New Cancer Treatments: The last 100 Years

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A Brief History of Radiation

- Wilhelm Roentgen discovered *X-rays* on November 8, 1895, while experimenting with a gas-filled cathode tube
  - He noted an image of the bones of his hand projected on a screen when placed between the tube and the fluorescent screen

- **He called this X-ray**

Early radiograph taken by Roentgen, January, 1896.

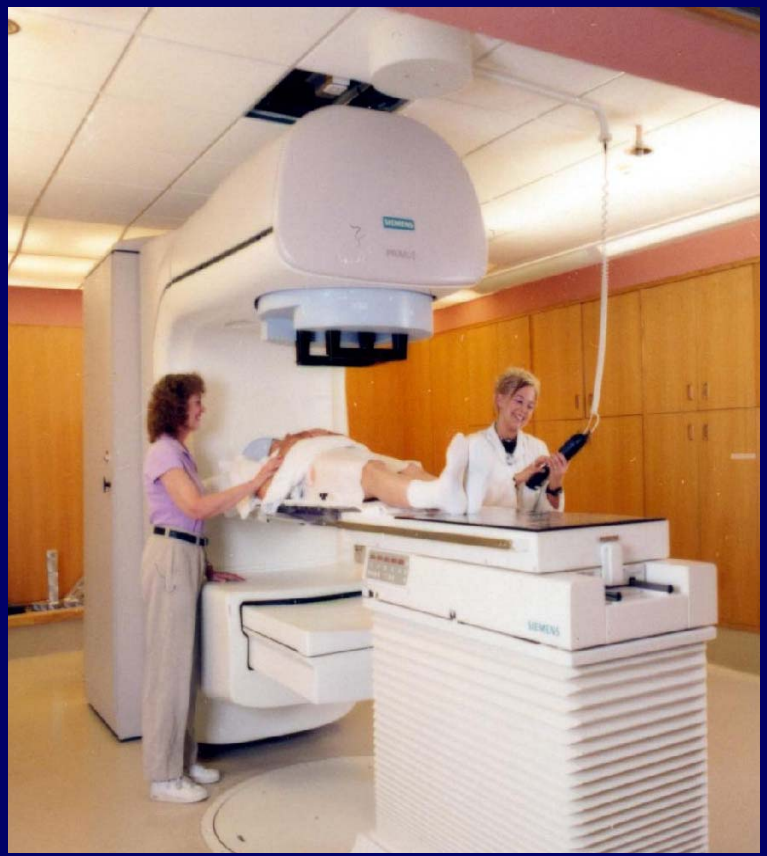
Brief History of Radiation Therapy

- The first patient was treated with radiation in 1896, two months after the discovery of the X-ray.
- Rapid technology advances began in the early 1950s with cobalt units followed by linear accelerators a few years later.
- Recent technology advances have made radiation more effective and precise.

Process of Care: Delivery of Radiation Therapy

- Radiation therapy can be delivered two ways
  - ***External beam*** radiation therapy typically delivers radiation using a linear accelerator
  - **Internal radiation** therapy, called *brachytherapy*, involves placing radioactive sources into or near the tumor

How Is Radiation Therapy Used?



Radiation therapy is used two different ways.

- **To cure cancer:**
  - Destroy tumors that have not spread to other body parts.
  - Reduce the risk that cancer will return after surgery or chemotherapy.
- **To reduce symptoms:**
  - Shrink tumors affecting quality of life, like a lung tumor that is causing shortness of breath.
  - Alleviate pain by reducing the size of a tumor.

Head and Neck Cancer

Xerostomia

- Xerostomia is the prominent long term RT side effect in the H&N ca pts

- **Permanent xerostomia affects QOL, causing**
  - **dental caries, difficulty chewing, swallowing, speaking, increased incidence of oral candidiasis and reflux esophagitis**

e 1. Severe radiation-induced mucositis.

Figure 2. Effects of radiation-induced xerostomia.

Xerostomia

- **Treatments**
  - siologogues - pilocarpine
  - radioprotectant - WR 2721
  - **<u>parotid sparing radiation - IMRT technique</u>**
  - Others - surgery, acupuncture

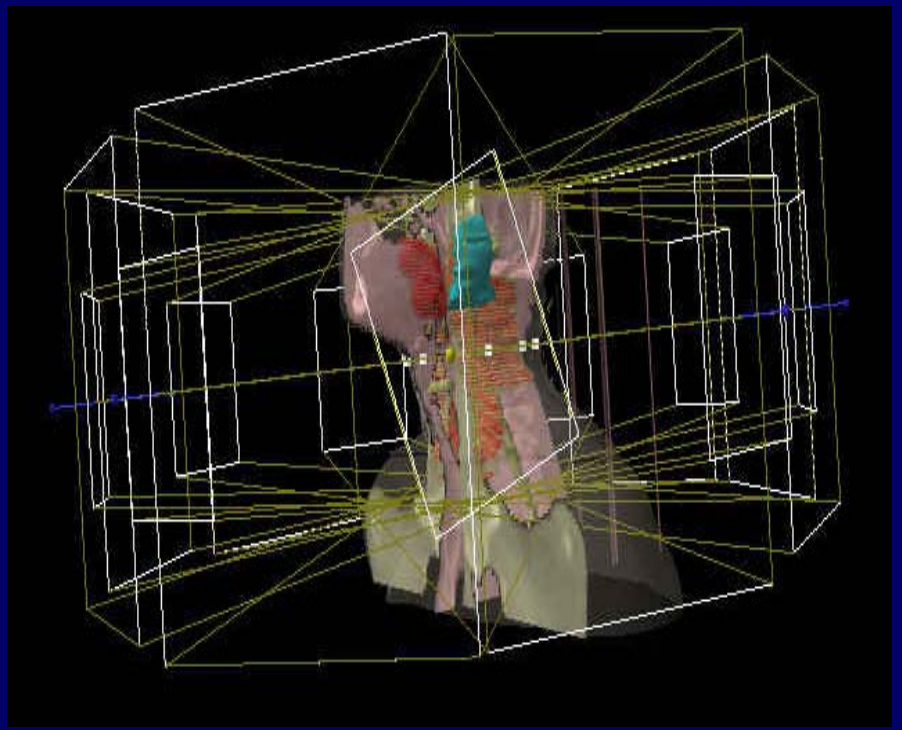
Teh et al., 1999

- IMRT is a new technology in RT that delivers radiation precisely to the tumor while relatively sparing the surrounding normal tissues.

