BIOLOGICAL BASIS OF CLINICAL PARTICLE PHYSICS

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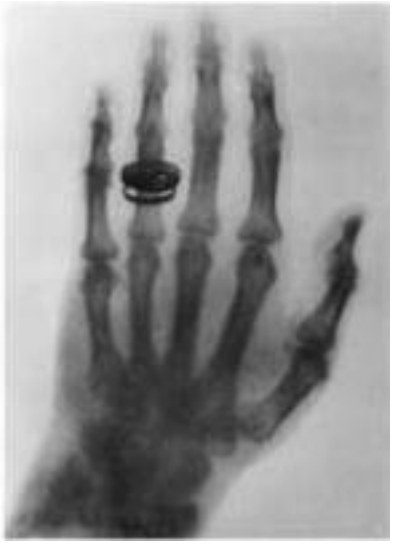
Outline

- Physics & Chemistry of Radiation Absorption
- Radiobiological basis of Radiotherapy
- Treatment Planning
- Charged particles

X-rays

- 1895 Roentgen discovery of X-rays
- 1896, 1st medical use reported in Lancet (Dx)
  - X-ray of sailor's backbone to remove piece of a knife

1896, L. Freund treatment of a hairy mole before Vienna Medical Society



1st Therapeutic use

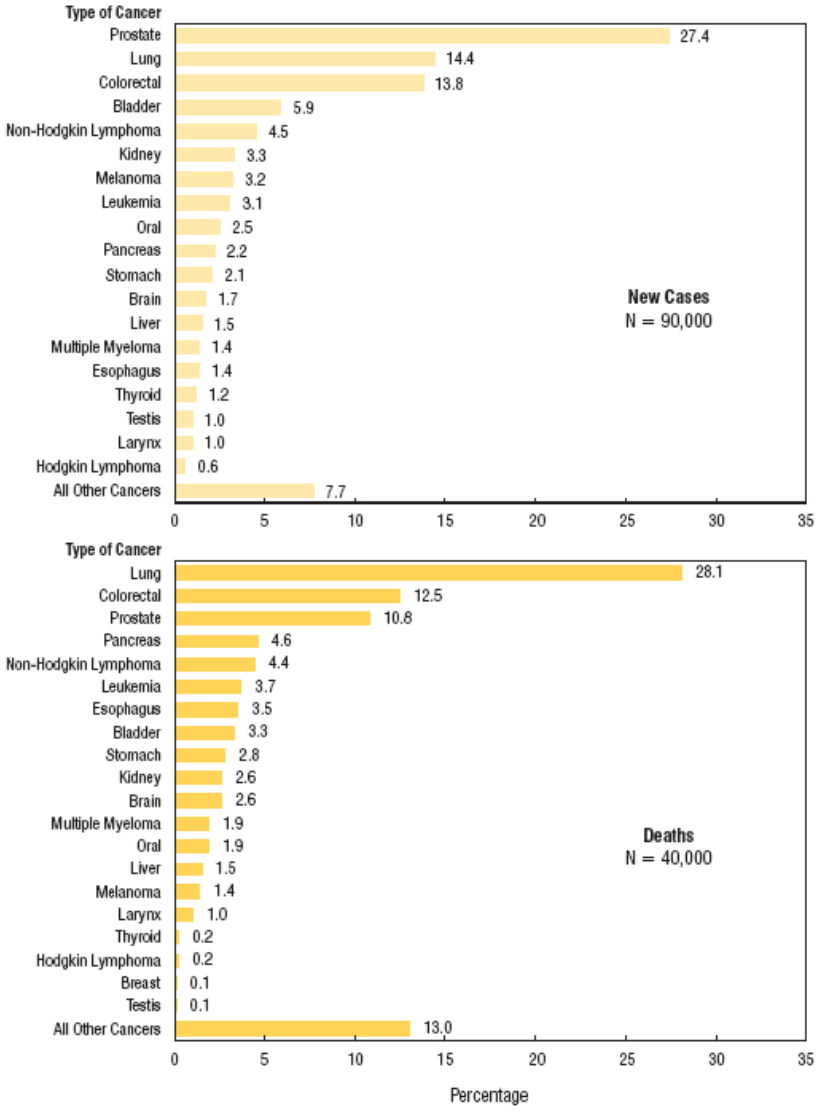
- 1896, , L. Freund treatment of a hairy mole before Vienna Medical Society
- A-H Becquerel discovery of radioactivity emitted by uranium compounds
- Becquerel INADVERTENTLY left radium container in his vest pocket

- 1901, Pierre Curie “radiation burn”

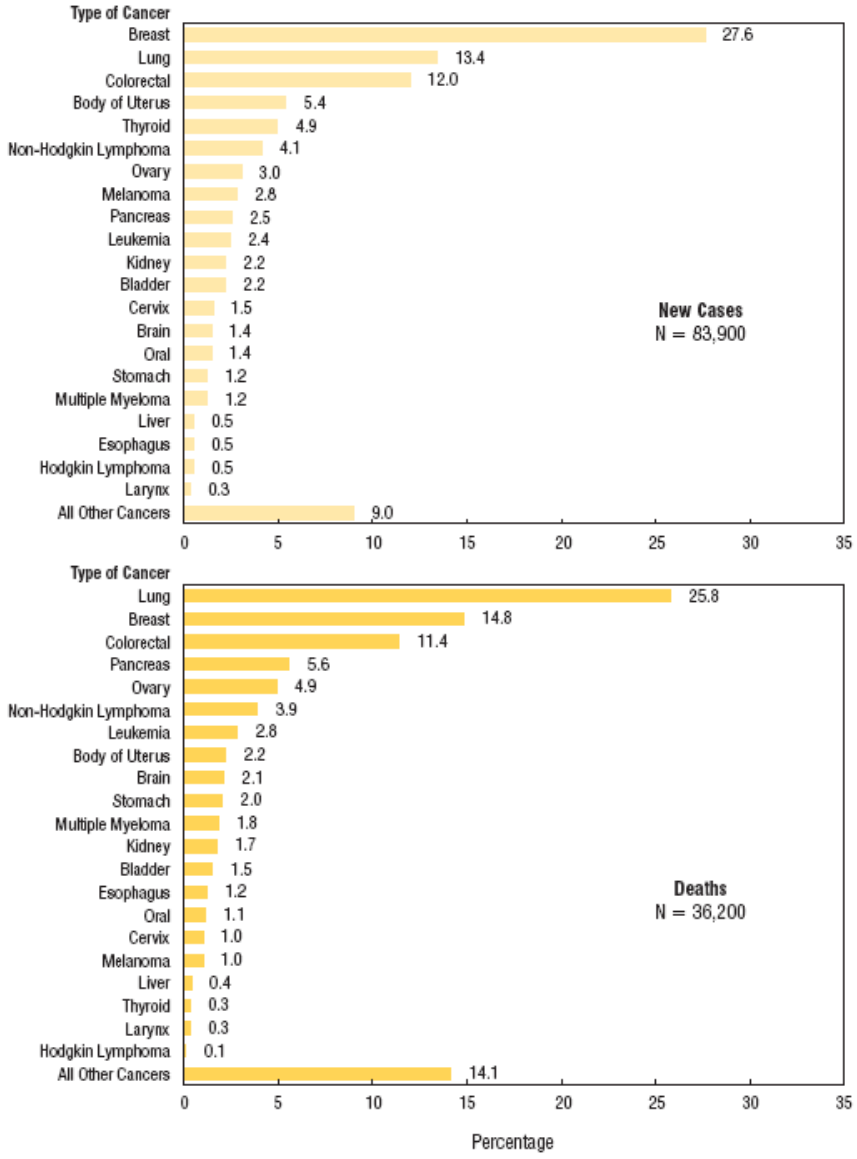
Mortality for the leading causes for death

- Heart diseases 36%
- Cancer 22%
- CVA diseases 7%
- Accidents 5%
- By 2003 statistics (Canada), cancer is equal to cardiovascular disease as a leading cause of death

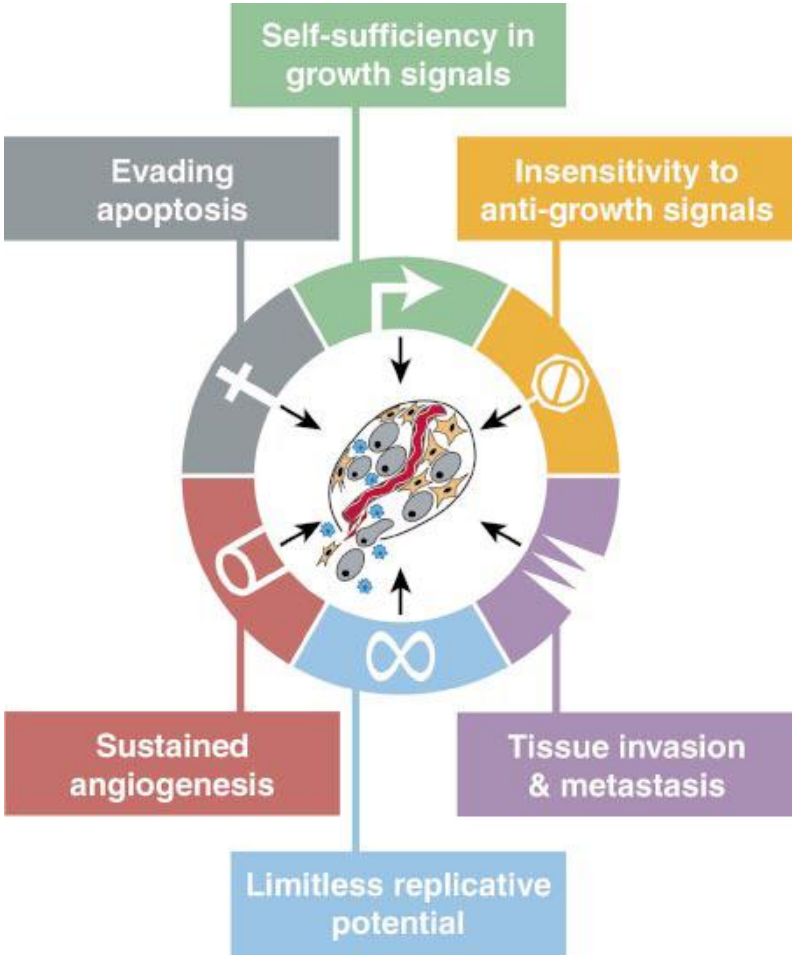
Percentage Distribution of Estimated New Cases and Deaths for Selected Cancers, Males, Canada, 2010

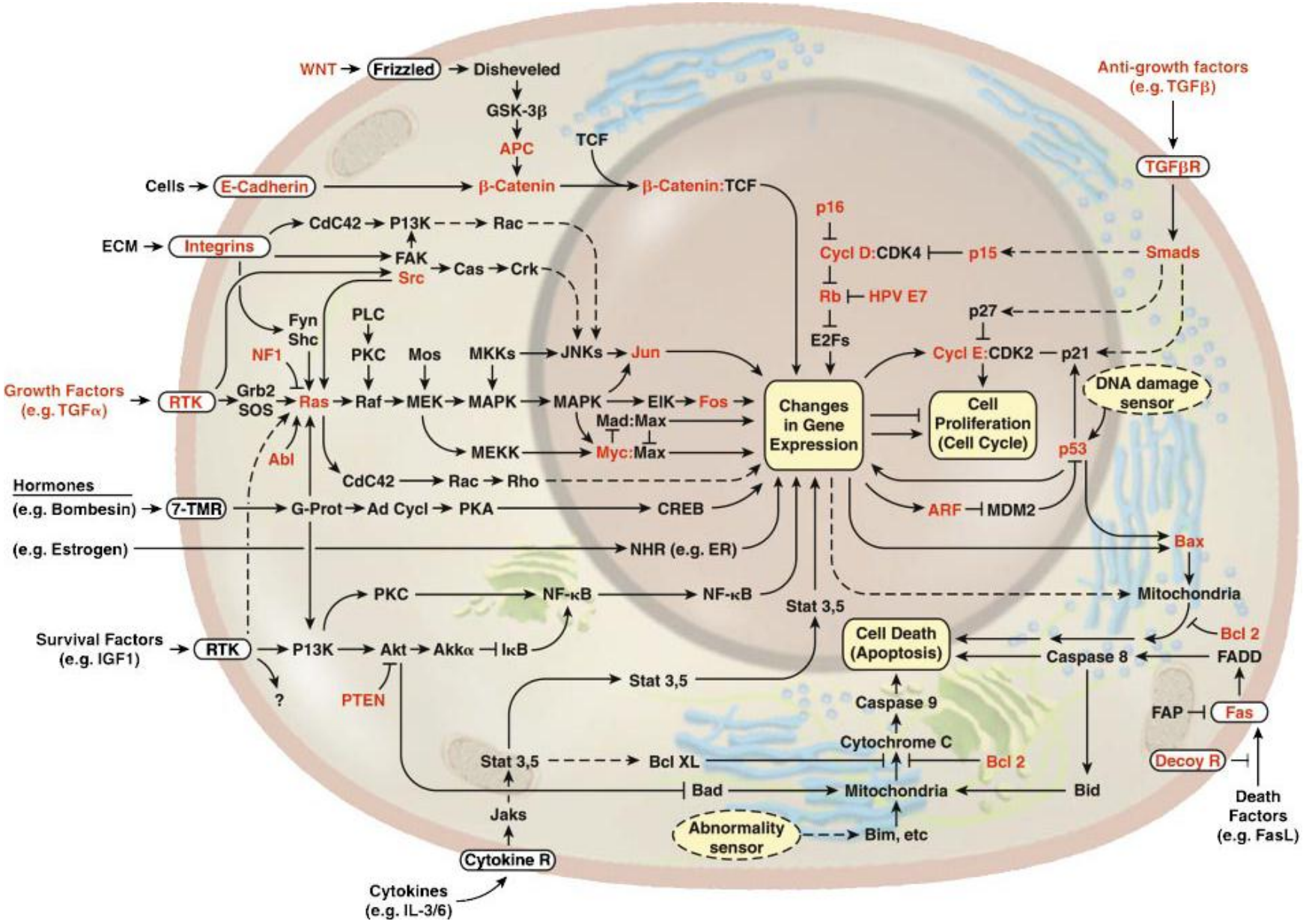


Percentage Distribution of Estimated New Cases and Deaths for Selected Cancers, Females, Canada, 2010



Hallmarks of Cancer





Radiobiology & Radiotherapy

- The study of the interaction of ionizing radiation on living things
  - excitation or ionization

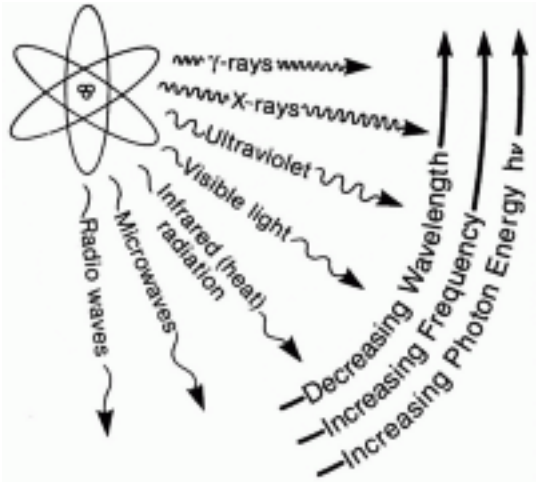
- The medical use of ionizing radiation to treat malignant disease.

