“Altered fractionation- hyper, hypo & accelerated fractionation”

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Introduction

Fractionation in Radiotherapy started after the French Experiments on ram in 1920

Basis of Fractionation in RT:

Dividing a dose into no. of #s which

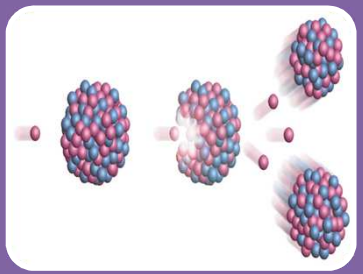
- Spares normal tissues by Repair of sublethal damage and Repopulation
- Increases damage to tumor by Reoxygenation and Reassortment

Introduction

Fractionation allows

- Normal tissue to recover & repair sub-lethal damage from previous #
- Killing of the tumor cells unable to sustain the first fraction

Most of cells exposed to low-LET rays experience a higher chance of sub-lethal damage than those with high-LET rays



When a single dose is divided into two fractions,

- An additional dose is required to compensate for repair.
- This dose is dependent on size of single dose & relative size of 2 smaller #s

Introduction

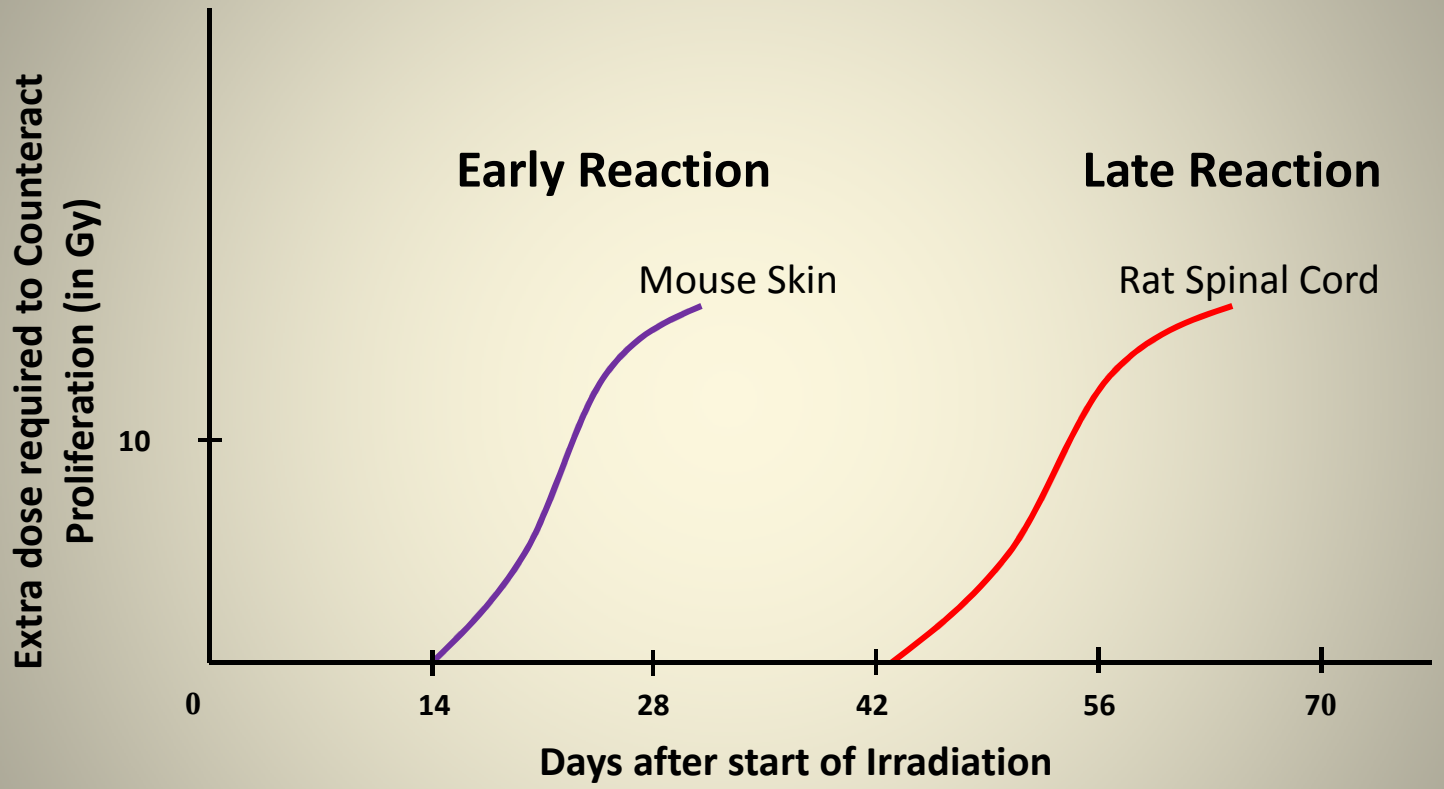
All normal tissues are not the same.

