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Review

Early-response multiple-parameter biodosimetry and dosimetry: risk predictions

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Abstract

The accepted generic multiple-parameter and early-response biodosimetry and dosimetry assessment approach for suspected high-dose radiation (i.e. life-threatening) exposure includes measuring radioactivity associated with the exposed individual (if appropriate); observing and recording prodromal signs/symptoms; obtaining serial complete blood counts with white-blood-cell differential; sampling blood for the chromosome-aberration cytogenetic bioassay using the 'gold standard' dicentric assay (premature chromosome condensation assay for exposures >5 Gy photon acute doses equivalent), measurement of proteomic biomarkers and gene expression assays for dose assessment; bioassay sampling, if appropriate, to determine radioactive internal contamination; physical dose reconstruction, and using other available opportunistic dosimetry approaches. Biodosimetry and dosimetry resources are identified and should be setup in advance along with agreements to access additional national, regional, and international resources. This multifaceted capability needs to be integrated into a biodosimetry/dosimetry 'concept of operations' for use in a radiological emergency. The combined use of traditional biological-, clinical-, and physical-dosimetry should be use in an integrated approach to provide: (a) early-phase diagnostics to guide the development

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of initial medical-management strategy, and (b) intermediate and definitive assessment of radiation dose and injury. Use of early-phase (a) clinical signs and symptoms, (b) blood chemistry biomarkers, and (c) triage cytogenetics shows diagnostic utility to predict acute radiation injury severity.

Supplementary material for this article is available online

Keywords: biodosimetry, physical dosimetry, radioactivity contamination, clinical signs and symptoms, blood chemistry, cytogenetic dose assessment, acute radiation syndrome (ARS) severity

(Some figures may appear in colour only in the online journal)

1. General guidance

In the case of a suspected radiation exposure to a high-dose (i.e. life-threatening dose) the early-phase (i.e. <2 weeks after exposure) general accepted guidance is to:

- Perform measurements, if appropriate, to determine radionuclide contamination and record physical dosimetry measurements, if available.
- Observe and record prodromal signs (i.e. body location of potential skin erythema) and symptoms.
- Obtain complete blood count (CBC) with white blood cell differential immediately, then every 6 h for 2 to 3 d, and then twice a day for 4 d.
- Sample blood for the chromosome-aberration cytogenetic bioassay using the 'gold standard' dicentric assay (or other suitable cytogenetic chromosome aberration assays).
- Bioassay sampling from various sources (i.e. urine, fecal, blood, nasal, oral), if appropriate, to determine radionuclide contamination.
- Biosampling blood for measurement of clinical blood chemistries, proteomic, and gene-expression radiation-responsive biomarkers.
- Biosampling nail clippings for measurement of free radicals by electron paramagnetic resonance (EPR).
- Consider other opportunistic dosimetry approaches as available [1–6].

2. Biodosimetry/dosimetry preplanning

A coordinated biodosimetry program should be established in advance of responding to a suspected radiation exposure. The program should consists of subject matter experts, who are equipped to initiate and coordinate a suitable biodosimetry/physical dose and injury assessment. Appropriate resources should be identified and available for rapid responses.

2.1. Radiation exposure assessment methods

Effective medical management of a suspected high-dose (i.e. life threatening) exposure necessitates a multiple parameter-based approach involving the combined use of (a) clinical, (b) biological, and (c) physical dosimetry. Table 1 illustrates early-phase radiation assessment methods. The accepted generic multiple parameter and early-response approach includes measuring radioactivity and monitoring the exposed individual; observing and recording

prodromal signs/symptoms and erythema; obtaining CBCs with white blood cell differential; sampling blood for the chromosome-aberration cytogenetic bioassay using the 'gold standard' dicentric assay (or other suitable cytogenetic chromosome aberration assay); blood proteomics, and gene expression for dose assessment; bioassay sampling, if appropriate, to determine radioactive contamination; physical dose reconstruction, and using other available dosimetry approaches (e.g. dose assessment by measurement of free radicals in solid matrix materials using EPR).

2.2. Radiation response teams and networks

National, regional, and international assets for response to radiological incidents are typically organized into expert teams with discrete functions as illustrated in table 2 [7]. In some nations these teams are components of a nuclear, biological, and chemical response teams [8].

The United Nations agencies have excellent resources to assist in biodosimetry response. The International Atomic Energy Agency (IAEA) established a 'Response and Assistance Network (RANET) consisting of teams suitably qualified to respond rapidly to a nuclear or radiological emergency, providing assistance including: (a) advisory, (b) assessment and evaluation, (c) monitoring, and (d) recovery [9]. The World Health Organization (WHO) established a Radiation Emergency Medical Preparedness and Assistance Network (REMPAN), which consists of biodosimetry laboratories with expertise in: cytogenetic, EPR, bioassays, and molecular biology methodology (table 3). In addition, regional and national networks are also established worldwide (table 3) [10]. Several of these networks support multiple parameter dosimetry assessment (i.e. cytogenetics, EPR-dosimetry, and physical dosimetry) capability.

2.3. Additional biodosimetry resources

Additional biodosimetry resources available include tools to assist in medical recording and software triage algorithms to assist responders to effectively diagnosis and manage a radiation incident.

