Sixth NCS Lustrum, 5 October 2012

Radiation dosimetry: balance between safety and cure

Cell survival following high dose rate flattening filter free (FFF) and conventional dose rate irradiation

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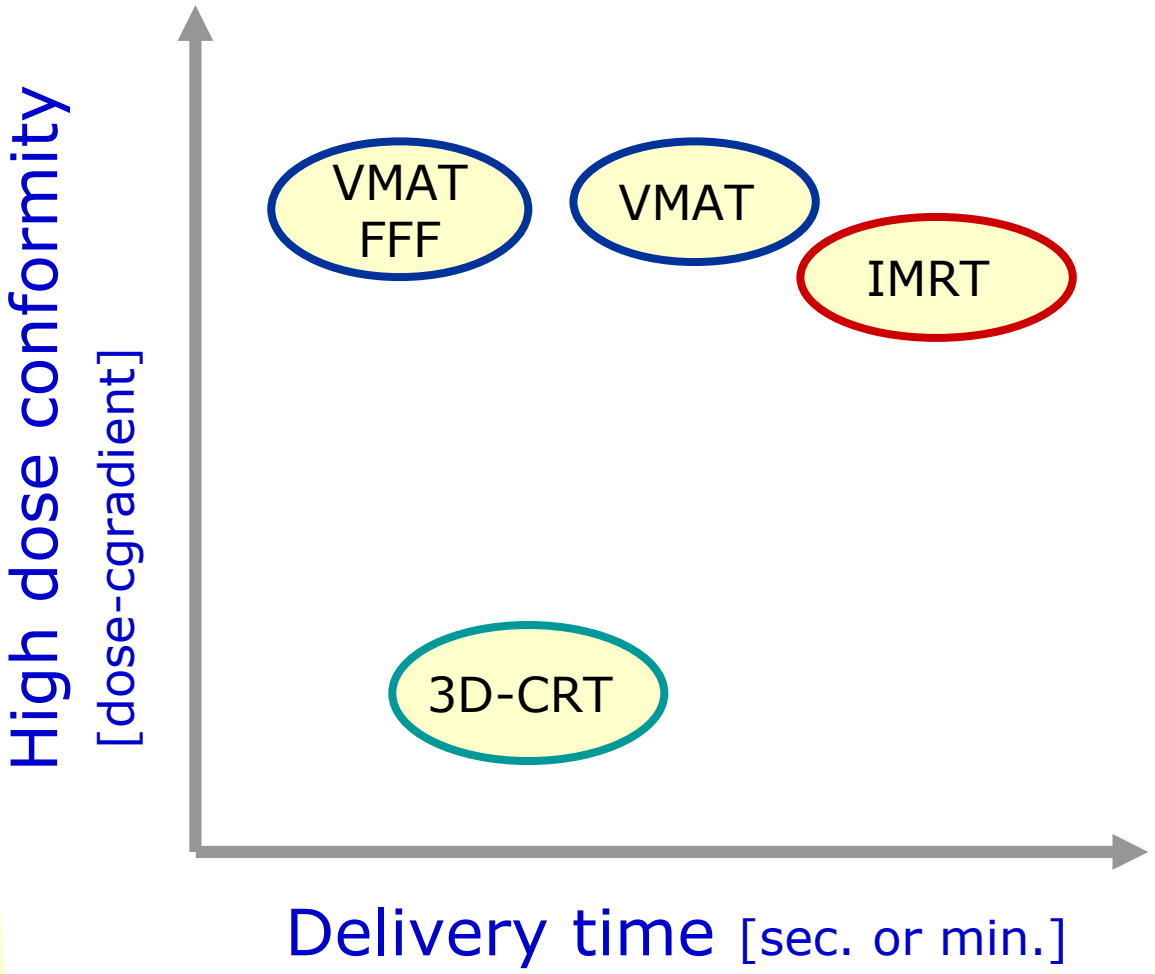
Progress in Radiotherapy: better conformity and shorter treatment time



VMAT

Volumetric Modulated Arc Therapy (VMAT) employs a linear accelerator to conduct dynamic modulation rotation radiotherapy.

VMAT allows high conformal three dimensional dose distributions to be delivered – in short time - to the target volume in one or two gantry arc rotations, with minimal exposure of surrounding normal tissues.

VMAT vs. IMRT: shorter delivery time and less Monitor Units (MU)

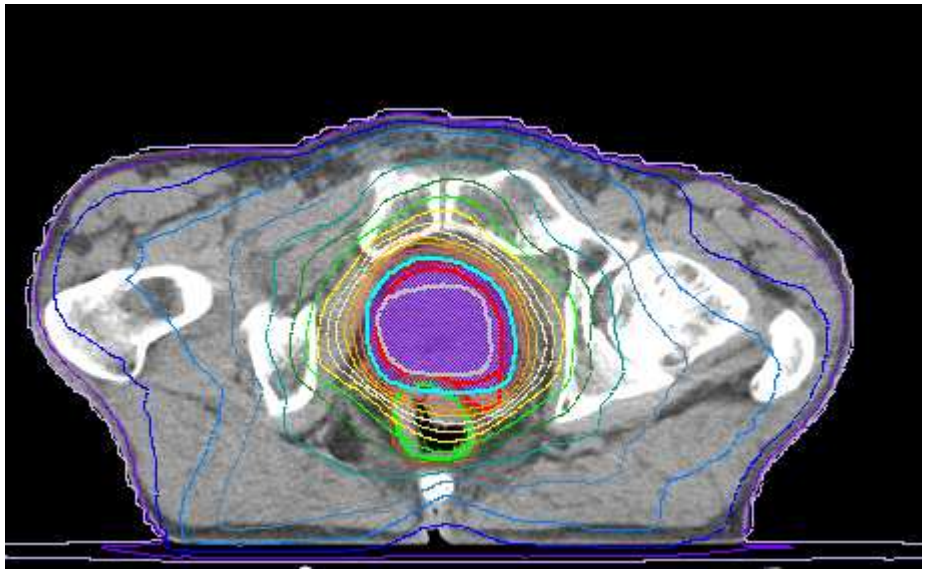
	IMRT			VMAT		
Treatment scheme	# beams	MU	time	# arcs	MU	time
Prostate (39 x 2Gy)	5	350	5 min	1	300	2 min
Rectum (25 x 2 Gy)	7	400	7 min	2	350	4 min
H&N (23 x 2 Gy)	6	550	9 min	2	450	6 min
Brain SRS (1 x 18Gy)	12	2600	15 min	2	2400	7 min
Lung SBRT (3 x 18 Gy)	14	3100	25 min	2	2900	8 min

