Workshop on Nuclear Data for Science and Technology: Medical Applications
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REVIEW OF NEUTRON AND PROTON THERAPY

Dan T L Jones[1,3] and André Wambersie[2,3]

[1] *iThemba Laboratory for Accelerator Based Sciences*
Somerset West, SOUTH AFRICA

[2] *Clinic Saint Luc / Université Catholique de Louvain*
Brussels, BELGIUM

[3] *International Commission on Radiation Units and Measurements*
Bethesda MD, USA

NUCLEAR PARTICLE THERAPY

- Proton therapy
- Heavy* ion therapy
  - ^{12}C (mainly)
  - ^{4}He, ^{20}Ne, ^{28}Si, ^{40}Ar
- Neutron therapy
  - Fast neutron therapy
  - Boron neutron capture therapy (BNCT)
  - ^{252}Cf brachytherapy
- Pion (π^-) therapy

**To distinguish from protons*

ICRU REPORTS:
NUCLEAR PARTICLE THERAPY (I)

- **NEUTRON DOSIMETRY FOR BIOLOGY AND MEDICINE**
  ICRU Report 26 (1976)
- **AN INTERNATIONAL NEUTRON DOSIMETRY INTERCOMPARISON**
  ICRU Report 27 (1978)
- **BASIC ASPECTS OF HIGH-ENERGY PARTICLE INTERACTIONS AND RADIATION DOSIMETRY**
  ICRU Report 28 (1978)
- **AVERAGE ENERGY REQUIRED TO PRODUCE AN ION PAIR**
  ICRU Report 31 (1979)
- **MICRODOSIMETRY**
  ICRU Report 36 (1983)

ICRU REPORTS:
NUCLEAR PARTICLE THERAPY (II)

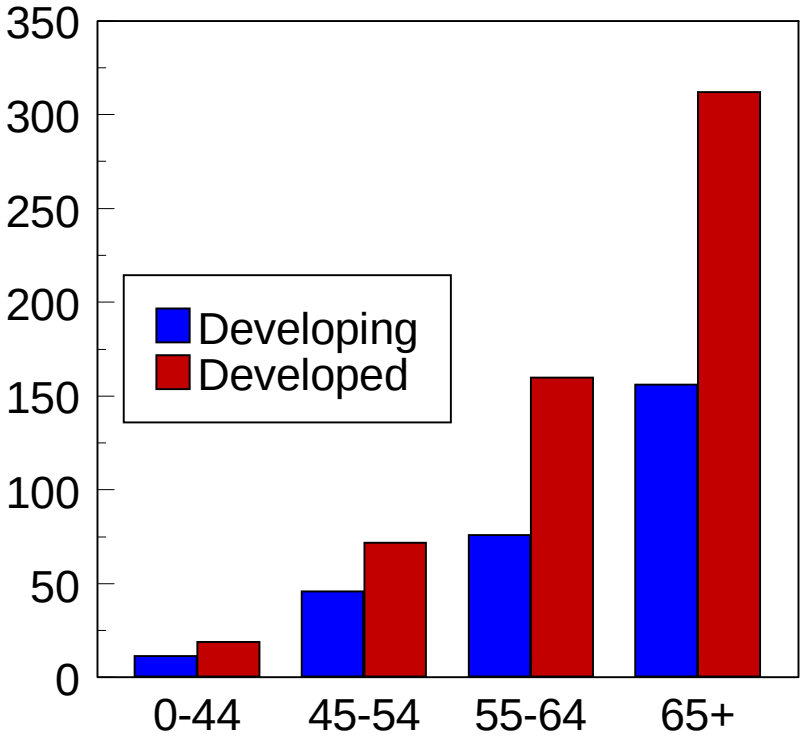
- **CLINICAL NEUTRON DOSIMETRY PART 1: DETERMINATION OF ABSORBED DOSE IN A PATIENT TREATED BY EXTERNAL BEAMS OF FAST NEUTRONS**
  ICRU Report 45, 1989
- **PHOTON, ELECTRON, PROTON AND NEUTRON INTERACTION DATA FOR BODY TISSUES**
  ICRU Report 46, 1992
- **STOPPING POWERS AND RANGES FOR PROTONS AND ALPHA PARTICLES**
  ICRU Report 49, 1993
- **CLINICAL PROTON DOSIMETRY PART I: BEAM PRODUCTION, BEAM DELIVERY AND MEASUREMENT OF ABSORBED DOSE**
  ICRU Report 59, 1998

ICRU REPORTS:
NUCLEAR PARTICLE THERAPY (III)

- **NUCLEAR DATA FOR NEUTRON AND PROTON RADIOTHERAPY AND FOR RADIATION PROTECTION**
  ICRU Report 63, 2000
- **STOPPING OF IONS HEAVIER THAN HELIUM**
  ICRU Report 73, 2005
- **PRESCRIBING, RECORDING, AND REPORTING PROTON-BEAM THERAPY**
  (Co-Chairs: D T L Jones, H D Suit)
  ICRU Report 78 (to be published in 2007)
- **PRESCRIBING, RECORDING, AND REPORTING CARBON ION-BEAM THERAPY**
  (Co-Chairs: W T Chu, H Tsujii)
  ICRU Report 81 (to be published in 2009)

CANCER INCIDENCE (I)

Rates of Cancer in Developing and Developed Countries, by Age (per 100000 per year)



The most common primary cancers in males in developed and developing countries (ranked by frequency)

Cancer Primary	Developing	Developed
Lung	1	1
Stomach	2	4
Liver	3	>10
Oesophagus	4	>10
Colon/rectum	5	3
Prostate	6	2
Oral cavity	7	9
Bladder	8	5

CANCER INCIDENCE (II)

- Cancer is the uncontrolled growth and spread of groups of abnormal cells
- 35 % of people in developed countries are diagnosed with cancer (USA: 41 %)
  - † nearly half of these die of it
- 10 million reported new cases world-wide per year (USA: 1 million, excluding non-melanoma skin cancer)
- ≈ 20 million new cases per year by 2020
  - † improved diagnosis in developing countries
  - † people are living longer
- **Modest improvements in cure rates will help a vast number of people**

CANCER INCIDENCE (III)

- Most common cases:
  - Men
    - lung, stomach (developing countries)
    - lung, prostate (developed countries)
    - *USA: prostate (30%), lung (14%)*
  - Women
    - breast, cervix (developing countries)
    - breast, colon (developed countries)
    - *USA: breast (31%), lung (12%), colon (12%)*
- Most radiation resistant tumors:
  - gliobastoma multiforme
  - malignant melanoma (+ brain metastases)
  - pancreatic cancer

CANCER INCIDENCE (IV)

- Prognosis varies greatly – depends on tumor type, size and location, stage of diagnosis, proximity of critical organs, heredity factors, lifestyle, and general health of patient, *etc*.
- 5−year survival rate without further symptoms (regarded as cure) of all treated cancer sufferers is about 45 %
- About 70 % of all cancer patients have no metastases (secondary tumors that spread from the primary site to other parts of the body) at diagnosis, *i.e.* tumor is confined to primary site

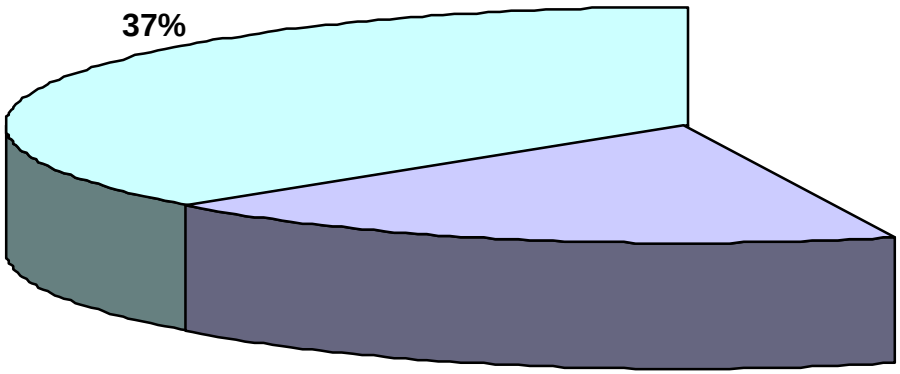
CANCER TREATMENT

- Treatment of primary tumor (radiotherapy, surgery) is responsible for 90 % of cancer cures
- Treatment of metastases (chemotherapy) is responsible for 10 % of cancer cures
- Patients cured (45 % of treated patients):
  - † 50 % - surgery
  - † 27 % - radiotherapy
  - † 13 % - radiotherapy + surgery } 40%
  - † 10 % - chemotherapy
- Causes of death:
  - † 33 % - uncontrolled primary tumor
  - † 67 % - uncontrolled metastases
- Cost of not curing a patient is very high

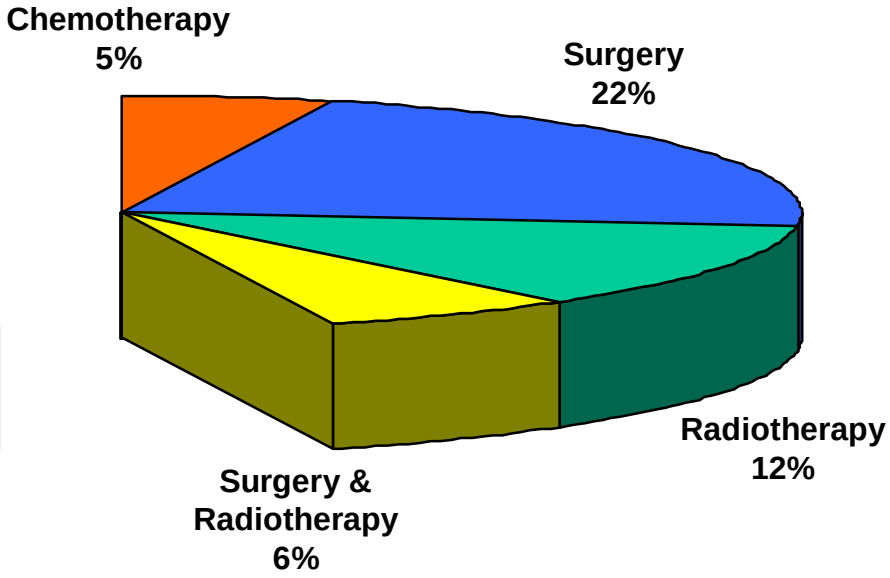
  (≥ 5 times more than cost of curing)

CANCER TREATMENT OUTCOMES

55%
PRESENTLY INCURABLE



45%
SUCCESSFULLY CURED



RADIOTHERAPY (I)

- Used mainly for control of local disease (primary tumor)
- Radiation modalities are characterized by LET (Linear Energy Transfer)
  - similar to linear stopping power, but excludes effects of radiative energy loss (Bremsstrahlung) and delta rays
- Objectives of radiotherapy
  - maximize effect on tumor
  - minimize effects on normal issues
  - avoid irradiating critical radiosensitive tissues and organs
    - can be accomplished by improving physical selectivity, crossfire irradiations, biological effect differentiation, fractionation optimization, use of radiosensitizers and/or radioprotectors, particle therapy, targeted radiation therapy, optimization of adjuvant therapy scheduling, ...

RADIOTHERAPY (II)

- Allows organ preservation in 40% of curable cases
- Improves quality of life
- Also used for palliation (relief of symptoms)
- Non-invasive and painless
- Patients can be treated on an outpatient basis
- There are little or no side effects
- Patients can carry on with normal activities
- Can be used in conjunction with other treatments
- Treatment takes from 1 day to 7 weeks
  - † depends on lesion site and radiation modality
- Requires accurate 3/4-dimensional *treatment planning*
- > 600 000 people undergo radiotherapy in the USA annually

ACCELERATORS (I)

LINEAR ACCELERATORS (neutron therapy)

- high energy consumption
- high beam intensity

SYNCHROTRONS (proton therapy)

- frequency of the high voltage acceleration system is increased with increasing particle speed
  - simultaneously the magnetic fields in the bending magnets are increased
- extraction at any energy by single turn or slow extraction (to achieve longer pulses)
- low intensities
- pulse-by-pulse energy change

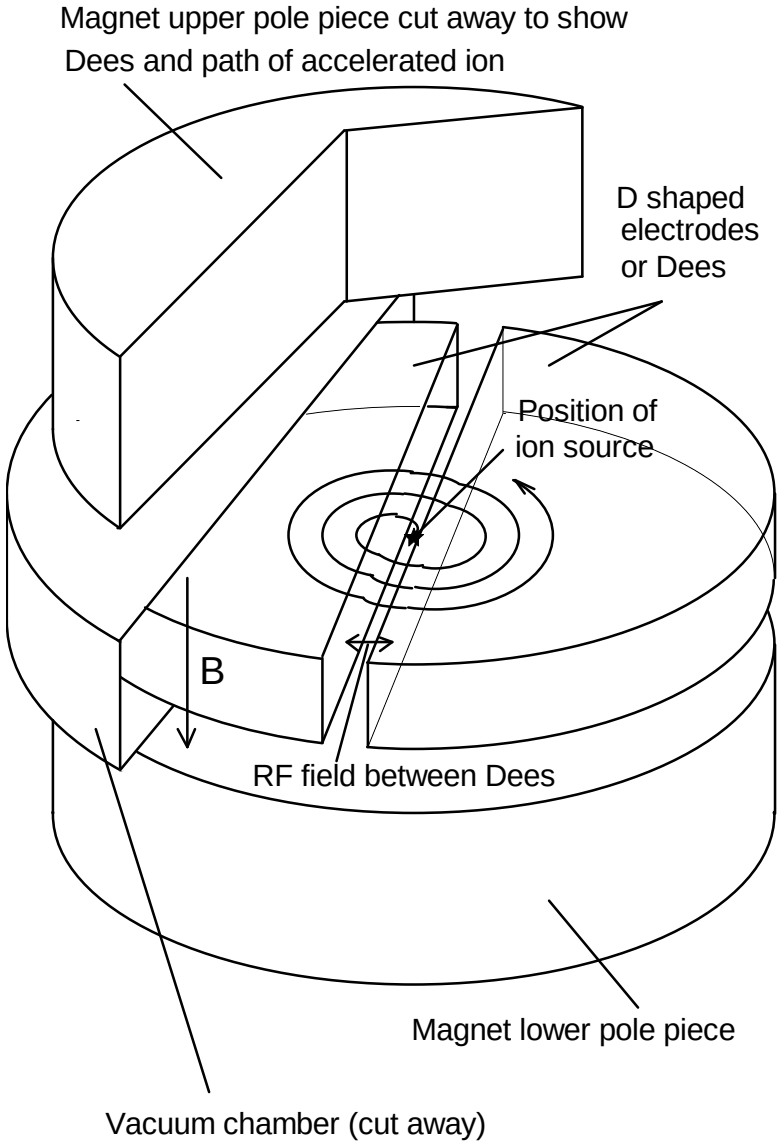
ACCELERATORS (II)

CYCLOTRONS

- † high intensities
- † degraders for energy change (if required)

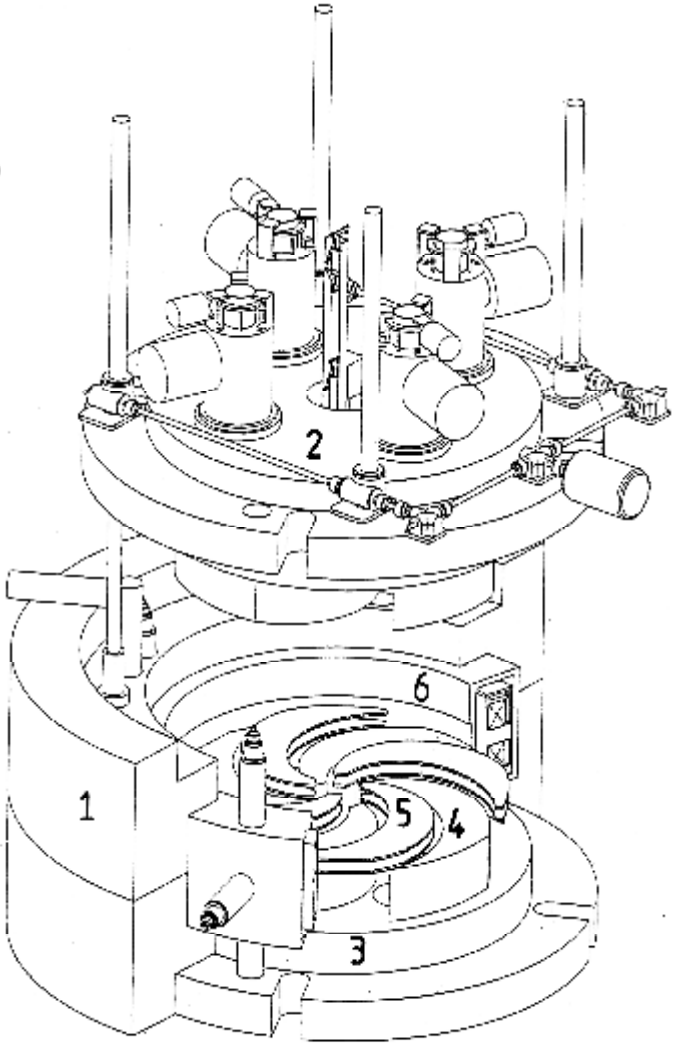
- ▶ Classical (neutron therapy)
  - † < 16 MeV (no relativistic mass increase)
- ▶ Isochronous (neutron and proton therapy)
  - † increasing magnetic field with radius compensates for relativistic effects
  - † room temperature or superconducting magnets
- ▶ Synchrocyclotron (proton therapy)
  - † decreasing frequency of accelerating voltage compensates for relativistic effects
  - † fixed energies
  - † pulsed operation

CLASSICAL CYCLOTRON



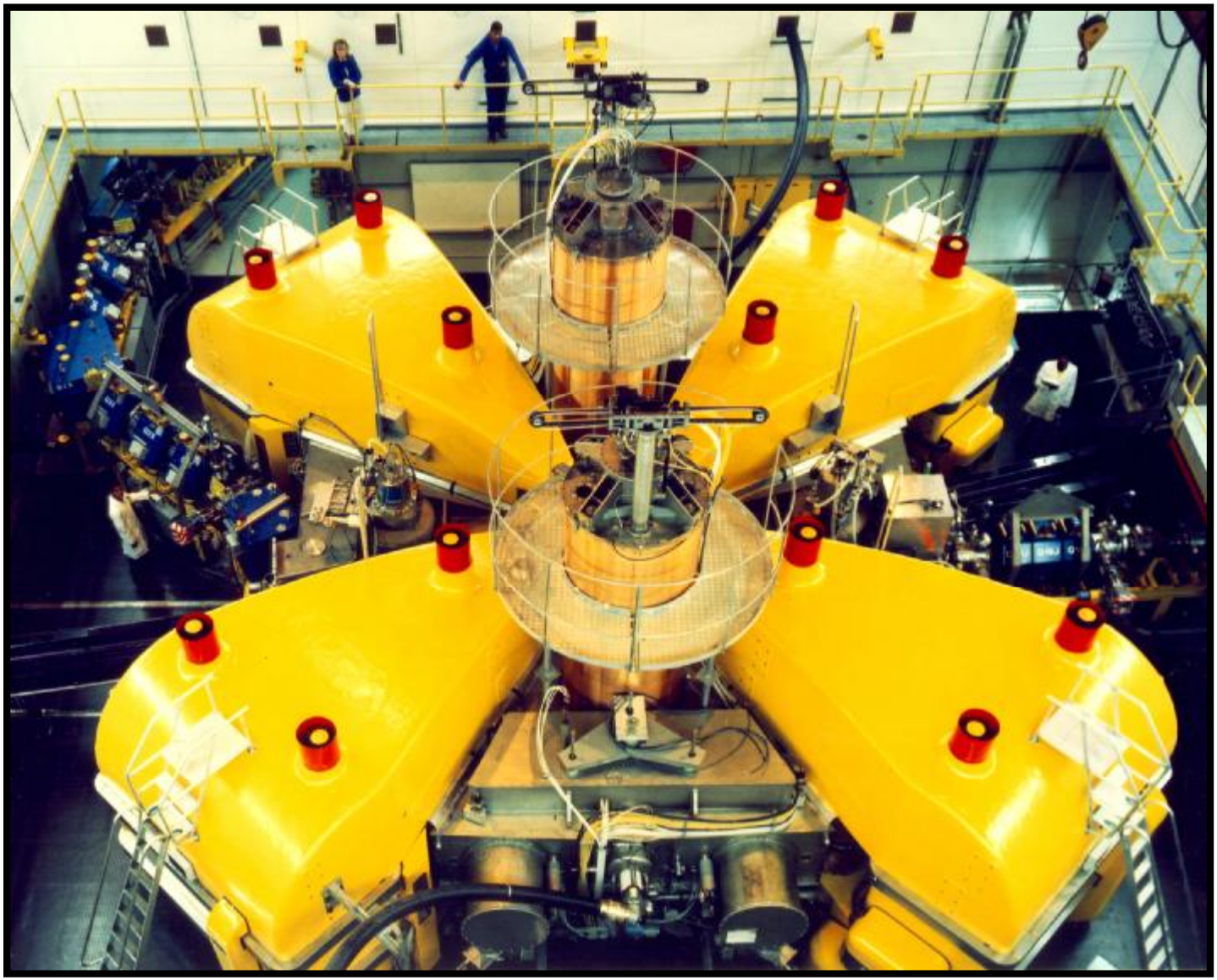
250 MeV ISOCHRONOUS CYCLOTRON
Superconducting

Diameter = 3.2 m
(room temperature: ~ 4.5 m)



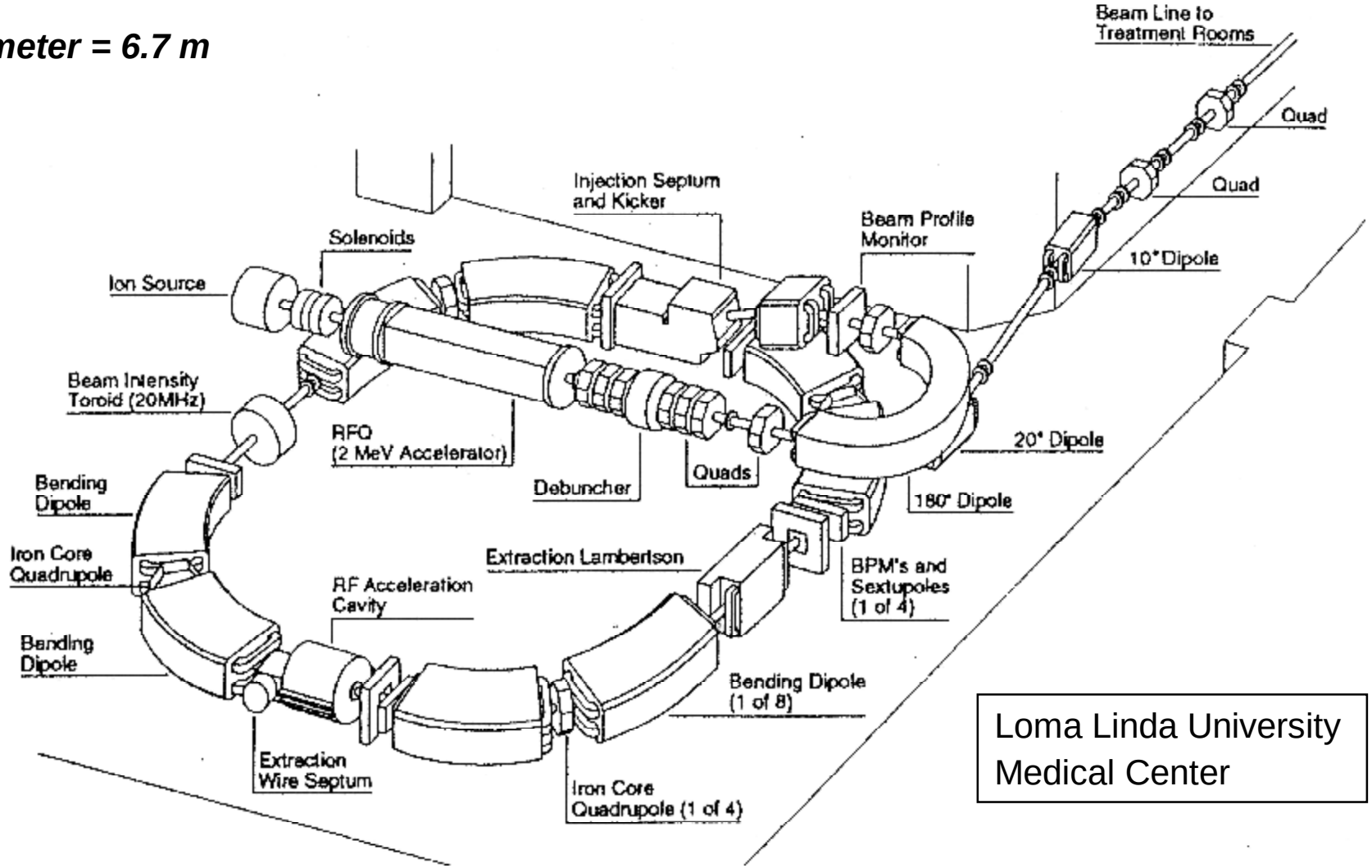
Blosser *et al*, 1993

SEPARATED-SECTOR CYCLOTRON (iTL)



250 MeV SYNCHROTRON

Diameter = 6.7 m



Loma Linda University Medical Center

NUCLEAR PARTICLE THERAPY
Beam production

DEVICE	NEUTRON	BNCT	PROTON	^{4}He	HI	π^-	TOTAL
Cyclotron	27		19			2	48
Synchrocyclotron			7	1			8
Superconductng cyclotron	1		1				2
Synchrotron	0		8		4		12
Linear Accelerator	2					1	3
Reactor	3	12					15
D-T generator	8						8
TOTAL	41	12	35	1	4	3	96

IDEAL PARTICLE THERAPY UNIT
Operational aspects

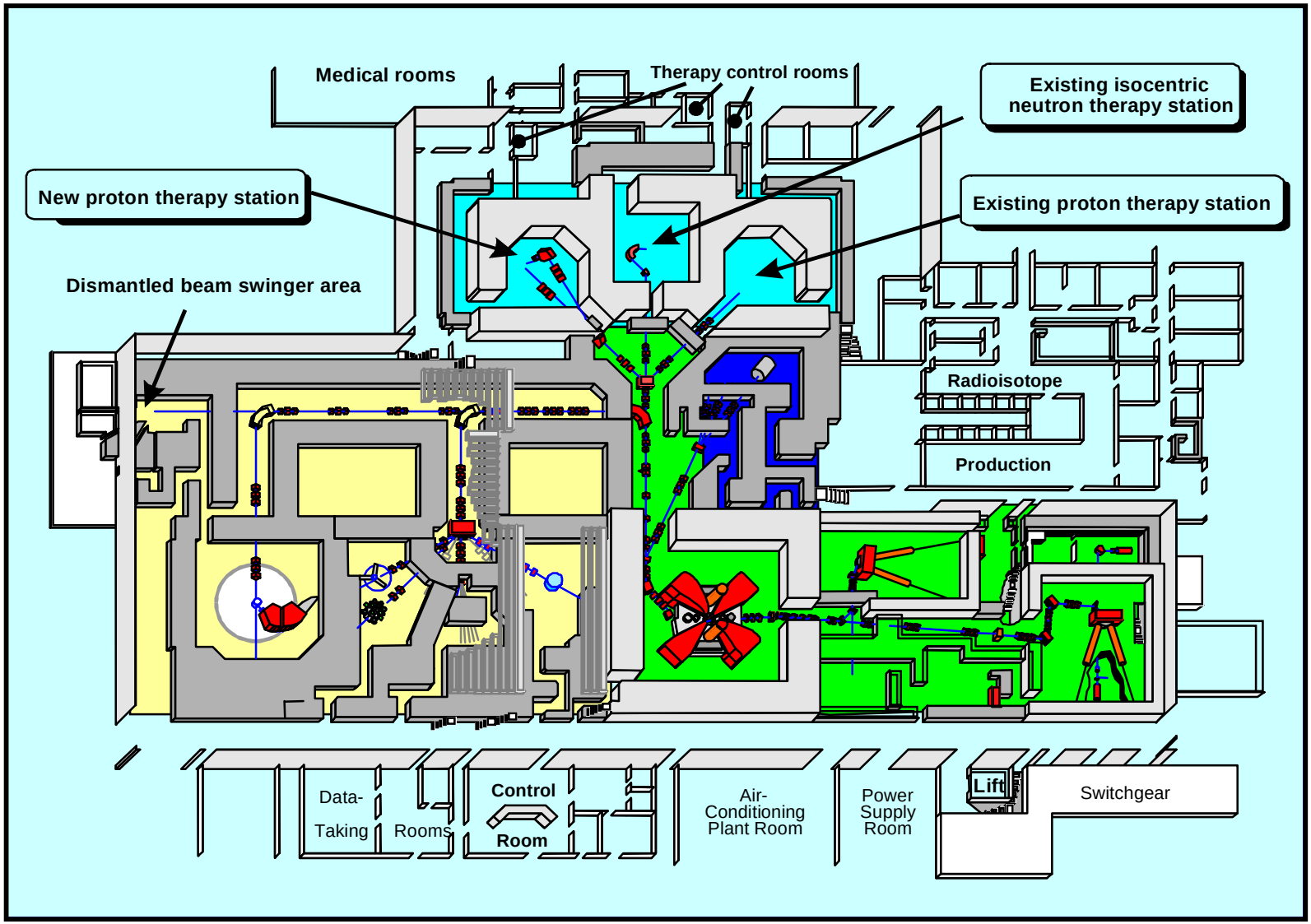
- Low capital costs
- Low operating costs
- Compact
- Located in or near large hospital
- Reliable (≥ 98% uptime)
- Accurate beam delivery
- Flexible beam configuration
- Simple to operate
- Maintenance personnel on site or nearby

IDEAL PARTICLE THERAPY UNIT
Technical aspects

- Intensity-modulated therapy
- Image-guided therapy
- Sufficient energy to adequately treat a lesion on the centerline of the thickest region of the body
- Compensation foe organ motion / respiratory gating
- Robotic patient support system
- Sophisticated treatment planning system
  - inverse planning, account for RBE variations, biological models.....
  - fast Monte Carlo dose calculations
- Real-time visualization of dose distributions
- Appropriate patient selection
  - predictive histological assays
- State-of-the-art diagnostic facilities
  - anatomical and functional **è** CT, MRI, PET/CT, ...

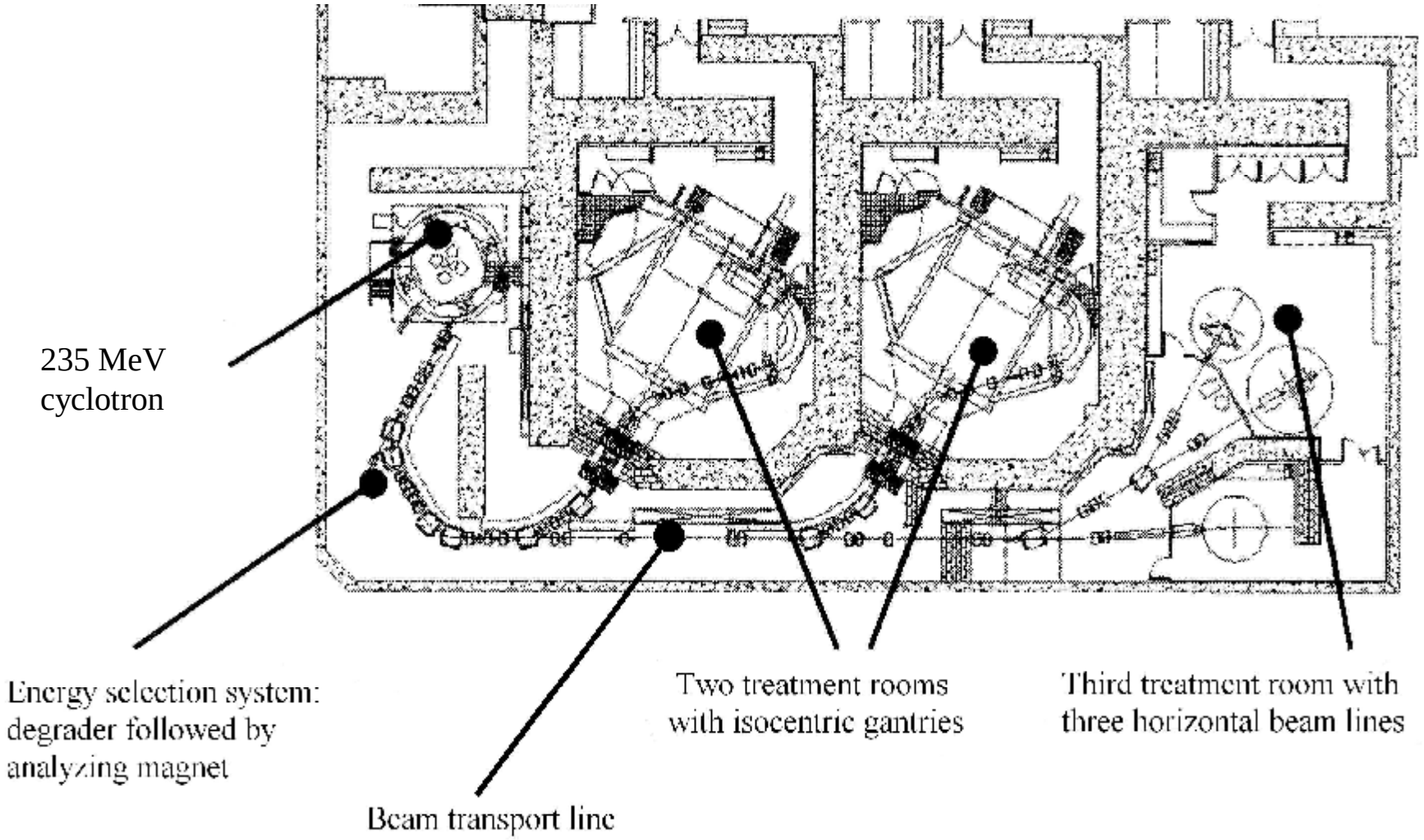
LABORATORY-BASED TREATMENT FACILITY

Neutron and proton therapy (iThemba LABS)

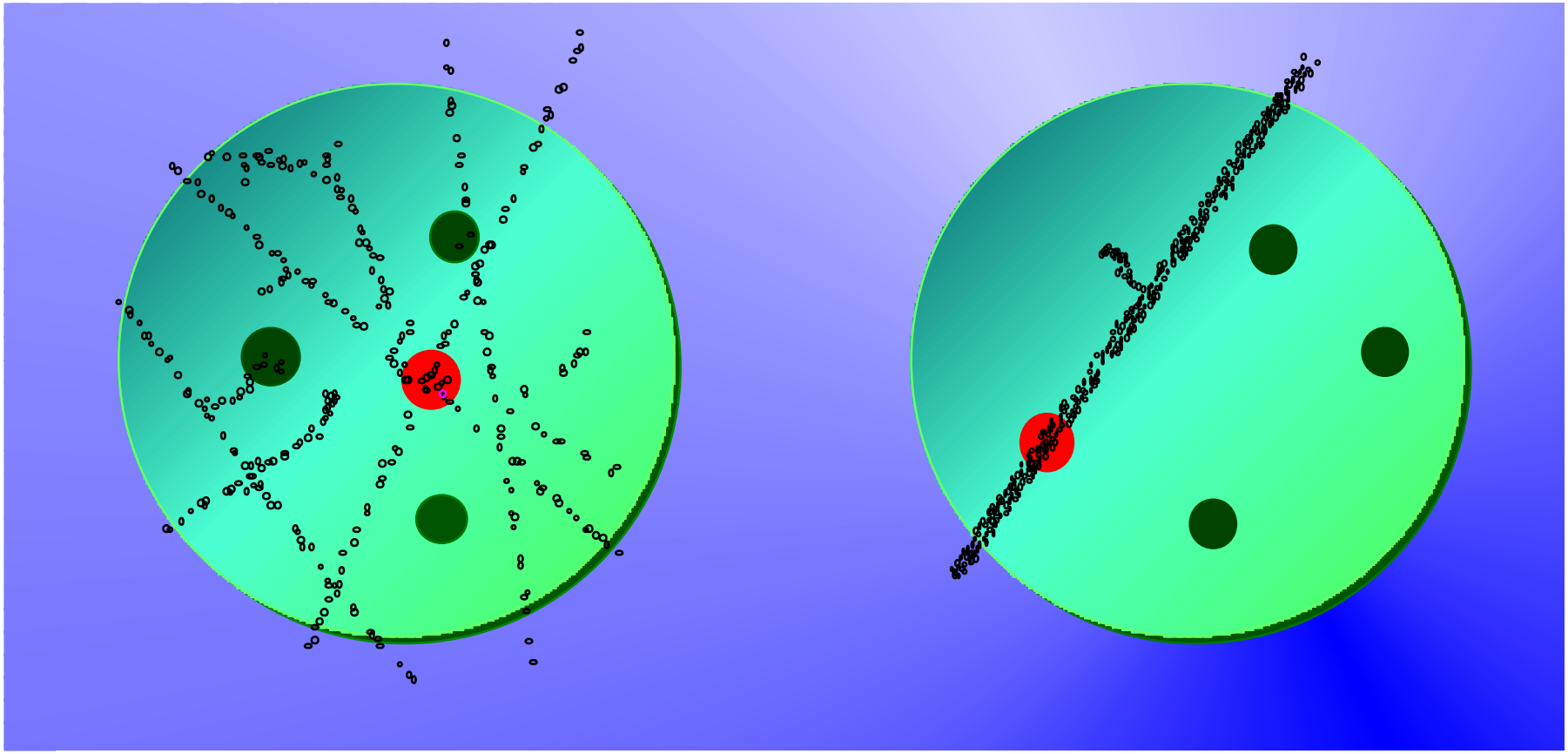


DEDICATED TREATMENT FACILITY

Proton therapy (Francis H Burr Proton Therapy Center)



IONIZATION DENSITY
Linear Energy Transfer



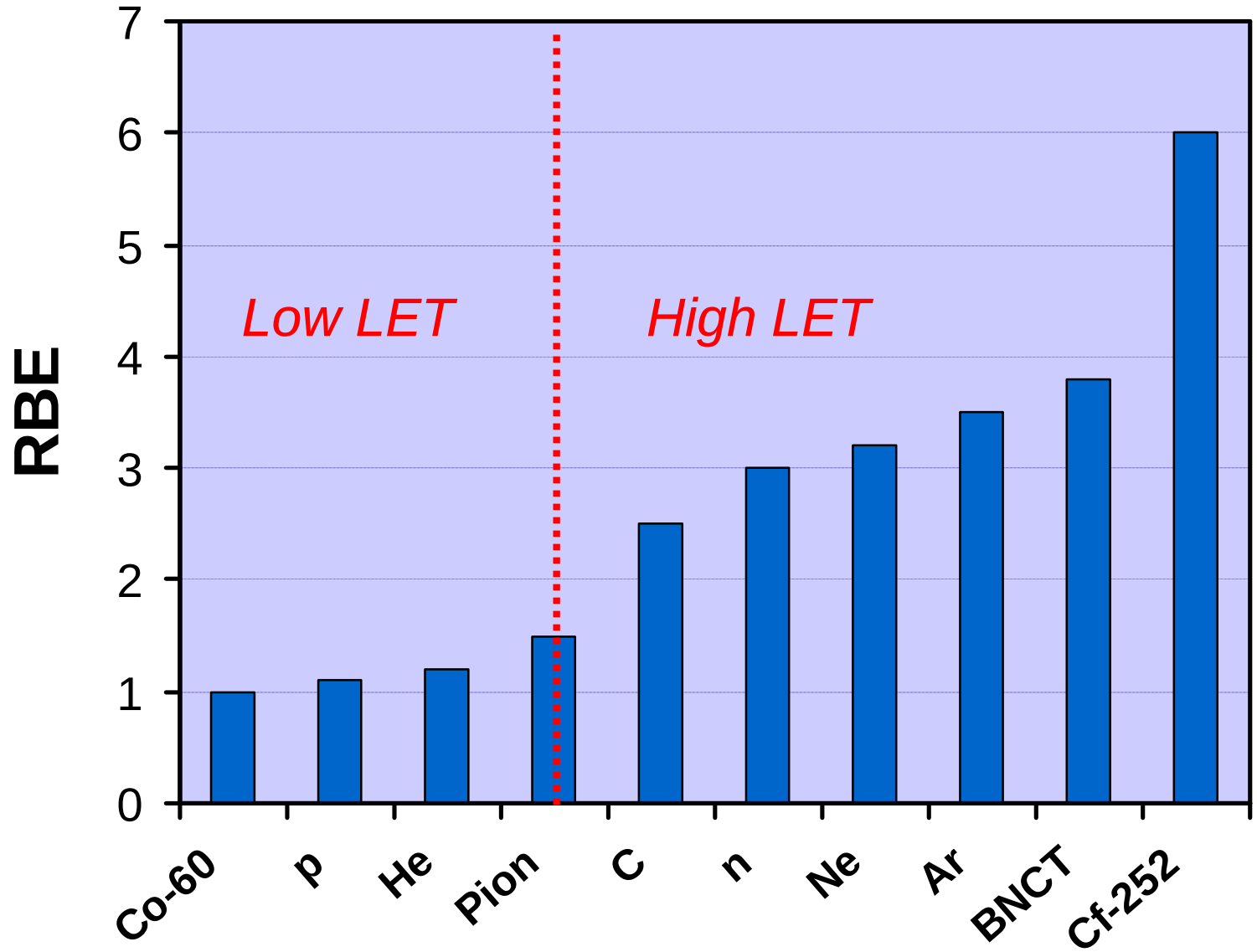
Low-LET
(PROTONS)

High-LET
(NEUTRONS)

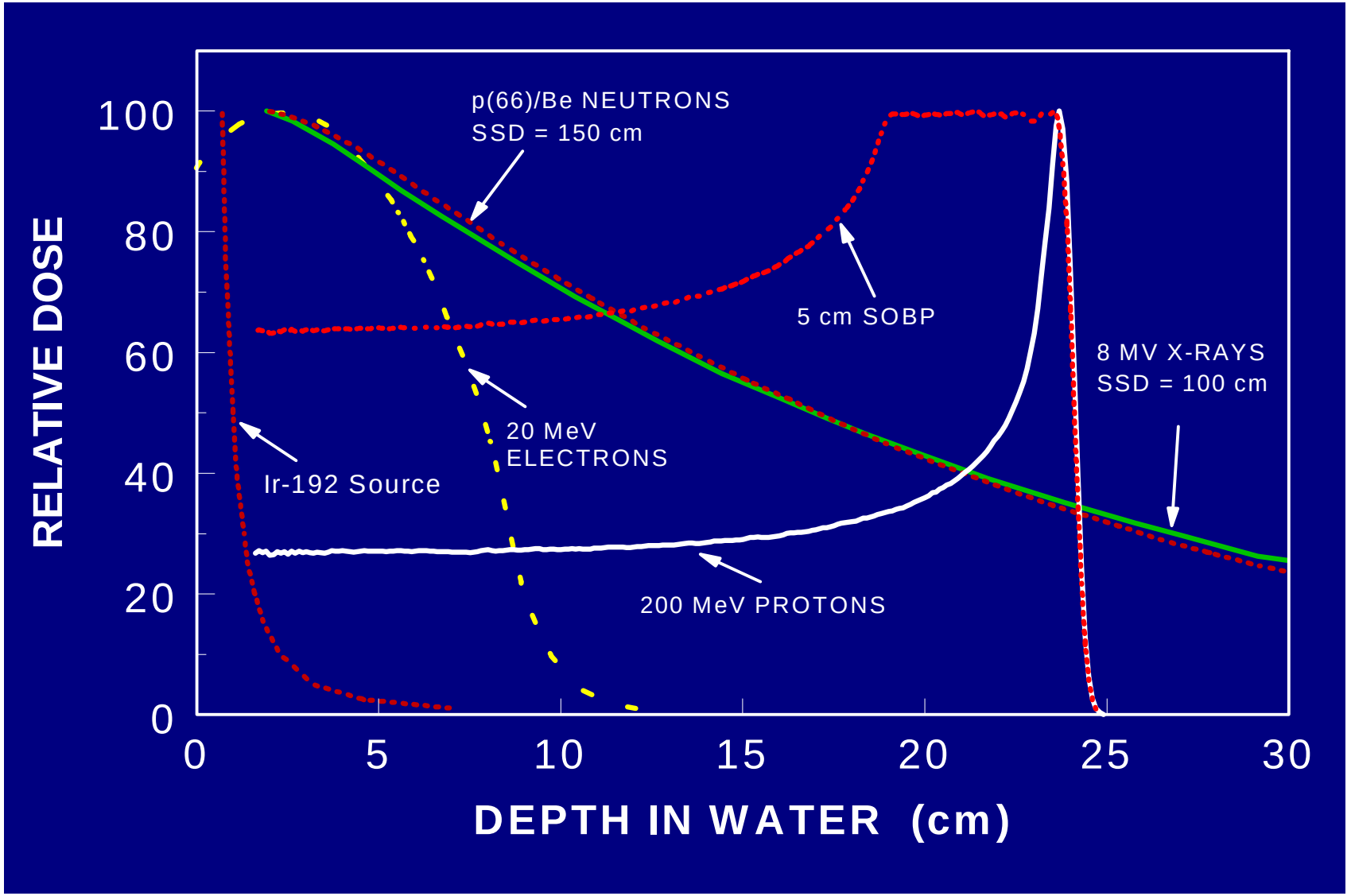
TYPICAL LET VALUES IN TISSUE

RADIATION	LET (keV μm^{-1})
^{60}Co γ-rays MV x-rays	7
Electrons	7
250 kV x-rays	10
Protons	10
^{4}He ions	15
p^- mesons	20
^{12}C ions	75
Fast neutrons	75
^{252}Cf	100
^{40}Ar ions	120
Boron neutron capture ^{4}He ^{7}Li	 200 160

