Introduction to Radiobiology
Lesson 6

Master of Advanced Studies in Medical Physics
A.Y. 2022-23

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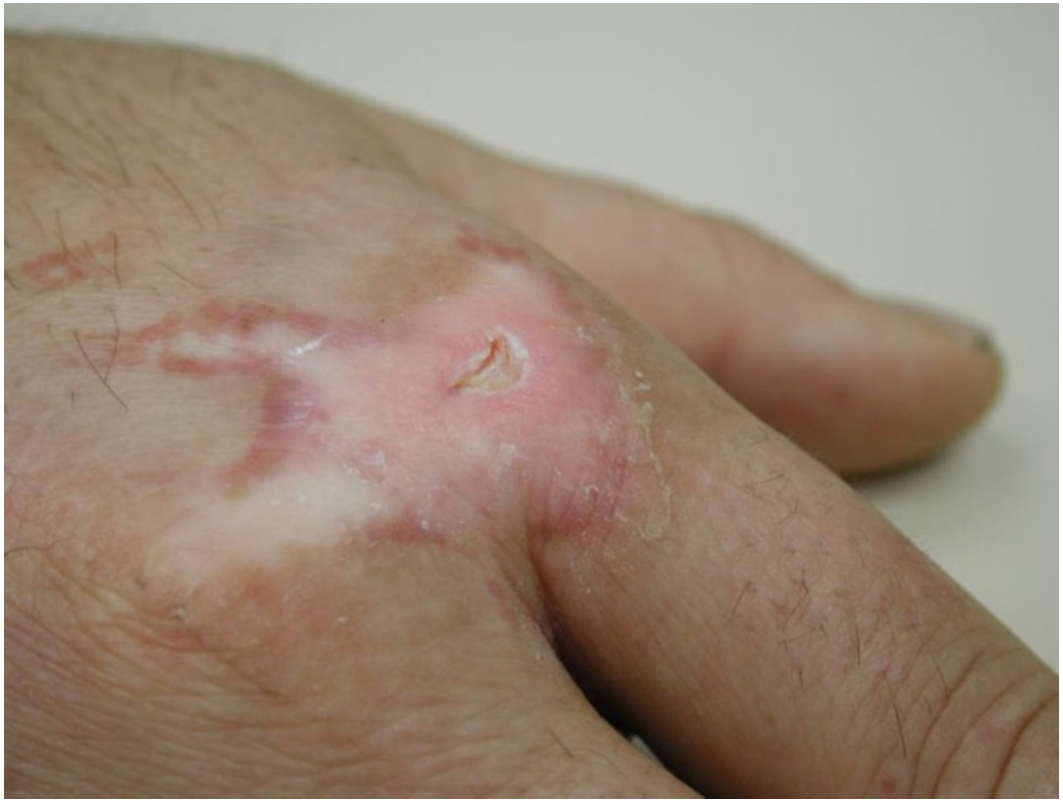
Radiation damages all kinds of human tissues – both healthy and diseased



An area of ulceration on the hand, caused by exposure to radiation therapy

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Radiotherapy and Oncology 63 (2002) 129–145

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

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Review article

The radiotherapeutic injury – a complex 'wound'

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Received 30 July 2001; received in revised form 12 February 2002; accepted 6 March 2002

Abstract

Radiotherapeutic normal tissue injury can be viewed as two simultaneously ongoing and interacting processes. The first has many features in common with the healing of traumatic wounds. The second is a set of transient or permanent alterations of cellular and extracellular components within the irradiated volume. In contrast to physical trauma, fractionated radiation therapy produces a series of repeated insults to tissues that undergo significant changes during the course of radiotherapy. Normal tissue responses are also influenced by rate of dose accumulation and other factors that relate to the radiation therapy schedule. This article reviews the principles of organised normal tissue responses during and after radiation therapy, the effect of radiation therapy on these responses, as well as some of the mechanisms underlying the development of recognisable injury. Important clinical implications relevant to these processes are also discussed.

Keywords: Radiation injury; Wound repair; Early and late effects

Radiation damage is more than the damage to individual cells, it affects tissue organization as well

1. Introduction

Radiotherapeutic injury is a complex process that occurs in *organised* tissues, i.e. tissues which comprise a large number of interacting, mutually dependent cellular lineages, as well as a multitude of biologically active extracellular molecules. This perspective is in some contrast to the more traditional (minimalist) approach that considers injury to individual cell lines that can be modelled by cell culture. All organised tissues are capable of mounting reparative responses to injury. This review examines some of these responses and draws attention to some unique phenomena that occur as a result of *repetitive* injuries – the series of exposures to ionising radiation that make up a course of radiotherapy.

The response of normal tissues to radiotherapy can be viewed as comprising two partially interacting components, each of which is very complex. The first is a process that in many, but not all, respects resembles the healing of traumatic wounds, while being subject to perturbation by the radiation treatment. The second is a set of specific injuries that affect virtually all cellular and extracellular components within the irradiated volume, and that may be responsible for the progression of injury over a period of many years.

The radiotherapy 'wound' differs in interesting ways from acute traumatic, thermal or chemical wounds, in which structural tissue damage occurs instantaneously, or nearly so. In contrast to these types of injury, exposure to ionising radiation produces a burst of free radicals, which, while obviously not re-arranging tissue components immediately, not only causes DNA damage, but also alters proteins, lipids, carbohydrates, and complex molecules. While the amount of energy deposited is minimal, each exposure inflicts considerable injury. Another important characteristic of radiation therapy is that it inflicts a *series* of small tissue insults as each fraction is delivered. In many tissues, each fraction thus contributes to accumulating inflammatory cell recruitment as well as to the accumulation of direct tissue injury. Furthermore, each fraction affects tissue that already exhibits a dynamic spectrum of cellular injury, ongoing repair, inflammation, and other pathophysiologic responses. Therefore, with repetitive radiation exposure, many cellular and molecular responses will be substantially exacerbated, suppressed, or substantially altered compared to the situation after a single exposure to radiation or traumatic injury.

Influence of dose-rate

For the same radiation dose, radiation delivered at a lower dose rate may produce less cell killing than radiation delivered at a higher dose rate, because sublethal damage repair may occur during the protracted exposure.

Typical dose rates used in radiotherapy are of the order of:

- 1 Gy/min in standard radiotherapy and high dose-rate (HDR) brachytherapy.
- 0.1 Gy/min in total body irradiation (TBI).
- 0.01 Gy/min in low dose-rate (LDR) brachytherapy

Note: **Brachytherapy**, also known as internal radiotherapy, sealed source radiotherapy, curietherapy or endocurietherapy, **is a form of radiotherapy where a radiation source is placed inside or next to the area requiring treatment**. Brachytherapy is commonly used as an effective treatment for cervical, prostate, breast, and skin cancer and can also be used to treat tumours in many other body sites.

Radiosensitizers

Radiosensitizers are chemical or pharmacologic agents that increase the lethal effects of radiation if administered in conjunction with it.

Many compounds that modify the radiation response of mammalian cells have been discovered, but most offer no practical gain in radiotherapy because they do not show a *differential effect* between tumors and normal tissues.
There is no point in employing a drug that increases the sensitivity of tumor and normal cells to the same extent.

Examples of radiosensitizers:

Halogenated pyrimidines sensitize cells to a degree dependent on the amount of the analogue incorporated. In this case, a differential effect is based on the premise that tumor cells cycle faster and therefore incorporate more of the drug than the surrounding normal tissues.

Hypoxic-cell sensitizers increase the radiosensitivity of cells deficient in molecular oxygen but have no effect on normally aerated cells. In this case, a differential effect is based on the premise that hypoxic cells occur only in tumors and not in normal tissues.

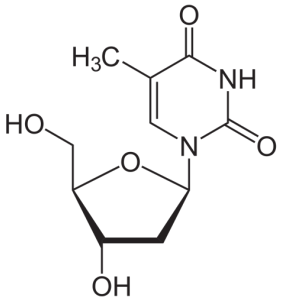
The halogenated pyrimidines

The combining size (the van der Waals radius) of an atom of chlorine, bromine, or iodine is very similar to that of the methyl group CH_3. The halogenated pyrimidines **5-iododeoxyuridine** and **5-bromodeoxyuridine** consequently are very similar to the normal DNA precursor thymidine, having a halogen substituted in place of the methyl group.

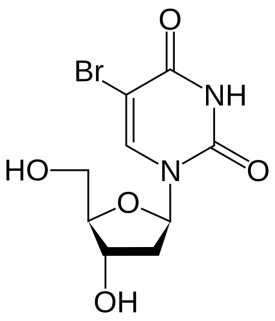
The similarity is so close that **they are incorporated into the DNA chain in place of thymine**.

This substitution "weakens" the DNA chain, making the cells more susceptible to damage by γ- rays or ultraviolet light.

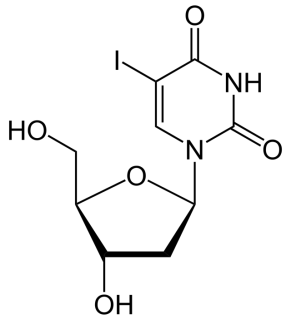
These substances are effective as sensitizers only if they are made available to cells for several cell generations so that an appreciable quantity of the analogue actually may be incorporated into the DNA. As the percentage of thymidine bases replaced increases, so does the extent of radiosensitization.



thymidine



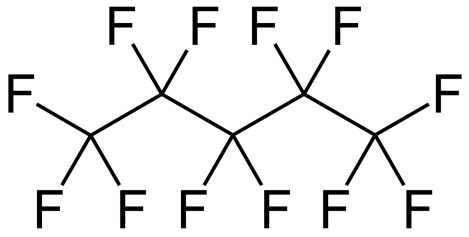
5-bromodeoxyuridine



5-iododeoxyuridine

Hypoxic cell sensitizer (dodecafluoropentane)

Hypoxic tumors require about three-fold higher radiation dose than normoxic tumors for comparable effect on tumor cells, and about two-thirds of all solid tumors are hypoxic.



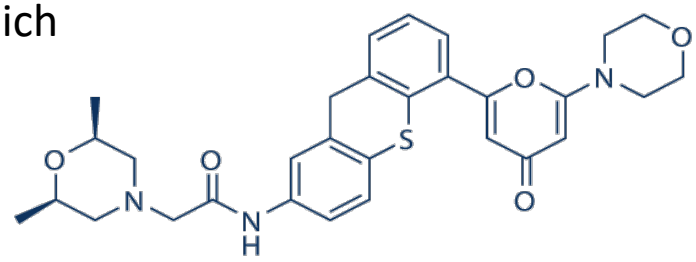
Hypoxia is predominant in tumors such as pancreas, head and neck, lung and high- grade brain neoplasms. In brain tumors hypoxia is associated with poor survival.

Normal tissues have interstitial pO2 values of about 25 mm of Hg (or greater) but in cancers pO2 values commonly range from 2 mm Hg (pancreas) to 14 mm Hg (sarcoma). Radiation sensitivity drops significantly below a critical oxygen level of about 25–30 mm Hg.

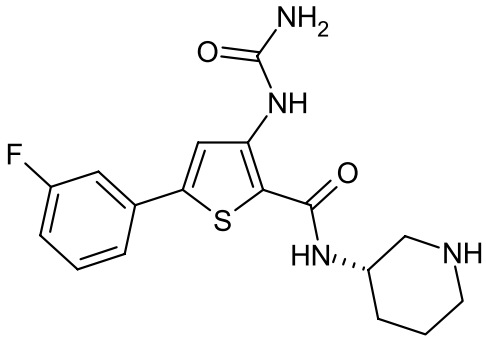
Dodecafluropentane forms nanobubbles that can transport oxygen to tissues. Dodefluoropentane nanoparticles are currently tested as a potential radiosensitizer that acts by reducing hypoxia (NVX-108 nanoemulsion).

