Fighting Cancer with Neutrons

Neutron Therapy Treatment
For Advanced and Radioresistant Tumors

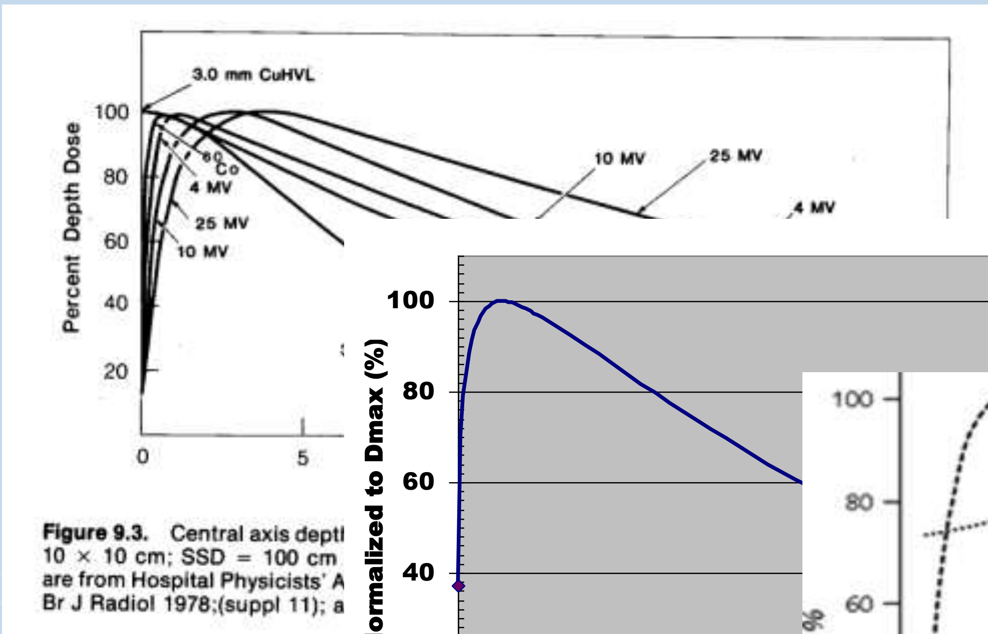
Neutron Therapy at Fermilab

- 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

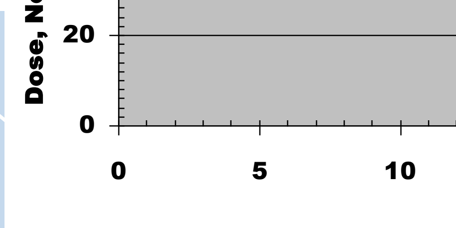
What is Radiation Therapy?
(External Beam Therapy)

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

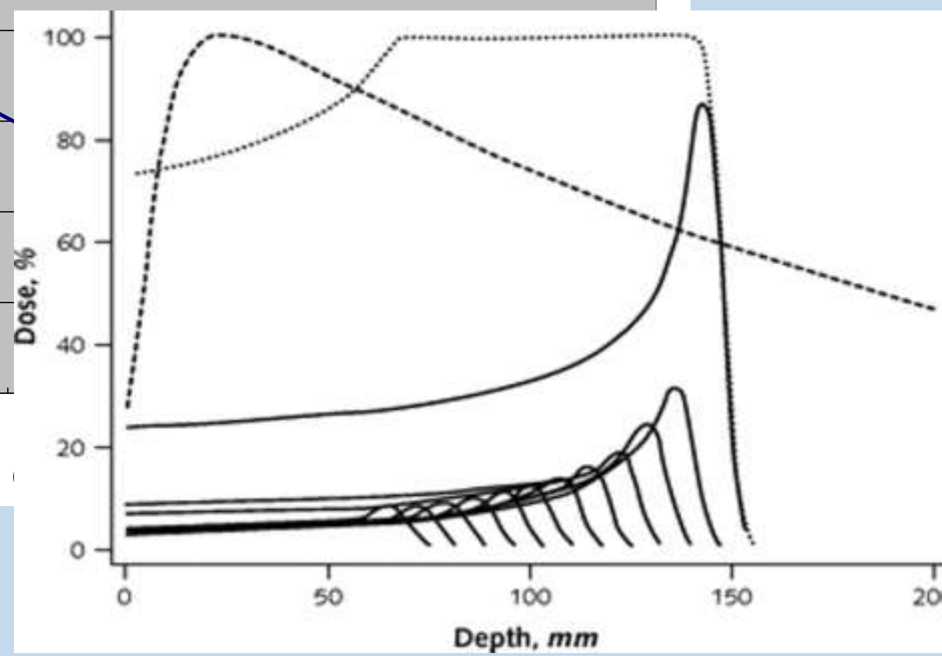
Where is the Energy Deposited?



