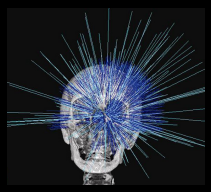
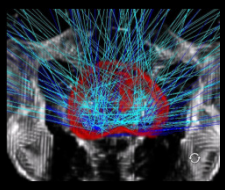
The Radiobiology of Small Fraction Numbers

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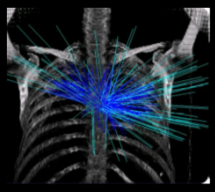
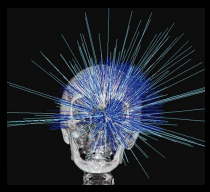
The Radiobiology of Small Fraction Numbers

1. Single-Fraction Radiotherapy

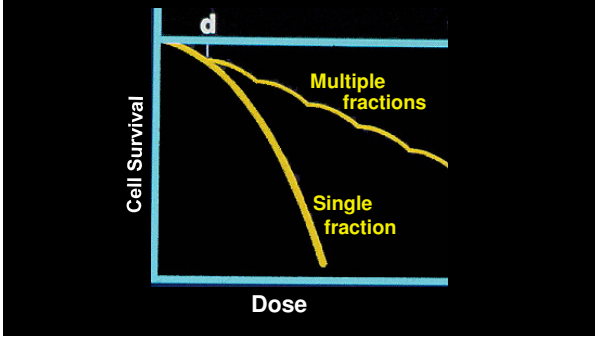



What determines optimal fractionation for conventional radiotherapy?

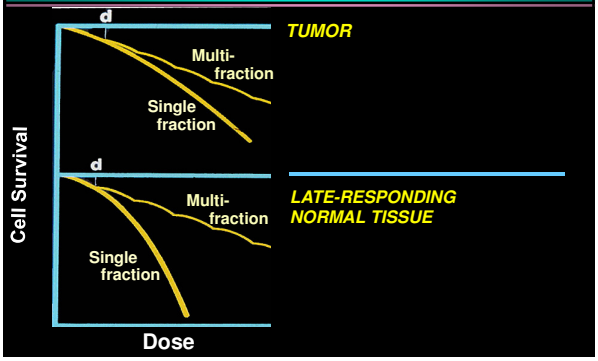
The Four R's

- ✓ Repair
- ✓ Reoxygenation
- ✓ Repopulation
- ✓ Redistribution

DNA repair results in reduced cell killing when a treatment is fractionated



Different types of tissue respond quantitatively differently to changes in fractionation



So why do we fractionate?

- Late-responding normal tissues are more sensitive to changes in fractionation (small α/β) than are early-responding tissues such as tumors (large α/β)
- So fractionation spares late-responding tissues compared to most tumors

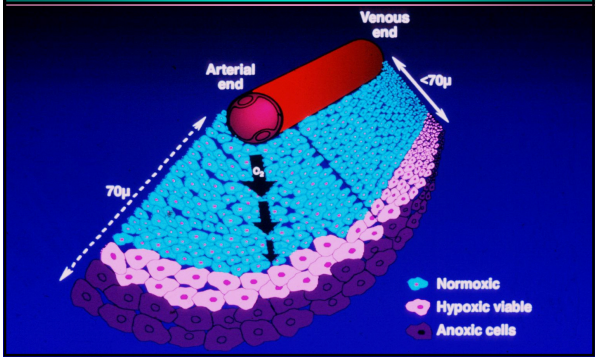
A basis for these α/β differences

- *In vitro*:
  - ✓ non-cycling cells are associated with low α/β
  - ✓ cycling cells are associated with high α/β

