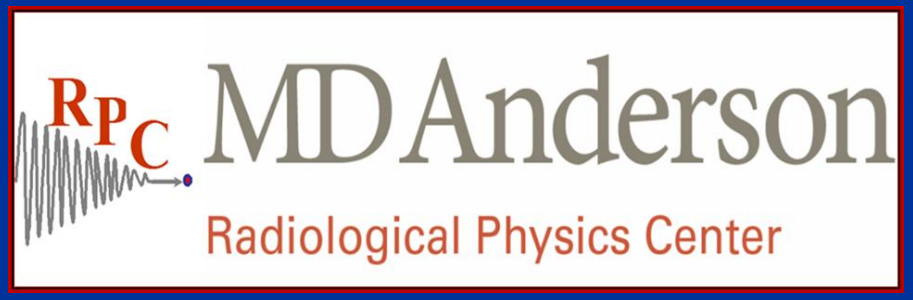
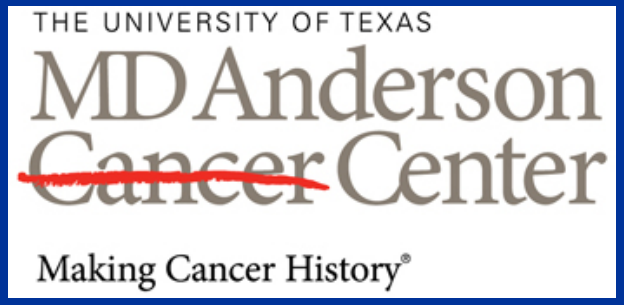
# Radiation Related Second Cancers

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



# Objectives

- Radiation is a well known carcinogen
  - Atomic bomb survivors
  - Accidental exposure
  - Occupational exposure
  - Medically exposed
- Radiotherapy can cause cancer

# Questions/Outline

- Magnitude of risk
- Causes of second cancers
- Location/Dose response
- Other Characteristics
- Impact of advanced techniques
- Options to reduce risk

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# Magnitude of the risk

- How many are there?
- How many are due to radiation?

## Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries

Amy Berrington de Gonzalez, Rochelle E Curtis, Stephen F Kry, Ethel Gilbert, Stephanie Lamart, Christine D Berg, Marilyn Stovall, Elaine Ron*

**Summary**

**Background** Improvements in cancer survival have made the long-term risks from treatments more important,

Lancet Oncol 2011; 12: 353–60

# Study

- 9 SEER registries (~10% of US population)
  - Lots of patients, limited information on each
  - 1973 – 2002
  - 15 different primary sites
- How many second cancers:
  - 5 year survivors
- How many from RT:
  - Radiation attributable second cancers
    - Excess second cancers in RT population versus non RT

| | # of RT patients |
|---|---|
| Oral/pharynx | 24880 |
| Larynx | 17070 |
| Lung (NSC) | 51270 |
| Breast | 150661 |
| Cervix | 14685 |
| Prostate | 128582 |
| Testes | 7862 |
| **Total** | **485481** |

| | # of RT patients | # Second cancers | Rate of second cancers (%) |
|---|---|---|---|
| Oral/pharynx | 24880 | 3683 | 15 |
| Larynx | 17070 | 3583 | 21 |
| Lung (NSC) | 51270 | 2395 | 5 |
| Breast | 150661 | 12450 | 8 |
| Cervix | 14685 | 1289 | 9 |
| Prostate | 128582 | 11292 | 9 |
| Testes | 7862 | 628 | 8 |
| **Total** | **485481** | **42294** | **9** |

# Second Cancer Risk

- 9% of patients developed a second cancer.
- Why?
- Many of these are expected
  - General population gets cancer
  - #1 cause of cancer: AGE
- Cancer patients get more cancer than general public
  - Common risk factors: genetic or environmental
- RT patients have additional risk factor
  - How important is this factor???

| | # of RT patients | # Second cancers | Rate of second cancers (%) |
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| | # of RT patients | # Second cancers | Rate of second cancers (%) | Excess cancers due to RT | % of excess cancers due to RT |
|---|---|---|---|---|---|
| Oral/pharynx | 24880 | 3683 | 15 | 182 | 5 |
| Larynx | 17070 | 3583 | 21 | 193 | 5 |
| Lung (NSC) | 51270 | 2395 | 5 | 152 | 6 |
| Breast | 150661 | 12450 | 8 | 660 | 5 |
| Cervix | 14685 | 1289 | 9 | 214 | 17 |
| Prostate | 128582 | 11292 | 9 | 1131 | 10 |
| Testes | 7862 | 628 | 8 | 150 | 24 |
| **Total** | **485481** | **42294** | **9** | **3266** | **8** |

| | # of RT patients | # Second cancers | Rate of second cancers (%) | Excess cancers due to RT | % of excess cancers due to RT | % of RT patients with RT induced second cancers |
|---|---|---|---|---|---|---|
| Oral/pharynx | 24880 | 3683 | 15 | 182 | 5 | 0.7 |
| Larynx | 17070 | 3583 | 21 | 193 | 5 | 1.1 |
| Lung (NSC) | 51270 | 2395 | 5 | 152 | 6 | 0.3 |
| Breast | 150661 | 12450 | 8 | 660 | 5 | 0.4 |
| Cervix | 14685 | 1289 | 9 | 214 | 17 | 1.5 |
| Prostate | 128582 | 11292 | 9 | 1131 | 10 | 0.9 |
| Testes | 7862 | 628 | 8 | 150 | 24 | 1.9 |
| **Total** | **485481** | **42294** | **9** | **3266** | **8** | **0.7** |

