Hadron therapy

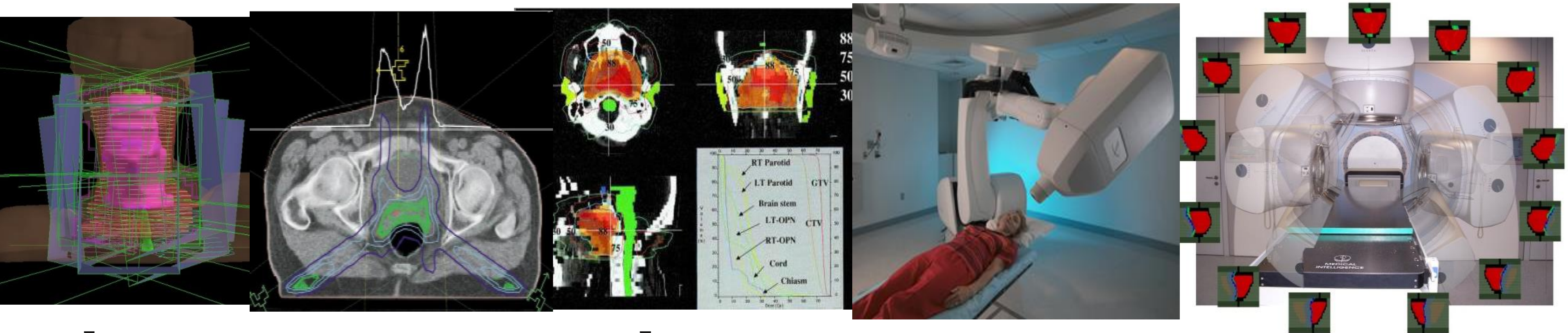
Katalin Hideghéty

LAMELIS 2016

Lasers in Medicine and Life Sciences

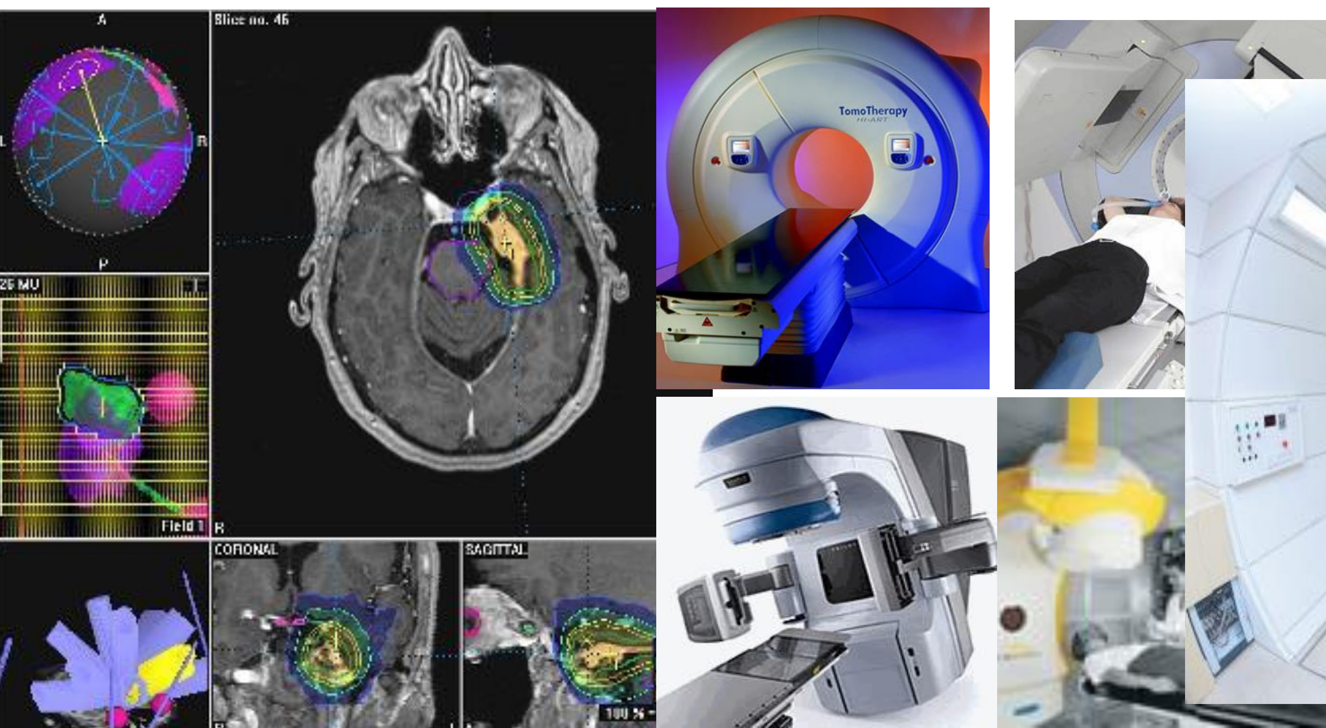
Advanced summer school for students of medicine and physics

30th June – 9th July 2016



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

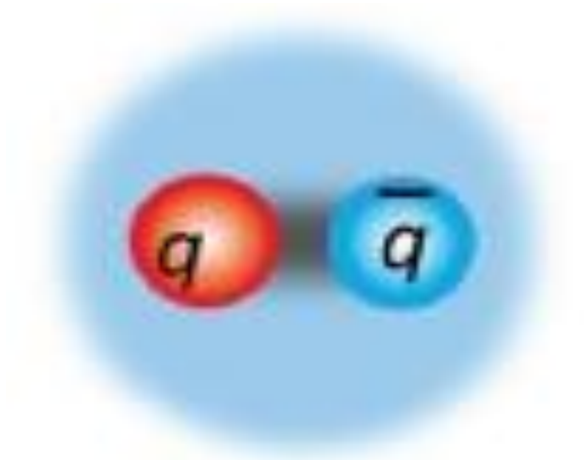
Selectivity, effectivity, accuracy



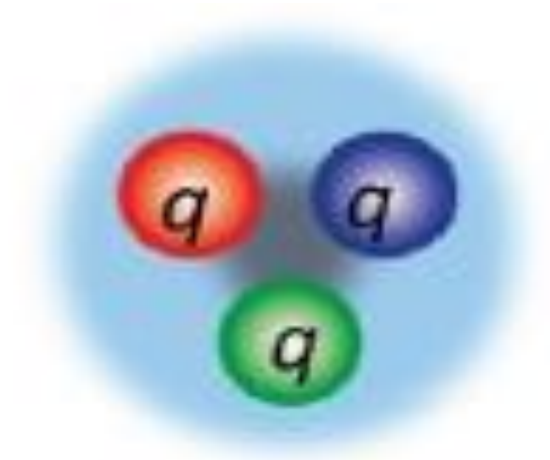
Hadron th.

Hadrons

Complex subatomic particles

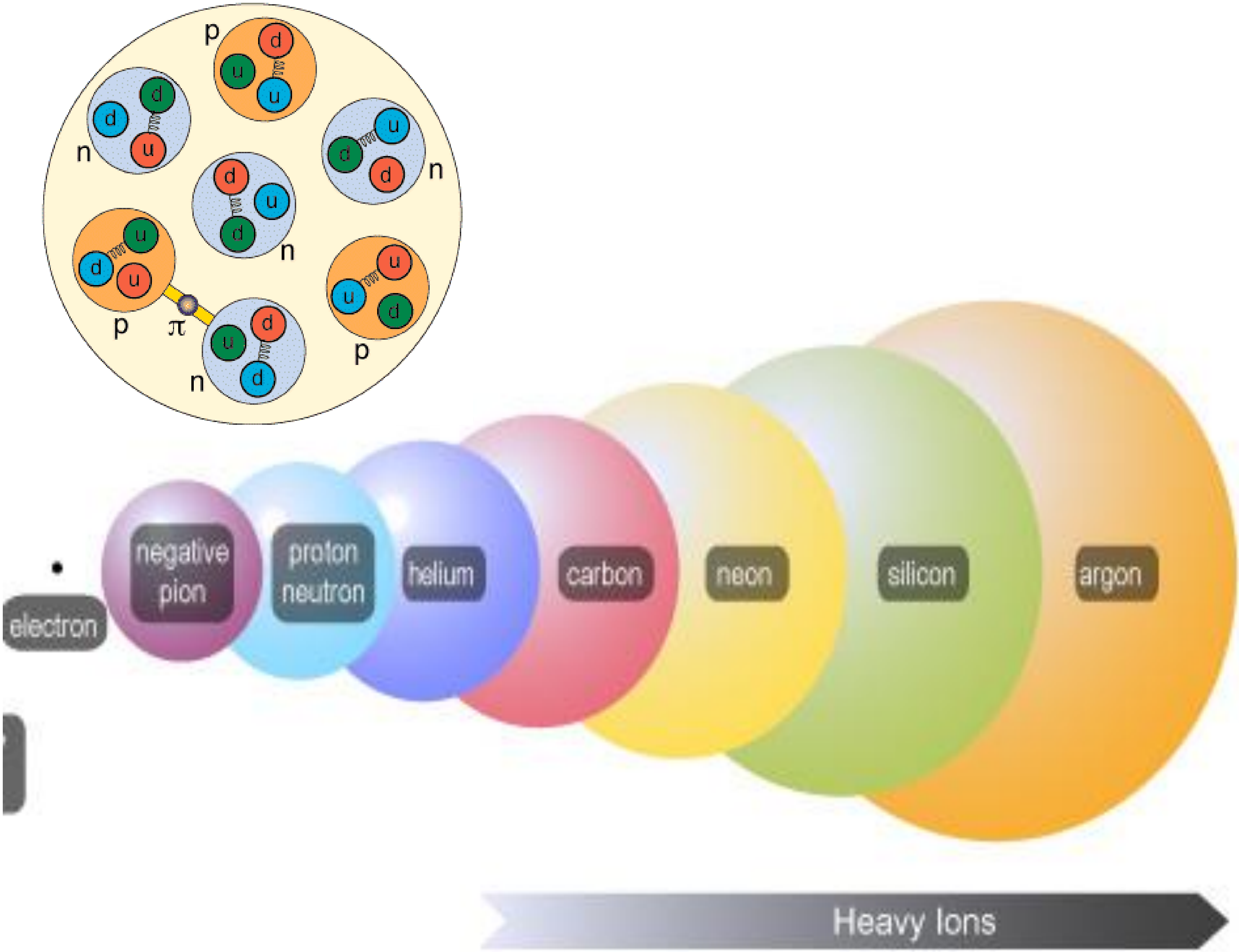


Meson



Barion

A.V. Anisovich, V.V. Anisovich, M.A. Matyeev, V.A. Nikonov, J. Nyiri, A.V. Sarantsev: Mesons and Baryons: Systematization and Methods of Analysis, 2009, World Scientific


p
n
π
u
d
electron
negative pion
proton neutron
helium
carbon
neon
silicon
argon
Heavy Ions

Nuclear particles

High physical selectivity

High LET
high RBE

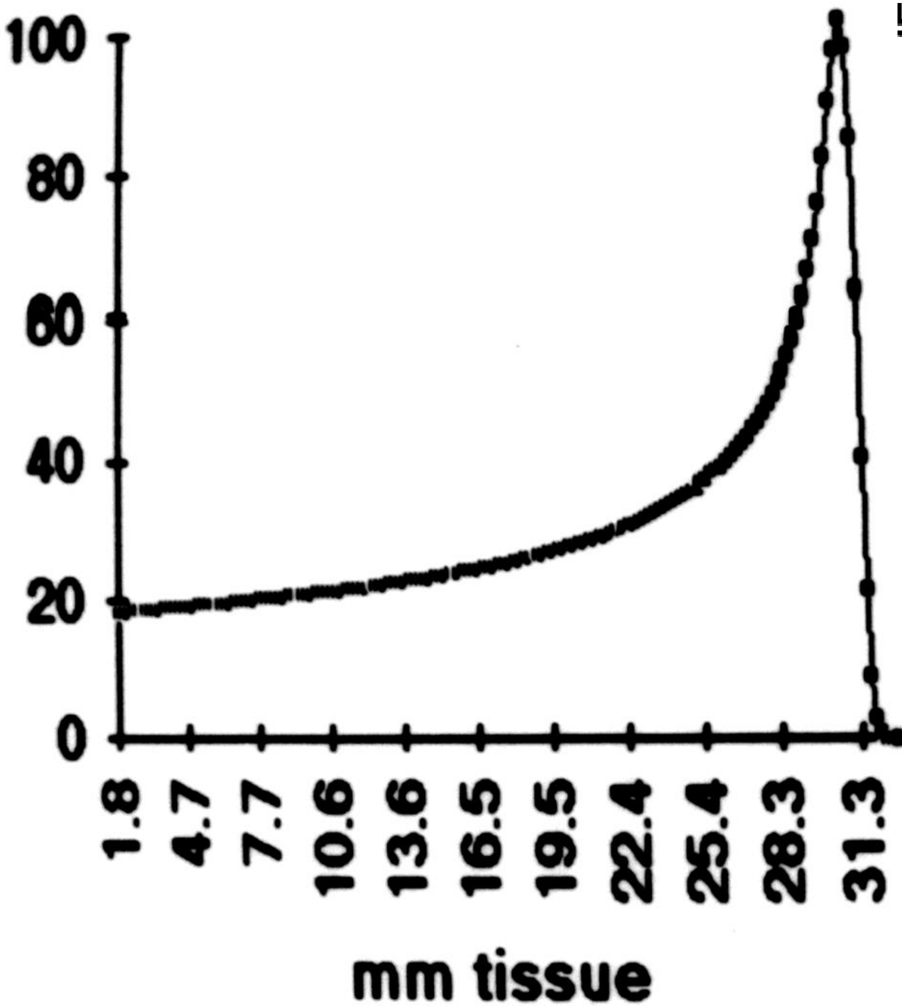
Proton
π-Meson

Fast neutron

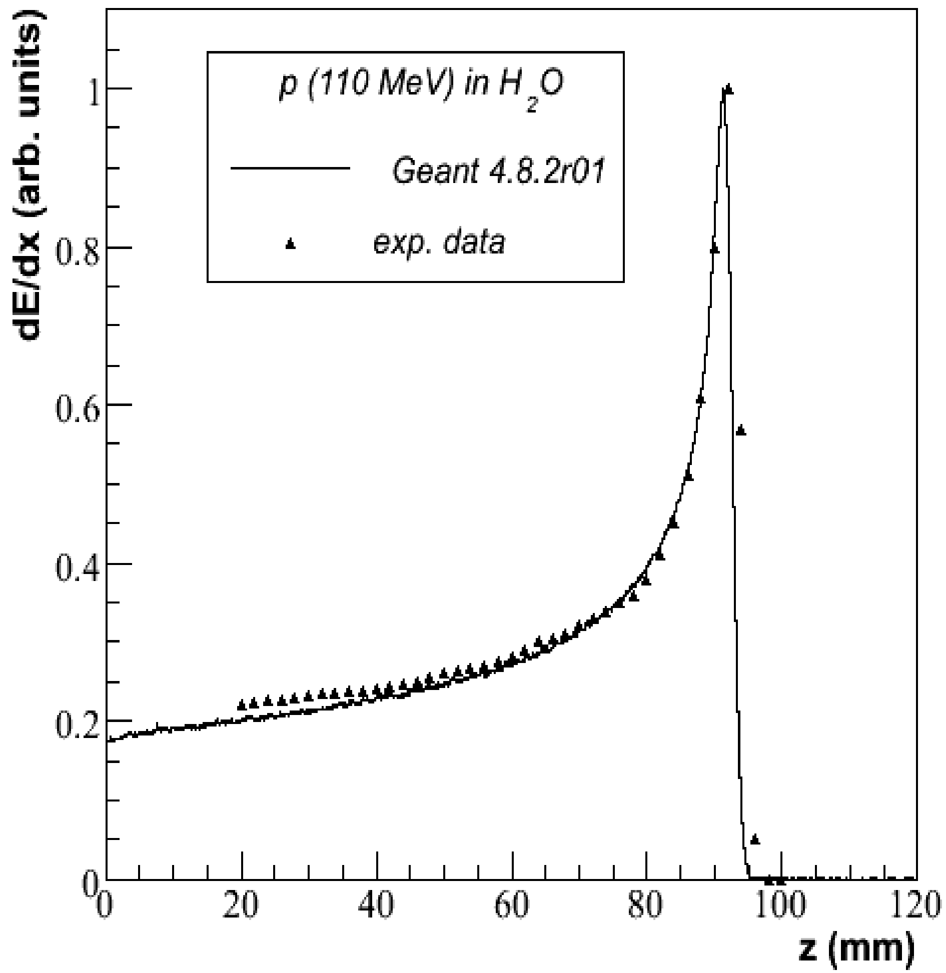
α-particle

heavy ions:
Carbon, Oxigen, Neon

Bragg Peak



100
80
60
40
20
0
1.8
4.7
7.7
10.6
13.6
16.5
19.5
22.4
25.4
28.3
31.3
mm tissue



p (110 MeV) in H2O
Geant 4.8.2r01
exp. data
dE/dx (arb. units)
z (mm)
0
0.2
0.4
0.6
0.8
1
20
40
60
80
100
120

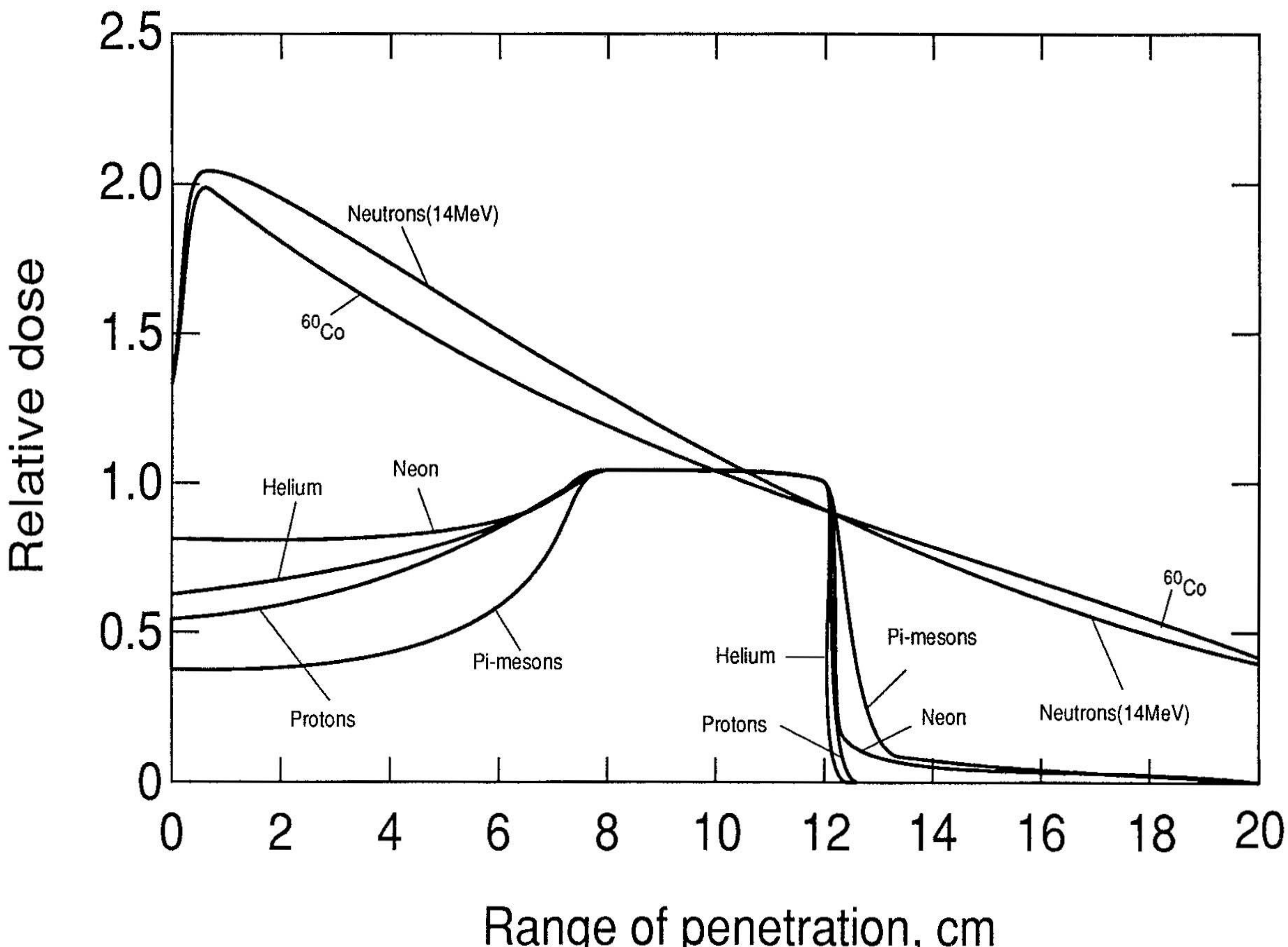
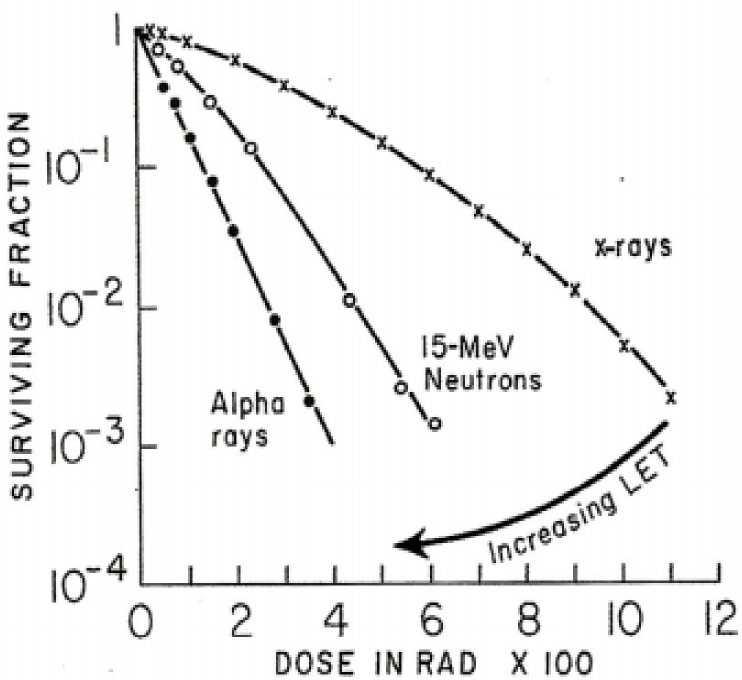
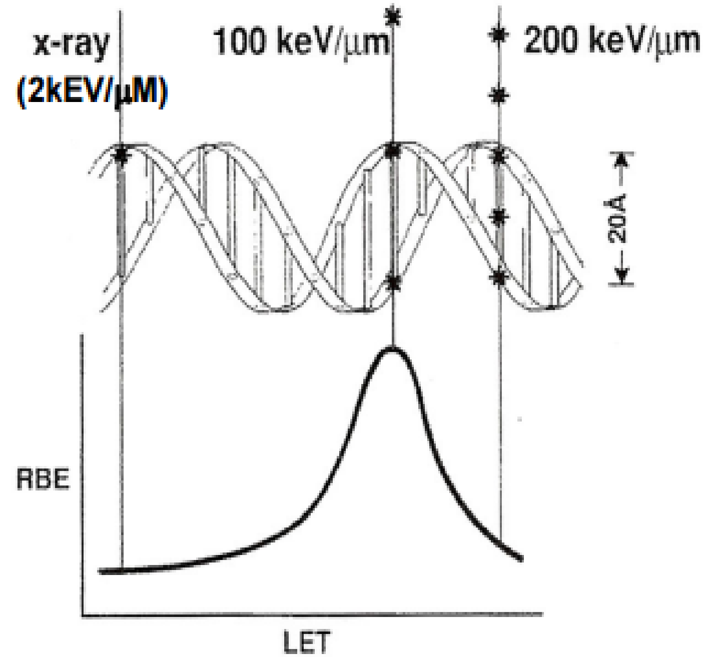


Fig. 2. "Depth-dose curves" for neutron, pion, proton and neon-ion beams as compared to the "gold standard", a photon beam produced by ^{60}Co. From published and unpublished data [2,3].

RBE: LET dependence





with increasing LET (linear energy transfer):

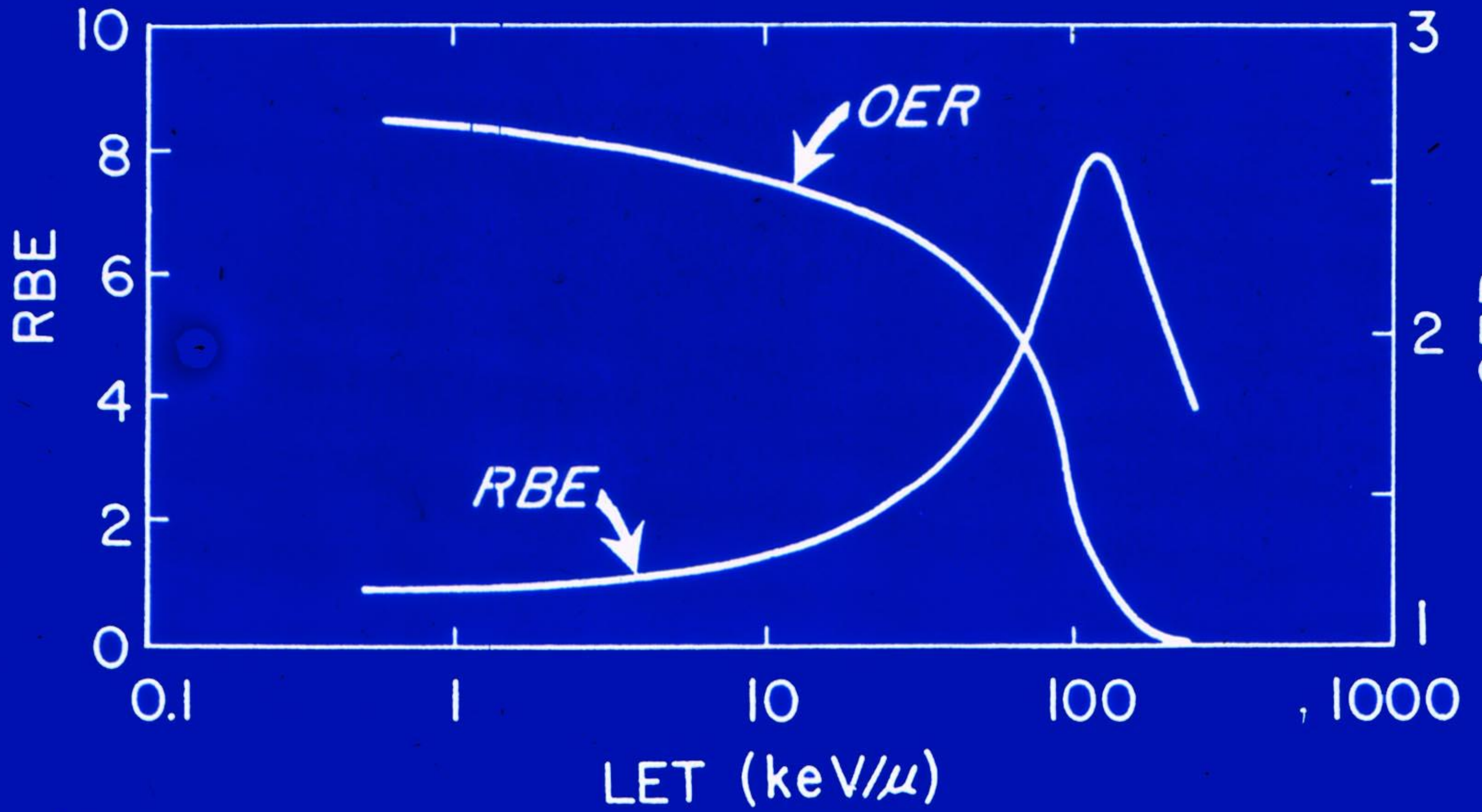
-the slope of the survival curve gets steeper
-size of initial shoulder gets smaller

Biological explanation for LET dependence /optimum

more than 1 track required for x-ray/proton-induced DSB: (sparsely ionizing)

LET: descriptor of energy transferred from the beam to the irradiated material per units of particle path length (e.g. keV/µm)

Variation of the OER and the RBE as a function of the LET of the radiation involved.



(Redrawn from Barendsen GW 1972)

HADRON THERAPY SOURCES

Tele/Percutan therapy	Isotop/Brachytherapy
Cyklotron, synchrotron	α-emitter (^{211}Astatin)
Atomreactor	neutr.(^{252}Californium)
Laser accelerated protons	

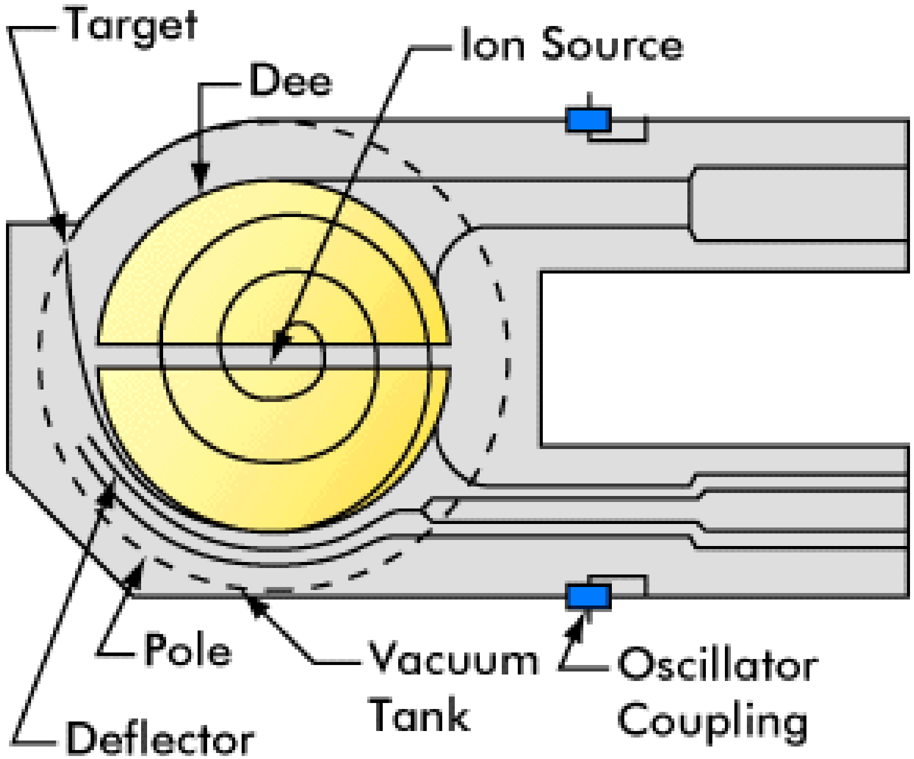
Thermal/epithermal neutron source research reactor

Capturing atom carrier

→ Neutron-capture therapy

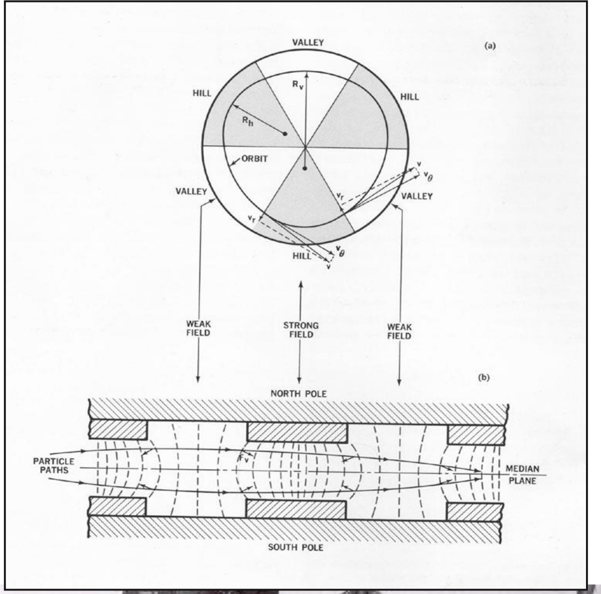
Cyclotron

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).



Sector focused cyclotron

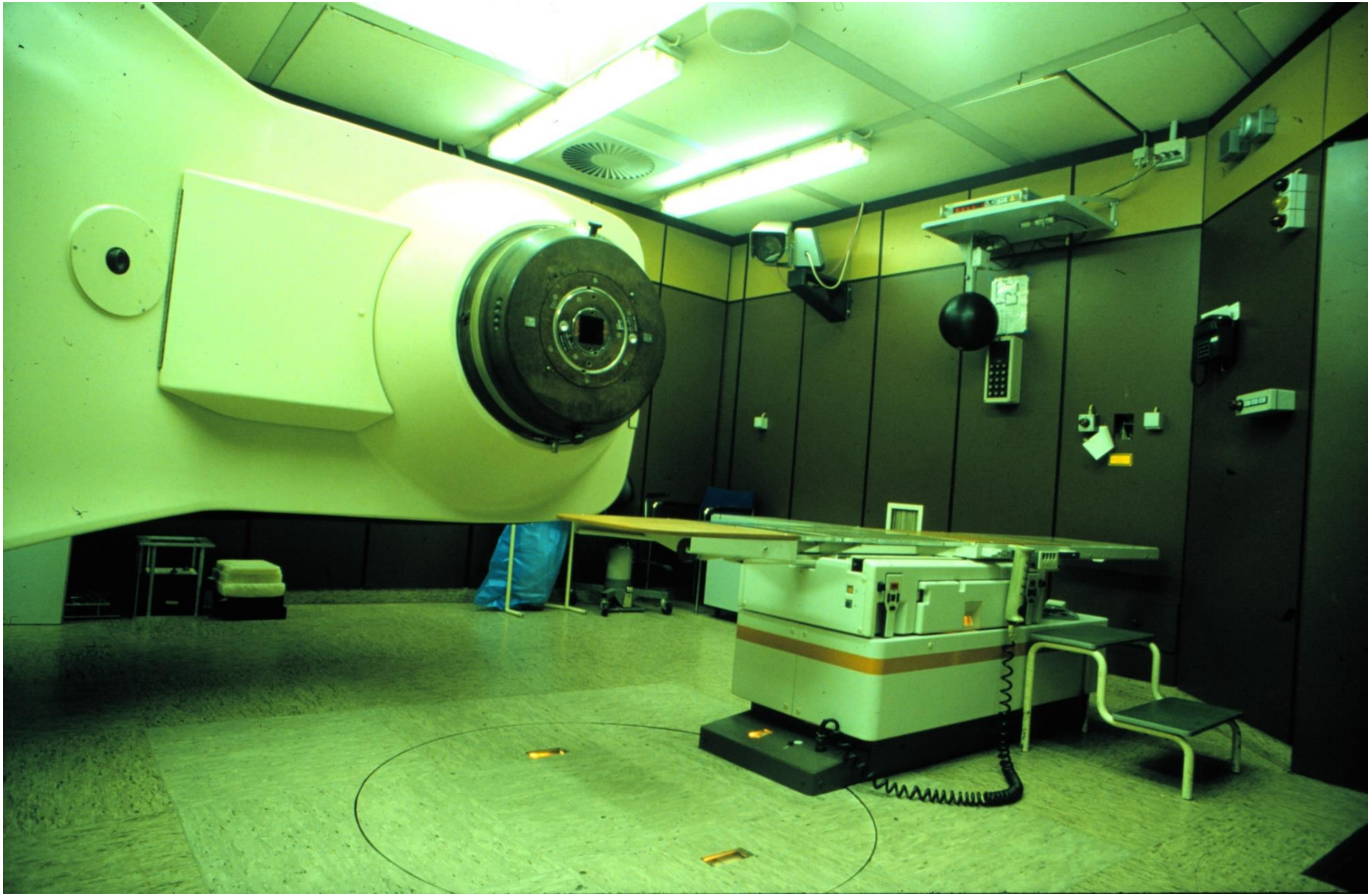
Synchrocyclotron



A history of fast neutron therapy

- 1930 Ernest O. Lawrence (principe of cyclotron) Zirkle, Abersold, Lampe, John Lawrence, Stone
- 1938 First clinical experiences (single fraction)
- 1939-41 Stone und Larkin 226 patients(fraktionated)
- 1948 Janaway Memorial Lecture
- `70 Gray and Caterall (Hammersmith Hospital London)
- 1981 Breur und Batterman

Hospital based cyclotron

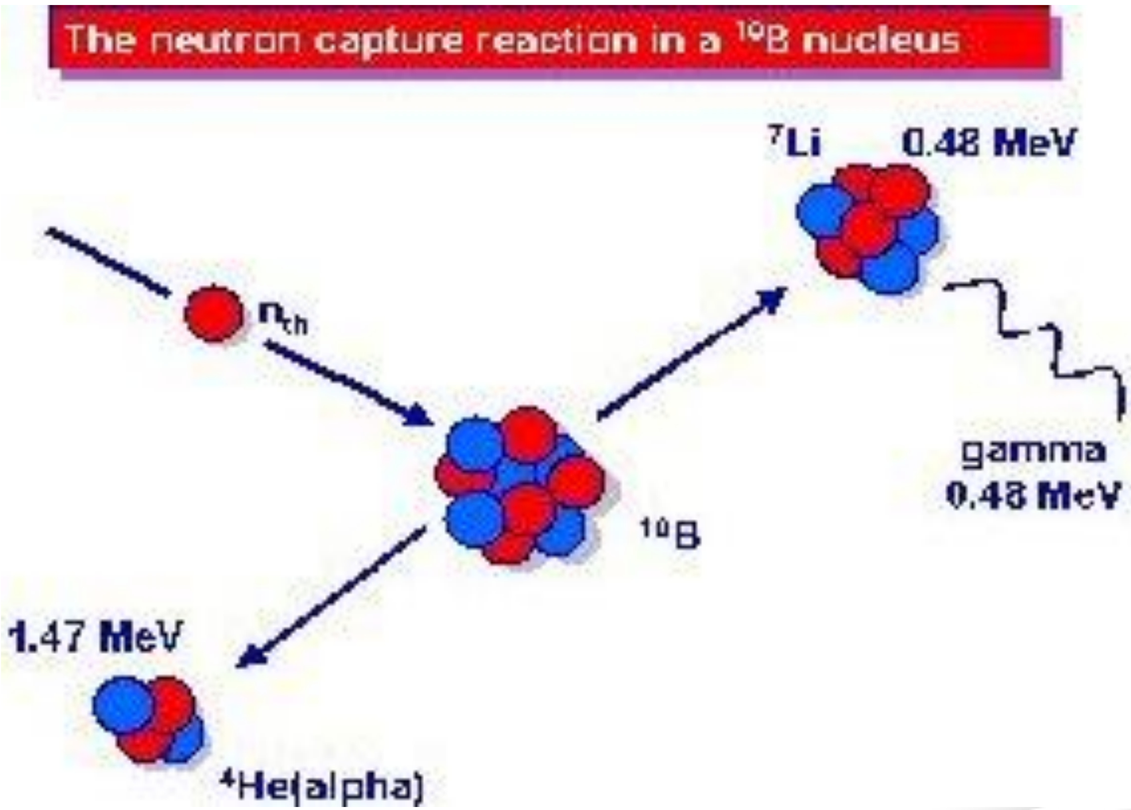


Neutron therapy centers

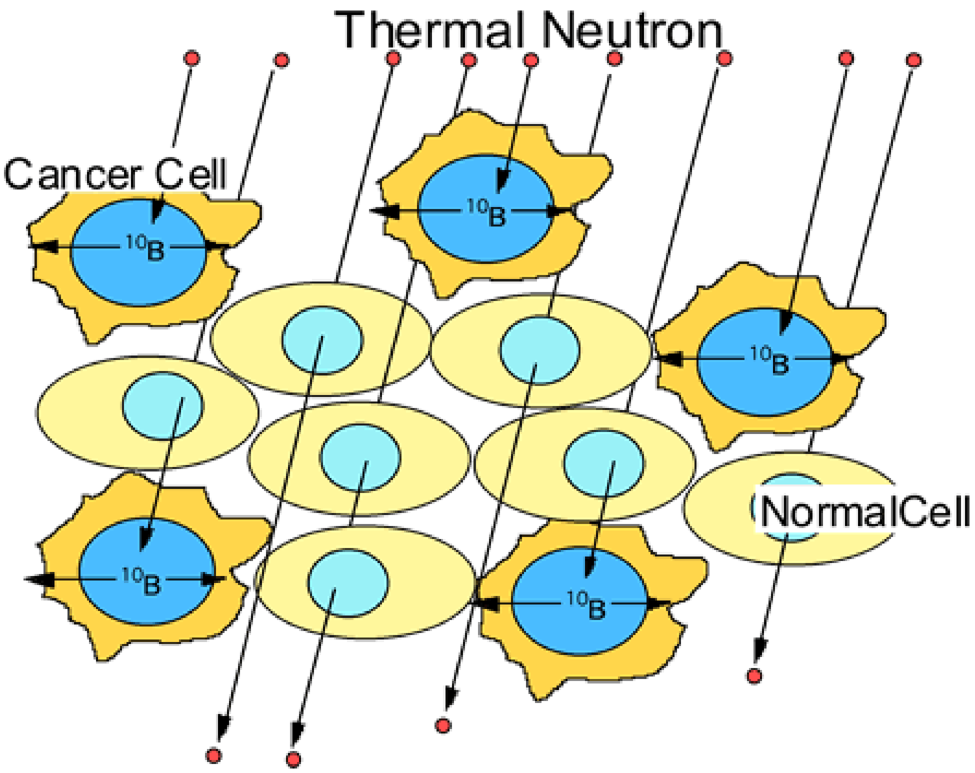
Essen	5,8MeV	salivarygl..,G1-2 sarc.
Orleans	14 MeV	MM.,gliobl
Nizza	40 MeV	-
Seattle	50 MeV	prostata.
Washington (Fermi)		sinus.,ut. sc.,lung
Faure	60 MeV	-“-

Boron Neutron Capture Therapy (BNCT)

Thermal neutrons captured by high probability by ^{10}B which desintegrates into two particles, whose absorption ranges in tissue (~9 mm and ~5 mm respectively) are as short as the diameter of a cell nucleus. All the energy is released inside the tumor cell.



Selective, cell-targetted energy deposition



High LET, dense

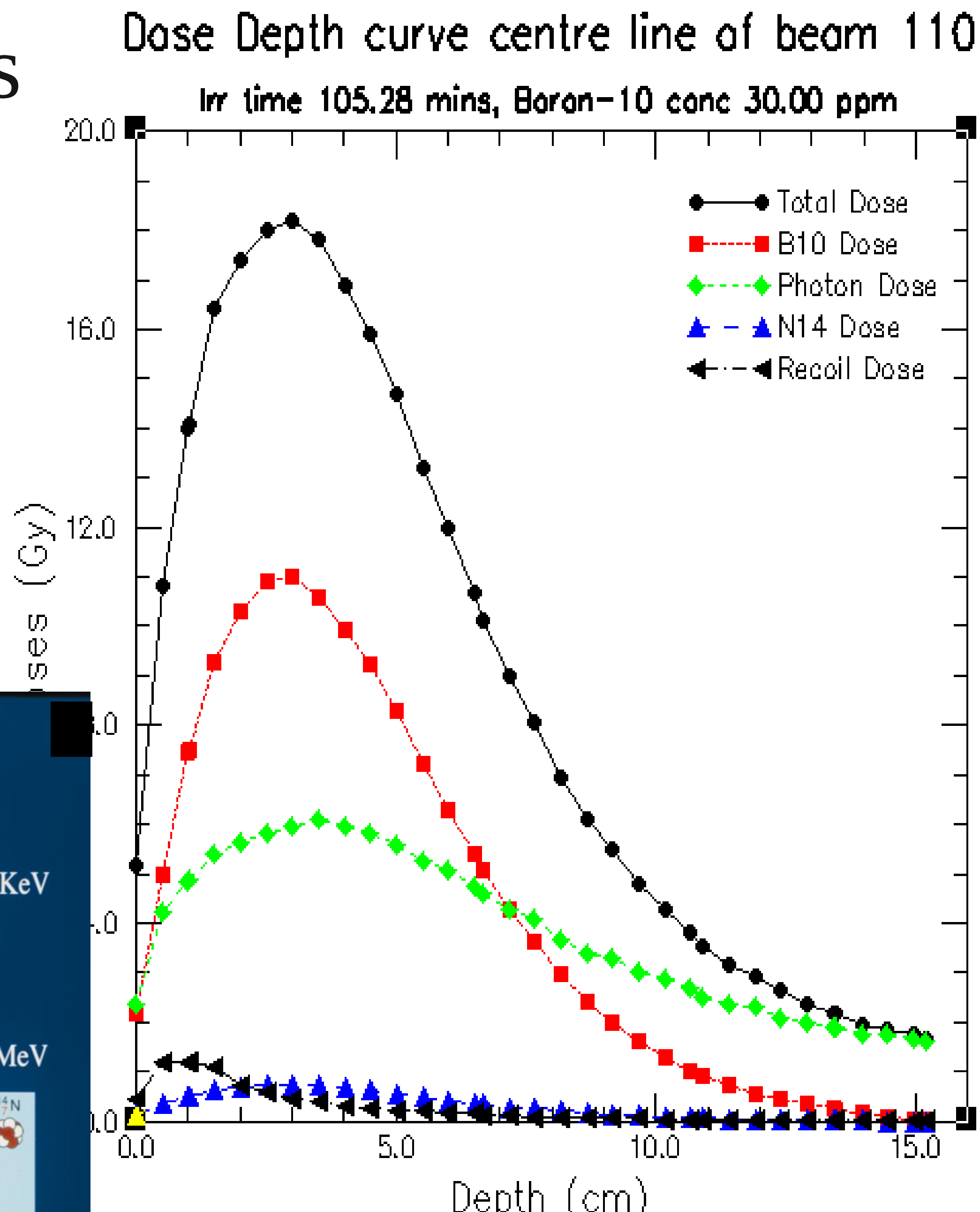
ionization

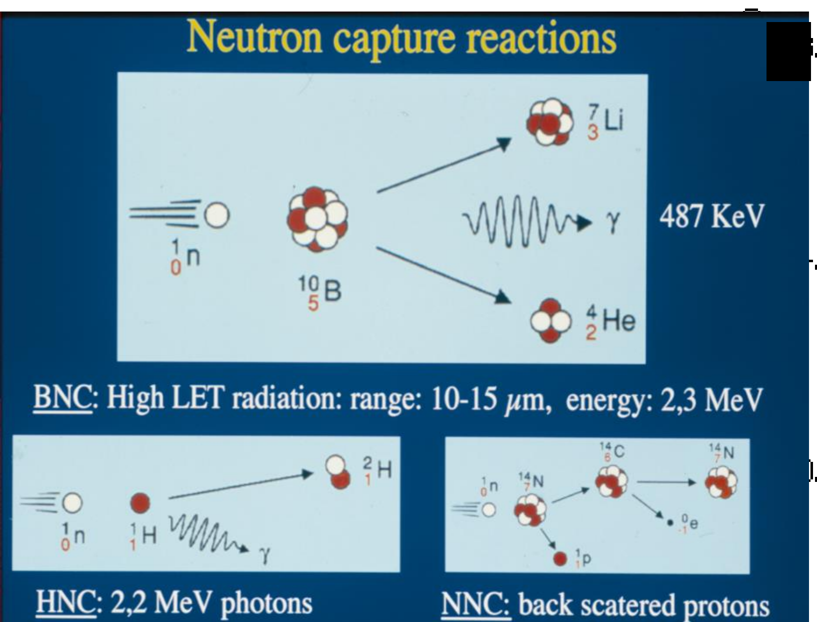
High RBE

Binary approach

Dose components

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





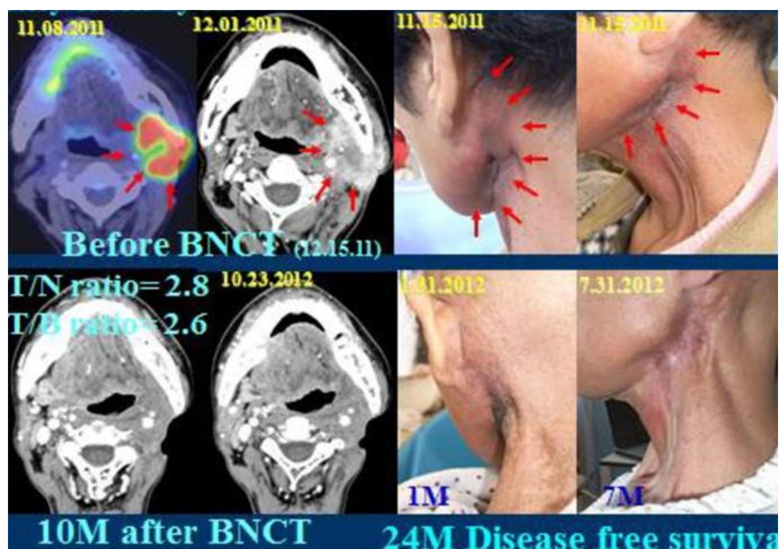
Boron Neutron Capture Therapy (BNCT) for GBM at the Petten facility - European phase I study

HFR Research reactor

<u>Boron carrier</u>

BSH

$Na_2B_{12}H_{11}SH$

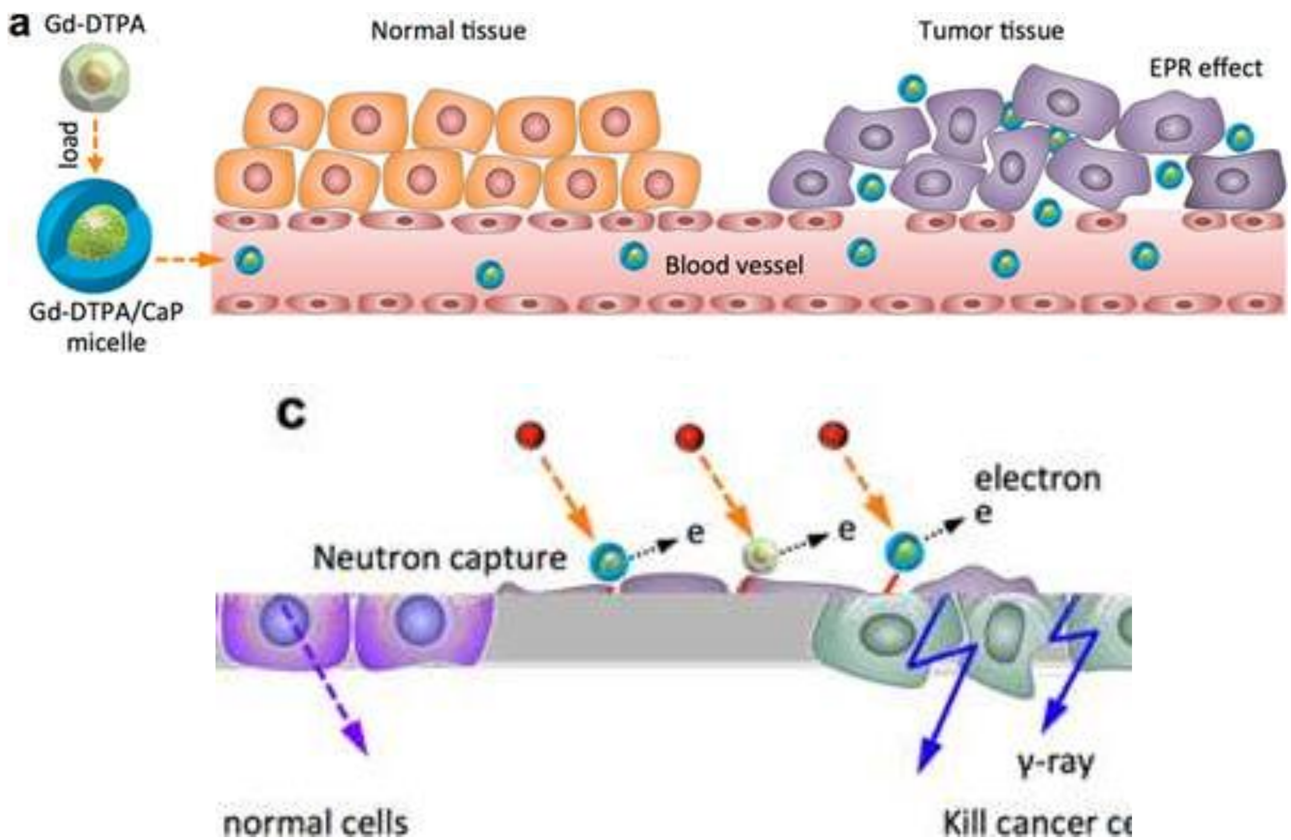


Recurrent H&N tumors

Boron carrier
BPA

^{157}Gd-NCT

- very high neutron capture cross section of 254,000 barns
- gadolinium compounds, such as Gd-DTPA (gadopentetate dimeglumine Magnevist®), are contrast agents for MRI of brain tumors, with high uptake by brain tumor cells in tissue culture
- neutron capture reaction: $^{157}Gd + n_{th}$ (0.025eV) → [^{158}Gd] → $^{158}Gd + \gamma$ + 7.94 MeV).



BNCT

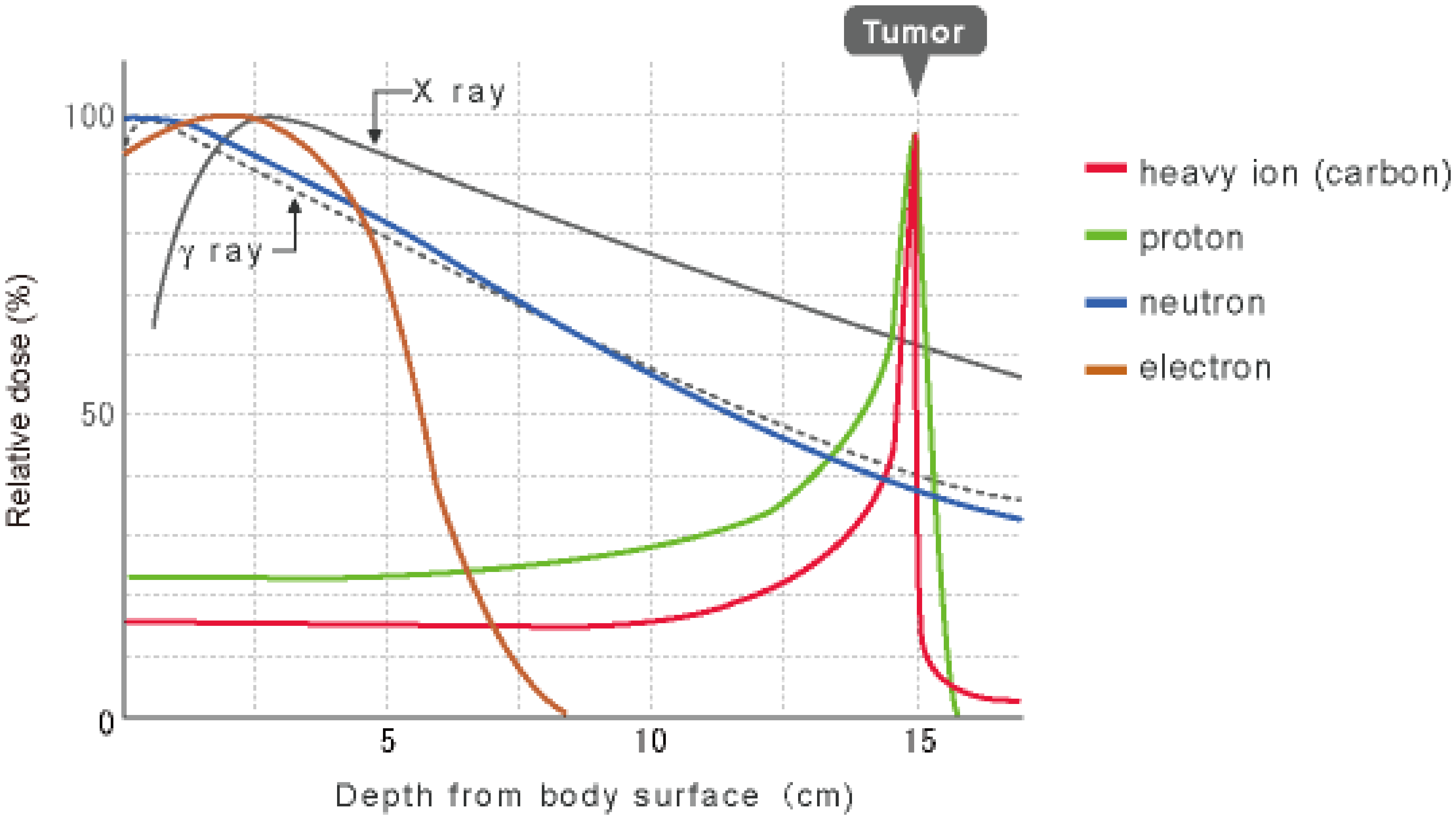
Up to now glioblastoma multiforme, melanoma malignum and reccurrent head and neck cancer were irradiated in the frame of clinical trials.

The clinical research is remarkably limited due to the lack of availability of proper epithermal, thermal neutron source.

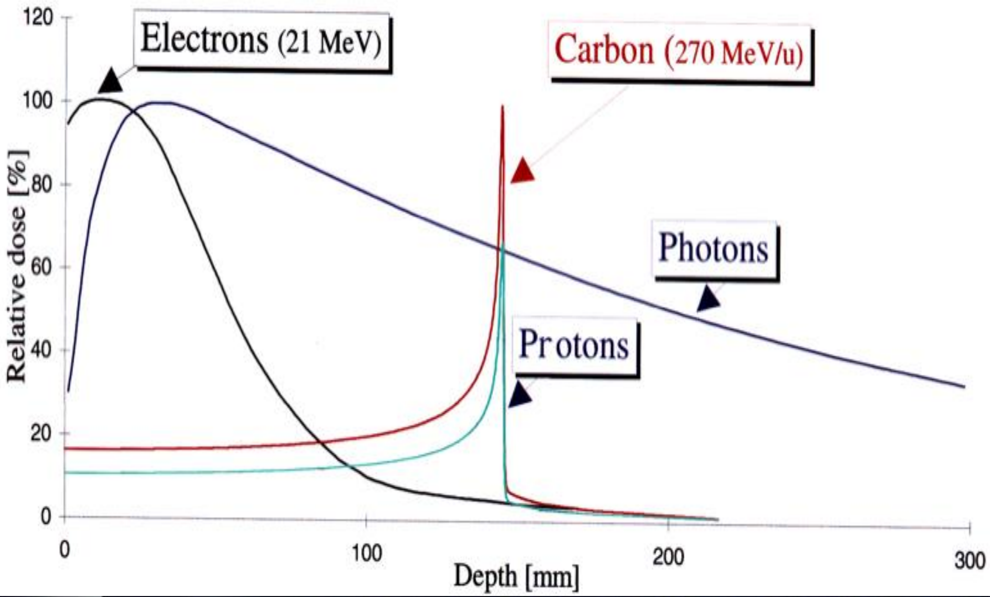
A LASER DRIVEN NEUTRON SOURCE COULD BE AN OPTION

Charged particle- therapy

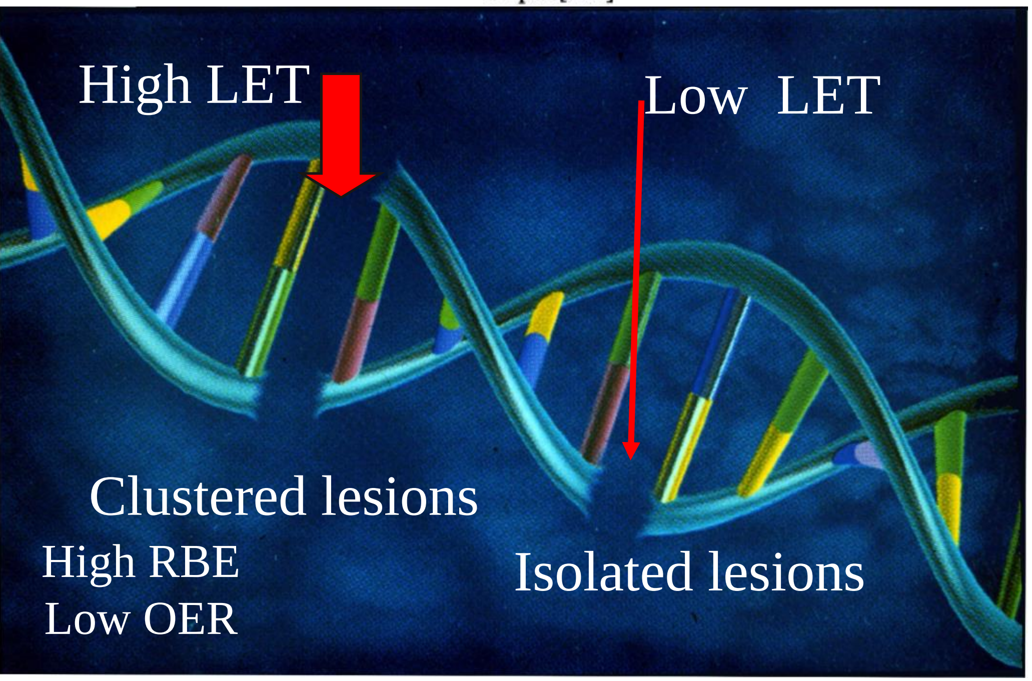
- Protontherapy,
- Heavy-ion therapy



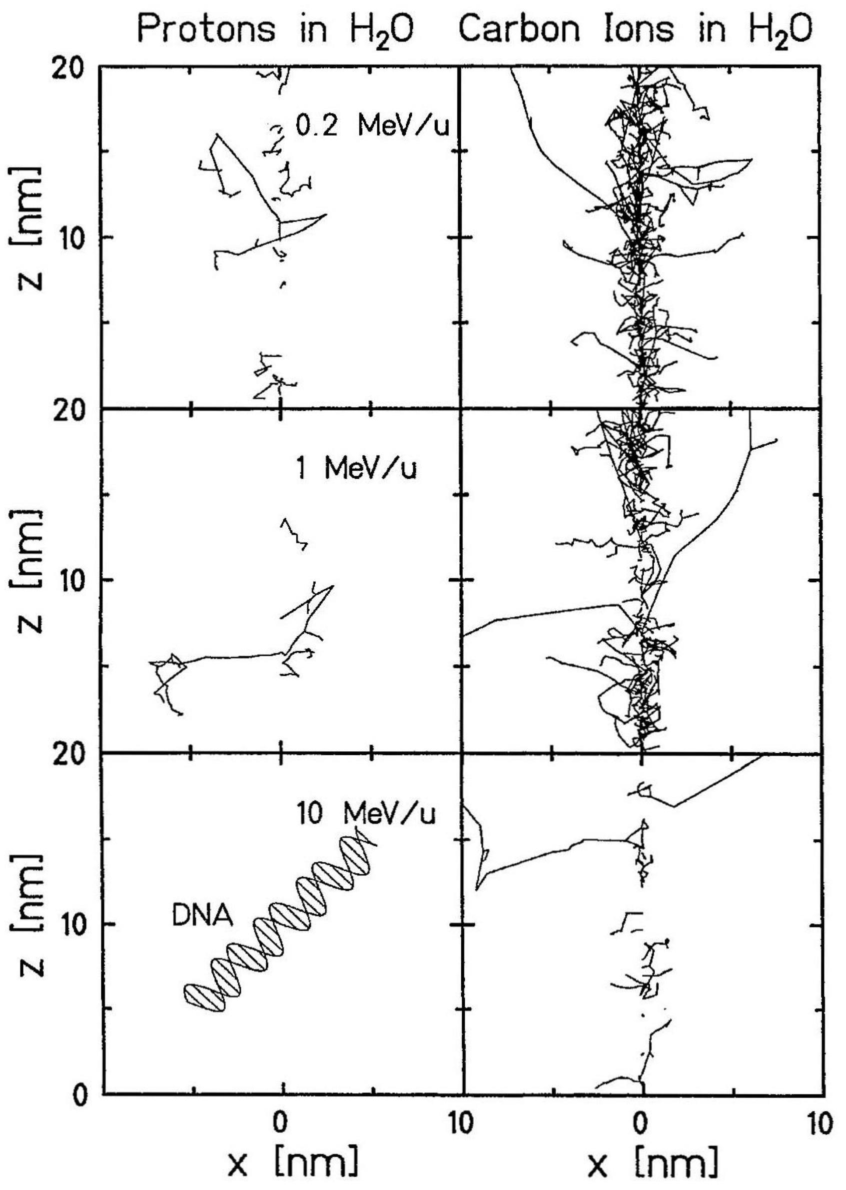
Tumor
X ray
γ ray
100
50
0
5
10
15
Relative dose (%)
Depth from body surface (cm)
heavy ion (carbon)
proton
neutron
electron



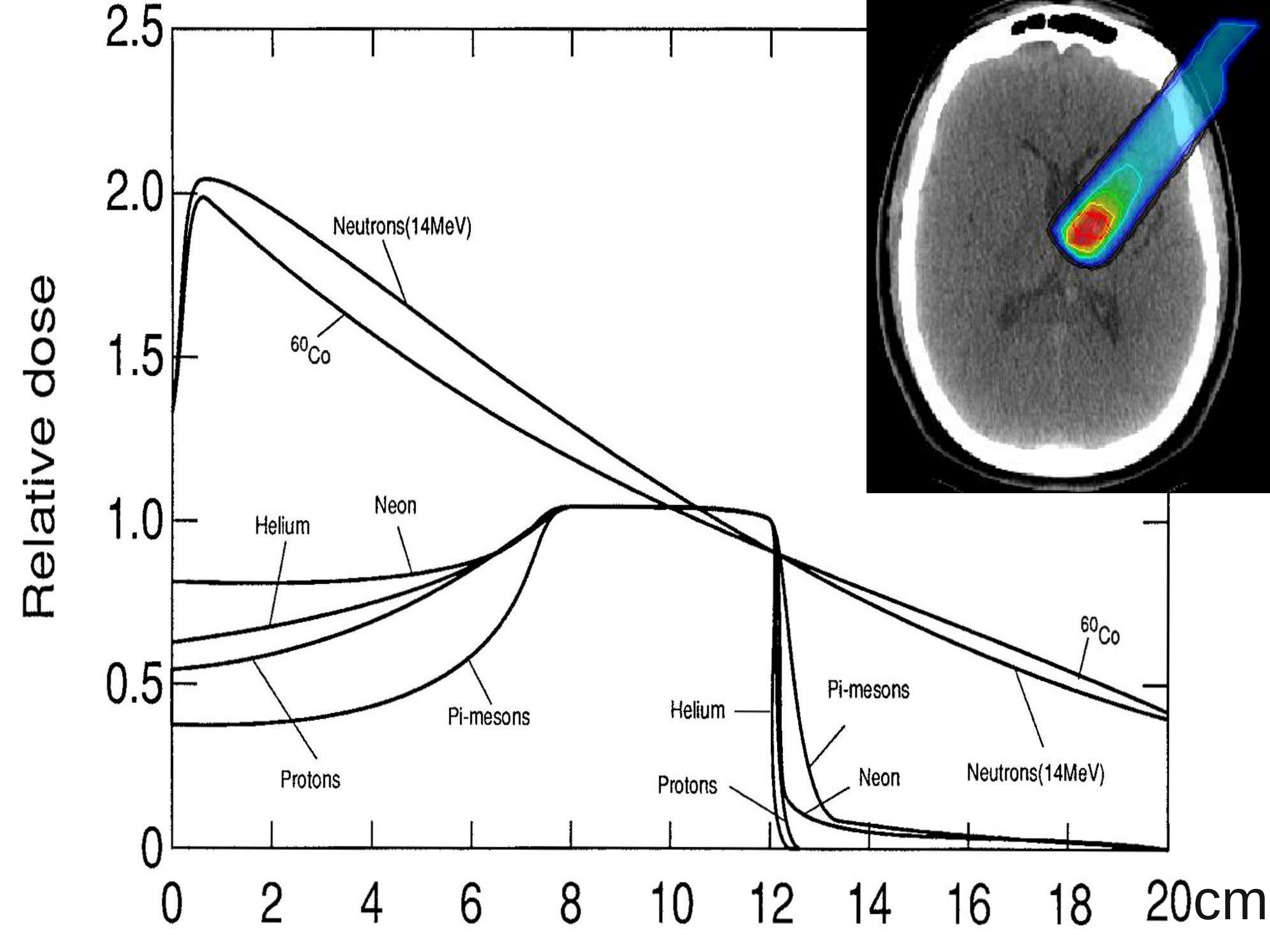
Electrons (21 MeV)
Carbon (270 MeV/u)
Photons
Protons
Relative dose [%]
Depth [mm]
0
20
40
60
80
100
120
0
100
200
300



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

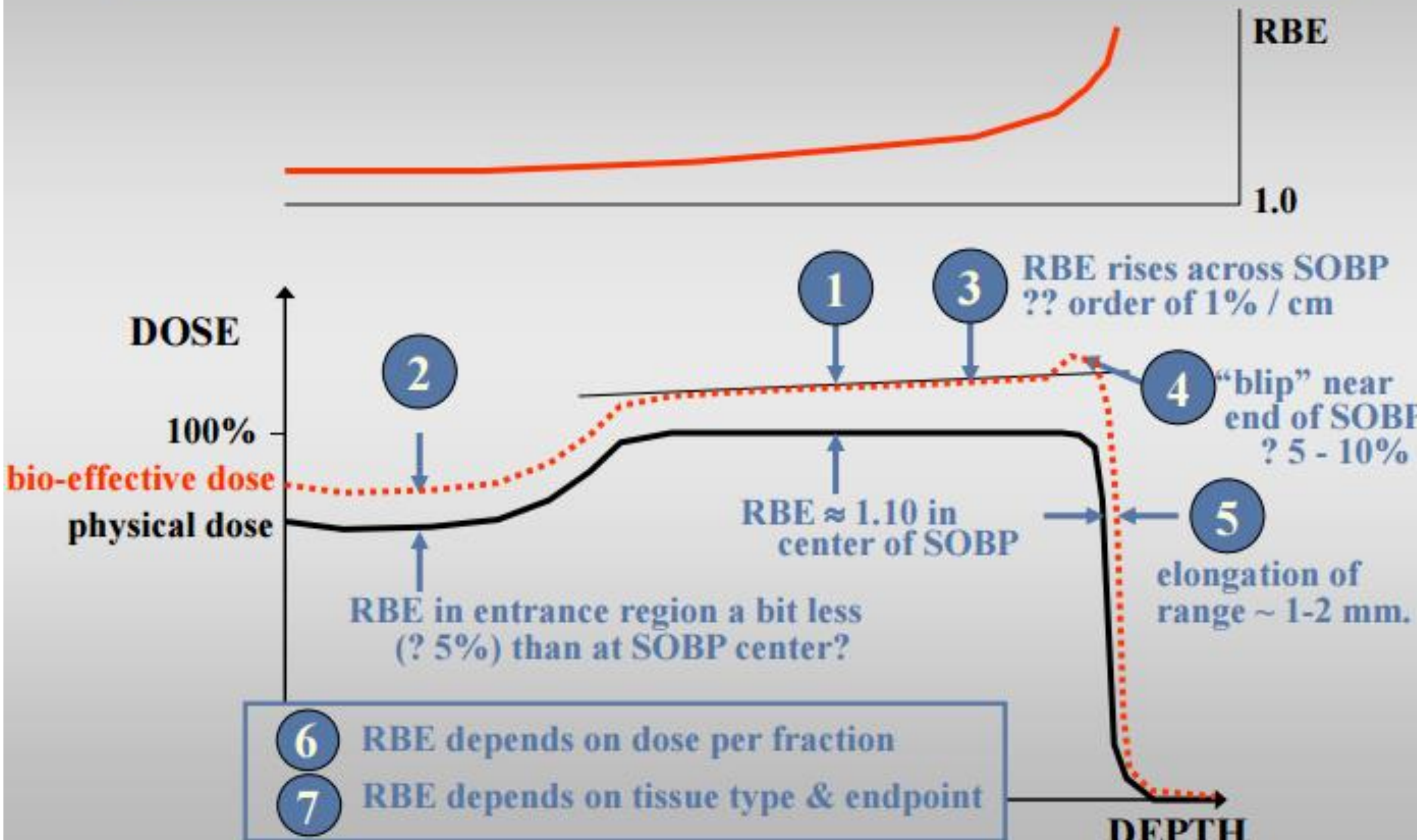


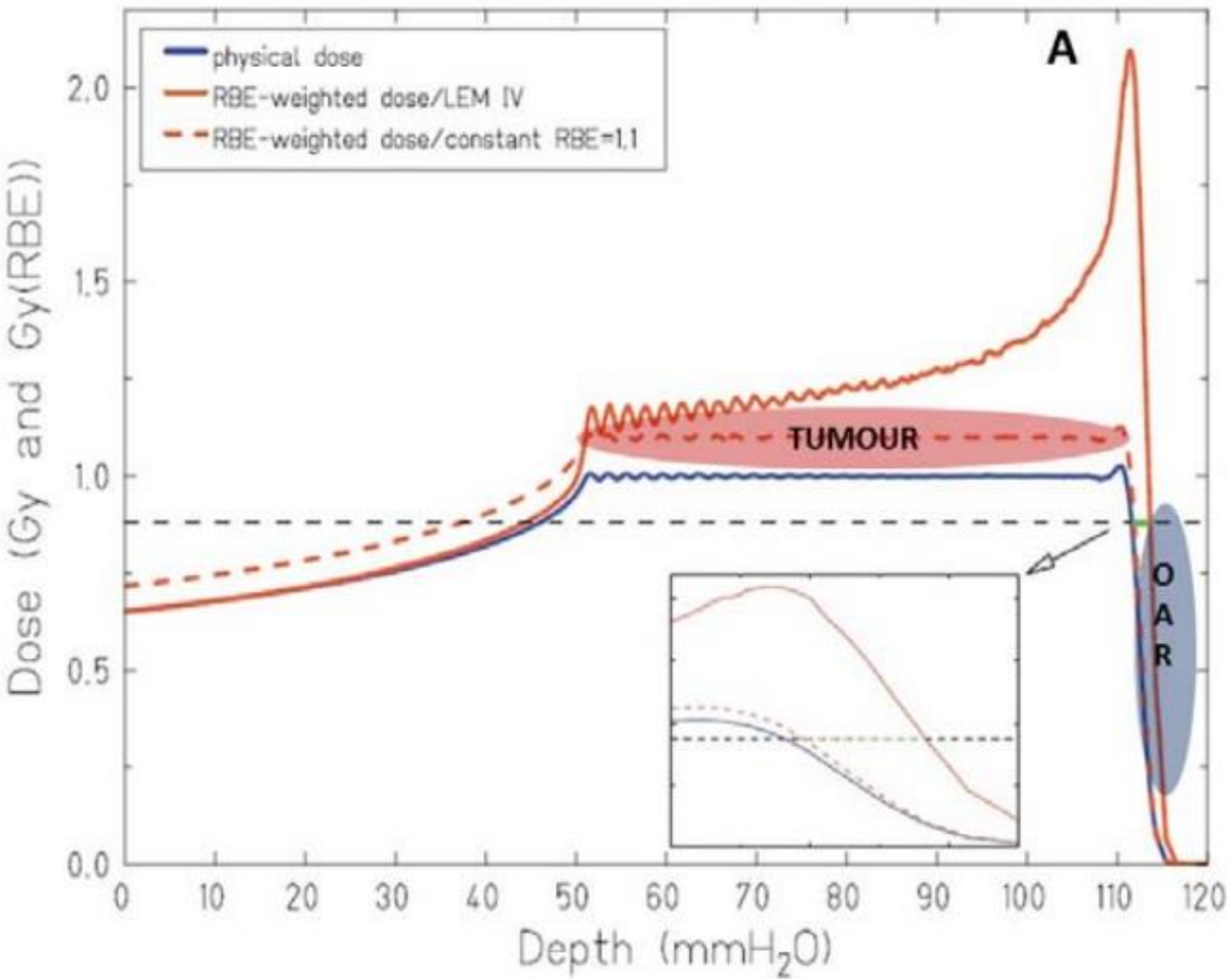
Protons in H_2O
Carbon Ions in H_2O
0.2 MeV/u
1 MeV/u
10 MeV/u
DNA
z [nm]
x [nm]
0
10
20



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

But, proton RBE needs (some) refinement



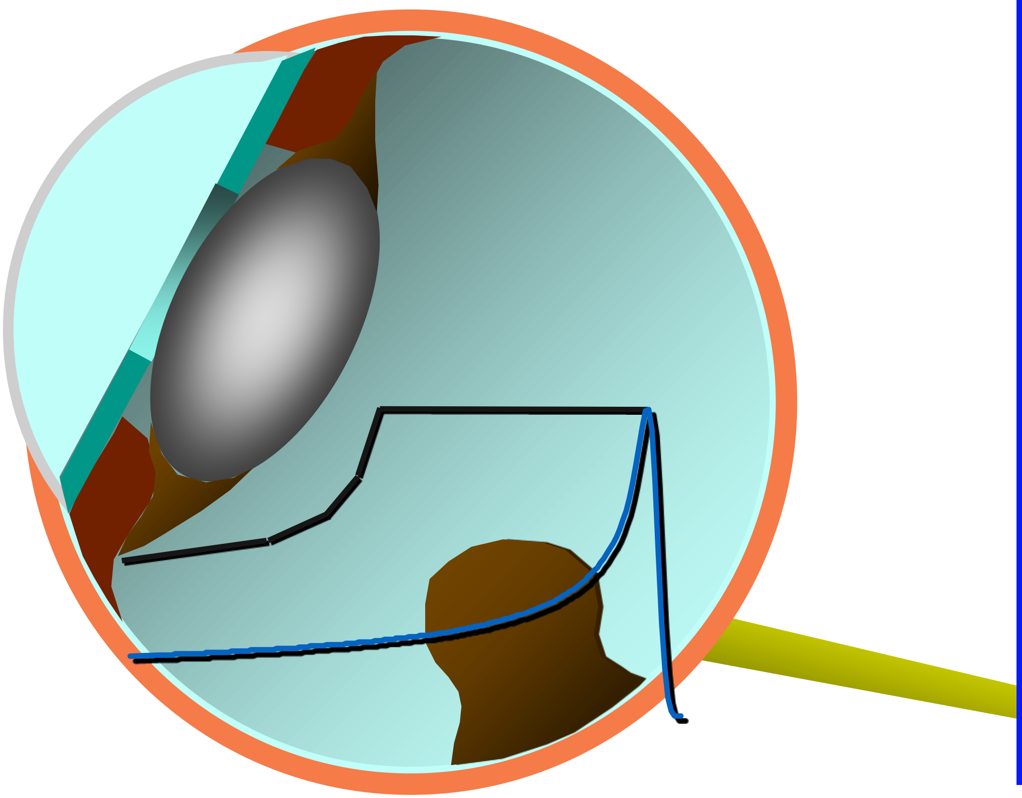


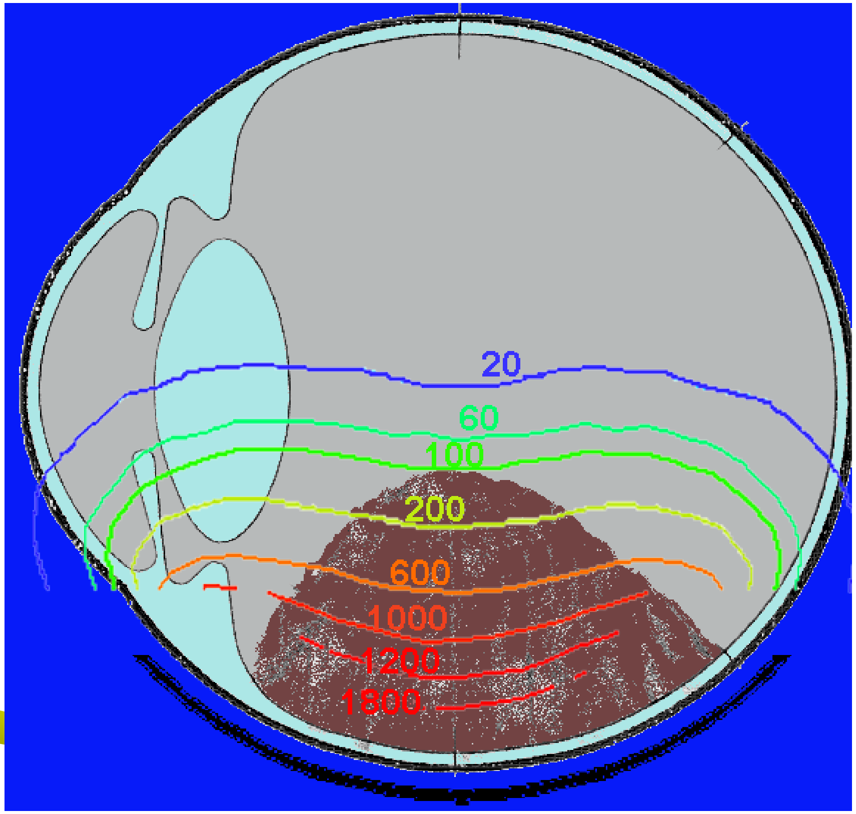
physical dose
RBE-weighted dose/LEM IV
RBE-weighted dose/constant RBE=1,1
A
TUMOUR
O
A
R
Dose (Gy and Gy(RBE))
Depth (mmH2O)
0,0
0,5
1,0
1,5
2,0
0
10
20
30
40
50
60
70
80
90
100
110
120

History of Proton Beam Therapy

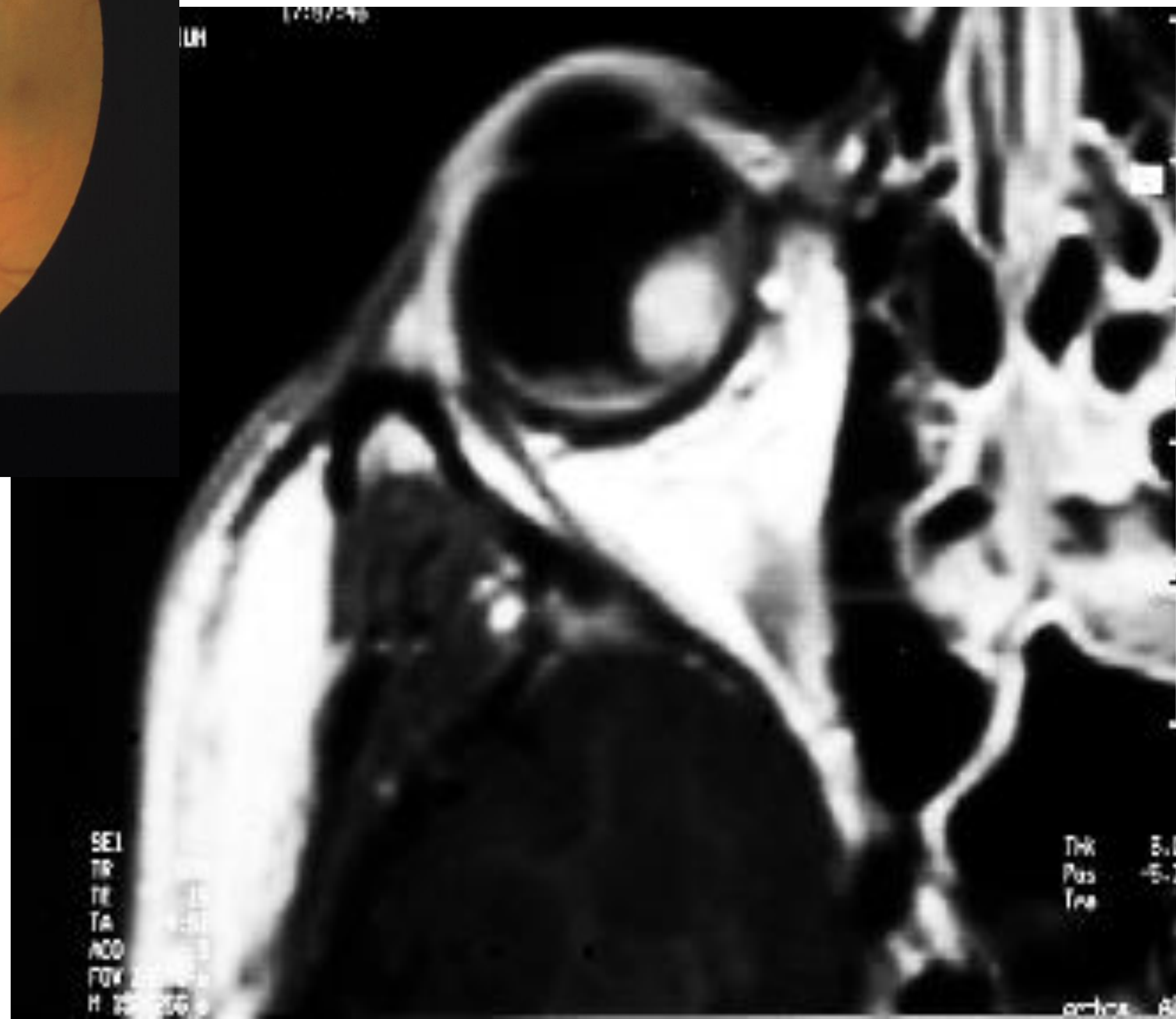
- 1946 Robert Wilson
- 1948 Tobias, Lawrence (Berkeley)(hypophysectomy)
- 1954-56 Boerje Larsson (Uppsala)
- 1960 Graffman 60 beteg.(Stereotactic neurosurgery)
- Early '60 Sweet, Koehler, (Kjellberg, Harvard)- AV. malform.
- 1969 Ganz (retinoblastoma), Constable (eye melanoma)
- 1970 Suit, Goitein (agyalapi daganatok)
- Russia, Japan (Tokio, Chiba)
- 1983 Tsukuba 250 MeV (tüdö, 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

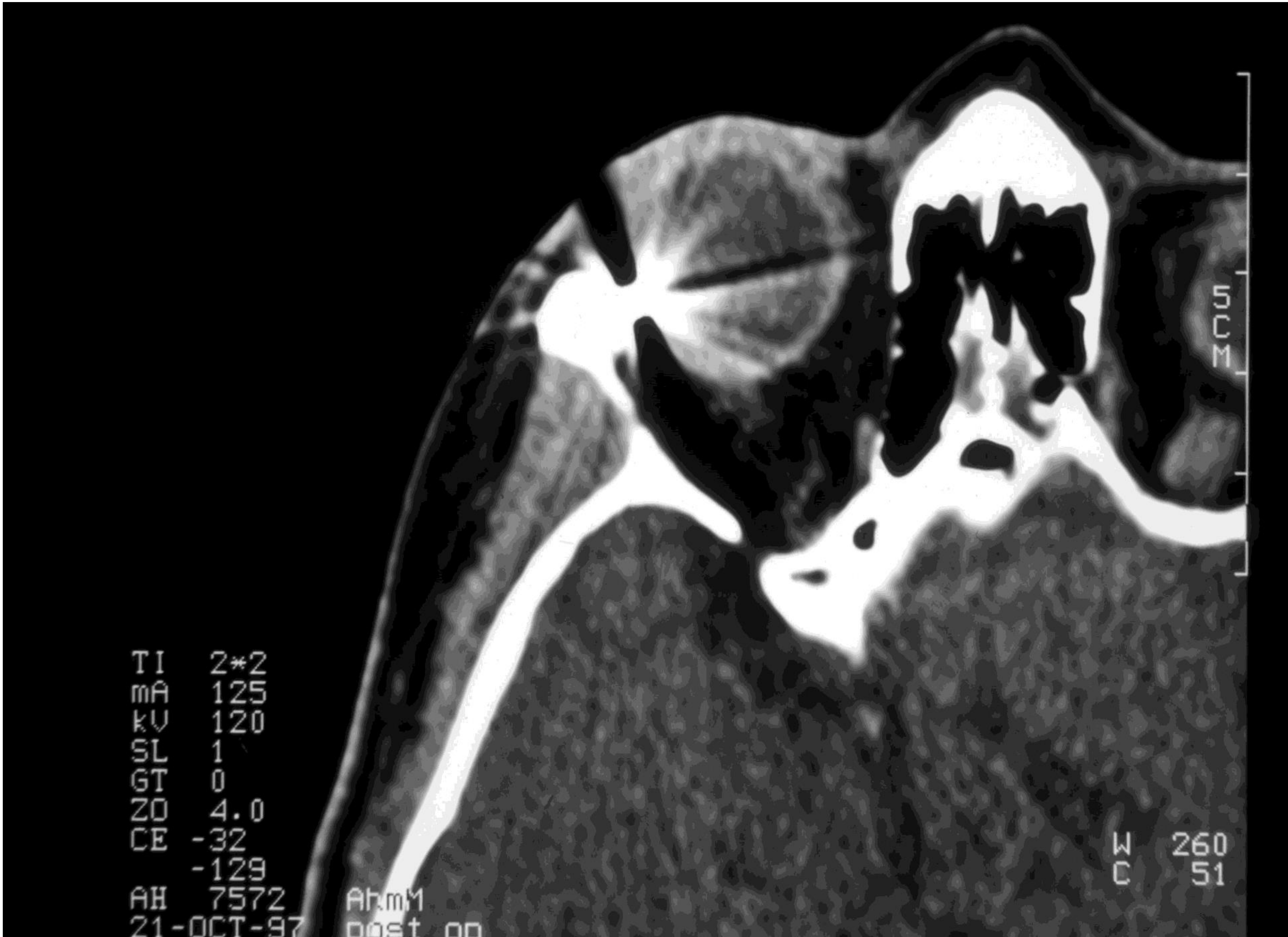
Uveal melanoma - proton therapy

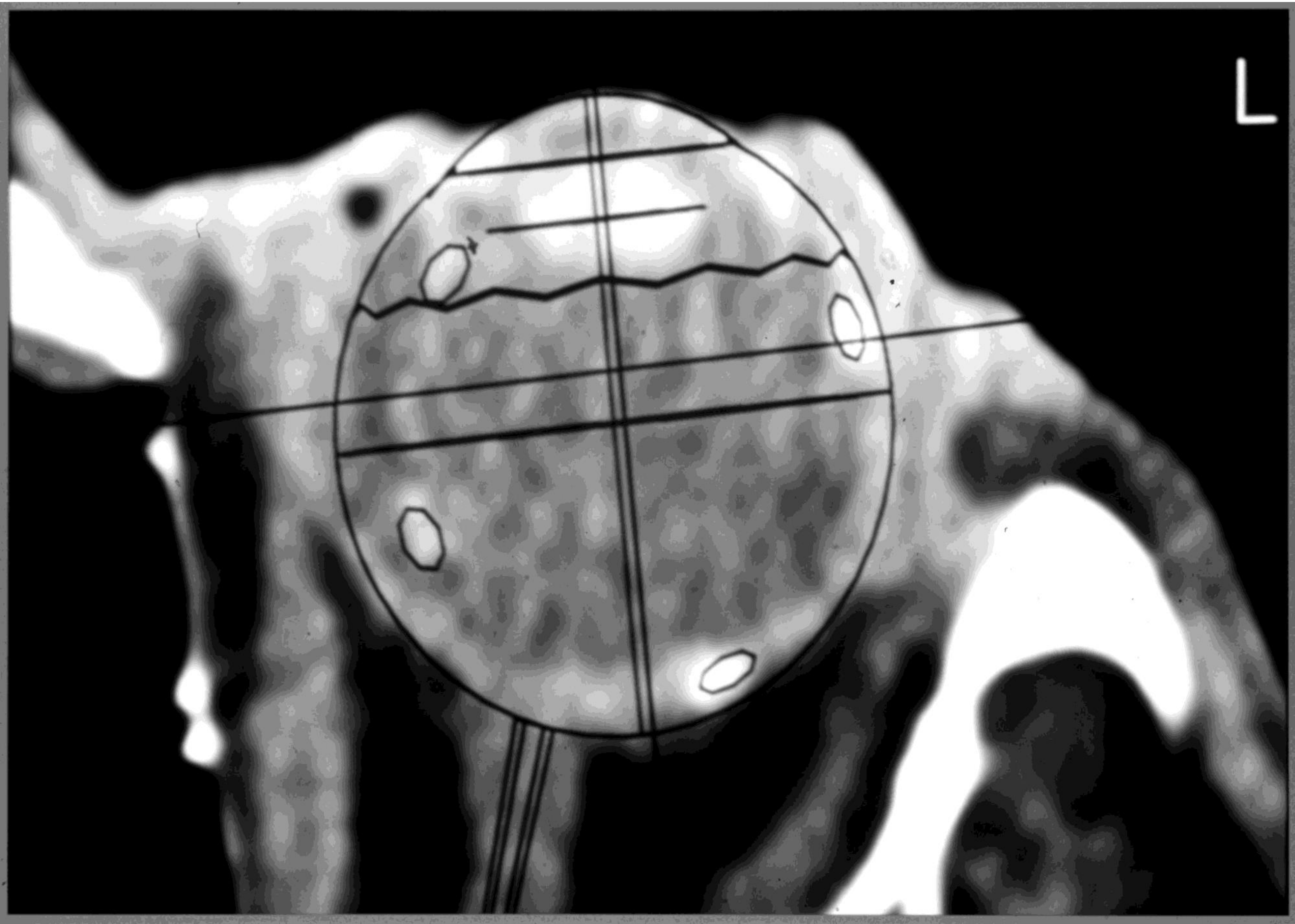


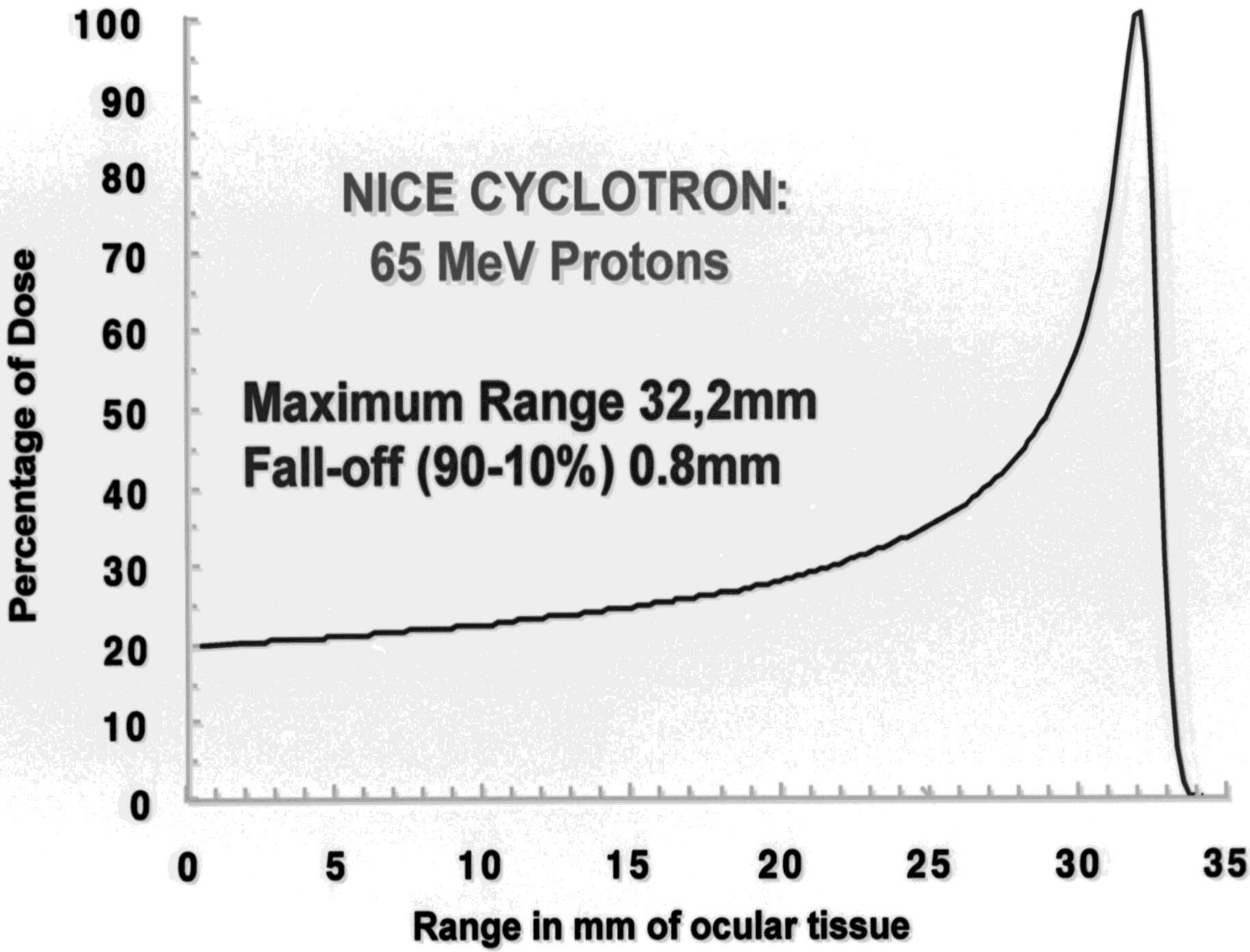


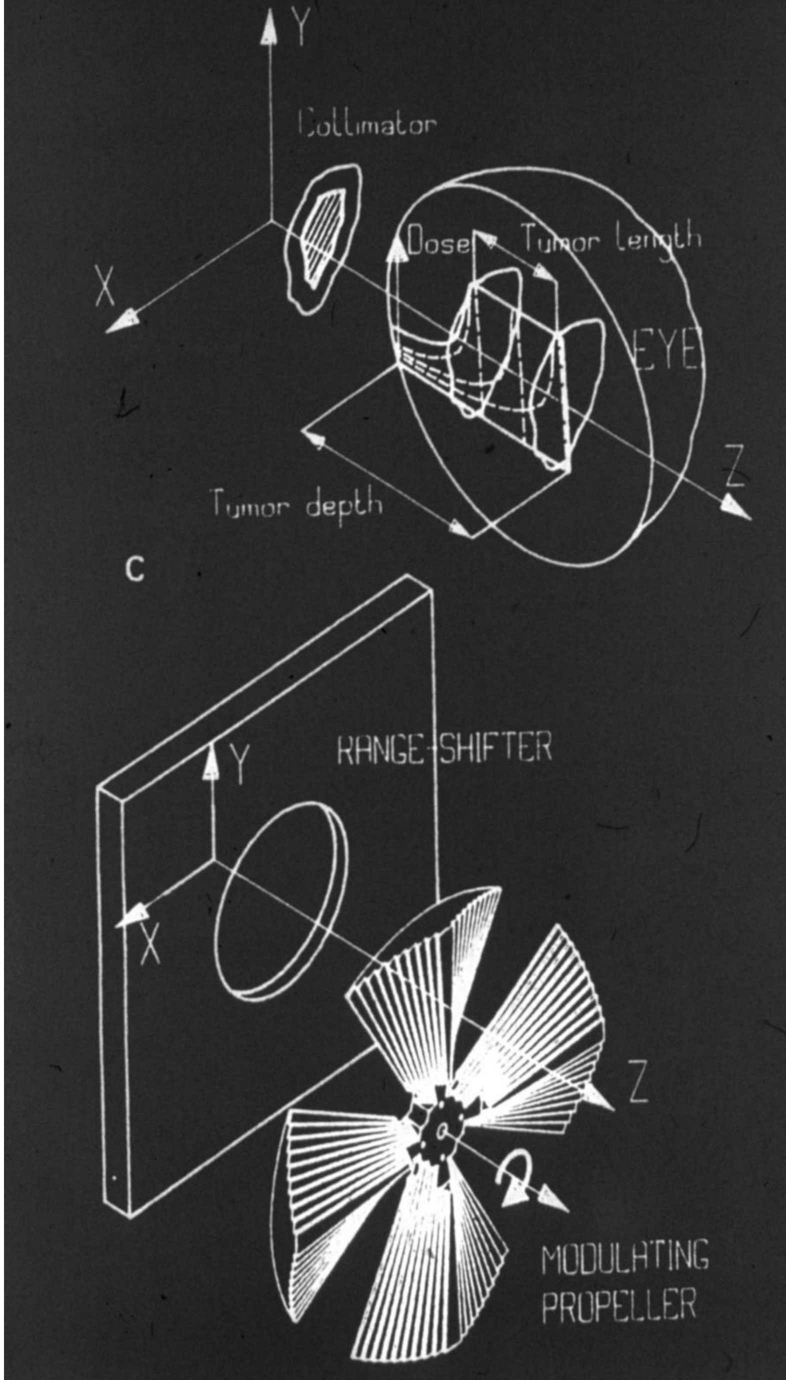
tumor: 8 mm ^{106}Ru/^{106}Rh apex: 100 Gy,
basis (sclera):2200 Gy opposite : 1Gy


SE1
TR
TE
TA
ACQ
FOV
THK 5.0
Pos -5.1

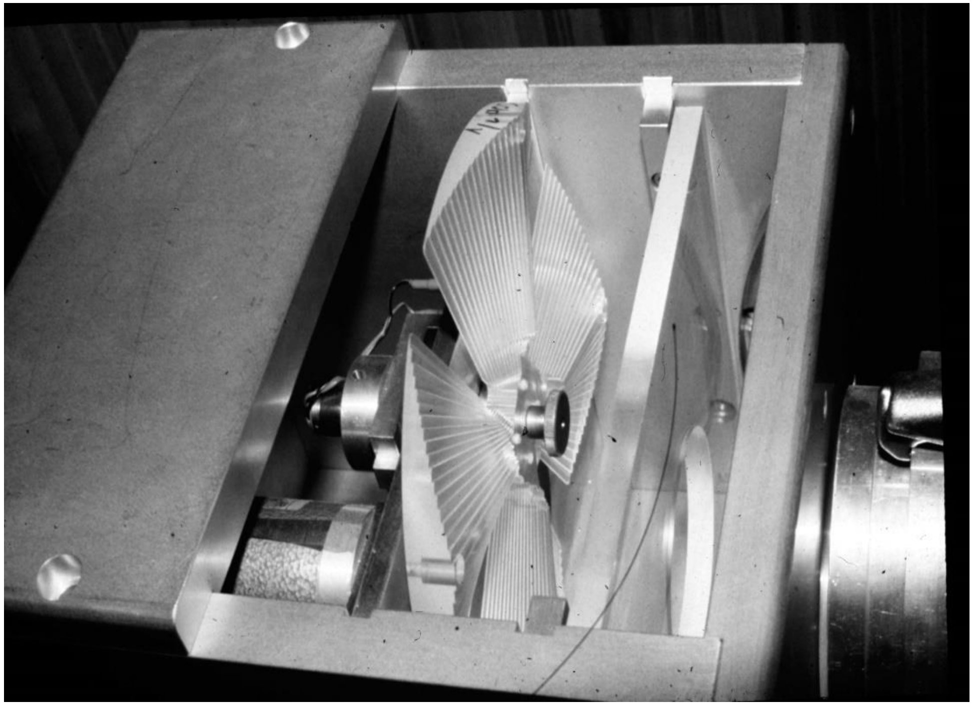

5CM
TI 2*2
mA 125
kV 120
SL 1
GT 0
ZO 4.0
CE -32
-129
AH 7572
21-OCT-97
AhmM
post op
W 260
C 51


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

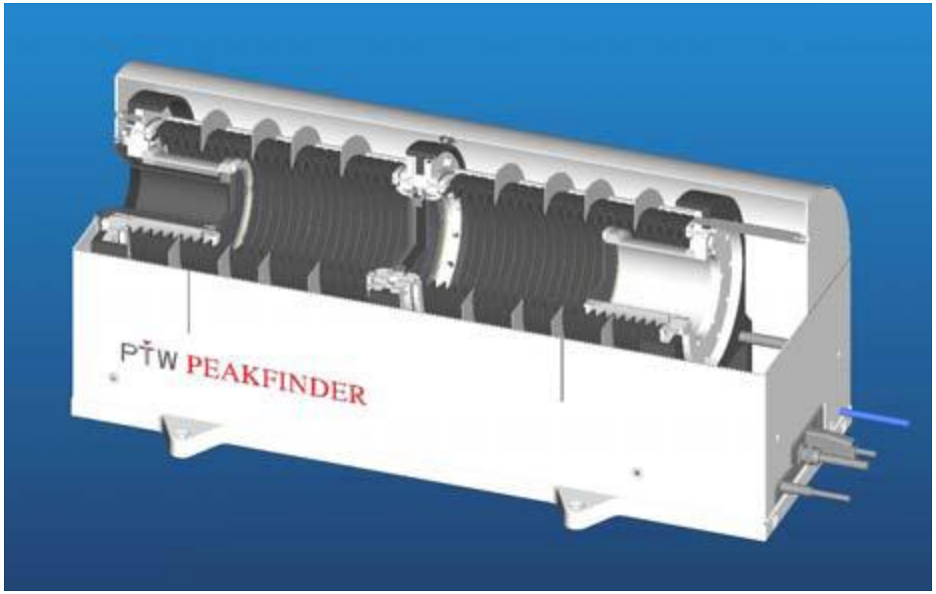


Wax bolus Cerrobend aperture Modulating wheels

Special dosimetric equipments

In the hadrontherapy used dosimetric devices mostly the same than in the traditional radiation therapy. Some examples for specifically developed equipments for measurement of the Bragg-peak:

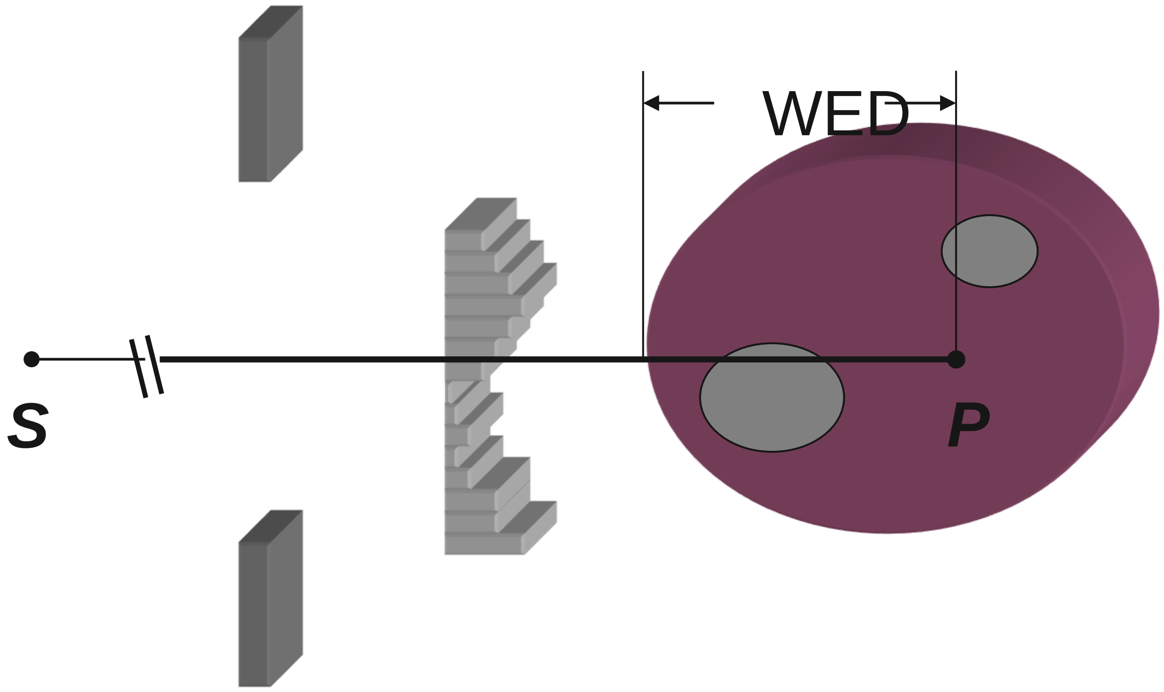
PEAKFINDER



BRAGG PEAK CHAMBER

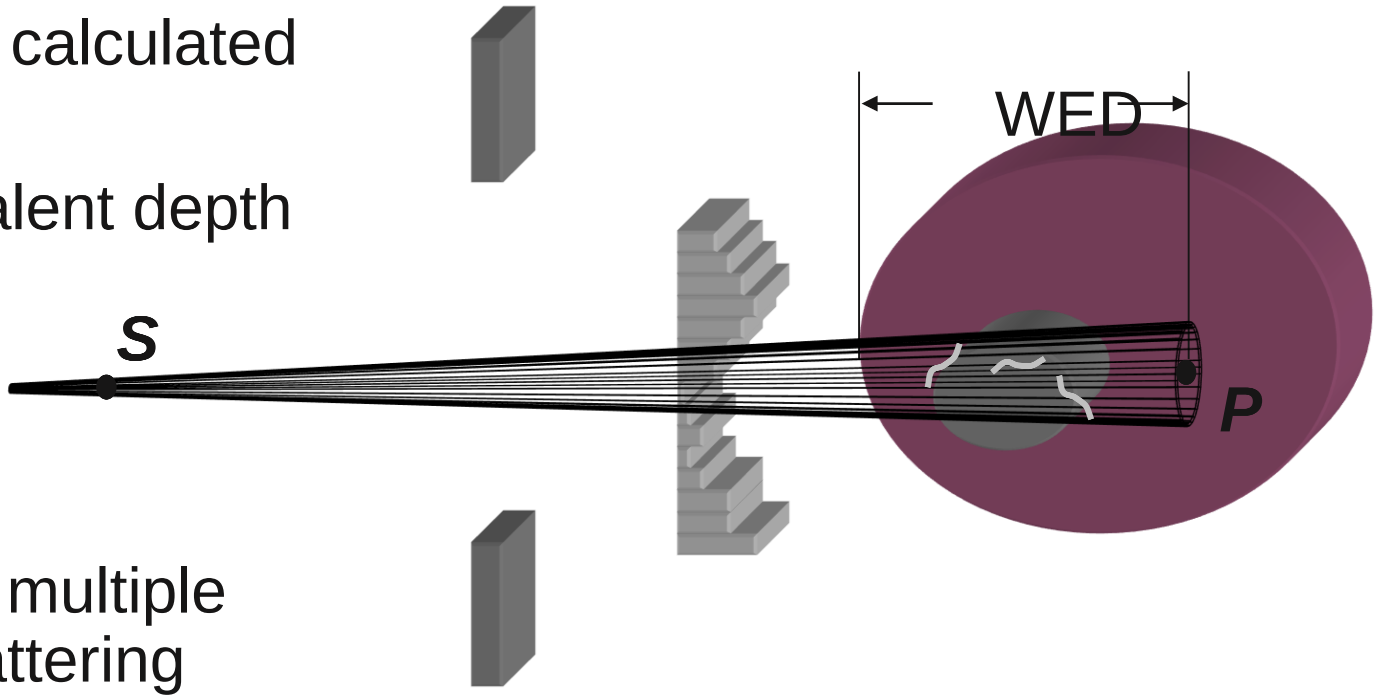
Ray-Tracing Dose Algorithm

- 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

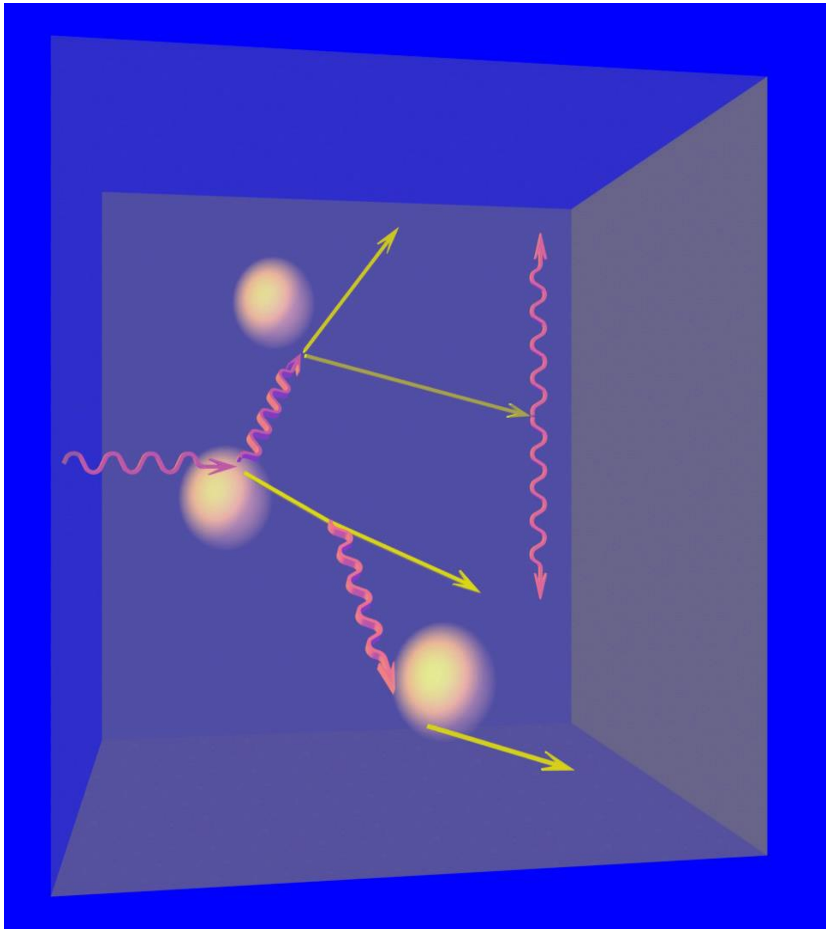
- Cylindrical coordinates
- Measured or calculated pencil kernel
- Water-equivalent depth

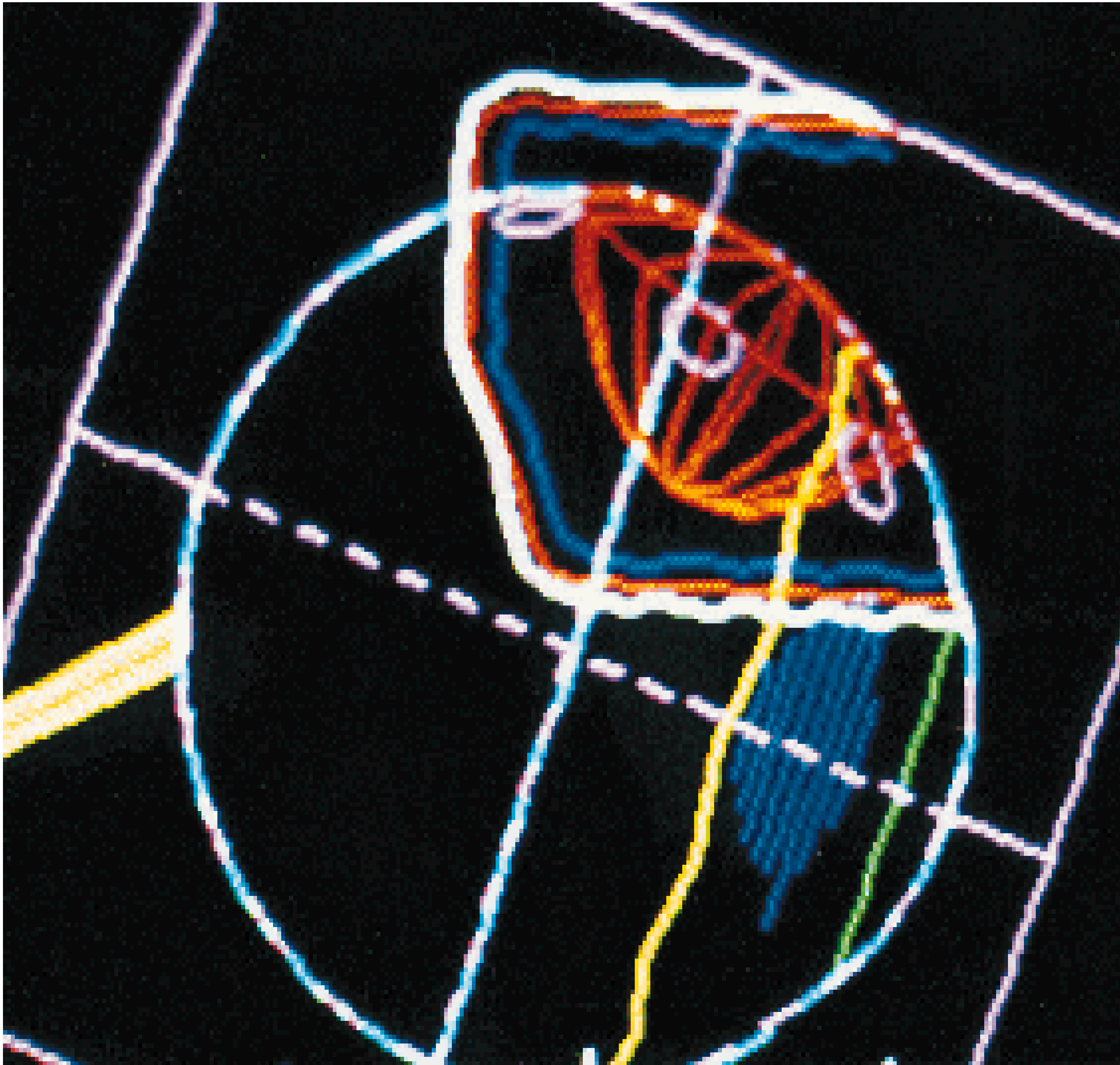


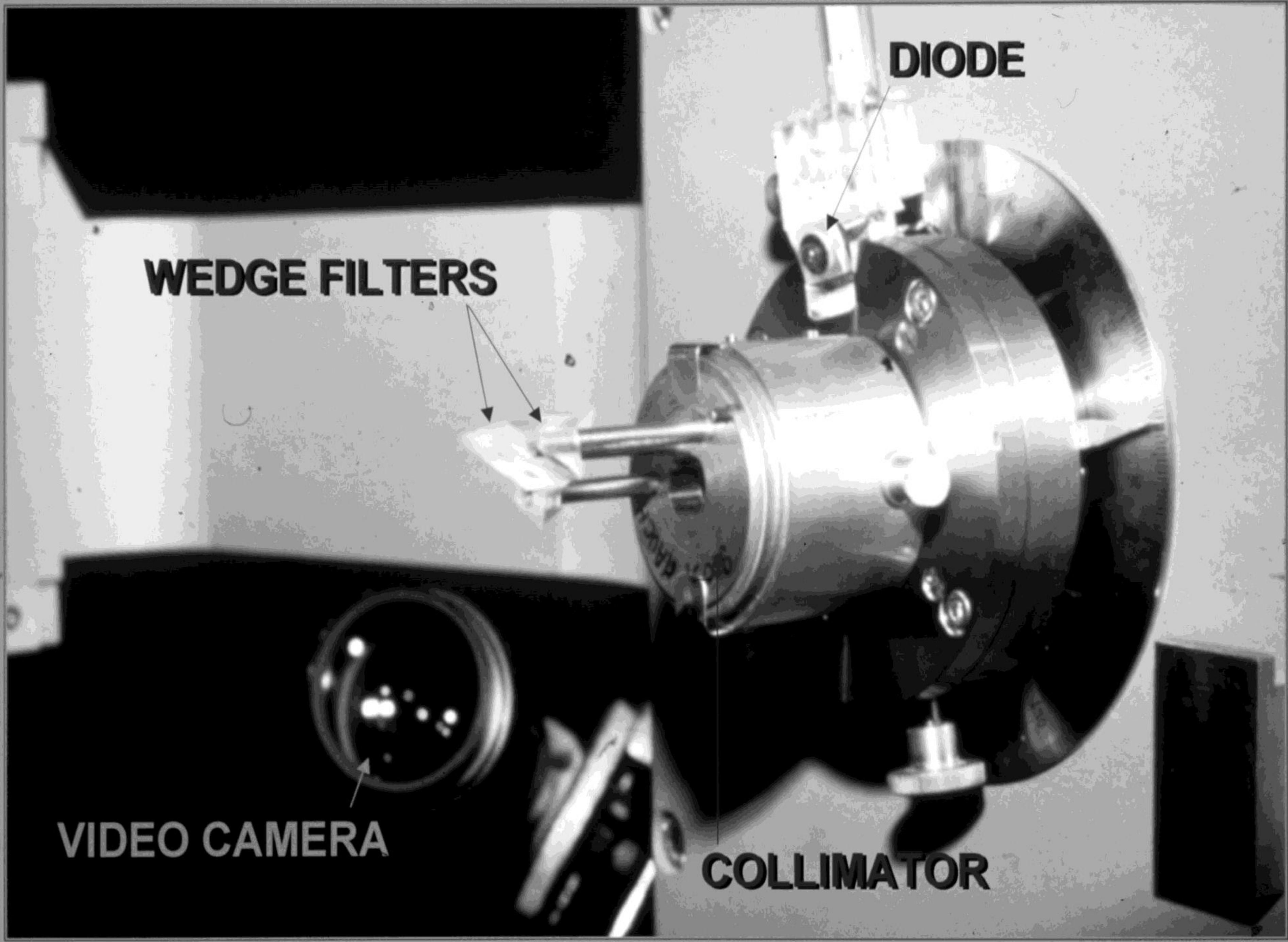
- Accounts for multiple Coloumb scattering
- more time consuming

Monte Carlo Dose Algorithm

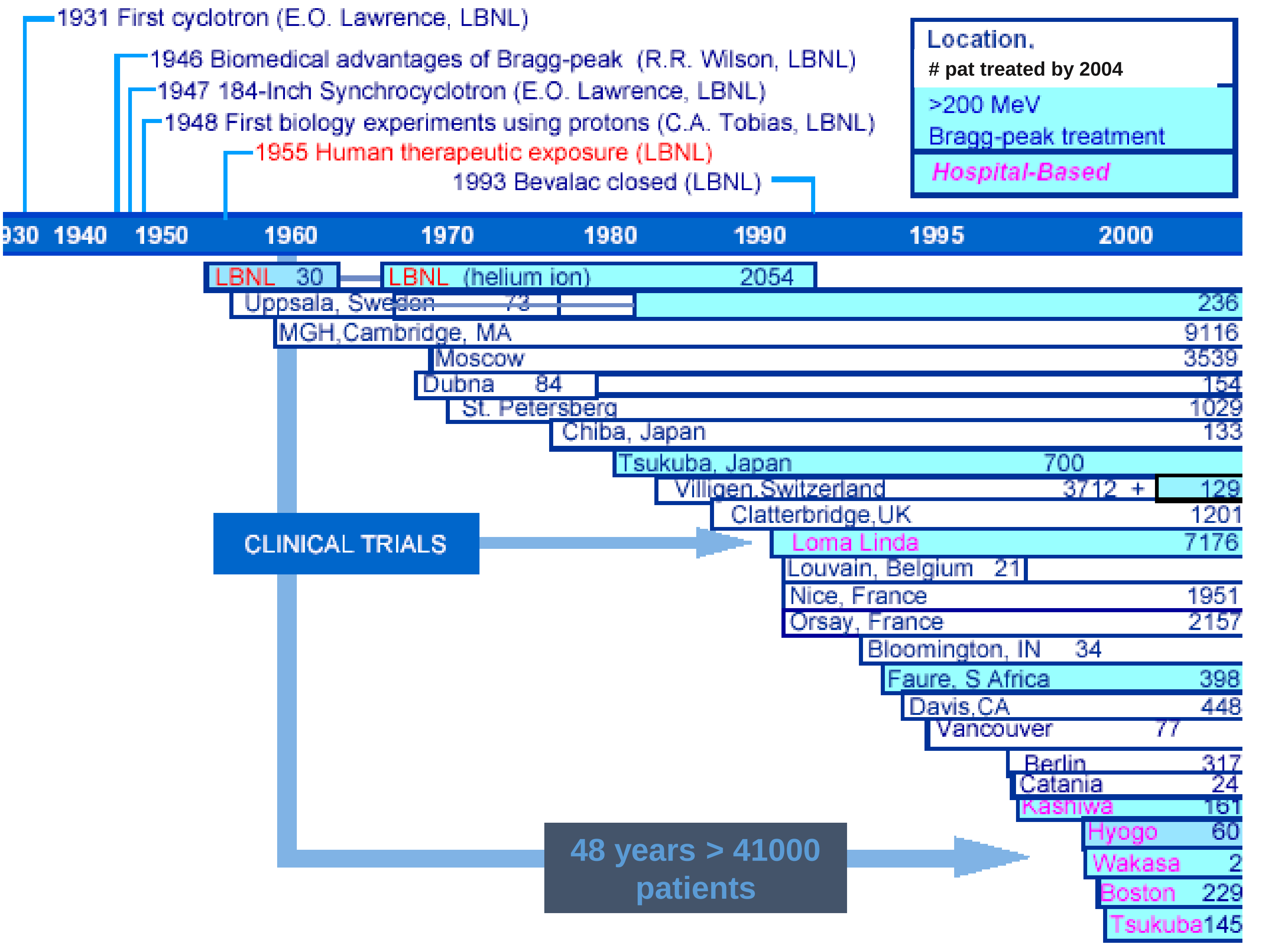
- Considered as “gold standard”
- Accounts for all relevant physical interactions
- Follows secondary particles
- Requires accurate cross section data bases
- Includes source geometry
- Very time consuming



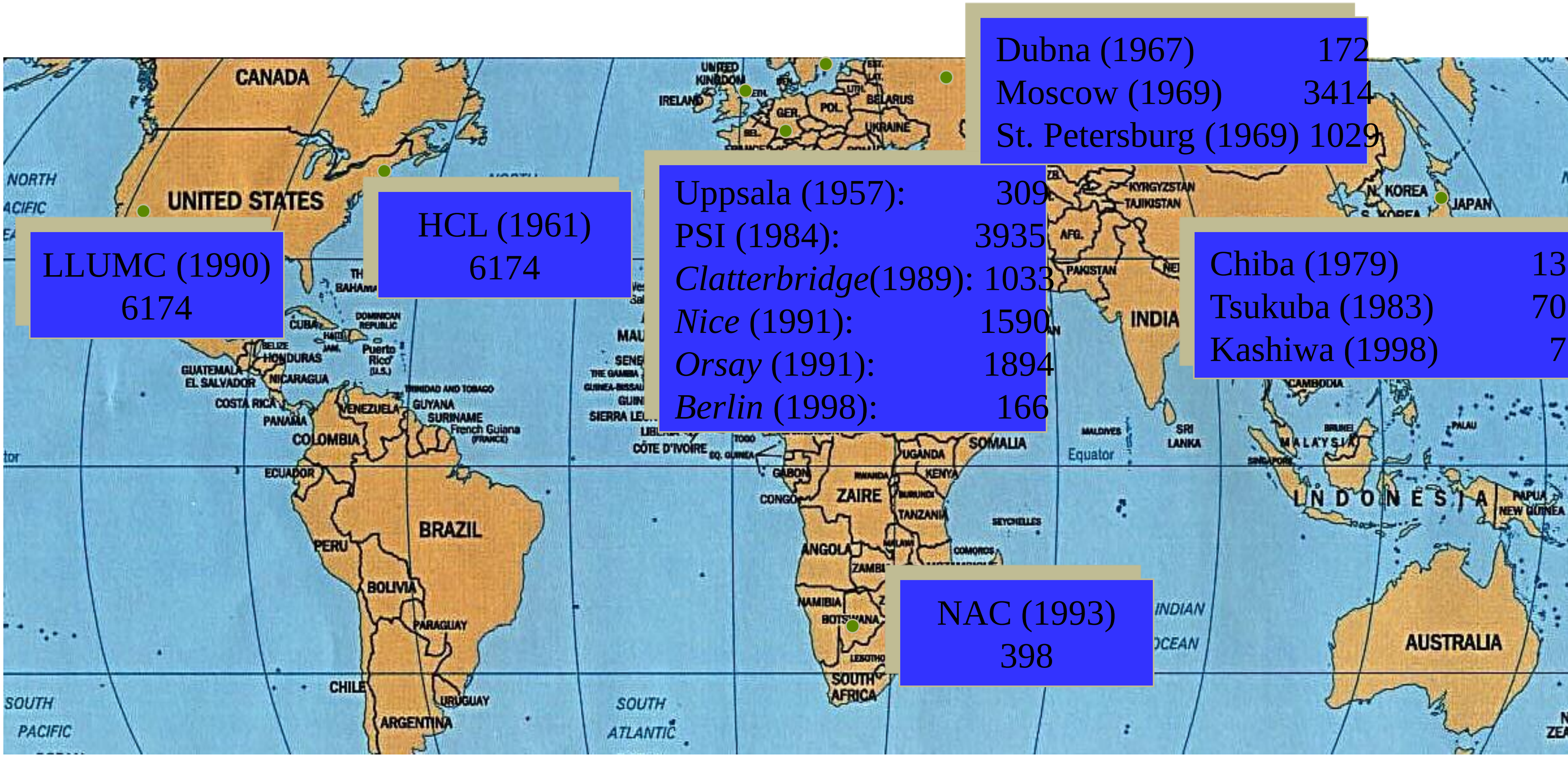


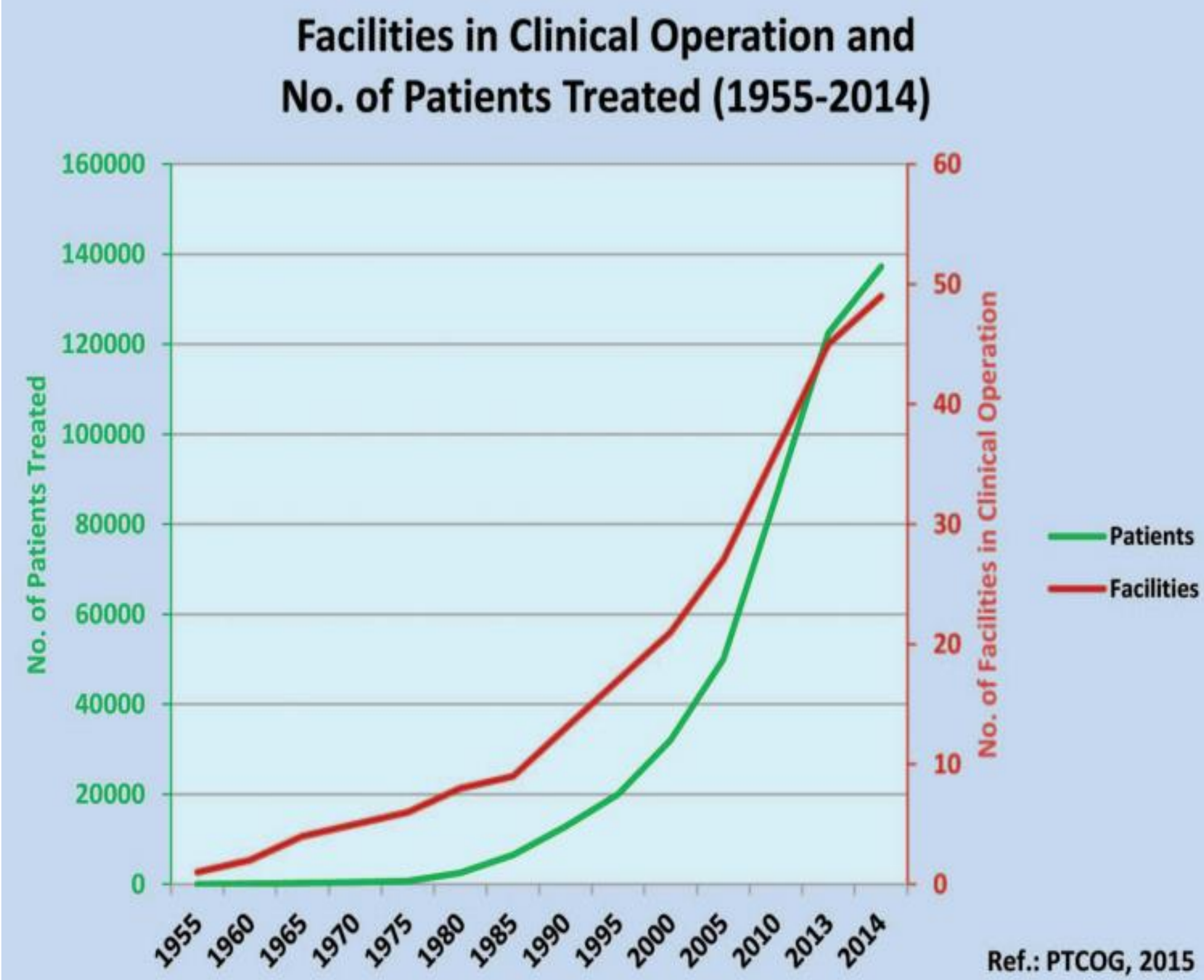

DIODE
WEDGE FILTERS
VIDEO CAMERA
COLLIMATOR

Proton Therapy Scientific Milestones



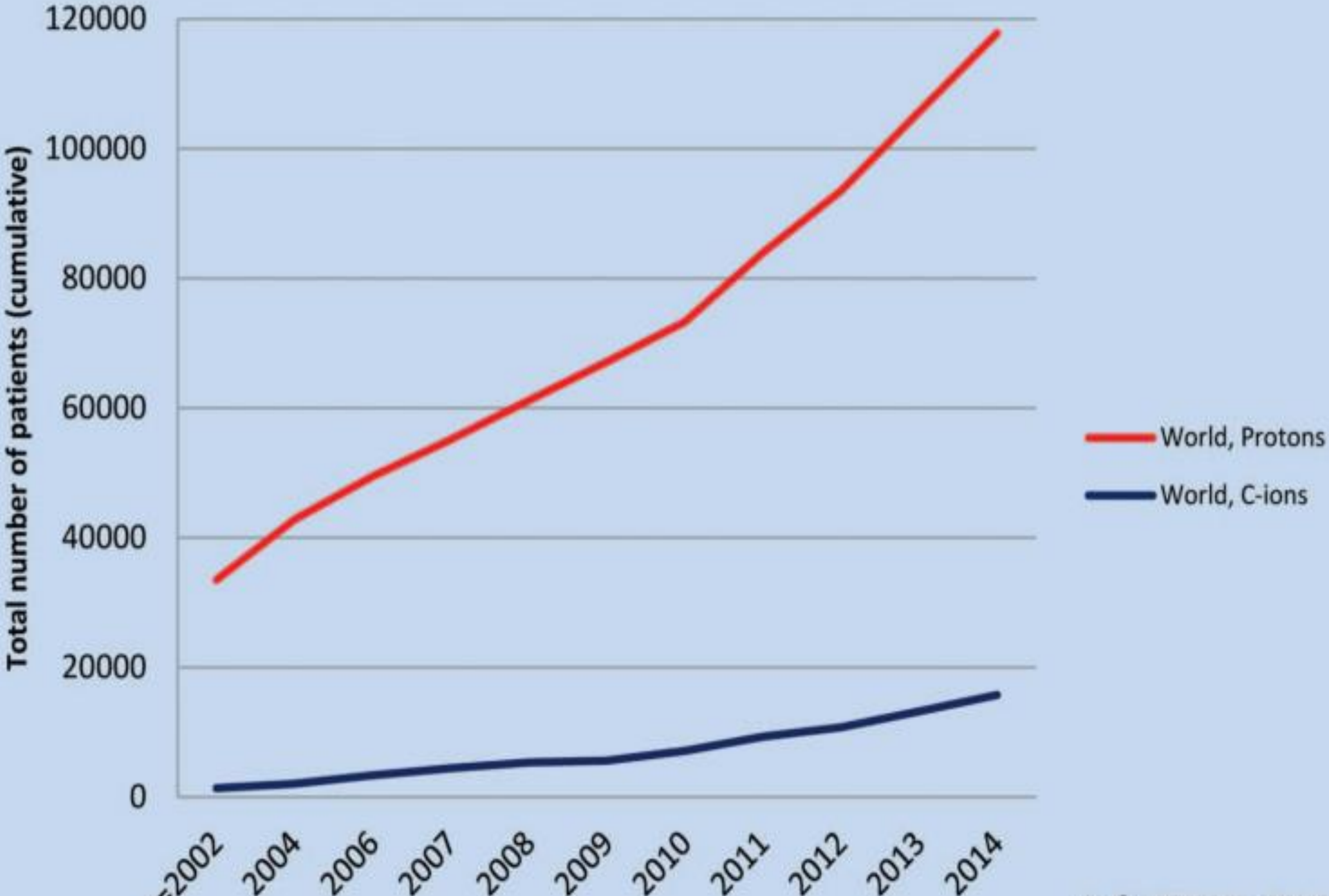
Number of treated patients





Total of all facilities (in and out of operation):		
He	2054	1957-1992
Pions	1100	1974-1994
C-ions	15736	1994-present
Other ions	433	1975-1992
Protons	118195	1954-present
Grand Total	137179	

Patients Treated with Protons and C-ions Worldwide



Ref.: PTCOG, 2015

Eye tumors

- Intraorbital neuroblastoma, retinoblastoma, conjunctival melanoma
- **Uveal melanoma**
  - Uvea: iris (6%), choroid (85%), corpus ciliare (9%)
  - Contains pigment
  - Cribriform
  - Fast growing
  - Visual impairment
  - If it breaks through the capsule of the eye, gives fast metastases

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

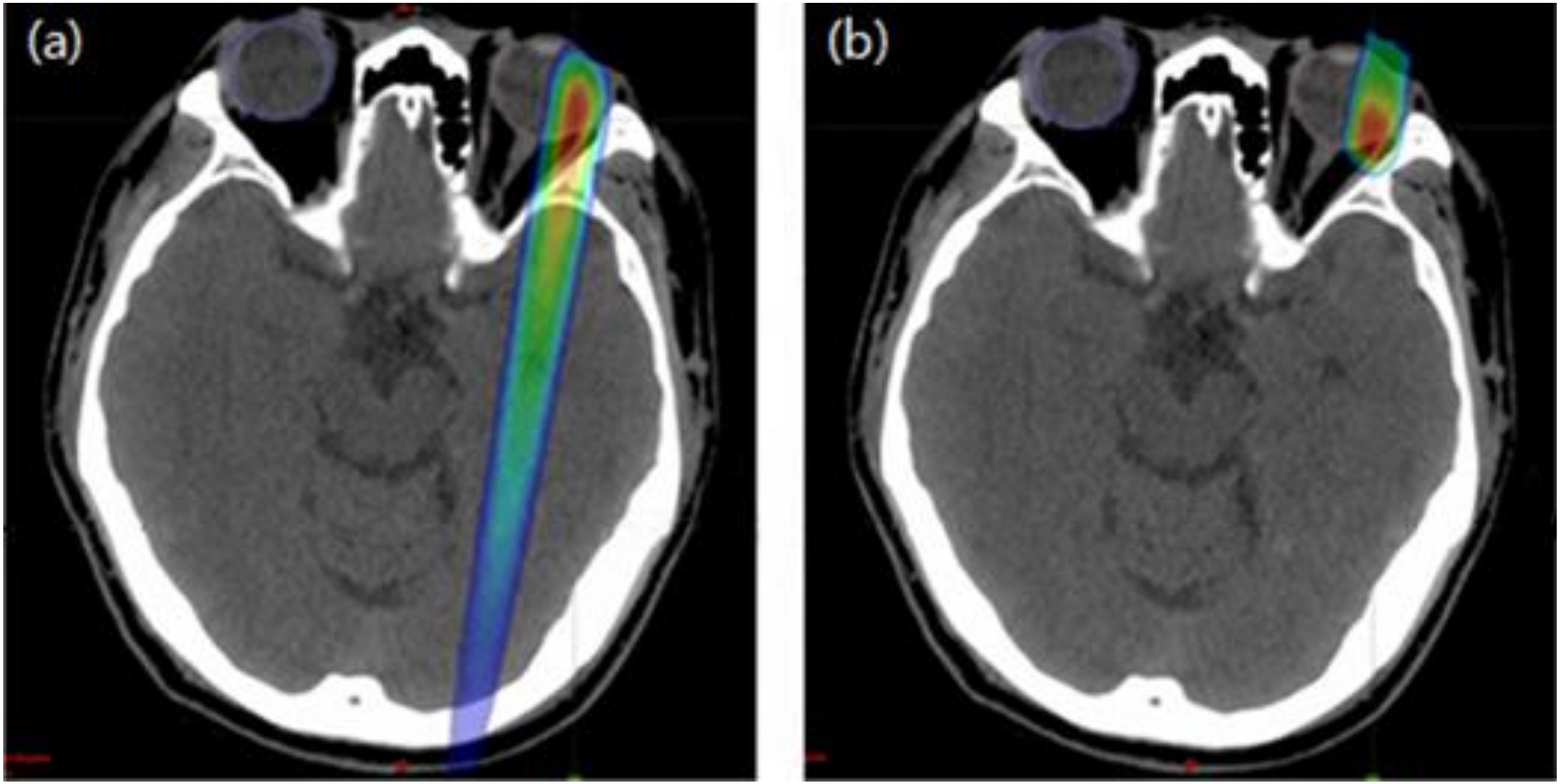


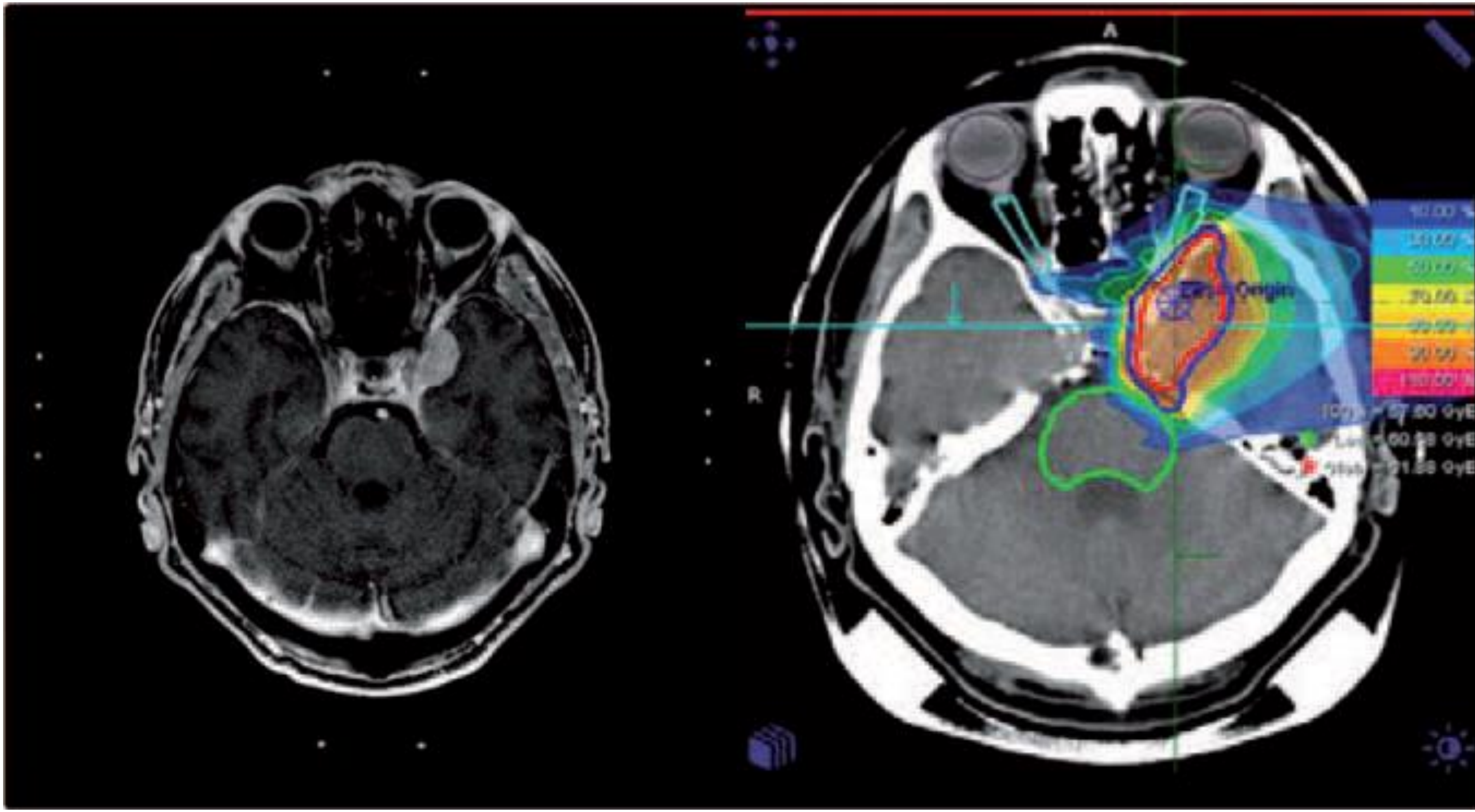
Fig. 11. www.nccproton.com

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.

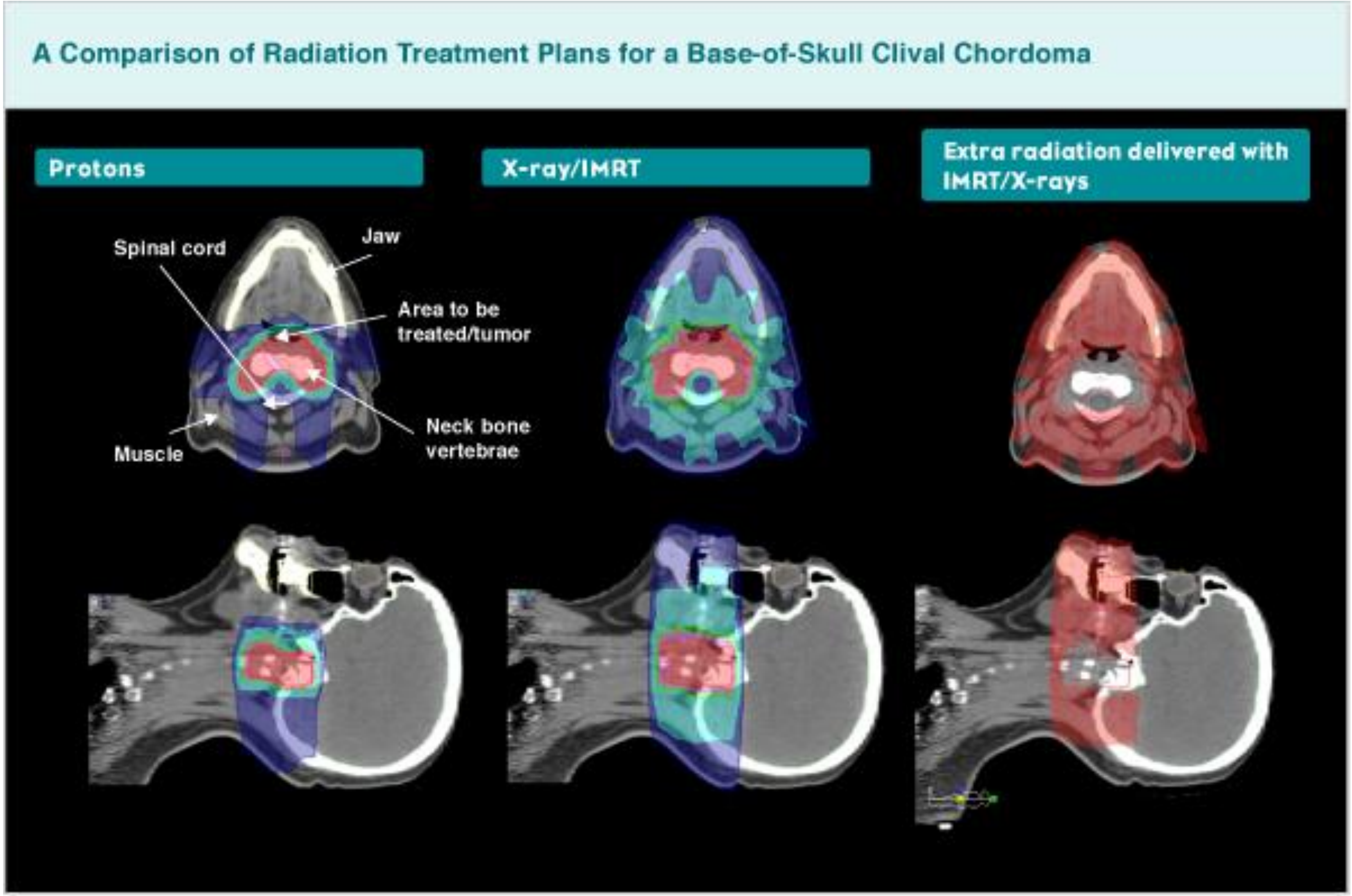


Fig. 14. www.procure.com

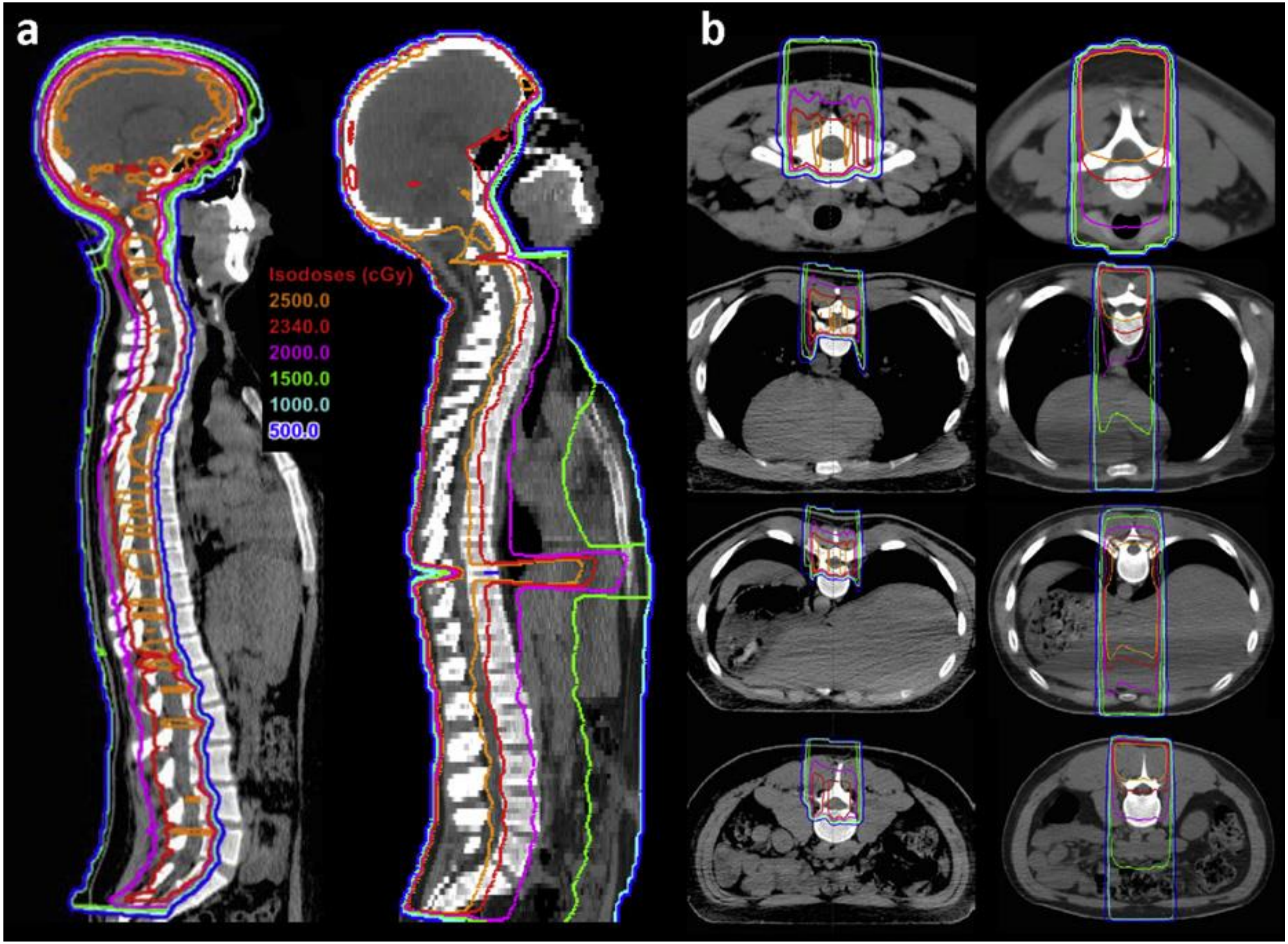
Childhood malignancies

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.

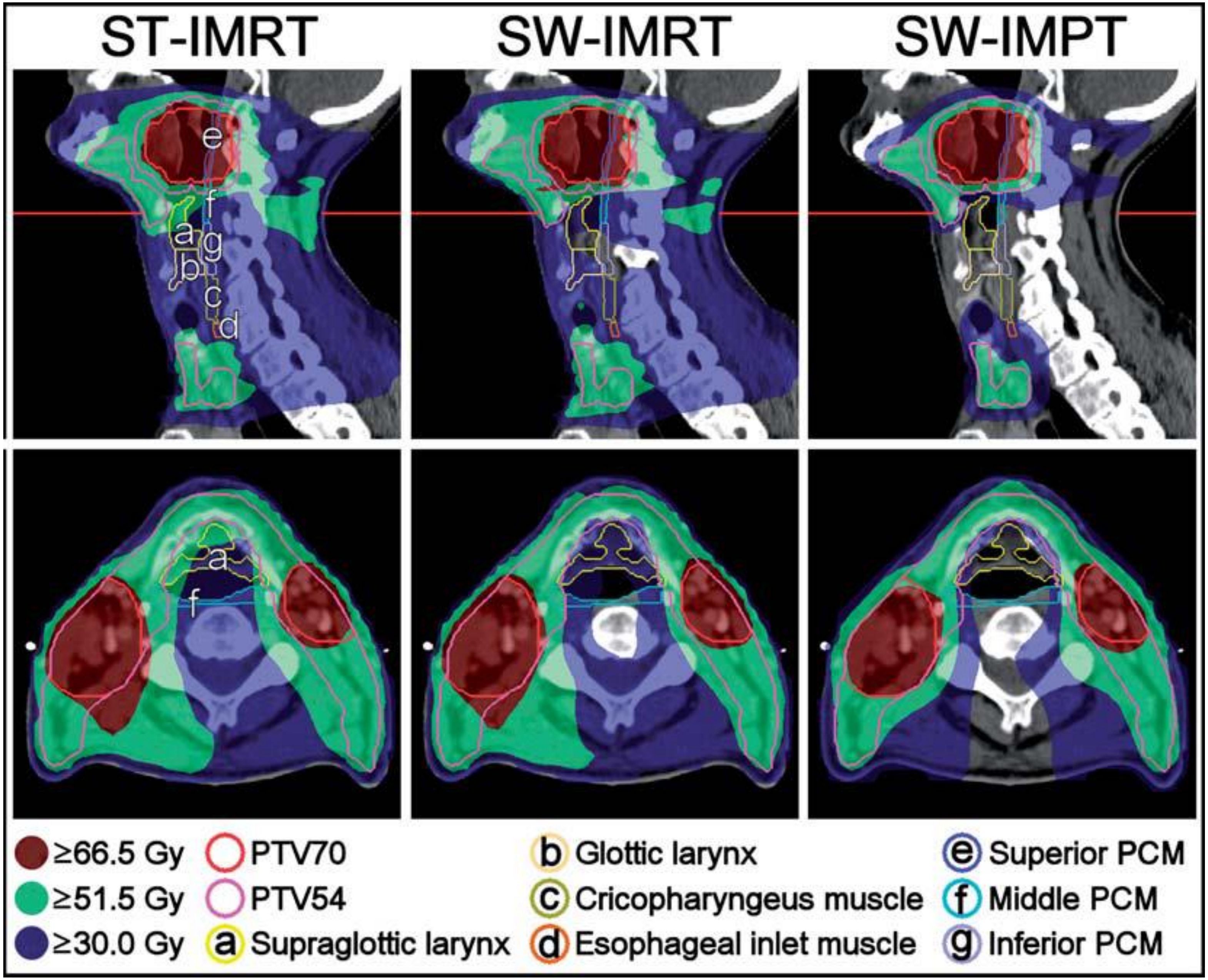
A Comparison of the Risk of Secondary Malignancies After Treating Medulloblastoma[3]

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 sinuse

- 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 stadium, 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

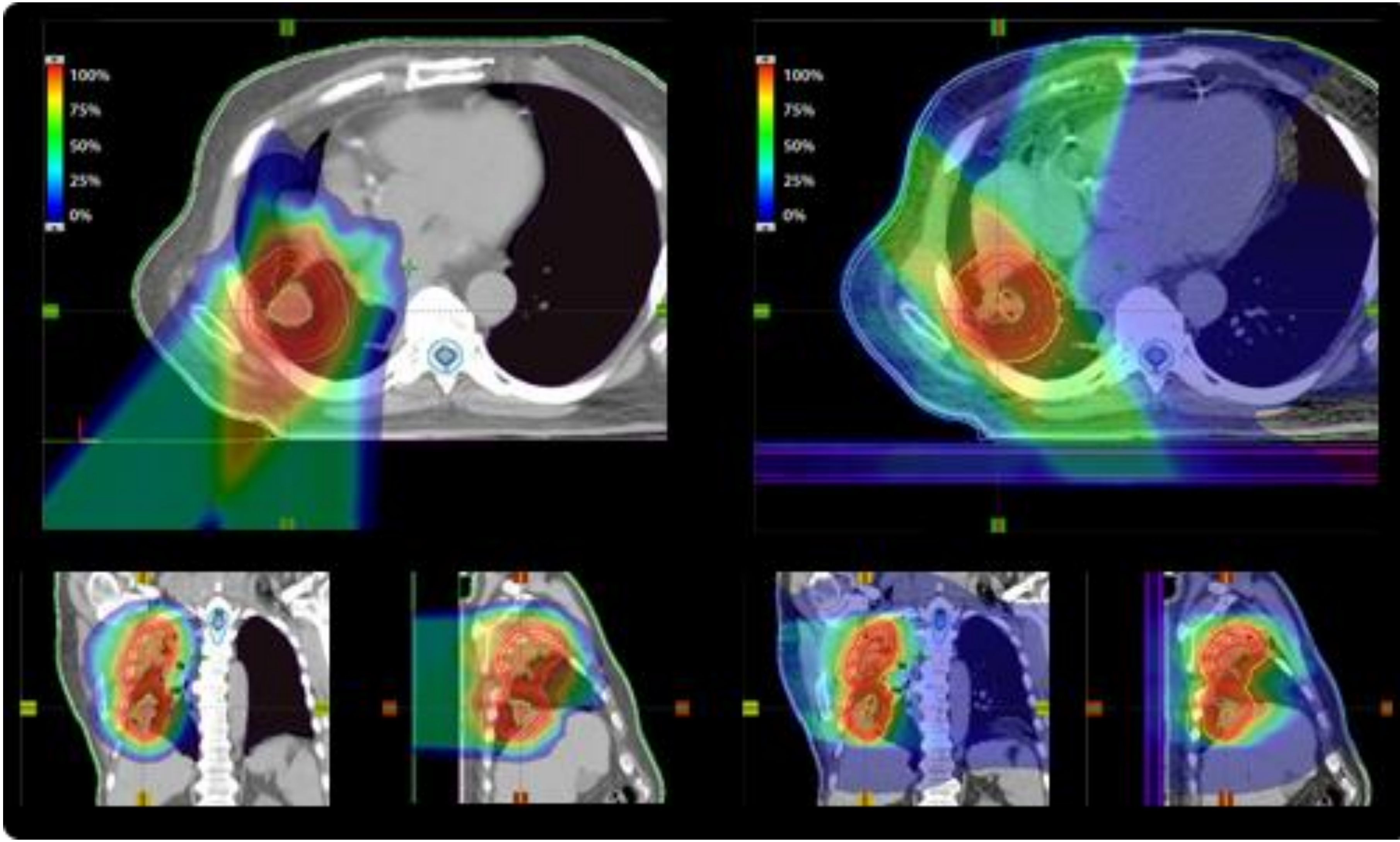
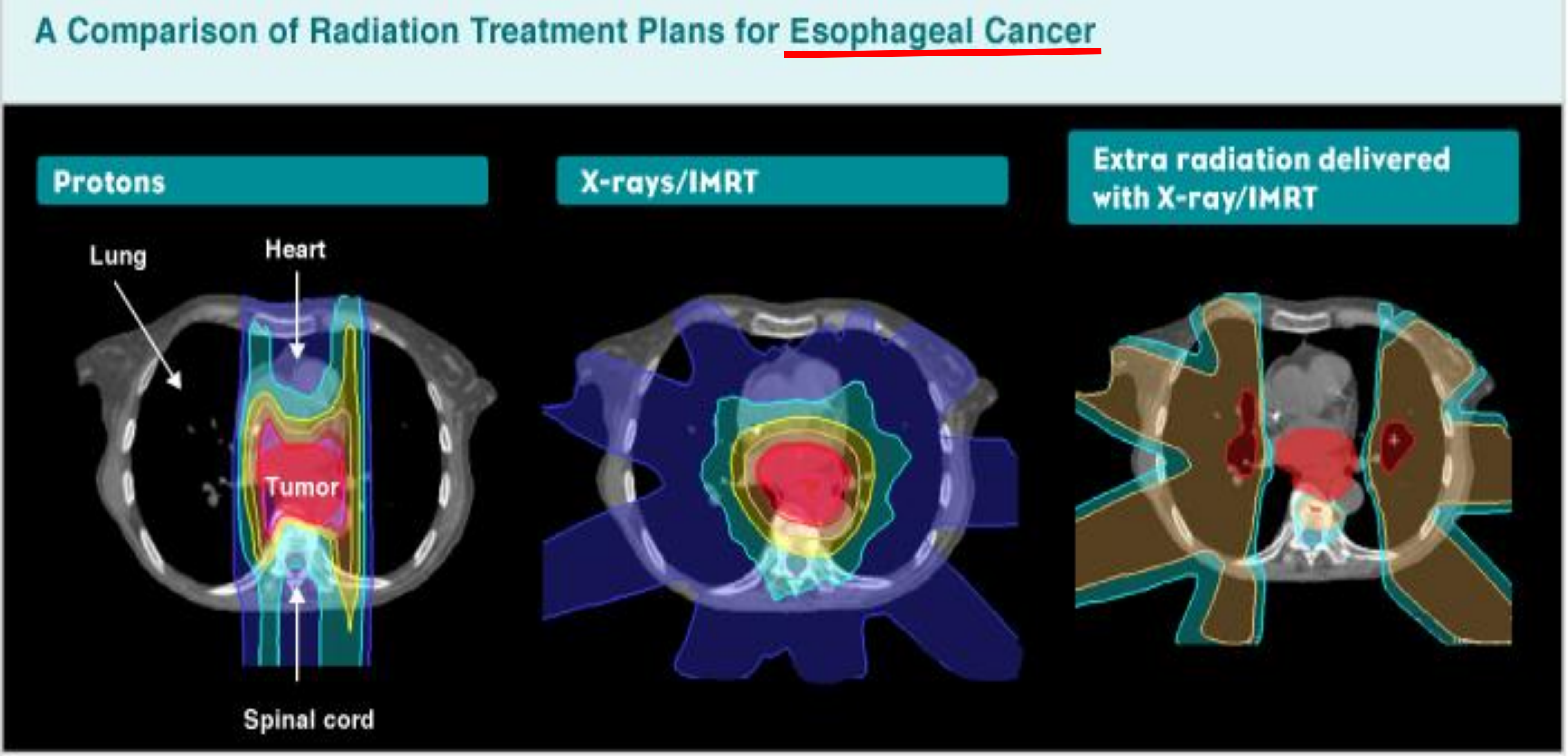


Fig. 20. www.iba-protontherapy.com



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

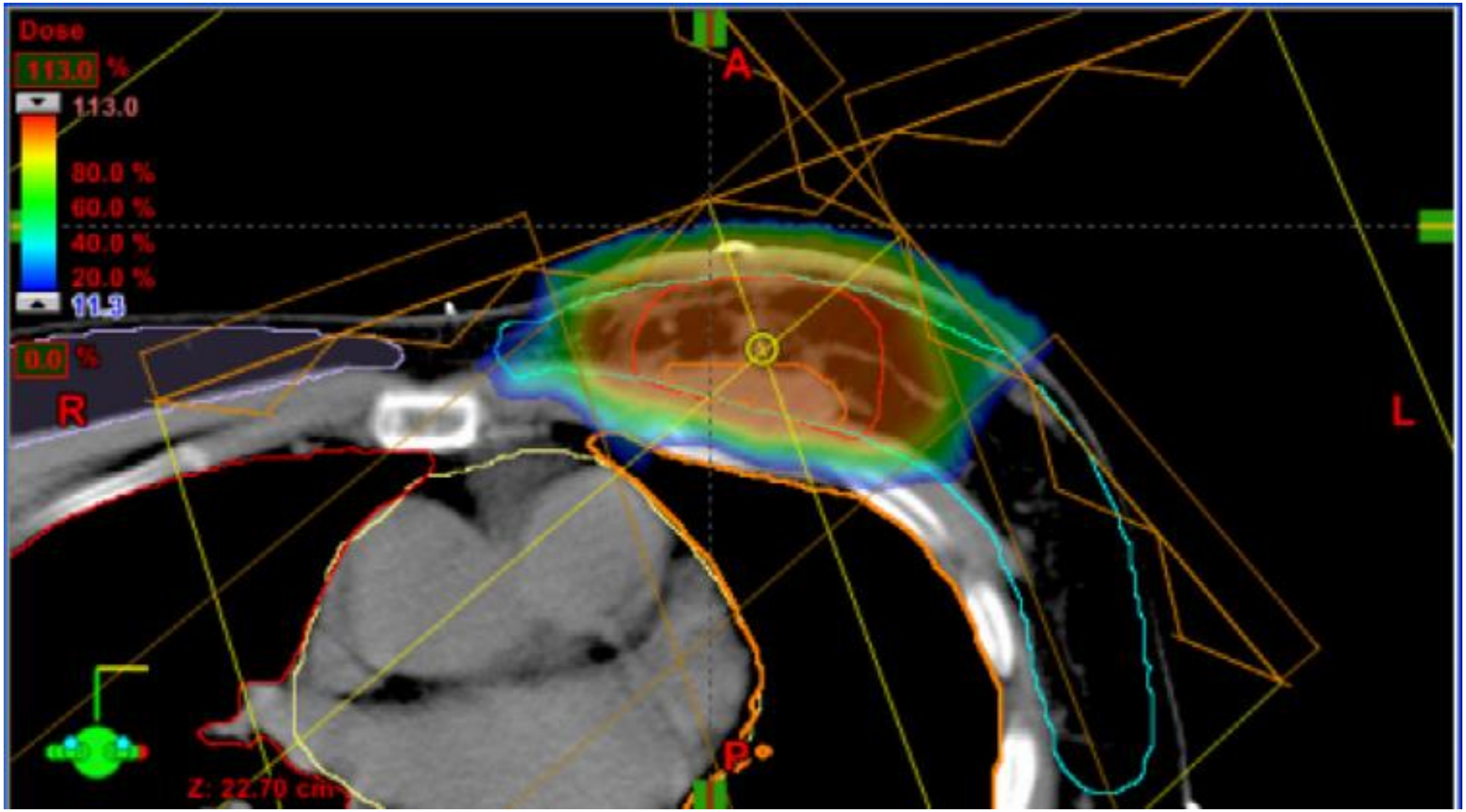
Source 21. www.procure.com

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

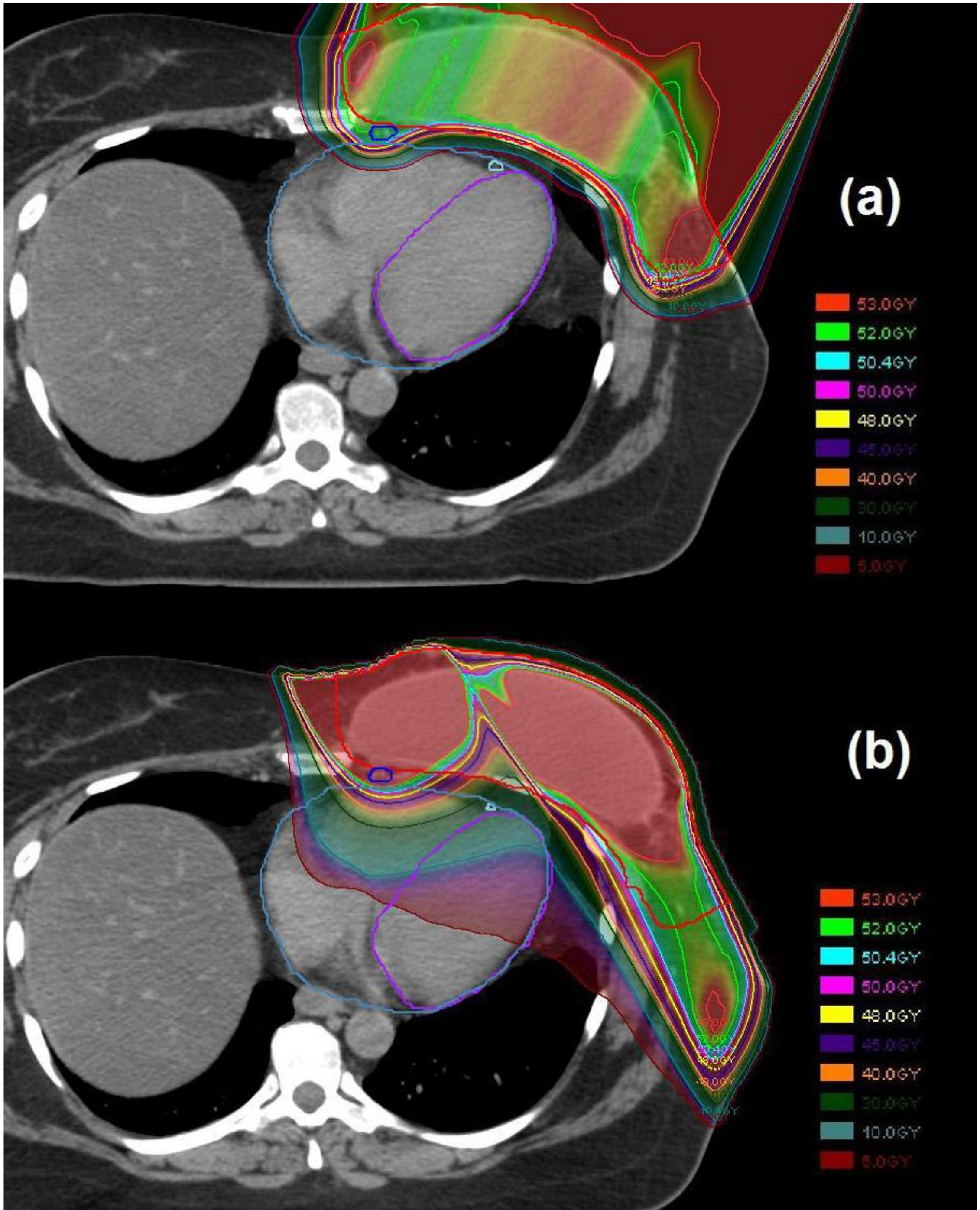
Chang et al 2013.

Proton RT



Source 22. Chang et al 2013.

Thoracic wall RT after complete mastectomy



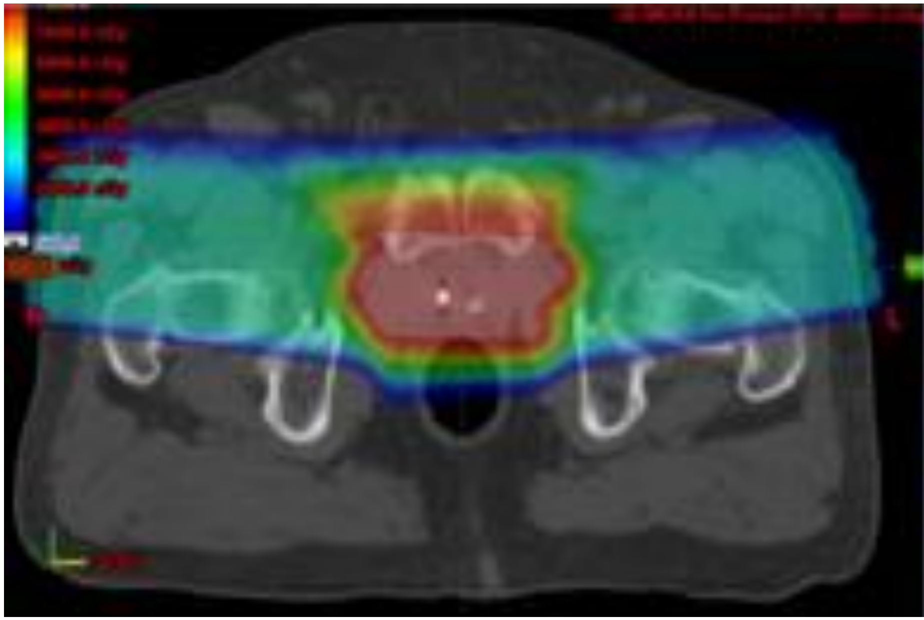
Proton RT

IMRT

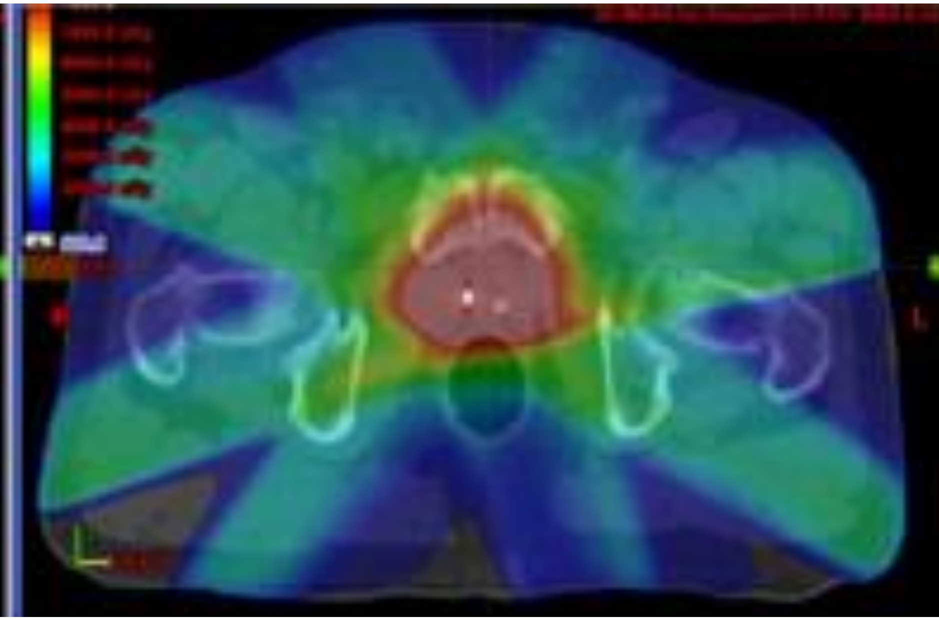
MacDonald et al 2013.