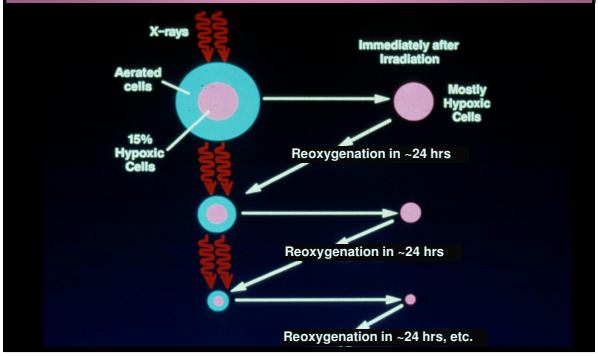
Tumor: Cycling cells: High α/β

Late-responding normal tissue: Few cycling cells: Low α/β

Hypoxia / Reoxygenation: The other reason we fractionate



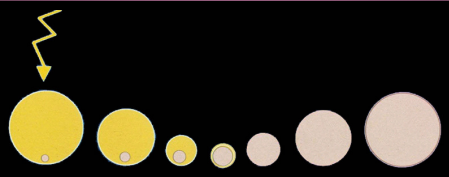
Fractionation results in reoxygenation



Hypoxia and malignancies

- Almost all malignant tumors, even a few mm in diameter, contain hypoxic cells
- A malignant tumor containing even a small hypoxic fraction would require an exceedingly high single-fraction dose for sterilization
- Therefore fractionation appears highly advantageous when attempting to cure malignant tumors

Accelerated Repopulation



As a tumor shrinks, surviving clonogens proliferate at an accelerated rate

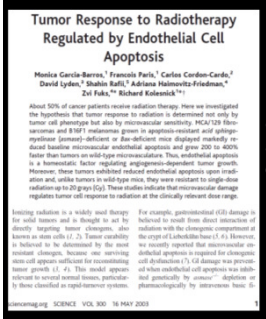
So… for external beam RT of tumors…

- Must fractionate treatment
  - to overcome hypoxia
  - for differential response with late effects
- Must prolong treatment
  - to limit early sequellae
- Would like to shorten treatment
  - to prevent accelerated repopulation

For stereotactic RT of malignant tumors..

- Must fractionate treatment
  - to overcome hypoxia
  - for differential response with late effects
- ~~Must prolong treatment~~
  - ~~to limit early sequellae~~
- Would like to shorten treatment
  - to prevent accelerated repopulation

Is the biology different at high doses per fraction?



Tumor Response to Radiotherapy Regulated by Endothelial Cell Apoptosis

Monica Garcia-Barros,[1] Francois Paris,[1] Carlos Cordon-Cardo,[2] David Lyden,[3] Shahin Rafii,[3] Adriana Haimovitz-Friedman,[4] Zvi Fuks,[4]* Richard Kolesnick[1]*

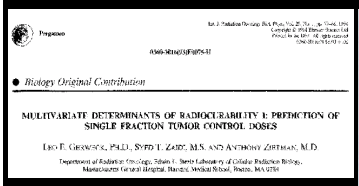
About 50% of cancer patients receive radiation therapy. Here we investigated the hypothesis that tumor response to radiation is determined not only by tumor cell phenotype but also by microvascular sensitivity. MCA/129 fibrosarcomas and B16F1 melanomas grown in apoptosis-resistant acid sphingomyelinase (asmase)–deficient or Bax-deficient mice displayed markedly reduced baseline microvascular endothelial apoptosis and grew 200 to 400% faster than tumors on wild-type microvasculature. Thus, endothelial apoptosis is a homeostatic factor regulating angiogenesis-dependent tumor growth. Moreover, these tumors exhibited reduced endothelial apoptosis upon irradiation and, unlike tumors in wild-type mice, they were resistant to single-dose radiation up to 20 grays (Gy). These studies indicate that microvascular damage regulates tumor cell response to radiation at the clinically relevant dose range.

Ionizing radiation is a widely used therapy for solid tumors and is thought to act by directly targeting tumor clonogens, also known as stem cells (1, 2). Tumor curability is believed to be determined by the most resistant clonogen, because one surviving stem cell appears sufficient for reconstituting tumor growth (3, 4). This model appears relevant to several normal tissues, particularly those classified as rapid-turnover systems. For example, gastrointestinal (GI) damage is believed to result from direct interaction of radiation with the clonogenic compartment at the crypt of Lieberkühn base (5, 6). However, we recently reported that microvascular endothelial apoptosis is required for clonogenic cell dysfunction (7). GI damage was prevented when endothelial cell apoptosis was inhibited genetically by *asmase*$^{-/-}$ depletion or pharmacologically by intravenous basic fi-

sciencemag.org SCIENCE VOL 300 16 MAY 2003 1

"Very high doses per fraction of radiation might trigger an entirely different method of cell kill via an anti-angiogenic pathway involving endothelial apoptosis"

Is the standard model (tumor control related primarily to radiation killing of tumor clonogens) inapplicable at high doses?