The Oncologist:4, 433, 1999

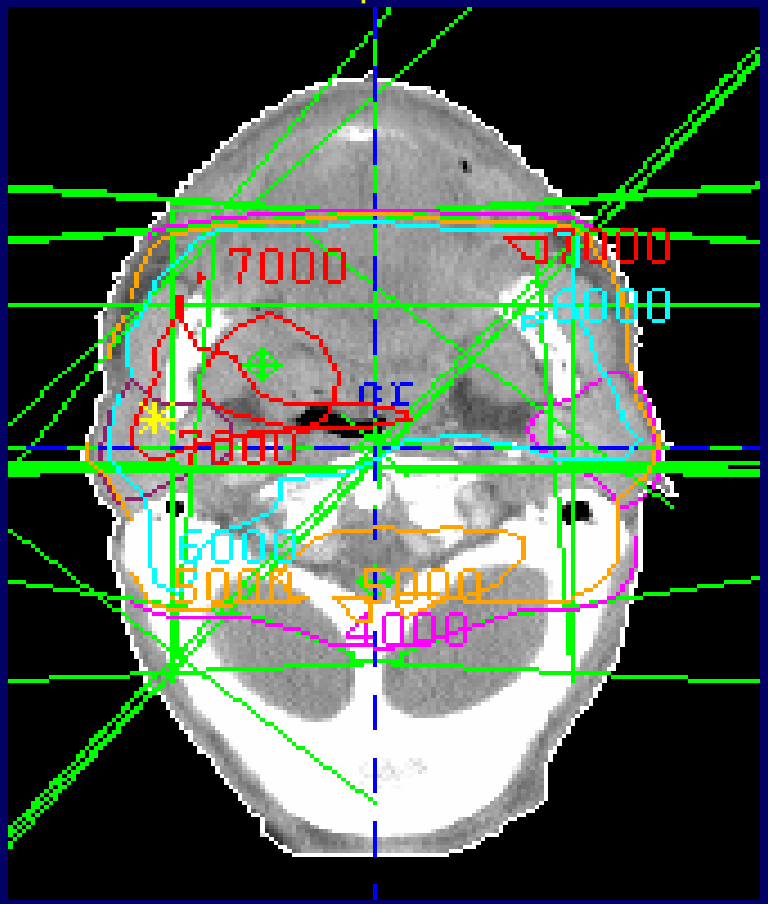
H&N IMRT

- 9 beam angles

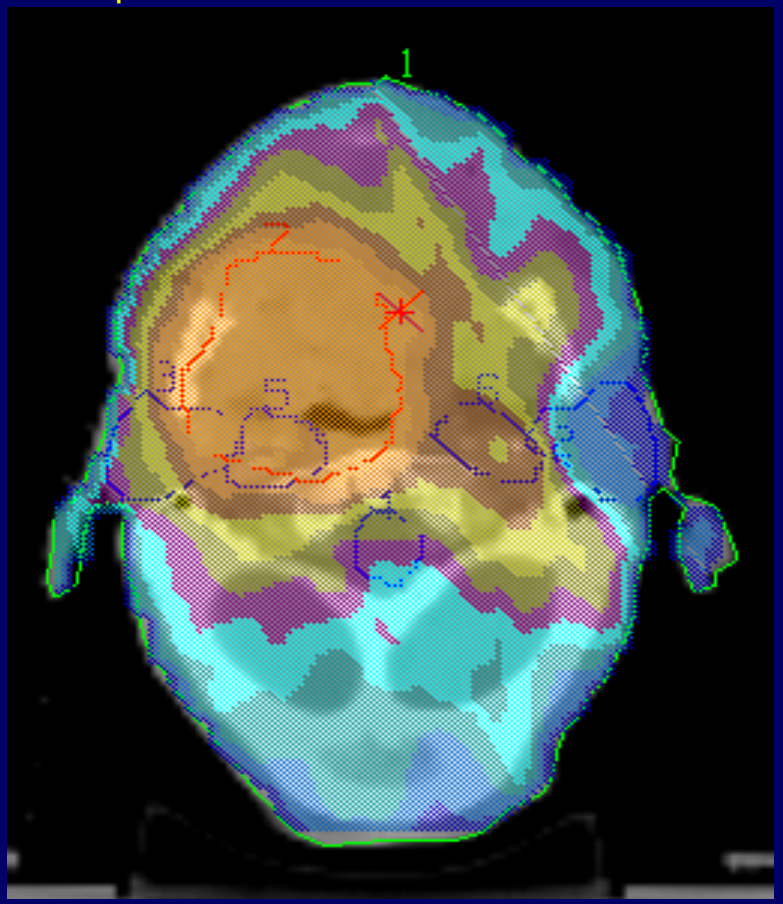


Compare conventional vs IMRT

- Case 1
- conventional plan



IMRT plan



WR 2721(Amifostine/Ethyol)

- US army synthesized 4000 compounds to identify a drug that would give protection to the infantry in the event of a nuclear conflict.

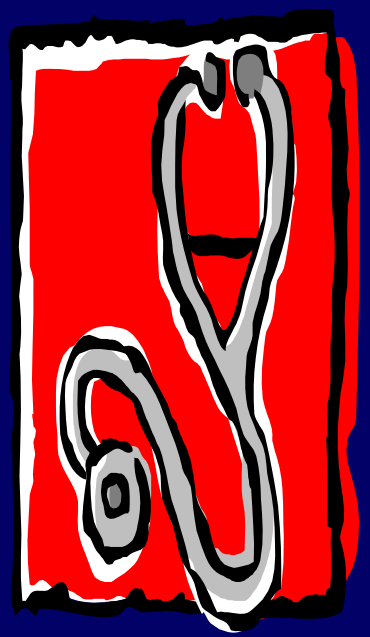
- Randomized study by Brizel D et al J Clin Oncol 2000

	acute dry	chronic dry	DFS	OS
	(%)	(%)	(%)	(%)
RT	78	57	53	71
RT+WR2721	51	34	57	66
P value	< .0001	0.002	NS	NS

Conclusion

- Xerostomia is a significant problem for HN cancer pts receiving radiation therapy

- IMRT and WR 2721 significantly spares the parotid gland and avoids xerostomia for HN cancer pts



Breast Cancer

William Halsted 1907

ORIGINAL MEMOIRS.

THE RESULTS OF RADICAL OPERATIONS FOR THE CURE OF CARCINOMA OF THE BREAST.*

BY WILLIAM STEWART HALSTED, M.D.,
OF BALTIMORE, MD.,
Surgeon to Johns Hopkins Hospital.

The Operation.—Though the area of disease extend from cranium to knee, breast cancer in the broad sense is a local affection, and there comes to the surgeon an encouragement to greater endeavor with the cognition that the metastases to bone, to pleura, to liver, are probably parts of the whole, and that the involvements are almost invariably by process of lymphatic permeation and not embolic by way of the blood. Extension,

Bernard Fisher 1981/ NSABP 4

- 1971-1974, 1655 pts, operable breast ca
- RM vs SM+RT vs SM(+LND)

- 10 yrs result

	LF/ N0	OS/ N0	LF/ N1	OS/ N1
	(%)	(%)	(%)	(%)
RM	2	57	1	38
SM + RT	2	57	12	38
SM (+LND)	18	57	not ran	not ran

- Concl
- No difference in OS in any groups

Cancer 48:1863-1872, 1981

Bernard Fisher 1995/ NSABP 6

- 1843 pts, stage I, II, randomized
- MRM vs lumpectomy+ALND vs Lumpectomy +ALND+RT
- 12 yrs result

	LF	LF/ N0	LF/ N1	OS
	(%)	(%)	(%)	(%)
MRM	59			60
Lump + LND	35	32	41	60
Lump + LND + RT	10	12	5	62

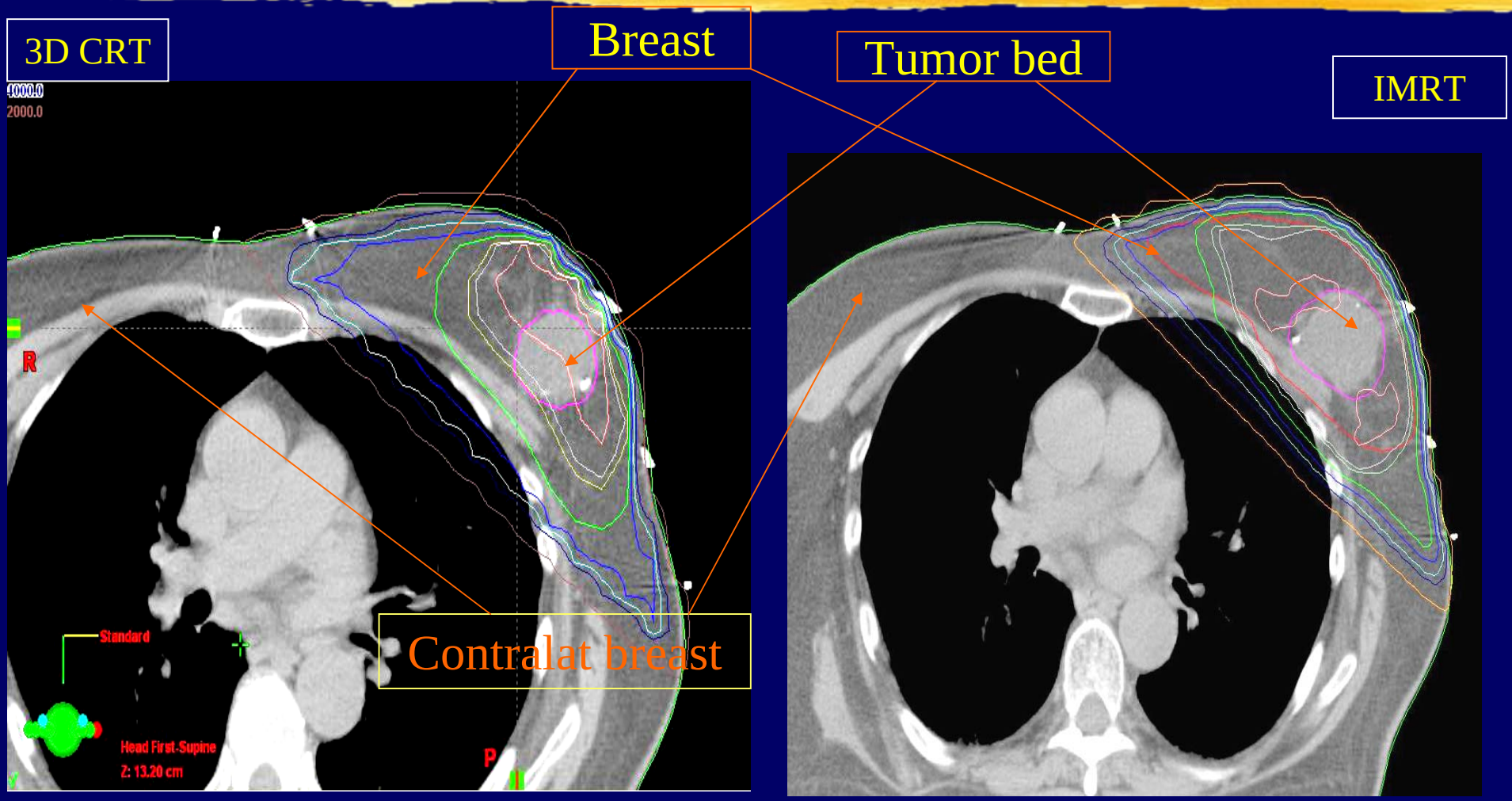
- Concl
- OS is independent of mastectomy vs lumpectomy
- RT reduces local failures and is crucial for BCT

