ON REDUCING DAMAGE FROM RADIOTHERAPY AND CHEMOTHERAPY

OR

USING ADAPTIVE RESPONSE IN THERAPY

CARE = Cell Adaptive Response Effect

RICHARD BLANKENBECLER

Professor Emeritus, SLAC, Stanford University

Adjunct Professor of Physics, VaTech

Adjunct Fellow, Nevada Cancer Institute

SCALE of the PROBLEM

New US cancers ≈ 1.5 million/year

After surgery: radiation ≈ 0.8 million

After surgery: chemotherapy ≈ 0.7 million

Many undergo Both treatments.

Length and Quality of Life Issues

- Need to Improve Effectiveness of Therapy
- Need to Reduce Unintended Side Effects
- Need to Reduce Secondary Cancers caused by the radiation treatment itself.

PROPOSAL

Use protective cell adaptive response effect

to LOW-DOSE radiation exposure (≈ CT Scan)

PREFACE

- **Low Dose** Effects can now be studied ($\leq$ 0.1Gy) using **microarray technology** (gene chip).

- Experimentally, a Low Radiation Dose induces a **cell adaptive response effect (CARE)** that offers protection against a subsequent high dose.

- Low Dose covers range 0.01-0.10 Gy where Chest CT scan $\approx$ 0.01 Gy.

- Almost all discussion of using adaptive response is about **radiation worker protection**.
  LNT:The Linear No-Threshold hypothesis

Main Point of this Talk:

Cell Adaptive Response can have different consequences for Therapy than for Protection.

Protection vs Therapy

Consider a person living in their own particular background radiation environment.

What is the risk associated with increasing their radiation exposure?

Consider a person about to receive high dose radiotherapy with its associated effects.

Is it possible to reduce the net damage to healthy cells arising from the therapy itself?

These are VERY different questions and require different approaches and different data.

Use of cellular adaptive response in therapy:

Simple Idea:

Prior to large dose radiotherapy,

irradiate with a low dose

only those healthy cells that will

inevitably receive a large dose.

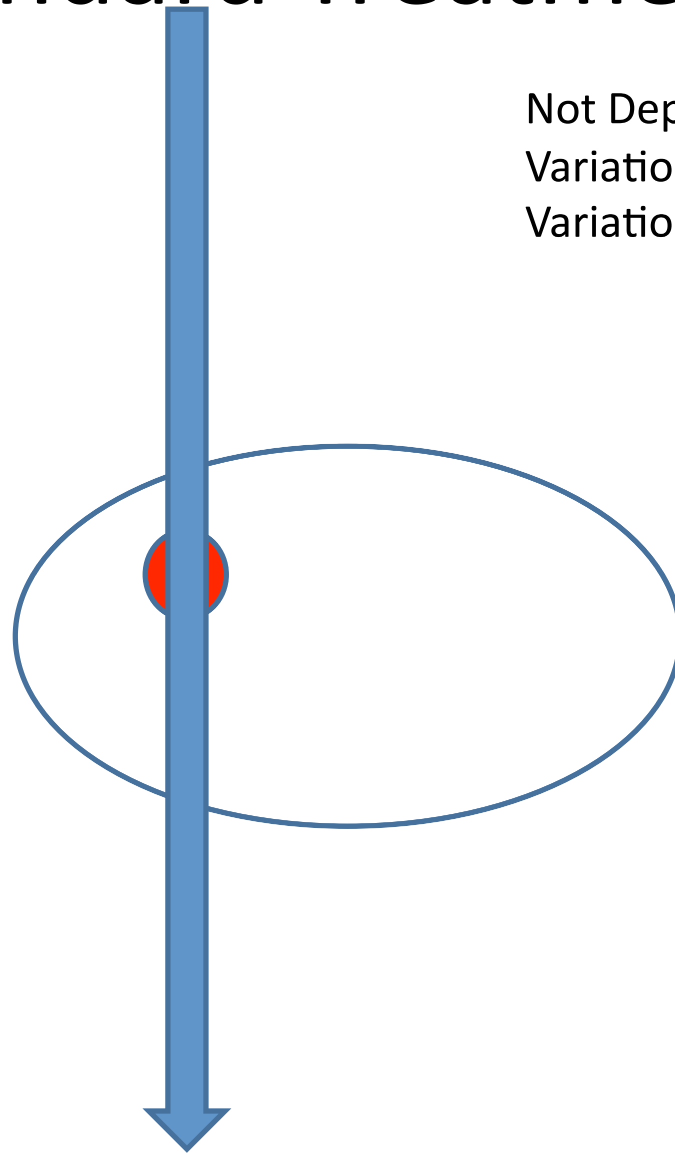
The cancerous cells are not irradiated at this stage.

