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der Universität Heidelberg

Universitätsklinikum Mannheim

Radiogene Zweittumoren

Frank Lohr, Mannheim

Disclosures

Elekta:

Travel Grants, Research Support, Teaching Honoraria

IBA:

Travel Grants, Advisory Board, Research Support, Teaching Honoraria

C-Rad:

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Problems with IMRT

Noncancer Problems

Secondary Tumors

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Second Malignancies

Synopsis

1. For **most patients**, second cancer is **not a relevant concern**. Young women with **breast cancer, Hodgkin‘s disease** and **pediatric** patients, however, **require attention** and an individual assessment if IMRT may carry more or less risk than 3D.

2. Most **Modelling** is based on Hiroshima Nagasaki data
–> valid for doses <2 Gy

3. **Therapeutic Data** have become available only relatively recently and suggest a linear relationship between SCI and Volume and at least a **linear relationship** between SCI and Dose

4. There is **no evidence for overkill/plateau** in relevant dose ranges for fractionated and single-dose RT, Incidence/dose relationship may be **supralinear** for fractionated RT

5. **Beam modalities other than MV** photons may have other characteristic

“The most important prerequisite for the development of a second neoplasm is cure of the primary malignancy”

Doerr, Hermann, SUON, 2008

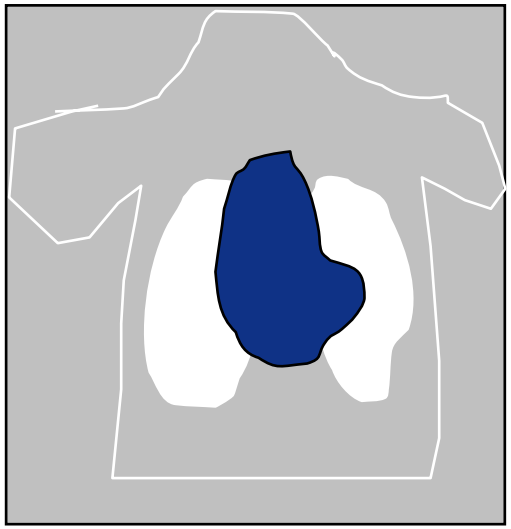
-> Death as confounding factor has to be compensated for in estimates

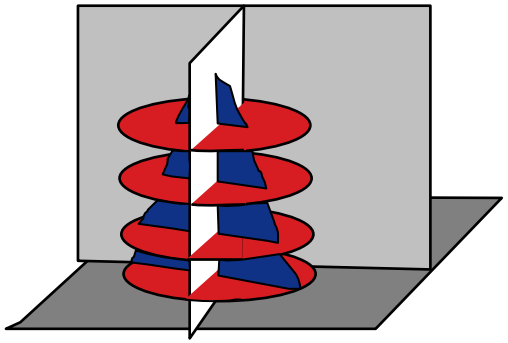
Radiotherapy Treatment Planning

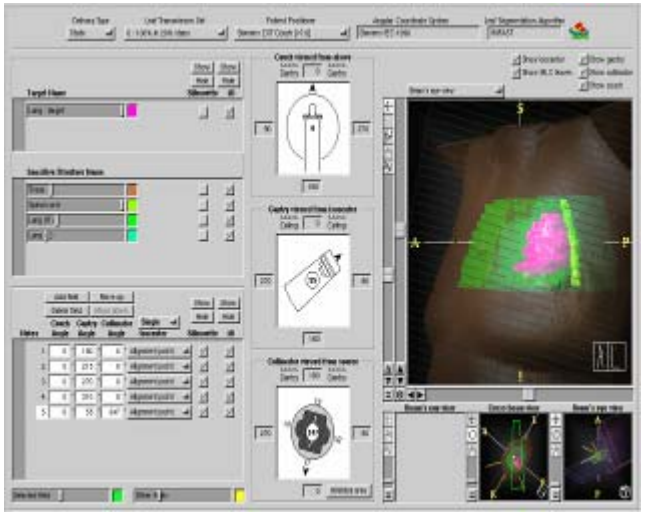
Simulator

2-D

3-D

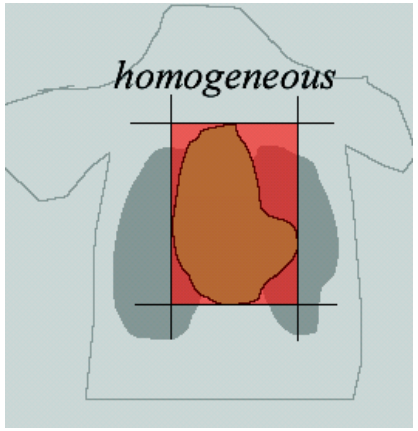


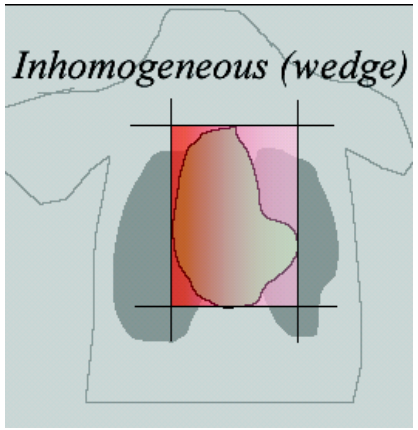




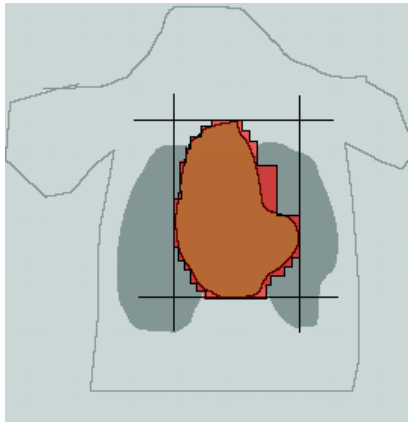
Treatment Delivery

Conventional

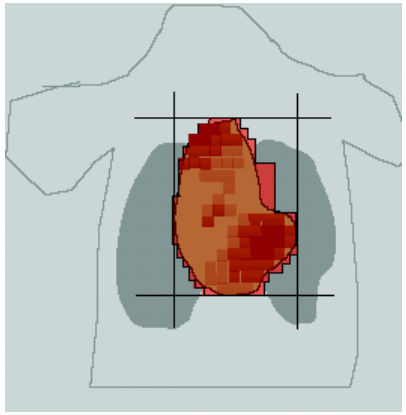




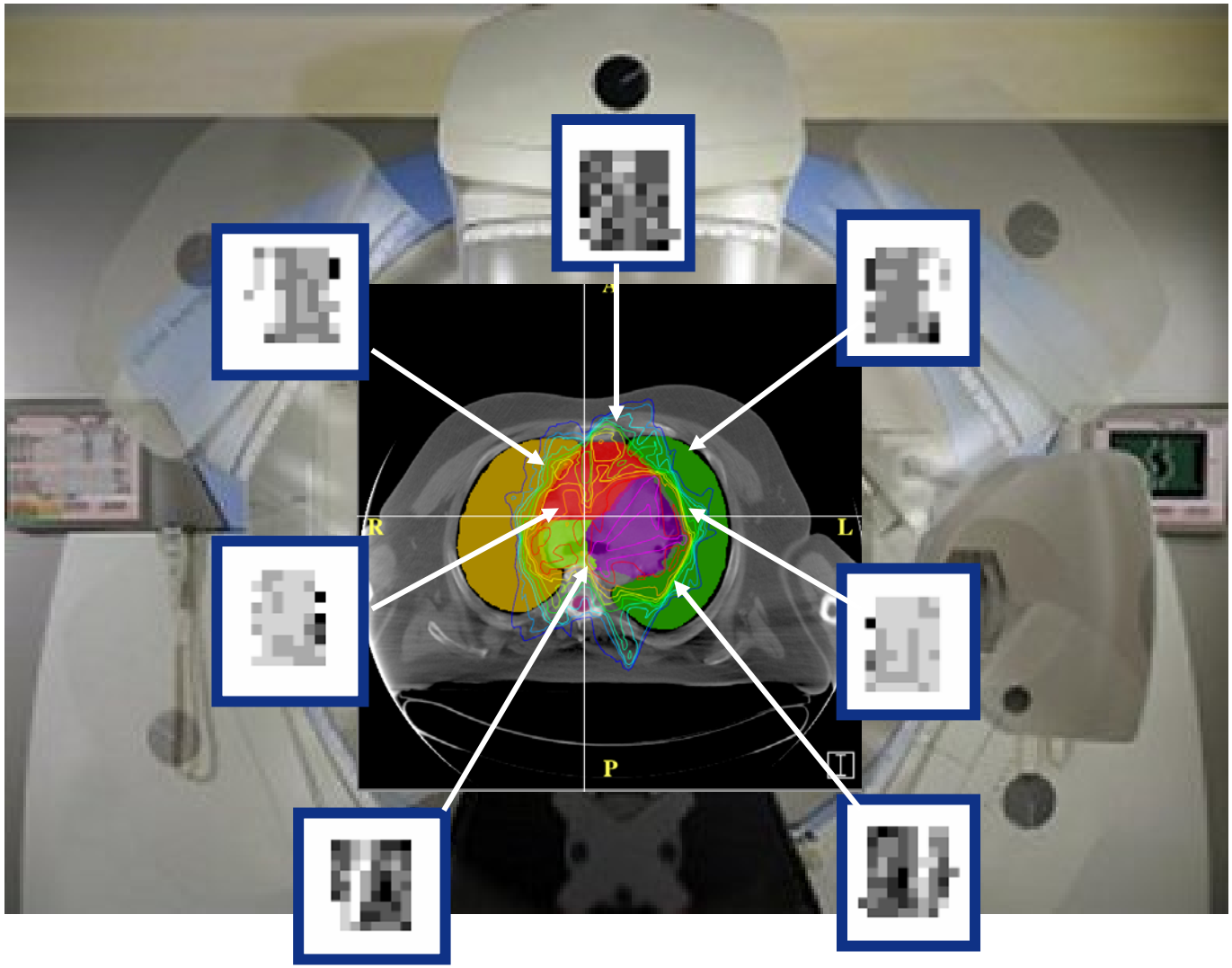
Conformal



IMRT

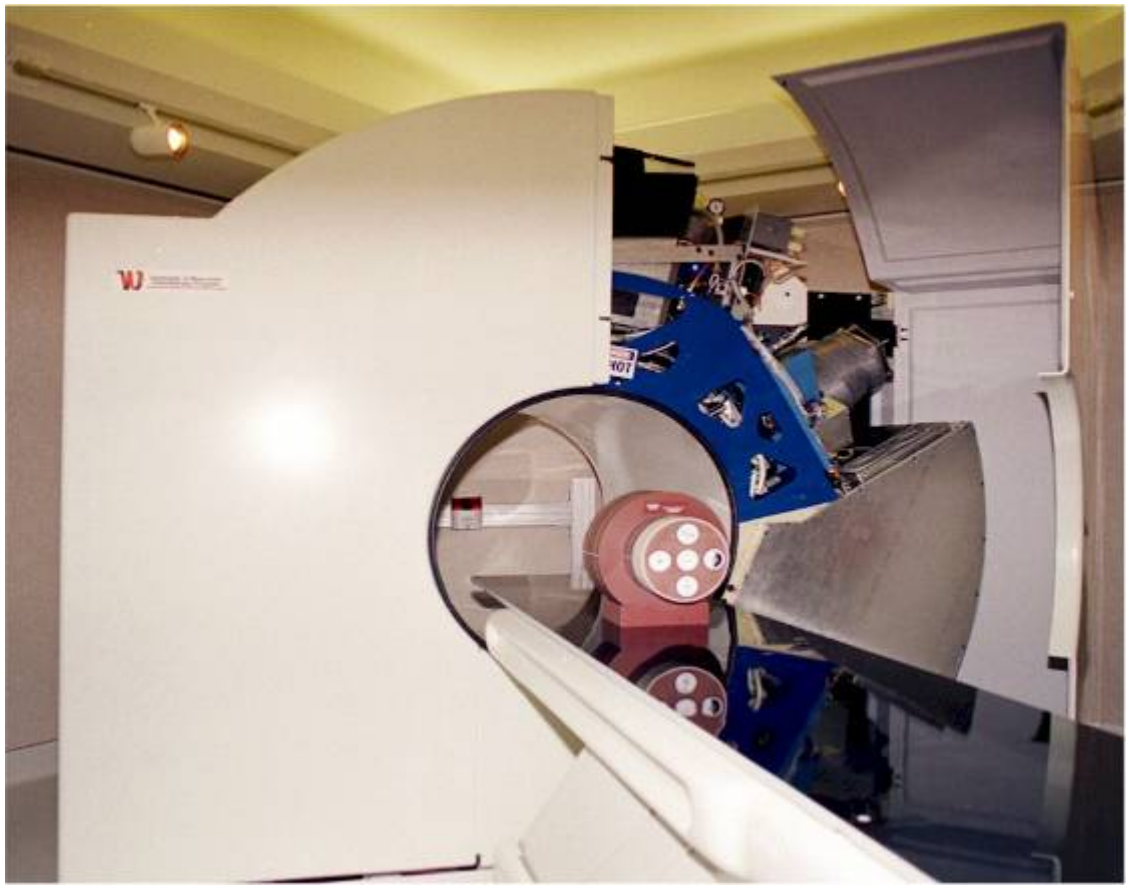


IMRT-Capable Delivery System



The HI•ART TomoTherapy System

UW Tomotherapy Research Unit



www.tomotherapy.com

There is nothing new under the sun……1

Klaus Welker und Jürgen Richter

2012

Die Geschichte
der Strahlentherapie
an der Robert-Rössle-Klinik
in Berlin-Buch
1950 bis 1984

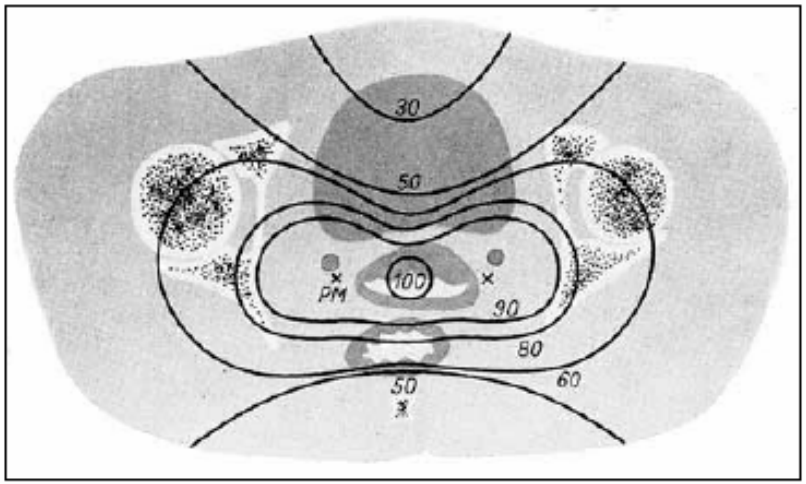


Abb. 2.6.1: Dosisverteilung für eine biaxiale Bewegungsbestrahlung.

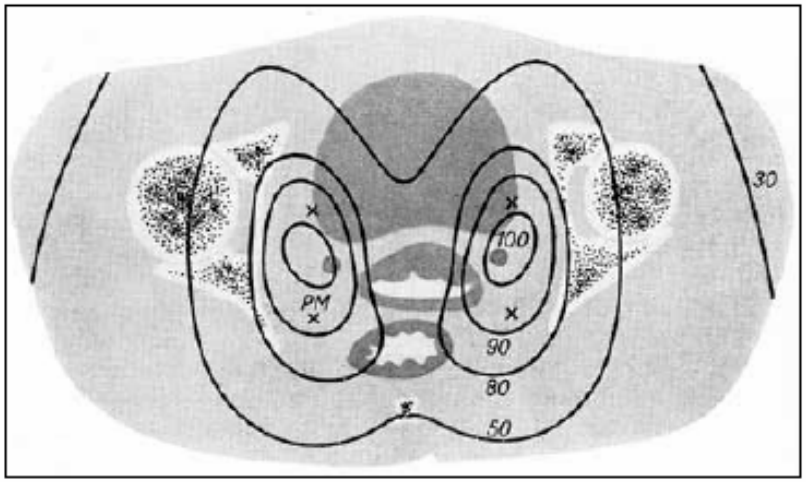


Abb. 2.6.2: Dosisverteilung für eine 4-axiale Bewegungsbestrahlung.