# Interesting considerations

- Elevated risk of second cancers even for primary sites with poor prognosis (lung)
  - RR: 1.18 (Berrington 2011), 6-7% attributable to RT
  - (Maddam 2008, Berrington 2011)

- Elevated risk of second cancers even for old patients (prostate).
  - RR: 1.26 (Berrington 2011), 5-10% attributable to RT
  - (Brenner 2000, Maddam 2008, Berrington 2011)

# Second Cancers from RT

- Most (~90%) of second cancers are not from RT.
  - Age, genes, environment…
- Rule of thumb:

  10% of survivors develop a second cancer

  10% of those are due to their radiation
- ~1% of 1 yr survivors treated with RT develop an RT-induced second cancer
  - Small number, but 12 million survivors and counting (NCRP 170)

# Questions/Outline

- Magnitude of risk
- Causes of second cancers
- Location/Dose response
- Other Characteristics
- Impact of advanced techniques
- Options to reduce risk

# Location

- Where do second cancers occur?
- Diallo et al., Int J Radiat Oncol Biol Phys 2009
  - 12% within geometric field
  - 66% beam-bordering region
    - Dosimetry is very challenging
  - 22% out-of-field (>5 cm away)

- Get most second cancers in high and intermediate dose regions

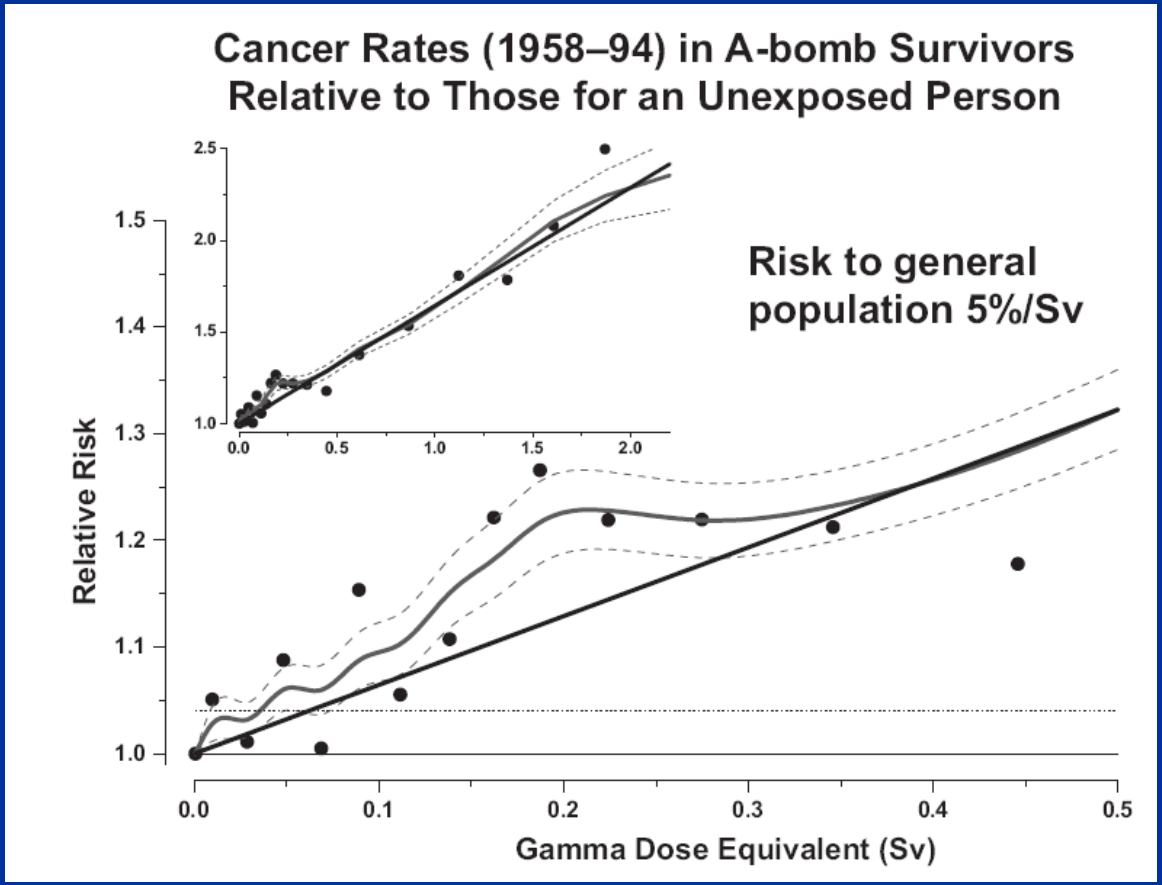
# Location

- 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
  - See carcinomas and sarcomas