Radiobiology & Radiotherapy

- IR local release of large amount of energy
- ~ 33eV dissipated / ionizing event, enough to break strong chemical bond
- energy associated C=C bond is 4.9 eV
- Types:
  - Electromagnetic
  - particulate

Electromagnetic Radiations

- X-rays and γ-rays
  - extranuclear and intranuclear production
- X-rays
  - electrical & magnetic energy
    - λν=c
  - Streams of photons/”packets” energy
    - hμ
    - λA=12.4/E(keV)



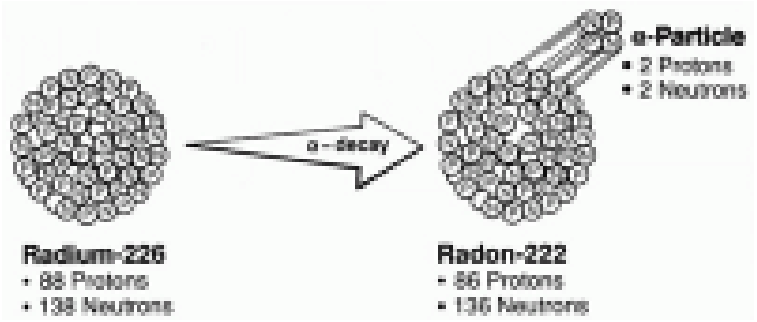
Radiobiology

- Concept of X-rays composed as photons is central in radiobiology
- Energy is deposited in tissues & cells unevenly in discrete packets culminates in biologic change

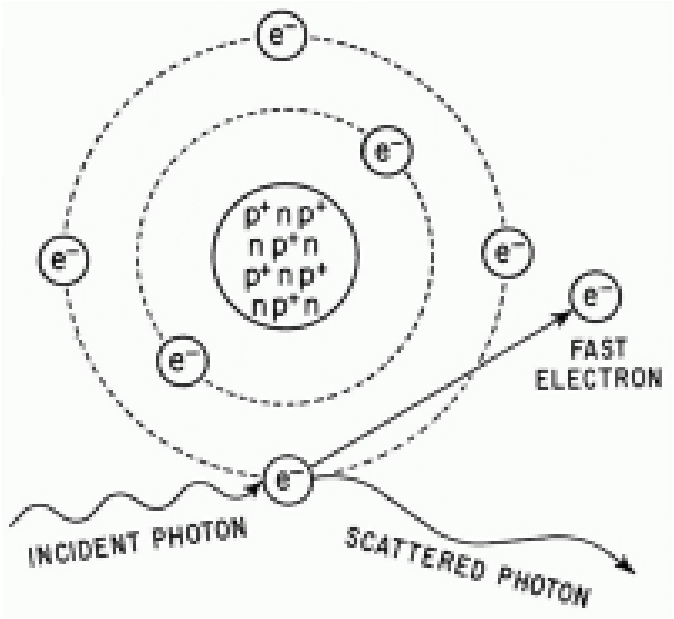
Particulate Radiations

- Electrons, protons, α-particles, neutrons, -π mesons, heavy charged ions
  - small - charged particles accelerated to high energy (betatron or linear accelerator)
  - + charged particles, relatively massive, accelerated to high energy (cyclotron)
  - mass like protons, no electrical charge
  - C, Ne, Fe + charged

- α-particles (+charged, decay) lung cancer in smokers (10-20,000 cases/year)

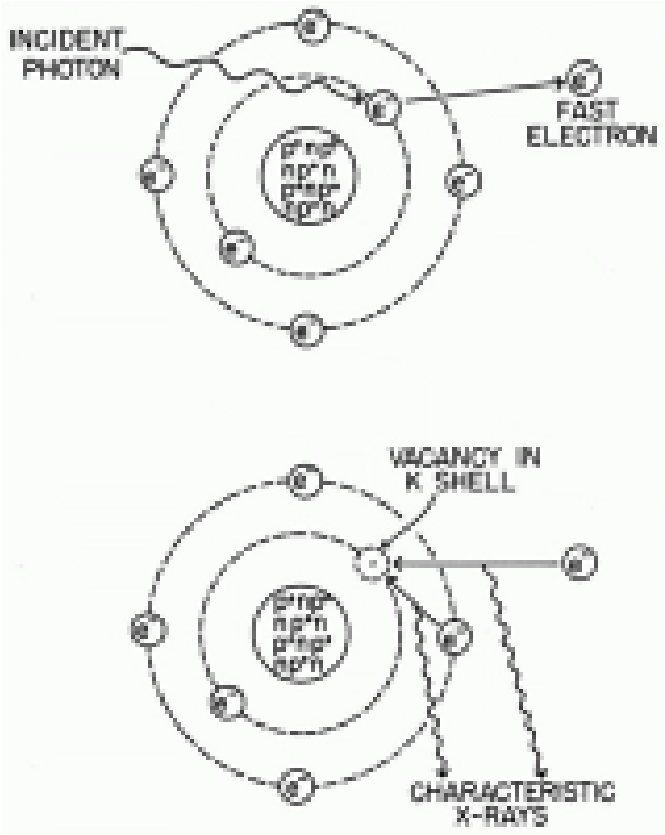


Absorptions of X-rays



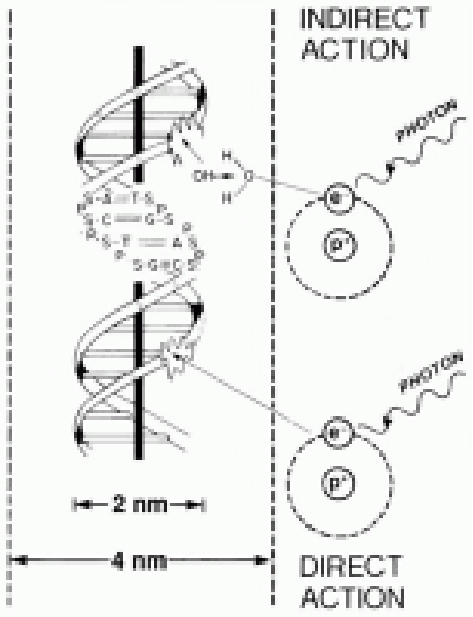
- Absorption of an x-ray photon by the Compton process (Co & linac).
- The photon interacts with a loosely bound planetary electron of an atom of the absorbing
- material. Part of the photon energy is given to the electron as kinetic energy. The photon, deflected from its original direction, proceeds with reduced energy.

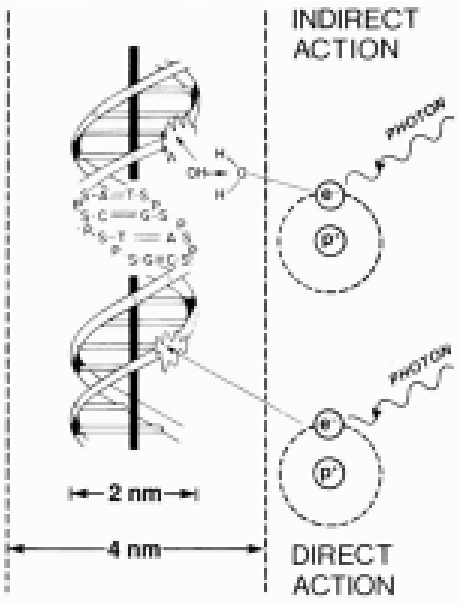
Absorptions of X-rays



- Absorption of a photon of x- or γ-rays by the Photoelectric process. The interaction involves the photon and a tightly bound orbital electron of an atom of the absorber. The photon gives up its energy entirely; the electron is ejected with a kinetic energy equal to the energy of the incident photon less the binding energy that previously held the electron in orbit **(top). The vacancy is filled either by an electron from an outer**
- orbit or by a free electron from outside the atom **(bottom). If**
- an electron changes energy levels, the difference in energy is
- emitted as a photon of characteristic x-rays. For soft tissue
- these x-rays are of very low energy.

Action of Radiation



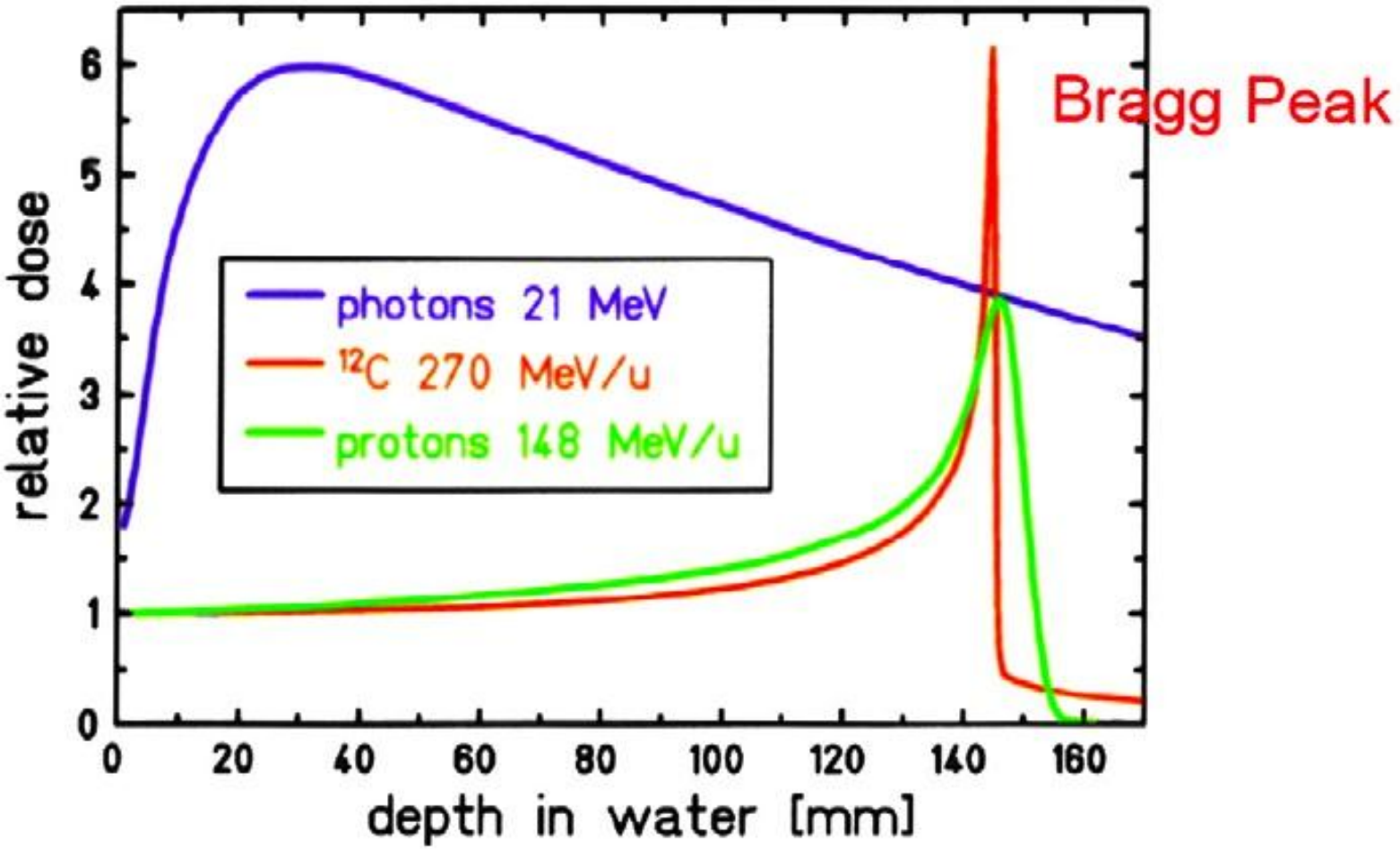


- Direct and indirect actions of radiation. The structure of DNA is shown schematically. In direct action, a secondary electron resulting from absorption of an x-ray photon interacts with the DNA to produce an effect. In indirect action, the secondary electron interacts with, for example, a water molecule to produce a hydroxyl radical (OH·), which in turn produces the damage to the DNA. The DNA helix has a diameter of about 20 Å (2 nm). It is estimated that free radicals produced in a cylinder with a diameter double that of the DNA helix can affect the DNA. Indirect action is dominant for sparsely ionizing radiation, such as x-rays. *S, sugar; P, phosphorus; A, adenine; T, thymine; G, guanine; C, cytosine.*

Interactions of Charged Particles

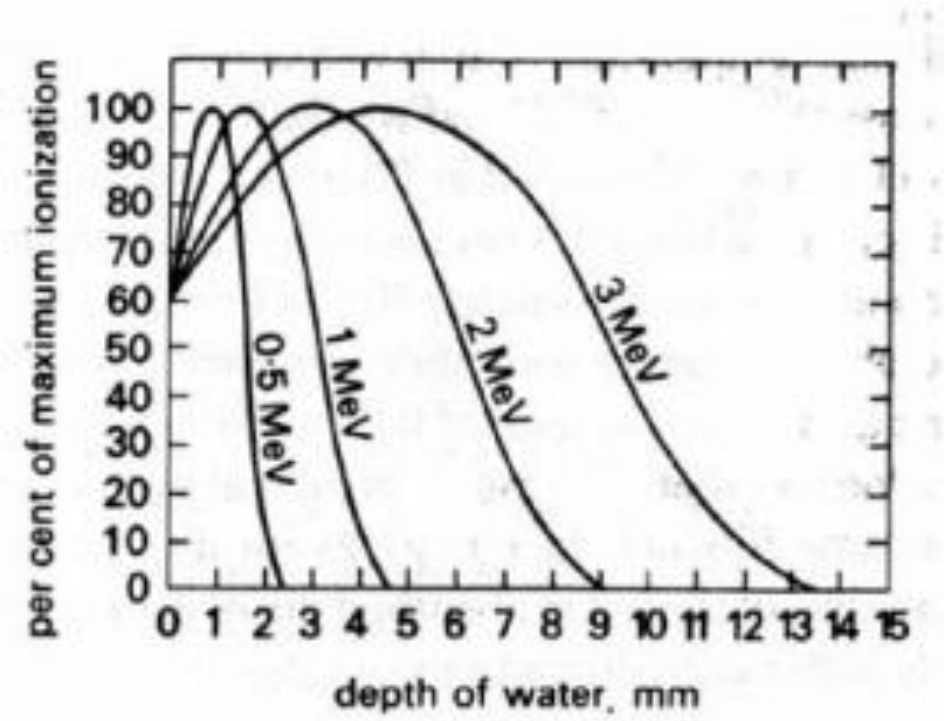
- Ionization and excitation
- Mediated by Coulomb force (electric fields of particle & material)
- Heavy charged particles give rises to nuclear reactions (positrons emitters)
  - Rate of energy loss proportional to square of charged particle and inversely to square of its velocity “Bragg peak”

