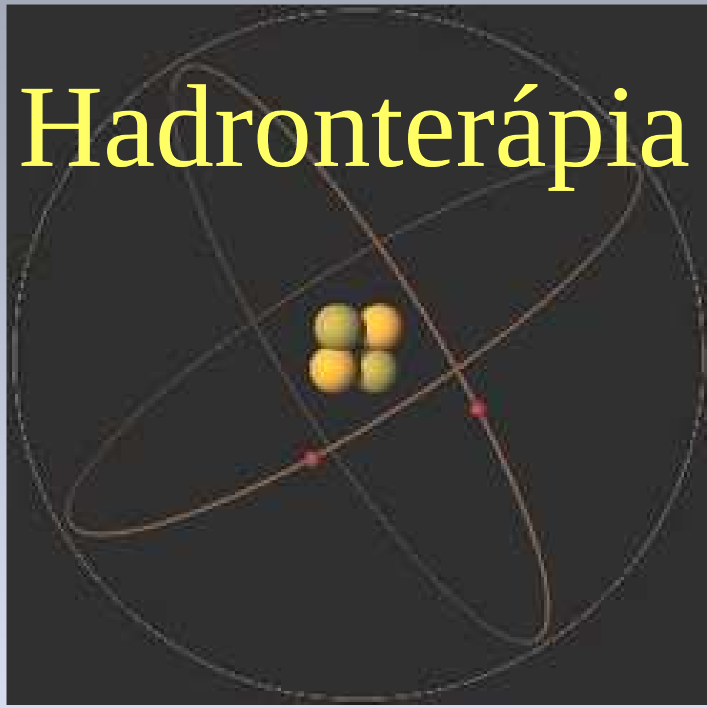
Onkoterápiás Klinika, Szegedi Tudományegyetem

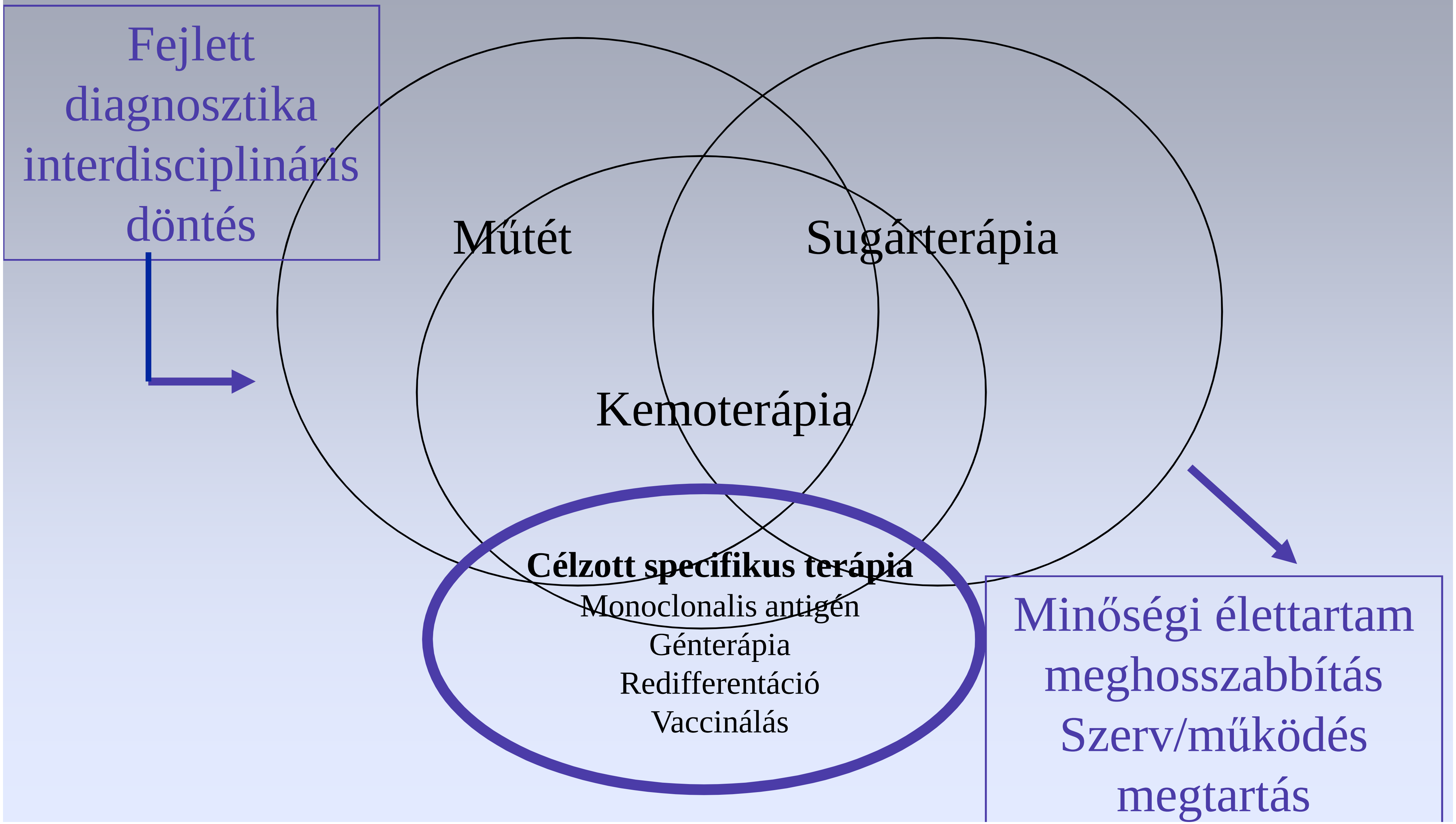
Hadronterápia



Hideghéty Katalin

ELI Téli Iskola 2012. 02. 2-4

Komplex tumorkezelés



Sugárzás hatása különböző szinteken

Atomi

Energia
Ionizáció

→

Molekuláris

Szabad oxygén gyökök

→

Makromolekuláris

Fehérje
DNS károsodás

→

Szubcelluláris

Anyagcsere
Szabályozás
Membrán,DNS

→

Celluláris

Sejthalál
Sejtkárosodás

→

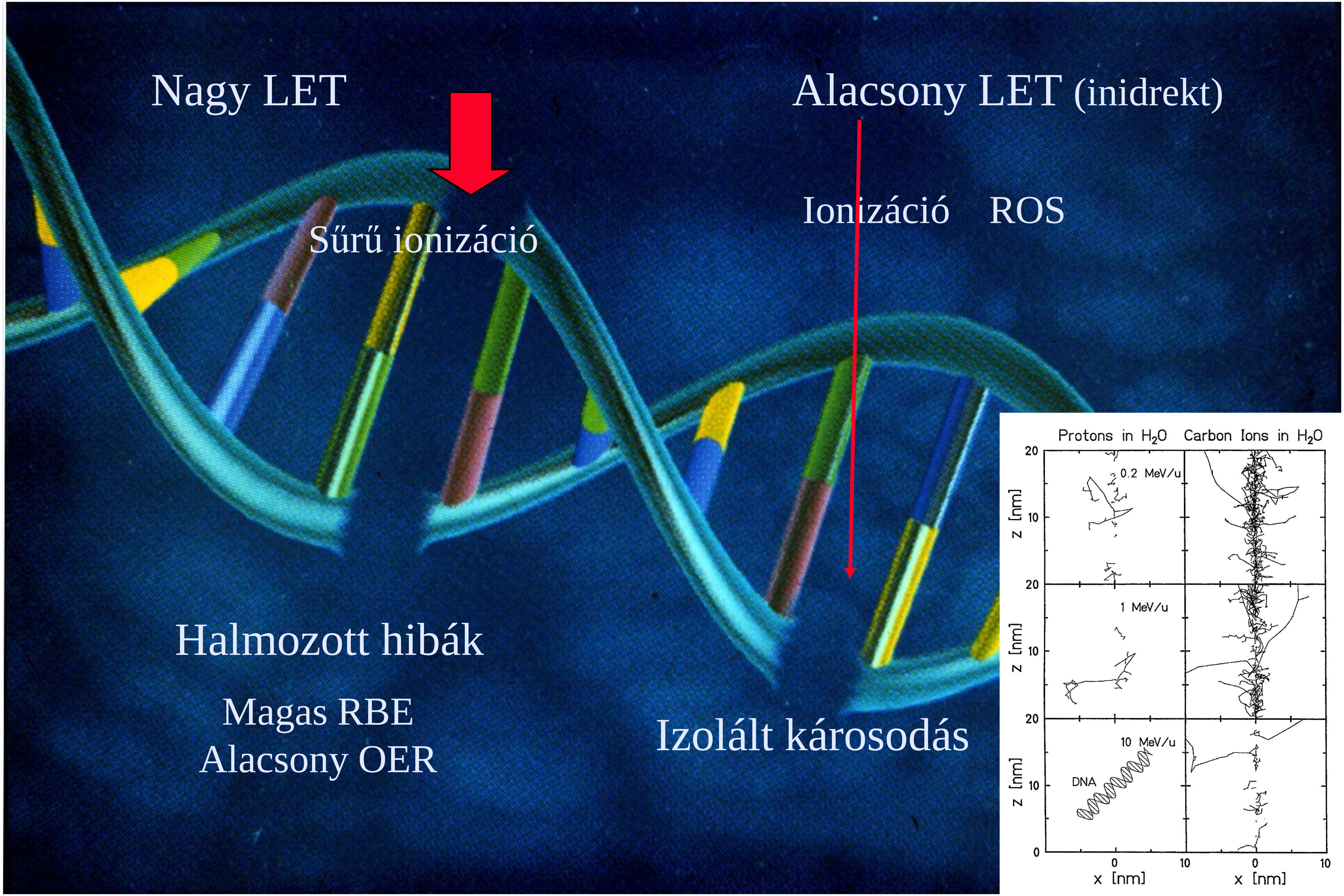
Szövetek

Citokinek
érfal
müködés

→

Makroszkópikus

Sugárreakciók
Nekrózis
Szerv-funkciózavar


Nagy LET
Alacsony LET (inidrekt)
Sűrű ionizáció
Ionizáció
ROS
Halmozott hibák
Magas RBE
Alacsony OER
Izolált károsodás
Protons in H_2O
Carbon Ions in H_2O
0.2 MeV/u
1 MeV/u
10 MeV/u
DNA
z [nm]
x [nm]
0
10
20

A sugárkezelés hatása, célja

A daganat (el)pusztítása

Tumor volumen csökkentés

Devitalizálás

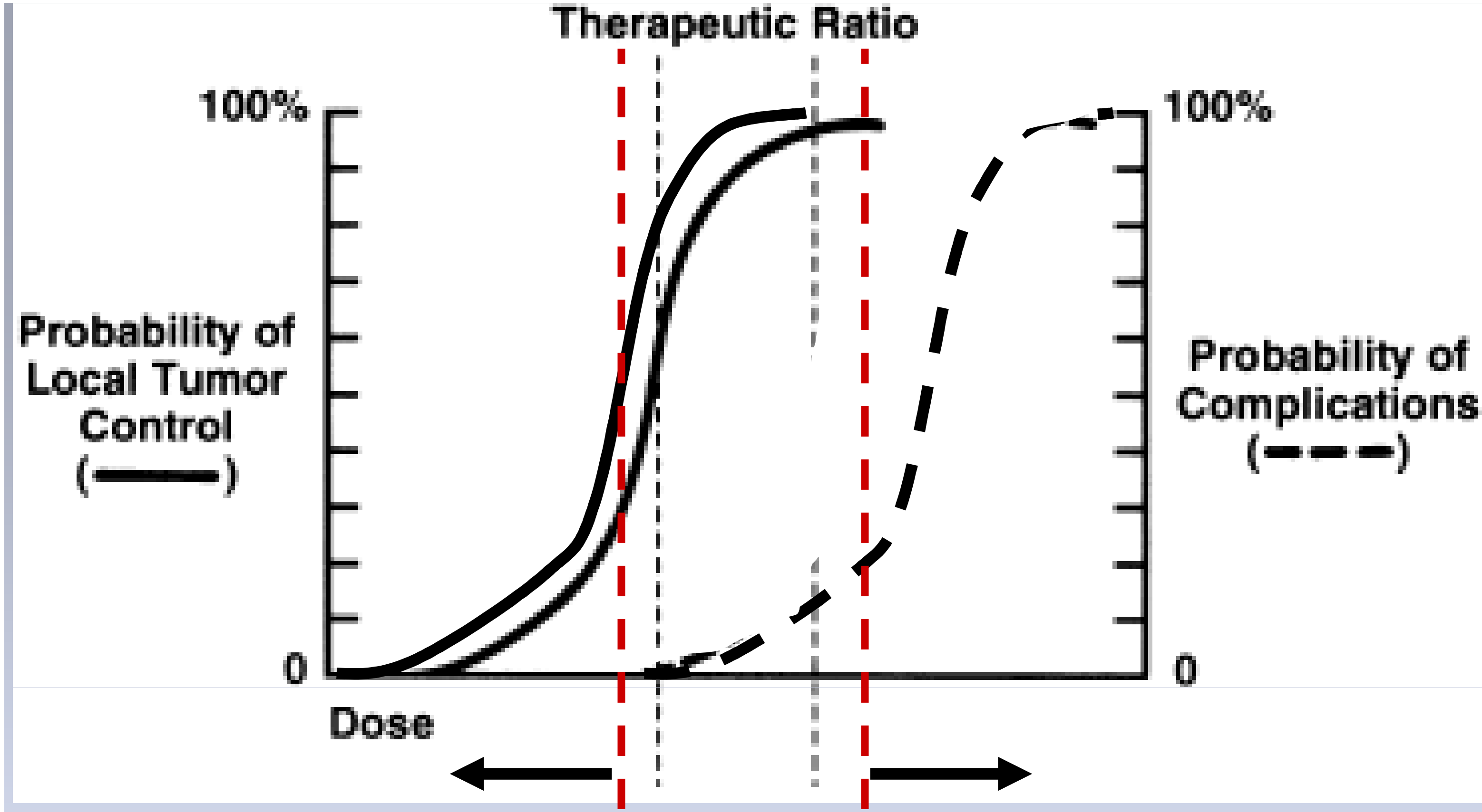
Apoptosis indukció

Proliferáció-gátlás

Gyógyítás (**Kuratív** kezelés)

A mütétek kiterjedésének csökkentése (Szerv-/müködés-megtartás

Panaszok csökkentése (**Palliatív** kezelés)



Frakcionálás

Hypofrakc.

Hyperfrack.

Accelerált hyperfr.
(CHART)

CHARTWELL

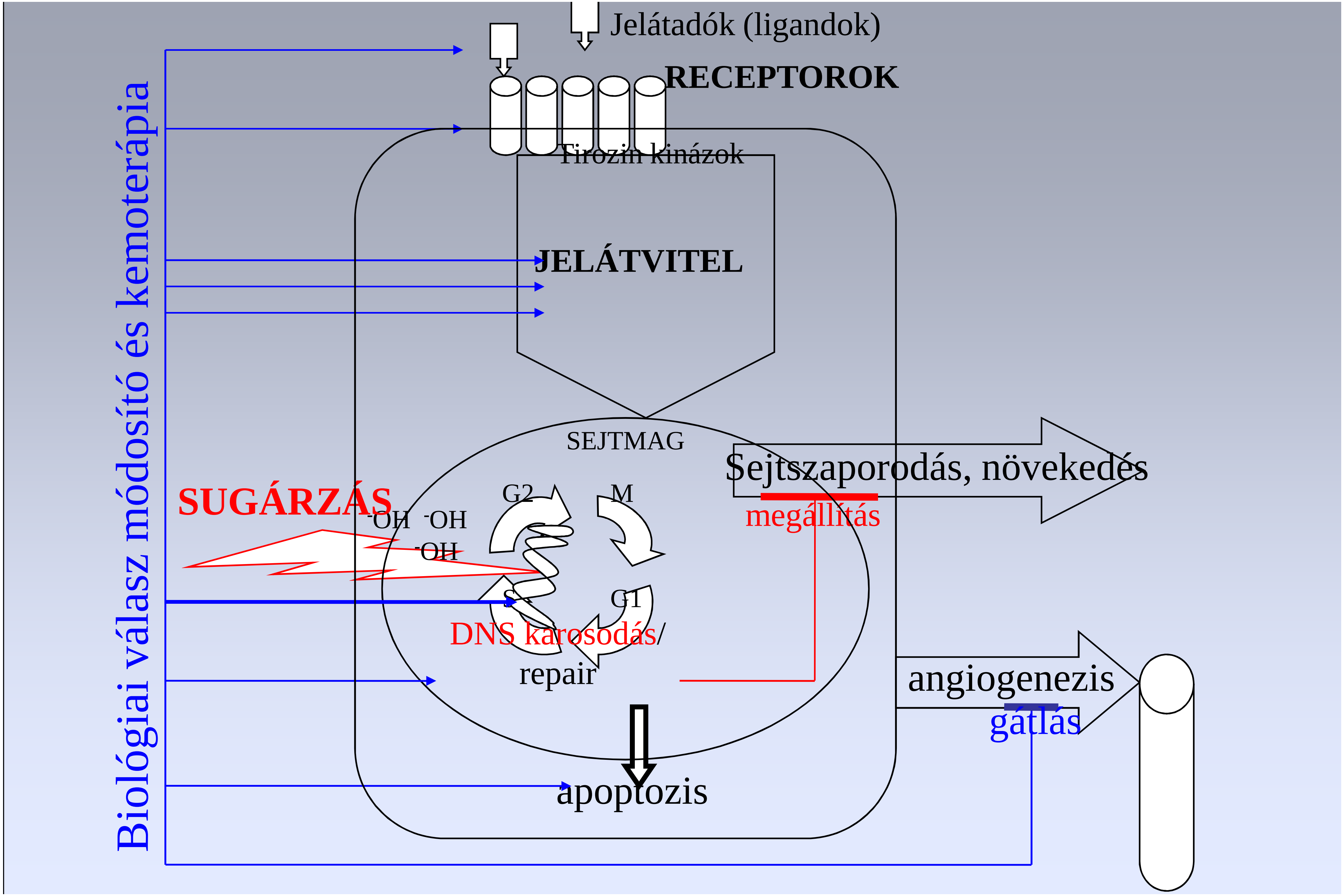
Sugárérzékenyítés

Chemo-, hormon, biol.m.

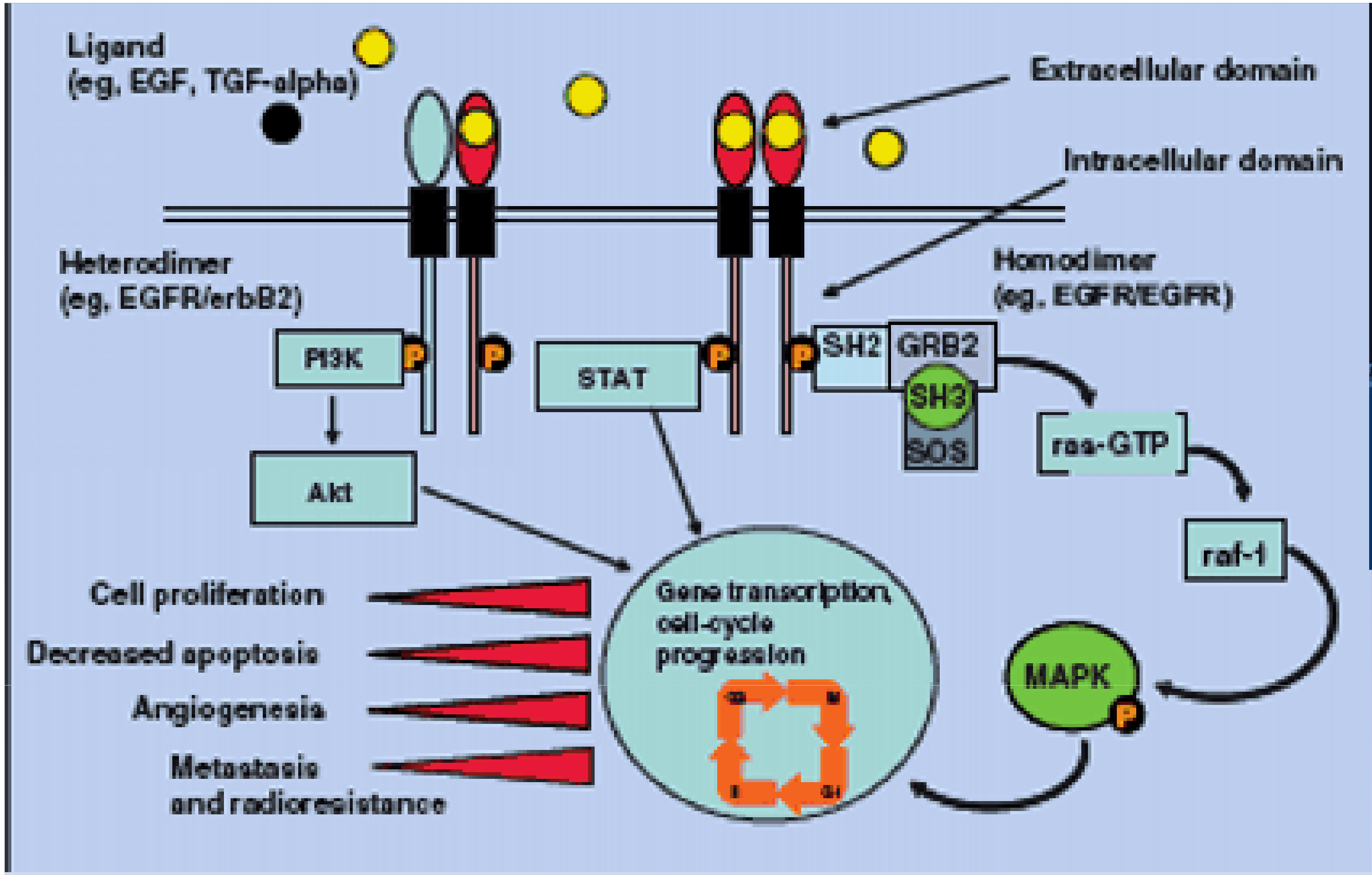
Hypoxiás szenzitizálók

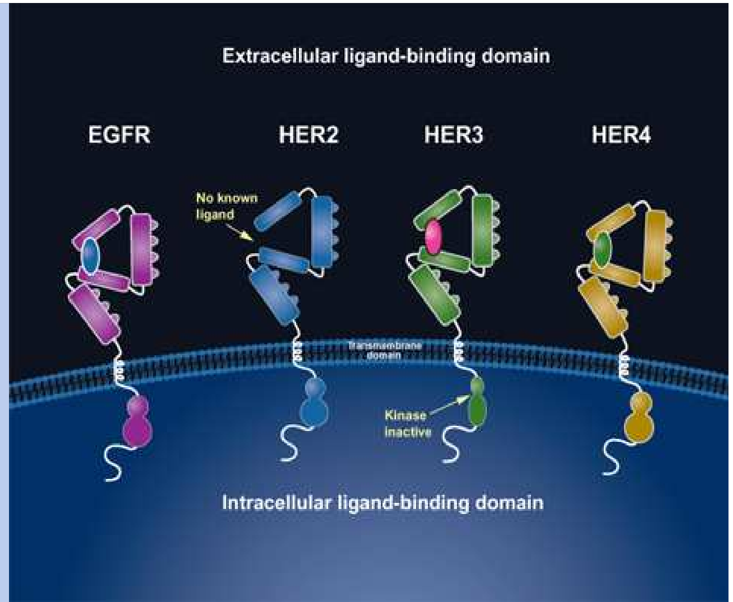
Technikai fejlődés

Fokozott szelektivitás



Jelátadók (ligandok)
RECEPTOROK
Tirozin kinázok
JELÁTVITEL
Biológiai válasz módosító és kemoterápia
SEJTMAG
Sejtszaporodás, növekedés
megállítás
SUGÁRZÁS
-OH -OH
-OH
G2
M
S
G1
DNS károsodás/
repair
angiogenezis
gátlás
apoptózis





Anti-EGFr

Cetuximab

Zalutumumab

Panitumumab

Nimotuzumab

TKI

Lapatinib

Erlotinib

Topov

PF-00299804

Multi-I

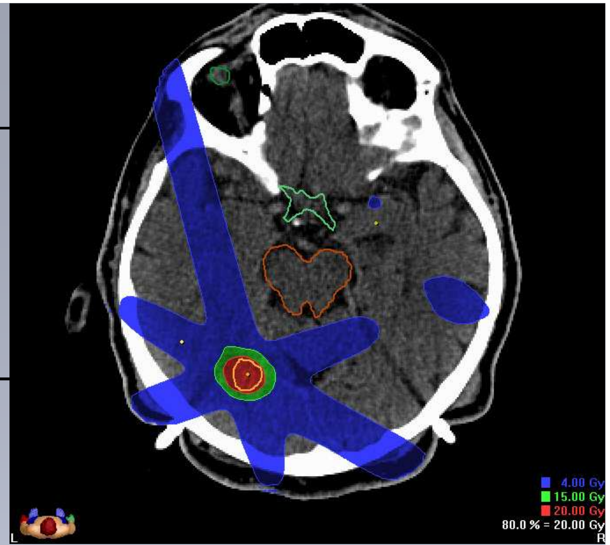
c-Raf, b-Raf VEGFR-1/2/3, PDGFR-β

Sorafenib

Proteosoma-I

Bortezomib

A fizikai specificitás növekedés



Céltérfogat

Szelektív, homogén, ill. tervezett inhomogén besugárzás

TCP ↑

Ép szövetek

Besugárzott térfogat és normál szöveti dózisterhelés csökkenése

NTCP ↓

Terápiás index növekszik

Szelektív sugárterápia

3D/IG brachyterápia

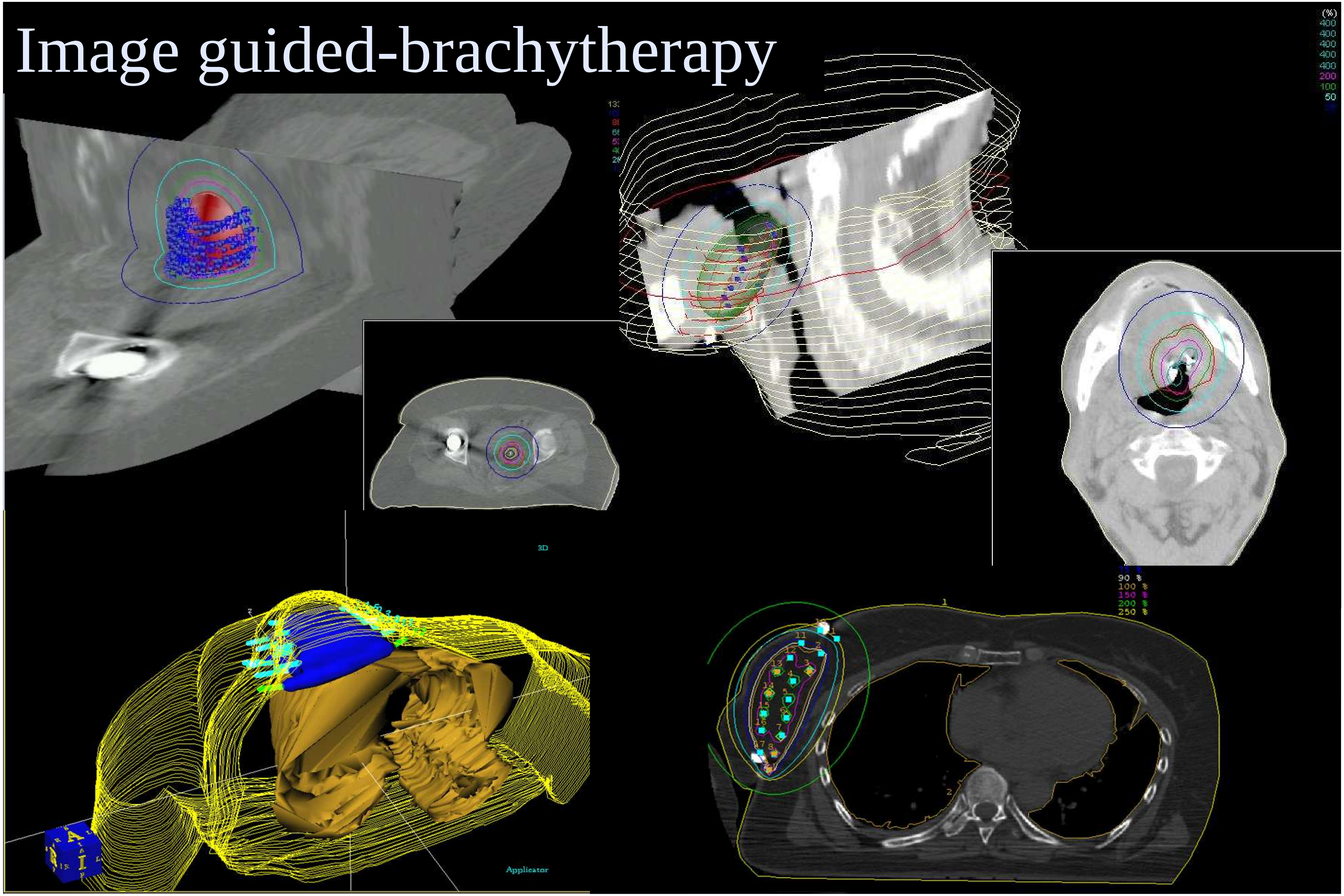
3DCRT/sztereotaxia

IMRT/HT/VMAT

HADRON TERÁPIA

IGRT

Image guided-brachytherapy



Sugárforrások

X-ray tube,Orthovolt (250KV)

