Radiobiological aspects of radiation-induced second cancers after particle radiotherapy

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Strandqvist J: Studien über die kumulative Wirkung der Röntgenstrahlung bei der Fraktionierung. Acta Oncologica Supplementum LV, Stockholm 1944

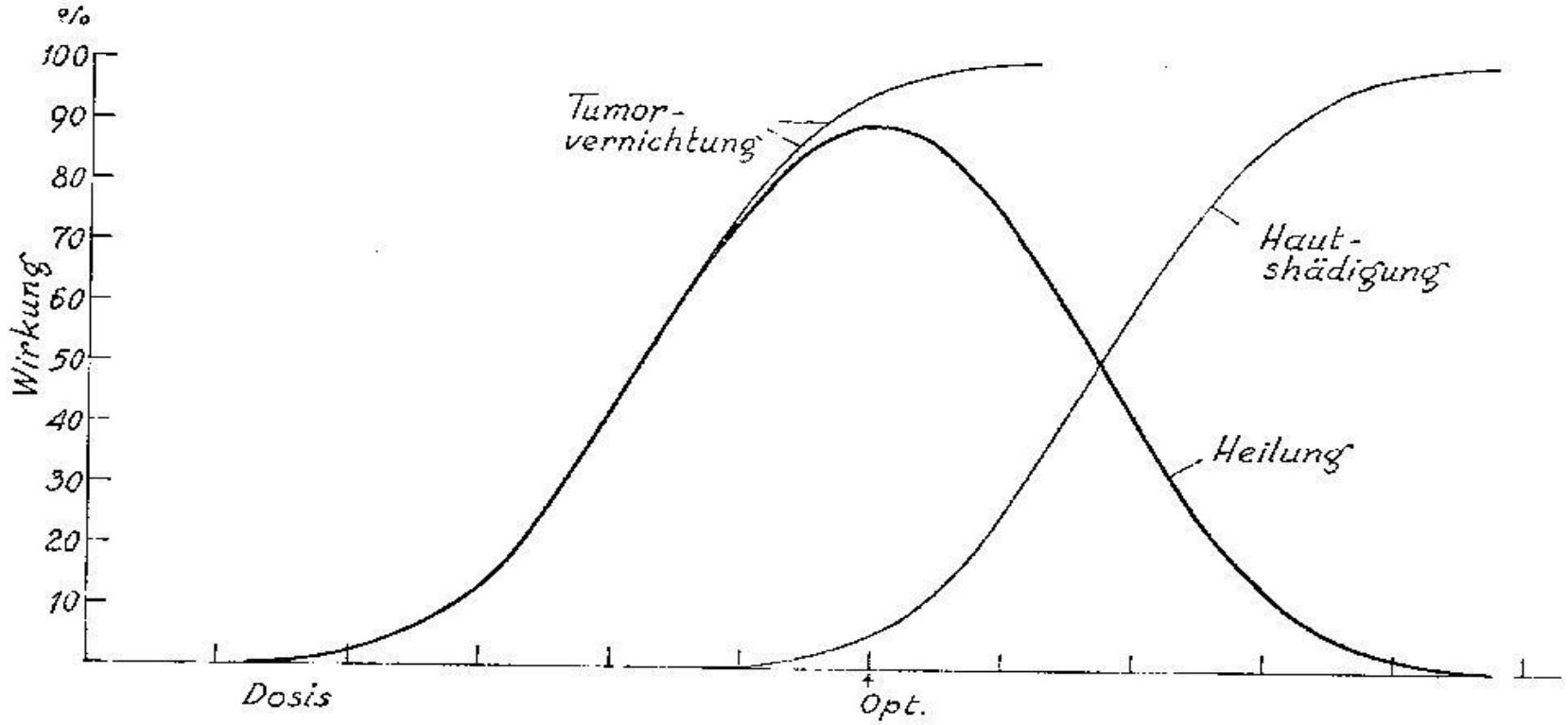
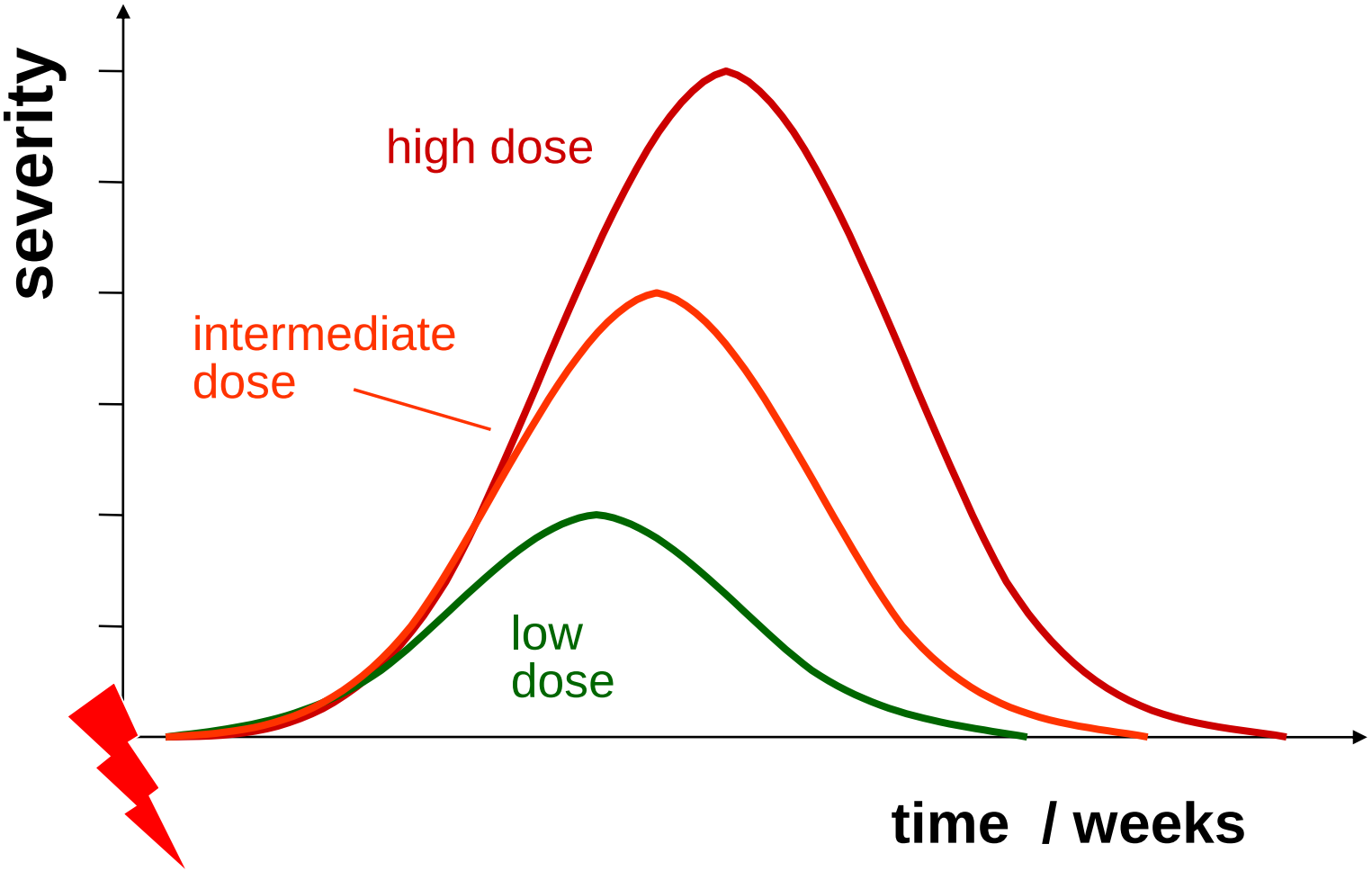


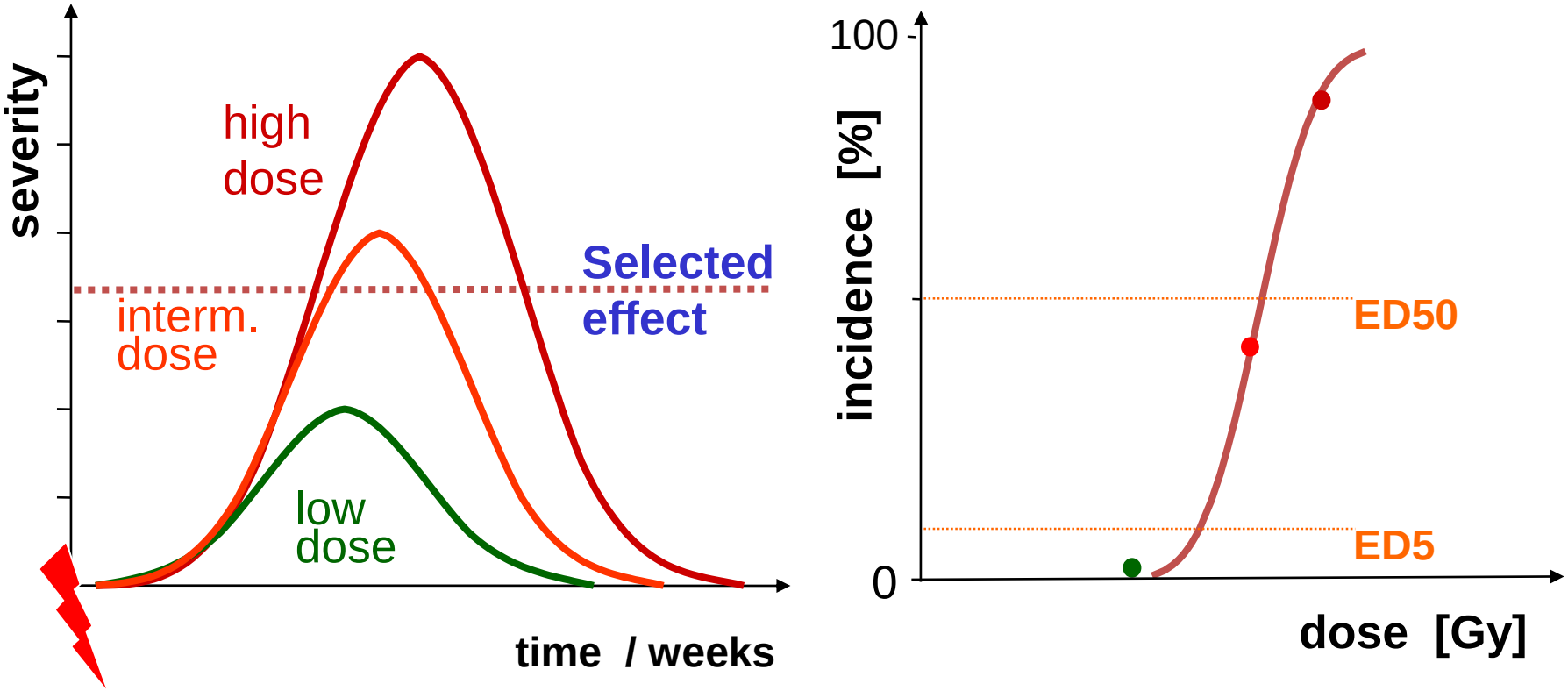
Abb. 2 a. Kurve über steigende prozentuale Tumorvernichtung bzw. chädigung und Heilung nach HOLTHUSEN