After a suitable time delay, the cancerous cells are HEAVILY irradiated.

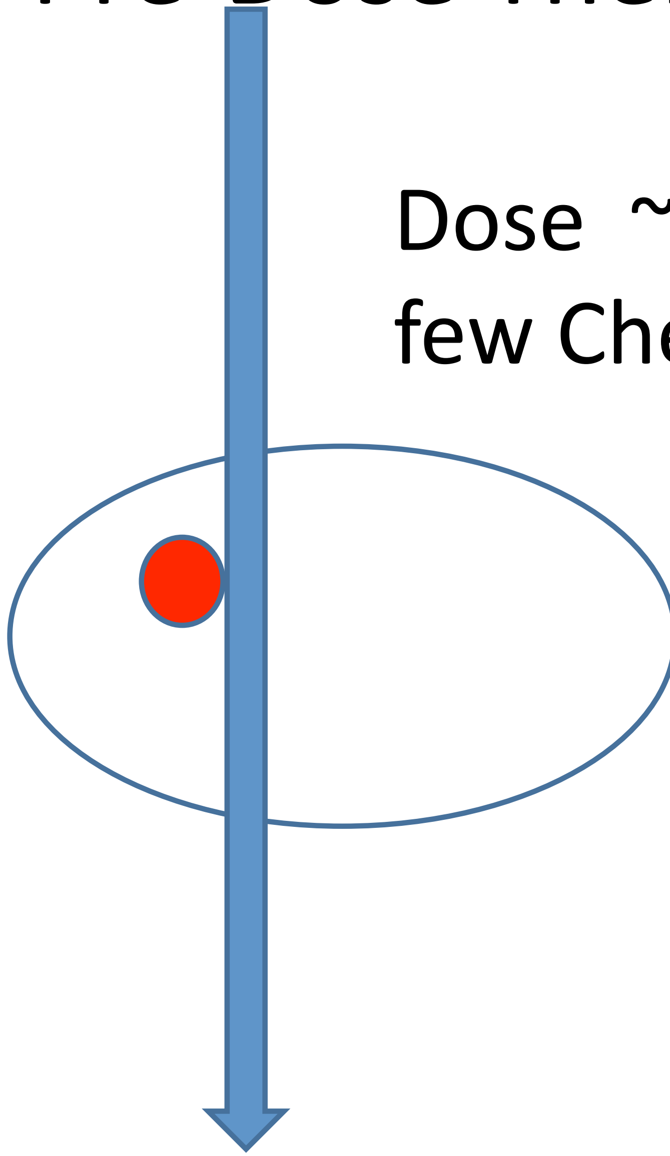
(standard treatment).

