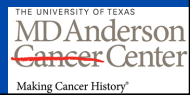
Second Cancers from Radiotherapy Procedures

Stephen F. Kry, Ph.D., D.ABR.



Outline

- Radiation and cancer induction
- Medically exposed people
- Estimating risk of second cancers
- Minimizing the risk

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Evidence of second cancers

- A-bomb
  - Most comprehensive cohort and most extensive studies
- Occupationally exposed
- Radiation accidents (Mayak)
- Medically exposed (Radiotherapy, also non-cancer radiation: peptic ulcers, tinea capitis)

A-bomb population

- ~120,000 people (Life Span Study)
- ~17,500 cancers (post 1958)
- 30% had doses 0.005 – 0.2 Gy
- 3% had doses >1 Gy
- Healthy population

compared to Hiroshima or Nagasaki residents who lived far from the bomb site or were not in the city at the time of the bombing

Initial Size of the Life Span Study Incidence Cohort[a] and Percentage Surviving[b] by Age at Exposure and Gender

Age at exposure	Male		Female		Total	
	People	Alive	People	Alive	People	Alive
<10	11,618	89%	11,917	94%	23,535	91%
10–19	11,202	73%	14,243	87%	25,445	81%
20–29	3,686	47%	11,680	72%	15,366	66%
30–39	5,716	17%	10,928	36%	16,644	29%
40–49	7,421	2%	9,469	5%	16,890	3%
≥50	6,237	0%	7,835	0%	14,072	0%
All ages	45,880	46%	66,072	55%	111,952	52%

Risks from A-bomb

Main findings:

- Significantly elevated risks of
  - Second cancers
  - Heart disease, stroke, digestive disease, respiratory disease (Preston et al, Radiation Research, 2003)
- Induced cancers are largest risk

  2/3 of the excess mortality
  - 440 solid cancer deaths and 250 noncancer deaths associated with radiation exposure (Preston et al, Radiation Research, 2003)

Cancer risk

- Significantly elevated risk for:
  - Oral cavity, esophagus, stomach, colon, liver, lung, non-melanoma skin, breast, ovary, bladder, nervous system, thyroid
- Consistent excess (not statistical)
  - Pancreas, prostate, kidney
- Radio-resistant organs:
  - Rectum, gallbladder, uterus
- Of 17,448 observed solid cancers (Preston 2007)
  - 96% carcinoma
  - <2% sarcoma

Attributable risk

- People get cancer normally!
- How much is the risk is elevated. Is it relevant?
- What fraction of the observed cancers are due to radiation?

Observed and Fitted[a] Solid Cancer Cases by Dose Category and Attributable Fraction

Dose category[b]	Subjects	Person years	Cases	Background	Fitted excess	Attributable fraction
<0.005	60,792	1,598,944	9,597	9,537	3	0.0%
0.005–0.1	27,789	729,603	4,406	4,374	81	1.8%
0.1–0.2	5,527	145,925	968	910	75	7.6%
0.2–0.5	5,935	153,886	1,144	963	179	15.7%
0.5–1	3,173	81,251	688	493	206	29.5%
1–2	1,647	41,412	460	248	196	44.2%
2–4	564	13,711	185	71	111	61.0%
Total	105,427	2,764,732	17,448	16,595	853	10.7%[c]

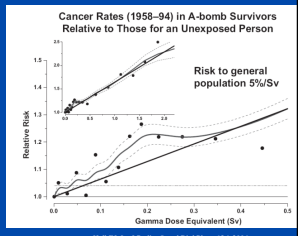
Preston et al, Radiation Research, 2007.

