Clinical Radiobiology

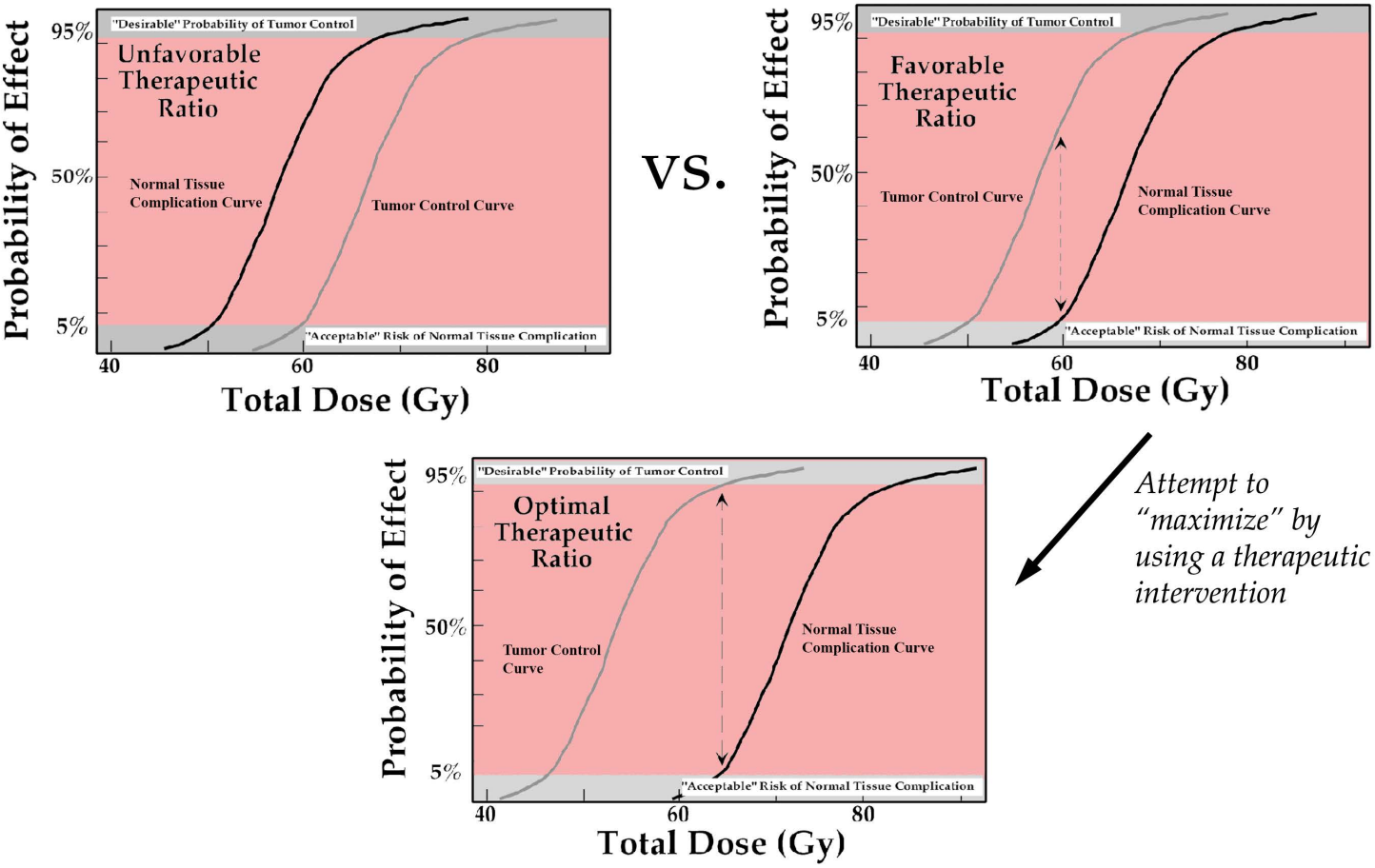
A. The Concept of Therapeutic Ratio

1. the goal of (curative) radiotherapy is to deliver a sufficiently high dose of radiation to kill all of the clonogenic tumor cells while at the same time, minimizing damage to the surrounding normal tissues such that they can continue to remain both structurally intact and functional

a) *this may sound fairly easy to accomplish in theory (i.e., just use a high enough tumor dose, but keep the normal tissue dose within tolerance limits), but in practice, it often isn't!*

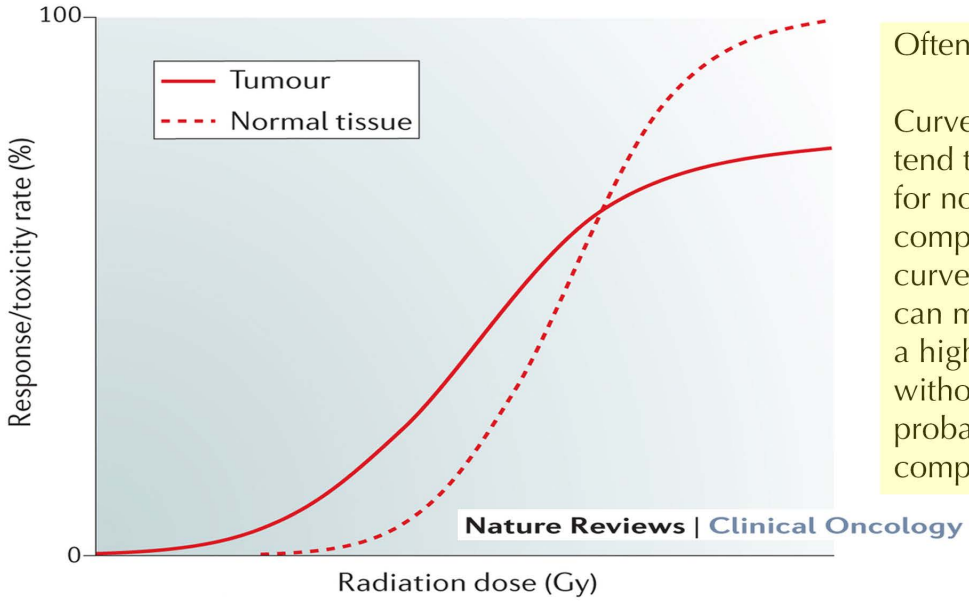
b) because of this, radiation therapy is often viewed as a trade-off...a weighing of possible risks versus possible benefits

1] the practice of designing a radiotherapy treatment which tries to reach an acceptable balance between risks and benefits is called "maximizing the therapeutic ratio"; usually, this concept is easiest to understand using the following graphical representation:



2] both the probability of curing the tumor and causing unacceptable normal tissue damage are dependent on the total dose given (includes the fractionation pattern and overall treatment time), but it is the <sometimes subtle> differences between these two that "make or break" the therapeutic ratio, and therefore, the treatment outcome

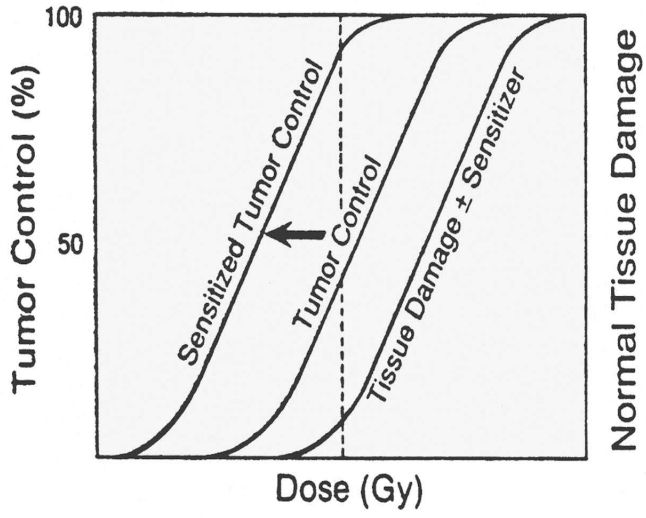
c) *that's all well and good for these theoretical dose response curves, but what do these things look like in the real world?*



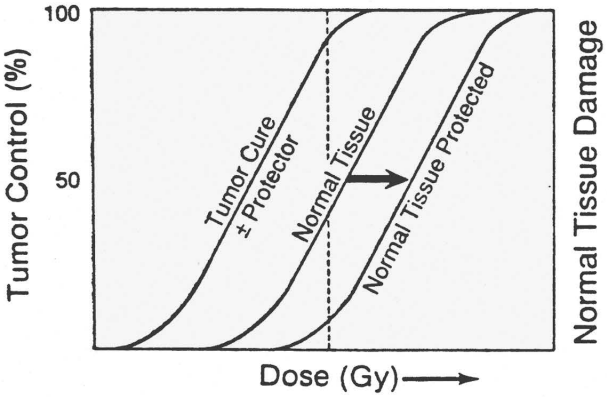
Often, like this.

Curves for tumor control tend to be shallower than for normal tissue complications, and the two curves often cross. This can make it difficult to get a high tumor control rate without also causing a high probability of normal tissue complications.

when the tumor cure and normal tissue complication curves are very close together, the outcome of therapy would be a toss-up; in such cases, it might be useful to try some chemical modifiers of radiation toxicity (see below) in an attempt to move these curves apart



Schematic of the rationale for using sensitizers in radiotherapy. The sensitizer shifts the tumor control curve to lower radiation doses while not affecting the normal tissue complication curve; therefore, the therapeutic ratio would increase because the sensitizer would affect only the tumor and not the normal tissue. (Adapted from Hall EJ: *Radiobiology for the Radiologist,* ed 3. Philadelphia, JB Lippincott Co, 1988.)



The rationale for the use of radioprotectors in clinical radiotherapy. Ideally, radioprotectors should shift the curve for normal tissue responses to higher total doses, while having no effect on the tumor. Thus, a higher therapeutic ratio is achieved by changing the dose range over which normal tissue damage occurs. (Adapted from Hall EJ: *Radiobiology for the Radiologist*, ed 3. Philadelphia, JB Lippincott Co, 1988.)

B. **Modifiers of Radiation Response**...*that are sometimes able to tip the balance of the therapeutic ratio in favor of tumor cure with minimal normal tissue complications*

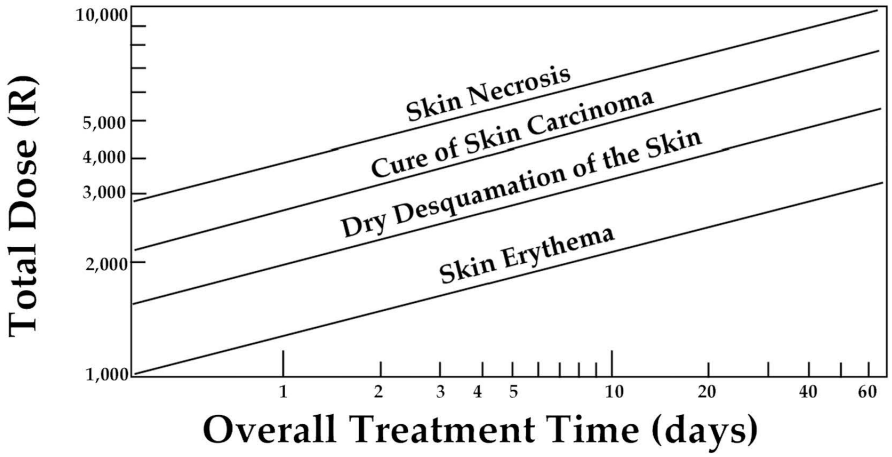
1) **Physical Modifiers** - factors that take advantage of the physical properties of electromagnetic radiation

a. ***Time, Dose, Fractionation and Isoffect Curves***

1] despite all we've learned about radiobiology, **the fact remains that the only parameters the radiation oncologist can vary in order to try to maximize the therapeutic ratio are the total dose, the dose per fraction and the overall treatment time (also, the treatment volume)**

2] *because of this, it becomes important to be able to compare and contrast different treatments in terms of both tumor control and normal tissue complications in order to look for patterns and especially, differences--this can be accomplished by constructing* ***isoeffect curves***

a. **the first person to use isoeffect curve analysis of clinical data was Strandqvist (1944)**, and his published curves (shown below) formed the basis of all subsequent studies of time, dose and fractionation effects for radiotherapy, even up to the present day!



Isoeffect curves, like these of Strandqvist, plot ***the log of the total dose it takes to cause a certain complication and/or cure a tumor, as a function of one of the varied treatment parameters*** **(i.e., overall time, number of fractions or dose per fraction).**

In this example, any combination of overall time and total dose that falls along the curve produces the same tissue "isoeffect".

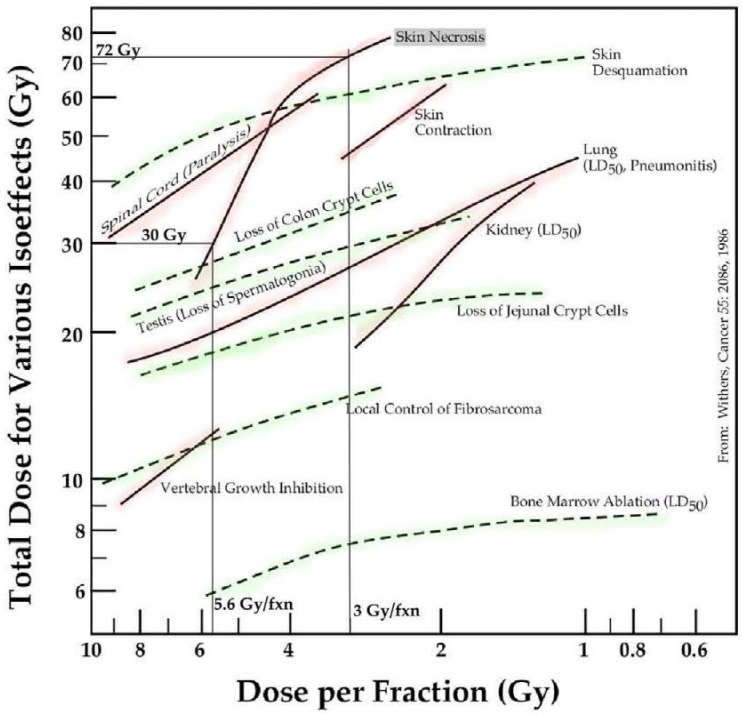
b. about 25 years after Strandqvist, **another investigator named Ellis used isoeffect curves to develop the NSD model, a technique for calculating radiotherapy treatment prescriptions that should give the same biological outcome (emphasis on "should")**

$$D = (NSD)\ N^{.24}\ T^{.11}$$

[where D = total dose prescribed, N = number of fractions, T = overall treatment time and NSD = a tissue-specific constant]

c. The NSD model has since been replaced by the linear-quadratic model (sometimes called the "alpha-beta model"), because the parameter α/β replaces NSD, and the model is based on the survival curve expression (discussed previously): $S = e^{-(\alpha D + \beta D^2)}$

4) **Thames, Withers, Peters and Fletcher (1982**, see: IJROBP *8*: 219-226, 1982) - were among those calculating α/β ratios for experimental animal and human tissues



Today's "higher resolution" isoeffect curves for normal tissue complications and tumor control are better fit by the alpha-beta isoeffect model (which discriminates between the behavior of early- and late-responding tisues and tumors) than the NSD model.

Whether these isoeffect curves are steep (late effects and a few tumors), or shallow (early effects and most tumors) is governed by the tissue's α/β ratio; low α/β = steep isoeffect curve and high α/β = shallow isoeffect curve

In this example, if the $TD_{5/5}$ for skin necrosis (late effect) is ~30 Gy when given in 5.6 Gy fractions, it's 72 Gy when given in 3 Gy fractions. A *huge* difference!

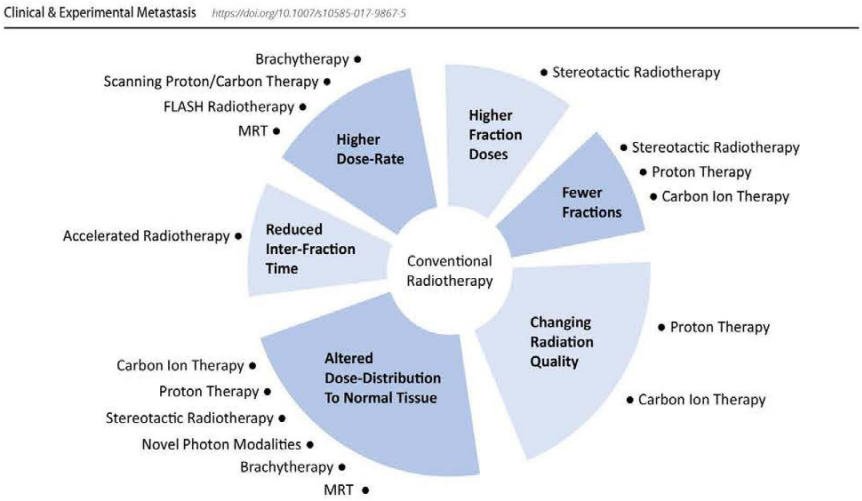
However, for bone marrow ablation (early effect), the change in tolerance dose in going from 5.6 Gy to 3 Gy fractions is quite small (~6 Gy to ~7.5 Gy).

The alpha-beta isoeffect model underlies many of the innovations over the last 35 years in how best to fractionate radiotherapy.

