

Fighting Cancer with Neutrons



**Neutron Therapy Treatment
For Advanced and Radioresistant Tumors**

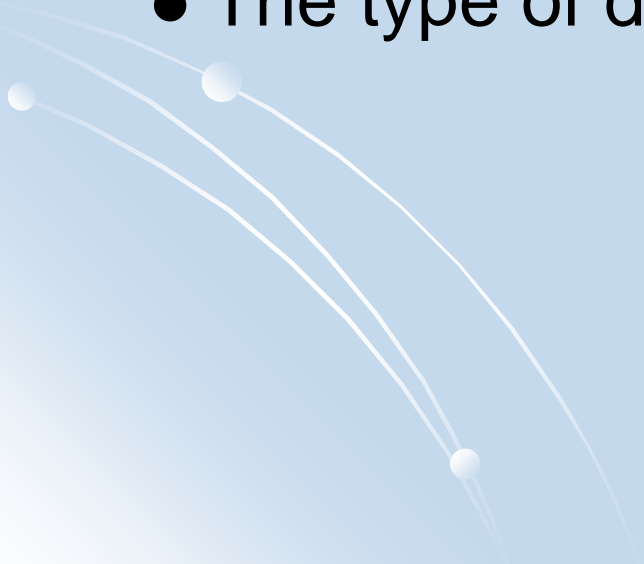
Neutron Therapy at Fermilab

- One of two (three ?) neutron therapy facilities in the US
- Operated in partnership with NIU
- Located in the Linac Gallery, synergistic w/HEP
- Have been treating since 1976, not experimental
- Radioresistant – not well controlled by conventional photon (x-ray) therapy
 - Depends on the type of tissue that is cancerous
 - Location & type

What is Radiation Therapy?

(External Beam Therapy)

- Radiation directed at the tumor from outside the body
- Two critical components
 - Where the energy is deposited
 - The type of damage produced



Where is the Energy Deposited?

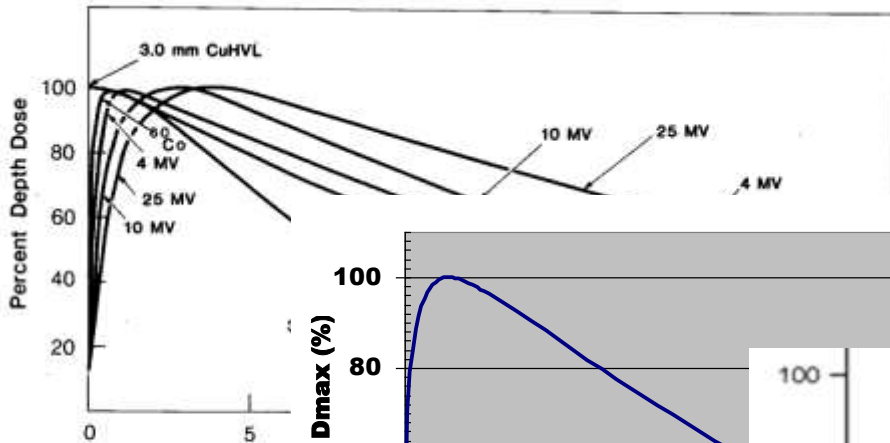
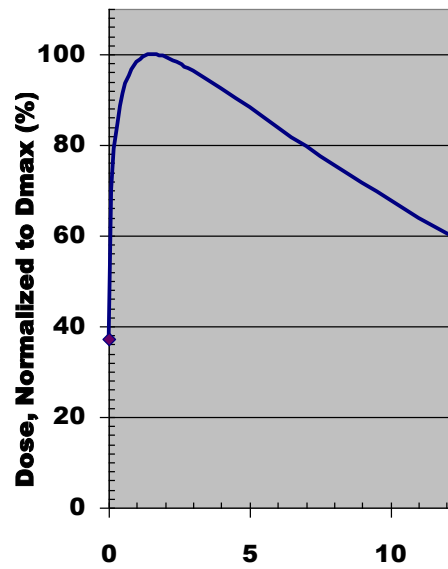
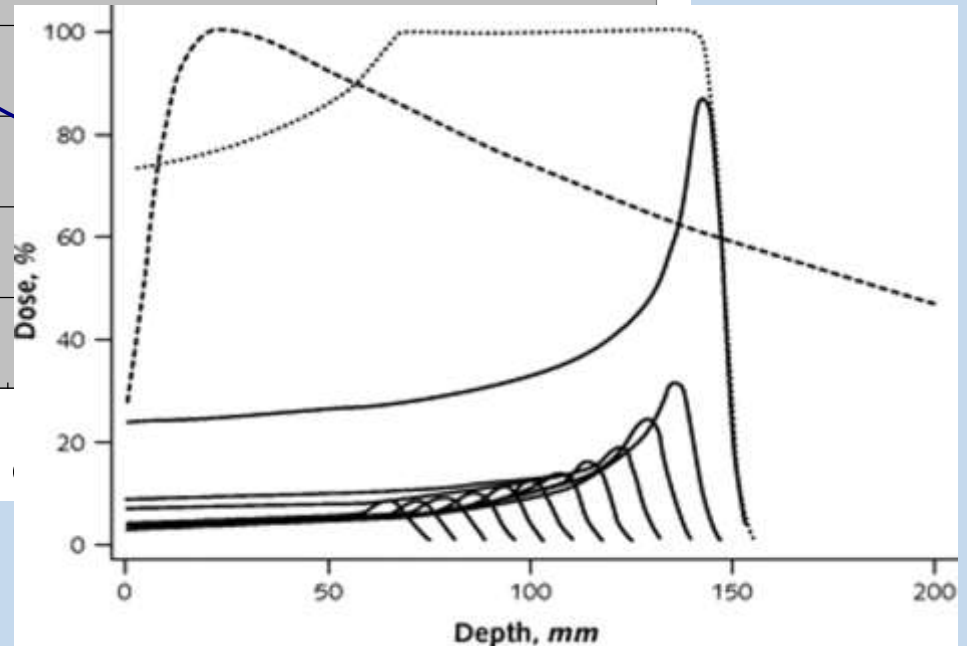


Figure 9.3. Central axis depth 10 × 10 cm; SSD = 100 cm are from Hospital Physicists' A Br J Radiol 1978;(suppl 11); a



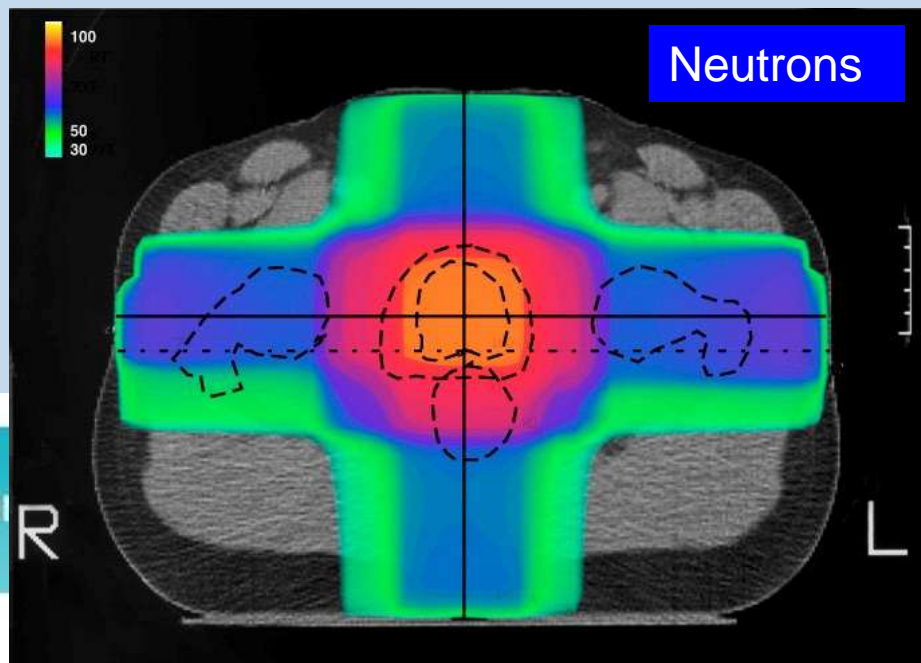
Photons

Neutrons

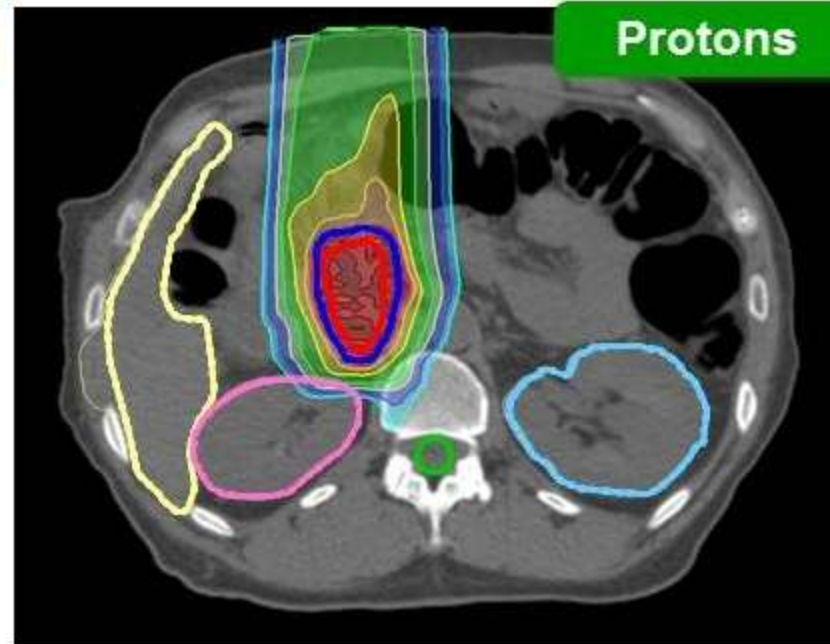
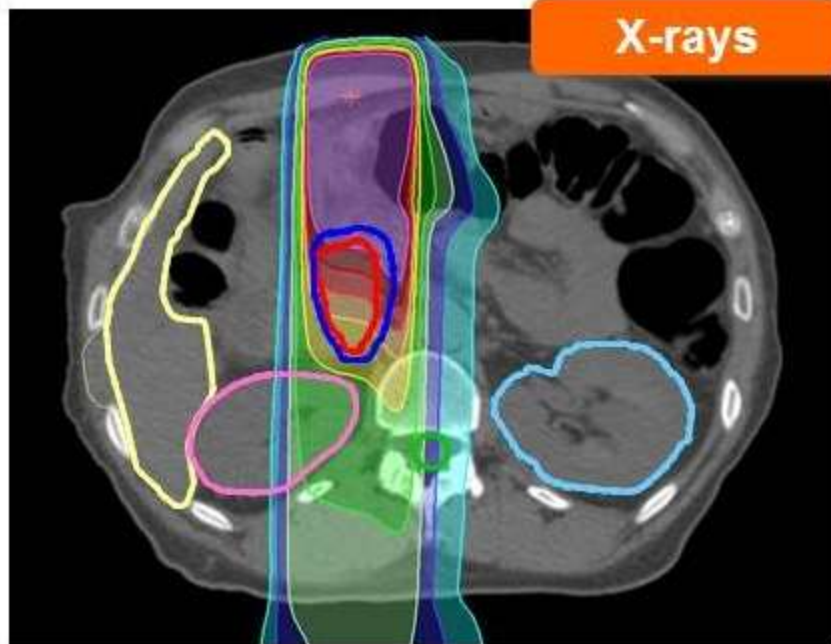


Protons

Image 2
Theoretical Comparison
Protons



 RINECKER
PROTON
THERAPY
CENTER



Why are Neutrons Needed?

