

Third Announcement

**ICRP-QST-RERF Workshop on
Individual Response to Ionising Radiation**

Current Scientific Evidence on Factors that Influence Individual Response

National Cancer Center, Research Institute, Tokyo, Japan

12 December, 2018

Organised by the International Commission on Radiological Protection (ICRP),
National Institutes for Quantum and Radiological Science and Technology (QST) and
Radiation Effect Research Foundation (RERF)

In collaboration with National Cancer Center Japan (NCC), Japanese Society for
Radiation Oncology (JASTRO), Japan Radiological Society (JRS), Japan Health
Physics Society (JHPS) and the Japanese Radiation Research Society (JRRS)

Registration

Attendance at the workshop is free of charge. However, advance registration is required as attendance is limited. Please send your name, affiliation, and e-mail address to Hiroki Fujita (ICRP Assistant Scientific Secretary) at register@icrp.org by 30 November 2018.

Workshop venue

Main Lecture Hall, National Cancer Center Research Building, Tsukiji Campus,

National Cancer Center, Tokyo, JAPAN

Access: <https://www.ncc.go.jp/en/about/access/index.html>

Program

09:00 – 09:30 **Welcome and Greetings (and Group Photo)**
T. Hirano (QST), R. Ullrich (RERF), T. Nishida (NCC)

09:30 – 17:00 **Scientific Session**

Chair: W. Rühm (ICRP), K. Ozasa (RERF)

Speaker:

1. W. Rühm and K. Applegate (ICRP): Setting the Scene

2. A. Wojcik (ICRP): Human Individual Radiation Sensitivity and Prospects for Prediction Factors

(10:30 – 10:45 Coffee break)

3. M. Hauptmann (ICRP): Genetic susceptibility to radiation induced breast cancer after Hodgkin Lymphoma.

4. A. Brenner (RERF): Age-dependence of breast cancer risk

5. K. Ozasa (RERF): Lifestyle-related cancer risk: Smoking and cancer

(12:15 – 13:15 Lunch break)

Chair: K. Applegate (ICRP), R. Kanda (QST)

6. M. Bourguignon (ICRP): Radiosensitivity and radiotherapy patients

7. Y. Suto (QST/NIRS): Individual difference of chromosome aberration in accidentally exposed workers

8. H. Onishi (JASTRO): Individual difference of post irradiated antitumor effect and lung damage in patients with lung cancer

9. M. Akahane (JRS): Individual variation in clinical practices and protocols

(15:15 – 15:30 Coffee break)

Chair: W. Rühm (ICRP), K. Applegate (ICRP)

10. Moderated Discussion

17:00 **Closing**
C. Clement (ICRP)

Abstracts

(1) Setting the Scene –The ICRP Task Group on “Factors Governing the Individual Response of Humans to Ionising Radiation”

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Abstract- Since a number of years, Committee 1 on “Radiation Effects” and Committee 3 on “Protection in Medicine” of the International Commission on Radiological Protection (ICRP) have identified individual response of humans to ionizing radiation as a topic with growing importance for international radiation protection. Accordingly, at its last meeting in October 2018 in Stockholm, Sweden, the ICRP Main Commission has approved a new Task Group (TG) on “Factors Governing the Individual Response of Humans to Ionising Radiation“, jointly organized by ICRP Committee 1 and Committee 3. The TG will review the currently available information on individual radiation responses with special focus on the following questions and issues: 1) What is the impact of age, sex and other determinants on normal tissue reactions and incidence of cancers and other diseases following radiation exposure? 2) What is the contribution of genetics to individual, normal tissue responses with respect to adverse reactions to varying doses such as given during radiotherapy? Would predictive tests contribute to a better radiation protection of radiotherapy patients without compromising cancer cure rates? 3) What is the contribution of genetics and epigenetic factors to tissue radiation response with respect to cancer induction at relevant doses and dose rates? 4) What is the evidence that modifiable factors can affect individual risk of radiation-induced cancer, tissue reactions and other non-cancer diseases? 5) 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? The final goal of the TG is development of a report for publication in the Annals of the ICRP that presents a review of the current science relevant to the topic of individual response to radiation.

