Risk of second cancers
Bridging epidemiology and modeling

Uwe Schneider
Department of Physics, Science Faculty, University of Zurich and Radiotherapy Hirslanden, Zurich, Switzerland
Table of Contents

1) Introduction
2) Risk factors and epidemiology
3) Combining epidemiology and modeling
4) Uncertainties of the models
5) The role of the dose distribution
6) Conclusions
Table of Contents

1) Introduction
2) Risk factors and epidemiology
3) Combining epidemiology and modeling
4) Uncertainties of the models
5) The role of the dose distribution
6) Conclusions
Cancer Survivors: A Booming Population

Estimated number of cancer survivors in the United States from 1971 to 2008

Long-term survivors of childhood cancer

Improved cure rates

5-y survival trends for children diagnosed with cancer at ages 0 to 19 y in SEER (solid lines) and Connecticut (dashed lines) areas.

For some types of cancers, secondary cancers cause more deaths than the primary cancer.
Why is there a need in predicting second cancers?

1) Increasing number of long-term cancer survivors

2) Treating cancer as a chronic disease

3) Distribution of dose in modern photon radiotherapy

4) Neutron dose in clinical ion therapy

We should optimize our treatment plans not only by taking early and late effects into account, but also second cancer estimates.
# Table of Contents

1) Introduction

2) Risk factors and epidemiology

3) Combining epidemiology and modeling

4) Uncertainties of the models

5) The role of the dose distribution

6) Conclusions
Risk factors for second cancers in modern radiation therapy

Risk factors for second cancers which impact dose-volume distribution

Uncertainties of the dose distribution

Has only recently been taken into consideration, as it was assumed that it can be neglected when compared to the uncertainties of the risk models.
Epidemiological studies of RT patients

Epidemiology
- Huge body of literature
- Patients treated 20 to 50 years ago
- Patients treated with techniques not used anymore
- Only few studies give insides on dose-response relationship

Modern treatment modalities
- IMRT / VMAT
- Protons and ions
- IGRT

Extrapolate cancer risk from “old” to “new” RT

Use biophysical models
Dose-response relationship from epidemiology

What we need

Dose-response:
Cancer risk as a function of
- dose to site of second cancer
for each organ
Standard model: “initiation + killing”

Conclusion: repopulation of normal tissue between dose fractions must be considered.

Stratifications of cancer risk as a function of dose to the tumor location: A-bomb survivors

- Organ at risk
- Homogenous dose distribution
- Dose at tumor location constant
Stratifications of cancer risk as a function of dose to the tumor location: A-bomb survivors
Stratifications of cancer risk as a function of dose to the tumor location: RT patients

Dose at tumor location varies significantly

inhomogenous dose distribution

Organ at risk
Determination of dose: RT patients

Fact: a detected second tumor is already a few cm in size

Table 5 Tumor size according to FH of BC. I. All patients; II. Tumors found by self-examination

<table>
<thead>
<tr>
<th></th>
<th>MD (95 % CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree of relationship</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0. no FH: 26.4 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. First-degree FH: 19.3 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Second-degree FH: 26.3 mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional uncertainties:
- Patient positioning
- Internal organ motion
- Anatomical changes
- Dose calculation

Determination of dose: Point dose

Point dose estimates are related to huge errors

Dose in the breast for Hodgkin’s treatment

Huge variations in dose

Axis tangential through breast [cm]
Stratifications of cancer risk as a function of dose to the tumor location

Table 2. Risk of Breast Cancer Among Young Women Diagnosed With Hodgkin Disease, by Treatment*

<table>
<thead>
<tr>
<th>Radiation Delivered to Specific Location in Breast†</th>
<th>Cases (n = 105)</th>
<th>Matched Controls (n = 266)</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose, median (range), Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2 (0-3.9)</td>
<td>15 (14.7)</td>
<td>76 (29.5)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>4.6 (4.0-6.9)</td>
<td>13 (12.7)</td>
<td>30 (11.7)</td>
<td>1.8 (0.7-4.5)</td>
<td>.21</td>
</tr>
<tr>
<td>21.0 (7.0-23.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.5 (23.2-27.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35.2 (28.0-37.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39.8 (37.2-40.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41.7 (40.5-61.3)</td>
<td>17 (16.7)</td>
<td>29 (11.2)</td>
<td>8.0 (2.6-26.4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Huge dose intervals: ~ 15 Gy

