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Review

Precision Radiotherapy and Radiation Risk Assessment: How Do We Overcome Radiogenomic Diversity?

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Precision medicine is a rapidly developing area that aims to deliver targeted therapies based on individual patient characteristics. However, current radiation treatment is not yet personalized; consequently, there is a critical need for specific patient characteristics of both tumor and normal tissues to be fully incorporated into dose prescription. Furthermore, current risk assessment following environmental, occupational, or accidental exposures to radiation is based on population effects, and does not account for individual diversity underpinning radiosensitivity. The lack of personalized approaches in both radiotherapy and radiation risk assessment resulted in the current situation where a population-based model, effective dose, is being used. In this review article, to stimulate scientific discussion for precision medicine in both radiotherapy and radiation risk assessment, we propose a novel radiological concept and metric – the personalized dose and the personalized risk index – that incorporate individual physiological, lifestyle-related and genomic variations and radiosensitivity, outlining the potential clinical application for precision medicine. We also review on recent progress in both genomics and biobanking research, which is promising for providing novel insights into individual radiosensitivity, and for creating a novel conceptual framework of precision radiotherapy and radiation risk assessment.

Keywords: biobank; genomics; precision medicine; radiation risk; radiotherapy
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Background

In 2015, US President Barack Obama announced the Precision Medicine Initiative in his State of the Union address (Ashley 2015), creating US$215 million in research funding to advance individualized healthcare, of which $70 million was allocated to the National Cancer Institute as part of the Cancer Moonshot Initiative (Tannock and Hickman 2016). Precision medicine is a powerful emerging approach with the potential to revolutionize disease prevention, diagnosis and treatment by taking into account specific differences in individuals' genetic, lifestyle-related, and environmental factors (McGrath and Ghersi 2016). However, the potential for precision medicine to improve radiotherapy remains at an early stage of development. In the specific context of dose estimation for both environmental and therapeutic radiation exposures, current empirical models, such as the concept of the effective dose, consider only the type of radiation (*e.g.*, X-rays, α-particles, and neutrons) and the characteristics of each exposed organ or tissue, without taking into account any individual genetic contribution to an individual's response (McCollough and Schueler 2000). Although the target of contemporary medical approaches is dramatically changing from the "average person" to "each person," when it comes to radiation protection and radiotherapy, this approach has not yet enjoyed widespread implementation. This delay may result in not only inaccurate risk assessment from accidental exposures but also in the prescription of sub-optimal radiotherapy treatment schedules that could be further improved through individualized treatment planning, dose escalation and de-escalation and altered fractionation.

In March 2011, the northeastern part of Japan was devastated by the triple disasters of an earthquake, a resulting tsunami and a consequent accident at the Fukushima Daiichi Nuclear Power Plant (FNPP). These events have continued to have major societal impacts on the area, including diverse radiation-related issues (Dauer et al.

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2011; Ten Hoeve and Jacobson 2012; World Health Organization 2013; United Nations Scientific Committee on the Effects of Atomic Radiation 2015). Previous statistical data based on population cohorts estimate that the long-term risk of cancer from radiation exposure will increase at least at doses exceeding 100 mGy (Pernot et al. 2012; Hall et al. 2017). Thus, according to the Fukushima Health Management Survey, personal dosimeters (for external exposure) and whole-body counters (for internal exposure) were used after the nuclear disaster to measure radiation exposure levels, which were used as the sole criterion in evaluating risk amongst local residents (Yasumura et al. 2012). However, individuals want to know their personalized radiation-induced health risk, not to be informed that the effective dose to their population group does not provide a measure of their personal risk. For accurately assessing the long-term environmental and health impacts of the FNPP accident, novel approaches for the precise estimation of radiation exposure and risk assessment at the individual level are needed; they must integrate the subject-specific variations in physiological, lifestyle and genomic factors that underpin responses to radiation exposure (Fukunaga and Yokoya 2016).

