Radiation exposures from CT scans in childhood and subsequent risk of leukaemia and brain tumours

Mark S. Pearce, PhD
CT scan history and usage

- A very useful tool
- Introduced in the early 1970’s for head scanning
- Available worldwide at over 30,000 centres (and continuing to increase)
- 4% of all medical imaging examinations in the UK
- >40% of total collective dose to UK population from medical x-ray examinations
Estimated that 5-10% of all CT exams are in children

- Though varies by country

Use has grown rapidly over the past two decades as procedures have become much faster
Why study young people?

- With their smaller mass, children tend to receive higher doses to specific organs
  - Great variability of doses, as procedures are not always adapted for young patients
  - Paediatric parameters are dependent on age and weight
  - Historically these parameters were often ignored
- Children have a longer remaining life span
What is known so far?

Generally:

• Other low dose exposures suggest increased cancer risks at the level of several CT scans

  • E.g. Japanese A-bomb survivors, nuclear workers, patients with high numbers of X-rays
What is known so far?

Specific to CT:

• Mostly risk projection studies extrapolating ‘expected’ doses and ‘expected’ cancer risks
  • i.e. no empirical data

• Projections often limited to certain scans, mortality outcomes only and made assumptions regarding modern protocol adjustments that may not have been possible historically
The UK CT Scan Study

- Long-term sequelae of radiation exposure due to computed tomography in childhood and early adulthood

- Funders:
  - US National Cancer Institute
  - UK Department of Health
Why in the UK?

- National Health Service (NHS)
  - Free access to healthcare for all
  - CT scans performed primarily in public hospitals
- NHS Central Register
- National and regional cancer registries
- Ability to obtain ‘umbrella consent’ & ethics
Any drawbacks to doing it in the UK?

• Expensive matching processes compared to Scandinavian countries
  • But a much bigger country/patient group

• Lower usage of CT compared to countries such as the USA and Japan
  • But more difficult to do the data linkage in these countries
The Study

- Primary Objective
  
  - To assess the risk of subsequent cancers in individuals exposed via CT scanning during childhood or as young adults
Cohort study

- Patients having one or more CT scans between 1985-2002
  - First scanned aged <22 years
  - Free from cancer at first CT

- Radiology departments with available electronic RIS data of sufficient quality
  - Film / paper records from small number of Trusts
A nested case-control study to assess dose response more precisely
Cohort study dosimetry

- Date and type of scan, age and sex available from electronic RIS records

- Typical CT machine settings for young people taken from 2 UK-wide surveys (1989 and 2001)

- These data combined with those from hybrid computational phantoms and Monte Carlo radiation transport techniques to give estimated absorbed organ doses (e.g. red bone marrow)

- Cumulative doses where more than one CT scan
Outcome data

- RIS data linked with the NHSCR (1985-2008)
  - Cancer incidence
  - Mortality
  - Loss-to-follow-up (e.g. notified emigrations)

- Excluded patients with existing cancer and those diagnosed with leukaemia within 2 years of first CT scan (5 years for brain tumours)
  - Sensitivity analyses with greater years of exclusion
Statistical Methods

- Used Poisson relative risk models fitted by maximum likelihood methods.
- Accrual of person-time began 2 or 5 years after the initial CT scan.
- Lag time of 2 or 5 years also included:
  - Sensitivity with longer time periods
Results - descriptive

- Initial cohort, including cancer patients: 245,000

- Excluding those with cancer and those that could not be linked by NHSCR left 178,604 patients in the leukaemia analysis and 176,587 in the brain tumour analysis

- These patients had 280,000 CT scans, over 60% of which were of the head
## Leukaemia - Excess relative risk per mGy organ-specific radiation doses received from CT scans

<table>
<thead>
<tr>
<th>Case Description</th>
<th>Cases</th>
<th>ERR per mGy (95% CI)</th>
<th>p value (test for dose-response)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red bone marrow dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All leukaemia, including myelodysplastic syndromes</td>
<td>74</td>
<td>0.0361 (0.0052 to 0.1198)</td>
<td>0.0097</td>
</tr>
<tr>
<td>Acute lymphoblastic leukaemia</td>
<td>26</td>
<td>1.719* (&gt;0 to 17.73†)</td>
<td>0.0053</td>
</tr>
<tr>
<td>Acute myeloid leukaemia</td>
<td>18</td>
<td>0.0208 (-0.0415† to 0.1554)</td>
<td>0.2653</td>
</tr>
<tr>
<td>Myelodysplastic syndromes</td>
<td>9</td>
<td>6.098* (&gt;0 to 145.4†)</td>
<td>0.0032</td>
</tr>
<tr>
<td>Leukaemia excluding myelodysplastic syndromes</td>
<td>65</td>
<td>0.0187 (-0.0119† to 0.0794)</td>
<td>0.1436</td>
</tr>
</tbody>
</table>