Percent Depth Dose



Interactions of Charged Particles

- Electrons small masses thus multiple scattering and changes in direction of motion resulting in a “smearing out” of the Bragg peak effect



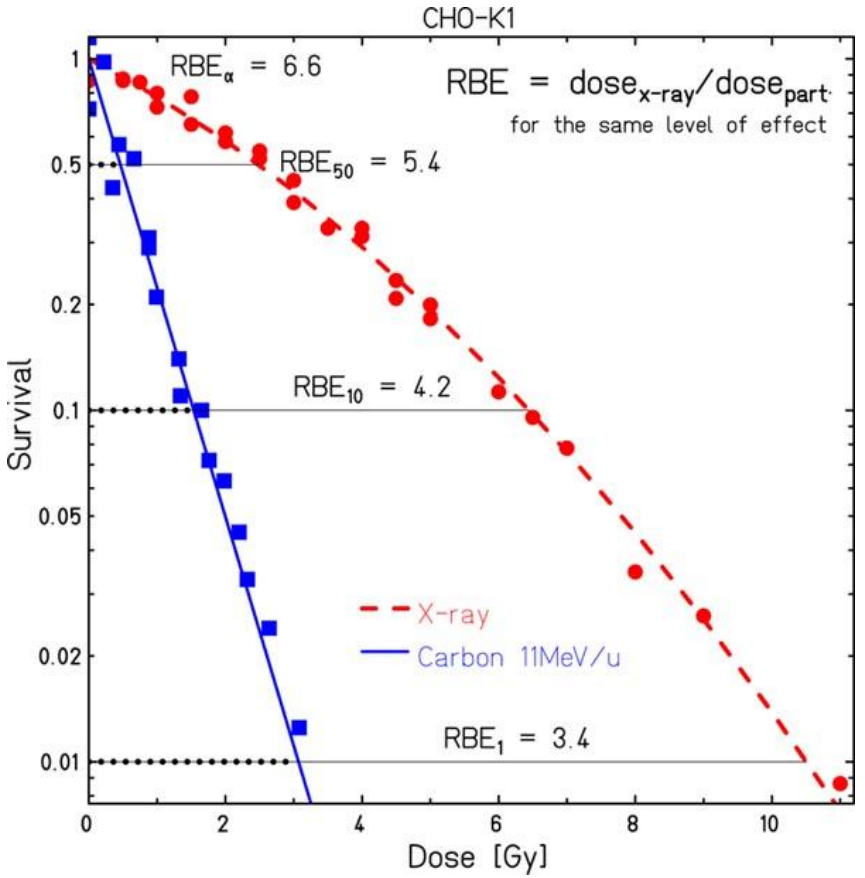
Interactions of Charged Particles

- Neutrons are indirectly ionizing interacting by 2 processes:
  - Recoiling protons: dose deposited in tissue is predominantly from recoil protons, dose absorbed by in fat is 20% > muscle due to differential H content
  - Nuclear disintegrations (charged particles & -rays) give rise to ~ 30% of the tissue dose

Relative Biological Effectiveness

RBE = Dose from reference radiation / Dose from test radiation, DT

Type and Energy Range	Radiation Weighting Factors
X and Gamma rays	1
Electrons	1
Neutrons (energy dependent)	5-20
Protons	5
Alpha Particles	20



Dose Response Curves

Tumor Radiobiology

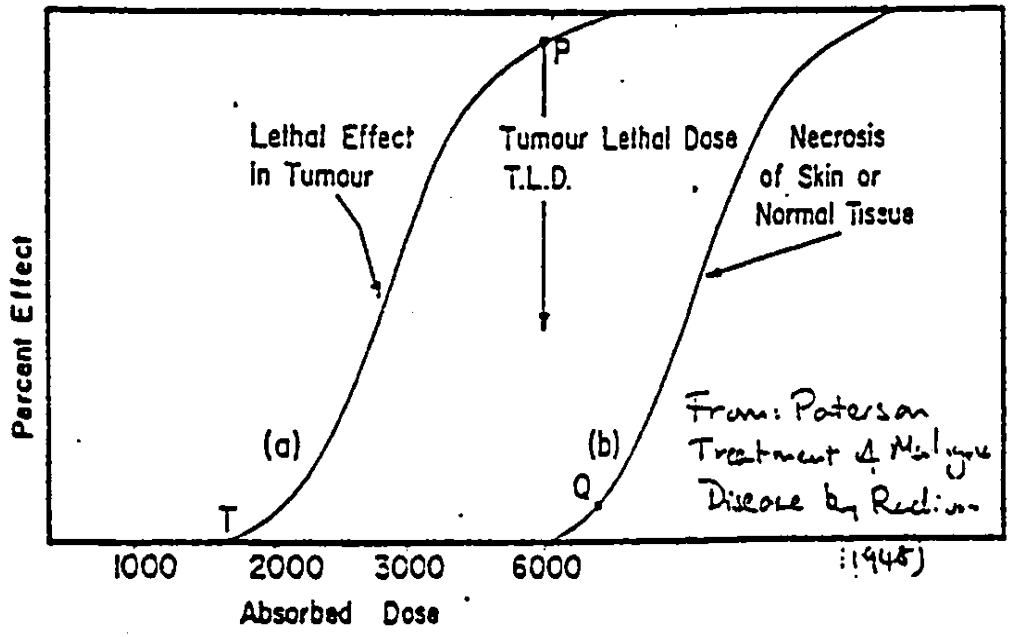


Figure 10.1: Therapeutic ratio.

Cell survival curves

Cell Radiation Biology

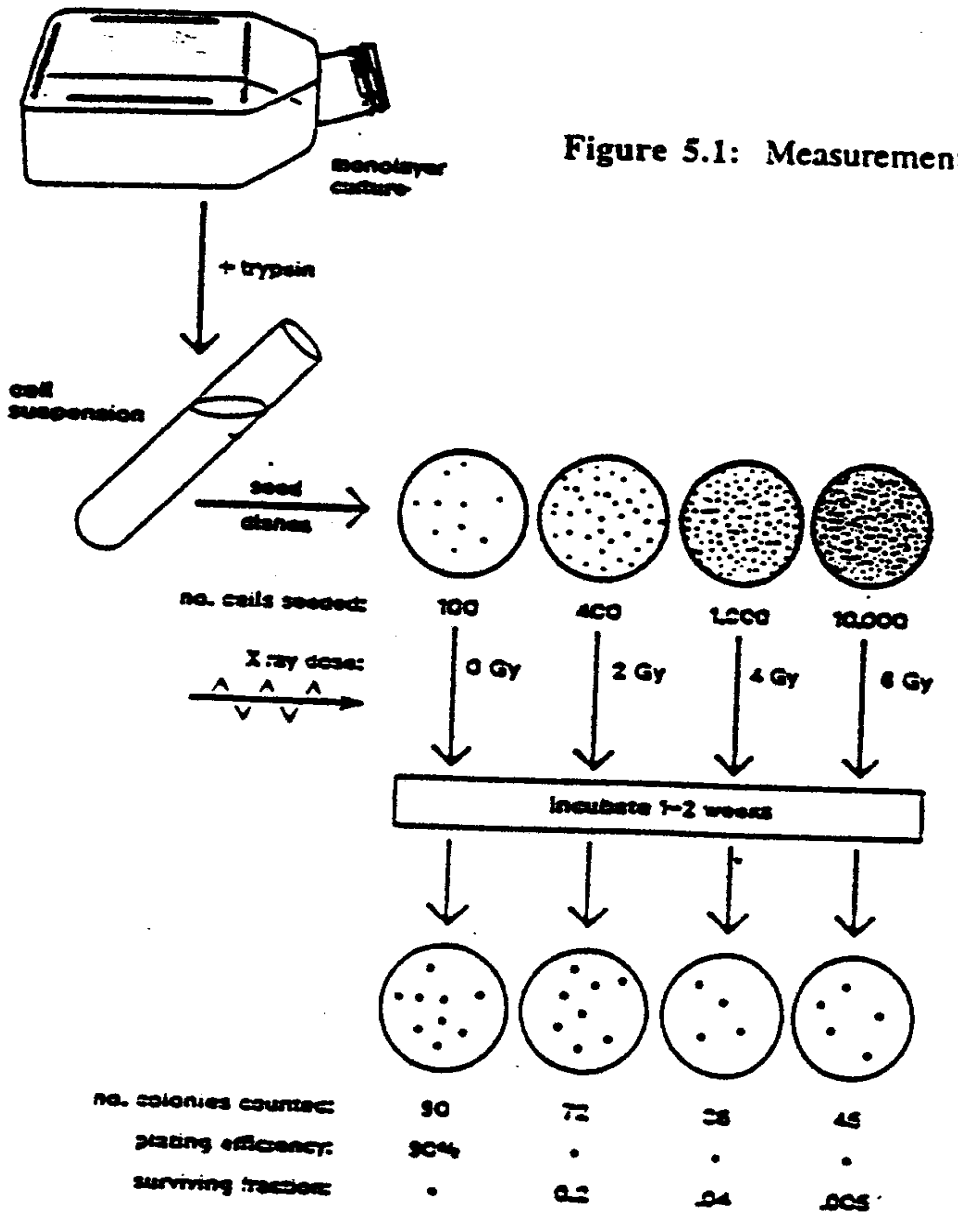
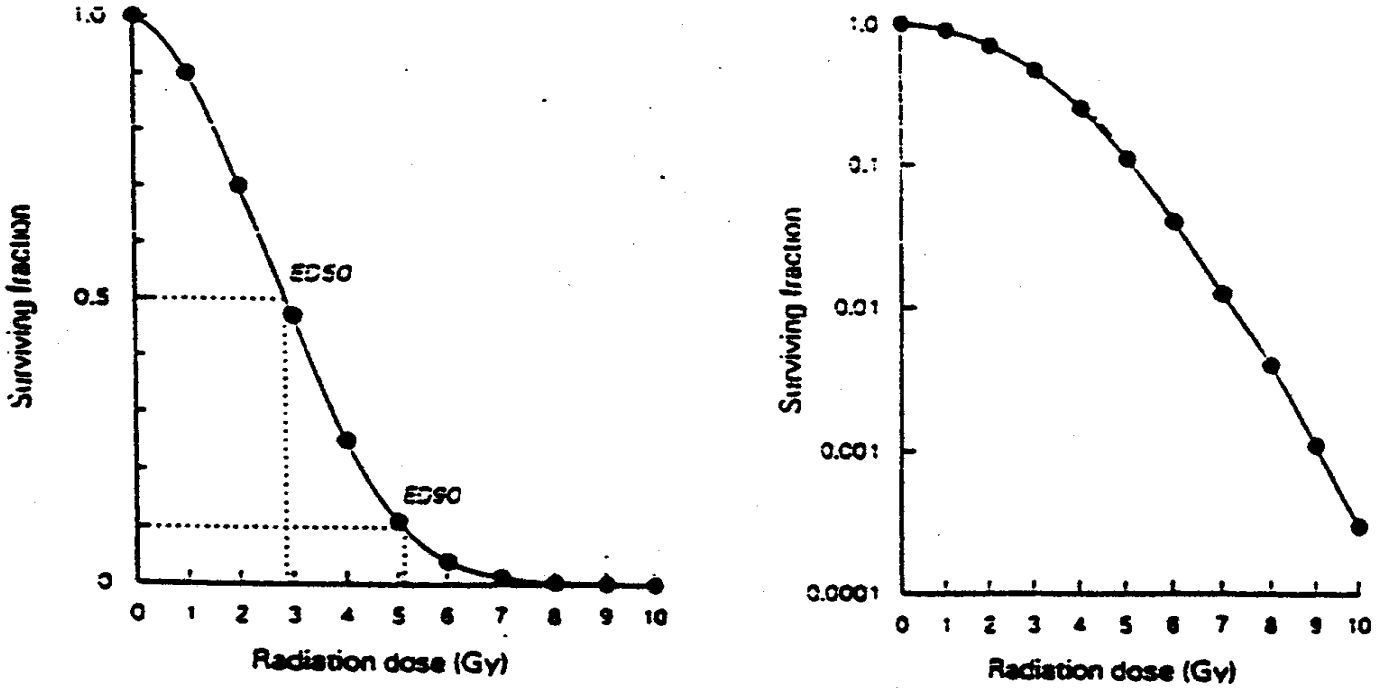


Figure 5.1: Measurement of cell survival.

