Altered Fractionation Radiotherapy in Head-Neck Cancer: Past, Present,….Future?

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Fractionation: What & Why?

- Dividing up the total dose of radiation to be delivered over multiple doses for the purposes of :
  - Tolerability

  &

  - Efficacy

Those 5 R's again

The basis of fractionation:

- Repair
- Repopulation
- Reoxygenation
- Reassortment
- Intrinsic Radiosensitvity

- By breaking up the radiotherapy dose into a number of different fractions, allows:
- Repair of sublethal damage of normal tissue
- Reoxygenation of hypoxic components of tumors
- Reassortment of tumor cells, from less radiosensitive to more radiosensitive phase of cell cycle (G2-M)

But…

- Repair of tumor cell damage can happen, depending on the interval between fractions

- Repopulation of tumor cells, depending on the total duration of the radiation course, can lead to part of the radiation dose being effectively “wasted” to counter the increased cell load

Accelerated repopulation

- Occurs after 3-4 weeks for squamous carcinomas
- Up to 0.6 Gy of each daily dose would be “wasted” due to increased tumor cell load
- For each extra day, local control would decrease by 1% due to accelerated repopulation

Intrinsic radiosensitivity

- Tumors can have variable degrees of radiosensitivity, from
- highly radioresistant (melanoma, renal cell carcinoma) to
- Highly radiosensitive (lymphomas)

- Based on the extent of sub-lethal damage repair

Conventional fractionation

- 1.8-2 Gy per fraction
- 1 fraction per day
- 5 fractions per week

- Everything else is altered fractionation!

- Conventional fractionation is a convention, founded on logistic, rather than radiobiological principles

- Various altered fractionation strategies have developed to exploit the different aspects of fractionation, as mentioned

Hyperfractionation

- Same/ higher total dose
- **Smaller dose/fraction**
- Multiple fractions/ day
- Higher number of fractions
- Approximately same duration