Cobalt beam1,26 MeV

Linearis gyorsító/ VMAT

Helical-/Robot-forrás

Synchrocyclotron/reaktor

Laser indukált hadron forrás

Céltérfogat meghatározás

2D becslés, Anatomia,Szimulátor

CT, PET-CT/MRI

Tervezés

Manuális, 2D

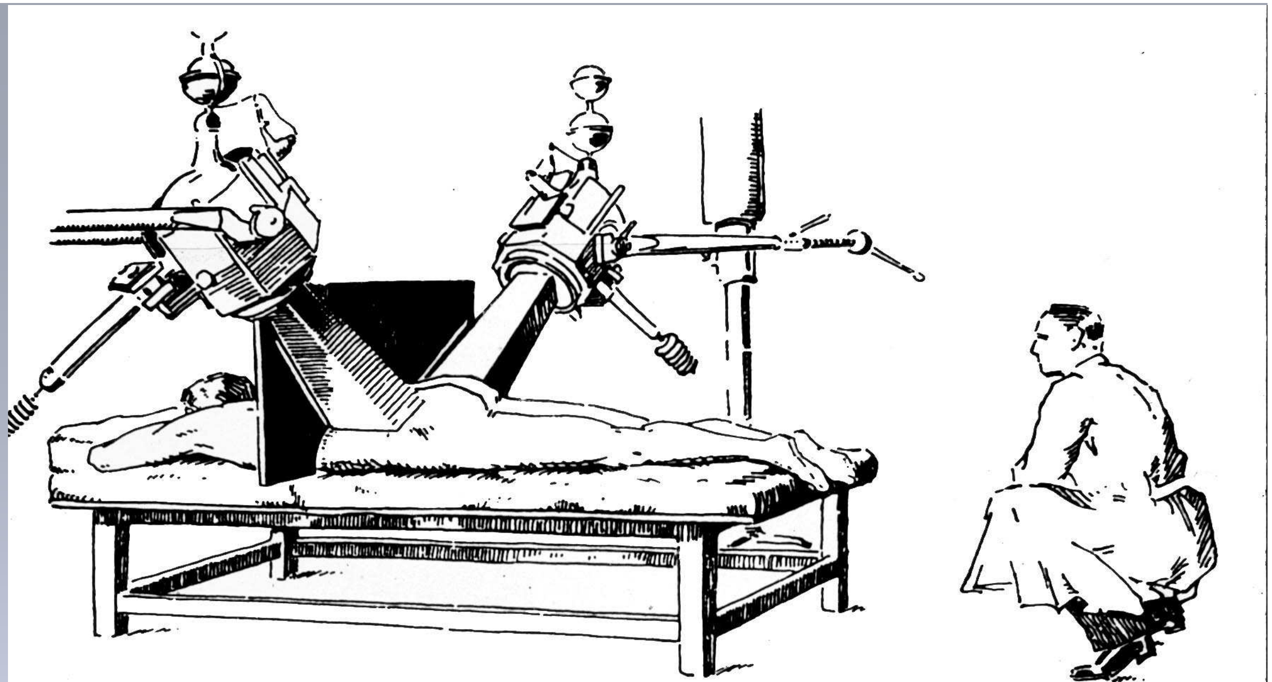
3D forward, inverz

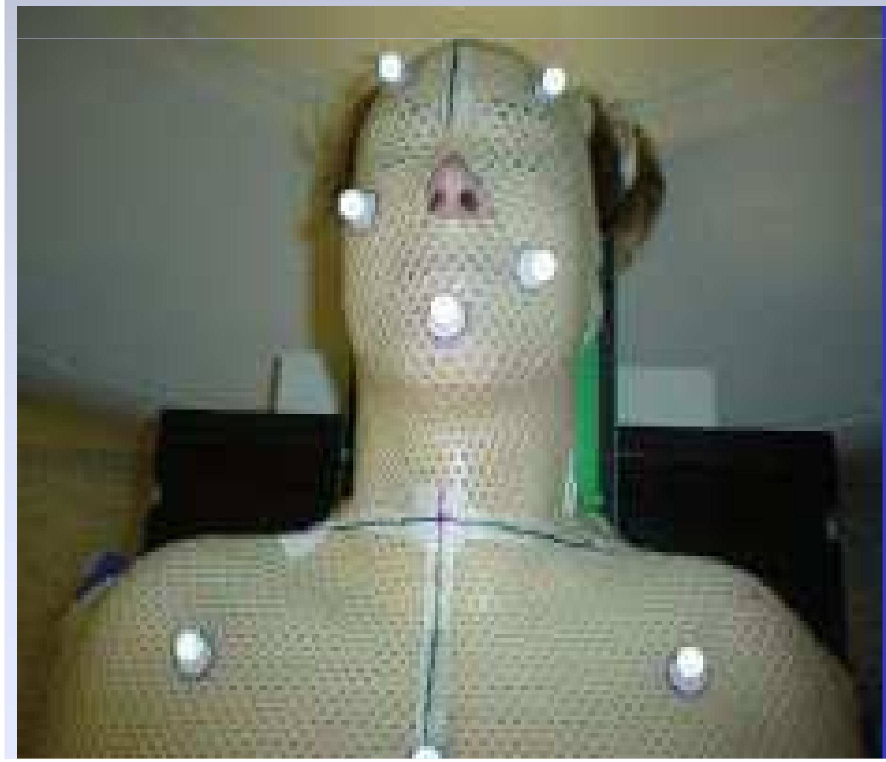
Kivitelezés

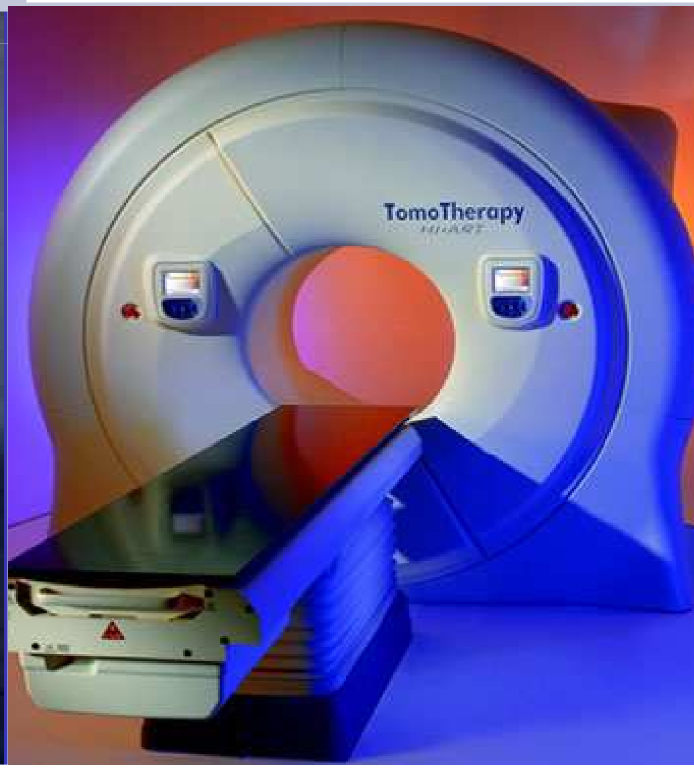
Pozícionálás/ beállítás

Kezelés verifikáció

Film, EPID, IGRT



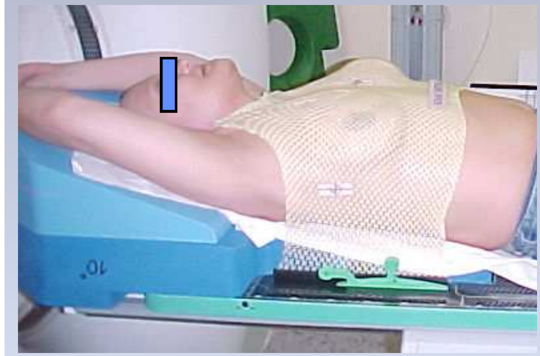


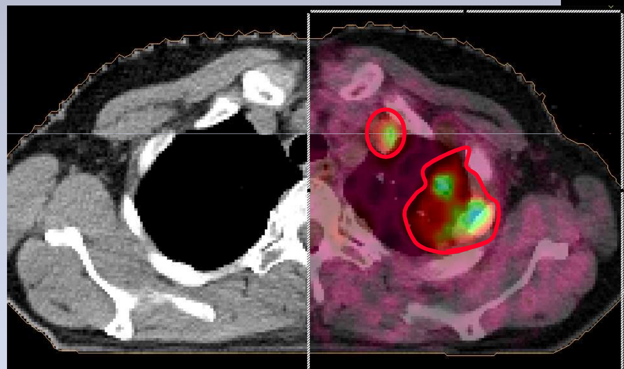


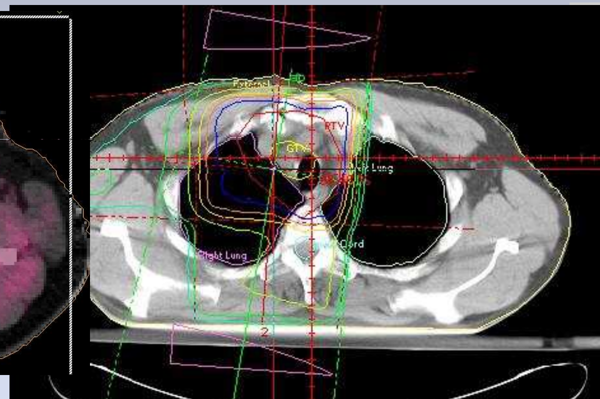
Folyamat-rendszer

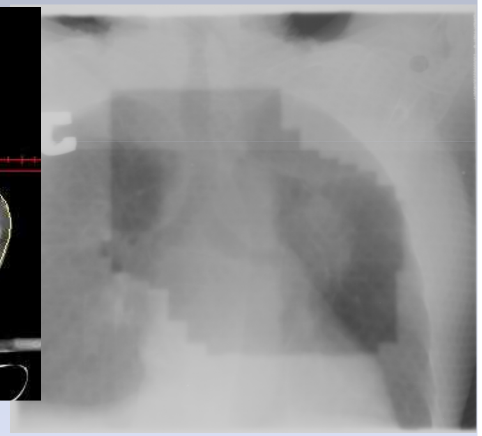
Beteg fektetés immobilizáció → Tervezési képalkotás(CT) → 3D tervezés → Beállítás, me-zőellenőrzés

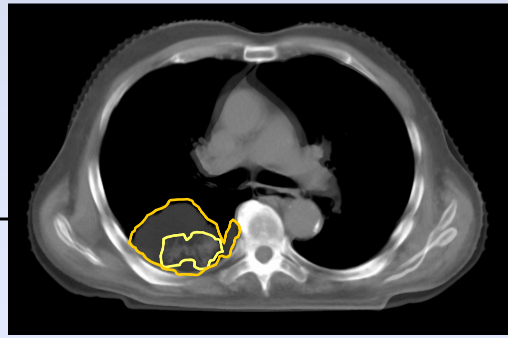
PET-CT/MRI



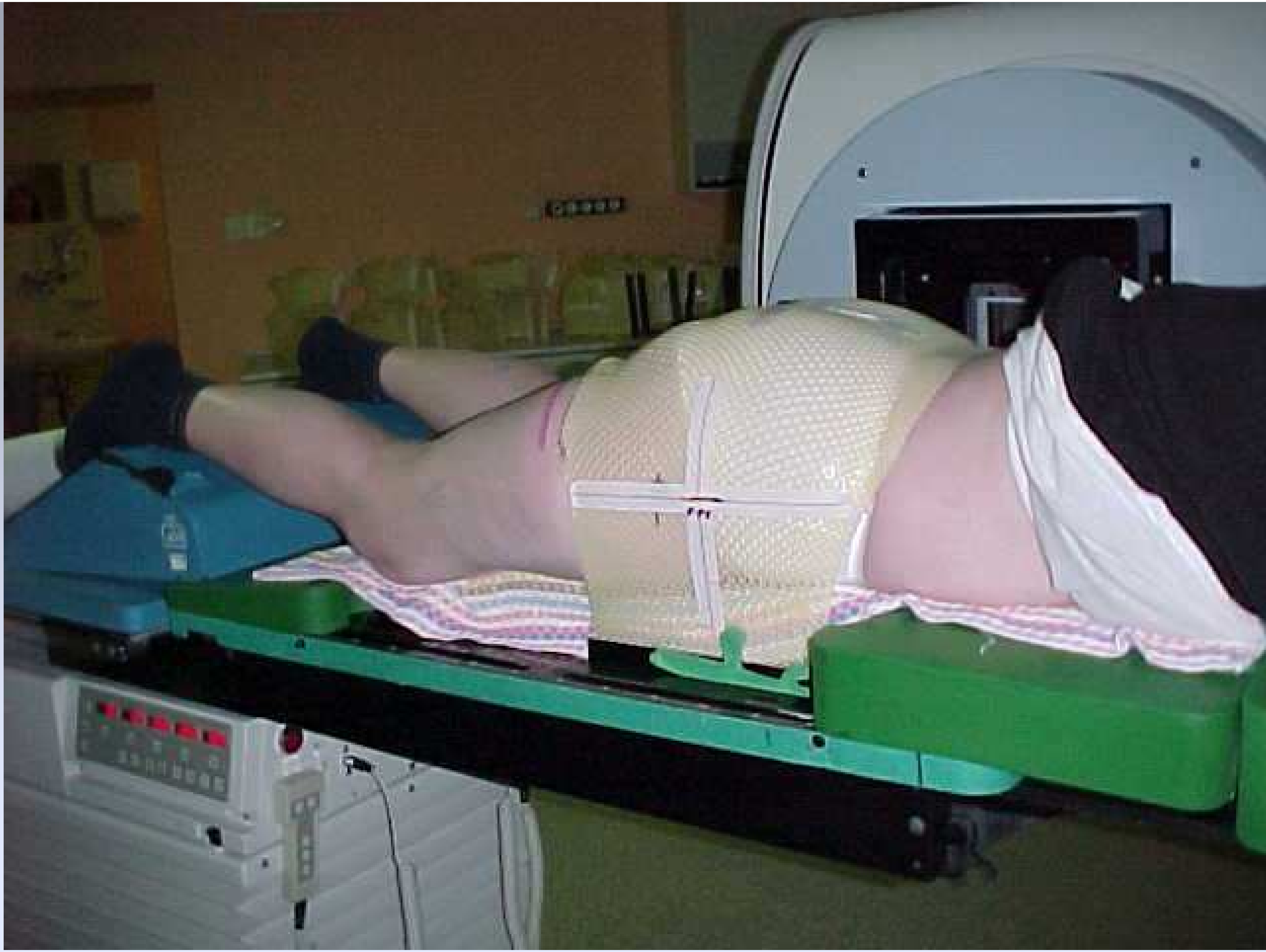






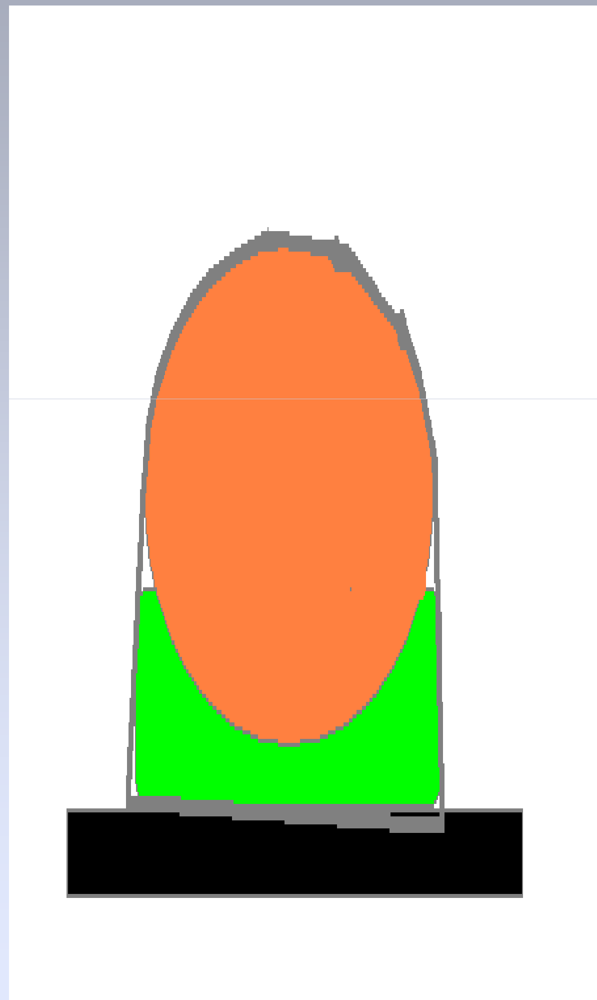


Re-CT- kép fúzió



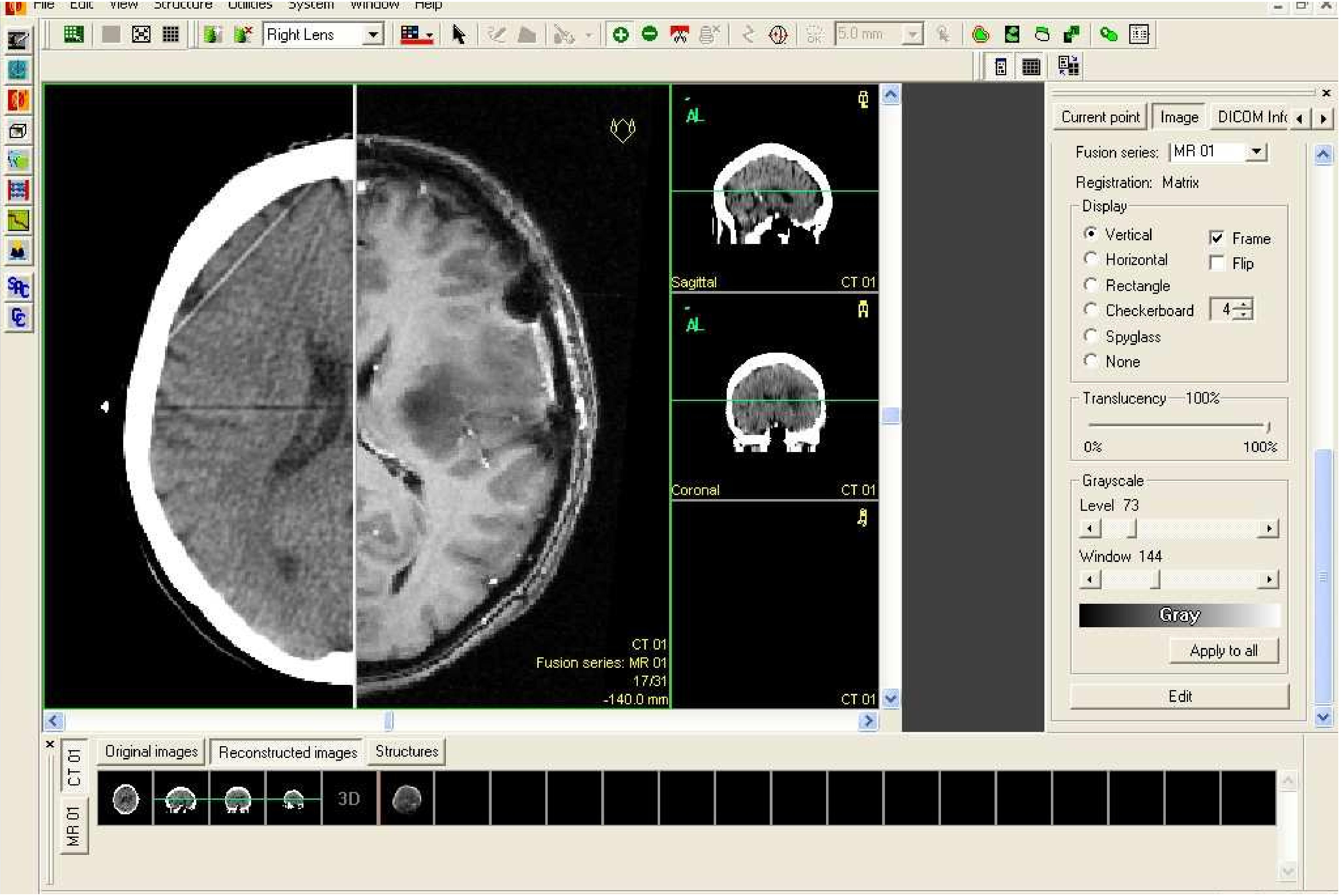



Combination of vacuum cushion and thermoplastic mask

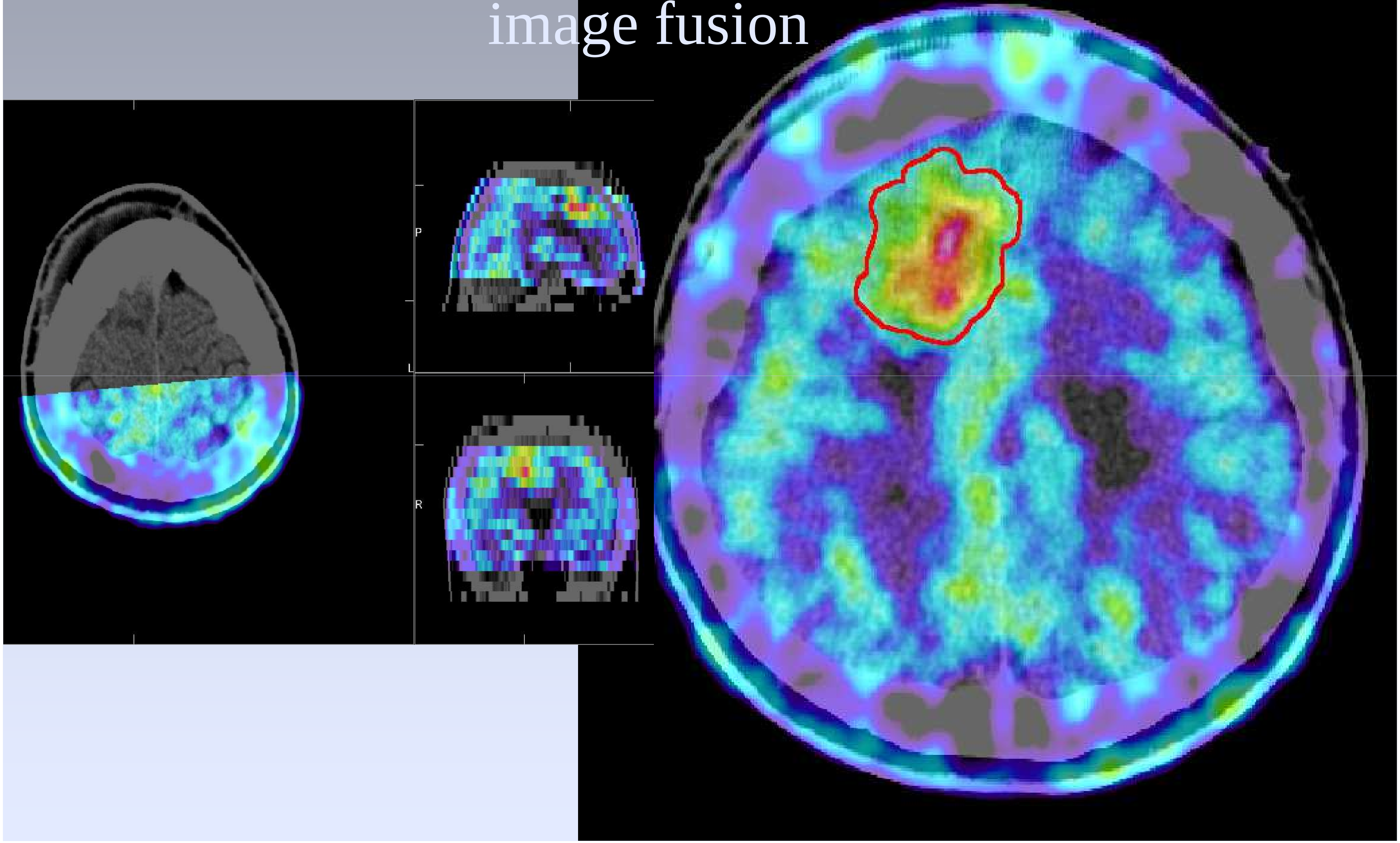


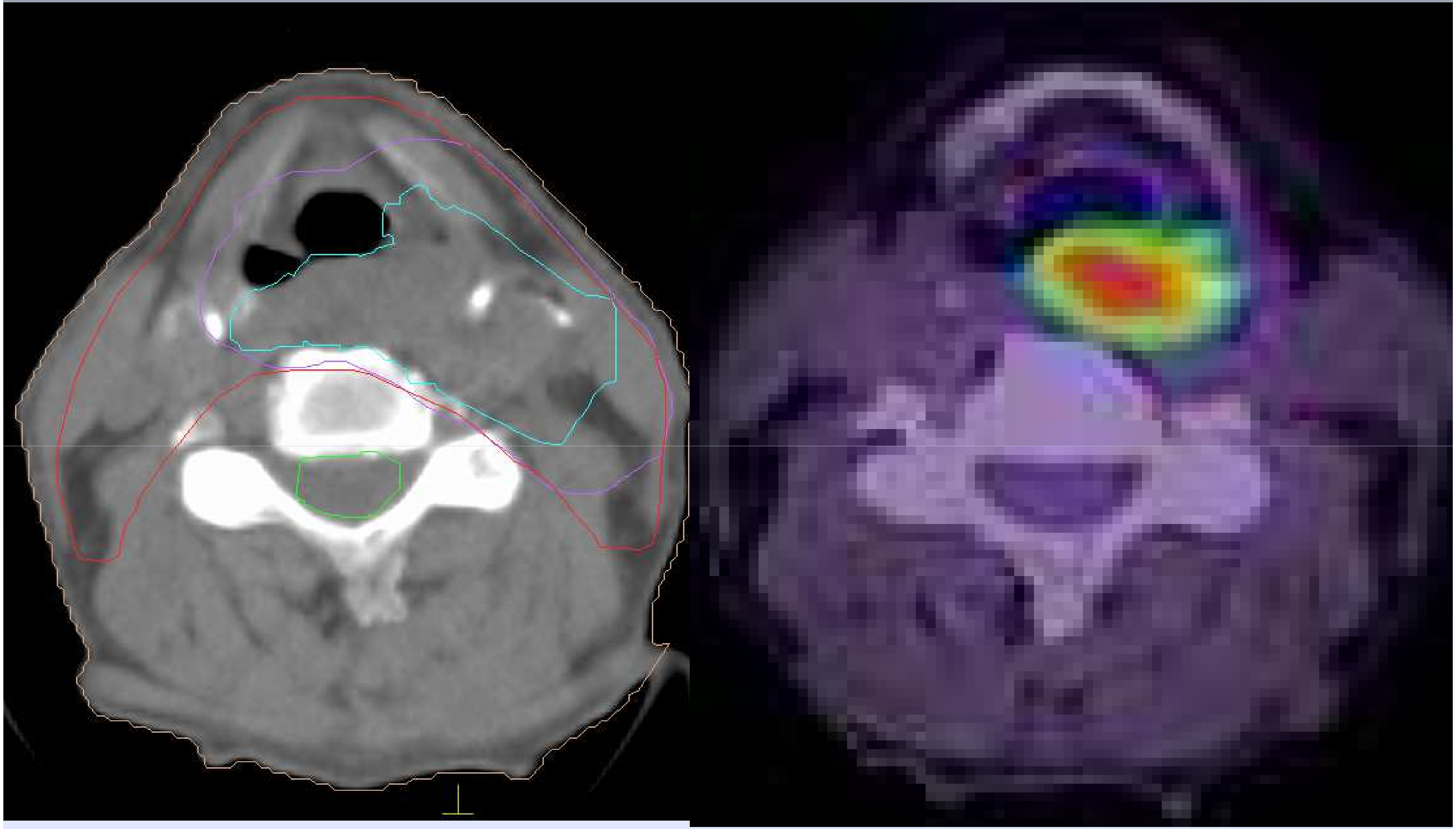

SOMATOM
Emotion 6

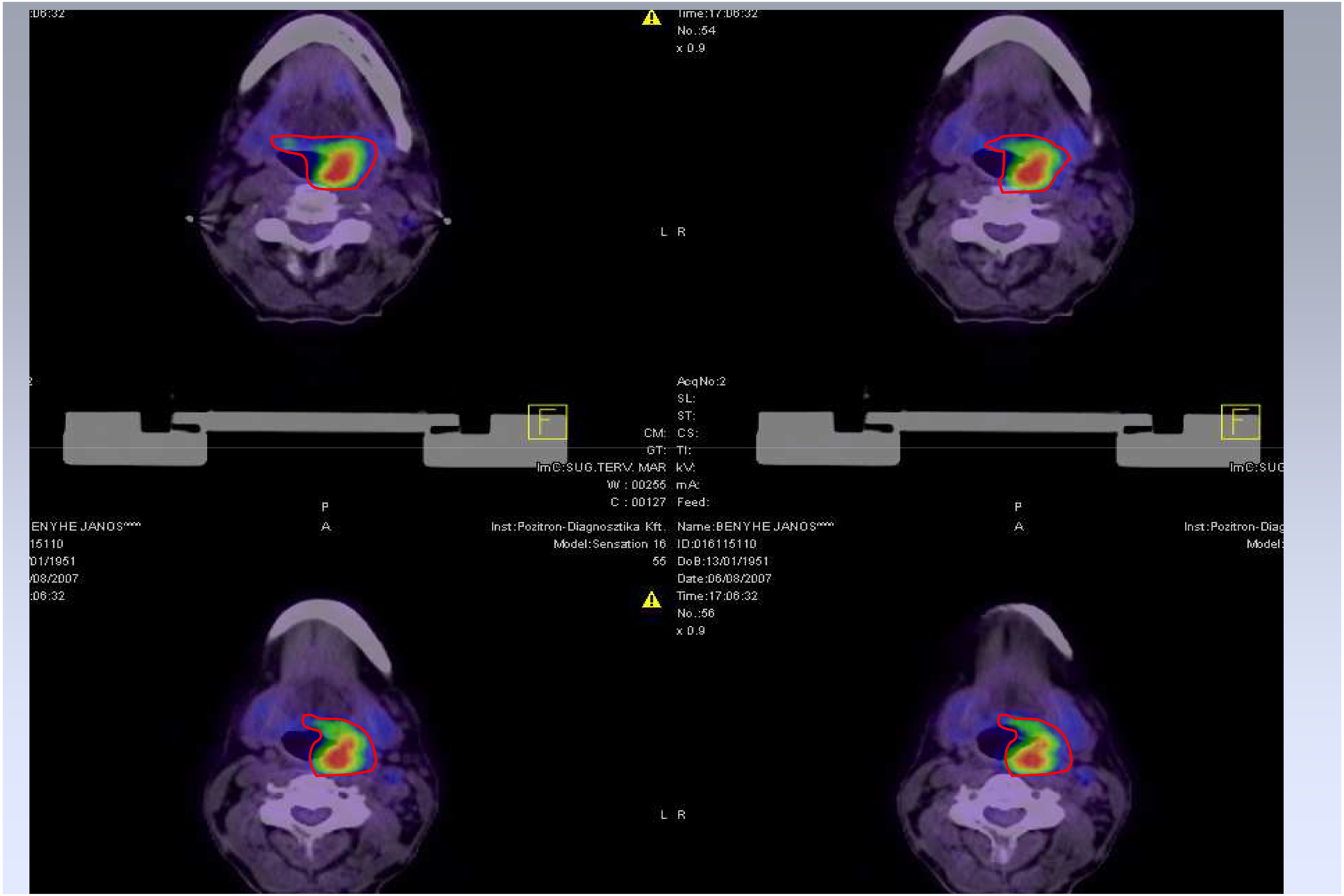
PET/CT

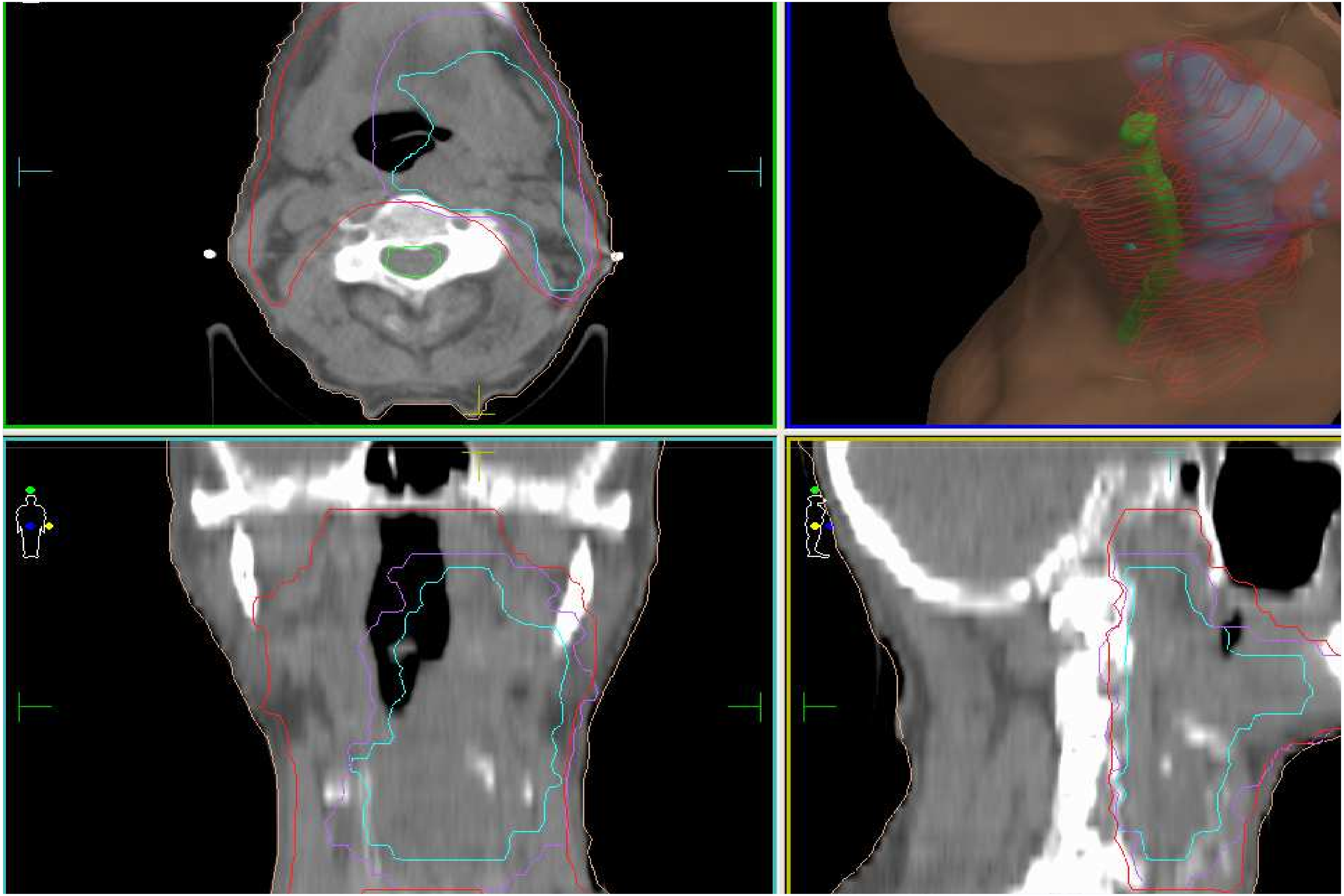

File Edit View Structure Utilities System Window Help
Right Lens
5.0 mm
Sagittal
CT 01
Coronal
CT 01
CT 01
Fusion series: MR 01
17/31
-140.0 mm
CT 01
Current point
Image
DICOM Info
Fusion series: MR 01
Registration: Matrix
Display
Vertical
Horizontal
Rectangle
Checkerboard
Spyglass
None
Frame
Flip
4
Translucency 100%
0%
100%
Grayscale
Level 73
Window 144
Gray
Apply to all
Edit
Original images
Reconstructed images
Structures
CT 01
MR 01
3D

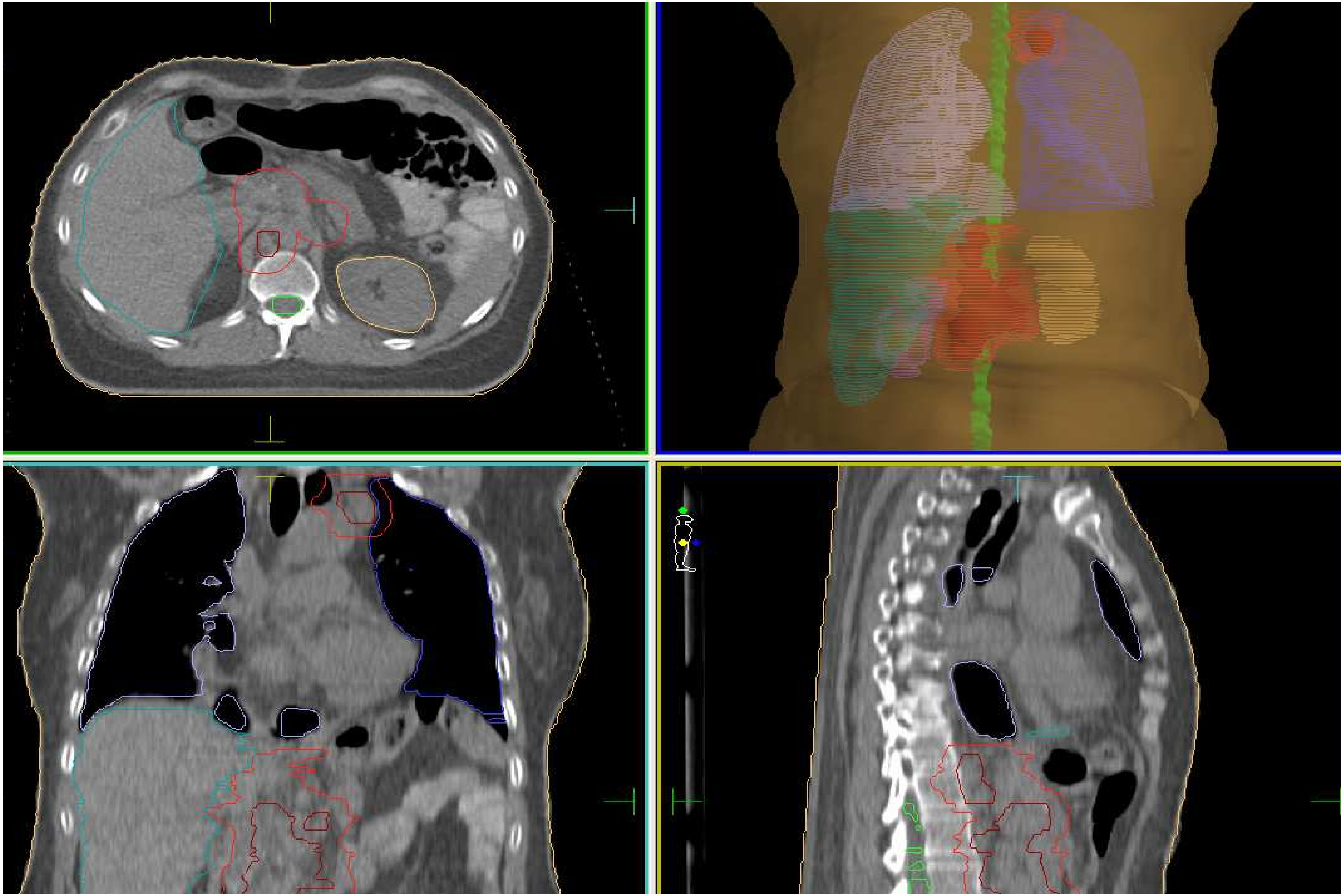
Indication of target volume on the basis of PET-CT image fusion