2.3.1. Medical recording forms and worksheets. Medical recording for radiation incidents should be consistent with an 'all hazards' approach used by first responders. AFRRI's adult/paediatric field medical record (AFRRI form 330) provides a medical record template in a convenient one-page form for gathering emergency medical information in the field [11]. It is applicable to both adult and paediatric cases. A version of the form is provided as appendix A (supplementary materials (available online at stacks.iop.org/JRP/41/R152/mmedia)).

The AFRRI biodosimetry worksheet (AFRRI form 331) represents a comprehensive data entry worksheet, recently expanded from four to six pages to accommodate a modified version of METRPOL acute radiation syndrome (ARS) severity scoring system [12]. It provides a place for recording the facts about a case of radiation exposure, including the source and type of radiation, the extent of exposure, relevant biodosimetry diagnostic information, and the nature of the resulting injuries. A version of the form applicable to both adult and paediatric cases and is provided as appendix B (supplementary materials).

Hick and colleagues introduced an exposure and symptom triage worksheet tool to assist first-responders to perform an initial triage of persons with radiation exposure (no/limited injury). The worksheet is used to prioritize suspected exposed individuals for evacuation/myeloid cytokine administration for use in a severe resource-poor environment after a nuclear denotation [13].

Table 1. Early-phase radiation assessment methods[a].

Assessment method	Applicable for internal contamination assessment	Applicable for scoring ARS[b] severity	Dose (Gy) or ARS RC level to select for priority cytogenetic triage analysis	
			Triage dose, Gy	RC levels
Direct recording of location history	Yes	—	3–7	—
Direct observation of clinical signs and symptoms	Yes	Yes	3–7	1–4
Personal monitoring (direct, non-invasive)				
In vivo EPR	—	—	3–7	—
Portable hand-held meters (triage/screening)	Yes	—	—	—
Portal monitors (triage/screening)	Yes	—	—	—
Whole-body counting	Yes	—	—	—
Personal monitoring (indirect, invasive)				
Blood chemistry (i.e. amylase activity, Flt-3 ligand, C-reactive protein, citrulline)	No	—	3–7	1–4 (CRP)
CBC and differential count	No	Yes	3–7	1–4
in vitro EPR (i.e. nails)	No	No	3–7	—
Nasal swab	Yes	No	—	—
Stool sample	Yes	No	—	—
Urine sample (Spot; 24 h)	Yes	No	—	—

(Continued.)

Table 1. (Continued.)

Assessment method	Applicable for internal contamination assessment	Applicable for scoring ARS[b] severity	Dose (Gy) or ARS RC level to select for priority cytogenetic triage analysis	
Cytogenetics (i.e. DCA[b] triage: 20–50 metaphase triage; DCA reference: 500–1000 metaphase analysis)	—	Yes (indirect)	—	—
Area monitoring Dosimetry results (e.g. TLDs, aerial measurements) combined with personal location information	—	—	3–7	—

[a] The table was modified a version reported [1, 2]. Note that the personal and area monitoring methods are listed in alphabetical order and, therefore, their location in the table does not infer priority or preference.
[b] ARS: acute radiation syndrome; DCA: dicentric chromosome aberration—metaphase-spread assay.

Table 2. Select list of radiological response teams and reach-back dosimetry components of networks supporting biodosimetry assessment.

Response teams:	Components of dosimetry networks:
Initial assessment	Radiobioassay assessment
Radiation source search	Cytogenetic biodosimetry
Biodosimetry sampling for haematology, proteomic, gene expression, and cytogenetic assessment	Proteomic biodosimetry
	Electron paramagnetic resonance dosimetry
Medical recording and registry	Gene expression biodosimetry
Radiation survey and sampling	

Table 3. Select list of global, regional and national biological dosimetry networks.

Global dosimetry/biodosimetry networks:
WHO REMPAN www.who.int/groups/rempan/about WHO BioDoseNet www.who.int/activities/strengthening-global-preparedness-to-radiation-emergencies/biodosenet
IAEA RANET www.iaea.org/services/networks/ranet
Global Health Security Initiative (GHSI) Rad-Nuc Threats Working Group [3]
Regional dosimetry/biodosimetry networks:
Running the European Network of Biological and Retrospective Physical Dosimetry (RENEB) www.reneb.net/
North America Biodosimetry Network
Latin American Biodosimetry Network
Asian Network of Biological Dosimetry (ARADOS) WG-03
European Radiation Dosimetry Group (EURADOS) WG-10
National cytogenetic biodosimetry networks:
Chromosome Network Council (Japan)
Biodose Network in China
Korean Cytogenetic Network
Canadian Biodosimetry Network

Comprehensive medical recording guidance and recording forms supporting the management of radiation casualties are also available from the IAEA (see worksheets of IAEA's Generic Procedures for Medical Response During Nuclear and Radiological Emergency, EPR-medical) [14].

