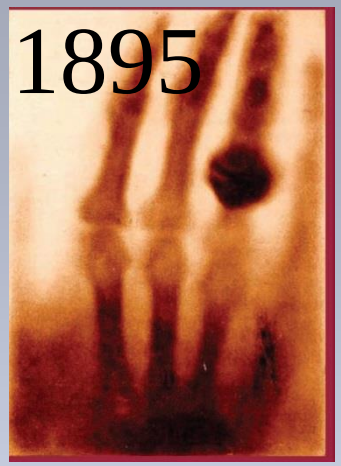
Effects of ionizing radiation

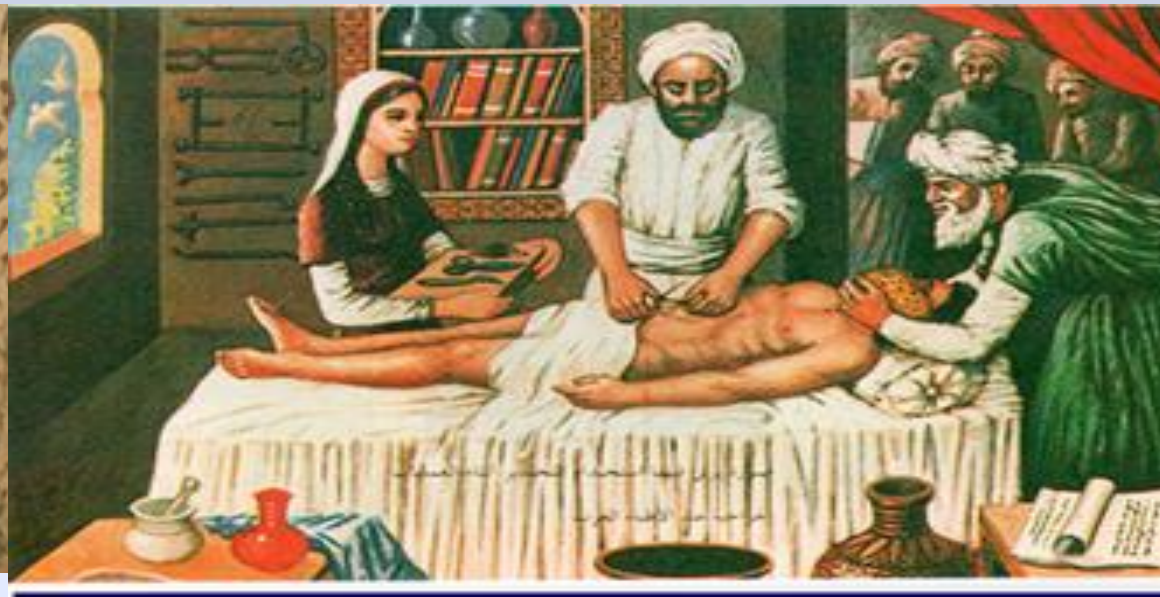
Katalin Hideghéty

Tumor therapy prior to 1895

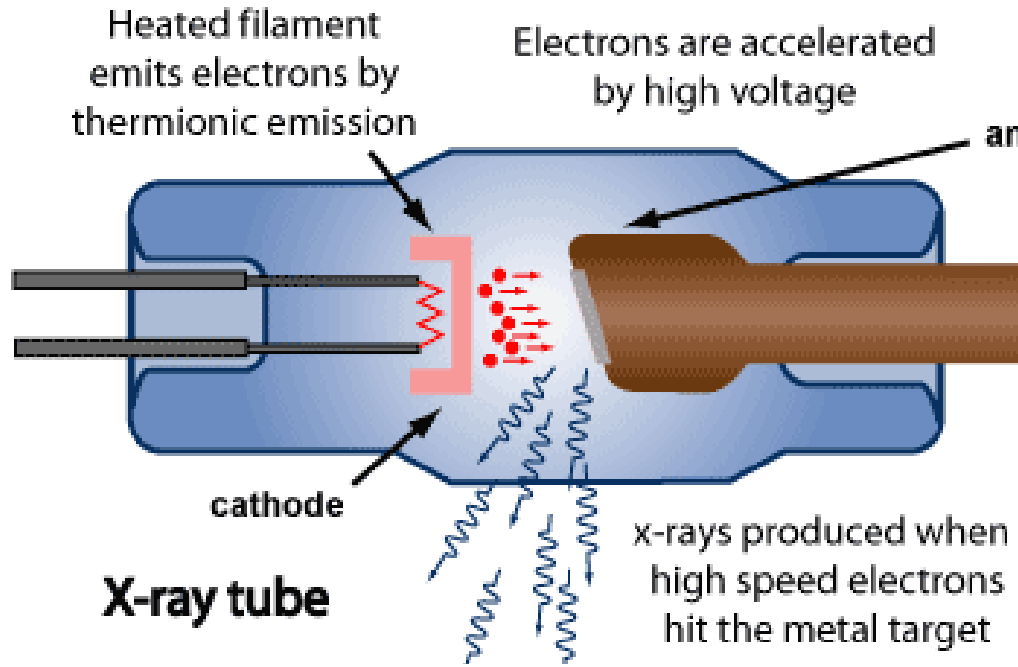
Surgery



Wilhelm Conrad Röntgen



1895

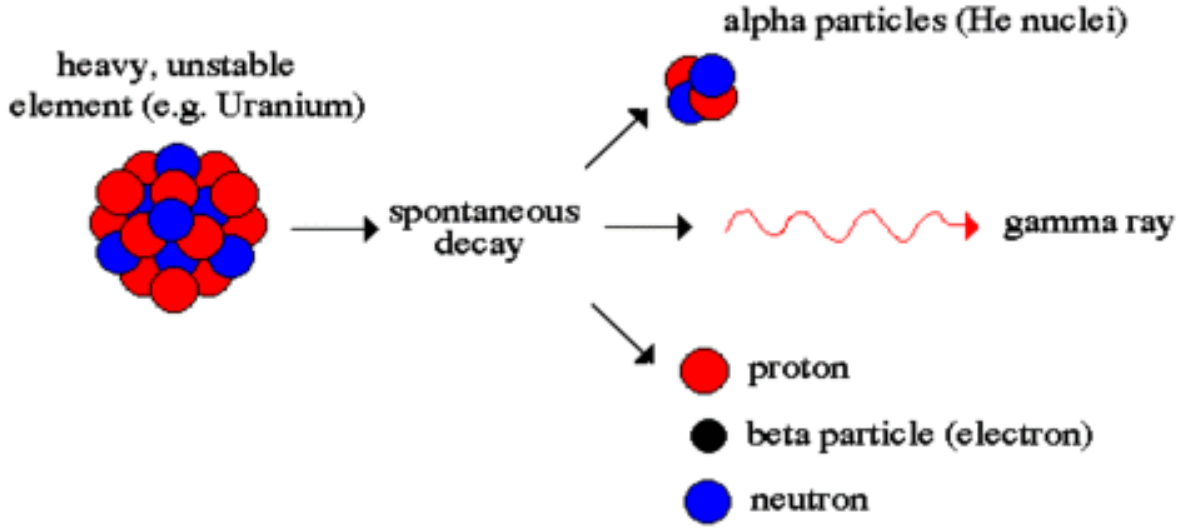


RADIOLOGY

RADIOTHERAPY

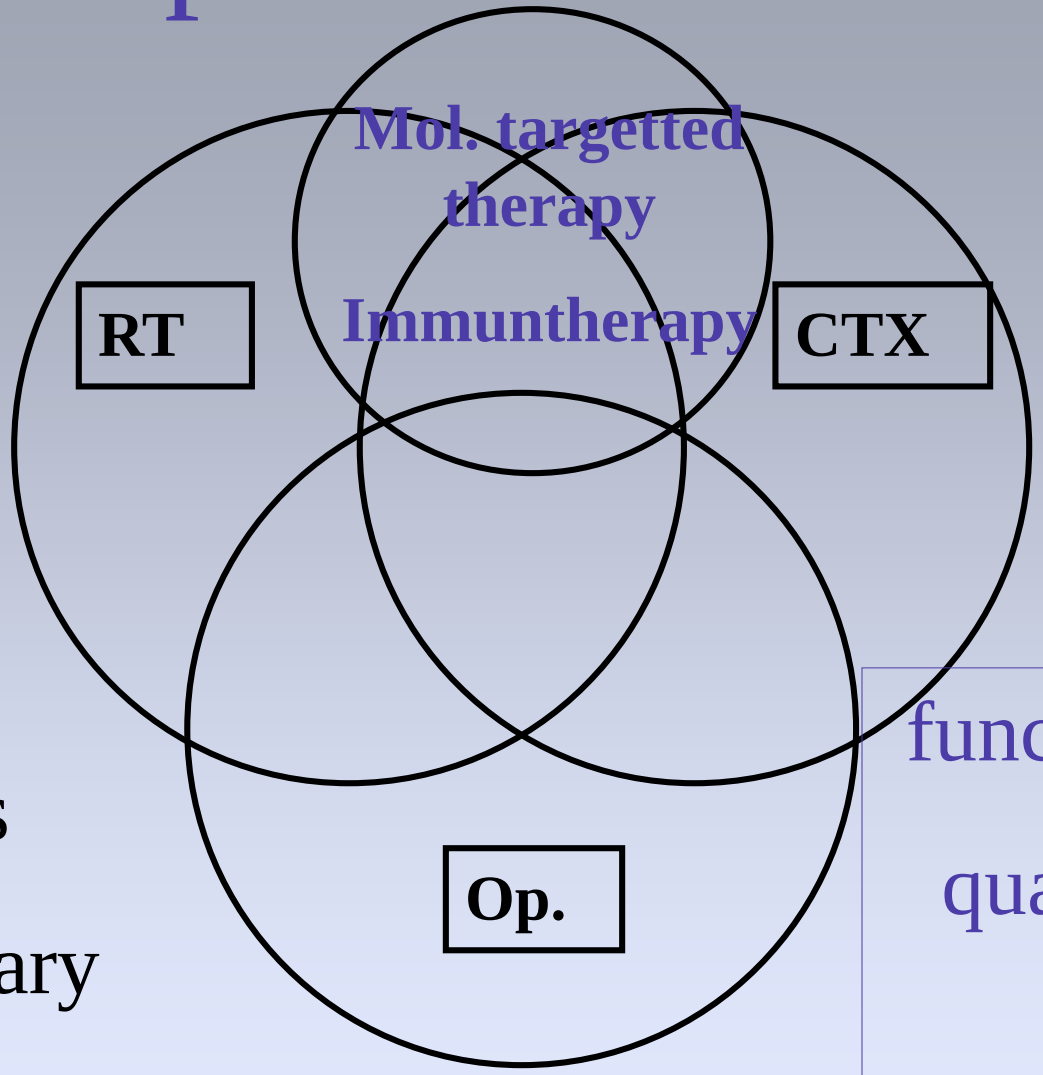
1896

Radioactivity



Complex tumor therapy

early detection



Advanced diagnostics

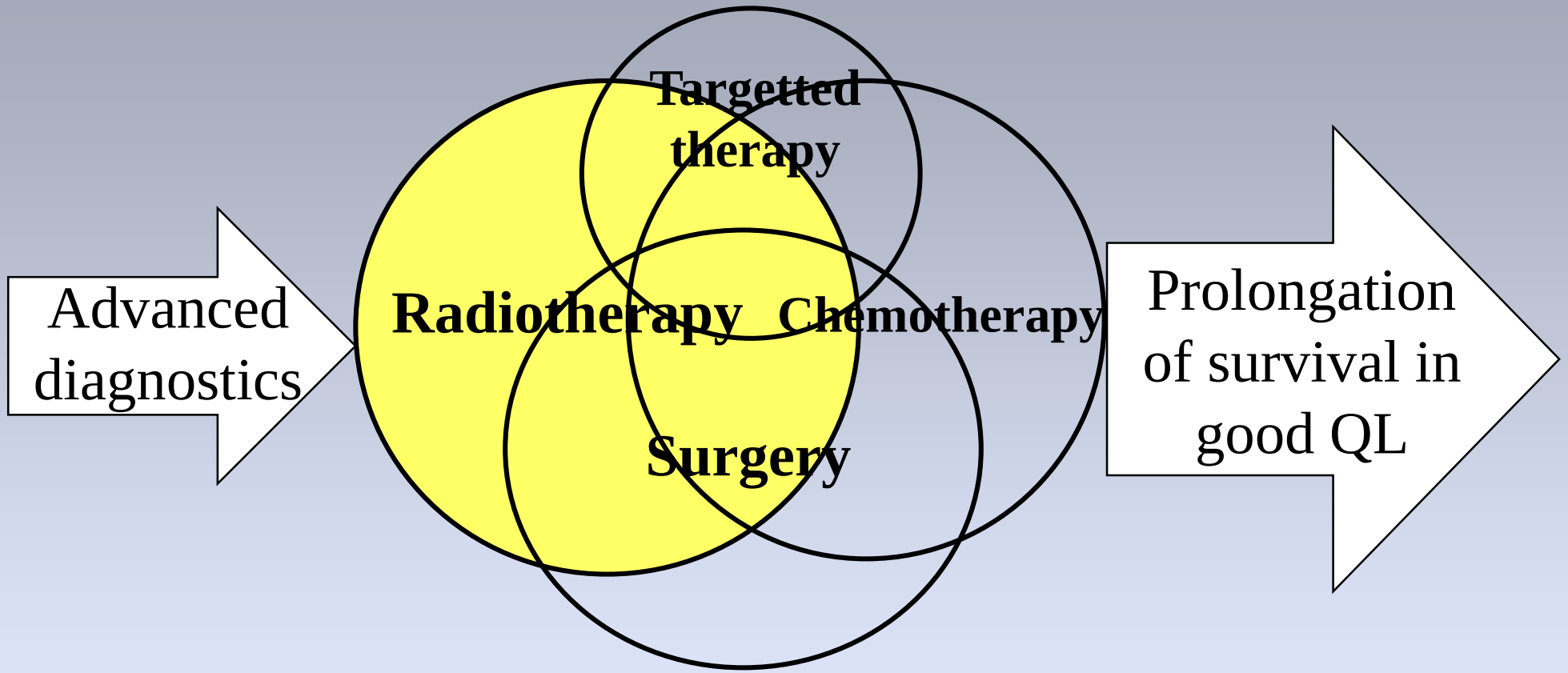
Interdisciplinary decision

function preservation

qualitative survival

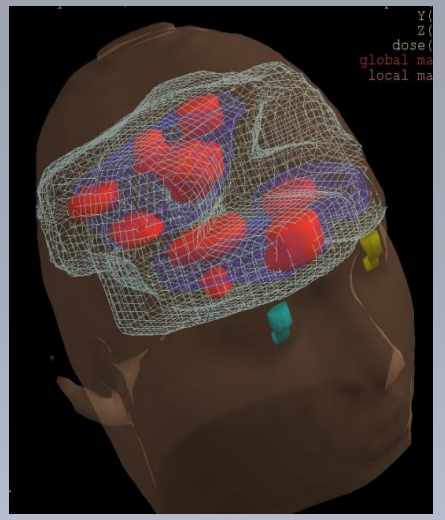
rehabilitation

Complex tumour therapy



10 million patients/year receive radiotherapy

Radiotherapy



Loco-regional treatment method

Directed energy deposition in the human body

$$\text{Dosis} = \frac{\text{energy}}{\text{mass}}$$

Unit Gy (Gray): 1Gy=1 J/kg

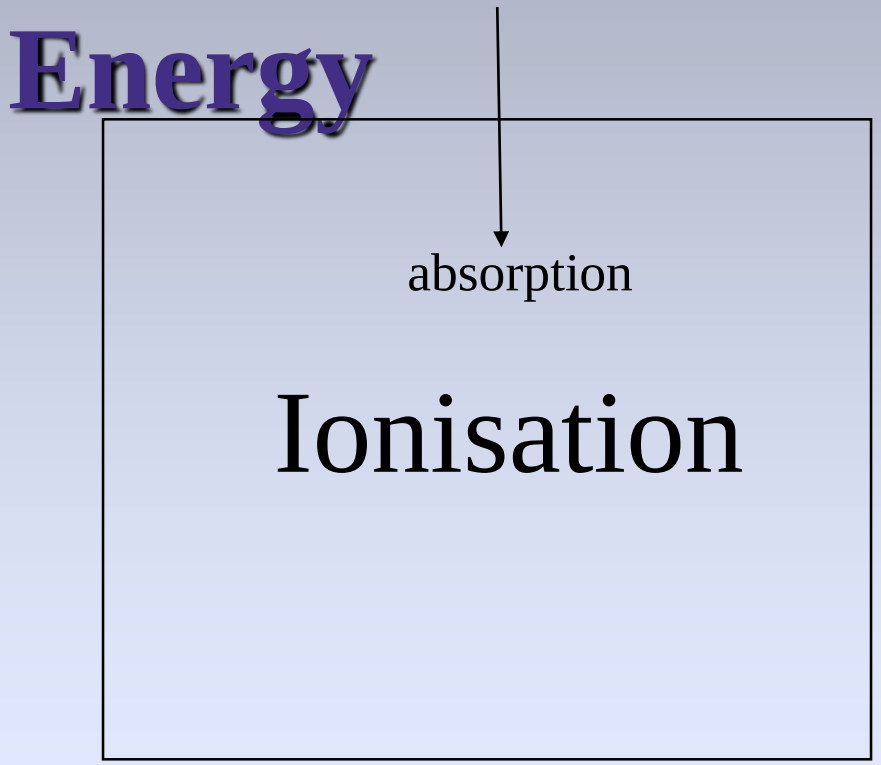
Physical process

RADIATION

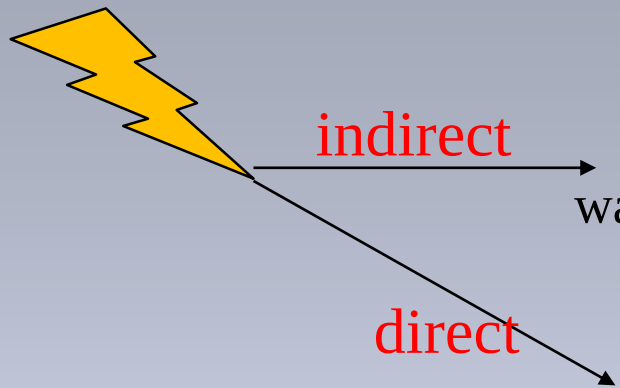
Radioactive isotope

Brachytherapy

Teletherapy (percutaneous)



Chemical procesess

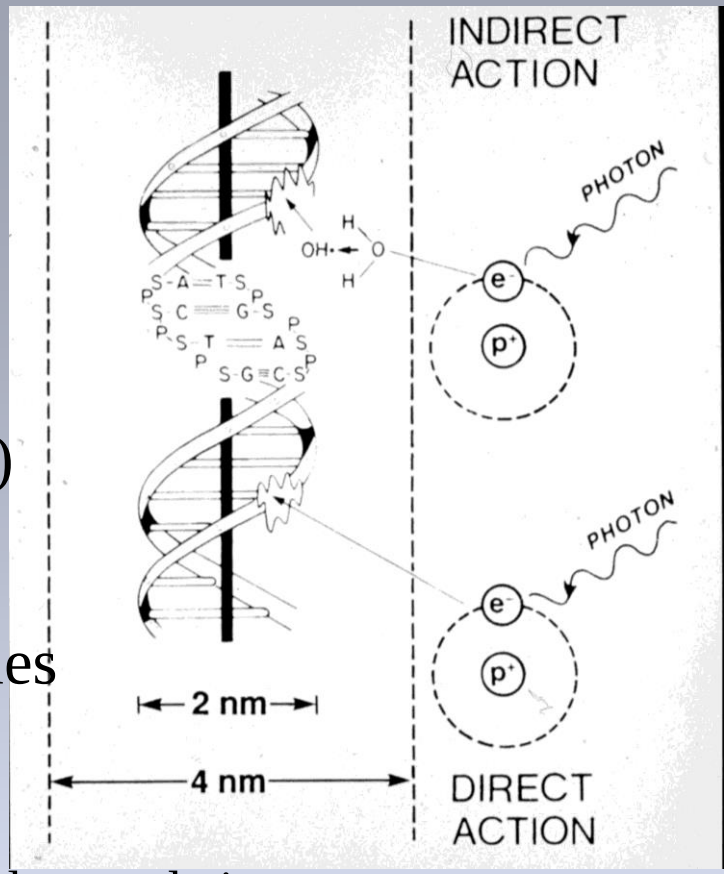


indirect

direct

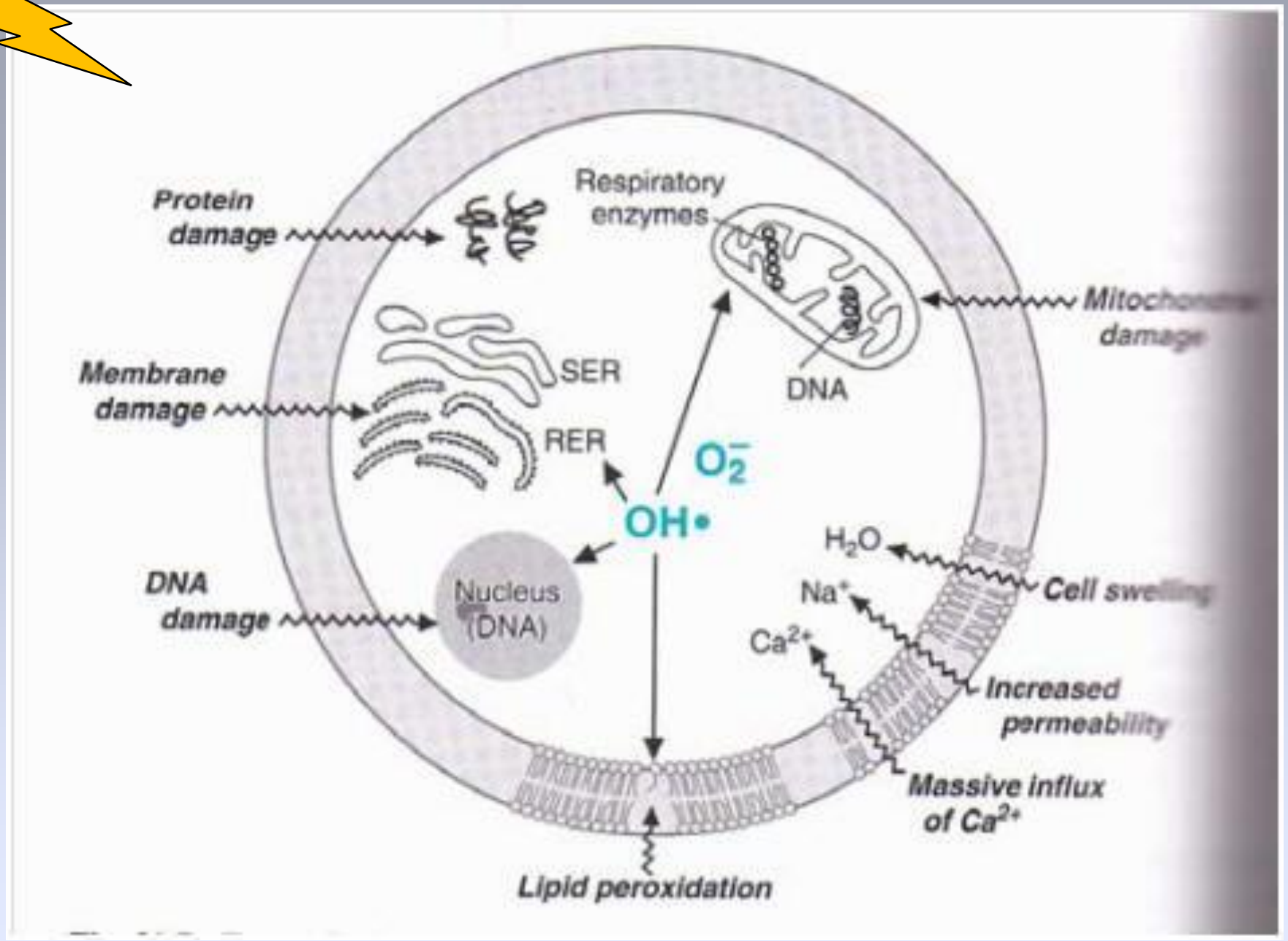
Free oxygen radicals*
water radiolysis, hydroxyl radical (OH)

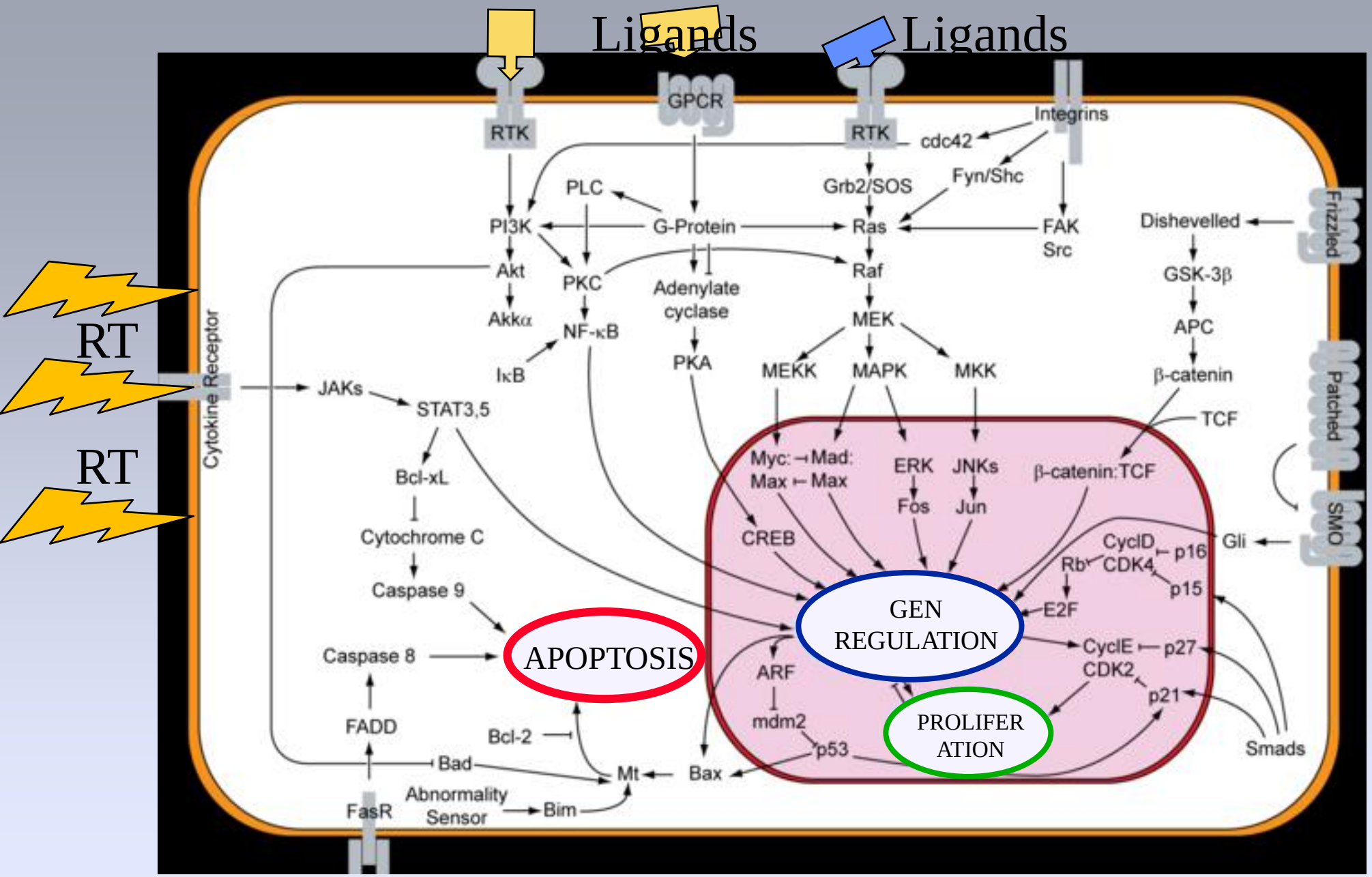
Changes in the macro-molecules
Lipids, proteins,DNA, RNA