A couple of recent examples:

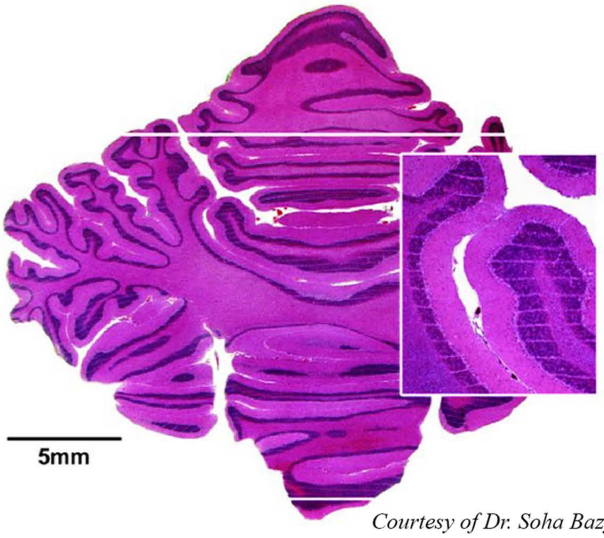
Spatially-fractionated radiotherapy = giving the daily dose non-uniformly in volume, i.e., cover the volume with **many "beamlets" (of differing size)** but with unirradiated zones in between

FLASH radiotherapy = giving the daily dose non-uniformly in time by using tiny "pulses" of dose delivered at a very high dose rate



Spatially-fractionated radiotherapy can use "thick" beamlets (GRID therapy), "thin" beamlets (minibeam therapy) or microscopic beamlets (microbeam therapy)

Piglet brain traversed by lots of microbeams...yet still seems to work just fine!



Courtesy of Dr. Soha Bazyar (2018)

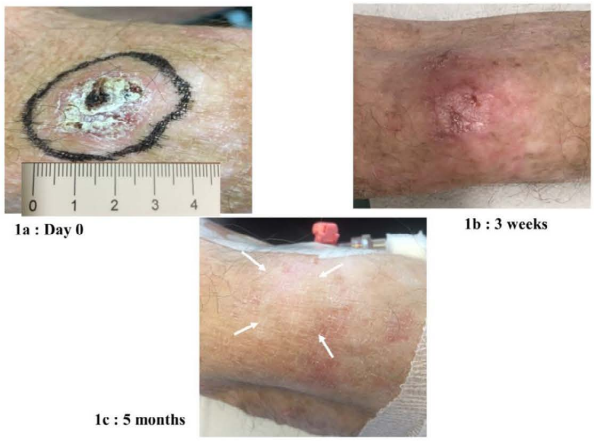
FLASH radiotherapy, where the total dose is delivered to the treatment volume at an extremely high dose rate (at least 40 Gy/second), given all at once

Cat with deeply-infiltrating SCC of the nose treated with a single dose of 27 Gy FLASH (electrons)

Vozenin et al. Clin Cancer Res; 25(1) January 1, 2019

First human patient, a 75 year old male with heavily-pretreated cutaneous T-cell lymphoma of ~20 years duration, received a single dose of 15 Gy FLASH electrons. (Overall treatment time = 90 ms.)

Patient claimed he saw a blue flash coming from the linac during/after treatment!



Temporal evolution of the treated lesion: (a) before treatment; the limits of th PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

Radiother Oncol 2019;*139*:18-22

1] *Both of these novel techniques seem to spare normal tissues but not tumors – suggesting a therapeutic advantage – although the exact mechanisms involved remain up for debate*

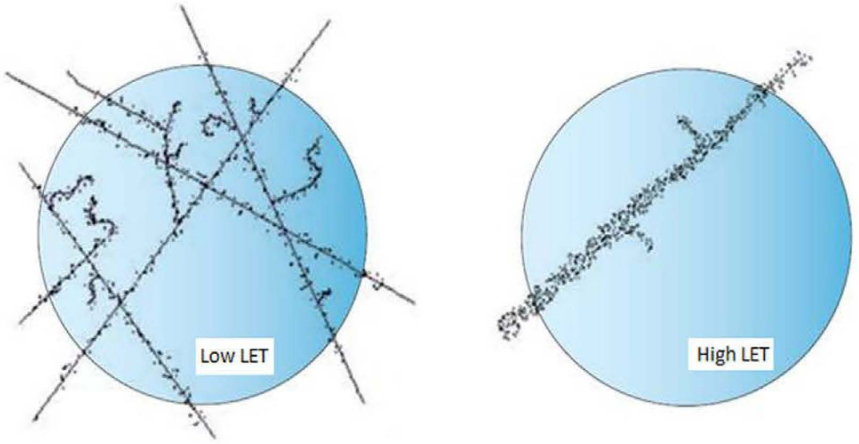
b. ***Changing the Type of Radiation: LET and RBE***

1] another approach to modifying the therapeutic ratio is to use a different type of radiation than conventional X- or γ-rays and electrons, in the hopes that it would have better physical (e.g., depth dose) and/or biological advantages

2] this involves an understanding of the differences between low and high LET radiation in terms of energy deposition patterns in matter, and in turn, what that means for biological effectiveness

(a) LET = *the average energy locally imparted to the absorbing medium by a charged particle of a specified energy divided by the distance traversed by that particle*

Translation: **LET refers to the relative density of "spurs" and "blobs" of energy deposited along the incident ionizing particle's track, that is, that LET is in units of energy per distance, or keV/μm**

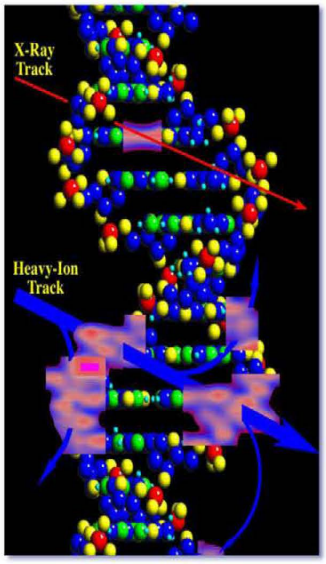


From Wambersie et al. J. Eur. Radiother. 5:248-264, 1985

In the examples shown for γ-rays (left) and neutrons (right), the macroscopic dose to the sensitive volume was the same, although microdosimetrically, the pattern of energy deposition was quite different.

This explains why the high LET neutrons are more biologically-damaging per unit dose than the low LET γ-rays.

DNA damage produced by high LET radiation (heavy ions in this case...see next page) tends to be more extensive and therefore harder to repair than after exposure to low LET radiation like X-rays.



Linear Energy Transfer (LET) of Various Radiations

Radiation	LET (keV/µm)
Photons	
^{60}Co (~1.2 MeV)	0.3
200-keV x-ray	2.5
Electrons	
1 Mev	0.2
100 keV	0.5
10 keV	2
1 keV	10
Charged particles	
Proton 2 MeV	17
Alpha 5 MeV	90
Carbon 100 MeV	160
Neutrons	
2.5 MeV	15 to 80
14.1 MeV	3 to 30

Important!

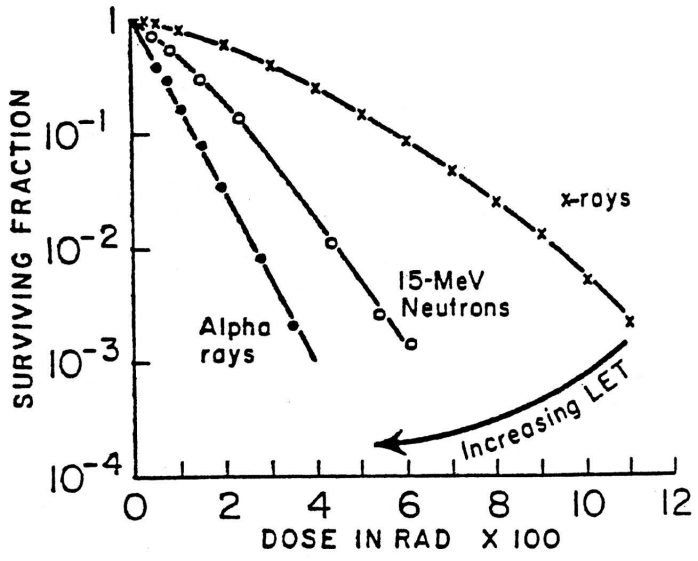
Particle-types of ionizing radiation with LETs greater than about 100 keV/µm are called "heavy ions"

high LET radiations, to a point, are more effective at producing biological damage than low LET radiations, and this is true for many different biological endpoints from tissue damage to cell survival to chromosome aberrations to DNA damage, etc.

...yet how can you express this differing biological effectiveness for different types of radiation on a common scale?

3] **Relative Biological Effectiveness or RBE**: a unit-less quantity used as a correction factor for the purposes of expressing the relative biological potency of radiations of different LET

(a) the formal definition of **relative biological effectiveness or RBE** is *the ratio of the dose of a standard type of radiation (usually, 250 kVp X-rays) to that of a test radiation which gives the same biological effect*

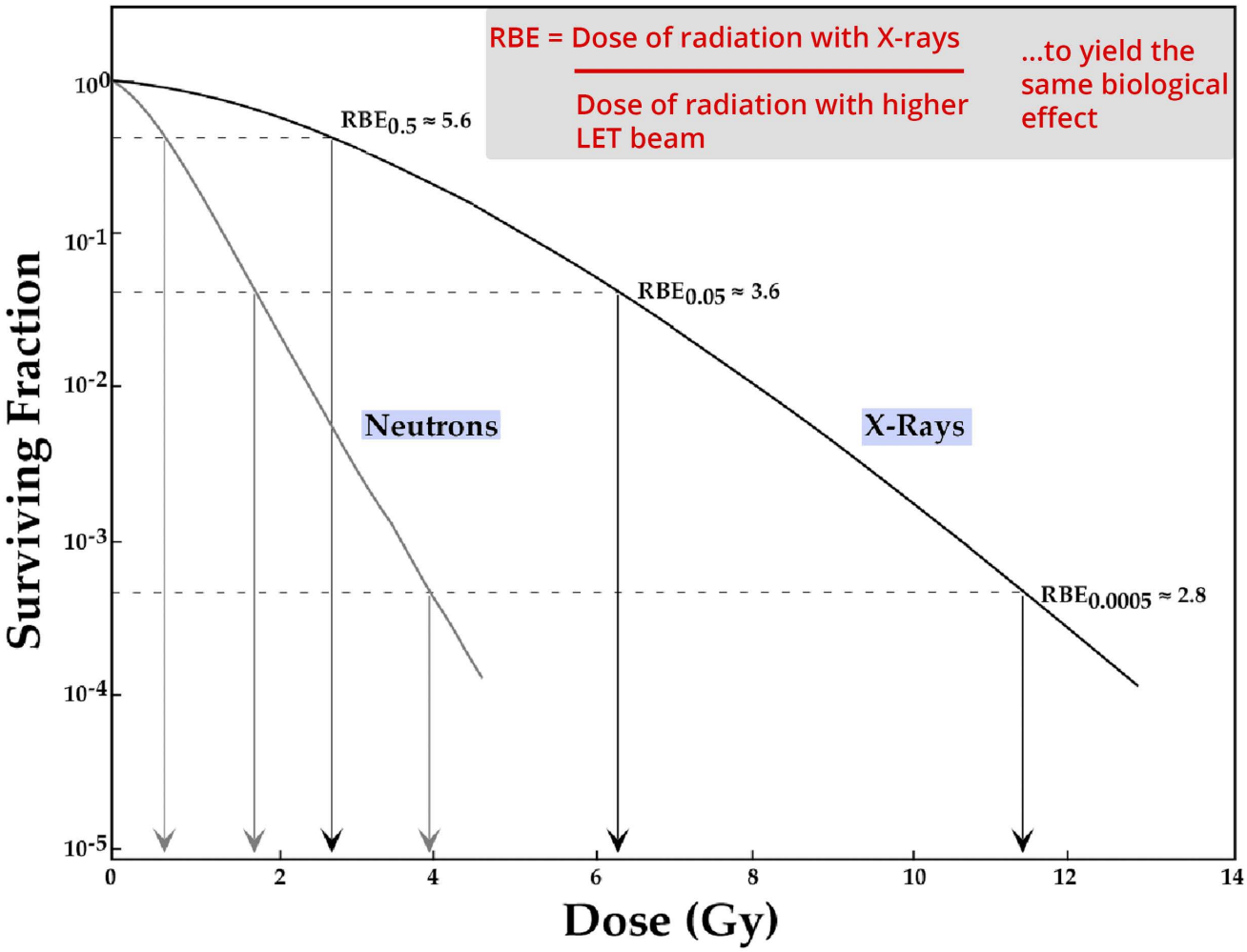


Survival curves for cultured cells of human origin exposed to 250-kVp x-rays, 15-MeV neutrons, and 4-MeV α-particles. As the LET of the radiation increases, the slope of the survival curves gets steeper and the size of the initial shoulder gets smaller.

From: Barendsen, Curr Top Radiat Res Q 4: 293-356, 1968

(b) **in terms of radiosensitivity of cells and tissues, survival curves for high(er) LET radiation are both steeper in final slope *and* have a reduced or absent survival curve shoulder**

Calculating the RBE from a survival curve plot



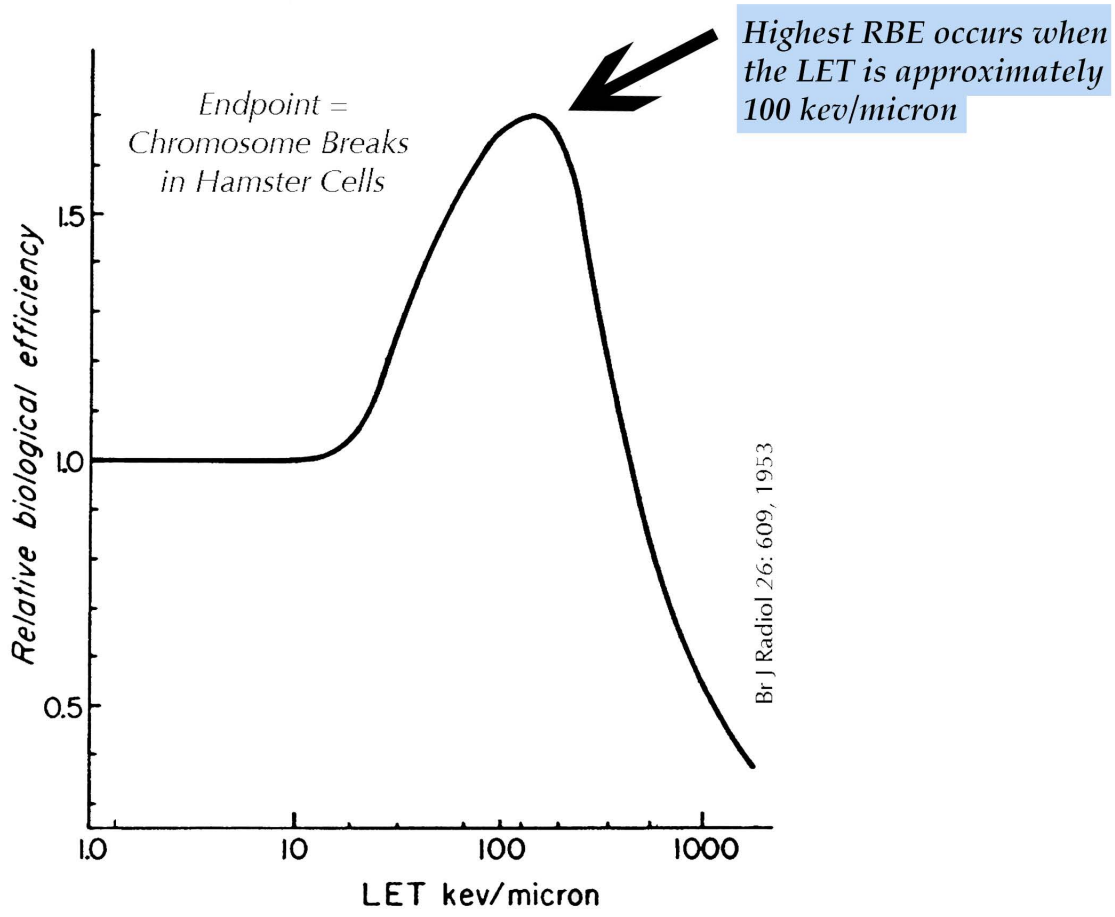
(c) because the survival curve for neutrons is both steeper *and* has a smaller shoulder compared to the curve for X-rays, it follows that the RBE will vary with the survival level chosen to construct the dose ratio

1) **Note that the RBE evaluated at low doses (where survival would be higher and the endpoint "milder") is greater than at high doses (where survival is lower and the endpoint more severe)**

2) **because of this, it is also true that the RBE for fractionated radiotherapy (consisting of repeated small doses) is higher than for single-dose treatment**

4] the dependence of RBE on LET:

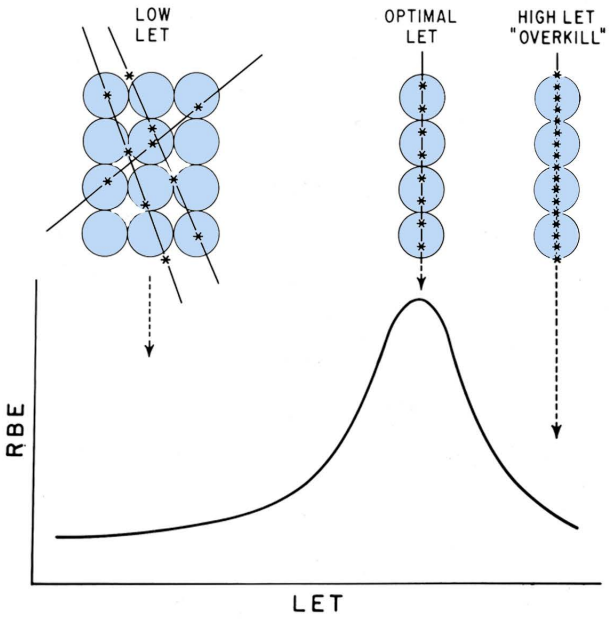
(a) the relationship between RBE and LET is a complicated one--the RBE first rises to a maximum at an LET of about 100 keV/μm, and then declines again



(b) Why would the RBE increase to a maximum and then decrease for even higher LETs?