- **Rationale**=lower late toxicity

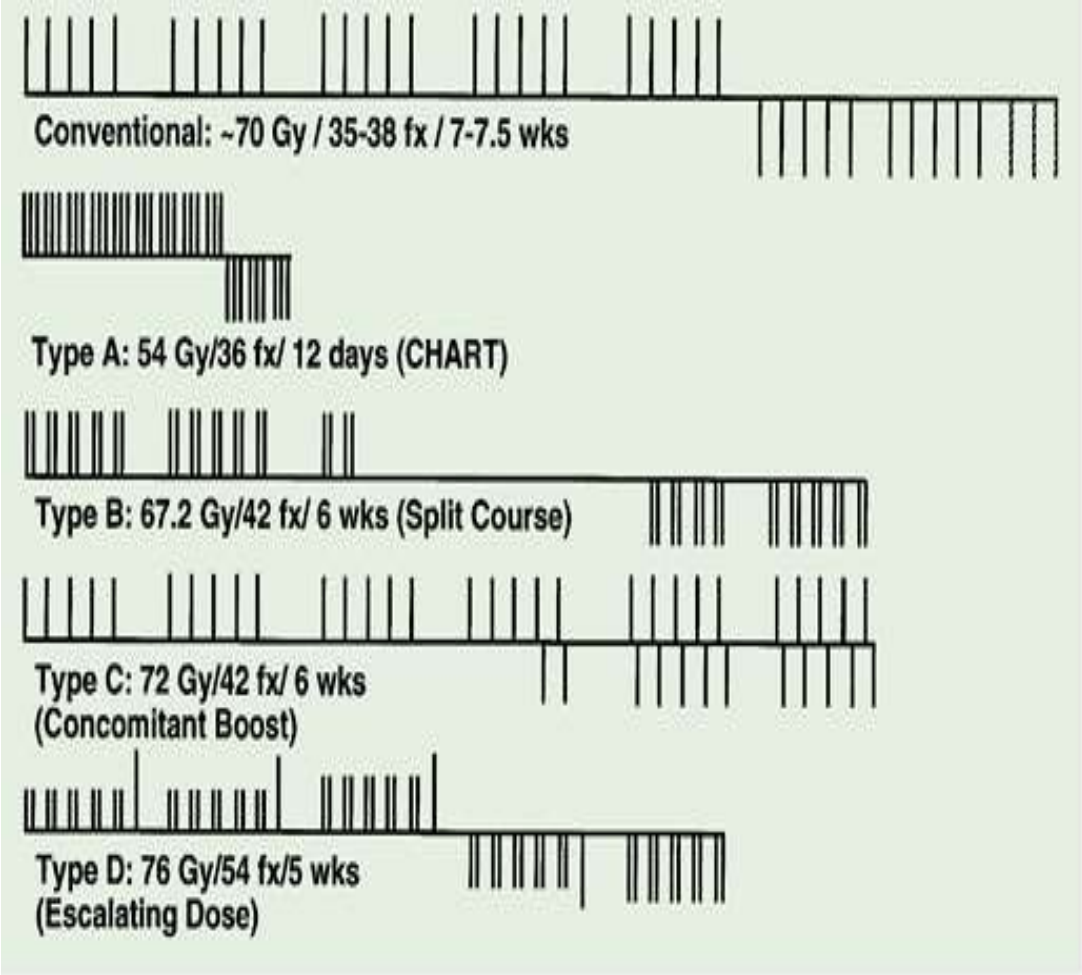
Accelerated fractionation

- Same/ lower total dose
- Lower dose/ fraction
- Multiple fractions/day
- Higher number of fractions
- **Shorter overall duration**

- **Rationale**=conclusion of radiation course before onset of accelerated repopulation

Strategies

- Concomitant boost
- Split-course
- Lower total dose



CHART

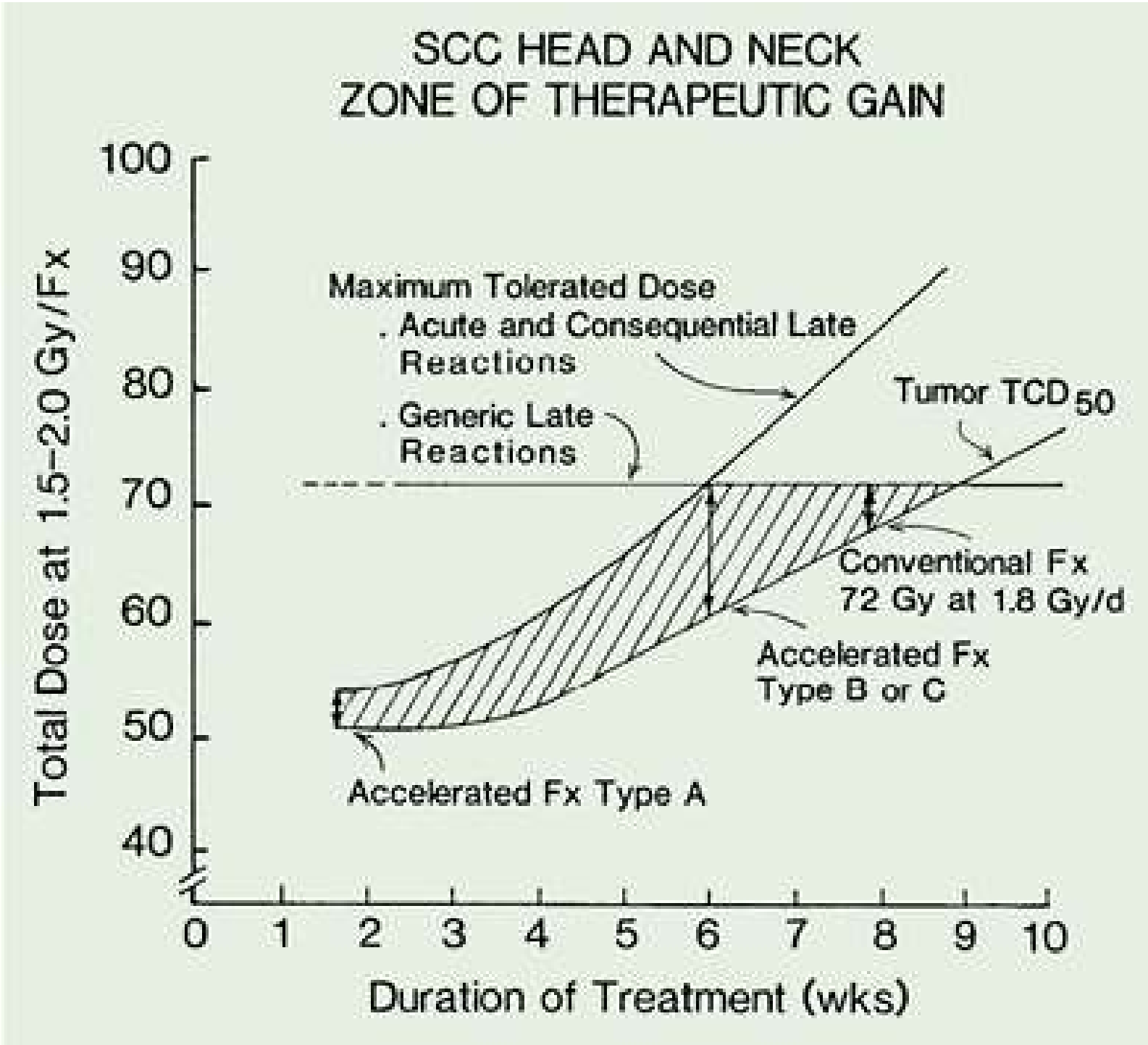
- Combines the twin advantages of:
- Hyperfractionation