# Dose relationship: Low Doses

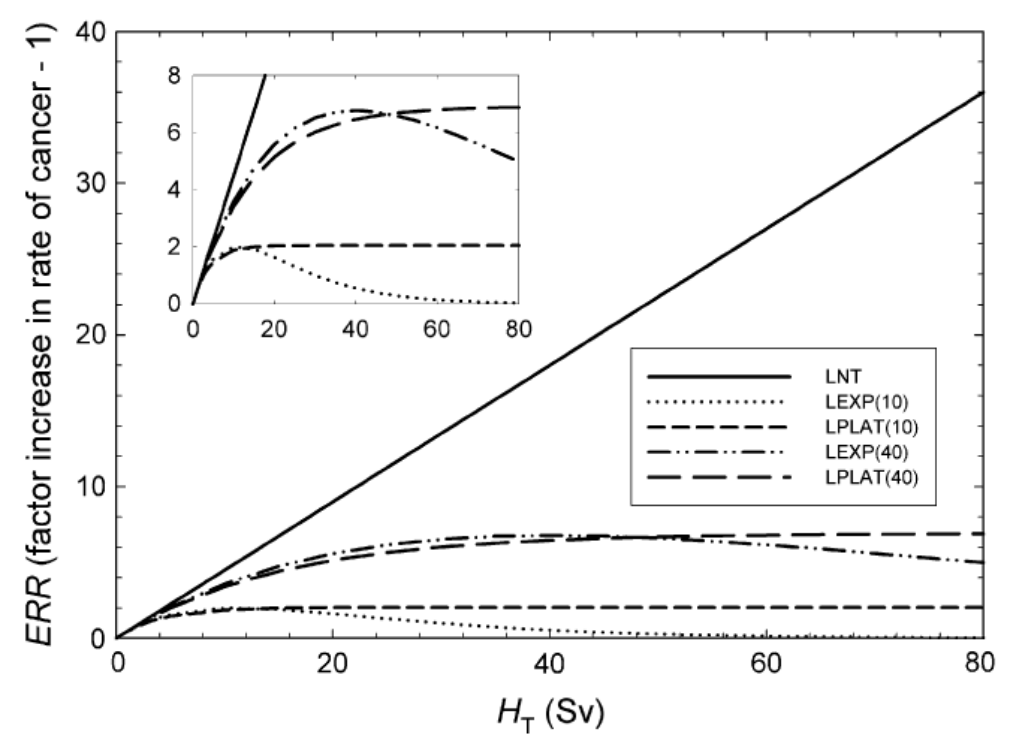
- 0.1 – 2.5 Sv: Linear
- 5%/Sv metric

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



# Dose relationship: High Doses

- > 2.5 Sv ???
- Linear?
- Linear exponential? (due to cell kill)
- Something in-between, e.g., linear plateau?



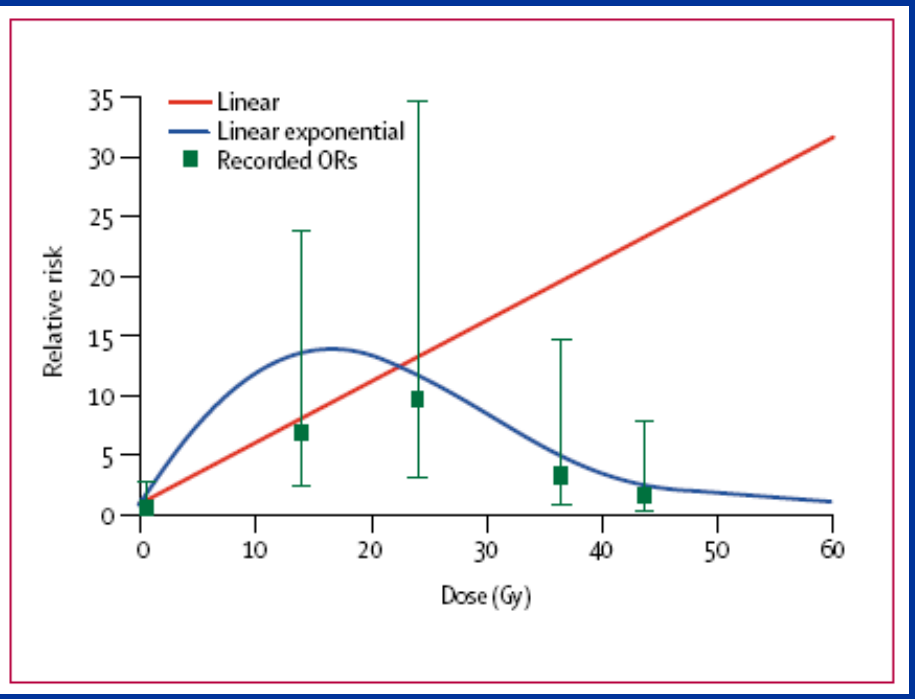

Fontenot et al.

