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
Questions/Outline

• Magnitude of risk
• Causes of second cancers
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• Options to reduce risk
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
<table>
<thead>
<tr>
<th>Cancer Site</th>
<th># of RT patients</th>
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<tbody>
<tr>
<td>Oral/pharynx</td>
<td>24880</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 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

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

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
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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

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Latency 5–9 years</th>
<th>Latency 10–14 years</th>
<th>Latency ≥15 years</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral/pharynx</td>
<td>1.12 (0.99 to 1.27)</td>
<td>1.14 (0.95 to 1.38)</td>
<td>0.95 (0.74 to 1.22)</td>
<td>0.34</td>
</tr>
<tr>
<td>Rectum</td>
<td>1.13 (0.94 to 1.35)</td>
<td>1.33 (1.03 to 1.70)</td>
<td>0.91 (0.64 to 1.27)</td>
<td>0.54</td>
</tr>
<tr>
<td>Larynx</td>
<td>1.17 (1.08 to 2.36)</td>
<td>1.04 (0.66 to 1.70)</td>
<td>1.29 (0.75 to 2.30)</td>
<td>0.45</td>
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<tr>
<td>Lung (non-small cell)</td>
<td>1.12 (0.98 to 1.27)</td>
<td>1.37 (1.12 to 1.65)</td>
<td>1.62 (1.23 to 2.09)</td>
<td>0.0079</td>
</tr>
<tr>
<td>Female breast</td>
<td>1.17 (1.05 to 1.30)</td>
<td>1.42 (1.24 to 1.62)</td>
<td>1.56 (1.34 to 1.81)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Cervix (external beam)*</td>
<td>1.18 (0.79 to 1.75)</td>
<td>1.55 (1.00 to 2.40)</td>
<td>2.59 (1.84 to 3.68)</td>
<td>0.0032</td>
</tr>
<tr>
<td>Endometrium (external beam)*</td>
<td>1.30 (1.08 to 1.56)</td>
<td>1.99 (1.60 to 2.47)</td>
<td>2.18 (1.78 to 2.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prostate (external beam)*</td>
<td>1.39 (1.29 to 1.50)</td>
<td>1.59 (1.41 to 1.80)</td>
<td>1.91 (1.53 to 2.38)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Thyroid*</td>
<td>0.89 (0.49 to 1.55)</td>
<td>1.03 (0.47 to 2.14)</td>
<td>1.21 (0.64 to 2.17)</td>
<td>0.47</td>
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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
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)

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
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!