2.3.2. Software applications and webtools. The biodosimetry assessment tool (BAT) program (version 1.0) for Windows XP was released on 21 September 2007 [15–19]. BAT was developed by AFRRI scientists as a tool to record and deliver diagnostic information (clinical signs and symptoms, physical dosimetry, etc) to federal health care providers responsible for the management of radiation casualties. It is designed primarily for early use after a radiation incident and permits collection, integration and archiving of data obtained from patients accidentally exposed to ionising radiation. Collection of relevant data is facilitated by use of structured templates and user-friendly software. This enables the generation of diagnostic indices for the development of a multiple parameter dose assessment. The BAT program is NOT a substitute for treatment decisions by physicians and other trained health care professionals. Additional clinical parameters (i.e. infection, treatments) useful for casualty management also are assessed. The resulting display of patient diagnostic information provides treating health care providers with concise and relevant information on which to base clinical decisions. This

information can be archived for further use in radiation protection management. An integrated, interactive human body map permits recording radioactivity detected by an appropriate radiation detection device. BAT is distributed on-line upon review of a download request application accessible at website www.usuhs.edu/afrri/biodosimetrytools.

The first-responders radiological assessment triage (FRAT) program enables first responders to triage suspected radiation casualties based on the initial, or prodromal, features listed in the Emergency Radiation Medicine Response—AFRRI Pocket Guide [20, 21]. FRAT was developed initially for the Palm operating system. A windows OS-based application (WinFRAT) for use on a desktop/laptop is also available on-line upon review of a download request application accessible at website www.usuhs.edu/afrri/biodosimetrytools. A version for use on mobile platforms (mFRAT) for use on smart phones (i.e. iphone, Android) is available [22]. With minimum text entry, FRAT will provide (a) signs and symptoms, (b) blood lymphocyte counts, and (c) dosimetry data. The program will assess the multiple-parameter triage dose or the exposure without an assigned dose, or it will indicate there is no evidence of overexposure. Additional FRAT output features include triage dose-specific messages addressing (a) reliability and diagnostic information, (b) hospitalisation estimations, and (c) mortality projections.

The Bundeswehr Institute of Raiobiology has developed a smartphone application, H-module, to perform clinical triage of radiation casualties [23–25]. The application is based on using peripheral blood cell counts measured within the 1st 3 d after radiation exposure to predict haematological acute radiation syndrome (H-ARS) severity. ARS severity degrees were defined based on the medical treatment protocols for radiation accident victims (METREPOL) [26]. Clinical case history data from the system for evaluation and archiving of radiation accidents based on case histories (SEARCH) database were used for developing the H-module [24].

Hu *et al* at NASA have developed software web tools (HemoDose) to estimate an exposed dose based on peripheral blood cell counts [27]. The HemoDose web tools are based on physiological understanding of mammalian hematopoietic systems, and bio-mathematical modelling. Using single or serial granulocyte, lymphocyte, leukocyte, or platelet counts after exposure, these tools can estimate absorbed doses of adult victims very rapidly and accurately. The HemoDose web tools establish robust correlations between the absorbed doses and victim's various types of blood cell counts not only in the early time window (1 or 2 d), but also in very late phase (up to 4 weeks) after exposure. Using a modified model prediction of clinical grading of H-ARS severity was accomplished [28]. HemoDose is distributed on-line at website https://federallabs.org/technology/hemodose-software-version-20.

Bader *et al* have established a comprehensive suite of web and mobile software application tools as part of the radiation emergency medical management (REMM); see website www.remm.nlm.gov/ [29, 30]. REMM provides numerous on-line tools related to biodosimetry (i.e. dose estimator for exposure, organ-based managing ARS). In addition, a REMM app that contains selected key features from the on-line full version of REMM, is also available for iphone/iPad and Android smartphones.

3. Concepts of operation

The primary purpose for early-response biodosimetry following suspected radiation overexposures is to rapidly provide first-responders and medical providers scientifically sound diagnostic radiation injury and dose assessment to support medical management treatment decisions. This will likely necessitate an initial reliance on diagnostic information based on

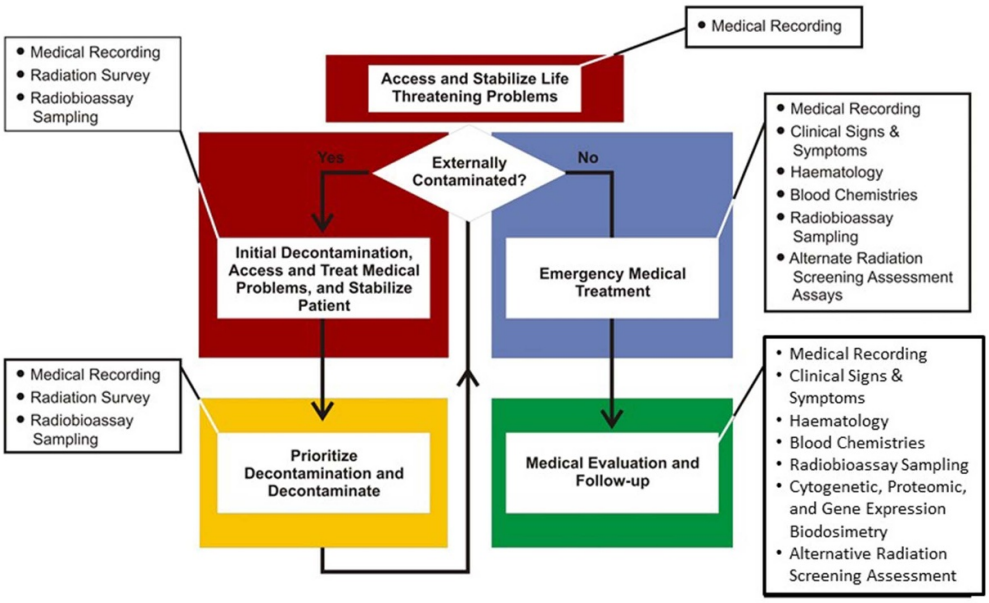

Figure 1. Biodosimetry concept of operations during management of radiation incident with trauma or illness. Biodosimetry functions are illustrated for the individual action steps of the 'Radiation Patient Treatment' algorithm.