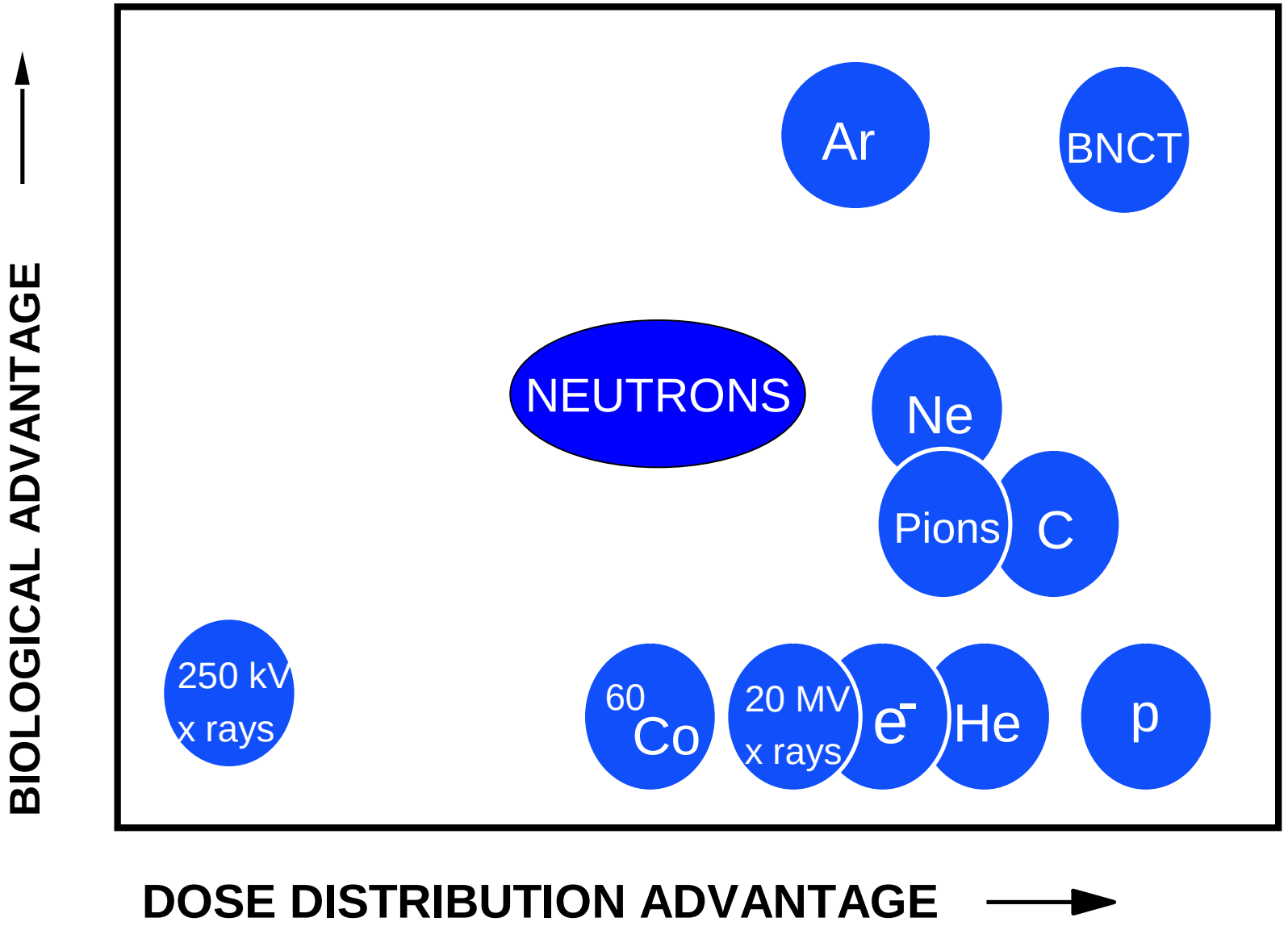
RELATIVE BIOLOGICAL EFFECTIVENESS



DEPTH DOSE DISTRIBUTIONS



RADIOTHERAPY MODALITIES



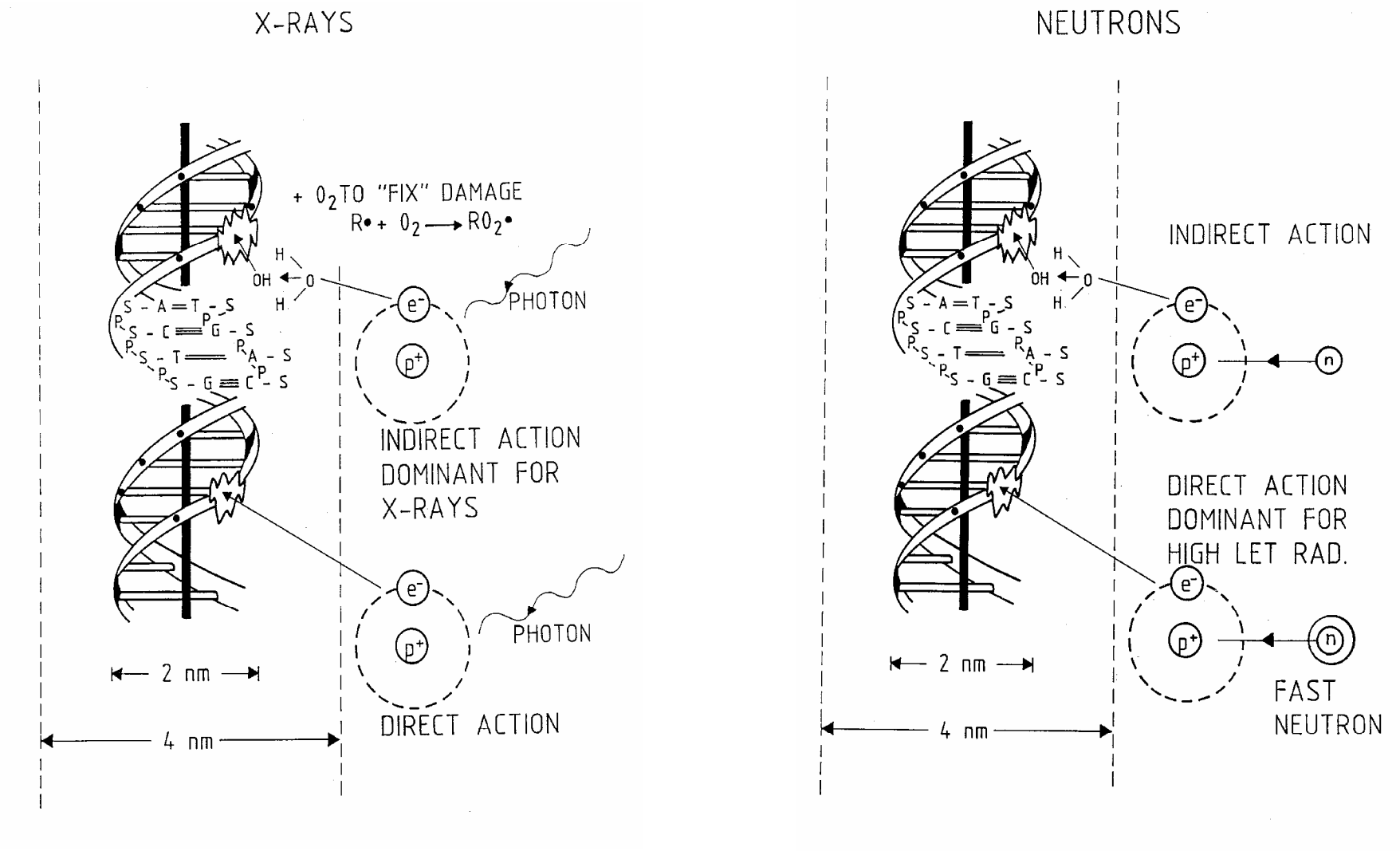
FAST NEUTRONS IN RADIOTHERAPY
Fundamental issues

- High−LET radiation
  - † reduced dependence on oxygen tension in tumor
  - † reduced repair of sublethal damage
  - † reduced variation of sensitivity within cell cycle
  - â ***more effective for treating larger, slow-growing tumors***
  - â ***fractionation schedule not as important as for low-LET***
- In tissue the predominant interaction is n−H scattering, but heavier recoils (^{4}He, ^{12}C, ^{14}N, ^{16}O .....) with higher LET values than protons are also produced
  - † bone sparing (less H)
  - † increased absorption in fat (more H)
- Gamma rays are always produced in surroundings and in patient

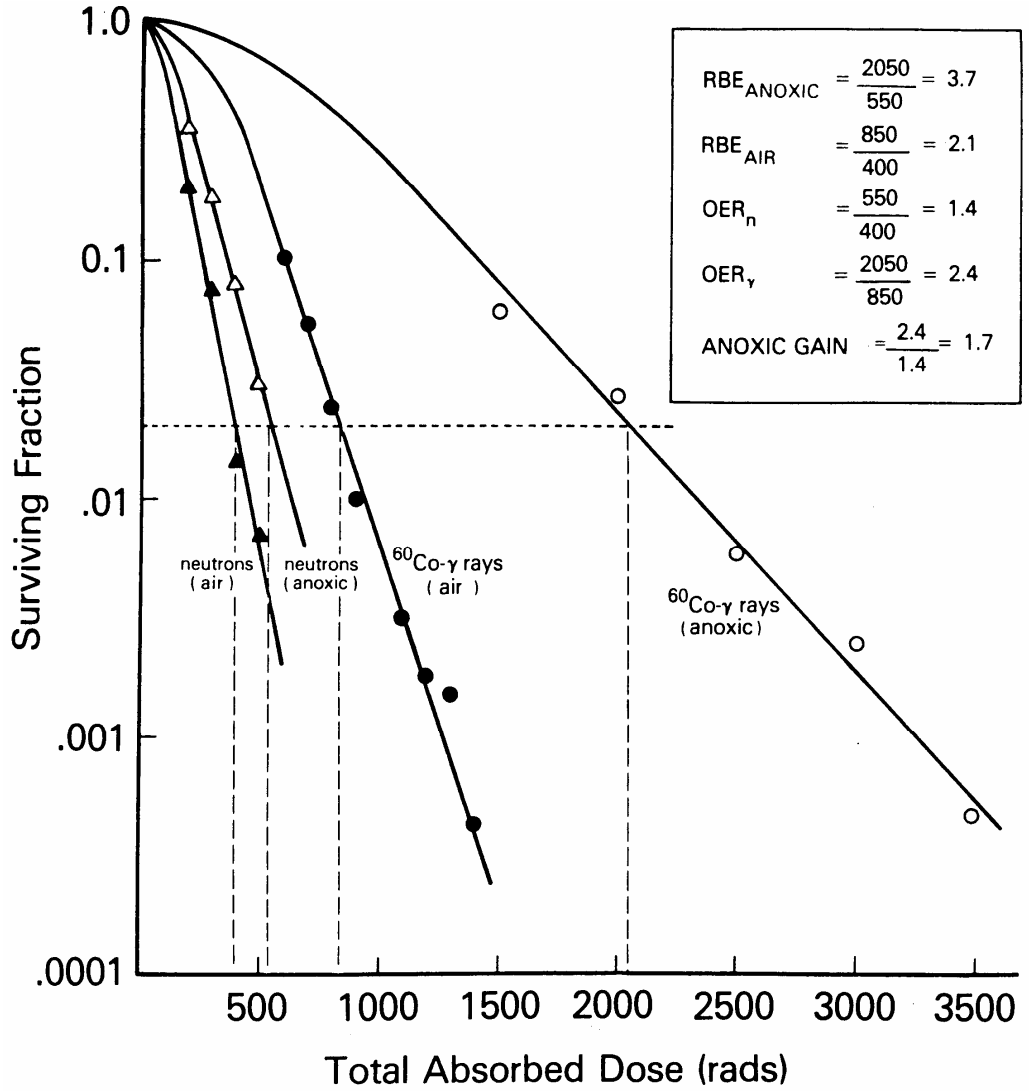
OXYGEN EFFECT

- Damage to DNA is done either directly by ionizing particles or indirectly by biochemical action
- Low-LET radiation damage is caused mostly by indirect biochemical action while high-LET radiation damage is mostly by direct interaction of ionizing particles
- In the indirect method the ionizing particles induce the formation of free radicals which damages the DNA. The presence of free oxygen is required to fix this radiation damage. In the absence of oxygen the effects of indirect action is limited

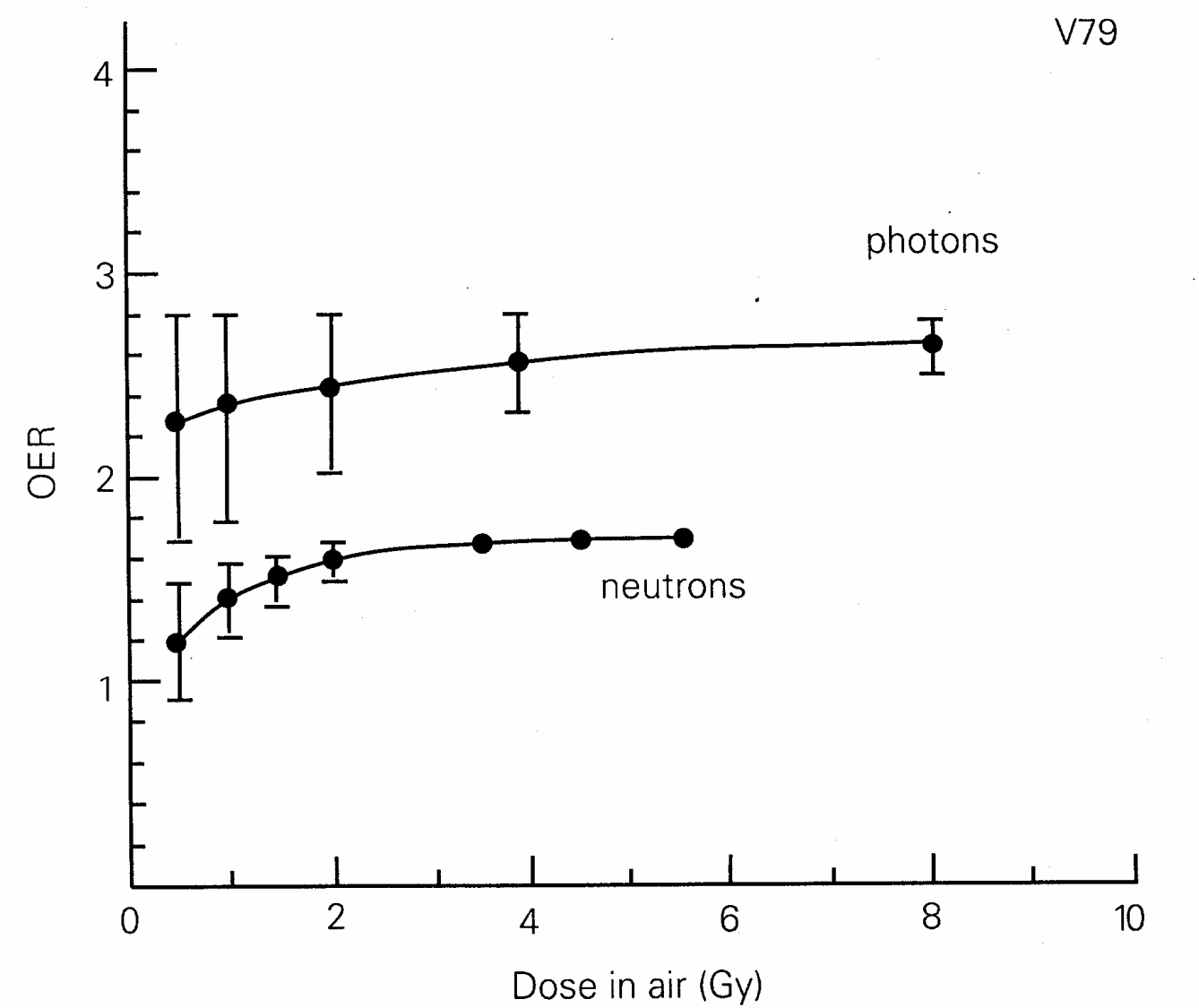
OXYGEN EFFECT



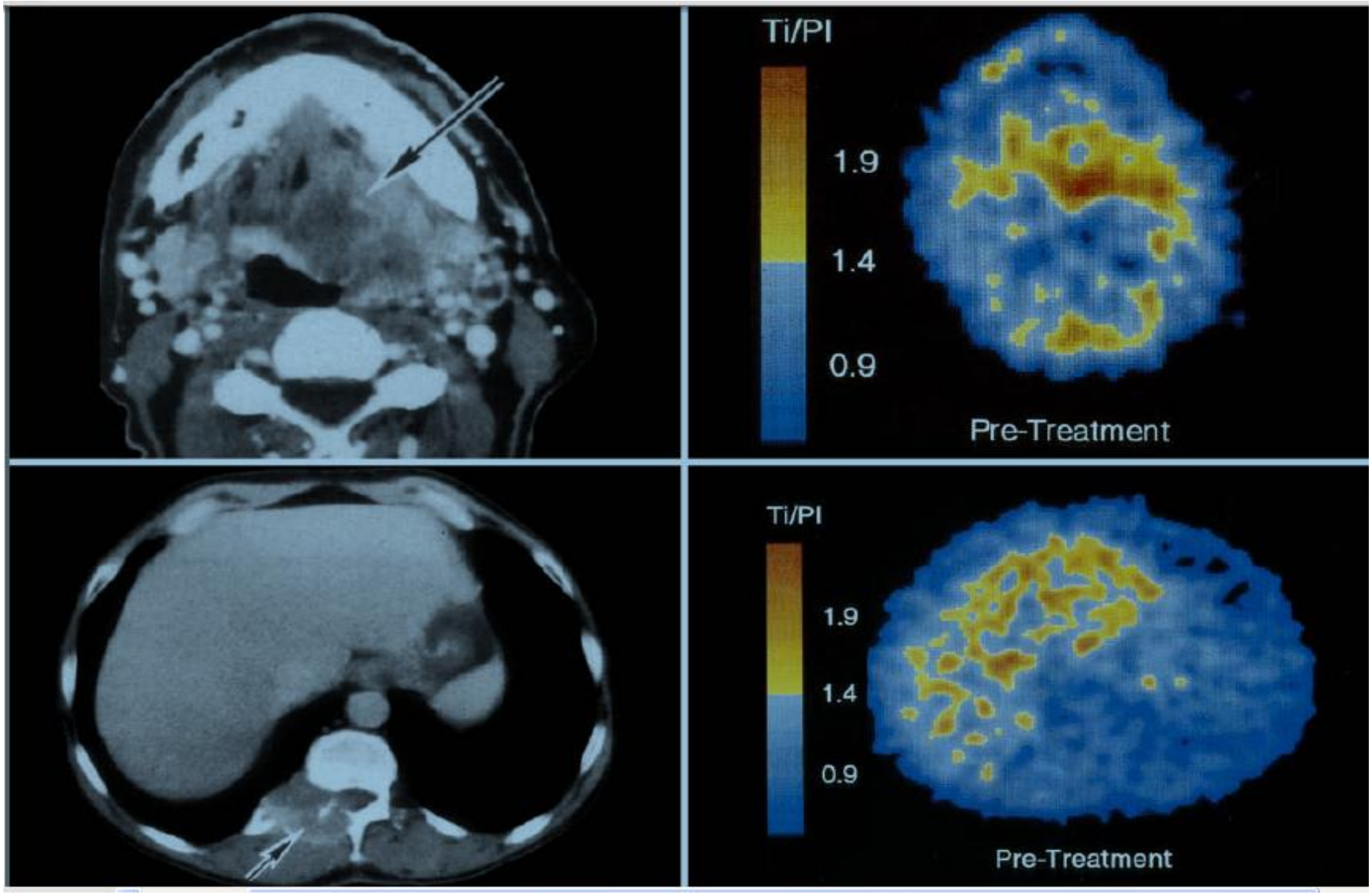
OXYGEN EFFECT

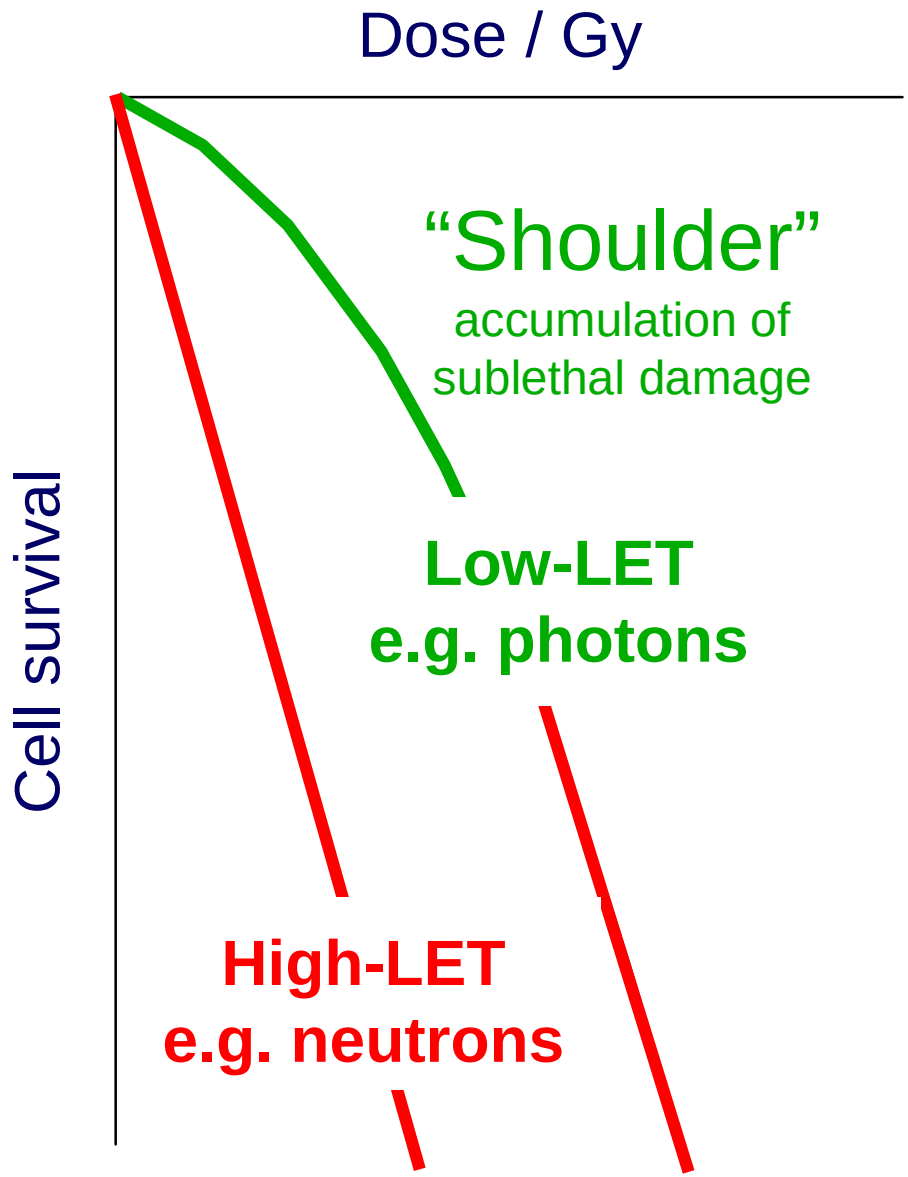


OXYGEN EFFECT (iTL)



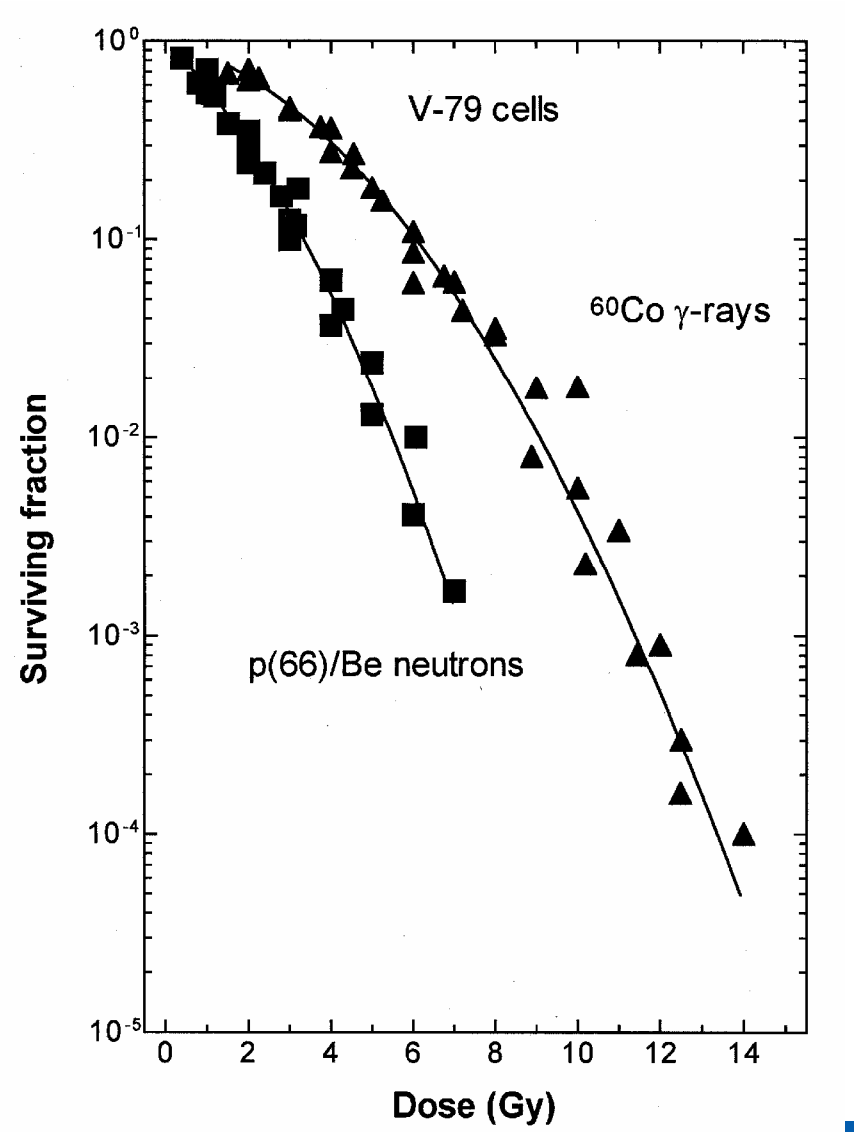
HYPOXIC CELLS: ^{18}F-Misonidazole



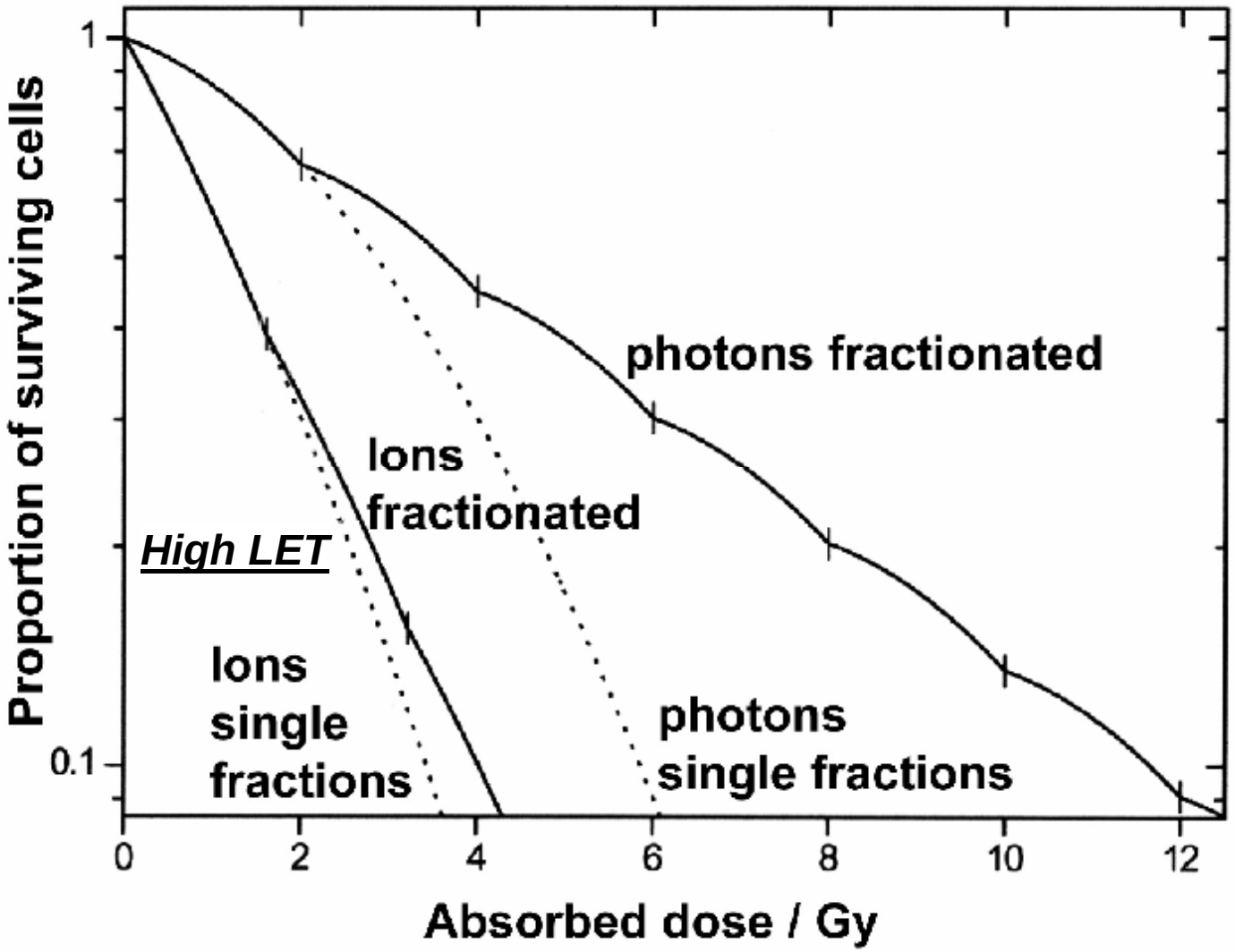


SURVIVAL CURVES

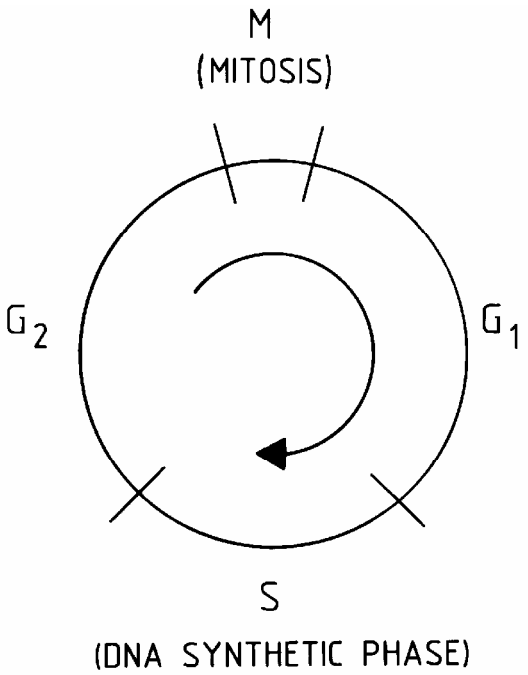
SURVIVAL CURVES (iTL)

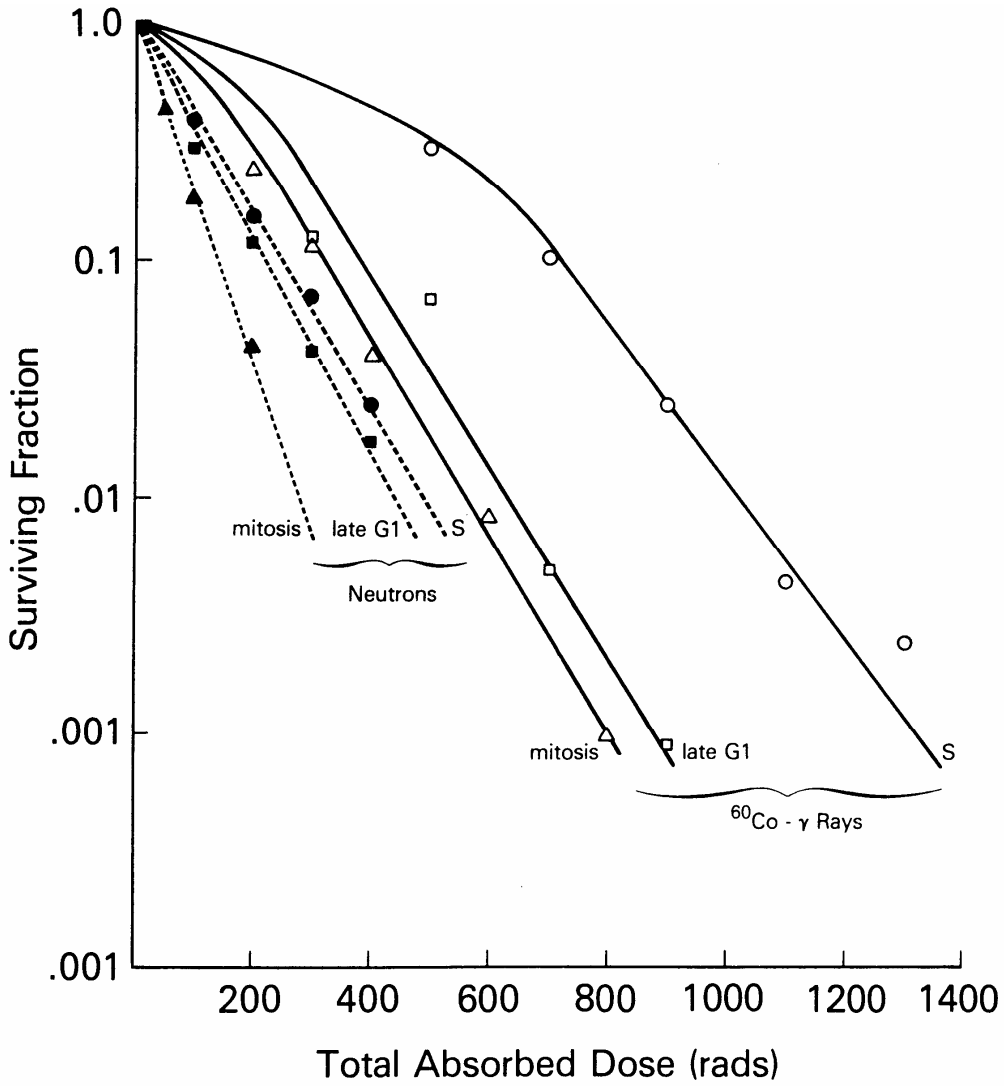


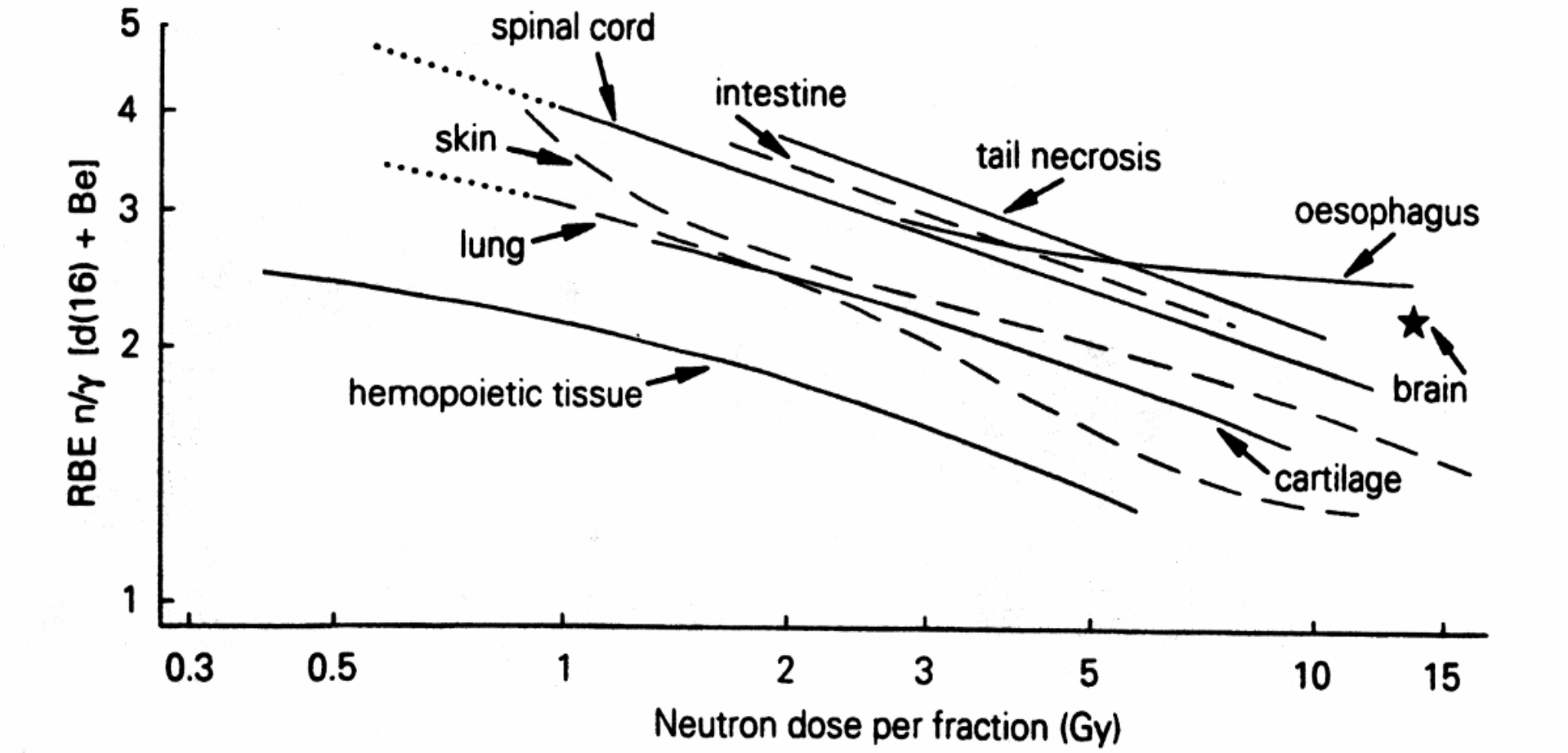
FRACTIONATION



CELL CYCLE EFFECTS






spinal cord
intestine
skin
tail necrosis
oesophagus
lung
brain
hemopoietic tissue
cartilage
RBE n/γ [d(16) + Be]
5
4
3
2
1
0.3
0.5
1
2
3
5
10
15
Neutron dose per fraction (Gy)

FAST NEUTRONS IN RADIOTHERAPY
Therapy issues

- Skin sparing (*dose build-up*)
- Dose distributions are similar to photons (uncharged)
  - † exponential attenuation in matter
- Induced activity in the treatment head (mainly target) and surroundings is a problem
- Isocentric gantry (rotating treatment head) is required
- Flexible beam shaping is needed for *conformal therapy* (*e.g.*, multileaf collimator)
- **Fewer treatment sessions/fractions (12 – 15) are required than for conventional radiation modalities (30 - 35)**

NEUTRON THERAPY HISTORY

1931 Ernest Lawrence invents the cyclotron

1932 James Chadwick discovers the neutron

1935 J and E Lawrence *et al*. begin biological experiments with fast neutrons on 37 inch cyclotron at University of California (UC), Berkeley

1936 G Locher postulates therapeutic possibilities of both fast and slow (capture) neutrons

1938 First patients treated with fast neutrons at UC, Berkeley

1943 Neutron therapy suspended (cyclotron required for atomic bomb project)

1951 Boron neutron capture therapy (BNCT) performed for first time with thermal beams at Brookhaven National Laboratory (BNL)

1966 Fast neutron therapy recommences at Hammersmith Hospital, London

1994 First epithermal beams used for BNCT treatments at BNL and Massachusetts Institute of Technology (MIT)

THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

Vol. 36 (1936) 1-13

BIOLOGICAL EFFECTS AND THERAPEUTIC POSSIBILITIES OF NEUTRONS

GORDON L. LOCHER, PhD.
Bartol Research Foundation of the Franklin Institute
SWARTHMORE, PENNSYLVANIA

It is now possible to obtain neutrons in sufficiently abundant intensities to make worthwhile the consideration of their biological and therapeutic possibilities

In the case of the organism exposed to heterogeneous neutrons, the absorption of energy is by a very different process. It is largely due to hydrogen atoms, except in regions where there are appreciable concentrations of atoms which absorb neutrons very strongly. The "absorption" by hydrogen atoms is mostly a scattering process; the neutrons undergo elastic collisions (i.e. non-capture collisions, or "billiard-ball collisions") ……

There exists, however, this important possibility: a high absorber of neutrons may be introduced, by injection or some other means, into the regions of the organism wherein it is desired to dissipate a great deal of energy in the form of ionization…(a simple illustration would be the injection of a soluble, non-toxic compound of boron, lithium, gadolinium, or gold into a superficial cancer, followed by bombardment with slower neutrons)

NEUTRON THERAPY INDICATIONS

REGION	TUMOR
Base of skull	Chordomas Chondrosarcomas
Head and neck	Salivary gland tumors Paranasal sinus tumors
Chest and abdomen	Breast tumors
Pelvis	Prostate tumors (T3, T4) Uterine sarcomas Chordomas Chondrosarcomas
Trunk and extremities	Osteosarcomas Malignant melamonas Soft tissue sarcomas

NEUTRON INTERACTIONS

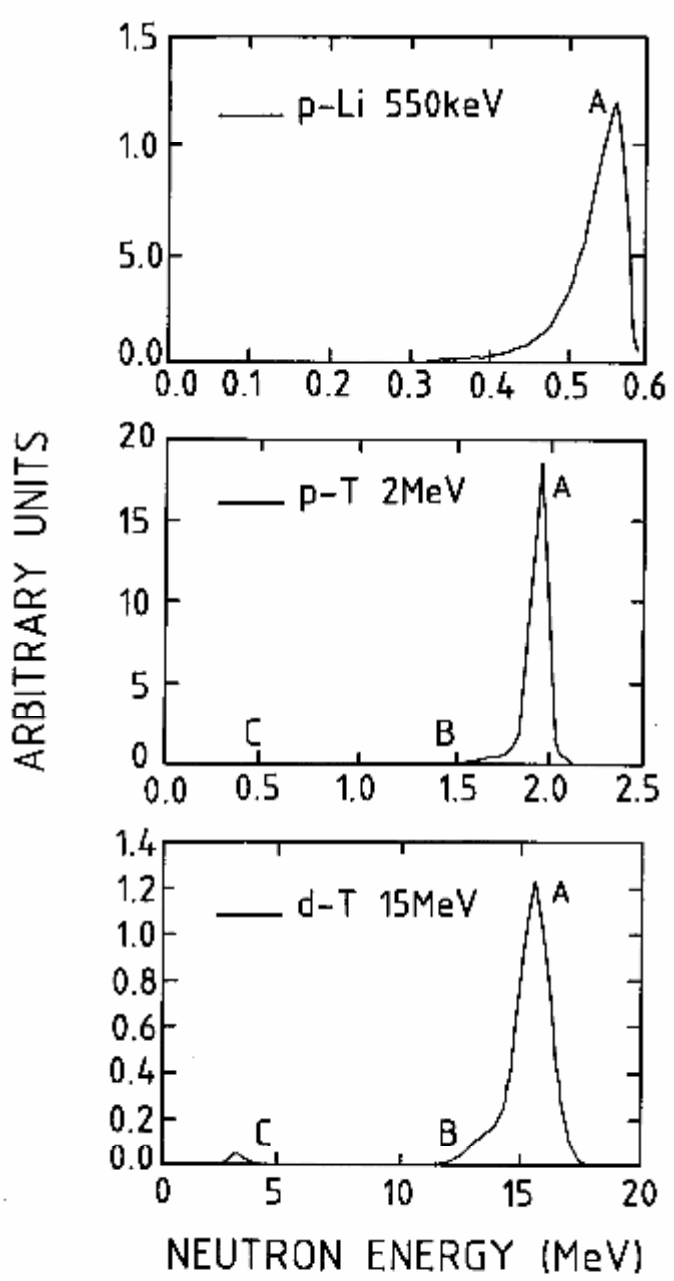
Neutrons are indirectly ionizing particles (no charge) and interact with nuclei. They transfer their energy to heavy charged particles by elastic and inelastic processes. Gamma rays are always produced in tissue.

- **Elastic scattering**
  - n-H collisions: predominant below 30 MeV [p recoils, $E_{av} = 0.5\ E_n$]
  - more H atoms than other elements
- **Inelastic scattering** (above 5 MeV)
  - struck nucleus left in excited state [C, N, O recoils, γ-rays]
  - incident neutron changes energy and direction
- **Non-elastic interactions** (above 5 MeV)
  - incident neutron absorbed [p, d, He, n, γ-rays]
- **Neutron capture**
  - thermal neutrons captured by H [2.2 MeV γ-rays]
- **Spallation**
  - above 100 MeV - not applicable in therapy

NEUTRON PRODUCTION

- **d-T reaction:** $d + T \rightarrow {}^{4}He + n + 17.59$ MeV
  - insufficient dose rate
  - E_d = 200 keV - 300 keV
  - monoenergetic neutrons (14 MeV - 15 MeV), isotropic emission
- **d-Be reaction:** $^{9}Be + d \rightarrow {}^{10}B + n + 4.36$ MeV
  - large number of reaction channels
  - broad energy spectrum, sharply forward peaked emission
  - E_n (avg) = 0.4 E_d (13 MeV ≤ E_d ≤ 50 MeV)
- **p-Be reaction:** $^{9}Be + p \rightarrow {}^{9}B + n$ - 1.85 MeV
  - large number of reaction channels
  - broad energy spectrum, forward peaked emission
  - large low energy tail - removed with hydrogenous filter
  - E_n (average) = 0.4 E_p (34 MeV ≤ E_p ≤ 66 MeV)

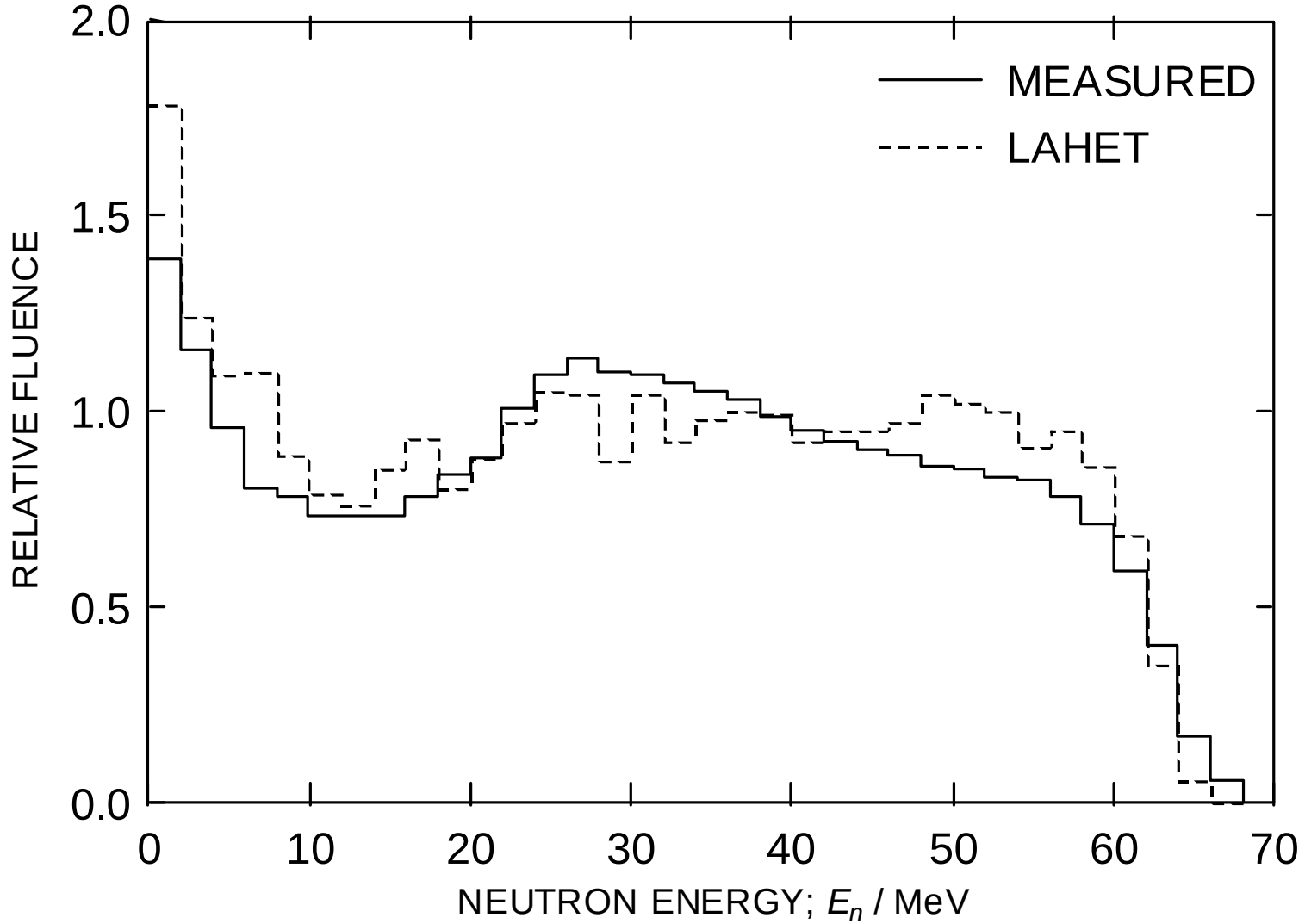
MONOENERGETIC NEUTRON SPECTRA



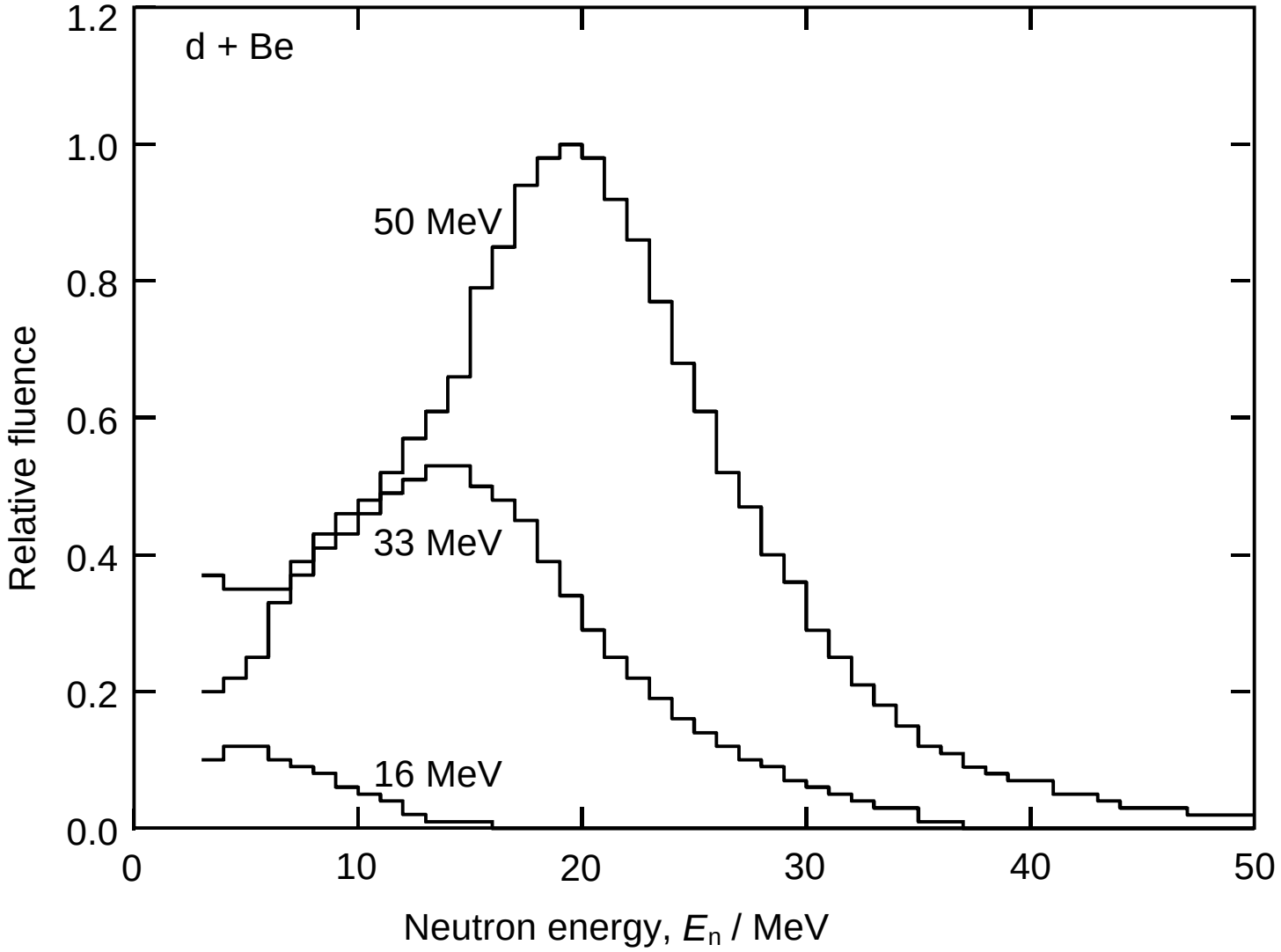
p + Be AND d + Be REACTIONS

REACTION	*Q* MeV	E_{th} MeV
$^{9}Be(p,n)^{9}B$	-1.652	2.058
$^{9}Be(p,n^{4}He)^{5}Li$	-3.541	3.934
$^{9}Be(p,pn)^{8}Be$	-1.666	1.851
$^{9}Be(p,np^{4}He)^{4}He$	-1.574	1.574
$^{9}Be(d,n)^{10}B$	4.361	-
$^{9}Be(d,2n)^{9}B$	-4.076	4.982
$^{9}Be(d,pn)^{9}Be$	-2.224	2.718
$^{9}Be(d,p2n)2^{4}He$	-3.798	4.642

