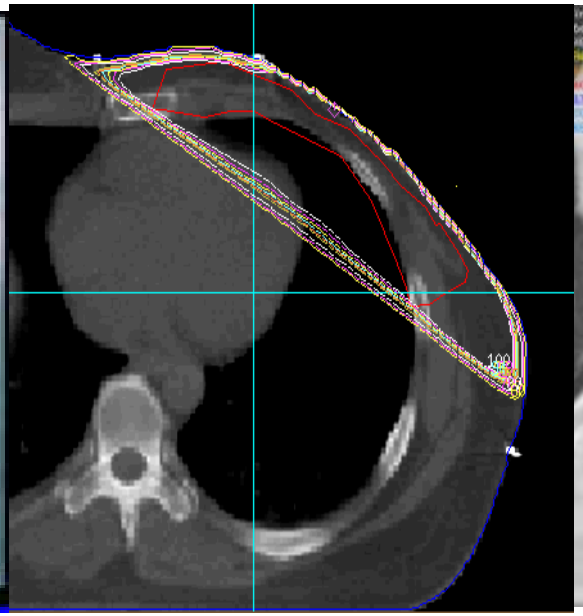
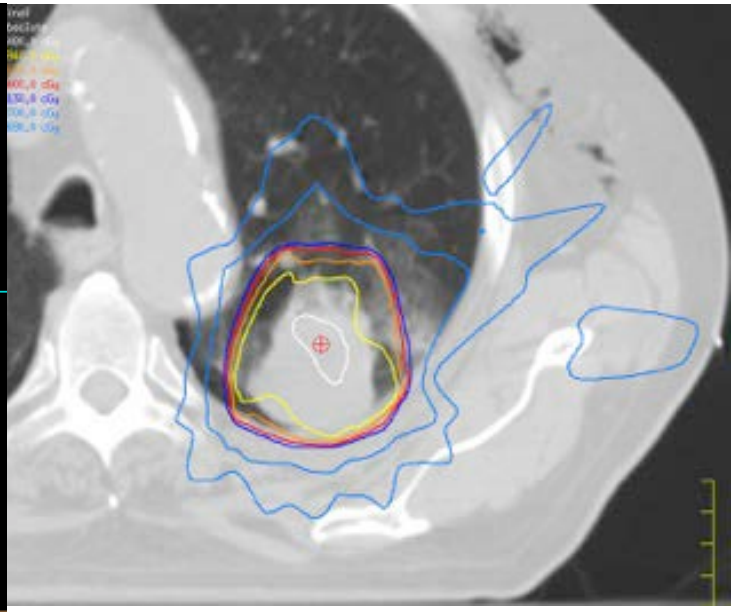
Science Behind New Photon Therapies

First known X-ray radiographs produced by Roentgen

2.5D planning



Stereotactic Body Radiotherapy to lung metastasis



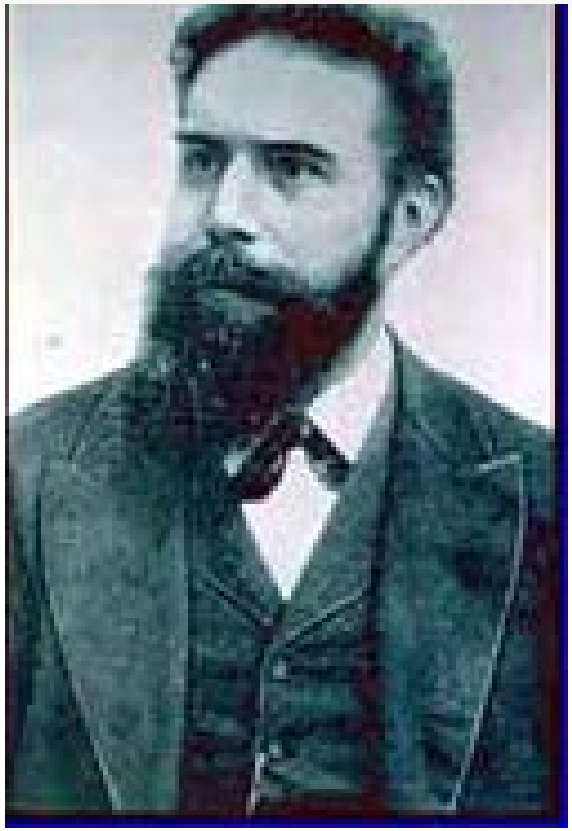
A Century of Sharpening the Knife

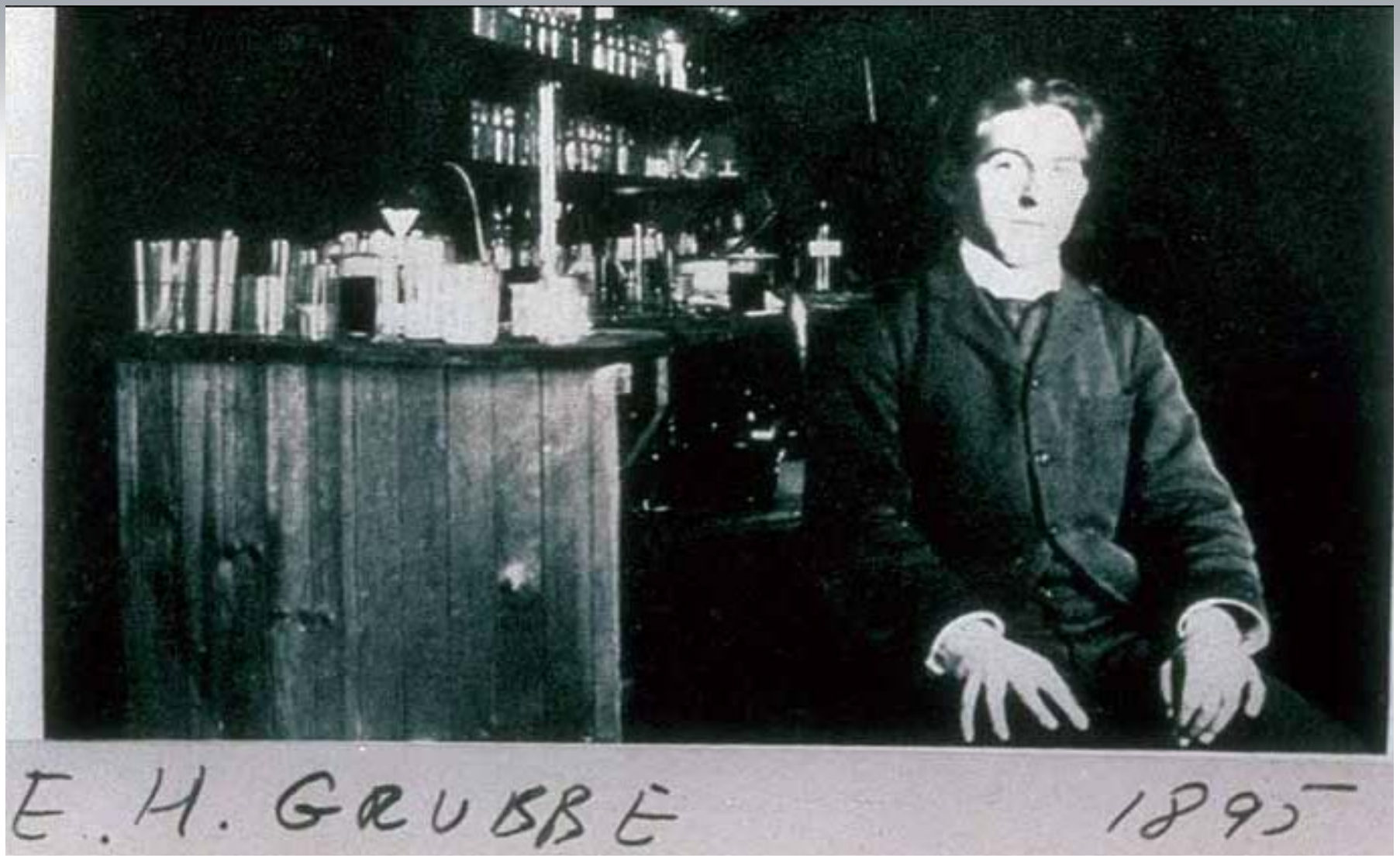
Steven J. Chmura MD, PhD
Associate Professor
Department of Radiation and Cellular Oncology
University of Chicago

20 Minute Outline

- Evolution of Photon therapy from 2D-> IMRT/IGRT
- Evidence that improvements in technology translate into improved cancer outcomes
- Can these technologies change the natural history of a cancer?
  - Oligometastases in breast cancer as an example

First known X-ray radiographs produced by Roentgen





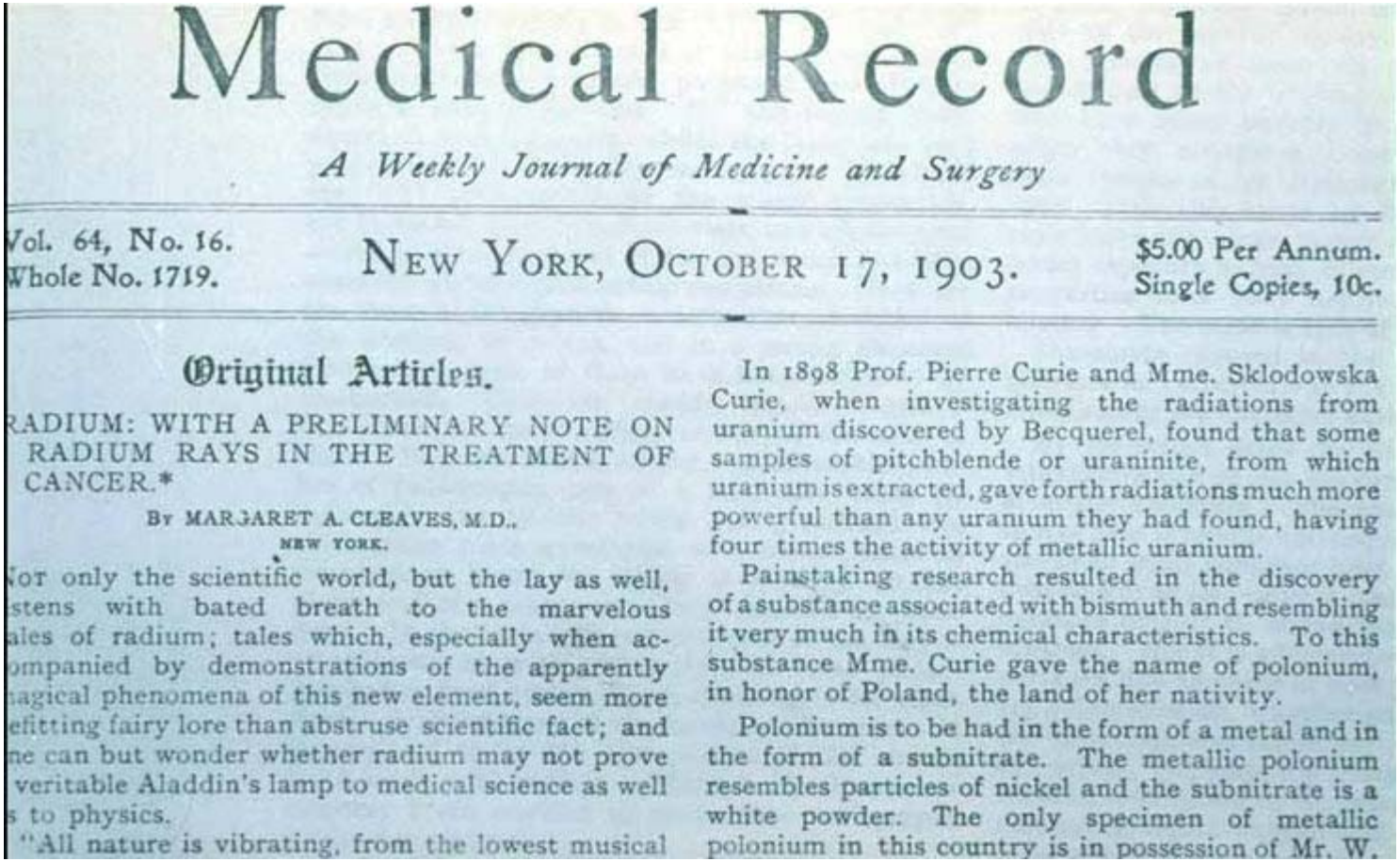
Emil Grubbe (1875-1960)
Over his lifetime, he required > 100 operations and amputations due to his excessive exposure to x-rays

First brachytherapy treatment of cervical cancer performed

By Margaret Cleaves M.D. (1848-1917)

Below is her original report of the first patient treated

Soon RT was being used instead of surgery in many countries



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.

Nor only the scientific world, but the lay as well, stens with bated breath to the marvelous ales of radium; tales which, especially when ac- ompanied by demonstrations of the apparently agical phenomena of this new element, seem more efitting fairy lore than abstruse scientific fact; and ne can but wonder whether radium may not prove veritable Aladdin's lamp to medical science as well s to physics.

"All nature is vibrating, from the lowest musical

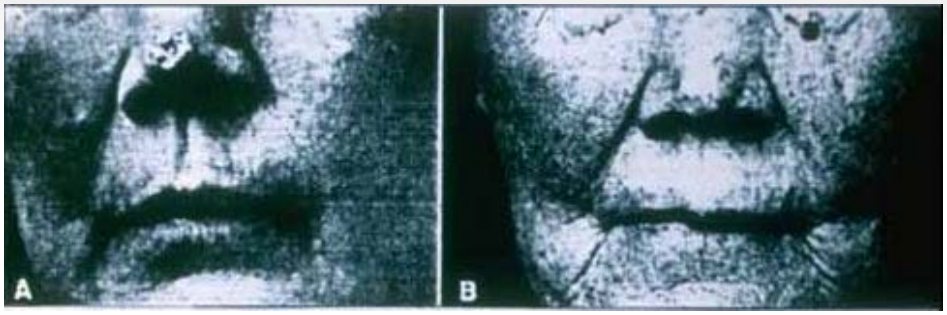
In 1898 Prof. Pierre Curie and Mme. Sklodowska Curie, when investigating the radiations from uranium discovered by Becquerel, found that some samples of pitchblende or uraninite, from which uranium is extracted, gave forth radiations much more powerful than any uranium they had found, having four times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

- Despeignes (France 1896) treats a patient with gastric cancer noting significant symptom relief