early bioindicators of radiation dose, which will then be replaced by bioindicators of the severity of ARS response as the clinical case evolves. The combined use of clinical signs and symptoms, biodosimetry, and physical dosimetry is encouraged. Based on the US Strategic National Stockpile Working Group the initial radiation exposure triage can be broken down into three photon acute dose rate dose windows: (a) <2 Gy—non-lethal, non-exposed, and concerned public, (b) 2–7 Gy—candidates for cytokine and antibiotic therapy, (c) >7 Gy—candidates for potential stem-cell transplant therapy [31].

AFRRI has modified a 'Radiation Patient Treatment' algorithm, initially developed by the US Radiation Emergency Assistance Centre/Training Site and incorporated early-response and multiple parameter biodosimetry protocols when responding to a radiation incident (figure 1). Use of a diagnostic pyramid triage concept involving initial use of early-phase rapid triage radiation assays (i.e. clinical signs and symptoms, dose by location), following by secondary bioassays involving potential use of hand-held devices (i.e. CBC device, C-reactive protein or CRP assay), and then tertiary radiation bioassays are recommended.

4. Early-response multiple parameter biodosimetry

4.1. Radioactivity contamination

The body location of radioactive contamination, internal contamination information, the dose estimation based on location, and the dose based on personnel dosimeters, if available, should be recorded by first responders and medical personnel. The biodosimetry worksheet (supplementary materials—appendix B) and BAT application provides templates for recording these

and other relevant parameters (location and activity of radiation source, patient location relative to radiation source, etc) that can contribute to medical management and dose reconstruction [19]. Metallic (or other) fragment samples should be collected for isotope classification, as appropriate, for identifying the radiation exposure scenario. In addition, biological samples (i.e. urinalysis, faecal, wound, swipes from body orifices) should also be collected for determining the committed dose. AFRRI's FRAT application uses information about radioactive contamination not eliminated after removal of clothes and washing as evidence for radiation exposure in a triage dose assessment algorithm [20–22].

4.2. Clinical signs and symptoms biodosimetry

The time onset and severity of early prodromal phase signs and symptoms can provide some valuable information regarding the absorbed 'dose range'. The early or prodromal phase response from exposure to ionising radiation is characterized by a dose-dependent expression of a constellation of signs and symptoms including nausea, vomiting, anorexia, and central nervous system function impairment [32]. The FRAT application integrates these prodromal signs to provide a triage dose assessment. Progressive increases in radiation dose result in an increased percentage of both the incidence and the constellation of prodromal signs and symptoms. The appearance of acute symptoms, such as vomiting, is directly dependent on the radiation dose to an overexposed individual [32]. Following photon and criticality accident exposures, the BAT program can be used to record prodromal symptoms and access dose prediction models for the prodromal symptom, time onset of vomiting [32–35]. An acute photon exposure dose of 2 Gy would cause ∼50% of individuals to exhibit emesis approximately 4.6 h post-irradiation. However, since potential confounders (flu epidemic, etc) can also induce similar symptoms, caution is warranted when using selective prodromal symptoms alone to assess dose for efficient treatment of the accident victim. For example, the incidence of psychogenic vomiting would likely be elevated during stressful events such as a radiological mass-casualty incident.

The location and time-course of radiation-induced cutaneous injury should be recorded. Reddening of the skin, or initial erythema, is generally seen within a few hours to a few days following exposure to a high radiation dose (>2 Gy) and lasts only for a day or two. This information provides diagnostic information concerning partial- or whole-body exposures and can later help define the boundary of the radiation exposure area when skin graphs are necessary. The biodosimetry worksheet (supplementary materials—appendix B) and BAT program provide data templates for this purpose. The skin's response to radiation is biphasic, and this type of skin reaction is largely due to capillary dilation caused by the release of histamine-like substances. Erythema increases during the 1st week following exposure and then generally subsides during the 2nd week. It may return 2 or 3 weeks after the initial insult and last up to 30 d, and additional changes, such as desquamation, bullae formation, or even skin sloughing may follow, all of which make even a crude estimation of radiation dose almost impossible.