There is clear distinction between early responding (skin, mucosa, intestinal epithelium) & late responding (spinal cord) tissues.

The time after the start of a fractionation regimen at which extra dose is required to compensate for cellular proliferation is quite different for late as opposed to early responding tissues.

Hence prolonging overall time within the normal radiotherapy range has no sparing effect on late reactions but a large sparing effect on early reactions.

Introduction



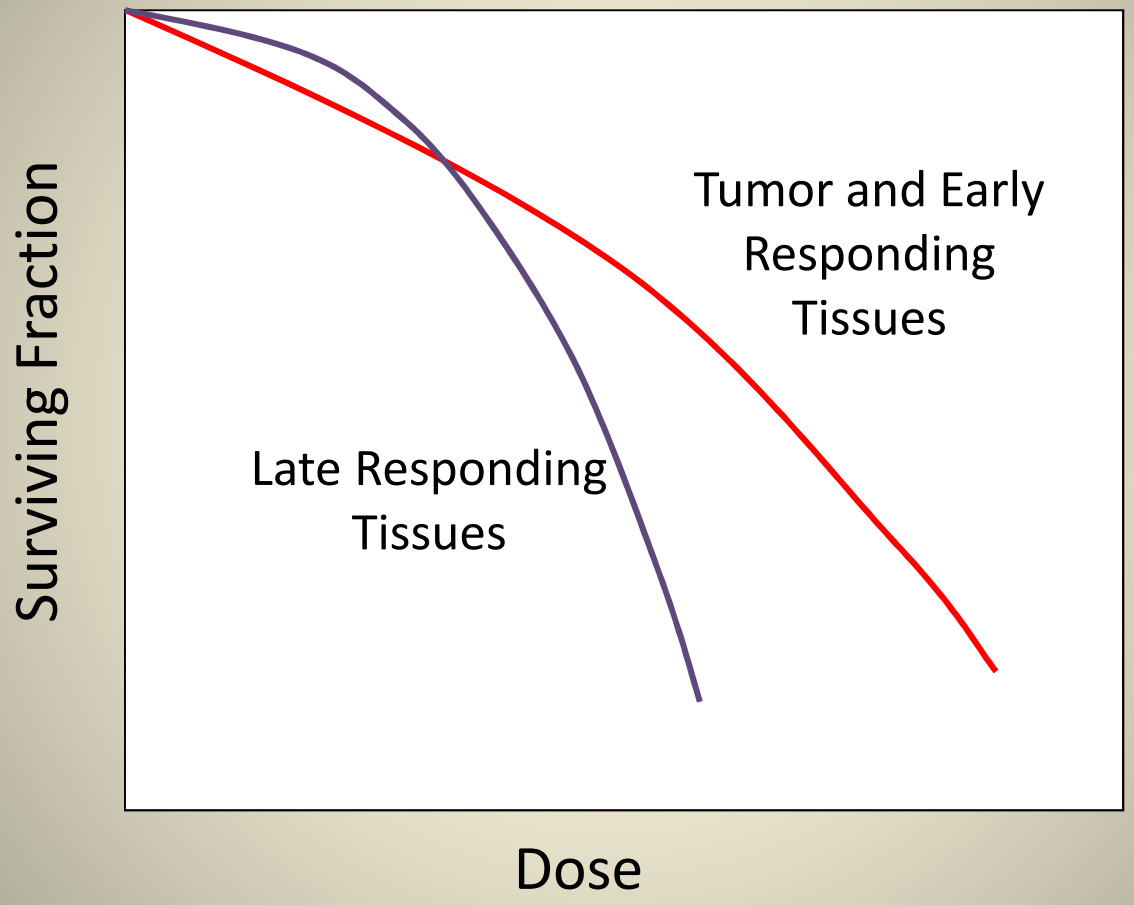
Extra dose required to counteract proliferation only as a function of time after starting daily irradiation in rodents.

