

# Radiation Oncology: physics meets biology

Gillies McKenna

Physics for Health in Europe

CERN 2010



MRC

Medical  
Research  
Council

CANCER RESEARCH UK

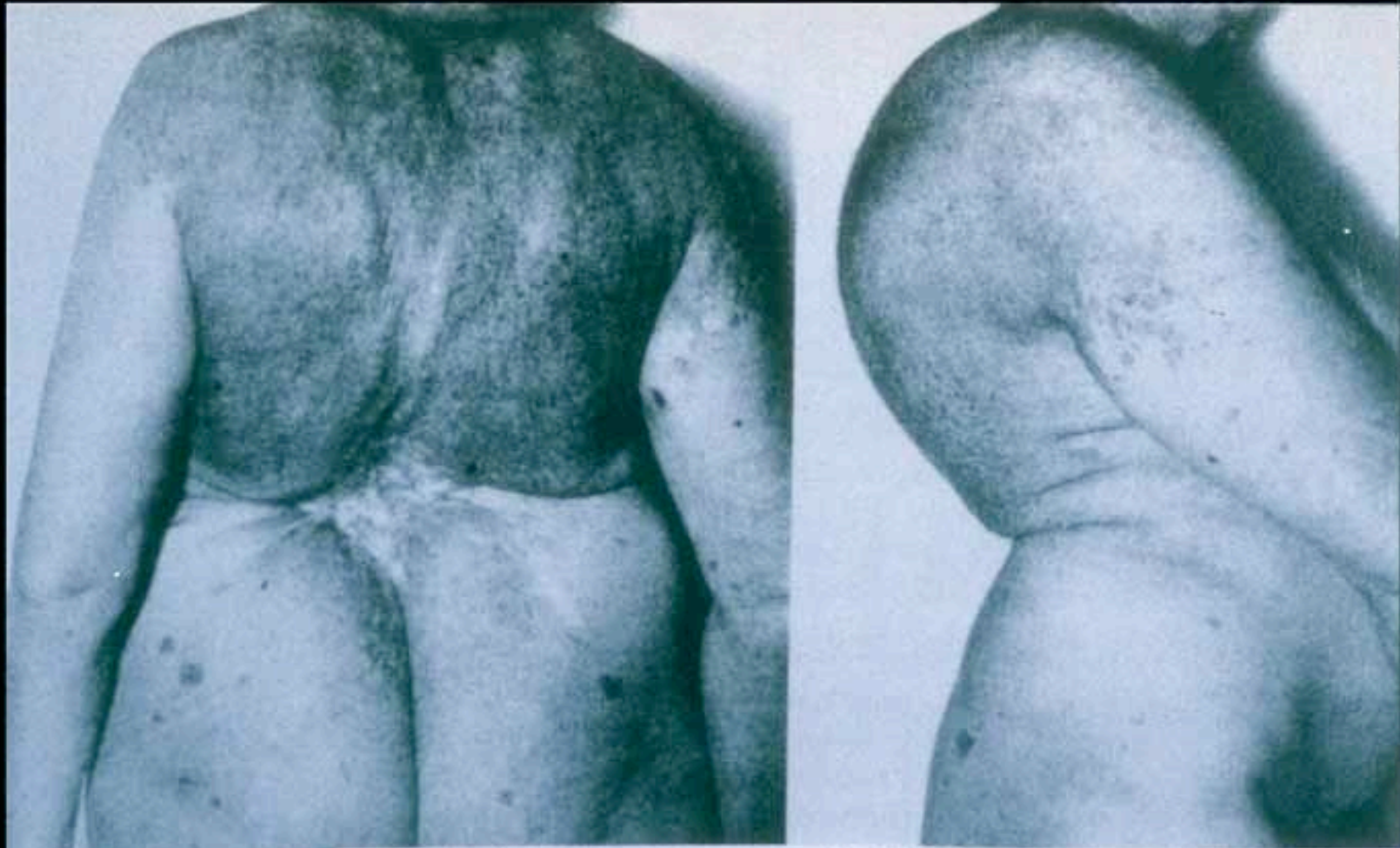




## Roentgen December 1895



## Radiation Therapy March 1896



1896 patient, Vienna: 70 years later

# Capabilities of Radiotherapy

- Small tumours where resection could be associated significant morbidity
  - Prostate
  - Vocal Cord
- Microscopic residual disease before or after surgical resection
  - Breast
  - Rectum
  - Head and Neck
  - Soft Tissue Sarcoma

# Limitations of Radiotherapy

- Prescribed dose is severely limited by adjacent normal tissues
  - Skin
  - Lung
  - Brain
  - Spinal cord
  - Bowel
- Effectiveness rapidly decreases with increasing tumour size

# Limitations of Radiotherapy

- Prescribed dose is severely limited by adjacent normal tissues

## Physics

- Brain
- Spinal cord
- Bowel

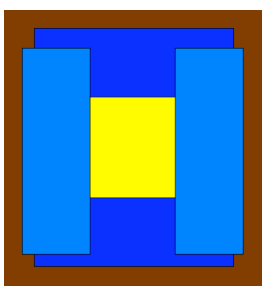
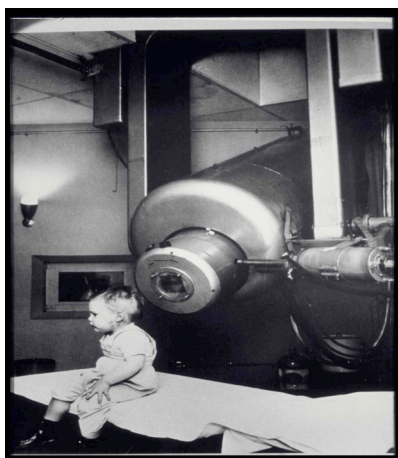
- Effectiveness is limited by the biological response to the dose
- Increasing the dose beyond a certain point does not increase the effectiveness of the treatment

## Biology or Physics?

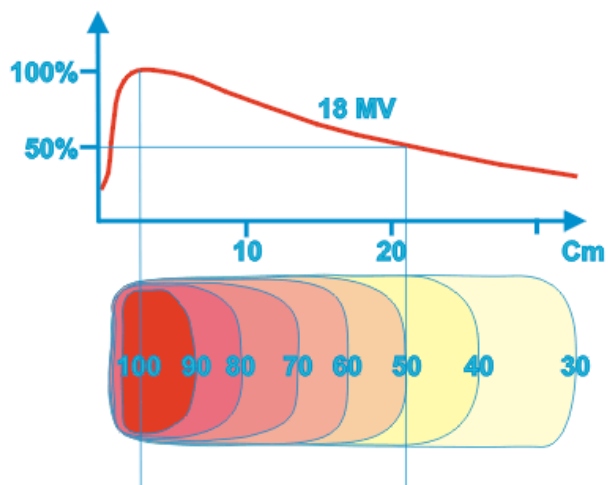
# The Evolution of Radiation Therapy

1960's

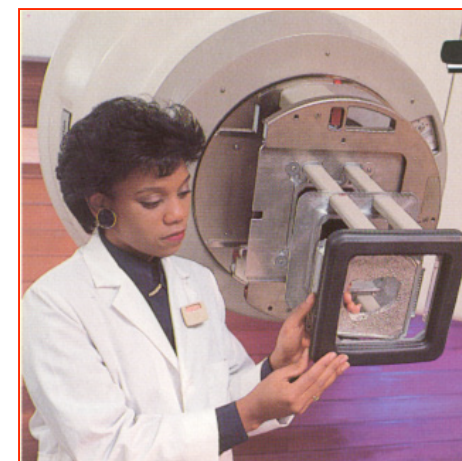
The First Clinac



Standard Collimator

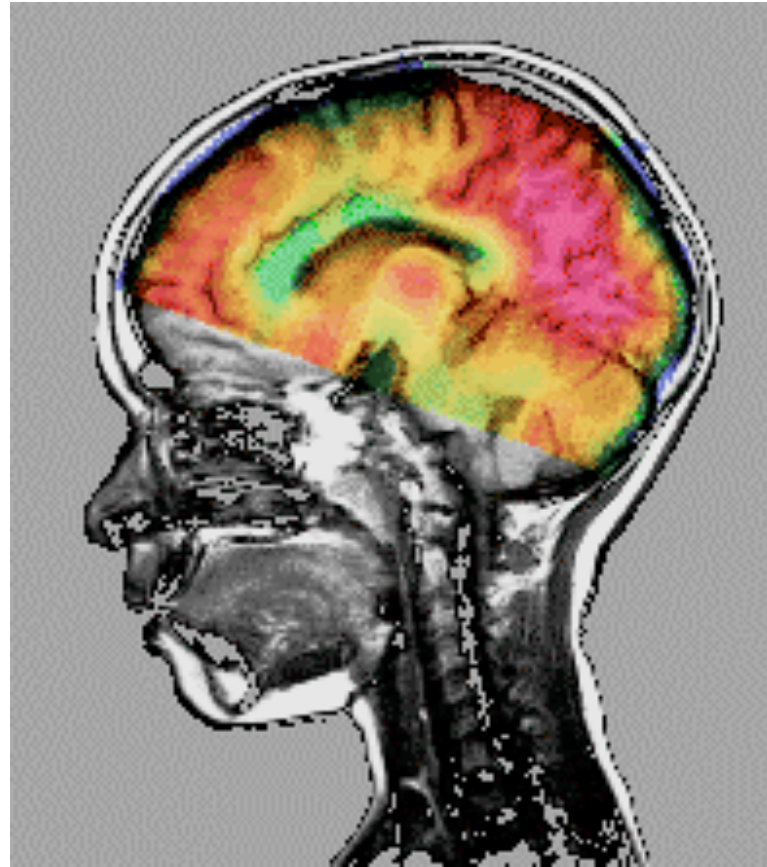


1970's



Cerrobend Blocks  
Electron Blocks

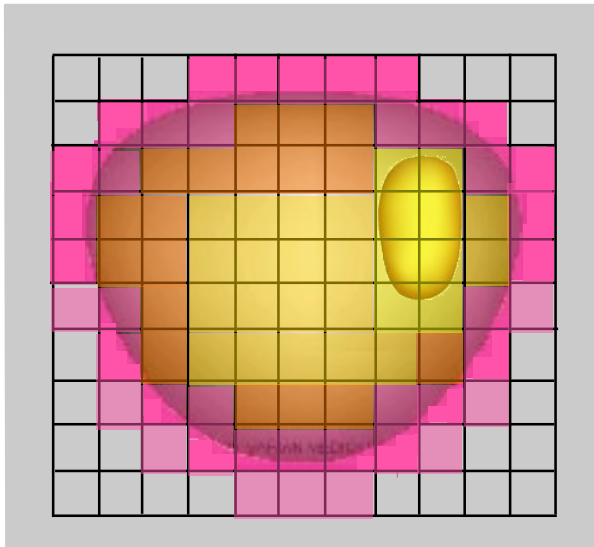
## Combining Image Data Sets



Pelizzari et al., Accurate three-dimensional registration of CT, PET and/or MR images of the brain. *J. Comput Assist Tomograph.* 13: 20. , 1989



# Intensity Modulated Radiation Therapy (IMRT) - mid 1990s

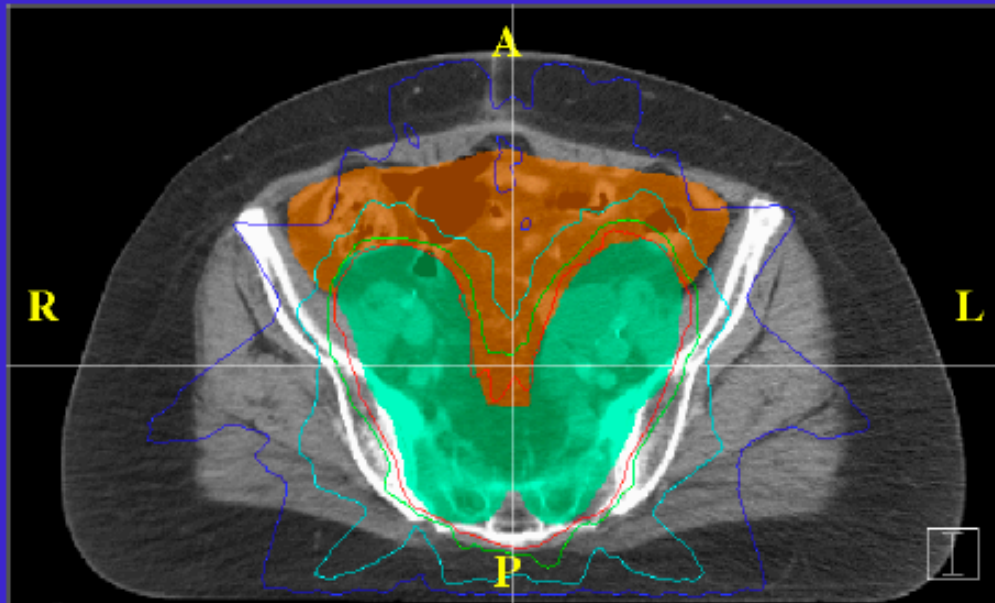


## The Evolution of Radiotherapy

- ◆ Divides each treatment field into multiple segments (up to 500/angle)
- ◆ Allows dose escalation to most aggressive tumor cells; best protection of healthy tissue
- ◆ Modulates radiation intensity; gives distinct dose to each segment
- ◆ Uses 9+ beam angles, thousands of segments
- ◆ Improves precision/accuracy
- ◆ Requires inverse treatment planning software to calculate dose distribution

