FRACTIONATION IN CLINICAL RADIATION ONCOLOGY

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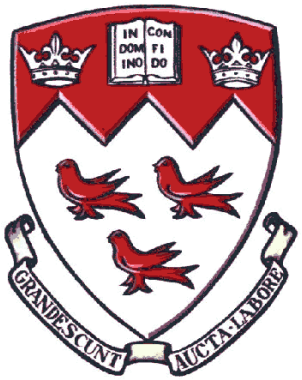


ALTERED FRACTIONATION SCHEDULES

CONVENTIONAL: 1.8 to 2 Gy daily fractions 5 fractions per week

HYPERFRACTIONATION: Total dose is increased, dose per fraction i decreased (1.1 to 1.2Gy per fraction), number of fractions i increased, with an overall time remaining unchanged

ACCELERATED FRACTIONATION: Total dose is unchanged, dose pe fraction is either unchanged or slightly reduced, number of fraction is unchanged or reduced and the overall treatment time is shortened

BACKGROUND RADIOBIOLOGY

Late effects normal tissues are more sensitive to changes in size o
dose per fraction than acute effects tissues

Acute reacting normal tissues are more sensitive to the changes i
the **rate of dose accumulation**

Accelerated repopulation is a major radiobiologica
pathophysiological mechanism explaining **reduction of tumor loca
control** after radiotherapy

RATIONALE FOR HYPERFRACTIONATION

The use of smaller dose/fraction allows the delivery of a higher tota
dose within the tolerance of late-responding normal tissues, resultin
in a higher biological effective dose in the tumor tissues

Radio sensitization by improving redistribution

Less dependency on oxygenation with lower dose/fraction

RATIONALE FOR ACCELERATED FRACTIONATION

The reduction in overall treatment time will decrease the probabilit of cancer cell regeneration/repopulation during an otherwise longe treatment delivery

A therapeutic gain is expected, with normal late effects as compare to conventional fractionation, provided that the dose/fraction i unchanged and the fractions are separated by a minimum inter fraction interval of > 6 hours an a single day

HYPERFRACTIONATED RADIOTHERAPY TRIALS

HEAD AND NECK TRIALS

EORTC TRIAL

EORTC 22791 compared Conventional fractionation (CF) of 70 Gy in 35-40 fractions in 7-8 weeks, to pure hyper fractionation (HF) of 80.5 Gy in 70 fractions in 7 weeks using 2 fractions of 1.15 Gy per day

From 1980 to 1987, 356 patients were entered.

At 5 years, 59% of patients are local disease-free in the HF arm compared to 40% in the CF arm.

The treatment regimen was an independent significant prognostic factor for loco regional control (p = 0.007 log-rank). This improvement of loco regional control was responsible for a trend to an improved survival (p = 0.08 log-rank).

There was no difference in late normal tissue damage between the two treatment modalities.

Horiot JC et al, Radiotherapy and Oncology, 25 (1992)

HYPERFRACTIONATED RADIOTHERAPY TRIALS
HEAD AND NECK TRIALS
The PMH Experience

Comparison of 58 Gy at 1.45 Gy/fraction twice a day over 4 weeks

Versus 51 Gy at 2.55 Gy/fraction (standard at PMH)

Loco regional control was improved from 37% to 45% and improved survival from 30% to 40% at 5 years

B Cummings Radiotherapy Oncology 2000

HYPERFRACTIONATED RADIOTHERAPY TRIALS
HEAD AND NECK TRIALS
RTOG 9003 Trial

The trial tested 81.6 Gy at 1.2 Gy/fraction twice daily over 6 weeks (HF) versus 70 Gy at 2 Gy/fraction over 7 weeks (CF)

Improved loco regional control from 46% (CF) to 54% (HF)

No increase in overall toxicities

K Fu et al Int J Rad Onc Biol Phys 2000

HYPERFRACTIONATED /ACCELERATED RADIOTHERAPY IN HEAD AND NECK CANCER: A META-ANALYSIS

Meta-analysis:

15 trials with 6515 patients were included.

The median follow-up was 6 years.

Tumours sites were mostly oropharynx and larynx; 5221 (74%) patients had stage III–IV

There was a significant survival benefit with altered fractionated radiotherapy, corresponding to an absolute benefit of 3·4% at 5 years (hazard ratio 0·92, 95% CI 0·86–0·97; p=0·003).

The benefit was significantly higher with hyperfractionated radiotherapy (8% at 5 years) than with accelerated radiotherapy (2% with accelerated fractionation without total dose reduction and 1·7% with total dose reduction at 5 years, p=0·02).