Photons



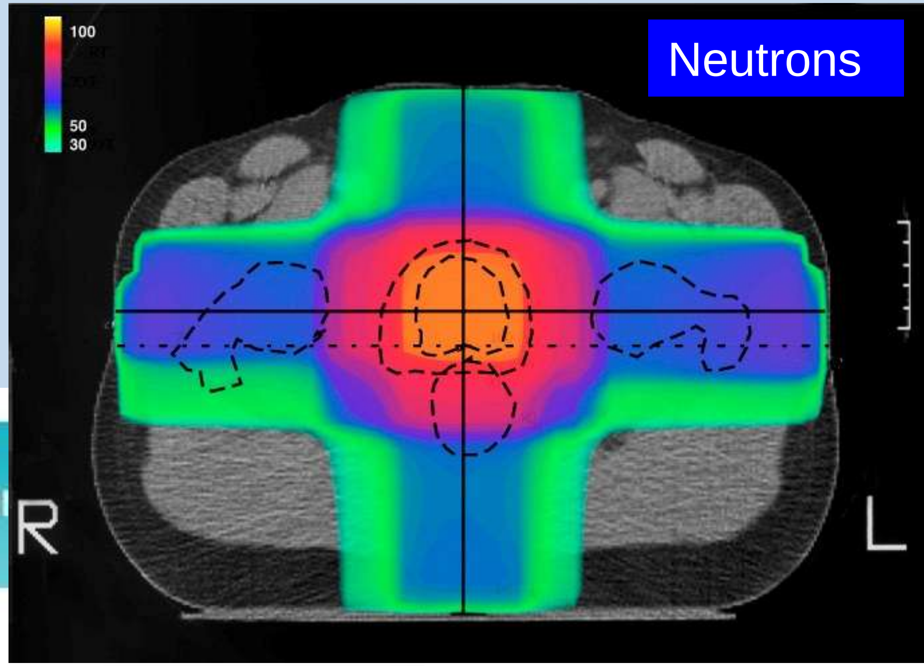
Neutrons

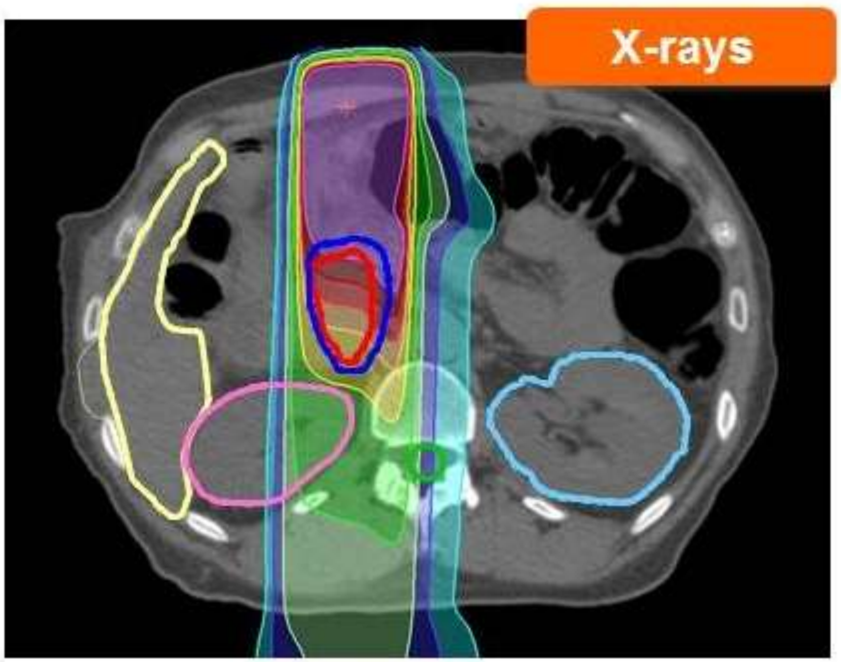


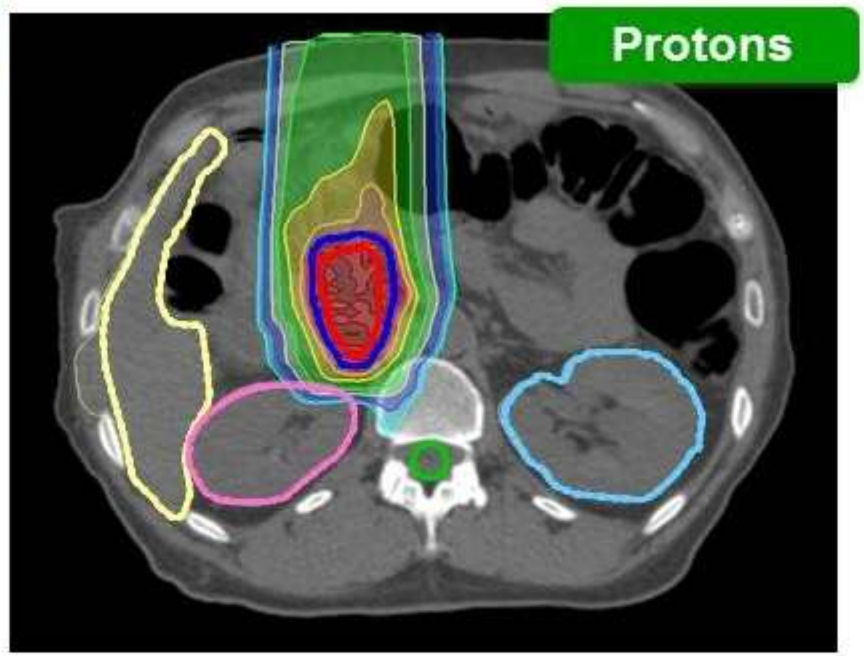
Protons

Image 2
Theoretical Compa
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?

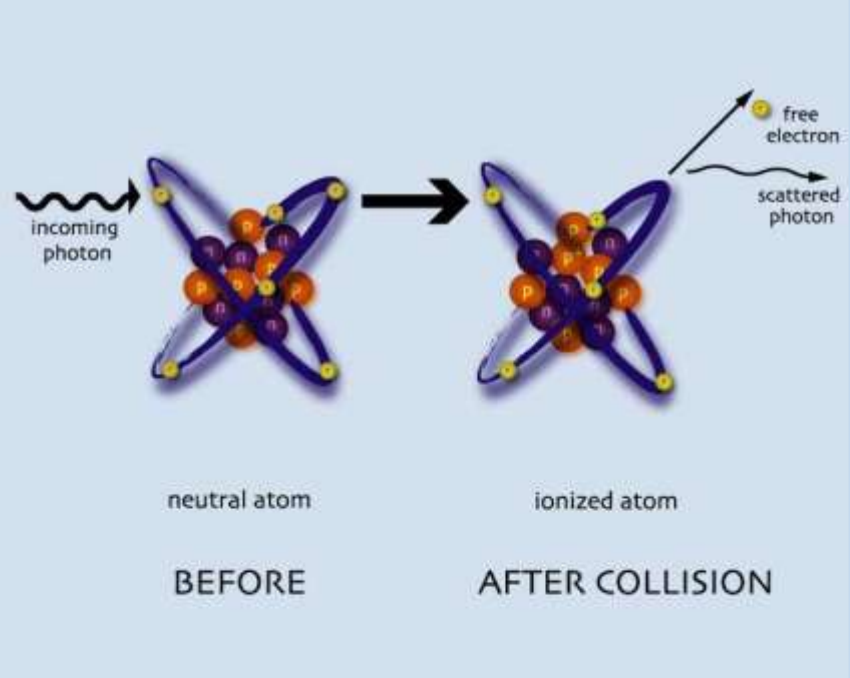
The Type of Damage Produced

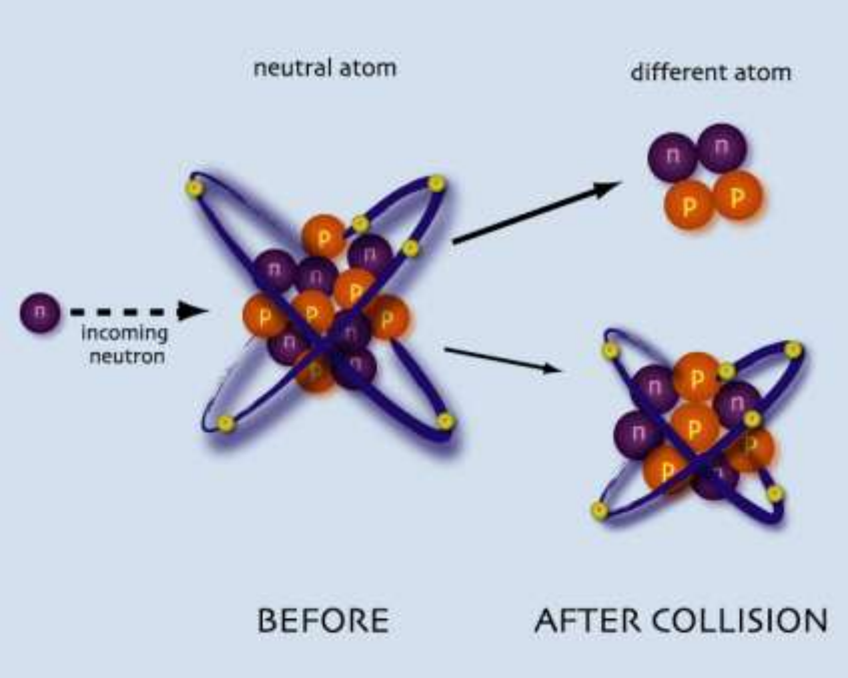
- Cell killing mechanisms are complicated
  - DNA damage
  - Free radicals
  - Bystander effect
  - Inflammation
  - Genetics
- Focus on DNA damage through:
  - Radiation Quality
  - Linear Energy Transfer - LET

Radiation Quality

Photons and Charged Particles

Neutrons





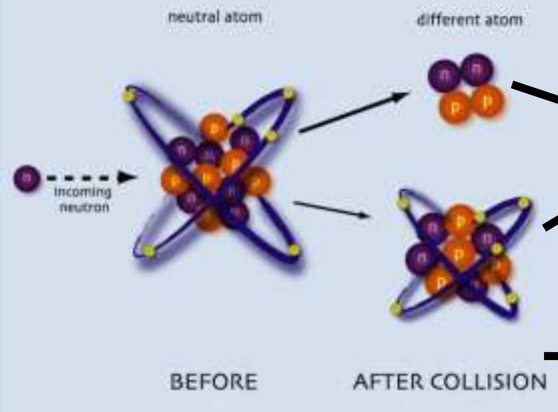
Low LET

High LET

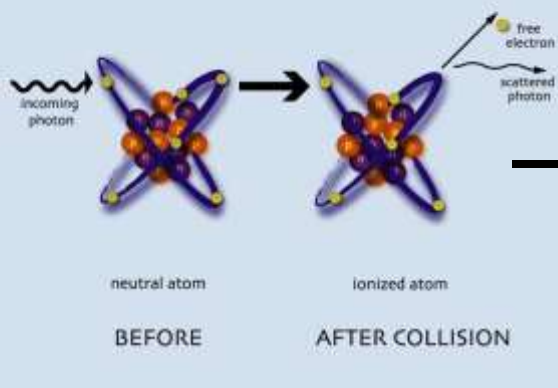
LET Comparison

(Linear Energy Transfer)