NEJM 333:1456-1461, 1995

Over the last 100 yrs

- Halstedian concept of RM does not improve OS
- Breast cancer is a systemic dz and systemic therapy was introduced to cure pts
- RT is essential for LC and is a critical part of multimodality management for breast cancer pts

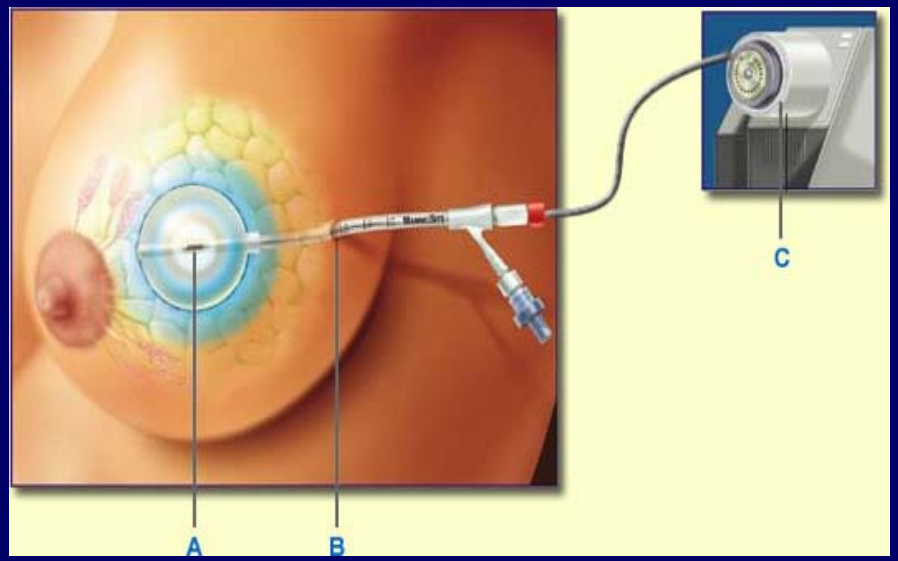
Case presentation/ Breast Tx 2007



Brachytherapy for Breast Ca

- Mammosite
  - **BID radiation over 1 week**

- High-Dose-Rate (HDR)
  - High energy source delivers the dose in a matter of minutes rather than days
    - > Gynecologic, breast and some prostate implants may use use high-dose-rate brachytherapy



HDR brachytherapy for breast cancer using MammoSite catheter (B) with an Iridium-192 source (A) and a high-dose-rate afterloader (C). This is an example of a temporary high-dose-rate implant.

BID RT over 1 week for Breast Cancer

- There have been several clinical studies since the MammoSite® Radiation Therapy System received FDA clearance in 2002.

- **5-year results from the initial 43-patient MammoSite clinical trial show:** No local recurrences and 82% of patients had good/excellent cosmetic results.[7]

- Five hundred and eighty patients have been enrolled in a manufacturer-sponsored registry trial designed to determine the technical reproducibility and acute toxicity involved in the large scale use of the device. This registry is now managed by the American Society of Breast Surgeons. The registry contains 81 sites (36 sites are enrolling patients) and 94 surgeons.

Keisch M, Vicini F, Kuske RR, et al: Int J Radiat Oncol Biol Phys 55:289-293, 2003.

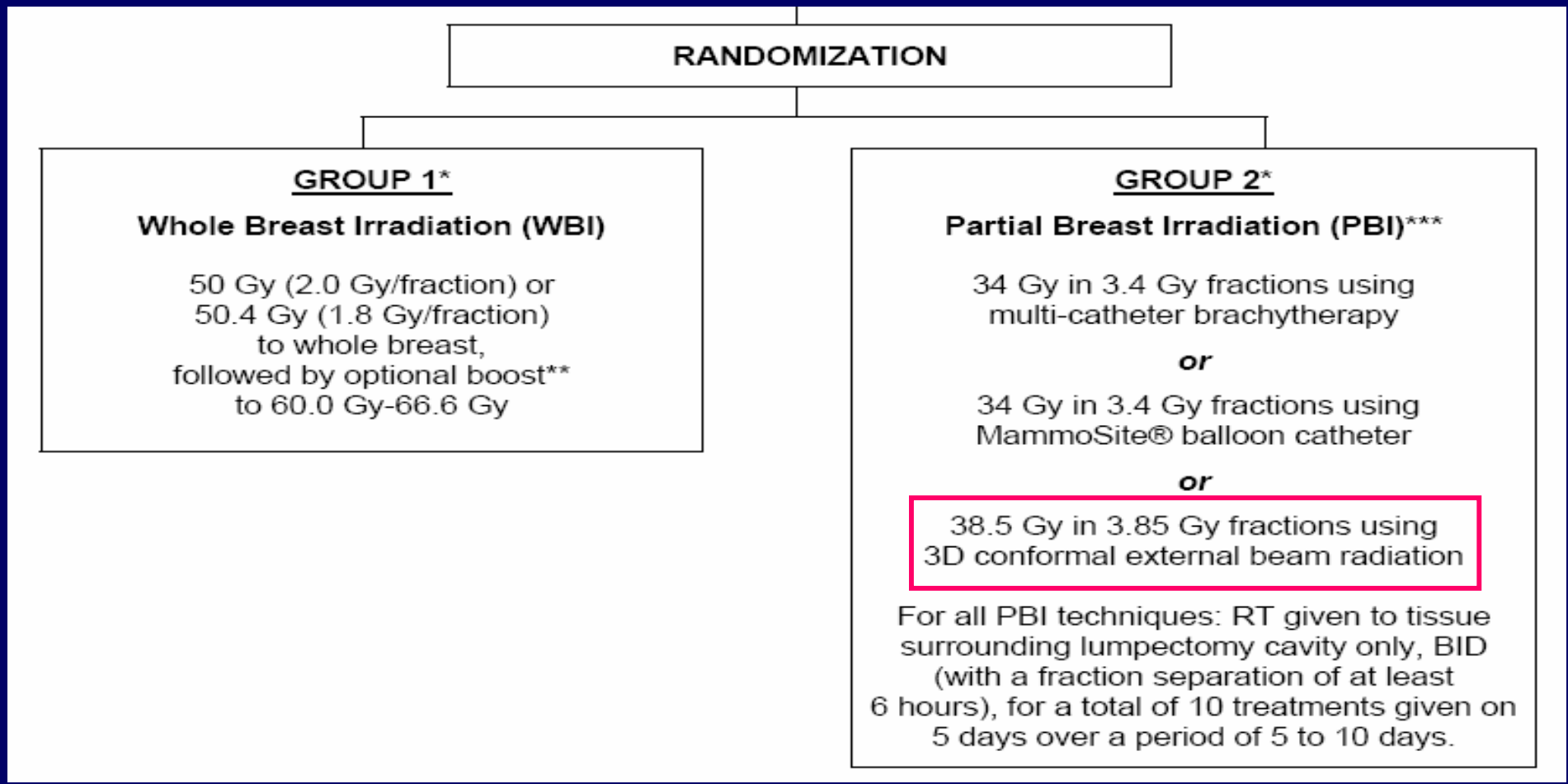
Ongoing Clinical Trial

NSABP PROTOCOL B-39
RTOG PROTOCOL 0413

A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer

National Surgical Adjuvant Breast and Bowel Project (NSABP)
Radiation Therapy Oncology Group (RTOG)