Turnover tissues: Clinical time course

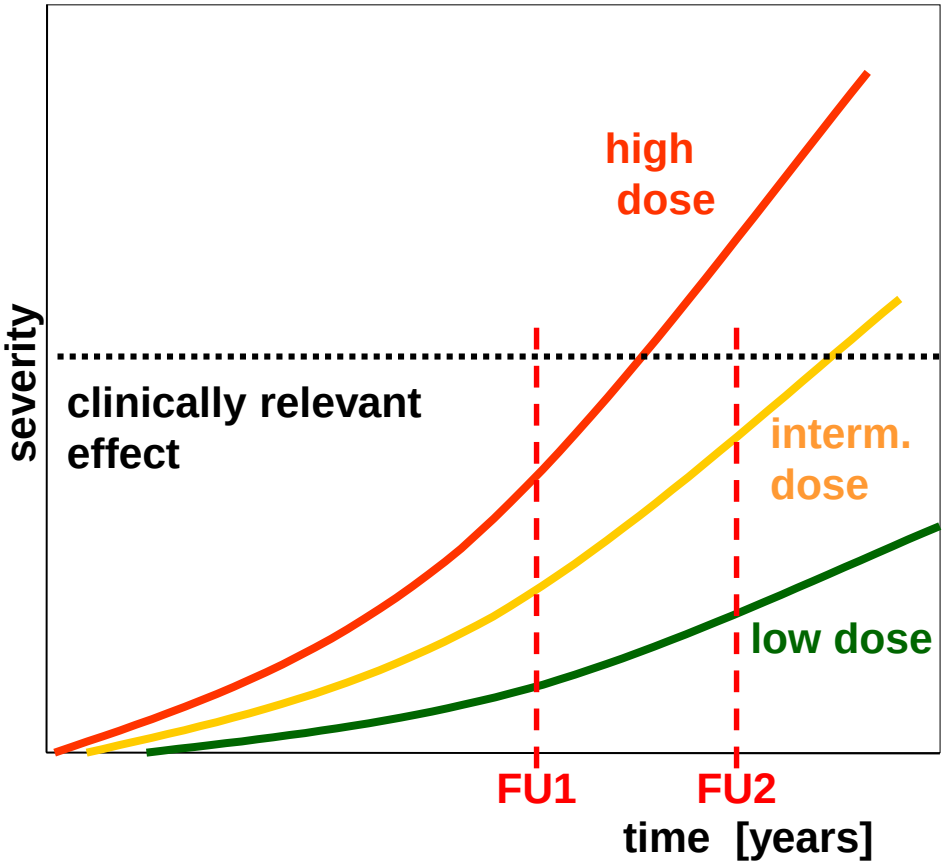


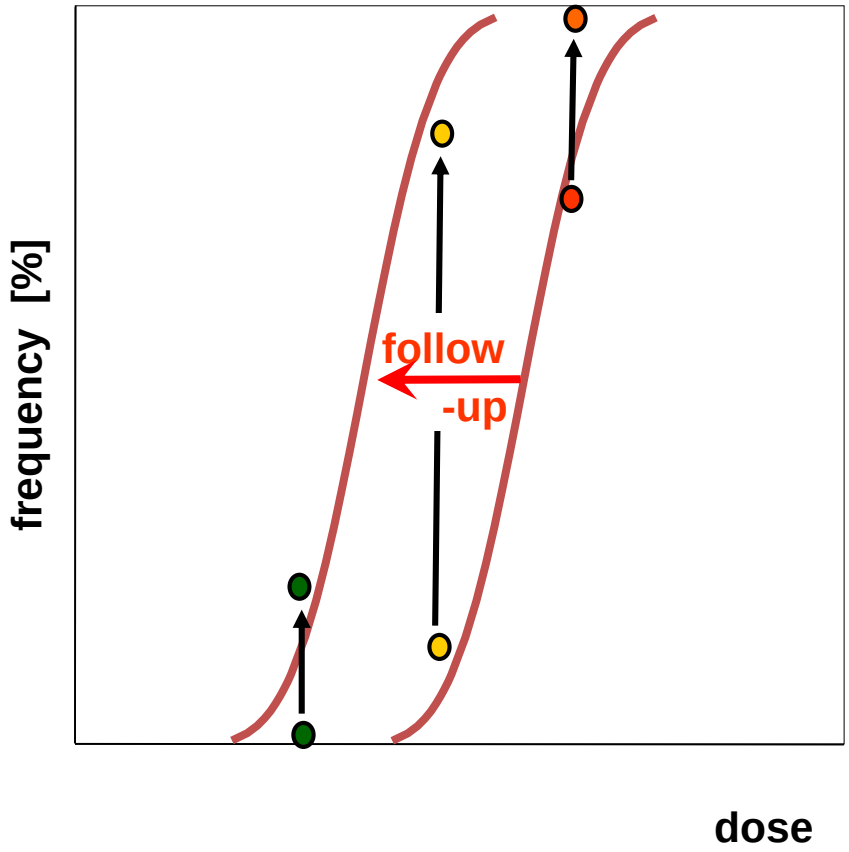
How to get a dose-effect relationship?

Quantalisation



Late effects – Dose-effect relationship





Tolerance doses for late responding tissues require information on the duration of follow up!

Second cancers after radiotherapy

the risk of radiotherapy-associated second cancers appears to

depend on radiation dose and radiation dose distribution in the critical organs

critical organs depend on age and sex.

Research on second cancers after radiotherapy

The popular method of pooling and averaging data from heterogeneous cohorts and pooling all types of cancer rather than studying organ-specific cancers for the reason of producing statistical significance is likely to produce biological and medical insignificance .

The undesired outcomes of radiotherapy

1. Local tumour recurrence
2. Early normal tissue damage
3. Late normal tissue damage
4. Second cancers (and other very late tissue damage)

Second primary cancers after adjuvant radiotherapy in early breast cancer patients: Danish Breast Cancer Cooperative Group

Trine Grantzau et al., Radiother.Oncol 106:42-49 (2013)

A Danish Cancer Registry – based cohort study on 46,176 breast cancer patients treated with/without postoperative radiotherapy according so sequential national protocols between 1982 and 2007.

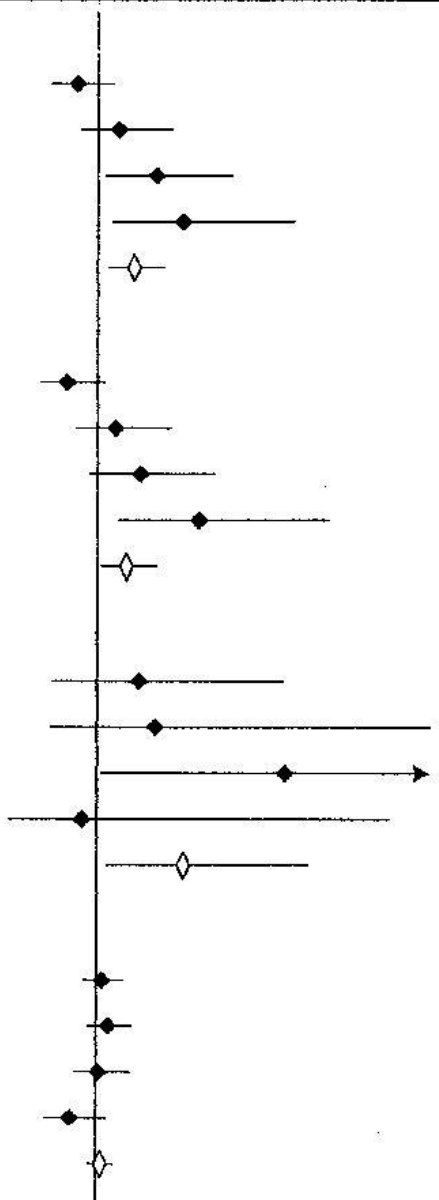
Second cancers (excluding second breast cancers) were identified in the Danish Cancer Registry

Study was part of the EU ALLEGRO Project)

Results:	yes	Radiotherapy	no
Patients	23,627		22,549
Median Latency so SPM	6 years		7 years
All second cancers		2,595	
Second cancers on potentially Irradiated sites		1,148	

SIRs after different follow-up were calculated

Second primary cancer site[1]	23,627 Irradiated women Obs	PY[2]	22,549 Non-Irradiated women Obs	PY	HR (95% CI)[3]
RT–associated sites[4]					
Latency 1–4 years	69	68,678	100	71,902	0.81 (0.58 - 1.14)
Latency 5–9 years	66	39,034	94	57,926	1.20 (0.86 - 1.69)
Latency 10–14 years	52	15,780	78	33,001	1.55 (1.08 - 2.24)
Latency >15 years	39	7,273	56	20,661	1.79 (1.14 - 2.81)
All	**226**	**130,765**	**328**	**183,490**	**1.34 (1.11 - 1.61)**
Lung					
Latency 1–4 years	52		88		0.72 (0.49 - 1.06)
Latency 5–9 years	57		84		1.17 (0.81 - 1.67)
Latency 10–14 years	41		70		1.40 (0.94 - 2.08)
Latency >15 years	36		50		1.94 (1.21 - 3.13)
All	**186**		**292**		**1.27 (1.04 - 1.55)**
RT–associated sites excl. lung					
Latency 1–4 years	17		12		1.39 (0.60 - 3.20)
Latency 5–9 years	9		10		1.54 (0.58 - 4.08)
Latency 10–14 years	11		8		2.74 (1.05 - 7.15)
Latency >15 years	3		6		0.86 (0.20 - 3.70)
All	**40**		**36**		**1.80 (1.10 - 2.95)**
Non RT–associated sites					
Latency 1–4 years	318		361		1.05 (0.89 - 1.25)
Latency 5–9 years	237		353		1.11 (0.93 - 1.32)
Latency 10–14 years	102		228		1.02 (0.81 - 1.31)
Latency >15 years	45		160		0.76 (0.53 - 1.09)
All	**702**		**1,102**		**1.04 (0.94 - 1.16)**



Second primary cancers after adjuvant radiotherapy in early breast cancer patients: Danish Breast Cancer Cooperative Group

Trine Grantzau et al., Radiother.Oncol 106:42-49 (2013)

Conclusion:

In absolute numbers, the risk of developing a radiation-induced second lung cancer remains relatively low and is equivalent to one radiation-induced cancer for every 200 women treated with radiotherapy.

A similar number is also estimated for radiation-induced fatal cardiac disease after treatment of breast cancer.

Risk of second primary lung cancer in women after radiotherapy for breast cancer
T.Grantzau et al., Radiother.Oncol. 111: 366-373 (2014)

A case-control study nested in the population-based cohort of 23.627 early breast cancer patients.

Cases were 151 cases of second primary lung cancer

Compared with 443 individually matched controls

Individual dose reconstructions were performed and the dose delivered to the centre of the second lung cancer determined (and the same location in controls).

Relative risk of second lung cancer increased by 8.5% per Gy.

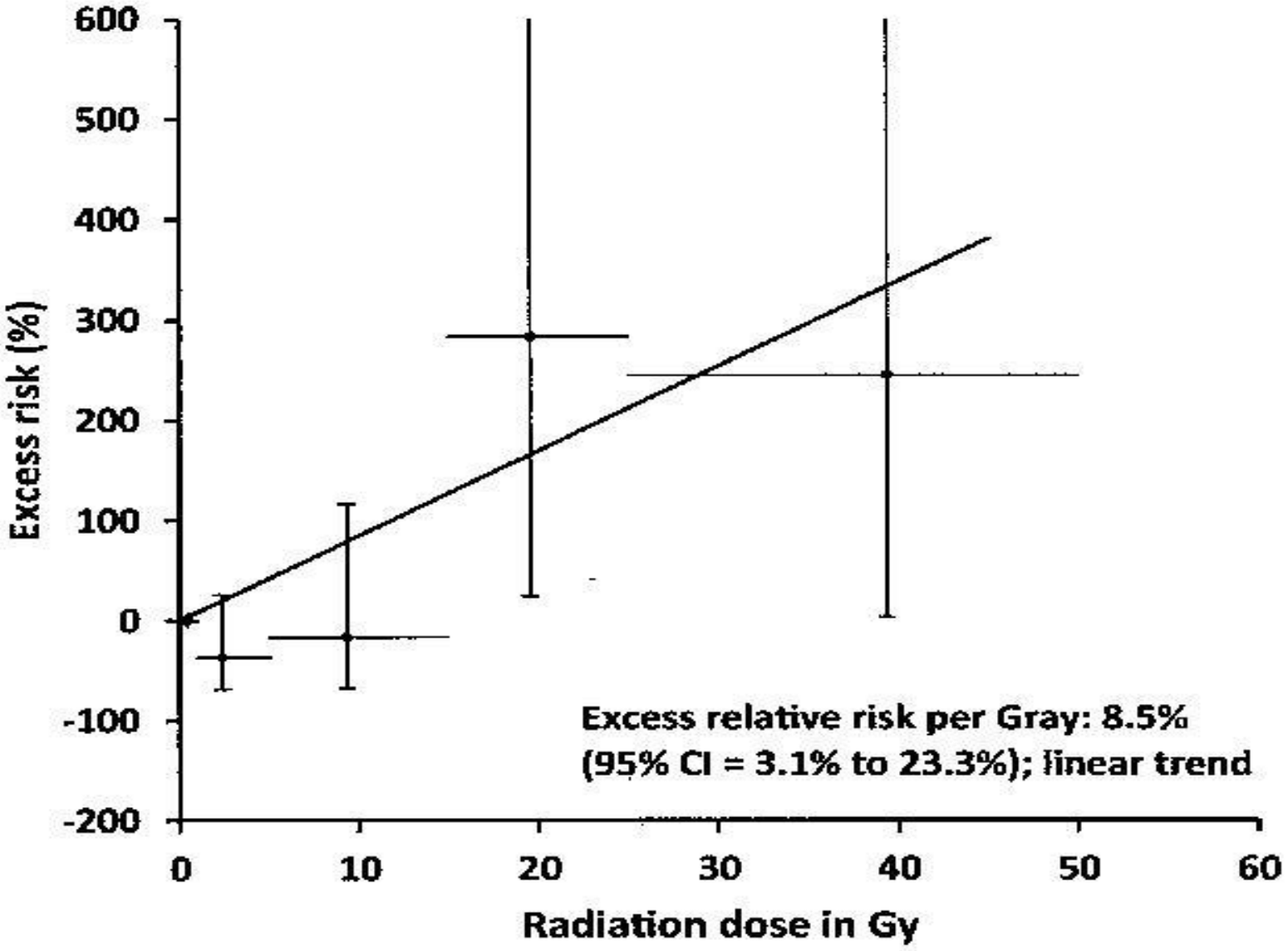
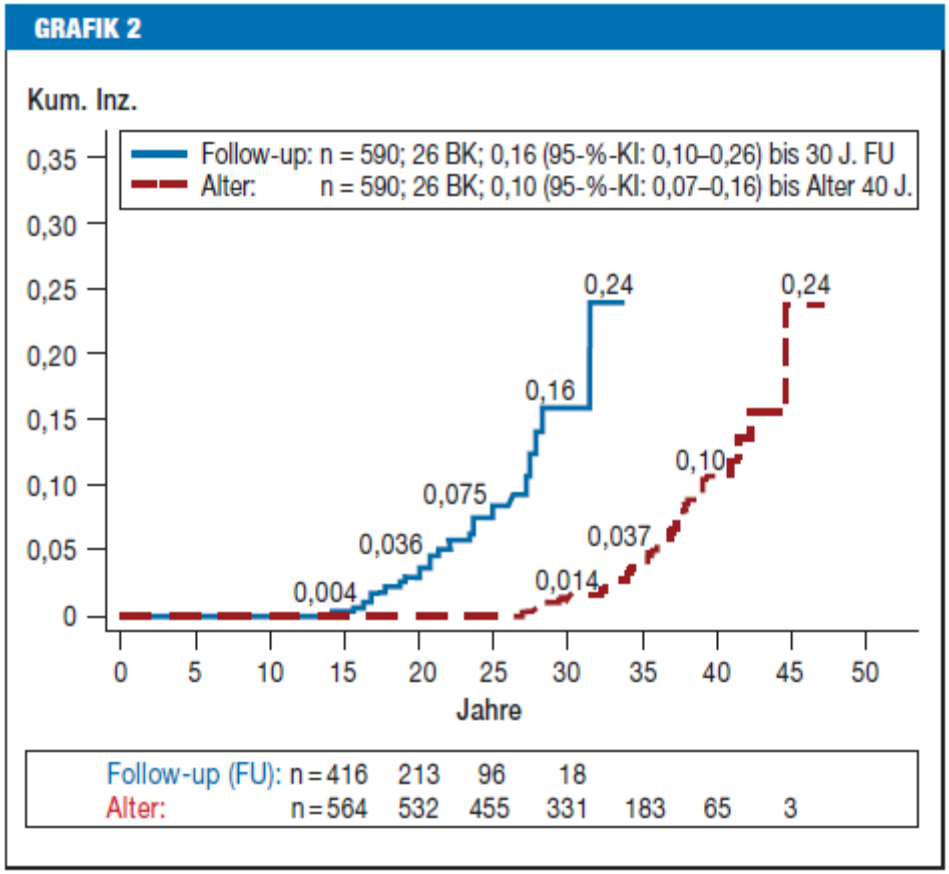