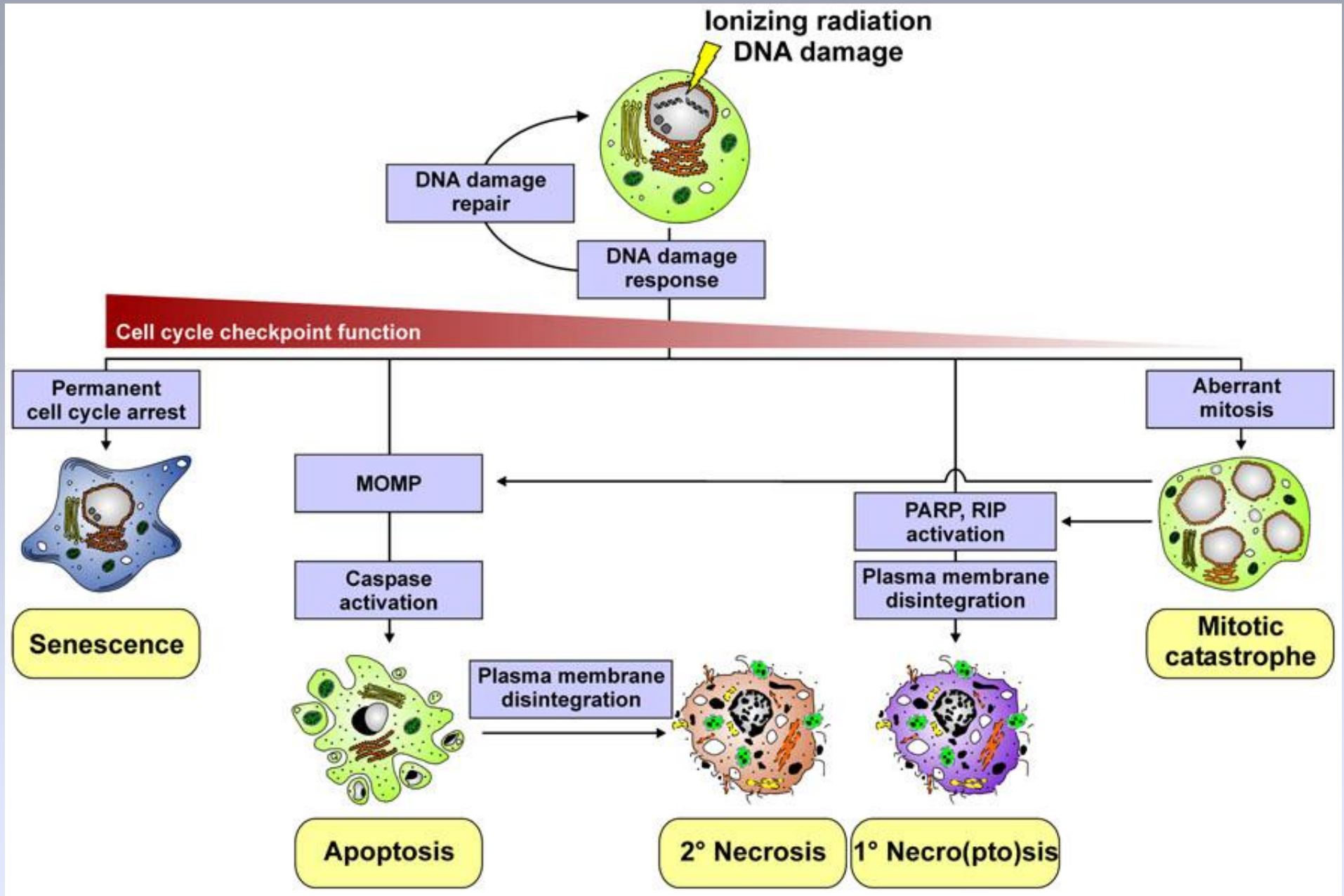


Chain reactions may also occur, particularly in lipids, and may play a role in damage to cell membranes

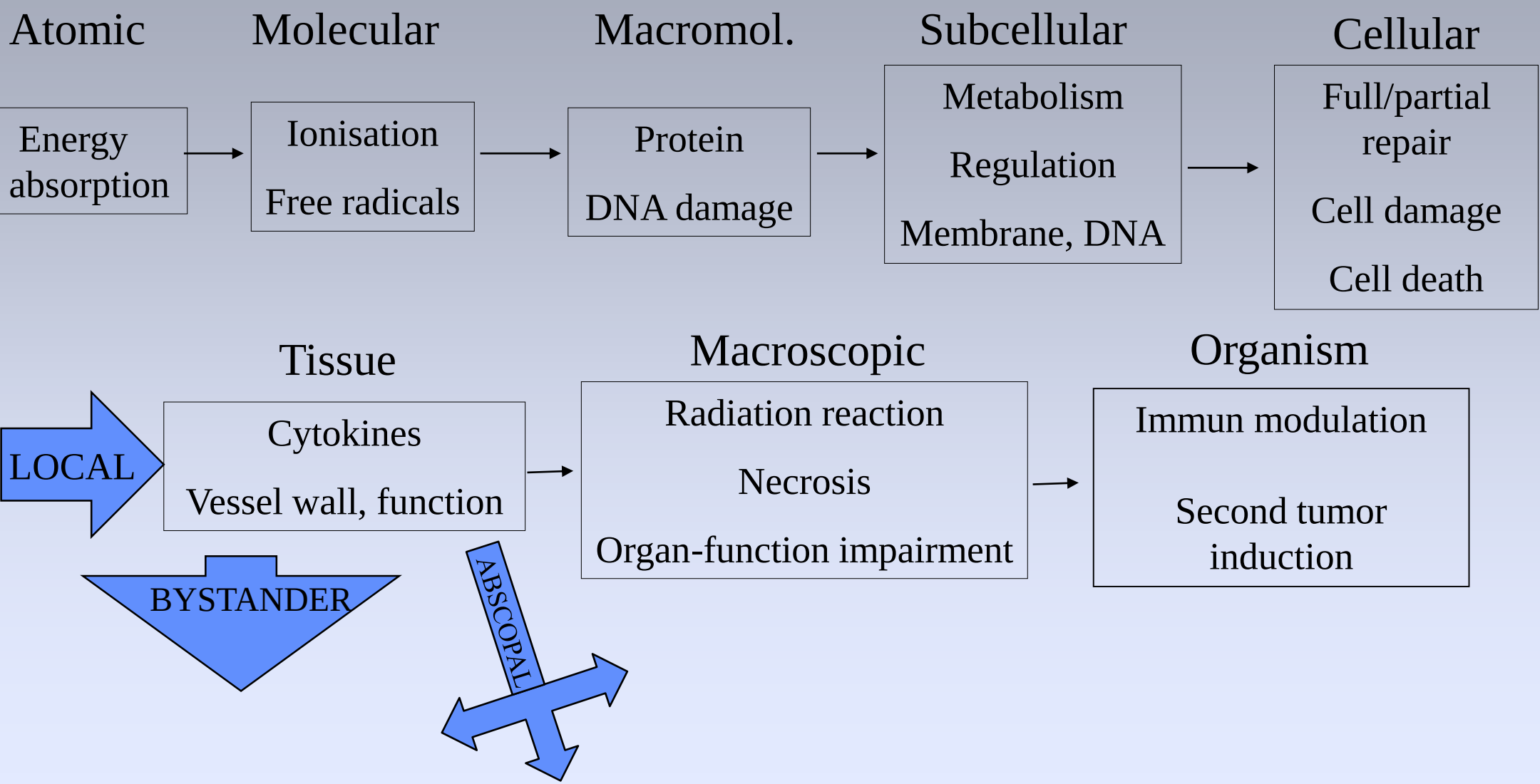
**Free radicals are highly reactive fragments of molecules having unpaired electrons*


Protein damage
Respiratory enzymes
Mitochondrial damage
Membrane damage
SER
RER
DNA
O_2^-
OH•
DNA damage
Nucleus (DNA)
H_2O
Cell swelling
Na^+
Ca^{2+}
Increased permeability
Massive influx of Ca^{2+}
Lipid peroxidation

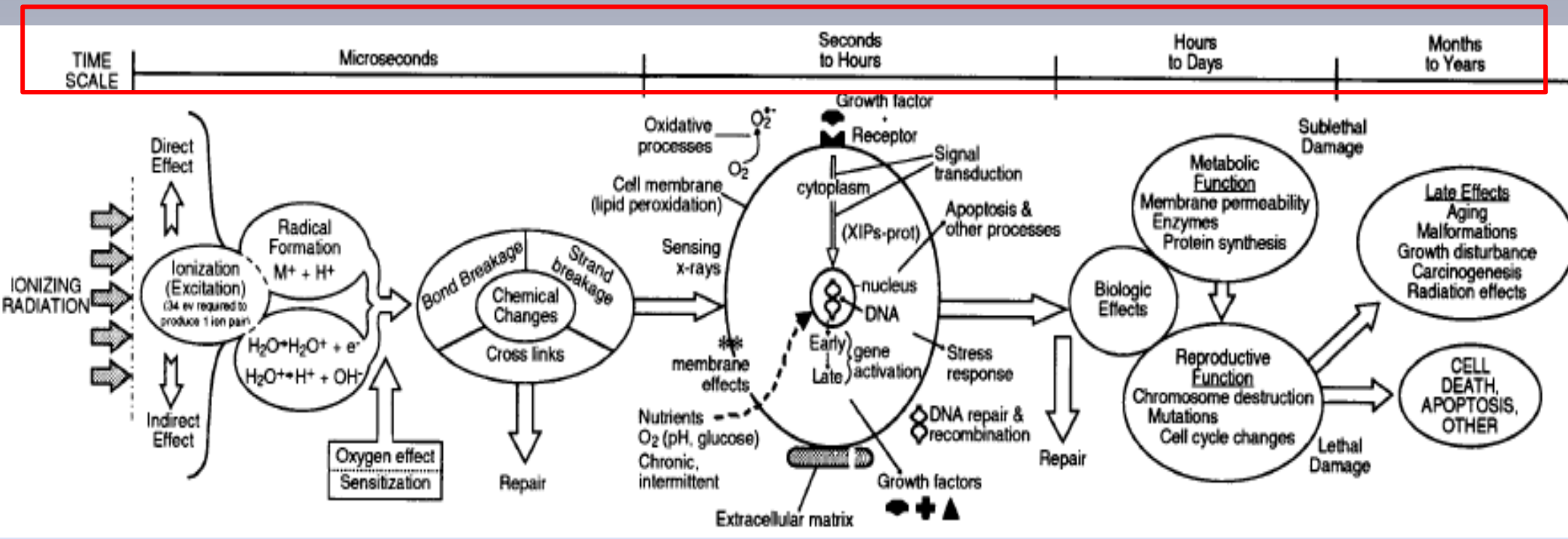

Ligands
Ligands
RT
RT
RTK
GPCR
RTK
Integrins
cdc42
Fyn/Shc
Grb2/SOS
PLC
PI3K
G-Protein
Ras
FAK
Src
Dishevelled
Frizzled
Akt
PKC
Adenylate cyclase
Raf
GSK-3β
Akkα
NF-κB
MEK
APC
IκB
PKA
MEKK
MAPK
MKK
β-catenin
Cytokine Receptor
JAKs
STAT3,5
TCF
Patched
SMO
Bcl-xL
Myc: ⊣ Mad:
Max ⊢ Max
ERK
JNKs
β-catenin:TCF
Fos
Jun
Cytochrome C
CREB
CyclD
p16
Gli
Rb
CDK4
p15
Caspase 9
E2F
GEN REGULATION
Caspase 8
APOPTOSIS
CyclE
p27
ARF
CDK2
p21
FADD
mdm2
PROLIFERATION
Bcl-2
p53
Smads
Bad
Mt
Bax
FasR
Abnormality Sensor
Bim


Ionizing radiation
DNA damage
DNA damage repair
DNA damage response
Cell cycle checkpoint function
Permanent cell cycle arrest
Senescence
MOMP
Caspase activation
Apoptosis
Plasma membrane disintegration
2° Necrosis
PARP, RIP activation
Plasma membrane disintegration
1° Necro(pto)sis
Aberrant mitosis
Mitotic catastrophe

Radiation effects

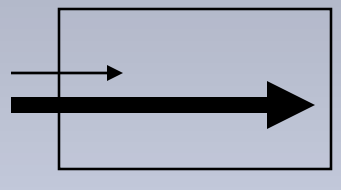


Radiation effects



Characteristic of radiation

- Quality (particle) photon, electron, proton…
- Energy (mean)



- Intensity

- Dose rate (dose/time)
- linear energy transfer LET/ biological effectivity RBE

High LET

Very dense ionisation

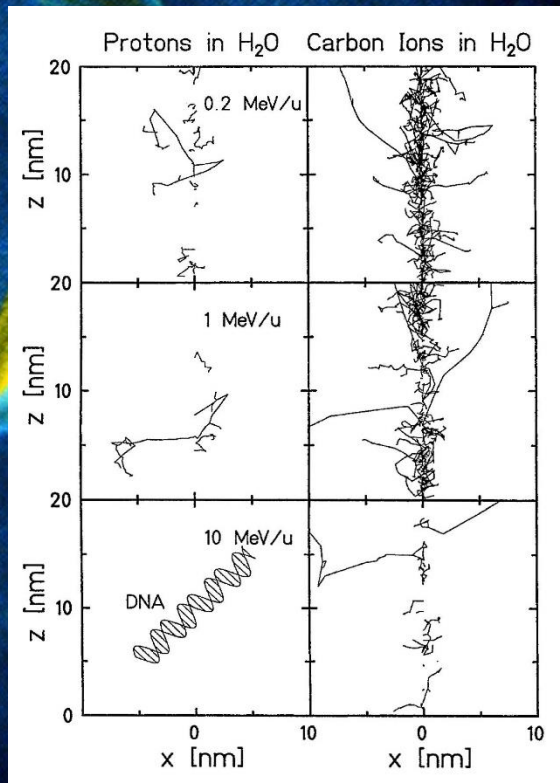
Low LET (inidrect action)

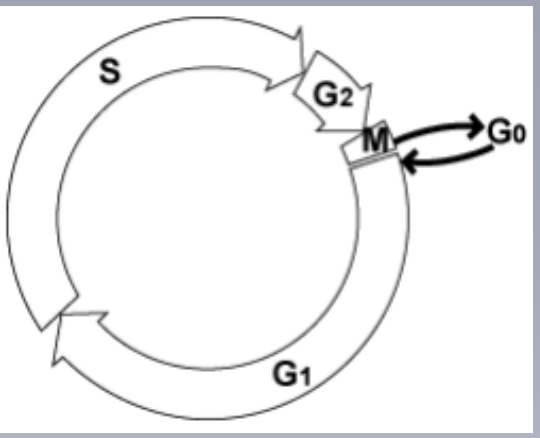
Ionisation Free oxygen radicals

Clustered lesions

High RBE
Low OER

Isolated lesions





Cell cycle effects

Radiosensitivity differs throughout the cell cycle

- late S-phase being most radioresistant,

- G2/M being most radiosensitive

- G1 phase taking an intermediate position.

Biological effects depend on

micr.

- cell cycle
- oxygenisation
- regeneration
- intrinsic radiosensitivity

macr.

- tumour size, -type, -vasc.
- age, nutrition, perf. status
- anaemia, co-morbidity, medication

Radiaton quality, dosis, fractionation, combination

RT

Aims

Tumour elimination

- Curation
- Organ/function preserv.
- Palliation

Side effects

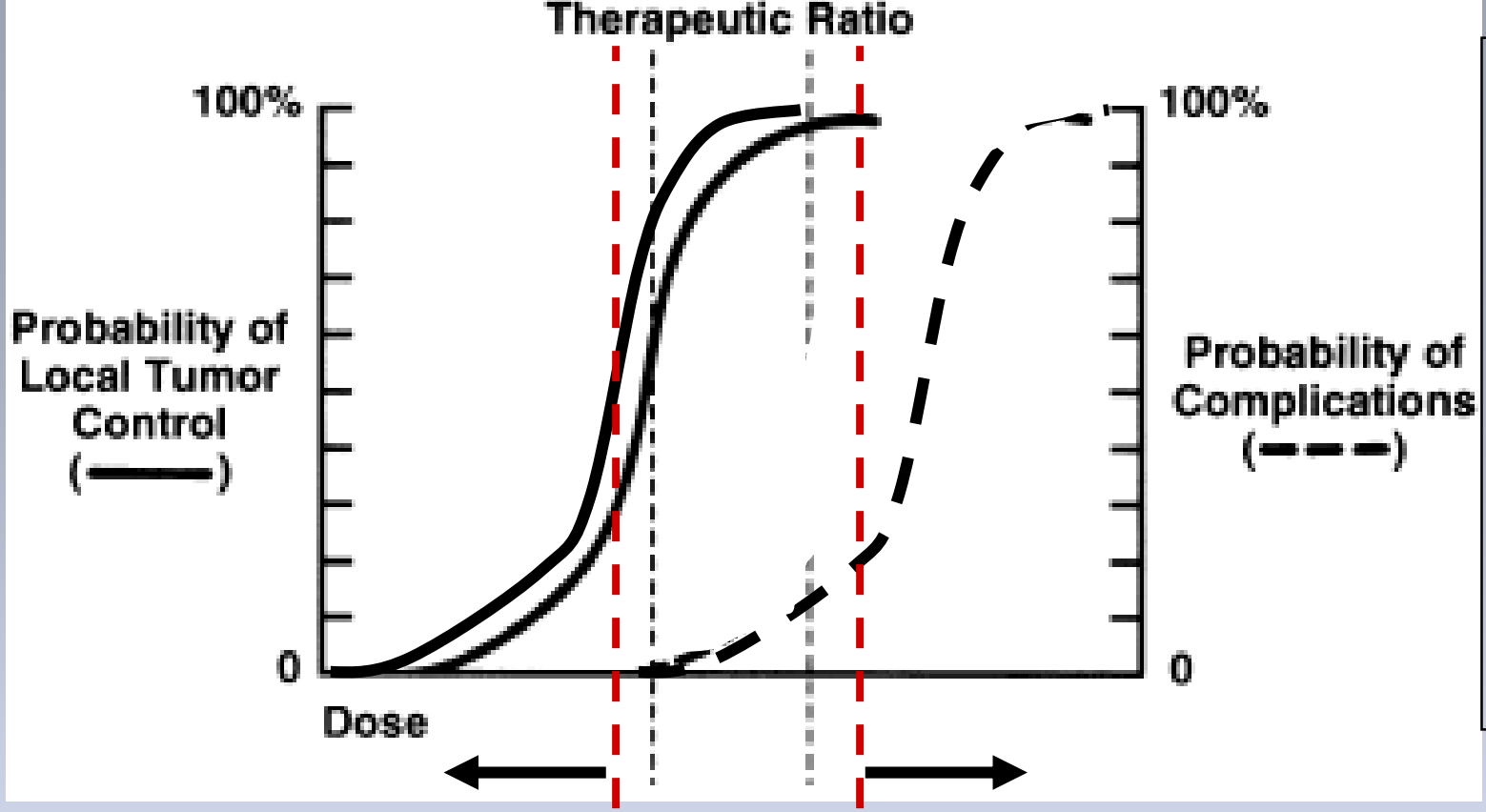
- **Acute reactions**
  - General /Local -**Inflammation**
- **Late sequales** (irreversibile)
  - **Scar tissue**, ulcus, organ function ↓
- (second) tumor induction

Therapeutic index

Tumour response / side effects

CR, PR, MC, SD, PD
LC, TFS, TTP, OS

Toxicity (grade. duration
impact on QL)



Fractionation

Hypofractionated

Hyperfractionated

Accelerated Hyperfractionated (CHART)

CHARTWELL

Radiation modifyers

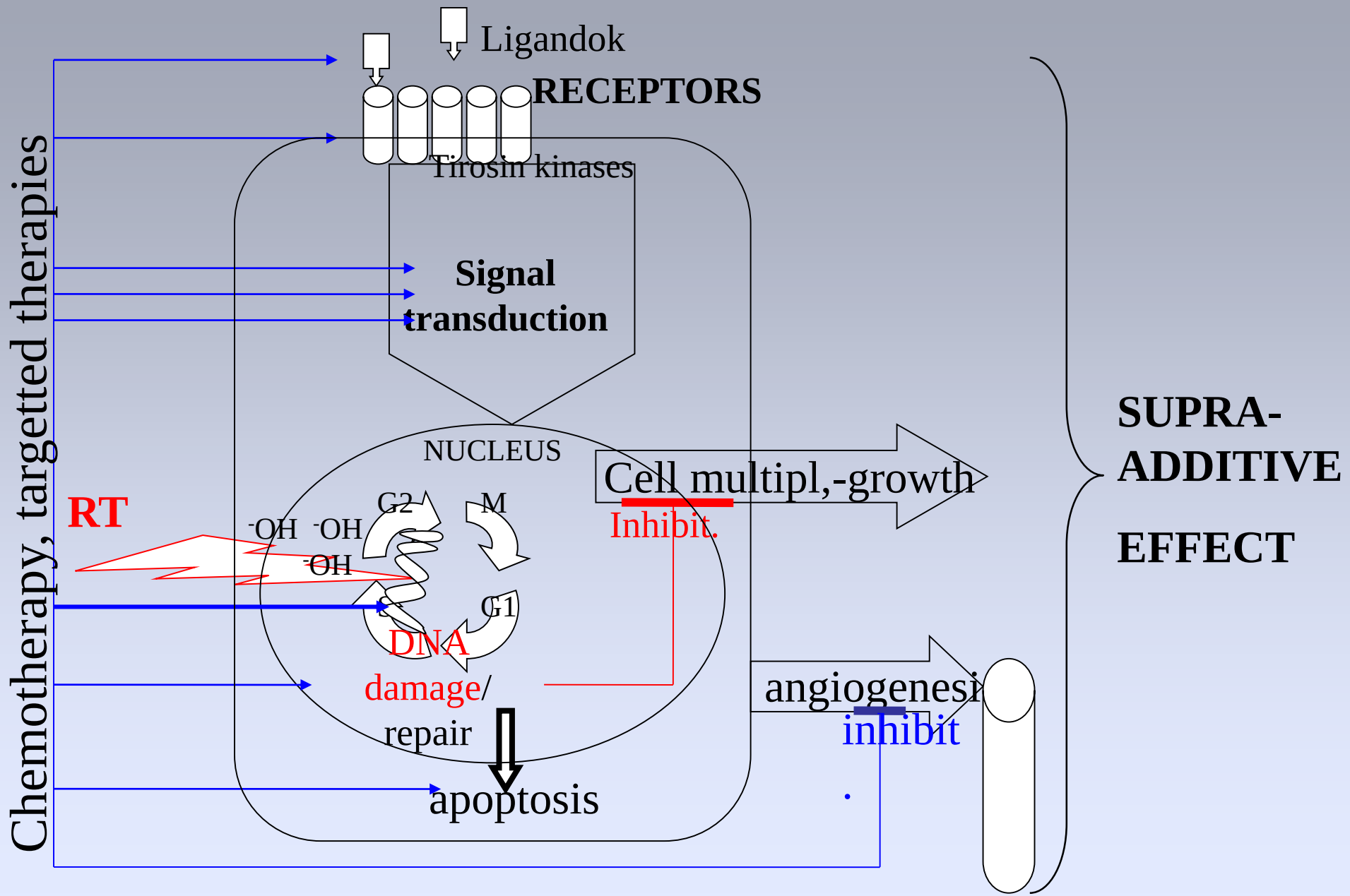
sensitisation/protection

Chemo-, hormon, biol.m.,hypoxic sens.