As radiation treatments become more effective and a growing number of individuals are living longer, the importance of accurate long-term risk assessment is increasing significantly. The risk of second cancer can be reduced not only by physical measures to lower radiation doses to normal tissues but also by biological means that interfere with the critical determinants of radiation-induced carcinogenesis (Imaoka et al. 2016). A 2011 cohort study showed that a relatively small proportion of secondary cancers are related to radiotherapy in adults, suggesting that most are due to other factors like lifestyle or genetics (Berrington de Gonzalez et al. 2011). However, our understanding of individual risk assessment during or after radiotherapy remains incompletely understood due to the limitation of population-based models, such as effective dose. For accelerating precision radiation oncology, novel approaches are needed that integrate subject-specific variations in physiological, lifestyle and genomic factors that underpin adverse effects following radiotherapy.

Differences between environmental and clinical radiation exposure scenarios include physical parameters such as radiation type, dose, dose-rate and irradiated time-scales (see Fig. 1). Environmental radiation exposure is continu-

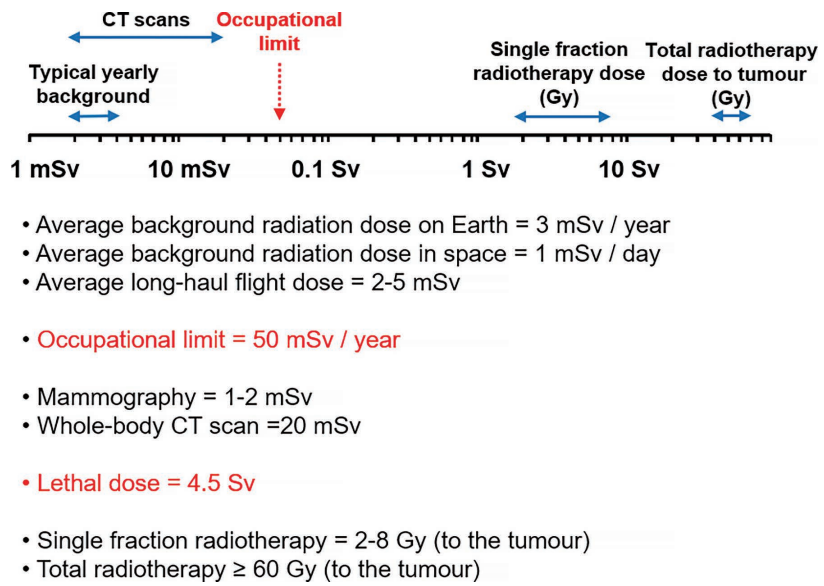

Fig. 1. Radiation dose ranges from natural background to therapeutic levels.
There are wide differences between natural background and therapeutic radiation dose ranges. The majority of background radiation occurs naturally from minerals and a small fraction comes from man-made elements. Naturally occurring radioactive minerals in the ground, soil, water and air produce background radiation, as does cosmic radiation from outer space. There can be large variances in natural background radiation levels from place to place, as well as changes in the same location over time but average background radiation levels are around 3 mSv. A small fraction of background radiation comes from human activities. Trace amounts of radioactive elements have dispersed in the environment from nuclear weapons tests and nuclear power plant accidents. Radiation exposures from diagnostic medical examinations are generally low (< 20 mSv) and are almost always justified by the benefits of accurate diagnosis of possible disease conditions. Therapeutic uses of radiation involve higher exposures and physicians need to consider the risks of the treatment against the potential benefits, but modern radiotherapy approaches deliver these as series of fractions of ~ 2 Gy, targeted to the tumor. The SI absorbed dose unit is the gray (Gy), which is defined as one joule of energy absorbed per kilogram of matter. As a physical quantity, the absorbed dose is not a satisfactory indicator of biological response, which may be driven by many additional factors. The SI unit for effective dose is the sievert (Sv), which currently represents, among the whole population, a 5.5% probability of developing cancer, weighted for detriment (ICRP 2007).

ous or intermittent over a long period of time, whilst in medical exposures, parts of the body are exposed to a large amount of radiation in a short period of time for diagnosis or treatment. However, in both medical and environmental radiation exposure scenarios, the same population-based concept, namely effective dose, is being used for radiological protection. This dosimetric quantity recommended by the International Commission on Radiological Protection (ICRP) is computed by age- and sex-averaging, and thus the estimates of fatality and detriment coefficients should not apply to specific individuals (ICRP 2007).

