Low dose exposure from pediatric CT scans and cancer risk

Elisabeth Cardis and Ausrele Kesminiene
Why are CTs of interest in radiation protection?

- Diagnostic radiation is an indispensable, sometimes life-saving, tool in modern medicine.

- But use of diagnostic X-rays and of high-dose techniques (CT, interventional procedures using X-rays) has grown dramatically in recent years
  - improvement of technology
  - more applications
  - markedly increased use
  - and increase in dose ...

... growing radiological protection and public health concern

Courtesy; F. Mettler, 2008
Questions

• What is the public health impact of this increase?
  – Brenner et al – predictions from A-bomb survivors
  – *But uncertainties regarding effects of low to moderate doses received in fractionated fashion*

• Are there subgroups with increased sensitivity?

• Need to optimise imaging protocols, particularly among young people?
The issue of children

• 5-10% of all CTs in children
• Because of their smaller mass, children tend to receive higher doses to specific organs
  – doses to target organs can be of the order of a few tens of mGy per examination
  – cumulative doses may reach 100 – 200 mGy (or more) if procedures are repeated
  – great variability of doses and procedures not always adapted to paediatric patients
• Children have a longer life span to express any radiation-related detriment
### Studies with estimate of risk per mGy

<table>
<thead>
<tr>
<th>Study</th>
<th>Population size and age range</th>
<th>ERR/mGy (95% CI)</th>
<th>Limitations - Organ-dose</th>
</tr>
</thead>
</table>
| Pearce et al, 2012, Berrington et al 2016 (UK) | 178,604 CT patients 0-22 years old | *Leukaemia* (74 cases) 0.036 (0.005, 0.120) 0.033 (0.004, 0.114) 0.037 (0.005, 0.125)  
*Brain tumours* (135 cases) 0.023 (0.010, 0.049) 0.012 (0.004, 0.031) | - Overall  
- excluding previous cancers  
- excluding leukaemia related cond. |
| Matthews et al, 2013 (Australia)           | 680,211 CT patients 0-19 years old | *Leukaemia* (246 cases) 0.039 (0.014, 0.070)  
*Brain tumours* (283 cases) 0.021 (0.014, 0.029) | - Exposure misclassification  
- Increase for all cancer types |
| Journy et al, 2014, 2015 (France)          | 67,274 patients 0-10 years old | *Leukaemia* (17 cases) 0.057 (-0.079, 0.193) 0.187 (NA)  
*Brain/CNS tumours* (22) 0.022 (-0.016, 0.061) 0.028 (NA) | - Short follow-up (4 years), few cases  
- Overall  
- excluding predisposing factors  
- Overall  
- excluding predisposing factors |
### Studies with no estimate of dose-related risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Population size and age range</th>
<th>Risk measures (95% CI)</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Huang et al, 2014      | 24,418 patients with brain CTs 0-18 years old | HR compared to population in health system  
All cancers (39)  
1.29 (0.90, 1.85)  
Leukaemia (8)  
1.90 (0.82–4.40)  
Brain tumours – all (19)  
2.56 (1.44–4.54)  
*HR increased with numbers of CTs* | - Short follow-up  
- Small numbers of cases  
- No dose estimation |
| Krille et al, 2015     | 80,000 patients 0-15 years old | SIR  
Leukaemia (12 cases)  
1.72 (0.89–3.01)  
1.79 (0.92–3.12)  
CNS (7 cases)  
1.35 (0.54–2.78)  
1.79 (0.92–3.12) | - No dose used in analysis  
- Small numbers  
Overall  
Excluding subjects at risk  
Overall  
Excluding subjects at risk |
Issues in interpreting results

- **Confound by predisposing condition**
  - UK, Netherlands, France ... little evidence
  - Miglioretti – US ...

- **Assessment of doses**
  - Very variable - type of scans, machine, protocol, organ, age/size variability
  - Missing doses (CTs in other hospitals, other procedures)

- **Individual sensitivity ?**
Study design

Records of radiology departments

Pediatric patients CT scans

Quantification of health risks from CT doses

Linkage with registries

Estimate individual radiation dose

Pediatric patients CT scans
<table>
<thead>
<tr>
<th>Country</th>
<th>Recruitment period</th>
<th>Age at 1st CT</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>2002 - 2012</td>
<td>0-18</td>
<td>14,002</td>
</tr>
<tr>
<td>Denmark</td>
<td>2002 - 2012</td>
<td>0-18</td>
<td>21,649</td>
</tr>
<tr>
<td>France</td>
<td>2000 - 2011</td>
<td>0-9</td>
<td>121,101</td>
</tr>
<tr>
<td>Germany</td>
<td>1983 - 2013</td>
<td>0-14</td>
<td>63,998</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1970 - 2014</td>
<td>0-17</td>
<td>158,130</td>
</tr>
<tr>
<td>Norway</td>
<td>1980 - 2013</td>
<td>0-20</td>
<td>80,225</td>
</tr>
<tr>
<td>Spain</td>
<td>1987 - 2013</td>
<td>0-20</td>
<td>171,336</td>
</tr>
<tr>
<td>Sweden</td>
<td>1984 - 2013</td>
<td>0-17</td>
<td>128,699</td>
</tr>
<tr>
<td>UK</td>
<td>1985 - 2013</td>
<td>0-21</td>
<td>411,046</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>1,170,186</strong></td>
</tr>
</tbody>
</table>
Particular attention was paid to

- Identification and assessment of sources of bias and uncertainty:
  - SES
  - missing CTs
  - missed doses from other procedures
  - confounding by indication
  - confounding by cancer susceptibility syndromes
  - incomplete follow-up (mortality, emigration, ...)
  - others (epidemiological surveillance ....)

