Cardiac Effects of Radiation Therapy

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DCEG Radiation Epidemiology and Dosimetry Course 2019
Radiotherapy cures cancers

What can currently cure cancer?

- Surgery: 49%
- Radiotherapy: 40%
- Chemotherapy: 11%

Professor Sir Mike Richards, NCRI 2011

DH Cancer Reform Strategy 2007 – Aim - ‘World Class Radiotherapy’
Types of Epidemiological Study

1. Descriptive studies
2. Randomised trials
3. Cohort studies
4. Nested case-control studies
Types of Epidemiological Study

1. Descriptive studies 1900s-1970s

Case reports

Case series
MANTLE IRRADIATION IN HODGKIN'S DISEASE
An Analysis of Technique, Tumor Eradication, and Complications

RICHARD J. CARMEL, MD, AND HENRY S. KAPLAN, MD

The “mantle” is a single anteroposterior radiation therapy field designed to treat in continuity the major lymph node-bearing areas above the diaphragm w
Descriptive studies

Mantle irradiation, Hodgkin Lymphoma

Radiotherapy planning X-ray

Dose reconstructed with modern techniques.

van Nimwegen et al, IJROBP, 2015
MANTLE IRRADIATION IN HODGKIN'S DISEASE
An Analysis of Technique, Tumor Eradication, and Complications

Richard J. Carmel, MD, and Henry S. Kaplan, MD

Mantle Treatment
The 377 patients within the study received mantle irradiation with a mean midline dose to the mediastinum of 4410 rads.

Descriptive studies

5 deaths from pericarditis

Interval from completion of radiotherapy to relapse/pericarditis

Cardiac Anatomy

- Pericardium
- Coronary arteries
- Valves
- Muscle

Duane, et al Radioth Oncol 2017
Types of Epidemiological Study

1. Descriptive studies
2. Randomised trials
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Types of Epidemiological Study

1. Descriptive studies
2. Randomised trials
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Randomised trial

**Experimental:** Randomization to exposure

Exposure:
- Yes: 😊😊😊😊😊
- No: 😊😊😊😊😊

Disease:
- ?
- ?
## Randomised trials

**Randomised to radiotherapy versus not**

75 trials, 40,000 women, median entry 1983

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>No. of trials</th>
<th>No. of women</th>
<th>Deaths with no recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy (for cancer)</td>
<td>36</td>
<td>16,156</td>
<td>2921</td>
</tr>
<tr>
<td>Breast conserving (for ca.)</td>
<td>18</td>
<td>11,655</td>
<td>1270</td>
</tr>
<tr>
<td>Various (for cancer)</td>
<td>17</td>
<td>9066</td>
<td>1666</td>
</tr>
<tr>
<td><strong>All trials</strong></td>
<td><strong>75</strong></td>
<td><strong>40,781</strong></td>
<td><strong>6064</strong></td>
</tr>
</tbody>
</table>

*EBCTCG, J Clin Oncol 2017*
## Randomised trials

### Heart disease mortality

<table>
<thead>
<tr>
<th>Cause</th>
<th>Total deaths</th>
<th>Excess deaths</th>
<th>Rate ratio (95% CI)</th>
<th>2p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>1253</td>
<td>143</td>
<td>1.30 (1.15-1.46)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischaemic heart dis.</td>
<td>751</td>
<td>90</td>
<td>1.31 (1.13-1.53)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Heart failure</td>
<td>96</td>
<td>28</td>
<td>1.94 (1.27-2.98)</td>
<td>0.002</td>
</tr>
<tr>
<td>Valve disease</td>
<td>46</td>
<td>14</td>
<td>1.97 (1.07-3.67)</td>
<td>0.03</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>360</td>
<td>11</td>
<td>1.08 (0.86-1.35)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

EBCTCG, J Clin Oncol 2017
Radiotherapy by decade in trials

1970s

1980s

1990s

c/o Dr Fran Duane
Randomised trials
Heart dose-response relationship
1253 cardiac deaths in 40,000 women

Percent increase per Gy: 4.1% (2.4 - 6.2)
2p<0.00001

Very approximate information on heart dose based just on trial description

Increase per Gy, 4.1% (95% CI 2.4-6.2) 2p<0.00001

EBCTCG, J Clin Oncol 2017
Still need ......

▪ Large studies in the *general* patient population

▪ Data on non-fatal and fatal events

▪ More detailed studies:
  ▪ Individual information on radiation heart dose
  ▪ Medical history at time of cancer diagnosis including, eg pre-existing heart disease
Types of Epidemiological Study

1. Descriptive studies
2. Randomised trials
3. Cohort studies
4. Nested case-control studies
Cohort Study

- Compare disease status in exposed vs. non-exposed
- Prospective
- May take many years to follow-up the cohort
In a randomised trial, the investigator allocates exposures using randomisation. In a cohort study, exposures are allocated through choice/circumstances.