Large *radioresistant* tumors are not well controlled by photon (or proton) therapy

- Resting cells are radioresistant
- Hypoxic (low oxygen) cells are radioresistant

Neutron therapy is less affected by cell cycle or oxygen content

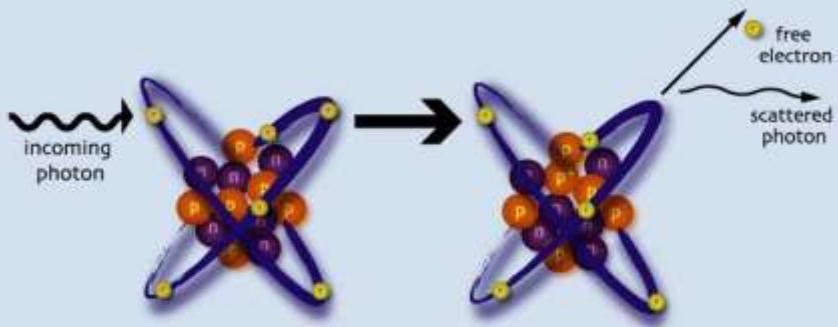
How Do Neutrons Overcome Resistance?

The Type of Damage Produced

- Cell killing mechanisms are complicated
 - DNA damage
 - Free radicals
 - Bystander effect
 - Inflammation
 - Genetics
- Focus on DNA damage through:
 - Radiation Quality
 - Linear Energy Transfer - LET

Radiation Quality

Photons and Charged Particles



neutral atom

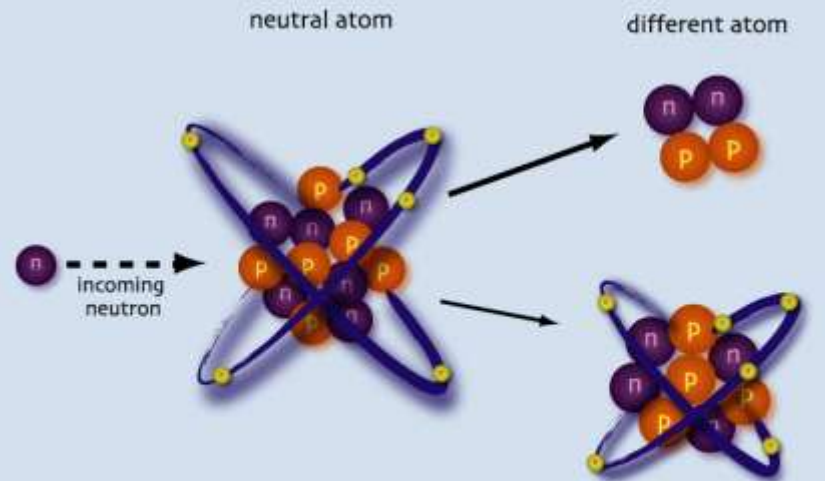
ionized atom

BEFORE

AFTER COLLISION

Low LET

Neutrons



neutral atom

different atom

BEFORE

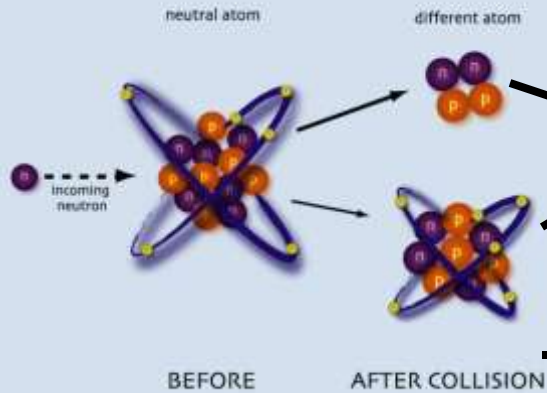
AFTER COLLISION

High LET

LET Comparison

(Linear Energy Transfer)

Neutrons



C-ions 1 MeV/u

α-particles 1 MeV/u

Protons 0.3 MeV
1 MeV
3 MeV

γ-rays

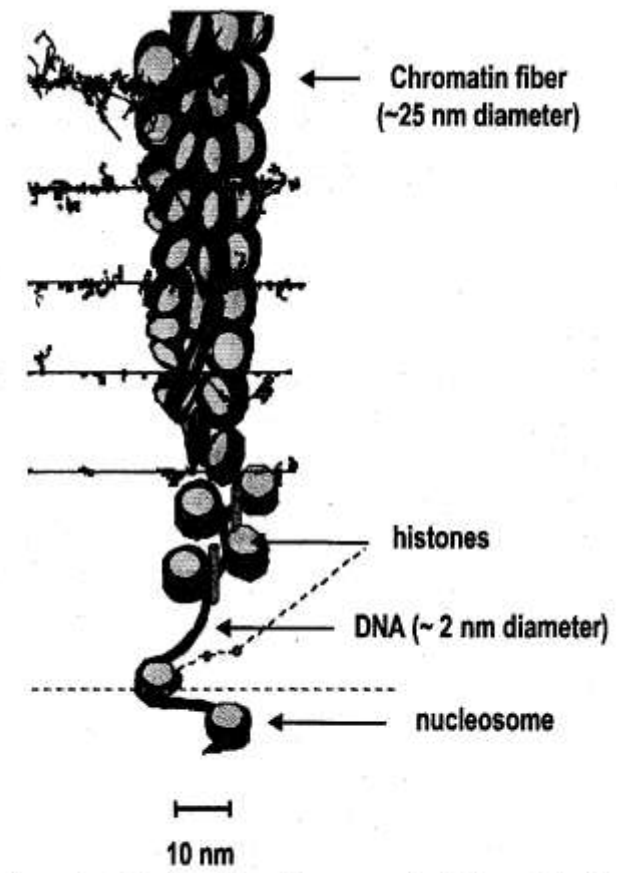
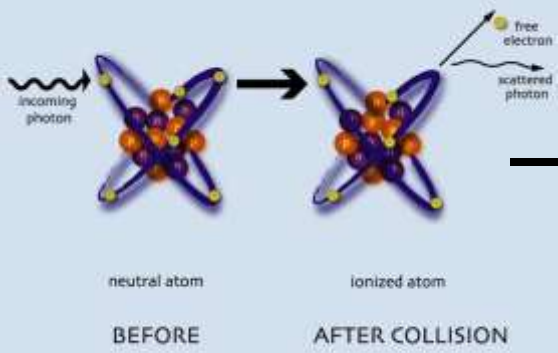


Fig. 1. Schematic representation of tracks of sparsely and densely ionizing radiations compared with relevant biological targets (chromatin fiber, nucleosomes and DNA double helix). Proton and alpha-particle tracks are based on the works of Paretzke¹²⁾ and carbon tracks on the works of Kramer and Kraft¹³⁾.

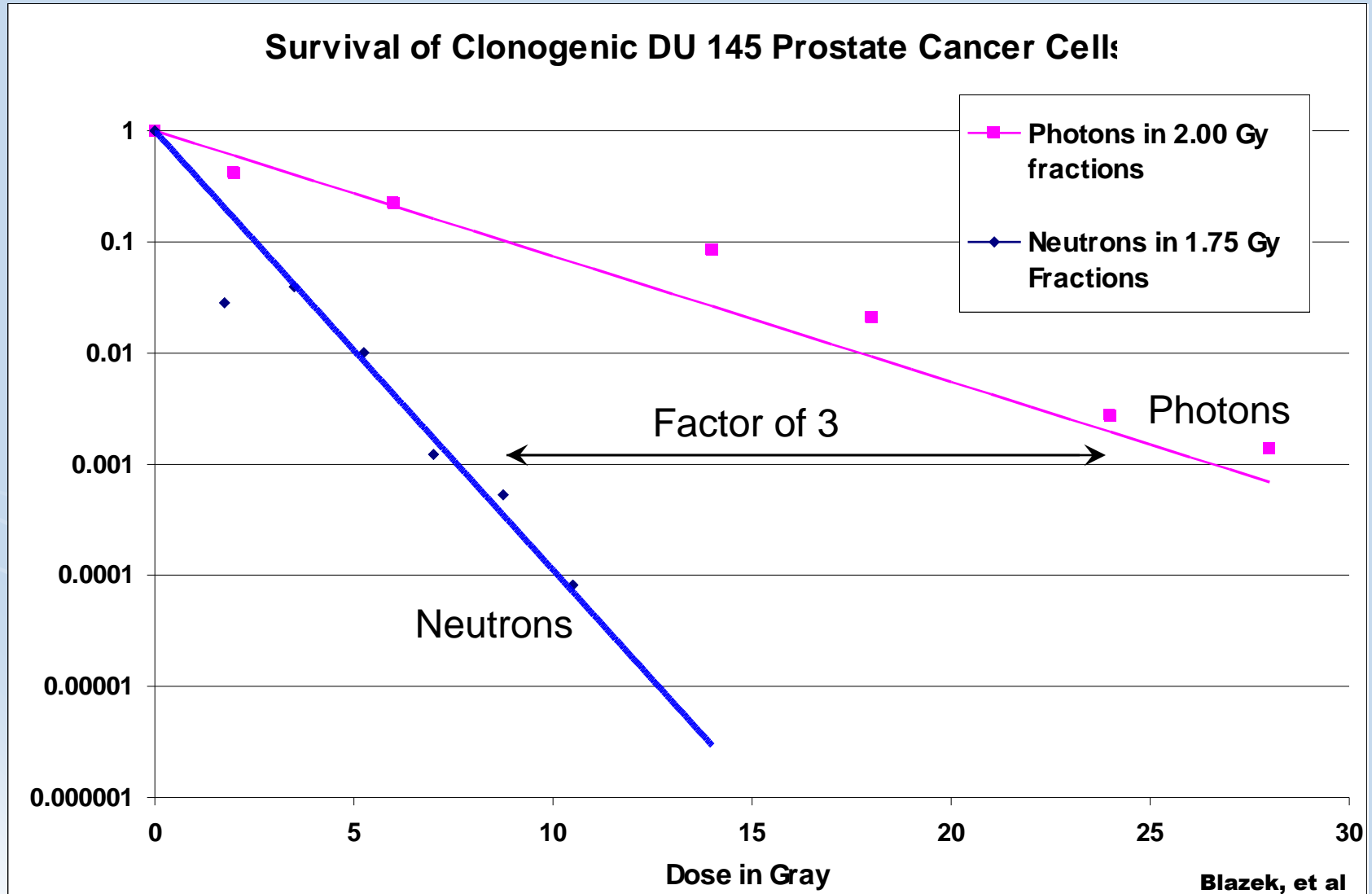
Photons & Protons



How can we turn LET,
radiation quality,
and all the other complexities of
cell killing
into something we can understand?



