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(12.12.1861-12.11.1946)
ALTERED FRACTIONATION
RADIOBIOLOGICAL BASIS
IMPROVING THERAPEUTIC RATIO
What to Discuss

- Altered Fractionation
- Radio sensitivity
- 4 R’s of Radiobiology
- Cell survival Curve
- L-Q Model
- Radiobiological Basis
- Clinical Experience
- Conclusion
History

- Jan. 29, 1896: 18 daily 1-hr RT fractions in Ca Breast; June, 1899: 50 # in ca cheek, at Stockholm, curative
- 1920s: Ram’s Experiment by Regaud in Paris
- 1932: Coutard published results and established Fractionation as standard of Practice
- Radiobiological basis recent
What is Fractionation

- Required Radiation Dose for Cure /Adjuvant /Palliation
- Total dose divided into several smaller parts, called fractions

- Total Dose – D in Gy
- Dose per fraction—d Gy
- No. of Fractions—N
- Total treat time—T days
- Inter fract time—t hrs
- D  d
- N
- T  t
**Conventional**

- **d**: 1.8-2.2 Gy
- **#/wk**: 5
- **D**: 60-70 Gy
- **N**: 30-35 #
- **T**: 6-7 wks

- Used for most patients Worldwide
- Established clinical experience
- Reached a plateau 60-70 Gy/30-35#/6-7 wks
Altered #

- What is Altered
- N
- d
- T
- t
- D

- Hyper #
- Hypo #
- Accelerated
- Accelerated Hyper/Hypo
- CHART/CHARTWEL
- Dynamic #
<table>
<thead>
<tr>
<th>Main characteristics of the conventional and altered fractionation schedules.</th>
<th>Fractionation regimen</th>
<th>Aim</th>
<th>Dose/fraction</th>
<th>Number of fractions/day</th>
<th>Days of treatment/week</th>
<th>Overall dose</th>
<th>Overall treatment time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>To control the tumour through redistribution and reoxygenation at the same time as sparing normal tissue through repair and repopulation</td>
<td>2 Gy</td>
<td>1</td>
<td>5</td>
<td>70 Gy</td>
<td>7 weeks</td>
<td></td>
</tr>
<tr>
<td>Hyperfractionated</td>
<td>To exploit the differences in radiosensitivity of tumour and healthy cells</td>
<td>&lt;2 Gy</td>
<td>2-3</td>
<td>6</td>
<td>&lt;70 Gy</td>
<td>5 weeks</td>
<td></td>
</tr>
<tr>
<td>Accelerated</td>
<td>To overcome tumour repopulation during treatment</td>
<td>≥2 Gy</td>
<td>1</td>
<td>6</td>
<td>&gt;70 Gy</td>
<td>7 weeks</td>
<td></td>
</tr>
</tbody>
</table>
Radiosensitivity

- Therapeutic Ratio
  - TR = Tissue Tolerance / Tumor Lethal Dose
  - > 1 - radiosensitive
  - < 1 - radioresistance
  - ~ 1 - tumor of limited sensitivity

- Sensitive - Seminoma, Lymphoma
- Resistant - Sarcoma, Melanoma
- Limited Sensitivity - Carcinomas
- Majority tumors of limited sensitivity
Dose-Response Relationships

![Graph showing dose-response relationships with tumor control and normal-tissue damage on the y-axis and dose on the x-axis. The graph illustrates the increase in tumor control and normal-tissue damage with increasing dose.](image-url)
Radiosensitivity

- **Therapeutic Ratio**
- \( TR = \frac{Tissue\ Tolerance}{Tumor\ Lethal\ Dose} \)
- \( > 1 \) - radiosensitive
- \( < 1 \) - radioresistance
- \( \sim 1 \) - tumor of limited sensitivity

- **Sensitive** - Seminoma, Lymphoma
- **Resistant** - Sarcoma, Melanoma
- **Limited Sensitivity** - Carcinomas
- **Majority** - tumors of limited sensitivity
4 R’s of Radiobiology

- Repair of Sub Lethal Damage
- Repopulation
- Reoxygenation
- Redistribution

- Saves normal tissue Vs Cancer
- Saves Cancer
- Increase cancer kill
- Increase Cancer kill
Cell survival curve