Other examples of radiosensitizers

KU-60019 is a novel, highly effective radiosensitizer, which **works by inactivating the ATM gene.**



AZD7762 is a novel drug that is administered in combination with DNA-damaging agents, to enhance the efficacy of both conventional chemotherapy and radiotherapy and increase patient response rates in a variety of settings. It **works by abrogating the S and G2 checkpoints.**



AZD7762

State-of-the-art: present knowledge is still incomplete, *radiation damage to healthy tissues during therapy is not yet completely understood*

"Radiation therapy is an integral part of the treatment of patients afflicted with cancer. It is estimated that over 60% of patients with cancer will have radiotherapy as part of their total course of treatment.

Radiation therapy affects both tumor cells and uninvolved normal cells; the former to the benefit and the latter to the detriment of patients.

With the goal of achieving uncomplicated local regional control of cancer, balancing between the two is both an art and a science of radiation oncology.

Unfortunately, after over 100 years of practicing radiation oncology and in spite of much recent progress, knowledge on either of the two is far from perfect. "

from B. Emami, Reports of Radiotherapy and Oncology **1** (2013) 1

Radiobiological knowledge is used to optimize treatment

Next, we consider some concepts associated with radiobiology and related to **treatment optimization**

1. Fractionation
2. The 4 R's (5R's) of radiobiology
3. Dose-volume histograms (DVH) and isodose curves
4. Equivalent Uniform Dose (EUD)
5. Introduction to Monte Carlo optimization methods

Conventional fractionated radiotherapy was based on experiments performed in Paris in the 1920s and in the 1930s.

Rams could not be sterilized with a single dose of x-rays without extensive skin damage, **whereas if the radiation were delivered in daily fractions over a period of time, sterilization was possible without skin damage**.

The testes were regarded as a model of a growing tumor and skin as dose-limiting normal tissue.

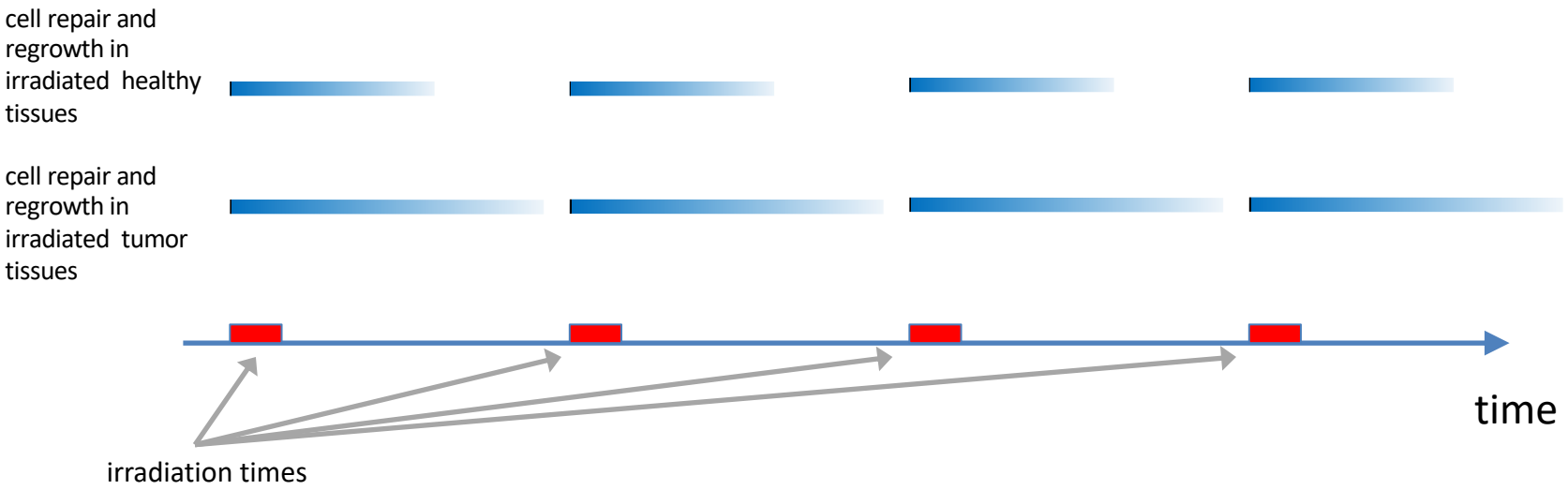
Dose fractionation

To minimize the toxic effects to healthy cells, the total dose is often subdivided in smaller doses.

However, to ensure that a tumor is properly treated, the total dose must be increased.

To achieve the desired level of biological damage the total dose in a fractionated treatment is considerably larger than that in a single treatment.

Fractionation and cell repair processes



- one expects to find differences in repair efficiency between normal cells and tumor cells
- proliferation restarts after repair
- most tissue repair occurs in about 3 hours and up to 24 hours post radiation

How effective is a radiation dose *with reference to the simple linear (Poisson model)*?

Because of the linear-quadratic law we know that

$$S(D) \approx e^{-\alpha D - \beta D^2}$$

instead of

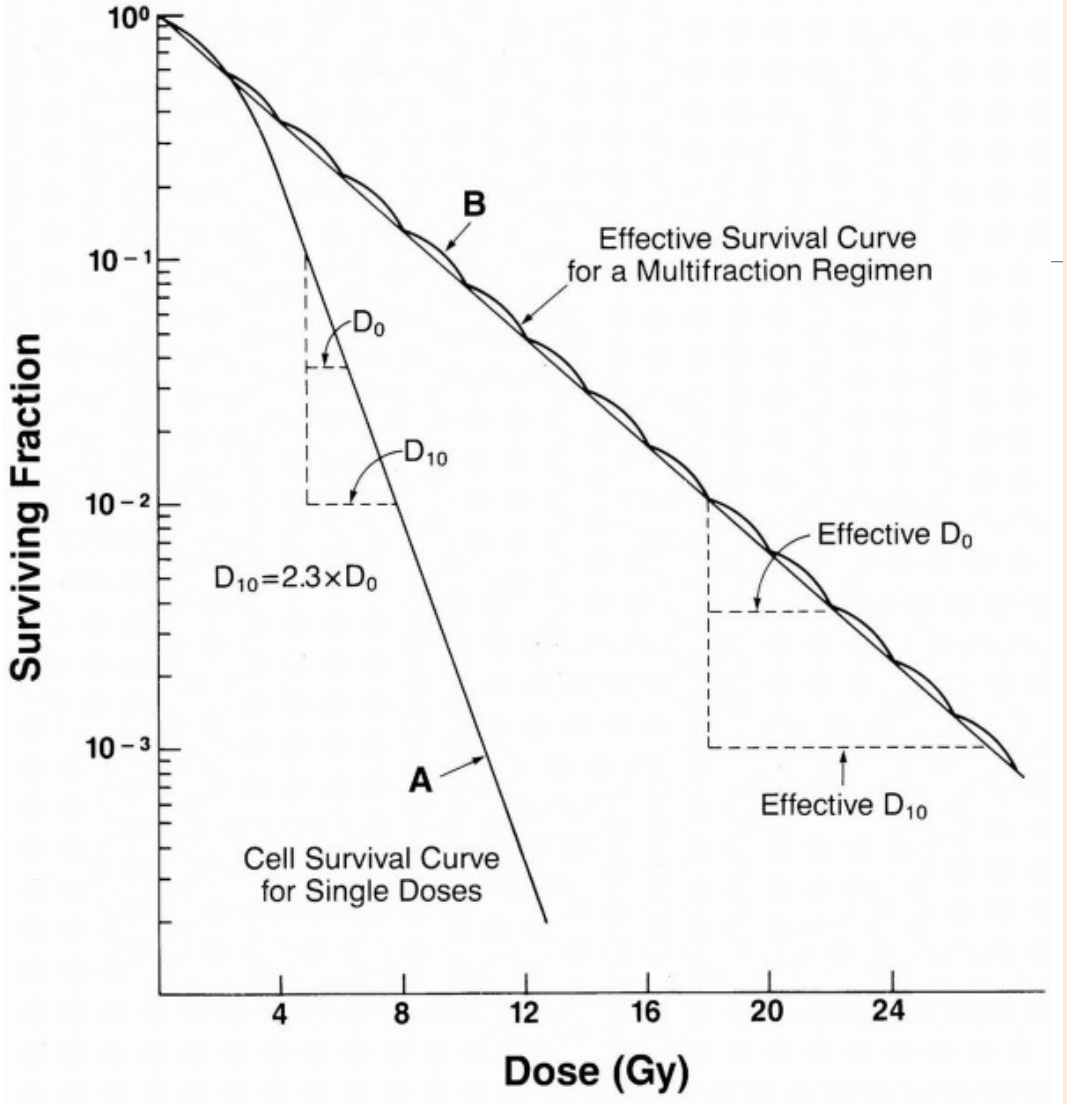
$$S_{\mathrm{lin}}(D) \approx e^{-D/D_0}$$

Therefore, the actual surviving fraction corresponds to the hypothetical dose D_e such that

$$E = \frac{D_e}{D_0} = \alpha D \left(1 + \frac{D}{\alpha/\beta}\right)$$

biological effect

relative effectiveness



A simple Poisson model of the surviving fraction has an exponent that is proportional to the dose.
Fractionation <u>approximates</u> this linear behavior.

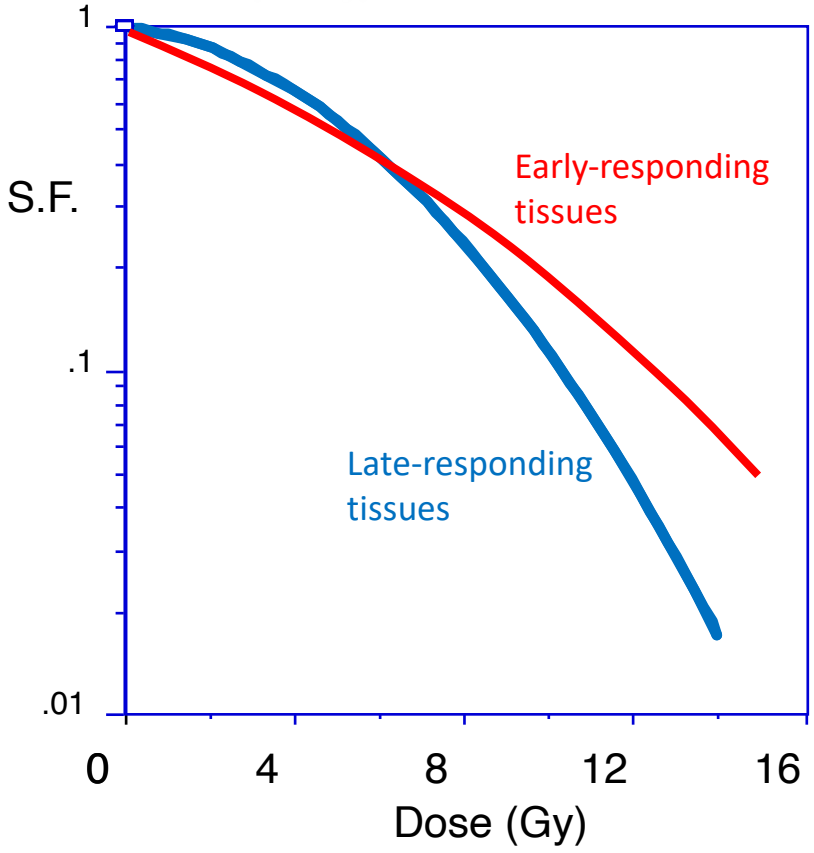
$$S(D) = e^{-D/D_0}$$
$$= 10^{D \log_{10} e/D_0}$$
$$= 10^{-D/D_{10}}$$