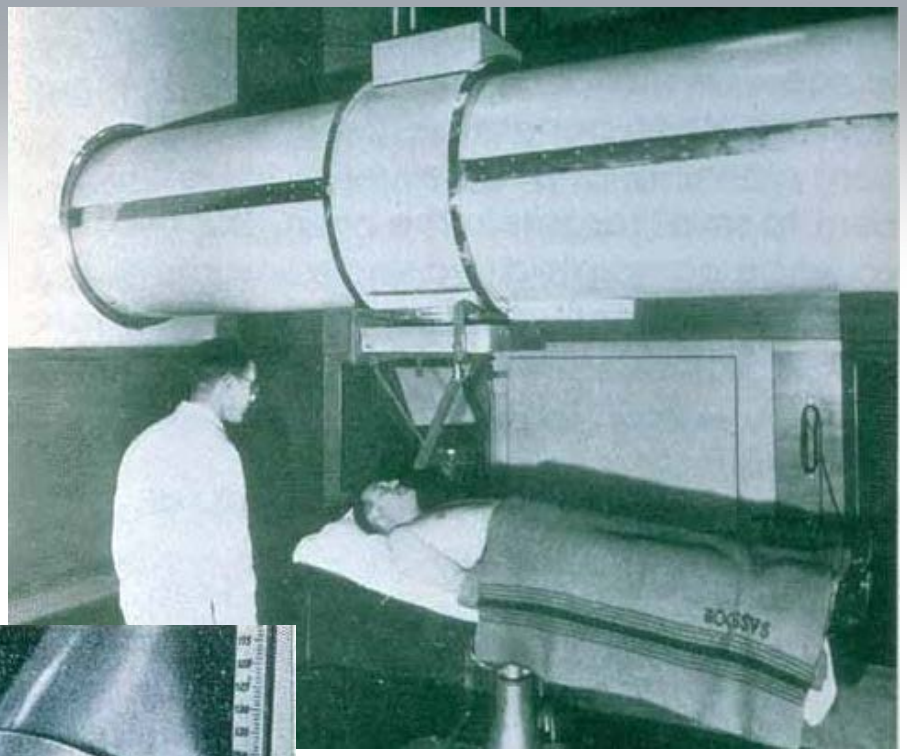
- Stenbeck (Sweden 1899) → Treats a 49 year old patient with a basal cell tumor on the nose (100 times over 9 months). The patient was alive and well 30 years later

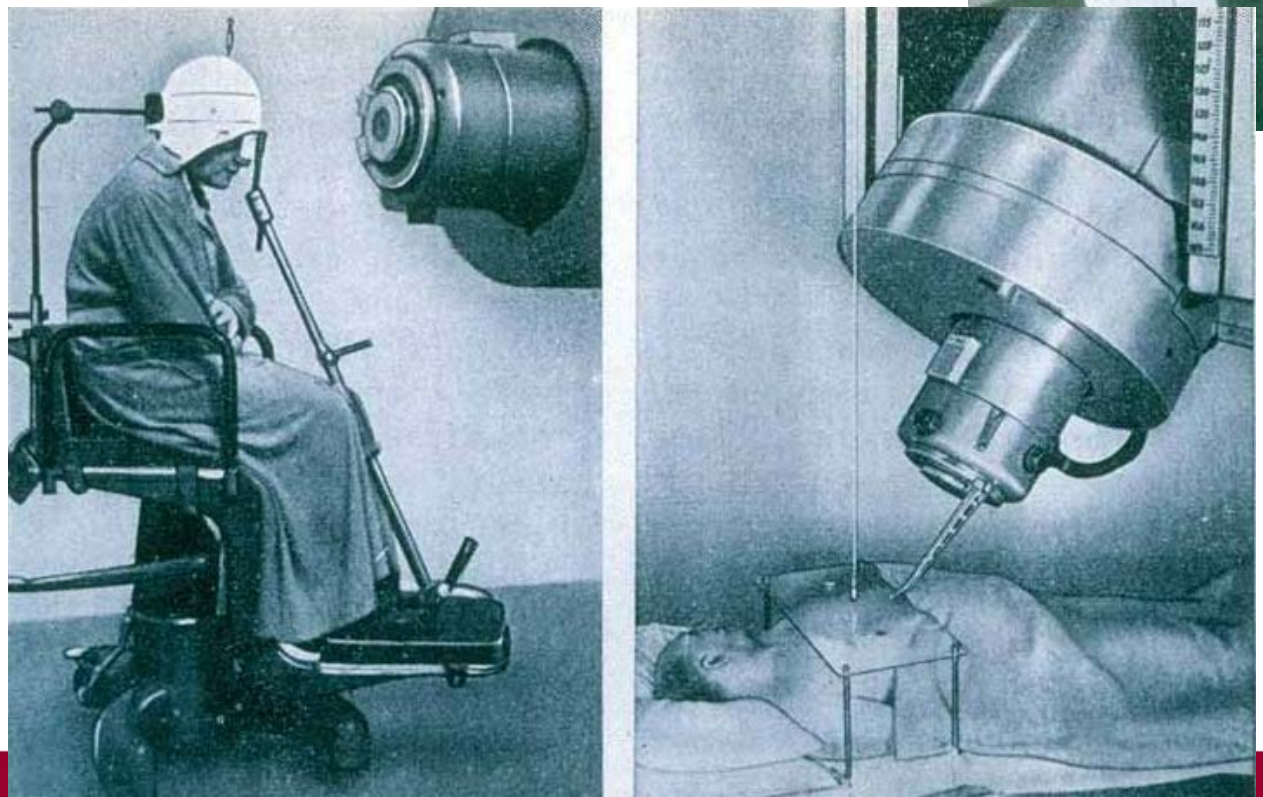


- Sjogren (Sweden 1900) → successfully treats a patient with a squamous cell cancer (50 times over 50 months)

Early Treatment Machines

1 MeV Vicker's Unit, St Bart's → Hospital London 1937
Equipped with a movable couch and variable field sizes





←1st Van de Graaf Generator, Royal Marsden Hospital, London, 1933

RSNA 100 YEARS
Radiology

December 1978
Volume 129, Issue 3

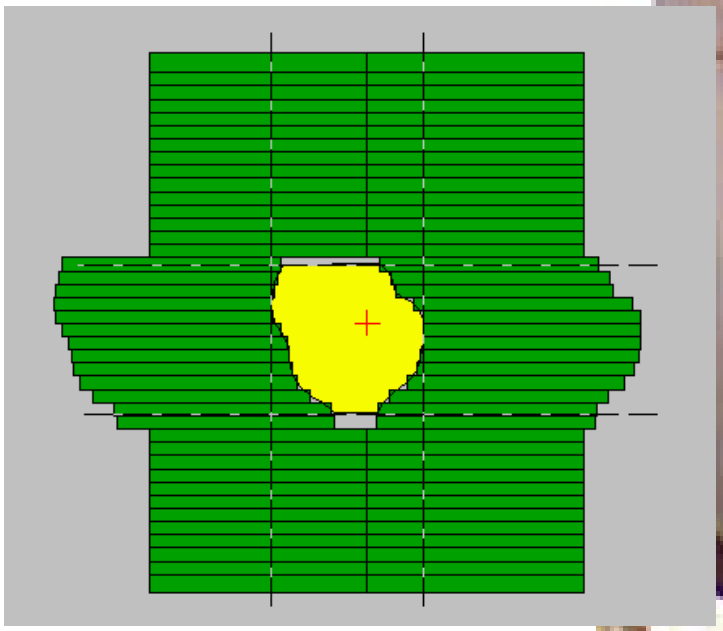
Computer-Controlled Radiation Therapy

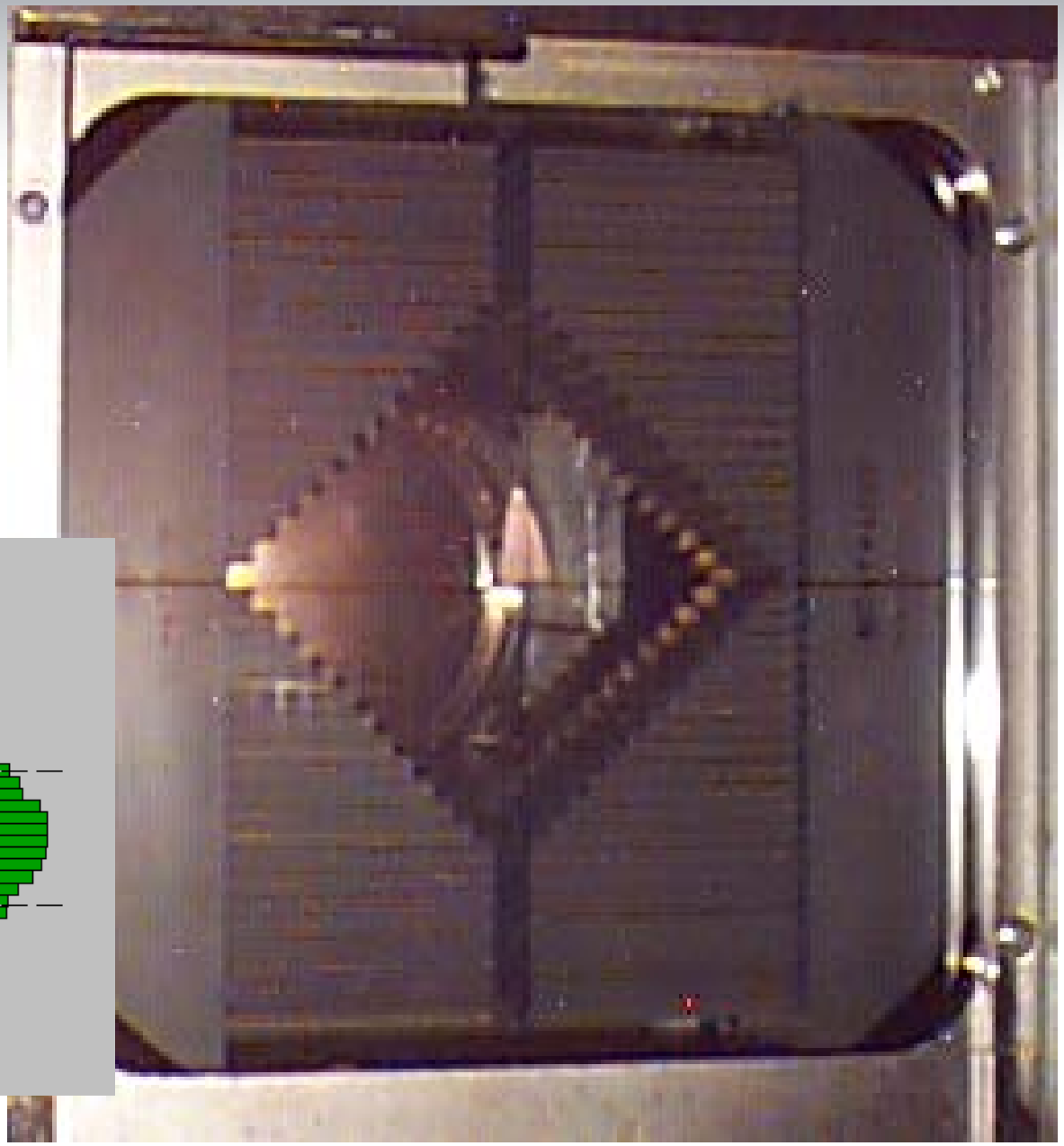
Martin B. Levene, M.D., , Peter K. Kijewski, Ph.D., , Lee M. Chin, S.M., , Bengt E. Bärngard, Ph.D., , and Samuel Hellman, M.D.,
Department of Radiation Therapy
Harvard Medical School Boston, MA 02115

Evolution of Technology form 2D-> Image Guided (IGRT) Intensity Modulated Radiotherapy (IMRT)

Medical linear accelerator

Metal leaves shape the radiation beam and shield normal tissue





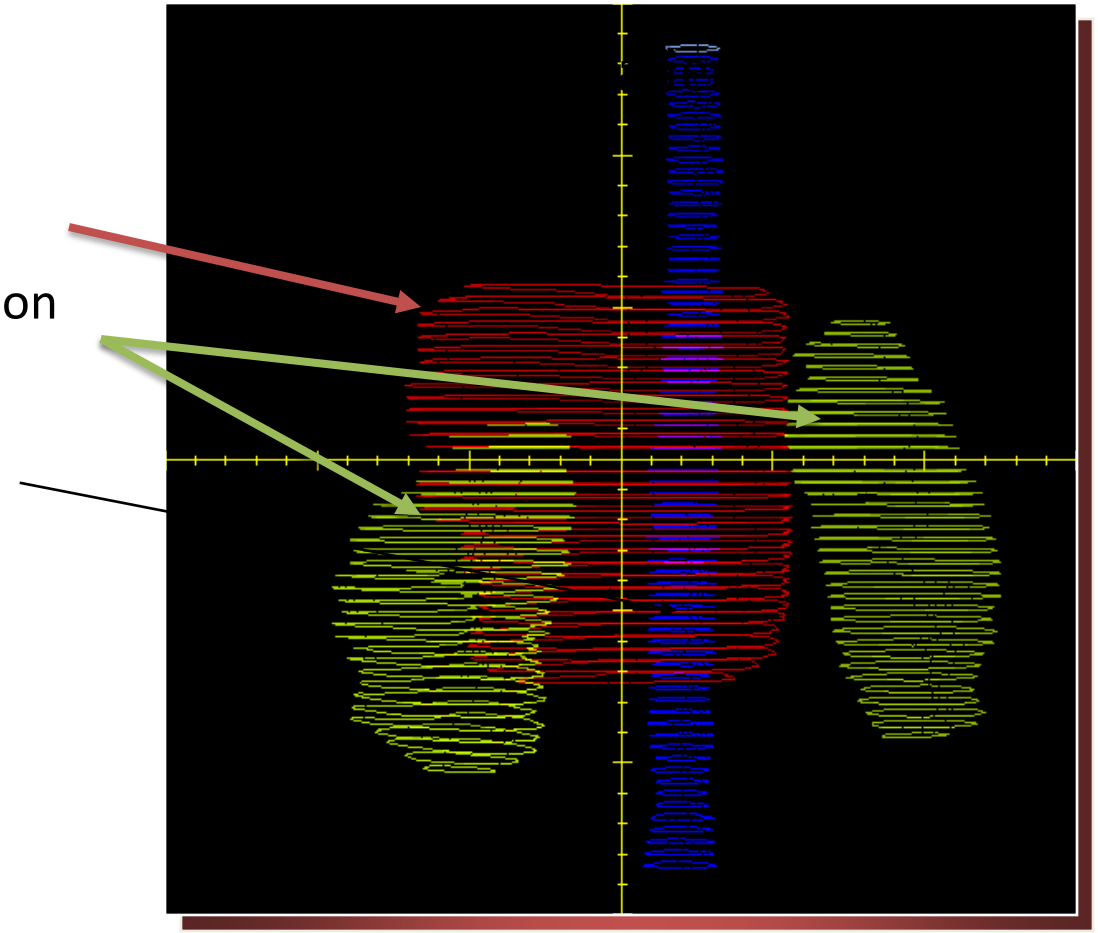
2D vs 3D

- 3D Planning with physician entering targets
  - Outlines targets in 3D
  - Outlines critical anatomy to avoid
  - Physicists generate plan based on targets/anatomy