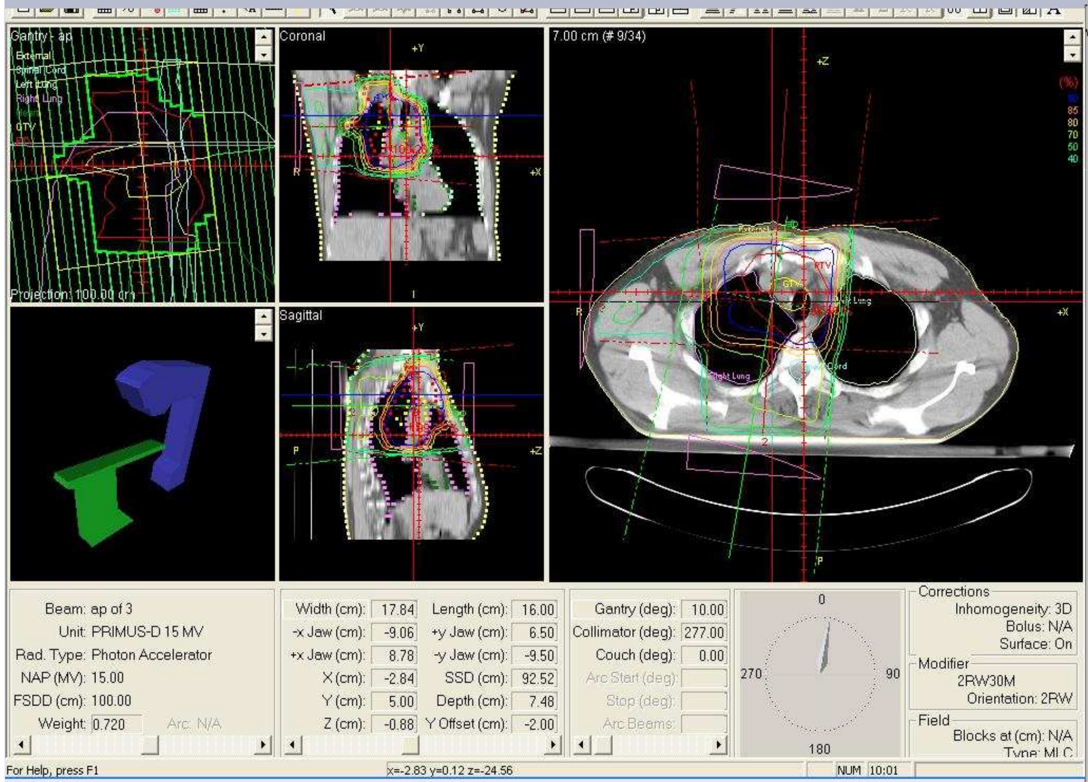

:06:32
Time:17:06:32
No.:54
x 0.9
L R
AcqNo:2
SL:
ST:
CM: CS:
GT: TI:
ImC:SUG.TERV. MAR kV:
W : 00255 mA:
C : 00127 Feed:
ImC:SUG
P
A
ENYHE JANOS****
15110
01/1951
/08/2007
:06:32
Inst:Pozitron-Diagnosztika Kft.
Model:Sensation 16
55
Name:BENYHE JANOS****
ID:016115110
DoB:13/01/1951
Date:06/08/2007
Time:17:06:32
No.:56
x 0.9
Inst:Pozitron-Diag
Model:
L R

