Cancer Risks from Conventional Radiotherapy

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DCEG Radiation Epidemiology and Dosimetry Course 2019
Cancer prognosis has improved over the last decades

- 1965-1970: introduction MOPP combination CT
- 1978: introduction cisplatinum-based combination CT
- 1978/1980 introduction adjuvant chemo (CMF) and hormonal (Tamoxifen) therapy, 1990 breast screening
Increasing numbers of cancer survivors

de Moor JS et al. Cancer Epidemiol Biomarkers Prev 2013

In 2016, 1 in 20 U.S. citizens = cancer survivor
More frequent diagnosis of subsequent cancers

Annual number of cancer diagnoses in the Netherlands

Source: Netherlands Cancer Registry

*19% in 9 U.S. SEER registries
Cancer Risks from Conventional Radiotherapy

• Introduction on second malignancy

• Magnitude of risks for various second malignancies after selected first primary malignancies

• Radiotherapy, dose and volume

• Modifying factors of radiation-associated risk (age, chemotherapy)

• Clinical implications
Second primary malignancy

- Originates in a new primary site/tissue
- Not a recurrence or metastasis

**Synonyms**
Second cancer / malignancy / neoplasm
Second primary (…)
Subsequent (…)
Multiple primaries / (…)
SMN
SPN
SPM
New primary cancers
Explanations for occurrence of 2 primary malignancies in one person

• Host susceptibility factors (genetic predisposition, immunodeficiency)

• Common carcinogenic influences (smoking, obesity, alcohol use)

• Treatment for the first tumor

• “Chance” (risk factors unrelated to first cancer)
Causes of second cancers

- Lifestyle & environmental factors (i.e. smoking, alcohol use, diet, weight, physical activity)
- Host susceptibility
  - Genetic susceptibility (i.e. BRCA, Lynch syndrome, SNP variants)
  - Immunodeficiency
- Cancer treatment (i.e. radiation dose & volume, chemo regimen)
Causes of second cancers in relation to age

Second cancers: impact of treatment

Treatment has **largest** impact on second cancer risk among patients treated for a **first cancer**:

- at a young age
- with excellent prognosis

Therefore second cancer research has a strong focus on survivors of:

- Childhood cancer
- Hodgkin lymphoma
- Breast cancer
- Testicular cancer

~ **27% of all cancer survivors**
Cancer Risks from Conventional Radiotherapy

• Introduction on second malignancy

• **Magnitude of risks for various second malignancies after selected first primary malignancies**

• Radiotherapy, dose and volume

• Modifying factors of radiation-associated risk (age, chemotherapy)

• Clinical implications
Radiotherapy

Classic radiation fields in treatment of Hodgkin lymphoma and testicular cancer

Hodgkin Lymphoma

36-44 Gray
2-Gray fractions

Testicular cancer

Seminoma subtype
26-40 Gray
2-Gray fractions

Organs in field

<table>
<thead>
<tr>
<th>Hodgkin</th>
<th>Testis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary glands</td>
<td>✓</td>
</tr>
<tr>
<td>Thyroid</td>
<td>x</td>
</tr>
<tr>
<td>Esophagus</td>
<td>✓</td>
</tr>
<tr>
<td>Pharynx/ Larynx</td>
<td>✓</td>
</tr>
<tr>
<td>Trachea/ Lung</td>
<td>✓</td>
</tr>
<tr>
<td>Breast</td>
<td>✓</td>
</tr>
<tr>
<td>Stomach</td>
<td>✓</td>
</tr>
<tr>
<td>Pancreas</td>
<td>✓</td>
</tr>
<tr>
<td>Colon</td>
<td>✓</td>
</tr>
<tr>
<td>Rectum</td>
<td>✓</td>
</tr>
<tr>
<td>Bladder</td>
<td>✓</td>
</tr>
<tr>
<td>Uterus</td>
<td>✓</td>
</tr>
<tr>
<td>Skin</td>
<td>✓</td>
</tr>
</tbody>
</table>
Changes in Hodgkin RT volumes

Mantle field radiotherapy till late 1980s

EORTC H9
Involved Field Radiotherapy
From 1985

EORTC H10
Involved Node Radiotherapy
After 2000

Courtesy: R vd Maazen Radboud
University Nijmegen Medical Center
Breast cancer radiation fields