Pancreas case

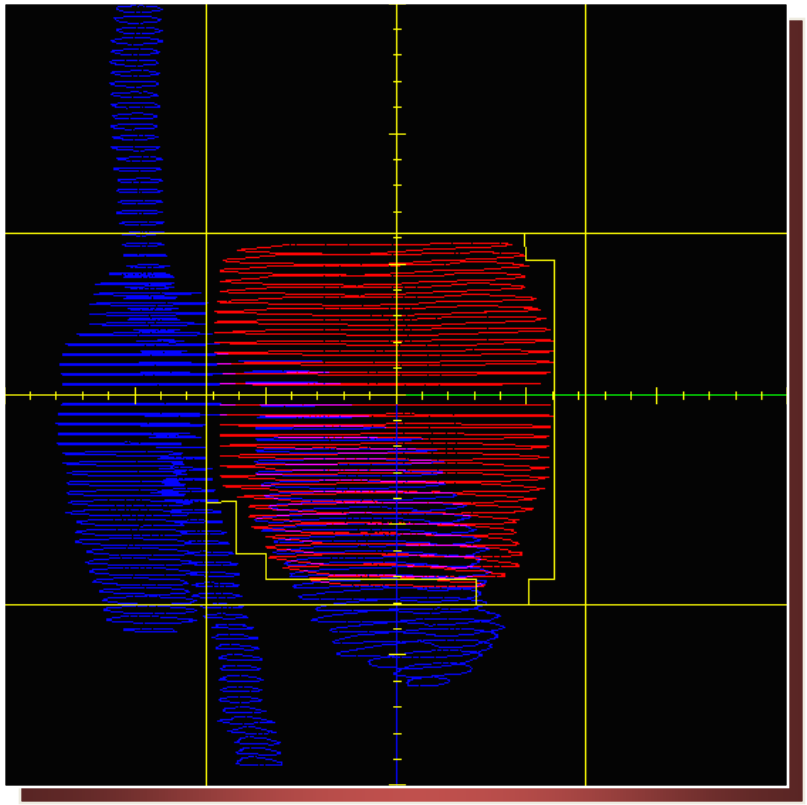
Pancreas

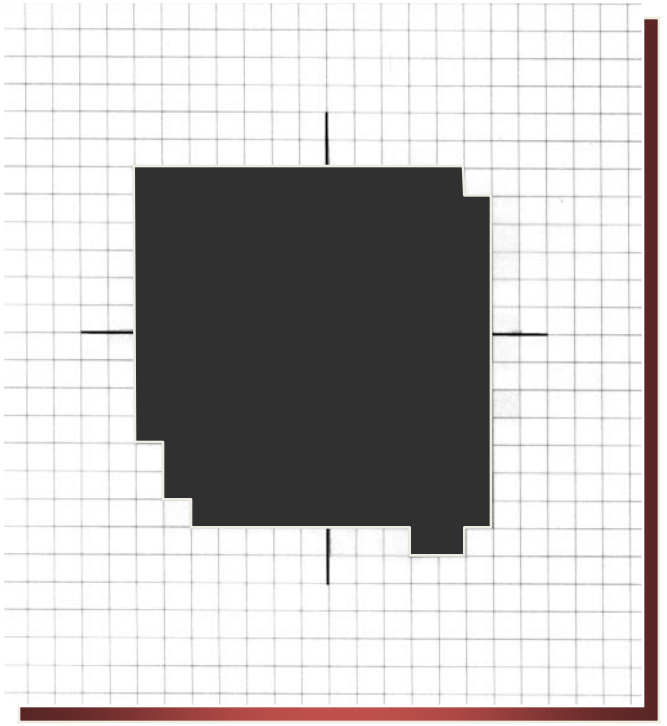
- Treat target to 55 Gy
- Preserve kidney function (dose limit = 20 Gy)
- Protect spinal cord (dose limit = 45 Gy)



3D Conventional beam

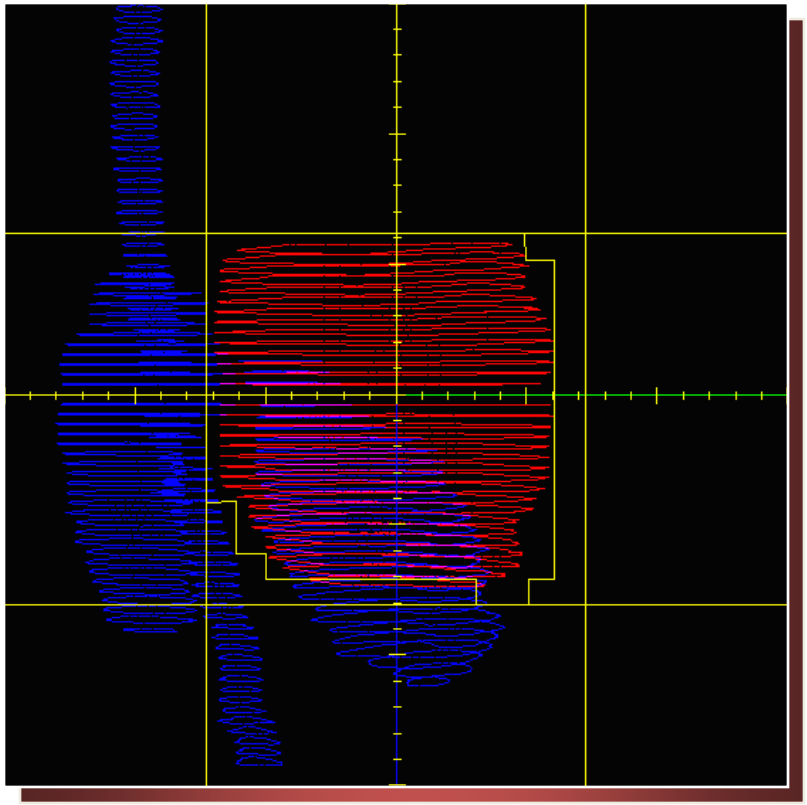
Each beam shaped to match 2D projection of target

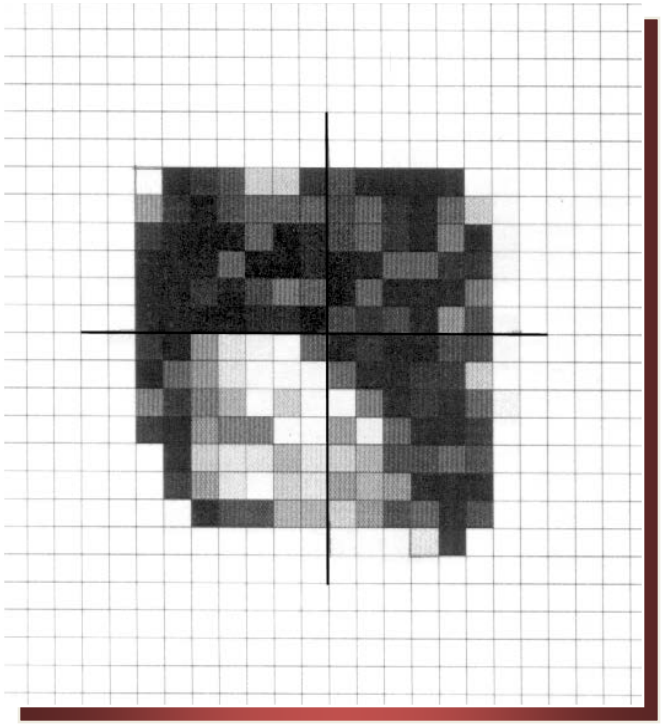




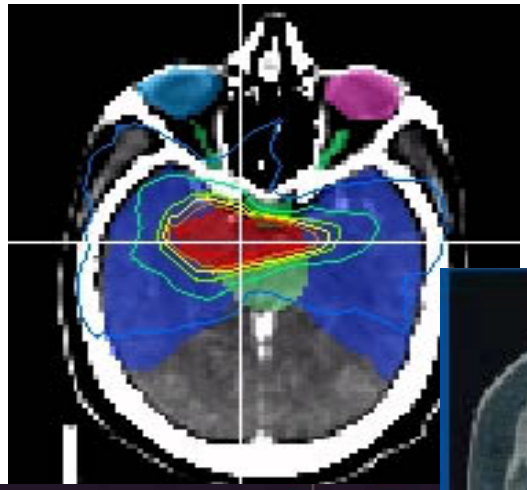
Intensity-modulated plan

Each beam divided into 1 x 1 cm beamlets





Intensity Modulated Radiation Therapy (IMRT): Sparing normal tissue

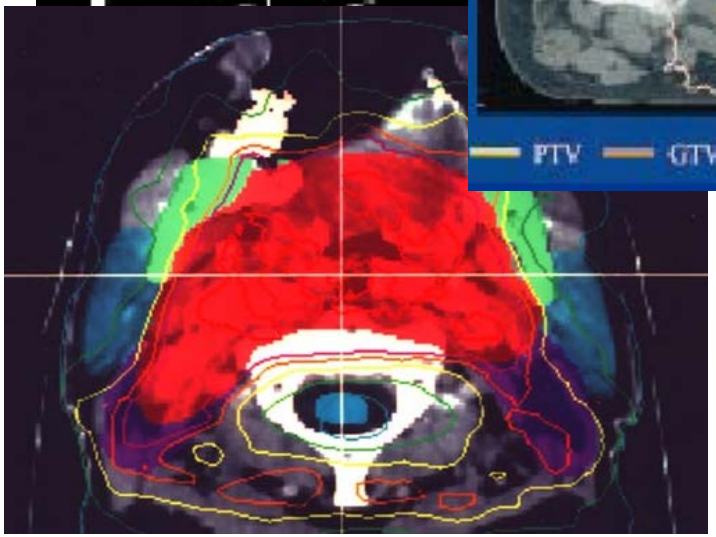


←Brain Tumors

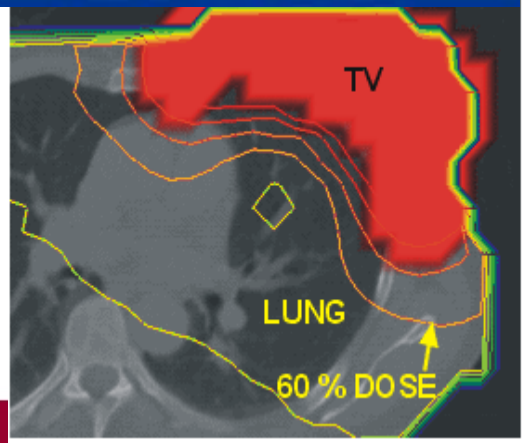
↓Prostate Cancer

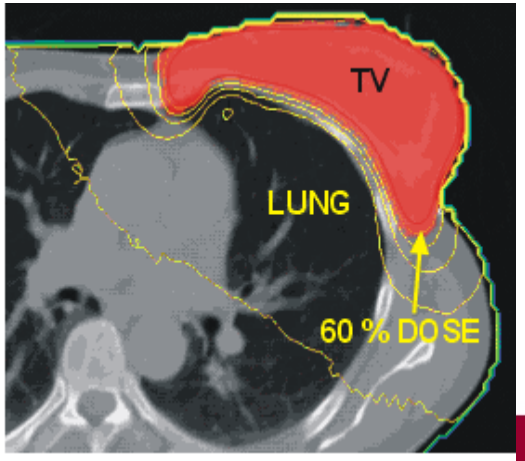
↑Cervix Cancer

↓Breast Cancer

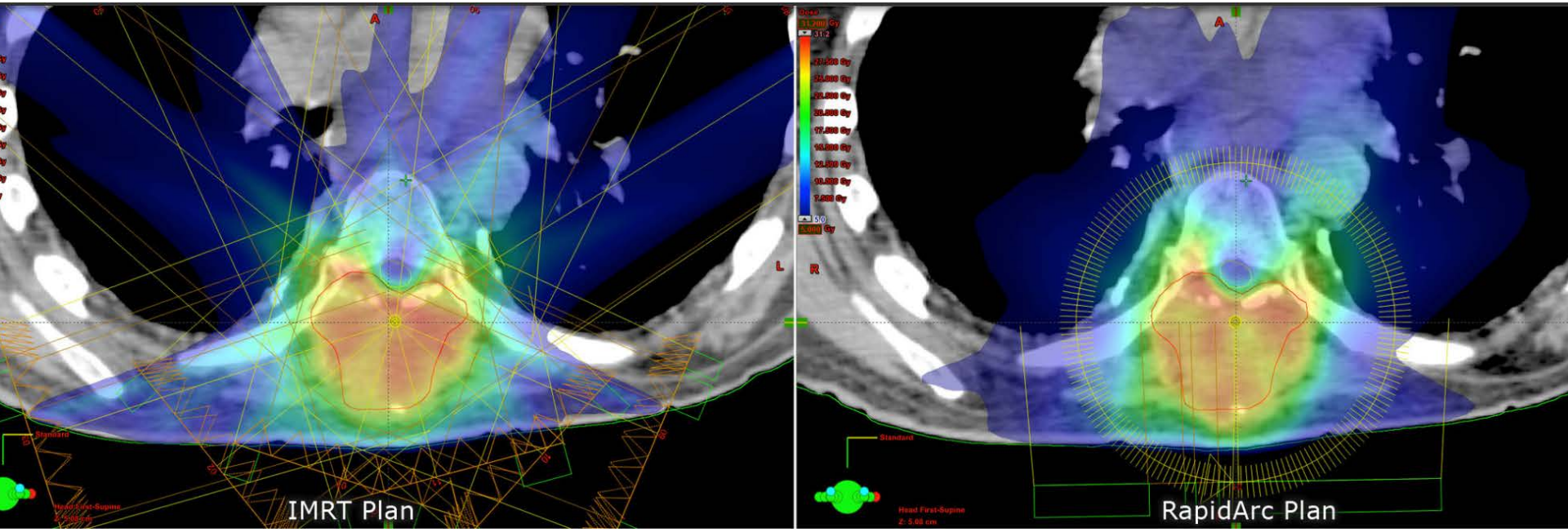


↑Head and Neck Cancer

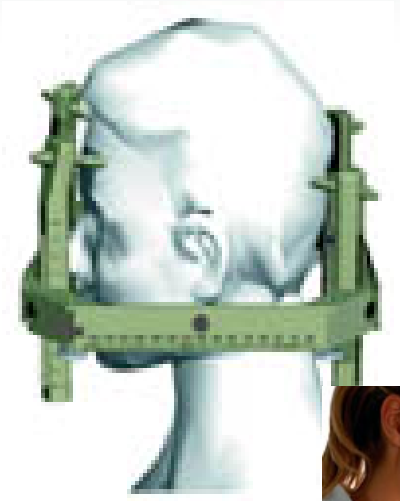


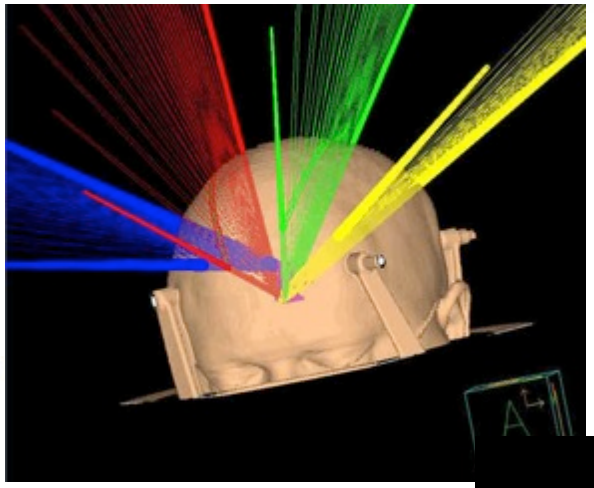


Variable Arc Radiotherapy (VMAT)

