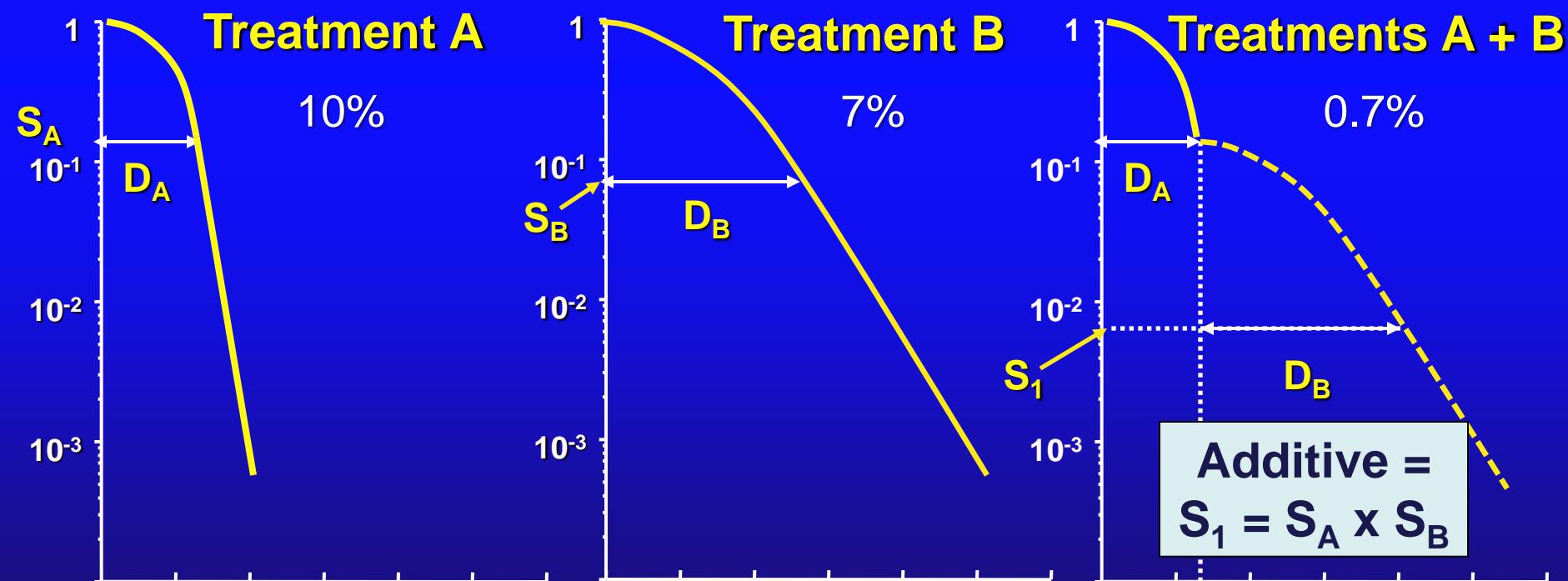


# **Chemo-radiation interactions, radiation sensitizers and protectors, bioreductive drugs**

Jacky Williams  
University of Rochester Medical Center

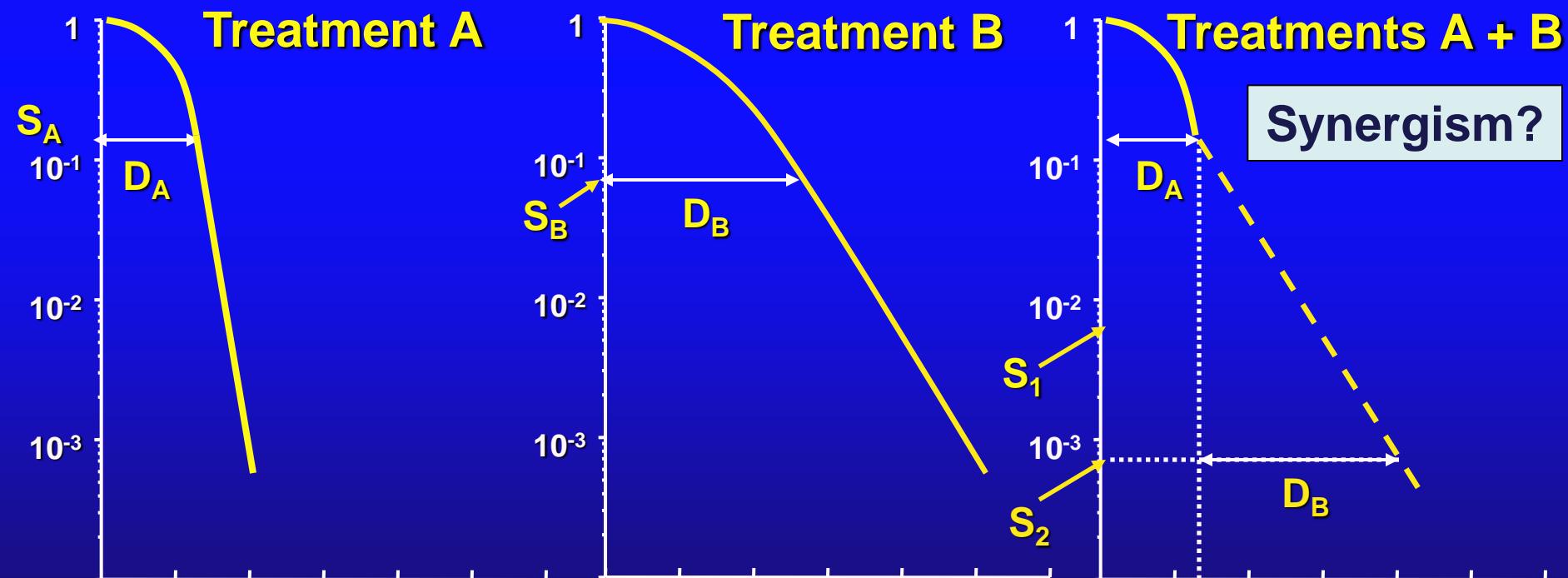
# Synergy vs. Additivity

- Frequent claims that agents/modalities are “synergistic”, i.e. more effective than expected
- Must take account of dose-effect relationships, not simple summation or multiplication of effects



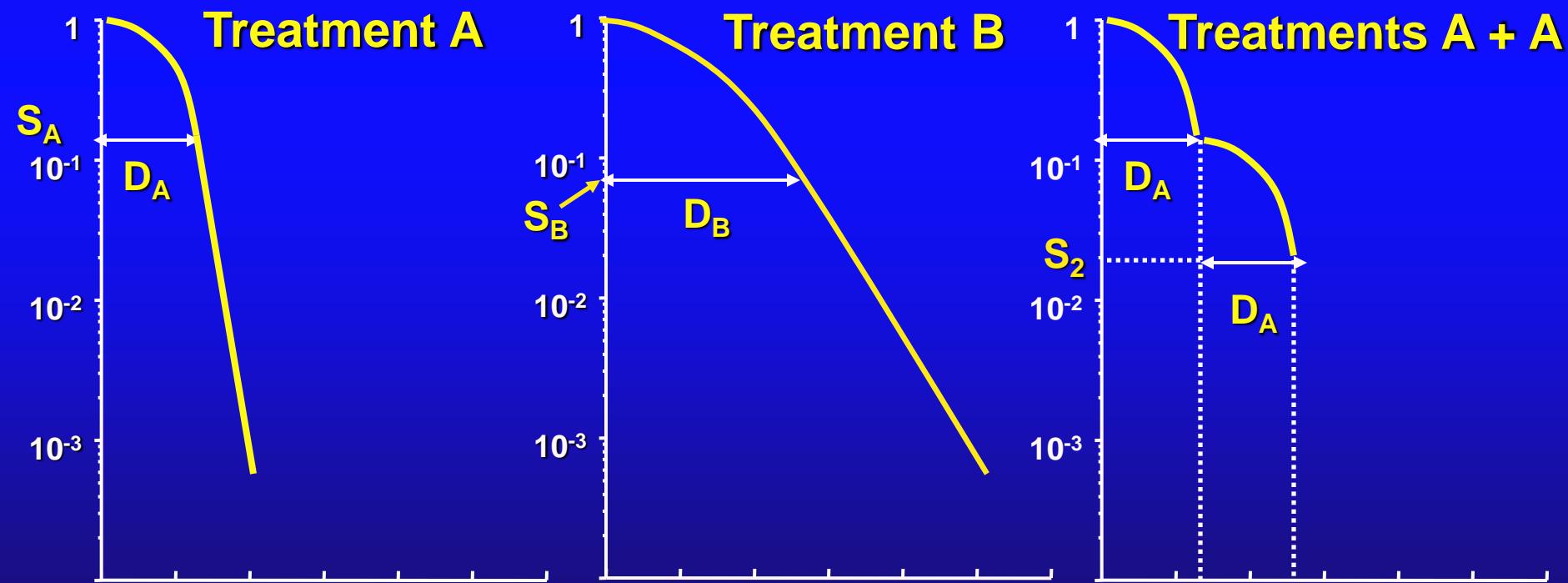
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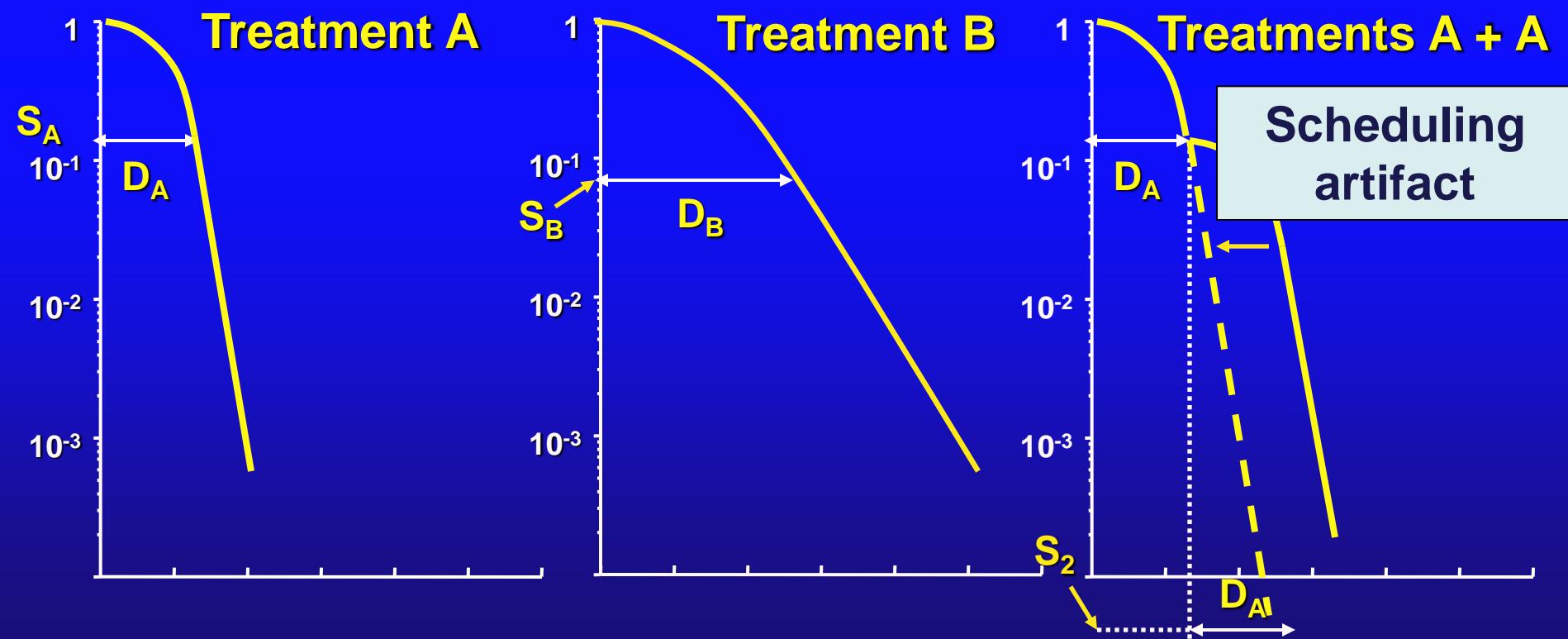
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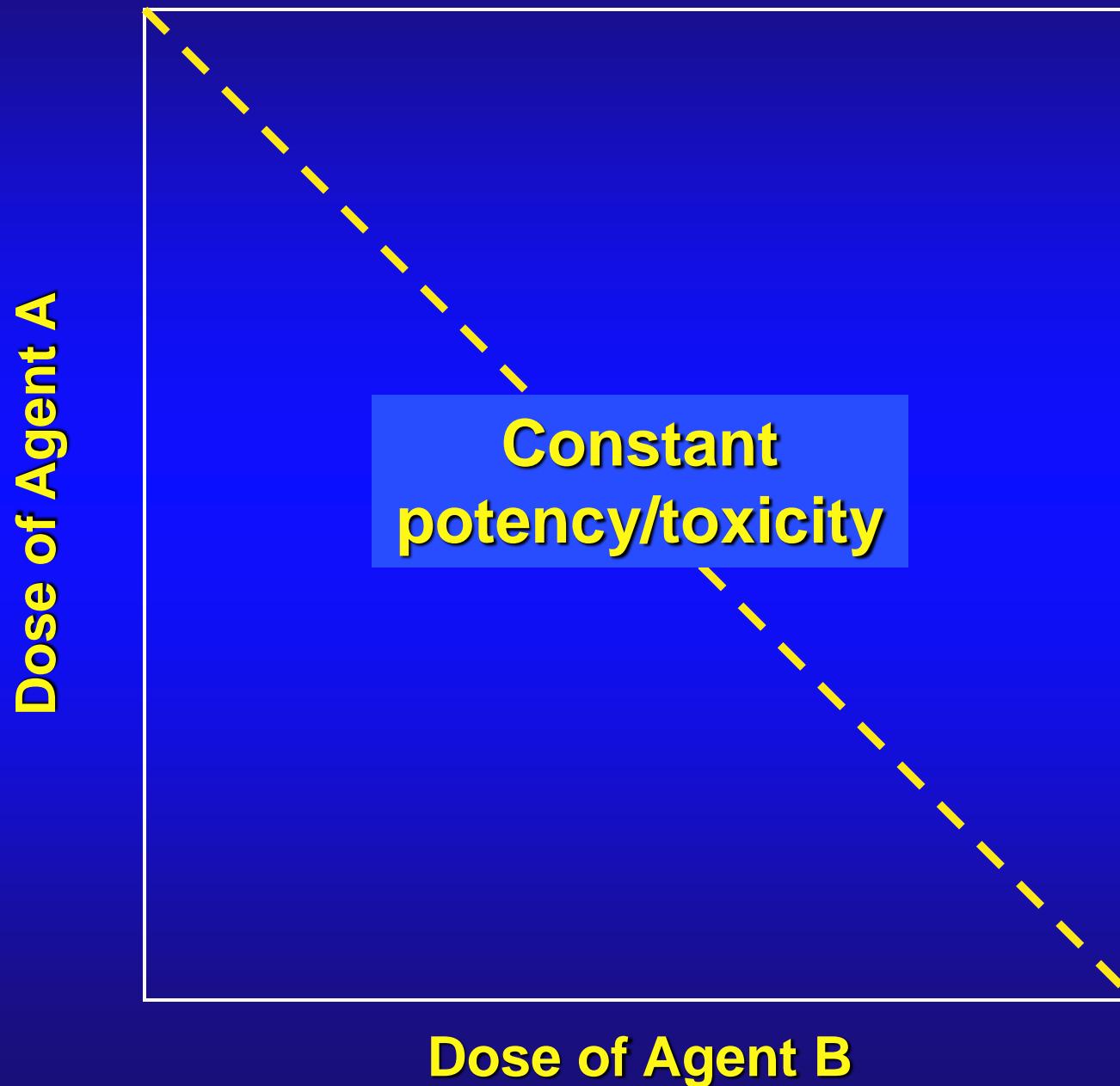