Relative Biological Effectiveness



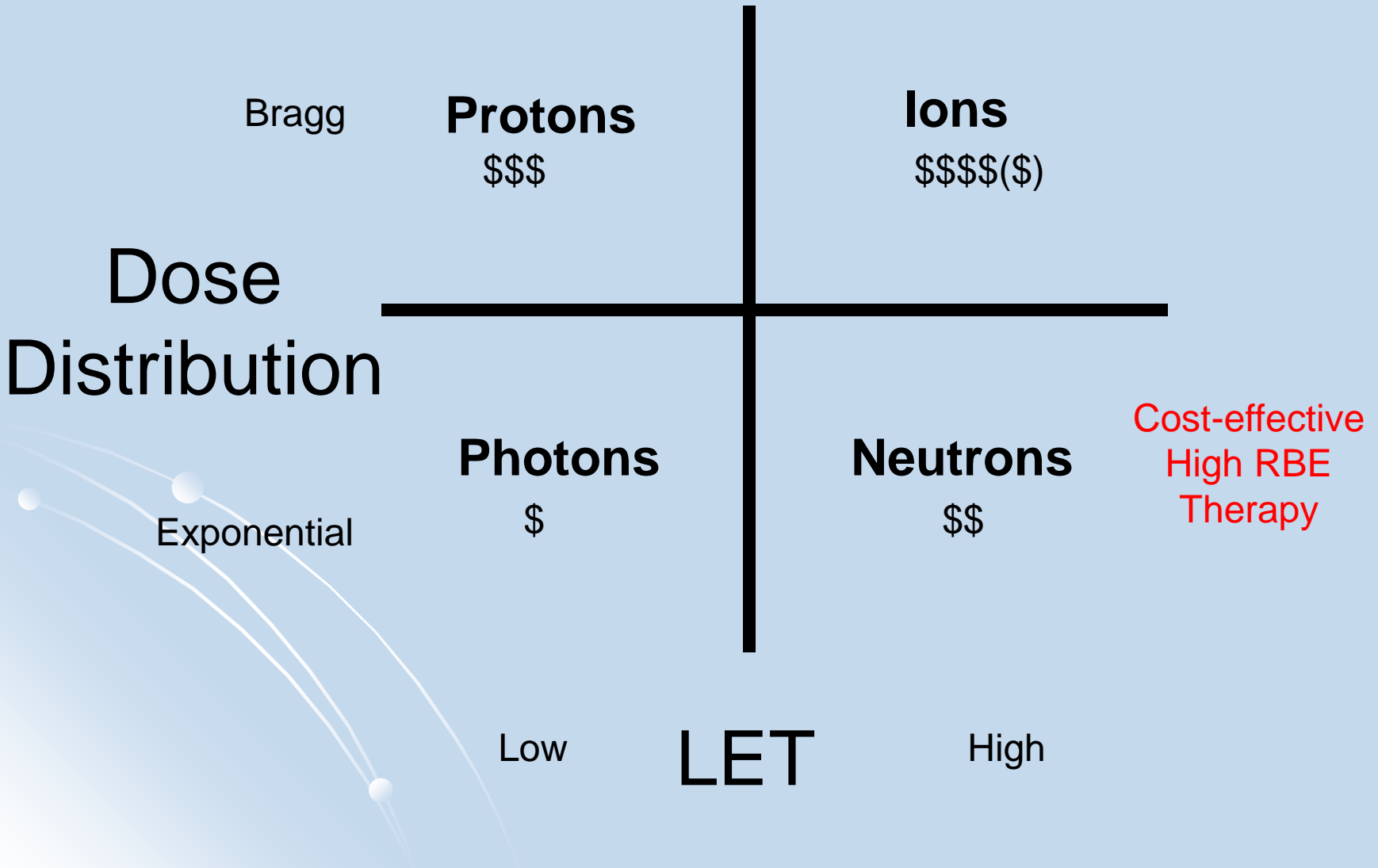
Relative Biological Effectiveness

- RBE -

is the reason for pursuing
Neutron Therapy



So What is the Best Therapy?



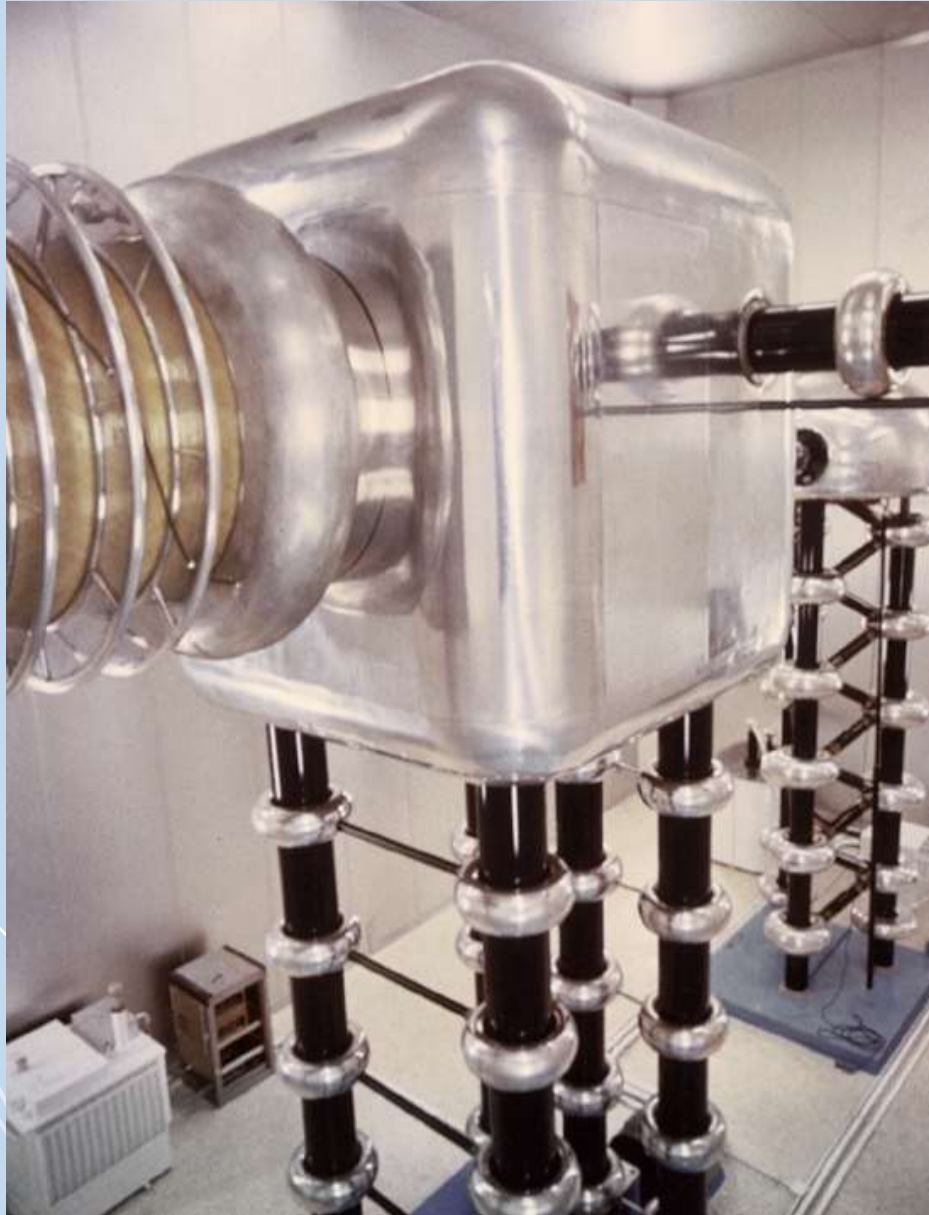
Why Fermilab?

- Robert Wilson – 1st director of Fermilab
 - Article in Radiology in 1946 proposing protons
- Paper by Louis Rosen of LASL
 - Use of accelerators for other than physics research – PAC '71
- Prof. Lester Skaggs – U of C & Argonne Cancer Hospital
 - Organized discussions looking at p, ions, π –1971
- Clinical results from Hammersmith Hosp
 - With neutrons - RBE
- September 7, 1976 – 1st patient treatment
 - With neutrons

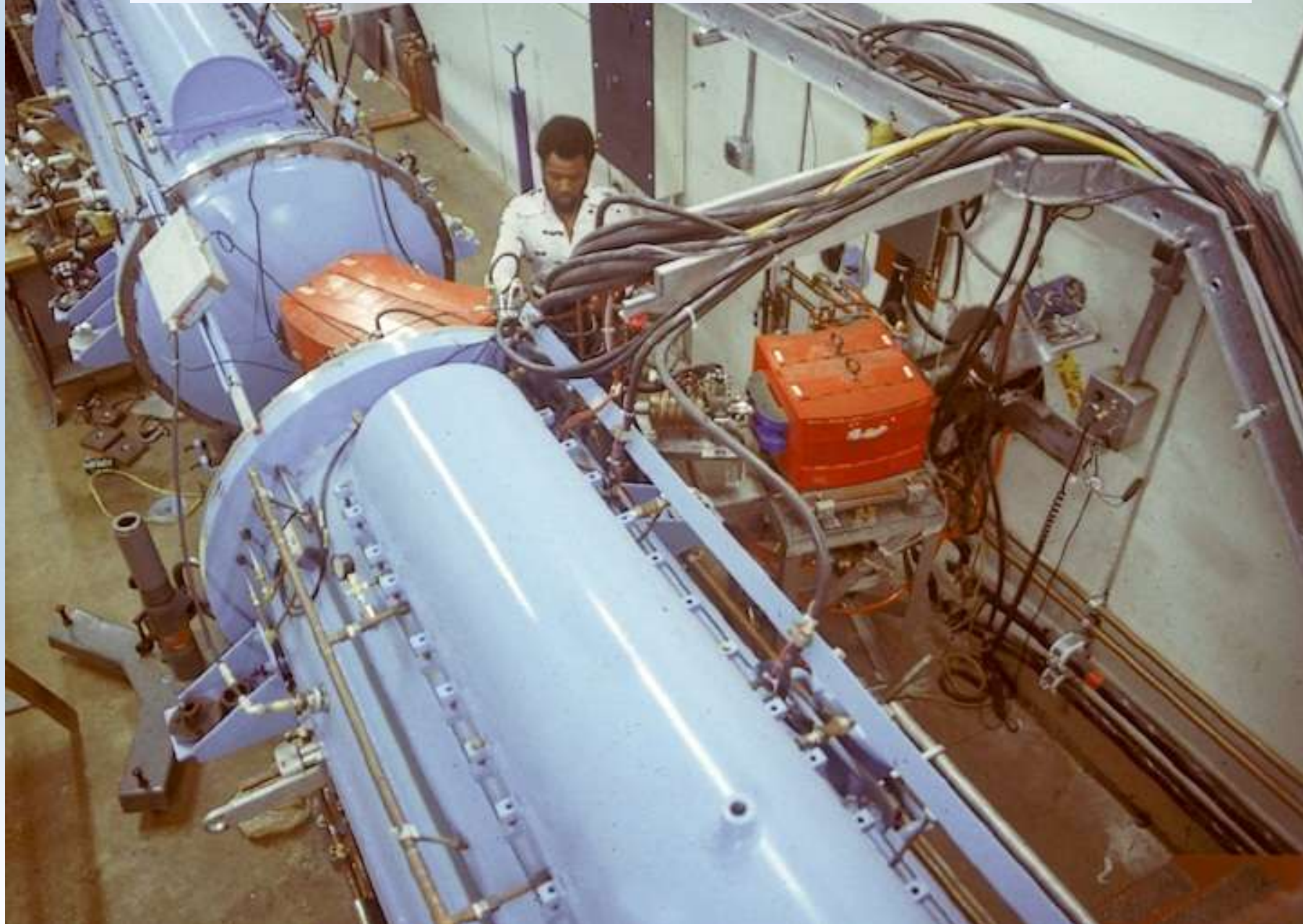
How is radiation therapy done?