- Individual dose (and uncertainty) reconstruction

- Feasibility of identifying biomarkers
Biological pilot study

Identification of markers of radiation sensitivity in very young ages

- In vitro chromosomal and comparative study of gamma-H2AX biomarker in blood
- Radiation-induced stress response in saliva
- Gene expression patterns before and after CT exposure
Biological pilot study: some results

- Chromosomal aberrations and induction of DNA double strand breaks following CT scanning - increased in blood samples from newborns and young children when compared to adults

- Differences also visible in the γ-H₂AX-foci assay

- Currently no biomarkers that can be obtained in non-invasive way - this makes difficult integration of molecular biology component in a large scale paediatric CT study
DOSE RECONSTRUCTION — AVAILABLE DATA

Early Years

Pre-PACS

RIS

Patient Information:
Age, Sex
Height & weight if available
Examination type

Recent Years

PACS

Questionnaire

Protocols:
- manufacturer
- model
- kV
- mAs
- pitch
- other parameters for additional analyses

PerMoS

Patient Information:
Age, Sex
Height & weight if available
Examination type
DICOM header
OVERALL STRATEGY FOR DOSE RECONSTRUCTION

- Analysis based on NCICT
  - To obtain an **ESTIMATION** of dose to the organs of the patients
THE problem ... missing data

Missing information on the type of machine used in a specific hospital (given time period)

Several machines were used in the same hospital

Machine settings for a given age and examination

Characteristics of the patient: Age (known), surrogate for height and weight

Body part scanned
2D Monte Carlo simulation

- Provides alternative realizations of possibly true sets of doses
  - The variability of dose for subjects with similar attributes is represented within each realization of the cohort;
  - The uncertainty of dose-related model parameters is represented across all the realizations of the cohort.

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Realization 1</th>
<th>Realization 2</th>
<th>Realization 3</th>
<th>...</th>
<th>...</th>
<th>...</th>
<th>Realization 1000</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>D_{1,1}</td>
<td>D_{1,2}</td>
<td>D_{1,3}</td>
<td></td>
<td></td>
<td></td>
<td>D_{1,1000}</td>
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<tr>
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<td>D_{2,1}</td>
<td>D_{2,2}</td>
<td>D_{2,3}</td>
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<td></td>
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<td>D_{2,1000}</td>
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<tr>
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<td>D_{3,1}</td>
<td>D_{3,2}</td>
<td>D_{3,3}</td>
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<td>D_{3,1000}</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>D_{N,1}</td>
<td>D_{N,2}</td>
<td>D_{N,3}</td>
<td></td>
<td></td>
<td></td>
<td>D_{N,1000}</td>
</tr>
</tbody>
</table>

- 2DMC is meant to separate uncertainties which are shared among individuals from those that are individual-specific
Example 1 — Missing questionnaires about scanner type and protocols

• Questionnaires to assess characteristics of typical protocols used over time sent to each participating hospital (by machine type, examination type and age group).

• No answer to our questionnaire for some hospitals
  - Unknown machine type (manufacturer and model)
  - Unknown protocols (kV, mAs and pitch)
Manufacturer and models

- Subjective probability density function
  - we believe it represents the relative likelihood of the use of CT machines in the country
## Selection of Machine

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Child 1</th>
<th>Child 2</th>
<th>Child 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital 1</td>
<td>2y/ Thorax</td>
<td>5y/ Thorax</td>
<td>newborn/ head</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>........</td>
</tr>
<tr>
<td>Hospital 2</td>
<td>2y/ Thorax</td>
<td>newborn/ head</td>
<td>5y/ head</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>........</td>
</tr>
<tr>
<td>Hospital 3</td>
<td>newborn/ head</td>
<td>newborn/thorax</td>
<td>5y/ head</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>........</td>
</tr>
</tbody>
</table>
NEXT STEPS

- Scanner model is determined for each realization
- All other parameters have to be considered
  - kVp, mAs, pitch