*Iteratively reweighted least-squares algorithm failed to converge, so parameter estimates might be unreliable.
† Calculated using Wald-based CI.
## Results for brain dose

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>ERR per mGy (95% CI)</th>
<th>p value (test for dose-response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All brain</td>
<td>135</td>
<td>0.0227 (0.0098 to 0.0494)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glioma</td>
<td>65</td>
<td>0.0186 (0.0034 to 0.0703)</td>
<td>0.0033</td>
</tr>
<tr>
<td>Schwannoma meningioma</td>
<td>20</td>
<td>0.0331 (0.0019 to 0.4388)</td>
<td>0.0195</td>
</tr>
</tbody>
</table>
Brain dose-response

![Graph showing brain dose-response relationship. The x-axis represents brain dose (mGy) ranging from 0 to 400, and the y-axis represents relative risk with 95% CI. The graph shows an increasing trend with data points and error bars indicating variability.]
More on the results

- For leukaemia, dose-response did not vary between age at exposure, time since exposure, sex or any of the other covariates examined.

- For brain tumours, the ERR increased with increasing age.

- Little evidence of non-linearity of the dose-response for either outcome.
Main findings

- Significant associations between the estimated radiation doses to red bone marrow and brain and subsequent incidence of leukaemia and brain tumours respectively
Critical appraisal of our study

- We used empirical data
- Cohort approach avoided recall bias (exposure data from medical records)
- The UK has free-to-access healthcare. Thus we should have a fairly representative sample.
- Nationwide cancer registration
  - Cancer ascertainment estimated at 97%
Patients not linked to registry records had similar characteristics to those included.

Our results are based on exposures in childhood or early adulthood.

- Not clear if we can extrapolate the results to adults.

Used a careful approach to avoid those with existing cancers.
Dosimetry was improved on previous estimates

- Provided organ doses, but unable to obtain individual-level parameter data for such a large and historical cohort

Uncertainties still exist

- Not expected to bias the findings
Comparisons with the Life Span Study

- Similar dose estimates with childhood exposure and similar follow-up time (<15 years)

- Life Span Study for leukaemia:
  - ERR = 0.045/mSv (95%CI 0.016-0.188)

- Our study:
  - ERR = 0.036/mGy (95%CI 0.005-0.120)
Interpretation

• Our results so far suggest that the risk of leukaemia is tripled with 5-10 head CTs in children aged under 15 years (based on 50mGy exposure)
  • And for brain tumours at 60mGy (2-3 head CTs)

• For every 10,000 head CTs in under 10s, expect one excess case of leukaemia and one excess brain tumour in the 1st decade after 1st CT
Interpretation

• The immediate benefits outweigh the (small) risks in most settings when CT is used appropriately.

• Of utmost importance is that, where CT is used, it should only be used where fully justified from a clinical perspective.
International collaboration

- Similar studies underway in:
  - Canada, Australia, Sweden, Israel and France
  - EU-funded collaborative study (EPI-CT) began in 2011
    - UK, France, Spain, Germany, Denmark, Sweden, Netherlands, Belgium, Norway and Luxembourg,
- All studies are using a similar study design and collaborations are underway re dosimetry
Acknowledgments

- Newcastle University, UK
  - Jane Salotti
  - Sir Alan Craft
  - Nicola Howe
  - Richard Hardy
  - Wenhua Metcalf
  - Claire-Louise Chapple
  - Katharine Kirton

- NCI
  - Amy Berrington de González
  - Choonsik Lee
  - Mark Little
  - Jay Lubin
  - Preetha Rajamaran
  - Elaine Ron
  - Cecile Ronckers

- Dalhousie University, Canada
  - Louise Parker

- Great Ormond Street Hospital, London
  - Kieran McHugh

- Kyung-Hee University, Korea
  - Kwang Pyo Kim