Total excludes "negligible" dose group

Also depended on age at exposure
20% for 0-9 year olds
6% for 40+ year olds

Dose relationship

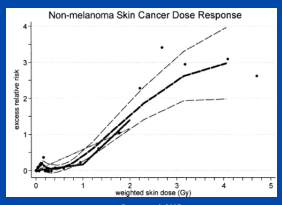
- 0.1 – 2.5 Sv: Linear
  0-0.15 Gy: elevated & linear
- High doses
  - No data because no survivors
- Low doses
  - Not enough power
  - Extrapolation via cell studies
    - largely linear
  - Radiation hormesis
    - BEIR VII Appendix D. Body of evidence suggests no such effect



Hall EJ, Int J Radiat Oncol Biol Phys. 65:1;2006

Dose relationship

- Most solid cancers are linear
- Leukemia typically fit with linear-quadratic function
- Some specific sites suggest non-linear behaviour



Preston et al. 2007

Age and time effects

- Risk also depends on age of exposure (younger people are more sensitive).
- Risk also depends on attained age/time since exposure (the longer you live, the more your risk increases). Relative risk becomes less elevated as time progresses after exposure, but absolute risk still elevated

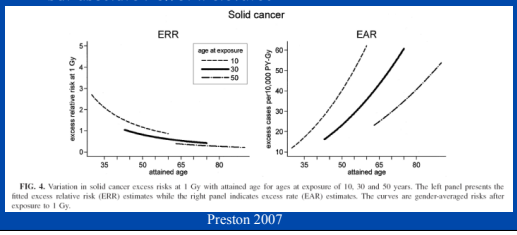
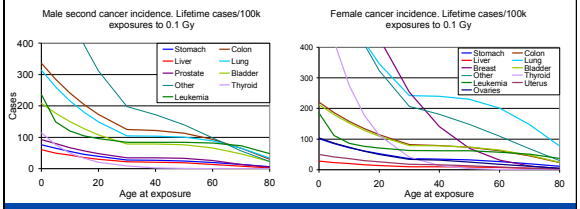


FIG. 4. Variation in solid cancer excess risks at 1 Gy with attained age for ages at exposure of 10, 30 and 50 years. The left panel presents the fitted excess relative risk (ERR) estimates while the right panel indicates excess rate (EAR) estimates. The curves are gender-averaged risks after exposure to 1 Gy.

Preston 2007

Gender effects



- Females more sensitive than males…?
  - Sensitive gender organs: breast
  - Higher relative risk
    - May be simply related to lower background rates and comparable sensitivity. (Preston 2007)

BEIR VII report: Committee on the Biological Effects of Ionizing Radiations. Health risks from exposure to low levels of ionizing radiation: BEIR VII phase 2. Washington DC: The National Academies Press; 2005

Q1: The organs most at risk of a second cancer for a 15 year old female are

5% 1. Breast, muscle tissue, thyroid
2% 2. Heart, lung, breast
92% 3. Breast, lung, thyroid
2% 4. Breast, lens of eye, lung
0% 5. Lung, thyroid, colon

A1: 3. Breast, lung, thyroid

- Breast, lung, and thyroid are the most sensitive organs for female pediatric patients
- Heart and lens of eye are also sensitive to damage and late effects, but not second cancers.
- Muscle/connective tissue, etc., are not sensitive at these doses. I.e., no sarcomas.

- BEIR VII report: Committee on the Biological Effects of Ionizing Radiations. Health risks from exposure to low levels of ionizing radiation: BEIR VII phase 2. Washington DC: The National Academies Press; 2005.

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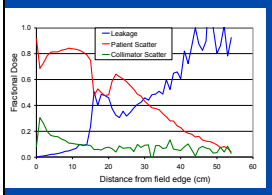
Medical Studies

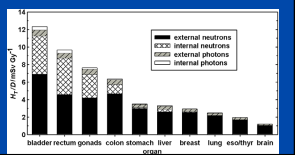
- We know radiation causes cancer, so no surprise that radiotherapy can cause second cancers.
- Radiation confers benefit, delivered for this purpose
  - Well, radiation delivered to CTV
  - Radiation to CTV-PTV only because we can't control setup and immobilization (and range uncertainty for protons)
  - Radiation outside PTV only because we can't control the radiation
    - Entrance and exit doses as well as out of field

Radiation sources

In field and build-up/exit regions are deposited by primary beam
Out-of-field source:



Photon therapy
10x10 field, 5 cm depth
6 MV
Kry et al, Phys Med Biol 2010



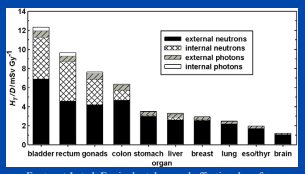
Proton therapy
250 MeV scanning beam
Fontenot et al, Phys Med Biol 2008

Q2: What is the dominant contributor to the second cancer risk from passive scatter proton therapy?

