Retrospective dosimetry concepts for triage / emergency situations
Status and future needs

The Task Group for the EURADOS WG10 SRA

Paola Fattibene
Istituto Superiore di Sanità, Italy

Clemens Woda
Helmholtz Zentrum Muenchen, Germany

Ulrike Kulka
Bundesamt fuer Strahlenschutz, Germany

Liz Ainsbury, Kai Rothkamm
Public Health England, United Kingdom

Natalia Maznyk
Institute Medical Radiology, Ukraine

Antonella Testa
Agenzia Nazionale per le Nuove Tecnologie, l’Energia e lo Sviluppo Economico Sostenibile, Italy
EURADOS WG10 Retrospective dosimetry: a group of physicists and biologists who have joined with the objective to set up a common ground for retrospective dosimetry (about 50 associate members)

This presentation reports the viewpoint of the SRA task group within EURADOS WG10.
Outline

• Definition of retrospective dosimetry
• Introduction to methods
• Requirements of retrospective dosimetry in emergencies
• Confounding factors with description of problems/solutions
• Short/medium and long term improvements
• Sinergy with other platforms
What is retrospective dosimetry

Retrospective dosimetry consists of methods that measure persistent chemical, biological or physical changes, in biological tissues or inert materials, which can be directly related to the absorbed dose of ionizing radiation.

In other words, retrospective dosimetry measures markers of radiation exposure which persist long enough to be able to assess doses received days, weeks or years before sampling.
Potential markers of biological changes

Potential markers of physical changes


### Currently proposed methods

<table>
<thead>
<tr>
<th>Hematologic techniques</th>
<th>• Lymphocyte counts (clinical dosimetry)</th>
</tr>
</thead>
</table>
| Cytogenetic techniques | • Dicentrics  
                          • Translocations  
                          • Premature chromosome condensation  
                          • Micronuclei |
| Genetic techniques     | • Somatic mutations  
                          • Gene expression |
| Protein biomarkers     | • $\gamma$H2AX  
                          • C-reactive protein |
| Physical techniques    | • EPR in teeth/bone  
                          • EPR in fingernails  
                          • OSL in teeth  
                          • Neutron activation of blood and hair  
                          • EPR in personal belongings  
                          • TL & OSL in electronic components  
                          • TL in dust |
| Computational techniques | • Analytical  
                          • Numerical |

**Biologically-based biodosimetry**

**Physically-based biodosimetry**

**Physically-based retrosp. dosimetry**

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When is RD needed in emergencies?

Main objective: to help to mitigate the health consequences where practicable

To reduce the occurrence of deterministic health effects in workers and the public

Triage: worried well and > 2 Gy

High doses (> 1 Gy)

48 hrs

days

To support management of treatment of radiation injuries

Timely

Sensitive

Specific

High capacity

ICRP 109 (2008)

External exposure!


ICRP 109 (2008)

- 10 Gy likely lethal
- 6-10 Gy severe
- 2-6 Gy moderate
- 0.5-2 Gy mild
- < 0.5 Gy minimal

Figure 5-1 Typical Lethality as a Function of Dose
Does the ideal dosimeter exists?

### Timely response
- $\gamma$H2AX (<24 hrs)
- OSL in some personal items (< 1 day)
- Micronuclei
- Dicentrics assay

### Specificity to IR
- TL/OSL in personal items
- Dicentrics assay
- EPR in calcified tissues
- Micronuclei
- gH2AX

### Stability (> 48 hrs)
- EPR in calcified tissues
- Dicentrics assay
- EPR/TL/OSL in personal items
- Micronuclei
- gH2AX

### Detection limit < 250 mGy
- $\gamma$H2AX
- TL/OSL in some personal items
- Dicentrics assay
- EPR in personal items

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Established methods of retrospective dosimetry

<table>
<thead>
<tr>
<th>Assay</th>
<th>Specificity to radiation</th>
<th>Sensitivity to radiation</th>
<th>Signal stability</th>
<th>Time for 50 samples (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dicentrics</td>
<td>Excellent</td>
<td>0.1 – 5 Gy</td>
<td>Months</td>
<td>4-6</td>
</tr>
<tr>
<td>FISH</td>
<td>Good</td>
<td>0.5 – 5 Gy</td>
<td>Years</td>
<td>4</td>
</tr>
<tr>
<td>Micronuclei</td>
<td>Good</td>
<td>0.5 – 5 Gy</td>
<td>Weeks</td>
<td>6</td>
</tr>
<tr>
<td>γ-H2AX</td>
<td>Good</td>
<td>0.01 - 10 Gy</td>
<td>hours</td>
<td>1</td>
</tr>
<tr>
<td>Proteomics</td>
<td>Good</td>
<td>0.5 – ca 10 Gy</td>
<td>Hours</td>
<td>1</td>
</tr>
<tr>
<td>EPR/OSL</td>
<td>Excellent</td>
<td>0.05 - &gt; 50 Gy</td>
<td>Months – years</td>
<td>1</td>
</tr>
</tbody>
</table>
Confounding factors