Pergamon

Int. J. Radiation Oncology Biol. Phys., Vol. 27, No. ... pp. ...

0360-3016/93/$6.00+0.00

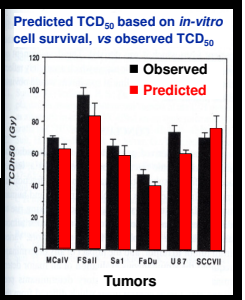
Biology Original Contribution

MULTIVARIATE DETERMINANTS OF RADIOCURABILITY I: PREDICTION OF SINGLE FRACTION TUMOR CONTROL DOSES

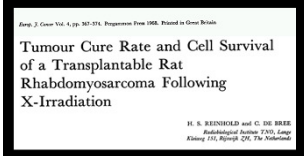
ERIC T. GERWECK, PH.D., SYED T. ZAIDI, M.S., AND ANTHONY ZIETMAN, M.D.

Department of Radiation Oncology, Sidney A. Farber Laboratory of Cellular Radiation Biology, Massachusetts General Hospital, Boston, Medical School, Boston, MA 02114

"The single-fraction dose to inactivate experimental tumors is well predicted by measured clonogenic fraction and *in-vitro* radiation-induced cell survival"

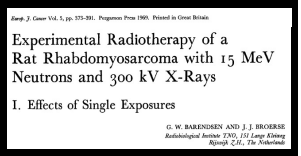


Other papers showing correlations between in vitro tumor-cell radiosensitivty and in vivo tumor control at high single doses / fraction



Tumour Cure Rate and Cell Survival of a Transplantable Rat Rhabdomyosarcoma Following X-Irradiation

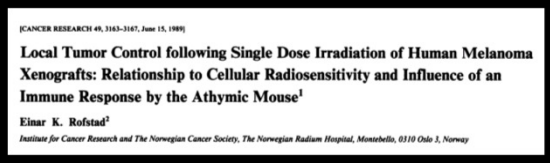
H. S. REINHOLD and C. DE BREE



Experimental Radiotherapy of a Rat Rhabdomyosarcoma with 15 MeV Neutrons and 300 kV X-Rays

I. Effects of Single Exposures

G. W. BARENDSEN AND J. J. BROERSE



[CANCER RESEARCH 49, 3163–3167, June 15, 1989]

Local Tumor Control following Single Dose Irradiation of Human Melanoma Xenografts: Relationship to Cellular Radiosensitivity and Influence of an Immune Response by the Athymic Mouse[1]

Einar K. Rofstad[2]

"Ablative" Radiotherapy: A different dominant mechanism for tumor control at high doses per fraction?

- The LQ model fails to predict high dose / Fx tumor control … *"so some new biology must be going on"*
- The LQ model will certainly fail at very high single doses
- But this doesn't imply that the standard model (*tumor control related primarily to radiation killing of tumor clonogens*) is wrong
- Nor does it contradict the rationale that fractionation will improve outcome after RT for tumors

Fractionation for malignant tumors

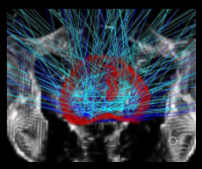
All malignant tumors, small or large, slow or fast growing, sensitive or resistant, will be more effectively treated with fractionation than with a single fraction

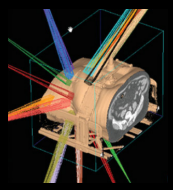
Stereotactic radiosurgery / ablative RT
The Bottom Line

- Stereotactic radiosurgery and SABR have had impressive success in treating some malignancies, particular in the brain and lung
  - But, for any given malignancy, better results should be obtained with fractionation
  - There is no need for conventional fractionation, 5-10 fractions is optimal
- For vascular disease and benign tumors, fractionation may only be needed if the lesions are large