72% 1. Neutrons generated in the accelerator head
19% 2. Neutrons generated in the patient
9% 3. Photons from capture gamma events
0% 4. Radiation from room activation
0% 5. No risk from this modality

A2: 1. Neutrons generated in the accelerator head

- Most dose equivalent will originate with neutrons generated in the accelerator.



Fontenot J et al. Equivalent dose and effective dose from stray radiation during passively scattered proton radiotherapy for prostate cancer. Phys Med Biol. 53 (2008) 1677-1688.

Dosimetry

- Dosimetry is challenging for medical radiation epidemiology studies
- Thousands of patients
- In-field
  - Usually no CT. Reconstruct from charts
- Near field
  - Estimate where field borders are (and patient anatomy)
- Out of field
  - Requires special programs

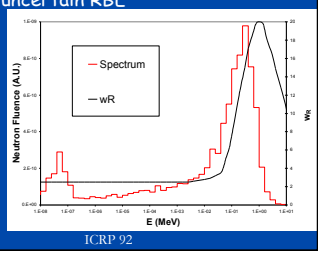
Dosimetry

- More complicated when neutrons are involved
  - Protons/High-energy photon therapy
- Neutrons are hard to measure
- Neutrons have high and uncertain RBE

$H\ (Sv) = w_R \times D\ (Gy)$

Or

$$H_{n+n_\gamma} = Q_{\text{eff}}(D_n + D_{n_\gamma}) = Q_n \cdot D_n + D_{n_\gamma}$$



ICRP 92

Neutron Dosimetry

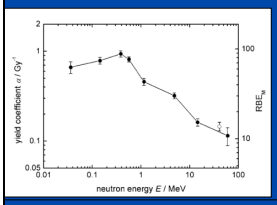


Table 2. Estimated relative biological effectiveness (RBE) for the 20-MV (γ + n) beams relative to the 6-MV (γ)

	20-MV (γ + n) beam relative to 6-MV (γ) beam	Neutrons from 20-MV beam relative to 6-MV (γ) beam
C^3H 10T½	4.8 ± 2.8	215 ± 124

Mutagenesis in mouse fibroblast cell line

Hall, 1995

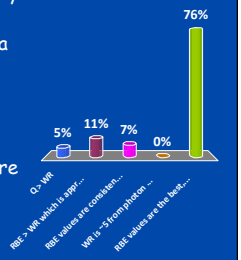
Dicentric chromosome induction in human lymphocytes

Nolte, 2005

- Other measurements have found RBE = 1 NCRP 104
- Depends on cell line, endpoint, dose, dose rate…
- Large uncertainties in neutron RBE

Q3: Which of the following statements about high-LET measures is true?

1. $Q > W_R$
2. RBE > W_R which is approximately equal to Q
3. RBE values are consistent for a given endpoint for a constant LET
4. W_R is ~5 from photon beam generated neutrons
5. RBE values are the best, but are nearly impossible to find or determine



A3: 5. RBE values are the best, but are nearly impossible to find or determine

1. $W_R > Q$ - Similar values
2. RBE > W_R which is approximately equal to Q - RBE has many values
3. RBE values are consistent for a given endpoint for a constant LET - RBE also varies with cell type, in vivo vs in vitro, etc.
4. W_R is ~5 from photon beam generated neutrons - The W_R maximum aligns with the fluence maximum

- ICRP 92: International Commission on Radiological Protection "Relative Biological Effectiveness (RBE), Quality Factor (Q), and Radiation Weighting Factor (wR)" ICRU Report 92 (ICRP, Bethesda, MD, 2003).

