Fundamental Radiobiology

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Cancer Treatment Options

SURGERY

CHEMOTHERAPY

Radiotherapy

HORMONE-THERAPY

BRACHYTHERAPY

IMMUNOTHERAPY

TELETHERAPY

RADIOBIOLOGY:

Radiobiology is a branch of science which combines the basic principles of physics and biology and is concerned with the action of ionizing radiation on biological tissues and living organisms.

LAW OF BERGOINE AND TRIBONDEAU

1906 Bergonie and Tribondeau realized that cells were most sensitive to radiation when they are:

Rapidly dividing

Undifferentiated

Have a long mitotic future

CELL RESPONSE TO RADIATION

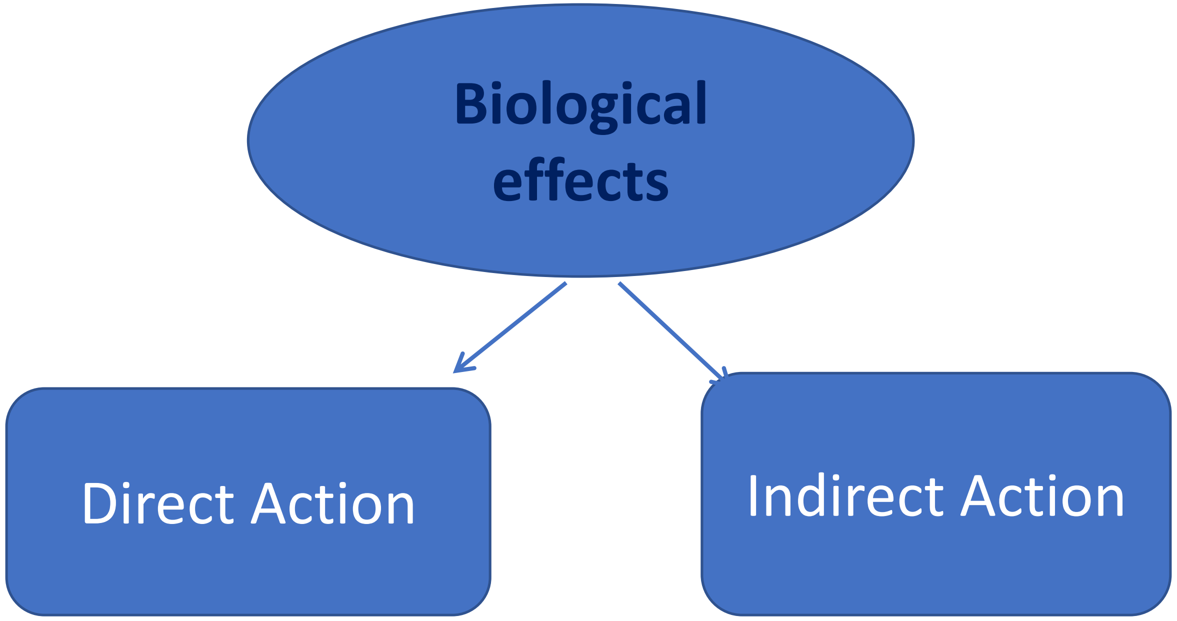
- LYNPHOCYTES
- SPERMATOGONIA

RADIOSENSITIVE

- OSTEOBLASTS
- SPERMATIDS
- MUSCLE CELL

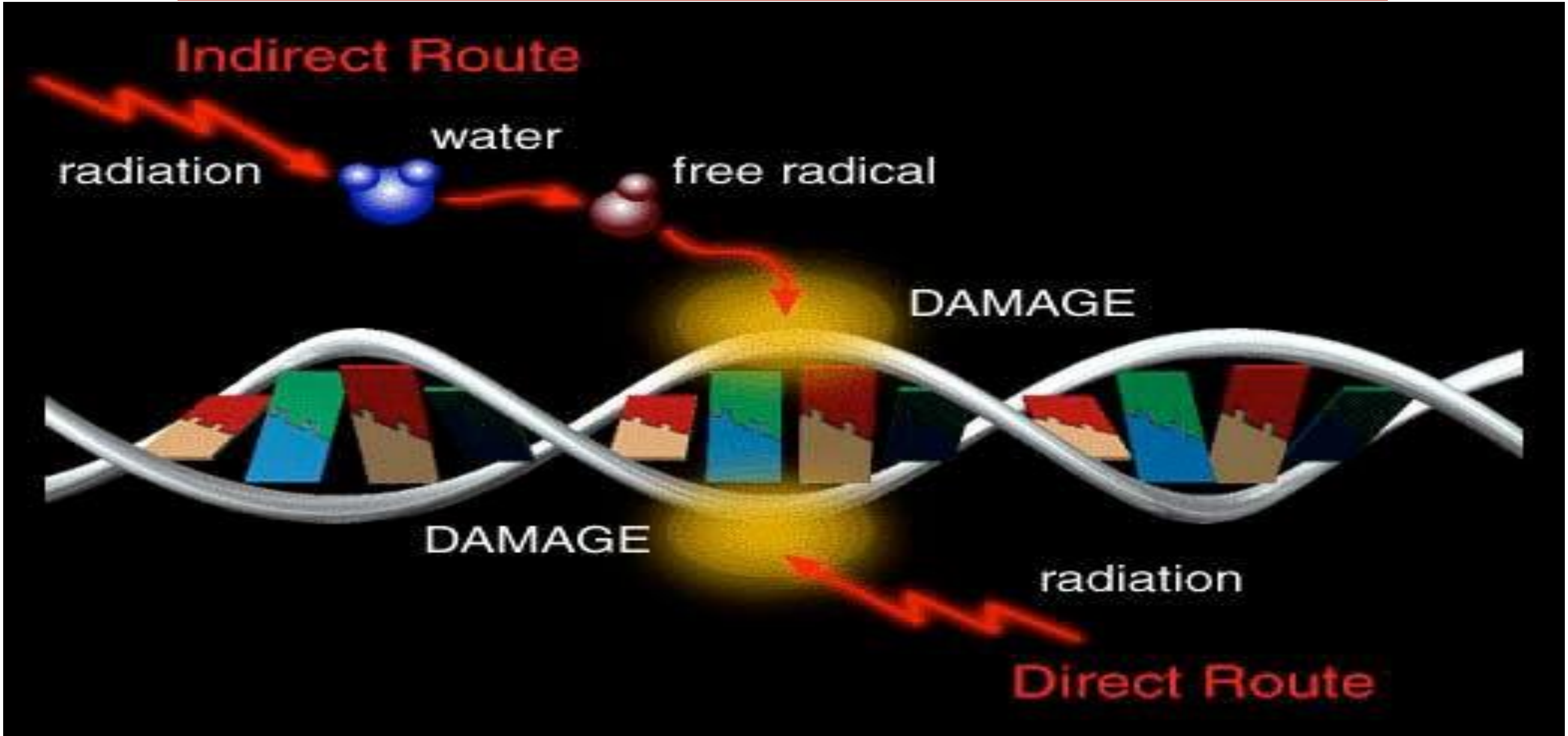
- NERVE CELL

RADIORESISTANT



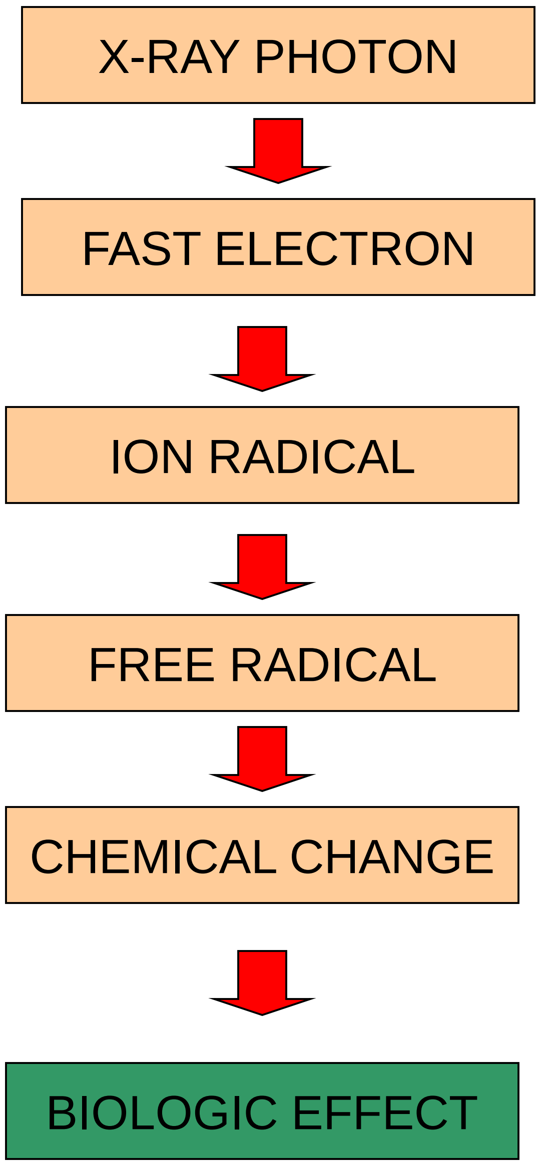
- **DIRECT ACTION** :- Radiation directly hit the critical target in the cell, causing ionization or excitation of the target atoms leading to biological change.
- **INDIRECT ACTION** :- Radiation interacts with other molecules & atoms in the cell, producing free radicals which further damage the critical target.

