Assenza di conflitto di interessi

UNIVERSITÀ DEGLI STUDI FIRENZE

HIGHLIGHTS IN RADIOTERAPIA

Gli studi del 2019 che modificano la pratica clinica in radioterapia esclusiva ed associazione farmacologica

Radiobiologia e frazionamenti alterati

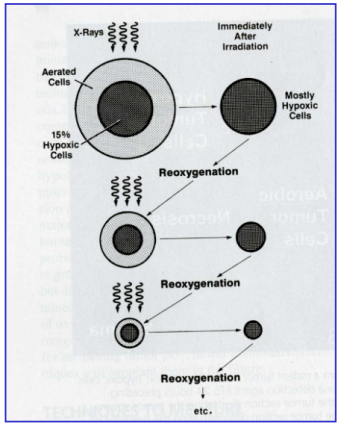
Monica Mangoni

Roma, 23 gennaio 2020

The introduction of Fractionation

FIGURE 23.1 Conventional multifraction radiotherapy was based on experiments performed in Paris in the 1920s and in the 1930s. Rams could not be sterilized with a single dose of x-rays without extensive skin damage, whereas if the radiation were delivered in daily fractions over a period of time, sterilization was possible without skin damage. The testes were regarded as a model of a growing tumor and skin as dose-limiting normal tissue.

Rational for fractionated radiotherapy



Reoxygenation

Redistribution

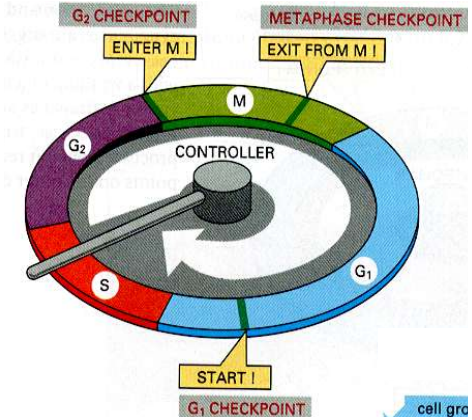
Repair

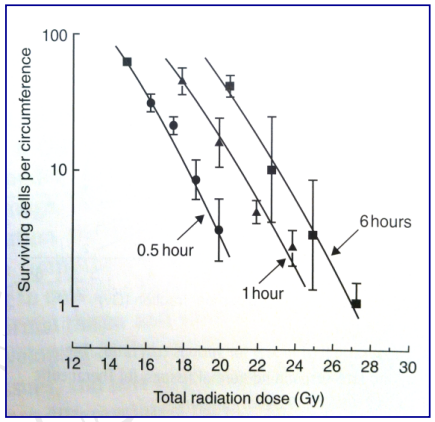
Repopulation

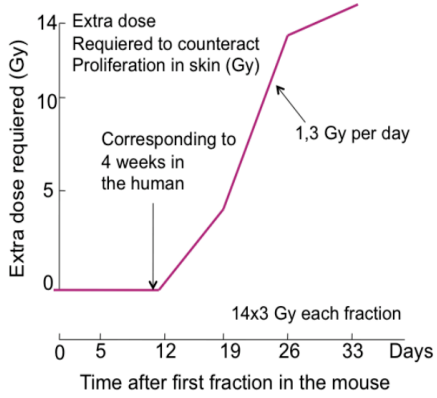
5R's

Radiosensitivity

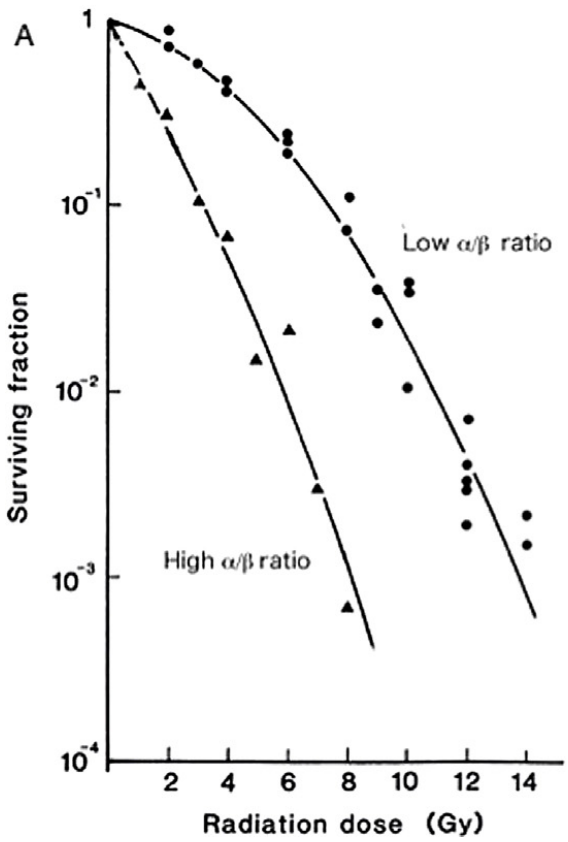
α/β







Linear-Quadratic model of dose response

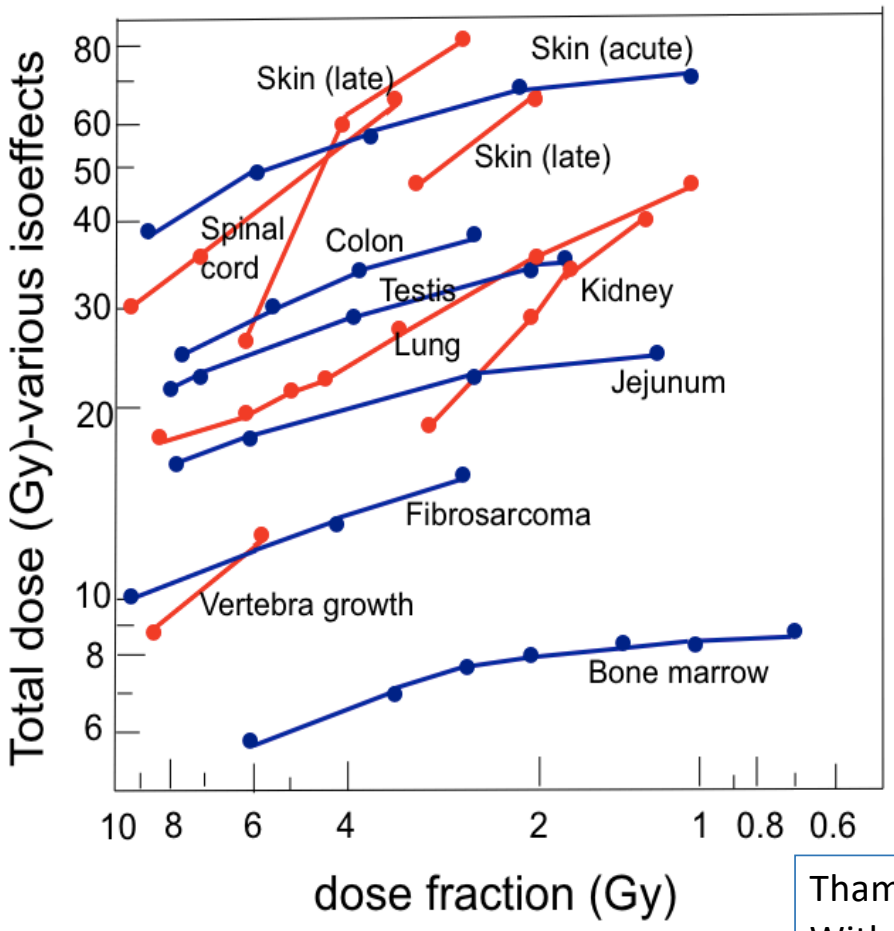


$$SF(d) = e^{-nd(\alpha+\beta d)}$$

BED Biologically effective dose

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right)$$

Relationship between total dose and dose per fraction



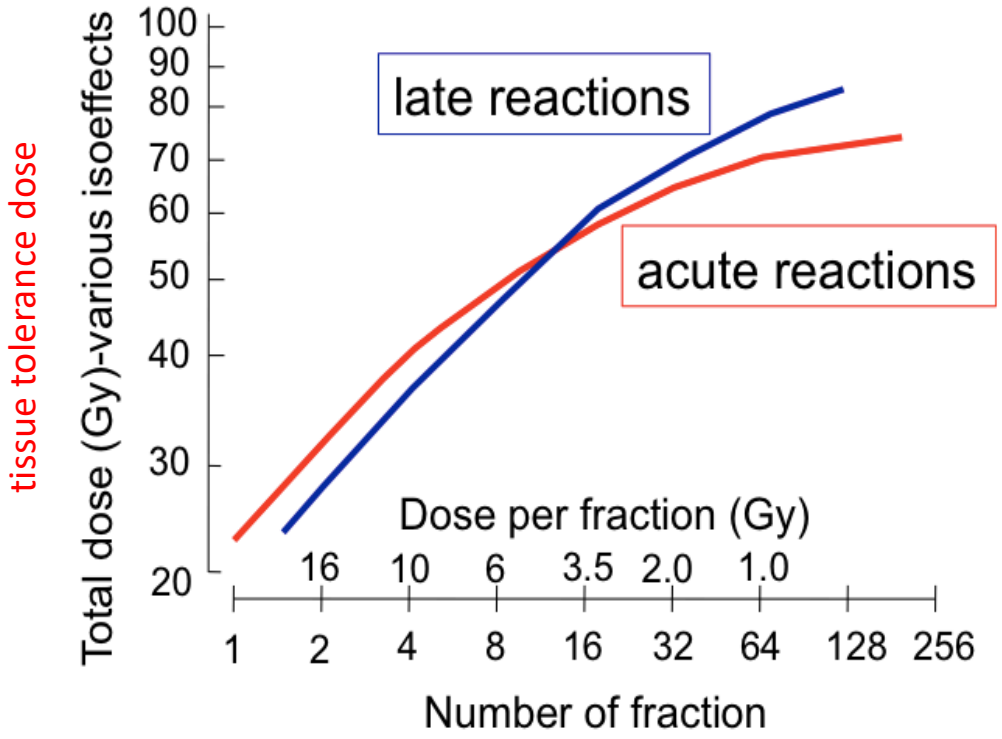
● = late responding issues
low α/β ratio

● =acutely responding issues
high α/β ratio

Thames HD, IJROBP 8:219-26, 1982
Withers HR, Cancer 55:2086-95, 1985

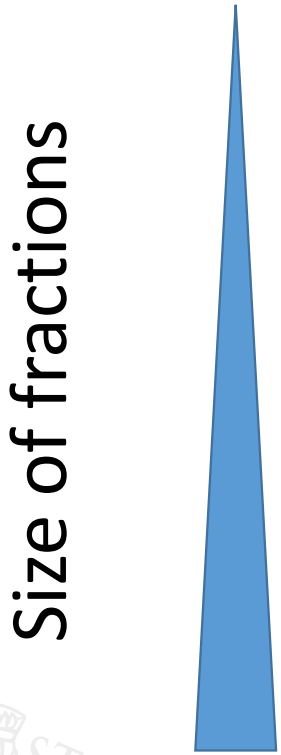
greater sensitivity of late responses to changes in dose per fraction

