LAMELIS 2019

Lasers in Medicine and Life Sciences

Advanced summer school for students of medicine and physics

eli attosecond

IONIZING RADIATION FOR CANCER TREATMENT

KATALIN HIDEGHÉTY

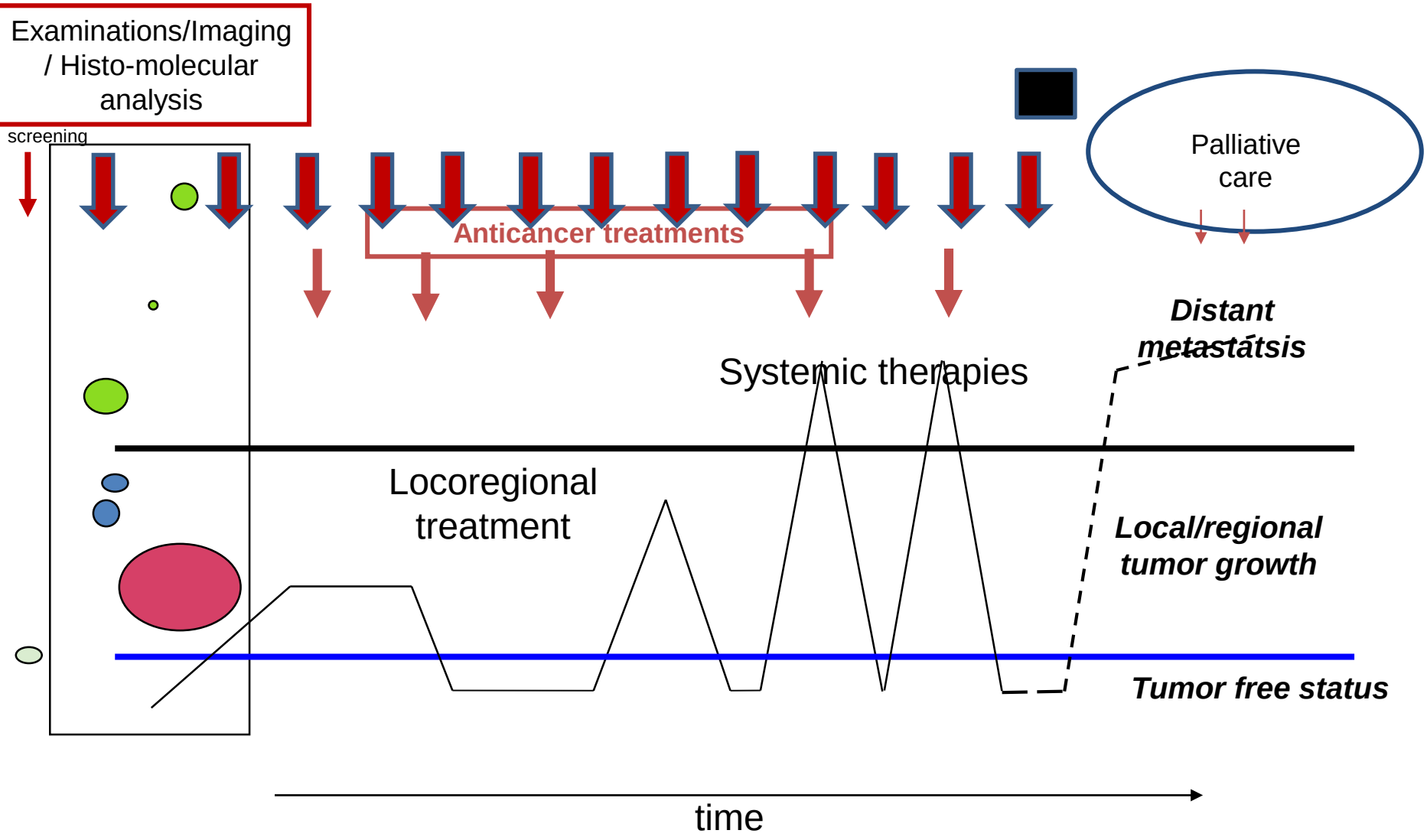
SZÉCHENYI 2020

HUNGARIAN GOVERNMENT

European Union
European Social Fund

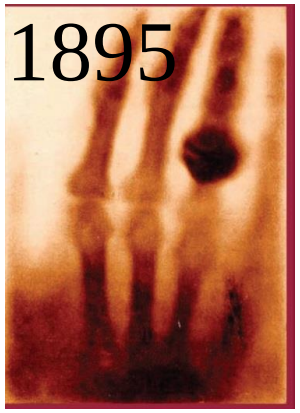
INVESTING IN YOUR FUTURE

Cancer is anarchic, autonom, progressive tissue, built of body identical, but pathologic cells on the basis of genetic error accumulation

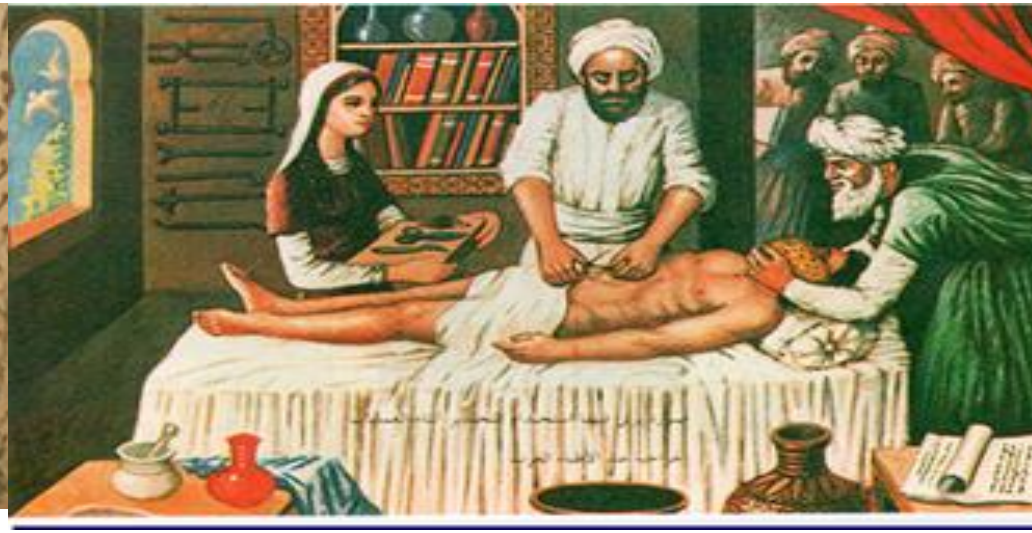


Cancer treatment prior to 1895

Surgery

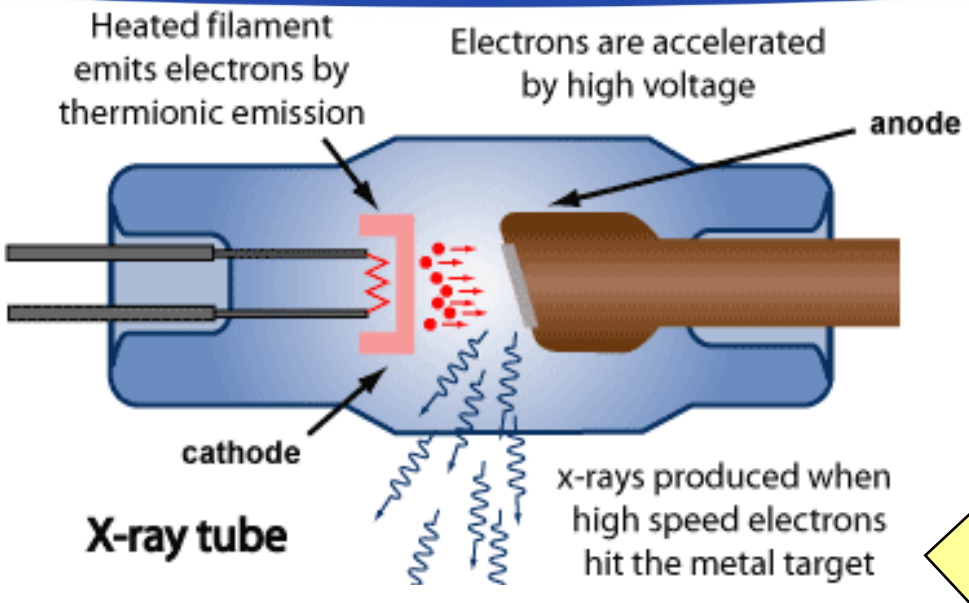


Wilhelm Conrad Röntgen



Discovery of the ionizing radiation

1895

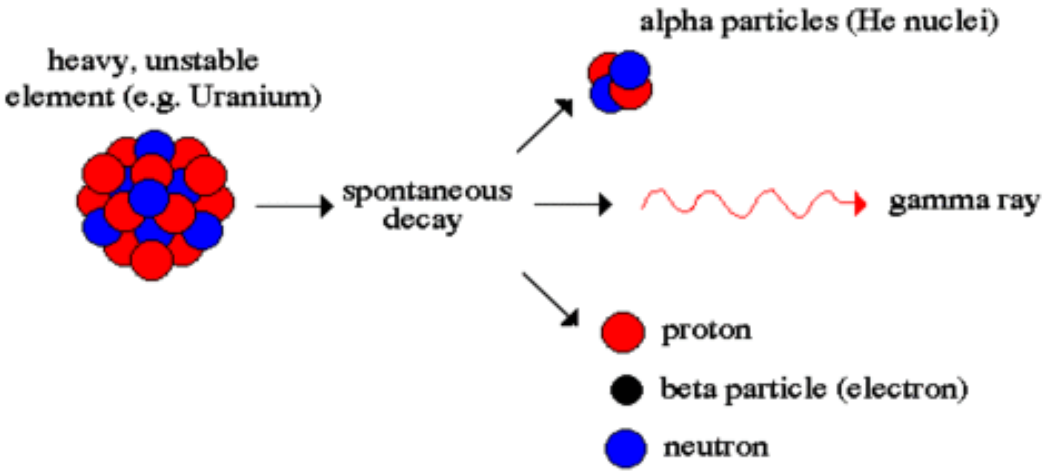


RADIOLOGY

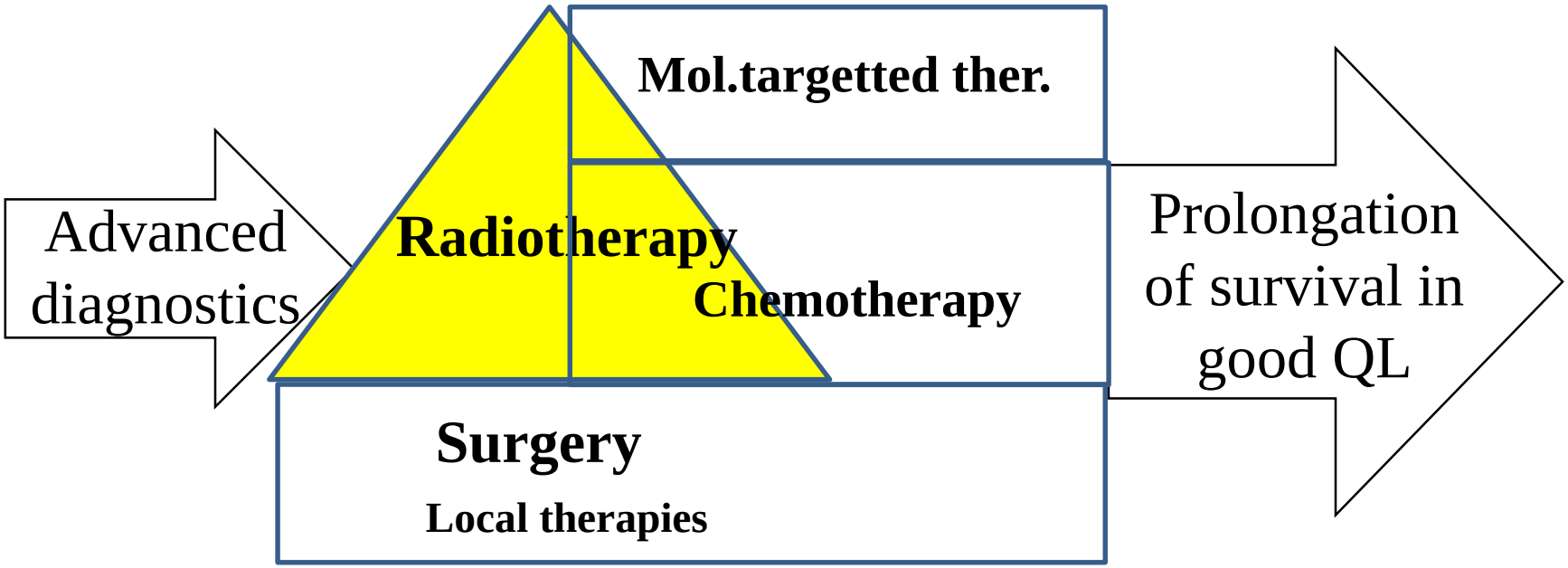
RADIOTHERAPY

Radioactivity

1896



COMPLEX TUMOR THERAPY



10 million patients/year receive radiotherapy

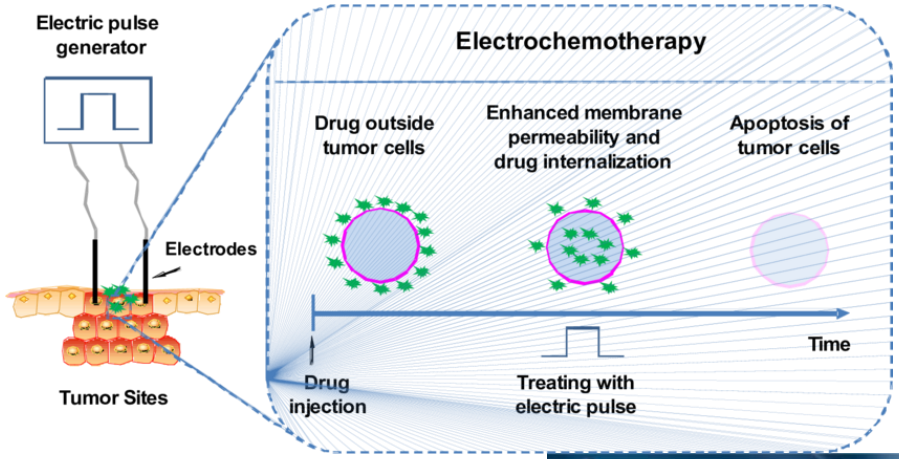
Local therapy modalities

Surgery (minimal invasive/endoscopic)

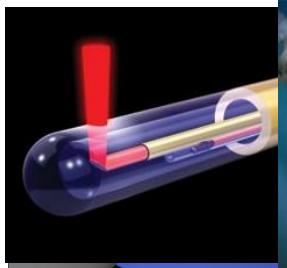
Radiotherapy

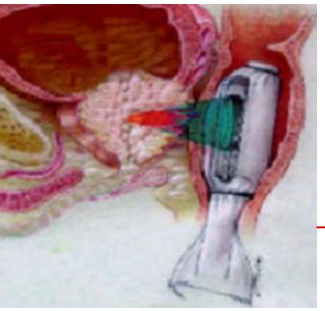
Intraarterial chemotherapy

Electro-chemotherapy



Thermo-ablative methods





Microwave coagulation therapy(MCT)

Radiofrecvention ablation (RFA)

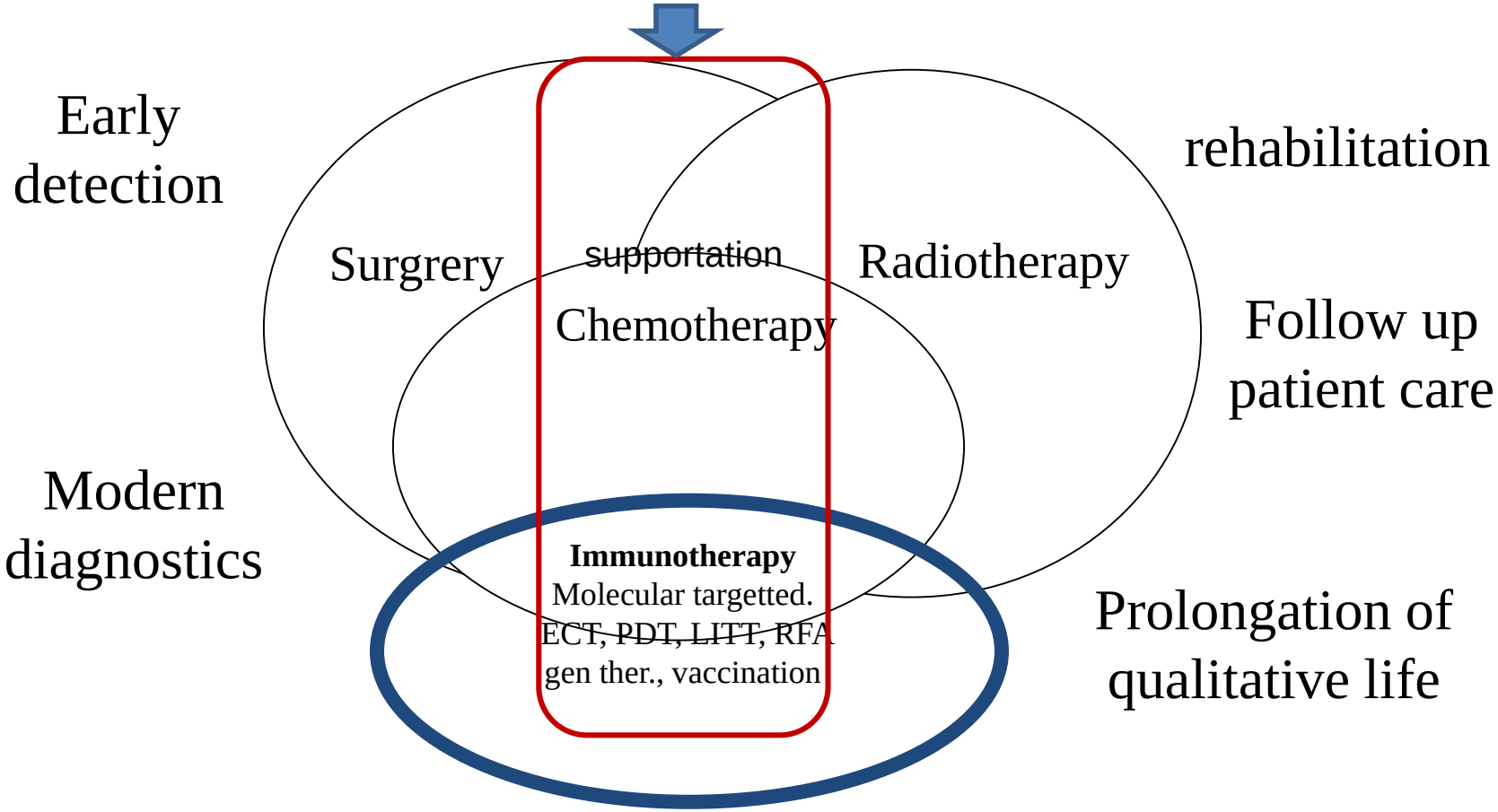
Laser interstitial thermo therapy (LITT)

High Intensity Focused Ultrasound (HIFU)

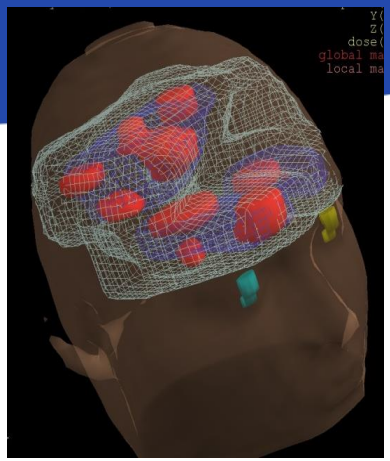
COMPLEX ONCOLOGICAL PATIENT MANAGEMENT

High throughput analysis (NGS) of the DNA, RNA, CSF/liquid biopsies

Personalized treatment



Ionizing radiation for treatment radiotherapy (RT)



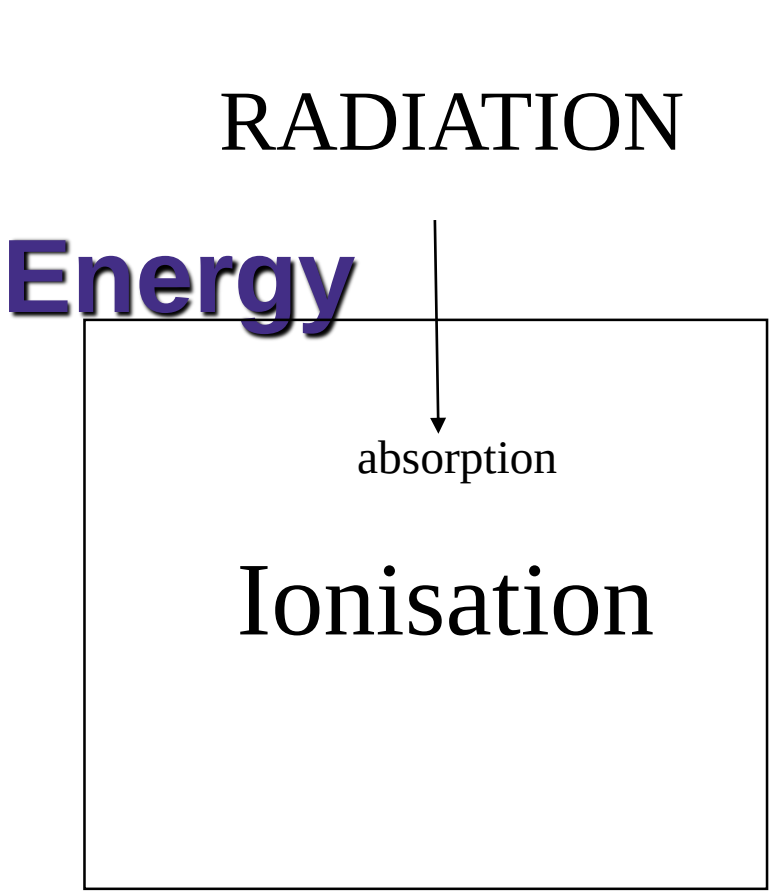
Loco-regional treatment method

Directed energy deposition in the human body

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

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

Physical process

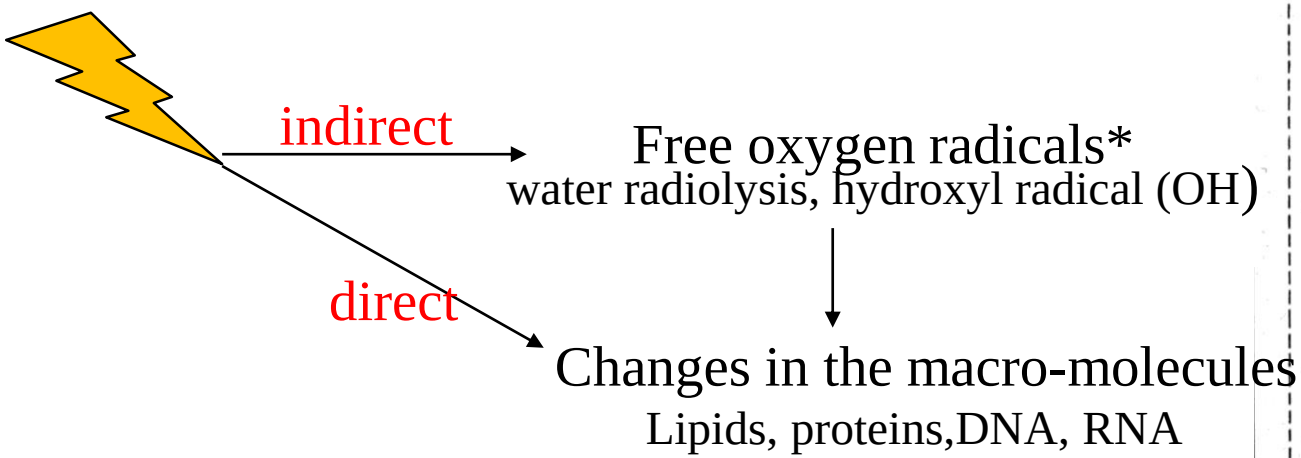


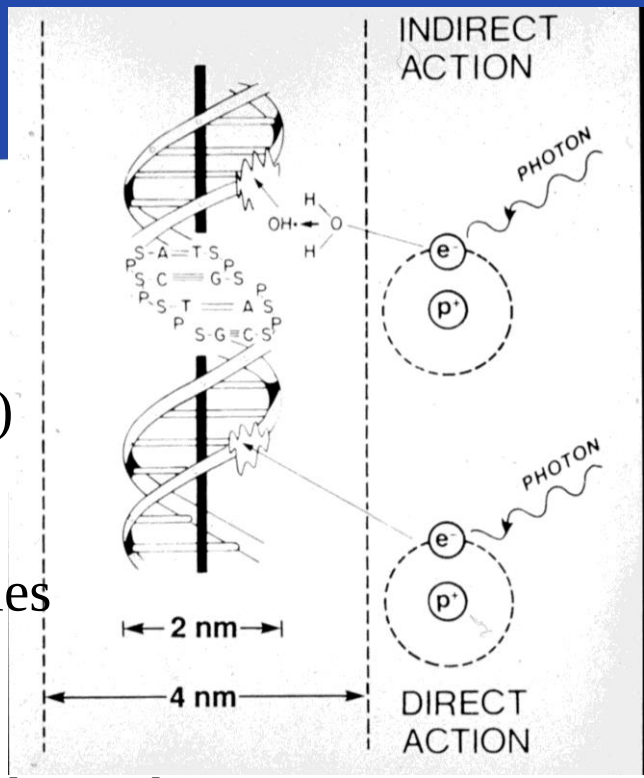
Radioactive isotope

Brachytherapy

Teletherapy (percutaneous)

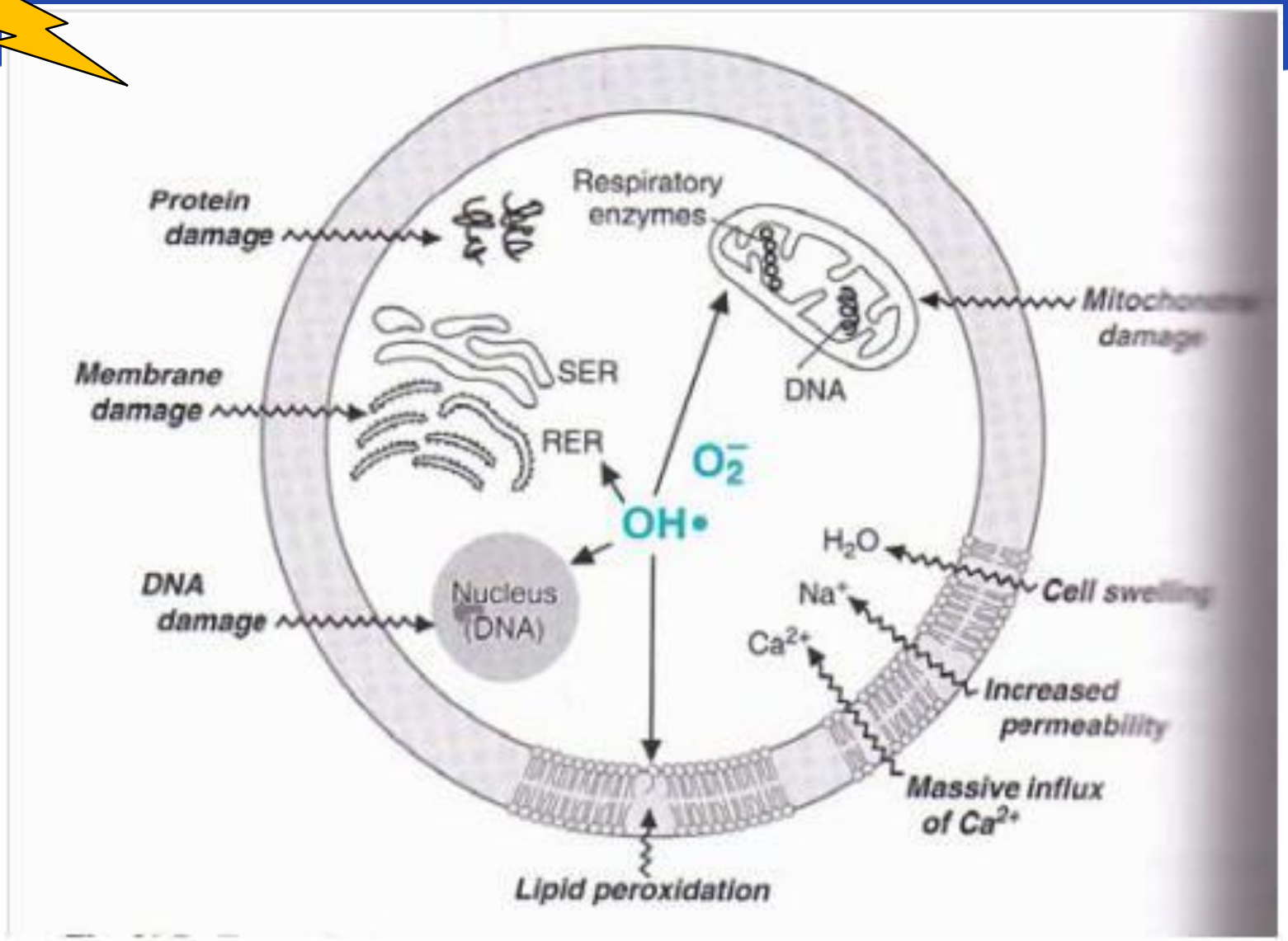
Chemical processess

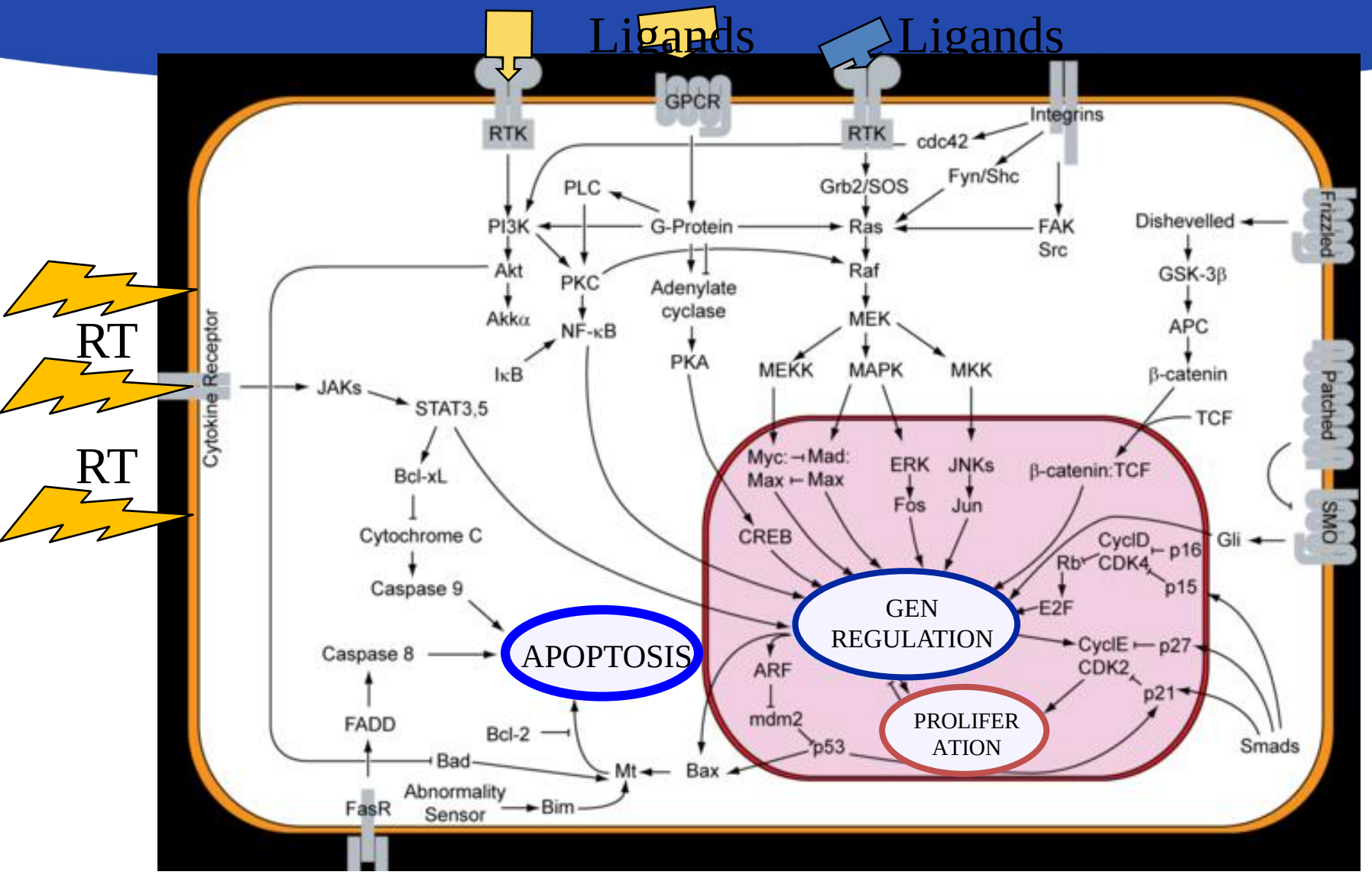




Chain reactions may also occur, particularly in lipids, and may play a role in damage to cell membranes

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


Protein damage
Respiratory enzymes
Mitochondrial damage
DNA
Membrane damage
SER
RER
O_2^-
OH•
H_2O
Cell swelling
Na^+
Ca^{2+}
Increased permeability
Massive influx of Ca^{2+}
DNA damage
Nucleus (DNA)
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
IκB
PKA
MEK
MEKK
MAPK
MKK
APC
β-catenin
TCF
Cytokine Receptor
JAKs
STAT3,5
Patched
SMO
Bcl-xL
Myc: Mad:
Max Max
ERK
JNKs
Fos
Jun
β-catenin:TCF
Cytochrome C
CREB
CyclD
CDK4
p16
p15
Gli
Rb
E2F
Caspase 9
GEN
REGULATION
Caspase 8
APOPTOSIS
CyclE
CDK2
p27
p21
ARF
mdm2
p53
PROLIFER
ATION
FADD
Bcl-2
Bad
Mt
Bax
Smads
FasR
Abnormality
Sensor
Bim

Radiation effects

Atomic

Energy absorption

Molecular

Ionisation

Free radicals

Macromol.

Protein

DNA damage

Subcellular

Metabolism

Regulation

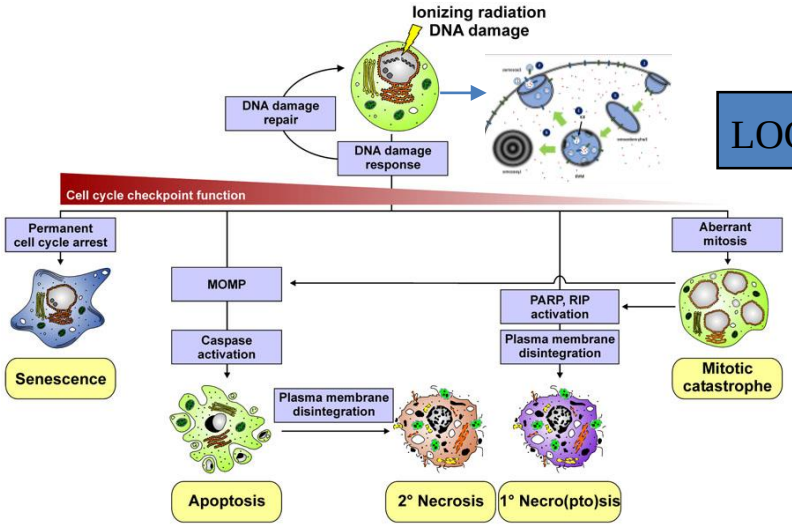
Membrane, DNA

Cellular

Full/partial repair

Cell damage

Cell death



LOCAL

Tissue

Cytokines/exosomas

Vessel wall, function

BYSTANDER

ABSCOPAL

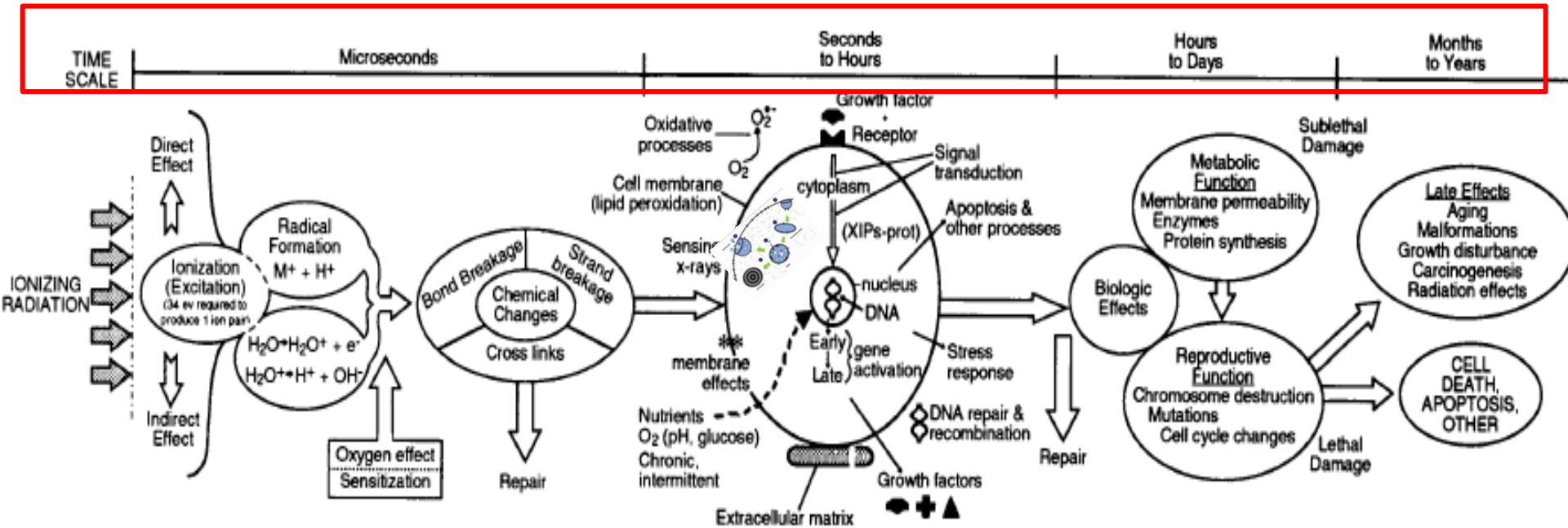
Macroscopic

Radiation reaction

Necrosis

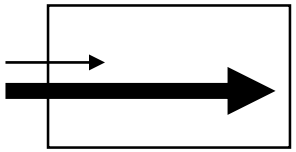
Organ-function det.

Radiation effects

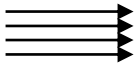


CHARACTERISTICS OF RADIATION

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



- Intensity



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

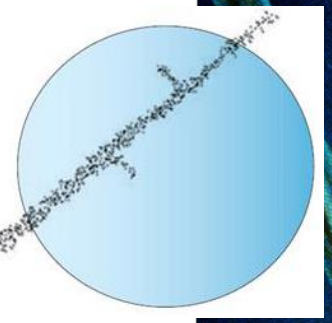
Linear energy transfer LET

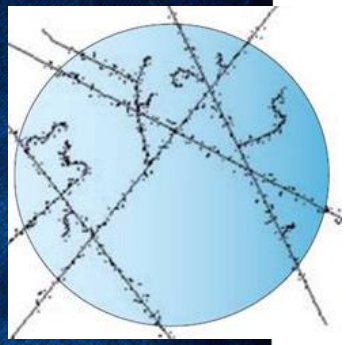
High LET

Very dense ionisation

Low LET

Mainly inidrect action $^{\cdot}OH$





Clustered lesions

Isolated lesions

High RBE
Low OER

Radiation		Linear Energy Transfer (keV/μm
Cobalt-60 γ-rays		0.2
250-kV x-rays		2.0
10-MeV protons		4.7
150-MeV proton		0.5
14-MeV neutrons	Track Avg. 12	
2.5-MeV α-particles		166
2-GeV Fe ions (space radiation)		1000

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

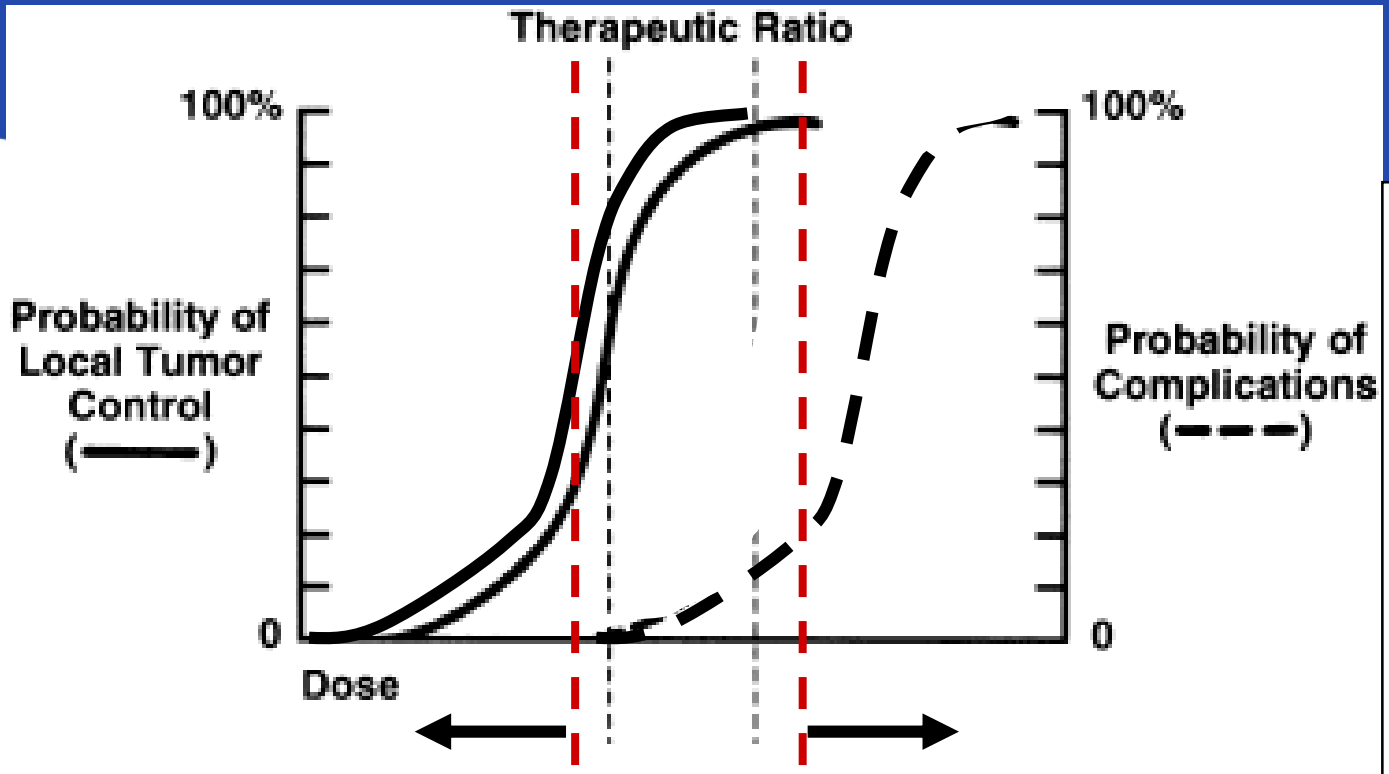
- **Acute reactions**
  - General /Local -**Inflammation**
- **Late sequales** (irreversibile)
  - **Scar tissue**, ulcus, organ function
- (second) tumor induction

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

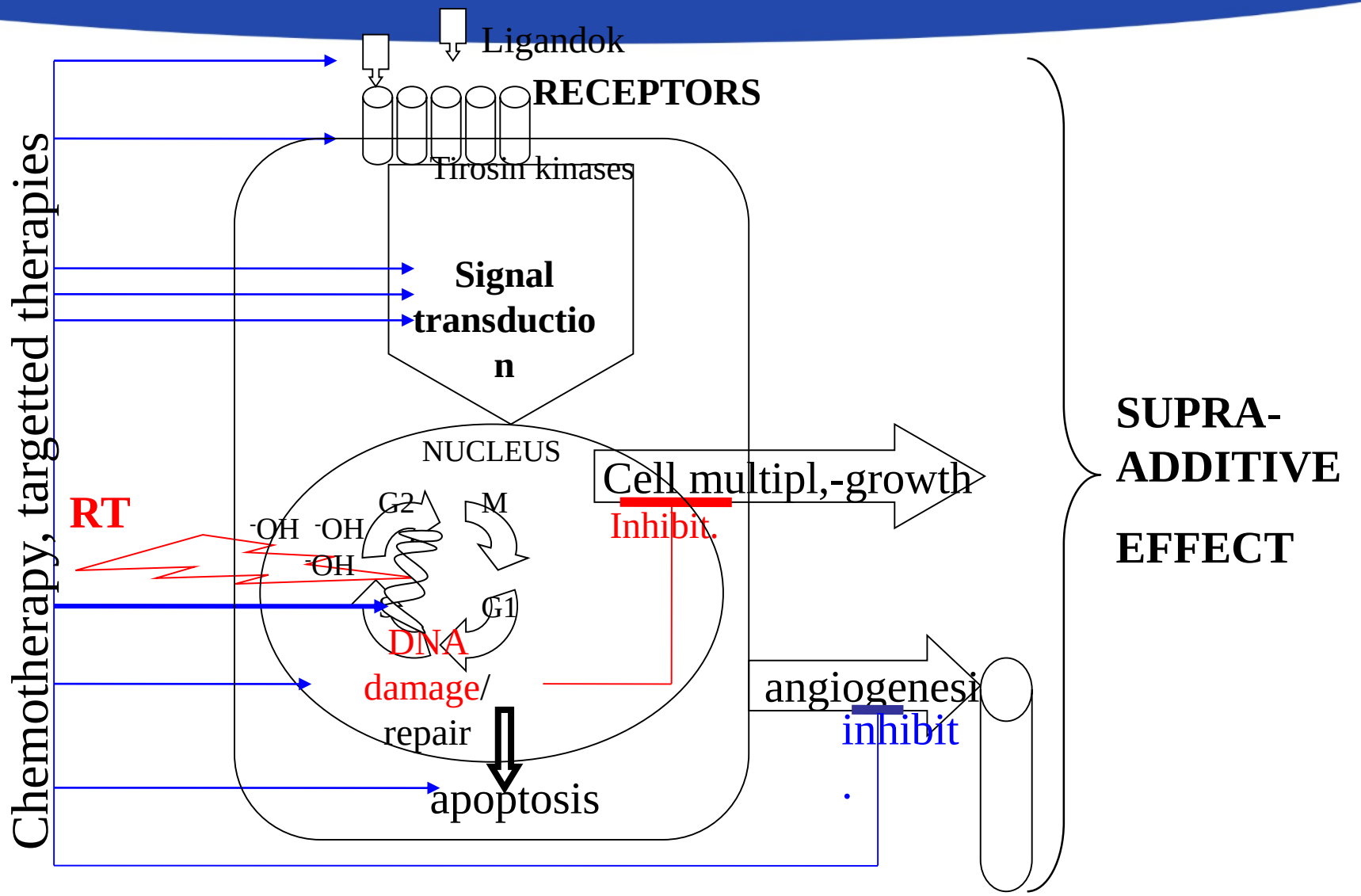
sensitisation/protection

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

Technical development

Increase of spatial selectivity

Radiosensitisation



Concomittant radio-chemotherapy NSCLC

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

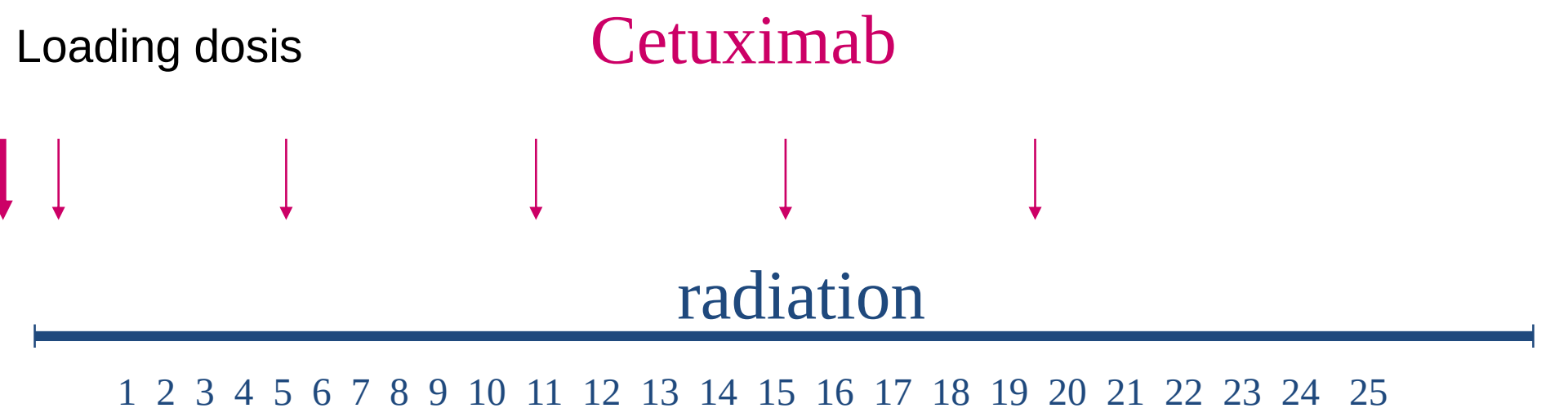
irradiation

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)

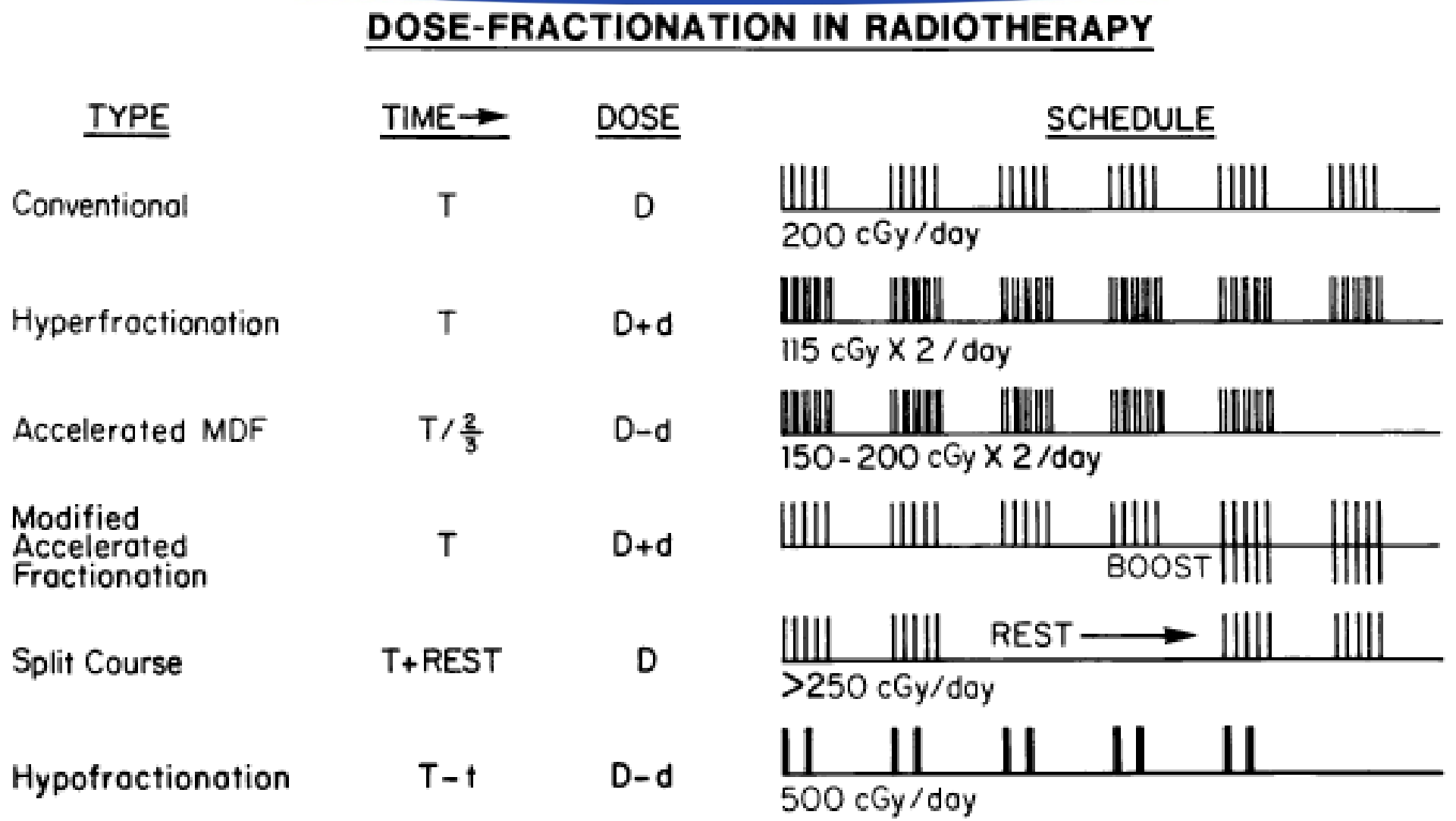
Concomittant anti-EGFr-radiotherapy
Head and neck



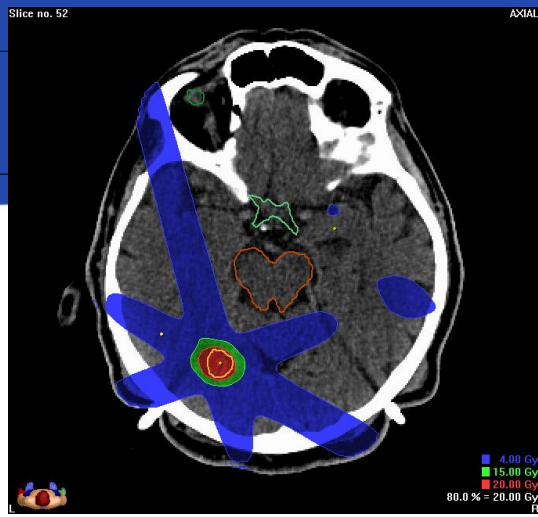
OPTIMISATION IN TIME

- **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)

Fractionation schemes



Increased selectivity



Target volume

Selective homogeneous painted RT (concomittant boost, hypoxic areas)

TCP ↑

Normal tissues

Decrease of the dose to the normal tissues

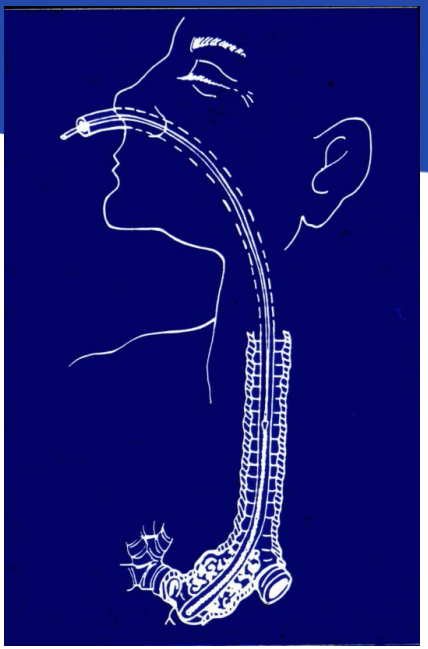
NTCP ↓

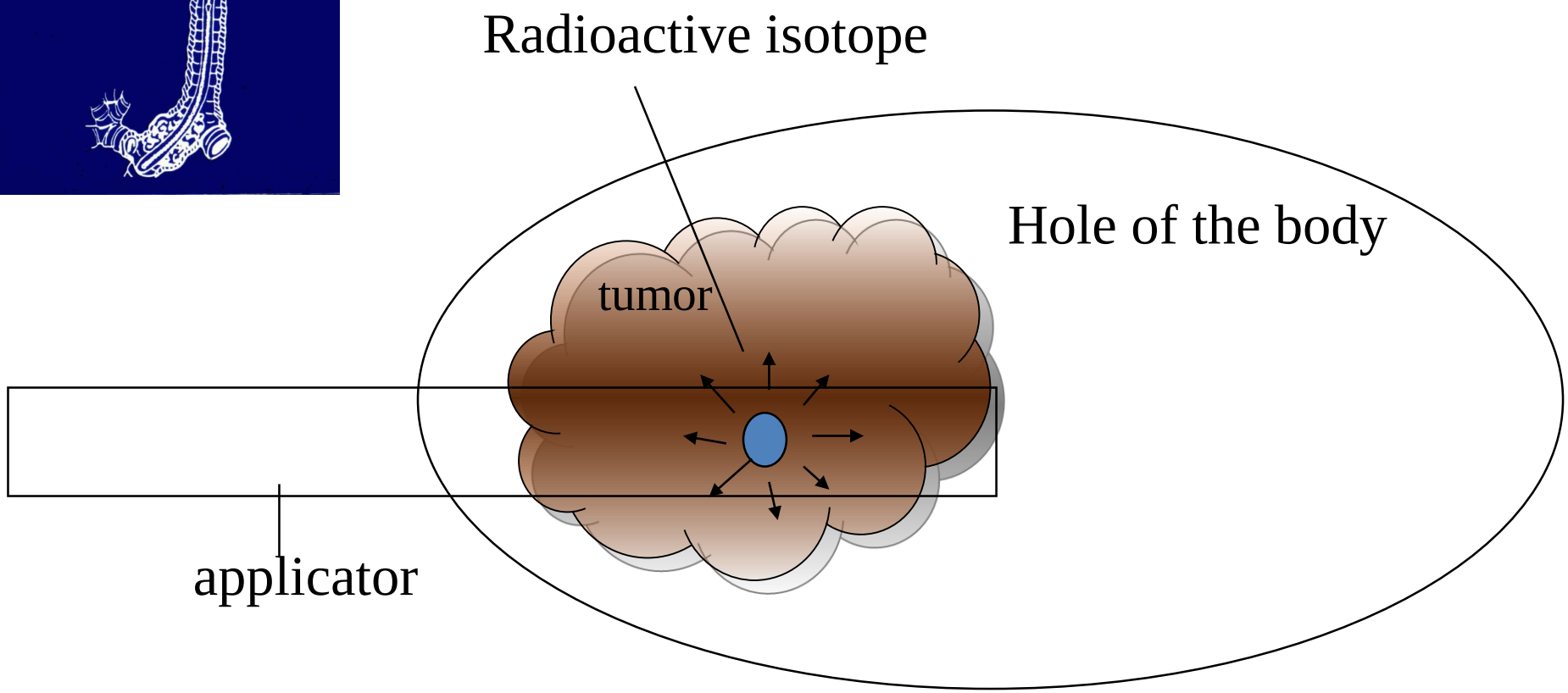
Increased therapeutic index

FORMS OF RADIOTHERAPY

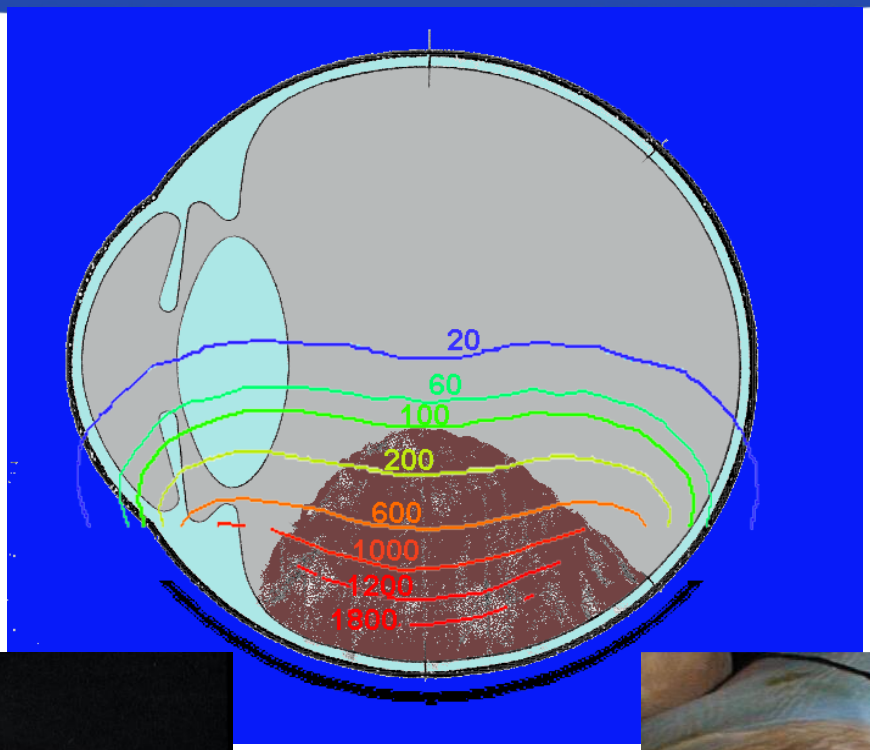
- Radioactive isotope
- Brachytherapy
- Teletherapy (percutanious)

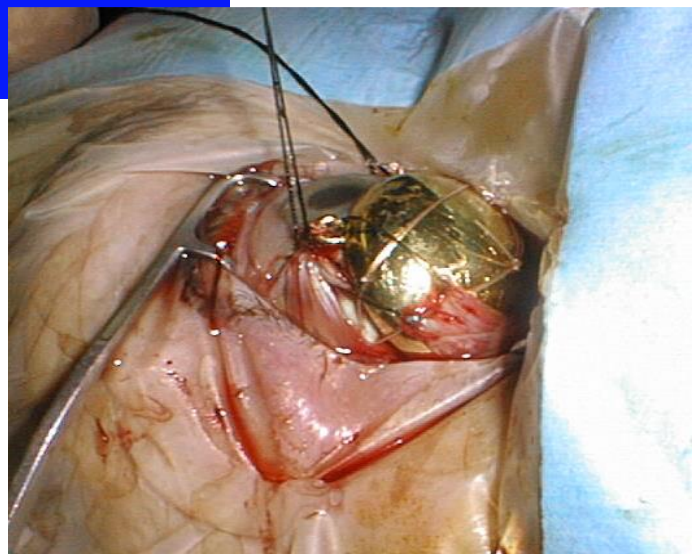
BRACHYTHERAPY



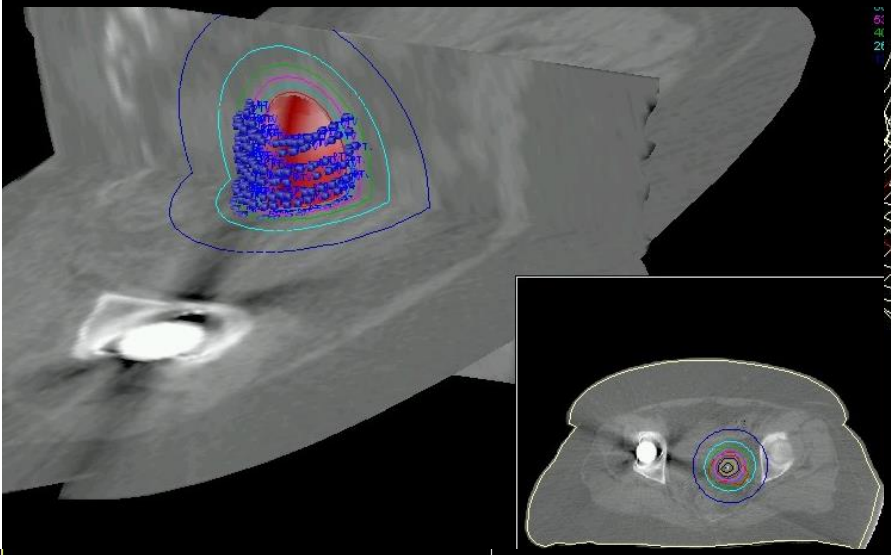


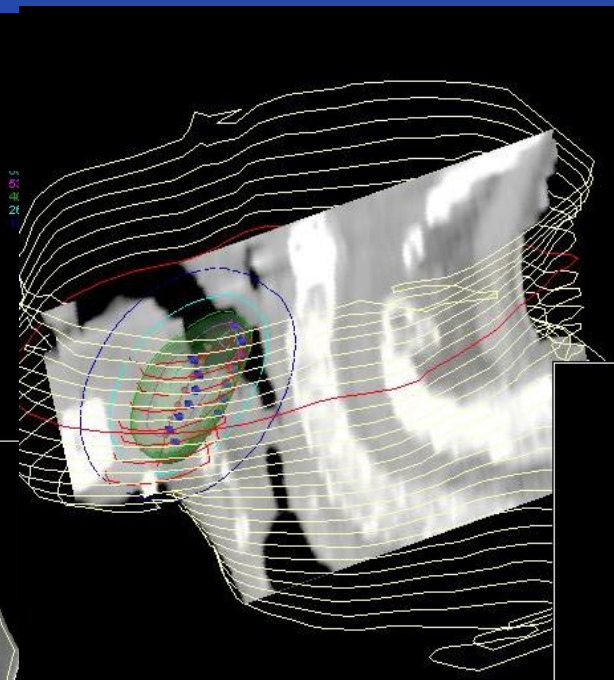
$^{106}Ru/^{106}Rh$ application

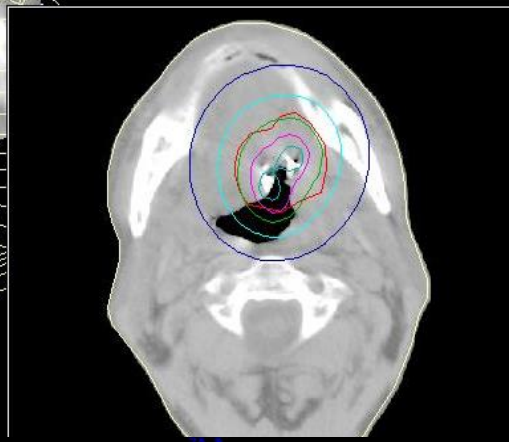


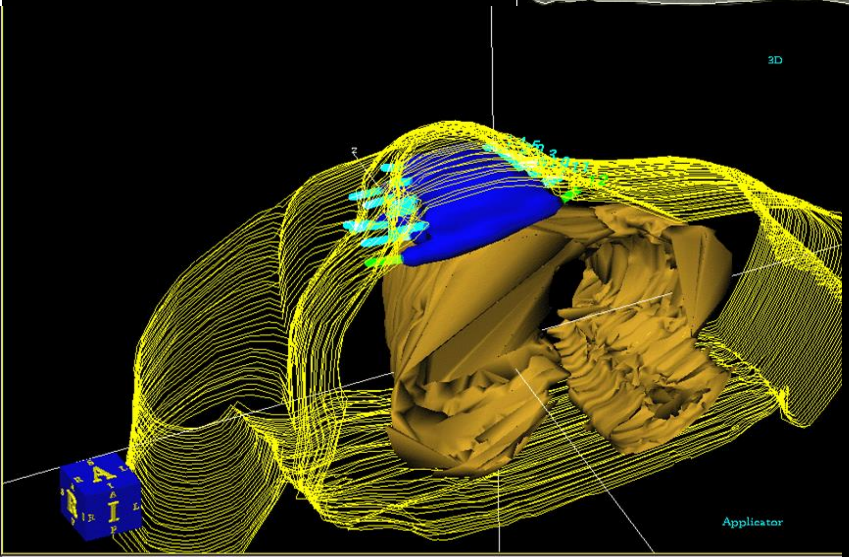


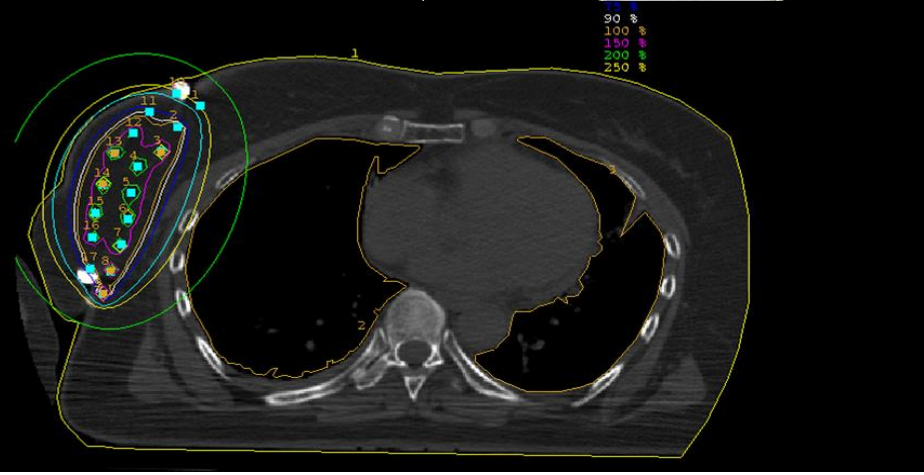
Brachytherapy - IGABT





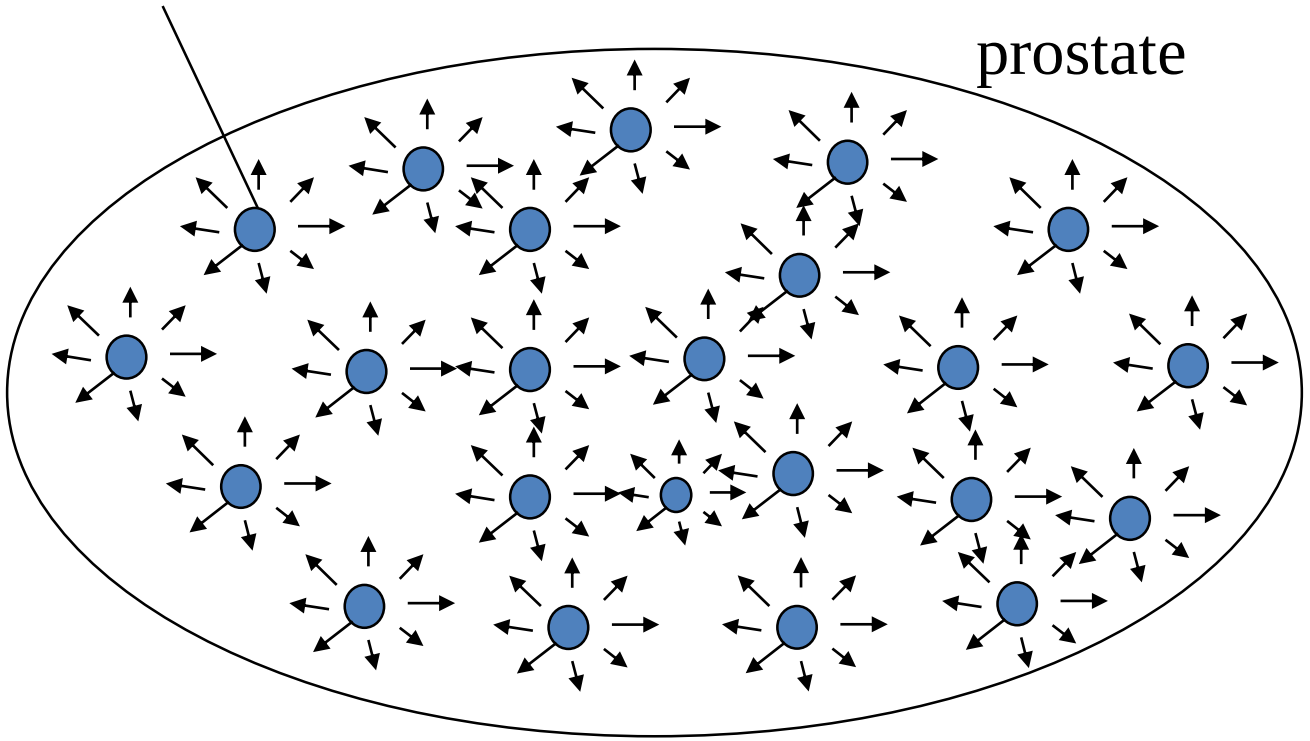


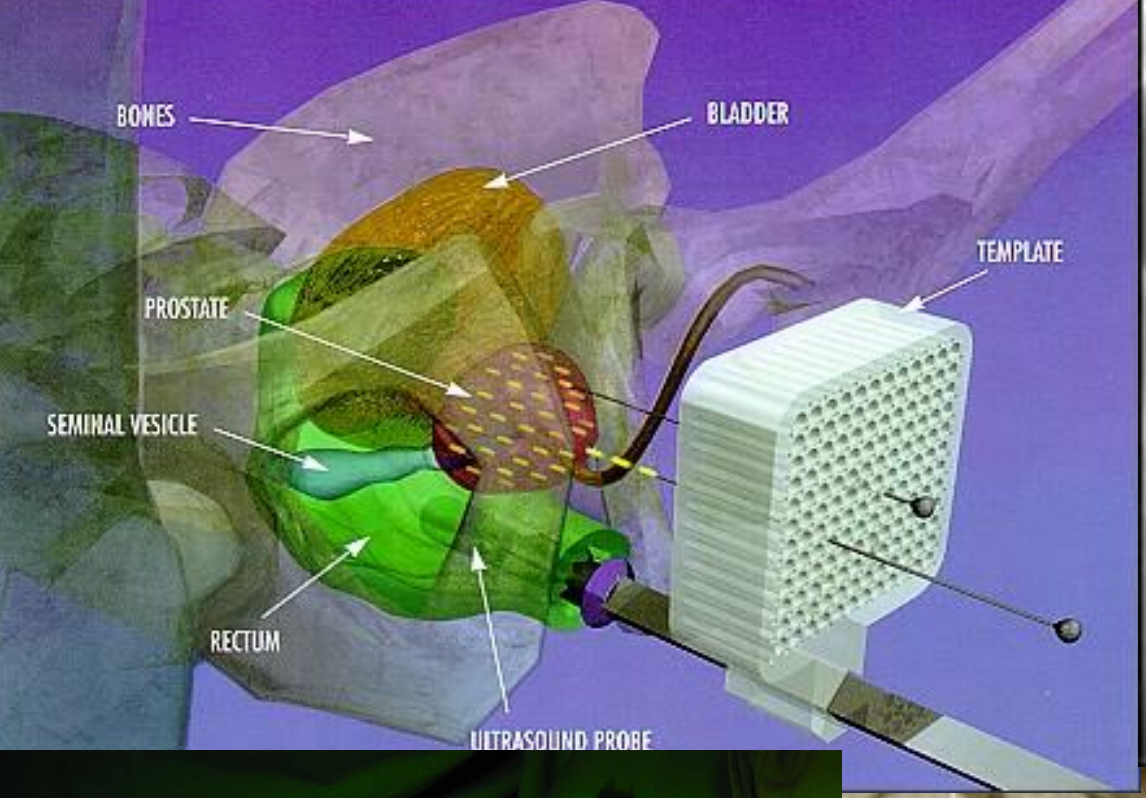


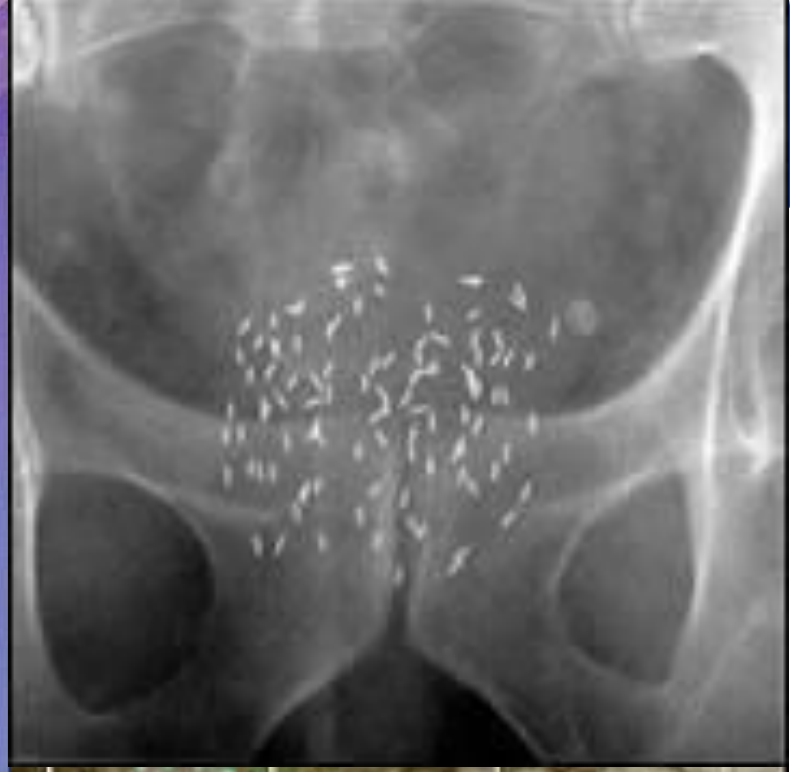


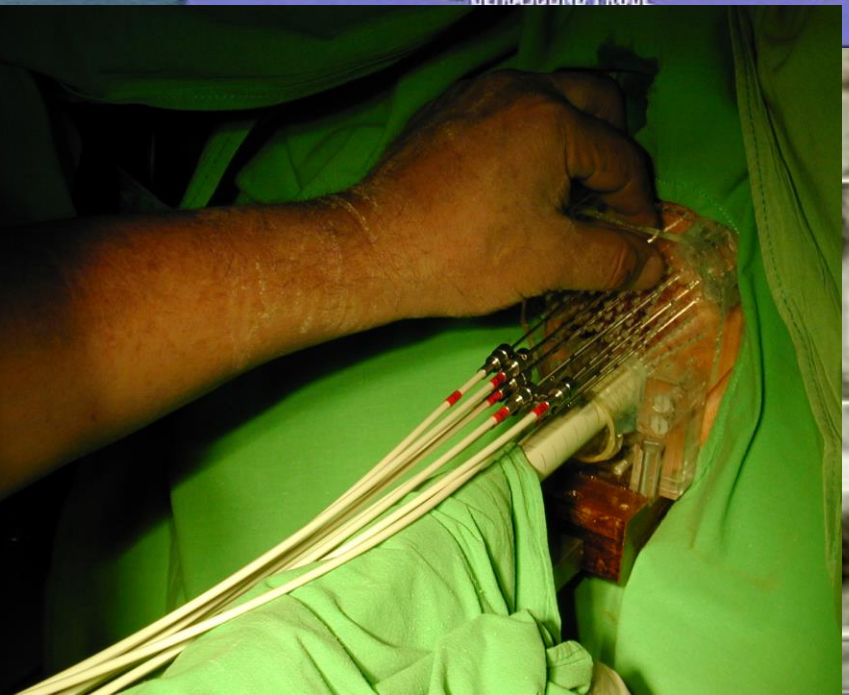
PROSTATE ^{125}IODINE SEED

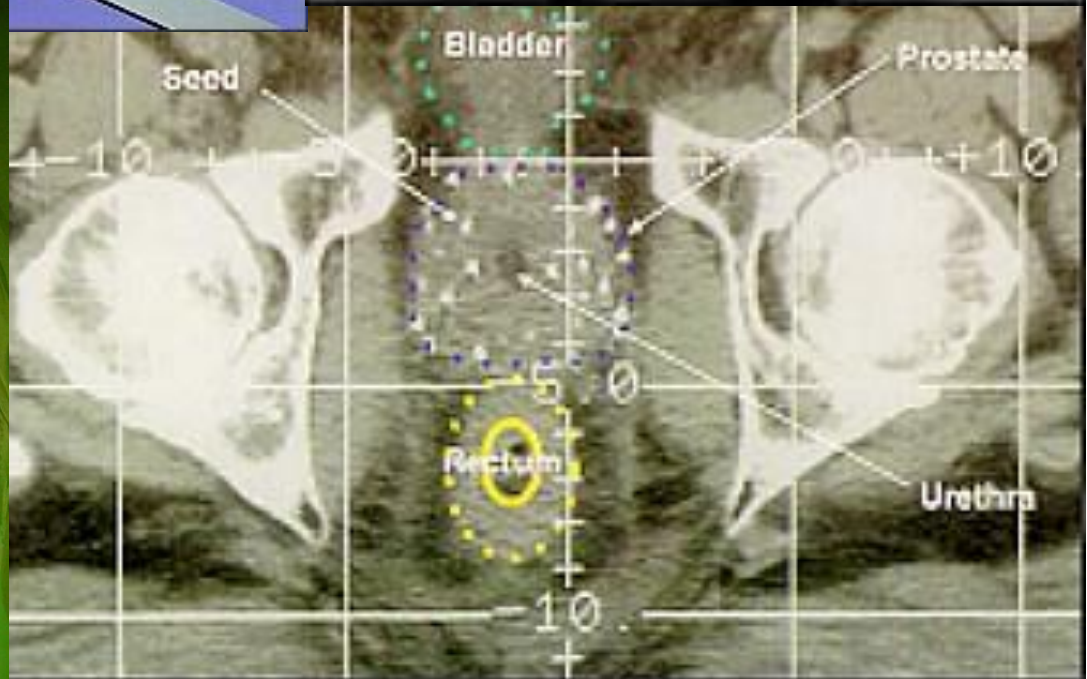
Radioactivev izotóp




BONES
BLADDER
TEMPLATE
PROSTATE
SEMINAL VESICLE
RECTUM
ULTRASOUND PROBE

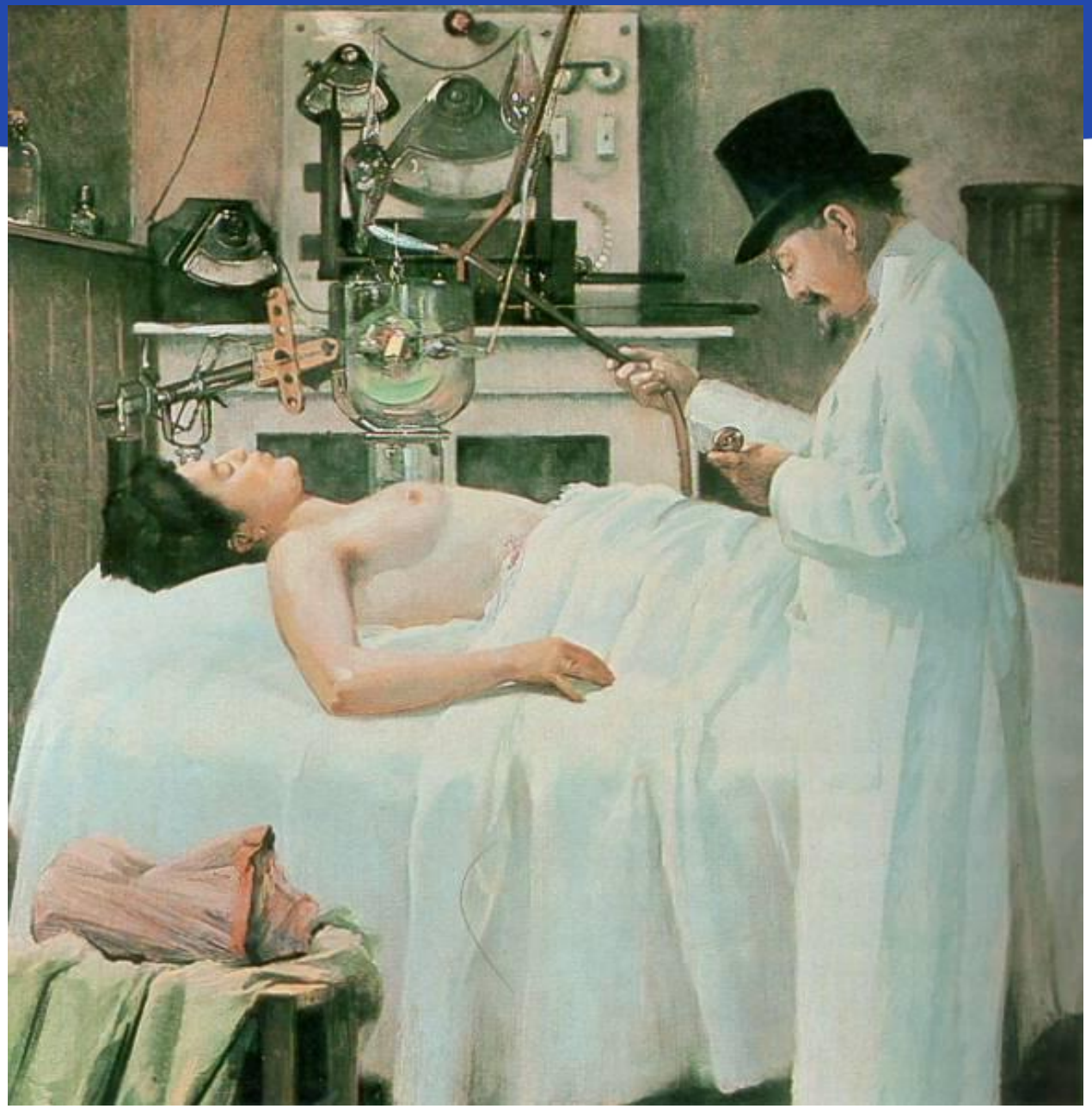





Bladder
Seed
Prostate
Rectum
Urethra

Teletherapy

After 1895



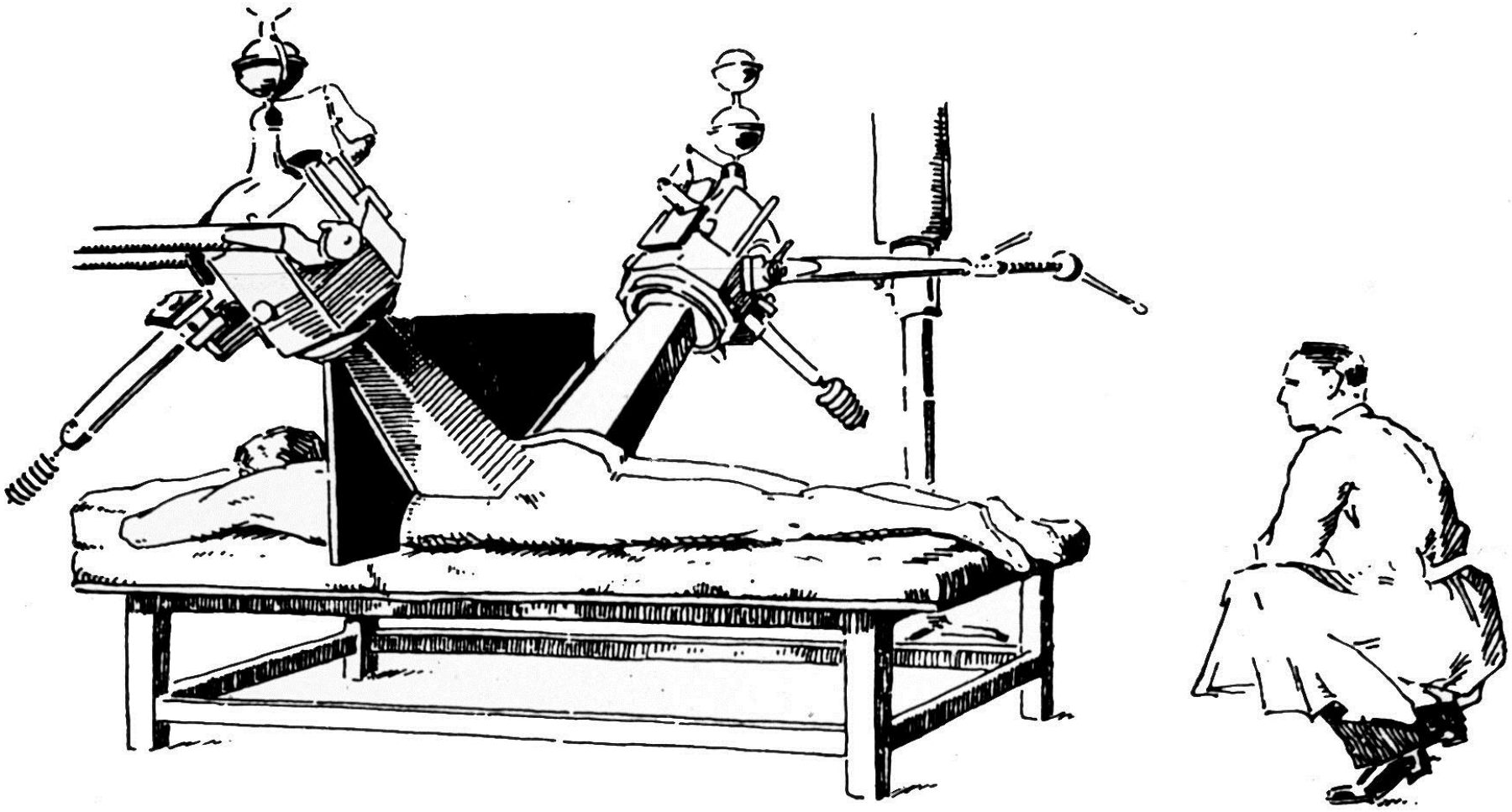
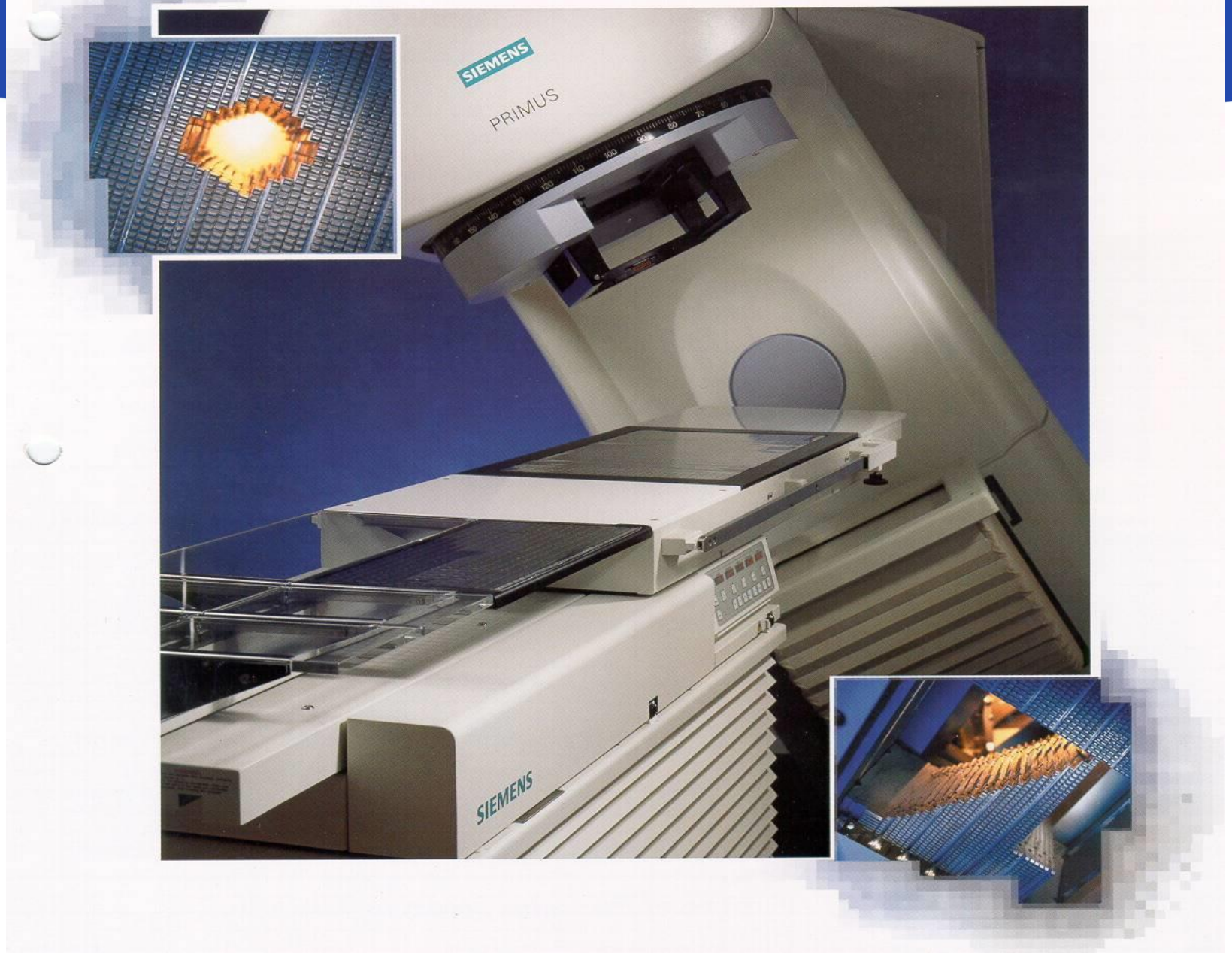


Abb. 51. Einrichten des Einfallswinkels der Strahlenkegel durch Vergleich aus einem entfernten Standpunkt mit den auf der Visierpappe aufgezeichneten Richtungslinien.


SIEMENS
PRIMUS
SIEMENS

Linear accelerators

TRUE Beam

Rapid arc

FFF

Integrated micro-multileaf

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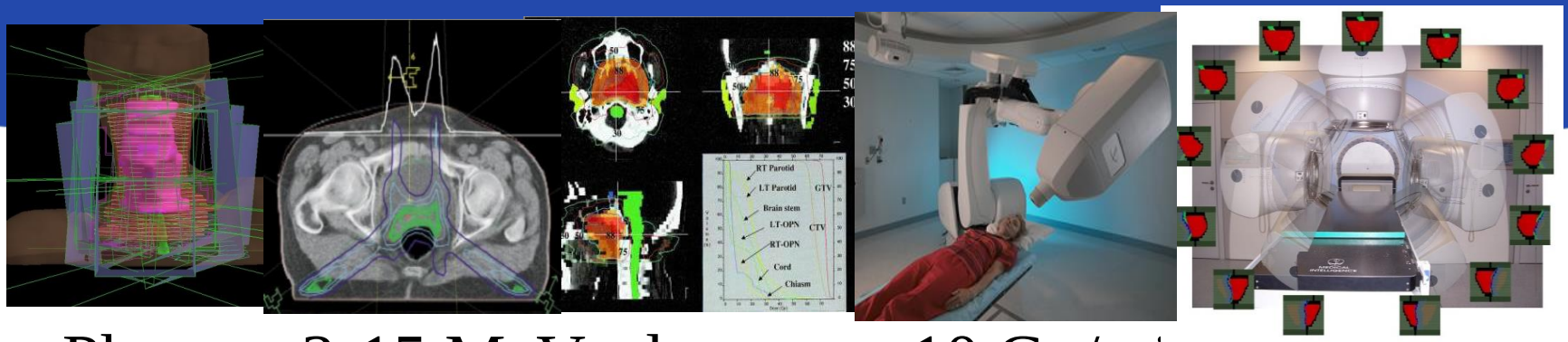
kV – CBCT

IMRT/SRS/SABR

SIB

IGRT/Adaptive RT



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

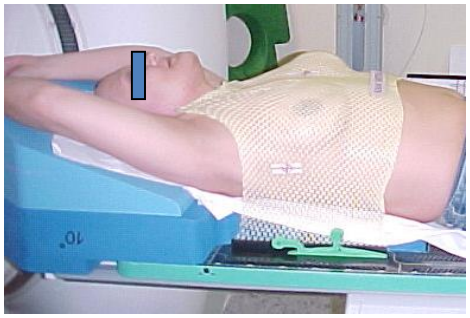
Selectivity, effectivity, accuracy

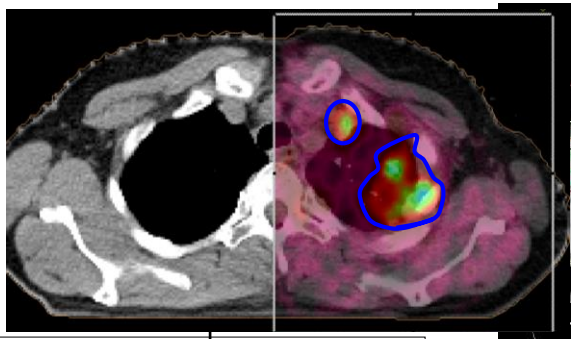
Hadron th.

Procedures

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

PET-CT/MRI





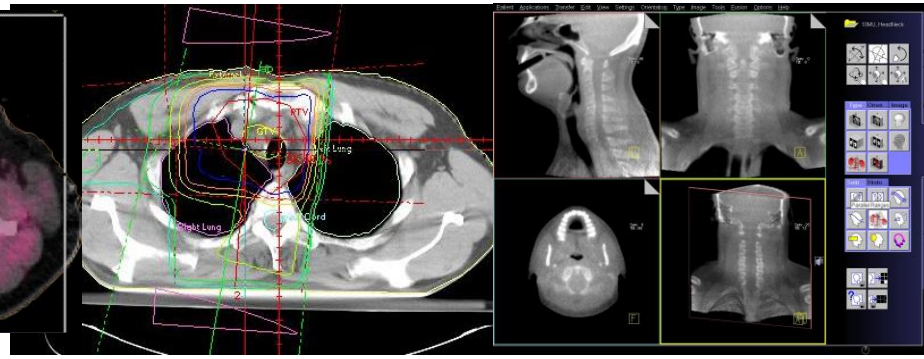
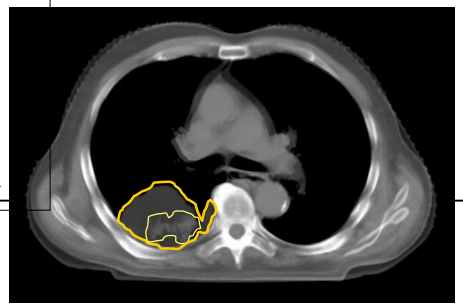
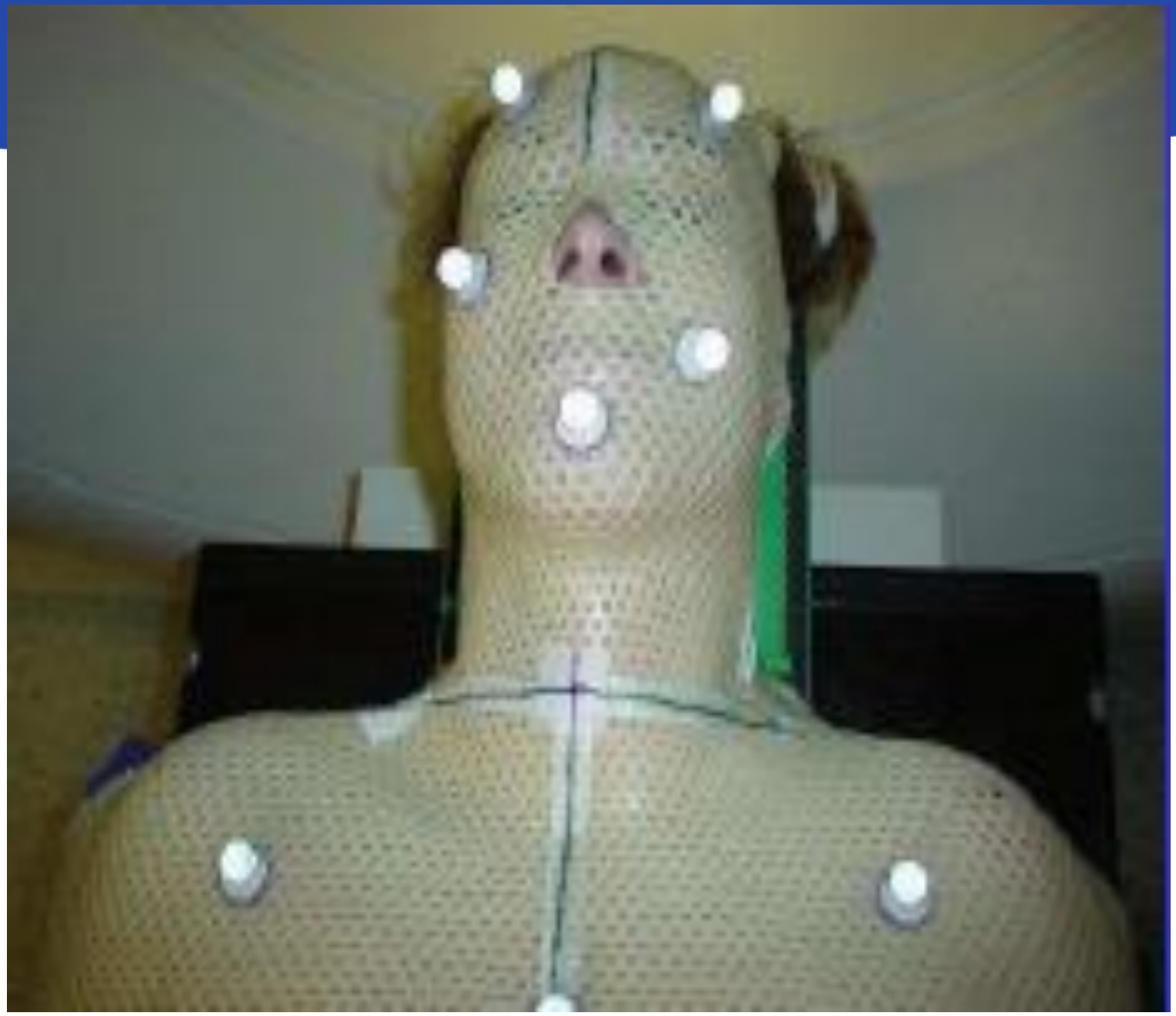
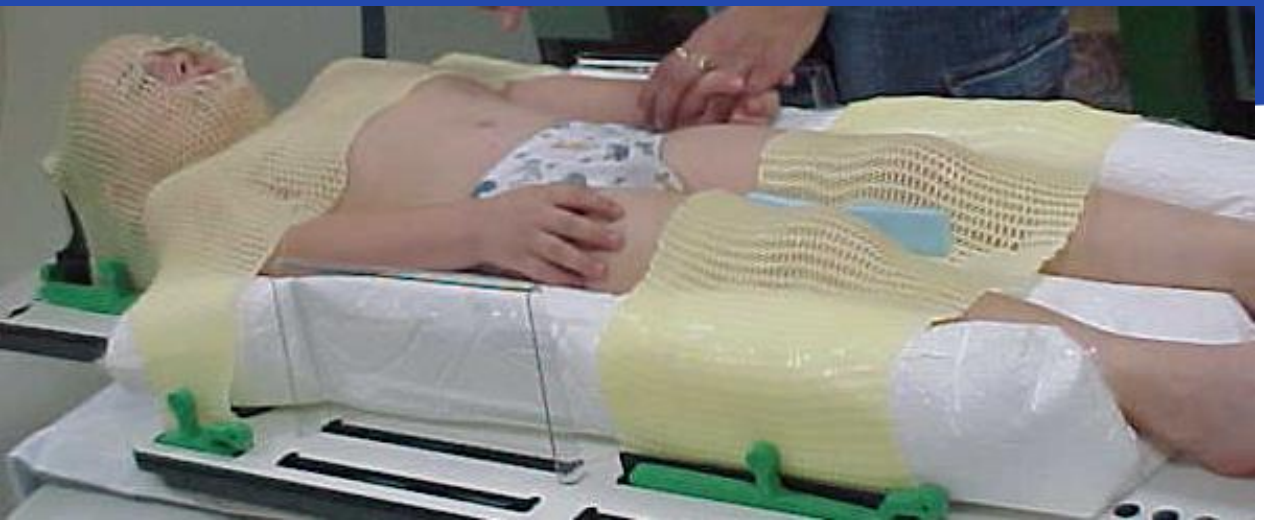


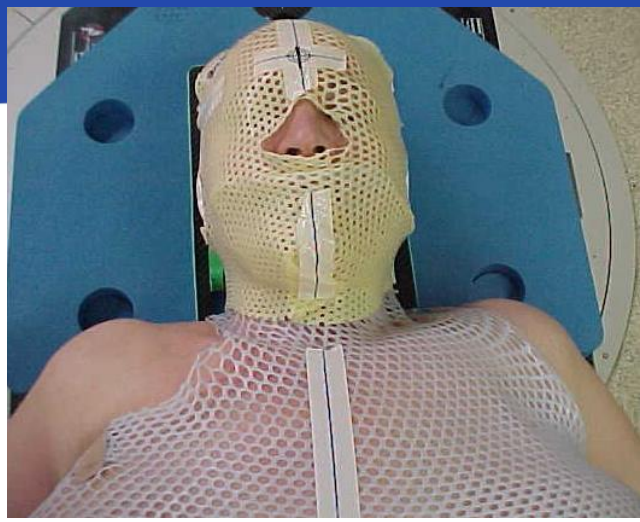
Image fusion
Target, OAR segment.
Dose prescription

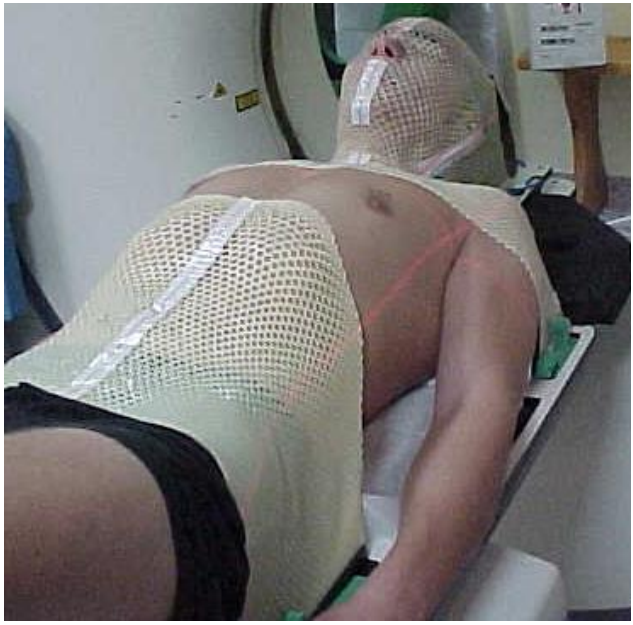


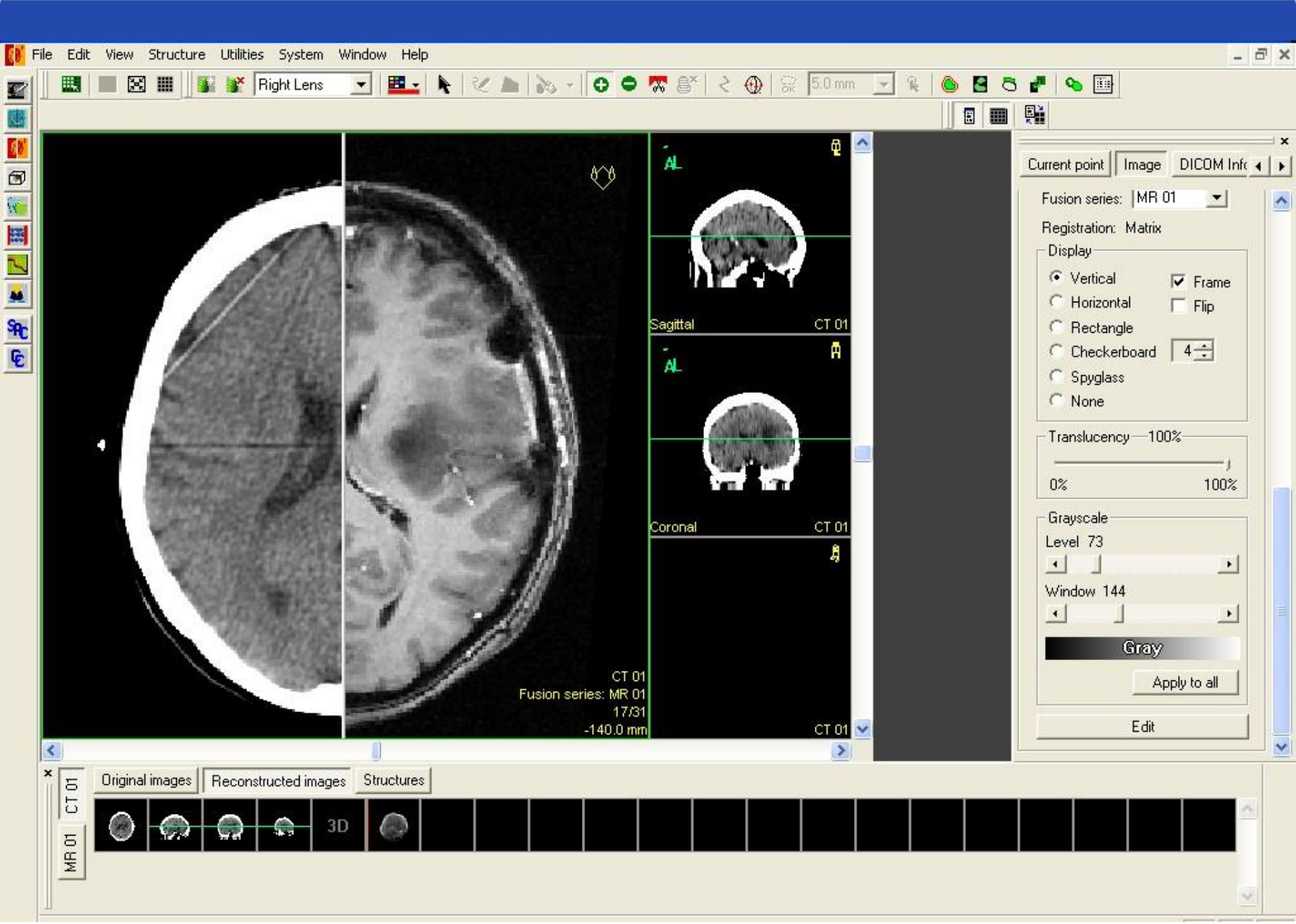
Re-CT- image fusion



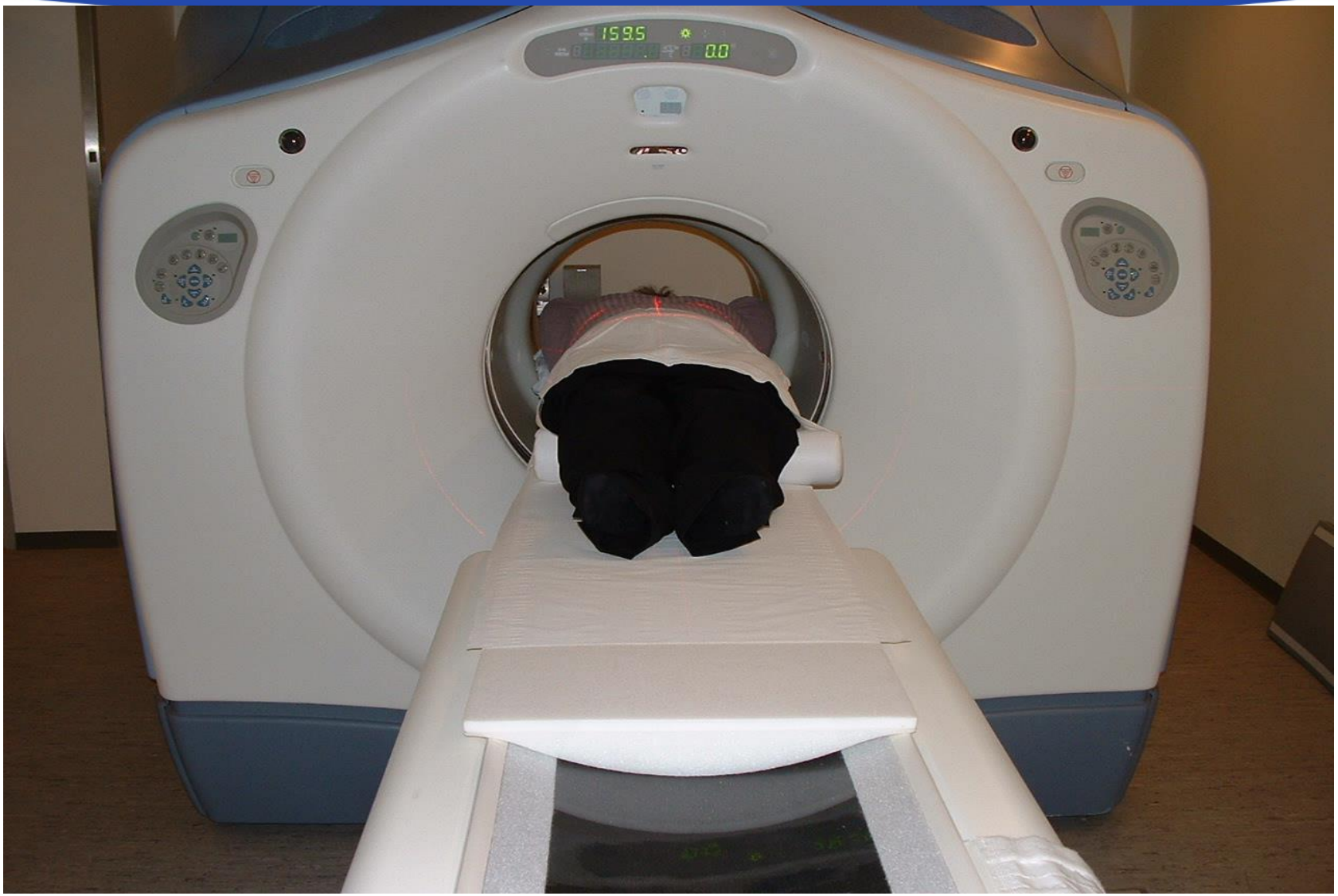




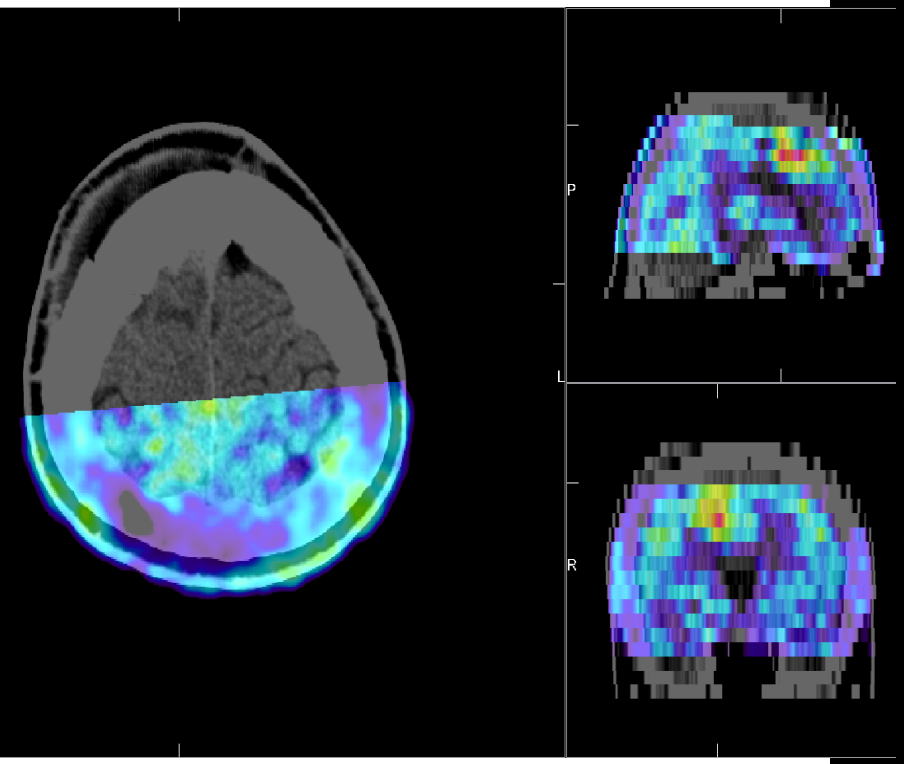


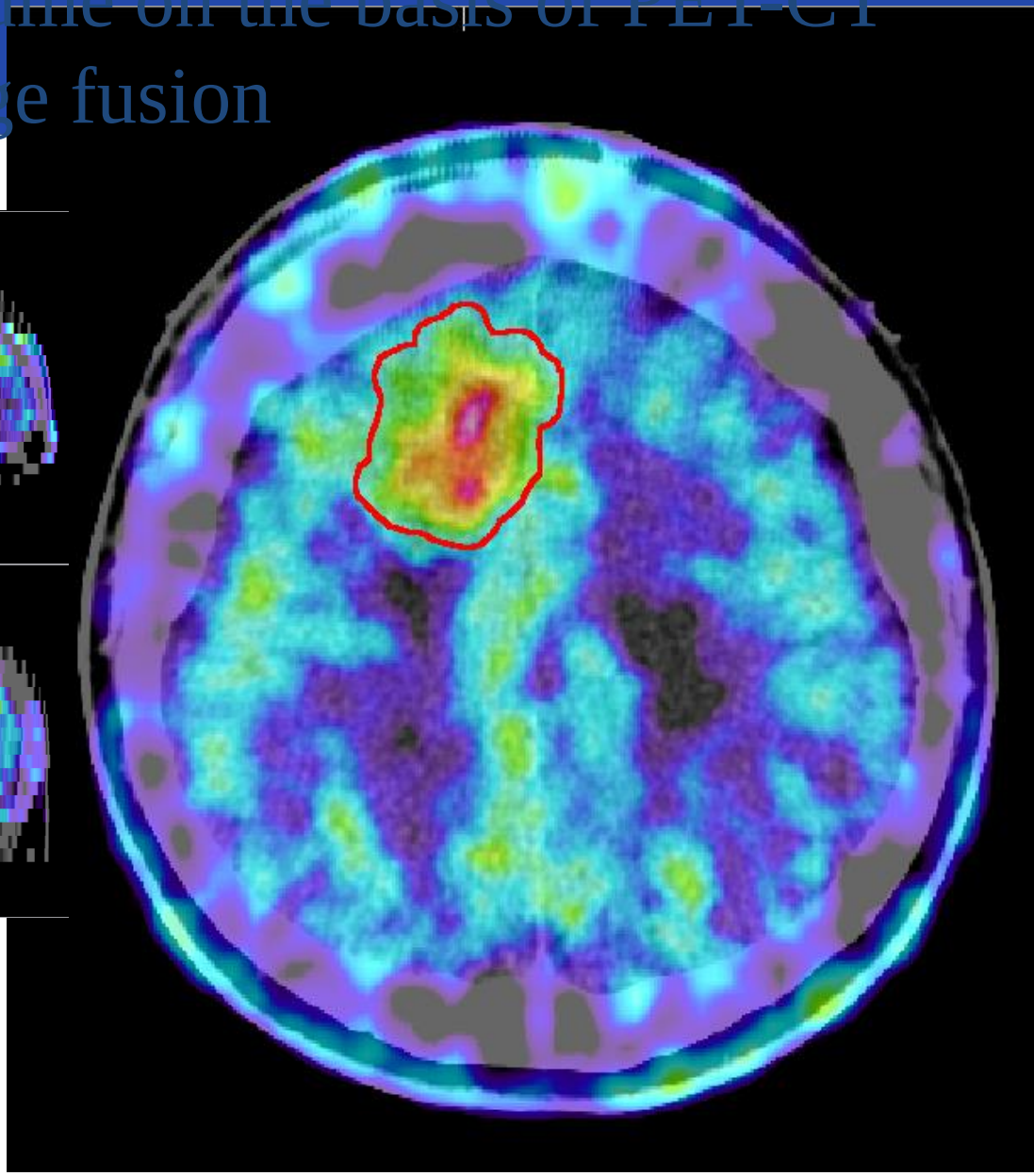

File Edit View Structure Utilities System Window Help
Right Lens
5.0 mm
Sagittal CT 01
Coronal CT 01
CT 01
Fusion series: MR 01
17/31
-140.0 mm
Current point
Image
DICOM Info
Fusion series: MR 01
Registration: Matrix
Display
Vertical
Horizontal
Rectangle
Checkerboard
Spyglass
None
Frame
Flip
4
Translucency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

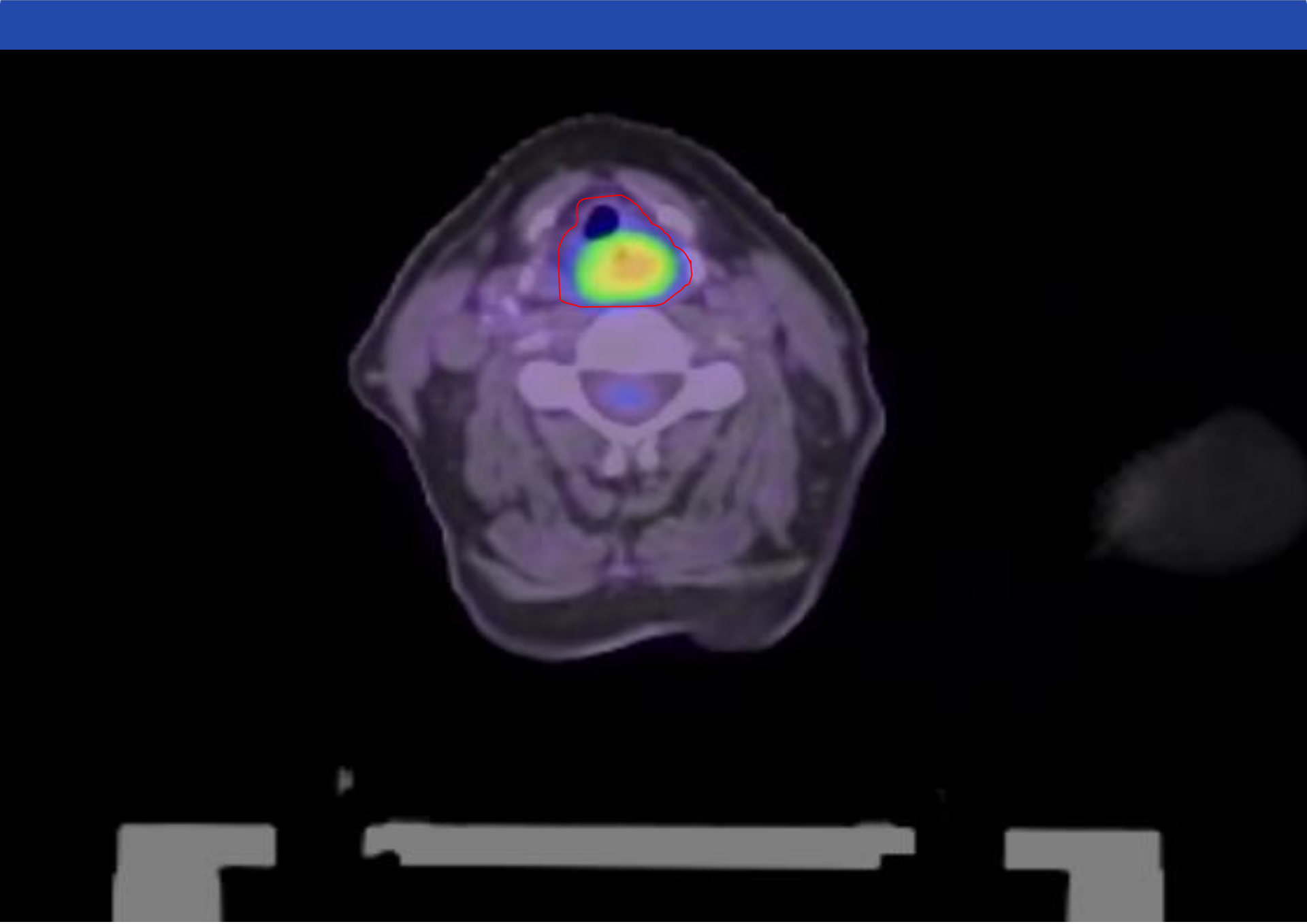
PET/CT

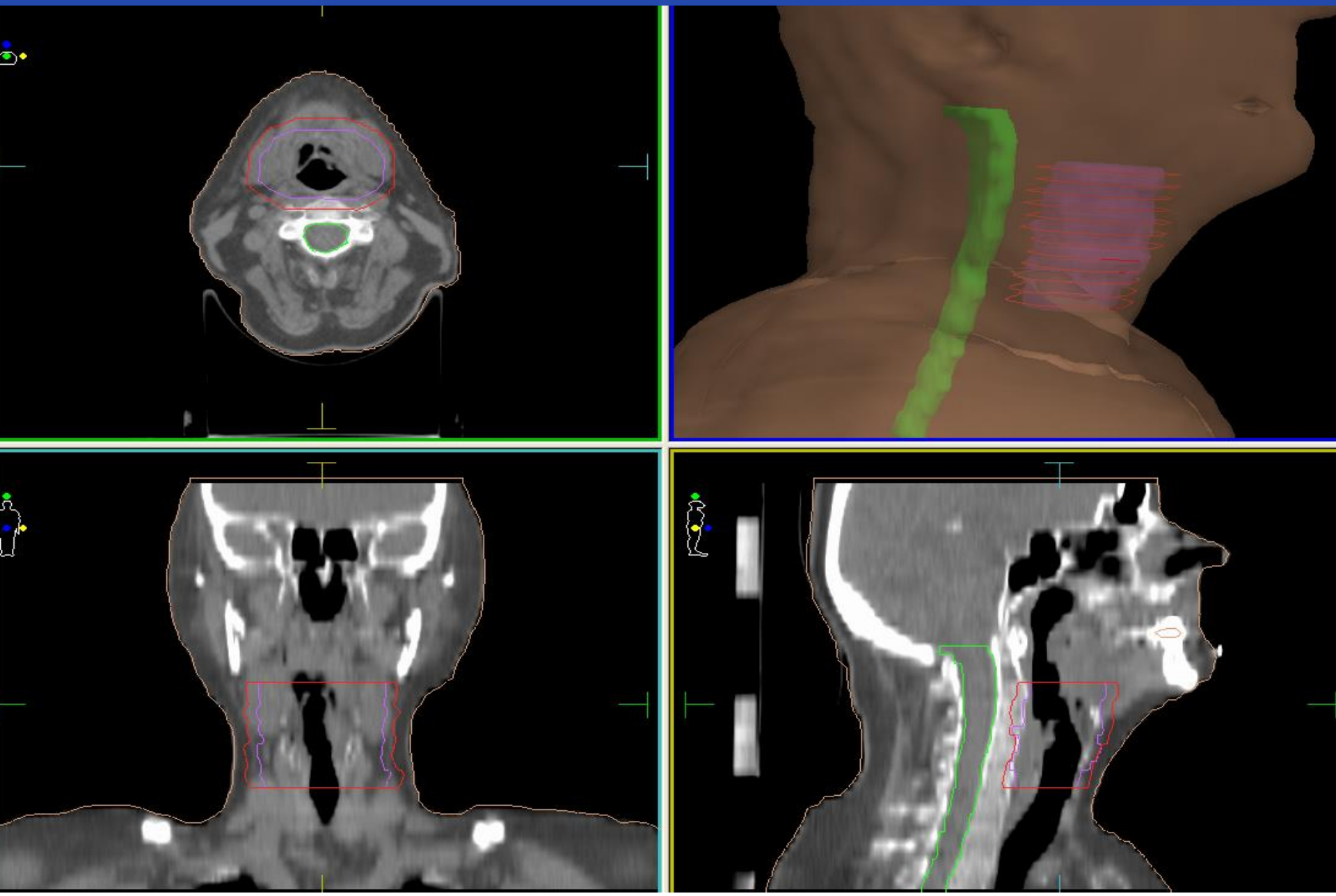


Indication of target volume on the basis of PET-CT image fusion



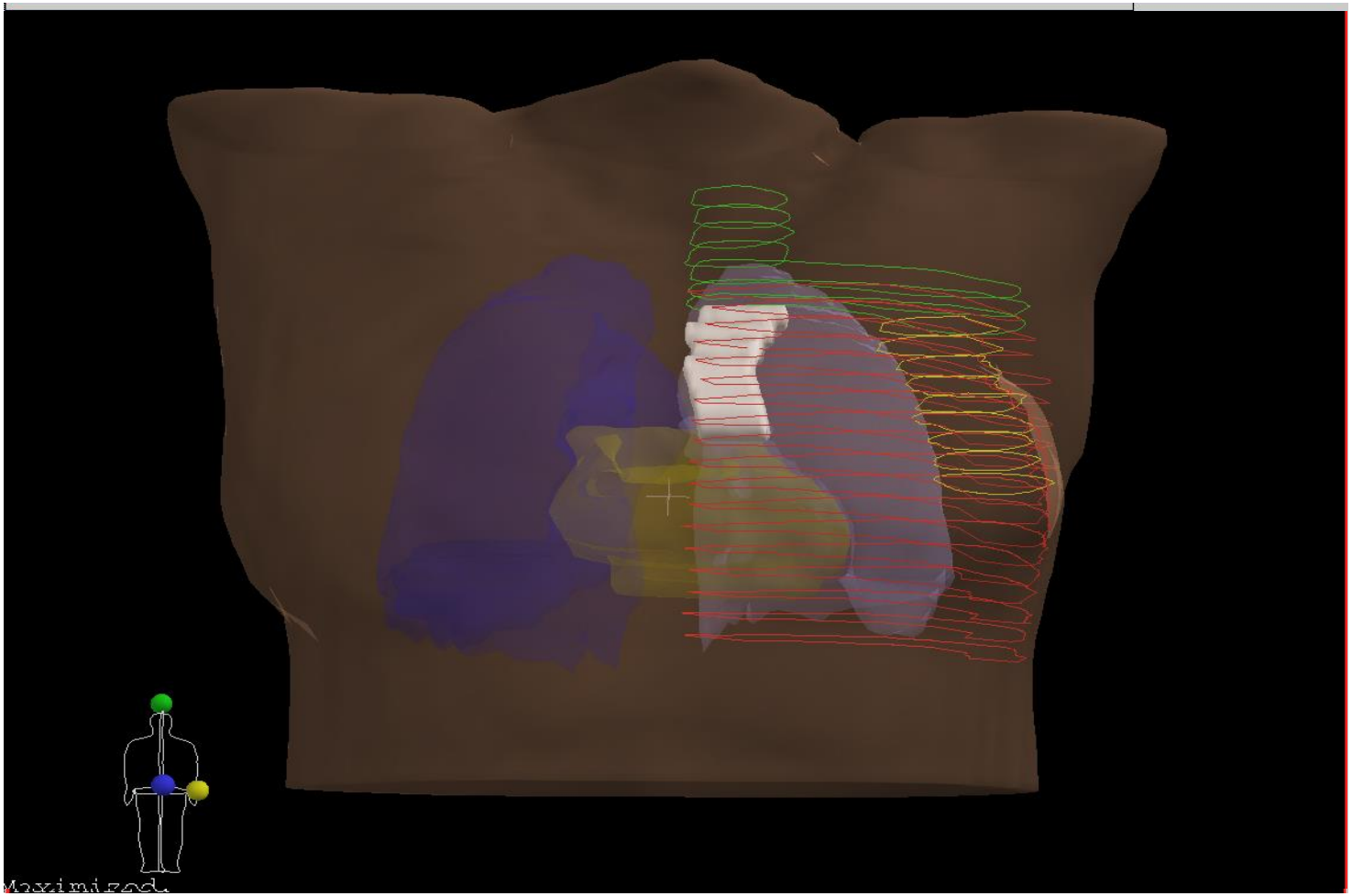






TREATMENT PLANNING

Contouring of target volumes and organs at risk



DOSE PRESCRIPTION - PROTOCOLS

- Target dose , fraction size
- Dose constraints for 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

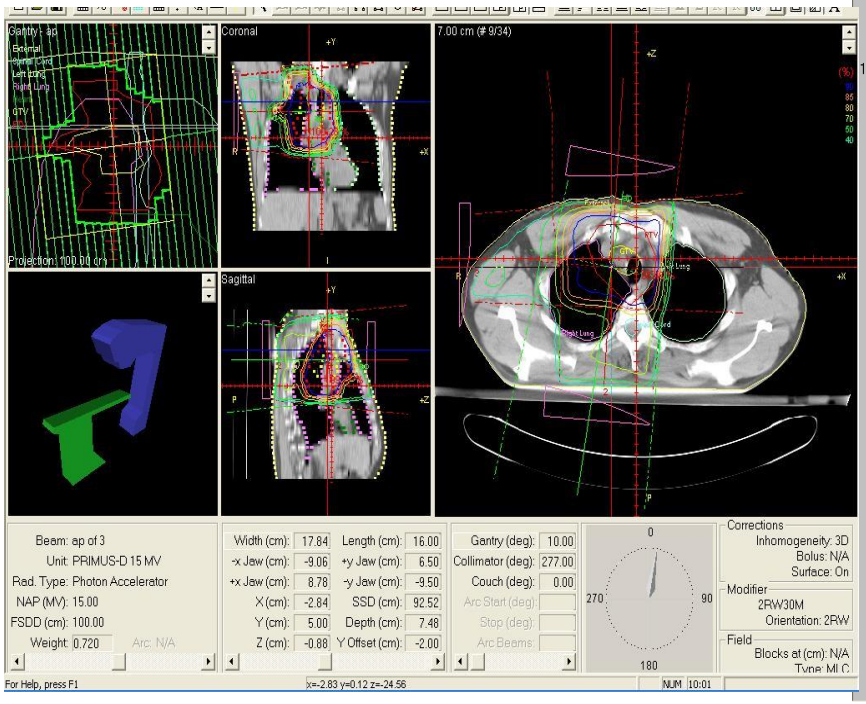
elementary photon beam → interactions → energy transmission and storing (dose kernel (core))

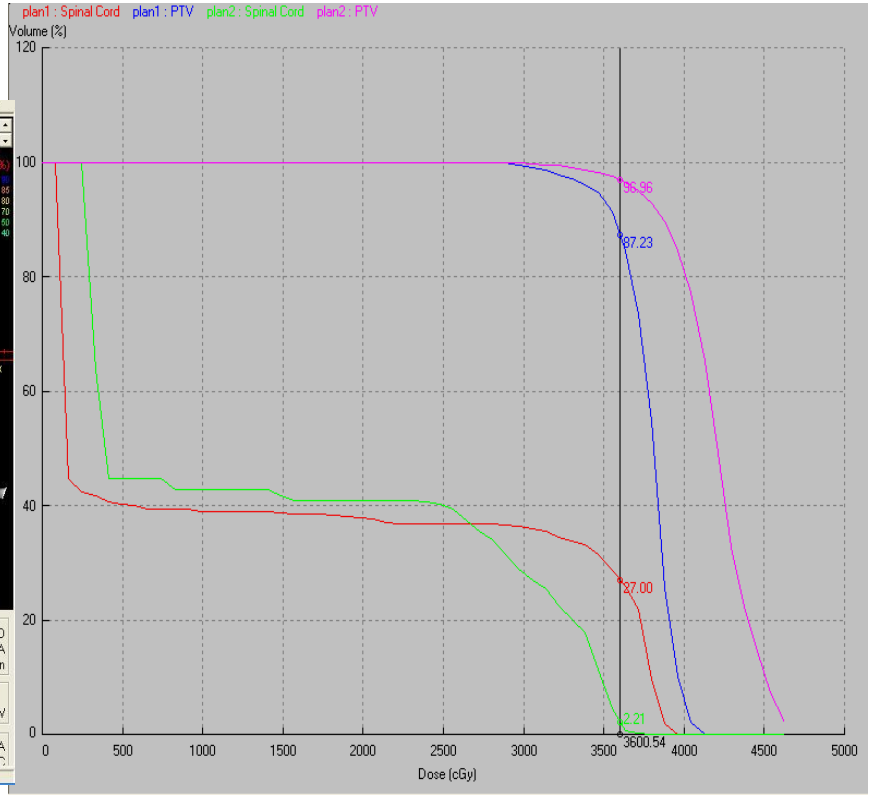
Sum of elementary beams → Sum of dose kernels

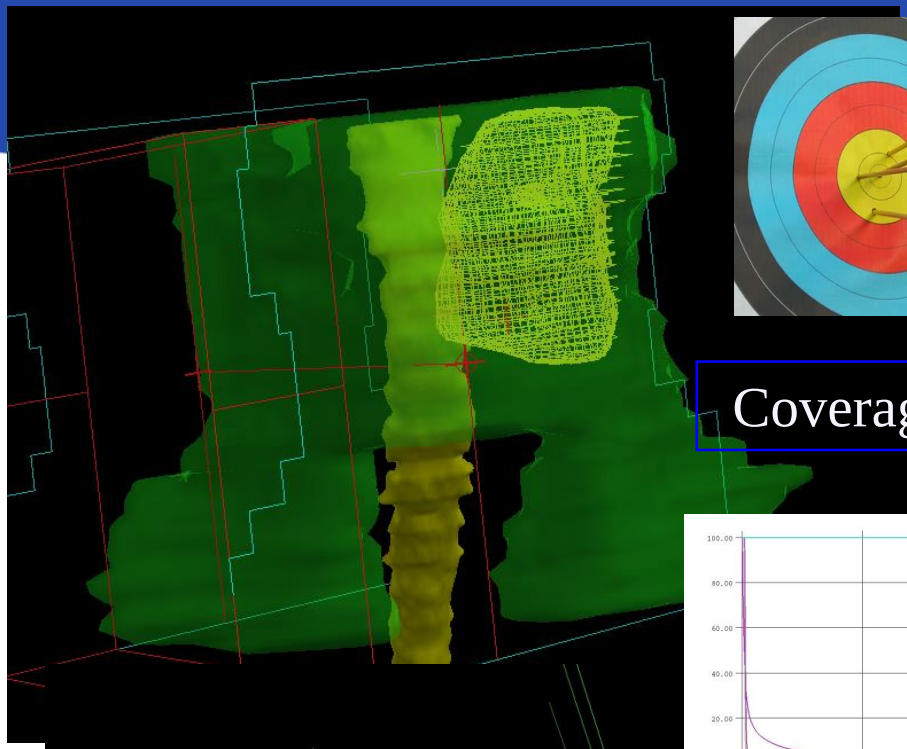
Monte Carlo simulation

Plan evaluation

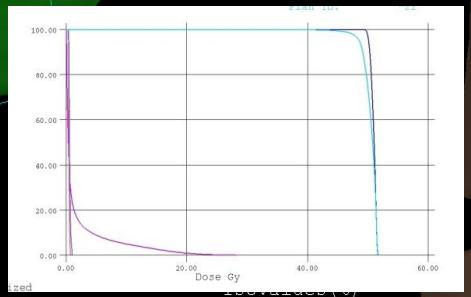
dose distribution - visual and quantitative, DVHs





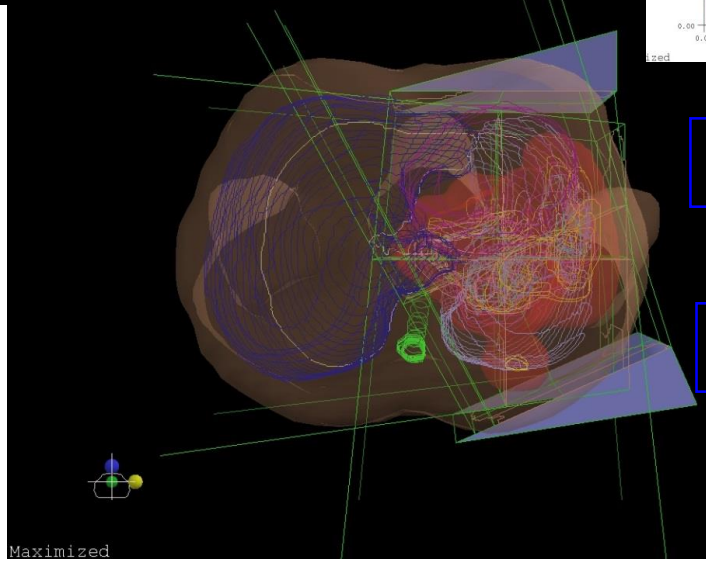


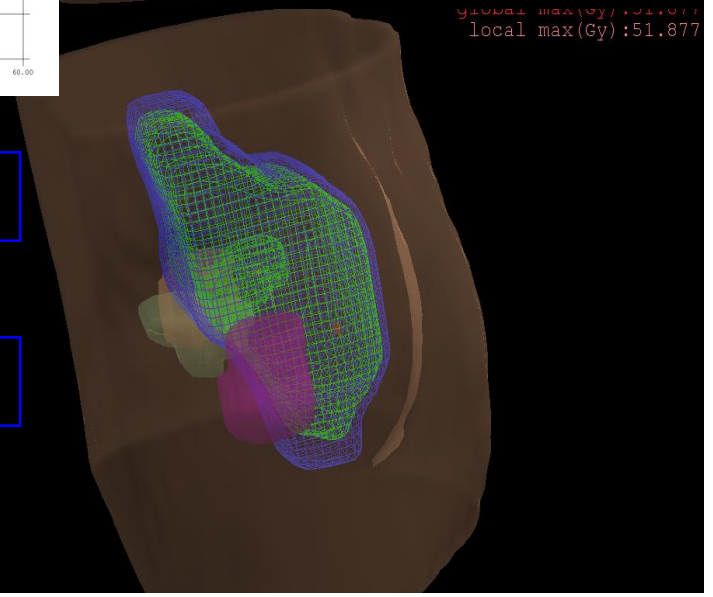
Coverage index

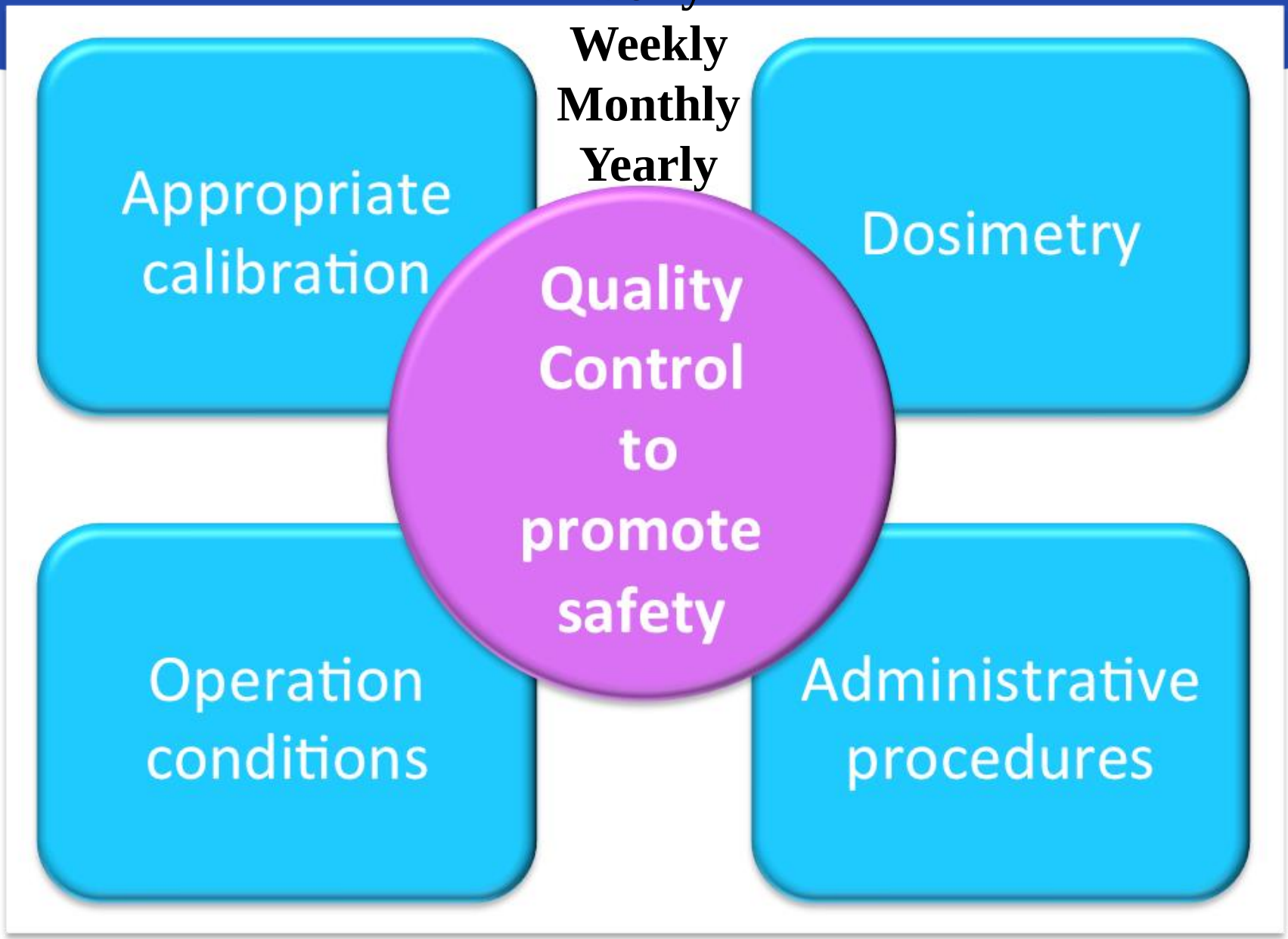


conformity

homogeneity






Daily
Weekly
Monthly
Yearly
Appropriate calibration
Dosimetry
Quality Control to promote safety
Operation conditions
Administrative procedures

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.

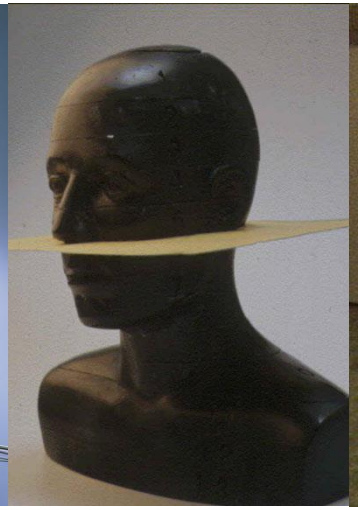
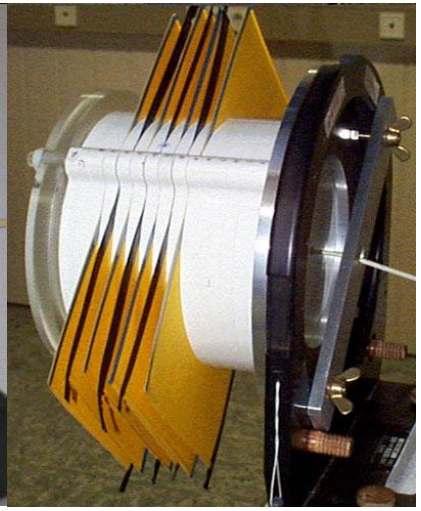
Standard phantoms

Water phantom: TBA (Therapy Beam Analyzer)

Anatomical phantoms: Alderson-Rando phantom

IMRT phantoms



TREATMENT

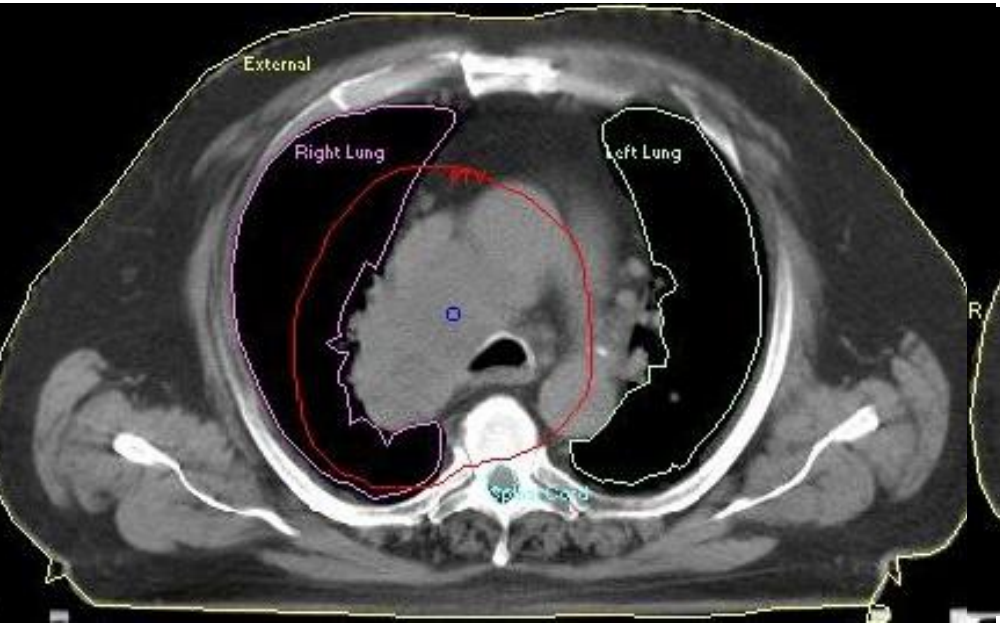
Simulation of the fields

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

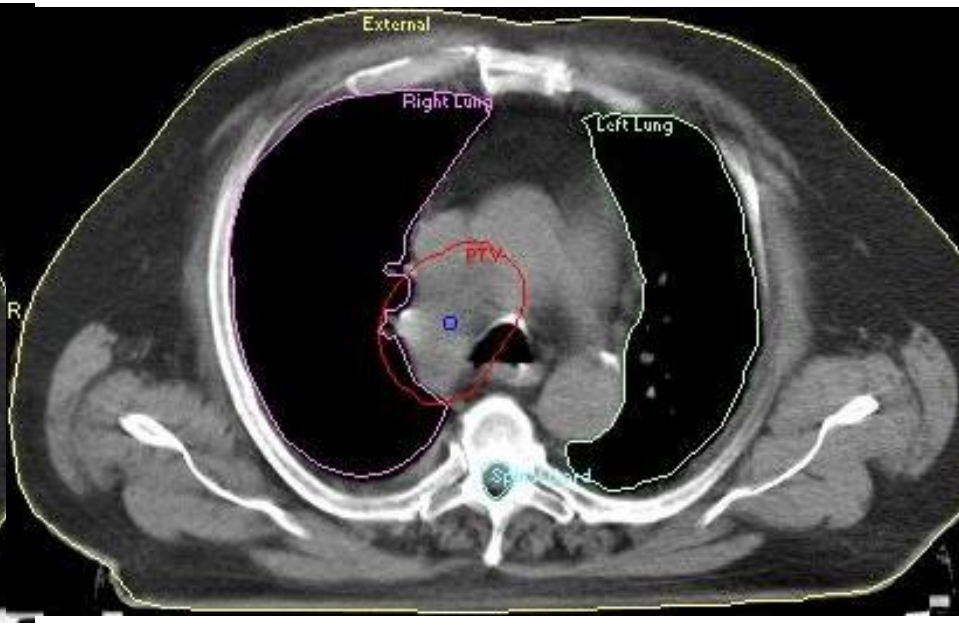
Treatment delivery with regular portal imaging and careful patient care

Adaptation to the changes during RT (repeated imaging)

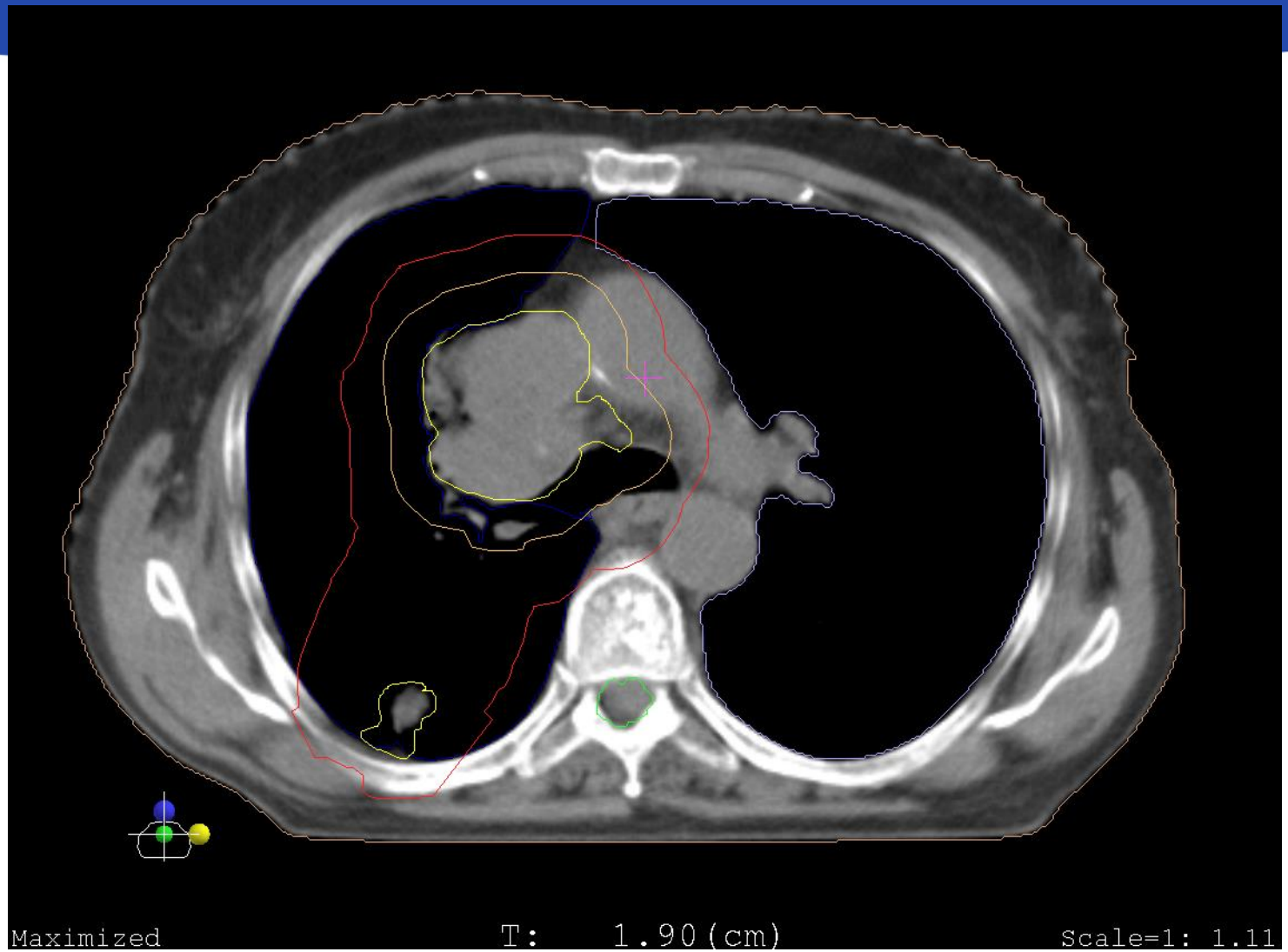
Adaptive radiation



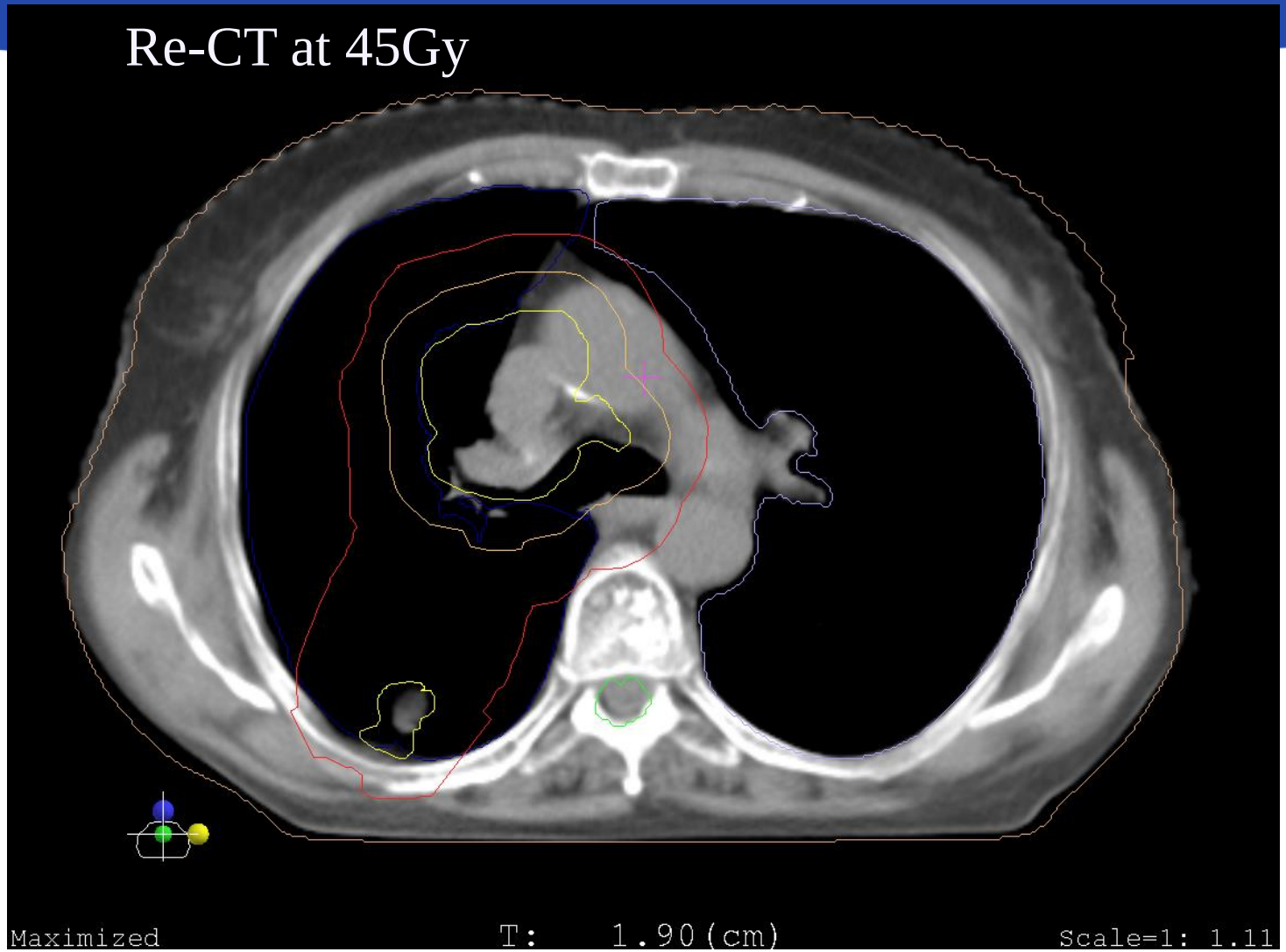
Prior to radiation



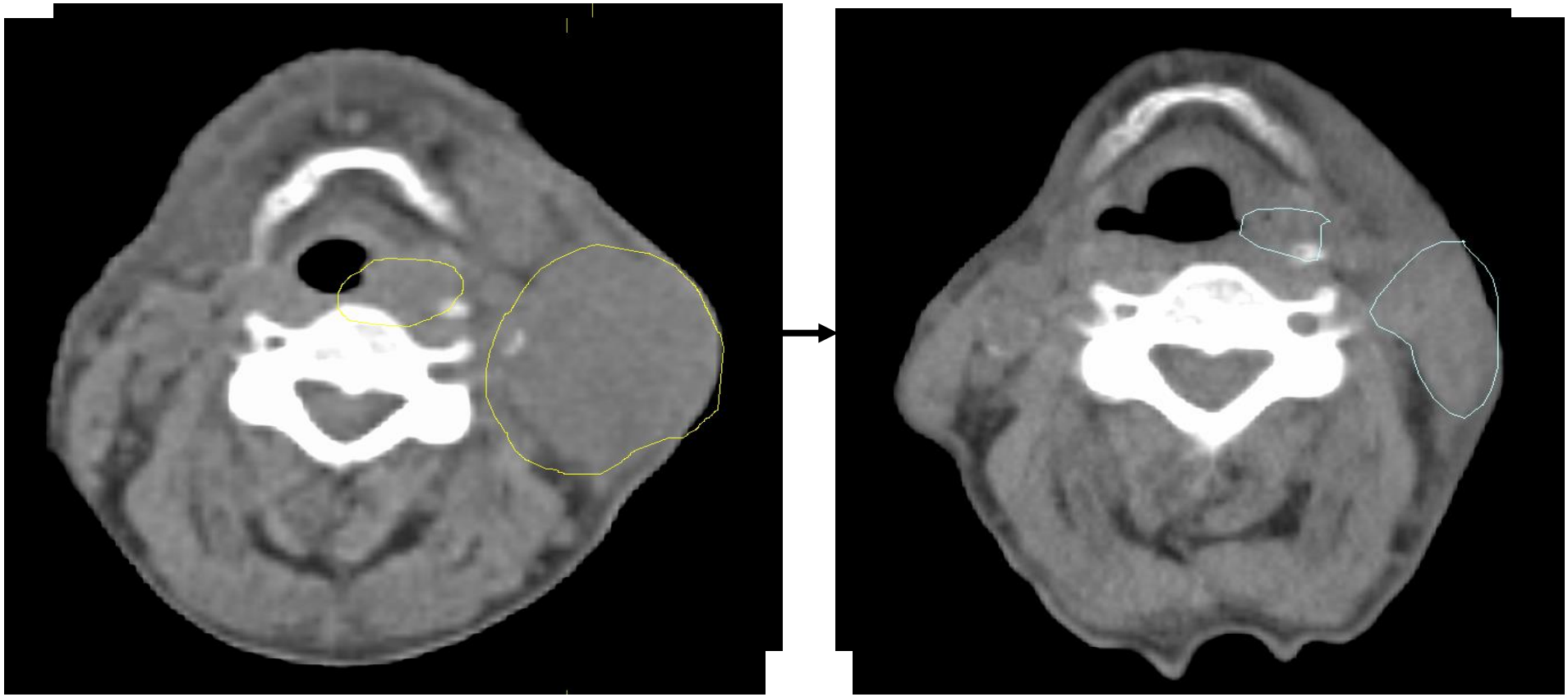
After 40 Gy

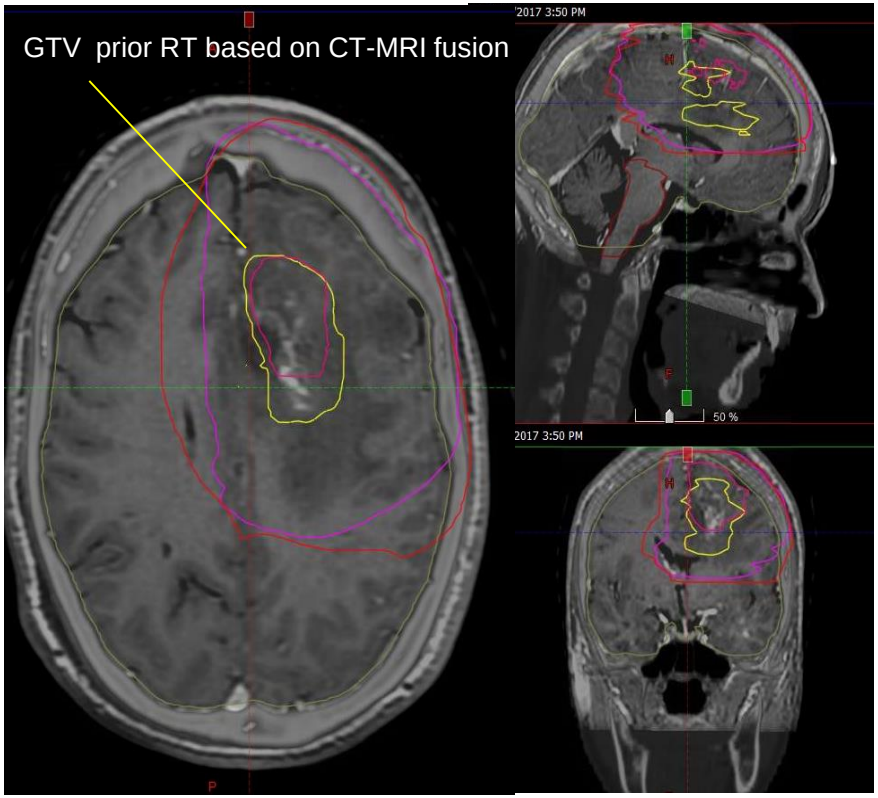

Maximized
T: 1.90(cm)
Scale=1: 1.11

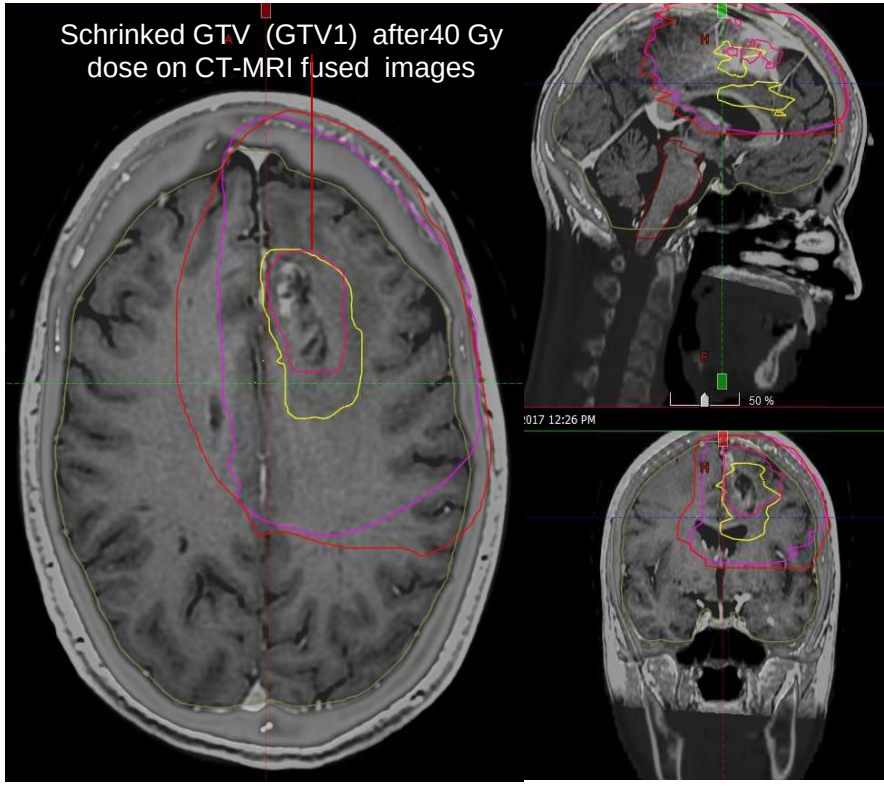
Re-CT at 45Gy

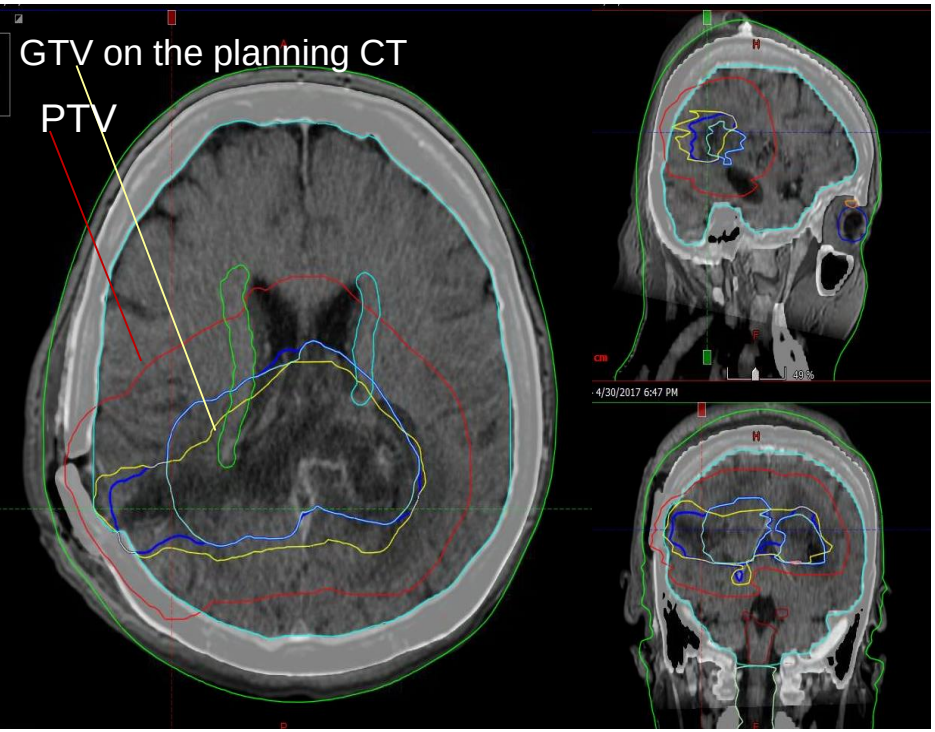


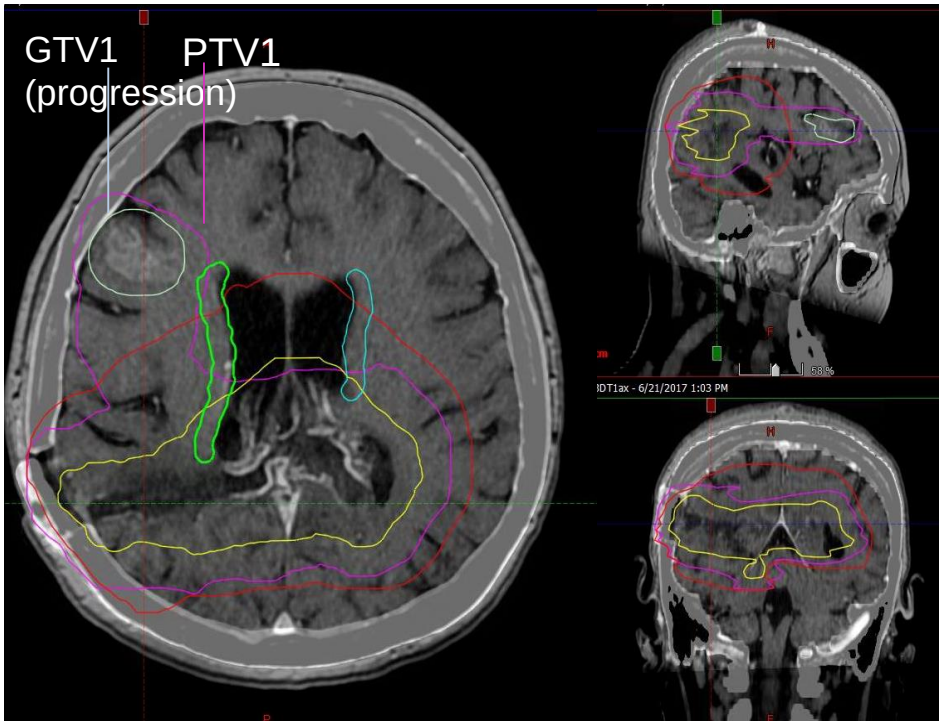
At 50,4 Gy CRT → tumor volume decrease **av. 39%**




GTV prior RT based on CT-MRI fusion
2017 3:50 PM
50 %
2017 3:50 PM


Schrinked GTV (GTV1) after40 Gy
dose on CT-MRI fused images
50 %
:017 12:26 PM


GTV on the planning CT
PTV


GTV1
(progression)
PTV1

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 care

Evaluation of the results- transparency

Nuclear particles

High physical selectivity

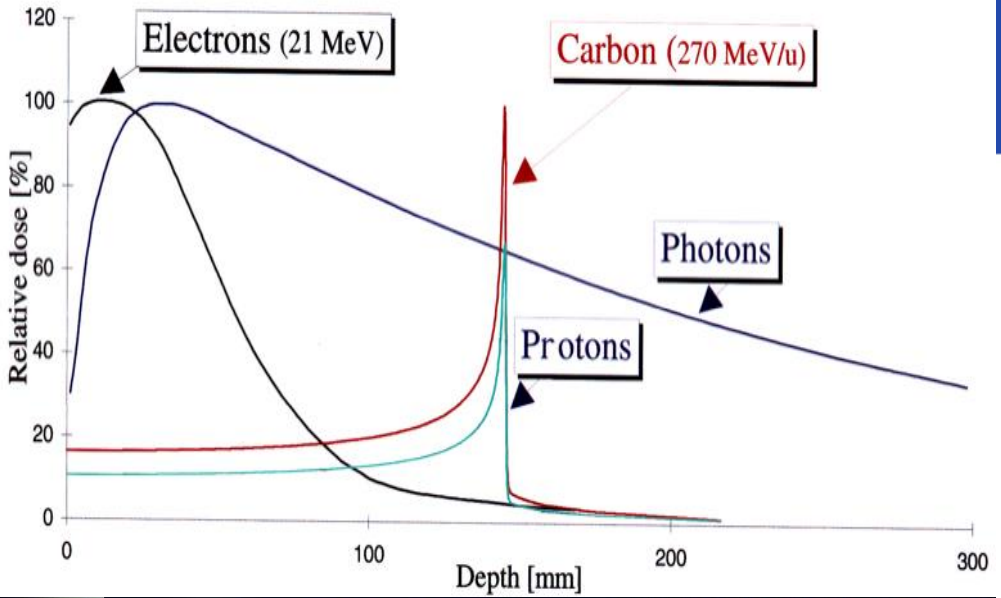
High LET
high RBE

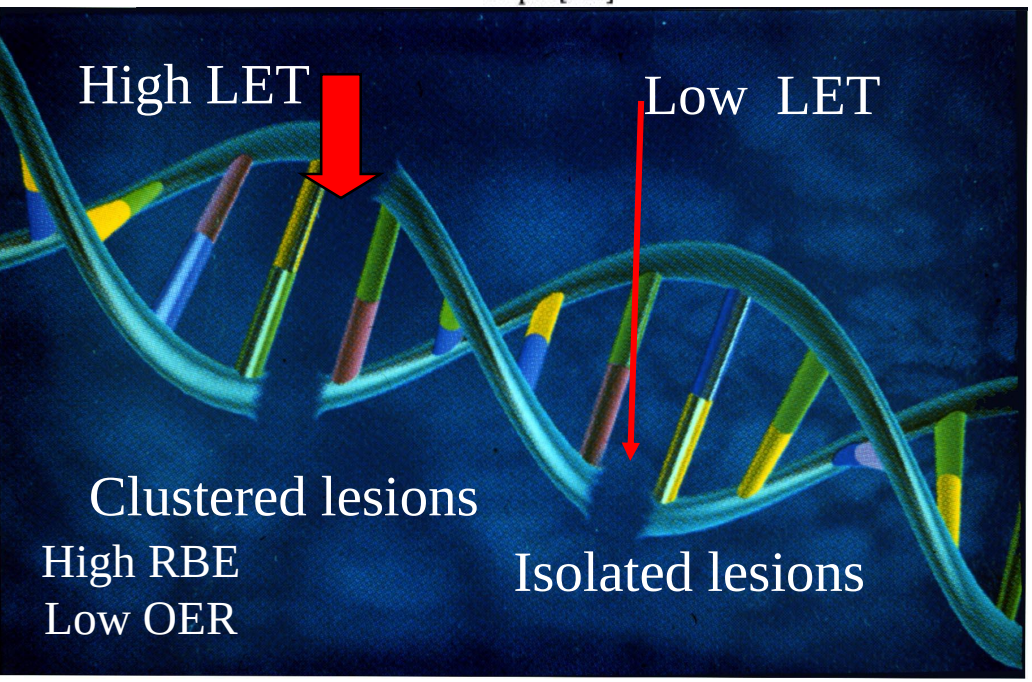
Proton
π-Meson

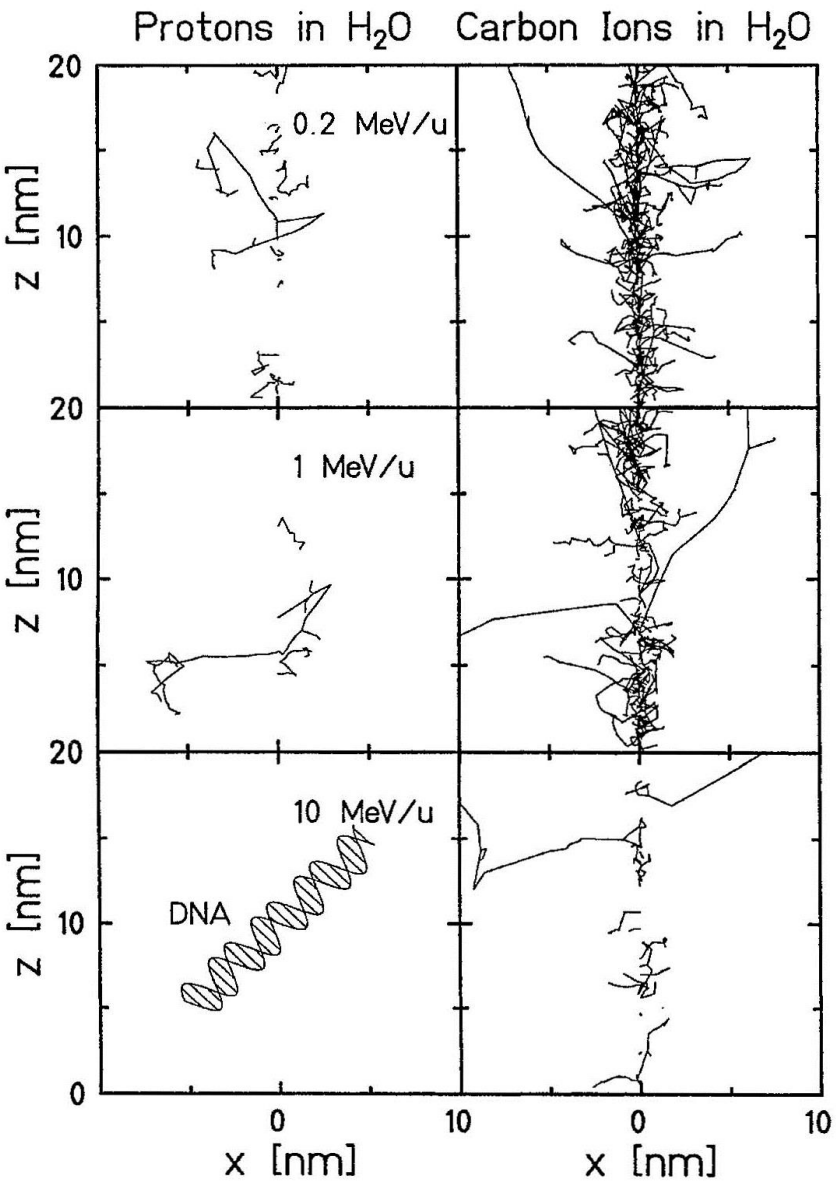
Fast neutron

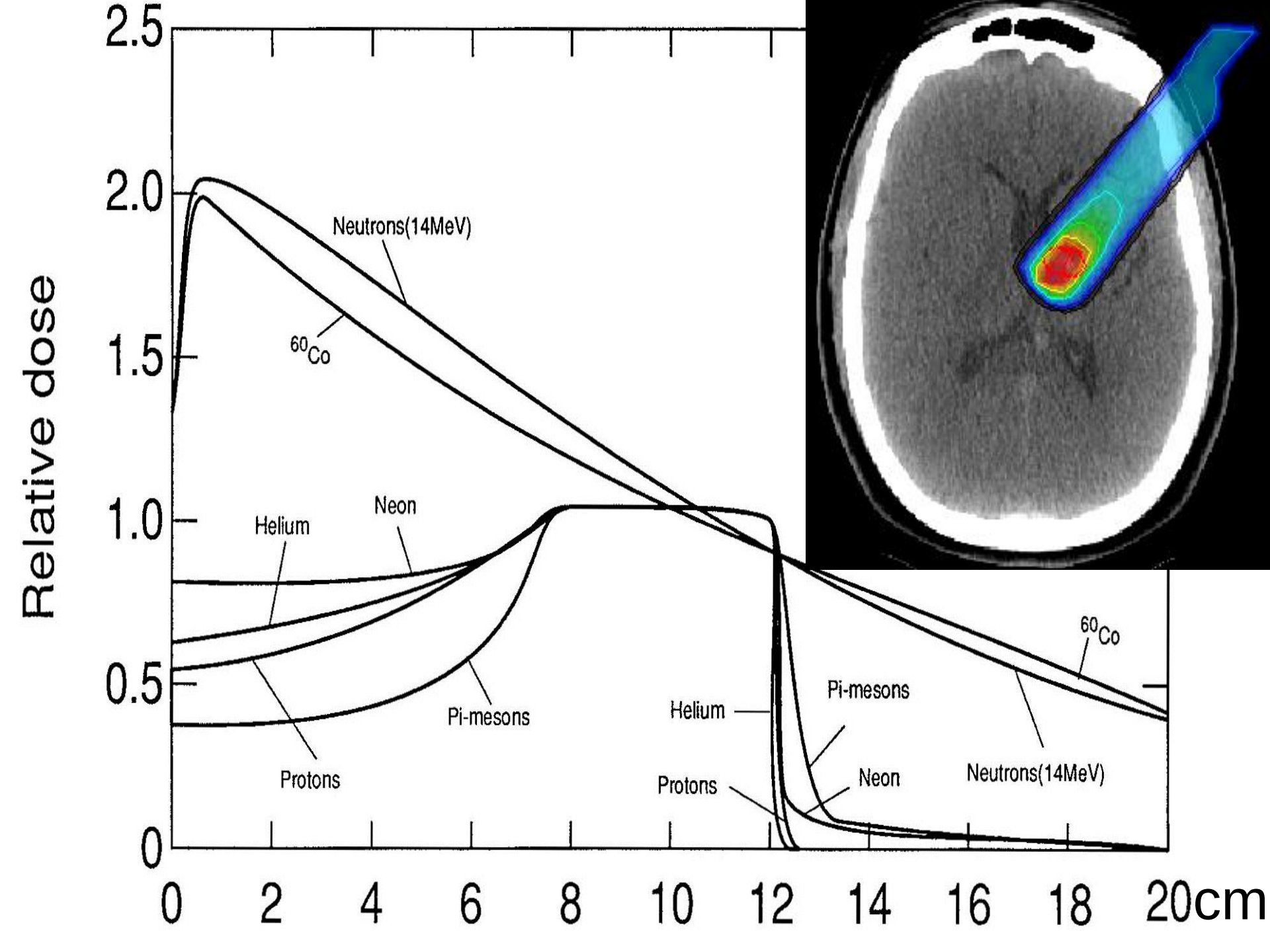
α-particle

heavy ions:
Carbon, Oxigen, Neon


Electrons (21 MeV)
Carbon (270 MeV/u)
Photons
Protons
Relative dose [%]
Depth [mm]
120
100
80
60
40
20
0
0
100
200
300

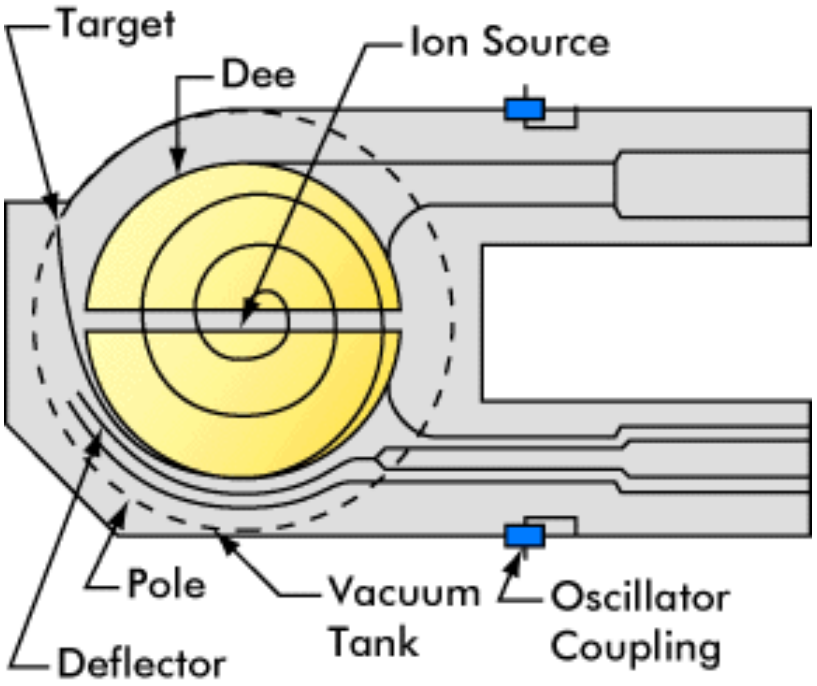

High LET
Low LET
Clustered lesions
High RBE
Low OER
Isolated lesions


Protons in H_2O
Carbon Ions in H_2O
0.2 MeV/u
1 MeV/u
10 MeV/u
DNA
z [nm]
x [nm]
20
10
0
10


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

CYCLOTRON

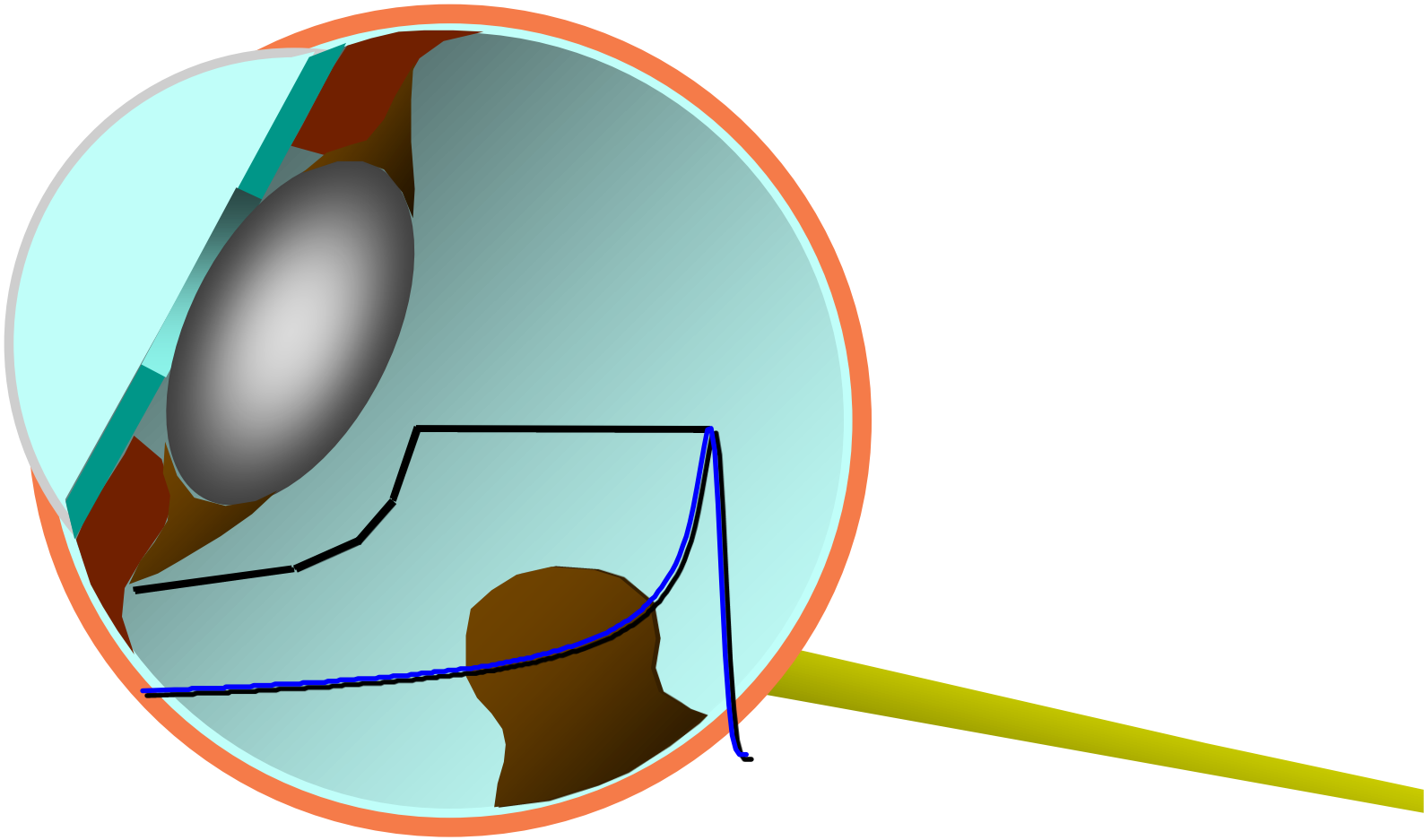
1929	Lawrence, inspired by Wideröe and Ising, conceives the cyclotron.
1931	Livingston demonstrates the cyclotron by accelerating hydrogen ions to 80 keV.
1932	Lawrence's cyclotron produces 1.25 MeV protons and he also splits the atom just a few weeks after Cockcroft and Walton (Lawrence received the Nobel Prize in 1939).

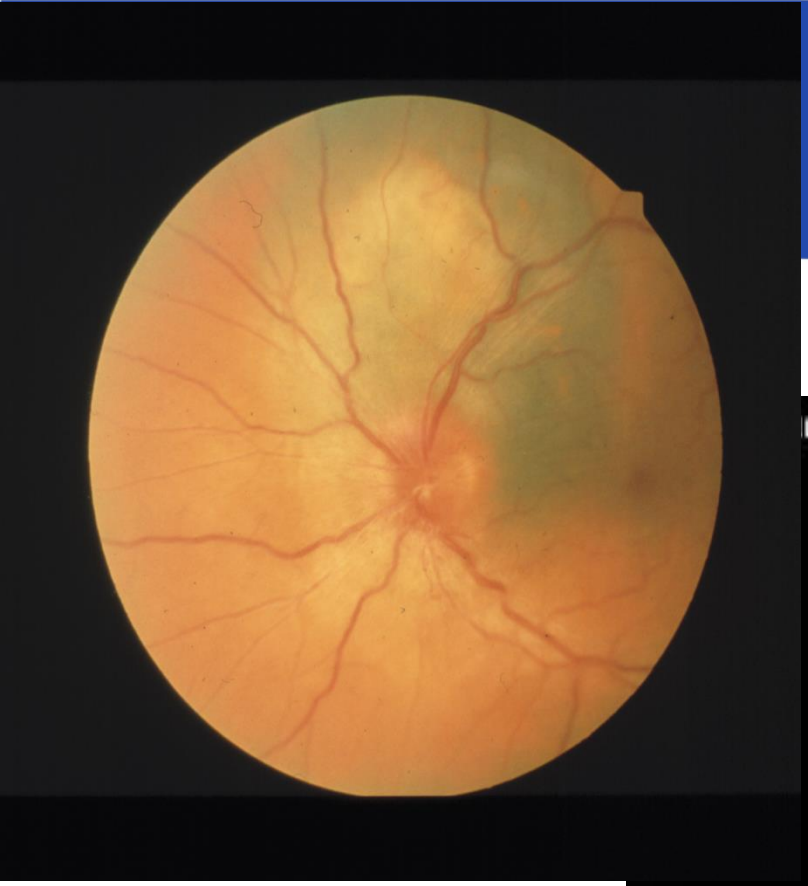


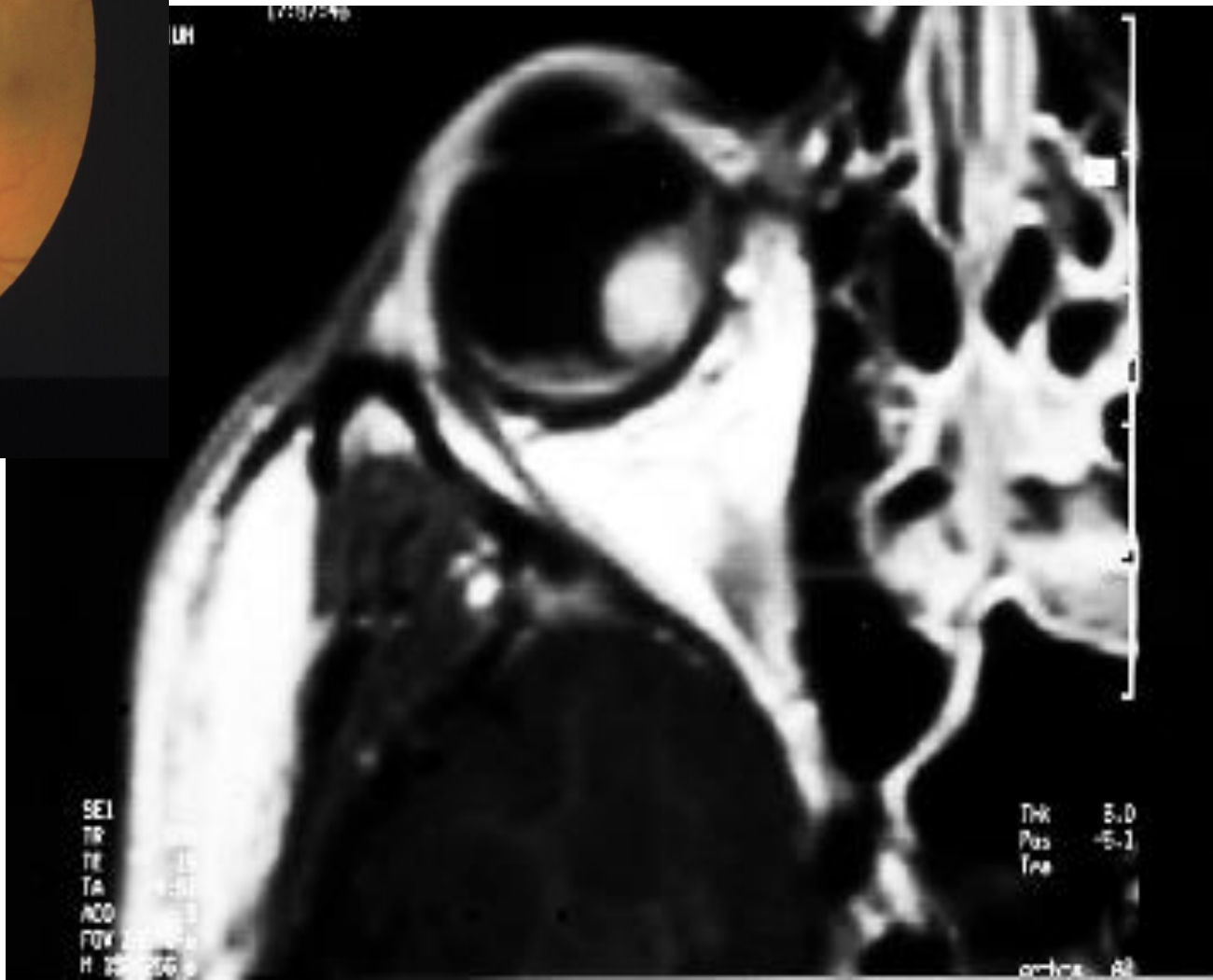
History of Proton Beam Therapy

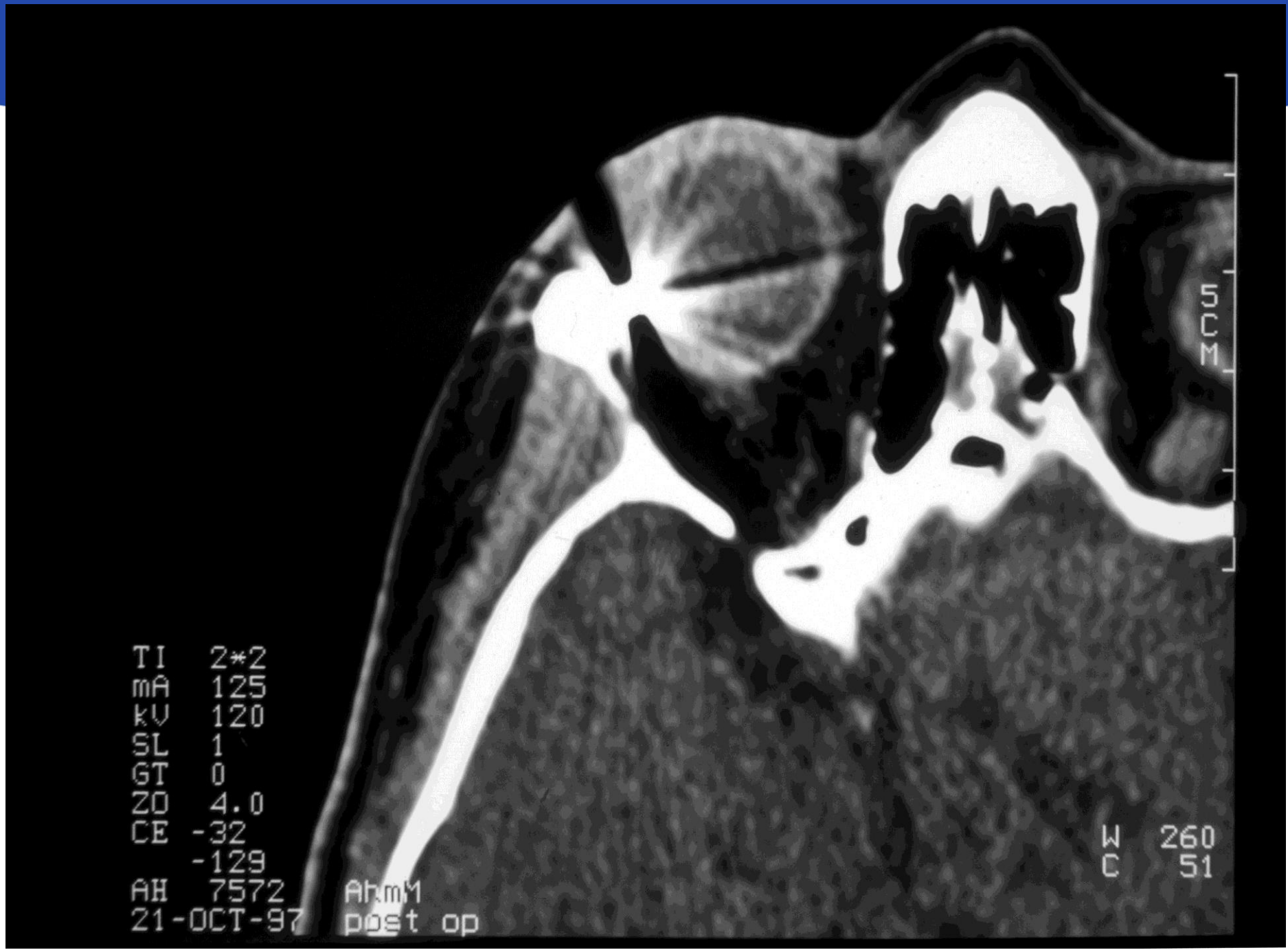
- 1946 Robert Wilson
- 1948 Tobias, Lawrence (Berkeley)(hypophysectomy)
- 1954-56 Boerje Larsson (Uppsala)
- 1960 Graffman 60 patients.(Stereotactic neurosurgery)
- Early ‘60 Sweet, Koehler, (Kjellberg, Harvard)- AV. malform.
- 1969 Ganz (retinoblastoma), Constable (eye melanoma)
- 1970 Suit, Goitein (skull base tumors)
- Russia, Japan (Tokio, Chiba)
- 1983 Tsukuba 250 MeV (lung, mediast, GI, Gyn,...)
- 1967 First large-field proton treatments in Sweden
- 1974 Large-field fractionated proton treatments program begins at HCL, Cambridge, MA
- 1990 First hospital-based proton treatment center opens at Loma Linda

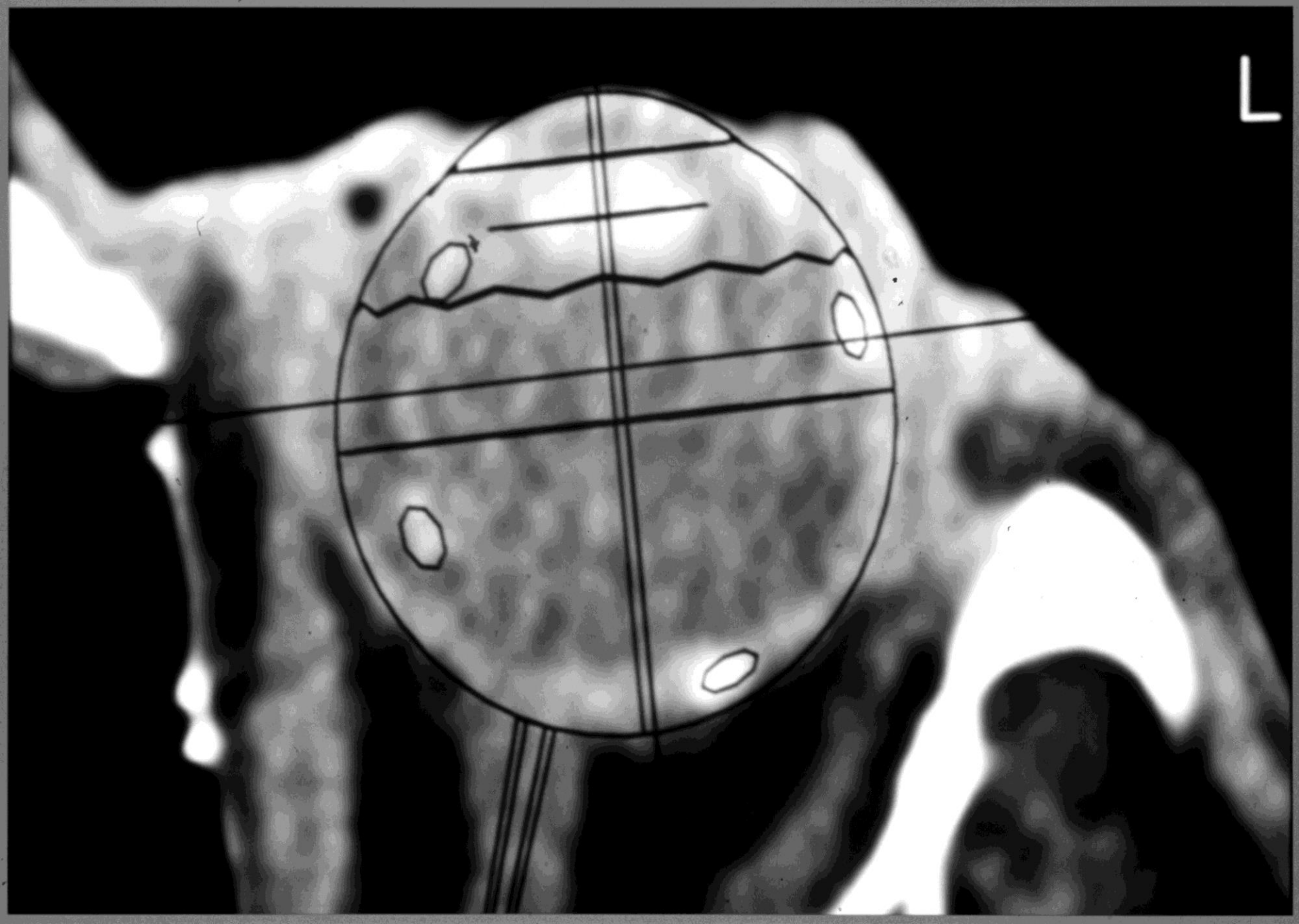
PROTON THERAPY OF UVEAL MELANOMA

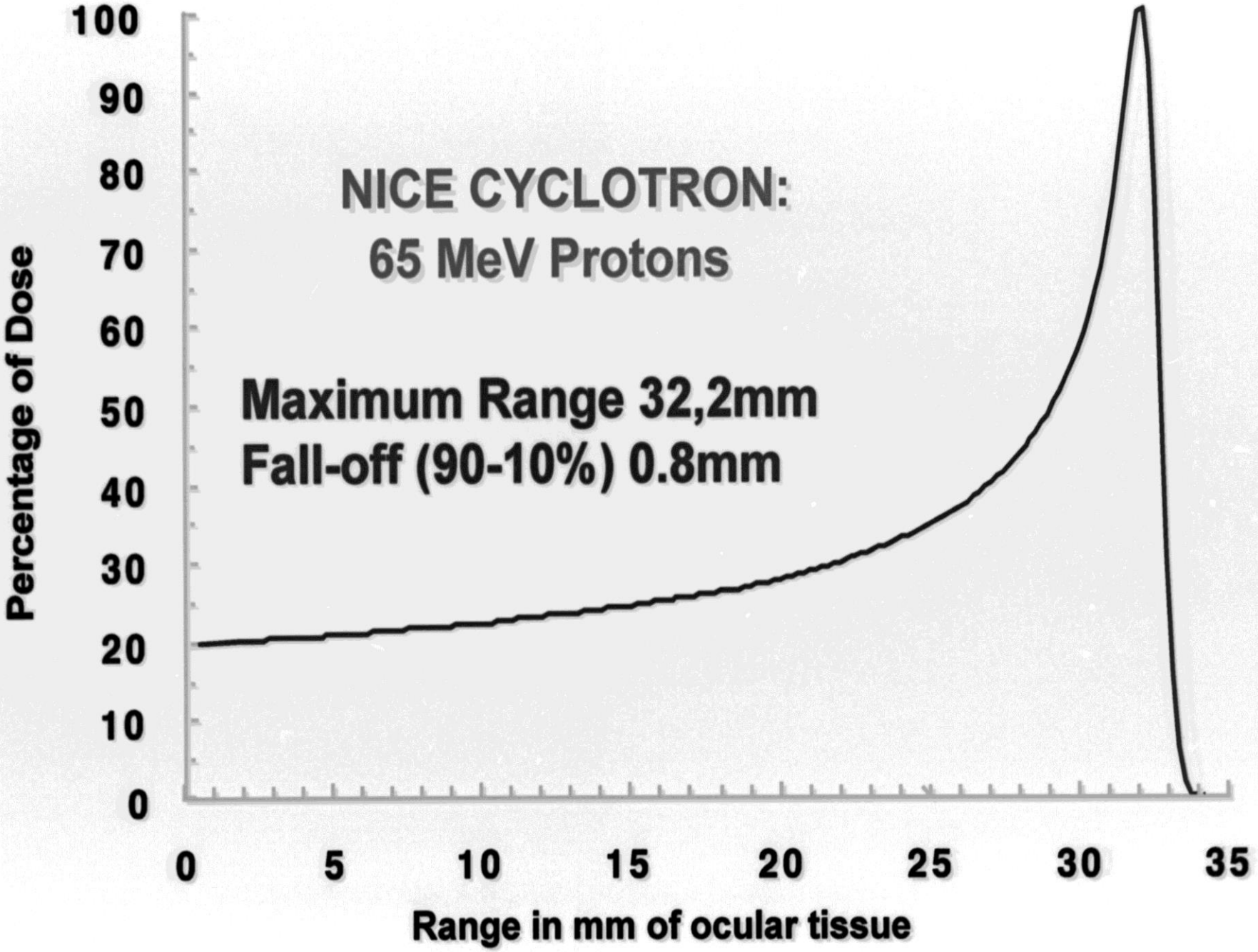


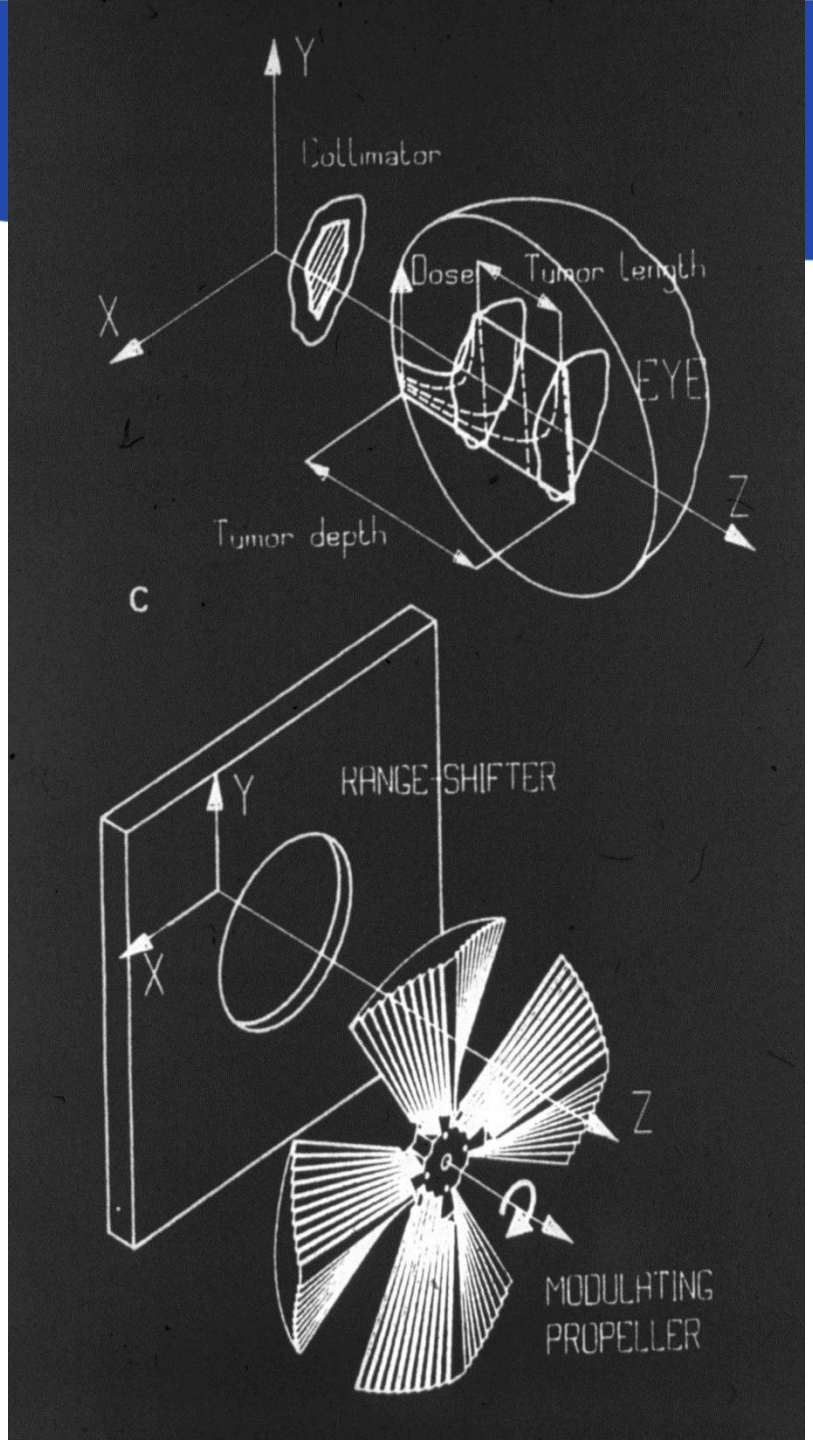


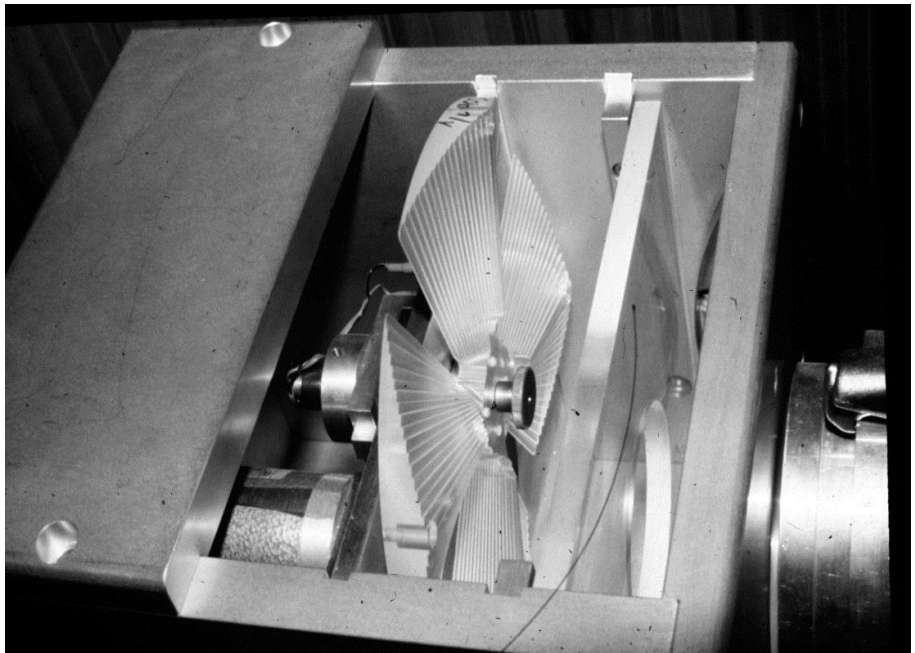

LH
SE1
TR
TE
TA
ACQ
FOV
Thk 5.0
Pos -5.1
Fre


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

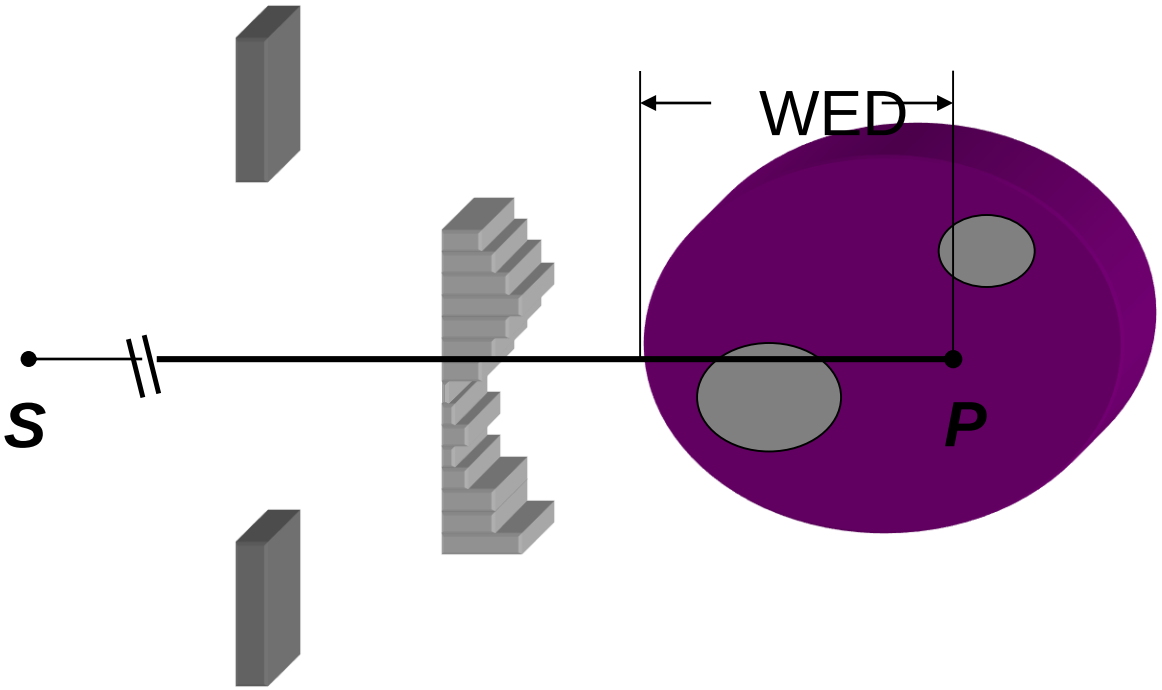

NICE CYCLOTRON:
65 MeV Protons
Maximum Range 32,2mm
Fall-off (90-10%) 0.8mm
Percentage of Dose
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
Range in mm of ocular tissue


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



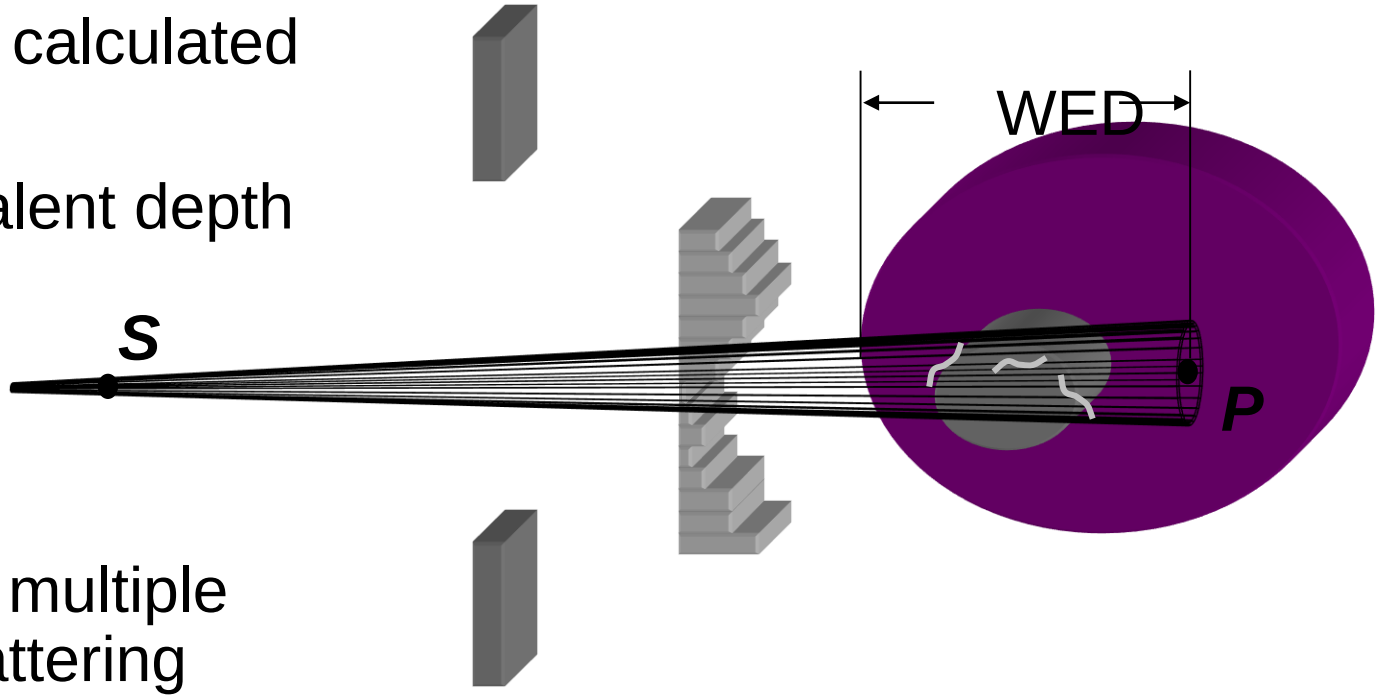
Ray-Tracing Dose Algorithm

- 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

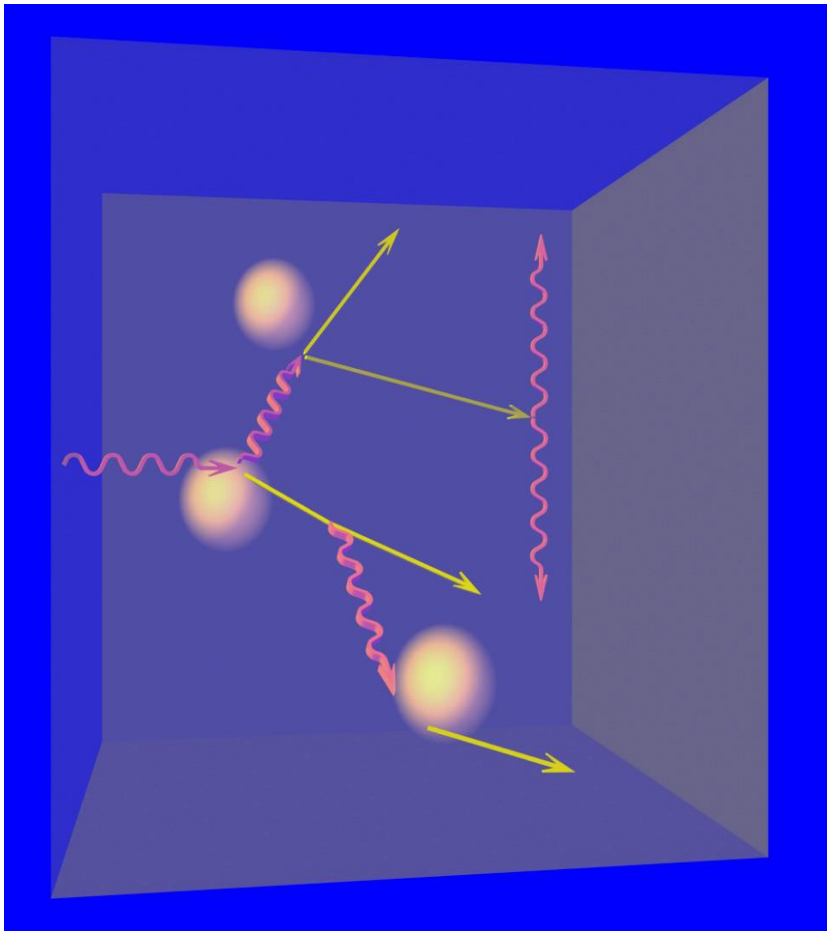
- Cylindrical coordinates
- Measured or calculated pencil kernel
- Water-equivalent depth

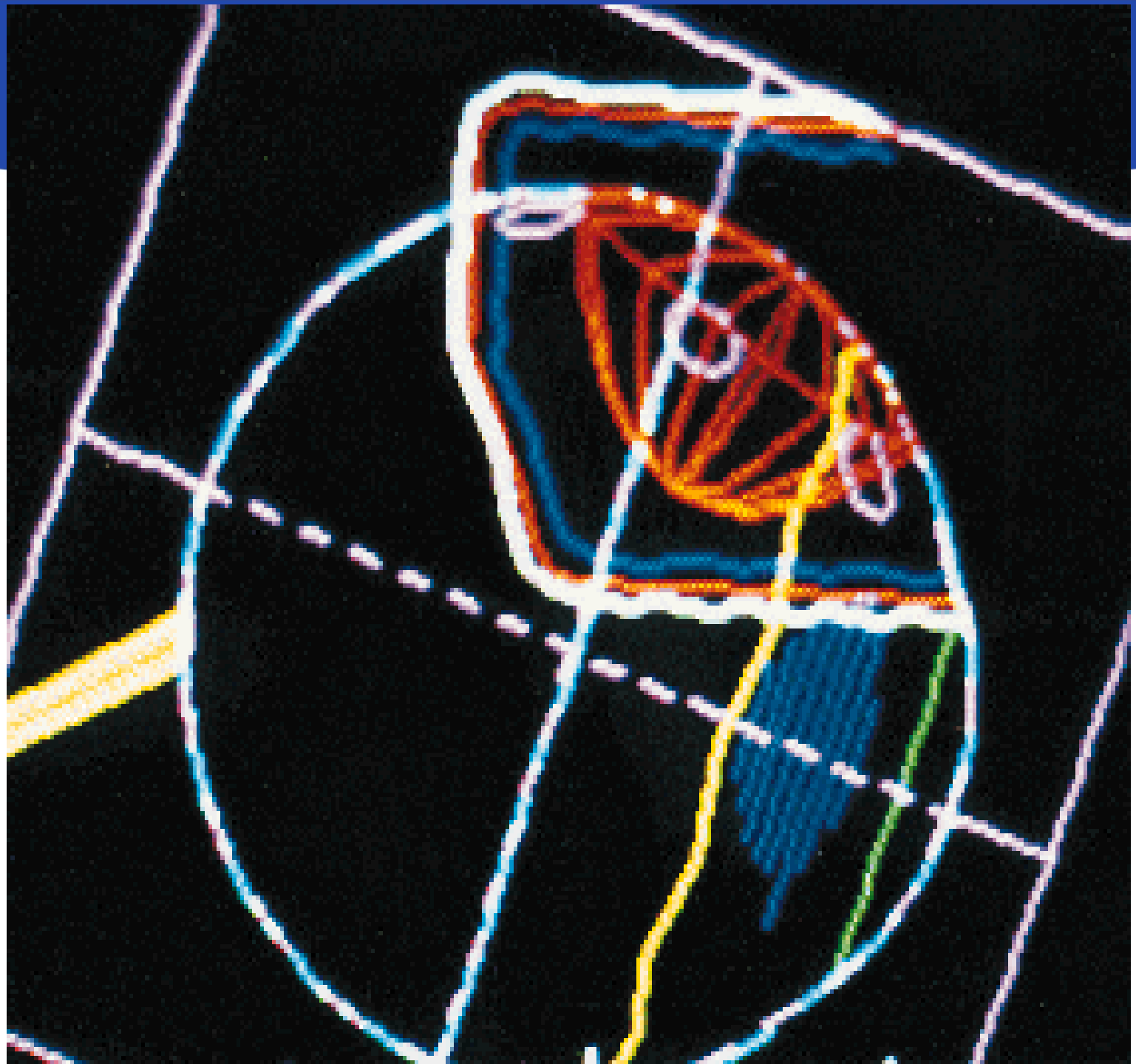


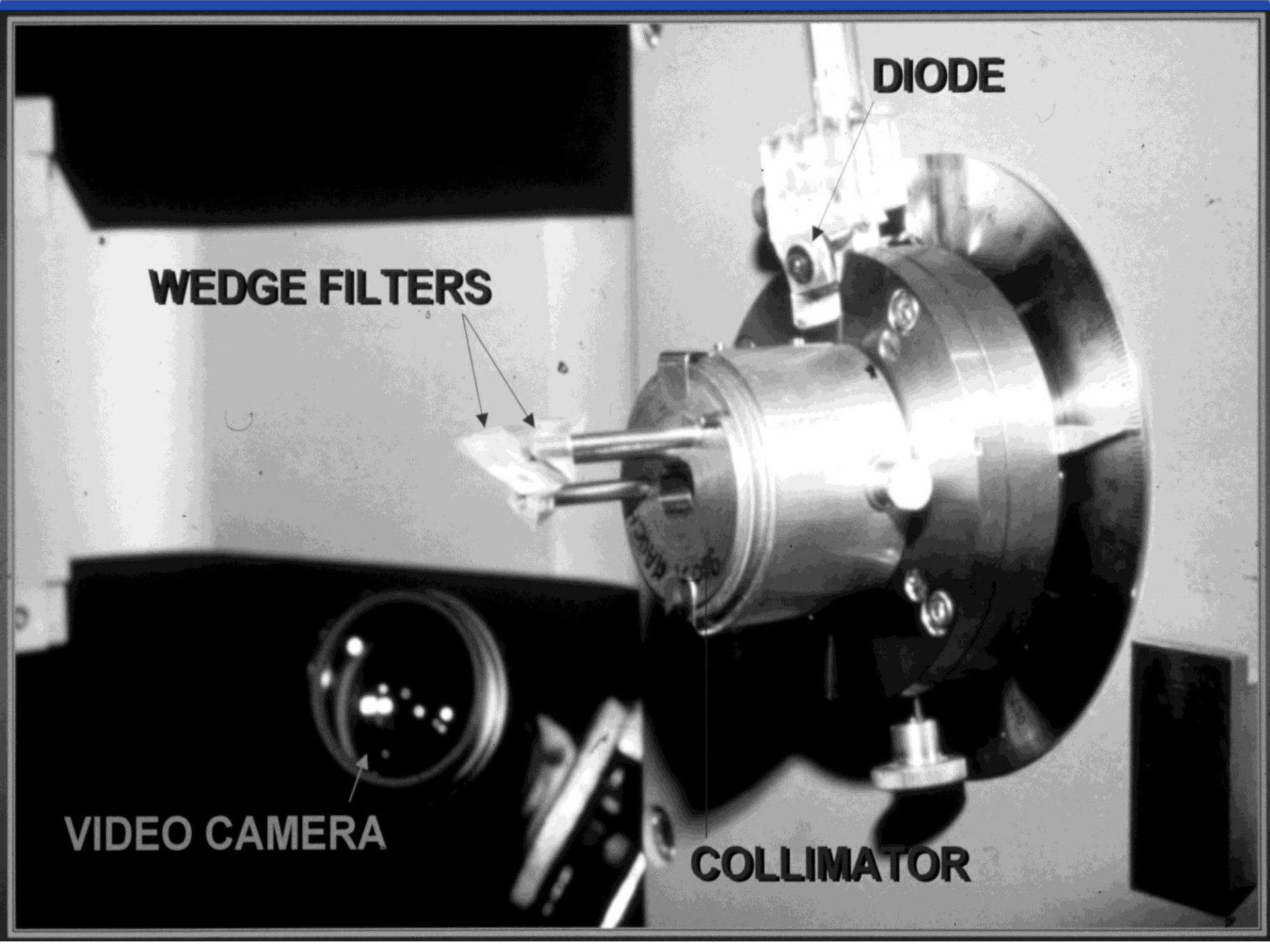
- Accounts for multiple Coloumb scattering
- more time consuming

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



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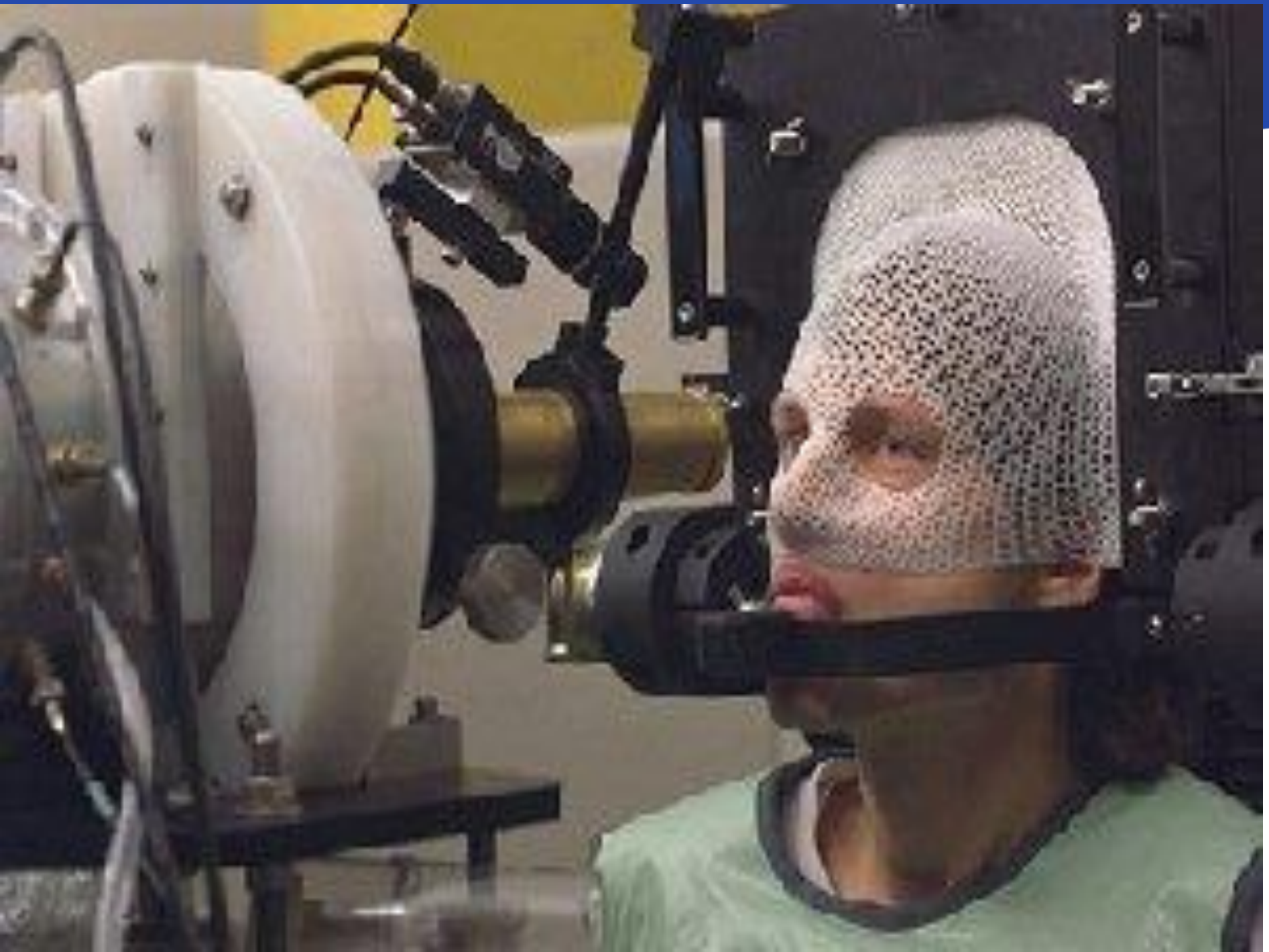
WEDGE FILTERS
VIDEO CAMERA
COLLIMATOR



E. Gragoudas: Proton Beam Irradiation of Uveal Melanomas: The First 30 Years

- Brachytherapy vs. **Hadron** therapy
  - Local recurrance rate is **lower**
  - Risk of developing cataract is **lower**
  - Enucleation is only **rarely** necessay

Source 10. Wang et al 2012.

IMRT

Proton RT

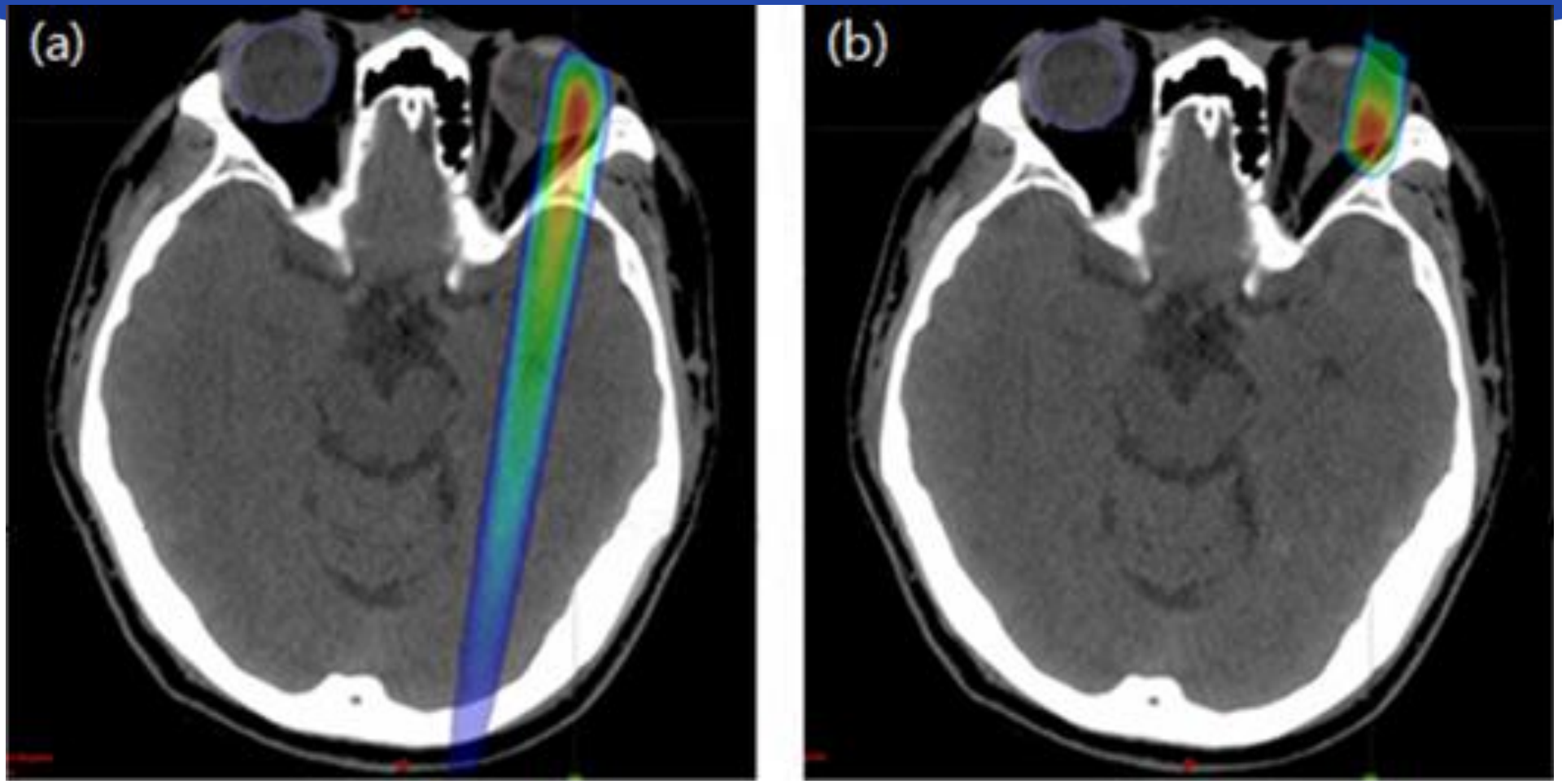


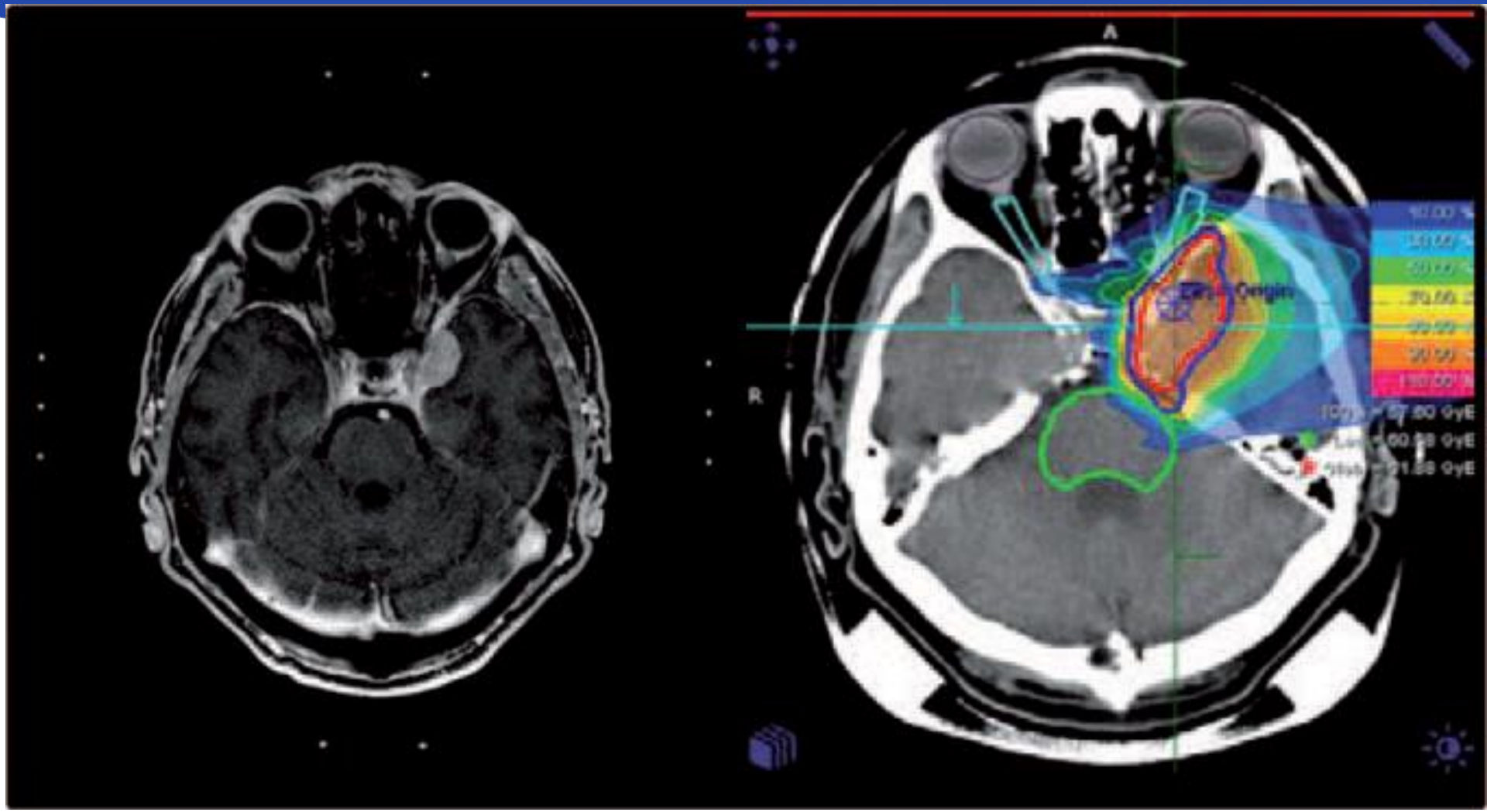
Fig. 11. www.nccproton.com

CNS tumors

- Meningeoma
  - 1/3 of primary CNS tumors
  - Initiates fom the meninx
  - Slow growing
  - Dose on the surrounding healthy tissues (skull base, otic nerve) can be minimized

Source 12. Combs et al 2010.

Proton/ion RT



Source 12. Combs et al 2010.

Skull base, proton/ion RT

- Chordoma: **73.5 Gy** (RBE)
- Chondrosarcoma: **68.4 Gy** (RBE) 1.8–2.0 Gy (RBE)/day
- 5 years local control (LC)
  - chordoma **81%**
  - chondrosarcoma **94%**
- Toxicity free survival at 5 years: **94%**

Source 13.Ares et al 2008.

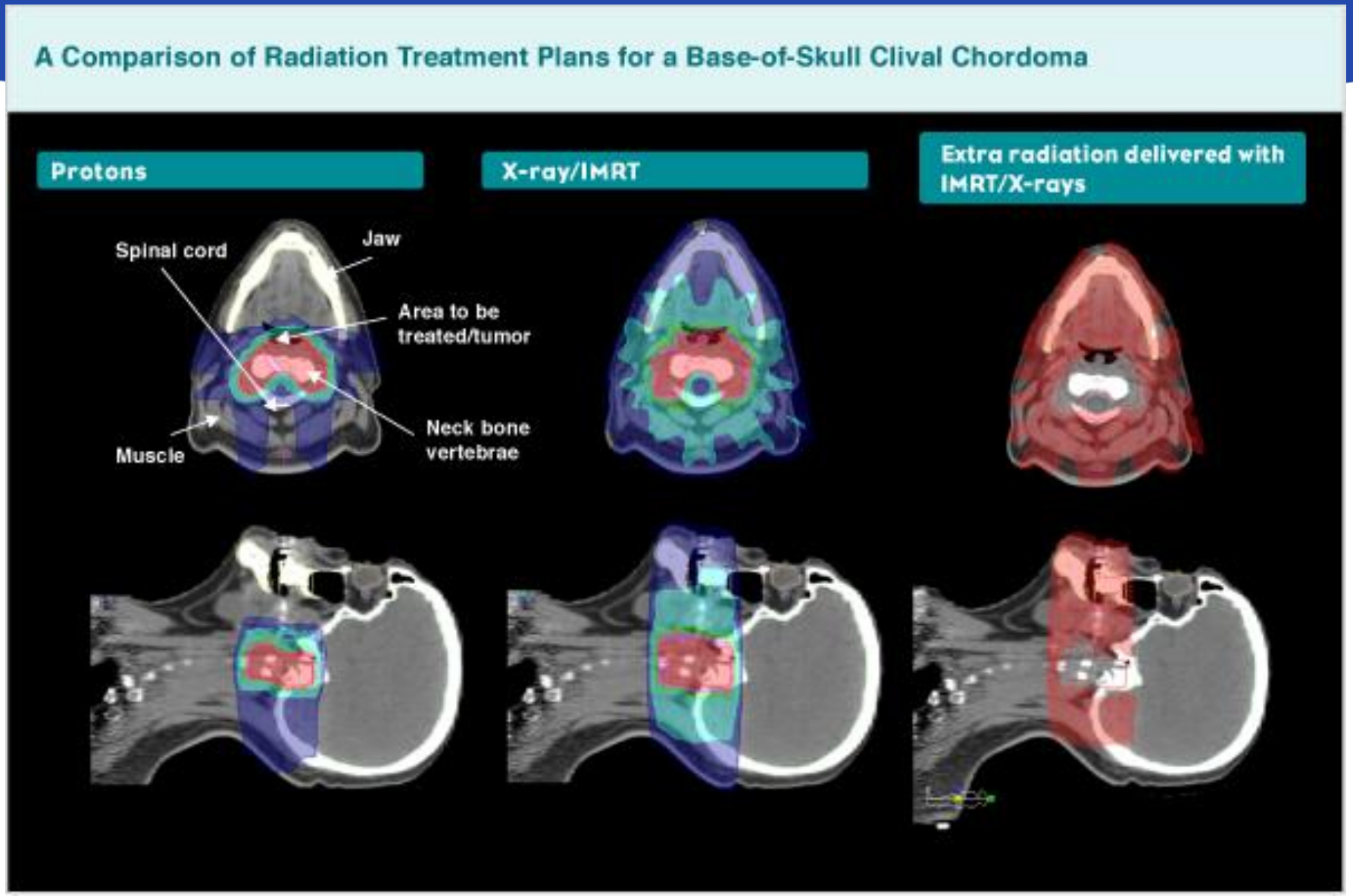


Fig. 14. www.procure.com

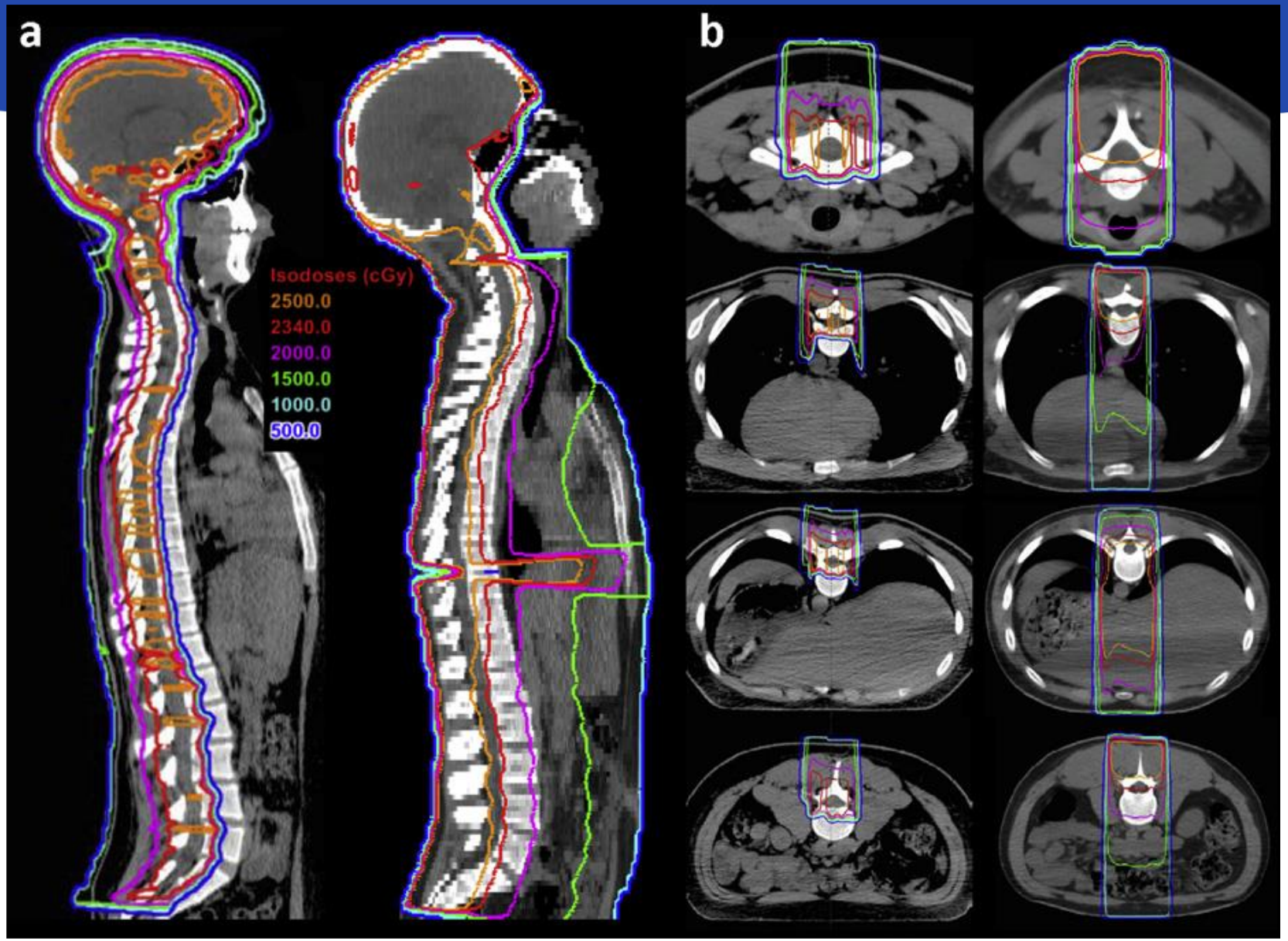
Childhood malignancies

Radisensitive embrional tumors, but the surrounding, healthy tissues are radiosensitive, growing tissues

Low dose is important – induction of second malignancy

- Skull base located CNS tumors
- Chordoma, chondrosarcoma
- Ewing and othe sarcomas
- Craniospinalis axis

- Medulloblastoma in adults
  - Rare (common at the age of 4-8)
  - Initiates from the cerebellum
  - Cemotherapeutical options are limited
  - High tendency of metastases by the liquor -> irradiation of the cranispinalis axis
  - 21 photon vs. 19 proton treated adult patients
  - **Low rate of acute side effects** in the proton group (weight loss, nausea, vomiting, oesophagitis, cell account depletation)
  - **Low dose on the vertebras**



Proton RT IMRT

Source 15. Brown et al 2013.

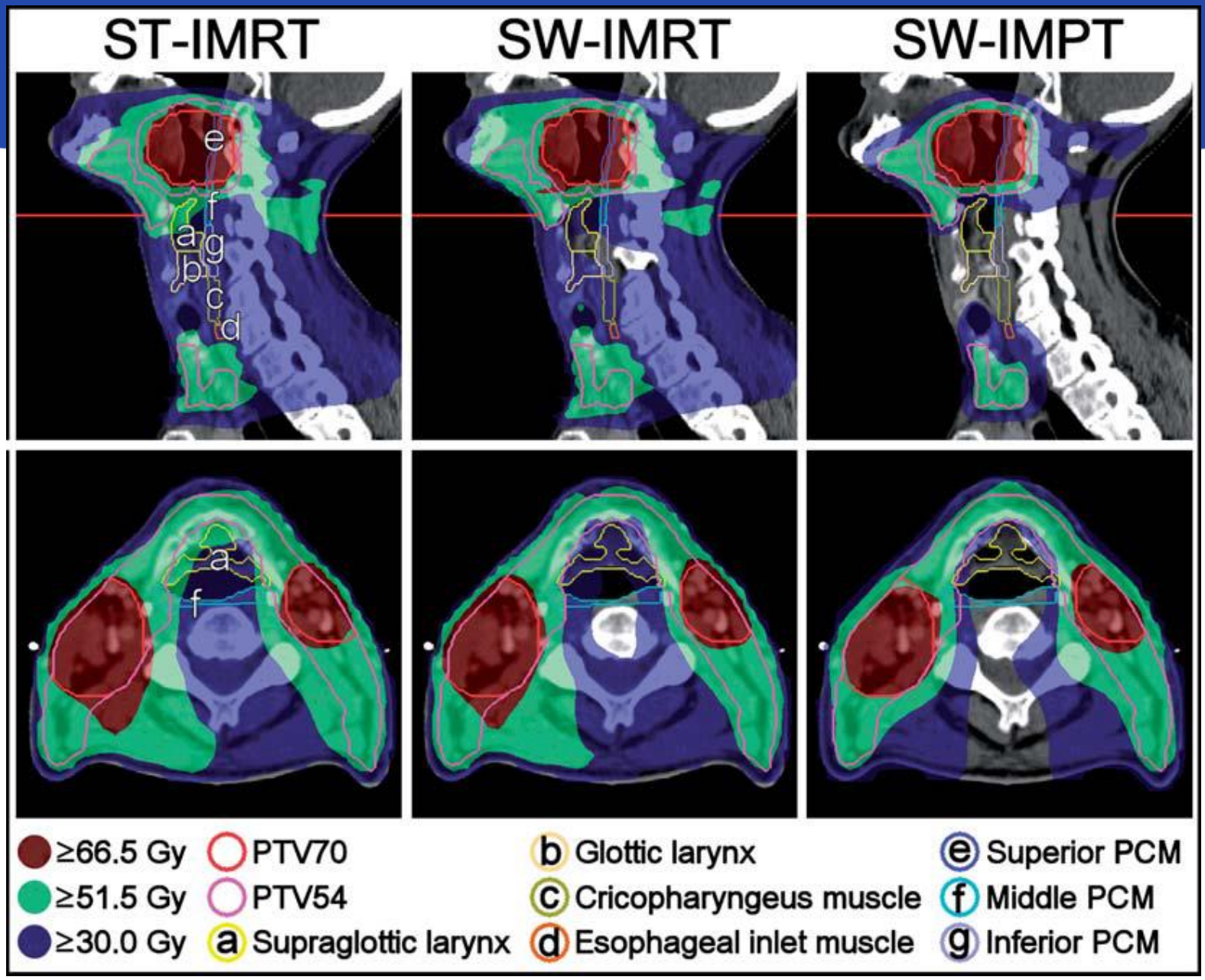
A Comparison of the Risk of Secondary Malignancies After Treating Medulloblastoma[3]

Tumor Site	IMRT X-Rays	Proton Therapy
Stomach and esophagus	11%	0%
Colon	7%	0%
Breast	0%	0%
Lung	7%	1%
Thyroid	6%	0%
Bone and connective tissue	2%	1%
Leukemia	5%	3%
All Secondary Cancers	**43%**	**5%**

Head and neck tumors

Salivary glands, mouth, pharynx, larynx

- Usually epithelial carcinomas
- Gives fast lymph node metastases because of lymphatic drenage
- Incidence of head and neck tumors increased 6 times since the ’50s
- Male:female=5:1
- Pain because of mucositis in the oral cavity leads often to therapeutic failure
- With IMPT the dose on the salivary glands is lower -> side effects are not so sevier



Source 16. Van der Laan et al 2013.

Tumors of the nasal cavity and sinuses

- Slow growing, locally destructive, in some cases radioresistant tumors, complete surgical removal is not always feasible
- Organs at risk (eye, optic nerve, chiasm)

- 2 years LC: 35%, OS: 47%
- 5 years LC: 17,5%, OS: 15,7%
- Therapy: proton RT ± IMRT
  - IMRT: 30-60 Gy
  - Proton, Carbon ion: 20- 80 GyE

Fukumitsu et al 2012.

Lung cancer

- T1 ill. T2 stad., N0, M0 central or periferial
- Hypofractionated proton therapy with 51, 60, 70 Gy
- 4 years OS: 51 Gy – 18%
  60 Gy – 32%
  70 Gy – 51%
- At priferial location 4 years OS: 60%

Source 18. Bush et al 2013.

Proton RT IMRT

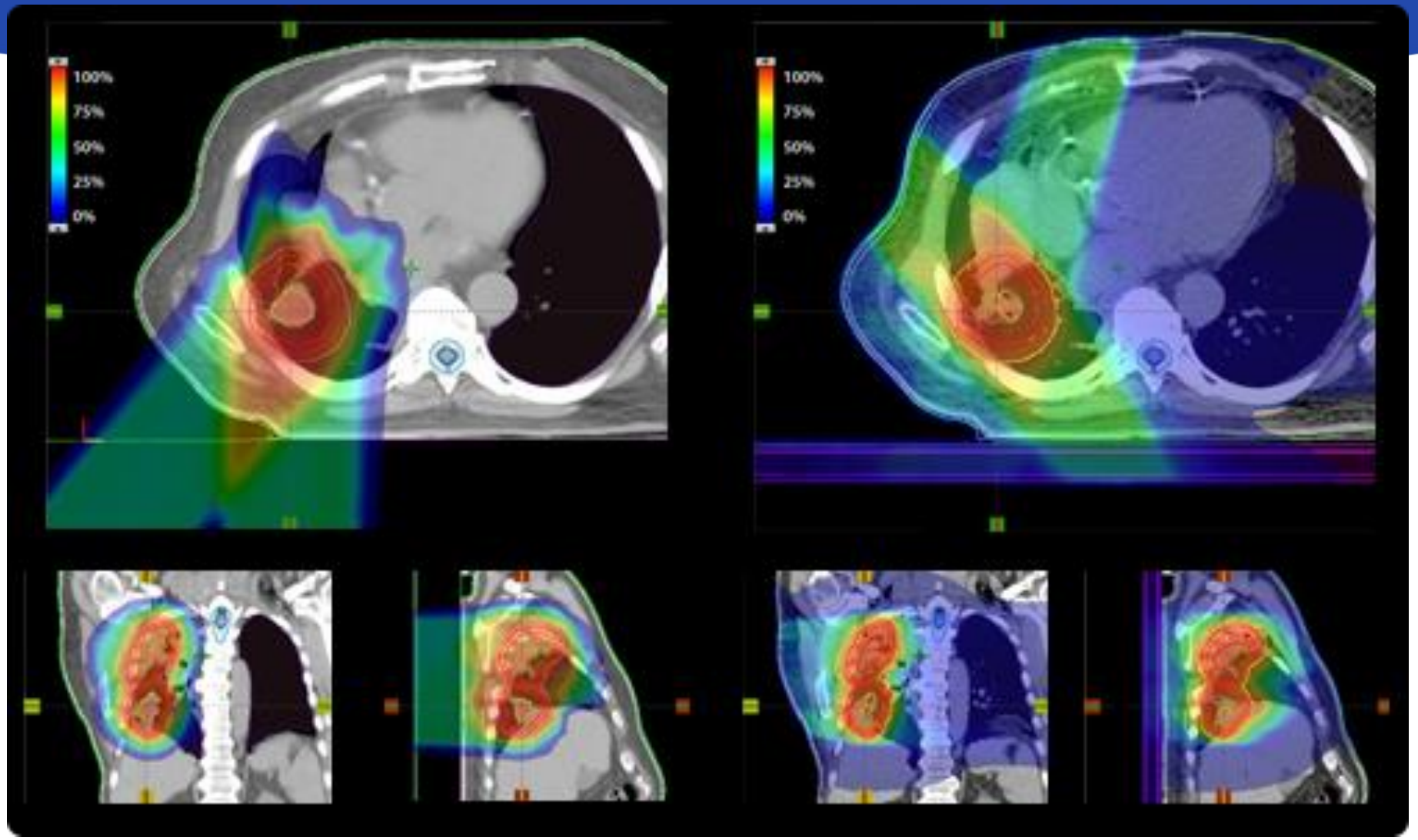
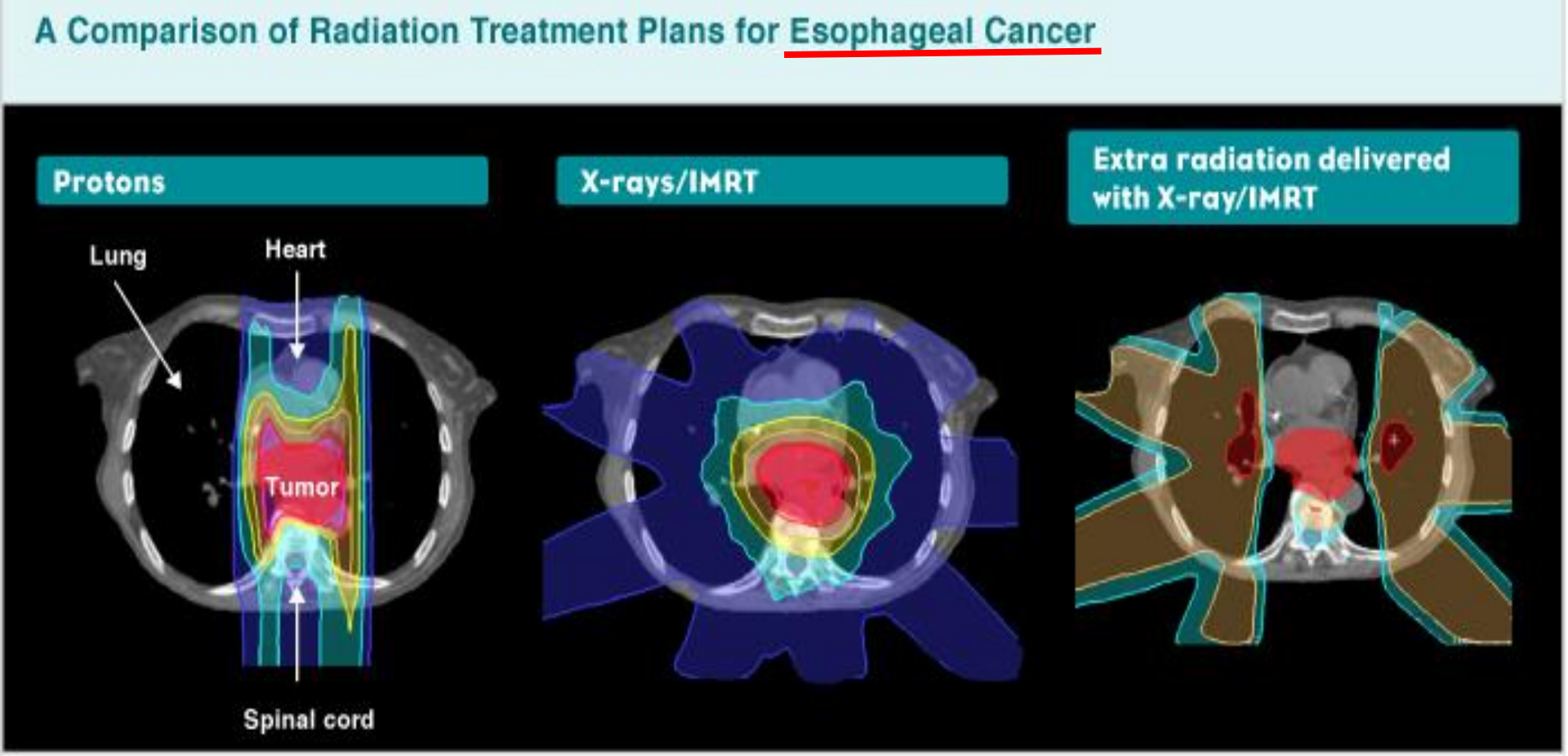


Fig. 20. www.iba-protontherapy.com



Research on the efficacy of proton therapy for esophageal cancer is ongoing, but at present only a few studies have been published. A retrospective study looked at 46 patients treated with proton therapy for locally confined esophageal cancer. The 5-year survival rate for all patient tumor locations was 34%, the 5-year local control rate for T1 patients was 83%, and the 5-year local control rate for T2 to T4 patients was 29%.38 These outcomes are comparable to those seen in patients treated with surgery.38

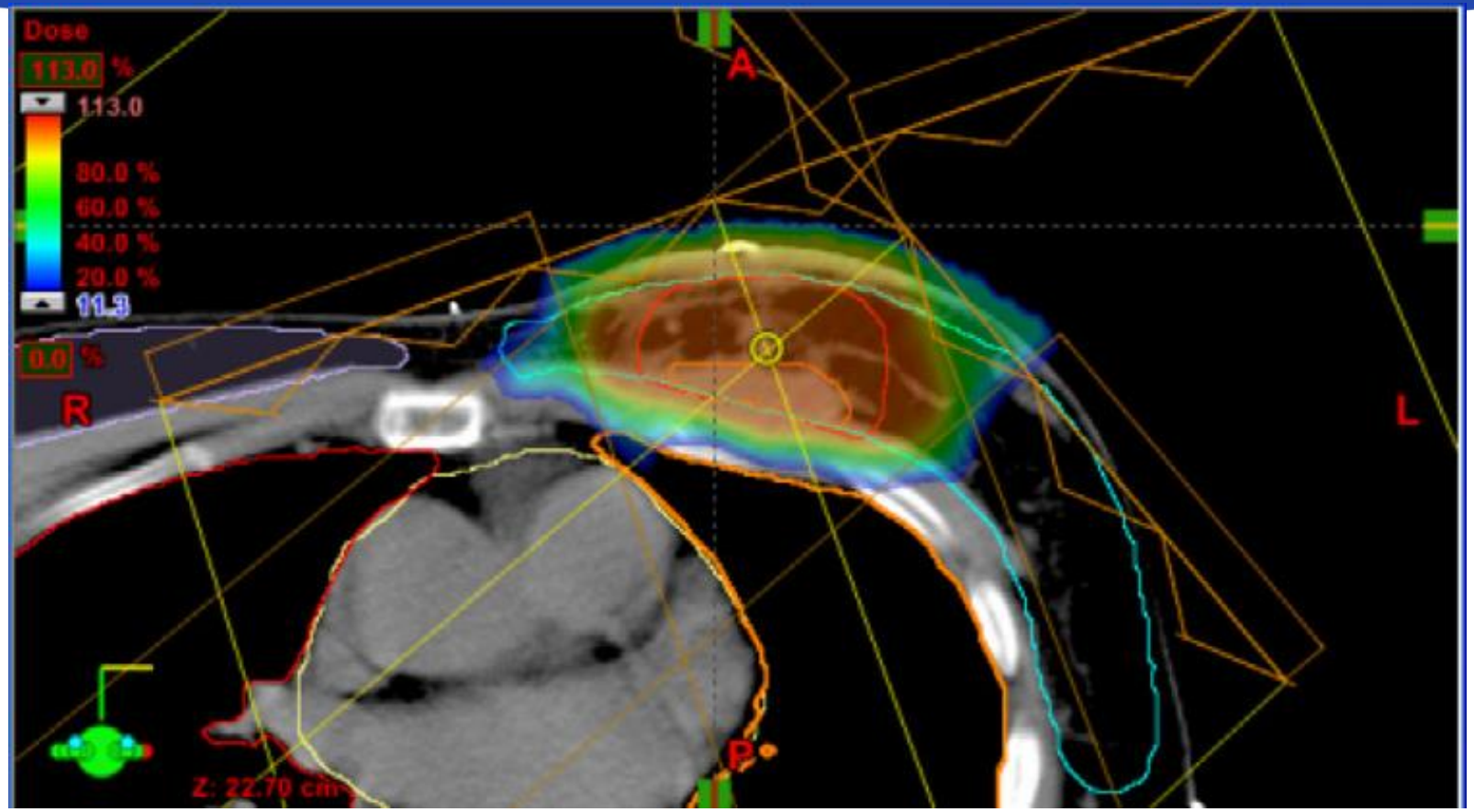
Source 21. www.procure.com

Breast cancer

- Partial breast irradiation
  - In selected patients (Ø lymph node metastasis, local, resection margins are free)
  - Phase 2. clinical study (30 patients)
  - Accelerated, partial proton RT: dose: 30 GyE, 6 GyE/day, 2 fields
  - Mean follow-up 60 months: every patient is disease-free

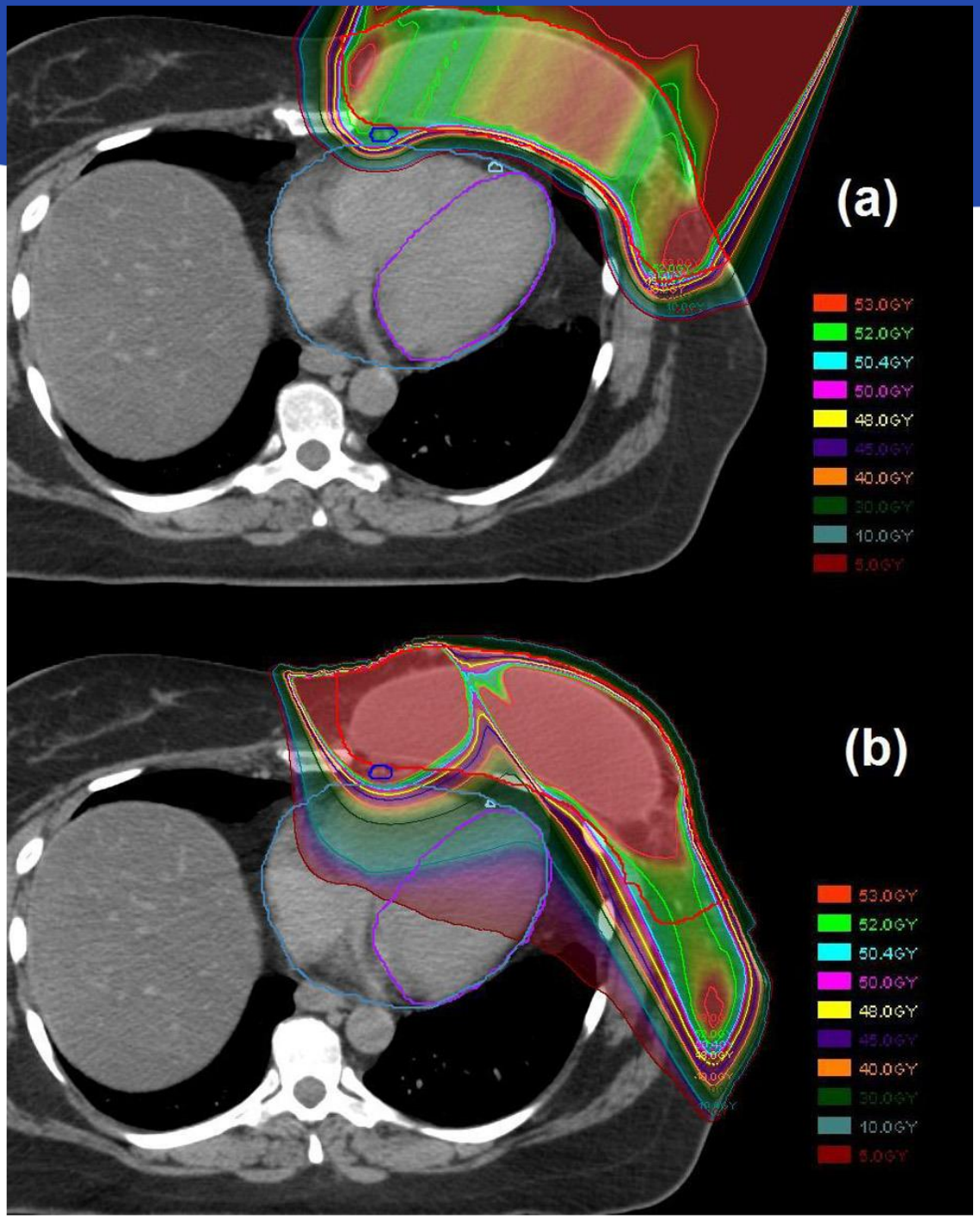
Chang et al 2013.

Proton RT



Source 22. Chang et al 2013.

Thoracic wall RT after mastectomy



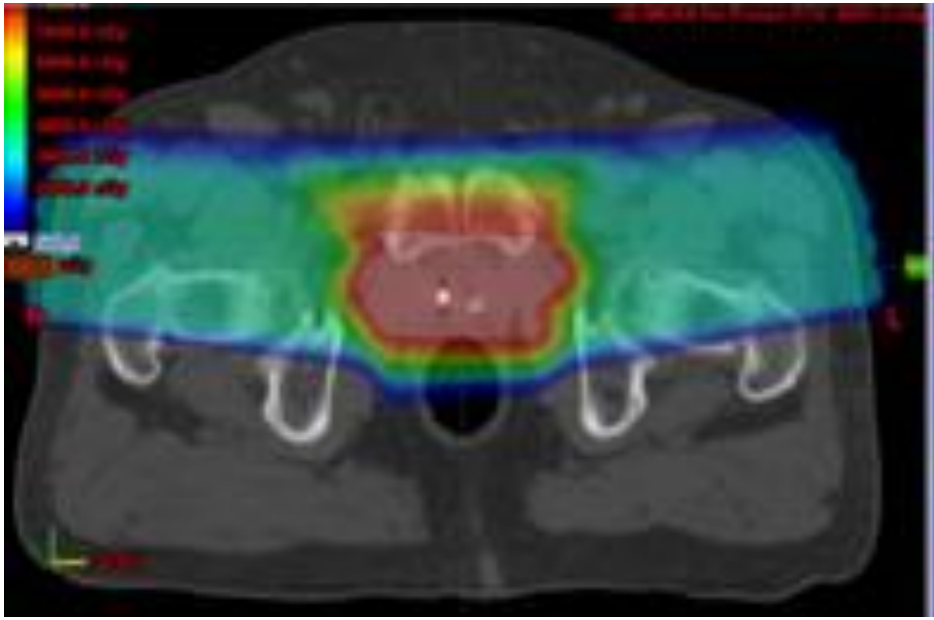
Proton RT

IMRT

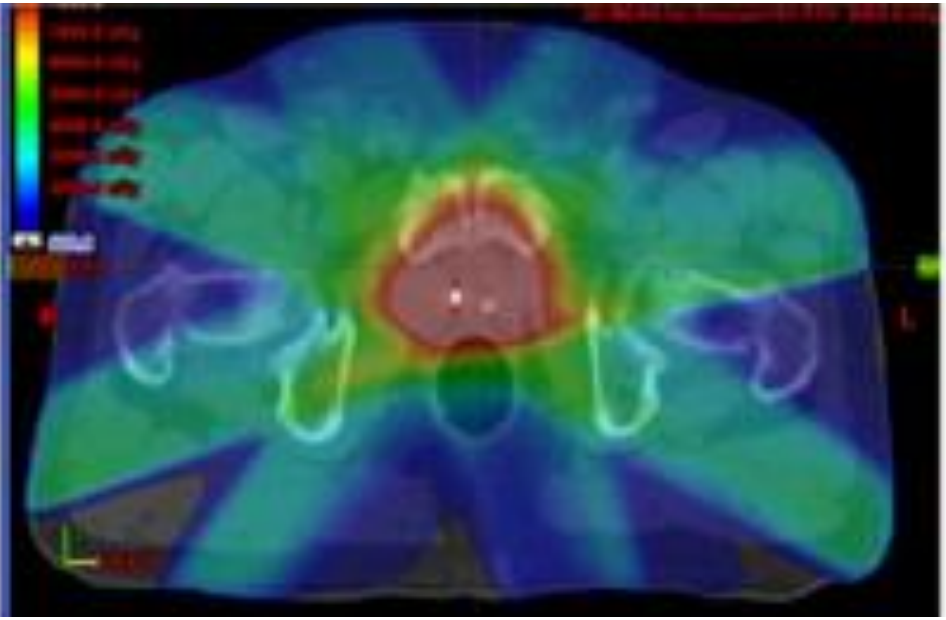
MacDonald et al 2013.

Prostate cancer

Proton RT dose distribution



IMRT dose distribution



=> low~high risk => 70-72,5 GyE, 2,5 GyE/day~76-82 GyE, 2 GyE/day

2 years after proton RT very low rate of side effects (erectil disfunction, urine or -, feces incontinence, diarrhoea)

www.floridaproton.org

Proton *versus* photon - radiochemotherapy in the treatment of locally advanced breast cancer

Retrospective analysis : N=1,483 (391 proton/1,092 photon).

Baseline toxicity and performance status were similar ($p > 0.05$).
Proton pat.: significantly older (median 66 vs. 61), had less favorable Charlson-Deyo comorbidity scores (median 3.0 vs. 2.0),

Proton: lower integral radiation dose to tissues outside the target ($p < 0.05$).

Proton chemo-radiotherapy

- significantly lower relative risk (RR) of 90-day grade ≥3 adverse events 11.5% vs 27.6%
- decline in performance status during treatment ($p < 0.01$).

There was no difference in DFS or OS.

Conclusions: In adults with locally advanced cancer, proton chemo-radiotherapy was associated with significantly reduced acute adverse events causing unplanned hospitalizations with similar disease-free and overall survival.

CONQUER CANCER® THE ASCO FOUNDATION | MERIT AWARD RECIPIENT

NATIONAL CANCER DATABASE

Risk of subsequent cancer diagnosis in patients treated with 3D conformal, intensity modulated, or proton beam radiation therapy

Michael Xiang[1,2], Daniel Chang[1], and Erqi Pollom[1,2]

1. Stanford Department of Radiation Oncology, 2. Palo Alto Veterans Affairs

June 3, 2019

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Presented By Michael Xiang at 2019 ASCO Annual Meeting

Aim, methodology, and data source

- **Aim:** Leverage scope of the **National Cancer Database (NCDB)** to determine second cancer risk associated with 3DCRT, IMRT, and PBRT
- Captures 70% of all cancers in US: enables assessment of a rare event
- Contains RT modality, dose, fractionation
- Other data: chemotherapy, surgery, sociodemographic factors (sex, race, insurance status, income quartile, etc.)

Boffa 2017

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Methods: 18 variables used for adjustment

- **Patient and sociodemographic:** age, sex, race, length of follow-up (measured from RT completion), comorbidity score, geographic region, insurance, income quartile, education quartile, urban/rural residence
- **RT:** total dose (Gy or GyE), dose per fraction, use of external beam boost
- **Tumor:** tumor type, stage group, year of diagnosis
- **Other treatments:** chemotherapy, surgery (including surgery/RT sequence)

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Results: Cohort description

- Total 450,373 patients
- 33.5% 3DCRT (151,020), 65.2% IMRT (293,486), 1.3% PBRT (5,867)
- Median follow-up after RT completion 5.1 years (range: 2-13.8 years)
- Total follow-up period 2.54 million person-years

Selected baseline characteristics

	3DCRT	IMRT	PBRT
Median age	60 years	64 years	63 years
Median RT dose	60 Gy	66 Gy	79.2 GyE
% chemo-therapy	48%	38%	17%
Median follow-up	5 years	5.2 years	5.2 years

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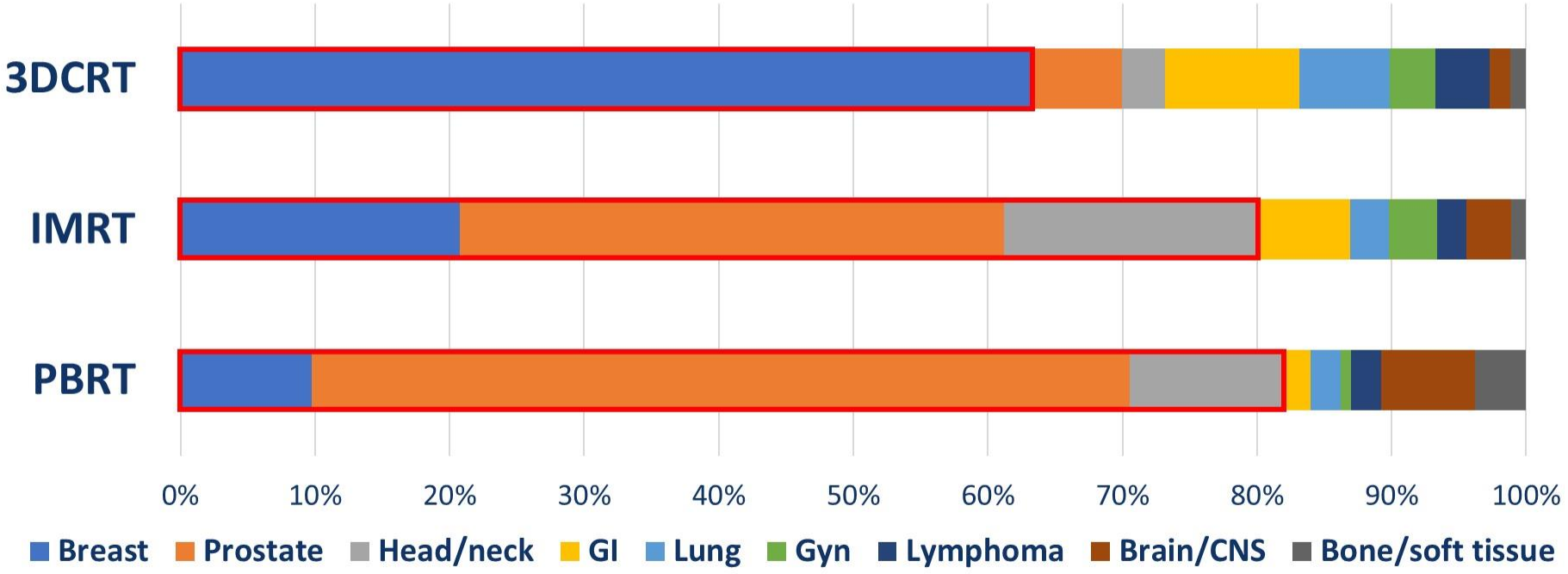
Results: Tumor type distribution by RT modality



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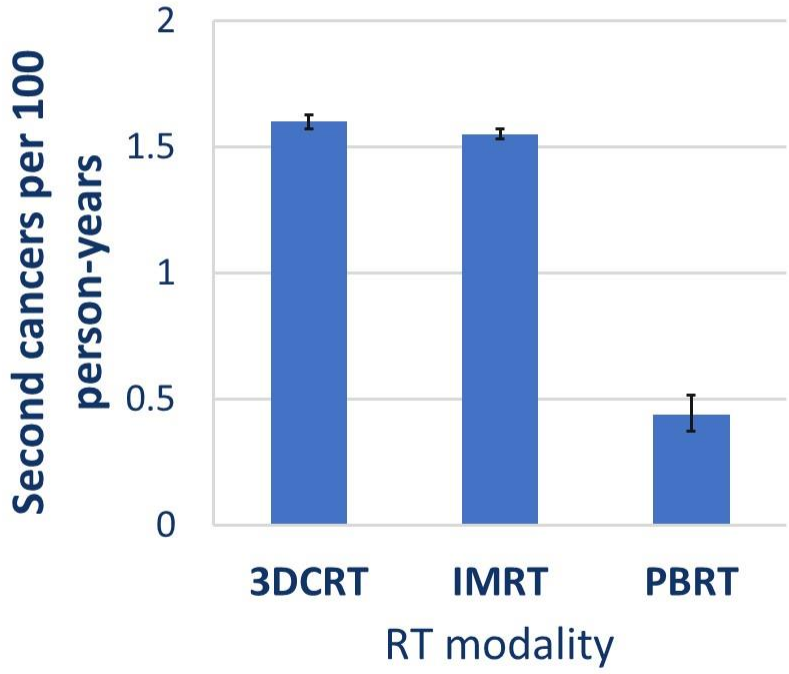
Results: Absolute crude incidence of second cancer

- **3DCRT:** 1.60 per 100 person-years (95% confidence interval [CI] 1.57-1.62)
- **IMRT:** 1.55 per 100 person-years (95% CI 1.53-1.57)
- **PBRT:** 0.44 per 100 person-years (95% CI 0.37-0.52)



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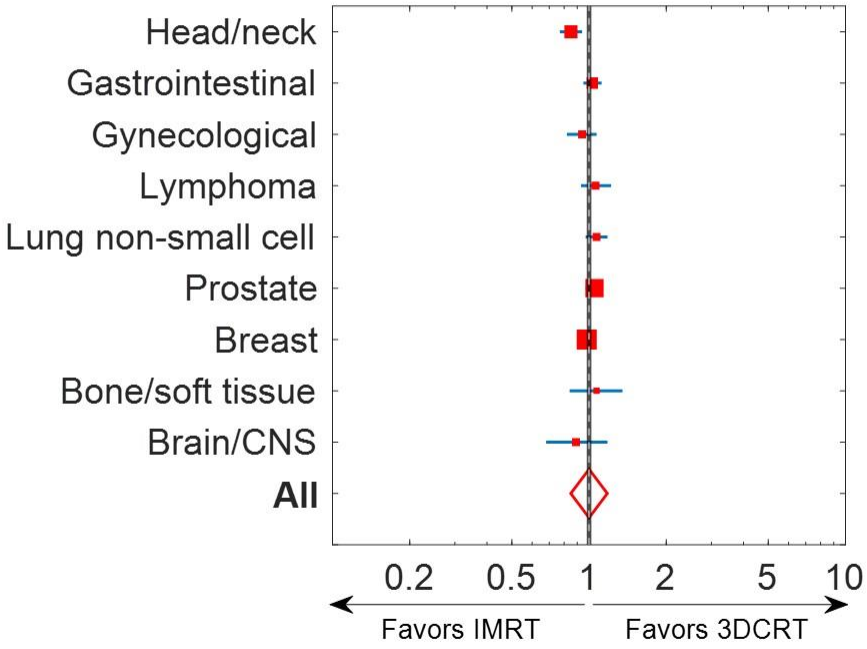
Results: IMRT has similar second cancers as 3DCRT

- Overall **adjusted OR 1.00** (95% CI 0.97-1.02), p = 0.75
- Head/neck: adjusted OR 0.85 (95% CI 0.77-0.94), p = 0.001



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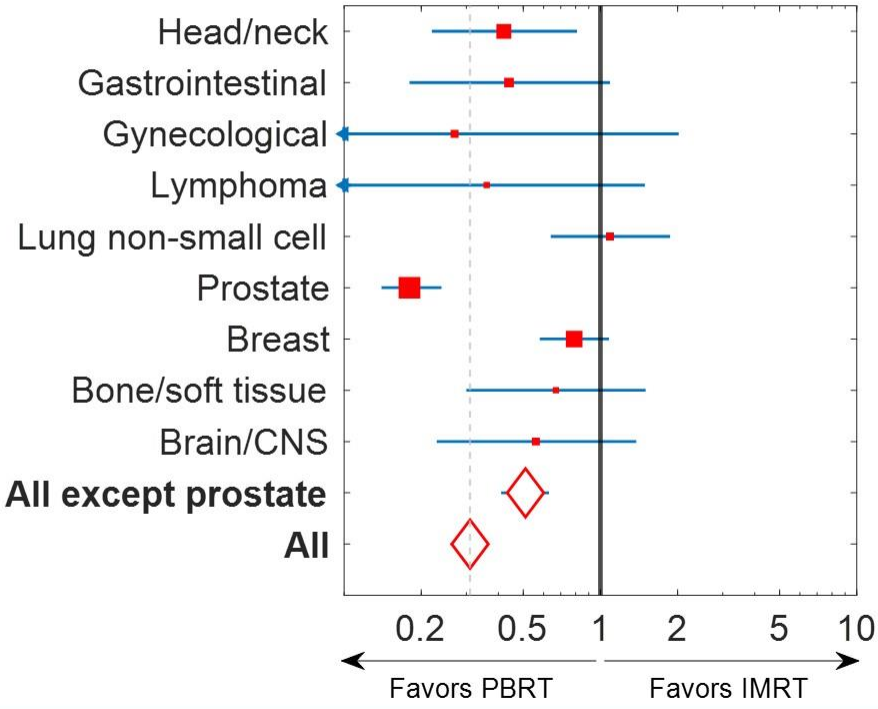
Results: PBRT significantly less second cancer vs IMRT

- Overall **adjusted OR 0.31** (95% CI 0.26-0.36), p < 0.0001
- Head/neck: adjusted OR 0.42 (95% CI 0.22-0.81), p = 0.009
- Prostate: adjusted OR 0.18 (95% CI 0.14-0.24), p < 0.0001
- All except prostate: **adjusted OR 0.51** (95% CI 0.41-0.63), p < 0.0001



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Conclusions and take-away message

- **In this large-scale, national epidemiological study, IMRT and 3DCRT had similar incidence of second cancers, while PBRT had significantly reduced second cancers compared to IMRT by 50-70%**
- Strengths: large sample size and follow-up period; adjustment for multiple treatment and sociodemographic factors; inclusion of diverse cancer types
- Limitations: type/location and timing of second cancers not available
- Patients most likely to benefit from PBRT may be pediatric and young adults due to potential for long life expectancy and increased susceptibility to treatment-related malignancies

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Indications for proton/ion therapy

Locally growing tumor sorrounded by radiosensitive healty tissues:

- Eye tumors (melanoma, retinobl.)
- Skull base tumors (chordoma, chondrosarcoma, meningioma, sinus tu.)
- CNS brain, spinal cord, paraspinal tu., AV malformation
- Childhood malignancies
- Prostate carcinoma
- Lung, breast, sarcomas...

Proton Therapy Scientific Milestones 60 years

1931 First cyclotron (E.O. Lawrence, LBNL)

1946 Biomedical advantages of Bragg-peak (R.R. Wilson, LBNL)

1947 184-Inch Synchrocyclotron (E.O. Lawrence, LBNL)

1948 First biology experiments using protons (C.A. Tobias, LBNL)

1955 Human therapeutic exposure (LBNL)

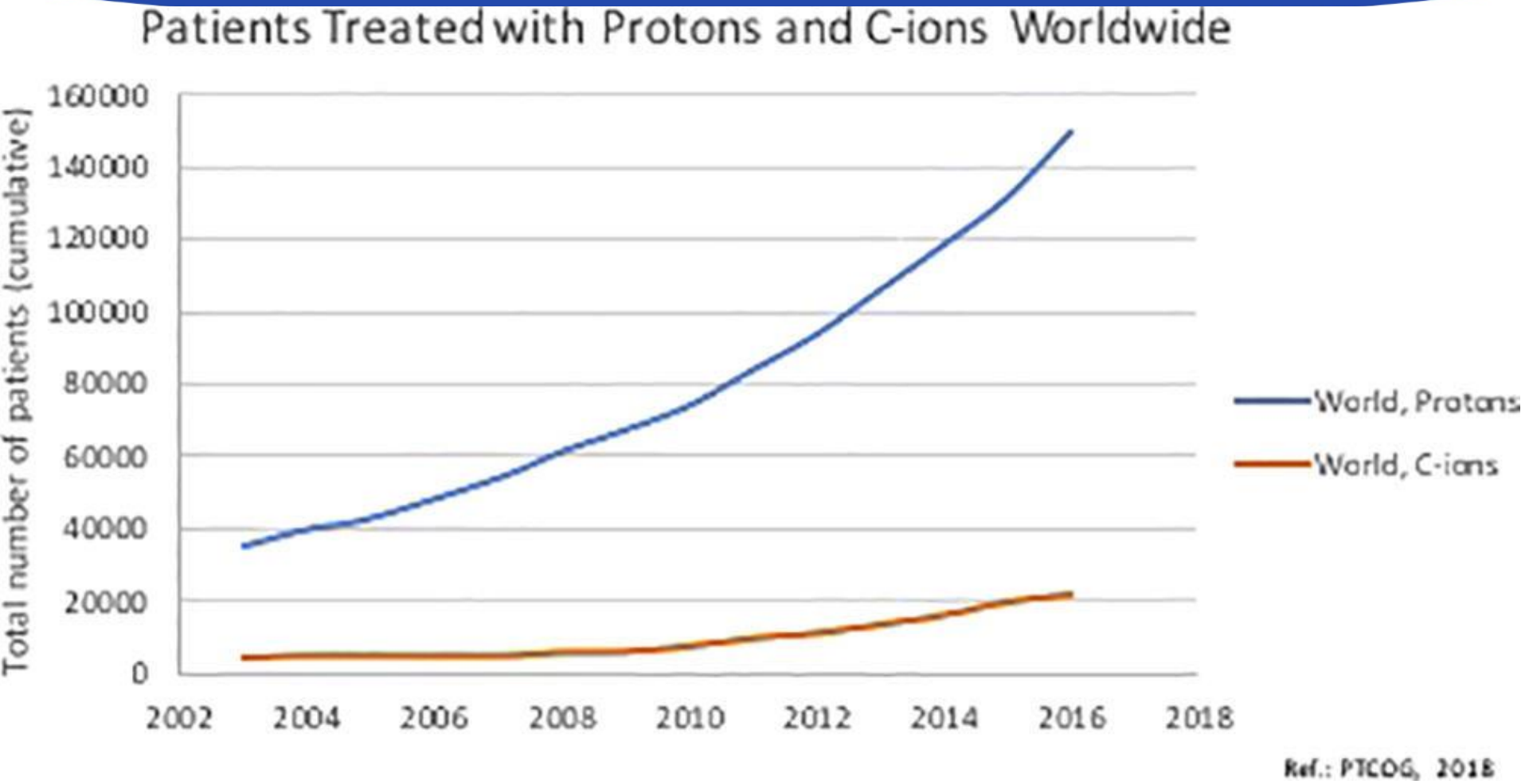
1993 Bevalac closed (LBNL)

Hospital-Based

930 1940 1950 1960 1970 1980 1990 1995 2000

LBNL 30
LBNL (helium ion) 2054
Uppsala, Sweden 73 236
MGH,Cambridge, MA 9116
Moscow 3539
Dubna 84 154
St. Petersberg 1029
Chiba, Japan 133
Tsukuba, Japan 700
Villigen,Switzerland 3712 + 129
Clatterbridge,UK 1201
Loma Linda 7176
Louvain, Belgium 21
Nice, France 1951
Orsay, France 2157
Bloomington, IN 34
Faure, S Africa 398
Davis,CA 448
Vancouver 77
Berlin 317
Catania 24
Kashiwa 161
Hyogo 60
Wakasa 2
Boston 229
Tsukuba145

1st Hospital based facility



Radiotherapy and Oncology DOI: (10.1016/j.radonc.2018.03.014)

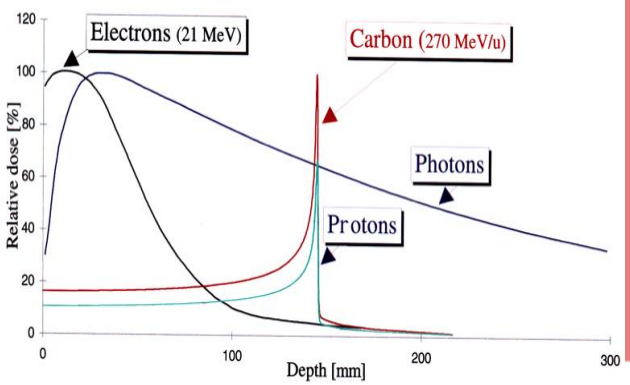
30 years High-LET Particle Therapy– Milestones

1956 Scientific justification of using HCP for therapy
1971 Heavy ions in Bevatron
1971 Radiobiology using neon ions
1975 Bevalac completed
1976 HCP therapy trial at Bevalac
1993 Bevalan stand down

1950 1960 1970 1980 1990 2000

LBNL, Berkeley 433
BHIC, Berkeley, design study
HIMAC, Chiba, Japan, 917
GSI, Darmstadt, Germany 84
EULIMA, EU, feasibility study
ITEP, Moscow, design study
Hyogyo, Japan, commissioned
Heildelberg, Germany, gb
Stockholm, Sweden
ADROTERAPIA, Italy,
MedAustron, Austria

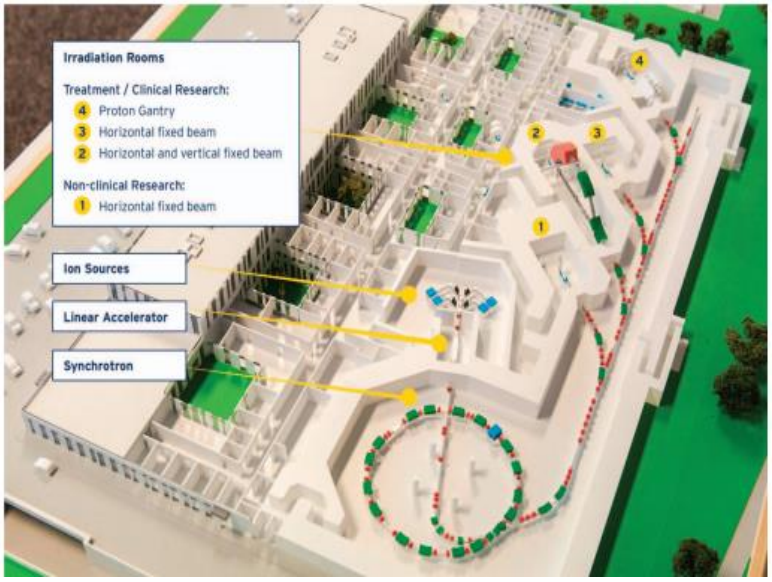
CLINICAL TRIAL



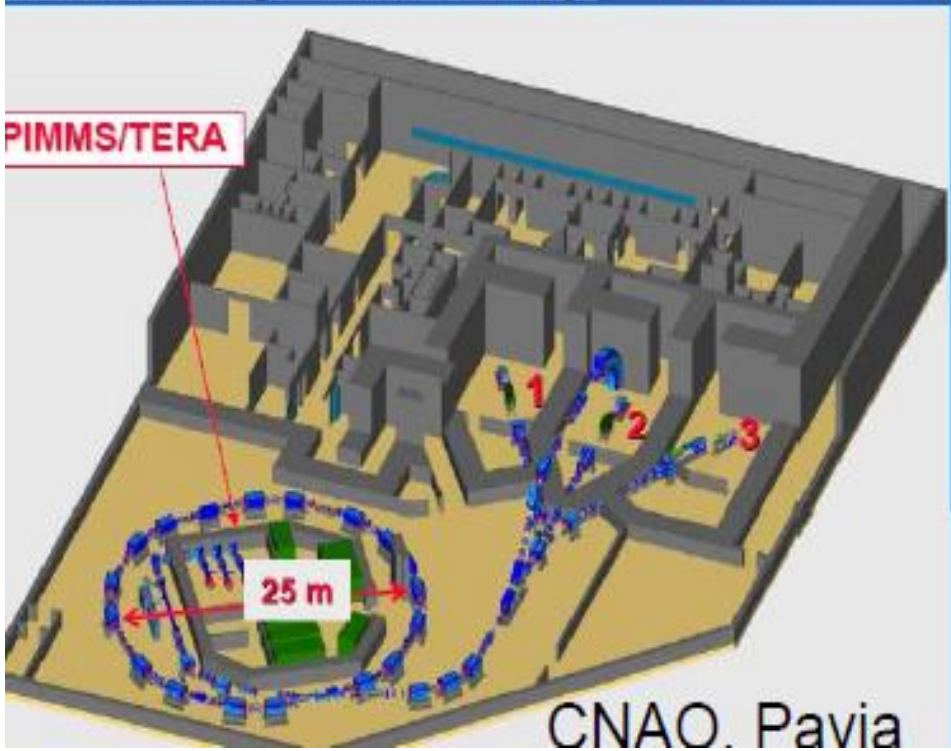
>25000

Hospital-Based Medical Accelerators

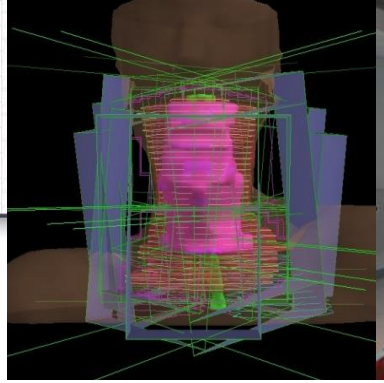
Hadron centers



<2% of all RT

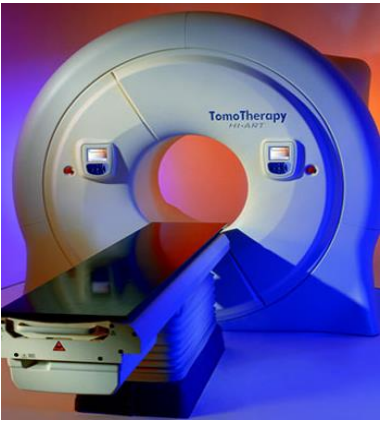


RT today



3DCRT IMRT/VMAT SRS/ SABR

Selectivity, effectivity, accuracy



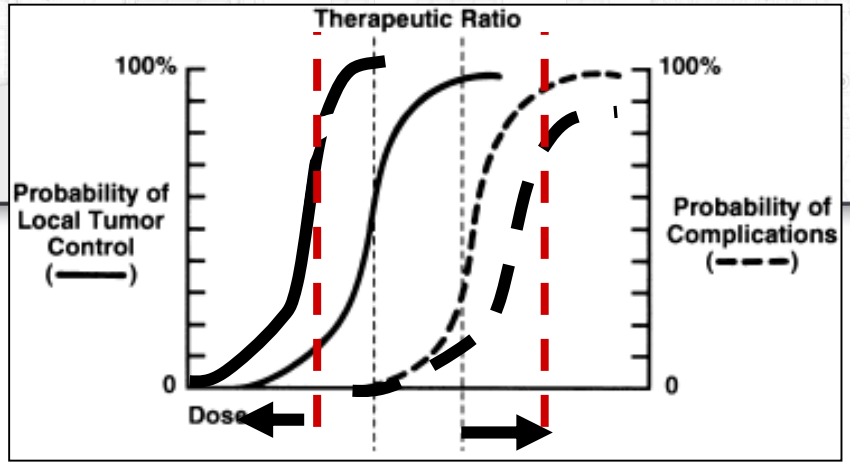
IGRT

Motion control

Hadron therapy

new gen. part. acc

Future of RT

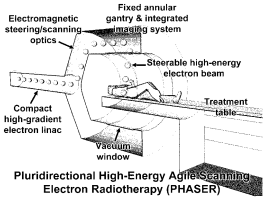


Novel approaches under clinical evaluation

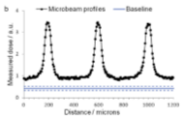
- **Fractionation:** hypofr./Acceler, Individ fr.
- **Technique:** Dose painting, **Hadron Th**
- Mixed energy RT
- **Combined treatment**
- sensitisation/protection
- Chemo-, hormon, biol.m., hypoxic sens.
- BNCT
- Immuno-Radiotherapy

Novel approaches under preclinical evaluation

- FLASH-RT 500ms pulses of >40 Gy/s
- VHEE -PHASER patented US20130231516



- Nanoparticles for RT sensitisation
- Mixed particle therapy
- Microbeam radiotherapy



- Dose and LET painting
- BPCEPT

PERSONALISED RT BASED ON RADIOMICS/GENOMIC

The implementation of precision medicine, such as genomics, radiomics, and mathematical modelling open the possibility to personalised RT adaptation and treatment.

THANK YOU FOR YOUR ATTENTION!

HUNGARIAN GOVERNMENT

European Union
European Social Fund

INVESTING IN YOUR FUTURE