The Evolution of Radiation Therapy Dose Fractionation

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

Common fractionation phases

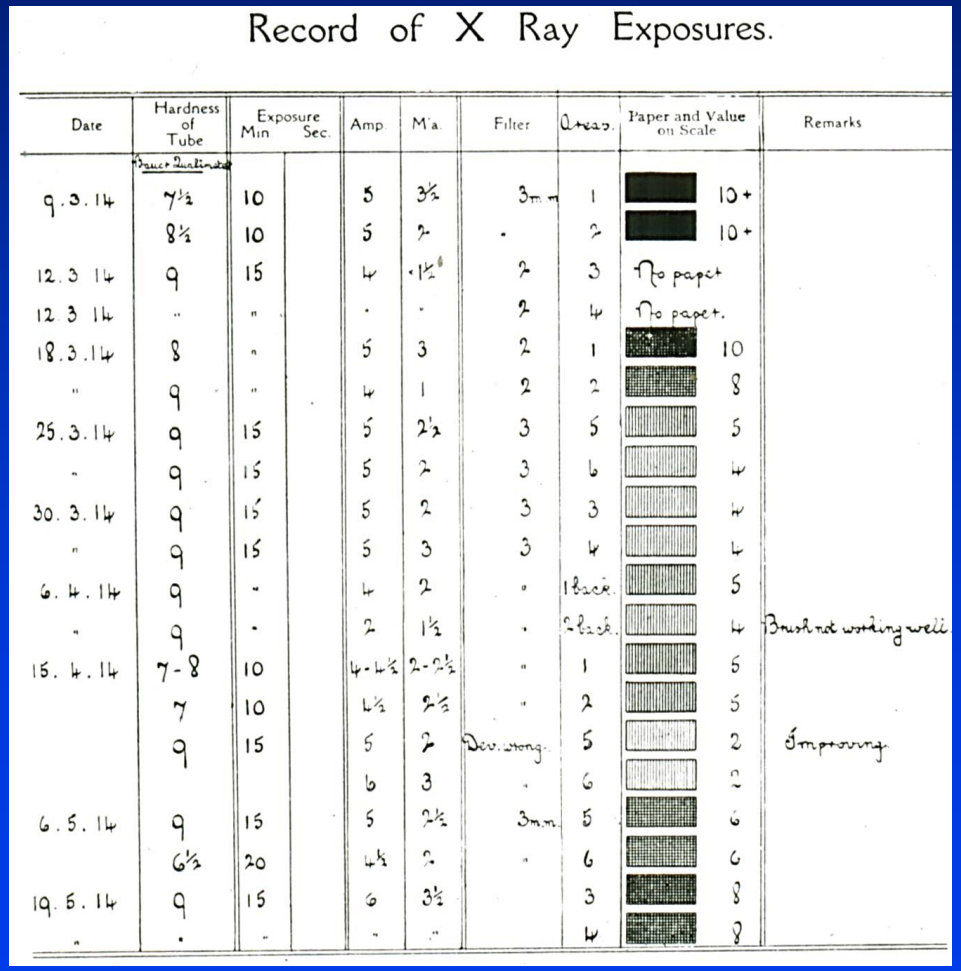
- Since the 1st radiotherapy treatments in 1896, fractionation has gone through several phases
  - *1896-1915: extreme hyperfractionation with as many as 100 fractions*
  - *1915-1935: two Schools of Thought, either extreme hypofractionation with just a single fraction or about 25-40 fractions*
  - *1935-2015: the fractionation school won out and 25-30 fractions became "standard fractionation" with occasional clinical trials of hyperfractionation, accelerated fractionation, and hypofractionation*
  - *2015-present: increased use of hypofractionation*

Physical, radiobiological and clinical rationales driving these phases

1895-1915 extreme hyperfractionation

- *Physical constraints* due to primitive x-ray units
  - *Very low output so needed numerous treatments to achieve sufficient total dose*
  - *Unpredictable exposures so had to measure each exposure to know what dose had been delivered for each fraction*

Typical Page of a Treatment Record



Record of X Ray Exposures.