Fractionation spares slowly responding tissues more than tissues and tumors that show an early response



$$\text{Effect}=\alpha d+\beta d^2$$

Altered fractionation



- Hyperfractionation (HF)
- Accelerated Fractionation (AF)
- Normofractionated RT
- Hypofractionation
- Ultra hypofractionation

Hyperfractionation

- Small fractions and increased total doses
- **Multiple fractions** are delivered on each treatment day, the **overall treatment time** is therefore **unchanged**

- Rationale: to **increase the total dose** translating into a higher probability of cure without an increase in late toxicity

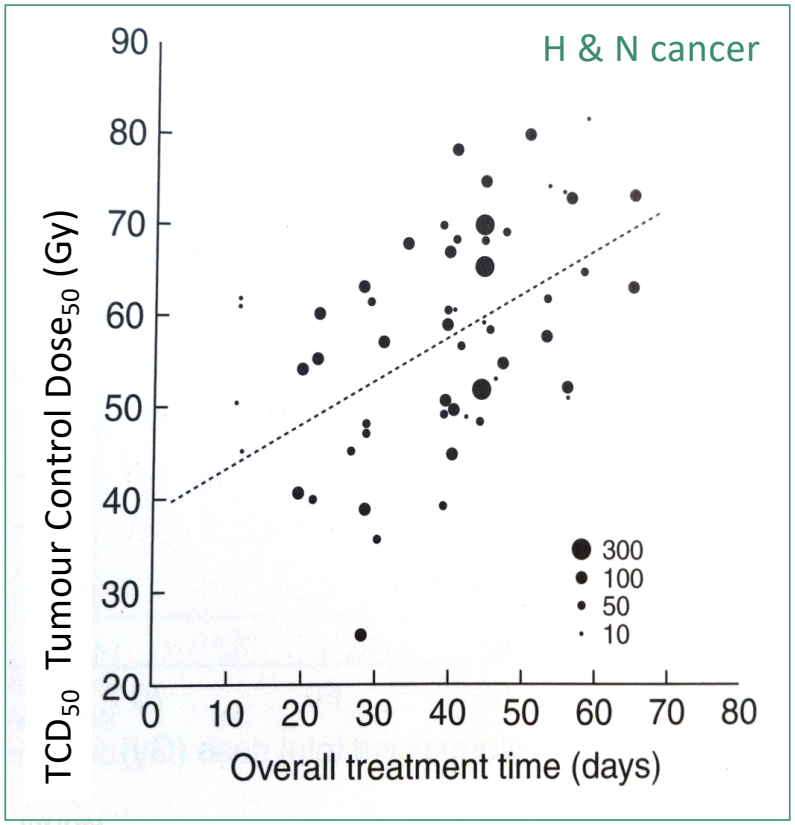
- Reduction of dose per fraction has **more effect on late-responding tissues**
- +++ Tumors with a rapidly proliferating clonogenic population, they mimic the acute-responding tissues and are not affected by the decrease in dose per fraction. No suitable for low α/β tumors

Accelerated fractionation

- Both the dose per fraction and the total dose are either the same or slightly lower than the doses used in standard fractionation. The key element is the **reduction in the overall time**.

- Rationale: shortening the overall treatment time helps overcome **accelerated tumor repopulation**

As overall time increases, a greater total radiation dose is requiered to control tumour



Bentzen SM, Radiother Oncol 1991; 22: 161-6
Withers HR, Acta Oncol 1988; 27: 131-46

For treatments longer than 4 weeks,
the effect of proliferation is equivalent to
a **loss of radiation dose of about 0,5-0,6 Gy/day**

View full text

Acta Oncol. 1988;27(2):131-46.

The hazard of accelerated tumor clonogen repopulation during radiotherapy.

Withers HR[1], Taylor JM, Maciejewski B.

Such a dose increment is consistent with a 4-day clonogen doubling rate, compared with a median of about 60 days in published reports of unperturbed tumor growth rates.

Accelerated repopulation

Int J Radiat Oncol Biol Phys. 2002 Sep 1;54(1):229-36.

How fast is repopulation of tumor cells during the treatment gap?

Tarnawski R[1], Fowler J, Skladowski K, Swierniak A, Suwiński R, Maciejewski B, Wygoda A.

1502 patients squamous cell carcinoma of the larynx or pharynx
The dose per fraction was in the range of 1.5 to 2.5 Gy.
The mean gap duration was 9 days
Significant tumor repopulation was found after the first 2 weeks of radiotherapy.
During the **treatment** gap, the proliferation rate was equal to 0.75 Gy/day.
During the days with irradiation, **repopulation** was slower and equal to 0.2 Gy/day.

Radiother Oncol. 2018 Apr;127(1):20-26. doi: 10.1016/j.radonc.2018.02.015. Epub 2018 Mar 10.

Dose dependence of accelerated repopulation in head and neck cancer: Supporting evidence and clinical implications.

Shuryak I[1], Hall EJ[2], Brenner DJ[2].

Standard Accelerated Repopulation (AR) models: AR begins at a fixed time, with repopulation rates independent of the number of clonogens killed.

Alternative model: onset-time and rate of AR depend on the number of clonogens killed, and thus on dose and dose-fractionation.

kick off time

$$S_{DI} = \exp\left[-\alpha D - \frac{\beta D^2}{n} + \gamma(T - T_k) + gT\right],$$

dose-independent AR rate

$$S_{DD} = \exp\left[-\alpha D - \frac{\beta D^2}{n} + \gamma_{DD}(T - T_{kDD}) + gT\right],$$

$$P_{kill} = 1 - \exp\left[\frac{(-\alpha d - \beta d^2)n}{T}\right],$$

mean proportion of tumor clonogens killed per day

$$C = \left(\alpha D + \frac{\beta D^2}{n}\right) T_{k_{DD}}/T,$$

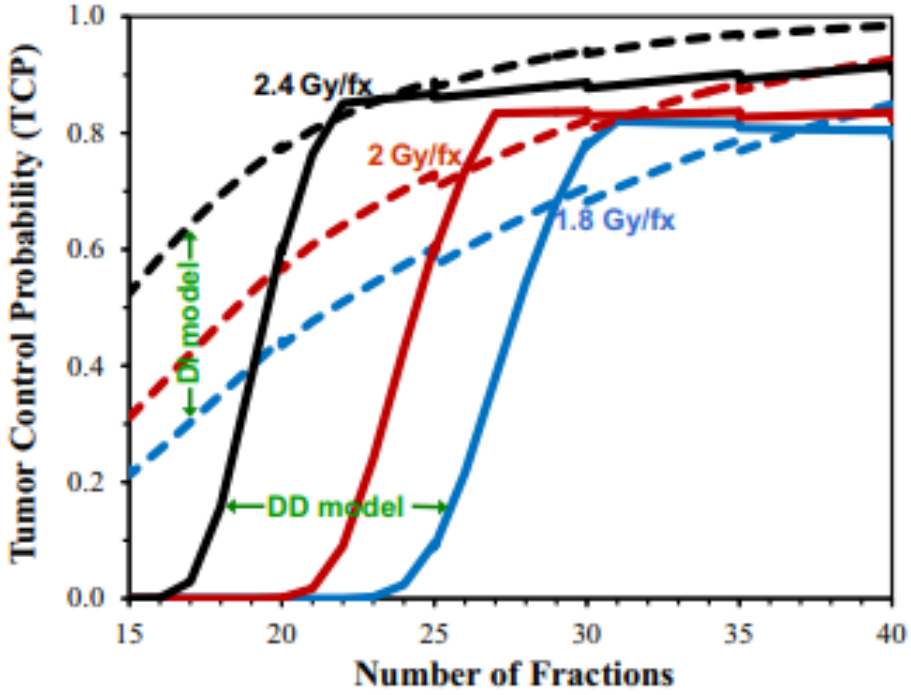
proportion of the total dose delivered before the onset of AR

Radiother Oncol. 2018 Apr;127(1):20-26. doi: 10.1016/j.radonc.2018.02.015. Epub 2018 Mar 10.

Dose dependence of accelerated repopulation in head and neck cancer: Supporting evidence and clinical implications.

Shuryak I[1], Hall EJ[2], Brenner DJ[2].

The alternative dose-dependent model of AR provides significantly-improved descriptions of a wide range of randomized clinical data



For currently-used HNC fractionation schemes, **the last 5 fractions do not increase TCP**, but simply compensate for increased accelerated repopulation.

Hyperfractionated and accelerated radiotherapy regimen without reduction of the total dose

Radiother Oncol. 1997 Aug;44(2):111-21.

Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial.

Horiot JC[1], Bontemps P, van den Bogaert W, Le Fur R, van den Weijngaert D, Bolla M, Bernier J, Lusinchi A, Stuschke M, Lopez-Torrecilla J, Begg AC, Pierart M, Collette L.

72 Gy in 45 fractions over 5 weeks
Split-course schedule
Fractions oh 1.6 Gy /three times a day
An approximate 2-week break administered after 28 Gy

Continuous hyperfractionated and accelerated radiotherapy regimen

ELSEVIER

International Journal of Radiation Oncology*Biology*Physics

Volume 19, Issue 5, November 1990, Pages 1317-1320

Oncology intelligence

The rationale for continuous, hyperfractionated, accelerated radiotherapy (chart) ☆

Stanley Dische M.D., F.R.C.R., Michele I. Saunders M.D., F.R.C.R.

54 Gy/36 fr
12 consecutive days
1.5 Gy /3 times a day

Radiother Oncol. 1999 Dec;53(3):219-26.

Repair halftimes estimated from observations of treatment-related morbidity after CHART or conventional radiotherapy in head and neck cancer.

Bentzen SM[1], Saunders MI, Dische S.

Estimated repair halftime of late treatment-related toxicities:

4.9 h (3.2, 6.4 CI) for laryngeal oedema

3.8 h (2.5, 4.6 CI) for skin telangiectasia

4.4 h (3.8, 4.9 CI) for subcutaneous fibrosis

only the hyperfractionated, and not the accelerated, schedules provide a substantial mortality benefit

MARCH

Lancet. 2006 Sep 2;368(9538):843-54.

Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis.

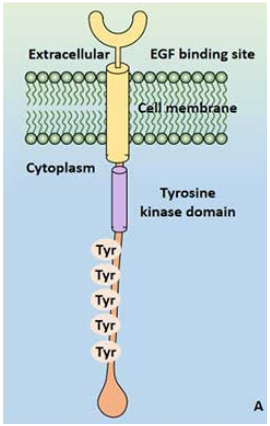
Bourhis J[1], Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, Horiot JC, Le Maître A, Pajak TF, Poulsen MG, O'Sullivan B, Dobrowsky W, Hliniak A, Skladowski K, Hay JH, Pinto LH, Fallai C, Fu KK, Sylvester R, Pignon JP; **Meta-Analysis** of **Radiotherapy** in (

Lancet Oncol. 2017 Sep;18(9):1221-1237.
Jul 27.

Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis.

Lacas B[1], Bourhis J[2], Overgaard J[3], Zhang Q[4], Grégoire V[5], Nankivell M[6], Zackrisson B[7], Szutkowski Z[8], Suwiński R[9], Poulsen M[10], O'Sullivan B[11], Corvò R[12], Laskar SG[13], Fallai C[14], Yamazaki H[15], Dobrowsky W[16], Cho KH[17], Beadle B[18], Langendijk JA[19], Viegas CMP[20], Hay J[21], Lotayef M[22], Parmar MKB[6], Aupérin A[1], van Herpen C[23], Maingon P[24], Trotti AM[25], Grau C[3], Pignon JP[26], Blanchard P[27]; **MARCH** Collaborative Group.

Role for the EGFR in determining the proliferative cellular response to fractionated radiotherapy in HNSCC



Int J Radiat Oncol Biol Phys. 2010 Jun 1;77(2):438-46. doi: 10.1016/j.ijrobp.2009.05.021. Epub 2009 Sep 3.

ELSEVIER FULL-TEXT ARTICLE

Predicting the effect of accelerated fractionation in postoperative radiotherapy for head and neck cancer based on molecular marker profiles: data from a randomized clinical trial.

Suwinski R[1], **Jaworska M**, **Nikiel B**, Grzegorz W, Bankowska-Wozniak M, Wojciech M, Krzysztof S, Dariusz L.

The molecular profile that benefited from accelerated treatment:

- ✓ **low Ki-67**
- ✓ **low p-53**
- ✓ **high EGFR**

J Clin Oncol. 2005 Aug 20;23(24):5560-7.

Epidermal growth factor receptor expression in pretreatment biopsies from head and neck squamous cell carcinoma as a predictive factor for a benefit from accelerated radiation therapy in a randomized controlled trial.

Bentzen SM[1], Atasoy BM, Daley FM, Dische S, Richman PI, Saunders MI, Trott KR, Wilson GD.

Acta Oncol. 2005;44(1):50-8.

The role of epidermal growth factor receptor and E-cadherin for the outcome of reduction in the overall treatment time of radiotherapy of supraglottic larynx squamous cell carcinoma.

Eriksen JG[1], Steiniche T, Overgaard J; Danish Head and Neck Cancer study group (DAHANCA).

Lancet. 1997 Jul 19;350(9072):161-5.

Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. CHART Steering Committee.

Saunders M[1], Dische S, Barrett A, Harvey A, Gibson D, Parmar M.

J Clin Oncol. **2012** Aug 1;30(22):2788-97. doi: 10.1200/JCO.**2012**.41.6677

Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis.

Mauguen A[1], Le Péchoux C, **Saunders MI**, **Schild SE**, **Turrisi AT**, **Baumann M**, Sause WT, Ball D, Belani CP, Bonner JA, Zajusz A, Dahlberg SE, Nankivell M, Mandrekar SJ, Paulus R, Behrendt K, Koch R, Bishop JF, Dische S, Arriagada R, De Ruysscher D, Pignon JP.

INDAR Individualized isotoxic accelerated radiotherapy

Radiother Oncol. 2012 Feb;102(2):228-33. doi: 10.1016/j.radonc.2011.10.010. Epub 2011 Nov 17.

Individualised isotoxic accelerated radiotherapy and chemotherapy are associated with improved long-term survival of patients with stage III NSCLC: a prospective population-based study.

De Ruysscher D[1], van Baardwijk A, Steevens J, Botterweck A, Bosmans G, Reymen B, Wanders R, Borger J, Dingemans AM, Bootsma G, Pitz C, Lunde R, Geraedts W, Oellers M, Dekker A, Lambin P.

Tailored approach based upon predefined organ at risk dose constraints

Eur J Cancer. 2012 Oct;48(15):2339-46. doi: 10.1016/j.ejca.2012.04.014. Epub 2012 May 18.

Mature results of a phase II trial on individualised accelerated radiotherapy based on normal tissue constraints in concurrent chemo-radiation for stage III non-small cell lung cancer.

van Baardwijk A[1], Reymen B, Wanders S, Borger J, Ollers M, Dingemans AM, Bootsma G, Geraedts W, Pitz C, Lunde R, Peters F, Lambin P, De Ruysscher D.

In the first three weeks:
30 twice daily fractions of 1.5 Gy

Next:
2 Gy fractions once a day until a mean lung dose of 19 Gy with a total ranging between 54 to 69 Gy in 5.5 weeks.

Hypofractionation

- Increased doses per fraction

- Rationale: better outcomes by **increasing BED** without lengthening treatment time and thereby preventing cancer cell repopulation.

van Leeuwen *et al. Radiation Oncology* (2018) 13:96
https://doi.org/10.1186/s13014-018-1040-z

Radiation Oncology

REVIEW Open Access

The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies

C. M. van Leeuwen[1], A. L. Oei[1,2], J. Crezee[1], A. Bel[1], N. A. P. Franken[1,2], L. J. A. Stalpers[1] and H. P. Kok[1*]

van Leeuwen *et al. Radiation Oncology* (2018) 13:96
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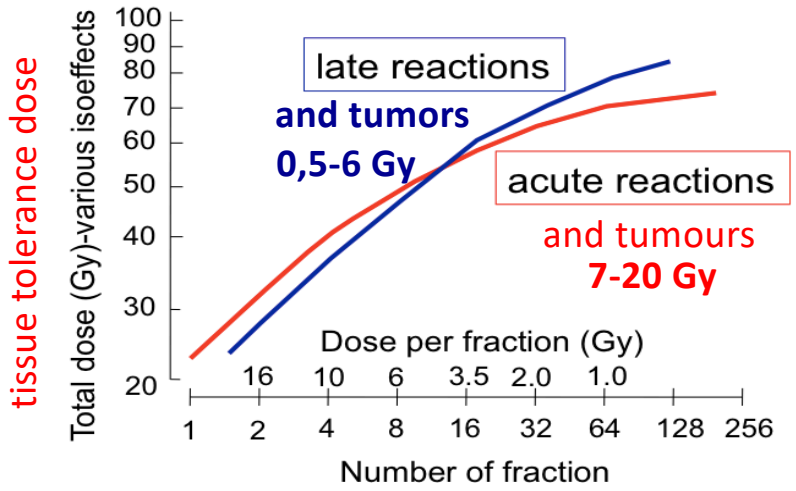

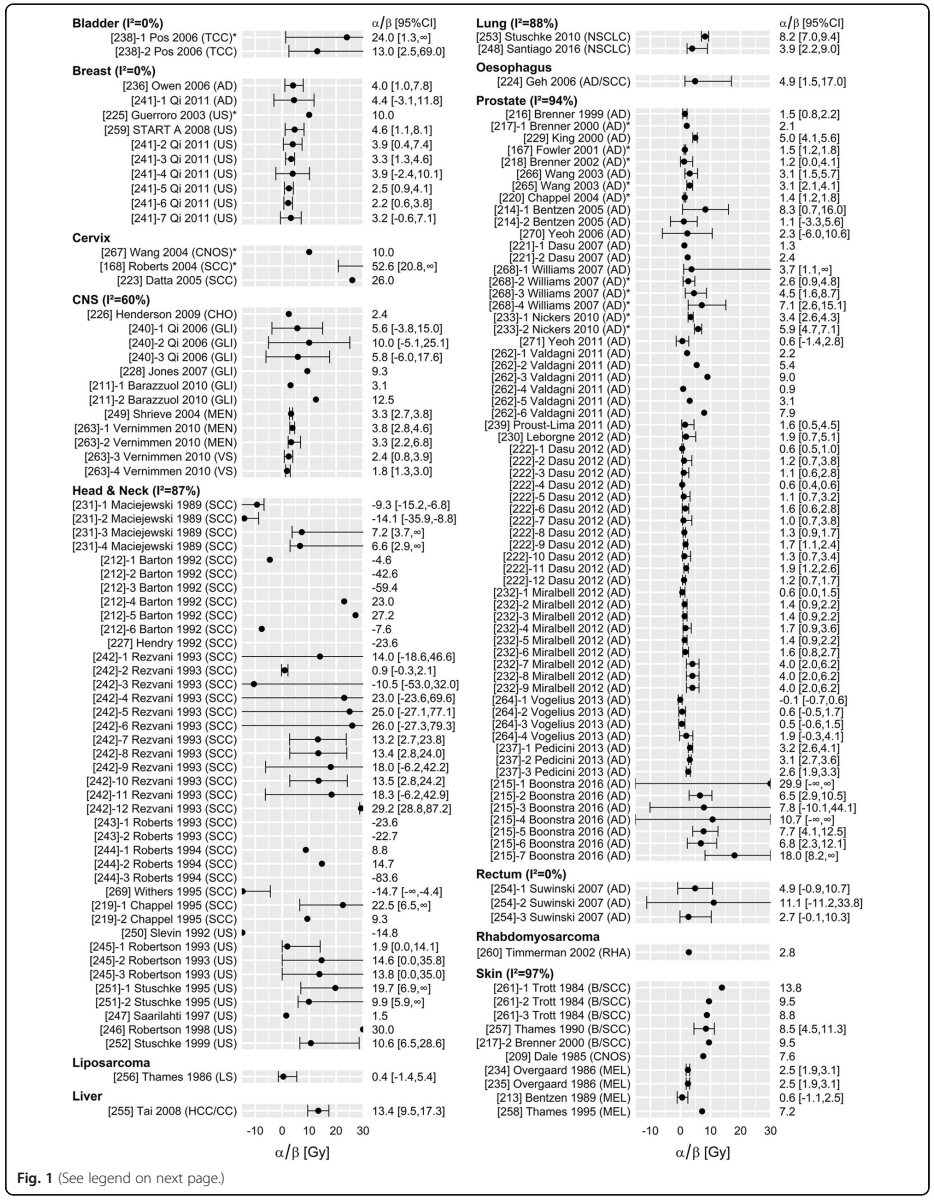

Fig. 1 (See legend on next page.)