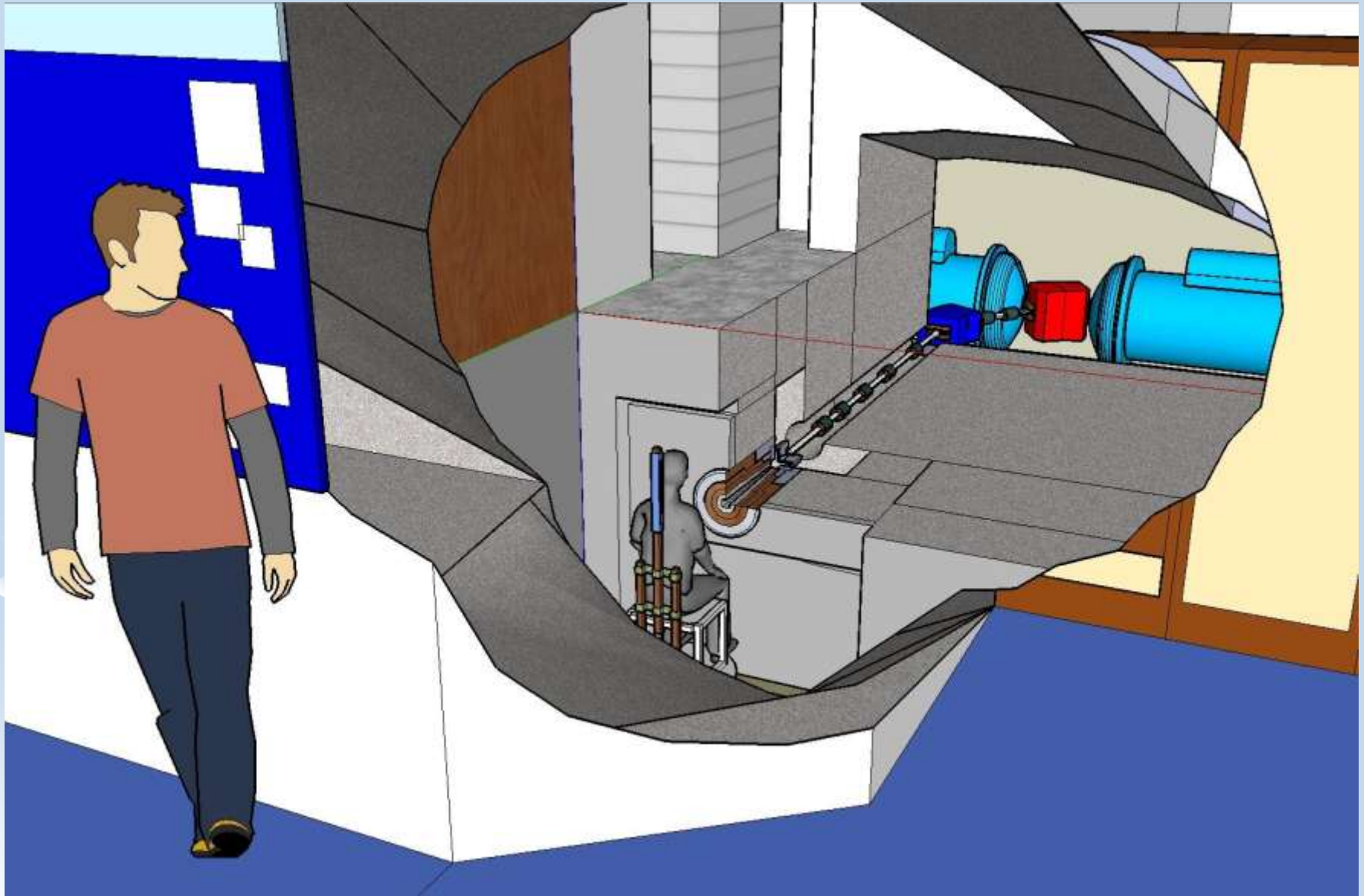
Proton linear accelerator for neutron therapy



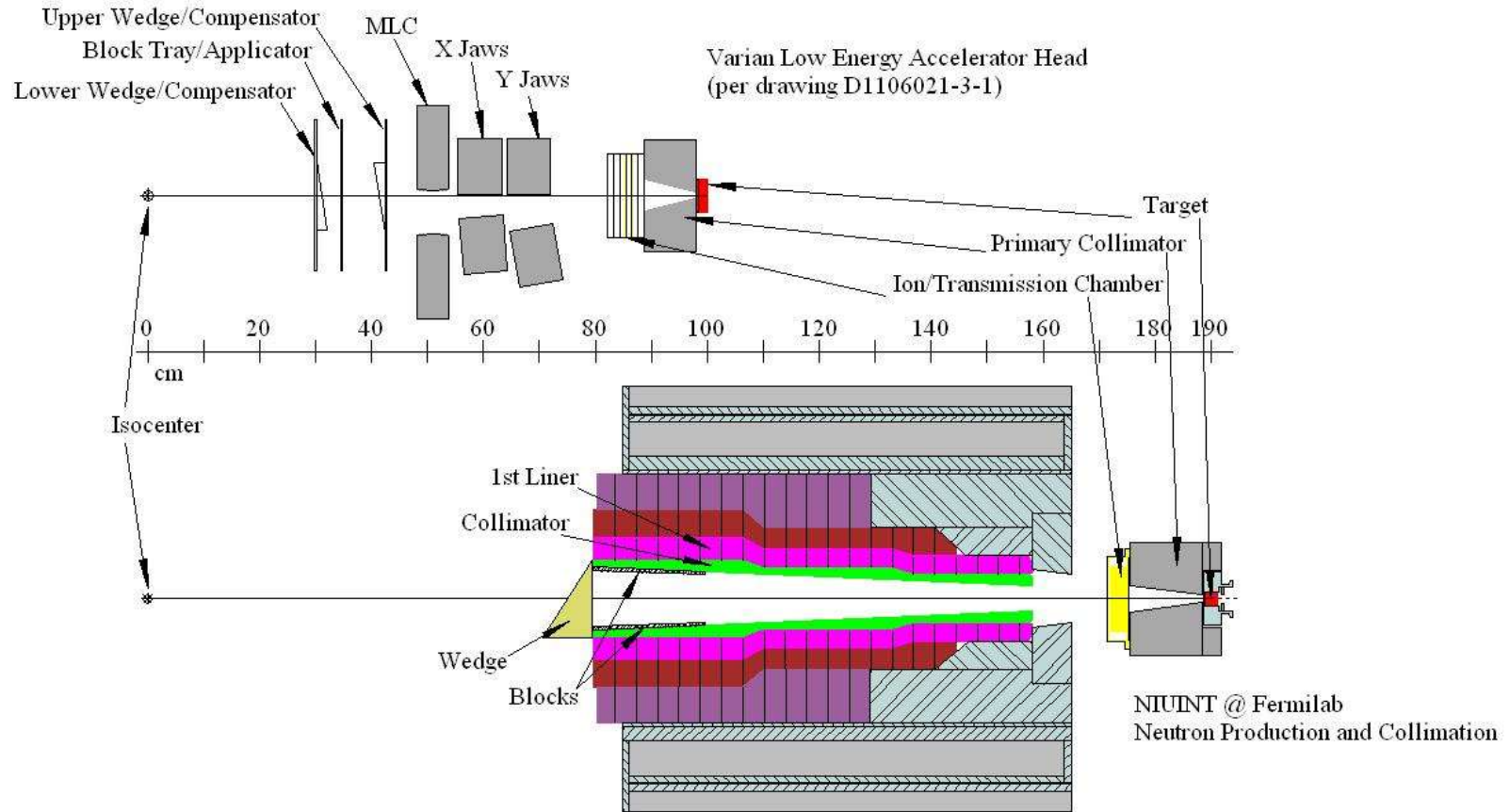
Proton linear accelerator for Neutron therapy



Proton linear accelerator for neutron therapy



Photon & Neutron Collimators



Collimators provide choice of rectangular field size ranging from 3x3 to 24x24 (square), 32x8 (rectangular).
Larger collimators (>14x14) are accommodated by removing the 1st liner.
Low carbon steel blocks (blocks, slabs, and triangles) allow additional choice in collimator size and
allow conformity of field shape to prescribed volume.