Technical development

Increase of spatial selectivity

Radiosensitisation



Concomittant radio-chemotherapy NSCLC

50mg/m2 Paclitaxel 200 mg/m2Carboplatin (AUC)

irradiation

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25

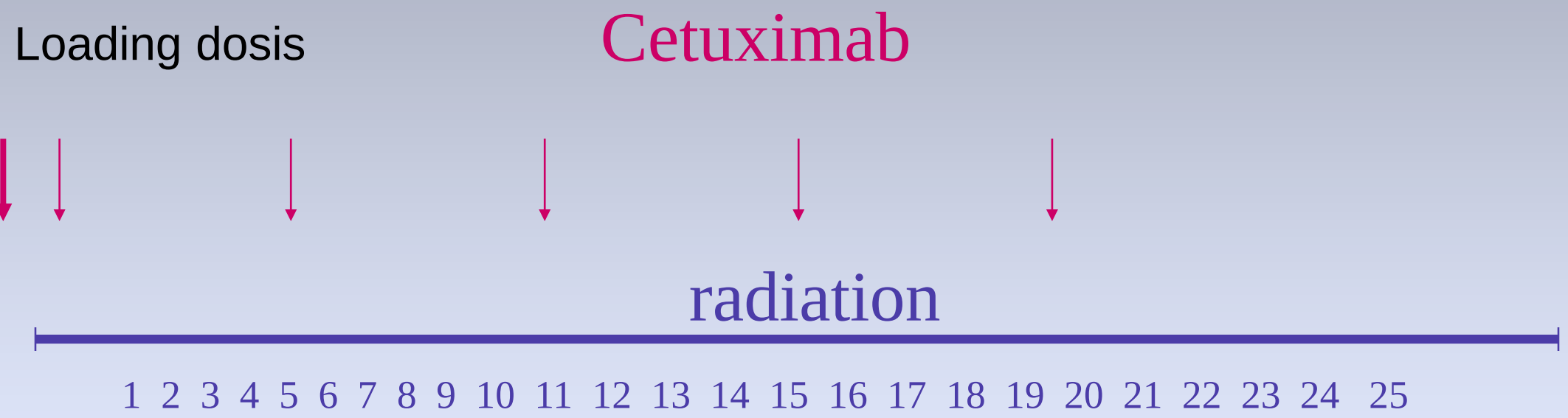
Concomittant radio-chemotherapy Glioblastoma

75mg/m^2/day temozolomid (during 42 days)

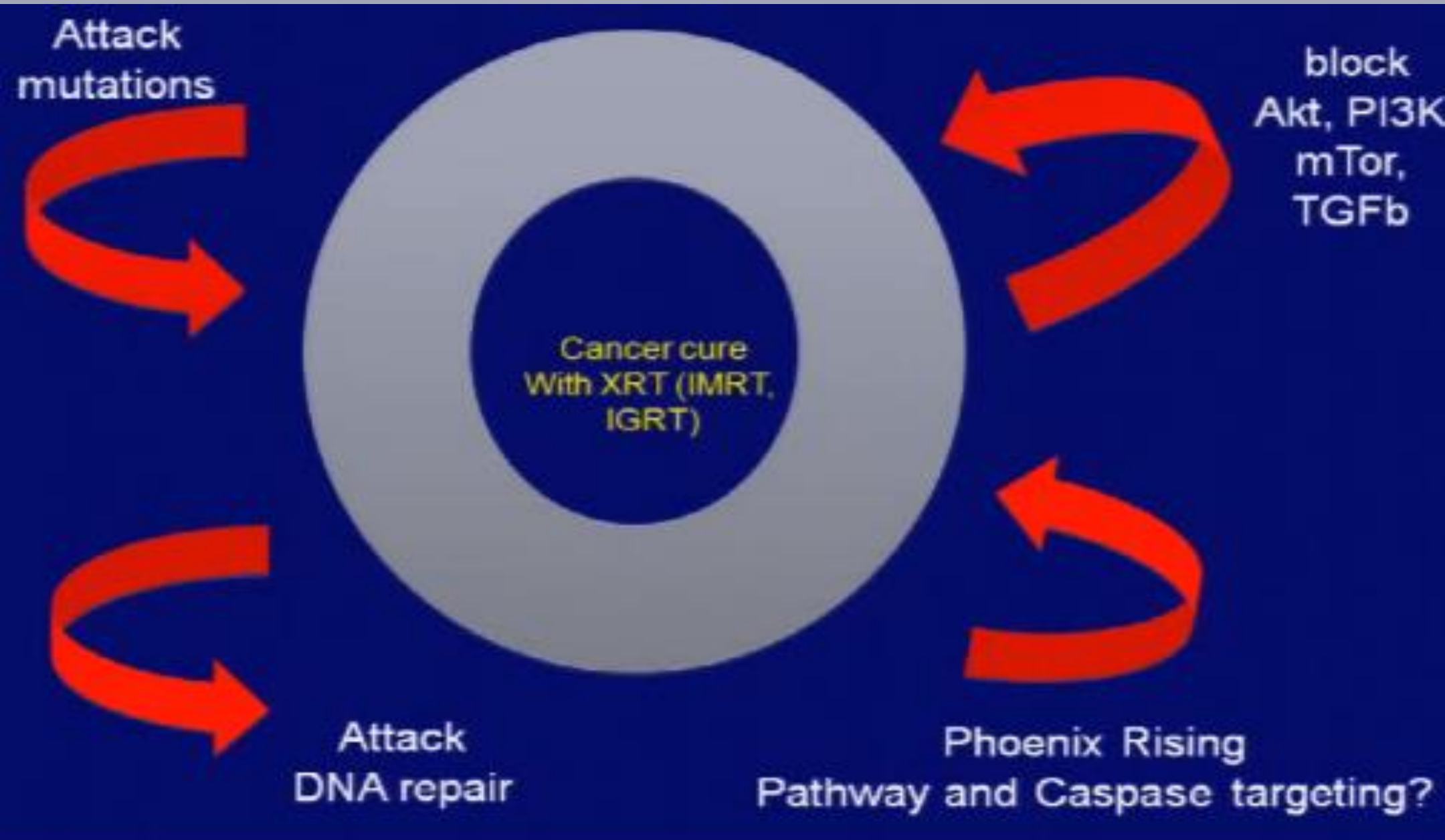
Irradiation

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25

Concomittant anti-EGFr-radiotherapy
Head and neck



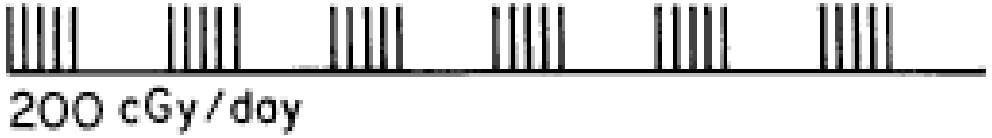
Molecular tagets in connection of radiotherapy

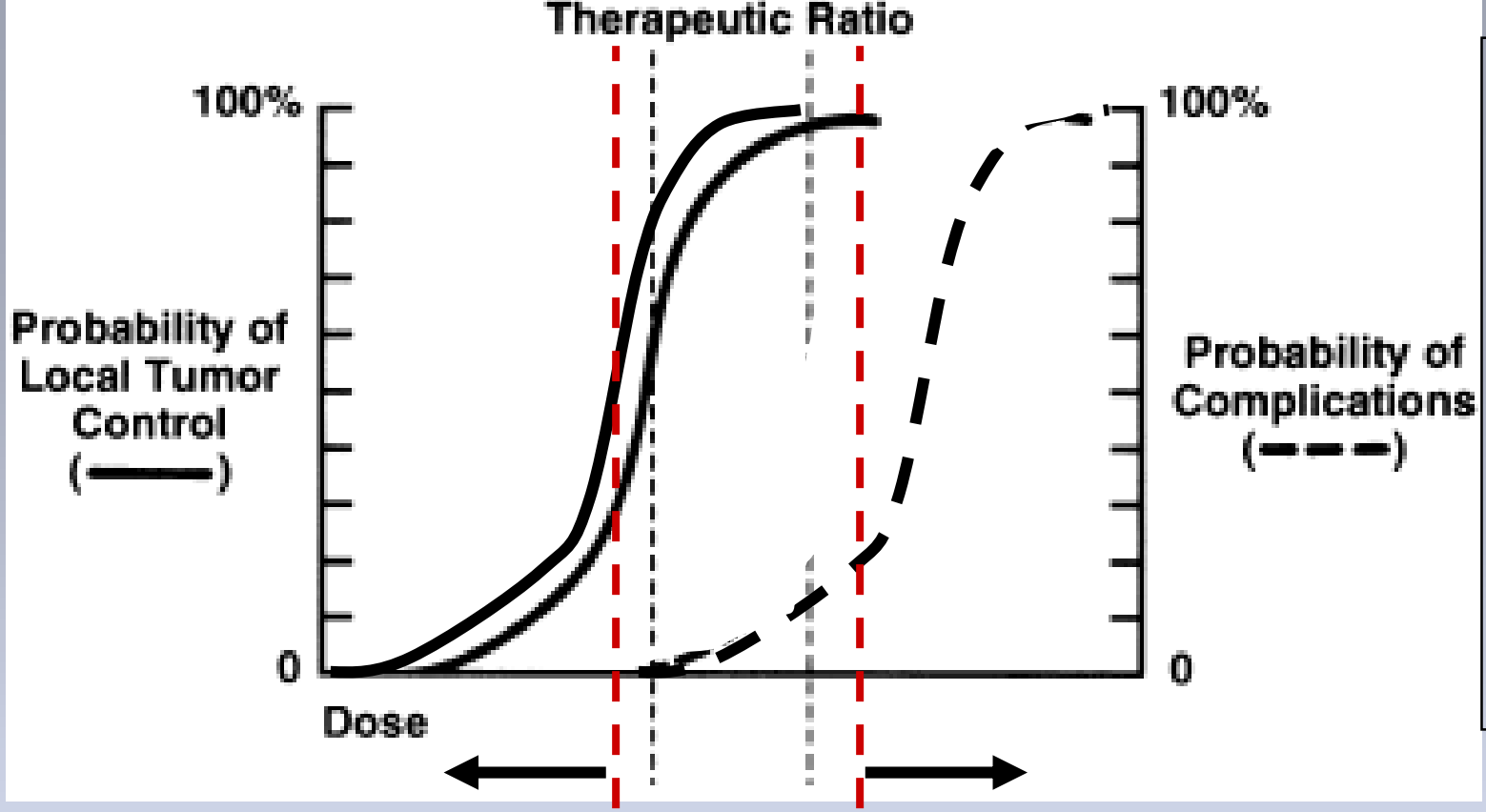


Optimisation in time

- **Fractionation**
  - daily dose (conventional, hyperfr., adapted-dinamic, chronobiology guided)
  - weekly dose
- **Overall treatment time**
- **Timing in relationship to other treatment modalities in combined scheme** (pre-, intra, peri, postoperative, sequential, altered, concomittant)

DOSE-FRACTIONATION IN RADIOTHERAPY

TYPE	TIME →	DOSE	SCHEDULE
Conventional	T	D	 200 cGy / day
Hyperfractionation	T	D+d	 115 cGy X 2 / day
Accelerated MDF	T/$\frac{2}{3}$	D-d	 150 - 200 cGy X 2 /day
Modified Accelerated Fractionation	T	D+d	
Split Course	T+REST	D	 >250 cGy/day
Hypofractionation	T-t	D-d	 500 cGy / day



Fractionation

Hypofractionated

Hyperfractionated

Accelerated Hyperfractionated (CHART)

CHARTWELL

Radiation modifyers

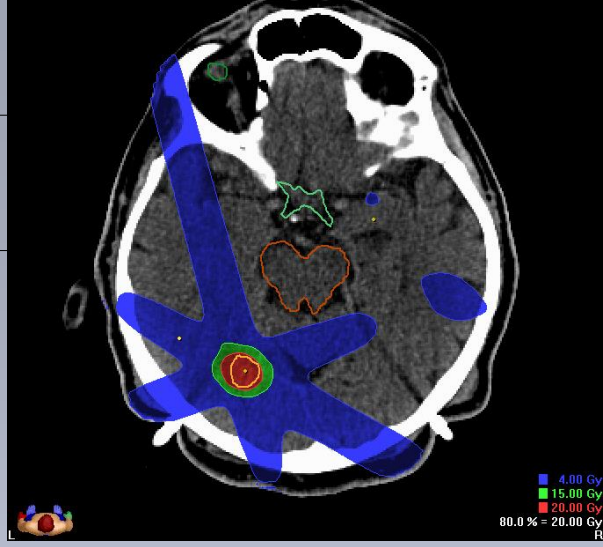
sensitisation/protection

Chemo-, hormon, biol.m.,hypoxic sens.

Technical development

Increase of spatial selectivity

Increased selectivity



Target volume

Selective homogeneous painted RT (concomittant boost, hypoxic areas)

TCP ↑

Normal tissues

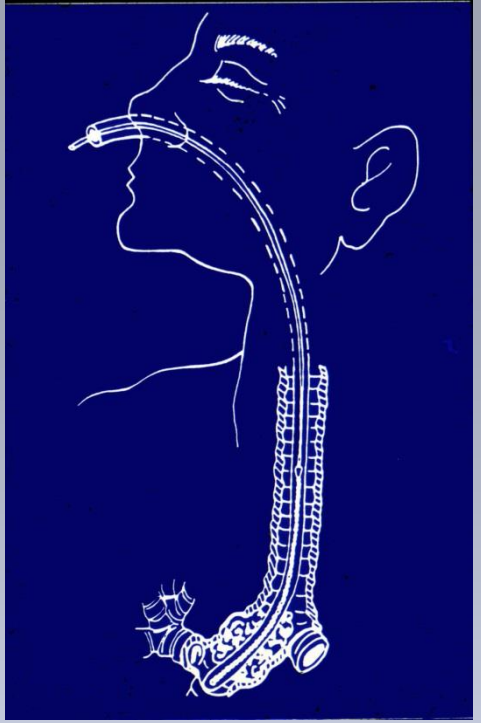
Decrease of the dose to the normal tissues

NTCP ↓

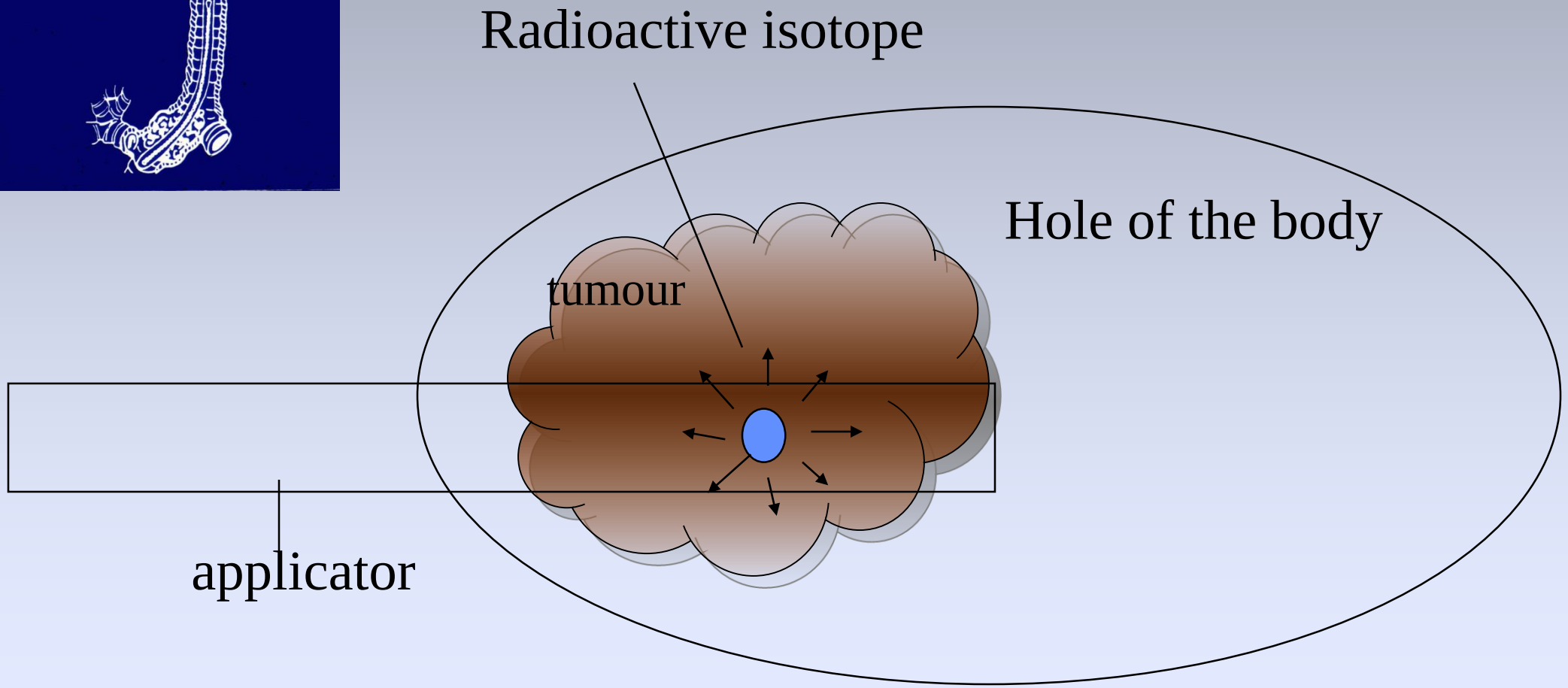
Increased therapeutic index

Forms of radiotherapy

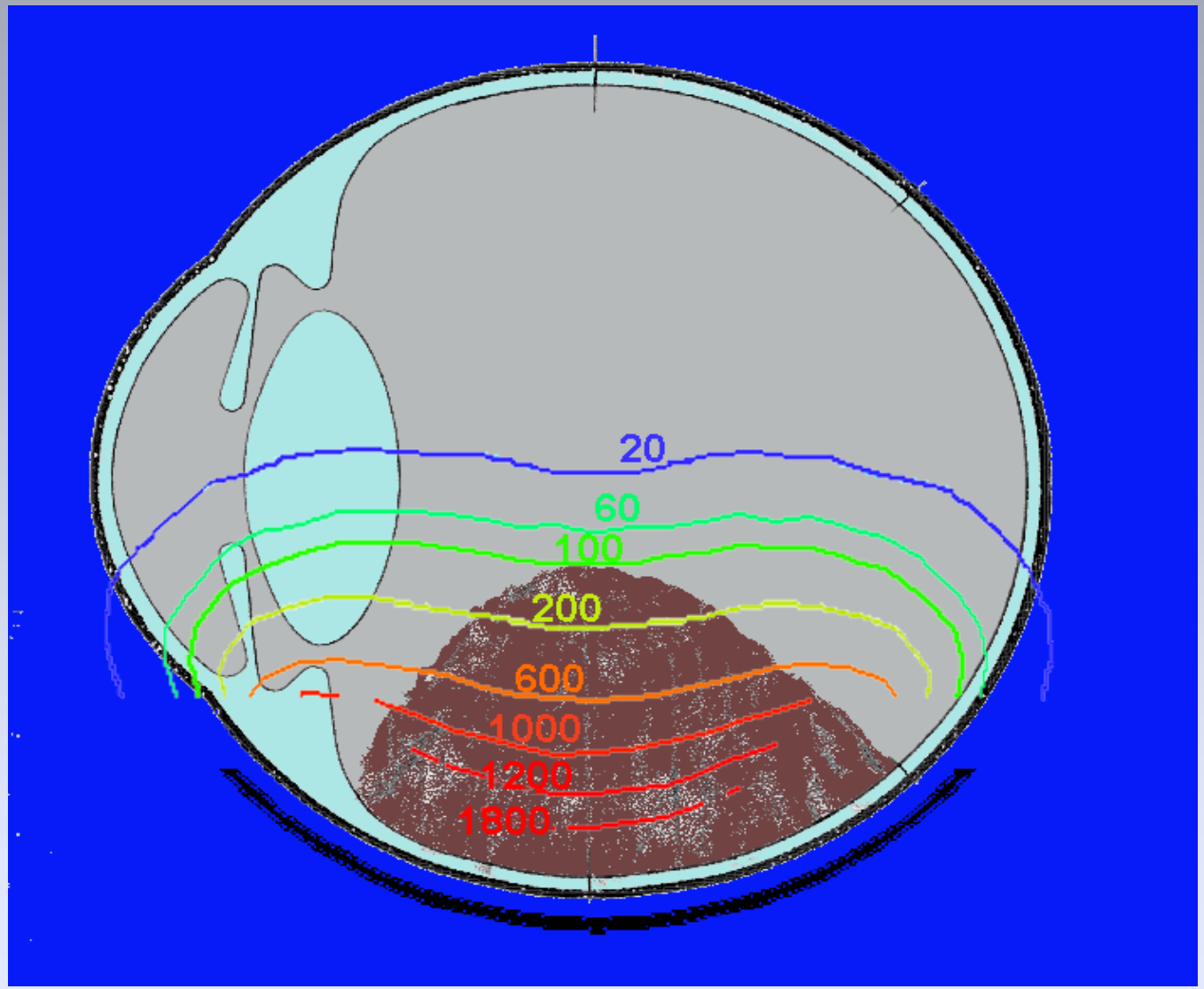
- Radioactive isotope
- Brachytherapy
- Teletherapy (percutanious)