1] there's one rather simplistic theory, and this is termed the **"Overkill Effect"**

a} the idea is that extra ionization energy keeps getting deposited in cells that have already been killed, meaning that cell killing gets less efficient (but not less effective) and the RBE drops



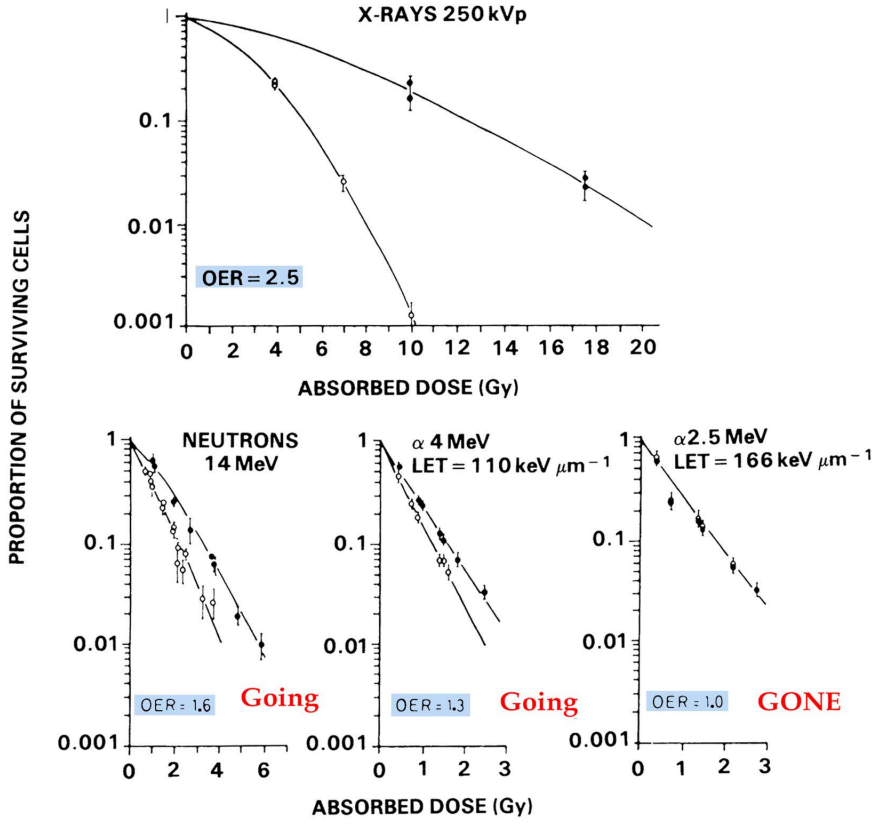
Diagrammatic representation of "overkill." For a cell to be killed, energy must be deposited in a number of critical sites within the cell. Sparsely ionizing radiation is inefficient because more than one particle must pass through the cell in order to kill it. Very densely ionizing radiation is also inefficient because it deposits more than enough energy in the critical sites within the cell; energy is wasted, the cells are "overkilled." Radiation of optimum LET deposits just enough energy to inactivate the critical targets. From: Hall, *Radiobiology for the Radiologist, First Edition*, 1973.

5] other radiobiological phenomena that vary with high versus low LET irradiation:

(a) **cellular recovery and dose rate effects** - *for high LET radiation, there is little or no sublethal damage recovery* (evidence that the types of DNA damage produced are more severe and less repairable), *meaning that there is little or no dose rate effect either*

(b) **cell cycle effects** - for low LET radiation, cells in different phases of the cell cycle have different inherent radiosensitivities (i.e., S phase cells are most resistant, and M phase most sensitive), but f*or high LET radiation, this age response effect is significantly "dampened" (neutrons), or absent (α-particles)*

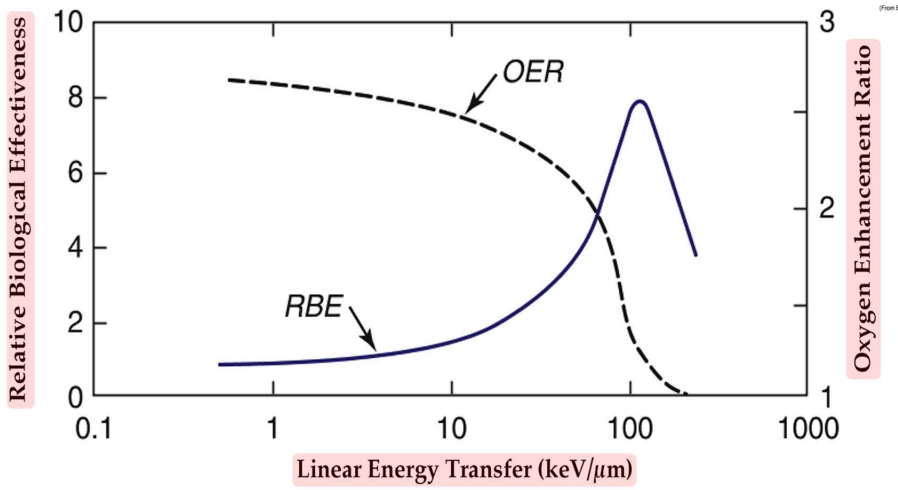
(c) **the oxygen effect** (see also, later in handout): *in the relative absence of oxygen at the time of irradiation, it can take up to 3 times the dose of low LET radiation to produce a comparable biological effect (like cell killing) to irradiation under well-oxygenated conditions; however, as the radiation's LET increases, the difference in radiosensitivity between aerated and hypoxic cells decreases...*



Survival curves of human kidney cells T1 irradiated under hypoxic and aerobic conditions with different qualities of radiation.

From: Barendsen, GW. Curr Top Radiat Res Q 4: 293-356, 1968

...until, at an LET of about 100 keV/μm (which corresponds to the maximum RBE), there is NO difference between the radioresponse of hypoxic and aerobic cells (i.e., the OER = 1.0)

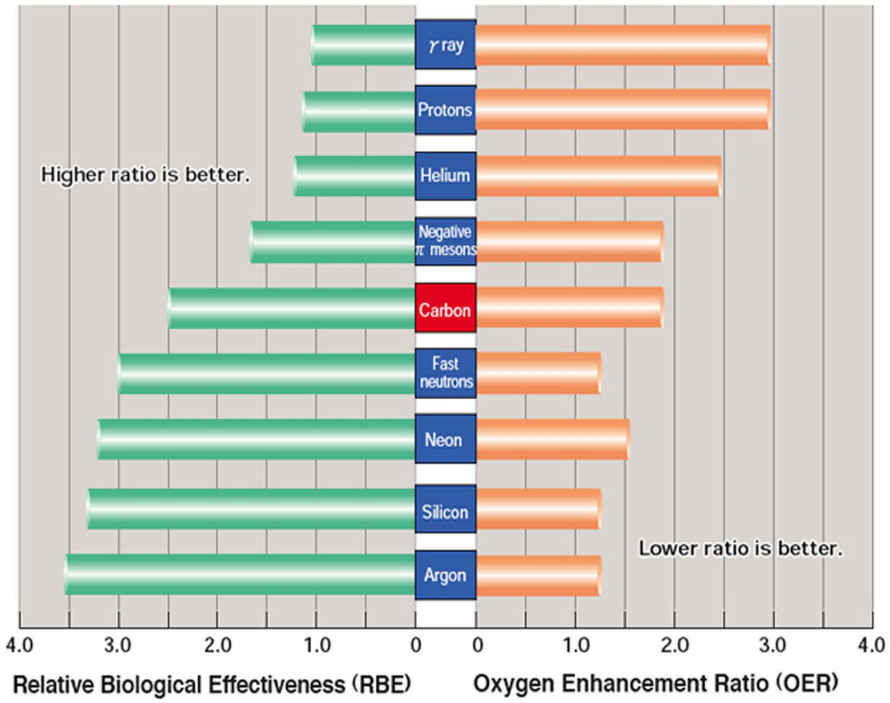


(From Barendsen GW. *Proceedings of the Conference on Particle Accelerators in Radiation Therapy*; LA-5160-C. Washington, DC: U.S. Atomic Energy Commission, Technical Information Center; 1972.)

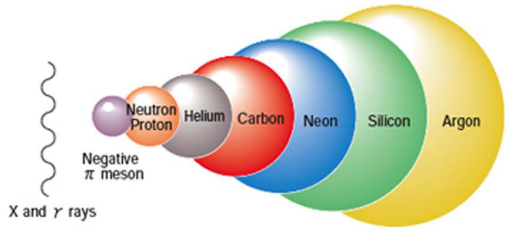
Variation of the oxygen enhancement ratio (OER) and the relative biological effectiveness (RBE) as a function of the LET of the radiation involved. The data were obtained by using T1 kidney cells of human origin, irradiated with various naturally occurring α-particles or with deuterons accelerated in the Hammersmith cyclotron. Note that the rapid increase of RBE and the rapid fall of OER occur at about the same LET, 100 keV/μm.

Types of high LET radiations that have been used in the clinic - do they work, and if so, why?

(a) when choosing to use high LET radiation, the decision is usually based on either the "tight", depth-dose distributions that allow almost surgical precision in dose delivery, or because of the radiobiological advantages (less repair, age response and oxygen effect), or some combination of both



From: National Institute of Radiological Sciences, Japan 2003



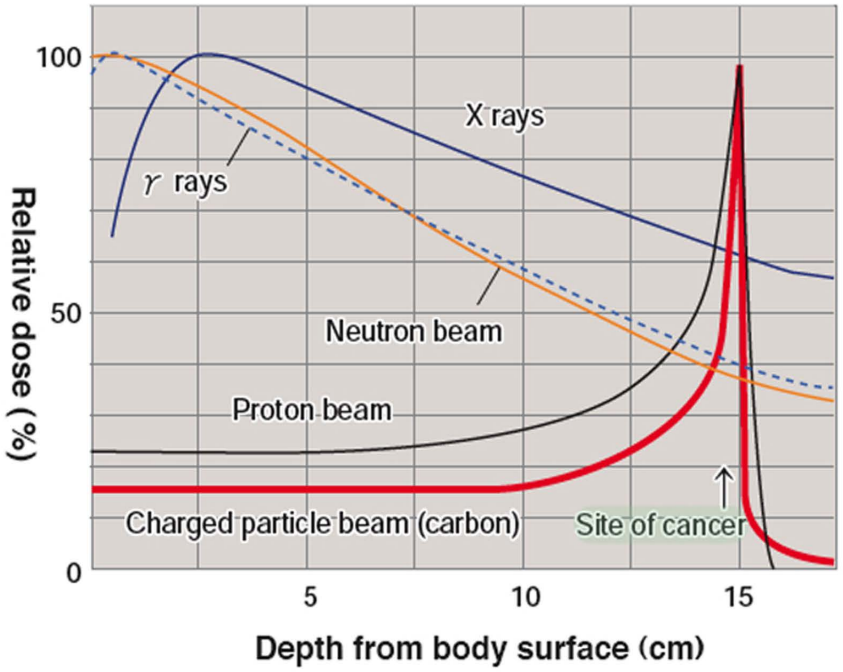
X and γ rays are forms of electromagnetic waves. Proton, fast neutron,and charged particle beams (carbon, neon, argon, etc.) are referred to as particle beams.

(b) *there are several types of high LET particles to choose from, but in practice, most are prohibitively expensive to use or else present serious radiation safety concerns, such that, in practice, the most feasible choices are neutrons, protons or (in Europe and Japan at least) carbon ions*

(c) *and what types of tumors are most likely to benefit from high LET therapy?*

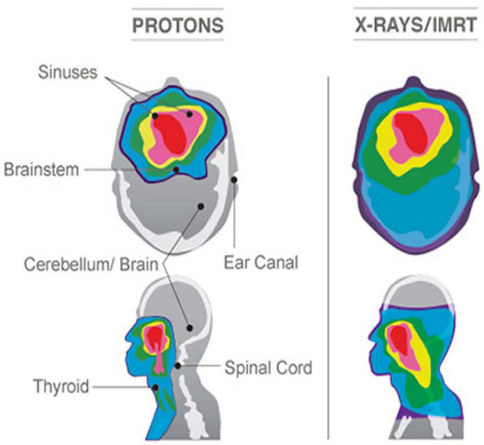
Answer: *slowly growing tumors like sarcomas, prostate cancer and salivary gland tumors, or a few other tumor types that tend to be located perilously close to critical normal structures and therefore require very precise treatment planning (choroidal melanoma of the eye, for example)*

Depth Dose Distribution for High and Low LET Radiations

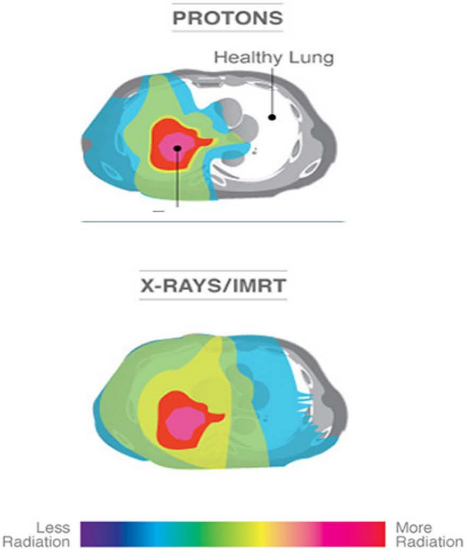


Examples of Treatment Plans for High LET beams

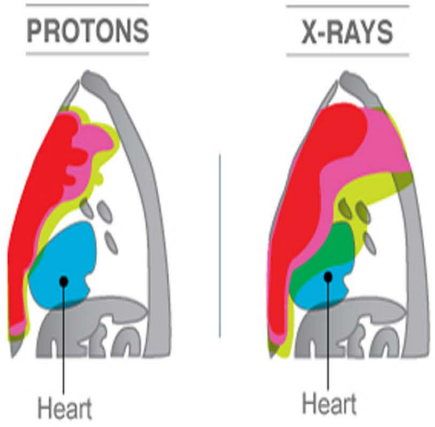
Nasopharynx

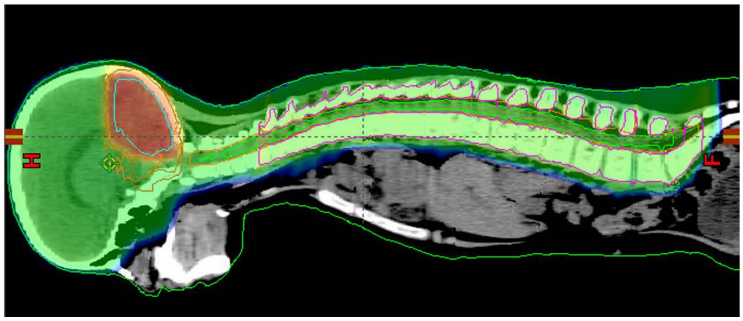


Lung



Breast





Craniospinal irradiation for pediatric cancer:

When using protons (or carbon ions), **there is NO exit dose**. *This is especially important when irradiating children whose tissues are still growing and therefore more radiosensitive, and who – if cured – would be expected to live a long time, so would hope to avoid complications.*

The Particles Summarized: Pros and Cons

neutrons: depth dose characteristics aren't much better than for conventional radiotherapy with x-rays or electrons, but neutrons do show a reduced OER and other biological advantages; in use today, particularly for salivary gland tumors and sarcomas, although radiation safety is a big issue

protons: these have biological properties similar to x- and γ-rays, but have excellent physical dose distributions, making this type of treatment particularly suitable for tumors that are perilously close to dose-limiting normal tissues (like the spinal cord or the retina, for example); in use today, and may be more popular in the future

heavy ions (such as accelerated carbon nuclei): were tried for radiotherapy in the past based both on perceived physics and biology advantages, but were found to be too expensive for too little improvement in tumor control; however, carbon ion beam therapy is making a mini-comeback these days in Japan, and at a couple of European sites

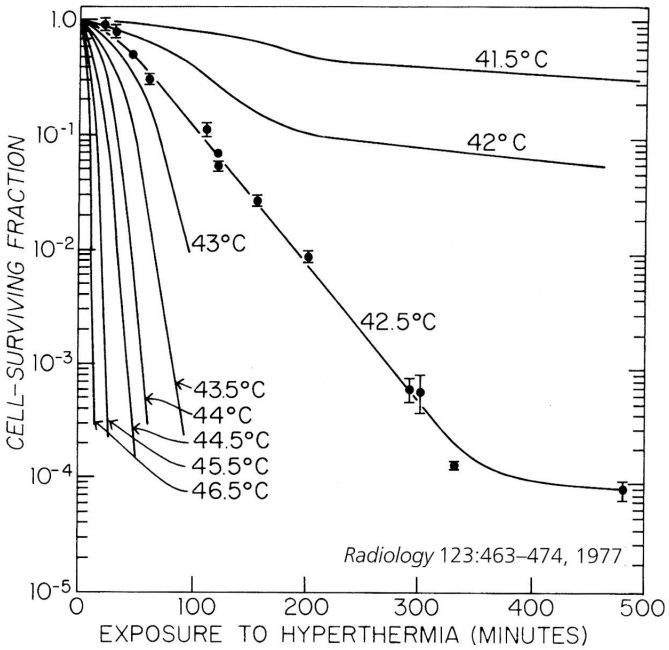
c. *Hyperthermia - a different type of electromagnetic radiation!*

1] the idea that heating a tumor might be useful in the treatment of cancer goes all the way back to antiquity, but interest in it has waxed and waned ever since due both to difficulties with thermal "dosimetry" and to erratic results in terms of tumor control and normal tissue complications

2] Hyperthermia Used Alone

(a) survival curves for heated cells and tissues are *qualitatively* similar to those for ionizing radiation (except that the dose axis is redrawn as "incubation time at a particular temperature")

1. the rate of cell killing by heat depends strongly on both the treatment temperature and duration



At higher temperatures (43°C/109°F and up), heat survival curves for rodent cells, look similar to medium-to-high LET radiation survival curves.

