Principles of Radiation Therapy

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Targeted Therapy in Oncology

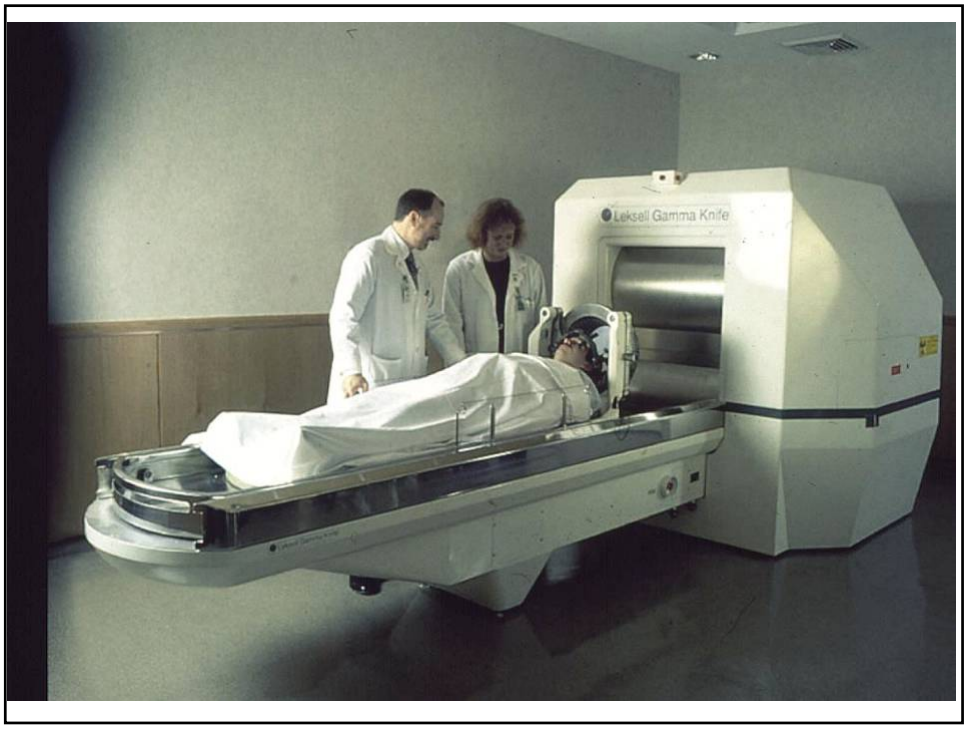
- Surgical Oncology
  - Minimal invasive techniques
- Medical Oncology
  - Tumor specific biological targets
- Radiation Oncology
  - IMRT
  - Brachytherapy
  - Protons
  - IGRT

TOPICS

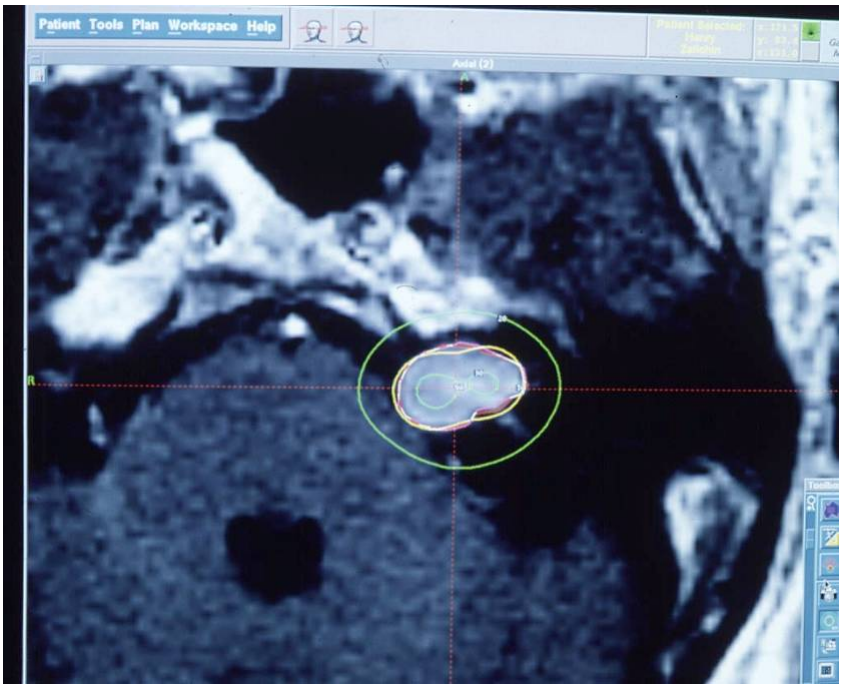
- Primary Radiation Therapy (Radiosurgery)
- Combing RT and Surgery
- Chemo/RT
  - Ca Esophagus
  - EGFR, monoclonal antibody cetuximab + RT for H&N Ca
- 3D-CRT Treatment of Localized CaP ± AD
- IGRT

