Extreme Hypo-fractionation

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Health Care Global

Famous Opinions

- "When the Paris electrical exhibition closes, no more will be heard of electricity again"

  - Prof Erasmus Wilson, Oxford University – from Book of Lists 2

- "Television will never appeal to the average American Family"

  - New York times editorial - from Book of Lists 2

Introduction

- Practical applications of extreme Hypo-fractionation (EHF) Guiding principle: High concern for devastating, irreversible damage. Kavanagh BD, McGarry RC, Timmerman RD: **Extracranial radiosurgery (stereotactic body radiation therapy) for oligometastases.** *Semin Radiat Oncol 2006, **16:77-84.***

- Results are rewarding in certain clinical situation
  - Local control can be improved from 30-40% to → 80-100%

- **Full Potential unexplored**

Definition of Extreme Fractionation

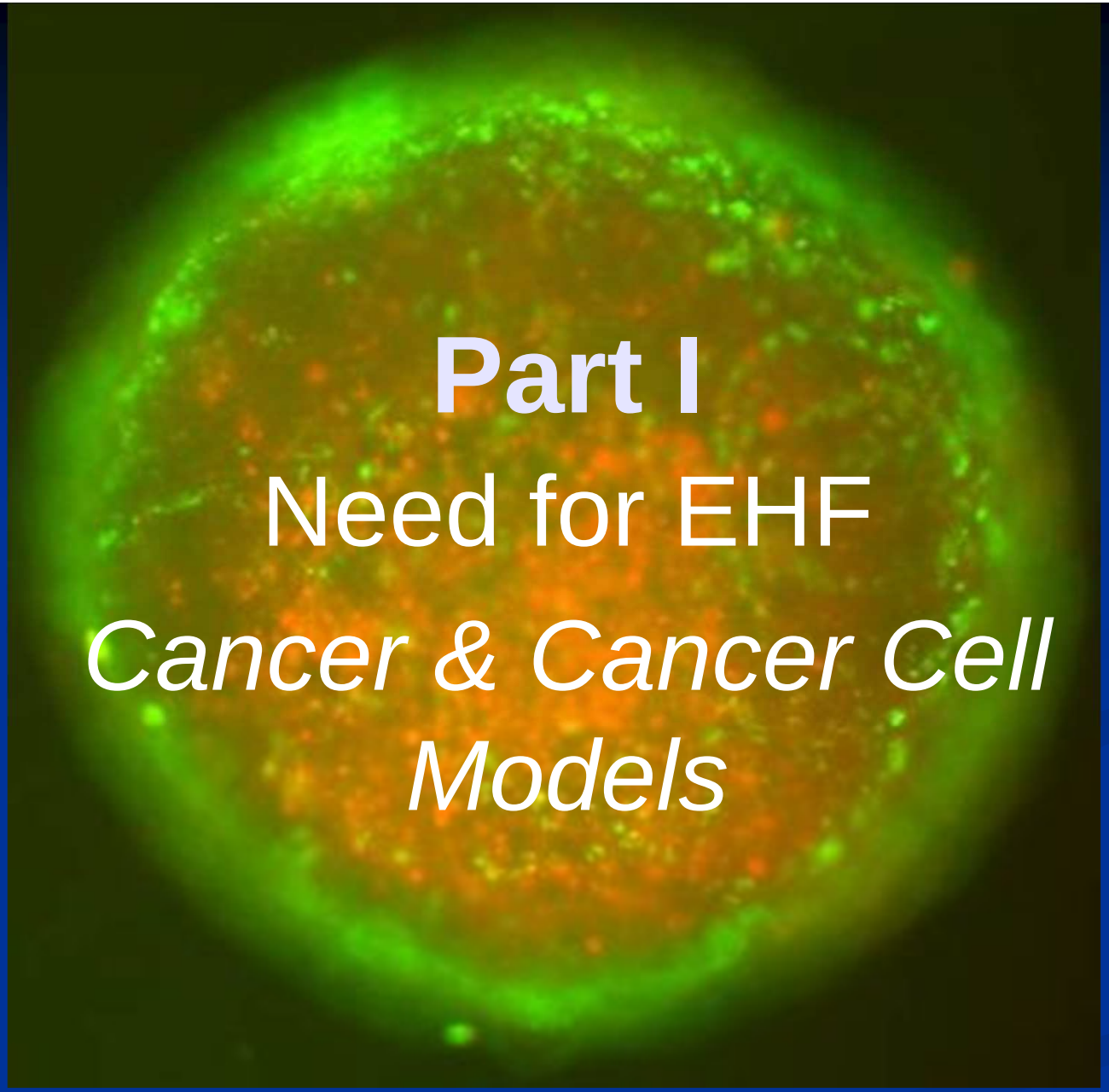
- Dose of radiation that causes ablation
- Ablative range starts from (>) 8 Gy
  - Hadziahmetovic M et al, Discov Med. 2010 May;9(48):411-7

History

- About 100 years earlier – RT started with single fraction
- By 1920 lesson a was learnt → RT should be given in fractions
- Initial practice standardized it to about 45 Gy/15 f, 250 to 300 cGy per fraction.
- Subsequent practice extended it up to 35 to 40 sittings with 180 to 200 cGy per fraction. Bone necrosis & soft tissue necrosis, transverse myelitis etc. decreased dramatically.

History

- Concept of “hypo fractionation techniques” persisted
- Now we are back to (almost) where we have started with extreme hypofactionation, *in selected clinical situations*



Part I

Need for EHF

Cancer & Cancer Cell Models

Fluorescent cancer cell, from internet…..