# Synergy vs. Additivity

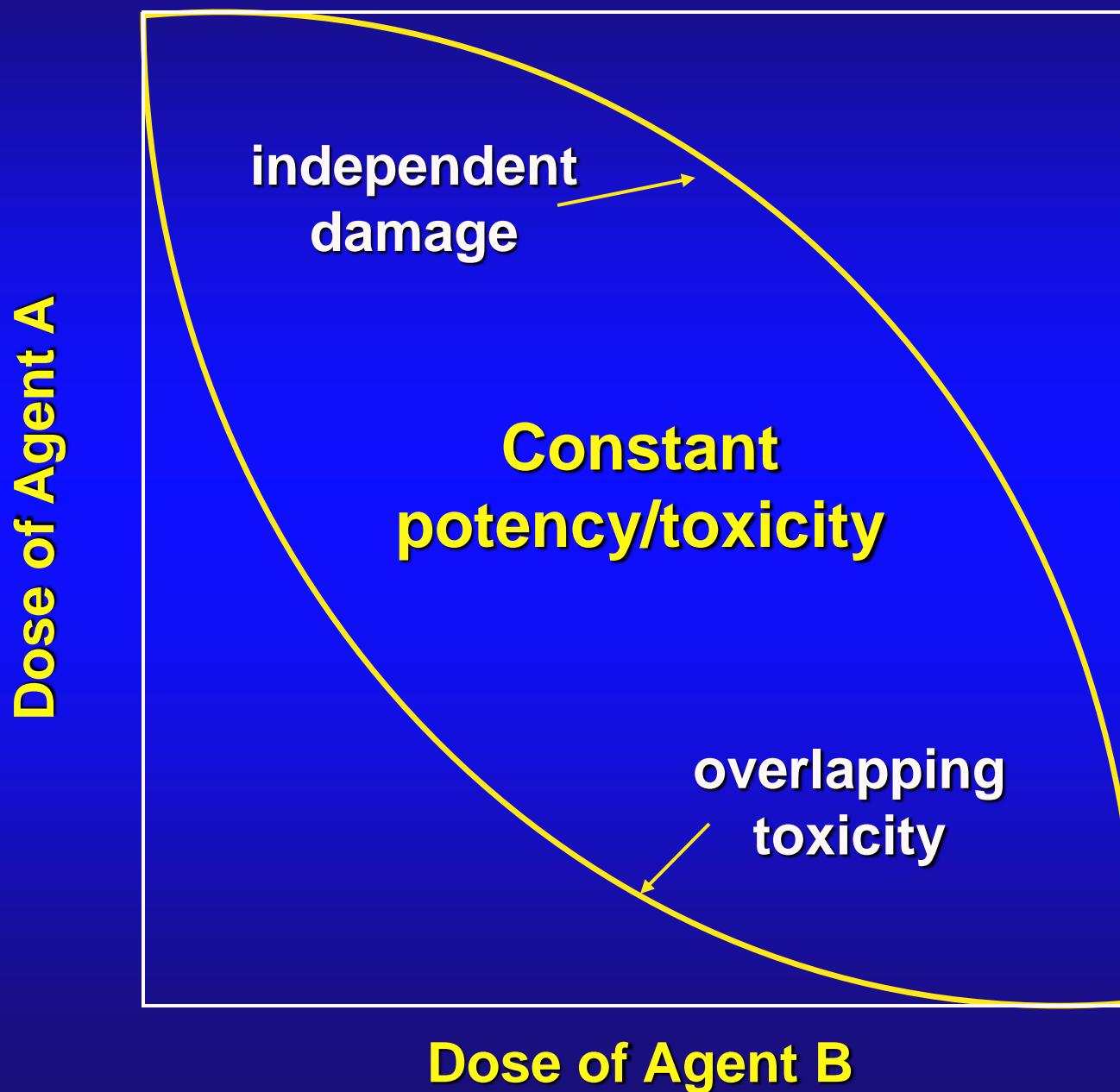
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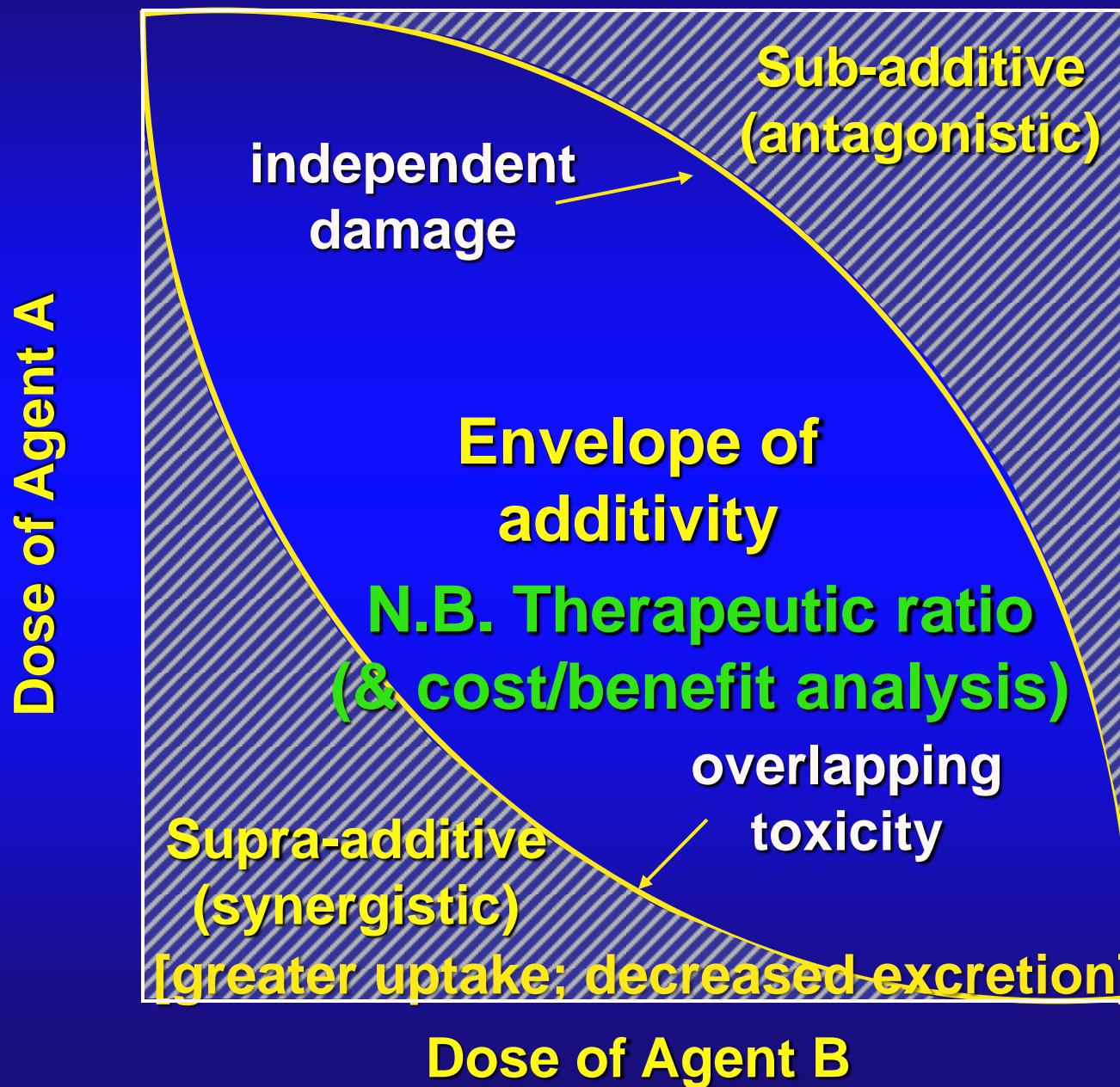
# Isobologram Analysis



# Isobologram Analysis



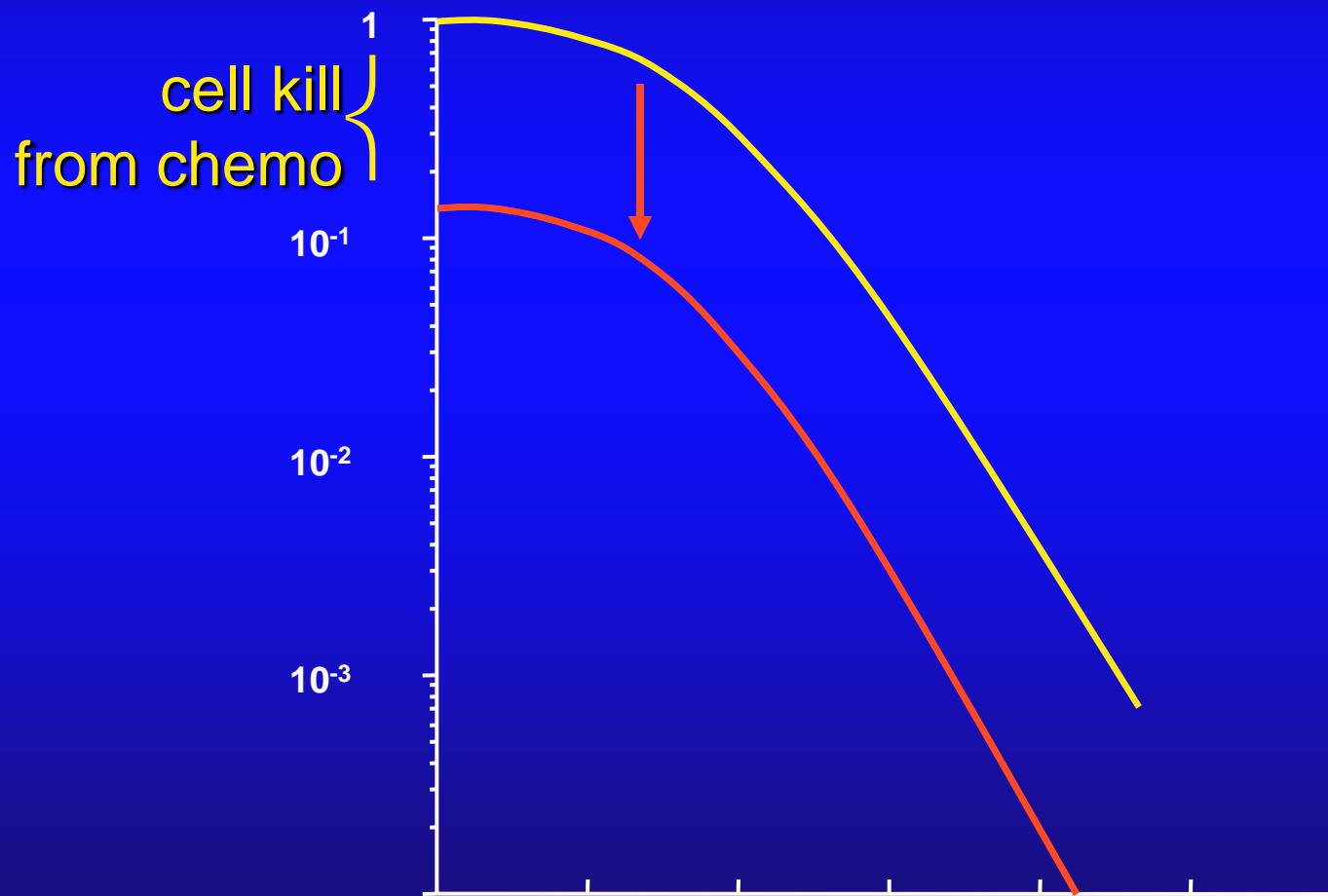
# Isobologram Analysis



# Chemotherapy and Radiation

Drugs can influence radiation by:

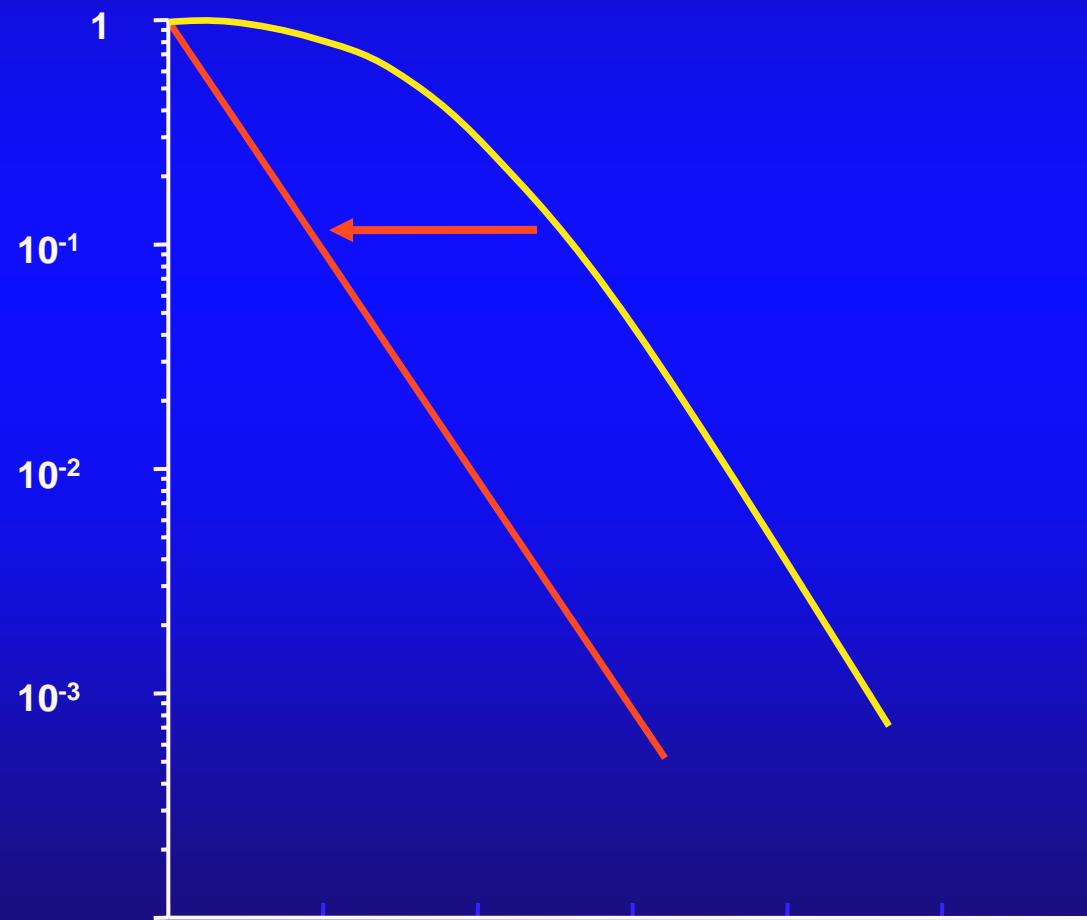
1. Displacing curve down (drug cell kill)



# Chemotherapy and Radiation

Drugs can influence radiation by:

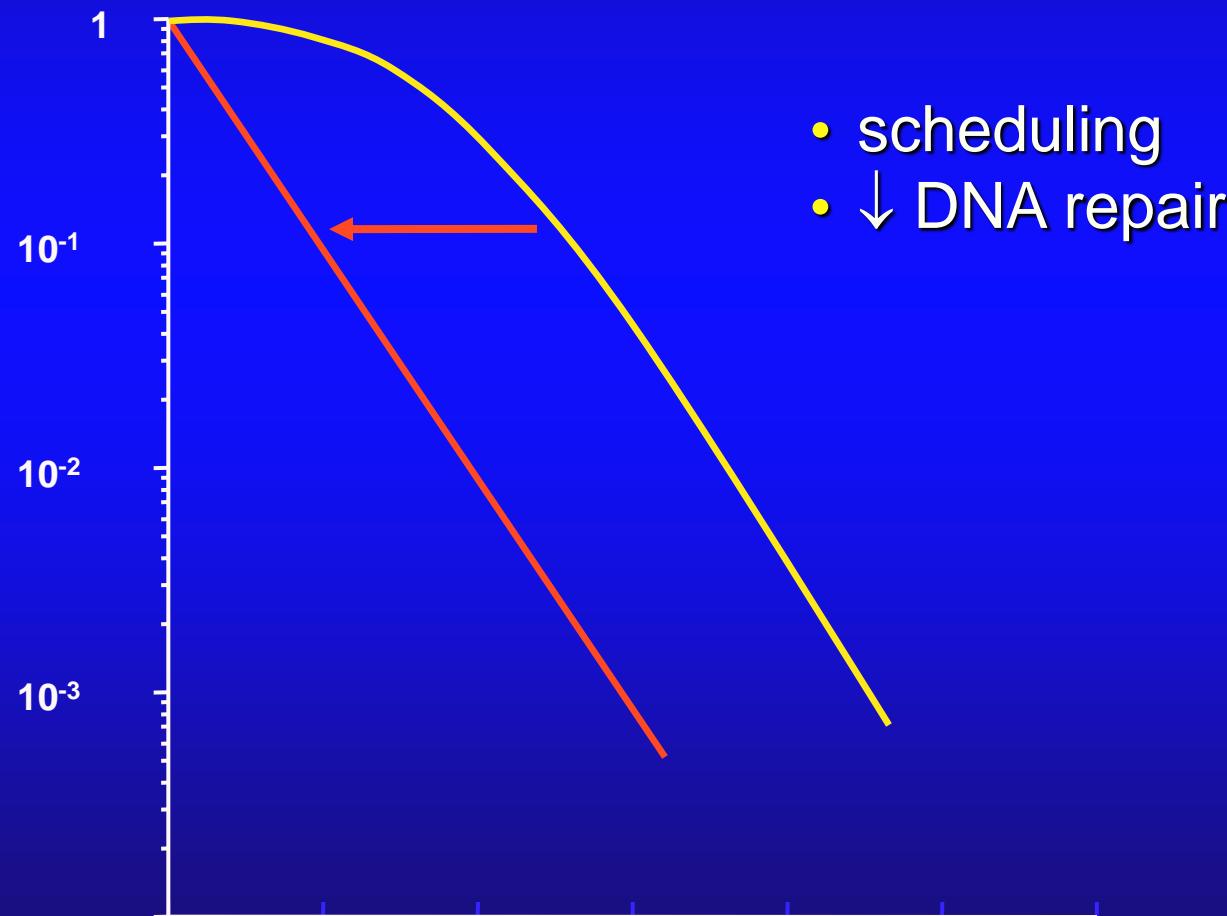
2. Losing the “shoulder”



# Chemotherapy and Radiation

Drugs can influence radiation by:

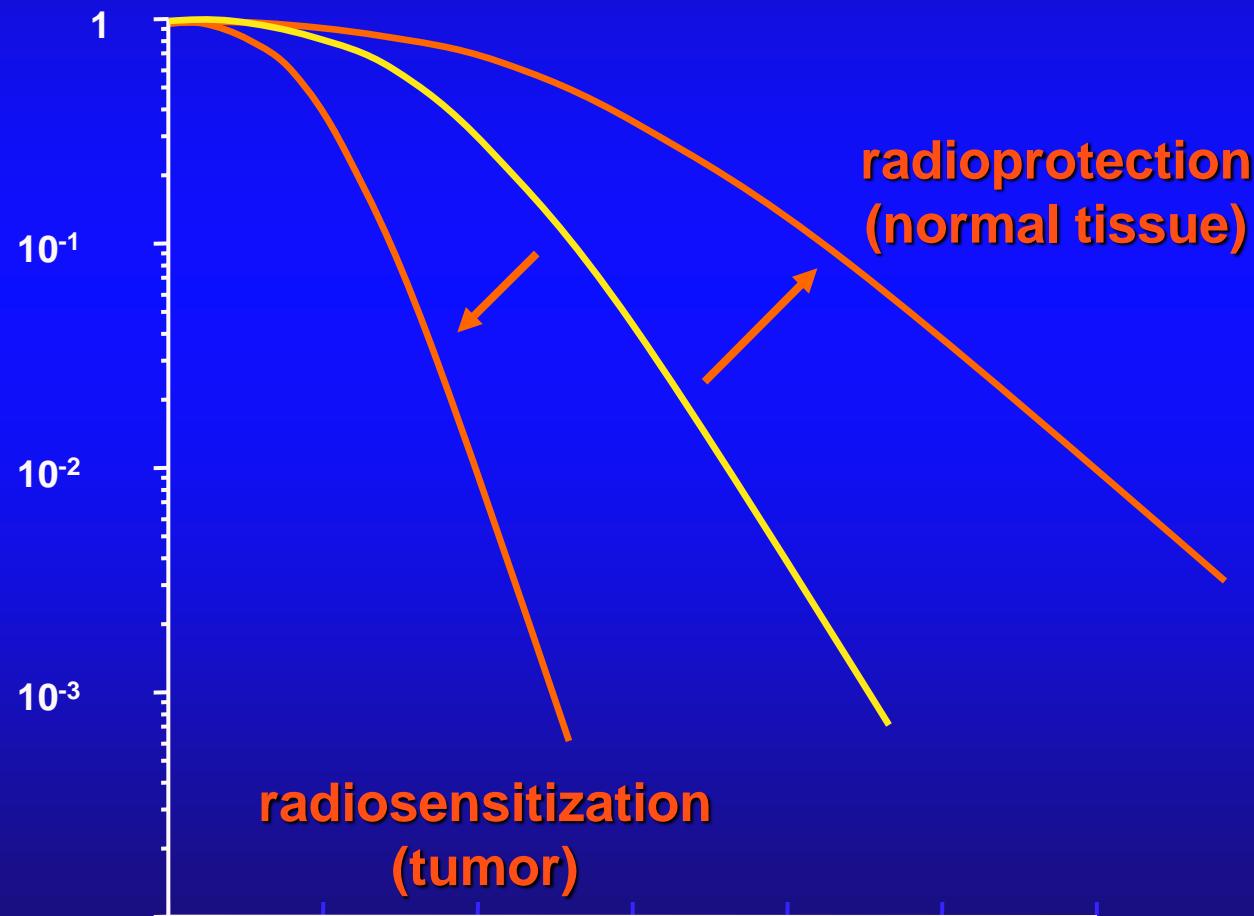
2. Losing the “shoulder” (drug effect on SLDR)



# Chemotherapy and Radiation

Drugs can influence radiation by:

3. Changing the shape of the curve



# Combined Treatment

- Includes combinations of drug(s) and radiation therapy [chemoradiation]
- Success = improved therapeutic ratio, i.e. any increase in normal tissue toxicity must be less than increase in toxicity to tumor or vice versa

# Combined Treatment

- Includes combinations of drug(s) and radiation therapy [chemoradiation]
- Success = improved therapeutic ratio, i.e. any increase in normal tissue toxicity must be less than increase in toxicity to tumor or vice versa

## Mechanisms of improved therapeutic ratio (Steel and Peckham, 1979):

- Spatial cooperation
- Independent toxicity
- Enhancement of tumor response
- Protection of normal tissue (radioprotectors, leuco)

# **Chemotherapy and Radiation**

- **Spatial cooperation**
  - Earliest/commonest mechanism of interaction

# Chemotherapy and Radiation

- **Spatial cooperation**

- Earliest/commonest mechanism of interaction
- Radiation treats bulk (primary) disease, chemotherapy treats smaller numbers (metastases)



# Chemotherapy and Radiation

- **Spatial cooperation**

- Earliest/commonest mechanism of interaction
- Chemotherapy treats primary and radiation used for sanctuary sites



# **Chemotherapy and Radiation**

- **Spatial cooperation**

- Earliest/commonest mechanism of interaction
- Radiation treats bulk (primary) disease, chemotherapy treats smaller numbers (metastases)
- Chemotherapy treats primary and radiation used for sanctuary sites
- Does not require interaction
- Different dose-limiting toxicities
- Significant gains have been made by improving radiation delivery (IMRT, IGRT, SBRT, brachytherapy)

# Combined Treatment

- Spatial cooperation
- Independent toxicity
- Majority of chemo agents – myelosuppressive
- Non-myelosuppressive: vincristine (neurotoxicity), cisplatin (neurotoxicity [nephrotoxicity]), bleomycin (mucositis, lung toxicity) – patients experience multiple toxicities ☹
  - bleomycin, etoposide, cisplatin (BEP) – testicular cancer
  - cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) – lymphoma
- Provides fundamental rationale for chemoradiation – systemic versus localized toxicities

# **Combined Treatment**

- **Spatial cooperation**
- **Independent toxicity**
  - Scheduling/timing:

# Combined Treatment

- Spatial cooperation
- Independent toxicity
  - Scheduling/timing:

Perez & Brady, 2008.

Strategy	Advantages	Disadvantages
<b>Sequential chemoradiation</b>	<ul style="list-style-type: none"><li>• Least toxic</li><li>• Maximizes systemic therapy</li><li>• Smaller radiation fields if induction shrinks tumor</li></ul>	<ul style="list-style-type: none"><li>• Increased treatment time</li><li>• Lack of local synergy</li></ul>
<b>Concurrent chemoradiation</b>	<ul style="list-style-type: none"><li>• Shorter treatment time</li><li>• Radiation enhancement</li></ul>	<ul style="list-style-type: none"><li>• Compromised systemic therapy</li><li>• Increased toxicity</li></ul>
<b>Concurrent chemoradiation and adjuvant chemotherapy</b>	<ul style="list-style-type: none"><li>• Maximizes systemic therapy</li><li>• Radiation enhancement</li><li>• Both local and distant therapy delivered upfront</li></ul>	<ul style="list-style-type: none"><li>• Increased toxicity</li><li>• Increased treatment time</li><li>• Difficult to complete chemotherapy after chemoradiation</li></ul>
<b>Induction chemotherapy and concurrent chemo-radiation</b>	<ul style="list-style-type: none"><li>• Maximizes systemic therapy</li><li>• Radiation enhancement</li></ul>	<ul style="list-style-type: none"><li>• Increased toxicity</li><li>• Increased treatment time</li><li>• Difficult to complete chemoradiation after induction therapy</li></ul>

# Combined Treatment

- Spatial cooperation
- Independent toxicity
  - Scheduling/timing:

Perez & Brady, 2008.

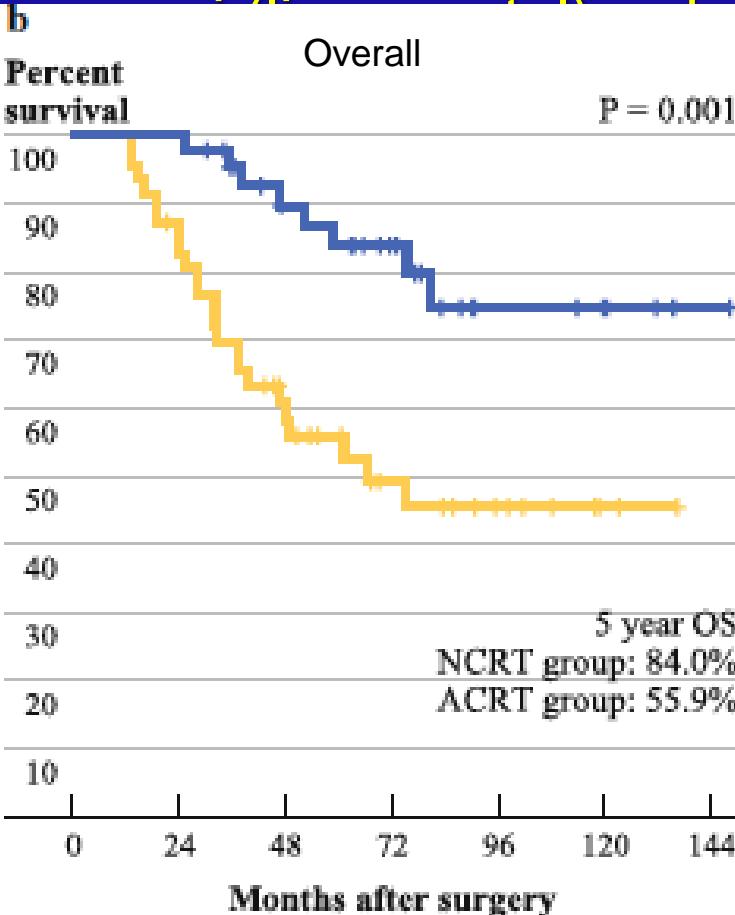
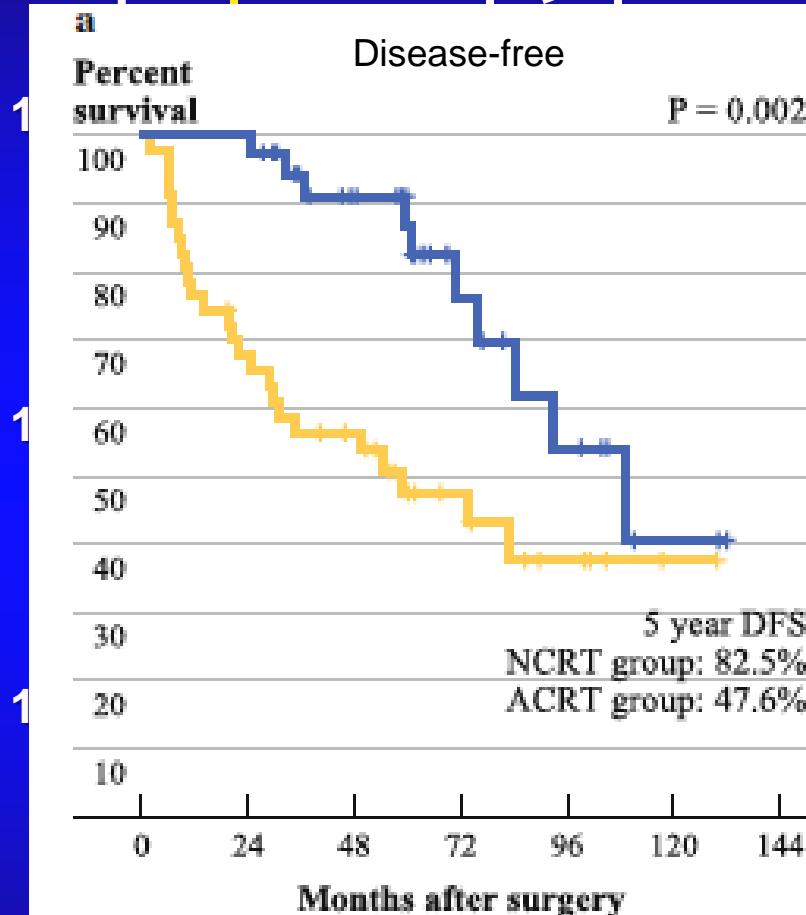
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Induction/neoadjuvant chemotherapy (primary tumor & disseminated disease):

- Treating metastases while they are few in number/small
- Reduce number of clonogens in primary tumor:
  - reduce number of surviving cells (large volume tumors)
  - reoxygenate surviving cells (hypoxic tumors)

# Shrinkage

Used in:  
- Radiotherapy  
- Surgery  
- Chemotherapy  
- Radiation fraction



Kang et al. Surg Oncol 2012: Neoadjuvant chemorad vs. adjuvant chemorad for stage III rectal

Radiation fractions

10<sup>10</sup>

L - 1 - 1



# Shrinkage

improved nutrition  
on

Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 3, pp. 717-724, 2005

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doi:10.1016/j.ijrobp.2005.03.001

## CLINICAL INVESTIGATION

## Head and Neck

### A PHASE I/II STUDY OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADIATION WITH BOOST CHEMOTHERAPY FOR ADVANCED T-STAGE NASOPHARYNGEAL CARCINOMA

FAYE M. JOHNSON, M.D., PH.D.,\* ADAM S. GARDEN, M.D.,† J. LYNN PALMER, PH.D.,‡  
DONG M. SHIN, M.D.,\*|| WILLIAM MORRISON, M.D.,† VASSILIKI PAPADIMITRAKOPOULOU, M.D.,\*  
FADLO KHURI, M.D.,\*|| GARY CLAYMAN, M.D.,§ HELMUTH GOEPFERT, M.D.,§  
K. KIAN ANG, M.D., PH.D.,† WAUN K. HONG, M.D.,\* AND BONNIE S. GLISSON, M.D.\*

Departments of \*Thoracic/Head & Neck Medical Oncology, †Radiation Oncology, ‡Biostatistics, and §Head and Neck Surgery,  
The University of Texas M. D. Anderson Cancer Center, Houston, TX; ||Winship Cancer Institute, Emory University, Atlanta, GA

**Purpose:** Local recurrence is the most common site of failure for locally advanced nasopharyngeal carcinoma (NPC) treated with neoadjuvant cisplatin/5-fluorouracil (PF) and definitive radiation at our center. Based on this, we studied the addition of chemotherapy during the boost phase of radiation after neoadjuvant PF for advanced

This study was based on theoretical radiosensitization with chemotherapy during accelerated repopulation of the tumor with relatively radioresistant clonogens.

Radiation fractions

# Combined Treatment

- Spatial cooperation
- Independent toxicity
  - Scheduling/timing:

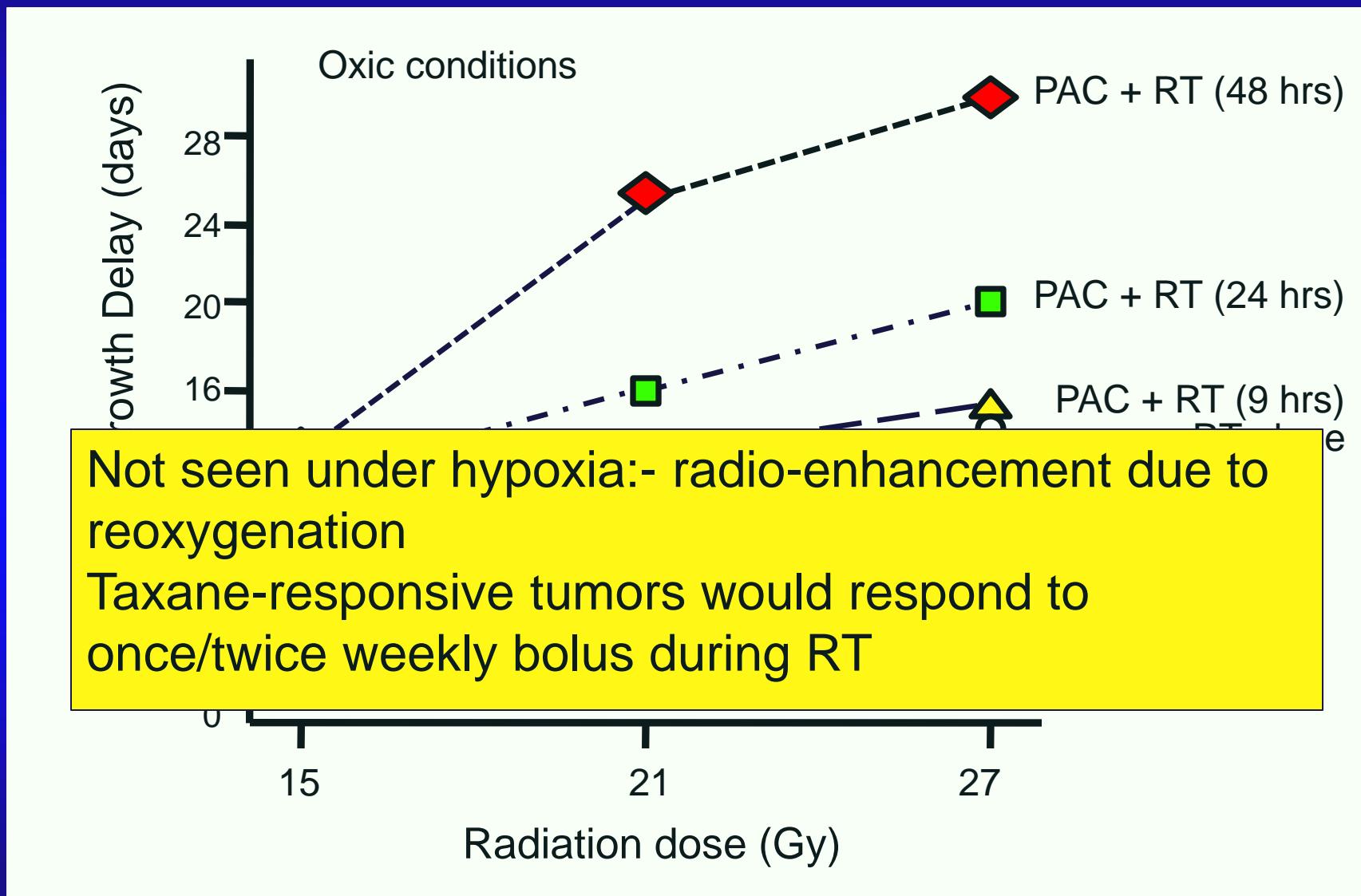
Perez & Brady, 2008.