(Beam-on time. Rough estimates based on Elekta/Pinnacle @ NKI)

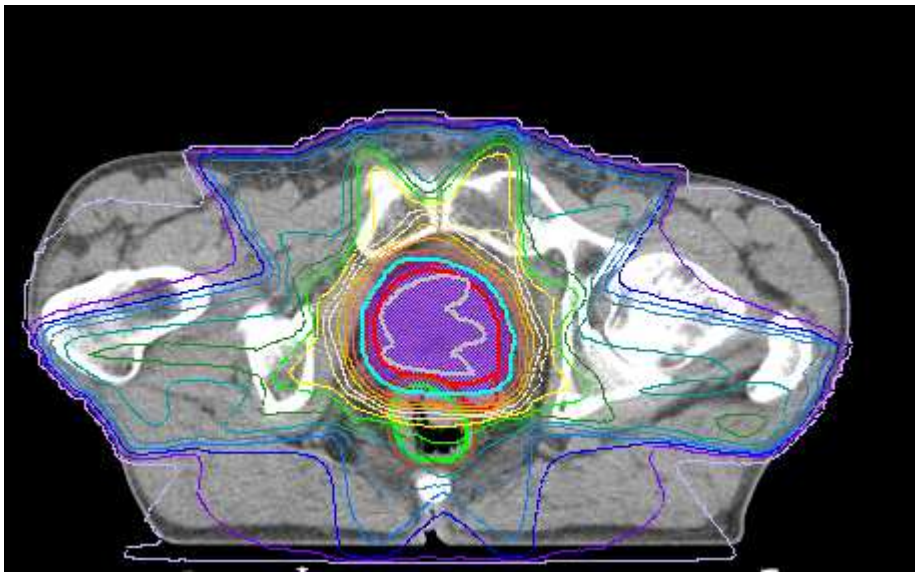
VMAT vs. IMRT: better conformity but larger normal tissue volume exposed to a low dose. Example prostate

8500.0 cGy
8346.0 cGy
8034.0 cGy
8000.0 cGy
7800.0 cGy
7500.0 cGy
7410.0 cGy
7000.0 cGy
6500.0 cGy
6000.0 cGy
5500.0 cGy
5000.0 cGy
4500.0 cGy
4000.0 cGy
3500.0 cGy
3000.0 cGy
2500.0 cGy
2000.0 cGy
1500.0 cGy
1000.0 cGy
500.0 cGy

VMAT→



IMRT→



VMAT FFF

- Because the beam is dynamic modulated, the original beam profile does not need a flattening filter anymore.
- However, removal of the flattening filter leads to a further increase in dose rate.
- Higher dose rate, shorter delivery time, *beneficial for the patient*, in particular in case of long, high single dose irradiation treatments like in SBRT and SRS.

Technical progress, clinical advantage,
but how about radiobiology?

VMAT FFF & Clinical / Radiobiological concerns

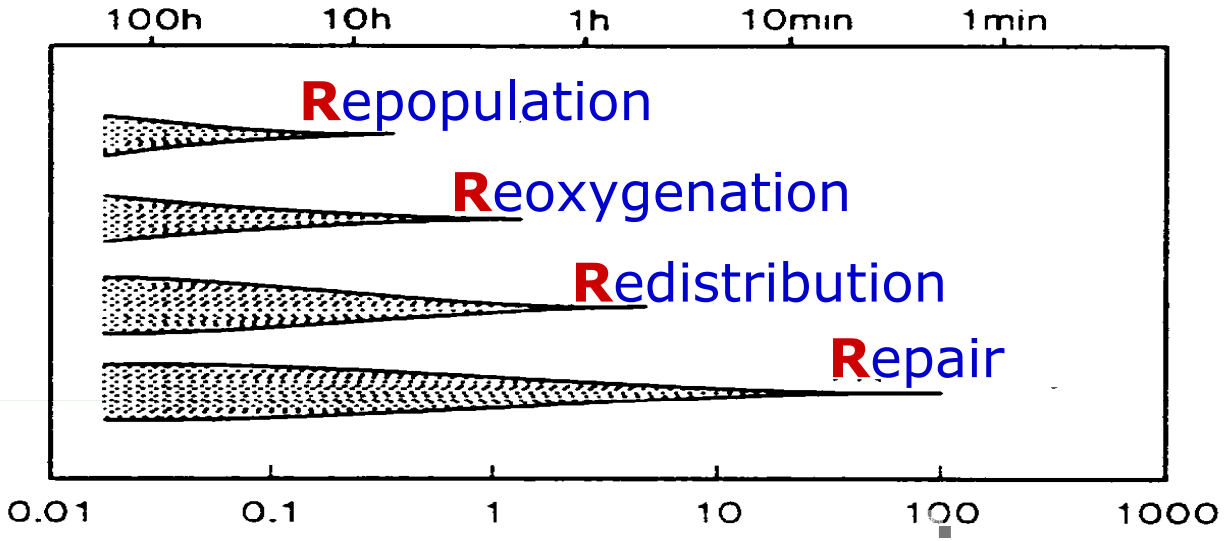
- Highly increased dose rate (MU/delivery time).
  - Dose rate FFF method ~ 3-4 times dose rate of FF
  - More detrimental for tumour and / or normal tissue cells?
- Larger normal tissue volume exposed to low radiation
  - Consequences regarding:
    - Late toxicity
    - Induction of secundary tumours

?