Principles of Radiation Therapy

Primary Radiation Therapy


Leksell Gamma Knife


B 35
B 36
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

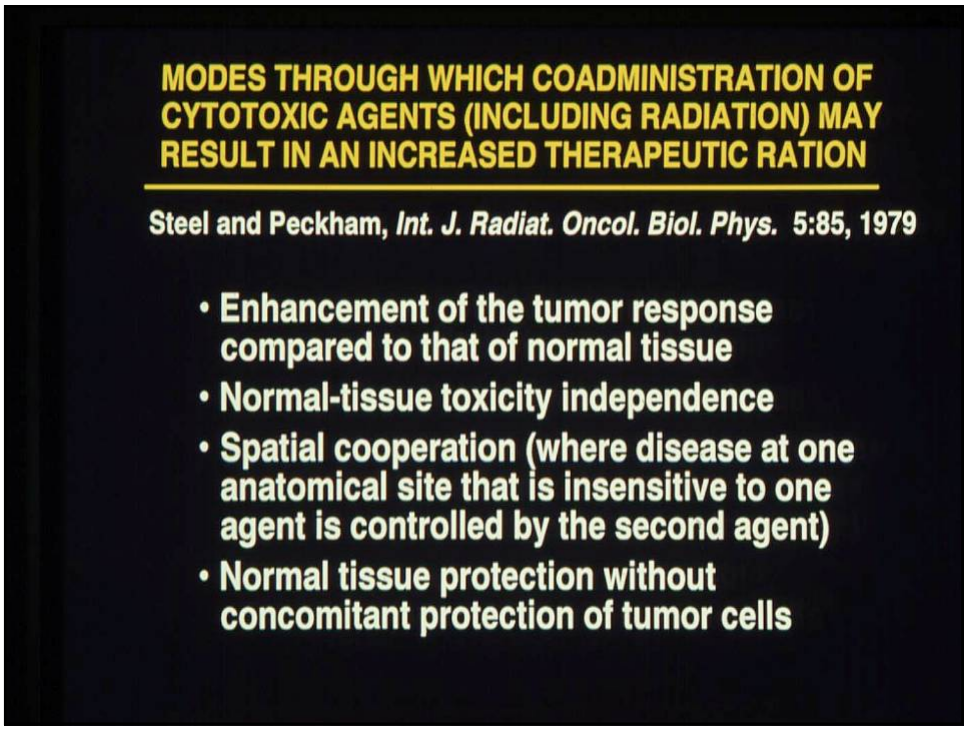
Pre-Operative vs. Post-Operative Radiation Therapy

Disadvantages of post-operative irradiation include:

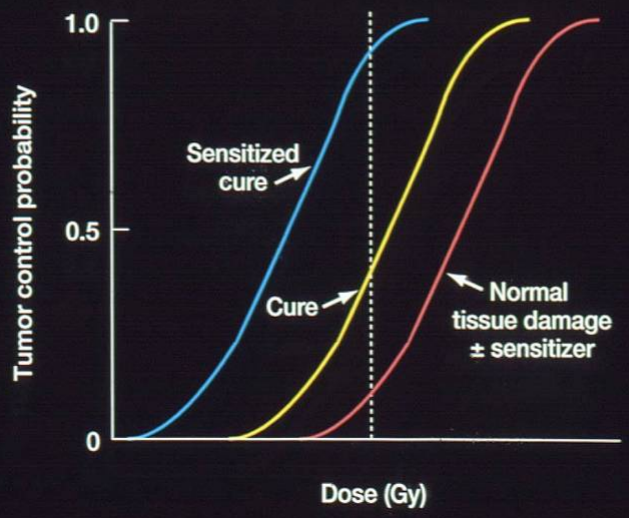
- Delivery of necessary irradiation may be delayed by poor wound healing or by surgical complications
- Tumor may be poorly oxygenated following disruption of blood supply and less sensitive to external beam irradiation
- Irradiation would have no effect on dissemination of tumor at the time of surgical 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

