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Editorial

Biological dosimetry to assess risks of health effects in victims of radiation accidents: Thirty years after Chernobyl

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April 26, 2016 marks 30 years since the Chernobyl accident. As a result of this catastrophic event, more than 200,000 km^2 were subjected to levels of radioactive deposits exceeding 37 kBq/m^2 of ^{137}Cs, the cut-off level to classify an area as contaminated [1]. As an immediate aftermath of the accident, two fatalities occurred among employees while 134 power plant employees and emergency workers were diagnosed with an acute radiation syndrome resulting in 28 deaths [2]. Following the accident, a significant clean-up operation was undertaken, as well as building the "sarcophagus" – a structure to contain the crippled building. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008 report summarized effective doses for 530,000 recovery operation workers which were received primarily from external irradiation [2]. The average effective dose was estimated at 120 mSv with recorded doses varying from <10 mSv to >1 Sv, with uncertainties as large as factor of five [2]. Doses to residents of the contaminated areas and evacuees primarily resulted from exposure to short-lived ^{131}I (half-life 8 days) and long-lived ^{137}Cs (half-life 30 years). The UNSCEAR 2008 report also presented thyroid and effective doses for 115,000 evacuees and 6,400,000 inhabitants of the contaminated areas [2] in Belarus, Russian Federation and Ukraine. The particular attention to thyroid dose was motivated by the observed excess incidence of thyroid cancer in individuals who were 18 years or younger at the time of the accident and were exposed to ^{131}I. Average dose to the thyroid among evacuees was estimated at 0.5 Gy ranging from <50 mGy to >5 Gy. For the residents of contaminated areas the average dose was 100 mGy although a small (<1%) proportion of individuals received >1 Gy. As of 2010, there were approximately 7000 reported cases of thyroid cancer in individuals exposed prenatally, as children or adolescents in Ukraine alone [3], and a significant dose–response for the induction of cancer has been reported [4]. While the background annual incidence of thyroid cancer among children 10 years old or younger is 2–4 per million, the crude annual incidence for children in this age group (at time of diagnosis) in Belarus reached approximately 34 per million among girls and 18 among boys during 1991–1995. Notably, the incidence for children born after 1986 who were 10 years or younger at diagnosis agreed with background levels, for 1996–2000 and 2001–2005 periods of observation, thus linking excess thyroid cancer to radiation exposure [2].

The Fukushima nuclear accident occurred 25 years after Chernobyl, with significant efforts spent on projecting doses and exploring remedial actions for regions contaminated with ^{134}Cs and ^{137}Cs [5]. The release of radioactivity in Fukushima resulted from a tsunami hitting the nuclear power plant and consequent loss of cooling capacity and damage to reactor cores. Of the 76,000 people residing 20 km or closer to the Daiichi power plant, 97% were evacuated within four days [6]. No increase over baseline in cancer incidence due to radiation is expected in the residents following the Fukushima accident.

Having accumulated decades of experience dealing with the health effects of radiation, we still mostly rely on cancer incidence in atomic bomb survivors to project radiation-induced cancer risk [7]. Analysis of health consequences of exposure to ionizing radiation as a result of large-scale accidents or medical errors has been challenged by reliability of the dosimetric data, in particular for the former. A significant effort has been spent since 1986 to develop guidelines, quality assurance (QA) procedures and benchmark methods of biological dosimetry [8,9]. Broadly, these methods use biological changes to reconstruct the radiation dose received. Biological dosimetry can be used to reconstruct an unknown dose or to validate the dose if an otherwise established estimate is available.

Medical physicists and radiation oncologists are most familiar with patient-related dose measurements for QA or verification of radiation therapy. For example, ionization chamber measurements in a solid water phantom are often performed prior to treatment delivery. In-vivo dosimetry is commonly performed for verification purposes, e.g., diode measurements are used to verify the total body irradiation dose and to check if the compensator thickness is appropriate, or optically stimulated luminescence dosimeters to measure dose to a pacemaker. These are point measurements meant to validate the dose from the radiation therapy plan.

Erroneous dose delivery in modern radiation therapy or diagnostic imaging settings is extremely rare. Such cases are well-documented [10] and causes are attributed to numerous components of the radiation therapy program, e.g., errors in

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machine calibration, incorrect data in the planning system or errors in transferring data to the treatment console [11]. Commonly, because of modern use of record and verify systems, the correct dose can be accurately reconstructed. However, record and verify systems only tell us what happened at the radiation beam end and do not account for unforeseen or erroneous events at the patient's end, for example excessive motion or erroneous setup.

Some methods of dose reconstruction are based on established physics where the location of the point of measurement is known. Specifically, electron spin resonance dosimetry allows us to accurately reconstruct individual doses [12]. This method, which has a solid physics foundation, is based on quantifying the concentration of radiation-induced radicals in a sample. It is commonly applied to tooth enamel samples, and thereby dose to teeth can be evaluated [13]. While this is perfectly acceptable for catastrophic events leading to whole body irradiation, it is not helpful following partial body irradiation. Commonly used chromosome aberration assays quantify dose to blood at short follow-up and dose to bone marrow at long follow-up. An example of the former is thyroid ablation, where blood cells accumulate dose as blood travels through the thyroid gland where ^{131}I is predominantly concentrated.