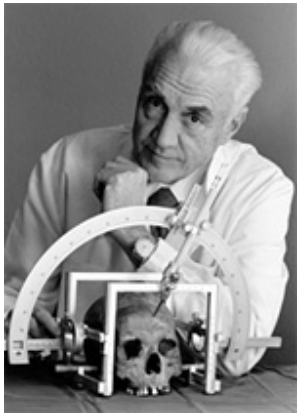


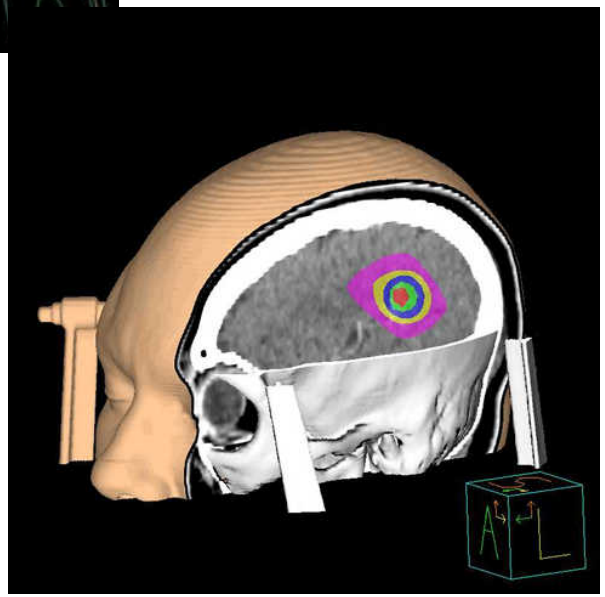
Stereotactic Radiosurgery



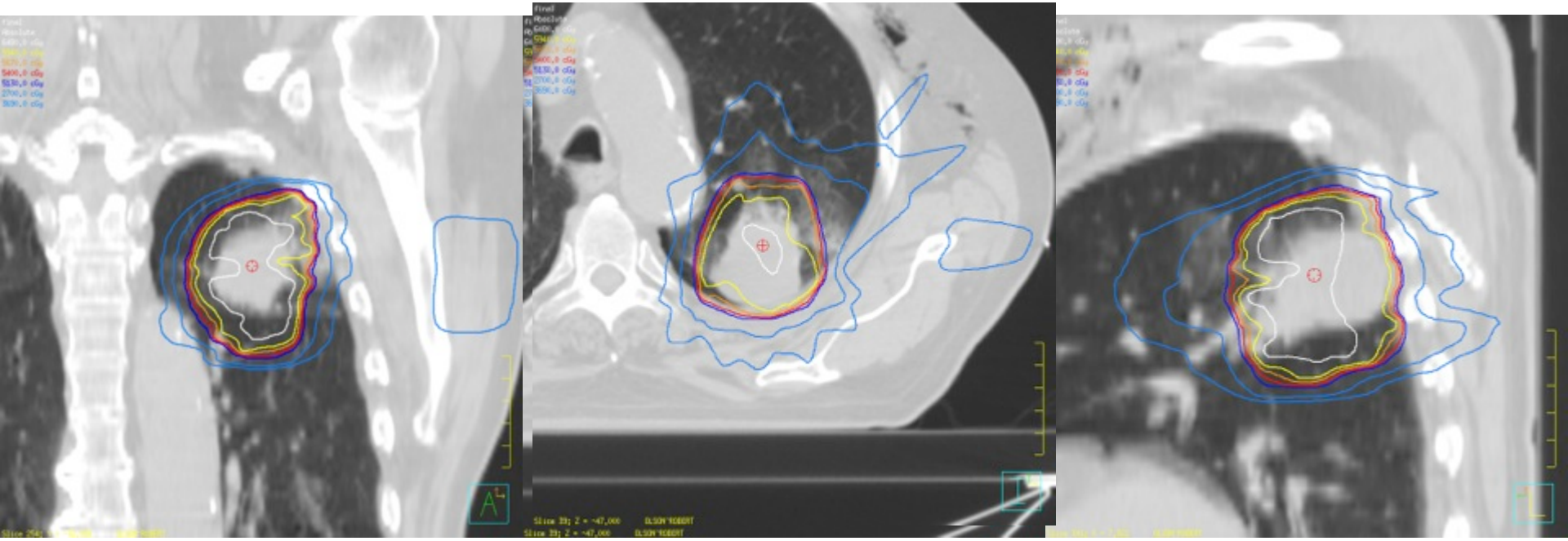


Local control 85-95%



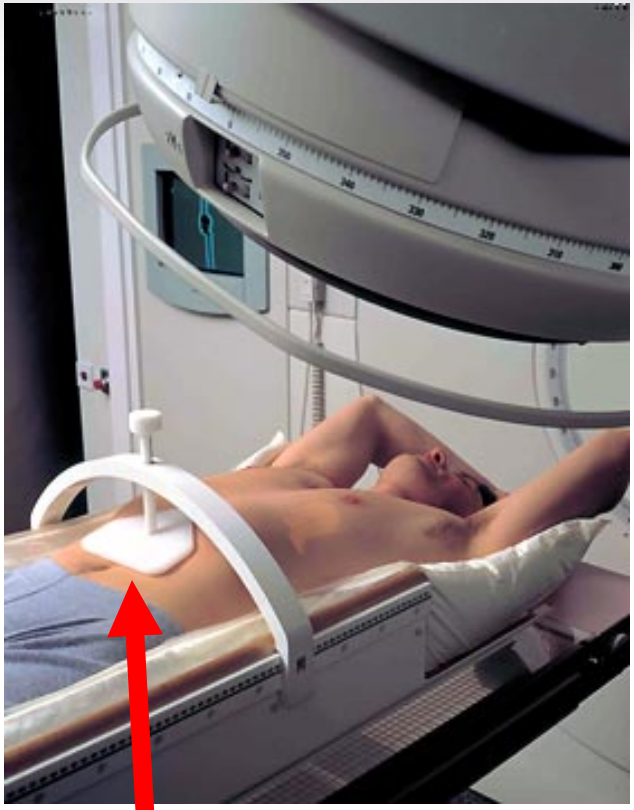


Stereotactic Body Radiotherapy SBRT/SABR/HIGRT

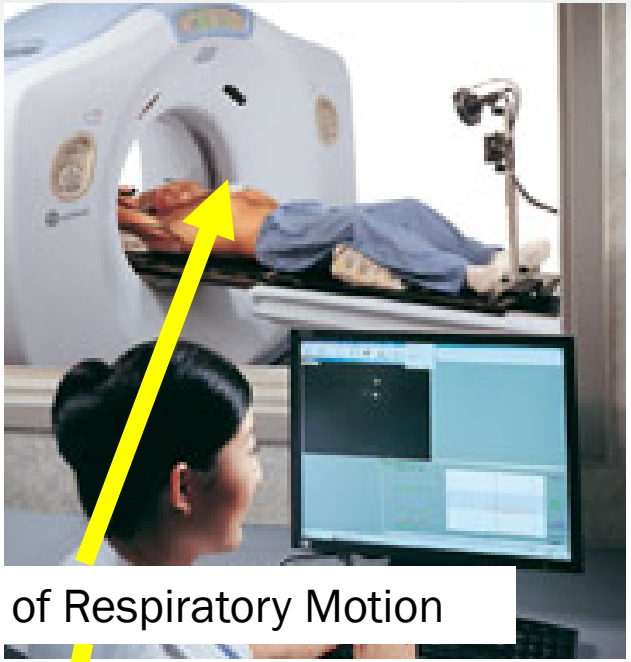


Sharper Knives:
Need imaging to visualize target

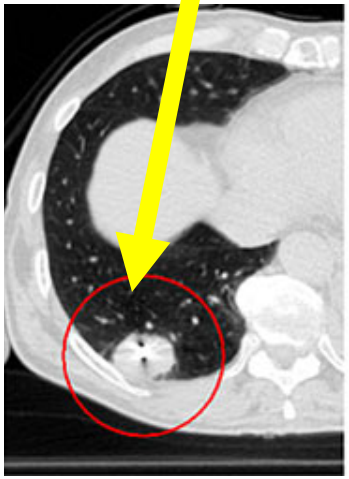
IGRT motion management



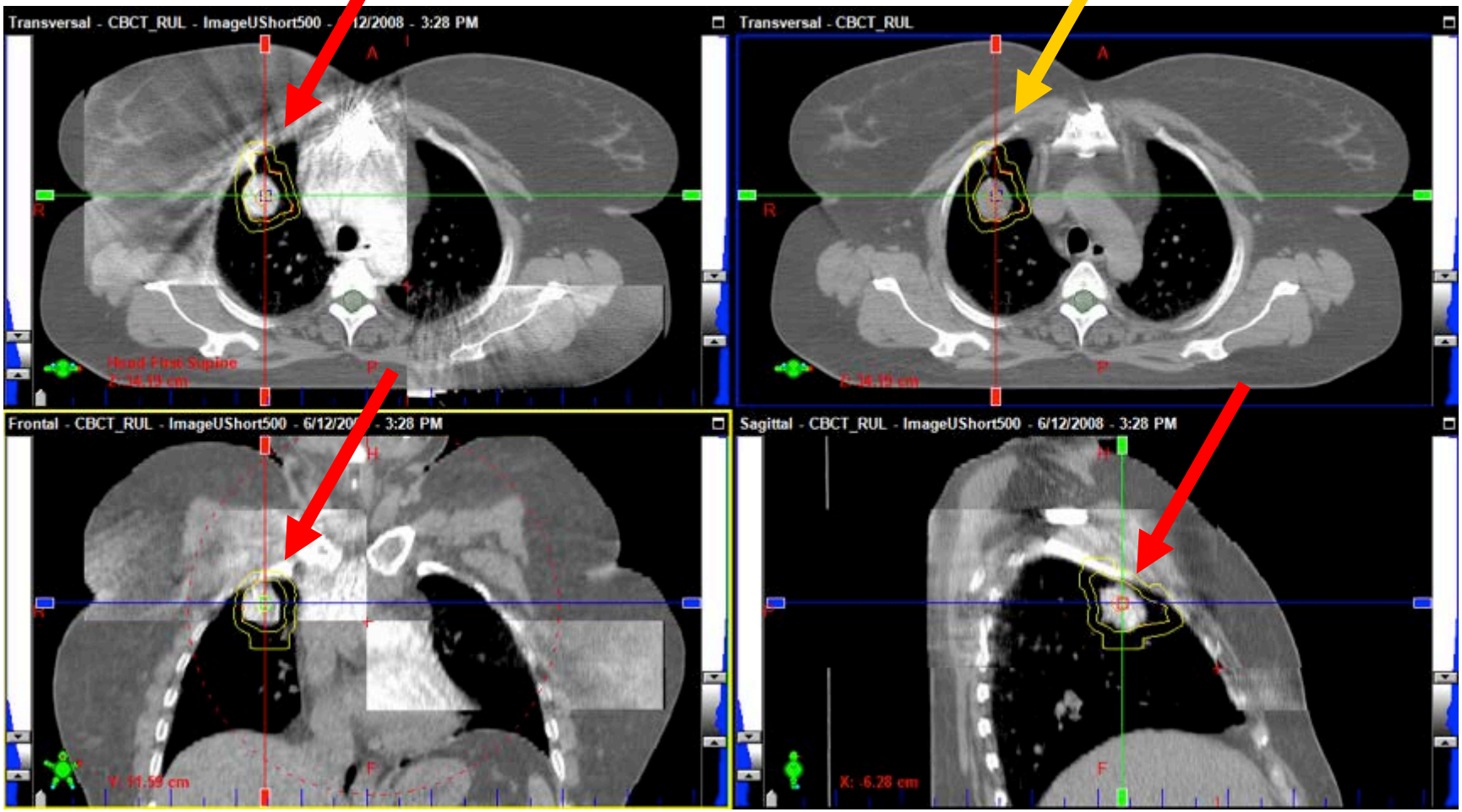
Control of Respiratory Motion



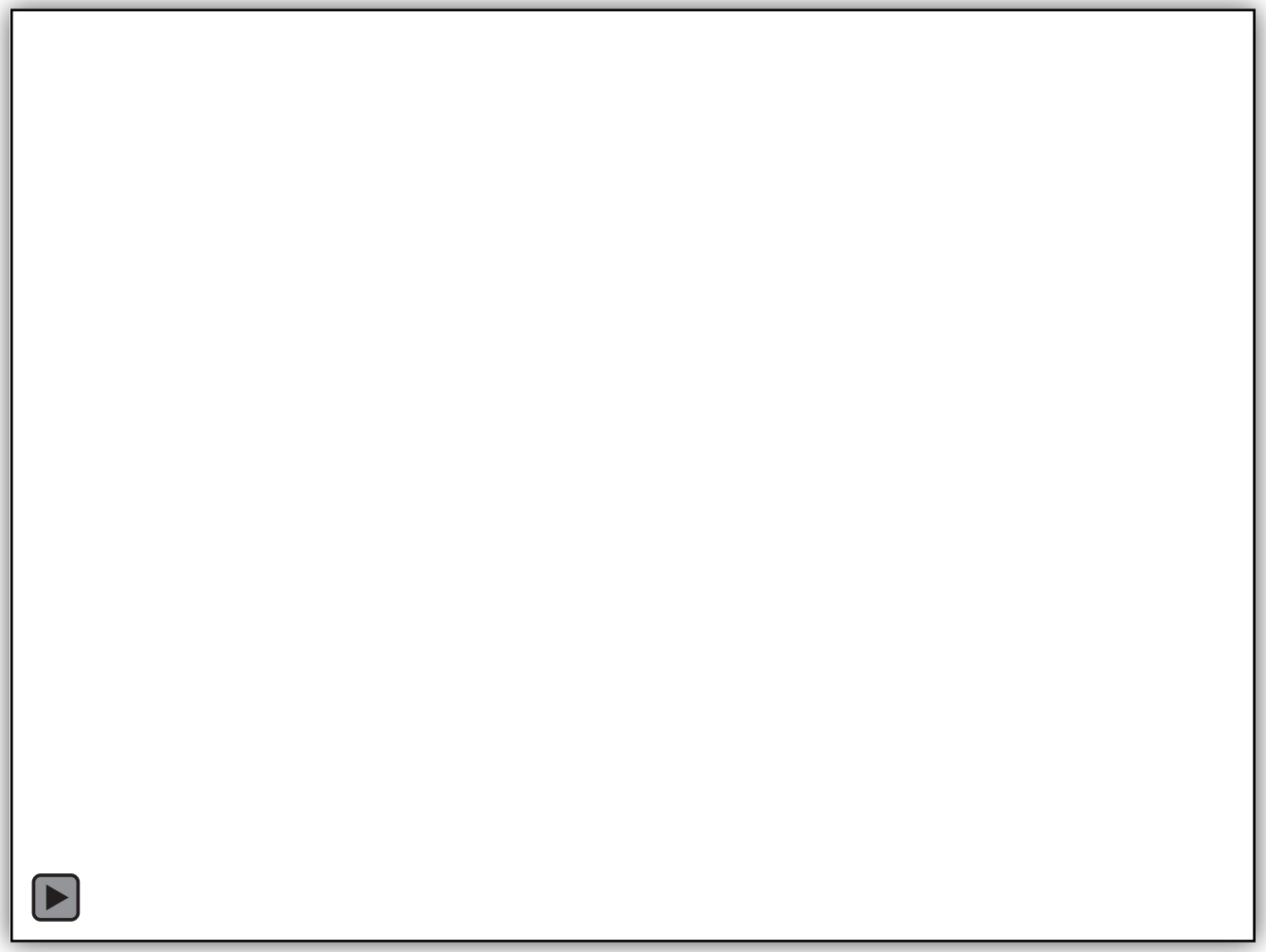
Tracking of Respiratory Motion



Pretreatment Imaging Confirmation



Monitoring and Tracking During Treatment



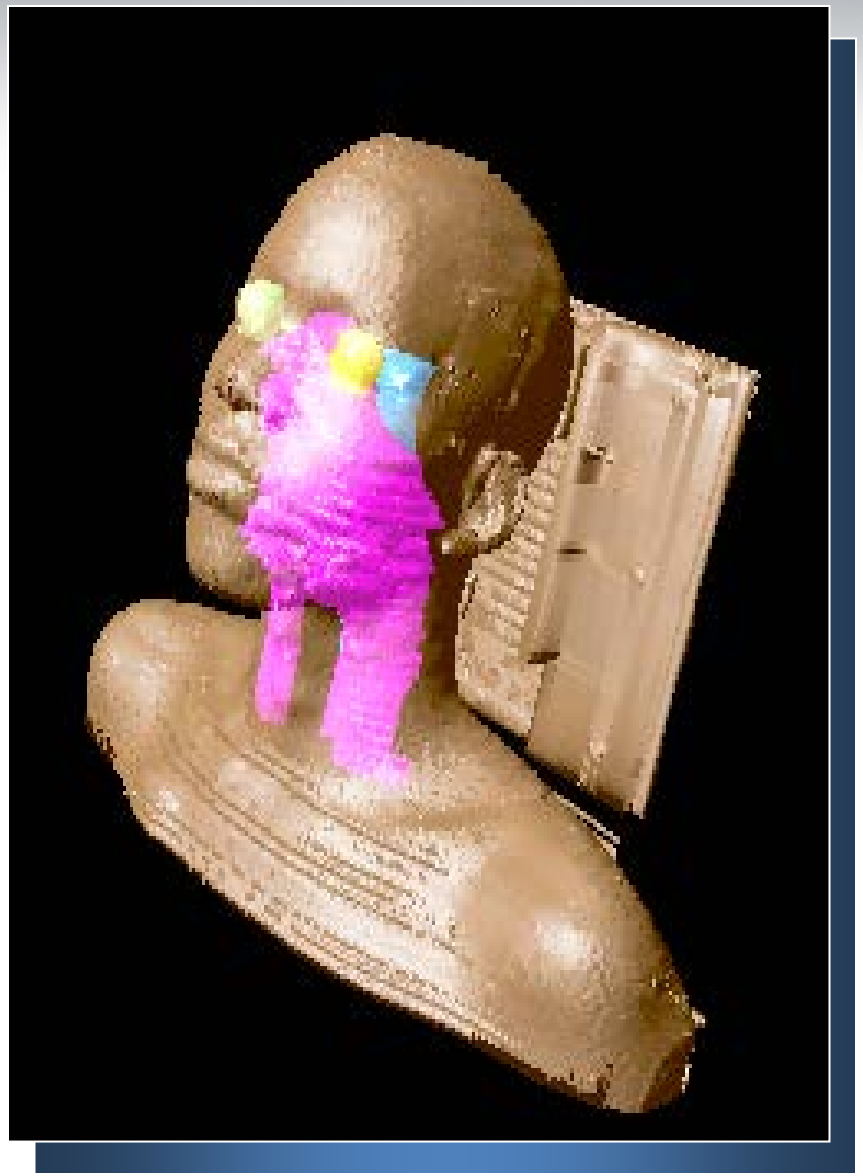
Summary of Evolving Photon Technology

- Evolution from large 2D fields to 3D conformal shapes