Date	Hardness of Tube (Bauer Qualimeter)	Exposure Min	Exposure Sec.	Amp.	M'a.	Filter	Area.	Paper and Value on Scale	Remarks
9.3.14	7½	10		5	3½	3m.m	1	10+	
	8½	10		5	2	"	2	10+	
12.3.14	9	15		4	1½	2	3	No paper	
12.3.14	"	"		"	"	2	4	No paper.	
18.3.14	8	"		5	3	2	1	10	
"	9	"		4	1	2	2	8	
25.3.14	9	15		5	2½	3	5	5	
"	9	15		5	2	3	6	4	
30.3.14	9	15		5	2	3	3	4	
"	9	15		5	3	3	4	4	
6.4.14	9	"		4	2	"	Black.	5	
"	9	"		2	1½	"	Black.	4	Brush not working well.
15.4.14	7-8	10		4-4½	2-2½	"	1	5	
	7	10		4½	2½	"	2	5	
	9	15		5	2	Dev. strong.	5	2	Improving.
				6	3	"	6	2	
6.5.14	9	15		5	2½	3m.m.	5	6	
	6½	20		4½	2	"	6	6	
19.5.14	9	15		6	3½		3	8	
"	"	"		"	"		4	8	

Film dosimeter on skin used to record each fraction

Wide variations in exposures showing complete unpredictability

Typically, treatments continued until acute skin reactions became intolerable

First documented successful cancer treatment

1899: Tor Stenbeck, in Sweden, treated a patient with a basal cell skin cancer using a total of 99 fractions

Before treatment

30 years later

1915-1935: two Schools of Thought

- Things changed dramatically after 1914 with the development of the hot-cathode x-ray tube by William D. Coolidge
  - *Much higher exposure rates*
  - *Outputs much more reproducible*
- It became possible to treat cancers with a very few, reproducible, fractions, or multiple, equal dose fractions, giving rise to the Erlangen and Paris Schools, respectively

Erlangen School headed by Hermann Wintz

- Fractionated radiotherapy is the “primitive method” and “weak irradiation”
  - *Long courses of fractionated treatments allow cancer cells to proliferate during treatment*
  - *To overcome this would require doses to be increased beyond the tolerance of normal tissues*

The Paris School headed by Henri Coutard

- Only with fractionation could sufficiently high doses be delivered without exceeding normal tissue tolerance
- Based upon the experiments of Claude Regaud:
  - *Rams could be sterilized by irradiation of the testes without exceeding the tolerance of the skin of the scrotum only if the exposures were fractionated*
  - *They argued that the testes were a good model for a proliferating tumor and the skin represented normal tissues*

The fractionation School won out

- Coutard, at the Institute Curie, Paris, published his excellent clinical results with fractionated radiotherapy in 1934
- Fractionation became the standard of practice
- Coutard's work did not initially define an optimal fractionation technique, however
- Fractionation was based on the size of the tumor and courses ranged from 1-7 weeks, often two fractions/day

1937: the "*Paris*" Technique

- All the early Institute Curie treatments were conducted at low dose-rate due to the primitive nature of the equipment
- François Baclesse took over from Coutard in 1937 and introduced equipment that operated at higher output
- He established the "*Paris*" technique of about 30 high dose-rate fractions of 2 Gy delivered in six weeks

