Evolution of Radiation Oncology: learning from the past and adapting to recent advances

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Historical Perspective

Wilhelm Conrad Röntgen

On the evening of November 8, 1895, he found that, if the discharge tube is enclosed in a sealed, thick black carton to exclude all light, and if he worked in a dark room, a paper plate covered on one side with barium

platinocyanide placed in the path of the rays became fluorescent even when it was as far as two meters from the discharge tube.

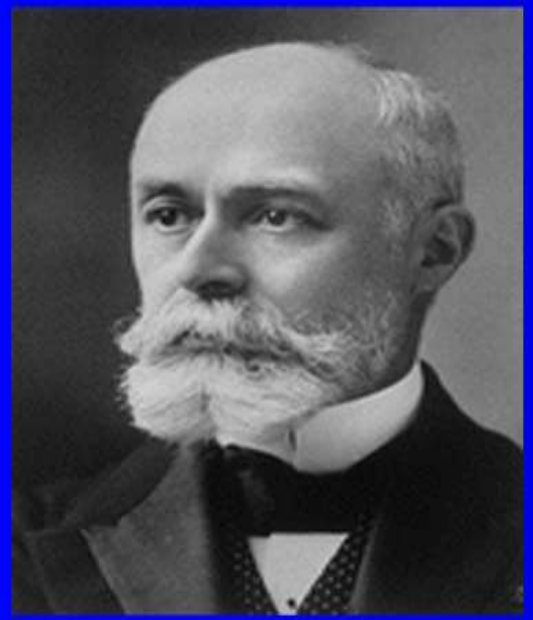
(27 March 1845 – 10 February 1923) was a German physicist, an achievement that earned him the first Nobel Prize in Physics in 1901

Emil Grubbe

Medical Student in Chicago

March 29, 1896 in an X-ray Tube factory in Chicago he began to bombard Rose Lee an elderly woman with recurrent breast cancer and had the first documented response to radiation

Antoine Henri Becquerel



In 1896, decided to investigate whether there was any connection between X-rays and naturally occurring phosphorescence. He had inherited from his father a supply of uranium salts, which phosphoresce on exposure to light. When the salts were placed near to a photographic plate covered with opaque paper, the plate was discovered to be fogged.

(15 December 1852 – 25 August 1908) was a French physicist, Nobel laureate, and the discoverer of radioactivity along with Marie Skłodowska-Curie and Pierre Curie, for which all three won the 1903 Nobel Prize in Physics.

Marie Curie

The discovery of radioactivity by Henri Becquerel led to in 1898 the Curies to the isolation of polonium, named after the country of Marie's birth, and radium. Mme. Curie developed methods for the separation of radium from radioactive residues in sufficient quantities to allow for its characterization and the careful study of its properties, therapeutic properties in particular.

(7 November 1867 – 4 July 1934) was a French-Polish physicist and chemist, She was the first person honored with two Nobel Prizes—in physics and chemistry. She was the first female professor at the University of Paris, and in 1995 became the first woman to be entombed on her own merits in the Pantheon in Paris.

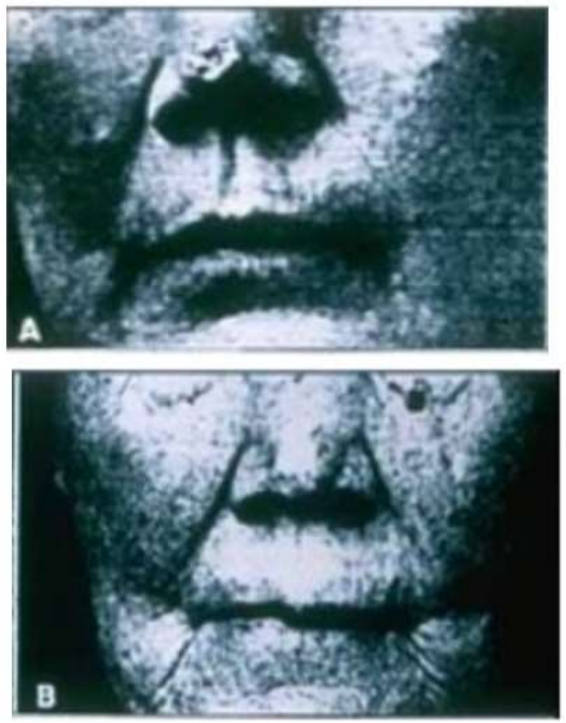
First few years of the twentieth century

Increased interest in the use of X-ray and Radium in medicine

FIRST EVER X-RAY TREATMENT???

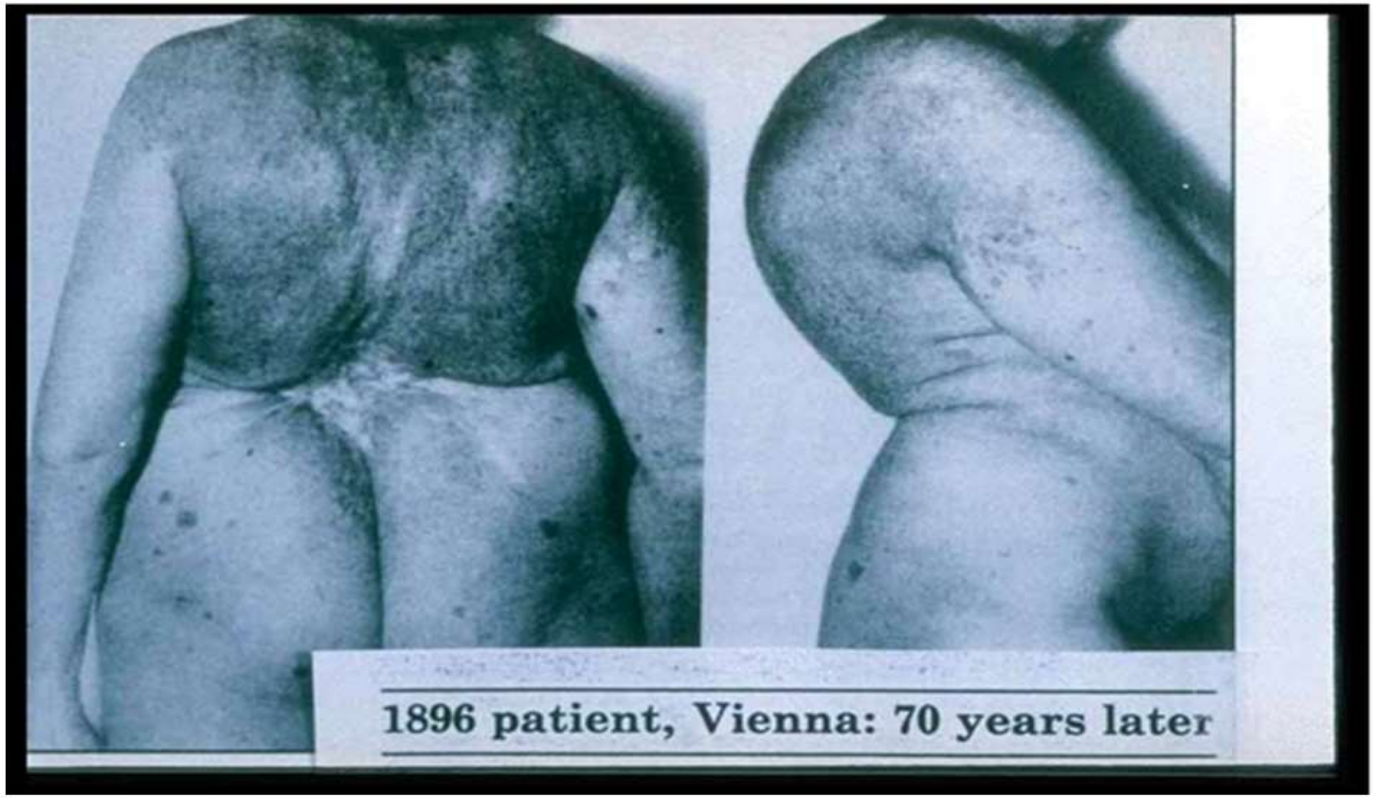
Jan 1896: Emile Grubbe therapeutically exposed a case of Carcinoma breast to a single treatment of x-rays for 1 hour

FIRST CANCER CURE BY X-RAYS

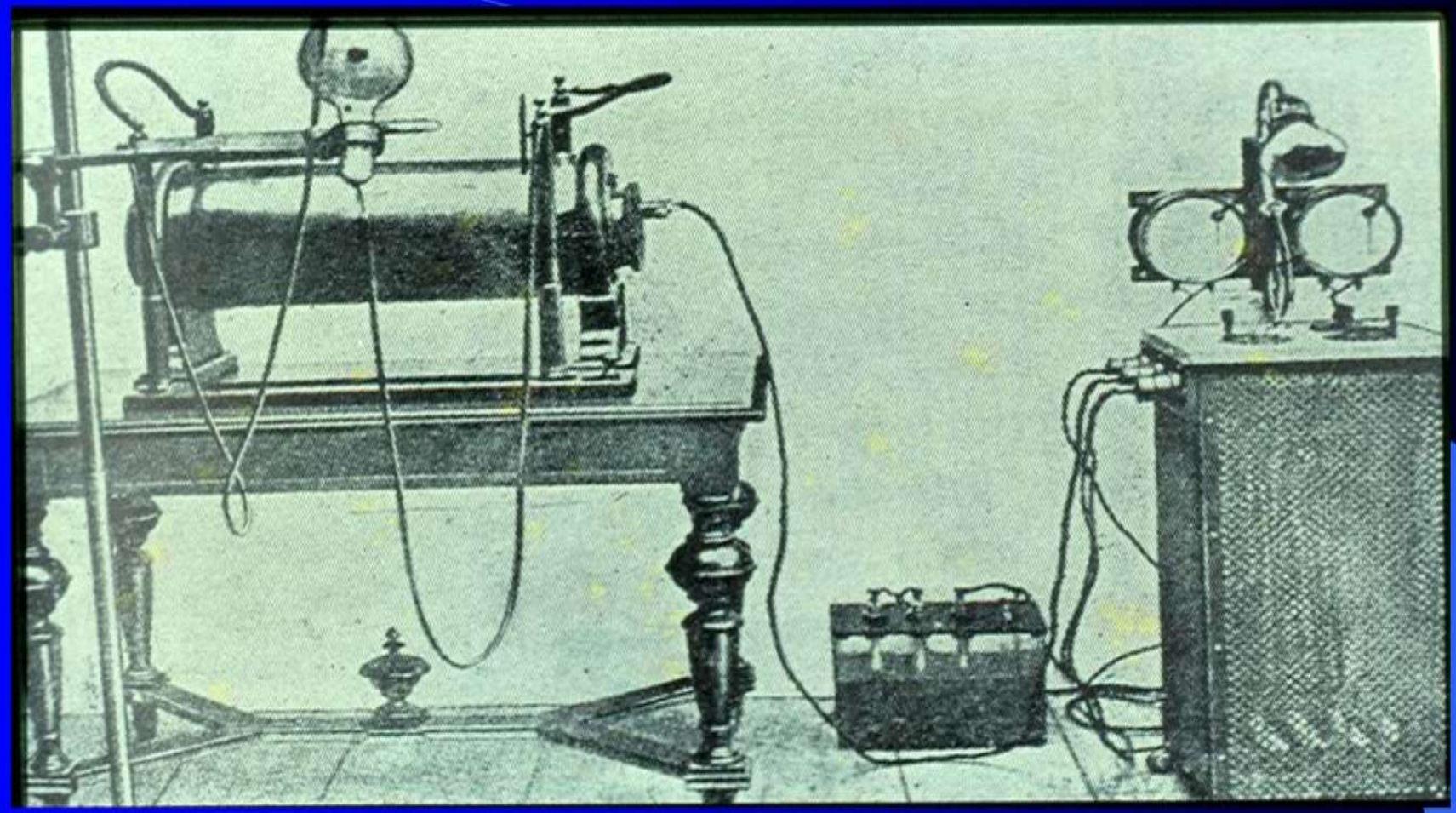


1899-1900 Stenbeck and Sjorgen first to cure BCC &SCC of skin using X-rays

FIRST EVER CURE BY X-RAYS



Nov 1896: Leopold Freund used fractionated X-ray therapy to treat a hairy nevus of a 5 year old girl child over 2 weeks.