At the lower temperatures however (about 39-42.5°C/102-108°F), heat survival curves "flatten out" after several hours of heating, meaning that the cells have adapted to the elevated temperature and are no longer killed. This acquired resistance to heat is called *thermotolerance*.

The phenomenon of thermotolerance explains why hyperthermia is not used alone for cancer therapy, i.e., that after a few heating sessions, it loses effectiveness almost completely.

3] Hyperthermia Combined wth Radiation and/or Chemotherapy

(a) *adding one or a few hyperthermia treatments to ongoing radiation therapy makes more clinical sense, because the heat can interact favorably with the radiation*; **usually, the best improvement in outcome occurs when the two modalities are given simultaneously (or nearly so, i.e., one right after the other)**

(b) *hyperthermia combined with chemotherapy is also used sometimes*

2) **Chemical Modifiers** - the addition (or subtraction) of drugs capable of modifying the radiosensitivity of cells, preferably in a differential way, i.e., by targeting either normal tissue cells or tumor cells, but not both

a. what is the ultimate goal of adding a "chemical modifier" to radiation therapy?

Answer: *to overcome the resistance of a subset of tumor cells whose presence is thought to make or break the ability of radiation to cure a tumor while remaining within the limits of normal tissue tolerance*

b. which types of cells in tumors are thought to be especially radioresistant?

- cells that are inherently resistant to radiation (such as, those with broad survival curve shoulders, shallow survival curve slopes, etc., like melanoma and possibly, glioblastoma, for example)
- cells that proliferate rapidly during treatment, and therefore can "negate" some of killing effect of radiotherapy (characteristic of some types of tumors, such as head and neck, and cervical carcinoma, but not others, like prostate cancer)
- hypoxic cells, those that are quite low in oxygen at the time of irradiation, although not so low as to kill them outright from sustained "nutrient deprivation" (many tumors types, although variable on a case-by-case basis)

c. ***Radiosensitizers - drugs that enhance radiation's toxicity***

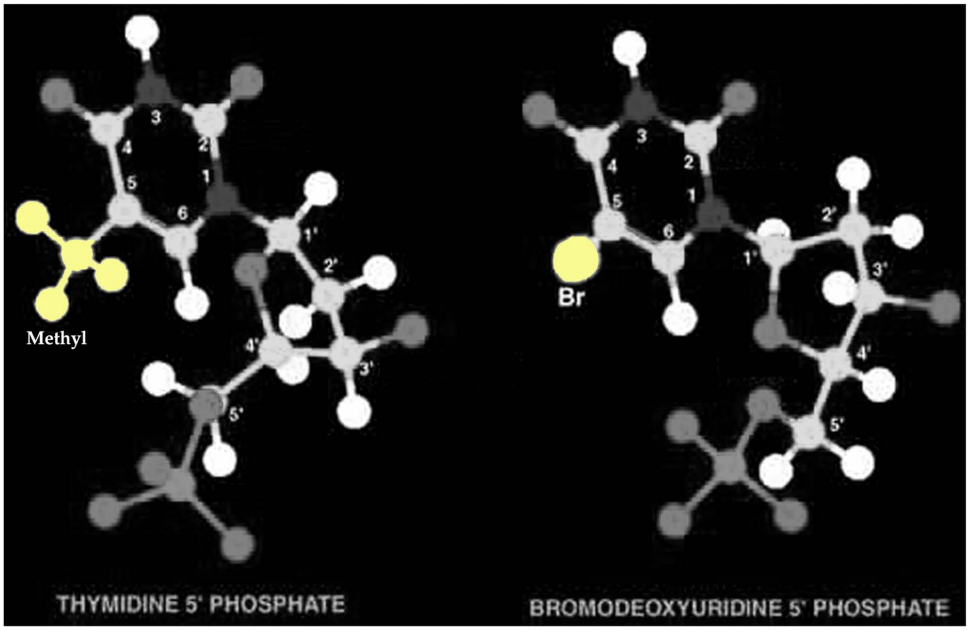
1] different classes of drugs are classified as radiation sensitizers

a. some drugs are both toxins *and* radiosensitizers, whereas other drugs are only radiosensitizers, and have little or no toxicity on their own

b. similarly, some drugs work as radiosensitizers at the level of free radical interactions (i.e., "fixing" radiation damage), and others behave after the fact by interfering with the ability of cells to recognize or repair the damage caused by radiation

2] **Radiosensitizers of Rapidly Proliferating and Resistant Cells**

(a) a class of drugs known as ***halogenated pyrimidines***, including ***bromodeoxyuridine (BUdR)*** and ***iododeoxyuridine (IUdR)***, have unique chemical structures such that they trick the cell into thinking they're DNA bases (usually, the "T" or thymidine) and end up being incorporated into cellular DNA

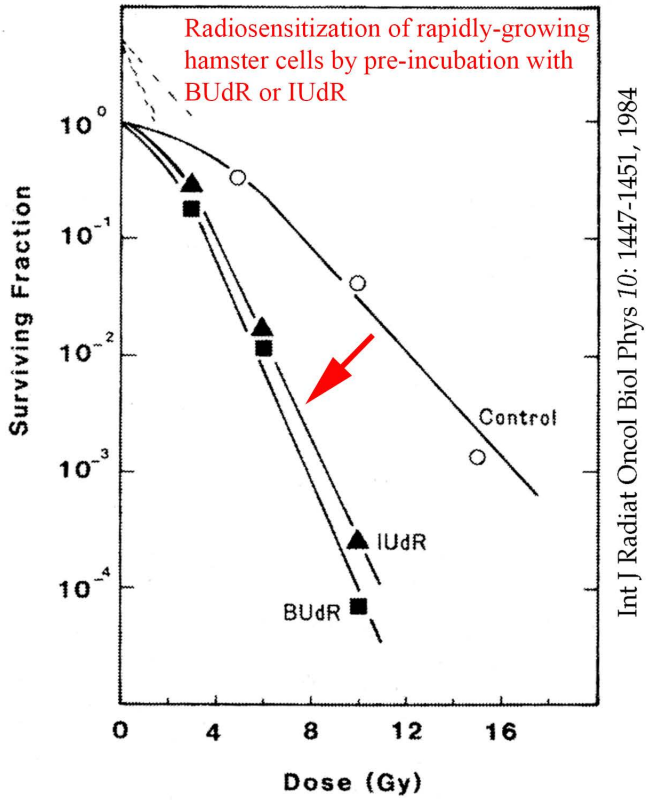


The structures of thymidine (left) and bromodeoxyuridine (right) are very similar.

No wonder the cell gets confused!

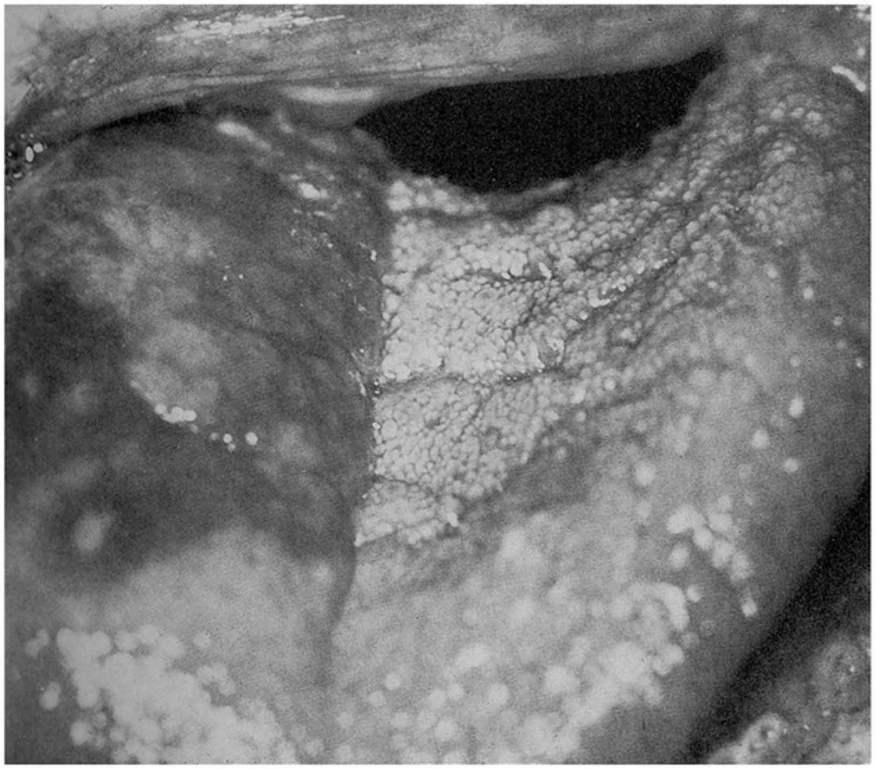
1. because of this, any cell that actively goes through S phase in the presence of BUdR (or IUdR) with have the drug inserted into their DNA in place of thymidine; therefore, ***incorporation of the drug only occurs in rapidly proliferating cells...ANY rapidly proliferating cell, normal or tumor***

2. and, as luck would have it, ***the presence of BUdR or IUdR in DNA "destabilizes" it, such that it becomes more susceptible to radiation damage and can't be repaired as well – this causes the cells that take it up to be radiosensitized, increasingly so the greater the amount of drug present in the DNA***



In retrospect, trying BUdR in patients with head and neck cancer was probably a poor choice, because there was too much rapidly proliferating normal tissue in the treatment field (oral mucosa), and it became radiosensitized as well as the tumor.

Brain tumors would have been a much better choice, because there, the tumor is proliferating, but presumably, nothing else is.

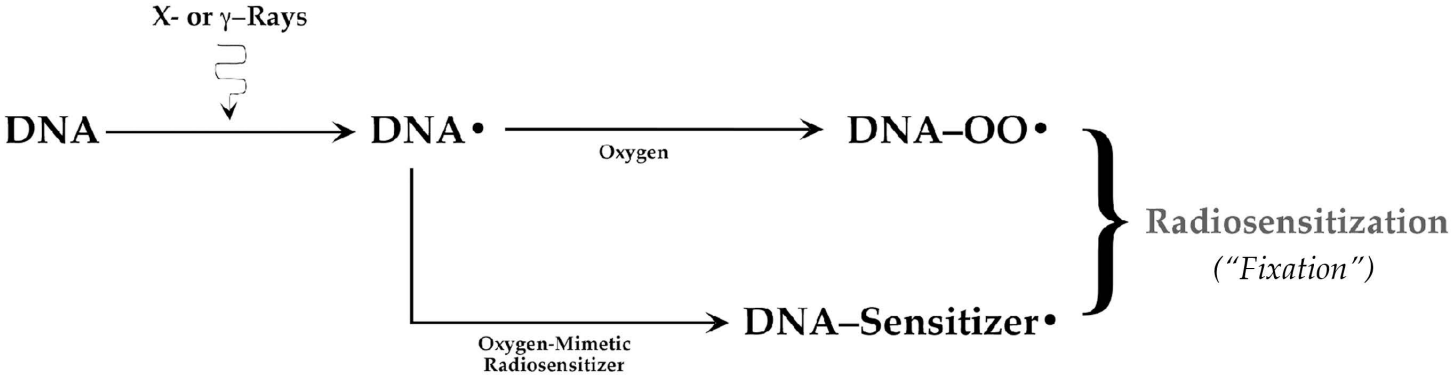


Photograph of the tongue of a patient at Stanford who received a BrdU infusion in the right carotid artery plus radiotherapy to the entire oral cavity. Note the vigorous mucositis on the right side only (left side of photograph). Courtesy of M. A. Bagshaw and R. L. S. Doggett.

Phillips, Radiation Research *158*: 389-417, 2002

(b) because BUdR needs time to get into the DNA of proliferating cells in order to work as a radiosensitizer, **the drug must be given to the patient as a continuous infusion for at least 24 hours prior to irradiation**

3] **Radiosensitizers of Hypoxic Cells** - these drugs mimic oxygen in its ability to "fix" free radical damage in the few milliseconds during and after irradiation



(a) *without question, the best hypoxic cell radiosensitizer there is is OXYGEN* (even if cells are kept at 1% oxygen – compared to room air at about 20% – they are fully radiosensitive; they don't start becoming radioresistant until the oxygen concentration falls below about 0.5 %)

(b) History of the Oxygen Effect: How long have we known or suspected that oxygen was a radiation sensitizer?

1] it has been recognized for over 120 years that *something* related to cutting off tissue blood flow during irradiation led to increased radioresistance

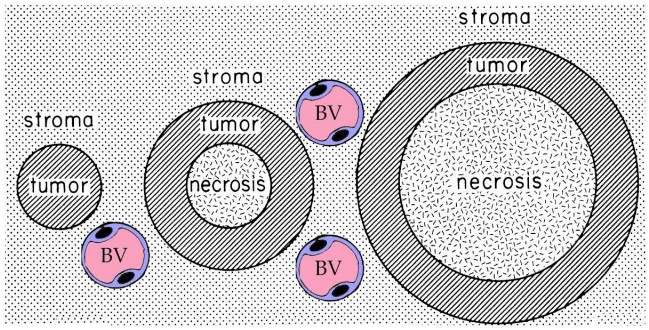
... it was much later however that the "something" was identified as (lack of) oxygen

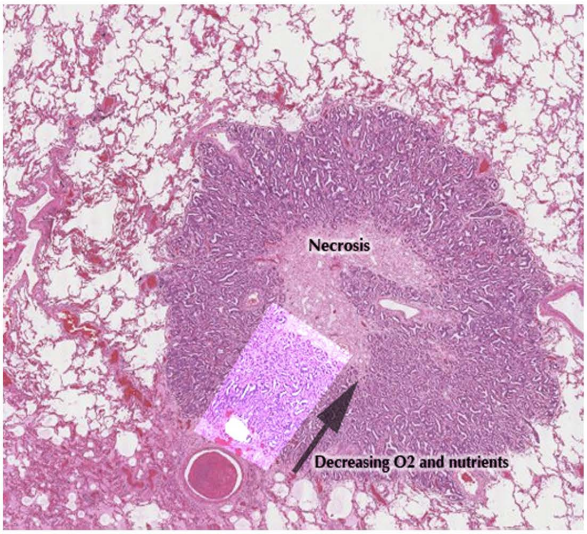
1. however, it wasn't until the 1950's and 1960's that the radiation oncology community sat up and took notice of the fact that hypoxia in human tumors might be a cause of treatment failure

a} an important paper by Thomlinson and Gray in 1955 became one of the most influential papers in the history of radiotherapy, because it offered up an explanation for why hypoxia might develop in tumors

(1) they studied biopsy specimens from bronchial carcinomas, and made the following observations:

Chronic Hypoxia

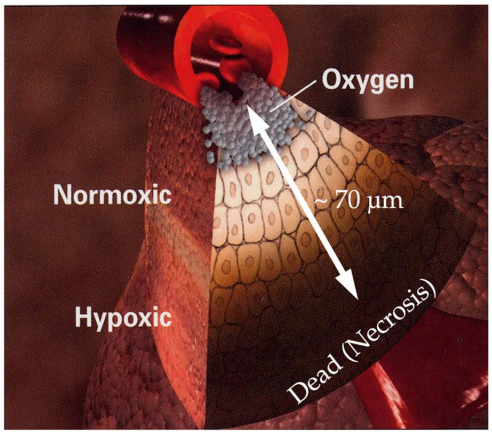




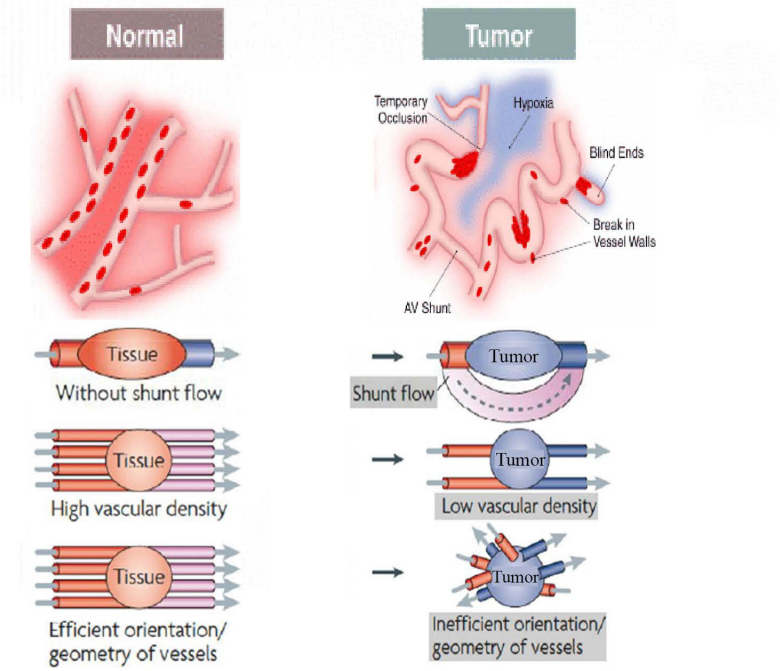
Thomlinson and Gray's histological studies showed that, no matter how big in diameter a tumor cord became, it was the region of necrosis that grew in size, NOT the tumor's apparently viable rim, which was much closer to blood vessels (BV). The viable rim of cells was around 100 µm in thickness, and if the entire tumor cord was that diameter or less, it had no region of necrosis at all.