(2) Human Individual Radiation Sensitivity and Prospects for Prediction Factors

Andrzej Wojcik

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Abstract- The idea of individual sensitivity to radiation in humans with respect to tissue effects has long been supported by data from patients with certain rare hereditary conditions such as ataxia telangiectasia or Nijmegen breakage syndrome. However, these monogenetic syndromes affect only a small proportion of the general population. More relevant to the majority of the population is that the genetic contribution defining radiation sensitivity follows a polygenic model, which predicts elevated risk resulting from the inheritance of an unknown number of low penetrance risk alleles. In this way individual radiosensitivity, both with respect to tissue effects and stochastic effects, can be regarded as a multifactorial trait. It is well known that multifactorial traits are influenced by the genotype and the environment. More recent investigations show that in addition to these two factors, there are non-inherited parental genetic variants, parental environment at the epigenetic level and stochastic molecular variations (noise). With respect to radiation sensitivity, an additional factor contributing to variability is the stochastic nature of radiation induced cell death. Hence, predicting the risk of adverse tissue reactions in a radiotherapy patient based on genotyping a single cell type (usually peripheral blood leukocytes) isolated from the patient or from the results of a functional assay may be difficult. Indeed, results of reports published so far are not promising. Also, as stated in the ICRP 79 report, in vitro human cellular radiosensitivity is not a reliable predictor of in vivo cancer proneness nor, by implication, tumorigenic radiosensitivity.

The aim of the presentation is to set the stage for discussions about factors modifying the risk of overreacting to radiation exposure by explaining the nature and relationship of monogenic and polygenic traits. Recent publications aiming at validating markers of individual radiosensitivity will be presented and the possible reasons for the conflicting results explained.

(3) Genetic susceptibility to radiation induced breast cancer after Hodgkin Lymphoma

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Abstract- Female Hodgkin lymphoma (HL) patients treated with chest radiotherapy (RT) have a very high risk of breast cancer. The contribution of genetic factors to this risk is unclear. We therefore examined 211,155 germline single nucleotide polymorphisms (SNPs) for gene-radiation interaction on breast cancer risk in a case-only analysis including 327 breast cancer patients after chest RT for HL and 4,671 first primary breast cancer patients. Nine SNPs showed statistically significant interaction with RT on breast cancer risk (false discovery rate <20%), of which one SNP in the PVT1 oncogene attained the Bonferroni threshold for statistical significance. A polygenic risk score (PRS) composed of these SNPs (RT-interaction-PRS) and a previously published breast cancer PRS (BC-PRS) derived in the general population were evaluated in a case-control analysis comprising the 327 chest-irradiated HL patients with breast cancer and 491 chest-irradiated HL patients without breast cancer. Patients in the highest tertile of the RT-interaction-PRS had a 1.6-fold higher breast cancer risk than those in the lowest tertile. Remarkably, we observed a 4-fold increased RT-induced breast cancer risk in the highest compared with the lowest decile of the BC-PRS. On a continuous scale, breast cancer risk increased 1.4-fold per standard deviation of the BC-PRS, similar to the effect size found in the general population. This study demonstrates that genetic factors influence breast cancer risk after chest RT for HL. Given the high absolute breast cancer risk in radiation-exposed women, these results can have important implications for the management of current HL survivors and future patients.

(4) Age-dependence of breast cancer risk

Alina V. Brenner

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Abstract- Studies of patients irradiated for diagnostic and therapeutic purposes, atomic bomb survivors, and environmentally exposed populations establish a strong and consistent association between breast cancer risk and radiation dose consistent with linearity. In a pooled analysis of eight cohort studies, age at exposure and attained age were important modifiers of radiation risk on excess relative risk (ERR) and excess absolute risk (EAR) scales, although the pattern was different. The ERR decreased with increasing age at exposure and attained age, while the EAR decreased with age at exposure and increased with attained age. In the Life Span Study (LSS) cohort of atomic bomb survivors, the relative importance of attained-age and age-at-exposure effects on radiation risks has evolved over the years. As follow-up increased, the correlation between attained age and age at exposure decreased markedly making possible an examination of age at exposure and attained age as separate effect modifiers. Over time, the evidence and estimated magnitude of a simple trend in the ERR with age at exposure has lessened, especially when the ERR was allowed to vary with attained age. In the most recent LSS breast cancer report with a follow-up through 2009, there was only weak evidence of a significant monotonic trend in the ERR per Gy with age-at-exposure without allowance for attained-age effect modification. By contrast, after allowing for attained age effect, the EAR decrease persisted. This study also provided new evidence that age-at-exposure effects on ERR and EAR might differ before and after menarche, with highest risks for exposures around menarche. For exposures prior to menarche, radiation effect increases (ERR) or remains stable (EAR) as the exposure age approaches menarche while, for exposures after menarche, radiation effects (ERR and EAR) decrease as exposure age increases. Independent of age-at-exposure and attained age effects, ERR and EAR also decreased with later age at menarche. While the new LSS findings require replication in independent studies, these suggest heightened breast tissue sensitivity to ionizing radiation during puberty. The LSS experience underscores the importance of long, perhaps life-long, follow-up of exposed populations in discerning the complex age patterns of radiation risk.

