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?

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
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<tr>
<th># of RT patients</th>
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<tr>
<td>Breast</td>
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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???
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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 2010)

• 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 2010)

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

Dose relationship: High Doses
• > 2.5 Sv ???
• Linear?
• Linear exponential? (due to cell kill)
• Something in-between, e.g., linear plateau?

Fontenot et al.

Dose Response: High Doses
• Apparently, every organ is different!

Thyroid
Rectum

Sigurdson, Lancet, 2005

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

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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 (Moore 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

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**Gender effects/organ risks**

- 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

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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

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)

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, 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 (Maric, Med Phys, 1993)
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


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!