# Intensity Modulated Pelvic RT

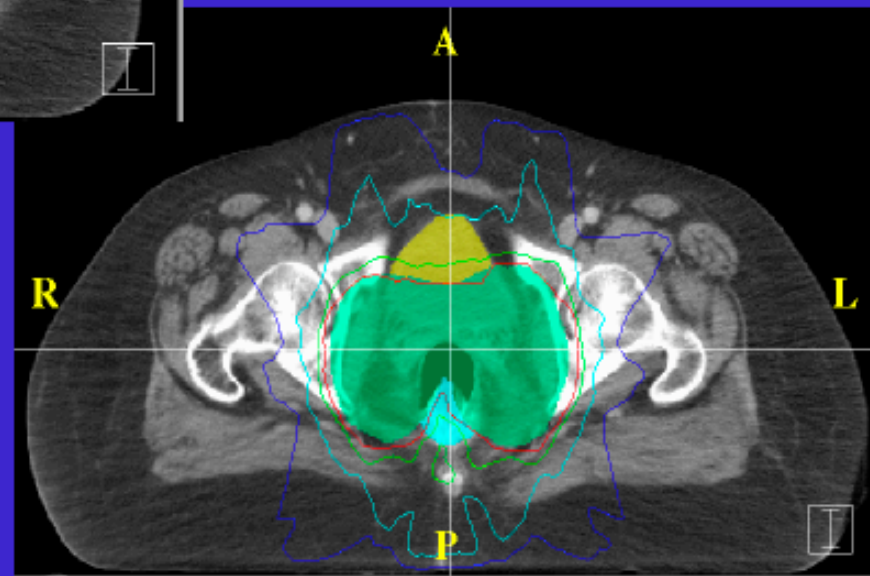
## Benefits



← In the upper pelvis,  
spares the small  
bowel

In the lower pelvis →  
spares the bladder  
and rectum

Roeske et al. (2000)



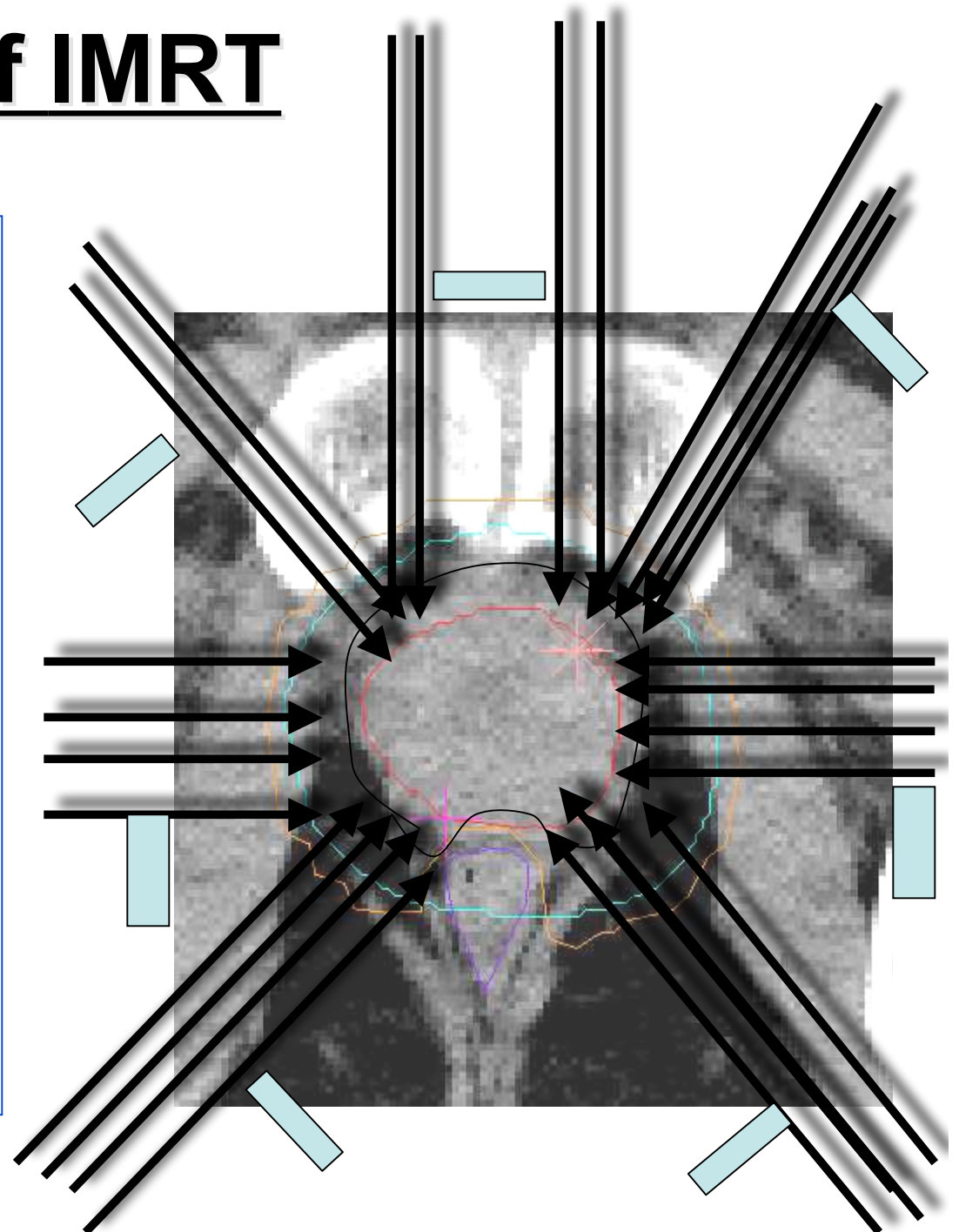
# Prostate Cancer: Improved Outcomes

Dose Level	Advanced Stage 2.5-Year Local Control (Biopsy)	Complication Rate (Grade 2 Bleeding)
68 Gy	43%	>6%
70 Gy	64%	6%
76 Gy	73%	17%
81 Gy – 3D CRT	96%	10%
81 Gy - inverse planned (IMRT)		2%

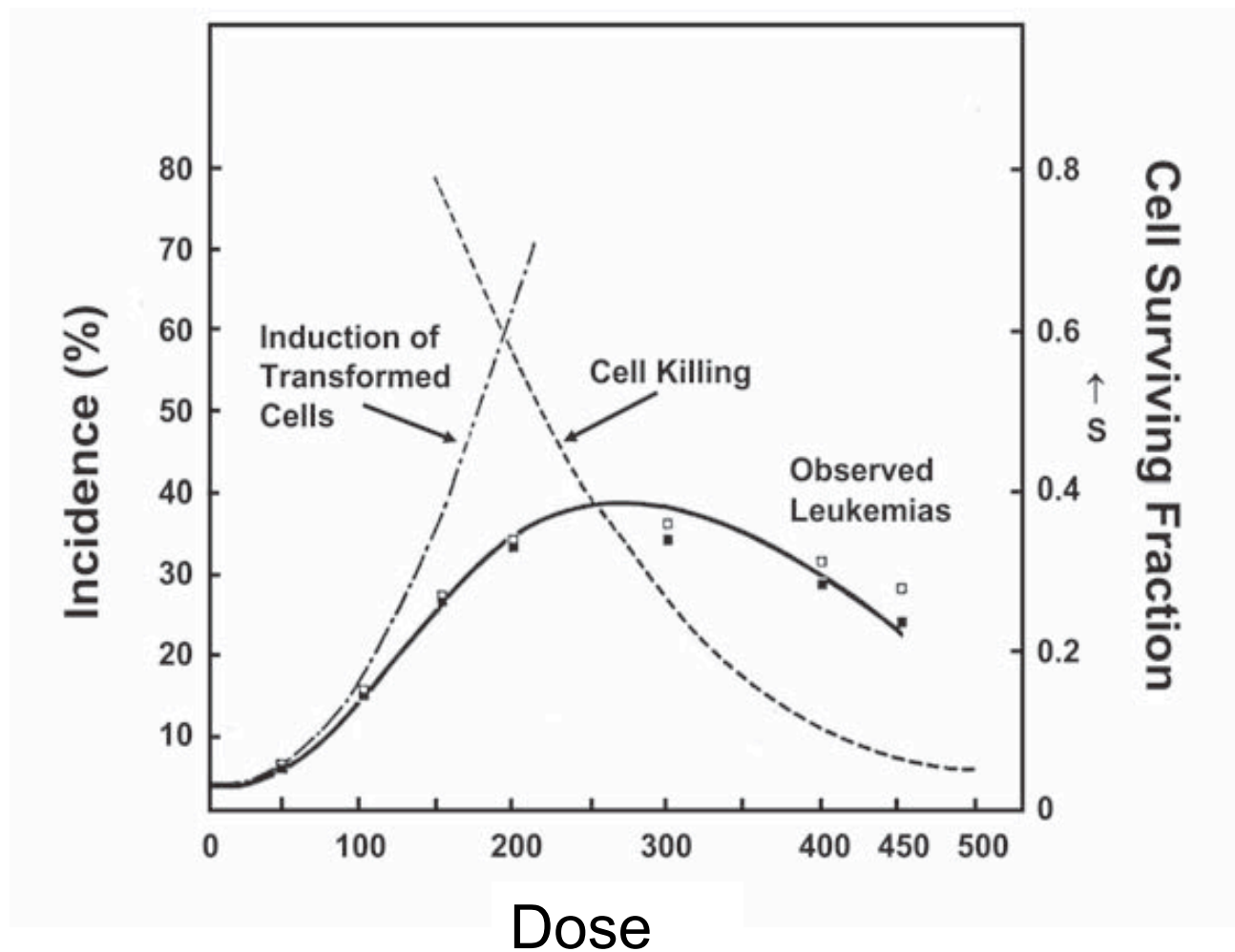
“Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer,” Zelefsky, et. al, *Radiotherapy & Oncology*, June 1, 2000

# The price of IMRT

**With IMRT There Is Spread of Low to Moderate Doses to Many Normal Tissues. Also, the Long Treatment Times Needed for IMRT Increase Total Body Exposure. This Is Critical For Children And Young Adults, But Also Important for Older Patients.**