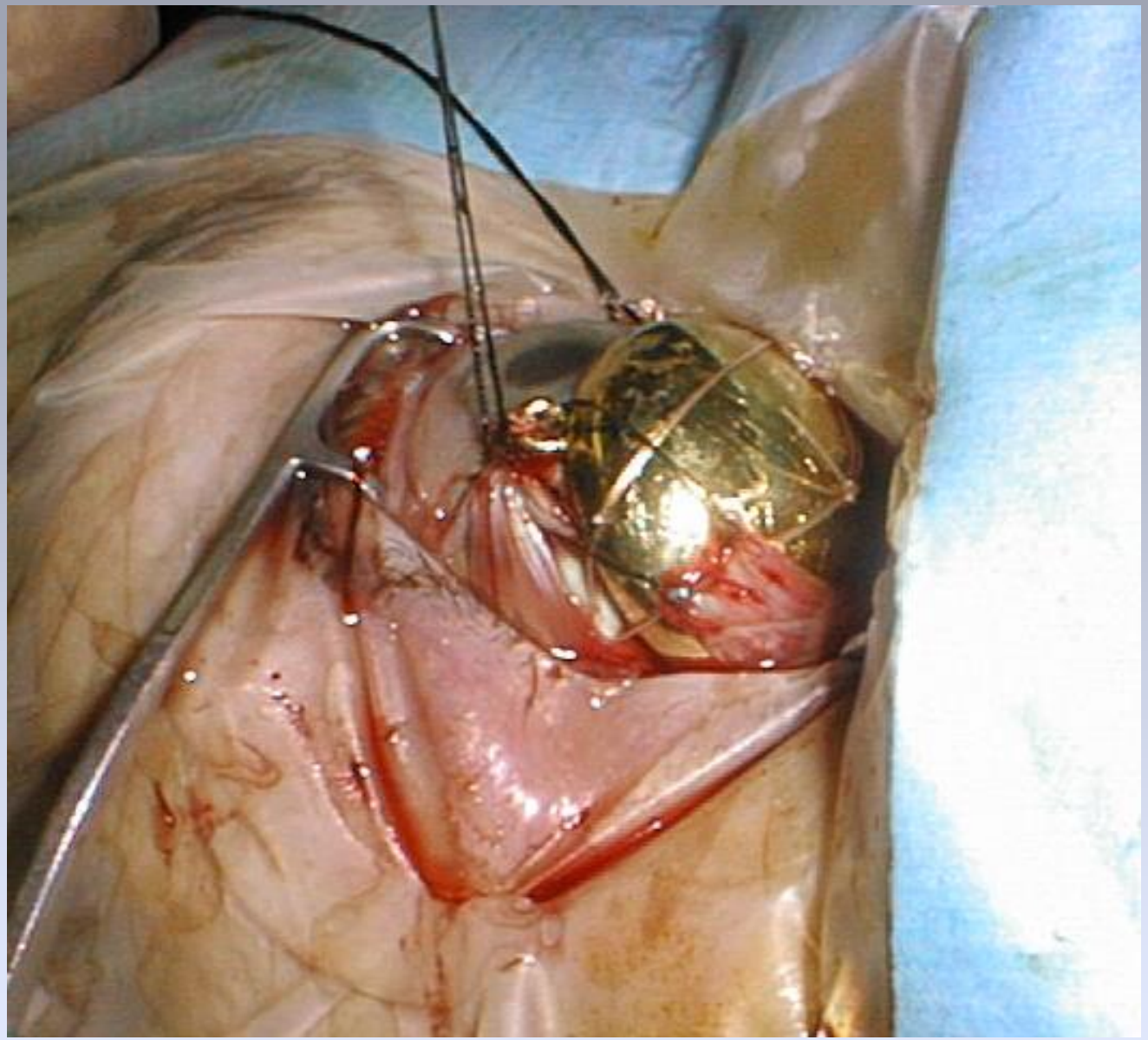
Brachytherapy



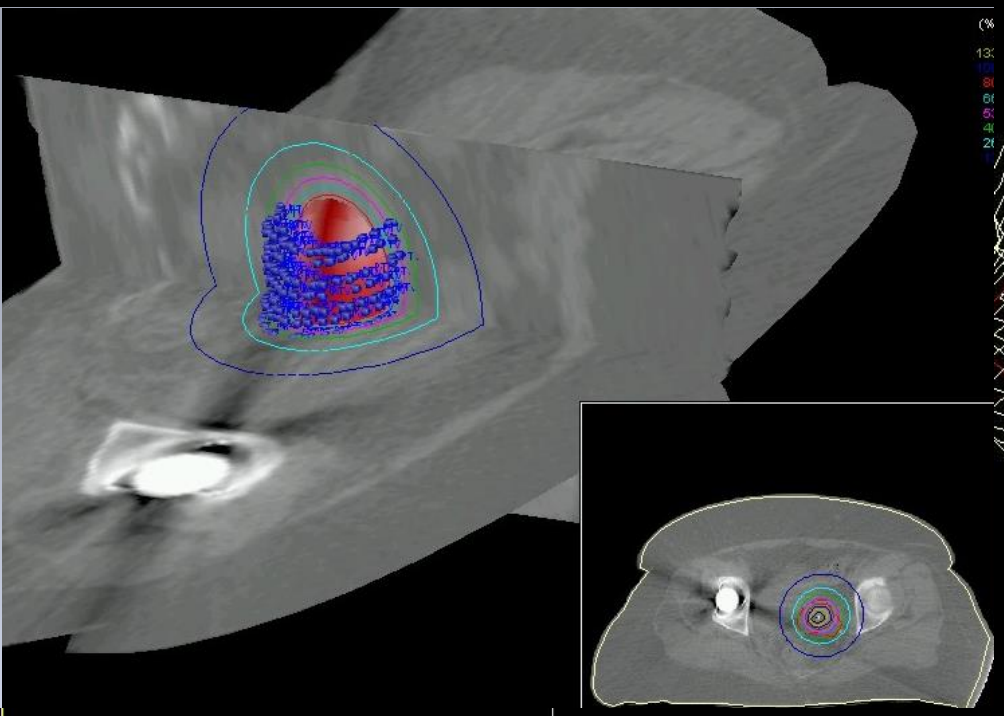
$^{106}Ru/^{106}Rh$ application

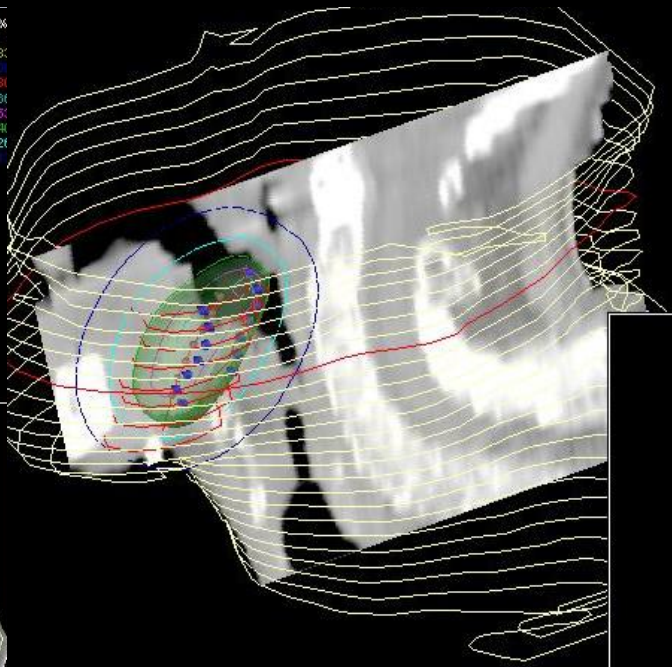


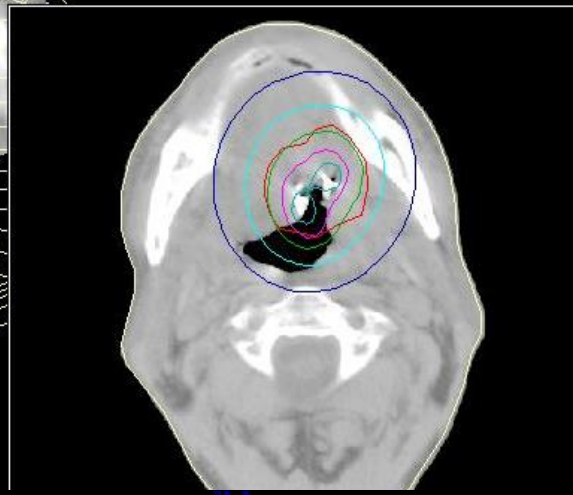

CCZ
CCB
CCA
CCC
CCB
CCA
CCV

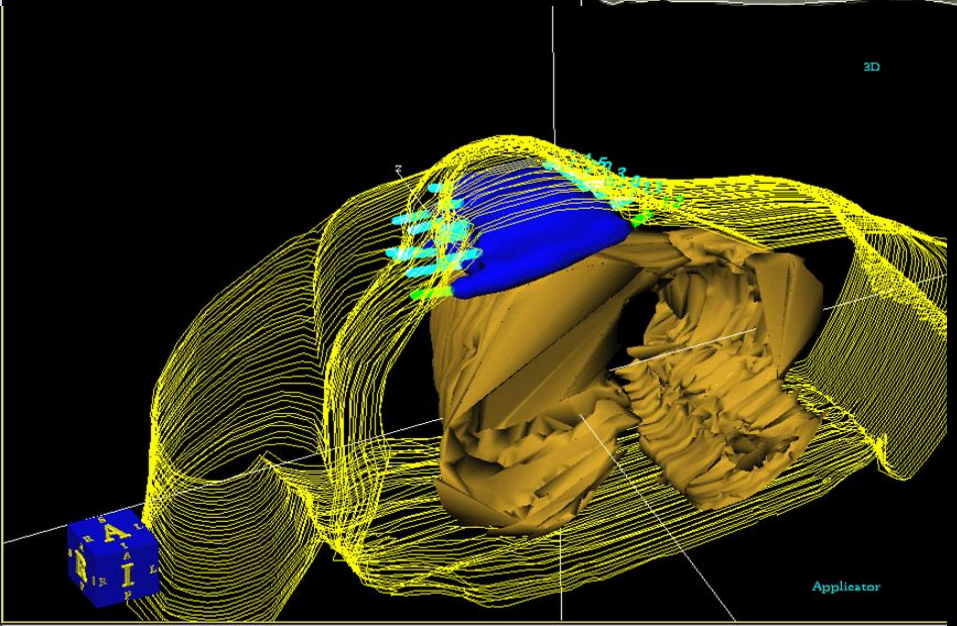


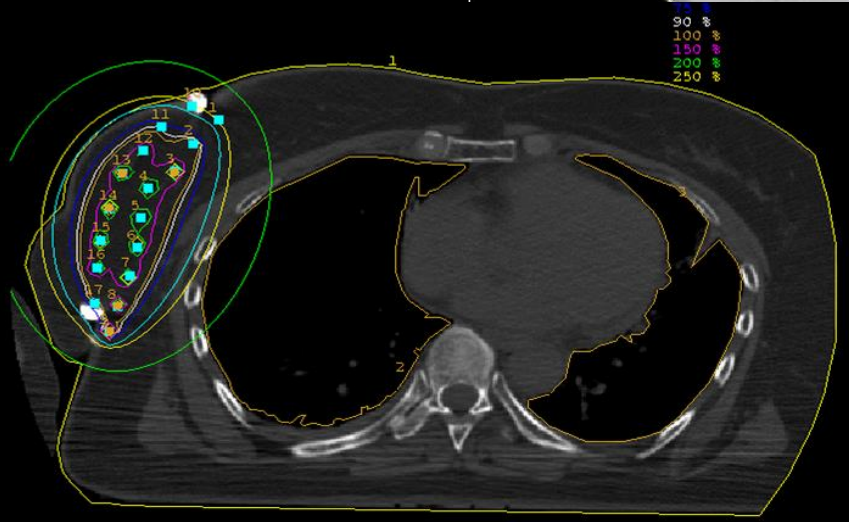
Brachytherapy

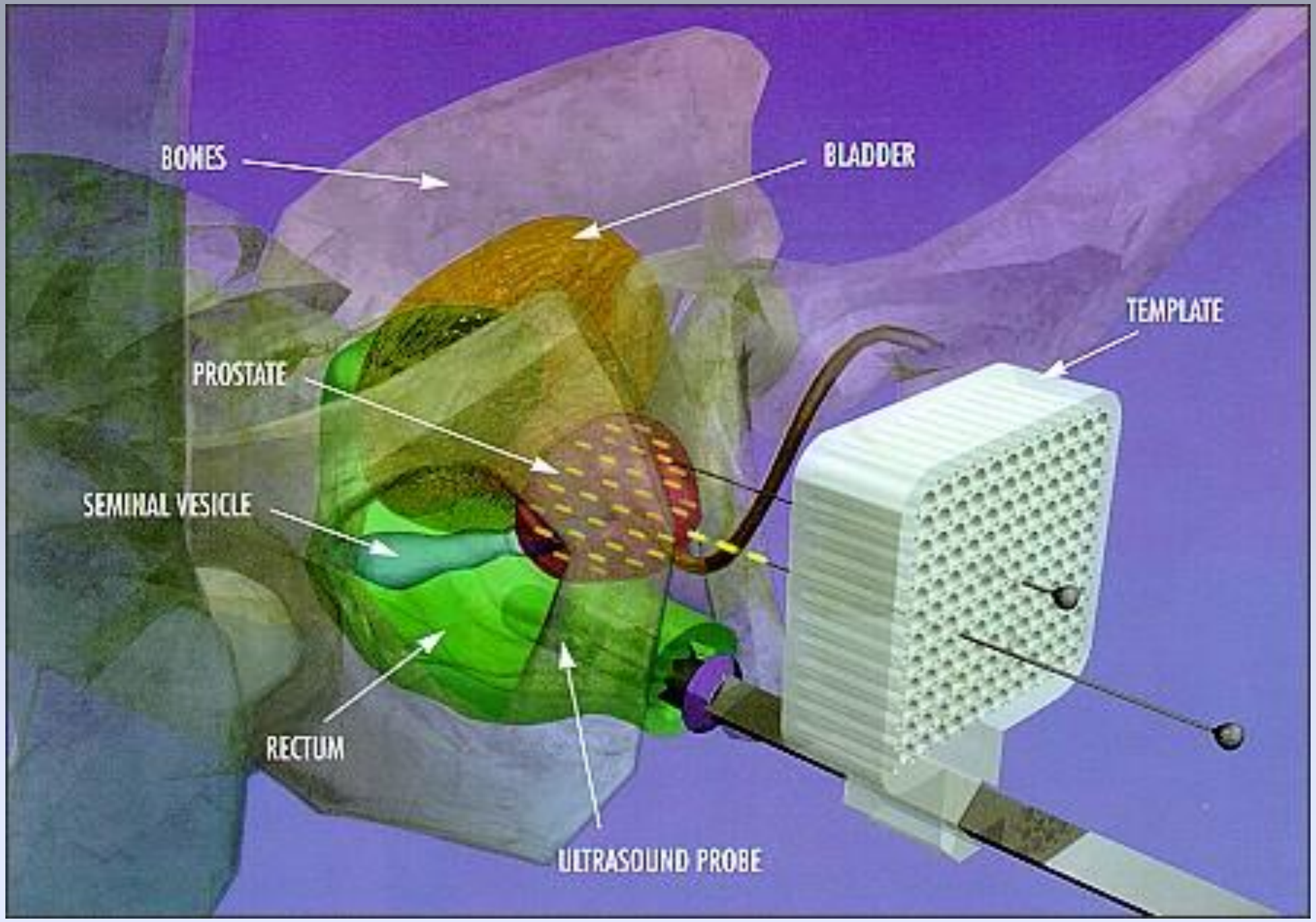








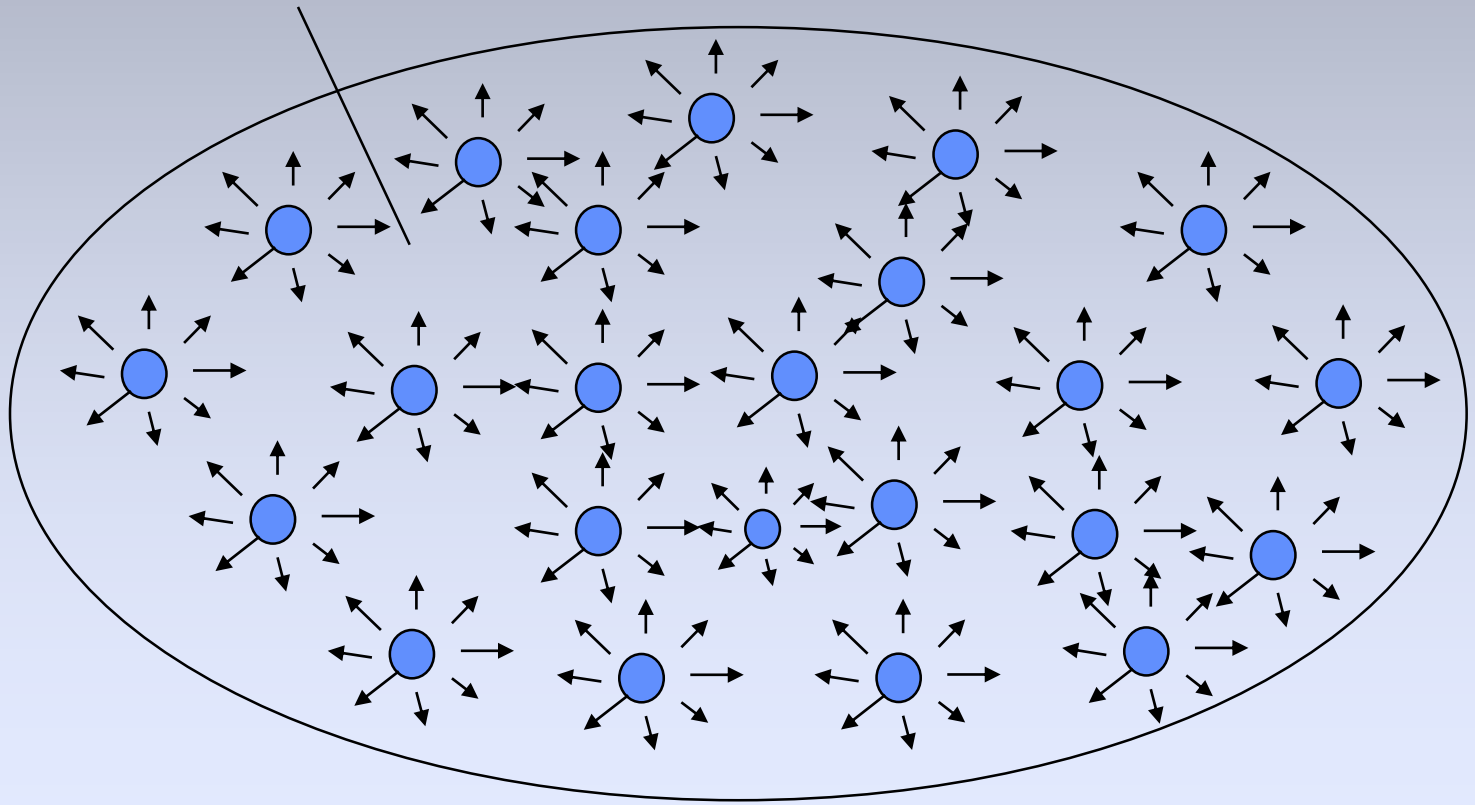


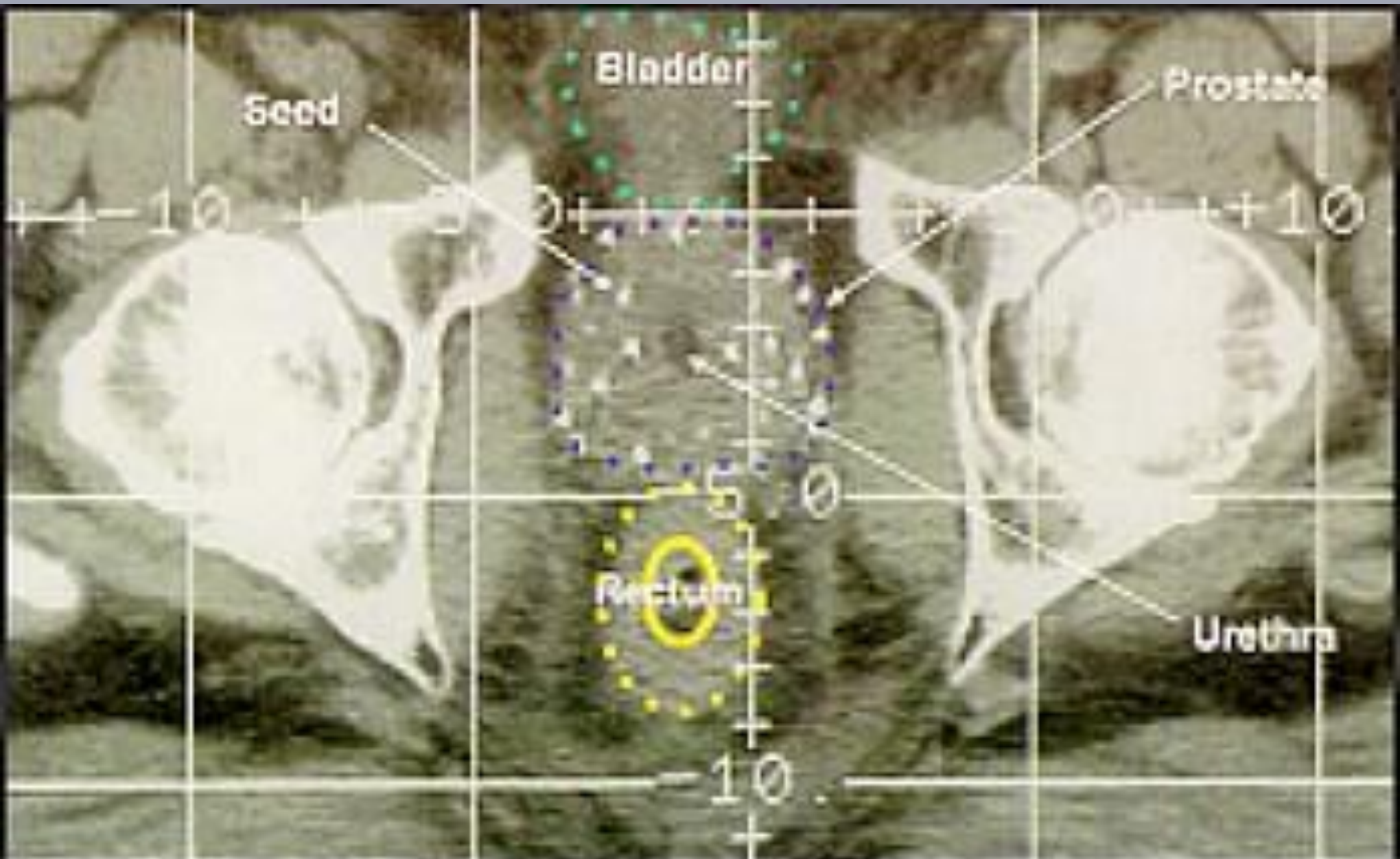

BONES
BLADDER
TEMPLATE
PROSTATE
SEMINAL VESICLE
RECTUM
ULTRASOUND PROBE

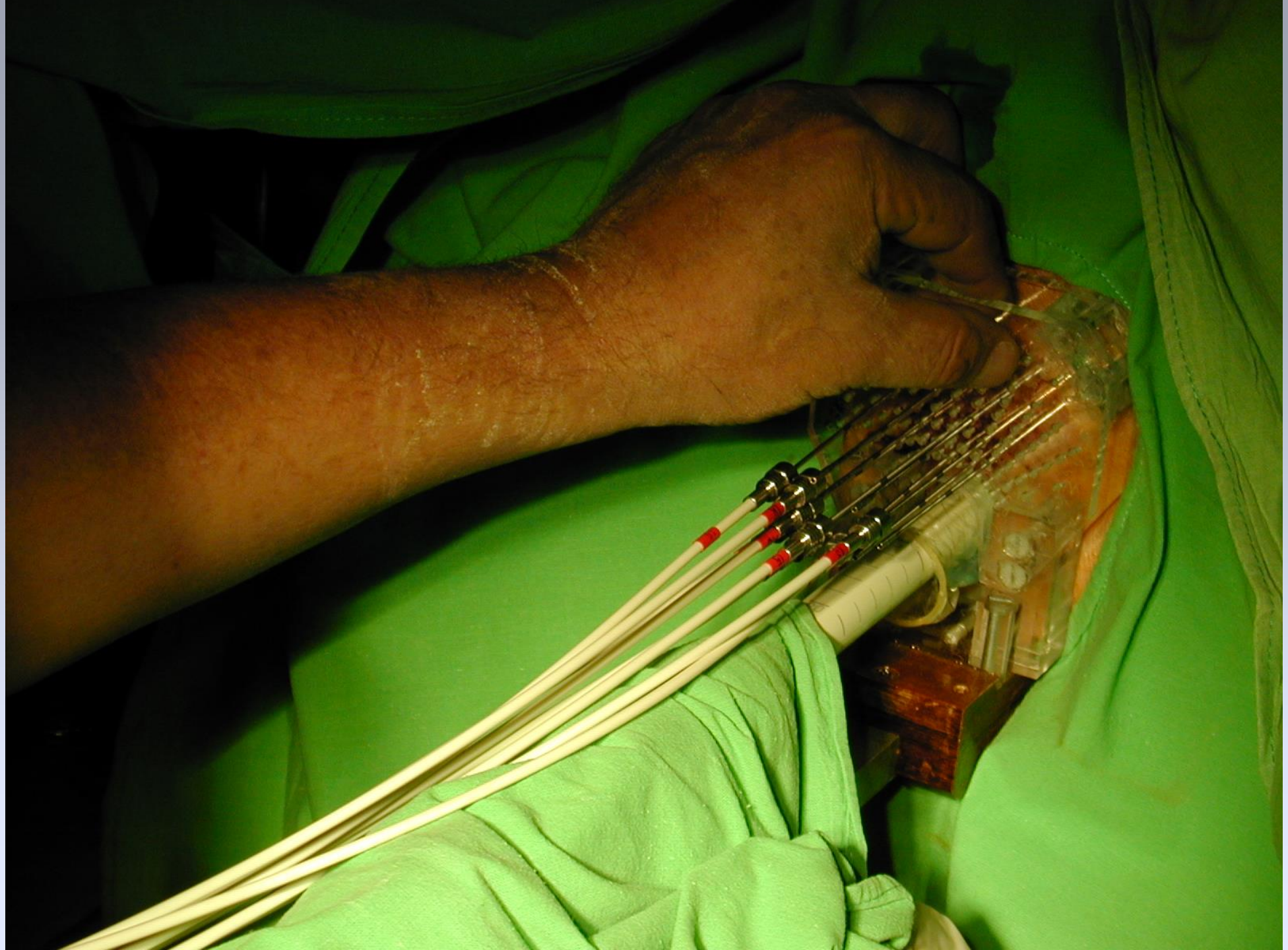
Prostate ^{125}Iodine seed

Radioactivev izotóp

prostate

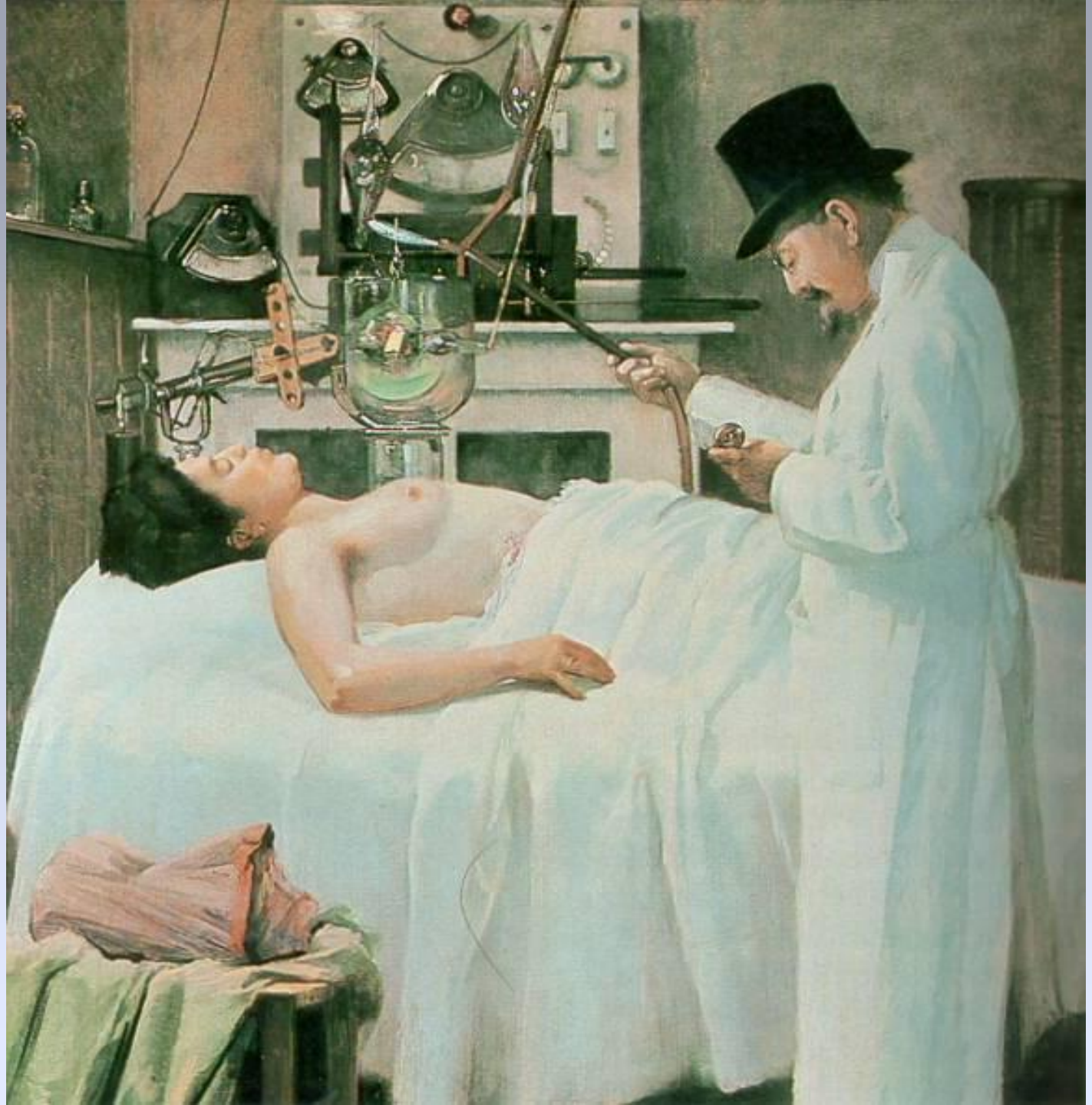



Bladder
Seed
Prostate
-10
0
+10
0
Rectum
Urethra
-10



Teletherapy

After 1895



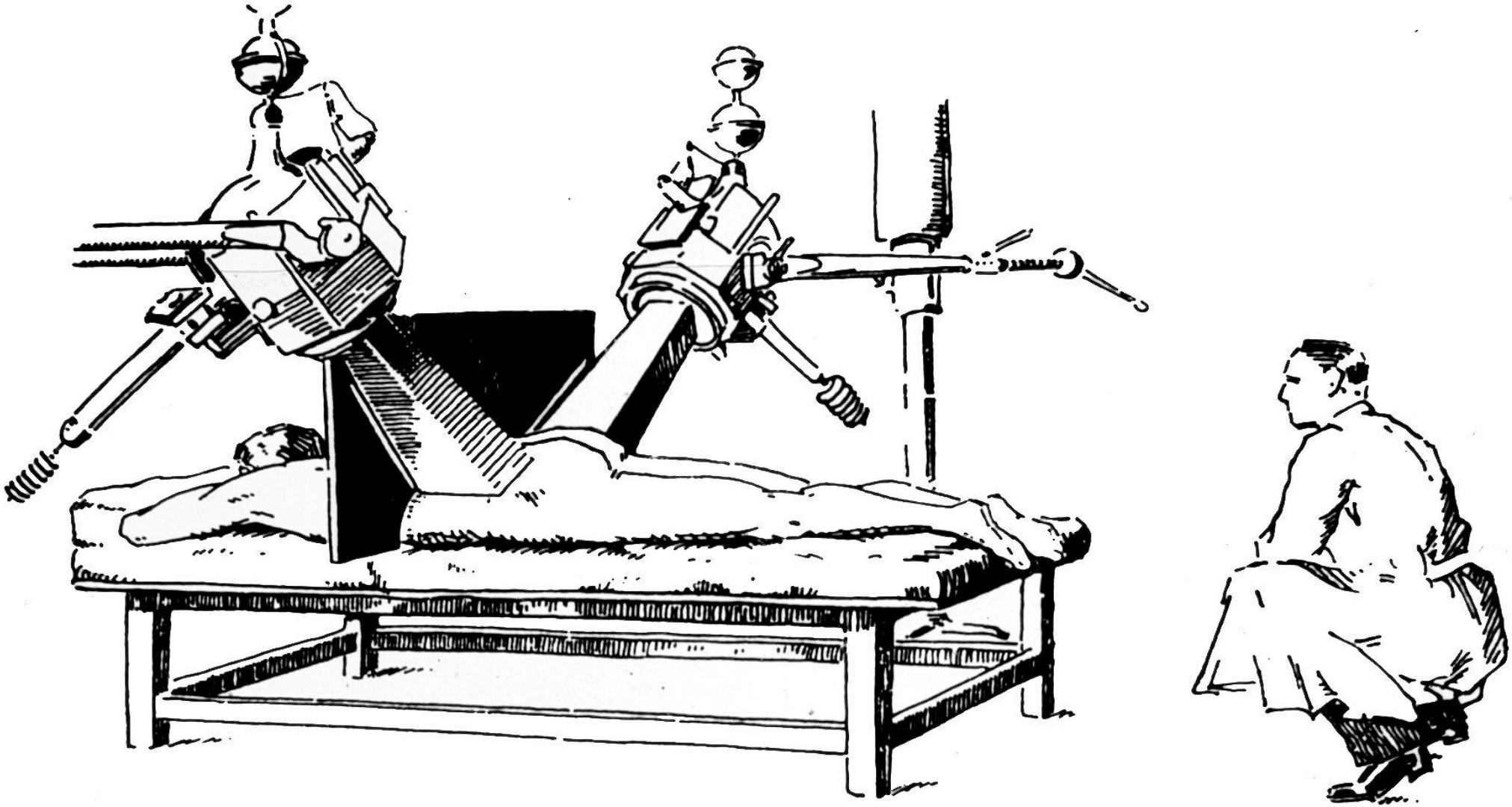
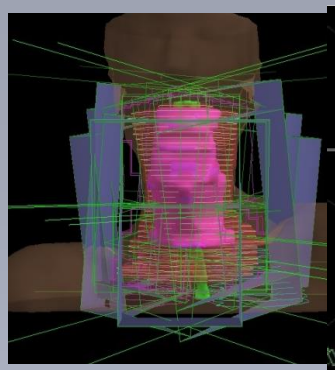
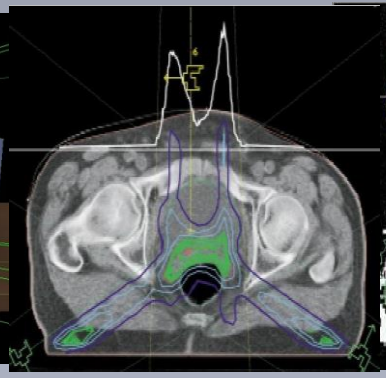
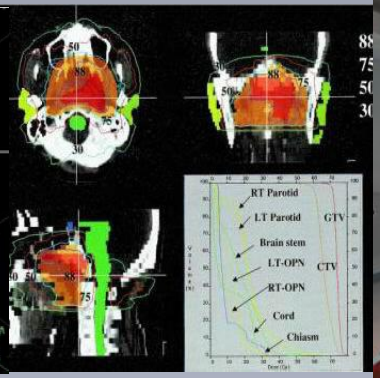
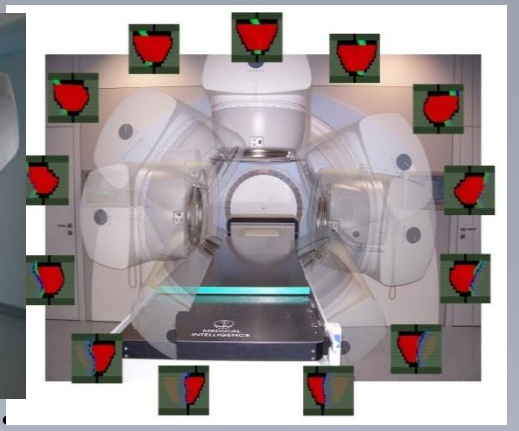