1948: Gilbert Fletcher introduces the "Paris" Technique to the USA

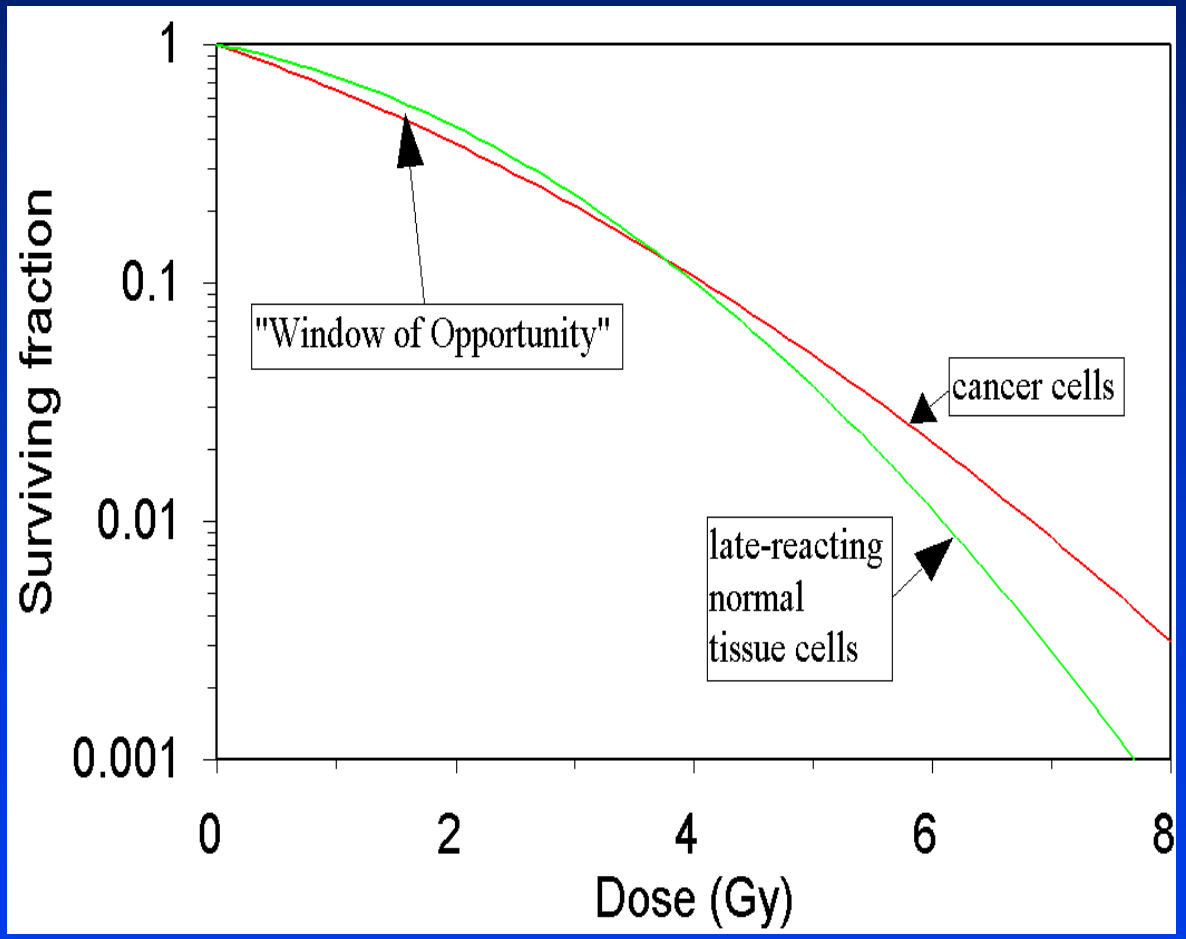
- Gilbert Fletcher was a student of Baclesse in Paris and brought the 2 Gy/fraction fractionation scheme to the USA when he was appointed to the M.D. Anderson Cancer Center in 1948
- This became the standard-or-practice in the USA for the next 60 years-or-so
- At about this same time, a different approach developed in the UK

UK fractionation after the 2nd World War

- Because of the shortage of equipment right after the 2nd World War, a higher dose/fraction was adopted in the UK using daily treatments of 3-3.5 Gy over 3-4 weeks
- This was developed at the Christie Hospital and was known as the "*Manchester*" technique
- This was abandoned after several years because of the high complication rates observed and about 2 Gy/fraction again became the standard

Do we know radiobiologically why 2 Gy/fraction was optimal?

- Yes. It was due to late-reacting normal tissue cells being better able to repair than cancer cells at low dose/fraction
- There is a “Window of Opportunity” centered around 2 Gy/fraction



Starting about 1960, many clinical trials of alternative fractionation were initiated

- Why?
  - *Total dose may be too low to control some resistant cancers*
  - *Total time may be too long and allow fast-growing cancers to proliferate*
  - *The desire to decrease the total number of fractions to make treatments less onerous to patients, more efficient, and less expensive*
- Clinical trials included *hyperfractionation, accelerated fractionation, accelerated hyperfractionation, continuous accelerated hyperfractionation, and hypofractionation*

Hyperfractionation

- Dose/fraction: 1.1 - 1.3 Gy
- Fractions/week: 10
  - *otherwise the overall time would have been too great and cancer cells would have had too much time to repopulate*
- Total dose: 70 - 80 Gy
- Used for treatment of resistant cancers when late normal tissue tolerance was a major problem (low dose/fraction means more repair)

Hyperfractionation problems

- Two fractions/day, with at least six hours between treatments to allow for complete repair, puts extra burden on patients, staff and equipment
- After many clinical trials, no clear benefit has been demonstrated that would justify these extra burdens

Accelerated fractionation

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

Accelerated fractionation problems

- Early responding normal tissues did not have sufficient time to repopulate in the 3 - 4 week course, so acute reactions were a major problem
  - *This frequently required patients to be given a rest, which negated the acceleration of the treatment*
  - *When the rest period was planned ahead, this was called "split-course" radiotherapy*
- No clear benefit was demonstrated in these clinical trials

Continuous hyperfractionated accelerated radiation therapy (CHART)

- Attempts were made to combine the benefits of hyperfractionation and accelerated fractionation
  - *Dose/fraction: 1.5 Gy*
  - *Fractions/week: 21 i.e. 3 fractions/day*
  - *Total dose: 54 Gy*
  - *Used for rapidly growing cancers*

CHART (cont'd.)