**Cohort Study**

- Compare disease status in exposed vs. non-exposed
- Prospective
- May take many years to follow-up the cohort
Cohort studies

Cardiac mortality: Radiotherapy versus not

~2 million women
57 cancer registries in 22 countries
55,000 deaths from heart disease
53% irradiated

Cardiac mortality ratio, RT versus not (95% CI)

| All women          | 0.94 (0.92-0.95) |

K Henson 2019 provisional results
### Cohort studies

**Cardiac mortality: Radiotherapy versus not**

<table>
<thead>
<tr>
<th>Treatment / no treatment</th>
<th>Number of deaths</th>
<th>Cardiac mortality rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>22,100 / 33,164</td>
<td>0.94 (0.92–0.95)</td>
</tr>
<tr>
<td>BCS</td>
<td>5,832 / 3,805</td>
<td>0.70 (0.67–0.73)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>3,315 / 13,727</td>
<td>1.24 (1.19–1.30)</td>
</tr>
<tr>
<td>Unknown/None</td>
<td>12,953 / 15,632</td>
<td>1.03 (1.00–1.06)</td>
</tr>
</tbody>
</table>

2p for difference < 0.0001

*K Henson 2019 provisional results*
***** WARNING *****

The comparison of irradiated and unirradiated women outside the context of a randomised trial may not provide information about the risk of radiation-related heart disease.

<table>
<thead>
<tr>
<th></th>
<th>No. of deaths</th>
<th>Cardiac mortality rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Europe: Britain &amp; Ireland</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS</td>
<td>812 / 388</td>
<td>0.86 (0.76-0.97)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>514 / 793</td>
<td>1.18 (1.05-1.32)</td>
</tr>
<tr>
<td>Unknown / None</td>
<td>1,407 / 2,385</td>
<td>0.85 (0.79-0.90)</td>
</tr>
<tr>
<td><strong>Europe: Nordic countries</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS</td>
<td>423 / 141</td>
<td>0.80 (0.65-1.00)</td>
</tr>
</tbody>
</table>

K Henson 2019 provisional results
# Cardiac mortality ratios

## Left-sided vs right-sided breast cancer

<table>
<thead>
<tr>
<th></th>
<th>Number of deaths</th>
<th>Cardiac mortality rate ratio (95% CI)</th>
<th>2p for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women diagnosed before 1990</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irradiated women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS</td>
<td>933 / 828</td>
<td>1.08 (0.98–1.19)</td>
<td>0.62</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>1,249 / 1,052</td>
<td>1.12 (1.03–1.21)</td>
<td></td>
</tr>
<tr>
<td>None/unknown</td>
<td>3,536 / 2,823</td>
<td>1.18 (1.13–1.24)</td>
<td></td>
</tr>
<tr>
<td>Not recorded</td>
<td>2,094 / 1,831</td>
<td>1.07 (1.01–1.14)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7,812 / 6,534</td>
<td>1.13 (1.09–1.17)</td>
<td></td>
</tr>
<tr>
<td>Unirradiated women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS</td>
<td>714 / 697</td>
<td>0.99 (0.89–1.10)</td>
<td>0.63</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>3,733 / 3,442</td>
<td>1.01 (0.97–1.06)</td>
<td></td>
</tr>
<tr>
<td>None/unknown</td>
<td>5,127 / 4,655</td>
<td>1.02 (0.98–1.06)</td>
<td></td>
</tr>
<tr>
<td>Not recorded</td>
<td>764 / 634</td>
<td>1.14 (1.03–1.27)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10,338 / 9,428</td>
<td>1.02 (0.99–1.05)</td>
<td></td>
</tr>
</tbody>
</table>

*K Henson 2019 provisional results*
Cohort studies

- If the decision to give radiotherapy did not depend on laterality of the breast cancer, then ..... 

- we can regard the heart disease rates in women with left-sided and right-sided breast cancer as equivalent to a randomised trial.
Cohort and case control studies

- Large studies in the general patient population
- Data on non-fatal and fatal events
- More detailed studies:
  - Individual information on radiation heart dose
  - Medical history at time of cancer diagnosis
Cohort studies

Cardiac morbidity

Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden

Paul McGale<sup>a</sup>, Sarah C. Darby<sup>a</sup>,<sup>*,</sup> Per Hall<sup>b</sup>, Jan Adolfsson<sup>c</sup>, Nils-Olof Bengtsson<sup>d</sup>, Anna M. Bennet<sup>b</sup>, Tommy Fornander<sup>c</sup>, Bruna Gigante<sup>f</sup>, Maj-Britt Jensen<sup>g</sup>, Richard Peto<sup>a</sup>, Kazem Rahimi<sup>b</sup>, Carolyn W. Taylor<sup>a</sup>, Marianne Ewertz<sup>i</sup>

Left vs right-sided breast cancer: Heart disease incidence ratios
Cardiac Anatomy

- Pericardium
- Coronary arteries
- Valves
- Muscle

Duane, et al Radioth Oncol 2017
Cohort studies
Left vs right-sided breast cancer:
35,000 women given breast cancer radiotherapy

