

Basic Radiobiology for the Radiotherapy Physicist

Colin G. Orton, Ph.D.
Professor Emeritus,
Wayne State University,
Detroit, Michigan, USA

Fractionation: why did we ever fractionate?

- Actually, initially there was considerable debate between two Schools of Thought
- The Single Fraction School (Germany) believed that fractionated treatments were inferior because they allowed cancer cells to proliferate during the course of treatment
- The Multiple Fractions School (Paris) believed that, only with fractionation, could high enough doses be delivered to cancers for cure without exceeding normal tissue tolerance

The Multiple Fractions School won!

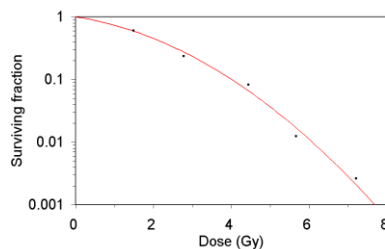
- It was not until 1932 that the debate was settled when Coutard in Paris published his excellent results using fractionated therapy with higher cure and lower complication rates than others had been able to achieve with single doses
- Single fraction radiotherapy was abandoned

Do we now know, radiobiologically, why fractionation is so important?

- Yes, it's because cells are able to repair radiation damage if this is not too great such as when
 - low doses and/or low doses/fraction are used and the radiation is not highly damaging i.e. not high-LET
- Most importantly, the cells of late-reacting normal tissues that are responsible for complications are better able to repair than are cancer cells
- At low doses cell survival of normal tissues will exceed that of cancers

As dose increases cell survival curves become steeper

Survival curves are less steep at low doses, especially for cells of late-reacting normal tissues, since most of the cells will be able to repair the radiation damage



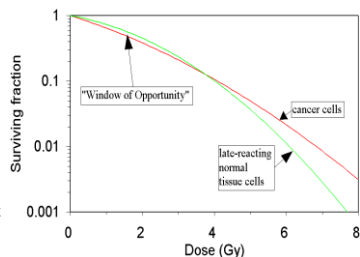
Survival curves: normal vs cancer cells

- Cancer cells do not “repair” damage at low doses as well as do normal tissue cells
 - Hence survival curves will be straighter
- ♦ There is a “Window of Opportunity” at low doses where the survival of late-reacting normal tissue cells exceeds that of cancer cells

Cell survival curve comparison: the “Window of Opportunity”

At low doses, the survival of normal tissue cells (green curve) exceeds that of cancer cells

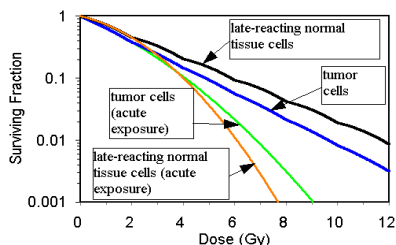
At high doses, the survival of cancer cells (red curve) exceeds that of normal tissues



Fractionation

- This is why we typically fractionate radiotherapy at low doses/fraction
- We need to fractionate at doses/fraction within this “Window of Opportunity” e.g. typically about 2 Gy/fraction

Normal vs cancer cells for fractionation at 2 Gy/fraction



The “Window of Opportunity”

- Note that, for these survival curves, we have assumed that the dose to normal tissues is the same as the dose to the cancer cells
- Is this a reasonable assumption if we are using conformal teletherapy?

No!

- Because the major advantage of conformal radiotherapy is that the dose to normal tissues is kept less than the tumor dose
- Hence the *effective dose** to normal tissues will usually be less than the *effective dose* to tumor

*the effective dose is the dose which, if delivered uniformly to the organ or tumor, will give the same complication or cure rate as the actual inhomogeneous dose distribution. Sometimes called the Equivalent Uniform Dose (EUD)

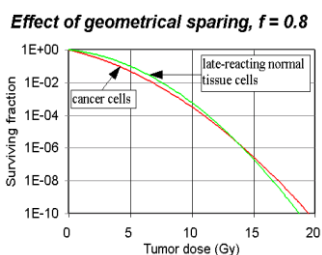
Geometrical sparing factor

We can define a “geometrical sparing factor”, f , such that:

$$f = \frac{\text{effective dose to normal tissues}}{\text{effective dose to tumor}}$$

The “Window of Opportunity” widens with geometrical sparing

Even with a modest geometrical sparing of only 20%, the “Window of Opportunity” extends to over 10 Gy



This means that:

With highly conformal therapy we can safely use much higher doses per fraction

- for teletherapy i.e. hypofractionation
- for brachytherapy i.e. HDR

What about dose rate and time between fractions?