- Radiation protection aspects

Dose rate and timescale of radiobiological processes

Delivery time for 2 Gy



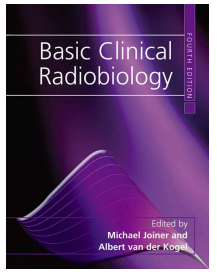


Figure 12.1

?

Radiation less effective

Radiation even more effective

Beyond ~ 1 Gy/min: no role for the 4 **R**'s during irradiation?

Dose rate effect on cell survival

Human melanoma cells

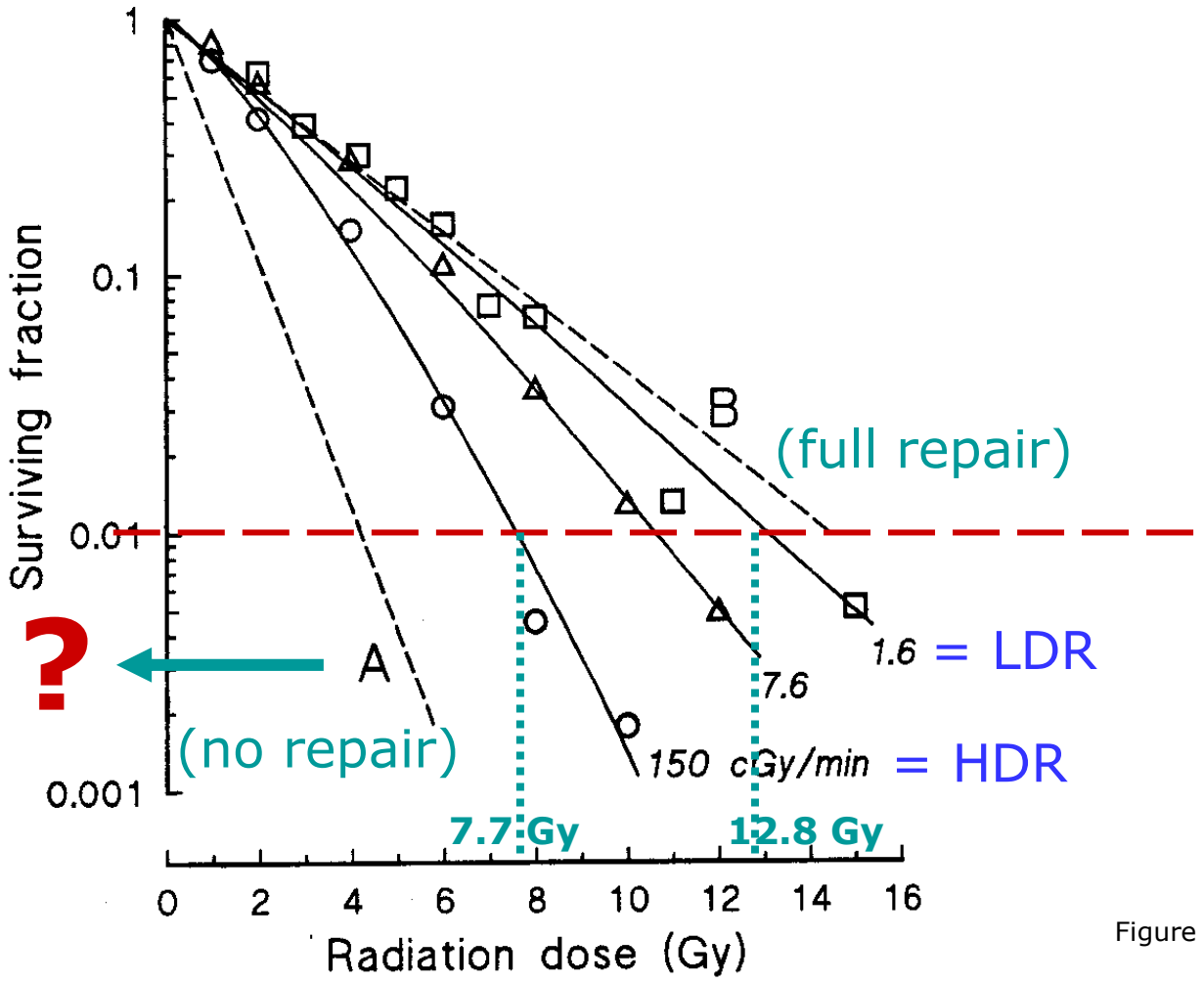


Figure 12.2

Dose rate sparing mainly because of DNA repair during exposure.

Dose rate effect on various normal tissues

Increase in dose-rate: decrease in total dose for isoeffect.

(dose decrease is inversely proportional to the α/β ratio)

LDR-MDR area (~< 20 cGy/min): large increase in tissue radiation tolerance.

Ultra high dose rate area?