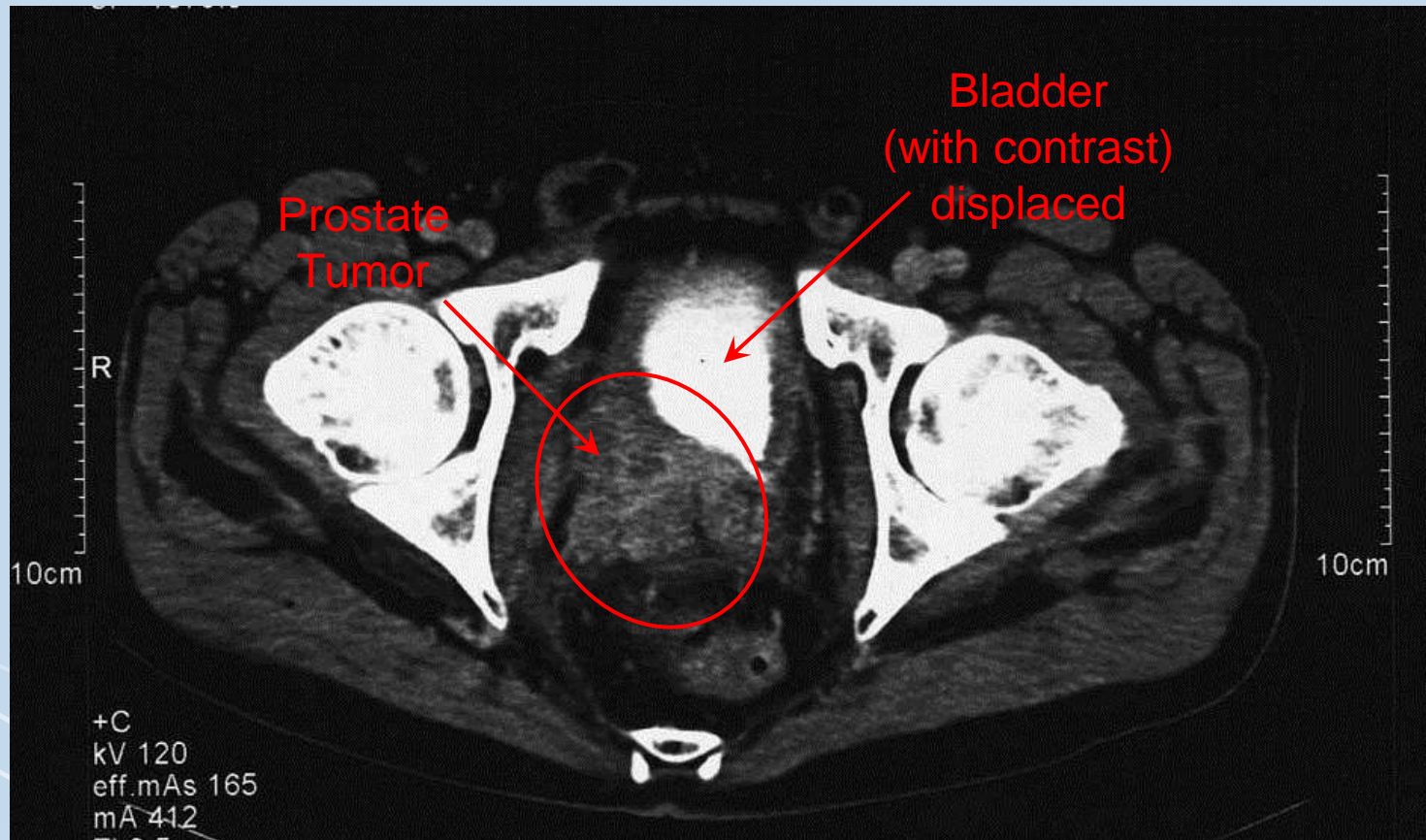
Some Clinical Results

How good is Neutron Therapy?

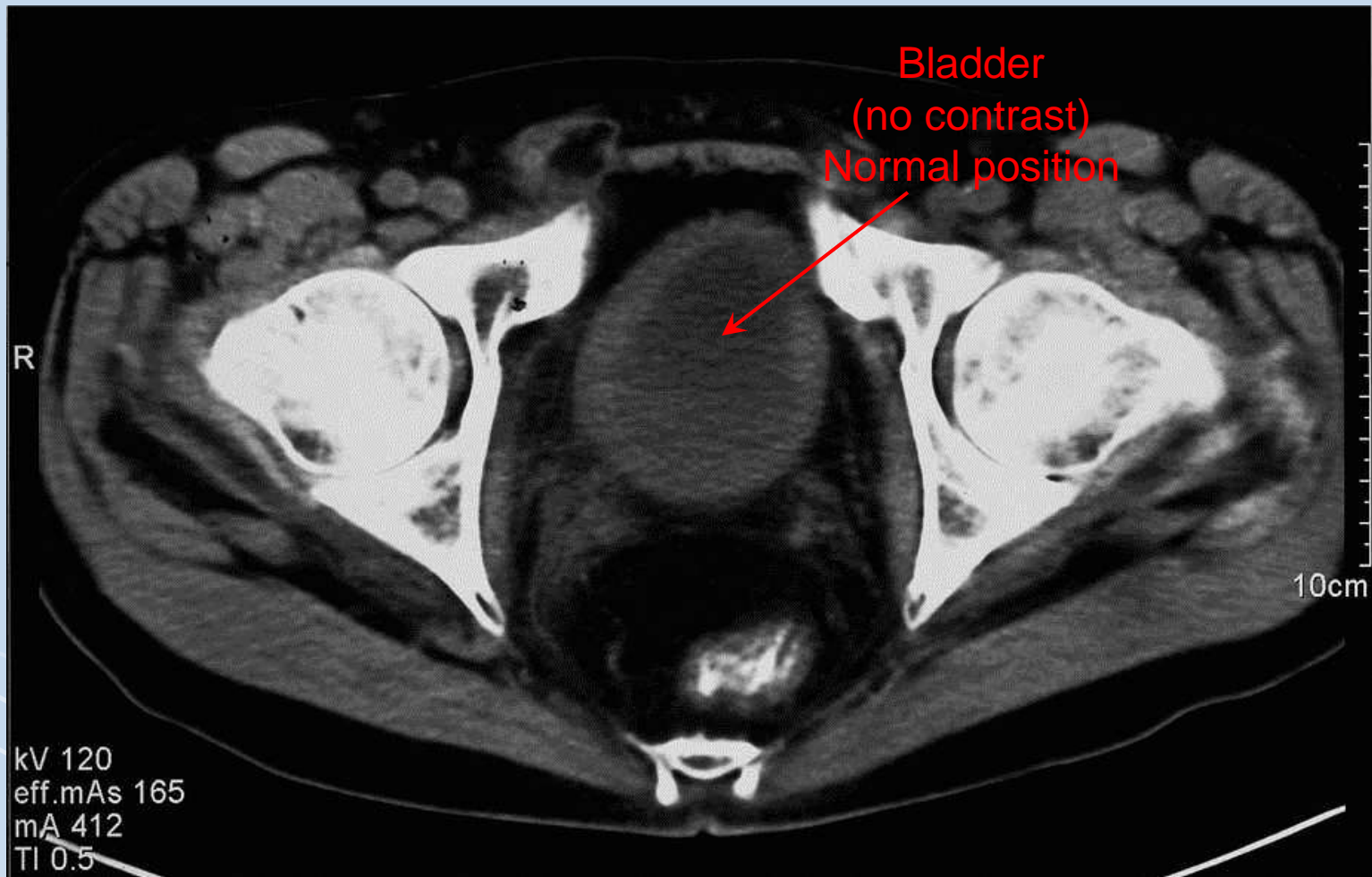
It depends.



CT scan of prostate cancer



Before Neutron Therapy



After 12.25 Gray of neutrons

Review of the loco-regional rates for malignant salivary gland tumors treated with radiation therapy.

| Fast Neutrons | | | |
|--------------------------------|--------------------|---------------------------|-------|
| Authors | Number of Patients | Loco-regional control (%) | |
| Saroja <i>et al.</i> (1987) | 113 | 71 | (63%) |
| Catterall and Errington (1987) | 65 | 50 | (77%) |
| Battermann and Mijnheer (1986) | 32 | 21 | (66%) |
| Griffin <i>et al.</i> (1988) | 32 | 26 | (81%) |
| Duncan <i>et al.</i> (1987) | 22 | 12 | (55%) |
| Tsunemoto <i>et al.</i> (1989) | 21 | 13 | (62%) |
| Maor <i>et al.</i> (1981) | 9 | 6 | (67%) |
| Ornitz <i>et al.</i> (1979) | 8 | 3 | (38%) |
| Eichhorn (1981) | 5 | 3 | (60%) |
| Skolyszewski (1982) | 3 | 2 | (67%) |
| Overall | 310 | 207 | (67%) |

| Low-LET Radiotherapy Photon and/or Electron beams and/or Radioactive Implants | | | |
|---|--------------------|---------------------------|-------|
| Authors | Number of Patients | Loco-regional control (%) | |
| Fitzpatrick and Theriault (1986) | 50 | 6 | (12%) |
| Vikramet <i>et al.</i> (1984) | 49 | 2 | (4%) |
| Borthne <i>et al.</i> (1986) | 35 | 8 | (23%) |
| Rafla (1977) | 25 | 9 | (36%) |
| Fu <i>et al.</i> (1977) | 19 | 6 | (32%) |
| Stewart <i>et al.</i> (1968) | 19 | 9 | (47%) |
| Dobrowsky <i>et al.</i> (1986) | 17 | 7 | (41%) |
| Shidnia <i>et al.</i> (1980) | 16 | 6 | (38%) |
| Elkon <i>et al.</i> (1978) | 13 | 2 | (15%) |
| Rossmann (1975) | 11 | 6 | (54%) |
| Overall | 254 | 61 | (24%) |

Table III. from IAEA-TECDOC-992, "Nuclear data for neutron therapy: Status and future needs," December 1997, pg. 12.

Salivary Gland Cancer Treatment (PDQ®)



Patient Version | Health Professional Version | En español

Last Modified: 02/17/2012

Salivary Gland Cancer Treatment (PDQ®)

- ▶ General Information About Salivary Gland Cancer
- ▶ Cellular Classification of Salivary Gland Cancer
- ▶ Stage Information for Salivary Gland Cancer
- ▶ Treatment Option Overview
- ▶ Stage I Major Salivary Gland Cancer
- ▶ Stage II Major Salivary Gland Cancer
- ▶ Stage III Major Salivary Gland Cancer
- ▶ Stage IV Major Salivary Gland Cancer
- ▶ **Recurrent Major Salivary Gland Cancer**
- ▶ Changes to This Summary (02/17/2012)
- ▶ About This PDQ Summary
- ▶ Get More Information From NCI

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Recurrent Major Salivary Gland Cancer[Current Clinical Trials](#)

The prognosis for any treated cancer patient with progressing or relapsing disease is poor, regardless of cell type or stage. Selecting further treatment depends on many factors, including the specific cancer, prior treatment, site of recurrence, and individual patient considerations. [Fast neutron-beam radiation therapy is superior to conventional radiation therapy using x-rays and may be curative in selected patients with recurrent disease.](#)^[1]

[Disease-free survival and overall survival for patients with inoperable, unresectable, or recurrent malignant salivary gland tumors is superior in patients treated with fast neutron-beam radiation therapy as compared to those treated with conventional x-ray radiation therapy.](#)^[2-5] Clinical trials are appropriate and should be considered when possible.

Current Clinical Trials

Check for U.S. clinical trials from NCI's list of cancer clinical trials that are now accepting patients with [recurrent salivary gland cancer](#). The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the [NCI Web site](#).