van Leeuwen et al. Radiation Oncology (2018) 13:96

Review of 64 clinical studies

A large heterogeneity in LQ parameters was found within and between studies

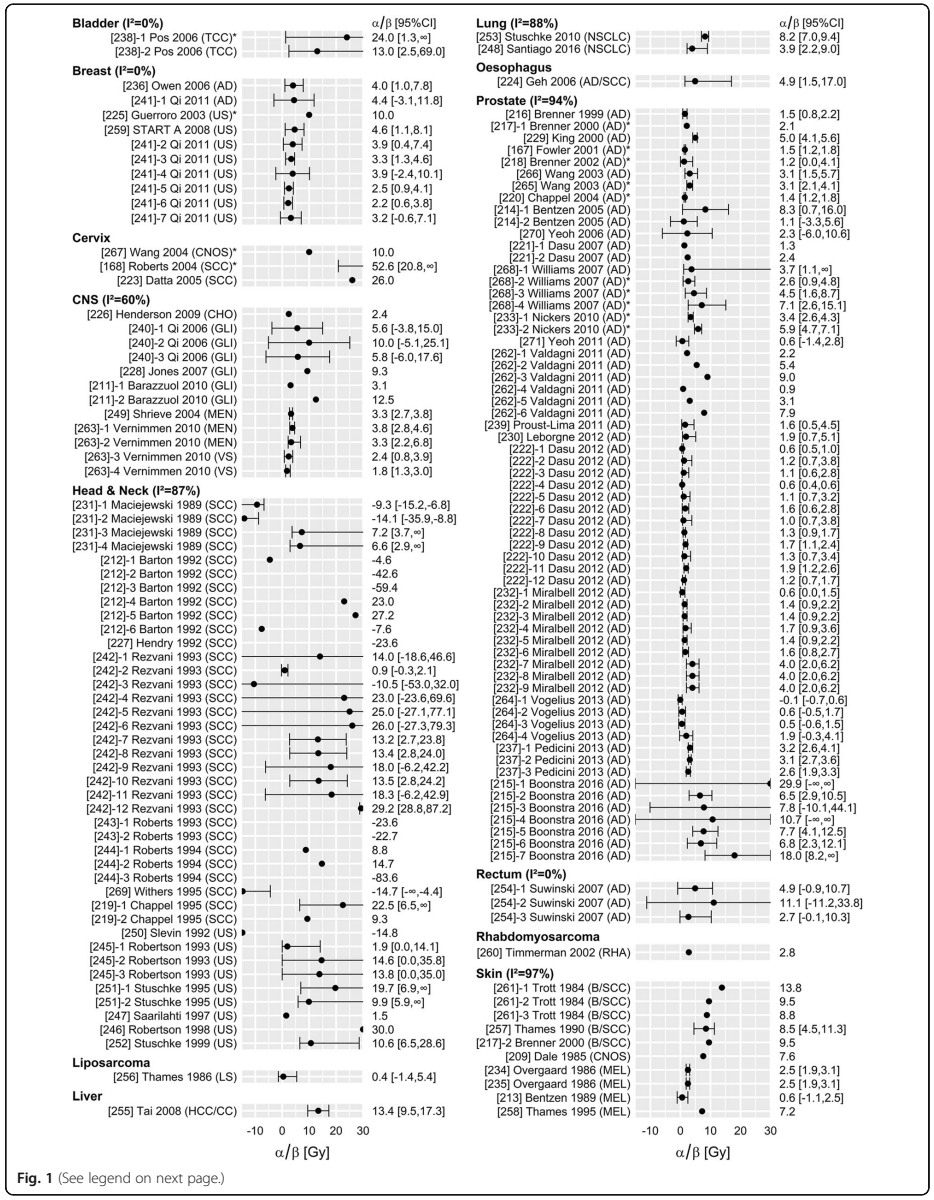

Fig. 1 (See legend on next page.)

van Leeuwen et al. Radiation Oncology (2018) 13:96

Review of 64 clinical studies

Effect of intratumor heterogeneity on the optimal fractionation in radiotherapy

↓

- temporal and spatial variations in tumor blood (hypoxia)
- rapid transitions between different phases of cell cycle
- repair of sublethal damage
- repopulation
- re-oxygenation

↓

heterogeneous radiosensitivity

↓

can **affect *BED*** achieved with standard fractionation or hypofractionated regimens

Physica Medica 67 (2019) 185–191

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journal homepage: www.elsevier.com/locate/ejmp

Original paper

Effect of heterogeneous radiosensitivity on the optimal fractionation in radiotherapy

V.Y. Kuperman

In the presence of heterogeneous alpha and beta in the tumor, hypofractionation can either increase or decrease *BEDtarget* depending on the variances $\sigma\alpha$ and $\sigma\beta$.

Intratumor heterogeneity is an important factor which can affect radiobiological comparison of different fractionation regimens.

ACTA ONCOLOGICA
2018, VOL. 57, NO. 7, 883–894
https://doi.org/10.1080/0284186X.2018.1433874

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ORIGINAL ARTICLE

Clinical estimation of α/β values for prostate cancer from isoeffective phase III randomized trials with moderately hypofractionated radiotherapy

Niloy R. Datta, Emanuel Stutz, Susanne Rogers and Stephan Bodis

slow growing tumors without significant tumor repopulation

α/βusually assumed to be low (**1.0–1.8 Gy**)
Eight trials from seven studies, randomized 6993 patients between CRT and HRT

Clinically estimated α/β ranged between**1.3 and 11.1Gy (4.9 ± 3.9 Gy**)

Modest Hypofractionated RT

CHHiP

Lancet Oncol. 2016 Aug;17(8):1047-1060. doi: 10.1016/S1470-2045(16)30102-4. Epub 2016 Jun 20.

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial.

Dearnaley D[1], Syndikus I[2], Mossop H[3], Khoo V[4], Birtle A[5], Bloomfield D[6], Graham J[7], Kirkbride P[8], Logue J[9], Malik Z[2], Money-Kyrle J[10], O'Sullivan JM[11], Panades M[12], Parker C[4], Patterson H[13], Scrase C[14], Staffurth J[15], Stockdale A[16], Tremlett J[6], Bidmead M[17], Mayles H[2], Naismith O[17], South C[10], Gao A[4], Cruickshank C[3], Hassan S[3], Pugh J[3], Griffin C[3], Hall E[3]; **CHHiP** Investigators.

74 Gy/2 Gy vs 60 and 57 Gy/3 Gy

J Clin Oncol. 2017 Jun 10;35(17):1891-1897. doi: 10.1200/JCO.2016.70.4189. Epub 2017 Mar 29.

Moderate Hypofractionation in High-Risk, Organ-Confined Prostate Cancer: Final Results of a Phase III Randomized Trial.

Arcangeli G[1], Saracino B[1], Arcangeli S[1], Gomellini S[1], Petrongari MG[1], Sanguineti G[1], Strigari L[1].

80 Gy /40 fr vs 62 Gy / 20 fr in 5 weeks

non-inferiority

Ultra-Hypofractionation

HYPO-RT-PC

Lancet. 2019 Aug 3;394(10196):385-395. doi: 10.1016/S0140-6736(19)31131-6. Epub 2019 Jun 18.

Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial.

Widmark A[1], Gunnlaugsson A[2], Beckman L[3], Thellenberg-Karlsson C[4], Hoyer M[5], Lagerlund M[6], Kindblom J[7], Ginman C[8], Johansson B[9], Björnlinger K[10], Seke M[11], Agrup M[12], Fransson P[13], Tavelin B[4], Norman D[4], Zackrisson B[4], Anderson H[14], Kjellén E[2], Franzén L[4], Nilsson P[2].

42,7 Gy/ 7 fr/ 3 days per week vs 78 Gy/ 39 fr/ 5 days

Lancet Oncol. 2019 Nov;20(11):1531-1543. doi: 10.1016/S1470-2045(19)30569-8. Epub 2019 Sep 17.

Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial.

Brand DH[1], Tree AC[1], Ostler P[2], van der Voet H[3], Loblaw A[4], Chu W[4], Ford D[5], Tolan S[6], Jain S[7], Martin A[8], Staffurth J[9], Camilleri P[10], Kancherla K[11], Frew J[12], Chan A[13], Dayes IS[14], Henderson D[5], Brown S[15], Cruickshank C[15], Burnett S[15], Duffton A[16], Griffin C[15], Hinder V[15], Morrison K[1], Naismith O[17], Hall E[15], van As N[18]; PACE Trial Investigators.

78 Gy/39 fr or 62 Gy/20 fr vs SBRT 36,25 Gy/5 fr/1-2 weeks

International Journal of Radiation Oncology*Biology*Physics
Volume 100, Issue 4, 15 March 2018, Pages 858-865

Clinical Investigation

Dose Response and Fractionation Sensitivity of Prostate Cancer After External Beam Radiation Therapy: A Meta-analysis of Randomized Trials

Ivan R. Vogelius PhD, DMSc * ✉, Søren M. Bentzen PhD, DSc †, ‡

Meta-analysis of 13 randomized trials

Time factor: α/β 1,2 →2,7 Gy

van Leeuwen *et al. Radiation Oncology* (2018) 13:96
https://doi.org/10.1186/s13014-018-1040-z

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The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies

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α/β≈4 Gy

ACTA ONCOLOGICA
2018, VOL. 57, NO. 7, 883–894
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ORIGINAL ARTICLE

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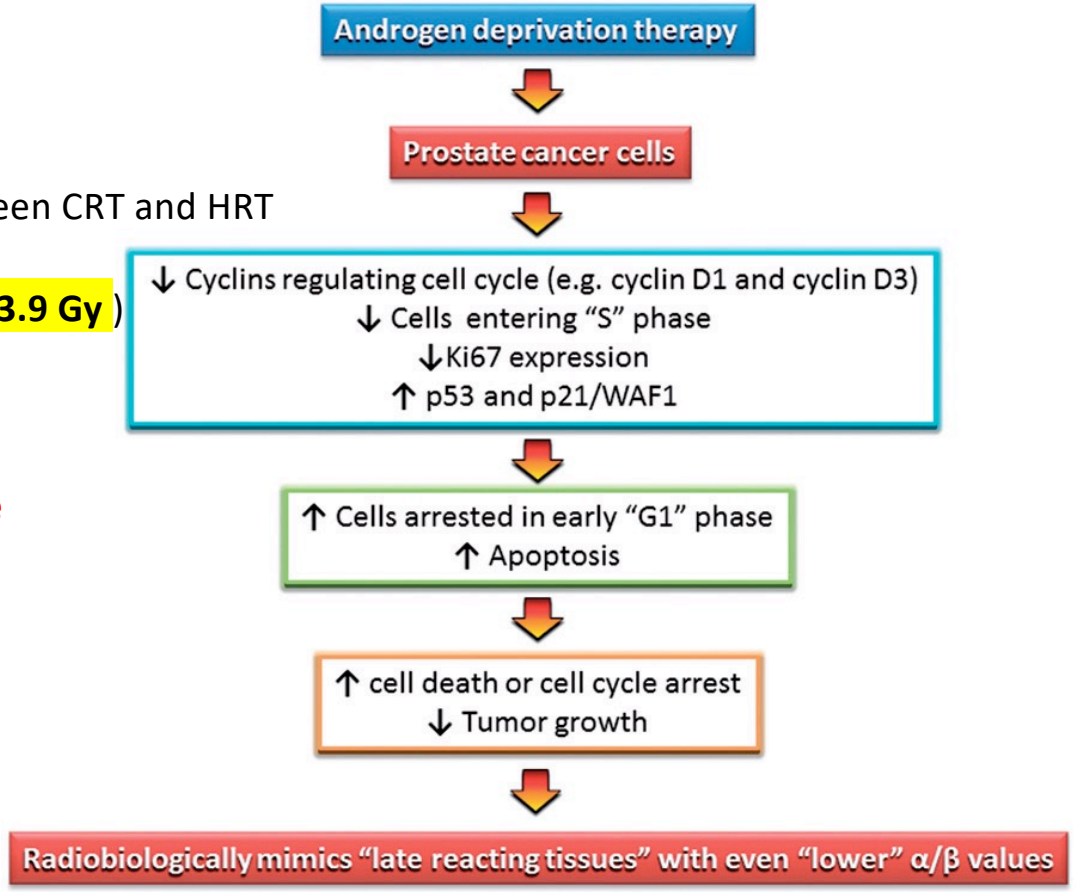
Eight trials from seven studies, randomized 6993 patients between CRT and HRT

Clinically estimated α/β ranged between **1.3 and 11.1Gy(4.9 ± 3.9 Gy)**

The estimated α/β values were inversely related to ADT usage



BJR https://doi.org/10.1259/bjr.20170849

Received: 09 November 2017 | Revised: 10 January 2018 | Accepted: 11 January 2018

Cite this article as:
Yarnold J. Changes in radiotherapy fractionation—breast cancer. *Br J Radiol* 2019; **92**: 20170849.