Neutrons



Photons & Protons



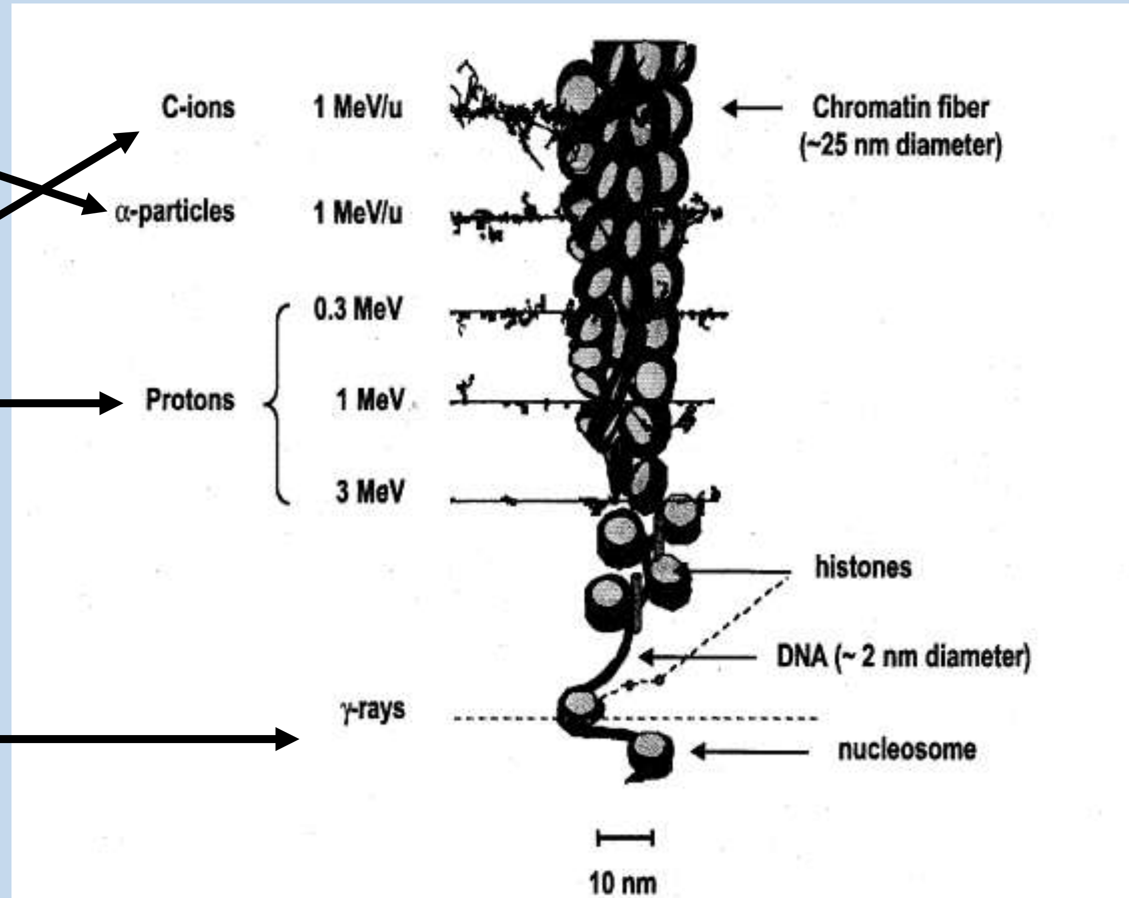
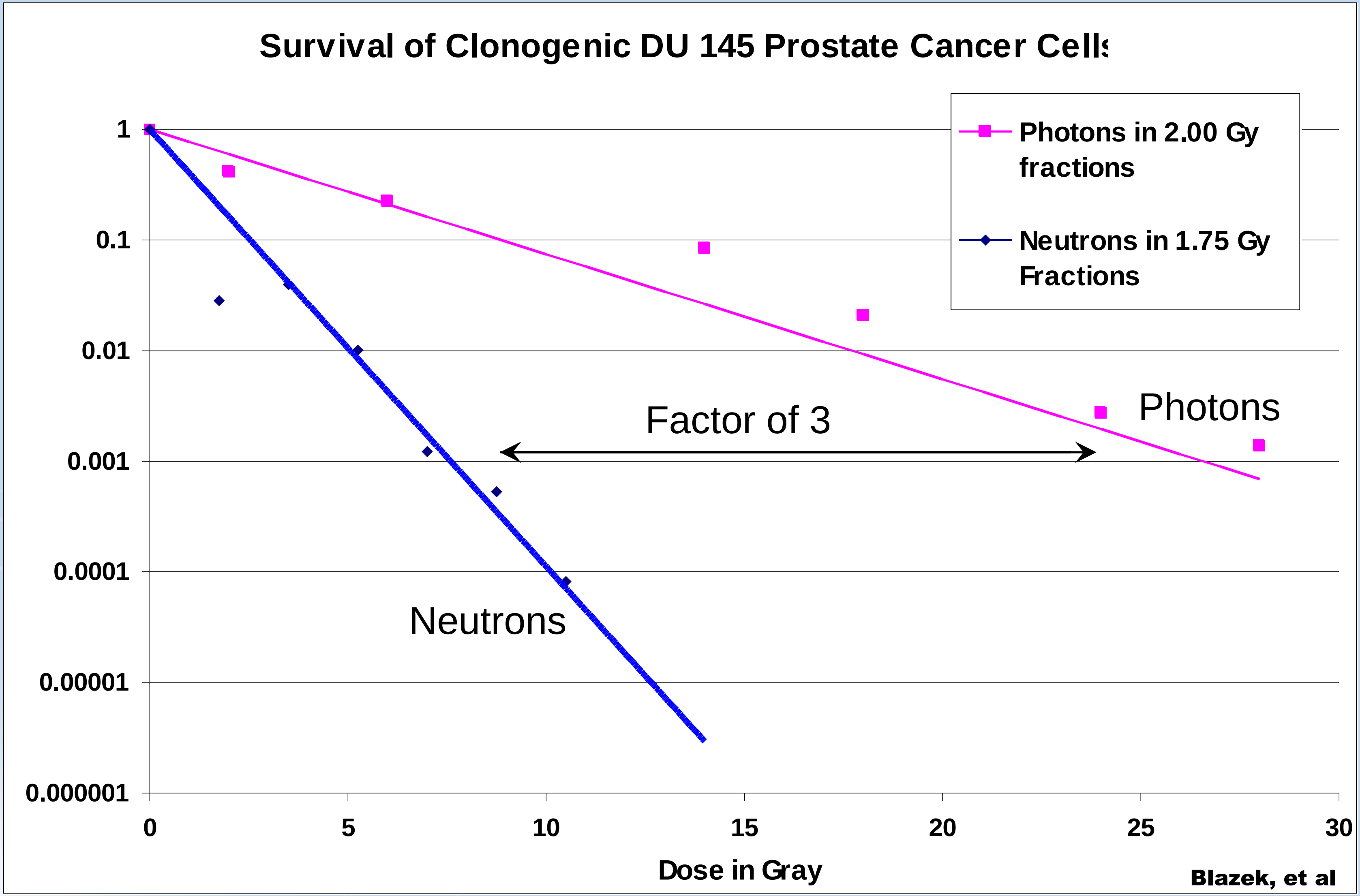


Fig. 1. Schematic representation of tracks of sparsely and densely ionizing radiations compared with relevant biological targets (chromatin fiber, nucleosomes and DNA double helix). Proton and alpha-particle tracks are based on the works of Paretzke[12] and carbon tracks on the works of Kramer and Kraft[13].

Belli, et. al., Molecular Targets in Cellular Response to Ionizing Radiation
and Implications in Space Radiation Protection, J. Radiat. Res.,43:Suppl.,S13-S19 (2002)

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?

Bragg

Protons

$$$

Ions

$$$$($)

Dose Distribution

Photons

$

Neutrons

$$

Cost-effective High RBE Therapy

Exponential

Low

LET

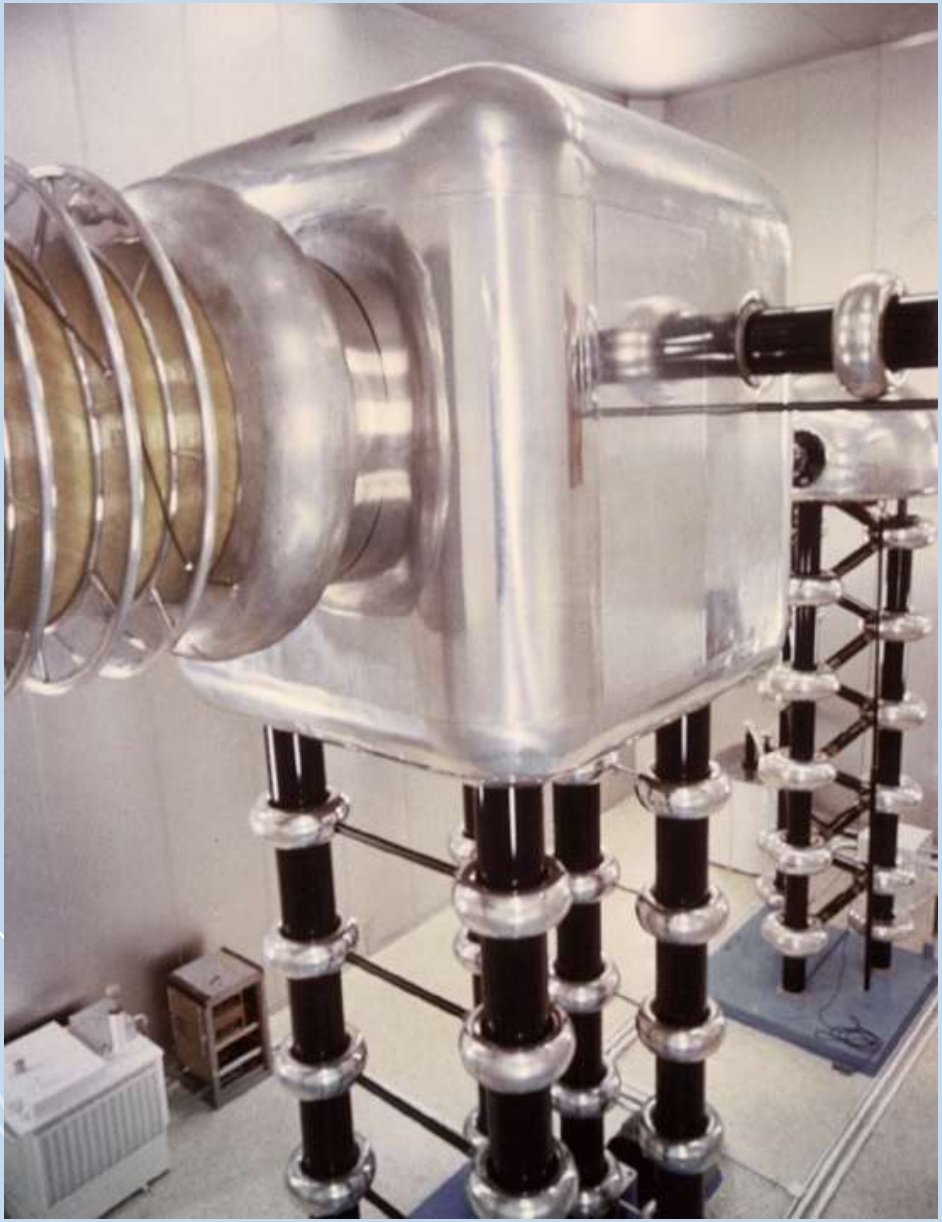
High

Why Fermilab?