There is nothing new under the sun……2

K. Bratengeier

In: Kiricuta, Definition of Target Volumes, 2001

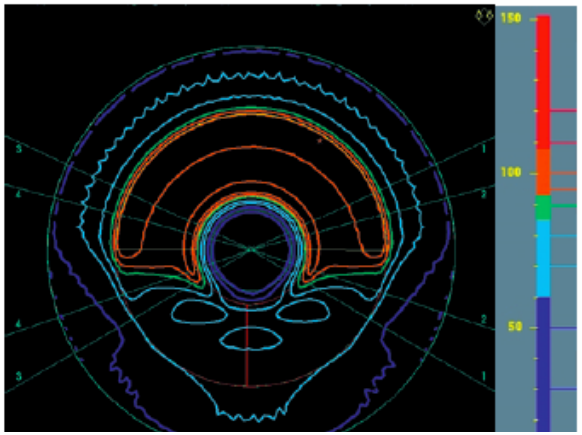
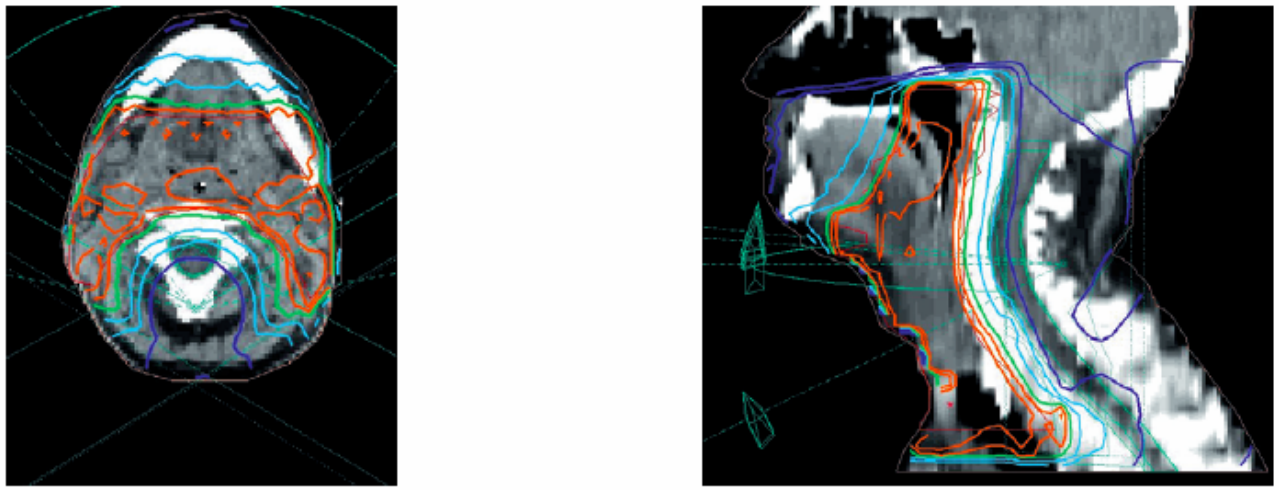
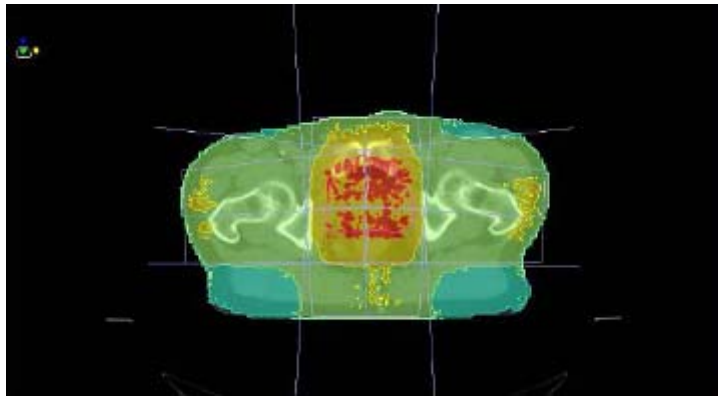
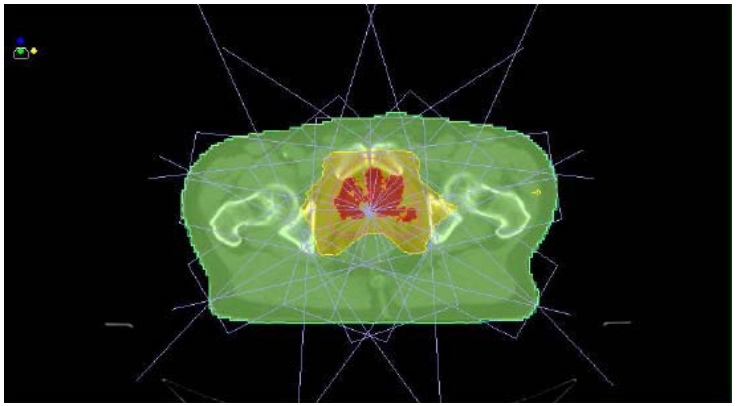


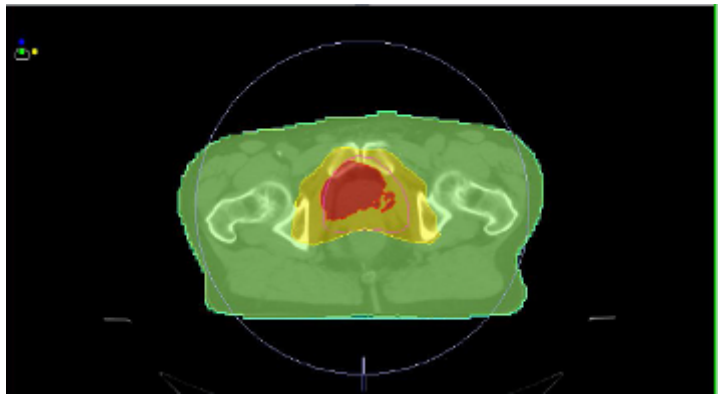
Figure 8. *Two-step IMAT in the case of a patient with Hypopharynx-Carcinoma. Left: transversal plane. Right: sagittal plane; 30%, 50%, 70%, 80%, 90% and 95% isodoses are shown in the same colors as labelled in figure 7.*

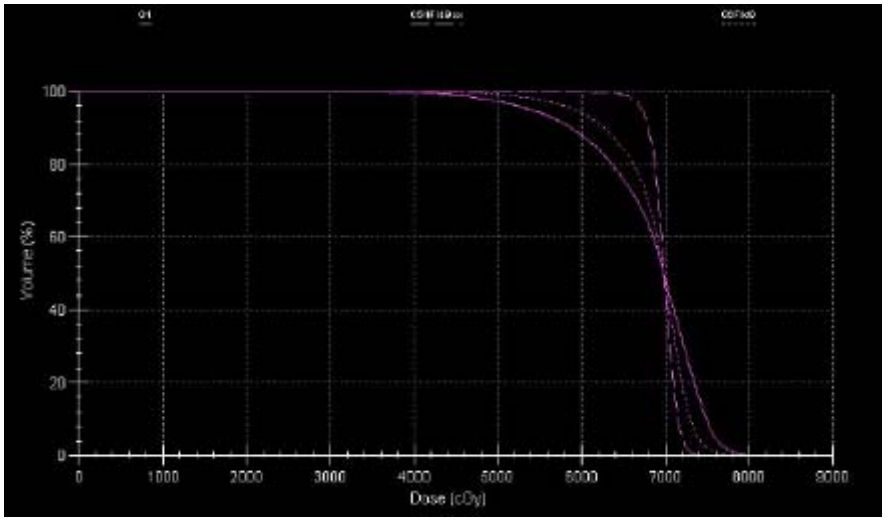


StrSchKomm – Stellungnahme zur IMRT









1 Gy (blue), 5 Gy (green), 45 Gy (yellow) and 70 Gy (red)

Risk estimates for secondary cancer after exposure to ionizing radiation

1. Low dose estimates (0-2 Gy single dose exposure, based on the Atomic Bomb Survivor Study (Life Span Study, LSS), that forms the basis for the Biological Effects of Ionizing Radiation (BEIR VII model)

2. High dose estimates (>2 or >5 Gy, based on clinical follow up data after radiotherapy for benign or malignant disease

Problems identifying true incidence numbers of secondary cancer after exposure to ionizing radiation

1. Low dose Estimates (LSS):

- Low number of events
- Uncertain Dosimetry
- Unclear effects of other toxins
- Difficulties to maintain long follow up
- Very limited dose range (limited by acute lethalty of exposure and explosion force to 0-2 Gy with emphasis on <1 Gy)

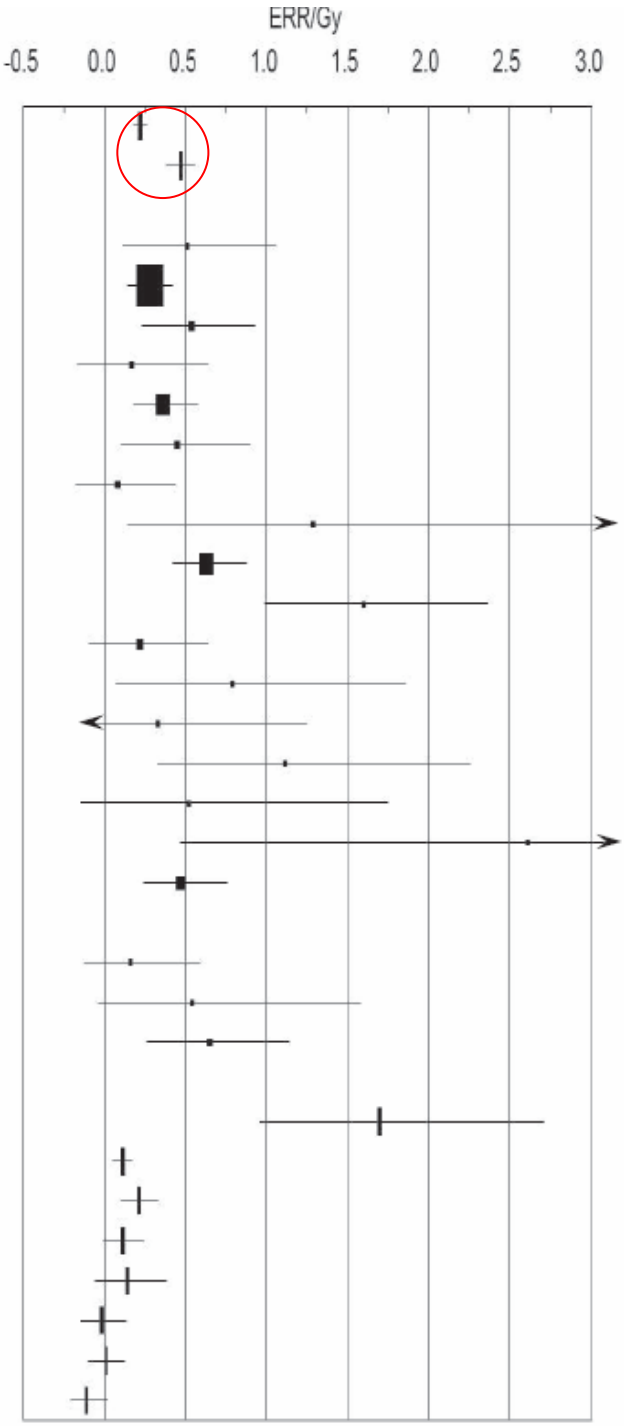
2. High dose Estimates (clinical)

- Low number of events
- Combination Therapies
- Information on precise localization and doses at the site of second malignancies hard to obtain (10 year documentation…..)
- Long follow up necessary, hard to obtain without institutional data collection

Modelling
(has severe limitations)

Low Dose Models

Cause of death	ERR/Gy [a] (95%CI [b])	Cases
All causes	0.22 (0.18, 0.26)	50,620
All solid cancer	0.47 (0.38, 0.56)	10,929
Cancers of Specific sites [c]		
Esophagus	051 (0.11, 1.06)	339
Stomach	0.28 (0.14, 0.42)	3,125
Colon	0.54 (0.23,0.93)	621
Rectum	0.17 (-0.17,0.64)	427
Liver	0.36 (0.18, 0.58)	1,519
Gallbladder	0.45 (0.10, 0.90)	419
Pancreas	0.08 (-0.18, 0.44)	513
Other digestive system	1.29 (0.14, 3.25)	84
Lung	0.63 (0.42, 0.88)	1,558
Breast	1.60 (0.99, 2.37)	324
Uterus	0.22 (-0.09, 0.64)	547
Ovary	0.79 (0.07, 1.86)	157
Prostate	0.33 (NA [e], 1.25)	130
Bladder	1.12 (0.33, 2.26)	183
Kidney parenchyma	0.52 (-0.15, 1.75)	80
Renal pelvis and ureter	2.62 (0.47,7.25)	33
Other solid cancer	0.47 (0.24, 0.76)	864
Lymphoid and hematopoietic malignancies [c, d]		
Malignant lymphoma	0.16 (-0.13,0.59)	284
Multiple myeloma	0.54 (-0.04,1.58)	93
Other neoplasms [c]	0.65 (0.26, 1.14)	518
Non-neoplastic diseases and other causes		
Blood diseases	1.70 (0.96, 2.70)	238
Circulatory diseases	0.11 (0.05, 0.17)	19,054
Respiratory diseases	0.21 (0.10, 0.33)	5,119
Digestive diseases	0.11 (-0.01, 0.24)	3,394
Genitourinary diseases	0.14 (-0.06, 0.38)	1,309
Infectious diseases	-0.02 (-0.15, 0.13)	1,962
Other diseases	0.01 (-0.1, 0.12)	4,847
External causes	-0.11 (-0.21, 0.02)	2,432



LSS, Ozasa, Rad Res, 2012

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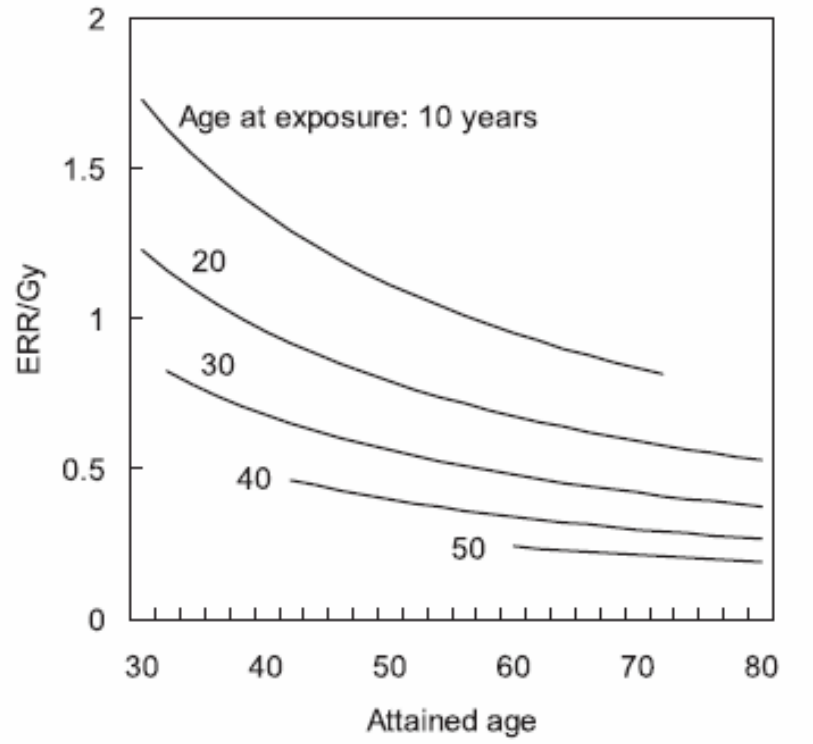


FIG. 2. Modification of the excess relative risk (ERR) for all solid cancer by age at exposure and attained age.

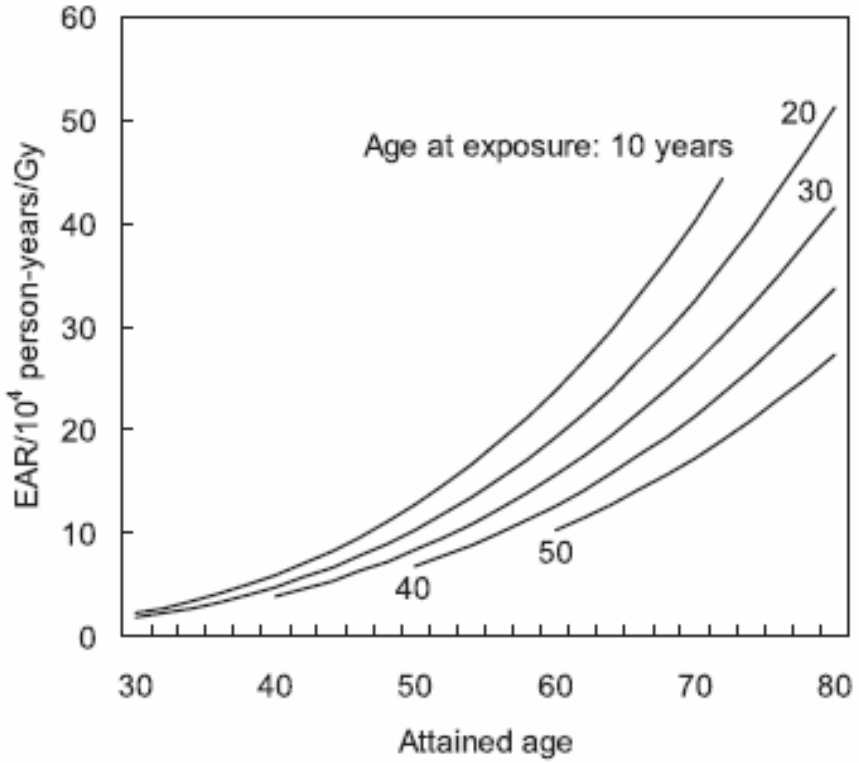


FIG. 3. Modification of the excess absolute risk (EAR) for all solid cancer by age at exposure and attained age.

LSS, Ozasa, Rad Res, 2012

Problems with Modelling

“The mean estimated ERR for breast, lung and thyroid were significantly ($p < 0.01$) lower with INRT than with IFRT planning, regardless of the radiation technique delivery used, assuming a linear dose-risk relationship. An ERR increase was however observed with the non-linear model. With the latter, mean ERR were significantly ($p < 0.01$) increased with IMRT or RA when compared to 3DCRT planning for the breast, lung and thyroid using an IFRT paradigm. After INRT planning, IMRT or RA increased the risk of RIC for lung and thyroid only. “

Weber et al., IJROBP, 2011

Does this sufficiently reflect reality?

$$\mathrm{OED}_{\mathrm{carcinoma}} = \frac{1}{N}\sum_i \frac{\exp(-\alpha_i' D_i)}{\alpha_i' R}\left(1 - 2R + R^2 \exp\left[\alpha_i' D_i\right] - [1-R]^2 \exp\left[-\frac{\alpha_i' R}{1-R} D_i\right]\right) \quad (1)$$

$$\mathrm{OED}_{\mathrm{sarcoma}} = \frac{1}{N}\sum_i \frac{\exp\left(-\alpha_i' D_i\right)}{\alpha_i' R}\left(1 - 2R + R^2 \exp\left[\alpha_i' D_i\right] - \alpha_i' R D_i - [1-R]^2 \exp\left[-\frac{\alpha_i' R}{1-R} D_i\right]\right) \quad (2)$$

$$\alpha_i' = \alpha + \beta D_i . \frac{d_F}{D}. \quad (3)$$

Paganetti et al., PMB, 2012

High(er) Dose Exposure

-> Therapeutic data is necessary

Clinical Data

(Are the definitive data source)

Hodgkin II (GHSG)

Behringer et al., IJROBP, 2004

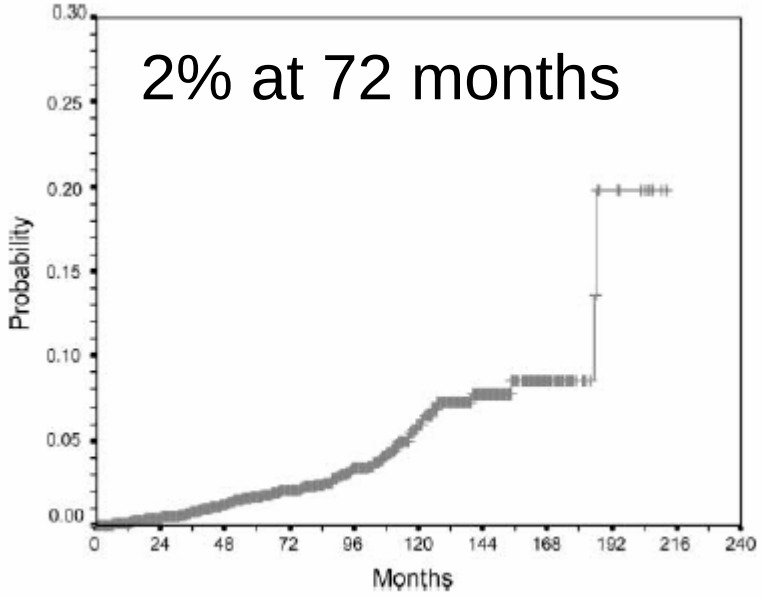


Figure 1. Cumulative risk of solid tumor by time since first treatment.