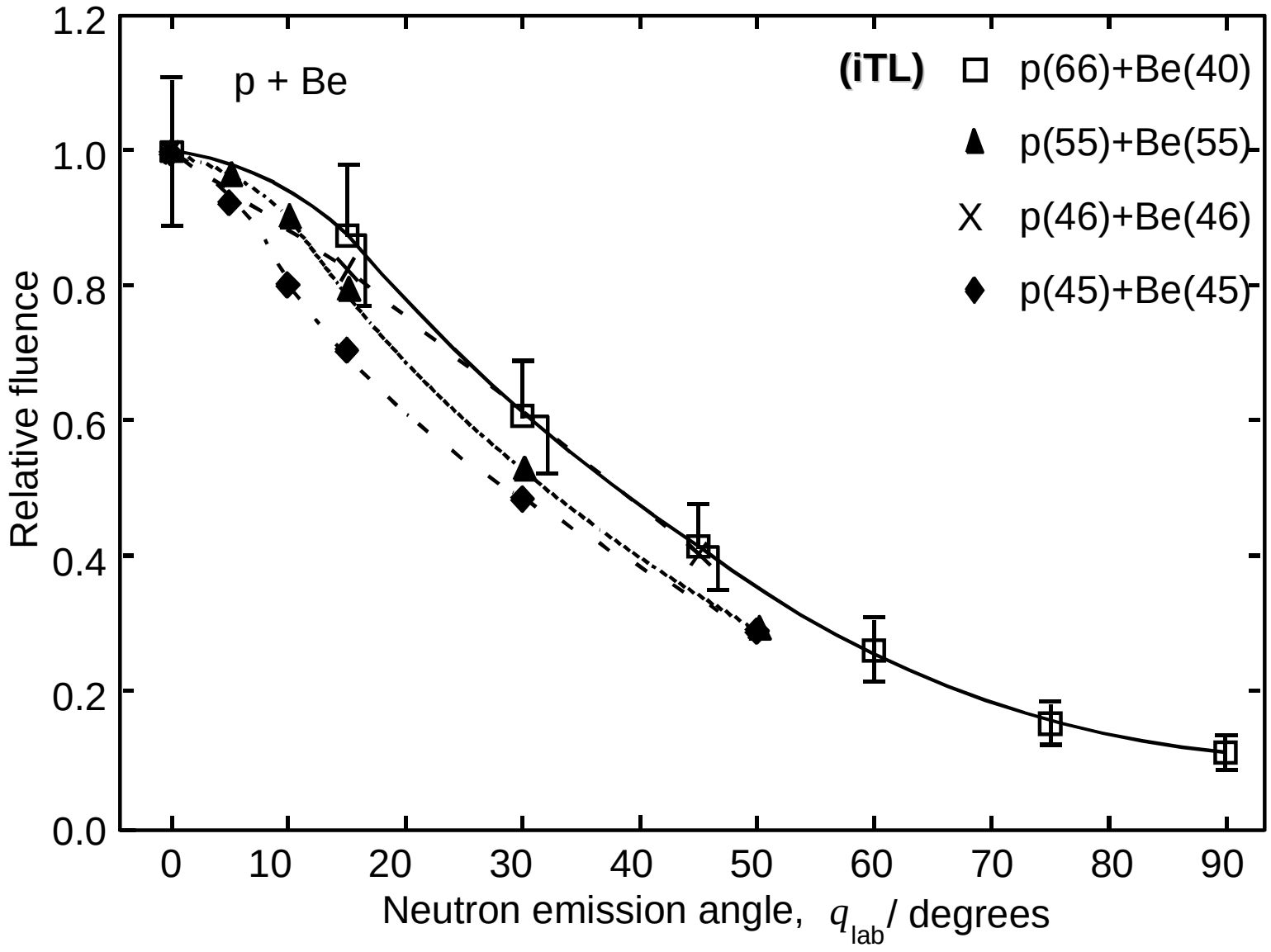
p(66) + Be SPECTRA [iTL]



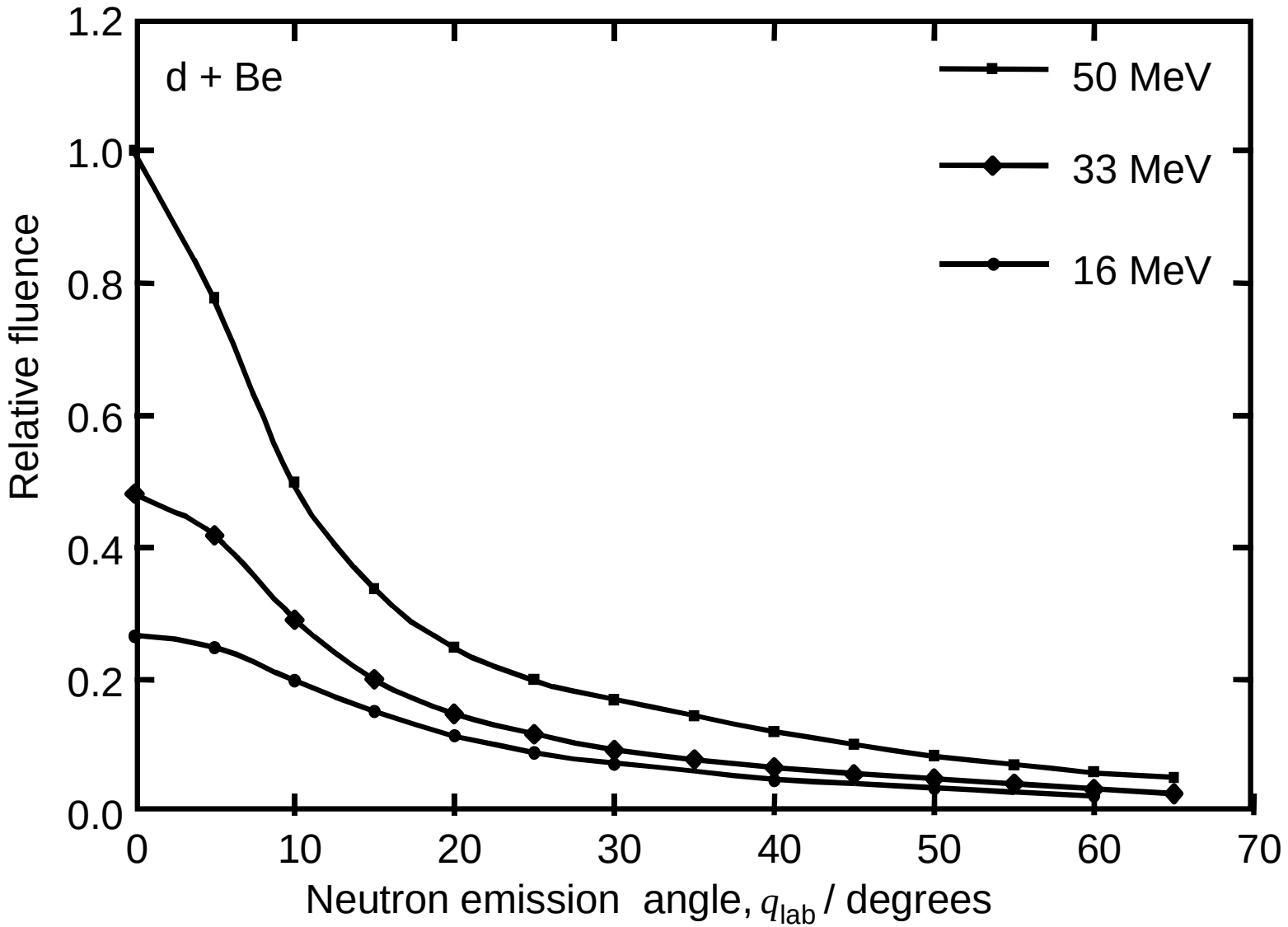
d + Be SPECTRA [UCL]



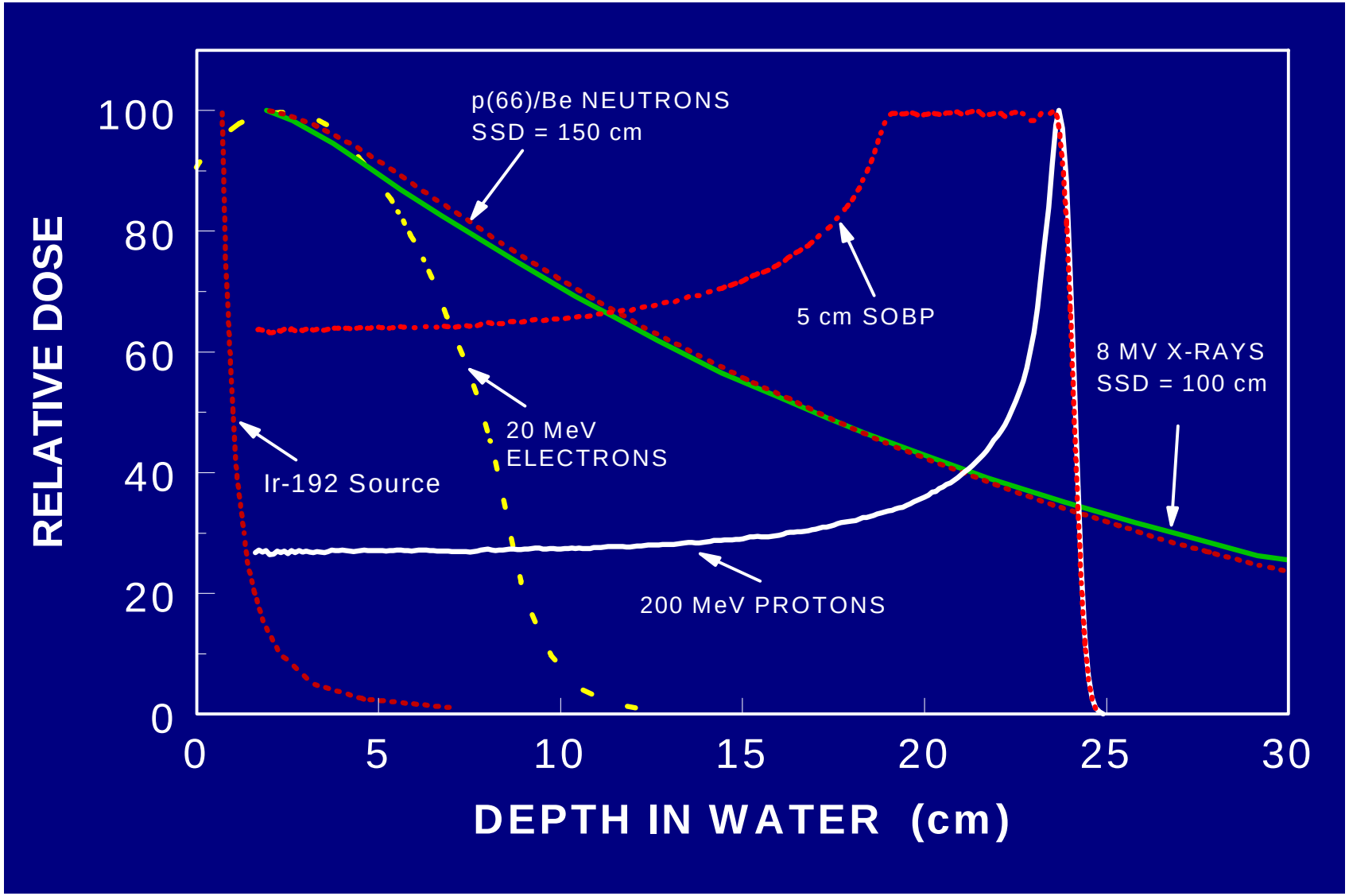
p + Be ANGULAR DISTRIBUTIONS



d+ Be ANGULAR DISTRIBUTIONS [UCL]



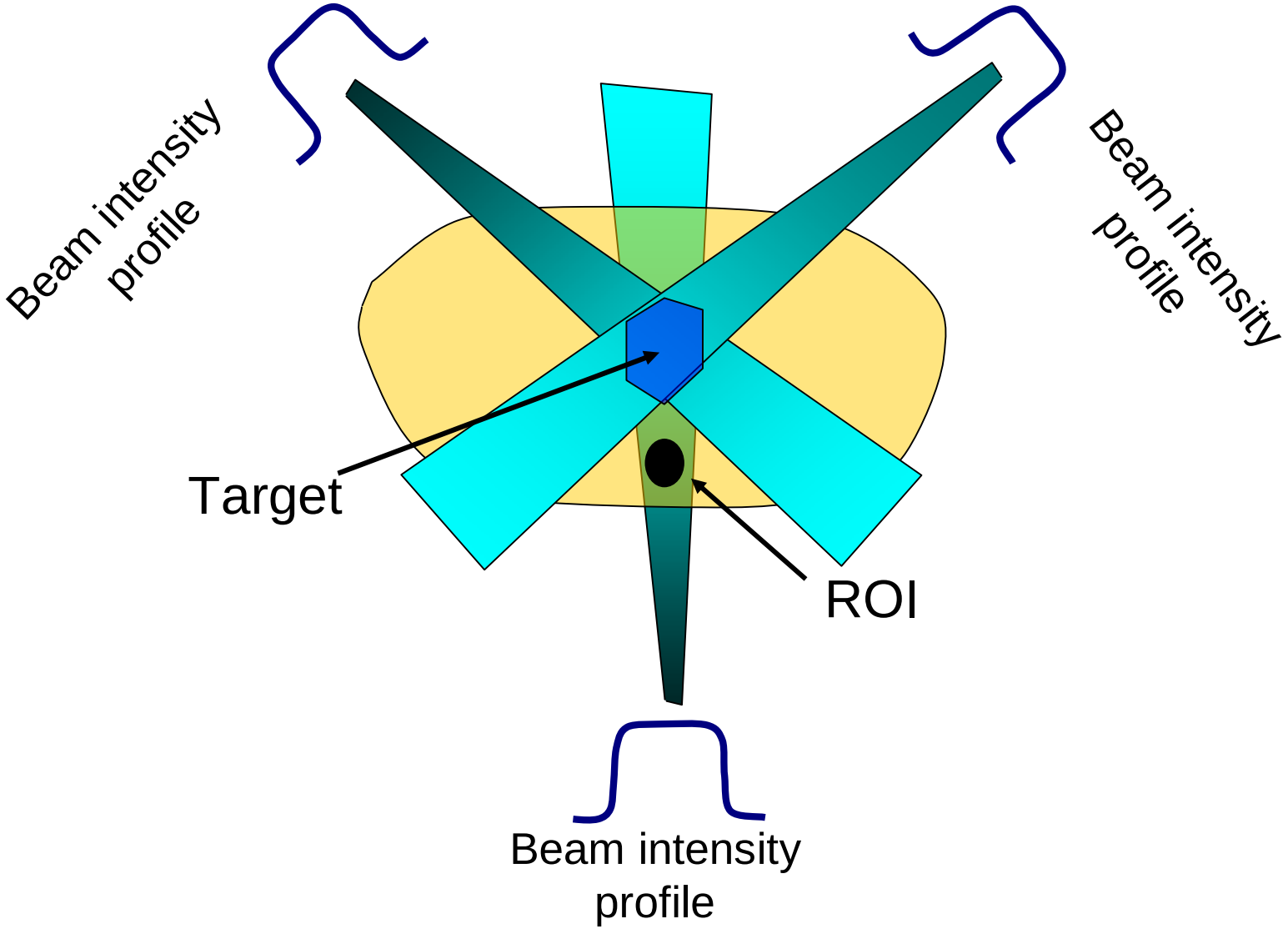
DEPTH DOSE CURVES



IDEAL NEUTRON THERAPY UNIT
Technical aspects

- Isocentric gantries + fixed beams
- Intensity modulated neutron therapy (IMNT)
  - compensators
  - dynamic multileaf collimator
  - source modulation (AIMA, France)
- Field sizes ≥ 30 × 30 cm^2
- Dose rate ≥ 0.5 Gy min^{-1}
- Dose distributions similar to 6 MV – 8 MV x-rays
  - 50% depth dose ≥ 15 cm
- Effective source-axis distance ≥ 1.50 m
  - reduced penumbra

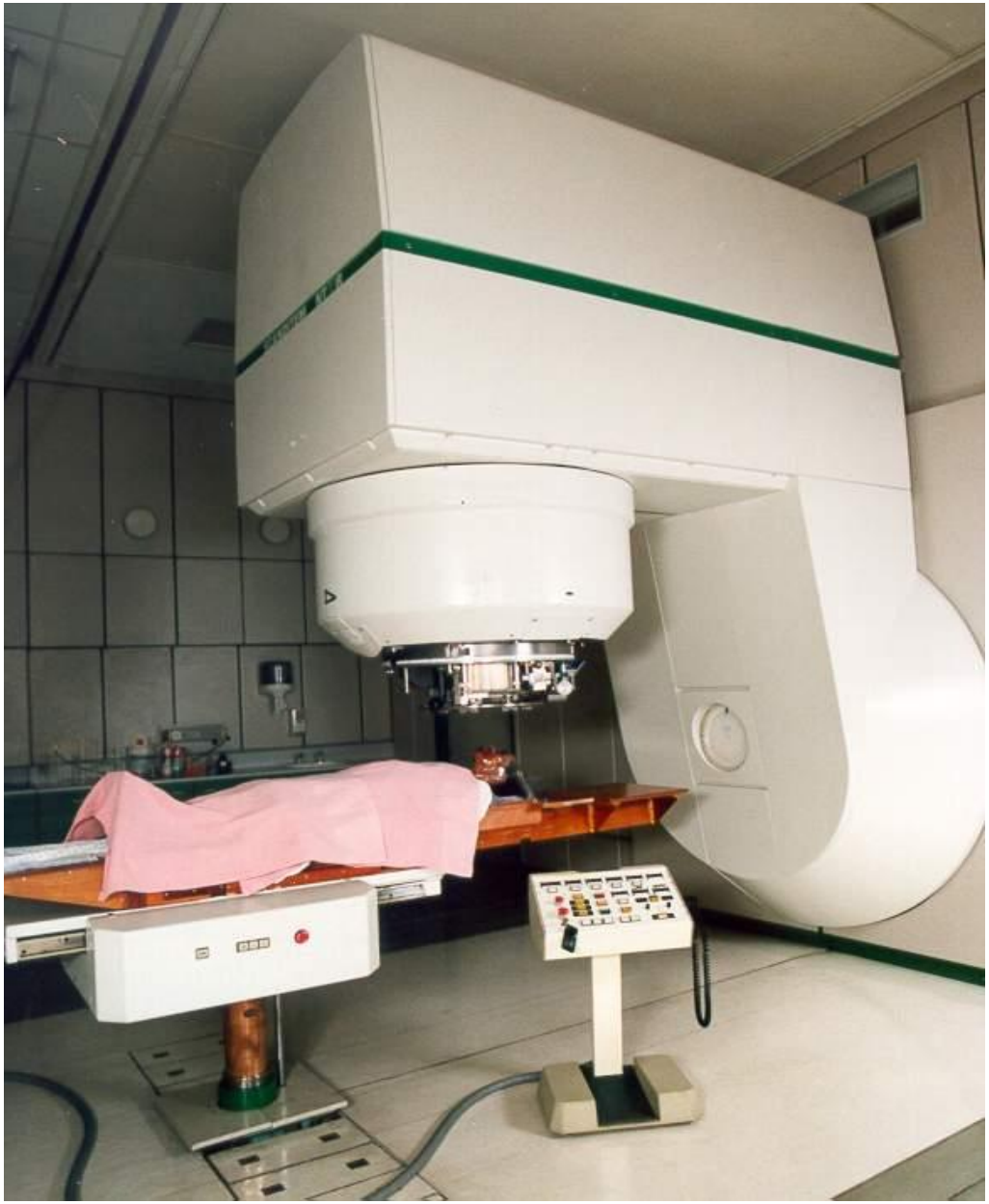
ISOCENTRIC BEAM DELIVERY



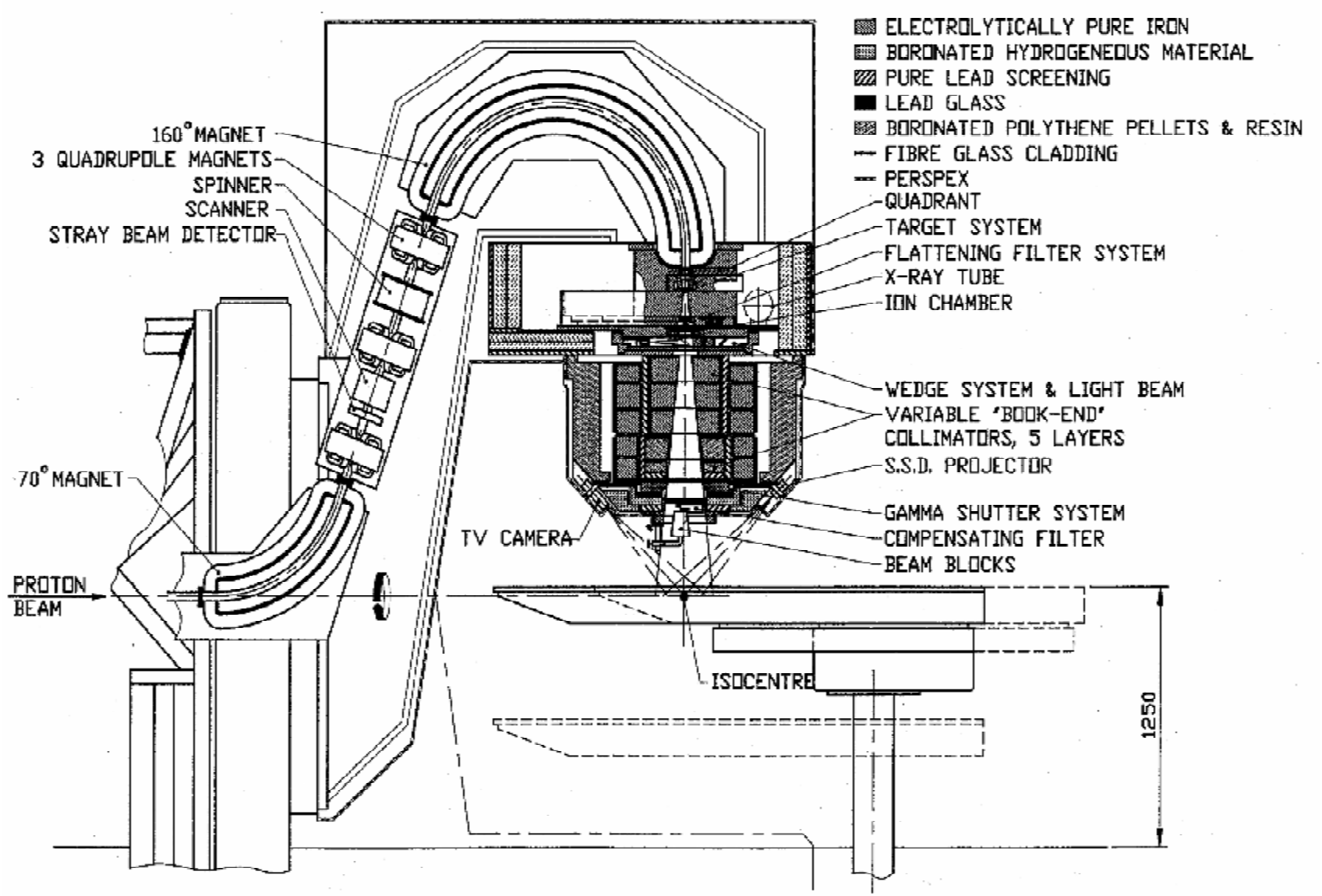
ISOCENTRIC GANTRY

- Beams can be directed from any angle leaving the patient in a fixed supine position while still avoiding sensitive structures.
- Treatment planning requires three-dimensional CT scanning with the patient fixed in the treatment position.
- Turning a supine patient, as is required with a fixed beam, reduces precision and can produce organ motion. Rotating a seated patient is often used for head and neck irradiations.
- Many international protocols require the beam to be rotated around the patient fixed in the treatment planning position for quality and intercomparison purposes.
- Treatment is much more efficient because the beam can be quickly rotated under computer control allowing for the treatment of 3 to 4 patients per hour rather than a few patients per day.

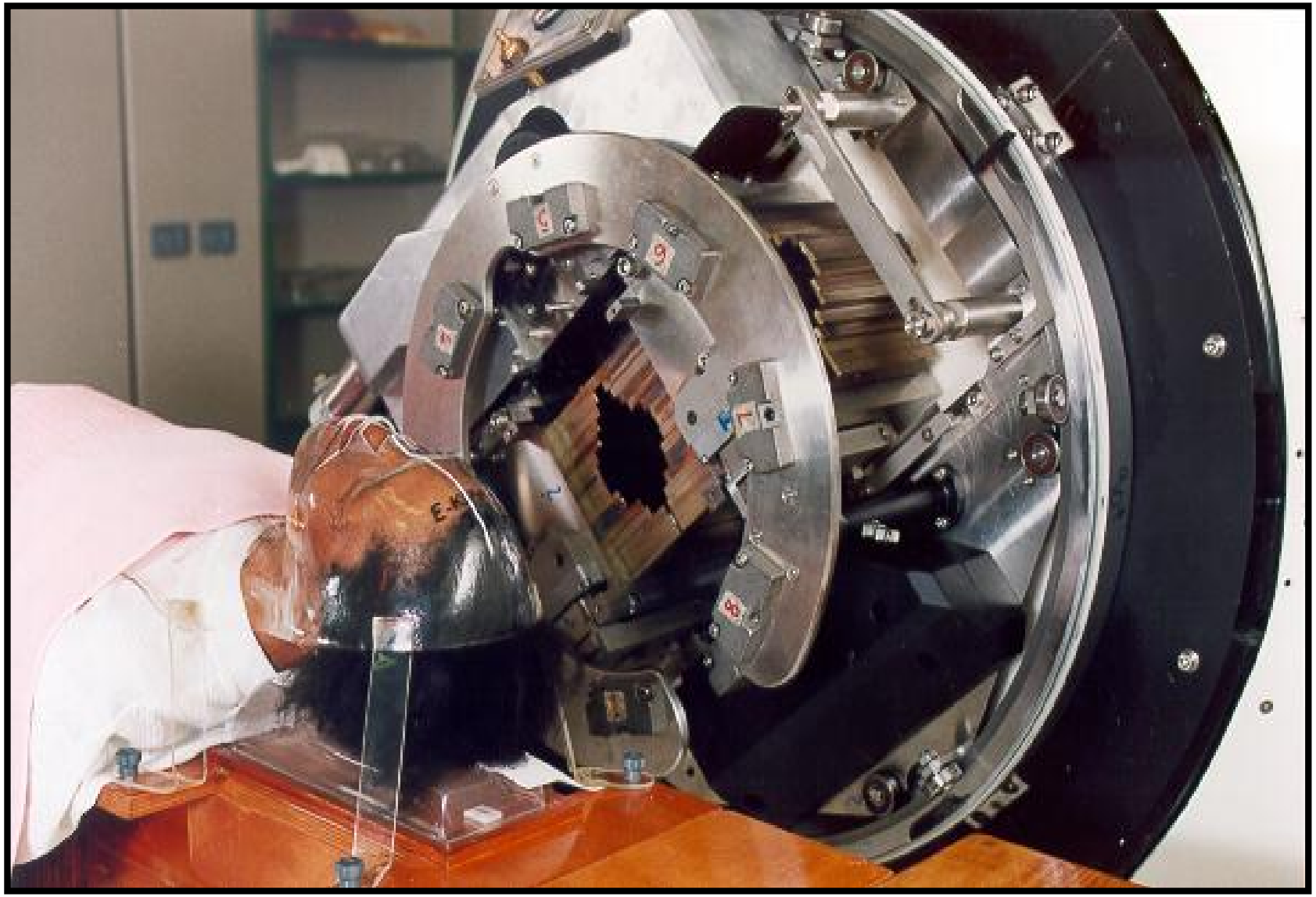
NEUTRON GANTRY [iTL]



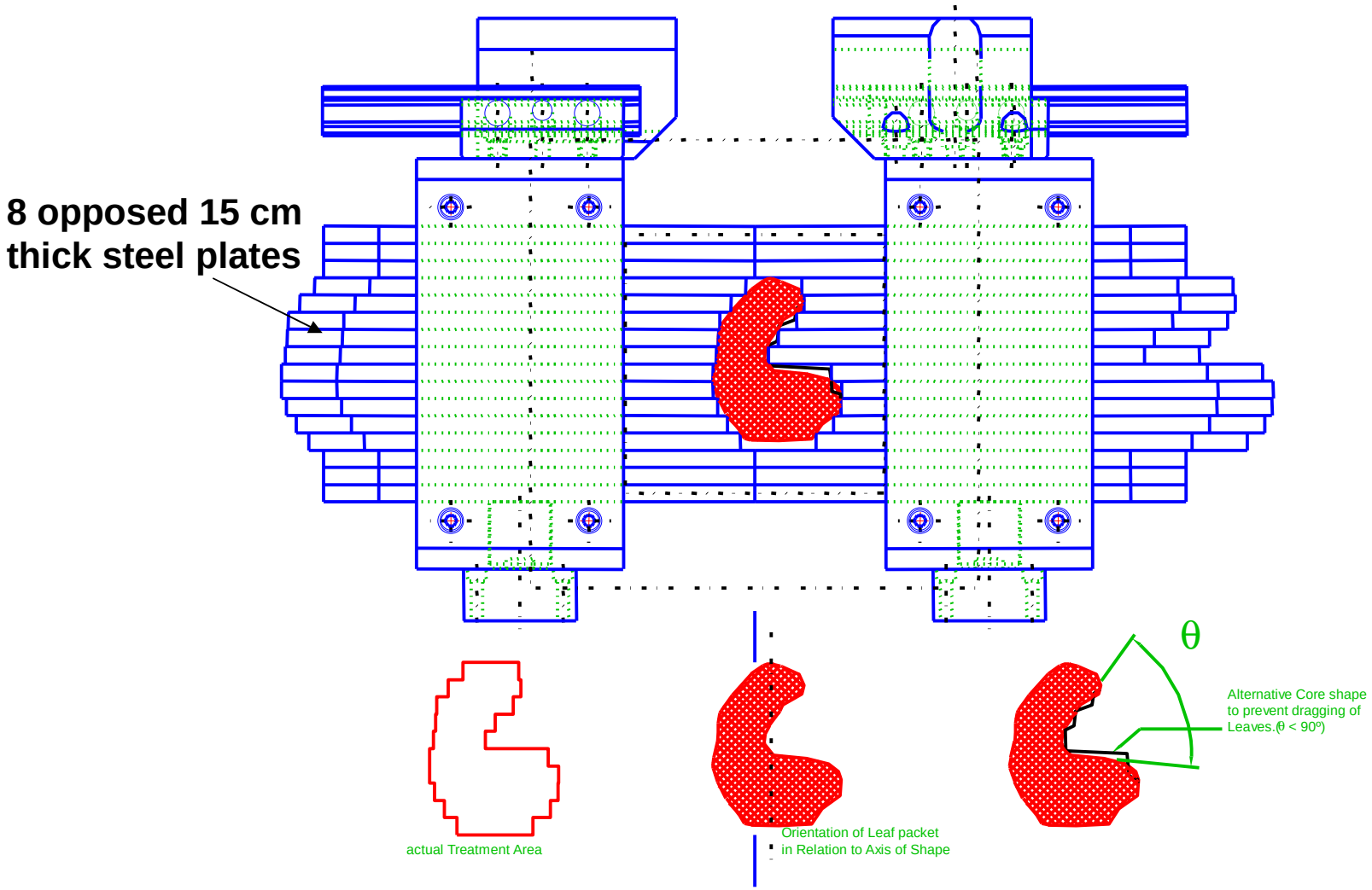
NEUTRON GANTRY [iTL]



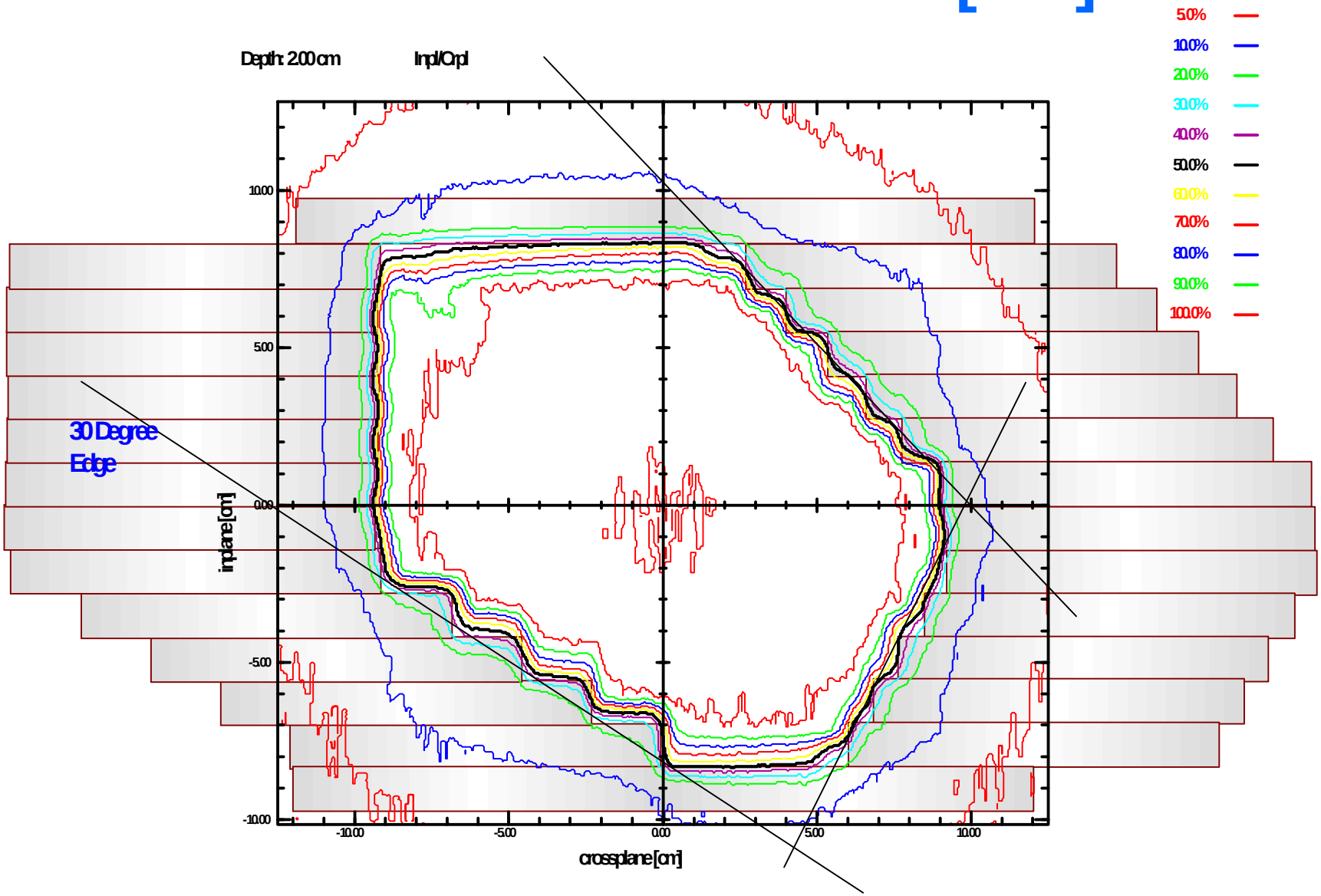
MULTIBLADE TRIMMER [iTL]



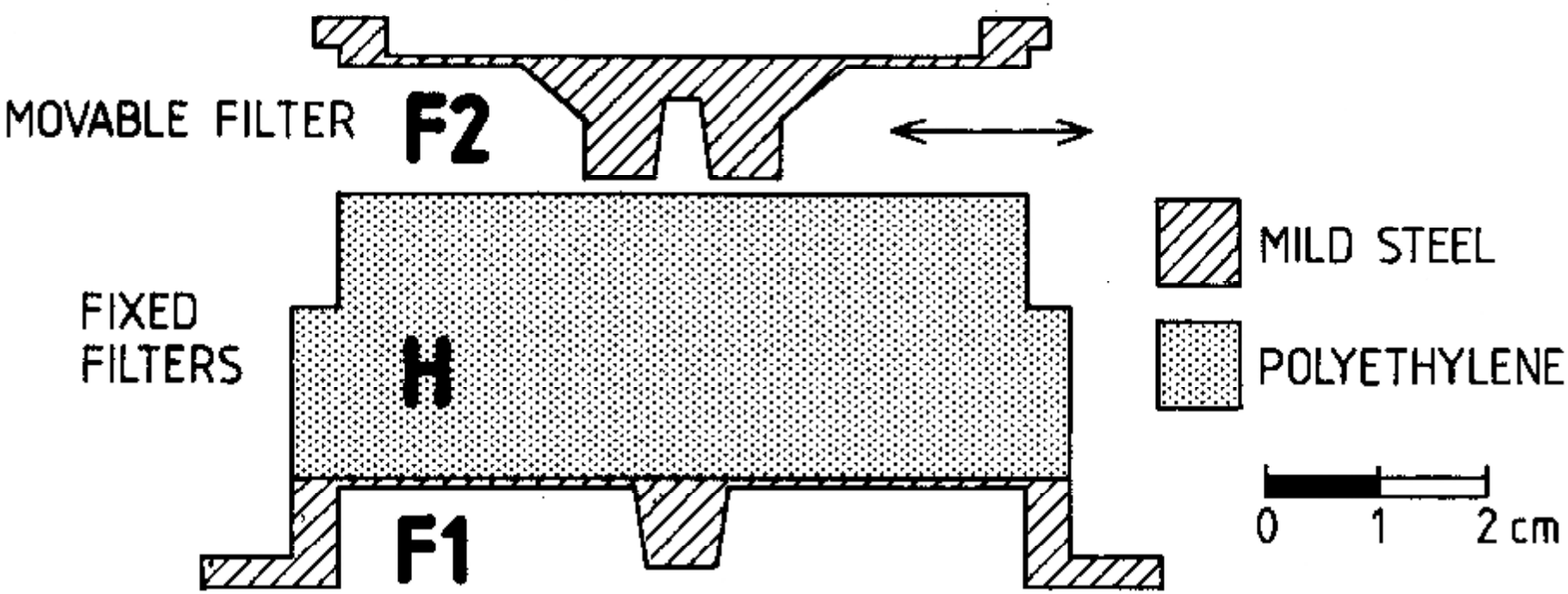
MULTBLADE TRIMMER [iTL]



MULTBLADE TRIMMER [iTL]

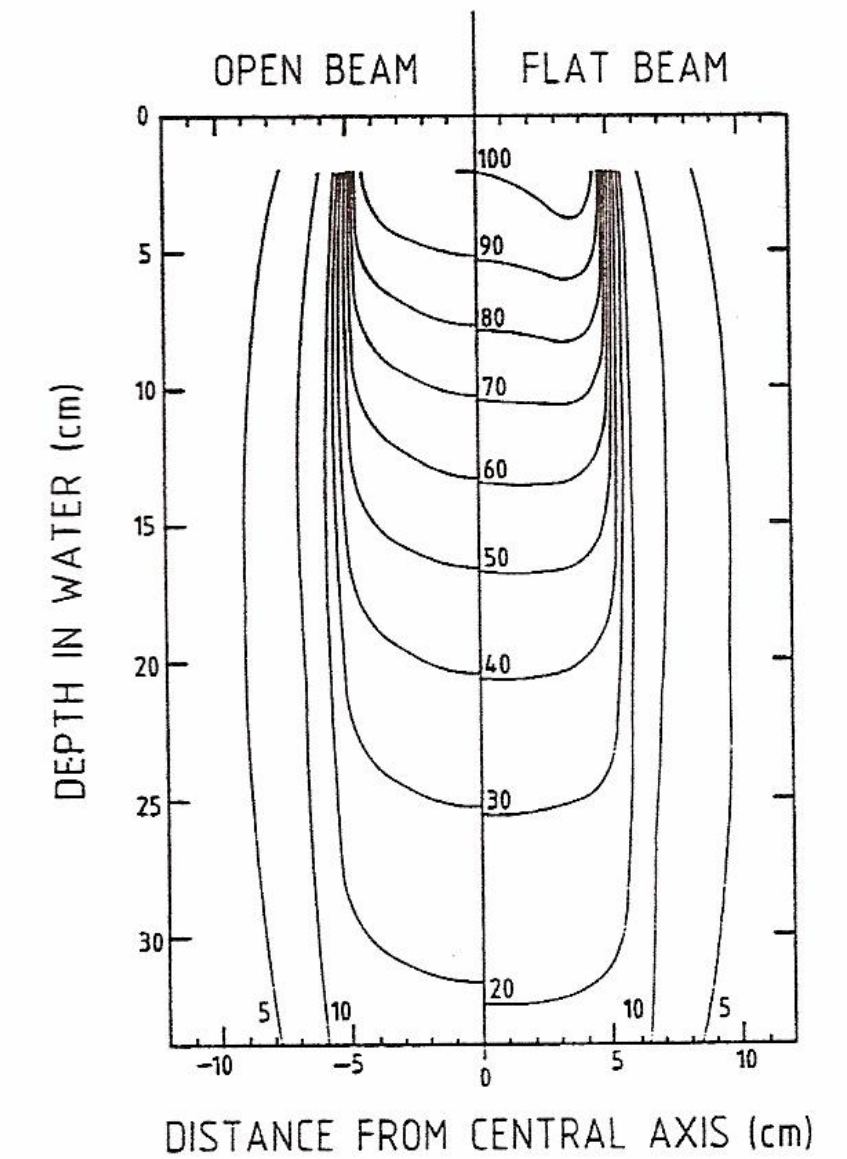


FLATTENING (F) AND HARDENING (H) FILTERS

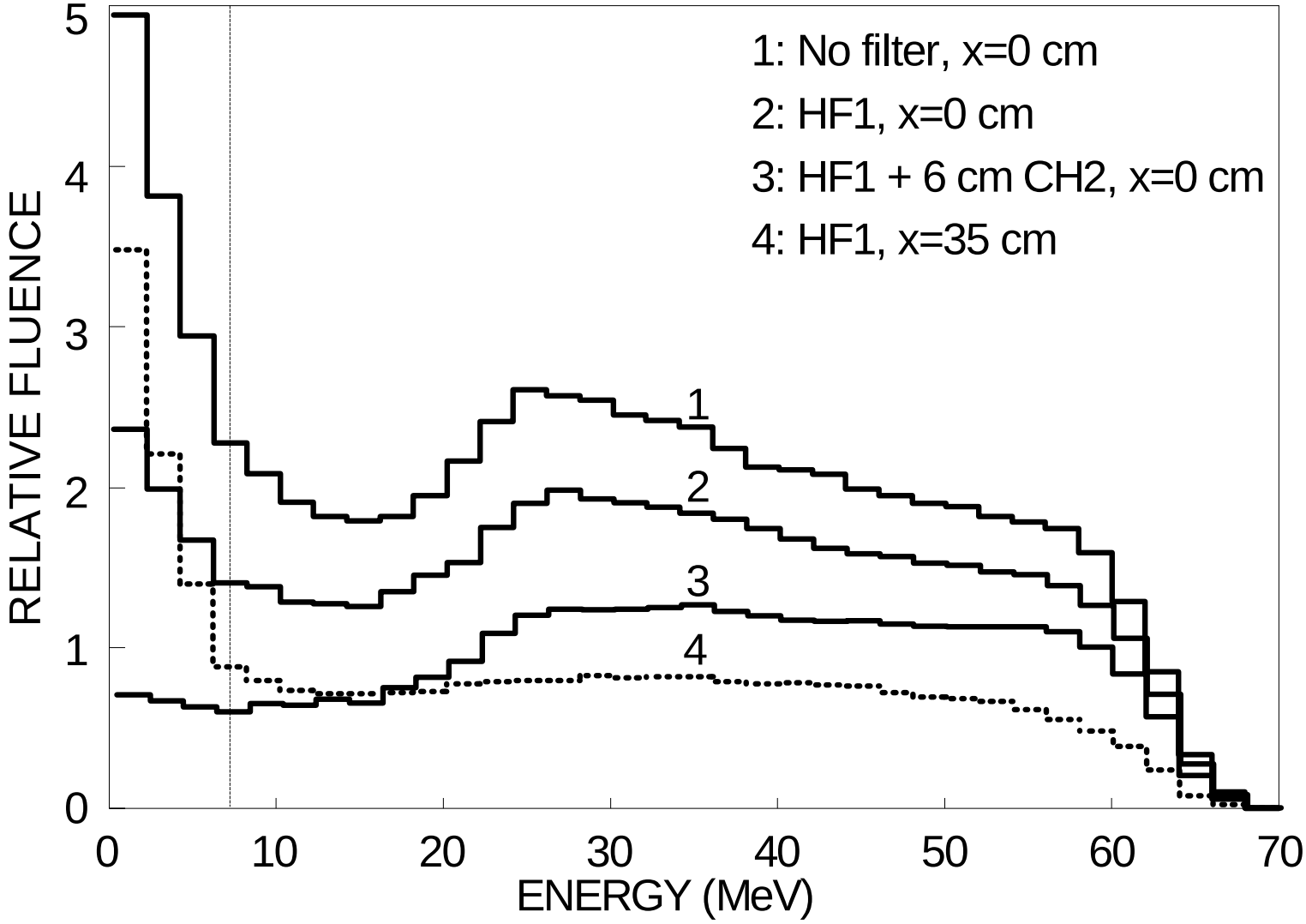


F1: ≤ 16 ´ 16 cm² **F1 + F2: > 16 ´ 16 cm²**

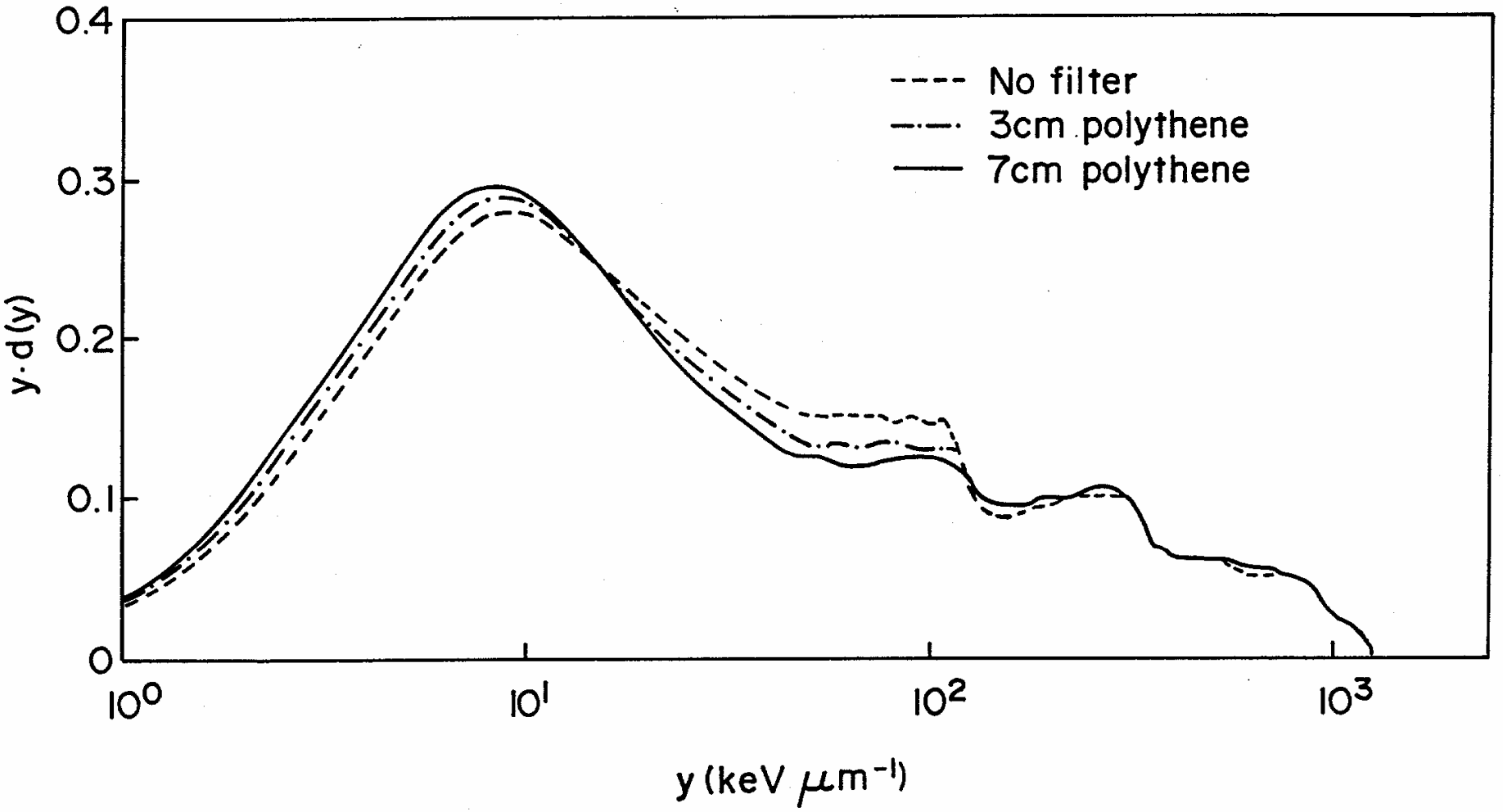
BEAM FLATTENING



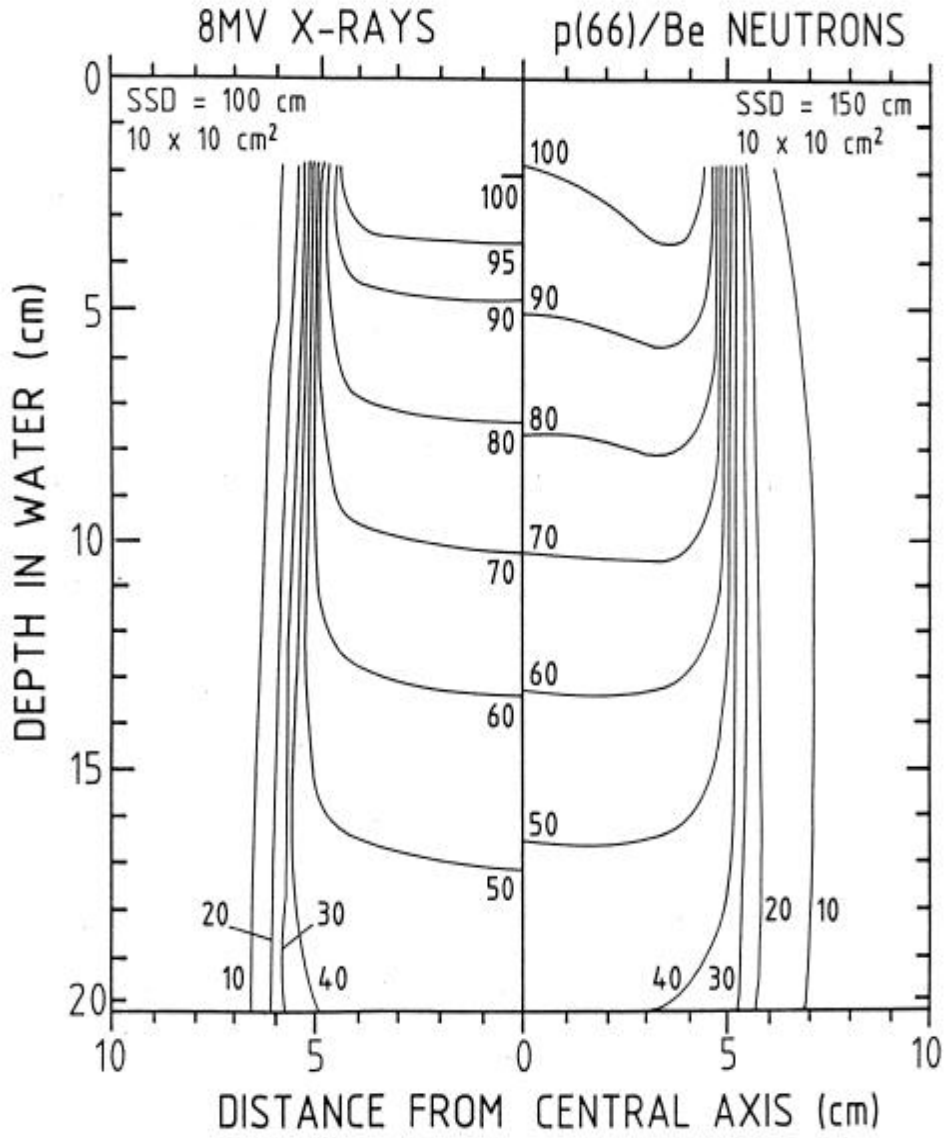
p(66)/Be SPECTRA [iTL]