Famous Opinions

- Heavier than air, flying machines are impossible

  - Lord Kelvin, President of Royal Society, 1895

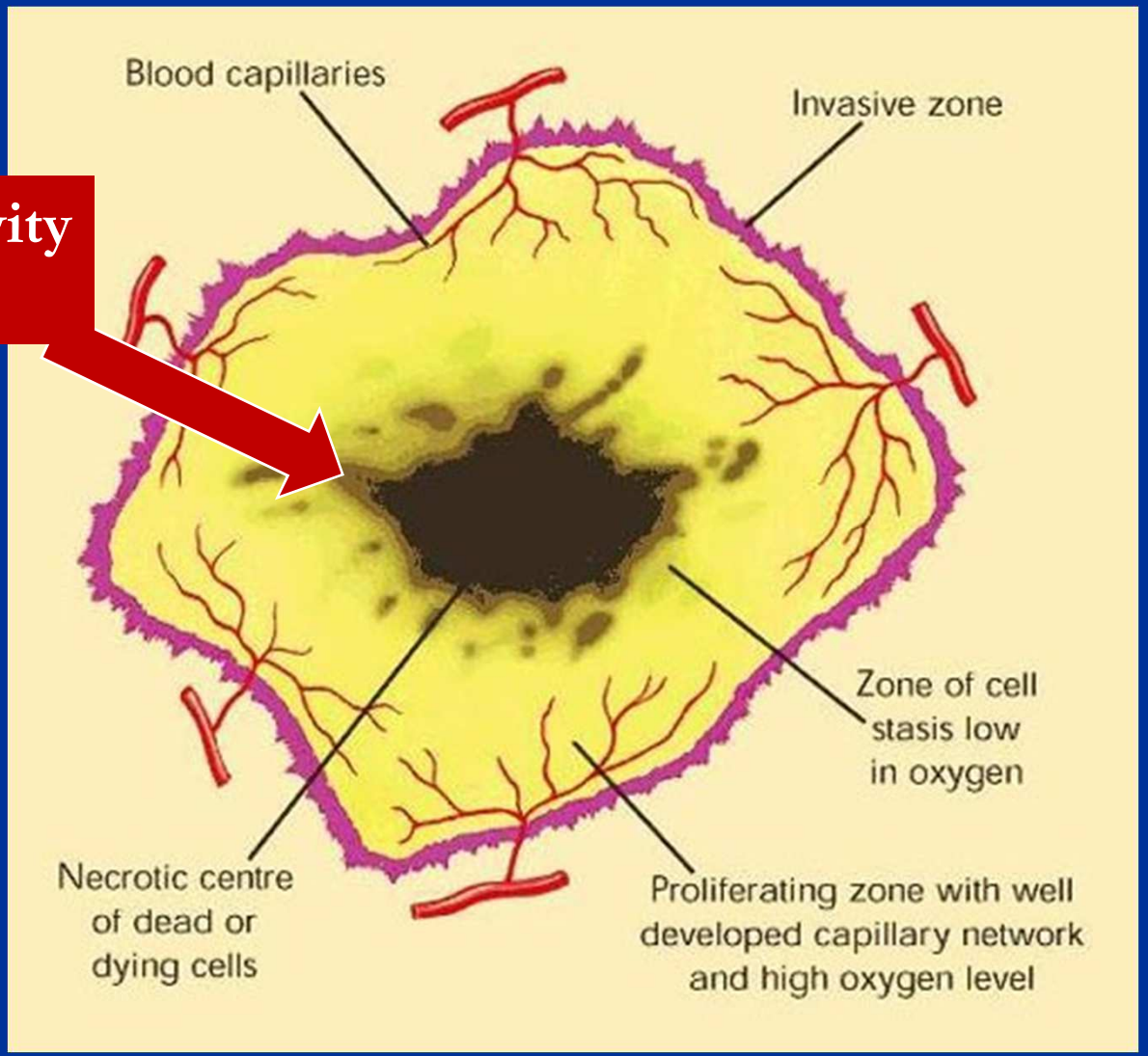
  – from Book of Lists 2

- What use could the company make of an electric toy

  - Western Union, when it turned down the rights for the telephone – *from Book of Lists 2*

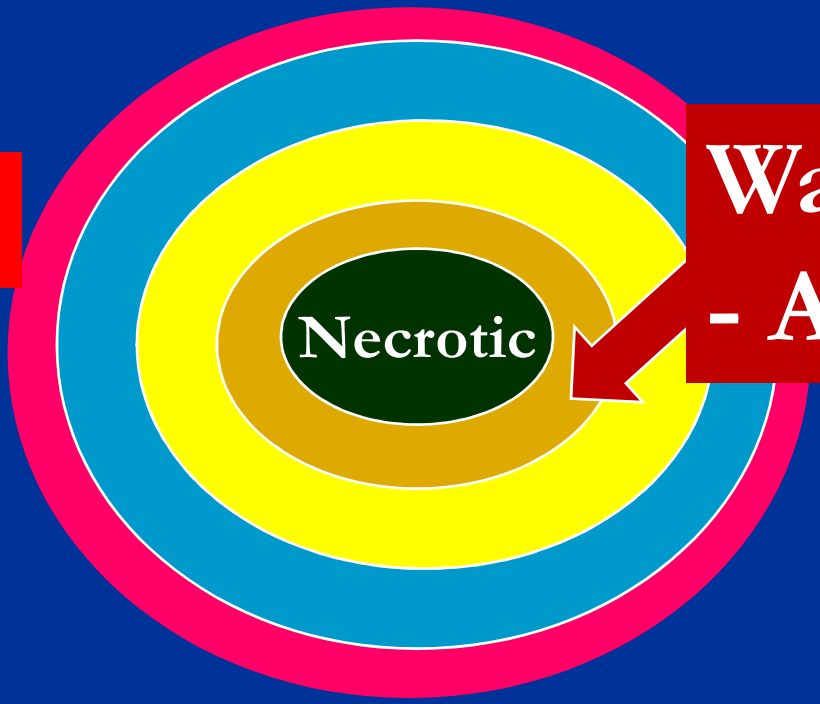
1. Morphological Model & Extracorporeal Radiation