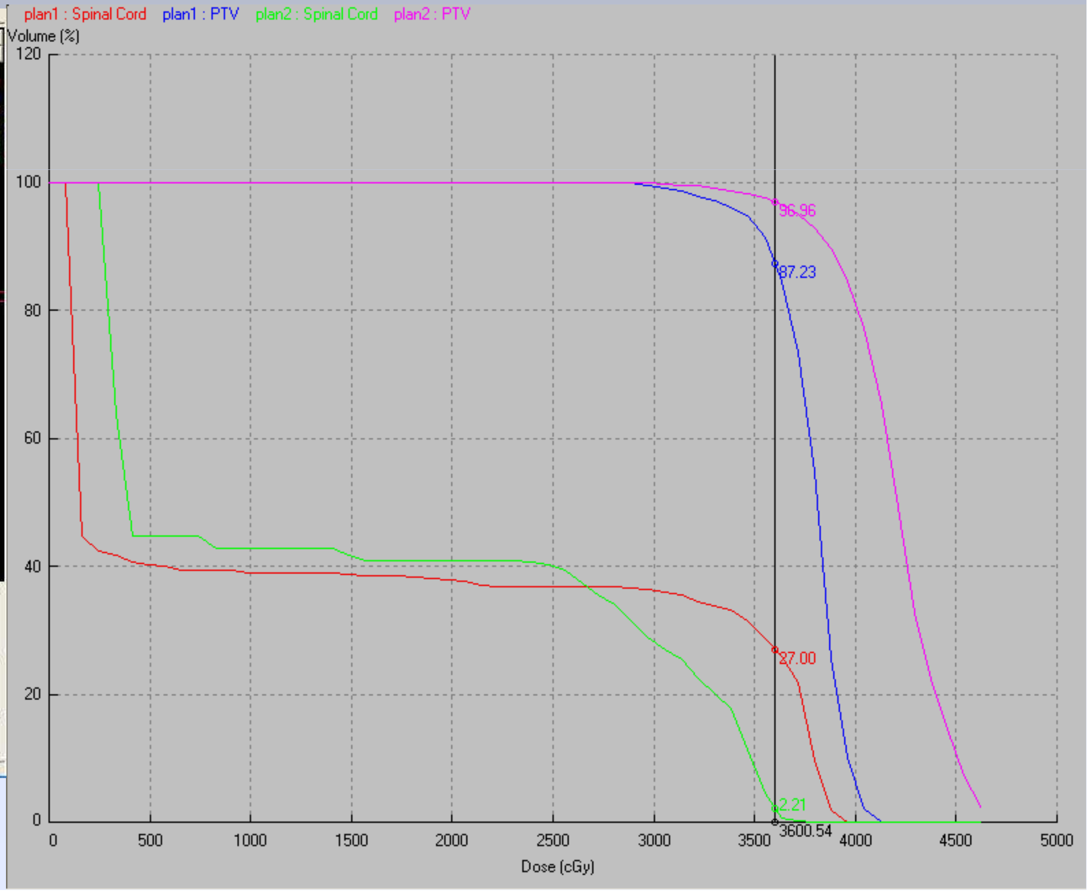




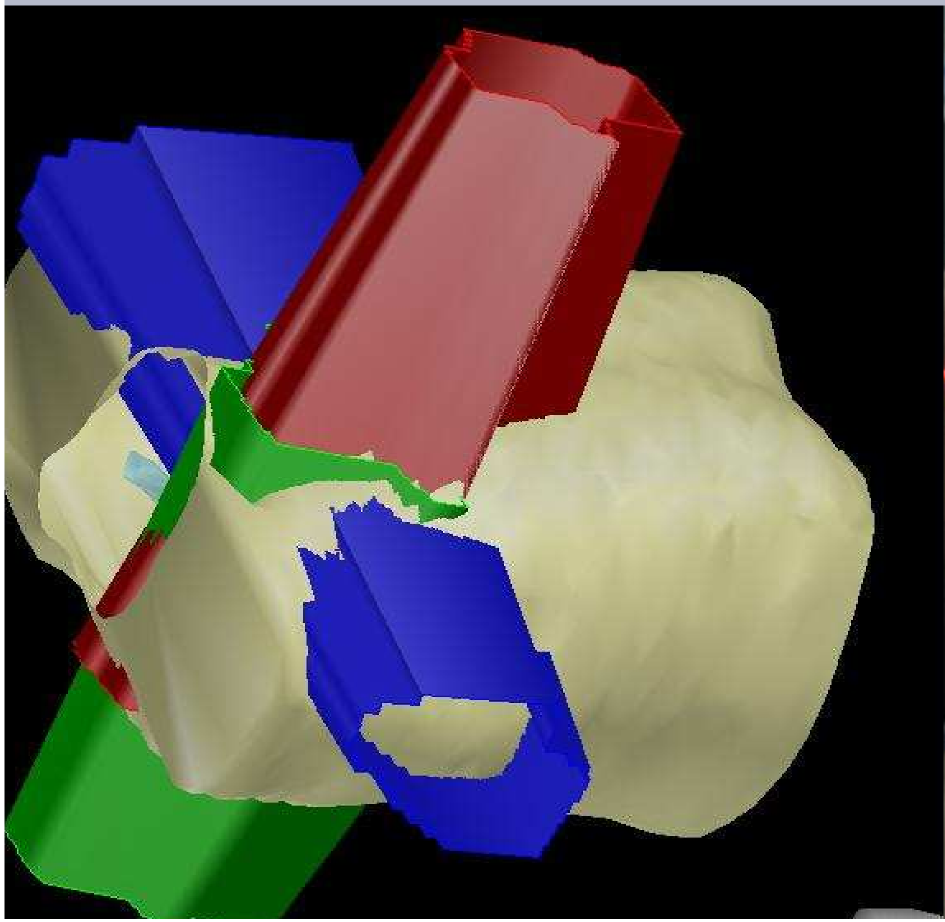
Besugárzás-tervezés- terv értékelés

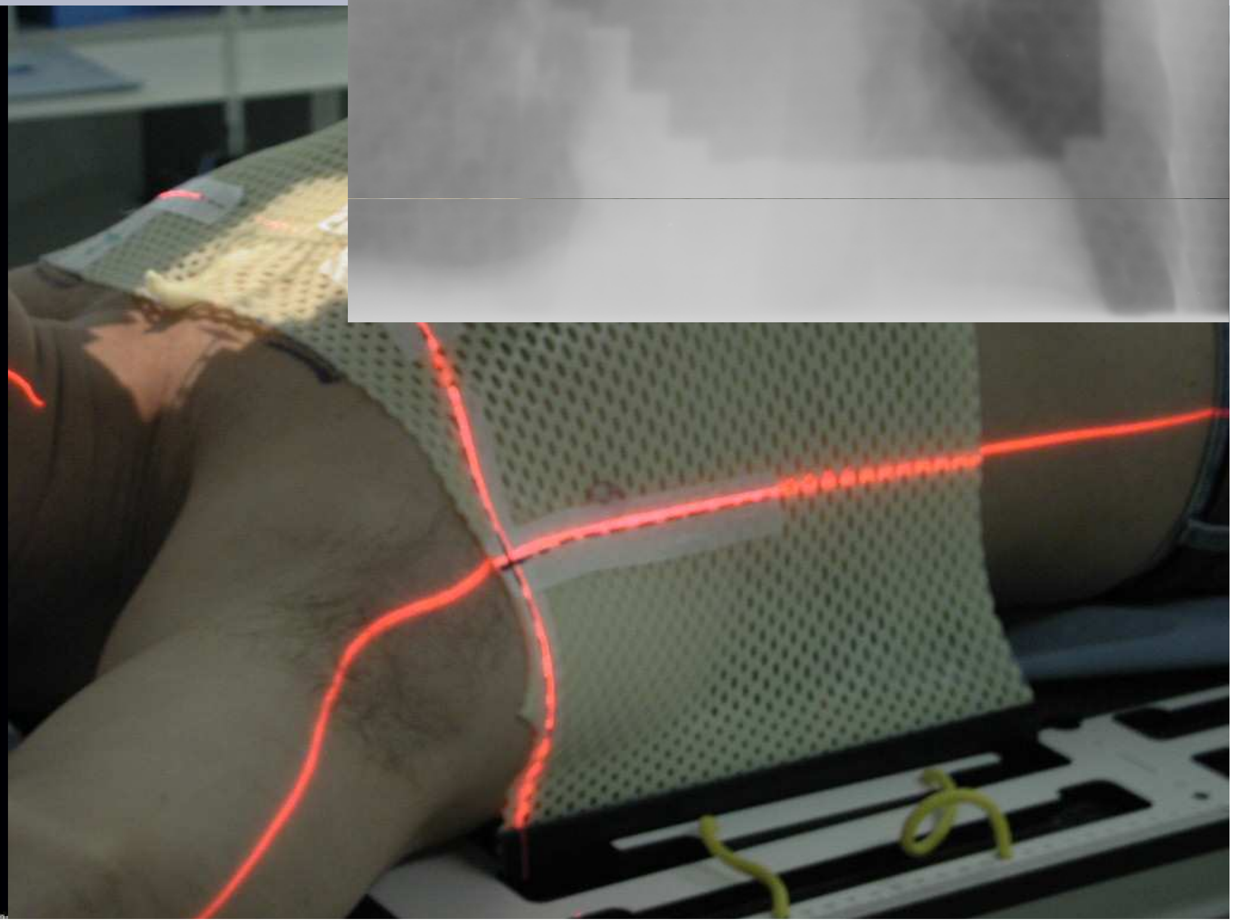
dóziseloszlás – numerikus, anat., DVH

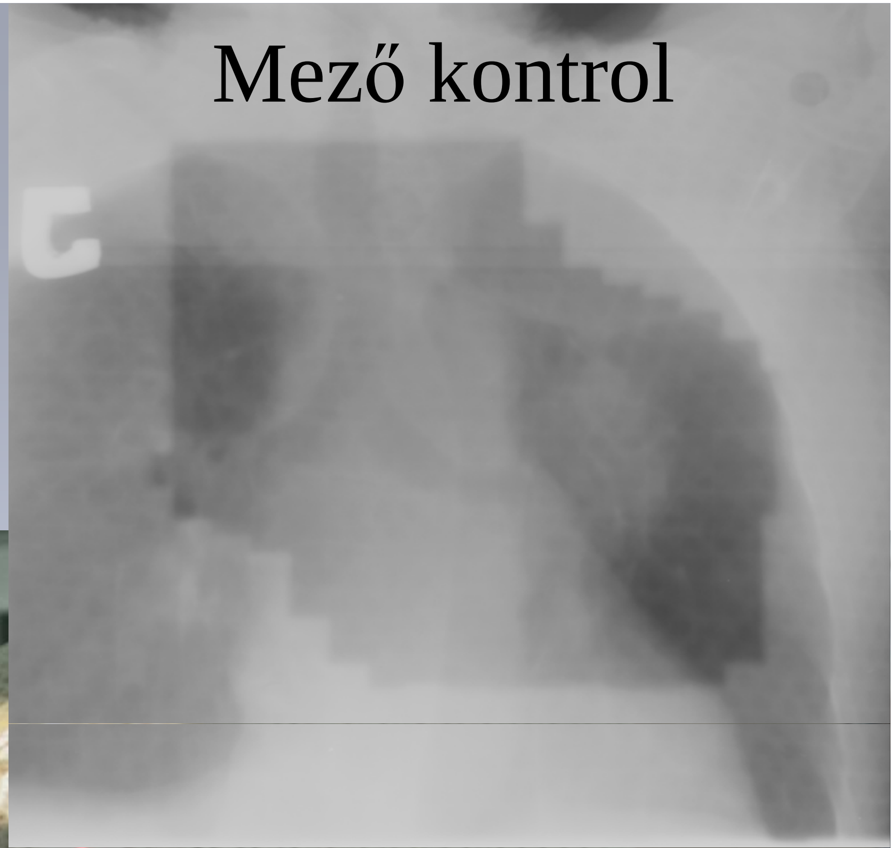


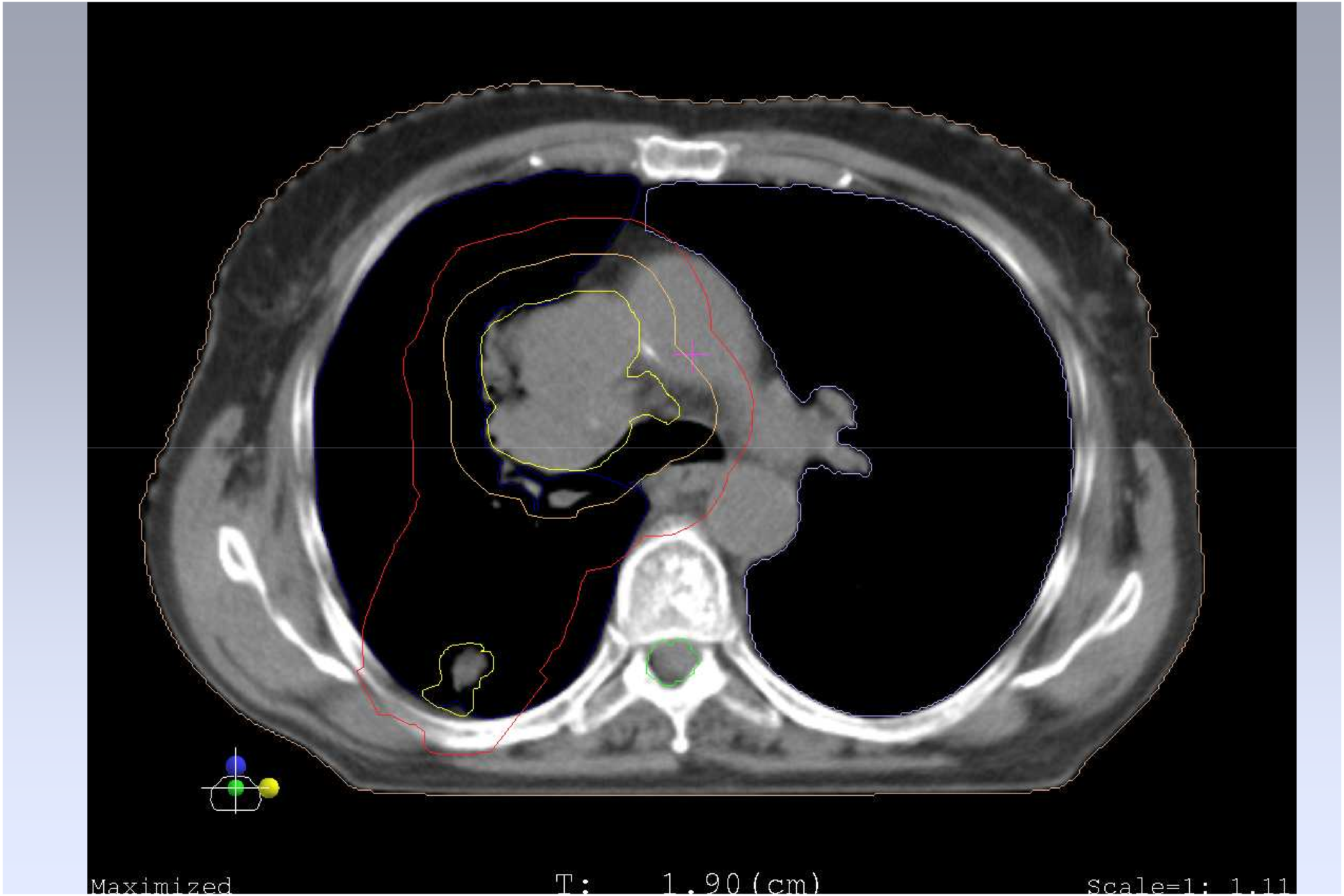


Besugárzás



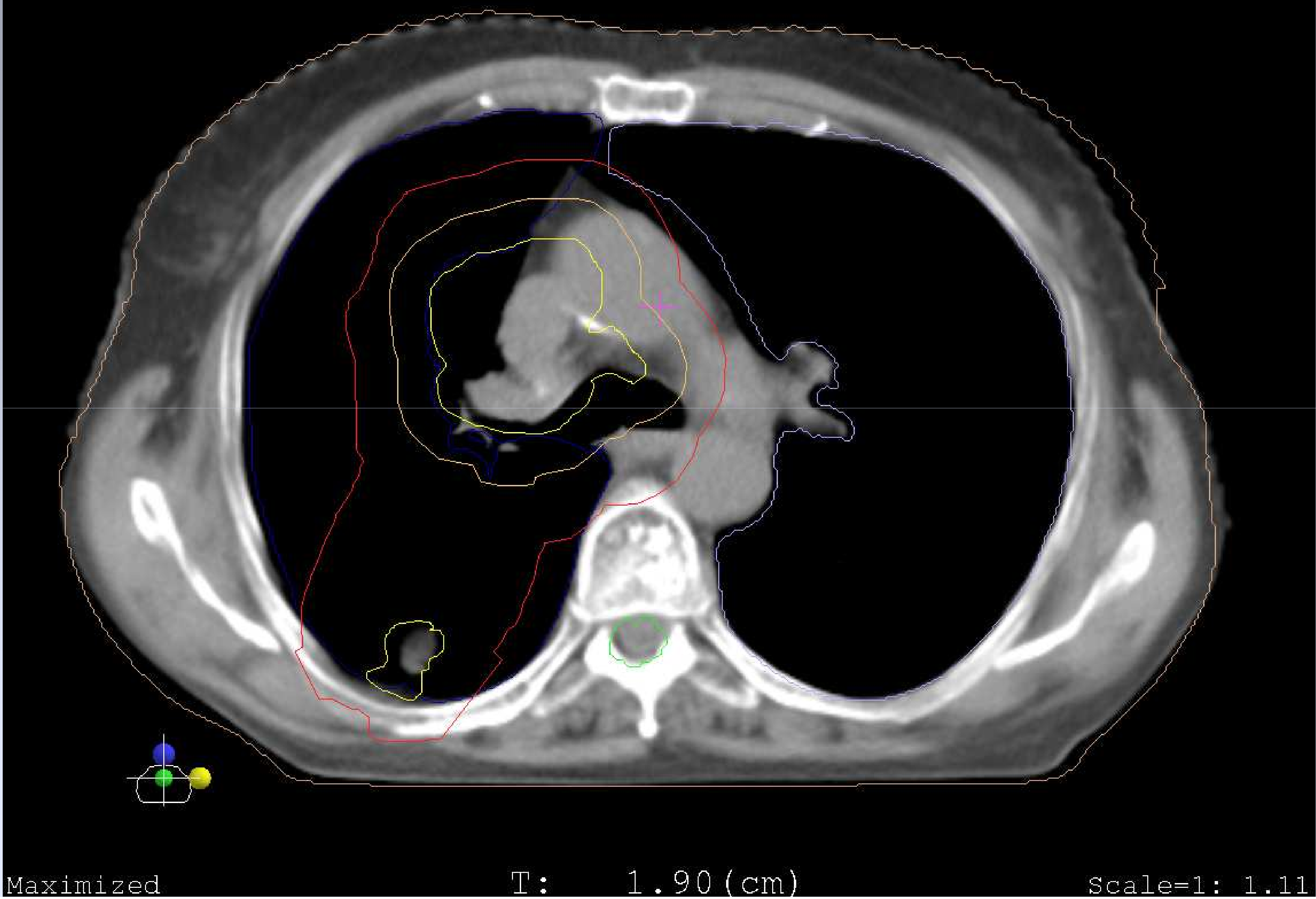


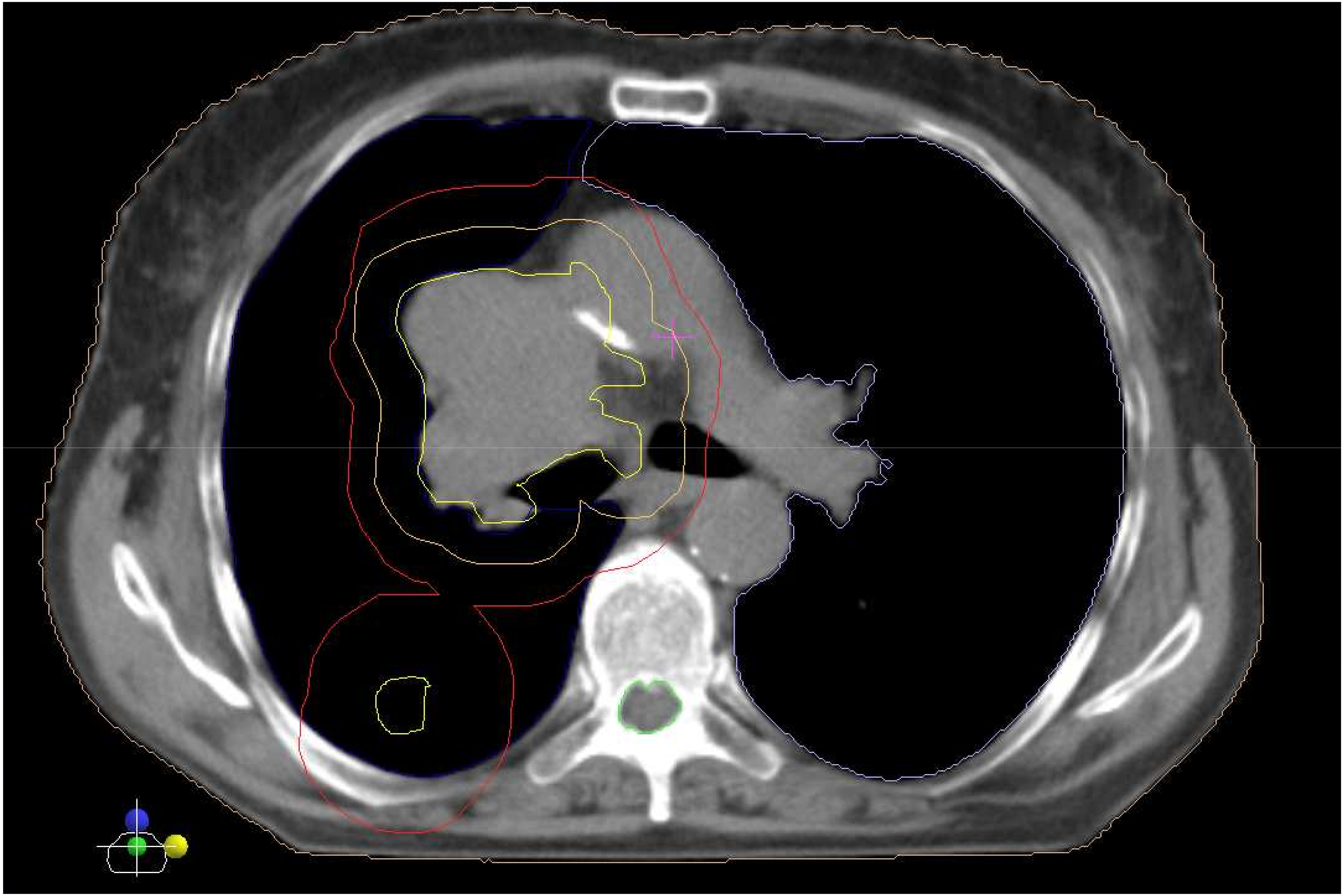


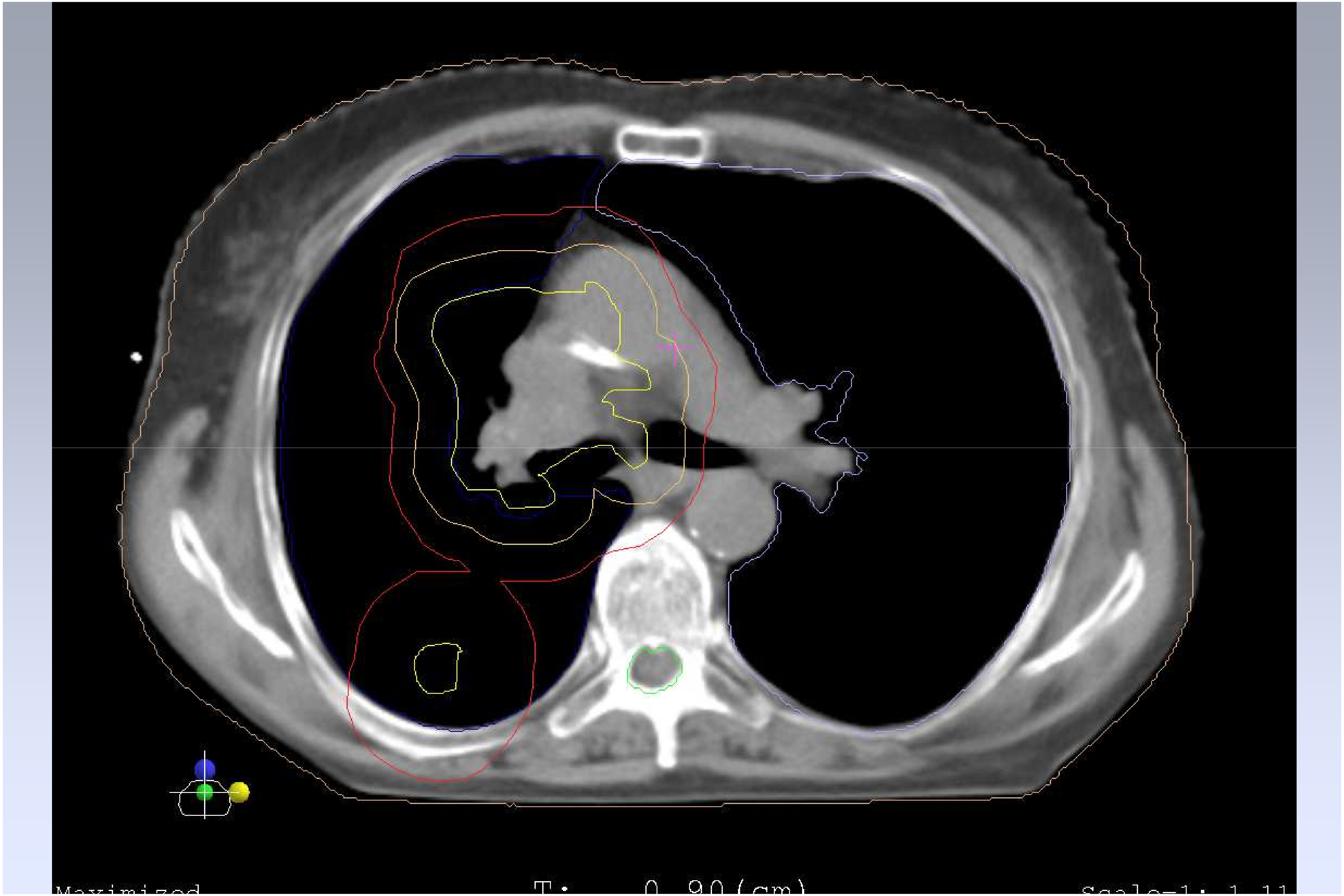


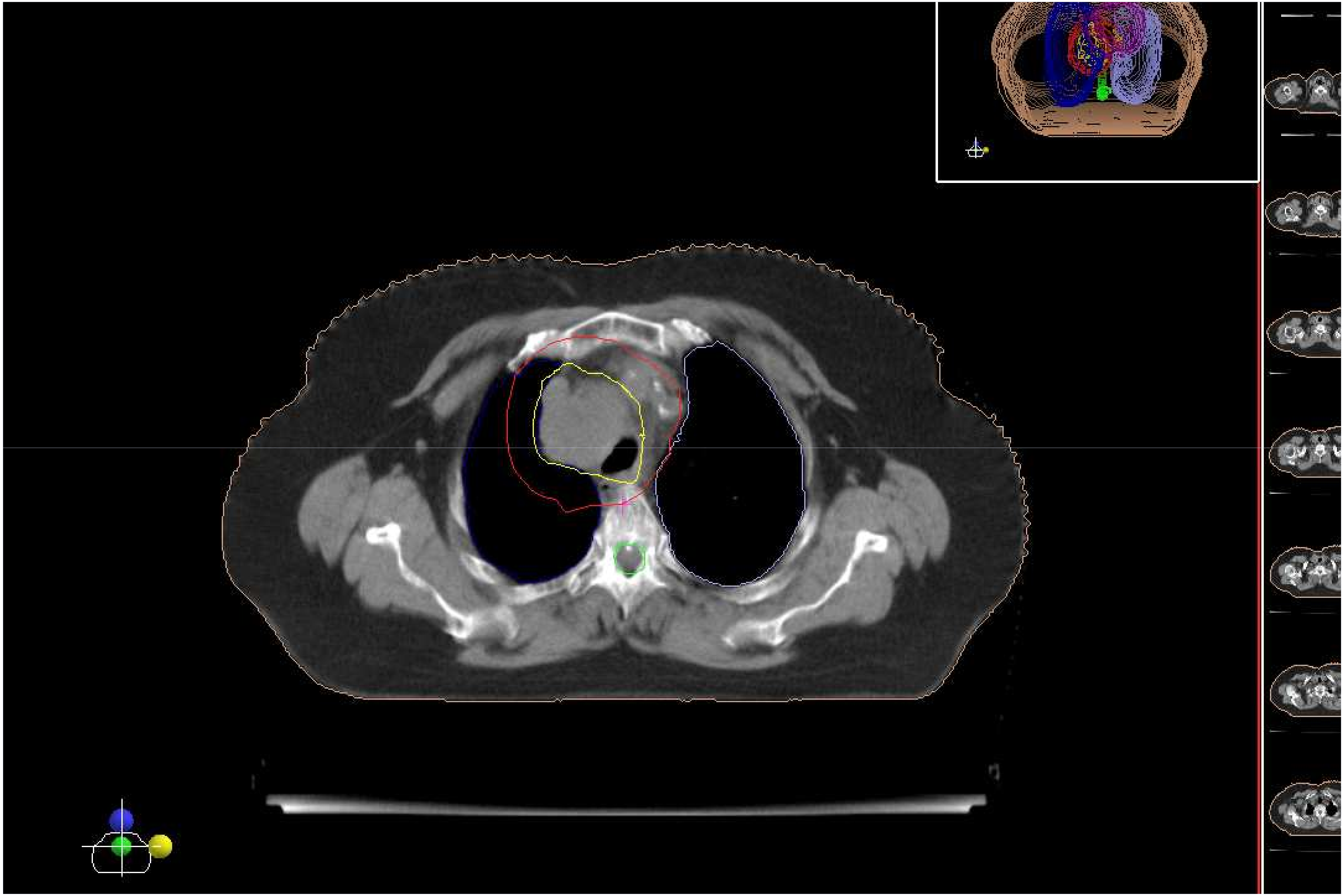
Maximized
T: 1.90(cm)
Scale=1: 1.11

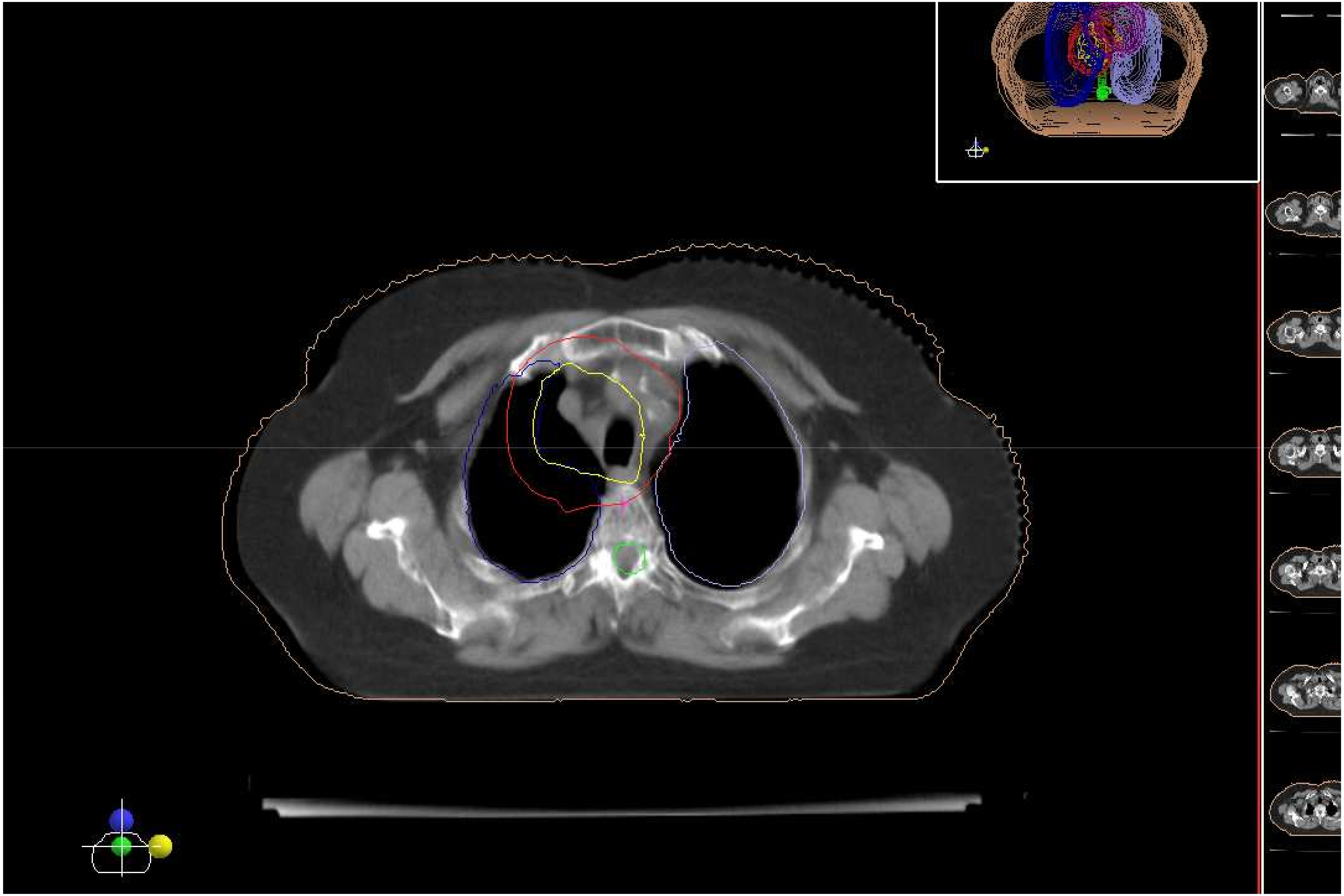
Re-CT 45Gy-nél











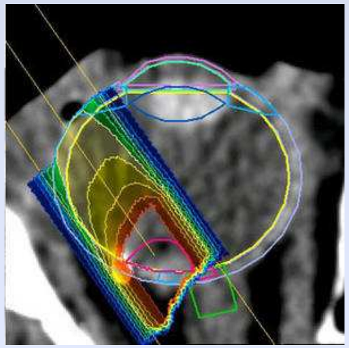
Atommag részecskék

Nagy fizikai szelektivitás

Magas LET, nagy RBE

Proton

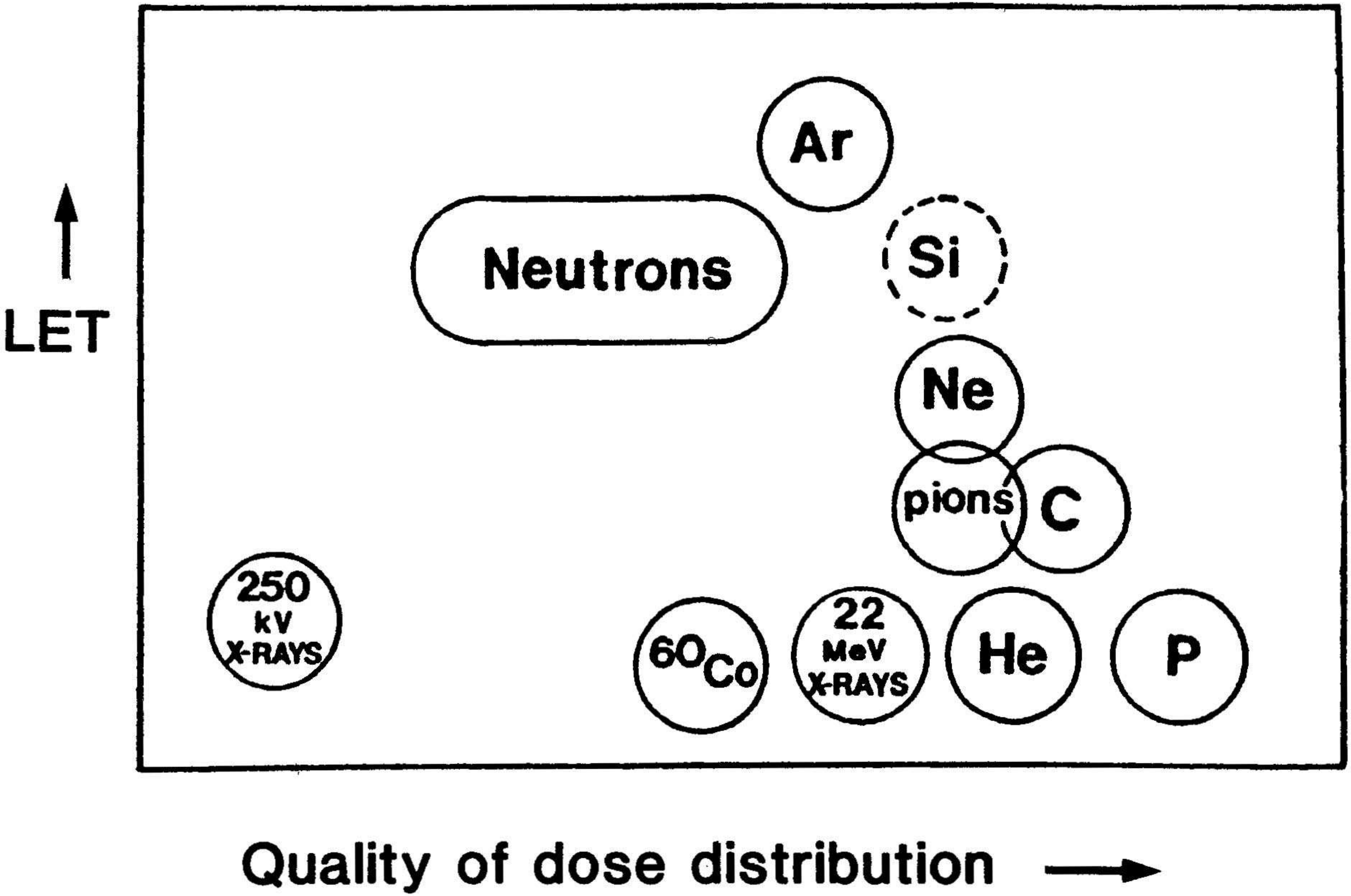
Neutron

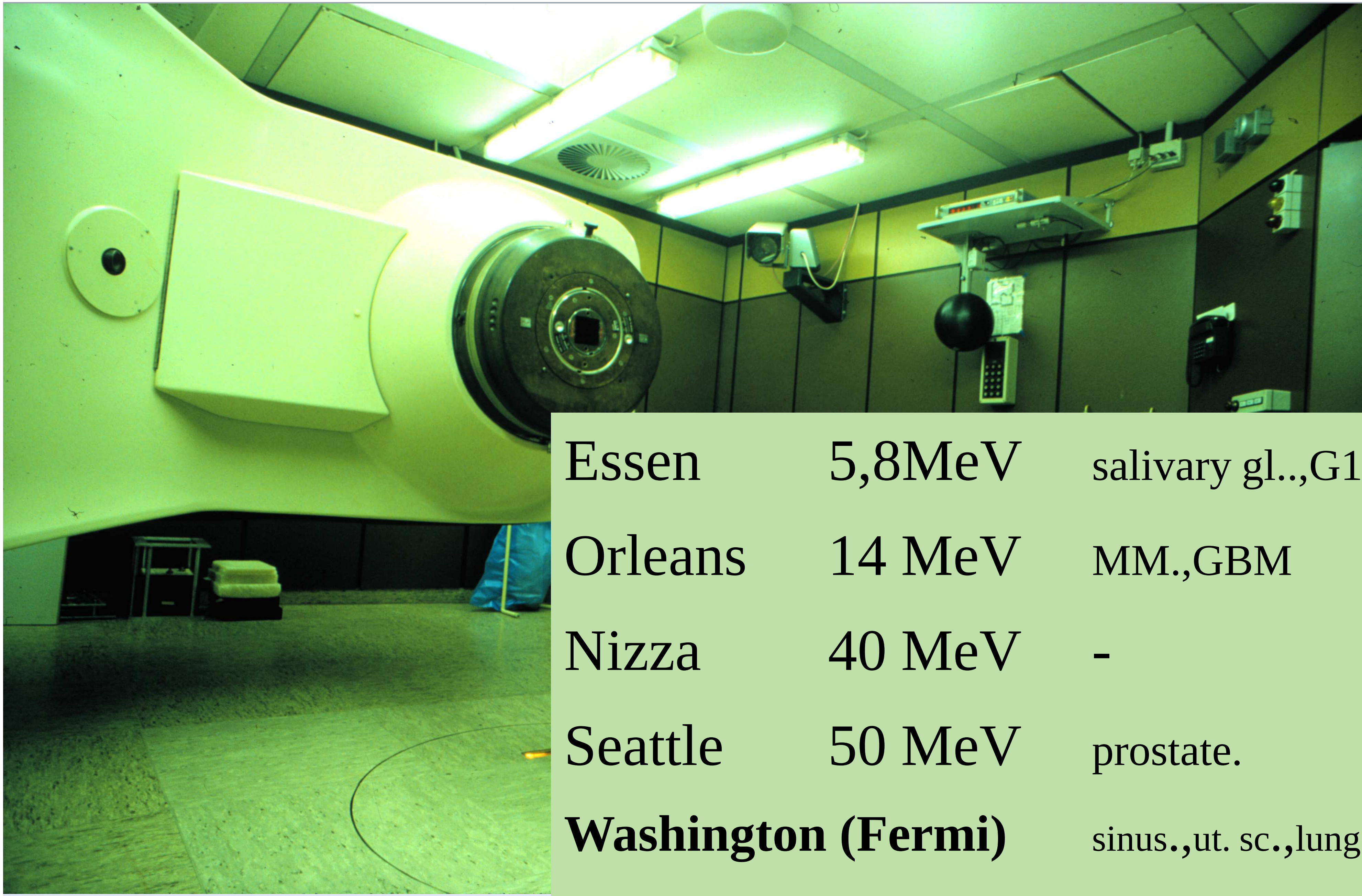


Nehéz ionok:

Szén, Oxigén, Neon

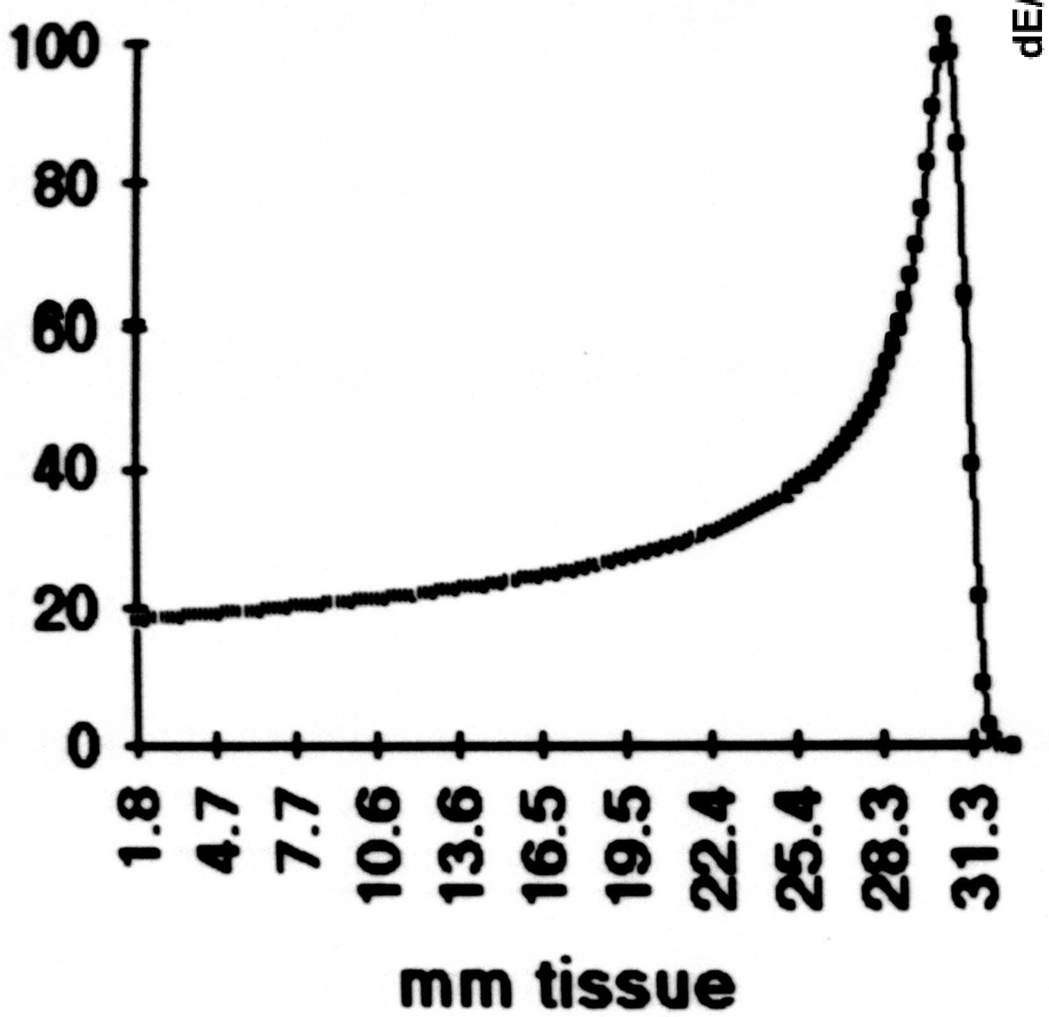
2010-ig >80.000 beteg

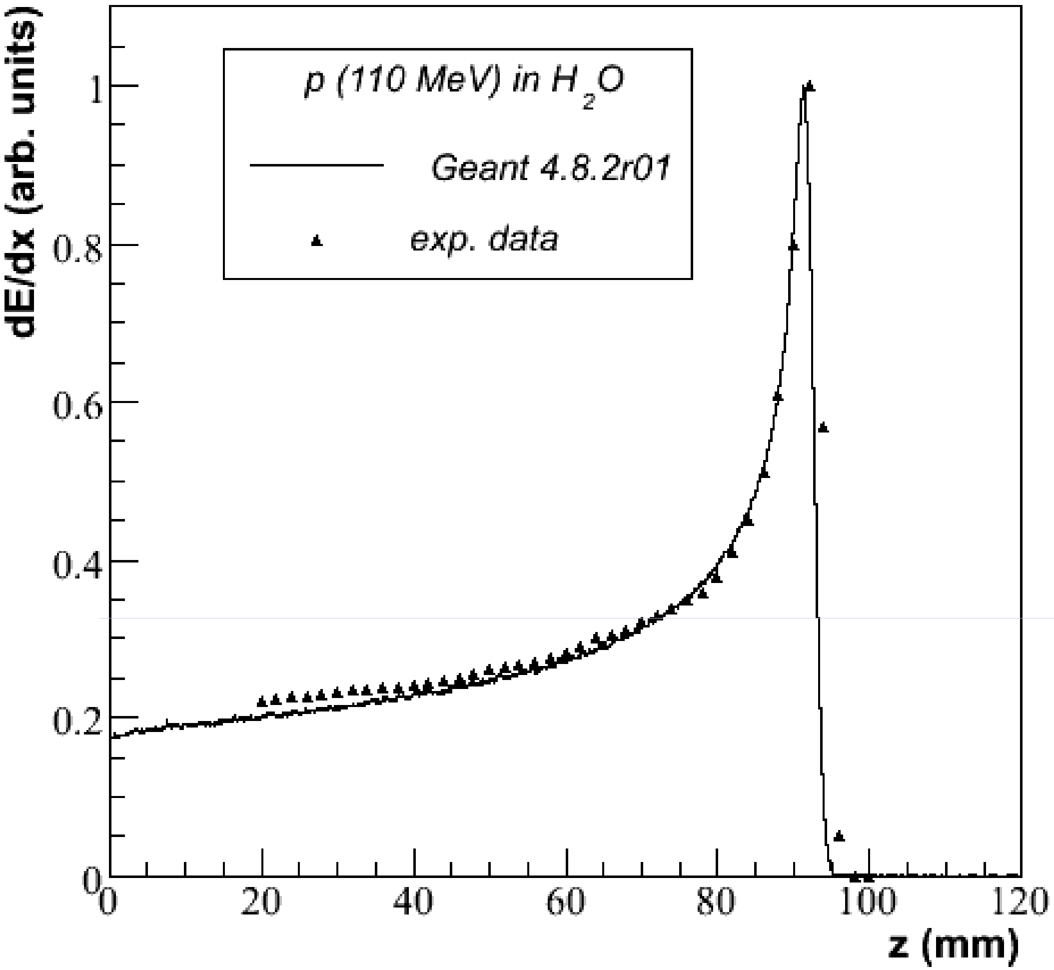

LET
Ar
Neutrons
Si
Ne
pions
C
250 kV X-RAYS
60Co
22 MeV X-RAYS
He
P
Quality of dose distribution



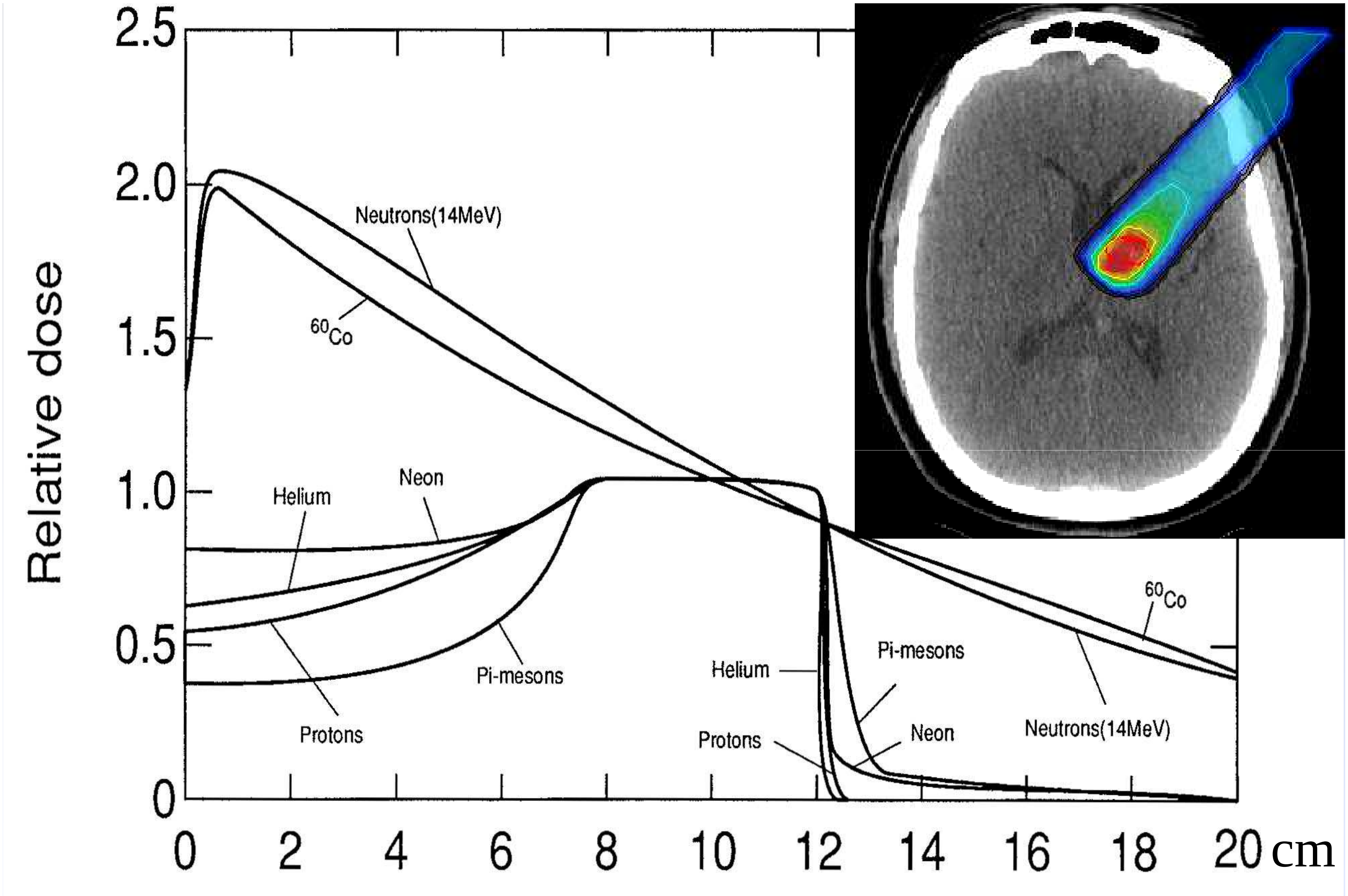
Essen	5,8MeV	salivary gl..,G1-2 sc.
Orleans	14 MeV	MM.,GBM
Nizza	40 MeV	-
Seattle	50 MeV	prostate.
Washington (Fermi)		sinus.,ut. sc.,lung
Faure	**60 MeV**	-“-

Töltött részecskék





Bragg Peak



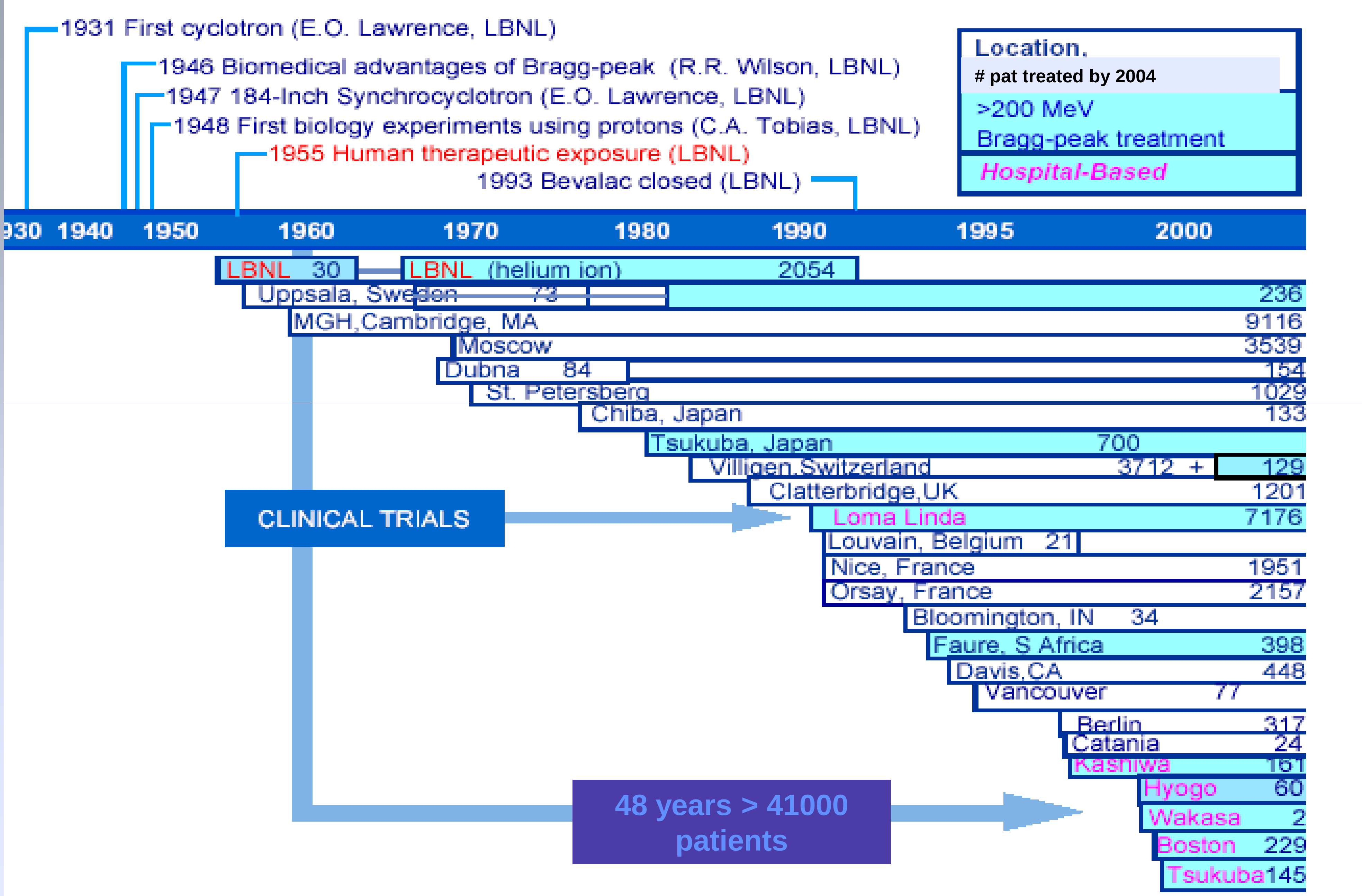
Relative dose
2.5
2.0
1.5
1.0
0.5
0
0
2
4
6
8
10
12
14
16
18
20 cm
Neutrons(14MeV)
^{60}Co
Neon
Helium
Protons
Pi-mesons
Helium
Protons
Pi-mesons
Neon
^{60}Co
Neutrons(14MeV)

A proton terápia története

- 1946 Robert Wilson
- 1948 Tobias, Lawrence (Berkeley)(hypophysectomy)
- 1954-56 Boerje Larsson (Uppsala)
- 1960 Graffman 60 beteg.(Stereotactic neurosurgery)
- Early ‘60 Sweet, Koehler, (Kjellberg, Harvard)- AV. malform.
- 1969 Ganz (retinoblastoma), Constable (eye melanoma)
- 1970 Suit, Goitein (agyalapi daganatok), Oroszo, Japán (Tokio, Chiba)
- 1983 Tsukuba 250 MeV (tüdö, mediast, GI, Gyn,...)
- 1967 Első nagymezős proton besugárzás Svédországban
- 1974 Nagymezős frakcionált proton kezelési program /HCL, Cambridge
- 1990 Első hospital-based proton kezelési kp. - Loma Linda


Heidelgberg Ion Therapy
HIT

Proton Therapy Scientific Milestones

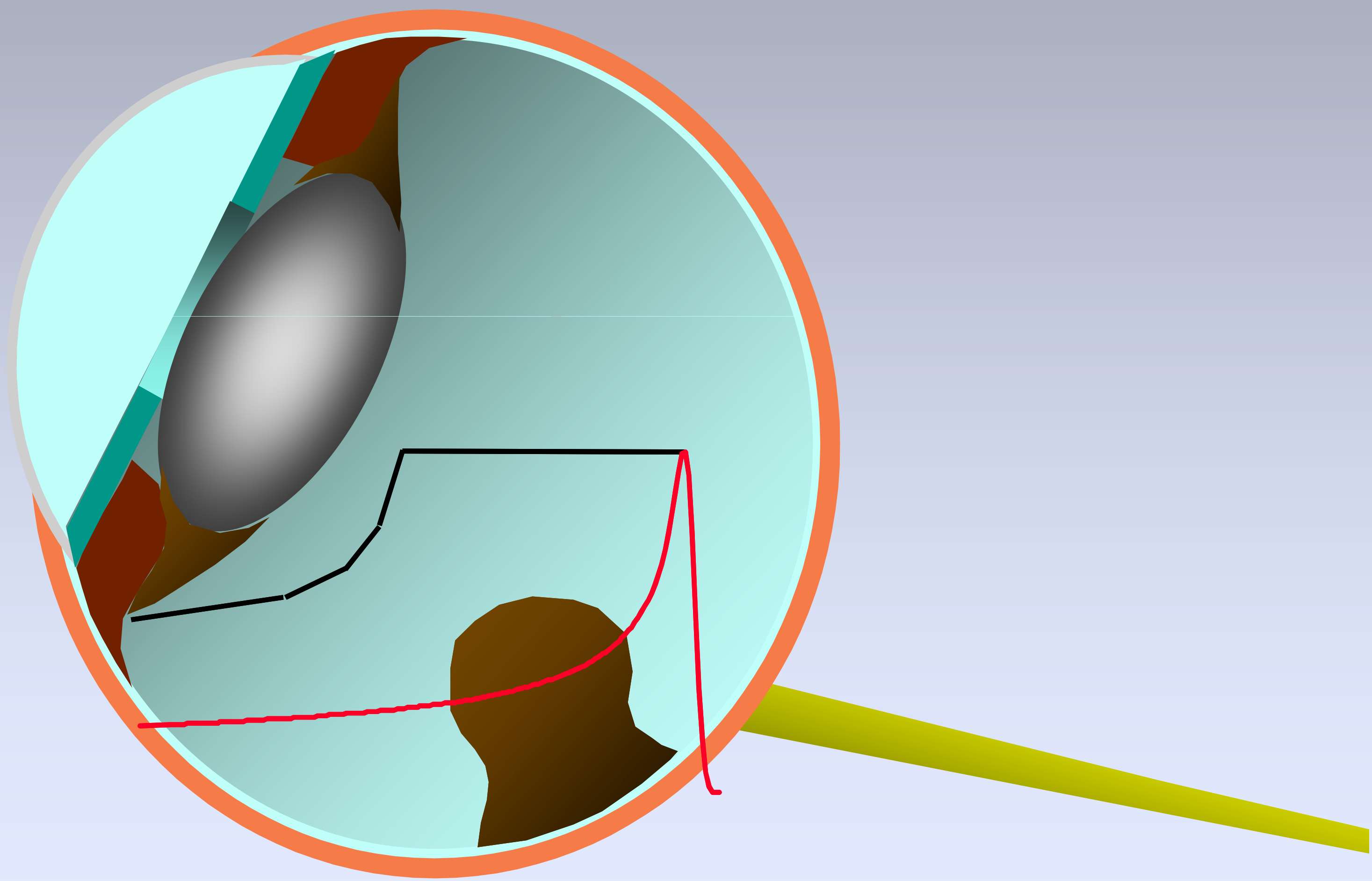


Patient Statistics (2011.május)