PUSHING THE FRONTIERS OF RADIOBIOLOGY: A SPECIAL FEATURE IN MEMORY OF SIR OLIVER SCOTT AND PROFESSOR JACK FOWLER: REVIEW ARTICLE

Changes in radiotherapy fractionation—breast cancer

JOHN YARNOLD, FRCR

Table 4. Unconfounded estimates of α/β: START-Pilot & START-A Trials[13]

Adverse effects (815 events/2263 pts): α/β = 3.1 Gy [95% CI (2.0–4.2)]
Tumour relapse (349 events/3646 pts): α/β = 3.5 Gy [95% CI (1.2–5.7)]

Trial	Randomisation (Gy/fraction)	% 5 year local relapse (95% CI)	% 10 year local relapse (95% CI)
START-P[9,13]	50.0/25	7.9 (5.4–10.4)	12.1 (8.8–15.5)
	42.9/13	7.1 (5.4–10.4)	9.6 (6.7–12.6)
	39.0/13	9.1 (6.4–11.7)	14.8 (11.2–18.3)
START-A[10,13]	50.0/25	3.4 (2.3–5.1)	6.7 (4.9–9.2)
	41.6/13	3.1 (2.0–4.7)	5.6 (4.1–7.8)
	39.0/13	4.4 (3.1–6.2)	8.1 (6.1–10.7)
START-B[11,13]	50.0/25	3.3 (2.4–4.6)	5.2 (2.7–5.2)
	40.0/15	1.9 (1.2–3.0)	3.8 (2.7–5.2)
Ontario[12]	50.0/25	3.2[a]	6.7[b]
	42.5/16	2.8[a]	6.2[b]

α/β-values

6 Gy

3 Gy

3 Gy

4 Gy.

Hickey BE, *Cochrane Database Syst Rev* 2016; **7**: CD003860.

San Antonio Breast Cancer Symposium®, December 10-14, 2019

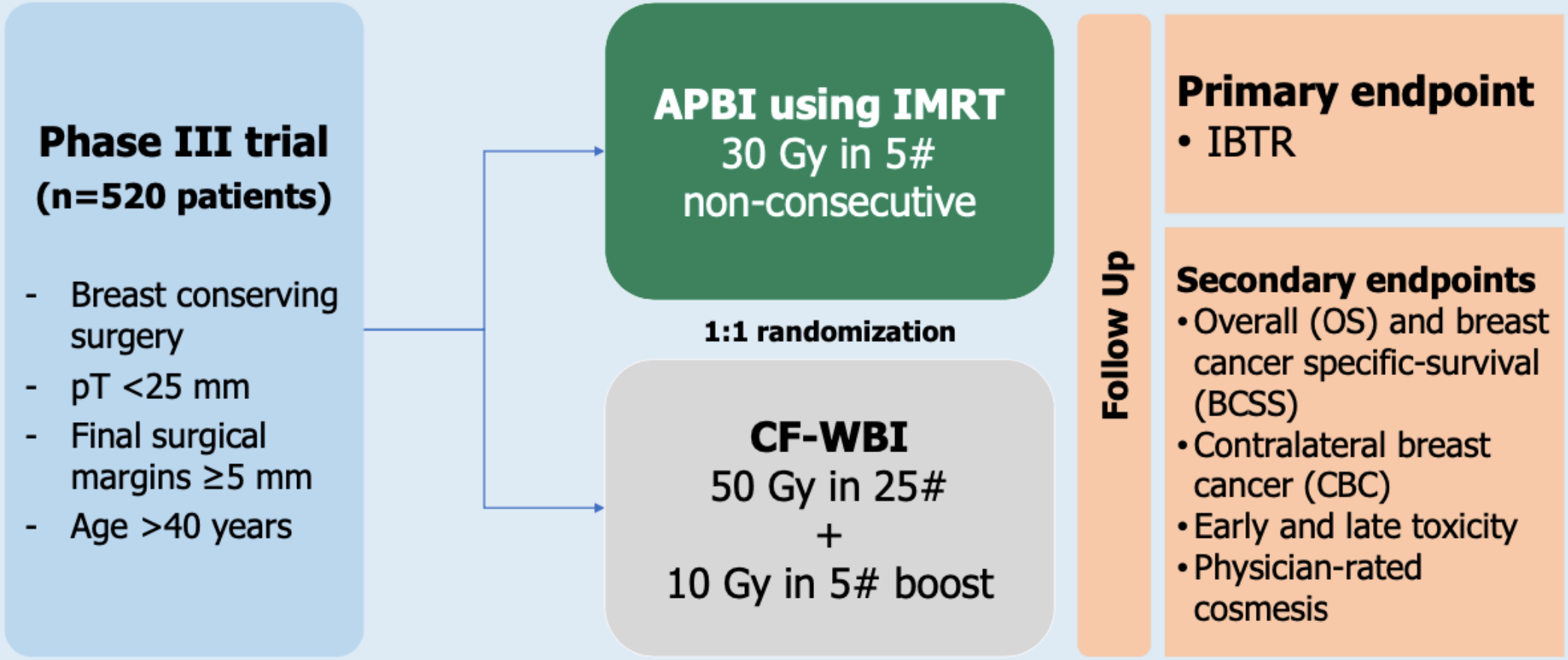
Accelerated partial breast or whole breast irradiation after breast conservation surgery for patients with early breast cancer

10-year follow up results of the APBI IMRT Florence randomized phase 3 trial

Icro Meattini[1,2], Calogero Saieva[3], Sara Lucidi[1], Monica lo Russo[1], Vieri Scotti[2], Isacco Desideri[1,2], Livia Marrazzo[2], Gabriele Simontacchi[2], Monica Mangoni[1,2], Carlotta Becherini[1], Lisa Paoletti[4], Erika Moretti[5], Luca Triggiani[6], Marco Bernini[2], Lorenzo Orzalesi[1,2], Luis Sanchez[2], Jacopo Nori[2], Stefania Pallotta[1,2], Simonetta Bianchi[1,2], and Lorenzo Livi[1,2]

[1]University of Florence, Florence; [2]Azienda Ospedaliero-Universitaria Careggi, Florence; [3]Istituto per lo Studio, la Prevenzione e la Rete Oncologica (ISPRO), Florence; [4]Ospedale Santa Maria Annunziata - Azienda Usl Toscana centro, Florence; [5]Ospedale S. Stefano - Azienda Usl Toscana centro, Prato; [6]University of Brescia, Brescia; Italy

Trial design – APBI IMRT Florence *(NCT 02104895)*



Livi L, et al. EJC 2015

Conclusions

10-year cumulative IBTR incidence in early breast cancer treated with **external APBI using IMRT** technique in **5 once-daily fractions (30 Gy in 5#)** is low and **not significantly different** from patients treated with CF-WBI

Comparable LRR, DM, CBC, BCSS, and **OS** rates

Acute & Late toxicity and **Cosmesis** evaluations significantly in **favor** of **APBI arm**

APBI might be considered a **standard alternative** to WBI in low risk early breast cancer patients

ARTICLE IN PRESS

Radiotherapy and Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Radical accelerated radiotherapy for non-small cell lung cancer (NSCLC): A 5-year retrospective review of two dose fractionation schedules

Stephen D. Robinson, Bilal A. Tahir, Katherine A.R. Absalom, Amila Lankathilake, Tathagata Das, Caroline Lee, Patricia M. Fisher, Emma Bates, Matthew Q.F. Hatton *

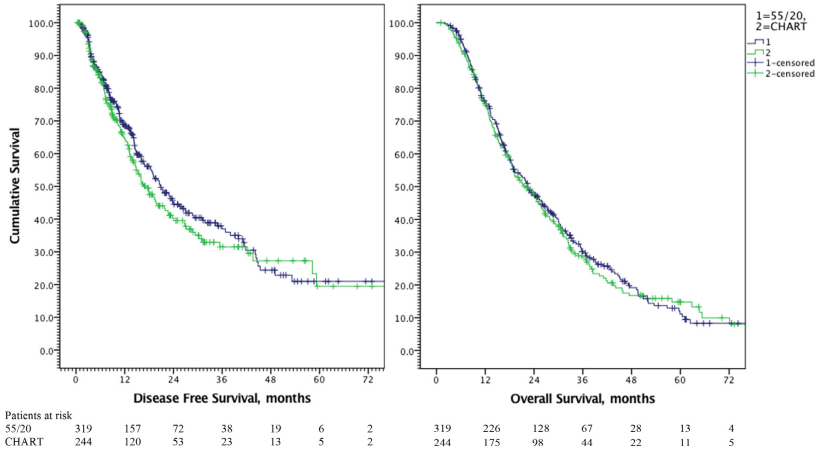


Fig. 1. Disease free and overall survival for CHART and the acclerated hypofractioned schedule (55/20).