Fig. 2. Estimated excess risk and 95% confidence interval of second primary lung

G. Schellong et al. (2014): Brustkrebs bei jungen Frauen nach Therapie eines Hodgkin Lymphoms im Kindes- und Jugendalter. Deutsches Ärzteblatt 111: 3 - 9

- Long-term follow-up of 590 female patients treated in childhood or adolescence for Hodgkin‘s disease within 5 consecutive randomized clinical trials between 1975 and 1995.
- Median follow-up 17.8 years, maximal follow-up 33.7 years
- 26 primary breast cancers diagnosed, between 14 and 31 years after radiotherapy. 25/26 were located in the treatment field which received between 20 and 45 Gy.
- The cumulative incidence of breast cancer at an attained age of 40 years was 10%, the standard incidence ratio was 25.
- The risk in women developing breast cancer after radiotherapy for Hodgkin‘s disease is similar to the risk of women carrying a BRCA-2 mutation.

G. Schellong et al. (2014) Reported cumulative incidences for secondary breast cancers from studies on childhood cancer. Deutsches Ärzteblatt 111: 3 - 9



French English Childhood Cancer Survivor Study

Diallo, I. and 10 other authors, senior author F.de Vathaire, International Journal of Radiation Oncology Biology Physics 74:876-883 (2009)

- Location of second cancers in relation to dose

Fatal second cancers		Location		
		in beam	border	distant
all	(115)	14	76	25
sarcomas	(52)	10	36	6
breast ca	(13)	1	9	3
CNS	(10)	0	4	6
thyroid	(17)	2	11	4

Second cancers after radiotherapy of prostate cancer

Brenner et al., Cancer 88: 398-406 (2000)

Out of the approximately 17,000 prostate cancer patients who survived more than five years after curative radiotherapy, 1.185 developed a second primary cancer.

More than 1,000 of those second cancers are due to cure from the first cancer and the subsequent increased life span of the cancer patients.

Approximately 120 to 150 of those second cancers among 51,584 prostate cancer patients are related to radiotherapy, i.e.:

approximately 50 cases of bladder cancer
approximately 15 cases of cancer of the rectum
approximately 50 cases of lung cancer
approximately 12 cases of leukaemia



Friedrich Dessaue in verschiedenem Alter

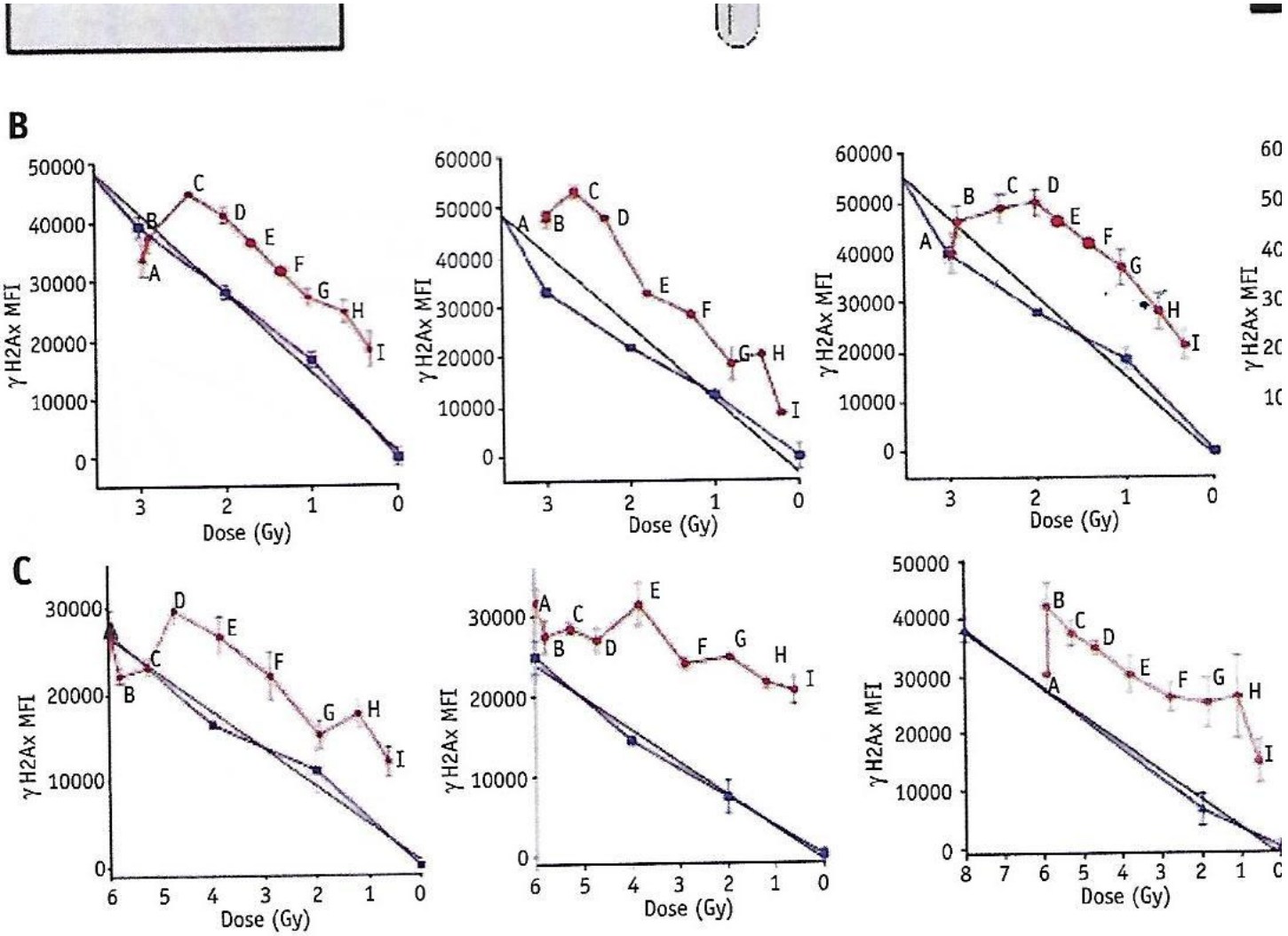
Three mechanisms leading to second cancers after radiotherapy

Dose	pathogenic mechanisms	organs
1. > 50 Gy threshold	consequential to late normal tissue damage: atrophy>hyperproliferation >chronic inflammation	e.g.rectum bladder in adults
2. 20-40 Gy threshold?	target cells:mesenchymal stem cells? Soft tissue sarcomas.Very little research	Specific for children
3. < 20 Gy? LNT ?	Mutation Initiation Progression etc. Carcinomas in children and adults	Lung, breast, thyroid et al.

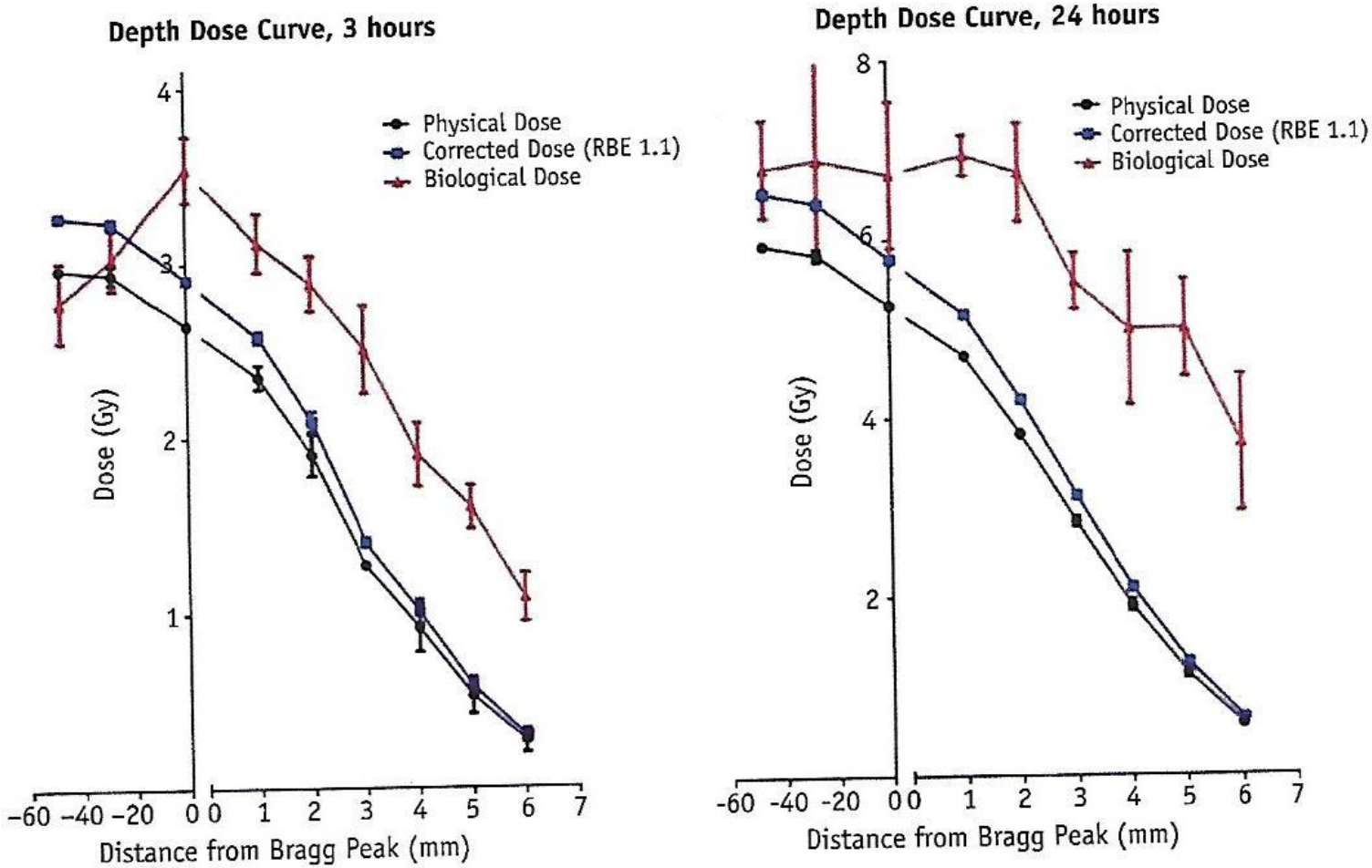
Radiobiological aspects of radiation-induced second cancers after particle radiotherapy

Organ / tissue weighting factors which have been proposed by ICRP for cancer risk estimations in the general population should not be used in medical radiation exposures.