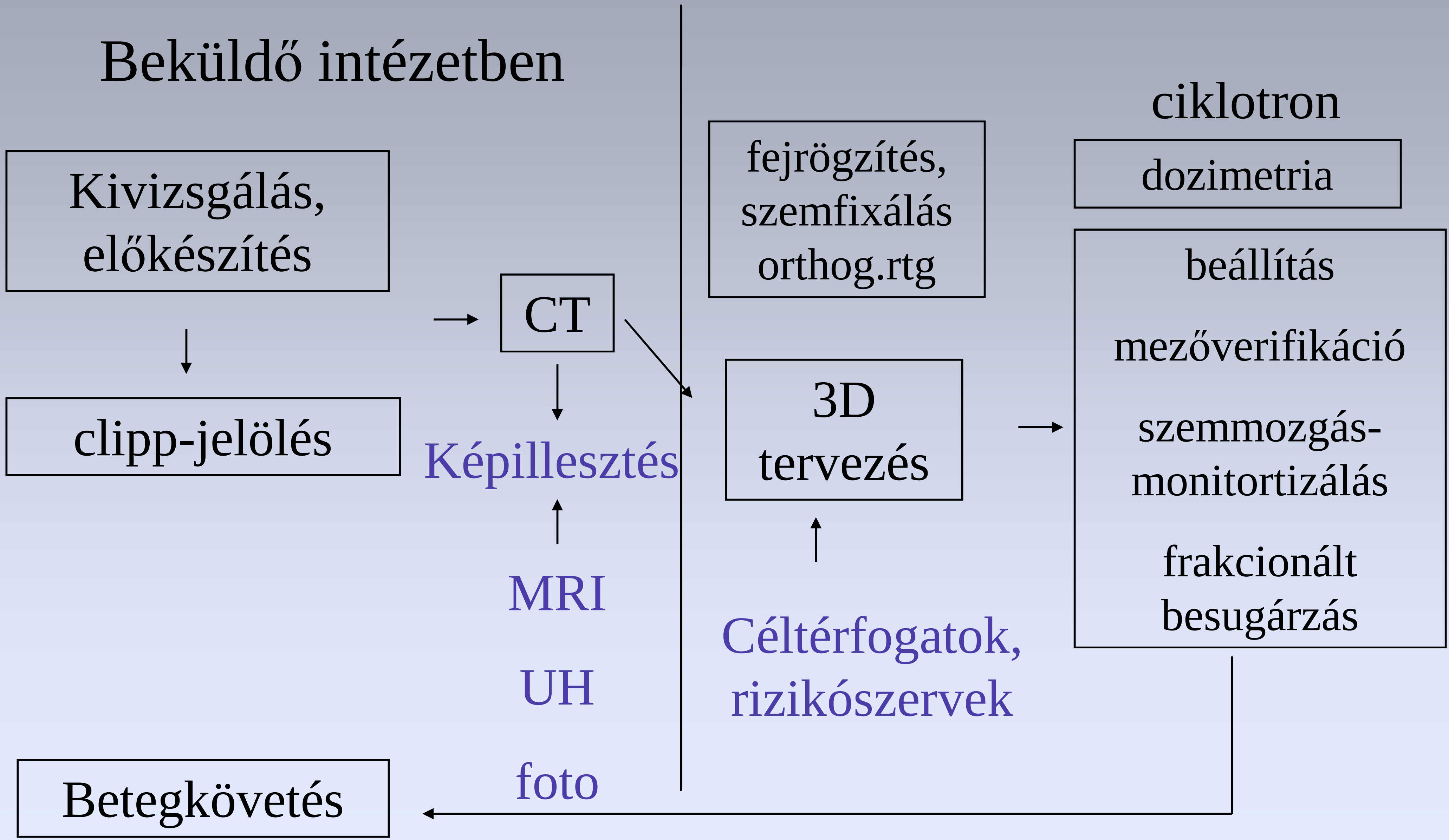
Canada Vancouver (TRIUMF)	p 1995	152	Dec-10	ocular tumors only
China Wanjie (WPTC)	p 2004	1078	Dec-10	
China Lanzhou	C ion 2006	126	Dec-10	
England Clatterbridge	p 1989	2021	Dec-10	ocular tumors only
France Nice (CAL)	p 1991	4209	Dec-10	ocular tumors only
France Orsay (CPO)	p 1991	5216	Dec-10	4245 ocular tumors
Germany Berlin (HMI)	p 1998	1660	Dec-10	ocular tumors only
Germany Munich (RPTC)	p 2009	446	Dec-10	
Germany HIT, Heidelberg	C ion 2010	400	Dec-10	estimate; has to be confirmed
Germany HIT, Heidelberg	p 2010	40	Dec-10	estimate; has to be confirmed
Italy Catania (INFN-LNS)	p 2002	174	Mar-09	ocular tumors only
Japan Chiba (HIMAC)	C ion 1994	5497	Aug-10	
Japan Kashiwa (NCC)	p 1998	772	Dec-10	
Japan Hyogo (HIBMC)	p 2001	2382	Nov-09	
Japan Hyogo (HIBMC)	C ion 2002	638	Nov-09	
Japan Tsukuba (PMRC, 2)	p 2001	1849	Dec-10	
Japan Shizuoka	p 2003	986	Dec-10	
Korea Ilsan, Korea	p 2007	648	Dec-10	
Russia Moscow (ITEP)	p 1969	4246	Dec-10	
Russia St. Petersburg	p 1975	1362	Dec-10	
Russia Dubna (JINR, 2)	p 1999	720	Dec-10	
South Africa iThemba LABS p 1993	511	Dec-09		
Sweden Uppsala (2)	p 1989	1000	Dec-10	
Switzerland Villigen PSI, incl OPTIS2	p 1996	772	Dec-10	47 ocular tumors
CA., USA UCSF - CNL	p 1994	1285	Dec-10	ocular tumors only
CA., USA Loma Linda (LLUMC)	p 1990	15000	Jan-11	
IN., USA Bloomington (MPRI, 2)	p 2004	1145	Dec-10	
MA., USA Boston (NPTC)	p 2001	4967	Dec-10	
TX, USA Houston	p 2006	2700	Dec-10	about 500 with scanning
FL, USA UFPTI Jacksonville	p 2006	2679	Dec-10	
OK, USA Oklahoma City (ProCure PTC)	p 2009	21	Dec-09	
IL, USA CDH Warrenville	p 2010		Oct-10	

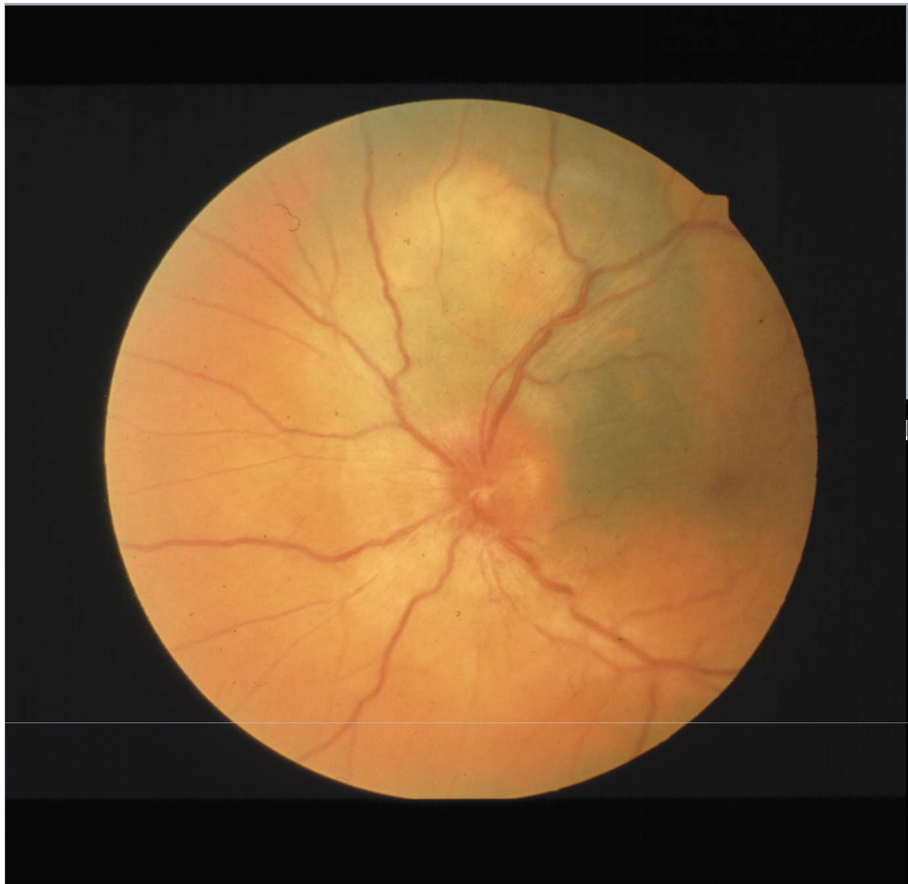
84492 Grand Total 64702 Total = 6661 C-ions + 58041 protons

Szem melanoma - proton terápia

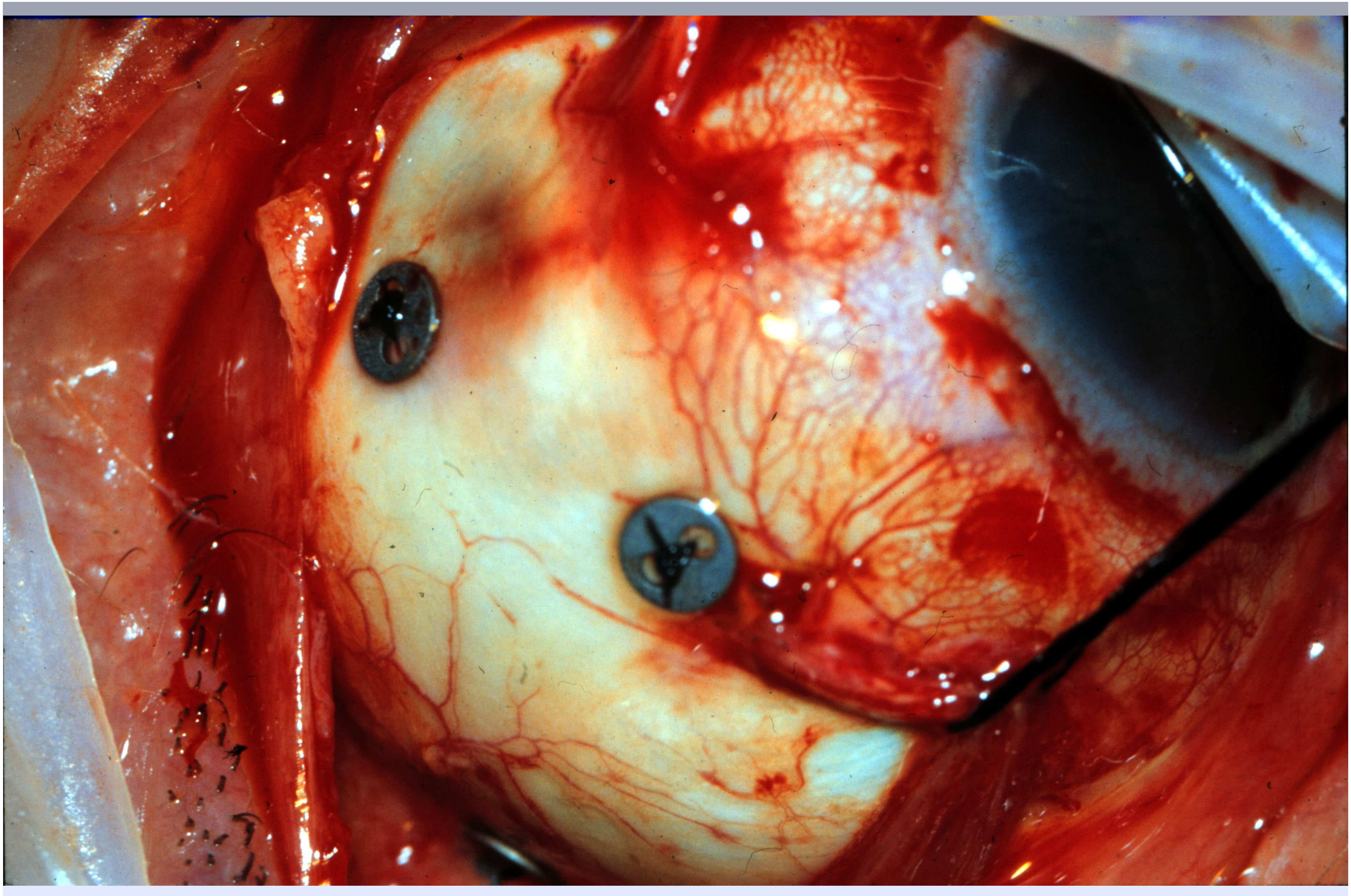


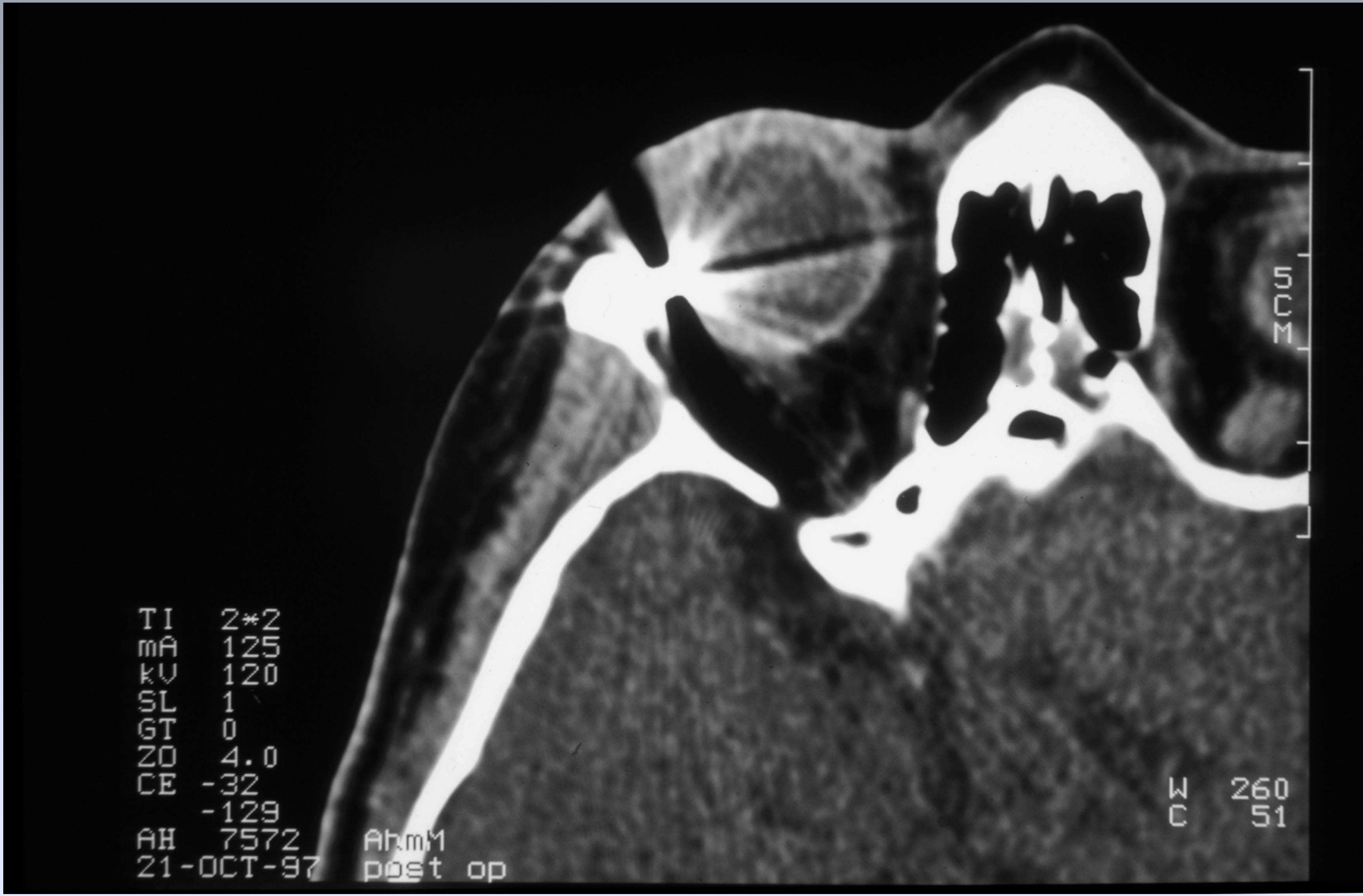
A protonterápia folyamatai

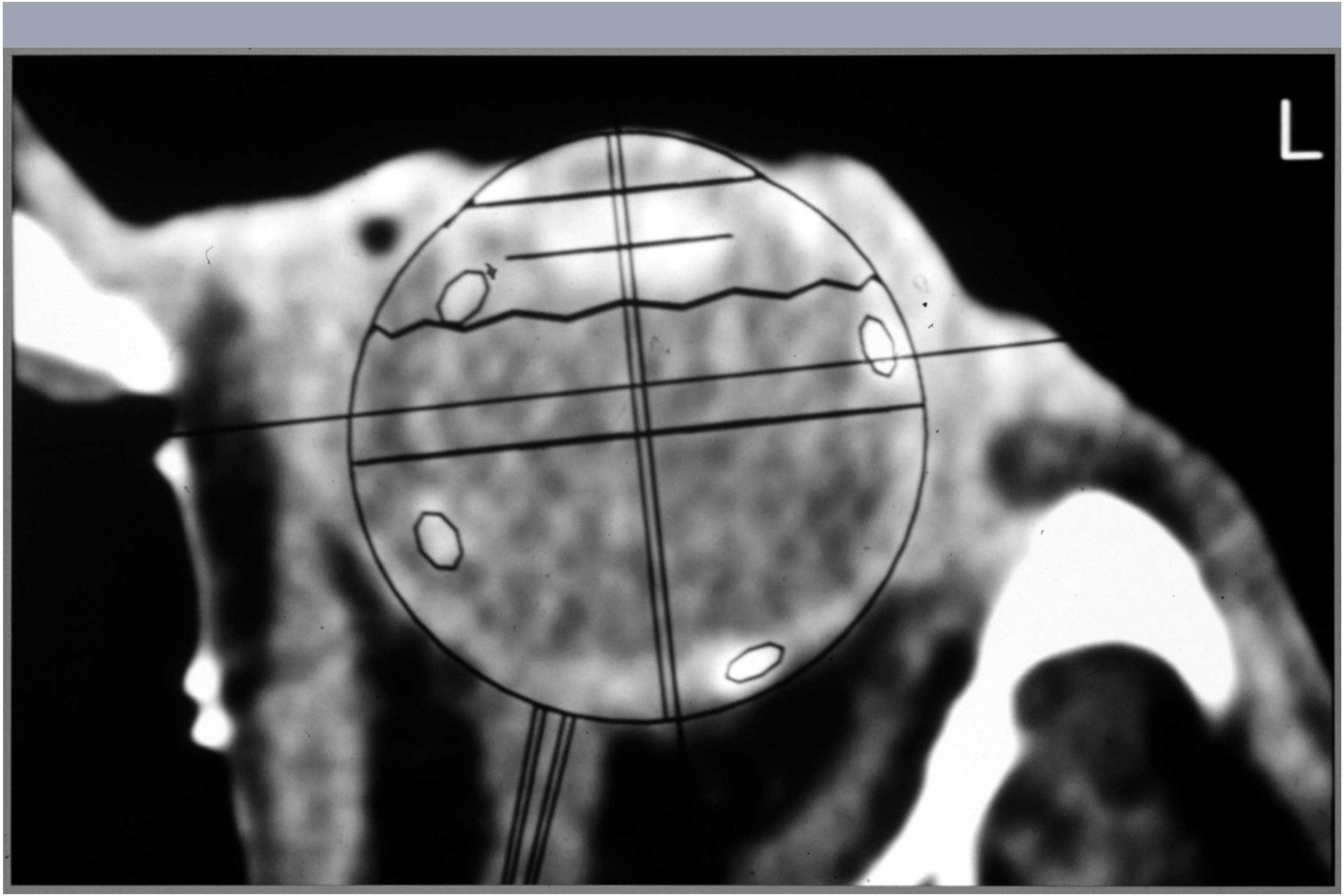


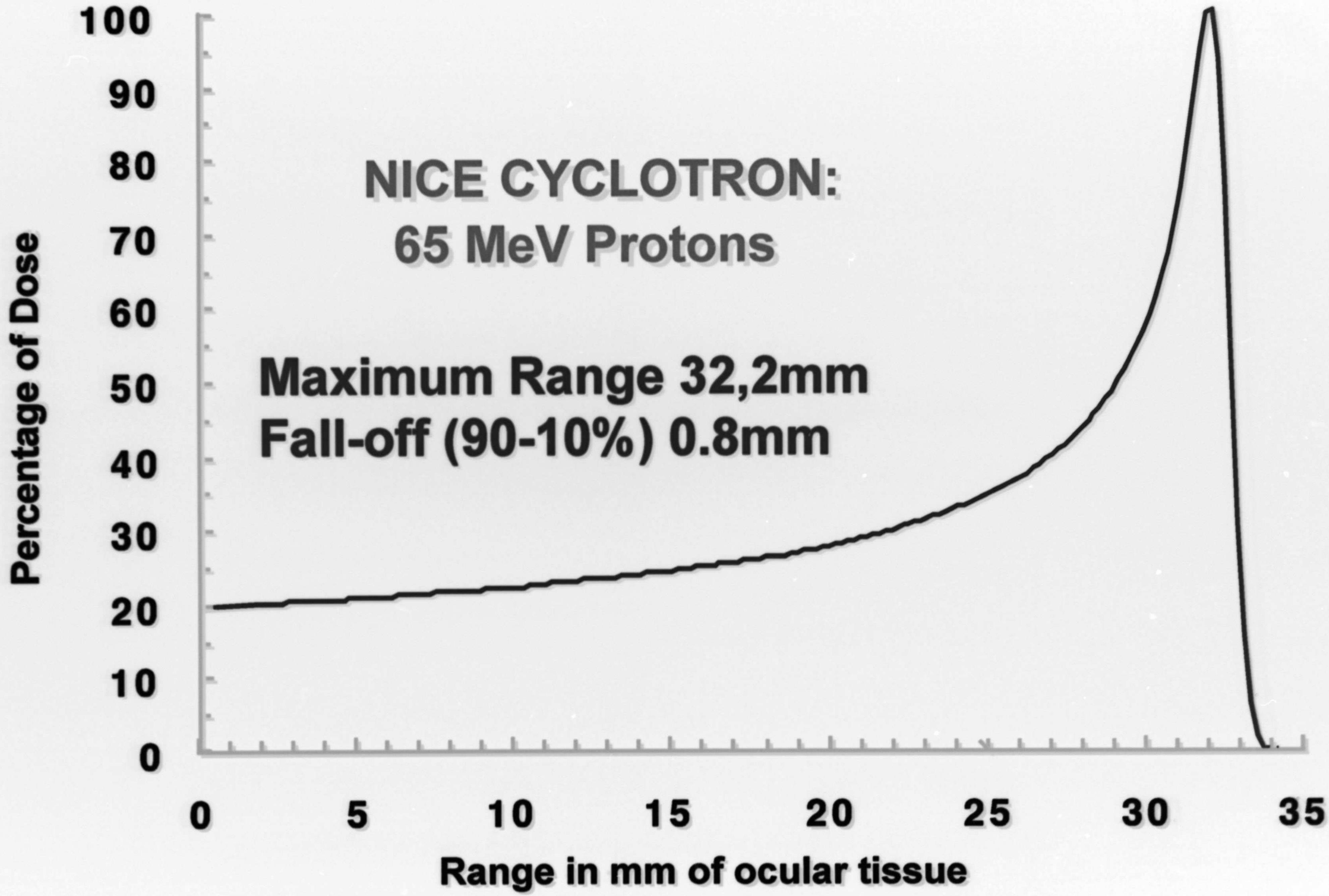



SE1
THK 5.0

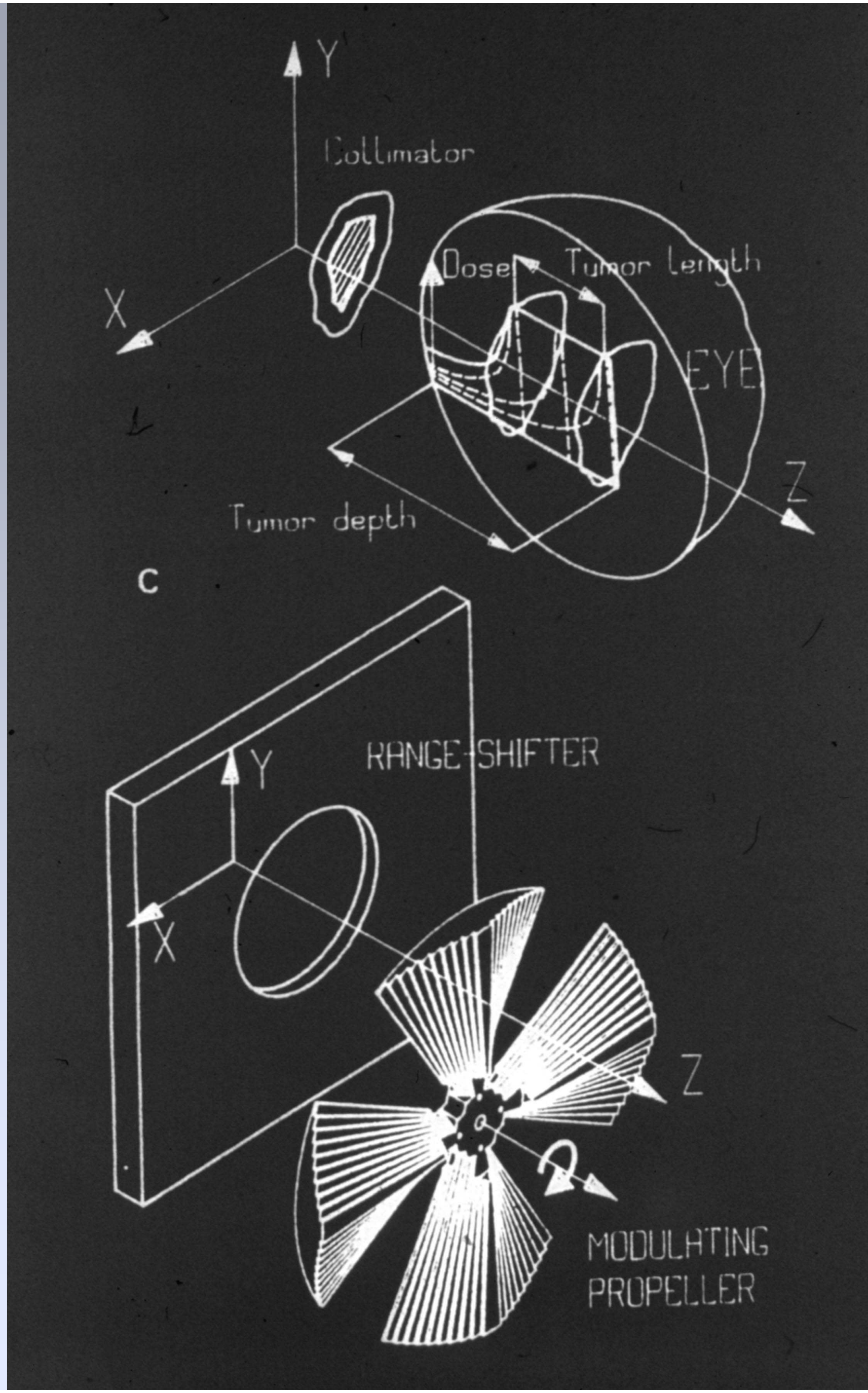



5CM
TI 2*2
mA 125
kV 120
SL 1
GT 0
ZO 4.0
CE -32
-129
AH 7572
21-OCT-97
AhmM
post op
W 260
C 51

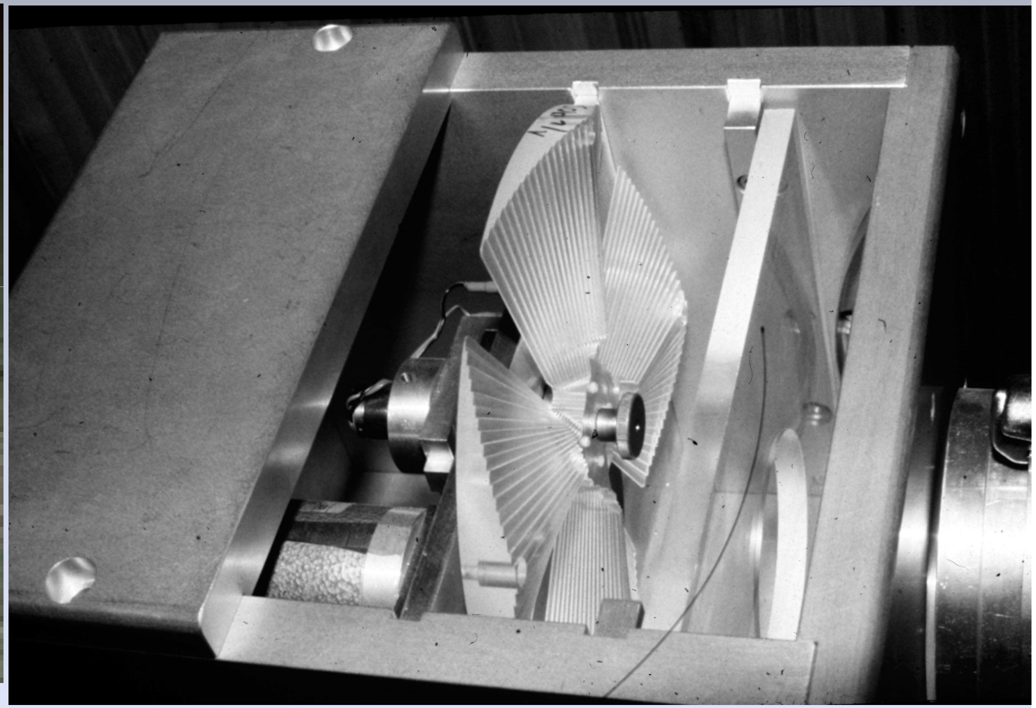

L



NICE CYCLOTRON:
65 MeV Protons
Maximum Range 32,2mm
Fall-off (90-10%) 0.8mm
Percentage of Dose
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
Range in mm of ocular tissue


Y
Collimator
X
Dose
Tumor length
EYE
Z
Tumor depth
c
RANGE-SHIFTER
Y
X
Z
MODULATING
PROPELLER

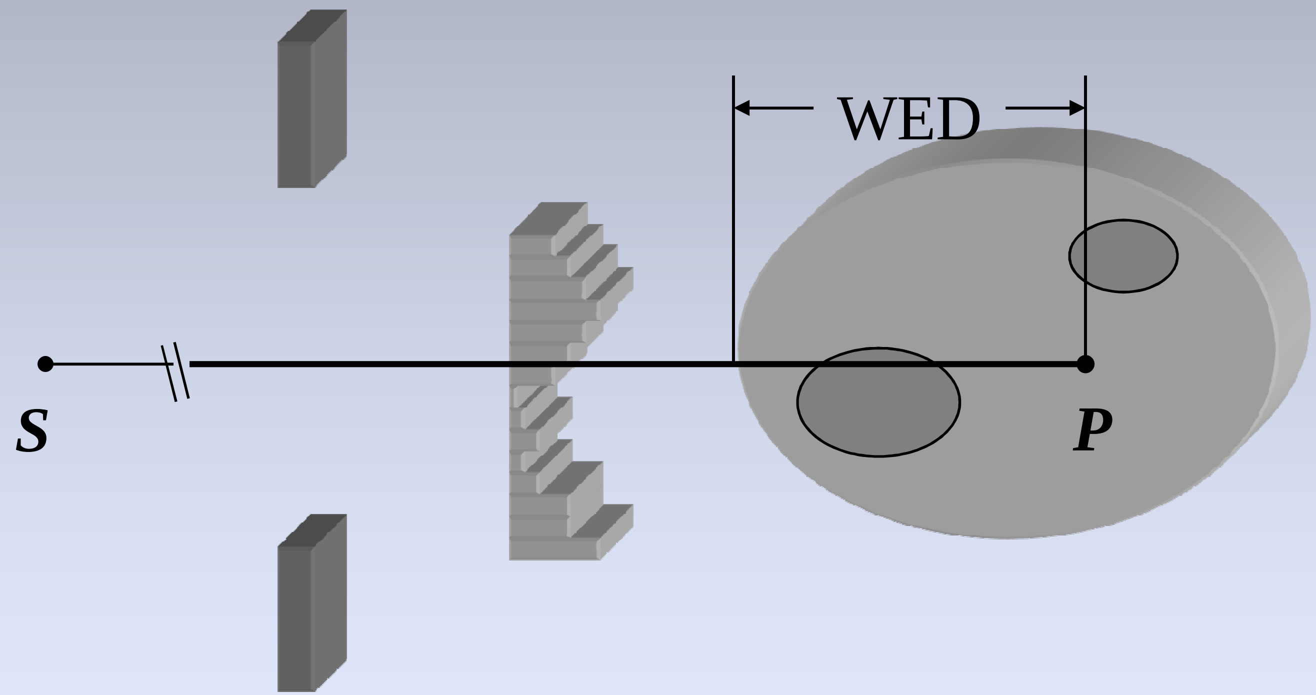
Proton Beam Shaping Devices



Wax bolus **Cerrobend aperture** **Modulating wheels**

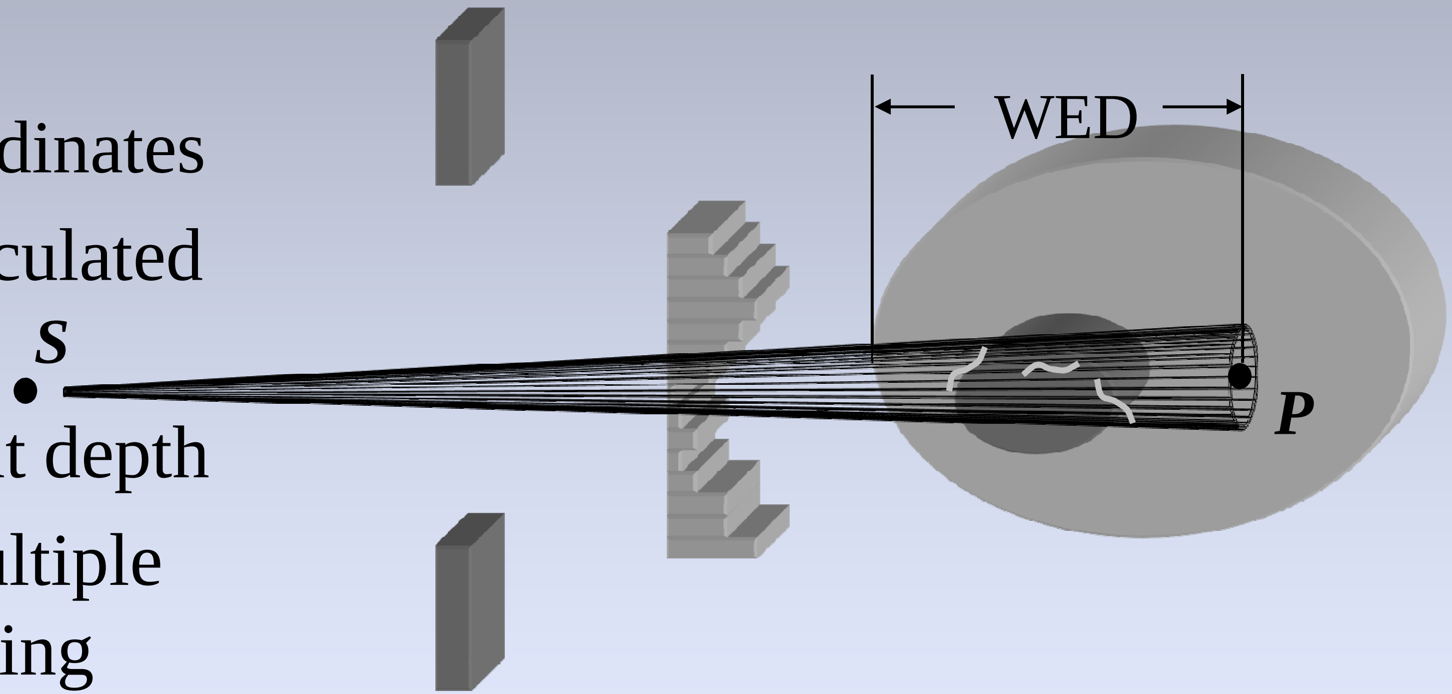
Ray-Tracing Dose Algorithm

- One-dimensional dose calculation
- Water-equivalent depth (WED) along single ray *SP*
- Look-up table
- Reasonably accurate for simple hetero-geneities
- Simple and fast