(5) Lifestyle-related Cancer Risk: Smoking and Cancer

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Abstract- Smoking is a definite and well-known carcinogen and causes many cancers, especially for lung cancer. In Japan, smoking habits became popular rapidly through recovery and development of economy after the World War II, peaked around 1970s at which more than 80% of adult men smoked, but smoking prevalence has decreased thereafter and reached at a level of 30% in 2010s. In women, smoking prevalence has been traditionally low as less than 20% although smoking prevalence among young women had peaked over 20% around the year of 2000. Mortality of lung cancer followed the trend of smoking habits in Japan, i.e., rapidly increased during the 20th century, but has decreased thereafter. It has been suggested that relative risk of smoking for lung cancer observed in Japanese population might be smaller than those observed in Western countries. The lower risk might be induced by possible overestimation of smoking intensity based on the surveys of epidemiological studies conducted in the late 20th century. Smoking status and its risk was examined in the LSS, which indicated low smoking intensity in older birth cohorts and smoking risks comparable to Western countries among smokers who started smoking at their young ages [1]. Smoking risk is high for small cell carcinoma among lung cancer subtypes, then squamous cell carcinoma, and the risk for adenocarcinoma was relatively low. In contrast, radiation risk of squamous cell carcinoma was relatively low compared to adenocarcinoma although small cell carcinoma showed the highest radiation risk. A positive interaction between radiation exposure and smoking was observed among smokers of low smoking intensity [2,3].

Recently it has been shown that mutations in the epidermal growth factor receptor genes (EGFR) are common in adenocarcinoma developed in East Asian non-smoking women. Smoking was not associated with EGFR-mutation lung cancer, but strongly associated with EGFR-wild-type lung cancer [4]. This finding may partially explain lower relative risks of smoking for lung cancer among Japanese and East Asian populations. Carcinogenetic process of smoking could be investigated through these analyses and that of radiation exposure might be, too.

- 1) Sakata R, et al. *BMJ*, 2012;345:e7093.
- 2) Furukawa K, et al. *Radiat Res*, 2010;174:72-82.
- 3) Egawa H, et al. *Radiat Res*, 2012;178:191-201.
- 4) Matsuo K, et al. *Cancer Sci* 2007;98:96-101.

(6) Radiosensitivity and radiotherapy patients

Michel Bourguignon

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Abstract- In a pragmatic clinical approach of the individual response to ionizing radiation (IR) in patients (Foray et al., 2016), three abnormal situations can be identified or envisaged: complications and undesirable side effects of radiotherapy with no error in dose delivery which affect the quality of life of patients, cancer proneness and degenerative diseases after exposures to IR. For the sake of clarity we have named the corresponding individual status radiosensitivity, radiosusceptibility and radiodegeneration respectively. This presentation deals with “Radiosensitivity and radiotherapy”.

Radiosensitivity was identified at the beginning of the XXth century but has been forgotten since. A first major classification of human diseases exhibiting radiosensitivity has been made on the basis of the cell survival fraction in vitro after exposures to IR (Deschavanne and Fertil, 1981). Radiosensitivity is clearly related to an excess of cell death after exposure even though the tissue response is important as well in vivo. All these diseases have a genetic component and about 70% of them concern a gene/protein directly involved in the DNA damage response (DDR), the most severe disease being related to mutated ATM^{-/-} in ataxia telangiectasia and the least severe with various heterozygous status. The other 30% are composed of genetic disease, mostly neuro-degenerative diseases with some degree of immunologic deficiency, where the abnormal gene/protein is not related to DDR. All these diseases account for about 5% of the population, ATM^{+/-} accounting by itself for 1.5% of the population.