Example: tube potential kV

- Probability density functions for GE Hispeed CT/i

- Similarly for all CT machines and examination types
<table>
<thead>
<tr>
<th>Hospital</th>
<th>Patient Age</th>
<th>Region</th>
<th>KVP 1</th>
<th>KVP 2</th>
<th>KVP 3</th>
<th>KVP Rn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital 1</td>
<td>Child 1: 2y/ Thorax</td>
<td>120</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>Hospital 1</td>
<td>Child 2: 5y/ Thorax</td>
<td>100</td>
<td>100</td>
<td>120</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>Hospital 1</td>
<td>Child 3: newborn/ head</td>
<td>150</td>
<td>150</td>
<td>100</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>Hospital 2</td>
<td>Child 1: 2y/ Thorax</td>
<td>120</td>
<td>80</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Hospital 2</td>
<td>Child 2: newborn/ head</td>
<td>100</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>Hospital 2</td>
<td>Child 3: 5y/ head</td>
<td>150</td>
<td>120</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Hospital 3</td>
<td>Child 1: newborn/ head</td>
<td>100</td>
<td>80</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Hospital 3</td>
<td>Child 2: newborn/thorax</td>
<td>100</td>
<td>100</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Hospital 3</td>
<td>Child 3: 5y/ head</td>
<td>100</td>
<td>140</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
**FIRST CASE — THORAX BOY 2 YEARS OLD**

- For each realization, we have selected **kVp, mAs and pitch** from the appropriate probability density functions.

<table>
<thead>
<tr>
<th>CT machine</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE-HiSpeed Adv., CT/i</td>
<td>120</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Toshiba-Aquilion-4</td>
<td></td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>GE-HiSpeed Adv., CT/i</td>
<td></td>
<td>200</td>
<td></td>
</tr>
<tr>
<td><strong>kVp</strong></td>
<td><strong>120</strong></td>
<td><strong>80</strong></td>
<td><strong>100</strong></td>
</tr>
<tr>
<td><strong>mAs</strong></td>
<td><strong>160</strong></td>
<td><strong>80</strong></td>
<td><strong>200</strong></td>
</tr>
<tr>
<td><strong>pitch</strong></td>
<td><strong>1</strong></td>
<td><strong>1</strong></td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>

**Resulting organ doses (mGy)**

<table>
<thead>
<tr>
<th>Organ</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>20</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Breast</td>
<td>17</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Heart wall</td>
<td>21</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>RBM</td>
<td>8</td>
<td>2</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Uncertainty on scanned area not taken into account.
The exposed part of the body assessed based on

- Type of examination
  - EU classification using 7 body regions divided into body part and specific organs
  - Expert judgment on scan position (uncertainty assessed)
- Analysis of mathematical descriptions of contours of the organs (for recent years)
  - Segmentation of the image for the HU (Hounsfield Unit) of bone, soft tissue and air, separately during data collection
  - Only segmented outlines are transferred to the database without collection of images
Probability density functions
ORGAN DOSES (mGy)

<table>
<thead>
<tr>
<th>CT machine</th>
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</thead>
<tbody>
<tr>
<td>kVp</td>
<td>120</td>
</tr>
<tr>
<td>mAs</td>
<td>160</td>
</tr>
<tr>
<td>pitch</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Thyroid</th>
<th>Breast</th>
<th>Heart wall</th>
<th>RBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mGy)</td>
<td>20</td>
<td>17</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Dose (mGy)</td>
<td>9</td>
<td>17</td>
<td>21</td>
<td>7.5</td>
</tr>
<tr>
<td>Dose (mGy)</td>
<td>23</td>
<td>17</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Dose (mGy)</td>
<td>5</td>
<td>16.5</td>
<td>20</td>
<td>6</td>
</tr>
</tbody>
</table>
Data collection:
- Cohort accrualment finished – EXPOSURE data
- Cancer and mortality data (finished) – OUTCOME data
- SES data, rare disease appraisal finished – CONFOUNDING data

Dose reconstruction:
- Dose reconstruction – with uncertainty – completed
- Last validations underway
- Final product: 500 realisations of doses

Analyses completed:
- Risk projection of radiation-related cancer for several sites (Germany, Spain, UK)
- Relation between CT scanning and SES (Netherlands, Spain, UK, Germany)
- Possible effect of cancer predisposing syndromes (France, Netherlands)
- Confounding by indication
Descriptive results

• Total size of cohort: ~1,003,700 (>1 year of follow-up)
• Person years of follow-up: ~9,500,000
• Median duration of follow-up: ~9.5 years
• Number of deaths: ~12,000
• Age at first CT: 0-21 (depends on country)
• Mean age at first CT: 10.8
• Average number of CT per subject: 1.5
• % of patients with >= 5 CTs: 5%

PRELIMINARY!
Analyses underway

• Estimates of leukemia and brain tumour risk and CT scan in Europe
• Simulations of impact of sources of bias on study results
• Modelling of impact of dosimetric uncertainty
• Timing – first draft result paper January 2018
Next step

- Nested case-control study – leukaemia, brain tumours (WP5)*
  - Questionnaire and medical records
    - Information about other CTs
    - Information about other procedures
    - Medical history – previous cancers, predisposing factors
    - Improve dosimetry (antropomorphical parameters, technical parameters)
  - Biological samples (saliva)
    - Genetic and epigenetic factors which may modify individual susceptibility

*involves contact with study subjects – subject to ethics approval and informed consent
Thank you!

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