Wall of Cavity
→ G0 cells



…modified from internet

2. Physiological/Functional model



Oxygen
Gradient

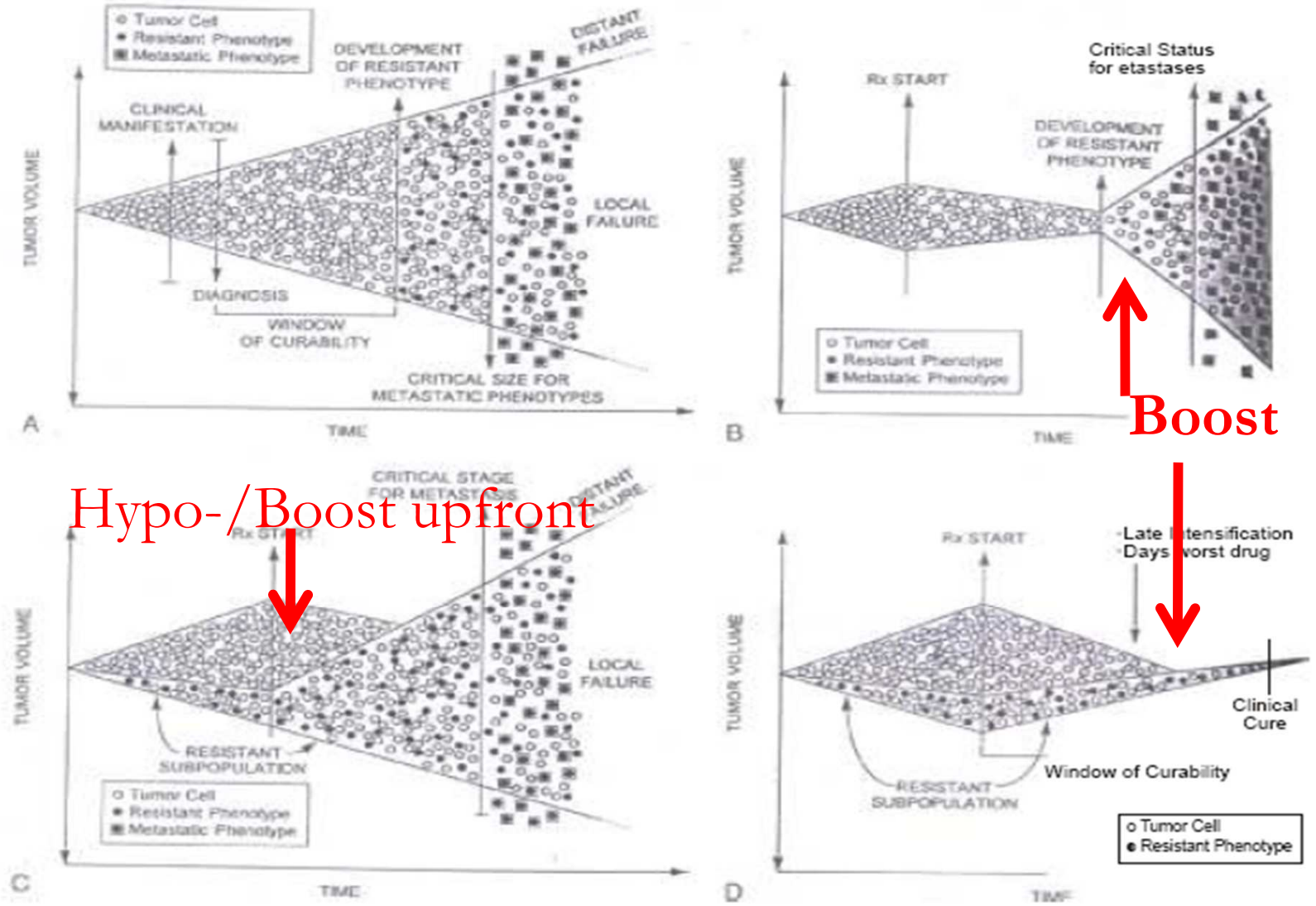
3. Biochemical Model

- Tumour ph and Immune surveillance deactivation

4. Biological Inhomogeniety Model

Oxic-clonogenic	Anoxic-hormone sensitive	Anoxic receptor +ve
Hypoxic-clonogenic	Hypoxic-nonclogenic	Oxic-nonapoptotic
Oxic-apoptic	Anoxic-clonogenic	Hypoxic receptor –ve
Hypoxic-apoptotic	Hypoxic-nonapoptotic	Oxic-receptor -ve
Oxic-nonclonogenic	Oxic-receptor +ve	Hypoxic-receptor +ve

5. Phenotypic MTMT model (Maximal Therapy Minimal Time) – *from Textbook of radiotherapy, Philip and Libel editors*



Phenotypic model

- Is it better to make use of apoptosis initially with conventional fractionation?
  - And then go for EHF during…
    - Accelerated repopulation *during 3-4th week*
    - *End of treatment*, before repopulation of resistant phenotype?
    - *2 to 3 months after regular treatment* when tumour size is small and in presence of persisting cancer stem cells
- or go for EHF upfront

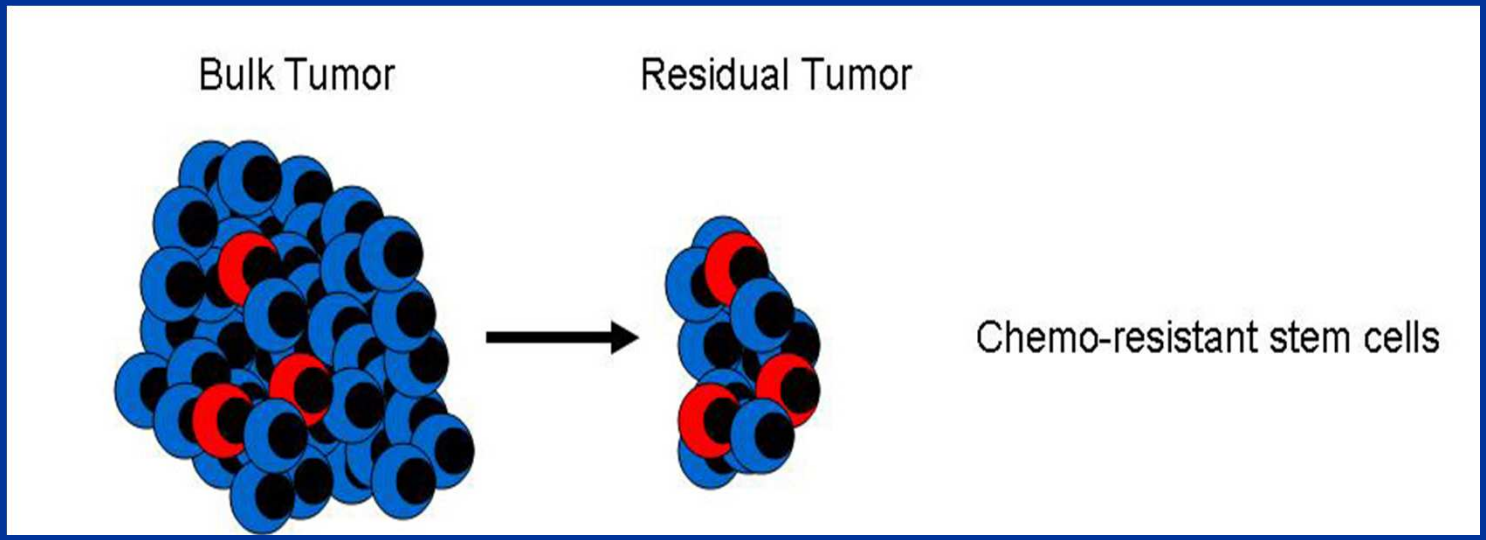
6. Cell survival Model

Dose/fraction	Reference	Estimated PFS - Lung
60 Gy/30fr	-	15%
70 Gy/35 fr	-	24%
SBRS/SBRT		
48 Gy/ 4 f	**Nagata Y et al, 2002**	**34%**
45 Gy/ 3 f	**Blomgren JM et al, 1995**	**95%**
48 Gy/ 3 f	**Blomgren JM et al, 1995**	**99%**
60 Gy/ 5 fr	Gomi K et al, 2003	>99%
60 Gy/ 3 fr	Blomgren H, 1988	>99%
69 Gy/ 3 fr	Emami B et al, 1991	>99%

Jack F. Fowler et al, Section 1, Chapter 1, Radiobiology of Stereotactic Body Radiation Therapy……

7. Cancer Stem Cell Model

- Primary
- Large tumours
- Non-responding part of tumour



.. Cell model from internet..

Cancer Stem Cell Model of resistance

- Adult male Fischer rats aged 3 to 4 months were subjected to single dose convergent beam irradiation (10 Gy).

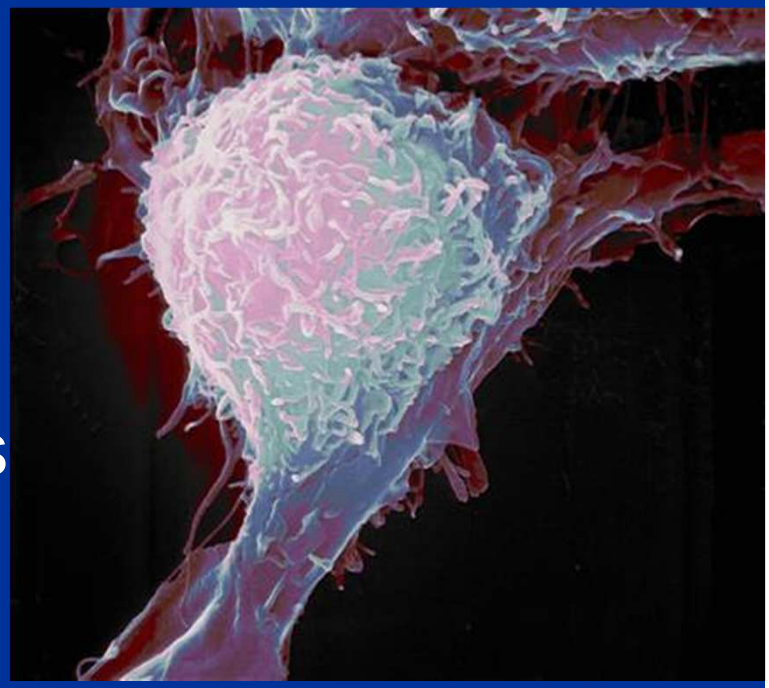
- Apoptotic cells belonged to the immature progenitor population responsible for neurogenesis

  - Wolfgang Peißner et al, 1999, Max-Planck-Institute for Neurological Research, Germany

8. Mathematical Model

Low Alpha/beta ratio

- E.g.. Prostate Ca alpha/beta of <3
- Also,
  - RCC,
  - melanoma,
  - sarcoma,
  - salivary gland tumours
  - skull base tumours



.. Cell model from internet..