Cohorts have been constituted with hundreds of patients exhibiting clinical radiosensitivity, e.g., the Copernic cohort (Granzotto, 2016) and most of them do not have the genetic diseases mentioned above since these patients are usually not treated by radiotherapy. Thus the status of radiosensitivity is observed in more than 5% of patients treated by radiotherapy and may reach up to 15 or 20 % if all grades from 2 to 4 (as classified by radiation oncologists with the EORTC or CTCEA scales) are included. These grades demonstrate some continuity between normality and severe syndromes.

Clonogenic survival, cytogenetic, DSB repair and gene expression assays have been proposed to predict radiosensitivity but these tests are difficult to use in routine practice mostly because of the delay in response. Among the most recent assays, CD8 T-lymphocyte apoptosis has been proposed to predict late toxicity after radiotherapy (Azria et al., 2015) but the inverse correlation with IR dose is surprising and still not understood. Gene expression assay of CDKN1A is also promising to identify severe early radiation toxicity (Finnon et al., 2012). Numerous immunofluorescence assays are nowadays available and allow to follow the cell kinetics of proteins in space (cytoplasm/nucleus) and time and thus to perform cell functional assessment. The kinetics of ATM has been modelled and it appears that the aforementioned neuro-

degenerative diseases exhibit an absence or a delay of translocation of ATM from the cytoplasm where it resides as dimers in the direction of nucleus as pATM monomers after exposure to IR (Granzotto, 2016). In the absence or delayed appearance of pATM in the nucleus the DNA DSBs are not properly repaired and this is the first time that a second clear mechanism of radiosensitivity, i.e., an indirect abnormal DDR is identified. Subsequently a pATM ELISA assay has been successfully developed in skin fibroblasts and lymphocytes for clinical use (Pereira et al., 2018).

At this stage it appears that radiosensitivity is clearly a public health issue since about 10 millions of patients benefit from radiotherapy worldwide every year and certainly more than 500,000 of them have a durable altered quality of life after their treatment. In order to progress in the prediction of radiosensitivity with the hope to avoid such poor clinical outcomes an international collaboration is necessary. Cross comparisons of assays in the different international cohorts of patients are certainly a good way to make significant progress and thus should be initiated.

Finally, about 8% of patients treated for cancer by radiotherapy exhibit a second cancer (Cosset et al., 2018). Although the issue is to know if it is a secondary cancer or a second primary cancer, these patients may be radiosusceptible and such a status of cancer proneness need to be explored in the future with pertinent biomarkers.

In conclusion, radiosensitivity, radiosusceptibility and radiodegeneration are key issues of the individual response to ionizing radiation and need to be addressed by the ICRP TG 111.

Main references

-Deschavanne PJ and Fertil B. A review of human cell radiosensitivity in vitro. *Int J Radiat Oncol Biol Phys.* 1996; 34(1):251-66

-Foray N, Bourguignon M, Hamada N. Individual response to ionizing radiation. *Mutation Research* 770 (2016) 369–386

-Granzotto a. et al. Influence of Nucleoshuttling of the ATM Protein in the Healthy Tissues Response to Radiation Therapy: Toward a Molecular Classification of Human Radiosensitivity. *Int J Radiation Oncol Biol Phys*, 2016, 94: 450-460

-Pereira S. et al. Fast and Binary Assay for Predicting Radiosensitivity Based on the Theory of ATM Nucleo-Shuttling: Development, Validation, and Performance. *Int J Radiation Oncol Biol Phys*, 2018, 100: 353-360

(7) Individual difference of chromosome aberration in accidentally exposed workers

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Abstract- Ionizing radiation exposure causes DNA strand breaks that lead to chromosome aberrations. Among radiation-induced chromosome aberrations, dicentric chromosomes have been considered sensitive and specific bio-indicators for assessing radiation dose. The dicentric chromosome assay (DCA) has been the ‘gold standard’ for biological dosimetry in accidental radiation exposure for more than three decades. A dicentric yield from a radiation-exposed patient is referred to a calibration curve (dose–response curve) experimentally prepared in advance from dicentric scoring data at several dose points from peripheral blood samples of one healthy donor or by pooling scoring data from several donors in considering inter-individual variability. In the latter cases, Van Buul and Natarajan (1980) and Kakati et al. (1986) noted a remarkable inter-individual variability. On the other hand, some reports showed moderate or no significant inter-individual variability so that data of all donors could be pooled (Vinnikov and Maznyk 2013; Al-Hadyan et al. 2014).