After mastectomy

Supraclavicular area + axilla

Internal mammary chain

Chest wall

After breast conserving treatment

Supraclavicular area + axilla

Internal mammary chain

Breast
Clinical epidemiology

• Comparison with risk in general population
• Comparison between treatments

APPROPRIATE STUDY DESIGNS

• Cohort study
• Case-control study

Risk measures

• Relative risk (SIR, HR)
• Absolute risk (AER, Cum. incidence)
Dutch HL cohort

- 3,905 HL patients from 6 (University Medical) Cancer Centers & 41 community hospitals
- Treatment period: 1965-2000
- Age at HL diagnosis: 15-50 years
- > 5-year survivors
- Follow-up through linkage with the Netherlands Cancer Registry
- 96% complete follow-up for second cancers

Schaapveld M et al. *NEJM* 2015;373(26):2499
Patient characteristics

- 3,905 HL survivors
- Median age at HL: 28.6 years
- Median follow-up time: 19 years, range: 5-47 yrs

![Pie chart showing treatment types]

- Radiation therapy alone: 60.5%
- Chemotherapy alone: 27.3%
- Radiation therapy & Chemotherapy: 12.1%
### Risk of second malignancy, Dutch HL cohort; 3,905 5-yr survivors, 15-50 yr at dx, 1965-2000

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Observed sec. cancers</th>
<th>SIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Malignancies</td>
<td>884</td>
<td>4.6</td>
</tr>
<tr>
<td>Oral cavity/pharynx</td>
<td>20</td>
<td>3.2</td>
</tr>
<tr>
<td>Esophagus</td>
<td>38</td>
<td>9.5</td>
</tr>
<tr>
<td>Stomach</td>
<td>39</td>
<td>7.4</td>
</tr>
<tr>
<td>Colon</td>
<td>42</td>
<td>2.9</td>
</tr>
<tr>
<td>Lung &amp; Bronchus</td>
<td>176</td>
<td>6.4</td>
</tr>
<tr>
<td>Pleura</td>
<td>17</td>
<td>15.1</td>
</tr>
<tr>
<td>Rectum &amp; Rectosigmoid</td>
<td>25</td>
<td>2.6</td>
</tr>
<tr>
<td>Pancreas</td>
<td>23</td>
<td>5.7</td>
</tr>
<tr>
<td>Female breast</td>
<td>183</td>
<td>4.7</td>
</tr>
<tr>
<td>Melanoma</td>
<td>34</td>
<td>2.8</td>
</tr>
<tr>
<td>Bladder</td>
<td>22</td>
<td>4.1</td>
</tr>
<tr>
<td>Thyroid</td>
<td>23</td>
<td>14.0</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>22</td>
<td>12.0</td>
</tr>
<tr>
<td>Leukemia</td>
<td>41</td>
<td>9.5</td>
</tr>
</tbody>
</table>

SIR = Standardized Incidence Ratio

Schaapveld M et al. *NEJM* 2015;373(26):2499
Cumulative incidence of second malignancies, in the presence of competing risks, Dutch HL cohort 1965-2000

High relative risk ≠ High absolute risk
Cumulative incidence of second malignancies, in the presence of competing risks, Dutch HL cohort 1965-2000 (2)

40-year risk of breast cancer = 22%

High relative risk ≠ High absolute risk
Absolute excess risk

• Excess number of second malignancies beyond number expected, per 10,000

• AER = (Obs – Exp)/Person-years x 10,000

• Most appropriate measure to judge which second cancers contribute most to SC burden
# Large absolute excess risk for solid cancers

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>SCs</th>
<th>SIR</th>
<th>AER/10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIRs and AERs of second</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>malignancy, Dutch HL cohort;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3,905 5-yr survivors,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>15-50 yr at dx,</strong></td>
<td></td>
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<tr>
<td><strong>1965-2000</strong></td>
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<td>6.1</td>
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AER= absolute excess number of cases per 10,000 patients/yr
Risk of second cancer after testicular cancer
Dutch nationwide testicular cancer cohort

• 5,848 1-year survivors
• Treated 1976-2007
• Median follow up: 14 years
• 50% seminoma, 50% non-seminoma
• 82% of seminoma patients received RT
• 58% of non-seminoma patients received platinum-based chemotherapy
• 38% of non-seminoma patients had orchidectomy alone