Cuaron JJ et al: Exponential increase in RBE along distal edge of a Bragg peak as measured by DNA double stand breaks. Int J Radiat Incol Biol Phys 93: 62 (2016)



Cuaron JJ et al: Exponential increase in RBE along distal edge of a Bragg peak as measured by DNA double stand breaks. Int J Radiat Incol Biol Phys 93: 62 (2016)



distal edge, using calculated relative biologic

Incidence of Second Malignancies among patients treated with proton versus photon radiation

Chung, C.S. et al, Int.J.Radiat.Oncol.Biol.Phys. 2013

Study design: Out of 5,398 patients treated between 1973 and 2001 at the Harvard Cycloton, 558 patients were selected and compared with individually matched 558 patients taken from the data basis of the SEER registry to look for second new malignancies.558 patients were treated for the following first cancers: one-third brain, one-third prostate, one-quarter head and neck. Mean follow-up 6.7 years.

29 SMC after proton, 42 SMC after photon radiotherapy

Adjusted hazard ratio: 0.52

Incidence of Second Malignancies among patients treated with proton versus photon radiation

Chung, C.S. et al, Int.J.Radiat.Oncol.Biol.Phys. 2013

More results:

- Among proton patients 10 SMN occurred within 5 years, among photon patients 24.
- 2 out of 29 SMN occurred in the PTV after protons

  7 out of 42 SMN after photons (5/186 after photon treatment of prostate cancer)
- In 44 pediatric proton patients no SMN developed after mean follow-up of 4 years, In 44 pediatric photon patients no SMN developed after mean follow-up of 4 years.

Animal experiments to study the RBE of neutrons for cancer incution

1. Oak Ridge National Laboratory, USA: Ullrich et al. 1977 and many to follow
2. Argonne National Laboratory, USA: Grahn et al. 1992
3. ENEA-CRE Casaccia Rome, Italy: Covelli et al. 1988
4. CEA Fontenay-aux-Roses, France: Lafuma et al, 1989, reanalysed 2000

Ullrich RL: Tumor induction in BALB/c female mice after fission neutron or gamma irradiation. Lung cancer Rad.Res.92:506(1983)

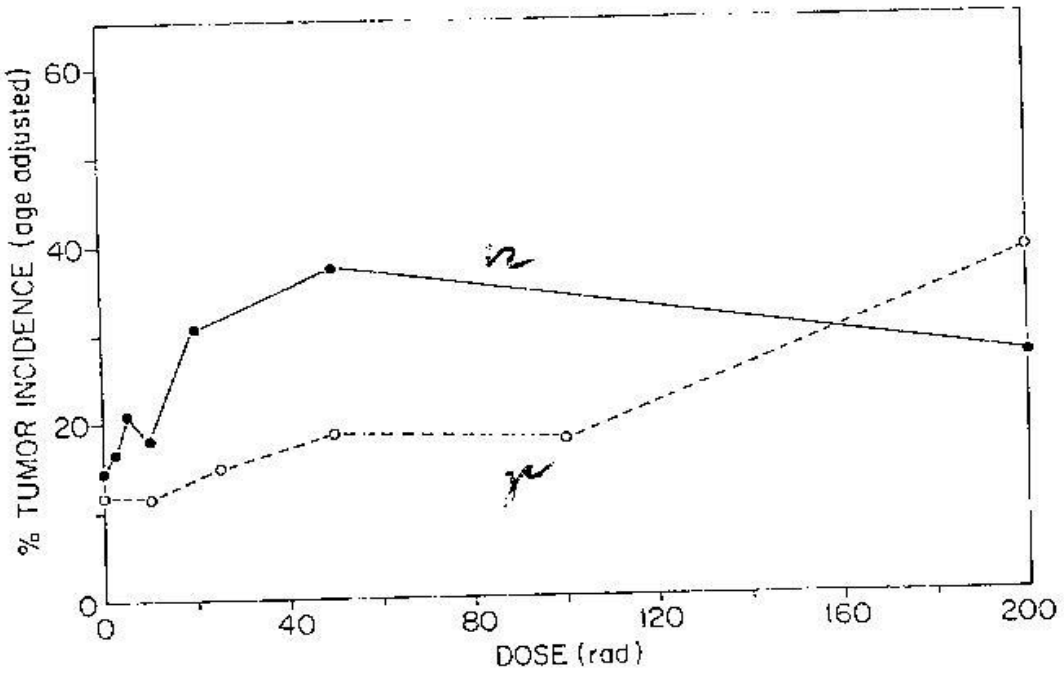


FIG. 3. Incidence of lung adenocarcinomas in female BALB/c mice as a function of dose after fissio neutron (●) or ^{137}Cs γ (○) irradiation.

Ullrich RL: Tumor induction in BALB/c female mice after fission neutron or gamma irradiation. Breast cancer Rad.Res.92:506(1983)

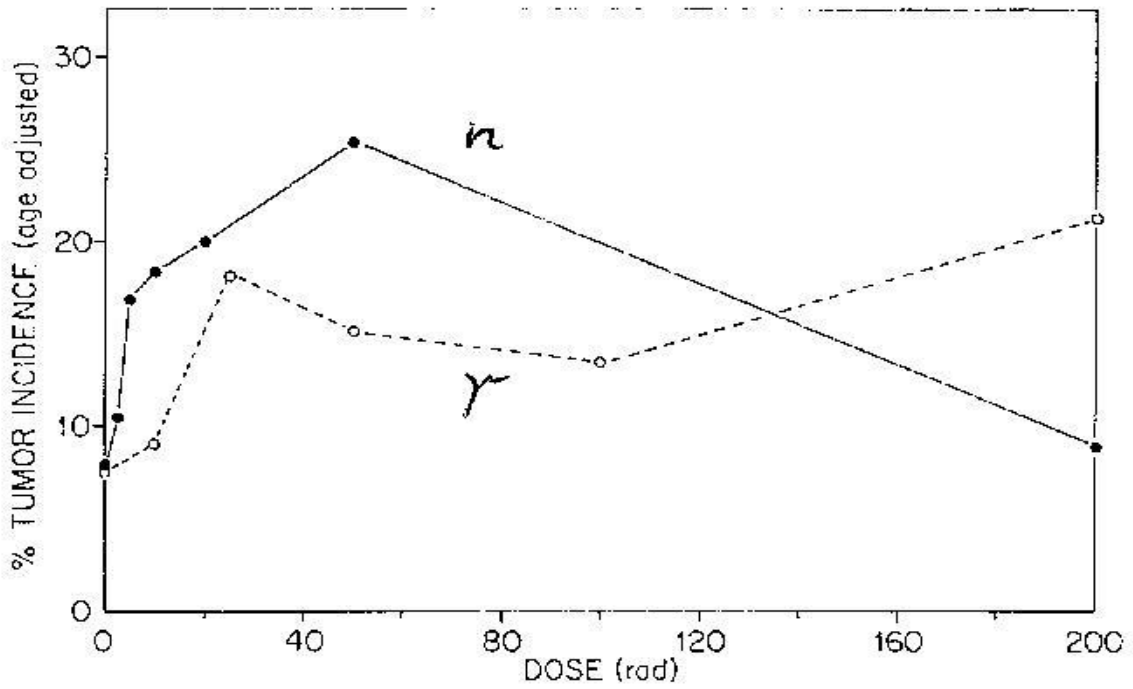


FIG. 2. Incidence of mammary adenocarcinomas in female BALB/c mice as a function of dose fission neutron (●) or ^{137}Cs γ (○) irradiation.

Grahn D et al.: The comparative tumorigenic effects of fission neutrons and cobalt-60 rays in the B6CF1 mouse. Radiat Res. 129: 19 (1992)

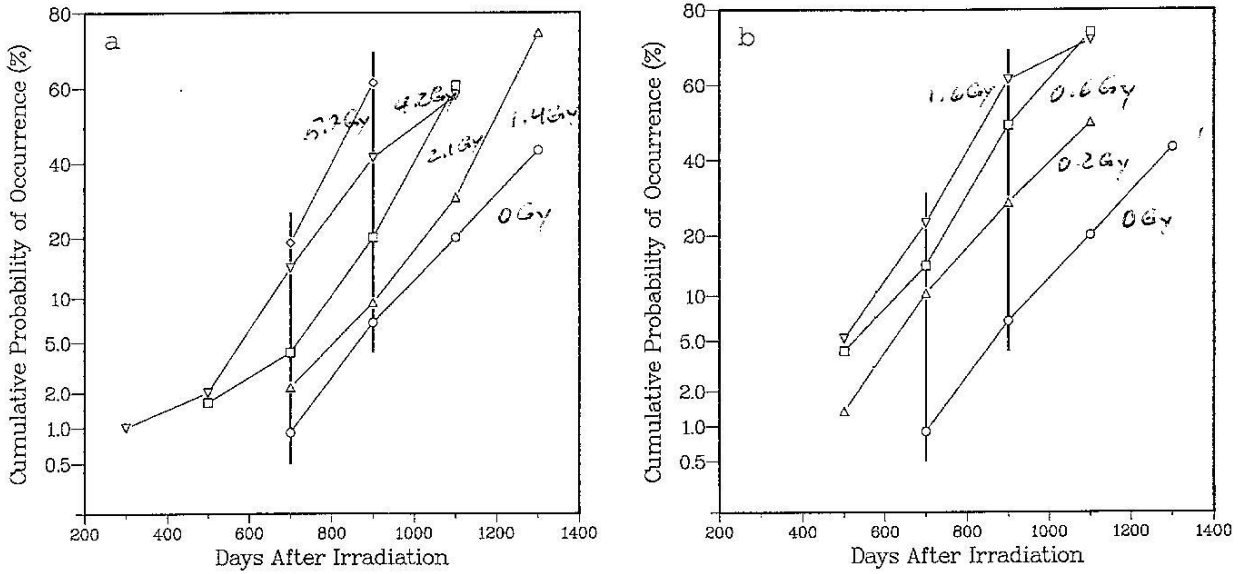


FIG. 3. Cumulative risks of occurrence versus age for selected data from experiment B (see Fig. 2). Vertical bars indicate the data points used for dose–response analysis. (a) Gamma radiation: (○) 0 Gy, (△) 1.43 Gy, (□) 2.06 Gy, (▽) 4.17 Gy, (◇) 5.69 Gy; (b) neutron irradiation: (△) 0.2 Gy, (□) 0.6 Gy, (▽) 1.6 Gy.

Covelli V et al.: Tumor induction and life shortening in BCeF female mice at low doses of fast neutrons and