- Repair takes time (half-time for repair typically 0.5 – 1.5 hours), hence repair decreases as
 - time between fractions decreases
 - dose rate increases

Importance of time between fractions

- Because repair is more important for normal tissues than for tumors, enough time must be left between fractions for full repair
 - based on clinical results, this is assumed to be at least six hours

Importance of dose rate

- Normal tissue cells repair better than cancer cells and low dose rate enhances repair
- This is the basis of low dose rate brachytherapy and, especially, permanent implants at very low dose rate

What about overall treatment time?

- Cancer cells and cells of acutely-reacting normal tissues proliferate during the course of therapy (called “repopulation”)
- Cells of late-reacting normal tissues proliferate little
- Hence the shorter the overall treatment time the better
 - but should not be too short otherwise acute reactions will prevent completion of treatment

What else do we know that effects radiotherapy?

- Hypoxia in tumors
 - Hypoxic cells are more resistant to radiation and some tumors are known to contain regions of hypoxia
 - However, hypoxic cells may reoxygenate between fractions
- The LET of the radiation
 - High-LET radiations are more damaging, exhibit less repair, and reduced effect of hypoxia

So how does all this effect the way we treat cancers?

- Different types of fractionation
- Different dose rates for brachytherapy
- Different types of radiation

Different fractionation schemes

- Conventional fractionation
- Hyperfractionation
- Accelerated fractionation
- Hyperfractionated accelerated fractionation
- Hypofractionation

Conventional fractionation

- Dose/fraction: 1.8 -2.2 Gy
- Fractions/week: 5
- Total dose: 50 - 65 Gy
- Used for most patients in the past

Conventional fractionation: potential problems

- May be too slow for the treatment of fast-growing cancers
- Total dose may be too low for some resistant cancers
 - We can go to higher doses without exceeding normal-tissue tolerance by giving lower dose/fraction

Hyperfractionation

- Dose/fraction: 1.1 - 1.3 Gy
- Fractions/week: 10
 - otherwise the overall time will be too great and cancer cells will have too much time to repopulate
- Total dose: 70 - 80 Gy
- Used when late normal tissue tolerance is a major problem (low dose/fraction means more repair) but we need to go to higher doses to control the tumor

Hyperfractionation problems

- Two fractions/day, with at least six hours between treatments, puts extra burden on patients, staff and equipment
- After many clinical trials, no clear benefit has been demonstrated

Accelerated fractionation

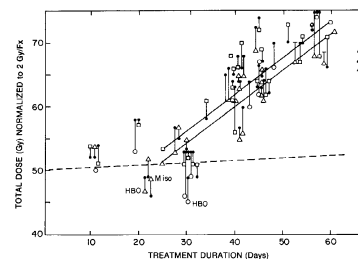
- Used for rapidly growing cancers
- Can be achieved by either using two fractions/day or a higher dose/fraction
- Dose/fraction: about 1.4 (with 2 fractions/day) - 2.5 Gy (with 1 fraction daily)
- Fractions/week: 5 - 10
- Total dose: 40 - 50 Gy

Accelerated fractionation problems

- Early responding normal tissues may not have time to repopulate in the 3 - 4 week course, so acute reactions have been a major problem
 - This has frequently required patients to be given a rest, which negates the acceleration of the treatment
- No clear benefit has been demonstrated in clinical trials

Accelerated repopulation

Withers' "hockey stick" showing that iso-effect dose for local control of H & N cancers increases significantly after 3 - 4 weeks of treatment, showing that even faster treatments might be better



Continuous hyperfractionated accelerated fractionation (CHART)

- Dose/fraction: 1.5 Gy
- Fractions/week: 21 i.e. 3 fractions/day
- Total dose: 54 Gy
- Used for rapidly growing cancers, especially if accelerated repopulation is suspected

CHART (cont'd.)

- Treatment completed in 12 days
- Acute reactions peak after the completion of treatment
 - Remember, with accelerated fractionation patients had to be given a rest due to excessive acute reactions
- Very inconvenient since have to treat for 12 consecutive days, including weekends

CHARTWEL (continuous hyperfractionated radiotherapy weekend less)

- Same as CHART but 5 days/week
- Treatment completed in 16 days
- Acute reactions peak after the completion of treatment (but it's close!)

CHART and CHARTWEL: potential problems

- Initially several patients were treated with as little as three hours between fractions
 - Late complication rates were excessive with these short inter-fraction times
 - A strict minimum of six hours between treatments had to be mandated
- This made these treatments highly inconvenient putting a very great burden on patients, staff and equipment

CHART and CHARTWEL: potential problems
(cont'd.)