Strategy	Advantages	Disadvantages
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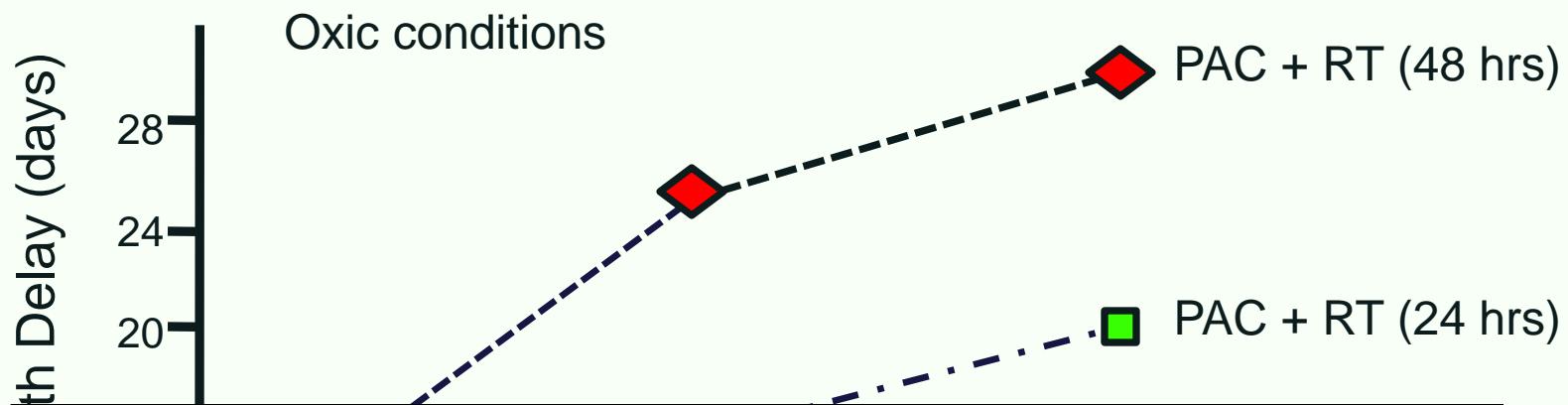
Concurrent chemotherapy (primary tumor & disseminated disease):

- Takes advantage of radiation-drug interactions to maximize tumor response
- Timing of drug is critical – optimal administration is based on:
  - mechanisms of tumor radio-enhancement by drug
  - drug's normal tissue toxicity
  - conditions under which maximum enhancement is achieved

# Effect of Paclitaxel on MCA-4 cells



# Effect of Paclitaxel on MCA-4 cells



Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 2, pp. 407-413, 2008  
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doi:10.1016/j.ijrobp.2007.10.011

## CLINICAL INVESTIGATION

Lung

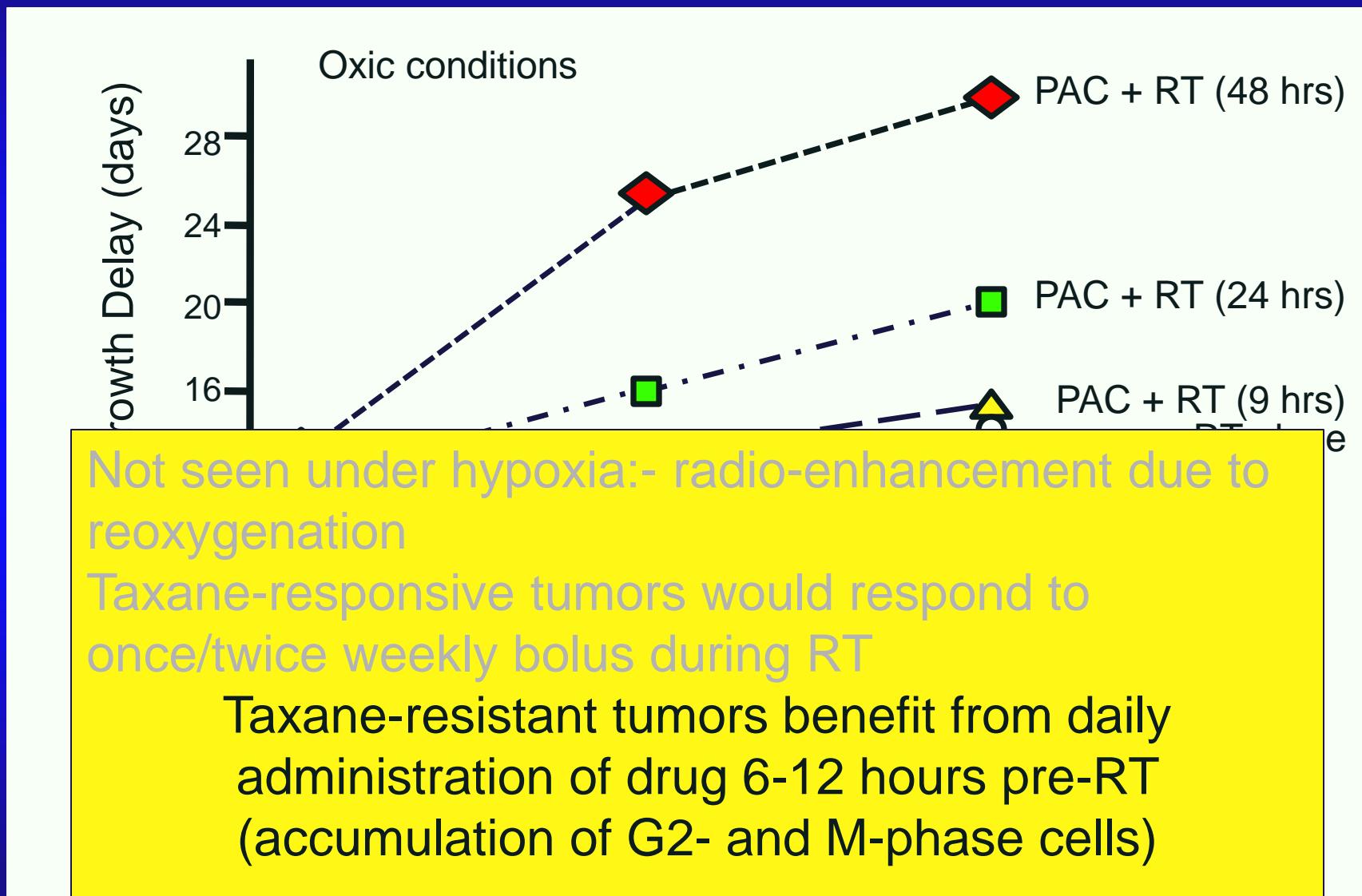
### TOXICITY PROFILE AND PHARMACOKINETIC STUDY OF A PHASE I LOW-DOSE SCHEDULE-DEPENDENT RADIOSENSITIZING PACLITAXEL CHEMORADIATION REGIMEN FOR INOPERABLE NON-SMALL-CELL LUNG CANCER

YUNCHYAU Chen, M.D., Ph.D., \* KISHAN J. PANDYA, M.D., † RICHARD FEINS, M.D., §  
DAVID W. JOHNSTONE, M.D., ¶ THOMAS WATSON, M.D., ‡ THERESE SMUDZIN, B.S., \*

AND Peter C. KING, Ph.D. \*

Milas et al., 1995

# Effect of Paclitaxel on MCA-4 cells



# Combined Treatment

- Spatial cooperation
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Perez & Brady, 2008.

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# Toxicity Concerns

- Sequential (SQ) vs. concurrent (CC) chemoRT for locally advanced, unresectable NSCLC (%WHO Grade 3 or 4 toxicity)

Trial Chemotherapy Radiation	Furuse Cis/vindesine/mito Split course 56 Gy		Zatloukal Cis/vinorelbine Standard 60 Gy		Fournel Cis/vinorelbine Standard 66 Gy	
	SQ	CC	SQ	CC	SQ	CC
Anemia	33%	10%	6%	12%	28%	20%
Leukopenia	77%	99%	19%	53%	--	--
Neutropenia	--	--	40%	65%	88%	77%
Thrombocytopenia	23%	53%	4%	6%	15%	16%
Febrile neutropenia/ infection	2%	3%	2%	8%	12%	14%
Nausea/vomiting	22%	23%	15%	39%	18%	24%
Pulmonary toxicity	1%	1%	2%	4%	11%	5%
Esophageal toxicity	2%	3%	4%	18%	3%	32%
Treatment-related death	--	--	0%	0%	5.6%	9.5%

# Toxicity Concerns

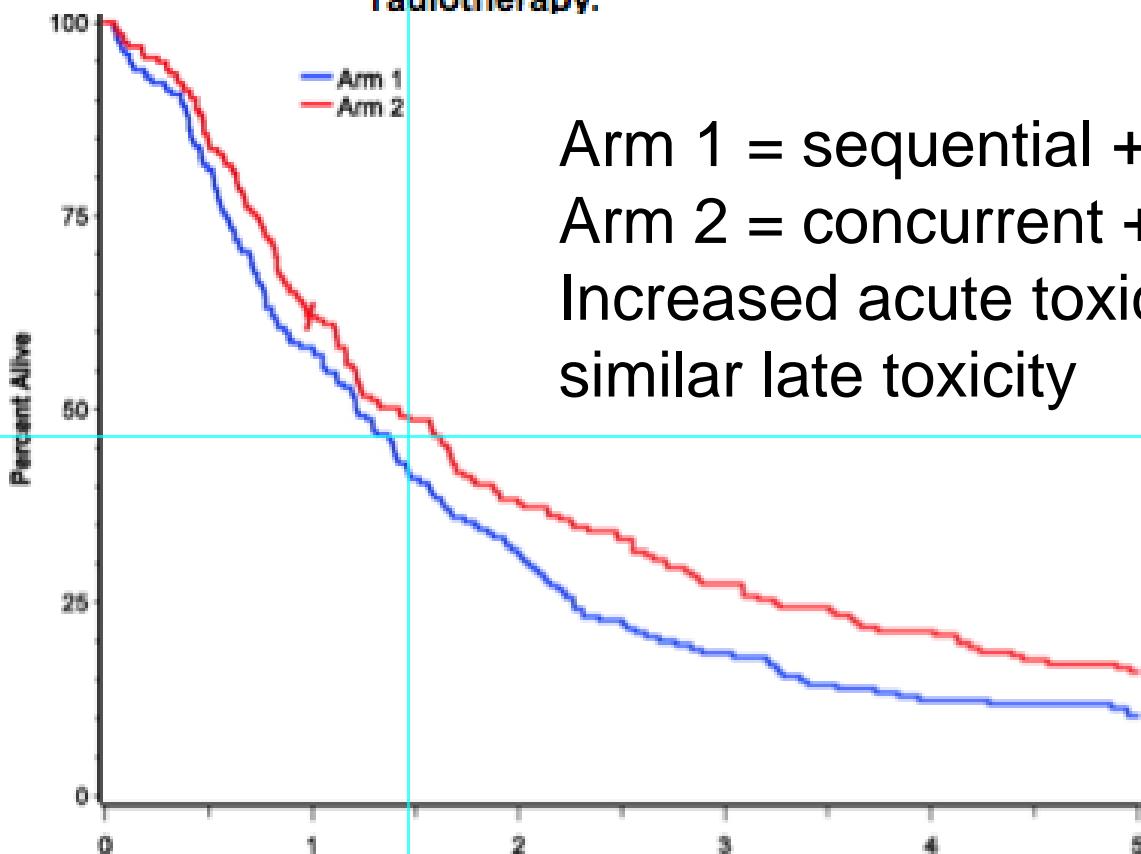
- Sequential (SQ) vs. concurrent (CC) chemoRT for locally advanced, unresectable NSCLC (%WHO Grade 3 or 4 toxicity)
- Concurrent doxirubicin/etoposide with radiation therapy **increases incidence of severe skin reactions** (and **esophagitis**) in breast cancer patients [*Van Helvoirt et al. Eur J Cancer 2000; Greget et al. Proc Am Soc Clin Oncol 2001*]
- Concurrent taxane-containing chemotherapy with RT **increases grade 2-3 skin toxicity** [*Hanna et al. Breast J 2002; Formenti et al. J Clin Oncol 2003*], **increases risk of pneumonitis** [*Hanna et al. Breast J 2002; Taghian et al. J Natl Cancer Inst 2001*] in breast cancer patients

# Toxicity Concerns

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- **Improved survival** in lung cancer [*Curran et al. J Clin Oncol 2003; Ausperin et al. J Thoracic Onc 2007*] and breast cancer [*Baldazzi et al. Cancer Treat Rev 2010*] **subgroups** of patients following concurrent vs. sequential chemoradiation

# RTOG 9410 – stage III NSCLC

Five-year survival results for patients assigned to receive standard radiation with concurrent chemotherapy compared with patients assigned to receive sequential chemotherapy and radiotherapy.



Arm 1 = sequential + RT  
Arm 2 = concurrent + RT  
Increased acute toxicity;  
similar late toxicity

## Patients at Risk:

Arm 1	195	113	61	36	24	20
Arm 2	195	120	73	53	41	31

Curran W J et al. JNCI J Natl Cancer Inst 2011;103:1452-1460

# Chemotherapy and Radiation

- Spatial cooperation
- Independent toxicity
- **Using inter-relationship(s) between modalities to improve tumor response**
  - Narrow therapeutic index
    - Agents are insufficient as monotherapy ± radiation
    - Normal tissue toxicity limits use of effective regimens
  - ? reached limits of improving radiation “targeting”
  - Alternative mechanisms

# **Chemotherapy and Radiation**

## **Exploitable cell properties:**

### **Property**

### **Effect of Combined Rx**

---

Genetic instability of tumors:  
resistance to drugs/radiation  
for different clones

# **Chemotherapy and Radiation**

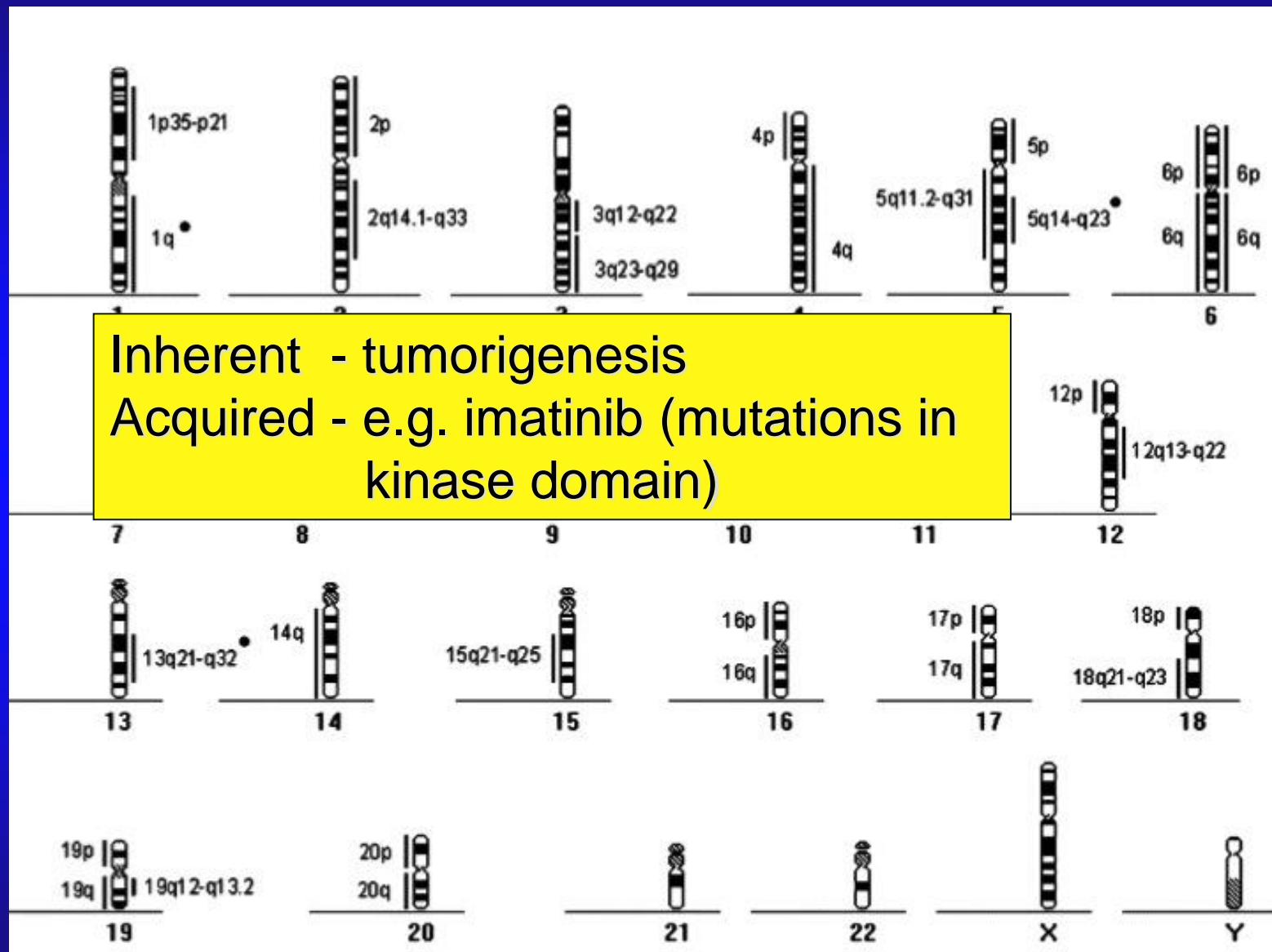
## **Radiation resistance:**

Marked variability in response to 2 Gy, therefore over standard fractionation course, survival will differ between cell populations

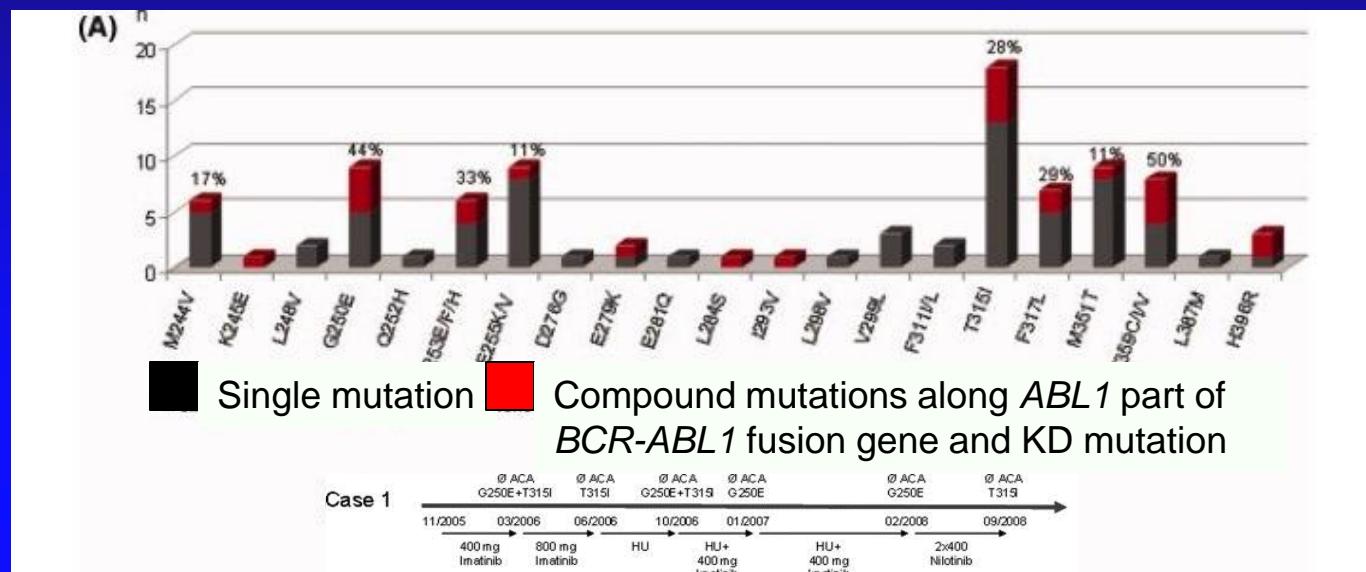
## **Target Mechanisms:**

- Survival phenotype:
  - Mutations associated with drug resistance

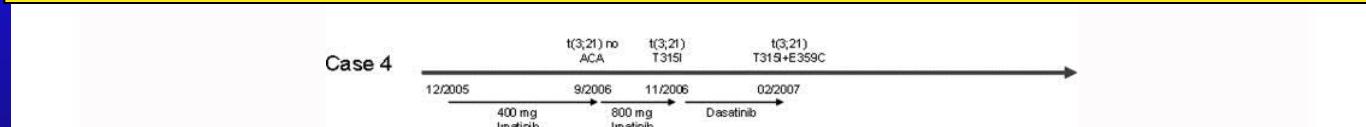
# Cytogenetic Alterations - Carboplatin



# Associations between imatinib resistance conferring mutations and Philadelphia positive clonal cytogenetic evolution in CML



Novel mutations developed during treatment (imatinib/dasatinib) showing that additional cytogenetic aberrations (ACAs) can precede or follow KD mutations.