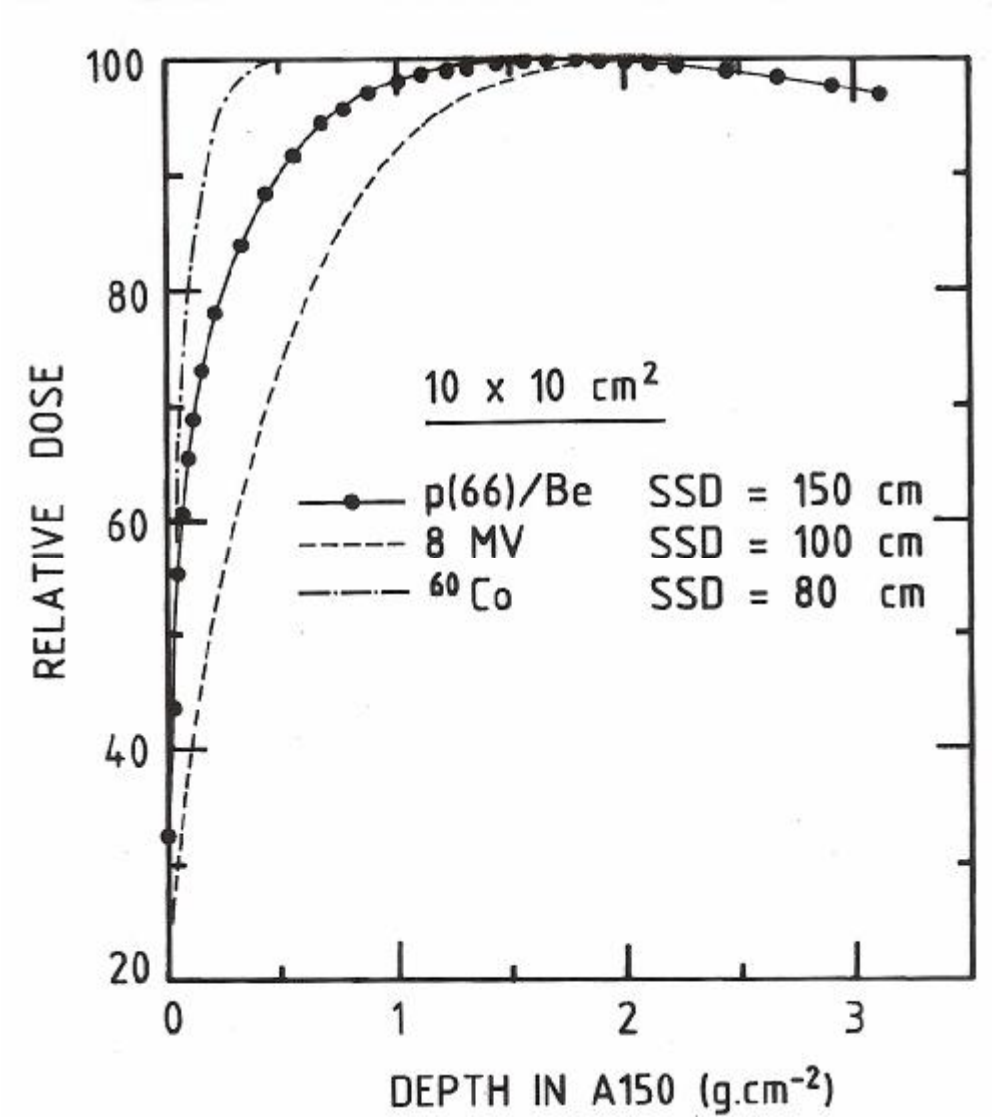
MICRODOSIMETRY



ISODOSE CURVES



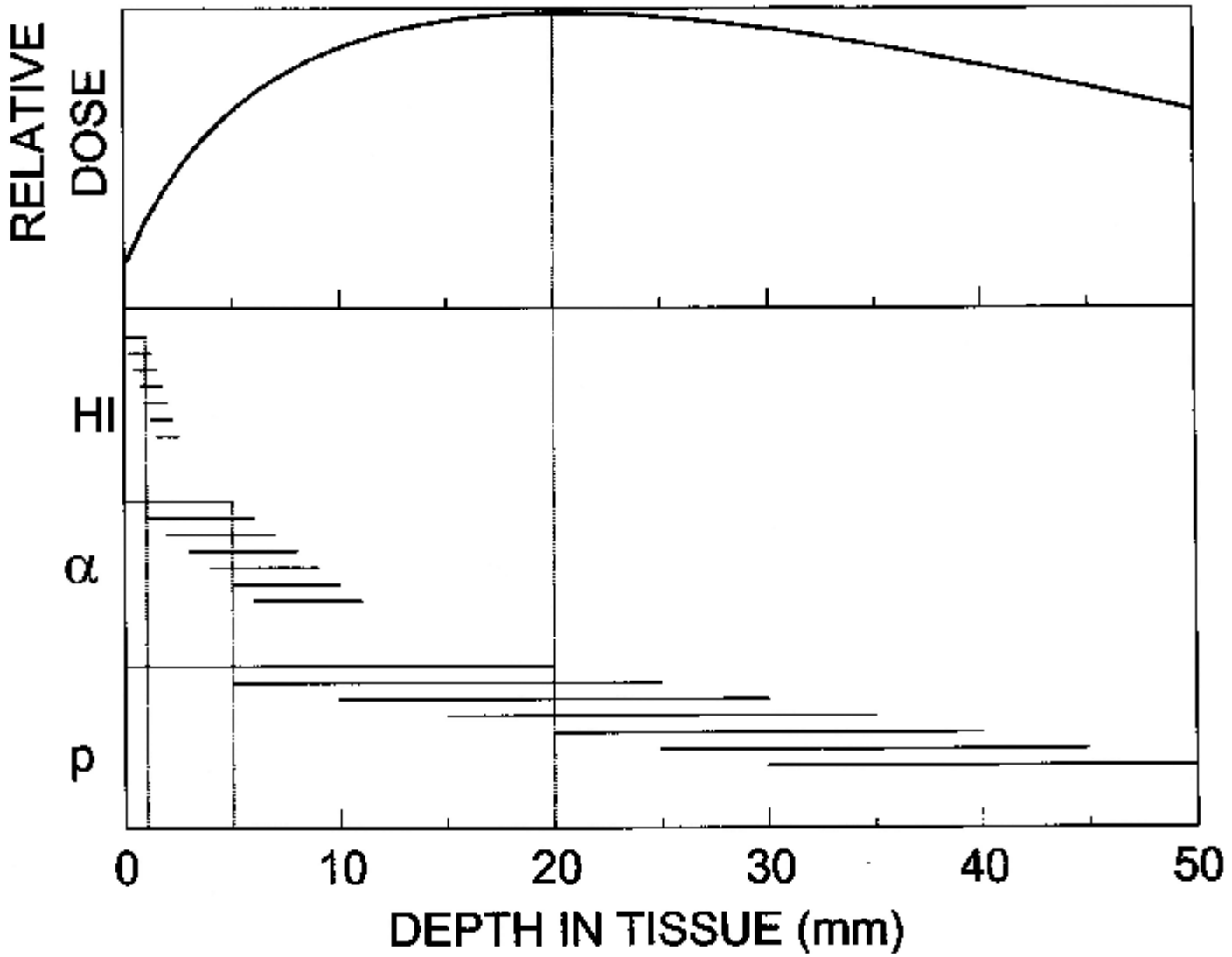
SKIN SPARING / DOSE BUILD-UP [iTL]



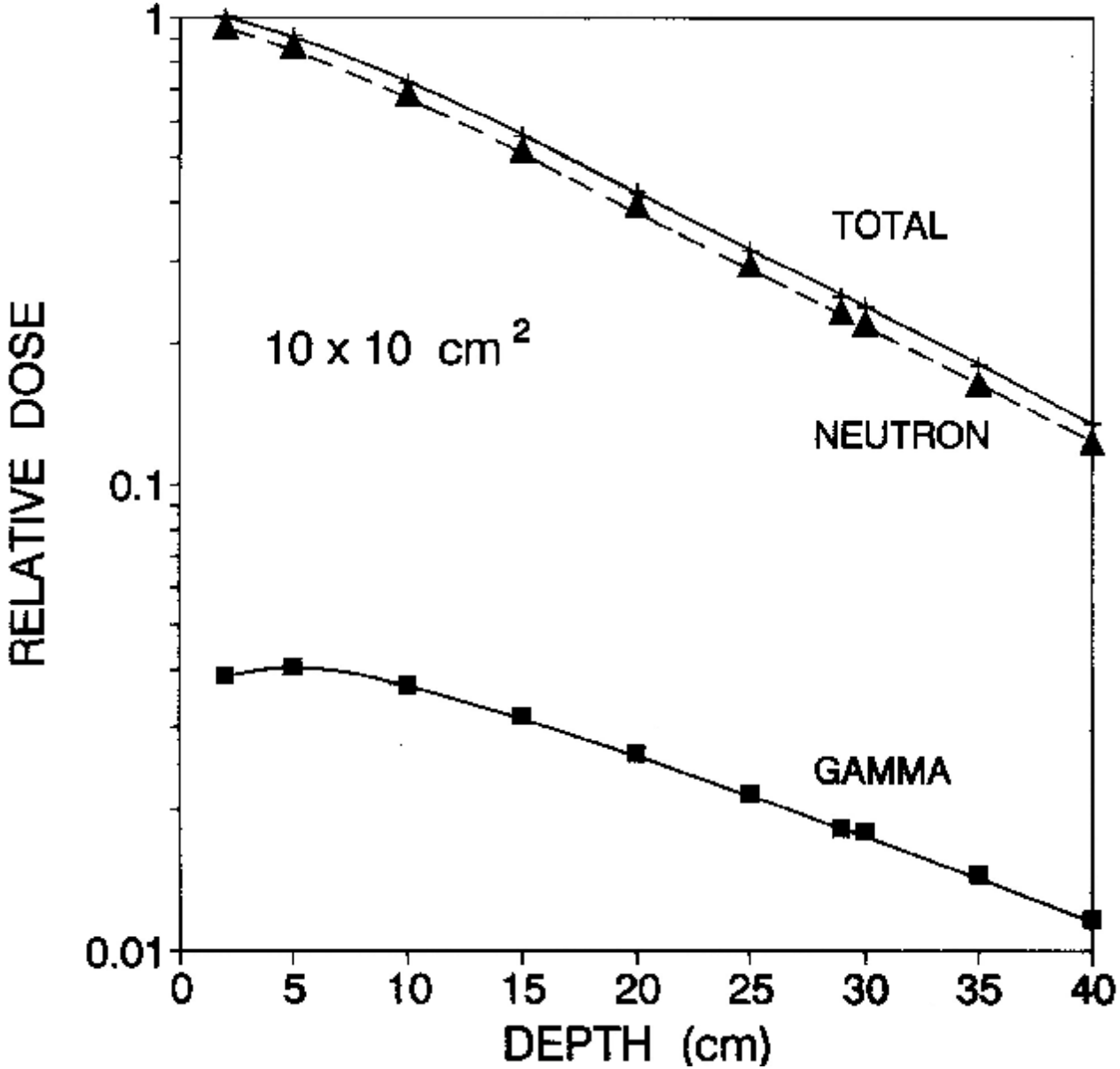
SKIN SPARING

- Neutron beams have high LET [linear energy transfer] and therefore high RBE [relative biological effectiveness] compared with photons
- Neutrons interact with atomic nuclei
- In tissue the predominant interaction is n-H scattering, but heavier recoils (α, ^{12}C, ^{14}N, ^{16}O) are also produced. These particles have higher LET values than protons
- Near the surface more particles leave a given volume element than stop in it. At some point charged particle equilibrium is established – the number of particles leaving a volume element is the same as the number stopping in it $\rightarrow$ *"dose build-up"*
- In the build-up region heavy ions and alpha particles come to rest before protons as they have shorter ranges. The effective LET is therefore higher at the surface, decreasing towards the region of maximum build-up, where proton equilibrium is established
- Beyond the depth of maximum build-up the LET is approximately constant as the neutron energy spectrum changes little with depth

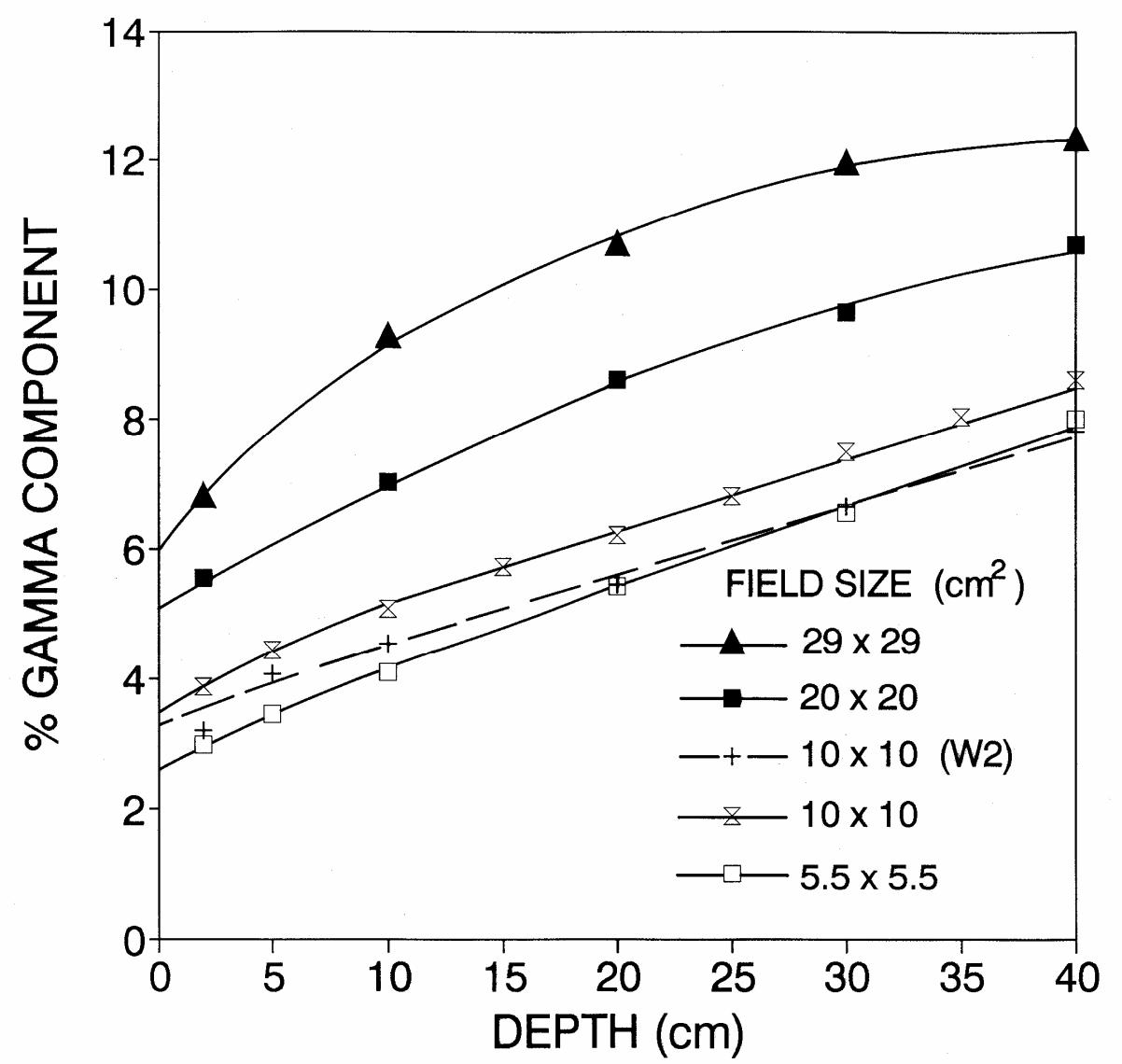
SKIN SPARING



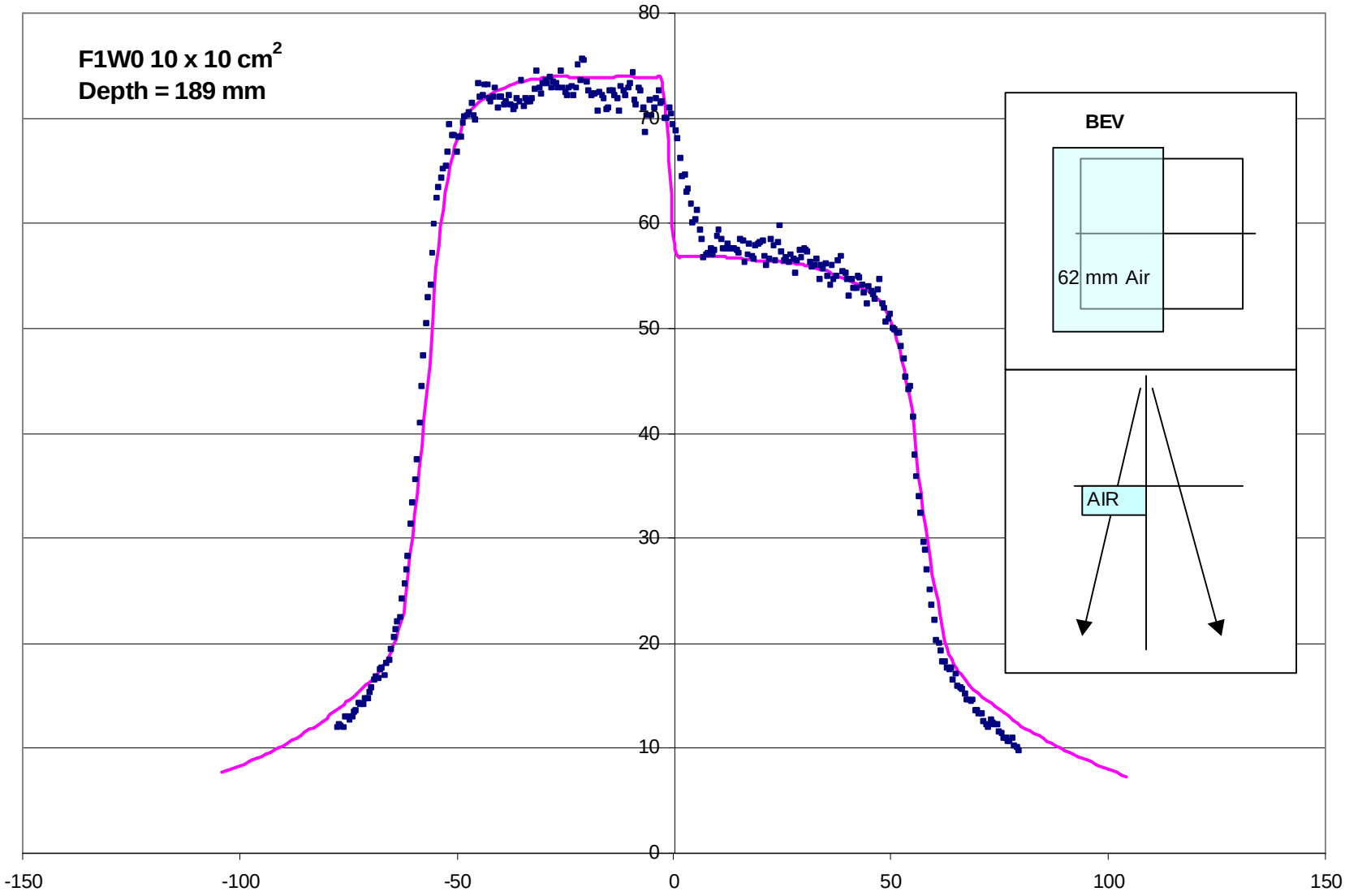
GAMMA DOSE


RELATIVE DOSE
1
0.1
0.01
0
5
10
15
20
25
30
35
40
DEPTH (cm)
10 x 10 cm 2
TOTAL
NEUTRON
GAMMA

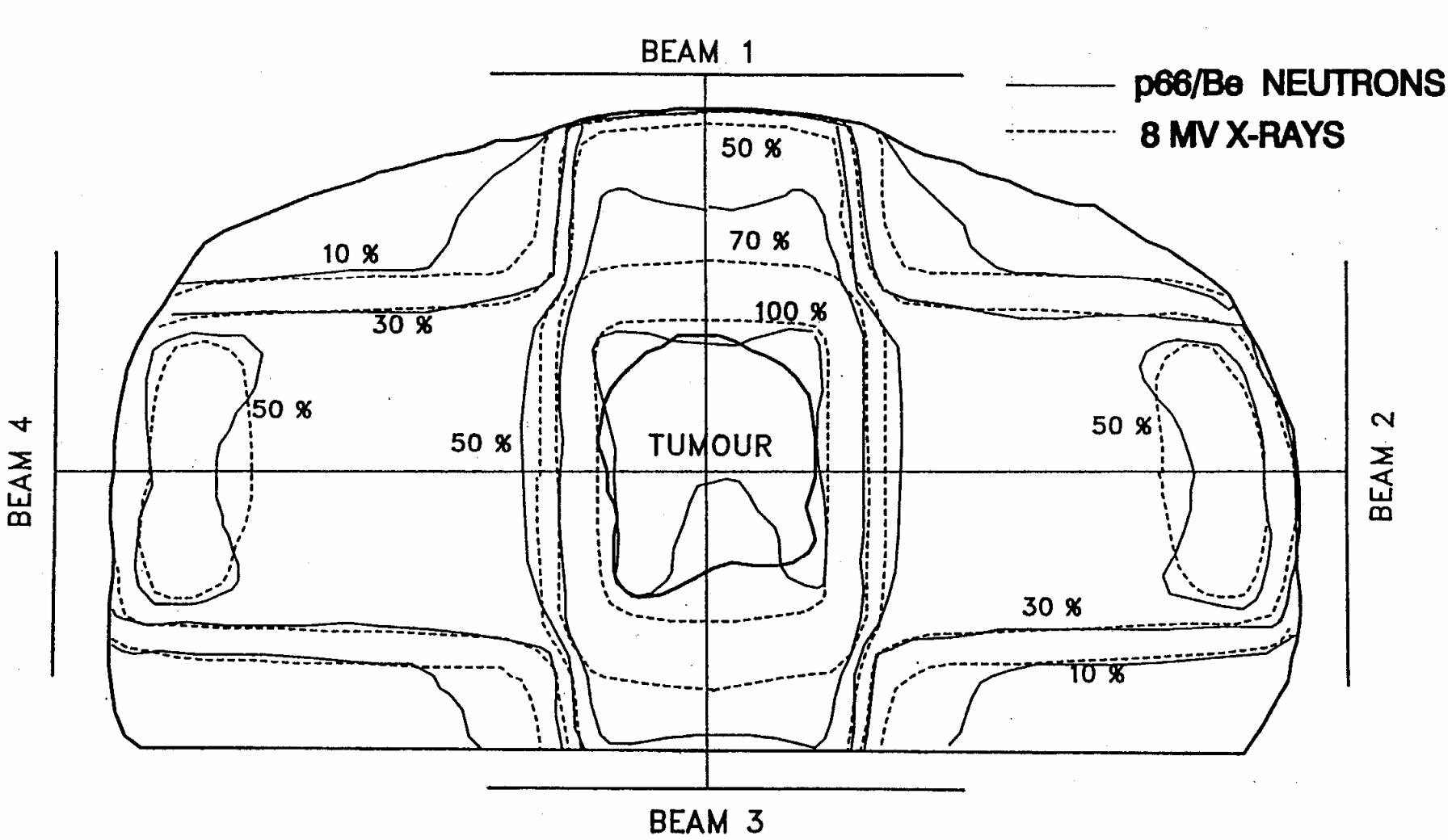
GAMMA COMPONENT



AIR INTERFACE



TREATMENT PLANS
x rays and neutrons

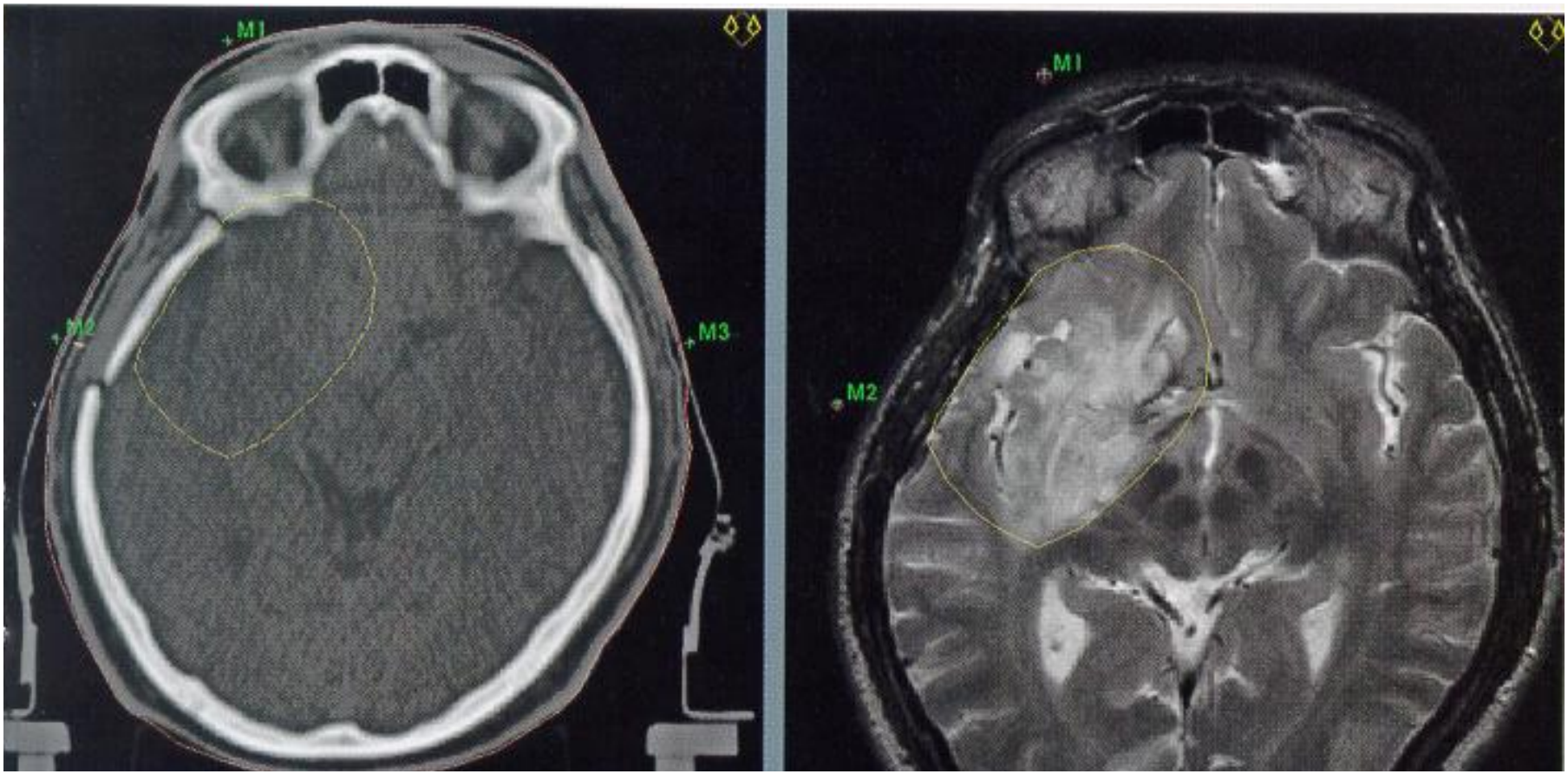


p(66)/Be(40) NEUTRONS AND 8 MV X RAYS

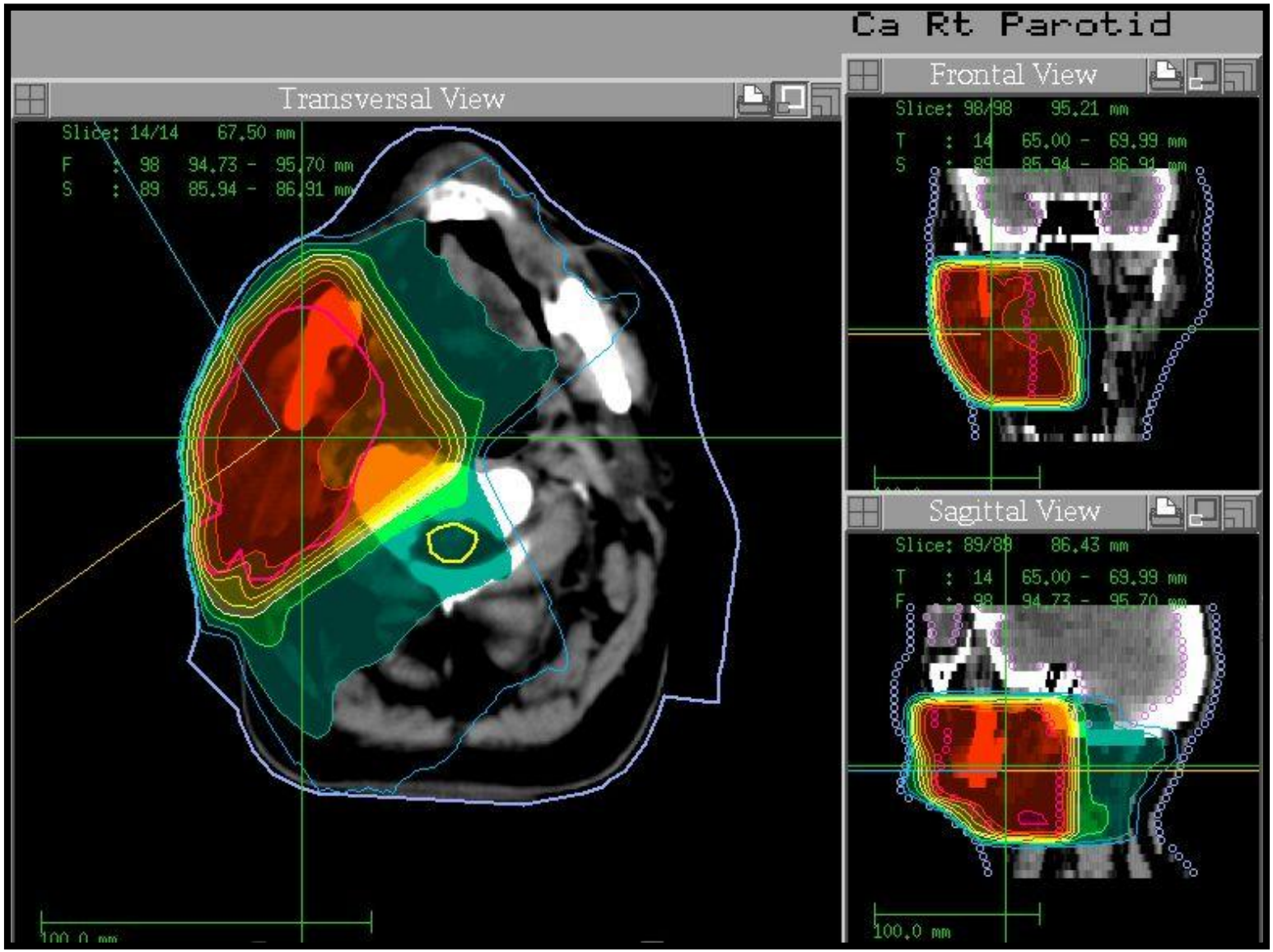
PARAMETER (10 ´ 10 cm^2 field)	p(66)/Be(40) (iThemba LABS)	8 MV x-rays
SAD (cm)	150	100
d_{max} (g cm^{-2})	1.7	1.8
$\dot{D}$ at d_{max} (Gy min^{-1})	0.6	4.0
90 % build-up (g cm^{-2})	0.5	0.9
$D_{surface}/D_{max}$	33 %	22 %
$d_{50\%}$ (cm)	16.7	17.1
$D_{10\ cm}/D_{max}$	71 %	71 %
20 % - 80 % penumbrae (cm) 2 cm 10 cm	 0.64 1.26	 0.70 1.00

DIAGNOSTIC SCANS

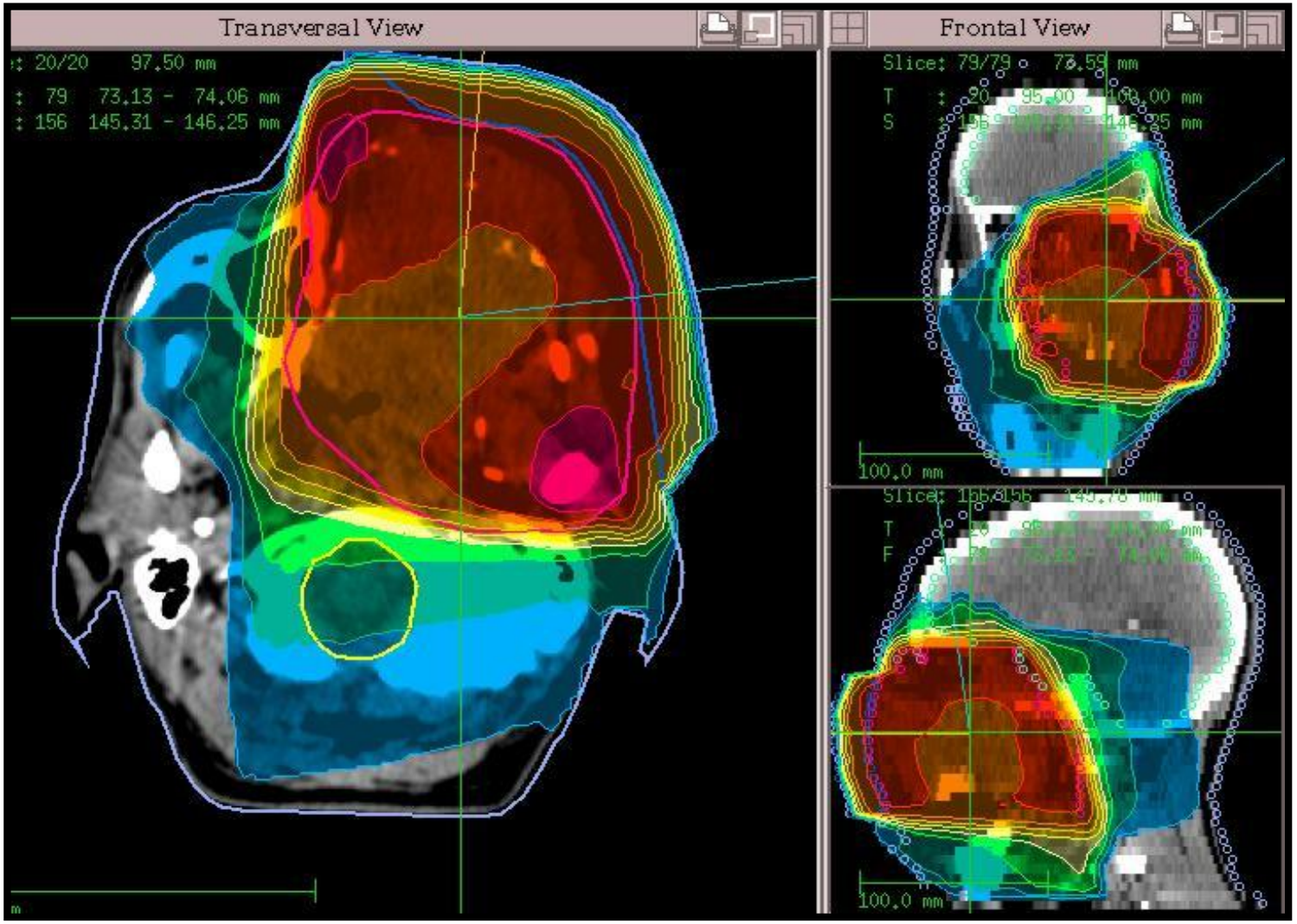
CT ***MRI***



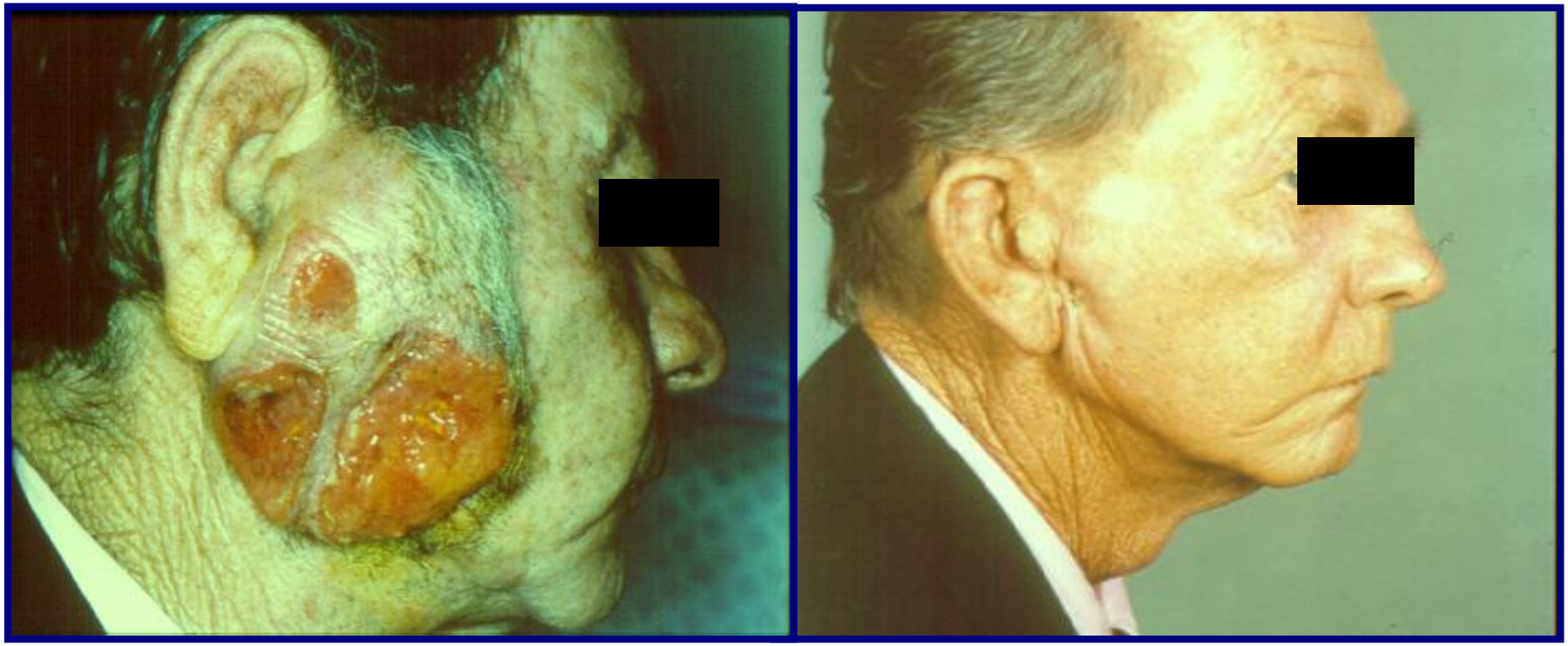
NEUTRON PLAN: PAROTID GLAND



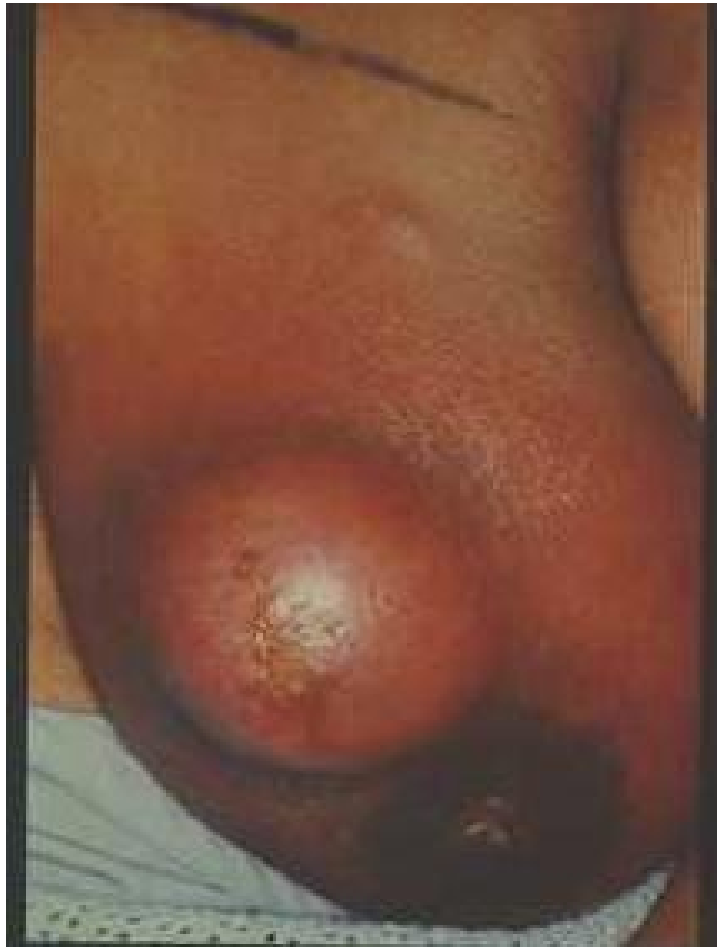
NEUTRON PLAN: MAXILLARY ANTRUM

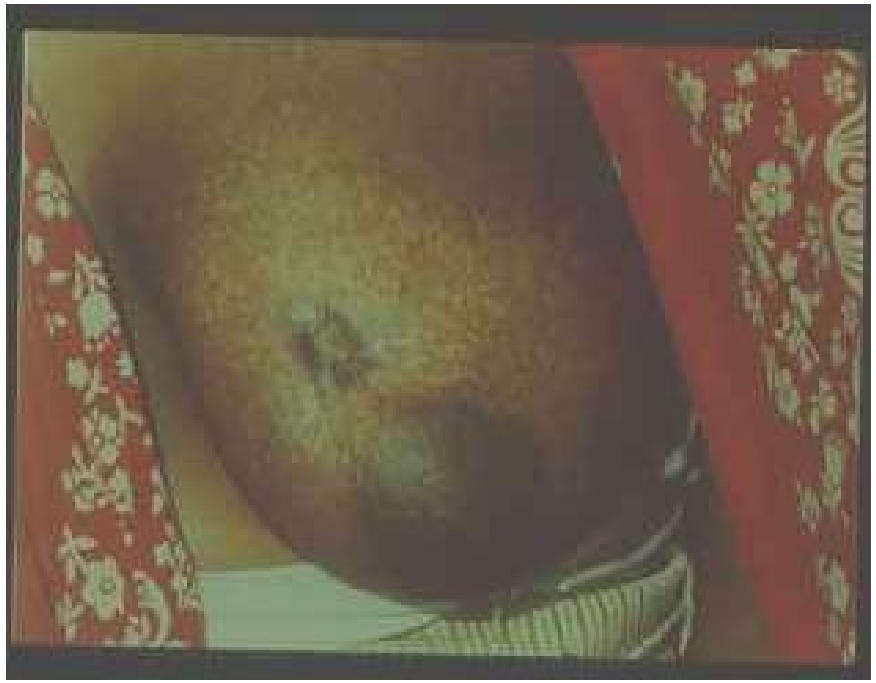


SALIVARY GLAND TUMOR
Before and after treatment



BREAST TUMOR
Before and after treatment





FAST NEUTRON THERAPY FACILITIES (6)