&

- Accelerated fractionation
- A common schedule is 54Gy/36#/12 days

Hypofractionation

- Lower total dose
- Higher dose/fraction
- Lesser number of fraction
- Shorter overall duration


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 TCD 50
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)

State-of-the-Art in Head-Neck Cancers: Pros & Cons

- IMRT allows parotid gland sparing→less xerostomia→ ? Better QoL
- IGRT allows margin reduction→less normal tissue irradiation→? Better QoL
- Advanced imaging techniques and delineation protocols also mean more accurate targetting
- Concurrent chemotherapy is a standard of care
- Biological therapies may allow superior tumor control

But what about fractionation?

- Hardly any modern trials genuinely address fractionation as a tool
- Barring use of Simultaneous Integrated Boost in IMRT, altered fractionation is hardly in our armamentarium
- In chasing after advanced technology, are we perhaps ignoring the entire biologic basis of radiotherapy?

Role of altered fractionation in other cancers

- Hypofractionation has emerged as a viable alternative in breast, prostate & lung cancers
- It may be better tolerated & even more effective
- Aside from tumor DNA damage, the extra effectiveness of hypofractionation may be due to its anti-angiogenic effect on micro-environment vasculature

What does the data in Head-Neck Cancer say?

- The MARCH (Meta-Analysis of Radiotherapy in Carcinomas of Head and neck) was done to evaluate the effect of altered fractionation radiotherapy on survival

Bourhis et al. Lancet Oncol 2010; 11: 553–60

- N= 6515 (15 trials)
- Median follow up =6 years
- Mostly oropharynx and larynx
- 5221 (74%) patients had stage III-IV disease

- **Significant benefit in 5-year locoregional control** (6.4%, $p < 0.0001$)

- The effect was more on local failure, whereas the benefit on nodal control was less pronounced.

- The benefit was significantly higher in the **youngest** patients (under 50 year old) (HR 0.78, 95% CI 0.65 to 0.94),

- **Significant 5-year overall survival benefit**, corresponding to an absolute benefit of **3.4%** (HR= 0.92, 95% CI 0.86 to 0.97; p = 0.003).

- The benefit was significantly higher with HFRT (**8%**) than with AFRT (2% without total dose reduction and 1.7% with total dose reduction) (p = 0.02)

MACH-NC (2009 update)

- 87 RCTs
- N=16485

Standard of Care

- Absolute survival benefit of chemotherapy **4.5%** at 5 years (HR=0.88)

- Absolute survival benefit of concurrent chemotherapy **6.5%** at 5 years (HR=0.81)

Pignon et al. Radiotherapy and Oncology 92 (2009) 4–14

THE CLASSICS

EORTC 22851

- RCT
- N=512
- T2-T4 HNC (hypopharynx excluded)
- Conventional RT (70Gy/35#/7weeks) vs Accelerated fractionation RT (72 Gy/45#/5weeks)

- **Significant increase in local tumor control** (13% at 5 years)
- **No** increase in survival
-
- Unexpected increase in late effects, some of which were lethal

Horiot et al. Radiotherapy and Oncology 44 (1997) 11 1 - 121

EORTC 22791

- RCT
- N=356
- T2-T3,N0-N1,M0 oropharyngeal carcinomas (excluding base of tongue)
- Conventional (70Gy/35#/7 weeks) vs hyperfractionated RT (80.5Gy/70#/7 weeks)

- **Significantly improved 5-year local tumor control** (from 40% to 59%)
- Trend towards improved survival
- **Similar** acute toxicities
- **Similar** late toxicities

Horiot et al. Radiotherapy & Oncology (1992) 25;4:231-41

CHART

- RCT
- N=918
- SCCHN (except T1N0 glottis)
- Conventional RT (66Gy/33#/6.5 weeks)

  vs
- CHART (54Gy/36#/12 days

- **No** difference in loco-regional control, primary tumour control, nodal control, disease-free interval, freedom from metastasis and survival

- **Acute** radiation mucositis more severe with CHART, occurred earlier but settled sooner.