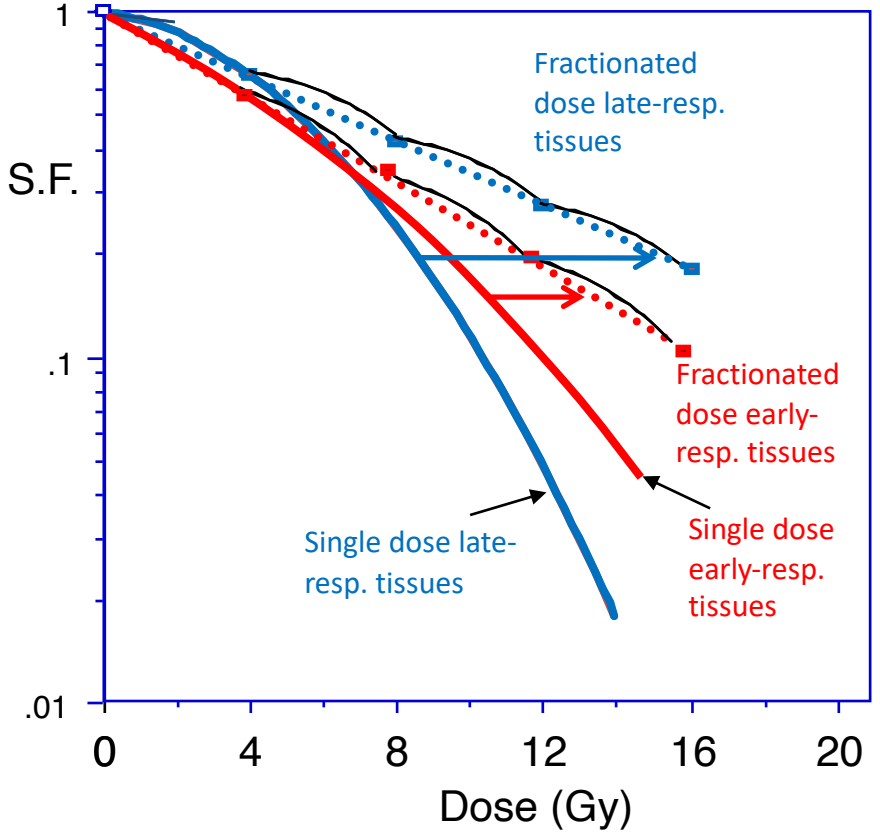
$$\ln S(D) = -D/D_0$$
$$D_0 = \frac{\Delta D}{\Delta \ln(1/S(D))}$$

$$D_{10} = D_0/\log_{10} e \approx 2.3 D_0$$
$$D_{10} = \frac{\Delta D}{\Delta \log_{10}(1/S(D))}$$

Response to fractionation varies with tissue, fractionation spares late responding tissues

When α/β is high (> 6 Gy) the survival curve is almost exponential, when α/β is low (1-4Gy) the shoulder is wide





The algebra of fractionation, using the linear-quadratic law

Survival probability with *n* doses *D* $[S(D)]^n$

The corresponding **biological effect** is

$$E = -\ln[S(D)]^n = -n \ln S(D)$$
$$= n(\alpha D + \beta D^2)$$
$$= \alpha(nD)\left(1 + \frac{D}{\alpha/\beta}\right)$$

total dose

relative effectiveness

Biologically Effective Dose: the dose that would give a given log cell kill in a very prolonged treatment (used to compare treatments)

$$\mathrm{BED} = \frac{E}{\alpha} = (nD)\left(1 + \frac{D}{\alpha/\beta}\right)$$

biologically effective dose

total dose

relative effectiveness

The relative effectiveness is always > 1,

therefore, in a fractionated treatment the biologically effective dose is always greater than the total dose.

In early responding tissues there is little difference between total dose and biologically effective dose.

Indeed, if

$$\alpha/\beta \gg D$$

then

$$\mathrm{BED} = (nD)\left(1 + \frac{D}{\alpha/\beta}\right) \approx (nD)$$

In this case the tissue responds as though the LQ response were essentially linear.

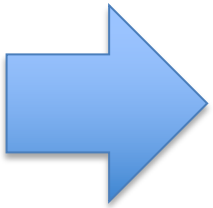
To assess the impact of fractionation on tissues, it is useful to turn to tables of α/β coefficients

Early-Responding Tissues	α/β	Late-Responding Tissues	α/β[b]
Jejunal mucosa	13	Spinal cord (110,166,245,284,285,322)	1.6–5
Colonic mucosa	7	Kidney (44,127,291,305)	0.5–5
Skin epithelium	10	Lung (90,211,214,275,289,295)	1.6–4.5
Spermatogenic cells	13	Liver (91)	1.4–3.5
Bone marrow	9	Human skin (32,211,279,280)	1.6–4.5
Melanocytes (302)	6.5	Cartilage and submucosa (171,329)	1.0–4.9
Tumors			
Mouse fibrosarcoma metastases (173)	10	Dermis (106)	2.5 ± 1.0
Human tumors (169,171,195,258)	6–25	Bladder (252,265)	5.0–10.0
Experimental tumors (306)	10–35	Bone (212)	1.8–2.5

Examples of conventional treatments

Fractionation: 30F x 2Gy/6 weeks

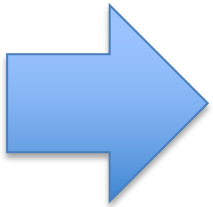
$$\begin{aligned}
\mathrm{BED(early)} &= (nD)\left(1+\frac{D}{\alpha/\beta}\right) \\
&= (60\ \mathrm{Gy})\left(1+\frac{2}{10}\right) \\
&= 72\ \mathrm{Gy}_{10} \\
\mathrm{BED(late)} &= (60\ \mathrm{Gy})\left(1+\frac{2}{3}\right) \\
&= 100\ \mathrm{Gy}_{3}
\end{aligned}$$



39% difference between early- and late-responding

Hyperfractionation: 70F x 1.15 Gy twice daily/7 weeks

$$\begin{aligned}
\mathrm{BED(early)} &= (nD)\left(1+\frac{D}{\alpha/\beta}\right) \\
&= (80.5\ \mathrm{Gy})\left(1+\frac{1.15}{10}\right) \\
&= 89.8\ \mathrm{Gy}_{10} \\
\mathrm{BED(late)} &= (80.5\ \mathrm{Gy})\left(1+\frac{1.15}{3}\right) \\
&= 111.4\ \mathrm{Gy}_{3}
\end{aligned}$$



24% difference between early- and late-responding

Isoeffect equation in dose fractionation

two fractionation strategies have the same BED if

$$D_1 \left[1 + d_1/(\alpha/\beta))\right] = D_2 \left[1 + d_2/(\alpha/\beta)\right]$$

For comparison purposes it is useful to define the **Equivalent Dose** at 2Gy:

$$\mathrm{EQD}_{2\mathrm{Gy}} = D \frac{d + \alpha/\beta}{2\mathrm{Gy} + \alpha/\beta}$$

equivalent total dose with 2Gy fractions

total dose delivered in *d* Gy fractions

The "Emami paper"

Int. J. Radiation Oncology Biol. Phys. Vol. 21, pp. 109–122
Printed in the U.S.A.

0360-3016/91 $3.00 + .00

● *Original Contribution*

TOLERANCE OF NORMAL TISSUE TO THERAPEUTIC IRRADIATION

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[1]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO 63110; [2]Memorial Sloan-Kettering Cancer Center, New York, NY 10021; [3]Department of Radiation Therapy, University of Pennsylvania School of Medicine and the Fox Chase Cancer Center, Philadelphia, PA 19111; [4]Massachusetts General Hospital, Department of Radiation Medicine, Boston, MA 02114 and Harvard Medical School; and [5]University of California-Lawrence Berkeley Laboratory, Research Medicine and Radiation Biophysics Division, Berkeley, CA 94720

The importance of knowledge on tolerance of normal tissue organs to irradiation by radiation oncologists cannot be overemphasized. Unfortunately, current knowledge is less than adequate. With the increasing use of 3-D treatment planning and dose delivery, this issue, particularly volumetric information, will become even more critical. As a part of the NCI contract N01 CM-47316, a task force, chaired by the primary author, was formed and an extensive literature search was carried out to address this issue. In this manuscript we present the updated information on tolerance of normal tissues of concern in the protocols of this contract, based on available data, with a special emphasis on partial volume effects. Due to a lack of precise and comprehensive data base, opinions and experience of the clinicians from four universities involved in the contract have also been contributory. Obviously, this is not and cannot be a comprehensive work, which is beyond the scope of this contract.

Additional material: QUANTEC guidelines (2010)

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines are a recent effort to review and summarize normal tissue toxicity, which may suggest dose-volume treatment planning guidelines and likely reduce the rates of side effects.

The primary goal is to provide a simple set of data to be used by the busy community of practitioners of radiation oncology, physicists and dosimetrists.

The second goal is to provide reliable predictive models of the relationships between dose-volume parameters and normal tissue complications to be used in the planning of radiation therapy.

The results of this large study can be found on this webpage

http://aapm.org/pubs/QUANTEC.asp

Note that these guidelines are not final and shall certainly be revised in the future as new data become available.

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PUBLICATIONS

Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)

Acknowledgement:

The QUANTEC effort was made possible, in part, by generous financial support from the American Society for Radiation Oncology (ASTRO) and the American Association of Physicists in Medicine (AAPM). The results were published in March 2010 in a special issue of the *International Journal of Radiation Oncology·Biology·Physics* (the Red Journal). The work is the result of the diligent efforts of numerous investigators, authors, reviewers, and support personnel. These important papers have heretofore only been available to Red Journal subscribers but ASTRO has now made this important effort open to all AAPM members through the following link. To avoid future delays in access to important papers like these members are encouraged to recommend the Red Journal to their institution's librarian. More information on the journal can be found at www.redjournal.org

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Tolerance of Normal Tissue to Therapeutic Radiation

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Introduction

Radiation therapy is an integral part of the treatment of patients inflicted with cancer. It is estimated that over 60% of patients with cancer will have radiotherapy as part of their total course of treatment [(1).] Radiation therapy affects both tumor cells and uninvolved normal cells; the former to the benefit and the later to the detriment of patients. With the goal of achieving uncomplicated local regional control of cancer, balancing between the two is both an art and a science of radiation oncology. Unfortunately, after over 100 years of practicing radiation oncology and in spite of much recent progress, knowledge on either of the two is far from perfect.

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Radiotherapy dose fractionation Third edition

https://www.rcr.ac.uk/publication/radiotherapy-dose-fractionation-third-edition

The 4 R's (5 !!!) of radiotherapy: a set of radiobiological rules of thumb for dose fractionated radiotherapy

Radiobiological mechanisms that impact on the efficacy of radiotherapy.
A summary list of what is important in radiotherapy (introduced by Withers in 1975)

A. ***Repair***

B. ***Redistribution of cells within the cell cycle***

C. ***Repopulation***

D. ***Reoxygenation***

… and

E. ***Radiosensitivity (the new, 5th R)***

A. Repair

The repair of sublethal damage must be taken into account

- because **it affects the tolerance of healthy tissue to radiotherapy** (allowing cells to repair we can continue a treatment that should otherwise be interrupted)

- because **tumor cells often have a reduced ability to repair damage**, e.g., when they have a mutated P53 gene

When considering repair one must keep into account the mean repair time of healthy tissue – e.g., the spinal cord tissue has a slow mean repair time of about 4 hours, and this means that daily doses must have at least this separation to spare that tissue.

Dose rate must also be taken into account: too low a dose rate means that both healthy and tumor tissues can start repair *during* a session.