9. Combined Model for Radiation failure

- Not Apoptotic
- Resistant
- Indolent
- Recurrent
- Receptor negative

→ Is Extreme Fractionation Answer to all the Models?

Extreme Hypo-fractionation: Mechanism of Action

Microvasculature

- Endothelial apoptosis becomes significant above a ~8–10 Gy single dose threshold Fuks Z, Kolesnick R: **Engaging the vascular component of the tumor response.** ***Cancer Cell 2005, 8:89-91.***-
- Endothelial apoptosis results in micro vascular disruption and death of the tissue supplied by that vasculature. Garcia-Barros M, Paris F, Cordon-Cardo C, Lyden D, Rafii S, Haimovitz- Friedman A, Fuks Z, Kolesnick R: **Tumor response to radiotherapy regulated by endothelial cell apoptosis.** ***Science 2003,*** **300:1155-1159.**
  - Large single fraction may bypass effect of radiation induced HIF-1 mediated release of VEGF on tumour vasculature in conventional RT

- hypofractionation actually results in a greater than expected tumor control → novel mechanisms which can overcome hypoxia. Brown JM, Koong AC: **High-dose single-fraction radiotherapy: exploiting a new biology?** ***Int J Radiat Oncol Biol Phys 2008,*** **71:324-325.**

Mechanism of Action - Others

- Radiation-induced stem cell depletion is also likely important.
  - Stem cell dysfunction for CNS is shown at 10 Gy
  - Stem cell dysfunction starting at 12 Gy in cells of Crypts of Lieberkuhn and no protection as dose approaches 18 Gy indicating target switch from GI endothelium to intestinal stem cells. - *Alan Alfieri et al , 2007*
- May also play a role in stimulating an immune response

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Evaluation of Immunological Changes in Patients Treated with SBRT and Radiotherapy - A Prospective cohort Study

Author Block: K. Swamy[1], B. S. Ajaikumar[1], N. Radheshyam[1], A. Verma[2], J. Chandra Rao[2], R. Premitha[1], B. Ramesh[1], P. S. Sridhar[1], S. Bhattacharjee[1], M. S. Bellappa[1], et al. [1]*HCG Bangalore Institute of Oncology, Bangalore, India*, [2]*Triesta Sciences, Bangalore, India*

Abstract:
Purpose/Objective(s):

Results: There was a significant increase in CD107a M (monocyte) (z=-2.03, p=0.04) and decrease in perforin M (z= 2.22, p=0.02) in SBRT group compared RT group on Mann Whitney test. There was a significant decrease in perforin M (z=-2.05,p=0.04) and perforin G (z=-2.16, p=0.03) following SBRT and a significant decrease in CD83 (z = -2.43, p=0.02), (with relative non significant increase in SBRT group) and CD107G (z = -2.44, p=0.02) in RT group on Wilcoxons Signed Rank test.

Conclusions. This is a preliminary study to evolve strategy for enhancement of cell-mediated immunity with SBRT. The results show that there is modulation of NK cell activity and relative improvement of dendritic cell population during SBRT of 3 to 5 sessions. Cross talk between these changes may trigger effective cell-mediated immunity.

:

Author Disclosure Information: K. Swamy: None. B.S. Ajaikumar: None. N. Radheshyam: None. A. Verma:

EHF Mechanism of Action at 18 Gy level; *from*

Alan Alfieri et al , 2007

Serine threonine kinase, phosphorylation

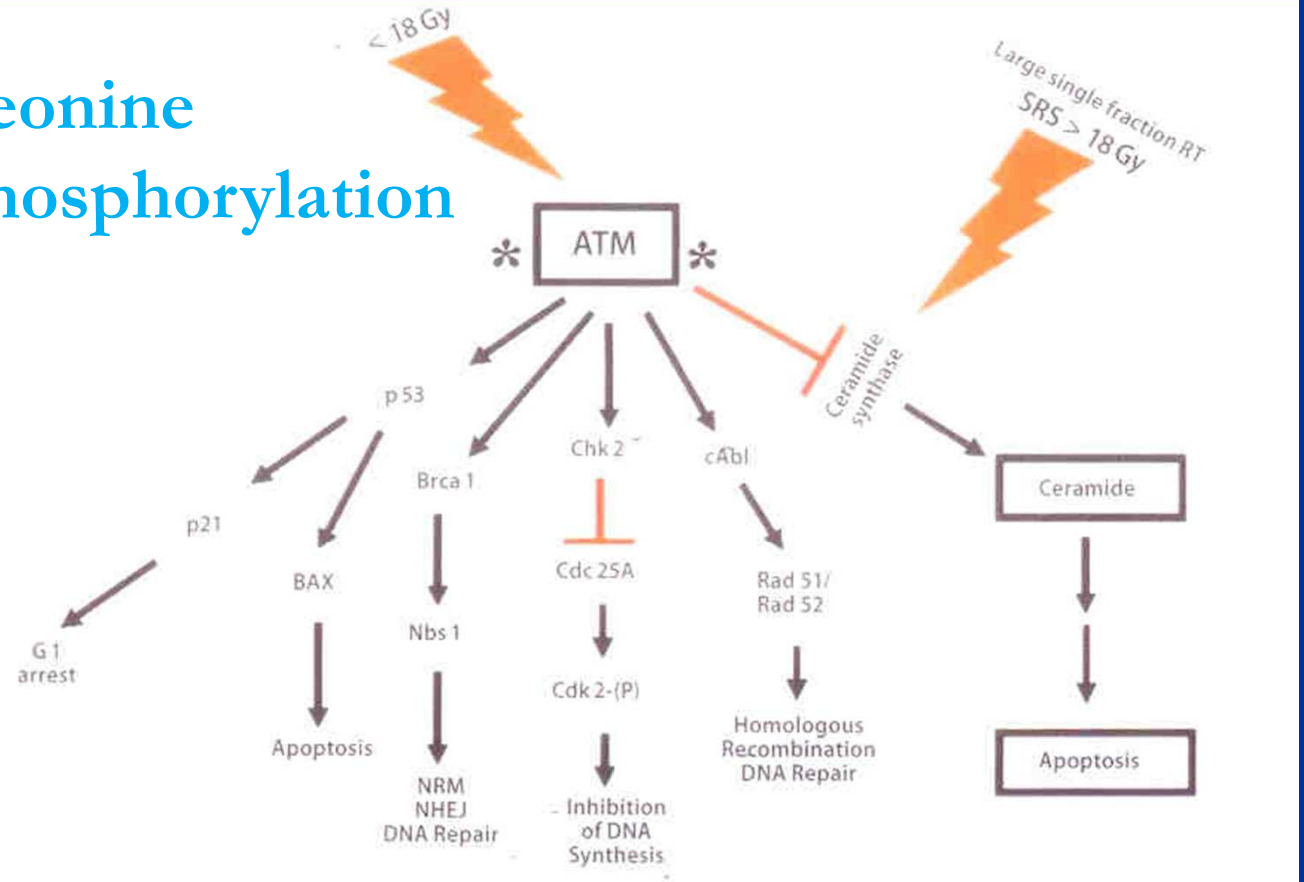


Fig. 4.4 Rationale for Hypofractionation. Conventional fractions of RT induce the DNA damage surveillance pathwa activating ATM. ATM, a serine-threonine kinase, phosphorylates a battery of proteins, some of which are shown. ATM-m ated phosphorylation events induce cell cycle arrest, inhibition of DNA synthesis, induce DNA repair, and promote sur of irradiated cells. Large single-fraction RT (>18 Gy) appears to overwhelm the radioprotective functions of ATM and in cell death in stem cells. Thus, large single fractions of RT delivered by SRS may bypass the ATM protective functions be more effective in killing tumor cells.