**Ideal scenarios:**
- Doses from 0.3 to 5 Gy
- Irradiation time known
- Homogeneous whole body exp.
- Few potentially exposed people
- Low-LET radiation
- Acute

**Real life:**
- Irradiation-sampling time delay not known
- Complex scenarios
  - Non homogeneous/partial exposure
  - Mixed fields
  - Internal/external sources
  - Protracted
  - Radiation/biological/chemical expos.
- High number of potentially exposed people
- Dose range from <0.3 Gy to > 5 Gy

**small scale accidents**
- That involve radiation sources used in industry or medicine: exposure of few people, usually high doses

**large scale accidents**: exposure of large groups of the general populations, usually at low doses

**mass casualties**, terrorist threats, exposure of large groups of the general populations, wide range of dose, unknown radiation
If the time of exposure is not known:

- Dicentrics and micronuclei are sufficiently stable within the time range of interest.
- EPR/OSL/TL signals typically decay within the first days/weeks and then reach a plateau. When the time of irradiation is known, correction for fading curve has shown to work reliably. If not, conservative correction can be used to provide a dose range.
Manage large number of potentially exposed people

If capacity of a single lab is too low then possible solutions are...

- Networking
- Web-based scoring
- Automation
- In vivo EPR
- Protocol adaptation
- Data acquisition
- Data interpretation
Networking

- 48h preparation of cells
- preparation of chromosomes (e.g.)
- small scale accident (<10)
- set up of cultures
- blood sampling
- analysis
- 0h

Manage large number of potentially exposed people
Manage large number of potentially exposed people

Networking

48h

preparation of cells

preparation of chromosomes (e.g.)

large scale accident (>50)

set up of cultures

blood sampling

Option: shipment to network partners

Option: shipment to network partners

0 h
Building networks: the WHO BIODOSENET

Manage large number of potentially exposed people
Building networks in Europe

Close collaboration among biologists and physicists
Manage large number of potentially exposed people

Sampling

Translocations

Dicentrics

Micronuclei

PCC

EPR

EPR

γH2AX

OSL
In vivo measurements

Manage large number of potentially exposed people

Grinberg et al. EPRBIODOSE 2010

De Witt et al. H Phys 2010
Shipping

- due to national regulations
- problems in transportation
- loss in infrastructure

Lessons learned from the Fukushima accident: “because of Tsunamis the transportation system was paralyzed, and the supply of electricity stopped for hours. Laboratories and suppliers of experimental reagents were damaged in Tohoku district” (Suto et al H Phys 2013)

Using the Internet to share images between laboratories has the potential to overcome this limitation (if no interruption of electricity power!) with a browser and no need of a dedicated software.
Measurement: High capacity techniques

Among the proposed methods, two have the potential of a high capacity of measurements:

\( \gamma H2AX \): 100 samples in 1 day (estimate from MULTIBIODOSE)

**Genetic techniques:** with microarrays and QPCR - fully automated, potentially hundreds of samples in a few hours.

Need to be tested in regards to specificity, radiation quality, interindividual variability, time dependency, in vivo-in vitro comparability

For both the information may be lost in a few hours
Measurement: Automation

A way to improve capacity is to automate the acquisition. In principle, any step might be automated, from cell culturing and slide preparations to data treatment/dose estimate.

In cytogenetic techniques: semi-automation: metaphase finder and image analysis instead of microscopy analysis.

<table>
<thead>
<tr>
<th></th>
<th>Total time to analyse samples¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time in days</td>
</tr>
<tr>
<td></td>
<td>1 sample 50 samples 100 samples 1000 samples</td>
</tr>
<tr>
<td></td>
<td>1 lab 1 lab 1 lab 1 lab 1 lab</td>
</tr>
<tr>
<td>Dicentrics manual</td>
<td>2.5 6 9 5 65 16</td>
</tr>
<tr>
<td>Dicentrics automated</td>
<td>2.5 4 5 3 24 7</td>
</tr>
</tbody>
</table>
Intercomparisons

A key issue of networking are the intercomparisons

Dicentrics

Micronuclei

EPR

OSL

Micronuclei: Horst et al. Radiat Res 2013
EPR results: Fattibene et al. Radiat Env Bioph submitted
Networking: laboratory QA & QM

ISO 19238:2004
Radiation Protection — Performance criteria for Service Laboratories performing Biological Dosimetry by Cytogenetics

ISO 21243:2008
Radiation protection — Performance criteria for laboratories performing cytogenetic triage for assessment of mass casualties in radiological or nuclear emergencies — General principles and application to dicentric assay

ISO 13304-1:2013
Radiological protection -- Minimum criteria for electron paramagnetic resonance (EPR) spectroscopy for retrospective dosimetry of ionizing radiation -- Part 1: General principles

Micronuclei: in preparation
when it comes to an emergency situation, it's too late for learning and training!