Principles of Radiation Therapy

Radiation Therapy and Chemotherapy



STRATEGY OF RADIOSENSITIZERS



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

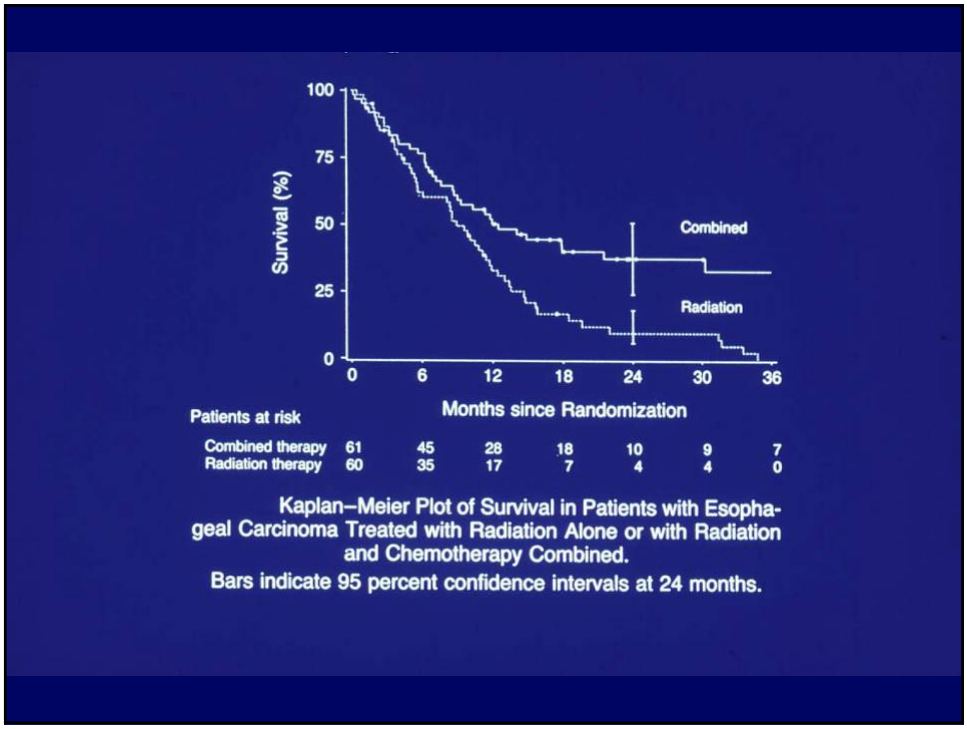
- Combination group: 4 cycles of combined 5-FU (1000 mg/m^2, for four days) and cisplatin (75 mg/m^2, day 1) plus RT (50 Gy)
- Radiation only group: 64 Gy

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%)



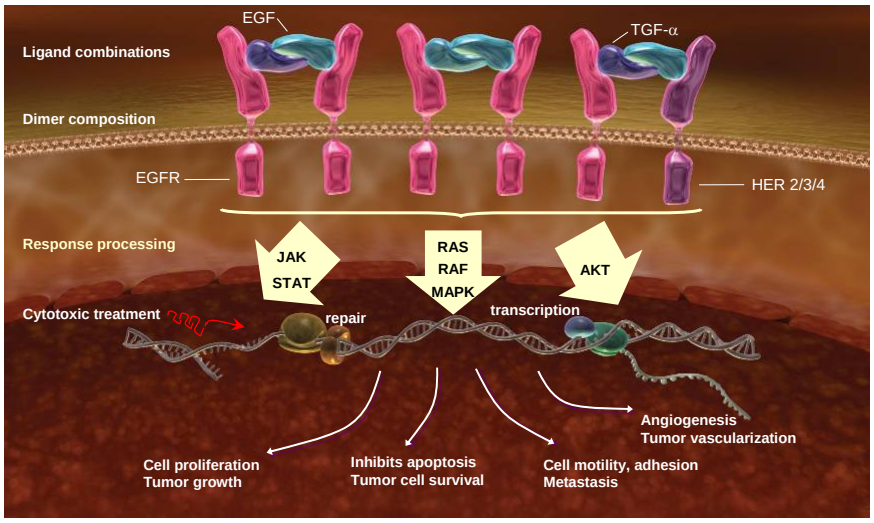
Kaplan–Meier Plot of Survival in Patients with Esophageal Carcinoma Treated with Radiation Alone or with Radiation and Chemotherapy Combined.
Bars indicate 95 percent confidence intervals at 24 months.

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

Bonner et al., NEJM 2006, 354:567

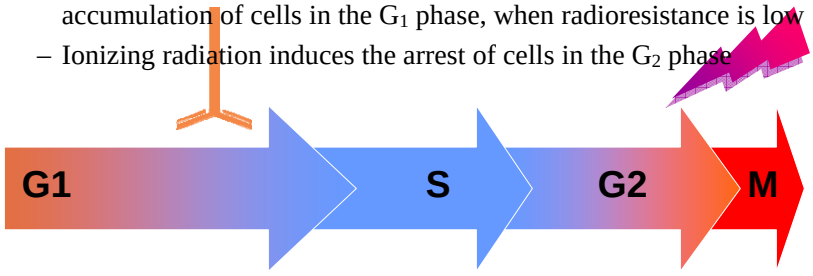
- Multinational, randomized clinical trial comparing RT alone (213 pts) with RT plus cetuximab (211 pts)
- Stage III or IV nonmetastatic SCC of oropharynx, hypopharynx or larynx
- RT up to 72 Gy
- Cetuximab iv 400 mg M^2 followed by weekly infusions of 250 mg M^2