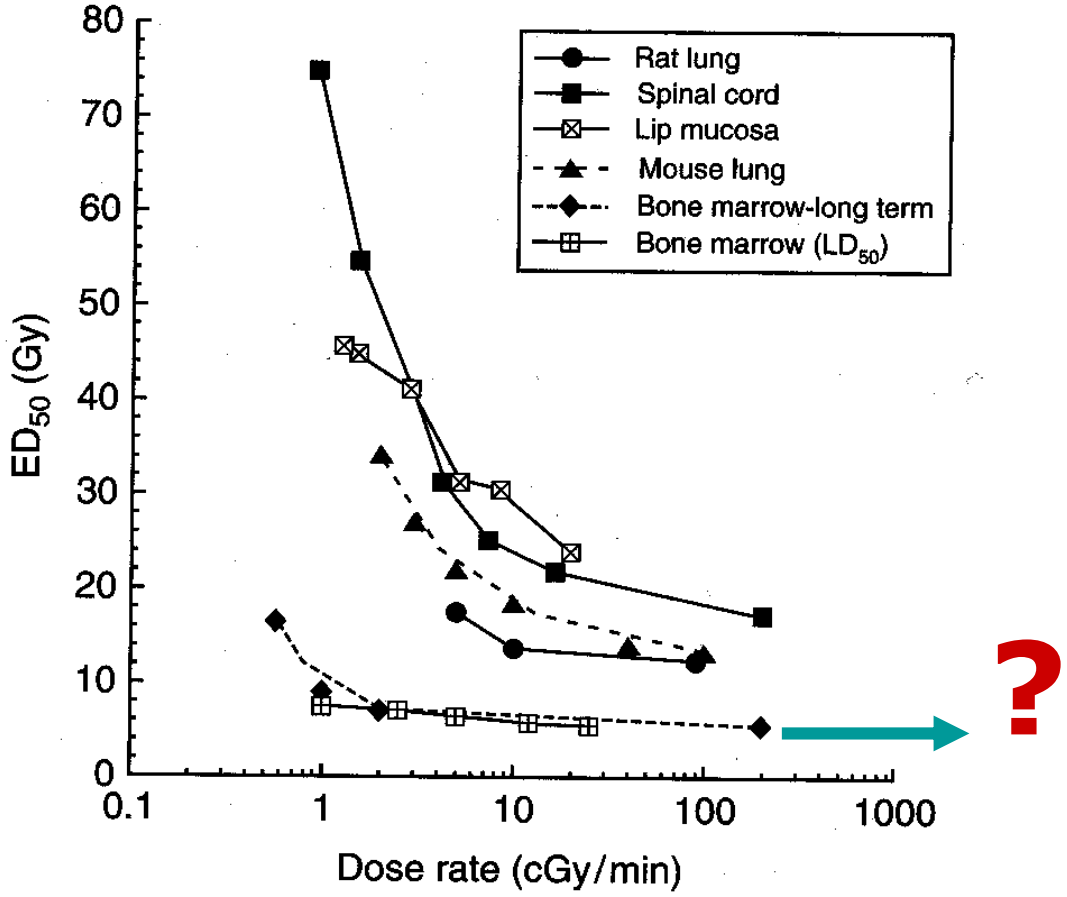


Figure 12.6 The dose-rate effect in various rodent normal tissues: lung, spinal cord, lip mucosa and bone marrow.

What happens at the ultra high dose rate site of the 'dose rate spectrum'. Difference between FFF and FF irradiation?

Recent in vitro studies – effects on cell survival:

Dose rate

Effect of high dose per pulse flattening filter-free beams on cancer cell survival

Ines Lohse [a], Stephanie Lang [a], Jan Hrbacek [a], Stephan Scheidegger [c], Stephan Bodis [b], Nadia S. Macedo [a], Jianhua Feng [a], Urs M. Lütolf [a], Kathrin Zaugg [a,*]

[a] *Department of Radiation Oncology, University Hospital Zürich, Switzerland;* [b] *Institute of Radiation Oncology, Kantonsspital Aarau, Switzerland;* [c] *Centre of Applied Mathematics and Physics, Zurich University of Applied Science, Switzerland*

Radiotherapy and Oncology 101 (2011) 226–232

Dose rate

Dependence of cell survival on instantaneous dose rate of a linear accelerator

Brita Singers Sørensen [a,*], Anne Vestergaard [b], Jens Overgaard [a], Lars Hjorth Præstegaard [b]

[a] *Department of Experimental Clinical Oncology; and* [b] *Department of Medical Physics, Aarhus University Hospital, Denmark*

Radiotherapy and Oncology 101 (2011) 223–225

Comparable cell survival between high dose rate flattening filter free and conventional dose rate irradiation

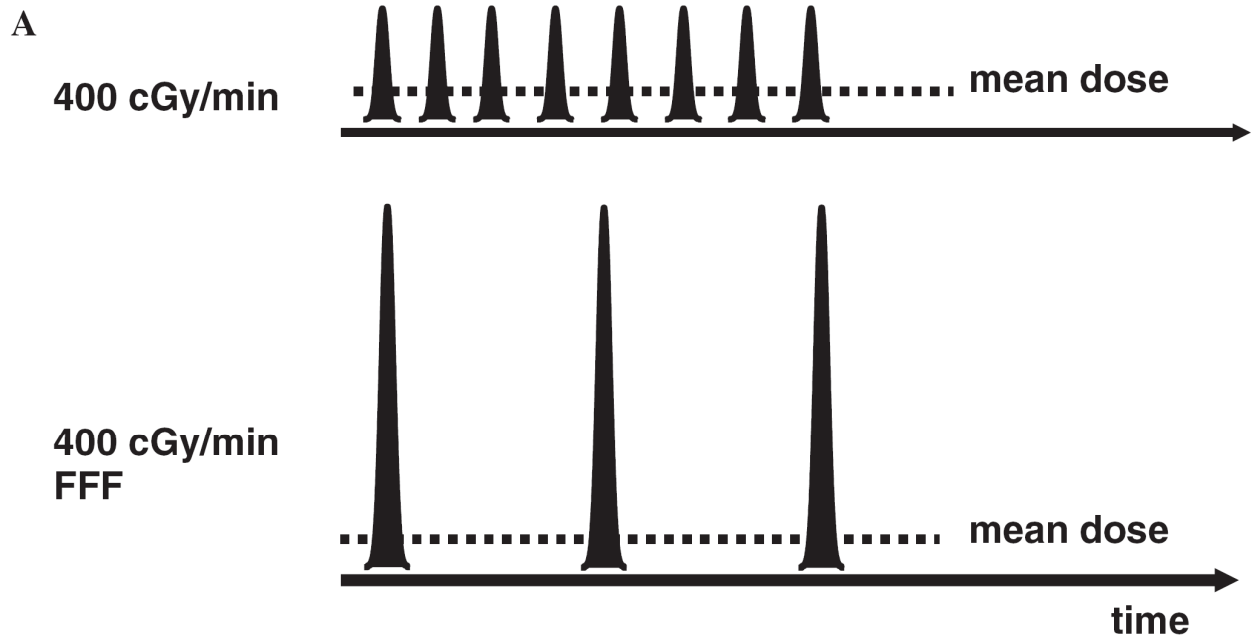
Wilko FAR Verbakel, Jaap van den Berg, Ben J. Slotman, Peter Sminia.