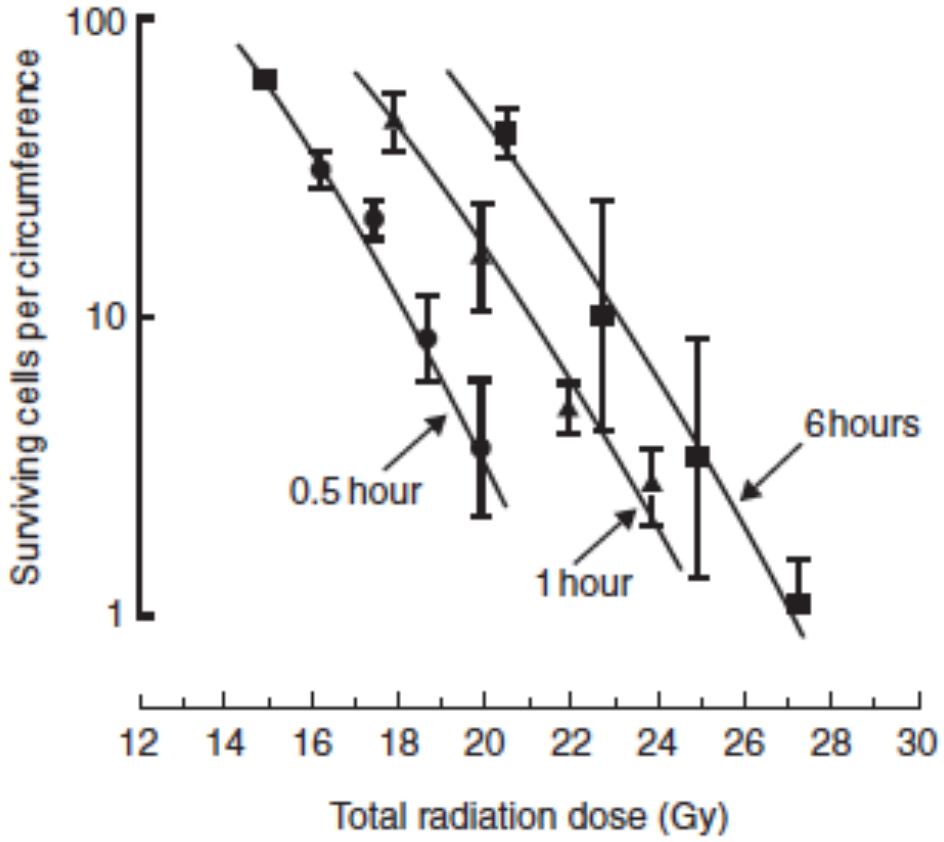


Figure 8.8 Effect of interfraction interval on intestinal radiation damage in mice. The total dose required in five fractions for a given level of effect is less for short intervals, illustrating incomplete repair between fractions. From Thames *et al.* (1984), with permission.

Dose fractionation must take into account the recovery time of normal tissues

Table 8.4 Halftimes for recovery from radiation damage in normal tissues of laboratory animals

Tissue	Species	Dose delivery	$T_{1/2}$ (hours)	Source
Haemopoietic	Mouse	CLDR	0.3	Thames *et al.* (1984)
Spermatogonia	Mouse	CLDR	0.3–0.4	Delic *et al.* (1987)
Jejunum	Mouse	F	0.45	Thames *et al.* (1984)
	Mouse	CLDR	0.2–0.7	Dale *et al.* (1988)
Colon (acute injury)	Mouse	F	0.8	Thames *et al.* (1984)
	Rat	F	1.5	Sassy *et al.* (1988)
Lip mucosa	Mouse	F	0.8	Ang *et al.* (1985)
	Mouse	CLDR	0.8	Scalliet *et al.* (1987)
	Mouse	FLDR	0.6	Stüben *et al.* (1991)
Tongue epithelium	Mouse	F	0.75	Dörr *et al.* (1993)
Skin (acute injury)	Mouse	F	1.5	Rojas *et al.* (1991)
	Mouse	CLDR	1.0	Joiner *et al.* (unpublished)
	Pig	F	0.4 + 1.2*	van den Aardweg and Hopewell (1992)
	Pig	F	0.2 + 6.6*	Millar *et al.* (1996)
Lung	Mouse	F	0.4 + 4.0*	van Rongen *et al.* (1993)
	Mouse	CLDR	0.85	Down *et al.* (1986)
	Rat	FLDR	1.0	van Rongen (1989)
Spinal cord	Rat	F	0.7 + 3.8*	Ang *et al.* (1992)
	Rat	CLDR	1.4	Scalliet *et al.* (1989)
	Rat	CLDR	1.43	Pop *et al.* (1996)
Kidney	Mouse	F	1.3	Joiner *et al.* (1993)
	Mouse	F	0.2 + 5.0	Millar *et al.* (1994)
	Rat	F	1.6–2.1	van Rongen *et al.* (1990)
Rectum (late injury)	Rat	CLDR	1.2	Kiszel *et al.* (1985)
Heart	Rat	F	>3	Schultz-Hector *et al.* (1992)

Dose delivery: F, acute dose fractions, FLDR, fractionated low dose rate; CLDR, continuous low dose rate.

*Two components of repair with different halftimes.

B. Redistribution

Proliferating cells have different radiosensitivities. After a session more of the cells in the S phase survive and **waiting for a redistribution of cells in different phases helps in killing them**.

A low dose rate means that redistribution can take place *during* a session, and this should be taken into account.

C. Repopulation

Repopulation takes place both in healthy and in diseased tissues.

Usually **healthy early-responding tissues begin repopulation at about 4 weeks into treatment**. Prolonging treatment over 4 weeks means a reduced early radiotoxicity for these tissues. This is not relevant for late-responding tissues.

At least some tumors display accelerated repopulation after 4-5 weeks into treatment. This means that this **repopulation must be countered in long treatments**.

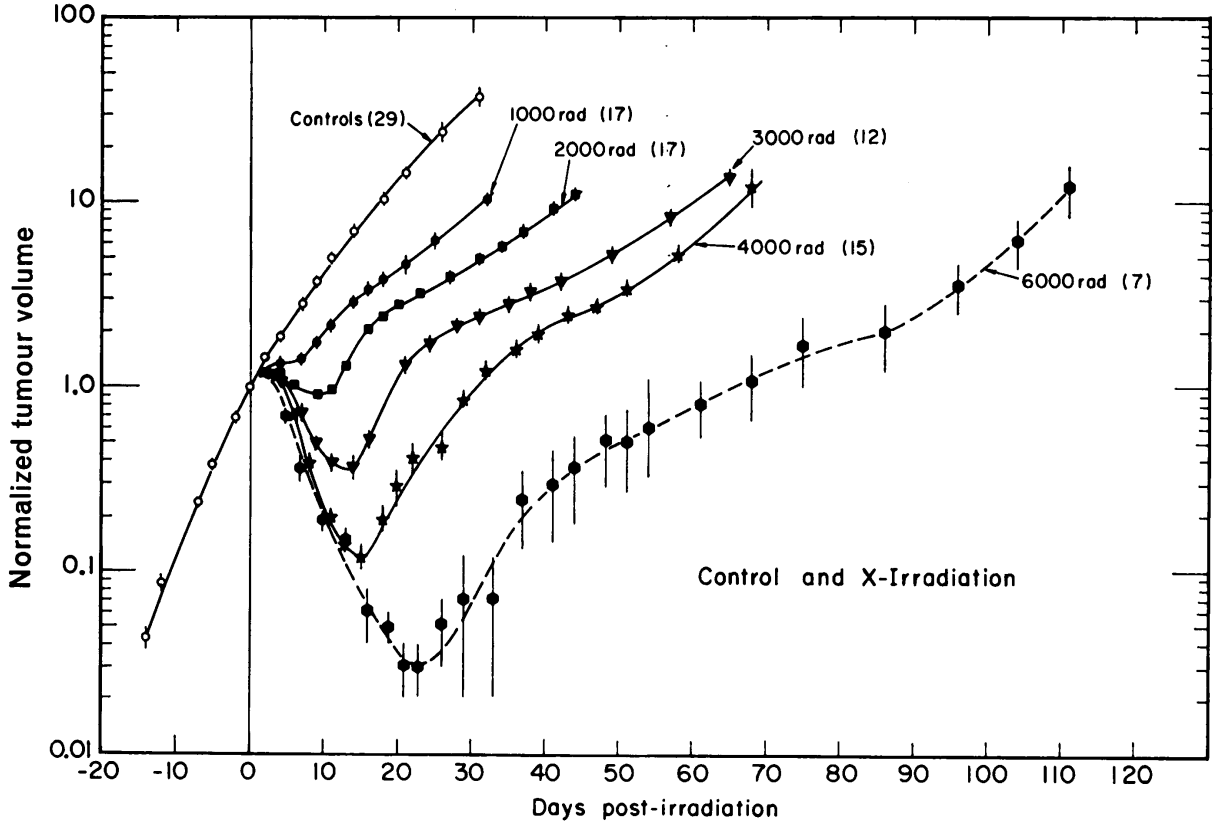


FIG. 1.—Volumes of R1/LBL tumours are plotted as a function of time for controls and for tumours receiving graded doses of 220-kV X-rays. The volumes have been normalized to unity on the day of irradiation. Numbers in parentheses represent the number of tumours exposed to each radiation dose. Error bars represent one standard error of the mean.

from Curtis & Tenforde: "Assessment of tumour response in a rat rhabdomyosarcoma", Br. J. Cancer 41 (1980), 266

A generalization of BED that includes tumor repopulation

After a "kickoff time" T_k, tumor cells start proliferating again, therefore the tumor population after treatment has changed by the total factor

$$N(T)/N_0 = [S(D)]^n 2^{(T-T_k)/T_p}$$

where T_p is the tumor cells' duplication time. Taking logarithms, we find

$$n \ln[S(D)] + \frac{T - T_k}{T_p/\ln 2} = -\alpha n D \left(1 + \frac{D}{\alpha/\beta}\right) + \frac{T - T_k}{T_p/\ln 2}$$

$$n \ln[S(D)] + \frac{T - T_k}{T_p / \ln 2} = -\alpha n D \left(1 + \frac{D}{\alpha/\beta}\right) + \frac{T - T_k}{T_p / \ln 2}$$

$$\begin{aligned} \mathrm{BED}(D, n, T) &= (nD)\left(1 + \frac{D}{\alpha/\beta}\right) - \frac{T - T_k}{\alpha T_p / \ln 2} \\ &= \mathrm{BED}(D, n) - \frac{T - T_k}{\alpha T_p / \ln 2} \end{aligned}$$

D. Reoxygenation

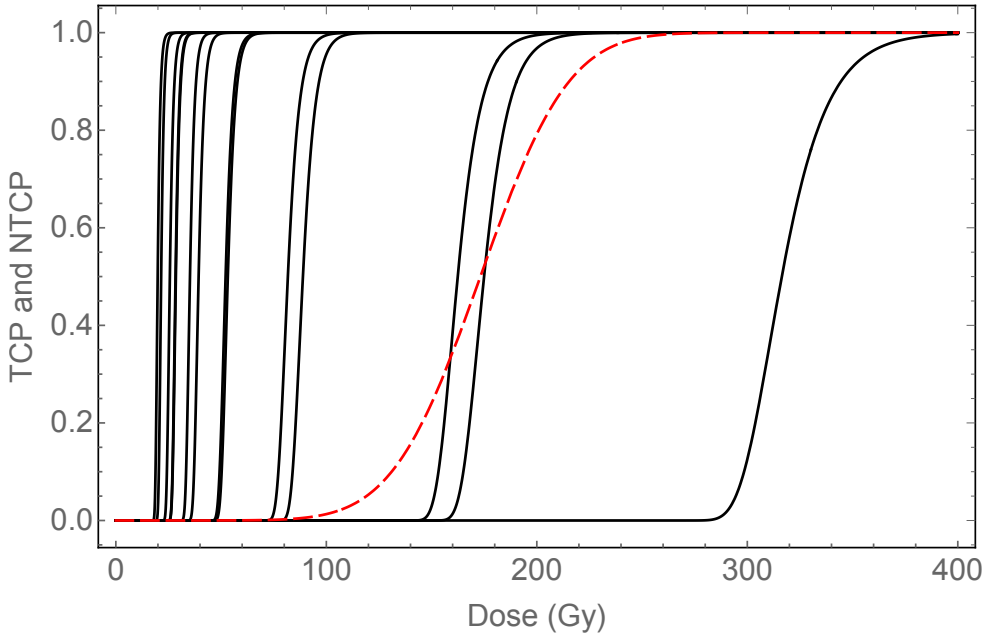
Many tumor tissues are hypoxic, and this protects tumor cells from radiation because of the Oxygen Effect. Therefore, one useful strategy consists in helping oxygen diffuse through tissues.

Reoxygenation can be achieved by killing cells closer to blood vessels, so that oxygen penetrates more deeply into the tumor tissue, **and also using growth factors that reestablish a healthier, more regular vascularization** in the tumor tissue (e.g, VEGF).

