FRACTIONATION IN CLINICAL RADIATION ONCOLOGY

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Mechanism of cytotoxicity
Chromosomal Damage

- Apoptosis
- Reproductive death
- Necrosis
Cell Radiation Biology

Figure 5.1: Measurement of cell survival.
Cell Survival Curves

(a): linear scale  
(b): same data on a logarithmic scale

Figure 5.2: Typical cell survival curve for mammalian cells irradiated in tissue culture.
History of Fractionation in Radiotherapy
Effect of fractionation on tissue damage

TUMOR
- rapidly cycling cells
- quiescent cells
- hypoxic cells

EARLY RESPONDING TISSUE
- rapid turnover

LATE RESPONDING TISSUE
- slow turnover

END OF TREATMENT
- tumor regressing
- few large fractions
- repair
- redistribution
- repopulation
- reoxygenation

MONTHS LATER
- tissue intact
- repopulation

YEARS LATER
- tissue breaks down
- cells die
- removed at slow rate
- latent damage in many cells
- tissue integrity intact
Effect of fractionation on tissue damage

Figure 12-9. The kinetic pattern following irradiation with many small dose fractions. A small dose fraction produces relatively less damage to late-responding than to early-responding tissues because of their curvy dose-response relationship. The tumor regresses and disappears. The early-responding tissues show a reaction but repopulate by rapid cell division. The late-responding tissues show little damage.
Effect of Cell Cycle
Re-oxygenation
Effect of Oxygen

A

High Dose Assay

OER = 3.5

Surviving Fraction

Dose (Gy)

Surviving Fraction

B

Low Dose Assay

OER = 2.5

Hypoxic

Aerated

Dose (Gy)
Tumor Oxygenation

- Aerated Proliferative Cell ¼ to ⅓
- Aerated Quiescent Cell
- Hypoxic Viable Cell
- Anoxic Necrotic Cell
Why Daily treatments?
Five R’s of Radiotherapy

• Repair of sub-lethal damage
• Re-oxygenation
• Repopulation
• Redistribution
• Radiosensitivity
Linear Quadratic Equation

- The linear quadratic equation is the most widely accepted method of fitting the survival of cells following radiation to an equation.

\[ S(D) = e^{-(\alpha D + \beta D^2)} \]

- Where \( S \) is the number of surviving cells following a dose of \( D \), and \( \alpha \) and \( \beta \) describe the linear and quadratic parts of the survival curve.

- The \( \alpha \) and \( \beta \) constants vary between different tissues and tumours.
  - The \( \alpha \) term describes the linear component to the curve.
  - The \( \beta \) term describes the quadratic part of the curve.
α/β Ratio

• This is the dose, in Gray, when the number of cells killed by the linear component $\alpha$ is equal to the cell kill from the quadratic $\beta$ constant.

• It is thought that the linear component $\alpha$ is related to a single hit and that the quadratic component $\beta$ is related to two hits mechanisms of cell killing.
  • Early responding tissues have a high alpha beta ratio
  • Late responding tissues have a low alpha beta ratio
  • Most tumours have a high alpha beta ratio
  • Some tumours (melanoma, sarcoma, prostate) have a low alpha beta ratio
Biologically Effective Dose (BED)

BED compare effects fractionation schedules
- need to know $\alpha/\beta$ ratio of the tissues concerned

$$BED = nd \left[ 1 + \frac{d}{\alpha/\beta} \right]$$
BED limitations

- need to know $\alpha/\beta$ ratio
- LQ fails at extremes of low dose rate and large fraction sizes
- Hot spots of treatment
- Previous cytotoxic chemotherapy
- Previous surgery
- Extremes of age
- Vascular pathology
- Breaks in treatment, compensation for accelerated proliferation
- Generic values of 10 Gy for tumors and 3 Gy for normal
FRACTIONATION SCHEDULES IN RADIOTHERAPY
ALTERED FRACTIONATION SCHEDULES

• **CONVENTIONAL**: 1.8 to 2 Gy daily fractions 5 fractions per week

• **HYPERFRACTIONATION**: Total dose is increased, dose per fraction is decreased (1.1 to 1.2 Gy per fraction), number of fractions is increased, with an overall time remaining unchanged

• **ACCELERATED FRACTIONATION**: Total dose is unchanged, dose per fraction is either unchanged or slightly reduced, number of fractions is unchanged or reduced and the overall treatment time is shortened.
Repopulation

• Repopulation is the increase in cell division that is seen in normal and malignant cells at some point after radiation is delivered.