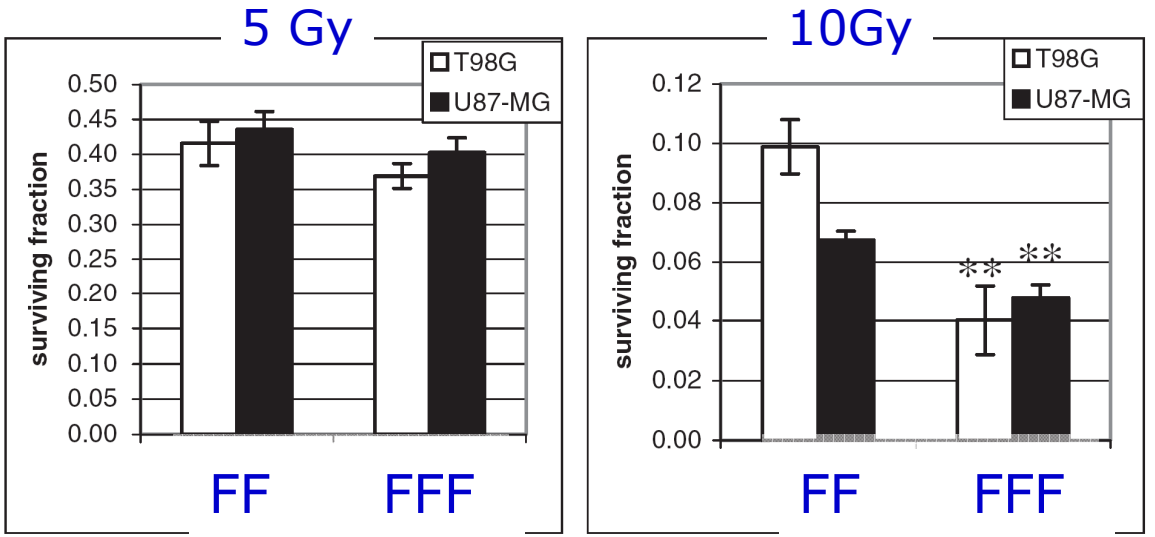
Acta Oncologica, in press

I. Lohse et al. / Radiotherapy and Oncology 101 (2011) 226–232

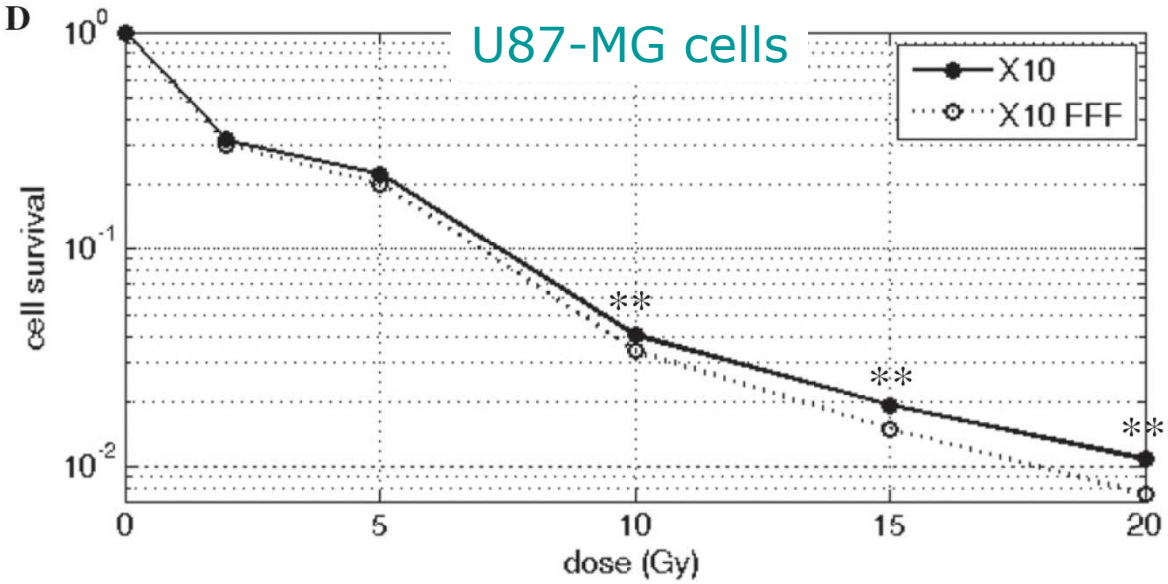
(A) Equal average dose, and lower pulse frequency with higher dose per pulse in FFF irradiation

