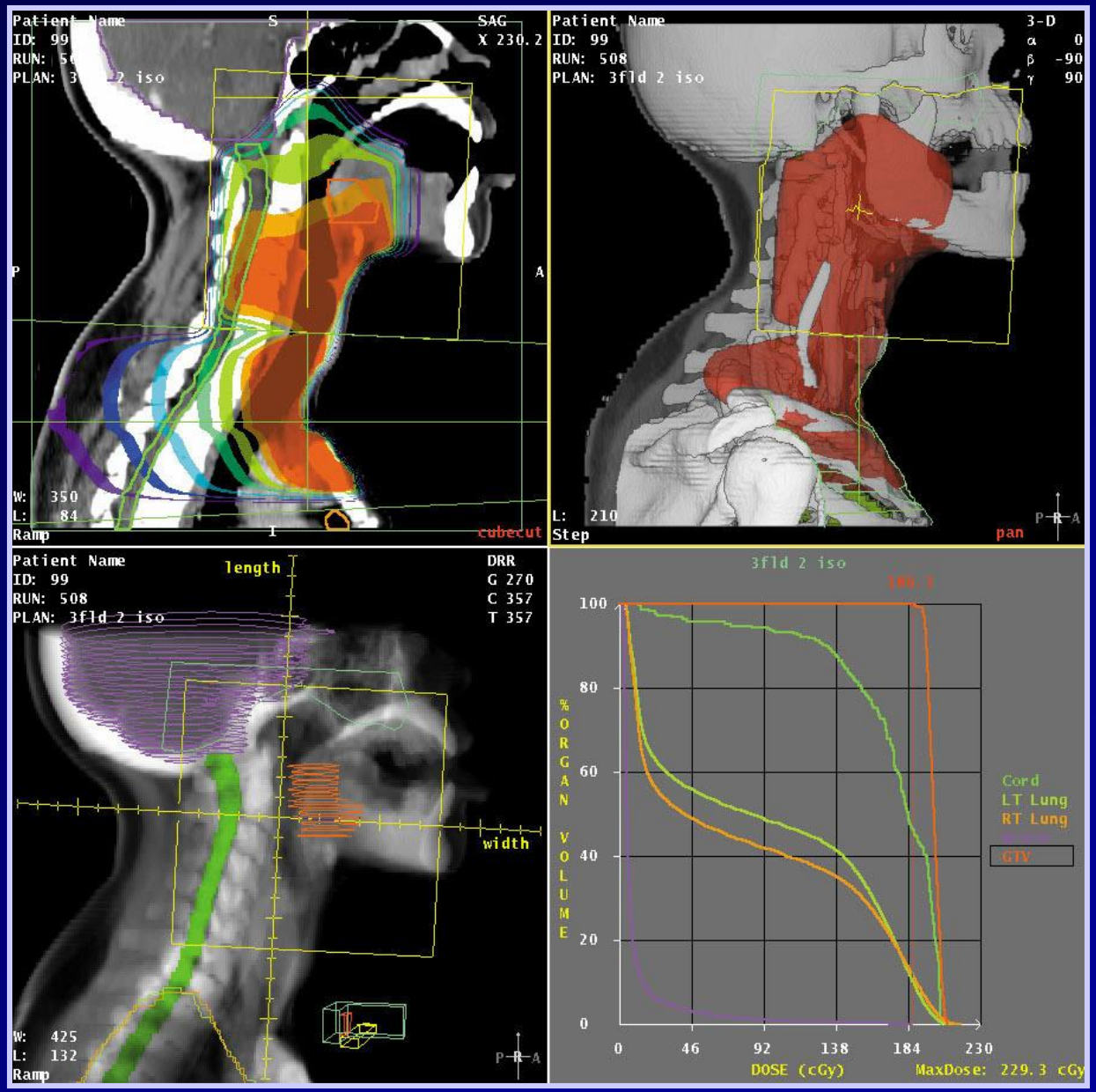
&

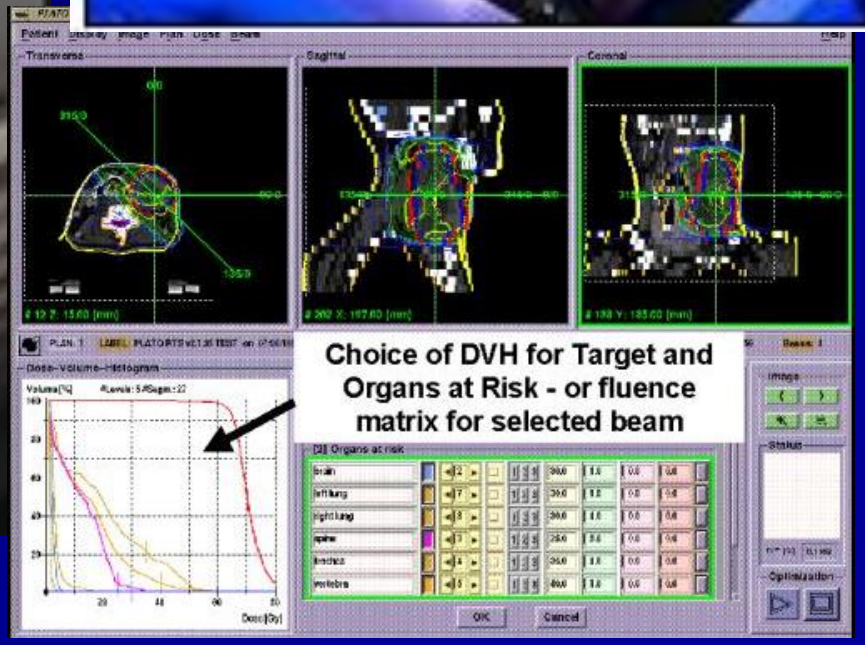
other
High Precision
Techniques

H&N DCR's

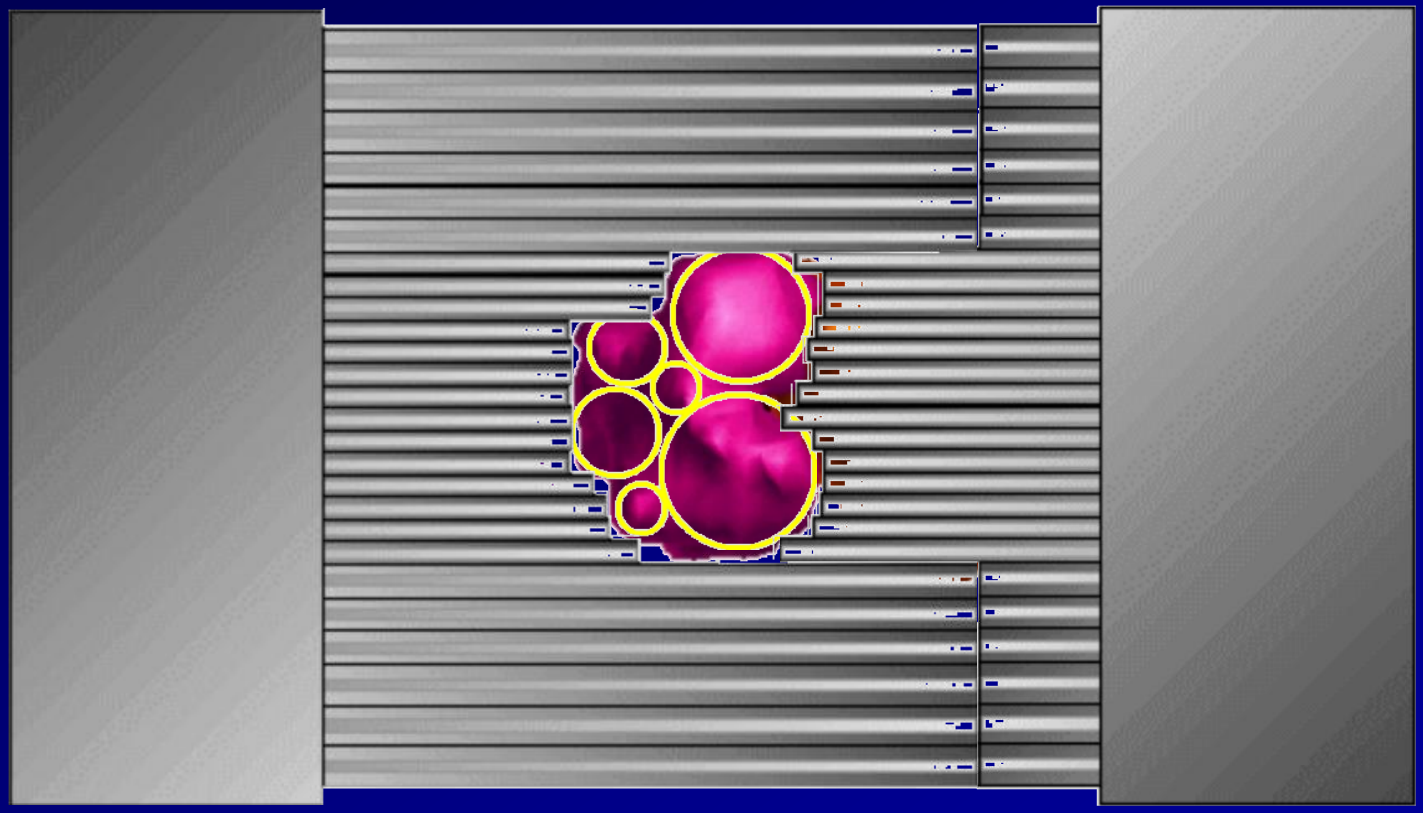

Marconi Medical Ctr.
PQ5000 508
Jan 27 19:29 2000
H&Neck
ID: 101
PHYN: lkl
PLAN: R/L Lat and
Zoom : 1.15 X
length
width
DC Radiograph
Field Marking
Unit : Emory 230
Gantry : 270.0°
Table : 360.0°
Collim : 0.0°
X1 cm 7.00
X2 cm 5.80
Y1 cm 9.00
Y2 cm 7.00
LFTsh cm 0.00
ANTsh cm 1.00
INFsh cm 0.00
SSD cm 94.07
P R A
Window: 750
Level: 15
Map: Ramp
Virtual Simulation
BEAM SETUP
Current Plan R/L Lat and S
Current Beam Field Marking
Machine Unit Emory 2300
Beam Energy 18 MV
Setup Mode Isocentric
BEAM ANGLES
Gantry deg 270.00
Collim deg 0.00
Table deg 360.00
FIELD SIZE
Collim Type ASYMM-XY
X1 cm 7.00
X2 cm 5.80
Y1 cm 9.00
Y2 cm 7.00
ISOCENTER
LATshf(+=LT)cm +0.00
AP shf(+=PO)cm -1.00
LNGshf(+=SU)cm -0.00
SSD (100SAD) 94.07
MODIFIERS
Wedge OPEN/No Wedge
Blocks / MLC MLC
Bolus No
HELP
DONE

Dose distribution and DVH

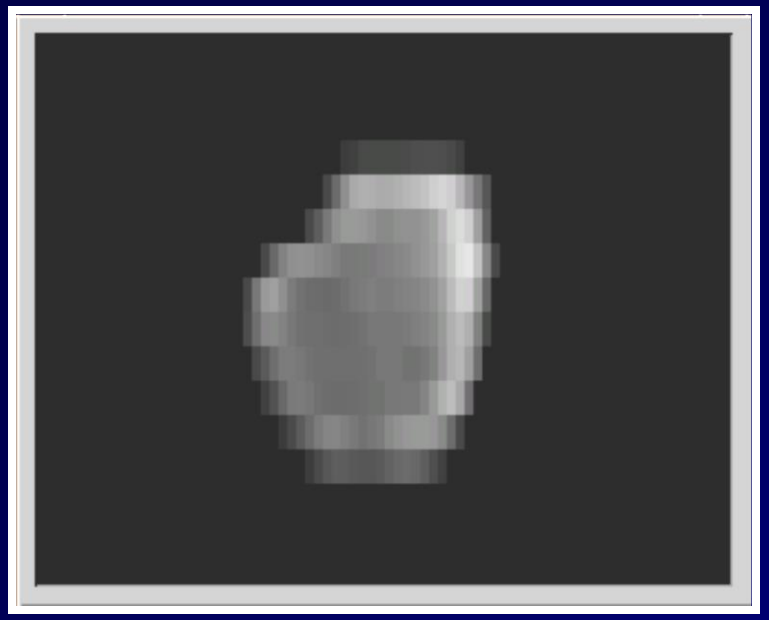



Choice of DVH for Target and Organs at Risk - or fluence matrix for selected beam

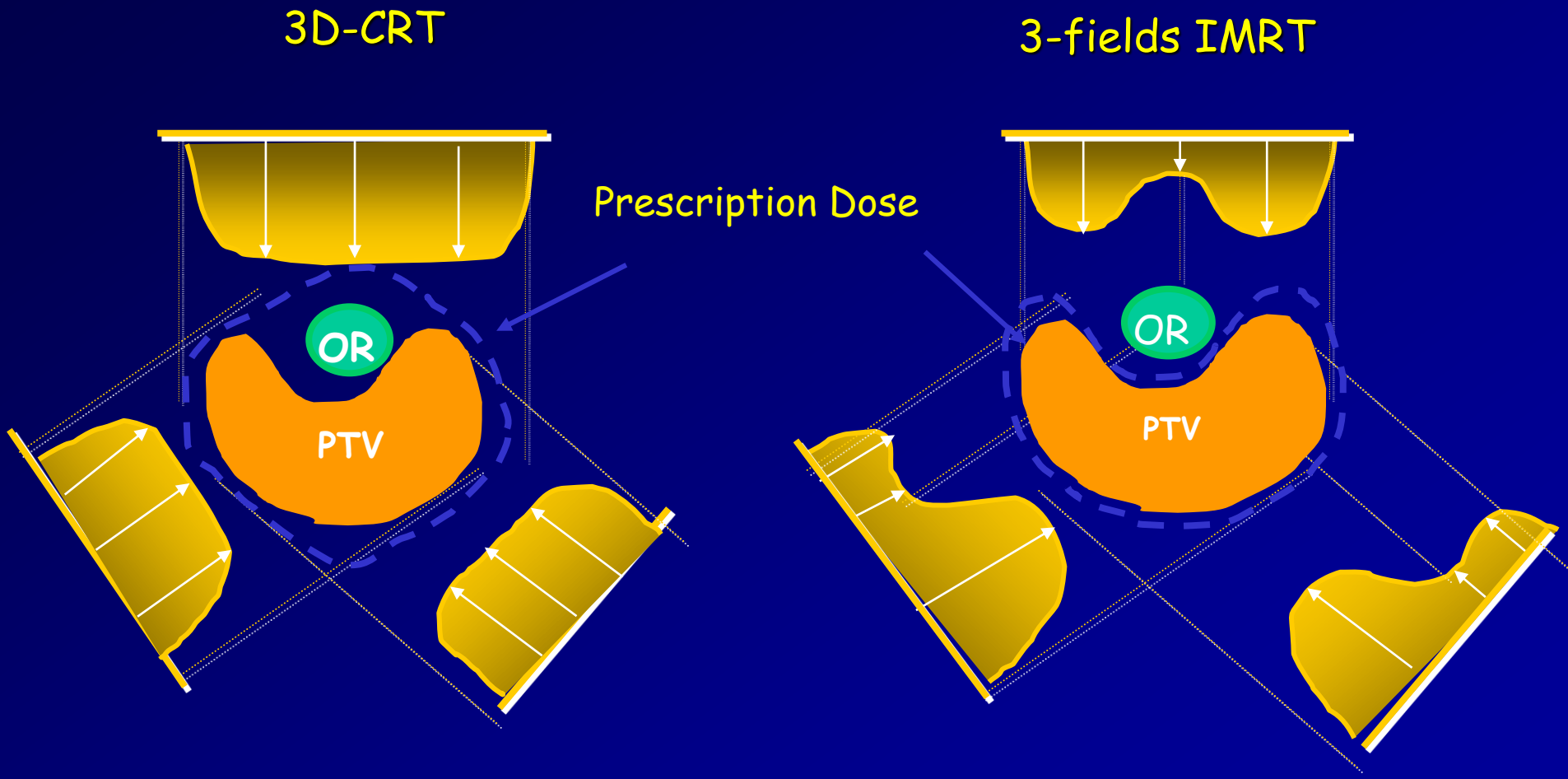
3D Conformal RT

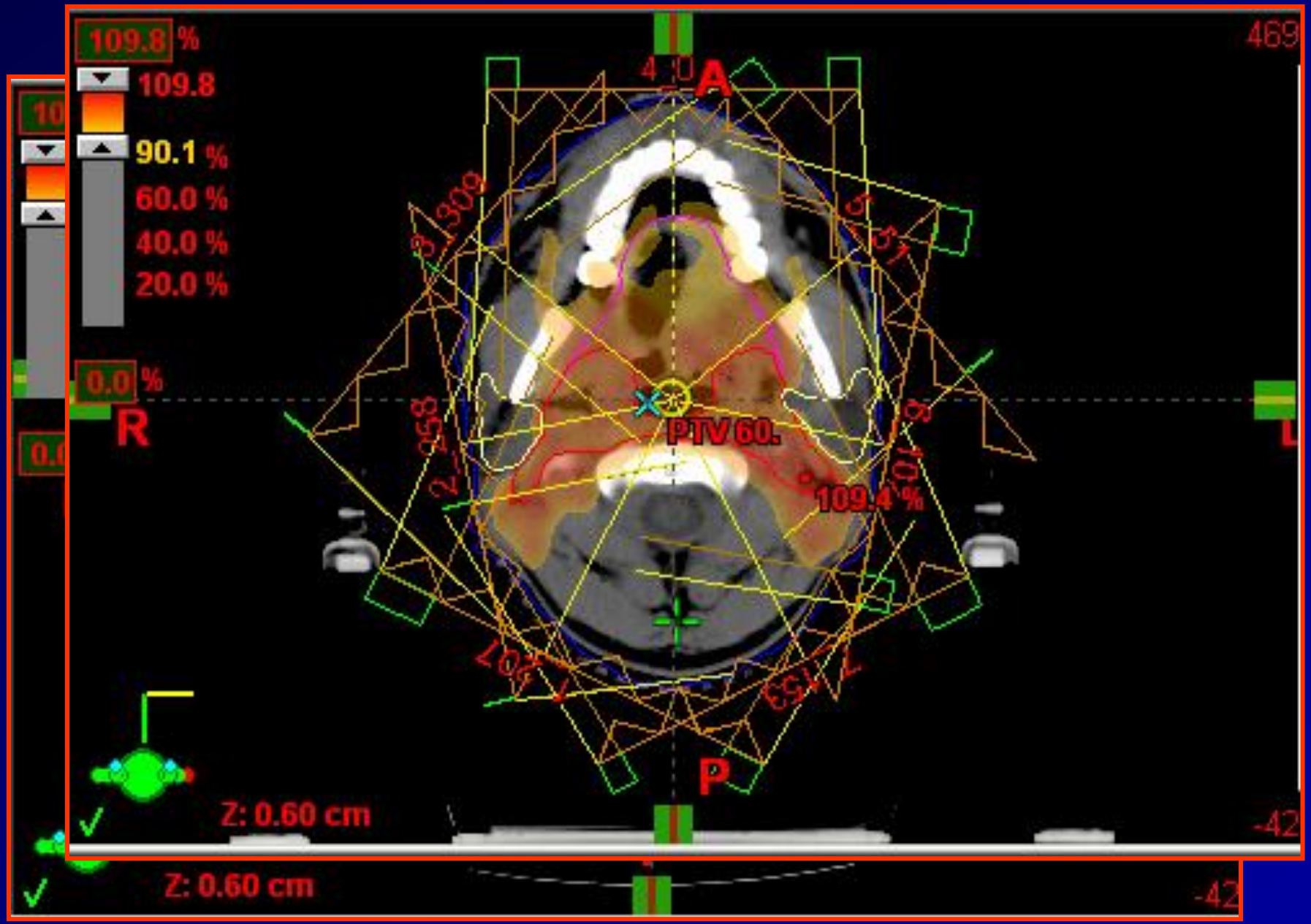


IMRT



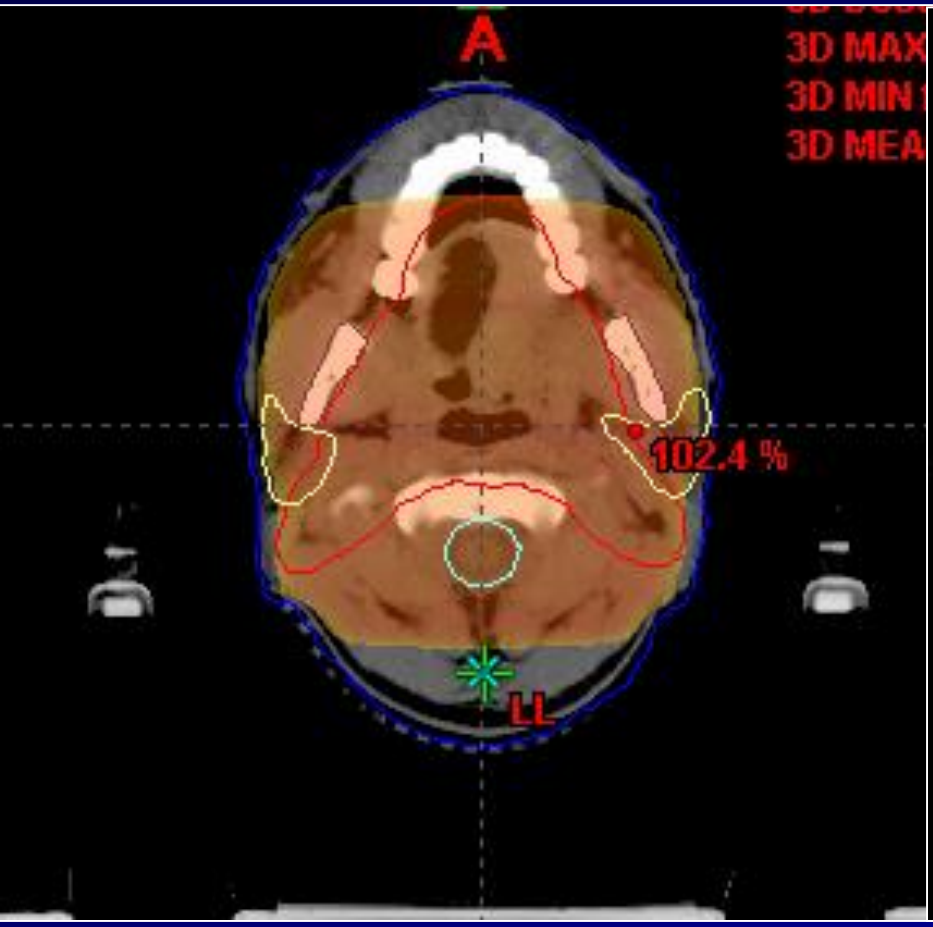
3D-CRT vs IMRT

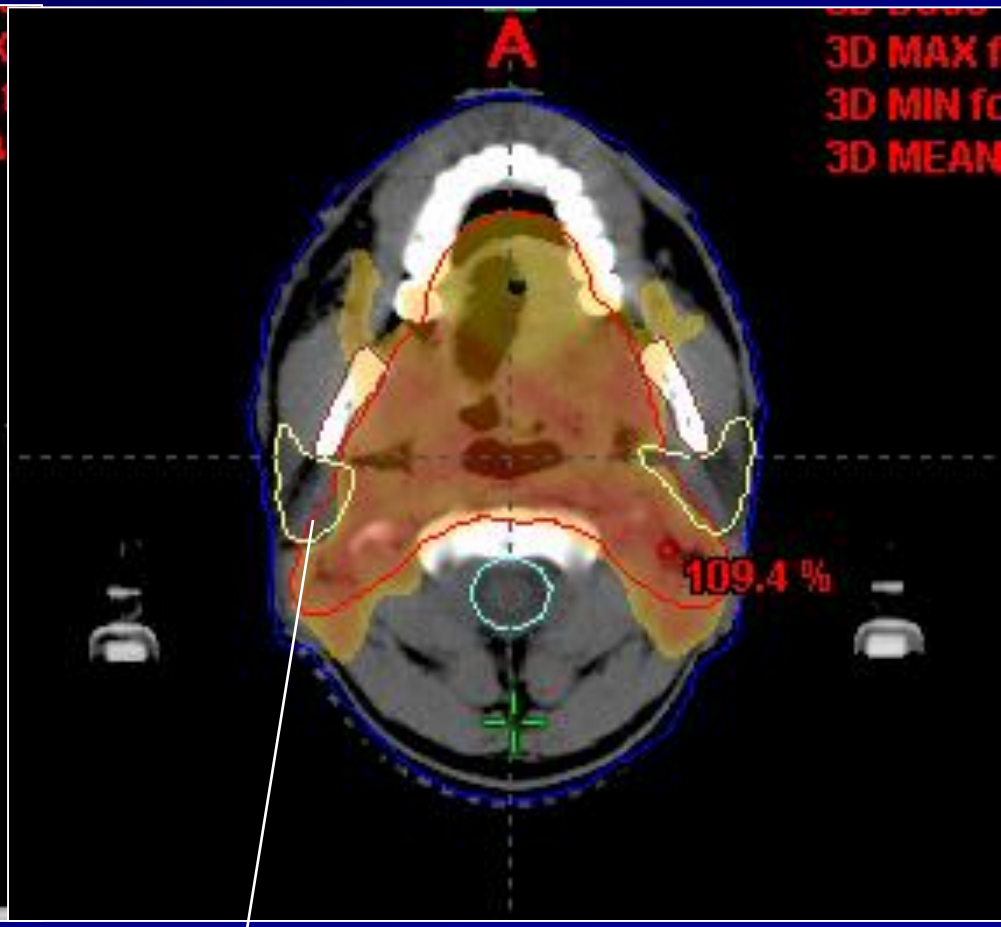



109.8 %
109.8
90.1 %
60.0 %
40.0 %
20.0 %
0.0 %
R
A
P
PTV 60.
109.4 %
Z: 0.60 cm
Z: 0.60 cm