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

CHARTWEL (continuous hyperfractionated accelerated radiotherapy weekend less)

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

CHART and CHARTWEL: problem with late reactions

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

CHART and CHARTWEL: problem with acute reactions

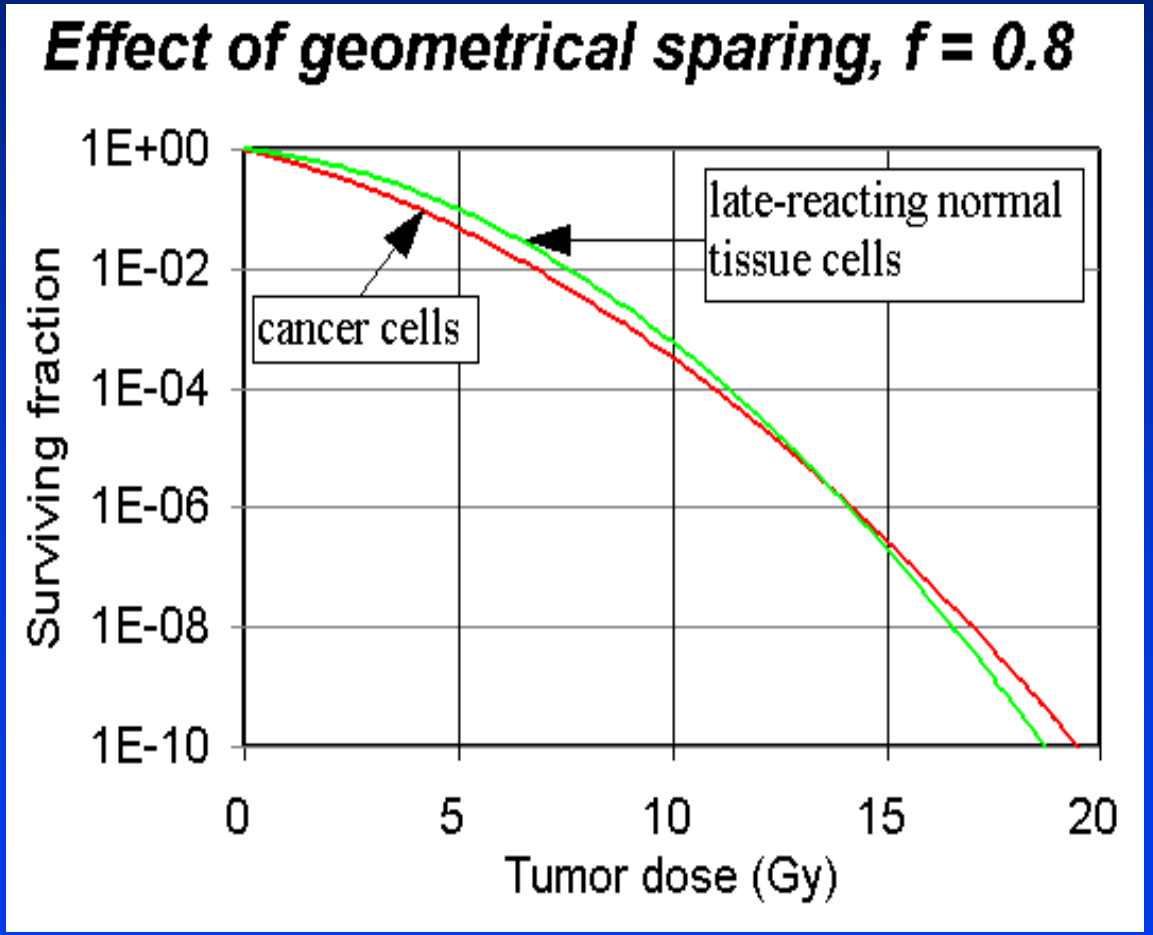
- Acute reactions were a major concern
  - *Most patients had to be hospitalized for treatment of excessive acute reactions as soon as they complete therapy*
  - *Results of clinical trials were not promising enough to justify the inconvenience and extra burdens on patients and staff entailed*

Hypofractionation

- Dose/fraction: above about 2.5 Gy
- Fractions/week: 1 – 5
- Total number of fractions: 1 - 20
- Total dose: 20 – 55 Gy (depends on fractionation used)

But can such high doses/fraction be tolerated?