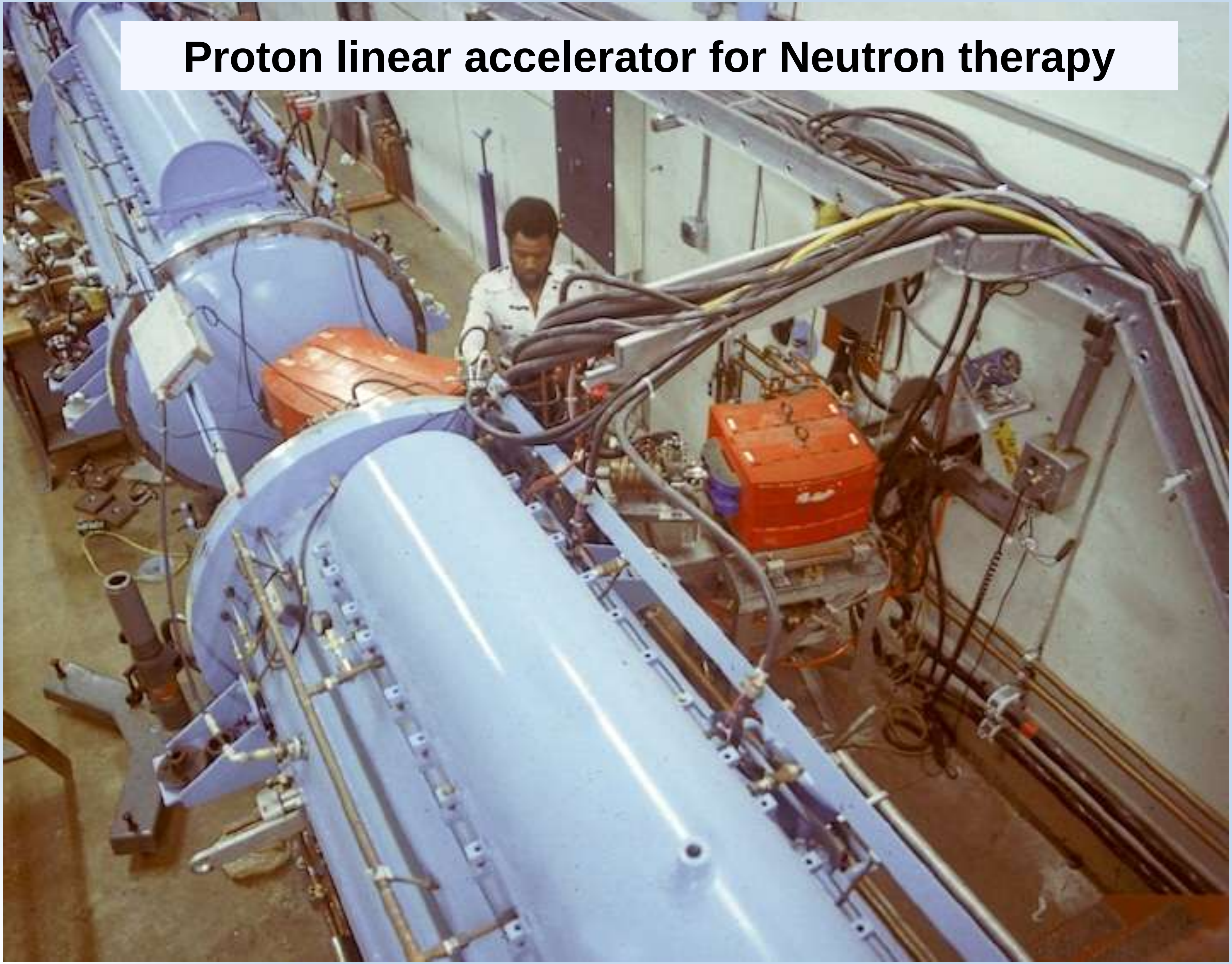
- Robert Wilson – 1st director of Fermilab
  - Article in Radiology in 1946 proposing protons
- Paper by Louis Rosen of LASL
  - Use of accelerators for other than physics research – PAC '71
- Prof. Lester Skaggs – U of C & Argonne Cancer Hospital
  - Organized discussions looking at p, ions, π –1971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

How is radiation therapy done?

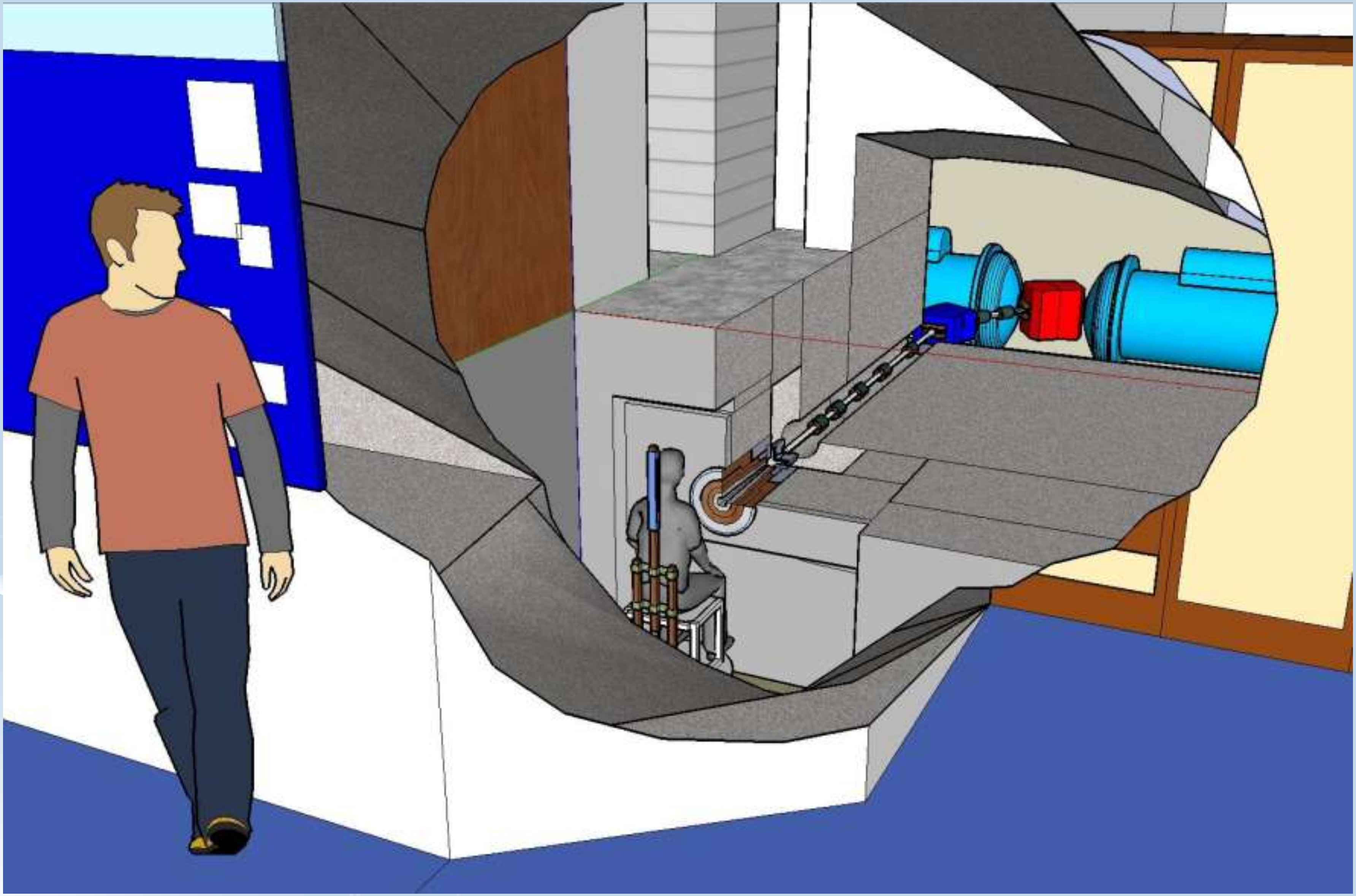
Proton linear accelerator for neutron therapy