The Radiobiology of Small Fraction Numbers

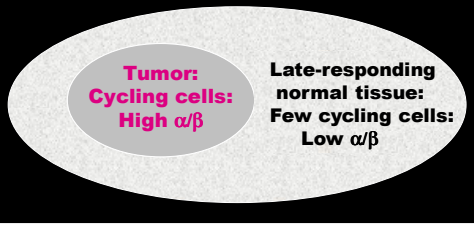
2. Hypofractionated radiotherapy





In most RT scenarios, we fractionate to take advantage of the differential α/β ratio between tumor and late responding normal tissue

- ✓ non-cycling cells are associated with low α/β
- ✓ cycling cells are associated with high α/β



Prostate Cancer

- Prostate tumors are not typical of most tumors, containing far fewer cycling cells
- Do prostate tumors have the typical differential response to fractionation for tumor control relative to late-responding tissues?
- What is an appropriate α/β value for prostate tumors?

Based on clinical data from implant and external beam data....

α/β for prostate cancer

= 1.5 Gy [95% CI: 0.8 - 2.2]

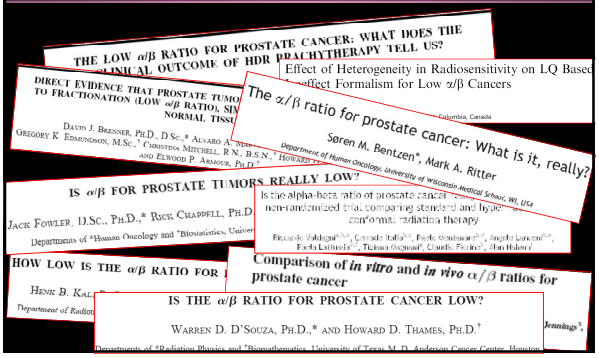
"comparable with typical α/β for late-responding normal tissues"

Brenner and Hall 1999

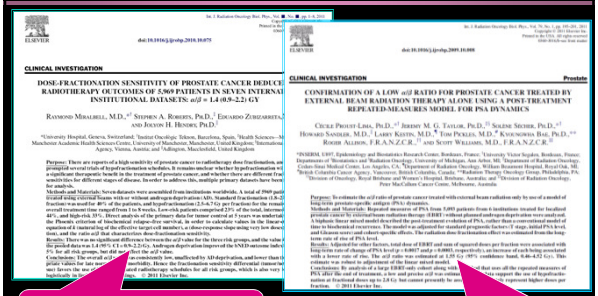
If the α/β ratio for prostate cancer is comparable to that for normal tissue….

- We lose one of the fundamental rationales for using many fractions or using low dose rate
- So hypo-fractionation or HDR rather than conventional fractionation or LDR become potential options for prostate RT

Since the 1999 estimate of α/β, there have been more than 70 further papers in the literature relating to α/β values for prostate



Two recent large studies of α/β for prostate



5,969 patients
α/β= 1.4 Gy (95% CI 0.9-2.2)

5,093 patients
α/β= 1.55 Gy (95% CI 0.46-4.52)

If α/β for prostate cancer is about the same as for surrounding late-responding normal tissue....

- ➔ Less rationale for using many fractions or LDR
- ➔ Fewer fractions at the right dose would give
  1. The same tumor control and late sequelae as current regimens
  2. Patient convenience
  3. Financial / resource advantages

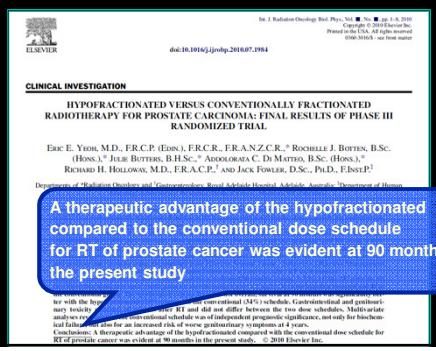
Tumor control / toxicity from randomized studies: Hypofractionation vs conventional fractionation