Standard Treatment

Not Depicted:
Variation in Intensity
Variation in shape



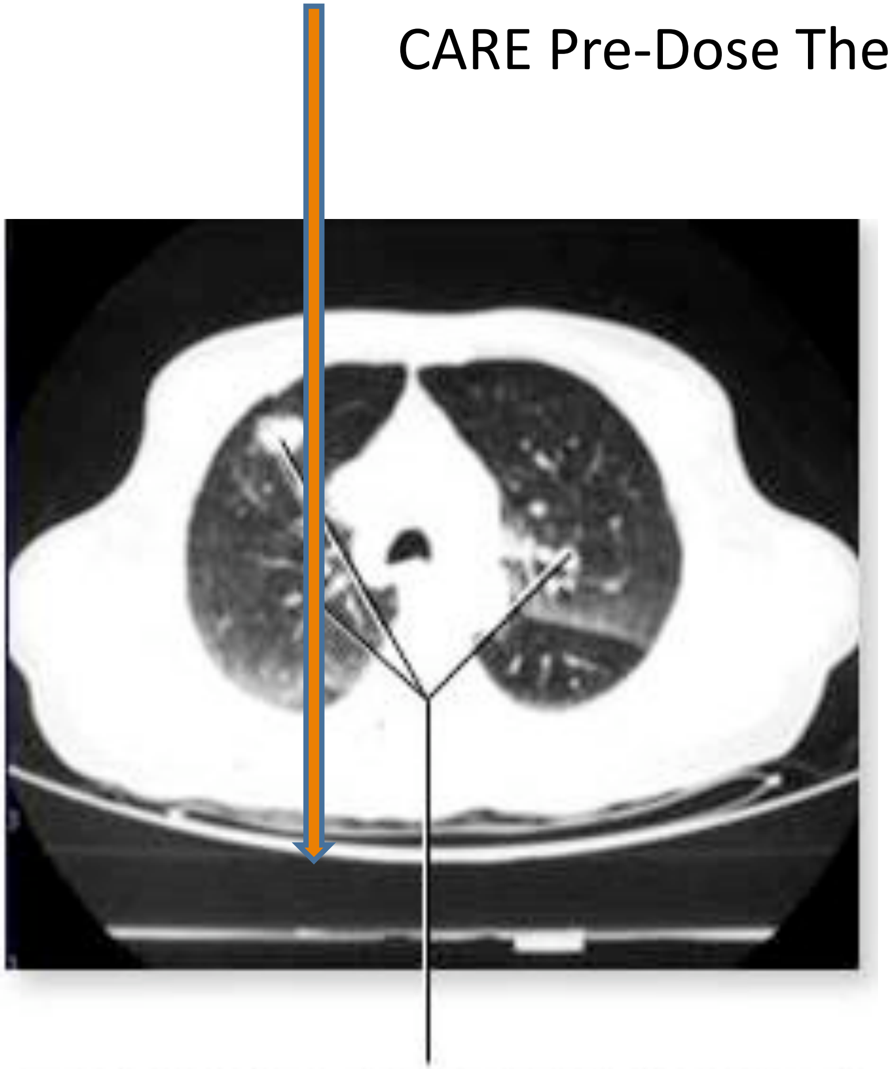
CARE Pre-Dose Therapy



Dose ~ equal to a few Chest CT Scans

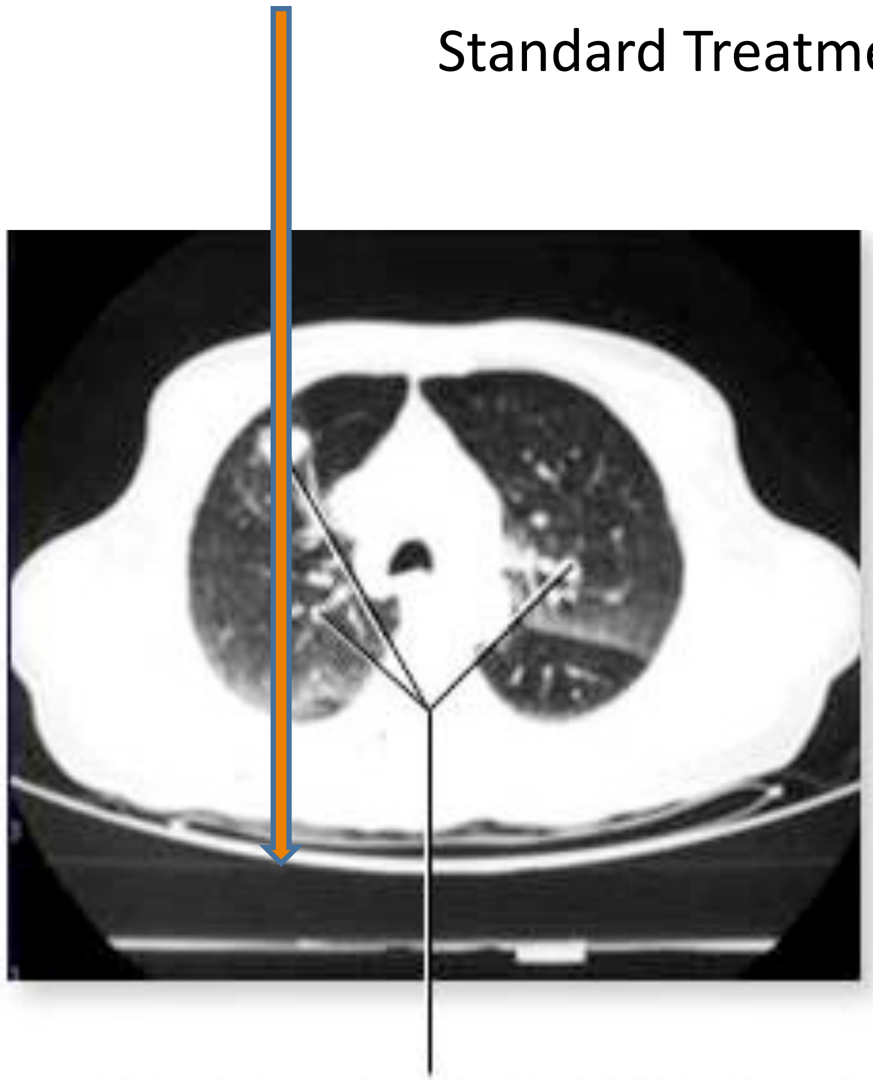
Now Reverse Order
and combine
for new therapy

CARE Pre-Dose Therapy



Bronchial cancer (white areas) in the lung (black area)

Standard Treatment



Bronchial cancer (white areas) in the lung (black area)

LOW DOSE EFFECTS NOW OBSERVABLE

DOE - Lawrence Livermore Laboratory

Biology and Biotechnology Research Program

A. Wyrobek, Health Effects Genetics Div.

Experiments done on mice and human cell cultures.

Microarrays: up to 20,000 different genes

Cells respond to low-level ionizing radiation by turning on or off hundreds of genes,

including those specialized in repairing

damaged chromosomes, membranes, and proteins

and countering cellular stress.

Genes involved at low dose are different from

the ones responding to high-dose radiation.

Livermore, cont'd

Mice - Cesium-137 Source - Number of Modulated Genes

Dose (Gy)	Wait Time 1/2 hr	Wait Time 4 hr	time independent
0.1	176	275	48
2.0	147	278	16

Note: The two gene sets are very different

Genes modulated at 0.1 Gy include:

DNA, RNA, protein synthesis and repair;

heat shock; stress response;

cell-cycle control; chemical stress;...

Quote - "Low Dose Exposure Can Protect"

Lymphoblastoid (blood) cells exhibited adaptive response.

Apply 0.05 Gy, wait 6 hours, apply 2.0 Gy

Chromosomal damage reduced by 20 to 50 percent compared to cells with no priming dose.