Their observations are consistent with ***the model of diffusion-limited or chronic hypoxia*** (right figure). **This model proposes that the diffusion distance of oxygen out of nearby blood vessels is only about 70 µm before it is totally used up by intervening cells. Beyond that distance, cells first become hypoxic, then anoxic and then they die by necrosis.**

The hypoxic cells are still viable however, but are also radioresistant



Acute Hypoxia



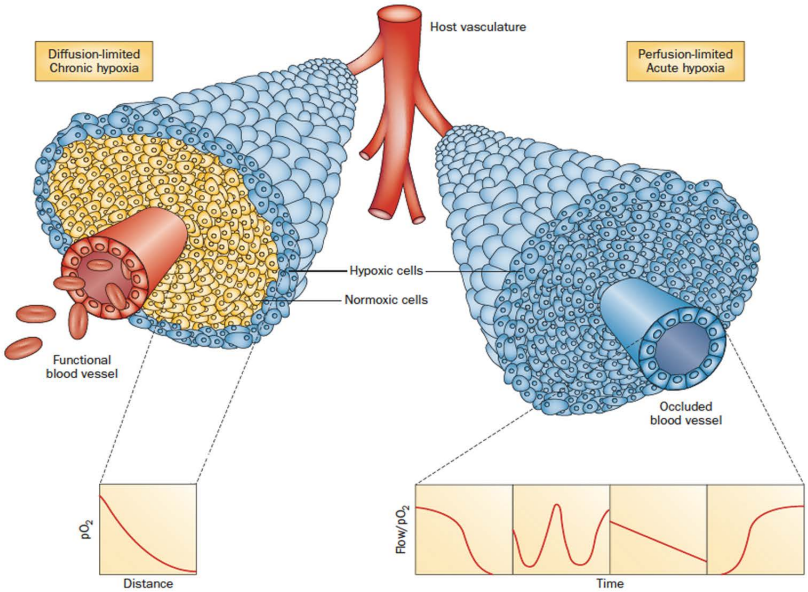
There is a second type of hypoxia however, that is a consequence of the abnormal blood vessels characteristic of most types of tumors.

Because of these abnormalities, ***blood flow through the vessel can be slowed, stopped or shunted elsewhere. When this happens, the cells close to that vessel become hypoxic acutely, due to perfusion-limited hypoxia.***

Then, ***often within minutes, these blood vessels will open again and the tumor cells will become reoxygenated.***

It would be unfortunate to be receiving one's daily dose of radiation during a time when many of the tumor's blood vessels are transiently closed.

The Two Types of Hypoxia Compared



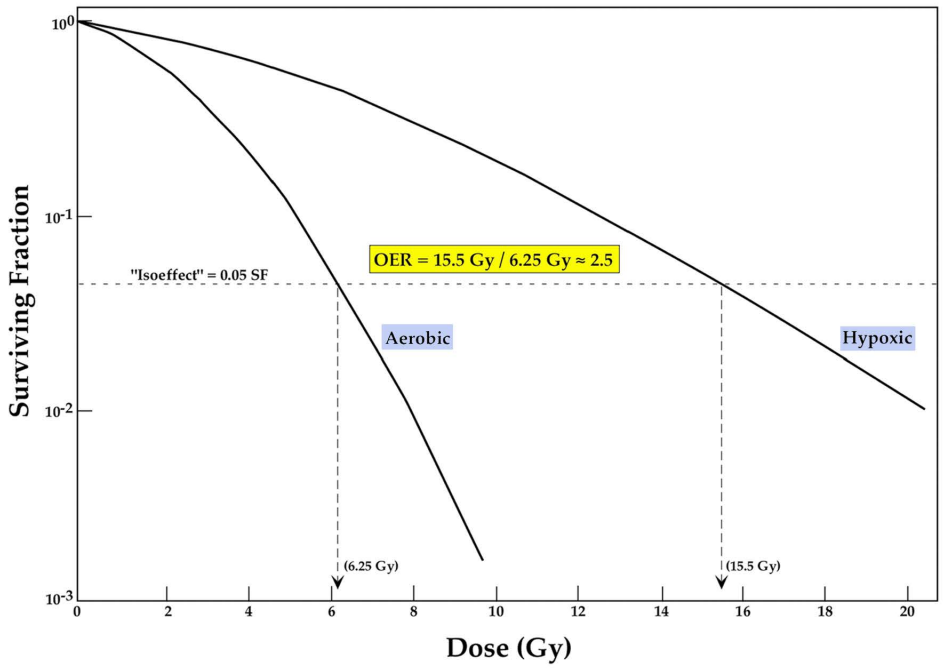
| Illustration of tumour cells growing as a cord around blood vessels from which they obtain oxygen and nutrients. The left side shows that, as oxygen diffuses from the vessels, it is used by the 'normoxic' (not radiobiologically hypoxic, but often still hypoxic to a certain degree) tumour cells, which results in a decrease in oxygen partial pressure (pO_2) as shown in the insert. This decrease in oxygen pressure eventually triggers the development of chronically hypoxic cells at the edge of the cord.

Schematic representation of diffusion-limited chronic *hypoxia and perfusion-limited* acute *hypoxia within tumour cords.*

2. Just how radioresistant are hypoxic cells?

a. the extent or degree of radiation resistance of hypoxic cells is quantified using a radiobiological parameter called the ***Oxygen Enhancement Ratio or OER***

$$OER = \frac{\text{Dose of Radiation Under Hypoxic Conditions}}{\text{Dose of Radiation Under Aerobic Conditions}} \text{ to achieve the same biological effect}$$



The oxygen enhancement ratio is a ratio of **doses** to yield the same effect, NOT a ratio of surviving fractions! For mammalian cells, the OER ranges between 1.0 and about 3.0 for exposure to ionizing radiation; it is a unit-less number.

3. Do human tumors contain hypoxic cells, and if so, which kind?

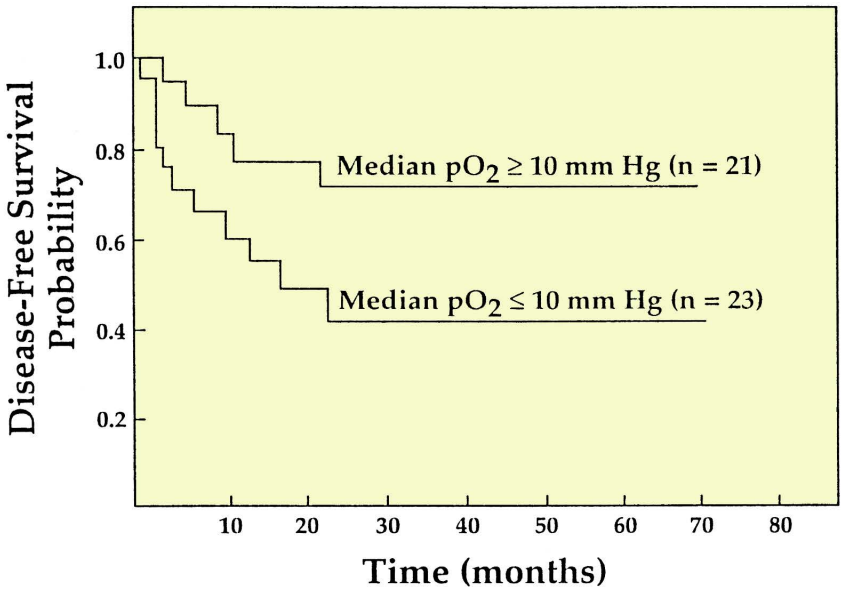
Answer: Human tumors do contain metabolically-active, presumably-clonogenic hypoxic cells, many of which seem to be chronically hypoxic. This doesn't eliminate the possibility that there are acutely hypoxic cells too however...it's just that these are harder to measure.

On average, human tumors contain 15-20% hypoxic cells (similar to rodent tumors), although there is a lot of variability from tumor type to tumor type, between tumors of the same type, and even within different regions of the same tumor.

One thing we still don't know is whether tumor hypoxia *really* exerts an influence on radiotherapy outcome, i.e., what if those hypoxic tumor cells weren't clonogenic, or what if they became reoxygenated during and regained their sensitivity to radiation?

We do have lots of (mostly-indirect) evidence that they are important though, at least for some types of tumors:

- Success of a few clinical trials in which women with cervical cancer breathed hyperbaric oxygen during each radiotherapy treatment; didn't work for most other tumor sites however.
- Association between patient anemia and poor radiotherapy outcome, with this trend partially reversed if patients received blood transfusions before and during radiotherapy.
- Success of a few clinical trials (emphasis on "a few") where patients received hypoxic cell radiosensitizers immediately prior to each dose fraction.



Direct evidence of the influence of hypoxia on radiotherapy outcome.

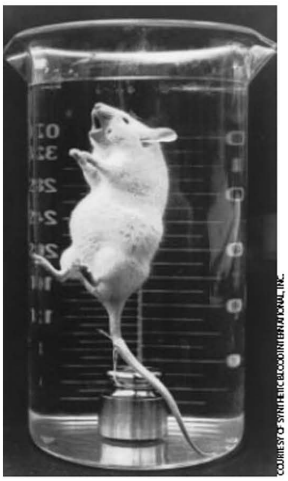
Cervical cancer patients whose tumors were low in oxygen as measured by an oxygen electrode* did worse in terms of disease-free survival than patients with tumors that were higher in oxygen.
(From Gatenby et al., 1988.)

*An oxygen electrode is to oxygen as a pH meter is to pH. The ultra-thin, glass oxygen electrode is inserted into the tumor repeatedly (in different locations) and measurements of the concentration of oxygen are made as the electrode is gradually pushed in and pulled out.

No fun for the patient.

(c) If oxygen is the best hypoxic cell radiosensitizer there is, why isn't *it* used, as opposed to other types of synthetic compounds?

1. it has been tried repeatedly (hyperbaric oxygen breathing, use of artificial blood substitutes that carry more oxygen than hemoglobin, etc.), but has only been successful at improving radiotherapy outcome in very few cases; the main reason for this is that ***administering extra oxygen is never going to work if: (a) the tumor blood vessels are closed at the time of irradiation (acute hypoxia): or (b) if the extra oxygen is consumed by the already well-aerated tumor cells close to vessels and never reaches the hypoxic ones (chronic hypoxia)***



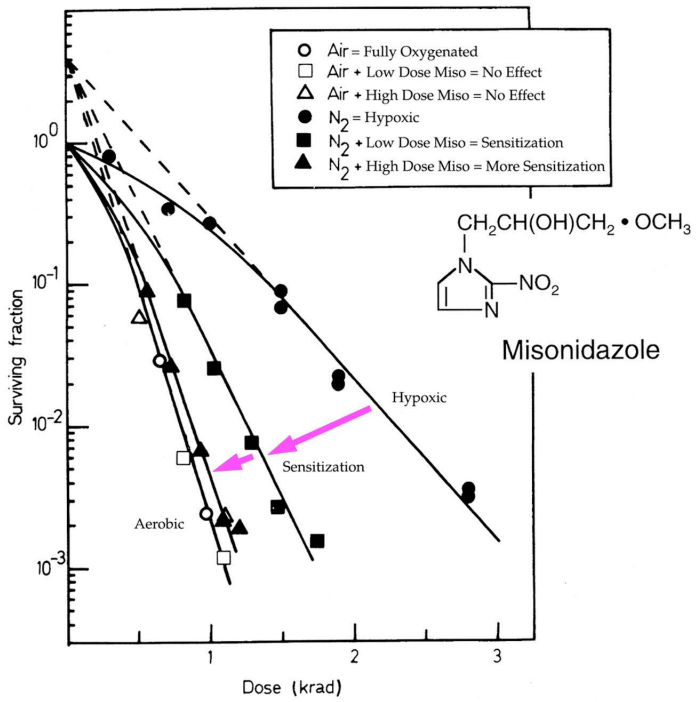
Fluosol-DA®, an artificial blood substitute originally invented for people whose religious beliefs preclude the acceptance of a blood transfusion, carries so much more oxygen than hemoglobin that it can literally be "breathed"...by a mouse in this case. Not really recommended however!

Pop culture reference: The movie "The Abyss".

Fluosol never did work very well as an injectable radiosensitizer however, plus, with repeated use, it sometimes caused liver damage.

(d) *Oxygen-Mimetic Hypoxic Cell Radiosensitizers*: these were thought to represent a reasonable trade-off when oxygen itself couldn't be used, or wouldn't work, as a radiosensitizer

1. ***although hypoxic cell radiosensitizers are not as good as oxygen at "fixing" the free radical damage caused by radiation, they do have an advantage because they are NOT used by the cell for other purposes like oxygen is (i.e., for energy generation and metabolism)...meaning that these drugs <u>can</u> diffuse deeper into tissue and reach the hypoxic cells***



Survival data for aerated and hypoxic Chinese hamster cells x-irradiated in the presence of various concentrations of misonidazole (Ro-07-0582). At a concentration of 10 mM of this drug the radiosensitivity of hypoxic cells approaches that of aerated cells. The response of aerated cells is not affected by the drug at all. (From Adams GE, Flockhart IR, Smithen CE, Stratford IJ, Wardman P, Watts ME: Radiat Res 67:9–20, 1976.)

Many of the hypoxic cell radiosensitizing drugs come from a chemical class called nitroimidazoles. Drugs of this type that act as radiosensitizers include: metronidazole, misonidazole (shown), etanidazole, pimonidazole and nimorazole.

Although they worked well in cells and experimental animals, these drugs did not pan out as good radiosensitizers in the clinic, so are not really used anymore (except for nimorazole, used in Europe).

The problem with the nitro-imidazoles was not so much that they didn't work, but rather that they caused intolerable side effects in patients (peripheral neuropathy) that severely limited the dose of drug that could be used.

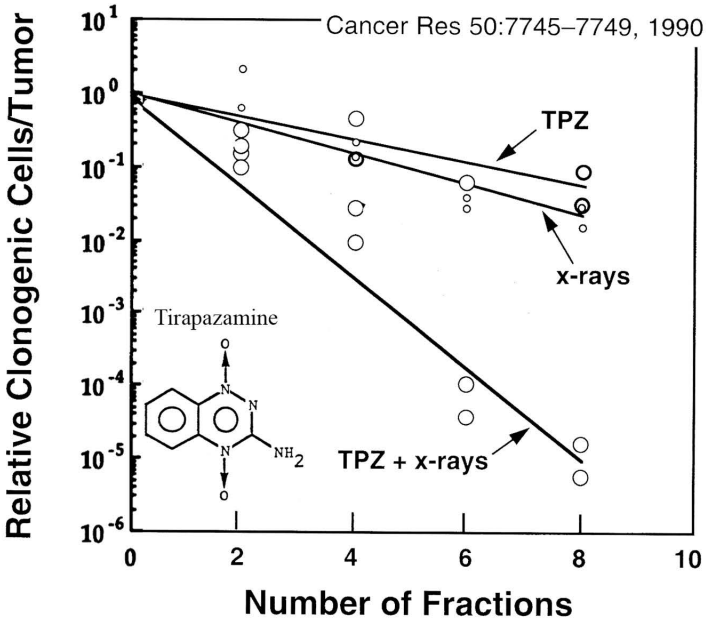
Sigh - oh well.

(e) *Bioreductive Drugs* - radiosensitizers, in that they *do* make tumors more sensitive to radiation overall, however their mechanism of action is different, plus, they're also toxic by themselves (which the nitroimidazoles and halogenated pyrimidines are not)

1. ***bioreductive drugs are different in that they don't mimic oxygen's free radical reactions...instead, they are simply toxic to hypoxic cells and kill them on contact***

a) because hypoxic cells are the ones resistant to radiation, killing them outright will make the tumor as a whole more radiosensitive, i.e., only aerated cells will be left, and they're more sensitive to radiation

b) meanwhile, bioreductive drugs don't affect already well-aerated cells at all, so the therapeutic ratio should improve (in theory)



Response of SCCVII mouse carcinomas to tirapazamine (TPZ) alone, radiation alone, or a combination of both. The radiation or drug treatment was given every 12 hours for up to eight fractions and the mice sacrificed for clonogenic cell survival 12 hours after the last dose.

One drug of this class that was the subject of several clinical trials (mostly in patients with advanced head and neck cancers) is called **Tirapazamine (TPZ)**.