RTOG PROTOCOL 0413/ BID RT over 1 week



RTOG PROTOCOL 0413/ BID RT over 1 week

Figure 2. Whole breast contour

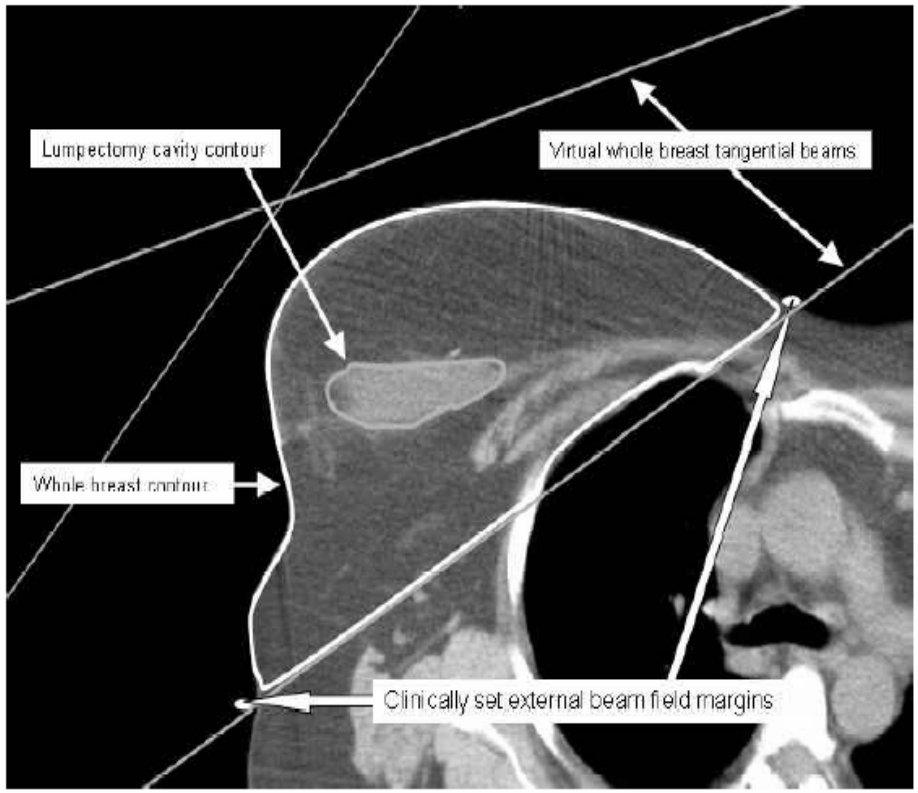
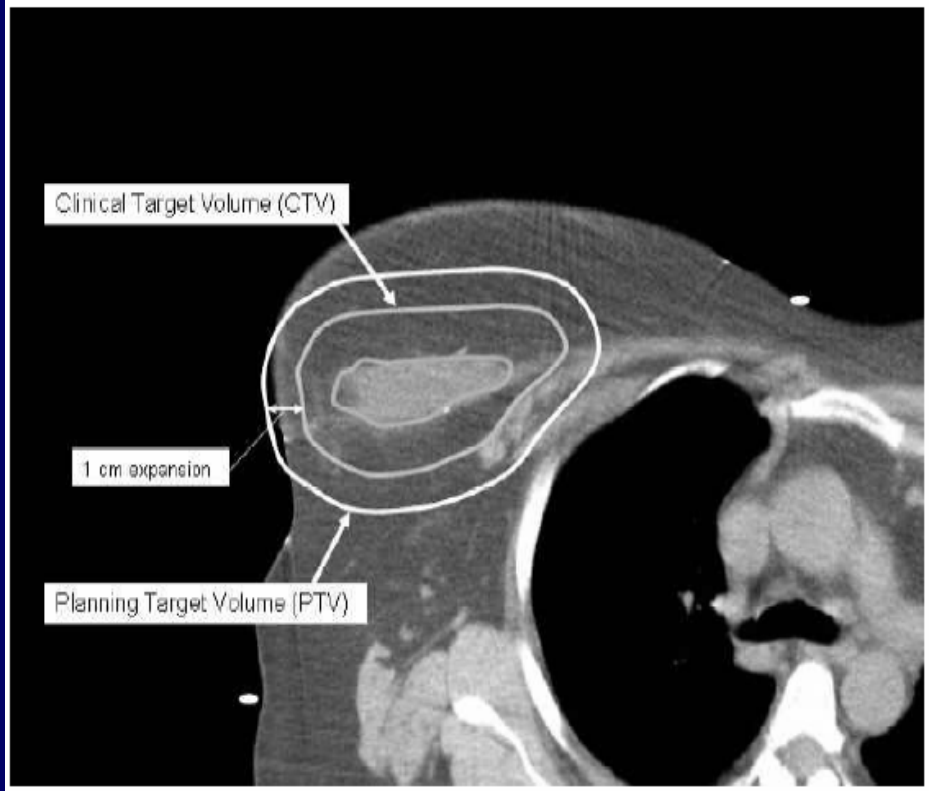


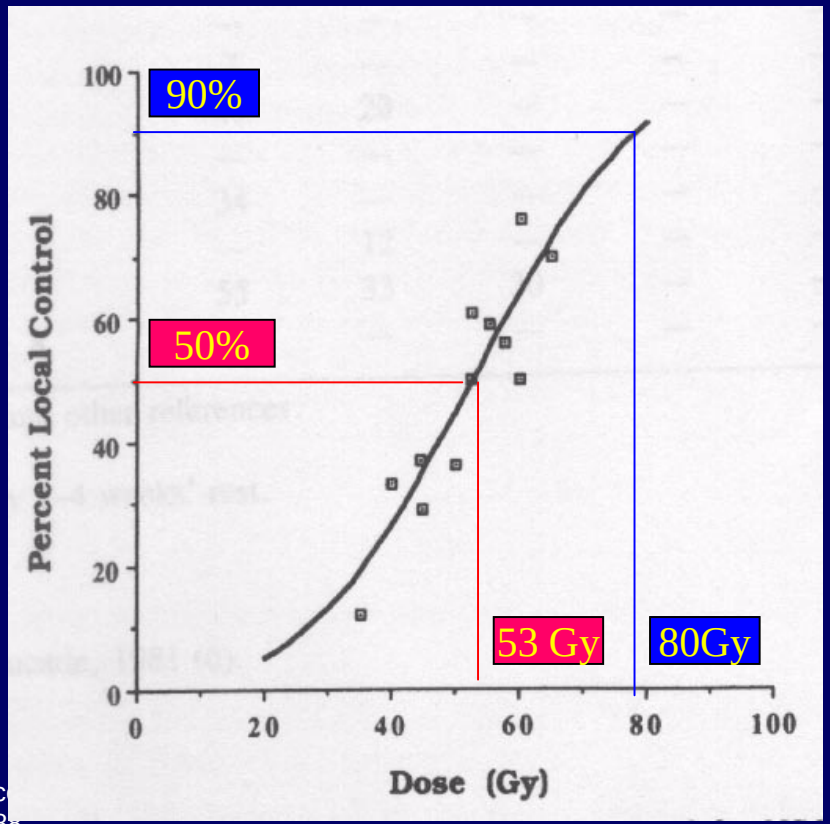
Figure 5. 3D-CRT



Lung Cancer

Statement of Problem

- Correlation between dose and LC for NSCLC from published data.
- Increasing RT dose improves LC.



Vijayakumar et al. Int J Radiat Onc
Aug; 21(30): 779-88

Statement of Problem

- Results: in multivariate only V20 significant.

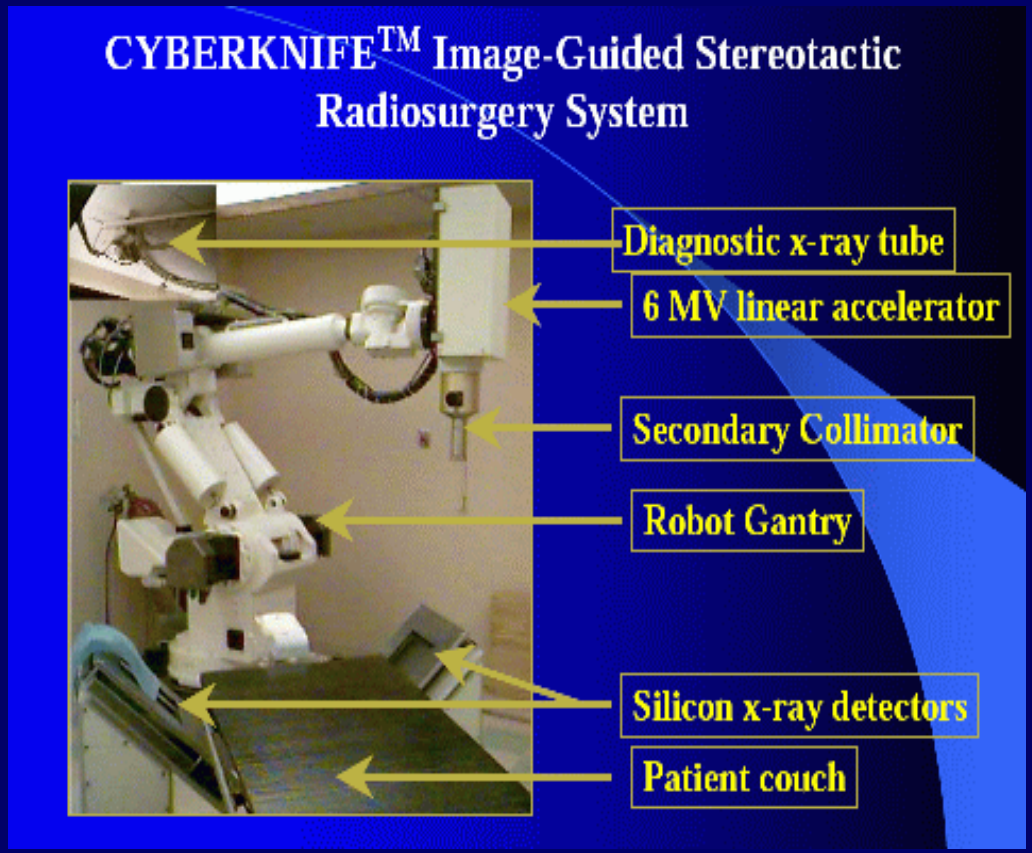
	Pneumonitis		
V20	gr 2	gr 3-5	fatal
(%)	(%)	(%)	(total pt)
< 22	0	0	
22-31	8	8	
32-40	13	5	1
> 40	19	23	3

- Concl:
  - Strong correlation between V20 and severity of pneumonitis.
  - V20 is a useful parameter to evaluate pneumonitis.