Summary of *dose per fraction effects*

- Conventional dose per fraction 180 to 200 cGy/f -sub lethal damage → recovery
- Normal tissue will have long term side effects if the dose per fraction exceeds 260 cGy per fraction
- 600 to 1200 Gy → lethal damage → to overcome the resistant cells
- 1200 – 1800 cGy → Some Cancer stem cells
- >1800 cGy/f → all cells sensitive (including glioma cancer stem cells)?

Hypo-Notes from literature

- Use of single fraction is probably worst of the radiobiologic alternative, without
  - Reoxygenation
  - Shift out of resistant phase
  - Nutritional deprivation
- Large amount of reoxygenation can occur in 24 hours

- Jack f Fowler et al

Hypo-Notes from literature

- Radiation is arguably the safest option for tumors abutting large vessels unlike surgery
  - Milano T et al
- (However, venous damage & lymphatic choking in non-collateral areas are of concern)

Hypo-Notes from literature

- Serial functioning tissues (i.e., spinal cord, esophagus, bronchi, hepatic ducts and bowel, which are linear or branching organs, in which functional subunits are undefined) may benefit from reduced high-dose volume exposure
- Small volumes (0.1%) can safely receive suprathreshold doses
- Stem cell migration may be of greater importance here
- However, heightened concern of devastating, irreversible downstream effects that can occur from damage to upstream portions of the organ is real and dose-volume levels are not well characterized as of now -Kavanagh BD, McGarry RC, Timmerman RD: **Extracranial radiosurgery (stereotactic body radiation therapy) for ligometastases.** *Semin Radiat Oncol 2006,* ***16:77-84.***

- Timmerman R, Bastasch M, Saha D, Abdulrahman R, Hittson W, Story M: **Optimizing dose and fractionation for stereotactic body radiation therapy. Normal tissue and tumor control effectswith large dose per fraction.** ***Front Radiat Ther Oncol 2007,*** **40:352-365.**

Disease (Approximate TDF equivalent)	Conventional	EX Hypo – 5 fr	Ex Hypo- 3 fr
Micro – low risk (with CT)	45--50 Gy	24 – 25 Gy **(5x5)**	22.5 Gy **(7.5 x3)**
Micro High risk (with CT)	50 – 60 Gy	28 - 30.5 Gy **(6x5)**	24 – 27 Gy **(8x3)**
Gross Disease	66 – 70 Gy	34 – 35.5 Gy **(7x5)**	28 – 30 Gy **(10x3)**
Hypoxic/low alpha beta disease	76 – 80 Gy	37.5 Gy **(7.5x5)**	31–32 Gy **(10.5x3)**
Anoxic disease	80 - 100 Gy	37.5 – 40 Gy **(8x5)**	32 - 33 Gy **(11x3)**
Cancer Stem Cells	>100 Gy	**>40 Gy (>8x5)**	**>33 Gy (>11x3)**

Normal issue tolerance – SBRT Lung 3 f

Organ	Volume	Dose (cGy)
Spinal Cord	Any point (0.1%)	18 Gy (6 Gy per fraction)
Esophagus	Any point	27 Gy (9 Gy per fraction)
Ipsilateral Brachial Plexus	Any point	24 Gy (8 Gy per fraction)
Heart	Any point	30 Gy (10 Gy per fraction)
Trachea and Ipsilateral Bronchus	Any point	30 Gy (10 Gy per fraction)

Spinal cord, Brain stem, Optic chiasm, **(critical veins?)** tolerance level – 8 to 12 Gy single fraction, 18 Gy 3 f, 24 Gy 5 f

Part II

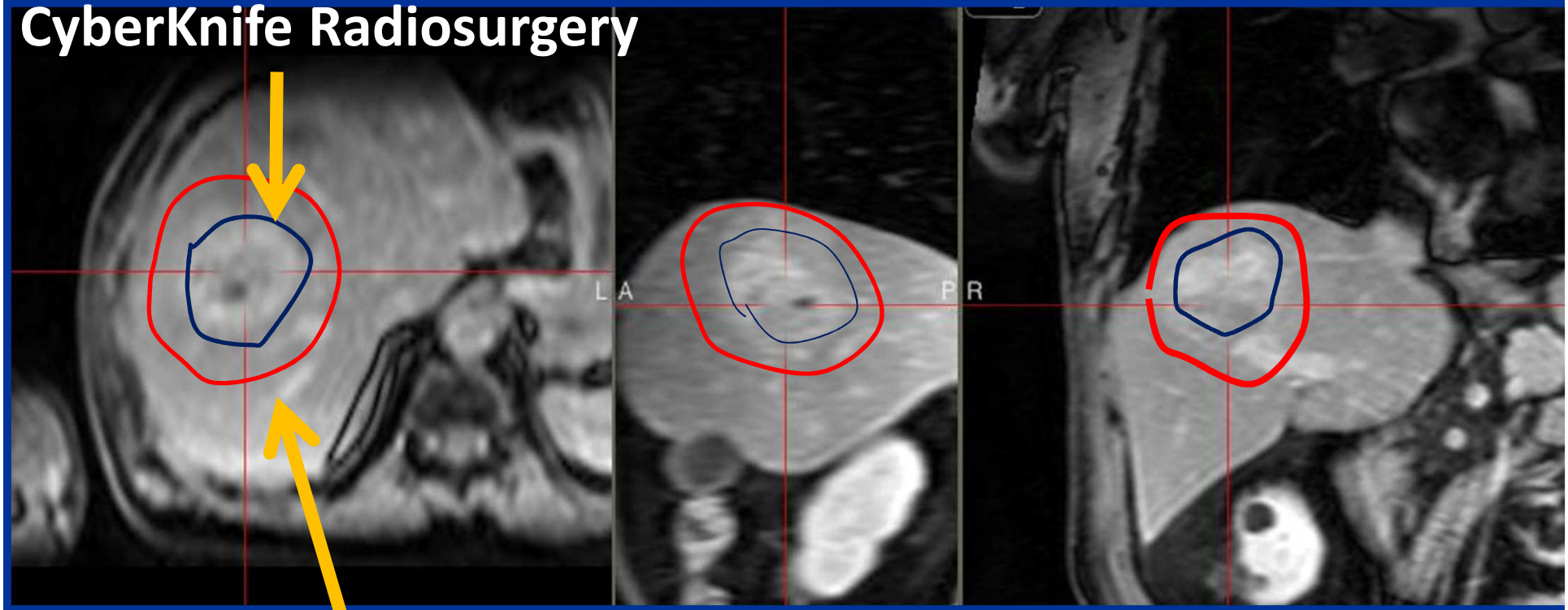
Application with CyberKnife

Picture from Accuray Inc..

