Altered fractionation
Aims

To **U**nderstand/ **I**nterprete/ **C**omprehend the basis of fractionation in radiotherapy, **K**now the various forms of altered fractionation, and **A**pply this knowledge to various clinical situations.
Specific Learning Objectives

• Understand the basis of fractionation in radiotherapy
• Radiobiological basis for the different forms of fractionation
• Apply this knowledge to clinical sites and illustrate the benefits and toxicity profile
The history of fractionation in radiotherapy essentially began with animal experiment in France in the 1920s – 1930s. It was shown that sterilisation by testicular irradiation was not possible with a single radiation fraction without extensive damage to the scrotum. By fractionating radiotherapy over several weeks, sterilisation was then possible without unacceptable skin damage.
The dose per fraction of radiation given is an important determinant in tissue reaction and complication rate. Early responding tissues are less sensitive to changes in fraction size while late responding tissue are more sensitive to large dose per fraction. In this example, although the total dose between the 2 radiotherapy schemes are similar, despite a lower total dose, the late complication of fibrosis is much higher (67% vs 5%) in the scheme with the higher dose per fraction of 4Gy.
Tumour control or cure is only possible when the number of surviving clonogenic tumour cells = 0. As radiotherapy kills a proportion of cells with every dose, increasing the dose increases the probability of cure by decreasing the probability of any cells surviving the radiation. TCP is a deterministic effect that is the probability of control begins at a certain dose level and then increases with subsequent dose. The graph indicates that TCP begins at about 40Gy but the probability of control is low (0.004%). By increasing the dose, the probability of cell surviving drops. If the average number of cells surviving is 1, then the cure rate is about 37%. The TCP then increases to 90% when the dose is increased so that the probability is that only 0.1 cell survives radiation.
To indicate the TCP in another way, we can plot the cell survival as a negative function on a semi-logarithmic scale. As cell survival is as a first order kinetic (proportional to dose rather than absolute) the plot as a log scale is a straight line with a negative gradient. We can add this graph to the earlier graph to get an estimate of the probability of cure with cell survival.
To show the effect of fractionation of normal tissues, different fraction size of radiation can be given to a radiation dose where an isoeffect of different tissues are seen. The figure shows that different tissue have different radiosensitivity for an effect. More importantly it shows the different sensitivity to fraction size according to tissue types.

The “acute responding” tissues eg jejunum and have a shallower slope indicating less sensitivity to fraction size. The spinal cord and kidneys are examples of late responding tissue which are more sensitive to changes in fraction size indicated by the steeper slopes of isoeffect.
The cell survival curves can be explained by the linear quadratic model with 2 components: alpha (\(\alpha\)) and Beta (\(\beta\)). Alpha determines the shape of the initial slope and beta determines the curvature of the subsequent segment of the plot.

Cells with a low \(\alpha/\beta\) ratio which are the late reacting tissues have a shallower initial slope (shoulder) but becomes more “bendy” with increasing dose per fraction. Cells with high \(\alpha/\beta\) ratio (early reacting tissues) have a steeper initial slope but is less “bendy” compare to cell with low \(\alpha/\beta\) ratio at higher doses. This indicates that early reacting tissues are less sensitive to fraction size changes.
The values for alpha and beta cannot be obtained from the cell survival curves. Alpha or linear cell kill is proportional to the dose given and Beta or quadratic cell kill is proportional to the $(dose)^2$. The values of $\alpha$ and $\beta$ cannot be obtained from the curve, but the $\alpha/\beta$ value is dose where the proportion of the linear and quadratic components are equal.

The graphs show cell survival for late reacting (left) and early tissues (right). The $\alpha/\beta$ ratio for late reacting tissues is about 3 Gy and for early reacting tissue is about 10 Gy.
Fractionation in radiotherapy is used mainly to spare the late reacting tissues.

The effect of fractionation is to reproduce the shoulder region of the cell survival curve. This has the effect of straightening out the curve somewhat. Note the difference between the curves (a) and (b) of the early reacting tissue is less compared to (c) and (d) of the late reacting tissue. As the shoulder region is larger for late reacting tissues, reproducing the shoulder with each radiation fraction results in a much higher survival compared to the same dose as single fraction. This indicates that cells with low $\alpha/\beta$ values are much more sensitive to fraction size changes.
Basis of fractionation in radiotherapy can be understood today in terms of the principles of

- **Repair** of sublethal damage
- **Reassortment** of cells within the cell cycle
- **Reoxygenation**
- **Repopulation**
- **Inherent radiosensitivity**