Graham et al. Int J Radiation Oncol Biol Phys 1999
Sep 1; 45(2): 223-9

Cyber Knife

- Cameras on the ceiling act as eyes -Map out movement caused by pts breathing
- Accuracy humans cannot achieve – sub millimeter
- The design came from the automotive industry

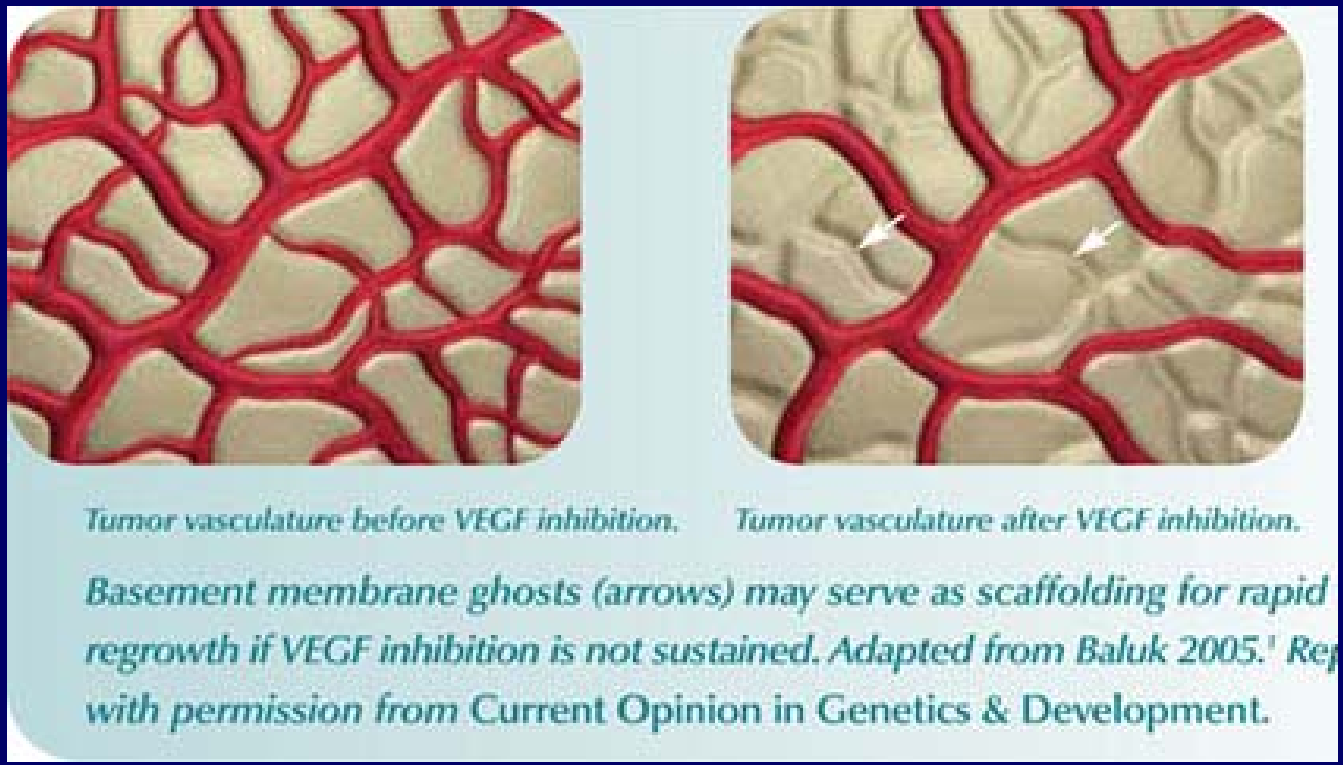


Conclusions

- New robotic radiation treatment significantly improved target coverage
- Reduced the volume of normal lung irradiated
- Reduced the volume of critical structures

Chemotherapy for Lung Cancer

- **Targeted drug therapy**
  - **Avastine**



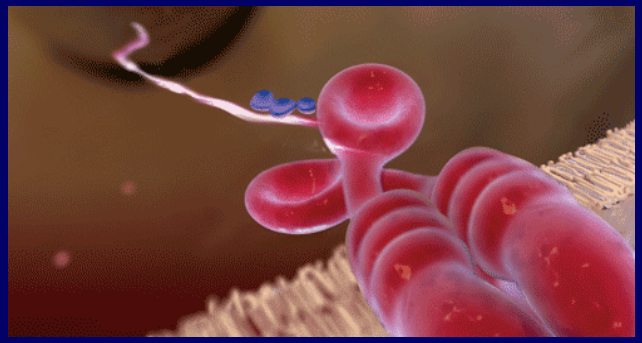
Tumor vasculature before VEGF inhibition. *Tumor vasculature after VEGF inhibition.*

Basement membrane ghosts (arrows) may serve as scaffolding for rapid regrowth if VEGF inhibition is not sustained. Adapted from Baluk 2005.[1] Rep with permission from Current Opinion in Genetics & Development.

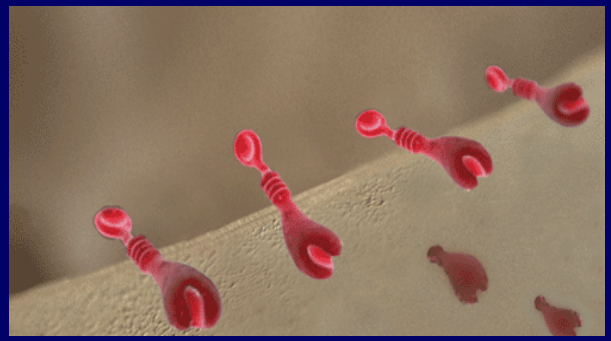
Chemotherapy for Lung Cancer

Targeted therapy
Tarceva

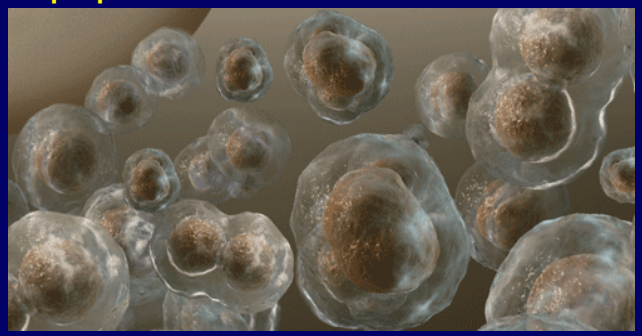
HER1/EGFR functions inappropriately



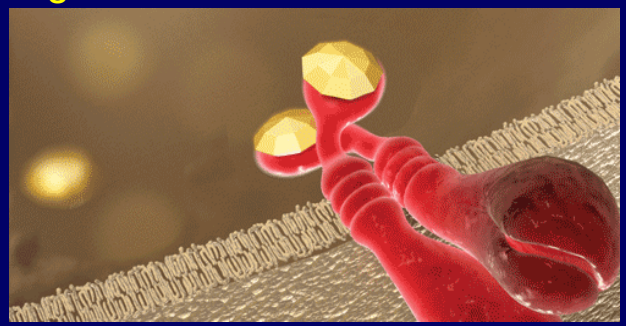
EGFR receptor overexpression



Cell proliferation and inhibit apoptosis



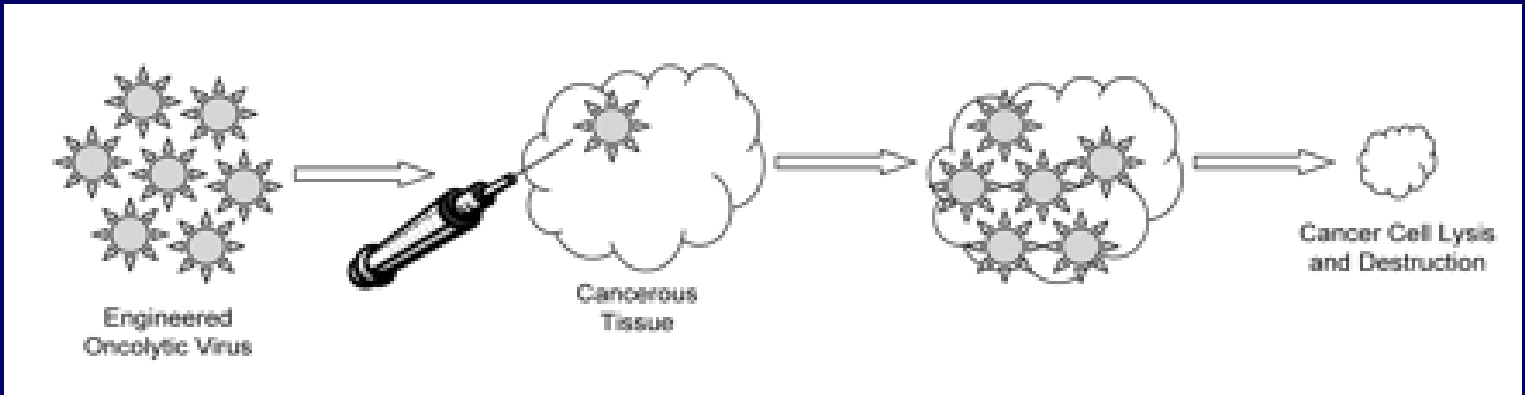
Blocks EGFR mediated downstream signals



Gene therapy for Lung Cancer

- Human Genome Study giving doctors new tools to fight lung cancer.