hypofractionated *accelerated* regimens (55Gy/20 fr) shorten the overall treatment time

for combating tumour repopulation

Volume 104 Number 2 2019

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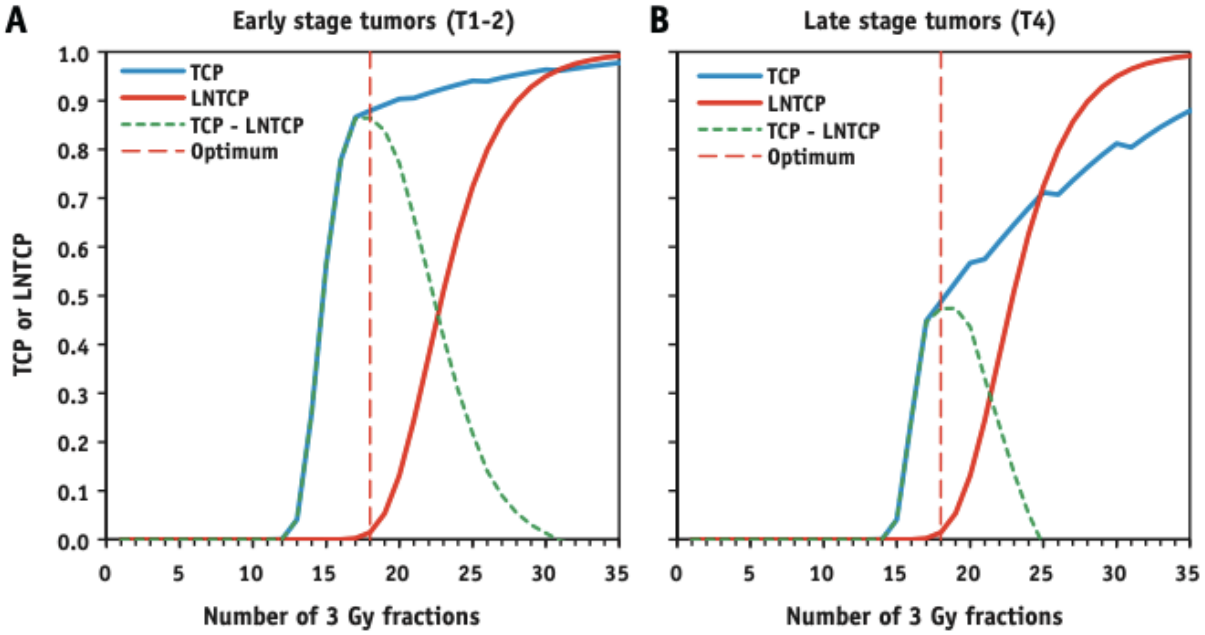
Biology Contribution

Optimized Hypofractionation Can Markedly Improve Tumor Control and Decrease Late Effects for Head and Neck Cancer

Igor Shuryak, MD, PhD, Eric J. Hall, DPhil, DSc, and David J. Brenner, PhD, DSc



fast-growing,
HPV negative, H&N cancers:

hypofractionation (**3 Gy x 18 fr**) or its close variant, *accelerated hyperfractionation* (**1.8 Gy BID x 38 fr**) **efficiently overcomes tumor repopulation**

Re-population

Hypofractionated ablative treatments do not provide the time needed for re-population which occurs 3-4 weeks after the start of radiotherapy

Kim MS(2005) Radiat Oncol J 33:265-275

Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2014 February 1; 88(2): 254–262. doi:10.1016/j.ijrobp.2013.07.022.

The Tumor Radiobiology of SRS and SBRT: Are More than the 5 R's Involved?

J. Martin Brown, PhD[1], **David J. Carlson, PhD**[2], and **David J. Brenner, PhD**[3]

Re-Oxygenation

As single fraction ablative treatments are associated with widespread vascular destruction of tumors, re-oxygenation plays little or no role in tumor response

The drastic drop in oxygen consumption due massive cell death could favor re-oxygenation of surviving hypoxic cells

Moderate doses per fraction 3-8 Gy may lead to some reoxygenation since vascular damage may be irrelevant

Shibamoto Y (2011) Cancer 118:2078-2084.
Story M (2008) Semin Radiat Oncol 18:244-248.

Repair

As hypofractionated schedules require prolonged delivery times, they may interfere with sublethal damage repair.

Around 10% loss of biological efficacy when irradiation lasts over 30 minutes

High-dose per fraction irradiation schedules may be assumed to overwhelm repair mechanisms due to enzymatic pool depletion

Fowler JF (2004). Int J Radiat Oncol Biol Phys 59:242-249.
Ling CC (2010) Radiother Oncol 95:261-268.
Brenner DJ (2008) Semin Radiat Oncol 18:234-239.

Re-distribution

High single-dose fractionation blocks the cell in the cycle phase, thus interfering with redistribution.

Kim MS (2005) Radiat Oncol J 33:265-275
Park H (2000) Radiat Res 153:295-304.

Main radiobiological target
of high-dose radiotherapy:

tumor or endothelial cells ?

Hypothesis of endothelial cell damage

- Tumor microenvironment deterioration and indirect cell death due to hypoxia
- Tumor endothelial cells were more radiosensitive than normal endothelial cells because of varying intrinsic radiosensitivity and structural differences
- Doses higher than 10 Gy in a single fraction caused vascular damage
- Clonogenic survival was lower in tumour-bearing mice that were irradiated with single dose 10 Gy than in *in vitro* tumour samples

But… radioinduced tumor death did not change when endothelial cells were genetically engineered by deleting the Bax pro-apoptotic gene

Song CW (2014) Int J Radiat Oncol Biol Phys 89:924-925
Clement JJ (1976) Int J Radiat Oncol Biol Phys 1:671–678
Moding EJ (2015) Sci Transl Med 7:278ra34

Acid sphingomyelinase (ASMase) pathway

- In ablative single-dose RT, apoptosis is mediated via the acid sphingomyelinase (ASMase) pathway

- ROS and RNS radiation-induced promote vasocontraction, which together with vascular wall inflammation leads to arterial hypertension and atherosclerosis

Fuks Z, Cancer Cell. 2005;8:89–91.
Marathe S, J Biol Chem. 1998;273:4081–8.
Garcia-Barros M, Science. 2003;300:1155–9
Soloviev AI, Biochem Pharmacol. 2019;159:121–39.

RESEARCH ARTICLE

The Journal of Clinical Investigation

jci.org Volume 129 Number 2 February 2019

Single-dose radiotherapy disables tumor cell homologous recombination via ischemia/reperfusion injury

Sahra Bodo,[1] Cécile Campagne,[1] Tin Htwe Thin,[1] Daniel S. Higginson,[1] H. Alberto Vargas,[2] Guoqiang Hua,[1] John D. Fuller,[3] Ellen Ackerstaff,[4] James Russell,[4] Zhigang Zhang,[5] Stefan Klingler,[3] HyungJoon Cho,[4] Matthew G. Kaag,[6] Yousef Mazaheri,[2] Andreas Rimner,[1] Katia Manova-Todorova,[7] Boris Epel,[8] Joan Zatcky,[1] Cristian R. Cleary,[1] Shyam S. Rao,[1] Yoshiya Yamada,[1] Michael J. Zelefsky,[1] Howard J. Halpern,[8] Jason A. Koutcher,[4] Carlos Cordon-Cardo,[9] Carlo Greco,[10] Adriana Haimovitz-Friedman,[1] Evis Sala,[2] Simon N. Powell,[1] Richard Kolesnick,[3] and Zvi Fuks[1,10]

[1]Department of Radiation Oncology, [2]Department of Radiology, [3]Laboratory of Signal Transduction, [4]Department of Medical Physics, [5]Department of Epidemiology and Biostatistics, [6]Department of Surgery,

ASMase-driven perfusion defects and consequent ROS/SSR–mediated HR inactivation

ASMase-mediated microcirculatory vasoconstriction after SDRT

↓

ischemic stress response within parenchymal tumor cells

↓

ROS

↓

SUMO stress response

↓

depletion of chromatin- associated free SUMO3 (indispensable for HR of DSBs)

24 Gy SDRT, but not 3×9 Gy fractionation, coupled early tumor ischemia/reperfusion to human cancer ablation.

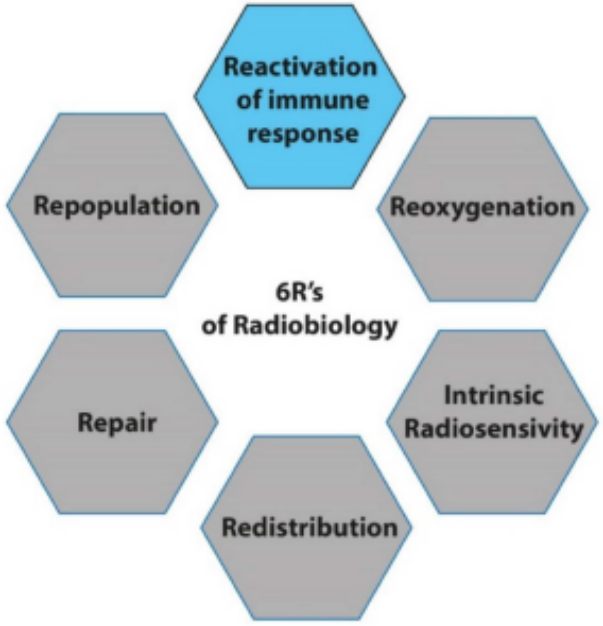
cancers

MDPI

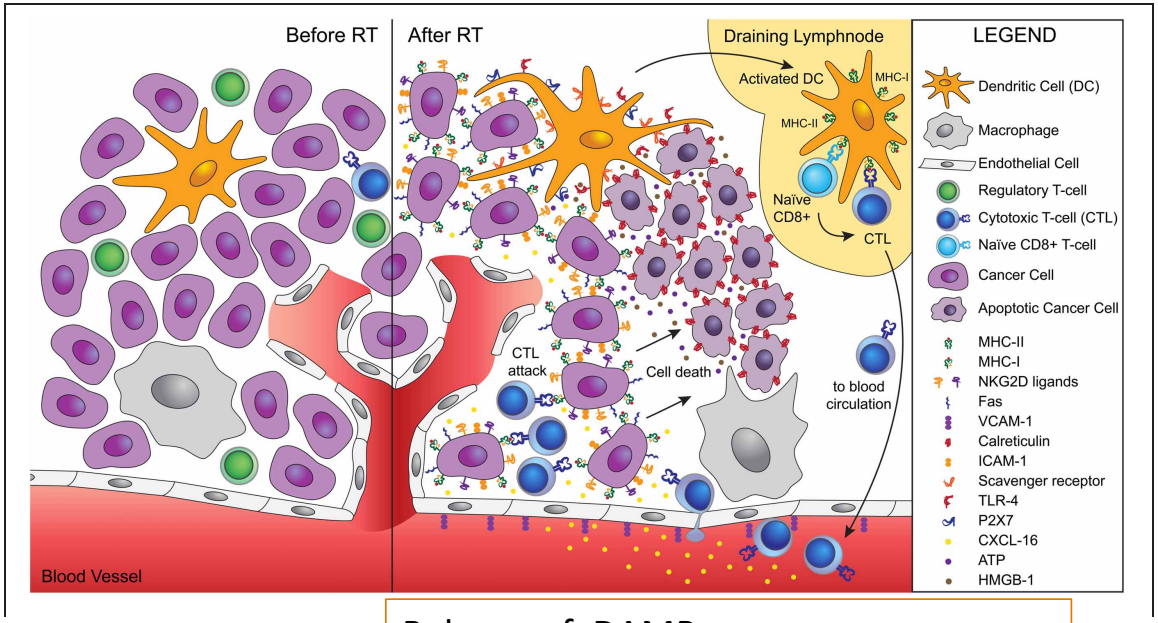
Review

The 6th R of Radiobiology: Reactivation of Anti-Tumor Immune Response

Jihane Boustani [1,†], Mathieu Grapin [1,†], Pierre-Antoine Laurent [1], Lionel Apetoh [2] and Céline Mirjolet [1,2,*]