4.3. Haematology biodosimetry

Haematological responses are an early response biomarker for radiation dose assessment and also contribute in the assessment of the severity of haematology ARS. Fliedner advocates the use of blood cell changes after whole-body radiation exposures are reliable bioindicators of injury and a critical aid to plan therapeutic treatments [36]. Figure 2(A) illustrated the radiation-induced decline in lymphocytes following exposure to acute photon doses. An approximate 50% decline occurs in peripheral blood lymphocyte counts over 12 h that fall

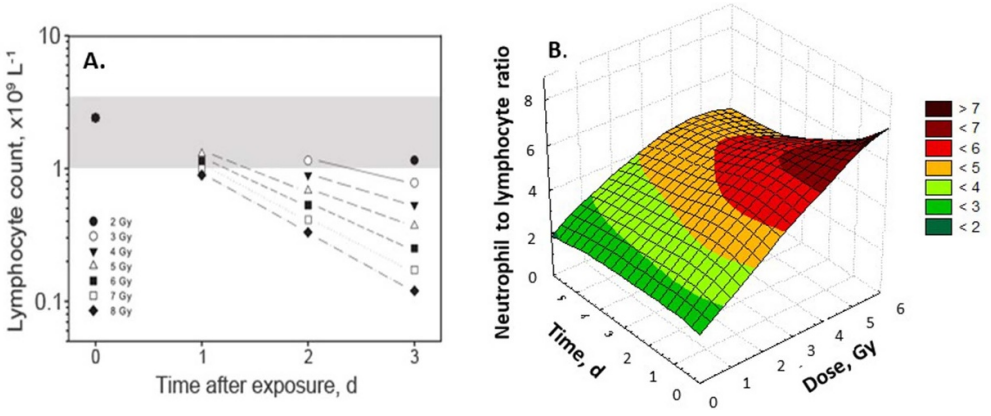

Figure 2. Haematology biomarkers for radiation exposure. (A) Lymphocyte counts after exposure to photon acute equivalent radiation doses. The shaded are reflect the normal baseline lymphocyte counts. Data taken from the dose prediction algorithm, which is part of the AFRRI's BAT software application. (B) Neutrophil to lymphocyte ratio after exposure to photon equivalent radiation doses. Data taken from the AFRRI's haematology radiation database as previously described [17].

below normal vales (1.4×10^9 L^{-1}) is indicative of a potential severe radiation overexposure [31]. Goans *et al* introduced lymphocyte depletion kinetic models for dose estimates based on human radiation accident registry data for whole-body acute gamma exposures [33] and for criticality accidents [34]. Immediately following exposure, a CBC with white cell differential should be obtained and then taken three times a day for the next 2 to 3 d and twice a day for the following 3–6 d. The BAT program permits the recording of peripheral blood lymphocyte counts and then converts them into dose predictions using lymphocyte depletion kinetic models based on previous dose responses in radiation accidents [32, 33, 35]. Lymphocyte cell counts and lymphocyte depletion kinetics provide dose assessment predictions that fall in the equivalent photon dose range of 1–10 Gy.

Neutrophil lymphocyte ratio (NLR) can also be used to assess radiation exposure. Figure 2(B) illustrates the dose- and time-dependence for changes in NLR. Goans and Iddins have recently reported the diagnostic utility of neutrophil to lymphocyte ratio as a triage tool in criticality accidents [37].

4.4. Blood chemistry biodosimetry

Blood biochemical markers of radiation exposure have also been advocated for use in early-phase triage of radiation casualties [38–41]. Table 4 illustrates a panel of radiation-induced proteomic biomarkers. The combined use of multiple blood chemistry biomarkers can enhance the reliability of the radiation exposure diagnostics. Currently all of biomarkers in this panel can currently be measured using commercially available ELISA kits. See article by Abend *et al* in this issue for additional information on proteomic biomarkers [42].

4.4.1. Amylase protein and activity. Hyperamylasemia, an increase in serum amylase activity, from the irradiation of salivary tissue has been proposed as a biochemical measure of early radiation effect in a normal tissue [44, 46, 62]. Cells in the salivary gland a few hours after radiation injury show acute inflammation and degenerative changes resulting in increases in serum

Table 4. Radiation-responsive proteomic biomarkers: tissue sources, time- and dose-windows for meaningful radiation diagnosis.

Target	Target class	Tissue or cell location	Biomarker functional test	Radiation pathology	Time window	Photon acute dose range (Gy) (Radiation therapy)	Photon acute dose range (Gy) (Radiation accidents)	References
α salivary amylase	Tissue enzyme	Parotid gland	↑ Serum or urinary amylase or amylase activity	Mucositis	12–36 h (peak increase at 24 h)	0.8–10	3.5, 8, 18	[38, 43–47]
C-reactive protein, Serum amyloid A	Acute phase reaction	Liver	↑ Serum or plasma CRP or SSA	ARS syndrome	6 h to 4 d	1–20	1–10	[41, 47–54]
Flt-3 ligand	Immunomodulatory effects	Bone marrow	↑Serum or plasma Flt-3 ligand	Haematology—ARS sub-syndrome	24 h to 10 d	—	0.25–4.5	[55–58]
Citrulline	Small bowel epitherlial damage	Small bowel	↓Serum or plasma citrulline	Gastrointestinal ARS sub-syndrome	>24 h (peak decline at 4 d)	1–20 (2 Gy daily)	∼4.5	[57, 59–61]

amylase activity. Confirmation that salivary glands are the source for radiation-induced amylase was determined using histochemical, isozyme analysis and partial-body exposure studies. Radiation induces peak levels of serum amylase activity between 18 and 30 h after exposure after head and neck irradiation of human [63], returning to normal levels within a few days [43]. In the early phase (1 d) after irradiation, sigmoidal dose-dependency for hyperamylasemia is shown based on radio-iodine therapy [64, 65], radiotherapy [38, 44, 45, 66] and from limited data from three individuals exposed in a criticality accident [67].