Direct and indirect mechanisms

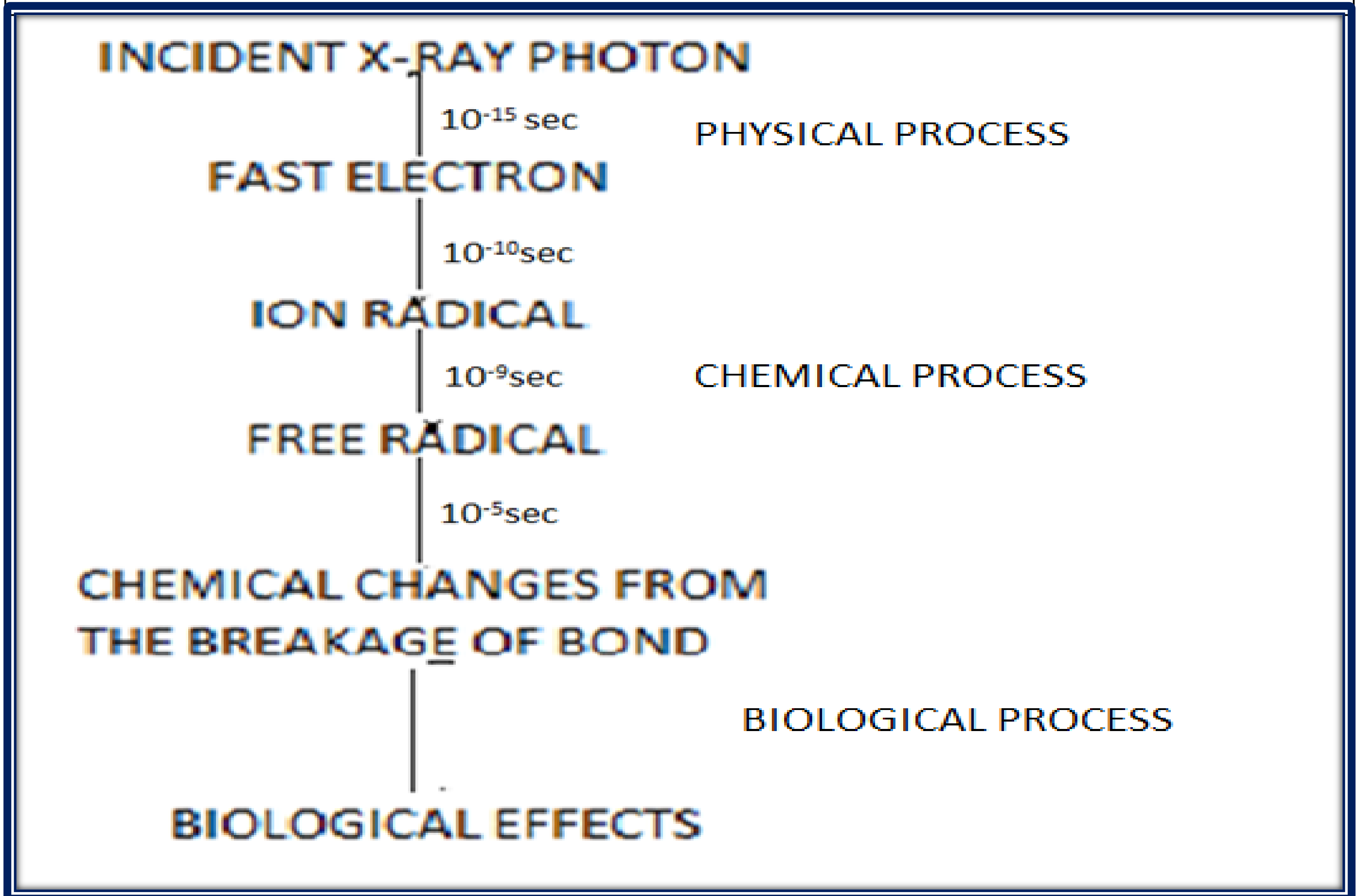


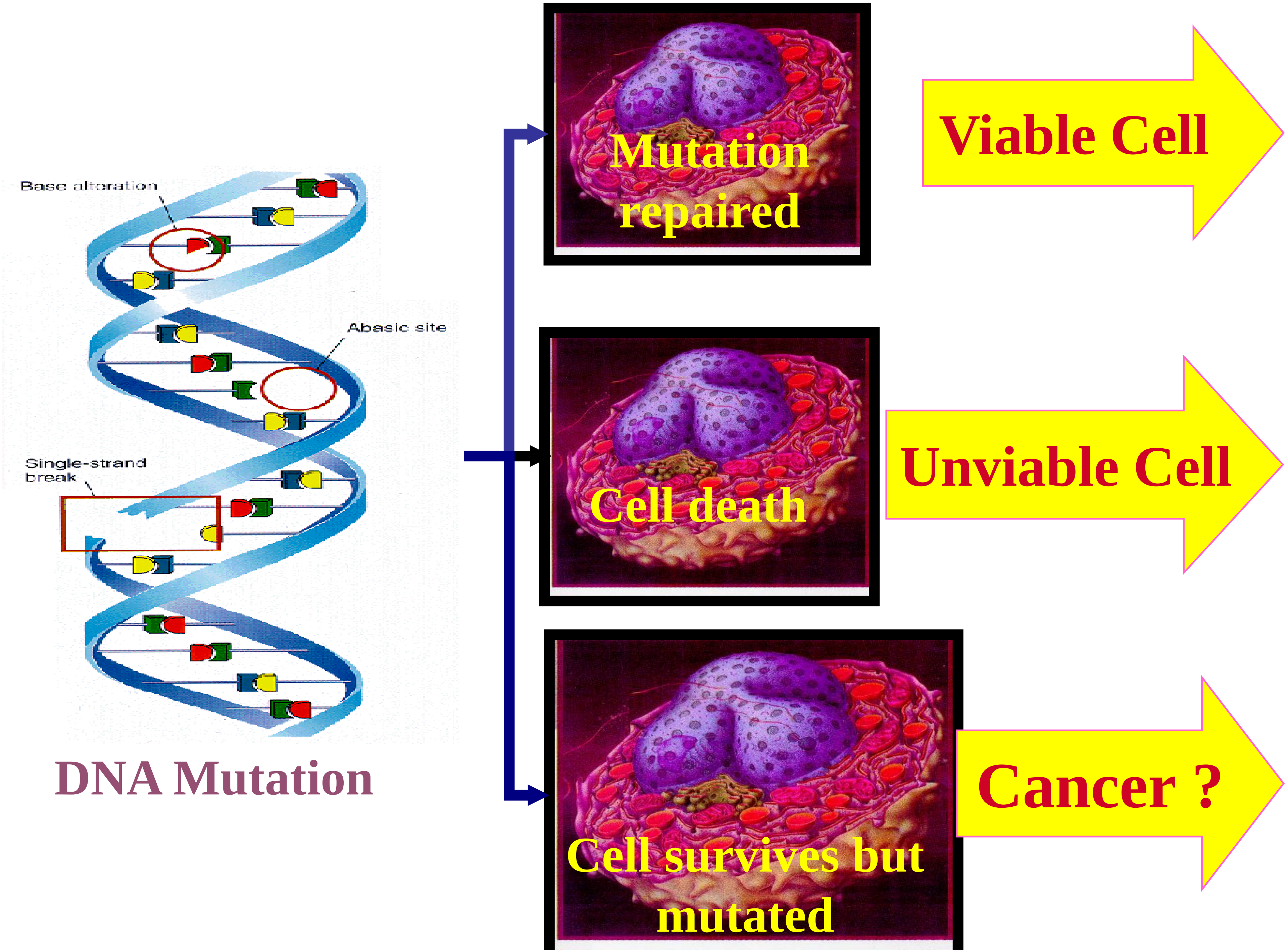
INDIRECT ACTION- RADI0LYSIS OF WATER

- HOH + RADIATION $\longrightarrow$ HOH^{+} + e
- HOH + e $\longrightarrow$ HOH^{-}
- HOH^{+} $\longrightarrow$ H^{+} + OH^{*}
- HOH^{-} $\longrightarrow$ OH^{-} + H^{*}


X-RAY PHOTON
FAST ELECTRON
ION RADICAL
FREE RADICAL
CHEMICAL CHANGE
BIOLOGIC EFFECT

Processes of Indirect Action




Base alteration
Abasic site
Single-strand break
DNA Mutation
Mutation repaired
Viable Cell
Cell death
Unviable Cell
Cell survives but mutated
Cancer ?

SENSITIVITY OF CELL

- Radiation effect depends on the sensitivity of the cell
- Sensitivity of cell depend on cell cycle, i. e. cell is in which phase,
- G1 phase in which cell grow and become mature.
- S   phase ,synthetic phase, in which
  DNA synthesis, very active phase,
- G2 phase in which cell division occur.
- M phase in which mitotic division occur

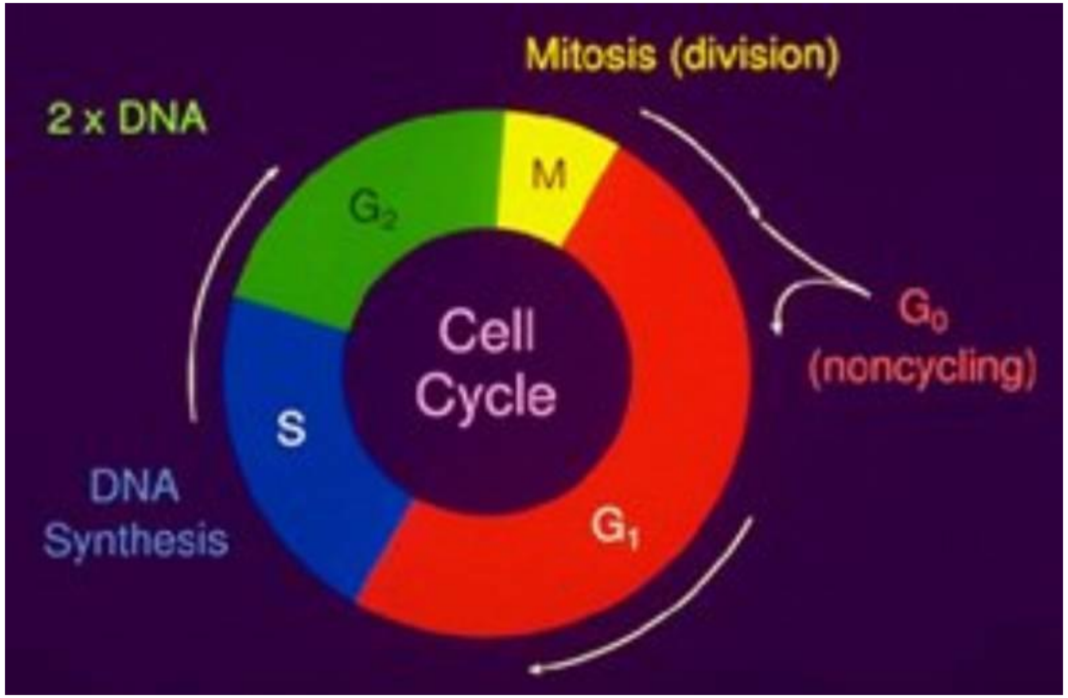
Cell Cycle.

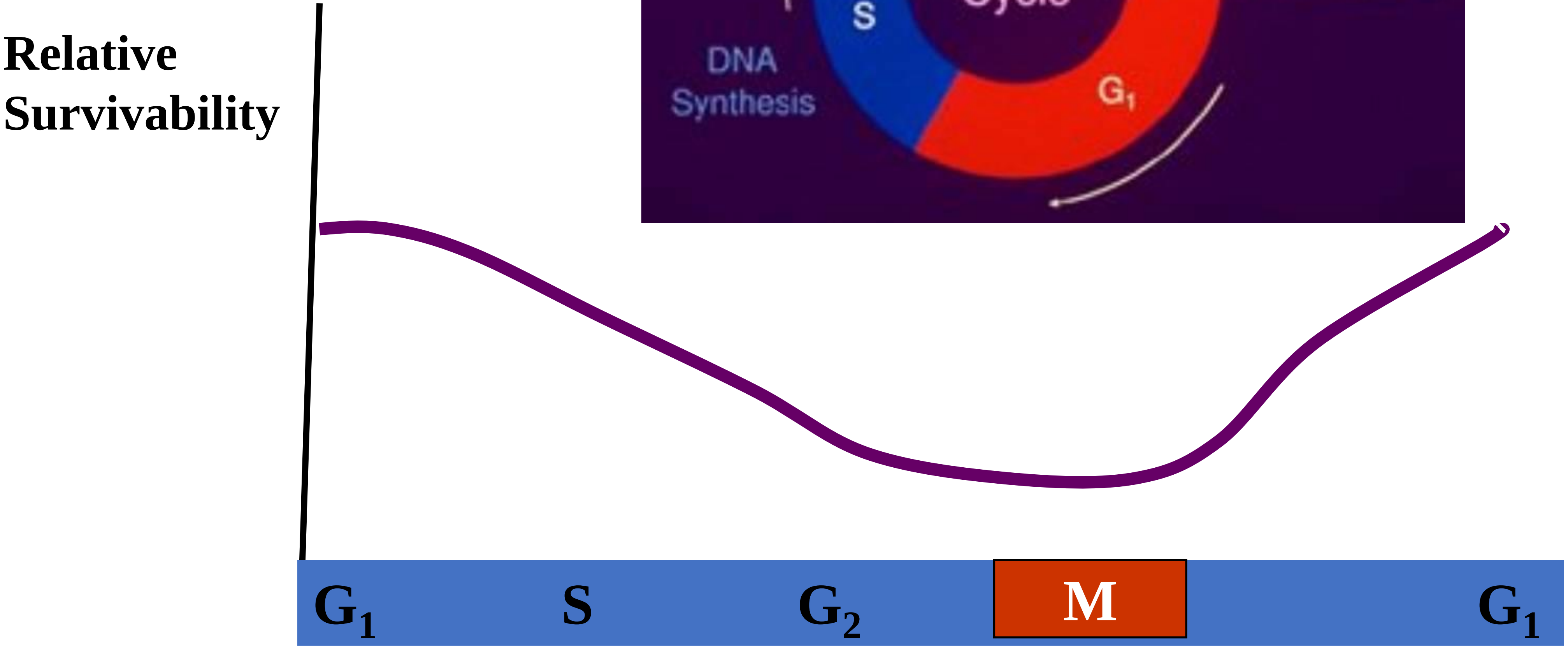
- The point that a cell is in the cell cycle has a marked influence on its response and survival of irradiation.
- G1 & G0 are relatively insensitive to radiation injury.
- S phase is generally considered to be the most resistant to radiation injury.

SENSITIVITY OF CELL PHASES

- G_1 Phase → More resistant
- S Phase → Less resistant
- G_2 Phase → sensitive
- M phase → most sensitive

Radiosensitivity of cell in cell cycle





Relative survivability of cells irradiated in different phases of the cell cycle. Synchronised cells in late G_2 and in mitosis (M) showed greatest sensitivity to cell killing.