LOCATION	COUNTRY	SOURCE REACTION	SAD (cm)	BEAM DIRECTION	COLLIMATOR TYPE	FIRST TREATMENT	PATIENTS (May 2007)
Garching (2)[1]	**Germany**	Reactor	620	Horizontal	Multileaf	2007	
Essen[2]	**Germany**	d(14.3) + Be^{n}	125	Isocentric	Inserts	1978	773
Detroit, MI[3]«	**USA**	d(48.5) + Be^{o}	183	Isocentric cyclotron	Multileaf	1990	2 214
Seattle, WA (2)[4]	**USA**	p(50.5) + Be^{n}	150	Isocentric Horizontal	Multileaf Inserts	1984	2 567
Batavia, IL[5]	**USA**	p(66) + Be^{Ò}	190	Horizontal	Inserts	1976	3 348
Somerset West[6]	**South Africa**	p(66) + Be^{n}	150	Isocentric	Variable jaws + Multiblade trimmer	1988	1 486

^{n} Cyclotron **^{o}Superconducting cyclotron** **^{Ò} Linac** **«Program suspended on 29 March 2007**

[1] Forschungsneutronenquelle Heinz Maier-Leibnitz (FRM-II)
[2] Universitätsklinikum Essen (UKE)
[3] Karmanos Cancer Institute (KCI)
[4] University of Washington (UW)
[5] Northern Illinois University Institute for Neutron Therapy at Fermilab (NIUINTF)
[6] iThemba Laboratory for Accelerator-Based Sciences (iTLABS)

FAST NEUTRON THERAPY
Status of facilities unknown (3)

LOCATION	COUNTRY	SOURCE REACTION
Chelyabinsk	**Russia**	d(0.5) + T
Minsk[n]	**Belarus**	d(14) + Be
Tomsk[n]	**Russia**	d(14) + Be

[n] Cyclotron

FAST NEUTRON THERAPY
Programs terminated: Cyclotrons (1-11/22)

LOCATION	COUNTRY	SOURCE REACTION	BEAM DIRECTION	COLLIMATOR TYPE	FIRST TREATMENT
Berkeley, CA (37″)	**USA**	d(8) + Be	Horizontal	Inserts	1938
Berkeley, CA (60″)	**USA**	d(16) + Be	Horizontal	Inserts	1939
London	**UK**	d(16) + Be	Horizontal	Inserts	1966
Anagawa	**Japan**	d(2.8) + Be	Horizontal	Inserts	1970
College Station, TX	**USA**	d(50) + Be	Horizontal	Inserts	1972
Dresden	**Germany**	d(13.5) + Be	Horizontal	Inserts	1972
Seattle, WA (1)	**USA**	d(22) + Be	Horizontal	Inserts	1973
Washington, DC	**USA**	d(35) + Be	Horizontal	Inserts	1973
Chiba	**Japan**	d(30) + Be	Vertical	Inserts	1975
Chicago, IL	**USA**	d(8) + D	Horizontal	Inserts	1976
Cleveland, OH	**USA**	d(25) + Be p(43) + Be	Horizontal	Inserts	1977

FAST NEUTRON THERAPY
Programs terminated: Cyclotrons (12-22/22)

LOCATION	COUNTRY	SOURCE REACTION	BEAM DIRECTION	COLLIMATOR TYPE	FIRST TREATMENT
Edinburgh	**UK**	d(16) + Be	Isocentric	Inserts	1977
Krakow	**Poland**	d(12.5) + Be	Horizontal	Inserts	1978
Tokyo	**Japan**	d(14) + Be	Horizontal	Inserts	1978
Louvain-la-Neuve	**Belgium**	p(65) + Be	Vertical	Multileaf	1978
Orleans	**France**	p(34) + Be	Vertical	Inserts	1981
Los Angeles, CA	**USA**	p(45) + Be	Isocentric	Variable jaws	1984
Clatterbridge	**UK**	p(62) + Be	Isocentric	Variable jaws	1985
Seoul	**South Korea**	p(50.5) + Be	Isocentric	Inserts	1986
Houston, TX	**USA**	p(42) + Be	Isocentric	Inserts	1988
Riyadh	**Saudi Arabia**	p(26) + Be	Isocentric	Inserts	1988
Nice	**France**	p(65) + Be	Vertical	Multileaf	1993

FAST NEUTRON THERAPY
Programs terminated: Other devices (10)

LOCATION	COUNTRY	SOURCE REACTION	FIRST TREATMENT
Amsterdam°	**The Netherlands**	D-T	1975
Hamburg°	**Germany**	D-T	1976
Glasgow	**UK**	D-T	1977
Manchester	**UK**	D-T	1977
Heidelberg°	**Germany**	D-T	1978
Philadelphia, PA	**USA**	D-T	1981
Münster	**Germany**	D-T	1984
Garching (1)	**Germany**	Reactor	1985
Obninsk	**Russia**	Reactor	1985
Beijing	**China**	p(35) + Be (Linac)	1991

°Rotating treatment head

FAST NEUTRON THERAPY
Assessment (I)

- ± 27 000 patients treated to date (estimated)
- Efficacy for several tumor types has been well established in randomized and other clinical trials
- Many facilities closed because of poor clinical results
  - † side effects due to poor physical beam characteristics
    - ¢ poor penetration (low energy)
    - ¢ lack of flexible beam delivery
  - † unethical to treat patients if x ray beams had similar characteristics
- Neutrons got a poor reputation, which has never been regained
- Viewed as outdated modality (~ radium)
- The advantages of neutrons are seriously underestimated

FAST NEUTRON THERAPY
Assessment (II)

- Same proton accelerator for neutron therapy can be used for
  - isotope production
  - proton treatments of eye tumors (E_p > 60 MeV)
  - NCT with spallation source
  - + booster accelerator for high-energy proton therapy
- Neutron fractionation schedules (12 - 15 fractions) provide enormous financial and logistic advantages over conventional therapy schedules (30 – 40 fractions)
- Similar clinical results obtained with heavy ions
- Fast neutron therapy is ideal for developing countries where patients often present with large, advanced tumors

FAST NEUTRON THERAPY
Assessment (III)

- Future is limited because of widespread interest in heavy ions (mainly ^{12}C) for high-LET therapy
- Favorable circumstances for fast neutron therapy
  - very high cost of heavy-ion facilities
    - relatively few patients treated
    - cost recovery limited
  - similar clinical results as with heavy ions
- New techniques should improve outcomes
  - intensity-modulated neutron therapy
  - neutron capture enhancement
  - Inverse planning optimization
  - biological treatment planning

PROTON BEAMS IN RADIOTHERAPY

- Radiobiologically equivalent to photons
  - † reduces the scope of preclinical studies
  - † conventional treatment schedules can be used
    - ¢ > 100 years of experience of treating millions of patients
- Favourable dose distributions
  - † higher dose to the tumor
  - † reduced dose to normal tissue
  - † avoids critical structures
- Requirements for effective treatment
  - † accurate patient set-up
  - † accurate tumor localization
  - † sophisticated 3-D treatment planning
  - † state-of-the-art beam delivery (scanning is best)
  - † allowance for organ motion

RADIOLOGY
Vol. 47 (1946) 487-491

RADIOLOGICAL USE OF FAST PROTONS

ROBERT R. WILSON
Research Laboratory of Physics, Harvard University
CAMBRIDGE, MASSACHUSETTS

It will be possible to treat a volume as small as 1.0 c.c. anywhere in the body and to give the volume several times the dose of any of the neighboring tissue. The exact behaviour of protons of the energy considered here will become known only when such protons are available for experiment.

In treating large tumors, for example, one will want to *cover the whole volume* with the very high ionization density which obtains over the last few millimeters. This can easily be accomplished by interposing a rotating wheel of variable thickness, corresponding to the tumor thickness, between the source and the patient.

ION THERAPY HISTORY

1946 Robert Wilson proposes use of protons and heavier ions for therapy

1948 Tobias *et al*. undertake experimental work with ion beams on 184 inch synchrocyclotron at UC, Berkeley

1954 Protons used for first time for treatment of human patients at Berkeley

1957 Proton therapy stopped at Berkeley after upgrade of synchrocyclotron results in proton energies too high for useful therapy

1957 Proton therapy starts at University of Uppsala, Sweden

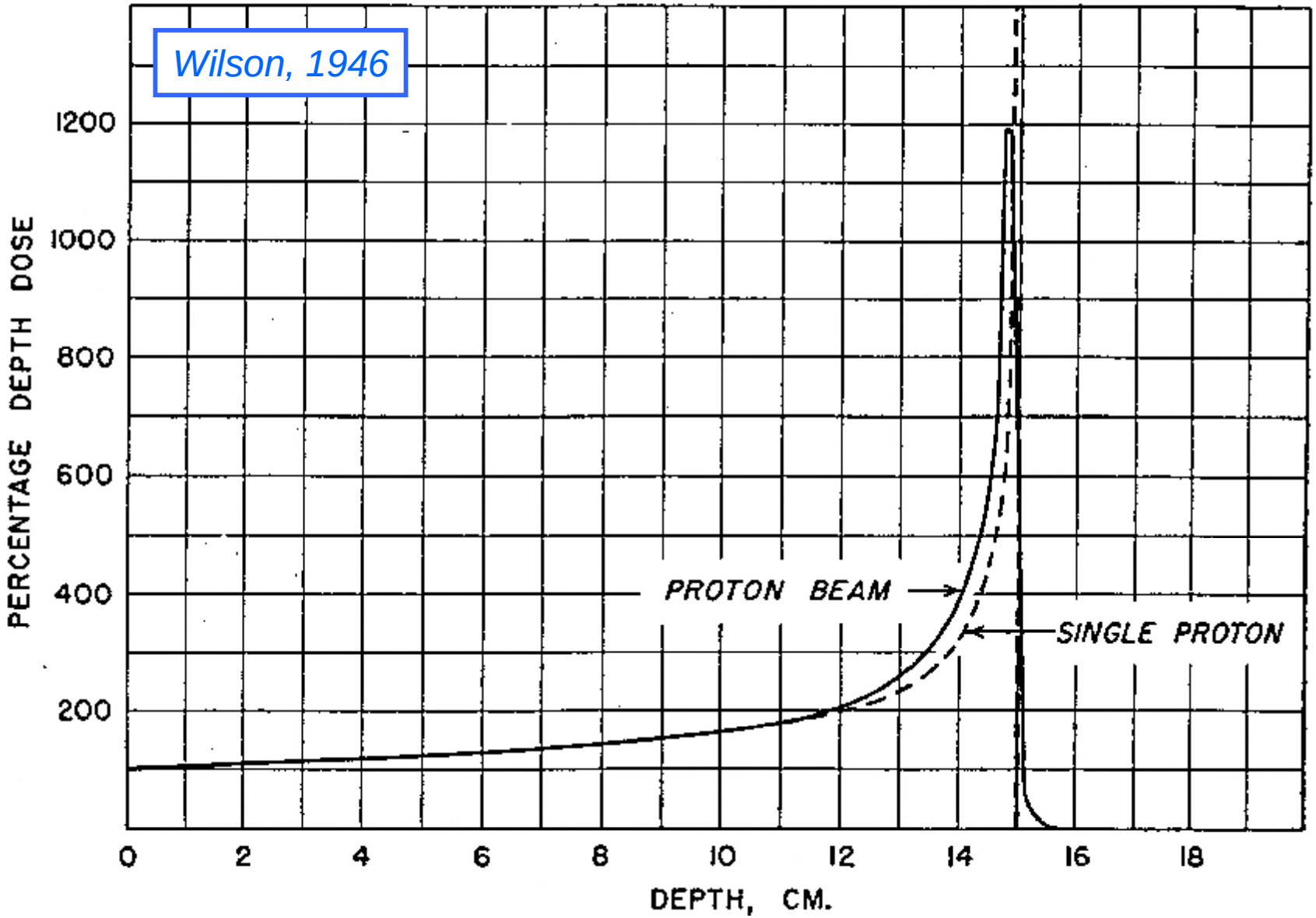
1957 Alpha particles used for first time for treatment at UC, Berkeley

1975 Heavy ions used for first time for treatment at UC, Berkeley

1992 Last alpha particle and heavy-ion treatments at UC, Berkeley

1994 Heavy ion therapy begins at National Institute of Radiological Sciences (NIRS), Chiba, Japan

PROTON DEPTH DOSE DISTRIBUTIONS



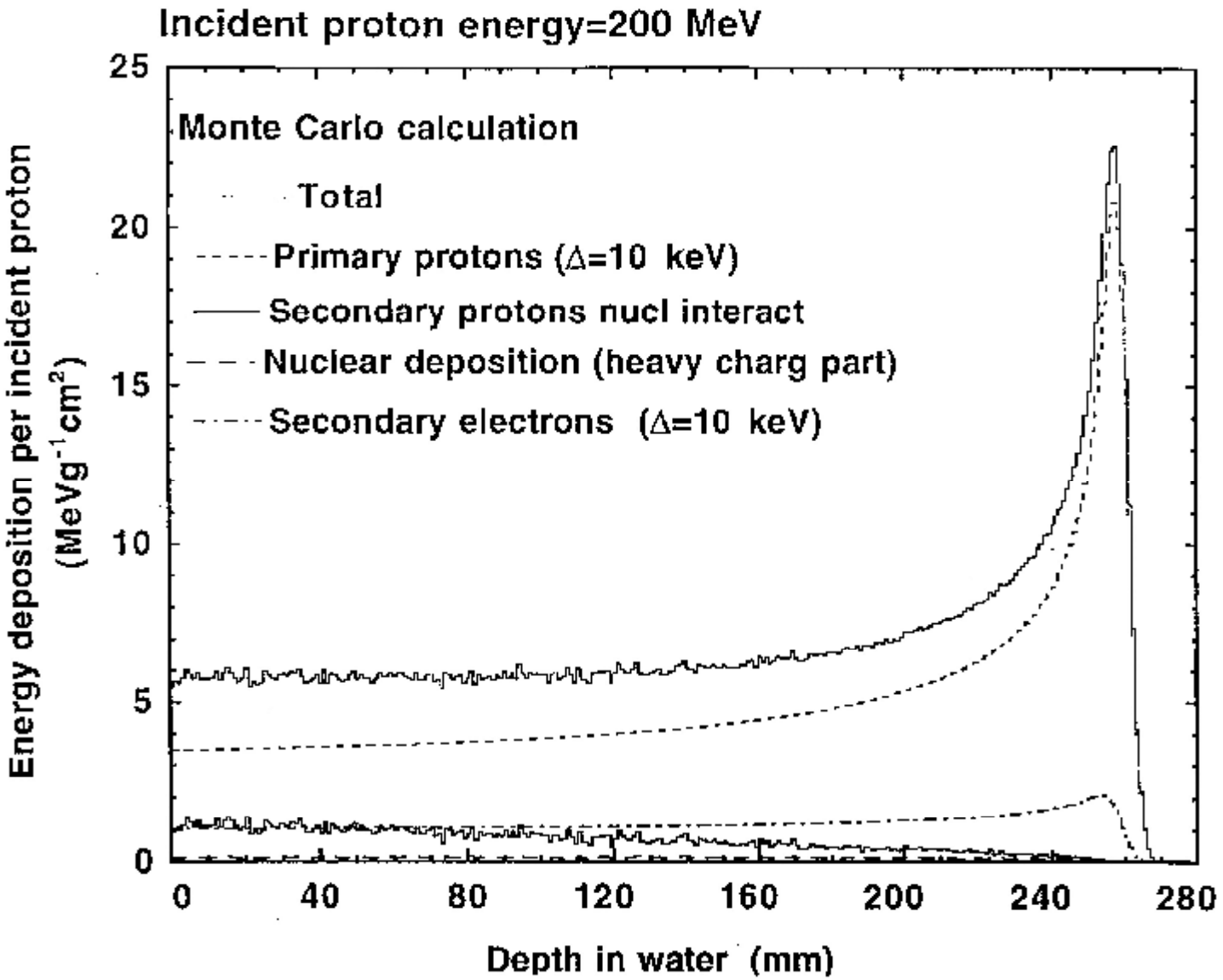
PROTON INTERACTIONS (I)

- Every interaction of a proton results in change of direction (scattering) or loss or energy
- At therapeutic energies (< 300 MeV) energy loss process is dominated by interaction of proton with bound outer shell electron of atoms or molecules in the matter penetrated
  - † excitation of atom or ionization with loss of electrons
  - † small energy loss per collision (max: 0.2 %, $m_p = 1840\ m_e$)
  - † continuous slowing down of protons
- Stopping power (energy loss per unit path length) is dominated by electronic interactions
  - † depends on material and proton energy
  - † $\propto 1/v^2$
    - ¢ increases with decreasing velocity
    - ¢ formation of Bragg peak
    - ¢ finite range in matter

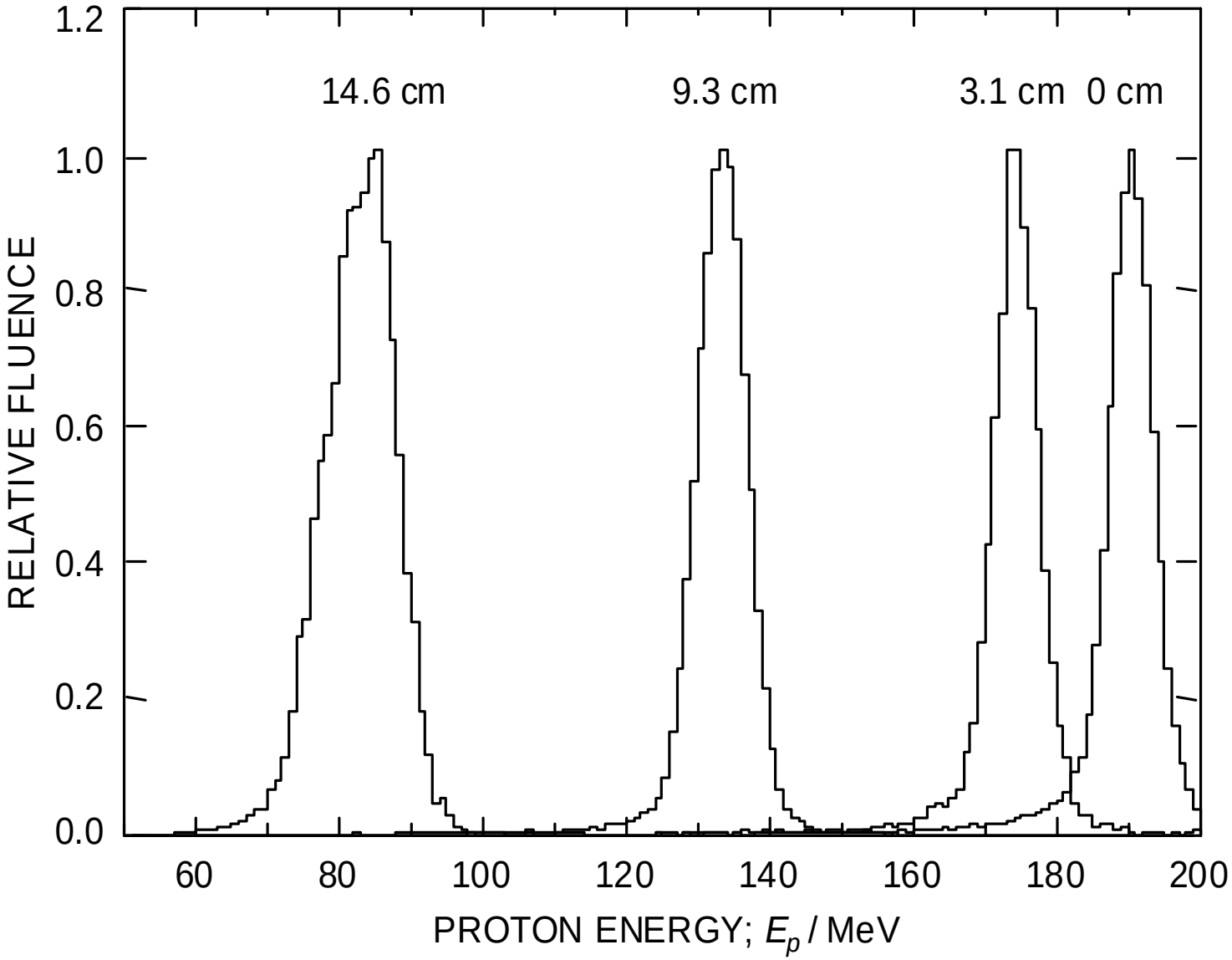
PROTON INTERACTIONS (II)

- Not all interactions are the same
  - protons move in slightly different paths
  - travel different distances
    - distribution of depths
    - range straggling (1% of mean range)
- Small angle (multiple scattering) results from Coulomb interactions with nuclei
  - lateral broadening of beam
  - sharp penumbrae decreasing with energy
    - more diffuse at Bragg peak (low energy)
- Nuclear interaction occur at high energies (>100 MeV)
  - loss of primary protons
  - production of secondary particles

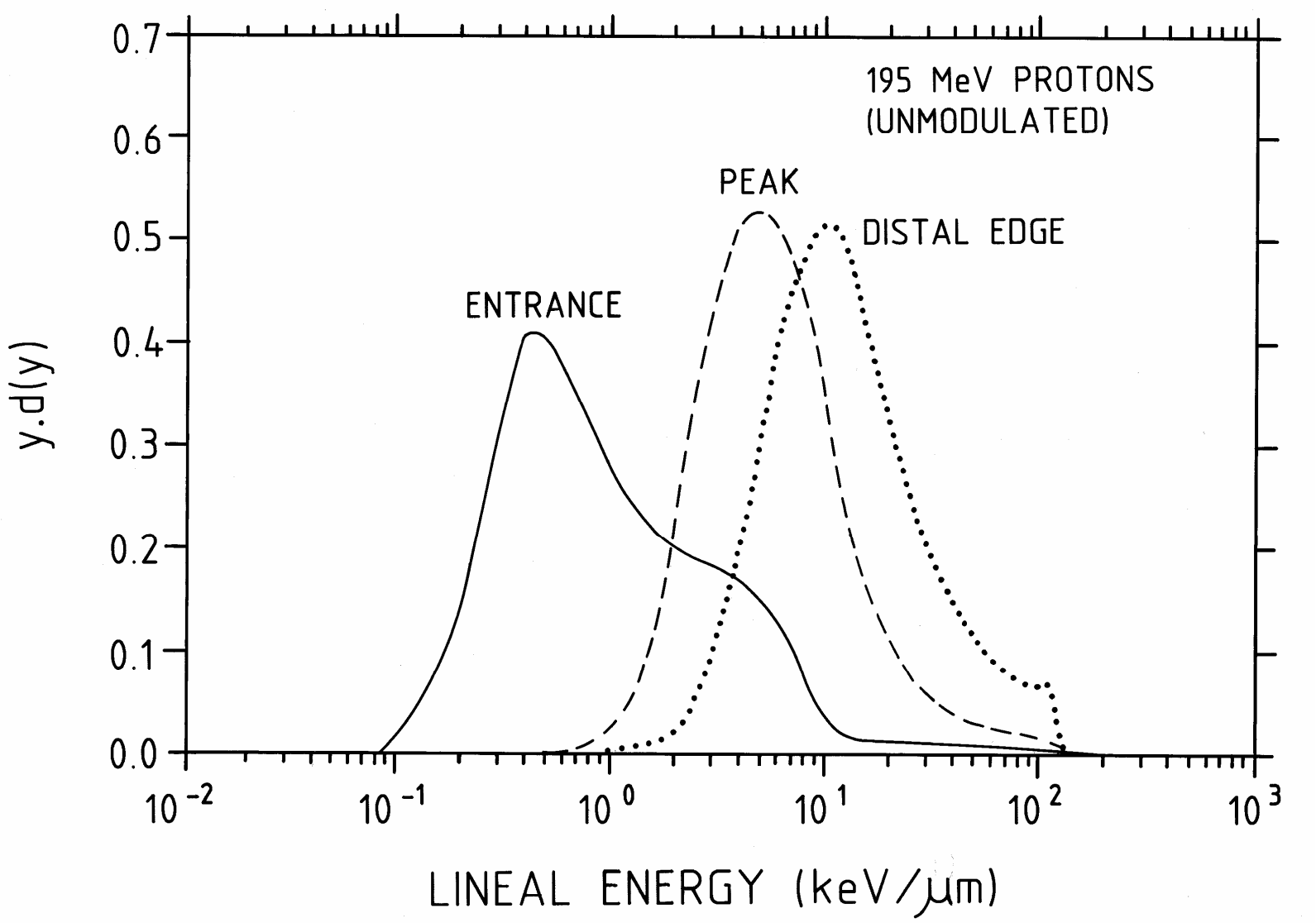
NUCLEAR INTERACTIONS



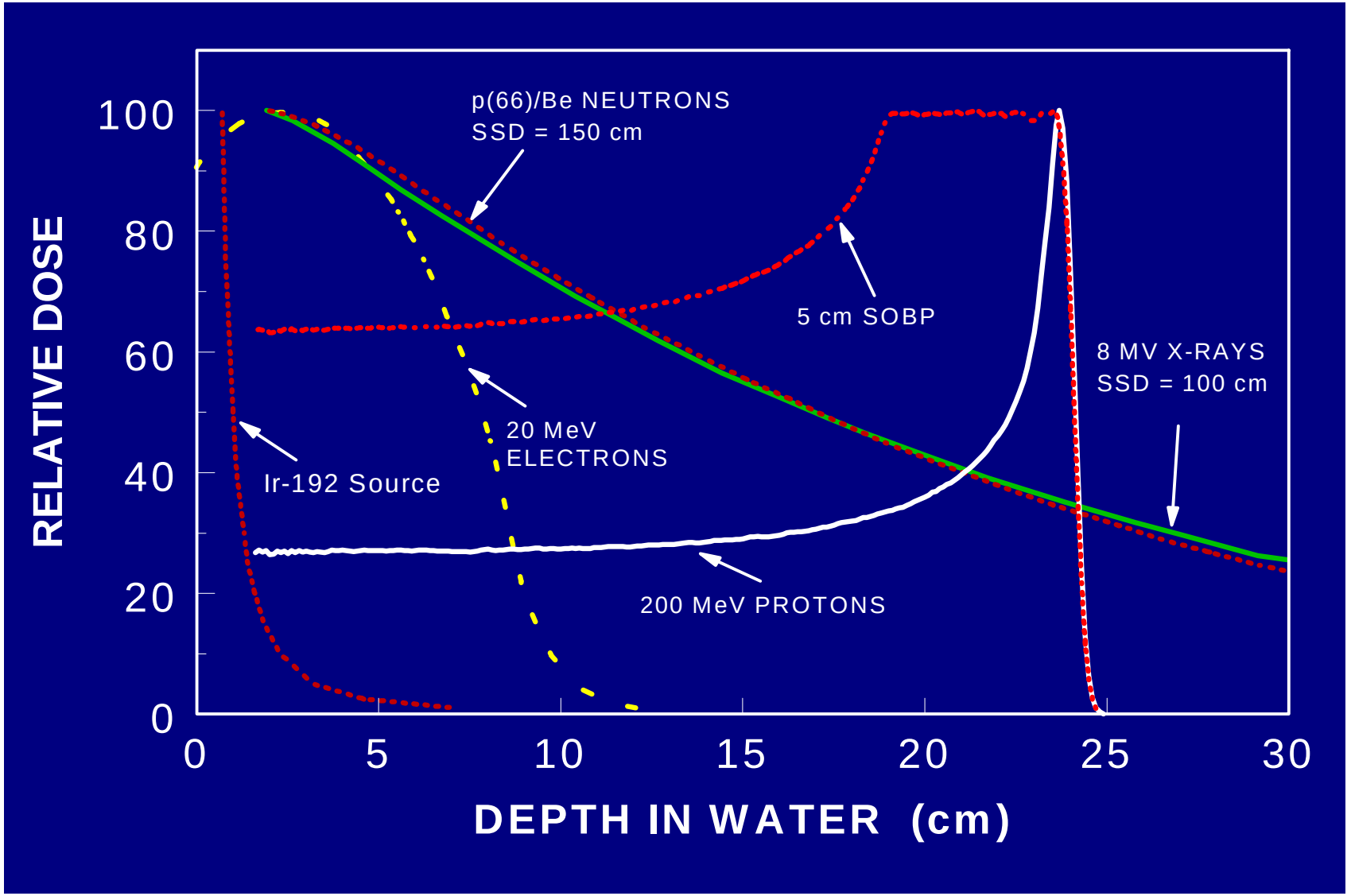
PROTON SPECTRA [iTL]



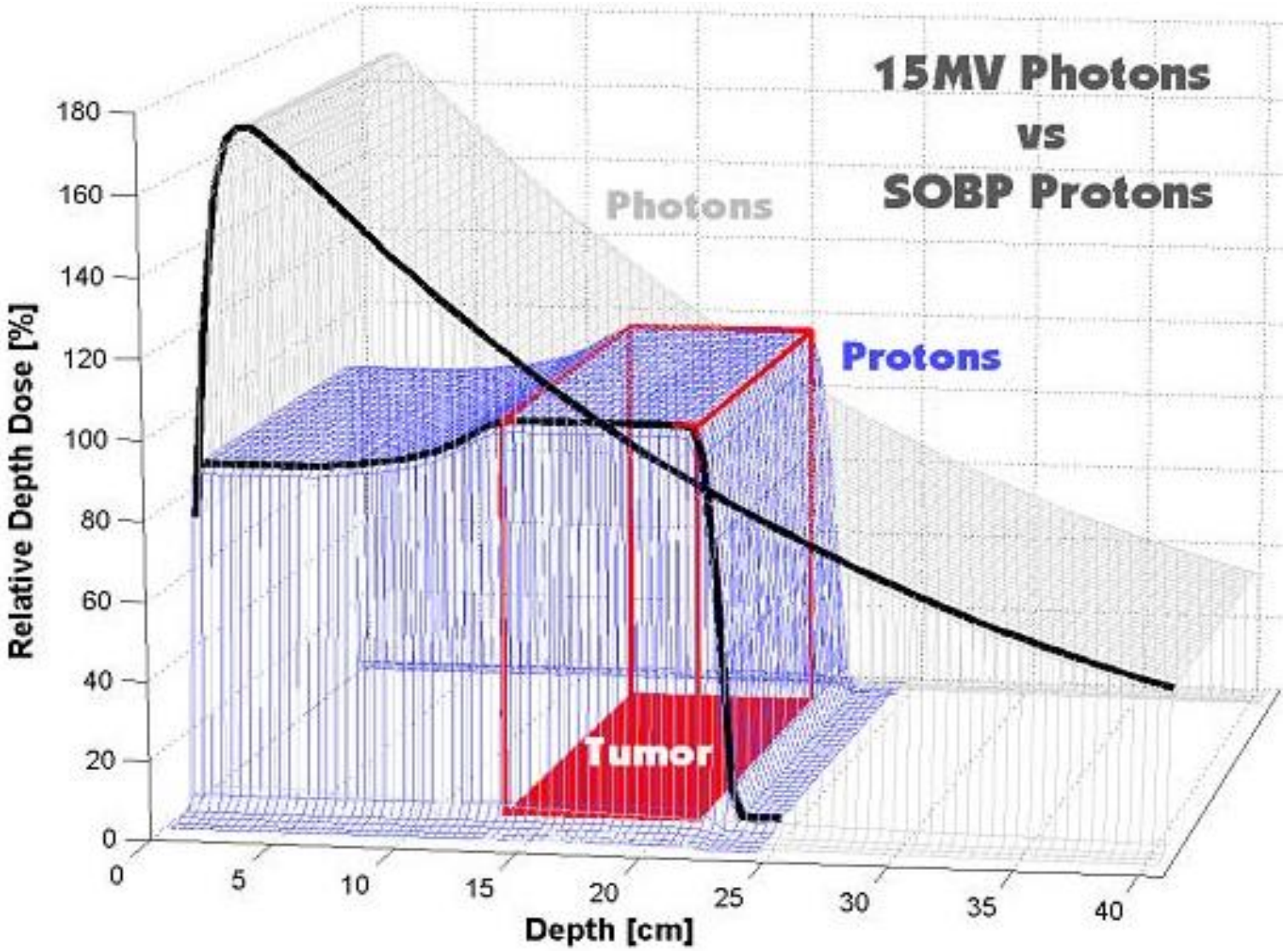
MICRODOSIMETRY



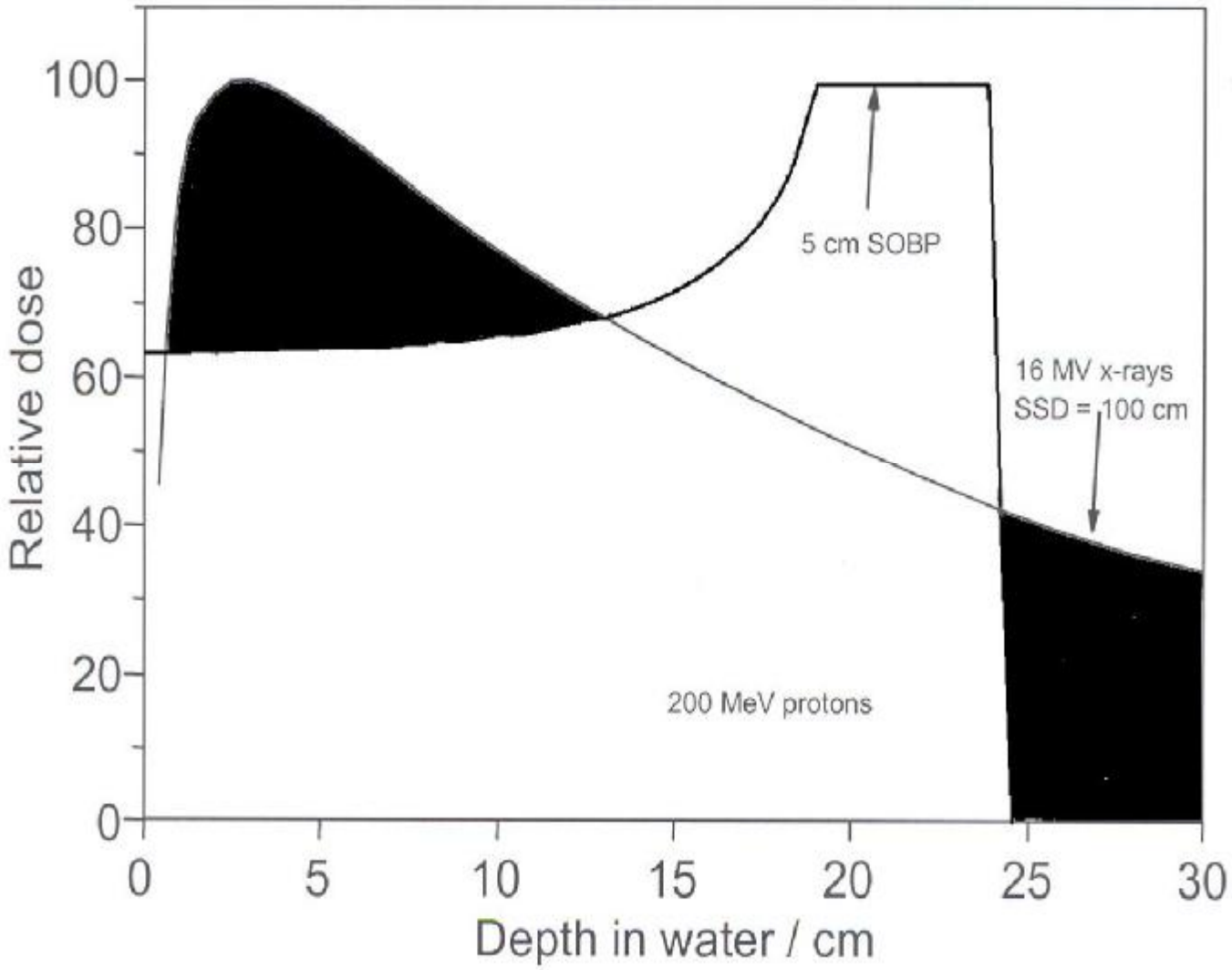
DEPTH DOSE DISTRIBUTIONS



DOSE DISTRIBUTIONS



PROTONS: DOSE ADVANTAGE

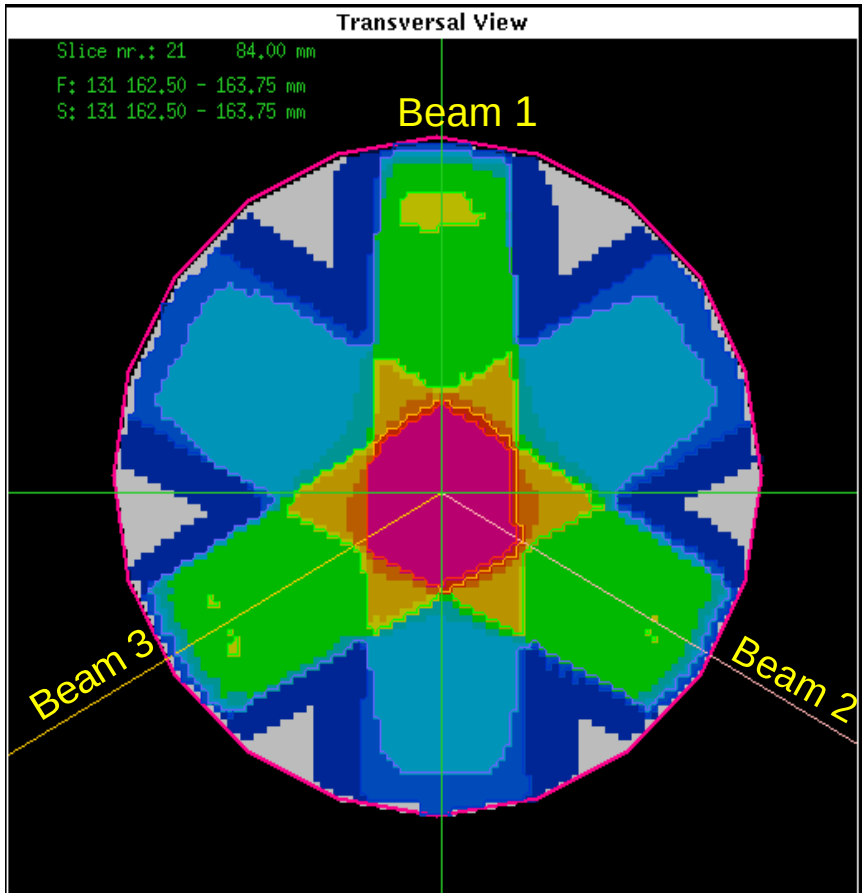


PROTON THERAPY

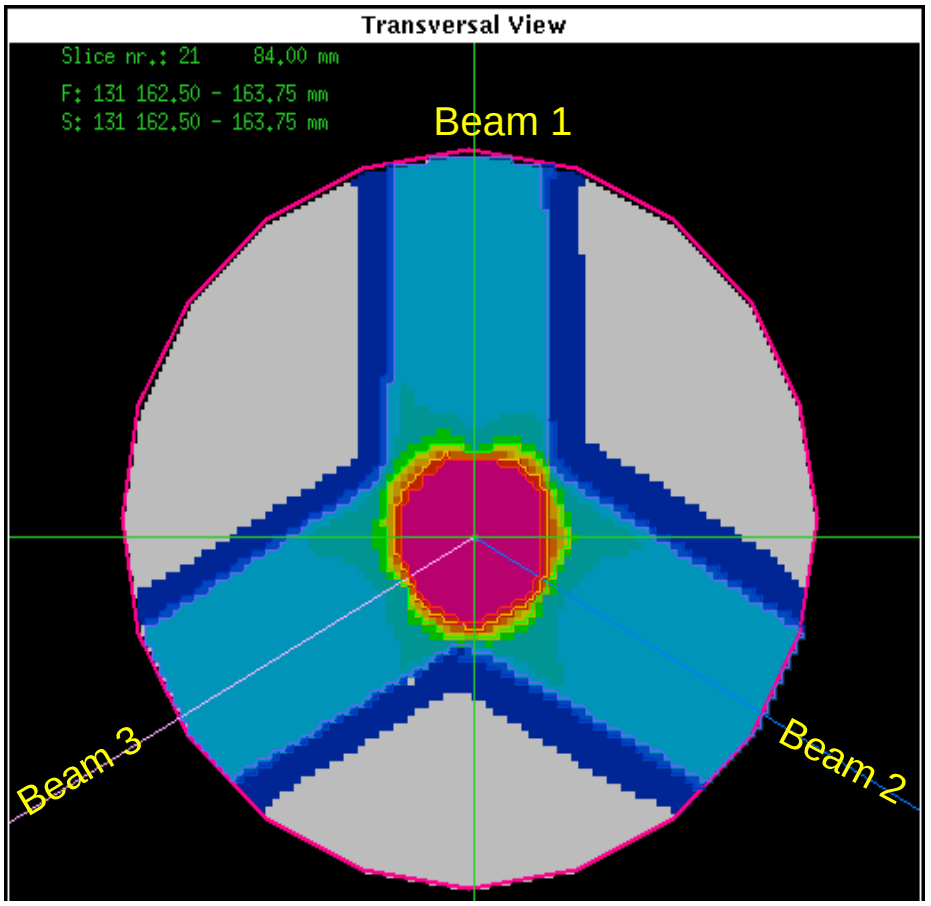
- The rationale for using protons for radiation therapy lies exclusively in their physical properties
  - near-zero dose distal to the target volume
    - avoidance of critical structures
  - steep lateral and distal dose gradients
- Beams are easy to modify
  - dose can be delivered with great precision
    - dose conforms more accurately to target volume
- Depth dose curve for a monoenergetic proton beam exhibits a relatively flat low-dose entrance region (the plateau) followed by a sharp high-dose peak (the Bragg peak), just beyond which the particles lose their energy in a few mm
  - spread-out Bragg peak (SOBP) provides a near-uniform dose across the target volume
- There are no known or predicted radiobiological advantages
  - conventional treatment schedules can be used
  - an RBE of 1.1 is adopted

3-FIELD TREATMENT

8 MV x rays



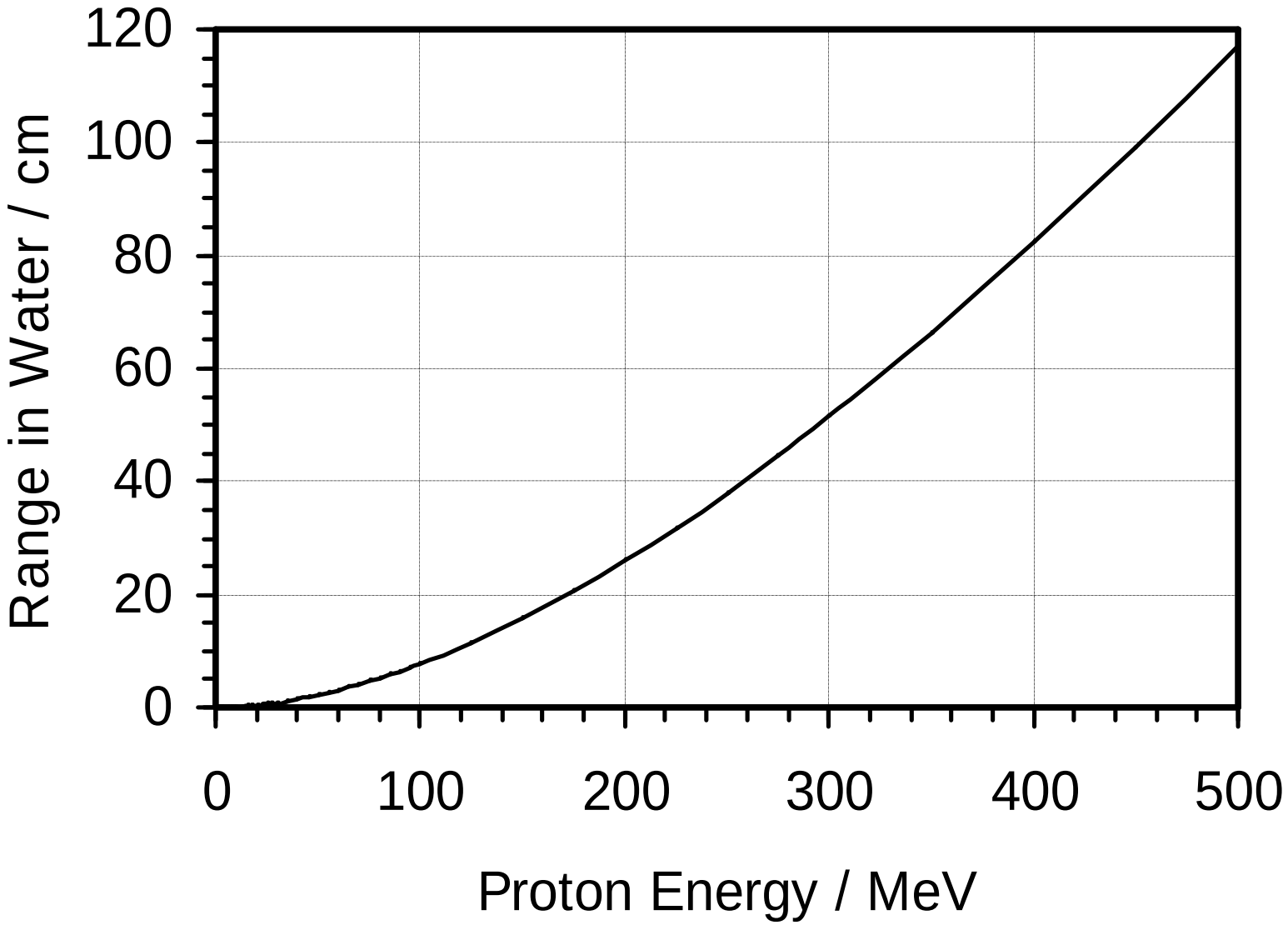
200 MeV protons



IDEAL ION THERAPY UNIT
Technical aspects

- Isocentric gantries + fixed beams
- Intensity modulated ion therapy (IMIT)
  - † scanning beam delivery
- Field sizes ≥ 35 × 35 cm^2
- Integral dose rate ≥ 3 Gy min^{-1}
- Beam range ≥ 30 cm
  - † 22 cm range (180 MeV) for 95% of tumors
  - † ≥ 50 cm for tomography
- Effective source-axis distance ≥ 3 m
  - † Cartesian scanning
- Automatic patient positioning and verification
  - † ≤ 1 mm