4.4.2. Acute phase reaction proteins. Mal'tsev *et al* showed that early-phase (1–6 d) CRP levels measured in Chernobyl victims were correlated with the bone-marrow ARS subsyndrome severity levels [48, 49]. CRP is one member of the acute-phase reactants and increases dramatically (>100-folds) during the inflammation process and is believed to play a role in innate immunity, as an early defence against infections. Normal concentration in healthy human serum is usually lower than 10 mg l^{-1}, slightly increasing with ageing. Elevations in acute phase reactants are not specific to exposure to ionising radiation. Moderate increases in CRP are associated with increased risk of diabetes, hypertension, and cardiovascular disease. Higher levels are found in late-stage pregnant women, mild inflammation and viral infections (10–40 mg L^{-1}), active inflammation, bacterial infection (40–200 mg l^{-1}), severe bacterial infections and burns (>200 mg l^{-1}) [68]. Despite these confounding factors, AFRRI scientists have advocated to use elevated CRP levels as an early-phase 'triage tool', combined with other radiation exposure bioindicators, to identify individuals suspected of severe life-threatening radiation exposure [47, 52].

4.4.3. Flt-3 ligand. Fms-related tyrosine kinase 3 ligand (Flt-3 ligand) is a hematopoietic four helical bundle cytokine, which stimulates the proliferation and differentiation of various blood cell progenitors. Bertho *et al* performed the seminal studies that support the use of this biomarker to assess radiation-induced aplasia (bone marrow) injury using animal radiation models [55]. Hutchet *et al* using patient samples from a fractionated radiotherapy study correlated plasma Flt-3 ligand levels with radiation-induced bone marrow damage [69]. In addition, the number of white blood cells and platelets inversely correlated with plasma Flt-3 ligand levels. In a radiation accident, the measured Flt-3 ligand levels were indicative of the severity of bone marrow aplasia [56, 58].

4.4.4. Citrulline. Plasma citrulline, an amino acid, is the current and most promising candidate for assessment of radiation-induced gastrointestinal (GI) injury [61]. Lutgens *et al* showed in mice both time- and radiation-dose dependent relationships, with the pronounced dose-dependency seen at 84 h post irradiation [59]. The citrullinemia significantly correlated with both jejunal crypt regeneration and measured circumference of the epithelial surface lining. Crenn *et al* reported significant decreases in plasma citrulline levels in a radiotherapy study with 57 patients undergoing bowel resection [70]. Citrullinemia levels were correlated with bowel length. In 2004 Lutgens *et al* measured a dose dependent decrease in plasma citrulline in patients undergoing abdominal fractionated radiotherapy [60].

4.5. Cytogenetic biodosimetry

The IAEA has established a manual for dose assessment by cytogenetics based on the use of several cytogenetic assays for dose assessment [71]. Table 5 illustrates a select list of cytogenetic assays used for dose assessment. These cytogenetic assays for dose assessment have

Table 5. Comparison of cytogenetic aberration assays used for dose assessments.

Assays	Endpoints	Radiation scenarios			Acute photon dose range (Gy)	Dose applications		ISO standard
		Acute	Protracted	Prior[b]		Partial-body	Triage	
DCA	Dicentrics[c] (and rings)	Yes	Yes	NA[d]	0.1–5	Yes	Yes	Yes
PCC	Excess fragments, Rings, dicentrics[c], and length ratio	Yes	Yes	NA	0.2–30	Yes	Yes	NA
CBMN	Micronuclei in binucleated cells, nucleoplasmic bridges	Yes	Yes	NA	0.3–5	No	Yes	Yes
γ-HA2X	Foci	Yes	Unknown	NA	0.5–8.5	Yes	Yes	No
FISH	Dicentrics[c] (and rings), translocations[d]	Yes	Yes	Yes	0.25–5	No	NA	Pending

[a] Table modified from IAEA cytogenetic manual [71].
[b] Prior: an assessment of cytogenetic dose when blood sampling is performed greater than 3 months after radiation exposure.
[c] Specific chromosome aberrations typically detected by use of centromeric and/or whole-chromosome specific DNA hybridisation probes.
[d] NA: not applicable/not available.

various features (i.e. dose range, persistency, applications for partial-body exposure assessment and/or triage), which need to be considered when a qualified laboratory considers when applying its use in a radiation incident.

The metaphase spread—dicentric (and ring) chromosome aberration (DCA) assay is commonly applied in the early-phase after radiation exposure. Variations of the premature chromosome condensation (PCC) assay) are useful for dose assessment at high doses and after partial-body exposures [72]. The cytokinesis blocked micronuclei (CBMN) assay has been advocated for use in radiological mass-casualty events. Redon *et al* using blood samples from an *in vivo* nonhuman primate radiation-dose response study showed the induction of γ-H2AX based signal by cytological scoring of lymphocytes [73]. These findings demonstrated that that the cytological-based γ-H2AX would be useful for days (i.e. 1 Gy: 1 d, 3.5 and 6.5 Gy: 4 d, 8.5 Gy: 14 d) post exposure. Similar findings were performed using a swine model following exposure using both an *in vivo* and *ex vivo* irradiations [74]. In addition, an analysis method for partial-body radiation exposure assessment using the γ-H2AX assay named as $Q_{(\gamma\text{-H2AX})}$ was introduced [75]. The metaphase-spread fluorescence *in situ* hybridisation (FISH) translocation assay is typically used in retrospective biodosimetry studies.