- For Single # dose vs Survival Fraction
- Initial slope – single particle event/single hit single target
- Shoulder - Repair SLD
- Subsequent linear curve
Cell survival curve
single # dose vs survival

- L-Q Model
- Irreparable damage
  - alpha d-A
- Reparable damage
  - beta d2-B
- Alpha/beta = dose in Gy at which A=B
- For cancer -5-20Gy
- Normal tissue -1-4 GY
Survival for cancer cells and late responding normal tissue

Cross over point / Window of Opportunity- 3-5 Gy normal tissue survival is higher than cancer cells

For cure of cancer ,higher dose is required

Solution:
  1. Fractionation within window of opportunity
  2. Geometrical sparing factor in conformal/IMRT/IGRT
The diagram illustrates the relationship between dose (in Gy) and surviving fraction for cancer cells and late-reacting normal tissue cells. The "Window of opportunity" is indicated on the graph, showing the range of doses where the therapeutic effect on cancer cells is expected to be maximal while minimizing harm to normal tissue.
Survival curve for fractionated RT

- RT within WOO will separate the survival curves for cancer cells and normal tissue with cancer cells suffering more damage.
- LQ model suggests infinite no. of # - not realistic
- Optimal dose per #
- Where the rate of increase in separation of 2 curves per # is a maximum, occurs at the point of maximum separation between two acute exposure curves
- = 1.5-2.5 Gy
Survival curve

- **Effective Dose** - dose if delivered uniformly to the tissue in question, would result in the same probability of local control / complications as the actual inhomogeneous dose distribution in that tissue - DVH

- **Geometrical sparing Factor** ($f$)
  
  ED in normal tissue / ED in tumor
  
  modest sparing $f=0.8$—increase cross over point from 3.8 to 14, and optimal dose of 7 Gy, Stereotactic RT, $f=0.6$—20 Gy SF are used; large tumor with $f>0.6$, #RT better
LQ Model
LQ model: Calculations

- Conventional: 70 Gy/35 #/7 weeks, d=2 Gy, 5 #/wk
- $\alpha/\beta=10$, for tumor and acutely responding normal tissue
- $\alpha/\beta=2.5$, for late responding normal tissue
- $E/\alpha=Nd\left(1+\frac{d}{\alpha/\beta}\right)$
- BED
  \[
  \frac{E}{\alpha} = (nd)\left(1 + \frac{d}{\alpha/\beta}\right) - 0.693 \frac{t}{T_{pot}}
  \]
BED = Nd(1+d/ α/β)-kT

= Nd(1+d/ α/β)-k(T-Tk)

k = repopulation rate parameter (estimated from loss of local control with prolongation with RT)

K = 0.6BED units per day for rapidly repopulating tumor

0.1BED for slow proliferating cells ex.prostate

K = 0 for late responding tissue

0.2-0.3 for acutely responding normal tissue
LQ Model to compare different fractionation

\[ \text{BED} = D_2 (1 + \frac{2}{\alpha/\beta}) = D_d (1 + \frac{d}{\alpha/\beta}) \]

Therefore, \( \frac{D_2}{D_d} = (1 + \frac{d}{\alpha/\beta}) / (1 + \frac{2}{\alpha/\beta}) \)
Radiobiological Basis of Altered #

**Hyper #**
- Large no. of #
- Smaller d
- Similar T
- Slightly higher D
- =
- Late respond tissue spared
- Acute toxicity –higher but can be managed
- Higher separation of curves for cancer cells and normal tissue
- TG achieved for HNC

**Hypo#**
- Smaller no. of #
- Larger d
- Similar T
- Slight reduction of D
- =
- More damage to normal tissue
- Acute toxicity -not
- Used for Palliation
- OR CURATIVE in Ca Prostate or highly conformal therapy
### Radiobiological Basis of Altered #

**Accelerated #**
- T is reduced
- d may be reduced or conventional or increased
- D may be reduced
- # per week may be increased to 5-10
- Higher acute toxicity
- Late toxicity may be similar
- Reduced Repopulation of cancer cells