Cell Survival Curves

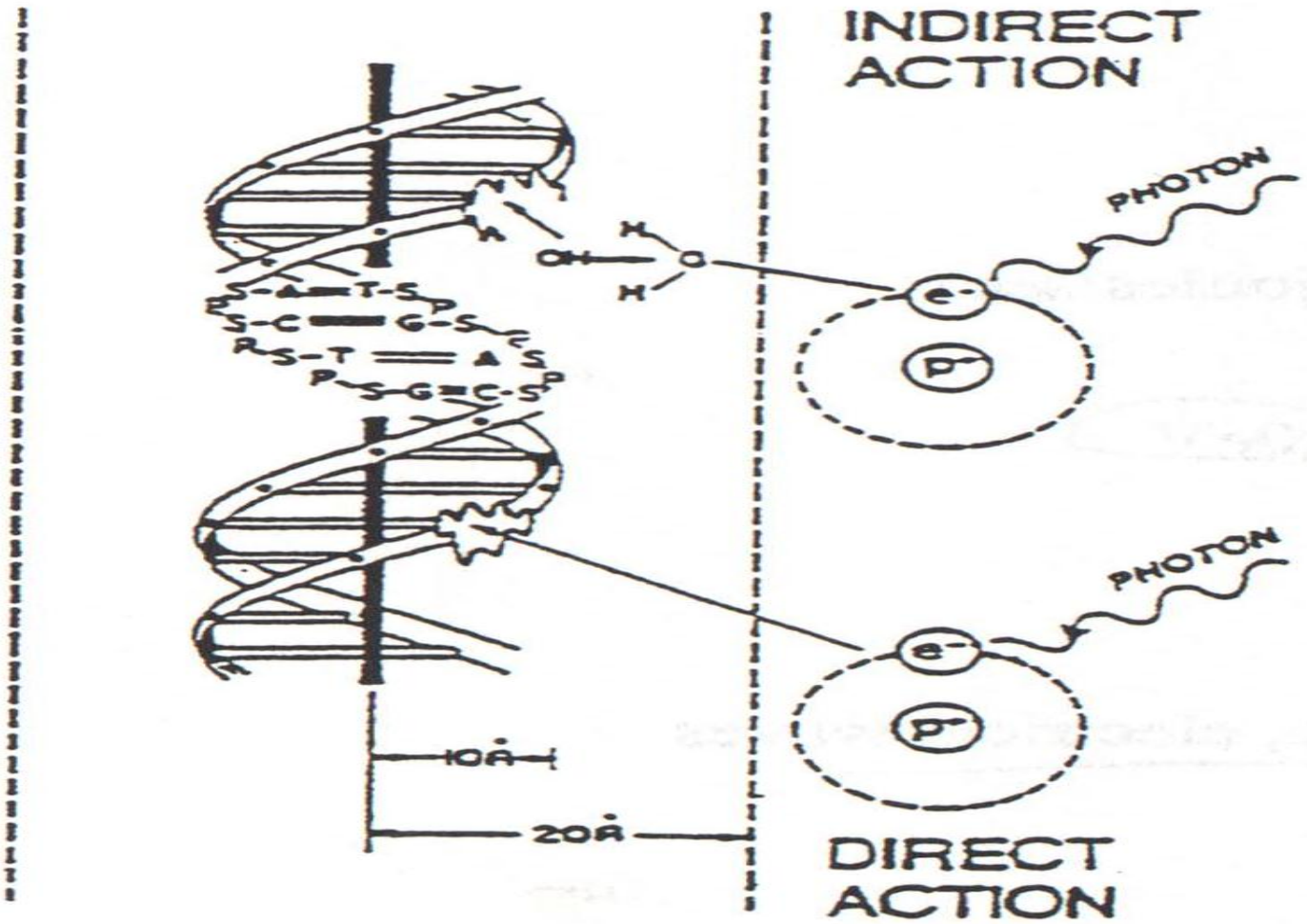


(a): linear scale

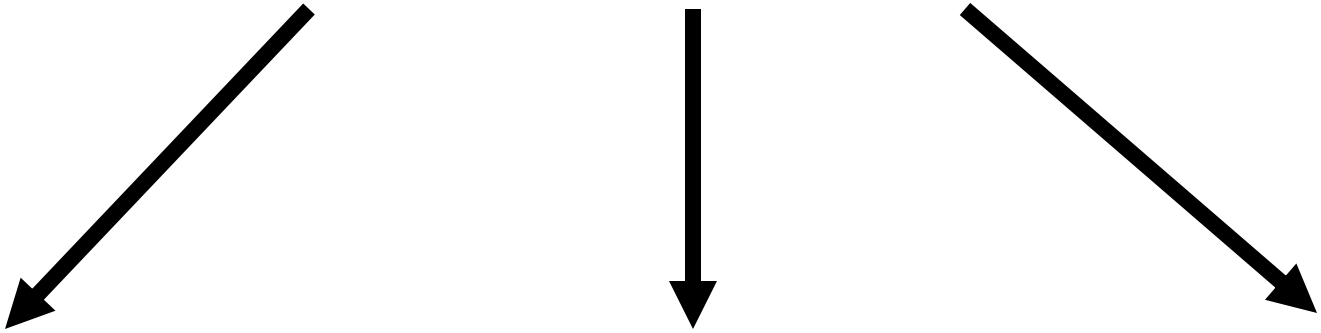
(b): same data on a logarithmic scale

Figure 5.2: Typical cell survival curve for mammalian cells irradiated in tissue culture.

Mechanism of cytotoxicity



Chromosomal Damage



Apoptosis

Reproductive death

Necrosis

Effect of Oxygen

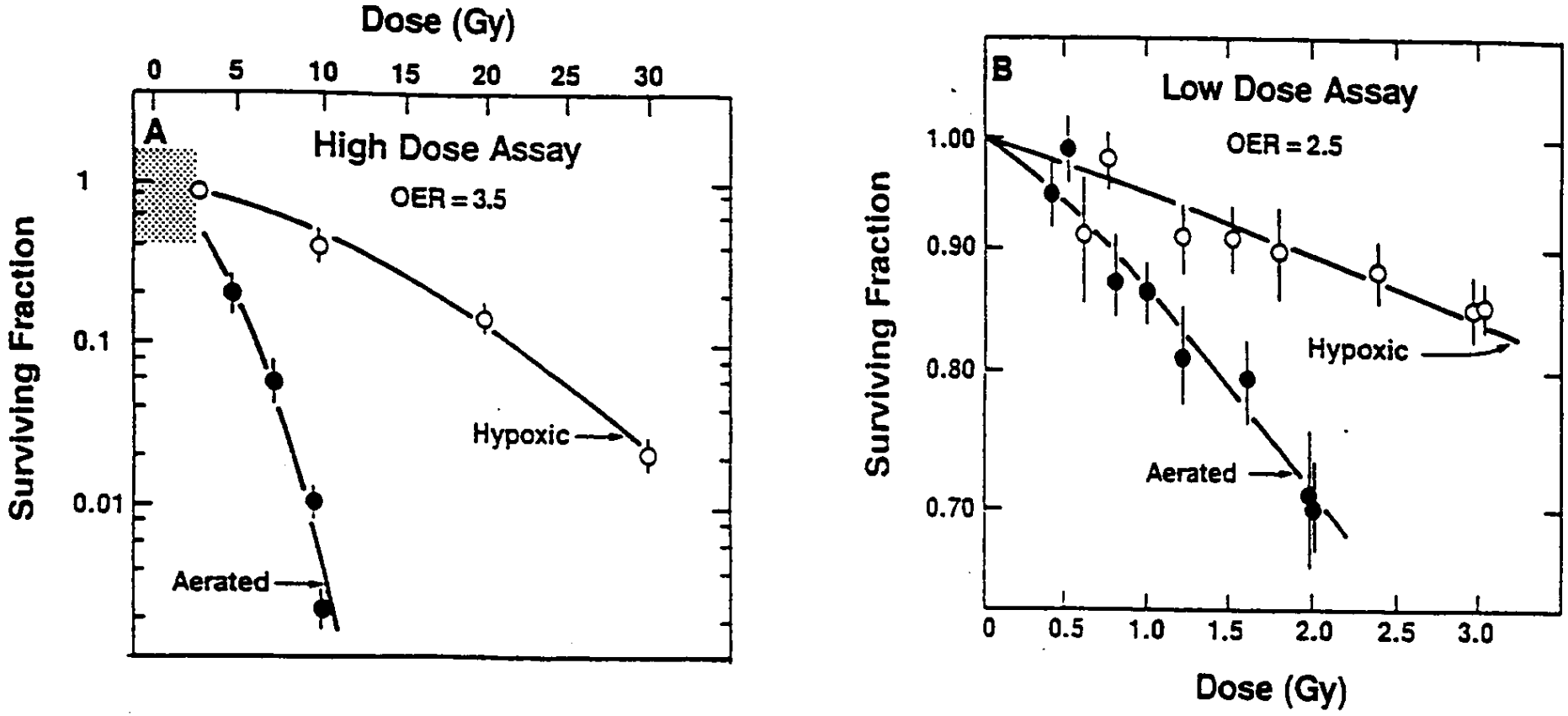
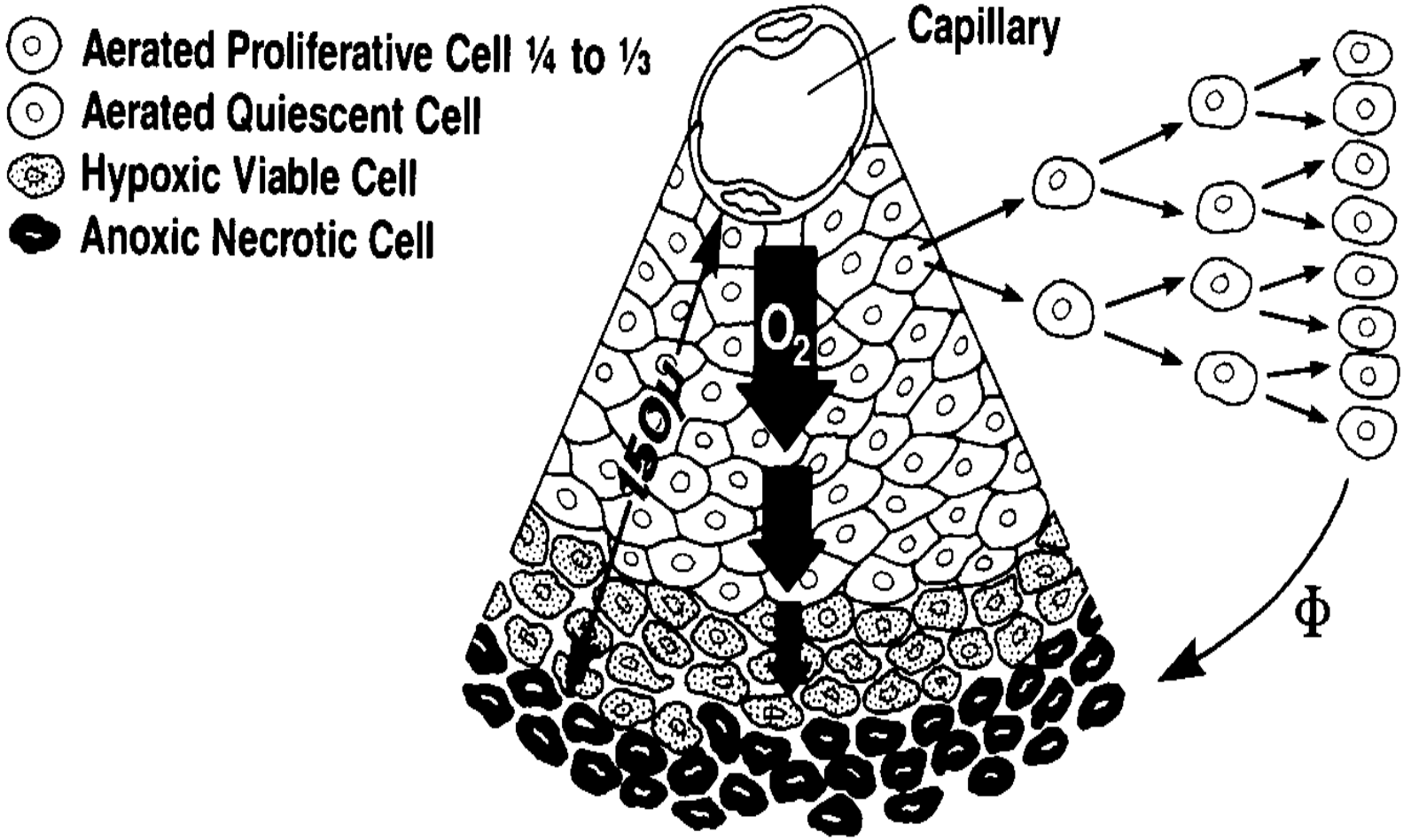
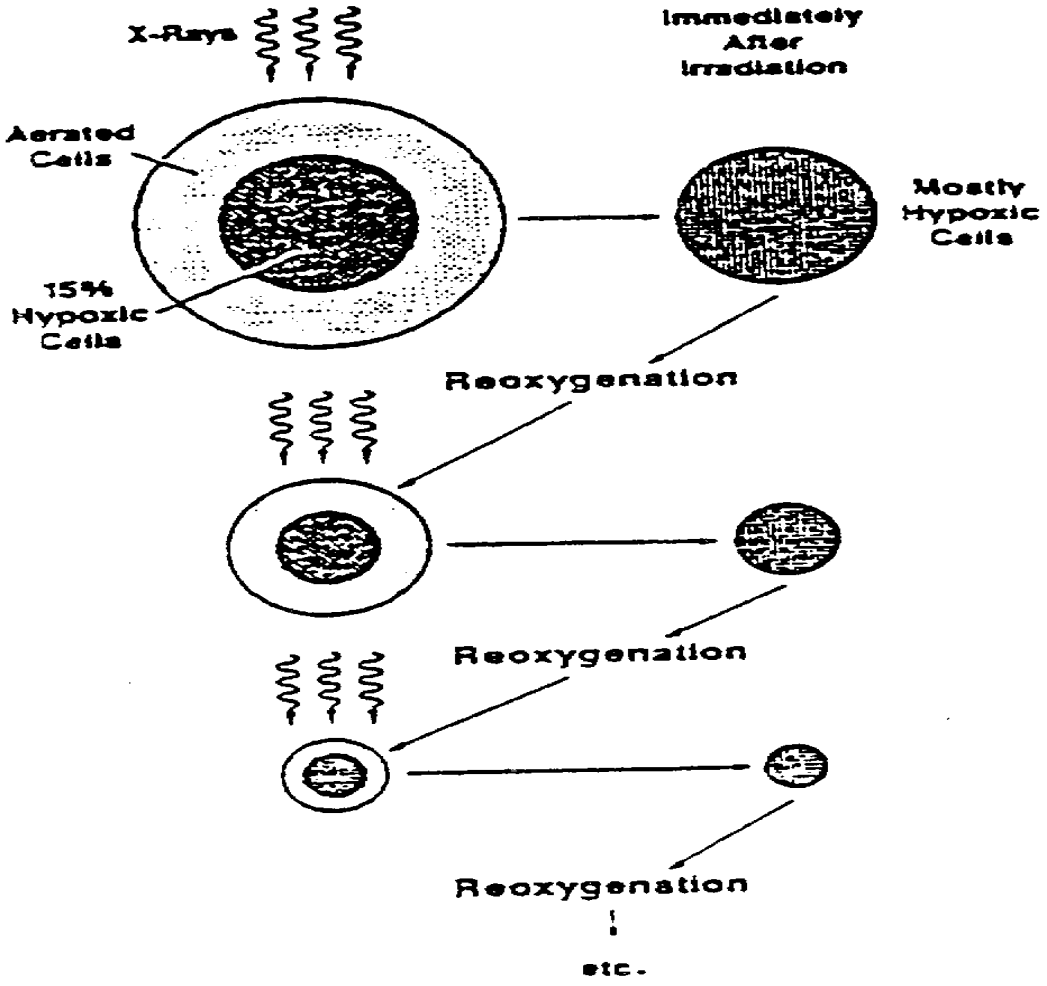


Figure 5.25: For sparsely ionizing radiation (x- and γ- rays) the OER is 2.5-3.0 at higher doses at which oxygen is dose modifying. At lower doses < 2.0 Gy, it may have a value of about 2.0.