The biological basis of fractionation in radiotherapy can be explained by the 5R’s. Within a tumour cell system in-vitro, repair is the most important component. Radiotherapy can cause different forms of damage including lethal and sub-lethal damage. Higher dose per fraction are more likely to induce higher proportion of irrepairable lethal damage. Smaller fractions allows repair of sub-lethal damage.
It would seem that the best way to deliver radiotherapy is by giving small doses per fraction. However, this will increase treatment time if the fractions are given on a daily basis. However this runs into the problem of another “R” namely repopulation. The figure indicates the local control and survival of patients with Head & Neck cancers treated with radiotherapy. In the past, planned gaps during the treatment was made to reduce the early tissue reactions. We can see that the longer OTT treatment schedules results in lower local control rates as well as survival. This is because with SCC, after 4 weeks of treatment tumours tend to undergo rapid repopulation which is faster than the rate of repopulation prior to therapy. Therefore the shortest fractionation schedule of 5.5 weeks had the best local control and overall survival in the Danish series of trials.

Overgaard et al (1997) IJROBP 39:S2:188; R&O 43:S2:55. (cannot find these citations)
So does this mean we should give smaller fractions within a shorter time? This is true to a certain extent. By giving more than 1 small fraction per day, we can shortened the OTT. However, the gap between the 2 fractions must be adequate to allow for tissue repair. The repair half times for normal tissue is 1-1.5 hours. A 6 hour gap between fractions is the minimum recommended to allow full repair of radiation damage to occur. If the second radiation dose is given in less than this time, the risk of complications increases. The graph shows percentage of late complications in patients including necrosis, with different time intervals between 2 fractions of radiotherapy. 4.5 hours gap between fractions is inadequate and results in unacceptable toxicity.
Hyperfractionation has been taken to the extreme by giving 8 fractions a day 2 hours apart. This scheme included a planned gap of 2 weeks. Modification of the schedule had to be done to include increasing the rest period to 4 weeks and lowering the total dose. Approximately 2/3 of the patients achieved remission but 56% recurred indicating a local control rate of about 38%. Late complication rate was 70% in the whole group.

In another trial, treatment gap of < 4.5 hours resulted in much higher complication rate compared to gaps over 4.5 hours. (Cox et al). Reducing the gap to < 6 hours was found to increase the rate of myelitis.

Rapid hyperfractionated radiotherapy. Clinical results in 178 advanced squamous cell carcinomas of the head and neck.
Nguyen TD, Demange L, Froissart D, Panis X, Loirette M.
ASTRO plenary: interfraction interval is a major determinant of late effects, with hyperfractionated radiation therapy of carcinomas of upper respiratory and digestive tracts: results from Radiation Therapy Oncology Group protocol 8313.
Cox JD, Pajak TF, Marcial VA, Coia L, Mohiuddin M, Fu KK, Selim H, Rubin P, Ortiz H.
Conventional fractionation in radiotherapy utilises fraction size of 1.8 - 2 Gy per day for 5 days a week resulting in a total dose of 9-10 Gy per week.
The efficacy of radiotherapy depend on the number of cells needed to be sterilised. The higher the number of cells, the larger the dose required for local control. Gross tumour require 70-80 Gy for sterilisation whereas microscopic disease requires less dose of about 45-50 Gy for sterilisation.
The table indicates that a dose of 50Gy may be adequate to control microscopic disease but will only control 50% of nodes 2-3 cm in size. Increasing the dose to 70 Gy will control about 90% of nodes of the same size. Small T1 tumour may require only 60Gy for control but larger T3-T4 tumours will need 70Gy or more for a similar control rate.
There are several ways of escalating the dose to the target as above. Here we will be focusing on alteration in fractionation schedule.
Various radiotherapy related parameters can be modified, these in turn determine the type of altered fractionation. Also, it should be realized that these parameters determine the outcomes both in terms of the total dose that can be delivered, the probability of tumor control and normal tissue toxicity.
Altered Fractionation - Biologic Rationale

a) Fraction size is the dominant factor in determining late effects, and the overall time has little influence

b) Fraction size and overall treatment time both determine the response of acutely responding tissues

The basis for accelerated fractionation patterns were the laboratory experiments that led to the conclusion that
a) the fraction size is the dominant factor in determining late effects, and the overall time has little influence
b) by contrast, the fraction size and overall treatment time both determine the response of acutely responding tissues
Altered fractionation schemes which have been tried include both hypo and hyperfractionated regimes. One extreme of hypofractionation is the “Manchester scheme” with large dose per fraction (3.3 Gy) with smaller total dose (50 Gy) resulting in a short overall treatment time. The other extreme is CHART giving 3 fractions per day and including treatment over weekend with a 12 day overall treatment time to a lower dose (52-54 Gy). The aim of these schemes is to accelerate treatment and reduce overall treatment time or to give higher total dose for the same rate of late complications.
A schematic diagram to illustrate the various forms of altered fractionation, in the radical radiotherapy setting. Hyperfractionation in the strictest form does not mean accelerated treatment although they are often combined.