E. Radiosensitivity

Radiosensitivity differs in different cell types, and this factor must be included in the therapeutic strategy.

Radiosensitivity can sometimes be enhanced in tumor cells with proper sensitizing chemicals.

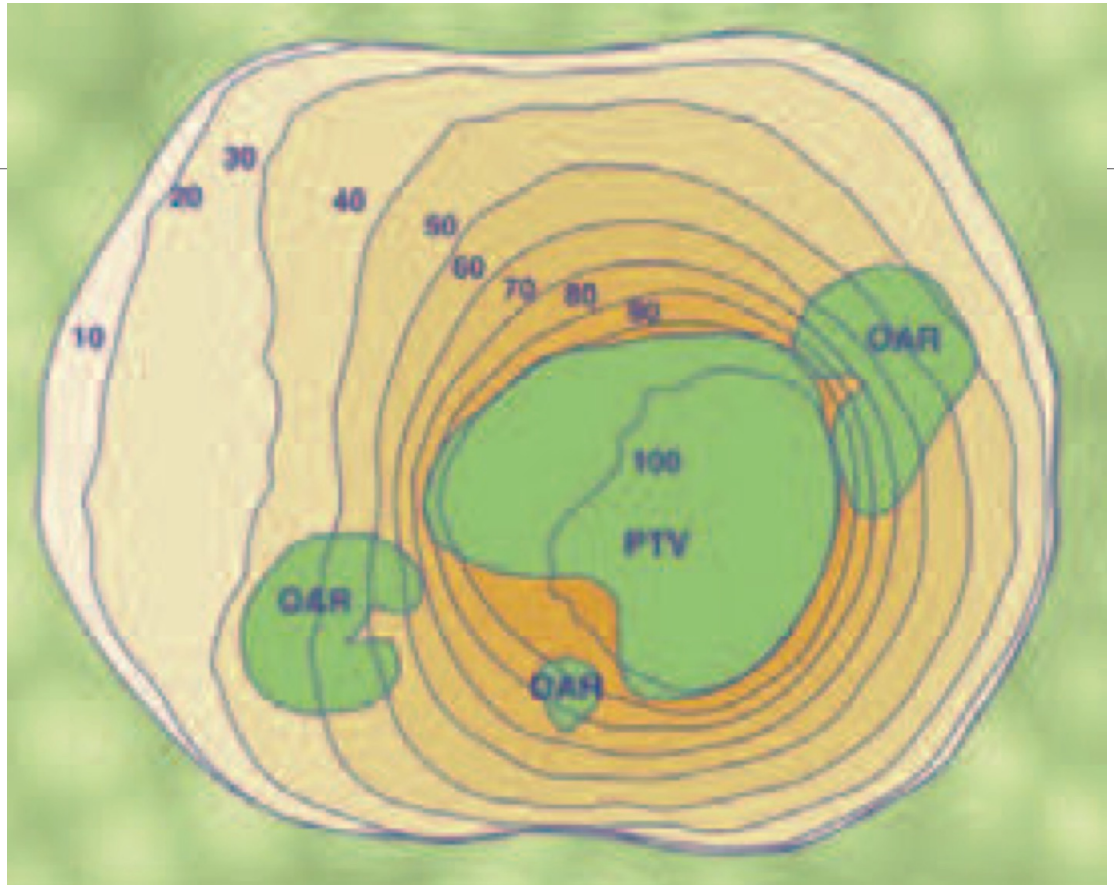


TCP curves (solid black lines) for various GBM histological types and NTCP curve (dashed red line) for brain tissue vs. dose D (Gy), for 10^9 cells (volume about 4 cm^3). The TCP curves have been drawn taking the linear extrapolation of the LQ model with the α and β parameters listed in the literature. The NTCP curve has been drawn with partial volume v = 5%.

Isodose curves and dose-volume histograms (DVH)

Dose is distributed in space and both tumor tissue and normal tissue are affected.

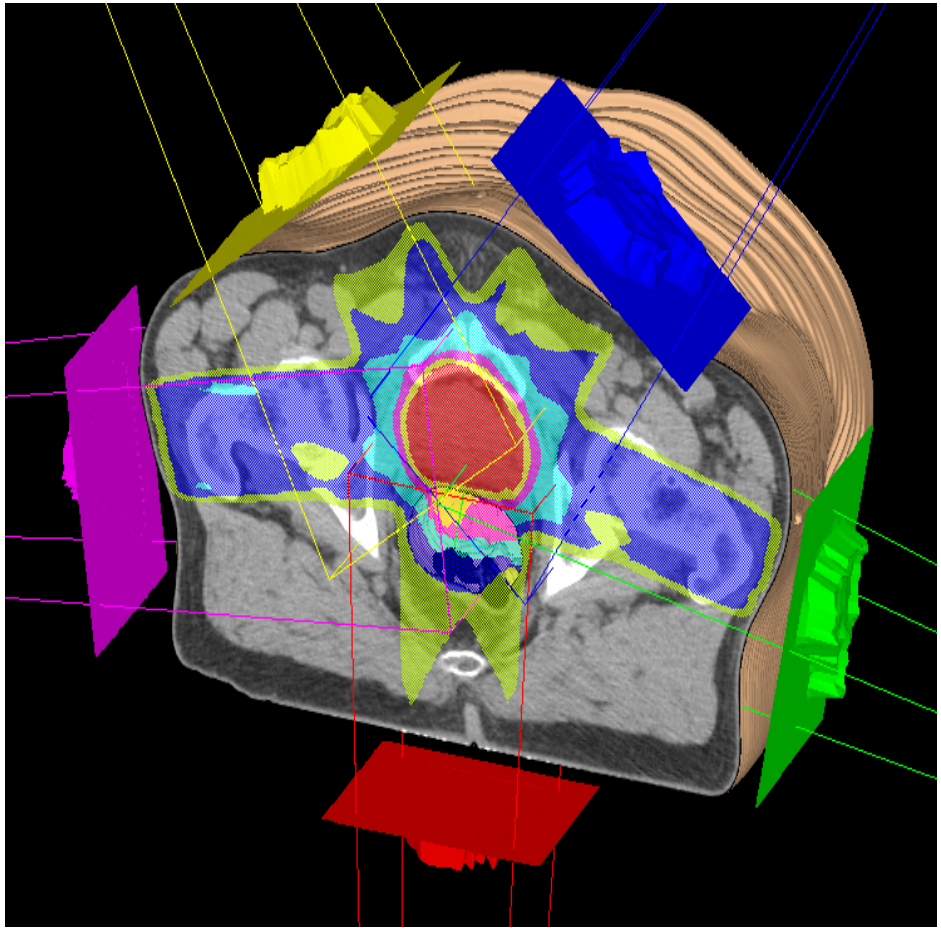
For this reason, it is important to characterize the dose received by both tumor tissue and normal tissue in a quantitative way.



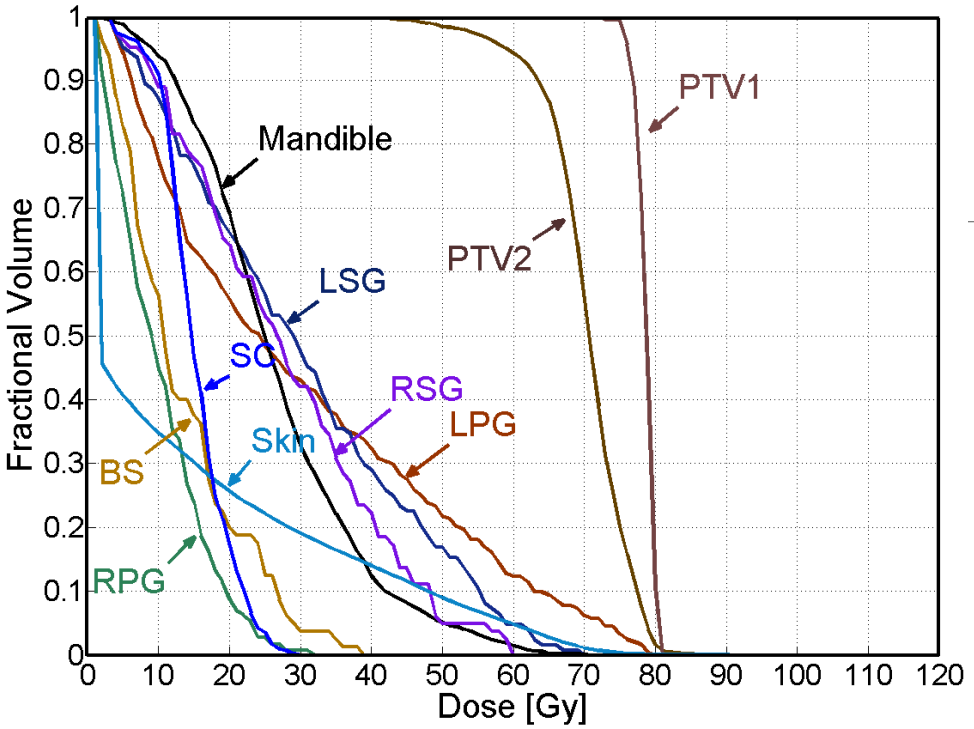
Example of two-dimensional isodose curves in the treatment of retroperitoneal liposarcoma, close to critical organs – kidneys and spinal cord.

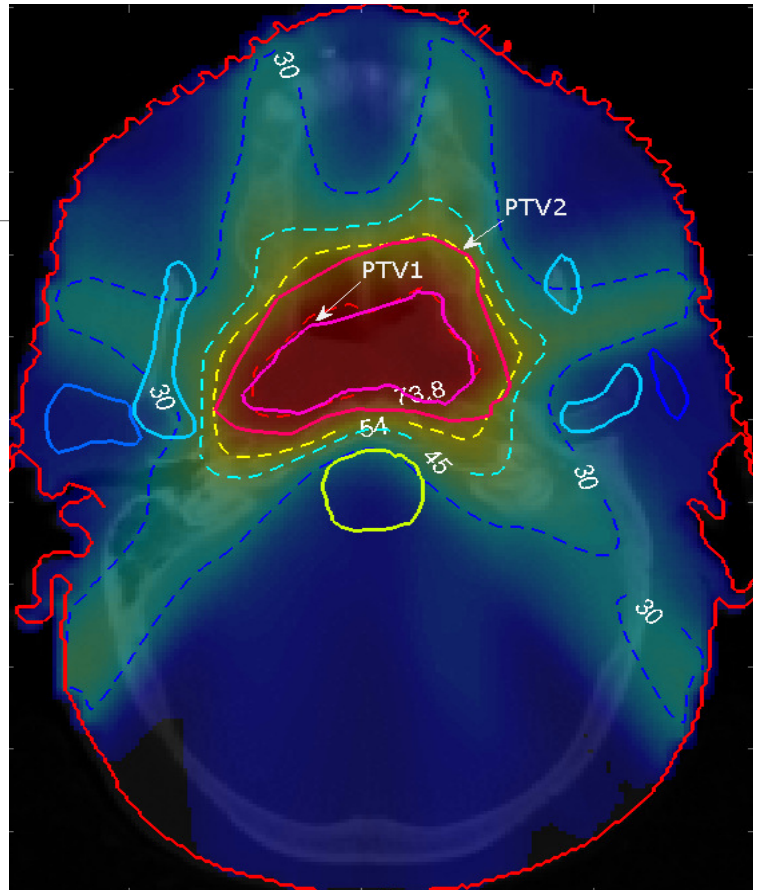
PTV = Planned Target Volume

OAR = Organ At Risk



Dose deposited in patient is measured using a fine cubical grid, and the cubes are called **voxels.**





Dose-volume histograms are cumulative distributions of the voxels receiving **at least** the given dose.

Differential dose-volume histograms are also used (fraction of the voxels receiving **exactly** the given dose).