H. Groot, JCO 2018;36(24):2504-2513
### Standardized incidence ratios for second malignancies after testicular cancer

#### Seminoma (N=2,827)

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Observed</th>
<th>SIR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any solid SMN</td>
<td>180</td>
<td>1.5</td>
<td>(1.3-1.8)</td>
</tr>
<tr>
<td>Lung</td>
<td>22</td>
<td>1.0</td>
<td>(0.7-1.6)</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>52</td>
<td>1.9</td>
<td>(1.4-2.4)</td>
</tr>
<tr>
<td>- Stomach</td>
<td>7</td>
<td>1.7</td>
<td>(0.7-3.5)</td>
</tr>
<tr>
<td>- Colon</td>
<td>13</td>
<td>1.3</td>
<td>(0.7-2.1)</td>
</tr>
<tr>
<td>- Rectum</td>
<td>8</td>
<td>1.0</td>
<td>(0.4-2.0)</td>
</tr>
<tr>
<td>- Pancreas</td>
<td>14</td>
<td>4.4</td>
<td>(2.4-7.4)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>28</td>
<td>2.7</td>
<td>(1.8-3.9)</td>
</tr>
<tr>
<td>- Kidney</td>
<td>10</td>
<td>2.1</td>
<td>(1.0-3.8)</td>
</tr>
<tr>
<td>- Bladder</td>
<td>17</td>
<td>3.4</td>
<td>(2.0-5.4)</td>
</tr>
<tr>
<td>- Prostate</td>
<td>26</td>
<td>1.2</td>
<td>(0.8-1.8)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>15</td>
<td>1.8</td>
<td>(1.0-2.9)</td>
</tr>
</tbody>
</table>

H. Groot, *JCO* 2018;36(24):2504-2513
Risks for selected SMNs after Hodgkin lymphoma and breast cancer *(SEER 1975-2010)*

Morton et al. *ASCO ed book 2014*
## Risk of second malignancy in Dutch childhood cancer survivors (DCOG-LATER cohort)

6,665 5-yr survivors 1963-2001, median follow-up 21 yrs

<table>
<thead>
<tr>
<th>Sec. Malign. Neopl.</th>
<th>Obs.</th>
<th>SIR (95% CI)</th>
<th>AER/10,000 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SMNs</td>
<td>261</td>
<td>5.2 (4.6-5.8)</td>
<td>20.3</td>
</tr>
<tr>
<td>Leukemia</td>
<td>17</td>
<td>6.1 (3.6-9.8)</td>
<td>1.3</td>
</tr>
<tr>
<td>All solid</td>
<td>230</td>
<td>5.5 (4.8-6.2)</td>
<td>18.1</td>
</tr>
<tr>
<td>Breast</td>
<td>45</td>
<td>5.1 (3.8-6.9)</td>
<td>7.6</td>
</tr>
<tr>
<td>Bone</td>
<td>21</td>
<td>17.1 (10.6-26.1)</td>
<td>1.9</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>24</td>
<td>19.3 (12.4-28.7)</td>
<td>2.2</td>
</tr>
<tr>
<td>CNS</td>
<td>24</td>
<td>8.5 (5.4-12.6)</td>
<td>2.0</td>
</tr>
<tr>
<td>Thyroid</td>
<td>25</td>
<td>17.1 (11.1-25.3)</td>
<td>2.2</td>
</tr>
<tr>
<td>Digestive tract</td>
<td>17</td>
<td>4.1 (2.4-6.6)</td>
<td>1.2</td>
</tr>
<tr>
<td>Lung</td>
<td>8</td>
<td>4.3 (1.9-8.5)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

SIR: Standardized Incidence Ratio, AER: Absolute Excess Risk

Risks for second cancers after childhood cancer in U.S. - SEER

Figure 17. Observed-to-expected (O/E) Ratios for Subsequent Cancers by Primary Site, Ages 0-19, 1973-2010

- **Retinoblastoma**: 11.9*
- **Hodgkin lymphoma, sarcoma, CNS, NHL, neuroblastoma**: 5 - 8*
- **Acute Lymphoblastic Leukemia (ALL)**: 3.8*

Source: SEER 1973-2010
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• Introduction on second malignancy

• Magnitude of risks for various second malignancies after selected first primary malignancies

• Radiotherapy, dose and volume

• Modifying factors of radiation-associated risk (age, chemotherapy)

• Clinical implications
Radiation dose – response for second cancer risk

Linear increase with higher dose for:
- Breast cancer
- Lung cancer
- Stomach cancer
- Pancreatic cancer
- Esophageal cancer
- Sarcoma
- Glioma
- Meningioma

For leukemia decreasing risk after 4 Gy
For thyroid cancer decreasing risk after 20-30 Gy

*Based on retrospective radiation dosimetry (simulation films, old RT charts, phantoms)*
Radiation dose – response for second cancer risk

Linear increase with higher dose for:
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For thyroid cancer decreasing risk after 20-30 Gy

*Based on retrospective radiation dosimetry (simulation films, old RT charts, phantoms)*
Breast cancer case-control study to assess radiation dose-response

- Compare treatment between:
  - Cases with breast cancer after HL
  - Matched controls without breast cancer

