Factors Governing the Individual Response of Humans to Ionising Radiation

The work of ICRP TG111

GT CIPR
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on behalf of TG111 members

Outline

- Formation and composition of TG111
- Issues under consideration (and those that are not)
- Progress to date
- A few provisional conclusions on the topic

Formation of TG111

- TG111 was established in 2018
- A joint TG of Committee 1 (Radiation Effects) and Committee 3 (Medical Aspects of Protection)
- Preceded by: joint C1/C3 meetings at Abu Dhabi Symposium, 2013 and Seoul Symposium, 2015; formation of a C1 working party on 'Individual Radiosensitivity' during C1 meeting in Chennai, 2016; presentations on the topic during Paris Symposium, 2017

Factors Governing the Individual Response of Humans to Ionising Radiation

Membership

Simon Bouffler (Chair)
Kyoji Furukawa
Michael Hauptmann
William McBride
Claudia E. Ruebe
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Dan Stram
Andrzej Wojcik
Julie Leblanc (Mentee)
Andreas Breitbarth (Mentee)
Sasha Jande (Mentee)

Terms of reference

The TG will review the currently available information on individual [illegible] responses with special focus on the following questions and issues:

- What is the impact of age, sex and other determinants [illegible] tissue reactions and incidence of cancers and other diseases follo[illegible]tion exposure?
- What is the contribution of genetics to indivi[illegible]al tissue responses with respect to adverse reactions to varying [illegible] as given during radiotherapy?
- Would predictive tests contribut[illegible] radiation protection of radiotherapy patients without compromi[illegible] cure rates?
- What is the contributi[illegible]etics and epigenetic factors to tissue radiation response with re[illegible]ancer induction at relevant doses and dose rates?
- What is th[illegible] that modifiable factors can affect individual risk of radiation-indu[illegible], tissue reactions and other non-cancer diseases?
- [illegible] the ways to quantify the potential impact of individual response to r[illegible]iation on the incidence of cancers, non-cancer diseases and normal tissue reactions?

Literature review – no consideration of the implications for RP

Scope

Health effects under consideration:

- Normal tissue reactions after radiotherapy
- Cancers
- Circulatory diseases
- Cognitive impairment
- Cataract

Types of evidence/study under consideration:

- Clinical studies
- Epidemiological studies
- Experimental animal studies
- Cellular assays

Terminology

- There are numerous ways of describing radiosensitivity, and some discussion of the best words to use – for example to distinguish between differing disease endpoints.

- In the draft report we do not adopt any specific 'naming convention' but ensure that the endpoint under consideration is specified, eg normal tissue radiosensitivity, sensitivity to cancer

Ways of working

Much of TG111 has been conducted under the restrictions due to the COVID-19 pandemic, nonetheless good progress is being made:

- Currently monthly web conference meetings with alternating late/early in the day timing to accommodate participation by all
- September 2021 web meeting with ICRP membership invited; September 2022 in person meeting
- Having identified key areas of interest, a systematic approach to review of the scientific literature is being taken
- A good basis is provided by the 1998 ICRP report on *Genetic susceptibility to cancer* and the 2013 AGIR report on *Human radiosensitivity* (https://www.gov.uk/government/publications/human-radiosensitivity)
- Anticipate publication of systematic reviews in the open literature as the work progresses

Importance of the topic

Currently the system of radiological protection aims to:

- **Avoid tissue injury (deterministic effects)**
- **Minimise risk of stochastic effects (cancer/hereditary)**
  - **justification, optimisation, dose limitation**
  - **limits derived from notional average that does not exist**

Where is variation in response observed?

- Variation in severity of normal tissue reactions following standardised radiotherapy regimens
- Variation in cellular responses to radiation exposure, eg cell killing, induction of chromosomal aberrations, DNA damage response-related mechanisms
- Variation between inbred strains, and GM strains, of mice in their specific susceptibilities to radiation-induced cancers
- Age- and sex-dependency of cancer risks observed in epidemiological analyses
- Smoking dependency of radon-exposure associated lung cancer risk

Potential contributors to variation in response

- Genetic factors
- Epigenetic modifications
- Lifestyle factors
- Co-exposures
- Underlying health conditions
- Stochasticity of responses
- .....

Current draft

- Approx 150 pages of text
- Introduction/context in good shape
- Good sections on Radiobiology of acute reactions in whole animals and tissues, cognitive function and on impact of age on normal tissue reactions
- LSS/cancer evidence and evidence from animal models of cancer well developed
- Clinical radiosensitivity – literature review near complete needs tabulation and interpretation
- Circulatory disease – biology and epidemiology sections in progress

Publications to date

- **Applegate et al (2020)** Individual response of humans to ionising radiation: governing factors and importance for radiological protection. Radiat Environ Biophys. 2020 May;59(2):185-209.
- **Wojcik and Pei (2021)** Individual Response to Ionising Radiation – Radiosensitivity of Children. In: Directorate-General for Energy (European Commission), EU Scientific Seminar 2020: "Radiosensitivity" of children – Health issues after radiation exposure at young age. Radiation Protection N° 196. Publications Office of the European Union, Luxembourg: 7–20
- **Abdelkarem et al (2022)** Effect of Race and Ethnicity on Risk of Radiotherapy Toxicity and Implications for Radiogenomics. Clin Oncol, online ahead of print - doi: 10.1016/j.clon.2022.03.013
- **Barnard & Hamada (2023)** Individual response of the ocular lens to ionizing radiation. Int J Radiat Biol, online ahead of print - doi: 10.1080/09553002.2022.2074166

Potential conclusions (could well change!)