WG10 “Retrospective dosimetry” Nehuerenberg (Germany) 2012
WG10 “Uncertainties for Retrospective dosimetry” 2014
RENEB training course on quality and statistics 2013
Complex scenarios

Non homogeneous/partial body exposure
Mixed fields
Internal/external sources
Protracted
Radiation/biological/chemical expos.
Partial body exposures

Dosimetry based on personal items may be suitable to map the dose on the body

Electronic components have shown suitable

<table>
<thead>
<tr>
<th>Nominal dose, Gy</th>
<th>Mean measured dose ± dev. st., Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>0.25 ± 0.15</td>
</tr>
<tr>
<td>1.7</td>
<td>1.41 ± 0.46</td>
</tr>
<tr>
<td>3.3</td>
<td>3.38 ± 0.98</td>
</tr>
</tbody>
</table>

Eurados/Multibiodose blind test of OSL in mobile phones

New markers, based on new materials or techniques, should be explored
Partial exposures: intercomparison with dicentrics

After partial exposure, irradiated cells are “diluted” in unirradiated blood. Overdispersion: values $\sigma^2/\mu \geq 1.5$

The estimated irradiated volume in % of “partial body” exposed samples

Also PCC has been shown to be reliable for partial exposure with high doses, but expensive and difficult to implement

By courtesy of H. Romm (BfS)
WHO BioDoseNet survey:
For which radiation qualities have you generated calibration curves?

Maznyk et al, 2010
Internal contamination

Bioassays

If radionuclides distributed uniformly in the body

Bioassay

EURADOS Task group

Complex scenarios

Kai Rothmann (PHE, UK) (on behalf of WG10)

Comparison of Physical and Biological Dosimetry for Internal Emitters

Section: Internal Emitters. Today 14:00-16:00
Concurrently C-B-R risk

- Study how the effects of radiation are changed when other contaminants or stressors (chemical, biological or others) are present

- Build a solid interaction (networking) with the chemical and biological (CB) risk assessment community

- In security there is a need for tools, or at least approaches, which can detect two or more C, B, R, N exposures
Dose range – lower limit

An ideal method should be able to:
- distinguish irradiated from non irradiated

The minimum detectable dose (MDD) depends roughly on the standard deviation of the spontaneous marker. MDD could be lowered by decreasing uncertainties. Depending on the protocol (e.g. the number of cells scored or the instrumentation used)

<table>
<thead>
<tr>
<th>Marker</th>
<th>MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dicentrics</td>
<td>&gt; 0.1-0.8 Gy</td>
</tr>
<tr>
<td>Micronuclei</td>
<td>&gt; 0.5 Gy or higher</td>
</tr>
<tr>
<td>gH2AX</td>
<td>&gt; 0.05 Gy</td>
</tr>
<tr>
<td>EPR in personal items</td>
<td>&gt; 2 Gy</td>
</tr>
<tr>
<td>OSL in personal items</td>
<td>&gt; 0.01-0.1 Gy</td>
</tr>
</tbody>
</table>

Even more important is to assess reliably and homogeneously the MDD EURADOS Task group “Uncertainties for Retrospective dosimetry”
An ideal method should be also able to:

- provide a reliable dose in a wide range

The largest measurable dose also varies between methods, due to saturation effects. This typically leads to a reduction of statistical confidence in doses within the high dose range.

Physically based methods generally work up to higher dose levels than biologically based methods.

This is an **intrinsic limitation** and a multiparametric approach can be the only solution.
Multi-parametric approach

Each tool is inherently limited with respect to some before mentioned requirements.

Despite the ongoing research, some of these and other radiation markers may not be suitable as stand-alone biodosimeters but would work as part of a multi-parametric dosimetric system.

Triage in acute and uniform low-LET exposure from 0,1 to 10 Gy
Is RD a useful tool for physicians?

Eventually, “the goal” is the post exposure management of patient. Dosimetry is only one tool among many to manage all the patient’s needs.

We should learn:
- how to communicate with emergency medical doctors
- what is helpful for physicians
- to convince physicians of the reliability and suitability of our data
On which scale are these improvements feasible?

Typically, the improvement of already existing and validated methods might be feasible in the short/medium term:

- networking
- web based scoring
- guidances for a multiparametric approach
- training
- validating the automated methods

Implementation of new methods will require long times:

*in vivo* EPR and OSL

- genetic assays
- new physical markers

Some improvements are difficult because of intrinsic limitations of the method, some others because of lack of resources (time, budget, human)
Synergy with other platforms

NERIS
- use of RD for improvement of existing Decision Support Systems in “difficult environments” such as explosions in buildings, subways, hidden sources ("New challenges for better dose assessments and decision support")
- use of RD to improve inverse estimation of unknown source term in urban areas and open spaces ("New challenges in atmospheric and aquatic model")

MELODI:
- need to further explore the potential for retrospective dosimetry in epidemiology, especially in the dose range < 100 mGy
- improvement of (existing or new) methods of biomarkers of exposure that are radiation specific, sensitive and high throughput

ALLIANCE
- RD for wildlife?
thank you for your attention and for any feedback!

clemens.woda@helmholtz-muenchen.de