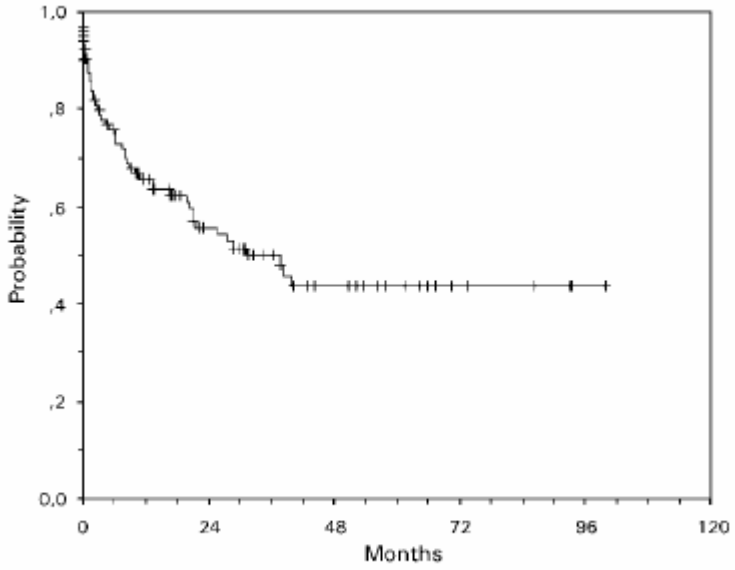


Figure 2. Overall survival from solid tumor.

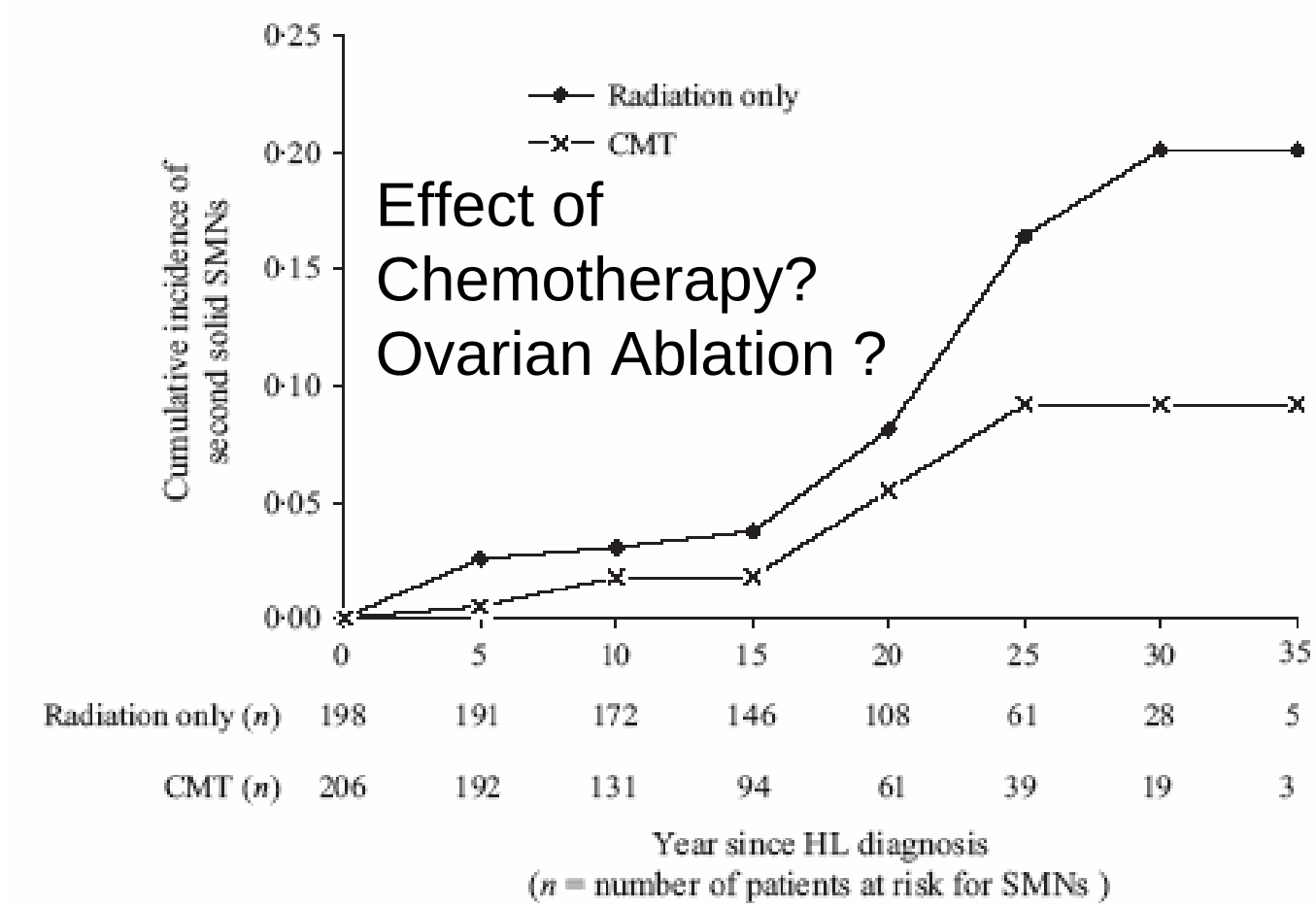
Table 8. Solid tumors within or adjacent to the initial irradiation field

Tumor entity	Location within the initial irradiation field		
	Probable	Not probable	Unknown
Breast	4	3	6
Lung	12	6	12
Thyroid	4	1	0

Uncertainty about SM-Location

Hodgkin III (Yale)

Omer et al., BJH, 2012



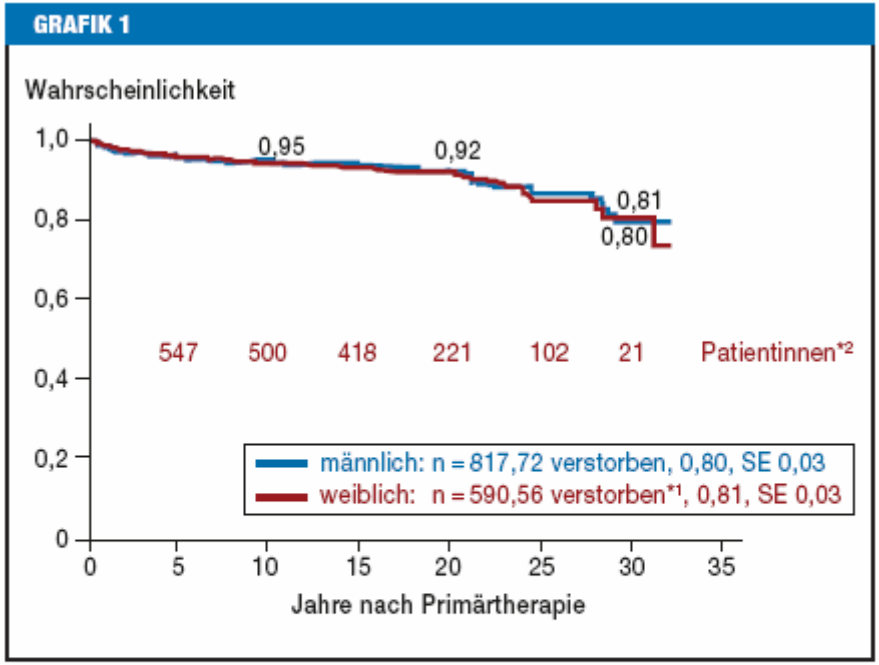
Effect of Chemotherapy? Ovarian Ablation ?

Vast Majority of SMNs in field

CMT Patients received lower doses than RT-only patients (20 vs. 40 Gy)

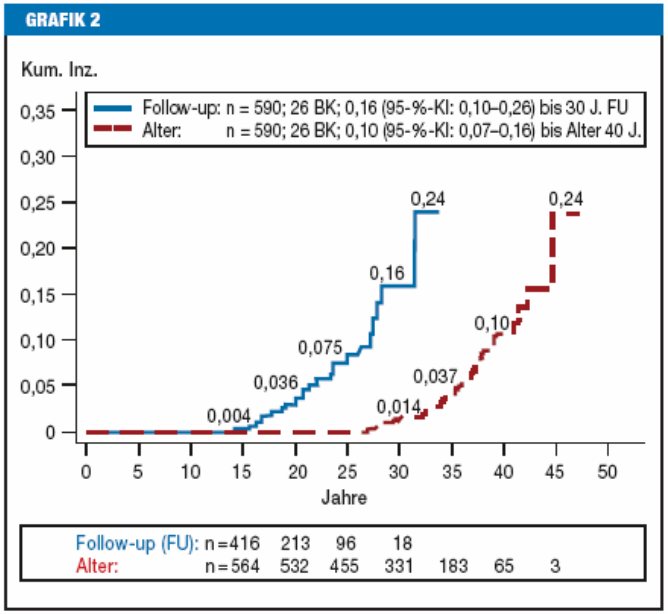
Hodgkin III: Pediatric HD

96% of Secondary Cancers in-field

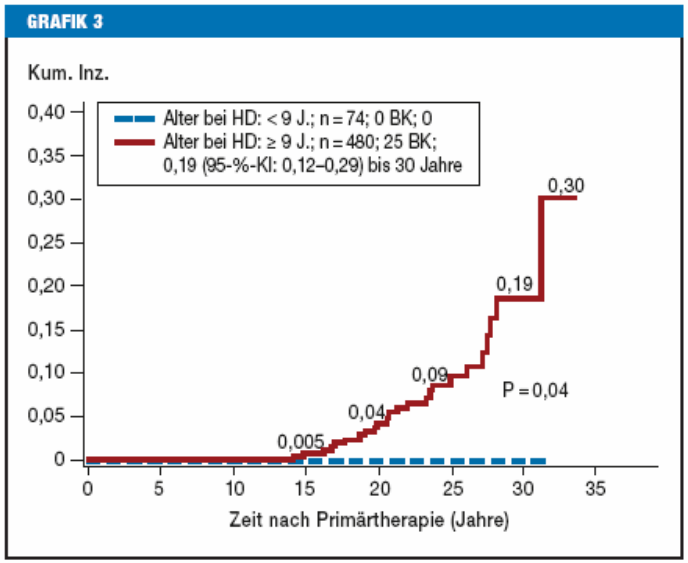


Gesamtüberleben („overall survival" [OS] nach 30 Jahren) in den Morbus-Hodgkin-Therapiestudien HD-78 bis HD-90 bei Jungen und Mädchen (Stand: 1. Juli 2012).
*1 Todesursachen bei den Patientinnen: Hodgkin-Lymphom (n = 18), Post-Splenektomie-Sepsis (n = 7), Sekundärmalignom (n = 15, davon 3 Brustkrebs), Herzerkrankungen (n = 6), sonstige (n = 10, inklusive Unfall, Suizid)
*2 mit dokumentierten Verlaufsinformationen
SE, „standard error"

Schellong, Dt. Ä-Blatt, 2014



Kumulative Inzidenz (Kum. Inz.) für Brustkrebs (BK) in der Gesamtgruppe der Patientinnen aus den pädiatrischen Therapiestudien HD-78 bis HD-90 in Abhängigkeit von der Zeit seit Primärtherapie (blaue Linie), bzw. vom erreichten Lebensalter (rote unterbrochene Linie) mit 95-%-Konfidenzintervall (95-%-KI). Stand: 1. Juli 2012



Kumulative Inzidenz (Kum. Inz.) für Brustkrebs (BK) mit 95-%-Konfidenzintervall (95-%-KI) in der Gruppe der Patientinnen aus den pädiatrischen Therapiestudien HD-78 bis HD-90, die im Brustbereich bestrahlt worden sind. (Stand: 1. Juli 2012)

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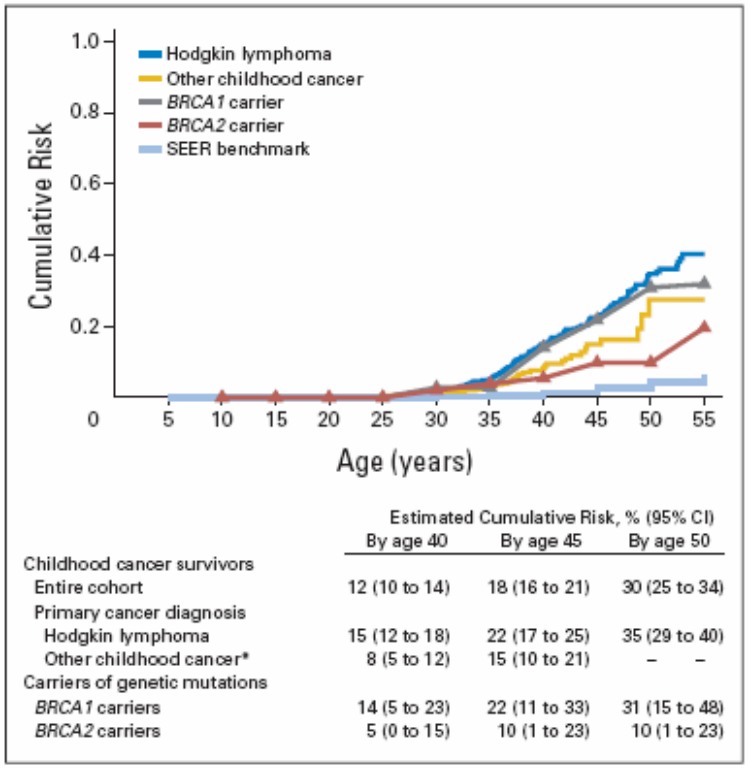
Hodgkin III: Pediatric HD

Moskowitz, JCO, 2014

Suggestive of Dose and Volume linearity at >10 Gy



	Estimated Cumulative Risk, % (95% CI)		
	By age 40	By age 45	By age 50
Childhood cancer survivors			
Entire cohort	12 (10 to 14)	18 (16 to 21)	30 (25 to 34)
Primary cancer diagnosis			
Hodgkin lymphoma	15 (12 to 18)	22 (17 to 25)	35 (29 to 40)
Other childhood cancer*	8 (5 to 12)	15 (10 to 21)	– –
Carriers of genetic mutations			
BRCA1 carriers	14 (5 to 23)	22 (11 to 33)	31 (15 to 48)
BRCA2 carriers	5 (0 to 15)	10 (1 to 23)	10 (1 to 23)

Fig 2. Cumulative risk of breast cancer. Breast cancer risk among women treated for childhood cancer with chest irradiation contrasted with breast cancer risk in female carriers of *BRCA1* or *BRCA2* deleterious mutations and women in general US population, with a birth-year distribution reflective of CCSS (Childhood Cancer Survivor Study) participants. (*) Insufficient follow-up in this group to provide reliable estimates of cumulative risk of breast cancer by age 50 years.

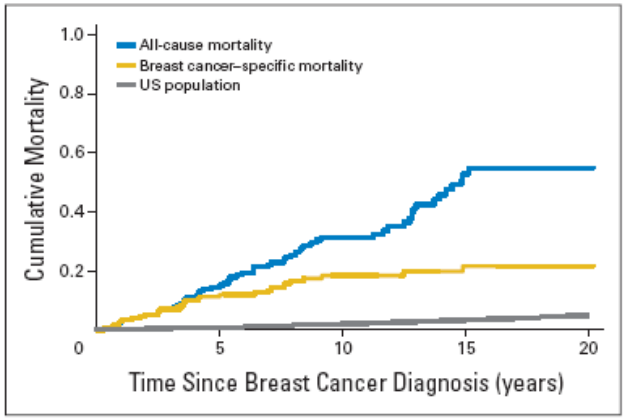


Fig 3. Death after breast cancer among childhood cancer survivors treated with chest irradiation. All-cause and breast cancer–specific mortality after breast cancer after chest radiotherapy for childhood cancer compared with expected mortality, age and year standardized to US population.

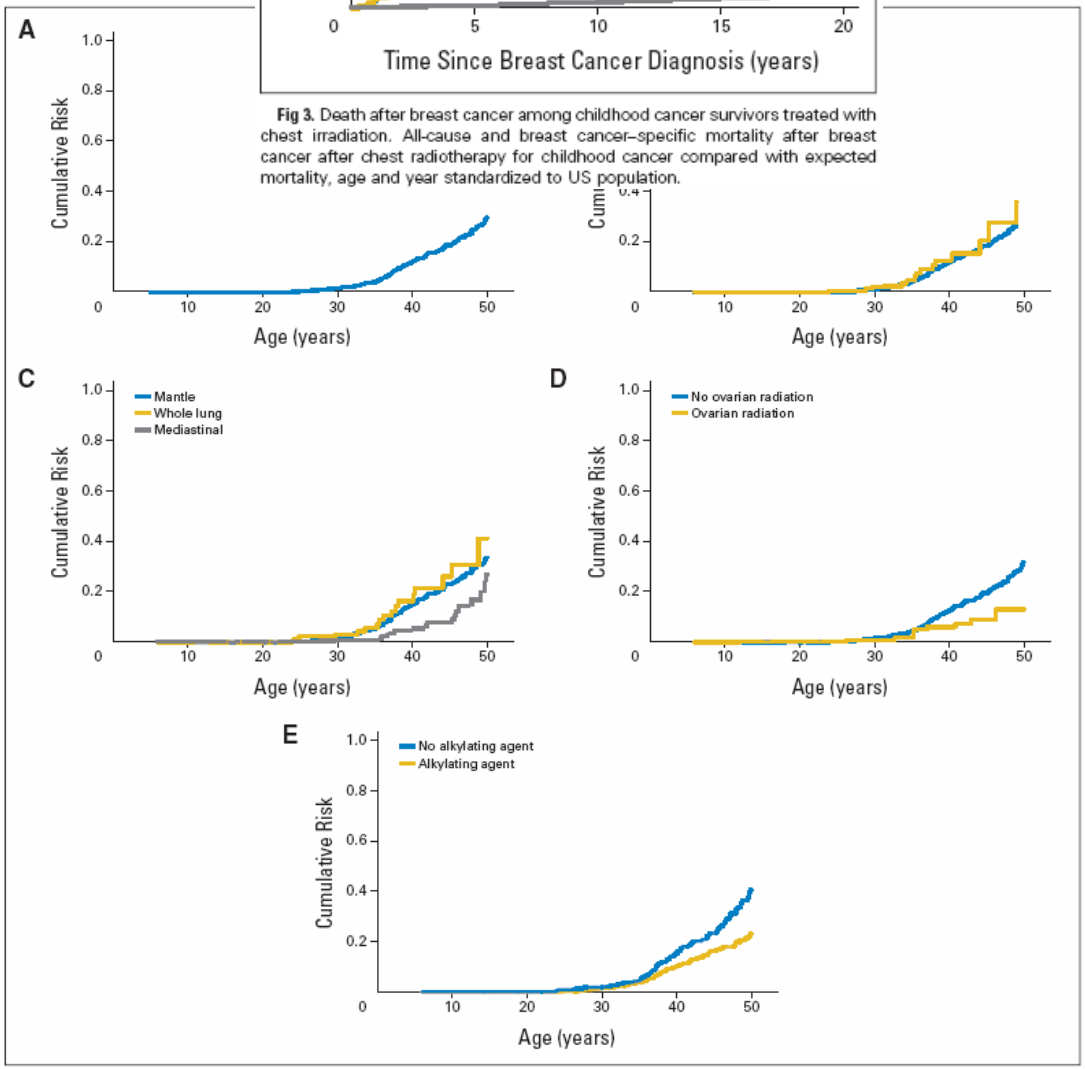


Fig 1. Cumulative risk of breast cancer among women treated for childhood cancer with chest irradiation (A) overall and by childhood cancer therapy: (B) chest radiation dose; (C) chest irradiation field; (D) ovaries in concurrent irradiation field; (E) alkylating agents.