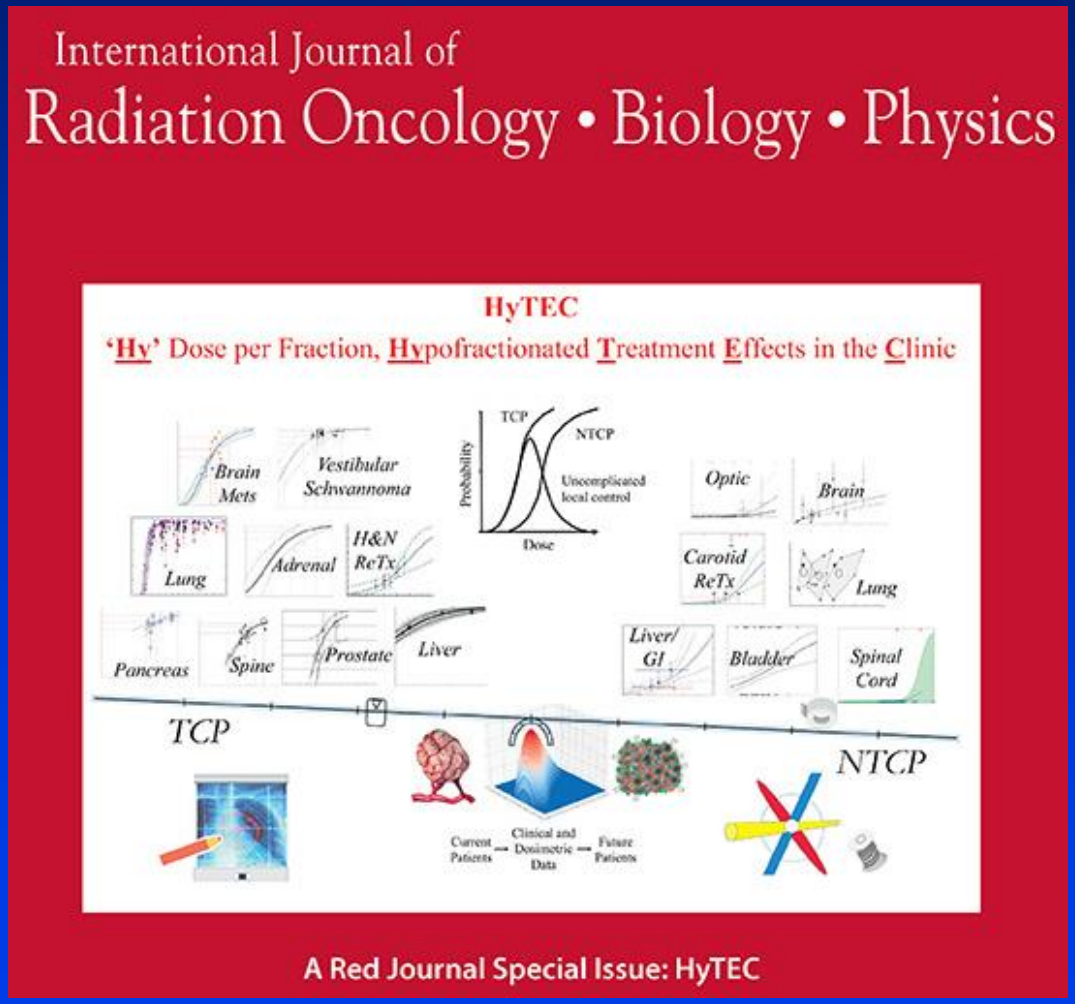
- Yes, by using highly conformal therapy such that the "*effective dose*" to normal tissues is less than that to cancers
- Even with a modest sparing of just 20%, the "Window of Opportunity" widens considerably



So what do we know?

- Clinical trials around the world 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*
  - *See the May 1, 2021 Special HyTEC issue of the IJROBP*

Red Journal May 1, 2021



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*

Summary

- Over the past hundred years-or-so, many different fractionation schemes have been used
- So-called “conventional fractionation” at about 2 Gy/fraction, five fractions/week, for about 30 fractions was the most common
- Recently, with the advent of highly conformal radiotherapy techniques, hypofractionation has begun to take over as the most common regime
- For details of all these clinical trials, see the latest issue of *Medical Physics International*

Latest issue of MPI

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A BRIEF HISTORY OF FRACTIONATION IN EXTERNAL-BEAM RADIOTHERAPY

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

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