- **HYPER FRACTIONATION**
  - Any schedule employing a dose per fraction of less than 1.8 Gy
- **ACCELERATED**
  - a schedule in which the rate of dose-accumulation exceeds 10 Gy/week
- **HYPOFRACTIONATION**
  - Any schedule employing a dose per fraction of greater than 1.8 – 2 Gy
A schematic diagram to illustrate the various forms of altered fractionation, in the radical radiotherapy setting.

Pure acceleration can be achieved by treating on saturdays or even continuously (in theory)

CHART incorporated hyperfractionation and acceleration together with weekend treatment. Other forms of accelerated hyperfractionation schemes usually utilises bid treatment, one in the morning and the second fraction in the evening.

In split course treatment, there is a planned break during therapy to allow recovery from acute side-effect.

Concomitant boost is often done for Head & Neck tumours where Phase 1 fields treats gross and microscopic disease while the “boost” Phase 2 fields covers gross disease and hence a smaller field. By treating large and small fields on the same day, again once in the morning and the boost field in the evening, it is meant to reduce the risk of severe side-effects of treating 2 large fields on the same day.
The basic aim of hyperfractionation is to further separate the early and late effects. The overall treatment time remains conventional at 6-8 wks, but since two fractions are used per day, the number of fractions are doubled to 60-80. The number of fractions must be increased because the dose per fraction has been decreased. The intent is to further reduce late effects while achieving the same or slightly increased early effects.

Note: the time between fractions should be at least 6 hours.
Hyperfractionation

- Utilizes higher fraction sensitivity of late responding normal tissues.
- Small dose fractions allow increase in total dose within tolerance limit of normal tissues.
  - As tumours are more sensitive to total dose rather than fraction size, increasing the dose would be advantageous for control.
- May induces radiosensitization through cell cycle reassortment.
- Oxygen effect is less profound at lower doses and hence hypoxic tumor cells would be less radioresistant.
Accelerated repopulation of SCC H&N occurs after 4 weeks of radiotherapy. The main aim of acceleration is to avoid tumour repopulation.

The tumour response to radiation is similar to acute responding tissues (with some exceptions eg prostate). The α/β ratio of tumours is similar to acute responding tissue or maybe higher eg squamous carcinomas of larynx. (Ref : Basic clinical radiobiology Van der Kogel et al). Therefore tumours are less sensitive to dose fractionation changes and are more sensitive to total dose and overall treatment time.

The radiobiological rationale for accelerated treatment are to reduce repopulation and greater acute effect as treatment is given over a shorter period. However the shorter treatment period would also increase the acute side-effects.
The alternative strategy of accelerated treatment involves an approximately conventional total dose with a conventional fraction number, but since two fractions are given, the overall time is approximately halved. In practice, it is never possible to quite achieve this, since the early effects become limiting. It is usually necessary either to interpose a rest period in the middle of the treatment or to slightly reduce the dose with early effects as the limiting factor. The intent of this strategy is to reduce repopulation in rapidly proliferating tumours with high $\alpha/\beta$ ratio like squamous cancers. Tumours with low $\alpha/\beta$ are unlikely to benefit from accelerated treatment.
Altered Fractionation in Head & Neck Cancers

Altered fractionation scheme has been extensively studied in H&N cancer and we will examine this in some detail.
Trials of accelerated radiotherapy in general has shown improved local control rates with accelerated treatment. Acute toxicities were usually higher in both percentage and severity. The Polish trial treated with 2 Gy per fraction every day of the week including sat and Sunday reducing OTT to 5 weeks. This scheme had to be modified as 22% of patients developed Grade 4 radiation necrosis. No grade 4 toxicity was seen when fraction size was reduced to 1.8Gy per fraction but OTT was then increased to 6 weeks similar to the trial of Overgaard et al.