Tumor Oxygenation



Re-oxygenation



Effect of Cell Cycle

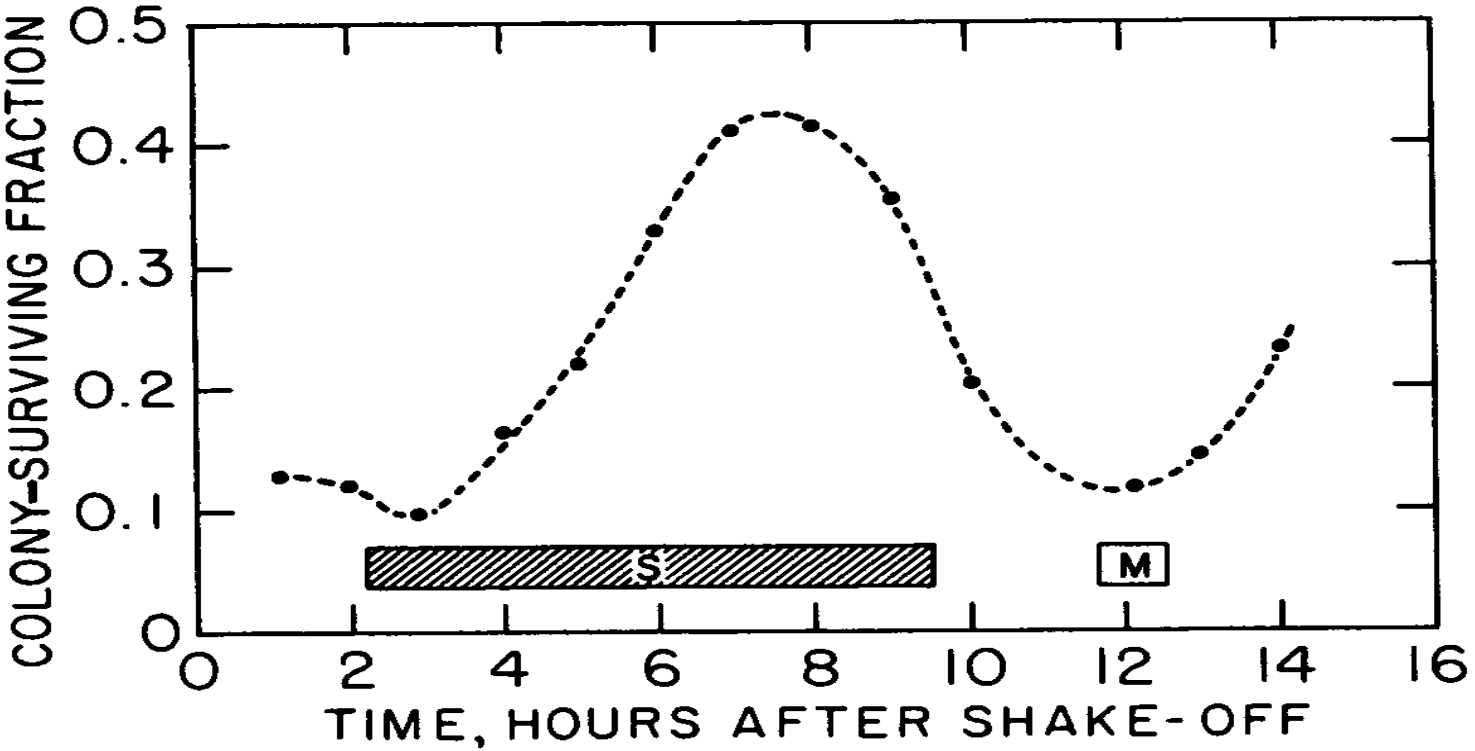


Figure 5–6. Fraction of Chinese hamster cells surviving a dose of 660 rads (6.6 Gy) of x-rays as a function of time. Time zero corresponds to the harvesting of mitotic cells. The cell-surviving fraction increases to a maximum late in *S*. (Redrawn from Sinclair WK, Morton RA: Radiat Res 29:450–474, 1966)

Why Daily treatments?
Four R's of radiotherapy:

- Repair of sub-lethal damage
- Re-oxygenation
- Repopulation
- Redistribution

Effect of fractionation on tissue damage

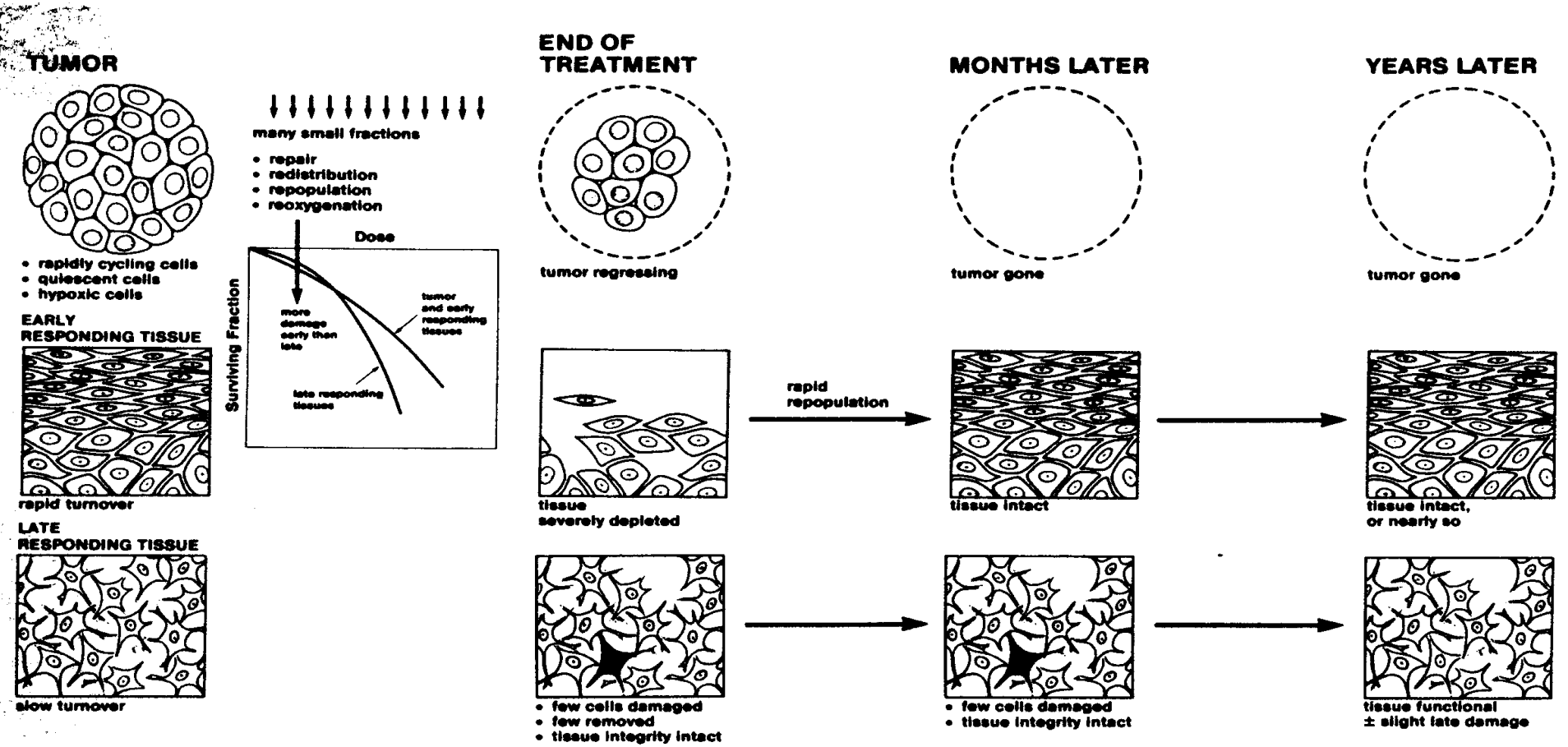
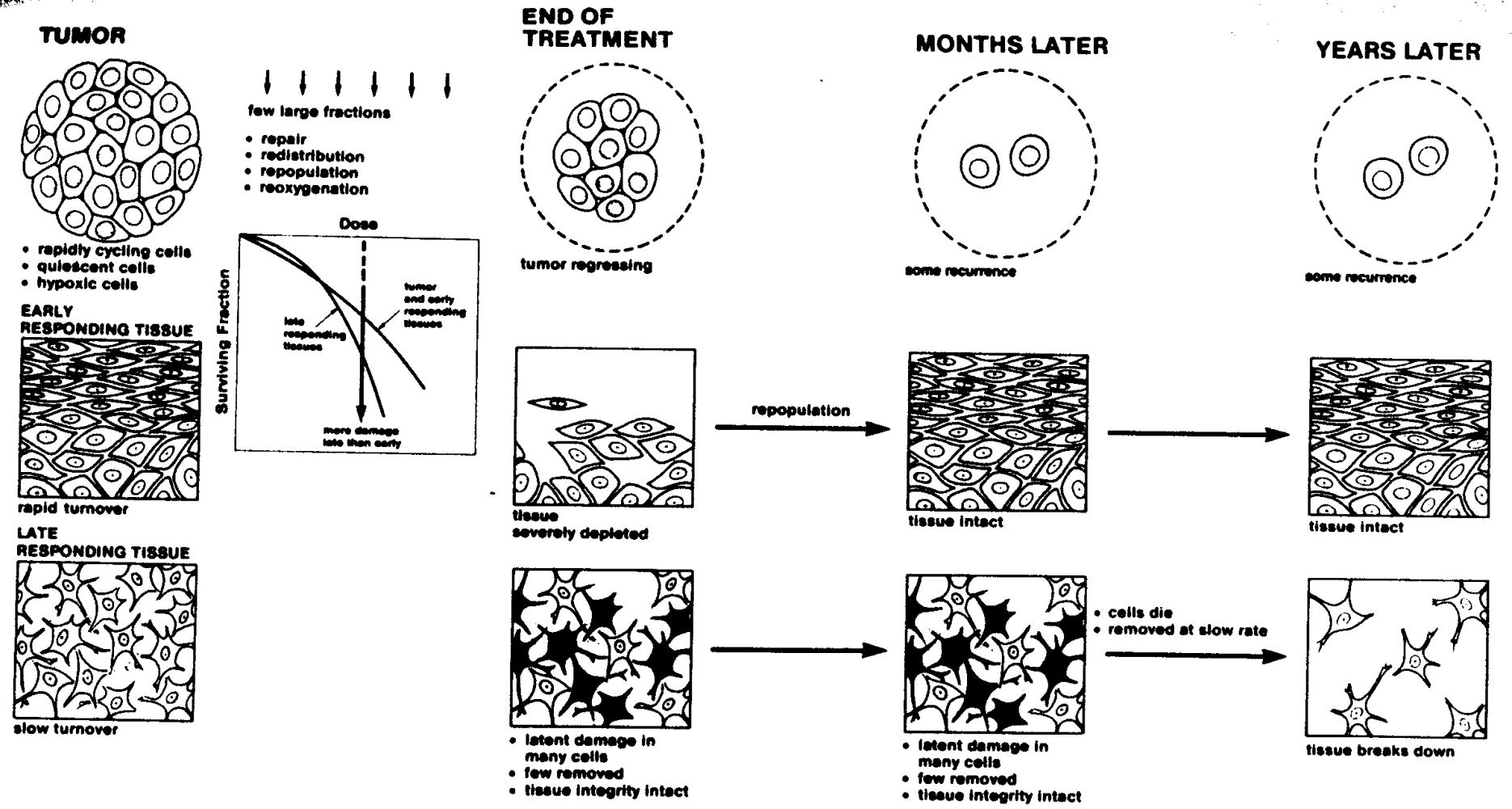


Figure 12–9. The kinetic pattern following irradiation with many small dose fractions. A small dose fraction produces relatively less damage to late-responding than to early-responding tissues because of their curvy dose-response relationship. The tumor regresses and disappears. The early-responding tissues show a reaction but repopulate by rapid cell division. The late responding tissues show little damage.

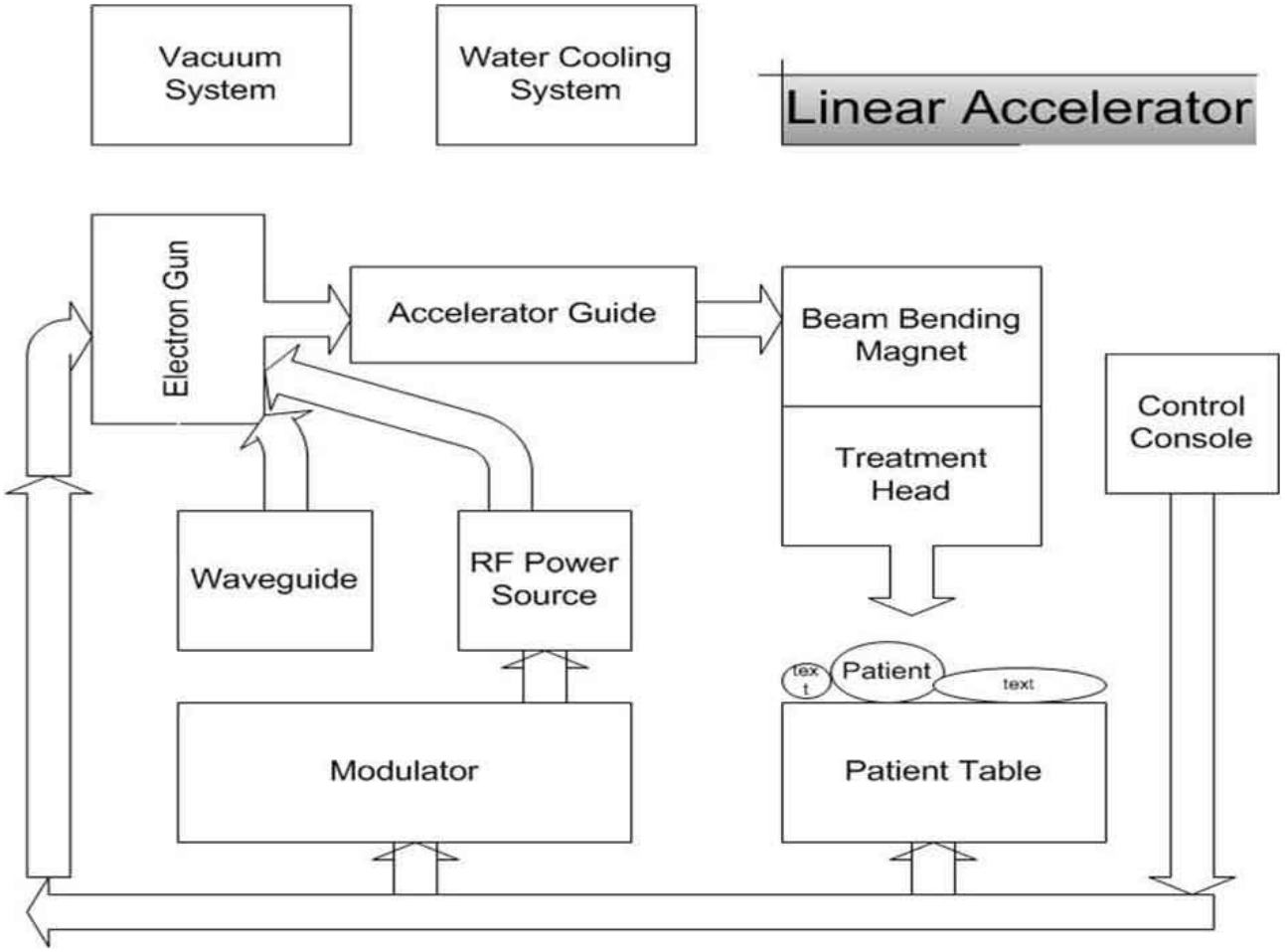
Effect of fractionation on tissue damage