3D-Conformal RT

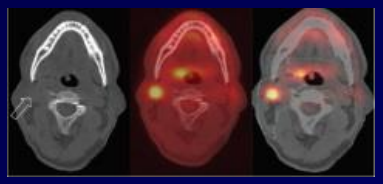
IMRT





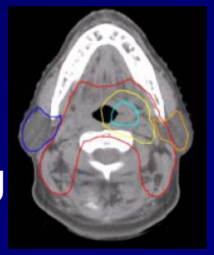
Parotid sparing

Imaging Treatment Planning Hardware

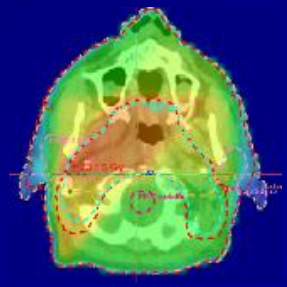


Localization

Contouring

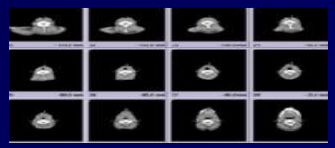


Dose prescription

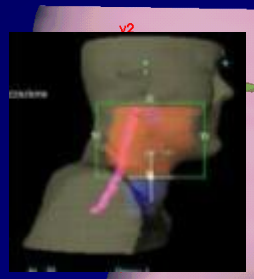


ImageFusion

Image acquisition

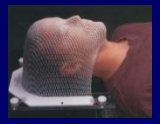


Targeting



Treatment technique

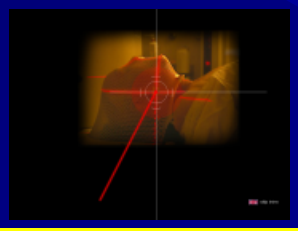
Immobilization Device



Dose evaluation

Export

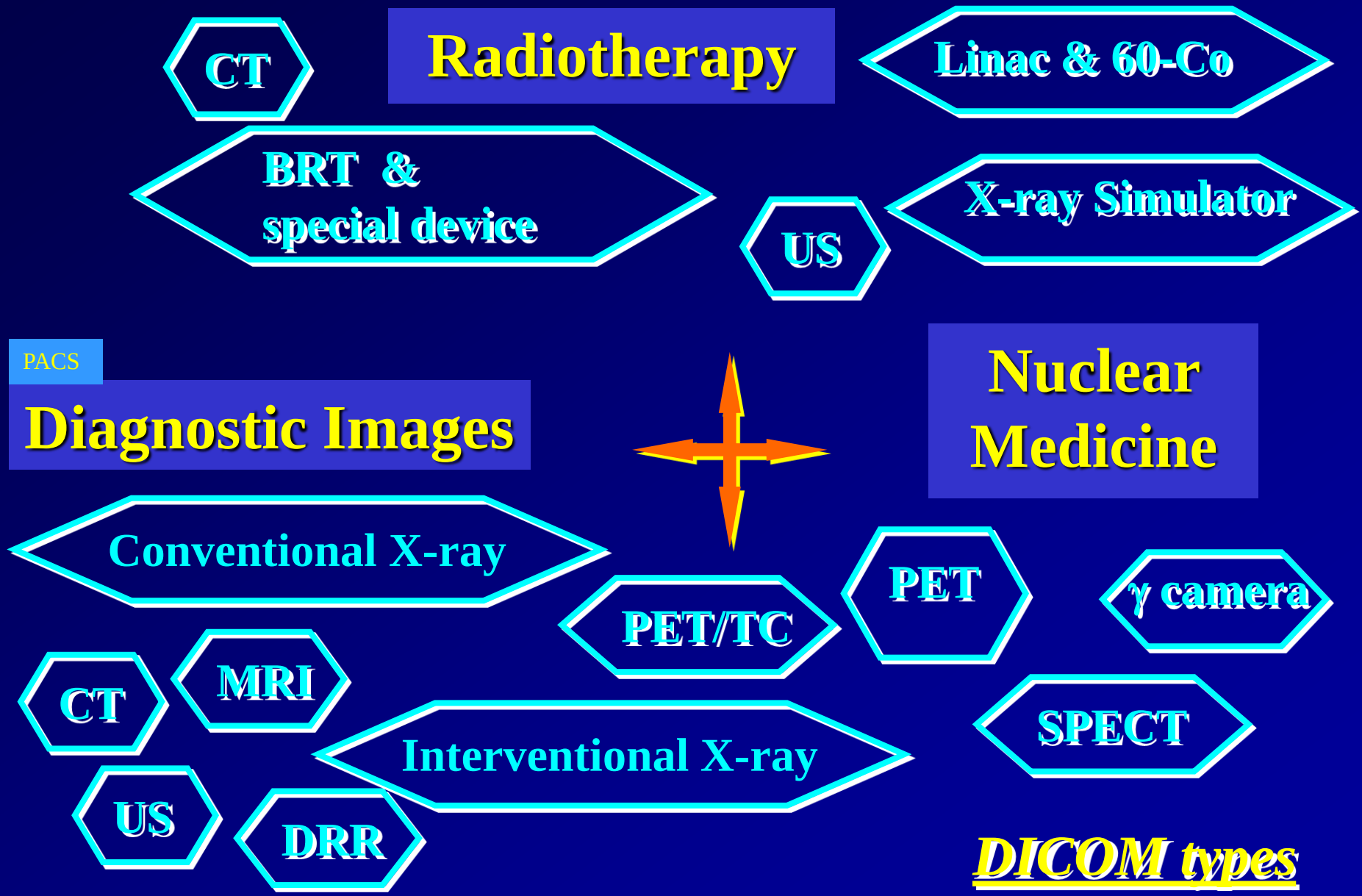
Treatment



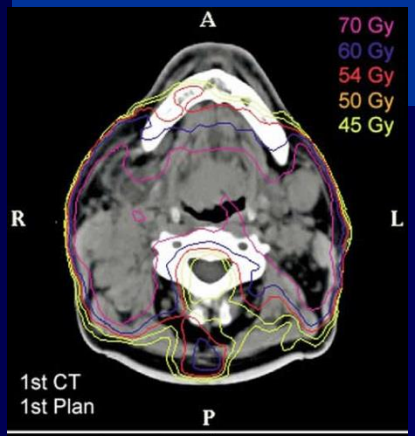
MLC/ MMLC

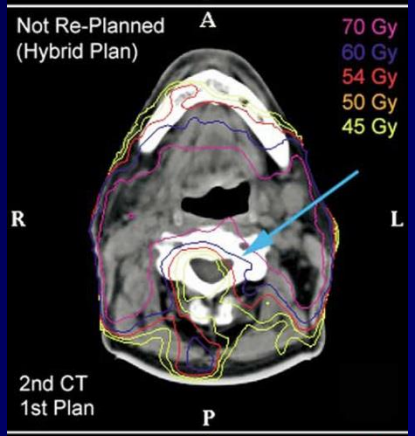
Patient set-up

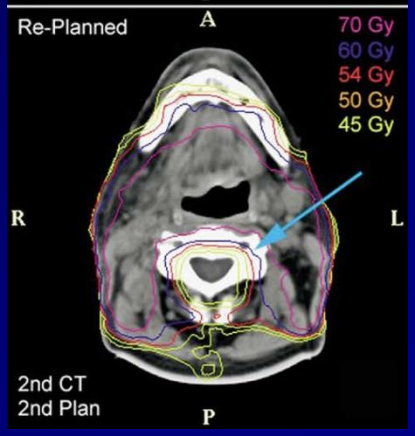
Diagnostic Images and Radiotherapy

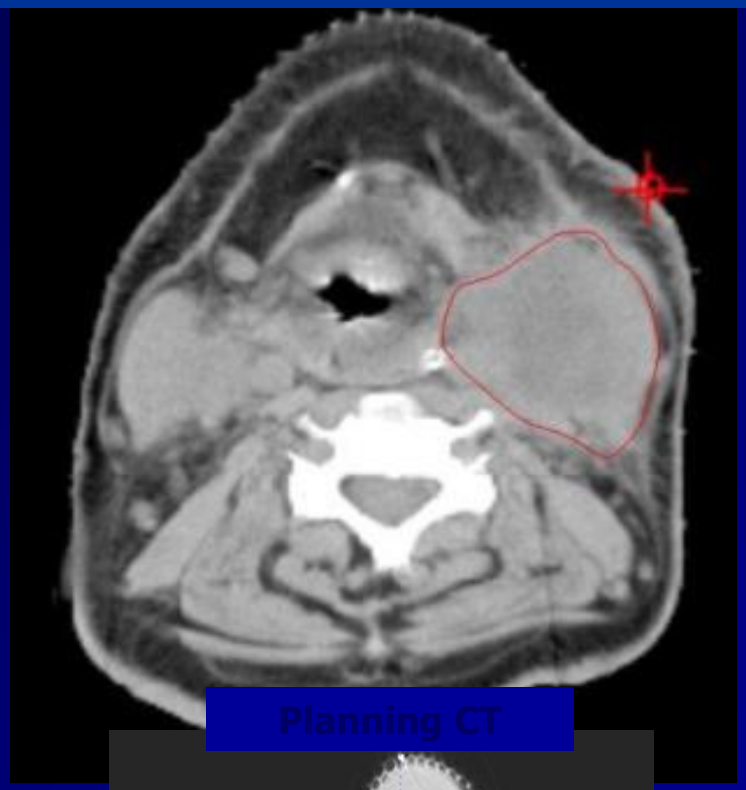


Physically Adapted Radiation Therapy

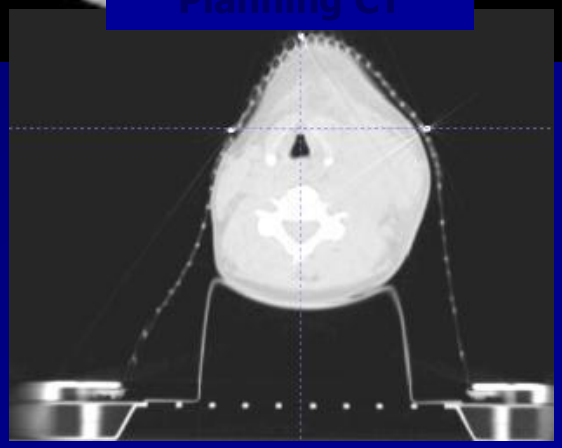


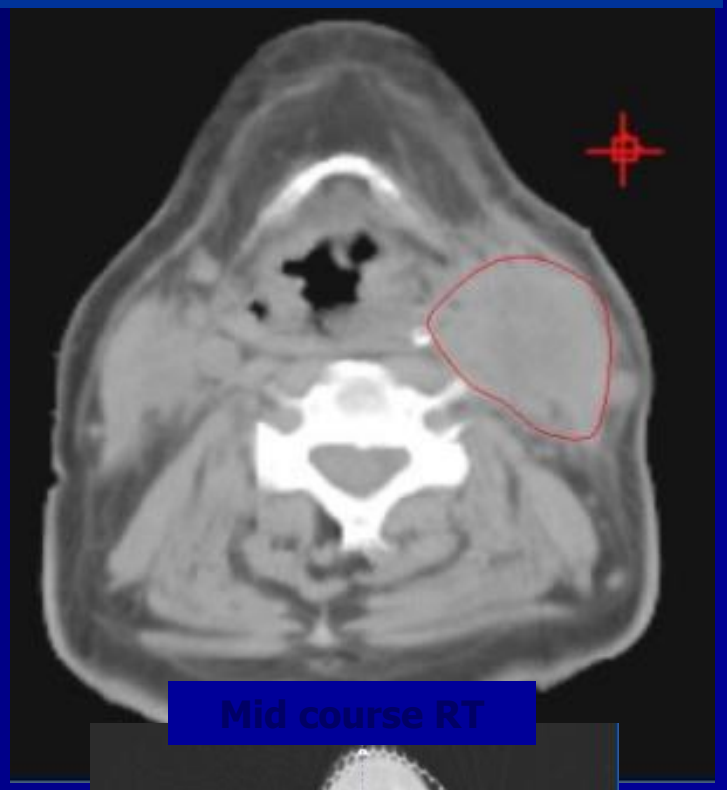




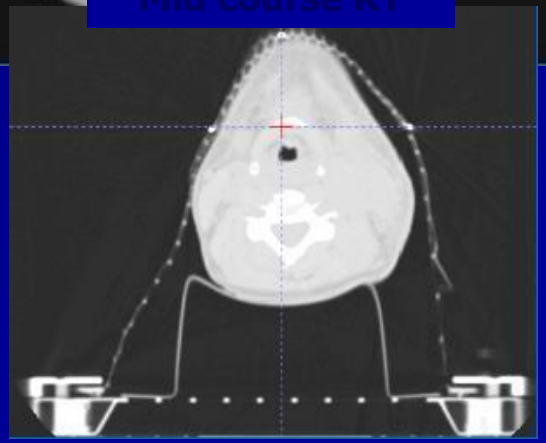


Planning CT





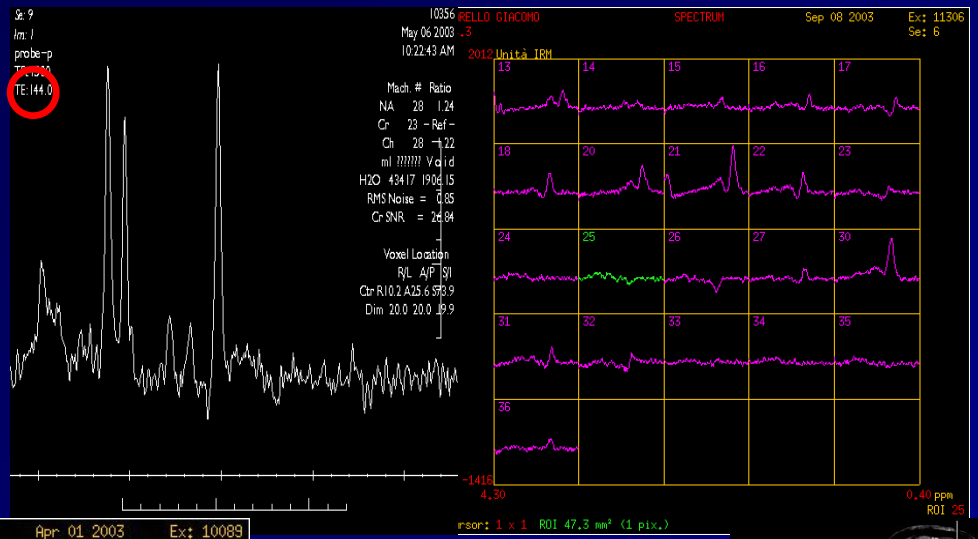
Mid course RT

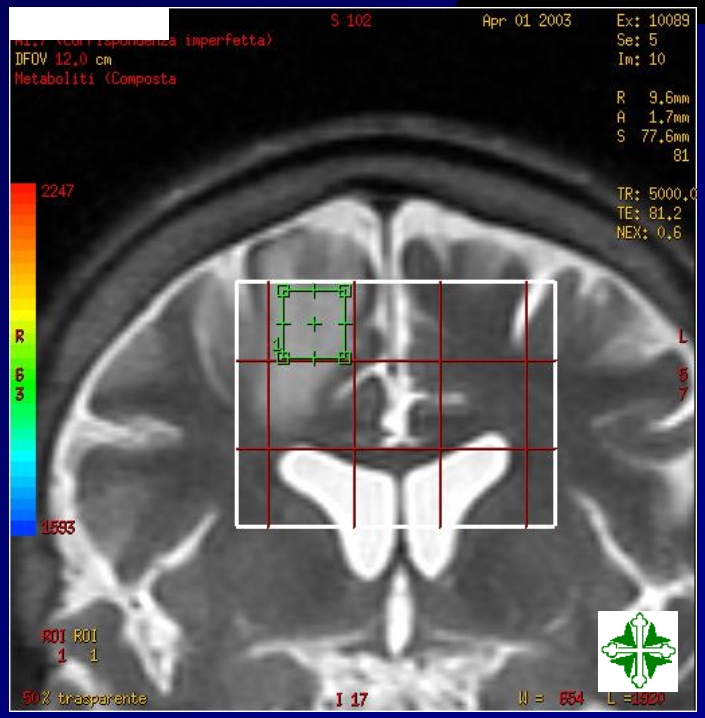


Morphofunctional imaging

Brain

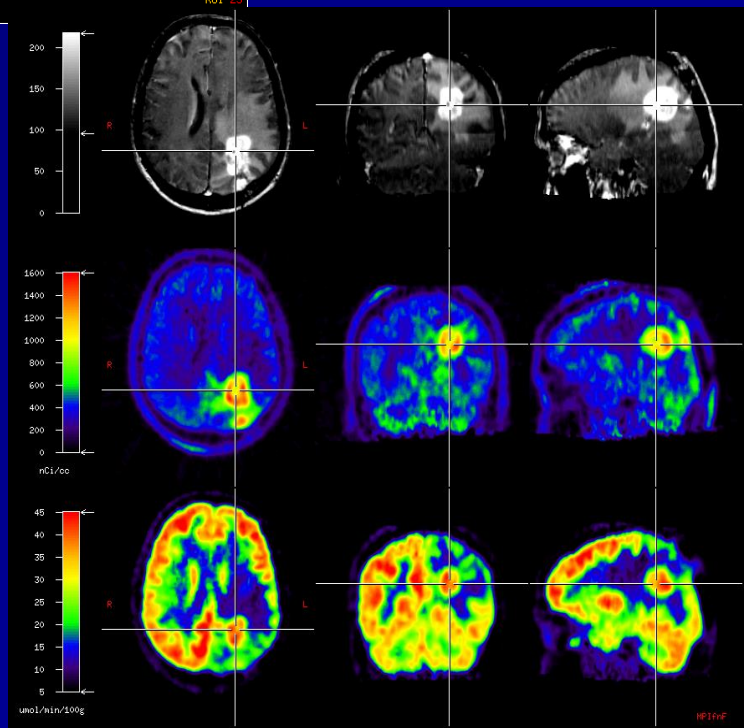
- Standard MRI imaging
- Spectroscopy on VOI



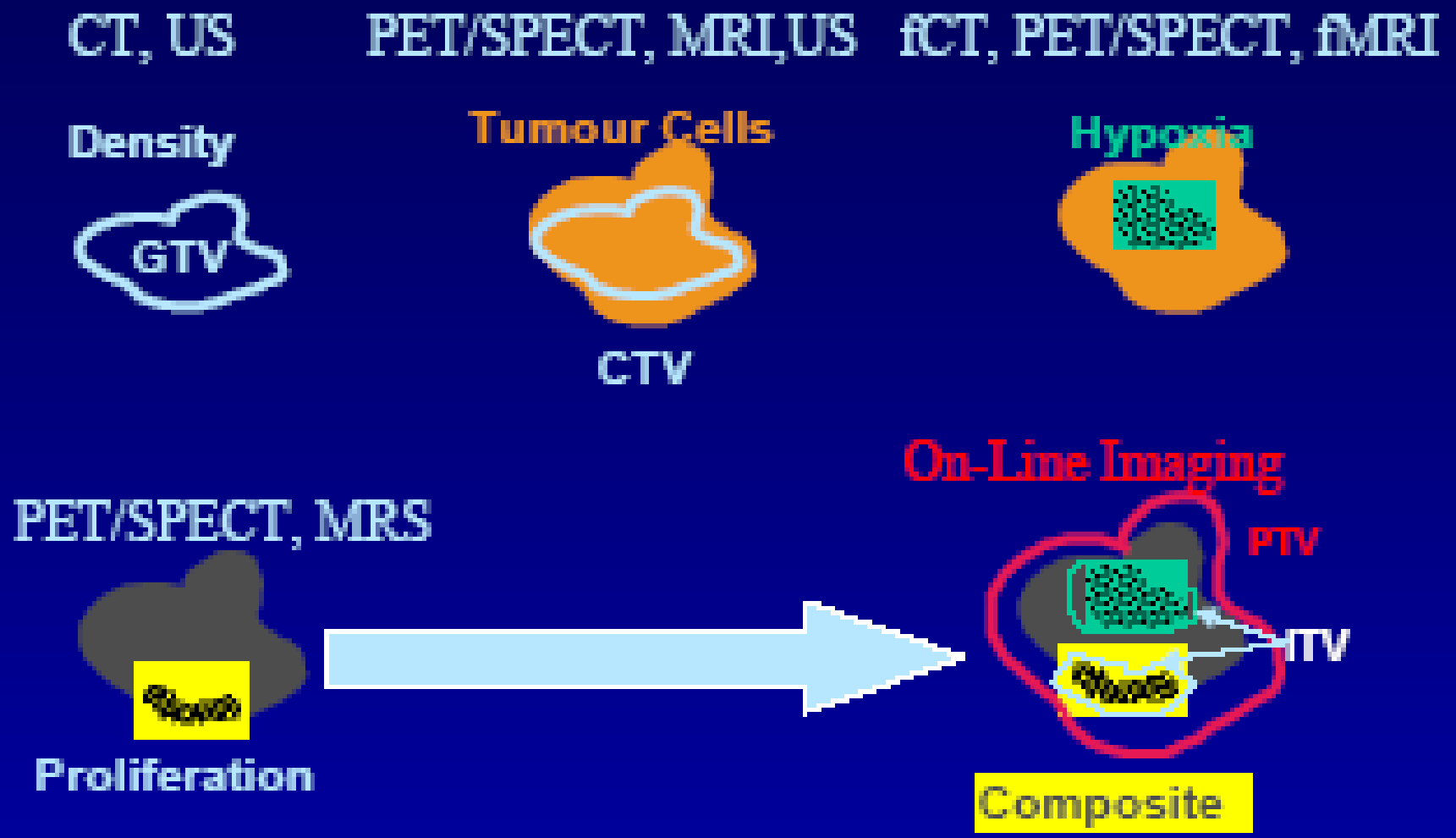


- Search of metaboilte peaks:

Myoinositol
Choline
Creatine
N-acetilaspartate
Lipids
Lactate

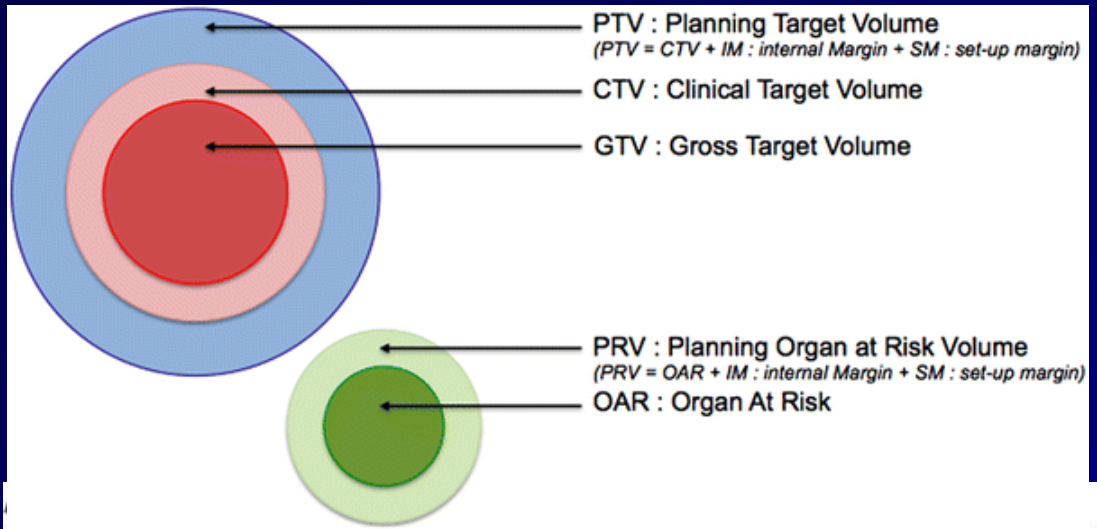


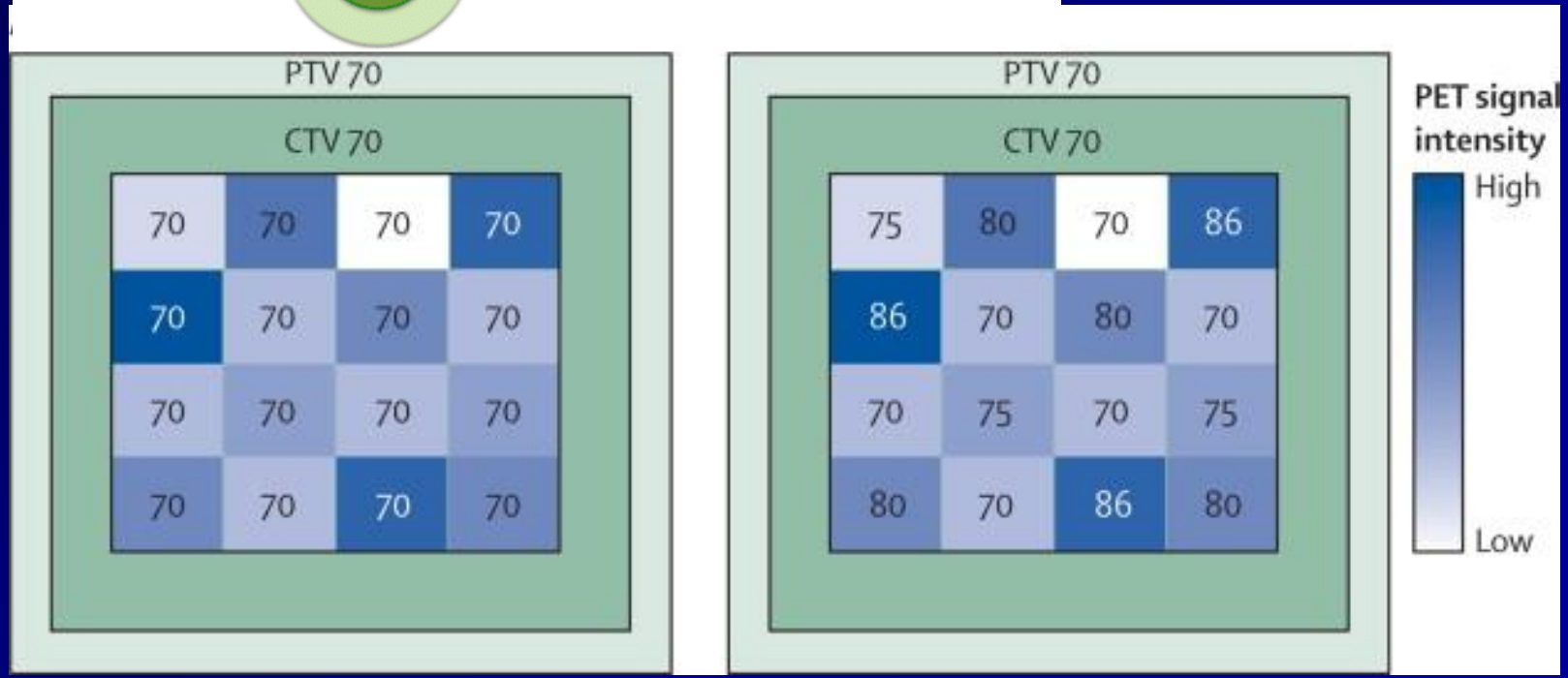
Biological Target Volume



Adapted from C. Ling et al...

Biologically Adapted Radiation Therapy





IMRT and dose-painting

Uptake Cu-diacetil-bis-metiltiosemicarbazone

GRAY CANCER INSTITUTE

SMB 07/04

^{60}Cu-ATSM guided IMRT

K.S.Clifford Chao et al. *IJROBP* 49: 1171 (2001)