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Breast i – Italian Data (Allegro Project)

„Our initial patient number is very high, but the incidence of a second cancer is relatively low (0.02% of all patients and 0.019% of the patients treated with adjuvant irradiation)“

Minimum F/U: 5 years

Median F/U: not given, but probably around 10 Years

Breast Cancers in High Dose Areas (in-field) excluded

Orecchia et al., Tumori, 2012

Breast II – DBCG Data (Allegro-Project)

Radiotherapy-associated sites:
HR 1.34 (95% CI 1.11–1.61)
10–14 years after RT: HR 1.55 (95% CI 1.08–2.24)
>15 years after: HR 1.79 (95% CI 1.14–2.81).

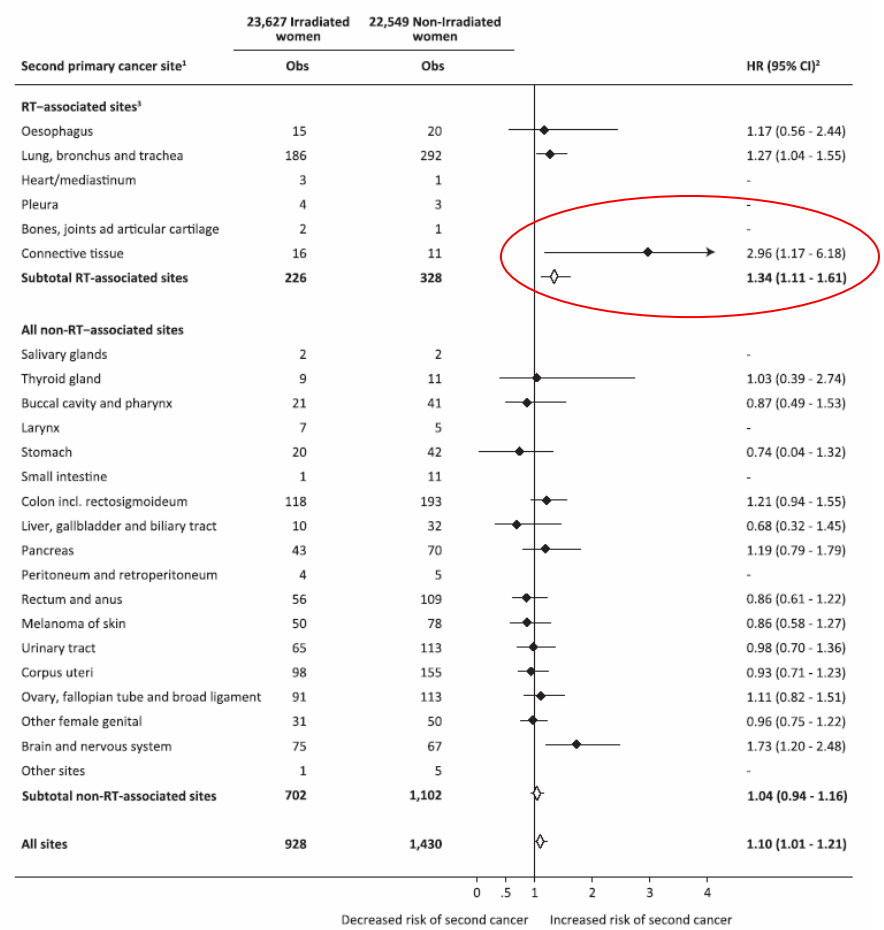
Non-radiotherapy-associated sites:
HR 1.04 (95% CI 0.94–1.1).

The estimated attributable risk related to radiotherapy for the radiotherapy-associated sites translates into one radiation-induced second cancer in every 200 women treated with radiotherapy.

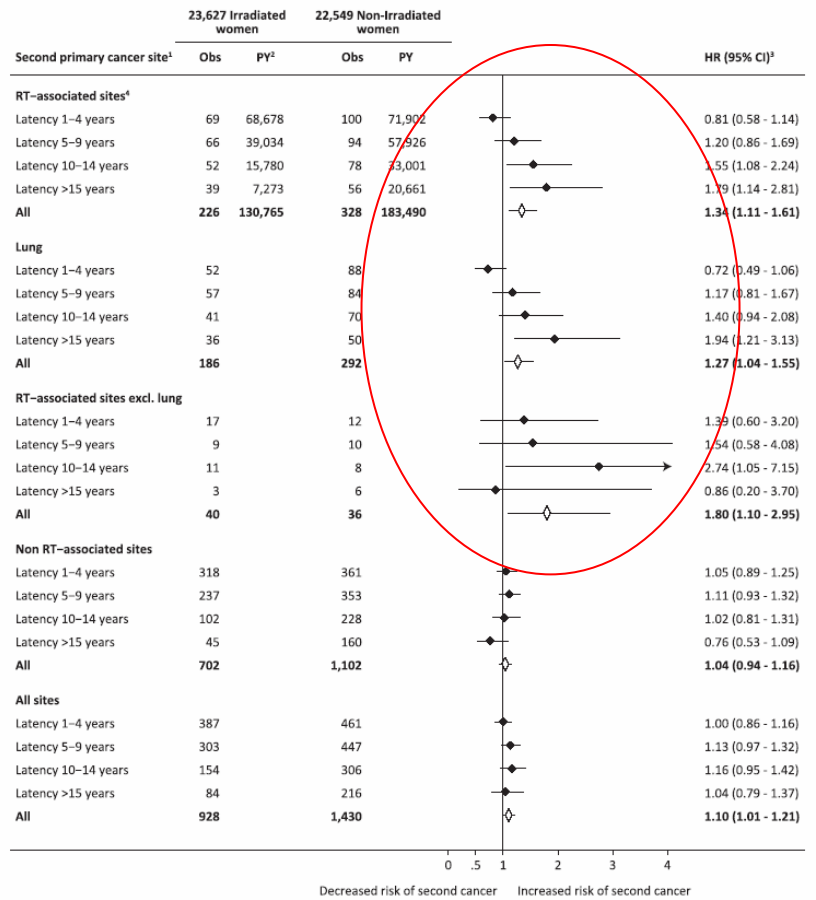
The observed temporal-pattern for the RT-associated sites is consistent with the suggestion that radiation induced solid tumors have a minimum latency of 5–9 years

Granzau et al., R&O, 2013

Breast III – DBCG Data (Allegro-Project)



Second primary cancer site[1]	23,627 Irradiated women Obs	22,549 Non-Irradiated women Obs	HR (95% CI)[2]
RT–associated sites[3]			
Oesophagus	15	20	1.17 (0.56 - 2.44)
Lung, bronchus and trachea	186	292	1.27 (1.04 - 1.55)
Heart/mediastinum	3	1	-
Pleura	4	3	-
Bones, joints ad articular cartilage	2	1	-
Connective tissue	16	11	2.96 (1.17 - 6.18)
Subtotal RT-associated sites	**226**	**328**	**1.34 (1.11 - 1.61)**
All non-RT–associated sites			
Salivary glands	2	2	-
Thyroid gland	9	11	1.03 (0.39 - 2.74)
Buccal cavity and pharynx	21	41	0.87 (0.49 - 1.53)
Larynx	7	5	-
Stomach	20	42	0.74 (0.04 - 1.32)
Small intestine	1	11	-
Colon incl. rectosigmoideum	118	193	1.21 (0.94 - 1.55)
Liver, gallbladder and biliary tract	10	32	0.68 (0.32 - 1.45)
Pancreas	43	70	1.19 (0.79 - 1.79)
Peritoneum and retroperitoneum	4	5	-
Rectum and anus	56	109	0.86 (0.61 - 1.22)
Melanoma of skin	50	78	0.86 (0.58 - 1.27)
Urinary tract	65	113	0.98 (0.70 - 1.36)
Corpus uteri	98	155	0.93 (0.71 - 1.23)
Ovary, fallopian tube and broad ligament	91	113	1.11 (0.82 - 1.51)
Other female genital	31	50	0.96 (0.75 - 1.22)
Brain and nervous system	75	67	1.73 (1.20 - 2.48)
Other sites	1	5	-
Subtotal non-RT-associated sites	**702**	**1,102**	**1.04 (0.94 - 1.16)**
All sites	**928**	**1,430**	**1.10 (1.01 - 1.21)**



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)**
All sites					
Latency 1–4 years	387		461		1.00 (0.86 - 1.16)
Latency 5–9 years	303		447		1.13 (0.97 - 1.32)
Latency 10–14 years	154		306		1.16 (0.95 - 1.42)
Latency >15 years	84		216		1.04 (0.79 - 1.37)
All	**928**		**1,430**		**1.10 (1.01 - 1.21)**

Soft Tissue Sarcoma of thorax and upper arm……

-> High Dose areas……

Granzau et al., R&O, 2013

Breast III – Prime II Trial

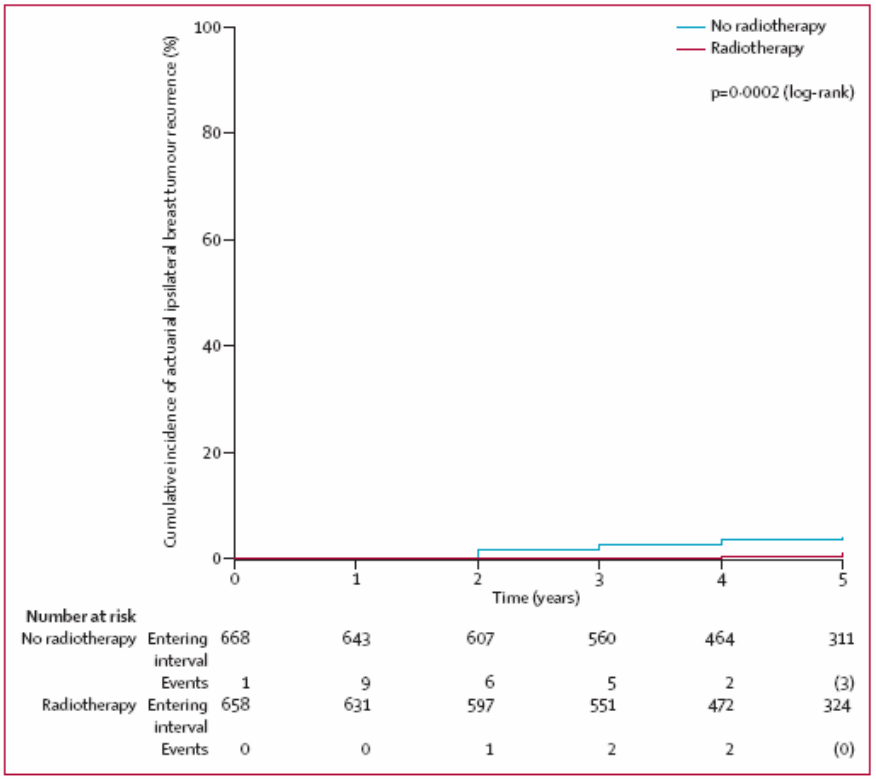


Figure 2: Time to actuarial ipsilateral breast tumour recurrence

	No radiotherapy (n=668)	Radiotherapy (n=658)
Regional recurrence	1·5% (0·5–2·4) (8)	0·5% (0–1·0) (3)
Distant recurrence	1·0% (0·1–1·7) (4)	0·5% (0–1·0) (5)
Contralateral breast cancer	0·7% (0·01–1·2) (4)	1·5% (0·4–2·5) (7)
New (non-breast) cancer	4·3% (2·6–5·7) (29)	3·7% (2·1–5·0) (26)

Data are Kaplan-Meier estimates of survival (95% CI) (number of events).

Table 4: **Other recurrences (as first event) or new cancers after 5 years**

Ipsilateral Reccurence at 5 ys:
1.3% vs. 4.1%
OS at 5 ys identical :
93.9% vs. 95%)

Kunkler et al., Lancet Oncol, 2015

Randomized Data: PORTEC etc.

Wiltink et al., JCO, 2015

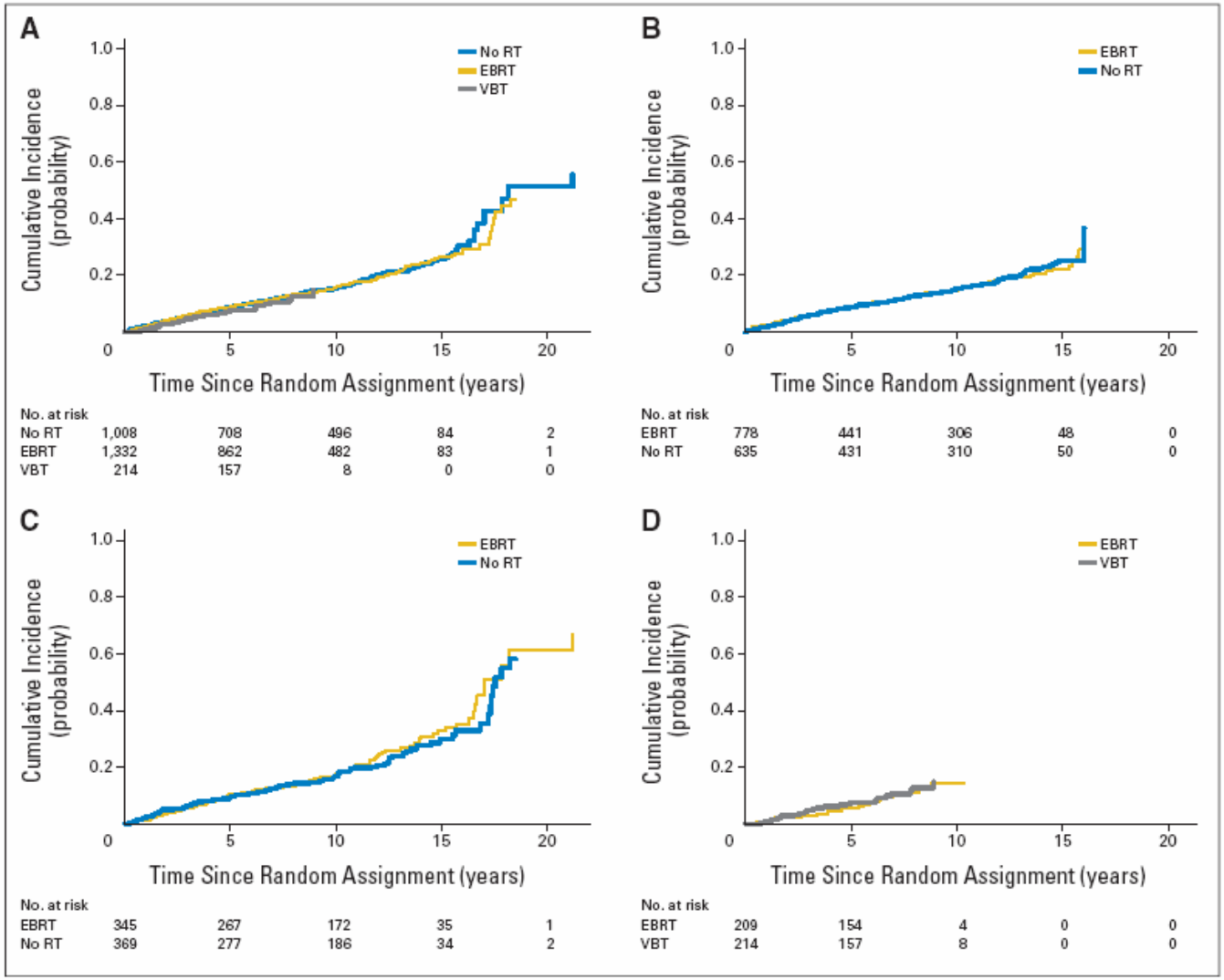


Fig 2. Cumulative probability of developing second cancer in (A) all, (B) TME (Total Mesorectal Excision), (C) PORTEC-1 (Post Operative Radiation Therapy in Endometrial Carcinoma 1), and (D) PORTEC-2 trials. NOTE. Because only four patients were included in no-RT group in the PORTEC-2 trial, these patients are not represented in panel D. EBRT, external-beam radiotherapy; RT, radiotherapy; VBT, vaginal brachytherapy.

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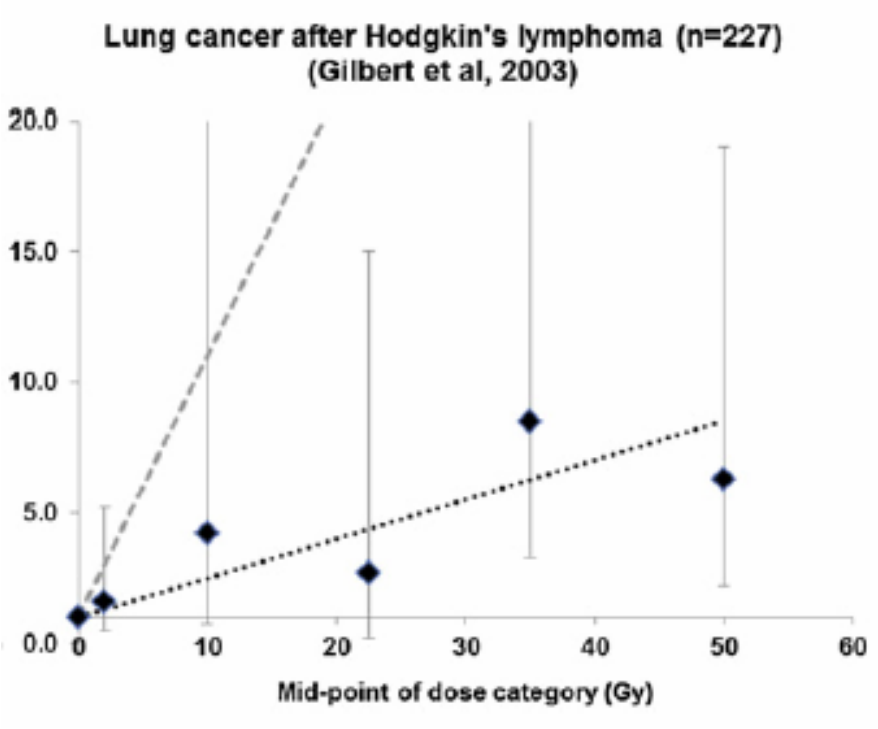
This just in…….

Overall, there was little evidence that the dose-response curve was nonlinear in the direction of a downturn in risk, even at organ doses of >60 Gy. Thyroid cancer was the only exception, with evidence of a downturn after 20 Gy. **Generally the excess relative risk per Gray, taking account of age and sex, was 5 to 10 times lower than the risk from acute exposures of <2 Gy among the Japanese atomic bomb survivors**.



