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COMMENTARY

Towards tailoring radiation protection strategies at an individual level

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Running title:
Individualized radiation protection strategies

ABSTRACT

Purpose: From radiation protection viewpoints, there have been continued discussions on potential individual differences in ionizing radiation responses. In October 2017, the International Commission on Radiological Protection (ICRP) and the European Radiological Protection Research Week (ERPW) held a joint meeting, of which key focus areas included individual responses. In March 2018, the European programs MELODI and CONCERT held a joint meeting on individual responses. This paper provides some highlights from these two meetings, and also briefly discusses pertinent issues on the tolerance dose concept used in radiation therapy vs the threshold dose concept used in radiation protection, a need of a longer follow up after exposure to lower doses and potential variations of individual responses depending on the levels of severity and onset time for tissue reactions, and radiomics.

Conclusions: There remains a long way ahead before a somewhat more individualized approach will be implemented in the radiation protection system, but discussions towards individualized strategies may be useful, such as for protection of medical patients, emergency workers, and astronauts, among which medicine will lead the way. Strategies to incorporate the individualized approach need to be considered, along with further developments of scientific knowledge and ethical foundations.

KEYWORDS

Individual response to ionizing radiation; cancer; tissue reactions; radiation protection; radiotherapy

Abbreviations: AGIR, Advisory Group on Ionising Radiation; ATM, ataxia telangiectasia mutated; C1, ICRP Committee 1 on radiation effects; C3, ICRP Committee 3 on medicine; ERPW, European Radiological Protection Research Week; ESTRO, European Society for Radiotherapy and Oncology; EURAMED, European Alliance for Medical Radiation Protection Research; GWAS, genome wide association studies; ICRP, International Commission on Radiological Protection; IR, ionizing radiation; MELODI, Multidisciplinary European Low Dose Initiative; PSC, posterior subcapsular cataract; RENEB, Realizing the European Network of Biodosimetry; SNP, single nucleotide polymorphism; SRA, strategic research agenda; TD, tolerance dose; VIC, vision impairing cataract; and WP, Working Party.

Introduction

Potential inter-individual differences in response to ionizing radiation (IR) exposures (referred hereinafter to as individual IR response), particularly in terms of cancer induction, have long been discussed from the context of radiation protection. In 1999, the International Commission on Radiological Protection (ICRP) issued Publication 79 "Genetic susceptibility to cancer" (ICRP 1998). In 2013, Advisory Group on Ionising Radiation (AGIR) of the UK Health Protection Agency (now called Public Health England) published a report on human radiosensitivity (HPA 2013). Besides these two major reports, there have been ongoing discussions.

Currently, ICRP has two active Working Parties (WPs). One is on "Radiation protection in medicine related to individual radiosusceptibility" established in 2015 under Committee 3 on medicine (C3) in conjunction with Committee 1 on radiation effects (C1), and chaired by Michel Bourguignon (hereafter C3–C1 WP) (Martin 2017). The other is on "individual radiosusceptibility" established in 2016 under C1, and chaired by Preetha Rajaraman (hereafter C1 WP) (Rühm 2017). On 13 October 2017, a joint C1–C3 session was held to discuss this issue. Taken together, ICRP Task Group 101 "Radiological protection in therapy with radiopharmaceuticals" held a workshop in Fukushima, Japan on 3 October 2017, in which Sören Mattsson proposed the use of lifetime attributable risk for individual risk estimates in radiology (Mattson & Andersson 2017; Andersson et al. 2017).

In Europe, the Multidisciplinary European Low Dose Initiative (MELODI) on Low Dose Effects has annually revised the strategic research agenda (SRA), and its latest (eighth) SRA issued in 2017 identified "individual radiation sensitivity" as one of three key research questions (Kreuzer et al. 2018). The European Alliance for Medical Radiation Protection Research (EURAMED) identified five major themes in its inaugural SRA issued in 2017: one major theme was "normal tissue reactions, radiation-induced morbidity and long-term health problems" where "individual patient-related radiation sensitivity" was included as one of the underlying key research questions (EANM et al. 2017).

This paper provides some highlights from the two recent meetings with particular emphasis on individual IR responses. Then, in the Discussion section, we briefly discuss the related issues such as on the tolerance dose concept used in radiation therapy vs the

threshold dose concept used in radiation protection, a need of a longer follow up after exposure to lower doses and potential variations of individual IR responses depending on the levels of severity and onset time for tissue reactions, and radiomics.

ICRP–ERPW 2017

On 10–12 October 2017, ICRP and European Radiological Protection Research Week (ERPW) held a joint meeting in Paris, France, of which one of the key focus areas was individual IR response.