(B) Clonogenic cell survival on two glioma cell lines





I. Lohse et al./Radiotherapy and Oncology 101 (2011) 226–232

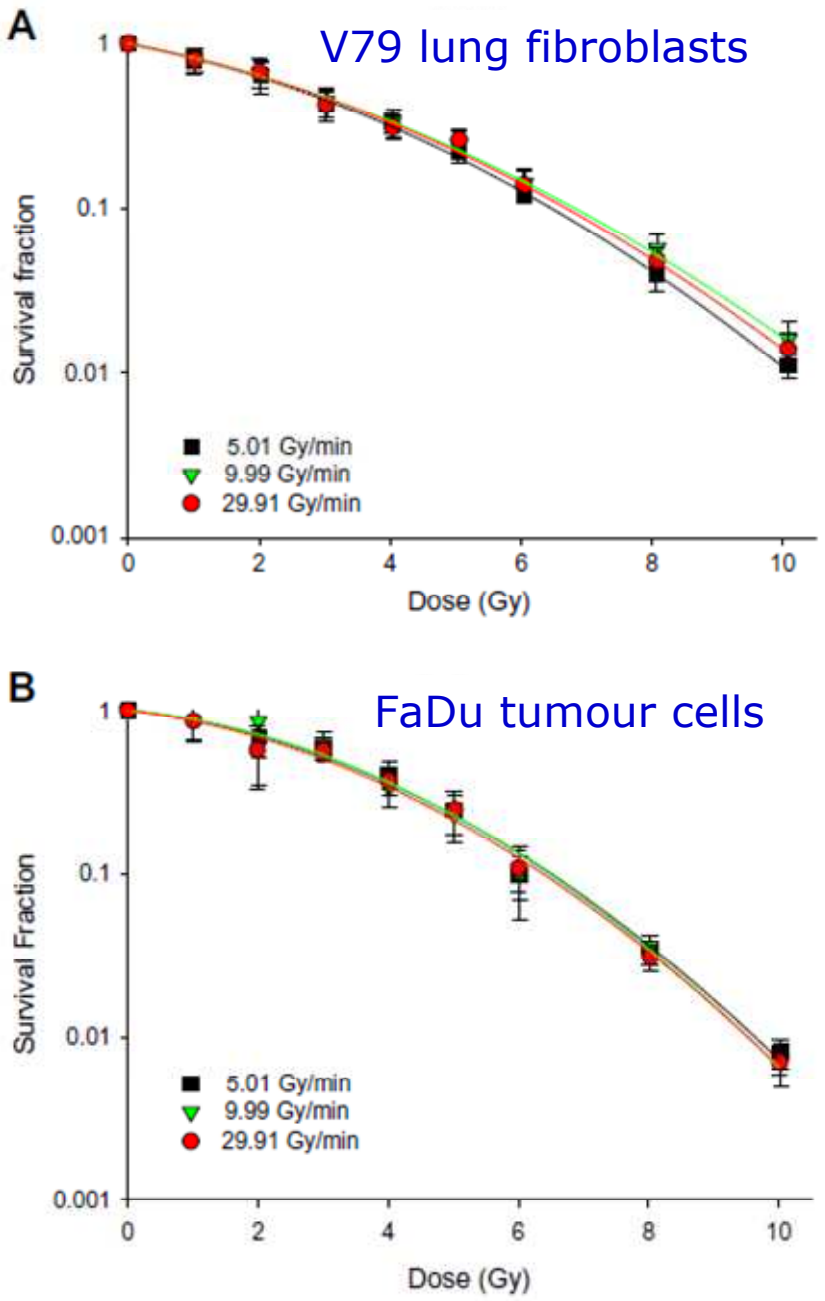


Cell survival curve U87-MG cells. FFF vs. FF irradiation

Significantly more cell kill after FFF irradiation $\geq$ 10 Gy vs. FF, which was attributed to the higher dose per pulse.

The cause?

'increase in DNA double strand breaks'
'so far unknown molecular mechanisms triggered by high radiation doses'

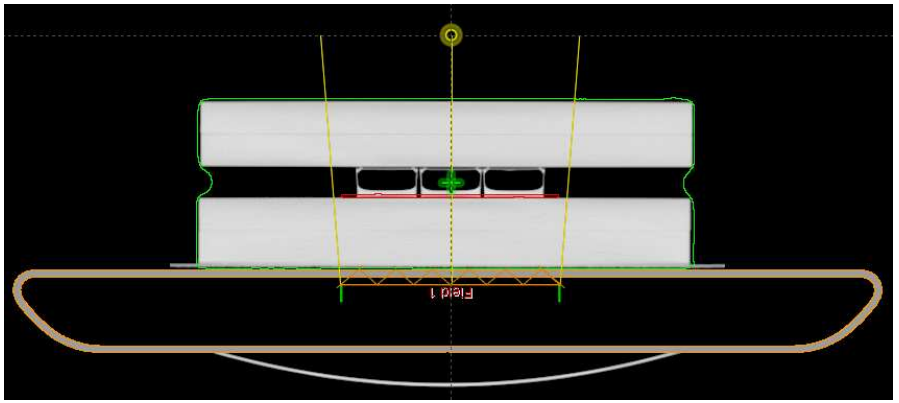


Average dose rate (Gy/min)	Instantaneous dose rate in pulse (Gy/s)
29.91	338
9.99	112.8
5.01	56.5

No effect of increase in average dose rate or instantaneous dose rate in the pulse on the survival of normal and tumour cells.