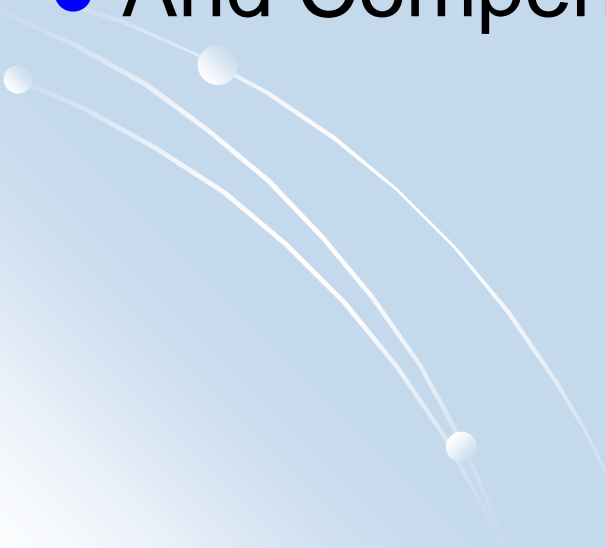
References

1. Laramore GE, Krall JM, Griffin TW, et al.: Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC randomized clinical trial. Radiation Therapy Oncology Group. Medical Research Council. *Int J Radiat Oncol Biol Phys* 27 (2): 235-40, 1993. [\[PUBMED Abstract\]](#)
2. Laramore GE: Fast neutron radiotherapy for inoperable salivary gland tumors: is it the treatment of choice? *Int J Radiat Oncol Biol Phys* 13 (9): 1421-3, 1987. [\[PUBMED Abstract\]](#)
3. Saroja KR, Mansell J, Hendrickson FR, et al.: An update on malignant salivary gland tumors treated with neutrons at Fermilab. *Int J Radiat Oncol Biol Phys* 13 (9): 1319-25, 1987. [\[PUBMED Abstract\]](#)
4. Buchholz TA, Laramore GE, Griffin BR, et al.: The role of fast neutron radiation therapy in the management of advanced salivary gland malignant neoplasms. *Cancer* 69 (11): 2779-88, 1992. [\[PUBMED Abstract\]](#)
5. Krüll A, Schwarz R, Engenhart R, et al.: European results in neutron therapy of malignant salivary gland tumors. *Bull Cancer Radiother* 83 (Suppl): 125-9s, 1996. [\[PUBMED Abstract\]](#)

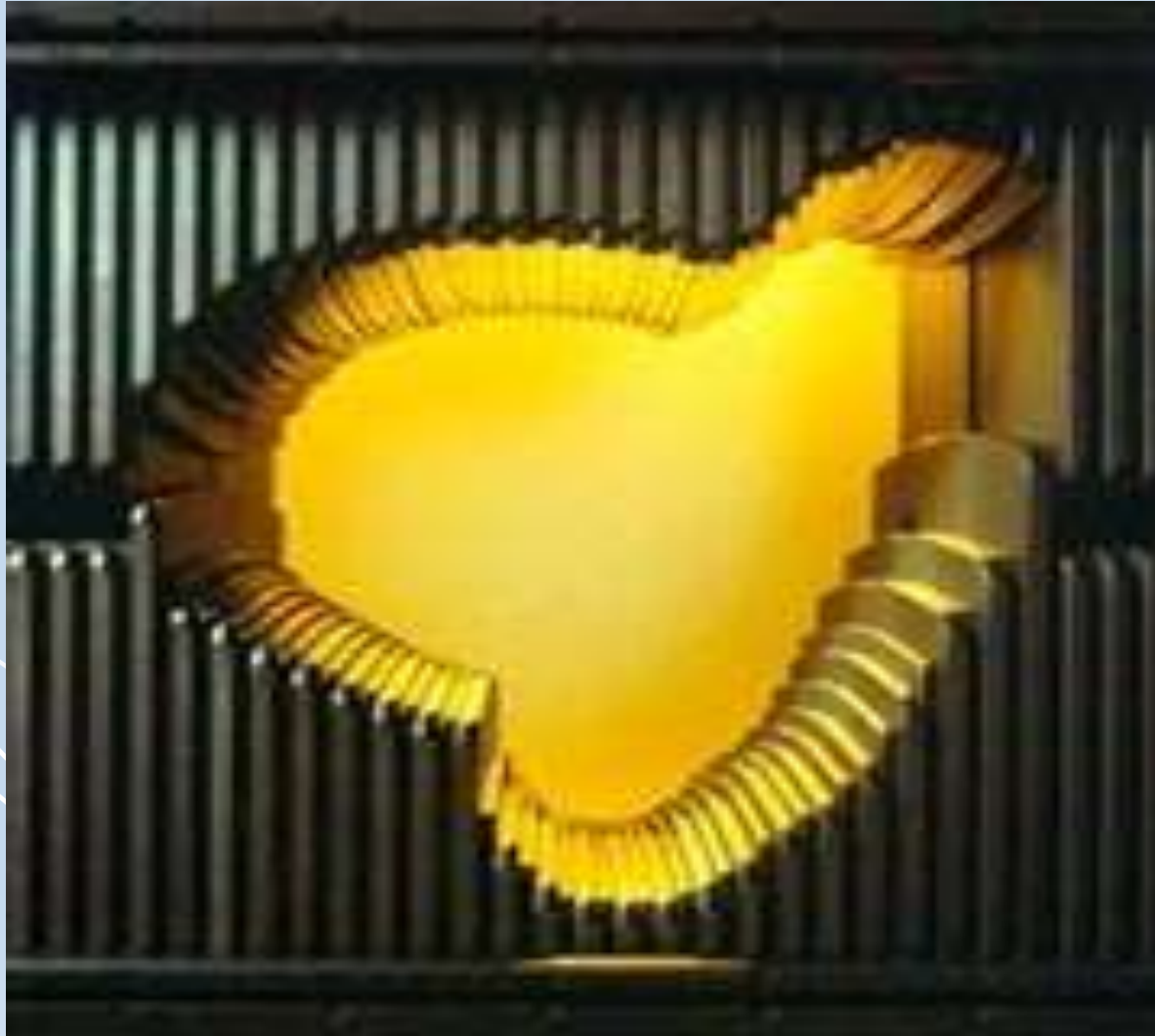
An Important Point for Potential Health Care Consumers

- Neutron Therapy is NOT a treatment of last resort.
- Healthy tissue can only tolerate a certain amount of any type of radiation.
- A specific tumor site cannot be retreated if it has already been treated with photons.
- Patients from both physician and self referral
- We presently treat up to 20 patients per year
 - Very underutilized

The Future

- Beam delivery for Neutron Therapy has fallen behind photon and proton therapy
 - We are working on addressing that by developing a Multi-Leaf Collimator (MLC)
 - And Compensator-Based IMRT
- 