Several radiogenomic studies have recently determined that individual variation in radiosensitivity is greater than expected, suggesting that conventional approaches to radiotherapy and radiation risk assessment are insufficient. Work in this area focuses on uncovering the underlying genomic causes of individual variation in radiosensitivity, which is of clinical importance (West and Barnett 2011). In fact, genome-wide association studies (GWAS), which investigate the association between single nucleotide polymorphisms (SNPs, the independent variable) and a phenotype of interest (the dependent variable) (Carter et al. 2017), were performed for personalized prediction of radiotherapy-induced second cancer risk. In 2011, GWAS data indicated that variants at 6q2 (rs4926728 and rs1040411) are strongly associated with risk for second malignant neoplasms after radiation treatment for Hodgkin's lymphoma in childhood (Best et al. 2011). Furthermore, for survivors who received 10 or higher Gy breast radiation exposure in childhood, a locus on 1q41 was associated with subsequent breast cancer risk (rs4342822, hazard ratio = 1.92, 95% confidence interval = 1.49 to 2.44, $P = 7.09 \times 10^{-9}$), and two rare variants also showed potentially promising associations (breast radiation $\geq$ 10 gray: rs74949440, $P = 5.84 \times 10^{-8}$; < 10 gray: rs17020562, $P = 6.68 \times 10^{-8}$) (Morton et al. 2017).

In response, our approach has been to develop a radiological concept by incorporating physiological, lifestyle and genomic variations into current empirical models (Fukunaga et al. 2016). In this article, we outline a novel radiological concept and metric called the "personalized dose" and "personalized risk index," respectively, and explore their utility for precision radiotherapy and radiation risk assessment.

Personalized Dose and Personalized Risk Index

Concept of effective dose and its limitation

In 1975, the effective dose concept was first developed by Jacobi (1975); it has since been established as a key measurement for assessing risks of the stochastic effects of radiation exposure and dose exposure limits by the ICRP (2007).

Ionizing radiation deposits energy directly into the matter being irradiated. The quantity used to express this energy is the absorbed dose, a physical dose quantity that depends on both the level of incident radiation and the absorption properties of the irradiated object. The SI absorbed dose unit is the gray (Gy), which is defined as one joule of energy absorbed per kilogram of matter. As a physical quantity, the absorbed dose is not a satisfactory indicator of biological response, which may be driven by many additional factors. To allow for the consideration of stochastic radiological risk (*e.g.*, carcinogenesis, hereditary effects), the dose quantity's equivalent dose and the effective dose were devised by the ICRP and the International Commission on Radiation Units and Measurements (ICRU) to estimate the biological effectiveness of a given absorbed dose. The SI unit for effective dose is the sievert (Sv), which currently represents, among the whole population, 5.5% probability of developing cancer, weighted for detriment (ICRP 2007). The effective dose accounts for the type of radiation and the characteristics of each organ or tissue being irradiated, because different organs in the human body have different radiosensitivities (Barnett et al. 2009). As shown in Fig. 1, the average annual effective dose from background radiation is around 3 mSv, while the typical effective doses of radiological and nuclear medical examinations are as follows: standard radiographic examinations (0.01-10 mSv), computed tomographic examinations (approximately 2-20 mSv), interventional radiological procedures (5-70 mSv) and most nuclear medicine procedures (0.3-20 mSv) (Mettler et al. 2008).

The concept of effective dose does not provide an individual-specific dose but uses a reference person for a given exposure situation. Furthermore, it does not take into consideration the genomic diversity of individual radiosensitivity, so it is not appropriate for estimating individual radiation-induced health risks for population members. In fact, as explained in *ICRP Publication 103*, effective dose is a risk-adjusted quantity for the control of exposures; it was not intended to be a measure of risk (ICRP 2007). It is calculated using reference phantoms for the purpose of enabling the summation of doses from all radiation exposures for comparison with limits, constraints and reference levels (set in the same quantity) and for the optimization of protection. Implicit in its use is the central assumption of a linear, non-threshold (LNT) dose-response relationship between dose and risk, a reasonable assumption for protection purposes but not proven for low doses. A single set of tissue weighting factors is used in the calculation of effective dose, despite previously recognized differences in the age and sex dependence of the relative contributions of cancer types to overall detriment and, crucially, in the overall magnitude of cancer detriment. Therefore, current radiological protection is achieved for members of the public using effective dose criteria that apply across populations (*i.e.*, optimization below 1 mSv limit for planned situations), although there are clear differences in risk per Sv between, for example, a three-year-old female and a 75-year-old male.

