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**eoxxygenation
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
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±1 weeks
Compensate with dose increase of about 0.6 Gy/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?

FRACTION SIZE

TIME

DOSE
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?
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 – 5 weeks 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
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 6 hours
  - 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 5 years 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
RECENT EVIDENCE

- MARCH Collaborative group, Sept’06
  - Meta-analysis 15 trials, 6515 patients
  - Median follow 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)
Bourhis et al May 2007

Meta analysis Chemo + altered #

120 randomised trials, 25000 patients

median follow up 6 years

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