Introduction

Hence early reactions such as skin or mucosal reactions can be dealt with by prolonging overall time.

While this strategy overcomes the problem of early reactions, it has no effect on the late reactions.

Dose–Response Relationship



The dose response relationship for late responding tissues is more curved than for early responding tissues.

Dose–Response Relationship

For Early effects α/β is large,

- α dominates at low doses
- The dose response curve has a marked initial slope and does not bend until higher doses.
- The linear and quadratic components of cell killing are not equal until about 10 Gy.

For late effects α/β is small

- β term has an influence at low doses.
- The dose response curve bends at lower doses at appear more curvy
- The linear and quadratic components of cell killing are equal by about 2 Gy.

Dose–Response Relationship

Clinical and lab data also suggests that there is a consistent difference between early and late responding tissues in their response to changing fractionation patterns.

The dose response relationship for late responding tissues is more curved than for early responding tissues.

There is larger α/β for early than for late effects.

α/β is the dose at which the linear (α) and the quadratic (β) components of cell killing are equal: i.e., $\alpha D = \beta D^2$.

Fraction Size & Overall Treatment Time

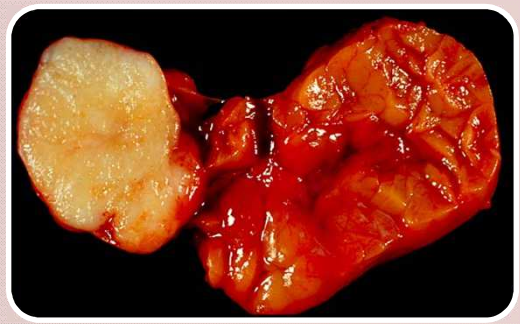
Factors determining Late Effects:

- Fraction size is the dominant factor
- But overall treatment time has no influence.