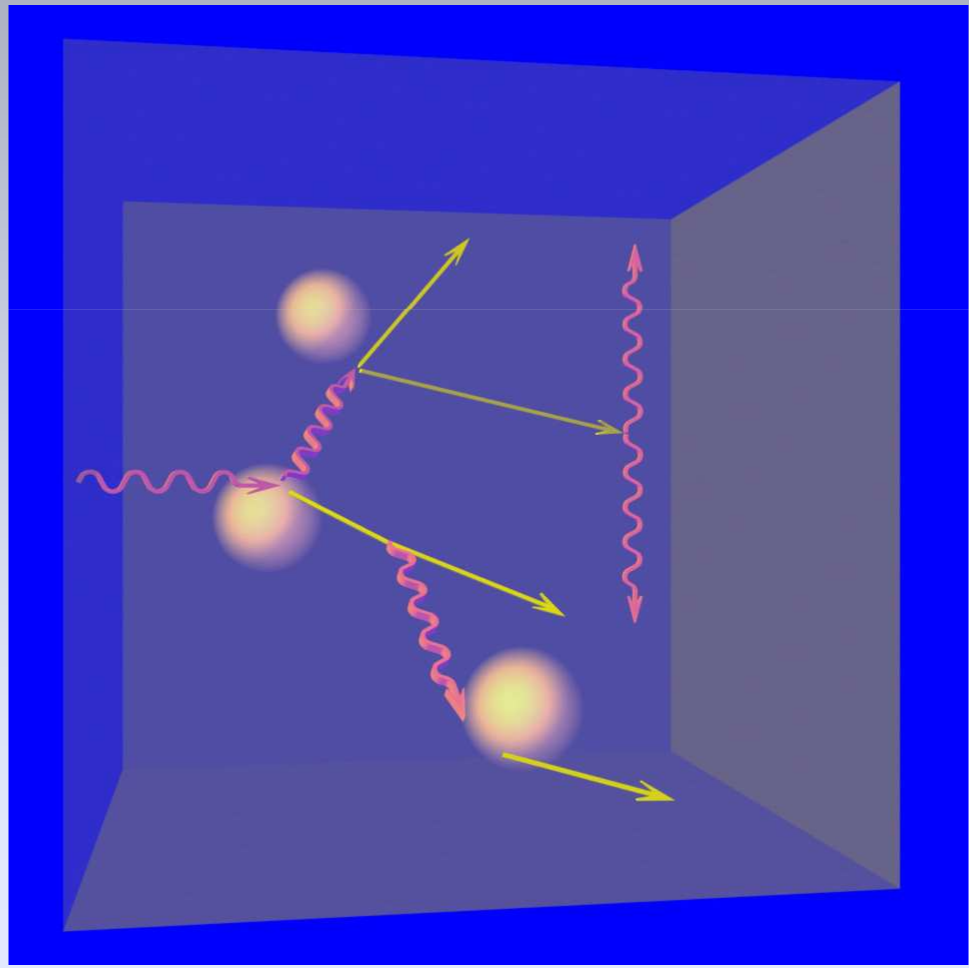
Pencil Beam Dose Algorithm

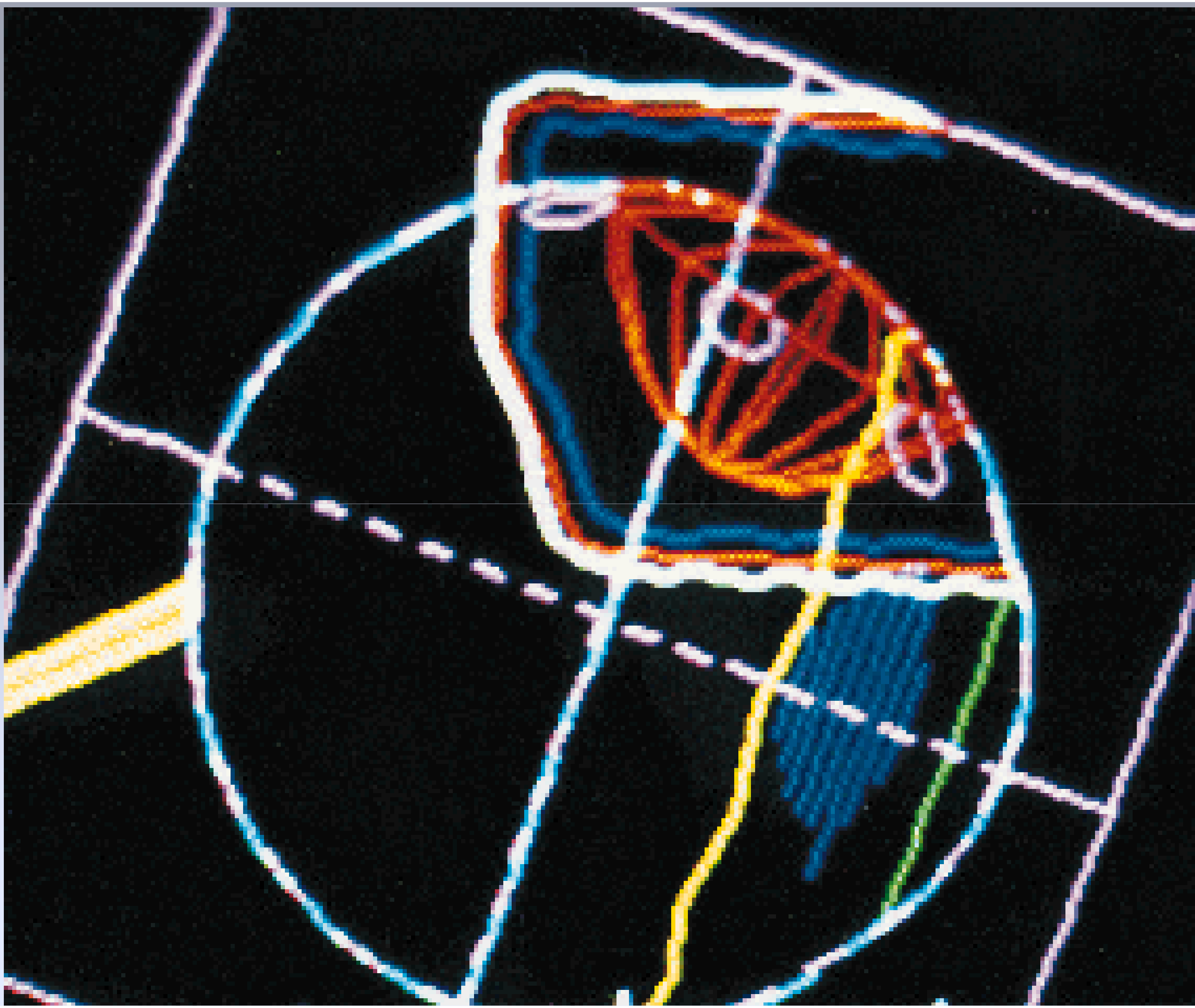
- Cylindrical coordinates
- Measured or calculated pencil kernel
- Water-equivalent depth
- Accounts for multiple Coloumb scattering
- more time consuming

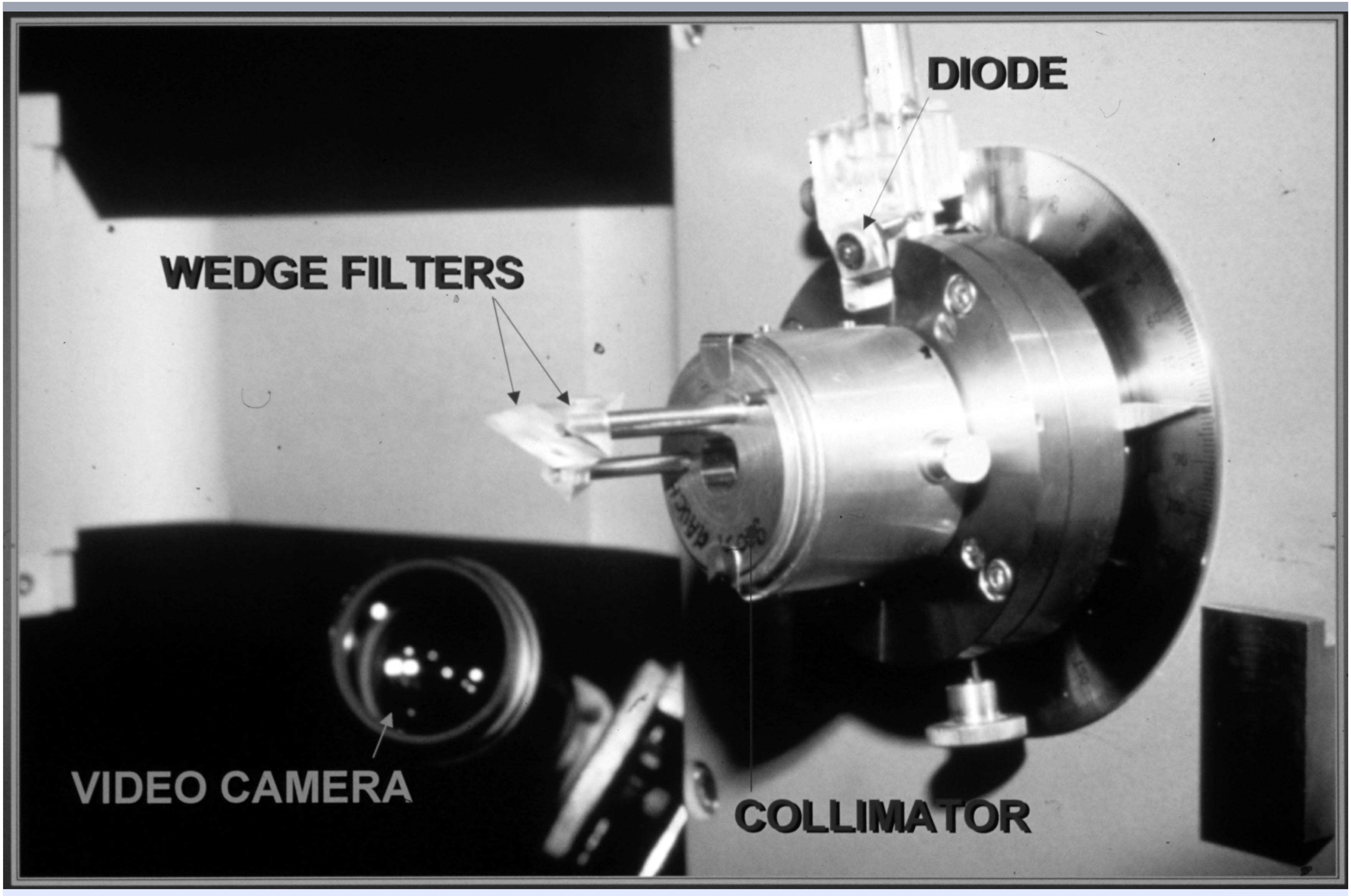


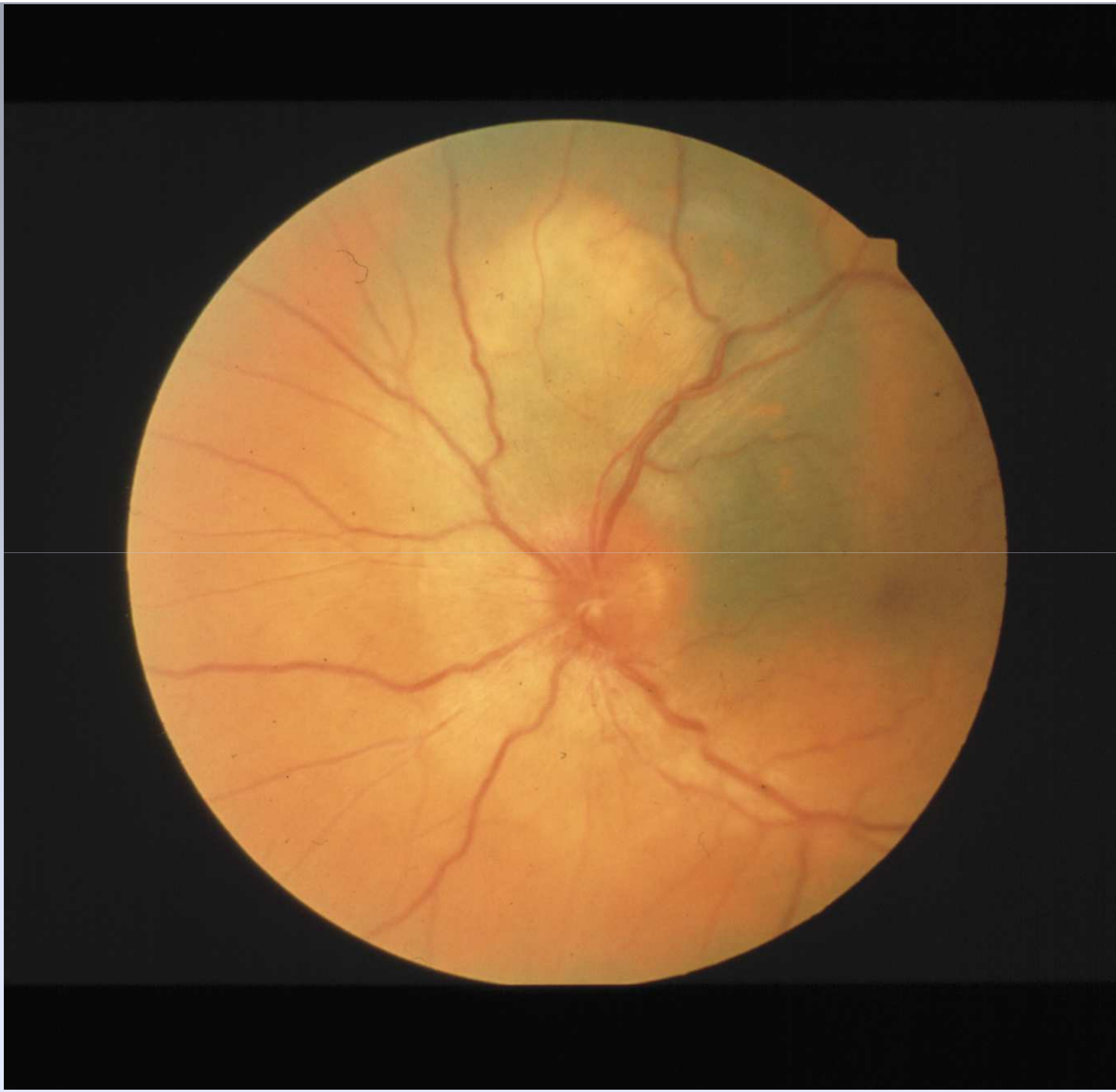
Monte Carlo Dose Algorithm

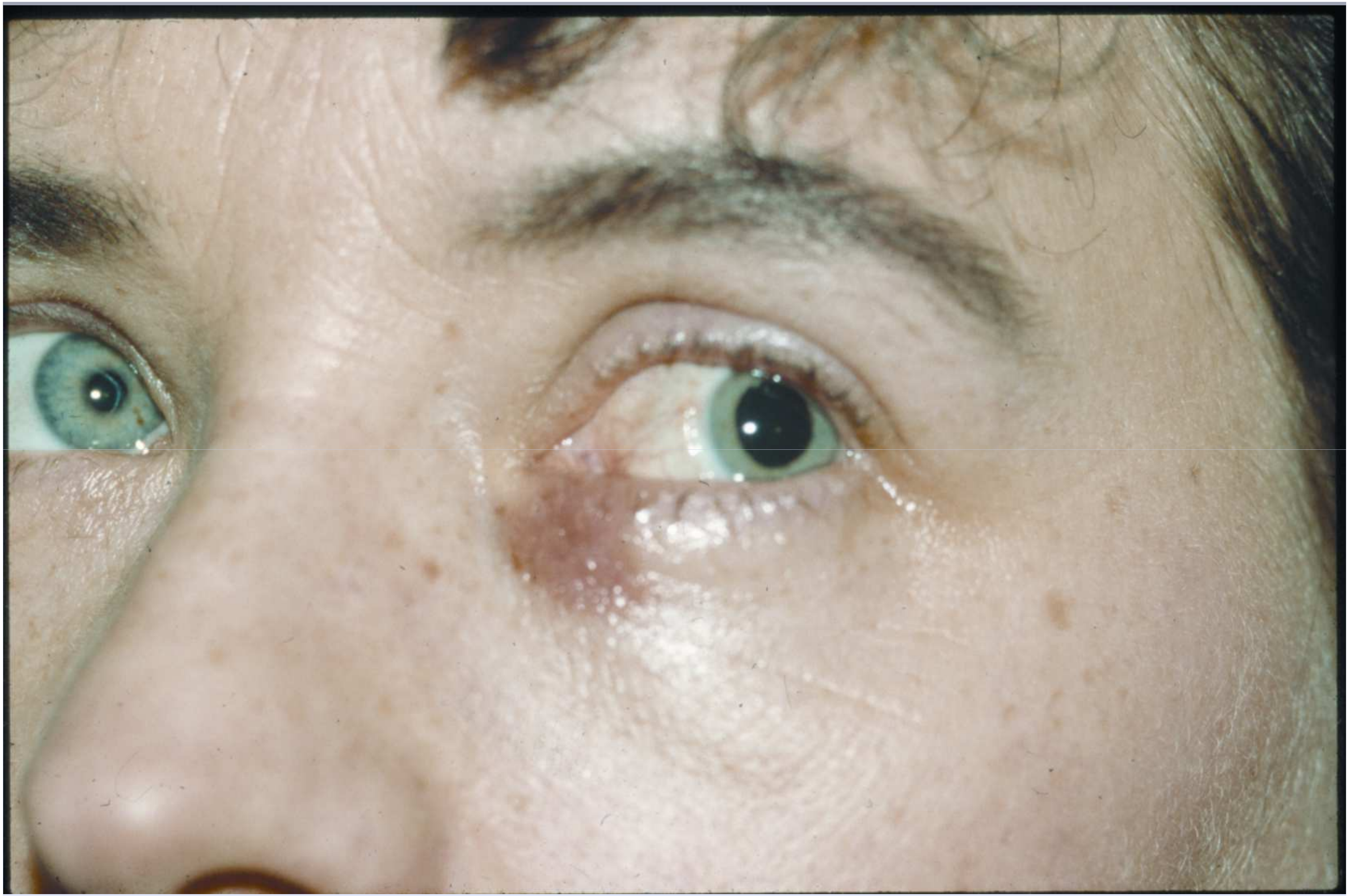
- Considered as "gold standard"
- Accounts for all relevant physical interactions
- Follows secondary particles
- Requires accurate cross section data bases
- Includes source geometry
- Very time consuming

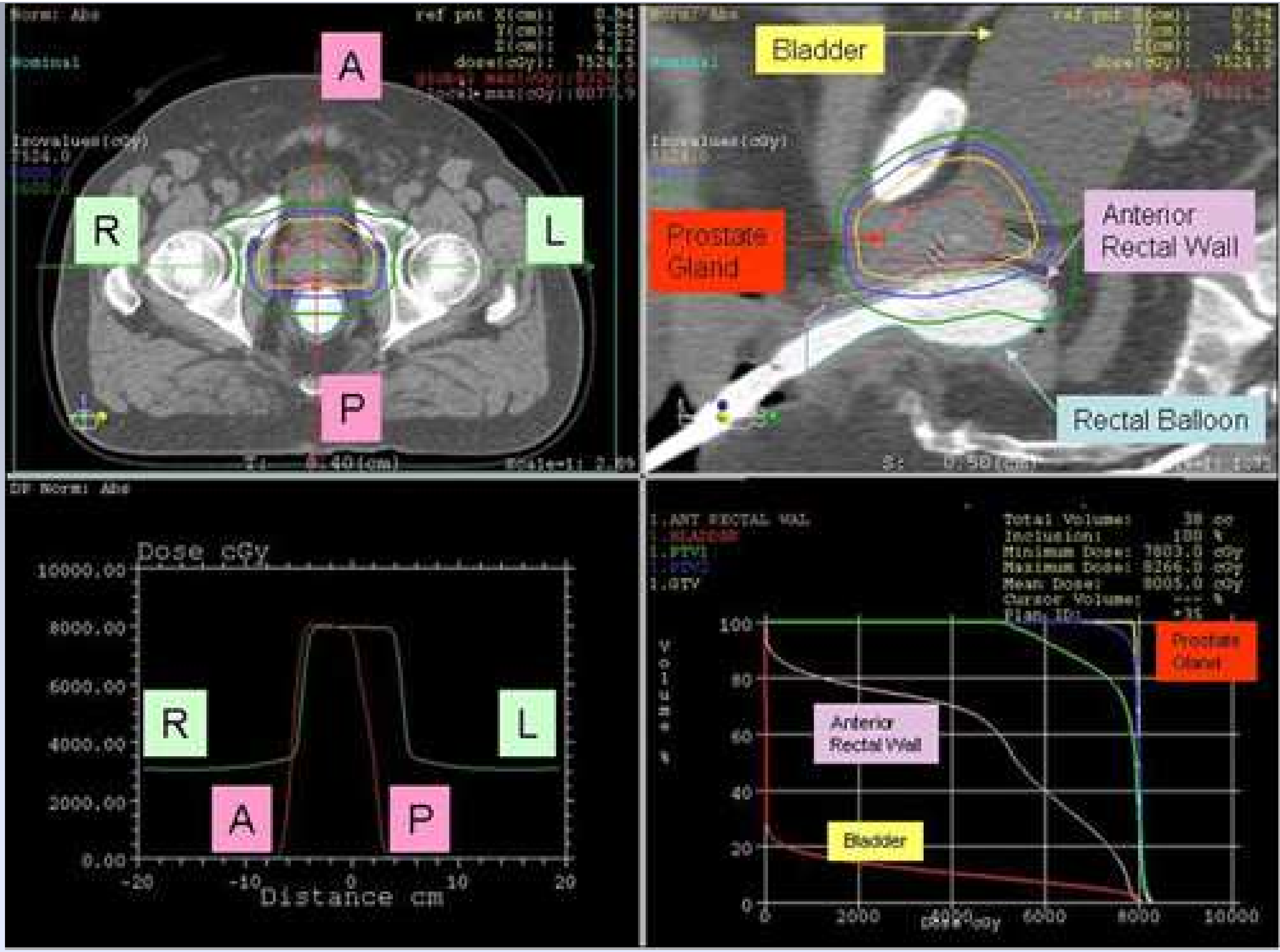


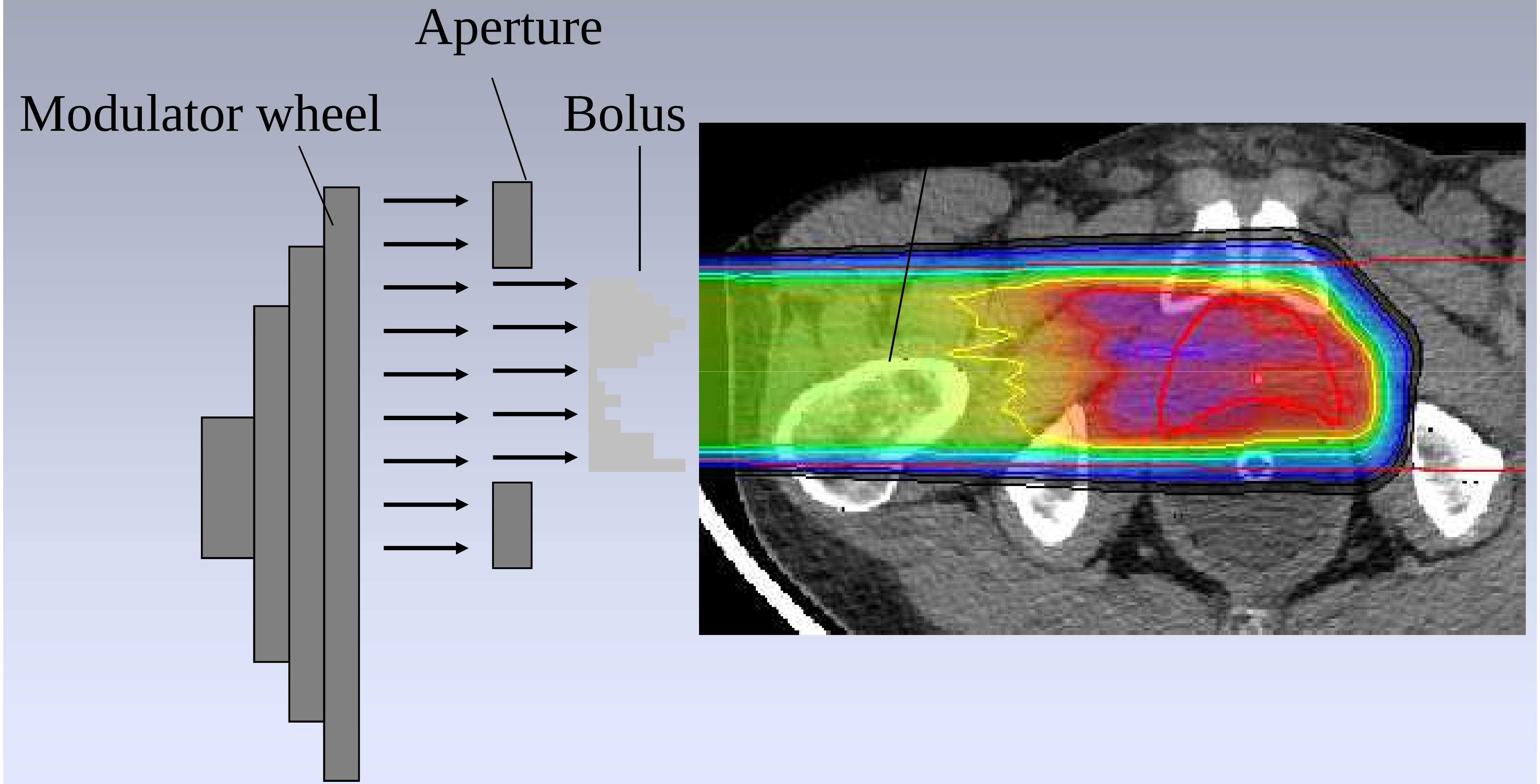



DIODE
WEDGE FILTERS
VIDEO CAMERA
COLLIMATOR






A
R
L
P
Bladder
Prostate Gland
Anterior Rectal Wall
Rectal Balloon
Dose cGy
Distance cm
R
L
A
P
1.ANT RECTAL WAL
1.PTV1
1.GTV
Prostate Gland
Anterior Rectal Wall
Bladder
Volume %


Aperture
Modulator wheel
Bolus

Hug E.B., Sweeney R.A., Nurre P.M., Holloway K.C., Slater J.D., Munzenrider J.E.

Proton radiotherapy in management of pediatric base of skull tumors

Int J Radiat Oncol Biol Phys. 2002 Vol. 52, No.4, pp 1017-1024

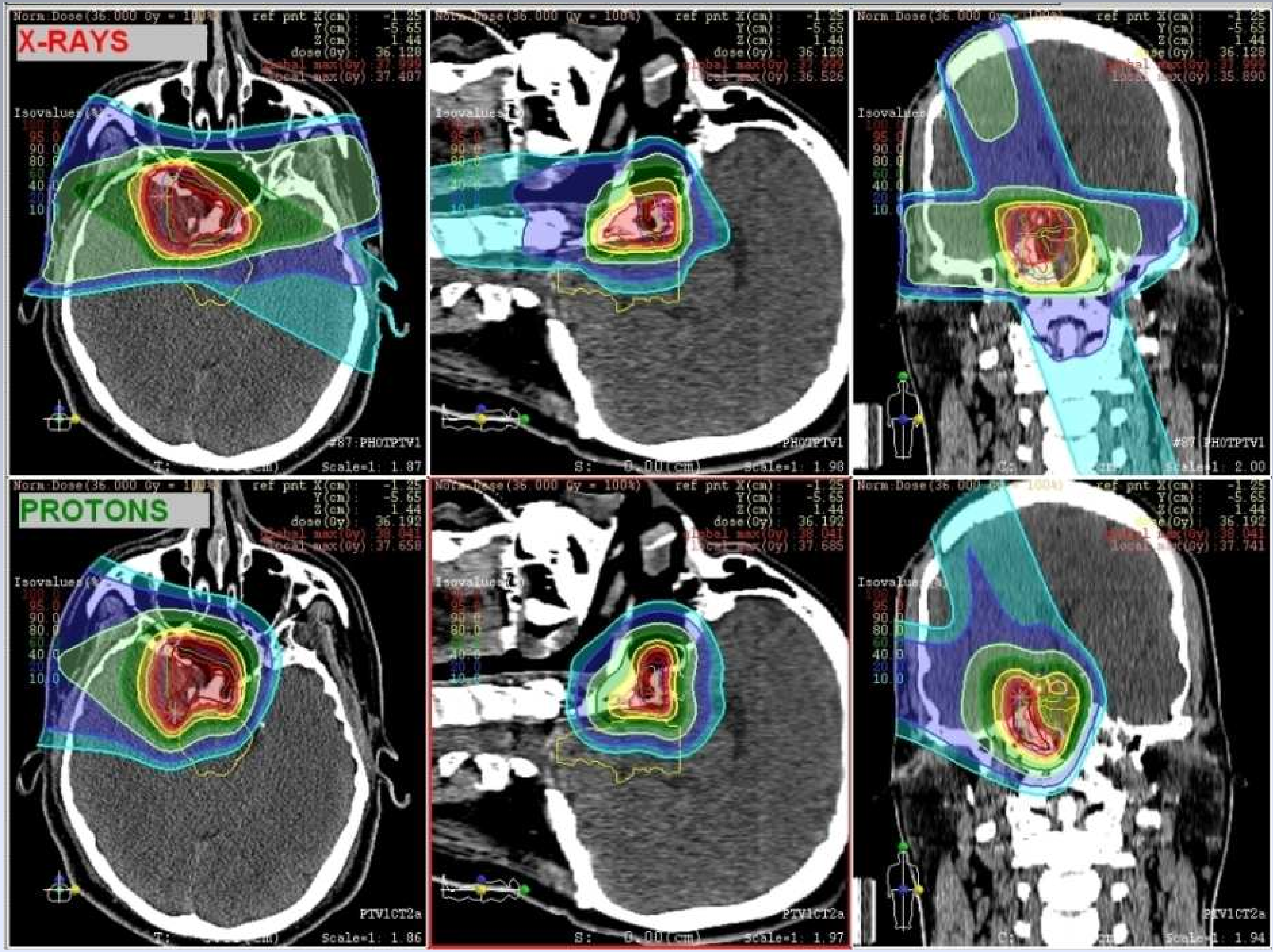
Locally advanced disease
16 chordoma, 9 chondrosc., 8 rhabdomyosc. 5 other sc