Abb. 51. Einrichten des Einfallswinkels der Strahlenkegel durch Vergleich aus einem entfernten Standpunkt mit den auf der Visierpappe aufgezeichneten Richtungslinien.

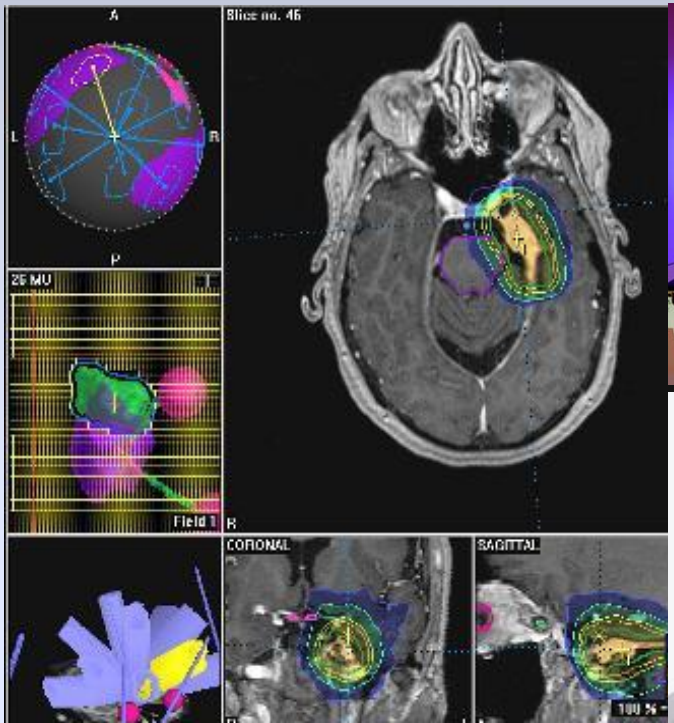

SIEMENS
PRIMUS
SIEMENS

Photons 3-15 MeV, dose rate: 10 Gy/min

Selectivity, effectivity, accuracy



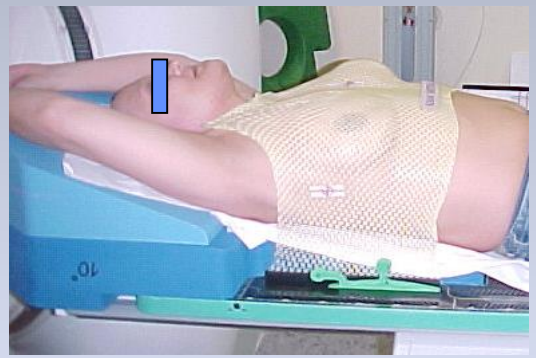


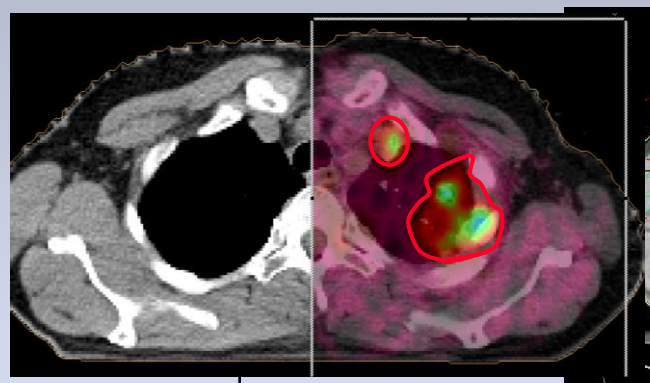
Hadron th.

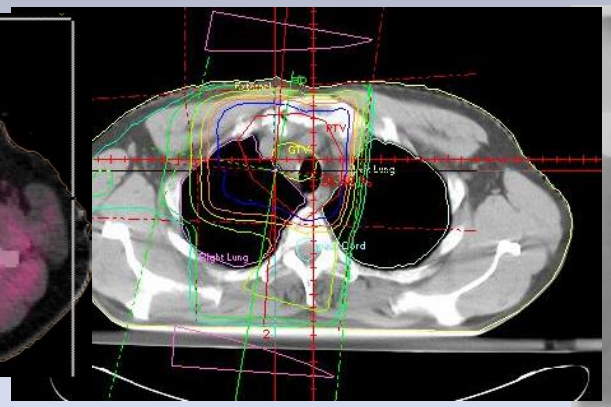
Procedures

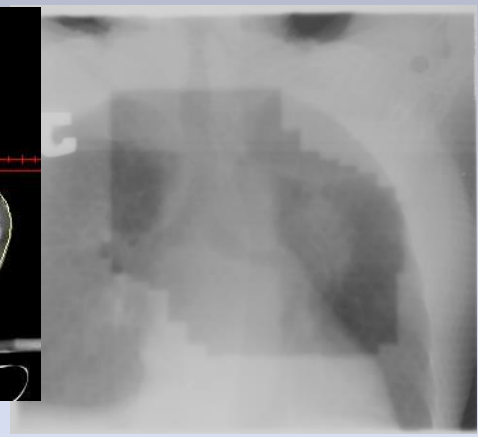
Patient positioning immobilisation → Planning imaging (CT) → 3D planning → Set up, field control