PROTON RANGE

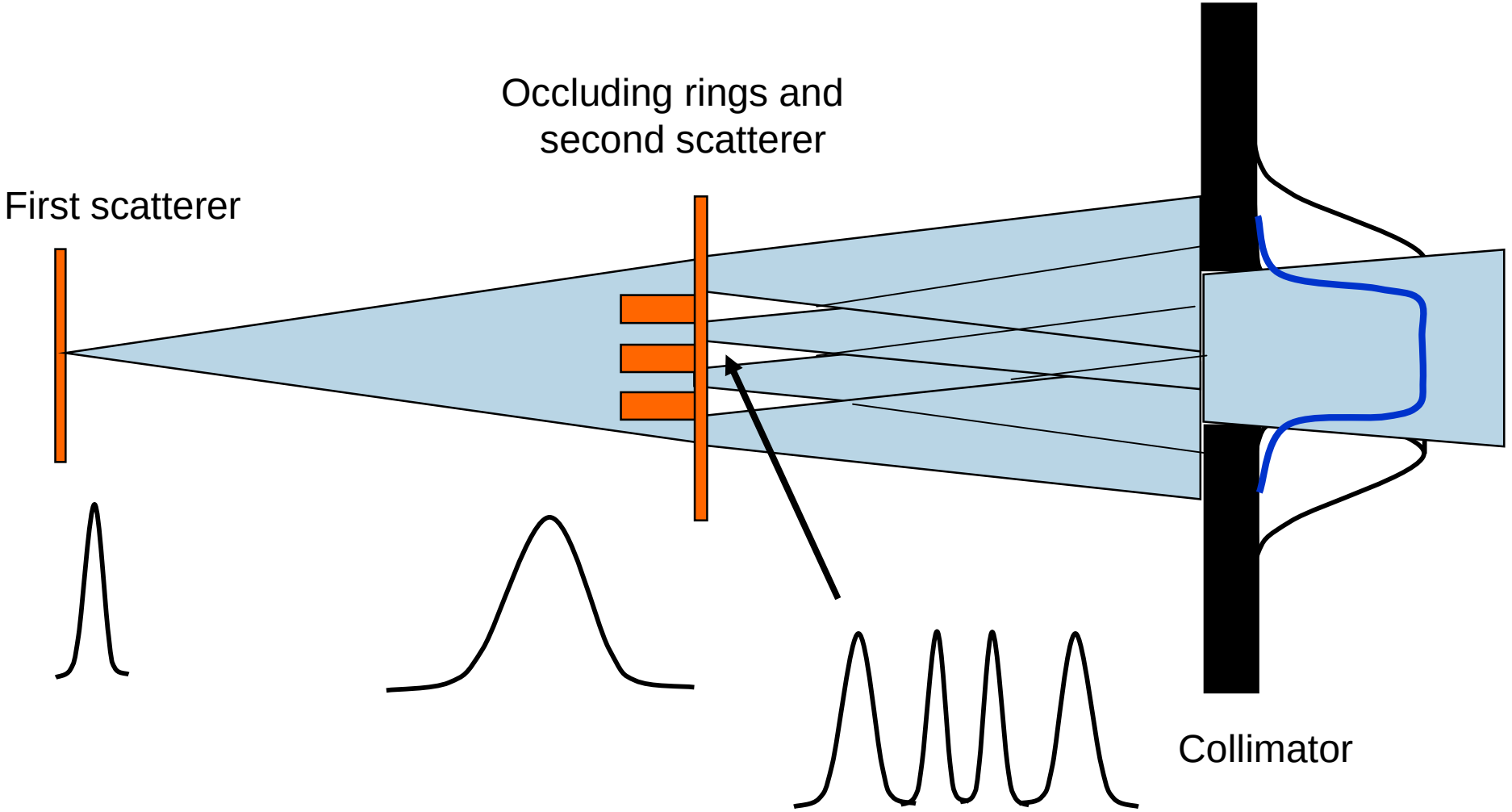


PROTON THERAPY INDICATIONS

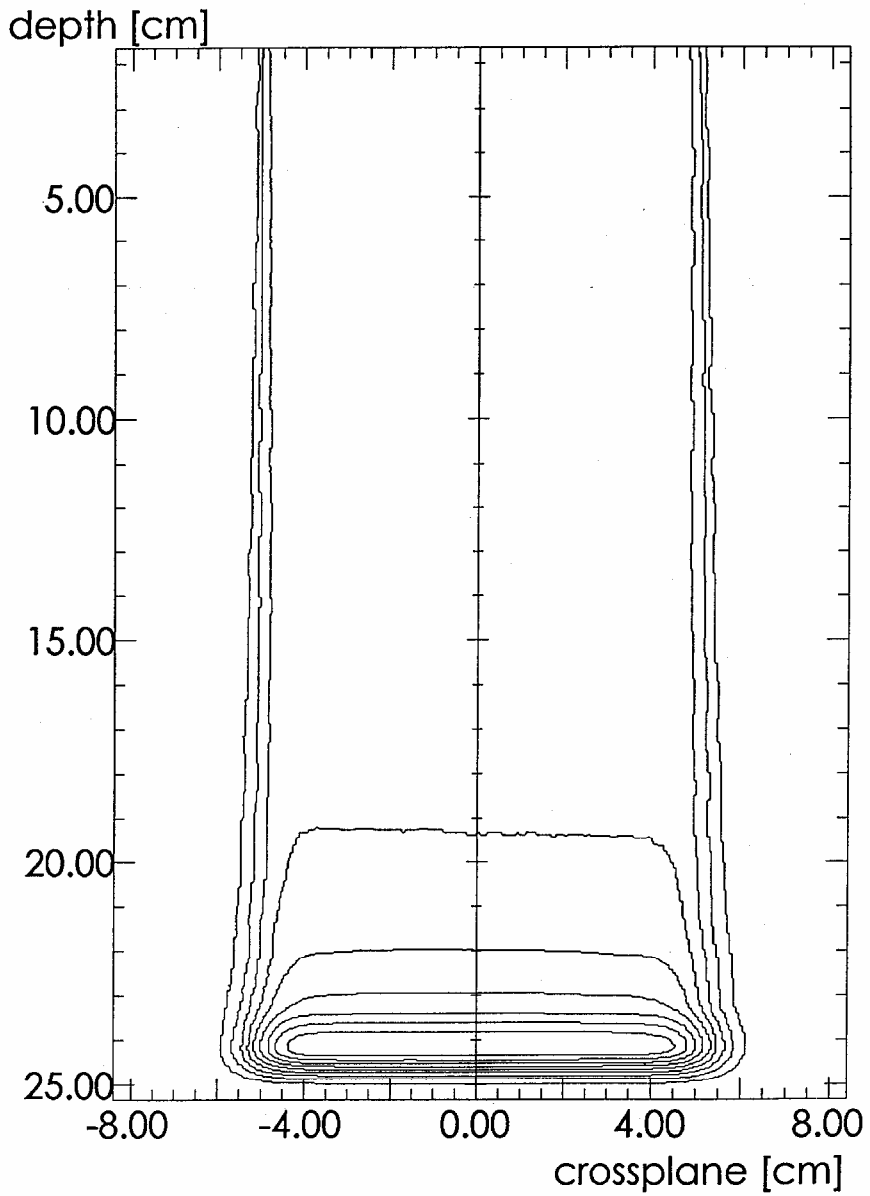
REGION	LESION
Brain and spinal cord	Isolated brain metastases Selected brain tumor recurrences Pituitary adenomas Arteriovenous malformations (AVMs)
Base of skull	Meningiomas Acoustic neuromas Chordomas and chondrosarcomas
Eye	Uveal melanomas Macular degeneration
Head and neck	Nasopharynx (primary and recurrent) tumors Oropharynx (locally advanced) tumors Paranasal sinus tumors
Chest and abdomen	Medically inoperable non-small-cell lung cancer Chordomas and chondrosarcomas Hepatic tumors Retroperitoneal tumors Paraspinal tumors
Pelvis	Prostate tumors Chordomas and chondrosarcomas
Pediatric lesions	Brain and spinal cord tumors Orbital and ocular tumors Sarcomas of the base of skull and spine Abdominal and pelvic tumors

LATERAL BEAM SPREADING SYSTEM

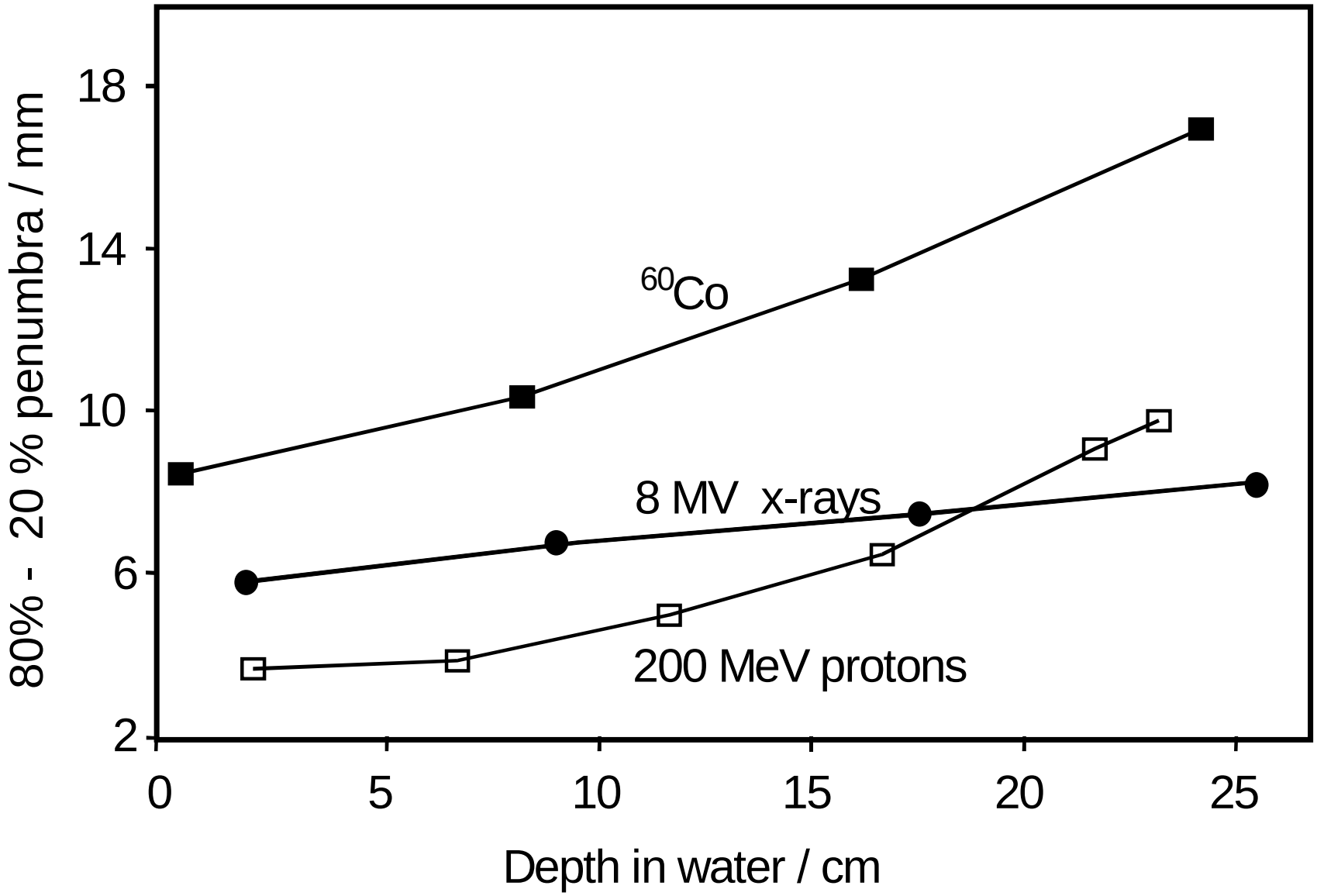
Passive scattering



ISODOSE DISTRIBUTIONS (191 MeV)

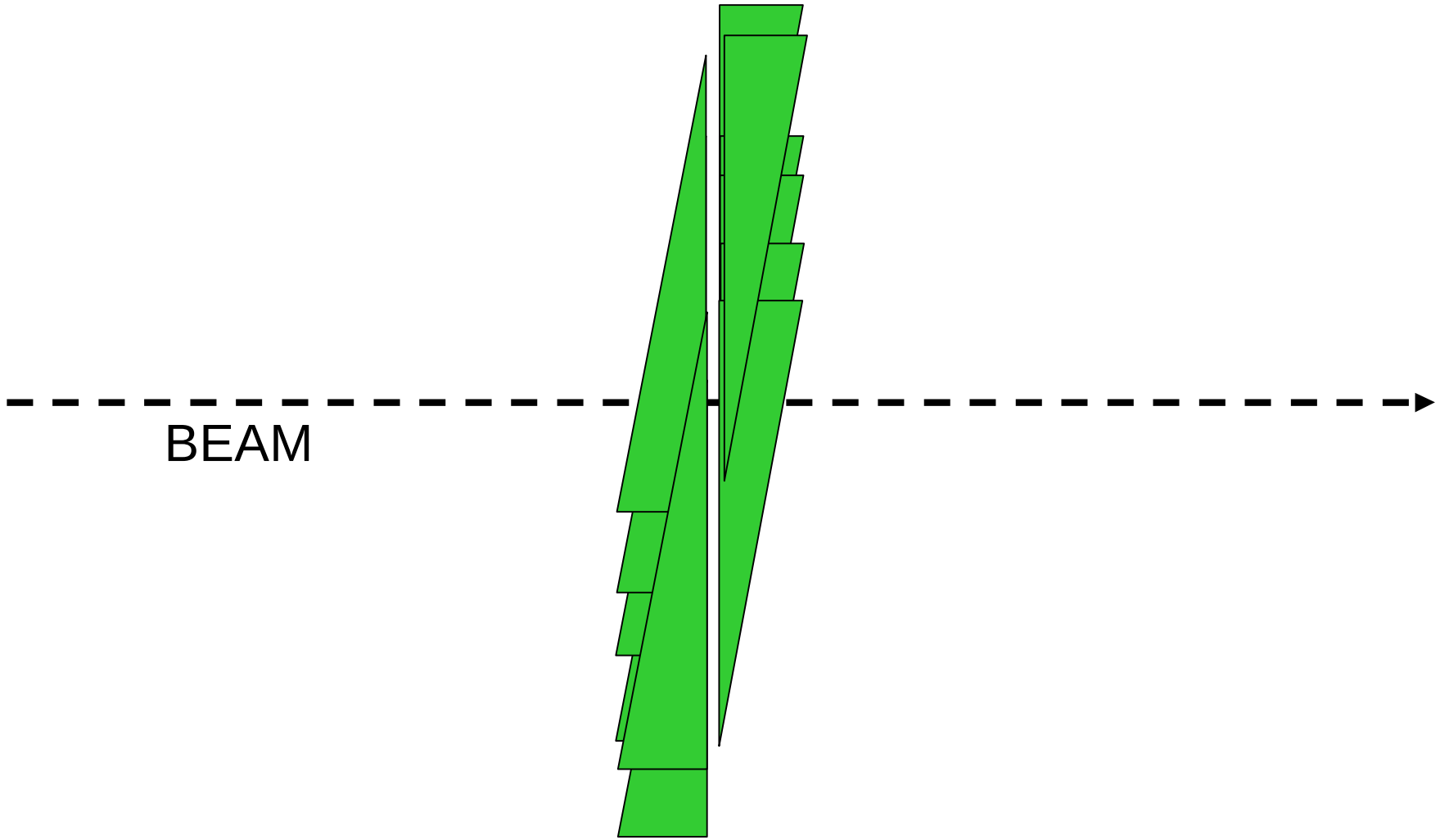


BEAM PENUMBRAE



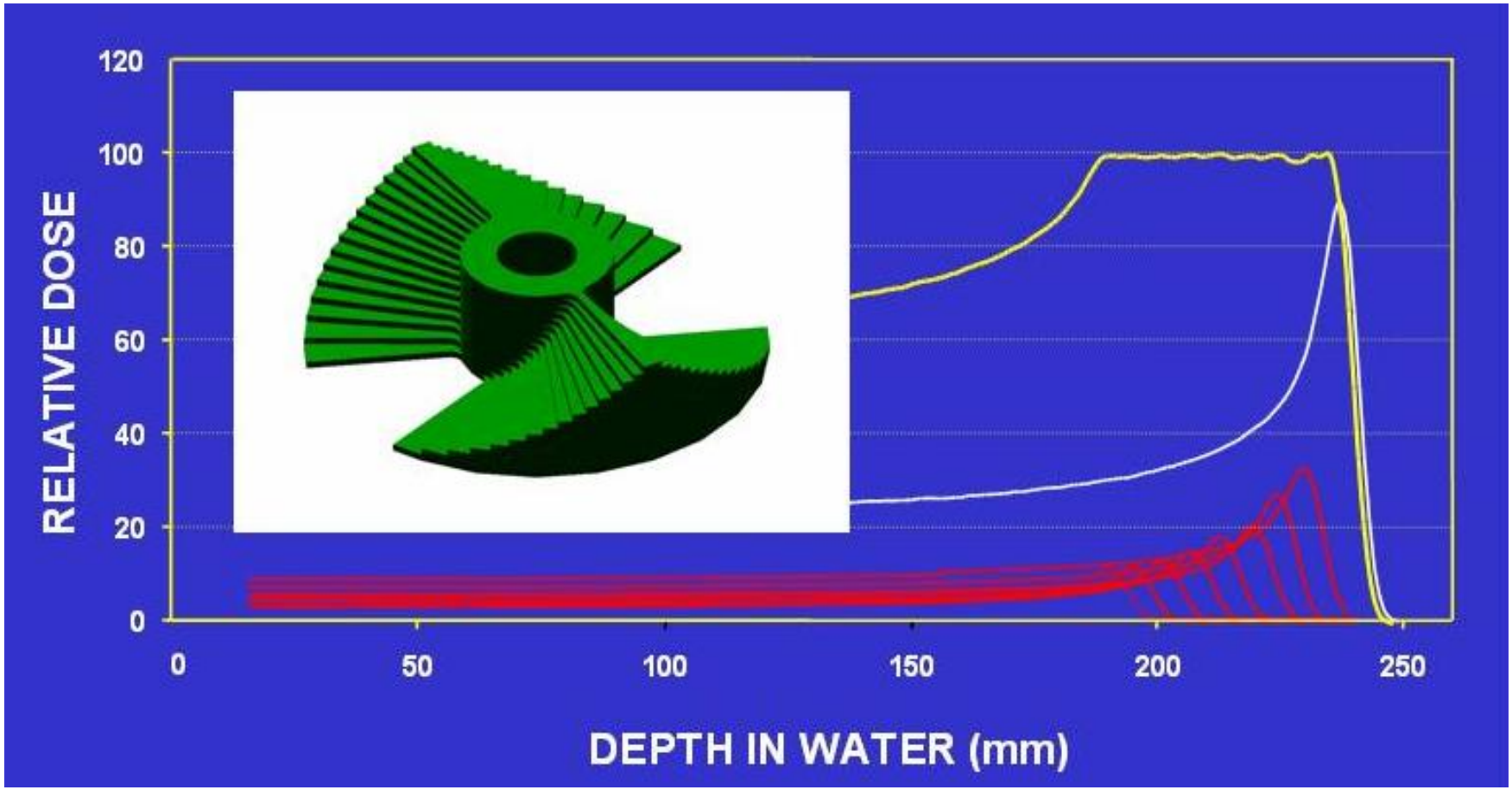
RANGE SHIFTER

TOTAL THICKNESS OF MATERIAL IN BEAM

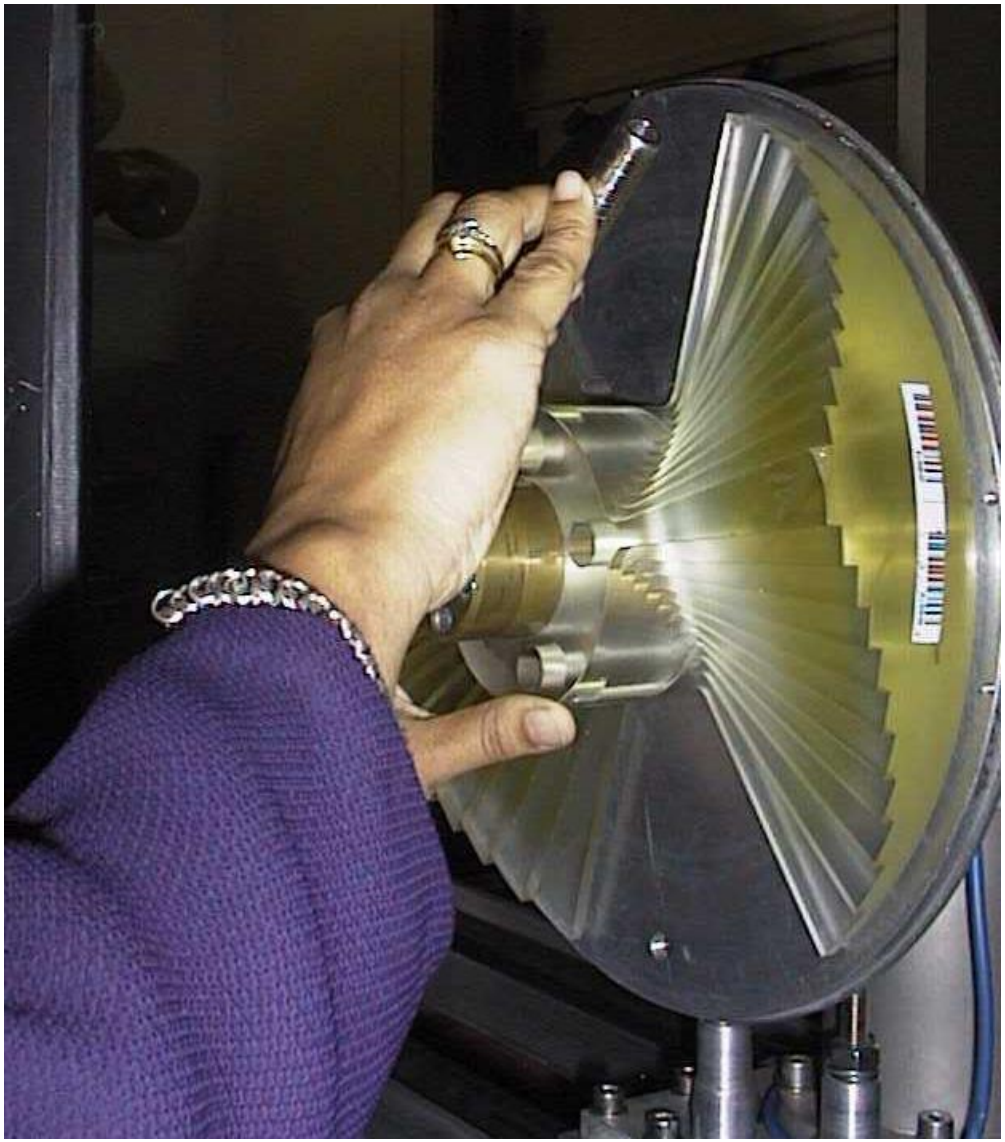


GRAPHITE WEDGES [iTL]

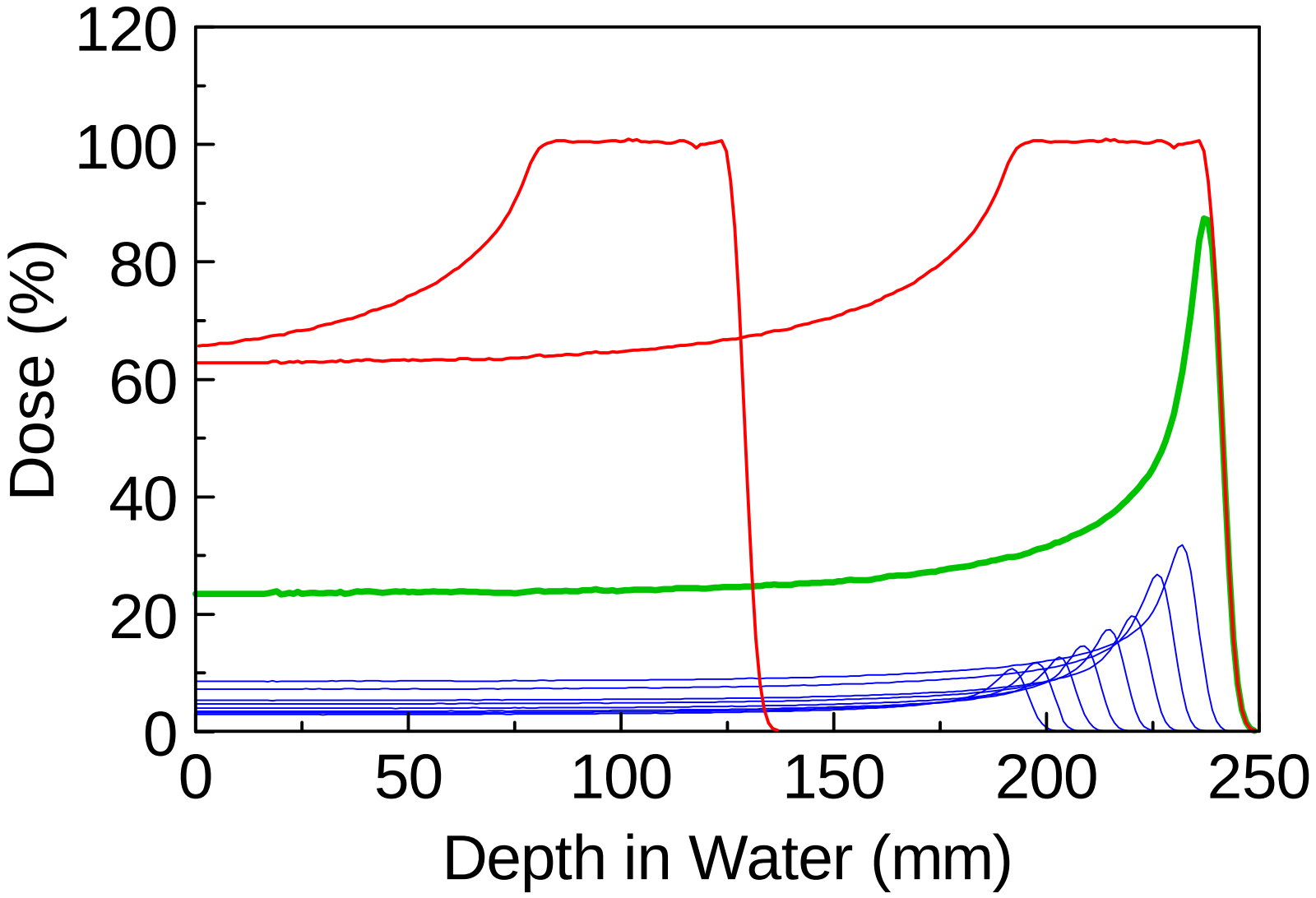
SPREAD-OUT BRAGG PEAK (SOBP)