- Skin reactions were less severe and settled more quickly.

- **Reduced** late morbidity (laryngeal oedema, ulceration & telegiectasia)

Dische et al. Radiotherapy and Oncology 44 (1997) 123- 136

RTOG 90-03

- RCT
- N=1073
- Locally advanced HNC
- 4 arm study:
- 1) standard fractionation (SFX)
- 2) hyperfractionation (HFX)
- 3) accelerated fractionation with split (AFX-S)
- 4) accelerated fractionation with concomitant boost (AFX-C).

Trotti et al. Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 2, S70-71, 2005

Updated results (2005): Disease Outcomes

- **HFX and AFX-C regimens :**
- **Significantly better 5-year local-regional control** (p=0.037 and p=0.042 respectively)
- **Significantly improved disease-free survival** (p=0.013 and p=0.042 respectively).

- **Trend toward improved overall survival** in patients treated with **hyperfractionation** (p=0.063).
- **No** significant difference in cause-specific survival.
- **No** significant differences in the incidence of distant metastasis.

- All three altered fractionation arms showed a **significantly higher crude incidence of patients with grade 3 acute side effects** when compared to SFX.

- **Trend toward an increased crude incidence of grade 3 late effects with AFX-C** compared to SFX (33.3% vs. 25.2%, p0.066)
- However, **the incidences for HFX and AFX-S arm were similar to SFX**. (27.4% and 26.8%)

TWEAK OR TREAT:
NEW STRATEGIES IN ALTERED FRACTIONATION

5 vs 6 fractions per week
IAEA trial

- RCT
- Stage I-IV LASCCHN (except NPC & T1-glottis)
- 70Gy/35#
- **2 arms:**
- 6#/week (N=456)

  Vs

  5#/week (N=450)

- **Significantly increased actuarial 5-year LCR** (42% vs 30%, p=0004**), 5-year DFS** (50% vs 40%, p=0.03)
- Trend towards increased actuarial 5-year OS (35% vs 28%, p=0.07)
- **Significantly increased acute morbidity**
- **Equivalent** late morbidity

Overgaard et al. Lancet Oncol 2010; 11: 553–60

Very Accelerated RT: GORTEC 94-02

- RCT
- N=268
- T3-T4,N0-N3 unresectable LASCCHN
- Conventional RT 70Gy/35#/7 weeks vs
- Very accelerated RT

64Gy/32#/3.5 weeks

(2Gy BID)

- **6-year LCR significantly increased** (by 24%)
- **No** DFS/OS benefit
- **Significantly increased acute toxicity** ($p<0.001$)
- **Similar** late toxicity