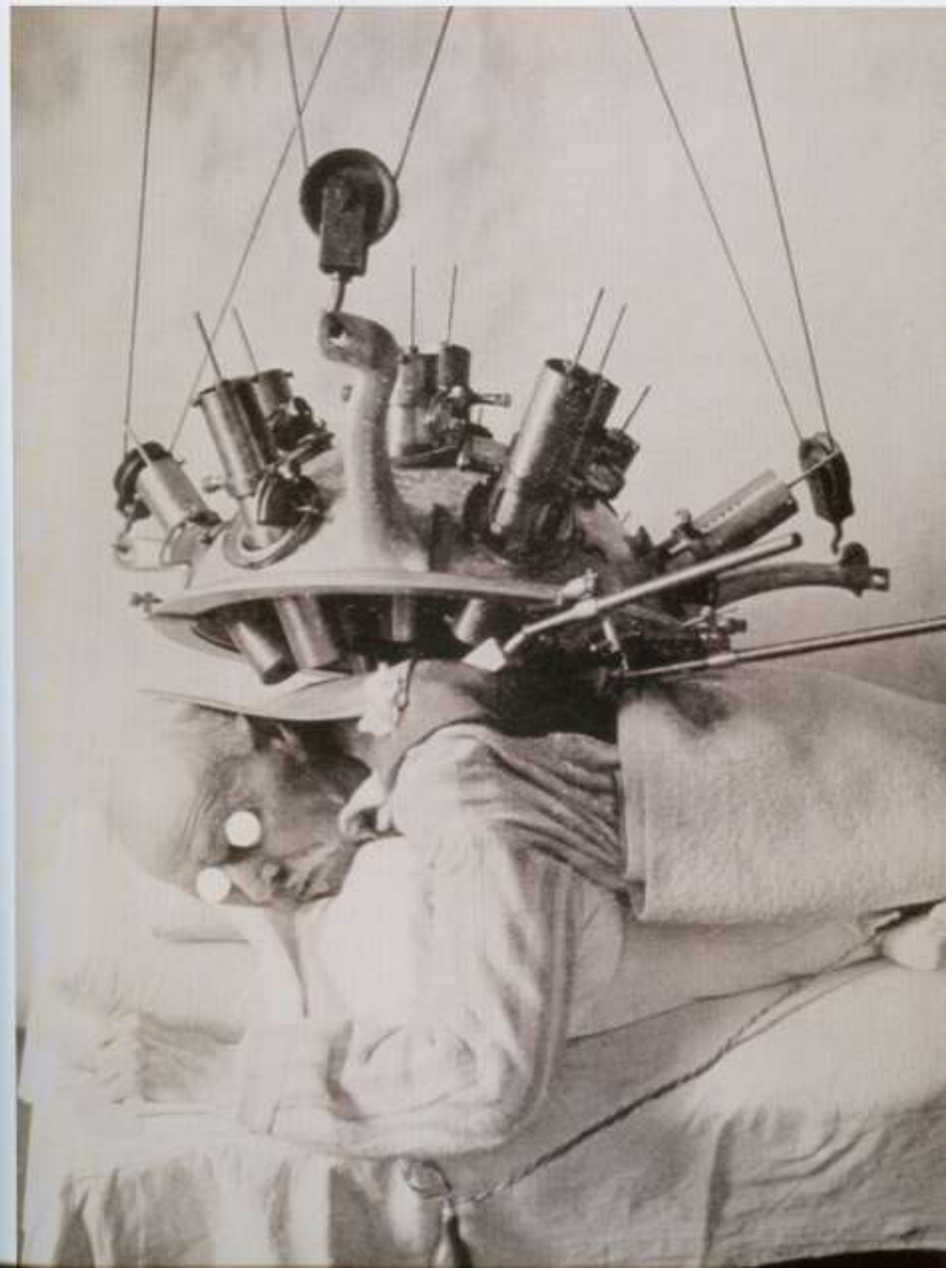


Pre- 1904 X-ray Machine

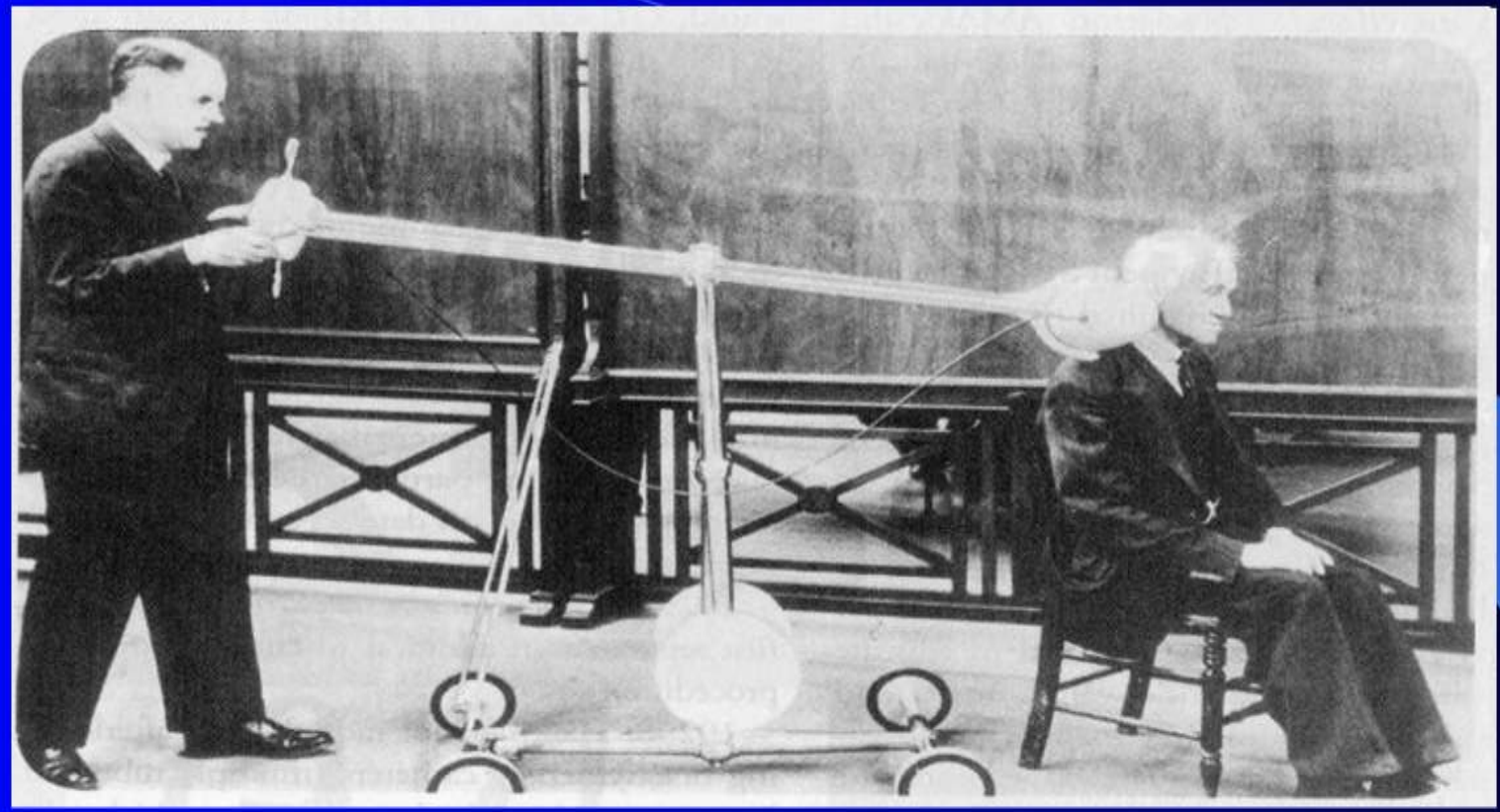
Sluys-Kessler

Radium Apparatus

Paris. 1930



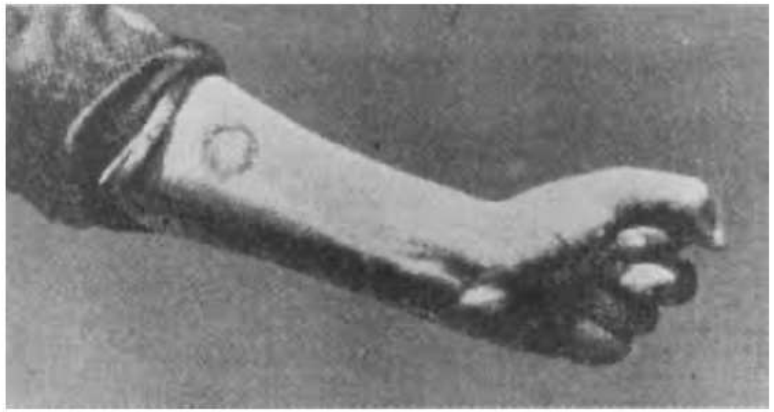
Radium Bomb London 1934

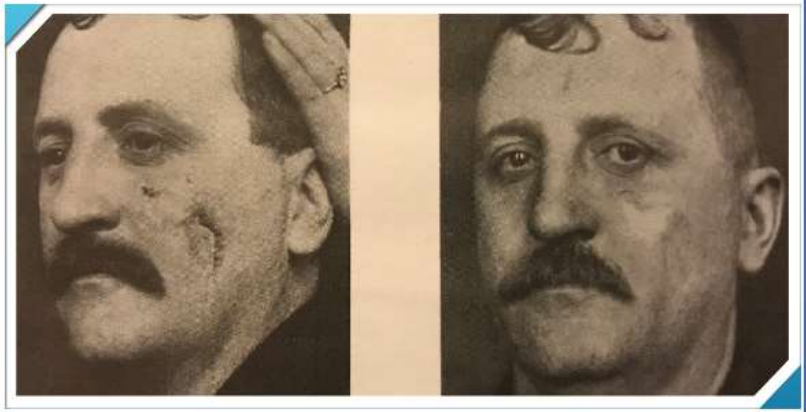


4 Radium sources close to the patient's skin. Each source focused on the cancer from a different angle, maximizing the dose to the localized area. Protective devices for the medical practitioner were non-existent at this time

RADIUM THE PANACEA?

- 1900: ***Radiumtherapy*** introduced by Danlos for treatment of lupus & other skin ailments
- 1903 : Margaret A. Cleaves in New York directly applied radium intracavitarily for the treatment of carcinoma of the cervix.
- 1905 : Robert Abbé, a New York surgeon, in 1905 implanted radium directly into a tumor.



