ALTERED FRACTIONATION SCHEDULES IN HEAD AND NECK CANCER – RADIOBIOLOGY AND CLINICAL APPLICATIONS

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FRACTIONATION – WHY?

- **FOUR 'R' s**
  - **R**epair of sublethal damage
  - **R**edistribution in cell cycle
  - **R**epopulation
  - **R**eoxygenation

FRACTIONATION – HOW?

- CONVENTIONAL
  - Developed empirically
  - Varied from place to place
  - Most common practice is
    - **ONE FRACTION PER DAY**
    - **DOSE 1.8 – 2 Gy / #**
    - **FIVE DAYS PER WEEK, MON – FRI**
    - **RADICAL DOSE 60 – 70 Gy**

RADIOBIOLOGY OF HEAD AND NECK CARCINOMAS

- Squamous cell carcinoma, higher α/β ratio as compared to late responding normal tissues
- Propensity for accelerated repopulation after onset of therapy
- Average lag period between onset of radiation and repopulation 4±1weeks
- Compensate with dose increase of about 0.6Gy/day

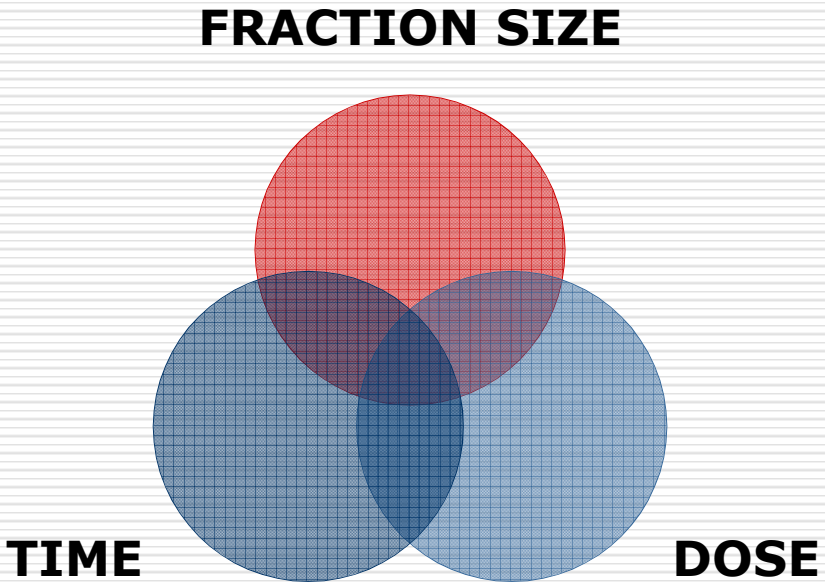
CONVENTIONAL FRACTIONATION IN HEAD AND NECK CARCINOMA

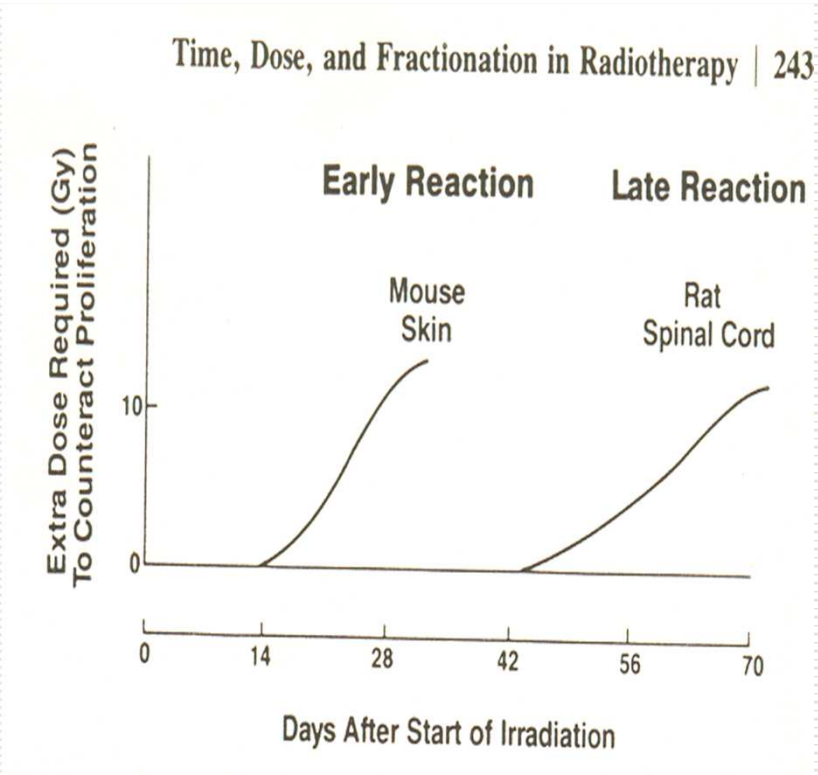
- Radical dose prescribed by most centres vary from 60 – 70 Gy in 6 – 7 weeks time
- Accelerated repopulation starts around 28 days after starting radiation
- Suboptimal results in locally advanced carcinomas

EVIDENCE?

