Radiation Therapy

Use of radiation to kill diseased cells.
Cancer is the disease that is almost always treated when using radiation.

- One person in three will develop some form of cancer in their lifetime.
- One person in five will die from that cancer.
- Cancer is the second leading cause of death but exceeds all other diseases in terms of years of working-life lost.

Diagrammatic representation of a slice through a large solid tumor.

[Image removed due to copyright concerns]

Webster's Medical Dictionary:
Cancer – A malignant tumor of potentially unlimited growth that expands locally by invasion and sytemically by metastasis.

Tumor – an abnormal mass of tissues that arises from cells of pre-existent tissue, and serves no useful purpose.

Malignant – dangerous and likely to be fatal (as opposed to "benign," which refers to a non-dangerous growth).

[Image removed due to copyright concerns]

Unlimited Growth:

- Cancer cells multiply in an unregulated manner independent of normal control mechanisms.
- Formation of a solid mass in organs.
- Multiplication of bone marrow stem cells gives rise to leukemia, a cancer of the blood.

Solid tumors:

- Primary tumor may be present in the body for months or years before clinical symptoms develop.
- Some tumors can be managed and the patient often cured provided there has been no significant invasion of vital organs.
- Patients do not often die of primary tumors---*brain tumors are the exception*.

Metastases:

- The spread of tumor cells from one part of the body to another, usually by the blood or lymph systems.
- Metastases are more usually the cause of death.
- Metastases are especially common in the bone marrow, liver, lungs and brain.

Cancer Treatment Modalities

Surgery

- Very important.
- For some tumors, surgery is the only or greatest chance for a complete cure
    - colorectal, small and large bowel cancer, some lung, ovarian, thyroid, testicular, stomach and uterine cancers.
- Often chemotherapy or radiation therapies are used to augment surgery.

Chemotherapy

- Drugs carried throughout the body (not like surgery or radiation, which are usually local).
- The only effective way, so far, for treatment of widespread, multiple metastases.
- Most successful against leukemias.
- Limited effectiveness against primary tumors or tumors greater than a few millimeters in diameter.
- About 30 chemotherapeutic drugs are in regular use in the treatment of cancer (but over 800,000 compounds have been tested).
- Usually used in combination with other treatment methods.

Hyperthermia

- Long reported that tumors stop growing during a fever bout.
- Not well studied; conflicting results.
- Difficult to quantitatively measure heat delivery and absorption, etc.
- Used in combination with other modalities.

Immunotherapy and Radioimmunotherapy

- Methods of stimulating the immune system are being investigated.
- Still experimental, not in clinical practice.

Radiation

- 50% of all cancer patients in the U.S. receive radiation therapy. 50% of these patients are potentially curable. (The rest receive radiation either as adjuvant or palliative treatment.)
- Any improvements to radiotherapy, even small improvements, will benefit a great many people.

Stats: 40% of all cancer patients “cured” by surgery, chemo, and radiation in various combinations. “Cure” usually means 5 year survival.

Surgery and radiation used with curative intent vs primary.

- Palliation: non-curative intent for more advanced disease.

The problem:

- Destroy the tumor with minimal damage to the normal tissues.
- However, normal tissues and tumor can have the same radiosensitivity.

X-ray dose-response curves of normal (N12) and transformed (T7) Chinese hamster cells

[Image removed due to copyright concerns]

Fractionation

- Standard radiotherapy is “fractionated” (usually five days a week for ~ 6 weeks).
- Fractionated radiotherapy relies on **biological effects** to obtain more cell kill in the tumor than in the surrounding normal tissue.

The 4 R’s of fractionated radiation therapy

- **R**epair
- **R**eoxygenation
- **R**edistribution
- **R**epopulation

Standard Radiation Therapy

Low-LET, electrons or photons, 5-25 MeV

A radiotherapy linear accelerator. The linac is isocentrically mounted so that when the tumor is placed at the axis of the treatment arm, the beam will be directed at the tumor from all angles.