• Repopulation occurs in different speeds depending on the tissue
  • Early responding tissues: short cell cycles, total dose and volumes
  • Late responding tissues: slow cell cycles, more sensitive to dose per fraction
  • Repopulation of malignant tissues

• Some tumors exhibit accelerated repopulation, a marked increase in their growth fraction and doubling time, at 4 - 5 weeks.

• Accelerated fractionation, BID, can counteract such scenario.
Radio-sensitivity

• Radiosensitivity is a newer member of the R's.
• An intrinsic radio-sensitivity or radio-resistance exists in different cell types.
• Radio-sensitive cells include hematological cells, epithelial stem cells, gametes and tumor cells from hematological or sex organ origin.
• Radio-resistant cells include myocytes, neurons and tumors cells such as melanoma or sarcoma.
RATIONALE FOR HYPERFRACTIONATION

• The use of smaller dose/fraction allows the delivery of a higher total dose within the tolerance of late-responding normal tissues, resulting in a higher biological effective dose in the tumor tissues.

• Radio sensitization by improving redistribution.

• Less dependency on oxygenation with lower dose/fraction.
RATIONALE FOR ACCELERATED FRACTIONATION

• The reduction in overall treatment time will decrease the probability of cancer cell regeneration/repopulation during an otherwise longer treatment delivery

• A therapeutic gain is expected, with normal late effects as compared to conventional fractionation, provided that the dose/fraction is unchanged and the fractions are separated by a minimum inter-fraction interval of > 6 hours an a single day
HYPERFRACTIONATED RADIOTHERAPY TRIALS
HEAD AND NECK TRIALS
EORTC TRIAL

• EORTC 22791 compared Conventional fractionation (CF) of 70 Gy in 35-40 fractions in 7-8 weeks, to pure hyper fractionation (HF) of 80.5 Gy in 70 fractions in 7 weeks using 2 fractions of 1.15 Gy per day

• From 1980 to 1987, 356 patients were entered.

• At 5 years, 59% of patients are local disease-free in the HF arm compared to 40% in the CF arm.

• The treatment regimen was an independent significant prognostic factor for loco regional control ($p = 0.007$ log-rank). This improvement of loco regional control was responsible for a trend to an improved survival ($p = 0.08$ log-rank).

• There was no difference in late normal tissue damage between the two treatment modalities.

• Horiot JC et al, Radiotherapy and Oncology, 25 (1992)
HYPERFRACTIONATED /ACCELERATED RADIOTHERAPY IN HEAD AND NECK CANCER: A META-ANALYSIS

• Meta-analysis:
  • 15 trials with 6515 patients were included.
  • The median follow-up was 6 years.
  • Tumours sites were mostly oropharynx and larynx; 5221 (74%) patients had stage III–IV
  • There was a significant survival benefit with altered fractionated radiotherapy, corresponding to an absolute benefit of 3·4% at 5 years (hazard ratio 0·92, 95% CI 0·86–0·97; p=0·003).
  • The benefit was significantly higher with hyperfractionated radiotherapy (8% at 5 years) than with accelerated radiotherapy (2% with accelerated fractionation without total dose reduction and 1·7% with total dose reduction at 5 years, p=0·02).
  • There was a benefit on loco regional control in favour of altered fractionation versus conventional radiotherapy (6·4% at 5 years; p<0·0001), which was particularly efficient in reducing local failure, whereas the benefit on nodal control was less pronounced.
  • The benefit was significantly higher in the youngest patients (hazard ratio 0·78 [0·65–0·94] for under 50 year olds, 0·95 [0·83–1·09] for 51–60 year olds, 0·92 [0·81–1·06] for 61–70 year olds, and 1·08 [0·89–1·30] for over 70 year olds; test for trends p=0·007).

• J Bourhis et al, The lancet 368; 843–854, 2006
HYPERFRACTIONATION TRIAL FOR T2 GLOTTIC CANCER
RTOG TRIAL

- Patients with T2 vocal cord cancer were randomly assigned to receive either hyperfractionation (HFX) to 79.2 Gy in 66 fractions of 1.2 Gy given twice a day, or standard fractionation
- 250 patients were enrolled.
- Median follow-up for all surviving patients was 7.9 years (range, 0.6-13.1 years).
- The 5-year local control (LC) rate was higher but not statistically significant (P=.14 for HFX [78%] vs SFX [70%]).
- The 5-year disease-free survival (DFS) was 49% versus 40% (P=.13) and overall survival (OS) was 72% versus 63% (P=.29).
- HFX was associated with higher rates of acute skin, mucosal, and laryngeal toxicity.
- Grade 3-4 late effects were similar with a 5-year cumulative incidence of 8.5% (3.4%-13.6%) after SFX and 8.5% (3.4%-13.5%) after HFX.
- The 5-year local control was modestly higher with HFX compared to SFX for T2 glottis carcinoma, but the difference was not statistically significant.