CLINICAL INVESTIGATION Prostate

A PROSPECTIVE PHASE III RANDOMIZED TRIAL OF HYPOFRACTIONATION VERSUS CONVENTIONAL FRACTIONATION IN PATIENTS WITH HIGH-RISK PROSTATE CANCER

Our findings suggest that late toxicity is equivalent between the two treatment groups, and that the hypofractionated schedule used in this trial is superior to the conventional fractionation in terms of FFBF

Tumor control / toxicity from randomized studies: Hypofractionation vs conventional fractionation



CLINICAL INVESTIGATION

HYPOFRACTIONATED VERSUS CONVENTIONALLY FRACTIONATED RADIOTHERAPY FOR PROSTATE CARCINOMA: FINAL RESULTS OF PHASE III RANDOMIZED TRIAL

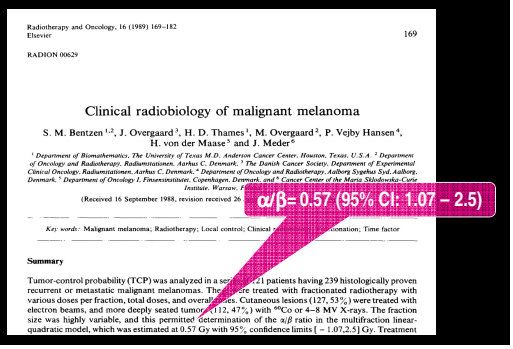
A therapeutic advantage of the hypofractionated compared to the conventional dose schedule for RT of prostate cancer was evident at 90 months in the present study

Is this mechanistically-based argument for hypofractionation unique to prostate?

"Prostate tumors are not typical of most tumors, containing far fewer cycling cells"

- This does not apply to most other tumor types
- Perhaps it applies to melanoma?

Melanoma is a slow-growing tumor with few dividing cells



Radiotherapy and Oncology, 16 (1989) 169–182
Elsevier

169

RADION 00629

Clinical radiobiology of malignant melanoma

S. M. Bentzen [1,2], J. Overgaard [3], H. D. Thames [1], M. Overgaard [2], P. Vejby Hansen [4], H. von der Maase [5] and J. Meder [6]

[1] Department of Biomathematics, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, U.S.A. [2] Department of Oncology and Radiotherapy, Radiumstationen, Aarhus C, Denmark, [3] The Danish Cancer Society, Department of Experimental Clinical Oncology, Radiumstationen, Aarhus C, Denmark, [4] Department of Oncology and Radiotherapy, Aalborg Sygehus Syd, Aalborg, Denmark, [5] Department of Oncology I, Finsencinstituttet, Copenhagen, Denmark, and [6] Cancer Center of the Maria Skłodowska-Curie Institute, Warsaw, P

(Received 16 September 1988, revision received 26

α/β= 0.57 (95% CI: 1.07 – 2.5)

Key words: Malignant melanoma; Radiotherapy; Local control; Clinical ; ionation; Time factor

Summary

Tumor-control probability (TCP) was analyzed in a ser 21 patients having 239 histologically proven recurrent or metastatic malignant melanomas. The re treated with fractionated radiotherapy with various doses per fraction, total doses, and overall ses. Cutaneous lesions (127, 53%) were treated with electron beams, and more deeply seated tumors (112, 47%) with ^{60}Co or 4–8 MV X-rays. The fraction size was highly variable, and this permitted determination of the α/β ratio in the multifraction linear-quadratic model, which was estimated at 0.57 Gy with 95% confidence limits [– 1.07,2.5] Gy. Treatment

Successful hypofractionation for choroidal melanoma

Int. J. Radiation Oncology Biol. Phys., Vol. 83, No. 1, pp. 199–205, 2011
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0360-3016/$ - see front matter

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doi:10.1016/j.ijrobp.2010.04.035

CLINICAL INVESTIGATION — Eye

LOCAL TUMOR CONTROL, VISUAL ACUITY, AND SURVIVAL AFTER HYPOFRACTIONATED STEREOTACTIC PHOTON RADIOTHERAPY OF CHOROIDAL MELANOMA IN 212 PATIENTS TREATED BETWEEN 1997 AND 2007