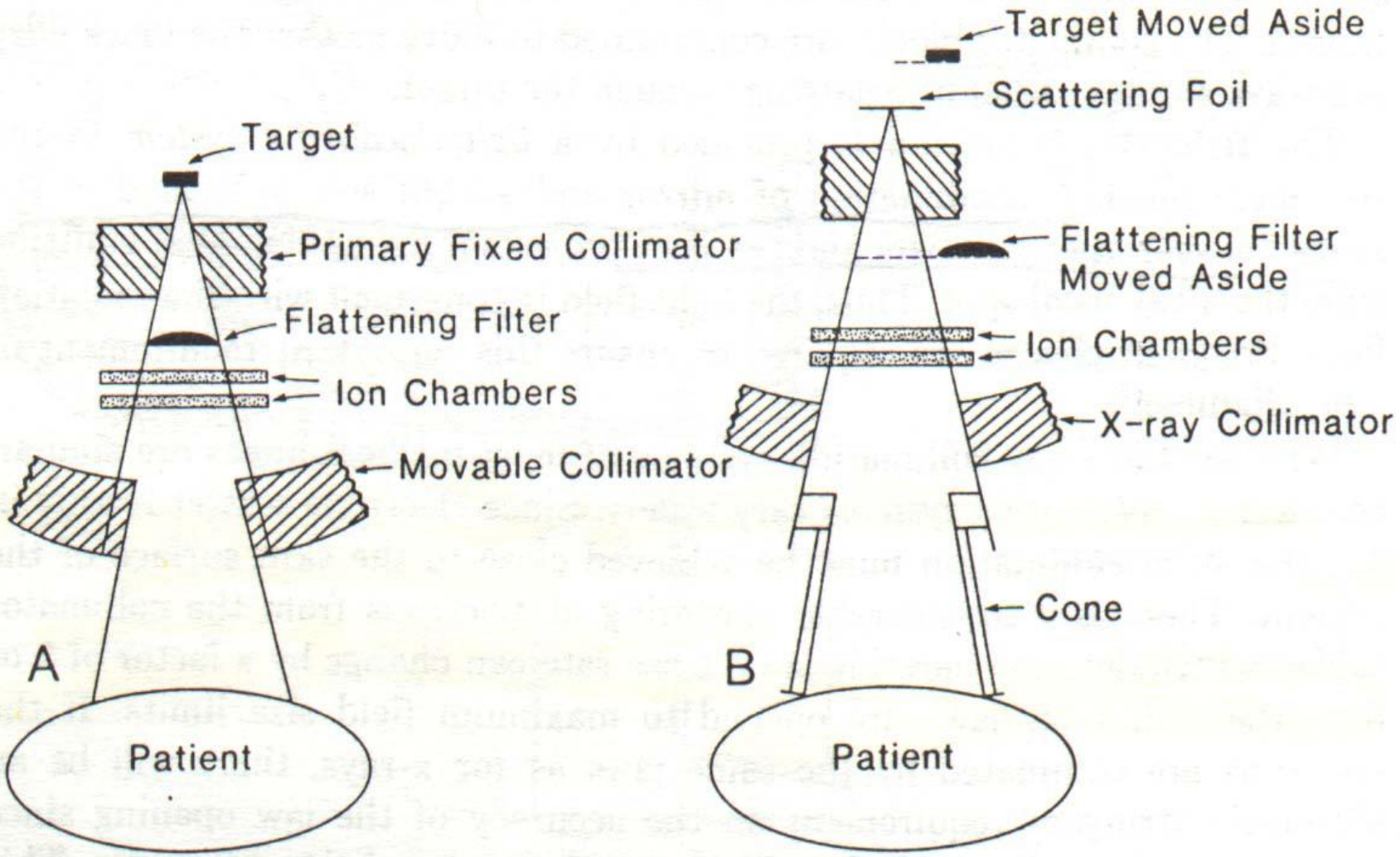


Radiotherapy delivery :

- External beam radiotherapy:
  - Photons:
    - X-rays: Linear accelerators.
    - γ-rays: Cobalt machines.
  - Particles:
    - Electrons.
    - Neutrons.
    - Protons.
- Brachytherapy:
  - Interstitial.
  - Intracavitary.

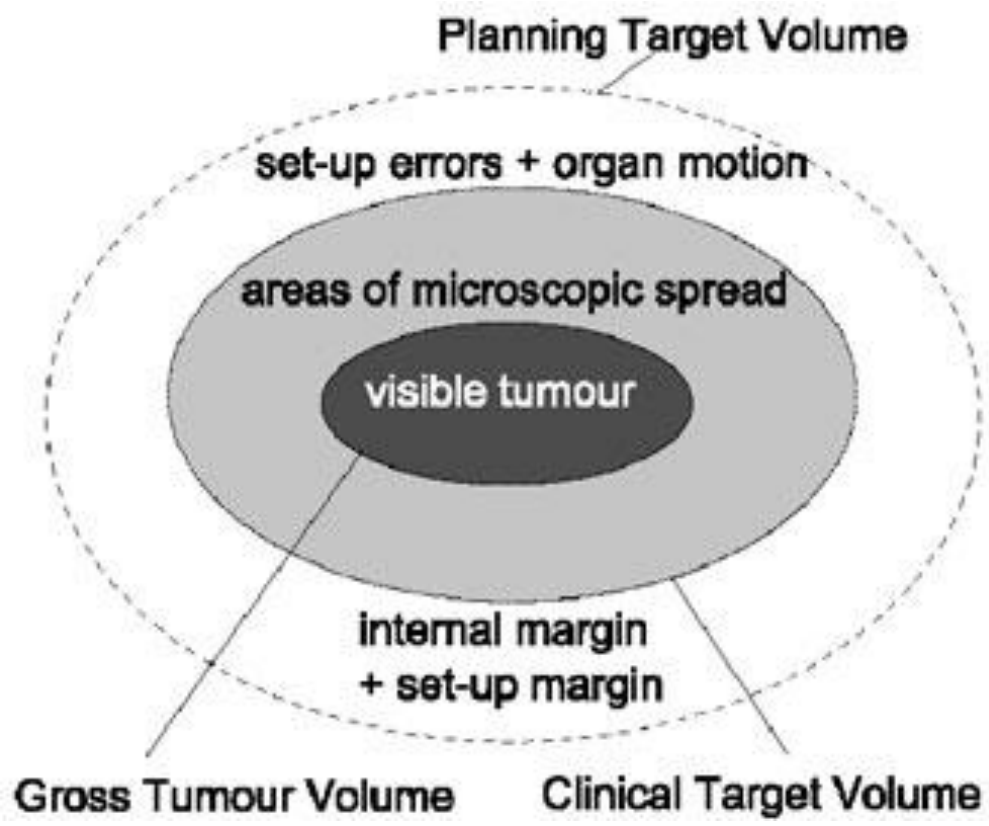
Linear Accelerator




Target
Primary Fixed Collimator
Flattening Filter
Ion Chambers
Movable Collimator
A
Patient
Target Moved Aside
Scattering Foil
Flattening Filter
Moved Aside
Ion Chambers
X-ray Collimator
Cone
B
Patient

LINAC

XRT Treatment Volumes



Treatment Sequence

Patient referral to oncology		
Investigations	History, physical examination, imaging, biopsy, pathology	
Cancer staging	T = tumor size N = lymph node extension M = metastasis	
Multidisciplinary Tumor Board	Surgeon, radiation oncologist, medical oncologist, pathologist & radiologist	Treatment recommendations / clinical trials
Radiotherapy	CT simulation: immobilisation, isocenter, marking CT planning: image fusion (US/MRI/PET) Target volumes delineation Treatment planning/dosimetry	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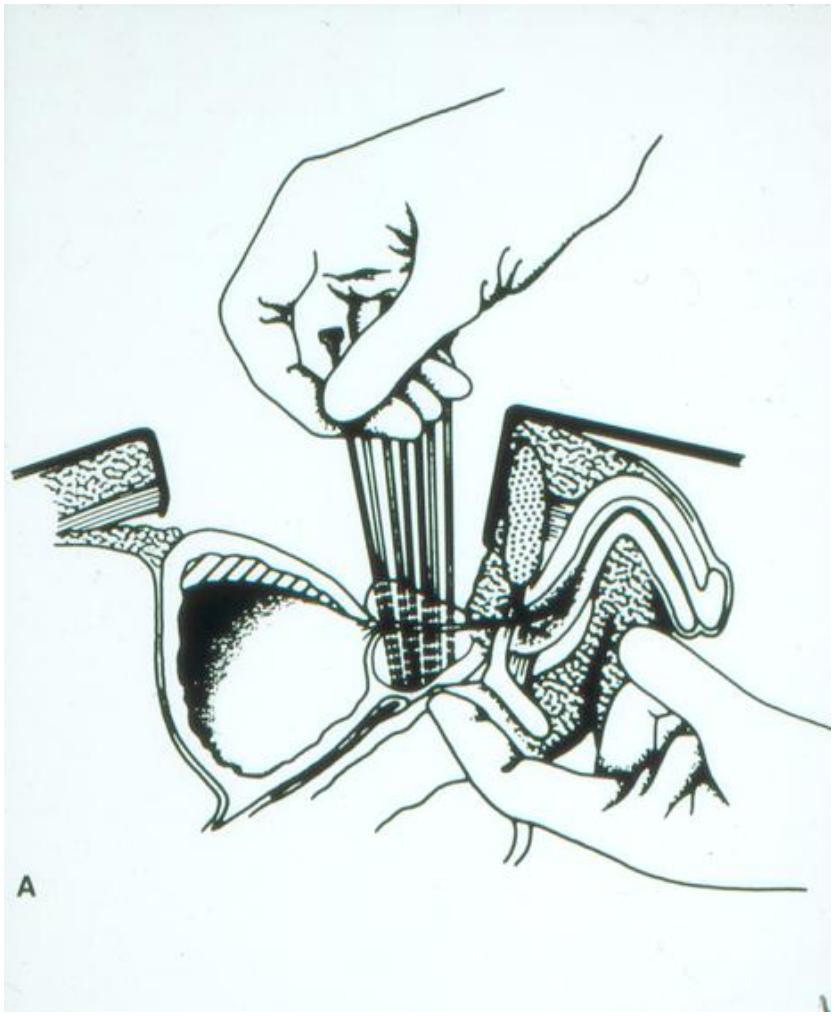
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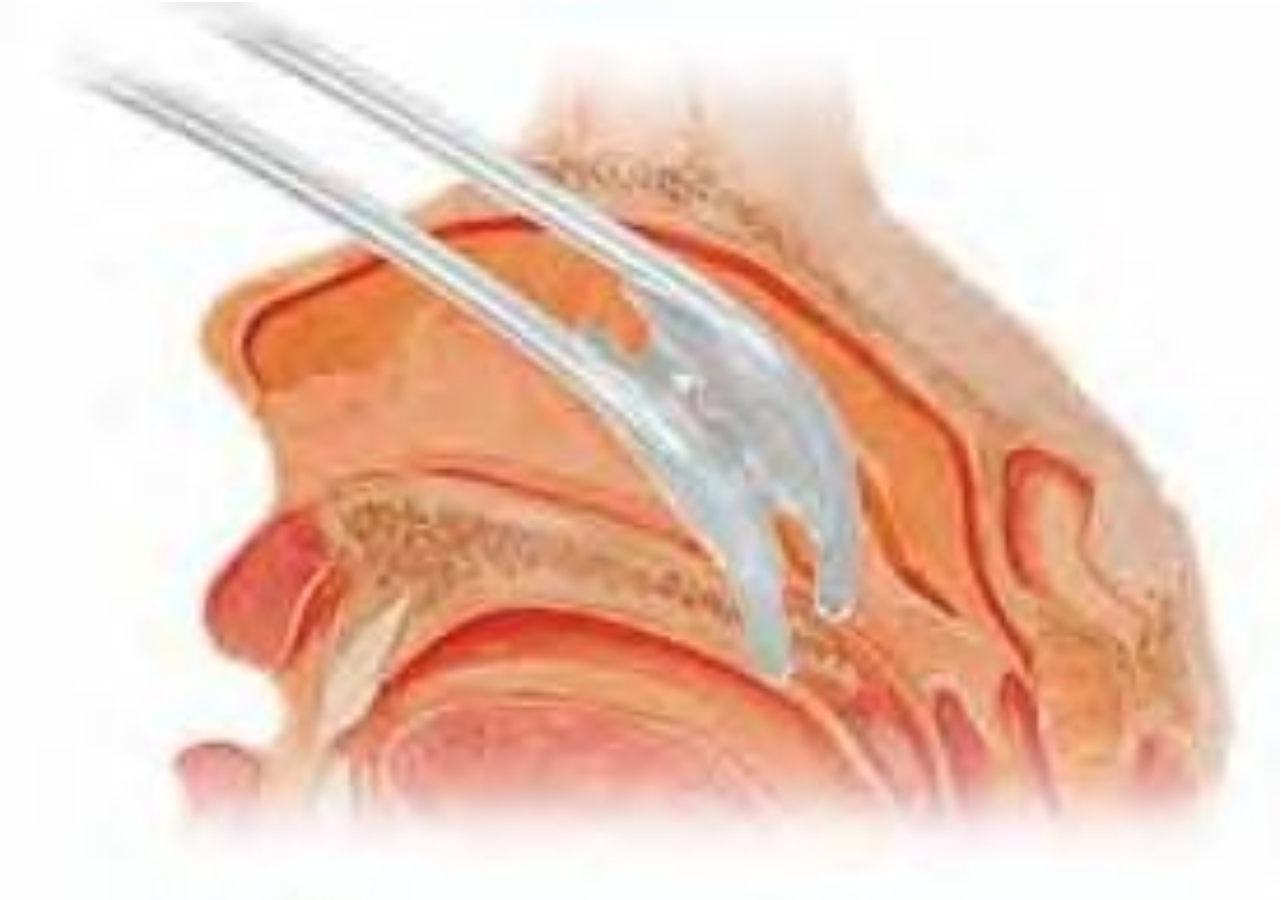
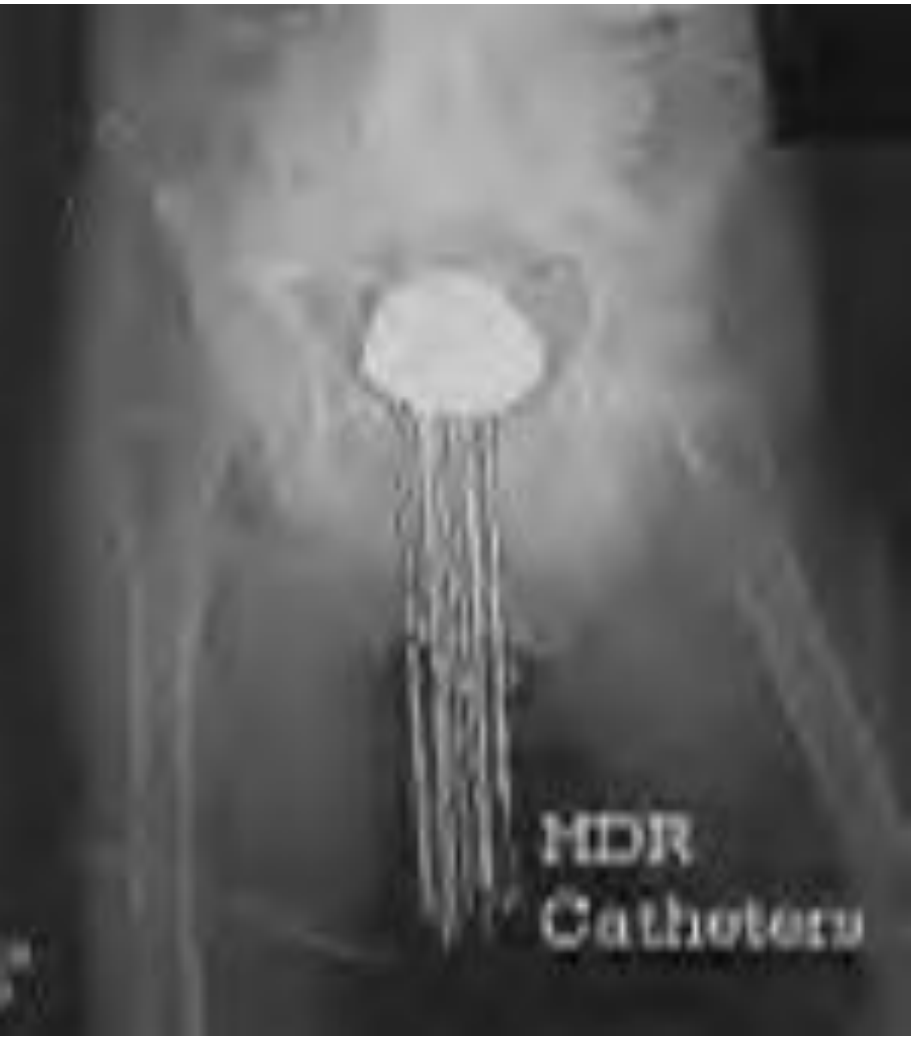
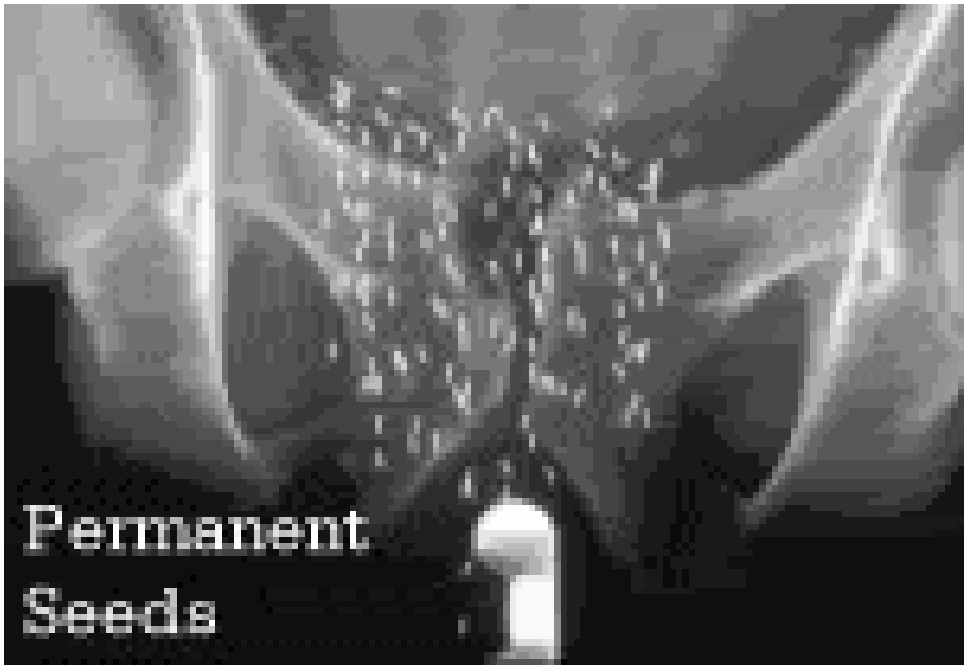