- Requires precise knowledge of anatomy to determine tumor AND organs at risk (OAR)
- Increasing Conformality necessitates improved imaging and tracking of motion (IGRT)

EVIDENCE FOR IMPORVED OUTCOMES IN PATINETS

EVIDENCE FOR IMPROVED OUTCOMES

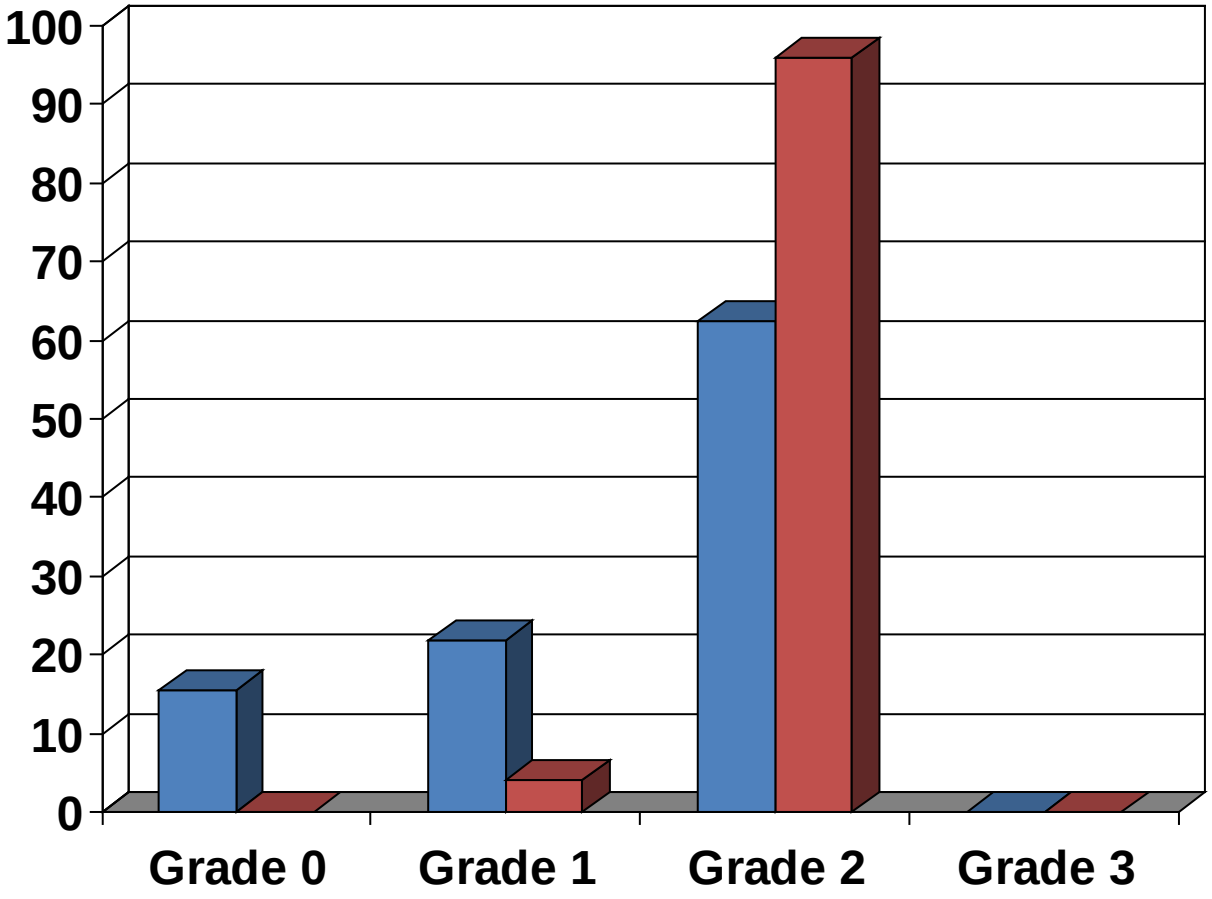
- Single institution series
- LEVEL 1 Evidence
- Always NEED RANDOMIZED TRIALS?



IMRT Literature

- Dosimetric studies demonstrate that IMRT *planning* → ↑tissue sparing and equivalent (or better) target coverage in nearly all tumor sites

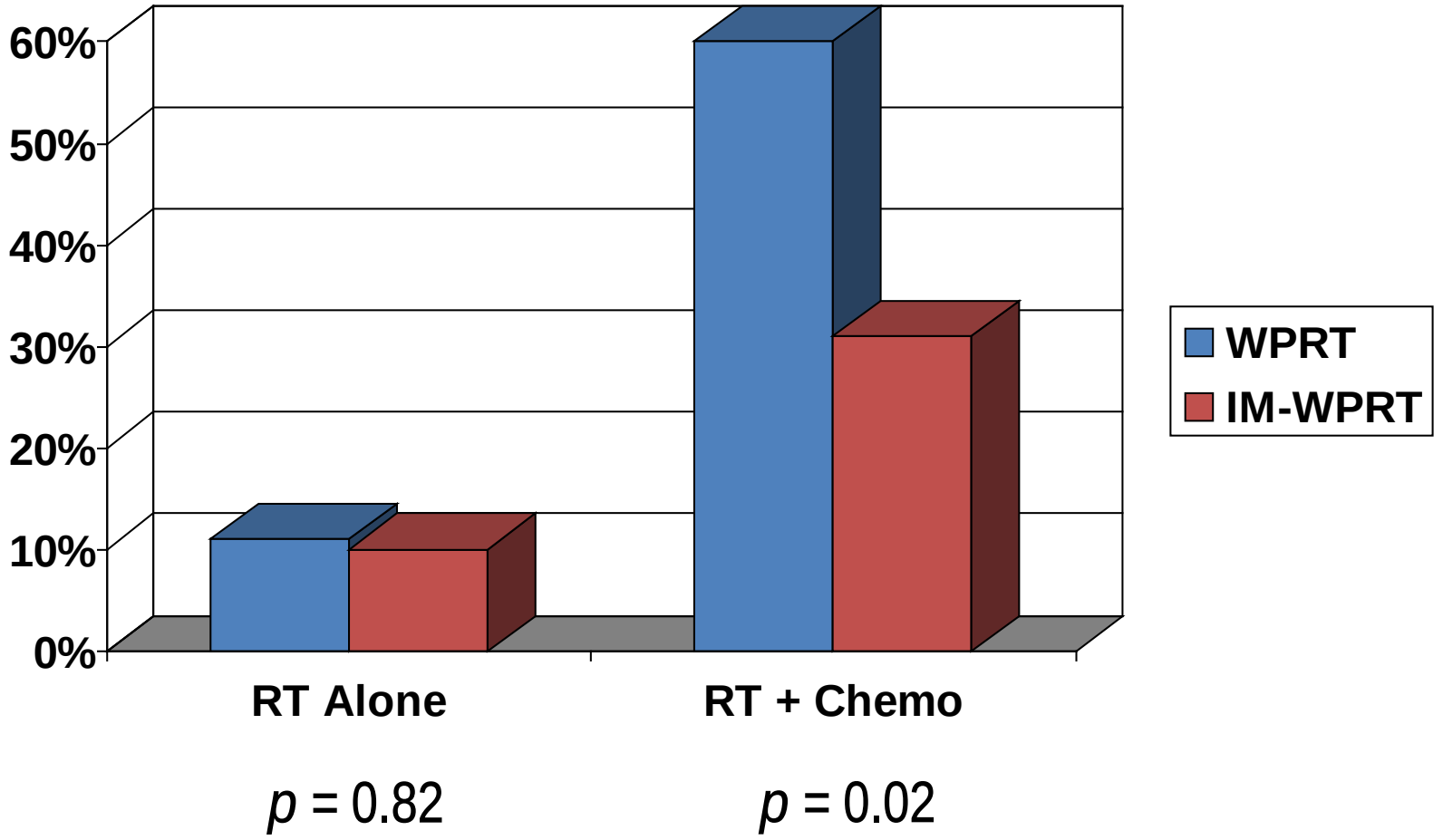
Acute GI toxicity
IM-WPRT vs. WPRT



P = 0.002

Mundt et al. *Int J Radiat Oncol Biol Phys* 52:1330-1337, 2002

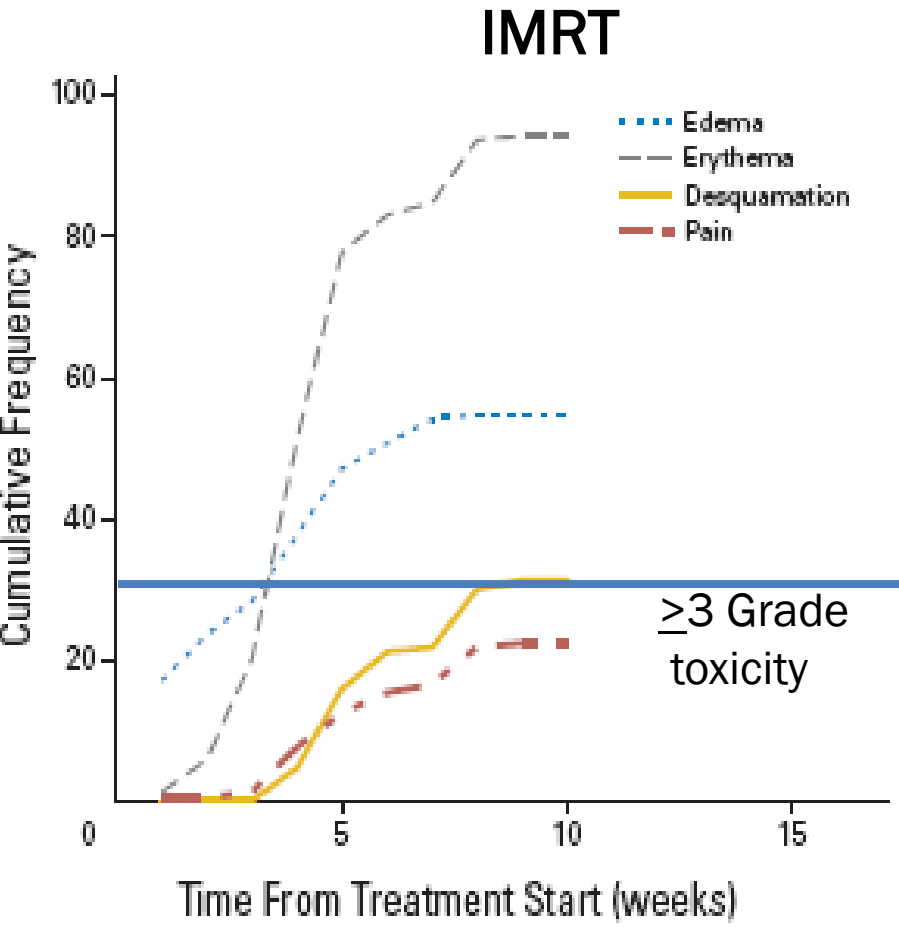
Grade ≥ 2 WBC Toxicity
WPRT versus IM-WPRT Patients