There was a benefit on loco regional control in favour of altered fractionation versus conventional radiotherapy (6·4% at years; p<0·0001), which was particularly efficient in reducing local failure, whereas the benefit on nodal control was less pronounced.

The benefit was significantly higher in the youngest patients (hazard ratio 0·78 [0·65–0·94] for under 50 year olds, 0·95 [0·83–1·09] for 51–60 year olds, 0·92 [0·81–1·06] for 61–70 year olds, and 1·08 [0·89–1·30] for over 70 year olds; test for trends p=0·007).

J Bourhis et al, The lancet 368; 843–854,2006

HYPERFRACTIONATED RADIOTHERAPY TRIALS
BLADDER CANCER

T2-4 Bladder cancer patients were randomized to:

- 84 Gy in 3, 1 Gy/fraction with 4 hours between fractions (HF)
- 64 Gy in 2 Gy daily fractions (CF)

Split course over 8 weeks

Cystoscopy CR was increased from 36% to 65%

Overall survival was also improved

Severe complications in the HF arm

Edsmyr et al, Radiotherapy Oncology, 1985

HYPERFRACTIONATION TRIAL FOR T2 GLOTTIC CANCER

RTOG TRIAL

Patients with T2 vocal cord cancer were randomly assigned to receive eithe hyperfractionation (HFX) to 79.2 Gy in 66 fractions of 1.2 Gy given twice a day, or standar fractionation

250 patients were enrolled.

Median follow-up for all surviving patients was 7.9 years (range, 0.6-13.1 years).

The 5-year local control (LC) rate was higher but not statistically significant (P=.14 for HFX [78% vs SFX [70%]).

The 5-year disease-free survival (DFS) was 49% versus 40% (P=.13) and overall survival (OS) wa 72% versus 63% (P=.29).

HFX was associated with higher rates of acute skin, mucosal, and laryngeal toxicity.

Grade 3-4 late effects were similar with a 5-year cumulative incidence of 8.5% (3.4%-13.6%) afte SFX and 8.5% (3.4%-13.5%) after HFX.

The 5-year local control was modestly higher with HFX compared to SFX for T2 glottis carcinoma but the difference was not statistically significant.

A Trotti et al, Int J Radiat Once Biol Phys. 2014 1;89(5):958-63.

ACCELERATED RADIOTHERAPY HEAD AND NECK DAHANCA 6&7 RIALS

Multicenter, controlled, randomised trial

1485 patients treated with primary radiotherapy alone, 1476 eligible patients were randomly assigned five (n=726) or six (n=750) fractions per week at the same total dose and fraction number (66–68 Gy in 33–34 fractions

Overall 5-year loco regional control rates were 70% and 60% for the six-fraction and five-fraction groups, respectively (p=0·0005).

Six compared with five fractions per week improved preservation of the voice among patients with laryngeal cancer (80 *vs*68%, p=0·007).

Disease-specific survival improved (73 *vs* 66% for six and five fractions, p=0·01) but not overall survival.

Acute morbidity was significantly more frequent with six than with five fractions, but was transient.

J Overgaard **The Lancet 362;**933–940, 20, 2003

HYPERFRACTIONATION TRIALS IN CNS

RTOG 8302

Phase I/II dose escalation altered fractionation trial in GBM:

- HF 1.2 Gy BID to 64.8, 72, 76, 81.6 Gy
- AH 1.6 Gy BID to 54.4 Gy

No differences in Median Overall Survival between arms

Late CNS toxicities were increased in the 72 Gy

Werner-Wasik et al, Cancer 1996;77,1535-1543.

RTOG 9006

- SF 60 Gy in 30 fractions
- HF 72 Gy in 1.2 Gy/fraction BID
- No difference in overall survival

- Scott C et al, Proc Am Soc Clin Oncol, 1998;16:384

ACCELERATED FRACTIONATION TYPES

Pure acceleration

Hybrid acceleration (split course)

Accelerated concomitant boost

ACCELERATED FRACTIONATION CLINICAL TRIALS
HEAD AND NECK CANCER

EORTC Cooperative Group of Radiotherapy (EORTC 22851) compared the experimental regimen (72 Gy in 45 fractions/5 weeks) to standard fractionation and overall treatment time (70 Gy/ 35 fractions/7 weeks) in T2, T3 and T4 head and neck cancers

Five hundred twelve patients were accrued.

Patients in the AF (accelerated fractionation) arm did significantly better with regard to loco-regional control ($P = 0.02$) resulting at 5 years in a 13% gain (95% CI 3–23% gain) in loco-regional control over the CF (conventiona fractionation) arm.

Specific survival shows a trend ($P = 0.06$) in favour of the AF arm.