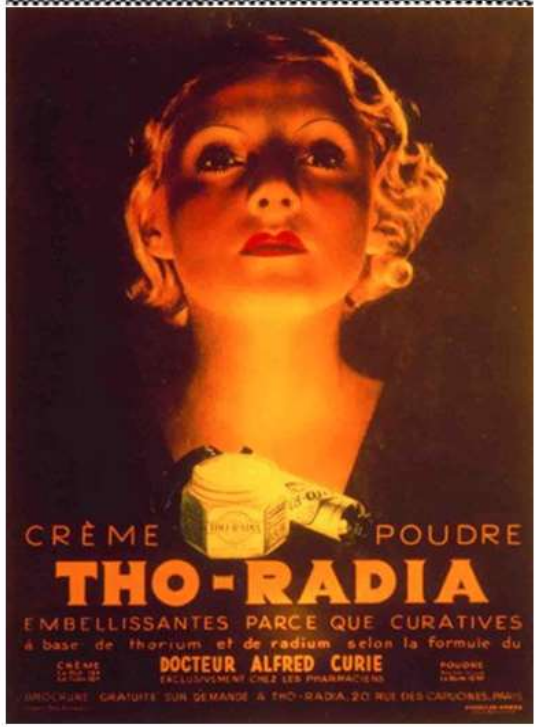


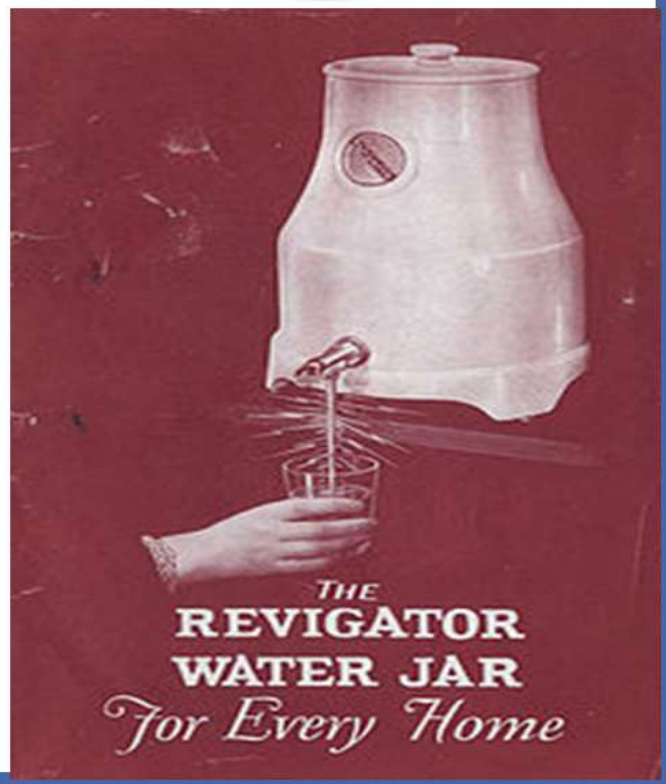
RADIUM AS A SUBSTITUTE FOR GAS, ELECTRICITY AND AS A POSITIVE CURE FOR EVERY DISEASE

Wonderful Things Learned About the New Metal by W. J. Hammer, Formerly Associated With Edison.

An Difficult to Obtain as Would Be a Specific of Flavoring Extract From the Waters of the Platte.

RADIOACTIVE QUACKERY



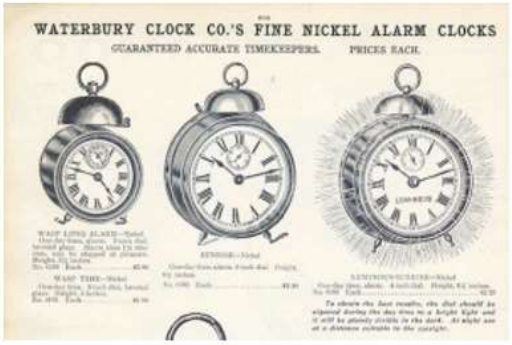


Enthusiastic use of X-rays and Radium without proper understanding of their physical and biological properties

led to more adverse effects

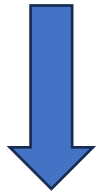
Undark and the Radium Girls

RADIUM GIRLS OF THE WATERBURY CLOCK COMPANY



Undark and the Radium Girls

Tumours could hardly be cured with these early approaches without incurring extensive normal tissue damage, due to the low energy and poor penetration power of beams



Initial failures stimulated a series of conceptual and technological developments

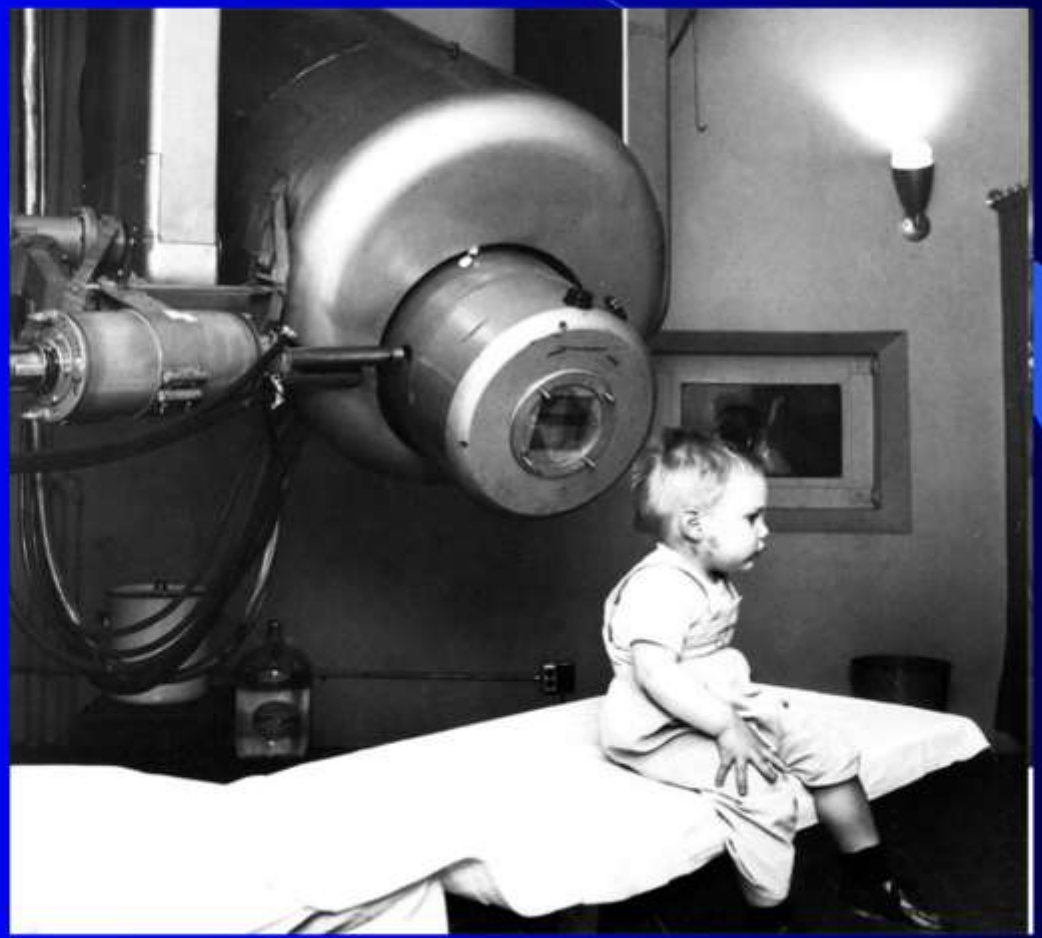
Technological advances in X-ray therapy

- Deep Xray/ Orthovolage therapy: 200 Kev range: 1913
- Gantry rotation introduced in 1920s
- Supervoltage Xray therapy by 1926
- LA developed by Sloan in 1930

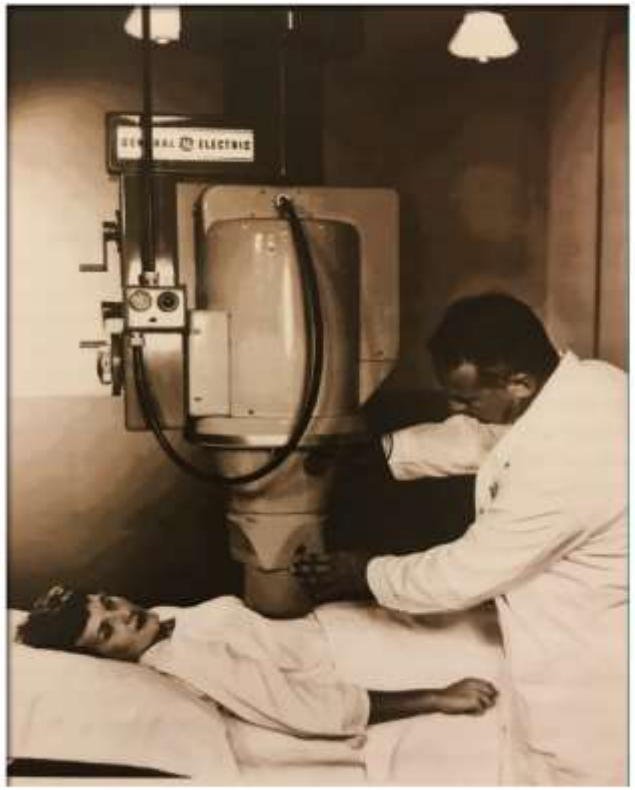
First Medical Linear Accelerator at Stanford in 1956

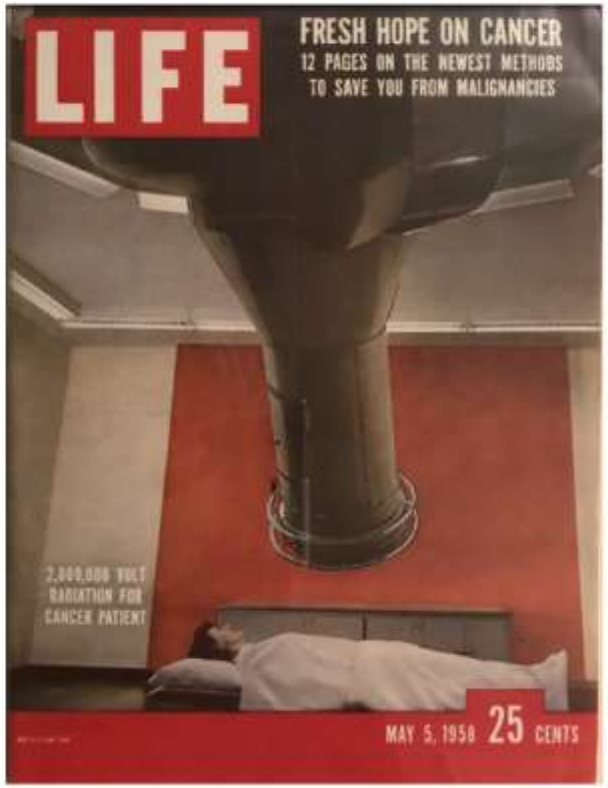
Click to add notes

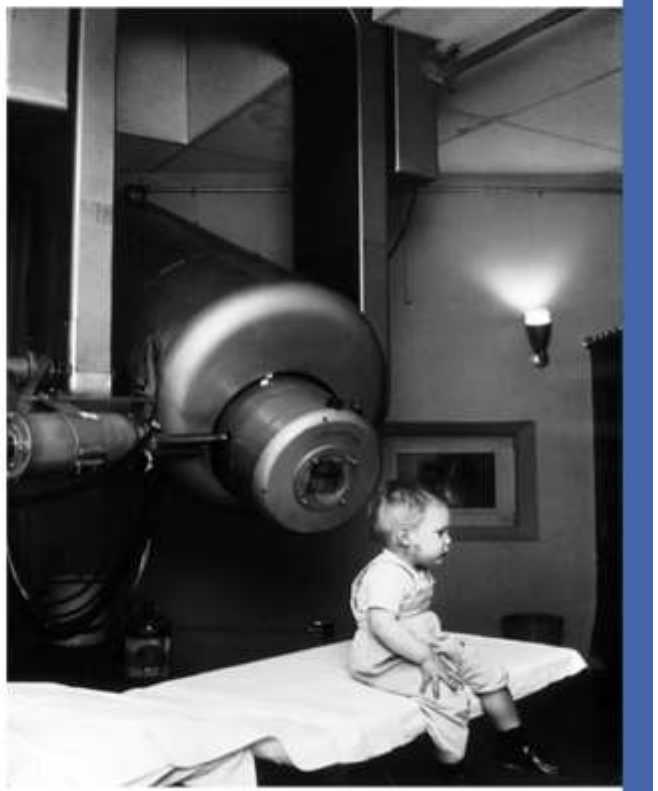
In January **1956** the machine was ready to be used on their first patient, a boy with retinoblastoma in his one remaining eye after surgeons had removed the tumor in the other eye. Destroying the tumor while sparing the eye would have been impossible with earlier, less-focused radiation sources.