- Withers et al, 1988
  - Rapid tumour re-growth when treatment time extended from 5 to 8 weeks
  - Lag period 4±1 weeks
  - Dose increment 0.6Gy/day required
- Fowler et al,1992
  - Review of 12 published clinical trials – 14% loss of local control/week of extra overall time

HOW TO TACKLE THE PROBLEM?





IMPROVING THERAPEUTIC INDEX IN HEAD AND NECK CANCERS

- AIM: To separate the sigmoid curve of complications from that of tumour control
  - ACUTE EFFECTS: Depend on rate of dose accumulation
  - LATE EFFECTS: Depend on total dose, dose per fraction, inter fraction interval
- Can the index be improved by giving small fractions over longer duration?

THERAPEUTIC INDEX….contd.

- The overall duration of radical radiation in head and neck cancer should not be extended beyond the period necessary to limit the acute normal tissue toxicity.
- Multiple fractions per day, respecting the tolerance of normal tissues, with overall duration <3 – 5weeks should be best way of improving this index.

MULTIPLE FRACTIONS/DAY

- HYPERFRACTIONATION
  - Total tumour dose: **INCREASED**
  - No. of fractions: **INCREASED**
  - Dose/fraction: **DECREASED**
  - Overall time: **UNCHANGED**
  - BED in tumour increased
  - Radiosensitisation through redistribution and lesser OER at low doses

MULTIPLE FRACTIONS/DAY contd.

- HYPERFRACTIONATION
  - For comparable toxicity in fibrovascular tissues, 2Gy/# replaced by two # per day, 1.15 – 1.2Gy/#
  - Inter-fraction interval not less than 6 hours
  - Useful when α/β ratio of tumour greater than dose limiting normal tissue
  - Inevitably, more severe acute reactions

CLINICAL TRIALS OF HYPERFRACTIONATION

- **EORTC Horiot et al, 1992**
  - Oropharynx T2-3, N0-1
  - 1.5Gy x 2/day at 6-8 hrs interval, total dose 80.5Gy in 7 weeks compared to conventional 70Gy/7weeks/35#
  - LR control rate 59% vs 40% (p=0.02)
  - More acute mucositis, late reactions comparable
  - Trend towards improved survival

CLINICAL TRIALS OF HYPERFRACTIONATION

- **PMH Cummings et al 2000**
  - Various sites, T3-4,N0 or any TN+
  - HF 1.45x2/day, 58Gy in 4 weeks compared to 51Gy/4weeks/20#
  - 5 years LRC 45% vs 37% (p=0.01)
  - 5 years OS 40% vs 30% (p=0.01)
  - More acute mucositis with HF but late complications comparable

CLINICAL TRIALS OF HYPERFRACTIONATION

- **RTOG Fu et al 2000**
  - Various sites, stage II – IV 1073 pts
  - 1.2x2/day, 81.6Gy in 6 weeks compared to 72Gy/7 weeks, 1.8Gy/#
  - Significant improvement in LR control rate and trend to improved DFS in favour of HF
  - Significantly higher Grade 3 mucositis, no difference in late toxicities

HYPERFRACTIONATION - recap

- Total dose increased
- Overall treatment time unchanged
- Multiple fractions at 6 – 8 hours interval
- Significant increase in locoregional control rate and acute mucositis
- Late toxicities unchanged
- Survival benefit?

MULTIPLE FRACTIONS/DAY

- ACCELERATED FRACTIONATION
  - Overall treatment time: significantly reduced
  - Total dose, fraction size: some change
  - Aim is to minimize tumour regeneration during therapy
  - ‘Pure’ and ‘hybrid’ types of schedules
  - No. of fractions/day varies

PURE ACCELERATION

- Reduction of overall treatment time
- No change in fraction size or total dose
- Once daily fraction, 6-7 days a week
- Two fractions per day during some or all weekdays

CLINICAL TRIAL PURE A.F.

- **DAHANCA Overgaard et al 2000**
  - 66 – 68 Gy in 33 – 34 fractions
  - 5 or 6 fractions per week
  - Overall treatment time 6 or 7 weeks
  - Significantly higher tumour control at 5 years 66% vs 57% (p=0.01)
  - DFS at 5 years 72% vs 65% (p=0.04)
  - Severe acute mucositis and dysphagia more with AF

CLINICAL TRIAL PURE A.F.