In situ Vaccine



cGAS/STING pathway→**IFN**

Release of DAMPs:
Calreticulin, HGPB1, ATP

Activation DC

Expression of CXCL9-10-16 on tumor cells
Vessel remodelling↑VCAM1

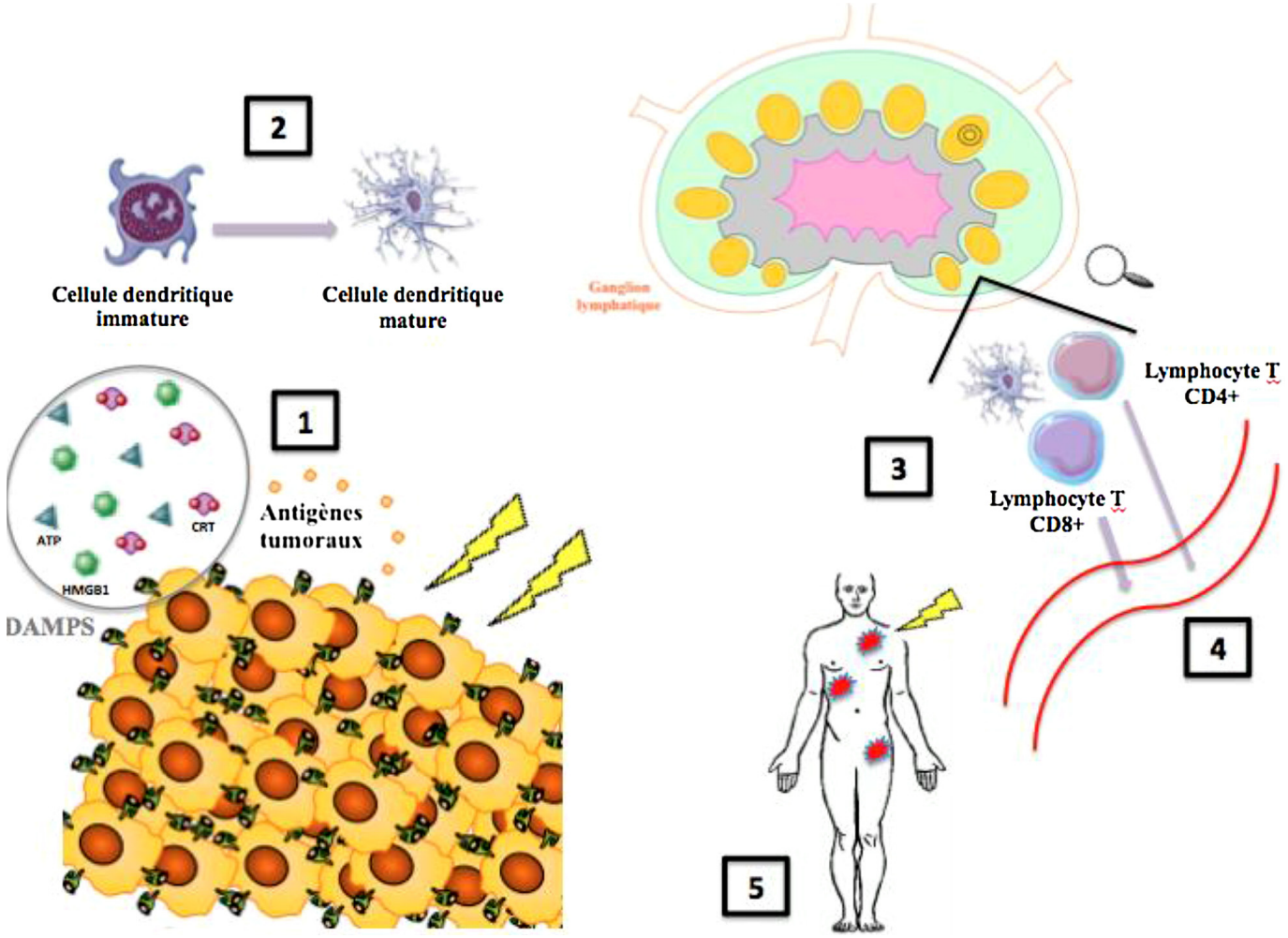
Recruitment T-Cells

Upregolation of MHC I, FAS/CD95

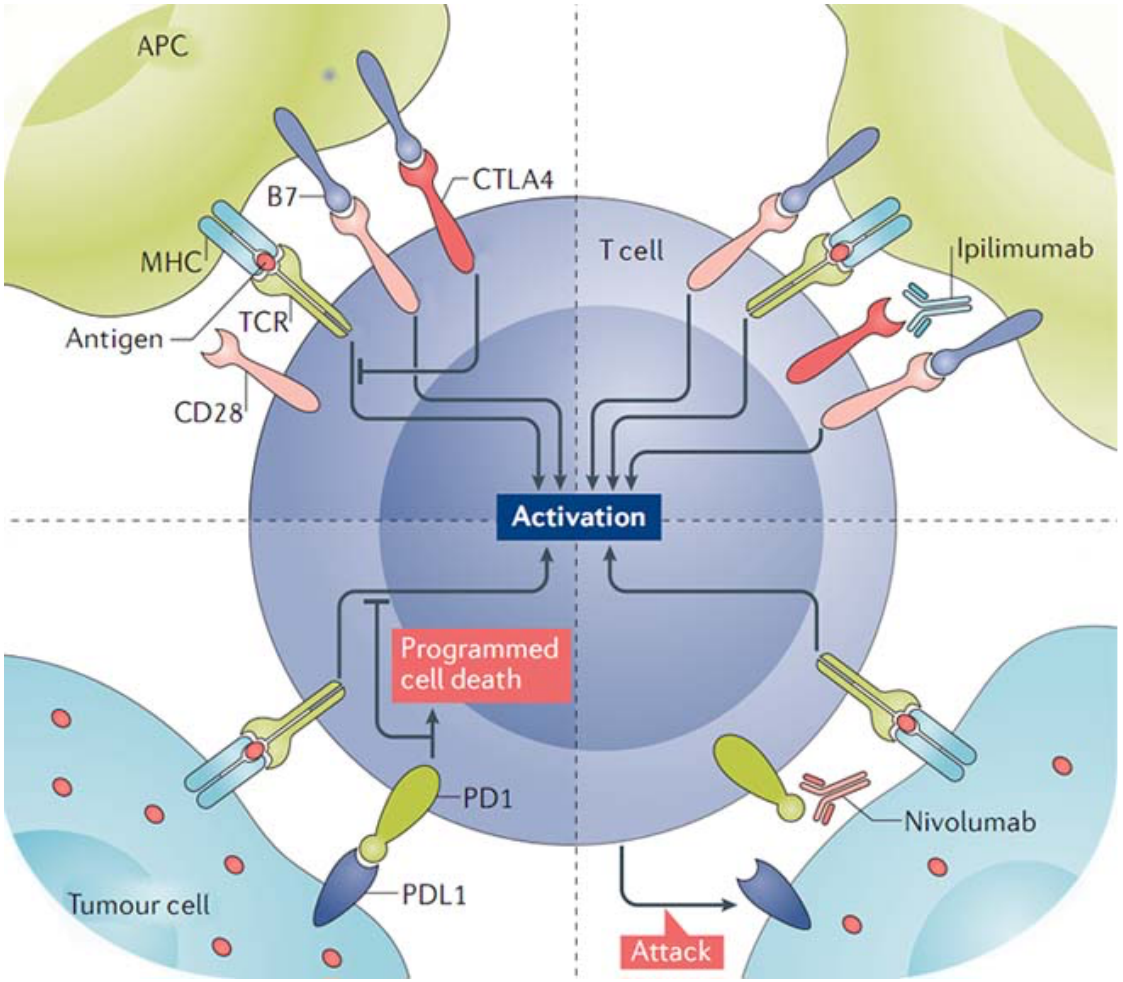
Strengthening of CTL

Demaria S, Frontiers in Oncology 2012
Vanpouille-Box C, Clin Canc Res 2018

Abscopal effect



RT + immune checkpoint inhibitors



CTLA4

PD1
PDL1

Weichselbaum RR, Nature review 2017, 14, 365
Kang et al. Journal for ImmunoTherapy of Cancer (2016) 4:51

Importance of dose per fraction

Advances in Radiation Oncology (2018) 3, 486-493

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in radiation oncology

www.advancesradonc.org

Critical Review

Generating antitumor immunity by targeted radiation therapy: Role of dose and fractionation

Eric C. Ko MD, PhD, Kimberly Thomas Benjamin MD, Silvia C. Formenti MD*

In preclinical models:
6 Gy x5 (IFN gamma)
8 Gy x3 (IFN gamma)

Dose >10-12 Gy: immunosuppressive effects
20-30 Gy (Treg)

Postow MA, N Engl J Med. 2012;366:925- 31.
Hiniker SM, Transl Oncol. 2012;5:404-7.
Golden EB, Cancer Immunol Res. 2013;1:365-72
Claire Vanpouille-Box, *Clin Cancer Res* 2017.

nature COMMUNICATIONS

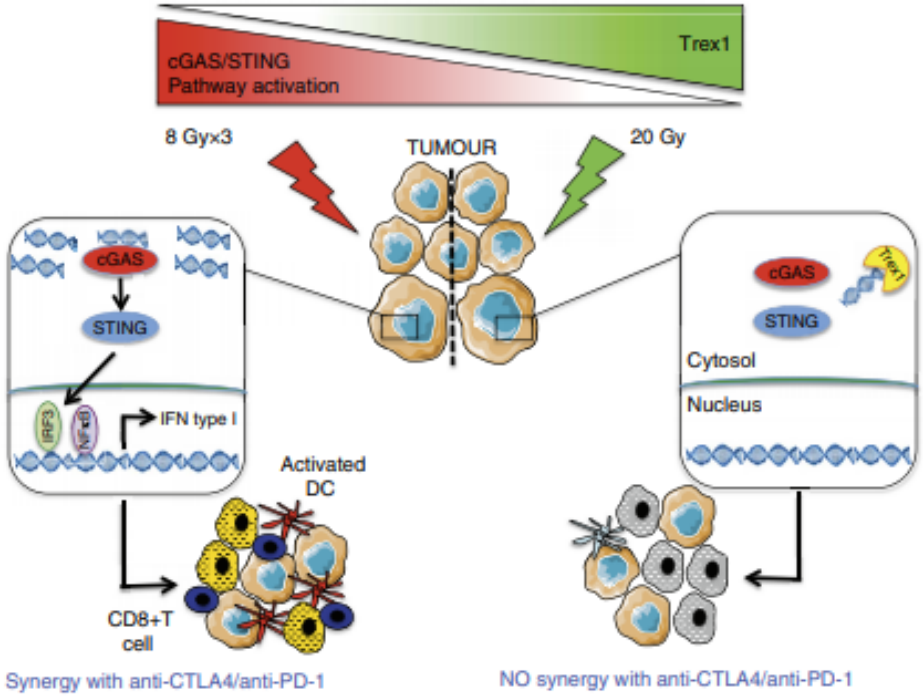
ARTICLE

Received 27 Mar 2017 | Accepted 12 Apr 2017 | Published 9 Jun 2017

DOI: 10.1038/ncomms15618 OPEN

DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity

Claire Vanpouille-Box[1], Amandine Alard[2,†], Molykutty J. Aryankalayil[3], Yasmeen Sarfraz[1], Julie M. Diamond[1], Robert J. Schneider[2], Giorgio Inghirami[4], C. Norman Coleman[3], Silvia C. Formenti[1] & Sandra Demaria[1,4]



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COMMENTARY

Optimizing Dose Per Fraction: A New Chapter in the Story of the Abscopal Effect?