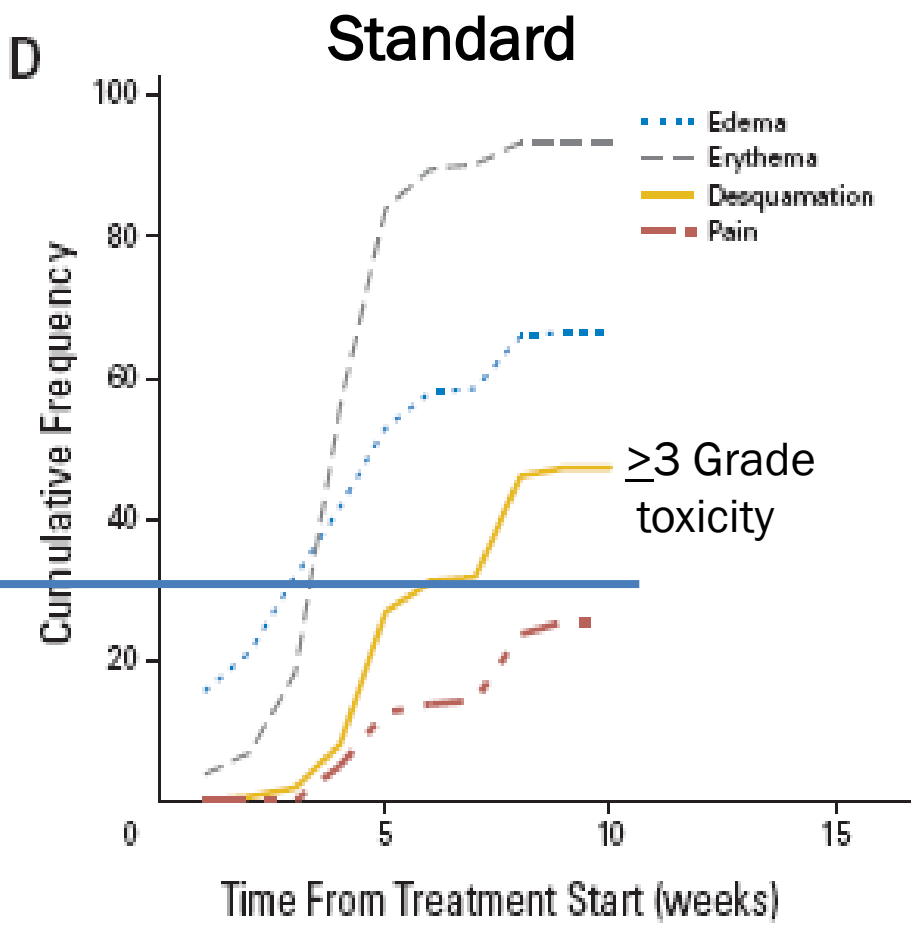


Brixey et al. *Int J Radiat Oncol Biol Phys* 52:1388-93, 2002

Level 1 Evidence IMRT/3DCRT vs 2D

IMRT improved Skin Toxicity and QOL





Primary endpoint: acute skin toxicity

Results: Moist desquamation: 31.2% vs 47.8% Correlated to pain and reduced QOL

Pignol, Toronto, JCO, 2008

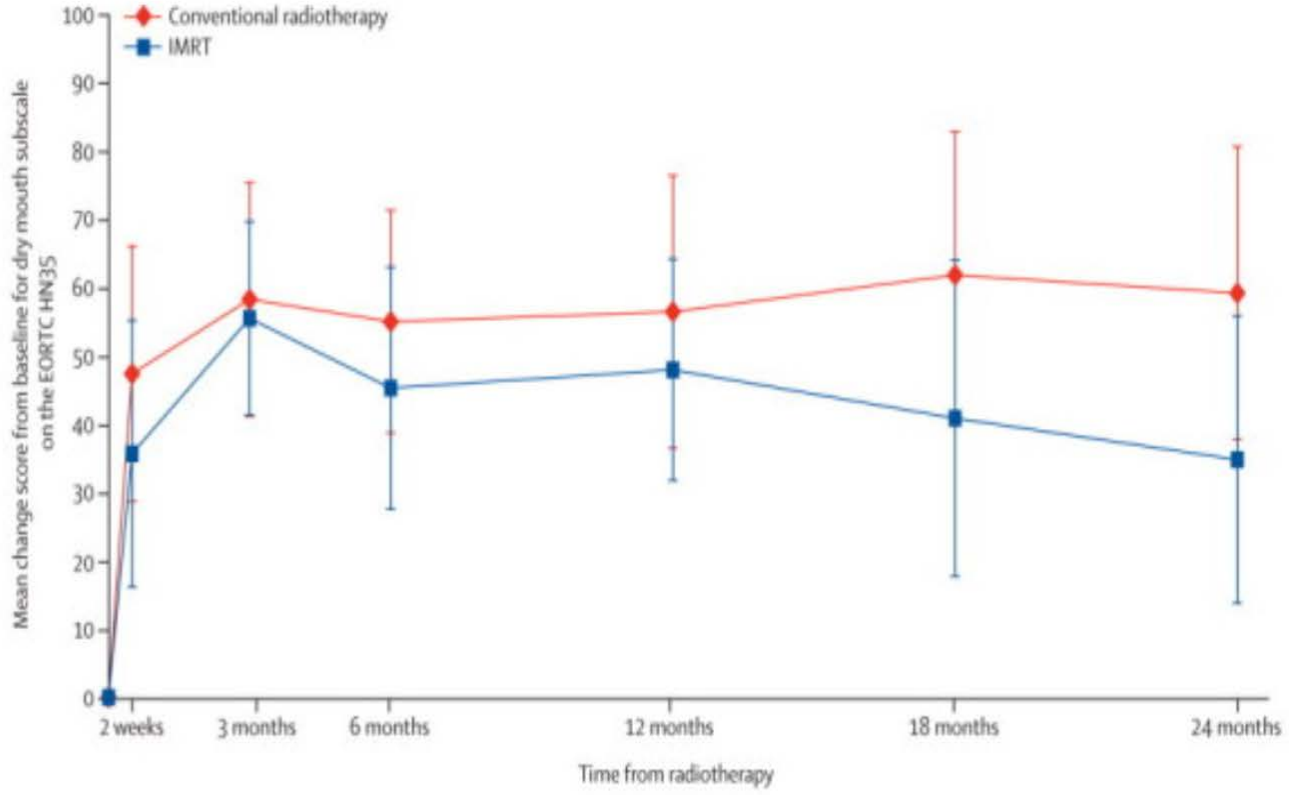
UK RND Trial: IMRT vs 2D Cosmesis Long Term Results (7y)

Results:

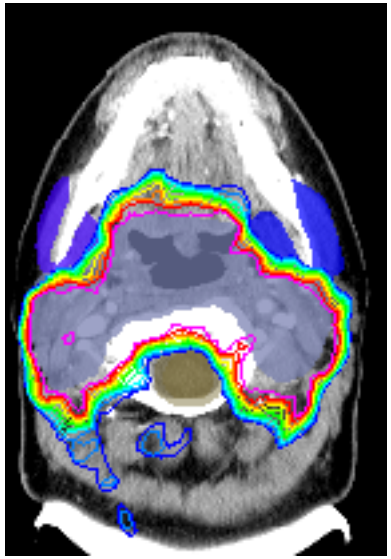
- Change in breast:
  - Photographs:
    - 58% (2D) vs.
    - 40% (IMRT) based on 5 yr photographs
  - Conformal plans (105%) predicted change in
    - 62% had no changes in breast appearance (<105%) vs.
    - 42.4% (>105%) SS
  - IMRT decreased 7y rates of
    - Palpable induration assessed in breast, pectoral fold, inframammary fold and boost site

***Conclusions**: IMRT can decrease dose inhomogeneity and long-term changes in the breast*

Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial.



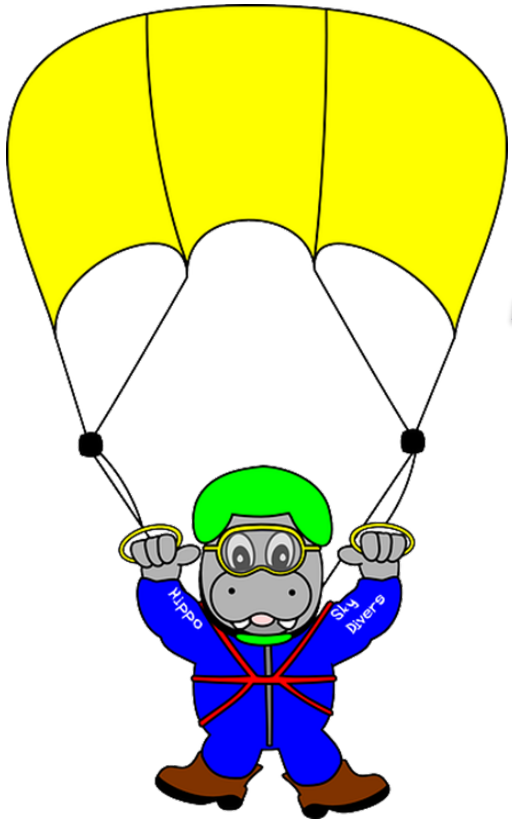
Conventional radiotherapy	26	24	23	23	21	18
IMRT	28	30	25	25	22	22
Difference in mean	11·7	2·8	9·7	8·5	21·0	24·4
(99% CI)	(−14·4 to 37·8)	(−18·4 to 24·0)	(−13·5 to 32·9)	(−15·9 to 33·0)	(−8·9 to 50·9)	(−4·3 to 53·2)

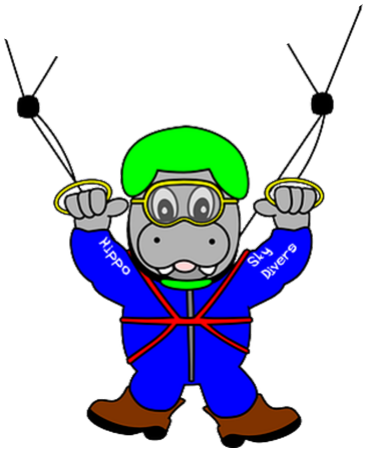


Lancet Oncol. 2011 Feb; 12(2): 127–136.

Do we always need Level 1 Evidence to adopt new technologies

RND

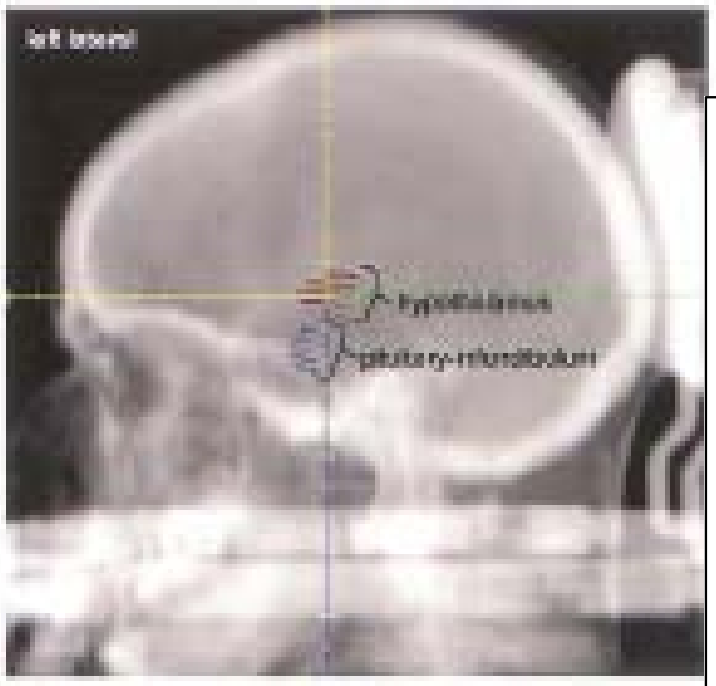


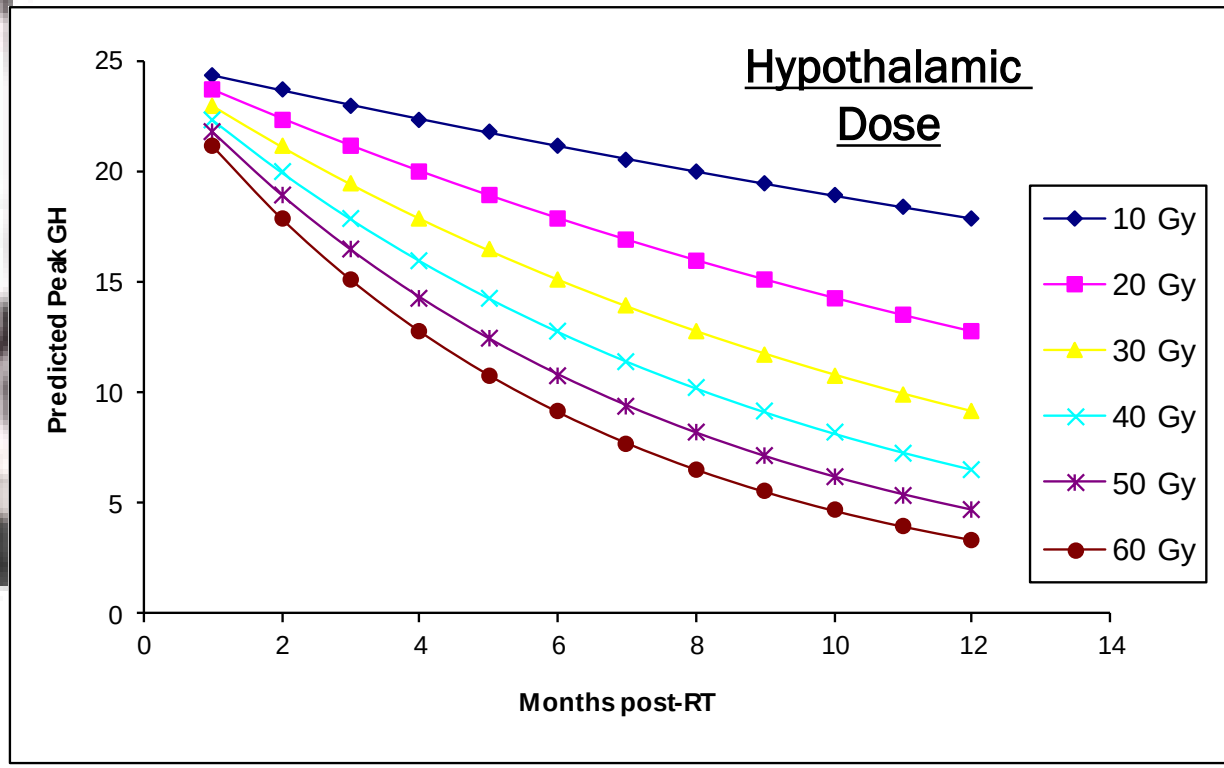


Overall Survival Primary Endpoint

Reducing Endocrine Dysfunction in Children

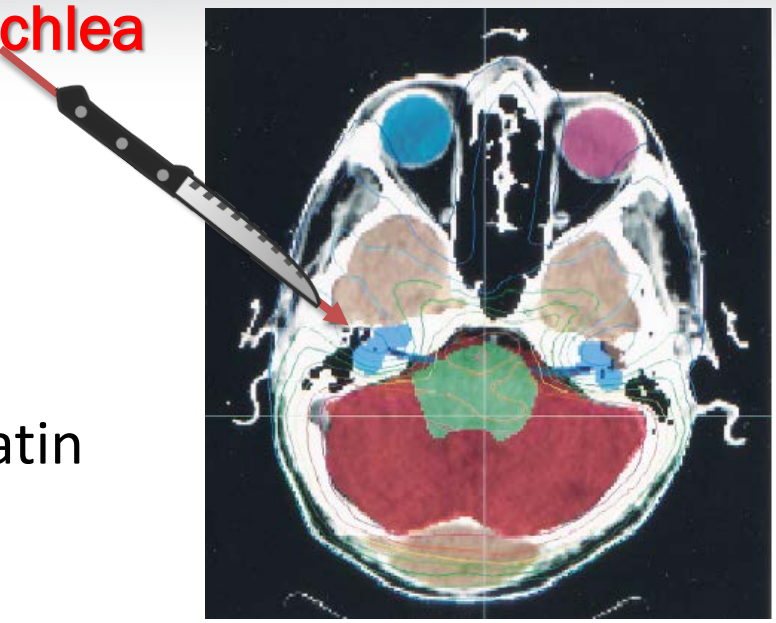
- GH deficiency modeled from data using serial arginine tolerance/L-dopa tests after RT:





Merchant TE et al, *IJROBP* 2006 Zhu Y et al, ASTRO 2003

Preserving Hearing in Children



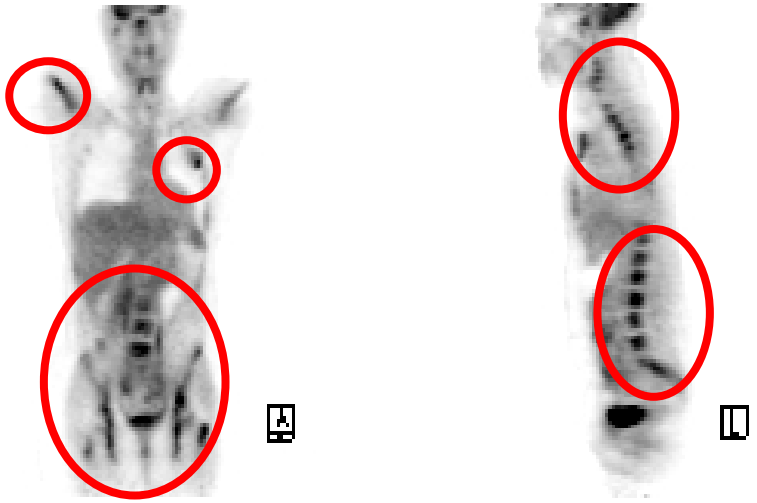
- 26 children with medulloblastoma
  - 15 IMRT versus 11 conventional RT
- Craniospinal RT and concomitant cisplatin
- IMRT planning significantly reduced the dose to the auditory apparatus (36 vs 54 Gy)
- IMRT was associated with significantly less severe hearing loss (13% vs 64%, $p < 0.01$)

Woo *et al.* (Baylor) *Int J Radiat Oncol* (2002)

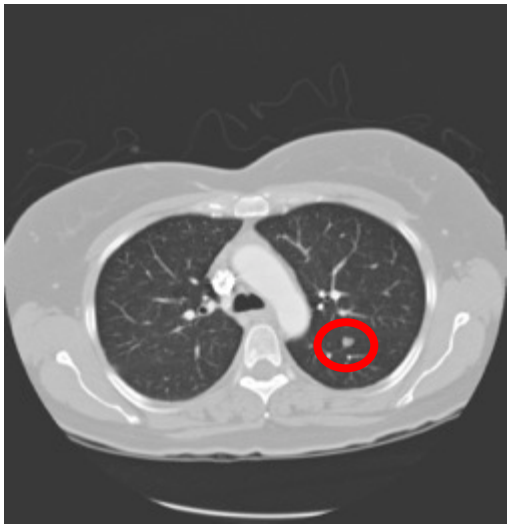
Can a sharper knife alter the natural history of cancer?