EHF – Clinical Application

- Radiosurgery is the method of delivery of EHF
- Modern day radiation therapy is all about margin around gross disease in EHF
- IGRT has helped to bring down the margin down to minimum of 5-3 mm. Intrafractional errors, random errors, rigid body errors, image resolution errors prevents us from clinically coming down below 3mm margin around the gross disease.
- Bringing down the treatment time to even 2 mts does not guarantee overcoming the intrafractional error. As of now Robotic Radiosurgery (Cyberknife) is the only technique available in correcting the extracranial intrafractional errors.

It is all about margin and VOLUME…

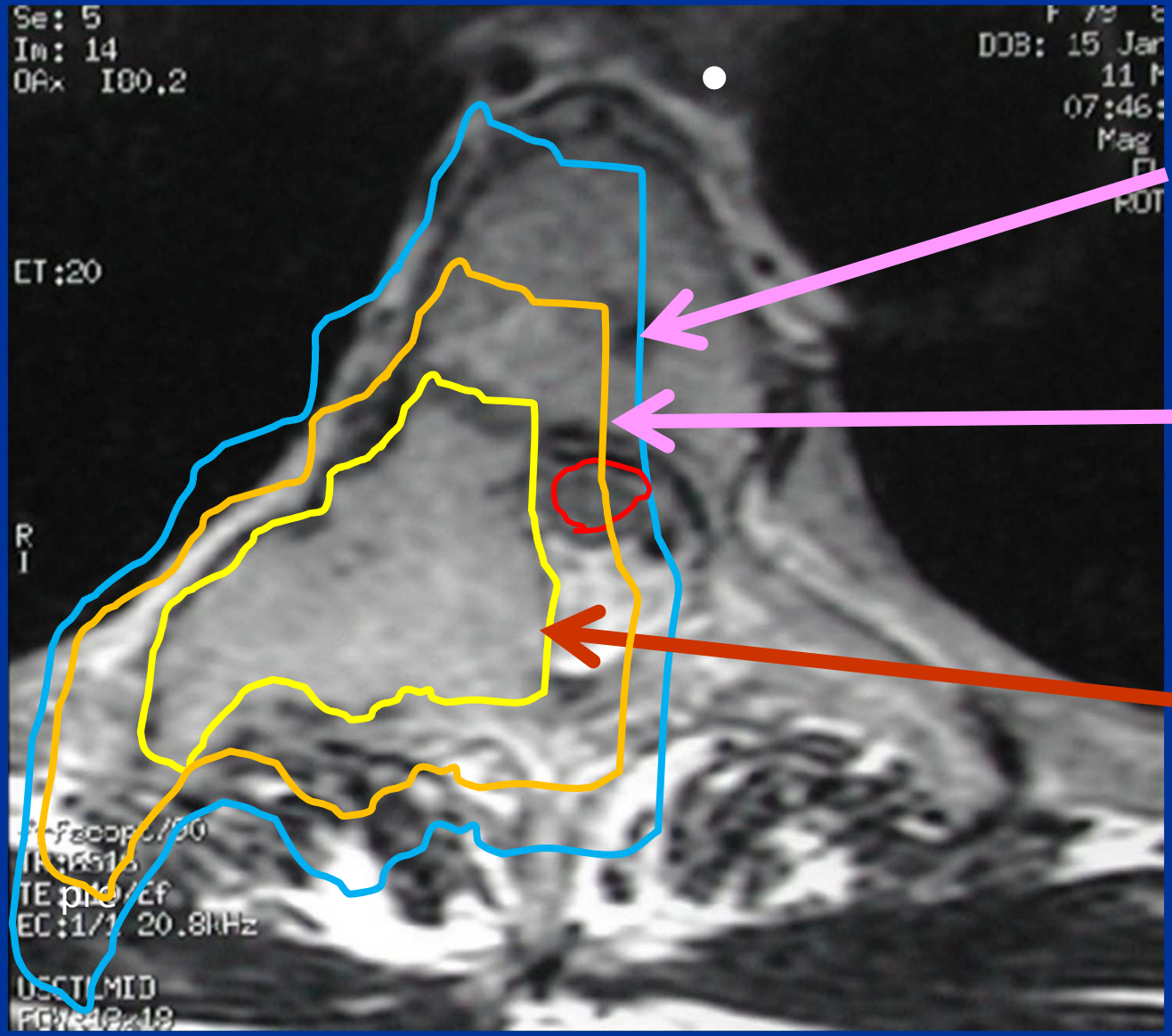


Cascading effect

1. *Less margin.*

2. *Ivolume of normal tissue decreases by half, for the same level of side effects, dose tolerated increases by 5 times,*

Gross disease and margin…



Radiotherapy hypo fractionation

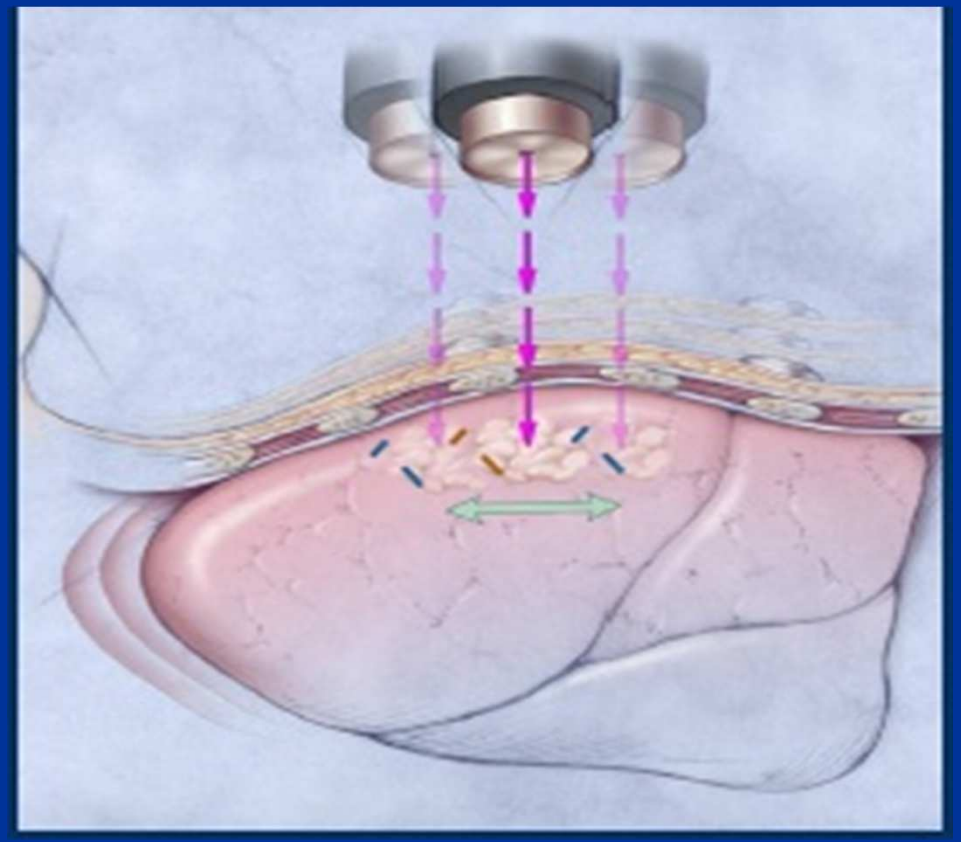
LA Radiosurgery *with margin for intrafractional error*

CyberKnife Radiosurgery

Picture modified from internet..