Acute and late toxicity were increased in the AF arm. Late severe functional irradiation damage occurred in 14% of patients of the AF arm versus 4% in the CF arm.

ACCELERATED VS. HYPERFRACTIONATED RADIOTHERAPY

RTOG 9003

atients with stage III or IV (or stage II base of tongue) SCC (n=1076) were randomized to 4 treatment arms:

(*1*) SFX, 70 Gy/35 daily fractions/7 weeks

(*2*) HFX, 81.6 Gy/68 twice-daily fractions/7 weeks

(*3*) AFX-S, 67.2 Gy/42 fractions/6 weeks with a 2-week rest after 38.4 Gy

(*4*) AFX-C, 72 Gy/42 fractions/6 weeks. The 3 experimental arms were to be compared with SFX

HFX with SFX was significantly different: HFX, hazard ratio (HR) 0.79 (95% confidence interval 0.62-1.00), *P*=.05

AFX-C, 0.82 (95% confidence interval 0.65-1.05)

HFX improved overall survival (HR 0.81, *P*=.05)

Prevalence of any grade 3, 4, or 5 toxicity at 5 years; any feeding tube use after 180 days; or feeding tube use at 1 year did not differ significantly when the experimental arms were compared with SFX.

When 7-week treatments were compared with 6-week treatments, accelerated fractionation appeared to increas grade 3, 4 or 5 toxicity at 5 years (*P*=.06)

ACCELERATED vs. CONVENTIONAL + CHEMOTHERAPY
RTOG 0129

AFX-C + CDDP x2 VS. SFX + CDDP x3 (100 mg/m^2, q3W).

There was no difference in the primary endpoint (5-Y survival: 59% vs. 56%; HR: 0.90, 0.72-1.13; p=0.18).

Each day of RT delay compromised OS, PFS, and LRP by 5%, 4%, and 4% (p=0.001, 0.006, and 0.02), respectively.

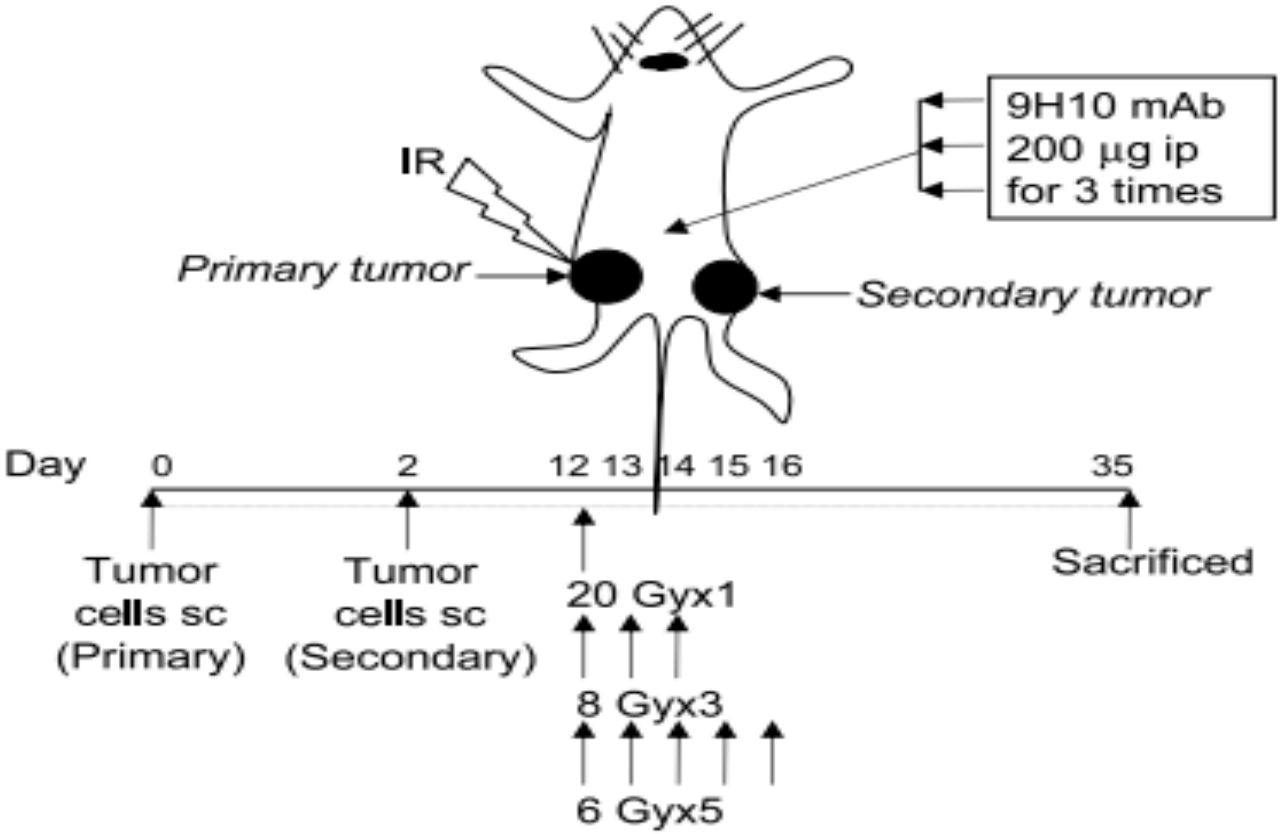
RT duration and CDDP dose affected survival significantly.