Oligometastatic breast cancer

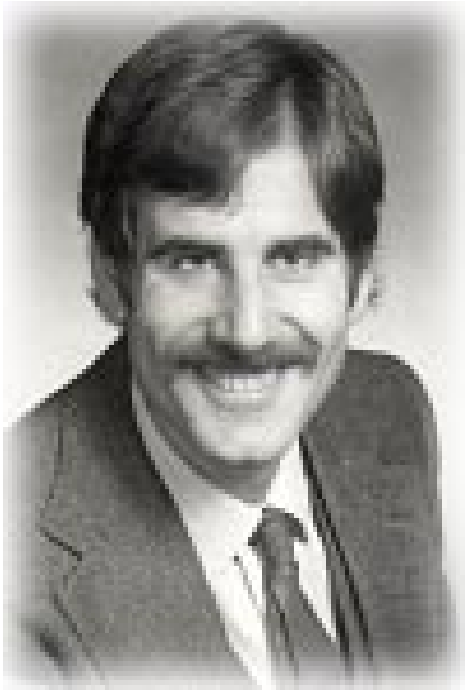
Widely Metastatic Disease



Limited Metastatic Disease



Oligometastases



Hellman and Weichselbaum, J Clin Oncol 13:8 (1995)

Pulmonary Metastasectomy

Number of Mets	Median Survival	5 yr OS	10 yr OS
One	43 months	43%	31%
2-3	31 months	34%	24%
>=4	27 months	27%	19%
>= 10	26 months	26%	17%

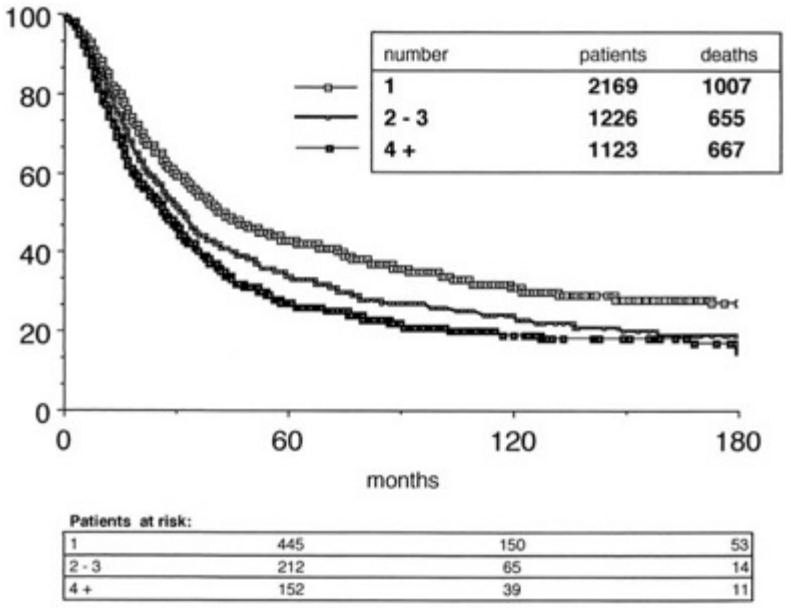
Survival after 2nd metastasectomy

- •5 yr: 44%
- •10 yr: 29%

•Survival with extrapulmonary resection:

- •5 yr: 29%
- •10 yr: 21%

Survival following complete resection:
N=4572



Int Registry of Lung Metastases J Thor Card Surg (1997) 113:37)

Hepatic Metastasectomy

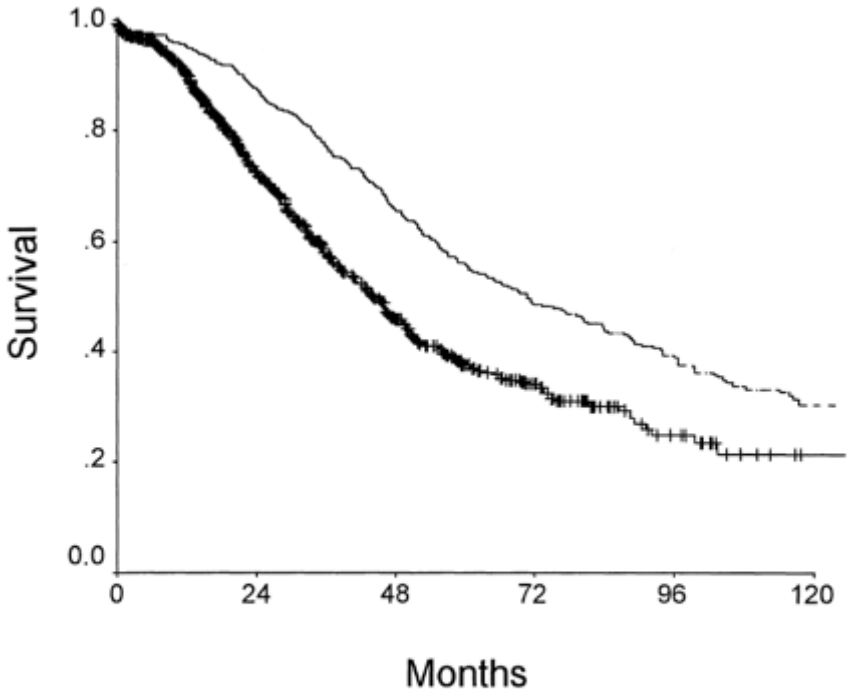
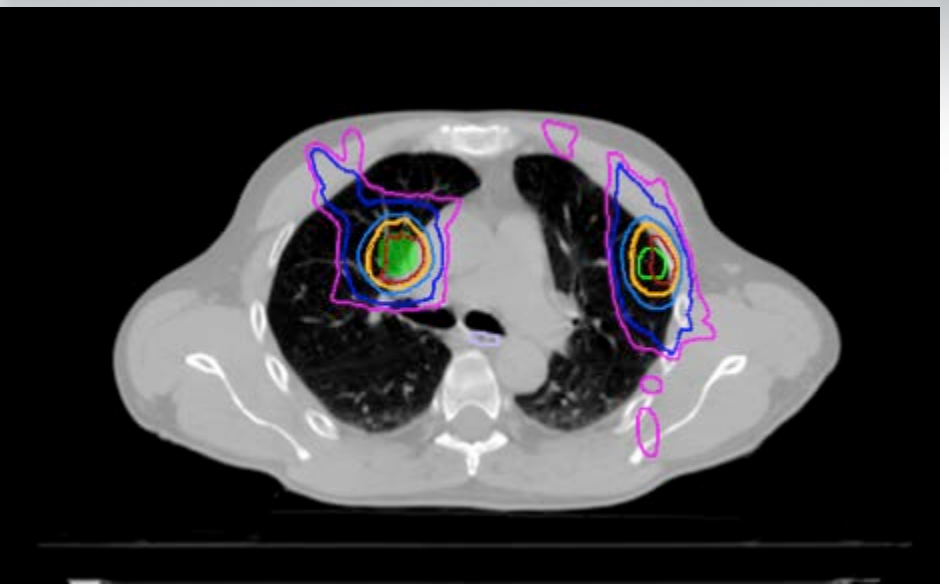
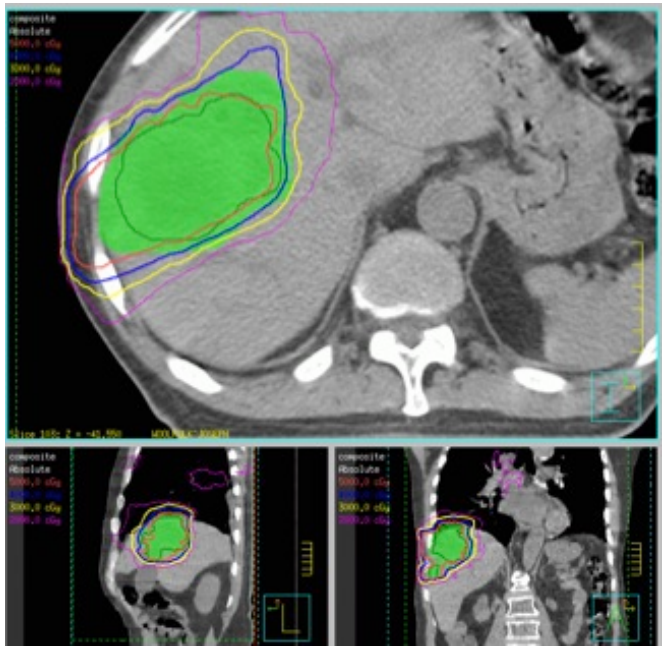


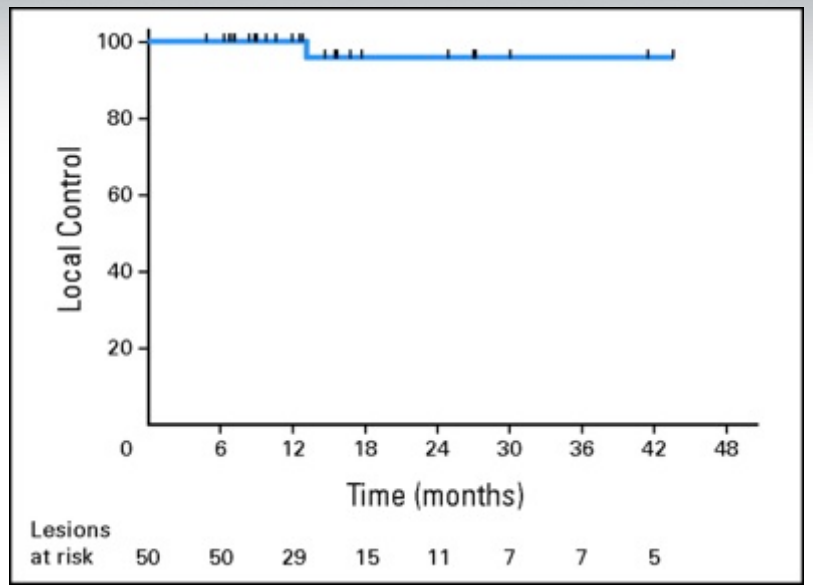
Figure 2. Survival after treatment for metastatic colorectal cancer to the liver. Bottom curve depicts survival as calculated from the time of liver resection. Top curve represents survival calculated from the time of resection of the primary colorectal cancer.

- 1001 consecutive patients
- 1985-1998
- Median # mets: 2 (1-20)
- Median size: 4.2 cm
- Extent of resection: 63% lobe or greater
- Mortality:
  - 2.8% within 30 days
  - 4.1 % if lobectomy or greater

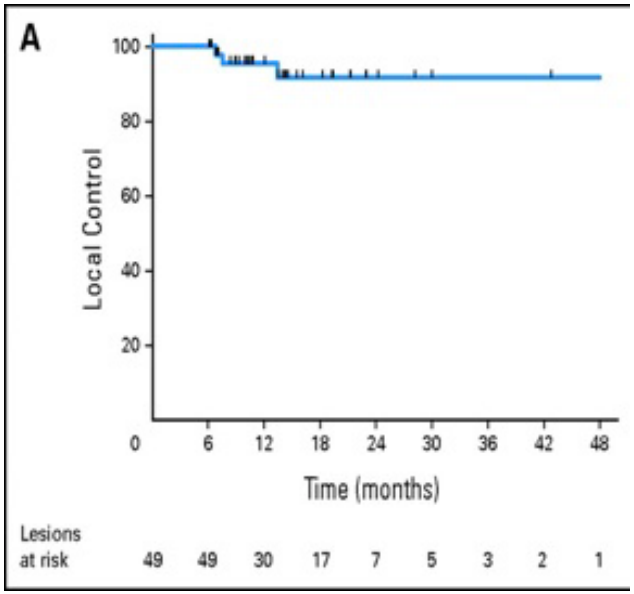
ANNALS OF SURGERY
Vol. 230, No. 3, 309–321