Multileaf Collimator



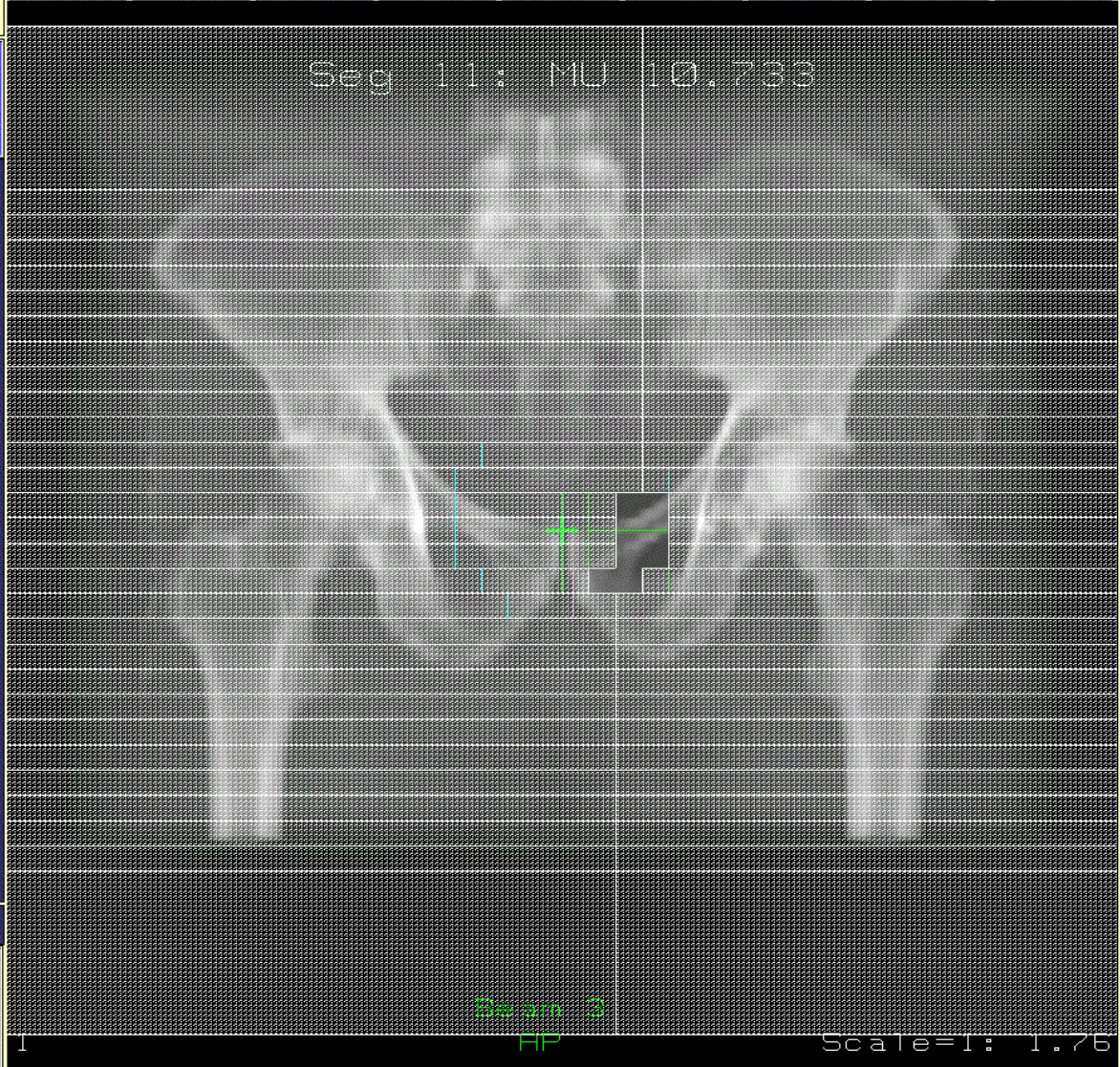
Courtesy of Mark Pankuch

Sep 05 2002
14:20

Good Samaritan
FOCUS - Release 3.2.1

SF1 HELP SF2 RESTART SF3 EDITPLAN SF4 DISPDOSE SF5 OPTIMIZE SF6 SAVEPLAN SF7 PLOT SF8 APPROVAL SF9 EXIT

Seg 11: MU 10.733



Graphics Area layout and contents

Window format: One

Display utilities

Scales off Spacing(cm): 1.0

Measure

Enhance contour

Object on/off

Graphics capture utilities

Capture Active Window

Capture Entire Graphics Area

Win. View Orient Ref(cm) Beam # *

1 BEV 3

Update Graphics Display

CANCEL

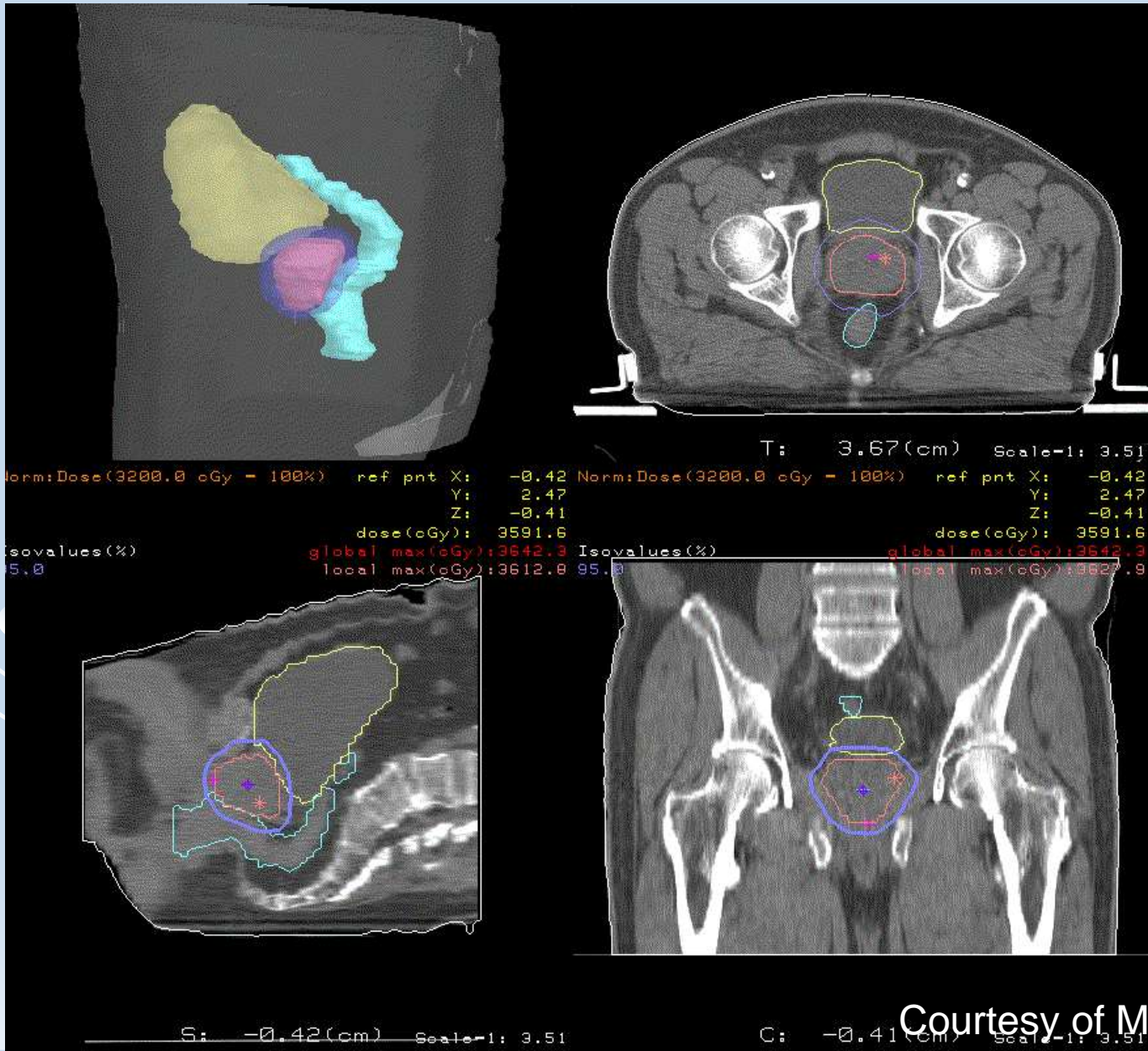
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SCALE

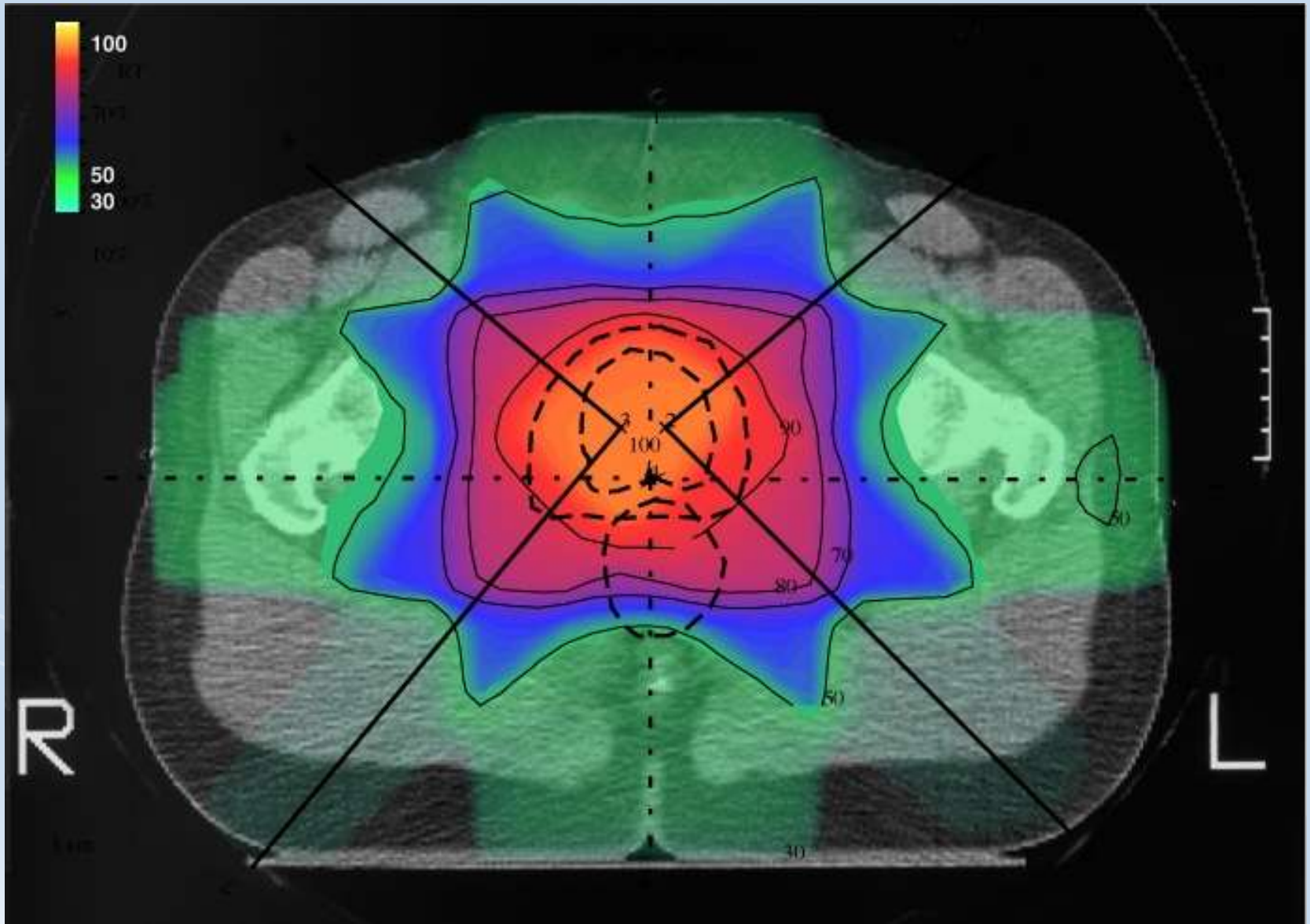
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F1 Isocurve F2 Weight F4 Time/MU F5 SourceIdx F6 Histogram F7 Biology F8 DoseProfile F9 DRR F10 Graphics

IMRT

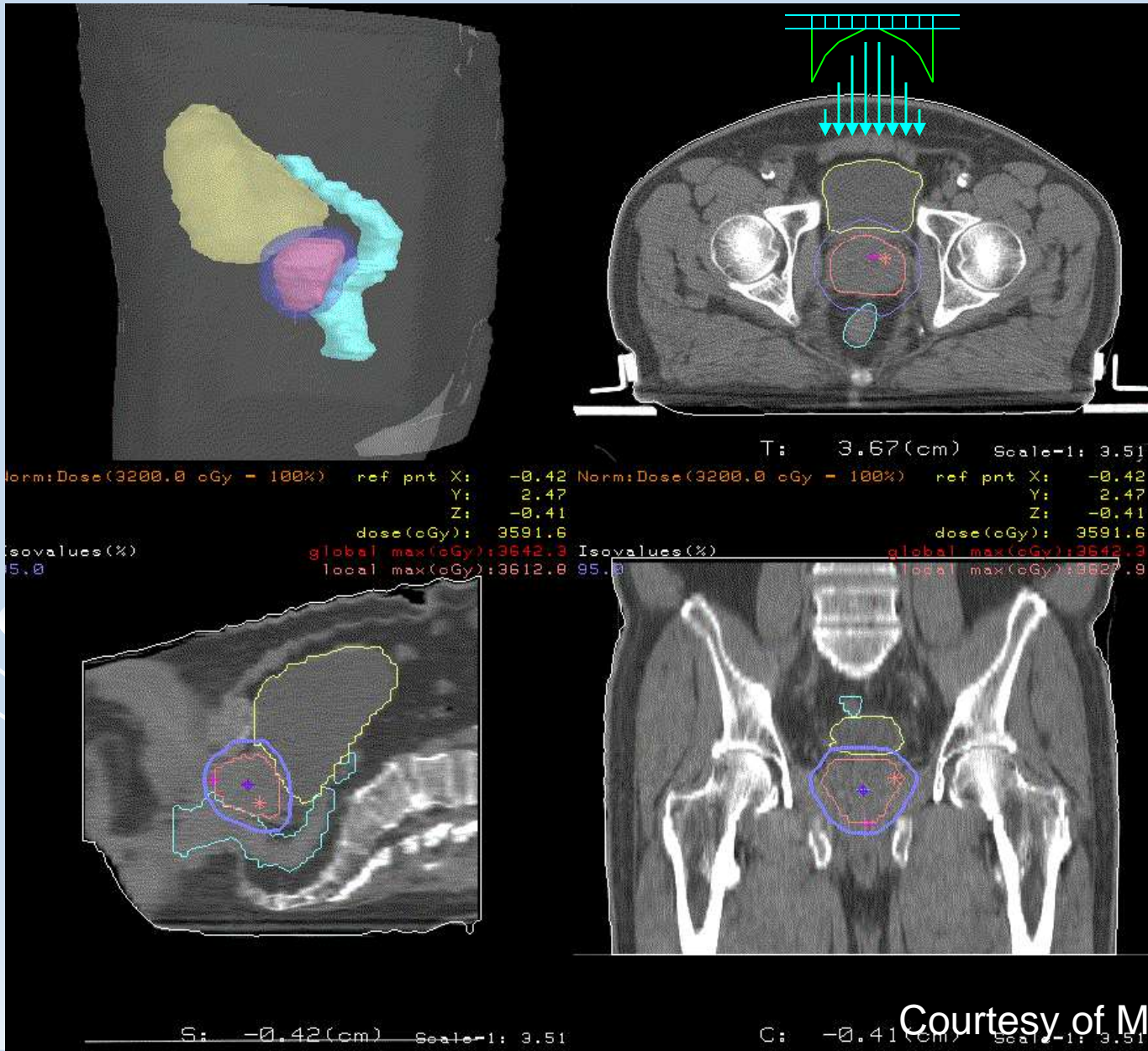


Courtesy of Mark Pankuch



Eight-Field Technique

IMRT



Courtesy of Mark Pankuch

The End – Thank you



Marty Murphy

How to find us

neutrontherapy.niu.edu

Or

neutrontherapy.org



Incidence of Life-Threatening or Fatal late normal tissue toxicity in the head and neck by prescribed tumor dose.