Ideally, biological dosimetry methods need to comply with the following requirements:

- Low detection threshold.
- Low person-to-person variation in dose–response for healthy individuals.
- Ability to obtain calibration curves in laboratory conditions, e.g. in vitro.
- Stability of the biological effect so that dose can be reconstructed at long time periods, years or decades, after exposure.

In addition, the ability to estimate non-uniformity of radiation exposure and radiation quality is desirable.

Scoring unstable chromosome aberrations in peripheral blood lymphocytes, with specific emphasis on dicentrics and centric rings, has been the enduring standard for biological dosimetry for photon radiation [9]. Calibration curves for various radiation types are well established, and a detection limit of 0.1–0.2 Gy can be reached. Notably, increased frequency of dicentrics was seen after a single chest or full upper body CT scan [14]. However, a larger number of metaphases, 2000 per patient, need to be analyzed in this case. Chromosome aberrations have also been studied in cancer patients and elevated levels have been reported for patients who received radiation therapy for lung cancer, Hodgkin's disease [15] and head and neck cancer [16]. In the latter case, elevated frequency of chromosome aberrations was seen after the first fraction and, after corrections for non-uniform exposure, the dose estimated using the cytogenetic assays agreed well with dose per fraction. The limitation of this assay is that because of natural turnover of lymphocytes (a half-life of 3–4 years has been reported [17]), retrospective dose reconstruction becomes unreliable at long follow-up.

Chromosome aberrations have an established track record in radiation protection, in particular when it comes to assessing risk of stochastic effects. Specific point mutations or translocations have been connected to multistage processes which eventually may lead to the development of cancer [18]. Chromosome aberrations therefore serve as a surrogate to study dose–response and the effect of radiation quality on cancer risk. Thereby, a contribution to the radiobiological foundation is made to justify extrapolating cancer risk to low doses and assigning radiation weighting factors [7]. Dose–response for dicentrics has been demonstrated to be linear down to about 20 mGy (below this level statistical noise dominates). On a more basic level, linear dose–response at even lower doses [19] was observed with γH2AX - a molecular assay employing antibody labeling of the phosphorylated form of H2AX. This method allows detecting radiation-induced DNA double-strand breaks (DSB) by identifying γH2AX foci which occur at the site of DSB [20]. This observed linearity of dose–response serves as a foundation for use of the linear-non-threshold model for extrapolating risk of stochastic effects to low doses. Direct human data on cancer induction in the healthy population following low dose exposure to neutrons and charged particles cannot be obtained. Therefore, alternative means to justify assigning radiation weighting factors, W_R, have to be explored. Low-dose relative biological effectiveness (RBE) for chromosome aberrations has therefore been used to underpin the judgment of W_R values using data derived from normal human cells [7].

While dicentrics lose their usefulness for dose reconstruction at longer follow-up, translocations in human lymphocytes, as scored using fluorescence in situ hybridization (FISH) can be used at longer follow-up. The premise is that, being stable, translocations will survive in marrow cells until differentiation when mature lymphocytes enter the bloodstream. This assumption appears to hold true for uniform irradiation, as was the case for clean-up personnel following the Chernobyl accident. This premise—that the frequency of translocations holds stable with time—had to be proven over decades after the radiation accident. This validation is particularly important for highly non-uniform irradiation, which is the case for radiation therapy [21]. FISH analysis, unlike scoring dicentrics, requires specialized equipment and expertise, which puts limitations on our ability to cope with the biological dosimetry demand following a large-scale accident.

The International Atomic Energy Agency Biodosimetry Manual published in 2011 [8] covers all aspects of using biological dosimetry, with emphasis on chromosome aberrations. This document describes suggested procedures for sample collection and handling, production of calibration curves in vitro, cell culture handling, fixing procedures, scoring criteria and handling the data. As such it provides a roadmap for a laboratory to establish its own practice. These components also form a foundation for quality assurance and quality control of biological dosimetry laboratories [9].

Biological dosimetry methods have been used to reconstruct doses for emergency workers, clean-up personnel, evacuees and residents of contaminated areas following the Chernobyl accident [22–25]. Major findings validate the expectation that translocations persist in blood lymphocytes and that the FISH-translocation method can be used years after exposure. A recent paper [26] reported persistence of translocations in 11 individuals over a span of a decade. These exposed individuals assessed the condition of the ruined Chernobyl reactor building, the "sarcophagus" structure enveloping the building, and gathered data regarding the distribution and state of the radioactive material. The self-reported individual dose estimates ranged from 0.6 to 17.1 Gy. FISH-translocations were stable with time and their frequency agreed broadly with self-reported doses [26].

While biological dosimetry may serve its purpose in the radiation therapy environment when an unknown dose was delivered [27], it may also be used following unsealed radionuclide therapy [28]. The dose in this case is literally unknown as it is activity, rather than dose, that is prescribed. Biological half-life varies greatly from person-to-person and biological dosimetry provides means for blood dose reconstruction [29].

Interest in the biological assays used in biological dosimetry has persisted in the radiation therapy community because these assays may uncover clinically useful patient-specific information [30,31]. This pertains to early response, specifically tumor response and acute adverse effects in normal tissues, as well as long-term effects such as late toxicity and risk of secondary malignancies. While the

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