RADIATION ENERGY TRANSFER DETERMINANTS

- Linear Energy Transfer - LET
- Radiobiological Effectiveness – RBE
- Oxygen Enhancement ratio - OER

Linear energy transfer (LET)

“*LET of ionsing radiation in a medium is the quotient dE/dl, where dE is the average energy locally imparted to the medium by a ionising radiation of specified energy in traversing a distance of dl.*”

LET < 10 keV / μm   low LET
LET > 10 keV / μm   high LET

- 250 kVp X rays: 2 keV/*μ*m.
- Cobalt-60 γ rays: 0.3 keV/*μ*m.
- 3 MeV X rays: 0.3 keV/*μ*m.
- 1 MeV electrons: 0.25 keV/*μ*m.
- 10 keV electrons: 2.3 keV/*μ*m.

—14 MeV neutrons: 12 keV/*μ*m.

—Heavy charged particles: 100–200 keV/*μ*m.

—1 keV electrons: 12.3 keV/*μ*m.

LET

LOW LET	HIGH LET
• GAMMA RAYS • X-RAYS	• ALPHA PARTICLES • IONS OF HEAVY NUCLEI • CHARGED PARTICLES • LOW ENERGY NEUTRONS

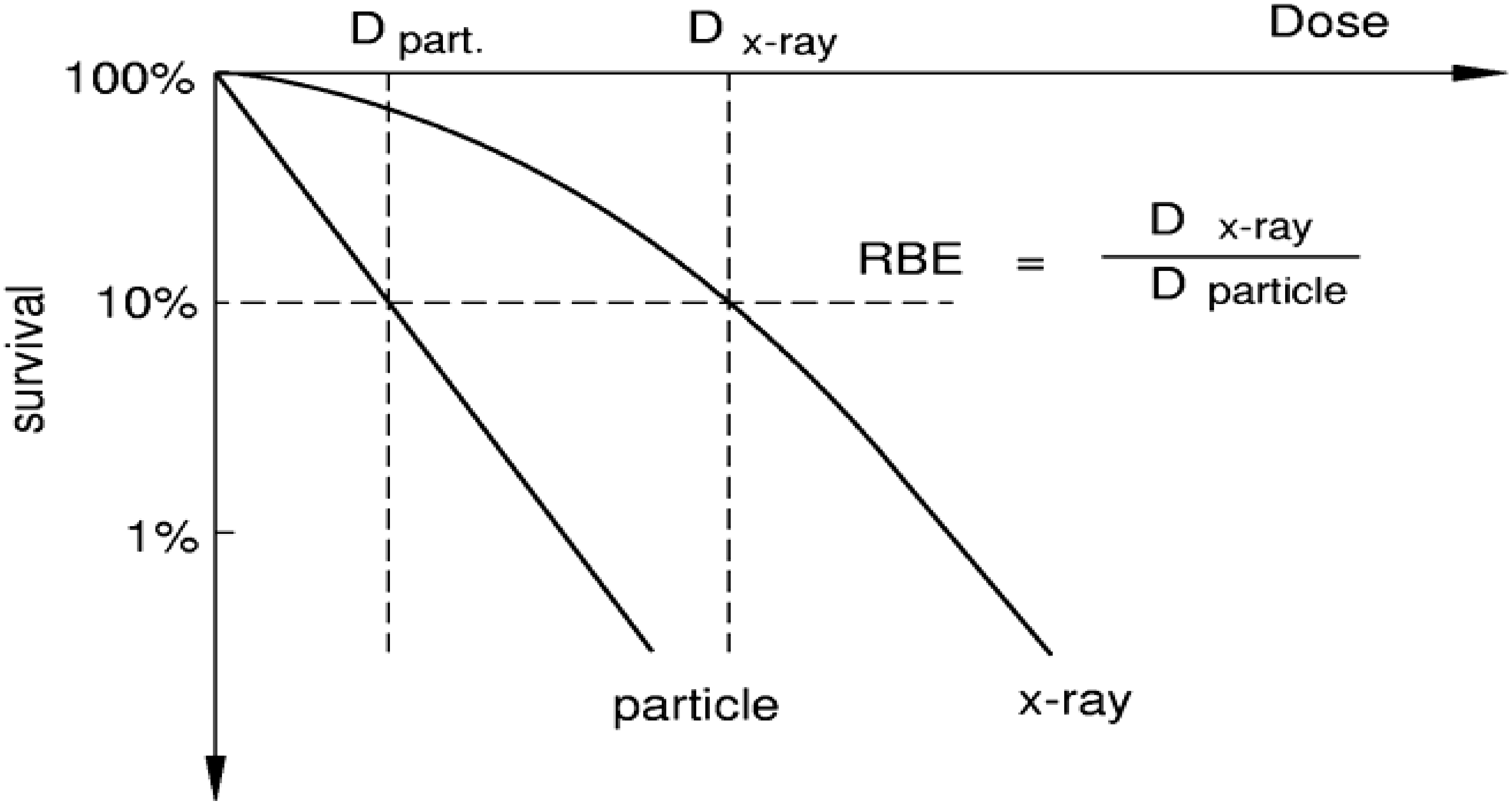
RBE –RELATIVE BIOLOGIC EFFECTIVENESS

- RELATIVE CAPABILITIES OF IONSISING RADIATION WITH DIFFERING LETs TO PRODUCE PARTICULAR BIOLOGIC RESPONSE

RBE

$$\text{RBE} = \frac{\text{DOSE IN Gy FROM 250 KVP X-RAYS}}{\text{DOSE IN GY OF TEST RADIATION}}$$