Shown here is an example of multifraction survival curves for mouse tumors in which TPZ plus radiation was compared to X-rays alone and TPZ alone. The particular mouse tumor type was called SCCVII, which was selected because it was known to have a high hypoxic fraction.

The combination of drug and radiation showed superior results to either treatment alone.

Like the nitroimidazoles though, TPZ worked much better in cells and mice than in human tumors. <Sigh>

f) Traditional Chemotherapy Agents and Targeted Therapies

The Good News: Many of these are also radiosensitizers because, when combined with radiation, the effect is greater than expected based on the toxicities of either agent alone

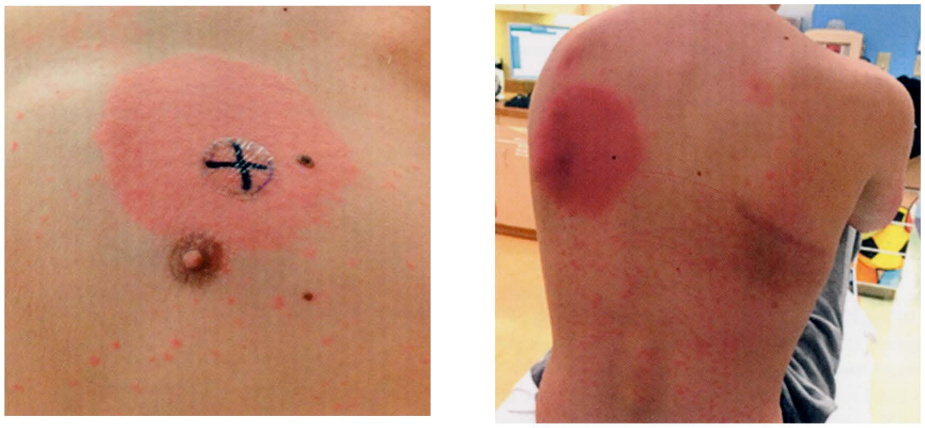
The Bad News: Normal tissue toxicity can also be greater, with certain tissues more affected than others; further, the types of complications in these tissues are sometimes unexpected (and different) compared to those produced by radiation or drugs alone

Summary of the clinical data regarding the toxicity of concomitant chemoradiation

	Early effects	Late effects
Antimetabolites		
5-Fluorouracil	+ (GI, skin)	?
Methotrexate	+ (GI)	?
Hydroxyurea	+ (GI)	?
Gemcitabine	+ (GI)	± (lung)
Fludarabine	+ (GI)	± (CNS)
Plant derivatives		
Vinca alkaloids	− (GI, BM)	?
Etoposide	?	?
Taxanes	+ (GI)	?
Antibiotics		
Doxorubicin	+ (GI, skin)	+ (heart, lung)
Mitomycin-C	+ (GI, BM)	+ (lung)
Bleomycin	+ (GI, skin)	+ (skin, lung)
Actinomycin-D	+ (GI, BM, skin)	+ (lung)
Alkylating agents		
Cisplatin	+ (GI)	+ (kidney)
BCNU	+ (GI)	+ (lung)
Cyclophosphamide	+ (GI, skin)	+ (lung, bladder, CNS)

BCNU, β-chloro-nitrosourea; BM, bone marrow; CNS, central nervous system; GI, gastrointestinal.
−, Not demonstrated; +, demonstrated; ±, conflicting data; ?, unknown.

Joiner and van der Kogel, *Basic Clinical Radiobiology, 4th Edition*, 2009



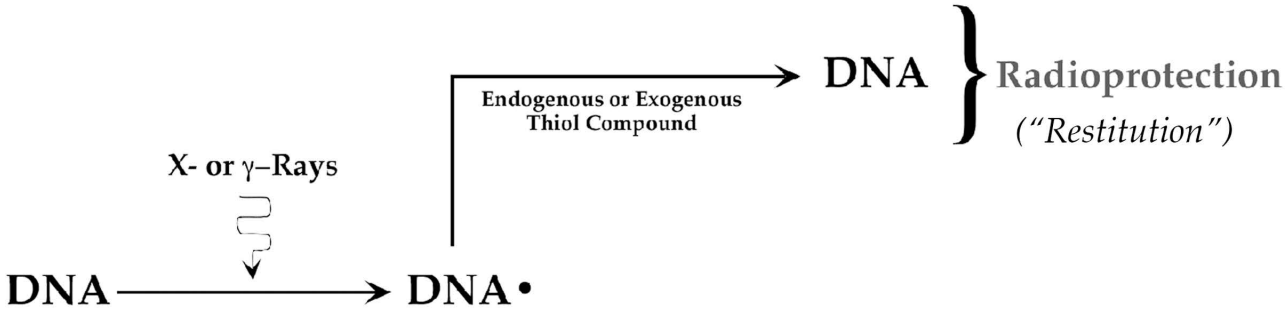
Enhanced Skin Reaction with Palliative Thoracic Radiotherapy and Sorafenib. A 15-year-old male with a 2-year history of multiply recurrent metastatic extremity osteosarcoma, initially diagnosed at age 13, presented with a left upper-lobe metastasis resulting in airway compression of the left hilum while on ifosfamide. He had a known germline retinoblastoma mutation with a history of bilateral retinoblastoma treated with intraocular chemotherapy, cryotherapy, and enucleation in infancy Given his multiple prior thoracotomies and extent of disease, he was deemed to be a suboptimal candidate for surgical resection.

As a radiation therapist or medical dosimetrist, you need to be aware whether your patients are receiving concurrent chemotherapy with their radiotherapy, and if so, which normal tissues might be at elevated risk of complications when the two treatments are combined. If such an enhancement of toxicity is already known or suspected, chances are that the total radiation dose has been reduced somewhat to compensate for the greater effectiveness of the drug-radiation combination.

5] **Normal Tissue Radioprotectors** - an alternate approach to dealing with the tumor hypoxia problem

(a) *a different approach to dealing with the radioresistance of hypoxic cells is to make the normal tissues equally as resistant (or as close as possible), thus allowing higher total doses to be given; this should result in a higher probability of tumor cure with little or no increase in the risk of normal tissue complications*

(b) taking the cue from the natural radioprotective compounds found in cells – such as glutathione – that detoxify free radicals and "repair" chemical damage, new drugs of similar structure were developed

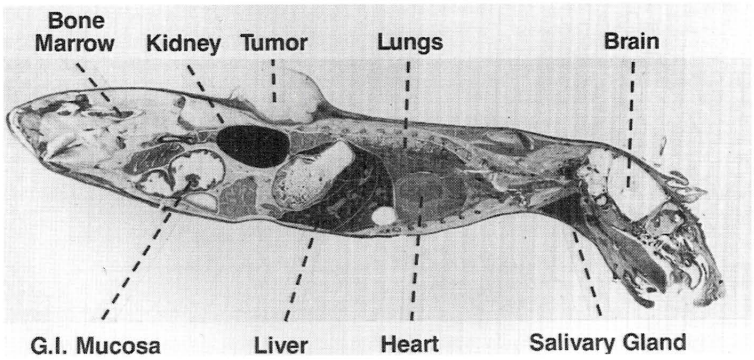


Summary of Normal-Tissue Responsiveness to Protection by WR-2721

Tissues Protected[a]	Tissues not Protected
Bone marrow (2.4–3)	Brain
Immune system (1.8–3.4)	Spinal cord
Skin (2–2.4)	
Small intestine (1.8–2)	
Colon (1.8)	
Lung (1.2–1.8)	
Esophagus (1.4)	
Kidney (1.5)	
Liver (2.7)	
Salivary gland (2.0)	
Oral mucosa (>1)	
Testes (2.1)	

[a]Numbers in parentheses are the dose reduction factors or factor increases in resistance associated with WR-2721 injection.

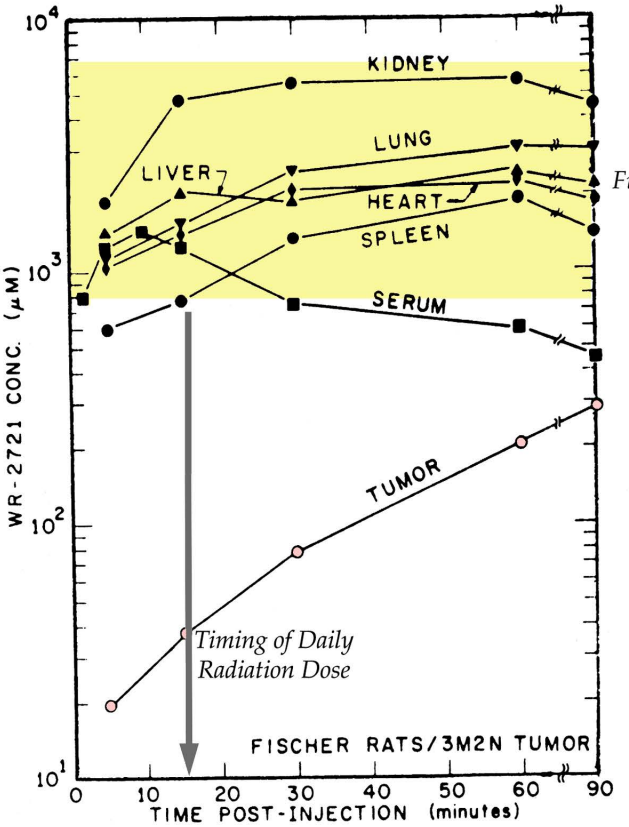
From Yuhas JM, Spellman JM, Culo F: The role of WR2721 in radiotherapy and/or chemotherapy. In Brady L (ed): Radiation Sensitizers, pp 303–308. New York, Masson, 1980



Autoradiograph of a mouse showing the distribution of amifostine, labeled with radioactive sulfur-35 at 6 minutes after intravenous injection. The greatest densities are seen in the kidney, liver, intestinal mucosa, and submandibular salivary gland. The brain shows little drug concentration because amifostine is hydrophilic and does not cross the blood–brain barrier. The drug has also not concentrated in the tumor (a transplanted EMT6). (From Utley JF, Marlowe C, Waddell WJ: Distribution of 35S-labeled WR-2721 in normal and malignant tissues of the mouse. Radiat Res 68:284–291, 1976.)

Amifostine has been shown to protect (by as much as a factor of three, above) a variety of normal tissues against radiation damage in both rodents and humans...although not all of them. The central nervous system is not protected, for example. Bummer!

None of this improvement in the therapeutic ratio would occur if amifostine diffused into tumors as quickly as it does into normal tissues following intravenous injection, i.e., that tumors would then be protected just as much. Luckily, this is NOT the case (below).



Full Dose Range for Amifostine

Serum, tissue, and tumor concentration of the radioprotector amifostine (WR-2721) as a function of time after intraperitoneal administration of the drug (200 mg/kg). The radioprotector penetrates more slowly into the tumor than into many normal tissues, so that if the radiation dose is delivered soon after the administration of the drug, there is a differential protection of normal tissues.

Cancer Res 40:1519–1524, 1980

(d) Newer types of radioprotectors: don't literally protect against radiation damage, but rather ***mitigate*** the injury

1] these are drugs that do NOT work by free radical mechanisms nor do they actually increase the survival of irradiated cells, ***but instead, they interfere with the chain of events that begins with dead or dying cells, and that ultimately leads to a normal tissue complication***...a (very) complicated process that may take months or years after irradiation

2] one class of radiation mitigators being used clinically is **cytokines**

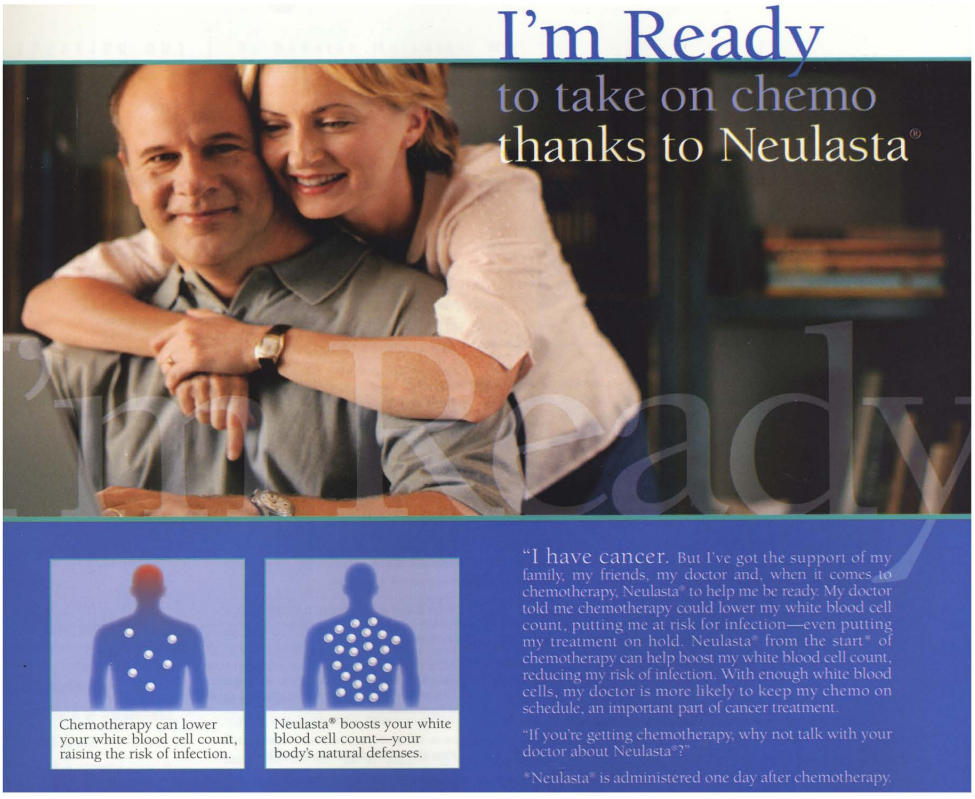
a. these act by increasing the rate of production of new cells, in an attempt to counteract the loss of cells killed by radiation or chemotherapy; this sometimes helps reduce or eliminate some normal tissue complications

b. examples:

1. **Palifermin** (discussed previously) = revs up the production of new epithelial cells in the hopes of reducing oral mucositis or skin desquamation

2. **Neulasta** = increases production of new white blood cells in the bone marrow, so that dropping blood counts cause less interference with the completion of radiation or, more commonly, chemotherapy

3. **Procrit** = similar to Neulasta, but instead of white blood cells, it increases production of new red blood cells, which in turn decreases treatment-induced anemia and fatigue



Please read the article attached at the back of this handout to see an example why the development of new protectors and mitigators of radiation injury to normal tissues could be so important to long-term cancer survivors (of which there are more and more with each passing year)

C. **The "4R's" of Radiotherapy** - clinical "shorthand" for remembering the important aspects of radiobiology that impact the success or failure of radiation therapy

1] historically, the Four R's of Radiotherapy include:

- **REPAIR**
- **REPOPULATION** or **REGENERATION**
- **REOXYGENATION**
- **REDISTRIBUTION** or **REASSORTMENT**

A fifth R was added later: **RADIOSENSITIVITY** (although this one is closedly related to repair)

2] which of the R's is the most important clinically?

(a) although it does vary depending on the exact clinical situation, **usually, Repair/Radiosensitivy is the most important determinant of treatment outcome, and Repopulation is second; and as for Redistribution/Reassortment (and related cell cycle effects),** this is known to occur, but seem to only play a minor role

(b) however, please note some fairly common exceptions:

1. for a *highly* hypoxic tumor, Reoxygenation (or lack thereof) is probably the most important
2. for a tumor *lacking* a hypoxic fraction, Reoxygenation doesn't matter
2. for a slowly-growing tumor (like prostate), Repopulation doesn't matter

3] is there a difference in the various R's for normal tissues versus for tumors, i.e., can the R's be exploited to help improve the therapeutic ratio?

(a) ***repair, repopulation and redistribution can happen for both tumors and normal tissues,*** and in general, there is NO systematic difference between the two...although there certainly can be individual differences from patient to patient

(b) ***reoxygenation, on the other hand, is tumor-specific,*** because normal tissues contain few if any hypoxic cells, and therefore are already well-aerated and don't need to be "reoxygenated"

REPAIR/RADIOSENSITIVITY

1] Which radiobiological processes are at play?

(a) "repair" can be assessed in a number of ways:

- Chemical "repair", i.e. free radical reactions
- DNA repair (the only real repair)
- Cellular "repair", i.e., sublethal damage recovery
- Tissue "repair", i.e., dose response curves, isoeffect curves

2] Which clinical parameters are influenced by radiobiological repair processes?