<table>
<thead>
<tr>
<th>Ref</th>
<th>#/day</th>
<th>#/week</th>
<th>Dose</th>
<th>Results</th>
</tr>
</thead>
</table>
| Jackson (Vancouver) | 2(2.0) 1(2.0) | 10 5 | 66.0 66.0 | CR 35% vs 29% (p=0.18) no diff in relapse free survival  
                      |             |        |       | Acute toxicity - 27% vs 8% (p=0.00006)       |
| Skaldowski CAIR (Polish) | 1(1.6-2) 1(1.6-2) | 7 5 | 70.0 70.0 | 5 yr LC 75% vs 33% (p<0.0001)  
                      |             |        |       | 5 yr OS 58% vs 20% (p<0.0001)  
                      |             |        |       | Acute toxicity-1.5 weeks earlier (94% vs 53%) |
| Overgaard DAHANCA | 1 (2.0) 1(2) | 6 5 | 66.0 66.0 | 5 yr LRC 66% vs 57% (p=0.01)  
                      |             |        |       | 5 yr DFS 72% vs 65% (p=0.004)     |
| Hliniak        | 1-2(2) 1(2) | 6 5 | 66.0 66.0 | 5yr LRC 52% vs 47% (p 0.3)  
                      |             |        |       | 5yr DFS 41% vs 35% (p=0.3)     |

Skladowski K et al IJROBP Vol. 66 No.3 pp 706 – 713 2006
Very accelerated radiotherapy without significant dose reduction run the risk of severe acute toxicity. One such trials had to be stopped due to treatment related deaths. CHART was a very accelerated form of radiotherapy with a compromise in the total dose. Although the 2 treatment arms showed similar results, it is interesting to note that tumours can be controlled with lower dose if the radiation schedule is short.

<table>
<thead>
<tr>
<th>ACCELERATION TYPE A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Dische CHART</td>
</tr>
<tr>
<td>Poulsen TTROG</td>
</tr>
<tr>
<td>Bourhis GORTEC</td>
</tr>
</tbody>
</table>

_Lancet Oncology vol3 Nov 2002_
Radiotherapy is often used in H&N cancer the post-operative setting with large tumours, node or margin positivity. This particular trial looked at the effect of shortening treatment time to 5 weeks for patients with high risk disease. This was coupled with an increased dose (64Gy) versus the standard dose (60 Gy).

Note the original manuscript has a mistake in the diagram where the high risk arm was started to have RT over 6 weeks.
There was no difference seen in loco-regional control or survival. However there was a doubling in the rate of confluent mucositis to 50%. The mucositis took the same time to heal as with conventional fractionation.
CHART is a very interesting form of very accelerated radiotherapy. It uses small hyperfractionated doses with a reduced overall dose and a greatly shortened treatment time of 12 days.
The Medical Research Council (MRC) of UK conducted a large multi-centre trial to evaluate the efficacy of CHART versus conventional radiotherapy. Although there was no significant difference for DFS there was a trend for benefit in patients with advanced cancers. The trend in benefit seen was in a sub-group analysis and therefore must be viewed with caution. There were also less late effect although the acute side-effects were worse and occurred earlier – in the 3rd week ie one week after treatment was completed.
Another method of accelerated radiotherapy is to give simultaneous small field boost together with the large fields. This is usually done towards the end of the large field radiation hence “delayed concomitant boost”
The RTOG did a complicated trial with 4 arms. The split course arm has a planned 2 week break after 24 fractions (38.4Gy). The arm with concomitnat boost treated the boost field simultaneously for the last 12 fractions.

### RTOG 9003 TRIAL (1073 patients)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Dose / #</th>
<th>No #</th>
<th>Total dose (Gy)</th>
<th>Tx time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>2Gy</td>
<td>35</td>
<td>70</td>
<td>7 weeks</td>
</tr>
<tr>
<td>Hyperfrac.</td>
<td>1.2Gy bid</td>
<td>68</td>
<td>81.6</td>
<td>7 weeks</td>
</tr>
<tr>
<td>Accelerated frac with split</td>
<td>1.6Gy bid</td>
<td>42</td>
<td>67.2</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Accel frac with concomitant boost</td>
<td>1.8Gy bid 1.5Gy</td>
<td>30 12</td>
<td>72</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

*Fu KK et al. JROBP, 48 (1) 7-16 (2000).*
In this trial, 2 treatment arms, hyperfractionation and Accelerated radiotherapy with concomitant boost had improved local control rates. This however did not translate into improve DFS or OS. Acute reactions were worse in all 3 accelerated radiotherapy arms and late effect increased at 24 months in the hyperfractionation arm.