# Chemotherapy and Radiation

## Radiation resistance:

Marked variability in response to 2 Gy, therefore over standard fractionation course, survival will differ between cell populations

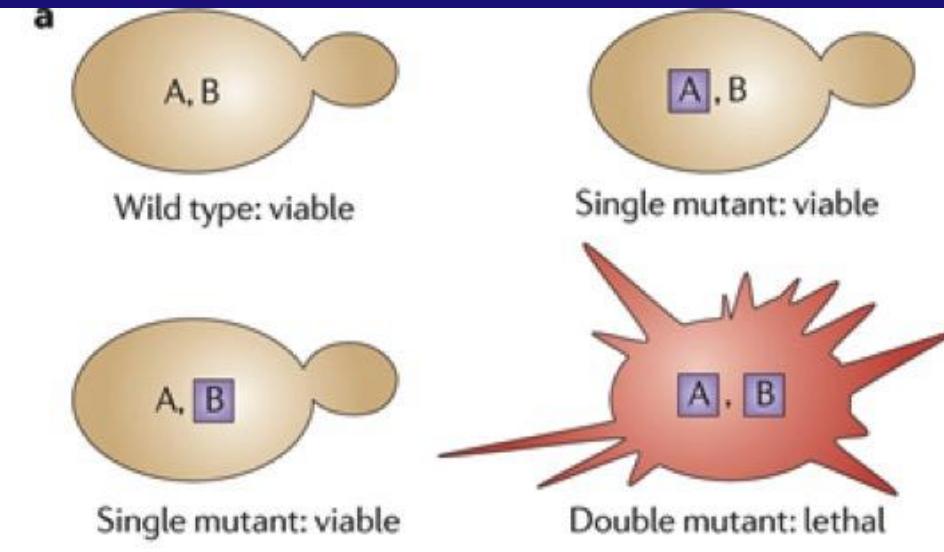
## Target Mechanisms:

- Survival phenotype:
  - Mutations associated with drug resistance
  - Target signaling pathways associated with resistance (limited efficacy of 3<sup>rd</sup> generation PGP-inhibitors, e.g. tariquidar)
  - Using “synthetic lethality”

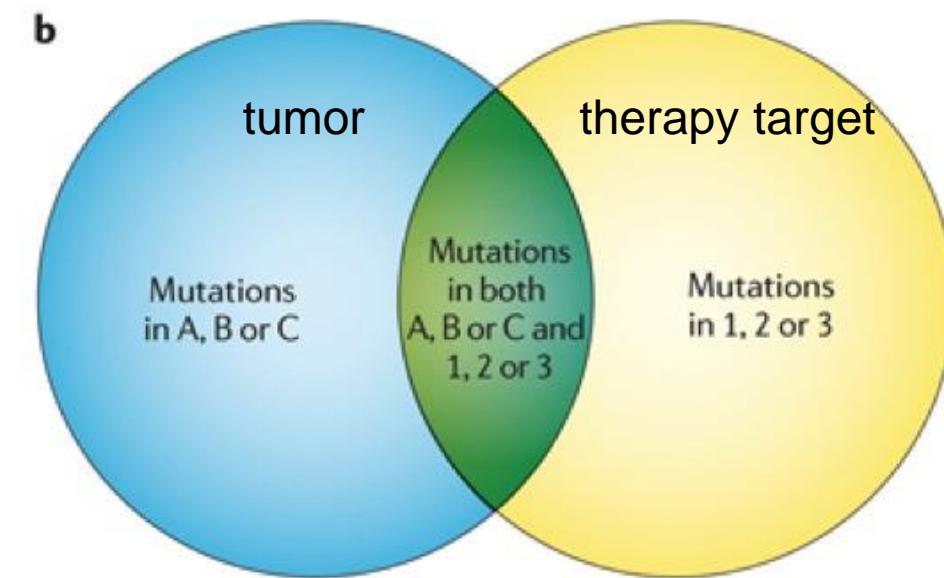
# Synthetic Lethality

- Coined in 1946 by Dobzhansky – describes complementary lethal systems
- Makes use of genetic interactions of two mutations where the presence of either single mutation has no effect on cell viability, but the presence of both results in cell death
- Exploit features of tumor cells instead of directly targeting oncogenic signaling (target alternative/salvage pathways)

## Organism lethality

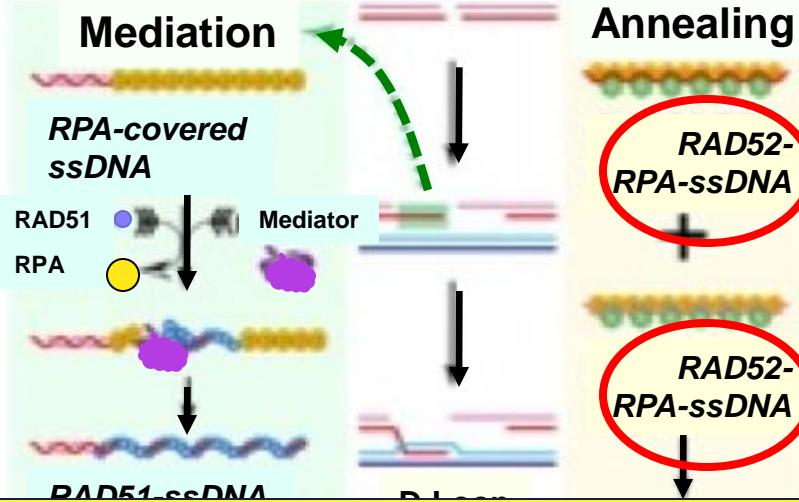


## Pathway lethality



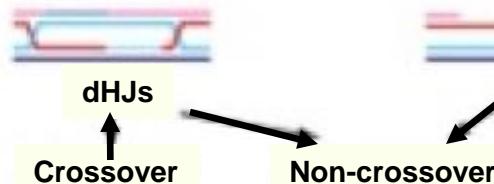
# Role of RAD52 in HR DNA Repair

## Homologous Recombination

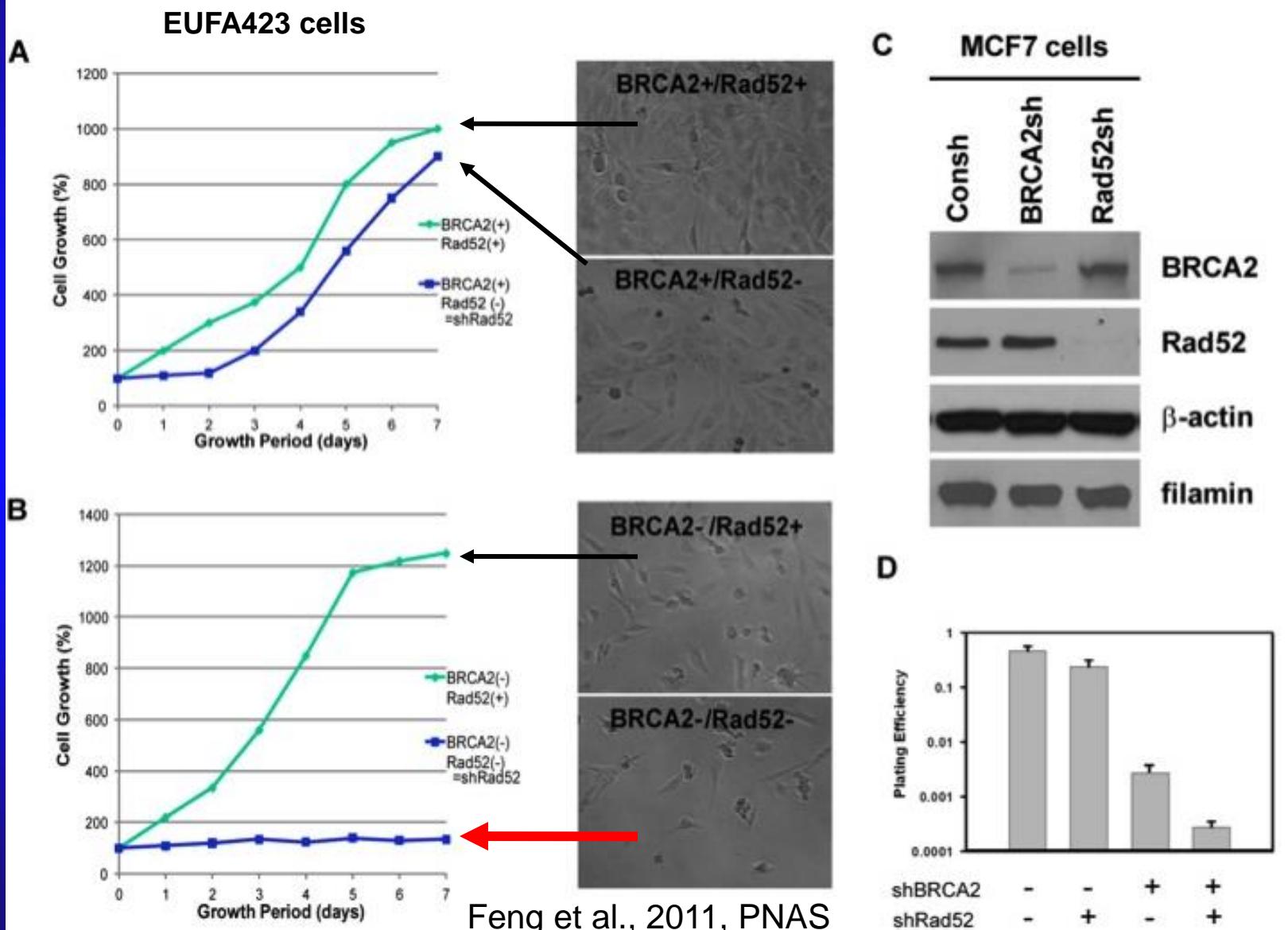


RAD52<sup>-/-</sup> mice – minimal or no phenotype for repair, recombination, or meiosis

BRCA2 (tumor suppressor protein) maintains central HR function

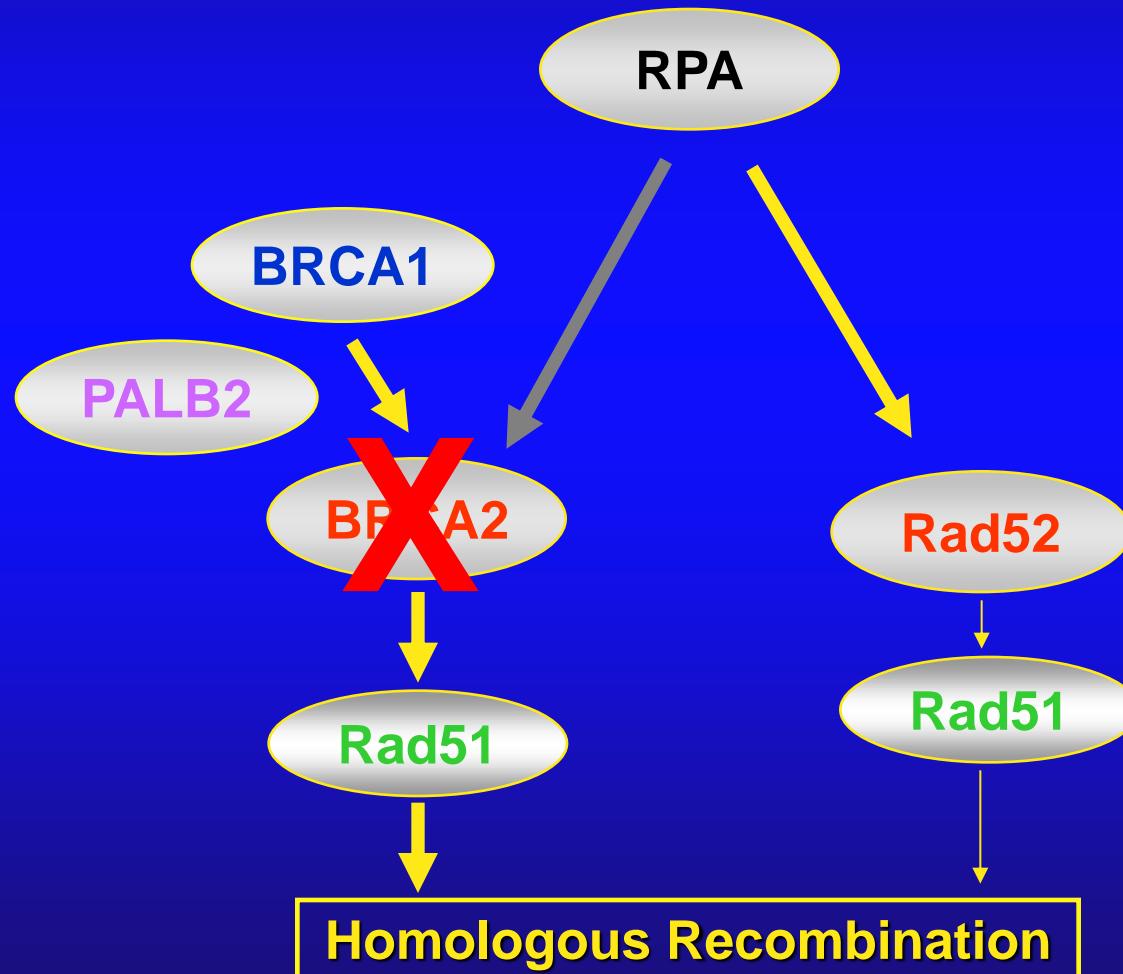


# Synthetic Lethality: Rad52 and BRCA2-deficient cells

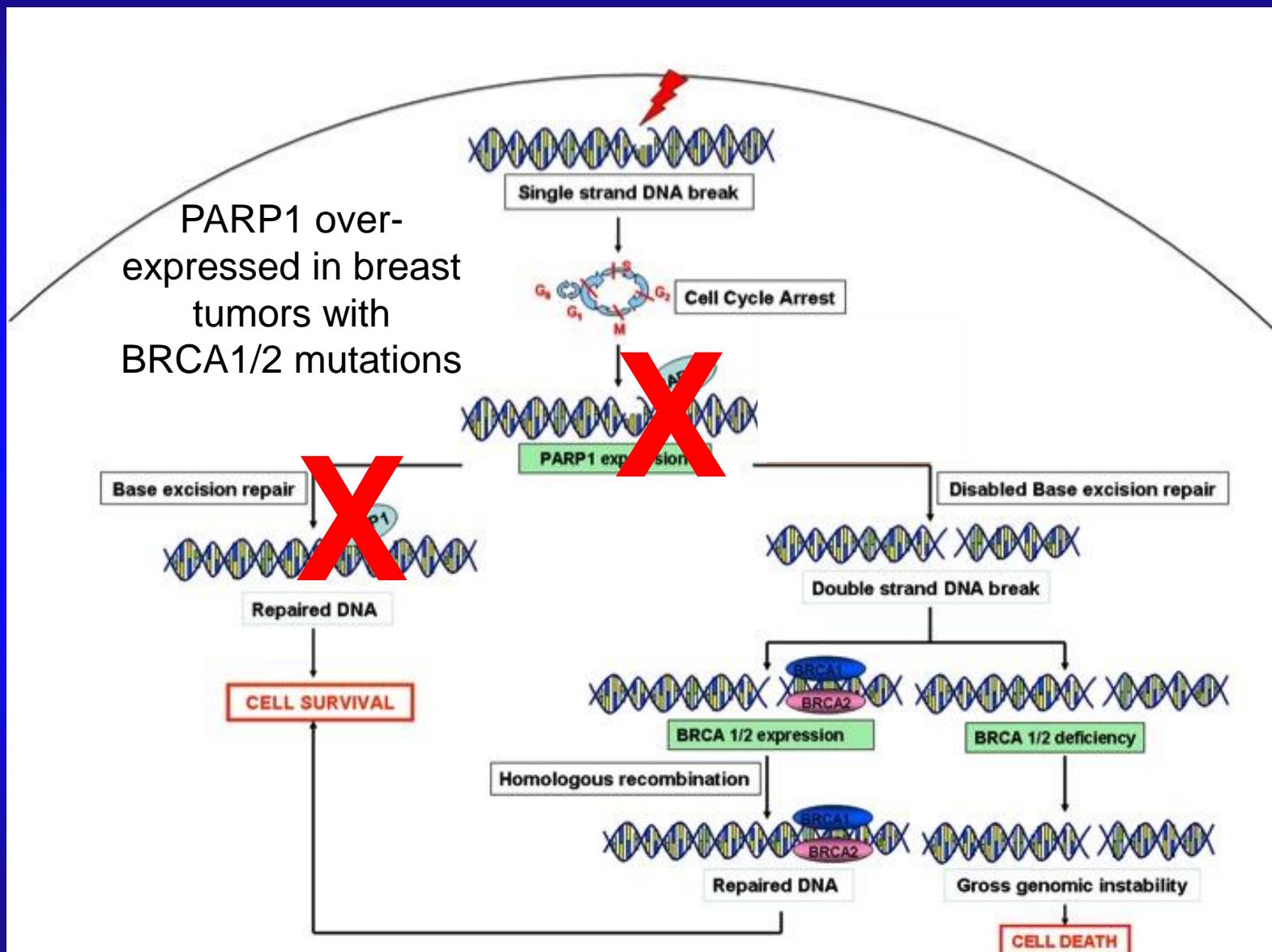


# Targeting Homologous Recombination

Rad52 becomes a salvage pathway when BRCA2 pathway is inactive – makes Rad52 a target for therapy in BRCA2-deficient tumors