HDR
Catheter


Permanent
Seeds

Role of Radiotherapy:

- Cancer treatment:
  - Curative Primary:
    - Prostate cancer.
    - Cancer of the head and neck region (early stage)
    - Hodgkin's disease.
    - Cervix cancer.
  - Curative as part of a combined approach:
    - Lung cancer.
    - Non-Hodgkin Lymphoma.
    - Cancer of the Head and Neck Region (advanced stage)
    - GI malignancies

Role of Radiotherapy:

- Cancer treatment:
  - Curative Adjuvant to surgery:
    - Breast cancer.
    - Sarcoma.
    - Cancer of the Head and Neck region.
    - Carcinoma of the rectum.
    - Tumors of the Central Nervous Systems

Role of Radiotherapy:

- Cancer treatment:
  - Palliative treatment:
    - Pain: Bone metastasis
    - Bleeding: Hemoptysis, Hematuria.
    - Obstructive or compressive symptoms:
      - Superior vena cava
      - Spinal cord compression
    - Brain metastasis.

Role of Radiotherapy:

- Treatment of begnin disease:
  - Prophylaxis of heterotopic bone formation.
  - Arterio-venous malformation.
  - Grave’s disease.
  - Keloids.
  - Pterygium.

Timing and clinical manifestation of radiation injury

- 1. Acute clinical period 0-6 months
- 2. Sub-acute period 6-12 months
- 3. Chronic clinical period 1-5 years
- 4. Late clinical period

Acute versus late injury

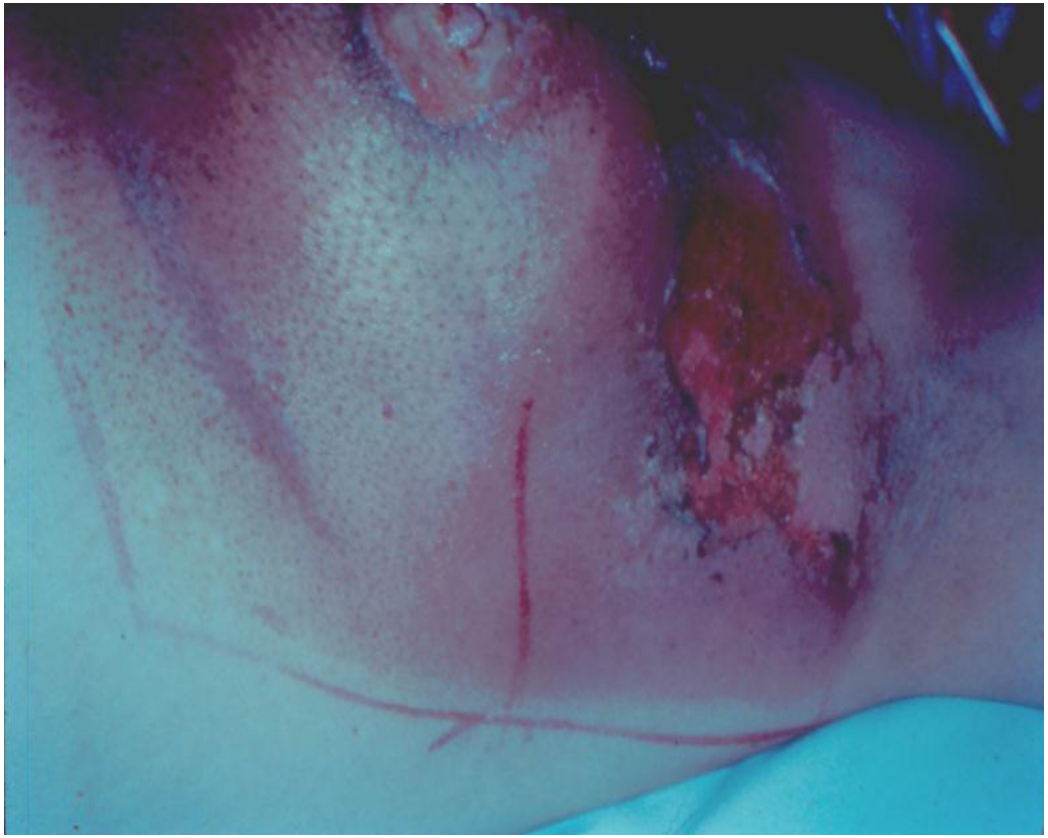
- Timing depends on cell cycle kinetics
- Clinical importance: reversible versus irreversible
- Correlation between acute and late complications

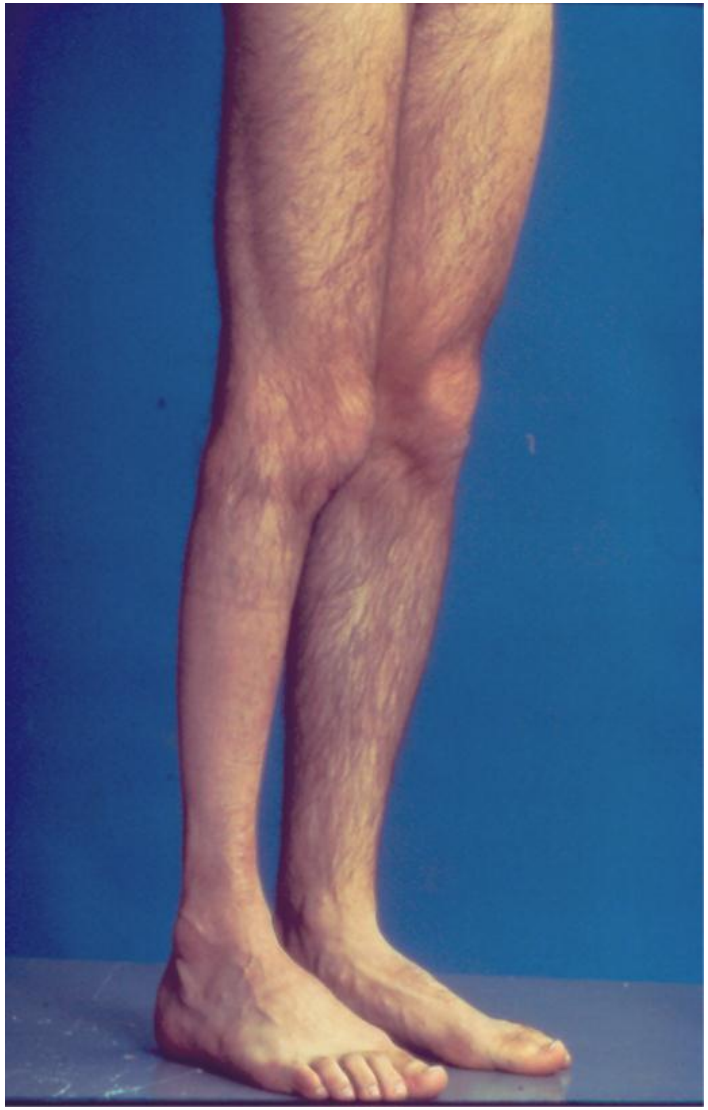
Factors affecting radiation damage

- 1. Volume to be irradiated
- 2. Total dose
- 3. Fraction size
- 4. Concomitant treatment

Total body irradiation

	Dose	Effects
Group I	0.5-1.5 Gy	Minimal
Group II	1.5- 4 Gy	Mild N/V
Group III	4- 6 Gy	Hemopoietic
Group IV	6- 14 Gy	GI
Group V	> 50 Gy	CNS





Radiation-Induced Malignancy

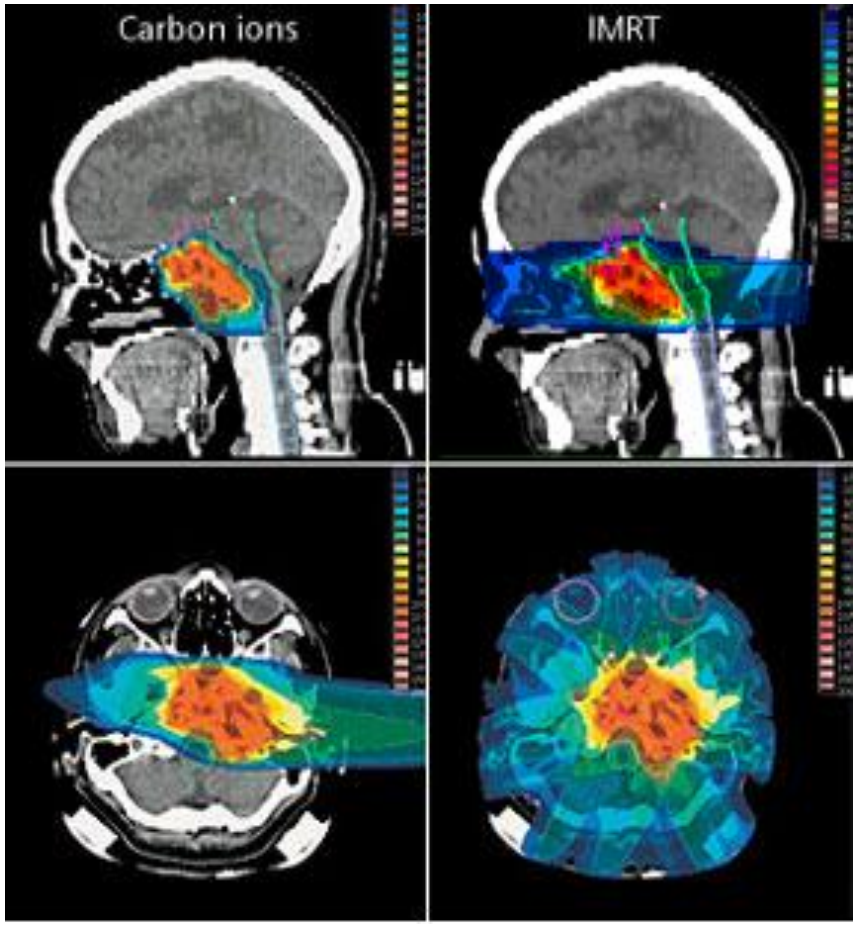
- 1. There is no threshold
- 2. Long latent period
- 3. Within the radiation ports
- 4. Different organ sensitivity
  - Thyroid, breast, lungs
  - Skeletal muscle

Image Guided RT

- IMRT
  - http://www.youtube.com/watch?v=eZS6DVGBx0k&feature=related
- Rapid Arc
  - http://www.youtube.com/watch?v=3s756awIl8o
- Cyber Knife
  - http://www.accuray.com/videos/lung_radiosurgery.aspx?video=Accuray_Lung
- Proton Therapy
  - http://www.youtube.com/watch?v=W0q5pmeRhu4&feature=related
- RESEARCH COOPERATION HYDRON THERAPY: ENLIGHT
  - http://enlight.web.cern.ch/enlight/cms/?file=home

Charged Particles Therapy

- Advantages
  - Superior dose distribution vs. photons
- Hypothesis
  - Improvement in treatment-related toxicity
  - Would allow for dose-escalation studies
  - Should improve local control
  - May improve overall survival



MAGICAL PROTONS?

MICHAEL GOITEIN, PH.D.

Harvard Medical School, Boston, MA; and Windisch, Switzerland

Proton therapy has enjoyed a recent surge of interest. Dozens of new proton centers are being planned, in addition to the approximately 24 now in operation worldwide (1). This enthusiasm is based, in part, on a conviction that the physical advantages of protons have been, in at least some sites, reflected in clinical advantages. The interest in protons has also been fueled by the perception that, although (or, perhaps, because) proton facilities are expensive, proton therapy can be highly profitable.