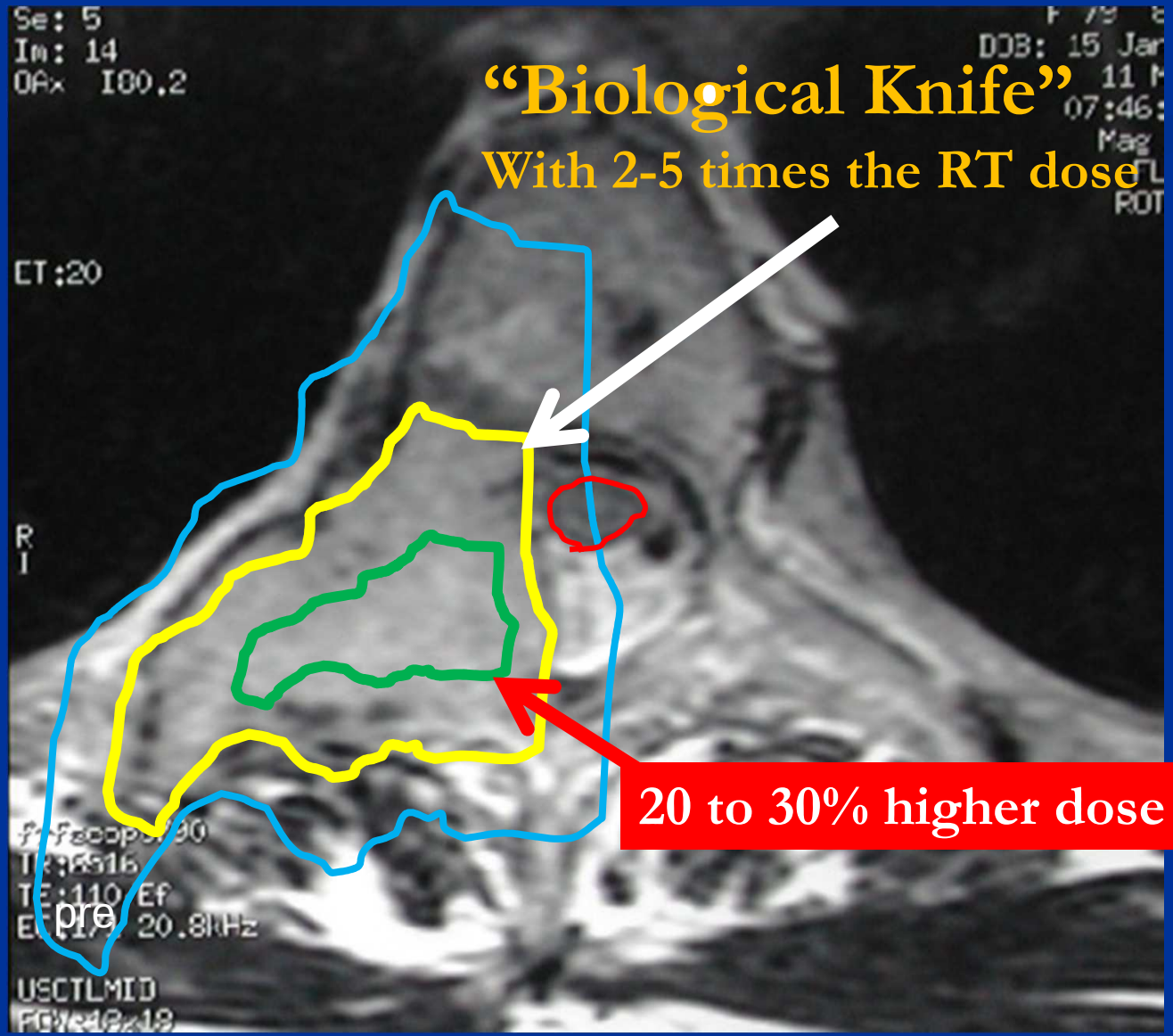
Synchrony Fidicial Tracking System

- Continuously tracks the internal movement via fidicial



Picture from Accuray inc…

Dynamic Tumour Tracking & Biological Knife



- Its dose distribution and prescription is similar to Gamma Knife.
- Usual edge prescription dose is to 65 to 80%
- Hypoxic core of tumour gets highest dose (ref morphological model) – can be manipulated to match hypoxic area in molecular imaging

Picture modified from internet..

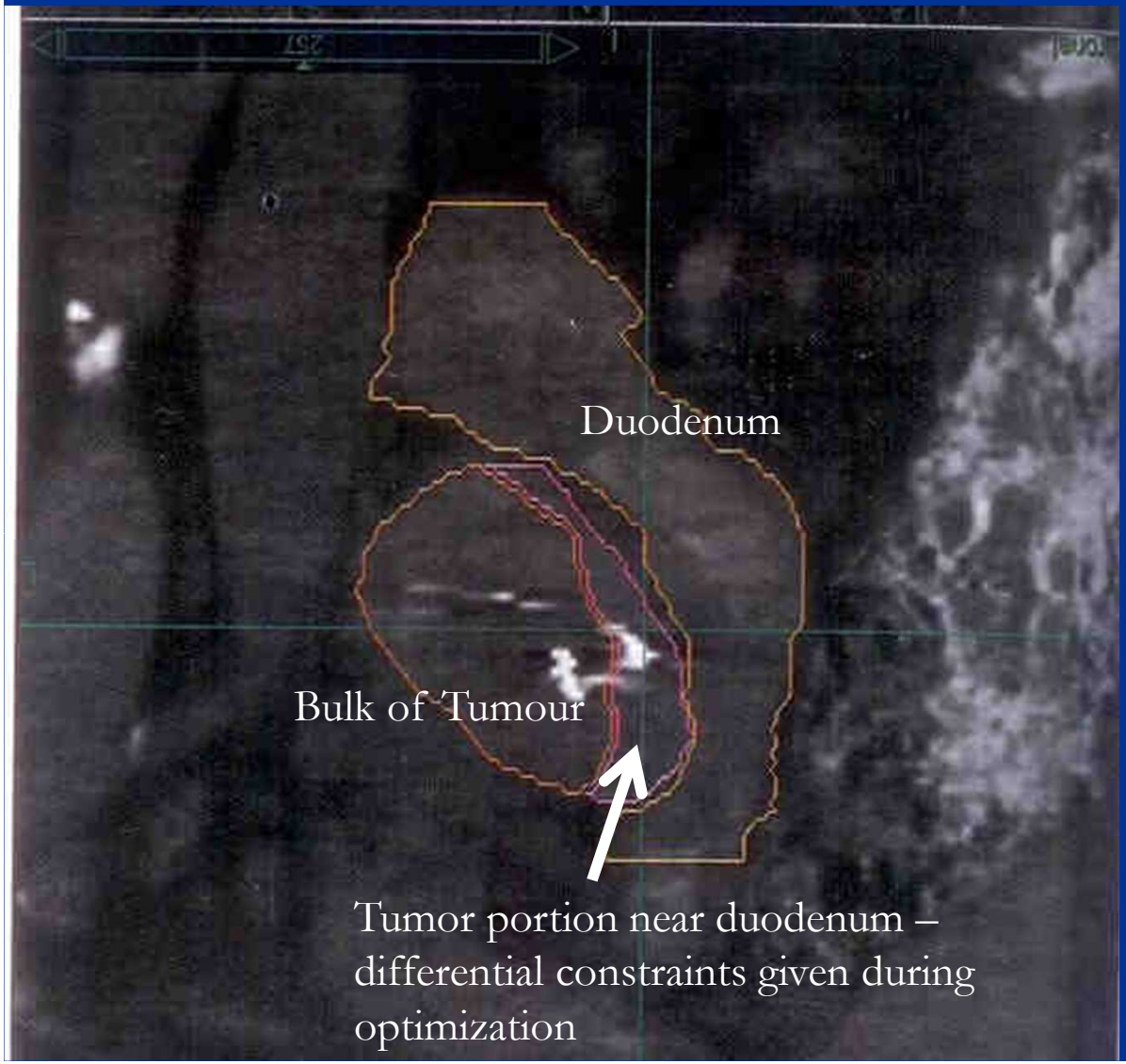
EHF – Clinical Application

- However, even with Cyberknife rigid body errors, image resolution errors etc are not totally compensated. Hence, when giving the dose prescription at least 3 mm margin should receive adequate dose along with higher dose gradient to the inner portion of the tumour (refer to morphological model).
- In EHF, beyond the prescription dose, effective dose is delivered to the *microscopic disease* for about 3 – 8 mm depending on the prescription dose