# Targeting Base Excision Repair





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Radia  
Marke

### Retinoid pathway and cancer therapeutics

Nathan Bushue, Yu-Jui Yvonne Wan \*

*Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS, 66160, USA*

Comments

### Does Vitamin E Prevent or Promote Cancer?

Chung S



Medical Hypotheses 77 (2011) 326–332

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The anticancer effects of Vitamin D and omega-3 PUFAs in combination via cod-liver oil: One plus one may equal more than two

Martin C. Dyck, David WL Ma, Kelly Anne Meckling \*

*Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, ON, Canada N1G 2W1*

# **Chemotherapy and Radiation**

## **Exploitable cell properties:**

### **Property**

### **Effect of Combined Rx**

Genetic instability of tumors:  
resistance to drugs/radiation  
for different clones

Exploiting tumor phenotype as  
means of improving cell kill

# Chemotherapy and Radiation

## Exploitable cell properties:

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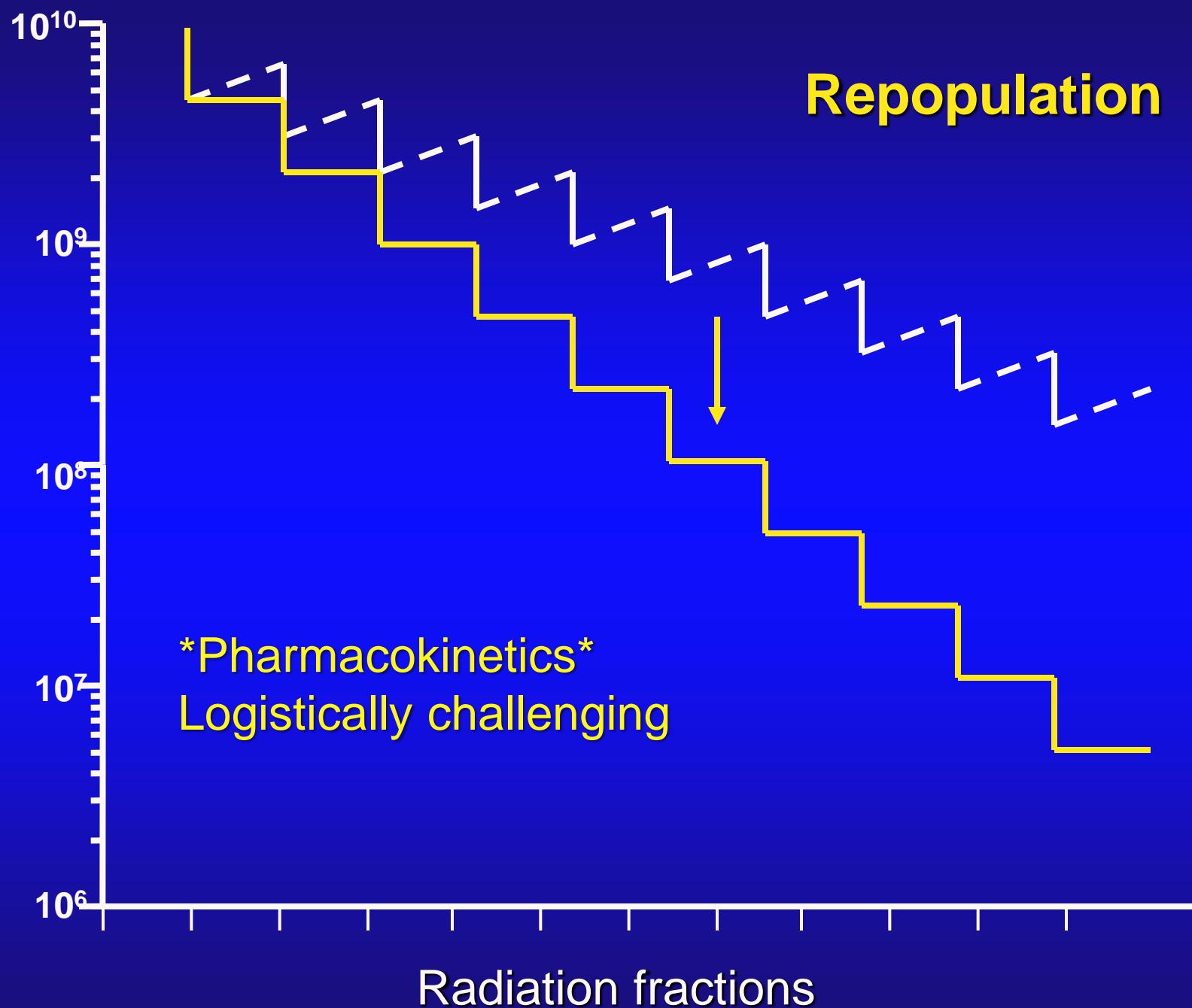
Exploiting tumor phenotype as  
means of improving cell kill

Differences in cell proliferation  
and especially repopulation  
during RT between tumor and  
normal tissue

# Chemotherapy and Radiation

## Repopulation: Counteracting strategies

1. Anticancer drugs given during fractionated radiation may reduce or even inhibit repopulation



# Chemotherapy and Radiation

## Repopulation: Counteracting strategies

1. Anticancer drugs given during fractionated radiation may reduce or even inhibit repopulation

Improves therapeutic ratio **only** if tumor cells are proliferating faster than surrounding normal tissue, e.g. tumors in slow or low proliferating tissues (lung & brain)

Therapeutic **disadvantage** if repopulation is faster in normal tissue, leading to ↑ acute effects, e.g. tumors next to mucous membranes in head and neck

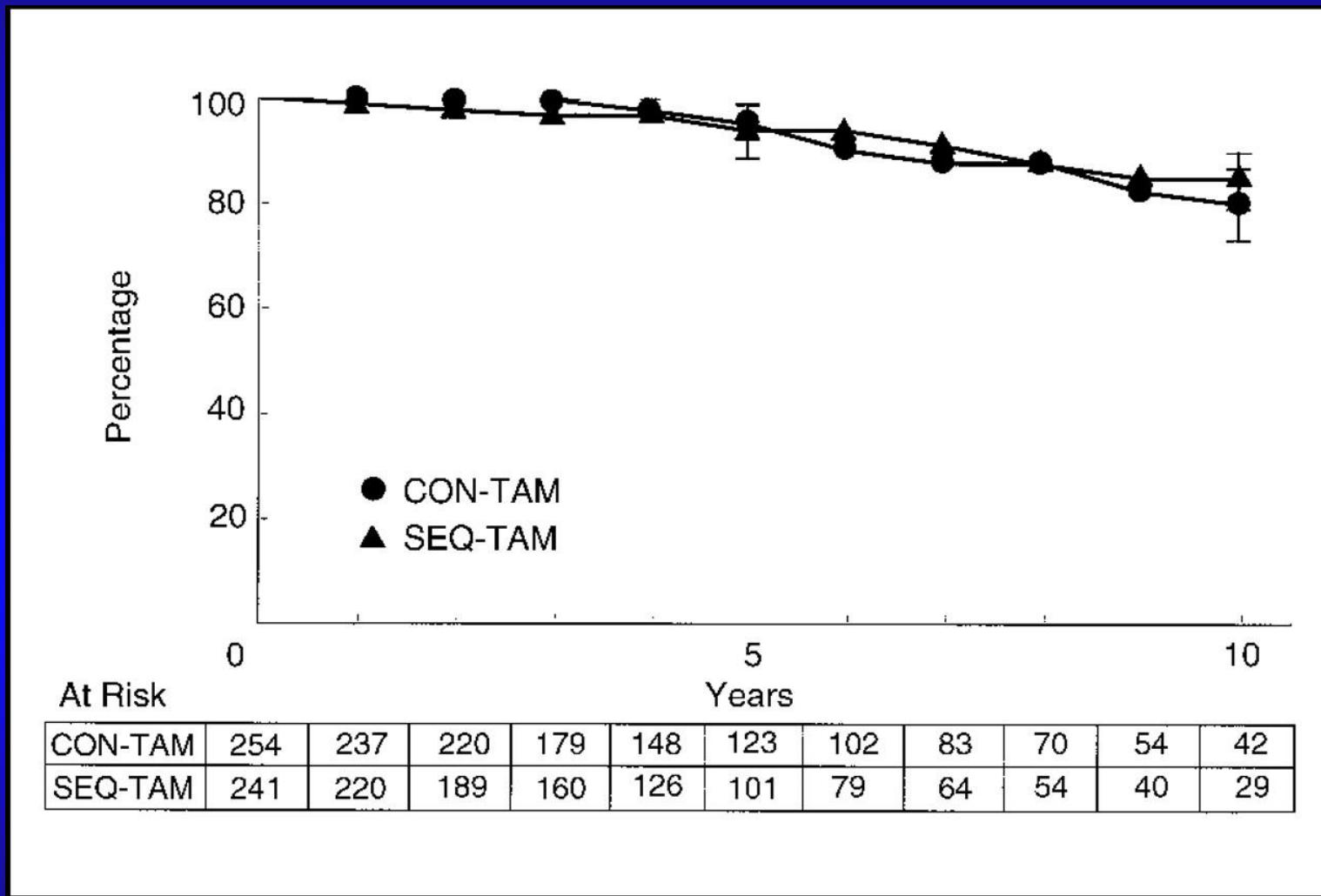
# Chemotherapy and Radiation

## Repopulation: Counteracting strategies

1. Anticancer drugs given during fractionated radiation may reduce or even inhibit repopulation
2. Increase specificity of drugs to proliferating tumor cells, e.g. hormonal agents (tamoxifen, anti-androgens) in breast and prostate cancers

## Overall survival by tamoxifen sequencing.

CON-TAM, concurrent tamoxifen; SEQ-TAM, sequential tamoxifen

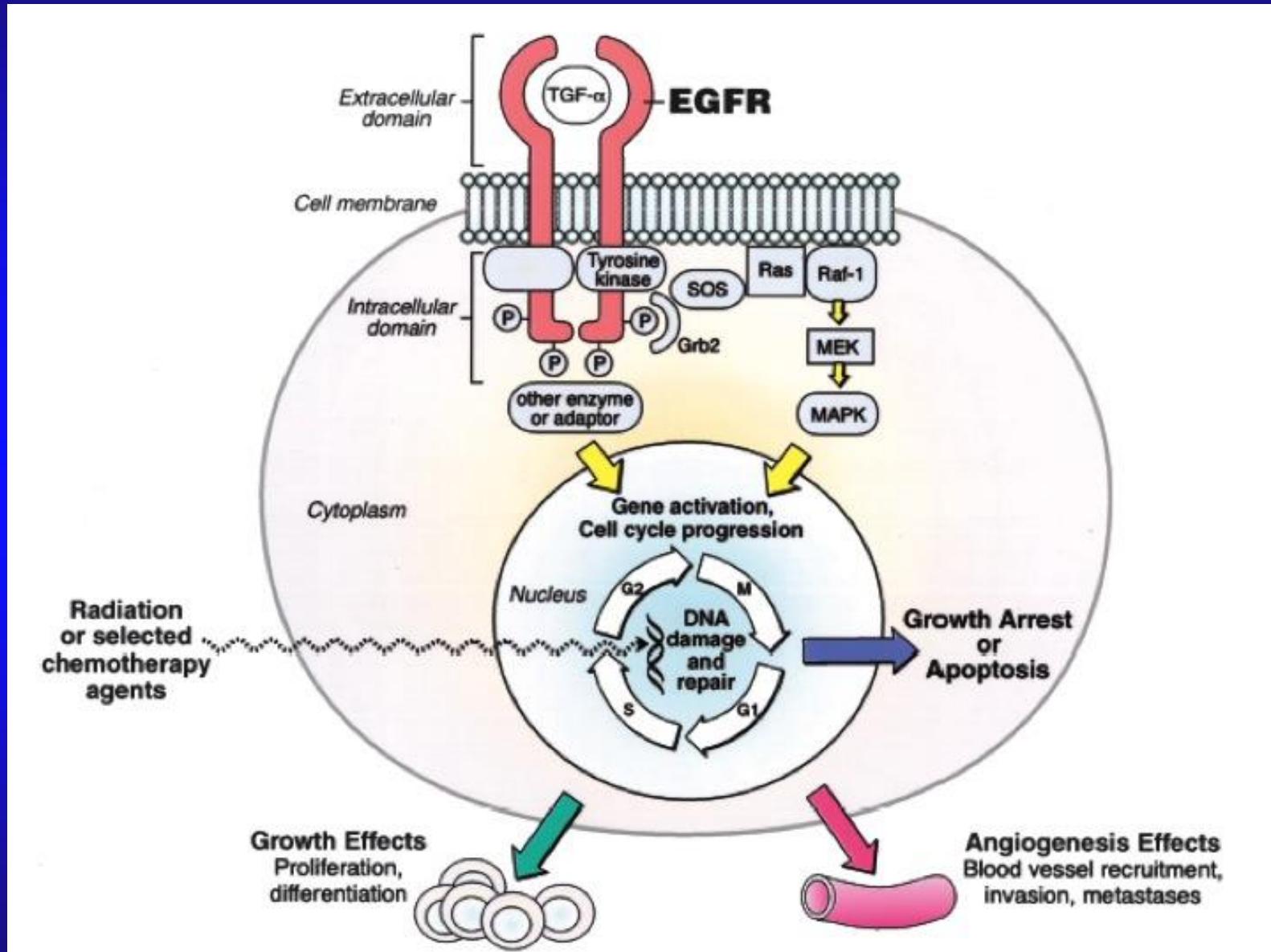


# Chemotherapy and Radiation

## Repopulation: Counteracting strategies

1. Anticancer drugs given during fractionated radiation may reduce or even inhibit repopulation
2. Increase specificity of drugs to proliferating tumor cells, e.g. hormonal agents (tamoxifen, anti-androgens) in breast and prostate cancers
3. Use of molecular targeting
  - epidermal growth factor inhibitors, e.g. VEGF (bevacizumab) or receptor blockers (if expressed on tumor cells), e.g. EGFR blockers (cetuximab, gefitinib)

# Cellular Role of EGFR



# EGFR trials in HNSCC

Study/phase	Regimen	# of patients	Outcome
Trigo et al. (stage III/IV recurrent metastatic HNSCC)	Cetuximab	103	PFS = 2.3mo, OS = 5.9mo
Baselga et al./II (cisplatin refractory HNSCC)	Cetuximab	96	PFS = 2.2mo, OS = 5.2mo
Herbst et al./II (cisplatin refractory HNSCC)	Cetuximab	76	RR = 10%, PFS = 2.8mo, OS = 6.1 mo
Bonner et al./III (locally advanced HNSCC)	Cetuximab + RT RT	211 213	<b>PFS = 17.1mo, OS = 49mo</b> <b>PFS = 12.4mo, OS = 29.3mo</b>
Burtness et al./II (metastatic/ recurrent HNSCC)	<p>Need for optimal timing and sequencing</p> <p>Need for biomarkers for subgroup identification</p>		
Vermoken et al./II (metastatic/ recurrent HNSCC)	Cetuximab Cetuximab + chemo	60 53	CP+PR+SD = 46%, TTP = 70d CP+PR+SD = 26%, TTP = 50d

# Chemotherapy and Radiation

## Exploitable cell properties:

### Property

### Effect of Combined Rx

Genetic instability of tumors  
drug/radiation resistance for  
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Exploiting tumor phenotype as  
means of improving cell kill

Differences in cell proliferation  
and especially repopulation  
during RT between tumor and  
normal tissue

Inhibition of repopulation by  
drugs if tumor repopulates  
faster than normal tissue;  
selective inhibition an  
advantage

# Chemotherapy and Radiation

- Spatial cooperation
- Independent toxicity
- **Using inter-relationship(s) between modalities to improve tumor response**
  - Narrow therapeutic index
    - Agents are insufficient as monotherapy ± radiation
    - Normal tissue toxicity limits use of effective regimens
  - ? reached limits of improving radiation “targeting”
  - Alternative mechanisms
  - Use a radiation sensitizer

# Radiation Sensitizers

- **Halogenated pyrimidines**
  - Activity is dependent on amount of incorporation
  - Differential presumes tumor cells cycle faster than normal tissue
- **Hypoxic cell sensitizers/cytotoxins**
  - Increases radiosensitivity of hypoxic not aerated cells
  - Differential presumes hypoxic cells only occur in tumors