I find it hard not to be pleased about this growth. However, it carries dangers. Protons are not magical; the mere exposure to protons does not, in itself, doom proliferating malignant cells to their graves. Protons must be used well and, in this connection, I want to sound a few notes of caution.

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JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Should Randomized Clinical Trials Be Required for Proton Radiotherapy? An Alternative View

Eli Glatstein, *Department of Radiation Oncology, University of Pennsylvania School of Medicine, Philadelphia, PA*
John Glick, *Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA*
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The facts offered by Goitein and Cox are incontrovertible in that the dose distribution of proton therapy is superior that of to x-rays. The question really has to do with whether or not these facts translate into *measurable benefits* for patients, and how significant those gains may be. The editorial in question alluded to a prior article in *JCO* by

Goitein and Cox believe that the superiority of protons rests largely on an improvement of the dose distribution that will almost certainly make for less morbidity. Exploiting that improvement in treatment-related toxicity suggests that dose escalation is feasible and that an improvement of local control should follow. Though local

Nonetheless, there is a potential for clinical benefit to be derived from proton therapy compared with conventional x-rays, either from dose escalation and improved local control and/or survival, or from reduced treatment-related morbidity, especially in children. Another important consideration is the potential for increased secondary cancers from proton therapy that has been postulated on a theoretical basis by Hall[3] in a recent article. Of course, Hall makes such predic-

community, whether we admit it or not. The enormous expenditures to build a proton center at the moment mean that during the next 5 to 10 years, there will be a relatively small number of facilities that have proton beam therapy.[12] The rest of the radiotherapeutic community will be interested in the outcomes to see if they really need to obtain such technology. It is likely that well-designed clinical trials that randomly assign proton beam therapy to patients would be supported by the National Cancer Institute and possibly even third-party payers themselves. To accrue the required numbers for such studies would probably require a concerted effort from virtually all the major centers

Meta-analysis

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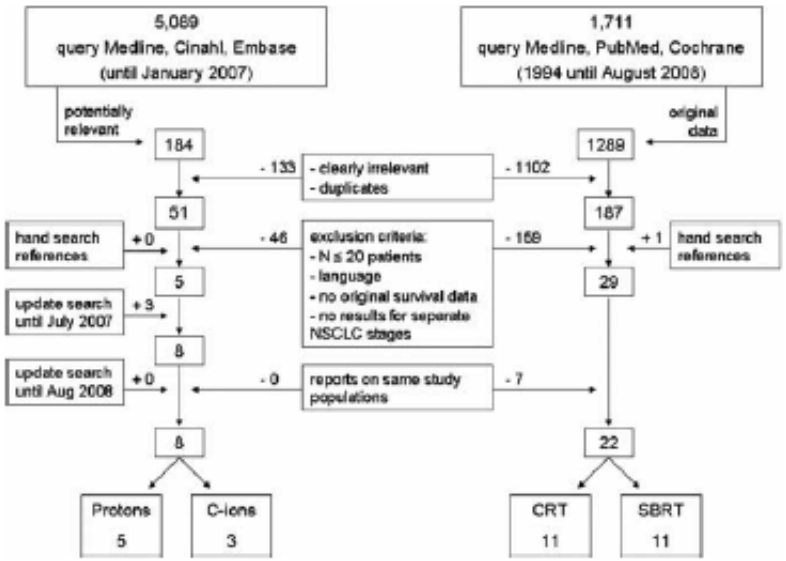
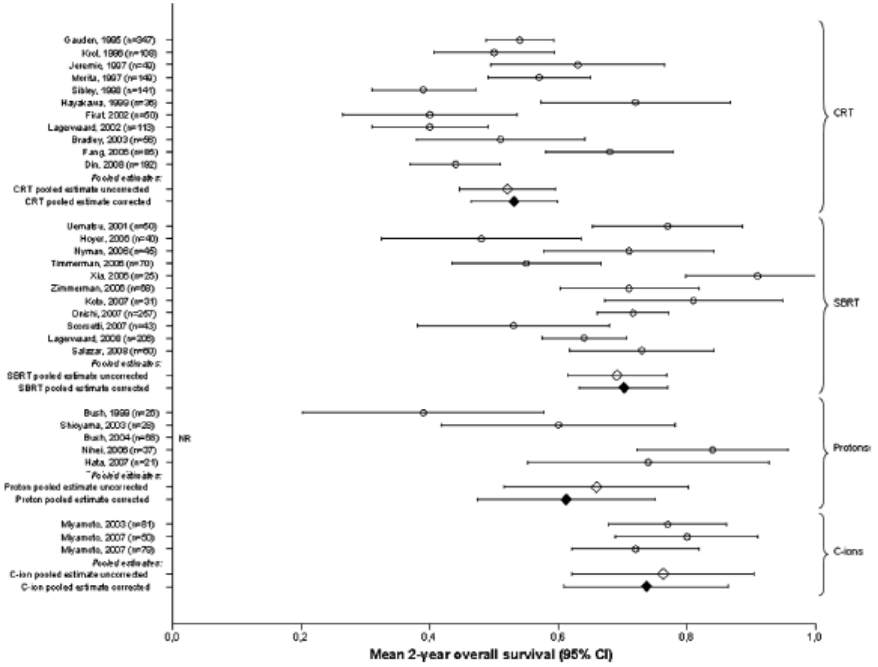
Appendix 1. Flow diagram of the search results for particle therapy (left) and photon therapy (right)





Study and population characteristics for studies on stage I NSCLC.

First author	Year	Study design	Treatment type	Sample size	Fraction dose (Gy)	Fraction number	Total dose (Gy)	OTT (weeks)	$EQD_{2,7}$	Median/mean age (range)	% tumors <3 cm	% Medically inoperable	Median FU in months (range)
Gaudien [30]	1995	R	CRT	347	2.5	20	50	4	48	70 (34–90)	48	64	22
Krol [36]	1996	R	CRT	108	2.5–3	20–26	60–65	5–7	51–57	74 (56–88)	47	94	NR
Jeremic [40]	1997	P	CRT	43	1.2	58	70	6	54	63 (51–70)	51	59	NR
Morita [32]	1997	R	CRT	149	2	27–38	55–74	5–8	46–57	74 (50–89)	40	83	31
Sibley [33]	1998	R	CRT	141	1.8–3	NR	50–80	4–10	NC	70 (46–95)	54	39	24 (7–132)
Hayakawa [35]	1999	R	CRT	36	2	30–40	60–81	6–8	47–59	NR	19	89	NR
Firat [34]	2002	R	CRT	50	NR	NR	31–77	NR	NC	69 (52–83)	50	NR	NR
Lagerwaard [31]	2002	R	CRT	113	2–2.5	28–35	60–72	5–7	47–60	74 (49–87)	58	90	29
Bradley [37]	2003	P	CRT	56	1.8–2	30–42	60–84	6–8	42–63	73 (52–90)	55	100	20 (15–72)
Fang [39]	2006	R	CRT	85	NR	NR	45–80	NR	NC	73	64	82	19 (2–77)
Din [38]	2008	P/R	CRT	102	1.5	36	54	2	57	71*	39	NR	Minimum 24
Uematsu [44]	2001	R	SBRT	50	5–12	5–10	50–60	1–2	63–110	71 (54–86)	48	42	36
Hoyer [21]	2006	II	SBRT	40	15	3	45	1	94	70 (48–80)	55	100	29 (13–58)
Nyman [43]	2006	P	SBRT	45	15	3	45	1	94	74 (58–84)	40	100	43 (24–74)
Timmerman [46]	2006	II	SBRT	70	20–22	3	60–66	1–2	150–176	70 (51–86)	50	100	18 (1–44)
Zimmerman [46]	2006	I/II	SBRT	68	6–12.5	3–5	24–40	NR	32–50	76 (59–92)	100	100	17 (3–44)
Xia [45]	2006	P	SBRT	25	7	10	70	2	99	71 (44–88)*	42	100	27 (24–34)
Koto [41]	2007	II	SBRT	31	7.5–15	3–8	45–60	1–2	88–94	77 (60–83)	61	65	32 (4–87)
Onishi [23]	2007	R	SBRT	257	4.4–35	1–14	30–84	NR	NC	74 (39–92)	64	61	38 (2–128)
Scorsetti [47]	2007	P	SBRT	43	7–10	2–4	20–32	NR	33–40	74 (52–90)	67	100	14 (6–36)
Lagerwaard [42]	2008	P	SBRT	206	7.5–20	3–8	60	NR	90–150	73	59	81	12 (3–44)
Salazar [49]	2008	P	SBRT	60	13	4	52	3	100	75 (53–93)*	75	100	38 (2–84)
Bush [50]	1990	P	Proton	26	1.8–5.1	10–41	51–74	2–5	64	72 (54–87)*	44	NR	14 (3–44)
Shioyama [54]	2003	R	Proton	28	2–6	7–32	49–93	1.5–11	NC	74 (25–87)*	32	NR	30 (18–153)
Bush [51]	2004	II	Proton	68	5.1–6	10	51–60	2	64–80	72 (52–87)	43	93	NR
Nihei [53]	2006	R	Proton	37	3.5–4.7	20	70–94	4–5	70–111	75 (63–87)	46	62	24 (3–62)
Hata [52]	2007	P	Proton	21	5–6	10	50–60	2	63–80	74 (51–85)	52	43	25 (10–54)
Miyamoto [57]	2003	I/II	Carbon-ion	81	3.3–8.8	9–18	59–95	3–6	53–124	72 (47–85)	50	74	53
Miyamoto [56]	2007	II	Carbon-ion	50	8	9	72	3	108	74 (61–84)	59	66	59 (6–83)
Miyamoto [55]	2007	I/II	Carbon-ion	79	13.2–15	4	53–60	1	102–125	75 (47–88)	53	78	39 (3–72)

Abbreviations: Gy, gray (for particle therapy gray equivalent (GyE) or cobalt gray equivalent (CGE)); $EQD_{2,7}$ biological equivalent dose for the tumor in 2 Gy fractions corrected for time (for SBRT studies when no OTT was reported we assumed an OTT <21 days); OTT, overall treatment time; FU, follow-up; P, prospective; R, retrospective; I, Phase I; II, Phase II; CRT = conventional radiotherapy with photons; SBRT, stereotactic body radiotherapy with photons; NR, not reported; NC, not calculable.

* Population characteristics are for total study population, including other disease stages.

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Results of meta-analysis for 2-year (disease-specific) survival.*

Treatment	2-year overall survival	(95% CI)	p-Value**		
			SBRT	Protons	Carbon-ions
CRT	0.531	(0.464–0.599)	<0.001	0.310	0.006
SBRT	0.702	(0.633–0.770)		0.262	0.638
Protons	0.612	(0.474–0.750)			0.180
Carbon-ions	0.737	(0.609–0.864)			
	2-year disease-specific survival				
CRT	0.674	(0.587–0.761)	0.006	0.430	0.065
SBRT	0.834	(0.751–0.917)		0.246	0.797
Protons	0.740	(0.607–0.874)			0.391
Carbon-ions	0.815	(0.700–0.930)			

Results of meta-analysis for 5-year (disease-specific) survival.*

Treatment	5-year overall survival	(95% CI)	p-Value**		
			SBRT	Protons	Carbon-ions
CRT	0.195	(0.148–0.242)	<0.001	0.014	<0.001
SBRT	0.421	(0.341–0.501)		0.782	0.985
Protons	0.397	(0.245–0.550)			0.790
Carbon-ions	0.421	(0.322–0.520)			
	5-year disease-specific survival				
CRT	0.435	(0.311–0.559)	0.045	0.471	0.051
SBRT	0.627	(0.500–0.754)		0.389	0.999
Protons	0.521	(0.319–0.724)			0.353
Carbon-ions	0.643	(0.486–0.801)			

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Occurrence of adverse events grade 3–5* for each treatment modality in patients with stage I NSCLC.

Treatment	N events	N at risk	Proportion	(95% CI**)	Source	N events	N at risk	Proportion	(95% CI**)	Source
	Pneumonitis grade 3/4					*Oesophagitis grade* 3/4				
CRT	2	867	0.0023	(0.0003–0.0083)	[30,32,33,35–37,40]	1	831	0.0012	(0.0000–0.0067)	[30,32,33,35–37,40]
SBRT	16	800	0.0200	(0.0115–0.0323)	[21,23,41–44,46,47,49]	2	840	0.0024	(0.0003–0.0086)	[21,23,41–44,46–49]
Protons	1	126	0.0079	(0.0002–0.0434)	[51–53]	0	126	0.0000	(0.0290)	[51–53]
Carbon-ions	3	210	0.0143	(0.0030–0.0412)	[55–57]	nr	nr	-	-	
	Irreversible dyspnoea grade 3/4					*Treatment-related death* (*grade* 5)				
CRT	5	980	0.0051	(0.0017–0.0119)	[30–33,35–37,40]	1	980	0.0010	(0.0000–0.0057)	[30–33,35–37,40]
SBRT	6	769	0.0078	(0.0029–0.0169)	[21,23,42–44,46,47,49]	6	870	0.0069	(0.0025–0.0150)	[21,23,41–44,46–49]
Protons	0	58	0.0000	(0.0620)	[52,53]	0	126	0.0000	(0.0290)	[51–53]
Carbon-ions	0	210	0.0000	(0.0170)	[55–57]	0	210	0.0000	(0.0170)	[55–57]

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ABSTRACT

Purpose: To provide a comparison between radiotherapy with photons, protons and carbon-ions in the treatment of Non-Small-Cell Lung Cancer (NSCLC), performing a meta-analysis of observational studies. *Methods:* Eligible studies on conventional radiotherapy (CRT), stereotactic radiotherapy (SBRT), concurrent chemoradiation (CCR), proton therapy and carbon-ion therapy were searched through a systematic review. To obtain pooled estimates of 2- and 5-year disease-specific and overall survival and the occurrence of severe adverse events for each treatment modality, a random effects meta-analysis was carried out. Pooled estimates were corrected for effect modifiers. *Results:* Corrected pooled estimates for 2-year overall survival in stage I inoperable NSCLC ranged from 53% for CRT to 74% for carbon-ion therapy. Five-year overall survival for CRT (20%) was statistically significantly lower than that for SBRT (42%), proton therapy (40%) and carbon-ion therapy (42%). However, caution is warranted due to the limited number of patients and limited length of follow-up of the particle studies. *Conclusion:* Survival rates for particle therapy were higher than those for CRT, but similar to SBRT in stage I inoperable NSCLC. Particle therapy may be more beneficial in stage III NSCLC, especially in reducing adverse events.

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References

- http://www.medphys.mcgill.ca/intro/mainintro.html
- Podgorsak, E.B., *Radiation Physics for Medical Physicists, 2nd ed., 2010, XXXIII, 745 p. 190 illus., 16 in color., HardcoverISBN: 978-3-642-00874-0*
- Khan, F.M. (1994*) The Physics of Radiation Therapy, Williams & Wilkins, Baltimore*
- Hall, E.J. (1988) *Radiobiology for the Radiologist, J.B. Lippincott Co., Philadelphia*