Lloyd *et al* introduced the concept to 'triage' cytogenetics for use to provide early-phase diagnostic information to guide medical providers in the development of treatment decisions [76]. In triage cytogenetic using the DCA assay fewer metaphase spreads (i.e. 50) are initially scored and used to provide a 'triage' dose assessment. Use of cytogenetic triage has been codified in inter-comparison exercises and standards.

Reference laboratories and standards are established for performance of dose assessment by cytogenetics [77, 78]. Experts from these laboratories apply the appropriate cytogenetic—chromosome aberration assay depending on the specific radiation scenarios encountered and for which they are qualified to perform. Cytogenetic biodosimetry networks, which are composed of expert laboratories from various nations, provide assistance to nations either without a reference cytogenetic biodosimetry laboratory or when the needs due to surge exceed their capabilities [10, 78].

4.6. Provisional, emerging, and candidate triage, clinical, and definitive dose-assessment methods

Several provisional and emerging approaches have been considered as methods to provide triage, clinical, and/or definitive dose assessment. For a review of these and other established dose assessment methods see reports by Alexander *et al* and Joint Interagency Working Group [1, 79]. Table 6 illustrates a select list of these methods. Radiation-induced exposure to cells and tissues results in changes detected by cytogenetic (i.e. Pseudo Pelger–Huet (PHA) anomaly, rapid interphase chromosome aberration (RICA)), molecular (i.e. blood proteins and gene expression changes) (see article by Abend *et al* in this issue for additional information) [38], induction of free radicals in solid matrix materials (i.e. nails, teeth) that are detected by EPR methods, and skin injury detected by ultrasound [117–123]. There are on-going efforts to optimize and validate these methods for applied biodosimetry applications. In the special case of criticality accidents, neutron activation is used to detection of neutron dose, typically at reactor facilities [80].

5. Prediction of radiation risk using early-phase biodosimetry

Radiation dose to unspecified locations on the body, when in fact it may not be homogeneous, may not be useful for predicting risk. Use of a multi-parameter biodosimetry approach for

Table 6. Select list of provisional, emerging, and candidate radiation injury and dose assessment methods.

Methods	Status	References
Cytogenetics		
PHA anomaly	Novel persistent cytogenetic assay being evaluated as a potential biodosimetric tool	[81–83]
RICA	Novel cytogenetic assay to identify radiation chromosomal damage in interphase cells undergoing further optimisation and validation	[84–86, 87, 88]
Blood proteomic		
Radiation proteomic panels	Proteomic panels proposed for use in radiation dose and injury assessment	[52, 89–92]
Gene expression		
mRNA miRNA	Multiple radiation responsive gene targets identified and used in the development of consensus dose-response and prediction of radiation injury	[93–107]
EPR		
Nails (ex vivo)	EPR X-band shows a lower limit of detection of 0.5–1 Gy	[108–111]
Teeth (*in vivo*)	EPR L-band is potentially able to measure doses as low as 2 to 3 Gy but needs additional development	[112–116]
Ultrasound and thermography		
Ultrasound, thermography	On-going studies evaluating use of ultrasound combined with thermography to characterize thickness of radiation-induced thermal burn	[117–123]
Neutron activation		
Neutron activation	Assessment of neutron dose based on neutron-induced activation on-going at nuclear centres with risk of criticality accidents	[80, 124–127]

radiation dose and injury assessment is recommend for incidents involving life-threatening exposures [128]. The combined use of traditional biological-, clinical-, and physical-dosimetry (with location body-specific doses) should be use in an integrated approach to provide: (a) early-phase diagnostics to guide the development of initial medical management strategy, and (b) intermediate and definitive assessment of radiation dose and injury.

Most radiation incidents involve partial-body exposure [129]. In cases of high-dose life-threatening exposures the use of ‘radiaton dose’ for diagnostic assessment has limited usefulness [130]. Additional confounders (i.e. fractionated dose, low-dose rate, radiation quality)