Short Answer: most of them

Long Answer:

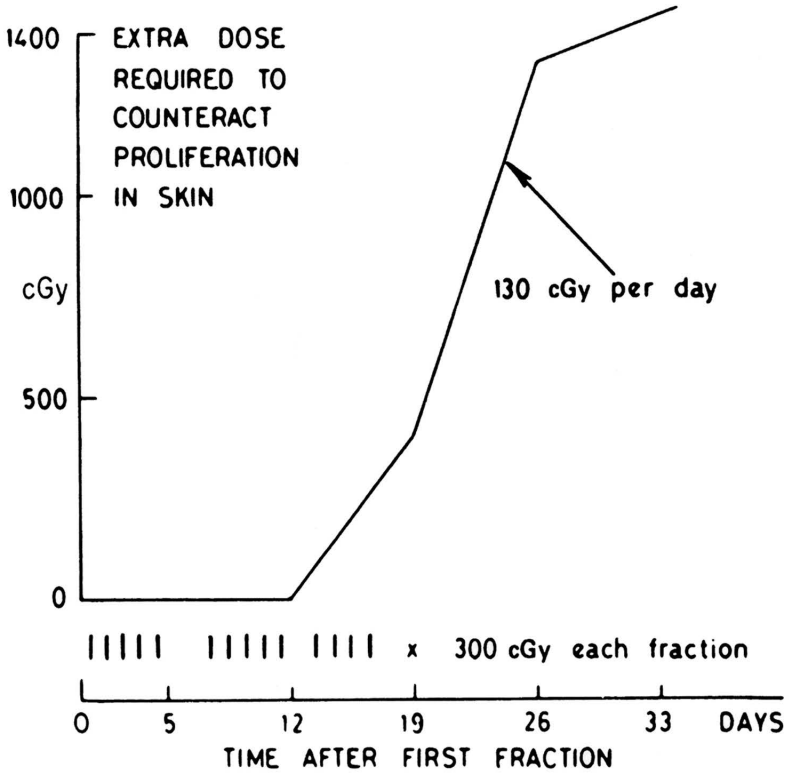
- shapes of dose response and isoeffect curves
- normal tissue tolerance doses and tumor control doses
- dose fractionation pattern and time between fractions (***usually, a minimum of 6 hrs***)
- whether to use a chemical modifier or not
- various aspects of treatment planning (e.g., to try to exclude sensitive normal tissues from the treatment field)

REPOPULATION (SOMETIMES CALLED "REGENERATION")

1] Which radiobiological processes are involved?

- how and when normal tissues and tumors "realize" that they are losing cells
- how quickly they then respond by increasing their production of new cells, if at all

2] examples of repopulation effects in normal tissues and tumors:

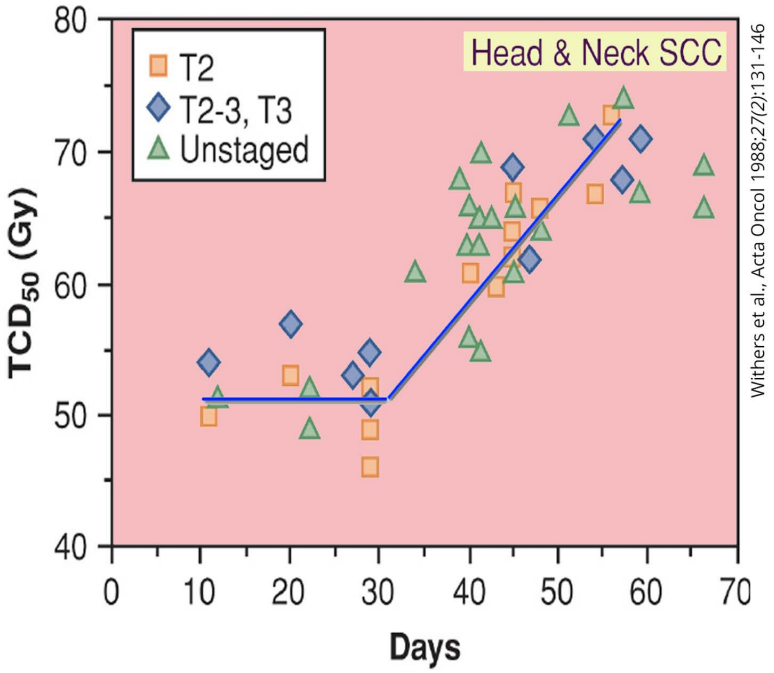


The repopulation response of mouse skin during fractionated radiotherapy, expressed as "amount of daily dose lost to proliferation". Note that repopulation starts *during* treatment.

In mouse skin, there is a delay of at least 2 weeks before the basal cells start revving-up new cell production in response to injury caused by daily radiation therapy. Once this revved-up proliferation begins however, it is very vigorous and can "negate" up to 130 cGy worth of radiation per dose fraction per day.

In humans, this "lag time" is usually a bit longer than in mice (3-4 weeks), but the vigor of the response is comparable.

When it comes to late-responding normal tissues however, they grow so slowly – if at all – that any effects of repopulation are delayed until *way* after the treatment is completed. Because of this, overall treatment time doesn't matter in the case of late effects.



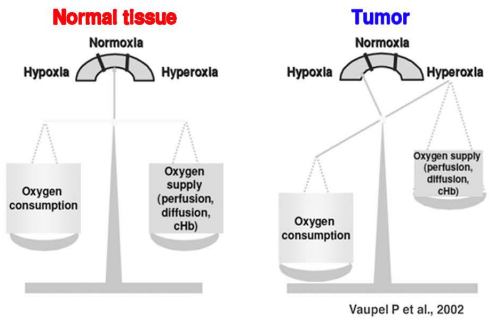
Human tumors also seem to show a delayed response before repopulation kicks in...about 4 weeks on average for head and neck tumors.

In this case, the proliferative response of head and neck tumors counteracts about 60 cGy of a typical 200 cGy dose per day.

3] Which clinical parameters are influenced by repopulation?

- overall treatment time (also, whether to schedule a gap during treatment)
- whether to intensify or "boost" during the last 2 weeks of treatment
- whether to add a chemical modifier that targets rapidly-growing cells (e.g., BUdR, or many traditional chemotherapy agents)

REOXYGENATION



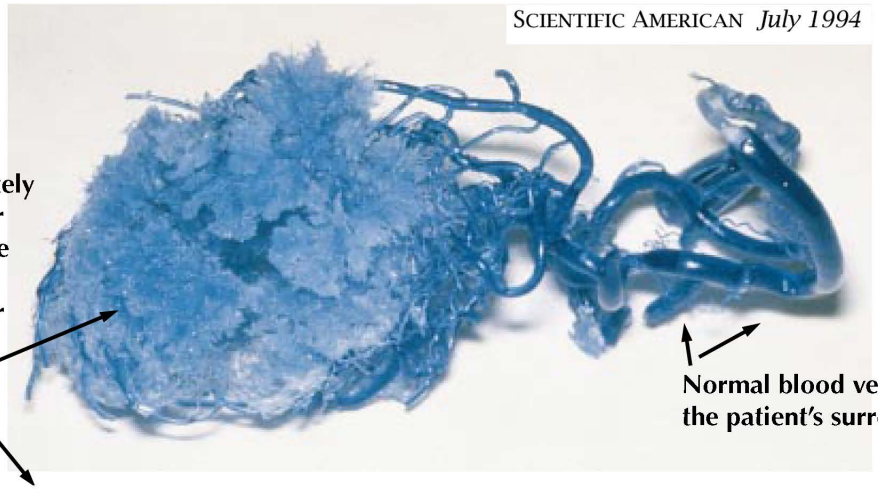
1] in order to understand how and why hypoxic cells in tumors get reoxygenated (and therefore much more radiosensitive), it is necessary to understand a bit more about tumor "physiology"

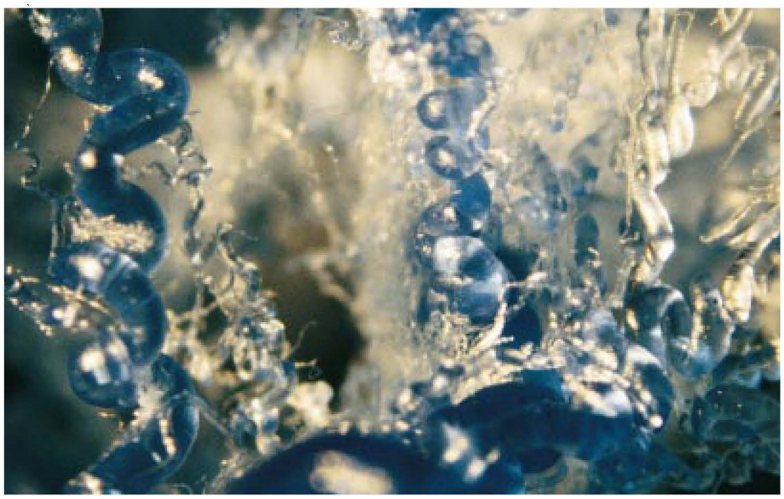
(a) first, just why are there hypoxic cells in tumors in the first place?

1. tumors contain hypoxic cells (and normal tissues don't) for two main reasons:

- ***tumor blood vessels tend to be very abnormal***: structurally, functionally, and "developmentally" (i.e., angiogensis - the process of making new blood vessels)

- because tumors continuously add new cells, and given the vascular abnormalities, ***they tend to outgrow and over-tax their own blood supply, and consume all the oxygen***





CAST OF BLOOD VESSELS in a half-pound human tumor is shown in two views. It was made by injecting a blue polymer into the vessels of a surgically excised colon cancer and then eliminating all tissue. The region resembling a crystal in the full cast (*left part of top image*) was formed by a chaotic cluster of microscopic vessels; the hole at the center of the region arose because the area lacked a blood supply. The close-up view (*bottom*) highlights one of many structural abnormalities of tumors: a number of the vessels are tortuous and twist into corkscrewlike coils that can contribute to a marked slowing of blood flow.

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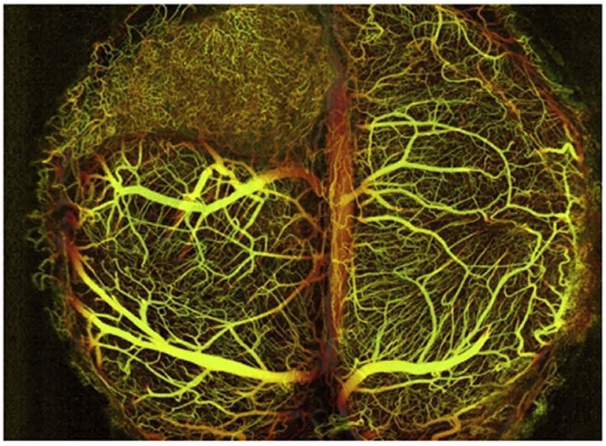
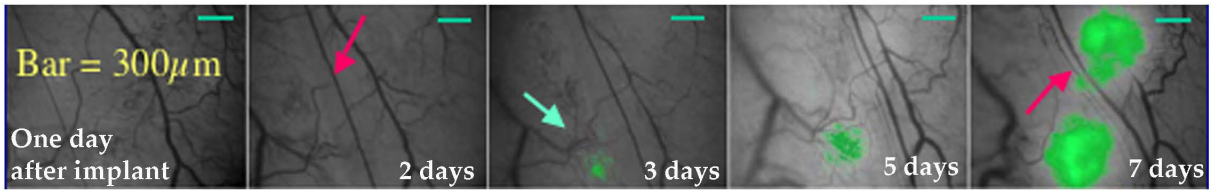


Vasculature of a brain tumor (upper left quadrant) and the surrounding brain of a mouse. The tumor vessels are abnormal, characterized by tortuousity and hyperpermeability.

(b) second, how big does a tumor have to be before it starts to develop hypoxia?

1. although the tumor shown in the example above is gigantic and would certainly be expected to contain hypoxic cells, *the reality is that even tiny tumors can contain (tiny) zones of hypoxia*



Mammary tumor cells implanted in the flank of a host mouse begin to grow into a solid tumor mass and already start to become hypoxic, even when they are no more than about 0.5 mm in diameter! (green staining indicates hypoxia).

2] Why, how, how much, and how fast do hypoxic tumor cells get reoxygenated?

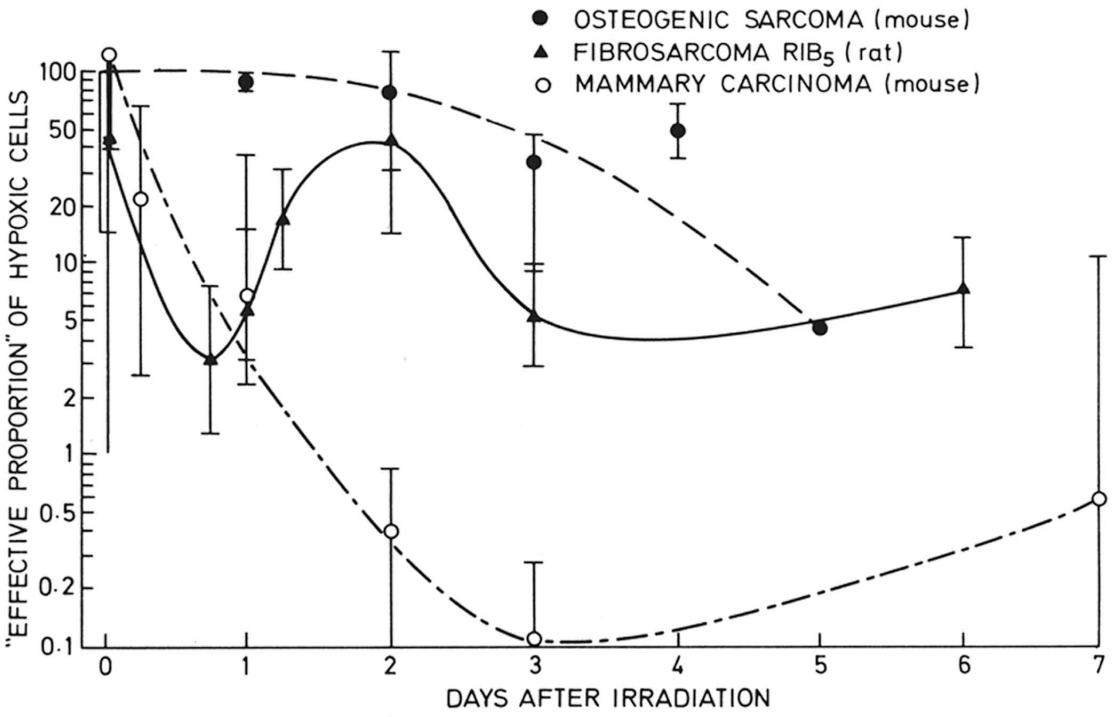
(a) ***for the acutely hypoxic cells, once the blocked or closed blood vessels reopen, the cells instantly get reoxygenated – this can take anywhere from minutes to a couple of hours in rodent tumors***

(b) ***for the chronically hypoxic cells***, there are two ways for them to become reoxygenated (assuming they haven't died in the interim):

1. ***well-aerated cells are killed by the radiotherapy , such that less oxygen is consumed and it can therefore diffuse further into the previously hypoxic regions***

2. ***many (but not all) tumors shrink once cells start to die in large numbers, which would have the effect of bringing the remaining hypoxic cells "closer in" to the tumor blood vessels such that they likewise receive more oxygen***

3. because it usually takes quite a while for dead cells to be cleared out of tumors or for it to start shrinking, ***it follows that chronically hypoxic cells would likely takes days or more to reoxygenate***



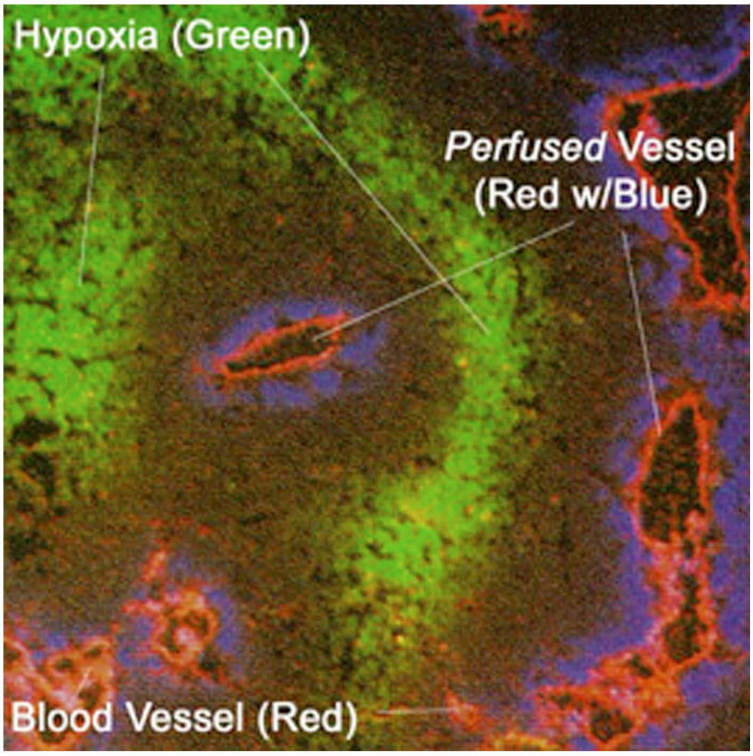
The temporal pattern of re-oxygenation of three experimental animal tumours after a high single dose of radiation (from Thomlinson 1970)

(c) What about reoxygenation in human tumors?