Berrington et al., IJROBP, 2013

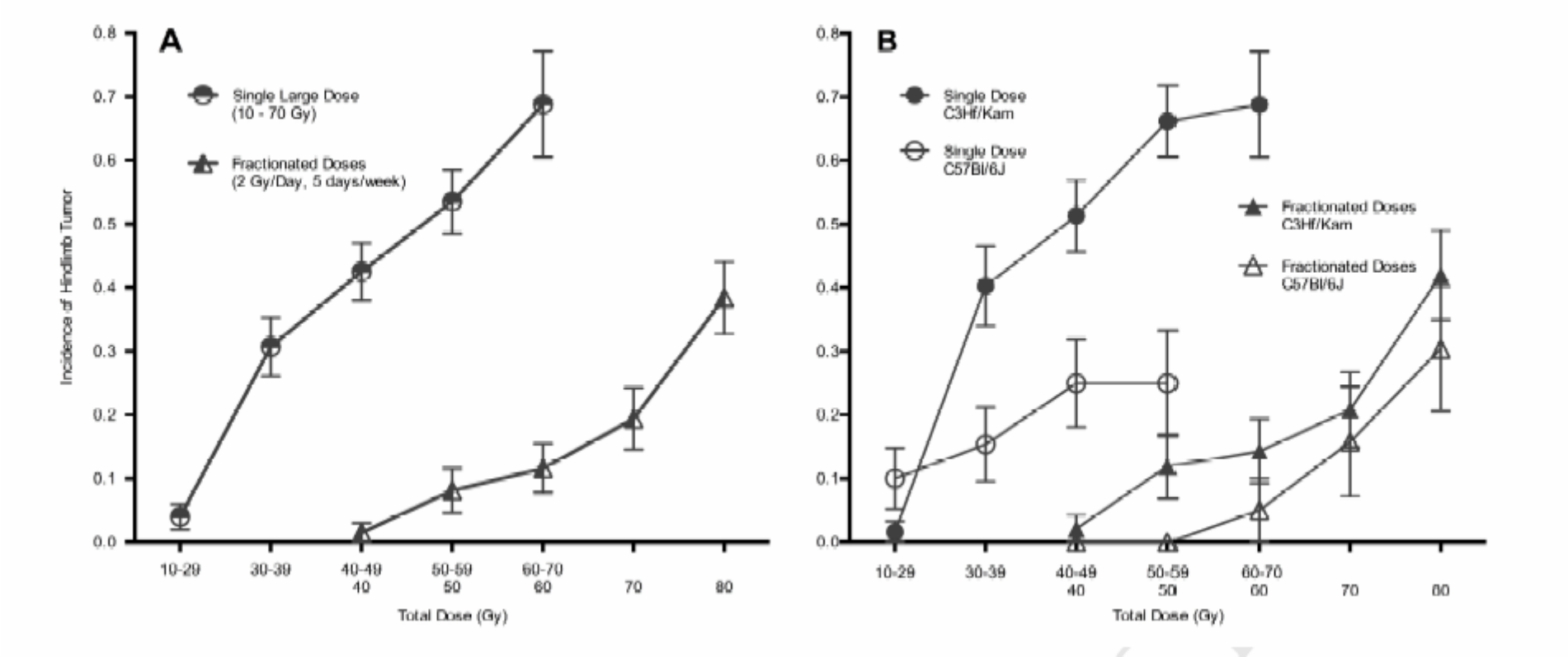


Figure 2. Incidence of hindlimb tumors by radiation dose. (A) Incidences of hindlimb tumors are significantly increased in mice exposed to a single large dose of radiation in comparison to mice exposed to fractionated radiation ($p < 0.001$). (B) Incidences of hindlimb tumors by radiation dose and mouse strain. C3Hf/Kam mice have a significantly higher incidence of hindlimb tumors following single dose exposures than C57BL/6J mice ($p < 0.001$). No significant difference in tumor incidence is observed between C3Hf/Kam and C57BL/6J mice following fractionated exposures. Single doses are grouped as 10-29, 30-39, 40-49, and 50-59 Gy. Fractionated doses were given as 2 Gy/day, 5 days/week for 4 to 8 weeks and are listed as total doses of 40, 50, 60 , 70, and 80 Gy

Edmondson et al., IJROBP, 2015

Using Logic
(is never wrong)

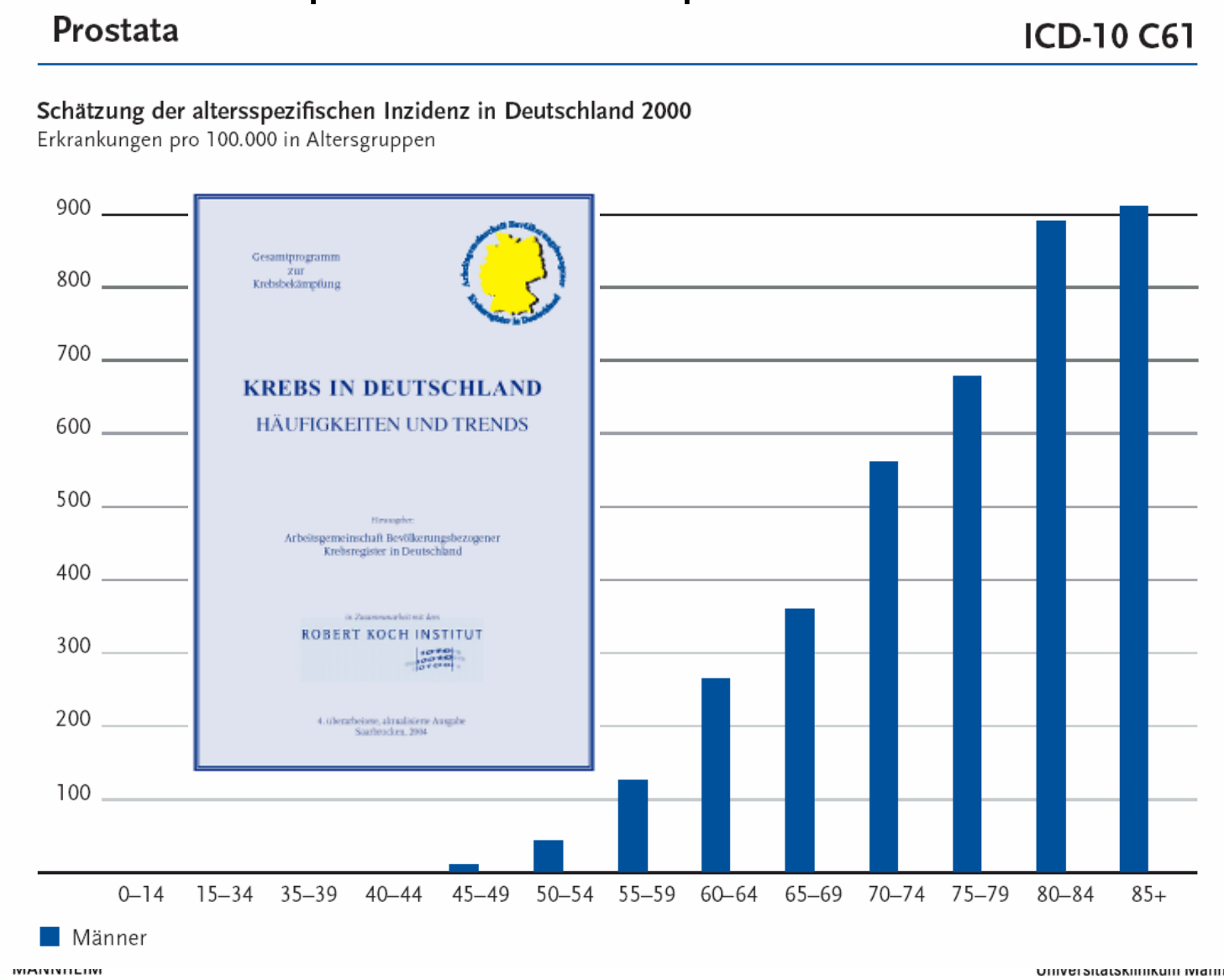
“The most important prerequisite for the development of a second neoplasm is cure of the primary malignancy”

Doerr, Hermann, SUON, 2008

-> Death as confounding factor has to be compensated for in estimates

Secondary Carcinoma

is not a relevant problem for old patients



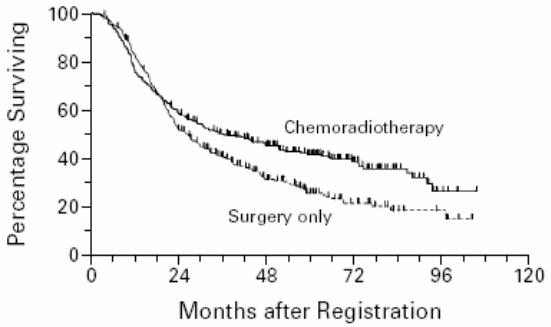


Figure 1. Overall Survival among All Eligible Patients, According to Treatment-Group Assignment.

The median duration of survival was 27 months in the surgery-only group and 36 months in the chemoradiotherapy group. The difference in overall survival was significant (P=0.005 by a two-sided log-rank test). A total of 169 of the 281 patients in the chemoradiotherapy group and 197 of the 275 patients in the surgery-only group died during the follow-up period.

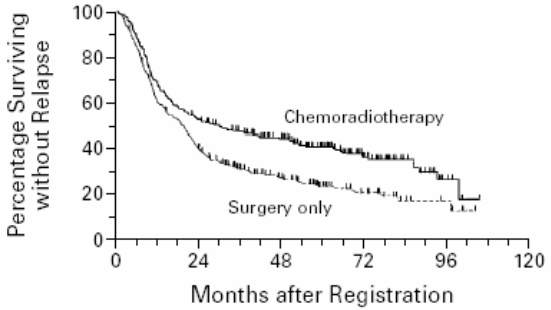


Figure 2. Relapse-free Survival among All Eligible Patients, According to Treatment-Group Assignments.

The median duration of relapse-free survival was 19 months in the surgery-only group and 30 months in the chemoradiotherapy group. This difference in relapse-free survival was significant (P<0.001 by a two-sided log-rank test). A total of 174 of the 281 patients in the chemoradiotherapy group and 206 of the 275 patients in the surgery-only group died or had a relapse during the follow-up period.

CHEMORADIOTHERAPY AFTER SURGERY COMPARED WITH SURGERY ALONE FOR ADENOCARCINOMA OF THE STOMACH OR GASTROESOPHAGEAL JUNCTION

John S. Macdonald, M.D., Stephen R. Smalley, M.D., Jacqueline Benedetti, Ph.D., Scott A. Hundahl, M.D., Norman C. Estes, M.D., Grant N. Stemmermann, M.D., Daniel G. Haller, M.D., Jaffer A. Ajani, M.D., Leonard L. Gunderson, M.D., J. Marvin Jessup, M.D., and James A. Martenson, M.D.

N Engl J Med, Vol. 345, No. 10 · September 6, 2001

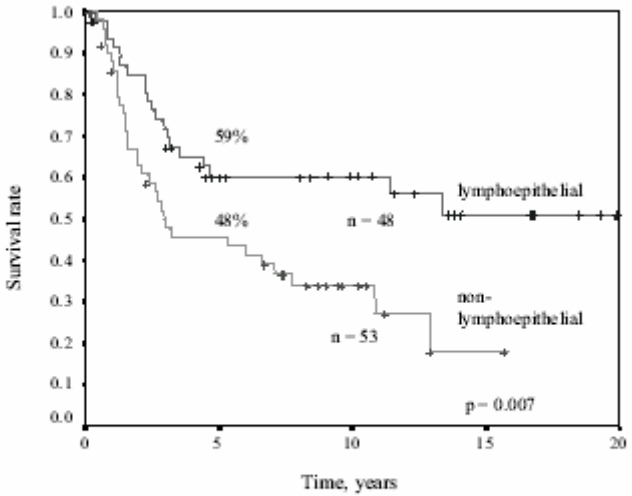


Fig. 1. Overall survival and histology: Upper curve represents 48 patients with lymphoepithelial cancer, lower curve represents 53 patients with other histology (p = 0.007).

Chemotherapy in Patients Onkologie 2003;26:12–18 mm

Patterns of Failure Following Radiation with and without

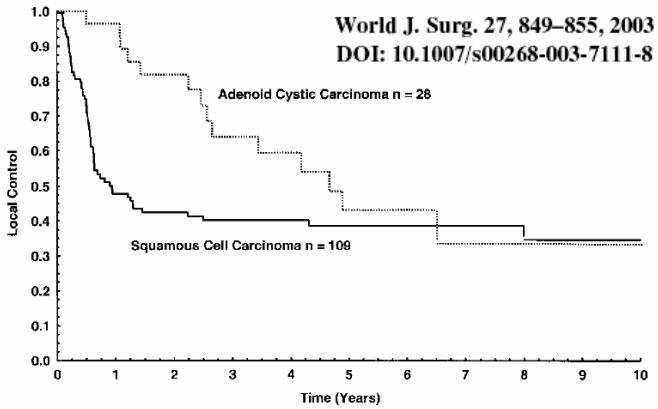


Fig. 2. Actuarial local control of paranasal sinus cancer according to histopathology: adenoid cystic carcinoma, $n = 28$; squamous cell carcinoma, $n = 109$. Data from Waldron et al. [4].

Paranasal Sinus Cancer: Caveats and Controversies

John Waldron, M.D., M.Sc.,[1] Ian Witterick, M.D.[2]

[1]Department of Radiation Oncology, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario, Canada M5G 2M9
[2]Division of Otolaryngology, Mt. Sinai Hospital, University of Toronto, 600 University Avenue, Toronto, Ontario, Canada M5G 1X5

Published Online: May 14, 2003

Secondary Carcinoma

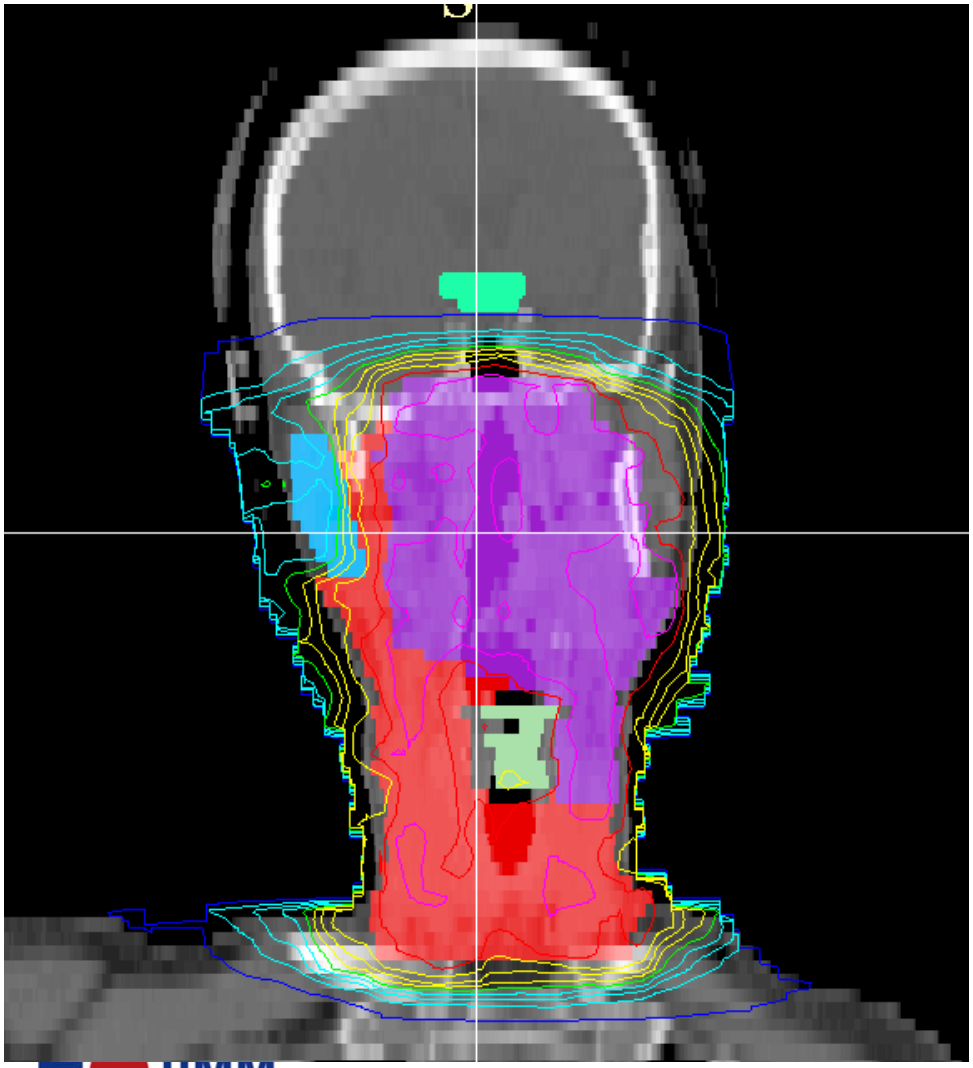
is not a relevant problem when patients with a bad prognosis (such as it is the case with advanced gastric cancer) are treated. Achieving cure is the problem for these patients.

Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

Secondary Tumors: H&N

Risk is not different from 3D if the whole diameter is irradiated



Head and Neck:
Irradiation of (more or less) the whole neck circumference with therapeutic doses (volume very similar to conventional 3D [paradigms changing slowly]) ->similar risk for secondary tumors for IMRT and 3D in the Neck area, probably slightly elevated risk outside neck due to elevated MU, increased scatter. High risk for secondary, non RT-induced cancer, though (Lung!!)

Specific Problems with IMRT

Reasons for a potentially increased incidence of secondary tumors by IMRT

1. Increased biological effectiveness of an elevated total body neutron dose

2. When compared to 3D-Conformal RT, IMRT irradiates a more tissue at lower doses

3. Increased scatter dose when dose-escalation is performed

4. Increased leakage radiation because of low MU-efficiency of IMRT

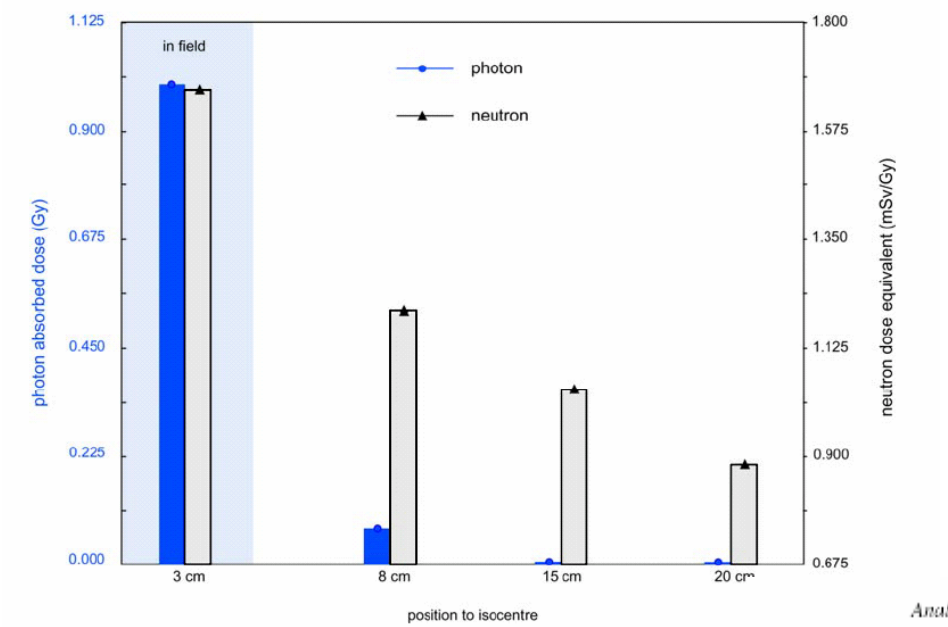


Figure 5. Siemens Mevatron. Integral photon absorbed dose (left-hand scal equivalent (right-hand scale) calculated with MCNP-GN at various positions isocentre.