- Treatment information from medical records

- Irradiated patients: individual radiation dosimetry; radiation dose to the site of breast cancer development, based on radiation charts, simulation films of previous RT treatment and mammograms (M. Stovall, M.D. Anderson, Houston)

### Radiation dose ↑ → Breast cancer risk ↑

- International NCI-coordinated nested case-control study, 105 cases with breast cancer after HL, 266 controls
- Radiation dosimetry: dose to affected site in breast

<table>
<thead>
<tr>
<th>Radiation dose</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 Gy</td>
<td>1.0</td>
<td>Ref</td>
</tr>
<tr>
<td>4-7 Gy</td>
<td>1.8</td>
<td>0.7-4.5</td>
</tr>
<tr>
<td>7-23 Gy</td>
<td>4.1</td>
<td>1.4-12.3</td>
</tr>
<tr>
<td>23-28 Gy</td>
<td>2.0</td>
<td>0.7-5.9</td>
</tr>
<tr>
<td>28-37 Gy</td>
<td>6.8</td>
<td>2.3-22.3</td>
</tr>
<tr>
<td>37-40 Gy</td>
<td>4.0</td>
<td>1.3-13.4</td>
</tr>
<tr>
<td>41-61 Gy</td>
<td>8.0</td>
<td>2.6-26.4</td>
</tr>
</tbody>
</table>

Linear ERR per Gy 0.05 – 0.15

Travis *JAMA* 2003; 290:465
Radiation dose–response relationship for stomach cancer following testicular cancer based on 92 cases and 180 controls

An international NCI-coordinated case-control study

Hauptmann M Br J Cancer. 2015;112(1):44-51.
Fitted radiation dose-response by type of second cancer, based on previous CCSS reports

Turcotte et al. J Clin Oncol., 2018
Changes in Hodgkin RT volumes

Mantle field radiotherapy till late 1980s

EORTC H9 Involved Field Radiotherapy From 1985

EORTC H10 Involved Node Radiotherapy After 2000

Courtesy: R vd Maazen Radboud University Nijmegen Medical Center
Lower risk with smaller radiation volumes

Mantle field radiotherapy

Involved Field Radiotherapy

60% reduction of breast cancer risk

De Bruin et al. JCO 2009; 27(26): 4239-4246
Schaapveld M et al. NEJM 2015;373(26):2499
Breast cancer after childhood cancer: Role of irradiated breast volume

Whole lung Irradiation (e.g. Wilms) similar risk as Mantle radiation (HL); higher than mediastinal irradiation, although RT dose is typically lower (10-19 Gy vs >20 Gy)

Separate and joint effects of RT dose and volume

What is worse:

• A lot (of dose) to a little (volume)
• A little (dose) to a lot (of volume)
• Dose-volume parameters
  \[ V_{40} = \text{part of organ that received 40 Gy or more} \]
Which part of second cancers can be attributed to radiotherapy?

- Cohort study in SEER cancer registries
- 647,672 5-yr survivors, ≥ 20 yr at diagnosis (1973-2002)
- Mean follow-up 12 yrs
- 60,271 (9%) with second solid tumor