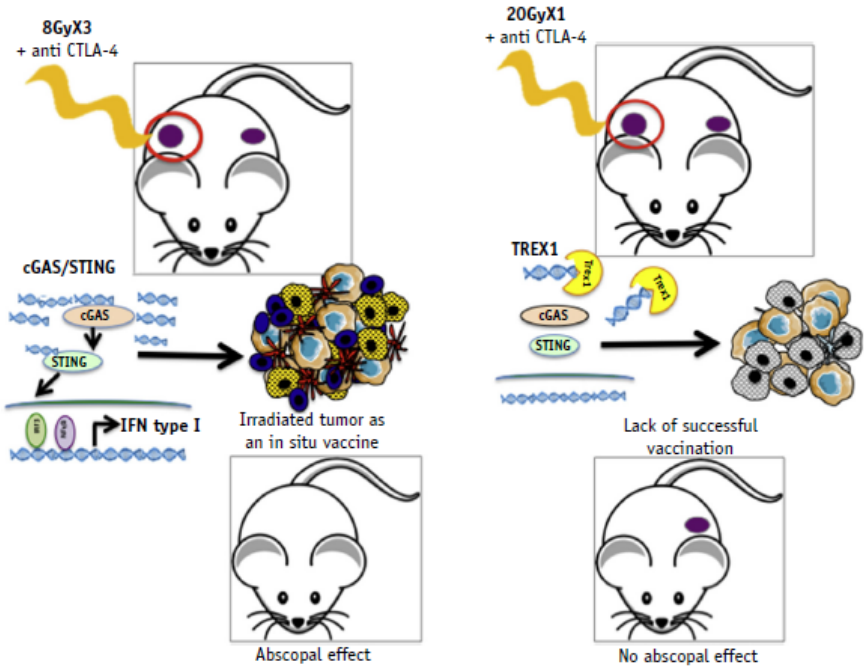
Silvia C. Formenti, MD

Challenge:

- ✓ Delivering enough dose per fraction to generate sufficient dsDNA to trigger cGAS/STING and induce IFN-mediated cross-priming while preventing Trex1 induction.

This ideal window of opportunity might be specific to the individual patient and tumor.

- ✓ The period of radiation delivery could also be relevant
- ✓ The timing of the administration of immunotherapies along with RT treatment is relevant as well.



www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 61), pp: 31812-31819

Research Paper

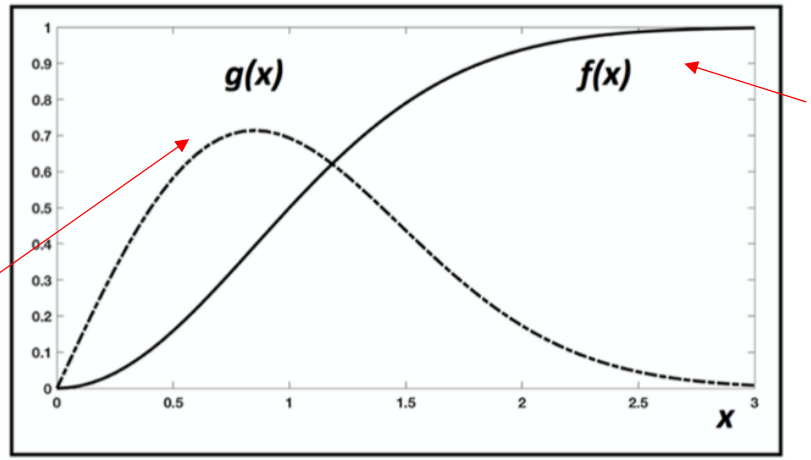
Immunologically effective dose: a practical model for immuno-radiotherapy

Raphaël Serre[1], Fabrice Barlesi[2], Xavier Muracciole[3] and Dominique Barbolosi[1]

[1]Simulation & Modelling Adaptive Response for Therapeutics in Cancer (SMARTc), Center for Research on Cancer of Marseille,

not much is known about the optimal size per fraction and inter-fraction time

IED models **an intrinsic immunogenicity of radiotherapy schedules: the fraction of immunogenicity that results from the choice of the dosing regimen.**



f(x) describes the gradual immune stimulation

g(x) gradual release of tumour antigens at time x,

Figure 4: Graphical description of the two functions used in the IED model. The number *g*(x) describes the gradual release of tumour antigens at time x, after irradiation at x = 0. The number *f*(x) describes the gradual immune stimulation, after tumour antigen release at x = 0. Here, x can be understood as a unit-less time variable, that is replaced by the ratio of an elapsed time over T_D (for *g*), or elapsed time over T_{IR} (for *f*). Their definitions are: $f(x)=1-\left(\frac{1}{2}\right)^{x^2}$ and $g(x)=\overset{\&}{f}(x)=2\ln(2)x\left(\frac{1}{2}\right)^{x^2}$, but other expressions could be used without changing the behaviour of the model, if the general shape of these curves is like this example.

Perspectives

Opportunities to optimize the biological efficacy of radiation beams

Lancet Oncol. 2017 Feb;18(2):202-211. doi: 10.1016/S1470-2045(16)30648-9. Epub 2016 Dec 18.

A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study.

Scott JG[1], Berglund A[2], Schell MJ[2], Mihaylov I[3], Fulp WJ[2], Yue B[2], Welsh E[2], Caudell JJ[4], Ahmed K[4], Strom TS[4], Mellon E[4], Venkat P[4], Johnstone P[4], Foekens J[5], Lee J[2], Moros E[4], Dalton WS[6], Eschrich SA[2], McLeod H[6], Harrison LB[4], Torres-Roca JF[7].

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Scott JG[1], Bergl
JJ[4], Ahmed K[4], S
Moros E[4], Daltor

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Physics Contribution

Utility of Normal Tissue-to-Tumor α/β Ratio When Evaluating Isodoses of Isoeffective Radiation Therapy Treatment Plans

Hiram A. Gay, MD,* Jian-Yue Jin, PhD,† Albert J. Chang, MD, PhD,‡ and Randall K. Ten Haken, PhD§

Table 1 LQ model predictions for the relative number of fractions offering an isodose% interval advantage for normal tissue sparing

Isodose% interval	Tissue sparing advantage for
$\text{isodose\%} < \left(\frac{\text{normal}\alpha/\beta}{\text{tumor}\alpha/\beta}\right) 100\%$	Fewer fractions
$\text{isodose\%} = \left(\frac{\text{normal}\alpha/\beta}{\text{tumor}\alpha/\beta}\right) 100\%$	Equivalent
$\left(\frac{\text{normal}\alpha/\beta}{\text{tumor}\alpha/\beta}\right) 100\% < \text{isodose\%}$	More fractions

The same BED is prescribed to the tumor but with a different number of fractions. Isodose z% = [normal α/β/tumor α/β] 100%.

Perspectives

Opportunities to optimize the biological efficacy of radiation beams

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Cured in a FLASH: Reducing Normal Tissue Toxicities Using Ultra-High-Dose Rates

By Hania Al-Hallaq, PhD, Minsong Cao, PhD, Jon Kruse, PhD, Eric Klein, PhD

FLASH

ultra-light dose rate irradiation to deliver a single high dose IR in a very short time (<200ms)

- Increase the differential effect tumors/normal tissues
- Possible role of depletion of oxygen to organic hydroperoxides and lipid peroxidation

- Extremely short time of exposure: early modulation of radiochemical events that depend upon oxygen concentration in irradiated volume. FLASH could cause a rapid consumption of local oxygen and elicit a transient radiation-induced hypoxia.
- Hyperoxygenation can abolish the FLASH effect in mice.

Bourhis J, Radioth Onc 2019, 139. 11-17

FLASH effect was found to be reproducibile with 1-10 pulses of 1,8-2 microsecond, an overall time of less than 200 ms and a dose rate within the pulse above $1,8x10^5$Gy

Table 1
Parameters with which the FLASH effect has been observed. Both Kinetron [5] and Oriatron (eRT6) [7] are irradiation devices dedicated to produce FLASH irradiation.

Animal model	Device	Volume (cm^2)	Duration of RT (ms)	Dose delivered (single dose in Gy)	Mean dose-rate (Gy/s)	Dose-rate within the pulse (Gy/s)	Ref.
Mice, Zebrafish	Kinetron Oriatron	< 2	< 200	> 8	> 40	> $1.8.10^5$	[5,11] (Montay-Gruel, in rev.)
Pig/Cats	Kinetron Oriatron	< 12	< 200	up to 41	300–400	> 1.10^6	[12]
Pig	Oriatron	100	< 200	31	160	$0.8,10^6$	[12]

the most relevant parameters for the FLASH effect are the combination of:

1)dose,

2)dose-rate within the pulse,

3) overall time of irradiation (<200 milliseconds)

1 patient:
CD30+ T-cell cutaneous lymphoma
3.5-cm diameter skin tumor
5.6-MeV linac specifically designed for FLASH-RT
15 Gy to PTV in 90 ms

Bourhis J, Radioth Onc 2019, 139. 11-17
Bourhis J, Radioth Onc 2019, 139. 18-22

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BRIEF REPORT

The Biology of SBRT: LQ or Something New?

J. Martin Brown, PhD

Department of Neurology, Stanford University School of Medicine, Palo Alto, California

Received Feb 15, 2018. Accepted for publication Feb 22, 2018.

If you want to cure a tumor
Then finish radiation sooner
Give it 3 × 20 Grays
And cut the time to just 5 days.
To figure dose just use LQ
With terms that are but two.
No need to add more bits
As the patient data already fits.
So keep it simple with nothing new
Just stick with straight LQ