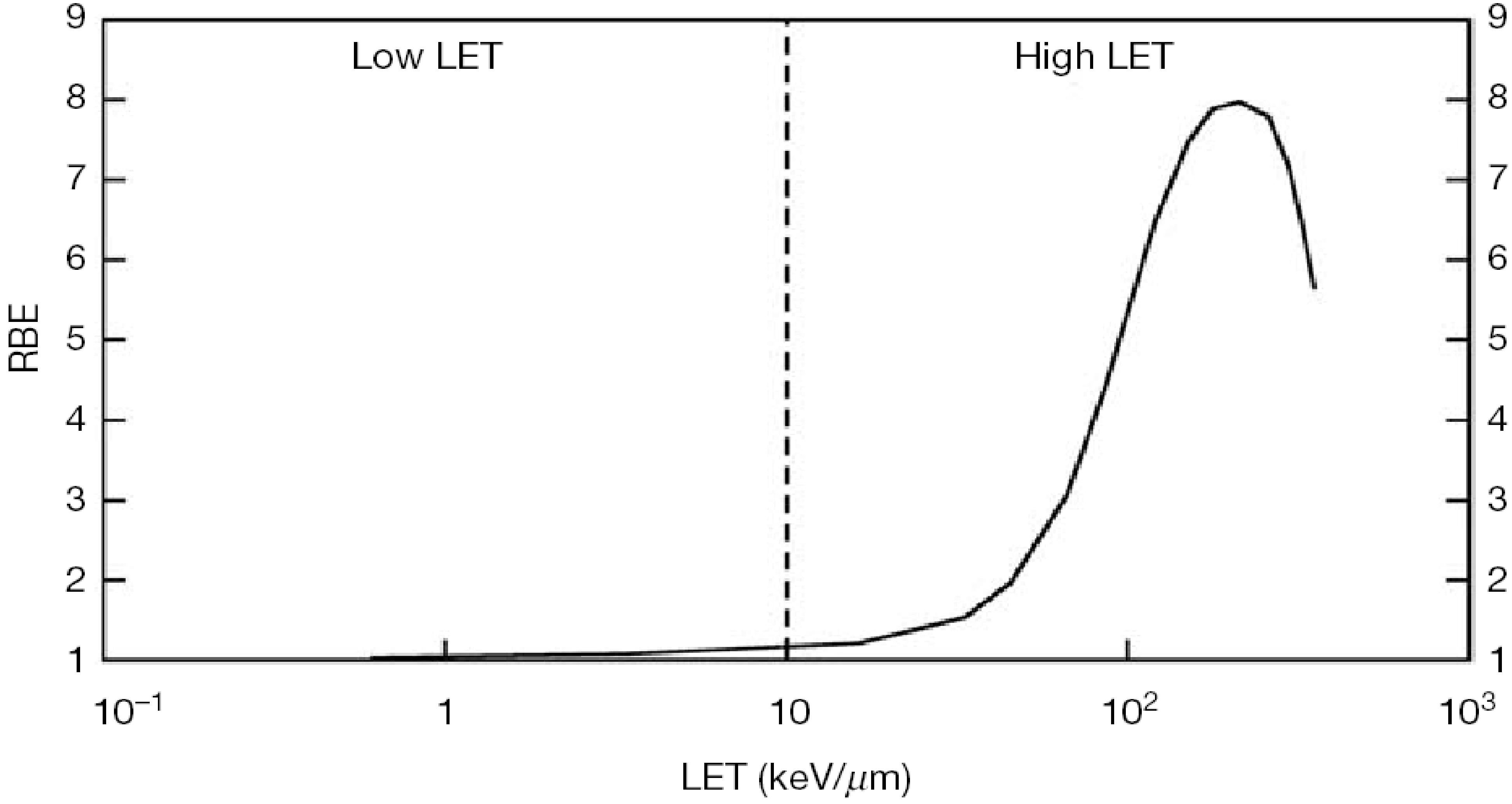
Definition of RBE



LET ↑

RBE ↑

LET and RBE RELATIONSHIP

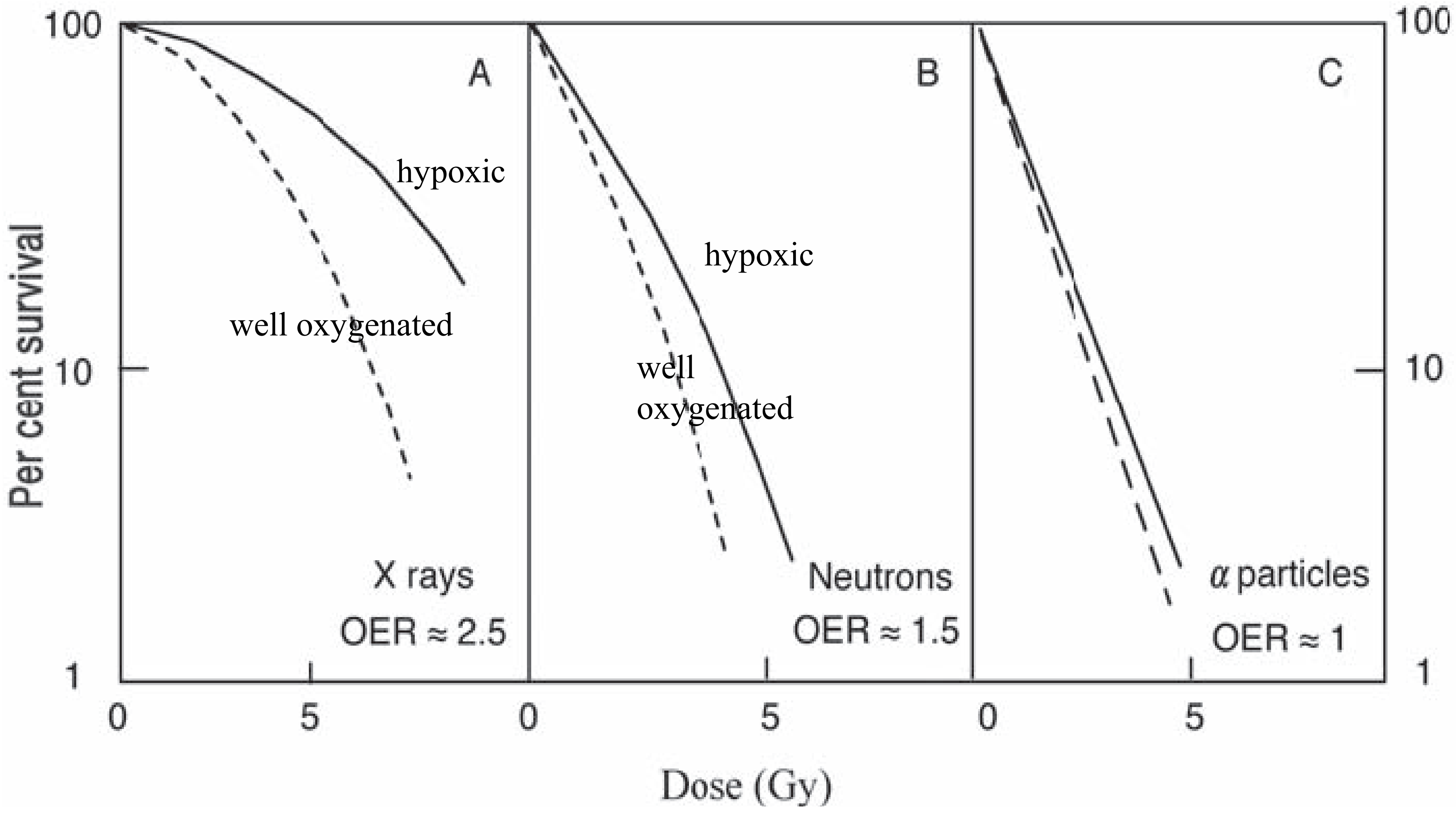


OER-OXYGEN ENHANCEMENT RATIO

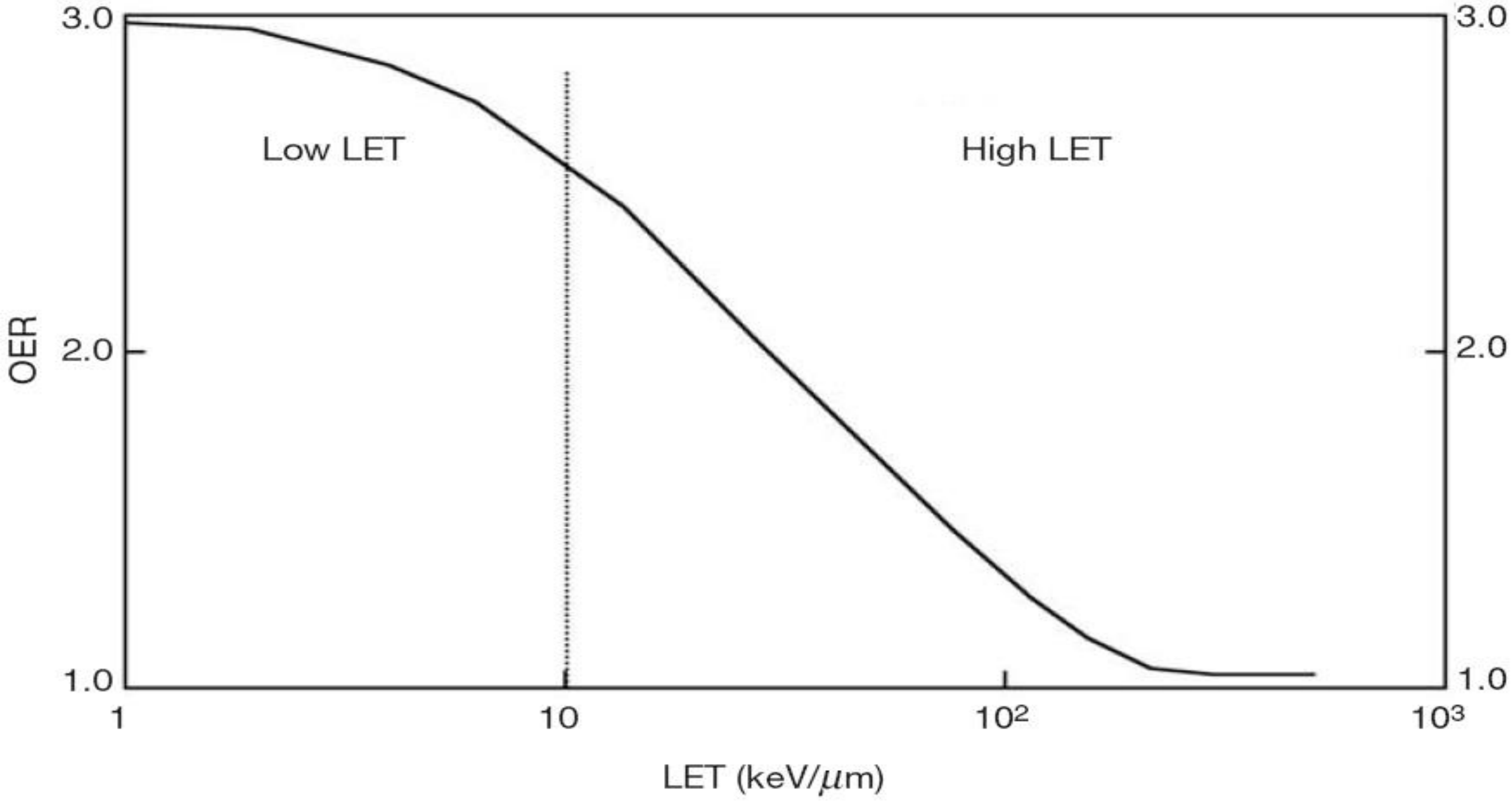
- THE RATIO OF THE RADIATION DOSE REQUIRED TO CAUSE A PARTICULAR BIOLOGIC RESPONSE OF CELLS OR ORGANISMS IN AN OXYGEN DEPRIVED ENVIRONMENT TO THE RADIATION DOSE REQUIRED TO CAUSE AN IDENTICAL RESPONSE UNDER NORMAL OXYGENATED CONDITIONS

$$\text{OER} = \frac{\text{Dose to produce a given effect without oxygen}}{\text{Dose to produce the same effect with oxygen}}$$

Oxygen enhancement ratio (OER)



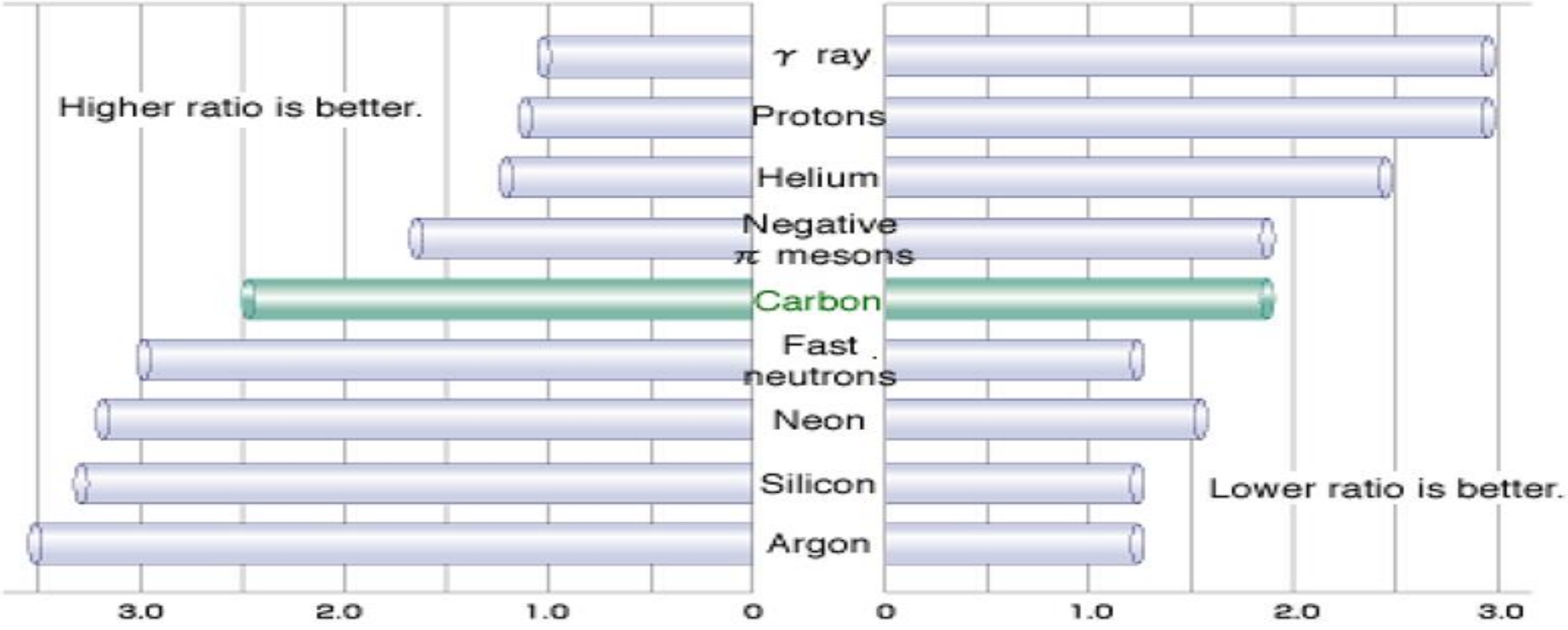
LET and OER RELATIONSHIP



LET ↑

OER ↓

Relative biological effectiveness (RBE) and oxygen enhancement ratio (OER) of various radiation types



RBE represents the biological effectiveness of radiation in the living body.
The larger the RBE, the greater the therapeutic effect on the cancer lesion.

OER represents the degree of sensitivity of hypoxic cancer cells to radiation.
The smaller the OER, the more effective the therapy for intractablecancer cells with low oxygen concentration.

RBE → QF (QUALITY FACTOR)

Biological Responses of cells to ionizing radiation

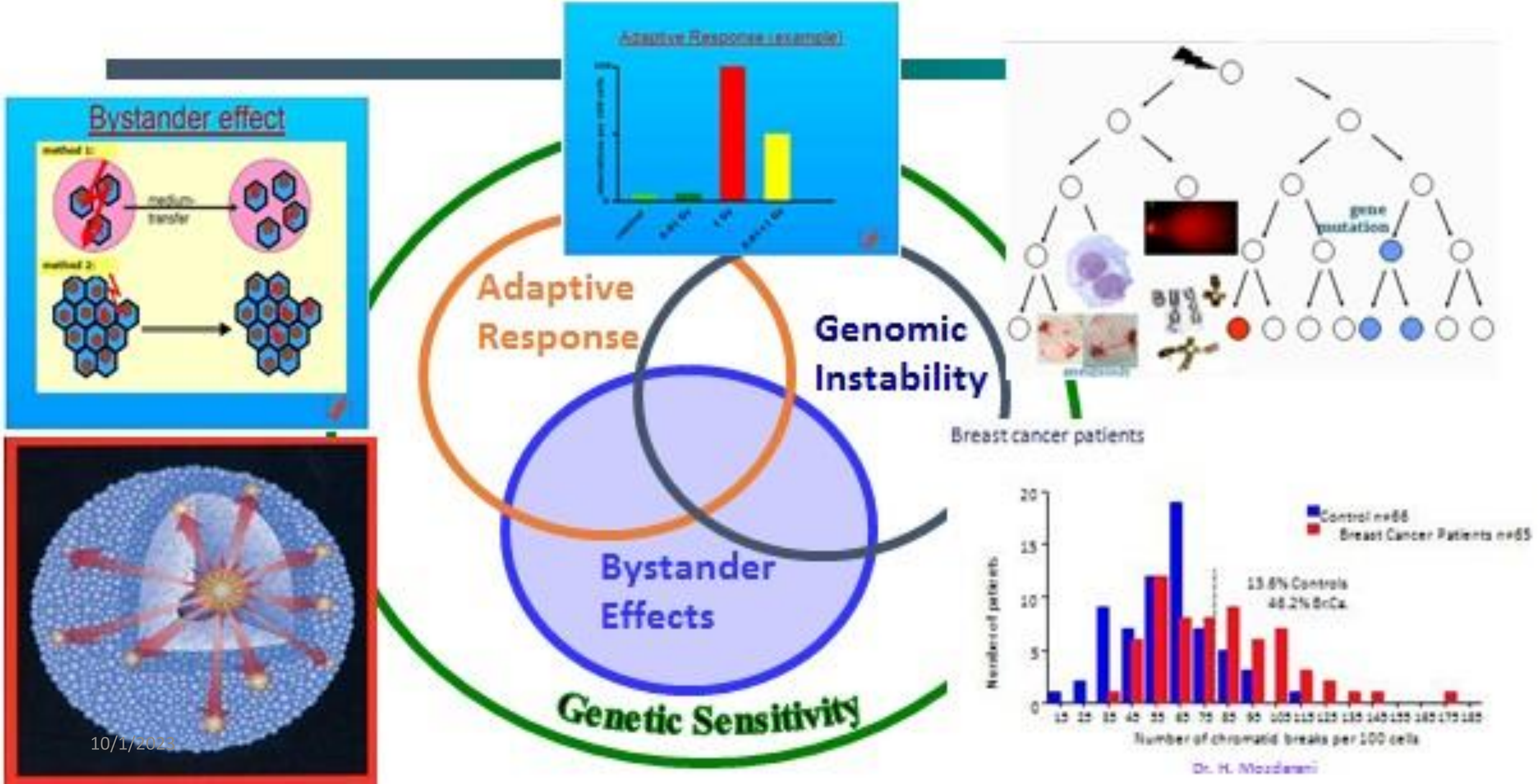


Figure 2. Advances in Radiotherapy: 1900–Present

Clinical Advances
Technologic Advances
Biologic Advances

Becquerel experiences skin burn while carrying radium in vest pocket (109)
1901

Radiation intensity related to inverse square of distance from source
1903

Cellular radiosensitivity depends on mitotic activities and levels of differentiation (47)
1906