Optimization (basic concepts of treatment plans)

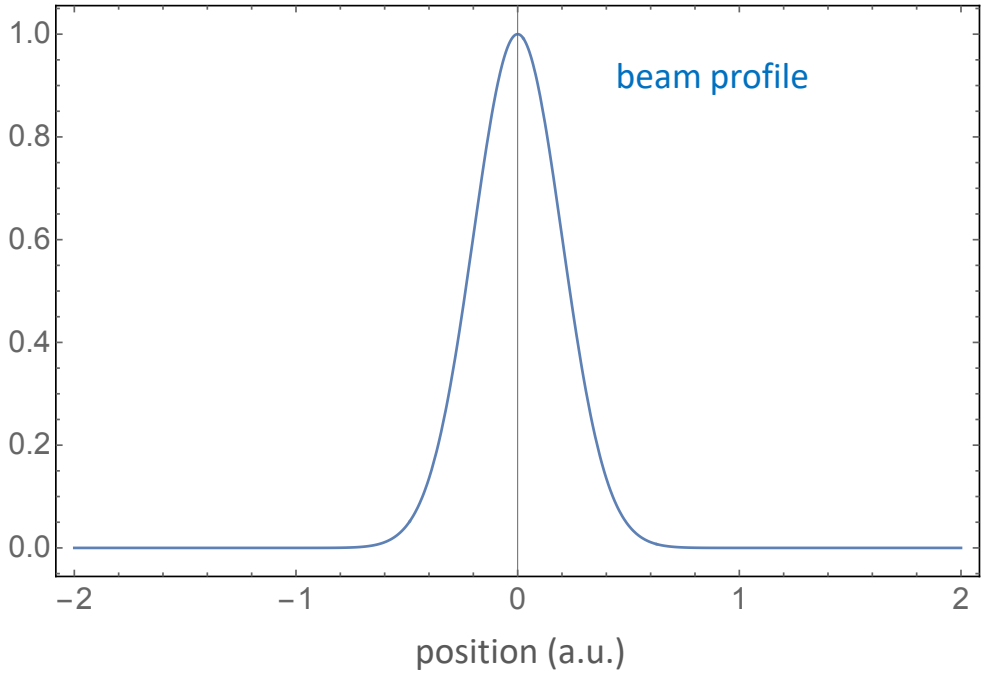
We optimize a treatment by

- maximizing damage to tumor tissue
- minimizing damage to normal tissue

This is a complex process that requires numerical solutions.

In the following slides we analyze a simple example that utilizes Monte Carlo simulation to analyze the effects of an IMRT (Intensity-Modulated Radiation Therapy) treatment (IMRT is an improved version of the 3D-treatment).

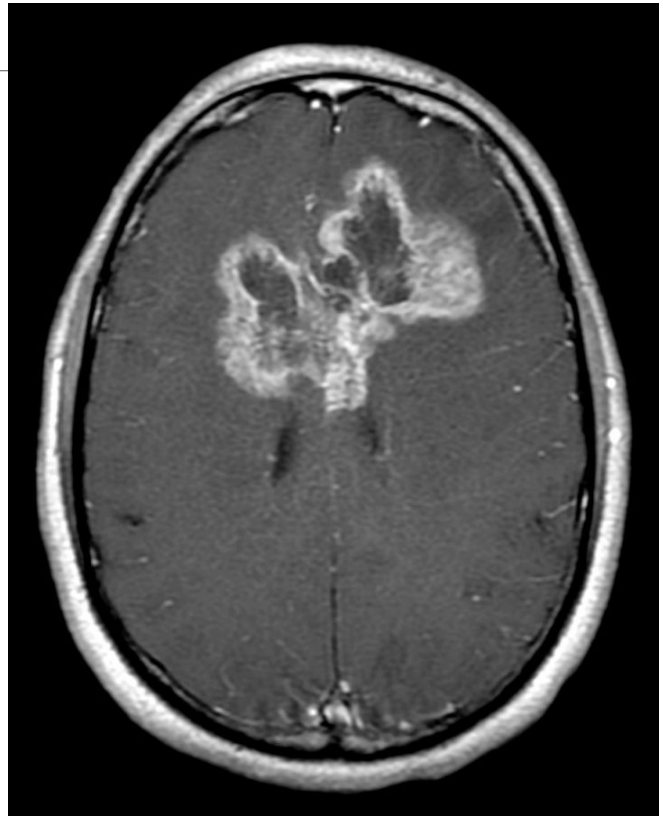
In this example the radiation is delivered by beams with the same Gaussian intensity modulation (this kind of intensity modulation is not realistic, it is just part of this specific example)



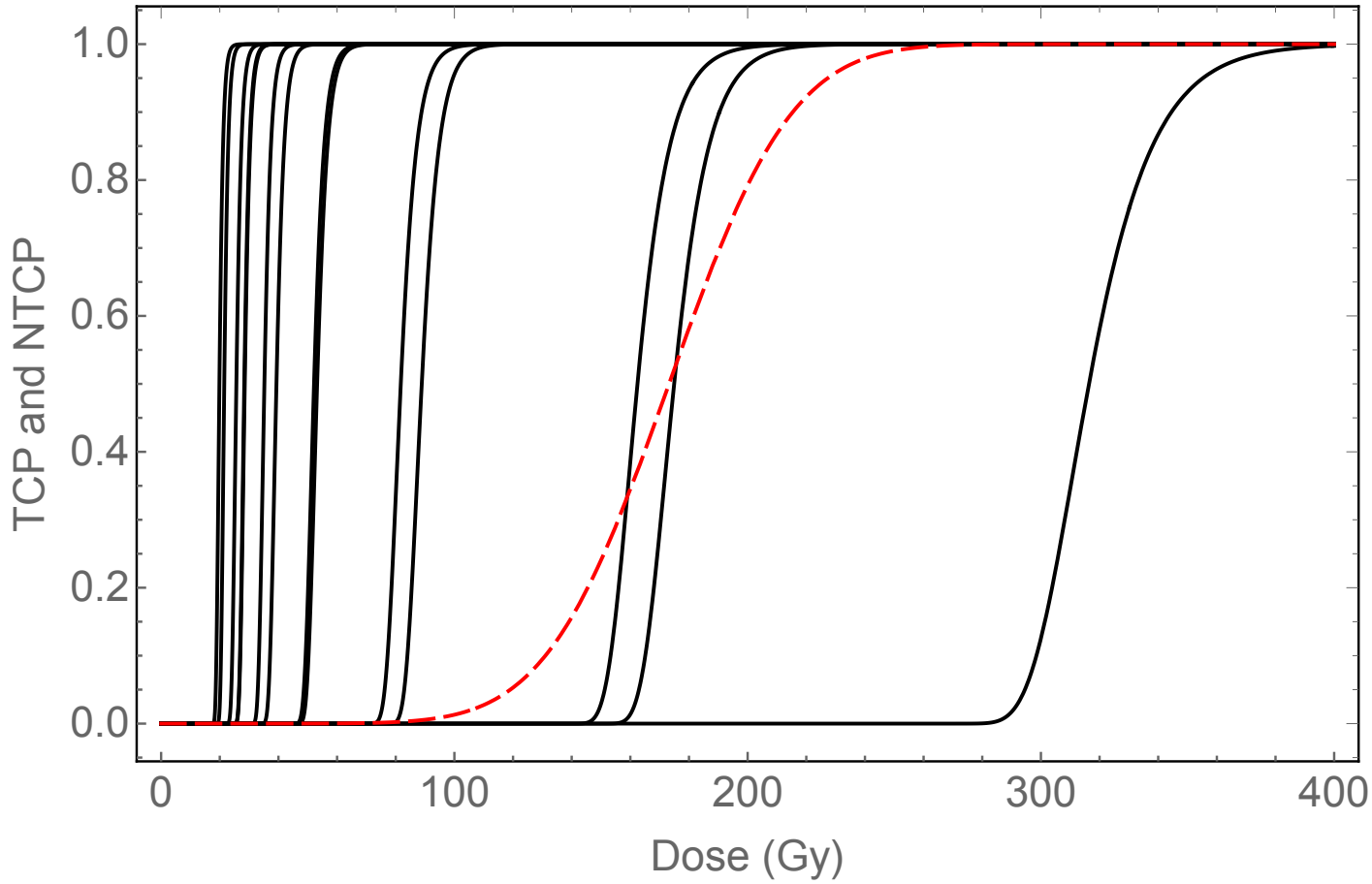
Simulation target: glioblastoma multiforme

Glioblastoma multiforme (GBM) is the most common and malignant brain tumor found in human beings, accounting for approximately 52% of all functional tissue brain tumor cases and 20% of all intracranial tumors.

GBM is comprised of heterogeneous groups of neoplasms that proliferate through various parts of the central nervous system. Although it is the most prevalent form of primary brain tumor, only 2-3 cases per 100,000 people in the Europe and North America are reported annually. However, the prognosis for patients afflicted with GBM is extremely poor, and is eventually fatal in the vast majority of cases.



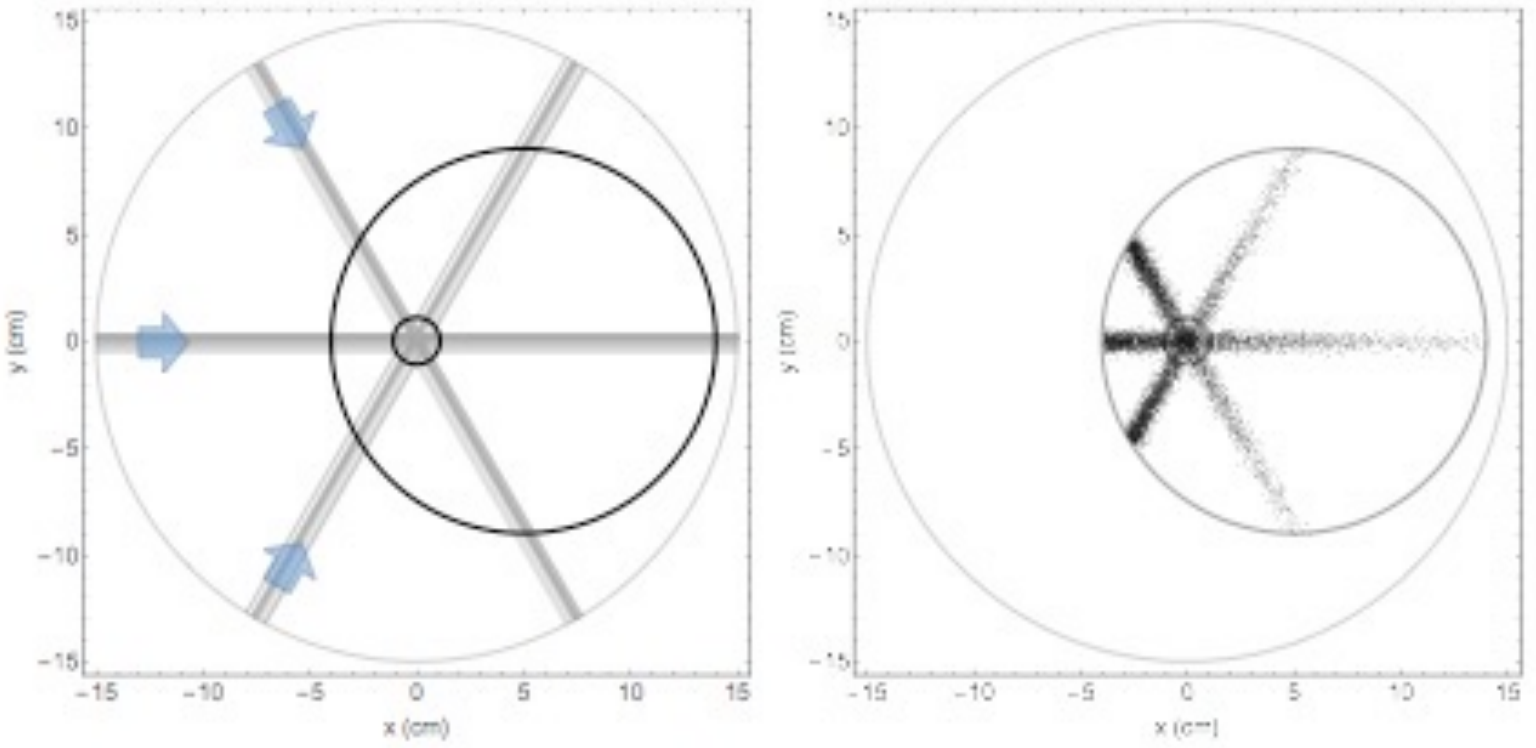
(from https://sites.google.com/site/whatisglioblastomamultiforme/pathophysiology)