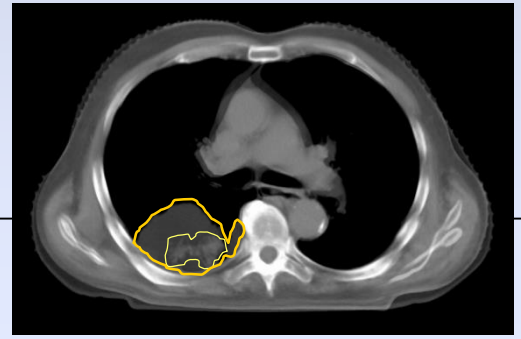
PET-CT/MRI





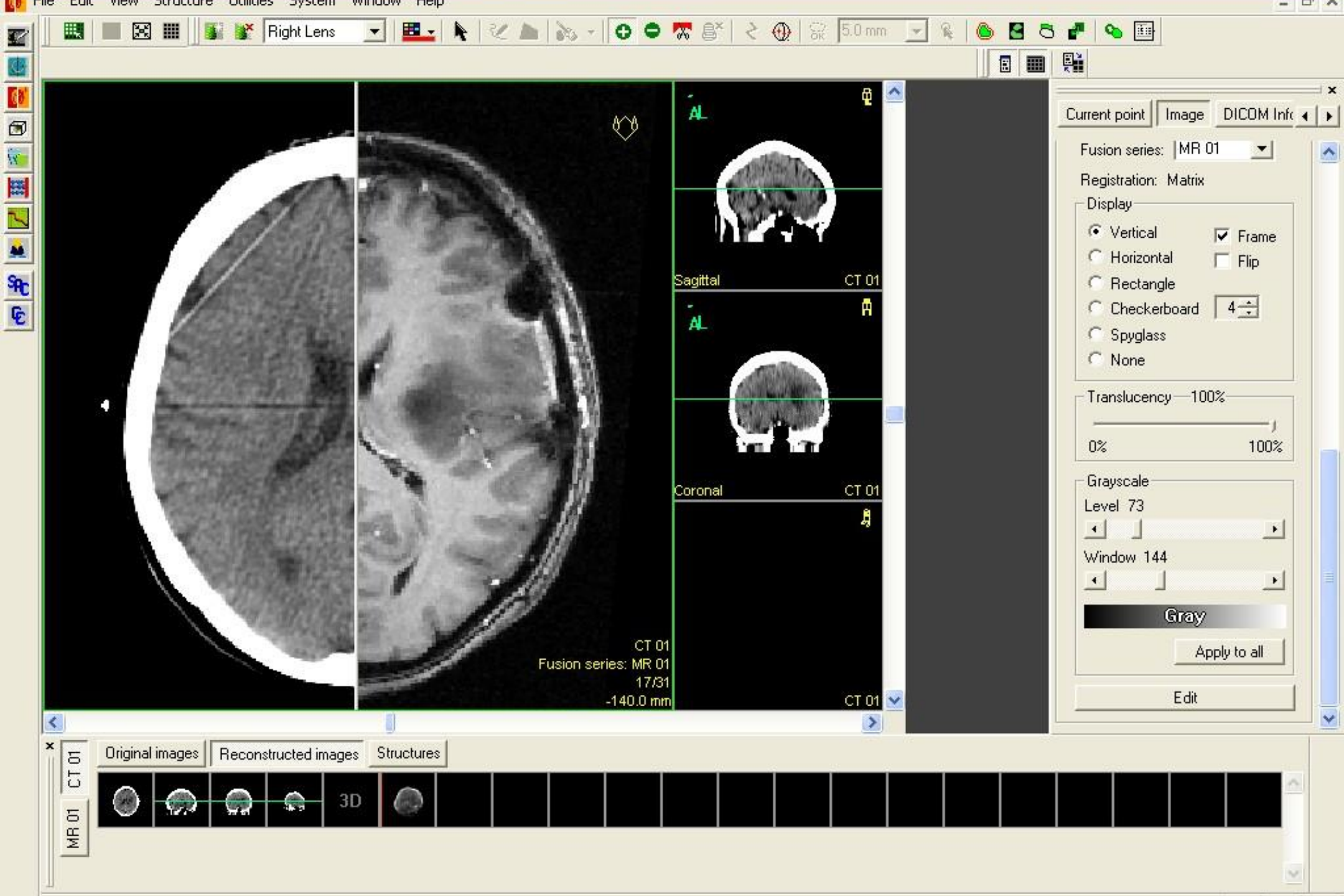




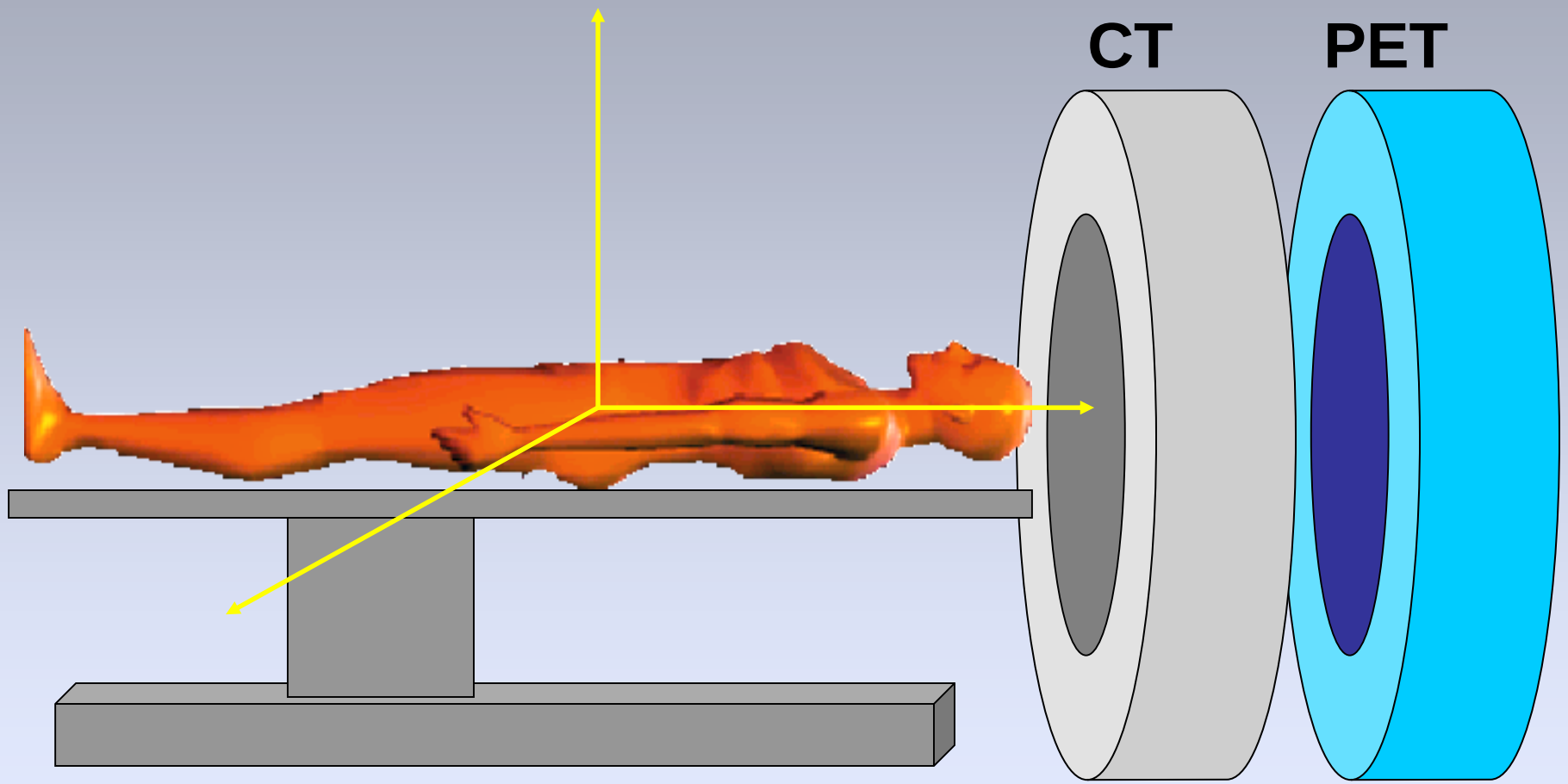


Re-CT- image fusion

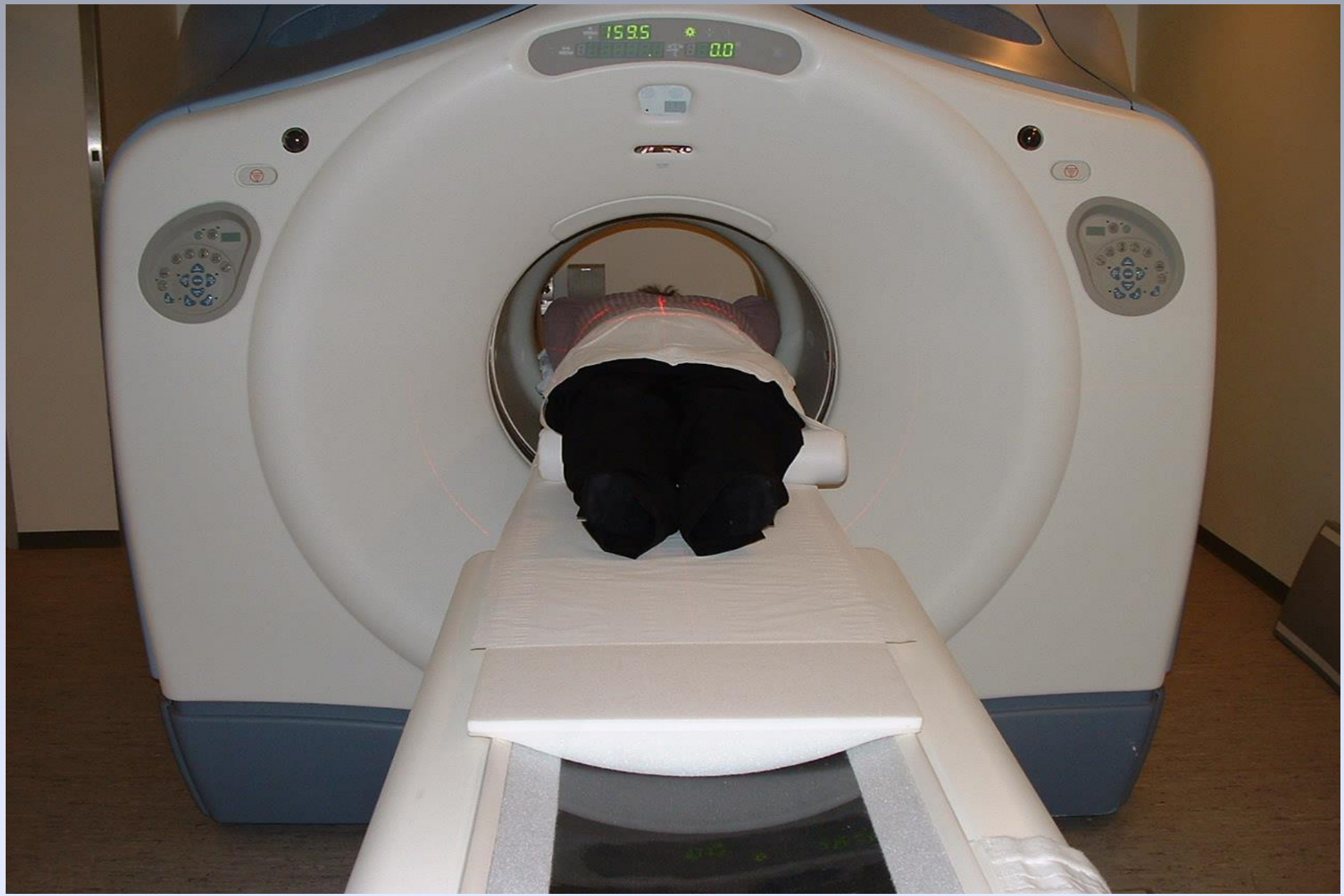

SIEMENS
SOMATOM
Emotion 6


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

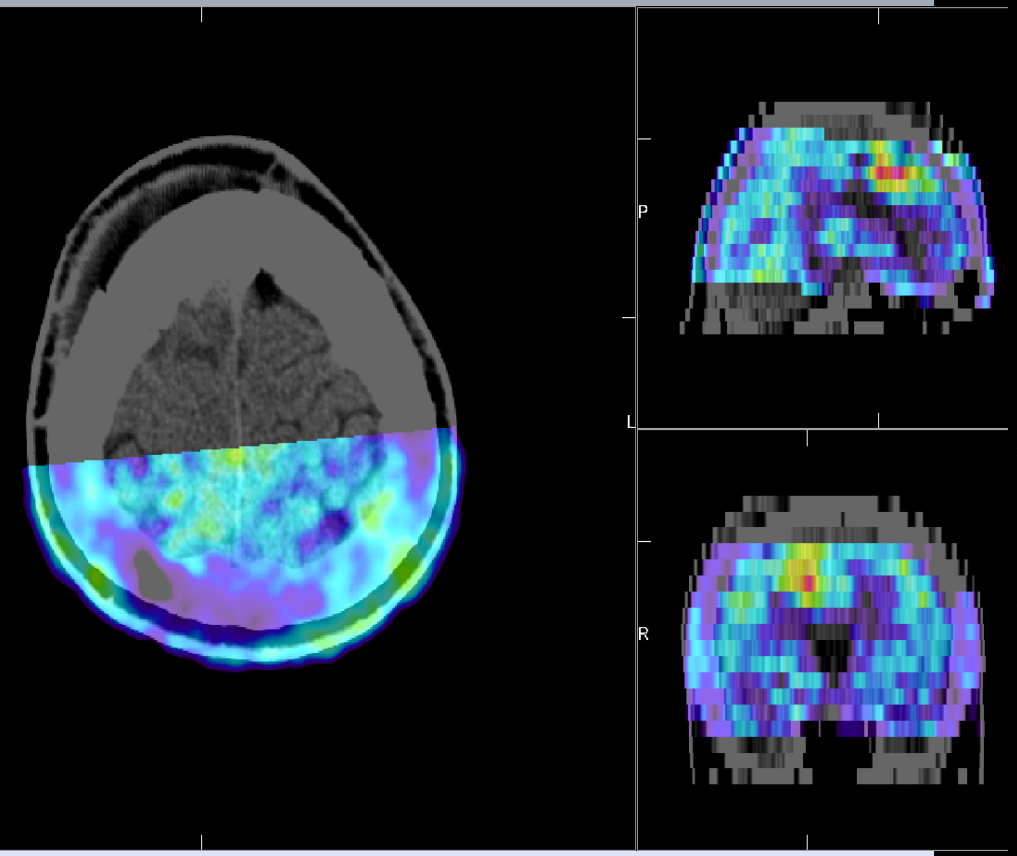
PET/CT

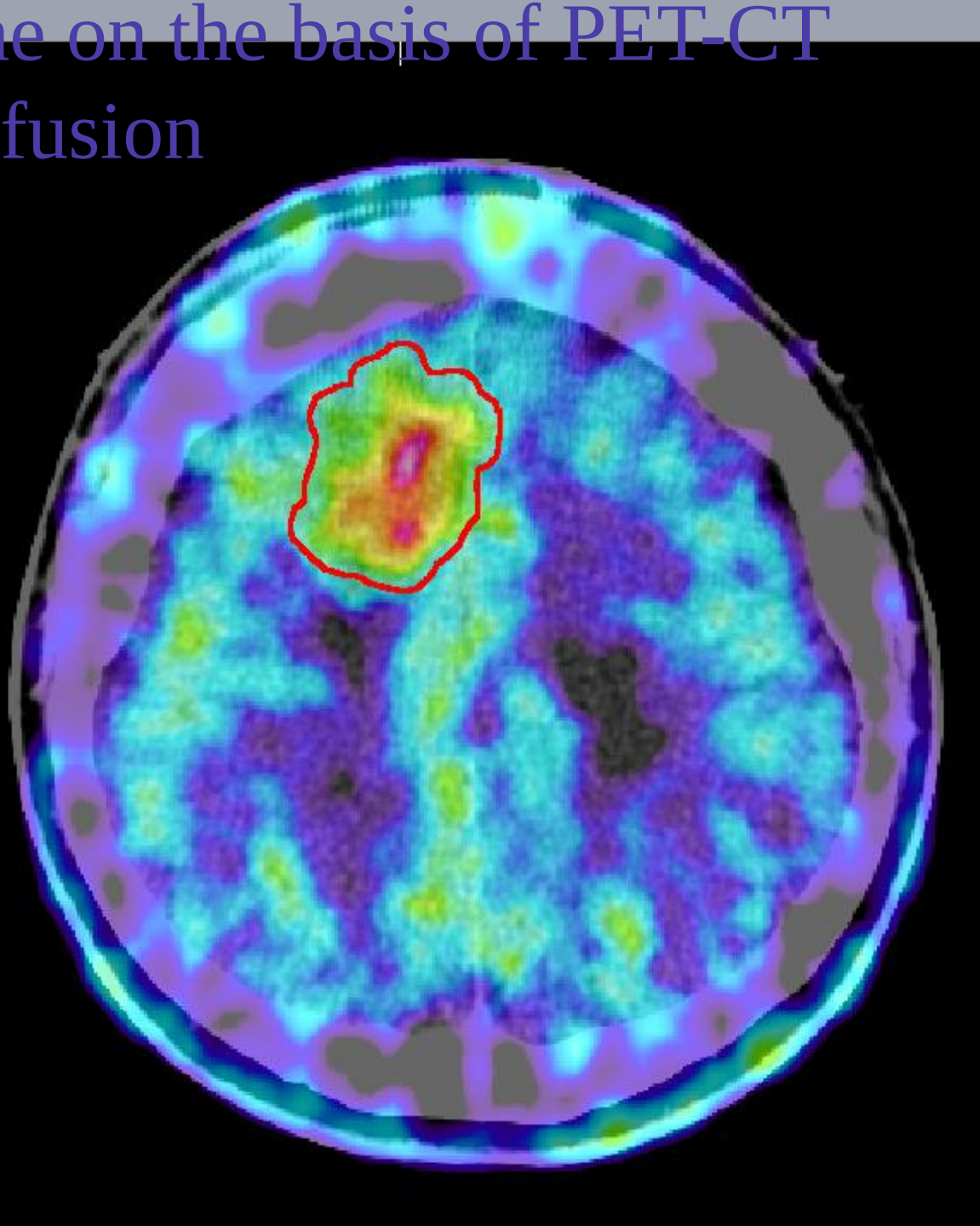


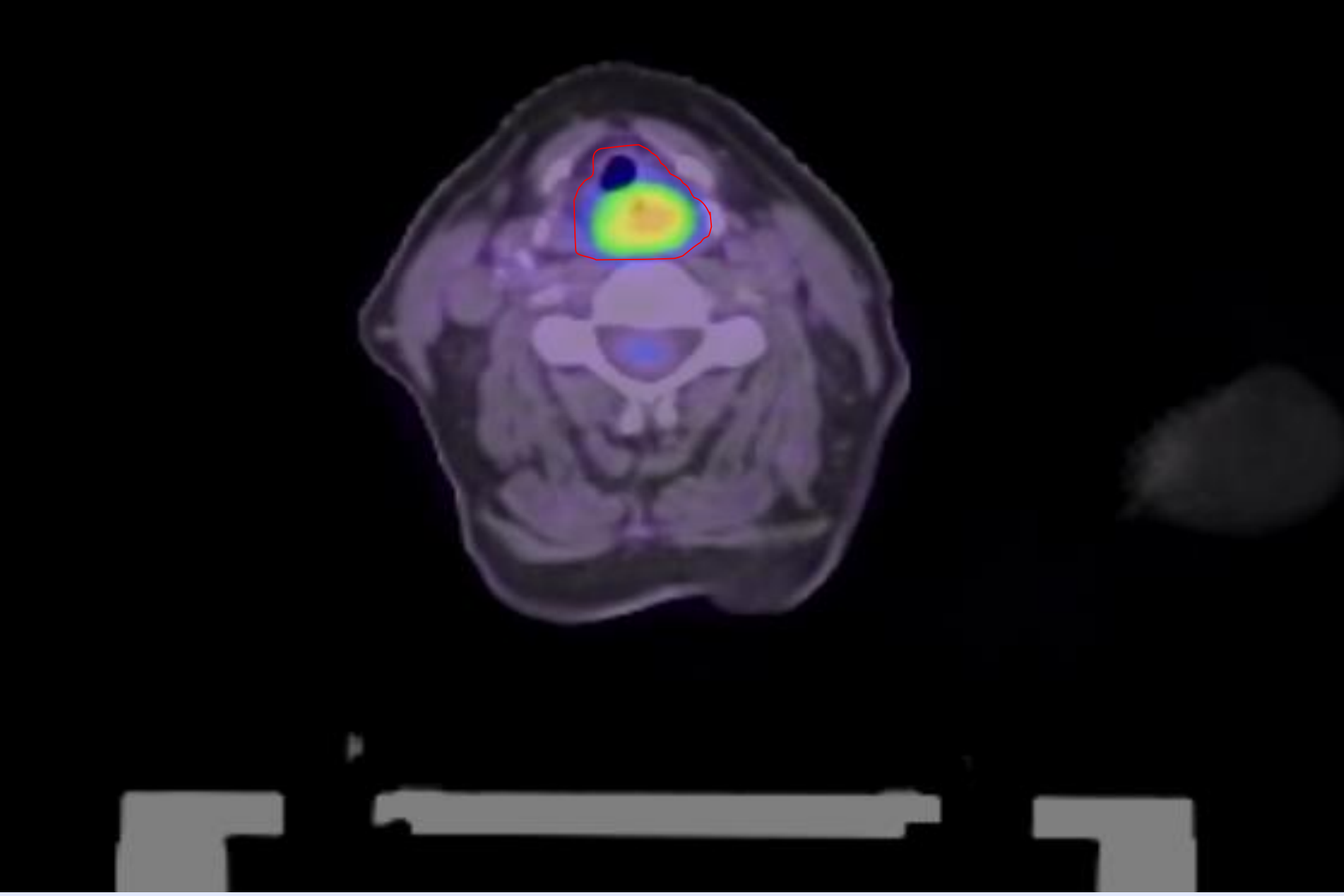
PET/CT

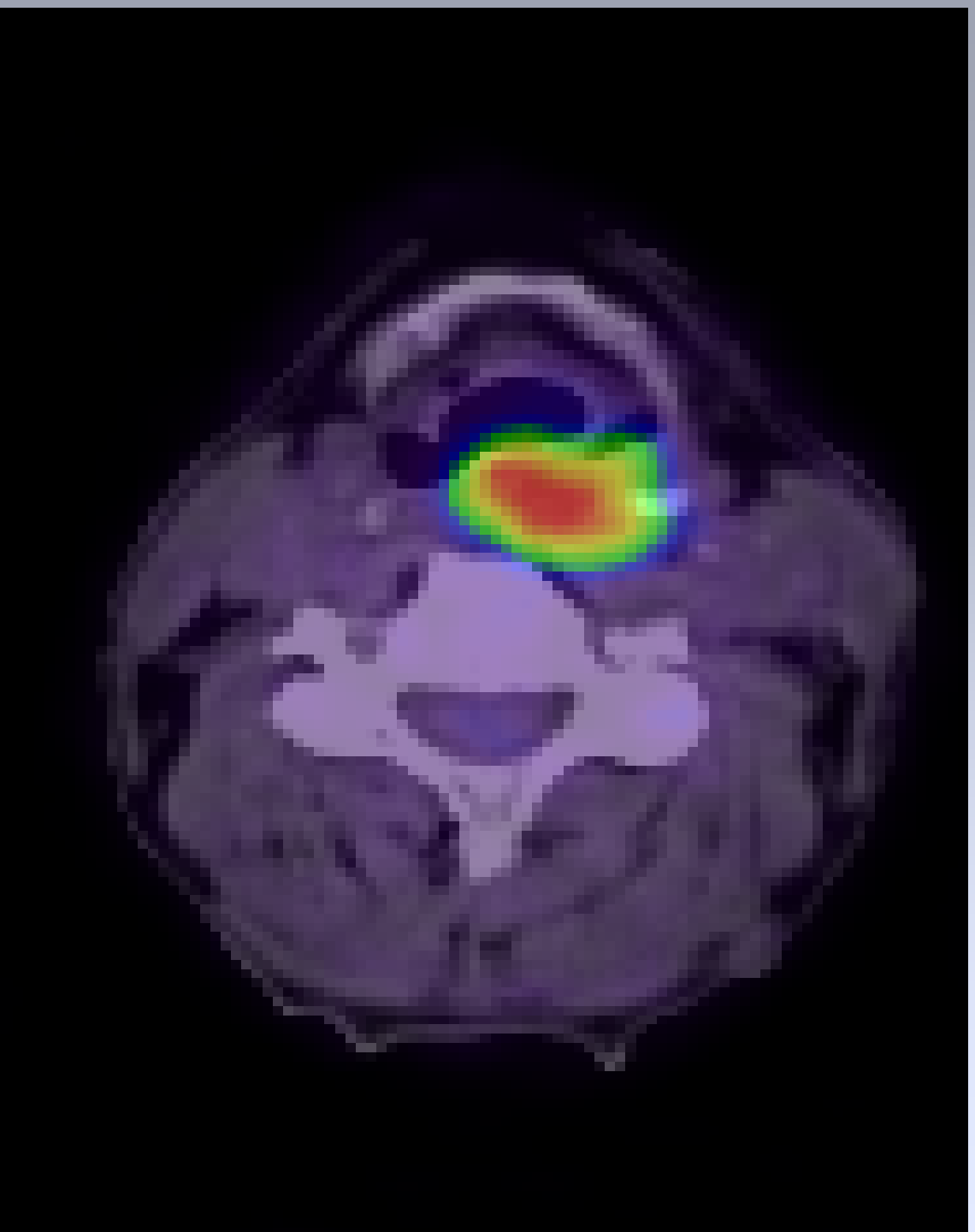


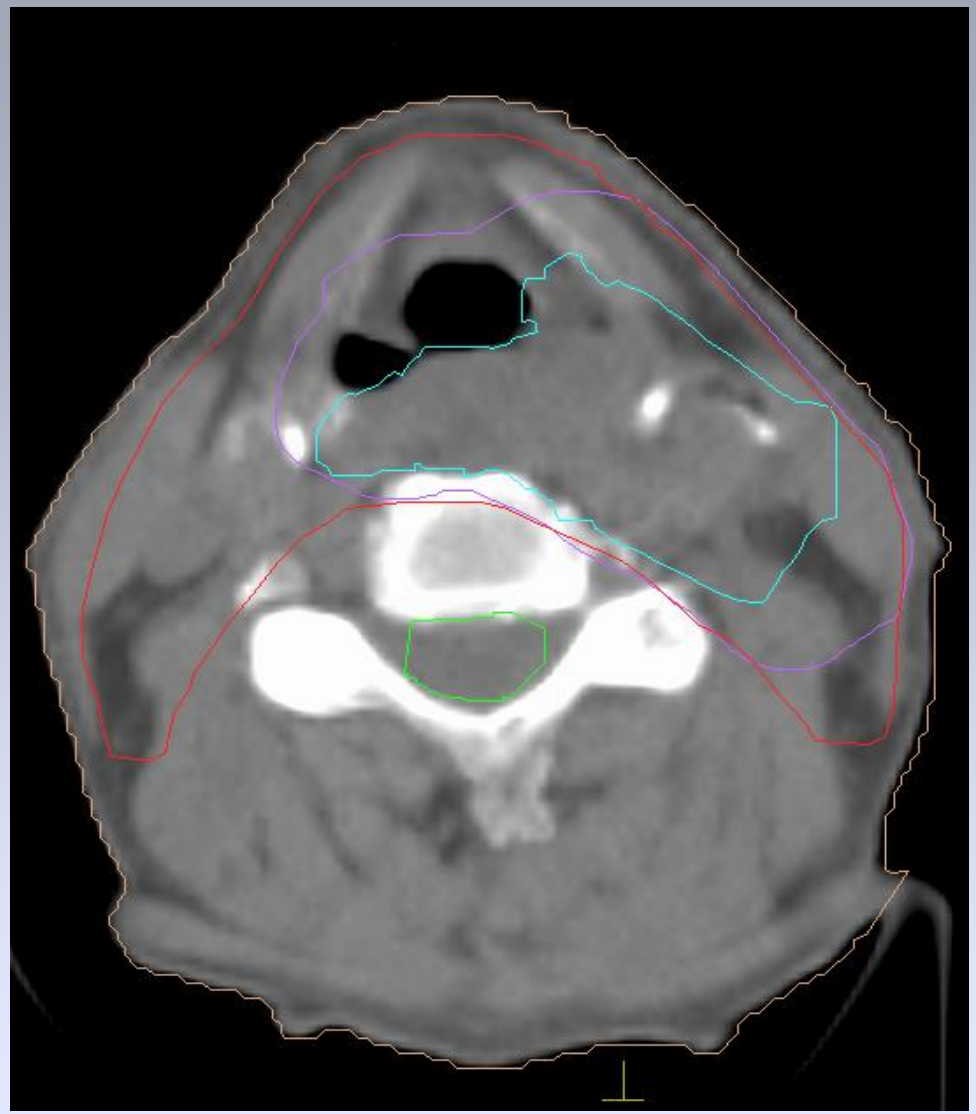
Indication of target volume on the basis of PET-CT image fusion

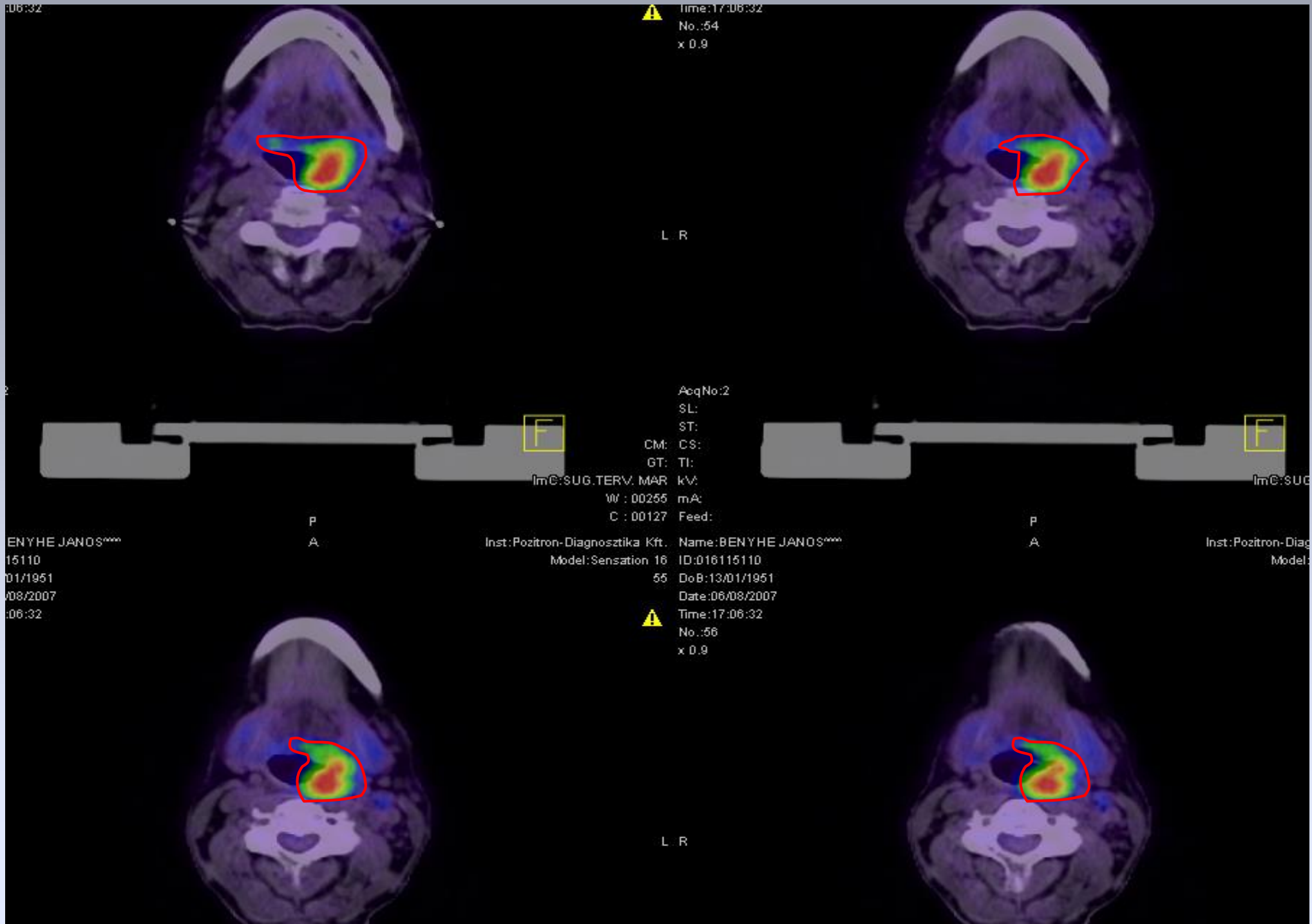


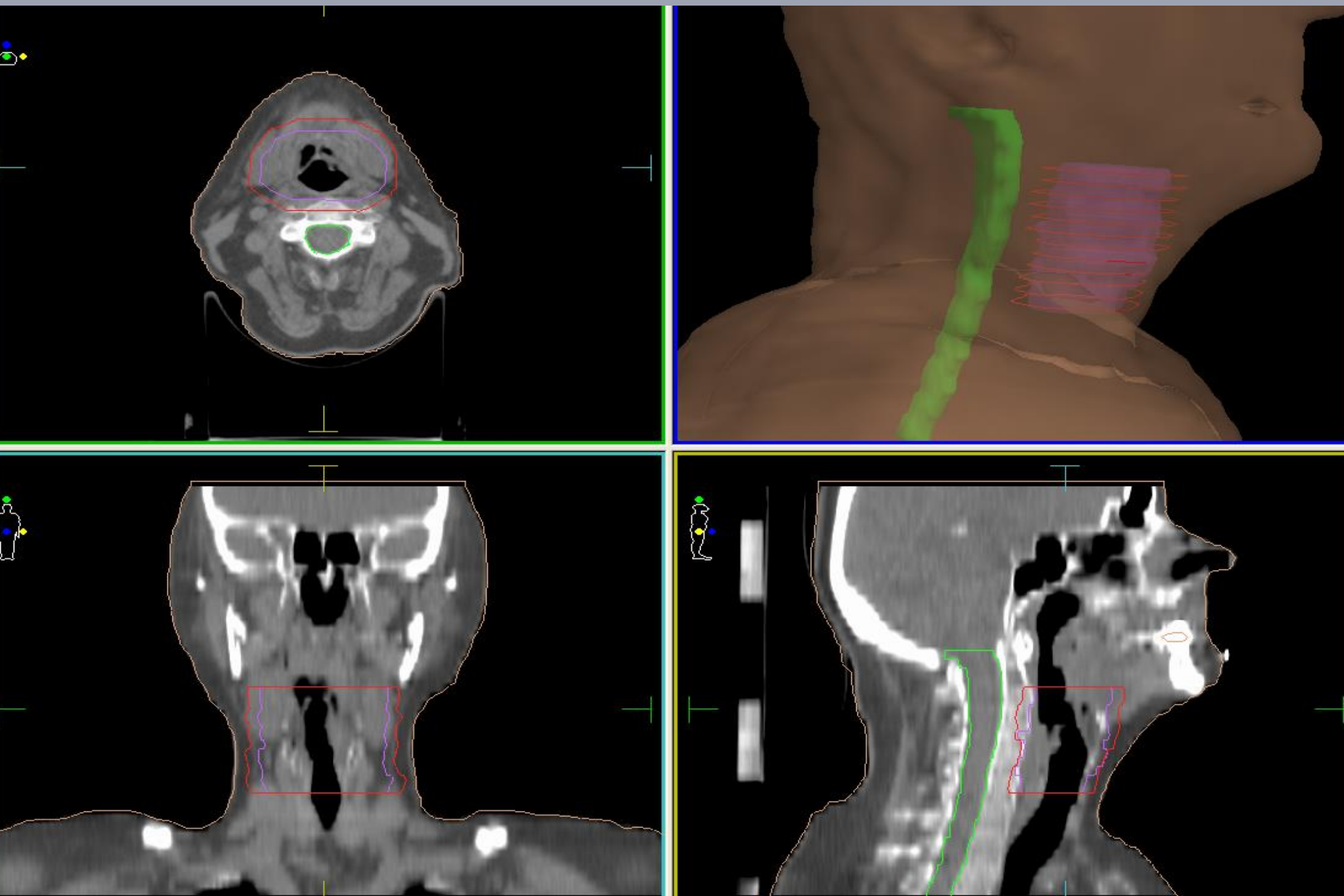






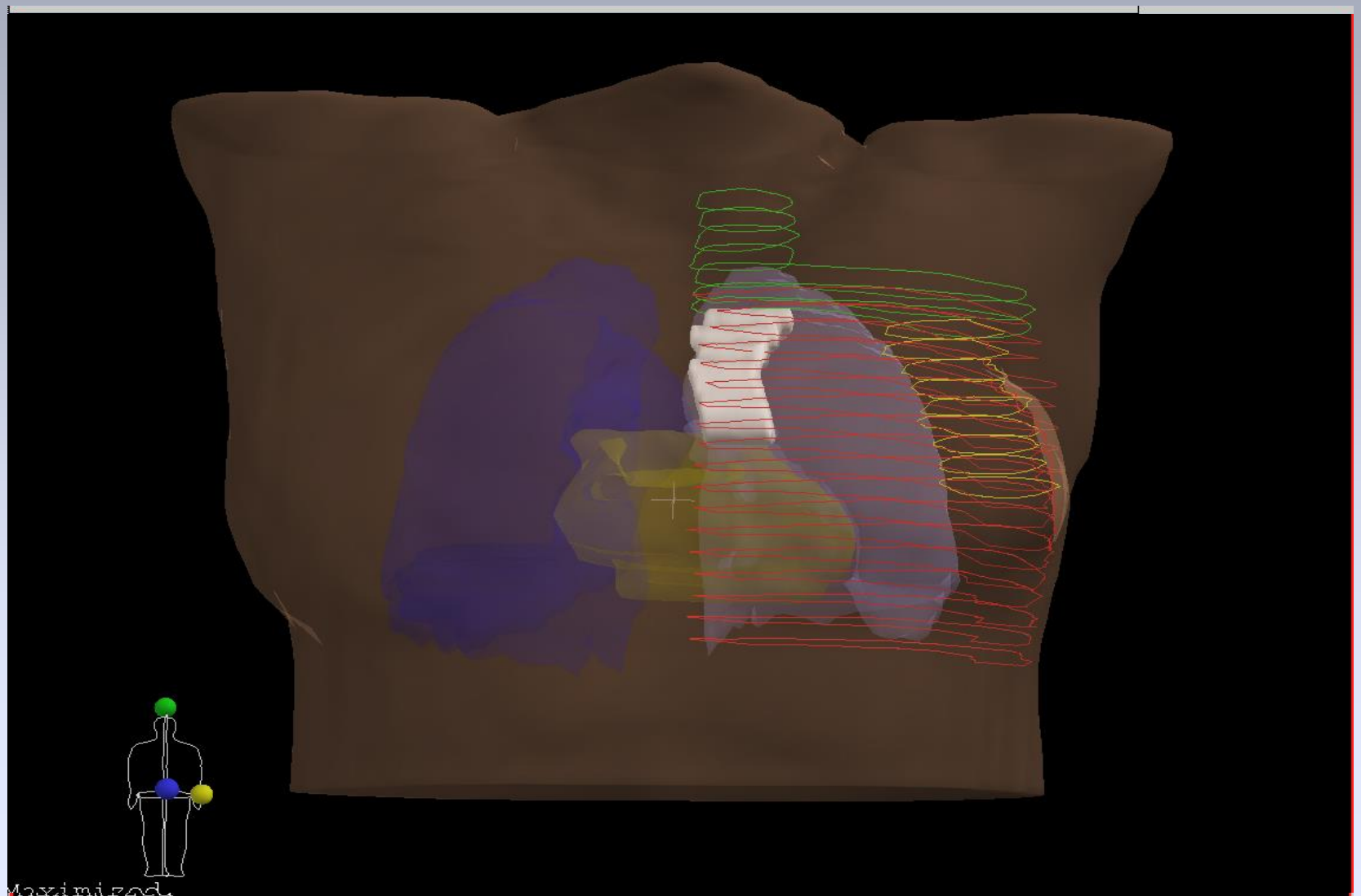



Time:17:06:32
No.:54
x 0.9
L R
AcqNo:2
SL:
ST:
CM: CS:
GT: TI:
ImC:SUG.TERV. MAR kV:
W : 00255 mA:
C : 00127 Feed:
P
A
Inst:Pozitron-Diagnosztika Kft.
Model:Sensation 16
55
Name:BENYHE JANOS****
ID:016115110
DoB:13/01/1951
Date:06/08/2007
Time:17:06:32
No.:56
x 0.9
L R



Treatment planning

Contouring of target volumes and organs at risk



Dose prescription - protocols

- Target dose , fraction size
- Dose constraints of normal tissues

Aim of the treatment (curative-pall.)

Tumour type and characteristics

Malignant cell amount (tumour size)

Other therapy modalities

Tolerance of surrounding normal tissues

Standard methods of dose calculation

Pure phenomenological models

Based on a parameterization of the dose distribution using measured data sets, the so called dosimetric base data.

Depth dose curve, doseprofile, collimator-scatter, head-scatter for open (square, rectangle shaped) fields

Inhomogeneity correction: A simple way is the scaling of the depth dose curve with the relative electron density of tissue to water.