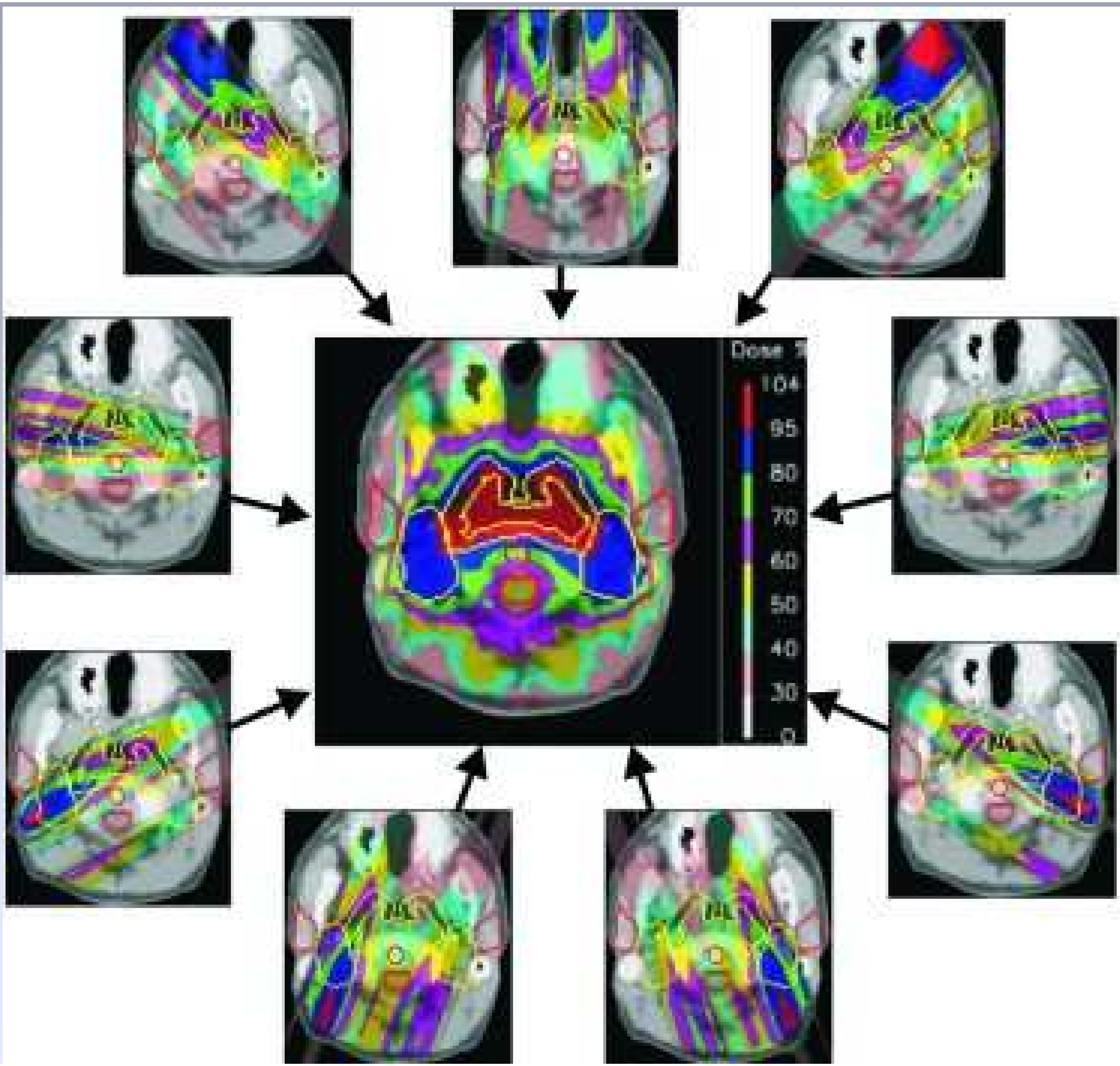
5 years local tumor control 72%:

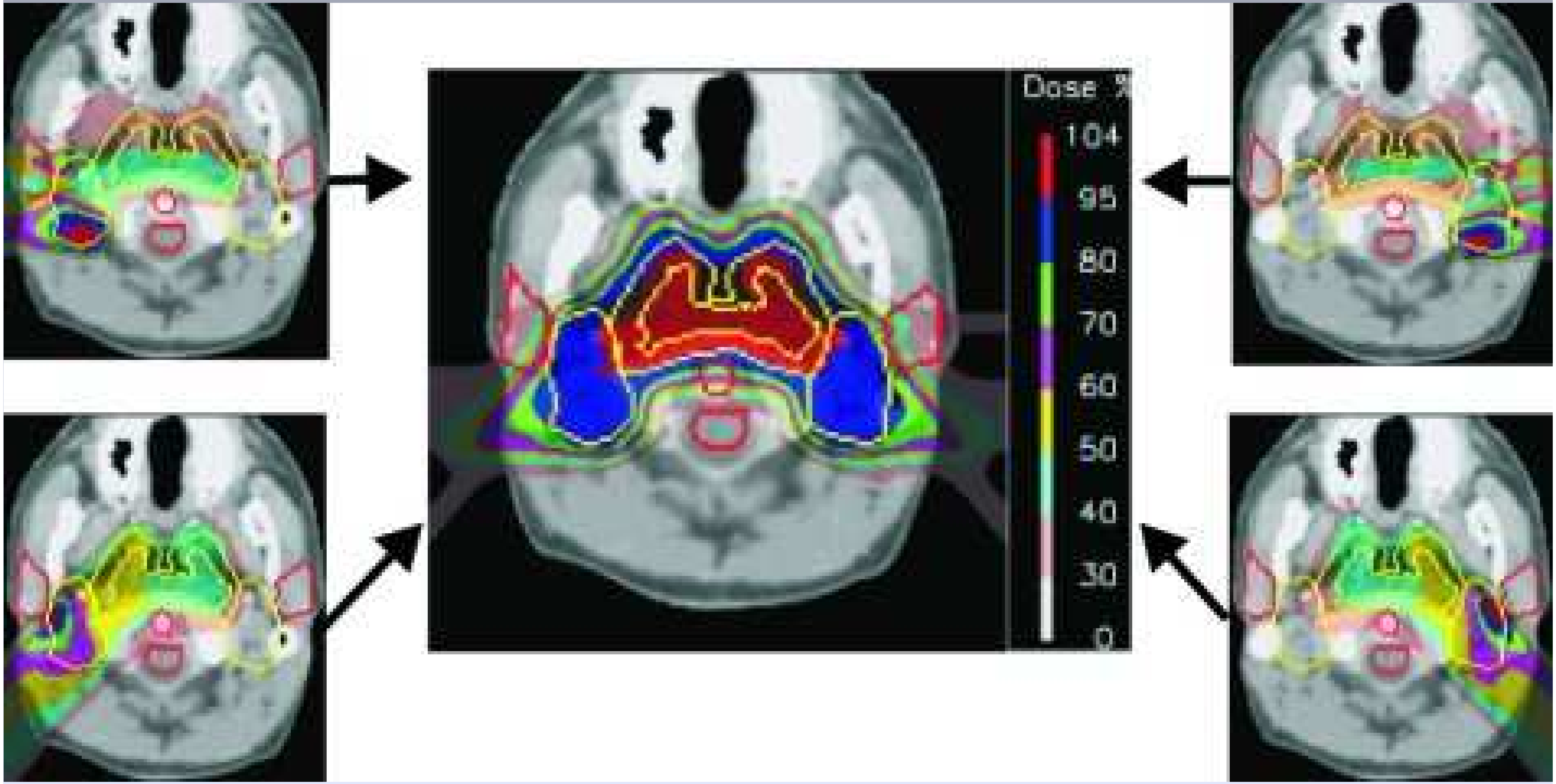
5 years overal survival 56%

Serious neurological complication 7 %
(motor/sensor function deterioration)

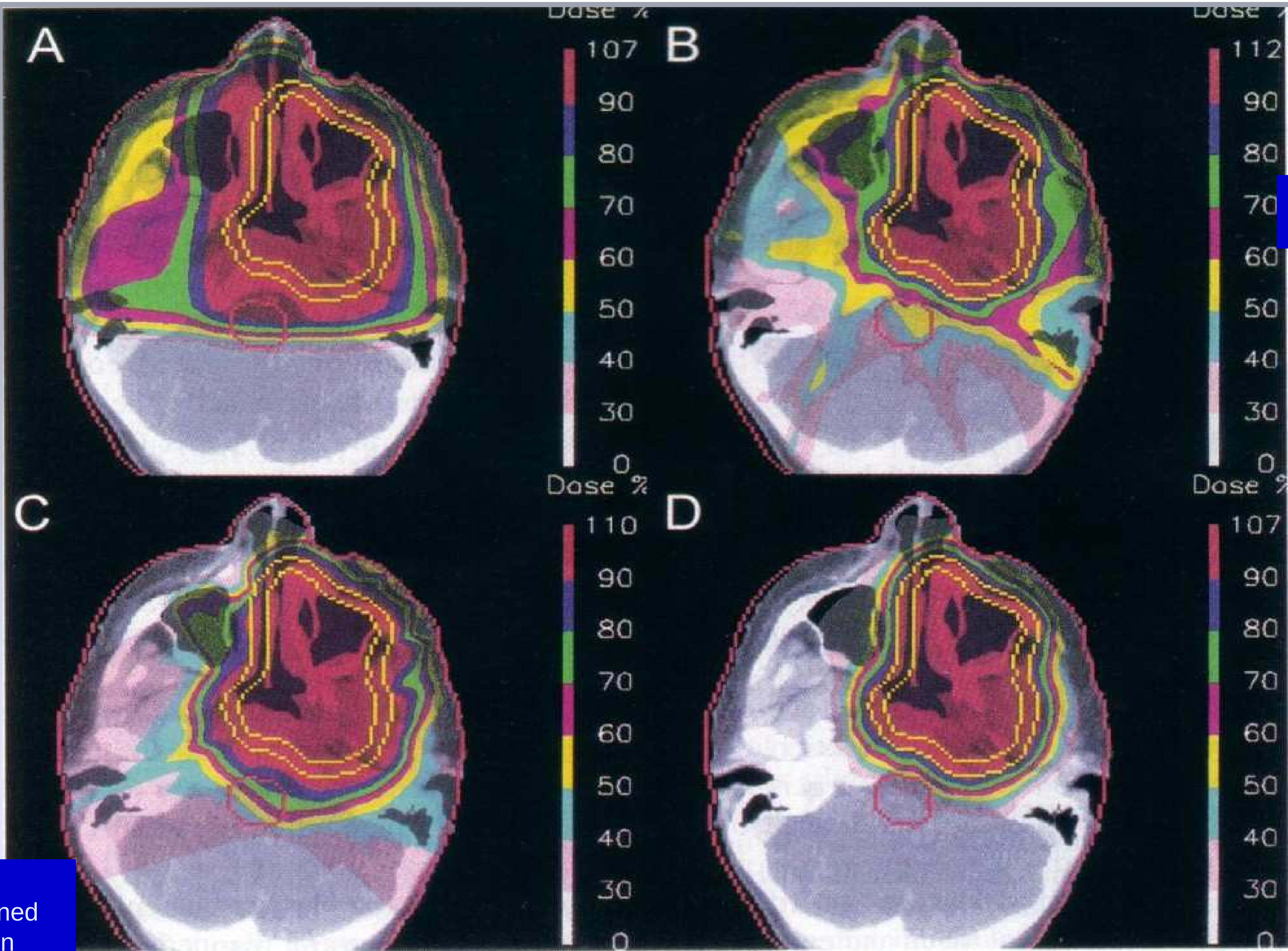

Eye
Optic Nerve
Optic Chiasm
Brainstem
Chordoma
Spinal Cord
Chordoma
Brainstem
Spinal Cord
Transverse Slice just Inferior to Chiasm


X-RAYS
PROTONS
Isovalues(%)
#87:PHOTPTV1
PHOTPTV1
PTV1CT2a


Dose %
104
95
80
70
60
50
40
30
0

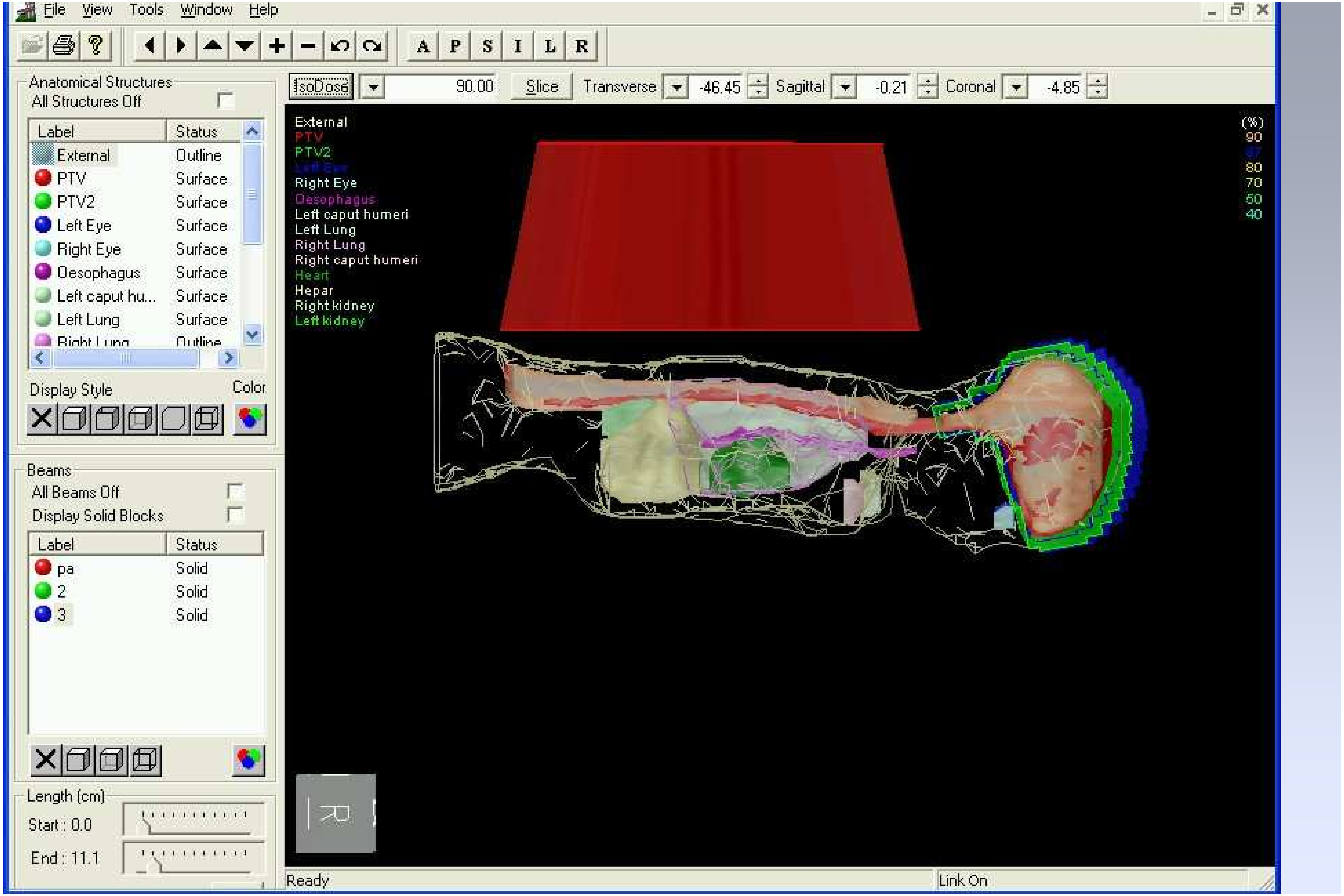


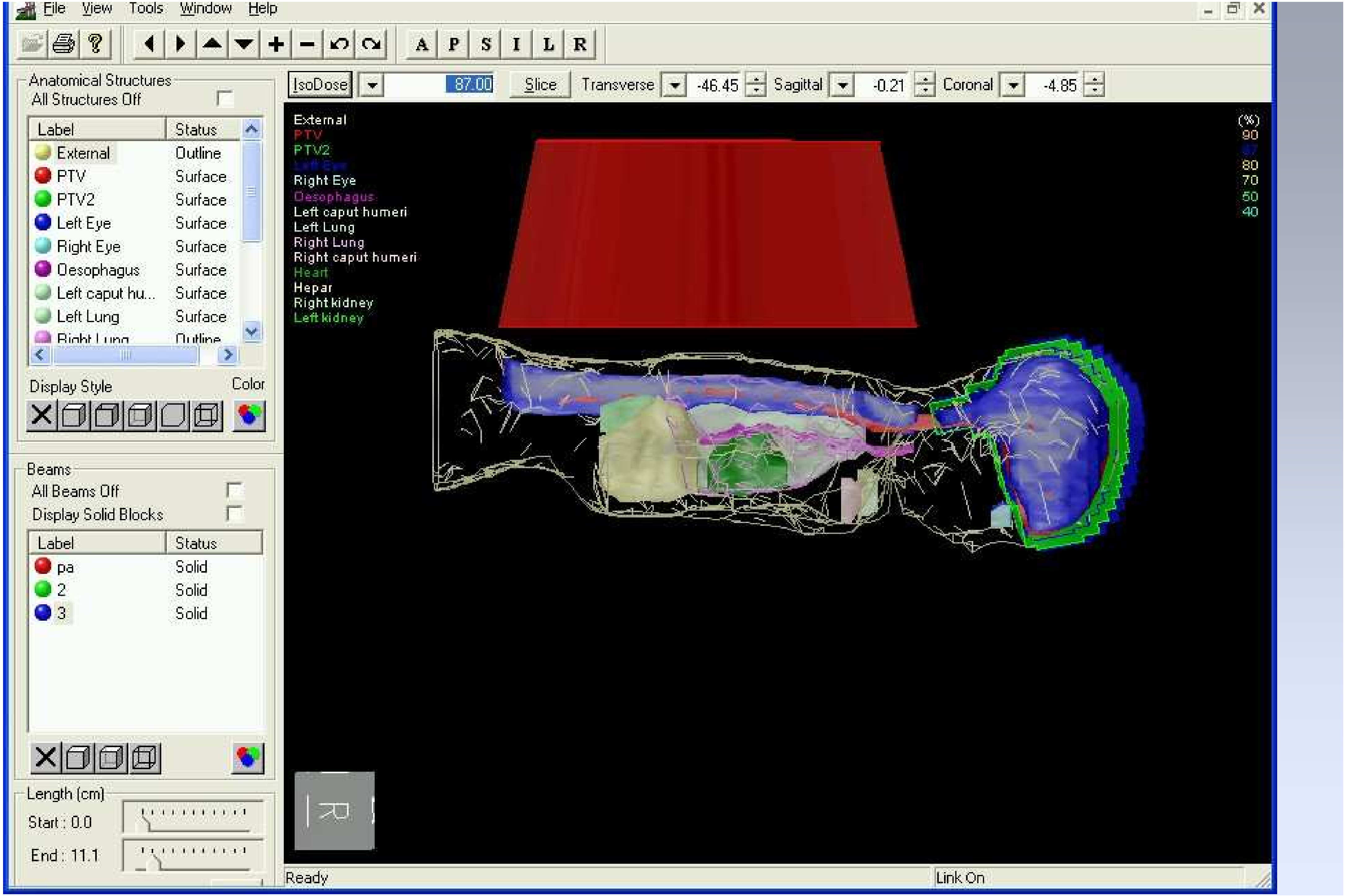
Dose %
104
95
80
70
60
50
40
30
0

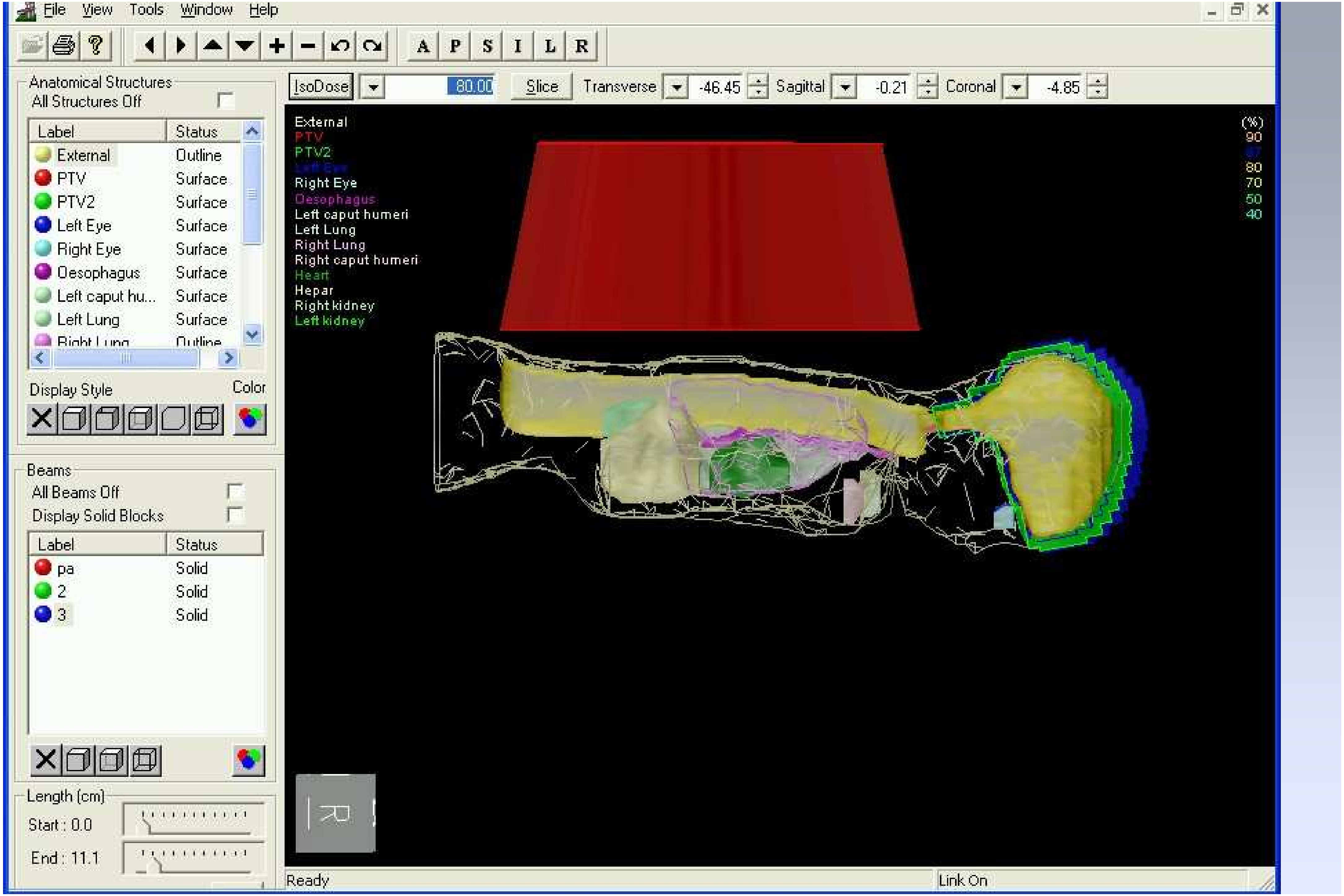


IM-photon

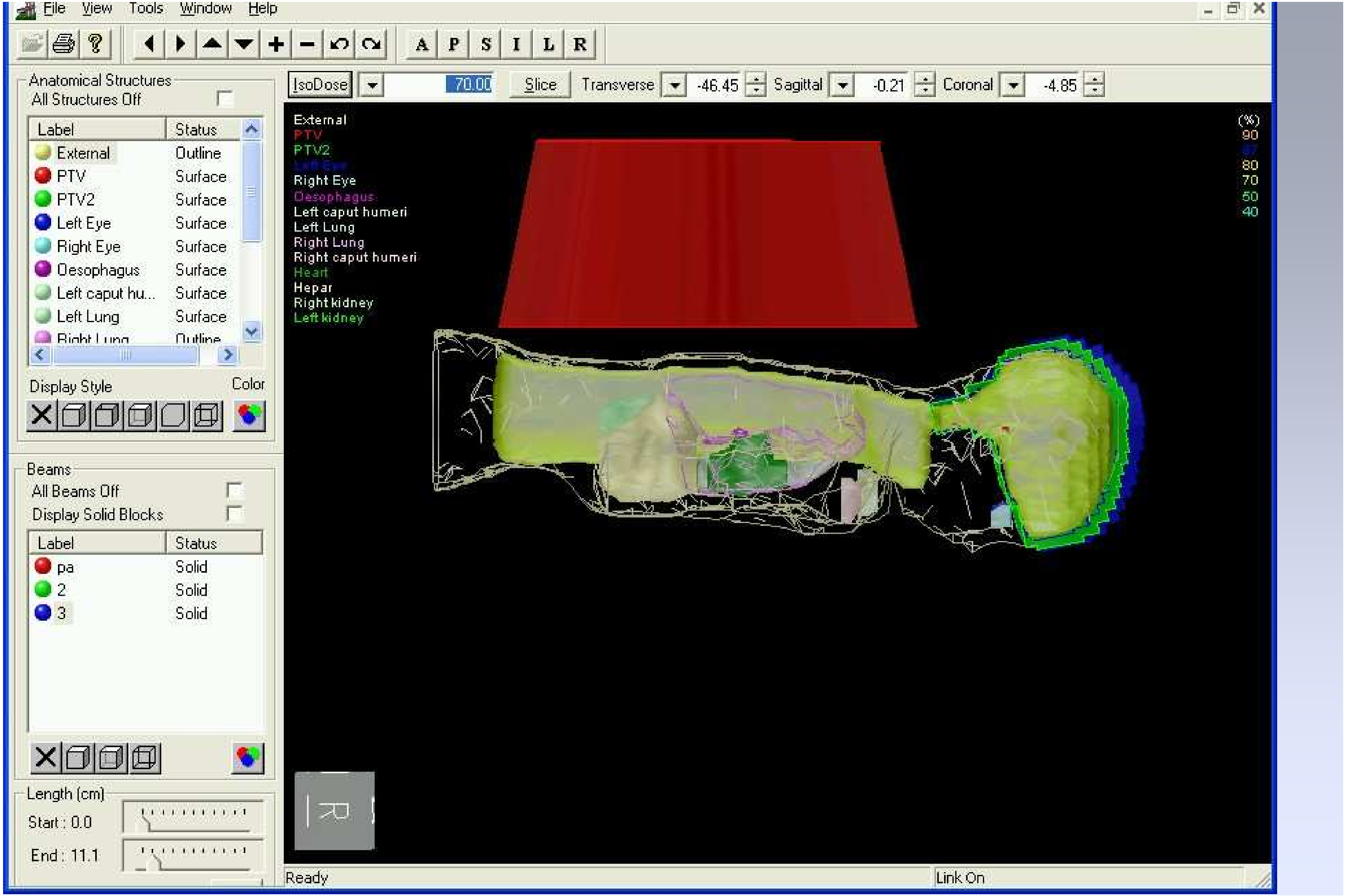
Spot scanned proton


File View Tools Window Help
A P S I L R
Anatomical Structures
All Structures Off
Label Status
External Outline
PTV Surface
PTV2 Surface
Left Eye Surface
Right Eye Surface
Oesophagus Surface
Left caput hu... Surface
Left Lung Surface
Display Style
Color
Beams
All Beams Off
Display Solid Blocks
Label Status
pa Solid
2 Solid
3 Solid
Length (cm)
Start : 0.0
End : 11.1
IsoDose 90.00 Slice Transverse -46.45 Sagittal -0.21 Coronal -4.85
External
PTV
PTV2
Right Eye
Oesophagus
Left caput humeri
Left Lung
Right Lung
Right caput humeri
Heart
Hepar
Right kidney
Left kidney
(%)
90
80
70
50
40
Ready
Link On

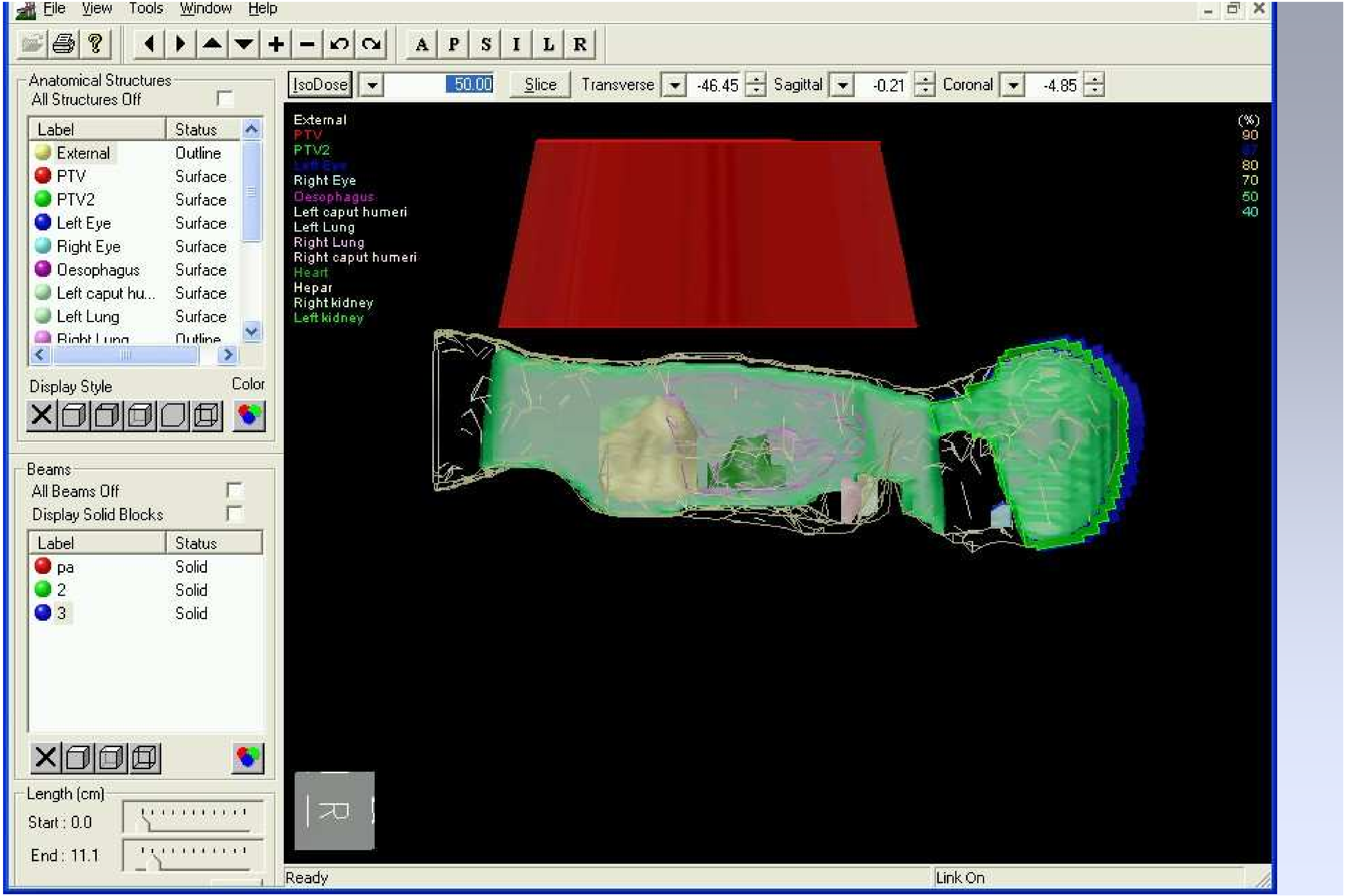

File View Tools Window Help
A P S I L R
Anatomical Structures
All Structures Off
Label Status
External Outline
PTV Surface
PTV2 Surface
Left Eye Surface
Right Eye Surface
Oesophagus Surface
Left caput hu... Surface
Left Lung Surface
Right Lung Outline
Display Style Color
Beams
All Beams Off
Display Solid Blocks
Label Status
pa Solid
2 Solid
3 Solid
Length (cm)
Start : 0.0
End : 11.1
IsoDose 87.00 Slice Transverse -46.45 Sagittal -0.21 Coronal -4.85
External
PTV
PTV2
Left Eye
Right Eye
Oesophagus
Left caput humeri
Left Lung
Right Lung
Right caput humeri
Heart
Hepar
Right kidney
Left kidney
(%)
90
87
80
70
50
40
Ready
Link On