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 2, pp. 616–622, 2009

# Dose Response: High Doses

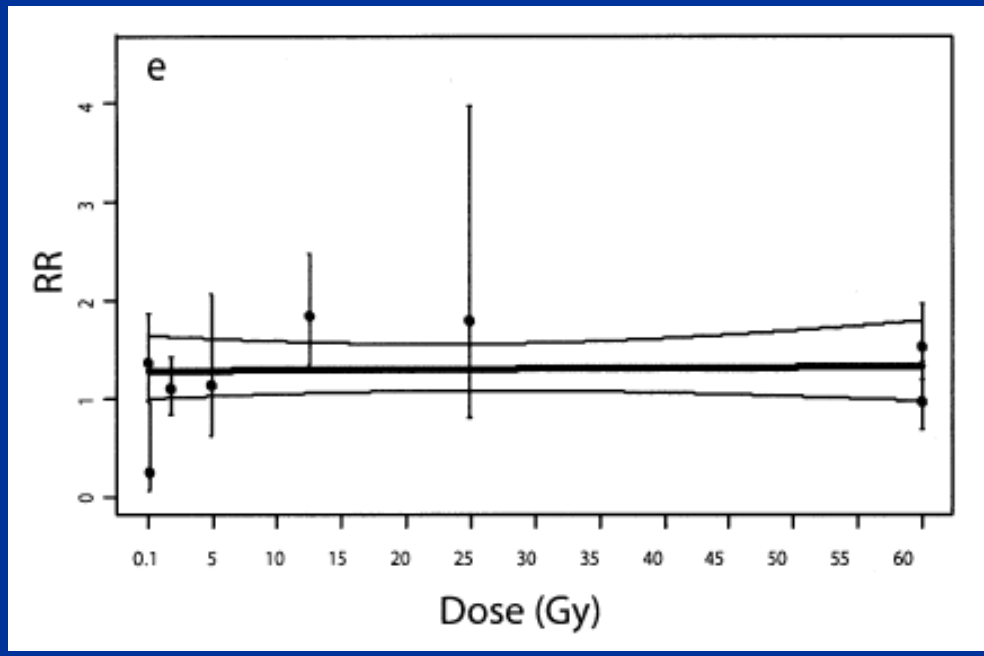
- Apparently, every organ is different!

Thyroid




Sigurdson, Lancet, 2005

Rectum

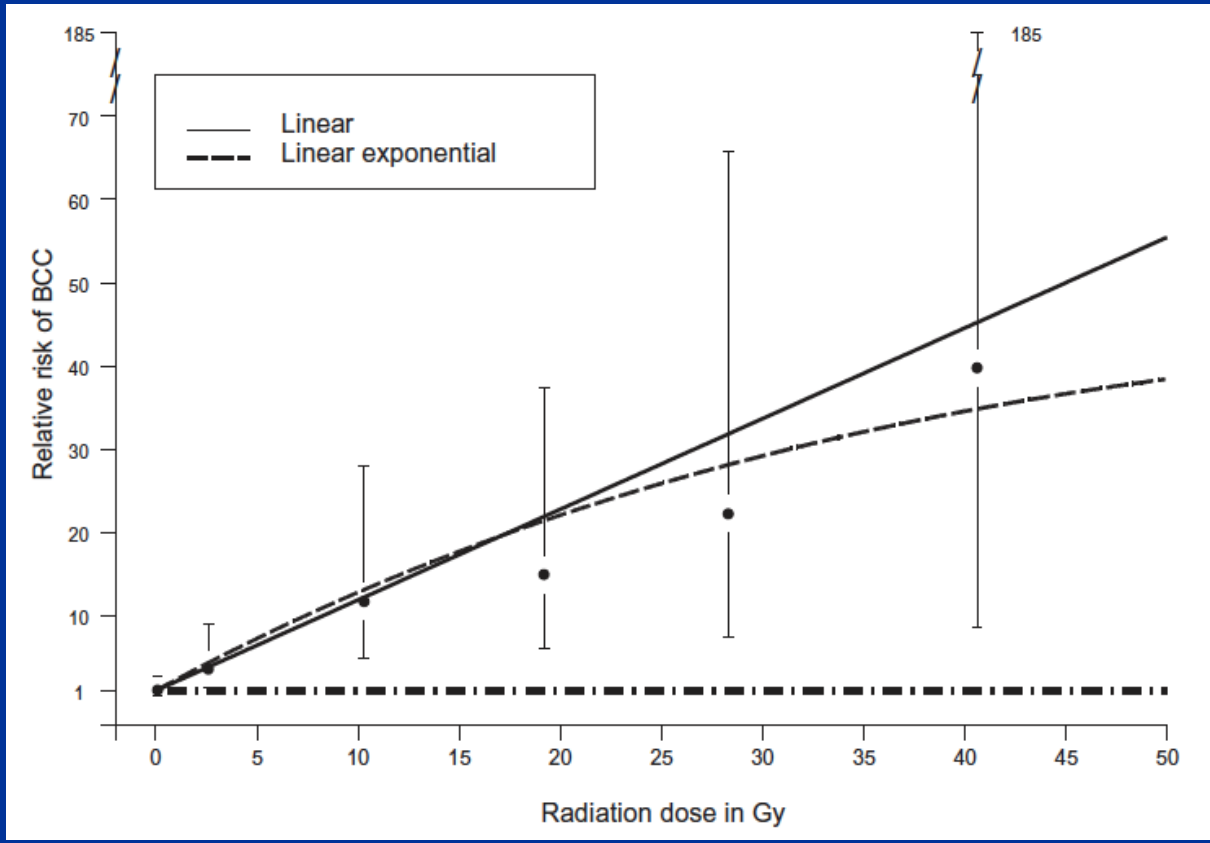



Suit, Rad Res, 2007

# Dose Response: High Doses

Skin

Watt et al., JNCI 2012



# Location/Dose Response Summary

- Distribution of second cancers over all dose ranges.
- Most occur in intermediate & high dose regions
  - Specifics will depend on primary site
  - Different tissues respond differently at high dose
- Substantial need for improved understanding
  - Particularly for risk estimation models
- Cautions for estimating risks
  - For RT applications, can't use simple linear no-threshold.
  - Most models (based on limited data or biological models) only assume linear exponential
  - This also doesn't describe most organs!
  - Need more good epidemiologic studies

# Questions/Outline

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# 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)

# Age effects

- Pediatrics have lots of second cancers
- Observed/Expected (O/E):
  - Adults: **1-2** (Moon 2006)
  - Pediatrics: **5-15** (Inskip 2006)
    - Genetic predisposition
    - More sensitive to radiation
    - Second cancers are a major concern
    - Hard to compare vs. unirradiated population

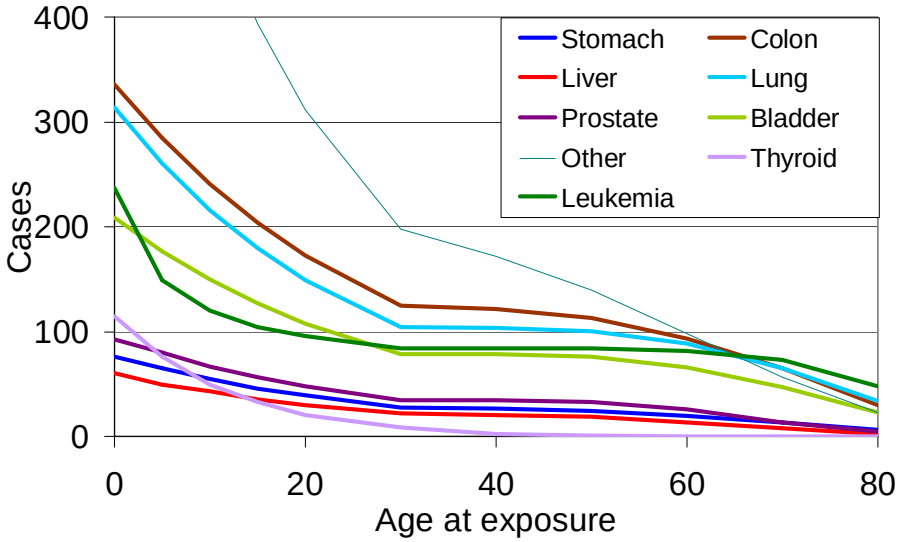
# Time since irradiation

- 5 year latency assumption
  - 2 years for leukemia
- RT versus non-RT

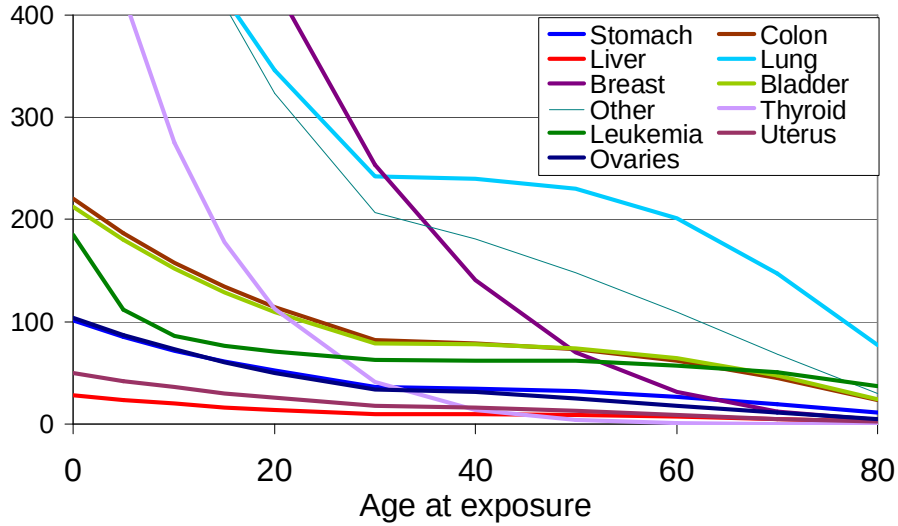
| | Latency 5–9 years | Latency 10–14 years | Latency ≥15 years | p-trend |
|---|---|---|---|---|
| Oral/pharynx | 1·12 (0·99 to 1·27) | 1·14 (0·95 to 1·38) | 0·95 (0·74 to 1·22) | 0·34 |
| Rectum* | 1·13 (0·94 to 1·35) | 1·33 (1·03 to 1·70) | 0·91 (0·64 to 1·27) | 0·54 |
| Larynx | 1·57 (1·08 to 2·36) | 1·04 (0·66 to 1·70) | 1·29 (0·75 to 2·30) | 0·45 |
| Lung (non-small cell) | 1·12 (0·98 to 1·27) | 1·37 (1·12 to 1·65) | 1·62 (1·23 to 2·09) | 0·0079 |
| Female breast | 1·17 (1·05 to 1·30) | 1·42 (1·24 to 1·62) | 1·56 (1·34 to 1·81) | 0·0013 |
| Cervix (external beam)* | 1·18 (0·79 to 1·75) | 1·55 (1·00 to 2·40) | 2·59 (1·84 to 3·68) | 0·0032 |
| Endometrium (external beam)* | 1·30 (1·08 to 1·56) | 1·99 (1·60 to 2·47) | 2·18 (1·78 to 2·65) | <0·0001 |
| Prostate (external beam)* | 1·39 (1·29 to 1·50) | 1·59 (1·41 to 1·80) | 1·91 (1·53 to 2·38) | 0·0031 |
| Thyroid* | 0·89 (0·49 to 1·55) | 1·03 (0·47 to 2·14) | 1·21 (0·64 to 2·17) | 0·47 |