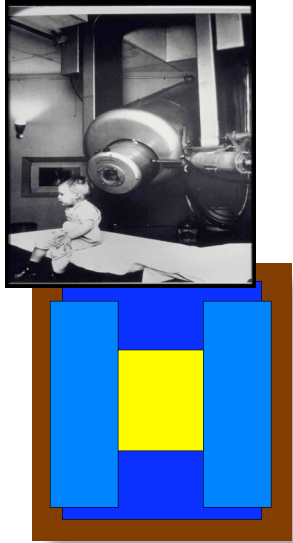


# Gray Model for Second Malignancies



# The Evolution of Radiation Therapy

1960's  
The First Clinac



Standard Collimator

1970's

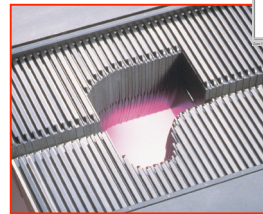


Cerrobend Blocks  
Electron Blocks

1980's Computerized 3D  
CT Treatment  
Planning



Multileaf Collimator

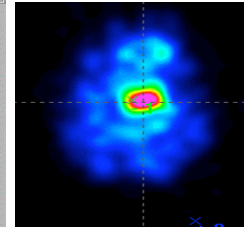


Dynamic MLC  
and IMRT  
High resolution  
IGRT

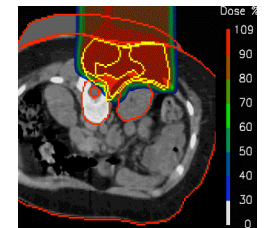
1990's



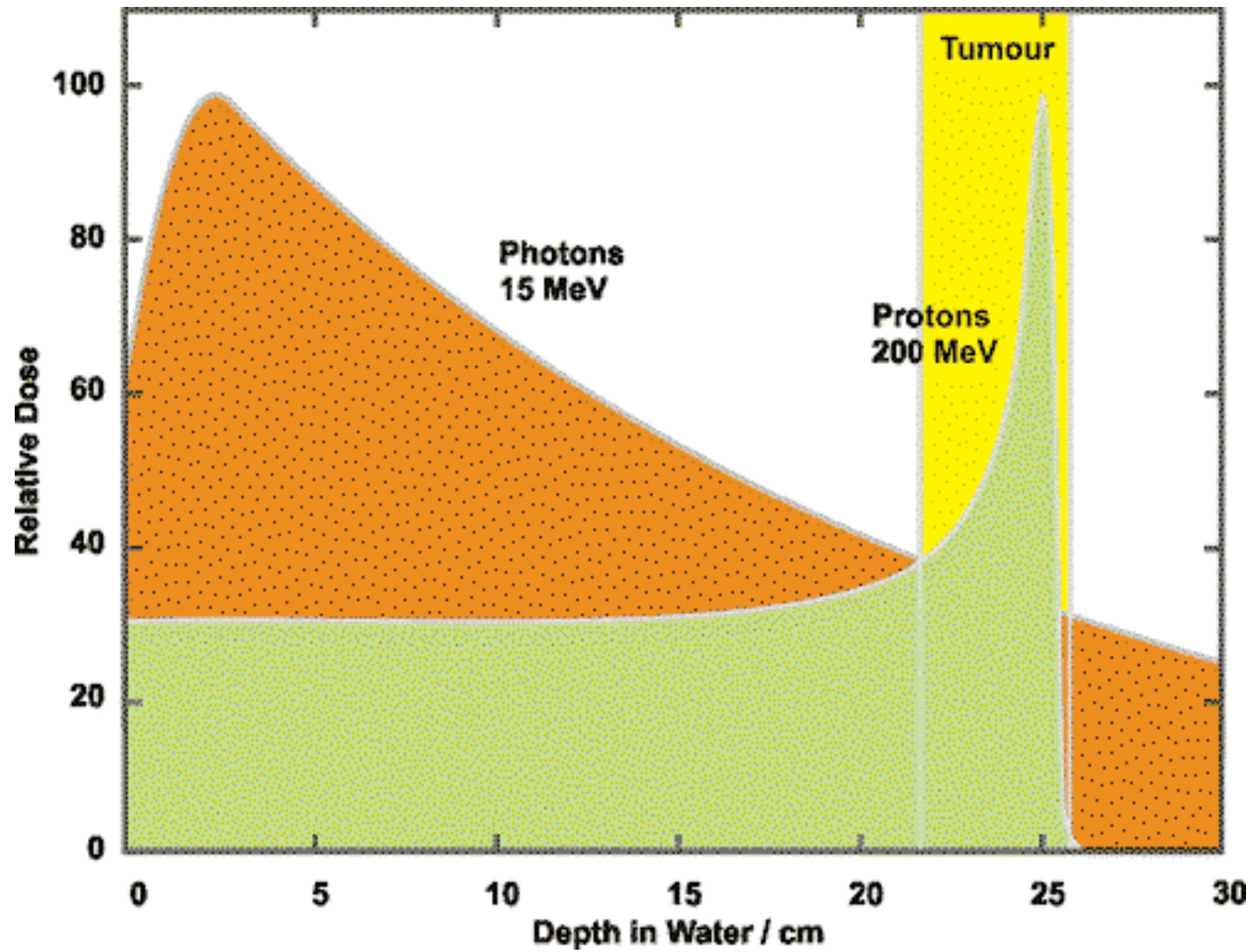
2000's?



Functional  
Imaging

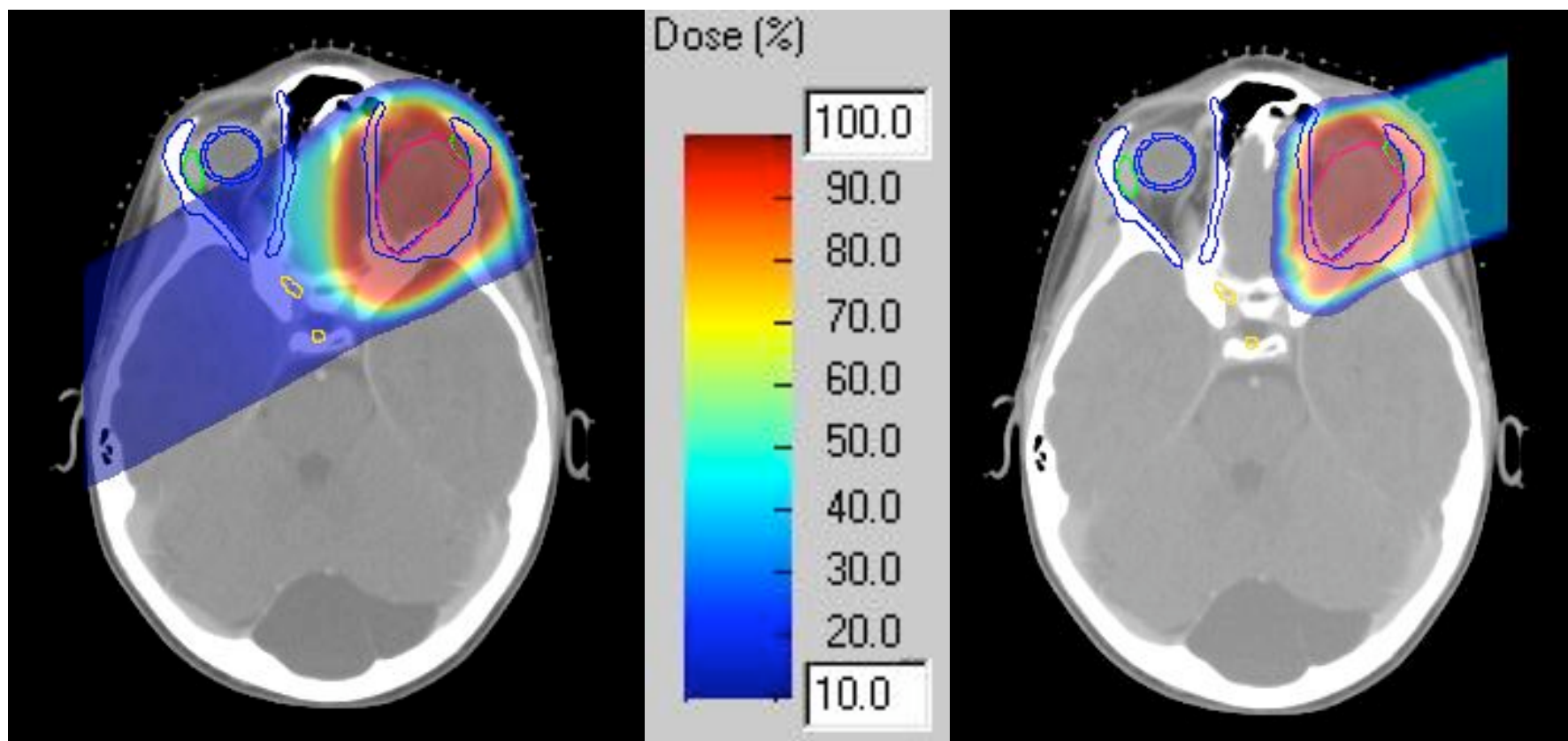


Particle  
Therapy



# X-Rays

# Protons



Yock et al, *IJROBP* 63:1161,2005



## Orbital RMS, pre, during, post



CPC, Friedmann, NEJM, 350:494, 2004

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# Limitations of Radiotherapy

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## Physics

- Brain
- Spinal cord
- Bowel

- Effectiveness is limited by the biological response of the tumor and normal tissues