Phys. Med. Biol. **45** (2000) L55–L61. Printed in the UK PII: S0031-9155(00)15010-9

RAPID COMMUNICATION

Analysis of photoneutron spectra produced in medical accelerators

Carla Ongaro†, Alba Zanini‡, U Nastasi§, José Rôdenas‖, Giuseppe Ottaviano† and Claudio Manfredotti†

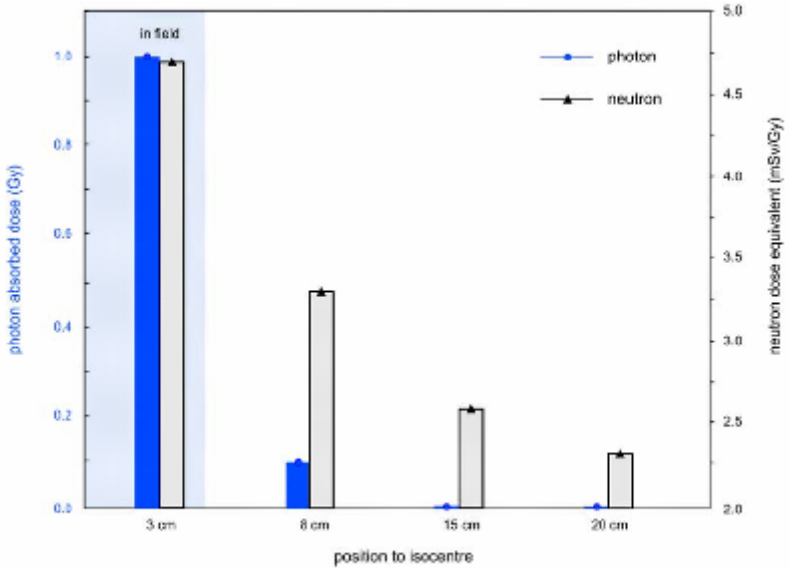


Figure 6. SELEKTA SL20i. Integral photon absorbed dose (left-hand scale) and neutron dose equivalent (right-hand scale) calculated with MCNP-GN at various positions with respect to the isocentre.

But:
Threshold energy for neutron generation is 6-8 MV,
thus relevant only at >10MV

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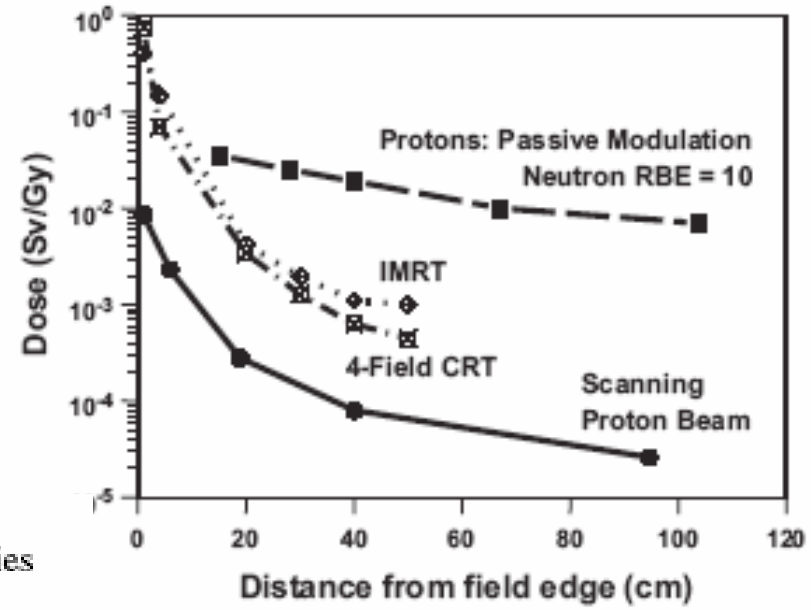


Table 3. Estimated risk of fatal radiation-induced malignancies after RT for prostate cancer (%/Sv)

Hall and Wuu (4)	
Conventional 6 MV	1.5
IMRT 6 MV	3.0
Kry *et al.* (5)	
Conventional 18-MV Varian	1.7
IMRT 6-MV Varian	2.9
Siemens	3.7
IMRT 10-MV Varian	2.1
IMRT 15-MV Varian	3.4
Siemens	4.0
IMRT 18-MV Varian	5.1

Abbreviations: IMRT = intensity-modulated radiation therapy; MV = megavoltage; RT = radiation therapy.

Secondary Tumors

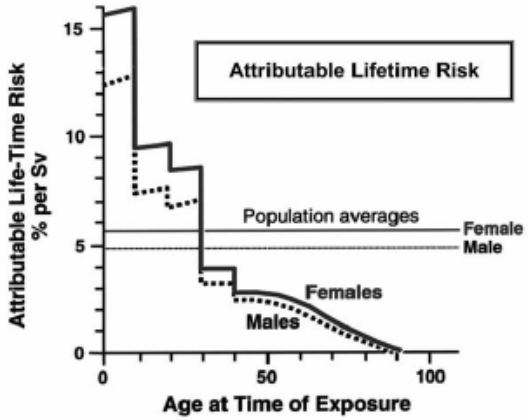


Fig. 6. The attributable lifetime risk from a single small dose of radiation at various ages at the time of exposure. Note the dramatic decrease in radiosensitivity with age. The higher risk for the younger age groups is not expressed until late in life. These estimates are based on a multiplicative model and on a dose and dose-rate effectiveness factor (DDREF) of 2. The figure was adapted from International Commission on Radiological Protection (ICRP) Publication 60 (14).

Same Leakage for Adult RT vs. Pediatric RT — But in Pediatric RT Scatter from the Treatment Volume Is More Significant

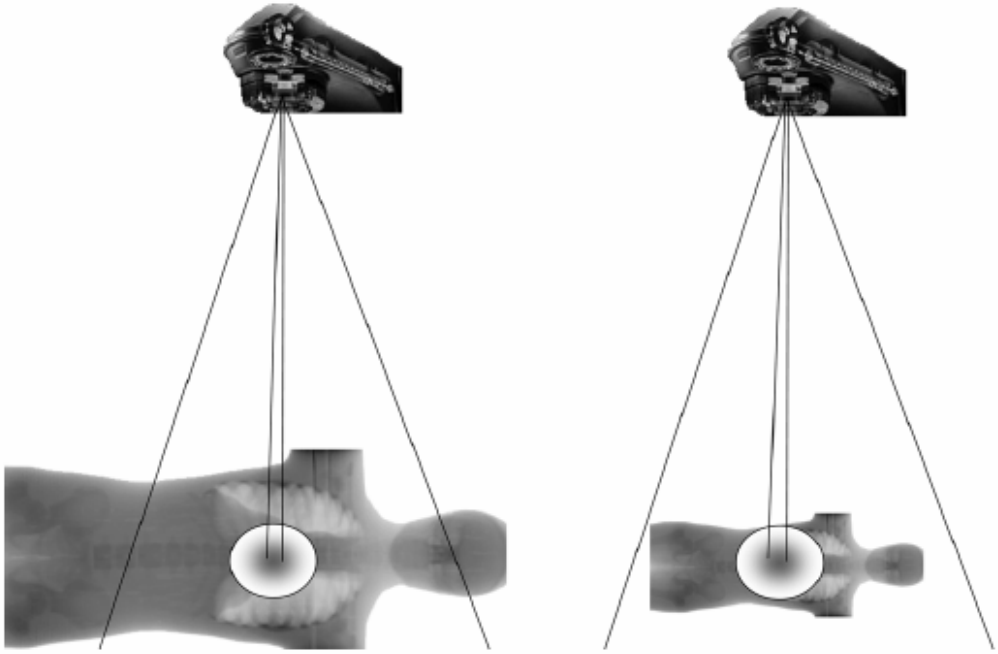


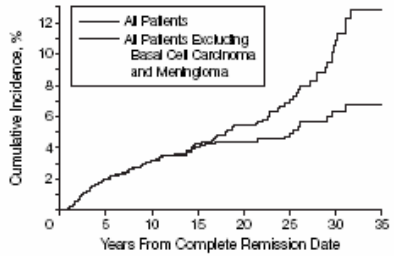
Fig. 7. When a primary tumor is treated with radiotherapy (RT) in a small child, nearby potentially radiogenic organs inevitably receive larger doses of radiation than when a comparable treatment is delivered to an adult, simply because of the closer proximity of organs in a child.

Pediatric Oncology is a problem…but not a disastrous one

The St. Jude Data….Conventional RT Techniques

Median is the line within each box; boxes indicates interquartile ranges and error bars indicate ranges.

Figure 2. Cumulative Incidence of Secondary Neoplasms Occurring in First Complete Remission



No. at Risk	2169	1265	1032	773	511	142
Incidence, % (SE)						
All Patients		1.95 (0.30)	3.14 (0.38)	4.17 (0.46)	5.37 (0.55)	10.85 (1.27)
All Patients Excluding Basal Cell Carcinoma and Meningioma		1.95 (0.30)	3.09 (0.38)	3.99 (0.44)	4.39 (0.48)	6.27 (0.83)

Hijiya, JAMA, 2007

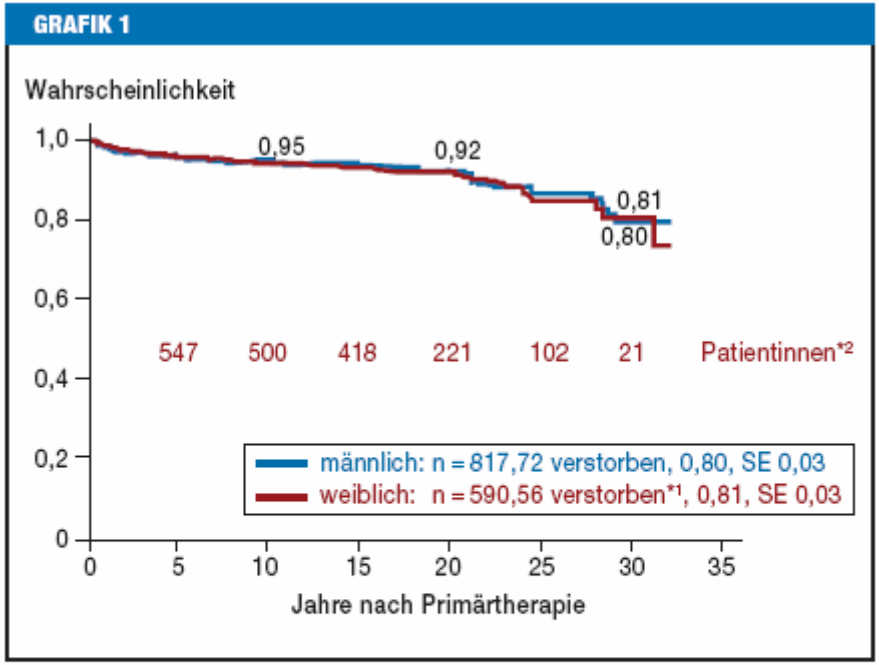
Table 3. Incidence of Secondary Neoplasm in Patients in First Complete Remission Who Were Treated for Acute Lymphoblastic Leukemia in 1962-1998 vs US General Population

Cancer Type/Site	No. of Events		Standardized Incidence Ratio (95% Confidence Interval)*
	Observed	Expected	
All tumors†			
All patients	87	6.4	13.5 (10.9-16.8)
Cranial/craniospinal irradiation	69	5.1	13.6 (10.5-17.1)
No cranial/craniospinal irradiation	18	1.4	13.3 (7.9-21.0)
Myeloid			
All patients	41	0.3	150.9 (98.1-185.4)
Cranial/craniospinal irradiation	27	0.2	138.6 (88.9-196.4)
No cranial/craniospinal irradiation	14	0.1	182.2 (99.5-306.1)
Central nervous system			
All patients	22	0.7	31.8 (19.7-47.6)
Cranial/craniospinal irradiation	21	0.5	45.8 (26.0-64.2)
No cranial/craniospinal irradiation	1	0.2	4.3 (0.1-24.0)
Lymphoma			
All patients	3	1.0	3.0 (0.6-8.8)
Cranial/craniospinal irradiation	2	0.7	2.7 (0.3-9.7)
No cranial/craniospinal irradiation	1	0.3	4.0 (0.1-22.3)
Other solid tumors†			
All patients	21	4.5	4.7 (2.9-7.1)
Cranial/craniospinal irradiation	19	3.7	5.1 (3.1-8.0)
No cranial/craniospinal irradiation	2	0.8	2.5 (0.3-9.0)

*See "Methods" section of the text for details on the calculation of standardized incidence ratios.
†These types of secondary neoplasms in first complete remission were omitted because they are not included or were only recently included in the Surveillance, Epidemiology, and End Results database: myelodysplastic syndrome (n = 7), meningioma (n = 16), and basal cell/squamous cell carcinoma (n = 16). Three malignancies occurring after meningioma or myelodysplastic syndrome were included (2 myeloid leukemias after myelodysplastic syndrome and 1 thyroid carcinoma after meningioma). See text for details.

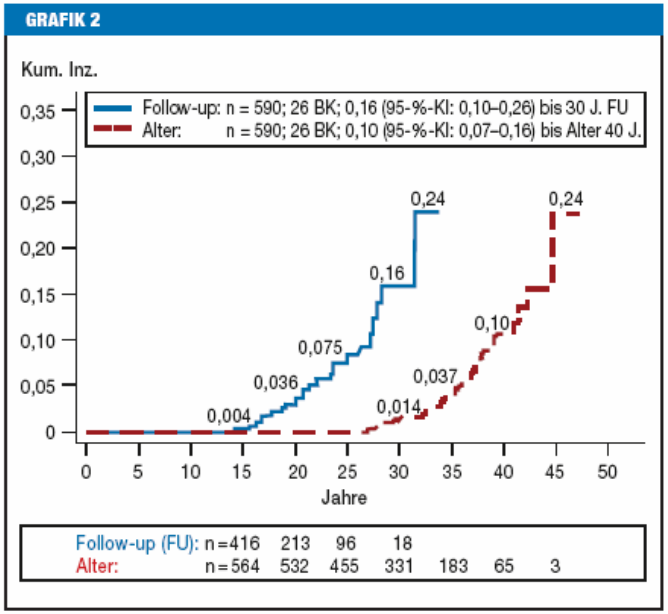
Hodgkin III: Pediatric HD

96% of Secondary Cancers in-field

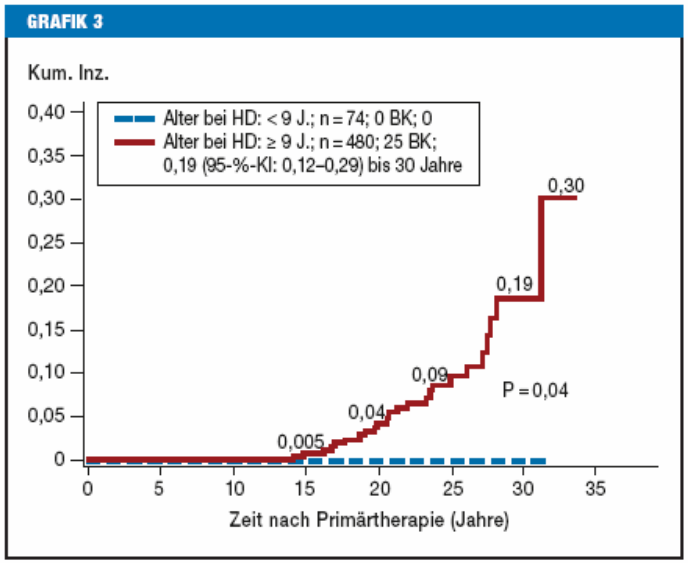


Gesamtüberleben („overall survival" [OS] nach 30 Jahren) in den Morbus-Hodgkin-Therapiestudien HD-78 bis HD-90 bei Jungen und Mädchen (Stand: 1. Juli 2012).
*1 Todesursachen bei den Patientinnen: Hodgkin-Lymphom (n = 18), Post-Splenektomie-Sepsis (n = 7), Sekundärmalignom (n = 15, davon 3 Brustkrebs), Herzerkrankungen (n = 6), sonstige (n = 10, inklusive Unfall, Suizid)
*2 mit dokumentierten Verlaufsinformationen
SE, „standard error"

Schellong, Dt. Ä-Blatt, 2014



Kumulative Inzidenz (Kum. Inz.) für Brustkrebs (BK) in der Gesamtgruppe der Patientinnen aus den pädiatrischen Therapiestudien HD-78 bis HD-90 in Abhängigkeit von der Zeit seit Primärtherapie (blaue Linie), bzw. vom erreichten Lebensalter (rote unterbrochene Linie) mit 95-%-Konfidenzintervall (95-%-KI). Stand: 1. Juli 2012



Kumulative Inzidenz (Kum. Inz.) für Brustkrebs (BK) mit 95-%-Konfidenzintervall (95-%-KI) in der Gruppe der Patientinnen aus den pädiatrischen Therapiestudien HD-78 bis HD-90, die im Brustbereich bestrahlt worden sind. (Stand: 1. Juli 2012)