Bourhis et al.JCO (2006) 24;18:2873-78

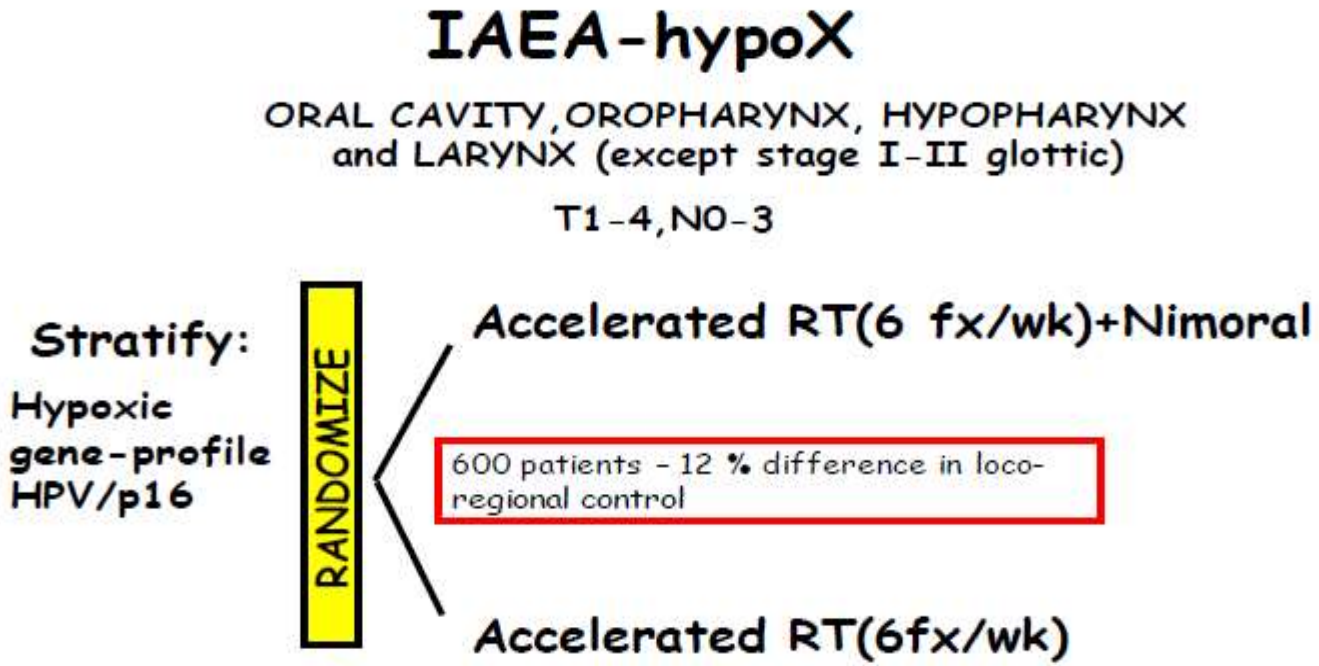
Altered fractionation + Chemotherapy: ORO 93-01

- RCT
- N=192
- Stage III-IV oropharyngeal cancers
- **3 arm study:**
- Arm A=Conventional RT
- Arm B=Split course accelerated RT
- Arm C=Split course accelerated RT + concurrent chemotherapy (Carboplatin+5FU)

- **No** difference in overall survival
- **2-year DFS significantly increased** in Arm C ($p<0.022$)
- **Slightly increased acute RT-toxicity** in Arm C
- **No** difference in late toxicity (xerostomia)

Olmi et al. Int. J. Radiation Oncology Biol. Phys., Vol. 55, No. 1, pp. 78–92, 2003

IAEA-HypoX:
Harnessing Altered fractionation & Radiosensitisers together



Accelerated Hypofractionation

- Retrospective study from Birmingham UK
- N=81
- Stage II-IV SCCHN
- EBRT 55Gy/20#/4 weeks with concurrent chemotherapy (MTX/ Carboplatin)

- Impressive disease outcomes:
- 2yr LCR=75.4%
- 2yr DFS rate=68.6%
- 2yr OS rate=71.6%

- Acute toxicities were tolerable
- No unexpected late toxicites at 24-month FU

Sanghera et al. Int J Radiat Oncol Biol Phys 2007 67;5:1342-51

Potential advantages

Biological:

- Avoids the effect of repopulation
- Delivers a lower BED_3, hence late toxicities should be comparable/ less
- Delivers similar BED_{10}, hence tumor control & acute toxicities should be at least equivalent

Logistic:

- Resource sparing (less number of treatment fractions/ days)

Hypofractionation for early glottic cancers

Yamazaki et al (2006)

- N=180
- T1N0M0
- 5-year LCR 77% (conv) vs 92% (hypo) (p=0.004)
- **No** significant difference in survival
- **No** significant difference in acute/ late toxicities.

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 1, pp. 77–82, 2006

KROG-0201 (2013)

- N=156
- T1-T2N0M0
- 5-year LFPS 77.8%(conv) vs 88.5%(hypo) (p=NS)
- 5-year LFPS for T1a 76.7% (conv) vs 93% (hypo) (p=0.056)
- **No** significant difference in survival
- **No** significant difference in acute/ late toxicity

Moon et al. Radiotherapy & Oncology, 2013 (ahead of print)

Take Home Messages

- Altered fractionation radiotherapy in head-neck cancer is effective and safe
- Significant logistical problems implementing multiple fractions/day protocol
- At present, logistic & funding considerations are focused on quality of radiotherapy treatment delivery
- Could the answer lie in quantity instead?