Second Cancers in RT patients

- Elevated risk of second cancers for patients undergoing RT
- Second cancers are one of the most common late effects for pediatric patients (NCI bulletin, 5:6 2008)
- SEER database (200,000+ RT patients)
  - Second cancers (RT patients):
    9% overall
    4-20% by primary site

Rates for medically exposed

- Not all are from radiation
  - Confounding genetics, environment, etc.
- What is the actual risk from RT?
- SEER registry, 12 year mean follow up, 1+ yr survivors
  - Berrington et al, Lancet Oncology, 2011
- 9% of patients developed a second cancer
- 8% of all observed second cancers were attributed to radiation
- ~1% of cancer patients that survive tx (1 yr) will develop a second cancer because of the radiation

Second Cancer Rates

- Fraction of second cancers attributable to radiation varies with primary site (Maddams et al. Int J Cancer, 2008)
- Hodgkin's disease: 17%
- Oral cavity: 18%

Interesting considerations

- Elevated risk of second cancers even for primary sites with poor prognosis (lung)
  - RR: 1.18 (Berrington 2011), 7% attributable to RT (Maddam 2008)
- Elevated risk of second cancers even for old patients (prostate).
  - RR: 1.26 (Berrington 2011), 5% attributable to RT(Maddam 2008)
  - 1 patient in 70 (10+ yr survivors) develops RT-attributable second cancer. (Brenner et al. Cancer 2000)
- Elevated risk of sarcoma (RR:1.29)
  - 15% of second cancers were sarcoma (Diallo 2009)

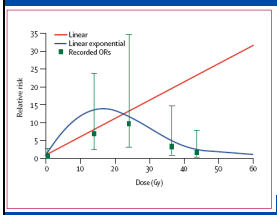
Severity of second cancers

- Limited study, but no indication that second cancers offer better or worse outcomes than primary cancers (Mery et al. Cancer 2009)

Dose Response

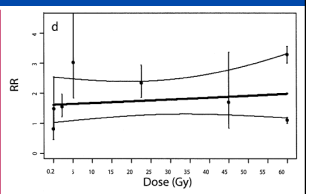
- Much larger dose range for medically exposed
- Linear, plateau, or linear exponential?
- Most organs aren't linear, but what?

Thyroid



Sigurdson, Lancet, 2005

Bladder



Suit, Rad Res, 2007

Location

- Where do second cancers occur?
  - 12% within geometric field
  - 66% beam-bordering region
  - 22% out-of-field (>5 cm away) Diallo IJROBP 2009
- Get most second cancers in high-intermediate dose regions

Location

- Low doses (<1 Gy; 10 cm from field edge)
  - Studies typically don't find increased risk
  - except for sensitive organs: lung after prostate (Brenner 2000)
    - Most likely too few patients
    - Low absolute risk
- Higher doses (in and near treatment field)
  - Most organs show elevated risk
  - Sarcomas inside the treatment field

Q4: Which is unique about medically induced second cancers to A-bomb induced cancers

2% 1. Over-expression of colon cancers
7% 2. Longer latency period
14% 3. Heightened sensitivity/risk
75% 4. Heightened incidence of sarcomas
2% 5. More aggressive tumors

A4: 4. Incidence of sarcomas

- Virtually no excess risk of sarcomas observed in A-bomb survivors; it is overwhelmingly associated with high doses.
- There is no evidence for any of the other differences.

- BEIR VII report: Committee on the Biological Effects of Ionizing Radiations. Health risks from exposure to low levels of ionizing radiation: BEIR VII phase 2. Washington DC: The National Academies Press; 2005.

