

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

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# FRACTIONATION – WHY?

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## □ **FOUR 'R' S**



- **R**epair of sublethal damage
  - **R**edistribution in cell cycle
  - **R**epopulation
  - **R**eoxygenation
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# FRACTIONATION – HOW?

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## 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**
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# RADIOBIOLOGY OF HEAD AND NECK CARCINOMAS

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- ❑ Squamous cell carcinoma, higher  $\alpha/\beta$  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  $4 \pm 1$  weeks
  - ❑ Compensate with dose increase of about 0.6Gy/day
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# CONVENTIONAL FRACTIONATION IN HEAD AND NECK CARCINOMA

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- ❑ 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
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# EVIDENCE?

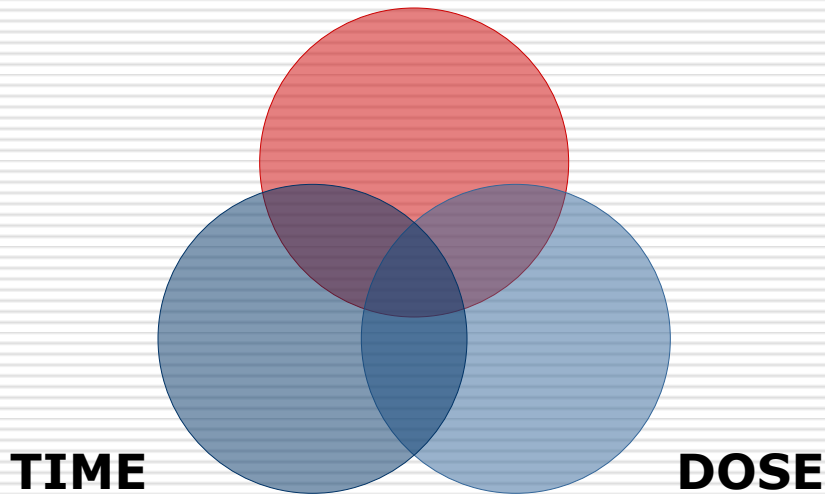
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- Withers et al, 1988
    - Rapid tumour re-growth when treatment time extended from 5 to 8 weeks
    - Lag period  $4 \pm 1$  weeks
    - Dose increment 0.6Gy/day required
  - Fowler et al, 1992
    - Review of 12 published clinical trials – 14% loss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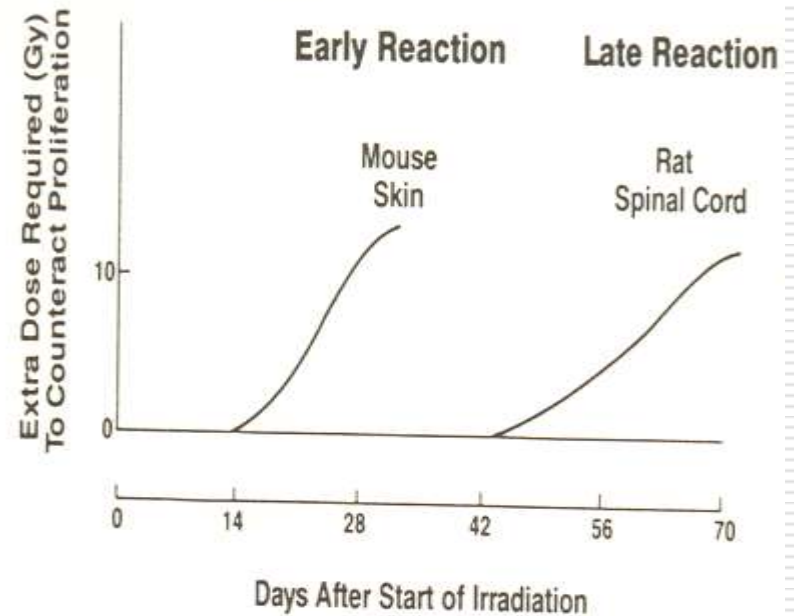
# HOW TO TACKLE THE PROBLEM?

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## FRACTION SIZE



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# IMPROVING THERAPEUTIC INDEX IN HEAD AND NECK CANCERS

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- 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?
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# THERAPEUTIC INDEX....contd.

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- 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.
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# MULTIPLE FRACTIONS/DAY

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## □ 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
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# MULTIPLE FRACTIONS/DAY contd.

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## □ 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  $\alpha/\beta$  ratio of tumour greater than dose limiting normal tissue
  - Inevitably, more severe acute reactions
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# CLINICAL TRIALS OF HYPERFRACTIONATION

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## □ **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
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# CLINICAL TRIALS OF HYPERFRACTIONATION

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## □ **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
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# CLINICAL TRIALS OF HYPERFRACTIONATION

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## □ **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
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# HYPERFRACTIONATION - recap

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- 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?
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# MULTIPLE FRACTIONS/DAY

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## □ 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
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# PURE ACCELERATION

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- ❑ 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
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# CLINICAL TRIAL PURE A.F.