## Biology or Physics?

# Radiosensitivity

## Intrinsic

Genetic

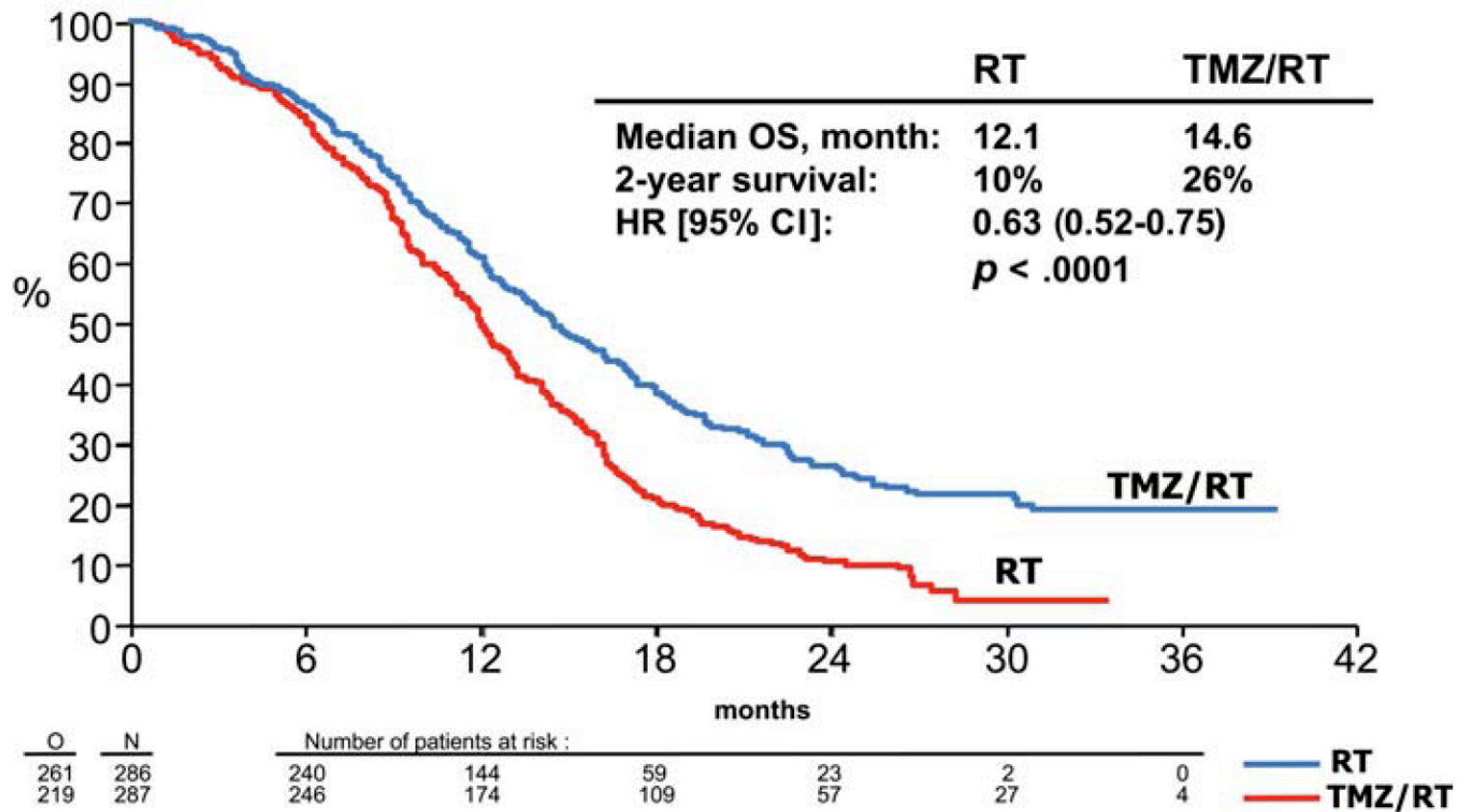
Epigenetic

## Extrinsic

Environmental

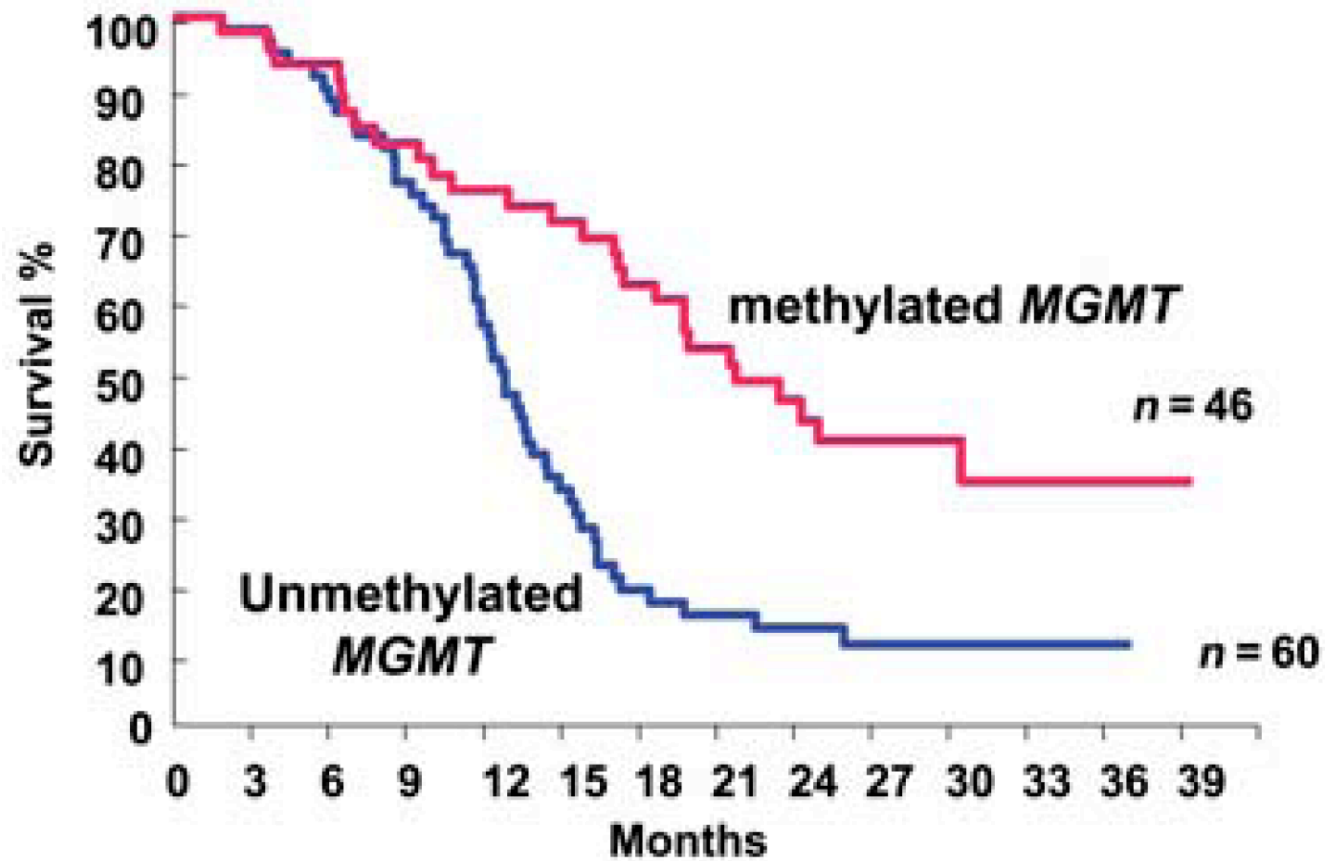
Hypoxia

# Genetics in Glioma



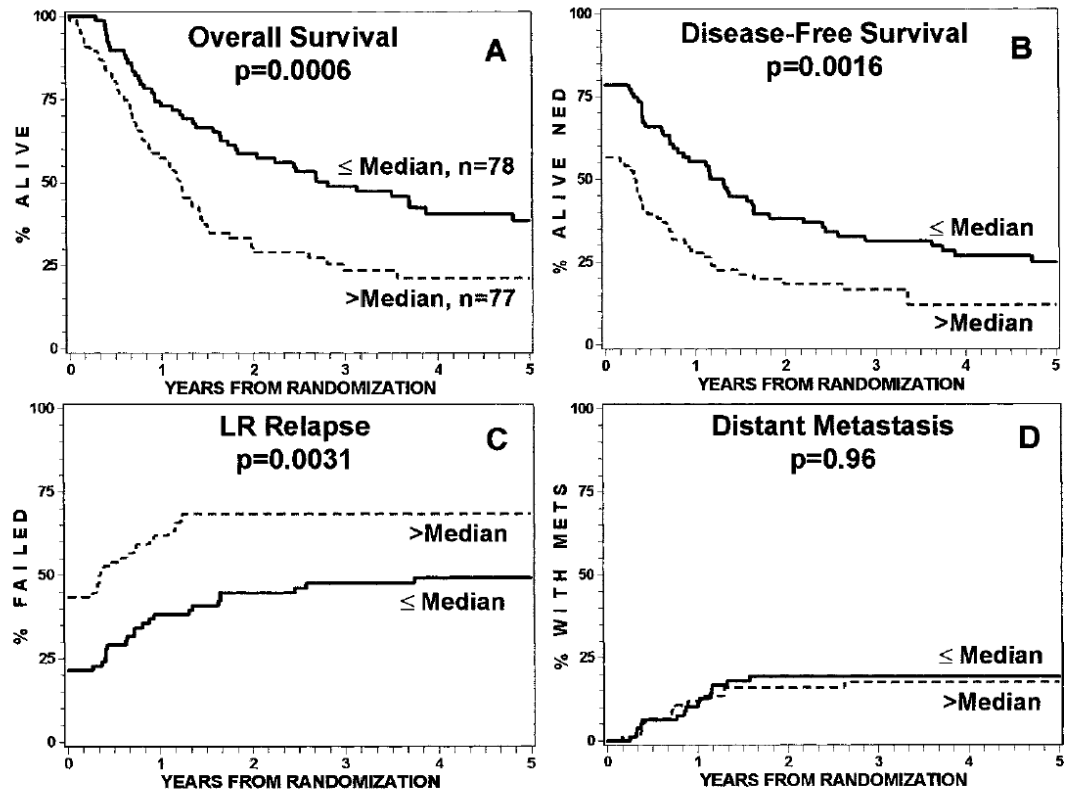
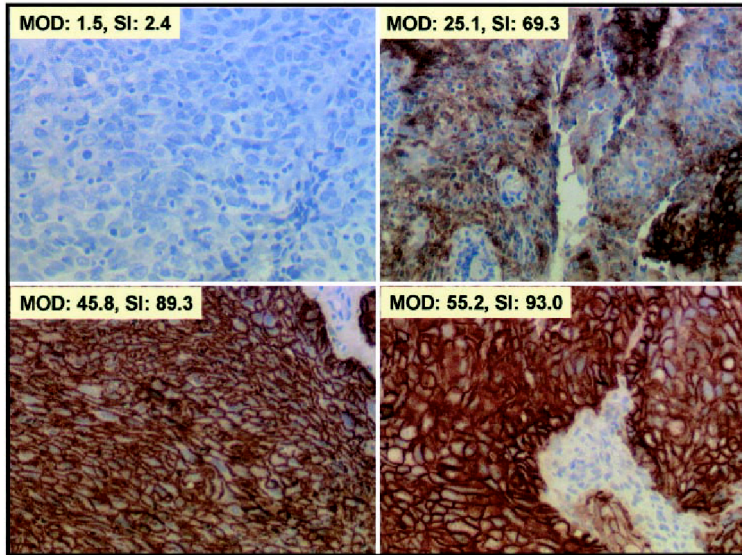
Stupp et al. Oncologist 11, 165 (2006)

# Genetics of Glioma



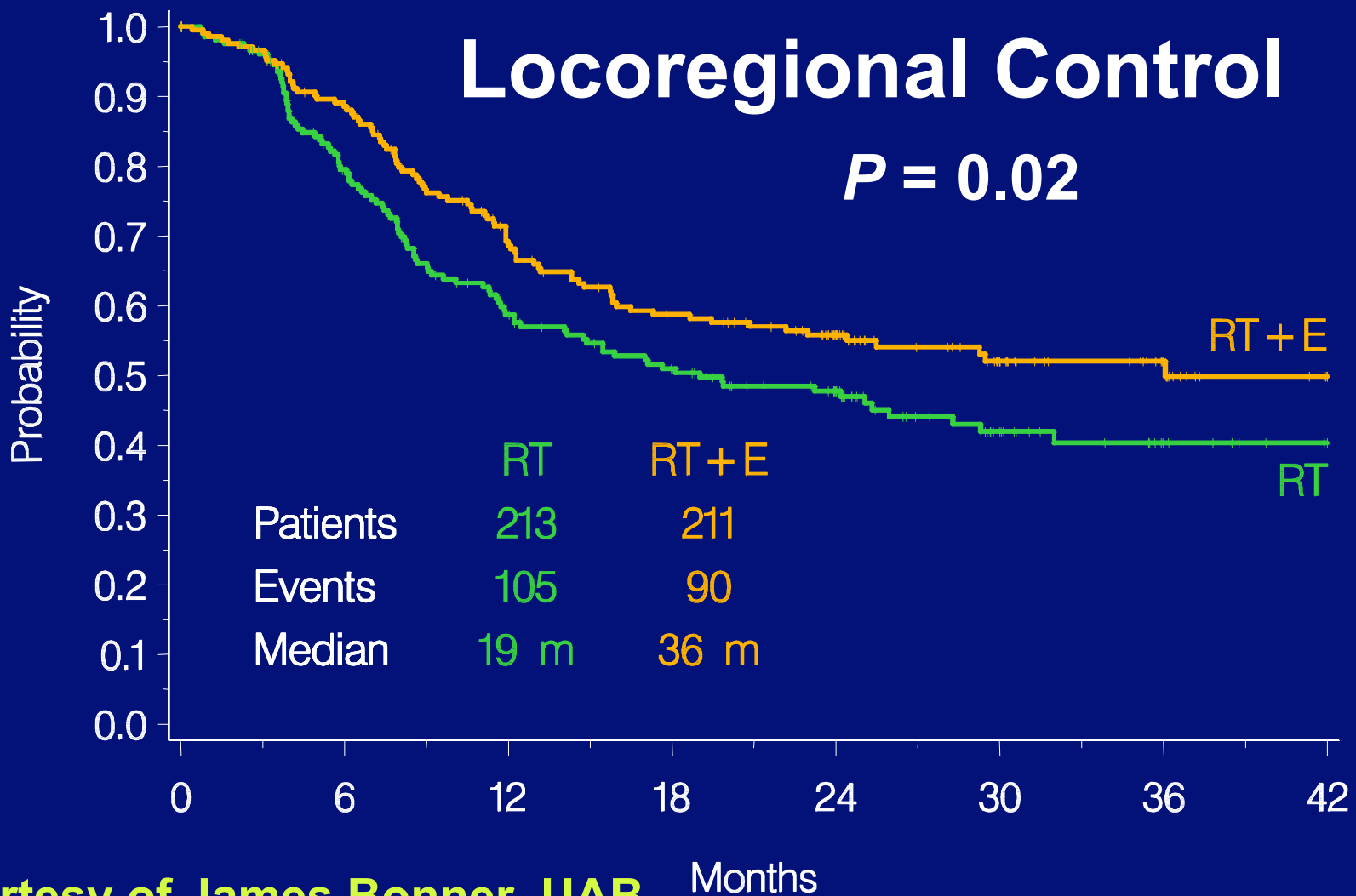
Stupp et al. Oncologist 11, 165 (2006)