CDDP improved OS but it also increased toxicity.

The effect of AFX-C approximated the third CDDP dose, suggesting that CDDP acted, in part, by inhibiting accelerated tumor repopulation.

FRACTIONATION AND THE ABSCOPAL EFFECT

Clin Cancer Res 2009;15(17):5379–88



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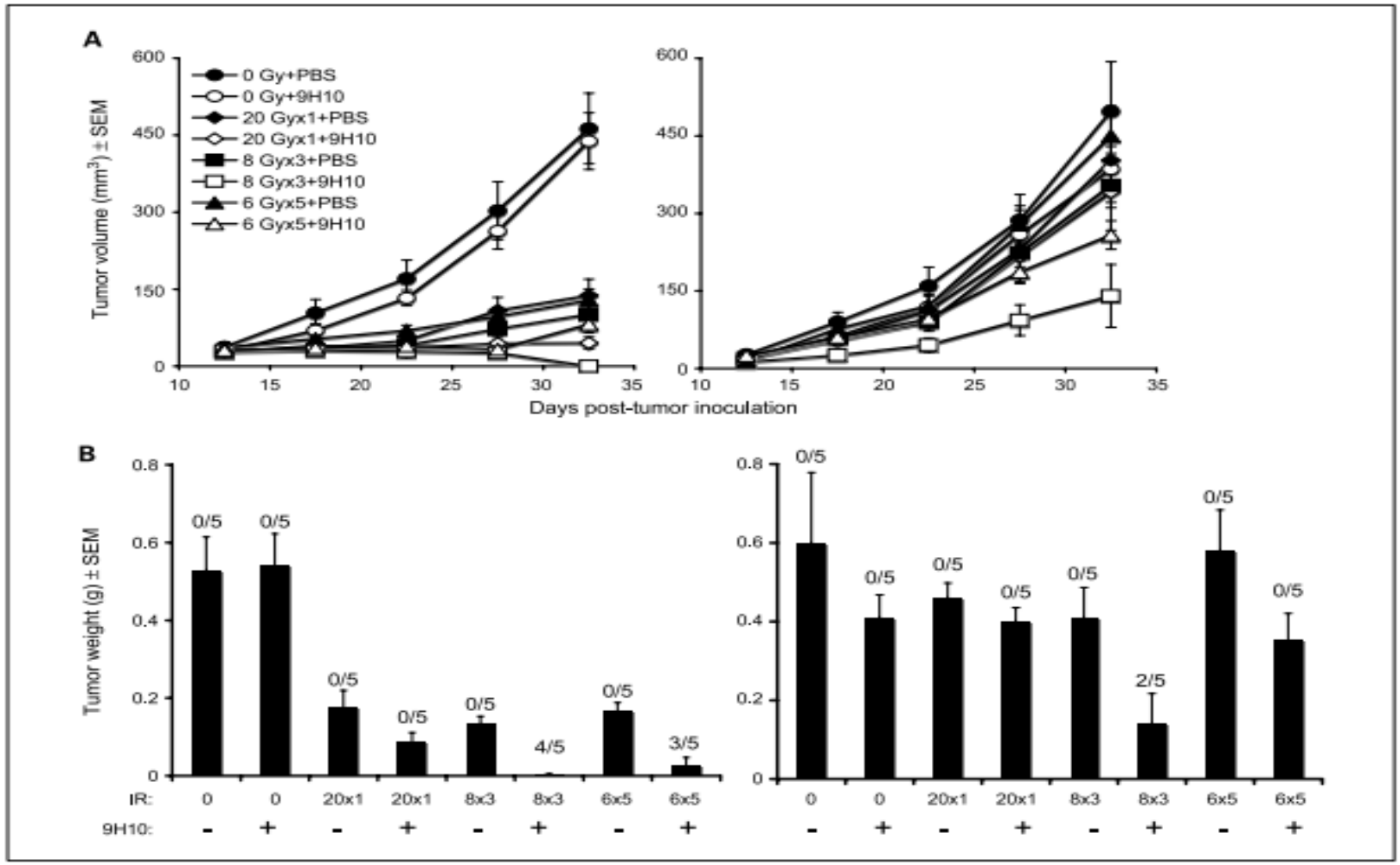
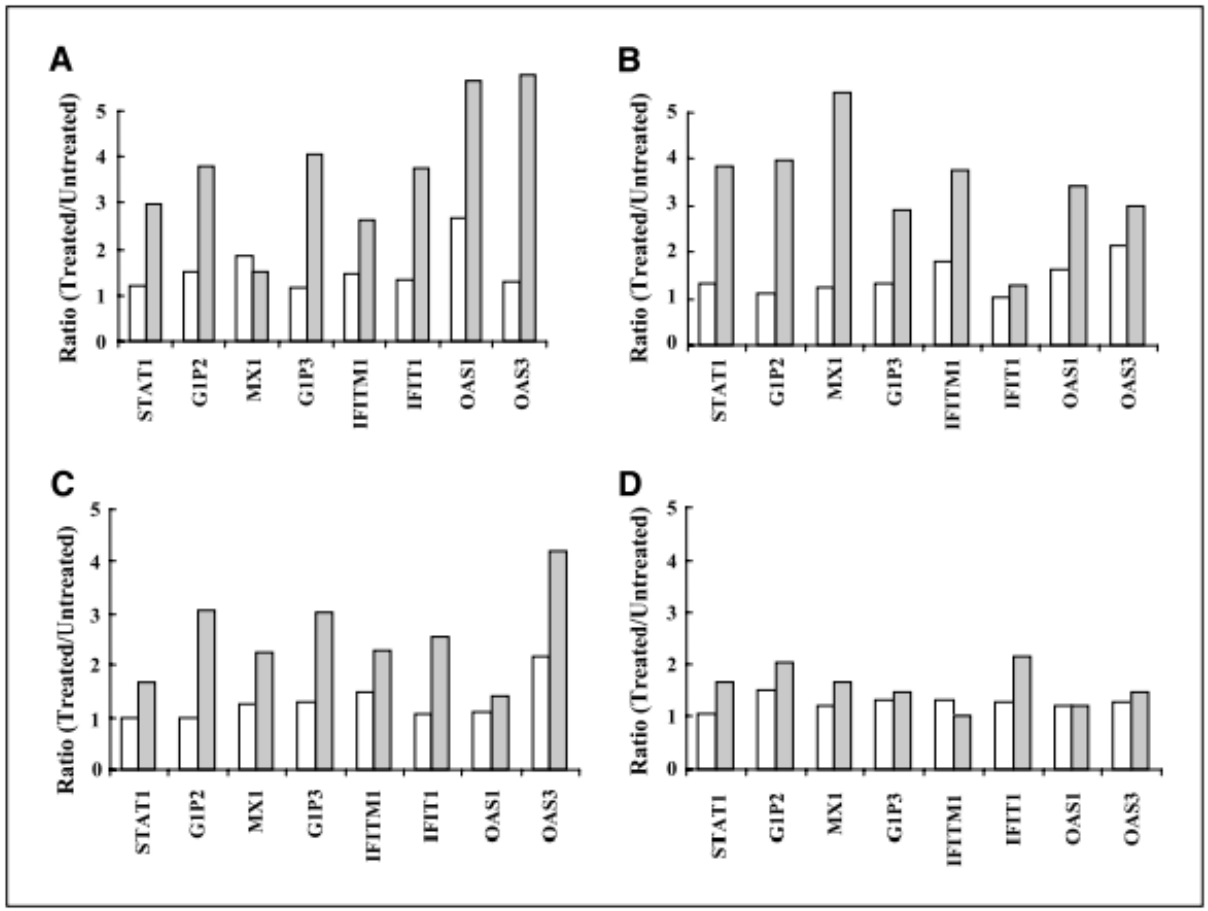


Gene Expression Profiling of Breast, Prostate, and Glioma Cells following Single versus Fractionated Doses of Radiation

Mong-Hsun Tsai, Cancer Res 2007;67(8):3845–52



CONCLUSIONS

Fractionation has a major impact on outcomes of radiotherapy

Careful attention has to be paid when conventional fractionation is altered in clinical trials

Practice must be guided by robust clinical level I evidence

Different fractionation schedules, specially single doses of ablative radiotherapy doses should carefully studied

The systemic effects of radiotherapy are being studied in the context of immuno-modulator molecules.