~ 8% of all solid tumors (~3.266) in irradiated patients attributable to RT

% differs with tumor type

Berrington de Gonzalez et al. *Lancet Oncology* 2011

---

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Number of second solid cancers in patients treated with radiotherapy*</th>
<th>Number of patients</th>
<th>Excess cancers (95% CI)†</th>
<th>Attributable risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral/pharynx</td>
<td>3683</td>
<td>24,880</td>
<td>182 (53 to 310)</td>
<td>5% (1 to 8)</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>309</td>
<td>3007</td>
<td>37 (1 to 71)</td>
<td>12% (0 to 23)</td>
</tr>
<tr>
<td>Rectum</td>
<td>1568</td>
<td>21,841</td>
<td>112 (41 to 184)</td>
<td>7% (3 to 12)</td>
</tr>
<tr>
<td>Anus</td>
<td>323</td>
<td>3444</td>
<td>32 (−14 to 74)</td>
<td>10% (−4 to 23)</td>
</tr>
<tr>
<td>Larynx</td>
<td>3583</td>
<td>17,070</td>
<td>193 (32 to 350)</td>
<td>5% (1 to 10)</td>
</tr>
<tr>
<td>Lung (non-small cell)</td>
<td>2395</td>
<td>51,270</td>
<td>152 (82 to 223)</td>
<td>6% (3 to 9)</td>
</tr>
<tr>
<td>Soft tissue (non-lims)</td>
<td>120</td>
<td>1602</td>
<td>18 (−2 to 39)</td>
<td>15% (−2 to 32)</td>
</tr>
<tr>
<td>Female breast</td>
<td>12,450</td>
<td>150,661</td>
<td>660 (454 to 866)</td>
<td>5% (4 to 7)</td>
</tr>
<tr>
<td>Cervix</td>
<td>1289</td>
<td>14,685</td>
<td>214 (130 to 295)</td>
<td>17% (10 to 23)</td>
</tr>
<tr>
<td>Endometrium</td>
<td>3269</td>
<td>29,338</td>
<td>286 (165 to 407)</td>
<td>9% (5 to 12)</td>
</tr>
<tr>
<td>Prostates</td>
<td>11,292</td>
<td>128,582</td>
<td>1131 (956 to 1307)</td>
<td>10% (8 to 12)</td>
</tr>
<tr>
<td>Testes (seminomas)</td>
<td>628</td>
<td>7,862</td>
<td>150 (56 to 233)</td>
<td>24% (9 to 37)</td>
</tr>
<tr>
<td>Eye and orbit</td>
<td>112</td>
<td>1085</td>
<td>4 (−12 to 22)</td>
<td>4% (−11 to 20)</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>314</td>
<td>13,220</td>
<td>28 (−11 to 66)</td>
<td>9% (−3 to 21)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>959</td>
<td>16,934</td>
<td>67 (6 to 128)</td>
<td>7% (1 to 13)</td>
</tr>
<tr>
<td>Total</td>
<td>42,294</td>
<td>485,481</td>
<td>3266 (2862 to 3670)</td>
<td>8% (7 to 9)</td>
</tr>
</tbody>
</table>

*In all patients (defined as ≥1 year survivors). †Estimated in 5 year or longer survivors calculated with the results from the Poisson regression model (figure 1). ‡Second cancers of the same site were excluded because standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate).
Which part of second cancers can be attributed to radiotherapy?

- Cohort study in SEER cancer registries
- 647,672 5-yr survivors, ≥ 20 yr at diagnosis (1973-2002)
- Mean follow-up only 12 yrs!!
- 60,271 (9%) with second solid tumor

~ 8% of all solid tumors (~3.266) in irradiated patients attributable to RT

% differs with tumor type

Berrington de Gonzalez et al. *Lancet Oncology* 2011
Solid cancer risk increased for >35 yrs
Dutch Hodgkin cohort (n=3940, 1965-2000)

AER per 10,000 patients/hrs

Schaapveld M et al. *NEJM* 2015;373(26):2499
Which part of second cancers can be attributed to radiotherapy?

- Cohort study in SEER cancer registries
- 647,672 5-yr survivors, ≥ 20 yr at diagnosis (1973-2002)
- Mean follow-up only 12 yrs!!
- 60,271 (9%) with second solid tumor
- ~ 8% of all solid tumors (~3.266) in irradiated patients attributable to RT
- overall estimate 15-25%
- % differs with tumor type: 40-50% for long-term Hodgkin survivors,

Berrington de Gonzalez et al. *Lancet Oncology* 2011

| Oral/pharynx | 3683 | 24,880 | 182 (53 to 310) | 5% (1 to 8) |
| Salivary gland | 309 | 3007 | 37 (1 to 71) | 12% (0 to 23) |
| Rectum | 1568 | 21,841 | 112 (41 to 184) | 7% (3 to 12) |
| Anus | 323 | 3444 | 32 (14 to 74) | 10% (-4 to 23) |
| Larynx | 3583 | 17,070 | 193 (32 to 350) | 5% (1 to 10) |
| Lung (non-small cell) | 2395 | 51,270 | 152 (82 to 223) | 6% (3 to 9) |
| Soft tissue (non-lims) | 120 | 1602 | 18 (-2 to 39) | 15% (-2 to 32) |
| Female breast | 12,450 | 150,661 | 660 (454 to 866) | **5% (4 to 7)** |
| Cervix | 1289 | 14,685 | 214 (130 to 295) | **17% (10 to 23)** |
| Endometrium | 3269 | 29,338 | 286 (165 to 407) | 9% (5 to 12) |
| Prostates | 11,292 | 128,582 | 1131 (956 to 1307) | 10% (8 to 12) |
| Testes (seminomas) | 628 | 7862 | 150 (56 to 233) | **24% (9 to 37)** |
| Eye and orbit | 112 | 1085 | 4 (-12 to 22) | **4% (-11 to 20)** |
| Brain/CNS | 314 | 13,220 | 28 (-11 to 66) | 9% (-3 to 21) |
| Thyroid | 959 | 16,934 | 67 (6 to 128) | 7% (1 to 13) |
| Total | 42,294 | 485,481 | 3266 (2862 to 3670) | 8% (7 to 9)