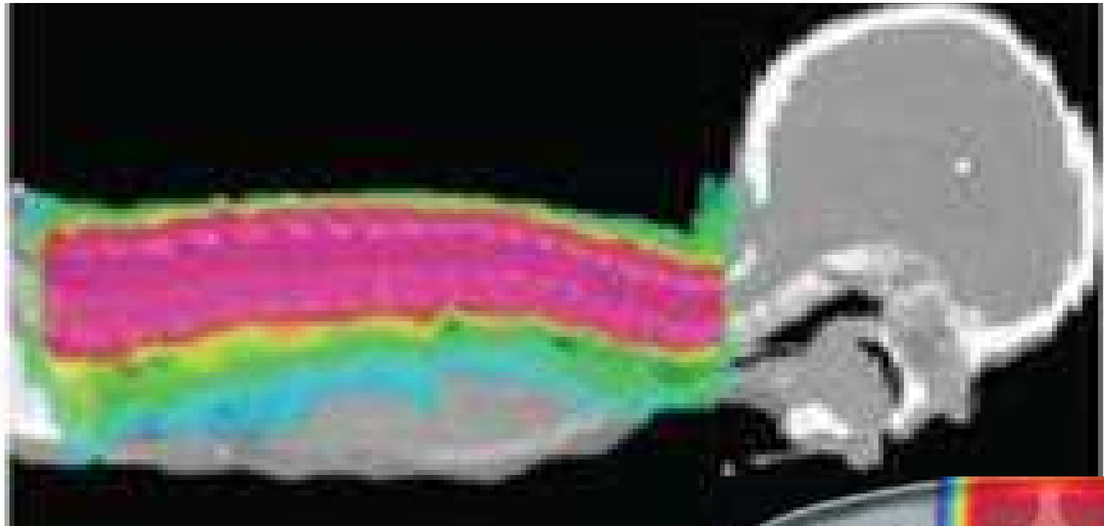


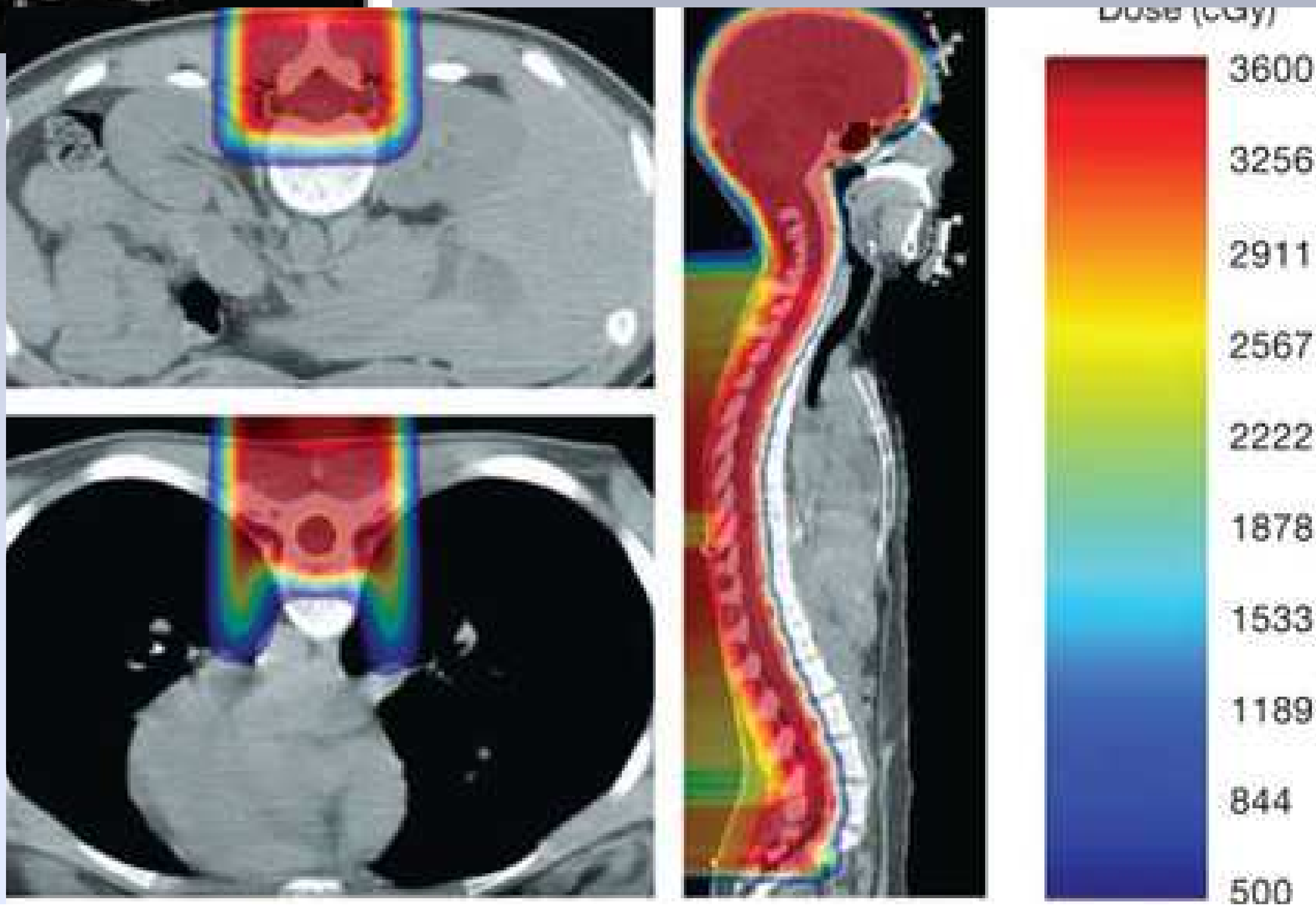
File View Tools Window Help
Anatomical Structures
All Structures Off
Label Status
External Outline
PTV Surface
PTV2 Surface
Left Eye Surface
Right Eye Surface
Oesophagus Surface
Left caput hu... Surface
Left Lung Surface
Right Lung Outline
Display Style
Color
Beams
All Beams Off
Display Solid Blocks
Label Status
pa Solid
2 Solid
3 Solid
Length (cm)
Start : 0.0
End : 11.1
IsoDose 80.00 Slice Transverse -46.45 Sagittal -0.21 Coronal -4.85
External
PTV
PTV2
Left Eye
Right Eye
Oesophagus
Left caput humeri
Left Lung
Right Lung
Right caput humeri
Heart
Hepar
Right kidney
Left kidney
(%)
90
80
70
50
40
Ready
Link On



File View Tools Window Help
A P S I L R
Anatomical Structures
All Structures Off
Label Status
External Outline
PTV Surface
PTV2 Surface
Left Eye Surface
Right Eye Surface
Oesophagus Surface
Left caput hu... Surface
Left Lung Surface
Right Lung Outline
Display Style Color
Beams
All Beams Off
Display Solid Blocks
Label Status
pa Solid
2 Solid
3 Solid
Length (cm)
Start : 0.0
End : 11.1
IsoDose 70.00 Slice Transverse -46.45 Sagittal -0.21 Coronal -4.85
External
PTV
PTV2
Left Eye
Right Eye
Oesophagus
Left caput humeri
Left Lung
Right Lung
Right caput humeri
Heart
Hepar
Right kidney
Left kidney
(%)
90
80
70
50
40
Ready
Link On


File View Tools Window Help
A P S I L R
Anatomical Structures
All Structures Off
Label Status
External Outline
PTV Surface
PTV2 Surface
Left Eye Surface
Right Eye Surface
Oesophagus Surface
Left caput hu... Surface
Left Lung Surface
Display Style
Color
Beams
All Beams Off
Display Solid Blocks
Label Status
pa Solid
2 Solid
3 Solid
Length (cm)
Start : 0.0
End : 11.1
IsoDose
50.00
Slice
Transverse
-46.45
Sagittal
-0.21
Coronal
-4.85
External
PTV
PTV2
Right Eye
Oesophagus
Left caput humeri
Left Lung
Right Lung
Right caput humeri
Heart
Hepar
Right kidney
Left kidney
(%)
90
80
70
50
40
Ready
Link On




Dose (cGy)
3600
3256
2911
2567
2222
1878
1533
1189
844
500

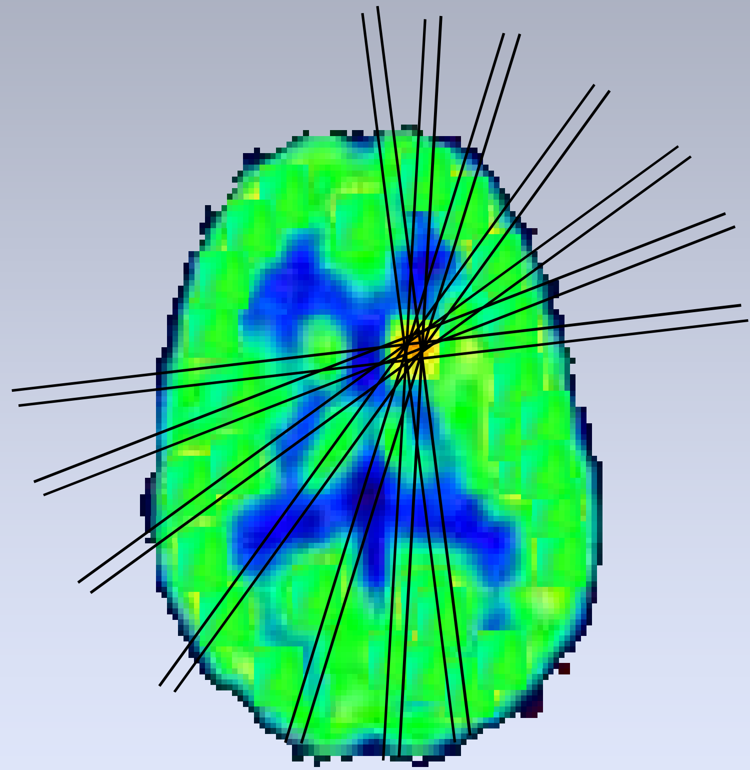
Protonterápia indikációja

Sugárérzékeny struktúrákkal övezett lokálisan növekvő tumorok:

- Szem tumorok (melanoma, retinobl.)
- Agyalapra terjedő tumorok (chordomak, chondrosarcomák, meningiomák, orrmelléküreg tu.)
- Kp.-i idegrsz :agydaganatok, gerincvelő ill. paraspinalis tumorok, AV malform.
- Gyermekkori daganatok
- Prostata karcinóma
- Emlő, fejnyak, nyelőcső, tüdő

PET Localization for Functional Proton Radiosurgery

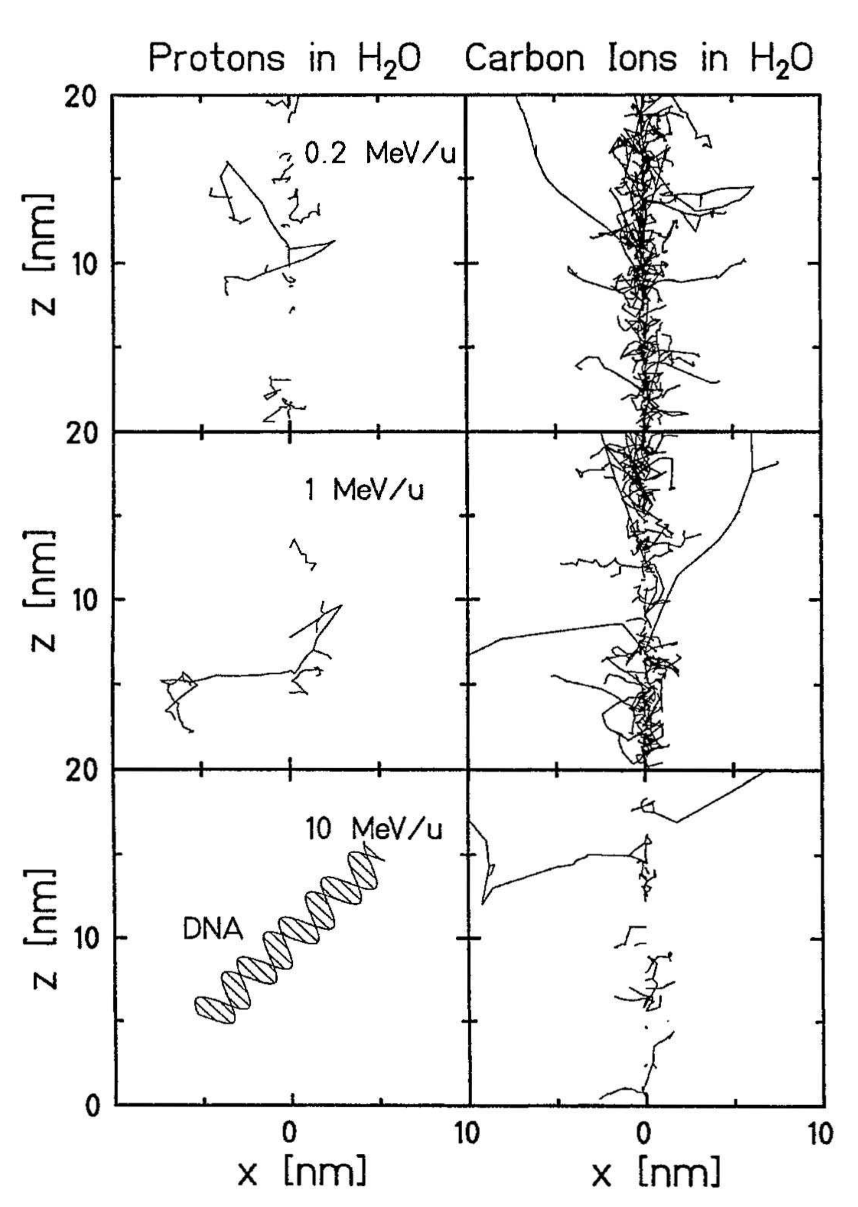
- Treatment of Parkinson’s disease
- Multiple narrow p beams of high energy (250 MeV)
- Focused shoot-through technique
- Very high local dose (> 100 Gy)
- PET verification possible after test dose



Positron Emission Tomography (PET) of Proton Beams

Reaction	Half-life	Threshold Energy (MeV)
$^{16}O(p,pn)^{15}O$	2.0 min	16.6
$^{16}O(p,2p2n)^{13}N$	10.0 min	5.5
$^{16}O(p,3p3n)^{13}C$	20.3 min	14.3
$^{14}N(p,pn)^{13}N$	10.0 min	11.3
$^{14}N(p,2p2n)^{11}C$	20.3 min	3.1
$^{12}C(p,pn)^{17}N$	20.3 min	20.3

Carbon ion terápia



^{10}C és ^{11}C positron kibocsájtók - kezelés monitorizálás PET-el.

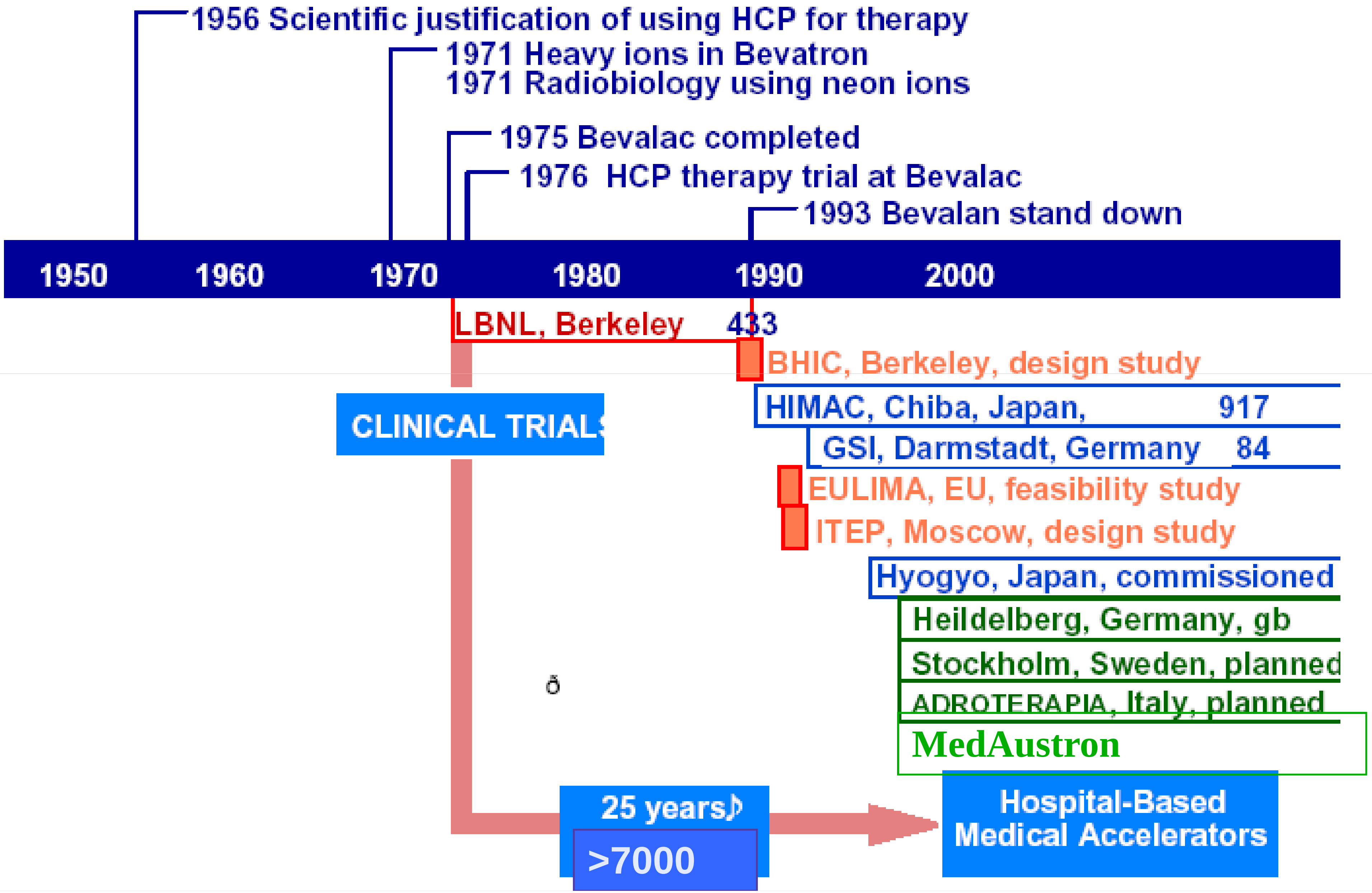
Nagy fizikai specificitás + nagy LET

Hátrányai

- drága
- korlátozottságok (fixált gantry)
- Tervezési, kivitelezési precizitás

[redacted]

High-LET Particle Therapy– Milestones



Neutron befogás terápia

Alapja egyes atomok relative nagy valószínűségű termikus neutron-befogása

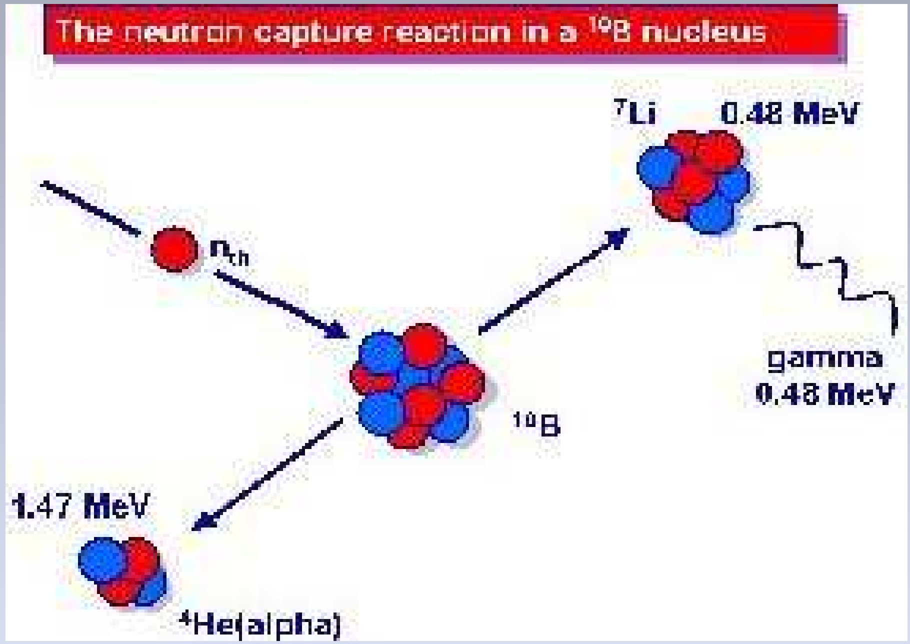
- Bór neutron befogás
- Gadolinium neutron befogás

↓

Nuclearis reakció

Bór Neutron Befogás Terápia BNCT

- Bináris rendszer
- High LET
- High RBE
- Cell-targeted RT



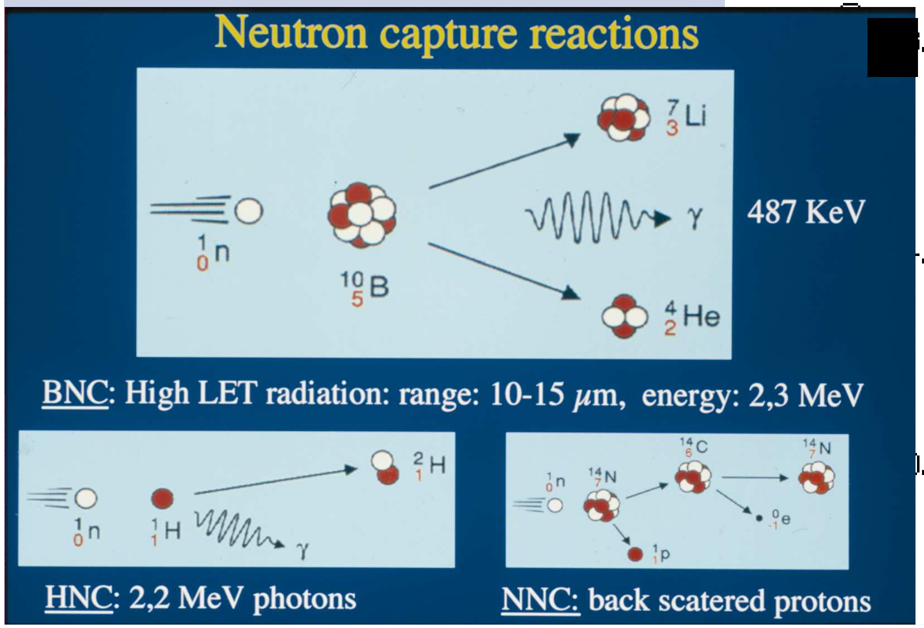
Boron carrier

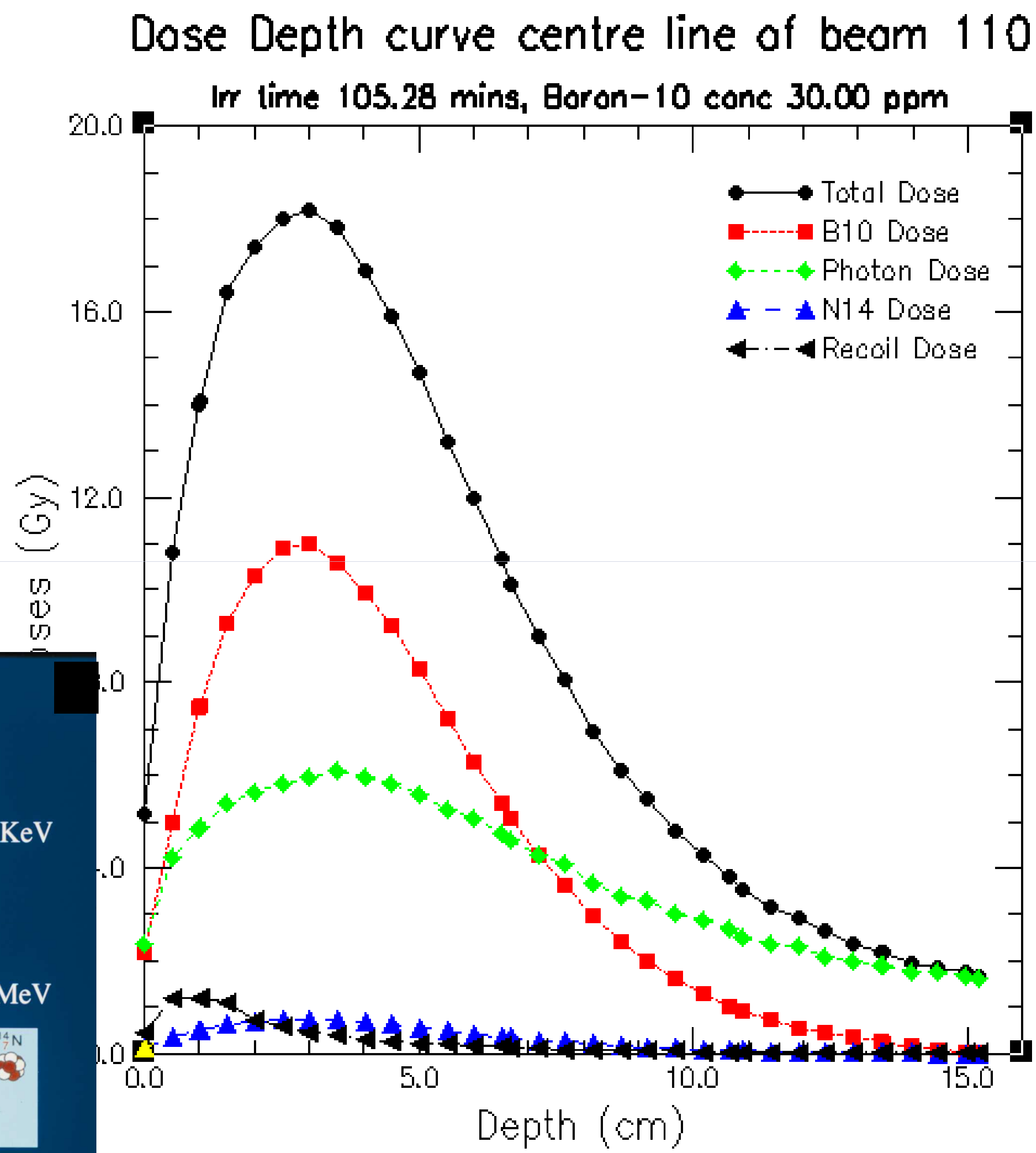
BPA (borophenylanalin)

BSH $Na_2B_{12}H_{11}SH$

Dose components

- D_{Boron}
- $D_{Nitrogen}$
- D_{Photon}
- $D_{neutron}$





Miért nem alkalmazzák szélesebbkörűbben a hadronterápiát?

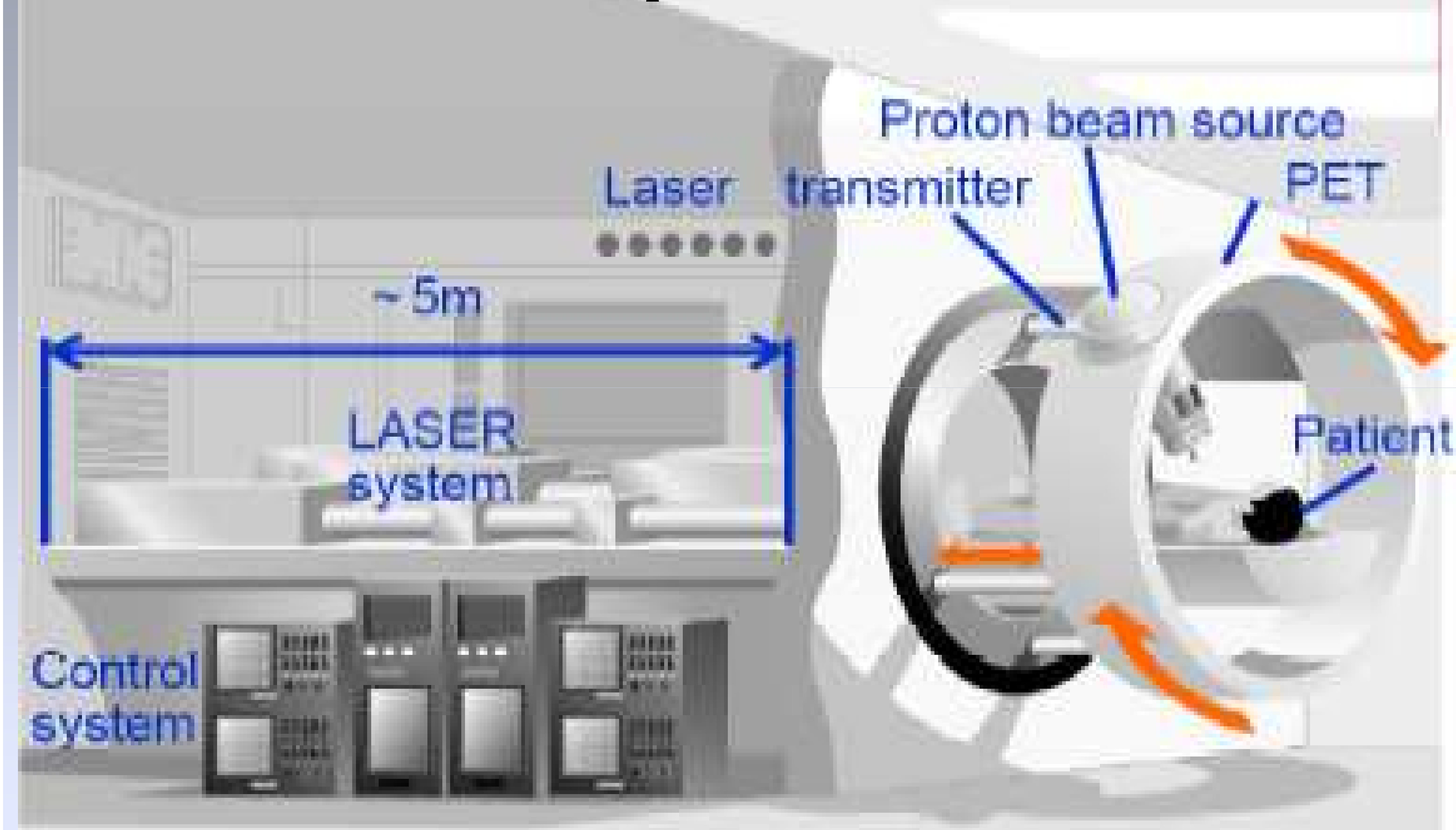
The main limitation to use widely the CPT is the enormous cost of cyclotron based proton/heavy ion accelerator (around 100 million ₤) and the high maintenance-operation costs. According to recent estimation the cost of a Laser-driven CPT facility can be 10 folds lower (cc. 10 million ₤).

Tsukuba

Injector (RFQ/DTL Linac): Max. energy: 7 MeV
Proton synchrotron:
Energy: 70 . 270 MeV
Repetition rate: 0.15 . 0.5 Hz
Extracted beam intensity:1.0 x 1011protons/pulse, (16 nC/pulse)

250-MeV Synchrotron (gated with respiratory motion) with 1 fixed-beam research and 2 gantry treatment rooms

„Table top” hadron forrás



Orvosi hadron forrás

- Intenzív sugárbiológiai kutatás
- Klinikai vizsgálatok
- BETEGKEZELÉS
- Frakcionálás optimalizálása/sugársebészet
- Kombináció
  - Más sugárkezelléssekkel
  - Kemoterápiával/ biol. válaszmódosítókkal
  - Sugárvédő anyagokkal

Célkitűzés

Kompakt, költség-hatékony Laser indukált proton/ion berendezés, amely betegek energia- és intenzitás-modulált, töltött részecske kezelésére (EIMCPT) alkalmas

Laser-hadron terápiás egység

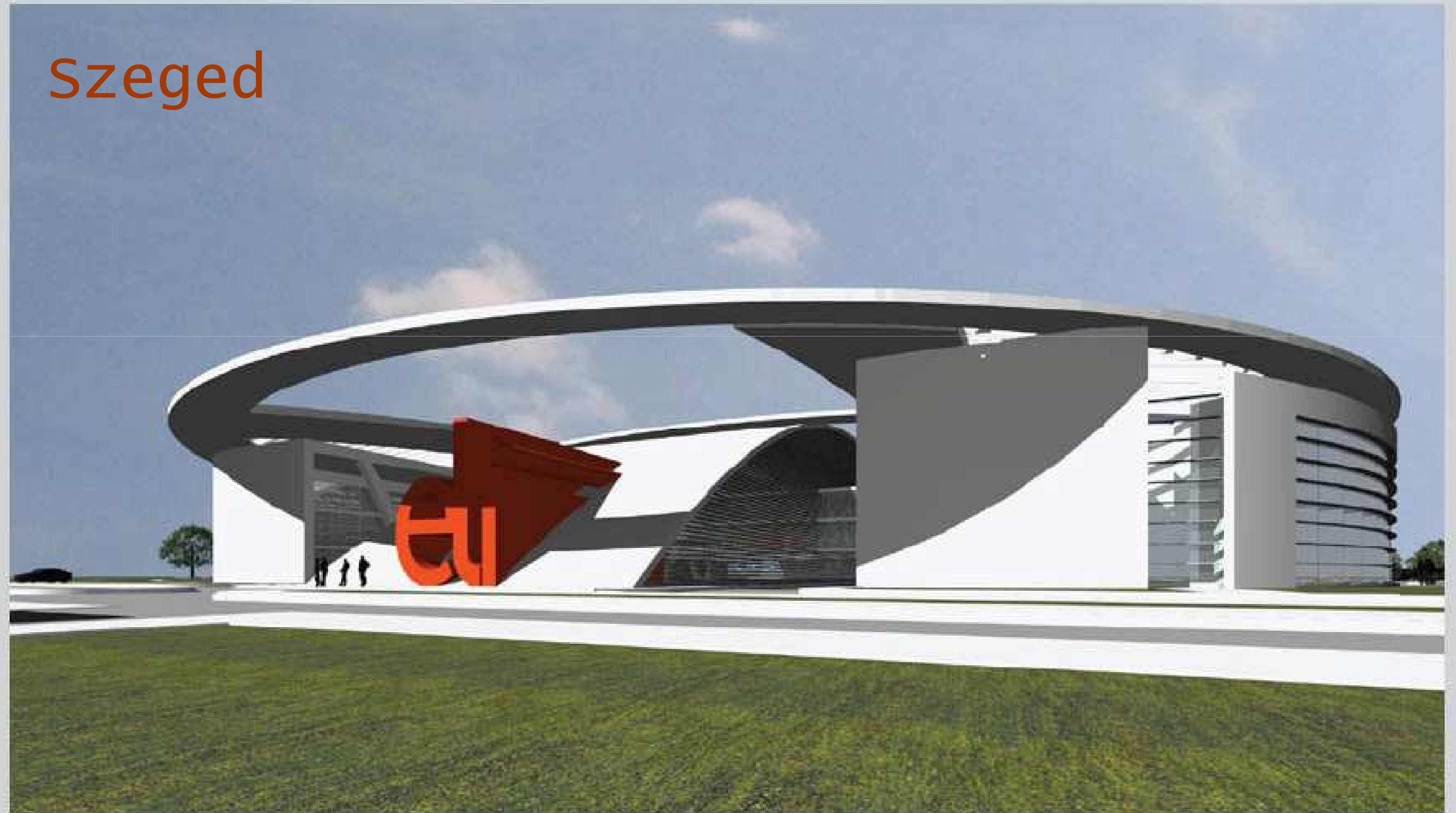
- 1. Laser technology and target design for proton/ion acceleration
- 2. Technology and system development for the particle source operated as a treating facility- QA *
- 3. Dosimetric measurement and calculation on the laser accelerated charged particle for therapeutic application *
- 4. Preclinical research on the biological effect of laser driven CPT
- 5. Development of advanced patient positioning, individual immobilization for planning and CPT delivery.

*

- *radiation protection*
- *particle /energy selection*
- *particle intensity, direction, dose rate*
- *beam collimation*
- *complex facility design*
- *proper room-buliding design*
- *beam operation*
- *treatment monitoring*
- *quality assurance*

Előkészítés: TÁMOP 4.2.B

Szeged



Sugárbiol. munkacsoport feladatai

I. Speciális pozícionáló és immobilizációs eszközfejlesztés hadronterápiához

II. Lézer indukált sugárforrások hatásának vizsgálatára alkalmas biológiai modelek kidolgozása

- konvencionális sugárforrásnál három fő biológiai rendszer beállítása

- Sugárkezelés- biológiai hatás vizsgálata