# Radiation Sensitizers

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# Radiation Sensitizers

- **Halogenated pyrimidines**

**Examples:** 5-iododeoxyuridine (IudR), 5-bromo-deoxyuridine (BrdU)

**Mechanisms:**

- The halogen groups (Cl, Br, I) are similar in size to  $\text{CH}_3$
- IudR and BrdU similar to thymidine; incorporate into DNA chain
- More substitution = more damage
- ↑ sensitivity to  $\gamma$ -rays and UV (BrdU phototoxic)
- **Disadvantage:** Needs several generations of incorporation → intra-arterial infusion

# Radiation Sensitizers

- Hypoxic cell sensitizers/cytotoxins

Non-pharmaceutical means of improving oxygen supply :

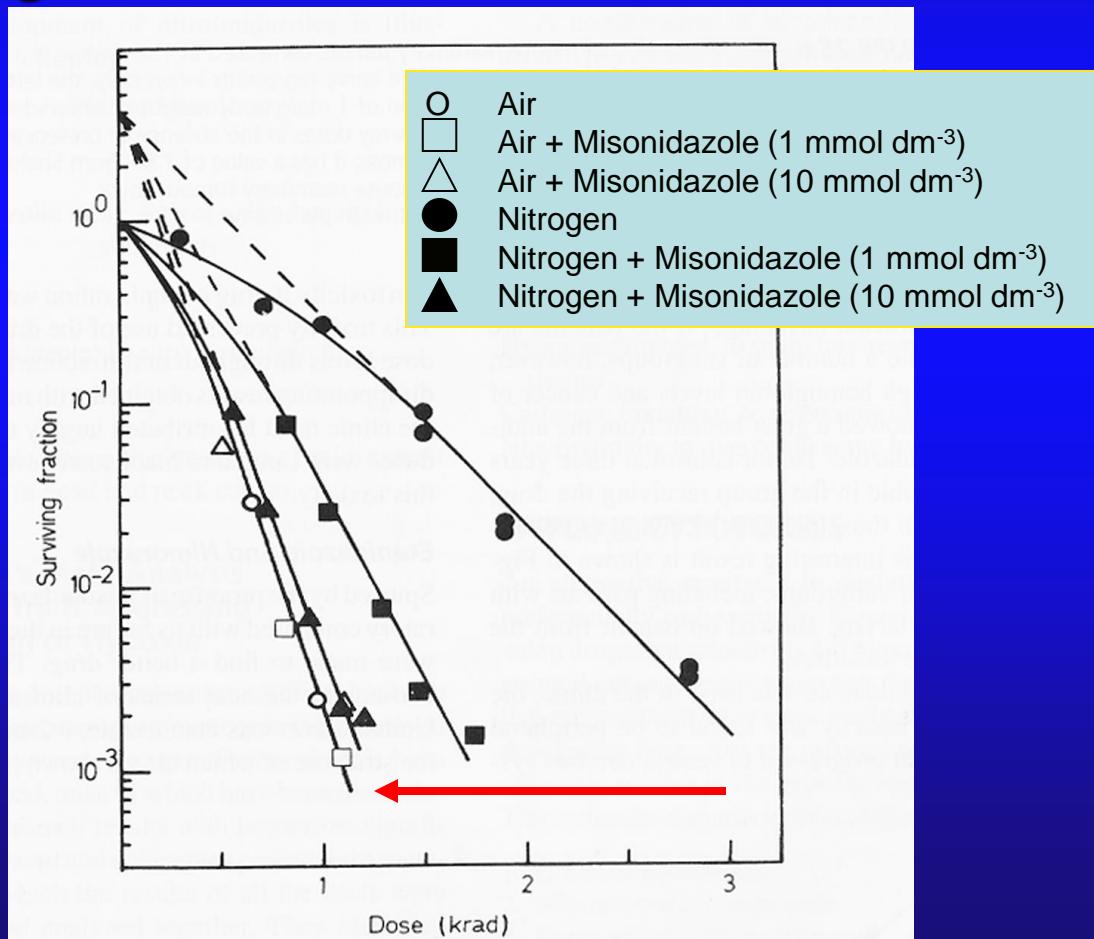
- Anemia -ive effect → blood transfusions
- Smoking (CO) ↓ oxygen unloading capacity ( $\text{VO}_2$ )
- ↑ oxygen carrying capacity of blood -- perfluorocarbon emulsions (? use in PDT/imaging)
- Efaproxiral: synthetic modifier of hemoglobin (brain mets for lung and breast)
- Nicotinamide (vitamin B3 analogue) [transient]
- + carbogen (95%  $\text{O}_2$ ; 5%  $\text{CO}_2$ ) [chronic]
- ARCON: **A**R = accelerated radiation; **C**O = carbogen; **N** = nicotinamide

# Radiation Sensitizers

- **Nitroimidazoles**

## Misonidazole:

- **In vitro:** good sensitization of cells in culture

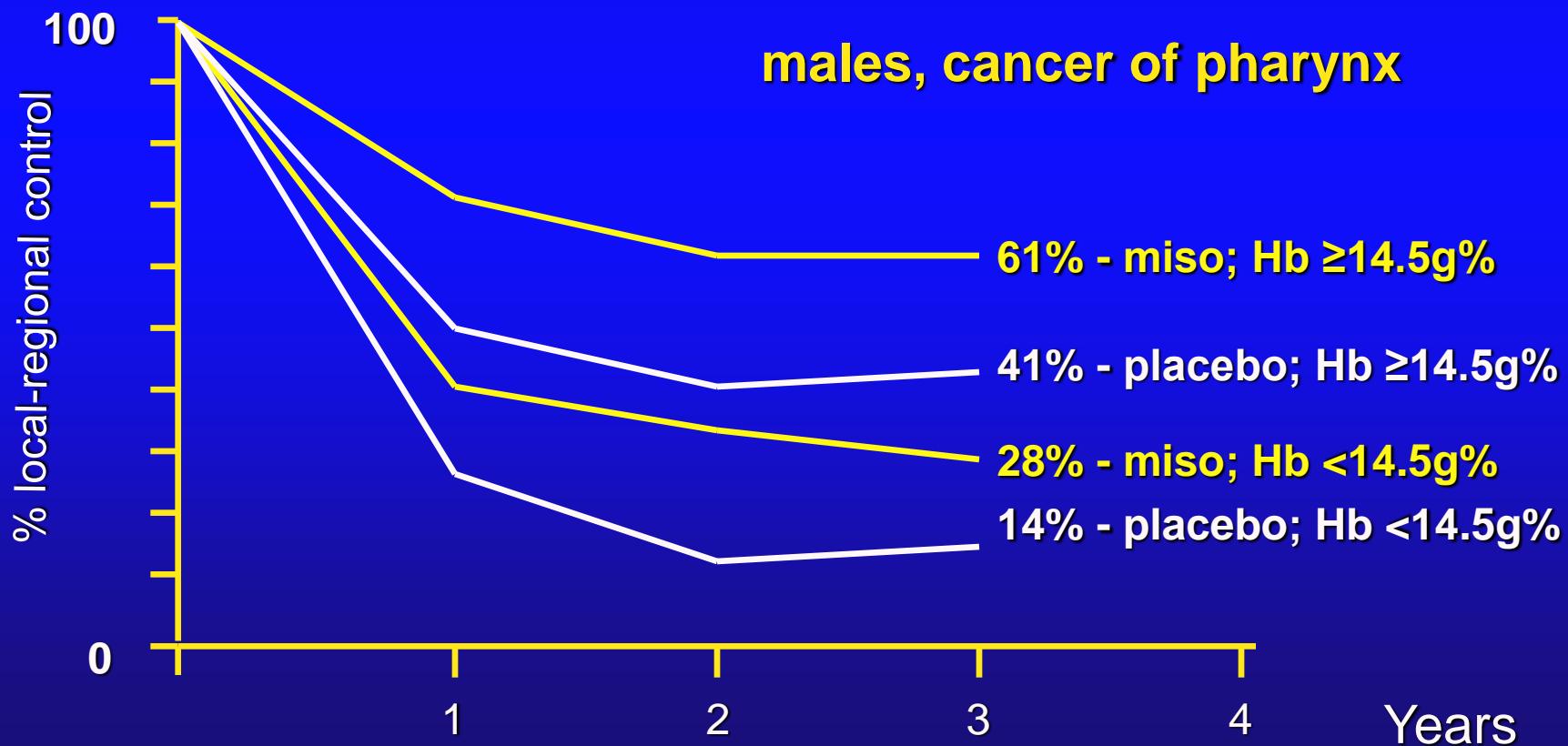


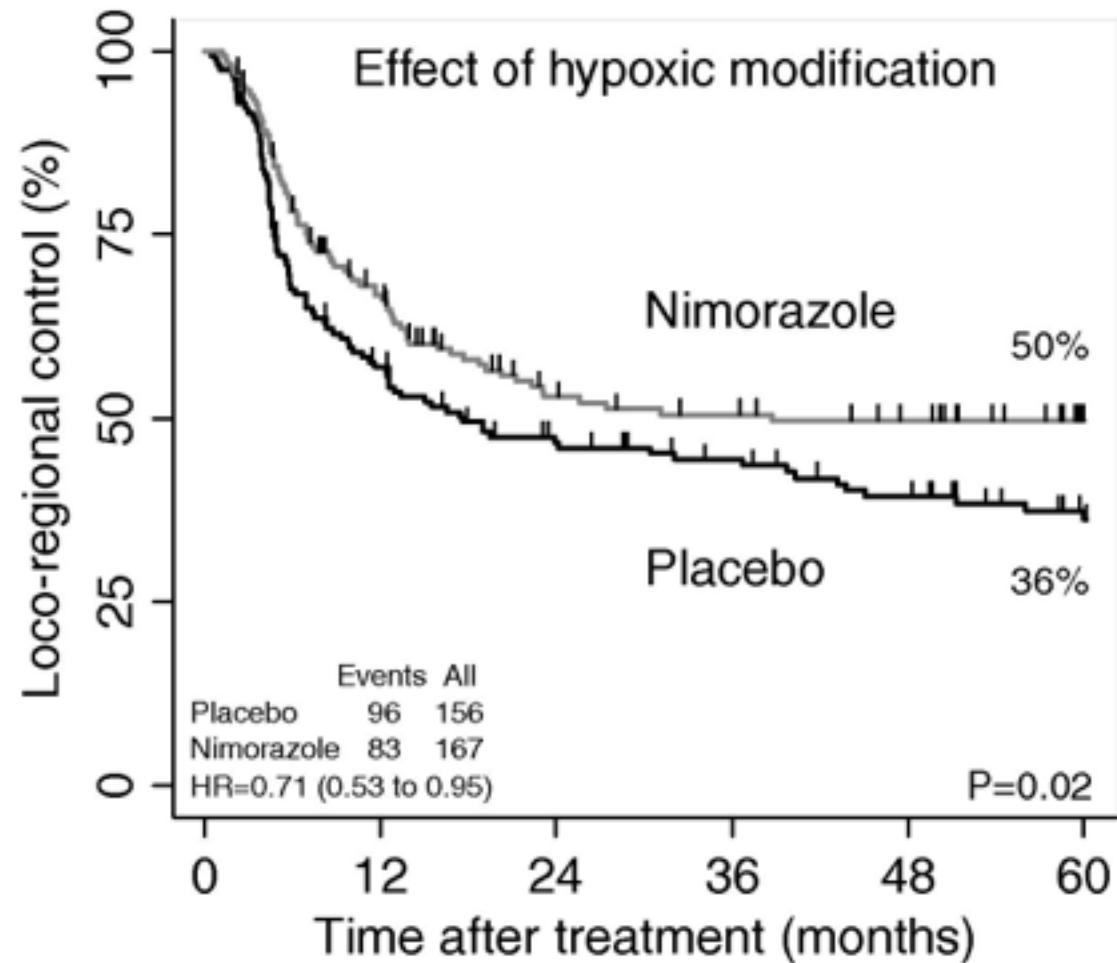
# Radiation Sensitizers

- Nitroimidazoles

## Misonidazole:

- **Clinic:** Only Danish head & neck trial +ive



**B**

At risk

Placebo	156	85	64	55	46	34
Nimorazole	167	102	70	64	58	38

CLINIC benefit in head & neck (DAHANCA)

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# Radiation Sensitizers

- **Hypoxia meta-analysis (Overgaard)**

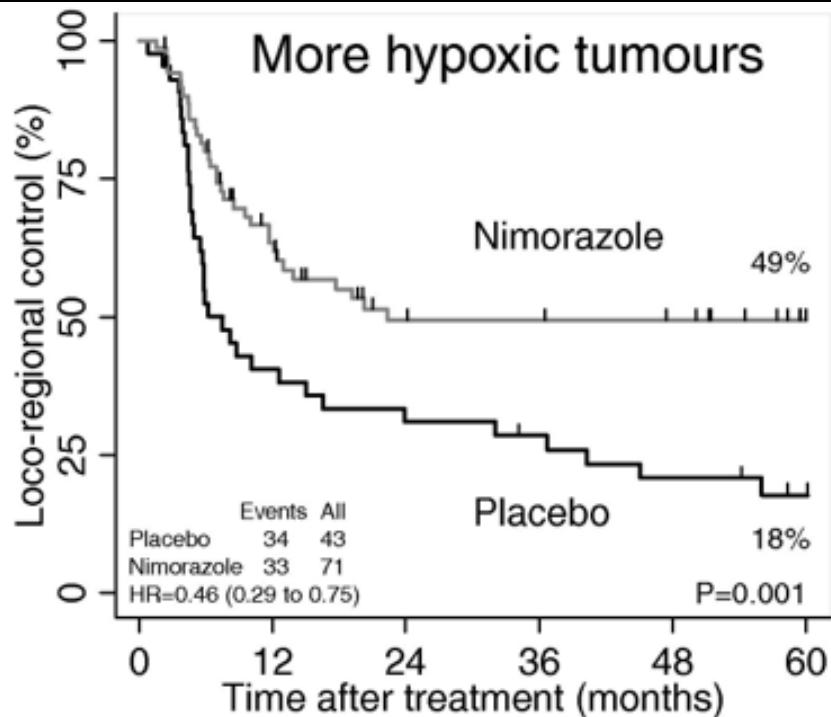
10,602 patients, 82 trials, HBO vs. sensitizers vs. carbogen vs. blood transfusions

- Greatest benefit in head & neck (largest group?)
- Hypoxia problem ↑ in squamous cell carcinomas,  
↓ in adenocarcinomas
- Improvement in local control = 5%; ↑ survival = 3%; ↑ complication rate = 0.6% (NS)