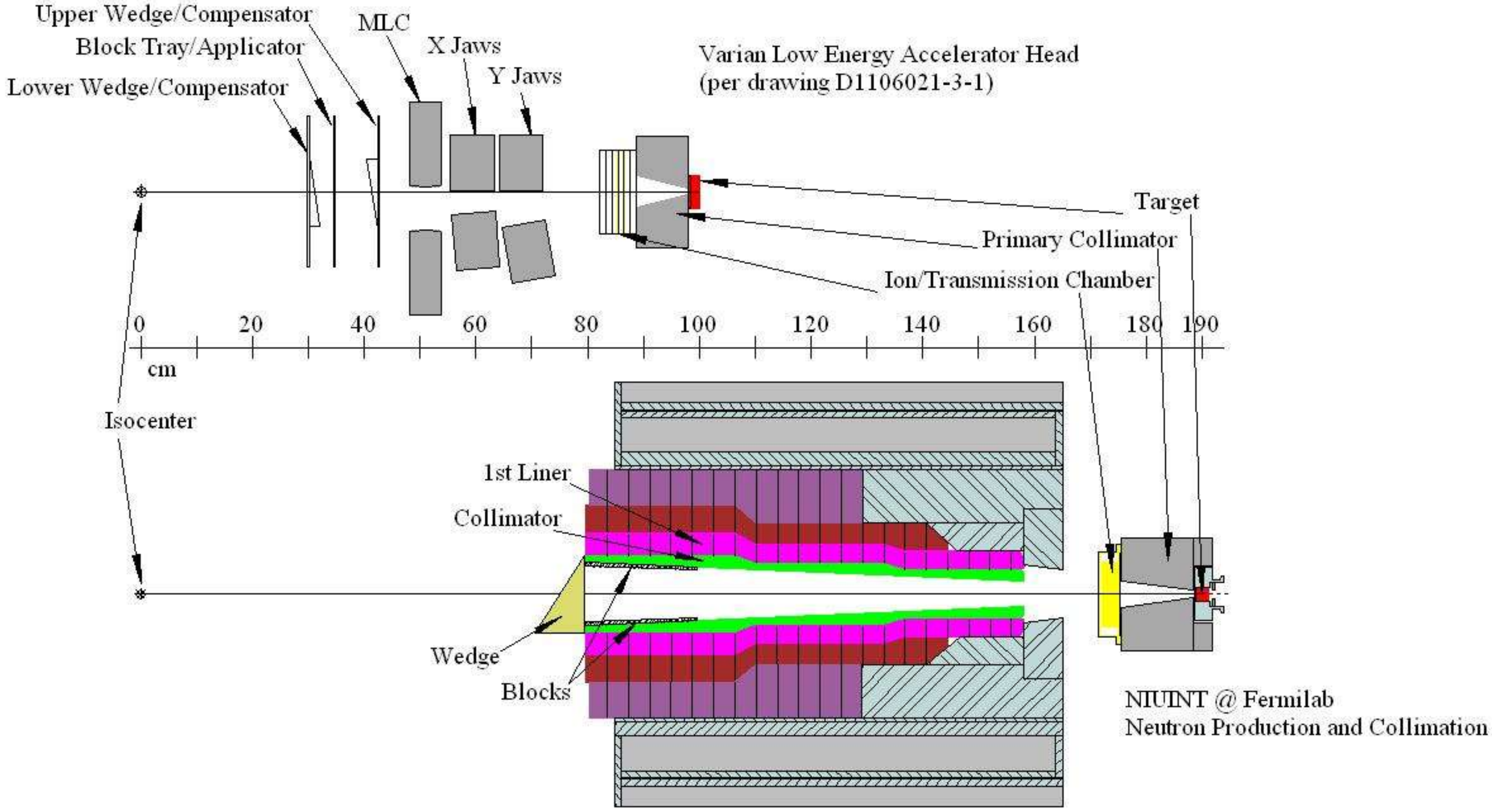
Proton linear accelerator for Neutron therapy



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 accomodated 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.