Cell survival studies VUmc: FFF vs. FF

- Human cancer cell lines: T98 glioma, D384 astrocytoma and SW1573 lung carcinoma.
- Single dose irradiation (0-12 Gy) and fractionated irradiation (5 daily fractions of 2 or 3 Gy) using FF and FFF
- Endpoints: ‘clonogenic cell survival’ and ‘number of clonogenic cells’

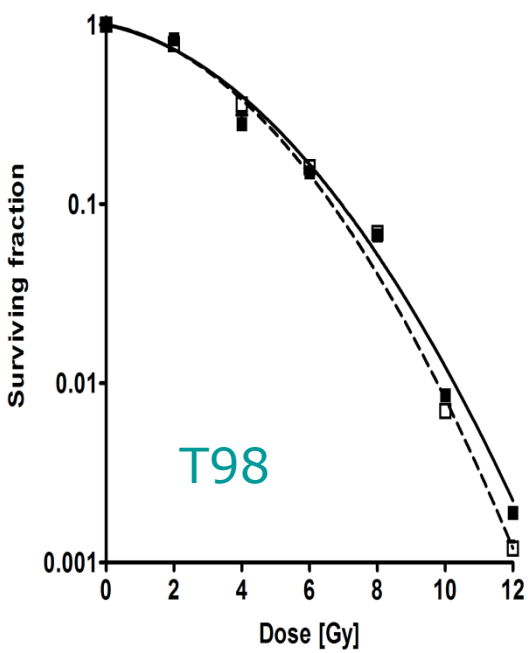


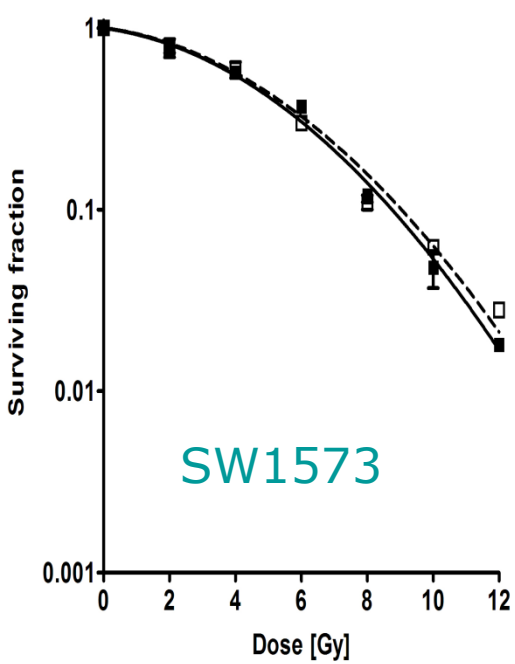
CT-scan of the phantom with flasks and a surrogate target volume

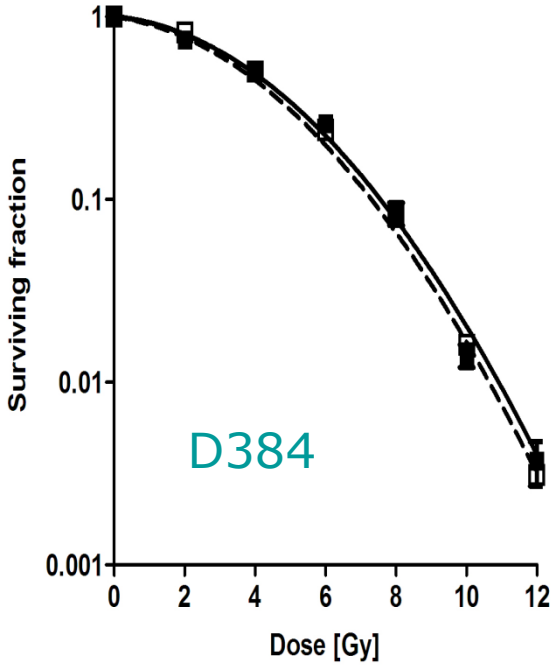
FFF vs. FF 'Truebeam' irradiation of cells

Irradiation details		FF	FFF
Monitor Units	[min^{-1}]	600	2400
Surface source distance	[cm]	95	86
Average dose rate	[Gy/min]	5.9	24
Instantaneous dose rate in the pulse	[Gy/min]	3.6×10^3	1.5×10^4
Pulse frequency	[s^{-1}]	360	360
Pulse width	[μs]	4.5	4.5