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## □ **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
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# CLINICAL TRIAL PURE A.F.

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## □ 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%
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# HYBRID ACCELERATION

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- ❑ 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
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# TYPE A ACCELERATION

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- ❑ 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
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# CLINICAL TRIAL TYPE A

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- 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
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# CLINICAL TRIAL TYPE A

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- 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
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# TYPE B ACCELERATION

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- 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
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# CLINICAL TRIAL TYPE B

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## □ **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
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# CLINICAL TRIAL TYPE B

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## **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
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# TYPE C ACCELERATION

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- 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
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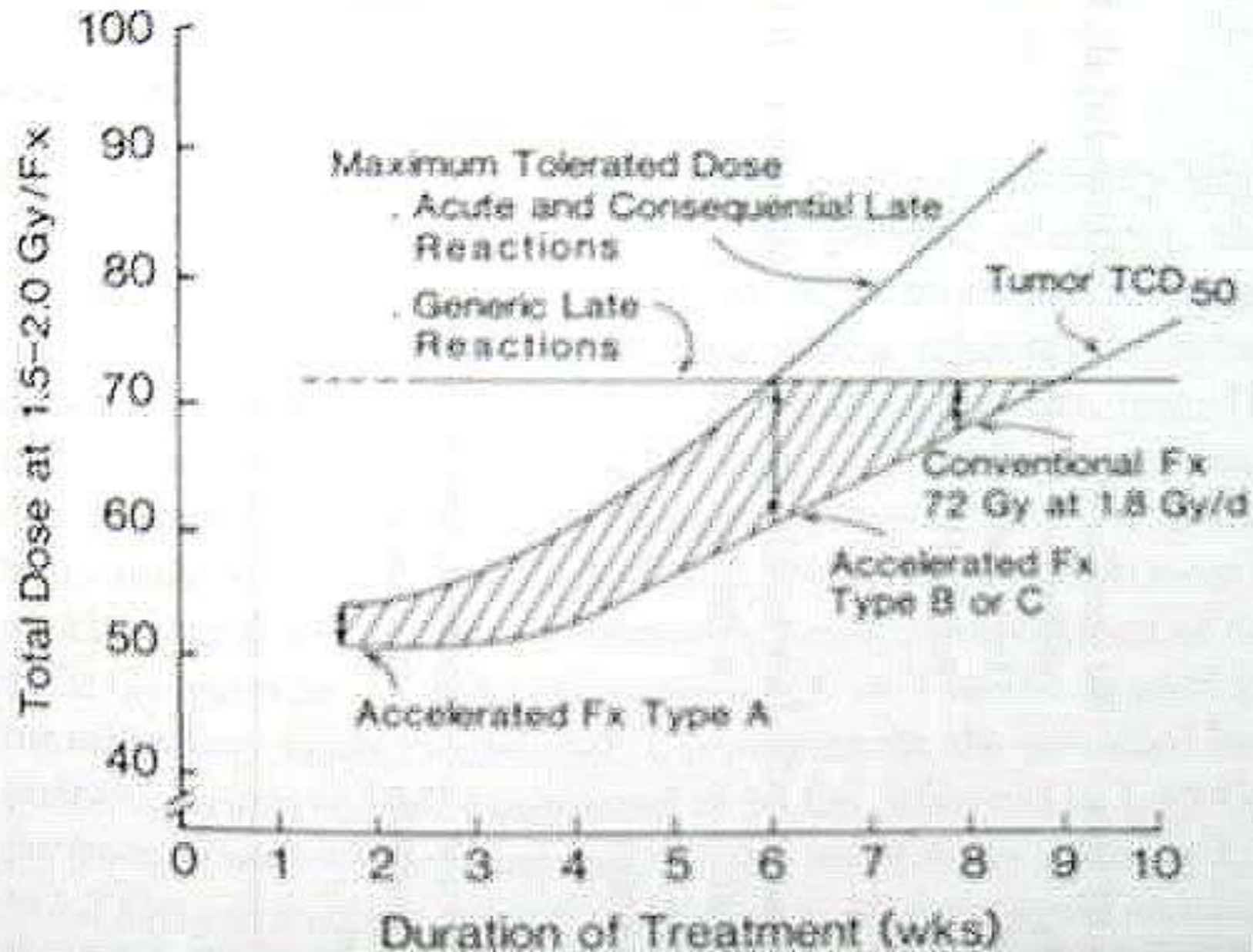
# CLINICAL TRIAL TYPE C

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## □ **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
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# SCC HEAD AND NECK ZONE OF THERAPEUTIC GAIN



# RECENT EVIDENCE

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- 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
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# MARCH contd

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- ❑ 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
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# RECENT EVIDENCE contd.

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## □ 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

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# RECENT EVIDENCE contd

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- 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)
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# RECENT EVIDENCE contd

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- 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
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# CONCLUSIONS

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- ❑ 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
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# CONCLUSIONS contd.

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- 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
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