- **Skladowski et al 2000**
  - 70 Gy ,1.8 – 2 Gy/#
  - Overall time 5 weeks or 7 weeks
  - LR control at 3 years 82% vs 37% ($p<0.0001$)
  - O.S. at 3 years 78% vs 32% ($p<0.0001$)
  - Severe mucositis 62% vs 26%
  - Late complications 10% vs 0%

HYBRID ACCELERATION

- Overall treatment reduced along with changes in fraction size and total dose
- Aim is to make treatment more tolerable
- Three main types of schedule tested with different strategies to avoid acute reactions

TYPE A ACCELERATION

- Intensive short course treatment
- Overall treatment time markedly reduced
- Multiple fractions delivered per day
- Total dose reduced in order to decrease acute reactions
- Spinal cord, if included, may not have full repair within 6 hours

CLINICAL TRIAL TYPE A

- CHART British MRC multicentre trial
  - Overall time 2 weeks
  - Dose per fraction 1.5 Gy
  - No. of fractions per day 3
  - Inter fraction interval 6hours
  - Total dose 54 Gy
- No difference in LRC, DFS, OS
- More acute mucositis, less telangiectasia

CLINICAL TRIAL TYPE A

- GORTEC Bourhis et al 2000
  - Overall treatment time 3.3 weeks compared to conventional 7 weeks
  - Dose per fraction 2Gy
  - No. of fractions 2 or 1
  - Total dose 63 Gy or 70 Gy
- LRC 58% vs 34% at 2 years ($p<0.01$)
- No survival benefit
- Significant increase in acute mucositis

TYPE B ACCELERATION

- Split course regimen
- Two short courses of multifraction radiation with a planned gap of two weeks
- Initially, the second part of treatment was given by once a day fractions
- Total treatment time lasted about 6 weeks

CLINICAL TRIAL TYPE B

- **EORTC Horiot et al 1997**
  - 28.8Gy/ 7 days, 1.6 Gy/#, 3 # /day
  - 2 weeks break
  - 43.2Gy/11days/27 #
- Compared to conventional 70Gy/7 weeks
- LRC at 5years 59% vs 46% (p=0.02)
- More severe acute and late morbidities

CLINICAL TRIAL TYPE B

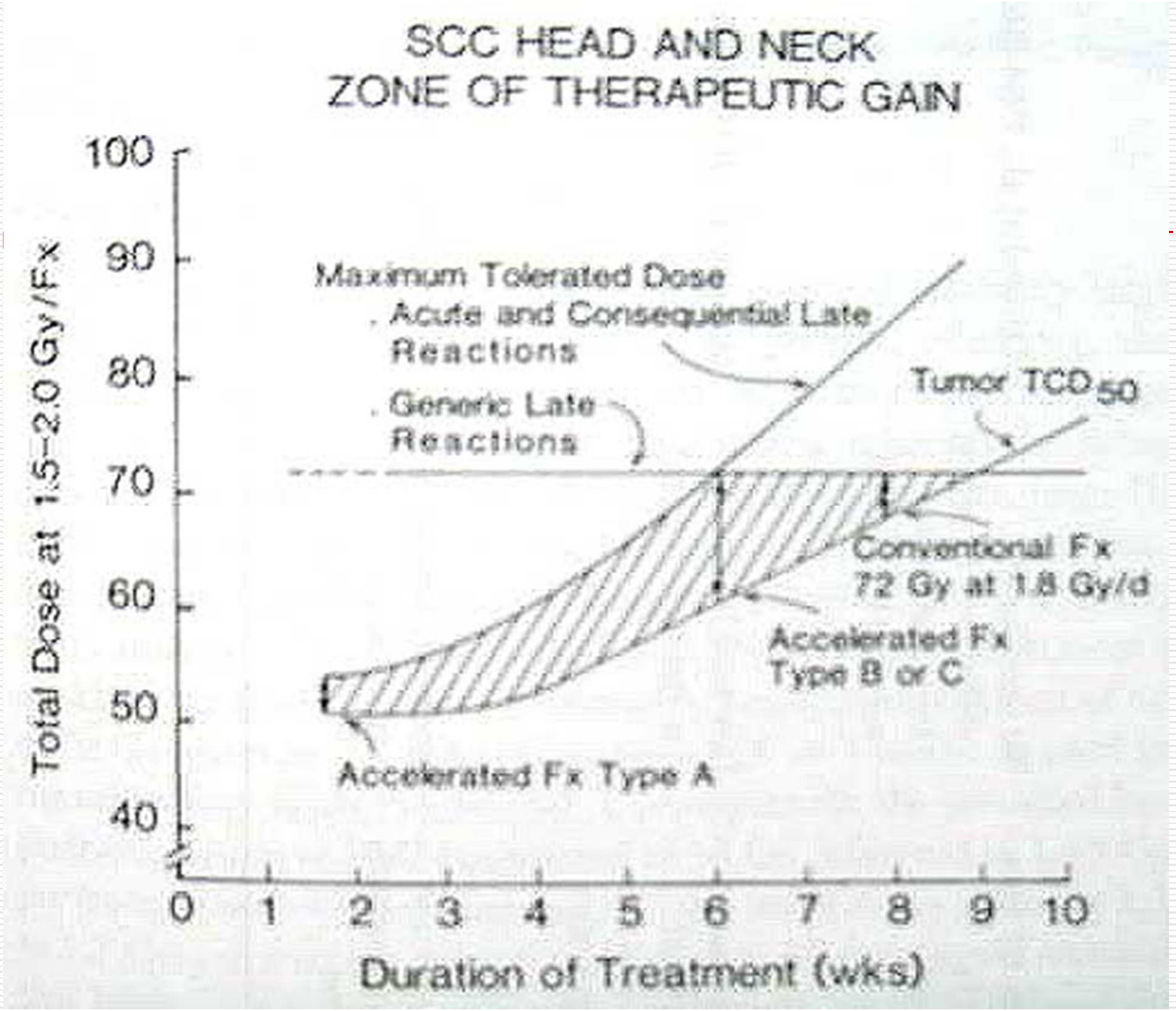
- **RTOG regimen**
  - Total dose 67.2 Gy/6 weeks
  - 1.6Gy/#, twice a day
  - Two weeks break after 34.8Gy
- Compared to standard 70Gy/7 weeks
- No improvement in LRC
- Acute mucositis increased