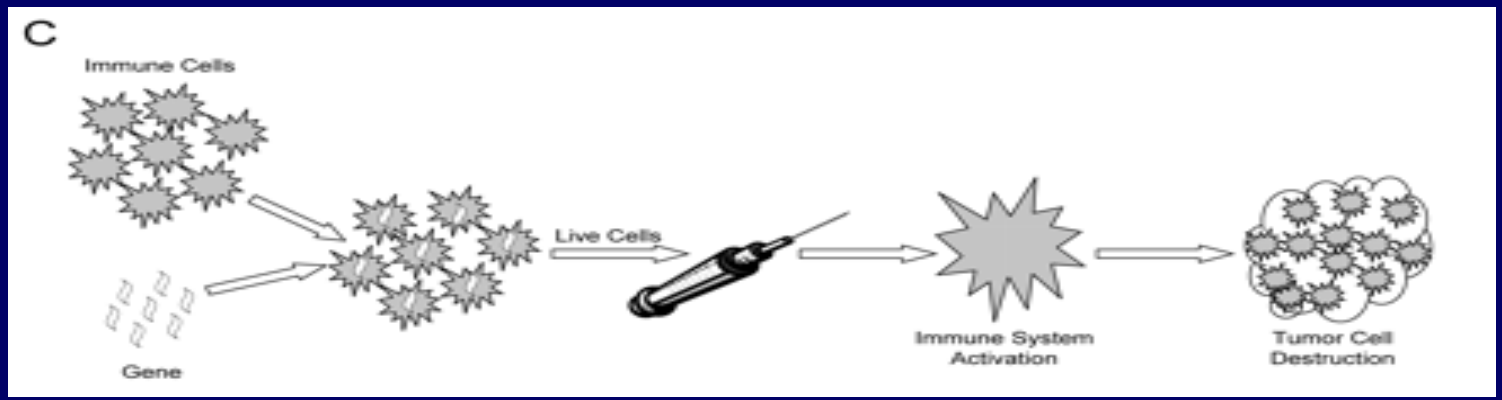
Gene therapy – healthy genetic materials are introduced into the cancer cells via artificially created viruses, causing cancer cell death



Immunotherapy for Lung Cancer

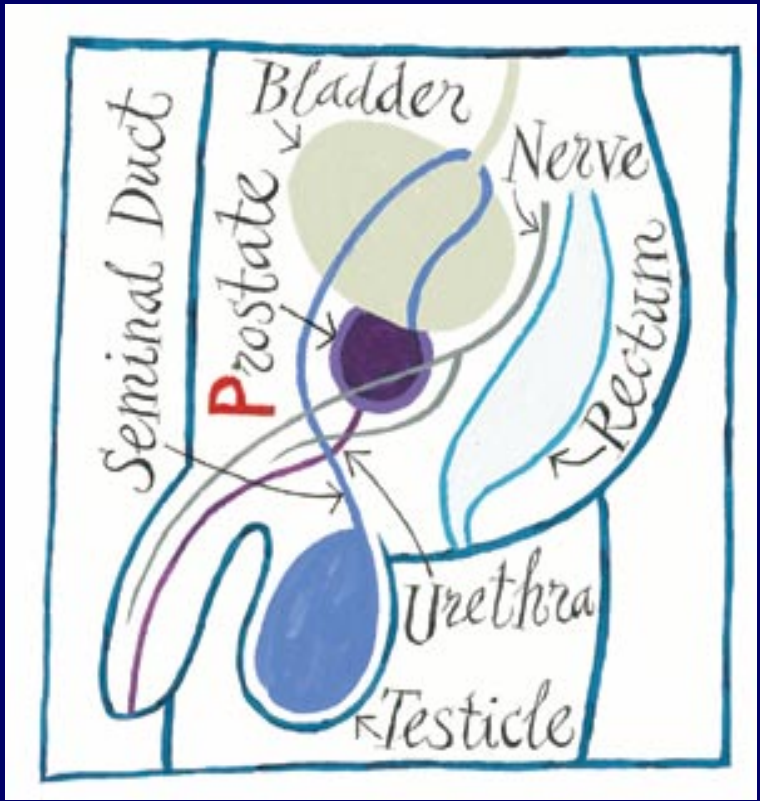
- Human Genome Study giving doctors new tools to fight lung cancer.

Immunotherapy – immune hormones alert the immune system of the body to create immune cells to kill cancer cells.



Prostate Cancer

Prostate Cancer



- **Prostate is surrounded – by the bladder, rectum, and urethra. The prostate is encircled by tissues and nerves - easily damaged during treatments – damage that can lead to cystitis, proctitis, impotence and incontinence.**

Pollack et al 2002/ 3DCRT

- FFF/OS results at 6 yrs

Doses	PSA	PSA	all	OS
	≤ 10	> 10	pt	all
	(%)	(%)	(%)	(%)
70 Gy	75	43	64	87
78 Gy	75	62	70	90
p value	ns	0.01	0.03	0.67

Int J Radiation Oncol Biol Phys: 53 (5), 1097, 2002

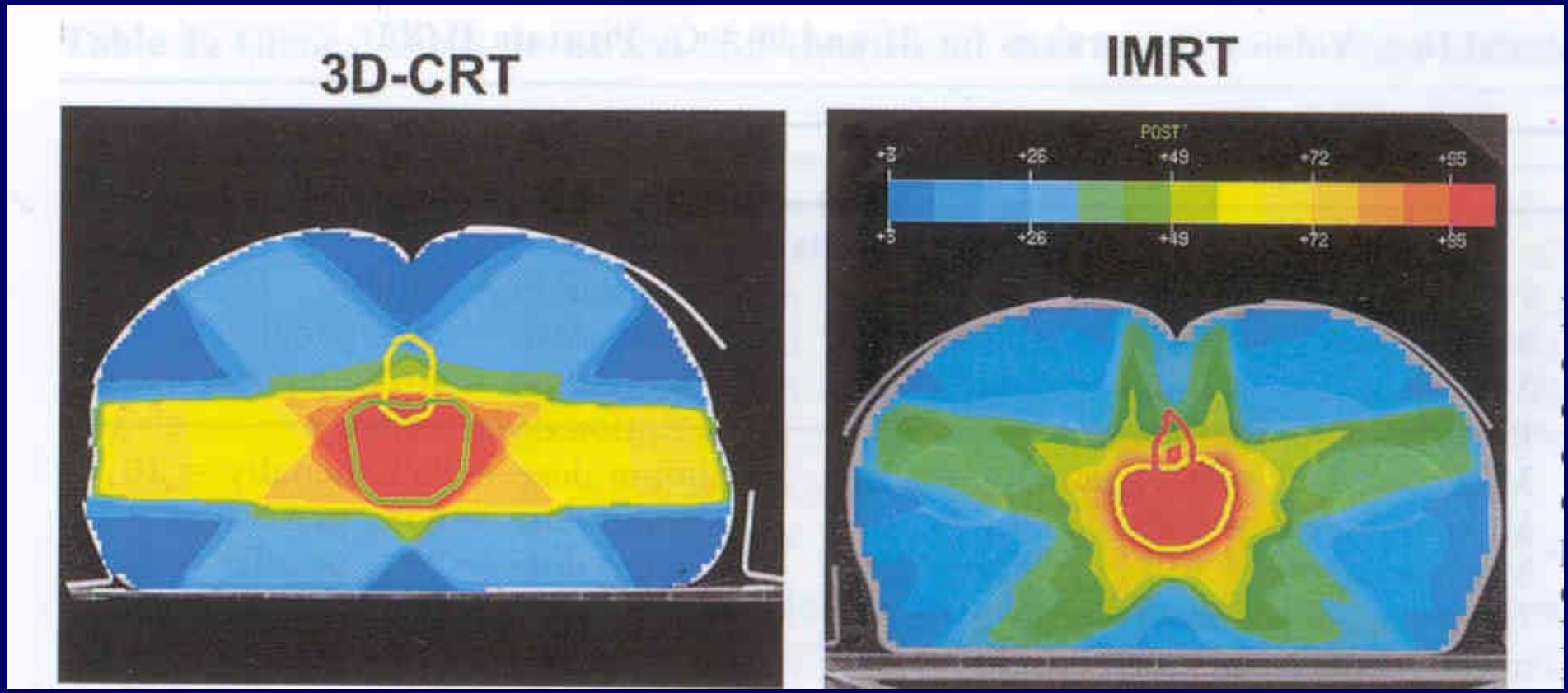
Pollack et al 2002/ 3DCRT

- Late toxicity results at 6 yrs

Doses	Rectal	Bladder
	gr ≥ 2 (%)	gr ≥ 2 (%)
70 Gy	12	10
78 Gy	26	10
p value	0.001	ns

Int J Radiation Oncol Biol Phys: 53 (5), 1097, 2002

Zelefsky et al 2002/ IMRT



Seminars in Radiation Oncology:12(3), 229, 2002

Zelefsky et al 2002/ IMRT

- Reslts: acturial PSA free survival
- Median f/u 24 m (6 - 60 m)

Risk	3D CRT	3DCRT	**IMRT**
group	64.8-70.2 Gy	75.6-86.4 Gy	**81- 86.4 Gy**
	at 5 yrs (%)	at 5 yrs (%)	**at 3 yrs (%)**
fav	77	90	**92**
int	50	70	**86**
unfav	21	47	**81**

Int J Radiation Oncol Biol Phys: 53 (5), 1111, 2002

Zelefsky et al 2002/ IMRT

- Reslts: acute and late toxicity
- Median f/u 24 m (6 - 60 m)

Tox grade	acute GI (%)	late GI (%)	acute GU (%)	late GU (%)
0	74	89	33	74
1	22	9	38	16
2	4	1.5	28	9.5
3	0	0.5	1	0.5

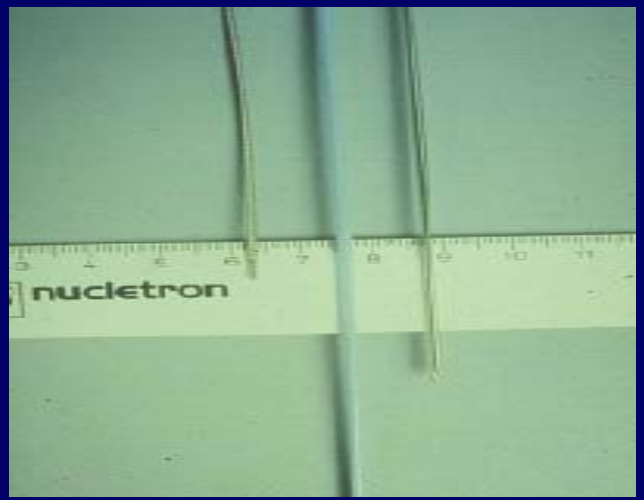
Int J Radiation Oncol Biol Phys: 53 (5), 1111, 2002

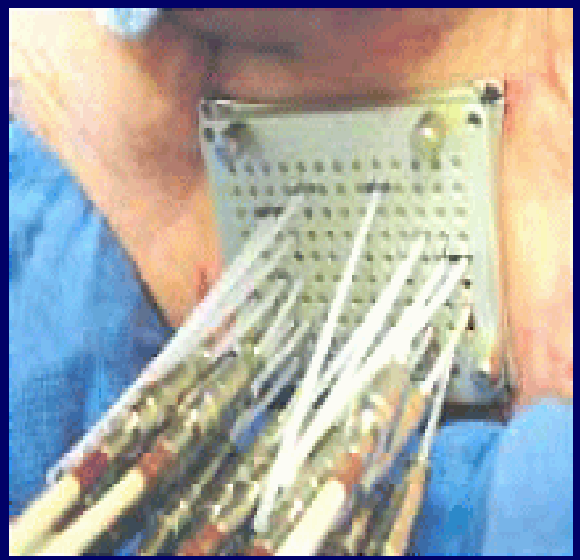
Conclusions/ Prostate

- IMRT can improve Prostate Cancer outcome.
- IMRT reduced GI toxicity in prostate cancer pts

High Dose Rate/ Prostate Cancer

- Temporary High Dose Rate (HDR) brachytherapy technique, commonly dubbed as ‘smart bomb’ is being popularized.





Cyber Knife/ Prostate Cancer

Gene therapy/ Prostate Cance

- Replacement of mutated tumor-suppressor gene
- Introduction of effector gene stimulating body's immune response
- Suicide gene activating pro drug into toxic chemotherapy
- **Gene injected before surgery**
- **Combination treatment involving the gene therapy with IMRT to see which treatment is most effective.**

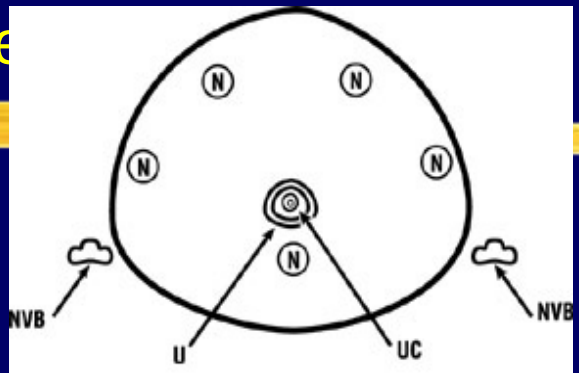


Fig 1. — Transverse section of a prostate showing the positions of 2 anterior and 3 posterior needles for p53 injection (N = needle for p53 injection, NVB = neurovascular bundle, U = urethra, UC = urethral catheter).

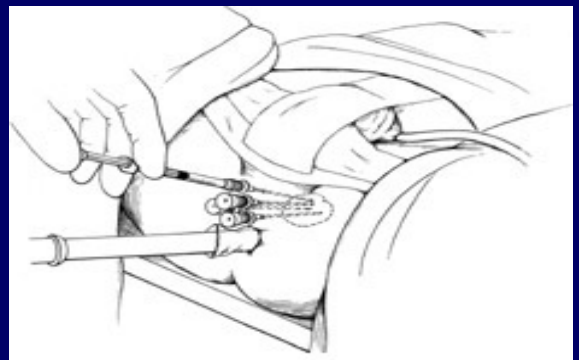


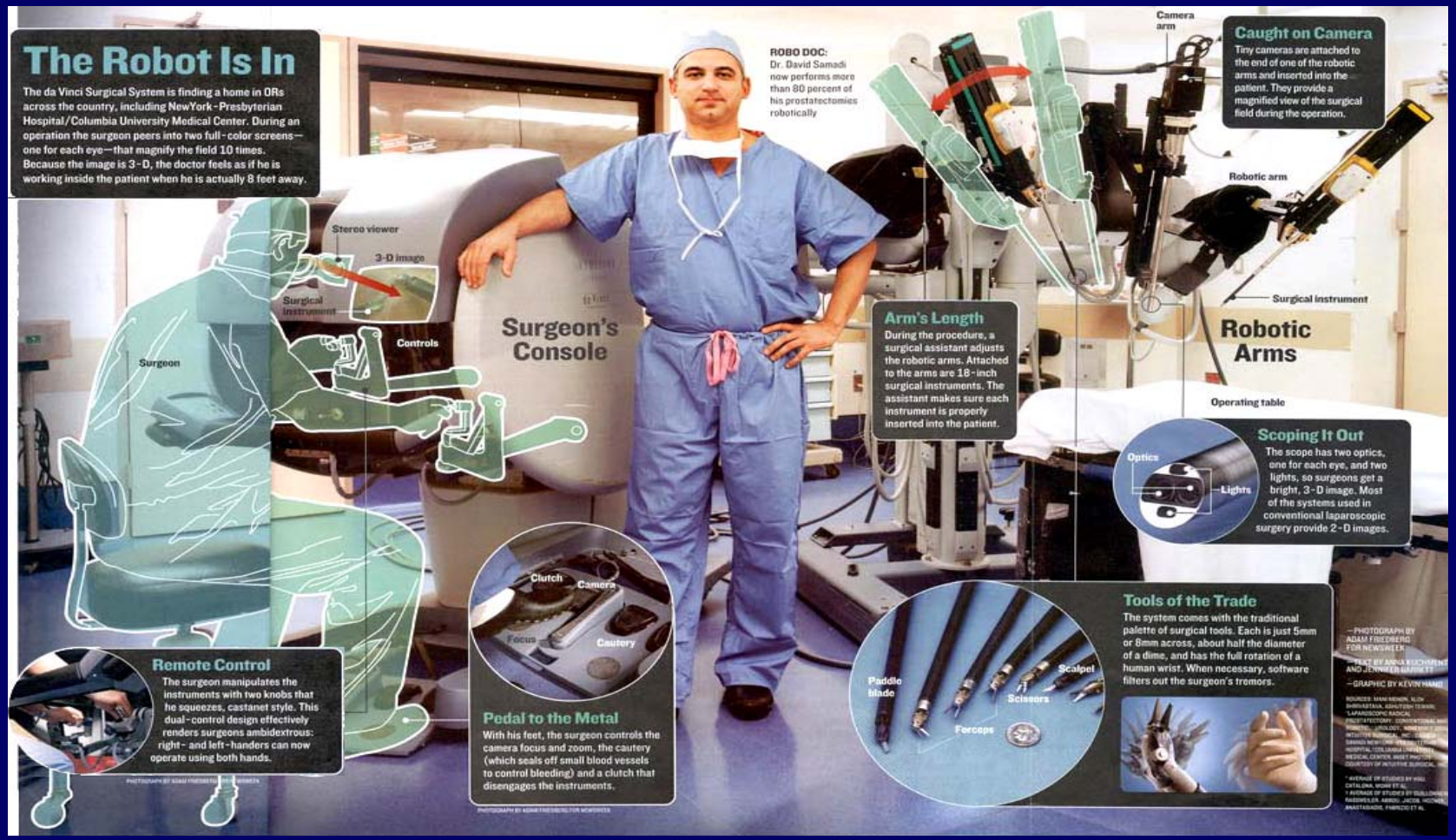
Fig 2. — The p53 gene in adenoviral vector is being injected into the prostate. During the injection, the needle is withdrawn from the base to the apex of the prostate to facilitate as extensive a distribution of vector as possible.