Single dose irradiation: FFF vs. FF



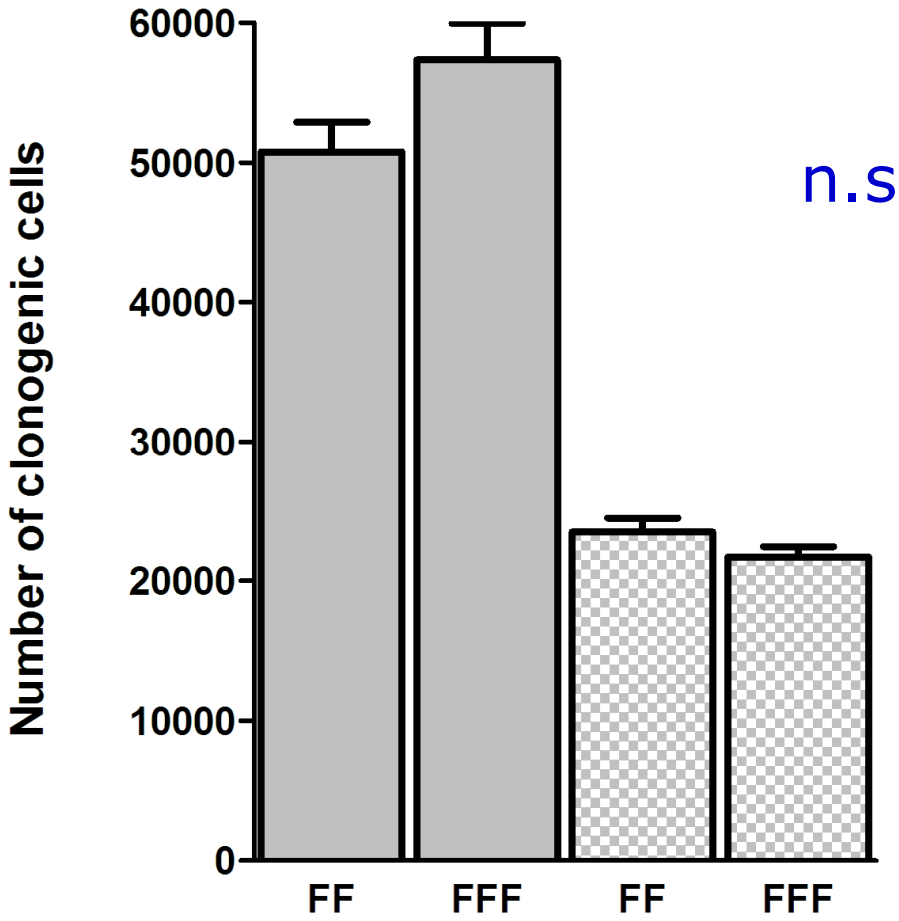




□ = FF ■ = FFF

Conclusion: equal cell survival

Fractionated irradiation: FFF vs. FF



n.s.

The number of clonogenic cells following flattening-filter (FF) and flattening-filter-free (FFF) fractionated irradiation of D384 (5x2Gy, p=0.08) and SW1573 (5x3Gy, p=0.20, dotted bars) cells. Error bars represent the standard error of the mean (n= 6).

Conclusion: equal effect following 5 daily fractions of irradiation

Ultra high dose rate and cell survival

MICHAELS, H. B., EPP, E. R., LING, C. C., AND PETERSON, E. C. Oxygen Sensitization of CHO Cells at Ultrahigh Dose Rates: Prelude to Oxygen Diffusion Studies. *Radiat. Res.* **76**, 510–521 (1978).

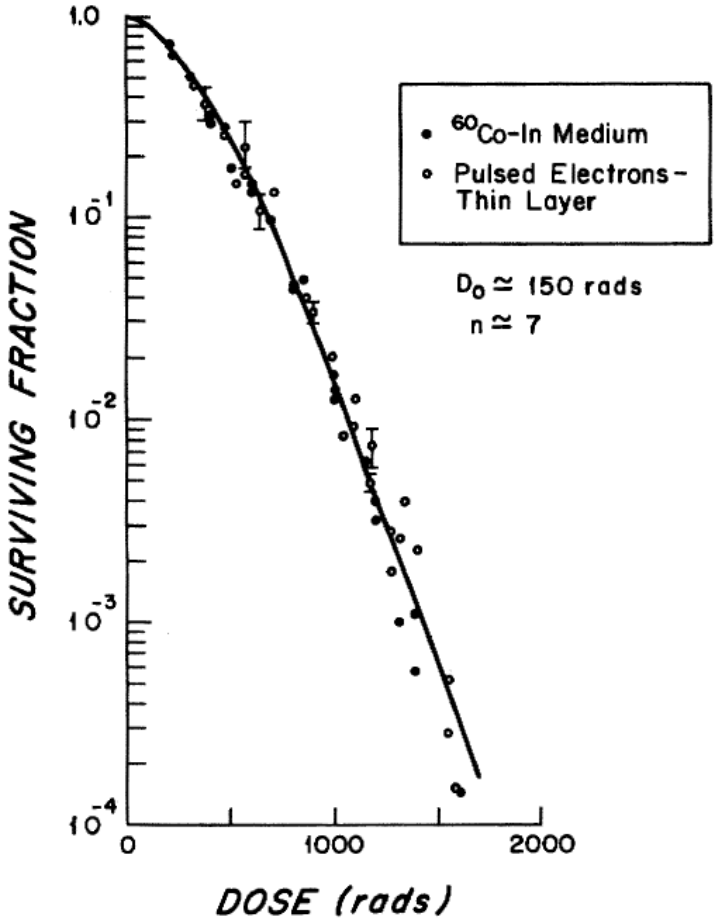


FIG. 3. Survival of CHO cells irradiated in air, as a thin layer with single pulses of electrons at ultrahigh dose rate (~10^{11} rad/sec), and in medium with ^{60}Co-γ rays at a conventional dose rate (~1 rad/sec).

Ultra high dose rate and cell death

Review

Dose-rate effects in external beam radiotherapy redux

C. Clifton Ling [a,b,*,1], Leo E. Gerweck [c,**], Marco Zaider [b], Ellen Yorke [b]

[a] *Varian Medical Systems, Palo Alto, CA, USA;* [b] *Department of Medical Physics, Memorial Hospital, New York, NY, USA;* [c] *Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA*

Radiotherapy and Oncology 95 (2010) 261–268
+ personal communication, August 2012

'The dose rate effect in external beam radiotherapy is governed by the overall beam-on-time, not by the average linac dose-rate, nor by the instantaneous dose-rate within individual linac pulses'

Radiobiological explanation

- Cell death following radiation is the result of lethal, non-repaired, DNA double strand breaks.

- DNAdsbs are ~ 70% caused by products of water radiolysis, mainly OH radicals. The production of radicals is *the same for the same unit dose*.

- Recombination of radicals, which might decrease the efficacy of cell killing per unit dose, is negligible within the range of dose rates used clinically.

Dose rate effect VMAT FFF vs. FF
Conclusion – Discussion

Dose–rate effect: in vitro data indicate equal cell survival following single dose and fractionated irradiation with the flattening filter and flattening filter free method.

[no differences to be expected for the reason of radio-physical and chemical processes leading to DNA damage and therewith cell death]

Final evidence:

- in vivo studies on normal tissues and tumours
- clinical data

[so far, no increase in toxicity has been observed when using VMAT FFF. Patients' follow-up time is however relatively short].

VUmc Cancer Center Amsterdam

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