# Gender effects/organ risks

Male second cancer incidence. Lifetime cases/100k exposures to 0.1 Gy




Female cancer incidence. Lifetime cases/100k exposures to 0.1 Gy




BEIR VII report:

- Different organs show different sensitivities
- Increased sensitivity for younger individuals
- Females more sensitive than males…?
  - Sensitive gender organs: breast
  - Lung? May be simply related to lower background rates and comparable sensitivity. (Preston 2007)

# Summary of other characteristics

- Most sensitive organs:
  - Breast, thyroid, lung
- Pediatrics most sensitive
- Females more sensitive
- 5 year latency
  - Continued elevated risk

# Questions/Outline

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# Reducing the risk

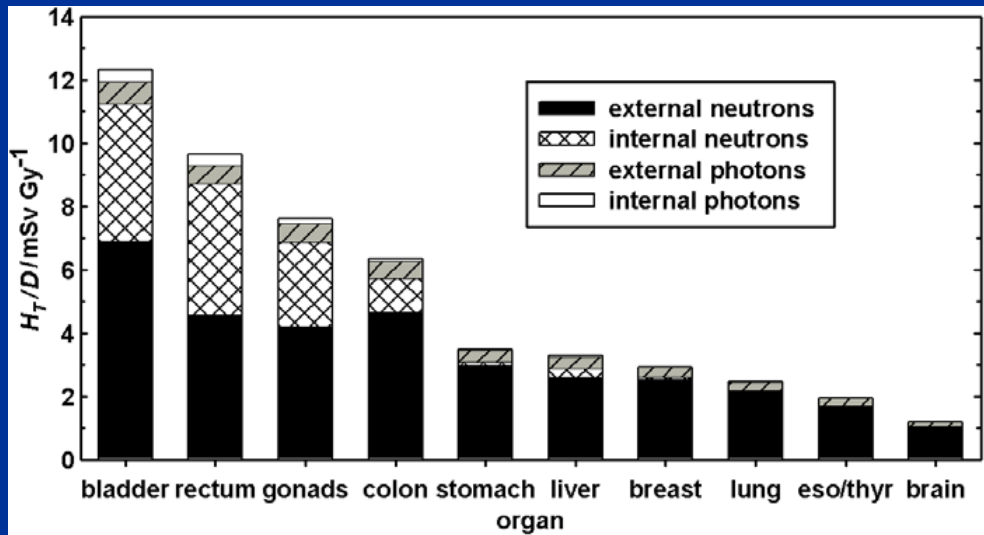
- Methods and thoughts on reducing the risk of second cancers

# 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

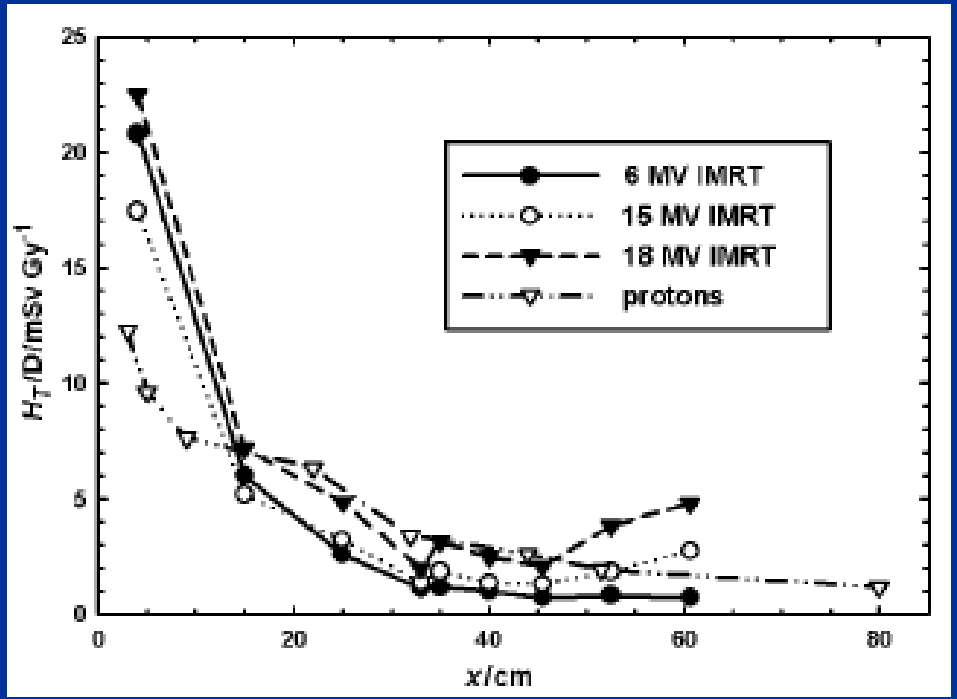



Fontenot et al. PMB 2008

# Modality: Scatter Protons vs. Photons

- Size of PTV?
- 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 risk
- Effect more pronounced at lower p+ energy
- Modeled results




**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)
- Overestimated neutron dose equivalent in literature

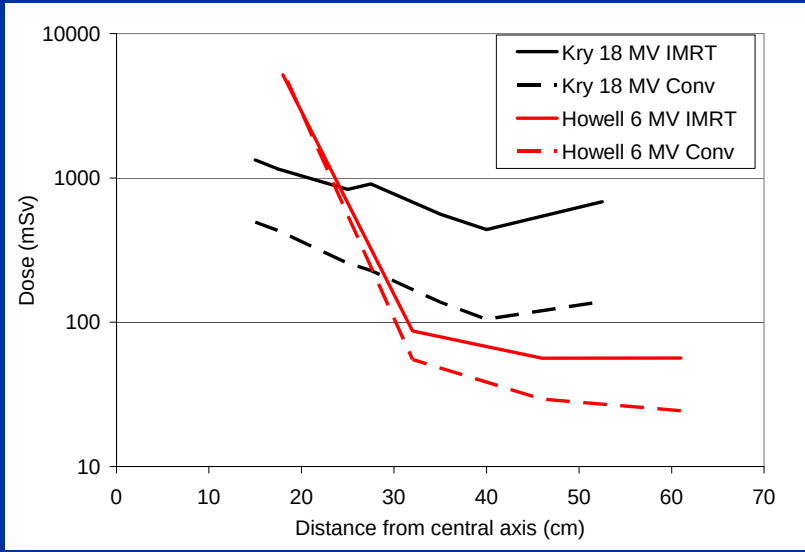
- 10 MV may be optimal
  energy for deep tumors

  (Kry 2005, Int J Radiat Oncol Biol Phys)

# IMRT vs. conformal

- Balance between increased out-of-field dose with decreased PTV

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



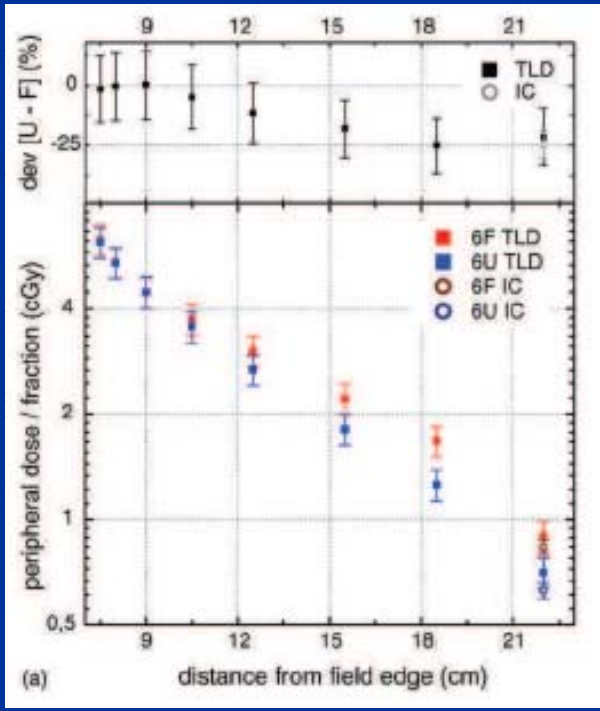

(Kry, 2005, Int J Radiat Oncol Biol Phys, Howell, 2006, Med Phys, Ruben et al Int J Radiat Oncol Biol Phys. 2008)

# Beam modifiers

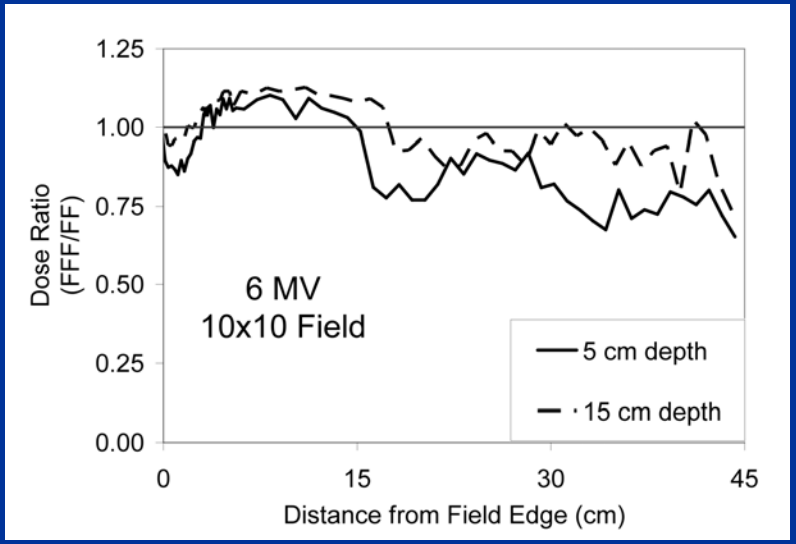
- Wedges
  - Physical wedges → increase out of field dose by 2-4 times (Sherazi et al, 1985, Int J Radiat Oncol Biol Phys)
  - Dynamic or universal wedges → no increase (Li et al, 1997, Int J Radiat Oncol Biol Phys)
- MLC orientation
  - Tertiary MLC reduces dose (extra shielding)
  - Align MLC along 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




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

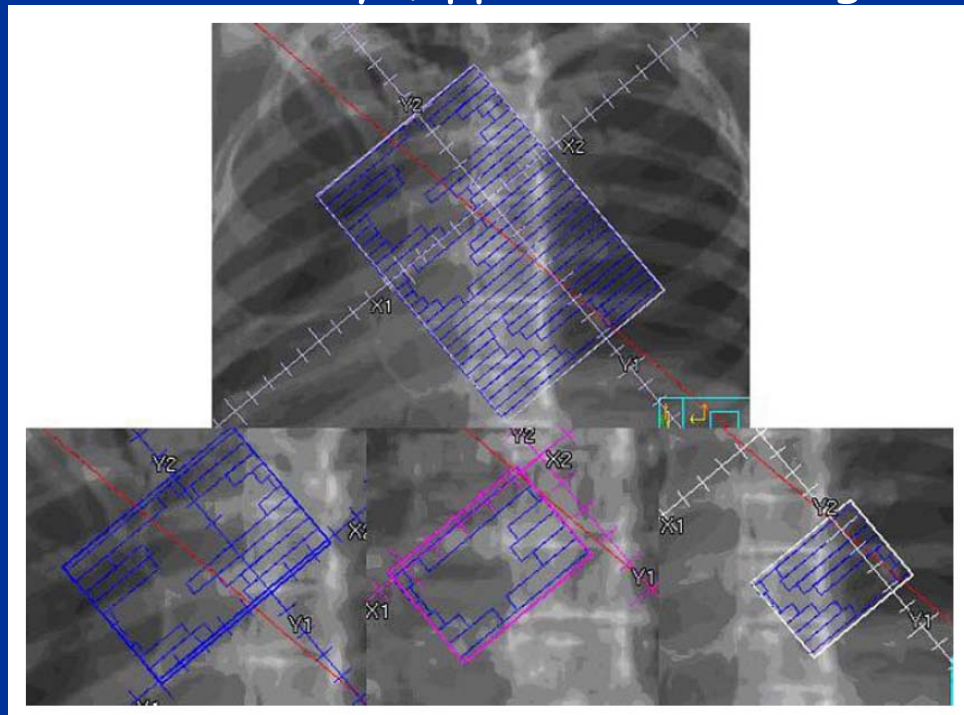



Kry et al. Phys Med Biol
2011;55:2155

# 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



# Summary of risk reduction

- There are methods to reduce the risk
- Some are complex
- Some are relatively simple

# Remaining Issues

- We do know a lot about second cancers, but many questions remain.

- Tools for answering these questions:
  - Epidemiologic studies
  - Calculational studies

# Challenges

- Epidemiology studies
  - Follow up means results are decades later, treatment modality obsolete
    - No IMRT/proton epidemiology studies
  - Studies have large populations OR patient specific data
  - Dosimetry is very difficult
  - Hard to coordinate
  - Expensive
- Calculational studies
  - Based on models
  - Dose response highly uncertain
  - Neutron RBE highly uncertain
  - Rarely account for different sizes of patients
  - Rarely account for range of different plans

# Final thoughts

- ~1% of RT survivors develop a second cancer due to RT (millions of survivors)
- Many remaining questions
  - Dose response/Dose-volume effects
  - Impact of modern technology
  - Causes of second cancers
- Cancer patients are not irradiated for the fun of it.
  - Therapeutic benefit outweighs risk.
  - Minimize the risk as much as possible.

Thank you!