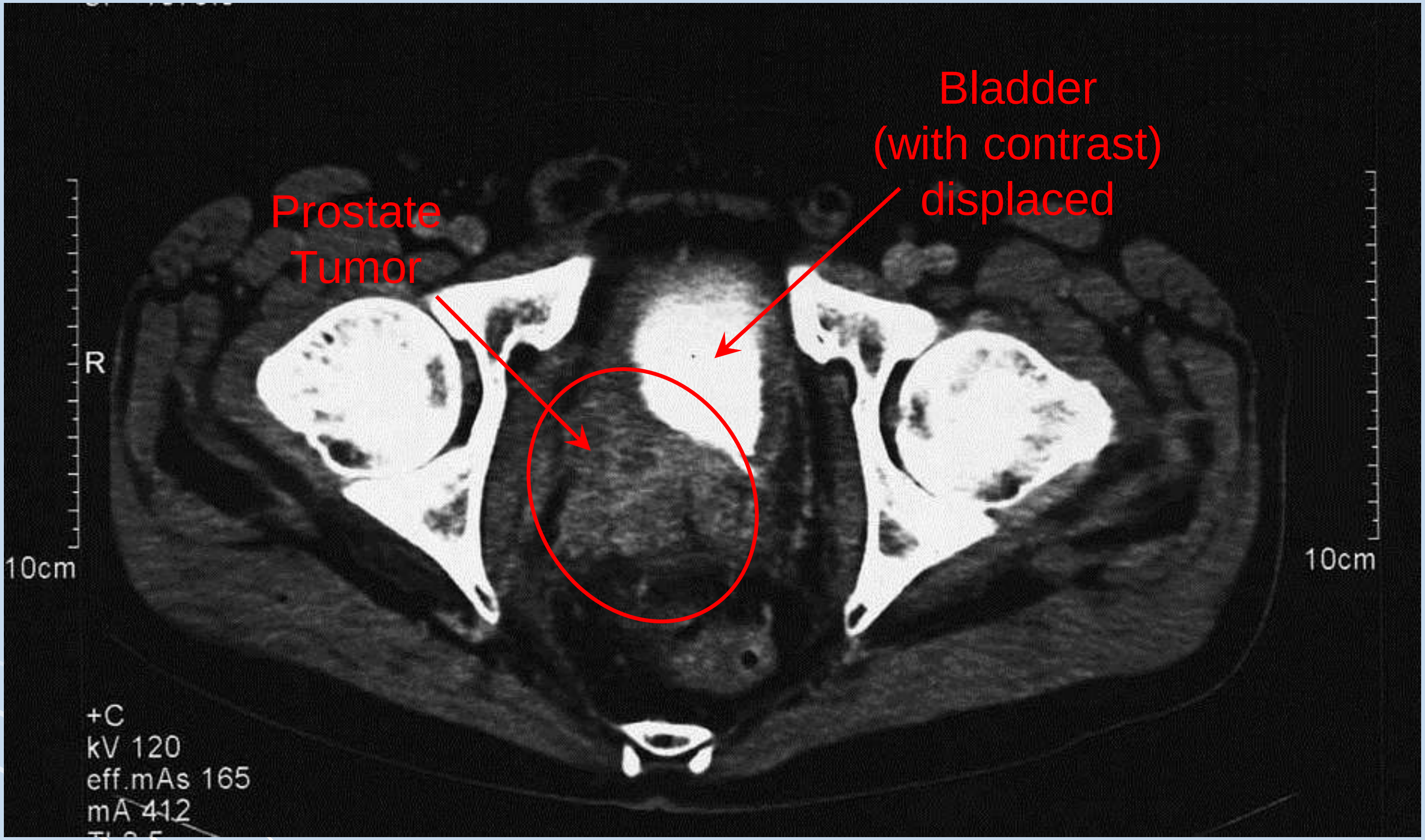
T. K. Kroc
10-9-07

Some Clinical Results

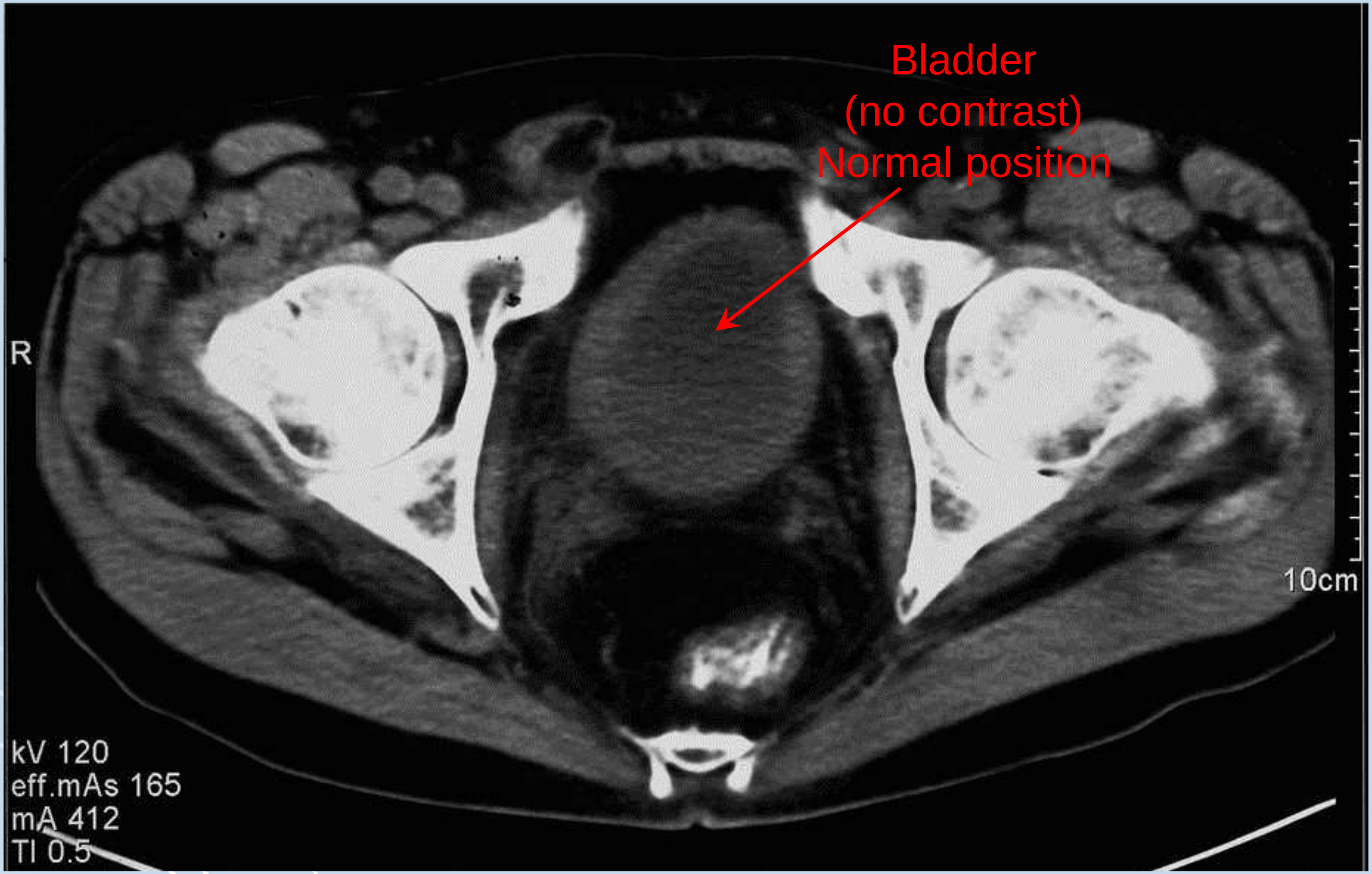
How good is Neutron Therapy?

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 *et al.* (1987)	113	71	(63%)
Catterall and Errington (1987)	65	50	(77%)
Battermann and Mijnheer (1986)	32	21	(66%)
Griffin *et al.* (1988)	32	26	(81%)
Duncan *et al.* (1987)	22	12	(55%)
Tsunemoto *et al.* (1989)	21	13	(62%)
Maor *et al.* (1981)	9	6	(67%)
Ornitz *et al.* (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 *et al.* (1984)	49	2	(4%)
Borthne et al. (1986)	35	8	(23%)
Rafla (1977)	25	9	(36%)
Fu *et al.* (1977)	19	6	(32%)
Stewart *et al.* (1968)	19	9	(47%)
Dobrowsky *et al.* (1986)	17	7	(41%)
Shidnia *et al.* (1980)	16	6	(38%)
Elkon *et al.* (1978)	13	2	(15%)
Rossman (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®)

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]

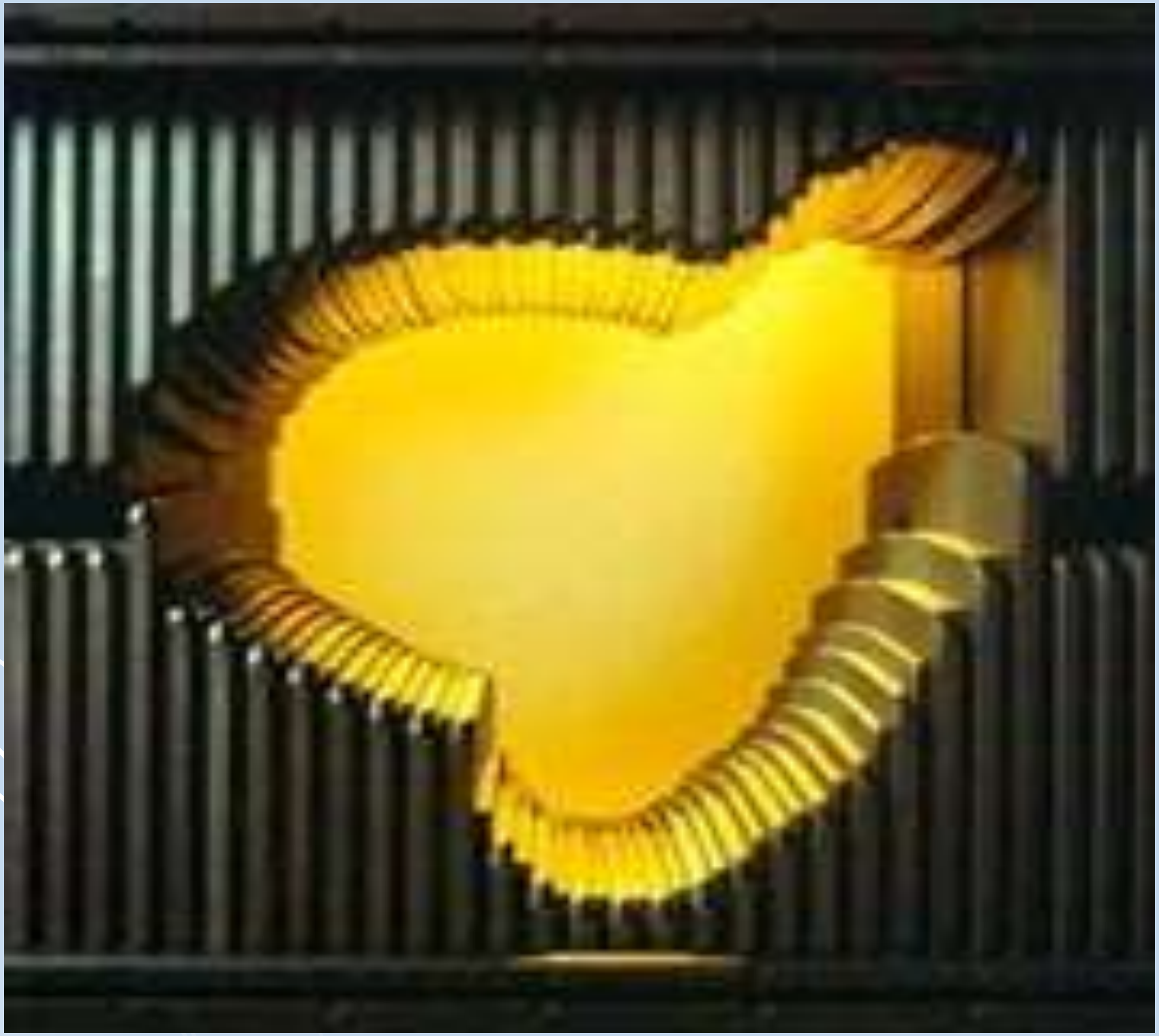
An Important Point for Potential Health Care Consumers