ROMAN DUNAVOELGYI, M.D.,* KARIN DIECKMANN, M.D.,† ANDREAS GLEISS, PH.D.,‡ STEFAN SACU, M.D.,* KARL KIRCHER, M.D.,* MICHAEL GEORGOPOULOS, M.D.,* DIETMAR GEORG, PH.D.,† MARTIN ZEHETMAYER, M.D.,* AND RICHARD POETTER, M.D.†

Departments of *Ophthalmology, †Radiotherapy and ‡Section of Clinical Biometrics, Medical University of Vienna, Vienna, Austria

International Journal of Radiation Oncology • Biology • Physics

www.redjournal.org

Clinical Investigation: Central Nervous System Tumor

Radiogenic Side Effects After Hypofractionated Stereotactic Photon Radiotherapy of Choroidal Melanoma in 212 Patients Treated Between 1997 and 2007

Roman Dunavoelgyi, M.D.,* Karin Dieckmann, M.D.,† Andreas Gleiss, Ph.D.,‡ Stefan Sacu, M.D.,* Karl Kircher, M.D.,* Michael Georgopoulos, M.D.,* Dietmar Georg, Ph.D.,† Martin Zehetmayer, M.D.,* and Richard Poetter, M.D.†

*From the Departments of *Ophthalmology and †Radiology and ‡Section of Clinical Biometrics, Medical University of Vienna, Vienna, Austria*

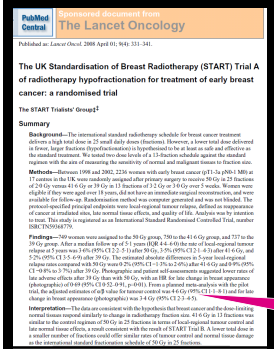
Received Nov 6, 2010, and in revised form Jan 3, 2011. Accepted for publication Jan 5, 2011

Is this mechanistically-based argument for hypofractionation unique to prostate?

"Prostate tumors are not typical of most tumors, containing far fewer cycling cells"

- This does not apply to most other tumor types
- Perhaps it applies to melanoma?
- Perhaps it applies to some other early-stage tumors?

What about early-stage breast cancer?



PubMed Central — Sponsored document from The Lancet Oncology

Published as: Lancet Oncol. 2008 April 01; 9(4): 331–341.

The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

The START Trialists' Group‡

Summary

Background—The international standard radiotherapy schedule for breast cancer treatment delivers a high total dose in 25 small daily doses (fractions). However, a lower total dose delivered in fewer, larger fractions (hypofractionation) is hypothesised to be at least as safe and effective as the standard treatment. We tested two dose levels of a 13-fraction schedule against the standard regimen with the aim of measuring the sensitivity of normal and malignant tissues to fraction size.

Methods—Between 1998 and 2002, 2236 women with early breast cancer (pT1–3a pN0–1 M0) at 17 centres in the UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2·0 Gy versus 41·6 Gy or 39 Gy in 13 fractions of 3·2 Gy or 3·0 Gy over 5 weeks. Women were eligible if they were aged over 18 years, did not have an immediate surgical reconstruction, and were available for follow-up. Randomisation method was computer generated and was not blinded. The protocol-specified principal endpoints were local-regional tumour relapse, defined as reappearance of cancer at irradiated sites, late normal tissue effects, and quality of life. Analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN50568779.

Findings—749 women were assigned to the 50 Gy group, 750 to the 41·6 Gy group, and 737 to the 39 Gy group. After a median follow-up of 5·1 years (IQR 4·4–6·0) the rate of local-regional tumour relapse at 5 years was 3·6% (95% CI 2·2–5·1) after 50 Gy, 3·5% (95% CI 2·1–5·0) after 41·6 Gy, and 5·2% (95% CI 3·5–6·9) after 39 Gy. The estimated absolute differences in 5-year local-regional relapse rates compared with 50 Gy were 0·2% (95% CI −1·3% to 2·6%) after 41·6 Gy and 0·9% (95% CI −0·8% to 3·7%) after 39 Gy. Photographic and patient self-assessments suggested lower rates of late adverse effects after 39 Gy than with 50 Gy, with an HR for late change in breast appearance (photographic) of 0·69 (95% CI 0·52–0·91, p=0·01). From a planned meta-analysis with the pilot trial, the adjusted estimates of α/β value for tumour control was 4·6 Gy (95% CI 1·1–8·1) and for late change in breast appearance (photographic) was 3·4 Gy (95% CI 2·3–4·5).