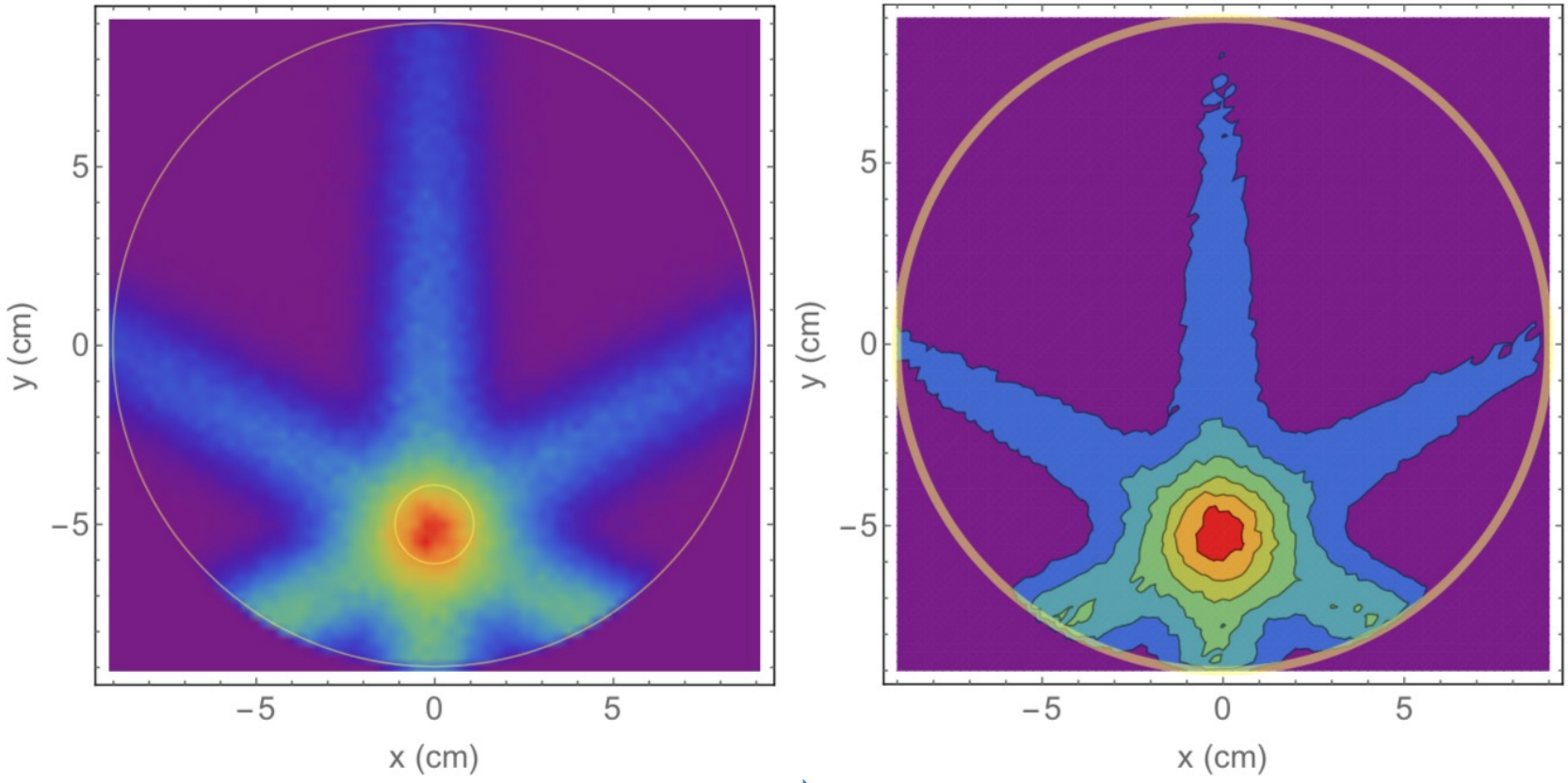
TCP curves (solid black lines) for various GBM histological types and NTCP curve (dashed red line) for brain tissue vs. dose D (Gy), for 10^9 cells (volume about 4 cm^3). The TCP curves have been drawn taking the linear extrapolation of the LQ model with the α and β parameters listed in the literature. The NTCP curve has been drawn with partial volume v = 5%.

Example distribution with 3 beams

Each dot represents the position of one absorbed photon. The local dot density is proportional to the local dose. The photon beams undergo exponential attenuation, and there is a corresponding energy absorption in tissue.