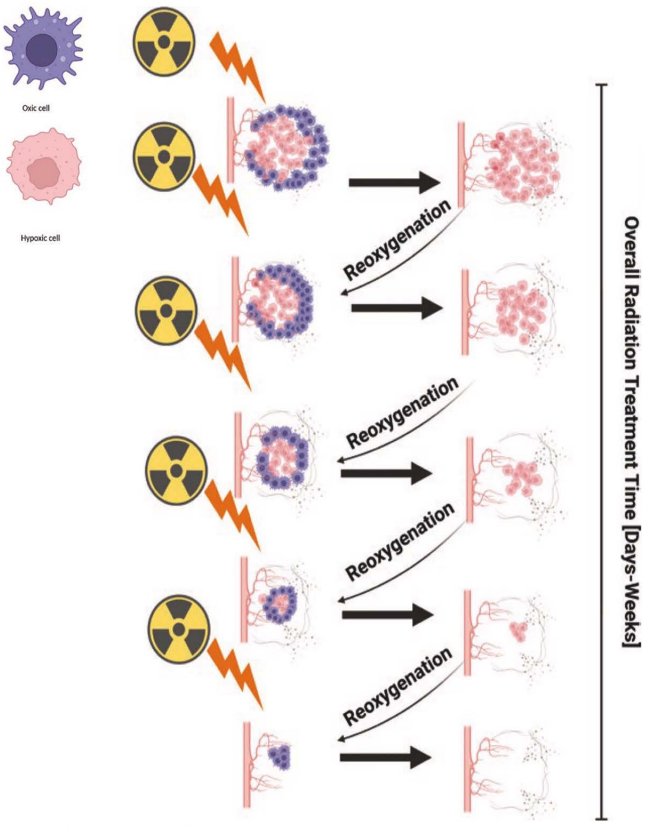
1. logistically, reoxygenation in human tumors is difficult to study, however ***we assume that the patterns of reoxygenation in rodent tumors are fairly representative of the human situation (emphasis on "fairly")***

2. ***it seems clear though that many types of human tumors must reoxygenate – completely or in part – because otherwise, we'd barely cure solid tumors at all (and yet, we do!)***

3] **clinical significance of reoxygenation** - if a patient's tumor FULLY reoxygenates during a course of radiotherapy lasting several weeks, then hypoxia should not be a problem after all, and the tumor should be much more curable; *if reoxygenation does not occur, occurs only partially, or occurs very slowly, then obtaining a cure would be much more difficult*



Fluorescent markers that can be applied to human tumor biopsies clearly indicate the locations of blood vessels (red), whether these vessels are flowing or not (red surrounded by blue), and where the chronically hypoxic cells are (green).



The process of reoxygenation.

Tumors contain a mixture of aerated and hypoxic cells. A dose of x-rays kills a greater proportion of aerated cells than hypoxic cells because aerated cells are more radiosensitive. Therefore, immediately after irradiation, most cells in the tumor are hypoxic. However, the preirradiation pattern tends to return because of reoxygenation. If the radiation is given in a series of fractions separated in time sufficient for reoxygenation to occur, the presence of hypoxic cells does not greatly influence the response of the tumor.

(a) Which clinical parameters are important vis-a-vis reoxygenation?

- Overall treatment time, i.e., is it long enought to allow complete reoxygenation?

  (Cases where the overall treatment time might NOT be long enough: HDR brachytherapy, IORT, SRS, and sometimes, SBRT/SABR)

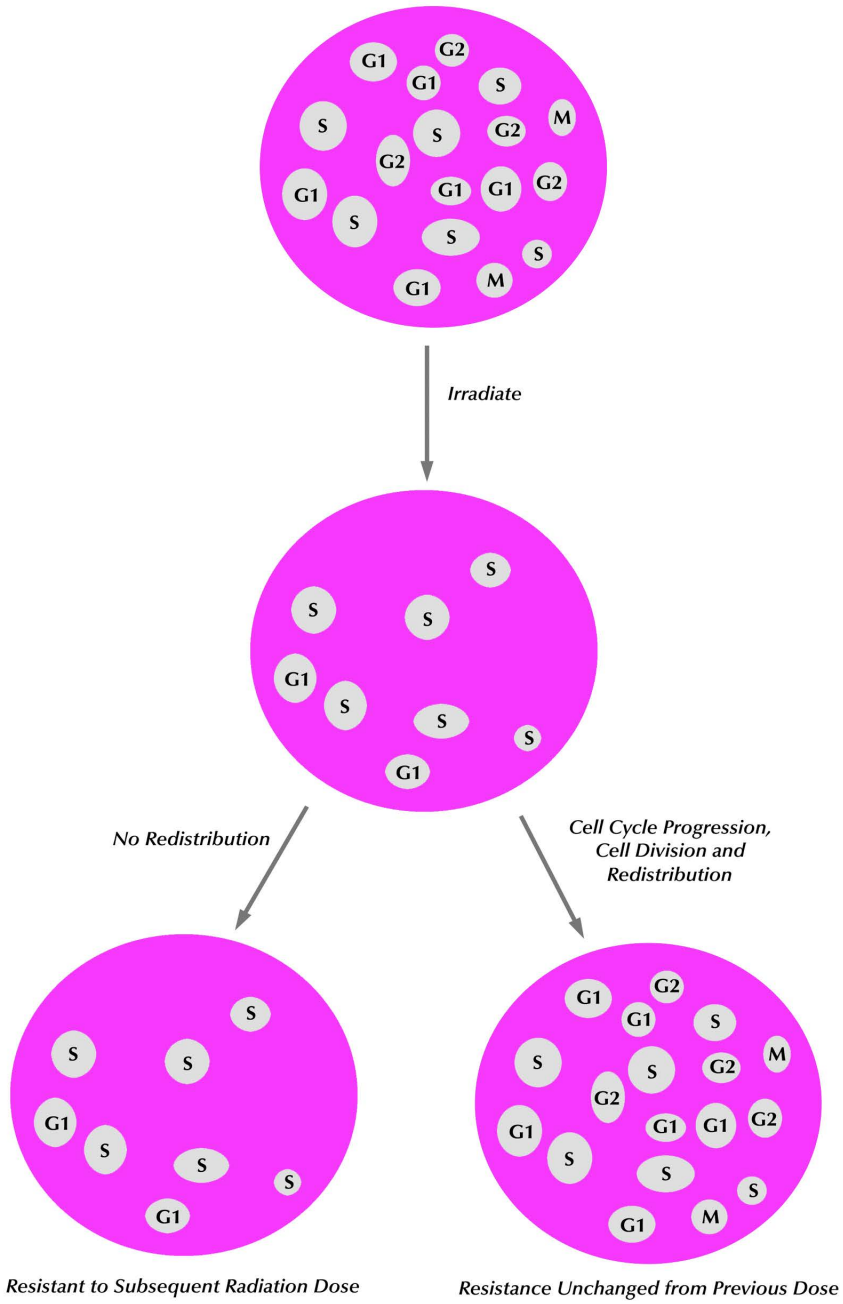
- Whether or not to add a hypoxic cell radiosensitizer…but only if we knew or suspected in advance that the particular patient's tumor contained regions of hypoxia. If not, doing so would be a waste of time. Unfortunately, we seldom have this kind of useful information.

Redistribution

1] redistribution effects can occur in tumors during radiotherapy because of the varying radiosensitivities of proliferating cells in different phases of the cell cycle (S phase most resistant, M phase most sensitive)

2] this is most likely to occur under conditions where the tumor has a high growth fraction and therefore contains lots of rapidly proliferating cells in different cell cycle phases, and especially, for low dose rate brachytherapy of short duration

(a) since these conditions don't occur often (exceptions: low dose rate implants for cervical cancer that are only left in place for a few days, or permanent, seed or wire implants for head and neck tumors), and because even the fastest growing tumor cells *in vivo* proliferate much more slowly than corresponding cells grown in Petri dishes, at best, ***redistribution is thought to be a minor effect, and therefore, the least important of the 4 R's***



When a mixed ("asynchronous") batch of cells receives a dose of radiation, the most resistant ones (S phase and a few G1 phase) tend to be the ones that survive.

If the situation remains unchanged by the time of the next dose fraction, the tumor will be more radioresistant as a whole due to enrichment with resistant cells.

However, if, during the time between the first and second dose, the surviving, resistant cells continue to move around the cell cycle and divide, they will re-establish the conditions of the original tumor prior to irradiation, and have the same overall radiosensitivity. This process is called "redistribution or reassortment".

Redistribution has the net effect of making each subsequent dose fraction equally as effective as the prior one; if redistribution *didn't* occur, the tumor would become more and more resistant with each dose.

art of oncology

The Arc of Therapy: From Cure to Humbling Legacy

Gene Bishop, MD[1]

In June 1965, at the age of 18, I sat in a room with my parents and heard an oncologist tell me that I had Hodgkin lymphoma. If I shared that diagnosis with people, he said, they would look at me as if I were dying because almost no one with this disease survived, but I would. With breathtaking confidence, the oncologist said a new treatment—radiation—would cure me.

In October 2018, at the age of 71, I sat in an oncologist's office as he told me I had stage IV non–small-cell lung cancer, presumably, a result of that radiation in 1965. He offered palliative therapy. His goal: "more good days than bad." He called me "our humbling legacy." I reflect now on that arc: from optimistic cure, through a mounting problem list of likely consequences of radiation, to the almost certainty that I will die of the treatment of a cancer I had in 1965.

I received the best treatment there was in 1965 and am getting the best treatment there is in 2019, but I am no longer being promised a cure. Both my oncologist and I are living with the reminder that no treatment does only what we want it to do and that one year's miracles may have serious consequences even 50 years later. And although some of these may be known, or theoretically possible, many are not even imagined until one, two, three, or many case reports begin to appear and random events turn into warnings and known consequences.

For the patient seeking cure and life, an unknown but potentially dangerous future is hard to imagine. Some new miracle will come along.[1] Physicians, waiting for data, recruiting patients for the next clinical trial, or facing pressure from patients for positive results, can also be focused more on immediate results. They may minimize the known or unknown future. How will physicians be both wise and humble?

The first oncologist was right. I was cured of lymphoma. I graduated, went to medical school, and had a family and a full life. I shared the story with friends, patients, and colleagues when I thought it was appropriate or helpful. "Look," I said to families facing radiation. "I had radiation and here I am, alive and well." A little hope never hurt anyone. I never thought of myself as a cancer survivor on an ongoing journey. I thought of myself as a cure. And I certainly didn't think about the difference until many years later.[2] If oncologists were no longer interested in me, then cancer was over.

There was no concept or field of study of adult survivors of childhood cancer. Certainly, no physician—neither the oncologists I saw initially nor the internists who later followed me when the oncologists lost interest— raised the issue. Why and when did I even begin to consider that I might be at some kind of risk? In 1979, 14 years after my treatment, the worst domestic nuclear power accident in US history occurred at the Three Mile Island nuclear plant in Pennsylvania. I was more than sympathetic to the nuclear disarmament movement, and although I understood that nuclear war and my radiation treatment were considerably different, I did begin to wonder if the treatment could have had unexpected consequences. I began to ask questions of physicians, with very few answers. Thus began almost 20 years of symptoms and consequences of being in the earliest cohort, not part of any study, before the age when anyone could request, if it occurred to them, weekly updates from the National Library of Medicine on consequences of earlier cancer treatment.

In 1981 (at age 34), I asked whether I should start mammograms early, and my internist asked the mammographers. We don't know, I was told, but it might be a good idea. In 1985, seeking answers to a persistent tachycardia, cardiopulmonary testing and a Holter monitor showed a baseline heart rate in the 90s. I was told I was deconditioned and anxious. In 1986, a physician studying effects of radiation on the heart—he had a 7-year follow-up at that point—told me the only known effect was constrictive pericarditis, which I did not have. Don't worry, I was told.

Both were correct. I was anxious. But my ectopy and tachycardia were not symptoms of anxiety, they were the cause of the anxiety. I was anxious about the effects of radiation. I never tried to be my own doctor, but only I looked through the lens of a radiation treatment survivor. Not until 2006 did I find early consensus-based guidelines, of which my physicians were unaware.[3] In the late 1980s, I was denied life insurance because of a new right bundle branch block, but not until 2001, 36 years after my initial treatment, did a cardiologist name it radiation-induced heart disease.

I imagined it as static, rather than dynamic. Not only was my heart not static but the entire field of radiation-induced heart disease was evolving. I didn't have a permanent scar, I had ongoing damage, and neither I nor my doctors had the evidence for where it was heading. I found a cardiologist who focused on cardiac consequences of cancer treatment. When I mentioned that hiking in the Canadian Rockies and trekking in Vietnam had ceased to be fun, the cardiologist found critical aortic stenosis. My already-damaged conduction system did not survive an aortic valve replacement, and I now had both a pacemaker and a new aortic valve.

Author affiliations and support information (if applicable) appear at the end of this article.

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In 2015 (at age 68), I read a published report of abnormal exercise response in long-term survivors of Hodgkin lymphoma treated with thoracic irradiation. I recognized myself in graphic detail.[4] No amount of training at the gym would get my heart rate below 90. That article appeared 50 years after radiation and 30 years after I first sought help, one of several sobering lessons in the length of time it can take to discover the effects of medical treatment.

The truth is, in my own therapy arc, I was lucky. Every consequence, until the lung cancer, was treatable, with the promise of a good outcome. I saw the article recommending breast magnetic resonance imaging for those who had received mantle radiation, appealed my insurance denial, and found my breast cancer early. However, two medical oncologists, two breast surgeons, and three radiation therapists all had vastly different treatment recommendations for my situation, reflecting the murky state of knowledge on treatment of Hodgkin survivors. A huge thyroid nodule was benign, but out came my thyroid, with a different small focus of cancer.

I faced each challenge, albeit with some depression and fear, with the knowledge that I would get better. Cure was still the operative word. In the arc of my disease, radiation had consequences, but they were not insurmountable.

As I reached more than 50 years out, I think I breathed an inward sigh of relief. I expected to have progressive cardiac disease. I imagined I would develop congestive heart failure. I worried about lung cancer—it had been reported 40 years out—but there were few studies on 50 years out. I thought I was done with my cancers.

When I developed a sudden and persistent cough, I began to worry. I could hear gurgles high in my midchest, but my doctors heard nothing. I doubted the pulmonologist's diagnosis of cough variant asthma, newly present in a 70-year-old. My doctors began gently suggesting what they do when a patient has unexplained symptoms. Perhaps you are anxious, they said. The classically trained psychiatrist noted he hadn't seen a conversion symptom in a long time, but thought I might never have really thought through what it meant having cancer at age 18. Several unexplained symptoms and normal computed tomography scans later, I contemplated what a nonphysician would do.

What if I weren't thinking like a doctor, but more like my fellow survivors? Off I went to Facebook, an unimaginable resource in 1965. I typed "Hodgkin's survivors" in the search box, and up popped a closed group: Hodgkins Lymphoma Disease Survival and Late Effects 1960s-early 2000s. Here were 500 people from around the world who had received radiation, chemotherapy, or both. It was hardly a tidy cohort. Their treatments for Hodgkin spanned the years from mantle radiation to chemotherapy, splenectomy, improved imaging, and actual staging.

As befits a social media site, they were seeking support, medical advice, and shared experiences. I was one of only two survivors on the site who were more than 50 years post treatment. Initially, I felt lucky, at least until the lung cancer diagnosis. The number of valve replacements, arrhythmias, pacemakers, and stents was extensive. Many had severe neck contractures from radiation. Breast cancer seemed to be an everyday occurrence; the question of prophylactic mastectomies frequently was raised. Cough, lung disease, and esophageal reflux with aspiration all appeared. I briefly let myself be reassured that my pulmonologist was correct, and my cough had a reflux component, even if I never had a classic reflux symptom and a gastroenterologist was doubtful.

If the medical world has been slow to recognize cancer survivorship, this nonrandom group has not. Many of them travel hundreds of miles to find survivorship clinics in various countries around the world. The more recently treated ones had both the good fortune to benefit from the new field of cancer survivorship, but the bad fortune to be beset constantly by worries about what the future holds. As with much of the lay public, many believe that screening and early diagnosis are always beneficial and are unaware that the evidence in our cohort is scant.[5]

I found myself alternately fascinated, riveted, terrified, and reassured, but refrained from diagnosing myself from Facebook. I also knew I had found my peeps—a cohort more aware of their risk factors than much of the medical world.

One woman expressed relief when her new oncologist said, "This is all our fault." Others chimed in they had never heard a physician acknowledge that. My new oncologist had fancier words: "You are our humbling legacy."

I am the living—or perhaps I should say dying—history of one of our more successful efforts to treat and cure cancer in the last 50 years. There are now numerous other efforts, especially to treat childhood malignancies. Awareness of long-term consequences, the concept of survivorship, and the concept of shared decision making are but a few of the inflections in the arc of therapy. Many patients make difficult decisions, choosing extremely toxic therapies that will extend life only months, with imminent consequences that are known. But many also make decisions on the basis of limited information, filled with hope. In early 2019, should an American woman wait while the Food and Drug Administration continues to investigate textured breast implants, or imagine she lives in France, where sales have been halted because of reports of an association with a rare lymphoma? What will be the effects of the successful immunotherapy in 10, 20, or 50 years? Of course, physicians are focused on near-term cure; yet, they must also acknowledge the uncertainty regarding possible late effects of the very treatment that is now saving their patients' lives.

But if I am a humbling legacy, humility is needed. We need clinicians to provide guidance and information to patients as they find themselves in unknown and often frightening

terrain years or decades after completing their course of treatment. In my primary care practice, I often told patients I had left my crystal ball at home, along with my magic wand. But I was usually referring to when they could return to work after a viral illness, not whether they would get a terminal illness 50 years later.

I try to imagine my 18-year-old self and the doctor peering into his crystal ball. *You will have symptoms no one will believe. You will happily marry and successfully have one child.* (As long as he has a crystal ball, I might as well learn everything.) *You will develop heart disease and require an artificial valve and a pacemaker. You will develop three other cancers, two of which will be treatable, but the third, at age 72, will be the cause of your death. Would you like the radiation and cure we can offer you now?*

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the author and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.00666.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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