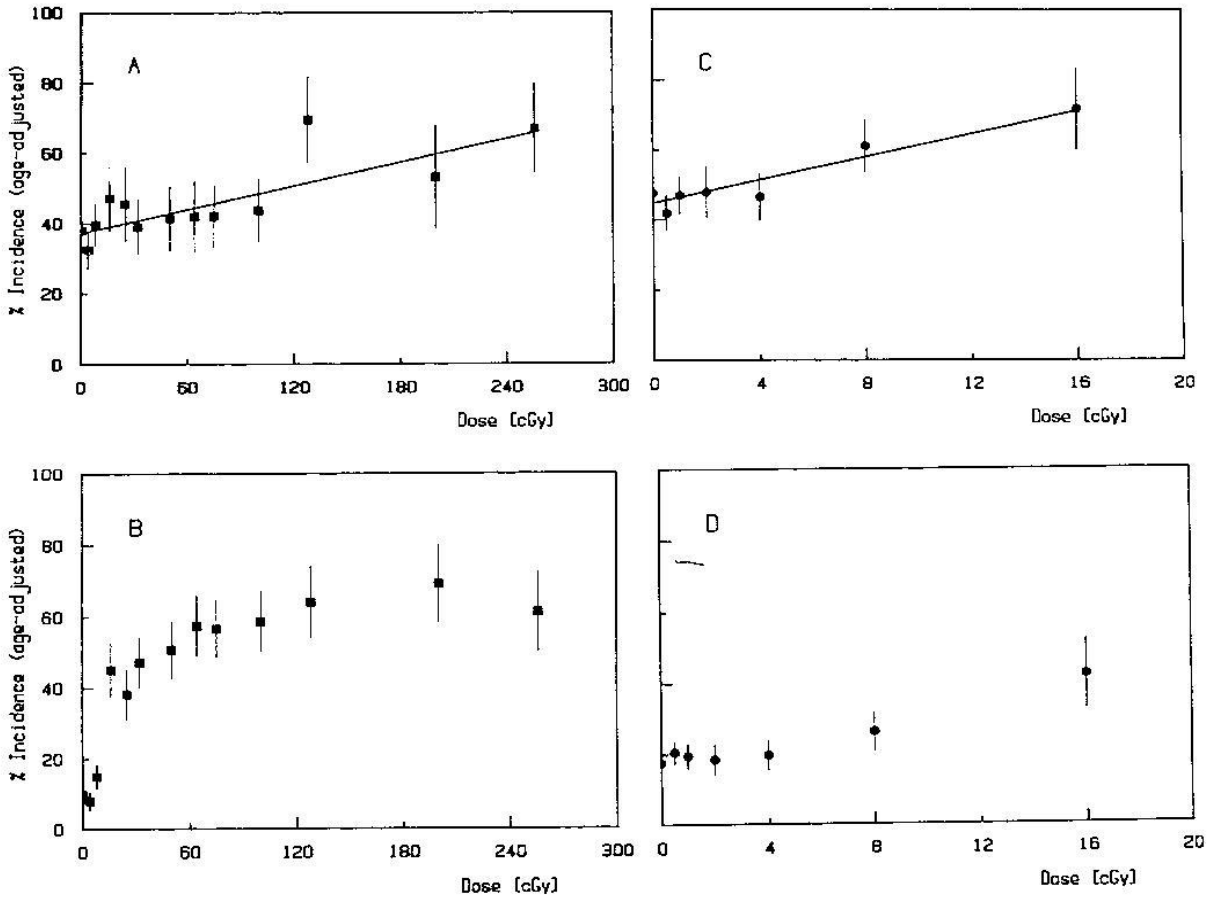
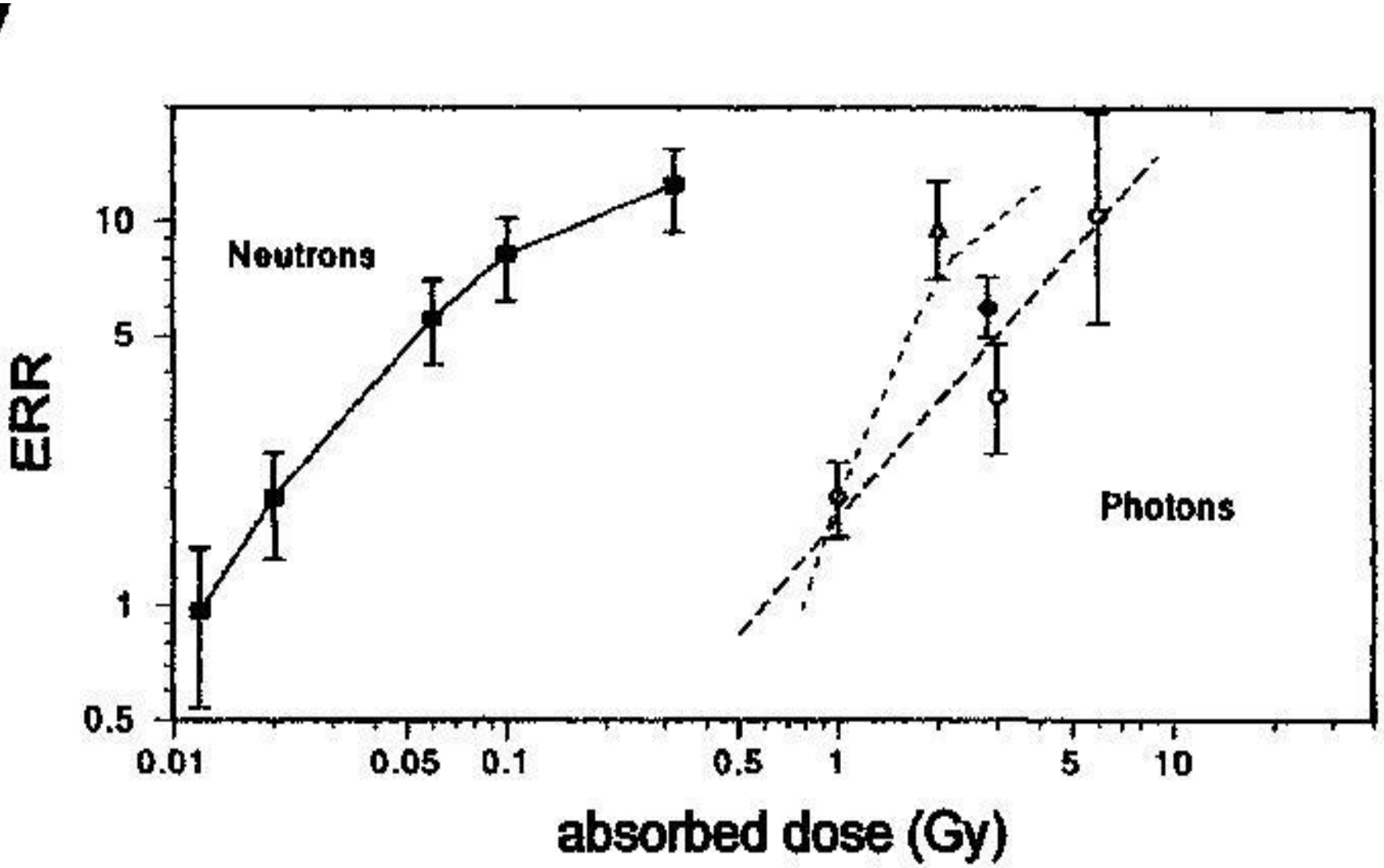


FIG. 1. Percentage incidences of solid tumors induced in mice irradiated with X rays (A) and neutrons (C). Fitted curves correspond to the linear dose–response model (see text). B and D show data of ovarian tumor induction after X and neutron irradiation, respectively. Bars are standard errors.

Neutron RBE for induction of tumors with high letality in Sprague Dawley rats.
Wolf, C., Lafuma, masse, R, Moris, M., Kellerer, A.M.J., Radiat.Res. 154:412-420 (2000)



Coggle J: Lung tumour induction in mice after X-rays and neutrons. Int.J.Radiat.Biol. 53:585 (1988)

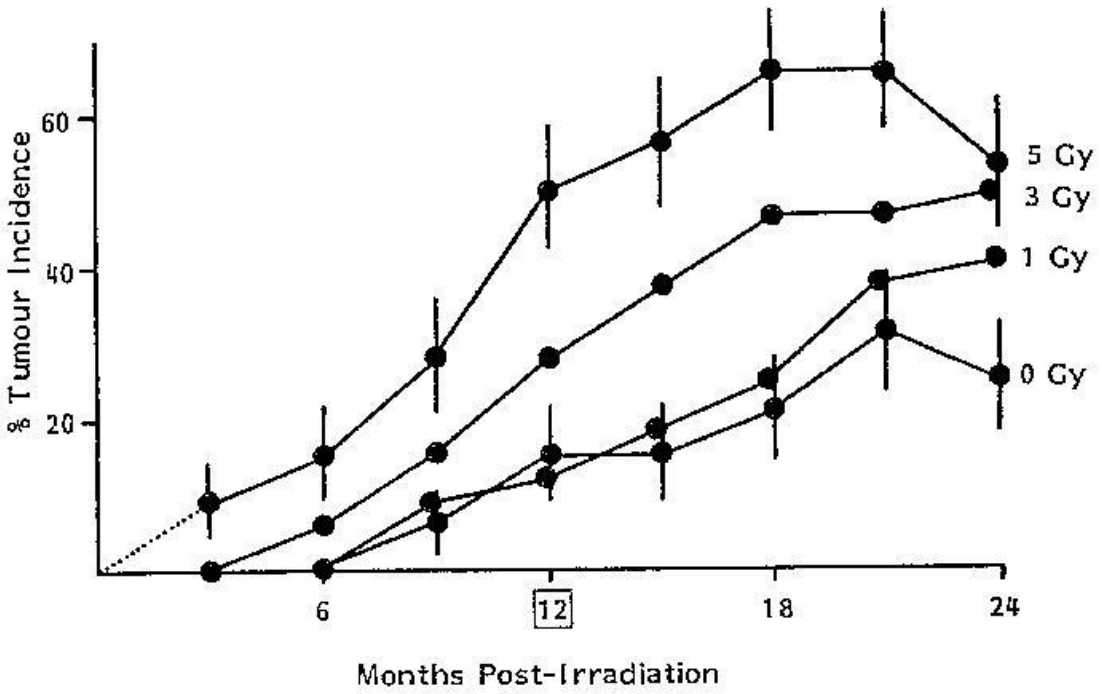


Figure 1. Lung tumour incidence (±SE) in SAS/4 male mice as a function of time in controls (0 Gy) and mice given 1, 3 and 5 Gy of X-rays.

Coggle J: Lung tumour induction in mice after X-rays and neutrons. Int.J.Radiat.Biol. 53:585 (1988)

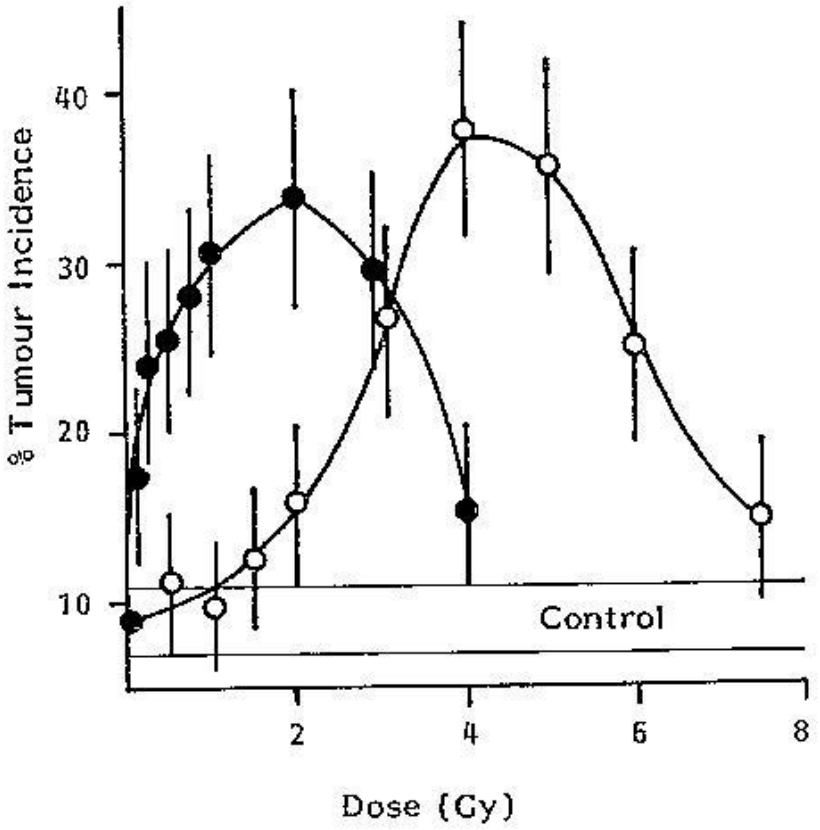


Figure 4. Lung tumour incidence (±SE) in SAS/4 female mice as a function of absorbed doses of X-rays (○) and cyclotron neutrons (●).

Hollander CF, Zurcher C, Broerse JJ: Tumorigenesis in High-Dose Total Body Irradiated Rhesus monkeys, a Life Span Study