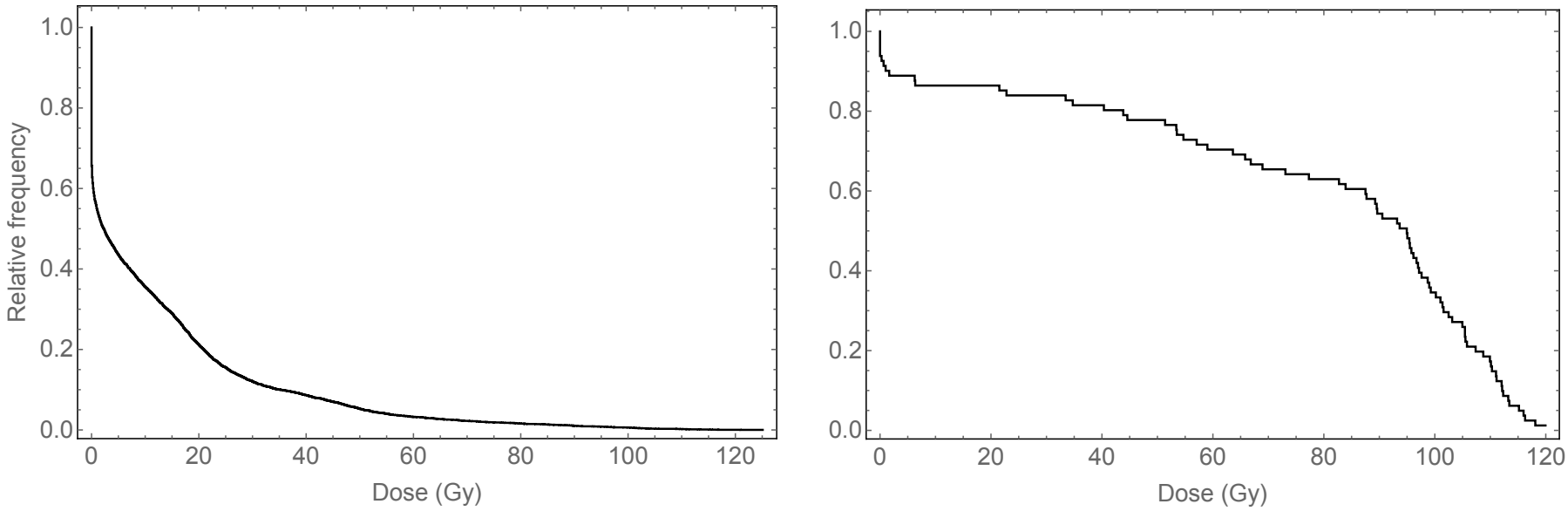
Isodose curves



From voxels to

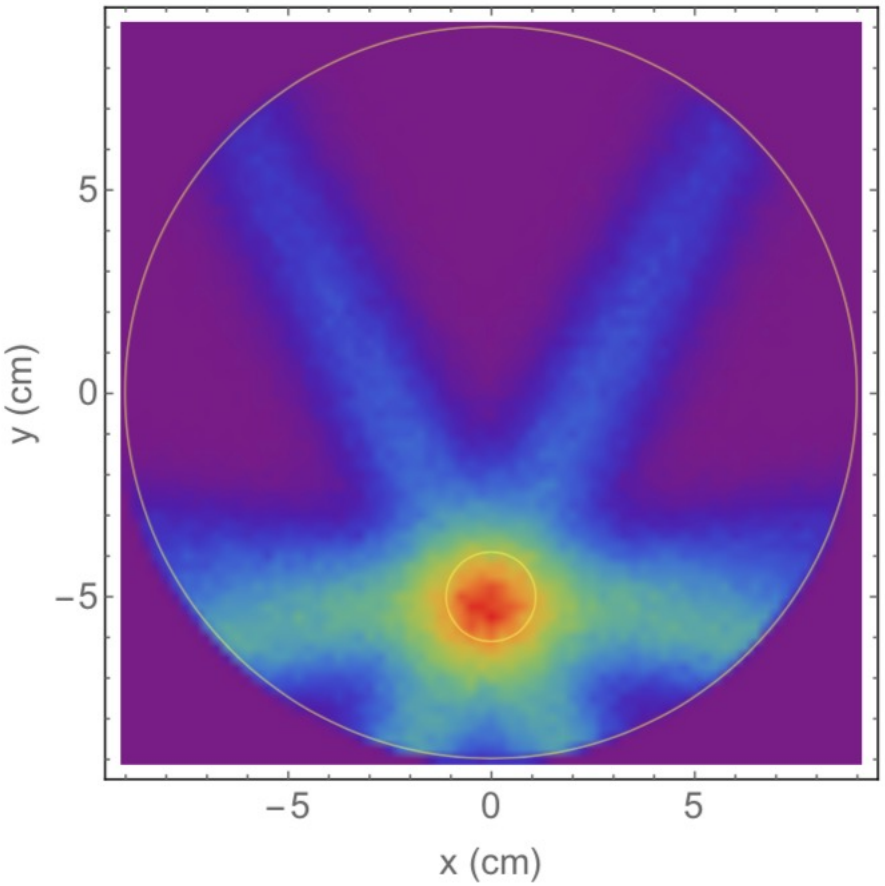
isodose curves

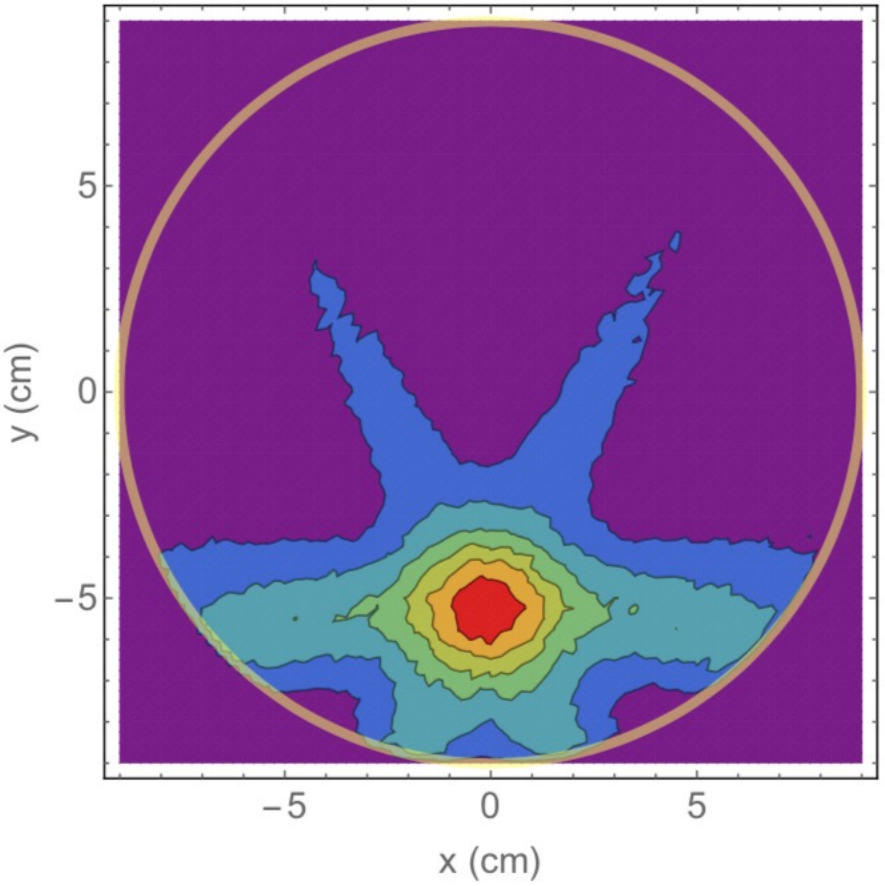
Dose-volume histograms



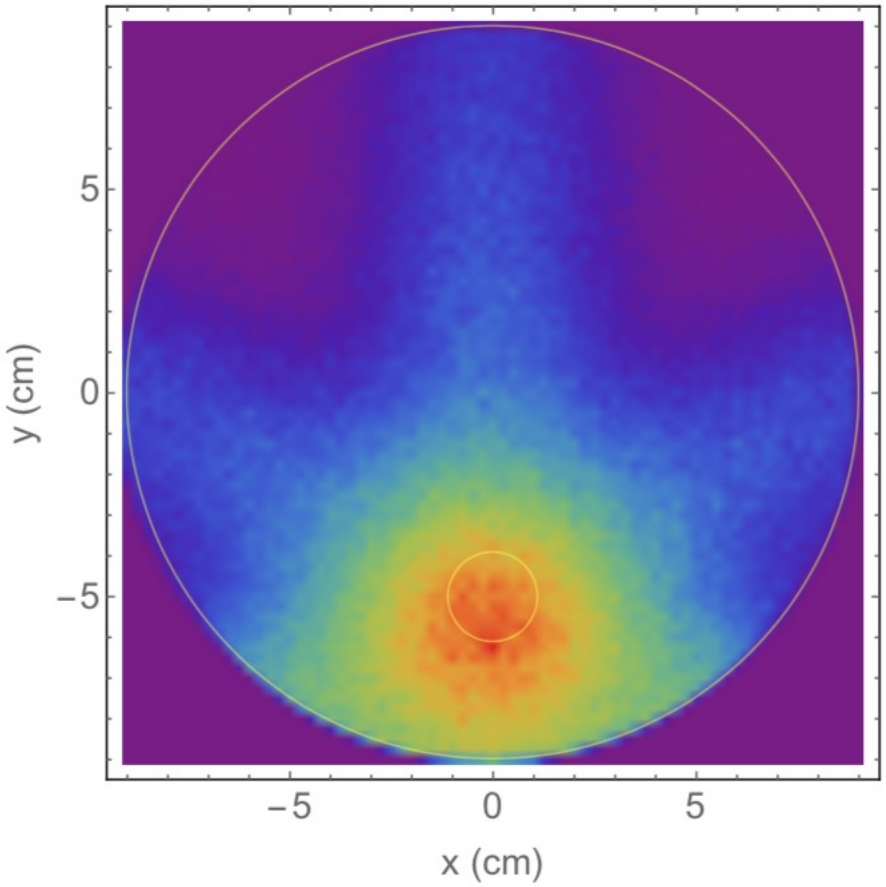
Dose-volume histograms (DVH) for the whole volume of the simulated head (left panel) and for the planning target volume (right panel). DVH's are empirical cumulative distributions of dose that are often used in radiotherapy, but they are read off differently from usual cumulative distributions. For instance, from the histogram on the right we find that about 70% of all voxels receives a dose larger than 60 Gy, and that about 30% of all voxels receives a dose larger than 100 Gy.

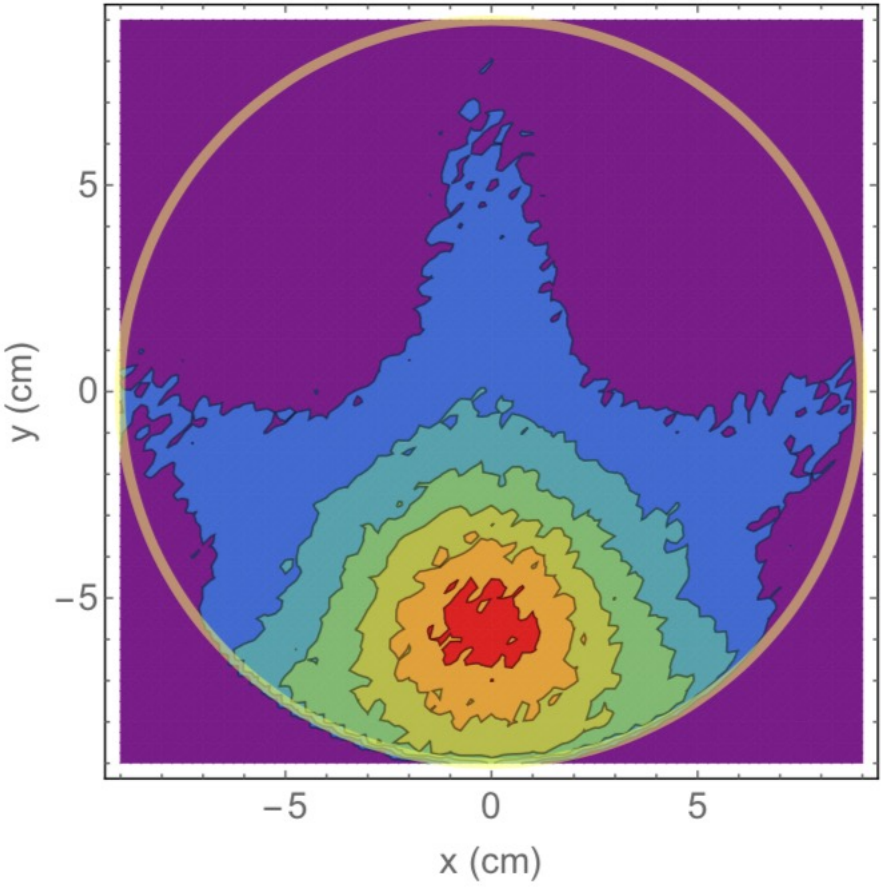
Simulation with 4 beams

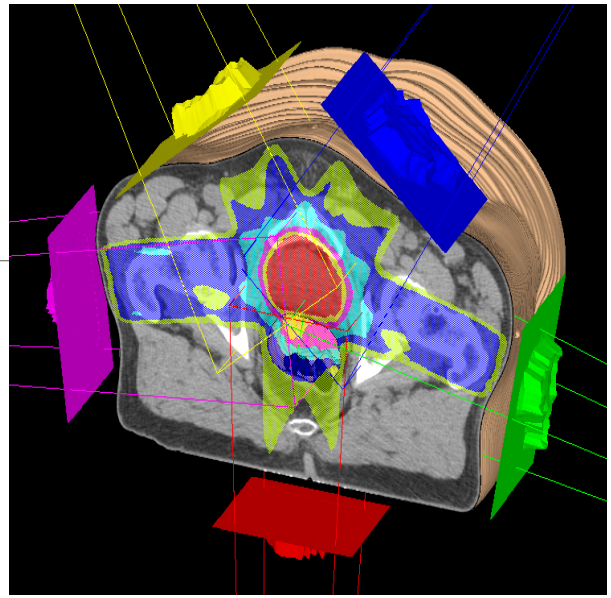




Simulation with 3 beams and doubled beam width







By carefully adjusting the beam parameters we can optimize the results of radiation therapy.

This simple example shows how to use the basic principles, however:

- example limited to 2D (real treatment plans must be 3D)
- no real physics (intensity does not change because of absorption, no Compton scattering of photons, etc.)
- quantification of damage with simplified TCP and NTCP curves
- simple structure with circular symmetry (real cases are much more complex)
- no organ-at-risk in the vicinity
- …

Test problems: an example from last year

1A. Consider the multistage model of colorectal cancer onset that we studied during the course. In this model there is a certain number of critical genes that must mutate, and therefore malfunction, to lead to the onset of cancer. What is the phenomenological power law that describes epidemiological data (probability of onset at age a vs. age a)?

1B. In the multistage model, we let r be the mutation rate per base per division. If L is the mean gene length, what is the mean mutation rate per gene per division?

1C. Using the definitions given in the previous questions, what is the probability that a given gene is not mutated over d consecutive divisions?

1D. Using the result of the previous question, what is the probability that a gene *is* mutated in at least one of the d consecutive divisions?

1E. If this process is replicated over k genes in the same cell, what is the probability that all the critical genes in the same cell have at least one mutation over d consecutive divisions? What is the probability that none of the critical genes is mutated over d consecutive divisions?

1F. Using the result of the previous question, what is the probability that no cell has mutations in all the critical genes? What is the probability that all the critical genes have at least one mutation in at least one cell after d consecutive divisions?

1F. Using the result of the previous question, what is the probability that no cell has mutations in all the critical genes? What is the probability that all the critical genes have at least one mutation in at least one cell after d consecutive divisions?

1G. Assuming that $rLd \ll 1$, expand the probability that all the critical genes have at least one mutation in at least one cell after d consecutive divisions (result of previous question), up to first order, and explain how this compares with the phenomenological power law of question 1A, recalling that if T is the mean duplication time, $d = a/T$.

1H. Take the following numerical values: $r = 10^{-9}$; $L = 400$; $T = 1$ day; $k = 6$; $n = 10^8$. How many days does it take to reach the value $p = 0.0001$ (corresponding to 10 cases in a population of 100000 people)?

1I. Go back to the previous question and repeat the evaluation of the number of days it takes to reach the value $p = 0.0001$, assuming a mutation rate r that is 10% larger (i.e., $r = 1.1 \times 10^{-9}$), due, e.g., to higher background radiation.

1J. If the cells in the previous questions correspond to a uniform layer of epithelial stem cells, with a thickness of just one cell, find the area covered by the epithelial stem cells, where each cell can be approximated by a sphere of radius 10 μm.

Solutions of the "standard" part

1A. The phenomenological power law is

$$p(onset\ of\ illness\ at\ age\ a)\ \approx\ ba^k$$

where a is the age (time) of cancer onset, and b and k are the power law parameters.

1B. The mean mutation rate per gene per division is rL.

1C. $(1-rL)^d$

1D. $1-(1-rL)^d$

1E. The probability that all the critical genes in the same cell have at least one mutation over d consecutive divisions is $[1-(1-rL)^d]^k$. The probability that none of the critical genes is mutated over d consecutive divisions is $1-[1-(1-rL)^d]^k$.

1F. The probability that no cell has mutations in all the critical genes is

$$\{1-[1-(1-rL)^d]^k\}^n$$

where n is the total number of cells. The probability that all the critical genes have at least one mutation in at least one cell after d consecutive divisions is

$$1-\{1-[1-(1-rL)^d]^k\}^n$$

1G. The power law is

$$p(onset\ of\ illness\ at\ age\ a)\ \approx\ n(drL)^k=\frac{n(rL)^k}{T^k}a^k=ba^k$$

Q: H-I

1H. Take the following numerical values: $r = 10^{-9}$; $L = 400$; $T = 1$ day; $k = 6$; $n = 10^8$. How many days does it take to reach the value $p = 0.0001$ (corresponding to 10 cases in a population of 100000 people)?

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A: H-I

1H. Using the result found in the previous question, we find

$$\frac{a}{T} = \frac{1}{rL}\left(\frac{p}{n}\right)^{1/k}$$

Clearly, since $T = 1$ day, the ratio a/T is the age expressed in days. We also find

$$\left(\frac{p}{n}\right)^{1/k} = (10^{-12})^{1/6} = 0.01$$

and therefore

$$\frac{a}{T} = \frac{1}{rL}\left(\frac{p}{n}\right)^{1/k} = 25000 \text{ days} \approx 68.5 \text{ years.}$$

1I. In this case $\frac{a}{T} \approx 22700$ days ≈ 62.3 years.

Q: J

1J. If the cells in the previous questions correspond to a uniform layer of epithelial stem cells, with a thickness of just one cell, find the area covered by the epithelial stem cells, where each cell can be approximated by a sphere of radius 10 μm.

A: J

1J. The approximate radius of a human cell is about 10 μm. This implies a cross-section area of about 3.14×10^{-10} m^2 and therefore 10^8 cells cover an area ~ 0.031 m^2.