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1) Repair of DNA damage

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Schematic illustration of the effect of fractionated radiotherapy on normal (--) and tumor (__) cell populations.

Normal tissues repair damage more efficiently than tumors.

Fractionation schedules developed empirically.
Typical: 1.8-2.0 Gy/day, 5 days/week for 6 weeks.

[Image removed due to copyright concerns]

Idealized fractionation experiment. With each fraction, the shoulder or repairable damage is repeated. Multiple small fractions approximate to a continuous low dose rate.

Normal Tissue Tolerance

[Image removed due to copyright concerns]

Tolerance of various normal tissues versus total number of fractions (left) or dose per fraction (right). Skin: dry desquamation in humans; bone marrow, intestine, lung: LD_{50} in mice.

Fractionation spares normal tissues

Greater total doses can be delivered if fractionated.

Tolerance doses can vary considerable for various normal tissues.

Note bone marrow: very little sparing with fractionation. Bone marrow stem cells radiosensitive, little or no shoulder on survival curve means no repair.

2) Reoxygenation

[Image removed due to copyright concerns]

Oxygen must diffuse from the capillary.

Diffusion limit ~ 70 μm.

Hypoxic cells may limit the radiocurability of the tumor.

[Image removed due to copyright concerns]

Tumor blood supply is dynamic.

Vessels may open and close periodically, affecting the oxygen distribution

Low-LET radiation is more effective at killing well-oxygenated cells:
"Direct vs indirect" effect

(Right)
Percent of hypoxic cells in a transplanted mouse tumor after a single dose of 10 Gy X rays.

Reoxygenation is rapid in this tumor.

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[Image removed due to copyright concerns]

Tumors "outgrow" their blood supply.

Large tumors develop hypoxic/necrotic centers.

Fractionation, given at the proper intervals to allow reoxygenation will continue to kill the reoxygenated fraction of cells.

3) Redistribution

- Radiation will kill cells in the more sensitive phases of the cell cycle.
- Radiation will also cause a G_2/M delay or block.
- Cells become partially synchronized after a dose of radiation.
- As these cells enter the more sensitive stages of the cell cycle together, the next fraction can kill more cells as the

Survivors of the initial dose are primarily in the radioresistant S phase. Six hours later this population of cells is in the radiosensitive G_2M phase.

[Image removed due to copyright concerns]

This split-dose experiment illustrates three of the 4 "R's" of radiobiology.
1) Prompt **repair** of sublethal damage within 2 hours.
2) Progression and **redistribution** of partially synchronized surviving cells through the cell cycle.
3) Increase in surviving population resulting from cell division (**repopulation**) if the interval between fractions is > the cell cycle time.

4) Repopulation

- Radiation can stimulate cell division in both tumor and normal tissues.
- Normal tissues have control mechanisms in place and will benefit from the repopulation.

Tumor cells may show accelerated repopulation during treatment.
Surviving tumor cells divide faster as overall tumor volume decreases.

[Image removed due to copyright concerns]

- Situation is more complicated during fractionated radiation therapy.
- Extra dose per fraction, or more fractions, may be needed to counteract tumor accelerated repopulation.
- Fractionation schedules may not be optimal from the radiation biology point of view: e.g., 1 fraction/day, 5 days/week, for 6 weeks.
- Experimental fractionation schedules (3 fractions/day, 12 days in a row) show improved tumor control with the same or less normal tissue complications.

Normal tissue complication probability (NTCP)
Tumor control probability (TCP)
10% NTCP is often considered the maximum allowable.

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Fractionated RT spares normal tissues because of **repair** and **repopulation**, but increases tumor damage because of **reoxygenation** and **redistribution**.

Radioresistant tumors: the 2 curves may be very close together.

Tumor response is a function of total treatment time and total dose.