Concept of personalized dose and personalized risk index

As Fig. 2 shows, we propose a novel radiation dose concept, "the personalized dose," which can be calculated from the effective dose to the entire organism and by a personalized risk index that is composed of physiological, lifestyle and genomics factors. A multivariable predictive model including such factors could be used to classify individuals based on their own personal radiation risk.

Physiological factors, such as age, sex and DNA repair-deficiency, are clearly important in estimating the biological effects induced by exposure to radiation. It is true that DNA repair-deficiency patients and carriers are relatively rare, but they should not be ignored (Health Protection Agency 2013). In fact, a number of adverse reactions to radiation therapy have been observed in individuals suffering from DNA damage response-defective disorders, such as ataxia telangiectasia (A-T), Nijmegen breakage syndrome, Fanconi anemia (Pollard and Gatti 2009). These patients and other heterozygous carriers can be associated with both radiation hypersensitivity and predisposition to cancer, although the underlying mechanisms of radiation-induced carcinogenesis in these individuals remains to be determined (Jongmans and Hall 1999). According to a systematic review in 2016, A-T carriers with heterozygous mutations in the ataxia telangiectasia-mutated (*ATM*) gene have a reduced life expectancy because of mortality from cancer and ischemic heart diseases (relative risk [RR] 1.7, 95% confidence interval [CI] 1.2-2.4) and an increased risk of developing cancer (RR 1.5, 95% CI 0.9-2.4), especially breast cancer (RR_{women} 3.0, 95% CI 2.1-4.5) (van Os et al. 2016). It is true that A-T is a rare disease with a frequency of ~1/40,000, but heterozygous carriers are hardly rare, with a frequency of ~1/100 (Watts et al. 2002). In addition, lifestyle factors, such as weight (Ector et al. 2007), diet (Sauvaget et al. 2004; Cardis et al. 2005), drug (Wardman 2007), smoking (Furukawa et al. 2010; Grant et al. 2012), pregnancy (Land et al. 1994), and childbirth (Land et al. 1994), can also modify the adverse effects induced by exposure to radiation. To estimate individual radiation risk precisely, we should consider not only the delivered dose but, at a minimum, these non-genomic risk factors.

The field of radiogenomics seeks to identify the link between genomic biomarkers and clinical variability in response to radiotherapy, with a view to predicting an individual's response to and toxicity of radiation therapy. Precision medicine relies on validated biomarkers with which to classify patients more accurately by their probable disease risk, prognosis, or response to treatment (Vargas and Harris 2016), so the clinical application of radiogenomics is highly promising for precision radiotherapy. The main approach used in radiogenomic analysis is the GWAS. For instance, the first GWAS for identifying the SNPs associated with erectile dysfunction (ED) among