*In all patients (defined as ≥1 year survivors). †Estimated in 5 year or longer survivors calculated with the results from the Poisson regression model (figure 1). §Second cancers of the same site were excluded because standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate).
Cancer Risks from Conventional Radiotherapy

• Introduction on second malignancy
• Magnitude of risks for various second malignancies after selected first primary malignancies
• Radiotherapy, dose and volume
• Modifying factors of radiation-associated risk
• Clinical implications
Potential modifiers of radiation-associated risk

- Age
- Chemotherapy
- Hormonal factors
- Smoking
- Genetic factors
Decreasing relative risks of solid tumors with increasing age at HL treatment

International cohort study: 32,591 HL patients
1,111 25-year survivors, population-based

(Adapted from Dores JCO 2002;20:3484)
Cumulative incidence of breast cancer after HL 5-yr survivors treated before age 21

Comparable to risk in BRCA 1 carriers

RR and AER of second cancers according to age at HL diagnosis and attained age.

Potential modifiers of radiation-associated risk (2)

- Age
- Chemotherapy
- Hormonal factors
- Smoking
- Genetic factors
Some chemotherapy regimens also increase solid cancer risk after Hodgkin lymphoma.

- **Lung Cancer**
  - Relative Risk (95% CI)
  - $P_{trend} < 0.001$
  - RRs adjusted for radiation dose

- **Stomach Cancer**
  - Relative Risk (95% CI)
  - $P_{trend} 0.02$
  - RRs adjusted for radiation dose

*Travis et al. JNCI 2002;94:182*

*Morton et al. JCO 2013;31:3369*
Risk of stomach cancer after HL according to procarbazine dose

An international NCI-coordinated case-control study

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>Cases</th>
<th>Controls</th>
<th>Mean</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>37</td>
<td>103</td>
<td>0.0</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>1-5599</td>
<td>12</td>
<td>39</td>
<td>3403</td>
<td>0.8 (0.3-1.9)</td>
</tr>
<tr>
<td>5600-8399</td>
<td>22</td>
<td>29</td>
<td>6938</td>
<td>2.9 (1.2-7.0)</td>
</tr>
<tr>
<td>≥8400</td>
<td>18</td>
<td>19</td>
<td>12,316</td>
<td>2.3 (1.0-5.5)</td>
</tr>
</tbody>
</table>

\( P_{\text{trend}} = 0.009 \)

* Adjusted for radiation dose and other alkylating agents.

Morton et al., JCO, 2013 Sep 20;31(27):3369-77
Stomach cancer after HL: interaction between radiation dose and procarbazine

Morton et al., JCO, 2013 Sep 20;31(27):3369-77
Colorectal cancer risk in HL patients

- Radiotherapy

- Chemotherapy (procarbazine)

Anja M. van Eggermond, Br J Cancer 2017
Risk of colorectal cancer by HL treatment

Higher risks for cancers in transverse colon!

Anja M. van Eggermond, *Br J Cancer* 2017

* P < 0.05
Risk of bone sarcoma after childhood cancer by radiation dose and alkylator score

Table 3. Matched Relative Risk of Bone Sarcoma, According to Radiation Dose and Alkylator Score.

<table>
<thead>
<tr>
<th>Radiation Dose</th>
<th>Alkylator Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>None None</td>
<td>1.0*</td>
</tr>
<tr>
<td>≤1000 rad</td>
<td>1.3</td>
</tr>
<tr>
<td>≥1000 rad</td>
<td>37.4‡</td>
</tr>
</tbody>
</table>

*Referent category.
†Trend in alkylator score in subjects not exposed to radiation, P = 0.05.
‡P<0.05.
Potential modifiers of radiation-associated risk (3)

- Age
- Chemotherapy
- Hormonal factors
- Smoking
- Genetic factors
Reduced risk of RT-induced breast cancer after alkylating chemotherapy or pelvic RT

- Van Leeuwen et al. JNCI 2003; 95(13):971-89
- Travis et al. JAMA 2003; 290(4):465-75
- De Bruin et al. JCO 2009; 27(26):4239-46
- Swerdlow et al. JCO 2012; 30(22):2745-52
- Schaapveld et al. NEJM 2015; 373(26):2499-511

40-yr cumulative risk of breast cancer after chest RT by no. of cycles of alkylating CT

Swerdlow et al. JCO 2012; 30(22):2745-52
Cumulative risk of premature menopause (< 40 yrs) by cumulative procarbazine dose in HL survivors