Five symposium sessions composed ICRP 2017 of which abstracts, slides and videos are downloadable from the ICRP website (ICRP 2017a): ICRP is also going to publish the proceedings in the Annals of the ICRP. Among them, in the ICRP/MELODI session on "Effects, risks, and detriment at low dose and low dose rates" (co-chaired by Simon Bouffler and Thomas Jung), Andrzej Wojcik as a member of C1 WP delivered a talk "Human radiosensitivity and prospects for prediction" (Wojcik 2017). Wojcik pointed out that the use of a common term "individual radiosensitivity" to describe the proneness to stochastic effects and tissue reactions is confusing (Foray et al. 2016). Wojcik also highlighted that testing of individual IR responses of low-dose occupationally exposed individuals is questionable from radiation protection viewpoints, owing to the limited contribution of genetic background. C1 WP is reviewing papers on individual IR responses that have come out since the 2013 AGIR report (HPA 2013), and is preparing a report that aims to address whether predictive assays/markers are available and to identify open questions (ICRP 2017b). Two papers related to C1 WP have thus far been published (Rajaraman et al. 2018; Wojcik et al. 2018).

Out of 14 symposium sessions at ERPW 2017, two sessions were dedicated to individual IR responses. Session 8 "Biomarkers and cohorts suitable for exploring low-dose/low-dose-rate exposure effects and individual susceptibility (humans, animals and plants)" (co-chaired by Almudena Real and Michaela Kreuzer) had two pertinent talks: one was "Cohorts for radiation research with focus on low-dose/low-dose-rate exposure effects and individual susceptibility" by Olivier Laurent from the viewpoint of epidemiology, the other being "Biomarkers for radiation research with a focus on human susceptibility" by Catharine West from the viewpoint of the REQUITE project (REQUITE 2018). West pointed out the need of a roadmap for the validation of

biomarkers in prospective cohorts. Perhaps surprisingly, many of the common genetic variants in terms of single nucleotide polymorphisms (SNPs) observed in the genome wide association studies (GWAS) on late radiation toxicity include not only genes involved in DNA damage response pathways but also those in various functions of the tissues, such as muscle cell regeneration (Fachal et al. 2014), regulation of angiogenesis (Kerns et al. 2013) and smooth muscle contraction (Barnett et al. 2014). In the radiation protection context, a roadmap was provided for development of biomarkers from discovery to implementation and used to summarize the current status of proposed biomarkers for epidemiological studies, but most potential biomarkers still remain in the discovery stage (Hall et al. 2017). All of four talks in Session 14 "Individualized approaches for radiation protection" (co-chaired by Hildegarde Vandenhove and Elisabeth Ainsbury) were relevant: "Challenges of individualized radiation protection: identification of individual radiation sensitivity" by Ulrike Kulka who raised the need of more scientific knowledge and ethical considerations, "Individual radiation protection approaches in medical applications" by Wolfgang Dörr from the medical viewpoint, "Individual approaches in emergency scenarios" by Andrzej Wojcik from the viewpoint of the Realizing the European Network of Biodosimetry (RENEB) project (RENEB 2018), and "Individual sensitivity; neither the issue or its solution should be thought of as radiation specific" by Christopher Kalman from the viewpoint of occupational protection. Individual variability in radiation sensitivity is of major concern in radiation protection. Established and novel biomarkers will allow for a more sensitive and fast identification. This applies for emergency and accident exposures. For all medical radiation applications, the "justifying indication" guarantees individualization. Moreover, radiotherapy in itself is a highly individualized procedure. It needs to be emphasized that the ethical, scientific and practical difficulties of standards based on individual sensitivity are huge; the ethical impact must not be underestimated.

MELODI–CONCERT workshop 2018

MELODI, at its management board meeting held on 9 October 2017, decided to hold the workshop on individual IR responses in Malta in March 2018, and actually held the MELODI–CONCERT workshop on individual radiosensitivity and radiosusceptibility on 12–14 March 2018 (MELODI 2018). Clinical and epidemiological observations,

mechanisms involved in radiation sensitivity, and identification of sensitive subpopulations were particularly discussed in the workshop.

About five percent of patients develop severe adverse effects and many more show moderate toxicity after radiotherapy. It would be useful to have a registry of overresponding patients; however, there are no standard criteria to identify them. There is a need for validated prediction tools to identify radiosensitive and radiosusceptible patients. If radiosensitive patient is identified, guidelines are then needed for alternative treatment. As for the reported outcomes, it was concluded that outcomes reported objectively by a physician and subjectively by a patient are both important. A long term follow-up of patients would be needed for effects such as heart/lung complications or second cancer. Recommendations on the collection of data and samples and on the follow-up were discussed and will be further developed. Cohorts of radiotherapy patients available for retrospective or prospective studies were reviewed, and alternative strategies by using non-radiotherapy cohorts with biosamples (such as national biobanks) were also considered. Even though there are rare genetic syndromes (e.g., ataxia telangiectasia) that come with very high sensitivity to radiation, the majority of overresponding patients do not carry mutations in the known DNA damage and damage response genes. It is not clear why they overrespond to radiotherapy and whether the underlying cause is genetic of environmental. Functional tests that would have the potential to identify overresponding patients were discussed. Among the most promising ones are levels of 8-oxo-dG in the serum or urine (Pour Khavari et al. 2018), the nuclear shuttling of ataxia telangiectasia mutated (ATM) proteins (Pereira et al. 2018), and the apoptosis of lymphocytes (Azria et al. 2015).