<table>
<thead>
<tr>
<th>Disease category</th>
<th>Events left/right</th>
<th>Incidence ratio, left vs. right (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>878/712</td>
<td>1.18 (1.07-1.30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>60/36</td>
<td>1.61 (1.06-2.43)</td>
<td>0.03</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>94/60</td>
<td>1.54 (1.11-2.13)</td>
<td>0.009</td>
</tr>
<tr>
<td>Conduction disorders</td>
<td>445/453</td>
<td>0.94 (0.82-1.07)</td>
<td>0.35</td>
</tr>
<tr>
<td>Heart failure</td>
<td>310/315</td>
<td>0.95 (0.81-1.11)</td>
<td>0.51</td>
</tr>
<tr>
<td>All heart disease</td>
<td>2275/2016</td>
<td>1.08 (1.02-1.15)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

McGale et al, Rad Onc 2011
Cohort and case control studies

- Large studies in the general patient population
- Data on non-fatal and fatal events
- More detailed studies:
  - Individual information on radiation heart dose
  - Medical history at time of cancer diagnosis
Types of Epidemiological Study

1. Descriptive studies
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3. Cohort studies
4. Nested case-control studies
Case-Control Study

- Compare exposure in cases vs. controls
- Retrospective
Case control studies

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Bronnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazug Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

Nested in cohort study
Danish Breast Cancer Cooperative Group and Swedish Cancer Registry
Case control studies

Population-based case-control study of major coronary events

- Population: Women irradiated for breast cancer
- 963 cases (Major Coronary Events)
- 1205 controls also irradiated for breast cancer
- Information from oncology records (medical history and radiotherapy plans)

Darby et al, NEJM 2013
Case control studies

Individual patient doses

Taylor et al, IJRBP 2007
Case control studies

Dose-response relationship for major coronary events

Darby et al, NEJM 2013

7.4% increase per Gy (95% CI 3-14; p=0.0001)
# Case control studies

## Major coronary event rate per Gy mean heart dose

<table>
<thead>
<tr>
<th>Cardiac risk factor</th>
<th>Average dose to heart (Gy)</th>
<th>% increase in MCE rate/Gy (95%CI)</th>
<th>2p for diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>5.1</td>
<td>7.4 (2.0-20.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Yes</td>
<td>4.9</td>
<td>7.4 (1.2-20.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Darby et al, NEJM 2013*
7.4% increase per Gy
(95% CI 3-14; p=0.0001)

Same slope for women with and without cardiac risk factors at time of breast cancer diagnosis

Darby et al, NEJM 2013
Case control studies

Risks by age 80 of radiotherapy at age 50

Darby et al, NEJM 2013
Ischaemic Heart Disease: Current position

- Risk proportional to whole heart dose
- No known threshold
- Radiation-related risk multiplies pre-existing risk
- Risk starts within first 5 years, continues for several decades
Case control studies

ARTICLE
Risk for Valvular Heart Disease After Treatment for Hodgkin Lymphoma

5-year survivors Hodgkin lymphoma
Nested in cohort of 1852 patients
Cases = valvular heart disease after radiotherapy
Cardiac Anatomy

- Pericardium
- Coronary arteries
- Valves
- Muscle

Duane, et al Radioth Oncol 2017
Case control studies
Valvular heart disease

Cutter, Schaapveld, et al JNCI 2015
Case control studies

Valvular Heart Disease: Current position

- Radiation increases the risk at >30 Gy
- Little evidence of risk from lower doses
- Risk starts after 10 years
Muscle: Heart failure can be caused by chemotherapy. Unclear about radiotherapy.
- Examples given for Hodgkin lymphoma and breast cancer.

- Good survival – many patients live a long time
Ten-year survival Hodgkin Lymphoma

Age-Standardised Ten-Year Net Survival, England and Wales
Age-standardised ten-year net survival, England and Wales
- Other adult cancers where radiotherapy involves heart:
  - Lung cancer
  - Oesophageal cancer

Survival poorer – few live a long time
Cohort study
Childhood cancer

Tukenova et al, JCO, 2010
Cohort study

Childhood cancer

- Linear relationship between heart dose and risk of cardiac mortality
- Estimated increase: 60% per Gy (7.4% for adults)
- Irradiating heart in childhood may affect growth of the heart
Clinical decisions

Clinicians need absolute risks ...

Balance absolute benefit and absolute risk
Radiotherapy has changed Hodgkin lymphoma

1970s
c/o Dr David Cutter

2010s
c/o Dr Georgios Ntentas
Radiotherapy has changed Breast cancer
Thank you
The commonest type of radiation-induced heart disease is:

a) Heart failure
b) Ischaemic heart disease
c) Valve disease
Quiz 1

The commonest type of radiation-induced heart disease is:

a) Heart failure
b) Ischaemic heart disease
c) Valve disease
Quiz 2

Heart radiation doses from today’s radiotherapy are similar to doses from 1970s radiotherapy

True/False
Quiz 2

Heart radiation doses from today’s radiotherapy are similar to doses from 1970s radiotherapy

True/False
Quiz 3

The cardiac risks from modern radiotherapy outweigh the benefits for most patients

True/False
Quiz 3

The cardiac risks from modern radiotherapy outweigh the benefits for most patients

True/False