Prostate cancer

Proton RT dose distribution



IMRT dose distribution



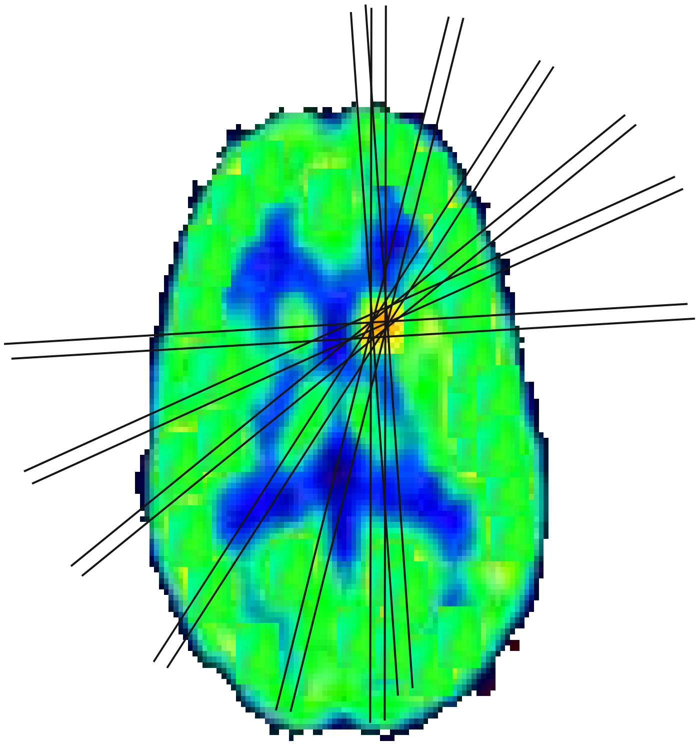
=> low~high risk => 70-72,5 GyE, 2,5 GyE/day~76-82 GyE, 2 GyE/day

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

www.floridaproton.org

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

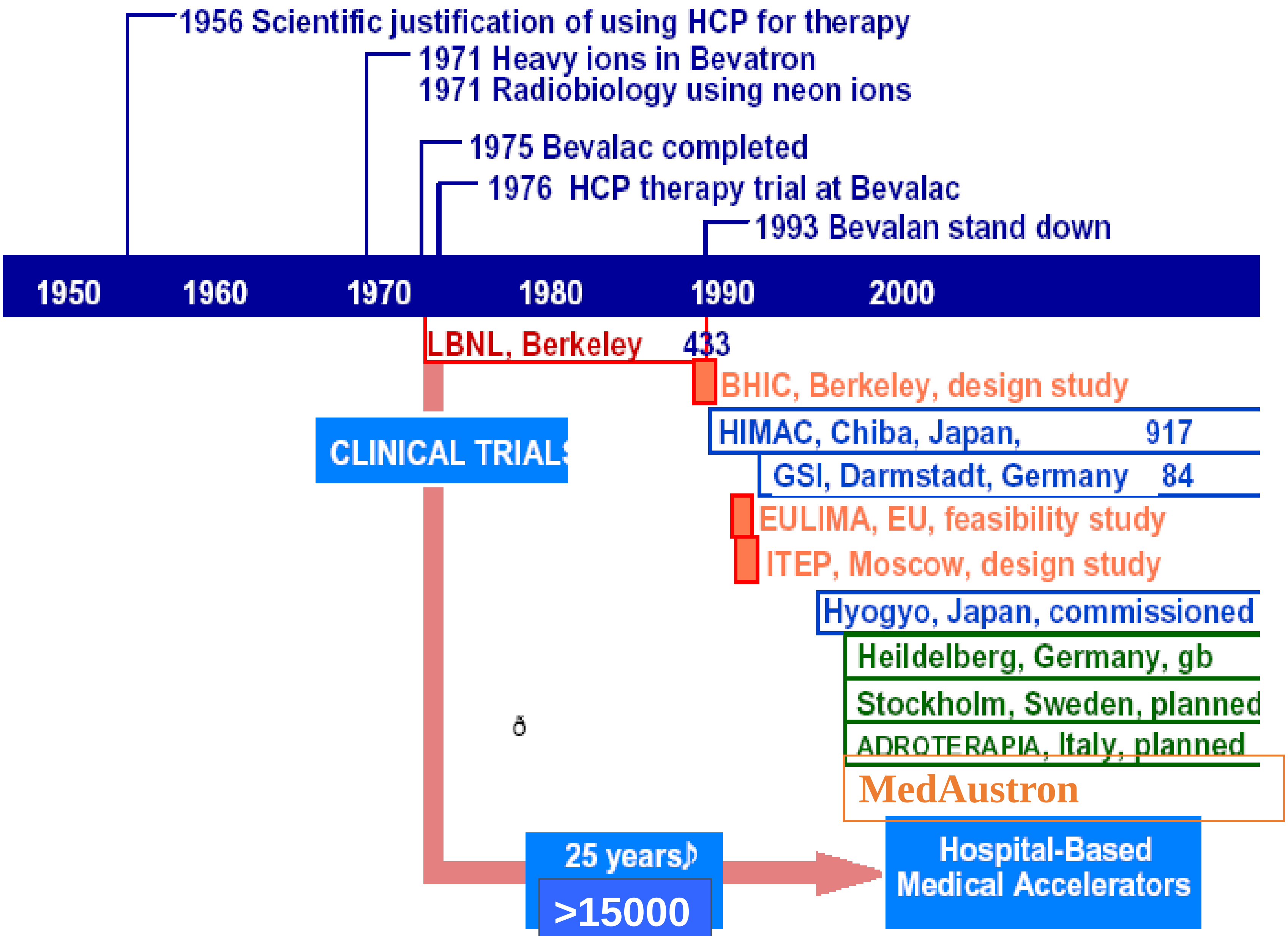


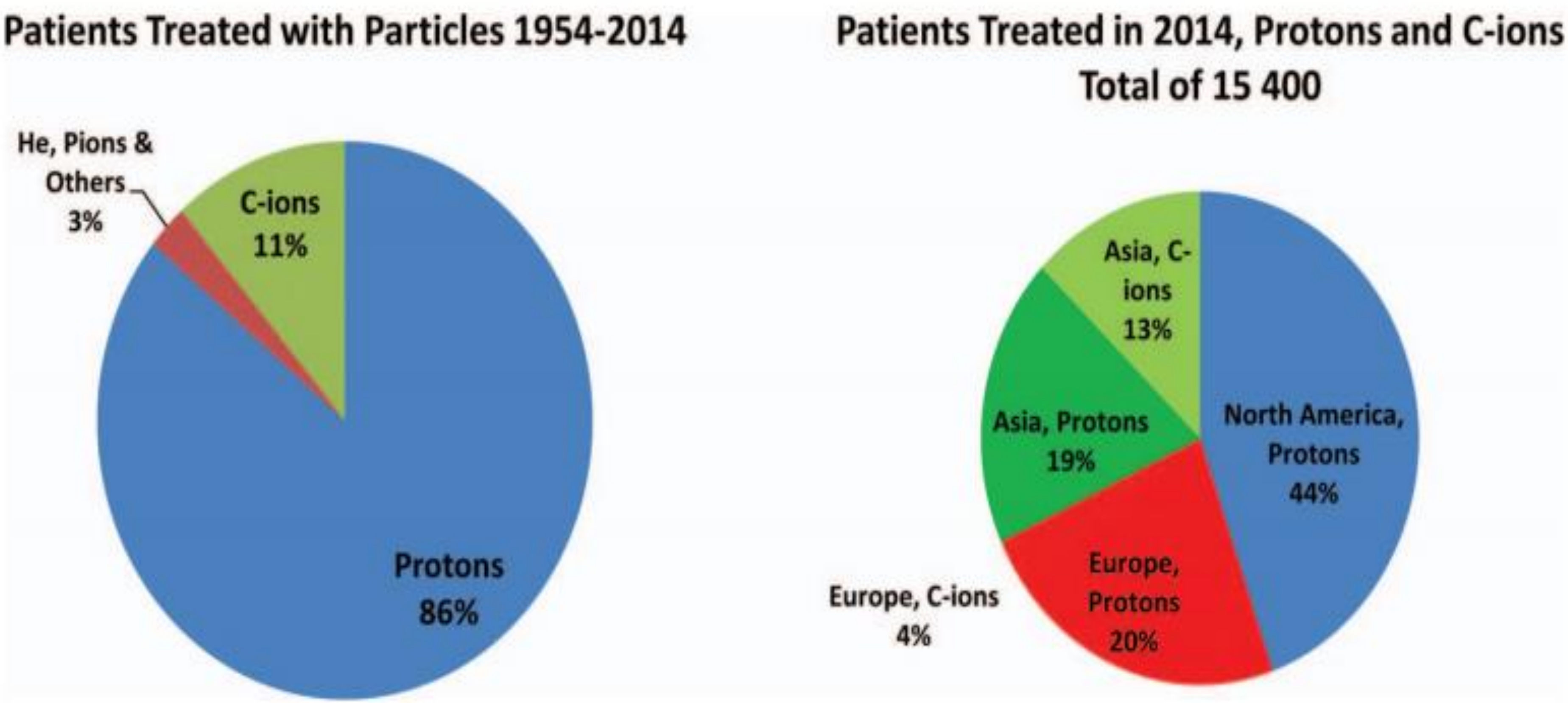
Indications of proton/ion therapy

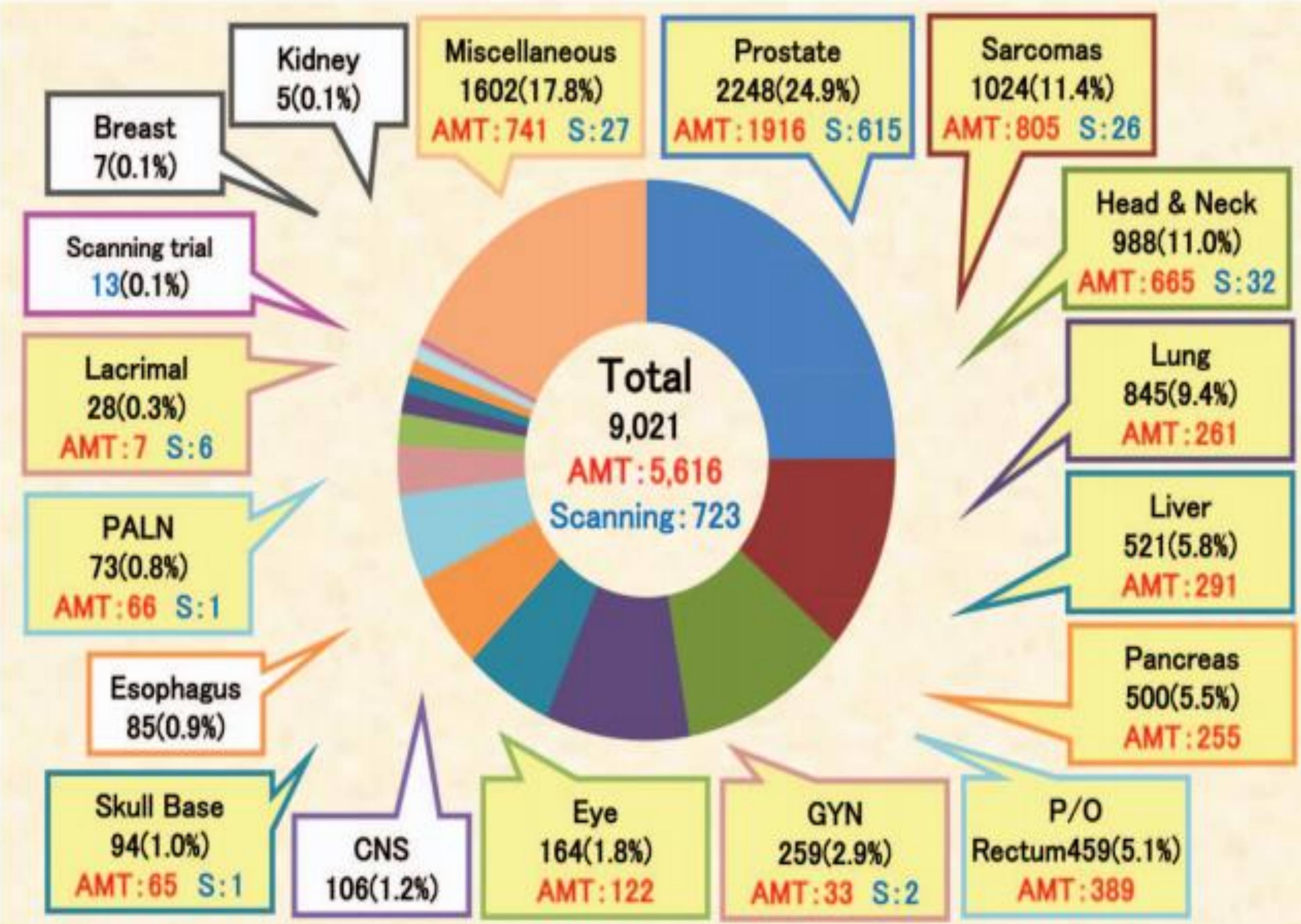
- Eye tumors (melanoma, retinobl.)
- Base of skull tumors (chordomas, chondrosarcomas, meningioma, sinonasal tu.)
- Brain- spinal cord tumors, AV malform.
- Childhood malignancies
- Prostate cancer
- Breast, chestwall, head and neck tumor esophagus, lung tumors

Ion therapy for radioresistant, hypoxic tumors: melanomas, sarcomas, pancreas tu. recurrant rectal cc.

High-LET Particle Therapy– Milestones




Patients Treated with Particles 1954-2014
He, Pions & Others 3%
C-ions 11%
Protons 86%
Patients Treated in 2014, Protons and C-ions
Total of 15 400
Asia, C-ions 13%
Asia, Protons 19%
North America, Protons 44%
Europe, Protons 20%
Europe, C-ions 4%



Kamada (2015), Int J Particle Ther

.

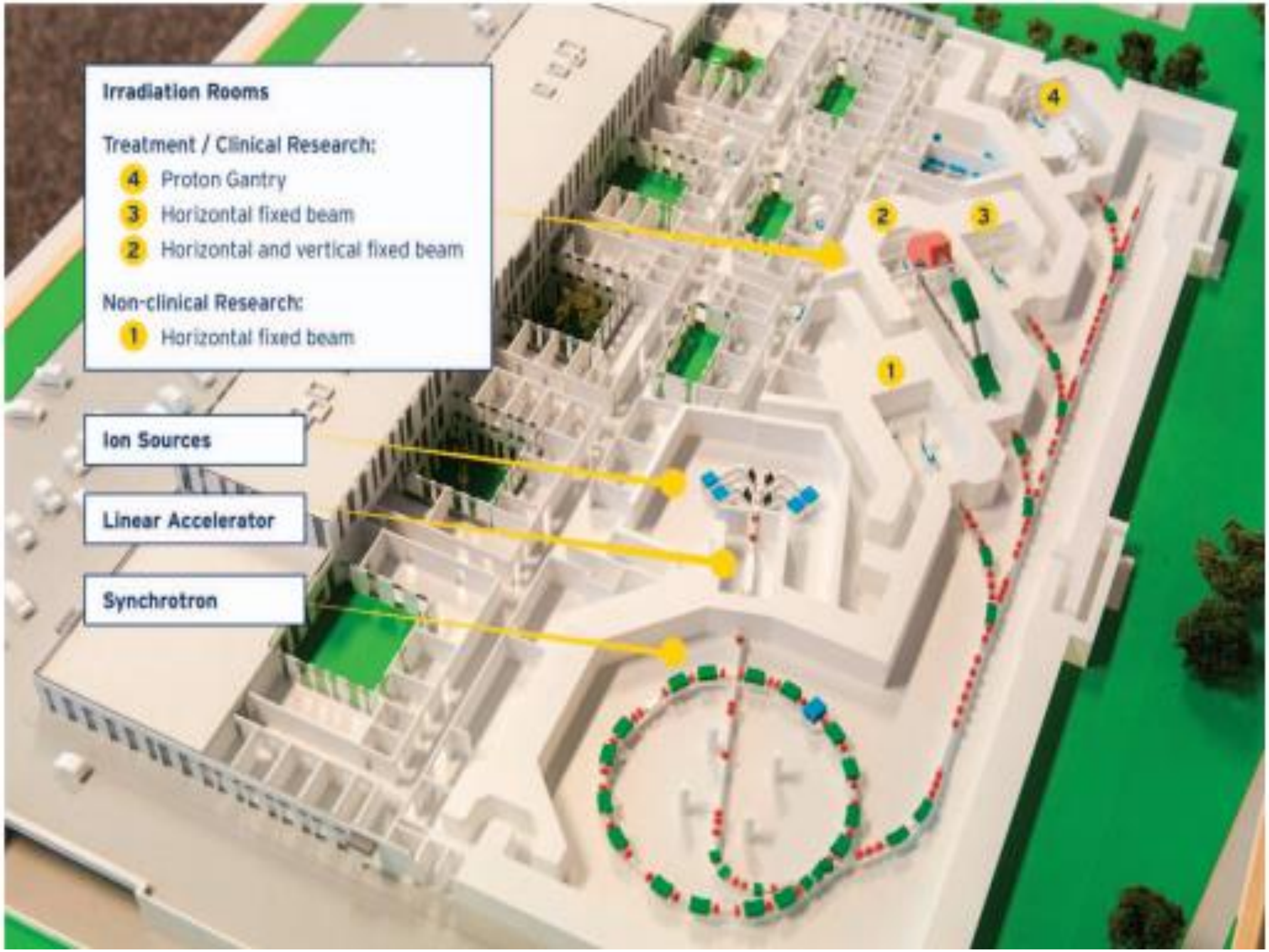
Laprie A, Hu Y. et al. **Paediatric brain tumours: A review of radiotherapy, state of the art and challenges for the future regarding protontherapy and carbontherapy.** Cancer Radiother. 2015 Dec;19(8):775-89.

A systematic review from 1966 to March of 2014.

A total of 7051 primary references published were retrieved, among which 40 clinical studies and 60 papers about quality of life, dose distribution and dosimetry were analysed, as well as the ongoing clinical trials.
Protontherapy allows outstanding ballistics to target the tumour area, while substantially decreasing radiation dose to the normal tissues.

There are many indications of protontherapy for paediatric brain tumours in curative intent, either for localized treatment of ependymomas, germ-cell tumours, craniopharyngiomas, low-grade gliomas; or panventricular irradiation of pure non-secreting germinoma; or craniospinal irradiation of medulloblastomas and metastatic pure germinomas.

Carbon ion therapy is just emerging and may be studied for highly aggressive and radioresistant tumours, as an initial treatment for diffuse brainstem gliomas, and for relapse of high-grade gliomas.



TPS RayStation includes scanned proton and carbon ion beams. Key features of the TPS for particle ther. are patient-specific Hounsfield unit-density scaling, proton and carbon ion Monte Carlo dose engines, beam-specific margins, machine parameter and treatment time optimization, robust optimization, multicriteria optimization, dose tracking, adaptive re-planning and 4D treatment planning

Figure 2. Ceiling-mounted robot for nonisocentric treatment equipped with imaging ring system for image-guided radiation therapy.

Clinical Trials for Particle Therapy (Up-date February 2016):

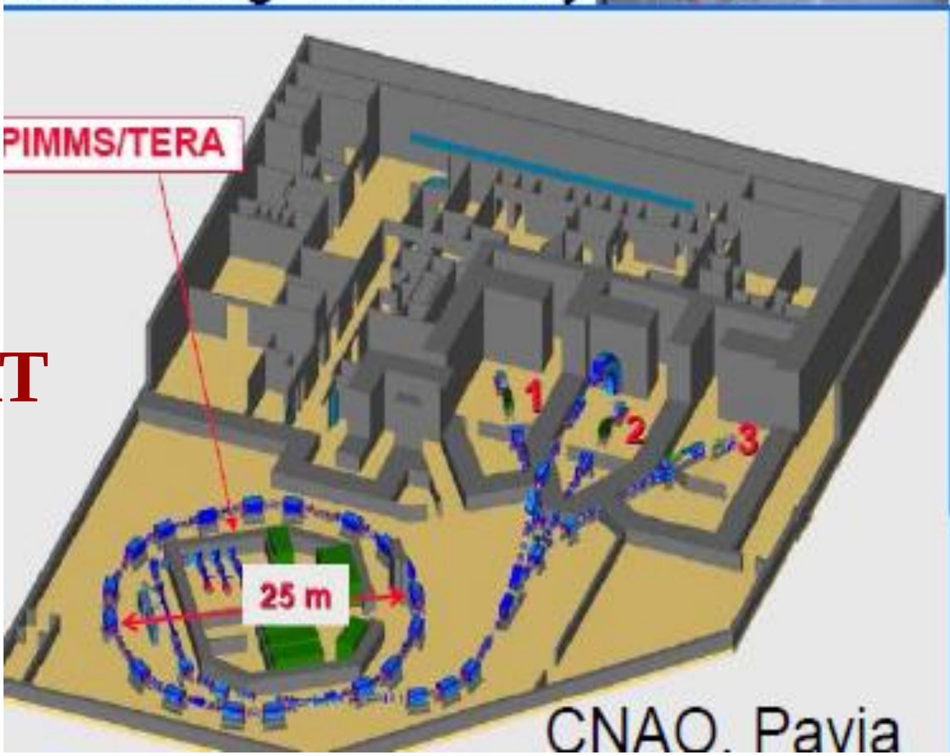
Indication:	Loc:	Links to protocol (clinicaltrials.gov):
Pediatrics	CNS, RMS, Meduloblastoma, H&N, Brain	MDA, MDA, NCC, NCC, NCC, UF, JUDE, JUDE, MGH, MGH, MGH, MGH, MGH, MGH, MGH, MGH, NCI, JUDE, SMC, IU, UW, CG,
Head & Neck	Nasal Cavity, Nasopharynx, Oropharynx, ...	MGH, MGH, MGH, HIT, HIT, HIT, HIT, UF, UF, UF, UF, MDA, MDA, MDA, MDA, TUD, MRO, SPHIC, IRCCS, IRCCS,
Lung	NSCLC	LL, MDA, MDA, MDA, MDA, MDA, MDA, UF, UF, UF, MRO, MRO, MGH, MGH, RTOG, UP, UP, UP, UP, MGH, MGH, MGH, UW, UW, UW, YU, NHS,
CNS	Base of Skull, Spine, ...	MDA, MDA, NCI, NCI, NCI, NRG, UP, UP, MGH, MGH, MGH, MGH, MGH, MGH, HIT, HIT, HIT, HIT, HIT, UF, NCC, NCC, RTOG, RTOG, UF, UW,
Breast	Partial Breast, Lymph-Nodes, Hodgkins, ...	UP, UP, UP, UP, IU, UF, UF, MGH, LL, LL, PCG, PCG, MDA, MAYO,
GI	Liver	LL, LL, LL, LL, MGH, MGH, MGH, NCC, NCC, NCC, NCC, MDA, UW, SMC, SMC, CG,
	Pancreas	MGH, MGH, MGH, MGH, NCC, NCC, UF, UF, UF, UF, LL, HIT,
	Upper GI, Esophageal, Rectum	UP, MDA, MDA, LL, UW, HIT,
GU	Prostate	IU, NCC, UP, UP, UP, MGH, PCPT, UF, UF, UF, UF, UF, UF, MDA, MDA, MDA, MDA, LL, PCG, PCG, PCG, EIO, HIT, NCI,
	Bladder	UP,
	Gyn	NCC,
Lymphoma	Hodgkin Lymphoma	IU, UF, UF, MGH,
Sarcoma	Chordoma, Chonrosarcoma, Spine, Retroperitonial, ...	UF, UF, UF, MGH, MGH, MGH, MGH, MDA, MDA, UP, UP, UP, HIT, HIT, KSA, JUDE, LL,
Eye	Melanoma, Retinoblasoma, Macular Degeneration	MDA, MEEI, UF, UC, UC, CAL, CAL, JUDE, CU,

Hadron centers

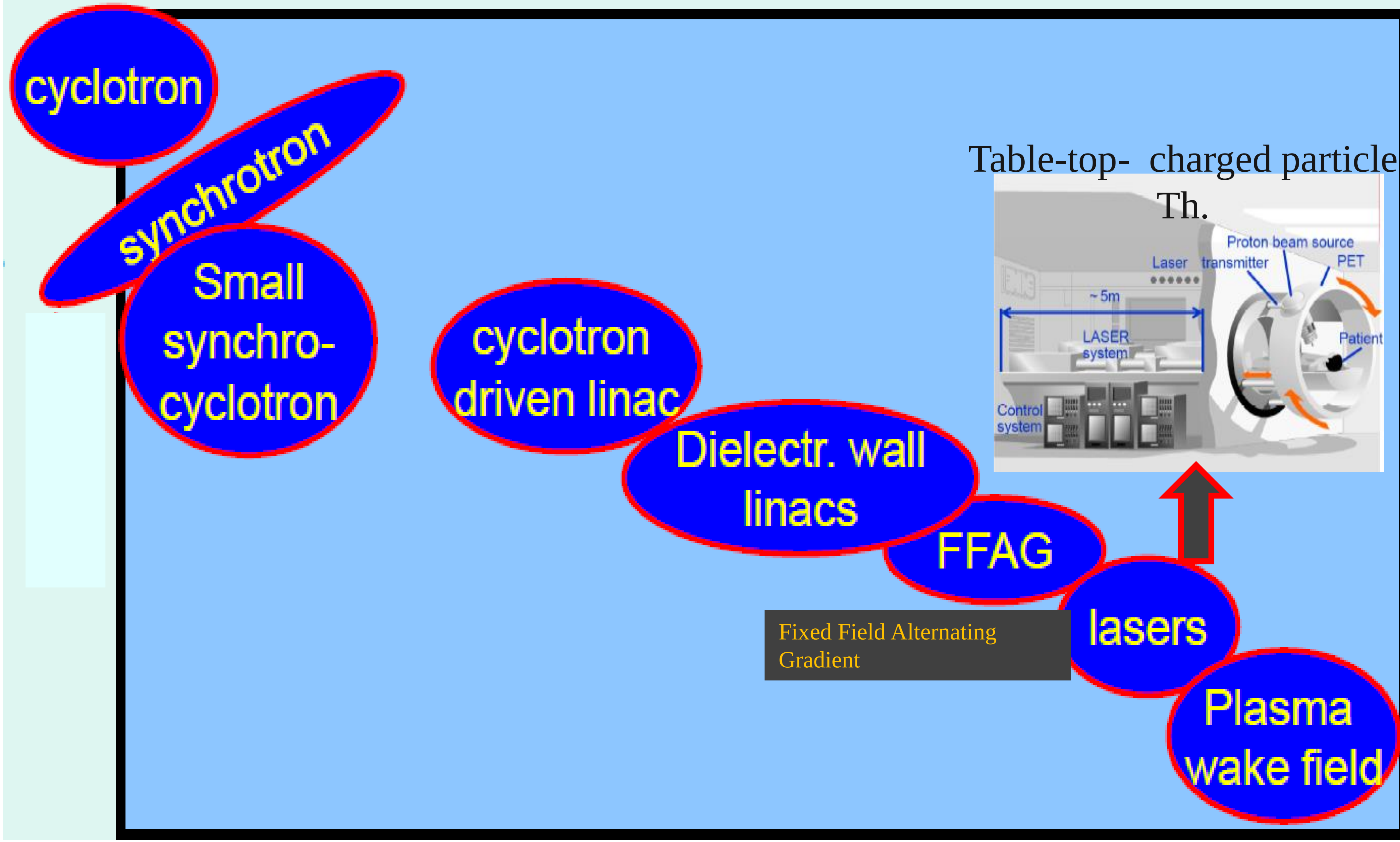
43 centers in operation and further 40 is planned

Total patients treated
2054 He
1100 pions
433 other ions
10756 C-ions
93895 protons
Total **108238** **<1% of all RT**

thereof 10316 C-ions
78132 protons



Proton/ion acceleration techniqes



Potential of laser driven ionizing radiation sources

For cost effective, compact, flexible hadrontherapy
economic aspect

Epithermic neutron, VHEE, microbeams, combined particle beams
physical aspect

To use the potential biological advantages of pulsed mode operation and ultra high dose rate- ultra high spatial and temporal resolution differential tumor- normal cell effect
biological aspect

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Thank you for your attention!

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