- 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

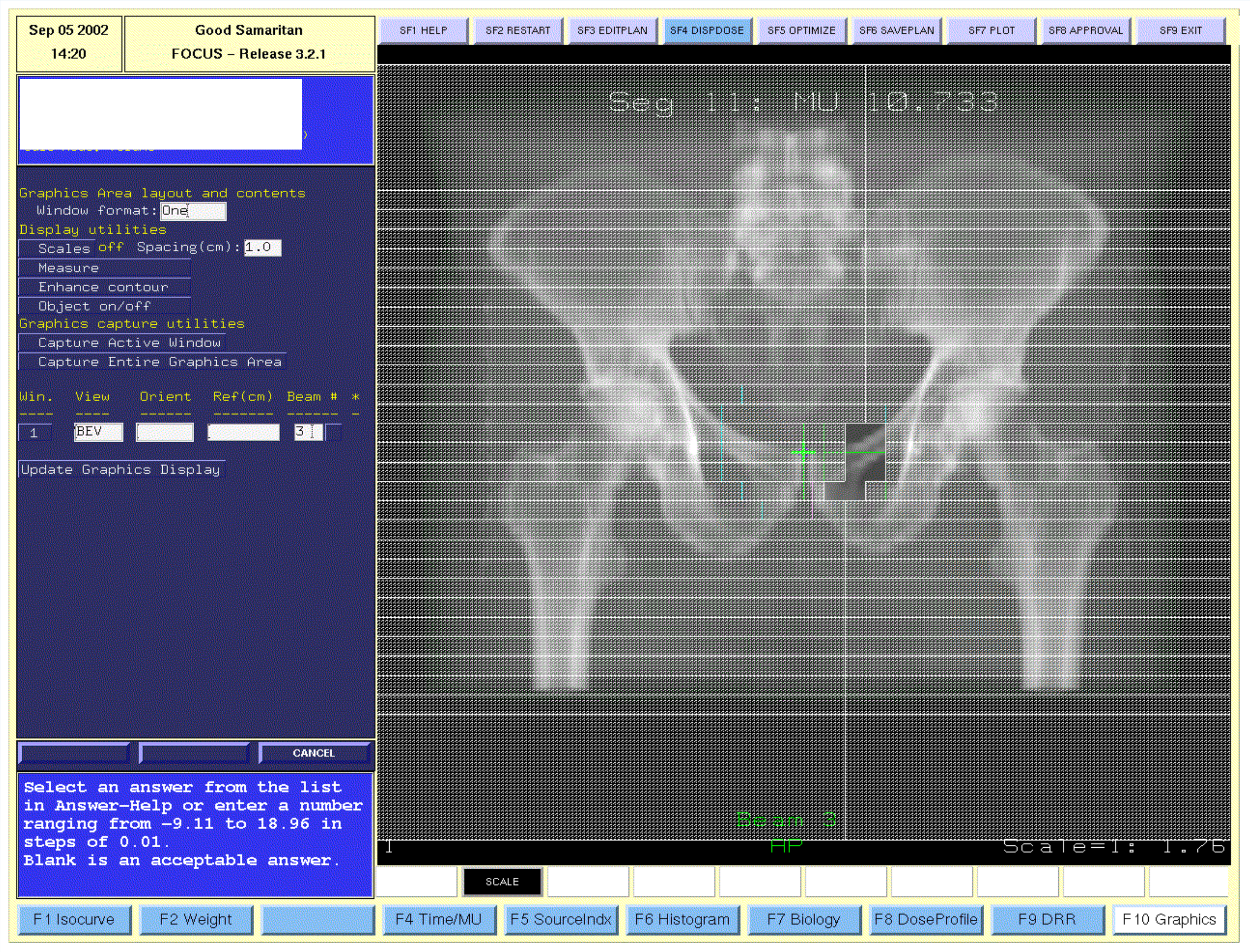
The Future

- 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



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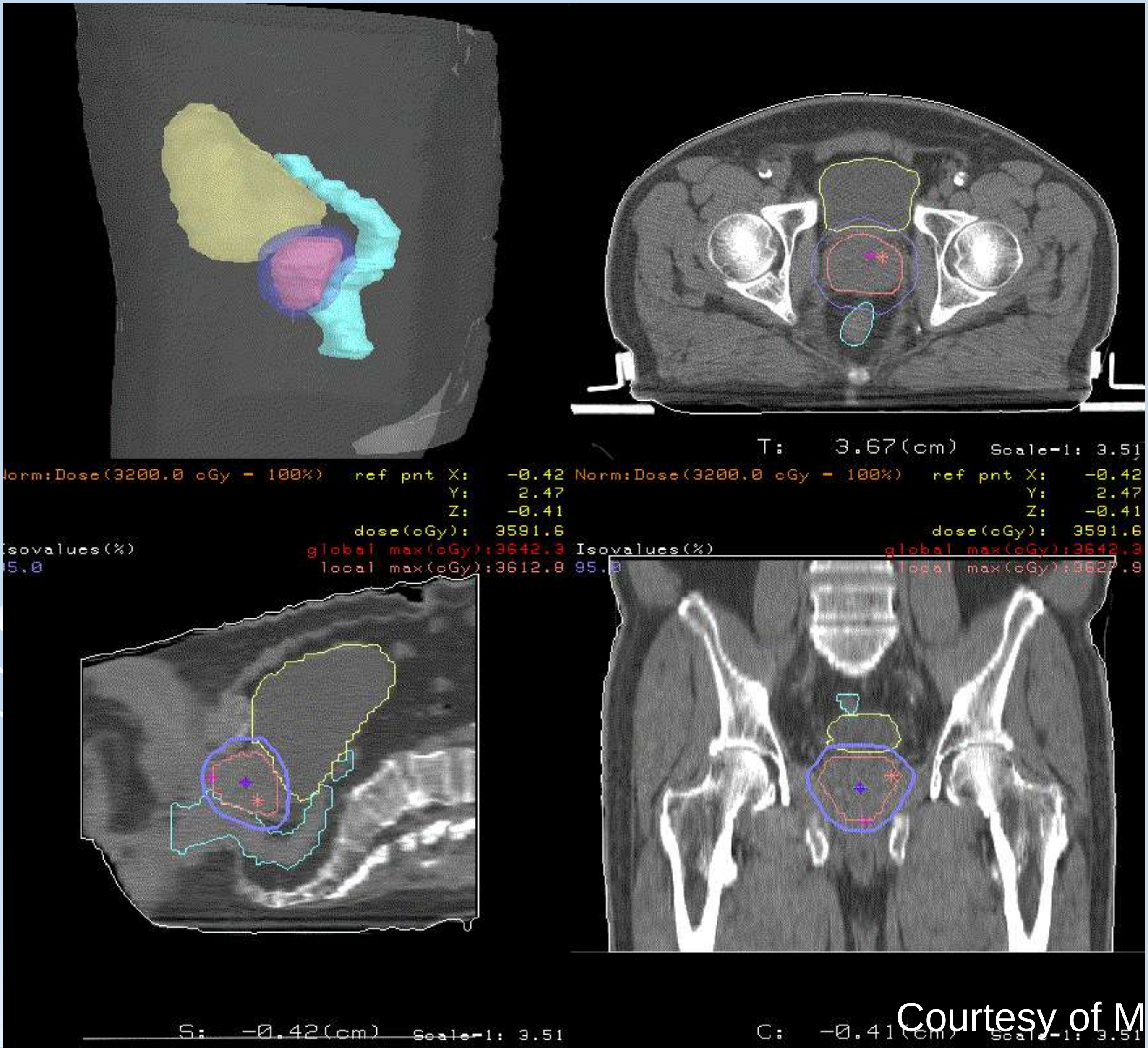
IMRT