TYPE C ACCELERATION

- Concomitant boost
  - Designed in MD Anderson Cancer Centre
  - Boost dose to a smaller area delivered concomitantly
  - Boost given as a second daily dose 4 – 6 hours after initial radiation
  - May be given throughout the main treatment or at the beginning or end

CLINICAL TRIAL TYPE C

- **RTOG TRIAL Fu et al 2000**
  - Basic field 54Gy/6 weeks, 1.8Gy/#
  - Boost field 18 Gy/2.5 weeks, 1.5Gy/# given as second daily dose during the last part of treatment
  - Higher LR control
  - Trend towards better DFS
  - More severe acute mucositis, late toxicities comparable


SCC HEAD AND NECK
ZONE OF THERAPEUTIC GAIN
Total Dose at 1.5–2.0 Gy/Fx
100
90
80
70
60
50
40
Maximum Tolerated Dose
. Acute and Consequential Late Reactions
. Generic Late Reactions
Tumor TCD50
Conventional Fx
72 Gy at 1.8 Gy/d
Accelerated Fx
Type B or C
Accelerated Fx Type A
0 1 2 3 4 5 6 7 8 9 10
Duration of Treatment (wks)

RECENT EVIDENCE

- MARCH Collaborative group, Sept'06
  - Meta-analysis 15 trials, 6515 patients
  - Median follw up 6 years
  - Sites: oropharynx and larynx, 74% stage III and IV
  - Significant survival benefit with altered fractionation
  - Absolute benefit 3.4% at 5 years; HR= 0.92, 95% CI 0.86-0.97,p=0.003

MARCH contd

- Significantly higher benefit with hyperfractionation 8% at 5 years
- Locoregional control with altered fractionation better than conventional 6.4% at 5 years ($p<0.0001$)
- Benefit less in older patients aged > 70 years

RECENT EVIDENCE contd.

- MACH – NC
  - Focuses on concomitant chemoradiation
  - Bourhis et al suggest that addition of chemotherapy to hyperfractionation and accelerated fractionation regime improve local control and survival outcome compared with radiation alone.
  - Acute and long term toxicity comparable
- Long term results need to be interpreted

RECENT EVIDENCE contd

- Budach et al meta analysis combined chemo+ altered fractionation
- 32 trials 10225 patients
  - Overall survival benefit of 12m with addition of chemo to conventional/ altered fractionation ($p<0.001$)
  - Substantial prolongation of median survival, 14.2m with HF compared to conventional RT (both without chemo)

RECENT EVIDENCE contd

- Bourhis et al May 2007
- Meta analysis Chemo + altered #
- 120 randomised trials, 25000 patients median follow up 6years
  - Concomitant cisplatin based chemotherapy and altered fractionation gives significant benefit in LR control and survival

CONCLUSIONS

- Altered fractionation regimens aim to improve the therapeutic ratio in head and neck malignancies
- Hyperfractionation enables dose escalation without increasing severe late toxicities
- Accelerated fractionation with split course or reduced total dose gives no benefit

CONCLUSIONS contd.

- Continuous RT without decreasing total dose improve local tumour control with non-significant survival benefit (More data needed in this subgroup)
- Addition of chemotherapy to altered fractionation schemes improve survival as shown by recent studies