MELODI is preparing a position paper predicated on discussions made in the workshop, and will have a continued discussion on individual IR responses at the third ERPW meeting in October 2018.

Discussion

Here we have provided some highlights from two recent meetings (ICRP–ERPW 2017 and MELODI–CONCERT workshop 2018) in the context of individual IR responses. We now briefly discuss the related issues such as on the tolerance dose concept used in radiation therapy vs the threshold dose concept used in radiation protection, a need of a

longer follow up after exposure to lower doses and potential variations of individual IR responses depending on the levels of severity and onset time for tissue reactions, and radiomics.

In 1972, Rubin and Casarett proposed a clinically acceptable minimum injurious tolerance dose, defined as a dose that causes severe normal tissue complications in '1–5%' and '25–50%' of patients within 5 years after radiotherapy (abbreviated as $TD_{5/5}$ and $TD_{50/5}$, respectively) (Rubin & Casarett 1972). Based on this proposal, tolerance dose has been used clinically, and its numerical values remain almost unchanged for a long time. On the other hand, in the field of radiation protection, ICRP first defined in 1984 a dose threshold for non-stochastic effects as the dose required to cause a particular effect in 'at least 1–5%' of exposed individuals (ICRP 1984), although ICRP first defined the threshold-type dose response in 1969 (ICRP 1969). In 1990, non-stochastic effects was renamed deterministic effects, with no change in definition of threshold (ICRP 1991). In 2007, ICRP defined a dose threshold for tissue reactions as the dose required to cause a particular effect in 'only 1%' of exposed individuals (ICRP 2007). ICRP has revised thresholds based on available scientific knowledge, and the latest revision was made in 2012 (ICRP 2012): now, threshold to the lens of the eye for vision impairing cataracts (VICs) is 0.5 Gy with a follow up of >20 years after exposure, and threshold to the heart and brain for cardio- and cerebrovascular disease respectively is now 0.5 Gy with a follow up of >10 years after exposure, such thresholds recommended being the same independent of the rate of dose delivery (ICRP 2012). It may be useful and efficient if these two different dose concepts (i.e., tolerance dose used in medicine at 5% at 5 years after exposure vs threshold dose used in radiation protection at 1% at 50 years after exposure) but with the same origin can be united into one dose concept applicable both to medicine and radiation protection. Such a dose concept may be defined for various levels of severity and follow-up time (years or decades) after exposure, levels of which can be judged depending on the situations. For example, in medicine, there is always justification for diagnostic or therapeutic exposures to ensure that the health benefits (diagnosing or curing a potentially fatal disease) outweigh the risks (e.g., cancer induction after diagnostic exposure, or tissue reactions and second cancer induction after therapeutic exposures). From radiation protection viewpoints, the very late occurring tissue reactions may exhibit less evident threshold and behave like stochastic effects, necessitating discussion on how to define an unacceptable level below which the

occurrence of reactions is kept (vs 1% level at which the occurrence of threshold type tissue reactions is avoided).

For tissue reactions, the latency period increases and severity decreases, with decreasing dose (ICRP 2012). A longer follow-up is hence needed when considering the lower dose (e.g., in assessing normal tissue complications after radiotherapy with modern techniques that deliver lower doses to normal tissues than conventional techniques). However, as a follow-up period increases, threshold dose decreases, the shape of the dose response curve becomes more linear, and risk needs to be derived from those with younger age at exposure.

Individual IR responses may also vary among the levels of severity or onset time. Take cataracts, for example. “Late” onset cataracts that appear months or years after IR exposure are mainly posterior subcapsular cataracts (PSCs) with a clear threshold, and “very late” onset cataracts that appear decades after IR exposure are PSCs or cortical cataracts with less clear threshold, behind which underlying etiological mechanisms and individual IR responses may be different (Hamada & Fujimichi 2015). Also, once the ocular lens develops VIC, the lens exhibits no more radiogenic cataracts later because of lens replacement surgery.

The properties of the tumor such as tumor radiosensitivity/radioresistance are also important for the individualized medical treatment. Extracting more information from medical images using advanced feature analysis is a promising noninvasive method, which provides information for the planning of treatment (Aerts et al. 2014). Signatures related to intratumor heterogeneity and irregularity can be identified from the image, where higher heterogeneity means worse prognosis. Decoding tumor phenotype by noninvasive imaging using a quantitative radiomics approach may well be part of the repertoire for the individualized treatment of cancer patients in the future (Lambin et al. 2012), as was also recently discussed at the 36th Annual Meeting of the European Society for Radiotherapy and Oncology (ESTRO 36) held on 5–9 May 2017 in Vienna, Austria.

Conclusions

There remains a long way ahead before a somewhat more individualized approach will be implemented in the radiation protection system, but discussions towards individualized strategies may be useful, such as for protection of medical patients, emergency workers,

and astronauts, among which medicine will lead the way. The current system of radiation protection is principally predicated on the nominal concept (averaging over age groups and gender), and the partial implantation of individual-specific parameters perturbs the nominal concept. As such, strategies to incorporate the individualized approach need to be considered, along with further developments of scientific knowledge and ethical foundations.

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Disclosure statement

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