TELECOBALT-60 (1951) & LINEAR ACCELERATOR (1953)



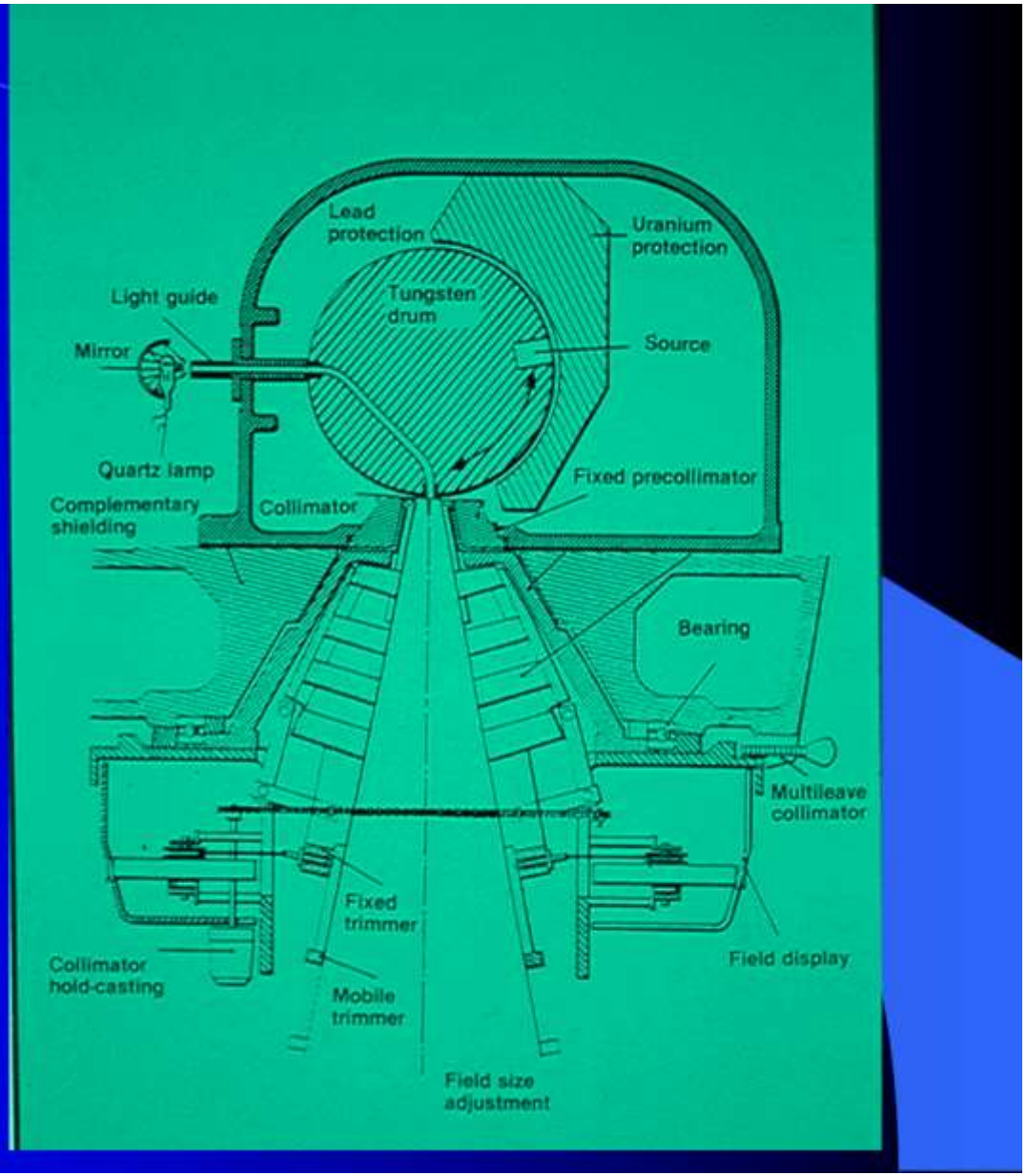




COBALT

The use of 60Co sources for teletherapy was begun in the **1950s** as a replacement for the 250 kVp x-ray treatment machines that were then in common use.

The skin-sparing effects of 60Co treatment were immediately recognized and such effects were no longer limitations on treatment.



Devolopements in Radiobiology

1911: Famous experiments on Ram's testis by Claudius Regaud:

Basis of modern fractionation in External Beam Therapy and
Continuous LDR application of Radium treatment

1920: Henri Coutard Popularized the concept of fractionation in curing a variety of Head and Neck malignancies
Applied custom Immobilization of patients and beam modification devices in external beam treatments

1930: Shift of interest from Radium to External Beam Therapy

Radiobiological developments

- 1934-41: Stranquivst: Iso-effect relationships based on radiotherapy induced skin reactions for comparibility between different dose schedules

- Orton and Ellis: NSD Formula-to compare the different fractionation schedules, based on total dose, number of fractions and overall treatment time

- Withers: Development of L-Q Model based on alfa and beta components of RT induced cell kill effects

Continuing developments in Radiobiology

- 4 RS of Radiobiology
  - Repair
  - Reoxygenation
  - Redistribution
  - Repopulation

- Development of Alternate fractionation schedules: EORTC & RTOG

  to increase the cure rates by exploring the differential recovery between normal and malignant tissues

Developments in Imaging

- Increasing application of CT, and MRI : for guiding modern radiotherapy planning and verification
- Fusion of Images –for better and more accurate planning

- PET Scan- for biological imaging and help in radiotherapy planning more accurately- especially useful in Lymphoma and Head & neck cancers
- Incorporation of Image verification systems into the radiotherapy delivery machine

PRESENT DAY TELETHERAPY

Developments in Computer dosimetry

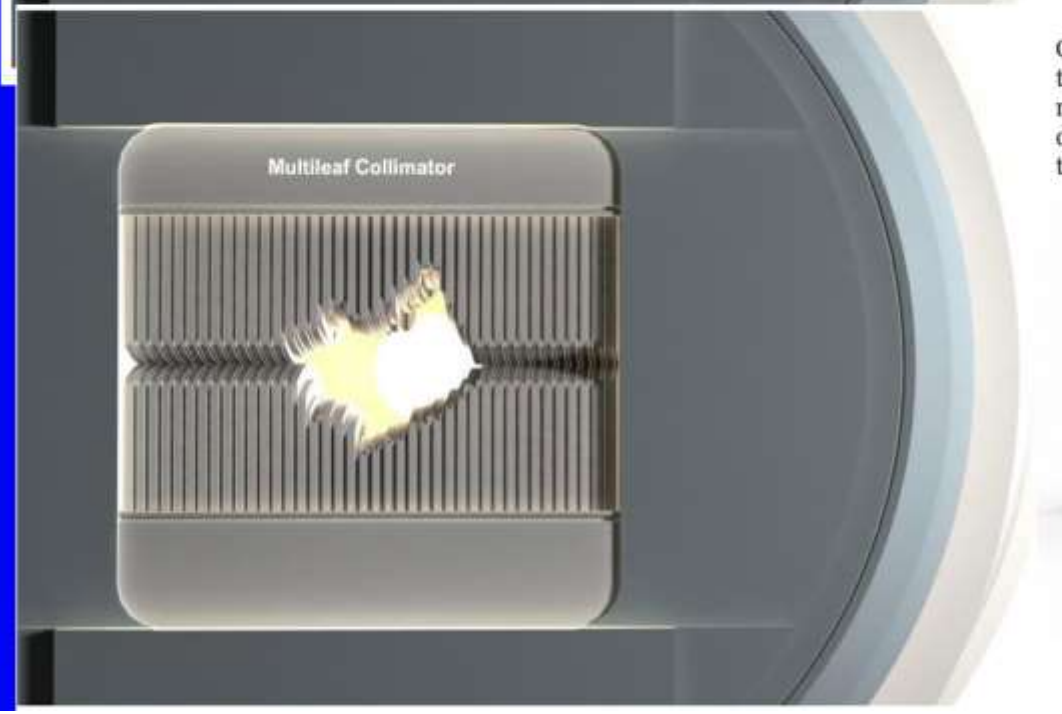
and different Planning Algorithms in Radiotherapy Planning

Customizing the beam

The X-rays are shaped and adjusted to destroy cancerous tissues while sparing healthy ones nearby.

A multileaf collimator uses metal "leaves" to determine how much radiation enters the patient at each point.

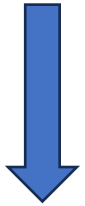
It is controlled by software which shapes and reshapes the beam during treatment.



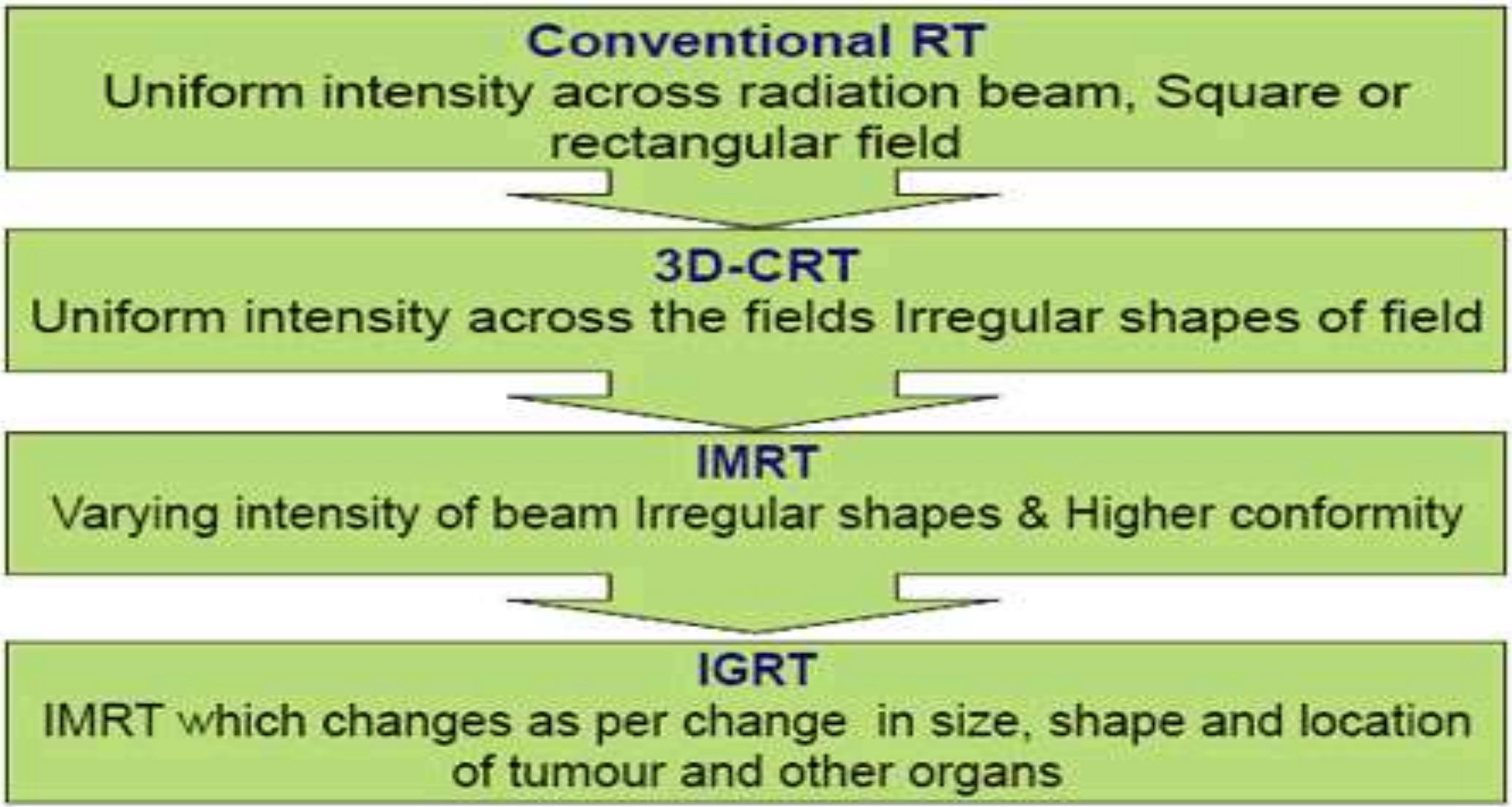
Guided by the computer-run treatment plan, a large gantry rotates around the patient, delivering radiation to cancerous tissues from different angles.