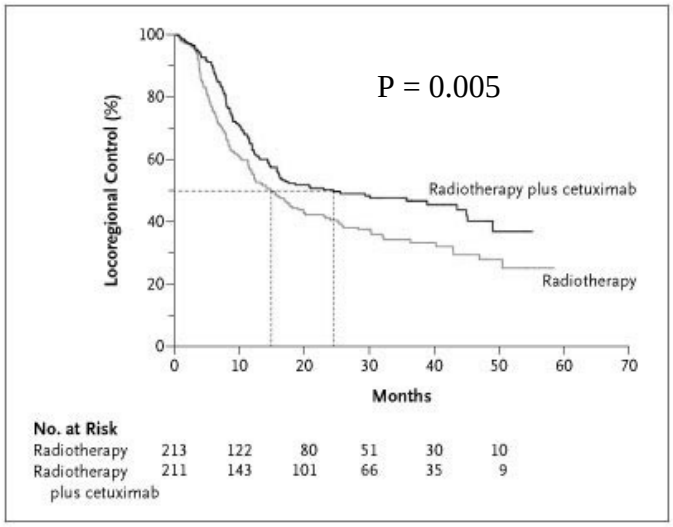
EGFR/HER1: A Key Factor in Tumorigenesis

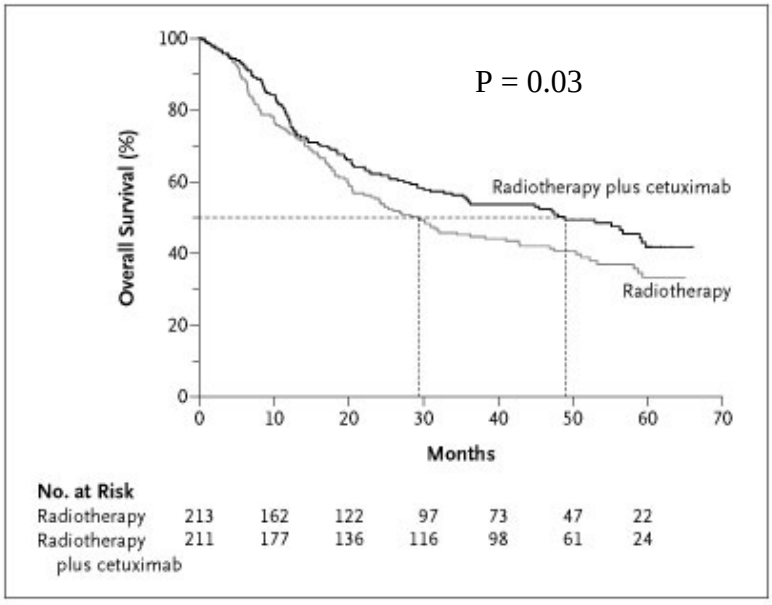


Cetuximab + RT: Enhances Antitumor Activity *In Vitro*

- As cells progress through the cell cycle, their sensitivity to ionizing radiation fluctuates. During S phase (DNA synthesis), resistance to radiation is greatest
  - *In vitro* studies have shown that Cetuximab causes the arrest and accumulation of cells in the G_1 phase, when radioresistance is low
  - Ionizing radiation induces the arrest of cells in the G_2 phase