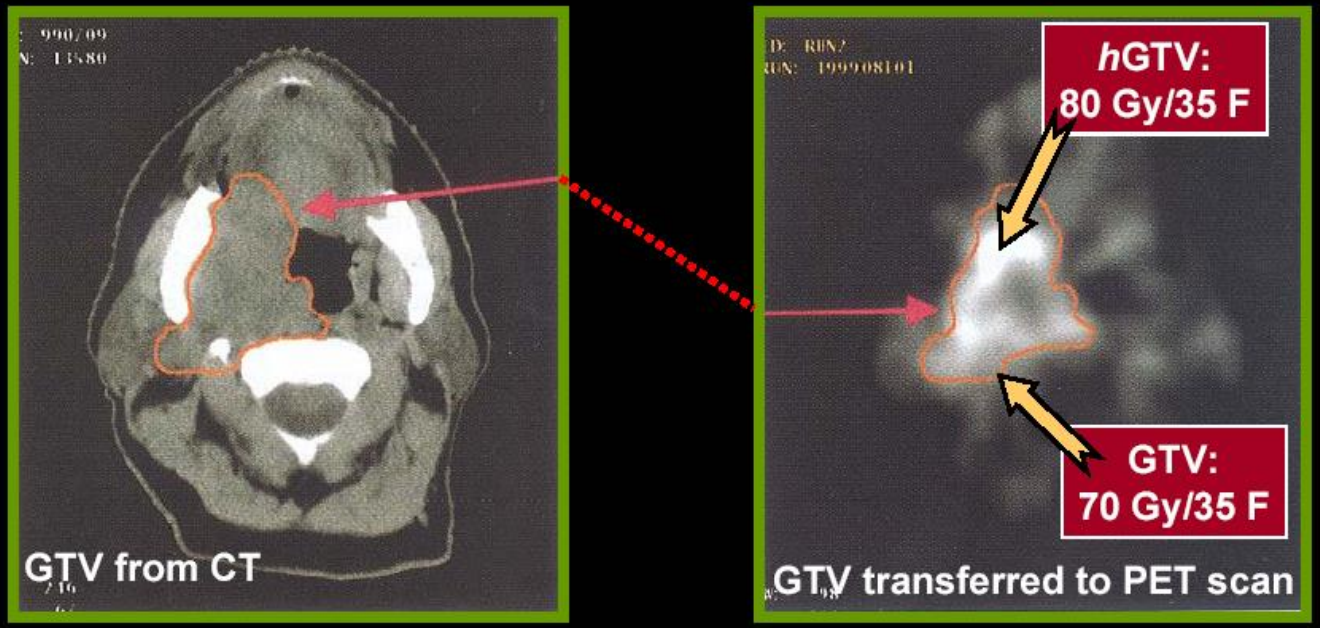


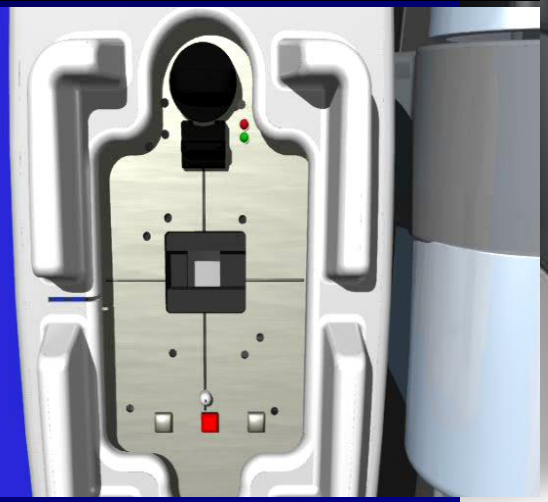
Image –Guided IMRT

Pencil Beam

Fan Beam

Cone Beam

On-Board kV Imaging Technology

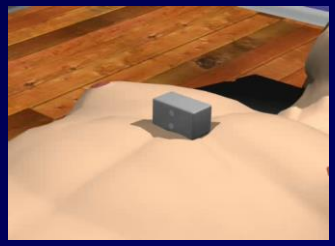


kV X-ray tube

kV On-Board Image Detector

PortalVision MV Imager

4D “gated” treatment



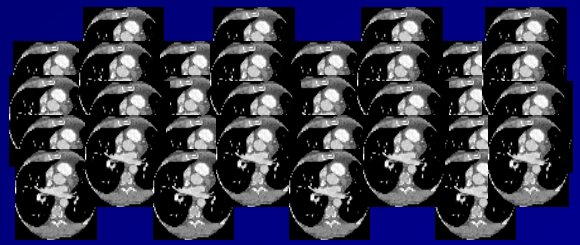
“Image acquired” signal to RPM system

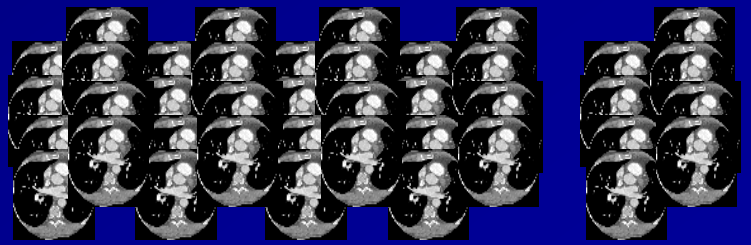
X-ray on

First couch position

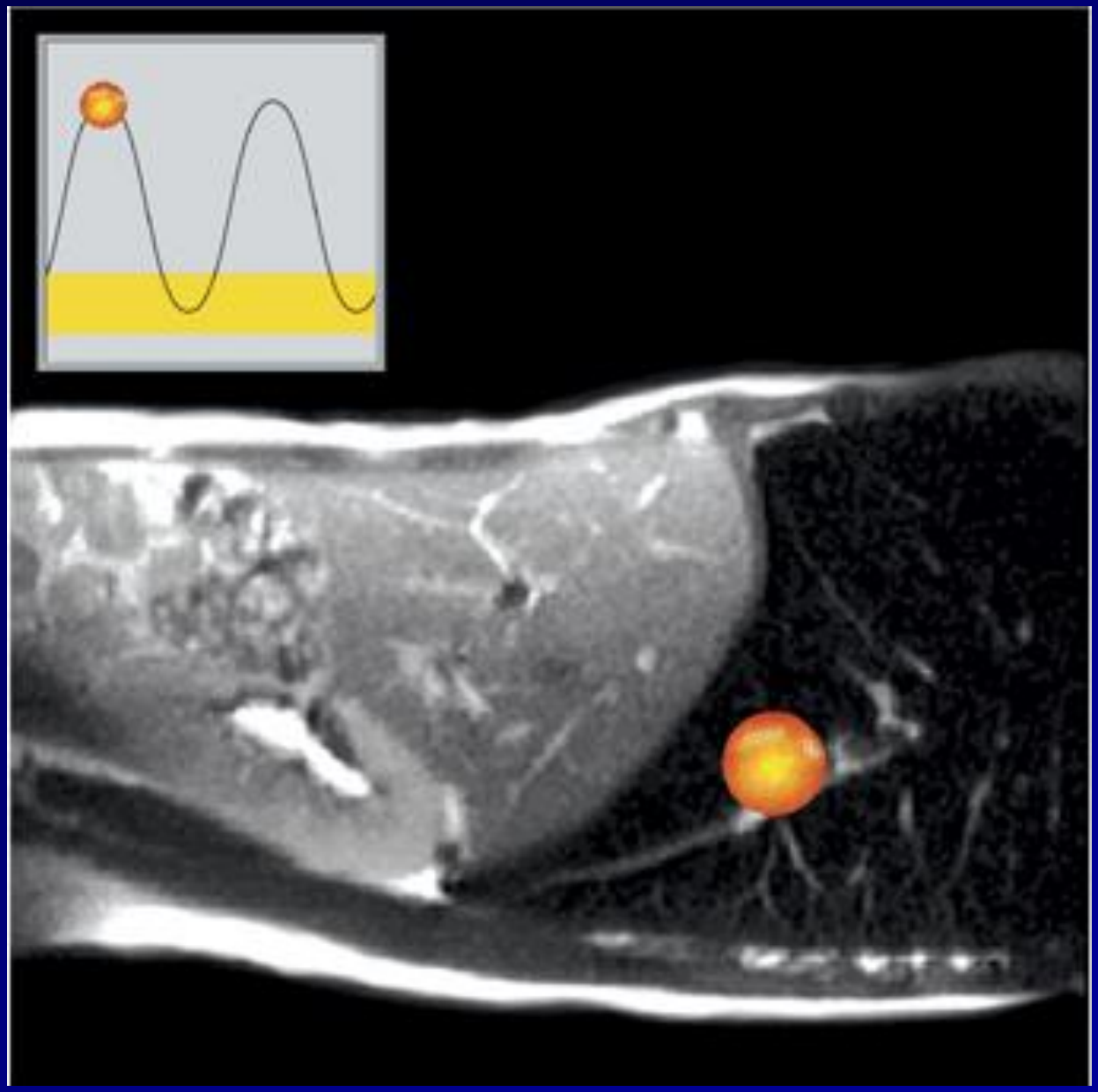
Second couch position

Third couch position

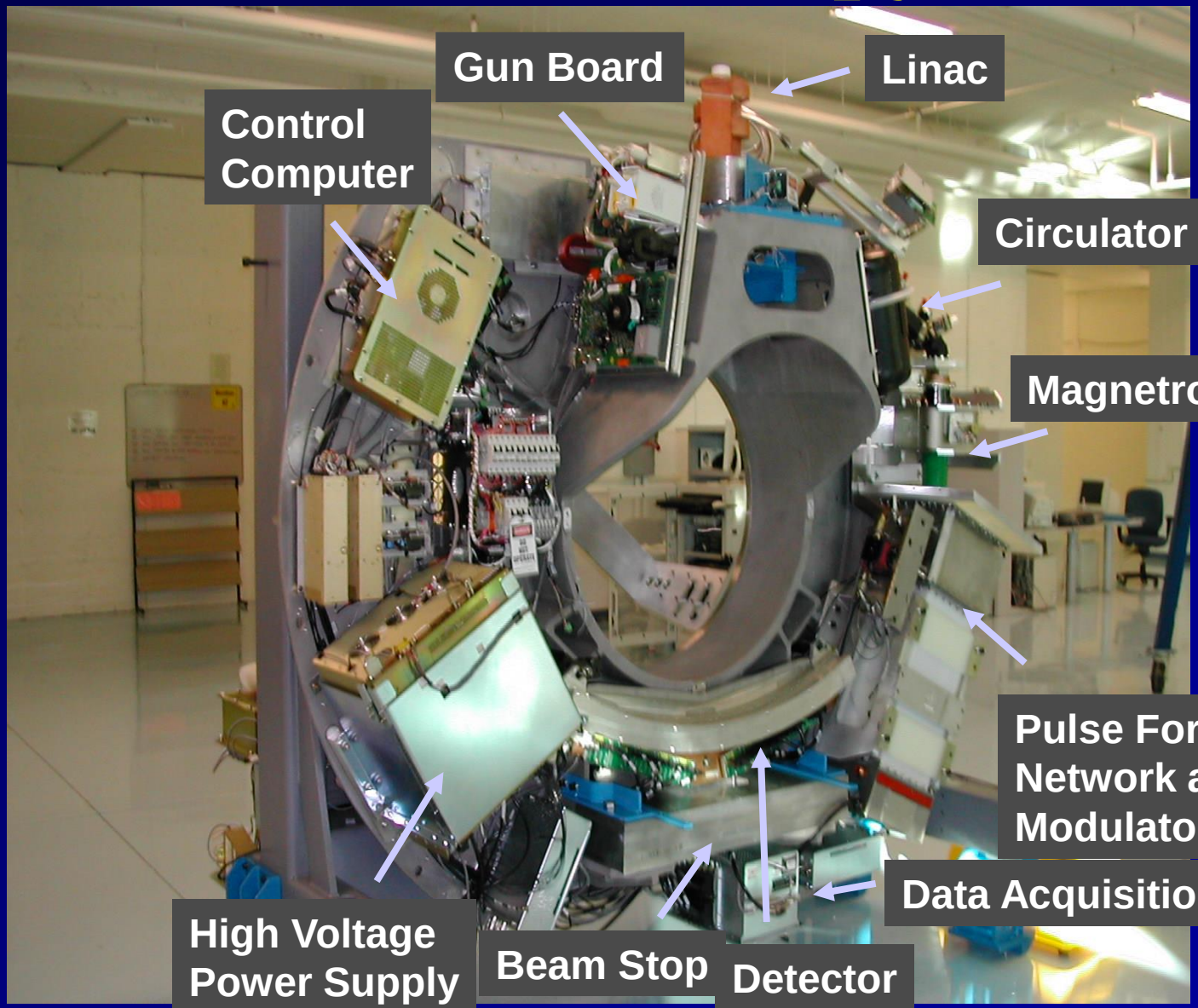




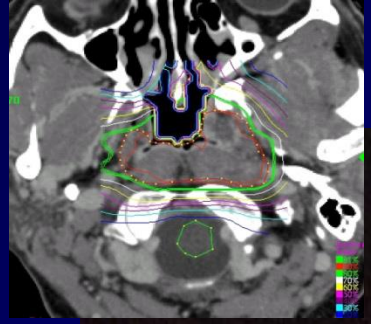
Respiratory Gating

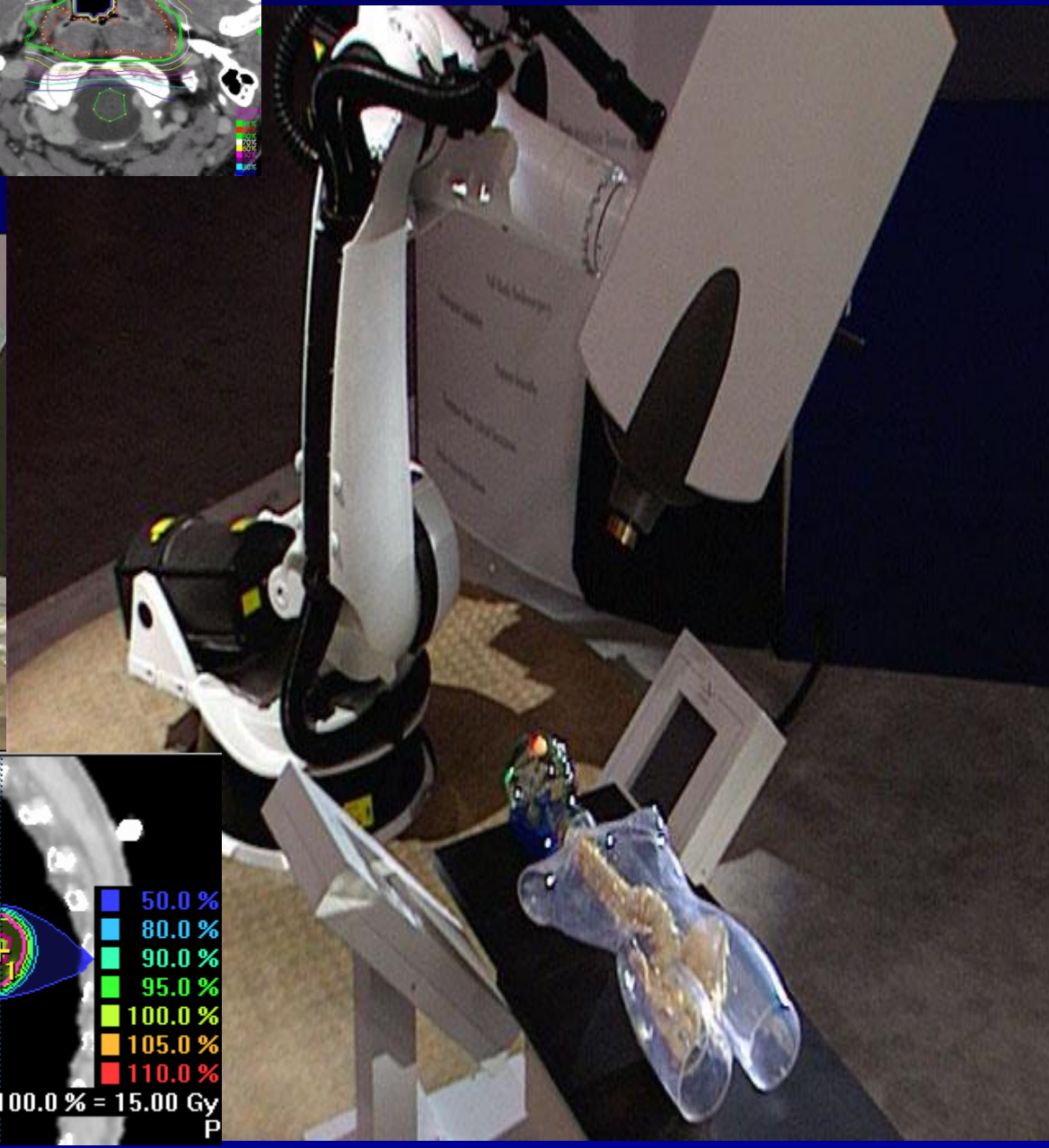


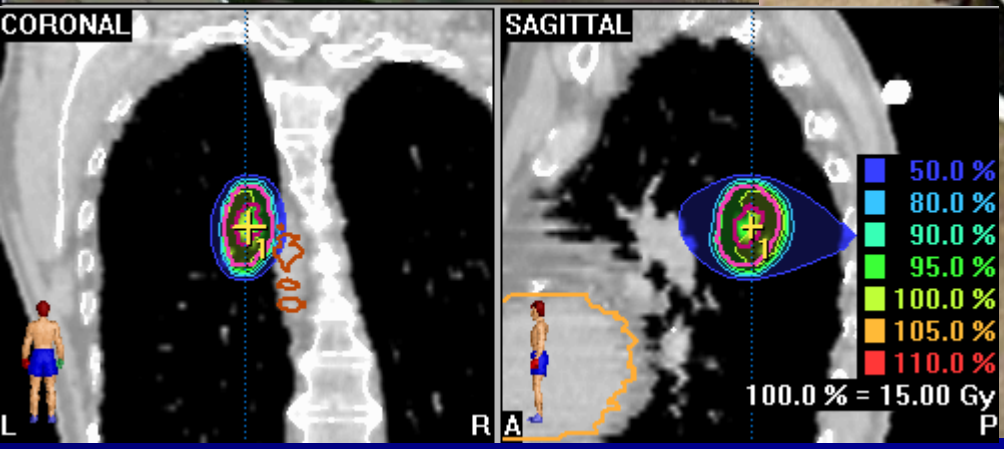
Tomotherapy



Cyberknife



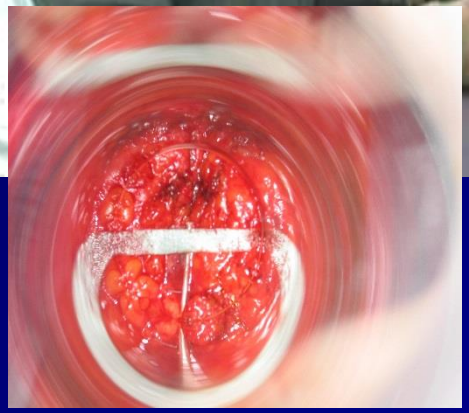


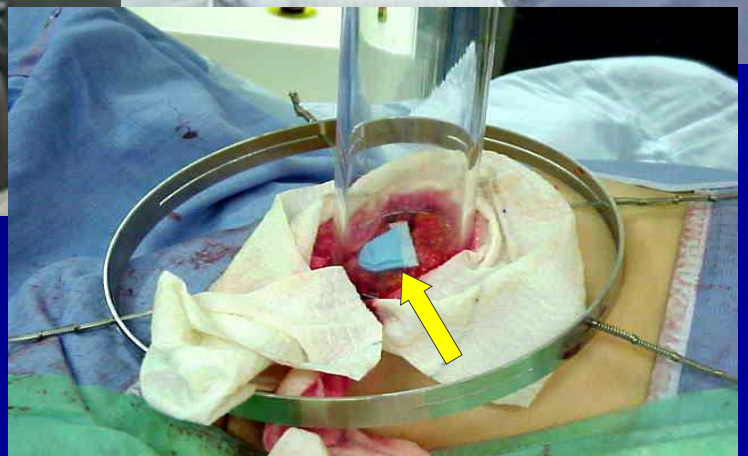

CORONAL
L
R

SAGITTAL
50.0 %
80.0 %
90.0 %
95.0 %
100.0 %
105.0 %
110.0 %
100.0 % = 15.00 Gy
A
P

Linac Dedicati

IOERT

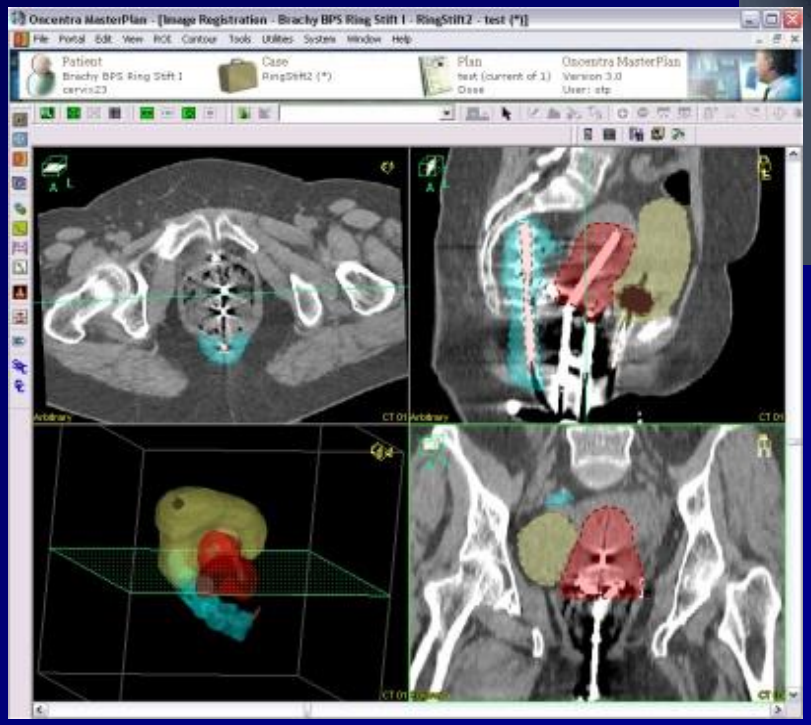




Brachytherapy. Key components

HDR/PDR/LDR Afterloader

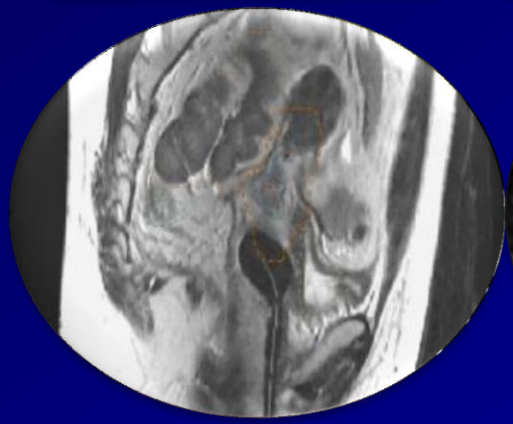
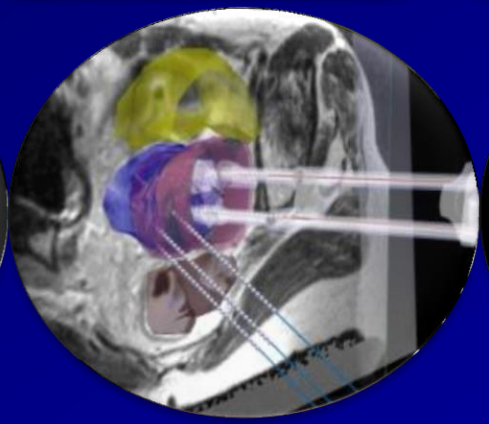
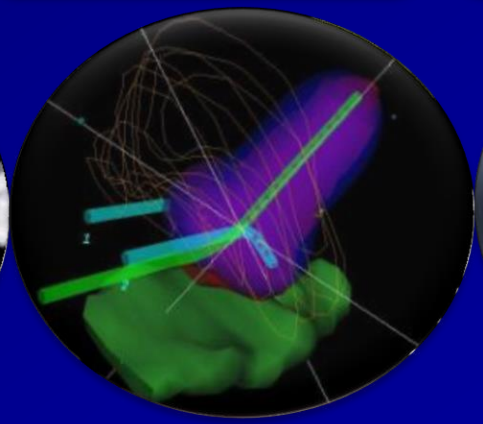
Treatment planning software



Specialized applicators

Process of BRT precision treatment

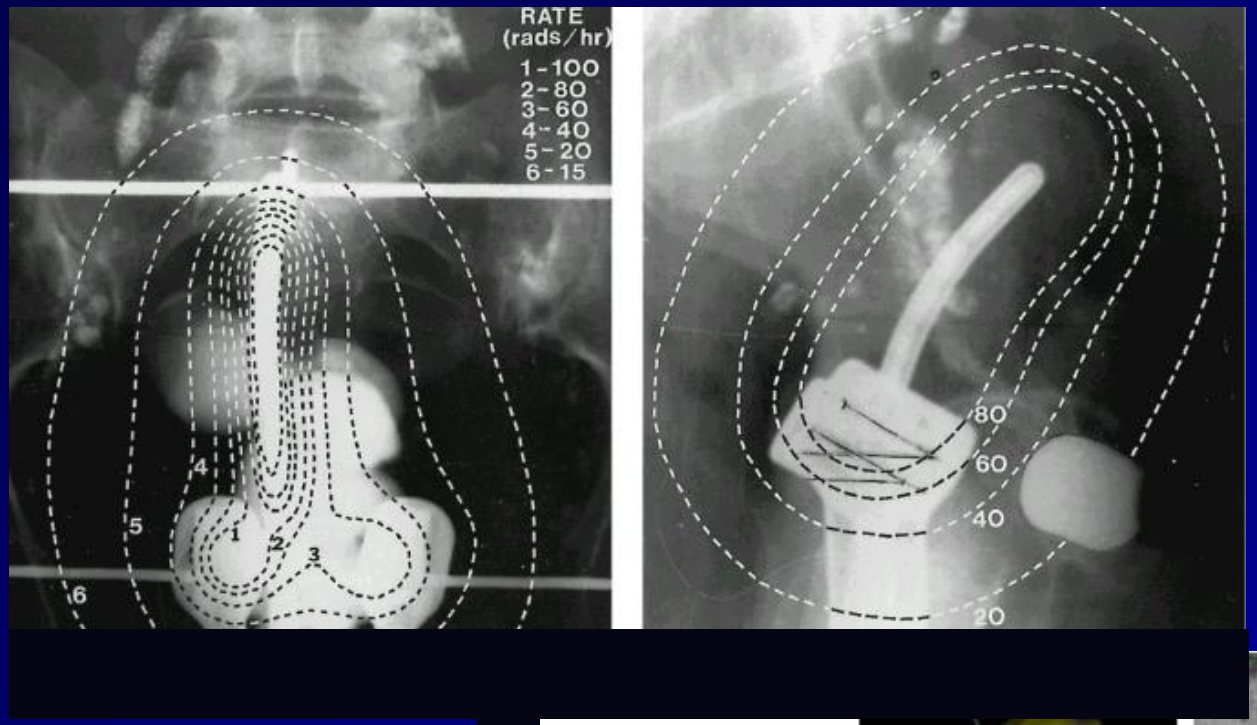
Imaging	Applicator implant	Optimizing treatment plan	Delivery
Clinical examination and tumor imaging	Source applicators placed in body for accurate positioning	Create virtual patient via visualization and refine	Sources delivered to treatment site via applicators

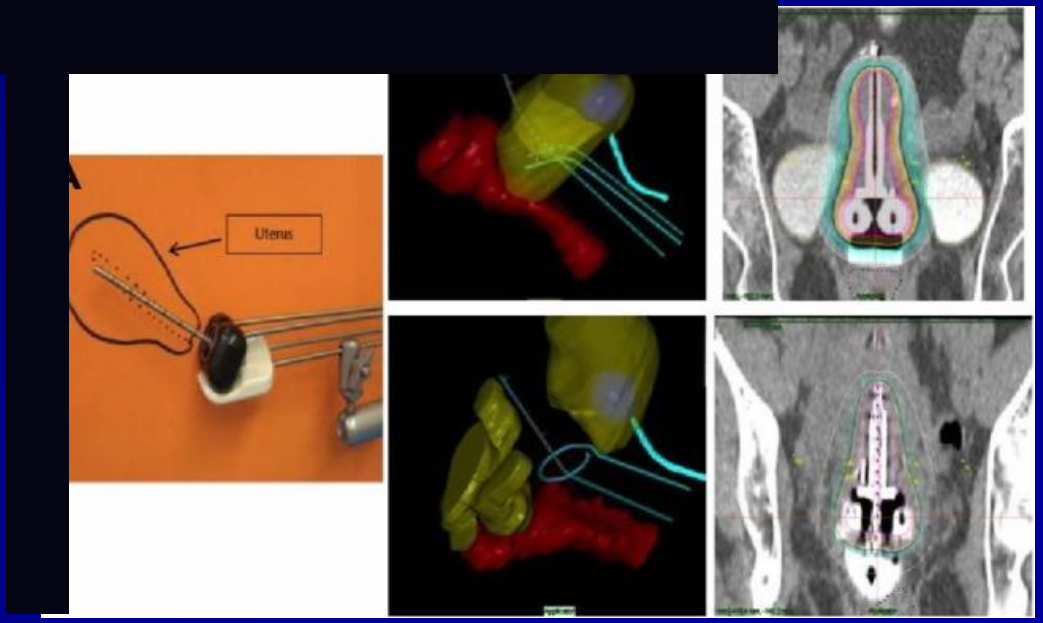





Features of cervical BRT: placement, duration, dose rate

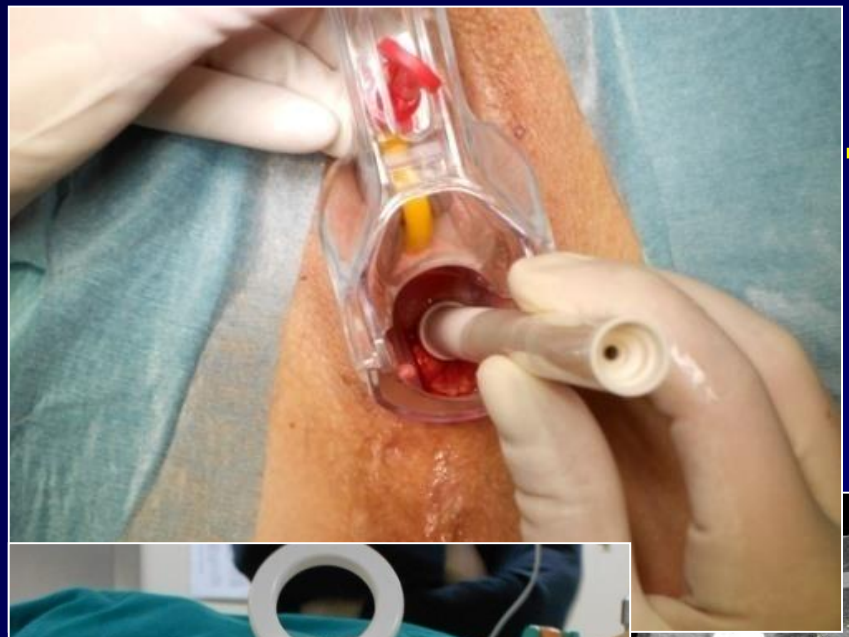
Characteristic	Type	Description
Source placement	Interstitial	Source placed within the tumor
	Intracavitary	Source placed next to the tumor
Duration	Temporary	Source implanted for specific treatment duration
Dose rate	Low (LDR)	<0.4 Gy/hour
	High (HDR)	> 12 Gy /hour
	Pulsed (PDR)	0.4-2 Gy/hour

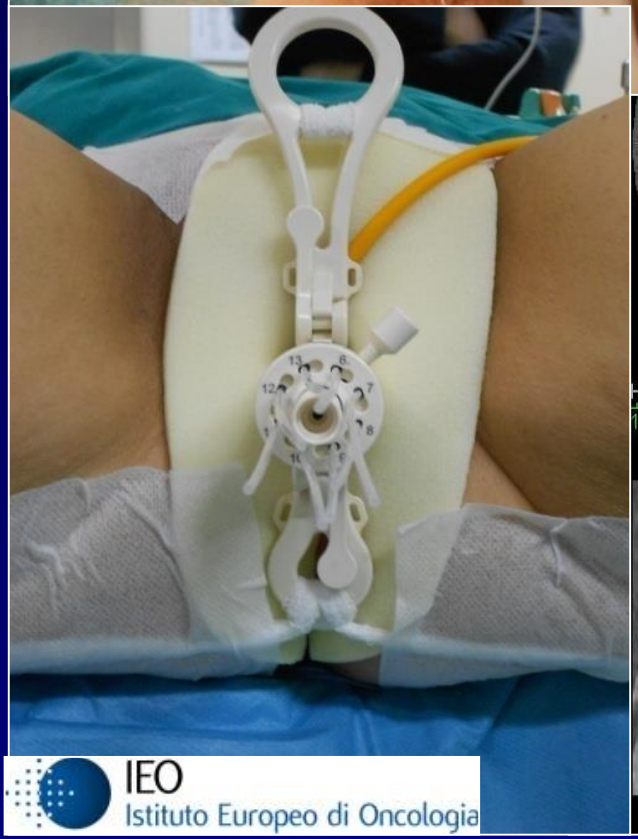
Intracavitary implant

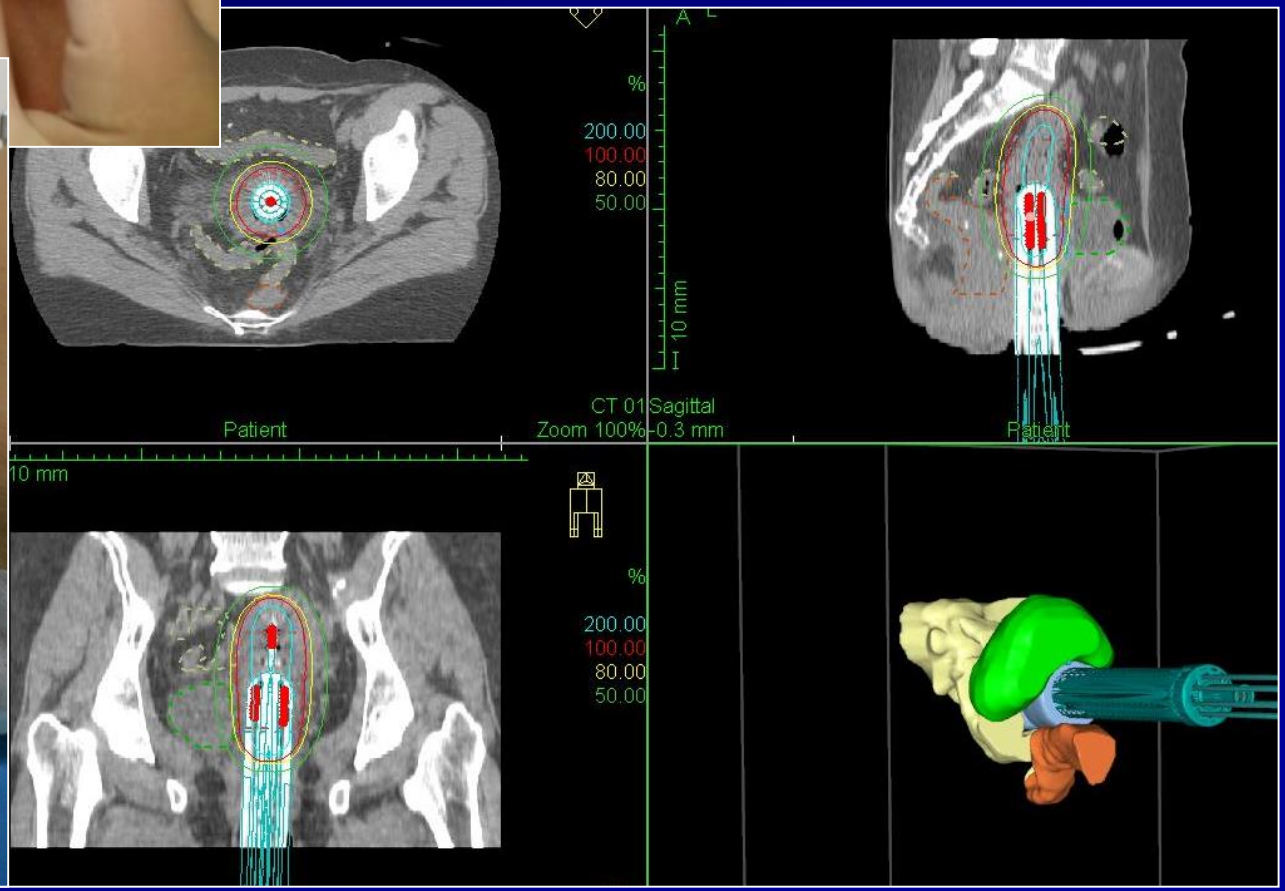




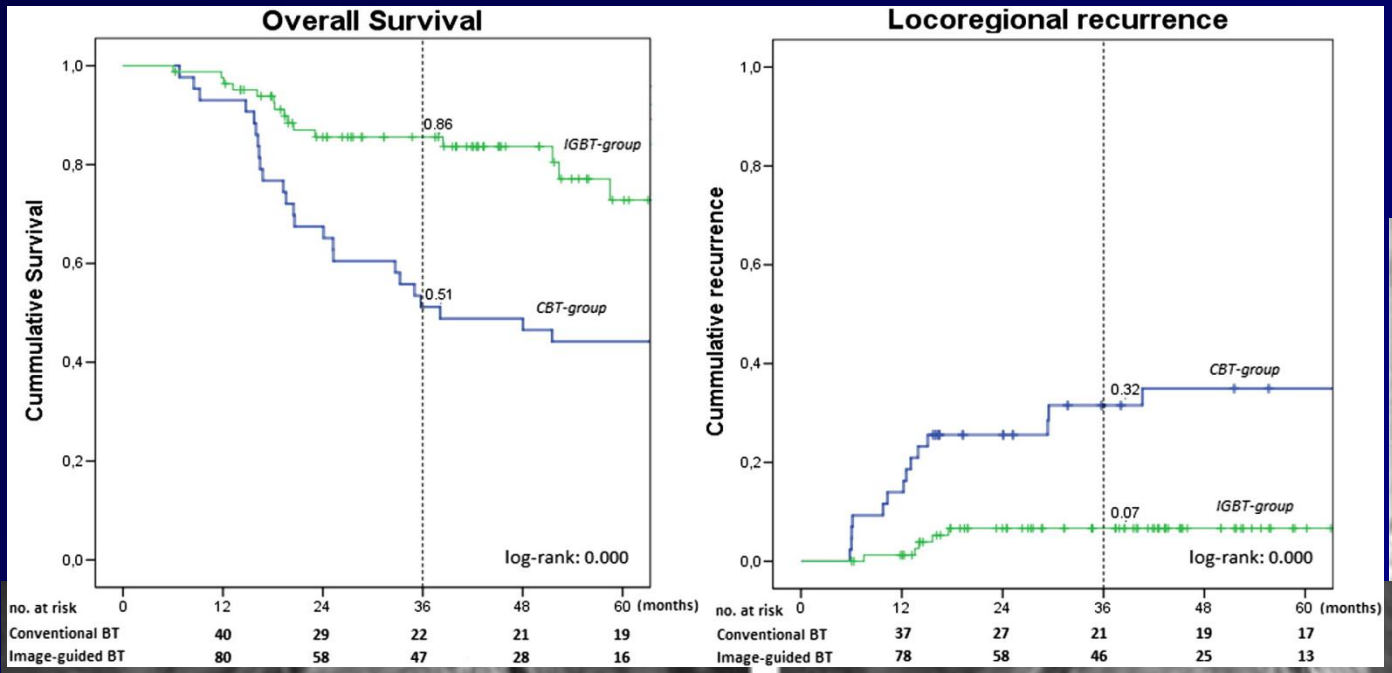
Tandem and cylinder (Multichannel)

