Radiation Therapy for Prostate Cancer: Where We are and What's Next

Ramesh Gopal, MD, PhD
Associate Professor of Radiation Oncology
MD Anderson Cancer Center
Medical Director MD Anderson Radiation Treatment Center at Presbyterian

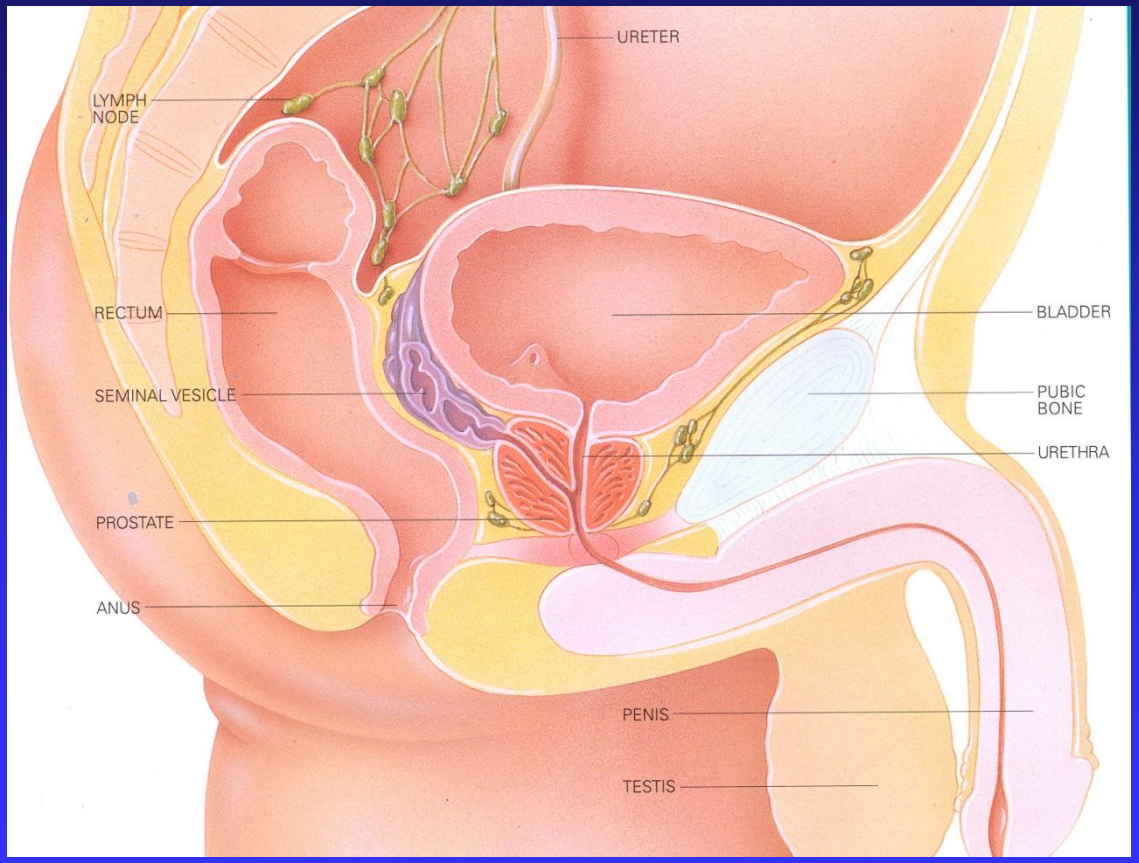
MD Anderson Cancer Center

Making Cancer History®

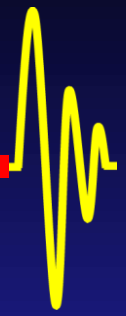
What is the Prostate?

- A gland about the size of a walnut
- Produces the prostatic fluid that carries the sperm
- Located just below the bladder and in front of the rectum

Prostate Anatomy



Prostate cancer is common



- ACS expects 161, 360 new cases in 2017
- Lifetime risk of developing prostate cancer is 1:7

Prostate cancer was commoner

- ACS expects 161, 360 new cases in 2017
- Lifetime risk of developing prostate cancer is 1:7
- How can this be?!

- ACS expects 220,800 new cases in 2015
- Lifetime risk of developing prostate cancer is 1:6
- Over age 80 approximately 75% have latent disease

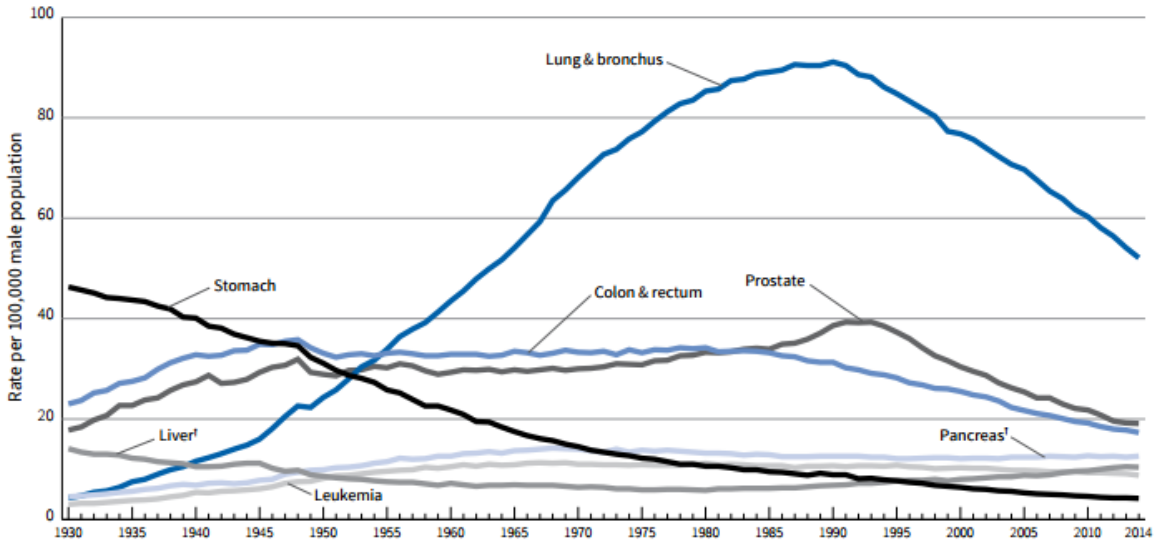
Less Prostate Cancer

- In fact in 2016 the expected number was 180, 890.
- These are extrapolations based on previous years.
- The extrapolation has changed!
  - ACS expects 161, 360 new cases in 2017
  - Lifetime risk of developing prostate cancer is 1:7
  - How can this be?!

- ACS expects 220,800 new cases in 2015
- Lifetime risk of developing prostate cancer is 1:6
- Over age 80 approximately 75% have latent disease

Most cancers are declining

Figure 1. Trends in Age-adjusted Cancer Death Rates* by Site, Males, US, 1930-2014

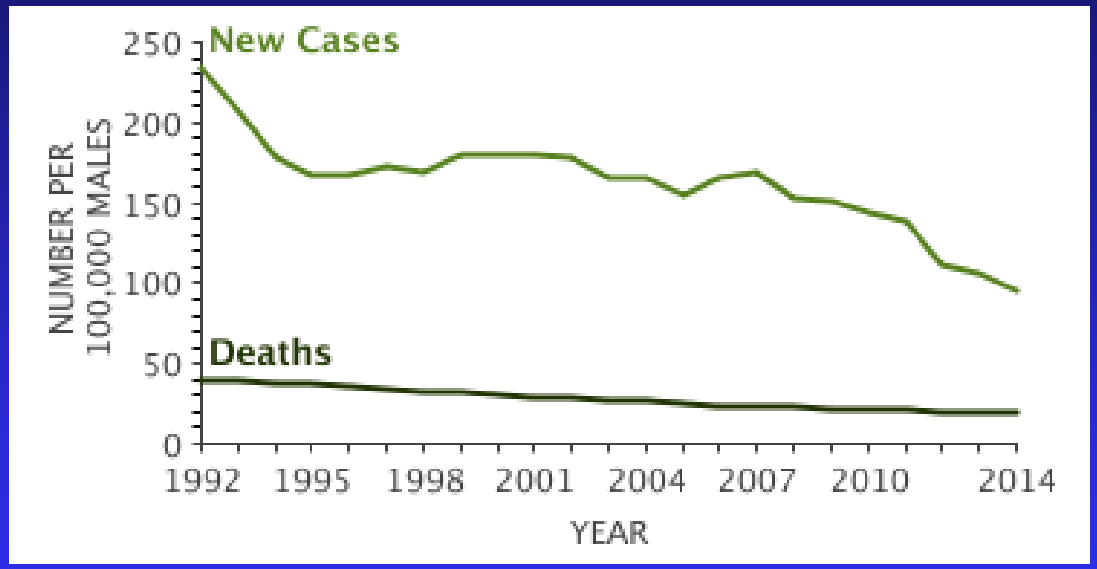


*Per 100,000, age adjusted to the 2000 US standard population. †Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, uterus, and colon and rectum are affected by these coding changes.

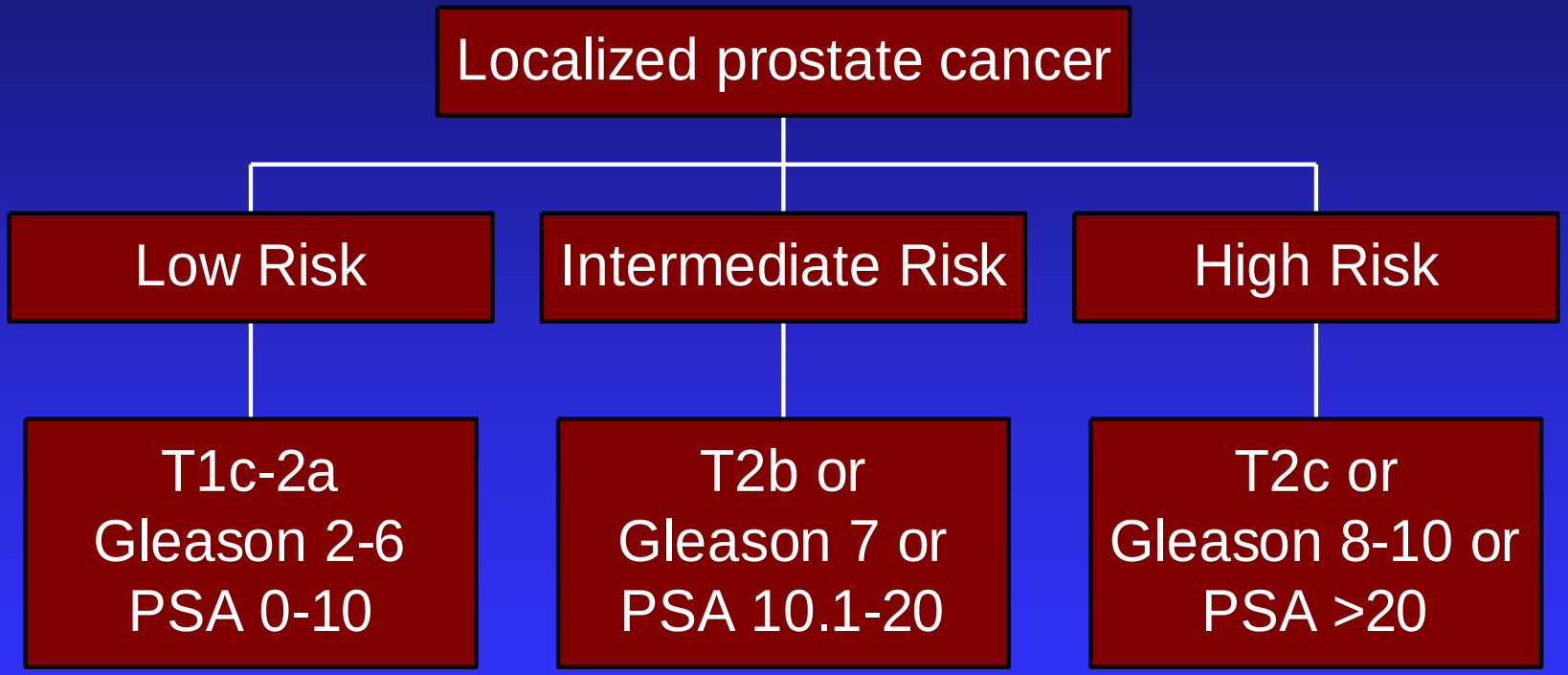
Source: US Mortality Volumes 1930 to 1959 and US Mortality Data 1960 to 2014, National Center for Health Statistics, Centers for Disease Control and Prevention.

There will be less prostate cancer



National Cancer Institute
Surveillance, Epidemiology and End Results Program (SEER)
Cancer Statistical Facts
https://seer.cancer.gov/statfacts/html/prost.html

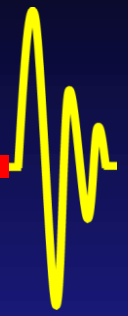
T-stage, Gleason, PSA define risk of failure



Which Prostate Cancer Needs Treatment?

- Unfavorable Group
  - High Gleason Score
  - High PSA
  - High Stage
- For Favorable Group
  - PSA velocity > 2ng/ml/yr
  - PSA doubling time < 3yrs

Rationale of Treatment



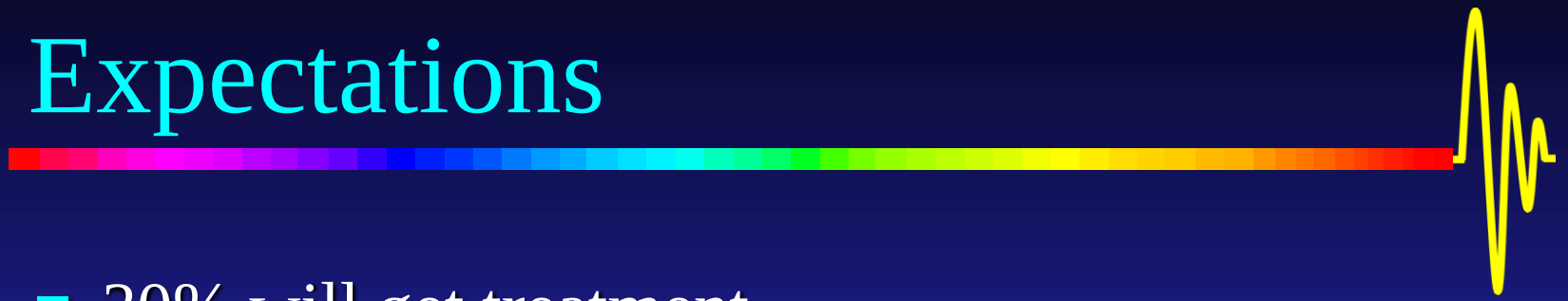
"There is a general rule, and I have seen great physicians acting on it, that the physician should not treat the disease but the patient who is suffering from it."

Maimonides (1135-1204)

Reasonable Active Surveillance Strategy

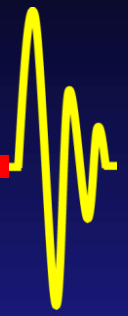
- Eligibility
  - PSA ≤ 10
  - Gleason ≤ 6
  - T1c–T2a
- Follow-up schedule
  - PSA, DRE every 3 months for 2 years, then every 6 months assuming PSA is stable
  - 10–12 core biopsy at 1 year, and then every 3–5 years until age 80
- In patients who appear borderline at 2 years consider more frequent biopsies
- Intervention
  - PSA doubling time < 3 years (based on at least eight determinations; approximately 20%)
  - For grade progression to Gleason 7 (4 + 3) or higher (approximately 5% of patients)

Expectations



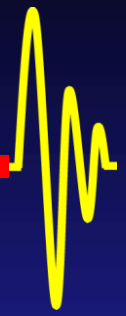
- 30% will get treatment
  - 20% because of PSA doubling time
  - 5-10% because of increased Gleason Score
- 70% will continue on surveillance
- Generally patients who need treatment will become known in 2 years.

Genomic Testing



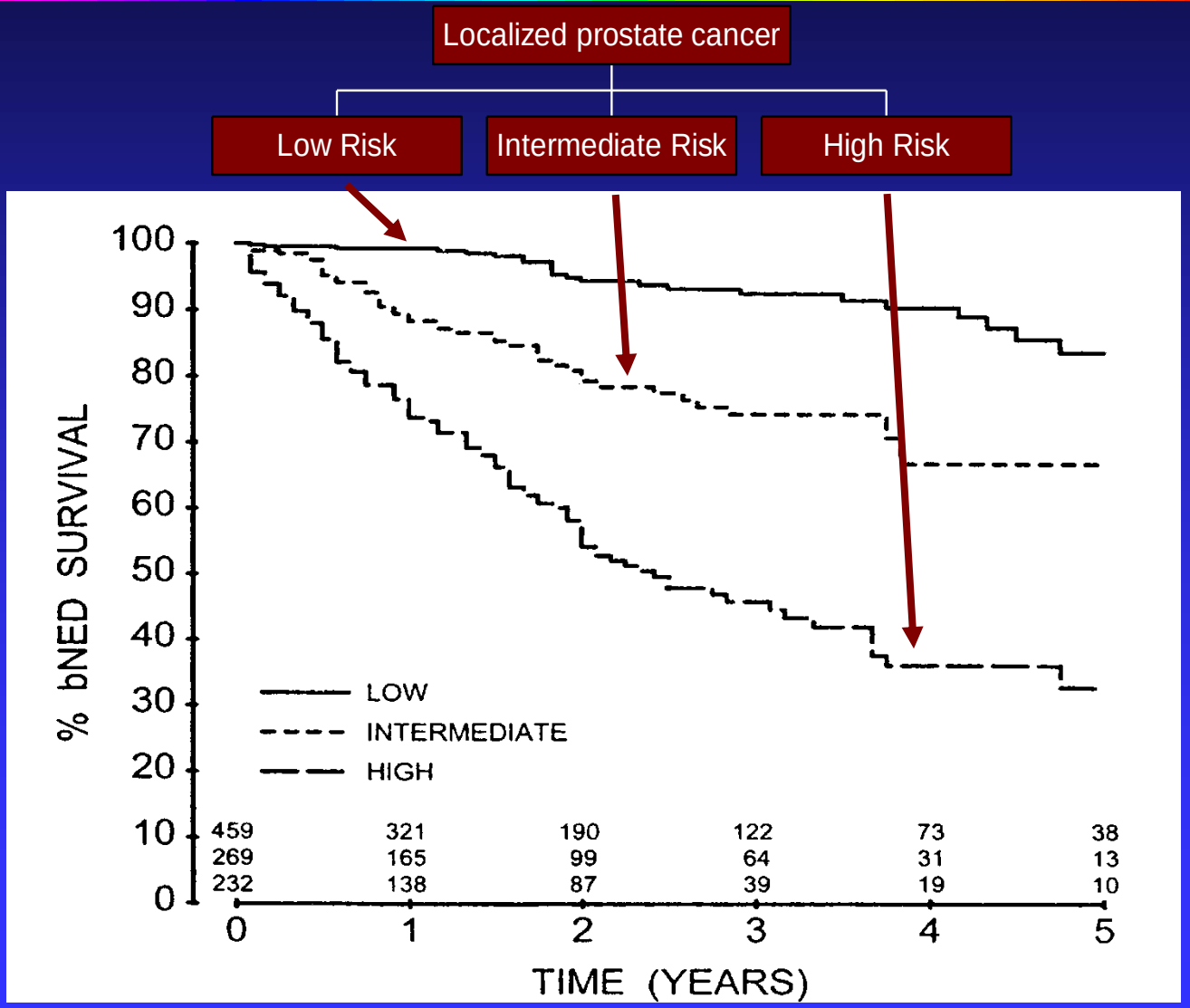
- Advances in molecular profiling can be expected to enhance treatment strategies.
  - The Oncotype DX test for prostate cancer evaluates 17 genes to estimate tumor behavior.
  - The Decipher test predicts the probability of metastasis after surgery by measuring the expression levels of 22 RNA biomarkers.

Present Prostate Cancer Treatment



- Surgery
  - Open
  - Laparoscopic
  - Robotic
- Radiation Therapy
  - IMRT/VMAT
  - Brachytherapy
  - Proton Therapy
  - Stereotactic Body Radiation Therapy (SBRT)
- Observation

PSA outcome after radical prostatectomy

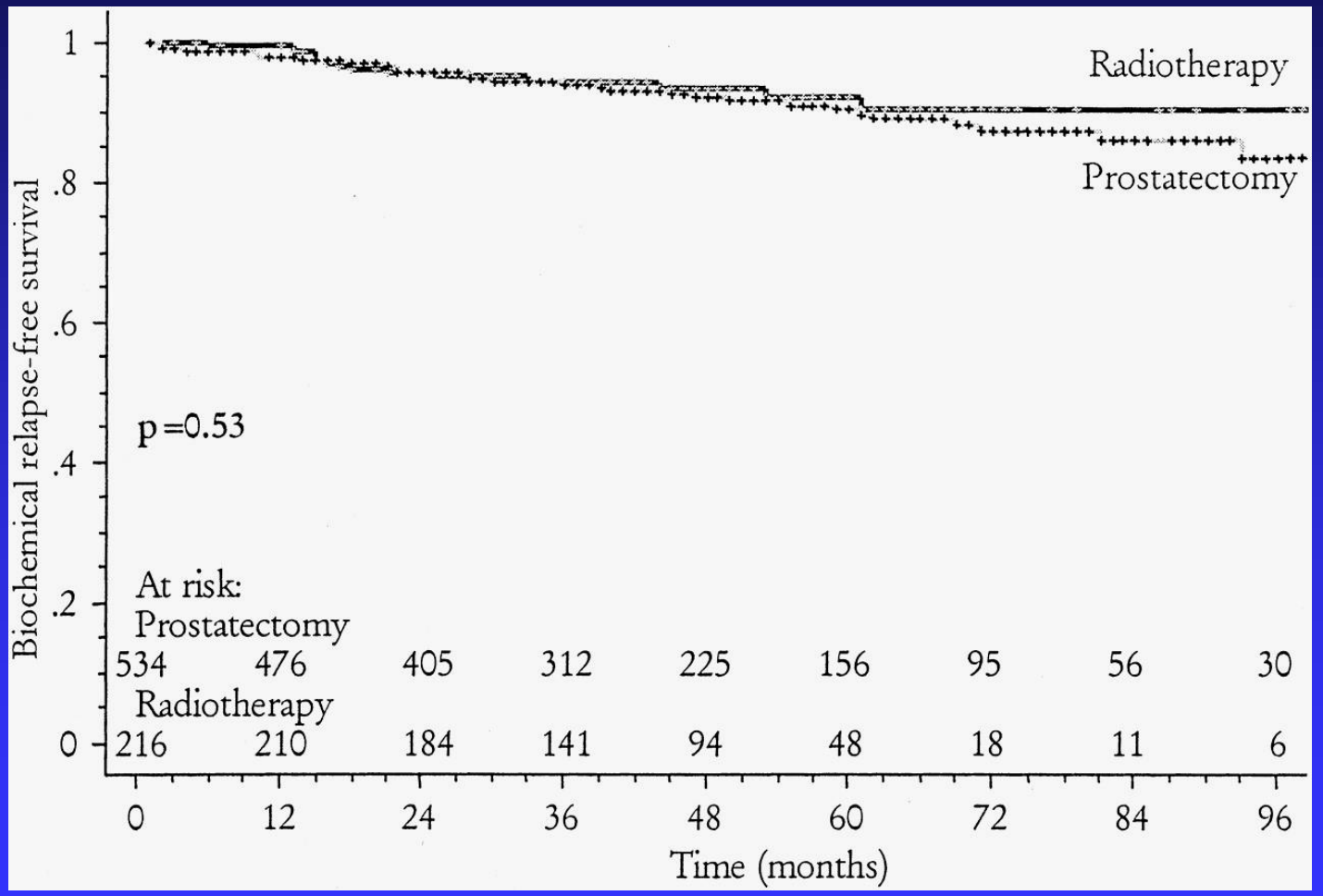


Cleveland Clinic Experience

- 1682 patients w/ T1-2 PC treated by RP (1054) or EBRT (628).
- Median RT dose 70.2 Gy [68-78Gy].
  - PSA failure for RP was >0.2
  - PSA failure for RT was ASTRO (3 consecutive rises)

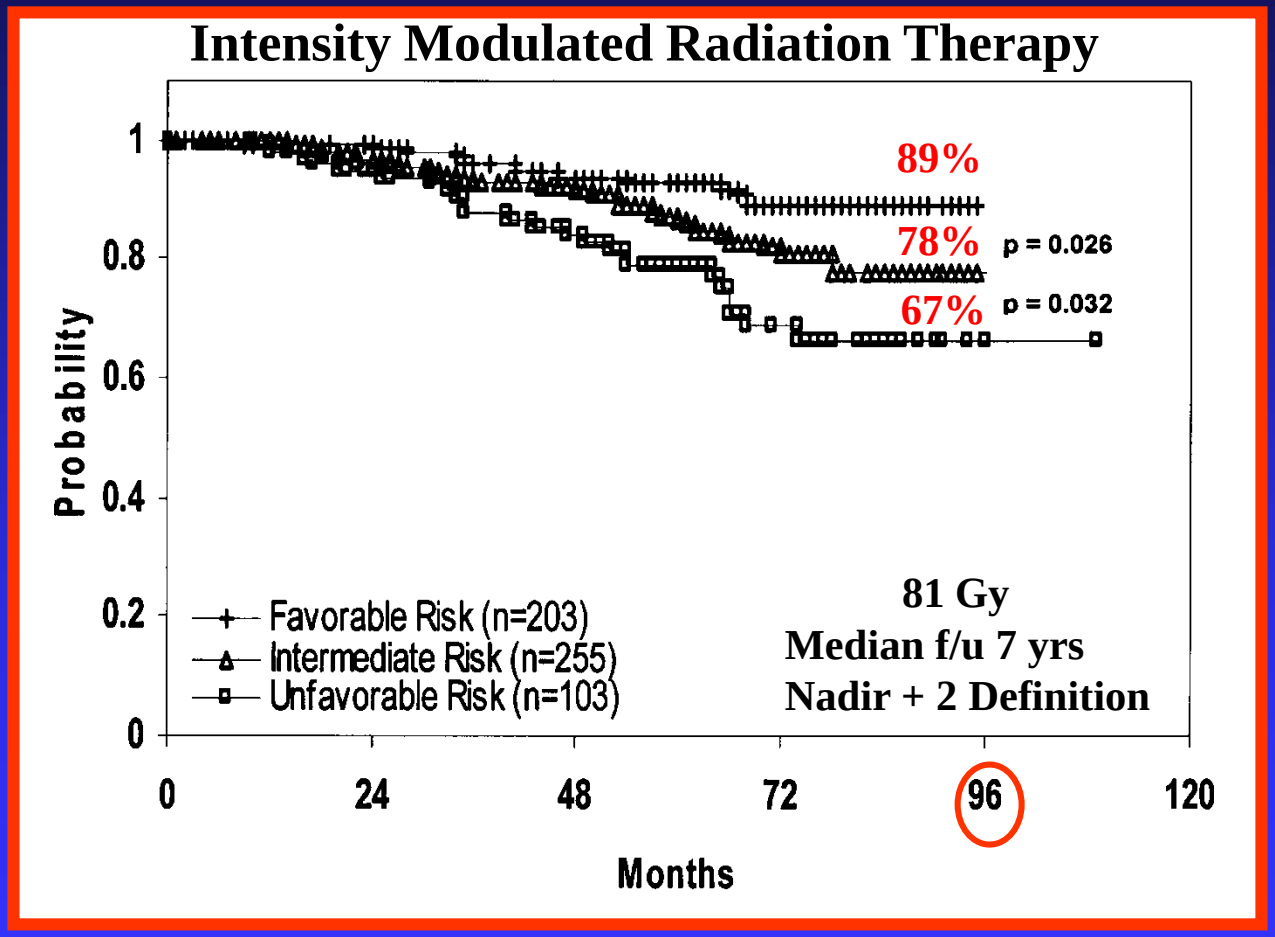
Kupelian et al. JCO 20:3376,2002

PSA-RFS in low risk



Kupelian et al. JCO 20:3376,2002

PSA Disease Free Survival



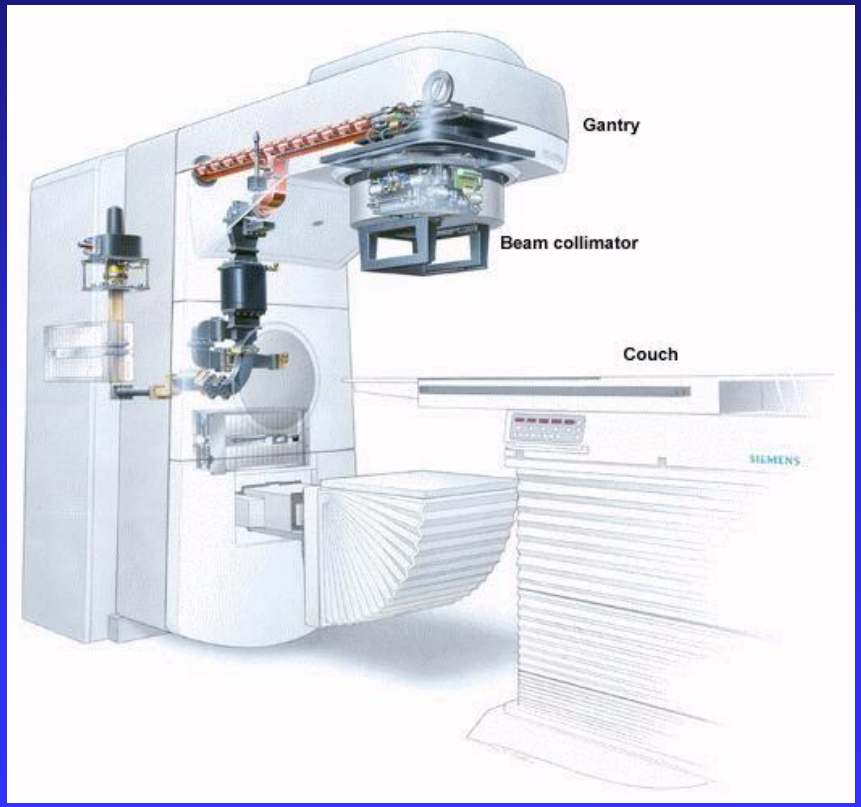
Zelefsky et al. , J Urol 176: 1415, 2006

External Beam Radiation Therapy

- Radiation is administered using a linear accelerator

The Working of a Linac

- A power source generates electrons
- The electrons are accelerated and...
- Either used for therapy, or...
- Directed at a target to produce photons for therapy



External Beam Radiation

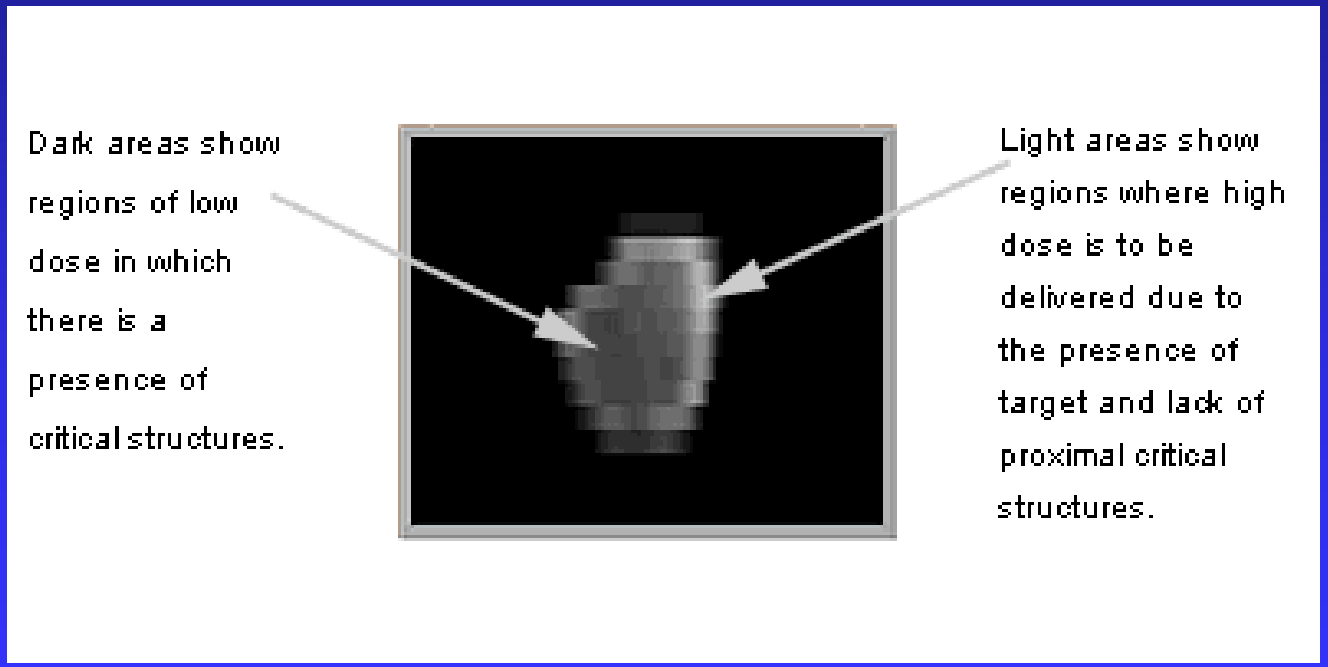
- Administered using a linear accelerator
  - Non-invasive
  - Can be used when extra-prostatic spread is likely
- 7 to 8 weeks of daily, M – F treatments

Treatment techniques

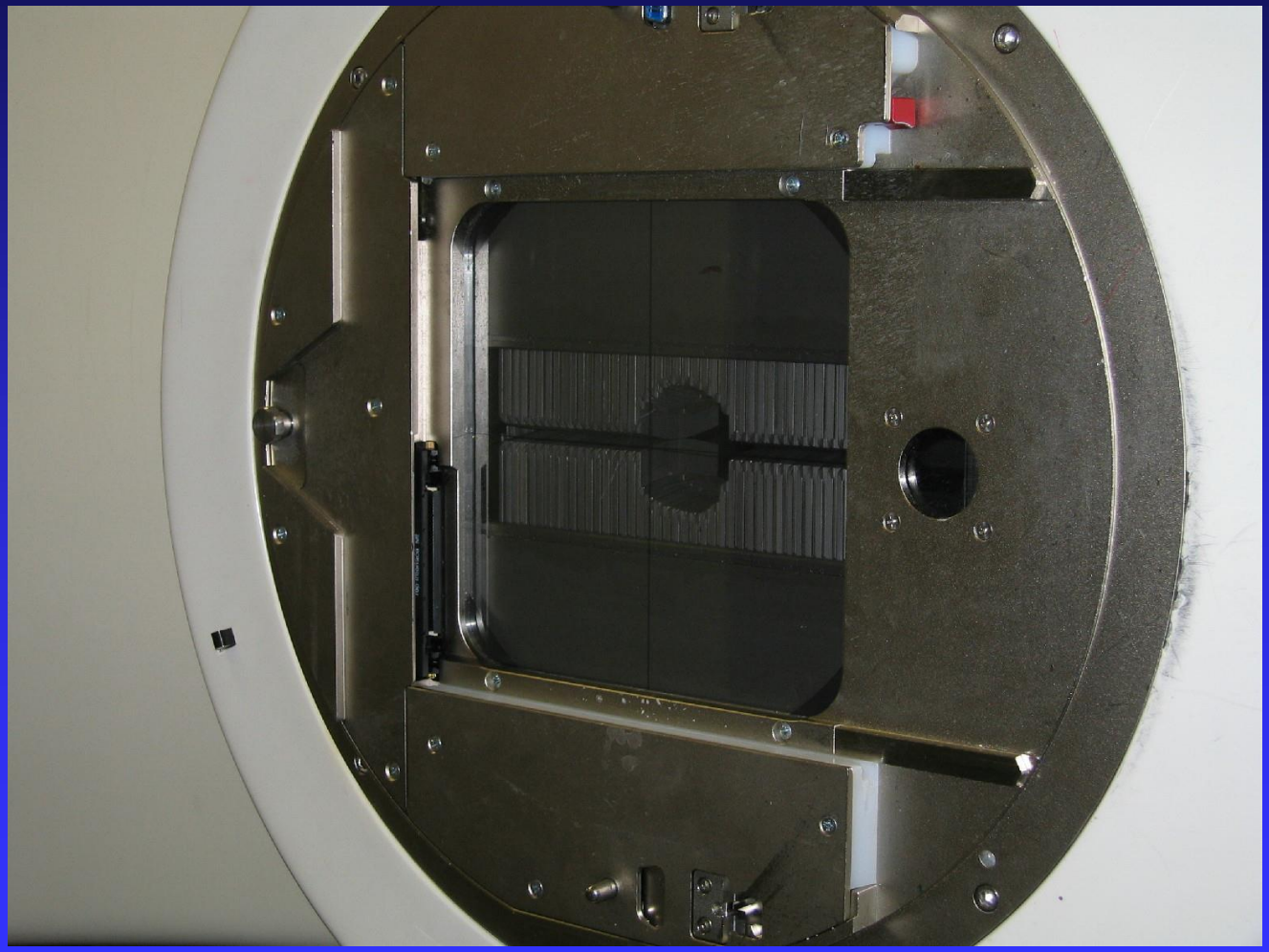
- Conformal radiation therapy
  - Radiation dose to the target is maximized, while dose to normal tissues is minimized
  - Inverse treatment planning is used
  - The goal is to minimize the volumes of rectum and bladder that are irradiated

IMRT

- Intensity Modulated Radiation Therapy



The Linac Head

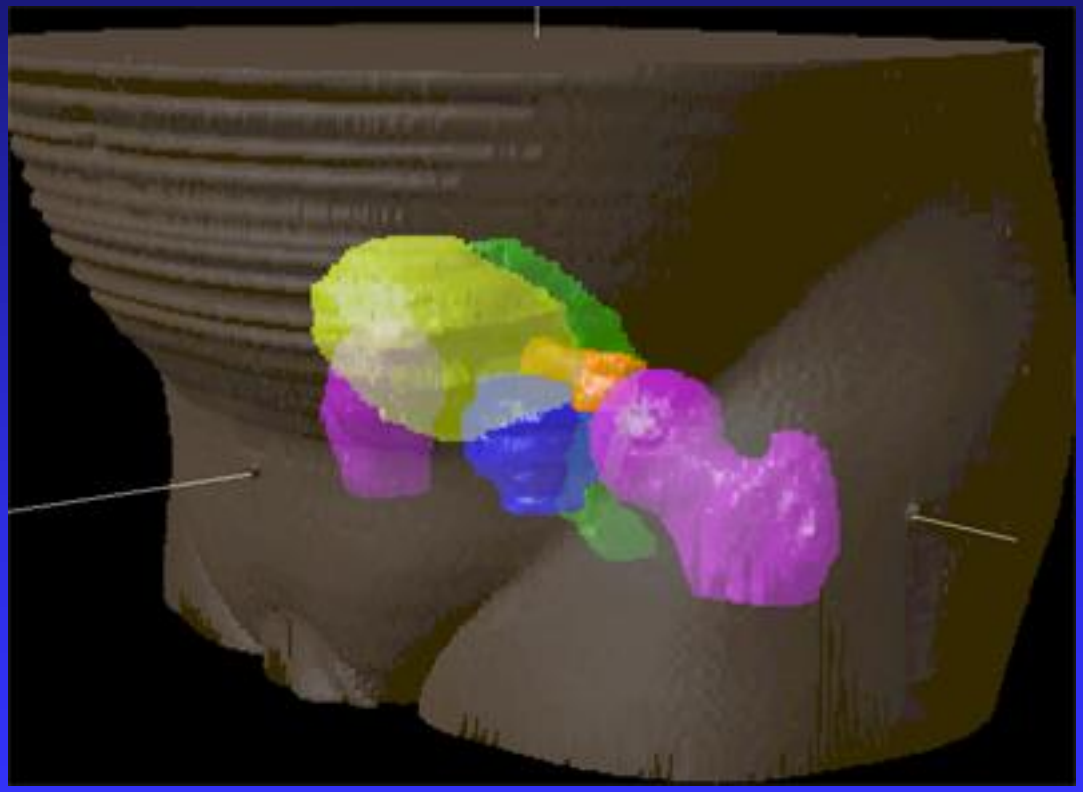


Multi-Leaf Collimators

Dose Painting

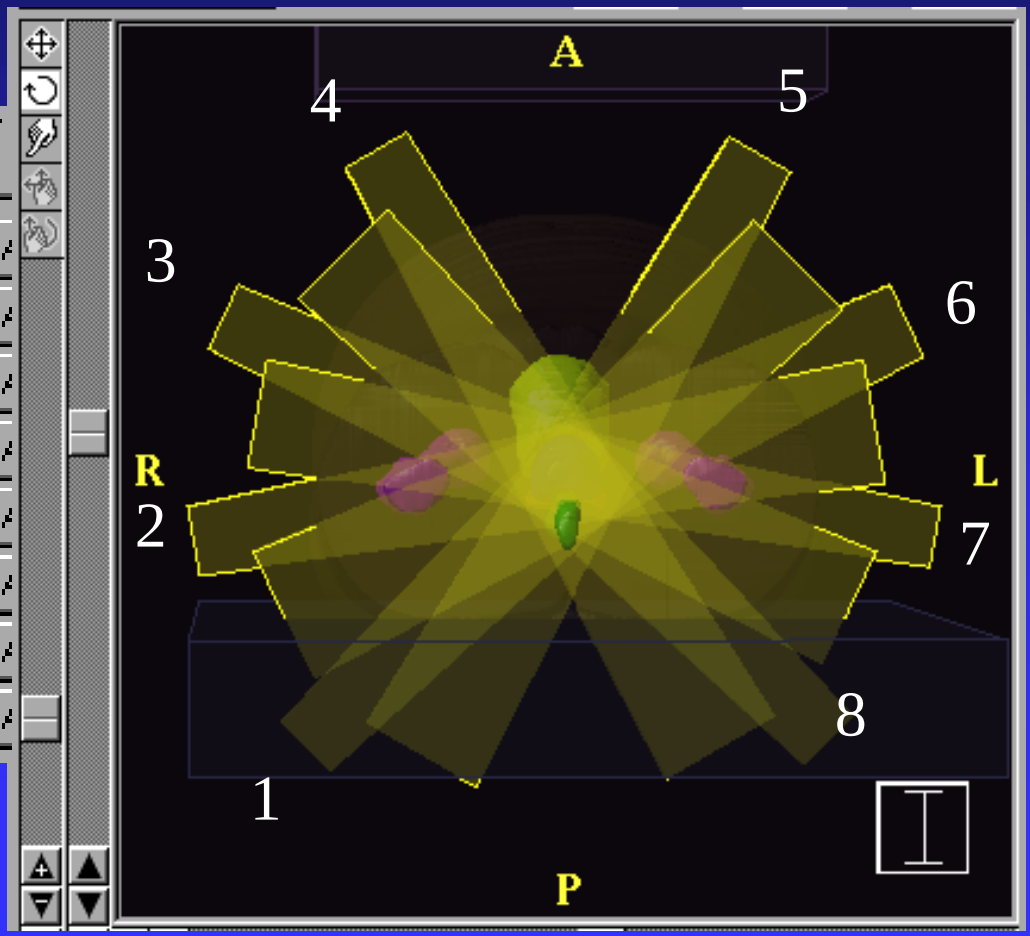
- Dose can literally be “painted” onto the target

Contouring the organs

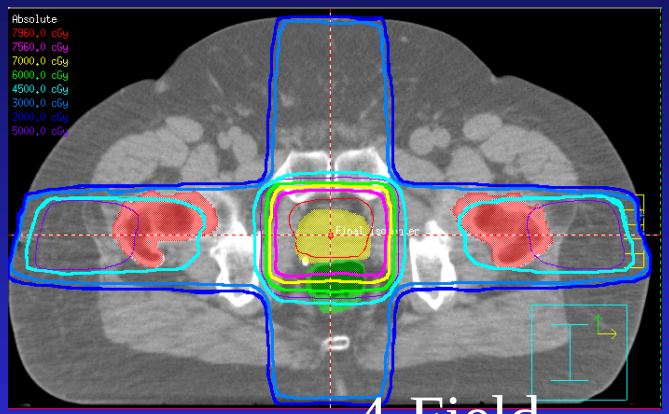


Beam angles

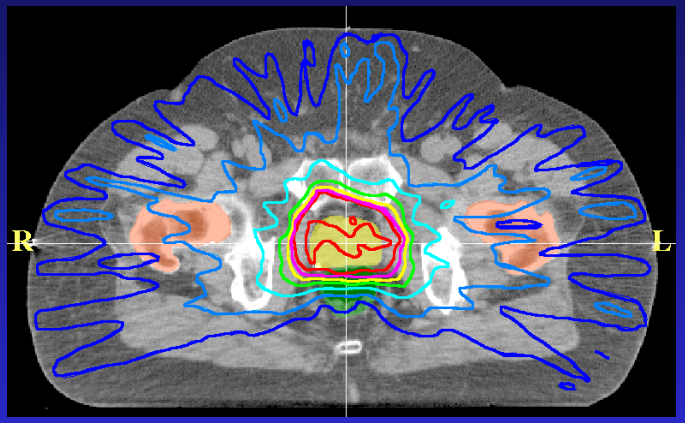
s	Couch Angle	Gantry Angle	Collimator Angle
1.	0 °	225 °	0 °
2.	0 °	260 °	0 °
3.	0 °	295 °	0 °
4.	0 °	330 °	0 °
5.	0 °	30 °	0 °
6.	0 °	65 °	0 °
7.	0 °	100 °	0 °
8.	0 °	135 °	0 °

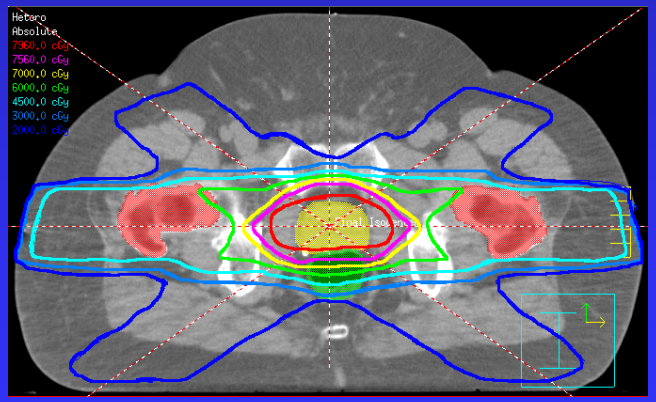


Dose distributions

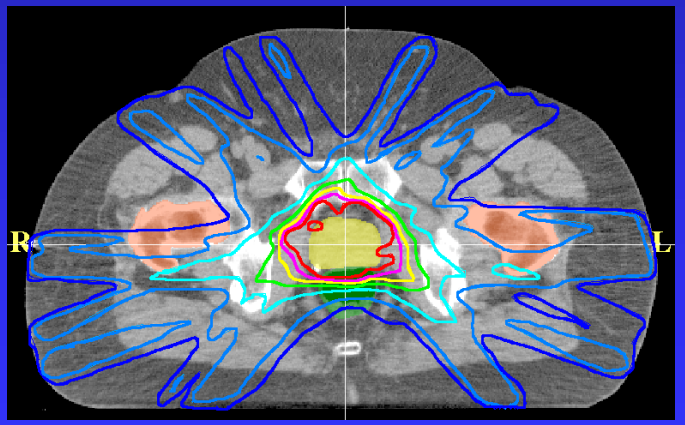


4-Field





7-Field



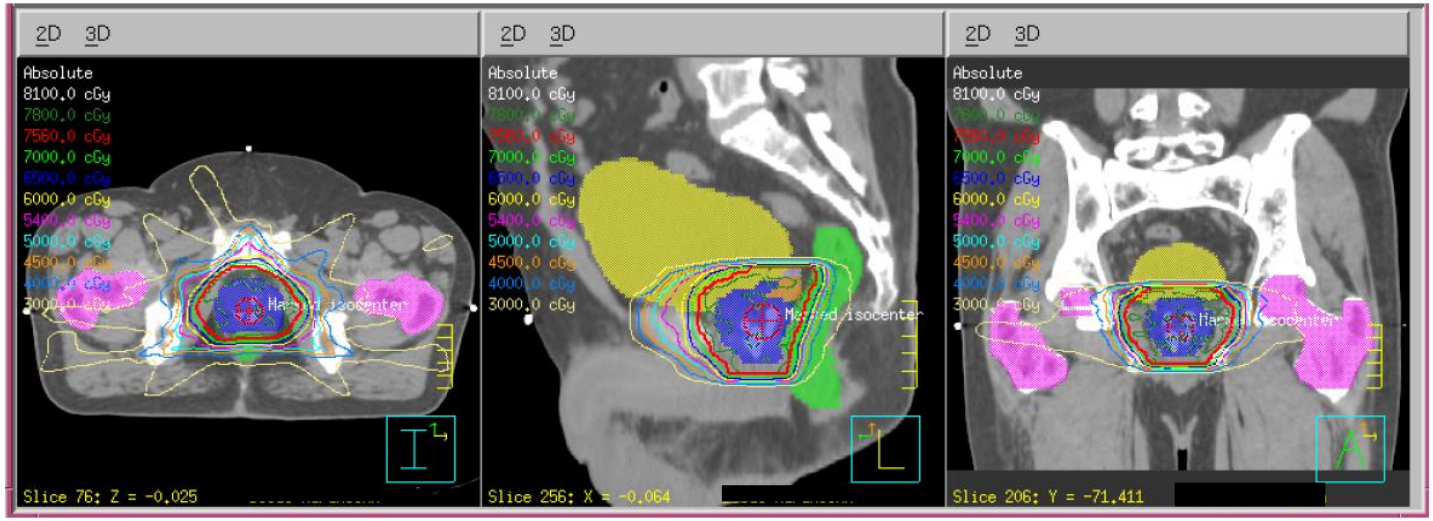
IMRT

79.6
75.6
70.0
60.0
45.0
30.0
20.0

IMRT

Pinnacle³ RTP System 7.6c

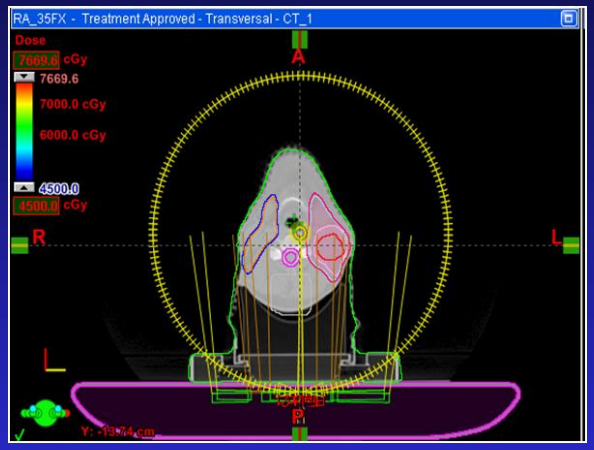
IMRT Prostate Plan



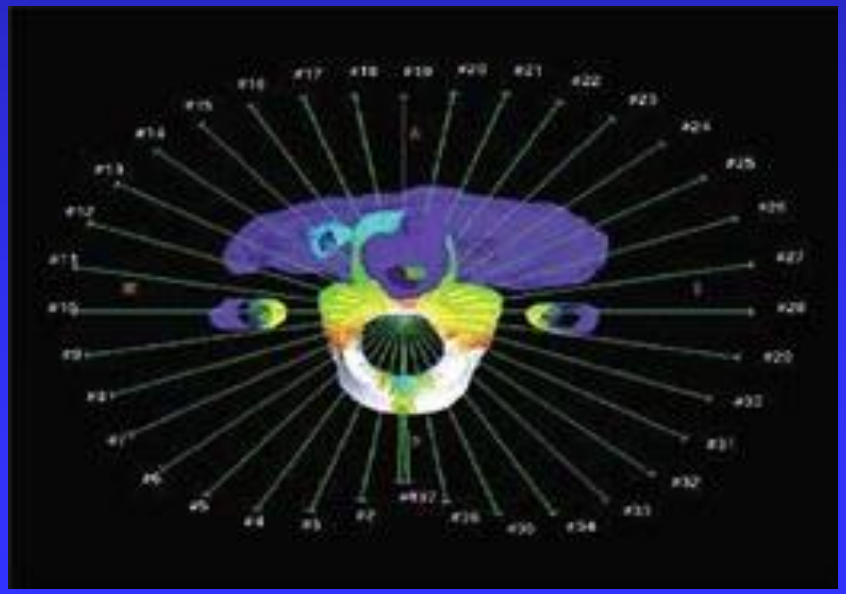
VMAT

- Volumetric Modulated Arc Therapy
- VMAT provides high dose conformance to the target, while reducing risk to critical structures
- VMAT can reduce treatment time which can also decrease the likelihood of patient movement

Dynamic Arcs Vs Static Beams



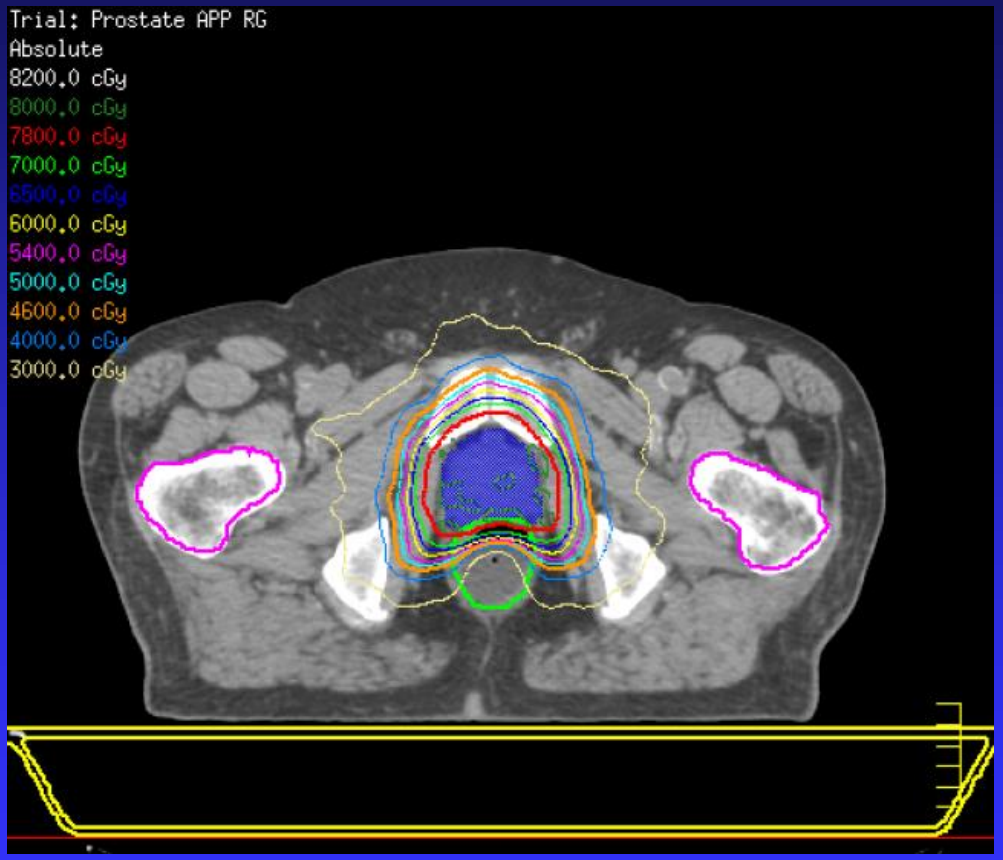
Multiple control points (≈ 90) per arc.



Arc Treatment

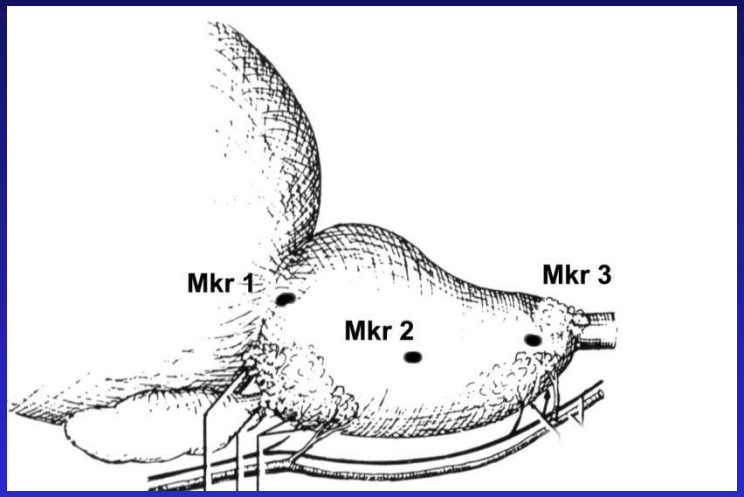
- The gantry rotates around the patients.
- Treatment is delivered continuously.
- This results in short treatment times.

VMAT in action



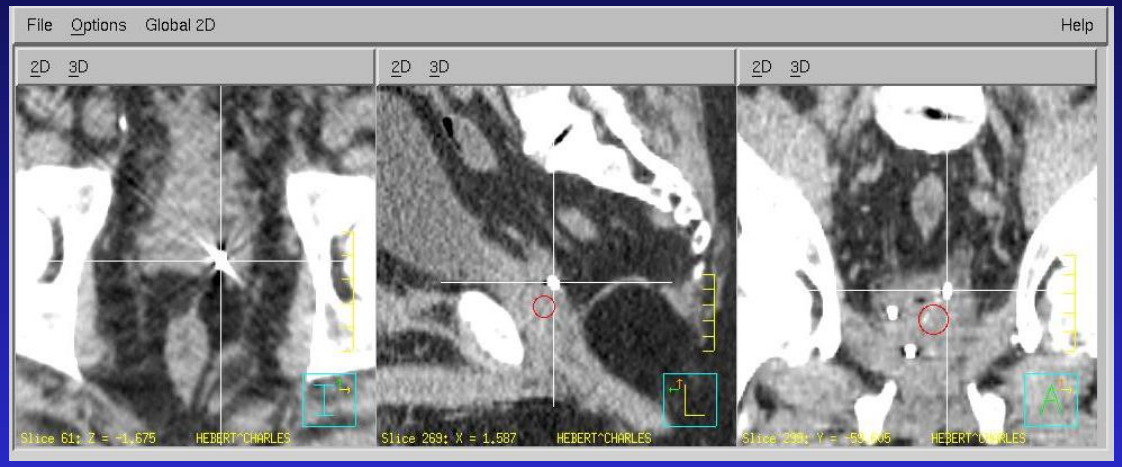
Treatment is delivered as 2 arcs.

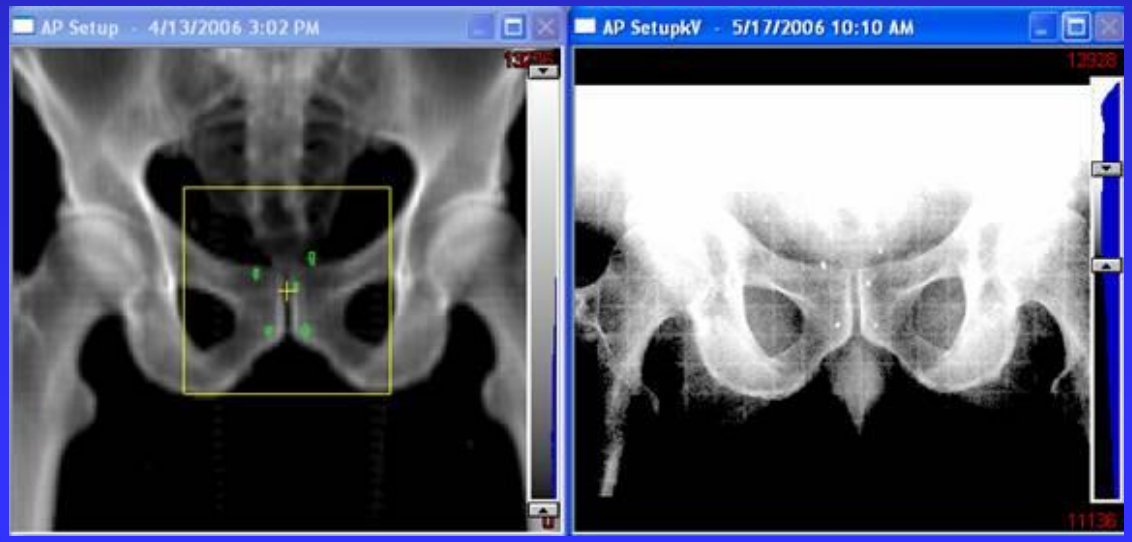
Image Guidance & Fiducial Markers



- Gold seeds implanted directly in the prostate can be visualized and adjustments made.

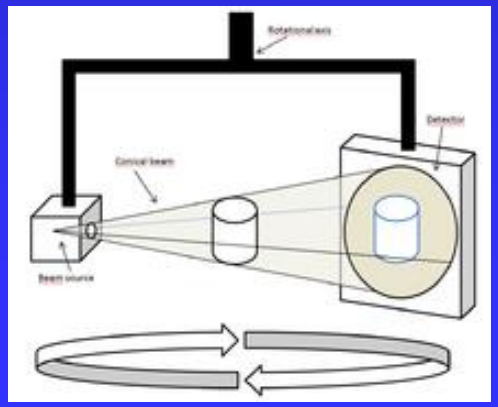
Markers used for set-up





- The markers are visible both on planning CT scans and on daily imaging.
- Used for daily set-up adjustments.

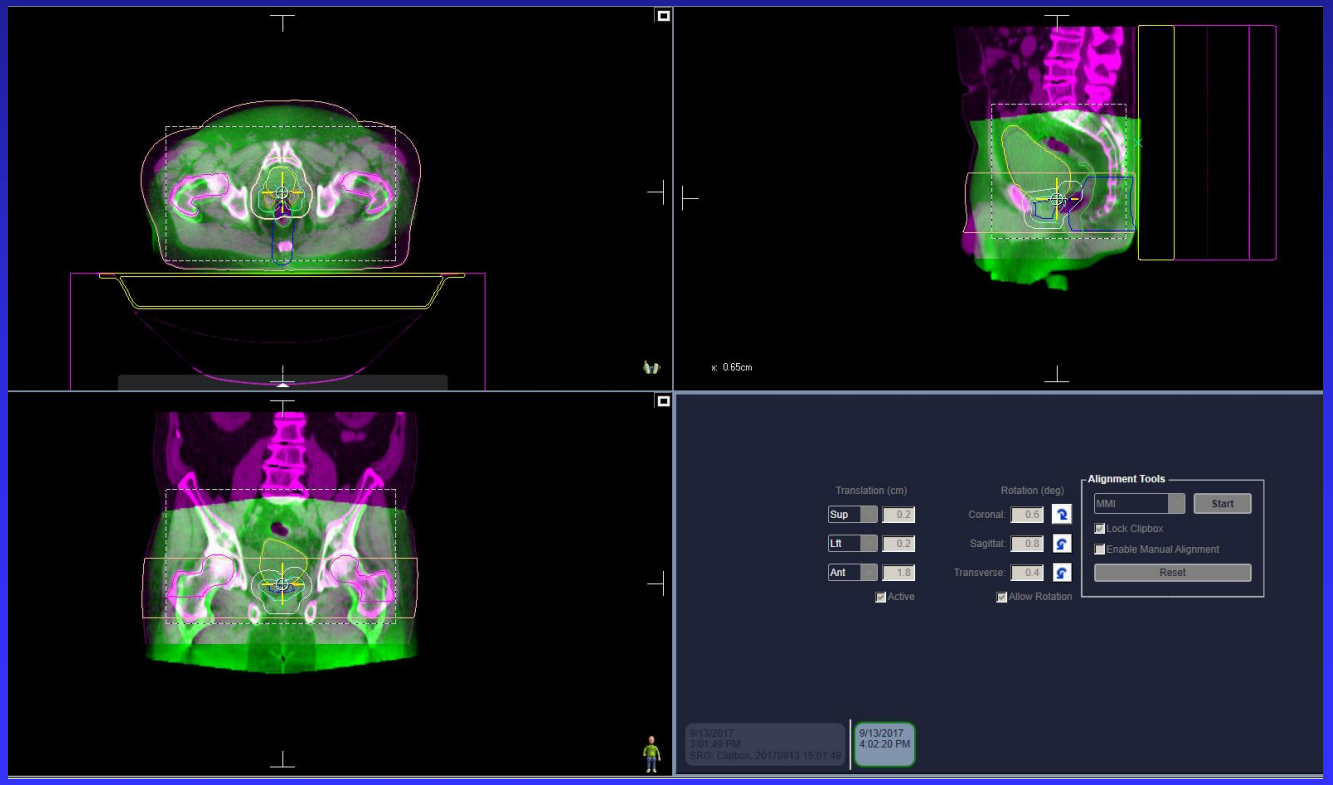
Cone Beam CT



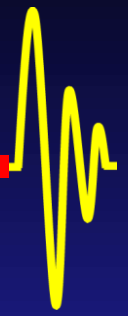
A separate kV x-ray source is used to capture 3D images, similar to a CT scan.

Image Guidance

- 3D imaging allows precise target localization.



Androgen Deprivation



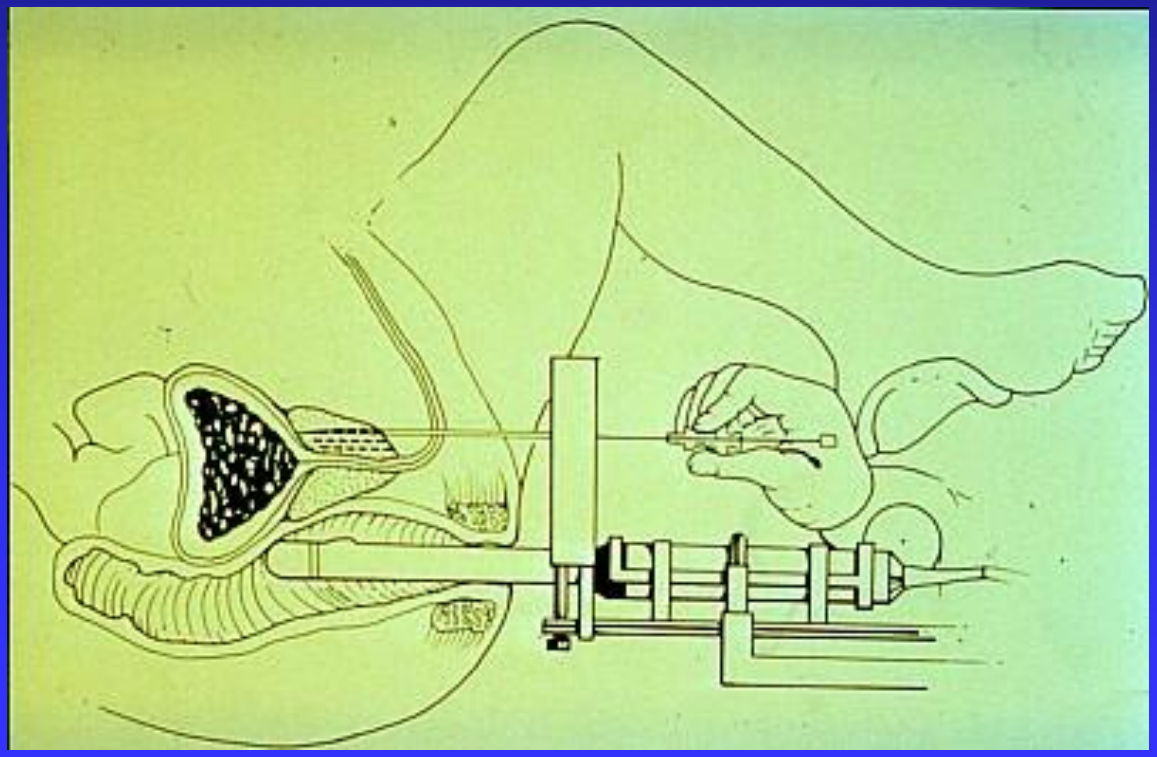
- Deprives prostate cancer of growth stimulus
- Available as 1 - 6 month injections
- Sometimes combined with oral agents for the first few weeks
- Eligard is the commonly used drug
- Used alone for metastatic cancers or combined with surgery/radiation for non-metastatic but unfavorable cancers

Prostate Brachytherapy

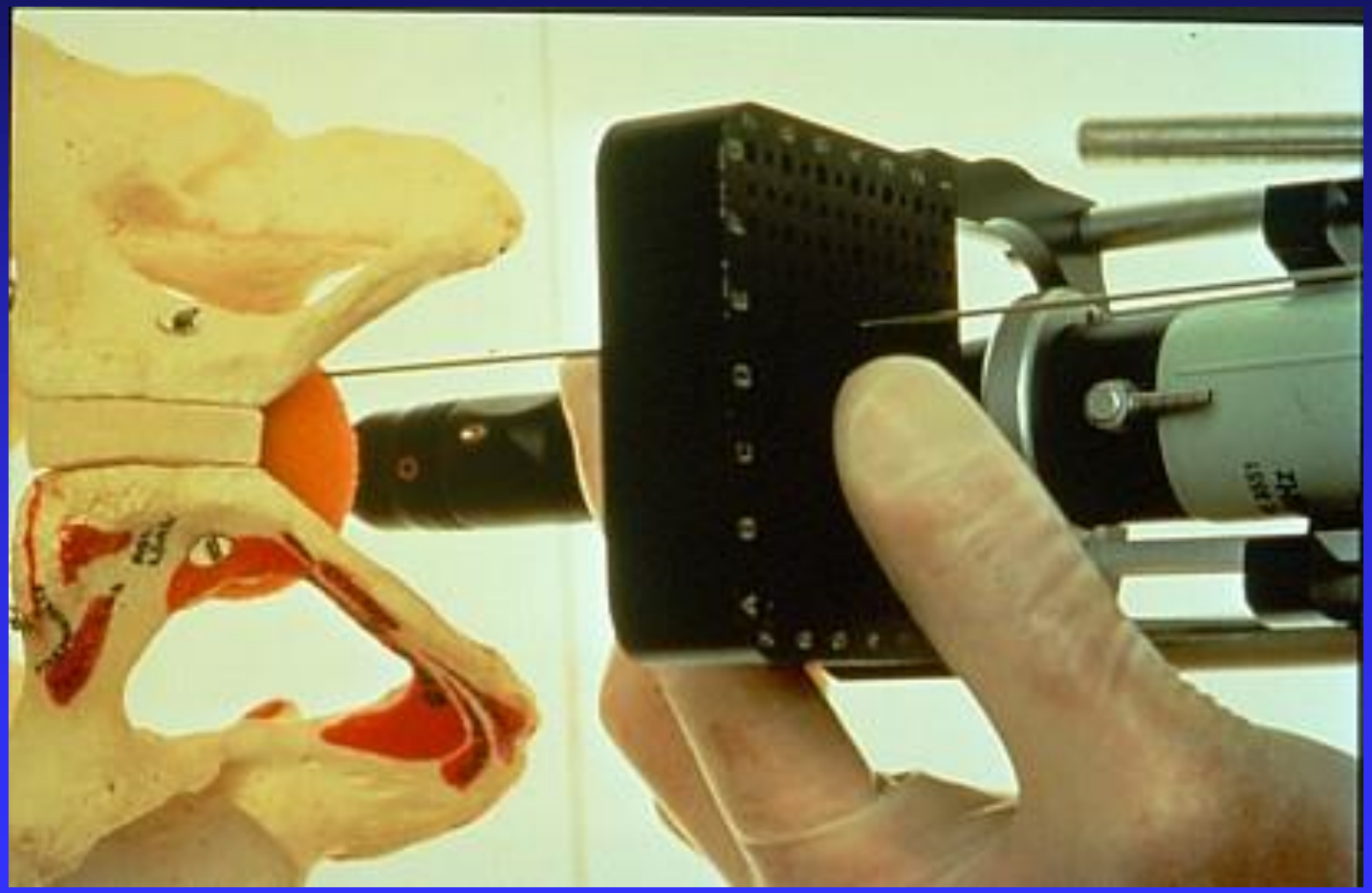
- Placement of radioactive material inside the prostate gland
- Low dose, permanent seed implant
  - Radioactive Iodine or Palladium Seeds

Prostate Brachytherapy

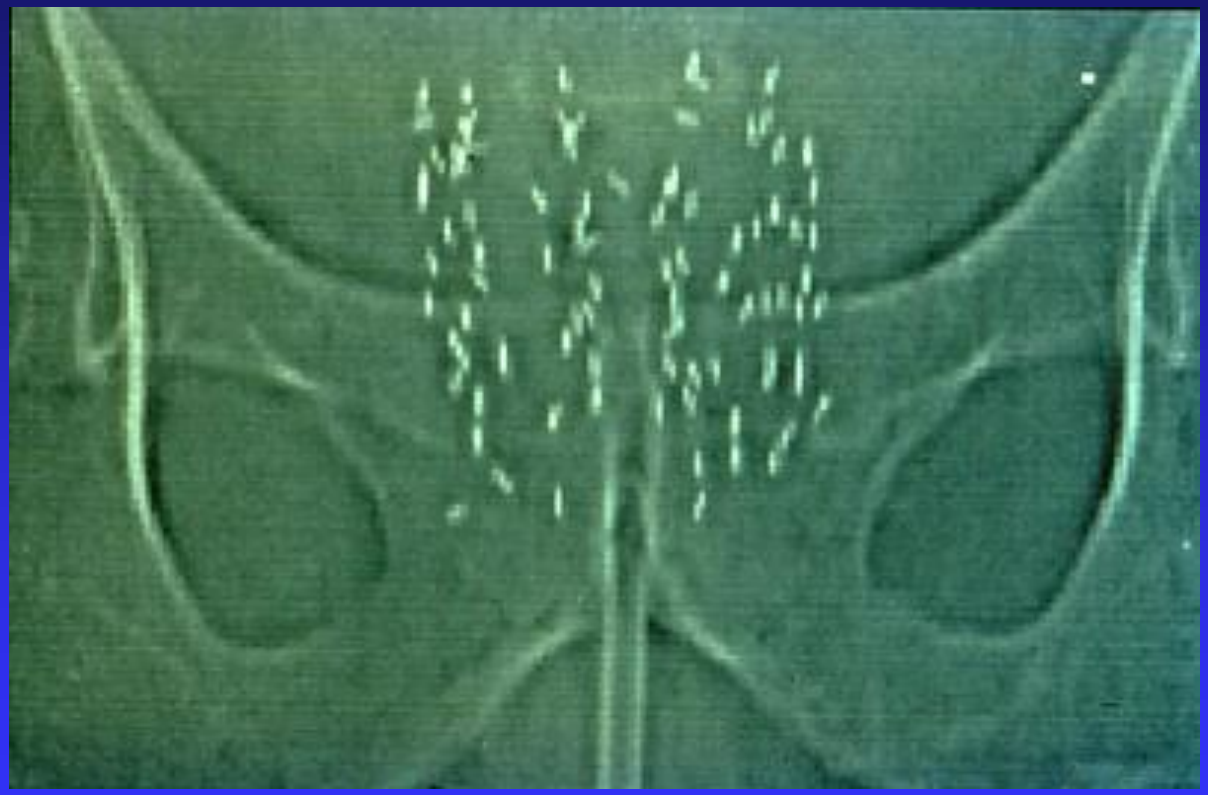
- Radioactive I-125 seeds are placed within the prostate under ultrasound guidance.



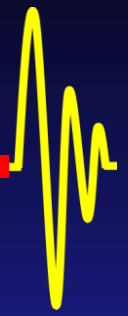
Seed Insertion



The completed implant



Brachytherapy



- Modern technique involves US-guided transperineal placement of radioactive sources (I-125 or Pd-103) into the prostate.
- Allows delivery of high doses (140 Gy) to discrete volumes.
- Superior to older retropubic technique.
- Minimally invasive (ambulatory, general or spinal anesthesia).
- Effective for appropriately selected patients.

Outcomes

- For low risk patients, multiple single-institution series have consistently reported 5y bNED of 85-90%.

- Grimm et al report >85% 10y bNED (2 rises) in consecutively treated cohort
  - [IJROBP 2001;51]

Variability

- Variable quality of seed implants

HEALTH

At V.A. Hospital, a Rogue Cancer Unit

By WALT BOGDANICH JUNE 20, 2009

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HE NAMED ME

For patients with prostate cancer, it is a common surgical procedure: a doctor implants dozens of radioactive seeds to attack the disease. But when Dr. Gary D. Kao treated one patient at the veterans' hospital in Philadelphia, his aim was more than a little off.

Most of the seeds, 40 in all, landed in the patient's healthy bladder, not the prostate.

It was a serious mistake, and under federal rules, regulators investigated. But Dr. Kao, with their consent, made his mistake all but disappear.

The Veterans Affairs Medical Center in Philadelphia. Jessica Kourkounis for The New York Times

- External beam technology delivers consistent quality assured treatment.

Proton Therapy

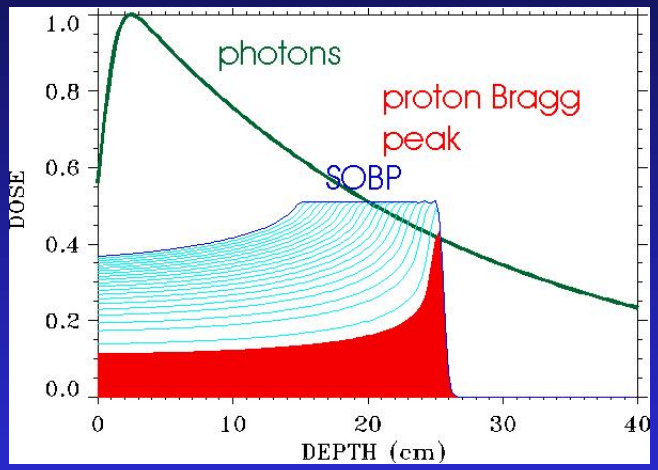
- Currently protons are accelerated in a cyclotron housed adjacent to the treatment suite.

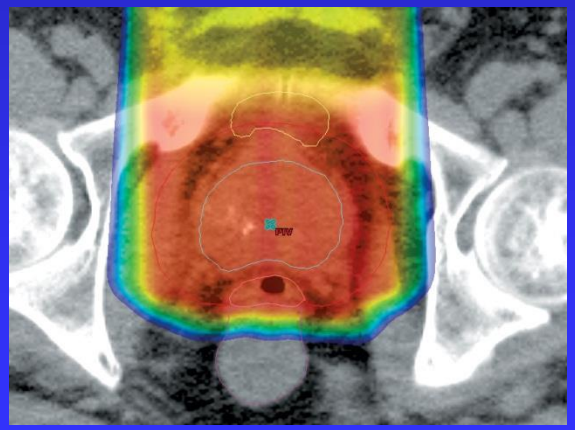
Treatment Center

Outside

Treatment Room

Proton Therapy

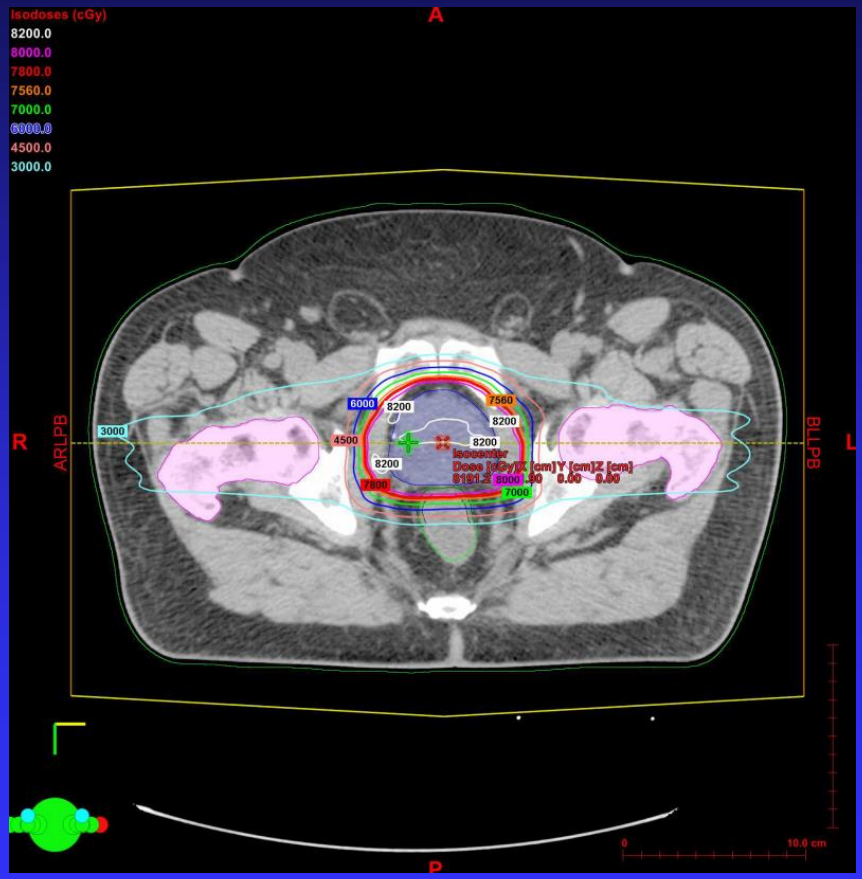




- The properties of therapeutic protons allow rapid beam “fall off”.
- This means tissues behind the tumor can be spared.

Proton Therapy Plan

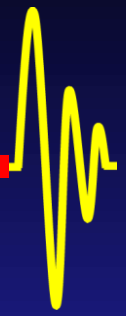
- Two lateral beams are used at M D Anderson



Proton Therapy vs. IMRT

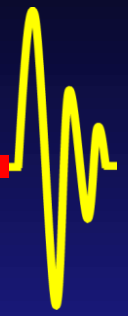
- No published evidence conclusively showing superiority of Proton Therapy to IMRT in regard to:
  - Better efficacy
  - Less Toxicity
- Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer (PARTIQoL) Trial
  - Primary endpoint: bowel toxicity at 2 yrs
  - Secondary endpoints: QOL, cost-effectiveness, survival, etc.
  - Expected to complete accrual in December 2018

Stereotactic Radiation



- Stereotactic Body Radiation Therapy (SBRT) is used to administer large doses in a few fractions.
  - 36.25 Gy in 5 (7.25 Gy fractions)
  - 37.5 Gy in 5 (7.5 Gy fractions)
  - 45 Gy in 5 (9 Gy fractions)
- Conventional RT uses ≈ 2 Gy fractions

Advantages



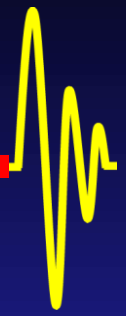
- SBRT is a short course of treatment
- Treatment is considered ‘ablative’
- The goal is to treat the tumor with a very tight margin
  - Very little surrounding normal tissue is treated.

SBRT

- CyberKnife®
  - McBride *et al*, Cancer, 2012
- TomoTherapy®
  - Boike *et al*, Journal of Clinical Oncology, 2011
- Linear Accelerator
  - Madsen *et al*, IJROBP, 2007

- The tool matters less than the plan.

Doses Higher or Equivalent



- Based on radiobiologic modeling for prostate cancer cells, treatment courses of approximately 40 Gy delivered in five fractions may be equivalent to approximately 90 Gy at 1.8-2 Gy per fraction.

SBRT Results

- The 5-year biochemical relapse free survival (bRFS) rate was 93% for all patients; 95%, 83% and 78% for GS ⩽6, 7 and ⩾8, respectively (p=0.001), and 95%, 84% and 81% for low-, intermediate- and high-risk patients, respectively (p<0.001).
  - King, CR, Radiother Oncol. 2013
- The rate of overall 3-yr actuarial biochemical failure free survival was 93.9% for low and intermediate risk prostate cancer.
  - Jeong BK, J Korean Med Sci. 2015

Results (Contd.)

- These are similar to results seen with standard radiation treatment of approximately 40 treatments over 8 weeks.
- A pooled analysis of over 800 men receiving SBRT for prostate cancer also showed good patient-reported quality of life with 5-year follow-up

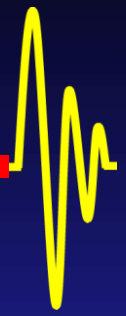
King CR, et al. Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiat Oncol 109:217-221, 2013.

Results (Contd.)

- 437 localized prostate cancer patients treated with SBRT at one of seventeen centers in the United States and Australia.
- Two year bRFS was found to be 99.0%, 94.5%, and 89.8% for low, intermediate and high-risk groups, respectively. Higher Gleason score was associated significantly with lower biochemical disease-free survival.
- SBRT treatments were well tolerated. No patients experienced high-grade genitourinary or gastrointestinal toxicity.

Davis J, et al. Stereotactic Body Radiotherapy for Clinically Localized Prostate Cancer: Toxicity and Biochemical Disease-Free Outcomes from a Multi-Institutional Patient Registry. Cureus 2015; 7: e395

SBRT Results Summary



- These regimens have delivered five fractions at 7-8 Gy per fraction for total doses on the order 35-40 Gy.
- In over 1000 men cancer control rates in multiple studies have approached 90% or better with severe toxicities reported at < 5-10%.

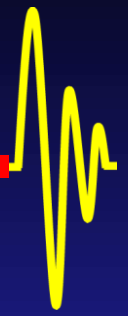
MDA SBRT Study Objectives

- Primary objective:
  - Evaluate the acute and long-term genitourinary (GU) and rectal toxicity
- Secondary objectives:
  - Quality of life
  - Correlate patient and radiation dosimetric factors with toxicity and/or QOL measures.
  - Evaluate prostate specific antigen (PSA) response after SBRT.

Eligibility Criteria

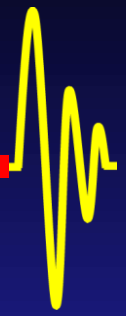
- Men with low to intermediate risk prostate adenocarcinoma
  - T1-T2b, pretreatment PSA <10, Gleason sum 7 or less.

Radiation Therapy Techniques



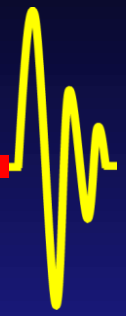
- Fiducial placement
- CT simulation, rectal balloon optional
- SBRT planning. VMAT preferred
- 8 Gy x 5 fractions, every other day
- Enema every day, bladder scan

Future of Prostate Cancer Treatment



- Less over-diagnosis
- Less surgery
- Less radiation therapy
- More observation
- Possibly more systemic therapy

Summary of Radiation Therapy



- Advances in engineering and computers continue to make radiation therapy more accurate, safe and effective in the treatment for prostate cancer.
- Future advances will focus on patient selection for treatment and shorter, more convenient regimens.