# EGFR expression is prognostic for the outcome of RT in H&N SCC



Ang et al., *Cancer Res* 62: 7350-7356, 2002

# Phase III Study of High Dose Radiation Therapy with or without Cetuximab

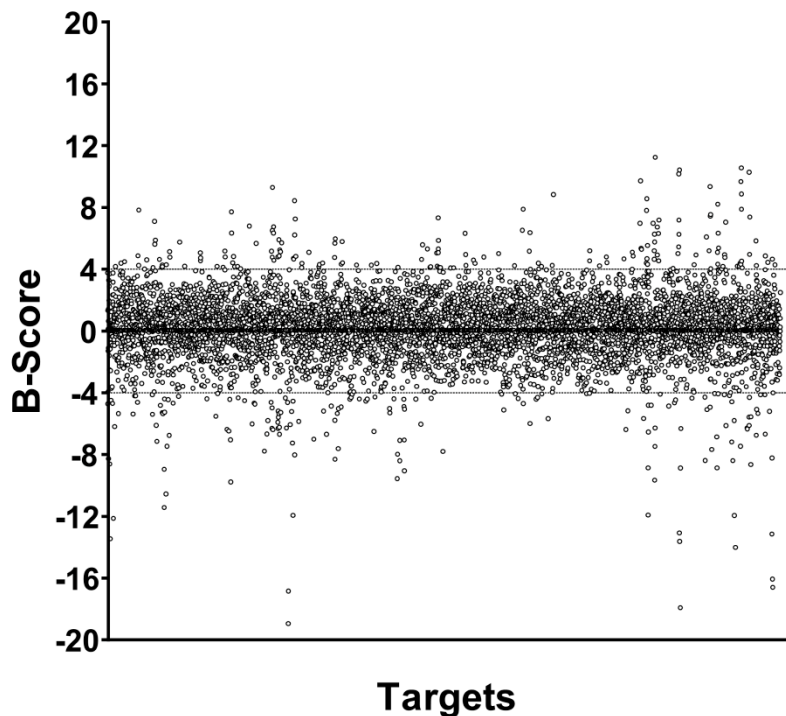


Courtesy of James Bonner, UAB

Months

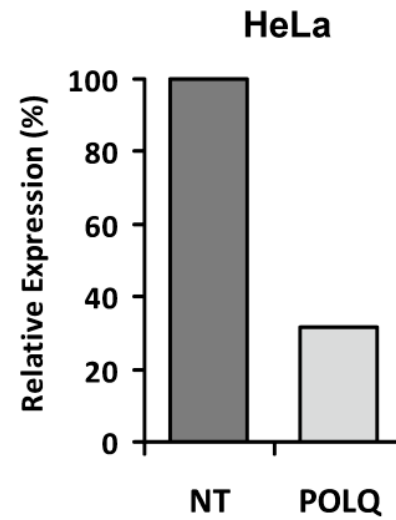
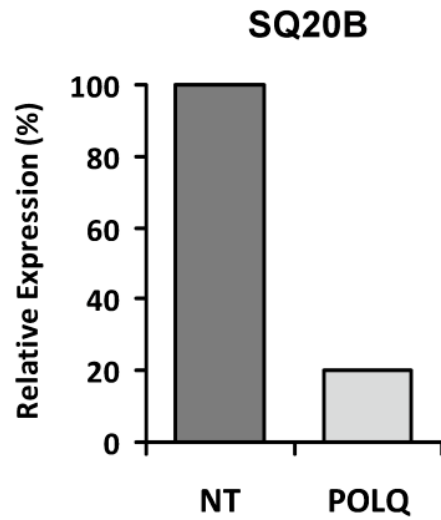
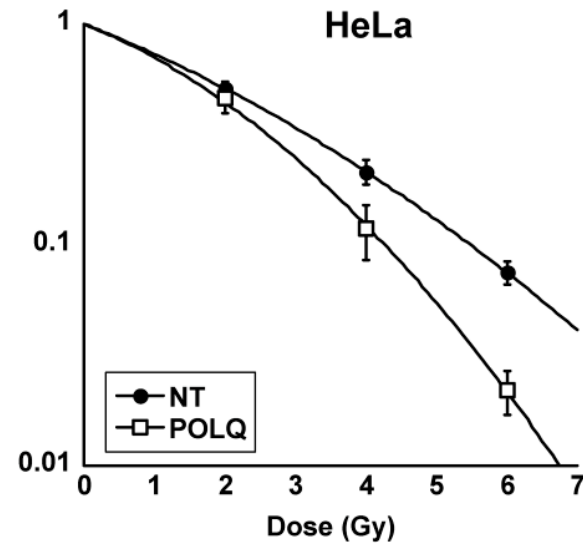
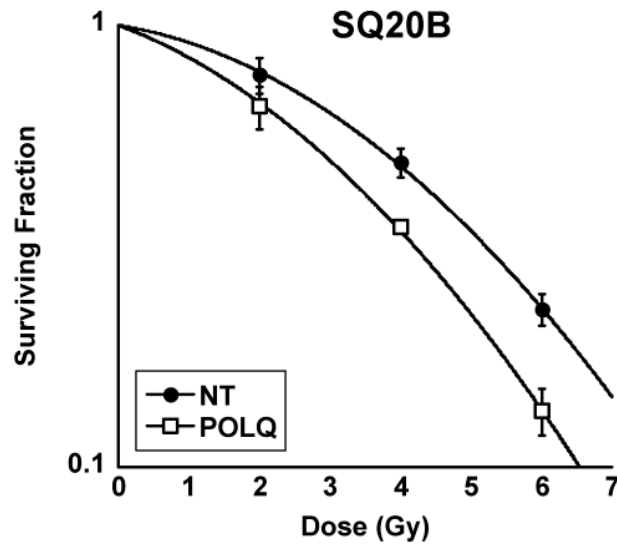


# High-Throughput Screening to detect novel genetic targets

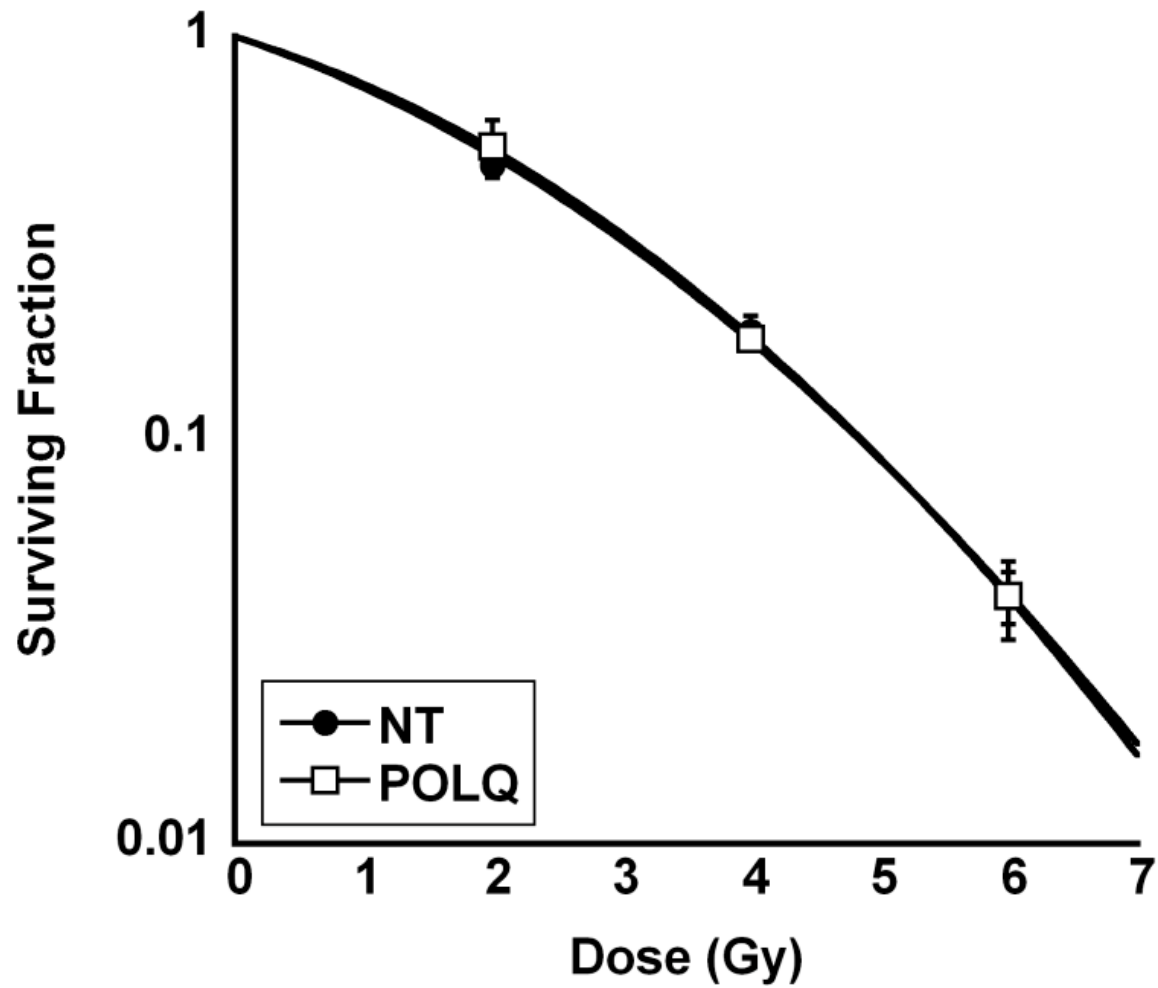


- **Dharmacon human siARRAY siRNA libraries**
  - 4 siRNAs pooled/gene
  - Protein Kinase (800 genes)
  - Druggable Genome (6080 genes)

# PolQ down-regulation in tumor cells



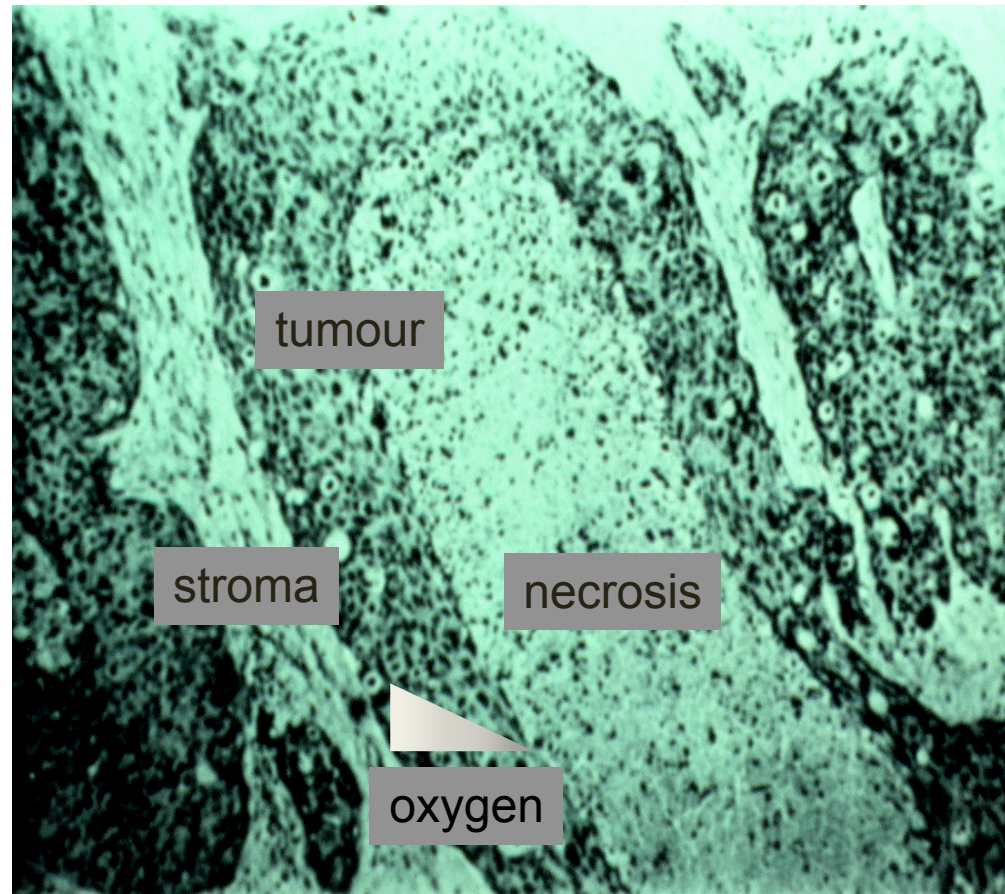
# PolQ in normal cells



# Extrinsic Factors

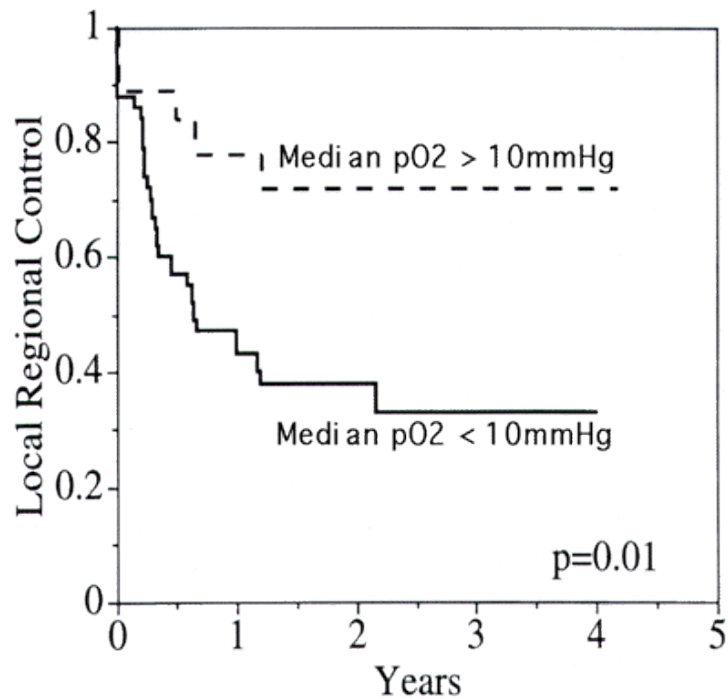
Hypoxia

# Etiology of hypoxic cells in human solid tumours



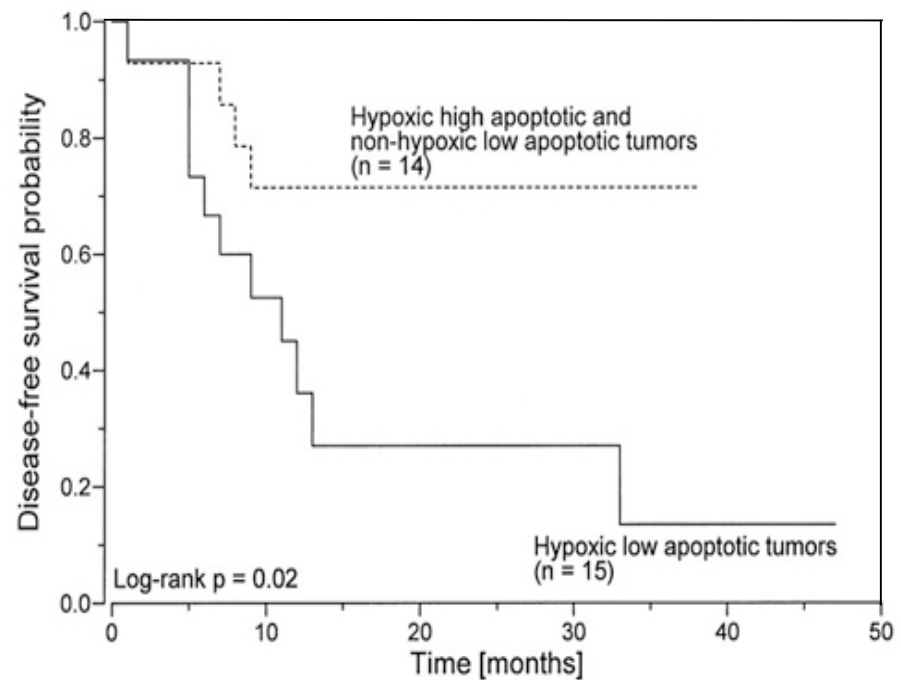
***Gray, Conger, Ebert, Hornsey and Scott, Br. J. Radiology, 1953***  
***Tomlinson and Gray, Br. J. Oncol., 1955***