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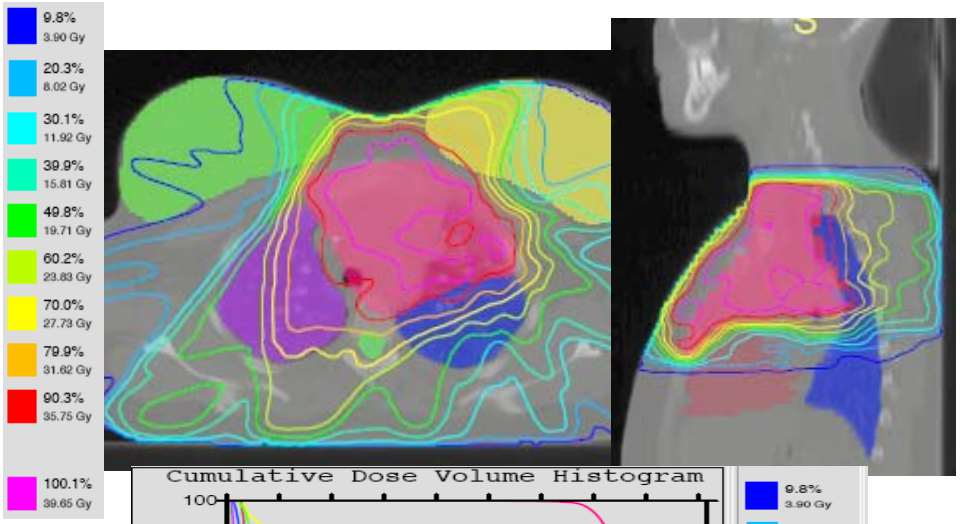
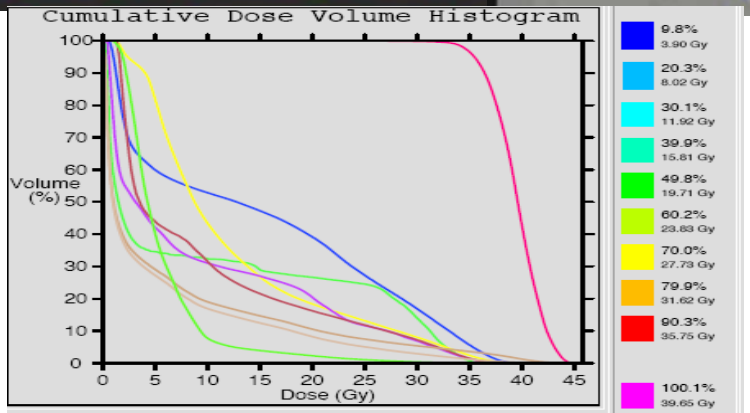
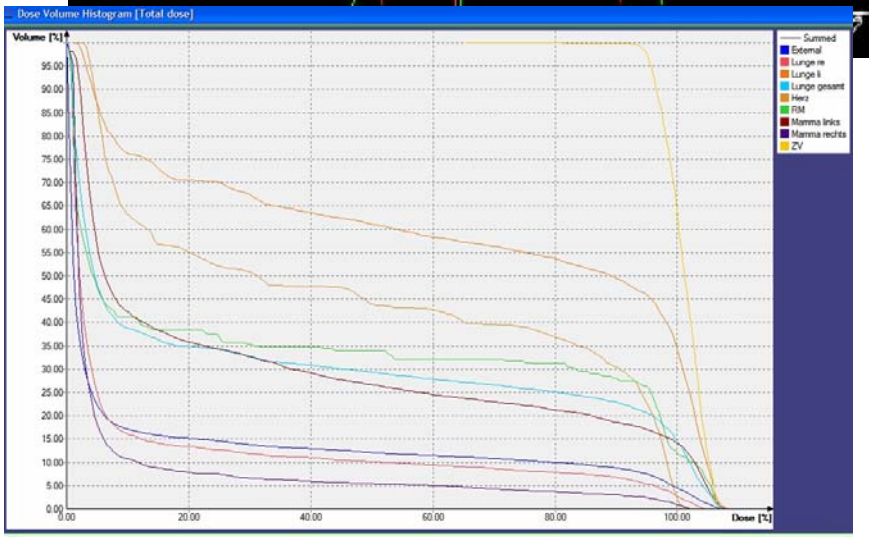
Mediastinal Tumors: Hodgkin‘s Disease

Elevated median but reduced mean breast dose as a result of improved heart protection -> Consequences???



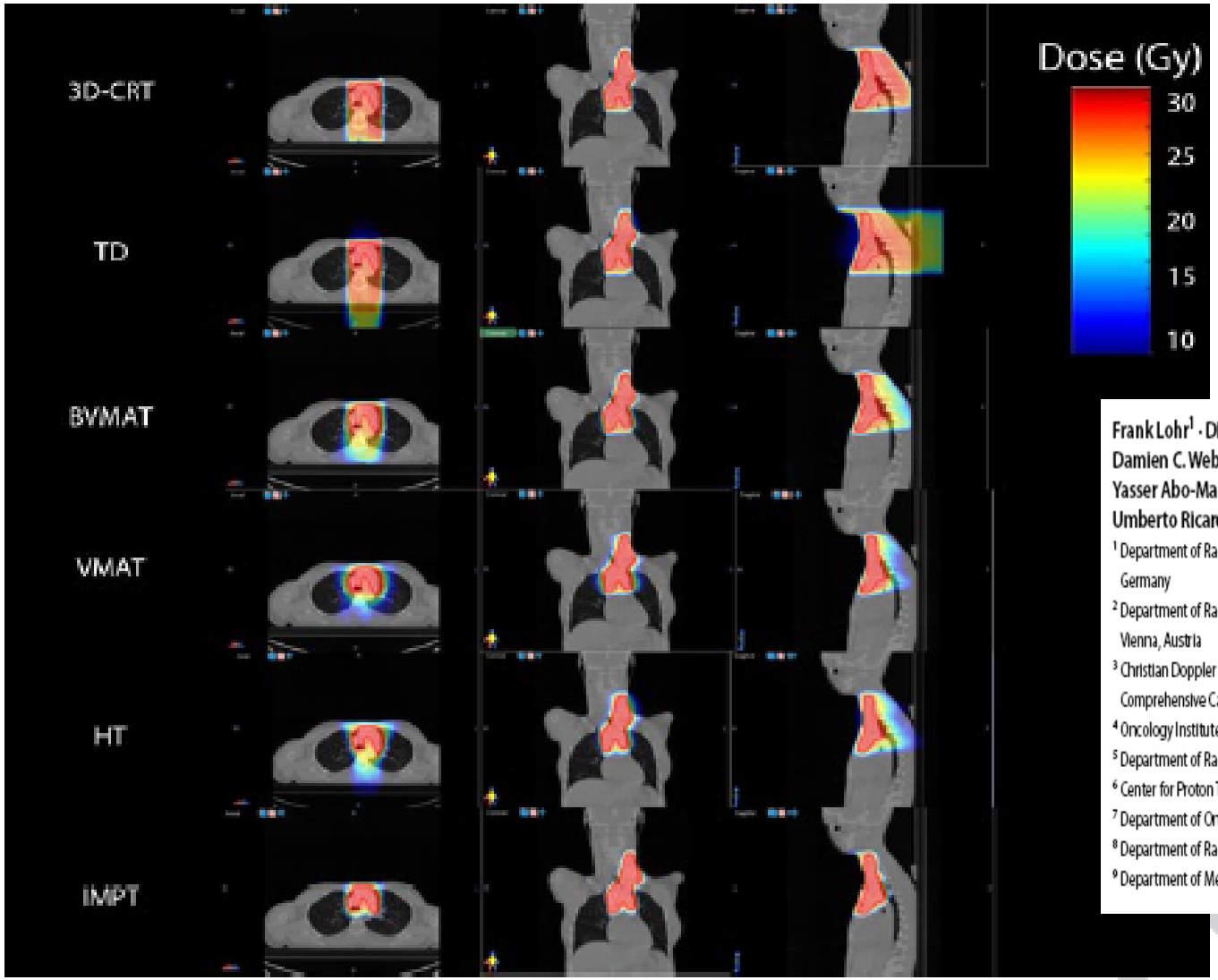




Dose Volume Histogram

Tissue
Lung (L)
Heart
Ref2 (
Spinal Cord
Lung (R)
Ref1 (
Target1 - target

Target1 - target	39.60 Limit (Gy)	49.92 Above Limit (%)	323.83 Limit (cc)	18.56 Min (Gy)	45.83 Max (Gy)	39.37 Mean (Gy)	2.33 S.D. (Gy)	648.64 Vol. (cc)
Non-target Tissue	40.00	0.14	36.20	0.00	43.54	4.96	8.26	25026.39
Tissue	40.00	1.22	313.88	0.00	45.83	5.83	9.79	25675.03
Spinal Cord	35.00	1.35	0.95	0.23	37.35	9.57	12.75	70.49
Lung (L)	14.00	48.50	318.60	0.46	41.02	14.58	12.57	656.85
Lung (R)	14.00	27.81	352.91	0.23	39.88	8.78	10.56	1268.99
Heart	10.00	31.54	114.03	1.15	38.73	8.99	9.83	361.58
Ref1 ( )	8.00	55.42	397.52	0.23	40.10	12.04	9.08	717.29
Ref2 ( )	6.00	30.57	215.19	0.46	36.67	5.42	4.27	704.03



Lohr et al., SUON, 2014

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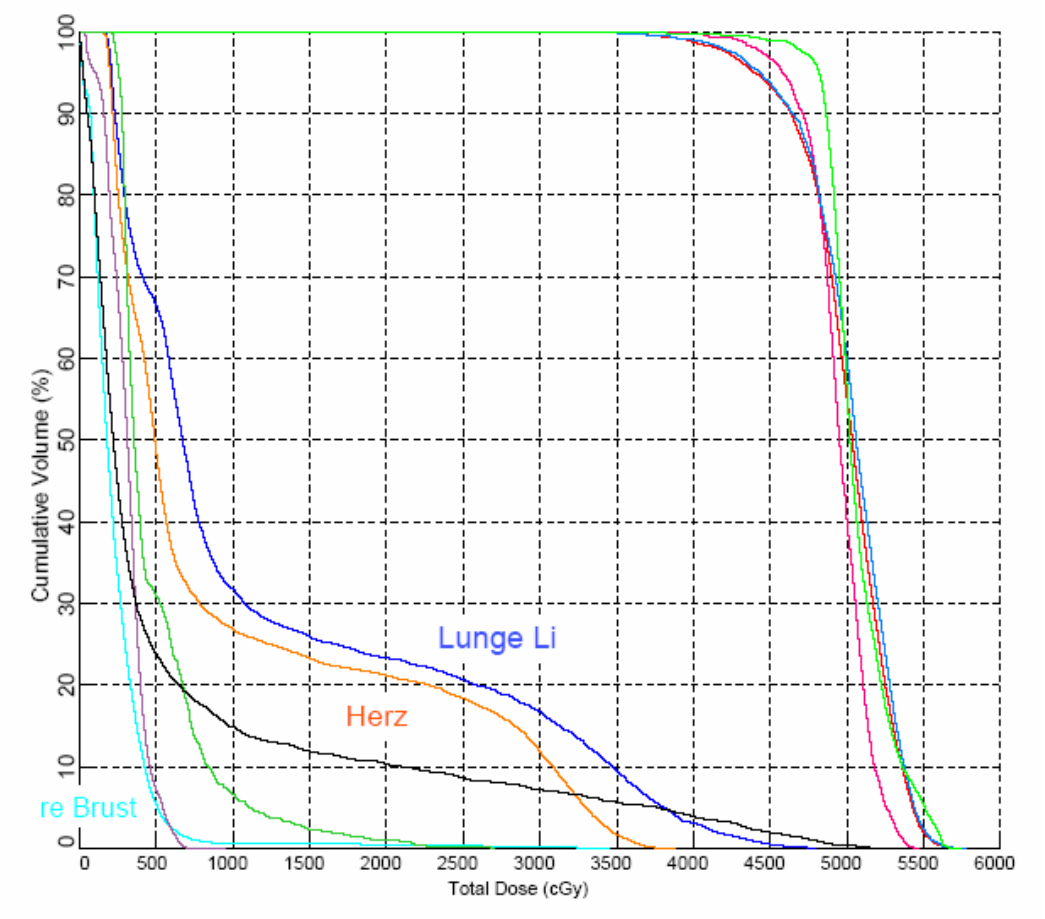
Fig. 1 ▲ Typical dose distributions for a 3D-RT plan in the various IMRT techniques: TomoDirect™, Butterfly-VMAT™ (BVMAT™), full VMAT™/RapidArc™, helical Tomotherapy™, and intensity-modulated proton RT (*IMPT*) in transversal, sagittal, and coronal planes for a patient with a typical planning target volume involving the mediastinal lymph nodes

Scatter Reduction with tangential IMRT

Table 2: Dose to various organs for various breast radiotherapy techniques.

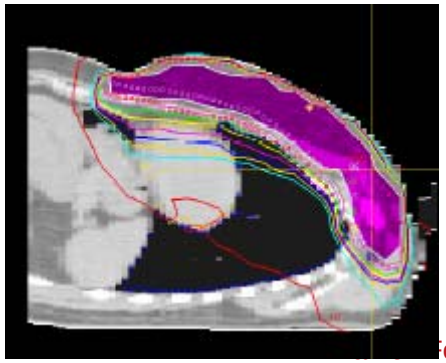
Technique	PBSI	HDR (catheters)	Wedge	IMRT	3D-CRT
Treated Breast	90 Gy	34 Gy	50 Gy	50 Gy	38.5 Gy
Contralateral Breast	2.2 mSv	230 mSv	1695 mSv	206 mSv	140 mSv
Spleen	44 mSv	1171 mSv	2300 mSv	810 mSv	130 mSv
Ipsilateral lung	790 mSv	2471 mSv	582 mSv	121 mSv	80 mSv
Heart (LAD)	0.7 Gy	3.6 Gy	2.7 Gy	1.1 Gy	0.7 Gy

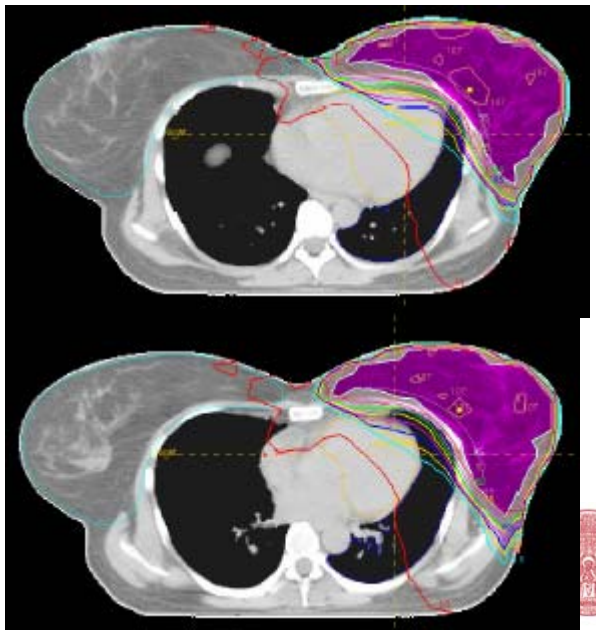
Pignol et al., 2011



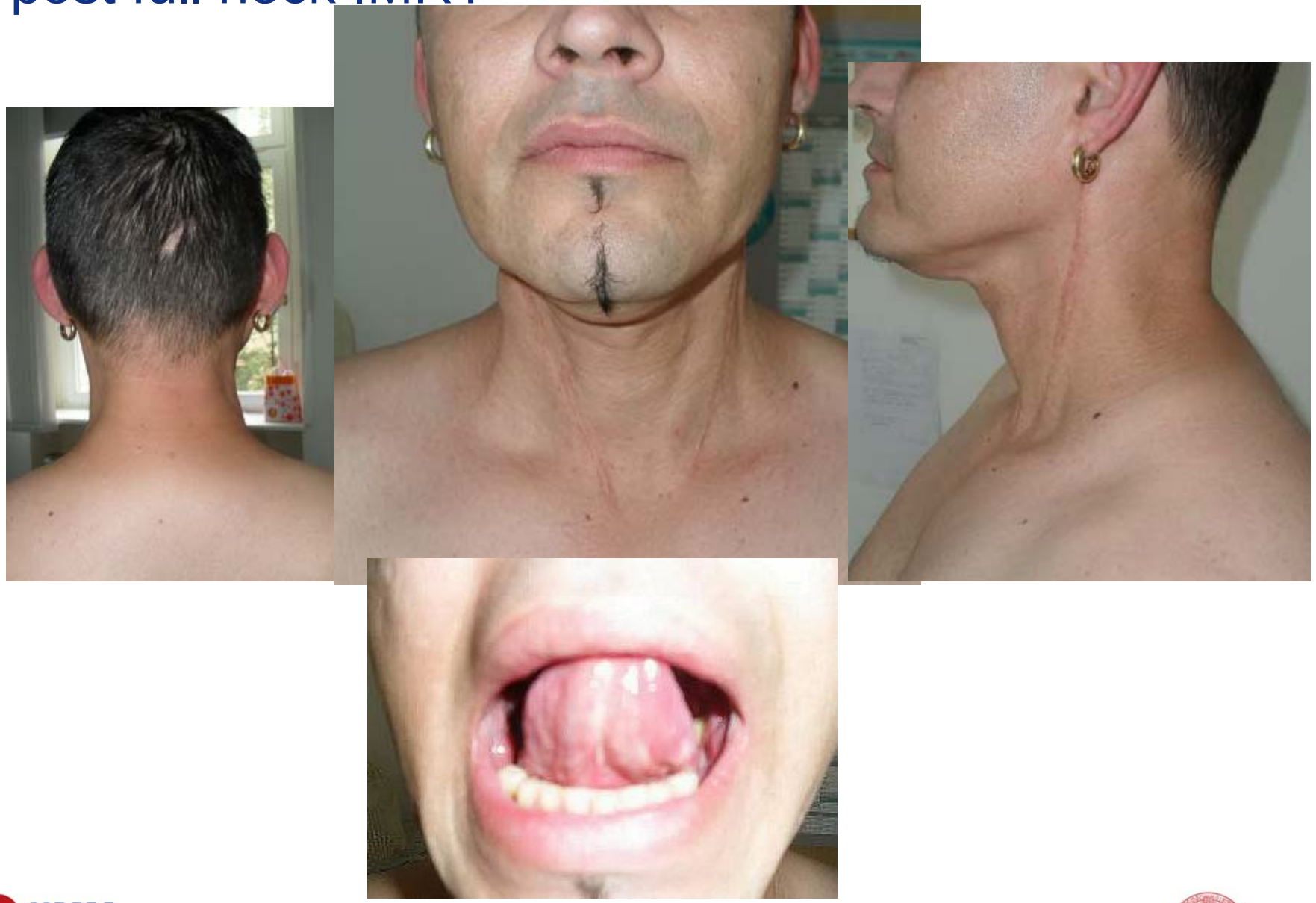
Breast:

Increase of mean and median contralateral breast dose very moderate (from 1.5 to 2.5 Gy) while improved heart protection can be achieved
(Example:
23 Segments - 7 Beams - 362 MUs)