### RTOG 9003 TRIAL (1073 patients)

<table>
<thead>
<tr>
<th>Arms</th>
<th>LRC</th>
<th>DFS (2 year)</th>
<th>OS (5 year)</th>
<th>Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>46%</td>
<td>32%</td>
<td>46%</td>
<td>30%</td>
</tr>
<tr>
<td>Hyperfrac.</td>
<td>54%</td>
<td>38%</td>
<td>55%</td>
<td>37%</td>
</tr>
<tr>
<td>Accel frac with split</td>
<td>48%</td>
<td>33%</td>
<td>46%</td>
<td>31%</td>
</tr>
<tr>
<td>Accel frac + concom boost</td>
<td>55%</td>
<td>39%</td>
<td>51%</td>
<td>34%</td>
</tr>
</tbody>
</table>

*Fu KK et al IJROBP. 48 (1) 7-16 (2000).*
*Trotti et al IJROBP Vo. 63, (S1)1 Oct 2005, Pp S70–S71*
The graph shows clear separation of local control rates for accelerated radiotherapy with boost and hyperfractionation.

All had significantly increased Grade 3 or worse acute side effects
- hyper fractionation $p<0.0001$
- split $p=0.0002$
- concomitant boost $p<0.0001$

*Fu KK et al IJROBP. 48 (1) 7-16 (2000).*
# RTOG 9003 TRIAL (1073 patients)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Dose/# No. of #</th>
<th>Dose</th>
<th>Tx time</th>
<th>LRC</th>
<th>DFS</th>
<th>OS</th>
<th>Grade III/IV reactions</th>
<th>Late toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard fractionation</td>
<td>2Gy/#;35#</td>
<td>70Gy</td>
<td>7wks</td>
<td>46%</td>
<td>31.7%</td>
<td>46%</td>
<td>35%</td>
<td>9%</td>
</tr>
<tr>
<td>Accelerated fractionation with split</td>
<td>1.6Gy/#;42#</td>
<td>67.2 Gy</td>
<td>6wks</td>
<td>47.5%</td>
<td>33.2%</td>
<td>46.2%</td>
<td>51%</td>
<td>8%</td>
</tr>
<tr>
<td>Hyperfractionation</td>
<td>1.2Gy/#;68#</td>
<td>81.6 Gy</td>
<td>7wks</td>
<td>54%</td>
<td>37.6%</td>
<td>54.5%</td>
<td>55%</td>
<td>9%</td>
</tr>
<tr>
<td>Accelerated fractionation with concomitant boost</td>
<td>1.8Gy/#;30+12#</td>
<td>50.4 Gy+18Gy</td>
<td>6wks</td>
<td>54.5%</td>
<td>39.3%</td>
<td>50.9%</td>
<td>59%</td>
<td>9%</td>
</tr>
</tbody>
</table>

*Fu K et al IJROBP 48 (1) 7-16 (2000).*
Other trials of hyperfractionated treatment have shown significant improvement in local control but with increased acute toxicity. Late toxicities however were similar.

<table>
<thead>
<tr>
<th>Trials of Hyperfractionation: Head &amp; Neck</th>
</tr>
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<tbody>
<tr>
<td><strong># per day</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Marcial RTOG</strong></td>
</tr>
<tr>
<td><strong>Horiot EORTC</strong></td>
</tr>
<tr>
<td><strong>Cummings PMH</strong></td>
</tr>
</tbody>
</table>
We need to review the issue of acute toxicity in H&N cancer as it causes great morbidity in terms of pain and dysphagia, limiting patient’s oral intake and nutrition.
As mentioned previously, continuous radiotherapy was associated with higher risk of acute side-effects. Data from Poland indicates severe dysphagia in $\frac{3}{4}$ of patients. Patients with SCC are often older, smokers with multiple co-morbidities.

<table>
<thead>
<tr>
<th></th>
<th>p-CAIR</th>
<th>p-CF</th>
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<tbody>
<tr>
<td>confluent mucositis</td>
<td>54%</td>
<td>27%</td>
</tr>
<tr>
<td>dysphagia</td>
<td>72%</td>
<td>62%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3.1%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Accelerated treatment can be considered tolerable with respect to acute toxicity.

Due to toxicity, compliance is an issue and many patients cannot complete the allocated protocol.

Compliance to prescribed dose and OTT in five randomized clinical trials of altered fractionation

IMPACT (Intergroup Merger of Patient data from Altered or Conventional Treatment schedules) study database.

Only in 767 patients (30%) was there an agreement between the overall treatment time and the ideal time

*Khalil AA et al IJROBP Vol. 55, No. 3, pp. 568–575, 2003*
We can see that various forms of accelerated treatment are all associated with increased severe acute toxicity.
Altered fractionation with or without chemotherapy demands good infrastructural and continuous nutritional support which possibly can be undertaken only at higher referral centres. Without proper support there is significant morbidity and even mortality during or soon after treatment.
To combine the results of all different trials, a meta-analysis of altered versus conventional radiotherapy for H&N cancer was published in 2006 and updated in 2010.
This analysis indicates a small overall advantage in altered fractionation radiotherapy with an 8% relative reduction of death or 3.4% absolute reduction. Although there is a suggestion that hyperfractionation regimes are better, there is significant heterogeneity between the trials and therefore interpretation of the results must be with some caution.

Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis
Jean Bourhis et al
Lancet 2006; 368: 843–54
The benefit on local control was more significant with 23% reduction in risk or about 8% absolute benefit. This time benefit was seen across all forms of altered fractionation.
This table shows the improvement in local control and overall survival by the different types of altered fractionation. For local control it is 6% absolute improvement and OS it is 3%.

Hyperfractionated or accelerated radiotherapy for head and neck cancer.
Baujat B et al.

<table>
<thead>
<tr>
<th></th>
<th>Overall survival</th>
<th>Local regional control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.4%</td>
<td>6.4%</td>
</tr>
<tr>
<td></td>
<td>(39.7/36.3)</td>
<td>(52.9/46.5)</td>
</tr>
<tr>
<td></td>
<td>p=0.003</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Hyper fractionation</td>
<td>8.2%</td>
<td>9.4%</td>
</tr>
<tr>
<td></td>
<td>(36.7/28.5)</td>
<td>(57.9/48.5)</td>
</tr>
<tr>
<td>Accelerated fractionation</td>
<td>2%</td>
<td>7.3%</td>
</tr>
<tr>
<td>without total dose reduction</td>
<td>(44.4/42.4)</td>
<td>(47.5/40.2)</td>
</tr>
<tr>
<td>Accelerated fractionation</td>
<td>1.7%</td>
<td>2.3%</td>
</tr>
<tr>
<td>with total dose reduction</td>
<td>(31.9/30.2)</td>
<td>(59.8/57.5)</td>
</tr>
</tbody>
</table>

Bourhis Lancet August 2006
In subset analysis, the effect of altered RT was more pronounced for local tumour, in younger patients and good performance status. Older patients may fare better with conventional RT.
MARCH (Meta-Analysis of Radiotherapy in Carcinomas of Head and neck) Collaborative Group

- Altered fractionated radiotherapy was better than conventional radiotherapy for tumour control and survival
- HF yield a more consistent advantage for survival than ART
- More diversity in ART regimens might be associated with higher non-cancer related death off setting its benefit in improving tumour control.
- Trials needed- whether the benefit persists when combined with concomitant chemotherapy
- Assess Strategies with IMRT or targeted therapies
Altered Fractionation Radiotherapy in Thoracic tumours.
The CHART scheme was also tried in lung cancer following the exact protocol.
The same CHART regime used in H&N cancer was also used in a NSCLC trial. The comparator arm was treatment with conventional fractionation Phase 1 44Gy in 22 fractions and 16 Gy in 8 fractions Phase 2. CHART resulted in significant difference of 22% risk reduction of death. The 2 year survival was 30% compared to 21% and 3—year survival was 20% compared to 13%.

The acute toxicities were similar except for dysphagia which was increased in CHART. In the mid term there was a slight increase in radiation pneumonitis in the conventional arm.
The current “standard” in inoperable lung cancer is chemotherapy with radiotherapy. The Forrest plot shows cisplatin chemotherapy improves the result over radiotherapy alone. However this improvement is less than that of CHART.
The previous slides demonstrated the efficacy of CHART in terms of the control rates. However while choosing an altered fractionation schedule it is imperative to understand the effect that this alteration would have on the normal tissues encountered during radiotherapy to the region. A thorough knowledge of the NTCP vis-à-vis the TCP is essential. The CHART trials are a classic example of modification or enhancement of controls at the cost of increased normal tissue toxicities. It also emphasizes the fact that enhanced supportive care is warranted with the employment of such strategies, especially in sites such as the head & neck, lung etc.

The reference quoted above, however examines the role of induction CT prior to CHART. What it also illustrates is that combination of these schedules with other concomitant modalities may enhance toxicity, again underlining the need for intense supportive care.
Despite the advantage of CHART, few centres offered this treatment as treatment over the weekends proved to be very challenging. CHARTWELL was developed to overcome this problem and the dose gradually increased to 60 Gy over 18 fractions.

In a randomised trial of over 400 patients, there was no difference seen in local control or survival for CHARTWELL versus conventional radiotherapy. Acute dysphagia and radiological pneumonitis were more pronounced after CHARTWELL. Again there was a trend (significant this time) for improvement in CHARTWELL for the more locally advanced tumours.

Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC).