<table>
<thead>
<tr>
<th>Dose Category</th>
<th>Numbers at Risk</th>
<th>Time since first treatment (years)</th>
<th>Cumulative risk 10 years after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=4.2 g/m² procarbazine (n=85)</td>
<td>85</td>
<td>76 66 58 51</td>
<td>41 15% [6-23%]</td>
</tr>
<tr>
<td>4.2-8.4 g/m² procarbazine (n=86)</td>
<td>86</td>
<td>68 59 51 44</td>
<td>36 37% [24-48%]</td>
</tr>
<tr>
<td>&gt;8.4 g/m² procarbazine (n=55)</td>
<td>55</td>
<td>39 19 14 9</td>
<td>7 65% [44-78%]</td>
</tr>
</tbody>
</table>
Ovarian hormones crucial in radiation-induced breast carcinogenesis

Breast cancer risk after childhood cancer according to radiation dose to breast and ovarian radiation

Inskip et al. JCO 2009; 27(24): 3901-07
Cumulative incidence of breast cancer in HL survivors according to RT field, prescribed dose, and duration of post-RT intact ovarian function.

Ovarian hormones, RT dose and volume equally important
## Lung cancer after HL
### Joint effects of smoking and treatment

Risks from smoking multiply risks from RT and CT

<table>
<thead>
<tr>
<th></th>
<th>RR non/light smokers</th>
<th>RR smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT (&lt; 5 Gy), no CT</td>
<td>1.0 (ref)</td>
<td>6.0 (1.9-20.4)</td>
</tr>
<tr>
<td>RT (≥ 5 Gy), no CT</td>
<td>7.2 (2.9-21.2)</td>
<td>20.2 (6.8-68)</td>
</tr>
<tr>
<td>No RT (&lt; 5 Gy), CT</td>
<td>4.3 (1.8-11.7)</td>
<td>16.8 (6.2-53)</td>
</tr>
<tr>
<td>RT (≥ 5 Gy), CT</td>
<td>7.2 (2.8-21.6)</td>
<td>49.1 (15.1-187)</td>
</tr>
</tbody>
</table>

- 10% of lung cancers due to treatment alone
- 24% of lung cancers due to smoking alone
- 63% of lung cancers due to treatment + smoking in combination

Travis et al. *JNCI* 2002; 94:182
Breast cancer after HL: 
*It’s not just chest radiotherapy…*

- High radiation dose
- Large irradiation volume
- Young age at treatment with RT
- Protective effect of premature menopause

About 60% of women who received high-dose chest RT (without gonadotoxic CT) do NOT develop breast cancer

Genetic susceptibility?
Genetic susceptibility for radiation-induced breast cancers?

Examined 14 breast cancer SNPs from general population
• 232 cases with breast cancer after HL, 461 controls
• OR of 1.59 (per allele) associated with FGFR2

GWAS of 207 patients with breast cancer after childhood cancer
• Comparison with 2274 CCS without second malignancy
• ~ 2-fold risk increase per allele for a genetic variant at 1q41 (nearest gene PROX1), only for survivors with ≥ 10Gy breast exposure

Dutch International Collaborative study:
Genetic susceptibility for breast cancer after chest RT for Hodgkin lymphoma

Aim: To examine the influence of
- Genetic variants interacting with radiotherapy
- 77 genetic variants associated with breast cancer in the general population

Opstal-van Winden et al., *Blood* 2019
Dutch study: Genetic susceptibility for breast cancer after chest RT for Hodgkin lymphoma

- Based on 327 cases with breast cancer after chest RT for HL from Dutch and UK Hodgkin cohorts and U.S. Childhood Cancer Survivor study
- 4,671 first primary breast cancers from BCAC
- 491 patients with chest RT for Hodgkin who did not develop breast cancer

1. iCOGS SNP-array (211,000 SNPs) → 9 SNPs interacting with RT (False Discovery Rate <20%)
2. Polygenic Risk Score based on these 9 SNPs
3. Internal validation in case-control study

Opstal-van Winden et al., *Blood* 2019
Study design

1\textsuperscript{st} step: Case-Case study

- RT for HL
- BC
- year & age
- 327 BC following HL cases
- 4,671 1\textsuperscript{st} primary BC cases

2\textsuperscript{nd} step: Case-Control study

- Compose Polygenic Risk Score (risk-weighted sum) of:
  - 9 SNPs significantly interacting with RT (\textit{RT-interaction PRS})
  - 77 SNPs associated with BC in general population* (\textit{BC-PRS})

- RT for HL
- BC
- year & age
- 327 BC following HL cases
- 491 HL controls

Opstal-van Winden et al., \textit{Blood} 2019
Risk of breast cancer after HL by RT-interaction Polygenic Risk Score