What is the impact of age, sex and other determinants on normal tissue reactions and incidence of cancers and other diseases following radiation exposure?

Normal tissue reactions:

- Some evidence that sex, increasing age, rheumatoid arthritis, prior surgery and chemotherapy increase the frequency of normal tissue reactions. Smoking generally increases the frequency of normal tissue reactions but in the lung protects against radiation-induced normal tissue reactions

Cataract

- The risk of cataract tends to be higher in females after radiation exposure, and in those of younger age at the time of exposure. Animal studies and limited human studies have indicated that genetic factors play a role, with some DNA repair related genes modifying risk. Some evidence indicates that co-morbidities (e.g., diabetes and glaucoma) and co-exposures (UV, antioxidants) modify risk. However, no firm conclusions can yet be drawn.

Diseases of the circulatory system (DCS)

- There is some suggestive evidence that younger age at exposure and concurrent chemotherapeutic (e.g., anthracycline and vinca alkaloids) exposure increase the risk of radiation induced DCS. The majority of evidence for these modifiers comes from high dose (radiotherapy) studies

Cognitive effects

- There is a clear age dependency of radiation-induced brain injury associated with cognitive dysfunction that can be explained by the higher radiosensitivity of numerous proliferating precursor cells in the developing brain. Other factors (such as sex, lifestyle and environmental factors) have no or significantly less influence on the development of neurocognitive disorders after exposure of the brain to ionizing radiation.

Potential conclusions (could well change!)

Cancers:

- Epidemiological and animal data indicate that younger age at exposure and female sex are associated with a higher relative risk for all solid cancers. However, there is variation between cancer sites. For breast cancer in females, the most sensitive age is the peri-pubertal period; human and animal studies are consistent in this finding
- In the case of leukaemia, absolute risk is higher at younger ages and in males.
- Both epidemiological and some experimental animal evidence suggest that smoking modifies the relative and absolute risk of radiation cancer in the lung.
- Animal studies provide some indication that excess body weight is associated with increased solid cancers and leukaemias.
- For breast cancer in animal studies hormonal factors (long-term estrogen exposure) increases risk.
- Animal studies provide some evidence that co-exposure to chemical agents is generally additive to radiation cancer risk, and radioprotectors and free radical scavengers reduce radiation cancer risk
- Variation in cancer risks in inbred strains provides good evidence that genetic factors modify radiation cancer risks. The use of genetically modified mouse strains indicates that deficiencies in genes that modify background cancer incidence also modify radiation cancer incidence

Potential conclusions (could well change!)

What is the contribution of genetics to individual, normal tissue responses with respect to adverse reactions to varying doses such as given during radiotherapy?

- There is clear evidence that rare homozygous mutations in some genes, such as ATM, have a large effect on normal tissue radiosensitivity. The combined effect of multiple common mutations will be smaller.

Would predictive tests contribute to a better radiation protection of radiotherapy patients without compromising cancer cure rates?

- Yes, in principle but there are no internationally validated assays available despite promise for some in certain centres

What are the ways to quantify the potential impact of individual response to radiation on the incidence of cancers, non-cancer diseases and normal tissue reactions?

- Very few

Task Group 128

Individualisation and Stratification in Radiological Protection: Implications and Areas of Application

- TG approved by the MC in March 2023
- A Task Group under Committee 1, 2, 3 and 4
- First meeting held on Monday 27th November 2023
- Open meeting planned as part of work, likely focus on medical sector

TG128 Membership

Simon Bouffler (Chair), UK Health Security Agency, United Kingdom
Julie Burtt (Member), Canadian Nuclear Safety Commission, Canada
Ahmed M. Alenezi (Member), Nuclear and Radiological Regulatory Commission, Saudi Arabia
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François Bochud (Member), IRA CHUV, Switzerland
Daniele Giuffrida (Member), Federal Authority for Nuclear Regulation (FANR), United Arab Emirates
Sakae Kinase (Member), Japan Atomic Energy Agency (JAEA)/ Ibaraki University, Japan
Andrea Magistrelli (Member), Children's Hospital Bambino Gesu' IRCCS, Italy
Colin Martin (Member), University of Glasgow, United Kingdom
Jose M. Soriano (Member), Spain
Richard Wakeford (Member), The University of Manchester, United Kingdom
Yeon Soo Yeom (Member), Yonsei University, Korea
Anna Denisova (Technical Secretary), Southern Urals Biophysics Institute (SUBI), Russian Federation

TG128 Mandate

Given the evolving work of Task Group 111 on Factors Governing the Individual Response of Humans to Ionising Radiation, it is timely to consider whether and for which situations the system of protection should adopt a more individualised/stratified approach, particularly when considering low dose, low dose-rate and chronic exposures. Therefore, this Task Group is mandated to:

- Identify the elements of individualisation or stratification (including treatment of sub-groups, such as age and sex) of dose, risk, and radiological protection already used in the current System, and in current practice.
- Identify situations where an additional individualisation / stratification of dose, risk, and radiological protection could be appropriate. These situations will especially, but not only, consider the protection of patients, bearing in mind that cumulative dose relates to lifetime radiation risks and these must be considered alongside all cancer risk factors, including other potentially carcinogenic exposures when evaluating risk to an individual.
- Identify situations where population averaging approaches are appropriate or not.
- Consider the impact of uncertainties, both in dose and risk, and opportunities for their reduction.
- Consider benefits, challenges of, and approaches to communication of risk on the individual/stratified level, and how this might be implemented.
- Identify potential consequences of adopting individualised/stratified approaches on the System and its application in different domains, illustrated with case studies and with specific consideration of ethical issues.

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