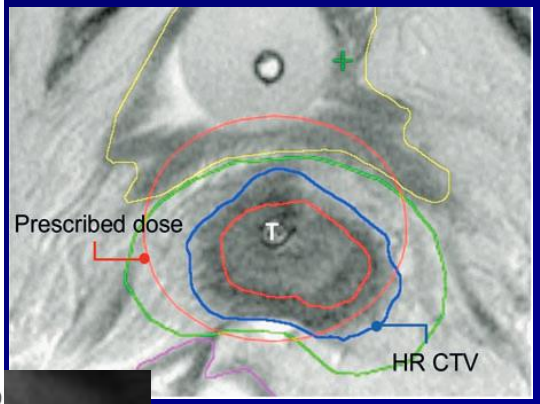


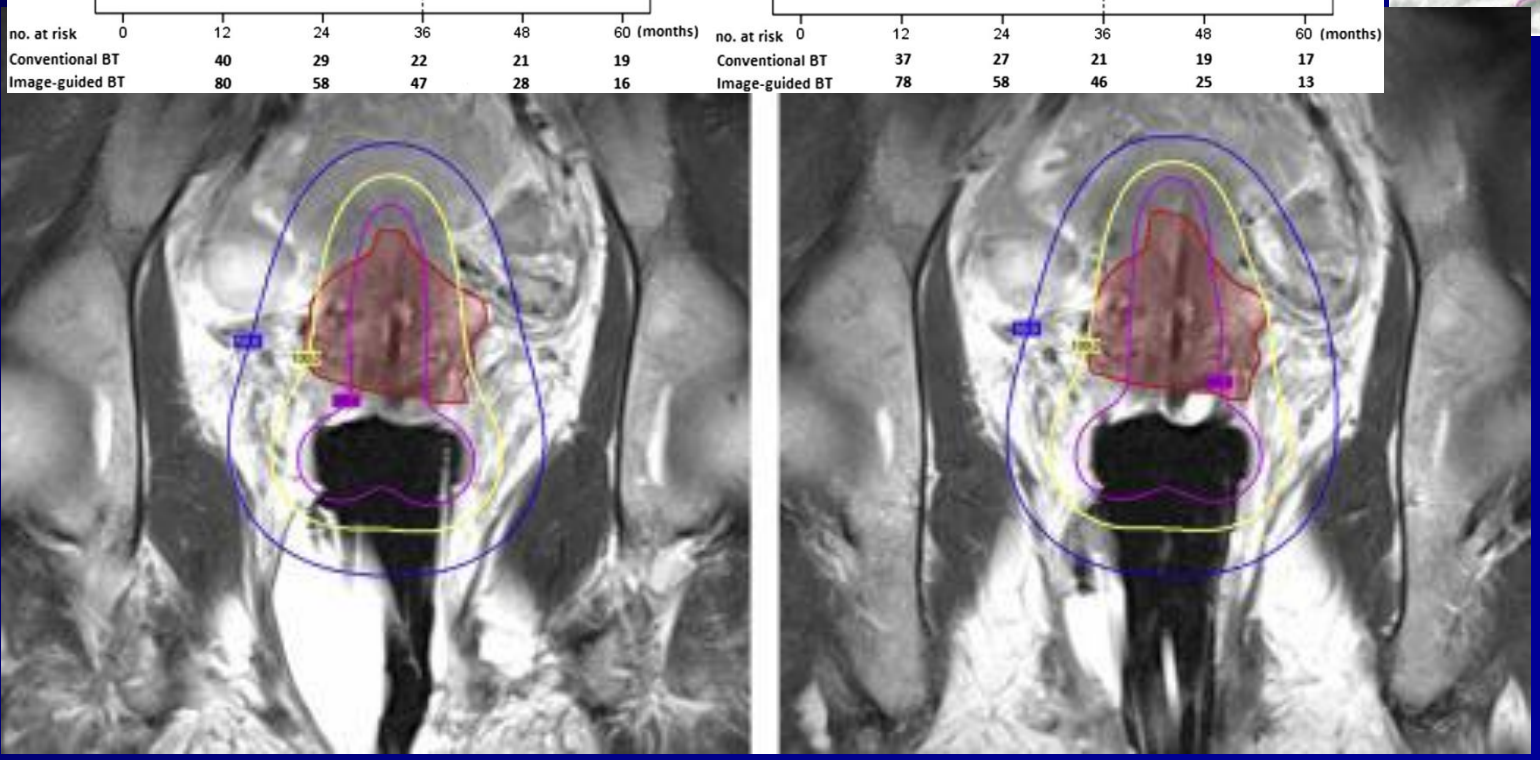




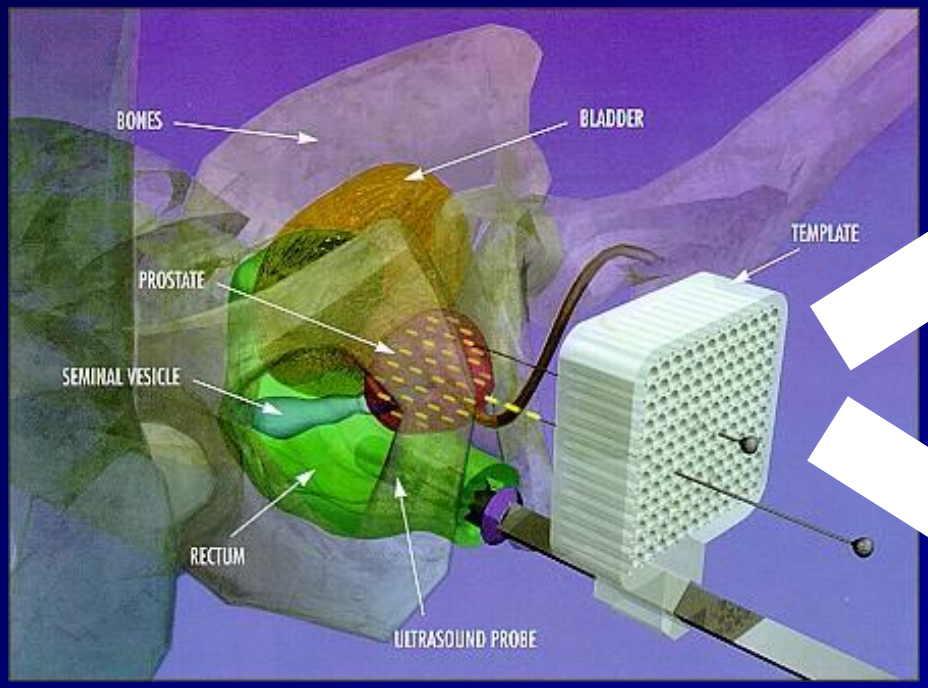
IEO
Istituto Europeo di Oncologia

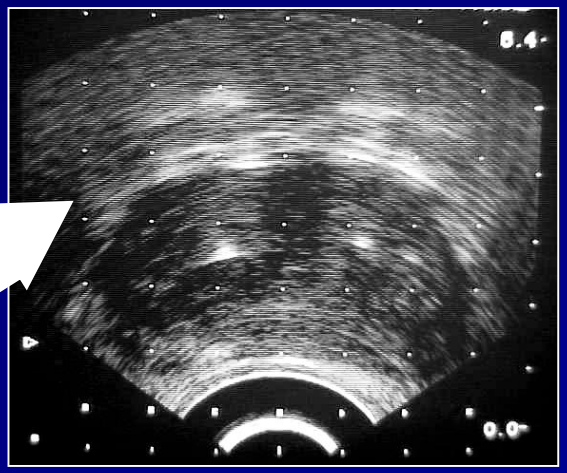

Overall Survival
Cummulative Survival
1,0
0,8
0,6
0,4
0,2
0,0
0.86
IGBT-group
0.51
CBT-group
log-rank: 0.000
no. at risk 0 12 24 36 48 60 (months)
Conventional BT 40 29 22 21 19
Image-guided BT 80 58 47 28 16
Locoregional recurrence
Cummulative recurrence
CBT-group
0.32
0.07
IGBT-group
log-rank: 0.000
no. at risk 0 12 24 36 48 60 (months)
Conventional BT 37 27 21 19 17
Image-guided BT 78 58 46 25 13

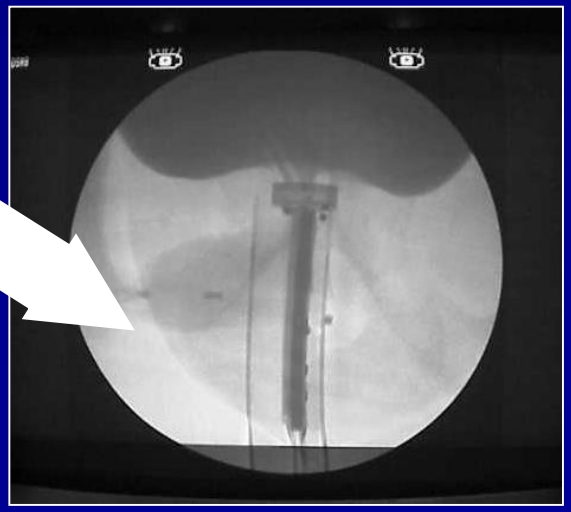

Prescribed dose
T
HR CTV

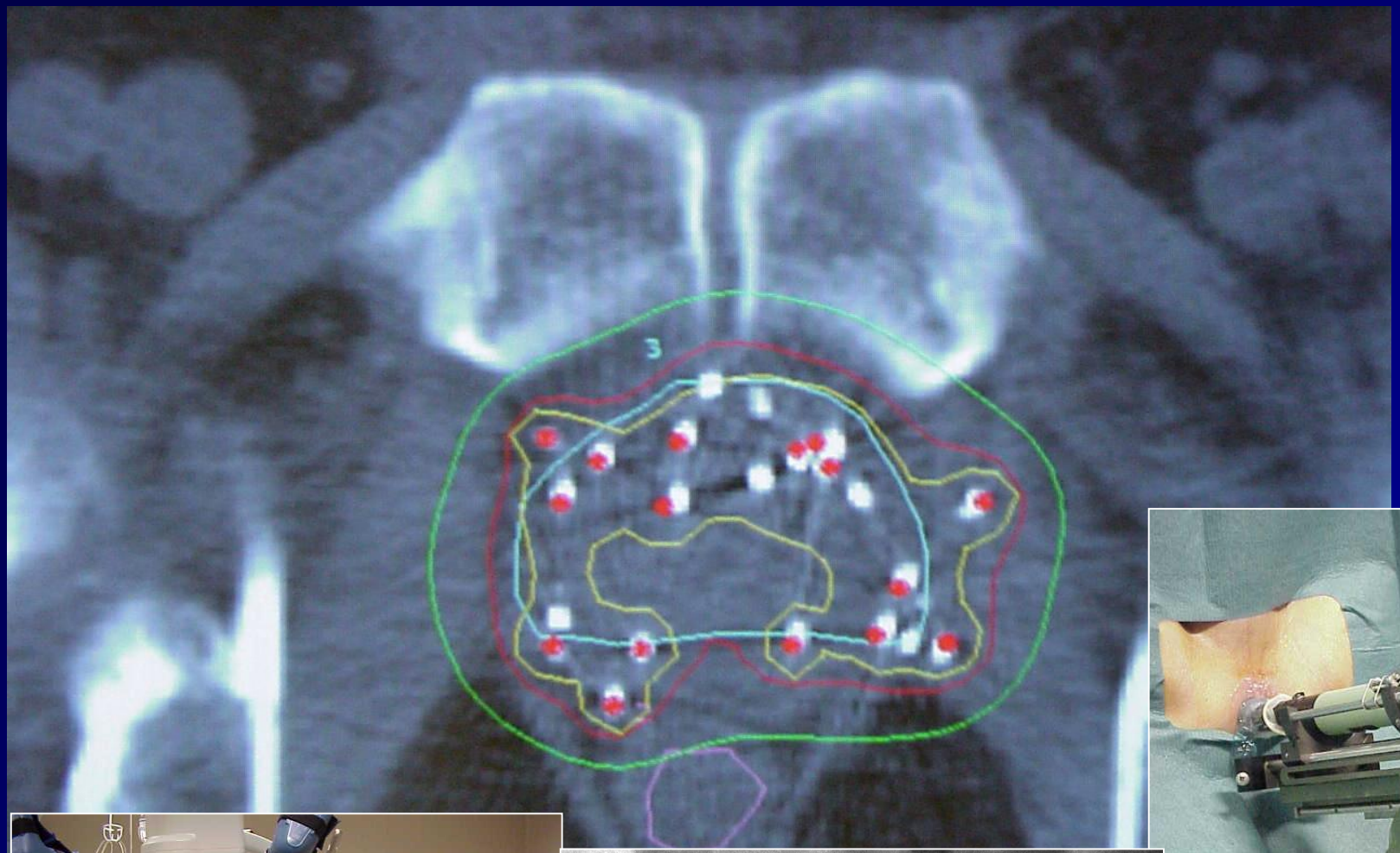


Brachiterapy (I-131)





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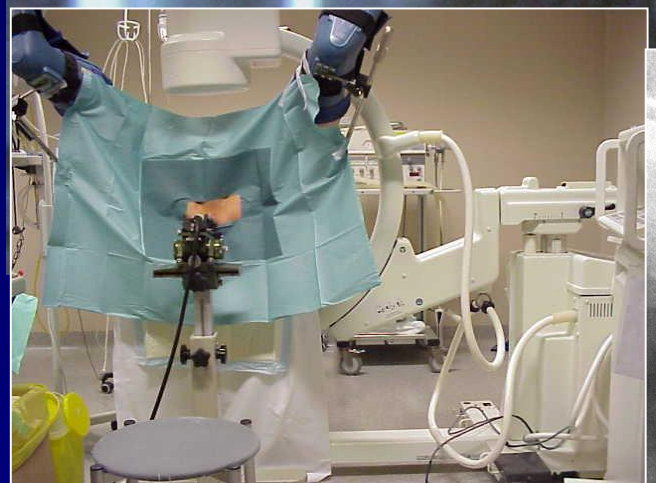
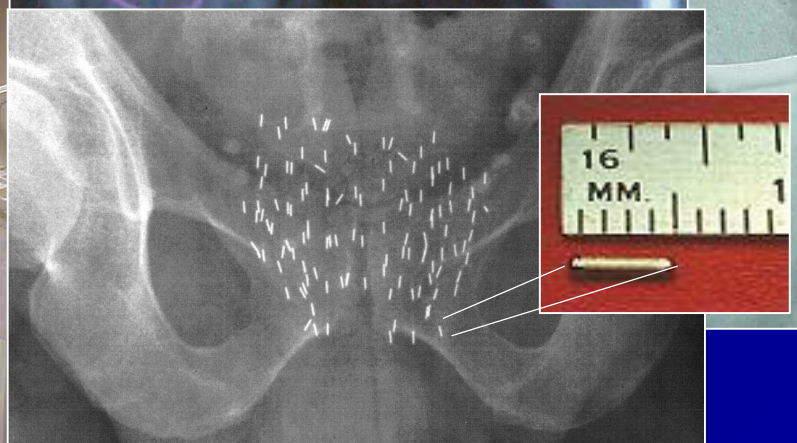
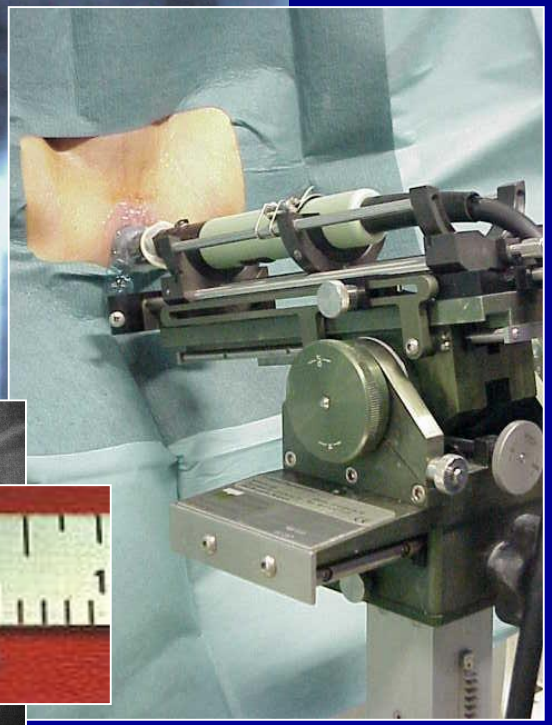
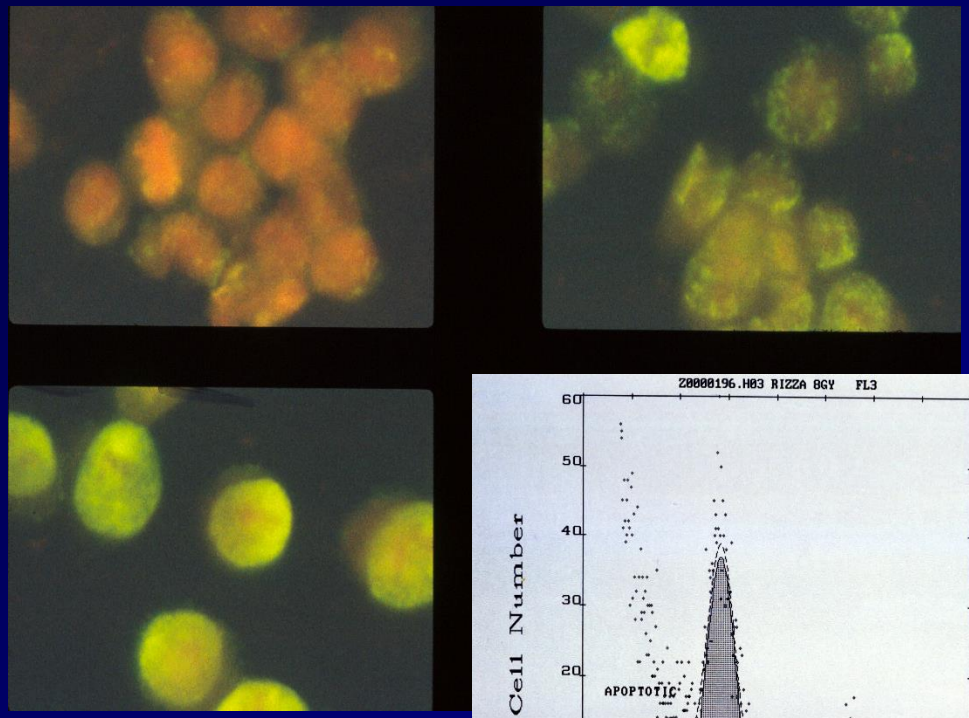
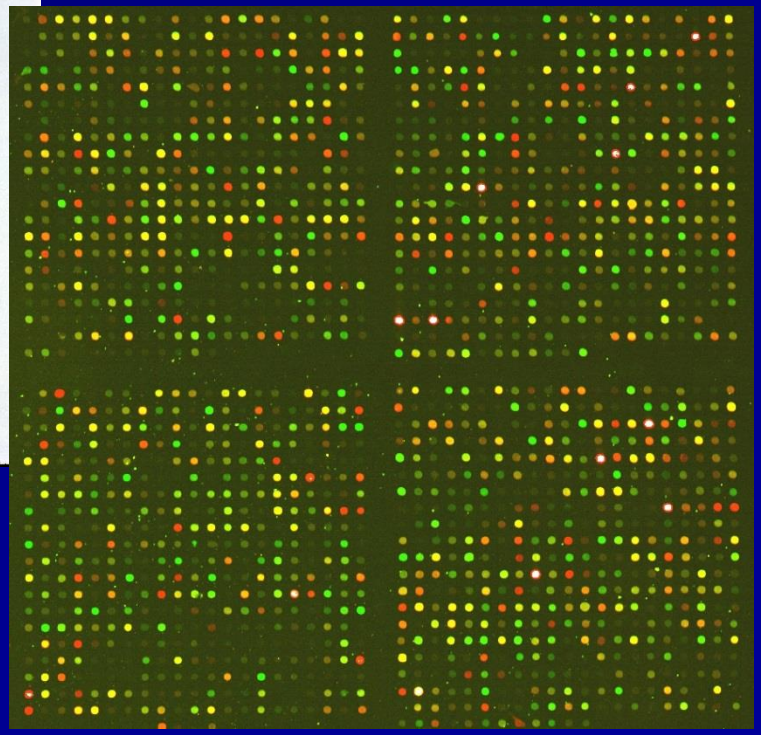



16
MM.
1

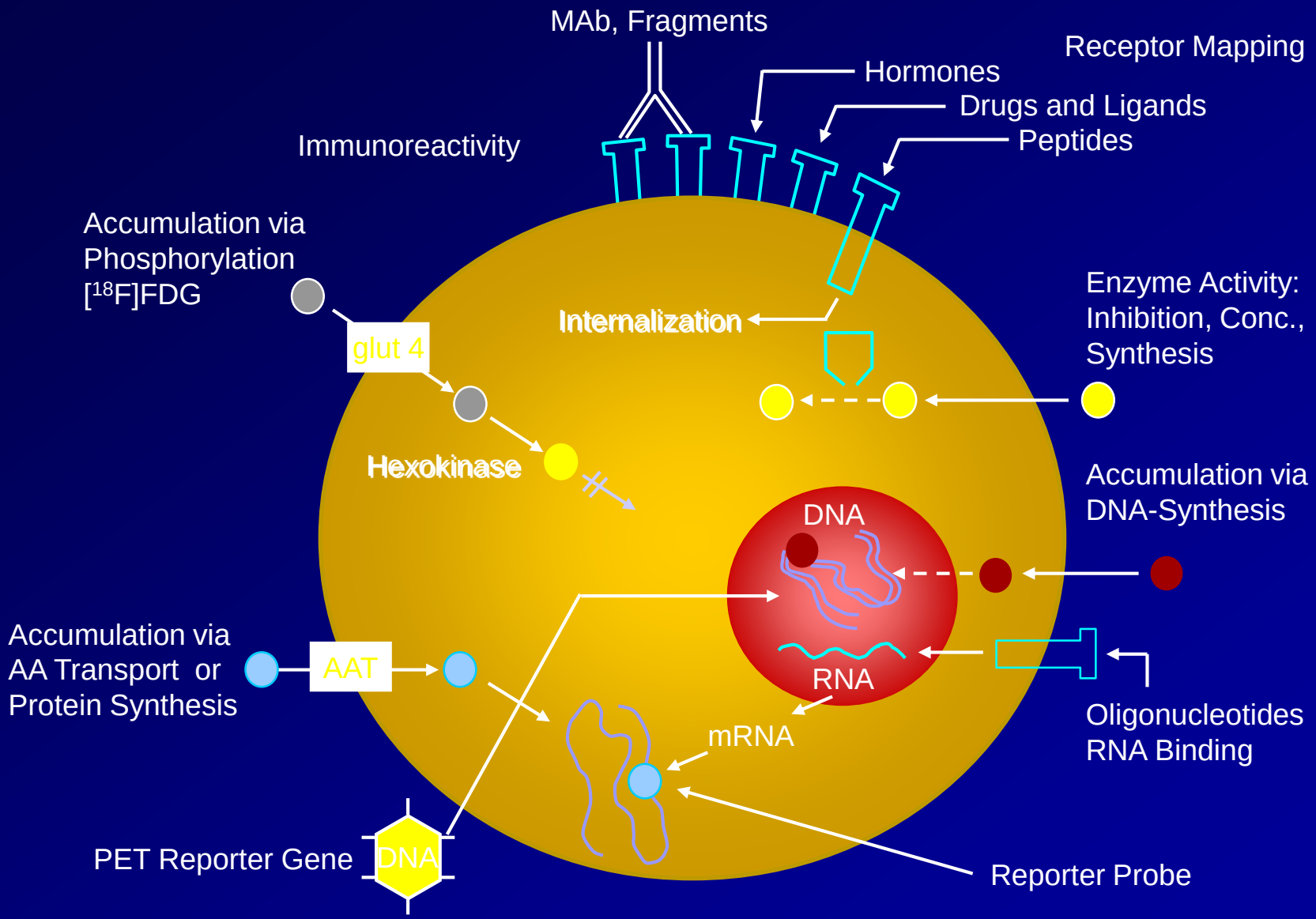


Molecular Radiation Therapy





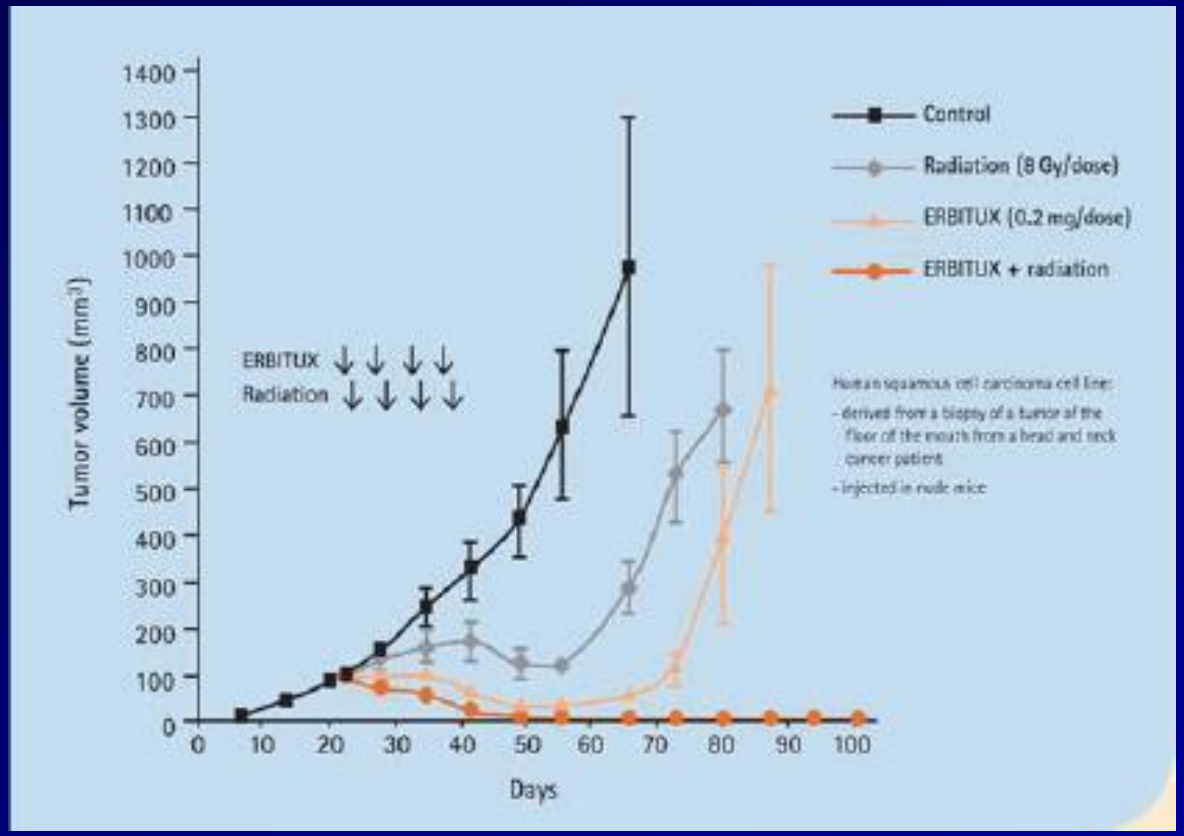
Cellular Targets



Pre-clinical evidence: anti-tumor activity of Erbitux + RT

Human squamous cell carcinoma cell line

- derived from a biopsy of a tumor of the floor of the mouth from a head and neck cancer patient
- injected in nude mice