Integration of improved technologies

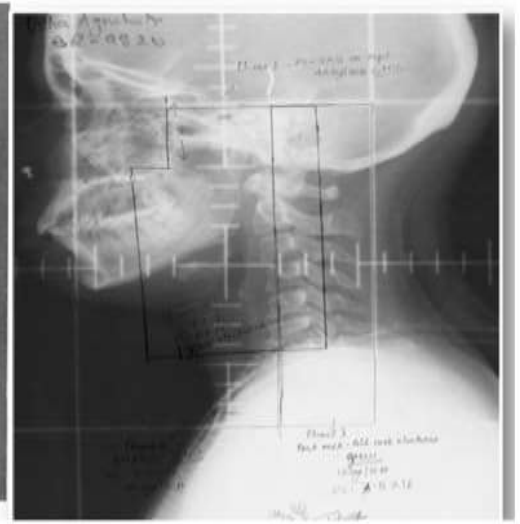
- Modern high energy linear accelerators with multileaf collimators ⟶ producing irregular fields
- Incorporation of Imaging technology
- Better planning algorithms for radiation planning

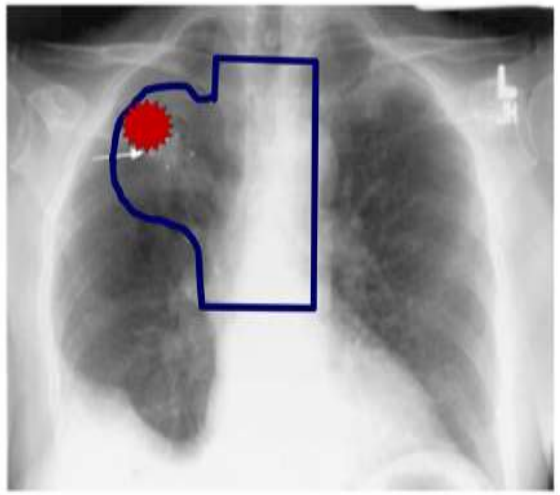


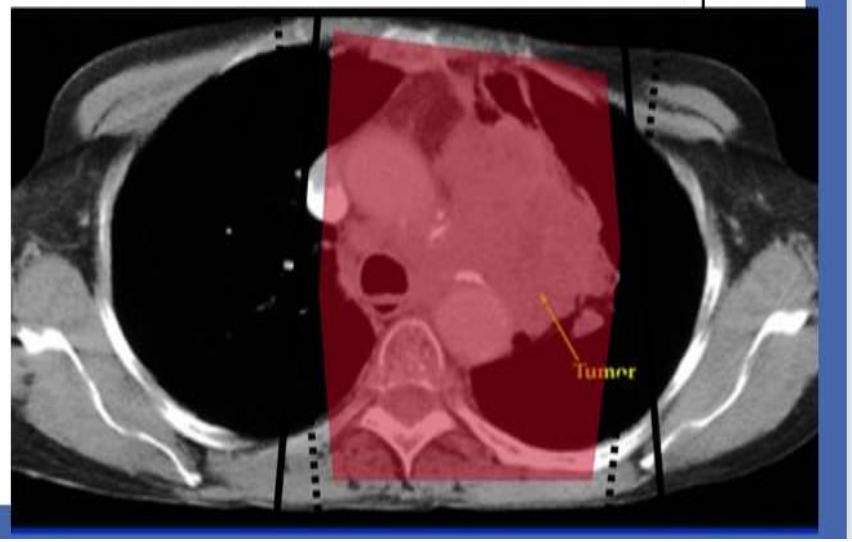
Improved plans for execution


Conventional RT
Uniform intensity across radiation beam, Square or rectangular field
3D-CRT
Uniform intensity across the fields Irregular shapes of field
IMRT
Varying intensity of beam Irregular shapes & Higher conformity
IGRT
IMRT which changes as per change in size, shape and location of tumour and other organs