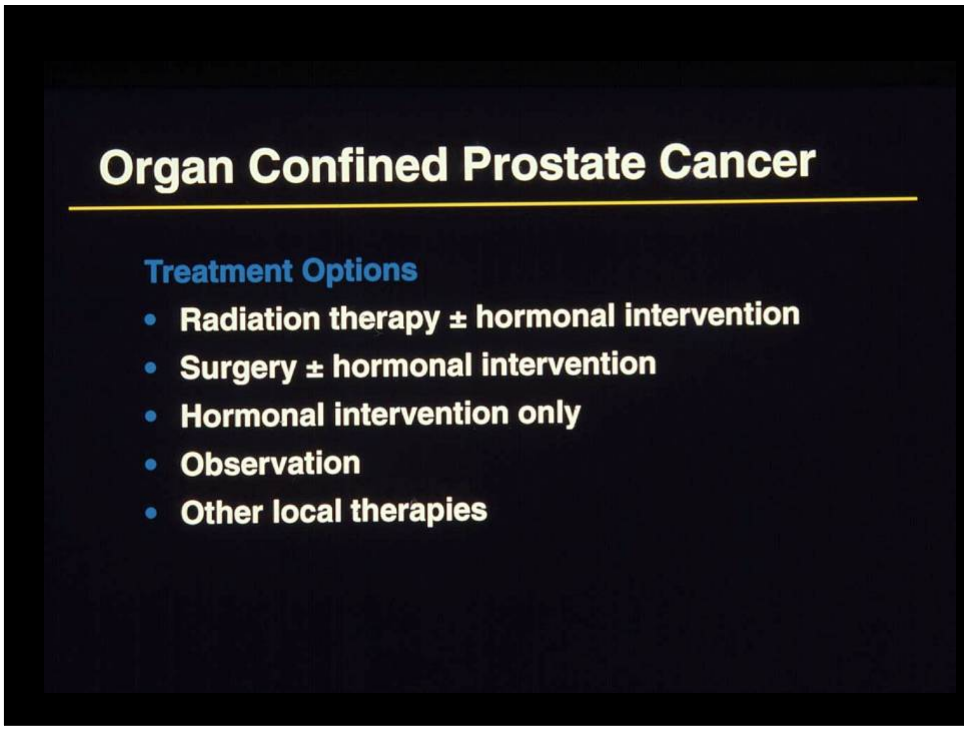

P = 0.005
Locoregional Control (%)
100
80
60
40
20
0
0 10 20 30 40 50 60 70
Months
Radiotherapy plus cetuximab
Radiotherapy
No. at Risk
Radiotherapy 213 122 80 51 30 10
Radiotherapy plus cetuximab 211 143 101 66 35 9


P = 0.03
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

Principles of Radiation Therapy

Treatment of Localized Prostate Cancer with Radiation Therapy

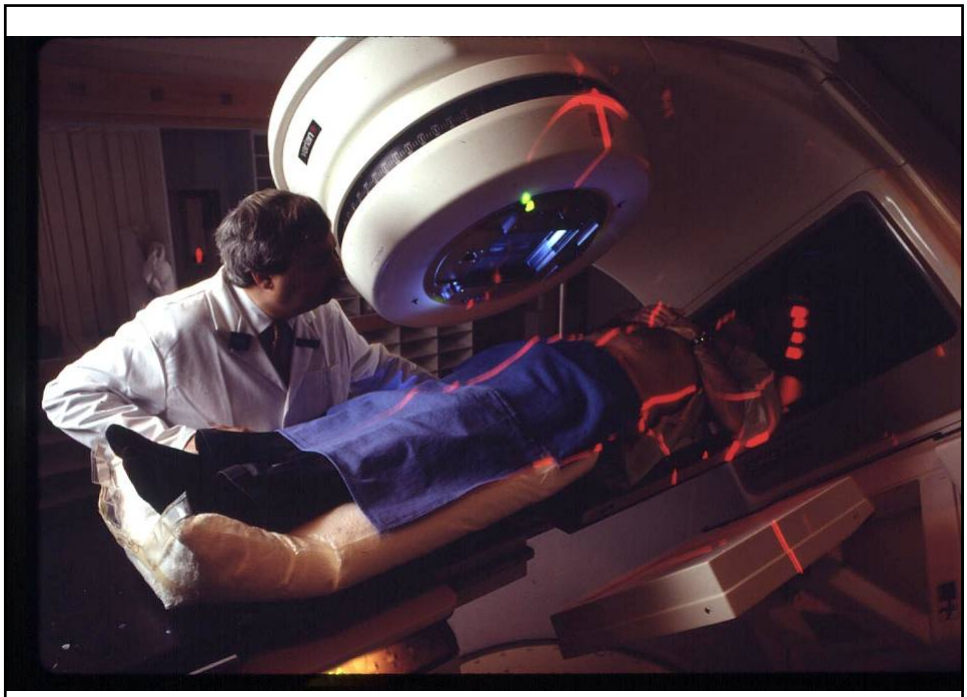
Combined Modality Treatment with AD
In Selected Patients



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

Principles of Radiation Therapy

IGRT

IGRT

New paradigms and other considerations

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

IGRT

- Respiratory motion of a lung tumor (axial view)

QuickTime™ and a
YUV420 codec decompressor
are needed to see this picture.

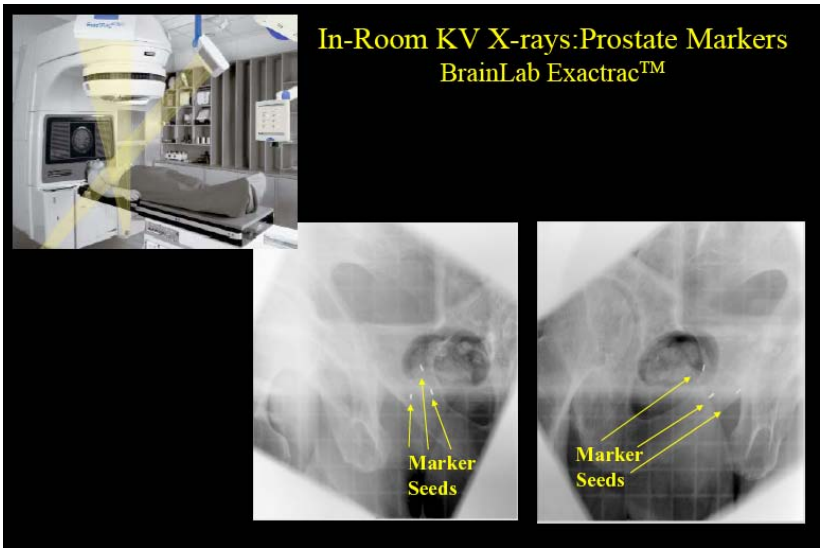
IGRT

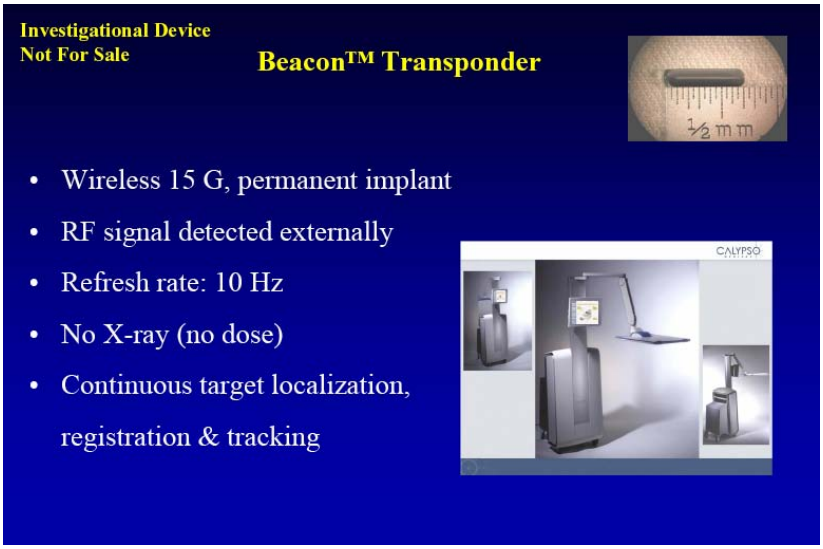
- Respiratory motion of a lung tumor (sagittal view)

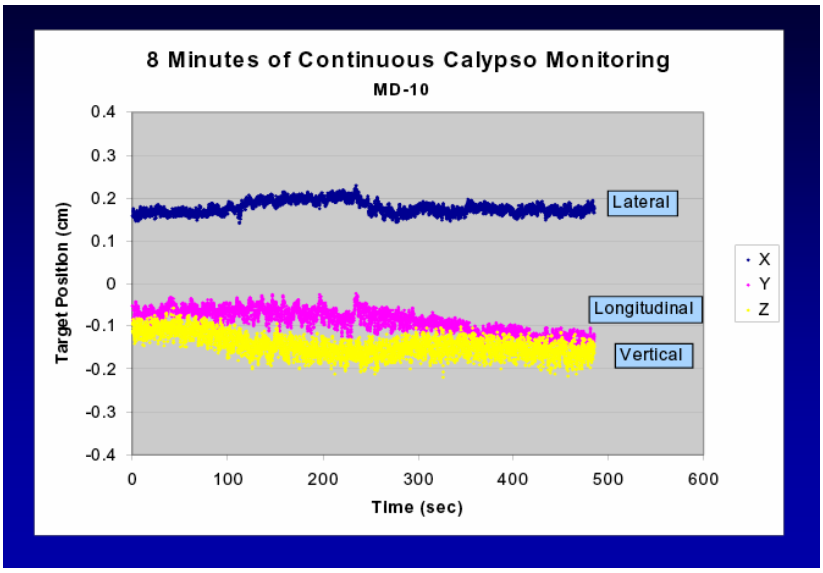
QuickTime™ and a YUV420 codec decompressor are needed to see this picture.

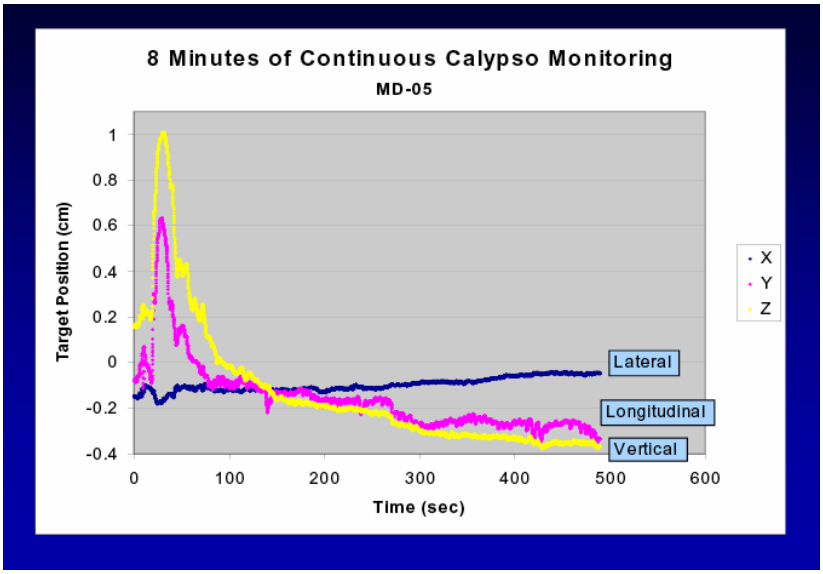
IGRT Technologies

- 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™
Marker Seeds
Marker Seeds


Investigational Device
Not For Sale
Beacon™ Transponder
½ mm
• Wireless 15 G, permanent implant
• RF signal detected externally
• Refresh rate: 10 Hz
• No X-ray (no dose)
• Continuous target localization, registration & tracking
CALYPSO


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

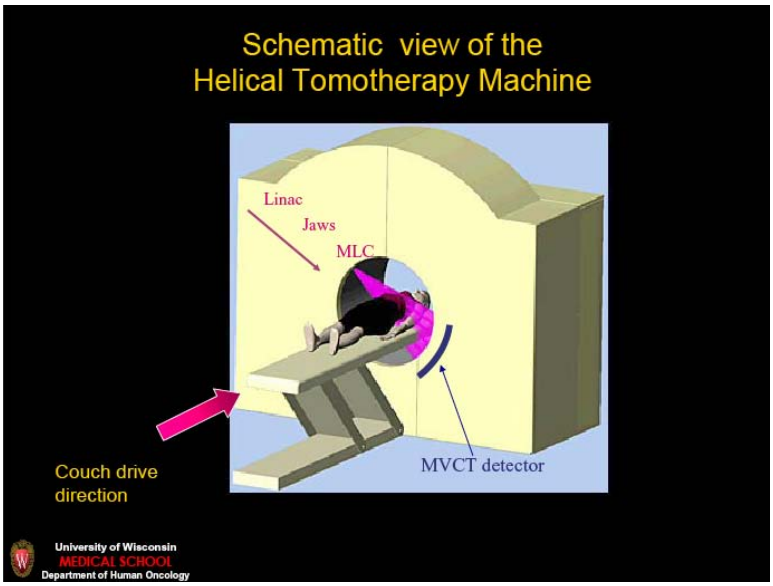
Cone Beam KV CT

Same Gantry
Coupled to delivery device
Volume acquisition

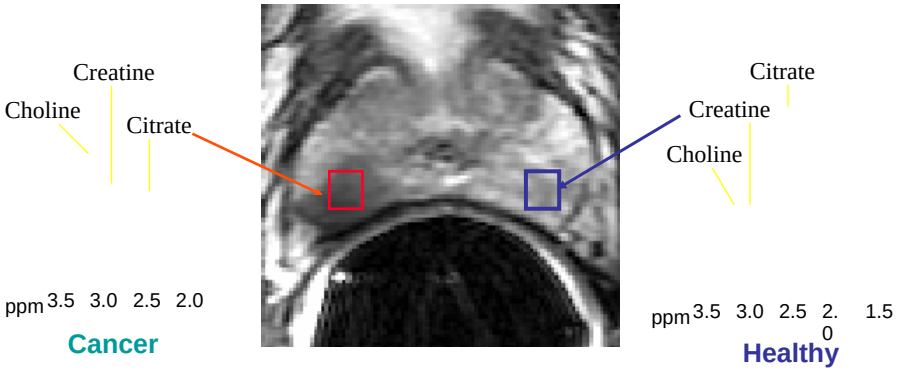
5-10 min for image guidance
1-2 cGy per scan