Robotic Prostatectomy

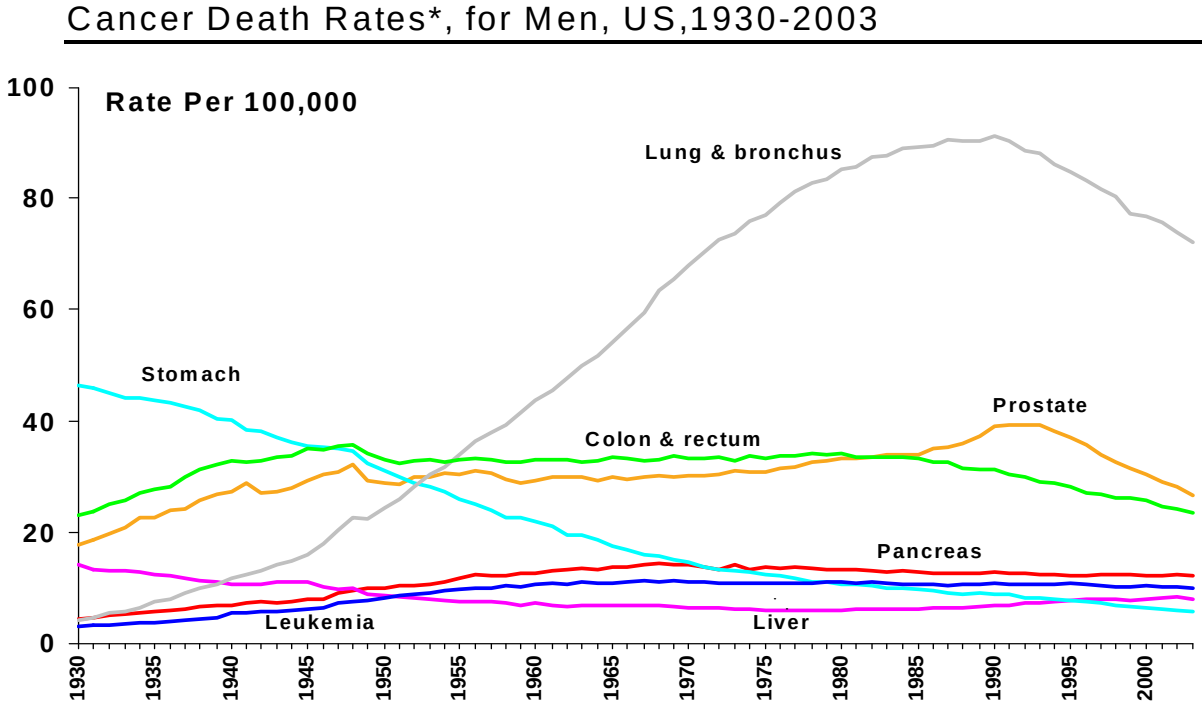
- **The latest advancements in robotic-assisted technology and allows a surgeon greater visualization, enhanced dexterity, precision, control and superior ergonomics.**

- > Shorter hospital stay
  > Less pain
  > Less risk of infection
  > Less blood loss and transfusions
  > Less scarring
  > Faster recovery
  > Quicker return to normal activities

Robotic Prostatectomy

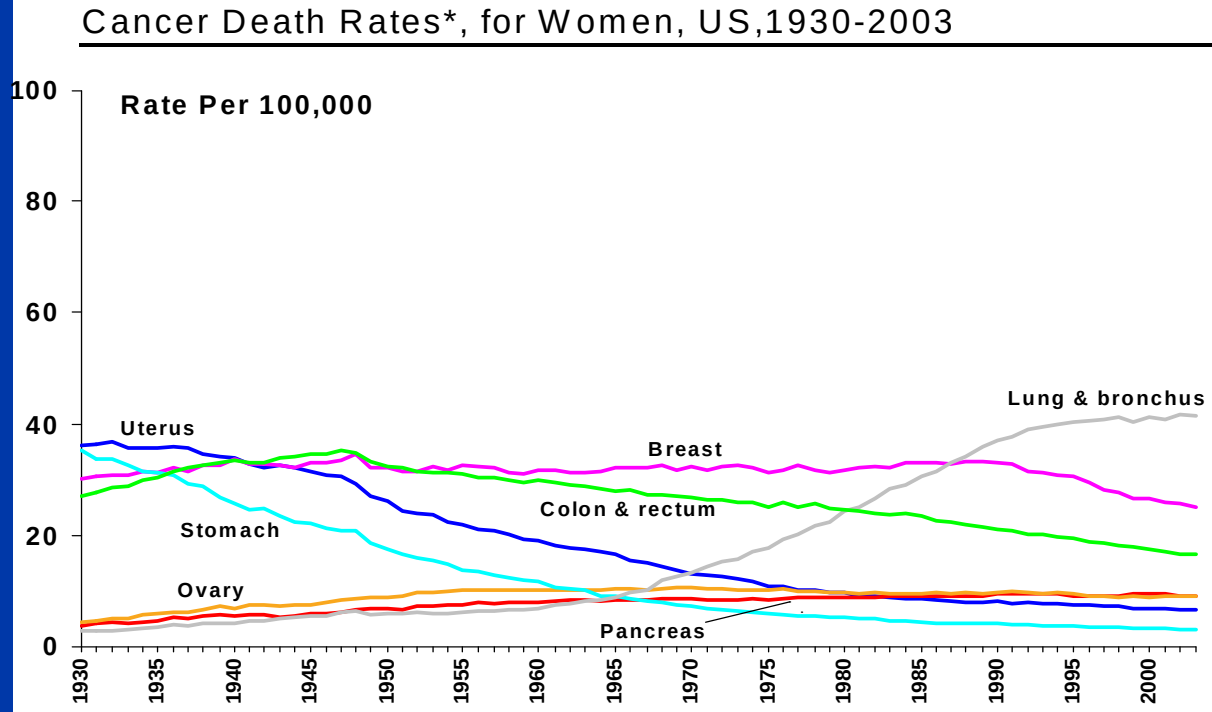


Cancer death rates 1930-2003



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes 1960-2003, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

Cancer death rates 1930-2003



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes 1960-2003, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

Conclusions

- Cancer treatments require a multi-modality management including surgery, chemotherapy and radiation.

- Each cancer pt should be consulted by all specialty, including a radiation oncologist.

Conclusions

- IMRT is the latest radiation therapy technique.
  - Preventing dry mouth for H&N cancer pts
  - Less skin dose for breast cancer pts
  - Higher cure rate/lower side effects for prostate cancer pt

Conclusions

- Newest cancer therapy
  - IMRT for Head & Neck cancer pts
  - Mammosite for breast cancer pts
  - Gene and immunotherapy for lung cancer pts
  - Robotic Cyber Knife for lung and prostate cancer pts
  - HDR radiation therapy for prostate cancer pts
  - Gene therapy for prostate cancer pts
  - Robotic surgery for prostate cancer pts

Conclusions

- Cancer treatments have come a long way in last 100 yrs, now actively contributing to cure of cancers.

Conclusions

- Still many treatments are on the horizon and will continue to be developed until cancer, like polio and smallpox, one day is a distant memory.