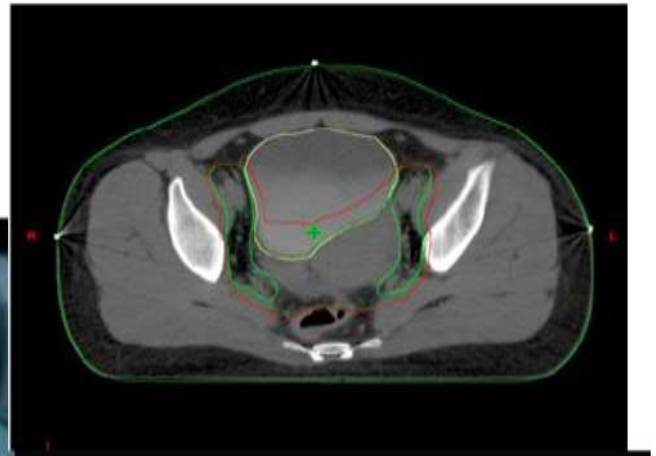
CONVENTIONAL 2D RADIOTHERAPY

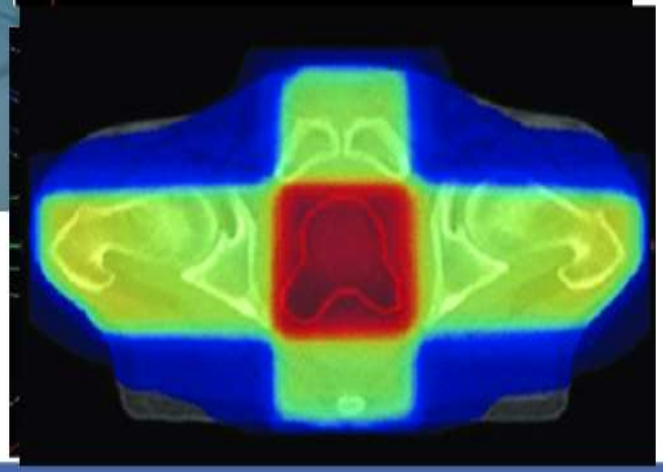




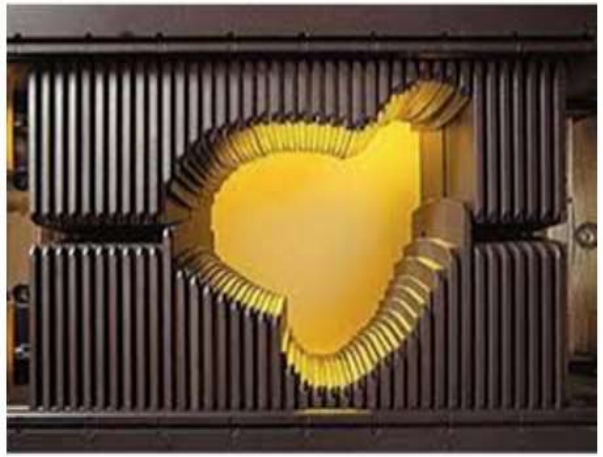


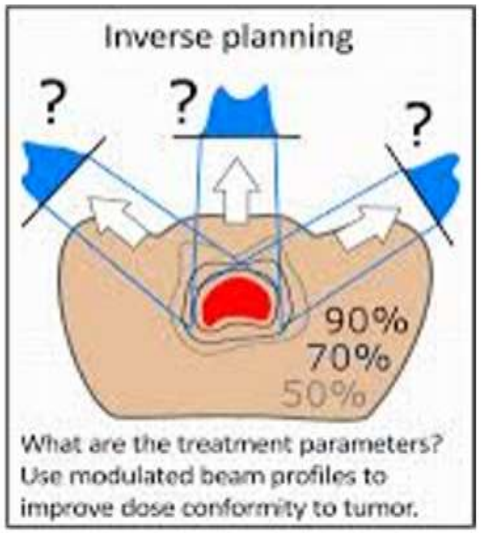
CT SIMULATION & 3D CONFORMAL RT

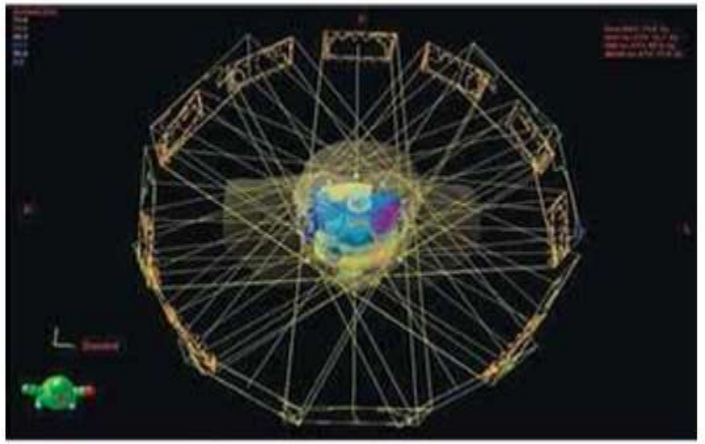


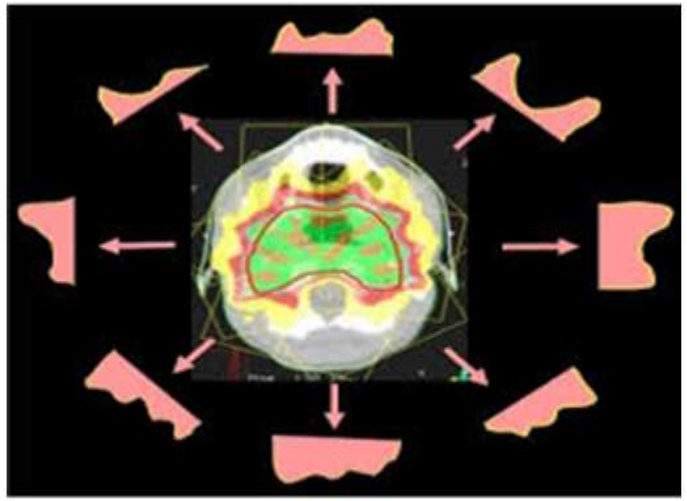


INTENSITY MODULATED RADIOTHERAPY



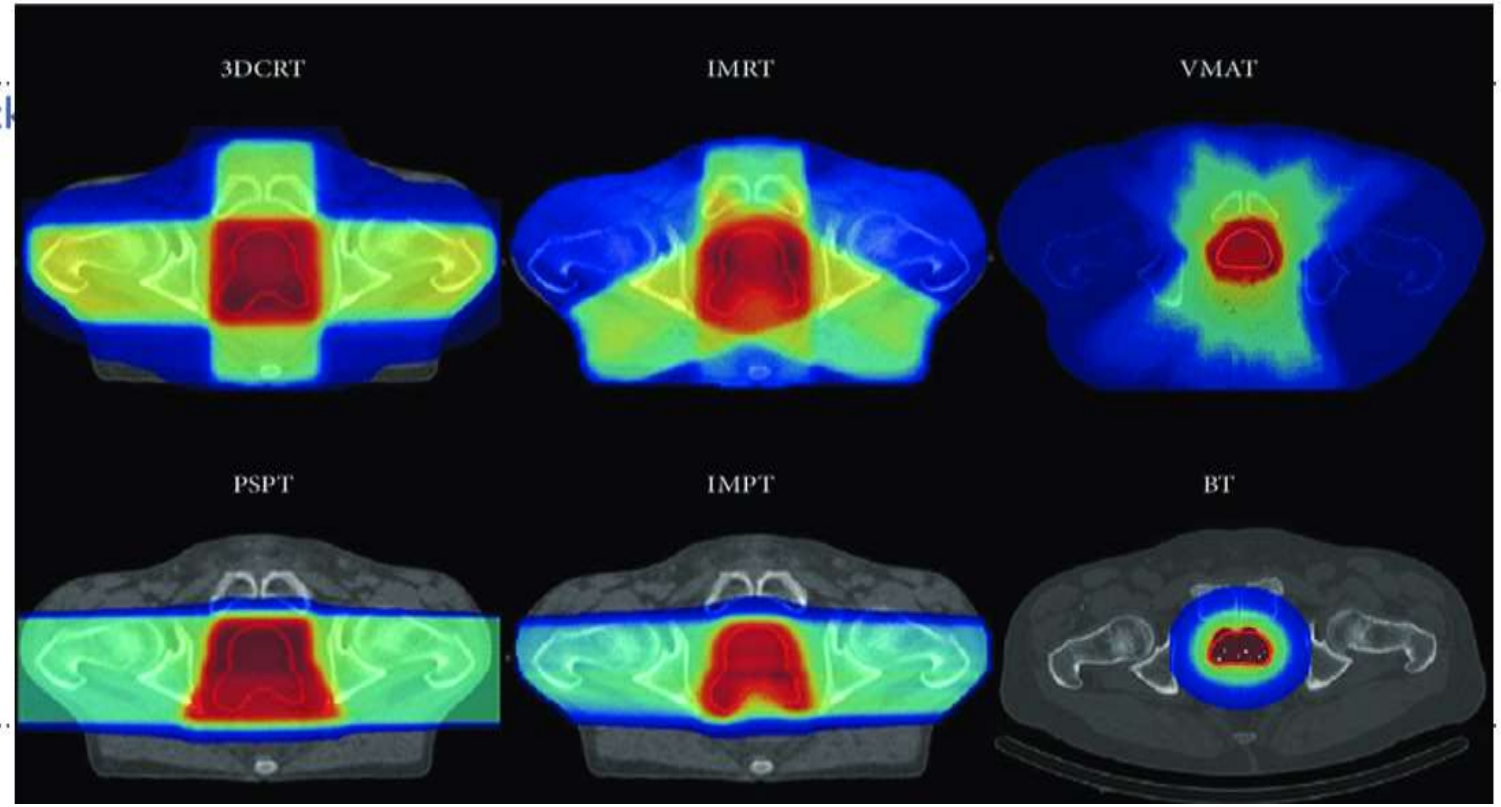






DOSIMETRIC COMPARISON

- Click



High dose Targeted Radiotherapy

- Stereotactic Radiosurgery (SRS)

  For small Cranial lesions

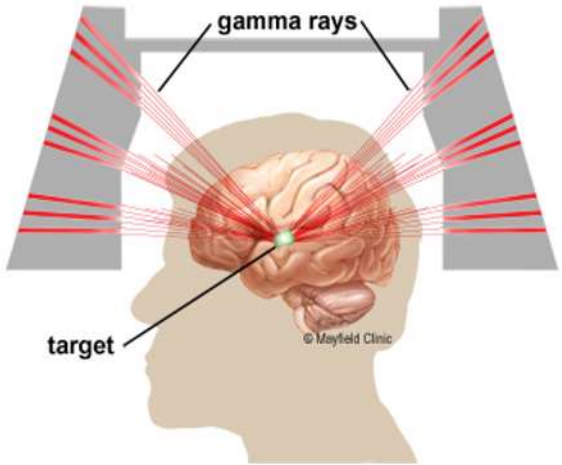
- Stereotactic Radiotherapy (SRT)

- SBRT

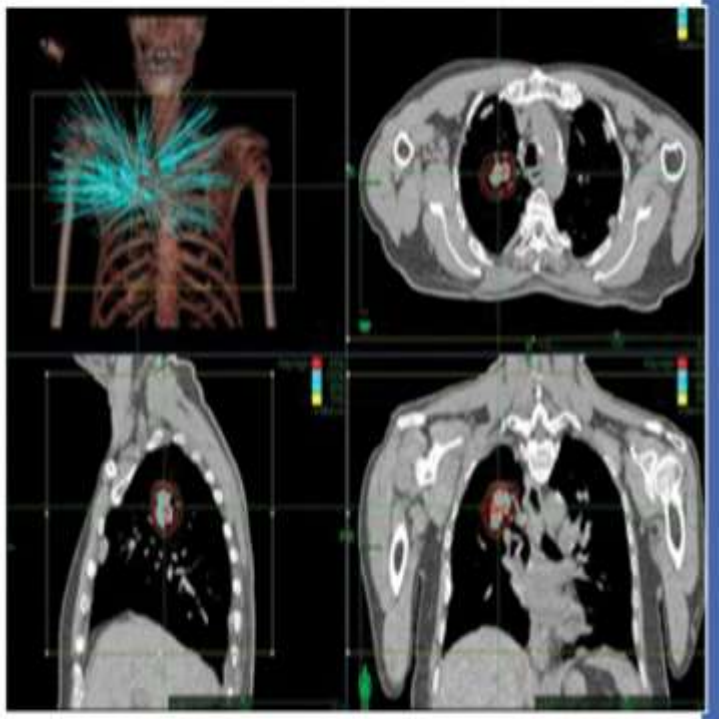
  For extracranial lesions

- Particle Therapy

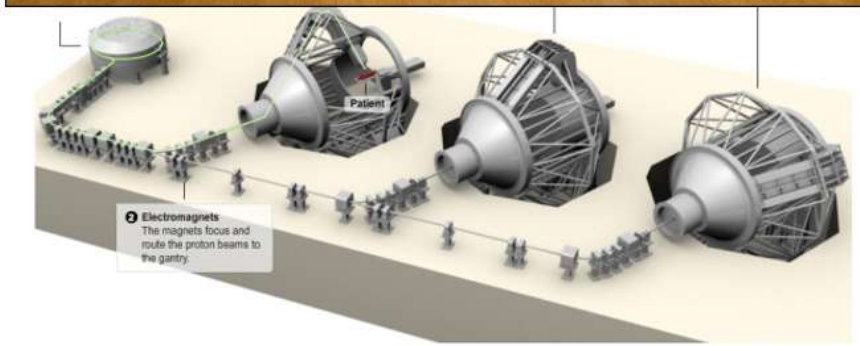
GAMMAKNIFE RADIOSURGERY

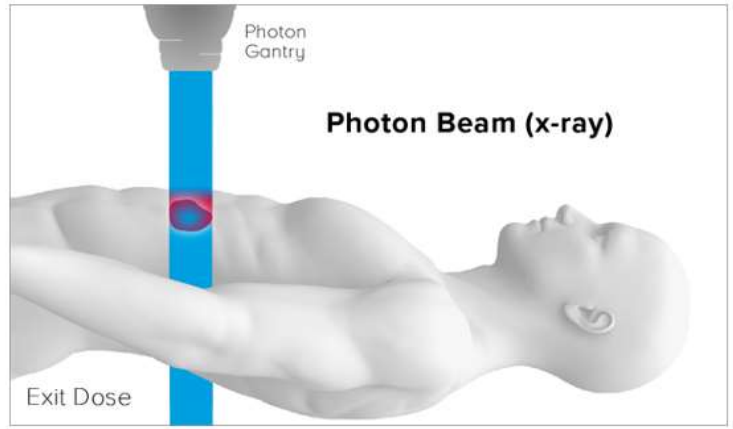


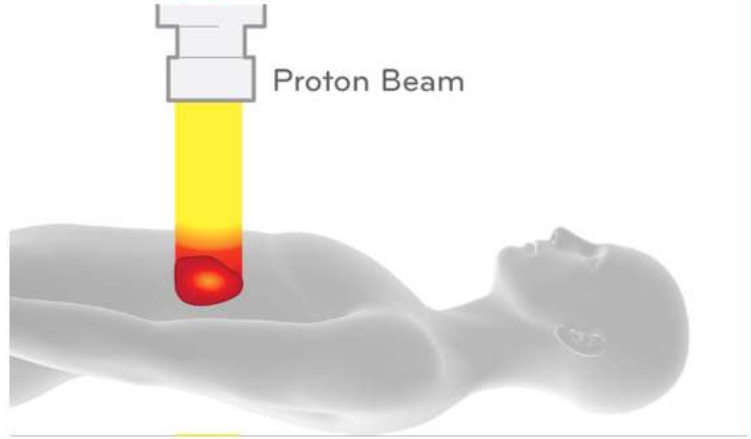
CYBERKNIFE RADIOSURGERY



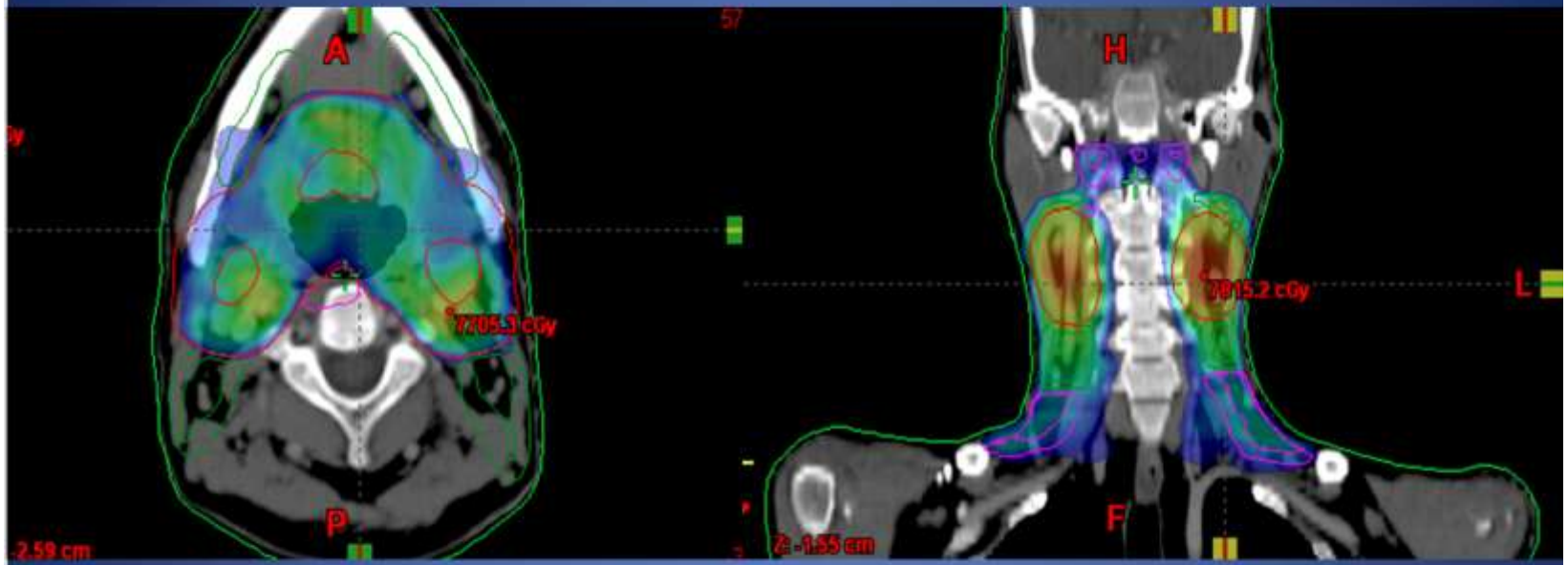
PROTON RADIOTHERAPY

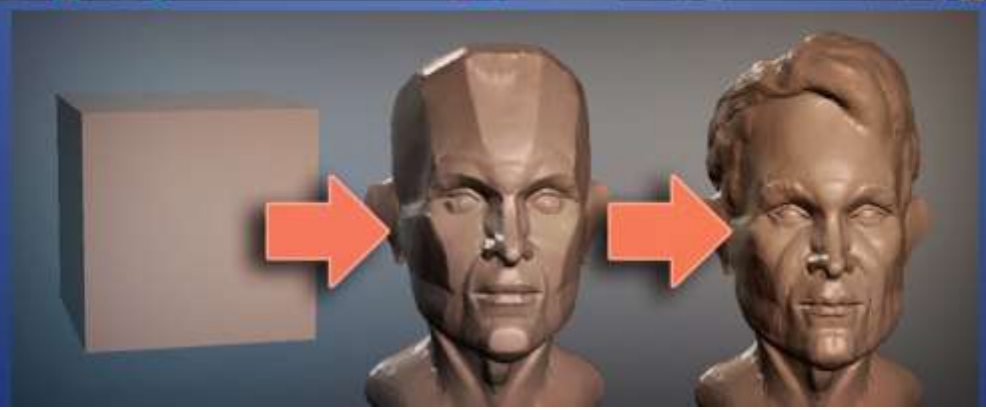






Dose sculpting/painting





Advances in RO: Improving outcomes

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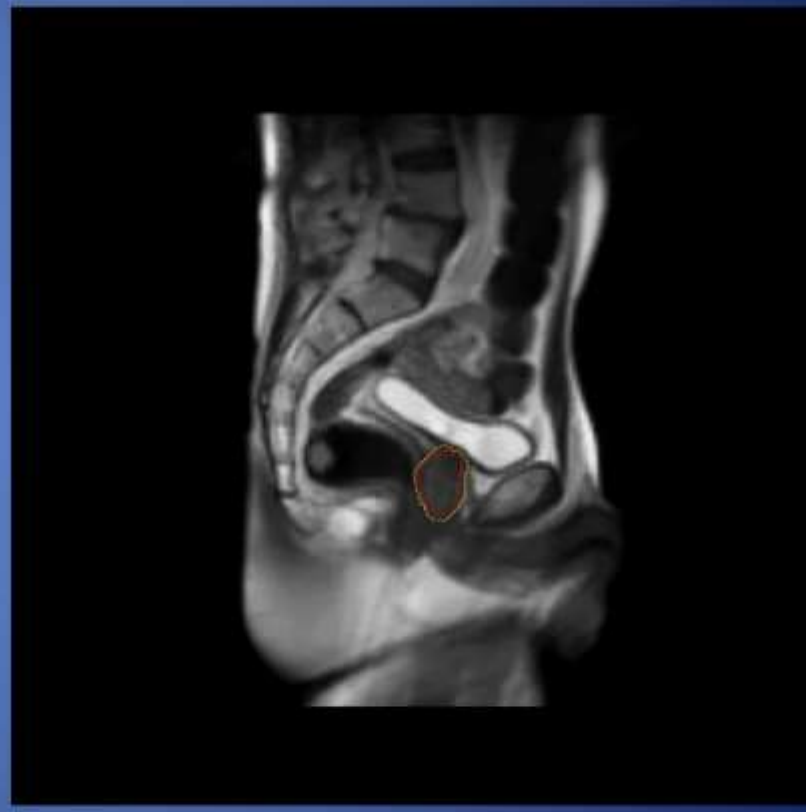


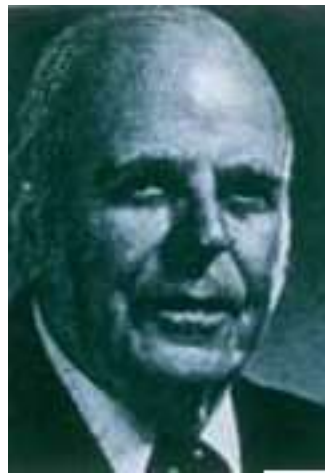
MRI-Guided Radiation therapy

History of Radiotherapy

- 1895 Roentgen discovers Xrays
- 1896 Becquerel discovers radioactivity
- 1898 Curie discovers radium
- late 1890's therapeutic use
- 1920's reliable Xray tubes (150-300Kv)
- 1950's Cobalt (1Mv or million volt)
- 1960's Linear Accelerator (4 - 25 million)
- 1970's computers and CT scans
- 1980's 3-D radiotherapy
- 1990's 3D conformal therapy
- 2002 IMRT (intensity modulated radiotherapy)
- 2002+ IGRT (image guided and radiosurgery)

Development of Brachytherapy

- 1900-1905: Insertion of Radium directly into the tumour by Danlos, Abbe and others, but dosimetry poorly understood



- 1938: Manchester system of intracavitary therapy in cervical cancer by Paterson and Parkar in Holt Radium Institute, Manchester

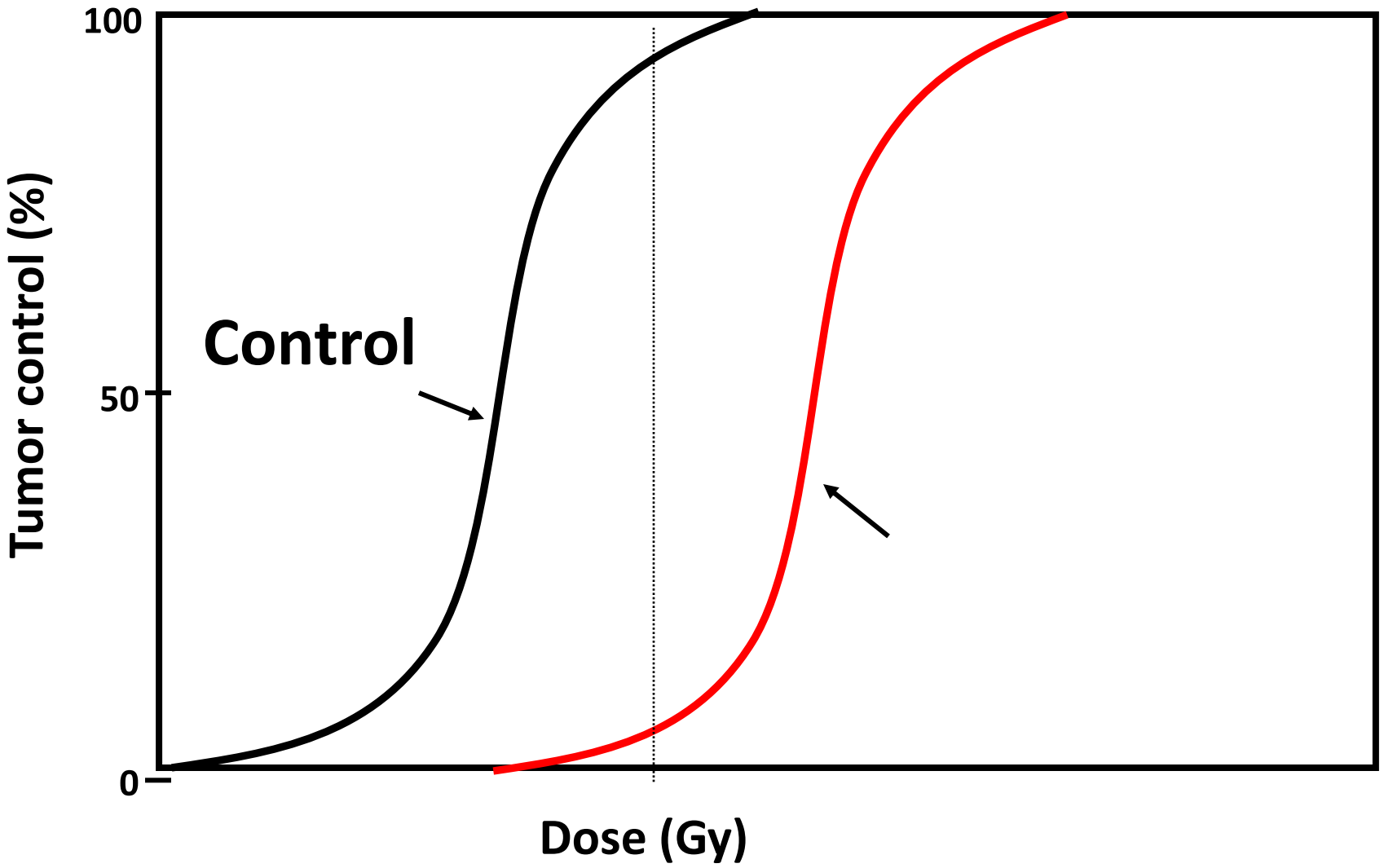
- Paterson-Parkar rules for Interstitial therapy

- Interest subsided in the middle of 20th century due to radiation hazards

Revival of interest in 1950s & 60s

- Development of Remote afterloading systems- to reduce radiation hazard
- Three-dimensional imaging modalities, computerised treatment planning systems and delivery equipment has made brachytherapy a safe and effective treatment
- Recent development of MR Guided Brachytherapy- in the 21st century