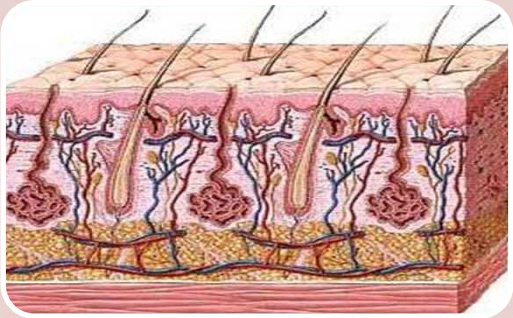
Factors determining Early Effects

- Both fraction size and overall treatment time

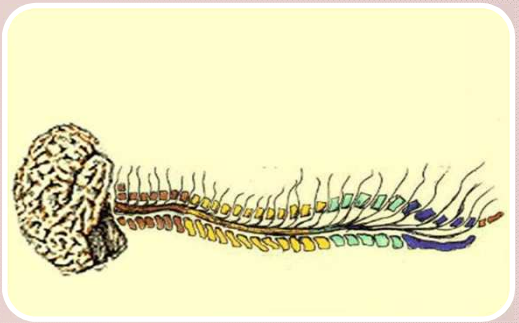
Response to Multiple small doses



Tumor shrinks and does not re-grow years later

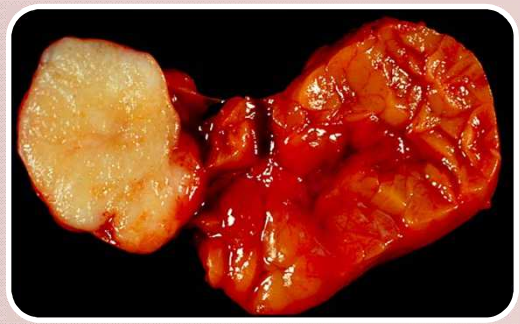


Shows considerable damage but repairs and is intact years later

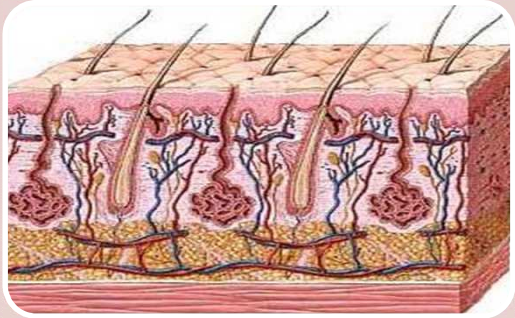


Very little damage to late responding tissues even years later

Response to Small no. of large



Tumor is shrinking and may be eradicated. Chance of recurrence higher



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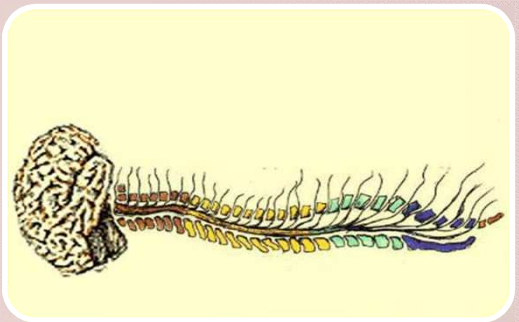

Show considerable damage. This will manifest only later when these tissues are called upon to divide.

Accelerated Repopulation

Treatment with any cytotoxic agent including radiation triggers surviving cells in a tumor to divide faster that before. This is **Accelerated Repopulation**.

Radiotherapy should be completed as soon after it has begun as is practicable.

It may be better to delay initiation of treatment than to introduce delays during treatment.

If overall treatment time is too long, the effect of later dose fractions will be prejudiced as the surviving clonogens in tumor have been triggered into rapid repopulation.

There is evidence in some human cancers that the RT produces poorer results if preceded by a course of CT caused due to AR triggered by CT.

Altered Fractionation

The "Standard Fractionation" for RT has evolved into 5 # a week by empiricism and convenience .

Other alternative fractionations proposed include:

- Hyperfractionation
- Accelerated Fractionation
- CHART
- Hypofractionation
- Split Course

Altered Fractionation

Fractionation Schedule	Schedule
Conventional	IIIII IIIII IIIII IIIII IIIII IIIII 200 cGy per day; 5 days a week
Hyperfractionation	II II II II II II II II II II II II II II II II II II II II II II II II II II II II II II 115 cGy X 2 per day; 5 days a week.
Accelerated Fractionation	II II II II II II II II II II II II II II II II II II II II II II II II II 150-200 cGy X 2 per day; 5 days a week
CHART	II II II II II II II II II II II II II II II II II II II II II II II II II 150-200 cGy X 2 per day; 7 days a week
Hypofractionation	I I I I I I I I I I 400 -500 cGy per day; twice a week
Split Course	IIIII IIIII Rest → IIIII IIIII > 250 cGy per day

Altered Fractionation

	Conventional	Split Course	Accelerated MDF	Hyperfractionation
For Tumors of growth rate	Average	Average/ Slow	Rapid	Slow
Acute effects	Standard	Standard/ Greater	Greater	Standard / Greater
Late effects	Standard	Greater	Standard /Greater	Lower
Advantages		Shorter treatment	Destroys more tumor cells and prevents tumor cell repopulation Less overall treatment time	Spares late damage, allows reoxygenation; allows stem cell repopulation
Disadvantages		May permit tumor repopulation		More fractions

Altered Fractionation

Peschel and Fisher reviewed the rationale for multiple daily fractionations

They emphasized that any alteration in fractionation schedule is potentially harmful and must be approached with great caution

They enlisted the following radiobiological principles for these altered fractionation:

Altered Fractionation

Prolonging overall treatment time favors acute over late tissues; provides for oxygenation of originally hypoxic cells.

Increase in number of fractions favors a cells that repairs sublethal damage; provides opportunity for redistribution through the cell cycle between the treatments.

Close spacing of radiation treatments could significantly favor a subpopulation of cells that repairs sublethal damage more rapidly.

Altered Fractionation

Multiple daily fractionation (MDF)

- Could be more effective in rapidly growing tumors with a high growth fraction,

Hypofractionation: (1, 2 or 3 fractions a week with higher doses)

- May be more efficacious for slow growing tumors (large D_o cell populations) or for tumor with a large D_q (e.g., melanoma).

Altered Fractionation

Thus the advantages of prolongation of treatment are

- To spare early reactions and
- To allow adequate reoxygenation in tumors.