Recently, the translocation analysis combined with fluorescence *in situ* hybridization (FISH) using differentially colored chromosome painting probes are also applied for biological dosimetry. This technique is useful particularly for retrospective dose assessment because translocations are more stable, allowing dose estimates to be made long time after exposure or after protracted exposures. It is well-known, however, that the background levels of translocations increase with age due to confounding factors (Sigurdson et al., 2008). Inter-individual variability of translocation yields could be larger than that of dicentric yields.

In the present session, current issues concerning inter-individual variability of chromosome aberration yields will be demonstrated and discussed.

(8) Individual difference of post irradiated antitumor effect and lung damage in patients with lung cancer

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Abstract- In the treatment of lung cancer, radiotherapy is one of the important therapies, despite its sometimes unpredictable side effects. Stereotactic body radiotherapy (SBRT) is a highly dose concentrated radiotherapy technique which can spare normal organ dose much more than conventional radiotherapy technique. Severe radiation pneumonitis (RP) after stereotactic SBRT for the patients with early stage primary lung cancer is generally rare toxicity but sometimes gets to be severe adverse effect. It is important but has not been achieved to predict patients who are at high risk of developing severe RP and its monitoring techniques. Therefore, identifying lung cancer patients who are at high risk of developing severe RP and applying effect intervention or monitoring techniques are important. Although human diversity to a certain amount is explained by clinical and dosimetric factors, the presence of specific genetic variants also influences the occurrence of radiation-induced damage.

In our multi-institutional study to search reliable biologic markers to predict the risk of RP after SBRT, we investigated the association between single nucleotide polymorphisms (SNPs) in inflammation-related genes and risk of radiation pneumonitis (RP) in the patients with stage I non-small-cell lung cancer (NSCLC) treated by SBRT. Using genomic DNA samples from totally 223 patients with stage I NSCLC treated by SBRT were acquired and genotyped 21 SNPs of inflammation-related genes by mainly MassARRAY system to detect the difference in the mass of nucleotides. In the result, grade ≥ 2 RP and inflammatory shadow outside of the irradiated volume were observed in 36 (16.1%) and 34 (15.2%), respectively. Multivariate analysis found a history of heart failure or steroid administration, the ratio of volume irradiated 10Gy or more in the total normal lung volume (V10), and genotypes of EGFR (rs11543848) to be significantly higher risk factors of grade ≥ 2 RP combined with inflammatory shadow outside of the irradiated volume. When excluding six cases with a history of steroid administration, only genotype of EGFR (rs11543848) was a significantly higher risk factor of grade ≥ 2 RP combined with inflammatory shadow outside of the irradiated volume. Though Replication studies with more patients are required to validate these results, the showed that the SNP with genotypes of EGFR might be a higher risk of severe RP in patients with NSCLC treated with SBRT.

In my presentation, the individual or racial difference of the ratio of RP and relationship of EGFR to post irradiation pneumonitis would be discussed.

(9) Individual variation in clinical practices and protocols

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Abstract- Justification in radiological protection of patients in clinical practices is different from justification of others, in that the very same person enjoys the benefits and suffers the risks associated with that particular radiological examination. The particular application of the examination should be judged to do more good than harm to the individual patient if properly optimized.

Imaging protocols are prepared for typical purposes or demands of the examination in each hospital, and an appropriate protocol for each examination is assigned by consensus of the referral physician and the radiologist. Tube current and voltage is adjusted and modulated to suit the body thickness of each patient. It is recommended prepare special protocols for pediatric and young patients, who are considered to be smaller in body size and more radiosensitive than the older patients. Tube current would be modified referring to some attributions of the patients, such as prognosis, expected life, planned therapy, past history (especially of the radiosensitivity syndromes such as ataxia telangiectasia), because these factors would affect the risk-benefit balance of the individual patient, although such modification tends to be subjective and not reproducible. Establishment of the system for objective and reproducible modification of the parameter of exposure should be warranted for further individualized patient care.