# Tumour Hypoxia and patient prognosis



Head and neck

*D.M. Brizel et al., Radiother. Oncol., 1999*



Cervical

*Hockel et al., 1999 Cancer Research*

# Tumour Microenvironment

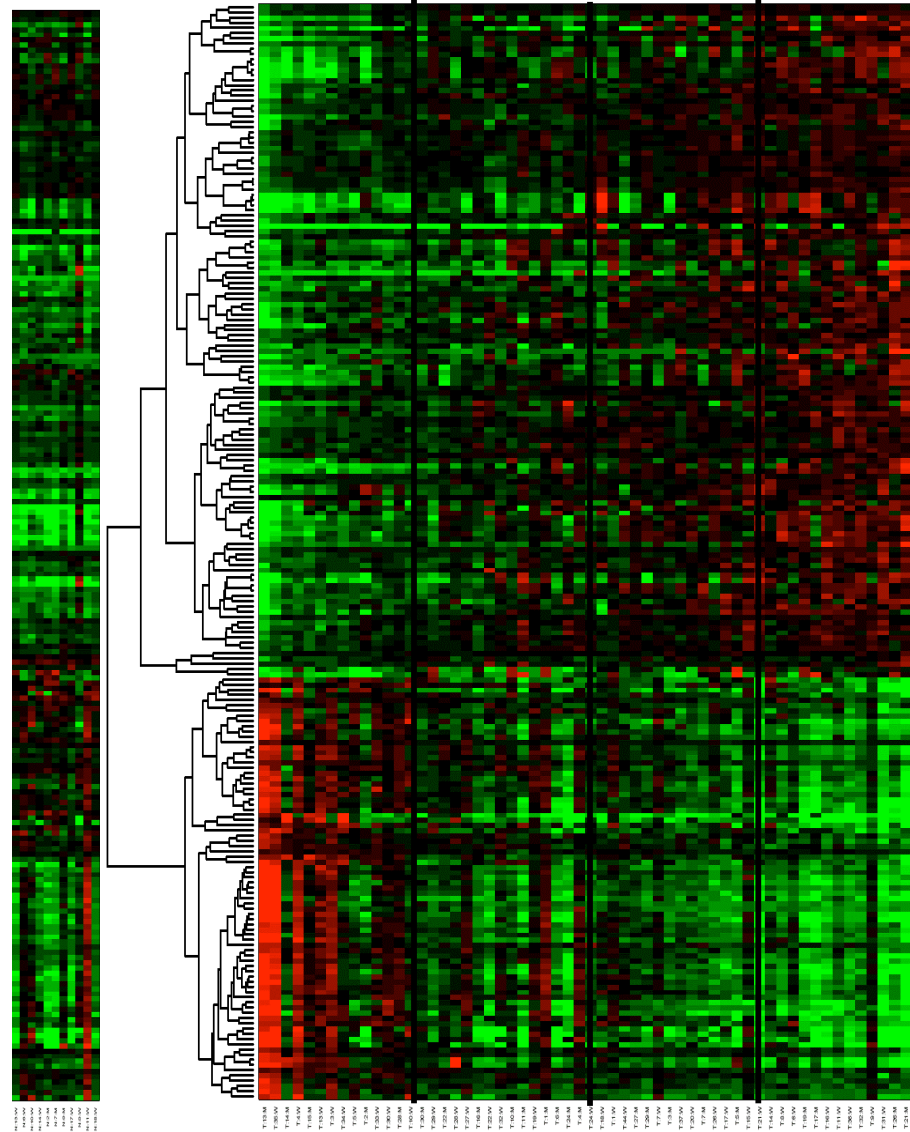
- Hypoxia
  - HIF-1,
    - VEGF, Glut1, etc

# Tumours ranked by H\* D50

median expression of hypoxia  
up-regulated profile

Normal  
Tissue

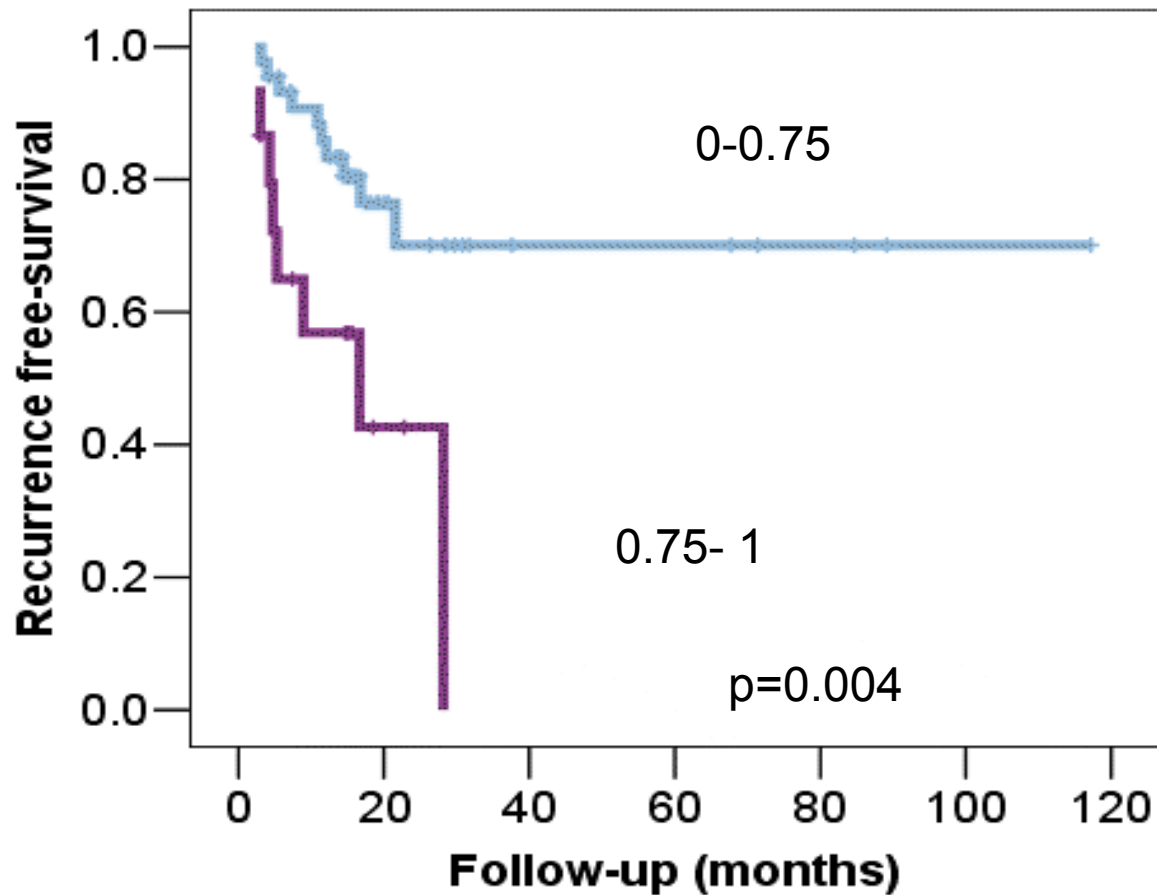
Tumours  
H\* (D>50)



Harris et al. 2007



# Chung et al (2004); RFS by highest 25% Hypoxia score

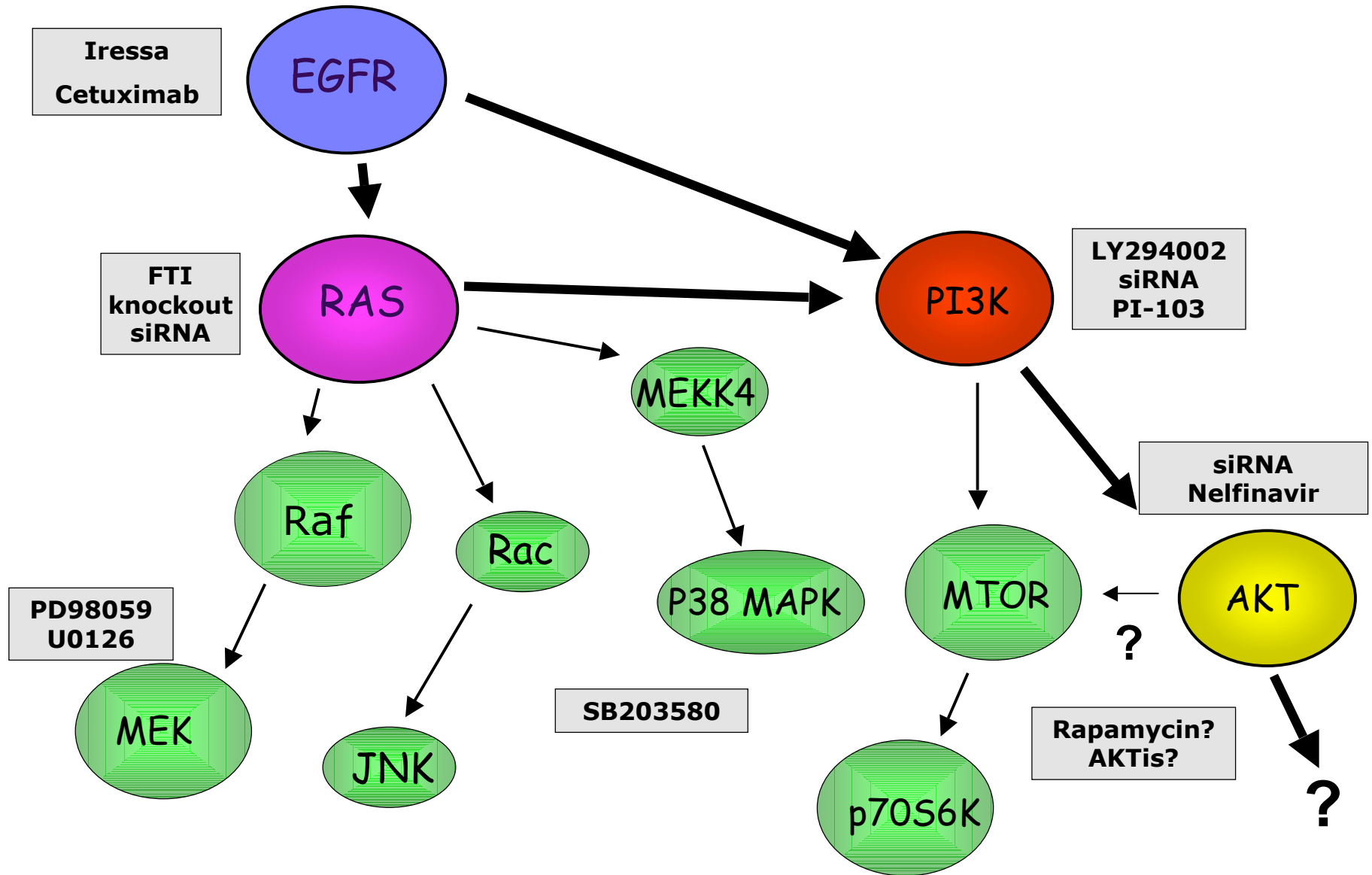


**Chung et al (2004). Molecular classification of head and neck squamous cell carcinomas using patterns of gene expression. Cancer Cell 5, 489-500.**