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Epidemiology studies

- Clearly the gold standard, but….
- Need follow up
  - Decades later, treatment modality obsolete
  - No IMRT epidemiology studies
  - No proton therapy studies
- Need lots of patients
  - Hard to coordinate
  - Expensive

Alternative

- Calculate estimate of risk
- Use risk models
- Small number of patients
- Use CT data and detailed dose calculations for the subset evaluated
- Can look at modern or theoretical treatments
- Results can depend on model assumptions and uncertainty

Estimating 2nd cancers

- Low doses: 5%/Sv (from A-bomb)
  - This value also includes dose rates effects to move from acute exposures to protracted exposure.
- More refined – look at age, gender, and organ specific risk coefficients
- Can also incorporate age at exposure and years of survival

What about at higher doses?

- Model dose response
- Available models derived from
  - Radiation biology (Dasu et al. Acta Oncology 2005)
  - Epidemiology data (Schneider et al. Int J Radiat Oncol Biol Phys 2005)
- Often reasonable, best available, but don't always match epidemiologic data.

Q5: Which of the following is not accounted for when estimating risk for medically exposed vs. A-bomb

5% 1. Age of the population
32% 2. Environmental factors
21% 3. Dose distributions
7% 4. LET of the radiation
35% 5. Duration of exposure

A5: 2. Environmental factors

- A-bomb survivors lived during war times and often in industrial areas. These effects are not well accounted for.
- Most risk estimates for cancer patients/ general population include:
- Age, dose, LET, prolonged exposure vs. acute

- BEIR VII report: Committee on the Biological Effects of Ionizing Radiations. Health risks from exposure to low levels of ionizing radiation: BEIR VII phase 2. Washington DC: The National Academies Press; 2005.

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Reducing the risk

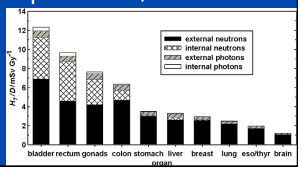
- Methods and thoughts on reducing the risk of second cancers

Reducing treatment volume

- Reducing CTV. Usually hard.
  - Testicular – volume treated with RT has been reduced
  - Hodgkin Lymphoma: involved fields rather than entire chest
  - TBI can be replaced by targeted bone marrow irradiation (Aydawan et al. Int J Radiat Oncol Biol Phys. 2010)
- Reducing PTV
  - Better setup
  - Better motion management

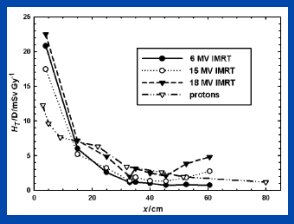
Modality: scanning protons

- Much interest in scanning beams
- No external neutrons
- Still internal neutrons, gammas
  - Up to half of dose equivalent to near organs
  - Negligible dose to distant organs
- Scanning beam is an improvement, but is not free from out-of-field dose



Modality: Scatter Protons vs. Photons

- Reduce exit dose can substantially reduce treated volume for some cases (CSI)
- Near to field, dose equivalent much lower with protons
  - Less lateral scatter
  - Less exit dose
- Less total out of field dose
- Effect more pronounced at lower p+ energy



Fontenot, 2008, Phys Med Biol. *HT/D* as a function of lateral distance (along the patient axis) from the isocenter from this work compared to IMRT values collected from Kry *et al* (2005) and Howell *et al* (2006).

Modality: photon IMRT

- High energy therapy (vs. low energy)
- Produces neutrons
- Requires fewer MU
- High energy photons scatter less
- No significant difference between 6 MV and 18 MV
  (Kry et al, Radioth Oncol 91:132,2009)
- 10 MV may be optimal energy for deep tumors
  (Kry 2005, Int J Radiat Oncol Biol Phys)

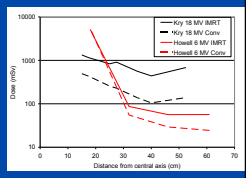
IMRT vs. conformal

- Overall: generally higher doses with IMRT

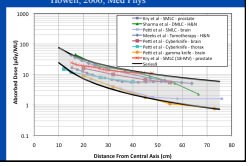
Risk:

- Depends on how much irradiated volume is reduced (reduced risk)
- Depends on how much modulation is employed (increased risk)

(Ruben et al Int J Radiat Oncol Biol Phys. 2008)



Kry, 2005, Int J Radiat Oncol Biol Phys
Howell, 2006, Med Phys

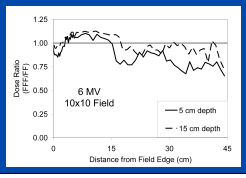


Beam modifiers

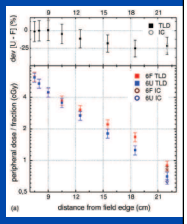
- Wedges
  - Physical wedges ➔ increase out of field dose by 2-4 times (Sherazi et al, 1985, Int J Radiat Oncol Biol Phys)
  - Dynamic or universal wedges ➔ no increase (Li et al, 1997, Int J Radiat Oncol Biol Phys)
- MLC orientation
  - Tertiary MLC reduces dose (extra shielding)
  - Align MLC along patient body reduces dose much more than across the patient (Mutic, Med Phys, 1999)

Flattening filter free

- Out of field dose usually (but not always) reduced for FFF
- Most reduced when head leakage is most important (i.e., FFF is best when):
  - Large distances from the treatment field
  - Small targets
  - High modulation



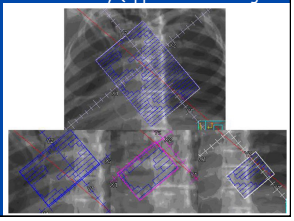
Kry et al. Phys Med Biol 2011;55:2155



Kragl et al. Z Med Phys 2011;21:91

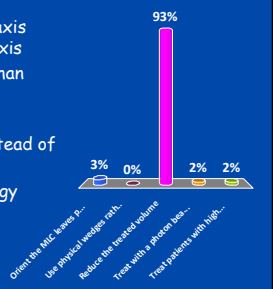
Other approaches

- Add head shielding
  - Pb for photons
    - Heavy -> manufacturing challenges
  - Steel and PMMA for protons (Taddei et al. Phys Med Biol 2008)
    - Could reduce external dose substantially (approach scanning beam doses)
- MLC jaw tracking (Joy et al. JACMP 2012)
  - Small reduction in integral dose



Q6: Which of the following is likely to reduce the risk of second cancers

1. Orient the MLC leaves perpendicular to the patient axis instead of along the patient axis
2. Use physical wedges rather than dynamic wedges
3. Reduce the treated volume
4. Treat with a photon beam instead of protons
5. Treat patients with high energy photon IMRT



A6: 3. Reduce the treated volume

- Alignment of the MLC along the patient axis reduces dose to the patient (Mutic S and Klein E, Int J Radiat Oncol Biol Phys 44:947;1999)
- Physical wedges have 2-3 times the dose outisde the field (Sherazi et al, 1985, Int J Radiat Oncol Biol Phys vs. Li et al, 1997, Int J Radiat Oncol Biol Phys)
- Reducing the treatment volume will reduce the high and intermediate dose volumes, where second tumors most often occur (Diallo I et al. Int J Radiat Oncol Biol Phys 74:876;2009)
- Proton therapy is associated with a lower risk (Fontenot J et al, Int J Radiat Oncol Biol Phys 74:616;2009)
- High energy IMRT has slight but not significantly elevated risk (Kry et al, Radioth Oncol 91:132;2009)

Thank you!

RBE uncertainty

- Often assume wR values or Q values

Table 2. Excess relative risk (*ERR*) in each tissue (ERR_T), sum of ERR_T values over all tissues ($ERR_{modality}$) and the ratio of ERR_{proton} to ERR_{IMRT} (*RRR*) for various scaling factors of the radiation weighting factor (w_R).