Four hundred and six patients with NSCLC were stratified according to stage, histology, neoadjuvant chemotherapy and centre and were randomized to receive 3D-planned radiotherapy to 60Gy/40 fractions/2.5weeks (CHARTWEL) or 66Gy/33 fractions/6.5weeks (conventional fractionation, CF).

RESULTS:
Overall survival (OS, primary endpoint) at 2, 3 and 5yr was not significantly different after CHARTWEL (31%, 22% and 11%) versus CF (32%, 18% and 7%; HR 0.92, 95% CI 0.75-1.13, p=0.43). Also local tumour control rates and distant metastases did not significantly differ., without differences in clinical
signs of pneumopathy).
Shortening treatment time seems to have had a limited effect on lung cancers. The next step is to examine the effect of increasing the dose to the tumour.
Phase 1/2 studies suggest a dose response curve for local control of NSCLC. Higher doses are needed for larger tumours with conventional fractionation.
When corrected for stage distribution, the dose-response relationship is clearer. Nevertheless, overall results of hyperfractionation in lung cancer has been disappointing.
Hypofractionation
Hypofractionated regimes are often used in palliative treatment of advanced cancer. It is very useful as it limits patient visit to the hospital especially for debilitated patients and offers good symptom control for the relatively short patient life span. Various hypofractionated regimes have been used in H&N cancers, each with its own merits.

<table>
<thead>
<tr>
<th>Study</th>
<th>Fraction</th>
<th>Total Dose</th>
<th>Fraction Count</th>
<th>Total Dose</th>
<th>Achieved Good Palliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGI</td>
<td>25</td>
<td>300cGy</td>
<td>10</td>
<td>30 Gy</td>
<td></td>
</tr>
<tr>
<td>Mohanti et al</td>
<td>50</td>
<td>400cGy</td>
<td>5</td>
<td>20 Gy</td>
<td>Achieved good palliation</td>
</tr>
<tr>
<td>Weissberg et al</td>
<td>64</td>
<td>400cGy</td>
<td>10-12</td>
<td>40-48 Gy</td>
<td></td>
</tr>
<tr>
<td>Paris et al</td>
<td>370 cGy</td>
<td>Twice daily x2days, Repeated every 3-4 wks</td>
<td>44 Gy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IN NSCLC, several case series indicate good local control and survival in early stage lung cancer using high doses per fraction for a few fraction. Lung toxicity specifically pneumonitis were acceptable in most series.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Median FU (months)</th>
<th>Tot Dose/ No fr</th>
<th>Actuarial Surv 2 year (%)</th>
<th>Prog Free Surv 2 year (%)</th>
<th>Toxicity Grade 2 Pneumo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onimaru R</td>
<td>25</td>
<td>18</td>
<td>48-60/8</td>
<td>47</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>Timmerman R</td>
<td>37</td>
<td>15</td>
<td>24-60/3</td>
<td>-</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td>Onishii H</td>
<td>245</td>
<td>24</td>
<td>18-75/1-22</td>
<td>70</td>
<td>87</td>
<td>7</td>
</tr>
<tr>
<td>Wuif J</td>
<td>20</td>
<td>11</td>
<td>30-37.5/3</td>
<td>32</td>
<td>92</td>
<td>3</td>
</tr>
<tr>
<td>Hoyer M</td>
<td>49</td>
<td>-</td>
<td>45/3</td>
<td>47</td>
<td>85</td>
<td>-</td>
</tr>
<tr>
<td>Nagata Y</td>
<td>45</td>
<td>30</td>
<td>48/4</td>
<td>StageA: 90 StageIB: 72</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Beitler JJ</td>
<td>75</td>
<td>17</td>
<td>30-90/4-12</td>
<td>45</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Xia T</td>
<td>43</td>
<td>27</td>
<td>50/10</td>
<td>78</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>Baumann P</td>
<td>138</td>
<td>33</td>
<td>30-48/2-4</td>
<td>65</td>
<td>91</td>
<td>1</td>
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<tr>
<td>Zimmermann FB</td>
<td>68</td>
<td>17</td>
<td>24-40/3-5</td>
<td>71</td>
<td>88</td>
<td>29</td>
</tr>
<tr>
<td>Faria SL</td>
<td>32</td>
<td>21</td>
<td>52.5/15</td>
<td>56</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Uematsu M</td>
<td>50</td>
<td>36</td>
<td>50-60/5-10</td>
<td>77</td>
<td>-</td>
<td>0</td>
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<tr>
<td>Hof H</td>
<td>42</td>
<td>15</td>
<td>19-30/1</td>
<td>65</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td>Lagenwaard FJ</td>
<td>206</td>
<td>12</td>
<td>60/3.5,8</td>
<td>64</td>
<td>68</td>
<td>3</td>
</tr>
</tbody>
</table>

Hatton MQF, Clinical Oncology 22 (2010), 356-364
Prostate cancers are thought to have a low $\alpha/\beta$ value, similar to late reacting tissue. Therefore they should be more sensitive to large fraction size radiation therapy. Some trial do indicate better biochemical control although the effect on overall survival is less clear.
Evidence from randomised trials has indicated that total doses >72 Gy are significantly better in cases of biochemical disease-free survival. Image-guided radiotherapy resulted in reduced safety margins around the prostate target volume and decreased acute and late side-effects. To date, data from two randomised controlled trials have indicated comparable results between hypofractionation and normofractionation without an increase of side-effects. During the few last years, there have been tremendous technological improvements with a focus on boosting the cure rate by increasing dose delivery while maintaining a similar or improved side-effect profile. Currently, efforts are also focused on shortening treatment times and improving efficacy through new technology.” - in the words of the authors of the above article.

Though we today have the technology to achieve this it is imperative that this knowledge be adapted to the expertise, infrastructure and logistics available at a particular Institute to achieve its primary objective: Uncomplicated cures.

Note that the series by Tsujii et al uses high LET radiation hence the dose is given as 66GyE (Gy equivalent)
Breast is an organ where hypofractionated treatment offers similar advantage to conventional treatment without compromise on overall recurrence rate or cosmesis.

The article refers to the use of hypofractionated RT in the treatment of the entire breast. The results need to be interpreted in the background of both local control and cosmetic outcome. There are various other case control series available to support the same. The experience and expertise should be able to guide selection of the optimal regimen and method.
An example in hypofractionation in the treatment of breast cancer: The START B trial. The intent is radical. The 2 fractions tested were 50Gy/ 25# and 40Gy/ 16 #. The endpoints both control and toxicity. The outcomes were similar in the 2 groups. What this emphasises is that hypofractionation has a definite place in the radical treatment of cancer. It would have an enormous bearing on the cost and logistic issues. However, good RT technique, attention to planning and proper patient selection are of paramount importance.
Partial breast radiation is also gaining acceptance. Here careful patient selection is required as the treatment is more suited to patients with small breast tumours. The local control rates appear comparable to standard radiotherapy.

Would refer participants to this article to review their knowledge and ideas on APBI, about the best method, patient selection etc.
Participants should refer to this document for an indepth understanding of patient selection, method of APBI, outcomes, both control rates and cosmesis.
Altered fractionation is a modification of dose per fraction, total dose based on tumor kinetics in an attempt to increase therapeutic ratio

To conclude-
It is a widely accepted hypothesis that hyperfractionation allows one to escalate total dose and thereby to enhance tumor control rate, without increasing the risk for late normal tissue complications. The number of studies on experimental tumours in a clinically relevant range is very limited. Although some of these data suggest that tumor response is not significantly altered by the use of smaller dose fractions below 1.6 Gy, other tumors show a clear fractionation effect.

Also the experimental evidence for dose sparing with small doses per fraction in late reacting tissues is very limited. The clinical data from various studies suggest that dose escalation accompanied by reduced doses per fraction might improve treatment outcome in some situations, but the line of evidence is not consistent. For the treatment of head and neck cancers there is even evidence that hyperfractionation regimens might even increase the incidence of severe late sequelae. It can be speculated whether such an increase might be due to insufficiently long intervals between daily fractions.

In conclusion it can be said that the experimental and clinical evidence for a consistent therapeutic gain from hyperfractionated radiotherapy is still lacking. The present studies indicate that the dose per fraction is a good choice. Nevertheless, disease control and survival that are achievable with standard radiotherapy are not satisfactory, and additional studies are warranted.
Summary

- Reduction of overall treatment time most effective in patients with well and moderately differentiated tumors.
- Shortening of overall treatment time by 1 wk optimum to strike a balance between tumor control and late tissue toxicity for Head & Neck cancers.
- Concomitant boost is an attractive mode to accelerate. Timing of boost is a significant factor for local control.
- Trials using Hyperfractionated schedules fared better, it should be preferred wherever logistically feasible.
Summary (2)

- Reduction in fraction size permits total dose escalation leading to increased tumor control without increase in late tissue toxicity.
- Choice between Accelerated and Hyperfractionated radiotherapy should be decided cost benefit ratio and logistics.
- Intense supportive care needs to be borne in mind
- Of relevance in present day use of combined modality approaches
- Toxicity profile could be modified with the use of Image based Radiotherapy techniques
- Hypofractionated regimes is important for palliative treatment and also in certain cancer sites
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