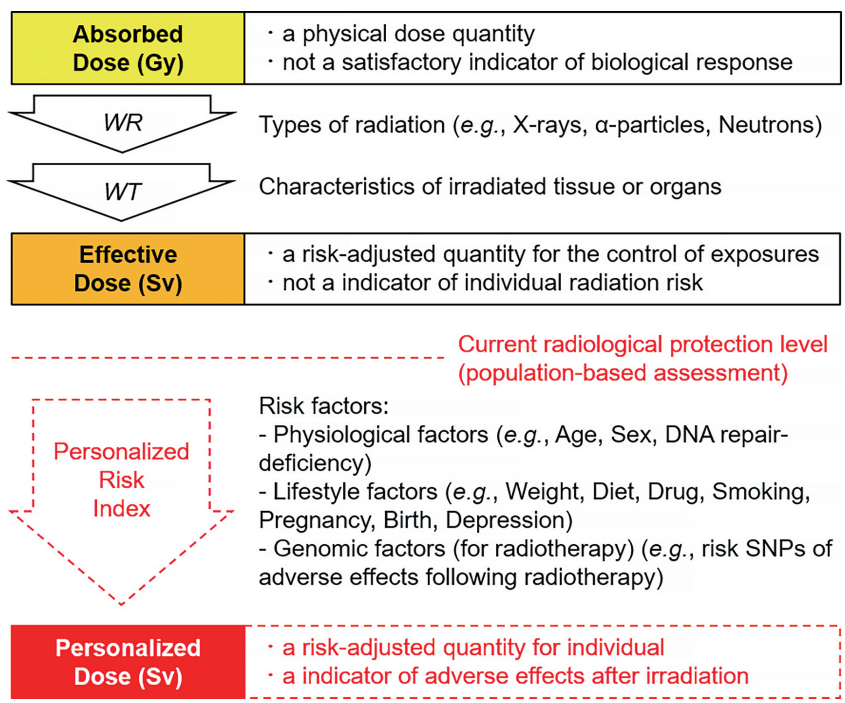

Fig. 2. Conceptual development of personalized dose.
The current concept of radiological protection, effective dose, takes into account only the absorbed dose, the radiation type using factor (*WR*) and the tissues or organs being irradiated using factor (*WT*). The novel concept, personalized dose, also takes into account the the physiological (*e.g.*, Age, Sex, DNA repair-deficiency), lifestyle (*e.g.*, Weight, Diet, Drug, Smoking, Pregnancy, Birth, Depression) and genomic factors (*e.g.*, risk SNPs of adverse effects following radiotherapy) that determine the personalized risk index. Genomic factors are especially suitable for predicting adverse effects following radiotherapy. The SI unit for personalized dose is the sievert (Sv).

African American prostate cancer patients treated with external beam radiation therapy showed that SNP rs2268363, located in the follicle-stimulating hormone receptor (*FSHR*) gene, was significantly associated with ED after correcting for multiple comparisons (odds ratio [OR] 7.03, 95% CI 3.4-14.7, unadjusted P value = 5.46×10^{-8}; Bonferroni P value = 0.028). These researchers also identified four additional SNPs that tended toward significant association (unadjusted P value < 10^{-6}) (Kerns et al. 2010). We must take such radiogenomic data into consideration to construct the multivariable predictive model, the personalized risk index.

Practice of personalized dose and personalized risk index

What people want to know is their own individual risk after accidental irradiation, such as occurred in the 2011 Fukushima nuclear disaster; however, they cannot access this vital information because the current effective dose for their population group does not provide a measure of their own individual risk. Since the diversity of individual radiosensitivity is significant, to precisely consider personalized radiation risk a converter from effective dose to inferred risks is needed for clinical practice. The personalized dose and the personalized risk index may enable us to assess individuals' radiation risks. For example, when a young female is accidentally exposed to just 20 mSv radiation, if her personalized risk index score is estimated at ~5-6 due to age, sex and mutations in DNA damage response genes, her personalized dose will be ~100-120 mSv, so her radiation risk is comparable to the risk of 100 rather than 20 mSv in terms of effective dose at the population level. As noted above, previous statistical data based on population cohorts estimate that the long-term risk of cancer from radiation exposure increases as a function of dose at least at doses exceeding 100 mGy (Pernot et al. 2012; Hall et al. 2017). However, to minimize future health risks following accidental irradiation such as radiation-related cancer risk, our young female can, as she matures, select appropriate medical checkups for cancer, such as ultrasonography, gastrointestinal endoscopy, measurements of tumor markers in blood and urine, and genetic testing, all combined in a balanced fashion. It is true that the concepts of personalized dose and personalized risk index that we have proposed are not perfect models in predicting long-term, radiation-induced health risk; however, this kind of personalized approach is important for precision radiation risk assessment.

We have also noticed that in radiotherapy, while the absorbed dose is currently used to assess the estimation of dose to tumor, a personalized dose would be useful to assess the possibility of adverse effects, including secondary cancer risk, to surrounding normal tissues during or after the course of treatment. There are relatively rare genomic variants that might produce enhanced risk of radiation injury and might differ in terms of what a specific variant would mean for different tissues. In that case, a personalized risk index would be useful as a screening panel for precision radiotherapy, because a specific personalized risk index for a certain organ would enable us to estimate more precisely the organ-specific adverse effects and toxicity following radiotherapy.

Radiogenomics for the Clinical Application of Personalized Risk Index

Candidate gene biomarkers associated with individual radiosensitivity

Several radiation oncological studies have aimed to understand the characteristics of tumor radiosensitivity. