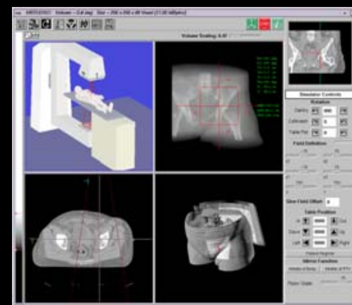
The Physical and Biological Basis of Radiation Therapy



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Wilhelm Conrad Roëntgen

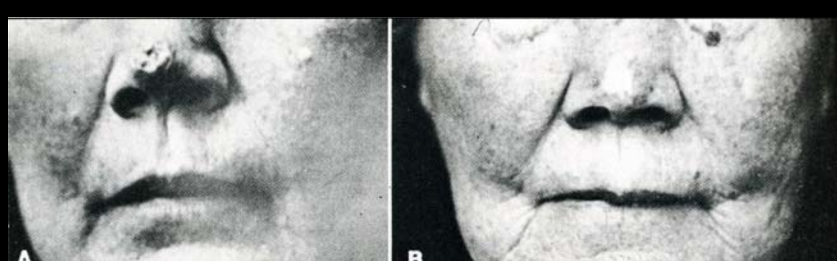
Discovered X rays in 1895

X rays were immediately big news at Columbia

"The College of Physicians and Surgeons is using x-rays to reflect diagrams directly on to the students' brains, making a more enduring impression than the normal method of learning"

New York Morning Journal, 1896

By 1899 X rays were being used for cancer therapy



1899 1929


Who gets radiotherapy?
HALF


Who gets radiotherapy?
Half of all
cancer patients
get radiotherapy

Who gets radiotherapy?

Half of all
RT patients
are treated with
curative intent

Who gets radiotherapy?

Half of all
RT patients
treated with
curative intent
are cured

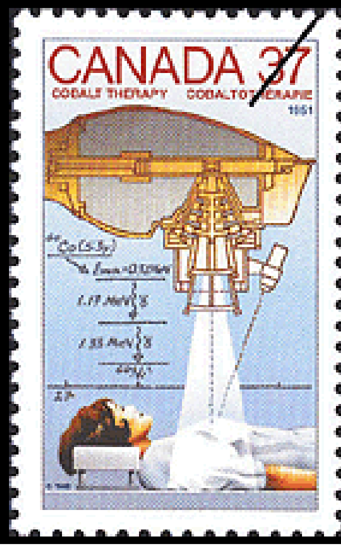
RT has both a physical and a biological basis

☞ The goal is always to produce as much cell killing as possible in the tumor, while minimizing damage to normal tissue

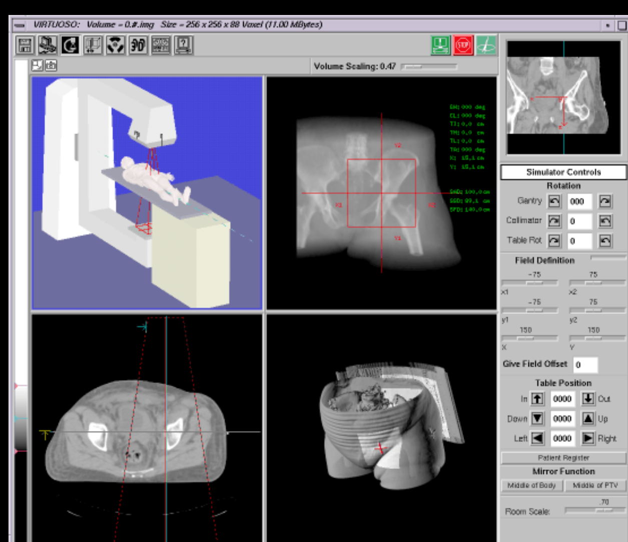
Physical Basis of Radiotherapy

- Aim beam at tumor
- Shape beam to conform to the tumor
- Minimize dose to normal tissue

External-beam radiotherapy: 1951

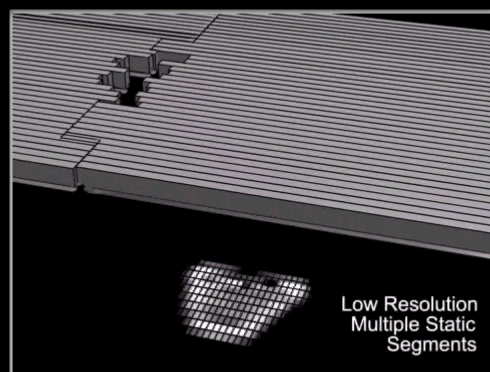


Higher energy beams and aiming at the tumor from more directions, made for better dose distributions

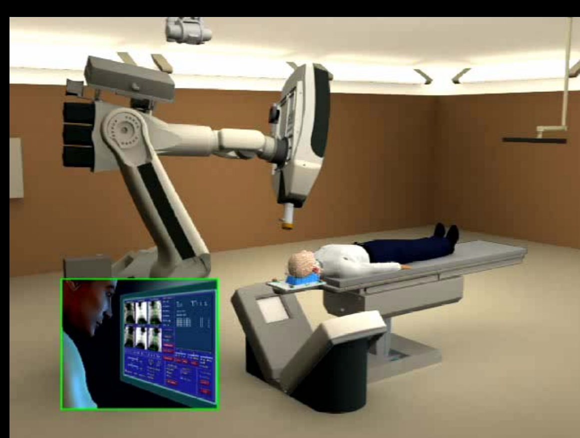


IMRT (intensity modulated radiation therapy)

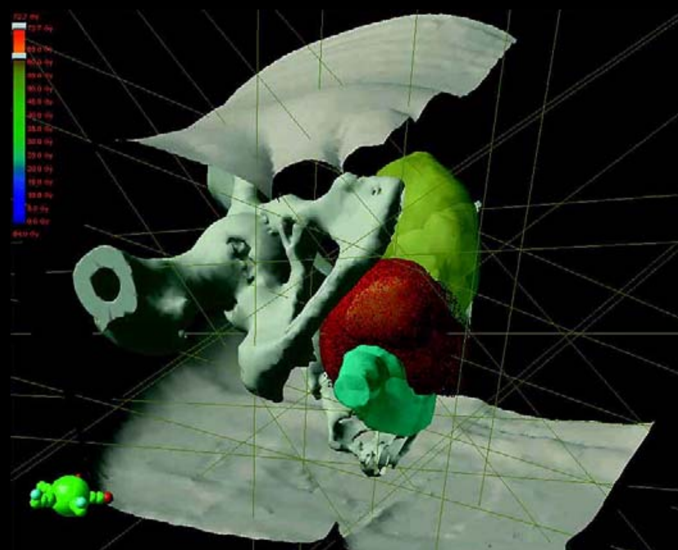
Continuously changing multi-leaf collimator



The CyberKnife, an x ray machine on the end of a robotic arm



The bottom line in 2006 is that far more normal-tissue dose sparing can be achieved than was previously possible



Correspondence American Medicine Aug. 15, 1903

The Uses of Radium

Dear Dr. Sowers:

I understand from you that the Röntgen rays, and the rays emitted by radium, have been found to have a marked curative effect upon external cancers, but that the effects upon deep-seated cancers have not thus far proved satisfactory.

It has occurred to me that one reason for the unsatisfactory nature of these latter experiments arises from the fact that the rays have been applied externally, thus having to pass through healthy tissues of various depths in order to reach the cancerous matter.

The Crookes' tube, from which the Röntgen rays are emitted, is of course too bulky to be admitted into the middle of a mass of cancer, *but there is no reason why a tiny fragment of radium sealed up in a fine glass tube should not be inserted into the very heart of the cancer, thus acting directly upon the diseased material.* Would it not be worth while making experiments along this line?

[signed] Alexander Graham Bell

By late 1903, the first treatment of cervical cancer with radium was reported from New York

Medical Record

A Weekly Journal of Medicine and Surgery

Vol. 64, No. 16.
Whole No. 1719.

New York, October 17, 1903.

$5.00 Per Annum.
Single Copies, 10c.

Original Articles.

RADIUM: WITH A PRELIMINARY NOTE ON RADIUM RAYS IN THE TREATMENT OF CANCER.*

By MARGARET A. CLEAVES, M.D.,
NEW YORK.

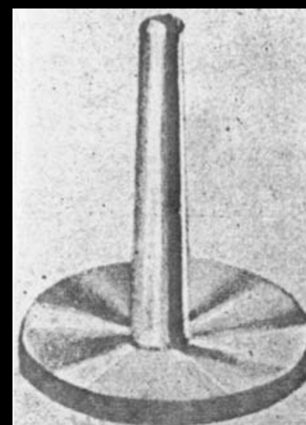
Not only the scientific world, but the lay as well, listens with bated breath to the marvelous tales of radium; tales which, especially when accompanied by demonstrations of the apparently magical phenomena of this new element, seem more befitting fairy lore than abstruse scientific fact; and one can but wonder whether radium may not prove a veritable Aladdin's lamp to medical science as well as to physics.

"All nature is vibrating, from the lowest musical note to the highest pitch of the chemical rays," and in radium the highest form of etheric vibration is to be found.

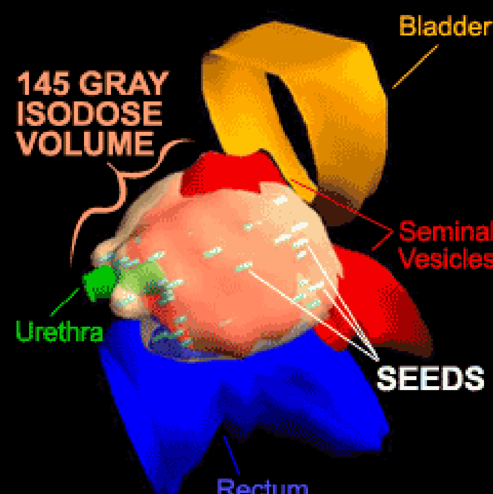
In 1898 Prof. Pierre Curie and Mme. Sklodowska Curie, when investigating the radiations from uranium discovered by Becquerel, found that some samples of pitchblende or uraninite, from which uranium is extracted, gave forth radiations much more powerful than any uranium they had found, having four times the activity of metallic uranium.

Painstaking research resulted in the discovery of a substance associated with bismuth and resembling it very much in its chemical characteristics. To this substance Mme. Curie gave the name of polonium, in honor of Poland, the land of her nativity.

Polonium is to be had in the form of a metal and in the form of a subnitrate. The metallic polonium resembles particles of nickel and the subnitrate is a white powder. The only specimen of metallic polonium in this country is in possession of Mr. W. J. Hammer, from whose exhaustive and interesting monograph[1] on radium many facts set forth herein have been gleaned. He also has the subnitrate, and



Radioactive seeds are increasingly used for treating prostate cancer

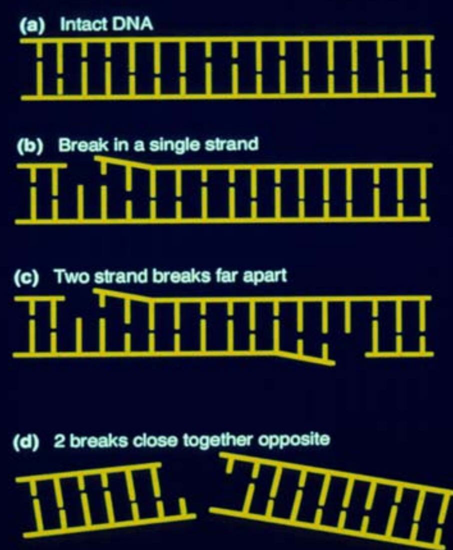


The Three R's of Radiotherapy

- Repair
- Reoxygenation
- Repopulation

Repair of DNA damage

Radiation-induced DNA Damage



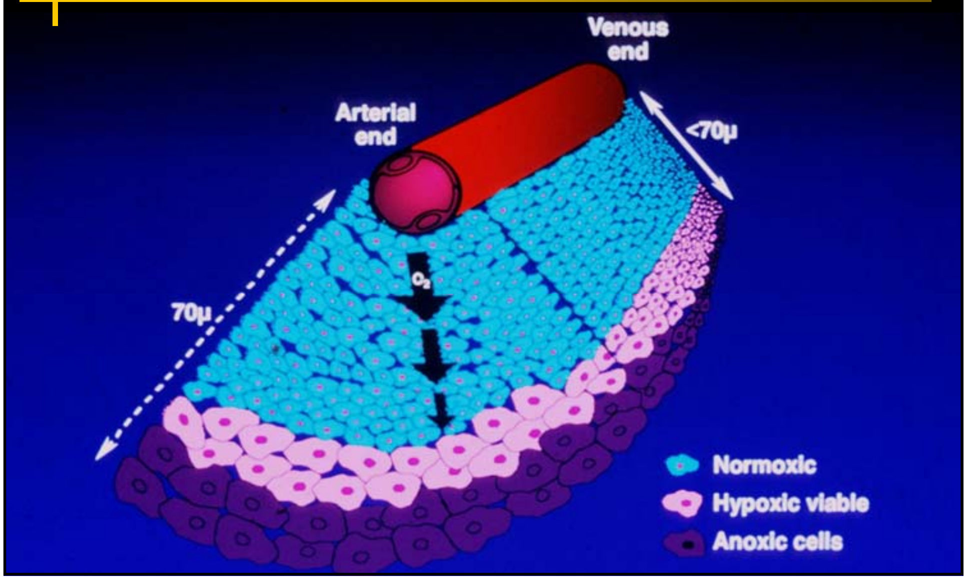
Taking advantage of DNA damage repair

- ☞ DNA repair is different for tumors (proliferating tissue) compared with late-responding normal tissues (slowly proliferating tissue)
- ☞ Dividing the treatment into many fractions takes advantage of this, allowing for more repair in late-responding normal tissue than in tumors

The significance of oxygenation:

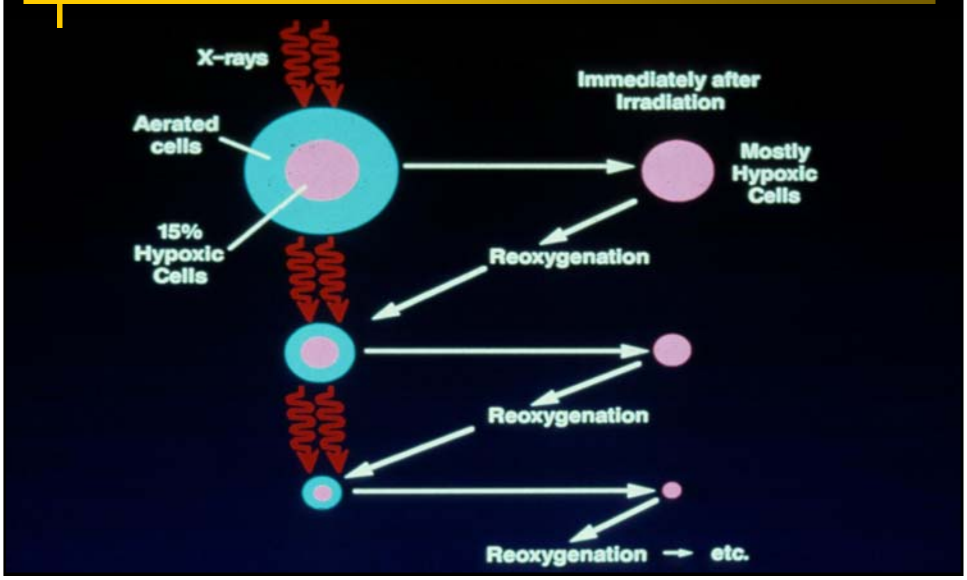
Hypoxic cells are very resistant to radiation killing

All tumors have significant proportions of hypoxic cells



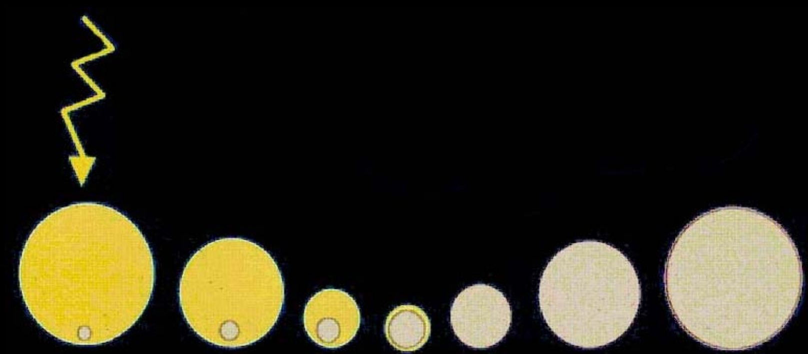
Solution is fractionation:

Allows reoxygenation between treatments



Accelerated Repopulation

As the tumor shrinks, the surviving tumor cells proliferate at an accelerated rate



Loss of tumor control as a result of increasing overall treatment time

- 2% per day for head and neck tumors
- 1% per day for cervix, bladder cancers

Biological Basis of Radiotherapy

- Exploit biological differences between tumor and normal tissues
- Minimize effects of hypoxic cells
- Fight accelerated repopulation

From a biological perspective:

Must divide radiotherapy treatment into many separate fractions

→ To overcome hypoxia

→ For differential response of tumor control and late side effects

From a biological perspective:

Must keep the treatment short

➔ To counteract accelerated population

Must prolong the treatment

➔ To limit early side effects

The Physical and Biological Bases of Radiation Therapy

- 1.4 million malignant cancers / yr in the US
- Half of them treated with radiotherapy
- Radiation therapy uses both physics biology to maximize the differential between tumor control and side effects

Clinical Principles of Radiation Therapy

Peter B. Schiff, M.D., Ph.D.
Department of Radiation Oncology
Columbia University Medical Center

Targeted Therapy in Oncology

- Surgical Oncology
  - Minimal invasive techniques
- Medical Oncology
  - Tumor specific biological targets
- Radiation Oncology
  - IMRT
  - Brachytherapy
  - Protons
  - IGRT

TOPICS

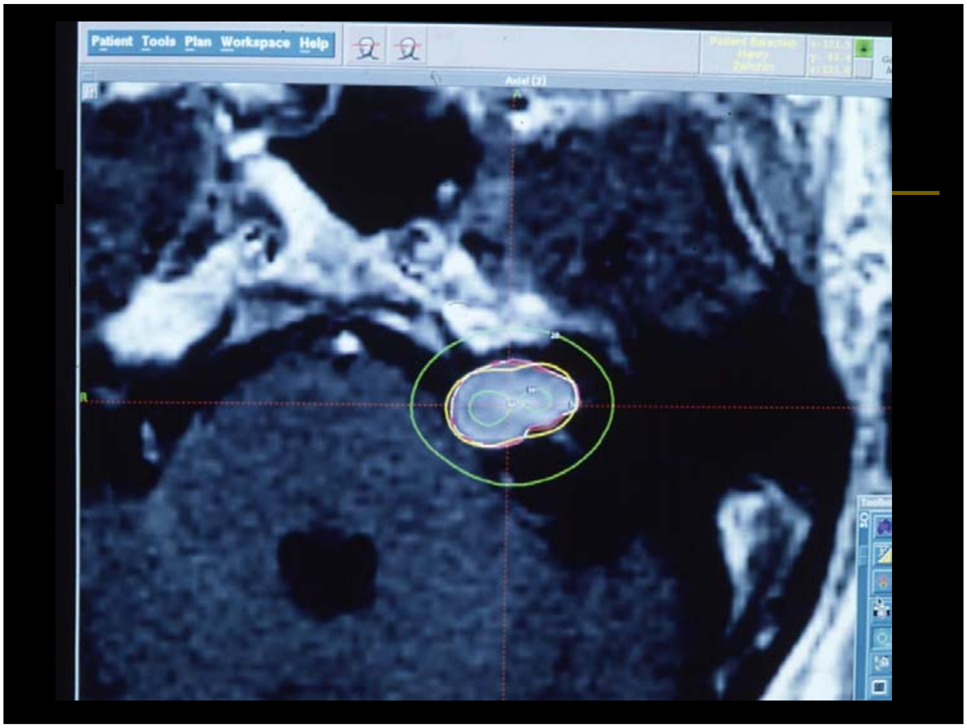
- Primary Radiation Therapy (Radiosurgery)
- Combing RT and Surgery
- Chemo/RT
  - Ca Esophagus
  - EGFR, monoclonal antibody cetuximab + RT for H&N Ca
- 3D-CRT Treatment of Localized CaP ± AD
- IGRT

Clinical Principles of Radiation Therapy

Primary Radiation Therapy


Leksell Gamma Knife


B 36
B 35
C 31
C 32
D 32
D 31
E 28
E 27



Combining Radiation Therapy and Surgery

Pre-0perative vs Post-Operative

Radiation Therapy

Pre-Operative vs. Post-Operative Radiation Therapy

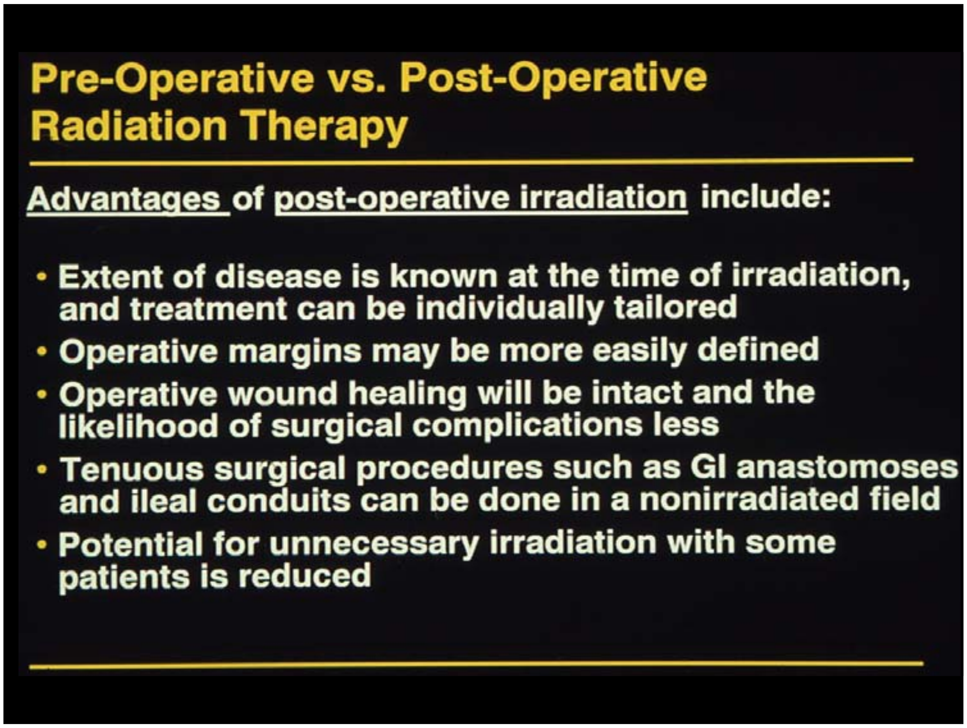
Pre-operative irradiation may:

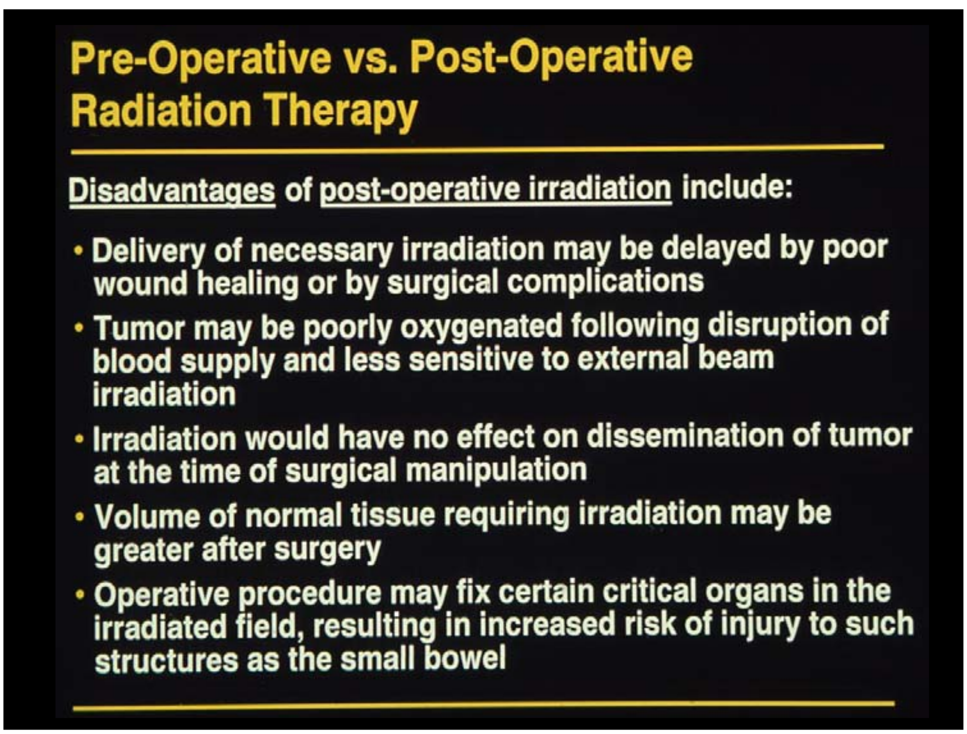
- Increase tumor's resectability
- Eliminate potential seeding of tumor during surgery
- Destroy microscopic foci of tumor that may extend beyond the surgical margins of resection
- Treat a relatively well-oxygenated tumor that may be more radiosensitive
- Allow a smaller treatment field because the operative bed has not been contaminated
- Decrease complications that may be associated with post-operative irradiation

Pre-Operative vs. Post-Operative Radiation Therapy

Disadvantages of pre-operative irradiation include:

- Inability to select patients on the basis of anatomical extent of disease
- Inability to tailor the irradiation to high-risk sites following the surgical procedure
- Delay primary treatment, which is surgery in most cases
- Increase incidence of post-operative complications associated primarily with wound healing
- Limitation of radiation total dose by the planned surgery
- Pathological downstaging, which may influence selection of adjuvant therapy


Pre-Operative vs. Post-Operative
Radiation Therapy
Advantages of post-operative irradiation include:
• Extent of disease is known at the time of irradiation, and treatment can be individually tailored
• Operative margins may be more easily defined
• Operative wound healing will be intact and the likelihood of surgical complications less
• Tenuous surgical procedures such as GI anastomoses and ileal conduits can be done in a nonirradiated field
• Potential for unnecessary irradiation with some patients is reduced


Pre-Operative vs. Post-Operative
Radiation Therapy
Disadvantages of post-operative irradiation include:
• Delivery of necessary irradiation may be delayed by poor wound healing or by surgical complications
• Tumor may be poorly oxygenated following disruption of blood supply and less sensitive to external beam irradiation
• Irradiation would have no effect on dissemination of tumor at the time of surgical manipulation
• Volume of normal tissue requiring irradiation may be greater after surgery
• Operative procedure may fix certain critical organs in the irradiated field, resulting in increased risk of injury to such structures as the small bowel

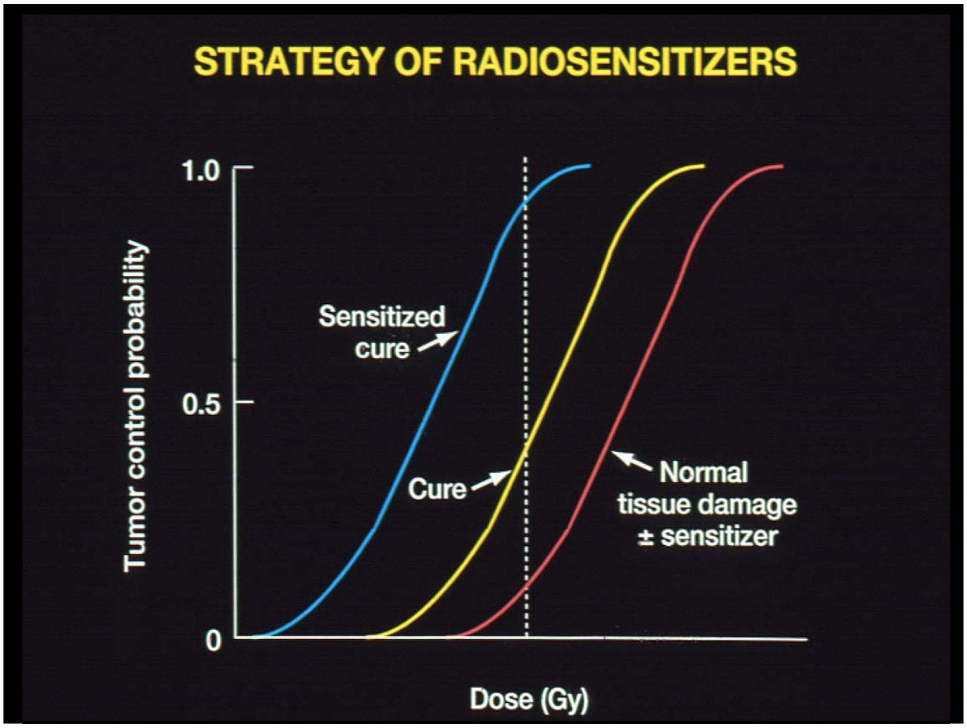
Clinical Principles of Radiation Therapy

Radiation Therapy and Chemotherapy

MODES THROUGH WHICH COADMINISTRATION OF CYTOTOXIC AGENTS (INCLUDING RADIATION) MAY RESULT IN AN INCREASED THERAPEUTIC RATION

Steel and Peckham, *Int. J. Radiat. Oncol. Biol. Phys.* 5:85, 1979

- Enhancement of the tumor response compared to that of normal tissue
- Normal-tissue toxicity independence
- Spatial cooperation (where disease at one anatomical site that is insensitive to one agent is controlled by the second agent)
- Normal tissue protection without concomitant protection of tumor cells



POTENTIAL ADVANTAGES AND DISADVANTAGES OF CHEMORADIATION

Advantages:

- Concurrent treatment may start soon after surgery
- Possible supra-additive effect on local tumor control
- Avoids treatment break between chemotherapy cycles associated with "sandwich" approach
- Shortens overall length of treatment program

POTENTIAL ADVANTAGES AND DISADVANTAGES OF CHEMORADIATION (cont)

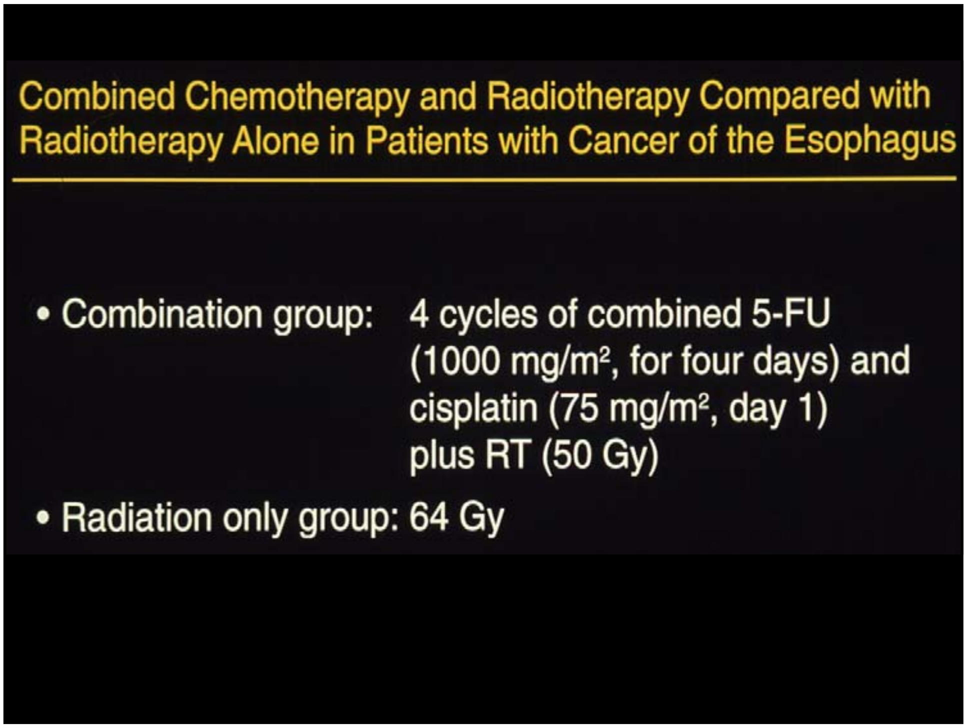
Disadvantages:

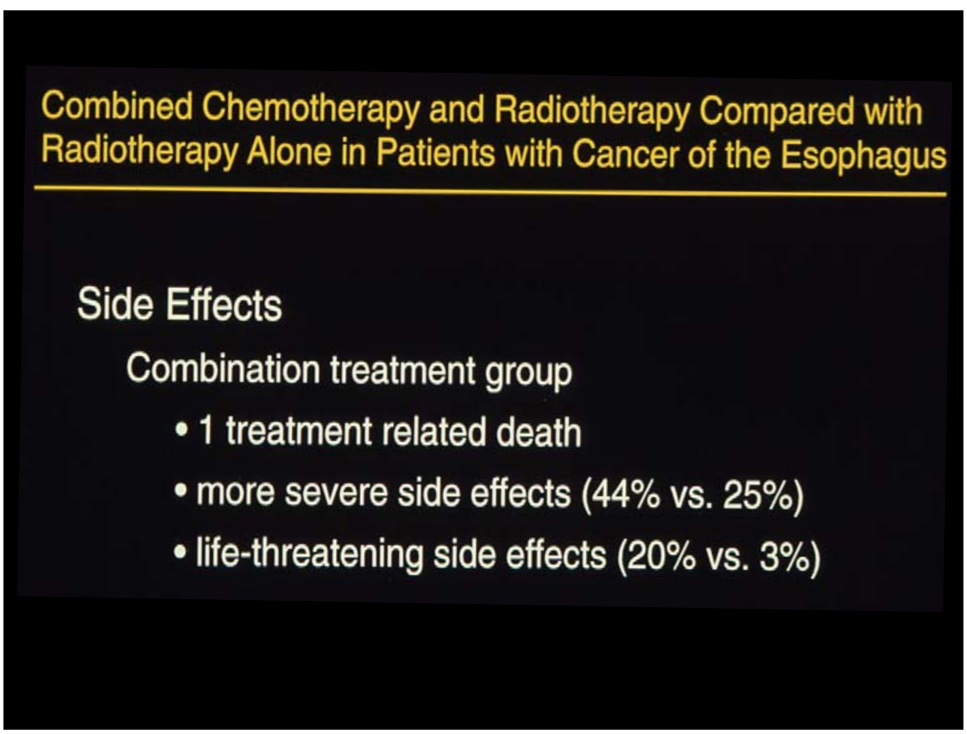
- Greater acute myelosuppression
- Increased acute skin reaction
- Acute side effects may result in delays or dose reductions of chemotherapy
- Increase risk of subacute side effects, such as pneumonitis
- Increase risk of chronic side effects, such as cardiotoxicity
- Worsened cosmetic outcome

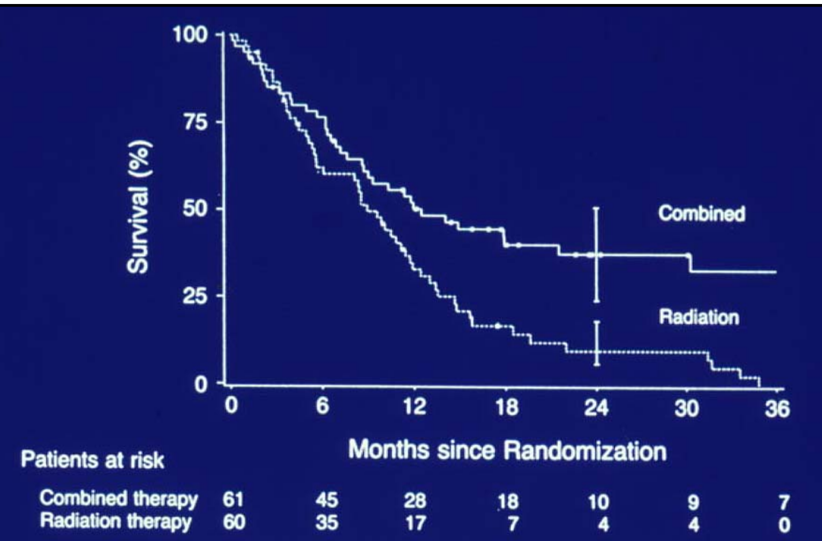
Combined Chemotherapy and Radiotherapy Compared with Radiotherapy Alone in Patients with Cancer of the Esophagus

RTOG

NEJM 326:1593-1598, 1992


Combined Chemotherapy and Radiotherapy Compared with Radiotherapy Alone in Patients with Cancer of the Esophagus
• Combination group: 4 cycles of combined 5-FU (1000 mg/m², for four days) and cisplatin (75 mg/m², day 1) plus RT (50 Gy)
• Radiation only group: 64 Gy


Combined Chemotherapy and Radiotherapy Compared with Radiotherapy Alone in Patients with Cancer of the Esophagus
Side Effects
Combination treatment group
• 1 treatment related death
• more severe side effects (44% vs. 25%)
• life-threatening side effects (20% vs. 3%)

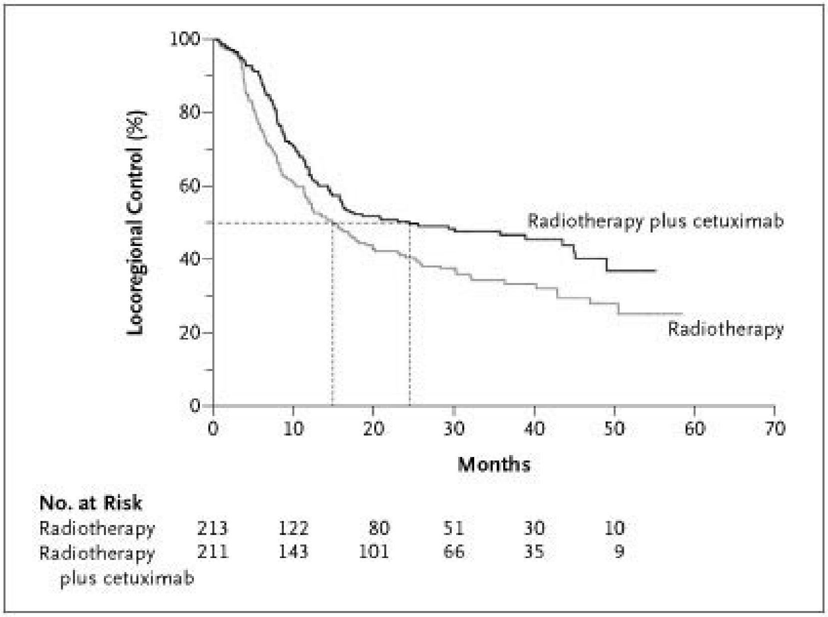


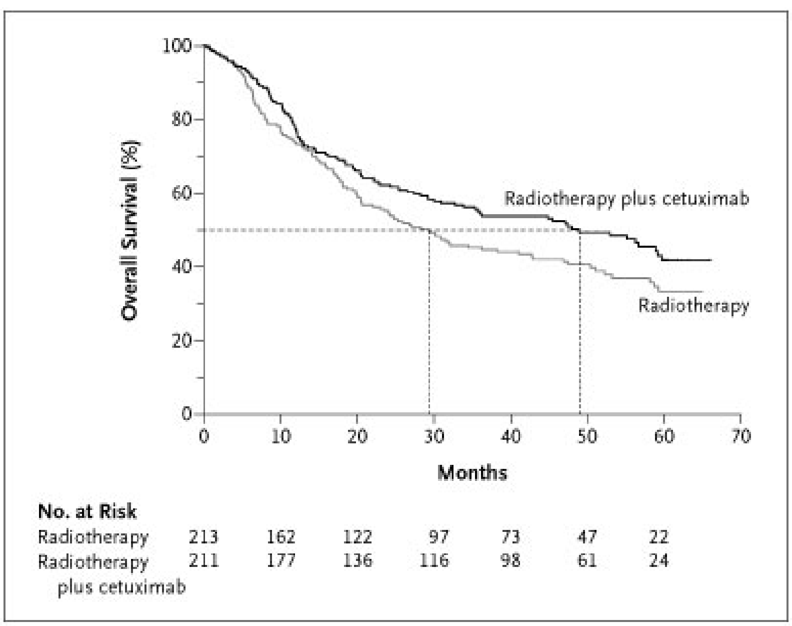
Kaplan–Meier Plot of Survival in Patients with Esophageal Carcinoma Treated with Radiation Alone or with Radiation and Chemotherapy Combined.
Bars indicate 95 percent confidence intervals at 24 months.

RT plus Cetuximab for Squamous-Cell Carcinoma of the Head & Neck

Bonner et al., NEJM 2006, 354:567

- Multinational, randomized clinical trial comparing RT alone (213 pts) with RT plus cetuximab (211 pts)
- Stage III or IV nonmetastatic SCC of oropharynx, hypopharynx or larynx
- RT up to 72 Gy
- Cetuximab iv 400 mg M^2 followed by weekly infusions of 250 mg M^2


Locoregional Control (%)
100
80
60
40
20
0
0 10 20 30 40 50 60 70
Months
Radiotherapy plus cetuximab
Radiotherapy
No. at Risk
Radiotherapy 213 122 80 51 30 10
Radiotherapy plus cetuximab 211 143 101 66 35 9


Overall Survival (%)
100
80
60
40
20
0
0 10 20 30 40 50 60 70
Months
Radiotherapy plus cetuximab
Radiotherapy
No. at Risk
Radiotherapy 213 162 122 97 73 47 22
Radiotherapy plus cetuximab 211 177 136 116 98 61 24

Treatment of Localized Prostate Cancer with Radiation Therapy

Combined Modality Treatment with AD

In Selected Patients

Organ Confined Prostate Cancer

Treatment Options

- Radiation therapy ± hormonal intervention
- Surgery ± hormonal intervention
- Hormonal intervention only
- Observation
- Other local therapies

Organ Confined Prostate Cancer

Radiation Therapy

- 3D-conformal radiation therapy (3D-CRT)
- Brachytherapy
- Combination of 3D conformal radiation therapy and brachytherapy

Columbia Biologic Classification of Clinically Localized Prostate Cancer

Class	Gleason	PSA	3-yr BDFS	3-yr BDFS (95% CI)
1	2-6	0-4	100.0	94.7 (67.5, 99.2)
	7	0-4	80.0	
2	2-6	4-15	58.4	54.8 (43.4, 64.8)
		15-50	50.6	
	7	4-15	48.5	
	8-10	0-4	50.0	
3	2-6	> 50	20.0	22.7 (8.8, 40.4)
	7	15-50	25.2	
	8-10	4-15	18.4	
4	7	> 50	0.0	4.6 (0.3, 19.6)
	8-10	15-50	7.0	
		> 50	0.0	

Columbia University, *Urology* 51:265-270, 1998

6-Month AD + 3D-CRT vs RT Alone for Patients Localized CaP

Harvard, JAMA 292:821-827, 2004

- **206 patients randomized to 3D-CRT (70 Gy) alone (n=104) or in combination with 6 months AD (n=102)**
- **Eligible patients included those with PSA ≥ 10 ng/mL, a Gleason score ≥ 7, or radiographic evidence of extracapsular disease**

6-Month AD + 3D-CRT vs RT Alone for Patients Localized CaP

Harvard, JAMA 292:821-827, 2004

	% 5-Year Overall Survival P = 0.04	% 5-Year Survival Without Progression P = 0.002
3D-CRT + AD	**90**	**80**
3D-CRT	**78**	**60**

Clinical Principles of Radiation Therapy

Image-Guided Radiation Therapy

IGRT

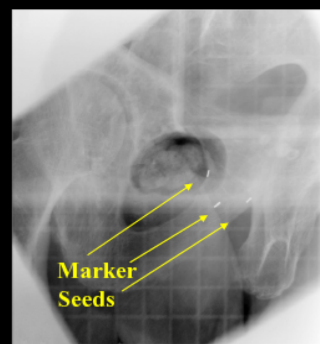
IGRT

- Medical professional teams working together
- Availability of new imaging modalities of tumors and normal tissues (CT/PET, MRI, MRS, USTT)
  - Anatomy now being fused with biologic function.
- Adaptive Radiotherapy (gating, organ motion, use of EPIDs, etc).
- CT/MRI virtual simulation

IGRT Technologies

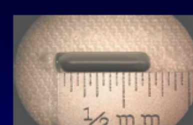
- CyberKnife (linear accelerator on robotic arm)
- Trilogy (linear accelerator with minimultileaf collimators and imaging arms)
- TomoTherapy (CT-like unit with linear accelerator)
- Protons
- Carbon ions

In-Room KV X-rays:Prostate Markers
BrainLab Exactrac™

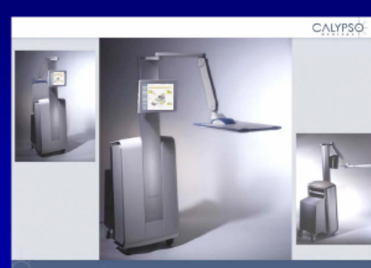


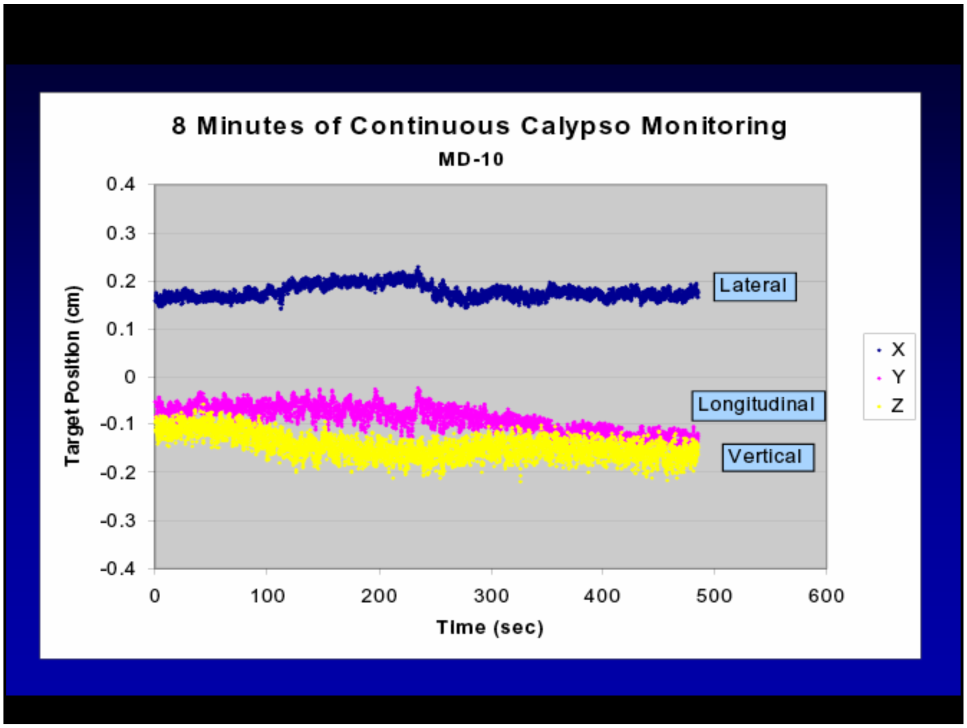
Investigational Device
Not For Sale

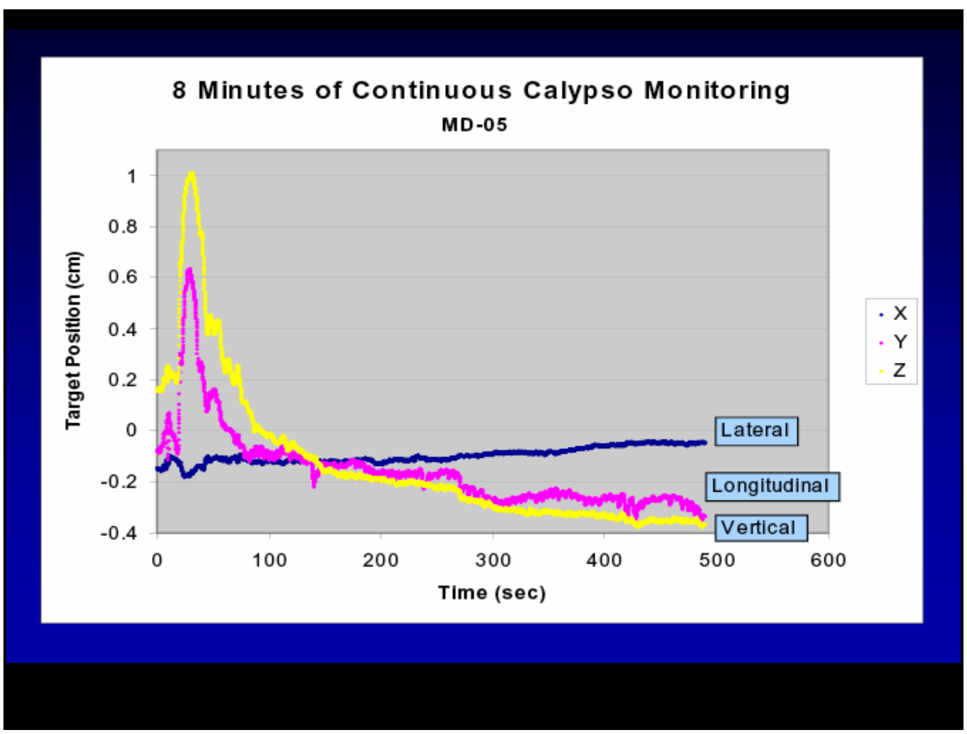
Beacon™ Transponder



- Wireless 15 G, permanent implant
- RF signal detected externally
- Refresh rate: 10 Hz
- No X-ray (no dose)
- Continuous target localization, registration & tracking




8 Minutes of Continuous Calypso Monitoring
MD-10
Target Position (cm)
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
0
100
200
300
400
500
600
Time (sec)
Lateral
Longitudinal
Vertical
X
Y
Z


8 Minutes of Continuous Calypso Monitoring
MD-05
Target Position (cm)
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
0
100
200
300
400
500
600
Time (sec)
Lateral
Longitudinal
Vertical
X
Y
Z

Cone Beam KV CT

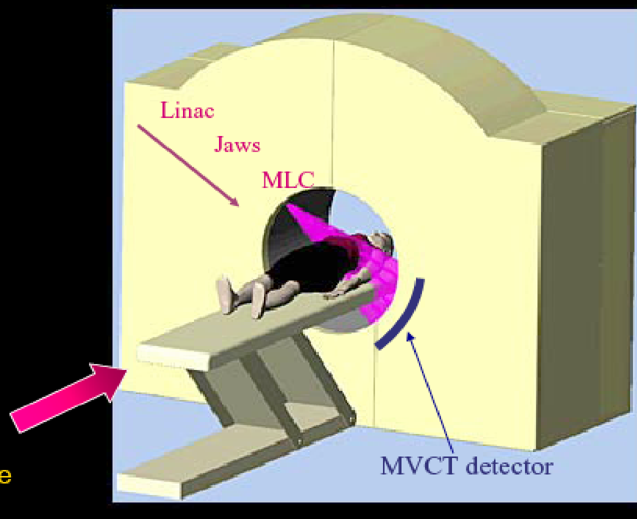
Same Gantry
Coupled to delivery device
Volume acquisition

5-10 min for image guidance
1-2 cGy per scan

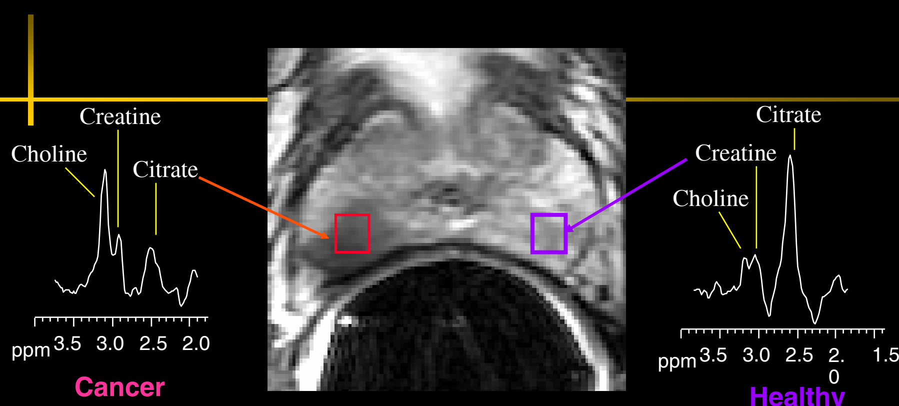
Elekta Synergy

Varian Trilogy

Schematic view of the Helical Tomotherapy Machine

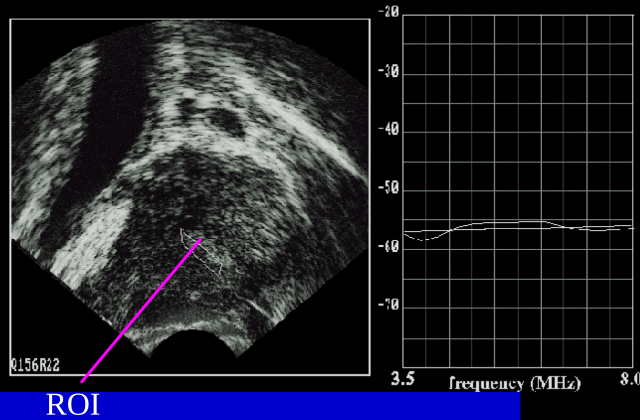


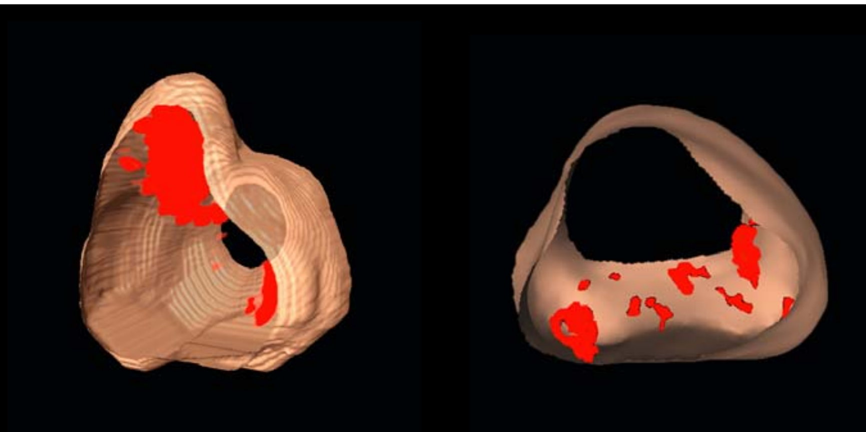
MRS Detection of Prostate Cancer



John Kurhanewicz, Ph.D.
Magnetic Resonance Science Center, Department of Radiology
University of California San Francisco

Region of Interest (ROI) and Spectrum (basis for characterizing tissue)



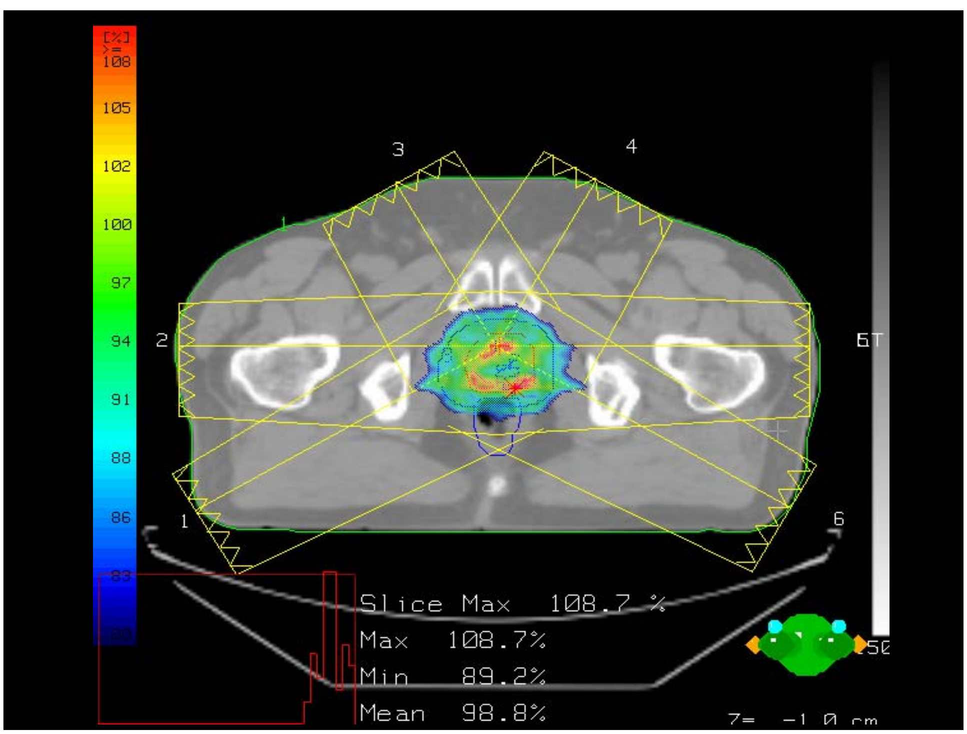


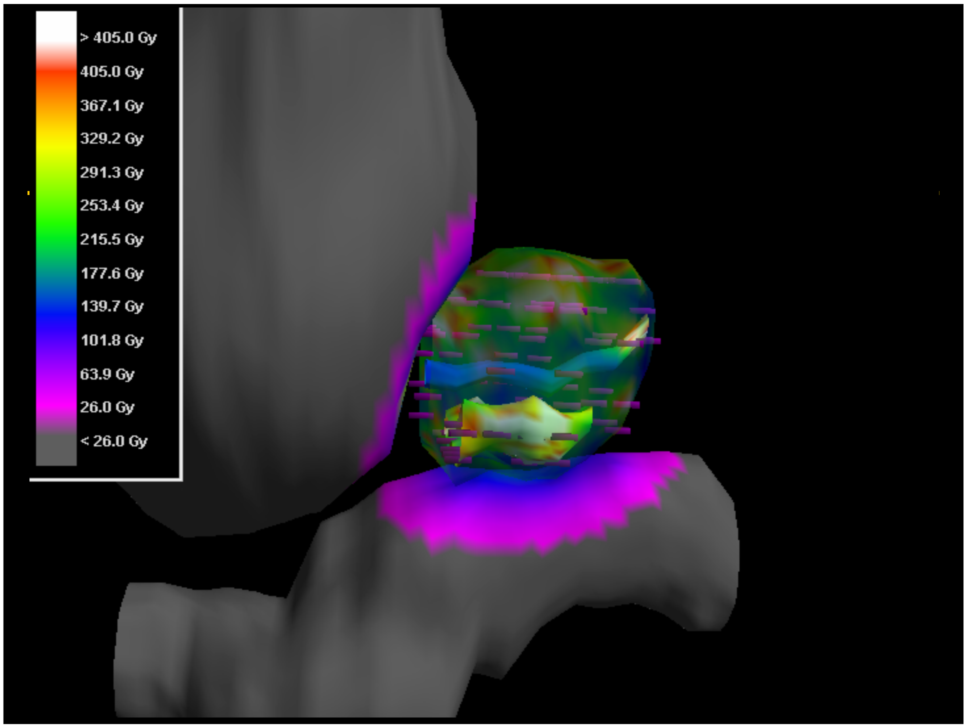
A. 3-D rendering of a prostate with a TZ protruding tumor and PZ tumor. View from the the base of the grand.

B. 3-D rendering of a prostate with cancer suspicious regions predominantly in the PZ.

Dose Sculpting & Imaging

- New imaging modalities combined with IMRT (or brachytherapy) open the way to modulating dose within diseased organs
- Success is dependent not only to the ability of IMRT (or brachytherapy) to modulate dose but also on the quality of imaging modalities





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