Determination of dose: RT patients

- Analyses of radiotherapy risks using mean dose to the stomach tumor location
- Evaluation of risk for the whole organ (e.g. case-control)
Dose-response relationship from epidemiology

What we get

Dose-response:
Cancer risk as a function of
- average dose in huge dose categories
- averaged dose over different treatment techniques
- average dose in a large part of the organ

Average dose implies linear dose-response
How to deal with inhomogeneous dose distributions in epidemiology

Problem:
Which dose do we assign to the "comparison organs" in the people who did not get cancer?
How to deal with inhomogeneous dose distributions in epidemiology

- Organ sub-division into sections where the dose is known

- Get the risks in these "organ sections" first
- Combine these risks to get the total organ risks.

Persons without cancer would provide "multiple comparisons" - one for each cancer free organ section
Table of Contents

1) Introduction
2) Risk factors and epidemiology
3) Combining epidemiology and modeling
4) Uncertainties of the models
5) The role of the dose distribution
6) Conclusions
Dose-response without dose stratification: Reduction of the DVH

Epidemiology:
- organ specific risk
  - e.g. Breast EAR = 10.5
  - O/E = 2.0 CI95(1.8-2.3)
- 3D-dose distribution or dose reconstruction

Apply dose-response model

Reduction of DVH into risk a equivalent variable: OED (similar to EUD-concept)

Reduction of the DVH: Hodgkin - Breast

Epidemiology:
- Combination with A-bomb survivor data

Risk ~ OED

Optimization of the model
- Linearize OED
- Change model
Result: optimized dose-response relationship without dose averaging

Result: optimized dose-response relationship without dose averaging

Convert DOSE to RISK
Second cancer web-tool from the University of Oxford

Table of Contents

1) Introduction
2) Risk factors and epidemiology
3) Combining epidemiology and modeling
4) Uncertainties of the models
5) The role of the dose distribution
6) Conclusions
Uncertainties of risk models

\[ \text{EAR}(D, df, agex, agea, s) = \beta(s) \cdot \mu(\text{agex}, \text{agea}, s) \cdot \text{OED}(D, df) \]

- **95 CI EAR \approx 100\%**
  - If you really need absolute risks

- **95 CI OED \approx 10\%**
  - If you want to compare risks for one patient: treatment planning

Risk variation with age

\[ \mu(\text{age}_{x, \text{age}_{a}}, s) \]

- Significant variation of risk with age
- Important for children

Table of Contents

1) Introduction
2) Risk factors and epidemiology
3) Combining epidemiology and modeling
4) Uncertainties of the models
5) The role of the dose distribution
6) Conclusions
Uncertainties of the dose distribution

Table of Contents

1) Introduction
2) Risk factors and epidemiology
3) Combining epidemiology and modeling
4) Uncertainties of the models
5) The role of the dose distribution
6) Conclusions
Conclusions I

- The number of cancer survivors is increasing
- Modern radiotherapy is changing the distribution of dose in the patient
- Epidemiological studies provide risk data for “old-fashioned RT”

Models of second cancer risk:
Extrapolate cancer risk from “old” to “new” RT
Conclusions II

- Epidemiology: **Analysis of the 3D-dose distribution** (avoid dose averaging)
- Epidemiology and inhomogeneous dose distributions: Dose stratification calculating **risk in organ sections**
- Epidemiology and modelling:
  - avoid dose stratification
  - use of **DVH and models together** with epidemiology
- **Fractionation effects**: animal experiments and epidemiology
- Neutrons and ions: **RBE** with regard to cancer induction
Thank you for your attention!

Acknowledgement:
- Roger Hälg, Pascal Hauri and the Radiotherapy Division of Hirslanden
- Linda Walsh and the Medical Physics research group @ University of Zürich