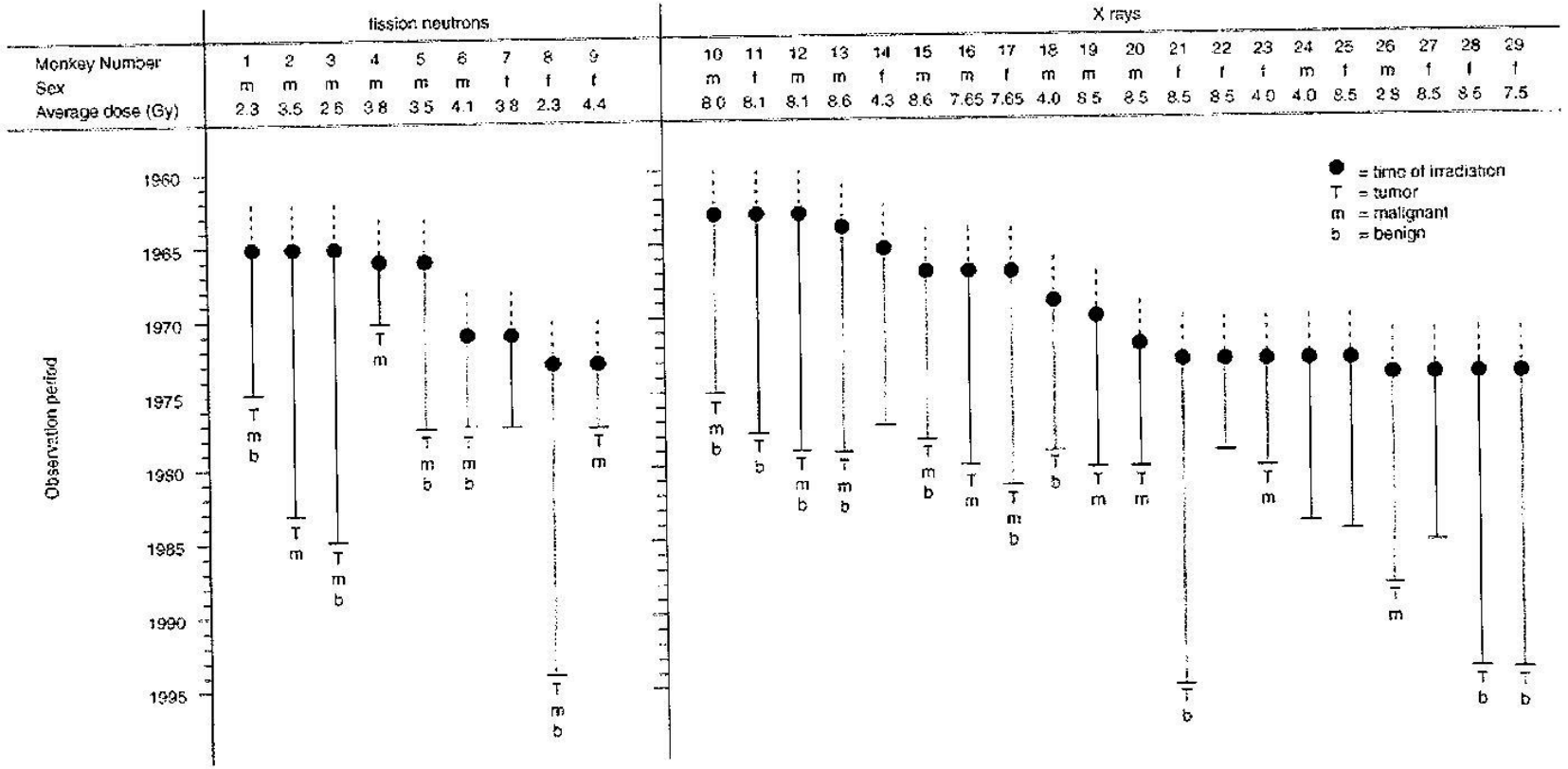
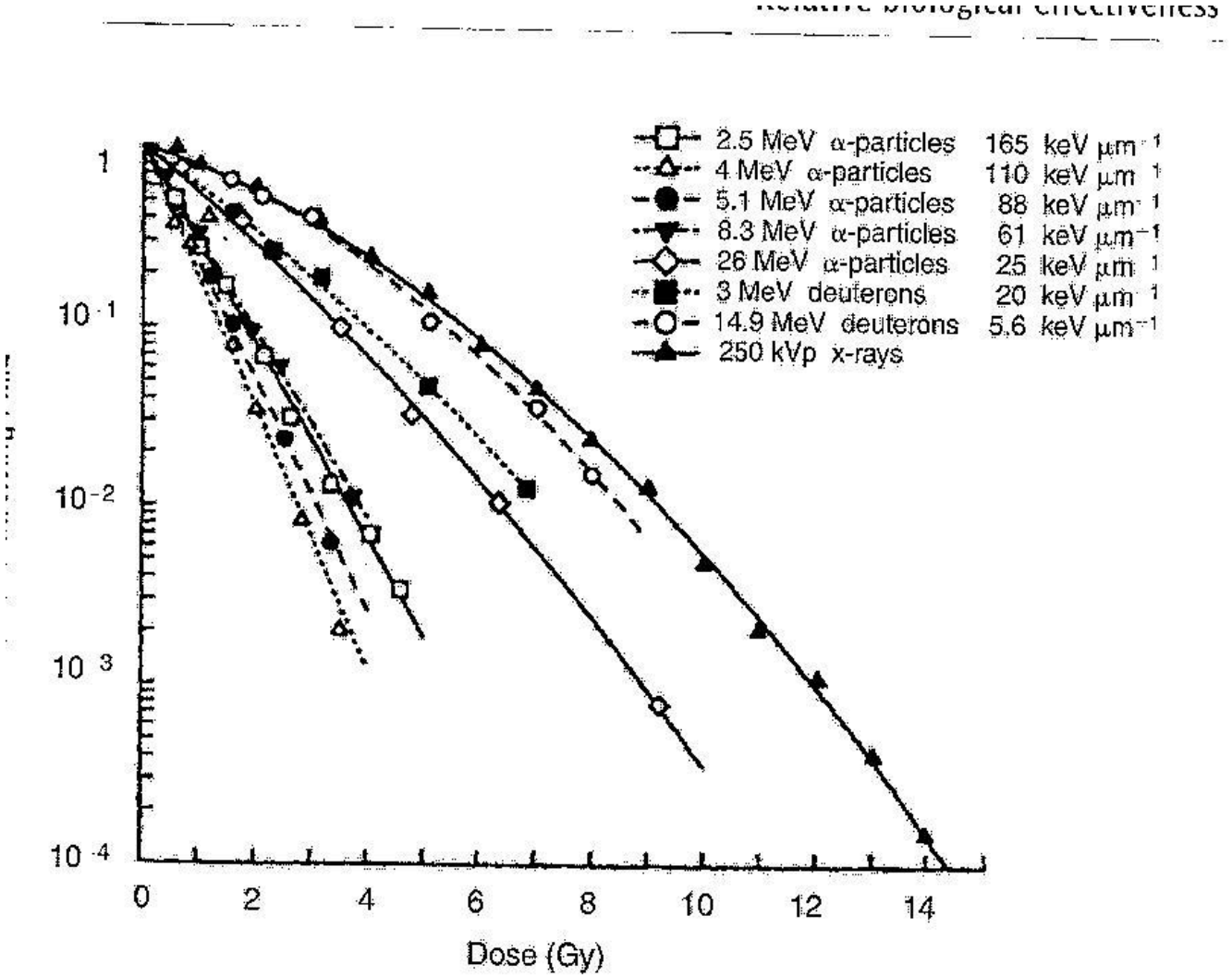
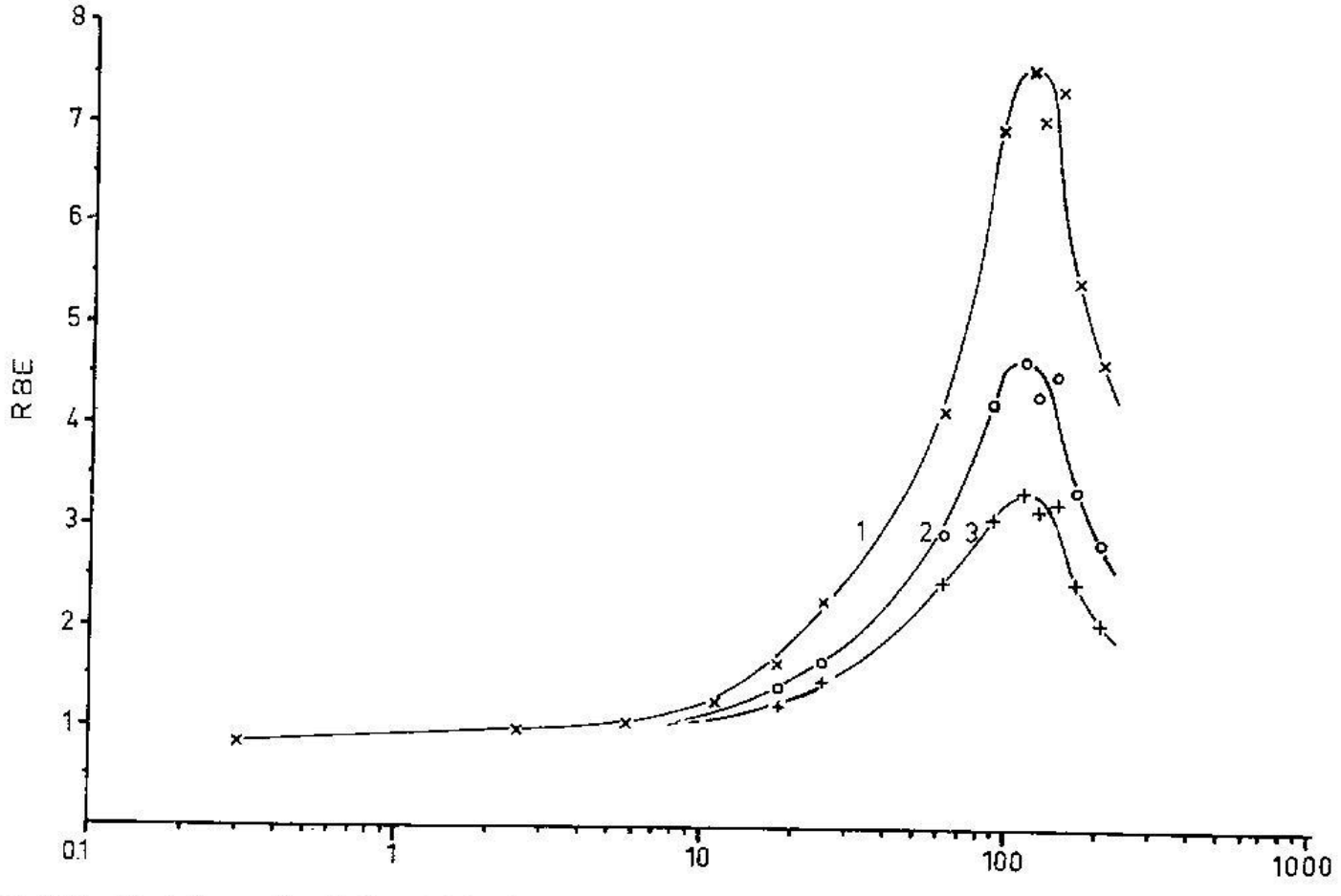


FIGURE 1.—Tumor incidence and post-irradiation observation periods for long-term surviving Rhesus monkeys of two genders (f: females and m: males) after whole-body irradiation and bone marrow transplantation. The dashed portions of the lines indicate the approximate age of monkeys before entering the experiment. Time of irradiation (●) and time of death with malignant (Tm) and/or benign (Tb) tumors are indicated.

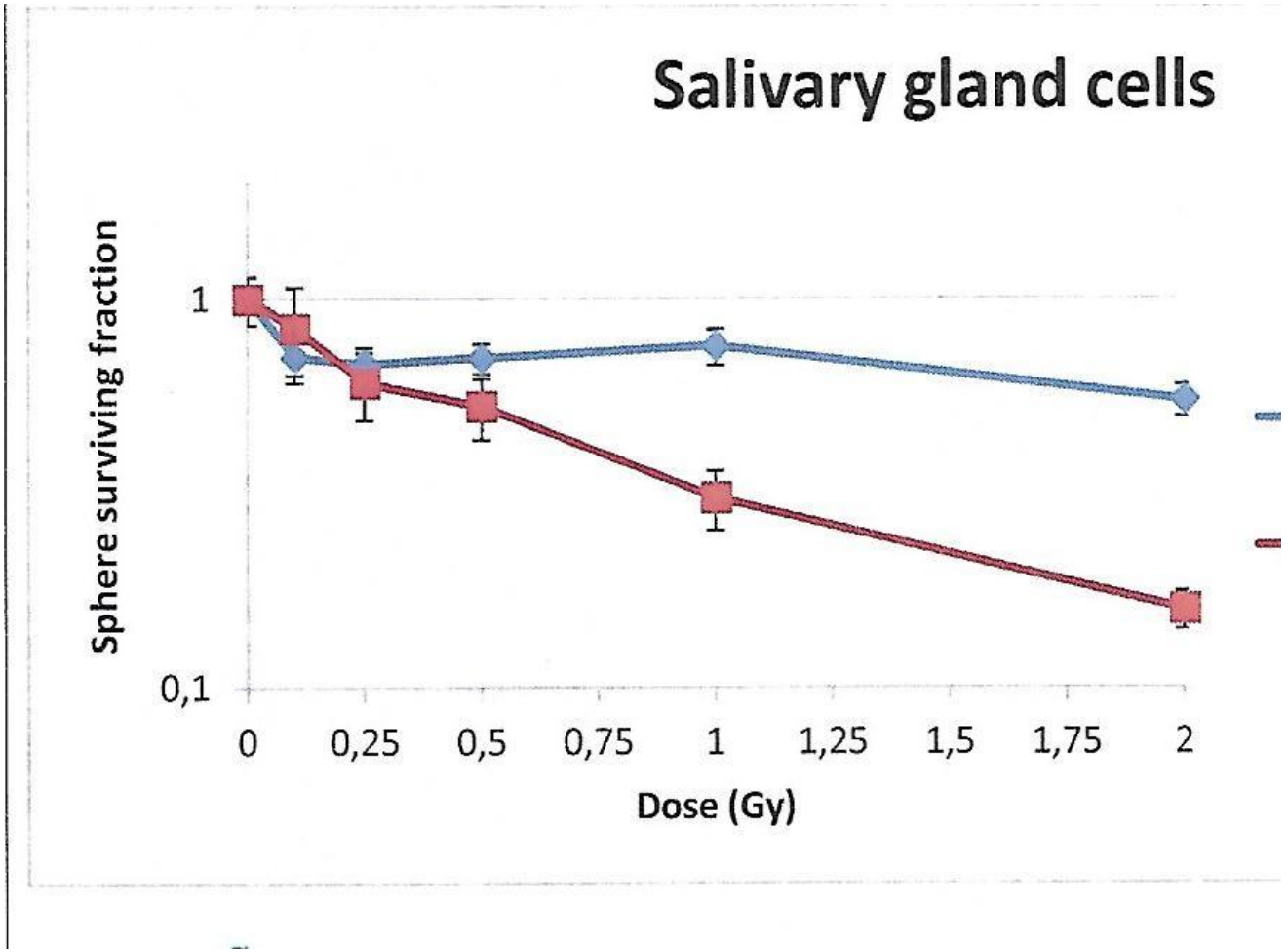
Barendsen E. in Current Topics of Radiation Research 4:293 (1968)