Elekta Synergy

Varian Trilogy

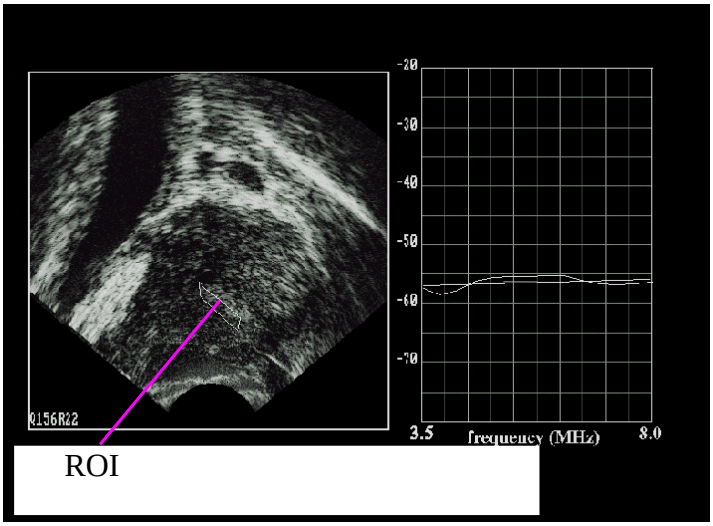


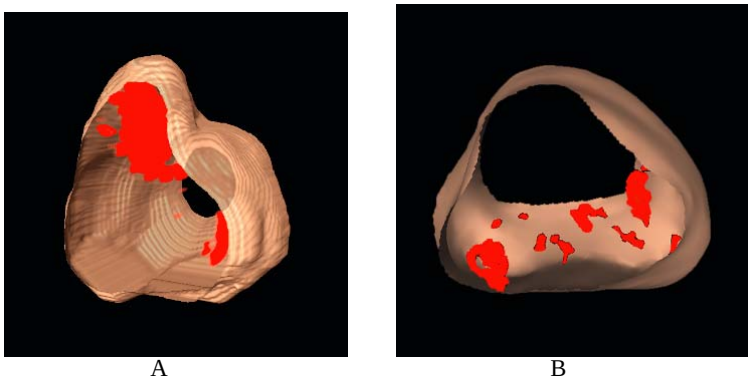
MRS Detection of Prostate Cancer



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)





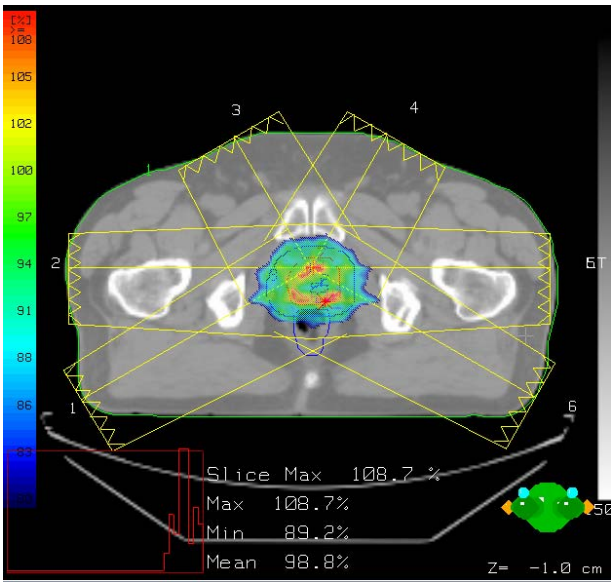
A B

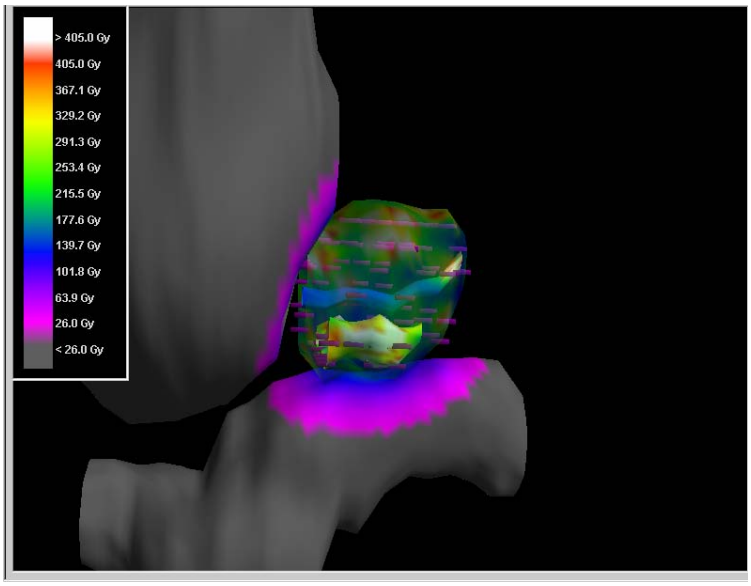
A. 3-D rendering of a prostate with a TZ protruding tumor and PZ tumor. View from the the base of the grand. Ultrasonic Imaging 23, 135-146, 2001.

B. 3-D rendering of a prostate with cancer suspicious regions predominantly in the PZ. Medical Imaging 2000: Ultrasonic Imaging and Signal Processing, Vol. 1, No 27: 68-76, 2000.

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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THANK YOU