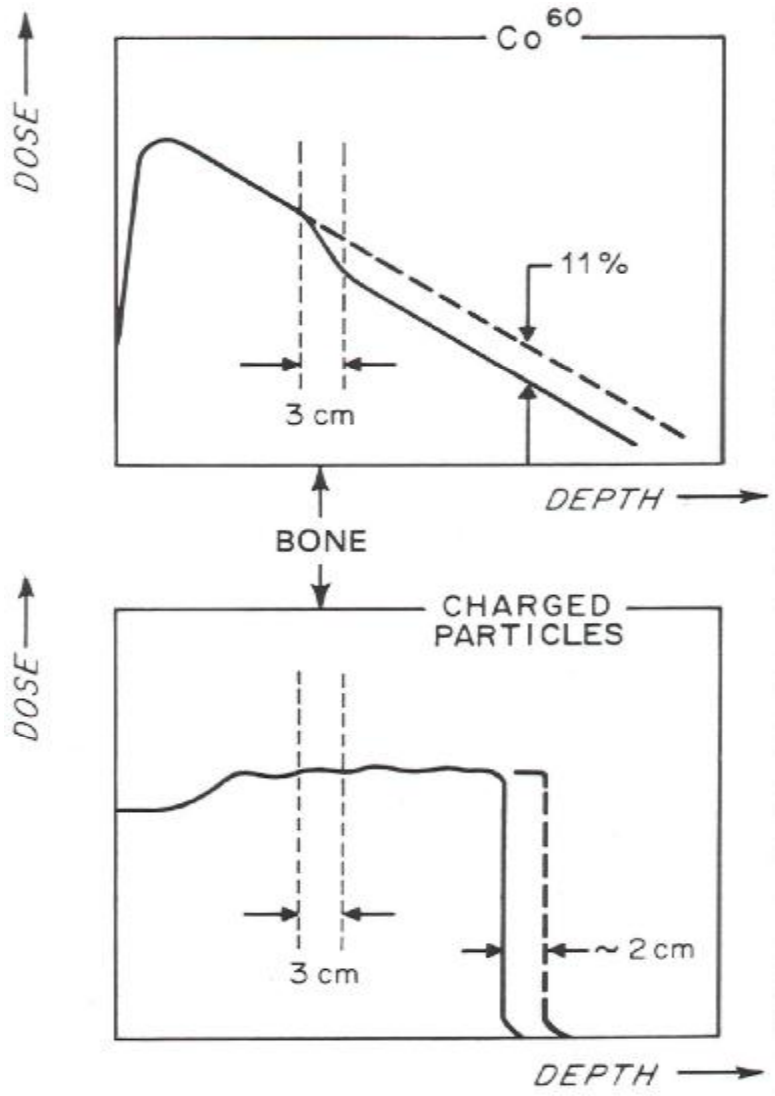
MODULATOR PROPELLER



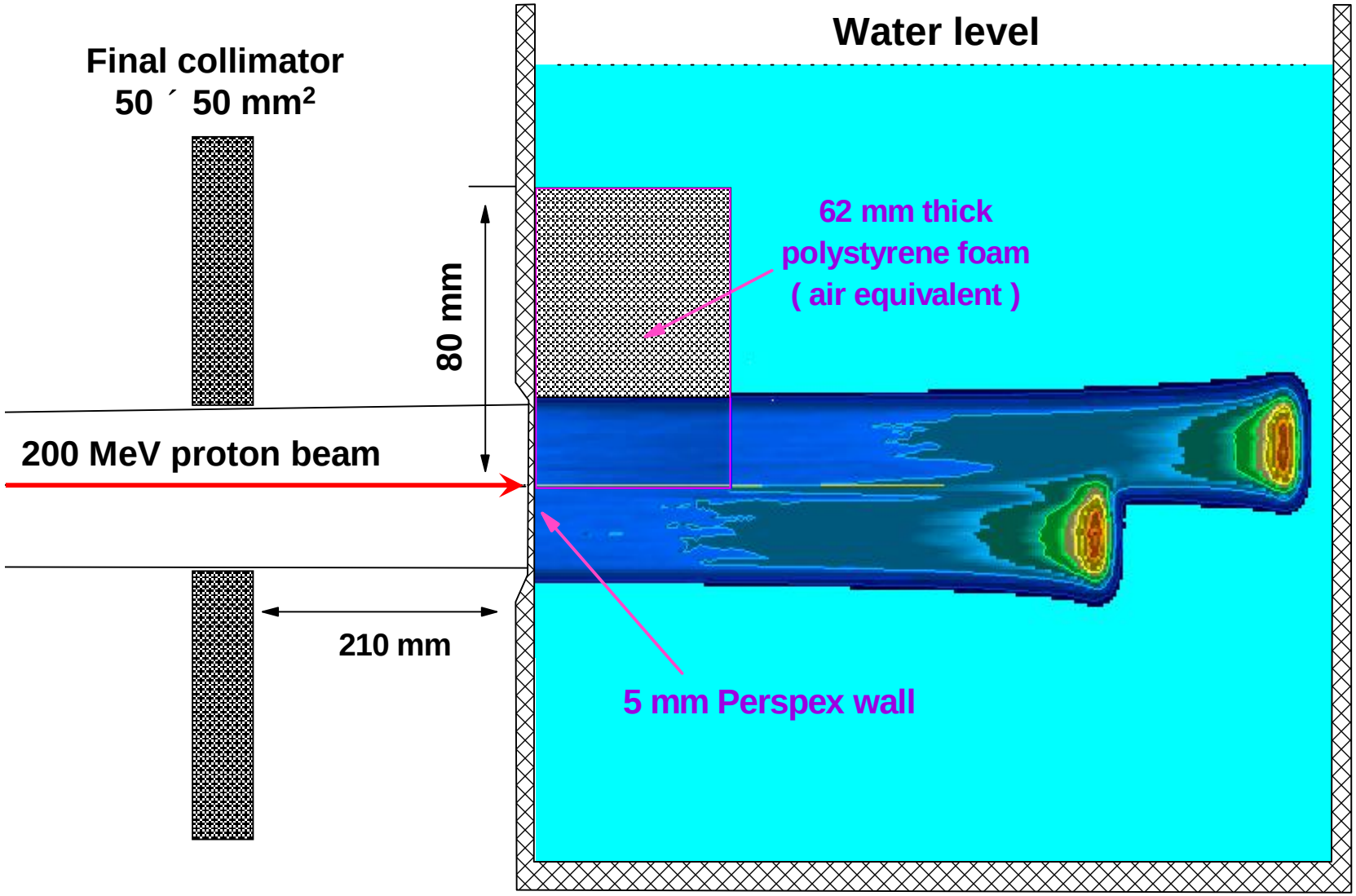
SPREAD OUT BRAGG PEAK + RANGE SHIFT



INHOMOGENIETY EFFECTS

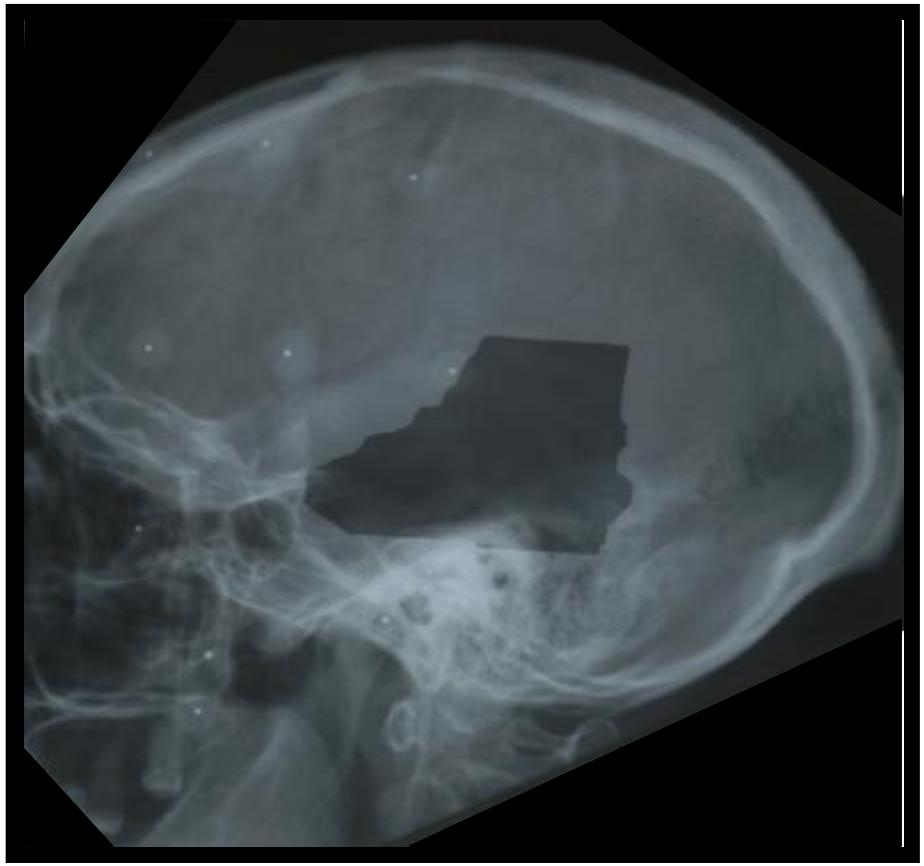


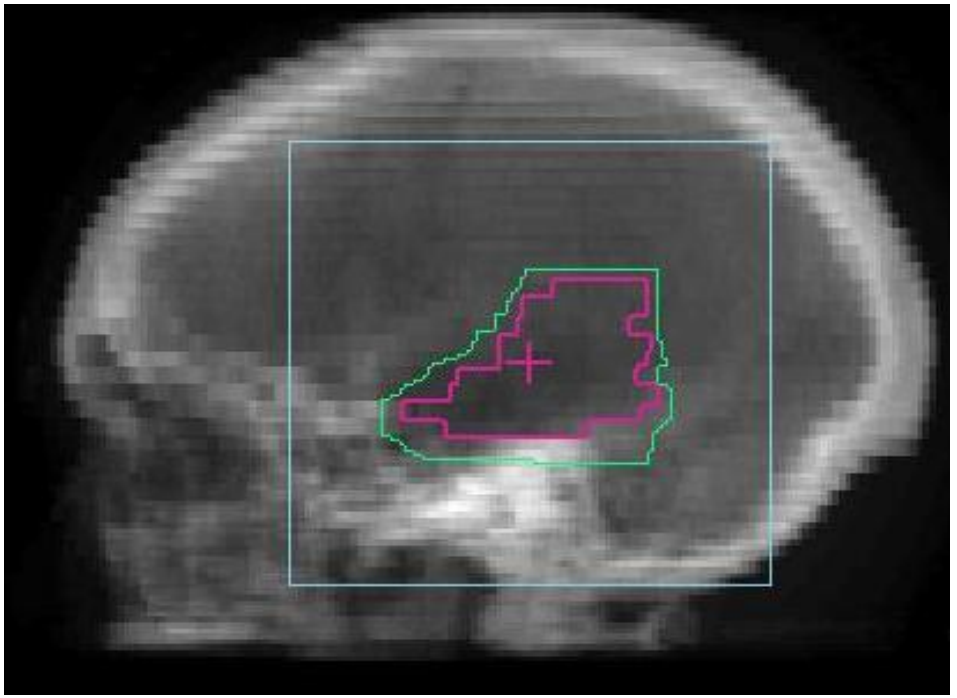
EFFECT OF INHOMOGENEITY



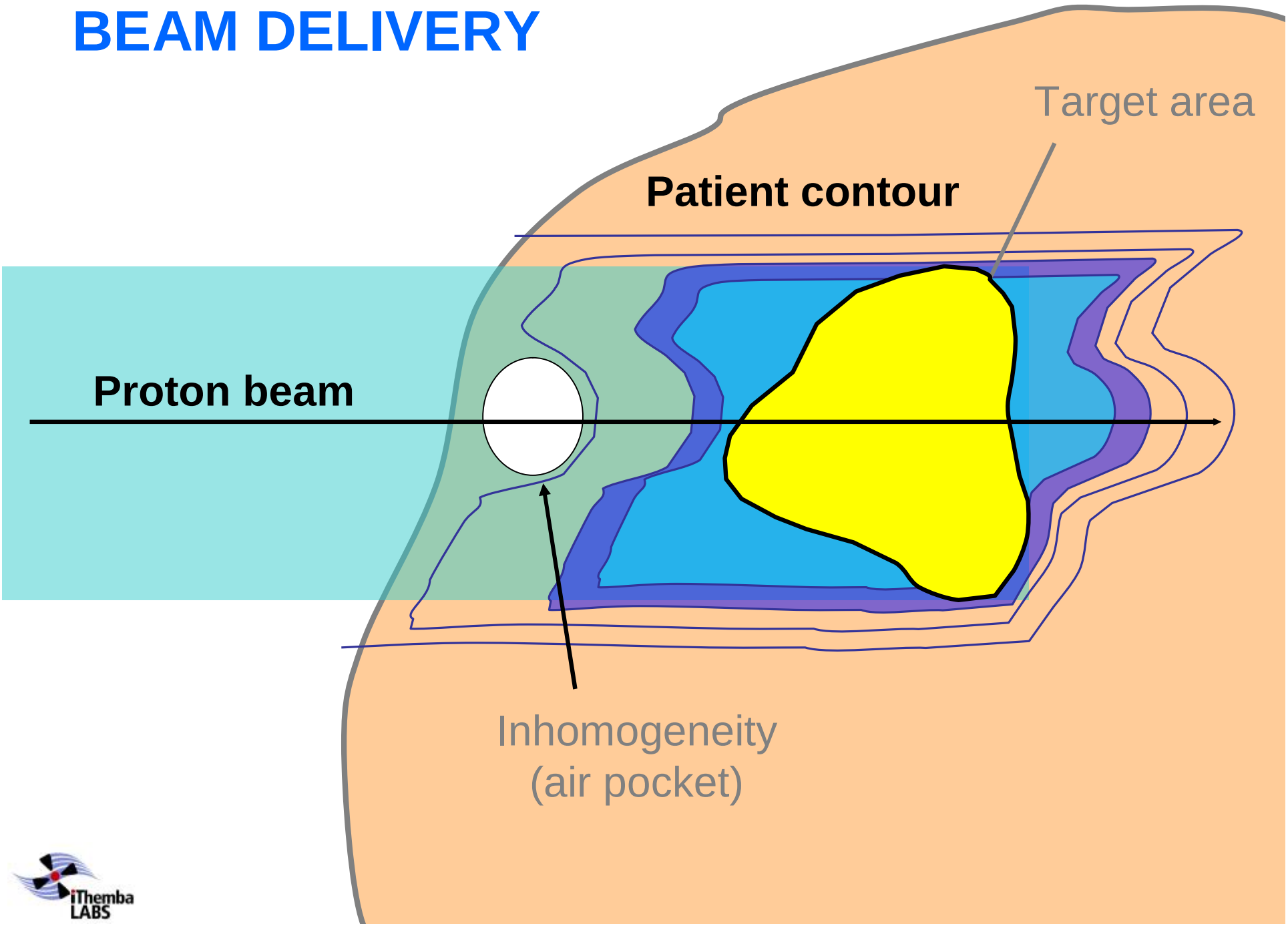
COLLIMATORS

POSITIONING VERIFICATION

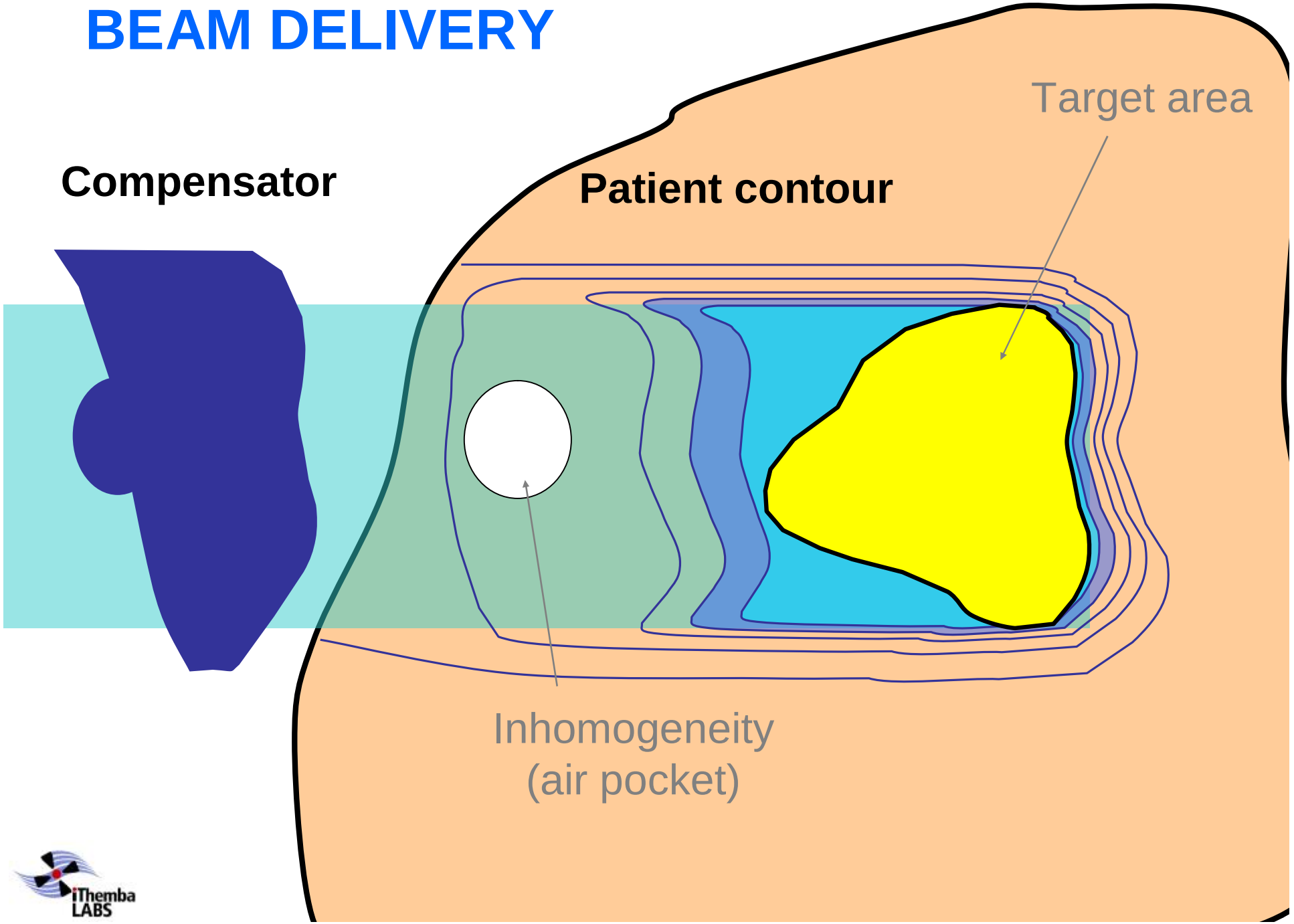




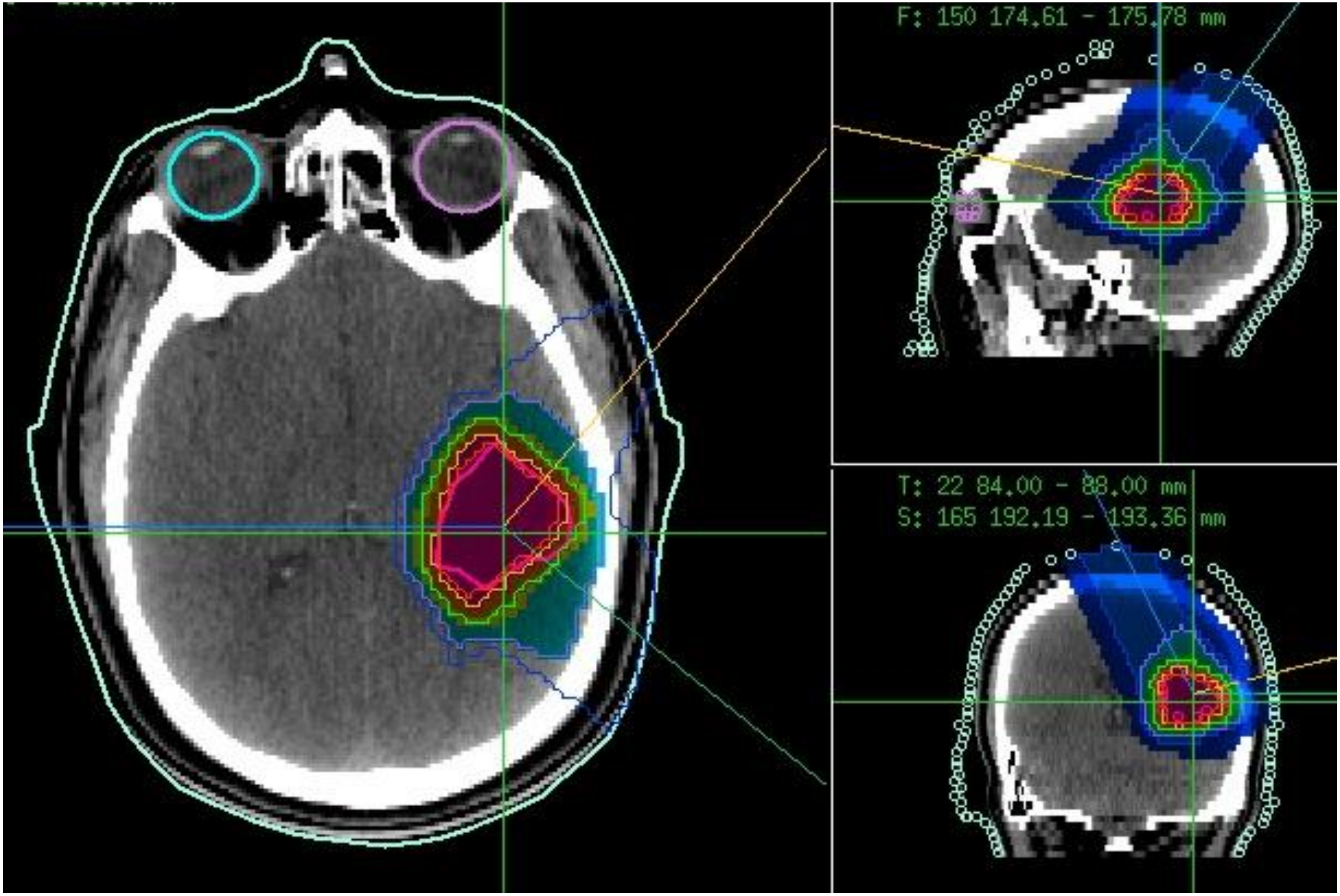
BEAM DELIVERY



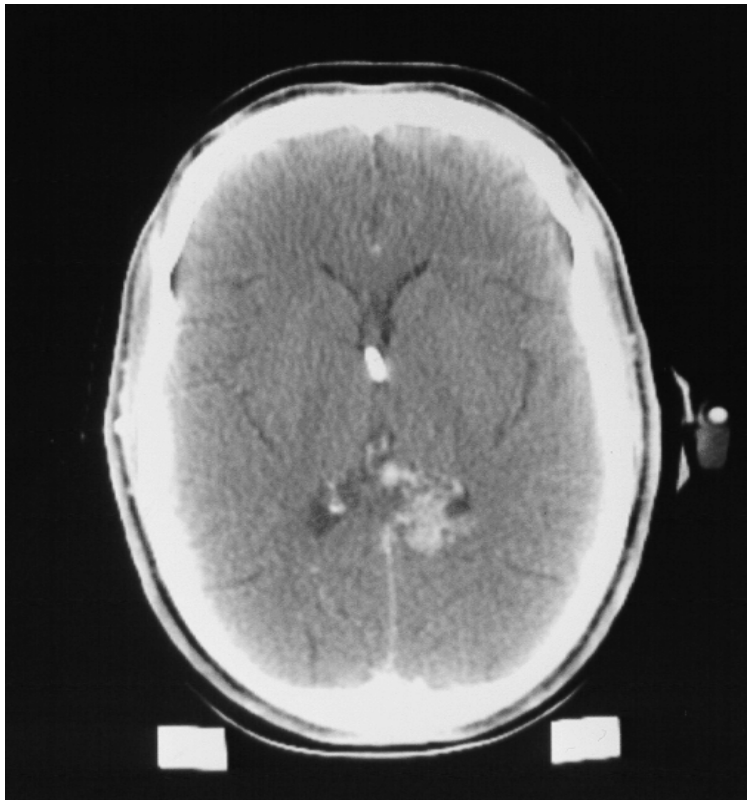
BEAM DELIVERY

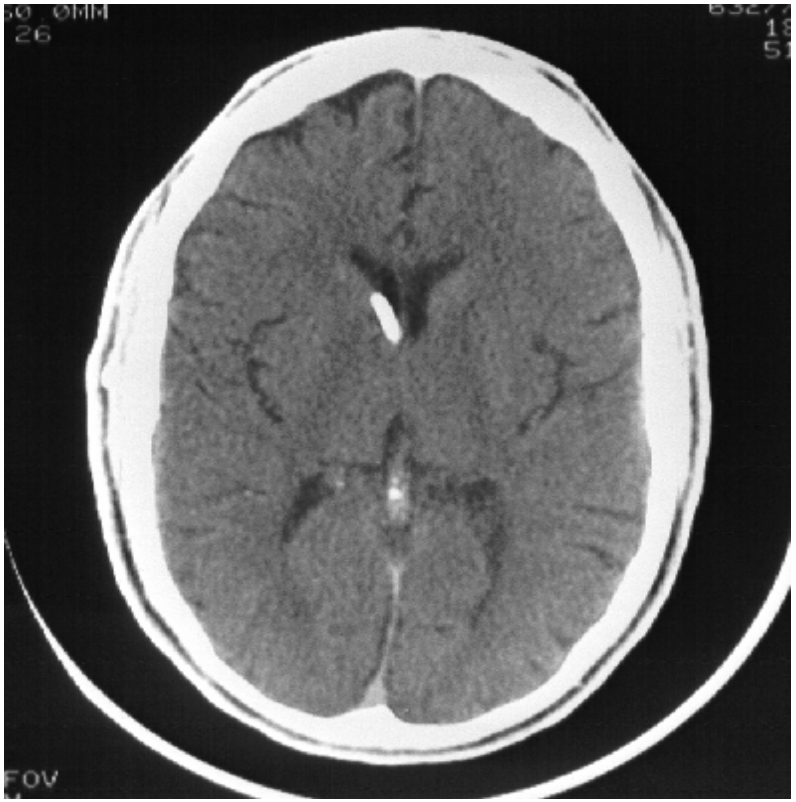


4-BEAM PROTON PLAN FOR AVM



ARTERIOVENOUS MALFORMATION

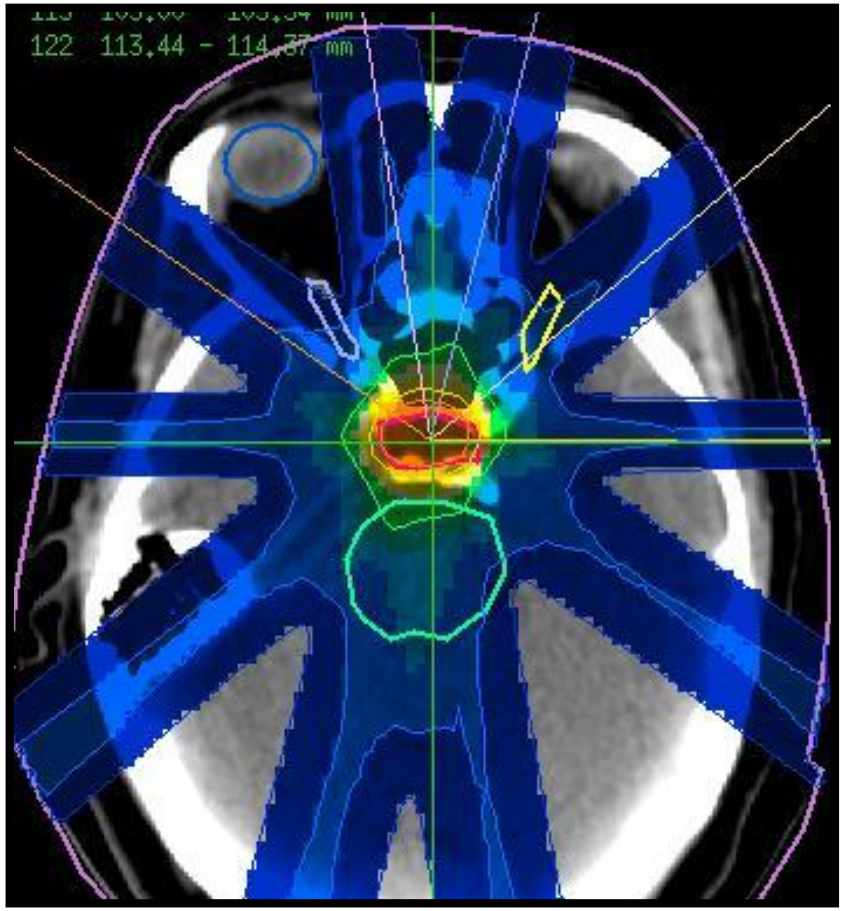


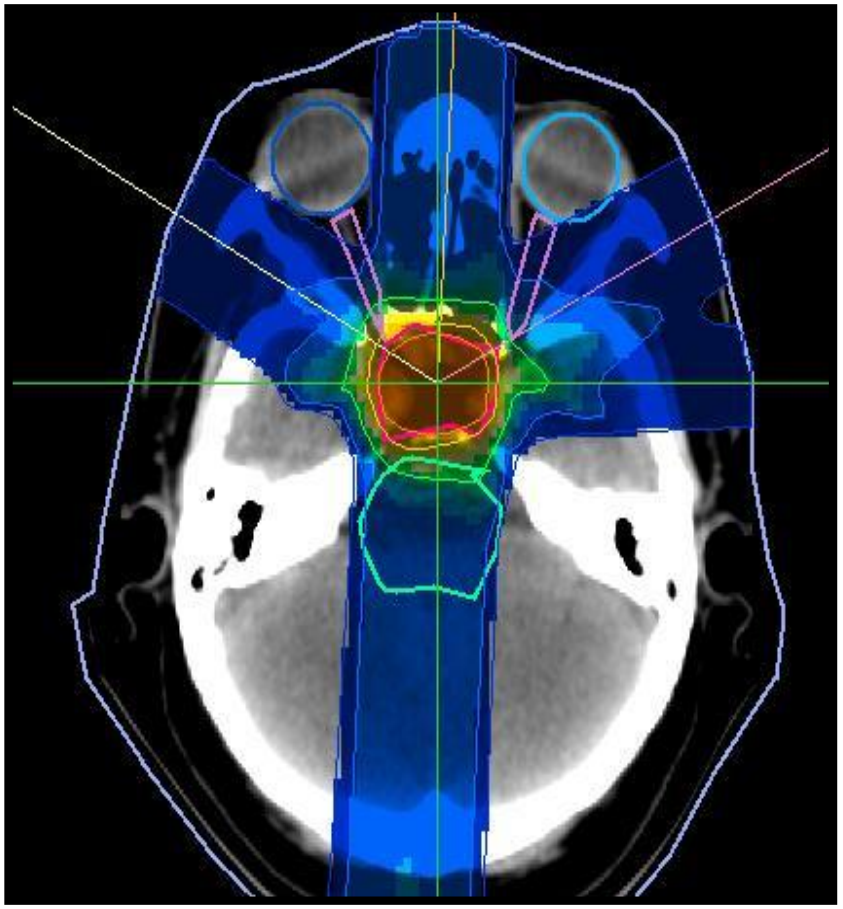


Before treatment

After treatment

PROTON PLANS: PITUITARY TUMOR

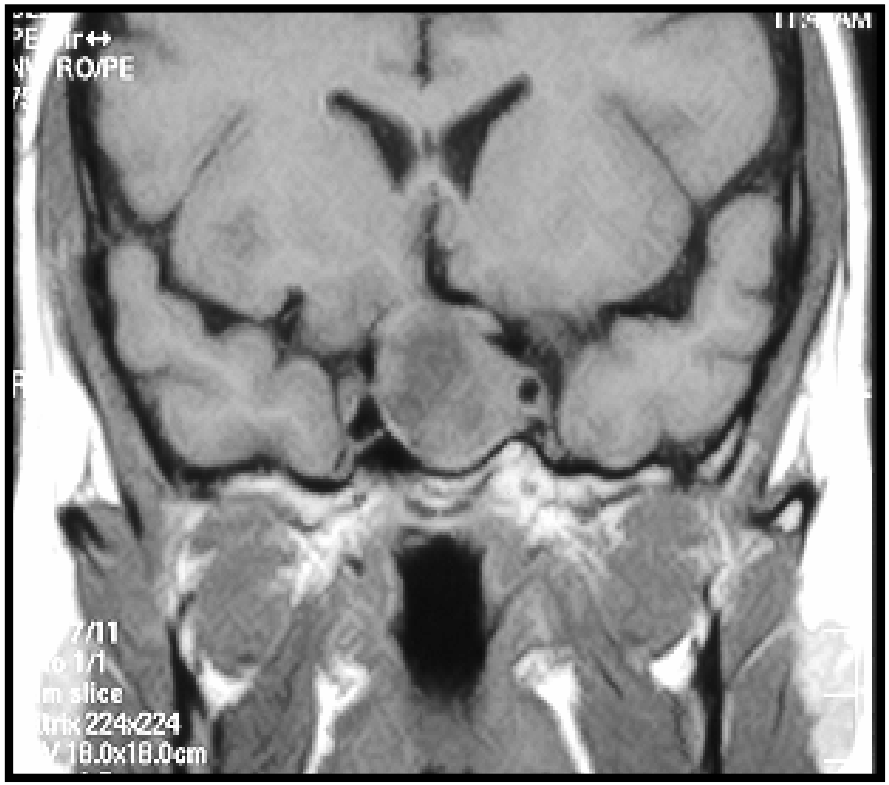


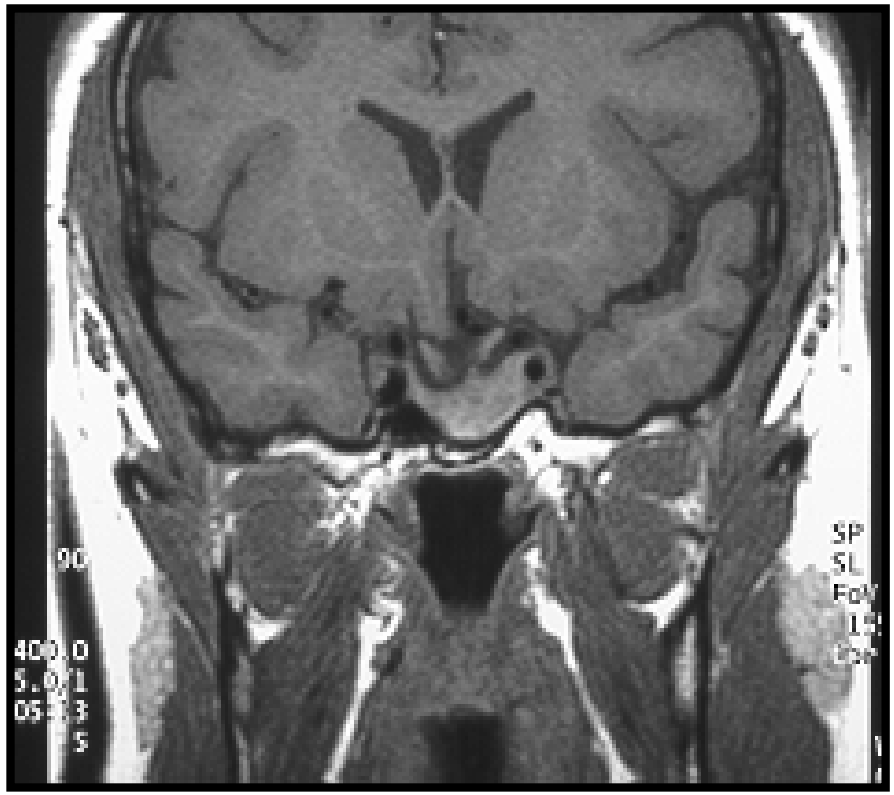


Plateau irradiations

COMBINATION
Plateau and SOBP beams

PITUITARY ADENOMA

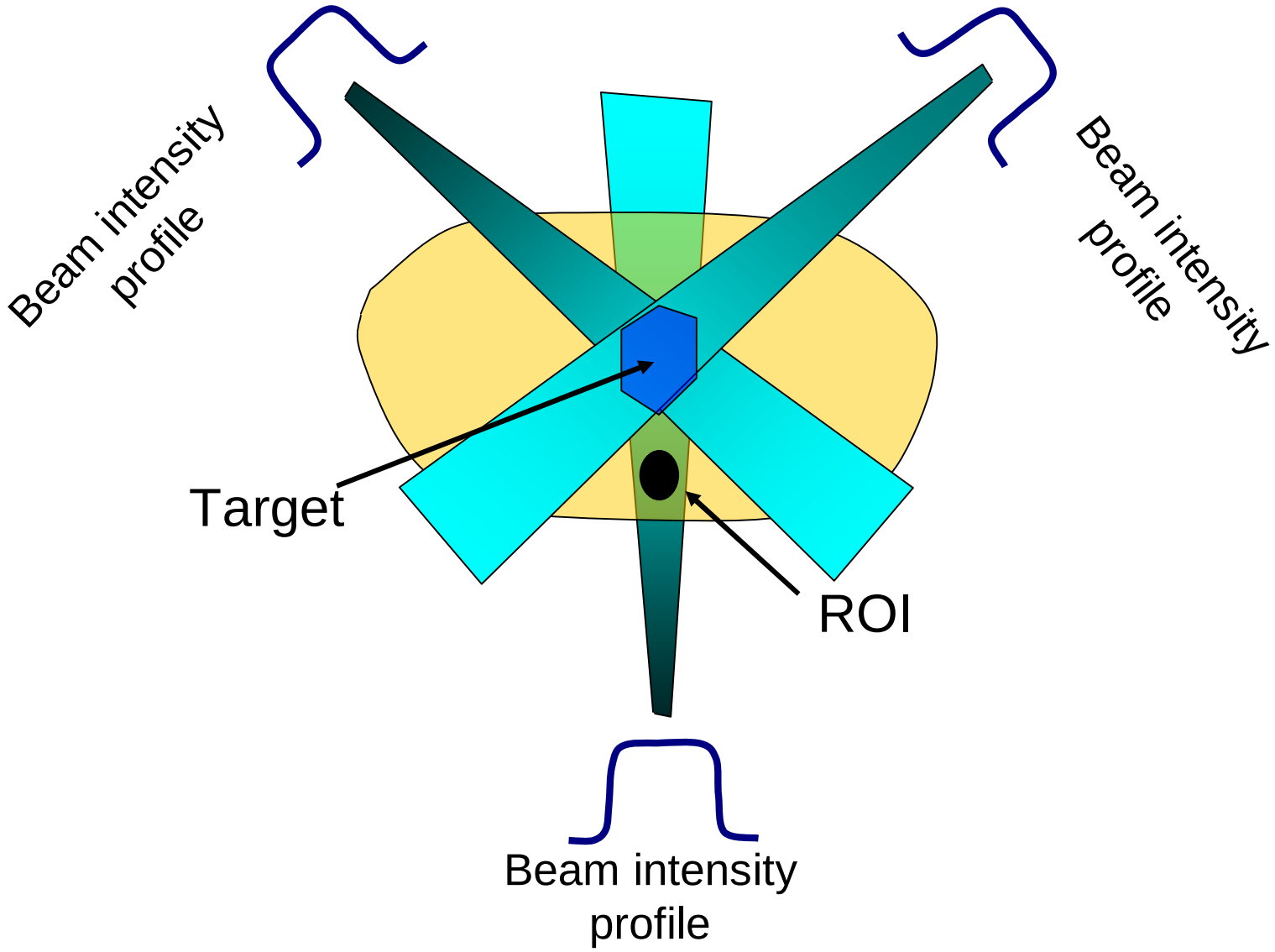




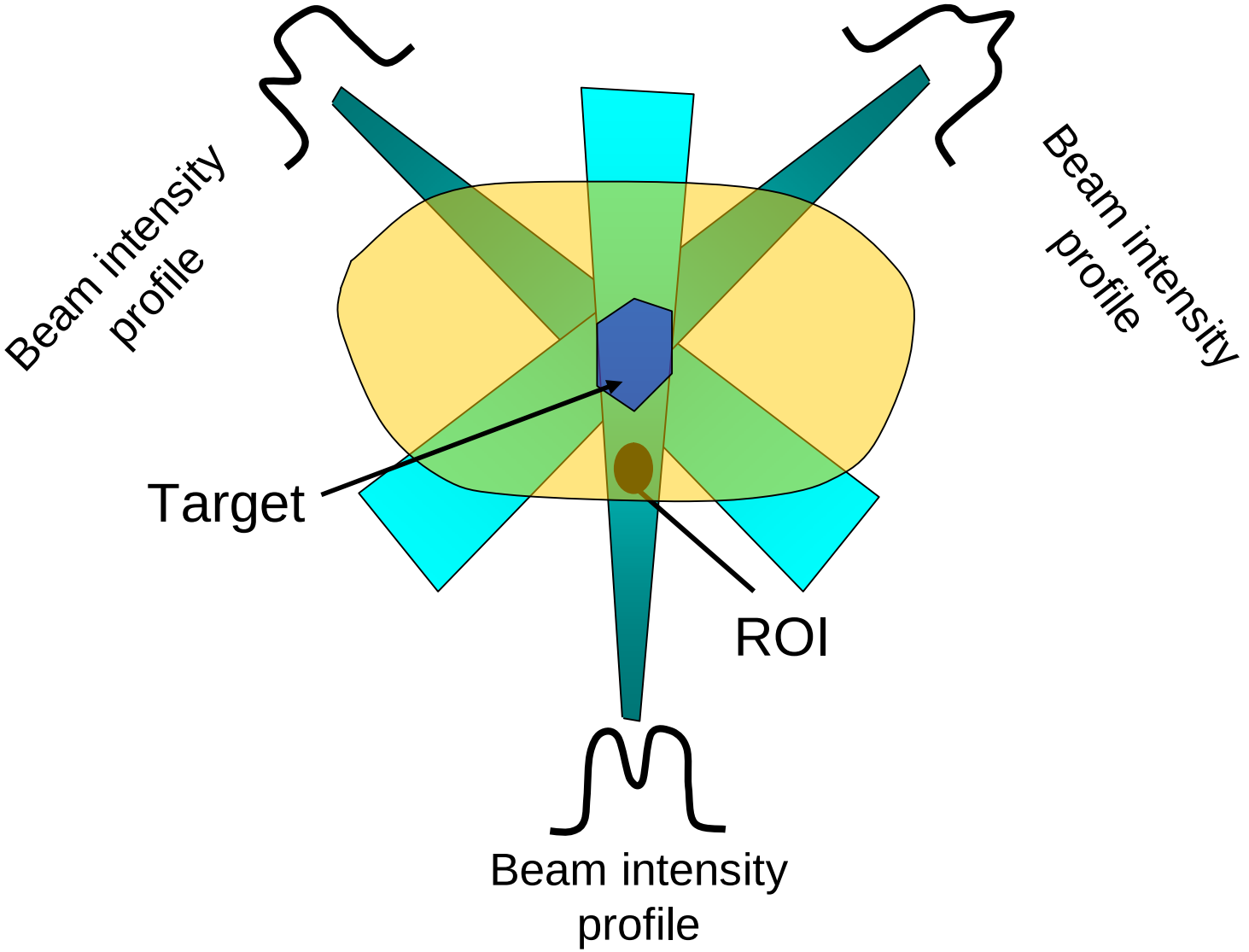
Before treatment

After treatment

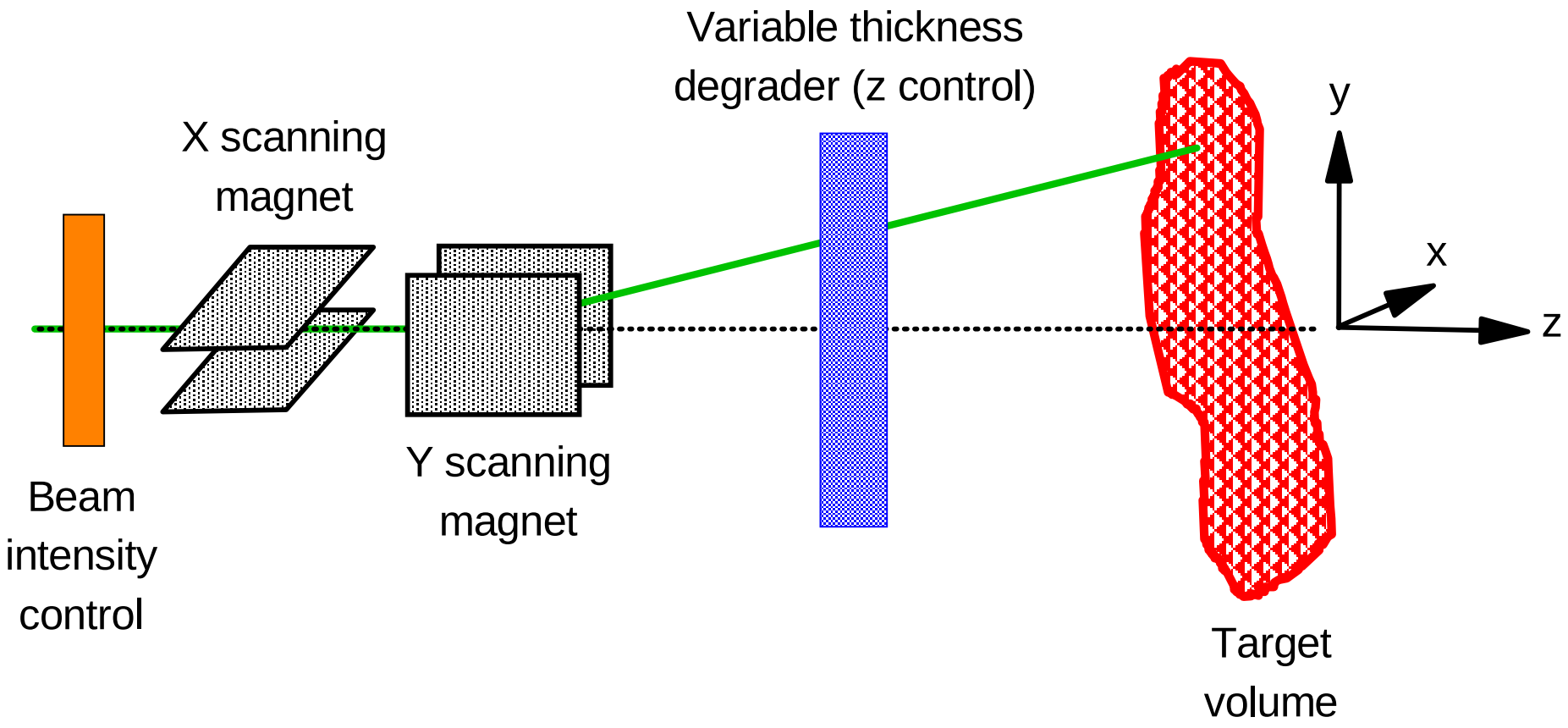
CLASSICAL RADIOTHERAPY



INTENSITY MODULATION



BEAM SCANNING



BEAM SCANNING RATIONALES

Used for beam spreading and intensity modulation

- Conforms dose accurately to lesion
- Competitive with modern x-ray therapy (IMRT)
- No loss of range
- Minimal loss of particles
- Less activation of components
- Small effective source size
  - smaller penumbrae
- Reduction of non-target dose
  - lower in-beam integral dose
  - less background radiation
    - essential for children and pregnant women

BEAM SCANNING TECHNIQUES

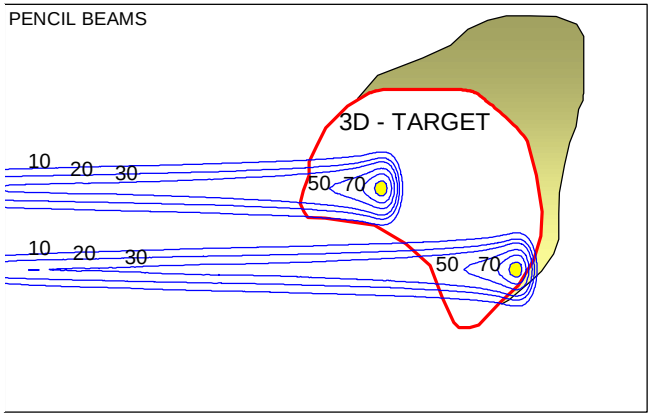
- Lateral beam spreading
  - 2-dimensional
    - circular (wobbling)
  - Linear
    - continuous (raster)
    - discrete (spot)
    - hybrid
    - 1-dimensional + mechanical motion (patient or magnet)
- Depth variation
  - interpose degraders (Cyclotrons)
  - change accelerator energy (Synchrotrons)
- Allowance for organ motion
  - multiple scans
  - closer “spots”
  - beam gating

BEAM SCANNING IMPLICATIONS

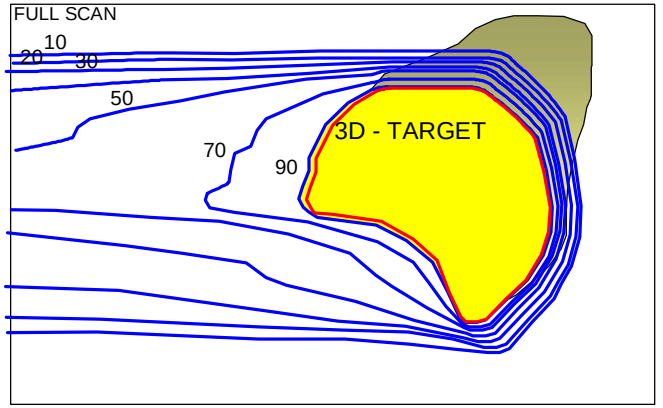
- No field- or patient-specific devices required
- No field-specific calibrations
- Flexible dose delivery patterns (computer-generated)
  - less staff
  - more patients
- Intensity modulated therapy
  - inverse planning optimization
  - fewer fields per treatment than IMXT **Ü** lower non-target dose
  - better clinical results
- Difficulties
  - complex technology **Ü** less reliable?
  - more stable beams required
  - dosimetry more difficult
  - patient positioning more important
  - organ and patient motion more critical
  - *not for small fields*

BEAM DELIVERY

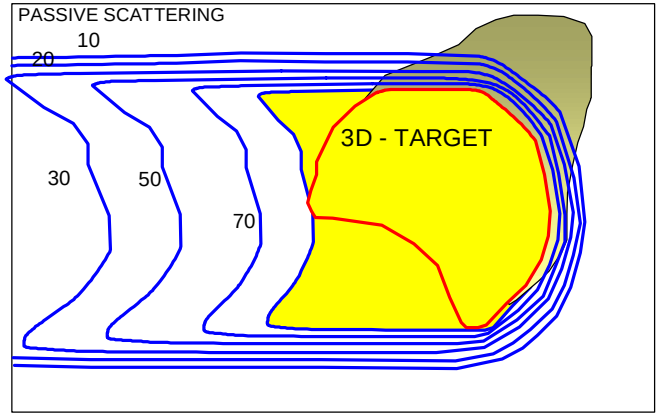
(Courtesy PSI)



BEAM SCANNING

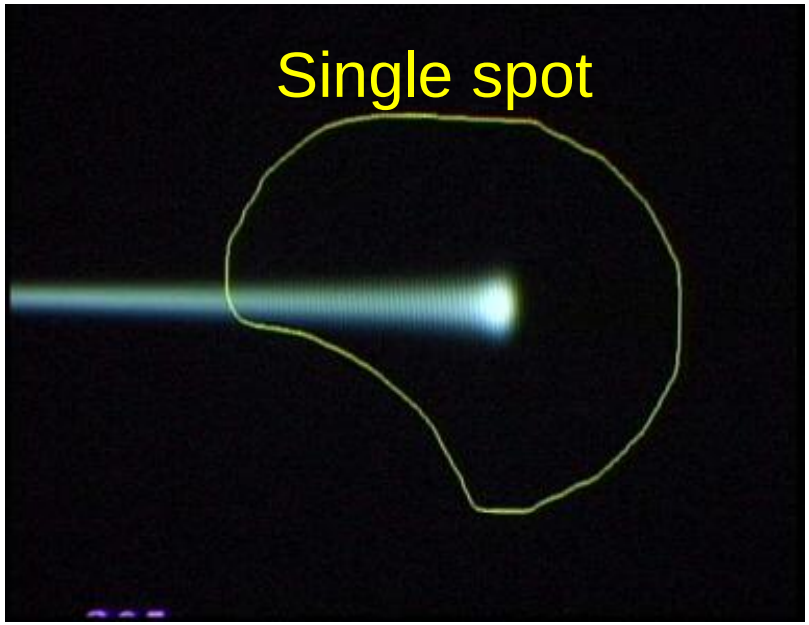


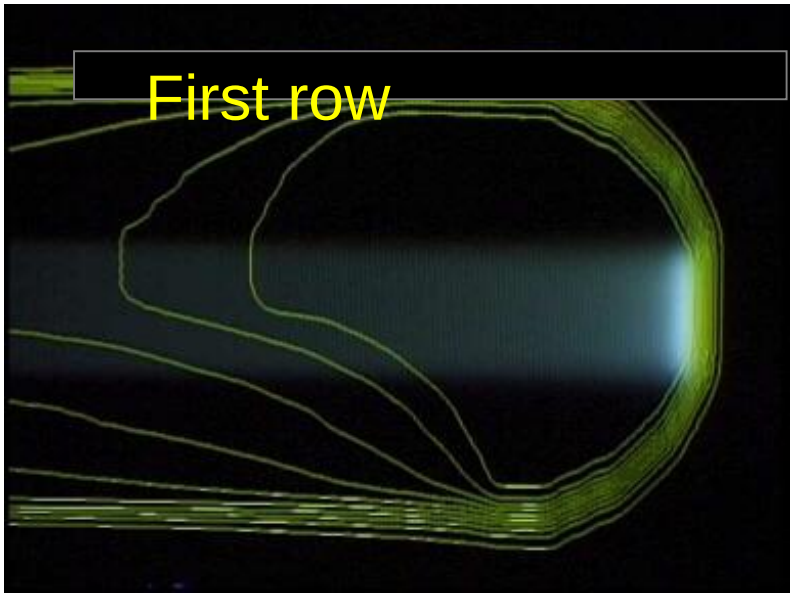
PASSIVE SCATTERING

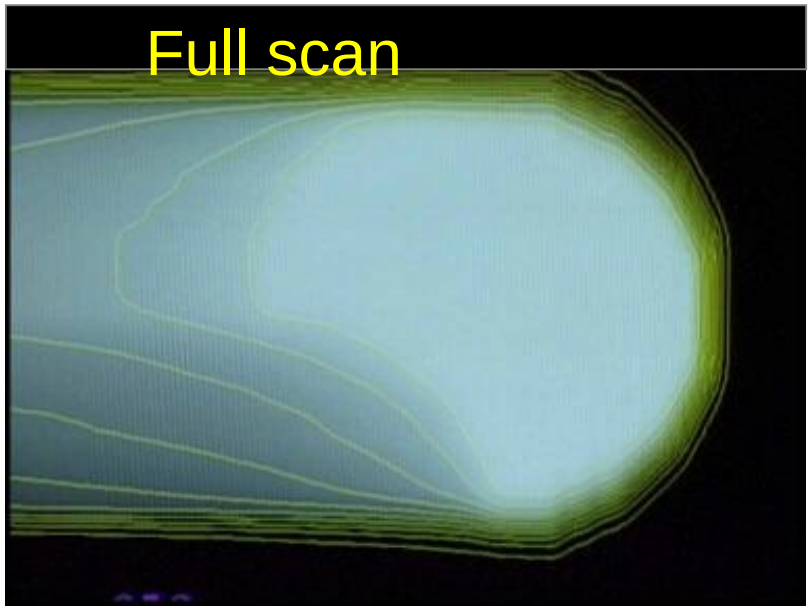


BEAM SCANNING

(Courtesy PSI)

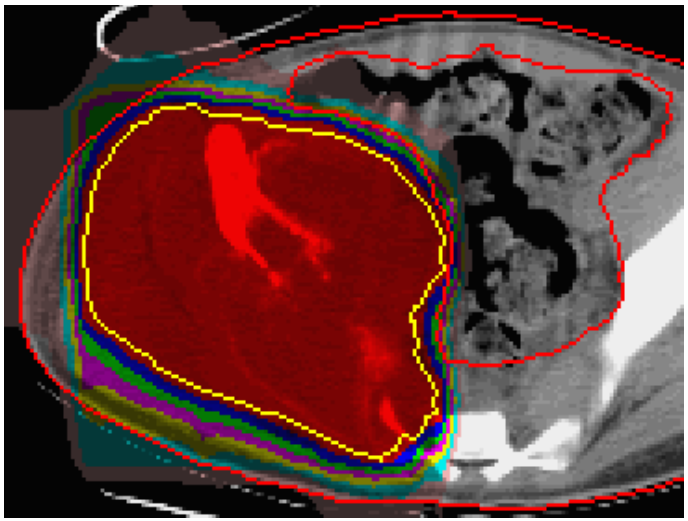


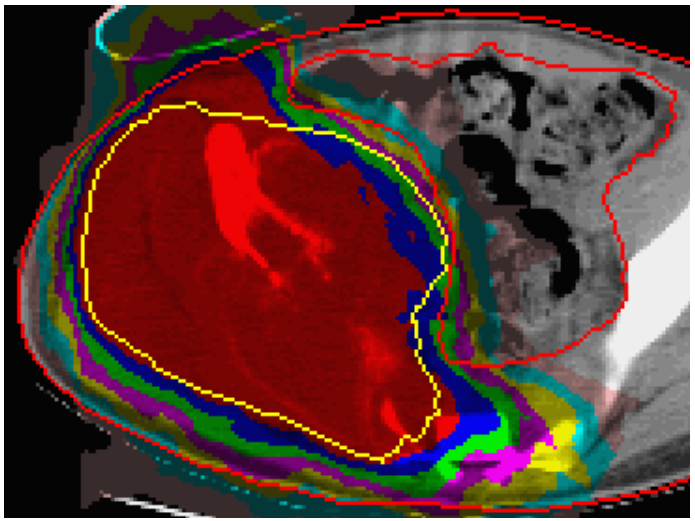


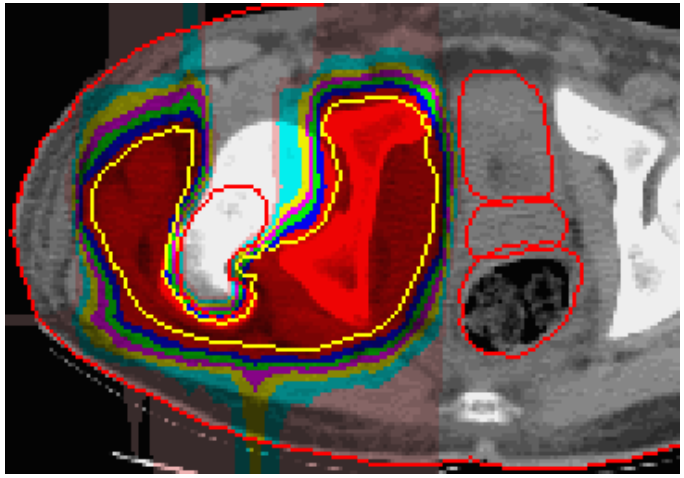


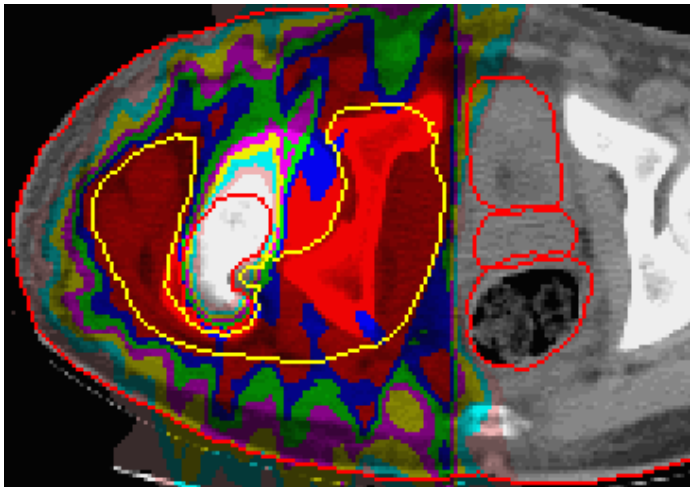
EWINGS SARCOMA

Reduced dose to intestine, femoral head and rectum



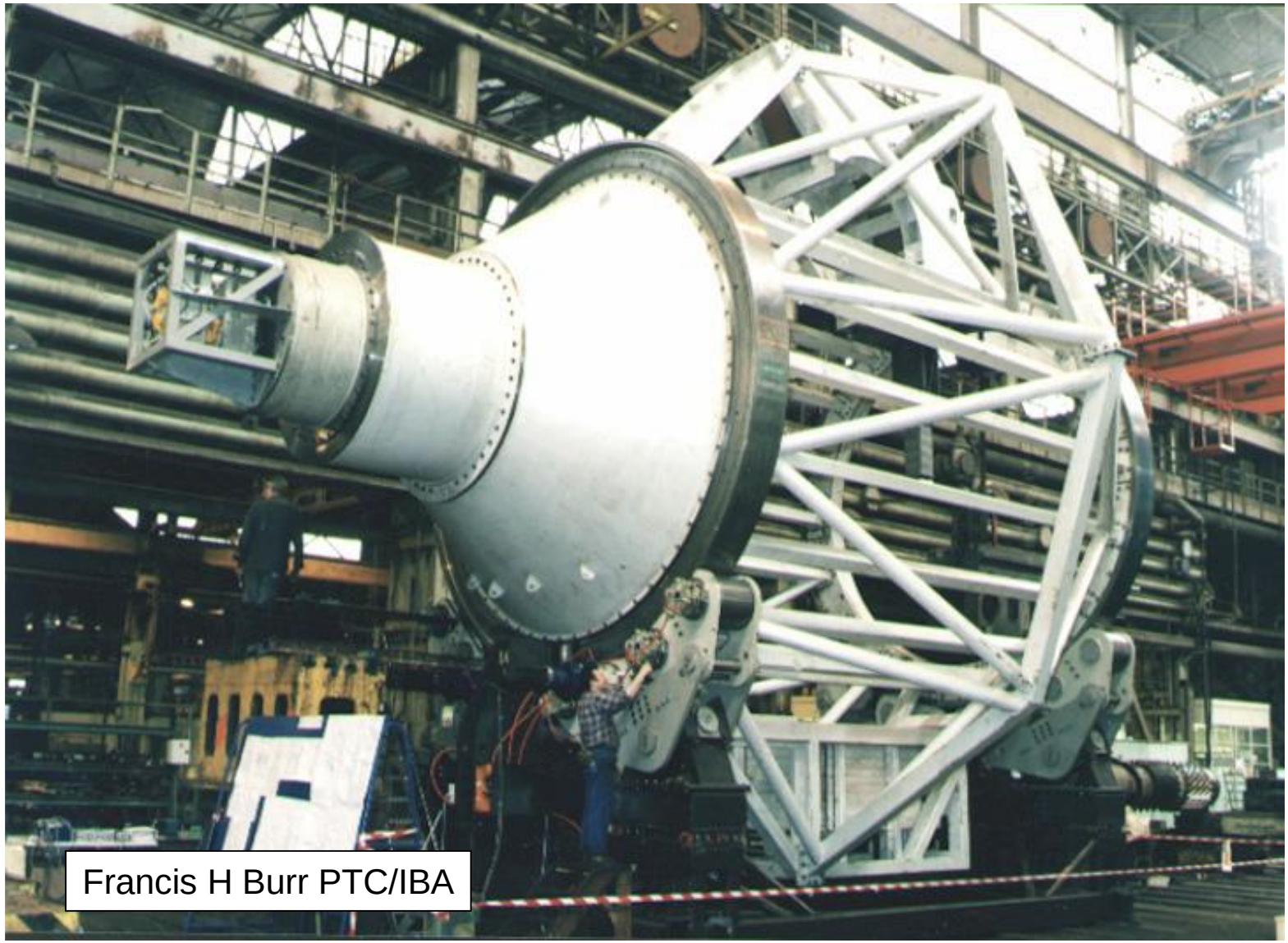






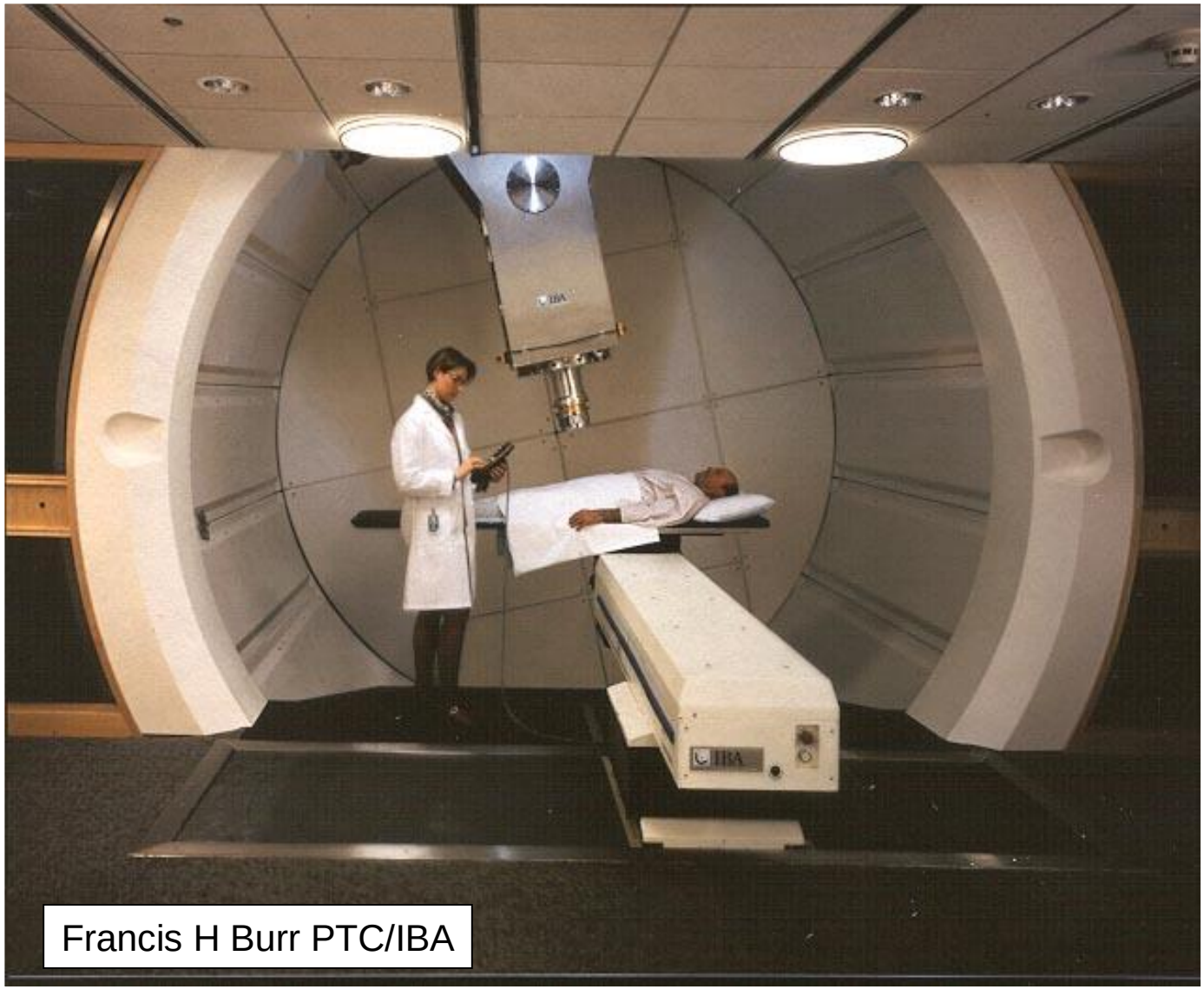
IMPT (3 fields) *(Courtesy PSI)* **IMXT (9 fields)**