| Dose | Neutron Source | | | |
|----------------|-----------------|-------------------------|----------------|---------|
| | High Energy (#) | Intermediate Energy (#) | Low Energy (#) | DT (#) |
| ≤ 15 Gy | 0 (4) | 0 (3) | 33% (6) | 0 (7) |
| 15.1 – 17.0 Gy | 0 (3) | 0 (2) | 21% (86) | 0 (18) |
| 17.1 – 19.0 Gy | 0 (3) | 0 (18) | 0 (5) | 66% (3) |
| 19.1 – 21.0 Gy | 4% (28) | 0 (19) | – | – |
| 21.1 – 23.0 Gy | 11% (56) | 24% (38) | – | – |
| 23.1 – 25.0 Gy | 9% (22) | 0 (2) | – | – |
| > 25 Gy | 50% (4) | 0 (3) | – | – |
| Total | 9% (120) | 10% (85) | 20% (97) | 8% (28) |

| Energy Range | Institution | Neutron Generator | Energy (mean) |
|---------------------|-----------------------------|-------------------|---------------------|
| High Energy | Fermilab | Linac | 66 MeV p->Be (25) |
| | MD Anderson /TAMVEC | Cyclotron | 50 MeV d->Be (19) |
| Intermediate Energy | MANTA | Cyclotron | 35 MeV d->Be (14) |
| | GLANTA | Cyclotron | 25 MeV d->Be (10) |
| | Univ. of Washington* | Cyclotron | 22 MeV d->Be (8) |
| Low Energy | Western General - Edinburgh | Cyclotron | 15 MeV d->Be (?) |
| DT | Antoni van Leeuwenhoek | DT Generator | 0.5 MeV d->T (14.3) |

* upgraded to 50 MeV->Be (22) since this study

T. Griffin, et. al., Analysis of neutron radiotherapy treatment complications, Bull. Cancer (Paris), 1986, 73, 5, 582-586.

DNA Damage

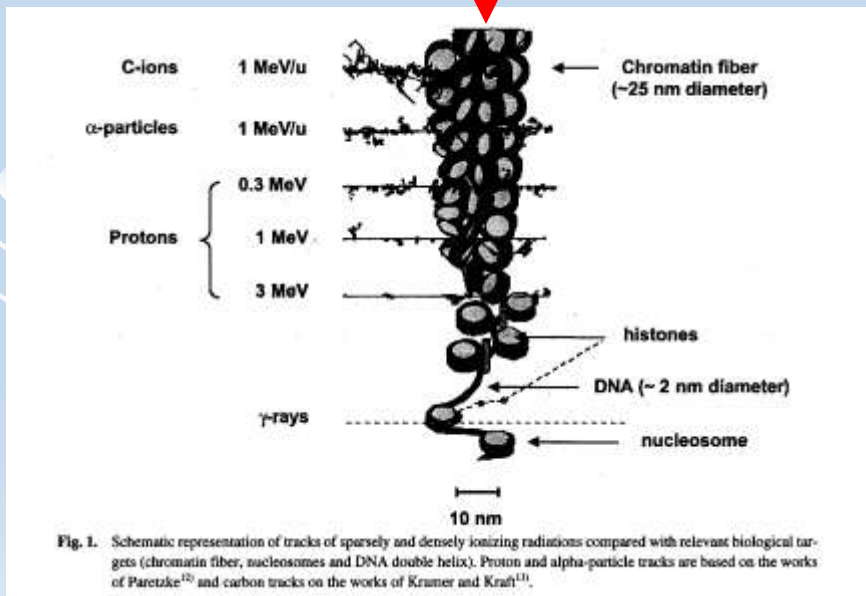
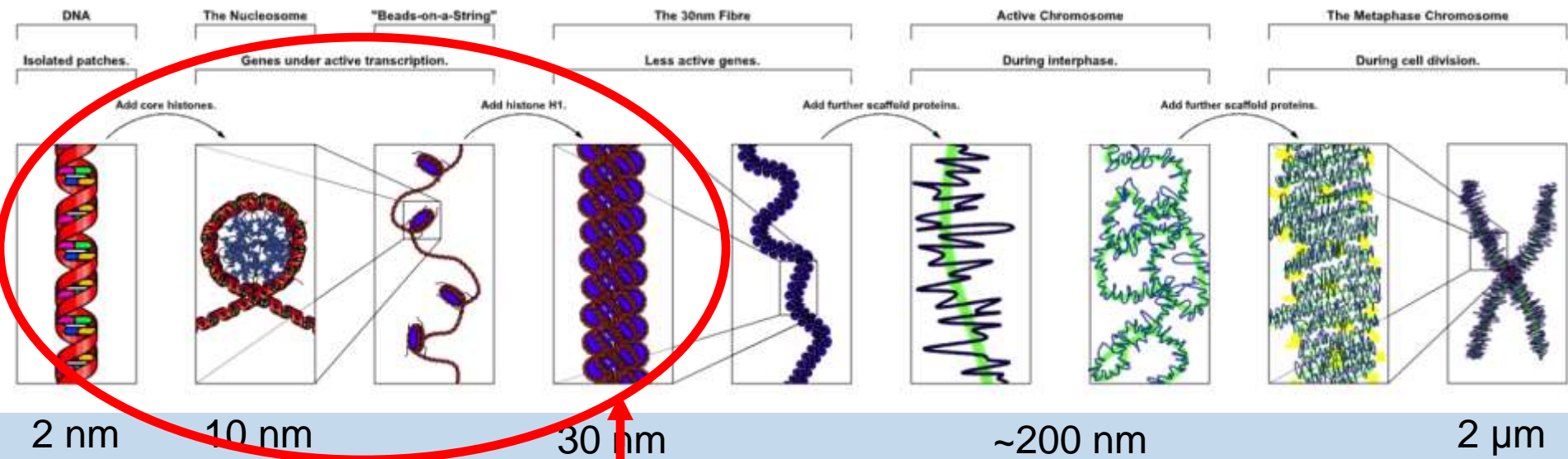
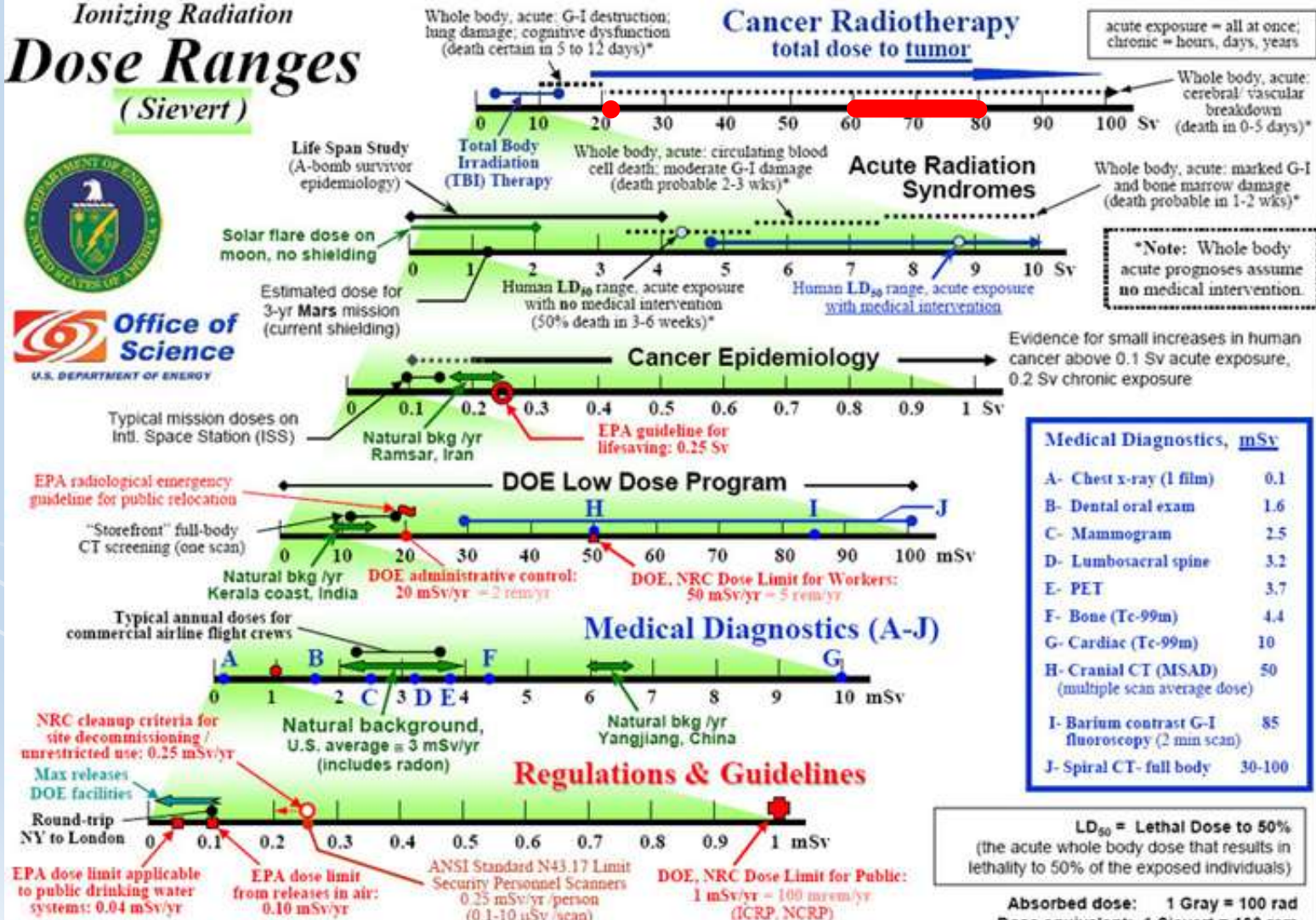


Fig. 1. Schematic representation of tracks of sparsely and densely ionizing radiations compared with relevant biological targets (chromatin fiber, nucleosomes and DNA double helix). Proton and alpha-particle tracks are based on the works of Paretzke⁽²⁾ and carbon tracks on the works of Kramer and Kraft⁽¹⁾.

Optimum LET
100 eV/nm
~3 ip

Understanding Dose

Ionizing Radiation **Dose Ranges** (Sievert)



LD₅₀ = Lethal Dose to 50%
(the acute whole body dose that results in lethality to 50% of the exposed individuals)

Absorbed dose: 1 Gray = 100 rad
Dose equivalent: 1 Sievert = 100 rem
1 mSv = 100 mrem
(1 Sv = 1 Gy for x- and gamma-rays)

Source: Office of Biological and Environmental Research (BER), Office of Science, U.S. Department of Energy
<http://www.science.doe.gov/ober/>

Note: This chart was constructed with the intention of providing a simple, user-friendly, "order-of-magnitude" reference for relative quantities of interest to scientists, managers, and the general public. In that spirit, some quantitative areas approximated to the more commonly used radiation protection units, the rem (or Sievert, 2nd page), and medical doses are given in "effective" dose. It is acknowledged that the decision to use one set of units does not address everyone's needs. DOE—US Nuclear Regulatory Commission, EPA—US Environmental Protection Agency
Disclaimer: Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information disclosed.

Chart compiled by NF Metting, Office of Science, DOE/BER
"Orders of Magnitude" revised March 2006