Erbitux enhanced the effect of radiation

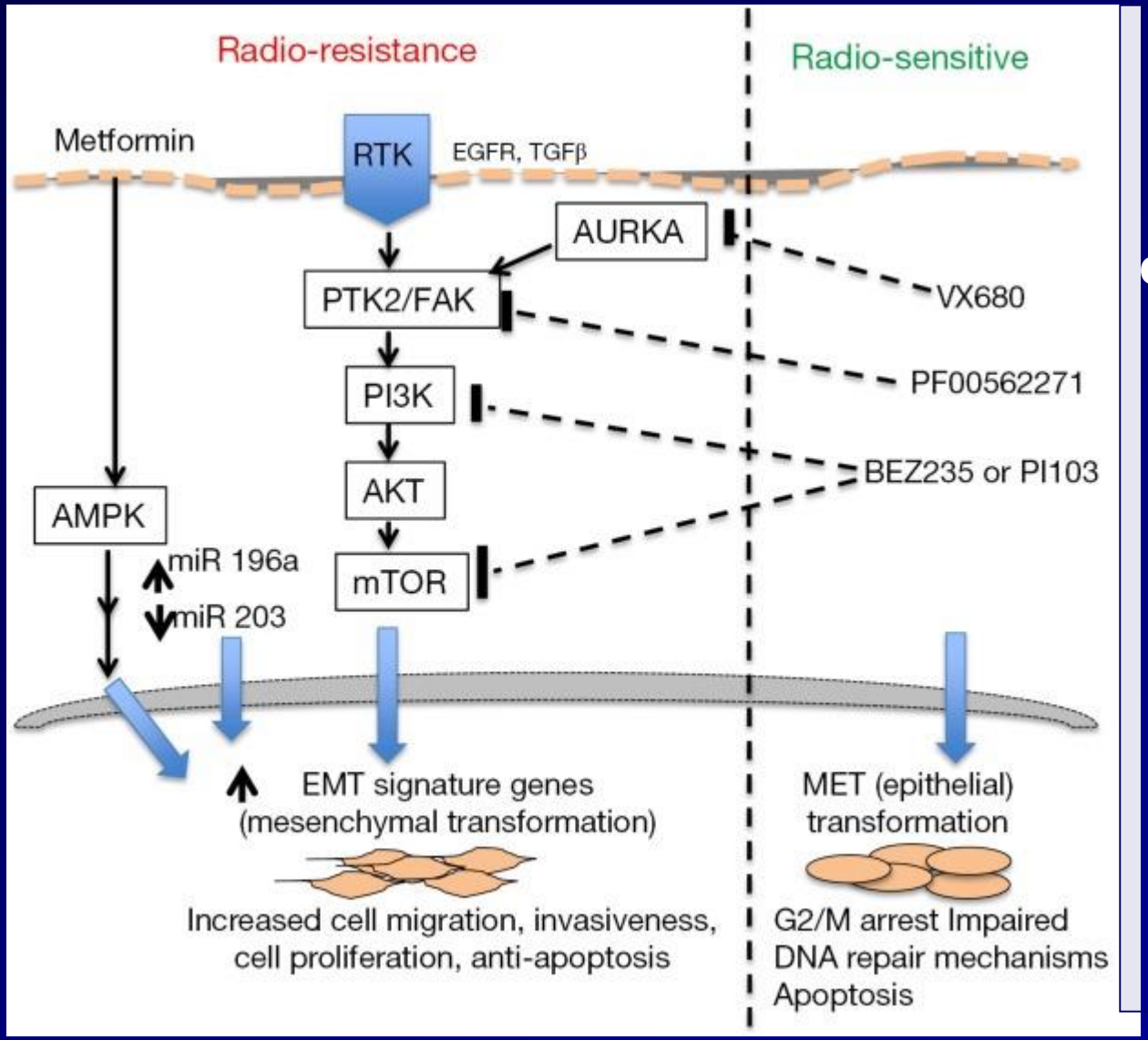
Erbitux has now been approved for use in SCCHN:

For the treatment of locally advanced tumors in combination with RT

	OS	DFS	LC
RT	29.3	12.4	14.9
RT+Cetuximab	49	17.1	24.4
P value	0.03	0.006	0.005

Bonner et al., 2006: in 424 locoregionally advanced SCCHN

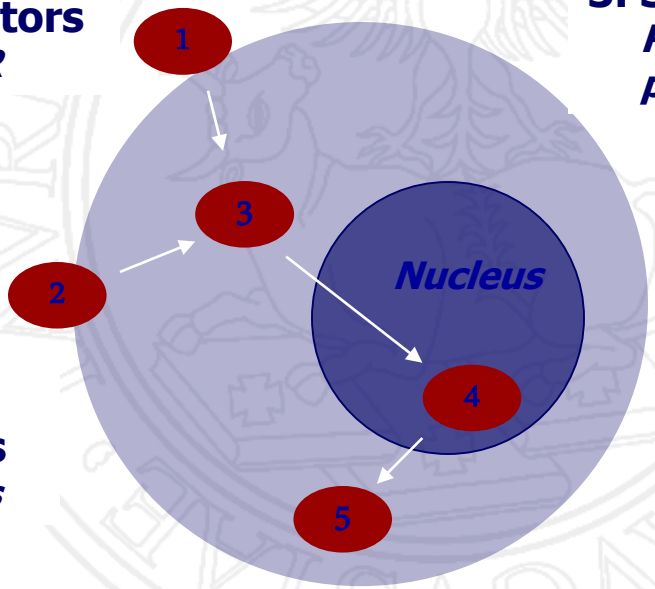
Molecular signature for H&N RT



There is a tremendous potential in this era of precision medicine to apply molecular signature to predict response to various tumors to RT

Many pathways are known to regulate radiation sensitivity, and novel markers are emerging to regulate such pathways

Targets for next-generation therapy



1. Growth factors and growth-factor receptors
HER family, c-kit/SCFR

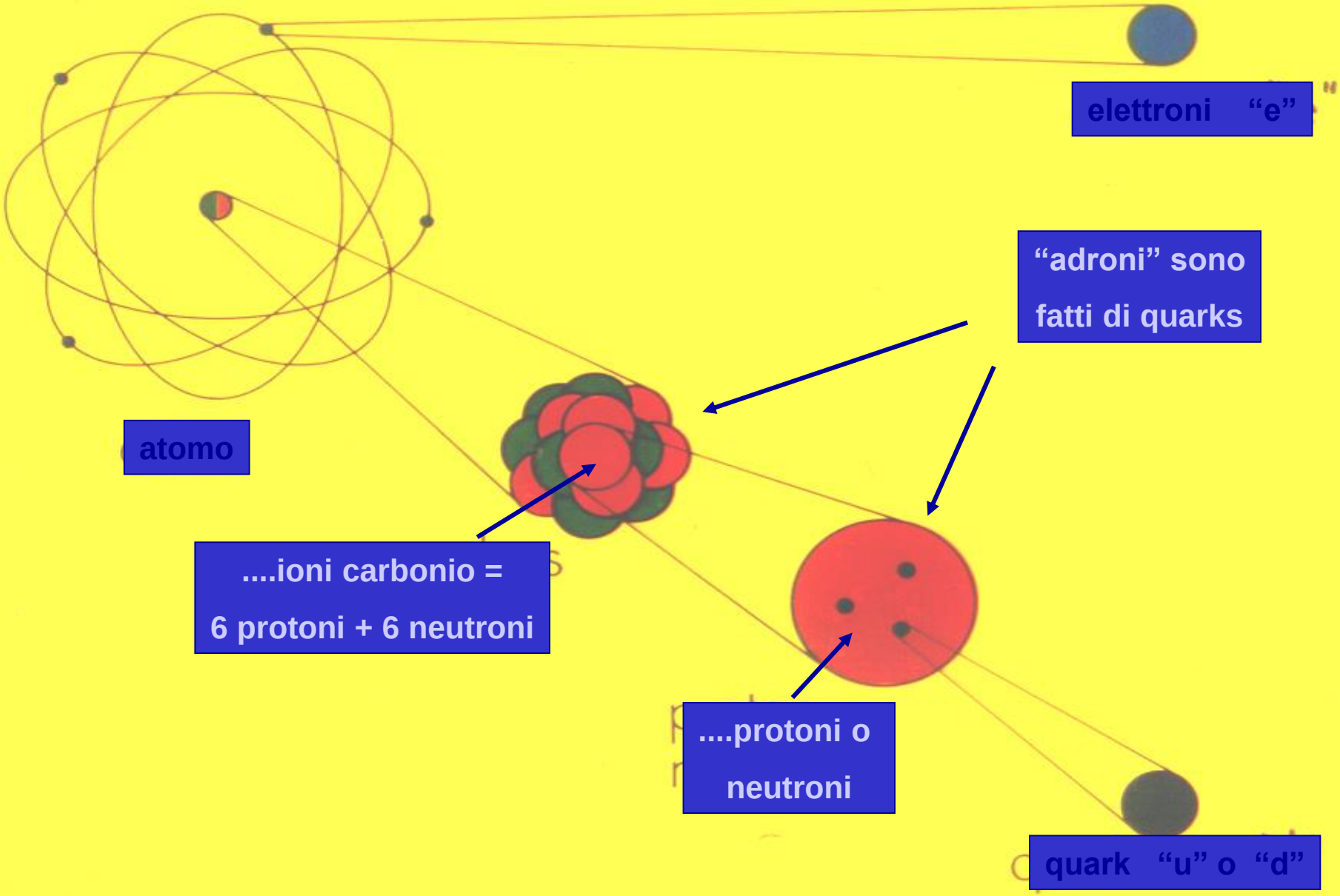
2. Extracellular matrix/ angiogenic pathways
VEGFR, integrins, MMPs

3. Signal transduction pathways
Ras, raf, MAPK, MEK, ERK, AKT protein kinase C, PI3K

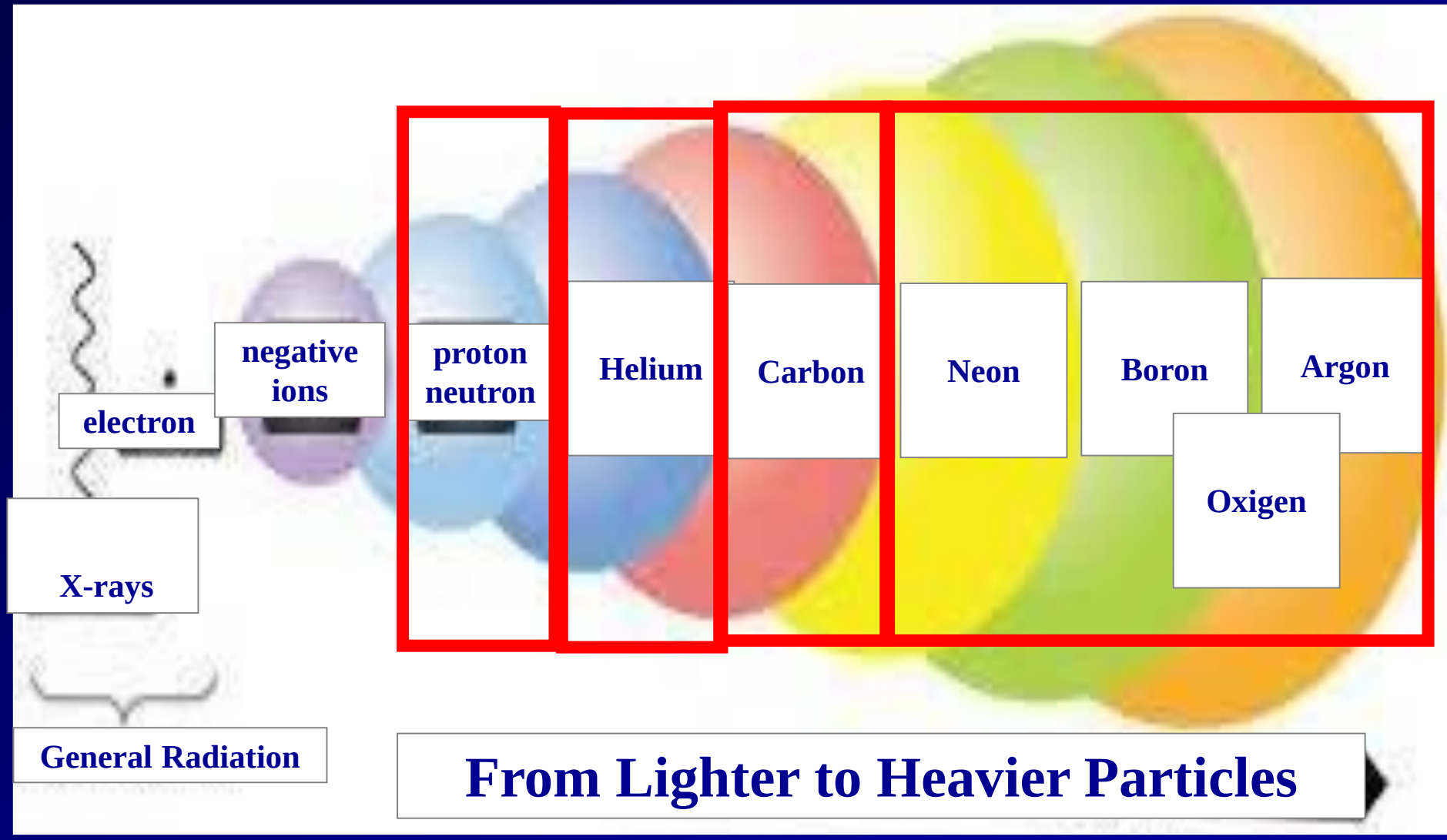
4. Cell-survival pathways
Cyclin-dependent kinases, mTOR, cGMP, COX-2, p53, Bcl-2

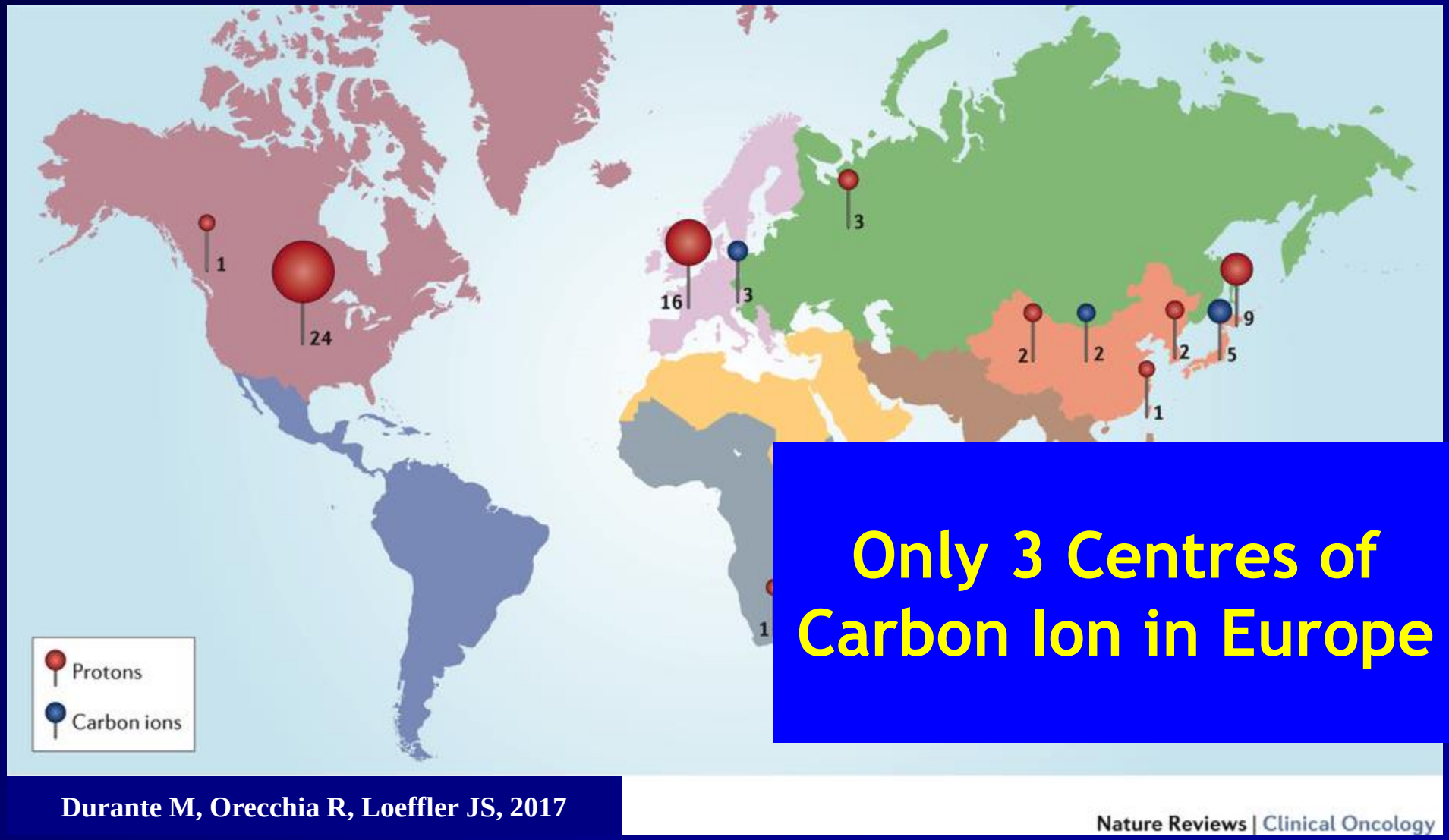
5. Protein production
Proteasome

Hadrons


elettroni “e”
“adroni” sono fatti di quarks
atomo
....ioni carbonio = 6 protoni + 6 neutroni
....protoni o neutroni
quark “u” o “d”