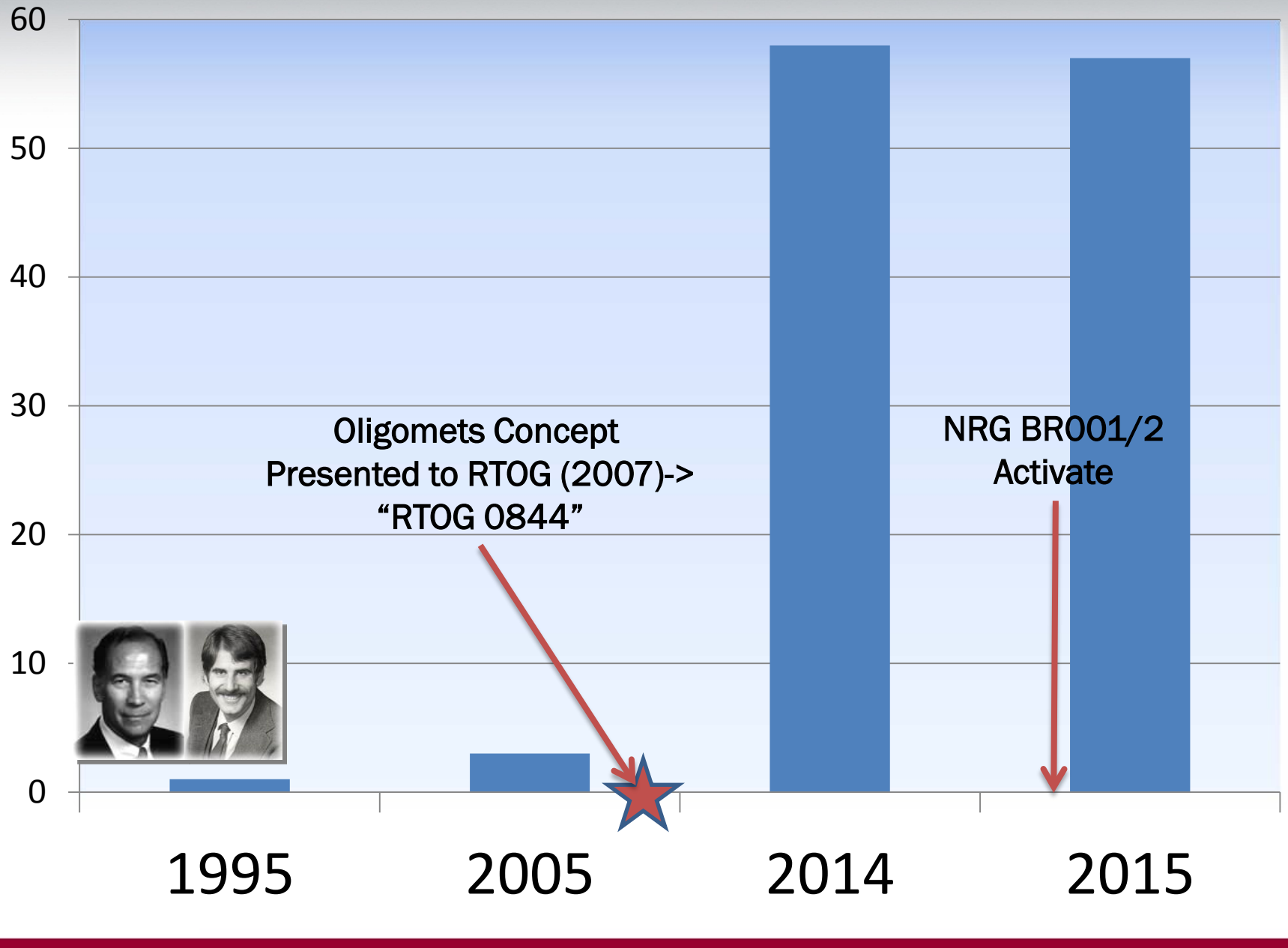


Rusthoven K E et al. JCO 2009;27:1579-1584



Rusthoven K E et al. JCO 2009;27:1572-1578

Pubmed Results: Interest in Oligomets over time



Definitive Stereotactic Body Radiotherapy (SBRT) for Extracranial Oligometastases

An International Survey of >1000 Radiation Oncologists

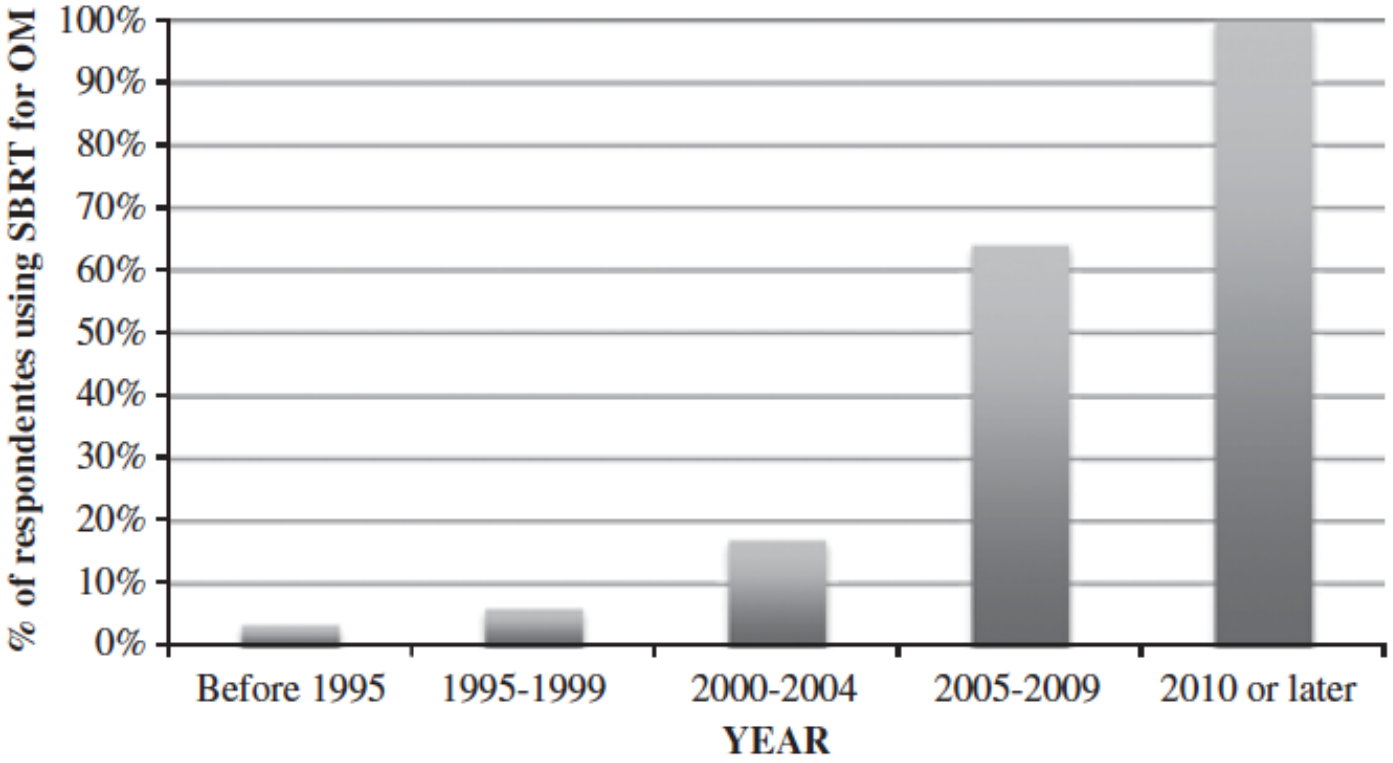


FIGURE 1. Cumulative percentage of respondents using stereotactic body radiotherapy (SBRT) for oligometastases during the defined time intervals.

Lewis et al. Am J Clin Oncol. 2015 Feb 2.

OLIGOMETASTATIC BREAST CANCER

Controlled Locoregional Disease and ≤ 2 Metastases
≤ 6 months systemic therapy without progression

NRG BR002

STRATIFICATION

1 v >1 metastasis
Hormone receptor status
Her 2 neu status
Chemotherapy for MBC (yes or no)

RANDOMIZATION

ARM 1

Standard *systemic* therapy

Symptom directed palliative therapy as needed

ARM 2

Total ablation of all metastases

Standard systemic therapy

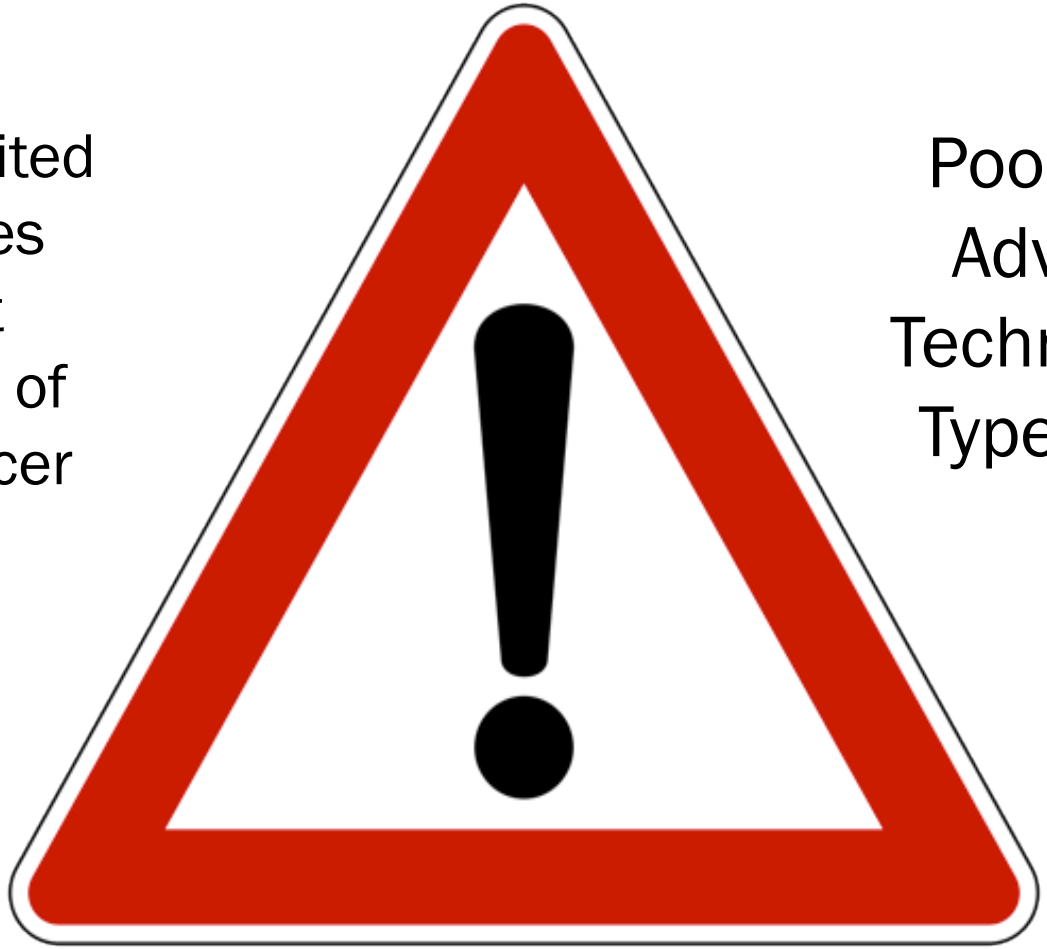
Anticipated Outcomes

- If Ablative Therapy of all Metastases ***improves OS*** when added to standard systemic therapy, then the **paradigm shifts** to multidisciplinary treatment

- If Ablative Therapy of all Metastases ***does not improve OS*** when added to standard systemic therapy, then ***off-protocol use of SBRT stops***
  - Cost reduction and toxicity avoidance

NRG BR002: If “No Benefit” to SBRT of Metastases

Ablating limited metastases does not change OS of breast cancer patients



Poor use of Advanced Technology -> Type 1 error

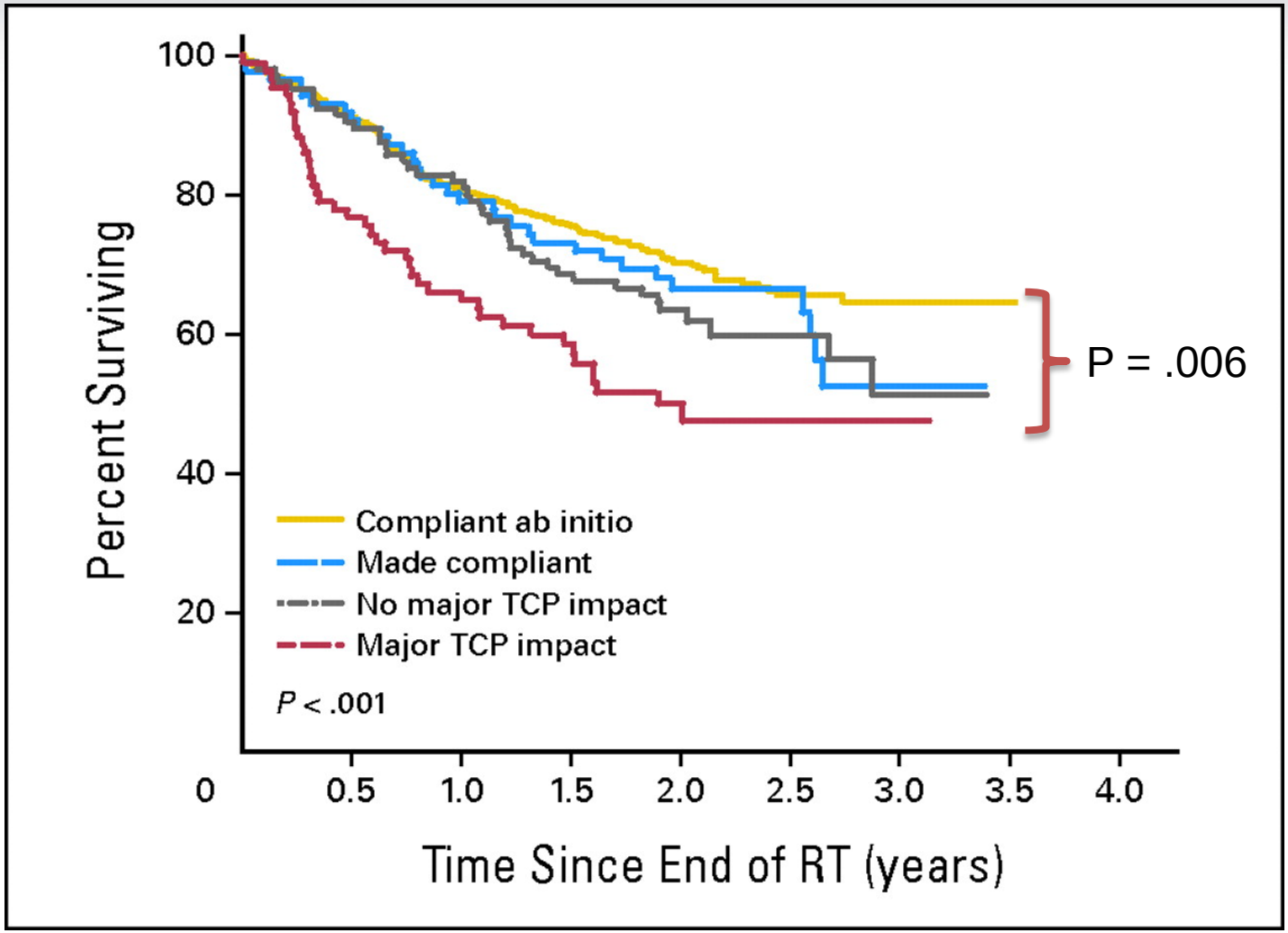
What do we want to conclude from trials of Advanced Technologies?

- Is Technology X rigorous enough to demonstrate a real world impact on the biology of disease today?

- Does the technology and its intended application alter the natural history of Cancer X?


thank you
danke
謝謝
gracias
merci
obrigado
dziękuję
bedankt
go raibh maith agat
teşekkür ederim
ngiyabonga
спасибо
рахмат
Баярлалаа
dank je
tapadh leat
mochchakkeram
sukriya
kop khun krap
terima kasih
arigatô
dakujem
grazie
sagolun
hvala
mauruuru
dhanyavadagalu
ευχαριστώ
감사합니다
তোমাকে ধন্যবাদ
merci
мерси

TROG 02.02 Phase III: Radiotherapy with concurrent cisplatin plus tirapazamine for advanced head and neck cancer



Overall survival by deviation status: (1) compliant from the outset (n = 502), (2) made compliant following a review by the Quality Assurance Review Center (n = 86), (3) noncompliant but without predicted major adverse impact on tumor control (n = 105), and...

Lester J. Peters et al. JCO 2010;28:2996-3001