- Acute reactions have been a major concern
 - Most patients have had to be hospitalized as soon as they complete therapy for treatment of excessive acute reactions
- Results of clinical trials have not been all that promising

Hypofractionation

- Dose/fraction: above about 2.5 Gy
- Fractions/week: 1 – 5
- Total number of fractions: 1 - 20
- Total dose: 10 - 30 Gy when used for palliation, 20 – 55 Gy when used for cure (depends on fractionation used)

What we know

- Clinical trials around the world are beginning to show that, with highly conformal therapy, hypofractionation can be just as effective as conventional fractionation (both for cure and avoidance of normal tissue complications)
 - we already knew this from stereotactic radiosurgery in the brain, but now know it for other sites

My prediction

- With even more conformation of dose distributions using more sophisticated imaging, image guidance, motion tracking, protons, etc., we'll be using as few as five fractions for most cancers in the near future
 - treatments will cost less and be more convenient
 - accelerated regimes will be more prevalent thus reducing cancer cell proliferation during treatment
 - cure rates will increase

There are some caveats however e.g.
hypoxic cells

- Hypoxic cells are radioresistant to radiation
- However, hypoxic cells may reoxygenate between fractions
- With hypofractionation there are fewer fractions so possibly less opportunity for reoxygenation
 - For hypoxic tumors, **hyper**fractionation might be the better way to go, not **hypo**fractionation

Hypofractionation Results in Reduced Tumor Cell Kill Compared to Conventional Fractionation for Tumors With Regions of Hypoxia

David J. Carlson, Ph.D., Paul J. Keall, Ph.D., Billy W. Loo, M.D., Ph.D., Zhe J. Chen, Ph.D. and J. Martin Brown, Ph.D.

International Journal of Radiation Oncology * Biology * Physics
Volume 79, Issue 4, Pages 1188-1195 (March 2011)



Another caveat: Repair *during* each fraction

- With higher doses/fraction the time to deliver each fraction increases
- If this time gets too long the cancer cells might repair significantly *during* the treatment
- This might be OK if normal cells repair at the same rate but some believe that their half-time for repair is longer than for cancer cells

Potential effects of long treatment times with IMRT for prostate cancer

- Because it is believed that prostate cancer cells have an unusually high propensity for repair (they have a low α/β), some concern has been expressed about the possibility that longer treatment sessions might reduce the efficacy of IMRT and other highly-conformal therapies
- This might be a problem for other cancers if late-responding normal tissue cells repair slower than tumor cells, as has been suggested

Potential effects of long treatment times for prostate treatments

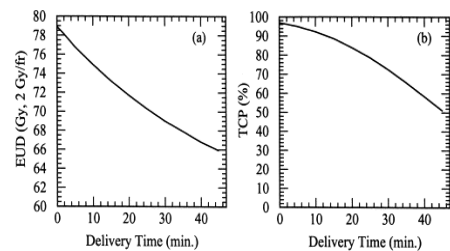
IMPACT OF PROLONGED FRACTION DELIVERY TIMES ON TUMOR CONTROL: A NOTE OF CAUTION FOR INTENSITY-MODULATED RADIATION THERAPY (IMRT)

JIAN Z. WANG, PH.D.,* X. ALLEN LI, PH.D.,* WARREN D. D'SOUZA, PH.D.,* AND ROBERT D. STEWART, PH.D.†

The prescription dose was 81 Gy in 1.8 Gy fractions

Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 2, pp. 543–552, 2003

EUD and TCP for an intermediate-risk patient group assuming the half-time for repair is 16 mins



Wang, et al (2003)

Wang et al conclusions

- *Our calculations indicate that fraction delivery times in the range of 15 - 45 min may significantly decrease cell killing*
- *The total time to deliver a single fraction may have a significant impact on IMRT treatment outcome for tumors with a low α/β ratio and a short repair half-time, such as prostate cancer*

Wang, et al (2003)

So what does all this tell us about hypofractionation?

- Hypofractionation looks very promising but might not be appropriate if:
 - the fraction of hypoxic cells is significant
 - treatment times get so long that cancer cells repair during each session of treatment, especially for tumors with short cancer cell repair half times and low α/β
- Only carefully controlled clinical trials will give us the answers

What else can we do about hypoxic or otherwise resistant cells?

- Maybe high-LET radiotherapy
 - Oxygen is the most powerful radiation sensitizer we know but, with high LET, the radiation is so damaging that it doesn't need oxygen to sensitize cells
 - Certain types of cancers are resistant because the cells are very efficient at repairing damage
 - With high-LET radiation, repair is minimal

So why aren't we all using high-LET radiotherapy?

- Cost!
 - High-LET machines are vast
 - They're extremely heavy
 - Very large
 - Require far more technical staff (especially physicists!)
 - Enormously expensive
- They have not yet been proven better than less expensive forms of radiotherapy

Summary

- We fractionate because late-reacting normal tissue cells repair better than tumor cells at low doses/fraction (the "Window of Opportunity")
- With highly conformal therapy we can treat at higher doses/fraction (the "Window of Opportunity" widens)
- In the future we are likely to increasingly use hypofractionation
- High-LET radiotherapy is very expensive and needs to be proven before most of us get a new toy to play with