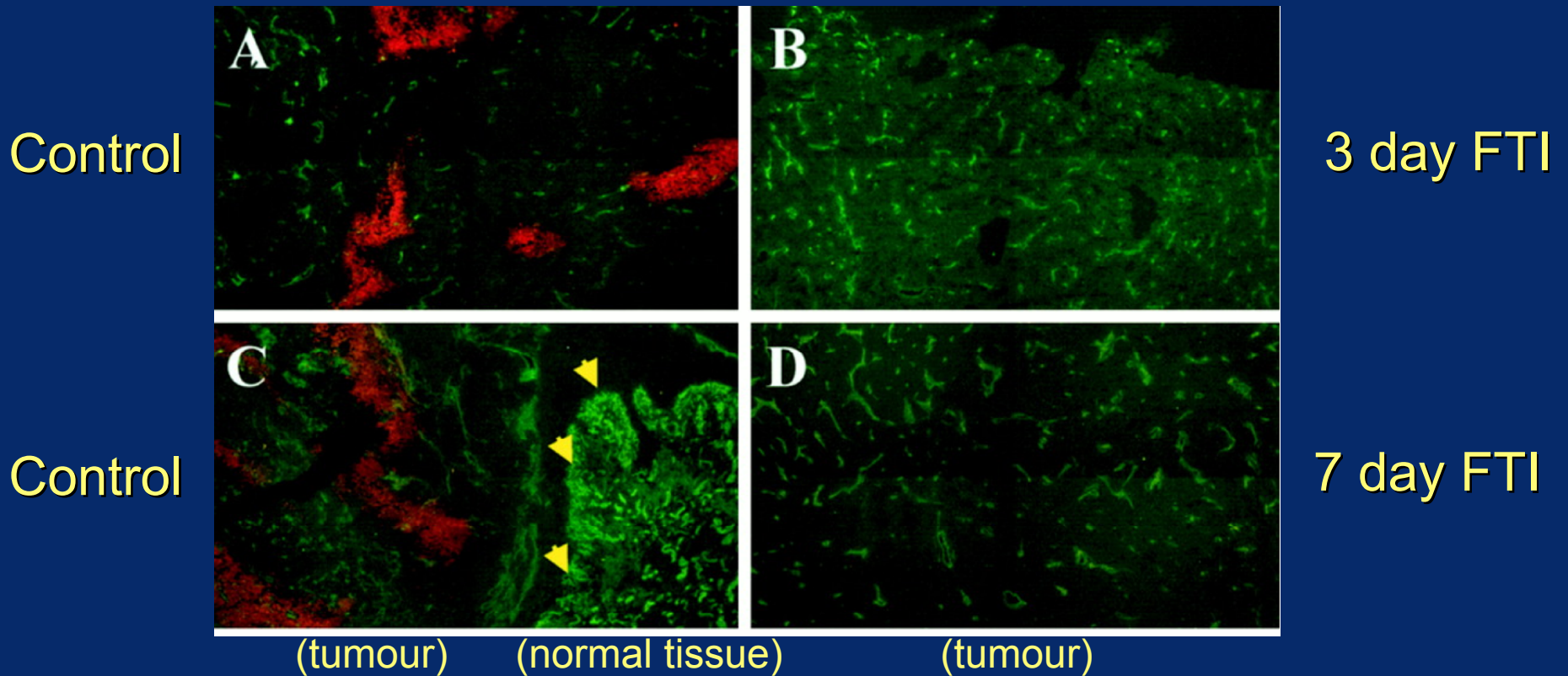
## Question

**Can the tumor  
microenvironment be genetically  
manipulated to make it less  
hostile to current therapies?**

# Tumor signalling and Radiosensitivity



# FTIs affect the tumour microenvironment (RAS?)

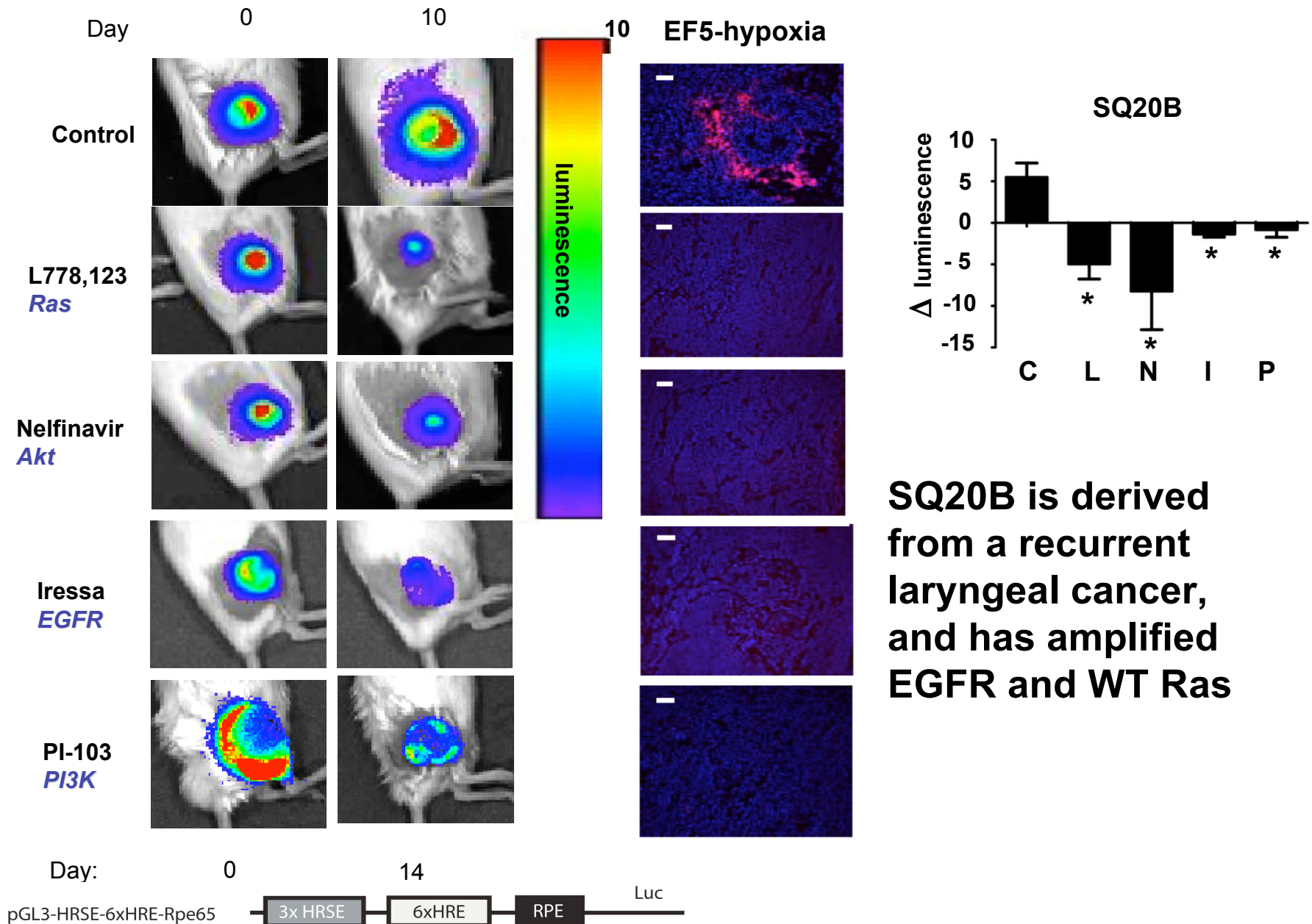


**HYPOXIA (EF5)**

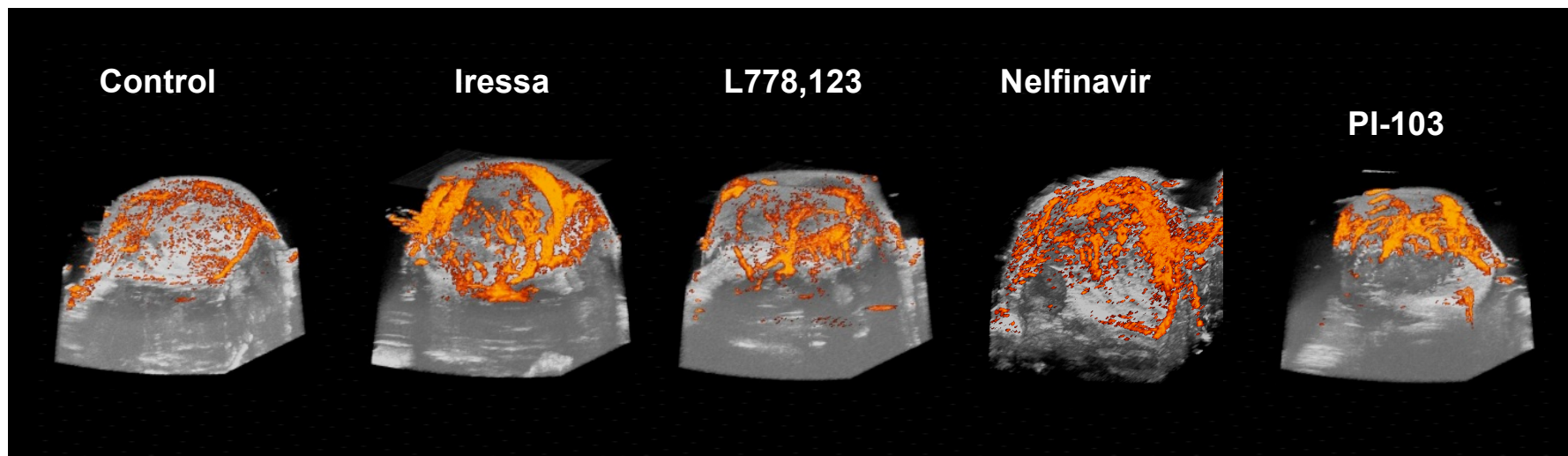
**VASCULATURE (CD31)**

From Cohen-Jonathan et al. Cancer Res. 61:2289, 2001

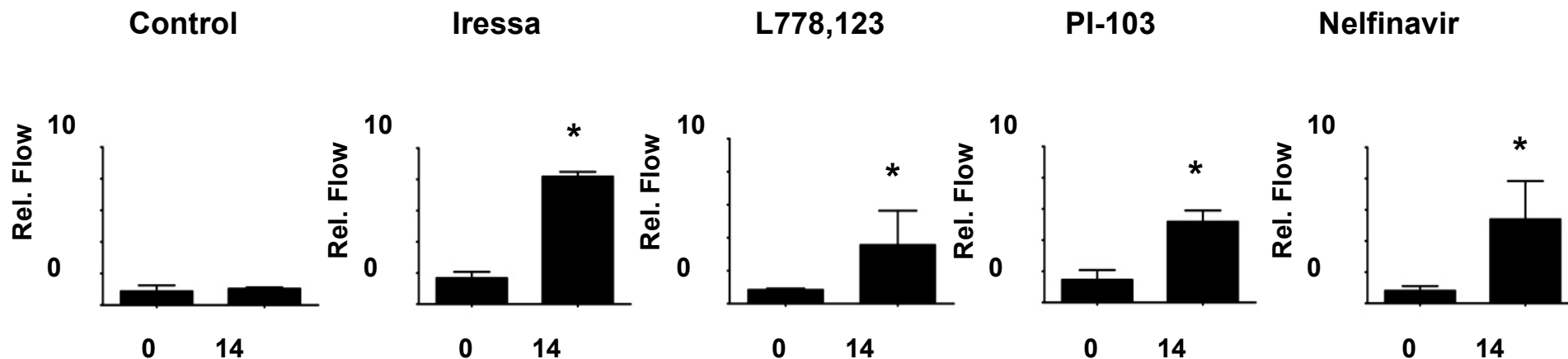
# Hypoxia is reduced by signalling inhibitors



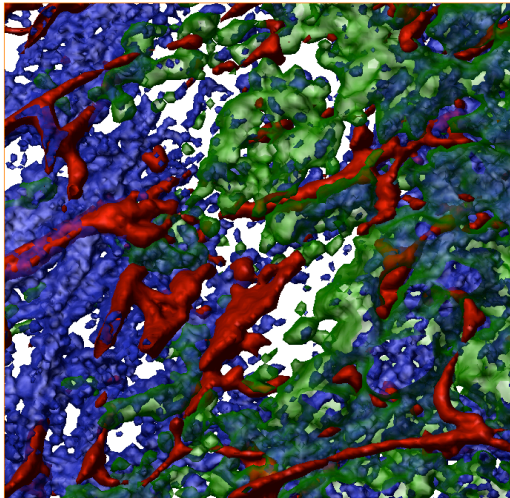
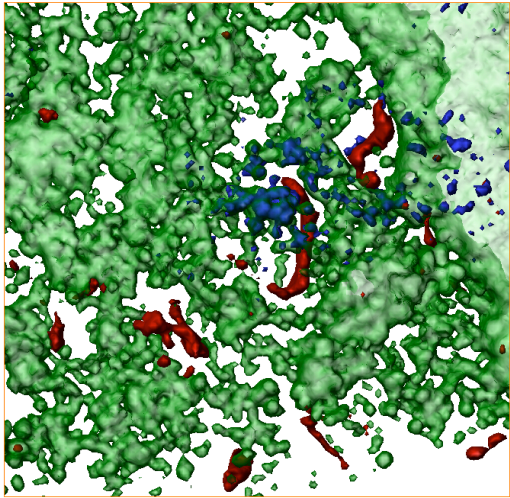
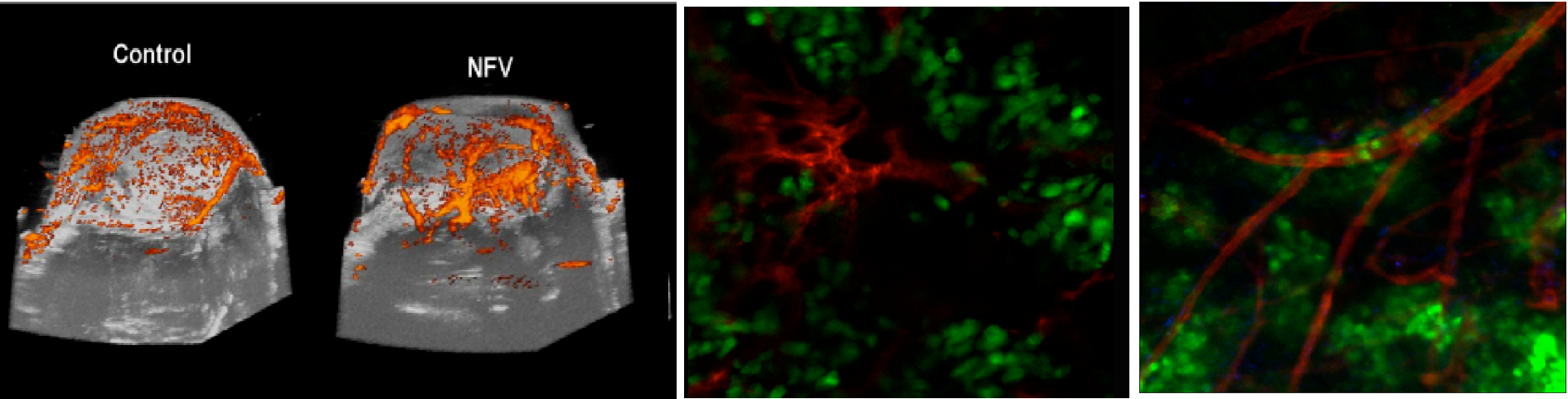
# Functional enhancement of tumour vasculature in SQ20B tumours