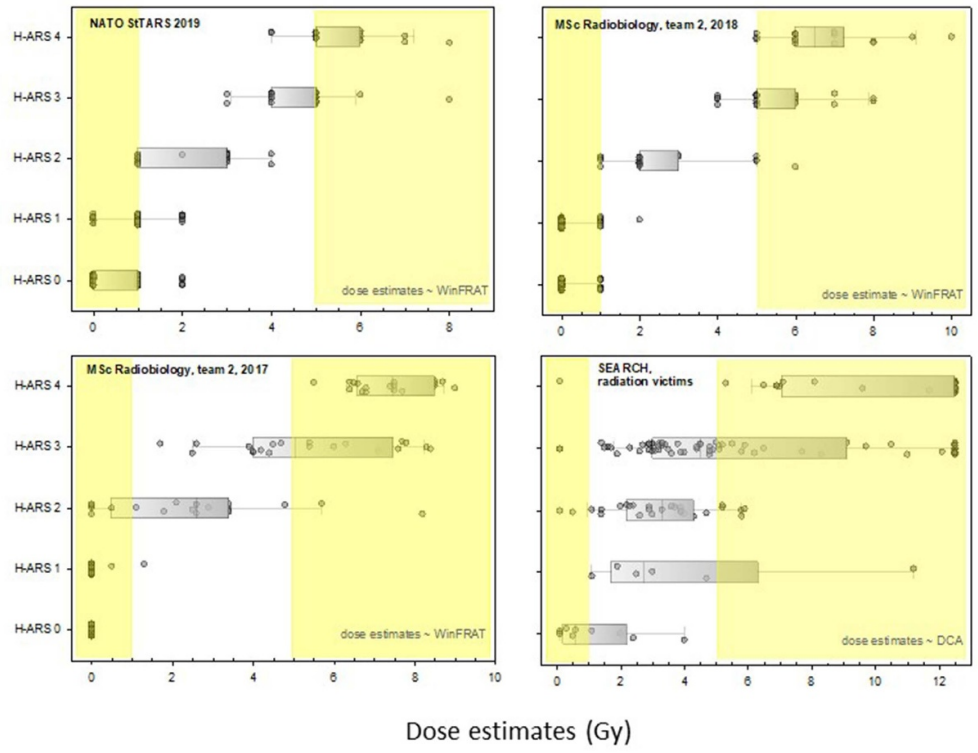

Figure 3. Clinical dose estimates generated from NATO StTARS workshop 2019 (top left), MSc Radiobiology 2018 team 2 (top right panel) and MSc radiobiology 2017 team 2 (bottom left panel) by using the provided software tools (WinFRAT) were correlated with the known H-ARS severity degrees 0–4. The last lower graph reflects the same correlation, but using biological dose estimates generated by the DCA assay documented in the SEARCH database and originating from real case histories [25]. Symbols (grey circle) represent single measurements and box plots (median, 10%; 25%, 75%, 90% percentile) reflect the corresponding estimated distribution of dose estimates per known HARS severity degree. Reproduced with permission from [21].

further substantiate the complications for use of the radiation dose approach. Fliedner METREPOL approach involves use of 'response categories (RC)' for graded levels of ARS severities represent an alternative approach to rank radiation injury [26].

In 2015 the NATO radiobiology research task group (HFM-222 RTG) conducted an exercise for prediction of METREPOL H-ARS severity degrees using human radiation accident and METREPOL database ($n = 190$ cases) and provided early-phase (i.e. 1–5 d after exposure) clinical signs and symptoms including CBC data to eight teams. Overall the teams using a variety of tools (i.e. BAT, winFRAT, H-module) were able to rapidly and accurately predict life-threatening ARS severity [131]. This suite of biodosimetry and ARS severity predicting software tools were further evaluated over a 5 years experience in a radiobiology masters course and one NATO workshop (figure 3) [25, 132]. These results confirm the consensus approach for use of clinical signs and symptoms to triage suspected radiation casualties.

Use of cytogenetic chromosomal aberrations yields also correlate well with ARS severity. Khvostunov *et al* reported that dicentric yields measured in individuals from radiation accidents correlated quite well with initial medical assessments of ARS severity [133]. However, ARS severity degrees were synonymously used to dose bands, e.g. a 1 to 2 Gy dose band was defined as ARS I and a 2–4 Gy dose band was defined as ARS II, thus, representing not a clinical, but an exposure related categorisation with associated limitations (see above). Port *et al* confirmed the correlation between dose estimates using the DCA assay to predict H-ARS severity based on using the METREPOL SEARCH database (figure 3) [23–25, 132]. Exposures below 1 Gy and doses >5 Gy roughly corresponded with grade H0 (not developing a H-ARS) and a severe grade (H3-4) HARS, respectively, and this was consistent with medical expectation. However, whole body doses between 1 and 5 Gy corresponded poorly to different H-ARS degrees of severity. This correlation with H-ARS was found as well when using clinical signs and symptoms for dose estimation in the context of the already mentioned radiobiology masters course and the NATO workshop (figure 3).

6. Summary

At present there is no FDA approved biodosimetry device.

- Capabilities to assess exposure, dose level, and the extent of potential radiation injury for: (a) operational, (b) early-phase medical treatment, and (c) late-effects monitoring decisions are needed to respond to potential life-threatening radiation exposures.
- Physical dosimeters, if available, to 'assess' exposure and dose are useful; FDA do not require that these devices be regulated for this purpose.
- Risk of radiation-induced lethality is significantly influenced by partial-body exposures, dose rate, and radiation quality, etc, which limits 'dose' alone as a guide for medical intervention for life-savings measures (i.e. G-CSF treatment).
- Use of prediction biomarkers (i.e. clinical signs and symptoms, blood cell counts, blood chemistries, cytogenetic biomarkers, proteomic biomarkers) of effect (i.e. risk of ARS severity) show useful diagnostic utility.
- Use of a combined multi-parameter based diagnostic approach using clinical, biological, and physical dosimeters is recommended for use to provide early-phase diagnostics to inform first-responders and medical professionals to formulate early-treatment decisions.

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