Tips, Traps & Tricks in EHF

- Alternate day fractionation
- Bone Marrow sparing EHF
  - Facilitate Chemo
  - Cell mediated immunity?
- Prophylactic anticoagulants. (low molecular weight clexate sc 0.4 ml daily for 2 to 3 weeks)
- Prophylactic pentoxyphylline

Tips, Traps & Tricks in EHF from literature – Split-contour Technique



Robotic radiosurgery . Treating tumors that move with respiration. Harold c. Urschel, Jr Ed in Chief, Springer pub.2007. Chapter 6, Treatment planning of abdominal lesions, Charles L Lee, Fig 6.3, page 69

Our EHF CyberKnife Dose Schedule Practice

- Until now, most often, 24 - 30 Gy/3 -5 fractions, daily/alternate days, 65-80% isodose prescription
- Occasionally > 20 Gy / 1f
- Now > 30 Gy / 3f especially in small volume tumours
- Prostate 37.5 Gy /5 fr/daily; also alternate days
- Lung T1-2N0M0, peripheral: 48–60 Gy/3f
- Boost 12-18 Gy in 1-3 f (after IMRT/IGRT)

Future of EHF

Famous Opinions

- I think there is a world market for may be 5 computers -

  - Thomas Wartson, Chairman IBM

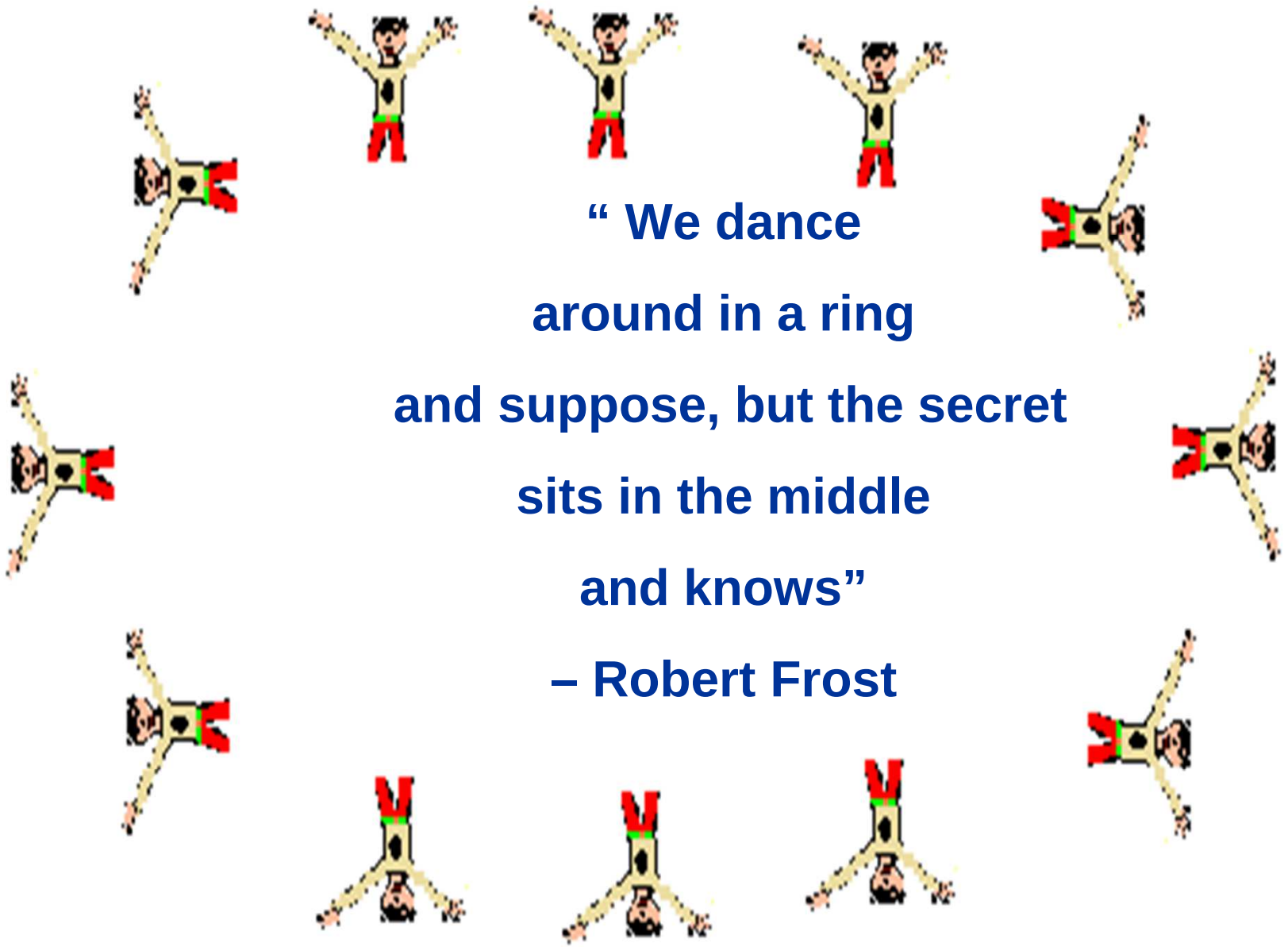
  1874- 1956 – *from Book of Lists 2*

- There is no likelihood that man ever tap the power of the atom

  - Robert Miliham, Nobel Prize in Physics, 1923 - *from Book of Lists 2*

EHF Potential Unexplored

- Right period of fractionation?
  - 3 →15 fraction?
  - Weekly ? Monthly? Based on disease burden?
- Right time for boost? – upfront, end or 3mo. post RT
- Right dose per fraction?
  - Min 6 → 20 Gy?
  - Sub-volume boost >18 Gy/fr?
- Right isodose *"titration" with metabolic imaging*
  - Molding to resistant sub-volumes
- Combination with other chemo/targeted therapies?
- Modulation of Cell mediated immunity?



“ We dance

around in a ring

and suppose, but the secret

sits in the middle

and knows”

– Robert Frost

" to use those principles of clinical radiobiology *that we have learned painstakingly over the last century* to drive clinical investigation, and not rely solely on the impetus of new technology"

"Had *Coutard and Baclesse not pioneered fractionation,* radiotherapy probably would have fallen into oblivion due to the morbidities of single shot treatment."

- **David I. Rosenthal, Eli Glatstein, M.D.** *The Oncologist 1997*

personally..higher.. (not the highest dose), the combinations and fractionation strategies …..

Future → your move…

Thank you…..

Picture from internet…