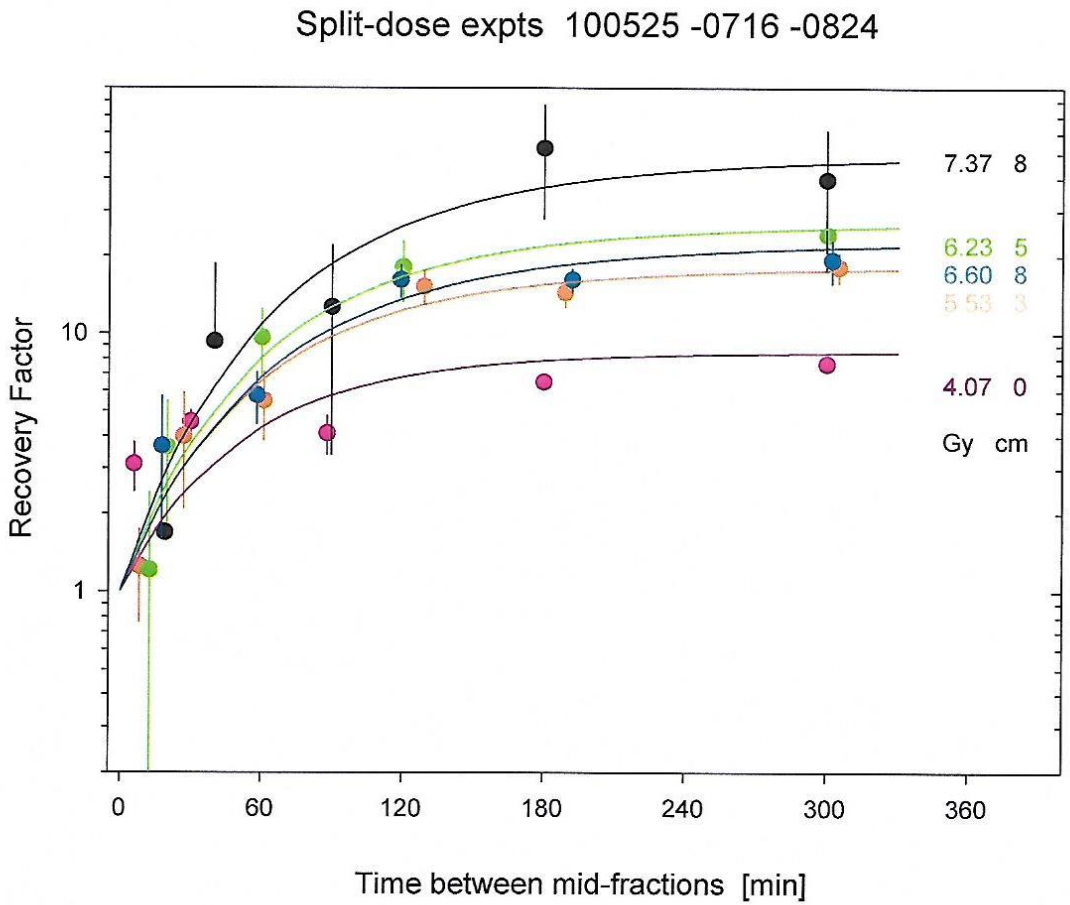
Barendsen E in Current Topics of Radiation Research 4:293 (1968)



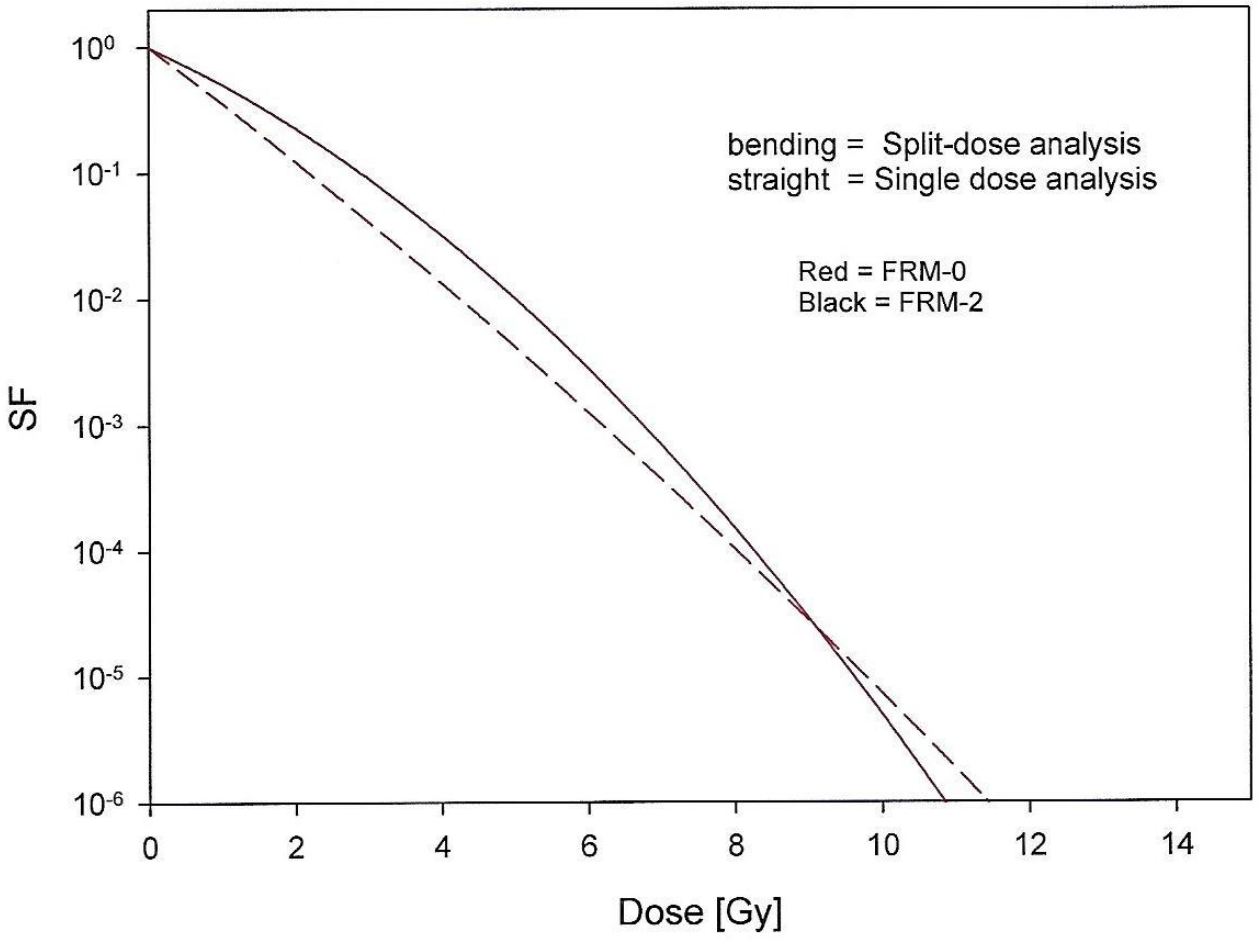
ANDANTE: Coppes R et al:
Sphere forming fraction one week after irradiation of salivary gland stem cells with X-rays or neutrons



Split dose irradiation with the therapeutic neutron beam from the TUM FRMII and recovery from sublethal radiation damage



Linear quadratic fit of single dose results and of split dose results of clonogenic cell survival after irradiation with the therapeutic neutron beam from FRMII



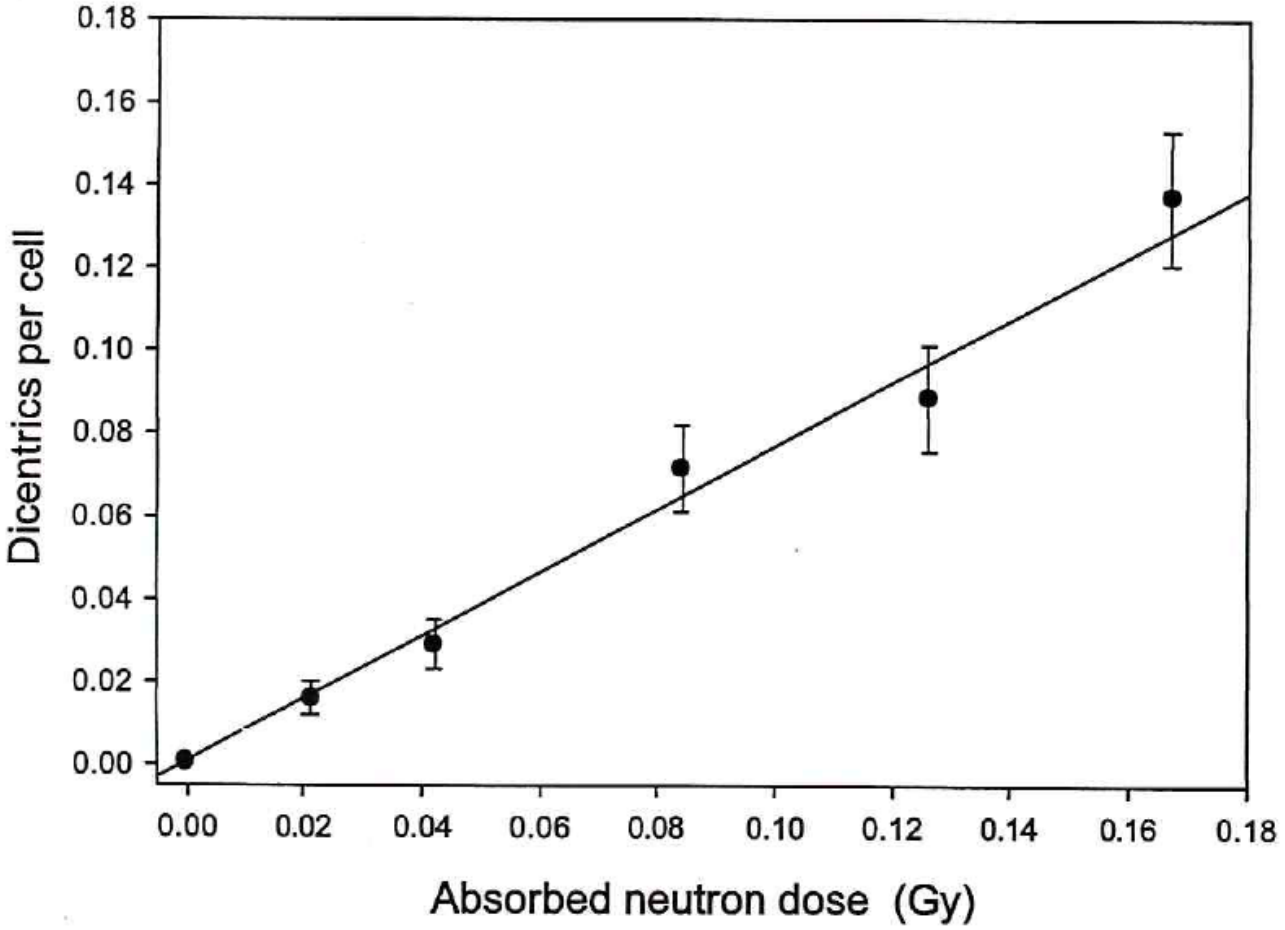


Figure: Dose dependence for the yield of dicentrics induced by monoenergetic neutrons at 565 keV energy.