Fractionated radiation sterilizes ram's testes without major burns (11, 12)
1911

Leukemia cases reported in radiation workers (10)
1911

Hot-cathode x-ray tube invented (33)
1913

How high-energy photons interact with tissue (Compton effect) (109)
1922

Radiosensitivity correlated with oxygen presence (52)
1923

Air wall ionization chambers accurately measure radiation intensities
1924

Roentgen adopted as standard exposure unit; radiation protection recommendations
1928

Head and neck cancers cured with fractionated X-rays (13)
1928

Cyclotron invented (37)
1932

Dosage system for gamma ray (36)
1934

Plant root studies show importance of oxygen in radiotherapy (52)
1935

First patient treated with neutron beams
1938

First self-sustaining nuclear chain reaction with uranium
1942

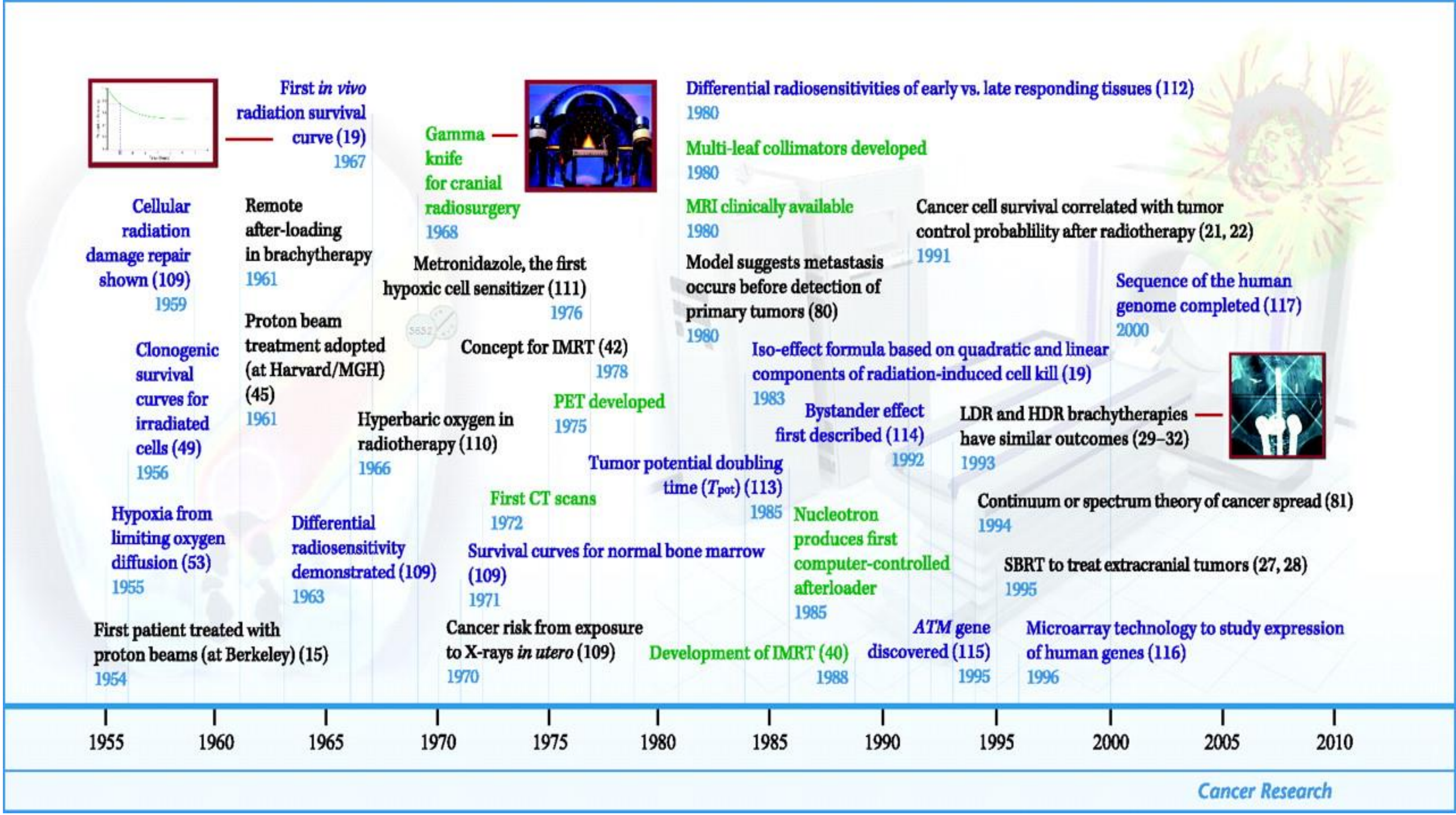
Skin iso-effects governed primarily by total dose and overall treatment time (17)
1944

Nobel Prize (Muller) for radiation-induced mutagenesis shown in Drosophila
1946

Cobalt-60 telotherapy units first used (15)
1951

Experimental quantification of the oxygen effect (109)
1952

1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950



First patient treated with proton beams (at Berkeley) (15)
1954
Hypoxia from limiting oxygen diffusion (53)
1955
Clonogenic survival curves for irradiated cells (49)
1956
Cellular radiation damage repair shown (109)
1959
Remote after-loading in brachytherapy
1961
Proton beam treatment adopted (at Harvard/MGH) (45)
1961
Differential radiosensitivity demonstrated (109)
1963
Hyperbaric oxygen in radiotherapy (110)
1966
First in vivo radiation survival curve (19)
1967
Gamma knife for cranial radiosurgery
1968
Cancer risk from exposure to X-rays in utero (109)
1970
Survival curves for normal bone marrow (109)
1971
First CT scans
1972
PET developed
1975
Metronidazole, the first hypoxic cell sensitizer (111)
1976
Concept for IMRT (42)
1978
Differential radiosensitivities of early vs. late responding tissues (112)
1980
Multi-leaf collimators developed
1980
MRI clinically available
1980
Model suggests metastasis occurs before detection of primary tumors (80)
1980
Iso-effect formula based on quadratic and linear components of radiation-induced cell kill (19)
1983
Tumor potential doubling time (T_{pot}) (113)
1985
Nucleotron produces first computer-controlled afterloader
1985
Development of IMRT (40)
1988
Cancer cell survival correlated with tumor control probablility after radiotherapy (21, 22)
1991
Bystander effect first described (114)
1992
LDR and HDR brachytherapies have similar outcomes (29–32)
1993
Continuum or spectrum theory of cancer spread (81)
1994
SBRT to treat extracranial tumors (27, 28)
1995
ATM gene discovered (115)
1995
Microarray technology to study expression of human genes (116)
1996
Sequence of the human genome completed (117)
2000
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
Cancer Research