**Accelerated Hyper #**
- T reduced
- N increased
- d may be reduced
- CHART-Continuous Hyper #
- Accelerated RT
- 54Gy/36#/15 days,3#/day,d=1.5 Gy
- CHARTWEL, week End Less
Dynamic #

- 1.2 Gy, bd/20#/2 wks
- 1.4 Gy, bd/20#/2 wks
- 1.6 Gy, bd/10#/1 wk
- =
- 68 Gy/50#/5 wks
<table>
<thead>
<tr>
<th>Fractionation scheme</th>
<th>Dose/fraction (Gy)</th>
<th>Fractions/week</th>
<th>Total dose (Gy)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>1.8€”2.0</td>
<td>5</td>
<td>~60</td>
<td>Used for most patients</td>
</tr>
<tr>
<td>Hyperfractionation</td>
<td>1.1€”1.3</td>
<td>10</td>
<td>~70</td>
<td>Allows higher doses to tumors without increased late complications</td>
</tr>
<tr>
<td>Accelerated fractionation</td>
<td>2€”2.2</td>
<td>7</td>
<td>~60</td>
<td>Used for rapidly proliferating tumors</td>
</tr>
<tr>
<td></td>
<td>2.2€”2.4</td>
<td>5</td>
<td>~50</td>
<td>Increased risk of acute complications</td>
</tr>
<tr>
<td></td>
<td>1.4€”1.6</td>
<td>10</td>
<td>~50</td>
<td></td>
</tr>
<tr>
<td>Hyperfractionated accelerated radiotherapy</td>
<td>~1.5</td>
<td>15 (CHARTWEL)</td>
<td>~54</td>
<td>Used for rapidly proliferating cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 (CHART)</td>
<td></td>
<td>High risk of severe acute complications</td>
</tr>
<tr>
<td>Dynamic fractionation</td>
<td>1.2€”2.0</td>
<td>10</td>
<td>~75</td>
<td>For rapidly proliferating tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gradually increasing the intensity of treatment in order to minimize acute reactions</td>
</tr>
<tr>
<td>Hypofractionation</td>
<td>3€”10</td>
<td>1€”5</td>
<td>10€”30 (palliation)</td>
<td>For palliation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40€”60 (€œure€œ )</td>
<td>Potential use for with highly conformal radiotherapy</td>
</tr>
</tbody>
</table>
Head & Neck Ca

- Options:
  - 1. hyper#, to exploit the diff.in radiosensitivity to increase TR
  - 2. Accelerated #, to overcome repopulation
  - 3. Combined = 2 or more # on all or some trt days

6 days / wk
54 Gy/36#/12 days, d=1.5 Gy
Results similar to conventional?
Low total dose delivered
Increasing the D will increase late toxicity
Similarly Trans-Tasman Oncology Group (TROG): reported no difference
59.4 Gy/33#, d=1.8, bd/24 days
TD was most significant factor
Best results obtained with regimens delivering conventional D with modest redn in T with fractions 6 days/wk. mod acclerated RT offers improved TR

Bourhis et al, 2006

Meta analysis

15 trials, N6515, FU 6 yrs: Alt# improves survival, locoregional control, Hyper# - greatest advantage

Conventional Rt is not standard care
<table>
<thead>
<tr>
<th>Trial/reference</th>
<th>Regimens compared</th>
<th>Overall dose (Gy)</th>
<th>Treatment duration (weeks)</th>
<th>Local tumour control (%)</th>
<th>Therapeutic gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAHANCA (Overgaard et al., 2003) [22]</td>
<td>Accelerated Conventional</td>
<td>66 66</td>
<td>6 7</td>
<td>70 60</td>
<td>Yes</td>
</tr>
<tr>
<td>RTOG (Fu et al., 2000) [23]</td>
<td>Accelerated-with concomitant boost Hyperfractionated Conventional</td>
<td>72 81.6 70</td>
<td>6 7</td>
<td>54.5 54.4 46</td>
<td>Yes Yes</td>
</tr>
<tr>
<td>Skladowski et al. (2000) [24]</td>
<td>Accelerated Conventional</td>
<td>70 70</td>
<td>5 7</td>
<td>82 37</td>
<td>Yes</td>
</tr>
<tr>
<td>TROG (Poulsen et al., 2001) [20]</td>
<td>Accelerated-hyperfractionated Conventional</td>
<td>59.4 70</td>
<td>3.5 7</td>
<td>No difference 46</td>
<td>No No (late toxicity nullified gain in tumour control)</td>
</tr>
<tr>
<td>EORTC (Horiot et al., 1997) [25]</td>
<td>Accelerated-hyperfractionated Conventional</td>
<td>72 70</td>
<td>5 7</td>
<td>59 46</td>
<td>No</td>
</tr>
<tr>
<td>CHART (Dische et al., 1997) [19]</td>
<td>Accelerated-hyperfractionated Conventional</td>
<td>54 66</td>
<td>1.7 6.5</td>
<td>No difference</td>
<td>No</td>
</tr>
</tbody>
</table>
Ca Prostate