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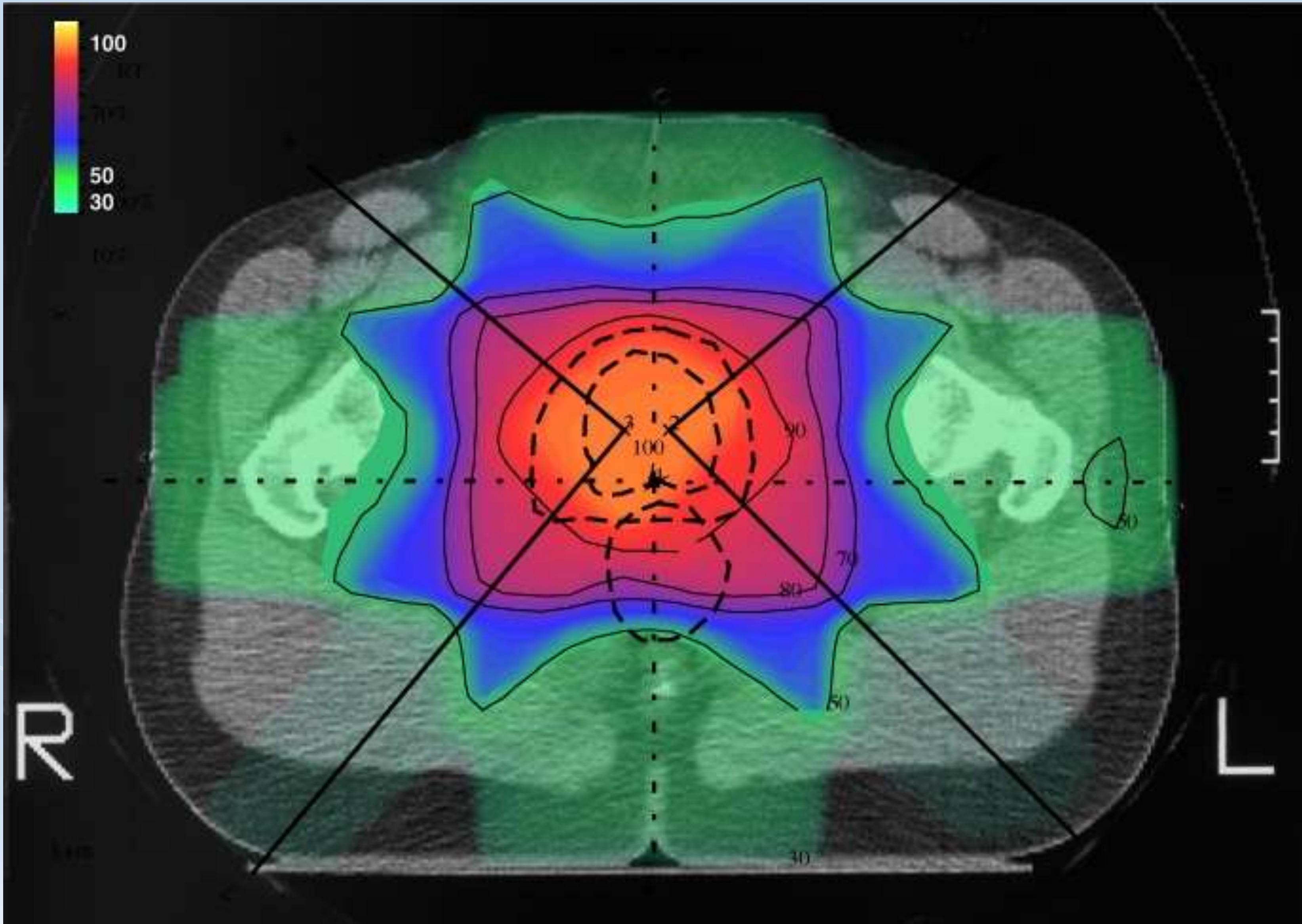
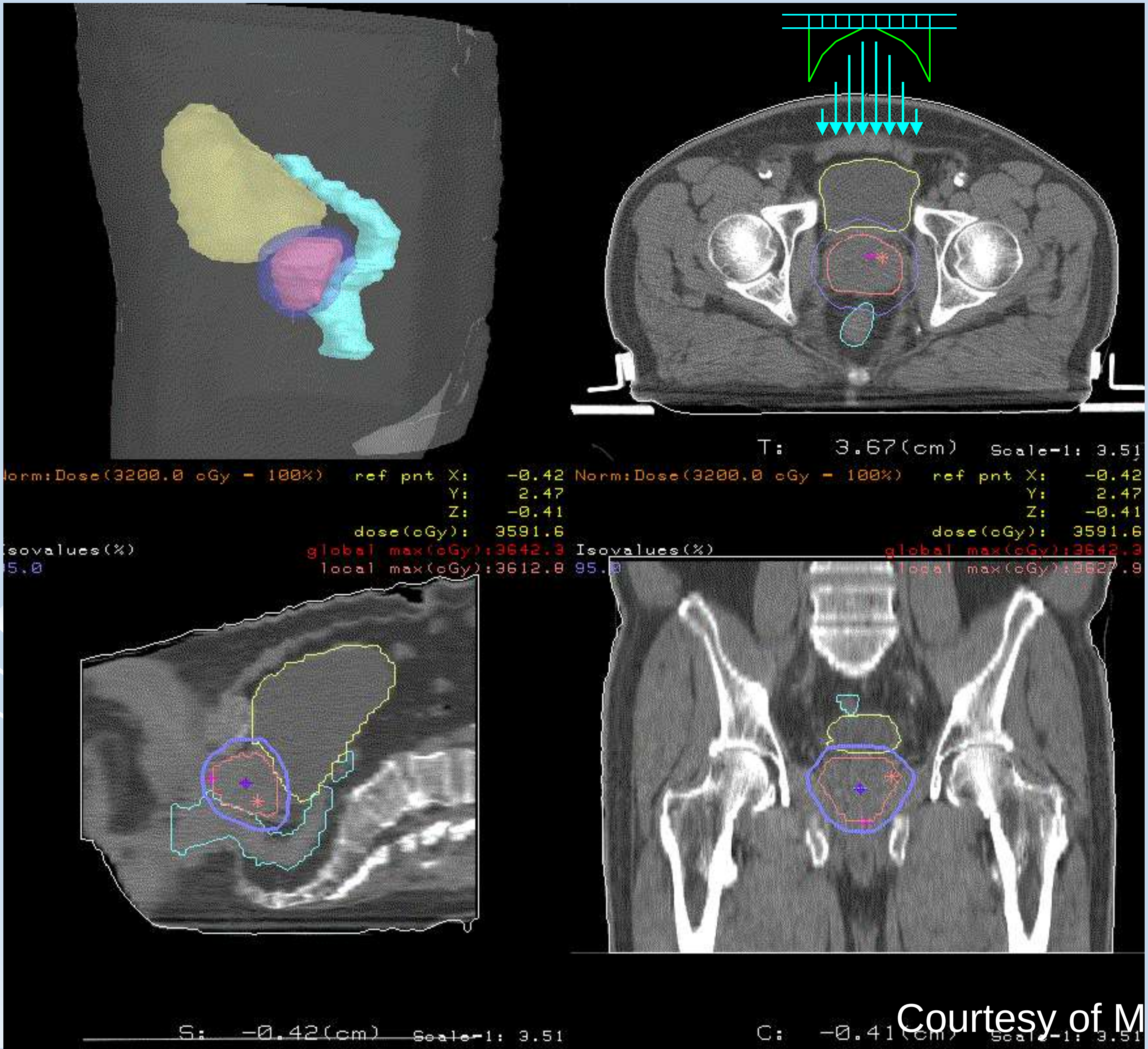


Eight-Field Technique

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.

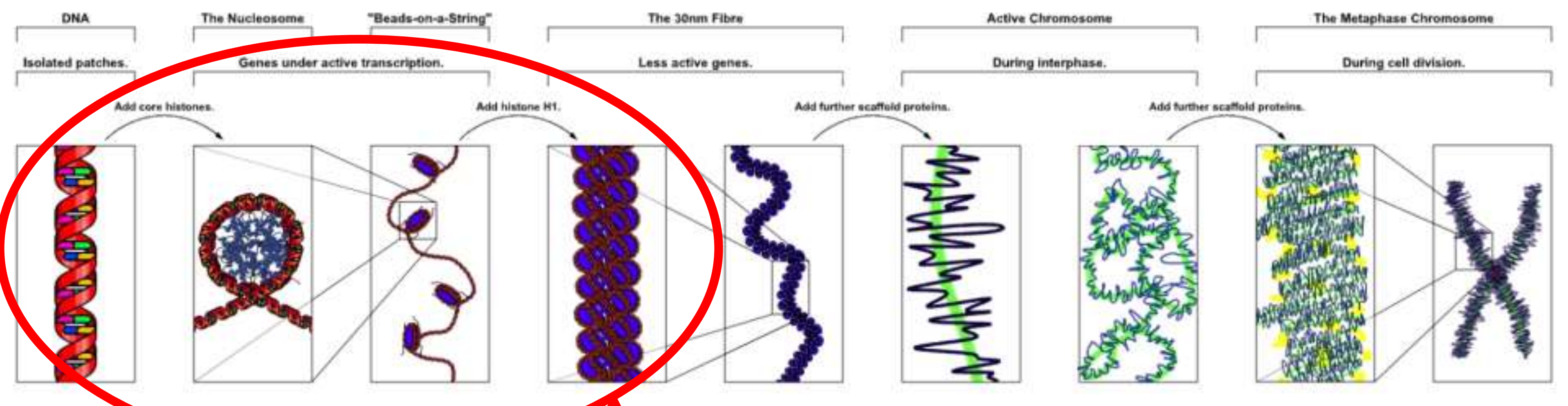
Dose	Neutron Source			
	High Energy (#)	Intermediate Energy (#)	Low Energy (#)	DT (#)
≤ 15 Gy	0 (4)	0 (3)	33% (6)	0 (7)
15.1 – 17.0 Gy	0 (3)	0 (2)	21% (86)	0 (18)
17.1 – 19.0 Gy	0 (3)	0 (18)	0 (5)	66% (3)
19.1 – 21.0 Gy	4% (28)	0 (19)	–	–
21.1 – 23.0 Gy	11% (56)	24% (38)	–	–
23.1 – 25.0 Gy	9% (22)	0 (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 Leewenhoeck	DT Generator	0.5 MeV d->T (14.3)

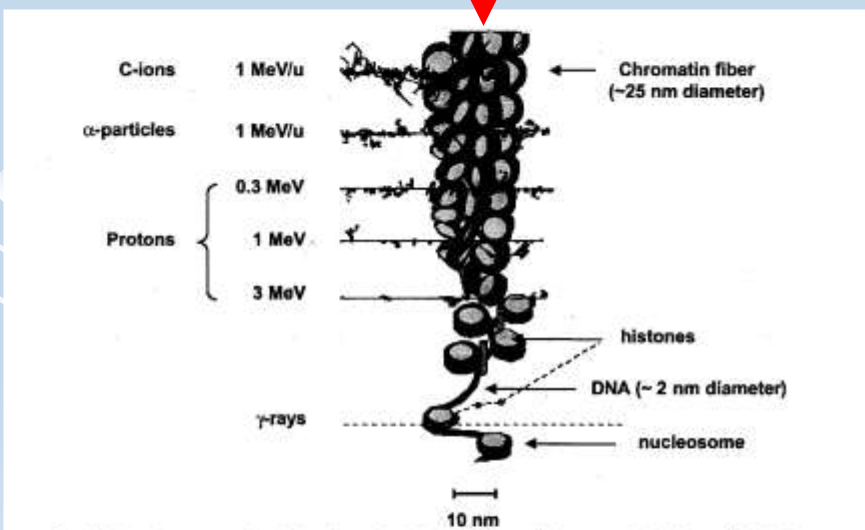
* upgraded to 50 MeV->Be (22) since this study

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

DNA Damage



2 nm 10 nm 30 nm ~200 nm 2 μm



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Optimum LET
100 eV/nm
~3 ip

Understanding Dose