## *Doppler ultrasound*



# Perfusion / Vascularisation after treatment with nelfinavir



# Pancreatic Cancer Radiotherapy with Nelfinavir

## Radiotherapy

33 x 1.8 Gy



50.4 Gy

59.4 Gy

## Nelfinavir

2 x 1,250 orally, start 3 days before XRT through last day of XRT



## Chemotherapy

Cis 30 mg/m<sup>2</sup>  
Gemzar 200 or  
300 mg/m<sup>2</sup>



Weeks

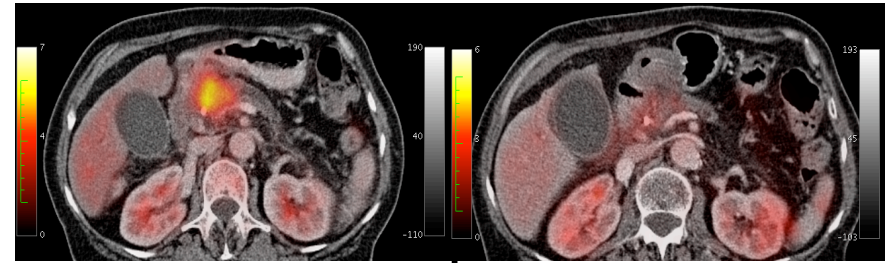
1 2 3 4 5 6

From Brunner et al. J Clin Onc, 2008

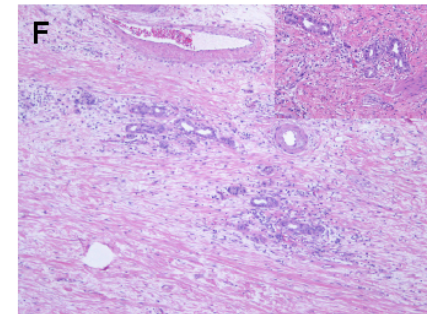
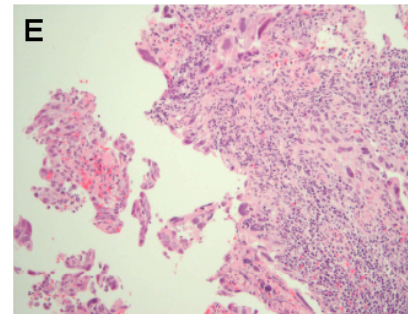
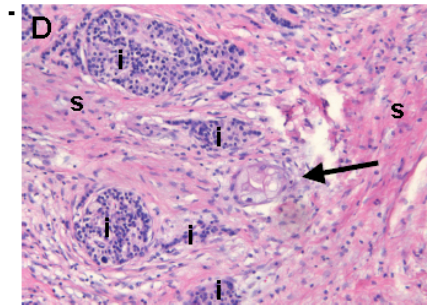
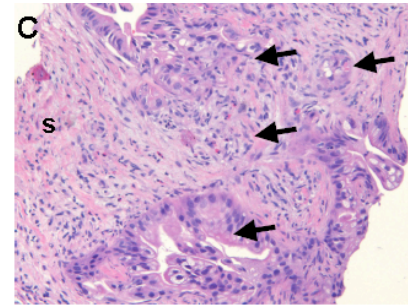


# Response

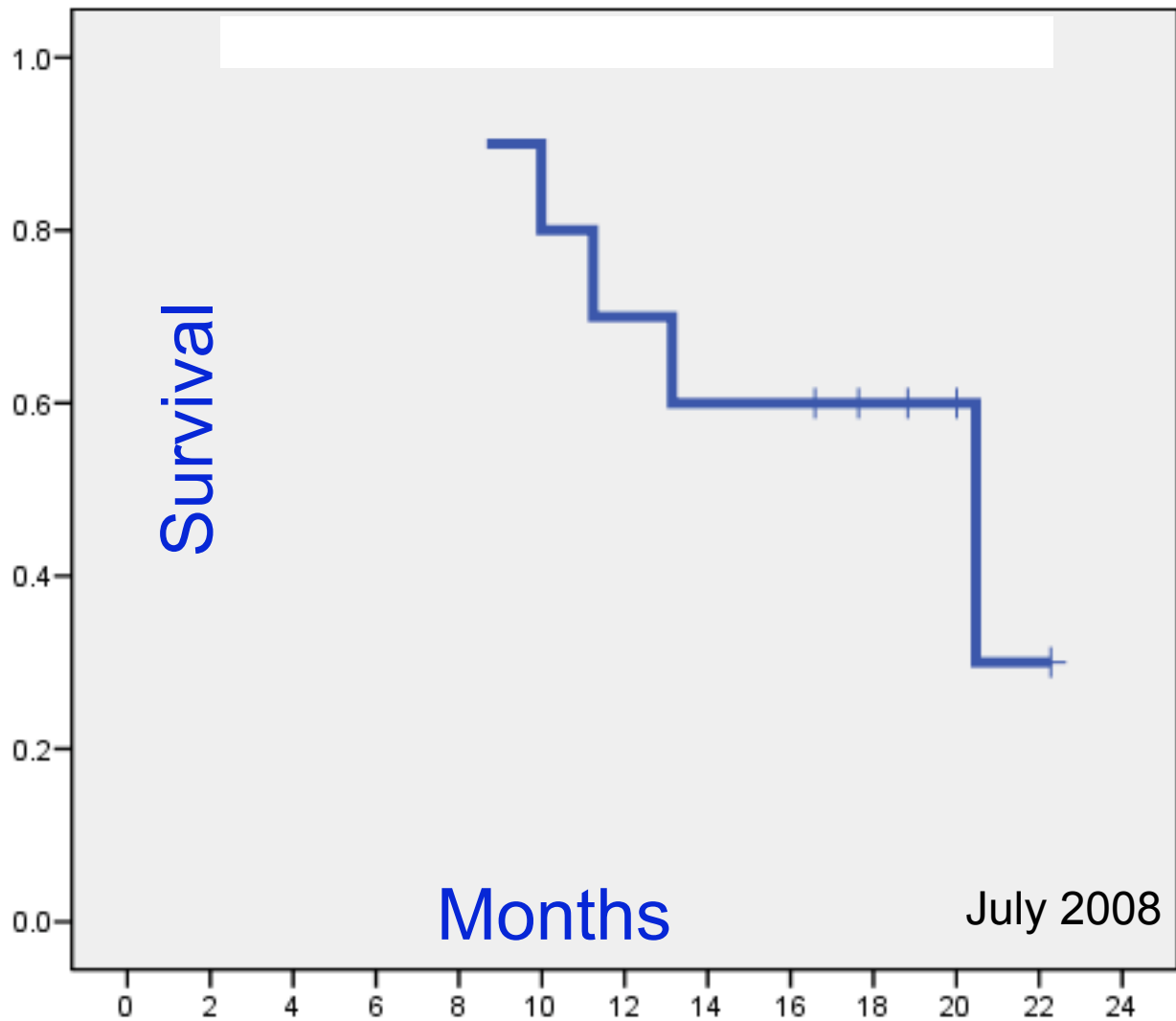
PET	CT	TRG
CR	mR	<10%
CR	PR	<10%
CR	PR	sterilized
CR	NC	
CR	PR	<80%
PR	PR	
PR	mR	<50%
NC	NC	
NC	NC	
n.a.	PR	<50%



**Pre** | **Post**



From Brunner et al. J Clin Onc, 2008



*Patients alive:*

3 resected

2 unresected

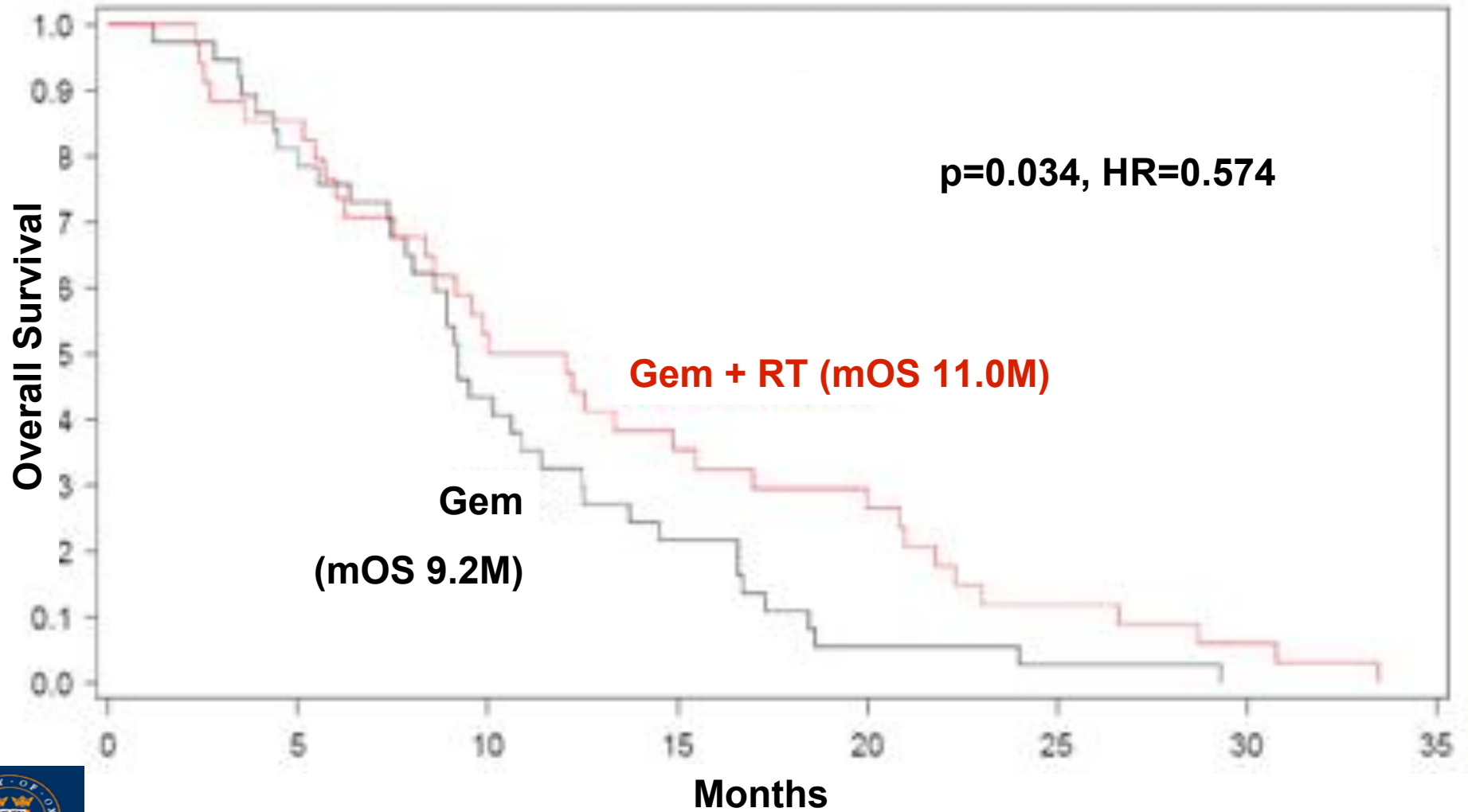
*Patients deceased:*

3 resected

2 unresected

**As of July 2009, median survival is approx 18m with longest survivor alive at 36m.**

# ECOG 4202



# Contributors:

## OXFORD

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**Grant Support from: Cancer Research UK, the Medical Research Council, EPSRC and NIH/NCI, Astra-Zeneca**  
**Reagents from: Merck, Plramed/Genentech/Roche, AstraZeneca, Vertex**