- Low alpha/beta ratio vs late rectal toxicity
- Case for Hypo #
- \( d = 2.7 \text{ Gy-4.5 Gy} \)
- Livsey et al, 2003: hypo#, conformal Rt, N-705, 50 Gy/13#/22 days, \( d = 3.13 \), similar tumor control, toxicity, as 65-70 Gy/d-1.8-2 Gy.
- Arcangeli et al, 2010: prospective, phase III, randomised trial, N-168, 62 Gy/20#/5 wks, 4#/per wk, \( d = 3.1 \text{ Gy}, \) vs 80 Gy/40#
- Achieved TG, reason higher dose
Calculated $\alpha/\beta$ ratios for prostate carcinoma and late rectal toxicity, respectively.

<table>
<thead>
<tr>
<th>$\alpha/\beta$ (Gy)</th>
<th>$\alpha/\beta$ (Gy)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate carcinoma</td>
<td>Late rectal toxicity</td>
<td></td>
</tr>
<tr>
<td>1.5 (assumed)</td>
<td>2.3</td>
<td>Marzi et al. (2009) [40]</td>
</tr>
<tr>
<td></td>
<td>5.4</td>
<td>Brenner (2004) [41]</td>
</tr>
<tr>
<td>3.1 (1.7–4.5)</td>
<td>–</td>
<td>Wang et al. (2003) [42]</td>
</tr>
<tr>
<td>1.2</td>
<td>–</td>
<td>Brenner et al. (2002) [43]</td>
</tr>
<tr>
<td>1.49 (1.25–1.76)</td>
<td>–</td>
<td>Fowler et al. (2001) [33]</td>
</tr>
<tr>
<td>1.5 (1.4–1.7)</td>
<td>–</td>
<td>Brenner and Hall (1999) [32]</td>
</tr>
<tr>
<td>–</td>
<td>3.87</td>
<td>Deore et al. (1993) [44]</td>
</tr>
</tbody>
</table>
Breast Ca

- Larger pDouble Time 10.4 d
- Alpha/beta ratio -4 Gy, similar to healthy normal tissue
- Hypo#, Better cosmesis, though no TG achieved

- IMRT-SIB
- Smaller double time for younger <50yrs & early breast ca? Accelerated Hypo#
- Accelerated Partial Breast Irradiation
Lung Ca

- Doubling time, adenoca-222d, nonsmall cell ca-46-81 days
- High repopulation during trt
- CHART trial, Saunders et al, 1999; vs 60 Gy/30 #
- N-563, TG achieved, 2 yr survival-20 to 29%, reducing relative risk of local progression by 27%, similar toxicity
- HICHART, unresectable tumor, phase I/II
- 68.4 Gy/38#/28d-2 yr survival 36% (=80Gy)
- Increase TD in CHART, CHARTWEL
Conclusion

- Low survival and high l-r trt failure led to modification of conventional RT
- Advanced HNC – hyper# RT better than accl RT = TG achieved
- Ca Prostate-Hypo # IMRT Promising, TG might be achieved
- Ca lung - CHART improved survival
- CHARTWEL with CTH might improve trt efficacy = TG might be achieved
- Ca breast = TG might be achieved
- Gliom = no benefit
Conclusion

- Rapidly proliferating tumors
  Aggressive trt-AcceleratedRT
  hyperfractionation RT

- Slowly growing Tumors
  Hypofractionation
THANK YOU