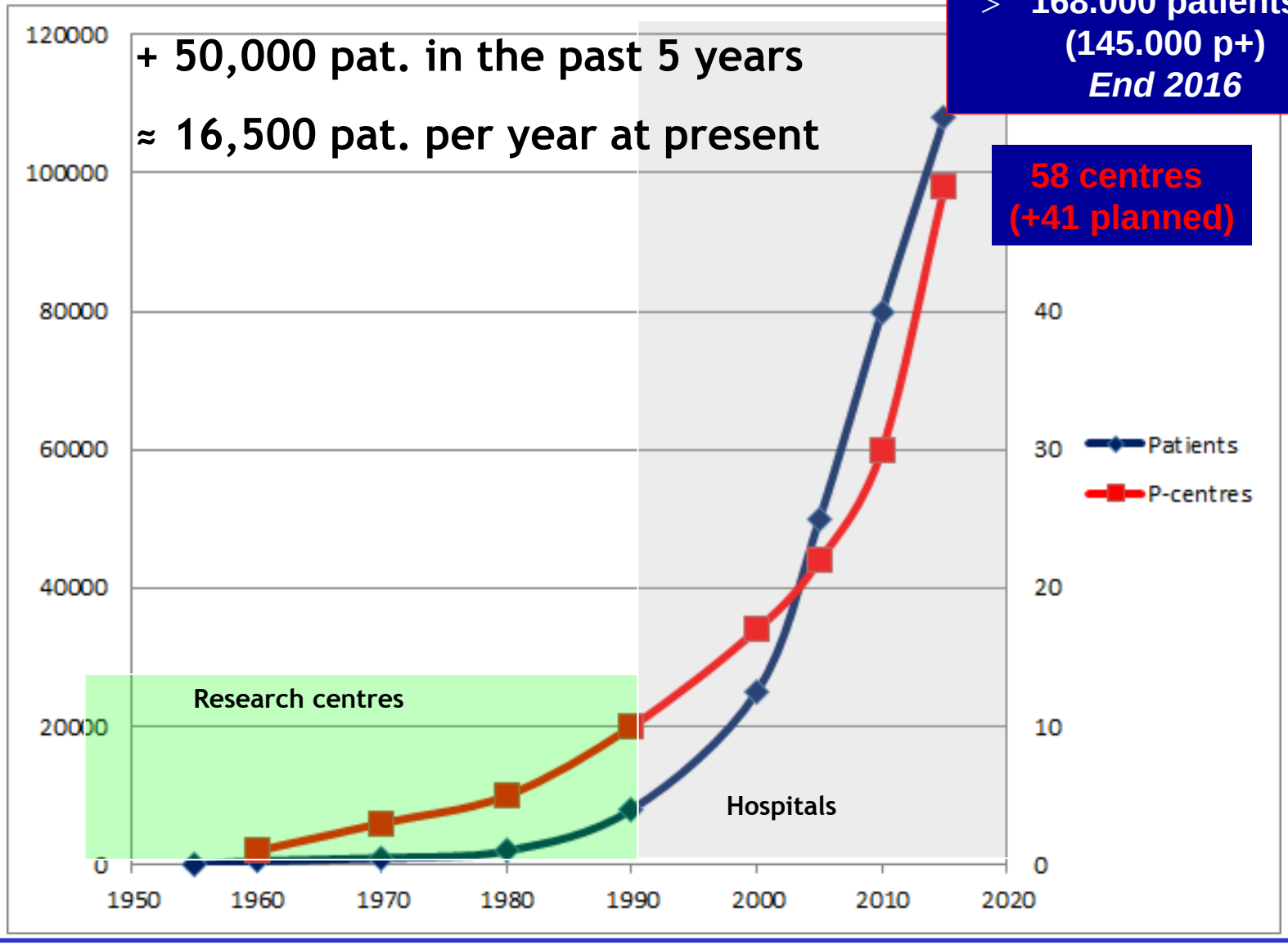
Hadron Therapy



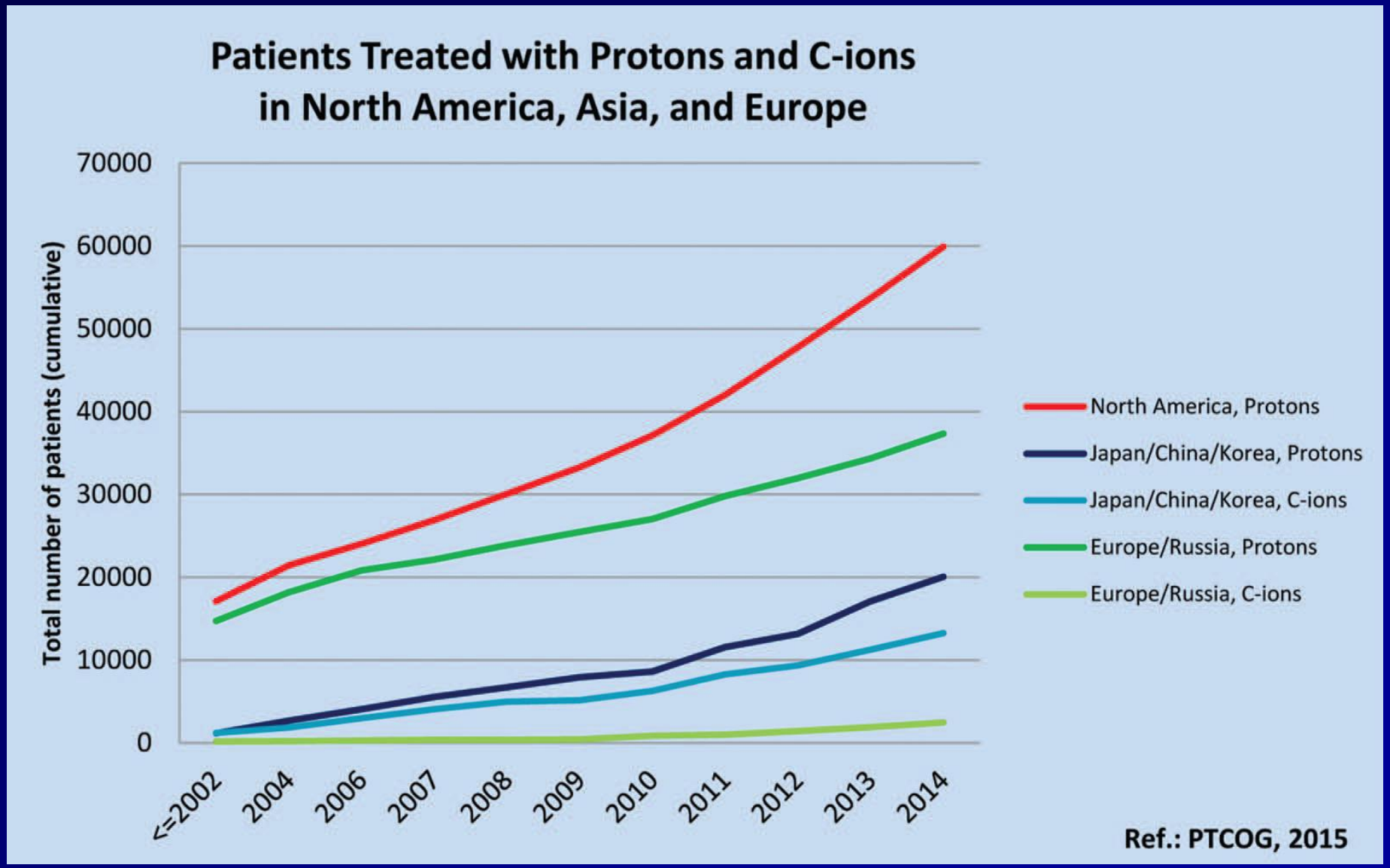


Charged Particle Therapy Centres

[Data from www.ptcog.ch]



Carbon Ions: > 23.000 patients; 10 centres (5 multi ions+2 in construction)


Patients Treated with Protons and C-ions
in North America, Asia, and Europe
Total number of patients (cumulative)
70000
60000
50000
40000
30000
20000
10000
0
<=2002
2004
2006
2007
2008
2009
2010
2011
2012
2013
2014
North America, Protons
Japan/China/Korea, Protons
Japan/China/Korea, C-ions
Europe/Russia, Protons
Europe/Russia, C-ions
Ref.: PTCOG, 2015

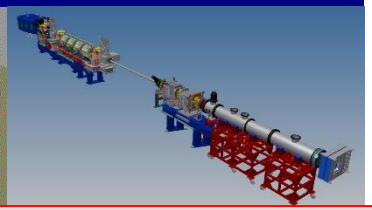
Experimental Phase
133 patients up to December 2013

http://folder.cnao.it

CNAO Pavia

in room 3D imaging

experimental room (2017)



Clinical Phase (National Health System) Started since January 2014

2014 – 2017 (30th April) Activity

Patients: 1279

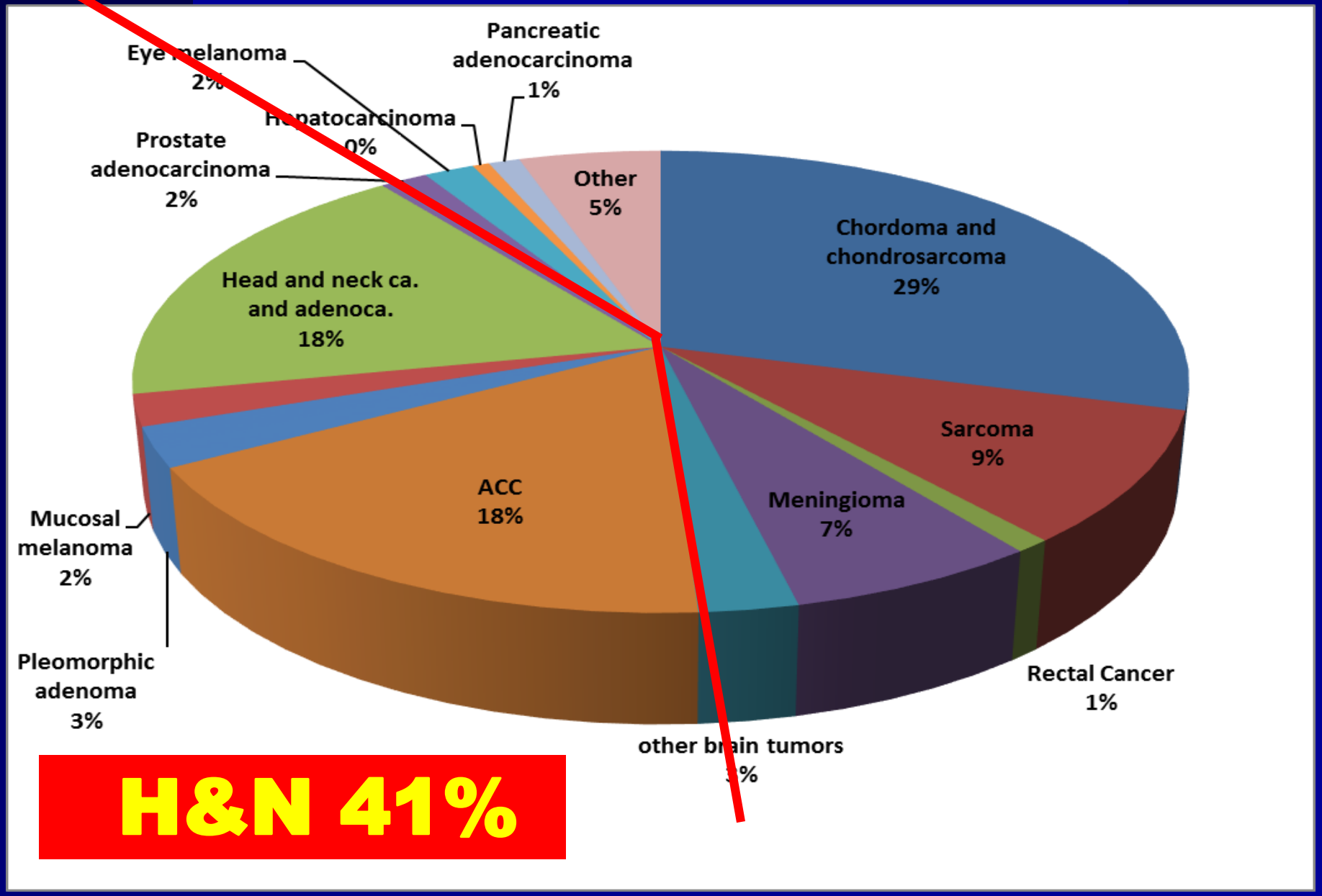
Synchrotron Operation: H24, 7/7
Maintenance: 4/year - 5 days each (Thursday to Tuesday)
Treatments: Mon to Fri – 8:00 to 21:00
QA: Mon to Fri – 0:00 to 6:00
Beam time for research over week-ends

Proton
Conventional fractionation
Patients: 372

Carbon ion
NIRS fractionation
Patients: 903

Mixed beam P+ / C-12
4 patients

2014 - 2017 Activity

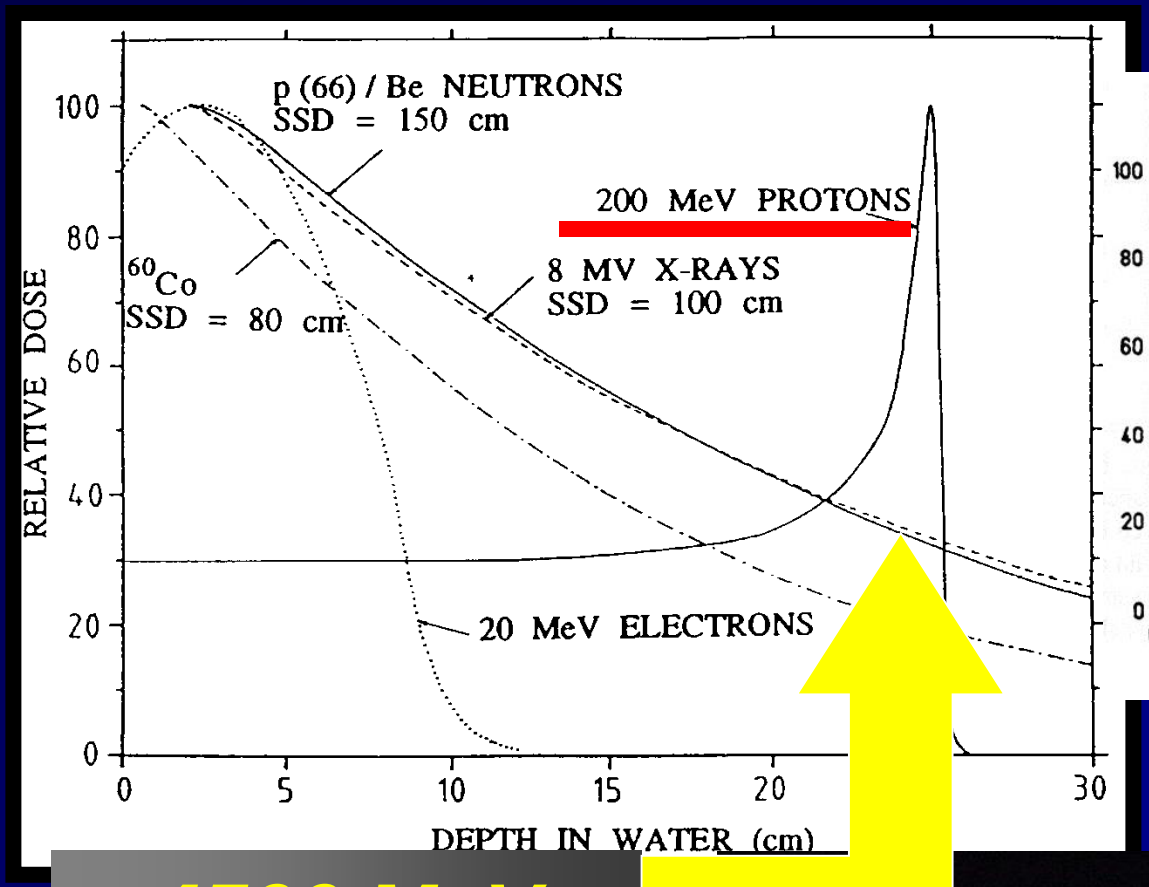


H&N 41%

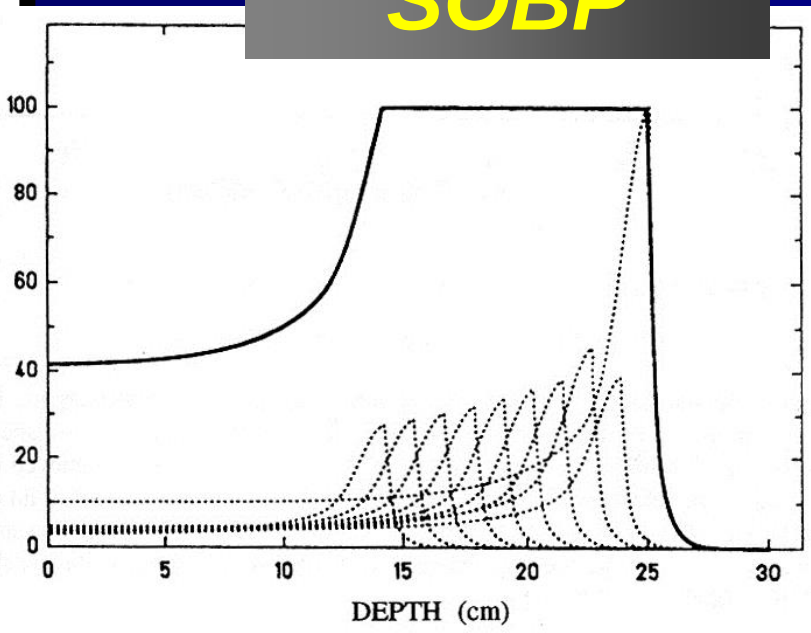
Hadrontherapy- LEA in NHS

1. Chordoma & chondrosarcoma base/spine
2. Meningiomas
3. Brain tumors (trunk)
4. ACC Salivary Glands
5. Orbit tumors including eye melanoma
6. Sinonasal carcinoma
7. Soft Tissue & bone Sarcoma (every sites)
8. Recurrent tumors (retreatment)
9. Patients with immulogical desorders
10. Pediatric solid tumors