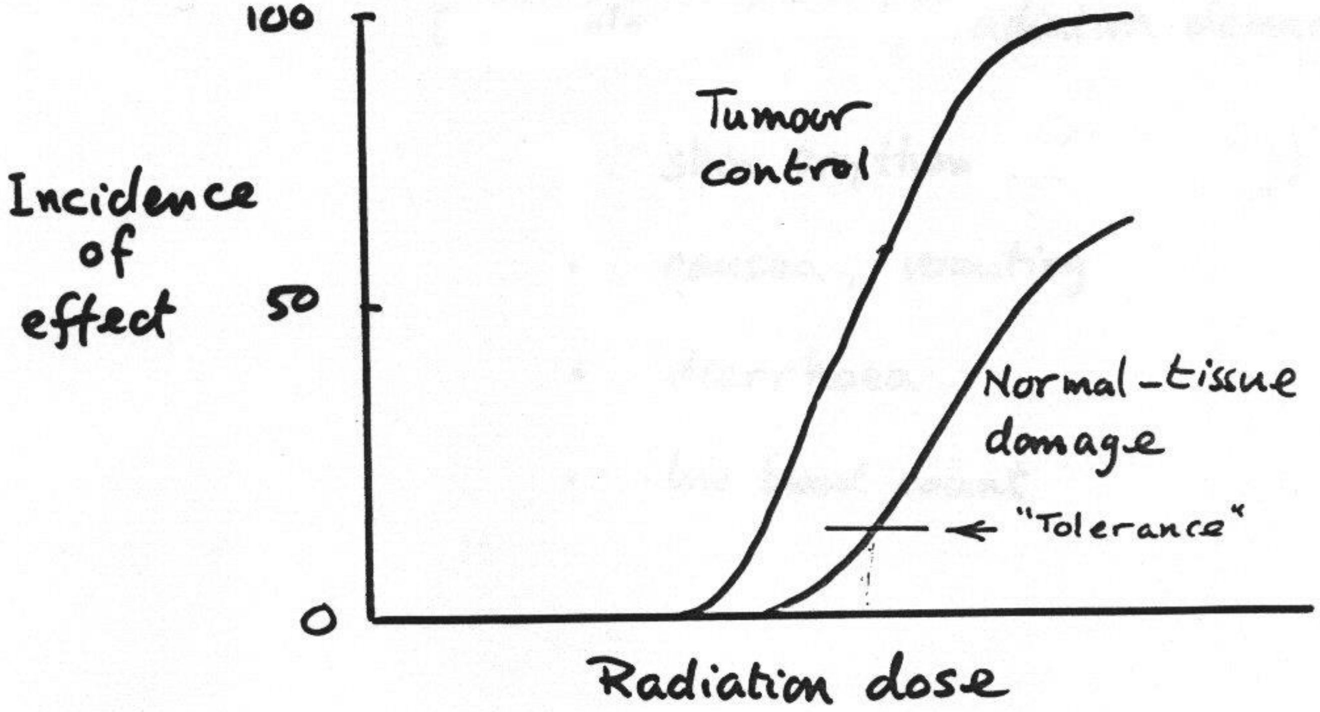
Primary aim of radiotherapy

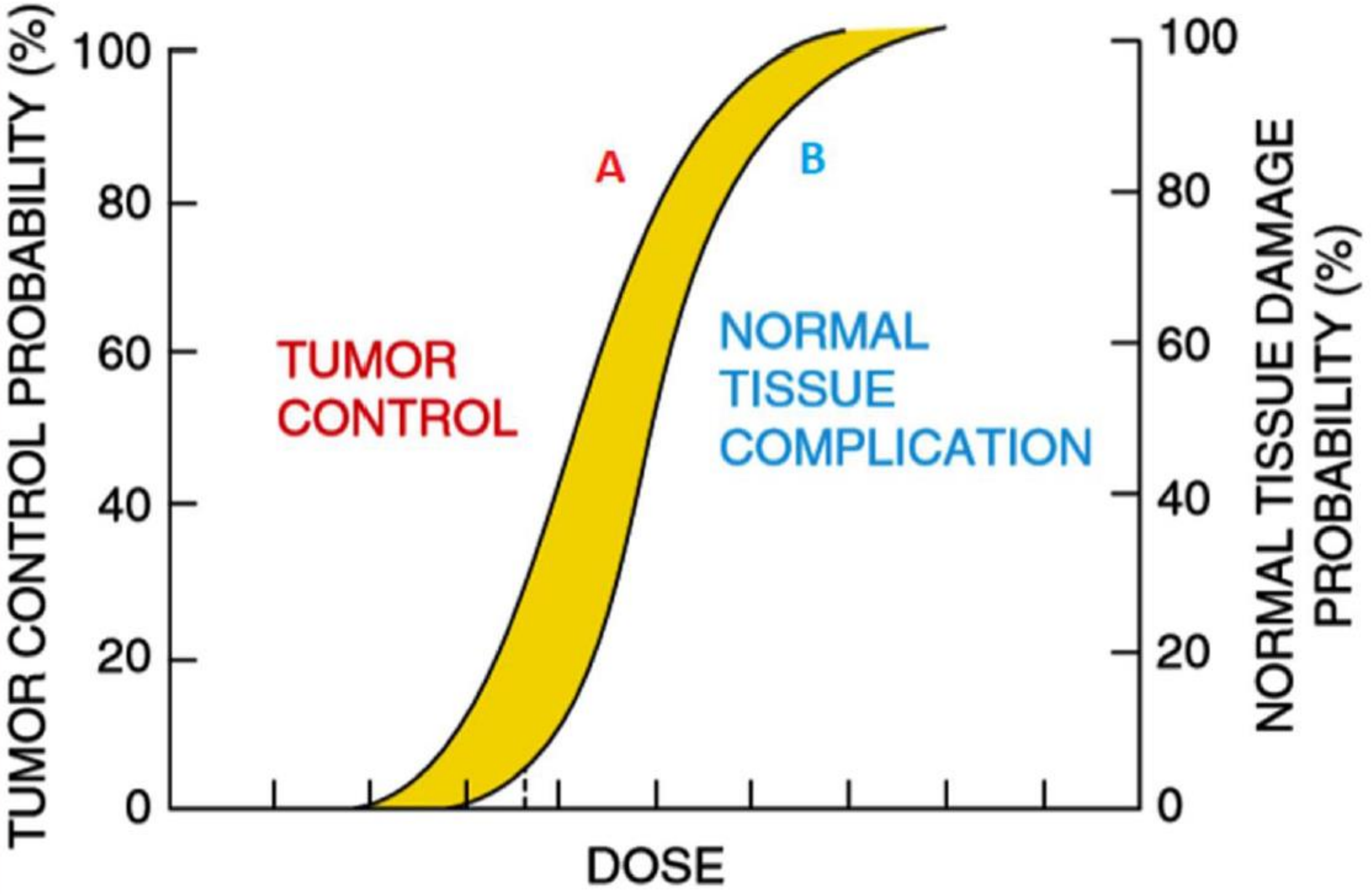
1. Deliver lethal dose to tumor
2. Spare normal tissue/ OAR

How to achieve
Art/ Science

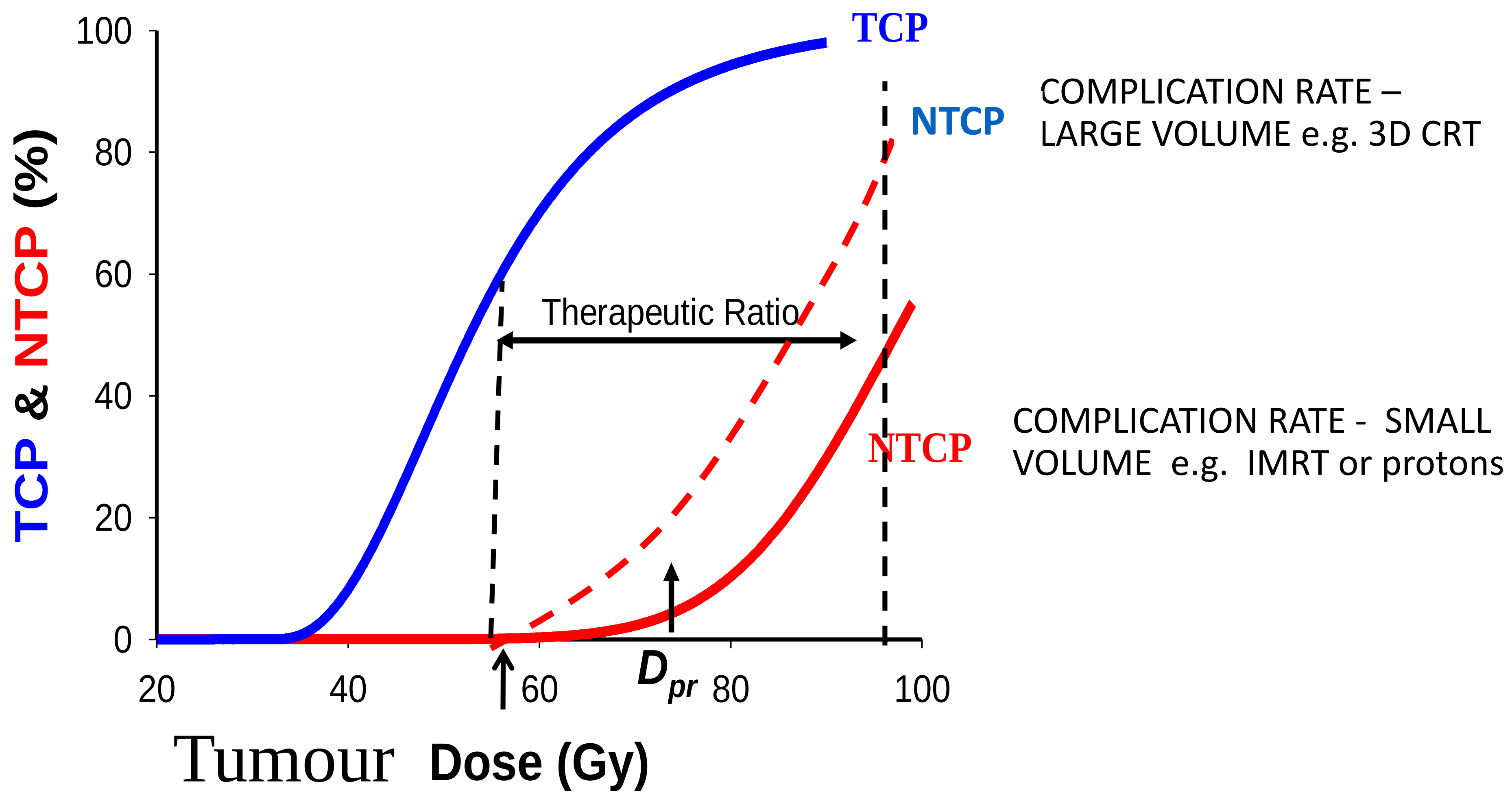
Radiobiology:
Tumour and normal tissue

- Radiation effect vs. dose
  - sigmoid behaviour
  - stochastic process
- Tumour control lower dose than normal tissue damage
  - Makes radiotherapy possible!
- Radiotherapy goals and research
  - separate two curves




TUMOR CONTROL PROBABILITY (%)
100
80
60
40
20
0
A
B
TUMOR
CONTROL
NORMAL
TISSUE
COMPLICATION
DOSE
NORMAL TISSUE DAMAGE
PROBABILITY (%)

For a given fraction size



4Rs OF DOSE FRACTIONATION

These are radiobiological mechanisms that impact the response to a fractionated course of radiation therapy

Repair of sublethal damage

spares late responding normal tissue preferentially

Redistribution of cells in the cell cycle

increases acute and tumor damage, no effect on late responding normal tissue

Repopulation

spares acute responding normal tissue, no effect on late effects,
danger of tumor repopulation

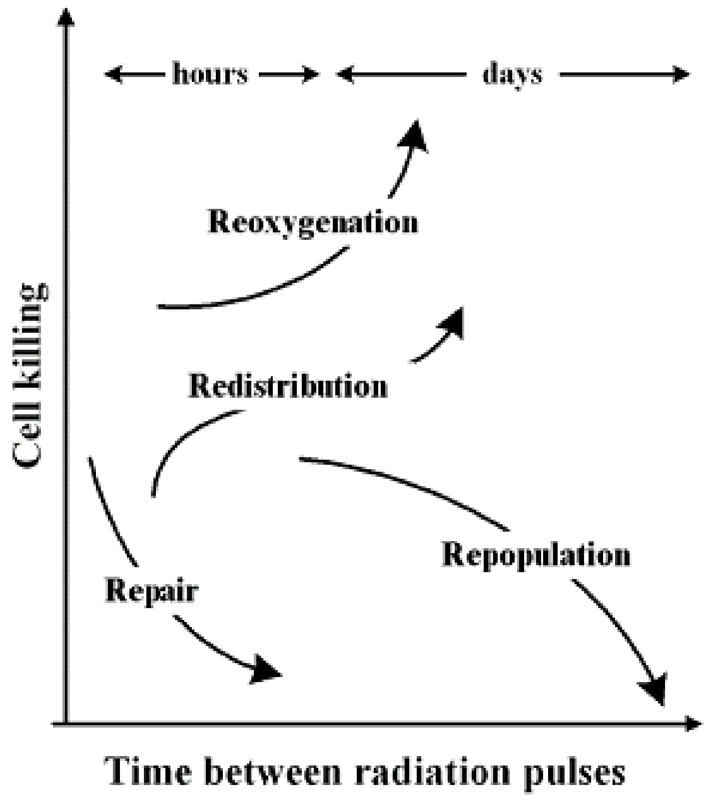
Reoxygenation

increases tumor damage, no effect in normal tissues

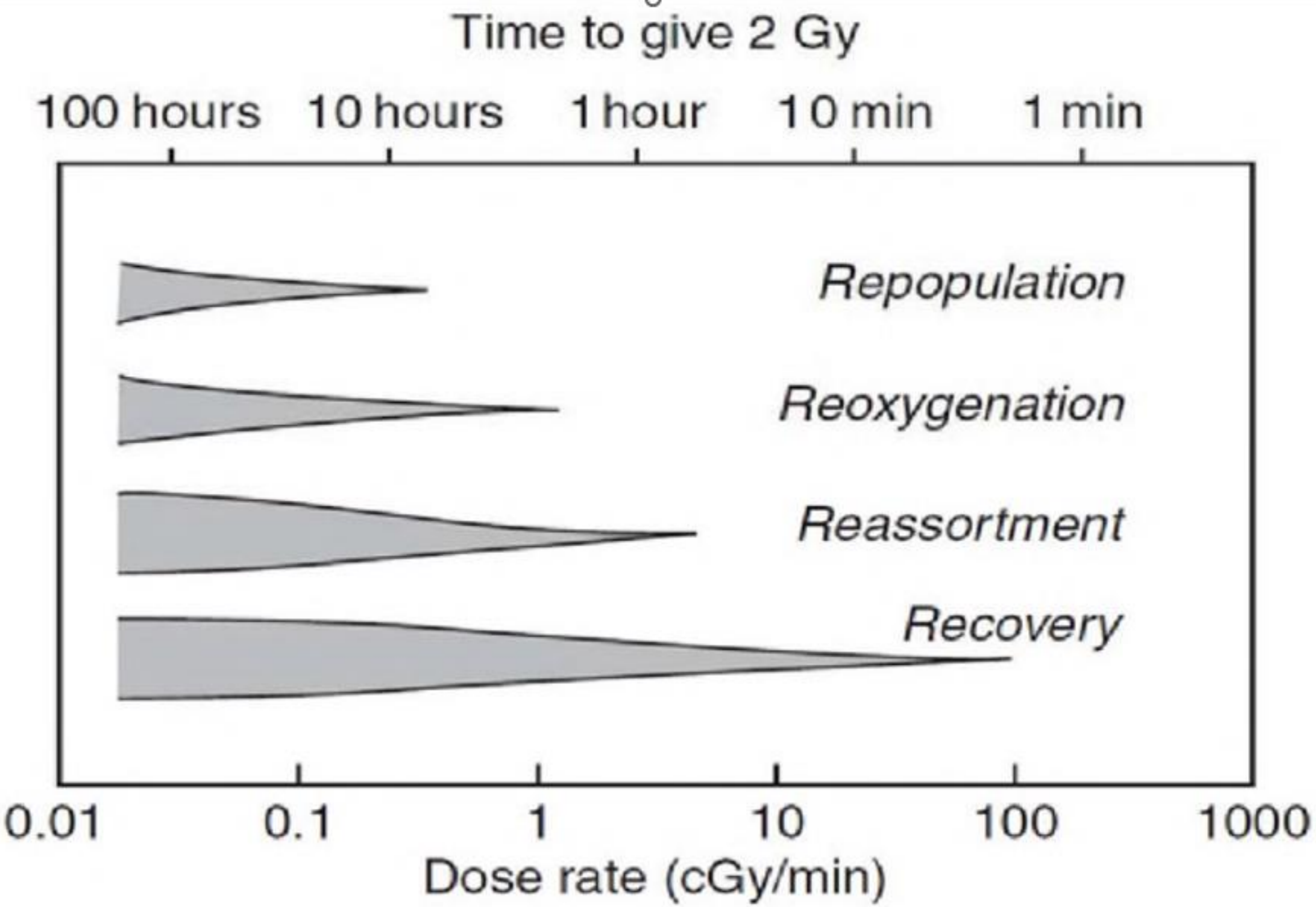
5 th R- Radiosensitivity

4 R's of radiation biology

- Repair of cellular damage
- Reoxygenation of the tumor
- Redistribution within the cell cycle
- Repopulation of cells



- **5 th R- Radiosensitivity-** the response to radiation varies by tumor intrinsic and individual radiosensitivity.
- 6th R - "Reactivation of anti-tumor immune response"- RT considerably modifies the immune landscape by affecting immune activation as well as immunosuppressive pathways.



The range of dose rates over which repair, reassortment and repopulation modify radiosensitivity depends upon the speed of these processes.

Steel, G.G., et al., Dose-rate effects and the repair of radiation damage. Radiother Oncol, 5 (1986) 321-331,

The 4 Rs of radiotherapy: Influence on time between fractions, t, and overall treatment time, T

- **R**eoxygenation
- **R**edistribution
- **R**epair
- **R**epopulation (or Regeneration)

- Need minimum T
- Need minimum t
- Need minimum t for normal tissues
- Need to reduce T for tumour

The 4 Rs of radiotherapy: Influence on time between fractions, t, and overall treatment time, T

- **R**eoxygenation
- **R**edistribution
- **R**epai
- **R**epo
  Regene

- Need minimum T
- Need minimum t
- m t for
  s
- e T for

Cannot achieve all at once - Optimization of schedule for individual circumstances

Time, dose and fractionation

- Need to optimize fractionation schedule for individual circumstances

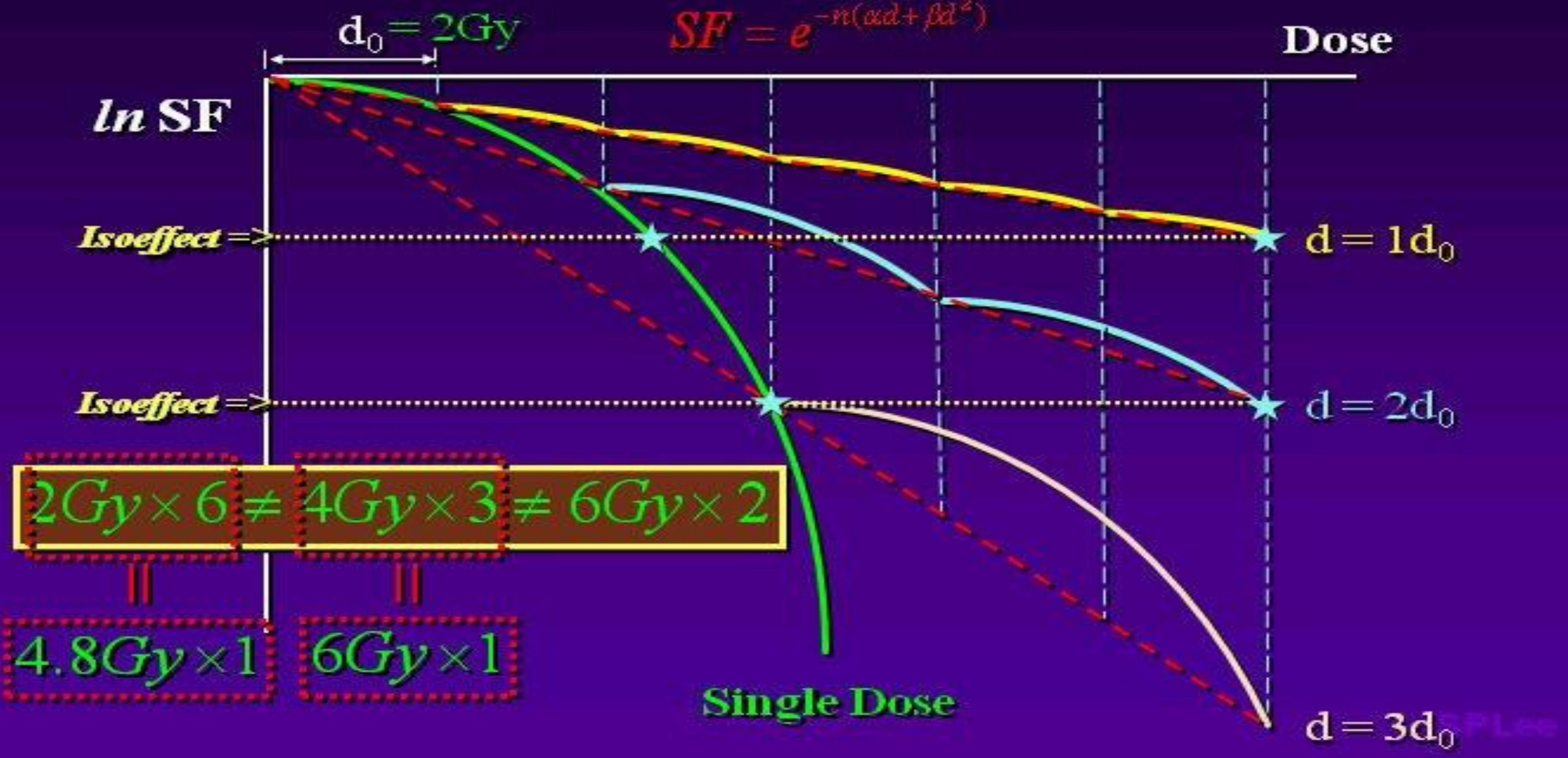
- Parameters:
  - Total dose
  - Dose per fraction
  - Time between fractions
  - Total treatment time

- The most important lessons that history has taught us are
- *There can be no single regimen of treatment delivery that will be appropriate for all tumors in all patients.*
- Fractionation cannot be considered in isolation. There is a complex interdependence between

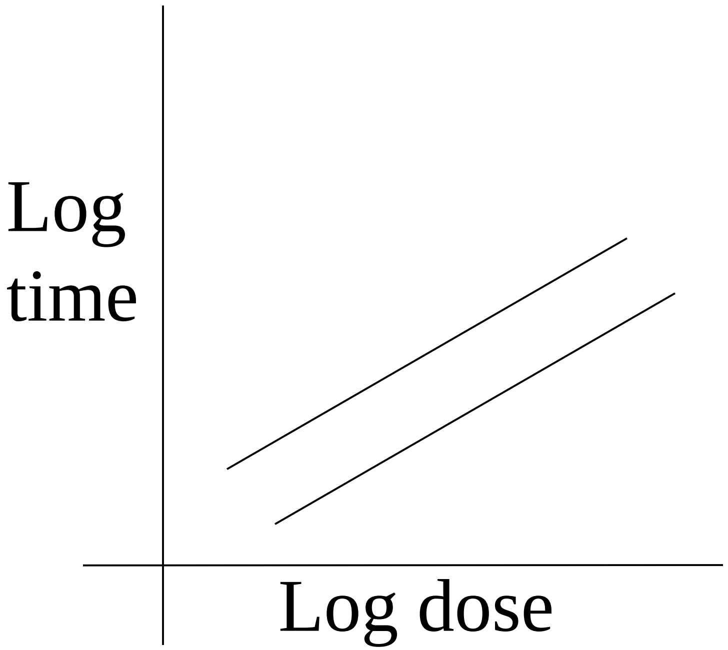
Total dose, dose-per-fraction, overall treatment time, treated volume, beam parameters

- Clinical advances precede, and are preceded by, advances in our basic understanding of radiation biology.
- *The tolerance of normal tissues to the late effects of radiation limits the dose that can safely be prescribed to the tumor.*
- The tolerance dose varies between tissues and is influenced by the proportion of the organ treated, the length of follow-up and the end point assessed.

Fractionation Effects



❖Strandqvist (1944)-first scientific approach - *related dose with overall treatment time for equivalent biological effect.*



❖Cohen (1949)-analyzed data of Reisner (1933), Quimby (1937) and Strandqvist (1944).

Definitions

- **Conventional fractionation**
  - **Daily doses (d) of 1.8 to 2 Gy**
  - **Dose per week of 9 to 10 Gy**
  - **Total dose (D) of 40 to 70 Gy**
- **Hyperfractionation**
  - **The number of fractions (N) is increased**
  - **T is kept the same**
  - **Dose per fraction (d) less than 1.8 Gy**
  - **Two or more fractions per day (t)**

  Rationale: Spares late responding tissues

Definitions

- **Accelerated fractionation**
  - Shorter overall treatment time
  - Dose per fraction of 1.8 to 2 Gy
  - More than 10 Gy per week

  Rationale: Overcome accelerated tumor repopulation
- **Hypofractionation**
  - Dose per fraction (d) higher than 2.2 Gy
  - Reduced total number of fractions (N)

  Rationale: Tumor has low α/β ratio and there is no therapeutic advantage to be gained with respect to late complications

Types of Hypofractionation

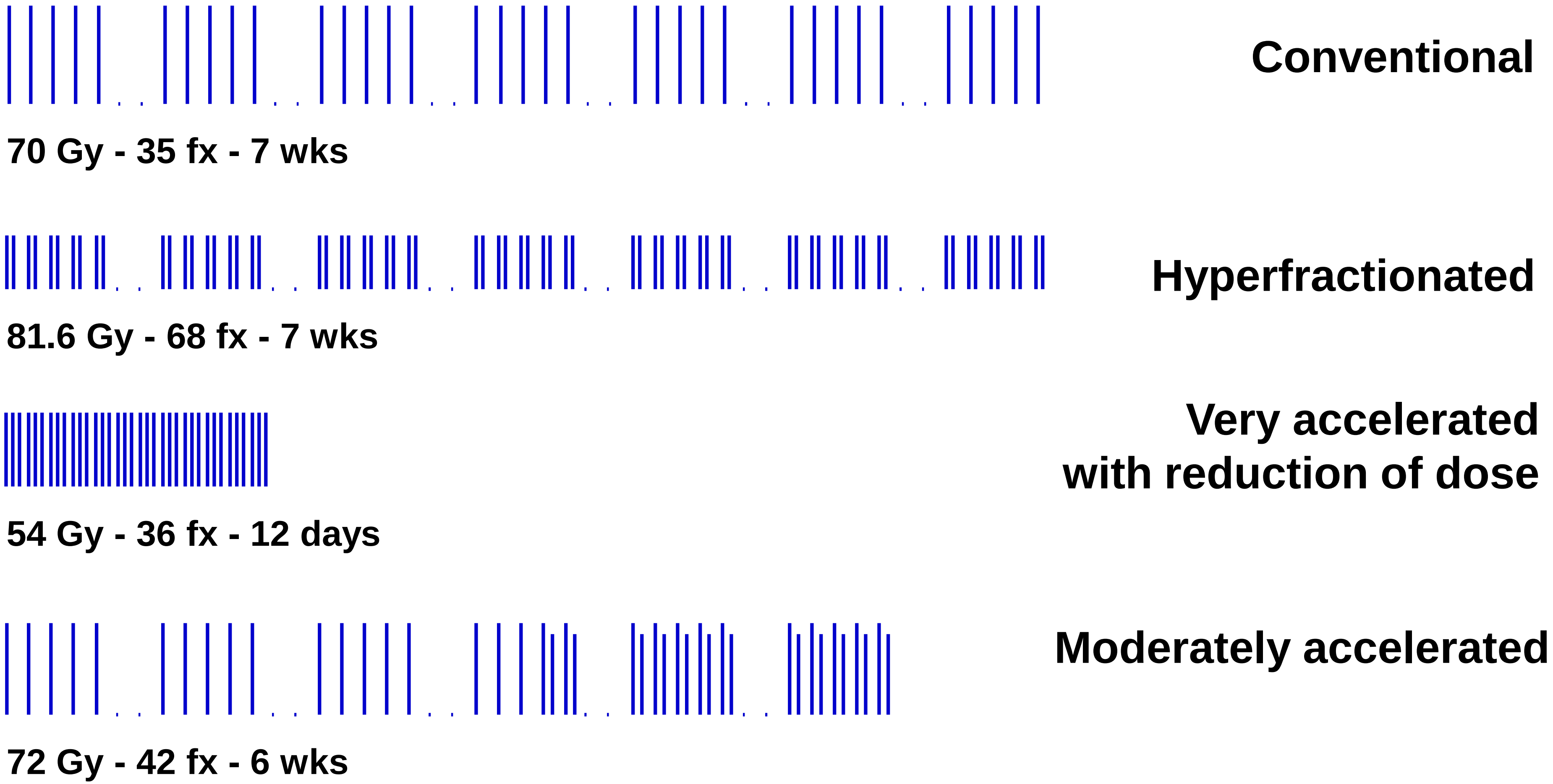
- Hypo fractionation has been further subdivided into two types:

1. Moderate hypo fractionation:

   (2.4 to 4 Gy/fraction for 15-30 fractions) and

2. *Extreme hypo fractionation*

   (6.5 to 10 Gy/fraction for 4-7 fractions)


Conventional
70 Gy - 35 fx - 7 wks
Hyperfractionated
81.6 Gy - 68 fx - 7 wks
Very accelerated
with reduction of dose
54 Gy - 36 fx - 12 days
Moderately accelerated
72 Gy - 42 fx - 6 wks

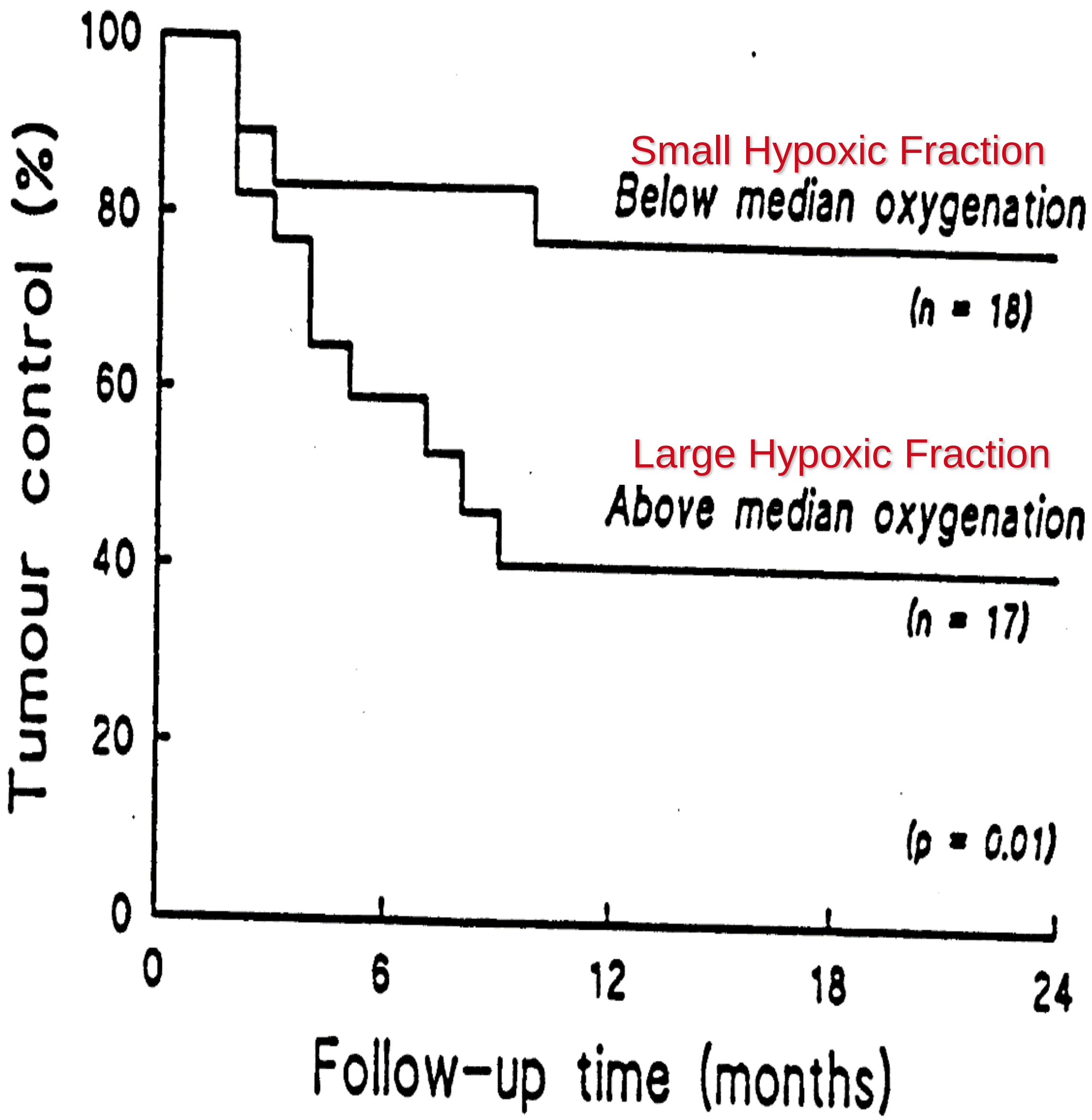
Fractination in RT

Fractionation	Typical Fraction Size	Typical No. of Fxs	Pros	Cons
Conventional	1.5-2.25 Gy /d	30-40	Spare early normal tissue reactions Allow Re-oxygenation & re-assortment in Tumors	Allow surviving Tumor cells to proliferate
Hyper Fx (same total dose in same time)	1.15-1.8 Gy Bid	60-70	Further separate early and late effects	Patient inconvenience
Accelerated Fx (same total dose in less time) •Continuous Hyper Fx Accelerated RT (CHART)	1.5-2.25 Gy bid (could include a break) 1.4-1.5 Gy tid separated by atleast 4-6 hrs	30-40 36 Fxs/12 days	Shorter time, reduces re-population of Tumor cells No change in late effects	Increase in acute effects
•Hypo Fx •HF-SRT, SBRT •SRS	2.5-3 Gy 4-6 Gy >8Gy	15-20 6-10 1-5	Reduced Treatment time, convenient Better efficacy with Hypoxic cells.	Increase Late effects

Fractionation sensitivity of different tumours in the clinical setting

Tumor fractionation sensitivity	Definition	Optimal fractionation schedule	Types offumor	Reference
Low	**α/β ratio of tumor higher** than that of late responding healthy tissues	**More, smaller-sized fr. with higher total dose**,	**head and neck and lung ca**	Nguyen et al.,2002 Overgaard et al., 2003 Saunders et al., 1999
Moderate to high	**α/β ratio of tumor similar or slightly higher than that of late responding healthy tissues**	**Fewer, larger-sized fractions might achieve same LC**	**BREAST CA**	Yarnold et al., 2005 Owen et al., 2006 Whelan et al., 2002 START A, 2008 START B, 2008
High	α/β ratio of tumor lower than that of late responding healthy tissues	**Fewer, larger-sized fr-> improve LC**	**prostate ca**	Fowler, 2005

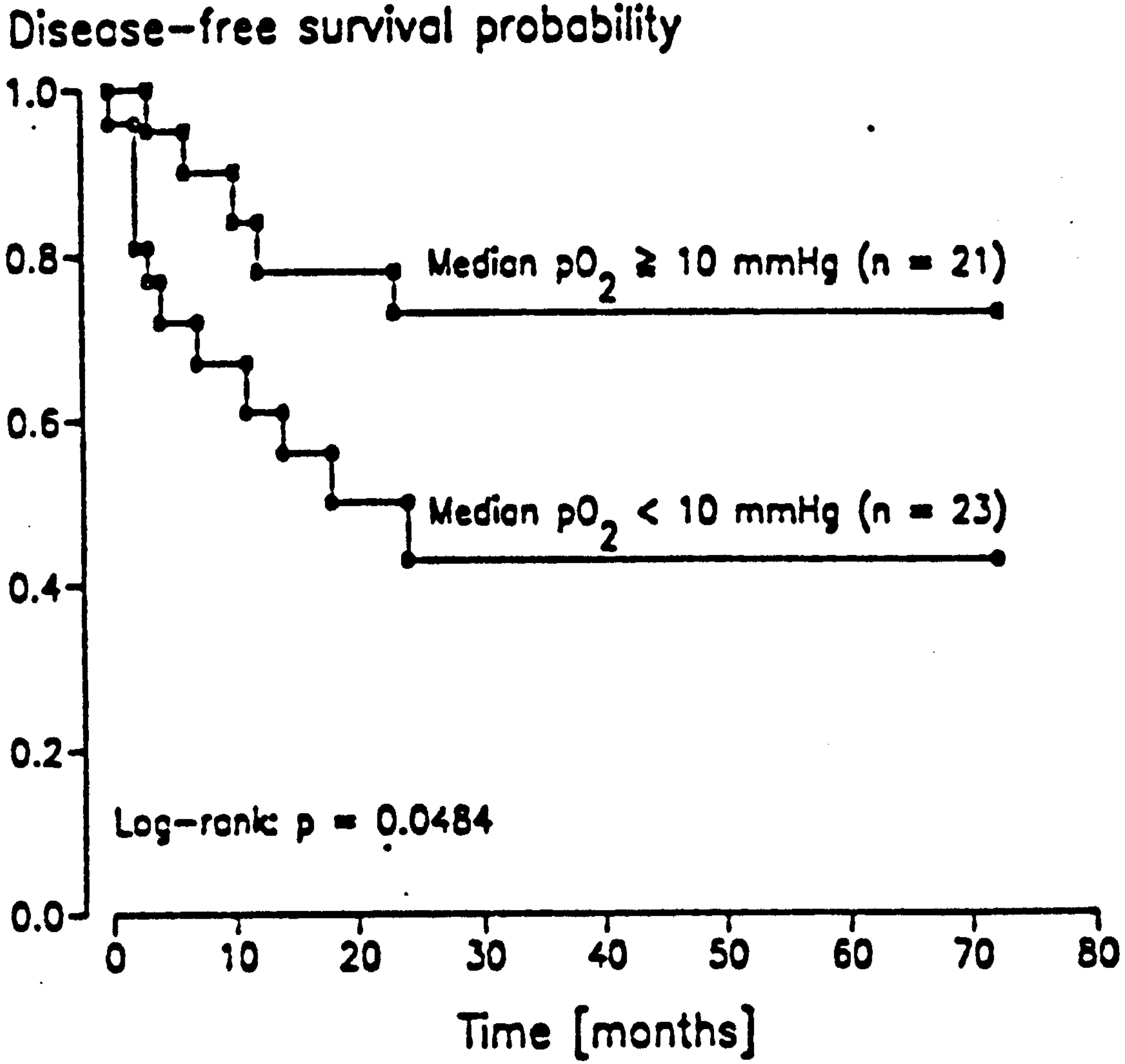
Hypoxia and Local Tumor Control



- Local tumor control correlates with pre-treatment oxygen levels in head and neck ca., as measured with an Eppendorf electrode. Tumors were stratified by whether the fraction of pO2 values less than 2.5 mm Hg was above or below the median (15%). 66-68 Gy was given in 33-34 Fx.
- Nordsmark et al Radiother Oncol 41, 31, 1996

Tumor Hypoxia and DFS

- DFS in cervix ca depends on pO_2, irrespective of type of treatment, surgery/RT. Hockel et al, Sem. Radiat. Oncol. 6:30, 1996.
- This suggests that hypoxia is linked to tumor aggression



Summary

Radiosensitivity depends on many intrinsic and extrinsic factors

Intrinsic factors

Cell type
Cell division phase
Repair, repopulation, reoxygenation, redistribution capabilities
Proliferative potential
Oxygen supply, vascularity , Metabolism
Host cell infiltrates, Interstitial pressure
Genetic composition- Oncogenes, Tumor suppressor genes

Extrinsic factors

Total dose
Time , dose rate, fraction size, type of radiation, volume

Questions ?