ISOCENTRIC GANTRY

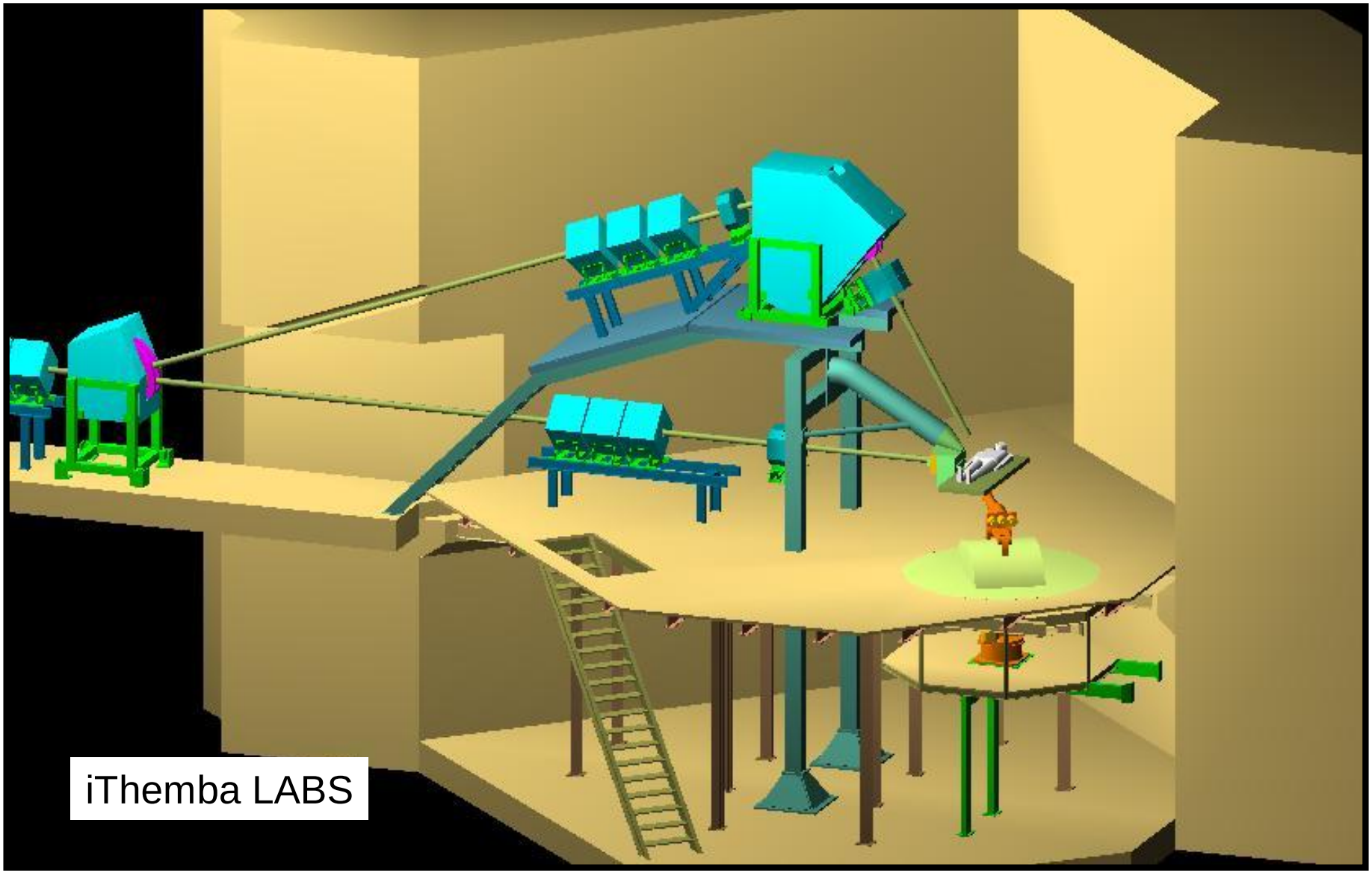


Francis H Burr PTC/IBA

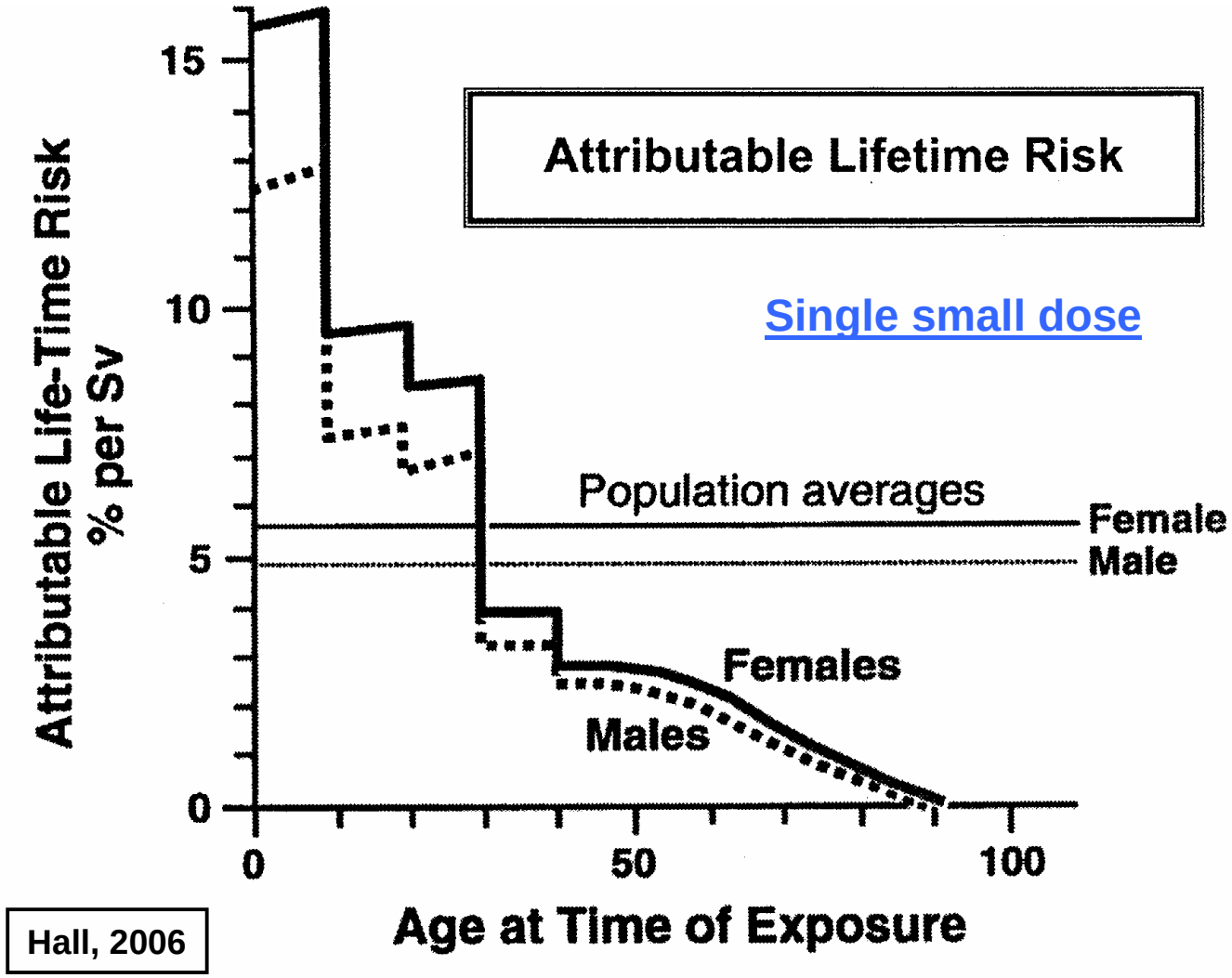
ISOCENTRIC GANTRY



FIXED BEAM CONFIGURATION

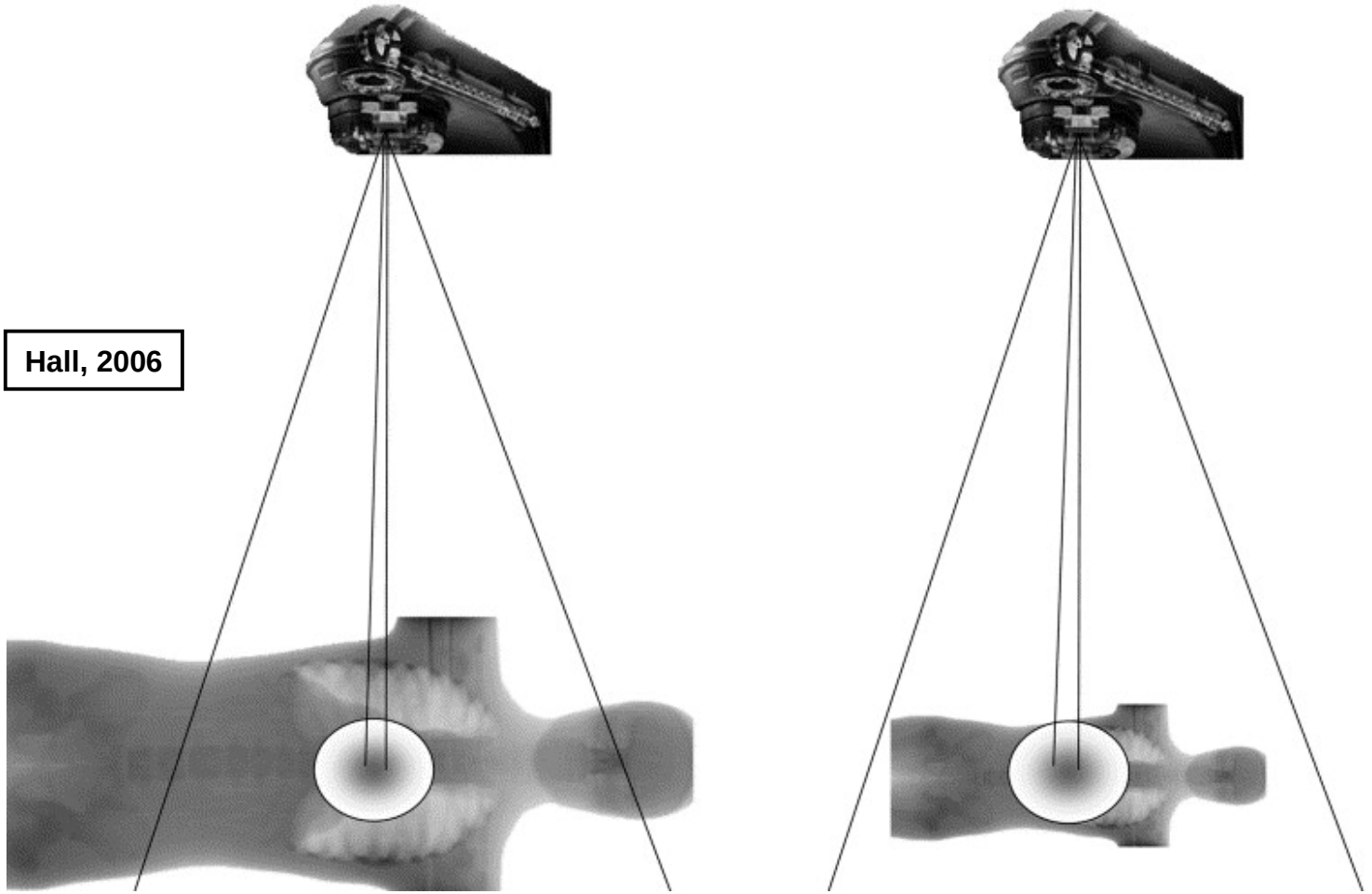


LIFETIME RISK OF CANCER INDUCTION



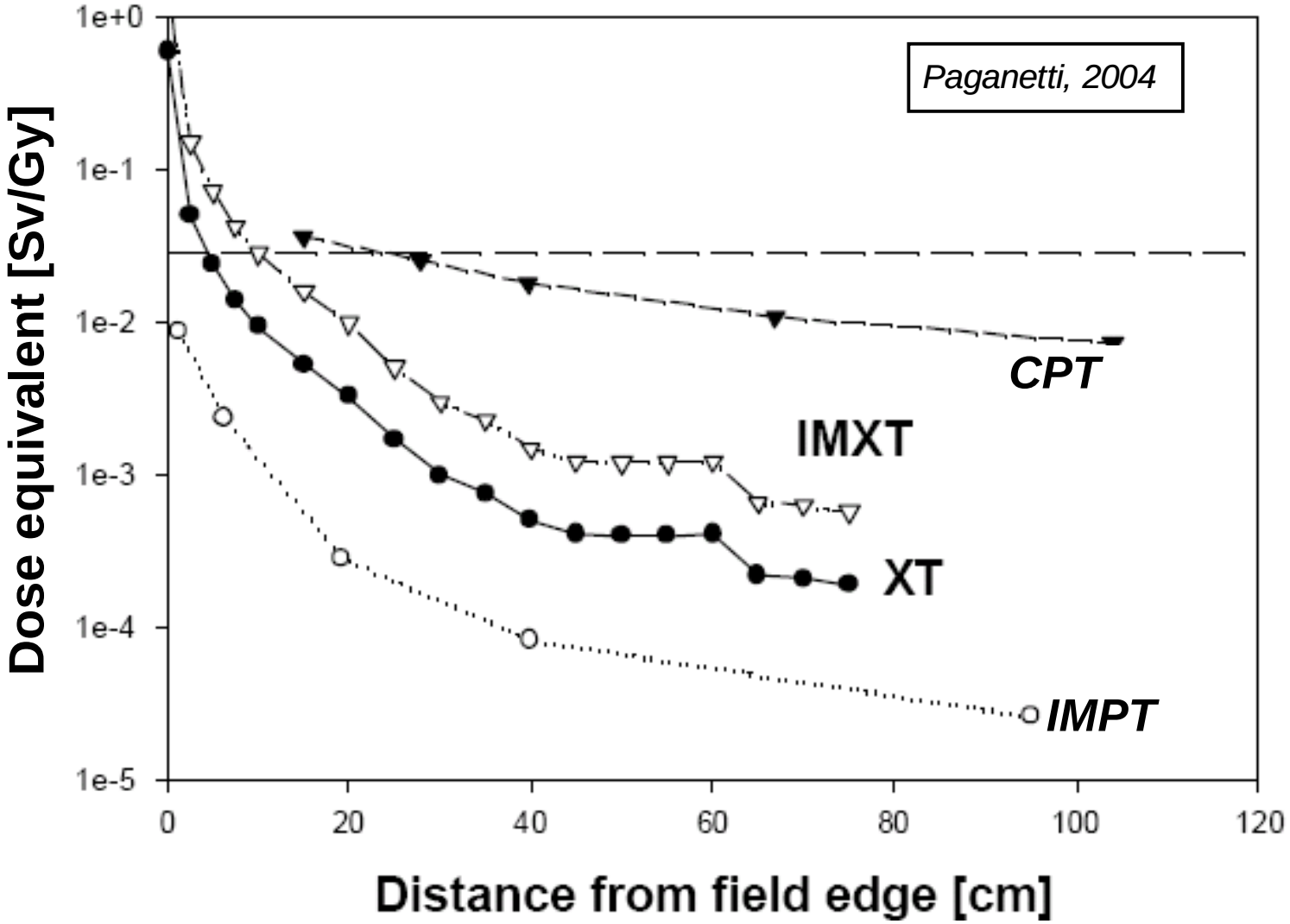
IRRADIATION OF CHILD

Same Leakage for Adult RT vs. Pediatric RT — But in Pediatric RT Scatter from the Treatment Volume Is More Significant



Hall, 2006

DOSE EQUIVALENT OUTSIDE FIELD



SECONDARY CANCER INDUCTION

- Low doses (outside primary field) can induce secondary cancer in long term
- Young people are most sensitive
- Scanned proton beams provide the lowest peripheral doses of all modalities
  - greater proportion of child's body receives background dose
  - most favorable for treating children and pregnant women (fetus is most susceptible)
- Children have long life expectancy
  - secondary cancer can result in severe deterioration in quality of life and expensive long-term chronic health care

PROTON THERAPY FACILITIES [≤ 90 MeV] (7/9)

LOCATION	COUNTRY	ACCEL-ERATOR	MAX. CLINICAL ENERGY MeV	RANGE IN WATER g cm^{-2}	BEAM DIRECTION	FIRST TREATMENT	PATIENTS TREATED (Feb 2007)
Davis CA[1]	**USA**	C	60	3.1	Horizontal	1994	632
Clatterbridge[2]	**UK**	C	62	3.3	Horizontal	1989	1 584
Nice[3]	**France**	C	65	3.6	Horizontal	1991	3 129
Chiba[4]	**Japan**	C	70	4.1	Vertical	1979-2002	145
Catania[5]	**Italy**	C	70	4.1	Horizontal	2002	114
Villigen[6]	**Switzerland**	C	72	4.3	Horizontal	1984	4 604
Vancouver[7]	**Canada**	C	72	4.3	Horizontal	1995	111
Berlin[8]	**Germany**	C	72	4.3	Horizontal	1998	829
Louvain-la-Neuve[9]	**Belgium**	C	90	6.4	Horizontal	1991-1993	21
							11 169

C cyclotron

[1]Crocker Nuclear Laboratory (CNL)
[2]Clatterbridge Centre for Oncology (CCO)
[3]Centre Antoine-Lacassagne (CAL)
[4]National Institute of Radiological Sciences (NIRS)
[5]Centro di Adro Terapia e Applicazioni Nucleari Avanzate (CATANA)
[6]Paul Scherrer Institute (PSI)
[7]Tri-University Meson Factory (TRIUMF)
[8]Hahn-Meitner-Institut (HMI)
[9]Université Catholique de Louvain (UCL)

PROTON THERAPY FACILITIES [160 MeV - 200 MeV] (7/11)

LOCATION	COUNTRY	ACCEL-ERATOR	MAX. CLINICAL ENERGY MeV	RANGE IN WATER g cm^{-2}	BEAM DIRECTION	FIRST TREATMENT	PATIENTS TREATED (Feb 2007)
Cambridge, MA[1]	**USA**	SC	160	17.7	Horizontal	1961-2002	9 116
Uppsala (1)[2]	**Sweden**	SC	185	22.8	Horizontal	1957-1976	73
Uppsala (2)[2]	**Sweden**	SC	200	26.0	Horizontal	1989	520
Moscow[3]	**Russia**	S	200	26.0	Horizontal	1969	3 858
Somerset West[4]	**South Africa**	C	200	26.0	Horizontal	1993	486
Bloomington, IN (1)[5]	**USA**	C	200	26.0	Horizontal	1993-1999	34
Bloomington, IN (2)[5]	**USA**	C	200	26.0	Iso(2), Horiz	2004	220
Orsay (1)[6]	**France**	SC	200	26.0	Horizontal	1991	3 766
Dubna (1)[7]	**Russia**	SC↓	200	26.0	Horizontal	1967-1996	124
Dubna (2)[7]	**Russia**	SC↓	200	26.0	Horizontal	1999	318
Wakasa Wan[8]	**Japan**	S	200	26.0	Vert, Horiz	2002	33
C cyclotron	**SC synchrocyclotron**		**S synchrotron**		**↓ degraded beam**		**18 548**

[1]Harvard Cyclotron Laboratory (HCL)
[2]The Svedberg Laboratory (TSL)
[3]Institute for Theoretical and Experimental Physics (ITEP)
[4]iThemba Laboratory for Accelerator Based Sciences (TLABS)
[5]Midwest Proton Radiotherapy Institute (MPRI)
[6]Centre de Protonthérapie de l'Institut Curie (CPIC)
[7] Institute for Nuclear Research (JINR)
[8]Wakasa Wan Energy Research Center (WERC)

PROTON THERAPY FACILITIES [230-235 MeV] (7/8)

LOCATION	COUNTRY	ACCEL-ERATOR	MAX. CLINICAL ENERGY MeV	RANGE IN WATER g cm^{-2}	BEAM DIRECTION	FIRST TREATMENT	PATIENTS TREATED (Feb 2007)
Villigen (1)[1]	**Switzerland**	C↓▪	230	32.9	Isocentric (1)	1996-2006	262
Nishi-Harima[2]	**Japan**	S	230	32.9	Is (2), Ve, Ho, 45º	2001	1 099
Jacksonville, FL[3]	**USA**	C	230	32.9	Iso (3), Horiz	2006	15
Kashiwa[4]	**Japan**	C	235	34.2	Iso (2), Horiz	1998	462
Boston, MA[5]	**USA**	C	235	34.2	Iso(2), Horiz	2001	2 080
Shizuoka[6]	**Japan**	S	235	34.2	Iso(2), Horiz	2003	410
Wanjie[7]	**China**	C	235	34.2	Iso (1→3) , Horiz	2004	270
Ilsan[8]	**South Korea**	C	235	34.2	Iso (2), Horiz(1)	2007	
							4 598

C cyclotron S synchrotron ↓ degraded beam ▪ scanned beam

[1]Paul Scherrer Institute (PSI)
[2]Hyogo Ion Beam Medical Center (HIBMC)
[3]University of Florida Proton Therapy Institute (UFPTI)
[4]National Cancer Center (NCC – Japan)
[5]Francis H Burr Proton Therapy Center (FHBPTC)
[6]Shizuoka Cancer Center (SCC)
[7]Wanjie Proton Therapy Center (WPTC)
[8]National Cancer Center (NCC – South Korea))

PROTON THERAPY FACILITIES [≥ 250 MeV] (5/7)

LOCATION	COUNTRY	ACCEL-ERATOR	MAX. CLINICAL ENERGY MeV	RANGE IN WATER g cm^{-2}	BEAM DIRECTION	FIRST TREATMENT	PATIENTS TREATED (Feb 2007)
Tsukuba (1)[1]	**Japan**	S↓	250	37.9	Vert, Horiz	1983-2000	700
Houston, TX[2]	**USA**	S	250	37.9	Iso (3), Horiz	2006	114
Villigen (2)[3]	**Switzerland**	sC▪	250	37.9	Iso (2), Horiz	2007	
Loma Linda, CA[4]	**USA**	S	270	43.2	Iso(3), Horiz	1990	11 414
Tsukuba (2)[1]	**Japan**	S	270	43.2	Isocentric (2)	2001	930
Berkeley CA[5]	**USA**	SC	340	63.3	Horizontal	1954-1957	30
St. Petersburg[6]	**Russia**	C	1 000	325.4	Horizontal	1975	1 320
							14 508

C cyclotron S synchrotron sC superconducting cyclotron SC synchrocyclotron

↓ degraded beam ▪ scanned beam

[1]Proton Medical Research Center (PMRC)
[2]M D Anderson Cancer Center (MDACC)
[3]Paul Scherrer Institute (PSI)
[4]Loma Linda University Medical Center (LLUMC)
[5]Lawrence Berkeley National Laboratory (LBNL)
[6]Petersburg Nuclear Physics Institute (PNPI)

PROTON THERAPY FACILITIES [≥ 230 MeV]

Under construction/funded (7)

LOCATION	COUNTRY	ACCEL-ERATOR	MAX. CLINICAL ENERGY MeV	RANGE IN WATER g cm^{-2}	BEAM DIRECTION	FIRST TREATMENT
Essen[1]	**Germany**	C	230	32.9	Iso (3), Horiz	2009 ?
Philadelphia, PA[2]	**USA**	C	230	32.9	Iso (4) , Horiz	2009 ?
Orsay (2)[3]	**France**	C	230	32.9	Iso, Horiz (4)	2010 ?
Oklahoma City, OK[4]	**USA**	C▪	230	32.9	Iso(1), Horiz (1), Dual fixed (2)	2009 ?
Hampton, VA[5]	**USA**	C	230	32.9	Iso (4), Horiz (1)	2010 ?
Beijing[6]	**China**	C	235	34.2	Iso (1) , Horiz	2007 ?
Munich[7]	**Germany**	sC▪	250	37.9	Iso (4), Horiz	2007 ?

C cyclotron sC superconducting cyclotron ▪ scanned beam

[1]Wesdeutsche Protontherapiezentrum (WPZ)
[2]University of Pennsylvania Health System Particle Therapy Center (UPHSPTC)
[3]Centre de Protonthérapie d'Orsay (CPO)
[4]Oklahoma ProCure Treatment Center (OPCTC)
[5]Hampton University Proton Beam Therapy Center (HUPBTC)
[6]Sino-Japanese Friendship Hospital (SJFH)
[7]Rinecker Proton Therapy Center (RPTC)

^{4}He AND HEAVY ION FACILITIES (3/5 + 6)

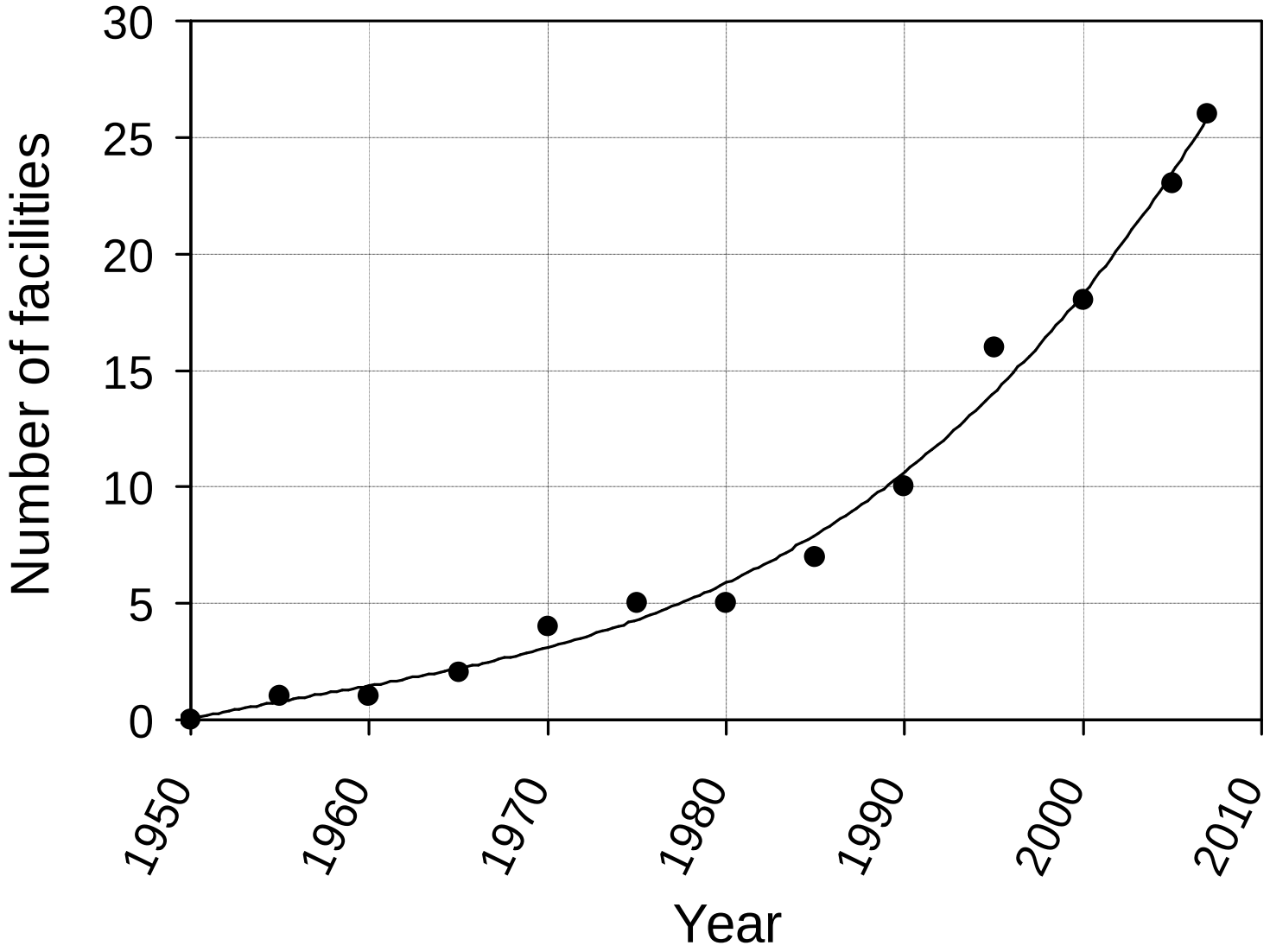
LOCATION	COUNTRY	ACCELERATOR	ION (ENERGY – MeV/u)	FIRST TREATMENT	PATIENTS TREATED (Feb 2007)
Berkeley CA[1]	**USA**	Synchrocyclotron Synchrotron	^{4}He (230)	1957 - 1992	2 054
Berkeley CA[1]	**USA**	Synchrotron	C, Ne, Si, Ar (670)	1975 - 1992	433
Chiba (1)[2]	**Japan**	Synchrotron	C (400)	1994	2 867
Darmstadt[3]■	**Germany**	Synchrotron	C (430)	1997	316
Nishi-Harima[4]	**Japan**	Synchrotron	C (320)	2002	131
Heidelberg[5]	**Germany**	Synchrotron	p, He, C, O (430)	2007	
Maebashi[6]	**Japan**	Synchrotron	p, C (400)	2009	
Pavia[7]	**Italy**	Synchrotron	p, C (430)	2009 ?	
Marburg[8]	**Germany**	Synchrotron	p, C (430)	2010 ?	
Wiener Neustadt[8]	**Austria**	Synchrotron	p, C (420)	2011 ?	
Lanzhou[10] ?	**China**	Synchrotron	p, C (120)	?	
				HI	**3 747**
				He + HI	**5 801**

■**Scanning beam**

Under construction/funded

[1]Lawrence Berkeley National Laboratory (LBNL)
[2]National Institute of Radiological Sciences (NIRS)
[3]Gesellschaf für Schwerionenforschung (GSI)
[4]Hyogo Ion Beam Medical Center (HIBMC)
[5]Heidelberger Ionstrahl-Therapiezentrum (HIT)
[6]Gunma University (GU)
[7]Centro Nazionale di Adroterapia (CNAO)
[8]Particle Therapy Center (PTC)
[9]MedAustron
[10]Institute of Modern Physics (IMP)

PROTON TREATMENT CENTERS



PROTON THERAPY
Assessment (I)

- Nearly 50 000 patients treated to date
- 26 facilities currently operational (7 low-energy)
- 13 new facilities are under construction
- Many new facilities proposed
- Established modality for
  - localized tumors
  - lesions close to critical structures
  - pediatric cases and pregnant women
  - large, irregular lesions
  - treatments for which no other modality can be used
- Proton therapy is the only viable treatment option for a variety of tumors
- No randomized clinical trials likely to be undertaken

PROTON THERAPY
Assessment (II)

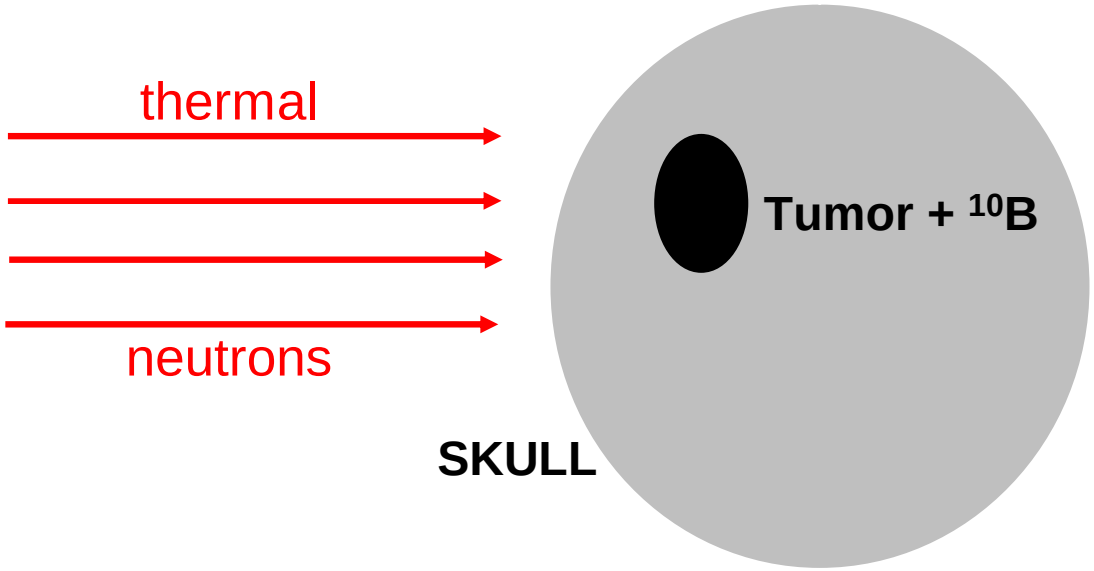
- Reduction in number of treatment fractions
  - † possible because of sparing of normal tissue
  - † reduces per fraction reimbursement
- Scanning beam delivery → IMPT will be universally used
- Economies of scale will bring about some cost reduction
  - † “single-room” facilities
- Accelerators: cyclotrons or synchrotrons
  - † lifetime (40-50 yr) much longer than linear accelerators
  - † one accelerator can serve multiple treatment rooms
- Proton therapy is expanding rapidly all over the world and will become an increasingly significant modality in the foreseeable future

PROTON THERAPY
Assessment (III)

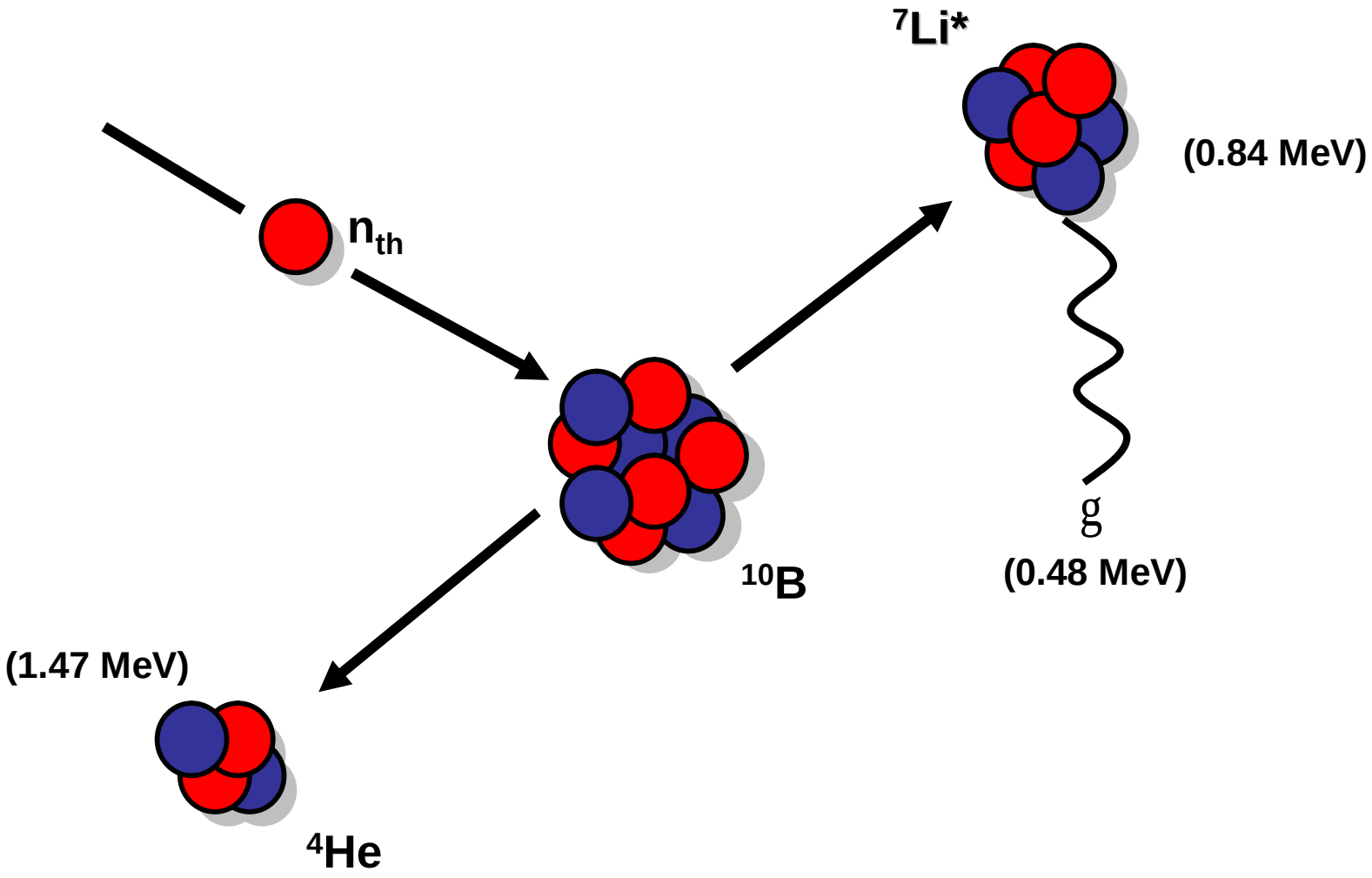
- There are ~ 12 000 x-ray linear accelerators currently operational (8 000 in the USA)
- The accelerators for particle therapy (cyclotrons, synchrotrons) are based on concepts developed 60 – 80 years ago (with many improvements)
- To be competitive with x rays revolutionary new technology is required
  - † compact low-cost accelerators under development
    - ¢ *e.g.*, dielectric wall linear accelerator (100 MeV m^{-1})
      - ´ robot mounted, will fit in x ray linac vault
- Little prospect of very substantial cost reductions with present technology
- More advanced x-ray equipment may be developed
  - † linear accelerators conceived in 1920s

BORON NEUTRON CAPTURE THERAPY

- Selective uptake of ^{10}B in tumor
- Exposure of tumor to thermal neutrons
  - † capture in ^{10}B (σ = 3838 b) produces highly ionizing ^{4}He and ^{7}Li ions, with ranges of the order of cell dimensions
- Used almost exclusively for treatments of glioblastoma multiforme and malignant melanoma with BSH and BPA (compounds developed in 1960s)
- Recent application involves irradiation of explanted livers
- New generation equipment (including accelerators) produces epithermal beams for better dose distributions



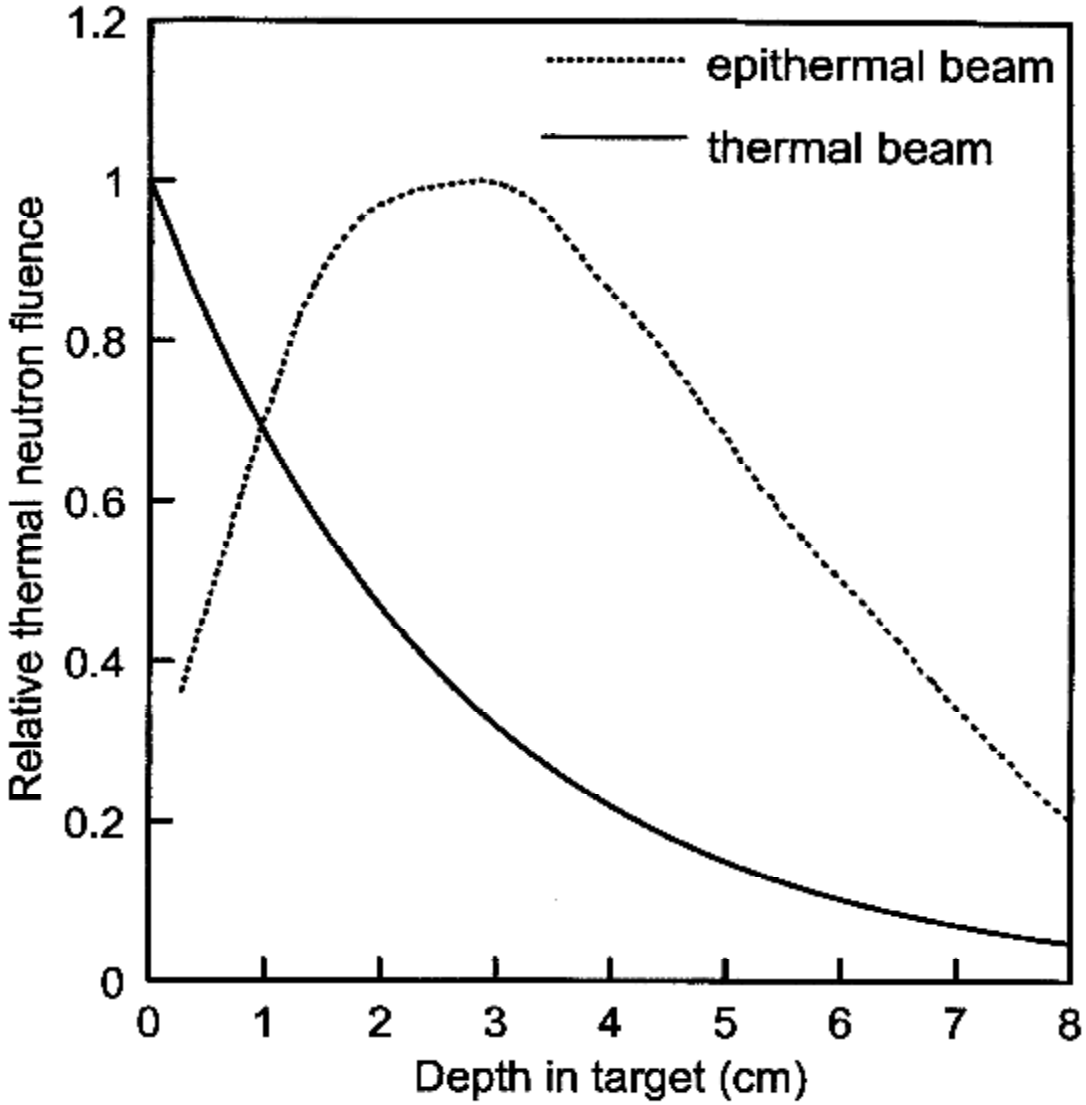
BORON NEUTRON CAPTURE



BORON NEUTRON CAPTURE

- Natural abundance of ^{10}B is 20 %
  - inexpensive to enrich
- n_{th} + ^{10}B cross section = 3 838 b
- Particle ranges in tissue:
  - ^{7}Li (5 µm), ^{4}He (9 µm) (LET ~ 180 keV/µm)
- Requires ^{10}B concentration in tumor:
  - 10^{9} atoms cell^{-1} (30 µg g^{-1} / 30 ppm)
    - not more than 30 % as much in normal tissue
- Competing reactions:
  - $^{1}H + n \rightarrow {}^{2}H + \gamma$ (2.22 MeV) [0.33 b]
  - $^{14}N + n \rightarrow {}^{14}C + p$ (0.63 MeV) [1.81 b]
  - $^{1}H + n \rightarrow {}^{1}H + n$ (fast neutrons)

DEPTH DOSE CURVES (NCT)



BNCT TREATMENTS
Physical aspects

- Most complex radiotherapy modality
- Short range ^{7}Li and ^{4}He ions deposit all energy in cells
- Poor penetration of thermal neutron beams (0.025 eV)
  - † remove section of skull for treatment of brain tumors
  - † improved penetration with epithermal beams (1 eV – 20 keV)
- Dose delivery problems (neutron fluence, ^{10}B concentration, fixed beam directions)
  - † long treatment times (≥ 40 min / fractionation difficult)

BNCT
Clinical aspects

- Glioblastoma multiforme (epithermal/BSH)
  - 1% of cancer diagnoses
  - 2.5% of all cancer deaths
  - 50% of primary brain tumours
  - Incidence increases with age
  - Patients die from uncontrolled local disease
  - Median survival
    - 6 months (untreated)
    - 9 months (photon irradiation)
    - 12 months (BNCT)
- Malignant melanoma (thermal, epithermal/BPA)
- Synovectomy, meningioma, brain metastases, arteriovenous malformation, lung, head and neck ?

NCT PHARMACEUTICALS

- ^{10}B chemistry is well known
  - † readily incorporated in stable chemical structures
- **BSH** Boronosulphydril hydride [$Na_2B_{12}H_{11}SH$]
- **BPA** *p*-boronophenylalanine [*p*-$(HO)_2B$-$C_6HCH_2CH(NH_2)COOH$]
- **GB-10** Polyhedral borane dianion [$Na_2B_{10}H_{10}$]
  - ***DEVELOPED IN EARLY 1960s ! NO OTHERS USED***
  - Many others developed, but not yet suitable for clinical use
    - † consider alternative capture agent, e.g.^{157}Gd
      - ¢ already used in medicine: MRI imaging
      - ¢ need not be deposited directly in cells

BNCT FACILITIES (8/12)[o]

FACILITY	LOCATION	COUNTRY	FIRST TREATMENT	NUMBER OF PATIENTS (June 2007)	
				THERMAL	EPITHERMAL
Brookhaven National Laboratory	Brookhaven, NY	USA	1951-1999	45	53
Massachusetts Institute of Technology	Cambridge, MA	USA	1959	18	25
Hitachi Training Reactor	Kawasaki	Japan	1968-1975	13	
Japan Atomic Energy Research Institute	Tokai	Japan	1969	47	>10
Kyoto University Research Reactor Institute	Osaka	Japan	1975	>60	>50
Musashi Institute of Technology	Kawasaki	Japan	1977-1989	>100	
Joint Research Centre	Petten	Netherlands	1997		30
Technical Research Centre of Finland	Espoo	Finland	1999		>100
Nuclear Research Institute	Řež	Czech Republic	2000		5
Nuclear Research Laboratory	Studsvik	Sweden	2001-2006		>40
Applied Nuclear Energy Laboratory	Pavia	Italy	2002		2
Centro Atómico	Bariloche	Argentina	2003		3
				>283	**>318**
				± 600	

[o]R L Moss (Private Communication)

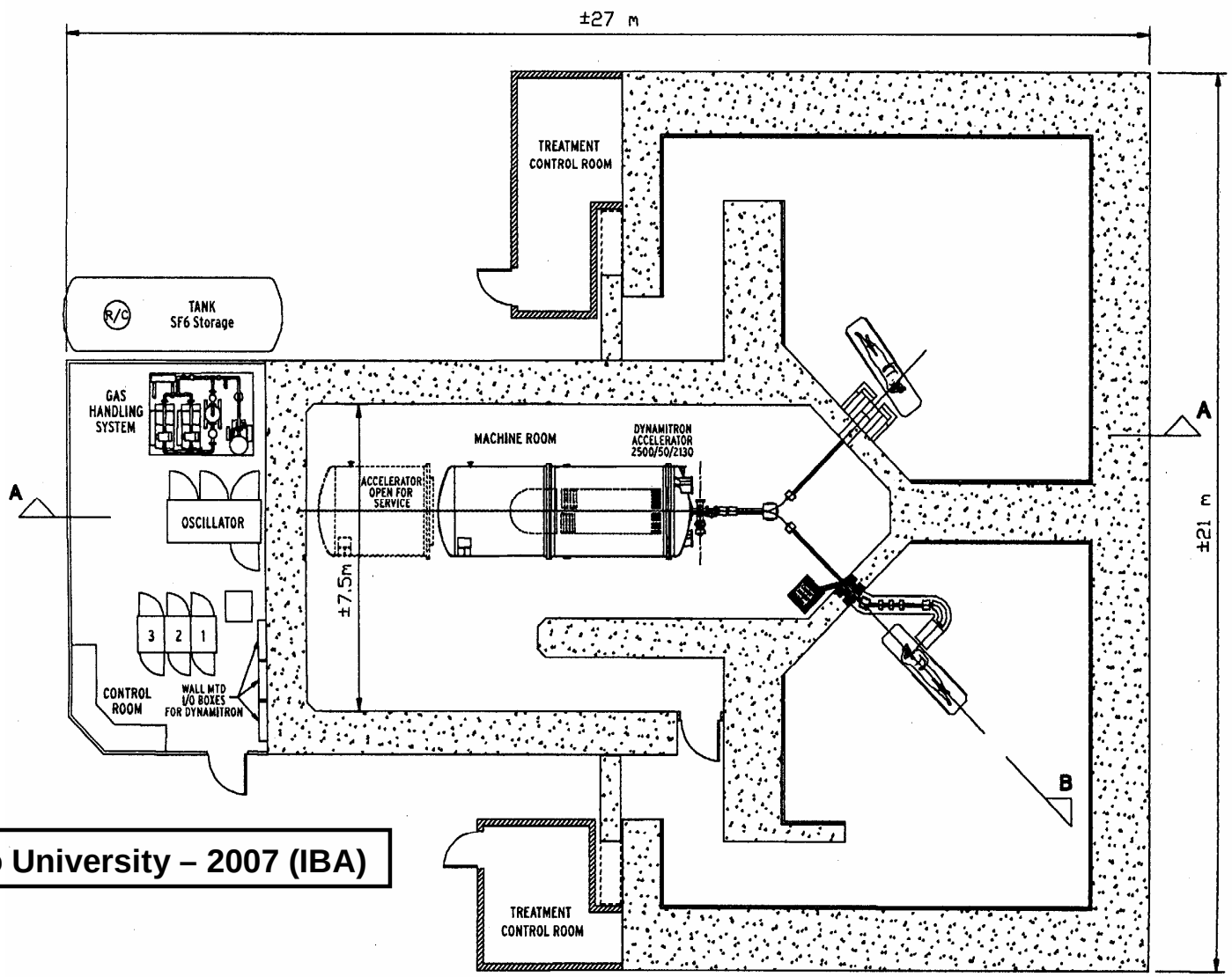
NEUTRON CAPTURE THERAPY
Assessment (I)

- ± 600 patients treated in 56 years
- Little clinical advantage with present techniques
  - establishment of new facilities is perceived as means to keep old reactors operational and staff employed
- Most complex of all radiation therapy modalities
- Dosimetry problems not solved
- Only reactor beams have been used
  - fixed beam directions
  - fixed collimators
  - long treatment times (≥ 40 minutes)
    - fractionation problematic
- Only B used as capture agent
  - compounds used (BSH, BPA) were developed in 1960s

NEUTRON CAPTURE THERAPY
Assessment (II)

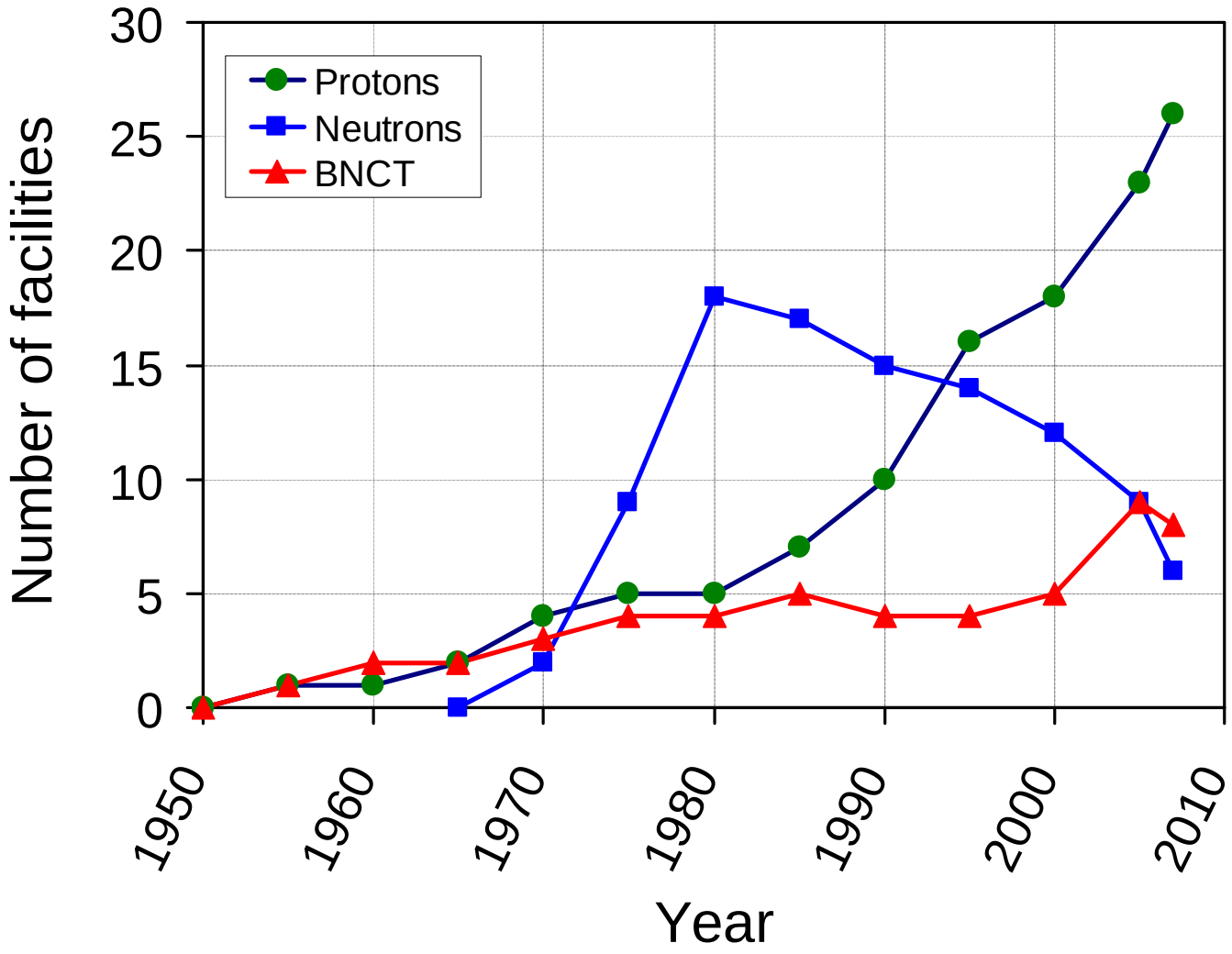
- Hospital-based accelerator facilities required
  - isocentric beam delivery
  - flexible collimation
  - shorter treatment times
    - fractionated treatments desirable
    - complicated schedules for fractionated drug administration?
    - very expensive drugs will limit number of fractions
- Commercial accelerator-based (Dynamitron) facility now available (IBA)
  - p(2.8 MeV) + ^{7}Li with isocentric gantry
  - installation at Kyoto University
- Different capture agent should be tried (*e.g.* ^{157}Gd: does not need to be taken up by cell, used in MRI))
- In vivo imaging (^{18}F labelling [PET], ^{11}B MRI)

ACCELERATOR-BASED BNCT FACILITY



Kyoto University – 2007 (IBA)

OPERATIONAL TREATMENT FACILITIES



THE END