Schmid E et al.: RBE of 144 kev neutrons in producing dicentric chromosomes in human lymphocytes.. Rad.Res.157:453(2002)

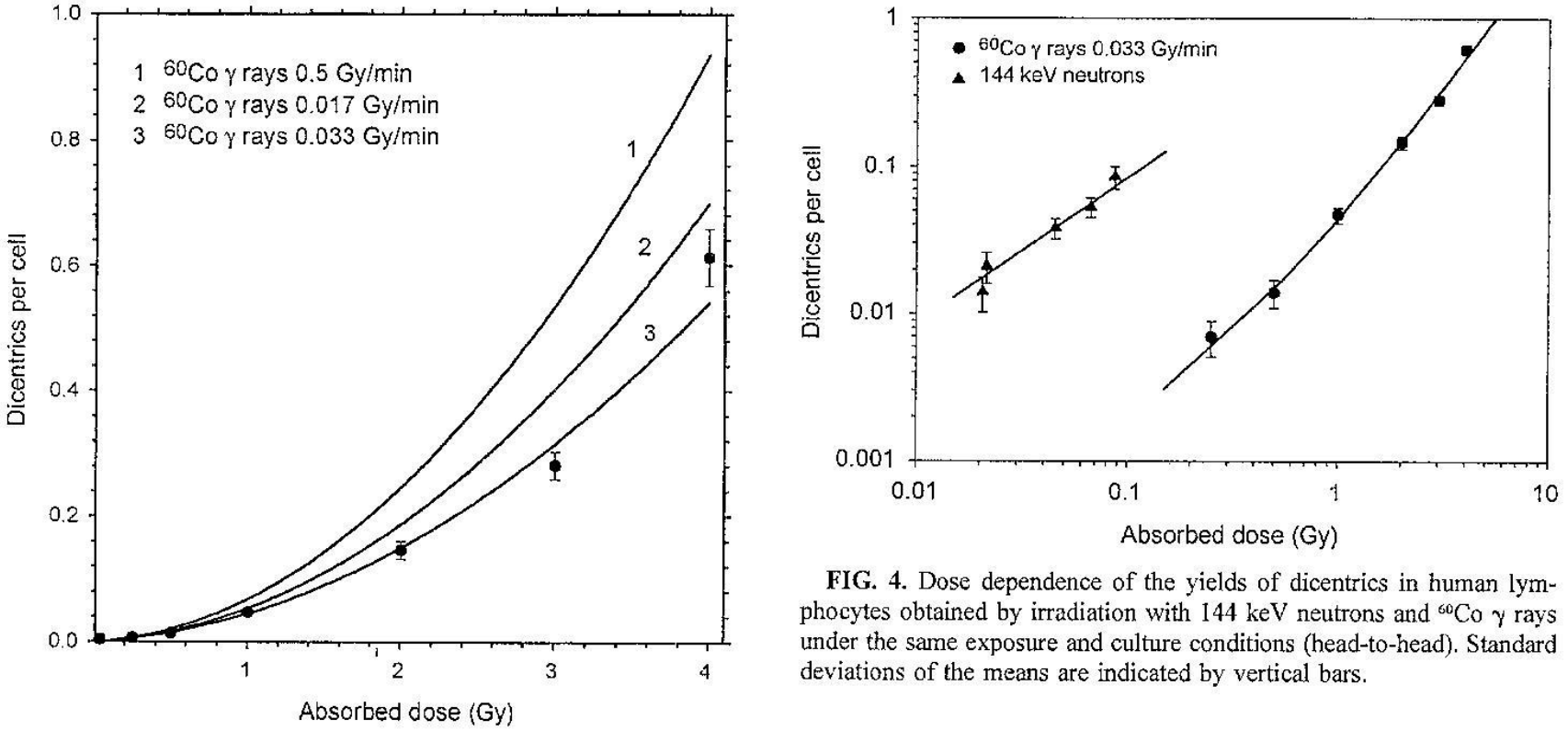
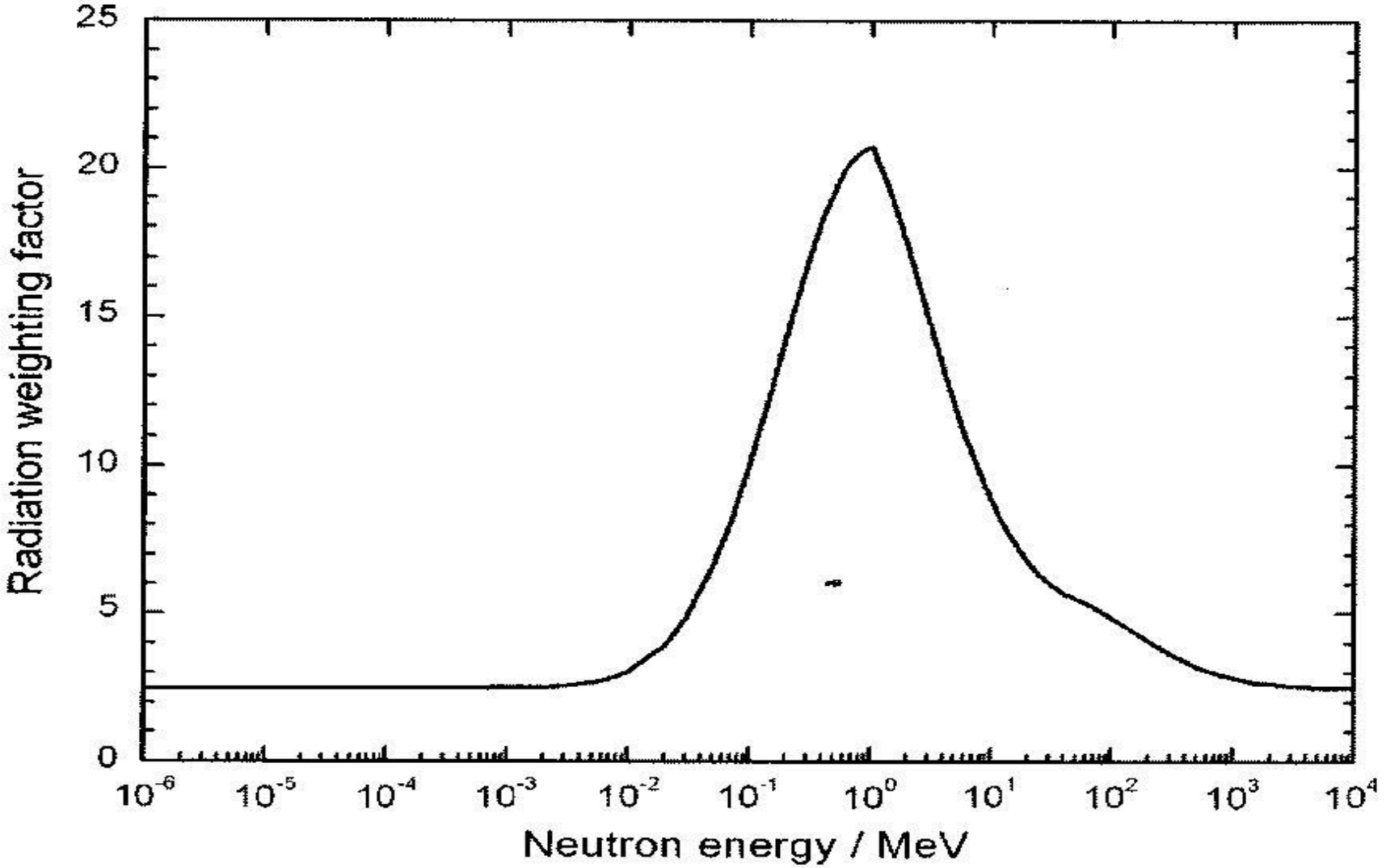


FIG. 4. Dose dependence of the yields of dicentrics in human lymphocytes obtained by irradiation with 144 keV neutrons and ^{60}Co γ rays under the same exposure and culture conditions (head-to-head). Standard deviations of the means are indicated by vertical bars.

Radiation weighting fctor as a function of neutron energy
ICRP 103 (2007)

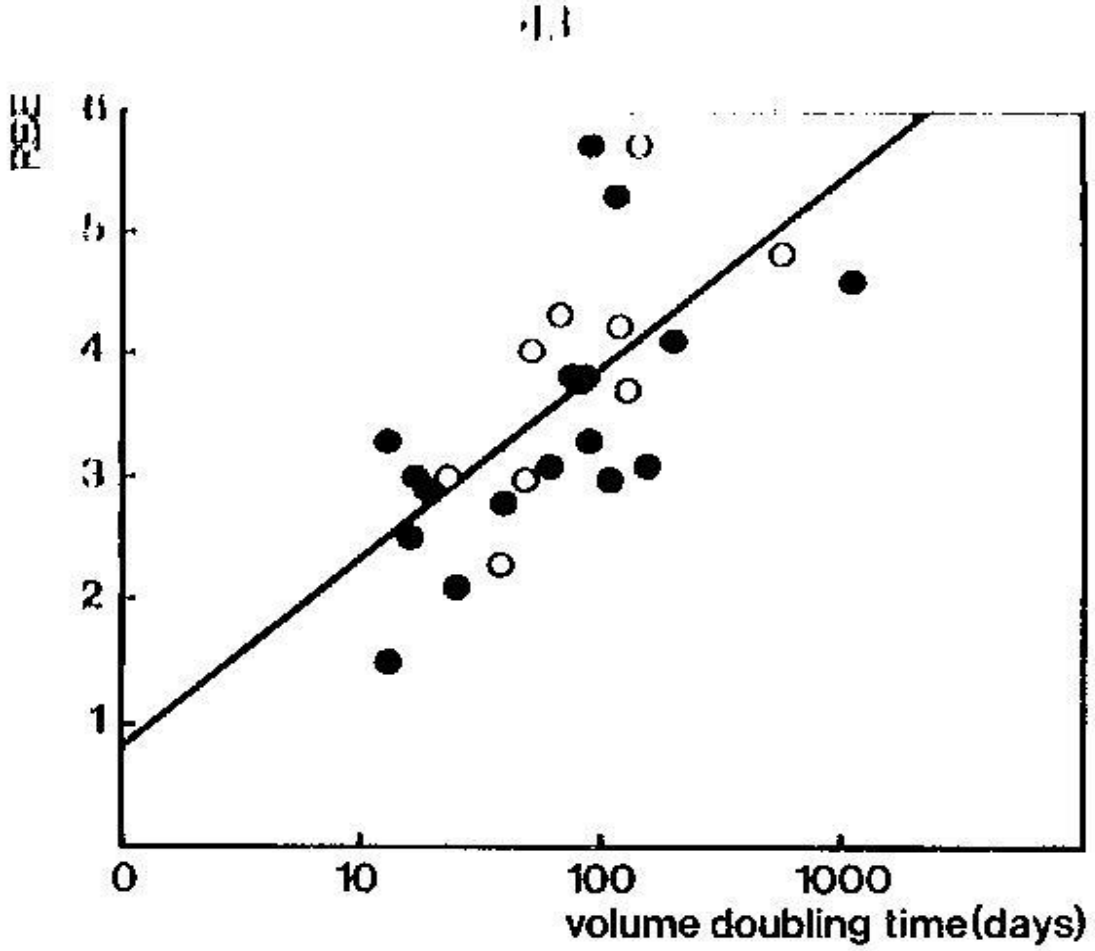


The potential clinical advantage of high LET radiations in radiation oncology

- Reduced radioresistance of hypoxic (tumour stem) cells
- Reduced induction and repair of sublethal radiation damage, less dose sparing of dose fractionation
- Less repair of clustered DNA damage, resulting in less heterogeneity of radiosensitivity of less lines
- Reduced dependence of radiosensitivity on the cell cycle phases
- Increased radiation effects on slow growing tumours

Battermann Jan J: Clinical application of fast neutrons. The Amsterdam Experience. Amsterdam 1981

The dependence of neutron RBE on human tumour growth rate



The ANDANTE project

- Comprehensive characterisation of the different neutron beams, most of which were provided by the PTB in Braunschweig,
- Characterisation of the neutron scatter fields from proton therapy beams,
- Track structure modelling of the initial damage to DNA, particularly clustered damage from the secondary particles from neutron absorption
- The exposure of primary, organ-specific stem cells (breast, thyroid, salivary glands) with different neutron beams and 220 kV X-rays. Long-term follow-up in vitro for many passages and investigation of pathological and molecular alterations in vivo after xenotransplantation,
- In silico design of a prospective study to estimate the RBE of neutrons by determining second cancer risk after proton radiotherapy by comparing the second cancer rate after scattered and scanned proton irradiation.

Neutron doses in different organs by various treatments of a pelvic malignancy (Hälg)

Table 2. Organ neutron dose equivalents H in μSv per treatment Gy for various treatment modalities with a standard uncertainty of 28%.

ICRP organ	Varian 3DCRT	Varian VMAT	Varian IMRT	Elekta IMRT	Siemens IMRT	Active protons	Passive protons
			μSv/treatment Gy				
Bone marrow	17	21	21	6	15	183	423
Colon	9	14	14	3	11	861	851
Lung	41	56	43	16	34	17	346
Stomach	6	7	12	3	7	24	232
Breast	71	106	83	39	86	17	328
Remainder	127	87	83	6	64	701	785
Bladder	485	278	257	12	218	3152	1913
Oesophagus	11	10	10	4	8	17	199
Liver	13	25	17	5	17	61	485
Thyroid	13	9	11	5	9	14	141
Bone surface	17	21	21	6	15	183	423
Brain	18	29	17	7	11	3	104
Salivary glands	45	77	48	18	32	5	210
Skin	159	166	148	54	161	34	647