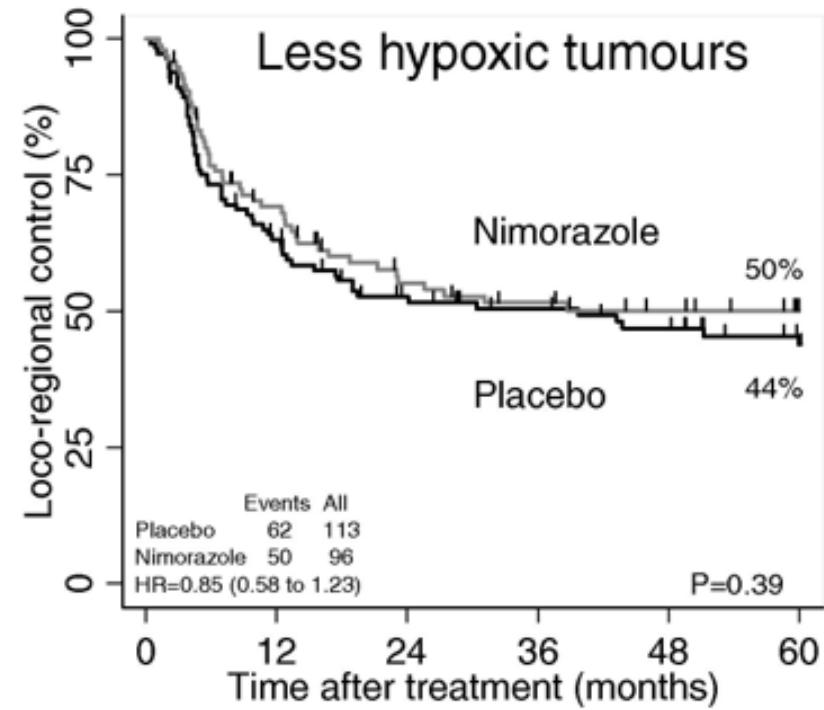
# Radiation Sensitizers

- Nitroimidazoles

A



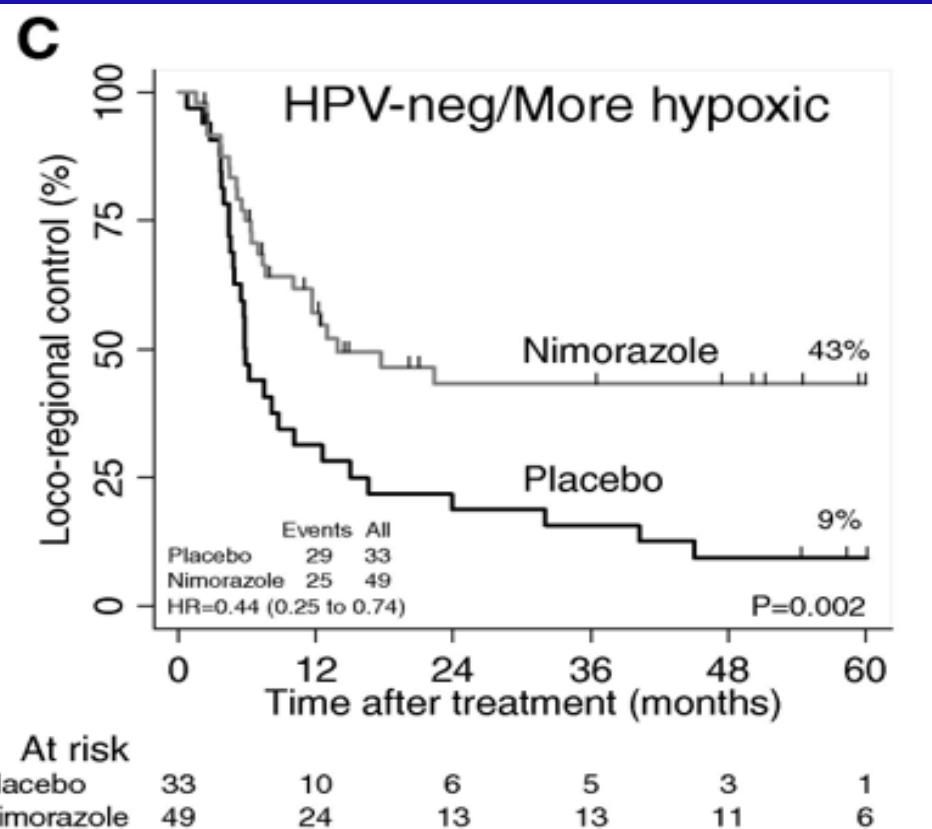
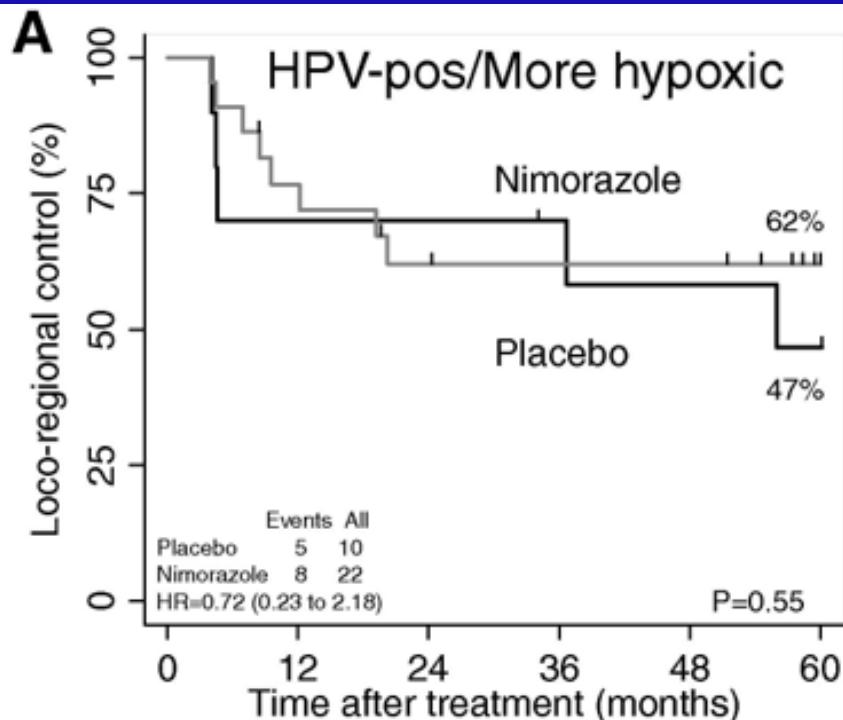
B



- **Clinic:** benefit in head & neck (DAHANCA)

# Radiation Sensitizers

- Nitroimidazoles

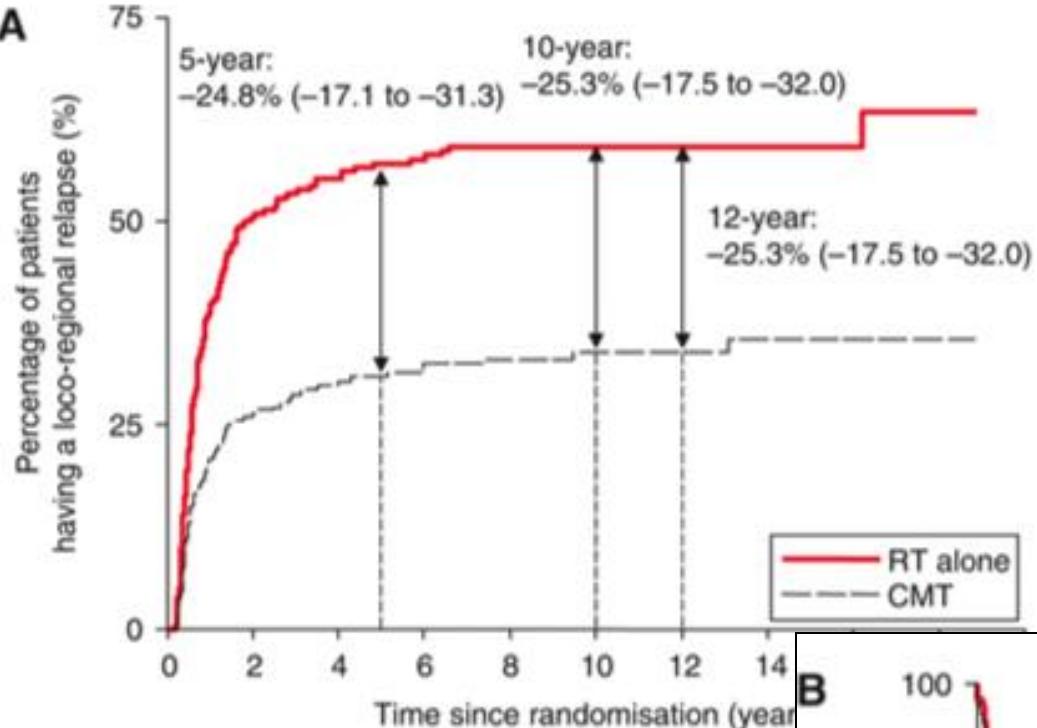
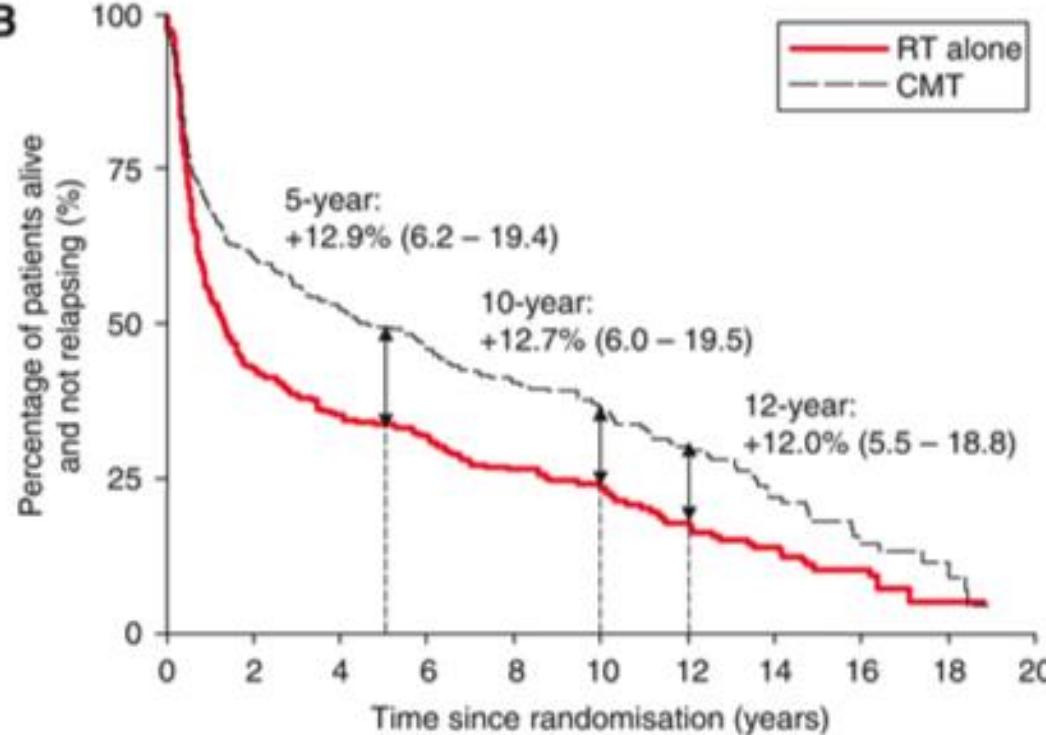


→ much less toxic (large doses)

- **Clinic:** benefit in head & neck (DAHANCA)

# Radiation Sensitizers

- Hypoxic cytotoxins
  - Quinone antibiotics
    - ❖ Examples: mitomycin C
    - ❖ Differential between hypoxic and oxic cells poor
    - ❖ Requires very low levels of oxygen for maximum cytotoxicity
  - Benzotriazine di-N-oxides

**A****B**

## UKCCR Anal Cancer Trial

# Radiation Sensitizers

- Hypoxic cytotoxins
  - Quinone antibiotics
    - ❖ Examples: mitomycin C
    - ❖ Differential between hypoxic and oxic cells poor
    - ❖ Requires very low levels of oxygen for maximum cytotoxicity
  - Benzotriazine di-N-oxides
    - ❖ Examples: tirapazamine
    - ❖ Hypoxia → oxidizing molecule (cyt P450)
    - ❖ Excellent differential between hypoxic and oxic cells, *in vivo* and *in vitro*

# **Chemotherapy and Radiation**

- Spatial cooperation
- Independent toxicity
- Using inter-relationship(s) between modalities to improve tumor response
- **Protection of normal tissue (radioprotectors)**

# Radiation Protectors

**Discovery:** substances that confer protection

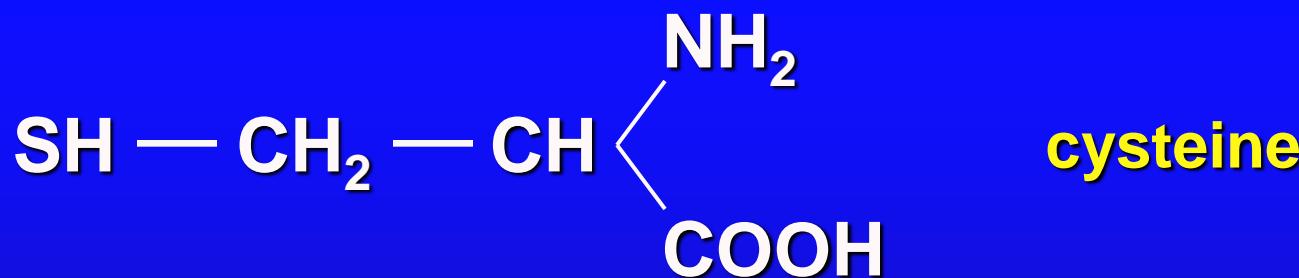
- **Examples:** sodium cyanide, carbon monoxide, epinephrine, histamine, serotonin
- **Mechanism:** cause vasoconstriction or alter metabolism causing reduction in oxygen concentration in tissue/organ
- **Radioprotectors:** substances that confer protection without directly affecting radiosensitivity of cells
- **Examples:** sulfhydryl compounds
- **Mechanism:** scavenge free radicals

# Radiation Protectors

- **Sulfhydryl compounds**

## Structure:

- Free (or potential) SH group at one end, strong base function at other, separated by short (2-3) straight carbon chain



# Radiation Protectors

- **Sulfhydryl compounds**

## Mechanisms:

Efficient radioprotectors against sparsely ionizing radiation

- Free-radical scavenging against O<sub>2</sub>-based free-radical generation (RT or drugs)
  - ❖ Examples: dimethyl sulfoxide (DMSO), superoxide dismutase enzymes (SODs)
  - ❖ Disadvantages: presence at time of radiation; differential between normal and tumor tissues

# Radiation Protectors

- **Sulfhydryl compounds**

## Mechanisms:

Efficient radioprotectors against sparsely ionizing radiation

- Free-radical scavenging against O<sub>2</sub>-based free-radical generation (RT or drugs)
- Hydrogen atom donation to facilitate direct repair to a radical site on a macromolecule, e.g. sites of DNA damage
  - ❖ Examples: glutathione, cysteine

# Radiation Protectors

- **Sulfhydryl compounds**

Cysteine, etc, are toxic (nausea & vomiting)

- Post-WWII, research at Walter Reed Institute for Research
- >4,000 compounds tested
- Addition of phosphate group reduced toxicity

# Radiation Protectors

- WR compounds

**WR-638 (cystaphos)**    $\text{NH}_2\text{CH}_2\text{CH}_2\text{SPO}_3\text{HNa}$

- Oral tablets carried by *Soviet* troops
- Requires intravenous or intraperitoneal administration

# Radiation Protectors

- WR compounds

**WR-638 (cystaphos)**    $\text{NH}_2\text{CH}_2\text{CH}_2\text{SPO}_3\text{HNa}$

- Oral tablets carried by Soviet troops
- Requires intravenous or intraperitoneal administration

**WR-1607**



- Effective radioprotector: dose of 10 mg/kg
- Cardiotoxicity
- Marketed as d-CON

# Radiation Protectors

- WR compounds

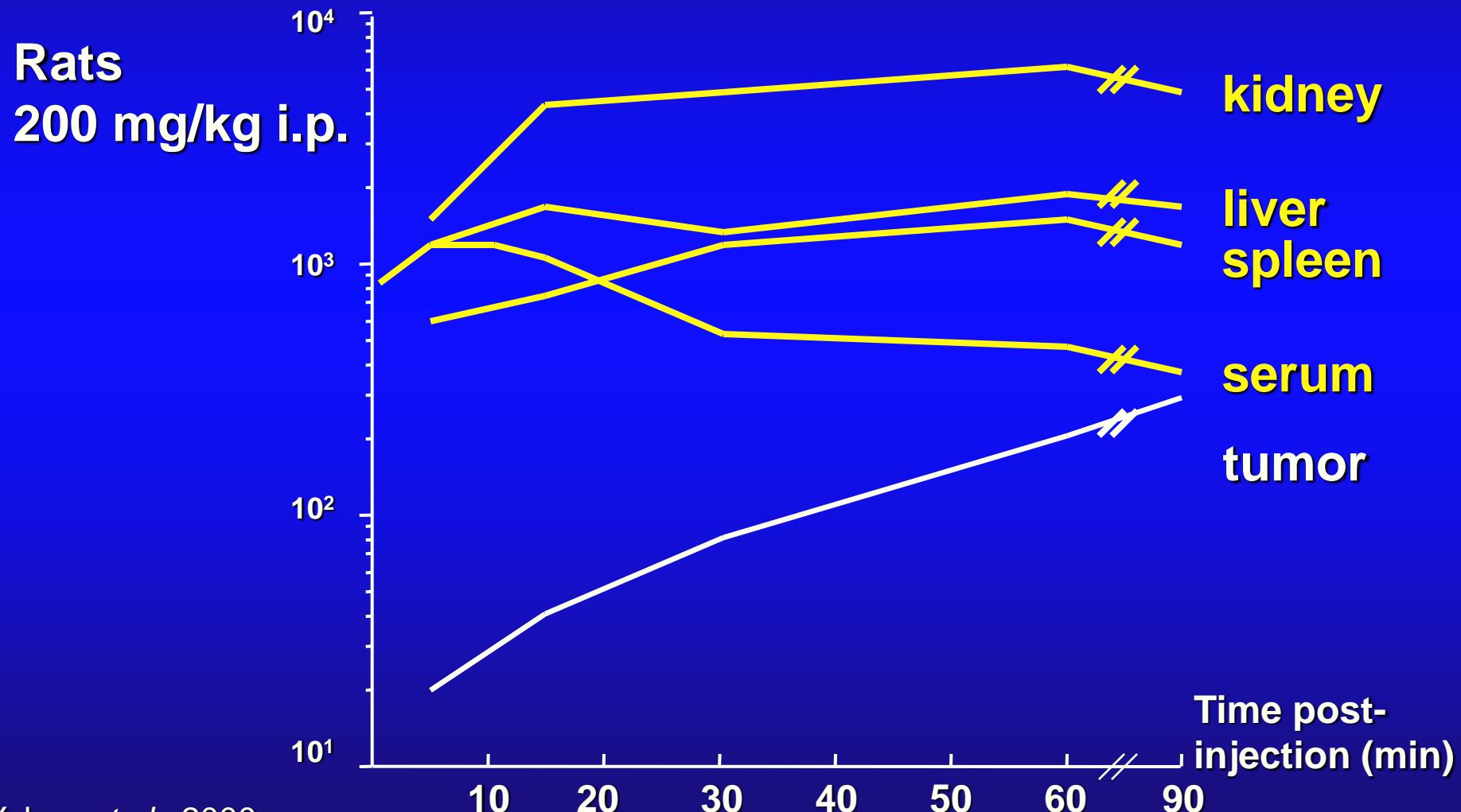
**WR-2721 (amifostine)**



- Phosphorothioate – prodrug
- Dephosphorylation (alkaline phosphatase)  
→ WR-1065
- Enters normal tissue cells by facilitated diffusion,  
tumor cells by passive diffusion,  
or
- differential from better normal tissue vasculature,  
or
- ↓ levels of alkaline phosphatase in tumors

# Radiation Protectors

- WR-2721 (amifostine)



# Radiation Protectors

- WR compounds

## WR-2721 (amifostine)

- Differential protection in normal tissues (bone marrow, gut, salivary glands > lungs > brain)
- For complete benefit, need to increase radiation dose ?
- **Clinical trials:** some benefit – RTOG phase III for xerostomia

# **Chemotherapy and Radiation**

## **Possible exploitable cell properties:**

### **Genetic instability**

- elimination of resistance
- selective lethality

### **Prevention of accelerated repopulation**

- sequencing
- inhibition of growth

# **Chemotherapy and Radiation**

## **Possible exploitable cell properties:**

Increased molecular targeting:

- alteration of chromatin structure
- DNA repair inhibitors
- farnesyltransferase inhibitors
- angiogenesis inhibitors
- cyclooxygenase-2 inhibitors
- proteasome inhibitors
- apoptosis inducers
- gene or siRNA transfer

# **Chemotherapy and Radiation**

## **Possible exploitable cell properties exist**

**However, for them to work:**

- Need biomarkers to identify target tumors/ patient subgroups that will benefit
- Need entire team of oncologists to work in close collaboration to identify optimal doses, timing, etc.
- Any new treatment must demonstrate improved therapeutic ratio