Opstal-van Winden et al., Blood 2019
Risk for breast cancer after HL by 77 SNP BC Polygenic Risk Score based on general population data

Significantly different risk for 20% of female HL survivors with extreme BC-PRS

Opstal-van Winden et al., Blood 2019

* Mavaddat et al. JNCI 2015
Conclusions genetic susceptibility for RT-induced breast cancer

Genetic susceptibility plays a role in RT-induced breast cancer

*Independent effects of:*

- PRS for breast cancer in the general population; implementation in risk prediction models for HL patients
- PRS based on 9 SNPs interacting with RT
- Validation of RT-interaction PRS required: *ongoing collaboration with NCI and Childhood Cancer Survivor Study: Lindsay Morton*
Summary of findings on second cancer risk

- Lower risk after testicular and breast cancer than after HL and childhood cancer
- **Solid cancer** risk after radiotherapy remains increased for >35 years
  - Higher risk with larger RT doses (linear dose-response) and volumes
  - Higher relative risk with treatment at younger age
- Chemotherapy also affects second cancer risk and can modify radiation-associated risk
  - Procarbazine → GI tract cancers, lung cancer
  - Alkylating agents and anthracyclines → sarcoma
- Genes, hormones and lifestyle appear to modify RT-associated solid cancer risk
Implications of second cancer studies

• Development of new treatment protocols with lower toxicity and equal therapeutic effectiveness (e.g. reduction of radiation dose)

• Identification of patient groups at high risk of second cancers → screening if effective methods available
Reduction of RT dose with modern treatments

Proportional Reduction in Mean Dose

Normalized Mean Dose

Organ Exposed

Bilateral Breast  Heart  Bilateral Lungs  Thyroid

Mantle 36Gy  IFRT 21Gy  INRT 21Gy

Courtesy: D. Hodgson
Is second cancer risk lower in more recent treatment periods?

- Evolution of second cancer risk in HL patients treated before age 51 between 1965-2000

Schaapveld M et al. *NEJM* 2015;373(26):2499
Cumulative incidence of solid cancers by treatment period

sHR 0.94 (95%CI 0.77-1.15)

Adjusted for age, gender and smoking status

Schaapveld M et al. NEJM 2015;373(26):2499
Cumulative incidence of breast cancer by treatment period

sHR 1.24 (95%CI 0.82-1.87)

Adjusted for age, gender and smoking status

Schaapveld M et al. *NEJM* 2015;373(26):2499
Why does solid tumor risk not decrease in recent treatment period?

• Favorable and unfavorable treatment changes
  - Less use of mantle field $\rightarrow$ breast cancer $\downarrow$
  - Less use of high dose gonadotoxic CT $\rightarrow$ breast cancer $\uparrow$
    $\rightarrow$ opposite effects on breast cancer risk
  - Anthracyclines?

• Surveillance (breast!) $\uparrow$

• Too early yet to observe a decline in second cancer risks; smaller RT volumes introduced rather recently!
A Dutch nationwide survivorship care program for lymphoma survivors
The “BETER”-project

Better care after (non-)Hodgkin lymphoma:
Evaluation of long-term treatment
Effects and screening
Recommendations

BETER Consortium: 26 hospitals
Second malignancies
Cardiovascular disease
Thyroid disease
Splenic dysfunction
Fertility and osteoporosis
Neck complaints

Patient recall: all HL 5-year survivors treated at ages 15 – 60 yrs
Challenges for future research

1. Contemporary RT regimens, IMRT, protons; lower doses to larger volumes
2. Dose-volume parameters
3. Search for susceptibility genes for RT/CT-associated second cancers
4. Genomic alterations in second cancers
5. Risk prediction models
6. Efficacy of screening
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University Medical Centre Groningen
Jourik Gietema

Netherlands Cancer Registry
Which proportion of second malignancies can be attributed to radiotherapy?

A. > 75%
B. < 5%
C. 10 – 25%
Which proportion of second malignancies can be attributed to radiotherapy?

A. > 75%
B. < 5%
C. 10 – 25%
The risk of breast cancer after chest radiotherapy increases with:

A. Radiation dose and younger age at treatment
B. Radiation dose, number of alkylating chemotherapy cycles and younger age at treatment
C. Radiation dose, number of alkylating chemotherapy cycles and older age at treatment
D. Radiation dose, longer exposure to ovarian hormones and younger age at treatment
The risk of breast cancer after chest radiotherapy increases with:

A. Radiation dose and younger age at treatment
B. Radiation dose, number of alkylating chemotherapy cycles and younger age at treatment
C. Radiation dose, number of alkylating chemotherapy cycles and older age at treatment
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