Excessive prolongation, however has two disadvantages.

- It can decrease deceptively the acute reactions without sparing the late injury
- It will allow the surviving tumor cells to proliferate during treatment

Hyperfractionation

Basic aim is to further separate the early and late effects.

The overall treatment time remains at 6-8 weeks, but since 2 # per day are used, the no. of fractions is doubled to 60 - 80.

The dose must be increased since the dose per fraction has been decreased.

The intent is to further reduce the late effects, while achieving the same or better tumor control and the same or slightly increased early effects.

Hyperfractionation

- Withers introduced a concept of *flexure dose*: The point at which the dose response curve starts to bend significantly.
- In practice this occurs at the dose of 0.1 of α/β.
- The curve bends at the dose 1/10 of that at which the linear & quadratic components are equal.
- α/β values are about 6-12 Gy for early tissues & 1-5 Gy for late tissues.
- Thus the flexure dose is 60 - 120 cGy for early tissues and 10 - 50 cGy for late tissues.

Hyperfractionation

- Prospective controlled clinical trials in the United States and by the European Cooperative Group have shown that the hyperfractionation can improve local control in head and neck cancer by 15%.

EORTC Trial:

- Comparison b/w conventional 70 Gy in 35 # over 7 weeks to 80.5 Gy in 1.15 Gy per fraction, 2 fractions per day and 5 days a week in 7 weeks.
- The results suggest that acute reactions were more severe but late reactions the same with an increased effect on the tumor.

Accelerated Fractionation

Involves an approx. conventional total dose and fraction, given 2 # a day, the overall treatment time is approx. halved.

In practice: It is never possible to achieve this since early effects become limiting.

Usually necessary to interpose rest period in the middle of Rx to slightly reduce the dose with early effects as the limiting factor.

Intent: to reduce repopulation in rapidly proliferating tumors.

No change in the late effects, since the number of fractions and the dose per fraction are unaltered.

Accelerated Fractionation

- Saunders et al, delivered accelerated fractionation, given 3 times a day for 12 consecutive days without a period of rest to a total dose of 50.4 Gy.
- The treatment was well tolerated in a series of patients with bronchial and head and neck cancers.

Saunders et al

CHART

CHART is similar to AF but patients are also treated at weekends to further reduce the overall treatment time.

CHART has recently been shown to improve survival in lung cancer patients compared to standard fractionation.

However both AF & CHART increase acute side effects and due to logistic problems they are not in wide use.

Hypofractionation

A small number of fractions but the dose per fraction is higher.

Overall dose must be lower than the conventional radiotherapy, due to the risk of late side effects.

This is particularly useful in palliative situations as:

- The overall treatment time is short &
- The large daily doses can be particularly effective in fast growing, aggressive symptomatic cancers.

Split Course Radiation

Large doses per fractions are used daily, increasing the risk of late side effects.

Therefore a treatment gap of few weeks rest is allowed before continuing.

This is mainly used in palliative conditions.

Conclusion

- Dividing a dose into a no. of # spares normal tissues by repair of sublethal damage and repopulation
- At the same time it increases the damage to tumor by reoxygenation & reassortment.
- 3 cell populations that govern radiation are “Tumor”, “Acute Responding Tissues” & “Late Responding Tissues”.
- Fraction size is a dominant factor in determining late effects, while overall treatment time has little influence.
- By contrast, fraction size and overall treatment time both determine the response of acutely responding tissues.

Conclusion

Altered Fraction	Overall Rx Time	Dose per #	No. of #	Total Dose	Intent
Hyper Fraction	Same	Reduced	Doubled/ More	Increased	Tumor Control: Same/ Better Acute Effects: Slightly more Late Effects: Less
Accelera ted Fraction	Reduced	Same	Same; but 2-3 # per day	Same	Tumor Control: Better Acute Effects: Pronounced Late Effects: Same
CHART	Reduced further	Same	Same	Same	Tumor Control: Better Acute Effects: Pronounced Late Effects: Same
Hypo Fraction	Reduced	Large	Less	Reduced	Tumor Control: Poor Acute Effects: Less Late Effects: High
Split Course	Reduced	Large	Less	Reduced	Tumor Control: Poor Acute Effects: Less Late Effects: High

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