	ERR_T							
	Nominal w_R		$w_R \times 0.5$		$w_R \times 2$		$w_R \times 5$	
Organ	Protons	IMRT	Protons	IMRT	Protons	IMRT	Protons	IMRT
Colon	2.25	2.73	2.11	2.73	2.52	2.73	3.33	2.73
Lung	0.05	0.02	0.02	0.02	0.10	0.02	0.24	0.02
Stomach	0.04	0.02	0.02	0.02	0.09	0.02	0.22	0.02
Bladder	3.99	6.92	3.80	6.92	4.36	6.92	5.47	6.92
Liver	0.07	0.03	0.03	0.03	0.13	0.03	0.33	0.03
Thyroid	0.01	0.00	0.00	0.00	0.01	0.00	0.03	0.00
Remainder	0.11	0.18	0.06	0.18	0.23	0.18	0.57	0.18
$ERR_{modality}$	6.50	9.90	6.10	9.90	7.40	9.90	10.20	9.90
RRR	0.66		0.61		0.75		1.03	
95% CI	0.63–0.69		0.59–0.63		0.72–0.78		0.99–1.07	

IMRT = intensity-modulated photon therapy; CI = confidence interval.

Dose response uncertainty

- Fontenot

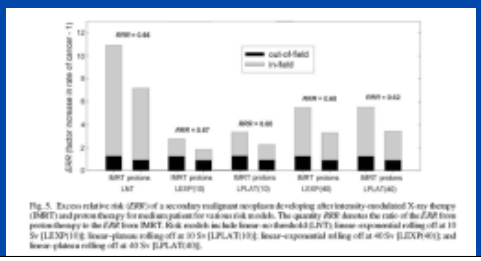


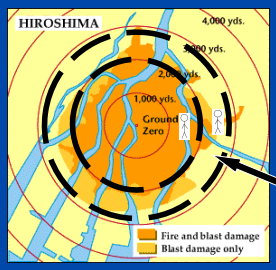
Fig. 5. Excess relative risk (*ERR*) of a secondary malignant neoplasm developing after intensity-modulated X-ray therapy (IMRT) and proton therapy for a medium patient for various risk models. The quantity *RRR* denotes the ratio of the *ERR* from proton therapy to the *ERR* from IMRT. Risk models include linear-no threshold (LNT), linear-exponential rolling off at 10 Sv [LEXP(10)], linear-plateau rolling off at 10 Sv [LPLAT(10)], linear-exponential rolling off at 40 Sv [LEXP(40)], and linear-plateau rolling off at 40 Sv [LPLAT(40)].

A-bomb Dosimetry

- Each individual was ascribed a dose
  - Depended on location, shielding, etc. (tricky)
  - Colon dose
- Atomic bomb included both photons and neutrons (small contribution: 10%).
  - Neutron dose weighted by 10 to account for RBE
- RBE and neutron dosimetry remain sources of uncertainty
- Exclude patients who died or developed cancer before latency period
  - Min 2 years leukemia, 5 years solid cancer
  - E.g., begin analysis in 1950 (Preston 2003)

What are the RT doses?

20 cm from the field edge



20-60 mSv, scanned proton beam

40-400 mSv, passive scatter protons

250 mSv, Conventional photons

300-450 mSv, IMRT

5-100 mSv

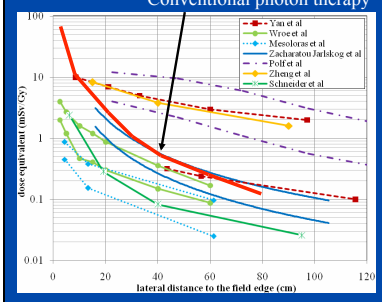
Courtesy of David Brenner

RT second cancers

- What is different about radiotherapy patients as compared to A-bomb survivors?
  - Not a healthy population (risk attributable to radiation?)
  - Different environment, different diet -> different background rates
  - Different ages
  - Fractionated exposure not acute
  - Higher doses (not capped at 4 Gy)
- How do these differences affect

Protons vs. Photons

Conventional photon therapy



Xu, 2008, Phys Med Biol
Stovall, 1995, Med Phys

- Photons:
  - More dose near treatment field
  - Comparable dose beyond 10-20 cm from field edge