Convolutional methods (Kernels and pencil beams)

A faster and more elegant method for a more accurate dose calculation of such irregular shaped fields

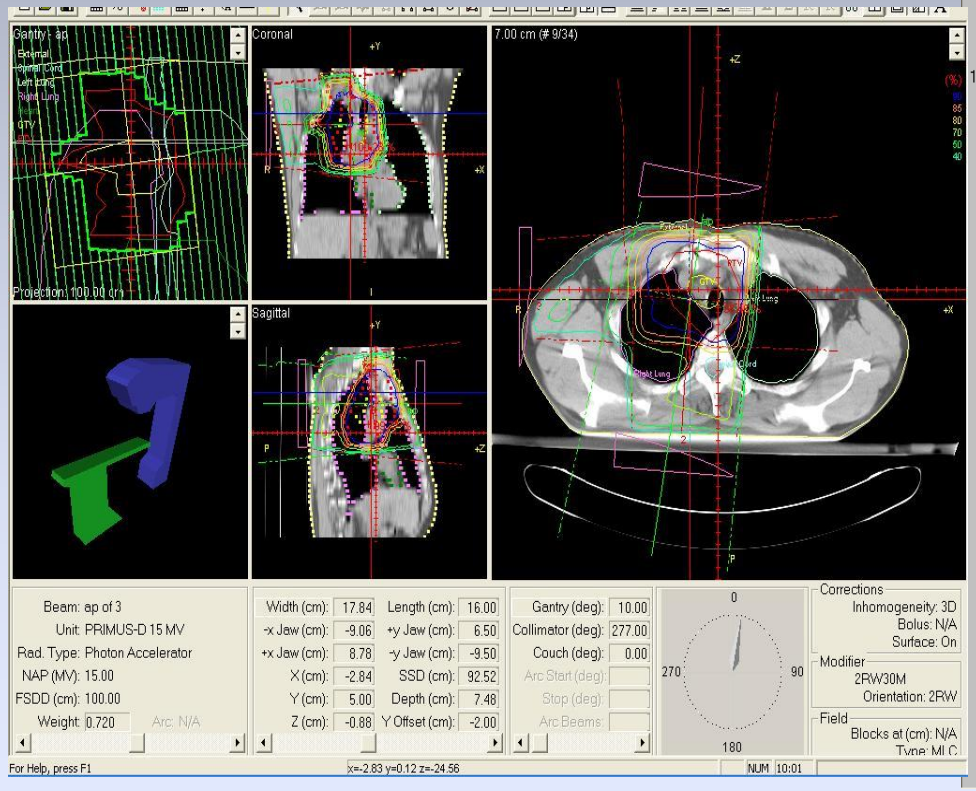
elementary photon beam $\longrightarrow$ interactions $\longrightarrow$ energy transmission and storing (dose kernel (core))

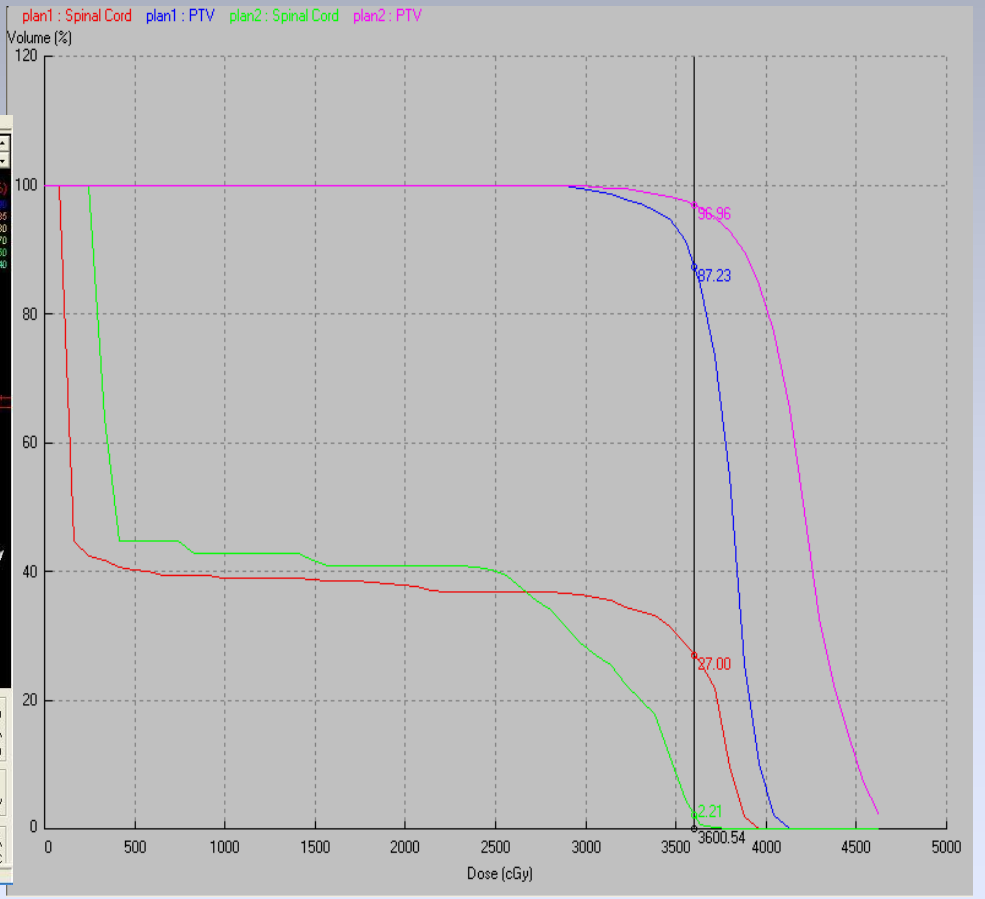
Sum of elementary beams $\longrightarrow$ Sum of dose kernels

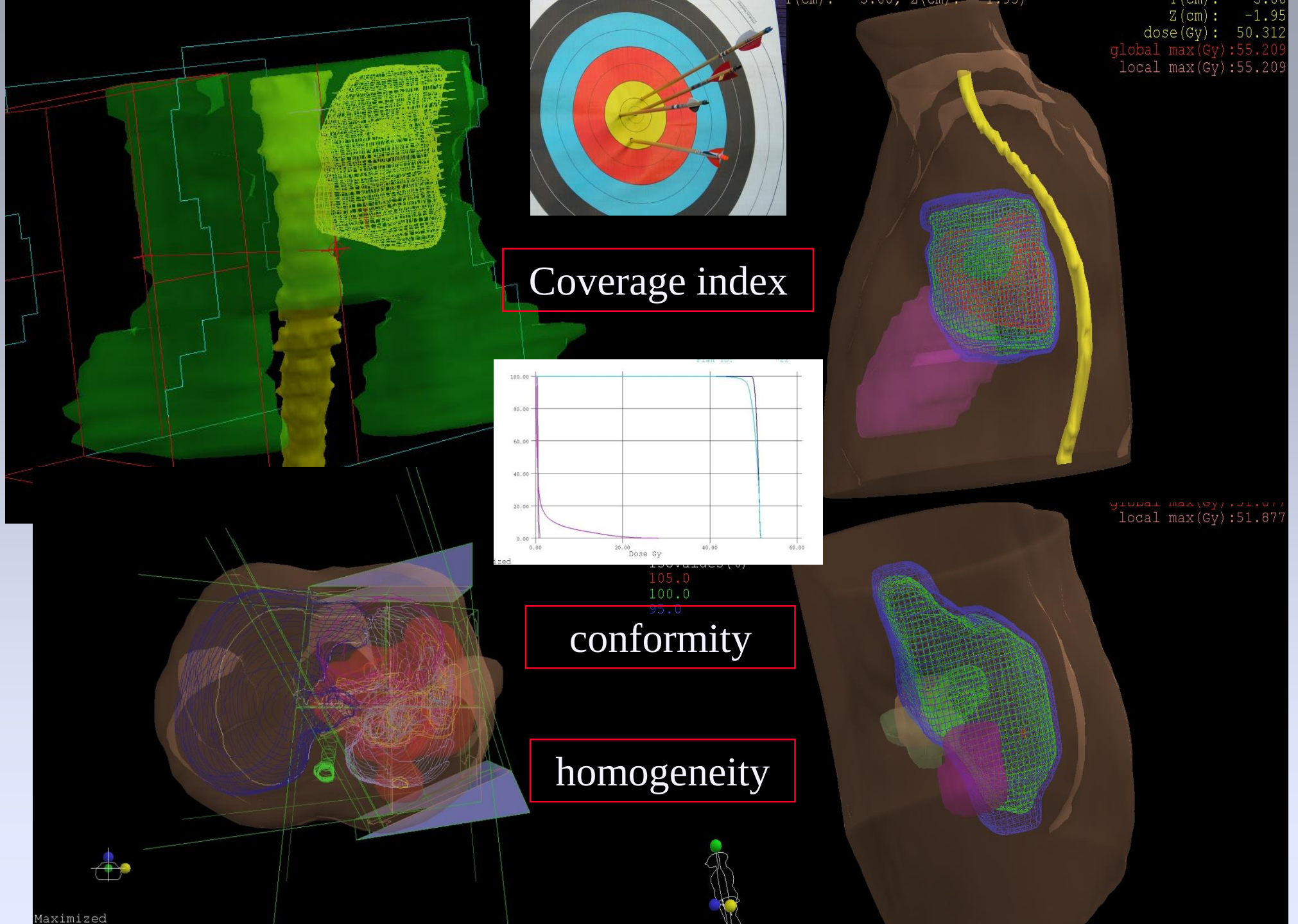
Monte Carlo simulation

Plan evaluation

dose distribution - visual and quantitative, DVHs






Z(cm): -1.95
dose(Gy): 50.312
global max(Gy):55.209
local max(Gy):55.209
Coverage index
100.00
80.00
60.00
40.00
20.00
0.00
0.00
20.00
40.00
60.00
Dose Gy
local max(Gy):51.877
105.0
100.0
95.0
conformity
homogeneity
Maximized

Measuring the dose

In order to determine a radiation dose, a variety of physical or chemical radiation effects can be used.

Radiation effect:		Detector of method:
Ionization in gas	→	ionization chamber
		proportional counter
		Geiger-Mueller counter
Ionization in solid	→	state semiconductor crystal
		conductivity detector
Luminescence	→	TLD
Chemcal effects	→	photographic film
		chemical dosimeters, gels
Thermal effect	→	calorimeter

Phantoms

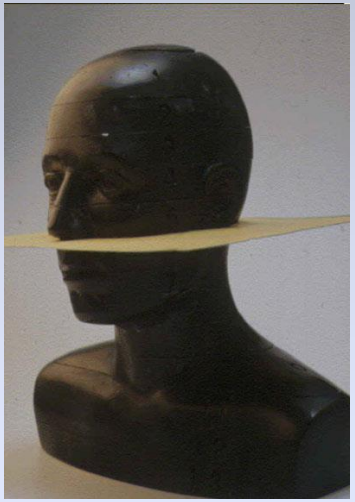
The measurement of water absorbed dose usually is performed within an absorbing medium called a phantom.

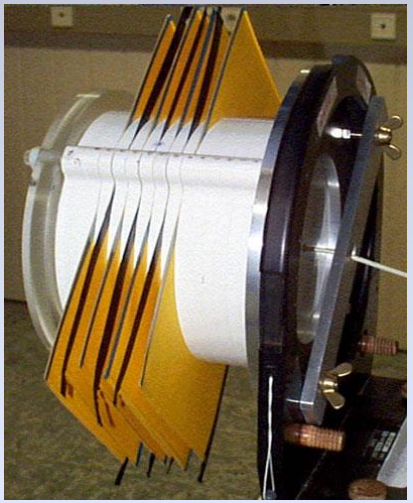
Standard phantoms

Water phantom: TBA (Therapy Beam Analyzer)

Anatomical phantoms: Alderson-Rando phantom

IMRT phantoms





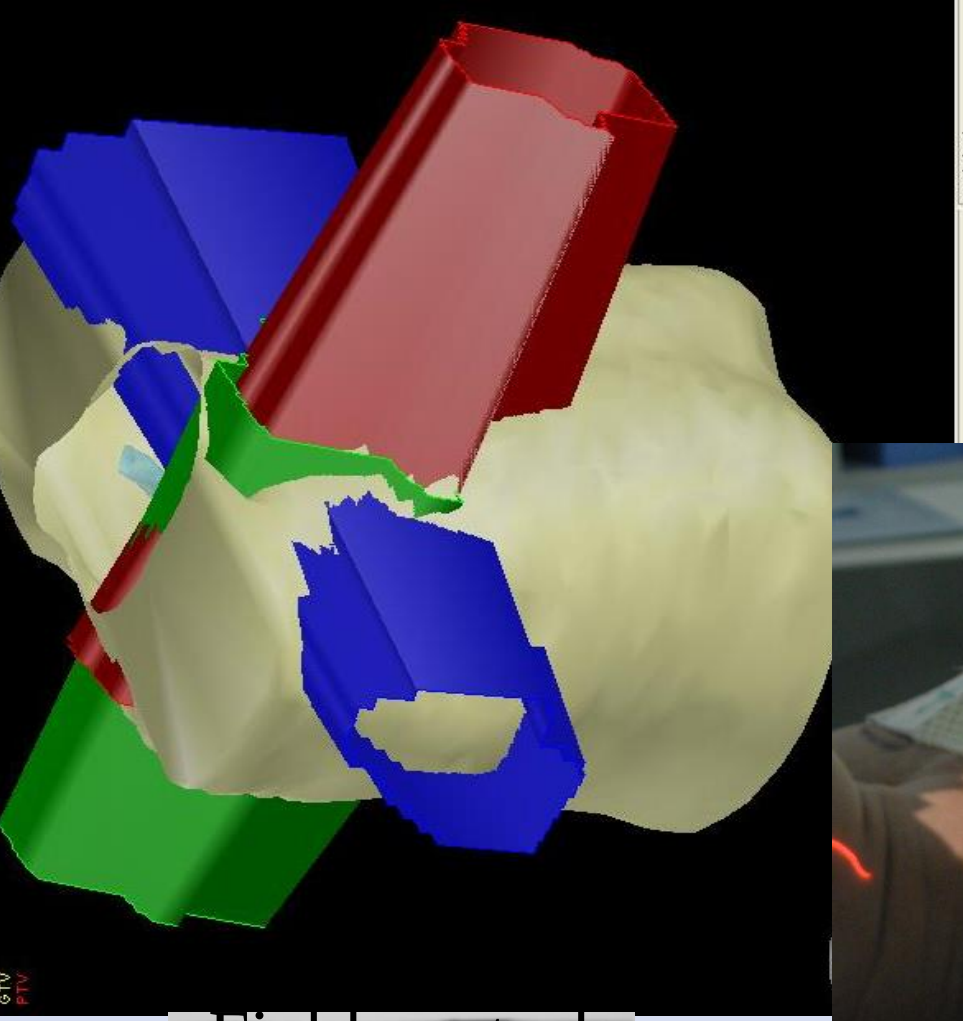
Treatment

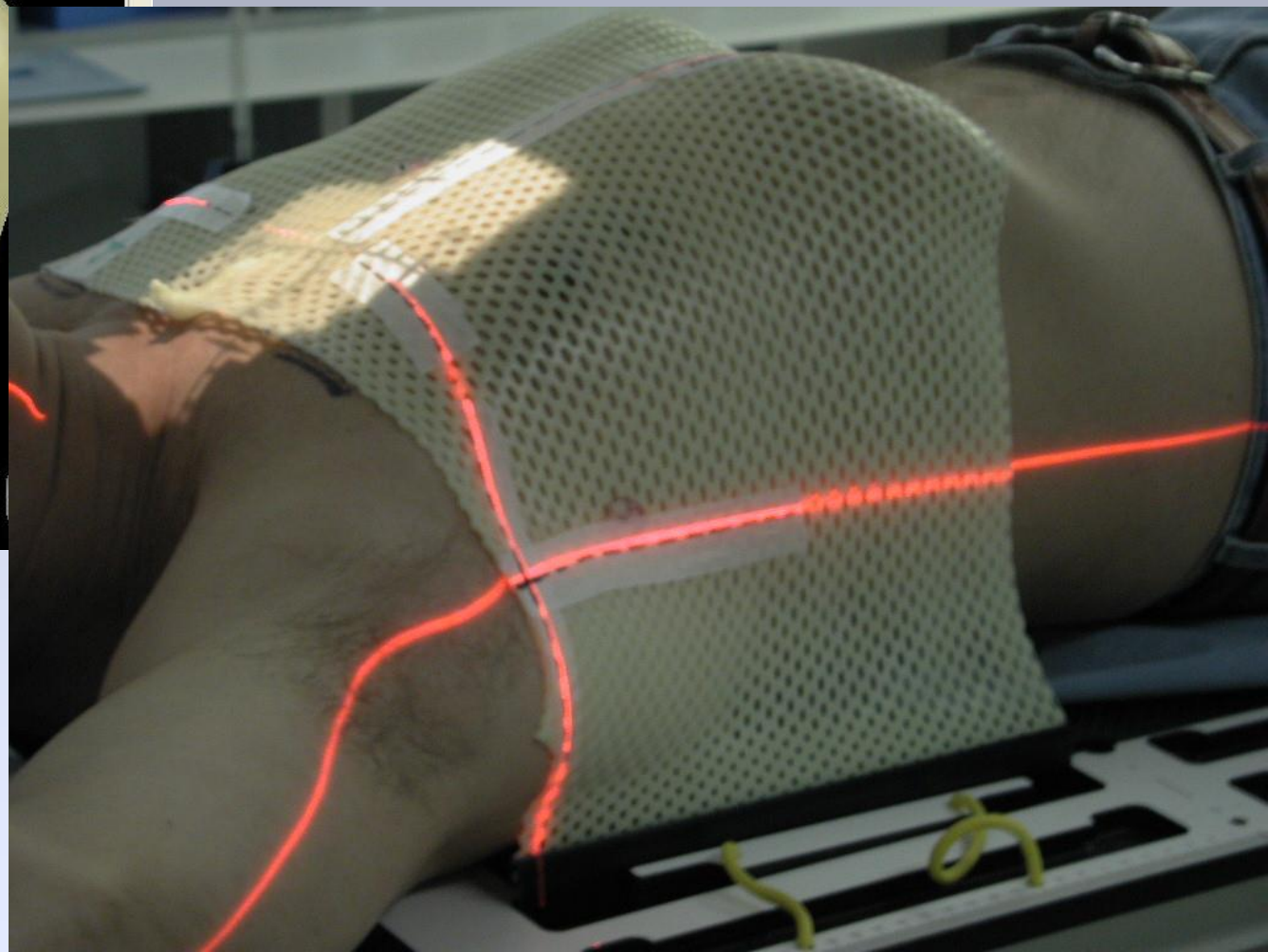
Simulation of the fields

Treatment set up – verification (EPID, orthogonal KV, MV images, Cone beam CT, MRI)

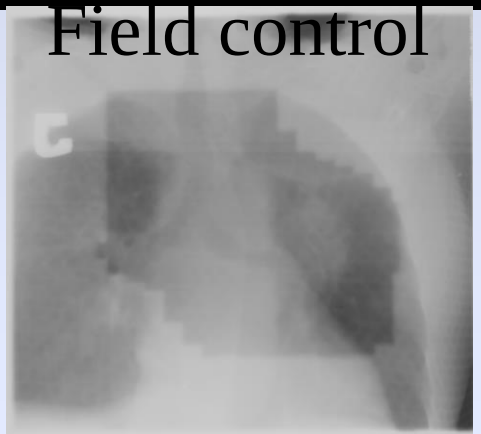
Treatment delivery with regular portal imaging and careful patient care

Adaptation to the changes during RT (repeated imaging)