Interpretation—The data are consistent with the hypothesis that breast cancer and the dose-limiting normal tissues respond similarly to change in radiotherapy fraction size. 41·6 Gy in 13 fractions was similar to the control regimen of 50 Gy in 25 fractions in terms of local-regional tumour control and late normal tissue effects, a result consistent with the result of START Trial B. A lower total dose in a smaller number of fractions could offer similar rates of tumour control and normal tissue damage as the international standard fractionation schedule of 50 Gy in 25 fractions.

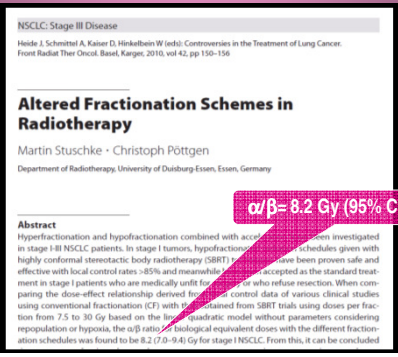
Much interest in accelerated partial breast irradiation for early-stage breast cancer

NSABP B-39/RTOG 0413:

3.4 or 3.85 x 10 fractions BID

2,236 patients
α/β= 4.6 Gy (95% CI 1.1-8.1)

What about lung?



NSCLC: Stage III Disease

Heide J, Schmittel A, Kaiser D, Hinkelbein W (eds): Controversies in the Treatment of Lung Cancer. Front Radiat Ther Oncol. Basel, Karger, 2010, vol 42, pp 150–156

Altered Fractionation Schemes in Radiotherapy

Martin Stuschke · Christoph Pöttgen

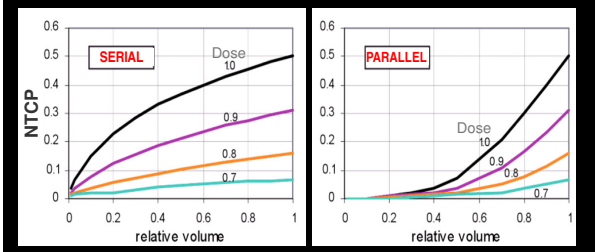
Department of Radiotherapy, University of Duisburg-Essen, Essen, Germany

Abstract

Hyperfractionation and hypofractionation combined with acce… been investigated in stage I-III NSCLC patients. In stage I tumors, hypofraction… schedules given with highly conformal stereotactic body radiotherapy (SBRT) h… ave been proven safe and effective with local control rates >85% and meanwhile … accepted as the standard treatment in stage I patients who are medically unfit for … or who refuse resection. When comparing the dose-effect relationship derived fro… control data of various clinical studies using conventional fractionation (CF) with t… obtained from SBRT trials using doses per fraction from 7.5 to 30 Gy based on the lin… quadratic model without parameters considering repopulation or hypoxia, the α/β ratio … biological equivalent doses with the different fractionation schedules was found to be 8.2 (7.0–9.4) Gy for stage I NSCLC. From this, it can be concluded

α/β= 8.2 Gy (95% CI 7.0-9.4)

How much you need to worry about the effects of hypofractionation on normal tissue will depend very much on whether the normal tissue is a serial or a parallel organ



e.g., brain, bladder, rectum, spinal cord

e.g., lung, kidney

Goitein 2008

Conclusions

- When the goal is to optimize the therapeutic ratio between tumor control and late complications, basic radiobiological principles tell us that we should fractionate
- Prostate is a mechanistically understood exception
- Melanoma and possibly early breast cancer may likewise be exceptions
- No such radiobiological rationale appears to exists for lung hypofractionation, but the parallel nature of normal lung tissue may well permit less fractionation than at other sites, *when the irradiated volume is small*
- ***This speaker does not think there is persuasive evidence for "new radiobiology" at high doses per fraction***

radiobiology radiobiology

Meet the new boss – same as the old boss!