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Other Radiation Therapy modalities

Brachytherapy: implant radioactive "seeds", or insert radioactive needles.
BNCT

Particles

Advantages of high-LET radiation

- Less, or no, oxygen effect
- Bragg Peak allows better dose localization

TABLE 64–1. Attributes of Particle Beams

Particle	Charge	Mass	RBE
Electron	−1	1 m_e	1
Proton	1	1832 m_e	1.1*
Neutron	0	1835 m_e	3.0–3.3†
Pions	−1	276 m_e	1.0–1.8†
Helium ion	2	4 amu	1.25‡
Neon ion	10	20 amu	2.5‡

*Value used clinically at Massachusetts General Hospital–Harvard Cyclotron Laboratory.
†Data from Raju.[56]
‡Values used clinically at University of California at San Francisco–Lawrence Berkeley Laboratory. Helium RBE: 8 cm spread-Bragg peak, 2.0 GyEq fractions; neon RBE: 8 cm Bragg peak, 3.0 GyEq fractions.
RBE, relative biologic effectiveness.

TABLE 64–2. Relative Advantages of Charged-Particle and Neutral Beams

	Dose Localization	Biologic Effect
Protons	+ + + +	+
Helium ions	+ + + + +	+
Carbon ions	+ + + + + +	+ + +
Neon ions	+ + +	+ + + +
Silicon ions	+ +	+ + + + +
Neutrons	+	+ + + +

Protons

[Image removed due to copyright concerns]

Dose localization
Normal tissue sparing
SOBP: spread out Bragg Peak

[Image removed due to copyright concerns]

[Image removed due to copyright concerns]

Protons

[Image removed due to copyright concerns]

Stereotactic Radiosurgery:
Uses accelerator

Gamma Knife:
Uses fixed Co-60 sources

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WORLD WIDE CHARGED PARTICLE PATIENT TOTALS

July 1999

WHO	WHERE	WHAT	DATE FIRST RX	DATE LAST RX	RECENT PATIENT TOTAL	DATE OF TOTAL
Berkeley 184	CA. USA	p	1954	— 1957	30	
Berkeley	CA. USA	He	1957	— 1992	2054	June-91
Uppsala	Sweden	p	1957	— 1976	73	
Harvard	MA. USA	p	1961		8160	Jun-99
Dubna	Russia	p	1967	— 1974	84	
Moscow	Russia	p	1969		3100	Dec-98
Los Alamos	NM. USA	π^-	1974	— 1982	230	
St. Petersburg	Russia	p	1975		1029	Jun-98
Berkeley	CA. USA	heavy ion	1975	— 1992	433	June-91
Chiba	Japan	p	1979		96	Oct-96
TRIUMF	Canada	π^-	1979	— 1994	367	Dec-93
PSI (SIN)	Switzerland	π^-	1980	— 1993	503	
PMRC, Tsukuba	Japan	p	1983		606	Mar-99
PSI (72 MeV)	Switzerland	p	1984		2753	Dec-98
Dubna	Russia	p	1987		41	Jun-99
Uppsala	Sweden	p	1989		147	Feb-98
Clatterbridge	England	p	1989		817	May-98
Loma Linda	CA. USA	p	1990		4330	May-99
Louvain-la-Neuve	Belgium	p	1991	– 1993	21	
Nice	France	p	1991		1350	Jun-99
Orsay	France	p	1991		1219	July-98
N.A.C.	South Africa	p	1993		310	May-99
MPRI	IN USA	p	1993		9	Dec-98
UCSF - CNL	CA USA	p	1994		214	Jun-99
HIMAC, Chiba	Japan	heavy ion	1994		473	Sept-98
TRIUMF	Canada	p	1995		47	Dec-98
PSI (200 MeV)	Switzerland	p	1996		20	Dec-98
G.S.I Darmstadt	Germany	heavy ion	1997		20	Dec-98
Berlin	Germany	p	1998		30	Dec-98
NCC, Kashiwa	Japan	p	1998		8	Jun-98
					1100	pions
					2980	ions
					24494	protons
				TOTAL	28574	all particles

- Protons are by far the most extensively used particle therapy.
- Heavier ions: carbon, neon,
- Clinical results not yet dramatic enough to justify the considerable cost of the accelerator required.