Brenda Rodgers and Kristen Holmes:
Radio-adaptive response to .. exposure at Chernobyl

Dose Response, 6:209-221, 2008

MN = MicroNucleus - broken chromosome fragments

Low Dose (cGy)	Dose Duration	Wait Time	High Dose (Gy)	MN Freq	
0	-	-	0	0.3	Natural
0	-	-	0	0.4	Backgrnd
9.8	20 da	-	0	0.3	Low
9.1	10 da	-	0	0.3	Dose
9.1	20min	-	0	1.0	only
0	-	-	1.5	4.5	High
9.8	20 da	24hr	1.5	4.1	Low
9.1	10 da	24hr	1.5	2.8	plus
9.1	20min	24hr	1.5	1.7	High

Adaptive Effect has been well established for some time.

"Radiation Biology of Low Doses"
by R. E. J. Mitchel, 2002.
Tested normal human skin cells ability to repair

subsequent DNA damage from radiation.

Compared High Dose with Low+High Dose Sequence.

Low+High Sequence - fewer broken chromosomes

Actually decreased cancer risk by 2-3 fold.

"The extra low dose application increased error-free DNA repair competence."

Not atypical Values in Experiments

Low dose = 0.01 to 0.1 Gy   High Dose ≈ 4 Gy

R. E. J. Mitchel, cont'd – Mice

treatment	Lifespan(days)
control	727
0.1 Gy →24hr →1.0 Gy	578
1.0 Gy	486

treatment	Malignant Transformation Freq.$\times 10^{-4}$
control	4
0.1 Gy →24hr →4.0 Gy	16
4.0 Gy	41

Repair of broken chromosomes - human fibroblasts

Moderate Dose(Gy)	Wait Time	High Dose (Gy)	MN Freq per cell	
0	-	0	0.06	Control
0.5	-	0	0.09	Low
0	-	4	1.1	High
0.5	-	4	0.7	Combo
0.5	5hr	4	0.45	Combo

Le, Xing, Lee, Leadon, Weinfeld:
Science (1998)

Repairing DNA damage.

Time required for 50% DNA lesion removal.

pre-dose	Delay	High dose	time
-	-	2.0 Gy	100 min
0.25 Gy	4 hr	2.0 Gy	50 min

CHEMO-THERAPY (Mitchel)

Low doses of in vivo beta-irradiation of mouse skin
24 hr prior to treatment with a
DNA damaging chemical carcinogen

reduced tumor frequency by about 5-fold.

Dr. John Robertson, head radiation oncology, VaTech

Dr. Blaise Burke, radiation oncology, Vet Hosp of San Diego

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(1) Microarray experiments on Low-Dose effects on canine

cell line - protective adaptive response seen.

Modulated genes identified.

(2) Tests of Treatment protocol on canine patients

have started - 8 dogs in study with control.

Minimal bad after effects – rapid recovery.

Cancers in remission. More trials to be performed.

(3) Both radiation and chemo-therapy will be tested.

"Does a low-dose pre-radiation induce cytoprotective gene activity in cells adjacent to tumors undergoing radiation therapy?"

R. Blankenbecler, B. Burke and J. Robertson, to be published

Madame Curie

Russ(1909) first showed that mice treated with low-level radiation were more resistant against bacterial disease.

Russ, V. K.,Consensus of the effect of X-rays on bacteria, Hygie,Vol. 56, pp. 341-344, (1909)

Yonezawa M., et.al.,(1996)- ICR-mice

treatment	% survival(30 days)
control	100
0.05 Gy →?delay? →8.0 Gy	70
8.0 Gy	30

Radiation Workers

Cell Adaptive Response can reduce total damage.

Workers and First Responders exposed due to a nuclear accident or terrorist attack.

Following exposure to low dose, workers retire.

After 12-24 hours, they return to contaminated area.

No need to increase allowed total exposure.

Conclusions

(1) Improve Effectiveness of Radiation Therapy
(higher dose/session)

(2) Reduce Treatment Duration

(3) Reduce bad side effects from treatment
(more healthy cells survive)

(4) Reduce probability of Follow-On Cancer
(caused by treatment itself)

(5) Radiation Worker and First Responder Protection