ACCELERATED RADIOTHERAPY
HEAD AND NECK DAHANCA 6&7 RIALS

• Multicenter, controlled, randomised trial
• 1485 patients treated with primary radiotherapy alone, 1476 eligible patients were randomly assigned five (n=726) or six (n=750) fractions per week at the same total dose and fraction number (66–68 Gy in 33–34 fractions
• Overall 5-year loco regional control rates were 70% and 60% for the six-fraction and five-fraction groups, respectively (p=0·0005).
• Six compared with five fractions per week improved preservation of the voice among patients with laryngeal cancer (80 vs 68%, p=0·007).
• Disease-specific survival improved (73 vs 66% for six and five fractions, p=0·01) but not overall survival.
• Acute morbidity was significantly more frequent with six than with five fractions, but was transient.

J Overgaard The Lancet 362;933–940, 20, 2003
HYPERFRACTIONATION TRIALS IN CNS

**RTOG 8302**
- Phase I/II dose escalation altered fractionation trial in GBM:
  - HF 1.2 Gy BID to 64.8, 72, 76, 81.6 Gy
  - AH 1.6 Gy BID to 54.4 Gy
- No differences in Median Overall Survival between arms
- Late CNS toxicities were increased in the 72 Gy

**RTOG 9006**
- SF 60 Gy in 30 fractions
- HF 72 Gy in 1.2 Gy/fraction BID
- No difference in overall survival


- Werner-Wasik et al, Cancer 1996;77,1535-1543.
ACCELERATED VS. HYPERFRACTIONATED RADIOTHERAPY

RTOG 9003

Patients with stage III or IV (or stage II base of tongue) SCC (n=1076) were randomized to 4 treatment arms:

- (1) SFX, 70 Gy/35 daily fractions/7 weeks
- (2) HFX, 81.6 Gy/68 twice-daily fractions/7 weeks
- (3) AFX-S, 67.2 Gy/42 fractions/6 weeks with a 2-week rest after 38.4 Gy
- (4) AFX-C, 72 Gy/42 fractions/6 weeks. The 3 experimental arms were to be compared with SFX

HFX with SFX was significantly different: HFX, hazard ratio (HR) 0.79 (95% confidence interval 0.62-1.00), \( P = .05 \)

- AFX-C, 0.82 (95% confidence interval 0.65-1.05)
- HFX improved overall survival (HR 0.81, \( P = .05 \))

- Prevalence of any grade 3, 4, or 5 toxicity at 5 years; any feeding tube use after 180 days; or feeding tube use at 1 year did not differ significantly when the experimental arms were compared with SFX.

- When 7-week treatments were compared with 6-week treatments, accelerated fractionation appeared to increase grade 3, 4 or 5 toxicity at 5 years (\( P = .06 \))
ACCELERATED vs. CONVENTIONAL + CHEMOTHERAPY
RTOG 0129

- AFX-C + CDDP x2 VS. SFX + CDDP x3 (100 mg/m², q3W).

- There was no difference in the primary endpoint (5-Y survival: 59% vs. 56%; HR: 0.90, 0.72-1.13; p=0.18).

- Each day of RT delay compromised OS, PFS, and LRP by 5%, 4%, and 4% (p=0.001, 0.006, and 0.02), respectively.

- RT duration and CDDP dose affected survival significantly.

- CDDP improved OS but it also increased toxicity.

- The effect of AFX-C approximated the third CDDP dose, suggesting that CDDP acted, in part, by inhibiting accelerated tumor repopulation.
FRACTIONATION AND THE ABSCOPAL EFFECT

FRACTIONATION AND THE ABSCOPAL EFFECT

CONCLUSIONS

• Fractionation has a major impact on outcomes of radiotherapy
• Careful attention has to be paid when conventional fractionation is altered in clinical trials
• Practice must be guided by robust clinical level I evidence
• Different fractionation schedules, specially single doses of ablative radiotherapy doses should carefully studied
• The systemic effects of radiotherapy are being studied in the context of immuno-modulator molecules.