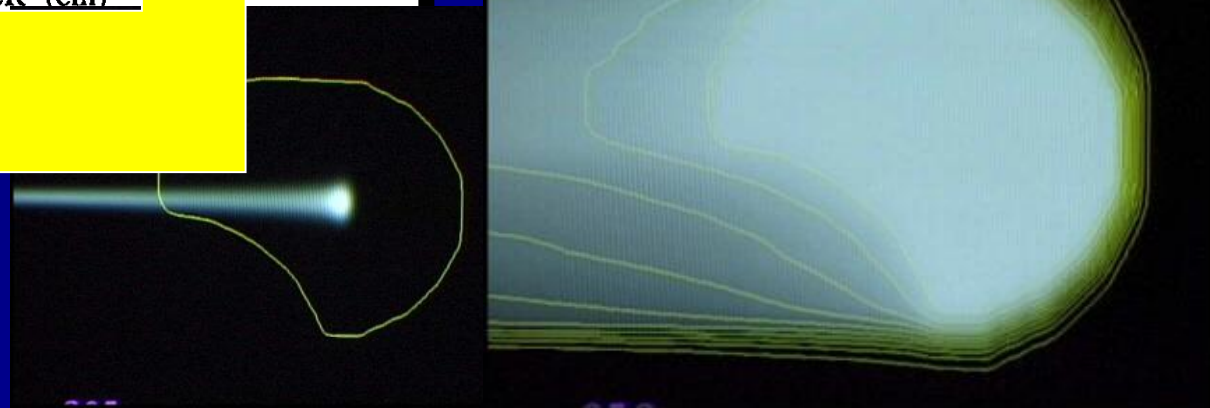
Physical Selectivy



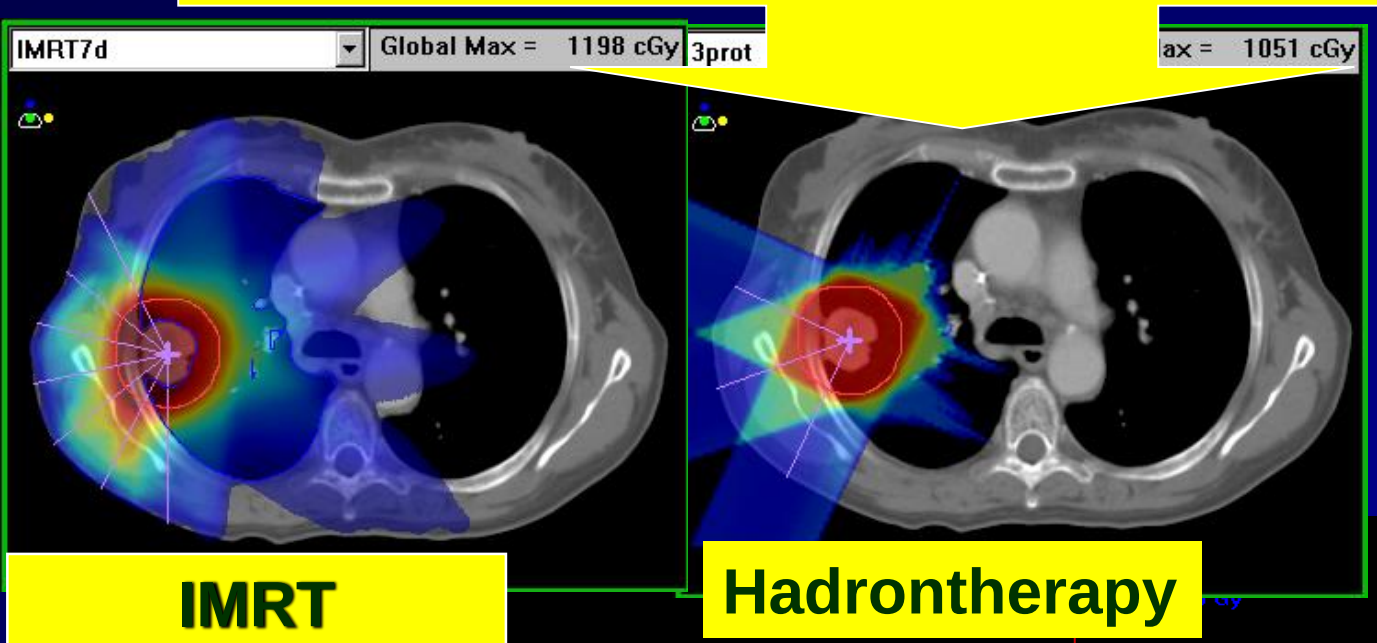
SOBP



4500 MeV Carbon Ion

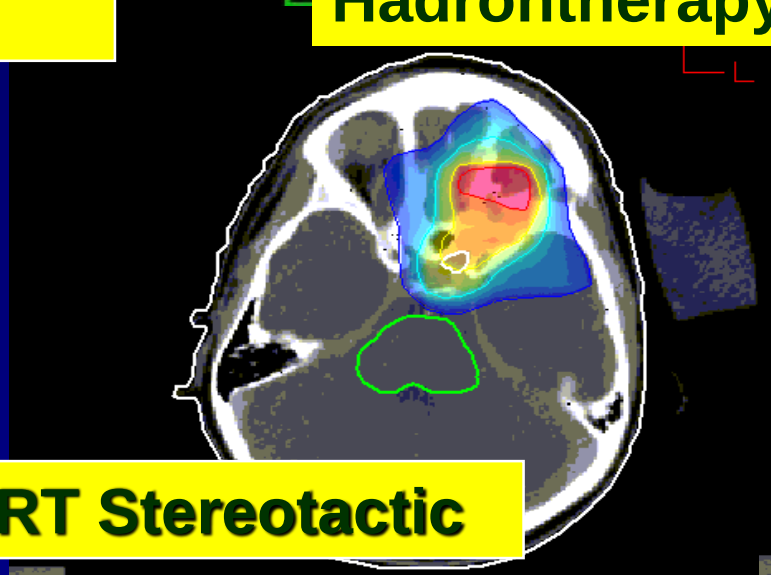


Physical Selectivity

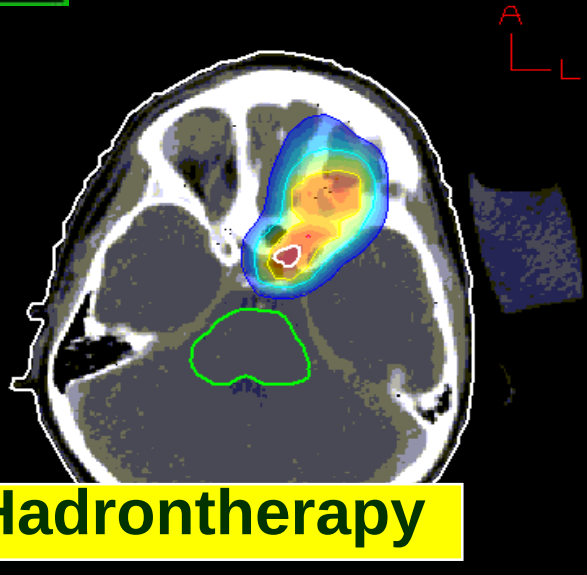


IMRT

Hadrontherapy

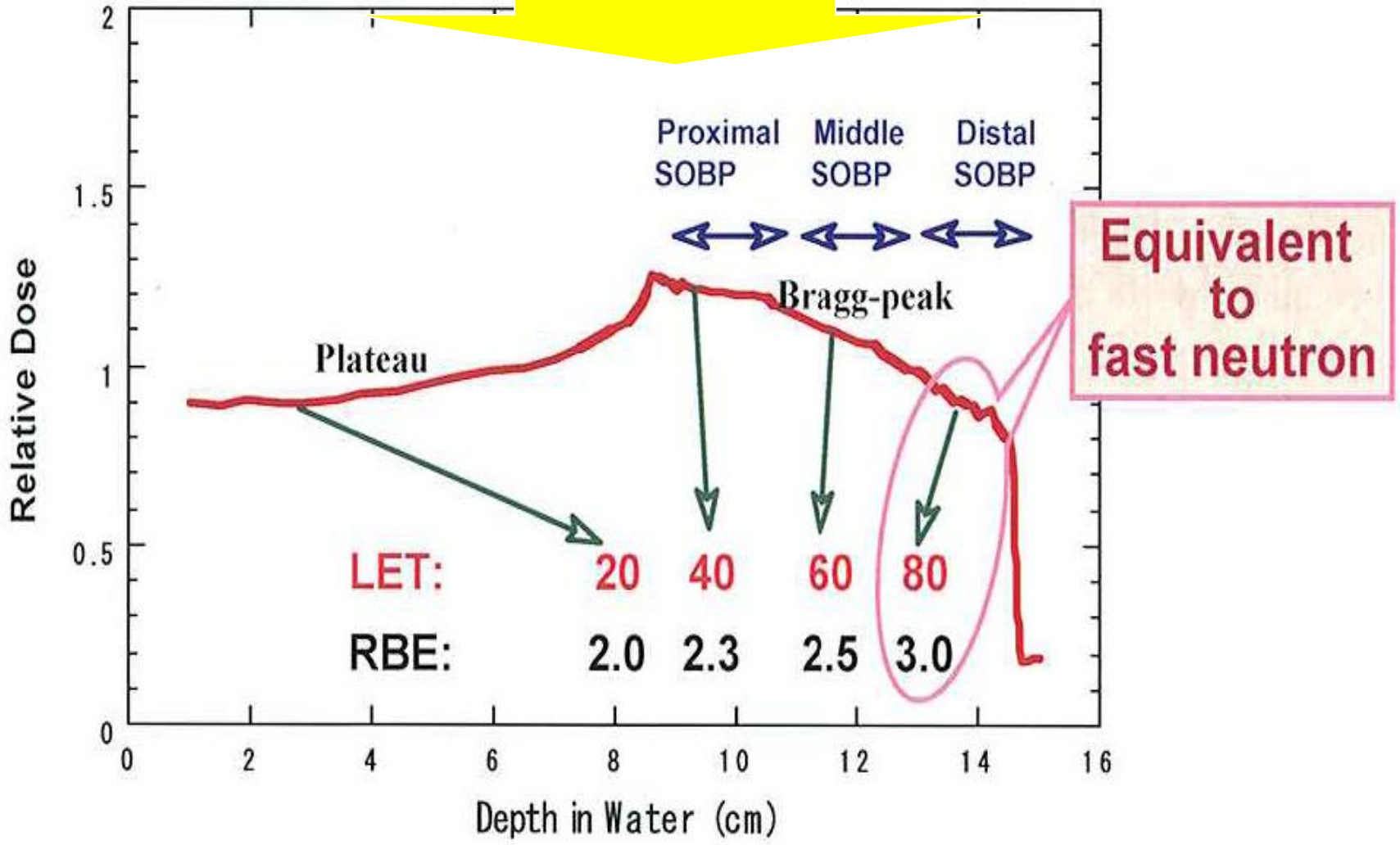


RT Stereotactic

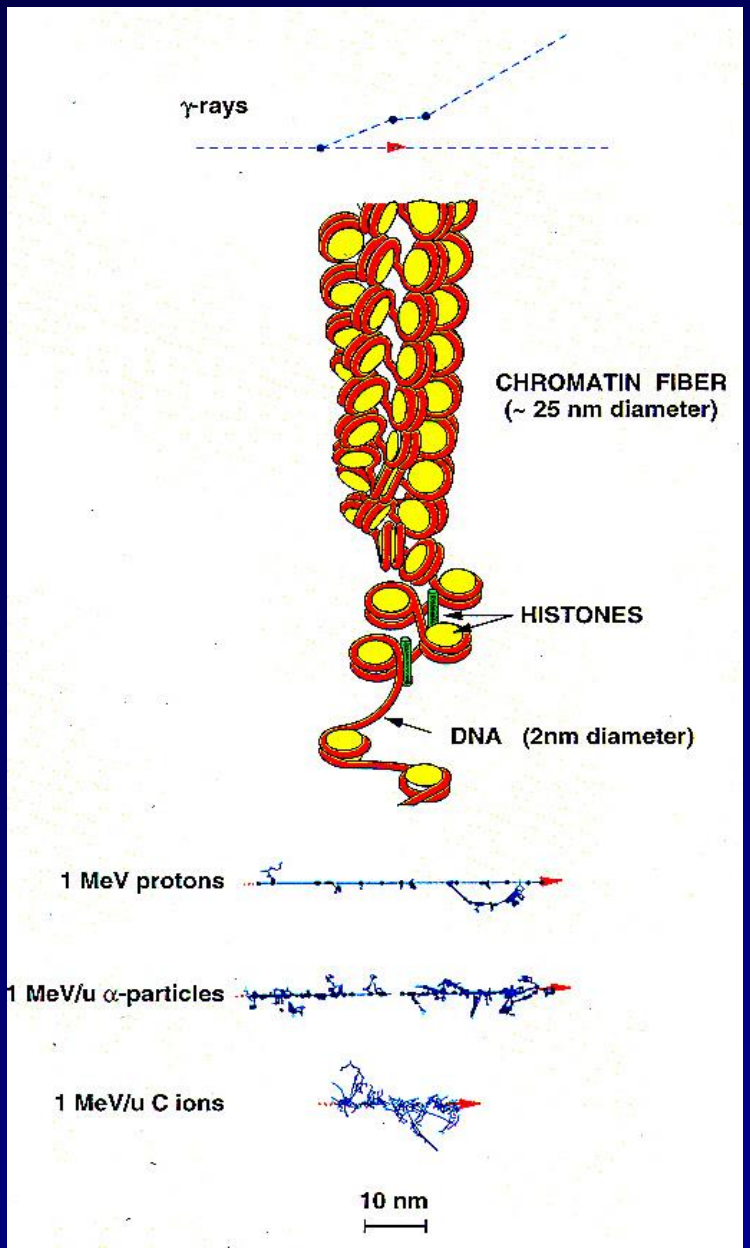


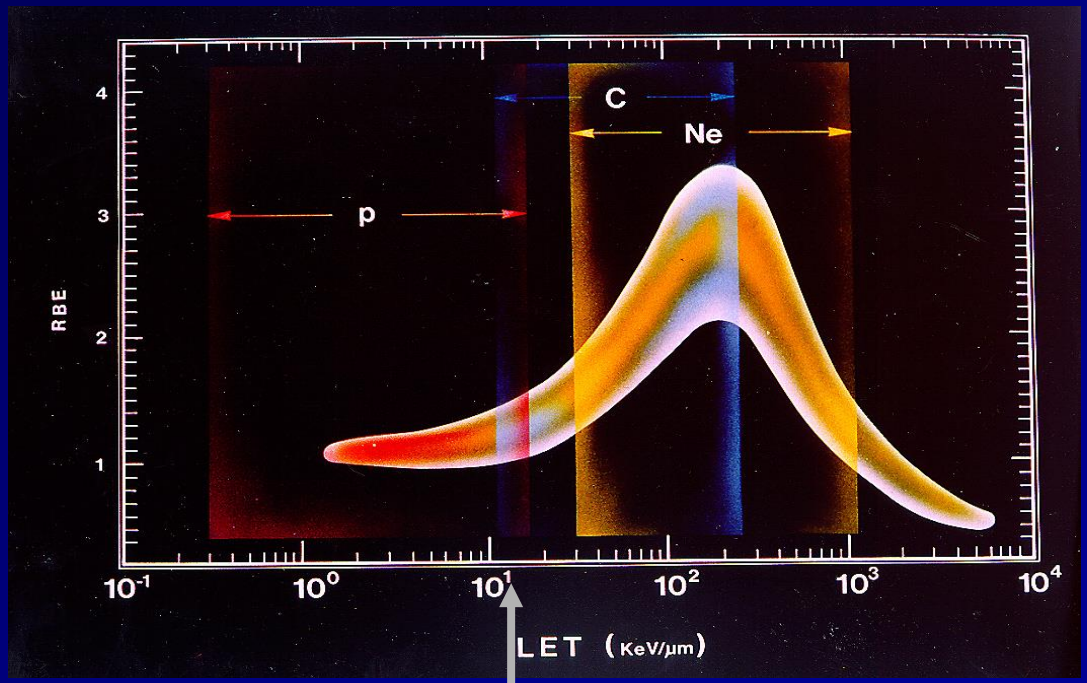
Hadrontherapy

Biological Selectivity



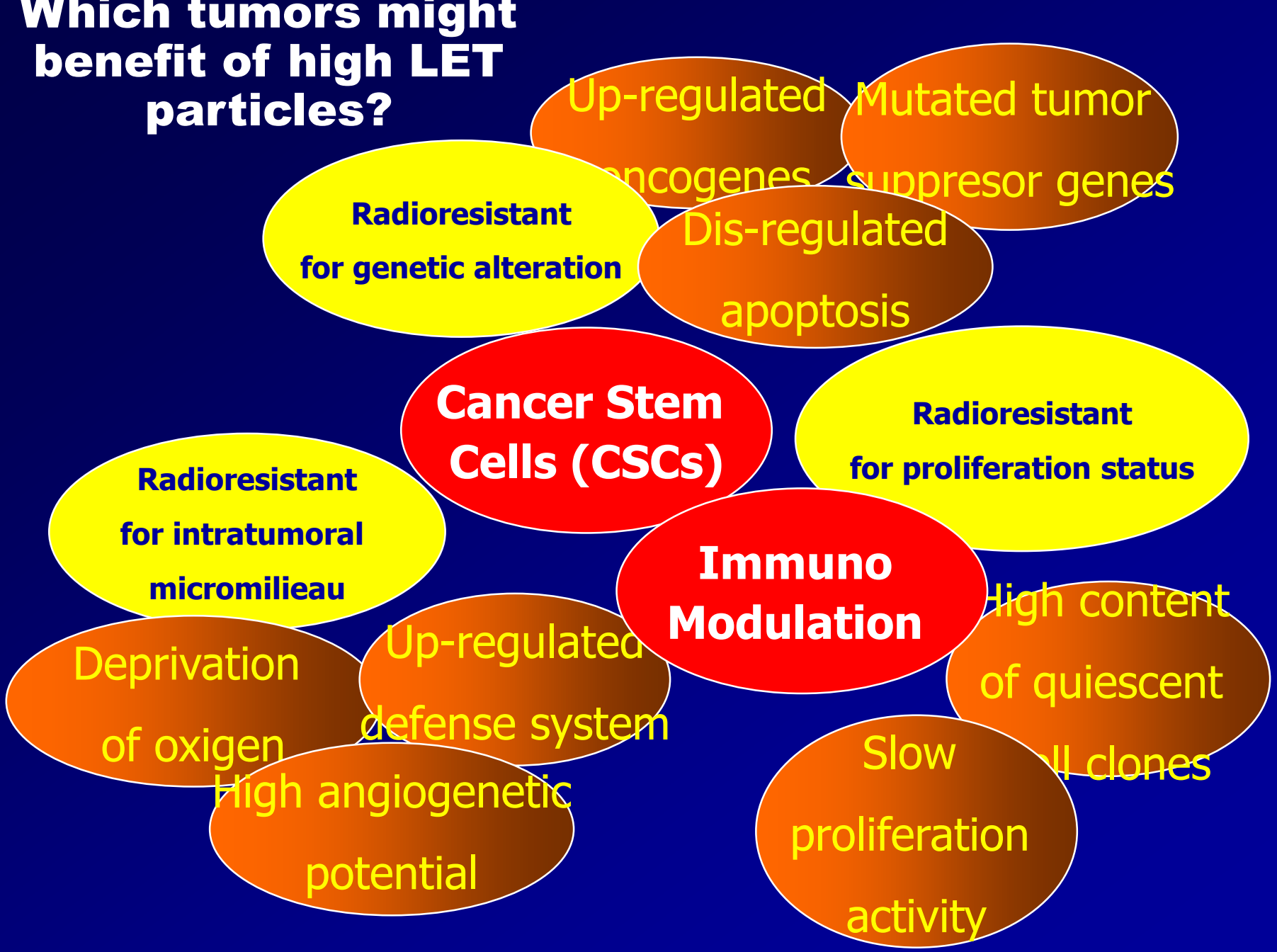
Biological selectivity. RBE

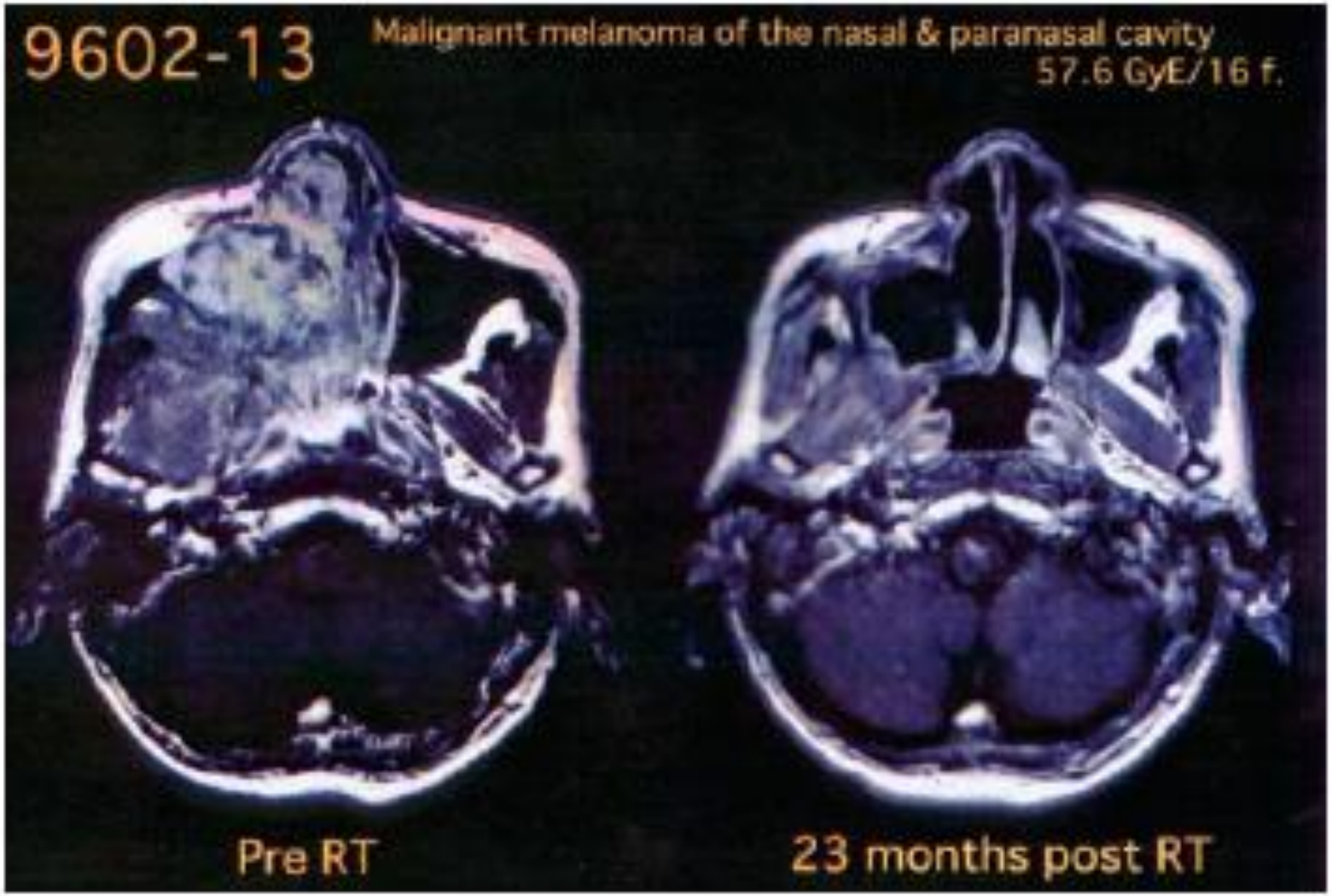




10 – 20 keV/μm = 100 – 200 MeV/cm =

20 – 40 eV/(2 nm)

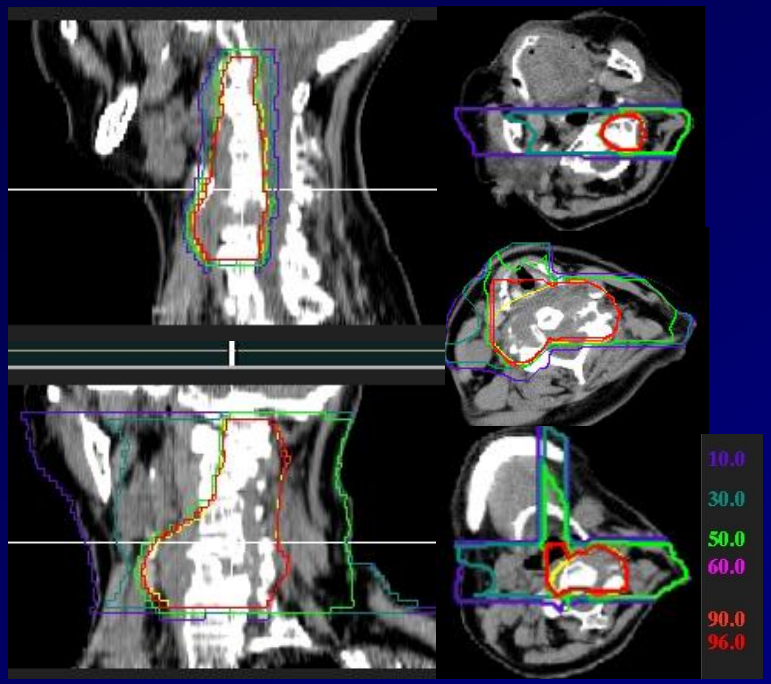

Which tumors might benefit of high LET particles?
Up-regulated
Mutated tumor
Radioresistant for genetic alteration
Dis-regulated apoptosis
Cancer Stem Cells (CSCs)
Radioresistant for proliferation status
Radioresistant for intratumoral micromilieau
Immuno Modulation
Deprivation of oxigen
Up-regulated defense system
High angiogenetic potential
Slow proliferation activity



Malignant melanoma

Nasal and paranasal sinuses

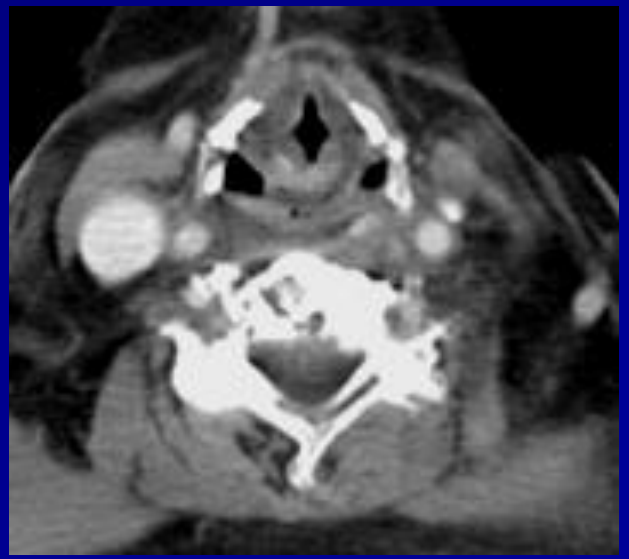
Osteosarcoma



64 GyE/16 fx
/4 weeks
Patch technique

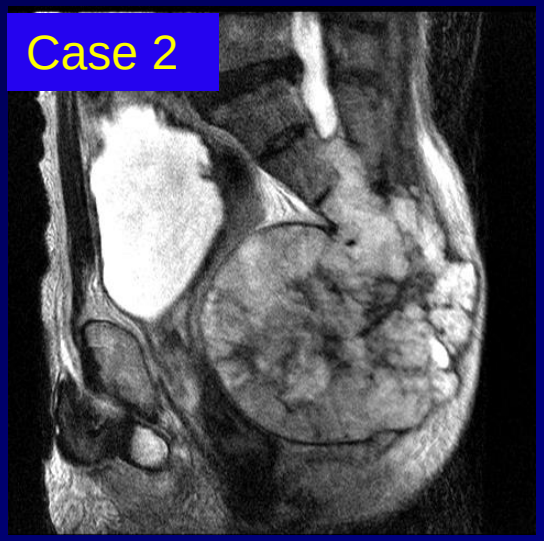
Before

7 years
after



(Lancet Oncology 2006)

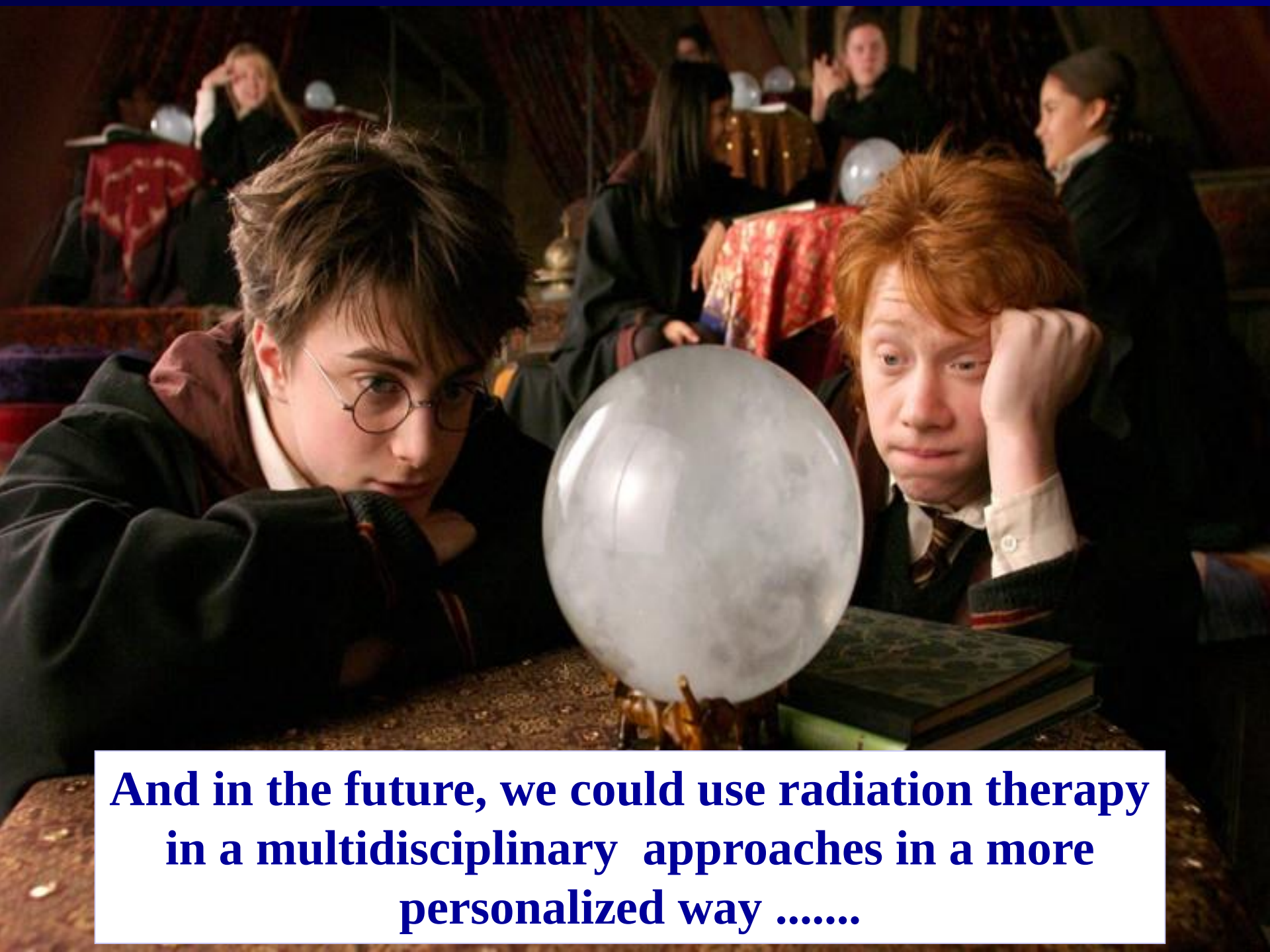
Chordoma of the sacrum



4 years

4 years

4.5 years



And in the future, we could use radiation therapy in a multidisciplinary approaches in a more personalized way .....