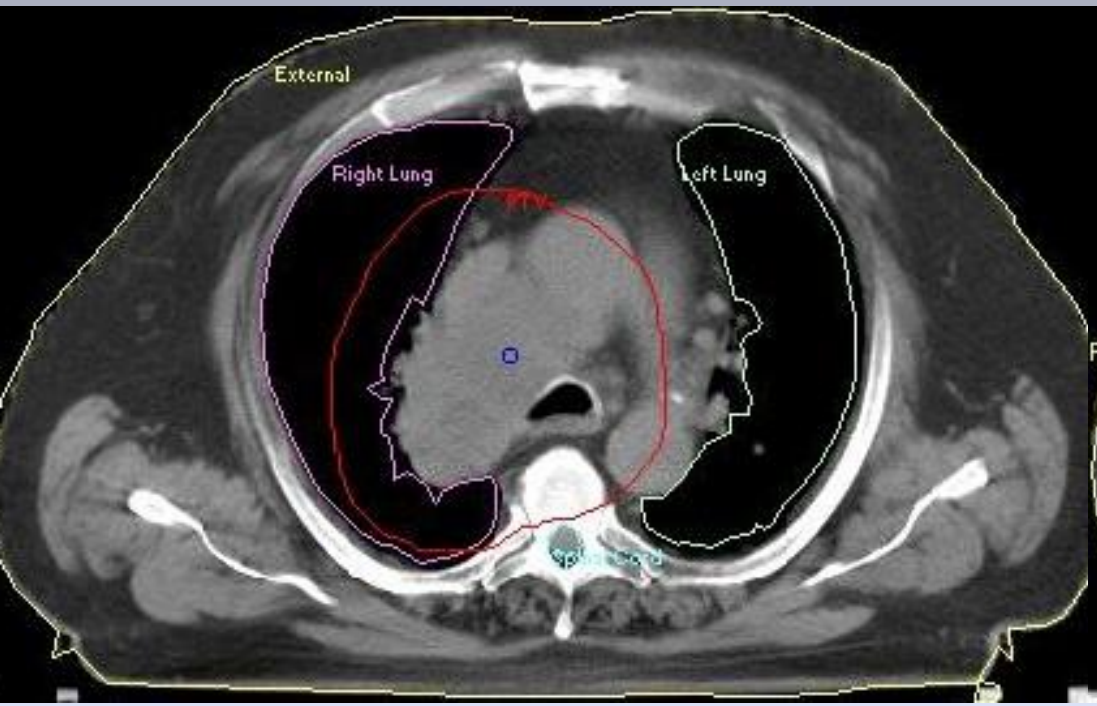




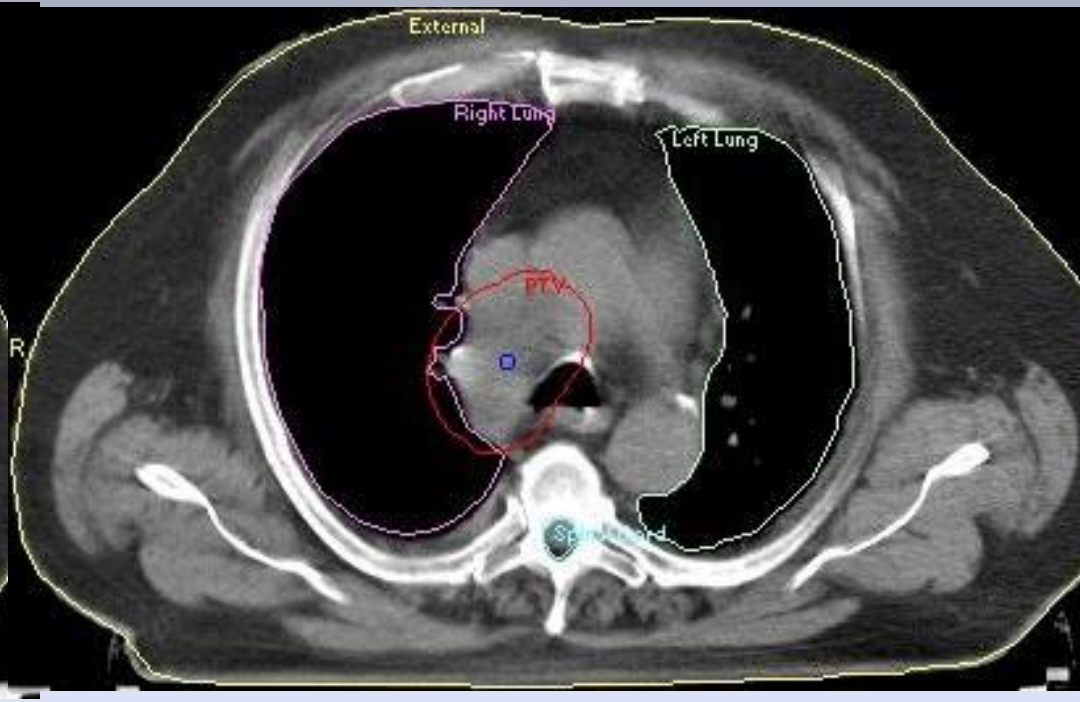
Field control



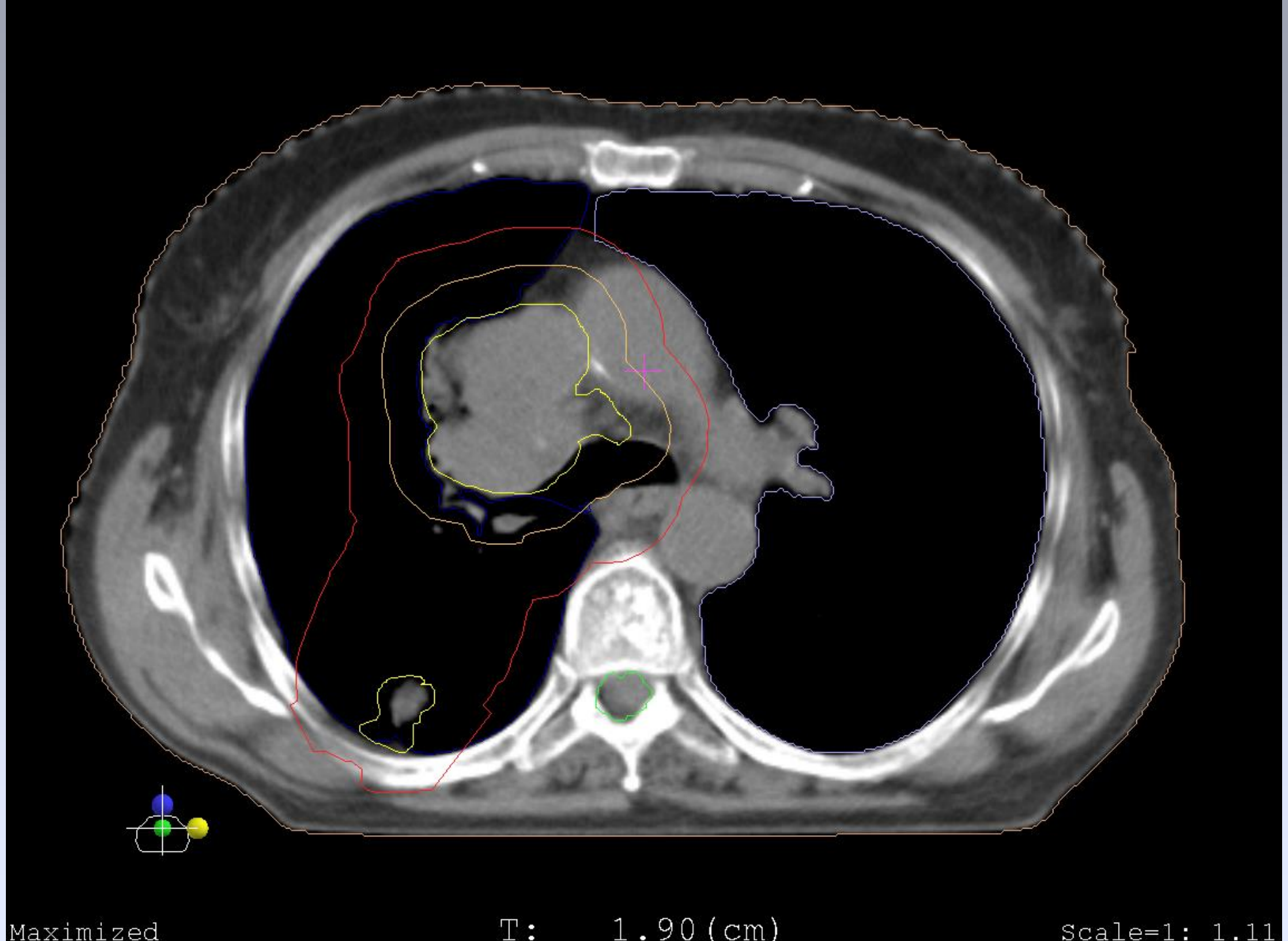
Adaptive radiation



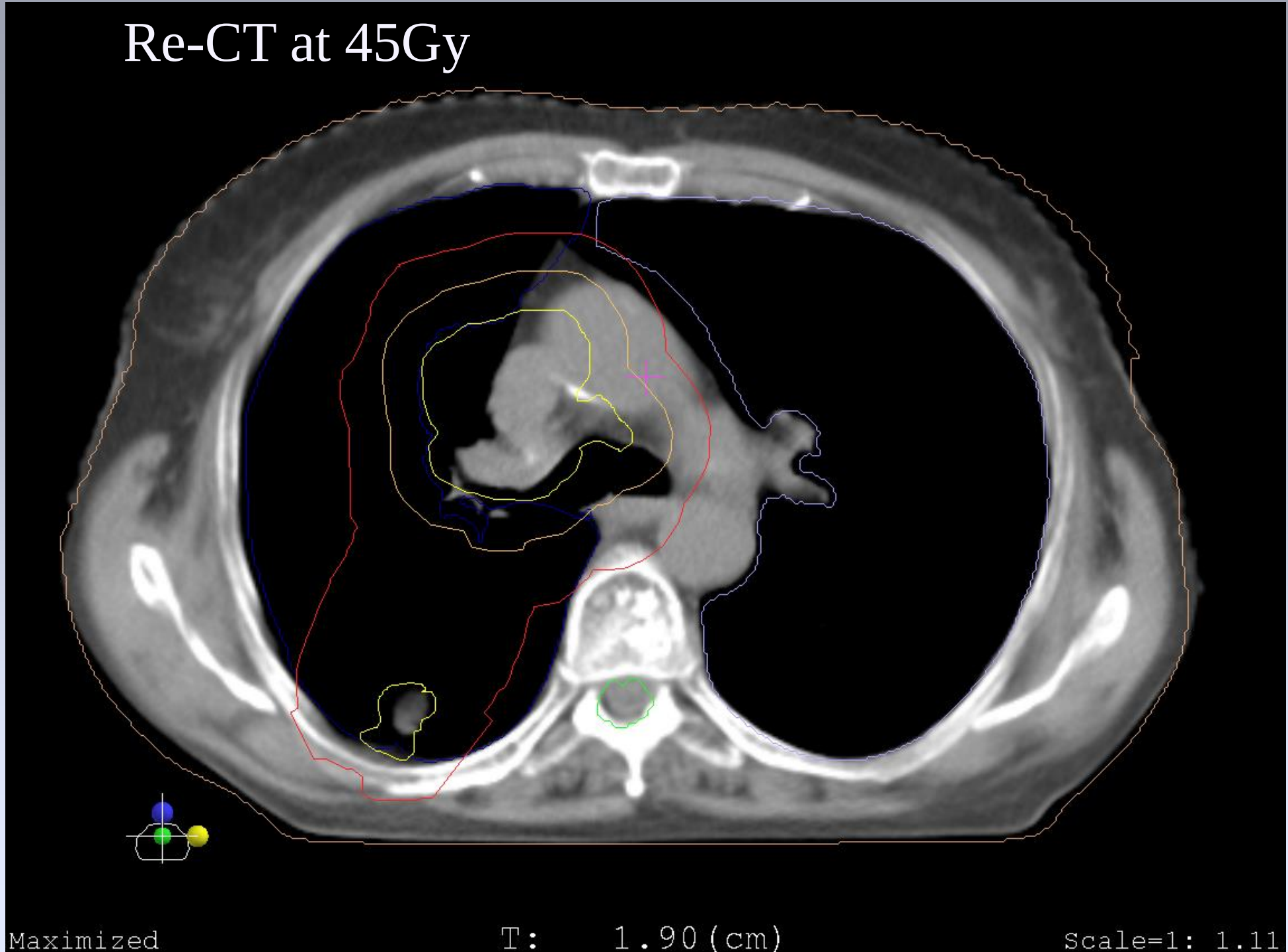
Prior to radiation

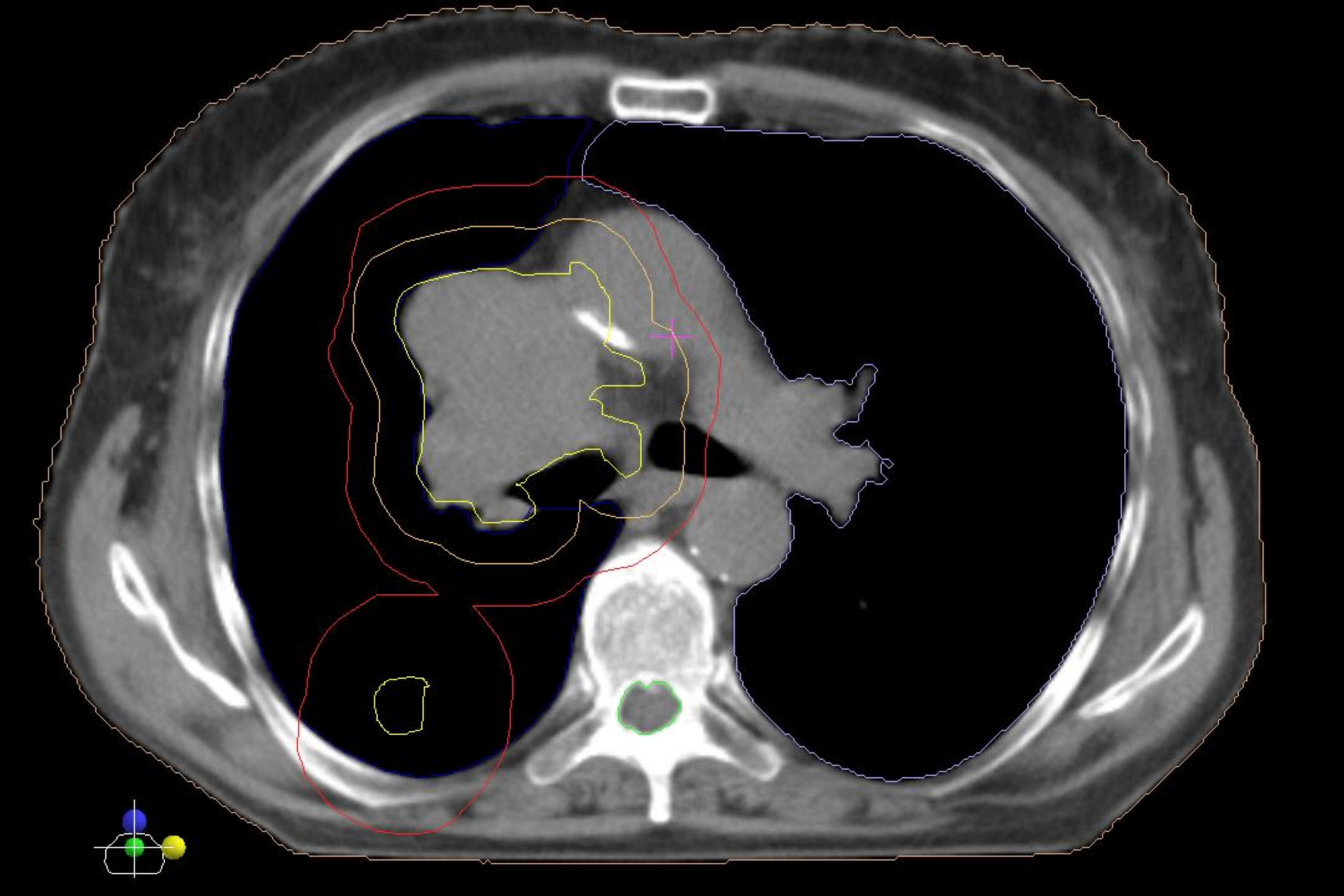


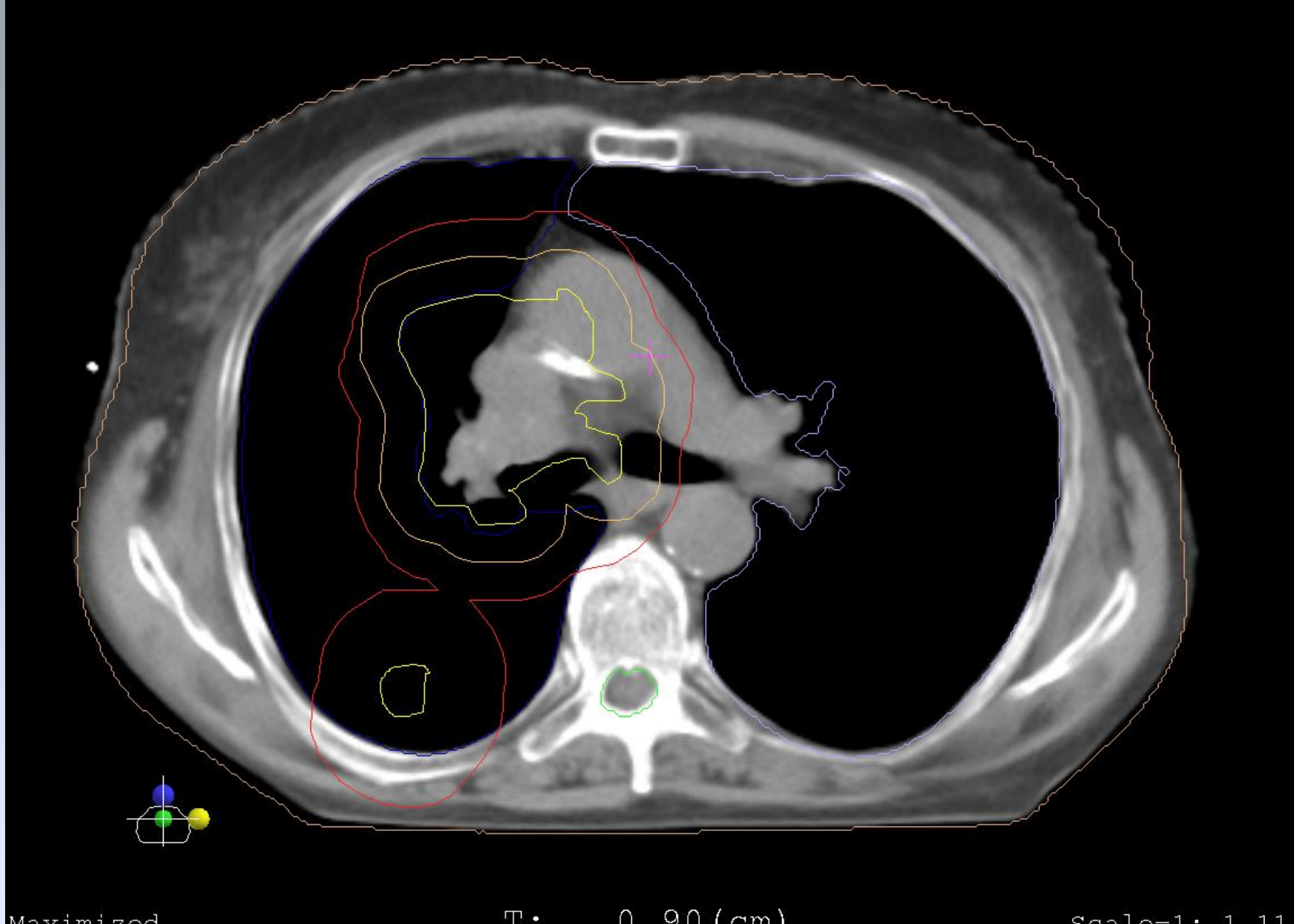
After 40 Gy

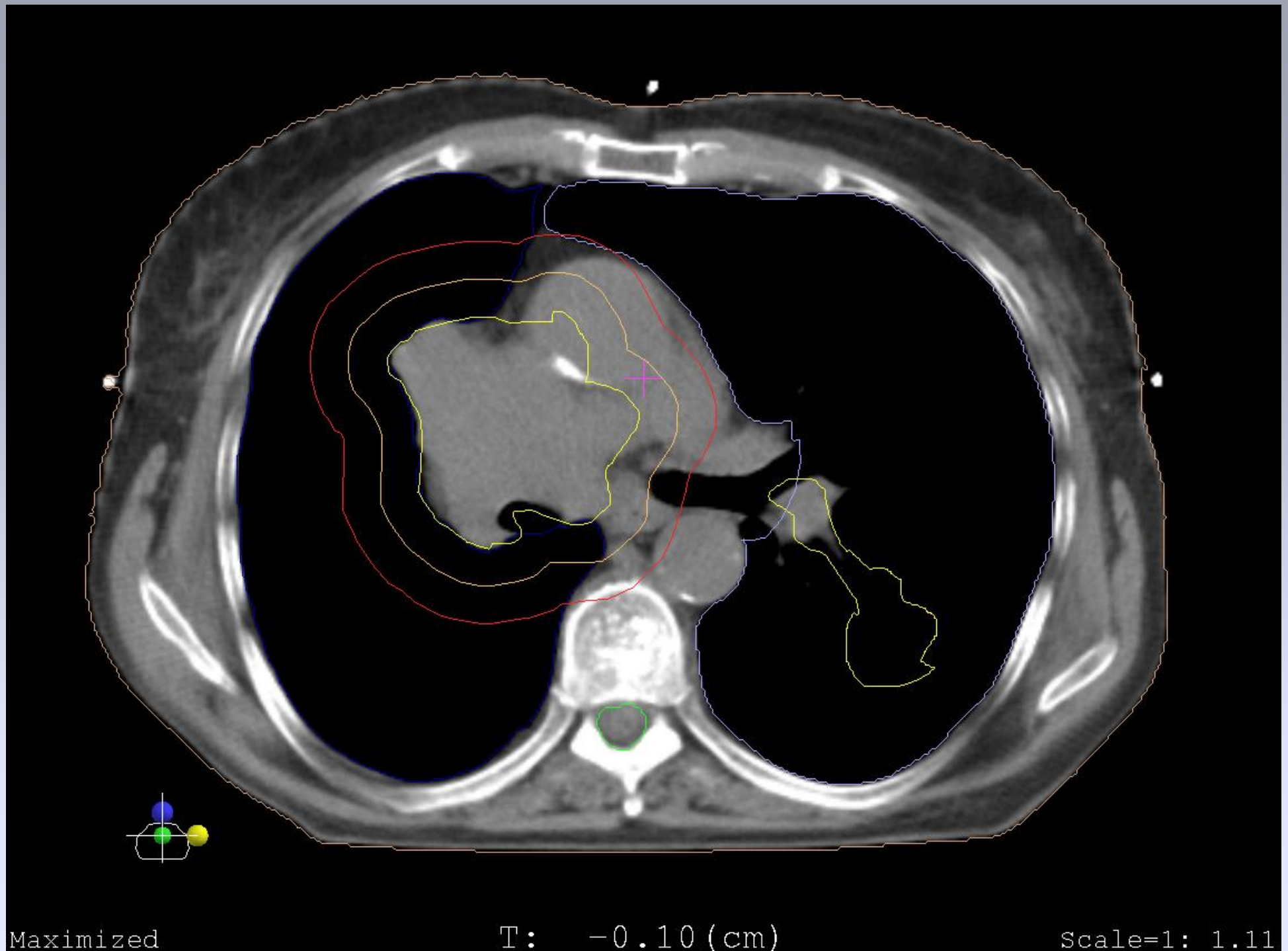

Maximized
T: 1.90(cm)
Scale=1: 1.11

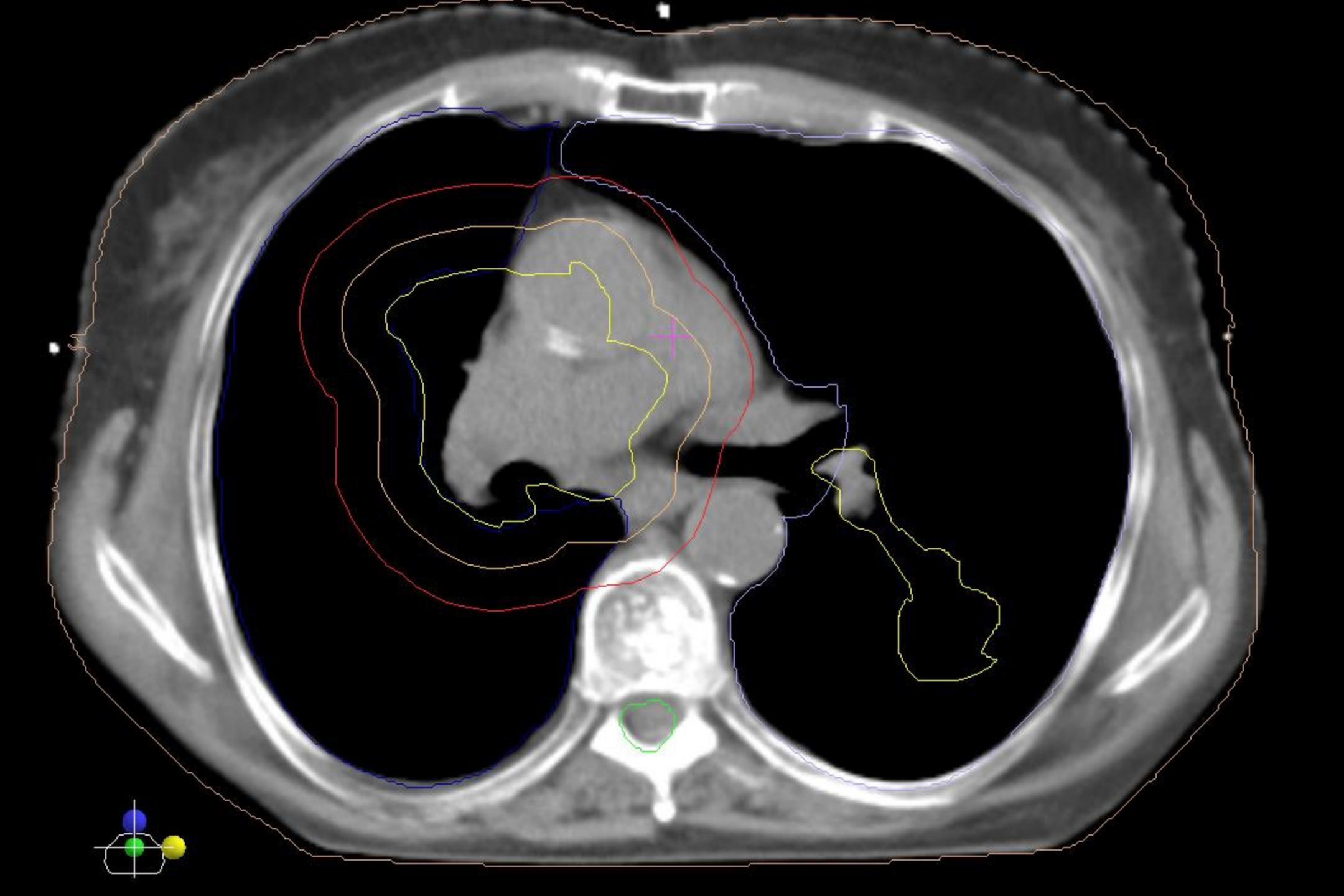
Re-CT at 45Gy

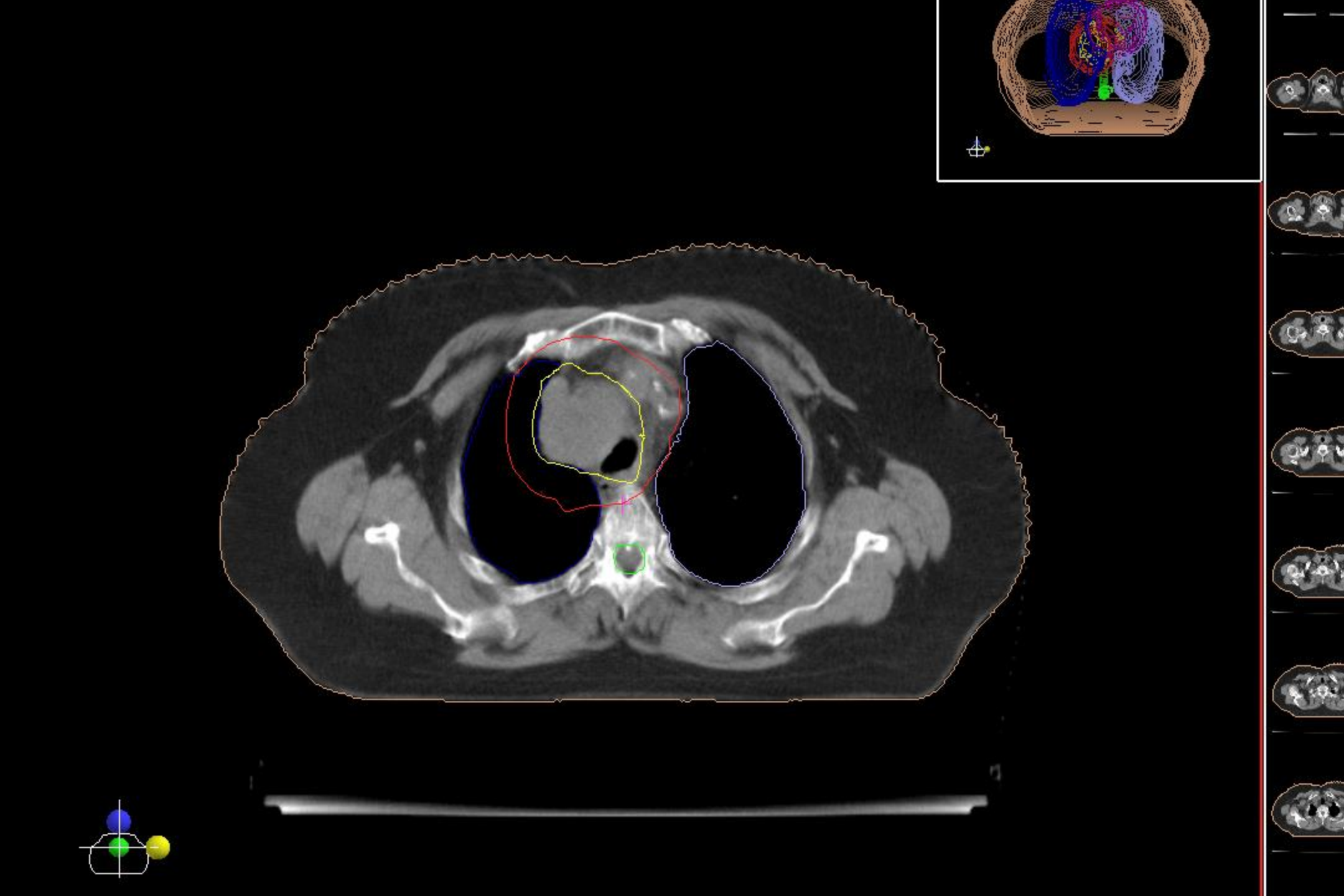


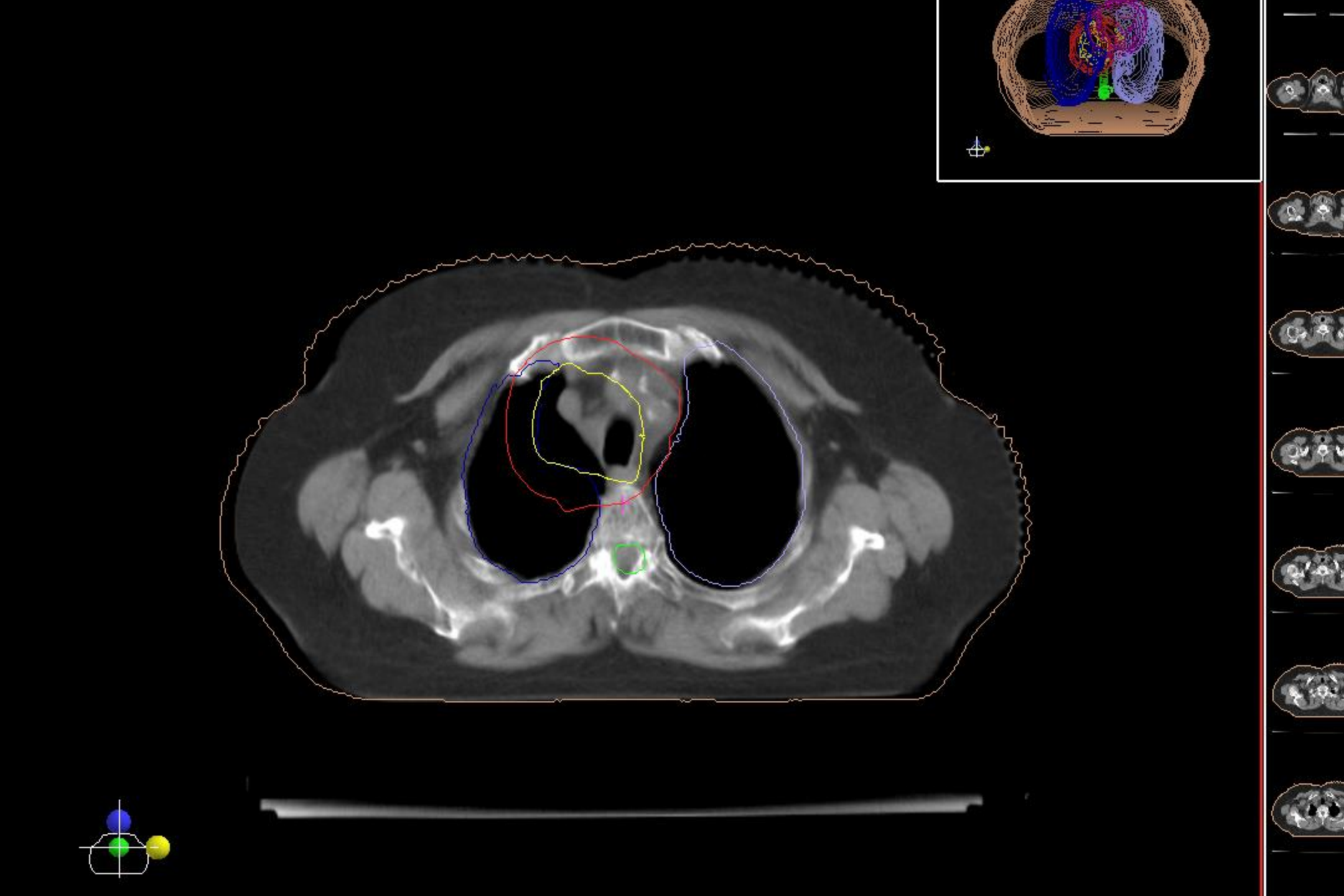



Maximized
T: 0.90(cm)
Scale=1: 1.11


Maximized
T: -0.10(cm)
Scale=1: 1.11







Quality Assurance

SOPs, defined tasks and responsibilities, regular updating
education, training

Control on medical decisions

Regular control of the machines

Control on procedures, treatment delivery and patient car

Evaluation of the results- transparency

Therapeutic index

Tumour response

CR, PR, MC, SD, PD
LC, TFS, TTP, OS

side effects

type, seriousity,
management, duration
impact on QL