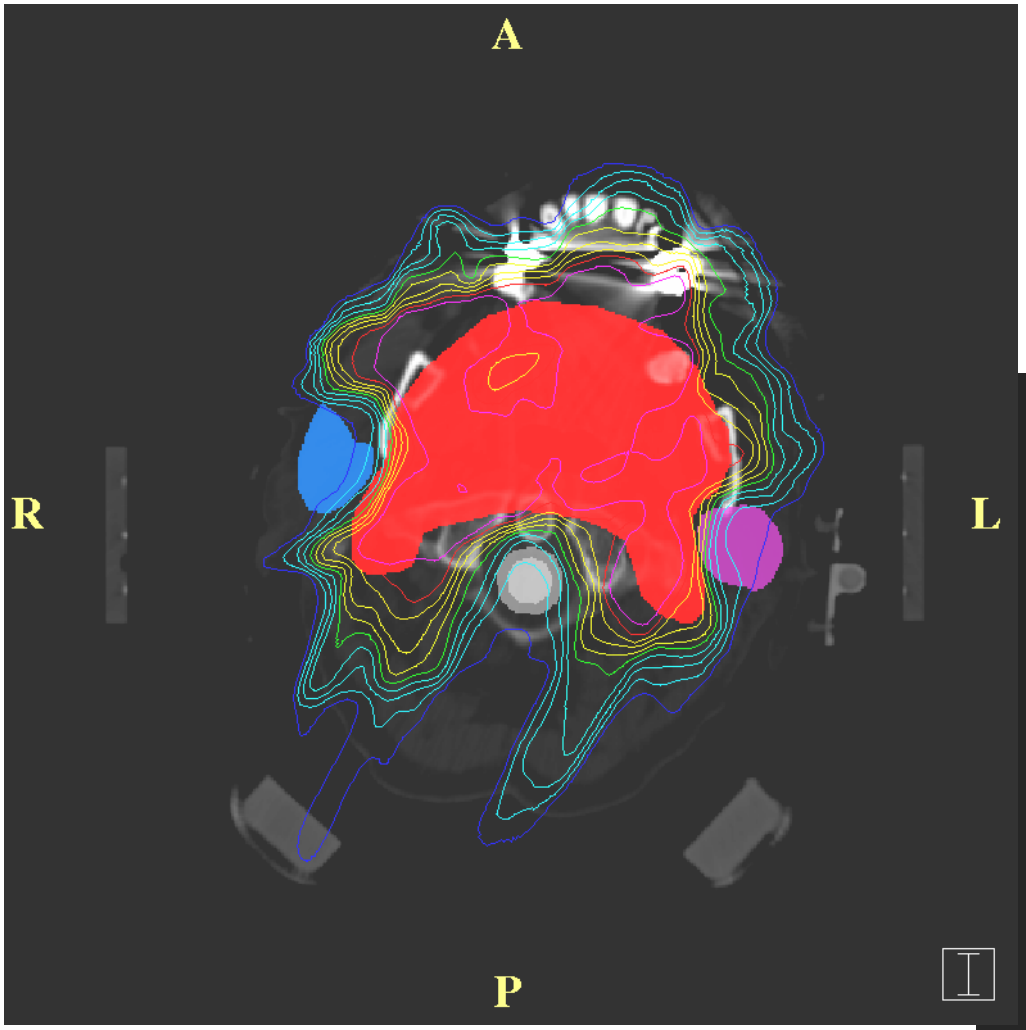


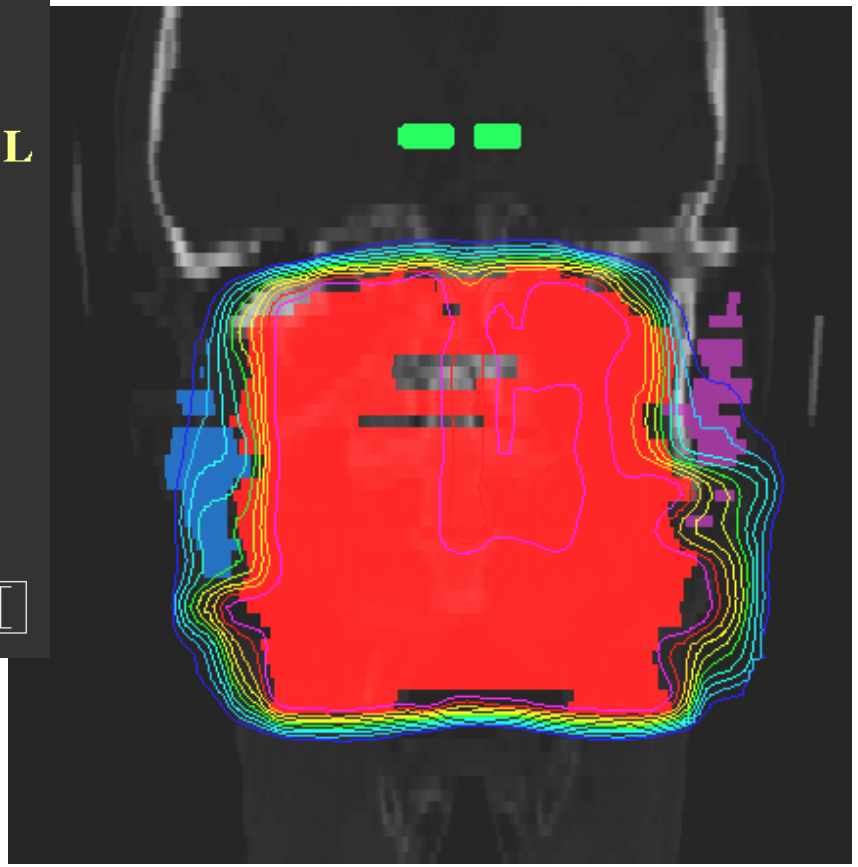


10J post full neck IMRT



Oropharnynx (Tongue) T3N0 Bilateral Parotid Sparing





Modelling

(depends on parameters one may not be aware of that they exist, which contributes to modellings‘ limitations)

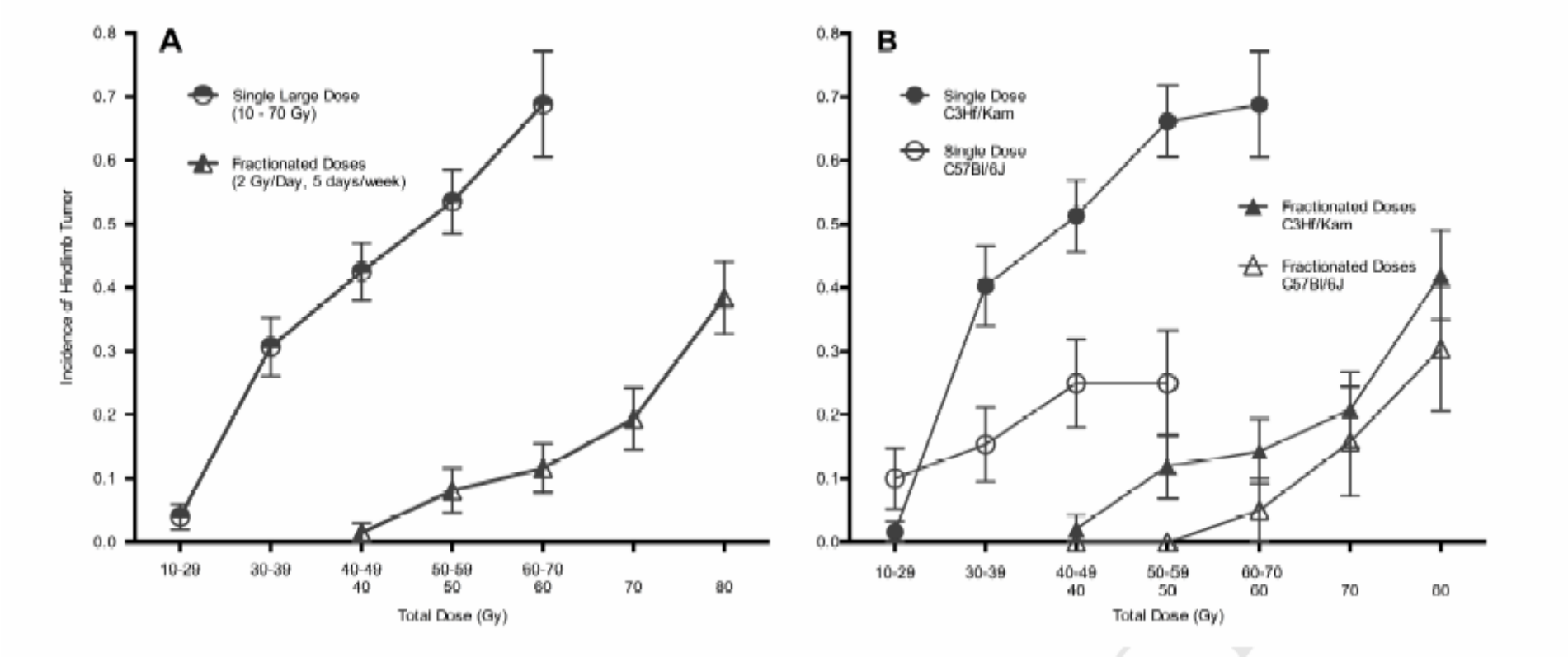


Figure 2. Incidence of hindlimb tumors by radiation dose. (A) Incidences of hindlimb tumors are significantly increased in mice exposed to a single large dose of radiation in comparison to mice exposed to fractionated radiation ($p < 0.001$). (B) Incidences of hindlimb tumors by radiation dose and mouse strain. C3Hf/Kam mice have a significantly higher incidence of hindlimb tumors following single dose exposures than C57BL/6J mice ($p < 0.001$). No significant difference in tumor incidence is observed between C3Hf/Kam and C57BL/6J mice following fractionated exposures. Single doses are grouped as 10-29, 30-39, 40-49, and 50-59 Gy. Fractionated doses were given as 2 Gy/day, 5 days/week for 4 to 8 weeks and are listed as total doses of 40, 50, 60 , 70, and 80 Gy

Edmondson et al., IJROBP, 2015

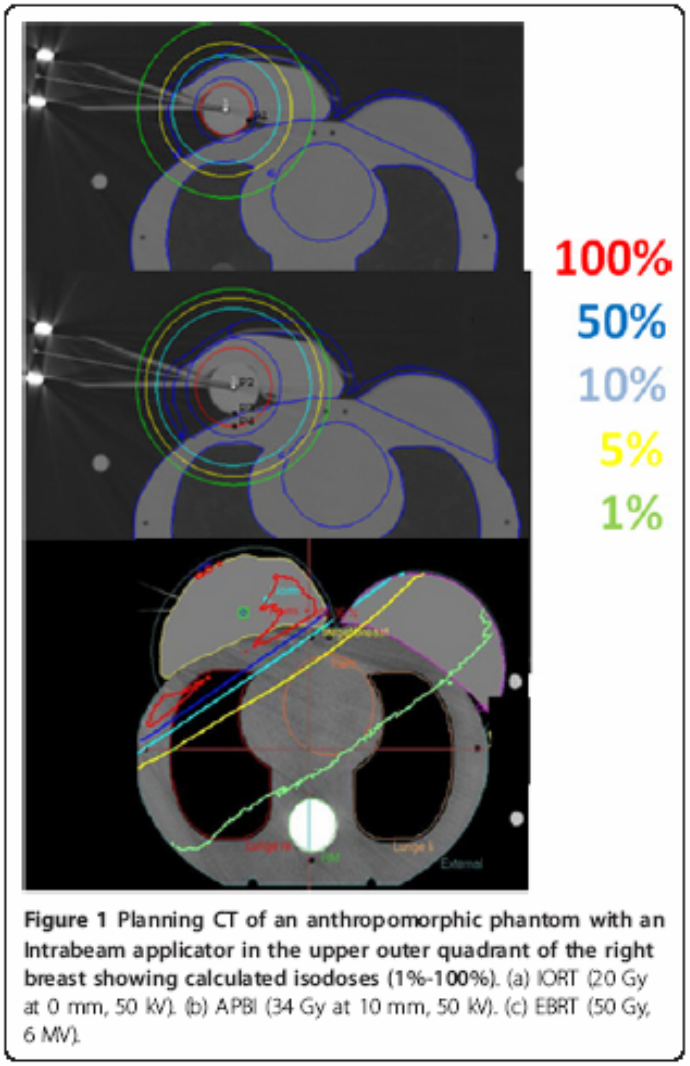


Figure 1 Planning CT of an anthropomorphic phantom with an Intrabeam applicator in the upper outer quadrant of the right breast showing calculated isodoses (1%-100%). (a) IORT (20 Gy at 0 mm, 50 kV). (b) APBI (34 Gy at 10 mm, 50 kV). (c) EBRT (50 Gy, 6 MV).

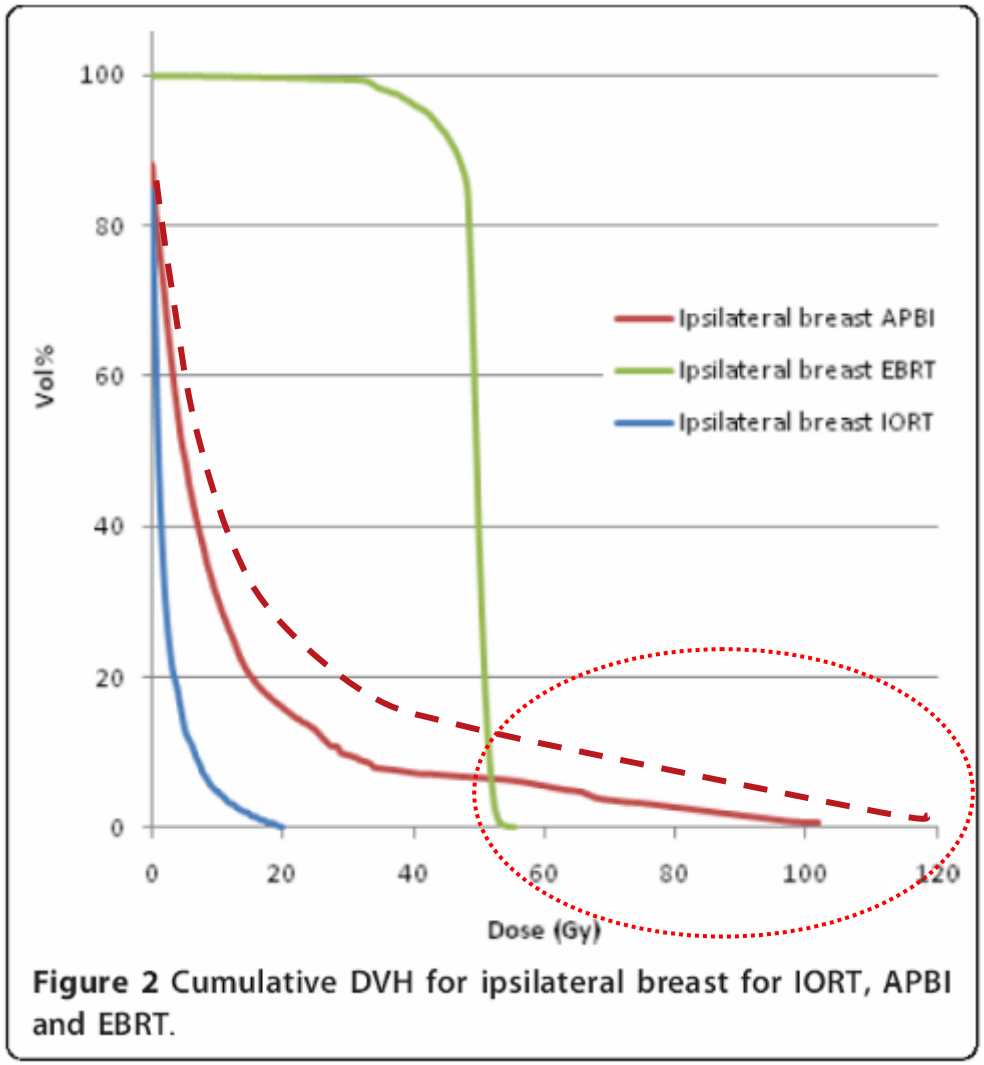


Figure 2 Cumulative DVH for ipsilateral breast for IORT, APBI and EBRT.

Aziz et al., Radiation Oncol, 2011

Synopsis

1. For **most patients**, second cancer is **not a relevant concern**. Young women with **breast cancer, Hodgkin‘s disease** and **pediatric** patients, however, **require attention** and an individual assessment if IMRT may carry more or less risk than 3D.

2. Most **Modelling** is based on Hiroshima Nagasaki data
–> valid for doses <2 Gy

3. **Therapeutic Data** have become available only relatively recently and suggest a linear relationship between SCI and Volume and at least a **linear relationship** between SCI and Dose

4. There is **no evidence for overkill/plateau** in relevant dose ranges for fractionated and single-dose RT, Incidence/dose relationship may be **supralinear** for fractionated RT

5. **Beam modalities other than MV** photons may have other characteristic

Where the real danger lurks……

Dental X-Rays and Risk of Meningioma

Elizabeth B. Claus, MD, PhD[1,2]; Lisa Calvocoressi, PhD[1]; Melissa L. Bondy, PhD[3]; Joellen M. Schildkraut, PhD[4]; Joseph L. Wiemels, PhD[5]; and Margaret Wrensch, PhD[5,6]

Cancer, 2012

Variable	Cases, n = 1433 No.	%	Controls, n = 1350 No.	%	OR (95% CI)[b]
Ever had Panorex					
Aged <10 y	22	2.1	5	0.4	4.9 (1.8-13.2)
Ages 10-19 y	91	8	69	6.1	1.5 (1.1-2.1)
Ages 20-49 y	349	30.3	355	31.5	0.9 (0.7-1.1)
Aged ≥50 y	253	29.9	223	27	1.2 (0.9-1.5)
Any age	536	46.7	541	46.7	1.0 (0.8-1.2)
Frequency of Panorex					
Aged <10 y					
Ever	22	2.1	5	0.4	4.9 (1.8-13.2)
Ages 10-19 y					
None	1040	92	1054	93.7	1.0
Less than yearly	74	6.5	63	5.6	1.3 (0.9-1.9)
Yearly or more	17	1.5	6	0.5	3.0 (1.2-7.8)
Ages 20-49 y					
None	803	69.7	773	68.5	1.0
Less than yearly	311	27	341	30.2	0.9 (0.7-1.0)
Yearly or more	38	3.3	14	1.2	2.7 (1.4-5.3)
Aged ≥50 y					
None	592	70.1	603	73	1.0
Less than yearly	214	25.3	209	25.3	1.0 (0.8-1.3)
Yearly or more	39	4.6	14	1.7	3.0 (1.6-5.6)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Individuals who received therapeutic radiation to the head, neck, face, or chest were not included (114 cases and 60 controls).
[b] Adjusted for age, sex, education, race (white vs nonwhite), and history of head computed tomography.

Table 3. Reported History of Therapeutic Radiation to Head, Neck, Face, or Chest Among Meningioma Cases and Controls

Radiation Treatment For	Cases, n = 1433 No.	%	Controls, n = 1350 No.	%	OR (95% CI)
Cancer	58	4.1	37	2.7	1.5 (1.0-2.2)[a]
Benign tumor	15	1	5	0.4	2.8 (1.0-7.8)[a]
Tonsils/adenoids	5	0.4	0	0	$P = .0628$[b]
Thyroid	9	0.6	2	0.2	$P = .0660$[b]
Acne	10	0.7	6	0.4	$P = .4565$[b]
Ringworm	4	0.4	0	0	$P = .1253$[b]
Ear	3	0.2	1	0.1	$P = .6254$[b]
Other	15	1.1	9	0.7	$P = .3087$[b]
Any	114	8	60	4.4	1.8 (1.3-2.5)[a]

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for age, sex, and race (white vs nonwhite).
[b] Fisher exact test (2-sided probability).

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