Tumour cure vs complication

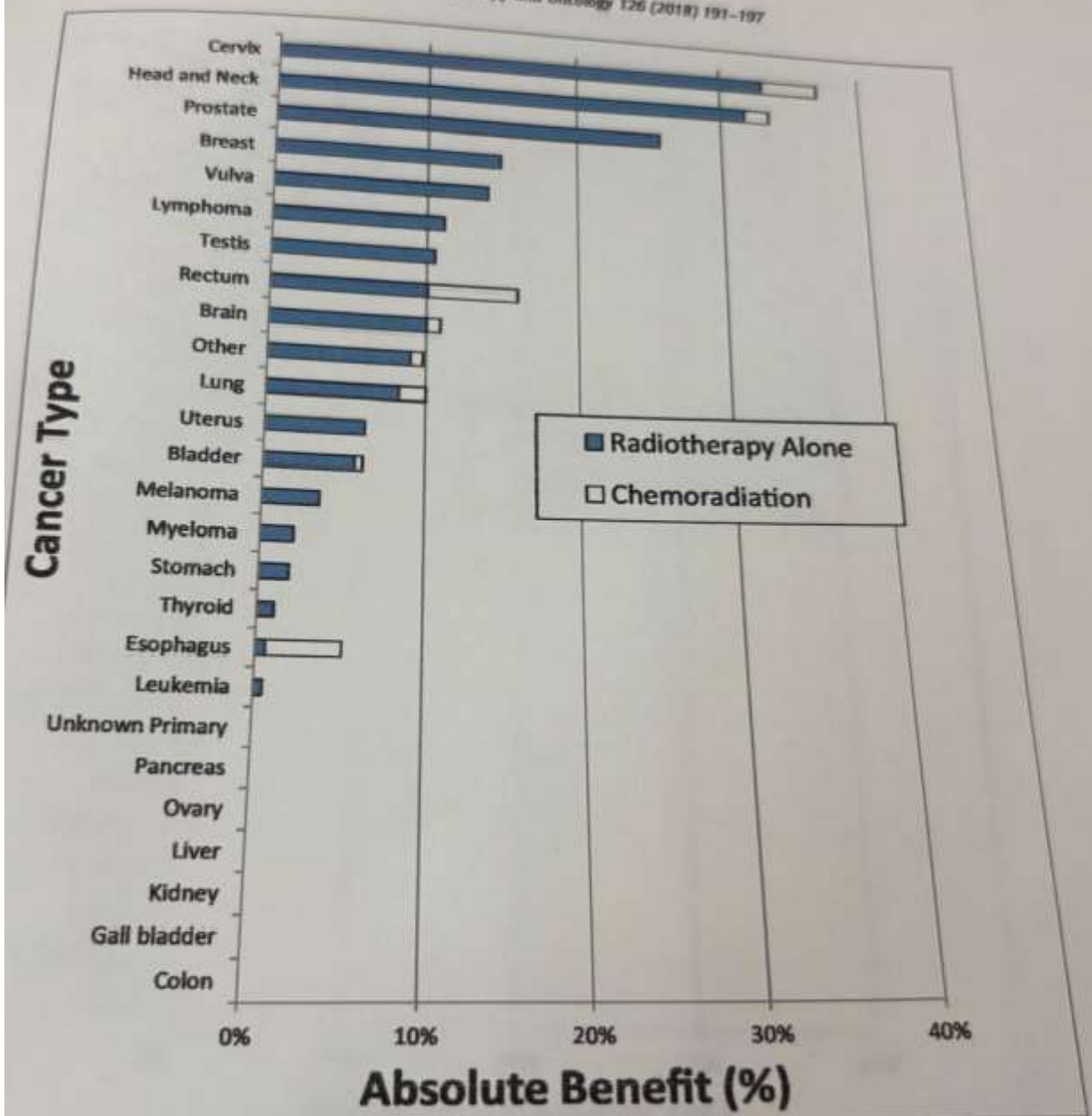


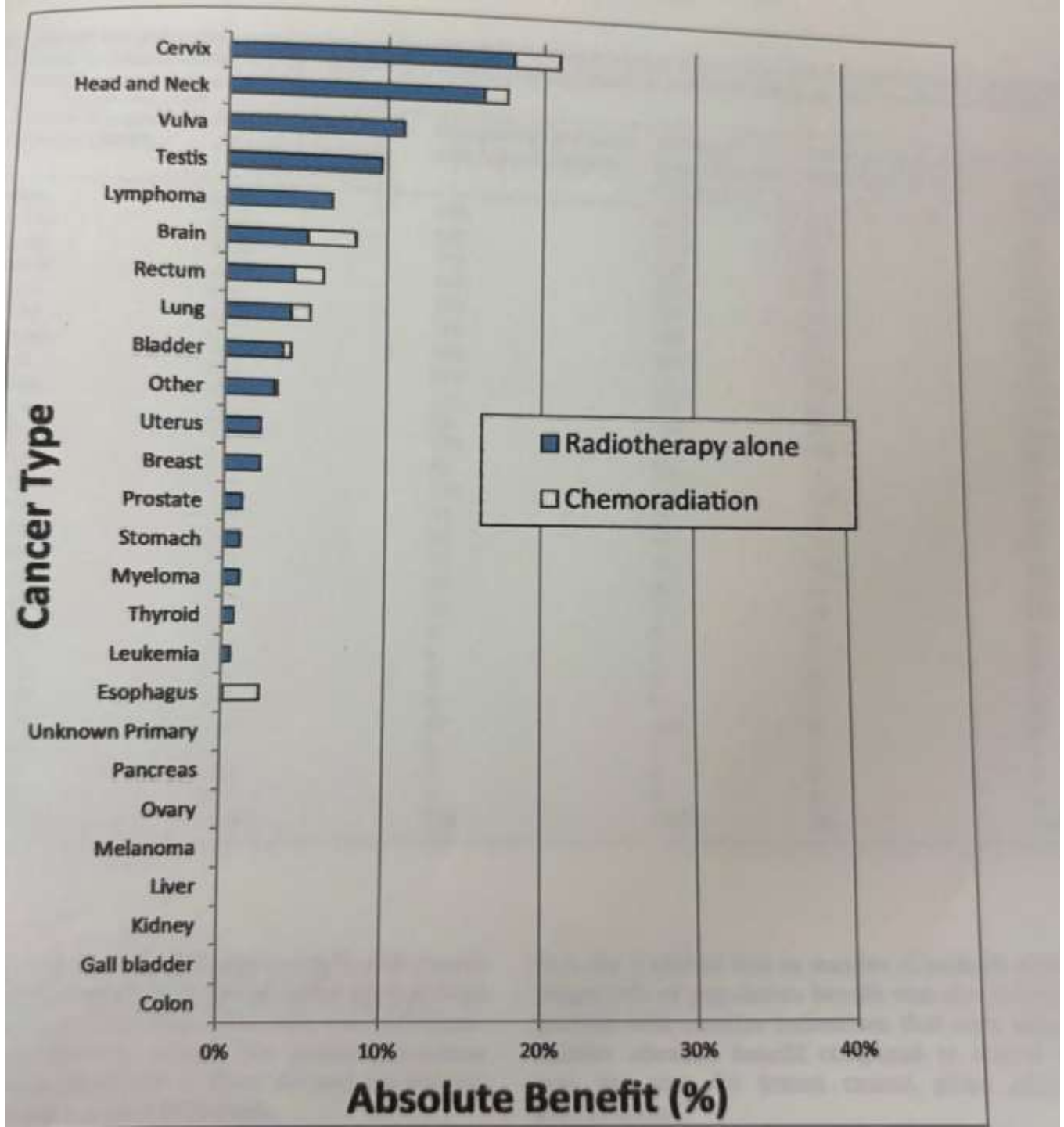
Common cancers curable at early stages with radiotherapy alone:

- Prostate carcinomas
- Head & neck carcinomas
- Non–small cell lung carcinomas
- Squamous and basal cell skin cancers
- Hodgkin lymphomas
- Uterine cervix carcinomas

Additional common cancers curable with regimens that include radiotherapy:

- Breast carcinomas
- Locally advanced lung carcinomas (non–small cell and small cell)
- Seminomas
- Endometrial carcinomas
- Locally advanced uterine cervix
- Several CNS tumors (e.g., ependymoma, glioma)
- Soft tissue sarcomas
- Rectal and anal carcinomas
- Lymphomas (Hodgkin and non–Hodgkin)
- Advanced head & neck carcinomas
- Bladder carcinomas
- Numerous pediatric malignancies (e.g., Wilms tumor, medulloblastoma, neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma)


Cervix
Head and Neck
Prostate
Breast
Vulva
Lymphoma
Testis
Rectum
Brain
Other
Lung
Uterus
Bladder
Melanoma
Myeloma
Stomach
Thyroid
Esophagus
Leukemia
Unknown Primary
Pancreas
Ovary
Liver
Kidney
Gall bladder
Colon
Cancer Type
Radiotherapy Alone
Chemoradiation
0%
10%
20%
30%
40%
Absolute Benefit (%)


Cervix
Head and Neck
Vulva
Testis
Lymphoma
Brain
Rectum
Lung
Bladder
Other
Uterus
Breast
Prostate
Stomach
Myeloma
Thyroid
Leukemia
Esophagus
Unknown Primary
Pancreas
Ovary
Melanoma
Liver
Kidney
Gall bladder
Colon
Cancer Type
Radiotherapy alone
Chemoradiation
0%
10%
20%
30%
40%
Absolute Benefit (%)

Clinical Advances
Technologic Advances
Biologic Advances

Becquerel experiences skin burn while carrying radium in vest pocket (109)
1901

Fractionated radiation sterilizes ram's testes without major burns (11, 12)
1911

Leukemia cases reported in radiation workers (10)
1911

Radiation intensity related to inverse square of distance from source
1903

Cellular radiosensitivity depends on mitotic activities and levels of differentiation (47)
1906

Hot-cathode x-ray tube invented (33)
1913

Radiosensitivity correlated with oxygen presence (52)
1923

How high-energy photons interact with tissue (Compton effect) (109)
1922

Roentgen adopted as standard exposure unit; radiation protection recommendations
1928

Head and neck cancers cured with fractionated X-rays (13)
1928

Air wall ionization chambers accurately measure radiation intensities
1924

Plant root studies show importance of oxygen in radiotherapy (52)
1935

Cyclotron invented (37)
1932

Nobel Prize (Muller) for radiation-induced mutagenesis shown in Drosophila
1946

First self-sustaining nuclear chain reaction with uranium
1942

Dosage system for gamma ray (36)
1934

First patient treated with neutron beams
1938

Experimental quantification of the oxygen effect (109)
1952

Cobalt-60 telotherapy units first used (15)
1951

Skin iso-effects governed primarily by total dose and overall treatment time (17)
1944

1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950

First *in vivo* radiation survival curve (19)
1967

Gamma knife for cranial radiosurgery
1968

Differential radiosensitivities of early vs. late responding tissues (112)
1980

Multi-leaf collimators developed
1980

MRI clinically available
1980

Cancer cell survival correlated with tumor control probablility after radiotherapy (21, 22)
1991

Sequence of the human genome completed (117)
2000

Cellular radiation damage repair shown (109)
1959

Remote after-loading in brachytherapy
1961

Metronidazole, the first hypoxic cell sensitizer (111)
1976

Model suggests metastasis occurs before detection of primary tumors (80)
1980

Clonogenic survival curves for irradiated cells (49)
1956

Proton beam treatment adopted (at Harvard/MGH) (45)
1961

Concept for IMRT (42)
1978

Iso-effect formula based on quadratic and linear components of radiation-induced cell kill (19)
1983

LDR and HDR brachytherapies have similar outcomes (29–32)
1993

Hyperbaric oxygen in radiotherapy (110)
1966

PET developed
1975

Bystander effect first described (114)
1992

Tumor potential doubling time (T_{pot}) (113)
1985

Hypoxia from limiting oxygen diffusion (53)
1955

Differential radiosensitivity demonstrated (109)
1963

First CT scans
1972

Survival curves for normal bone marrow (109)
1971

Nucleotron produces first computer-controlled afterloader
1985

Continuum or spectrum theory of cancer spread (81)
1994

SBRT to treat extracranial tumors (27, 28)
1995

First patient treated with proton beams (at Berkeley) (15)
1954

Cancer risk from exposure to X-rays *in utero* (109)
1970

Development of IMRT (40)
1988

ATM gene discovered (115)
1995

Microarray technology to study expression of human genes (116)
1996

1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010

Future developments in radiotherapy

- FLASH Radiotherapy
- Immuno-radiotherapy
- Adaptive radiotherapy
- Personalized radiotherapy
- More use of Radiogenomics

THANK YOU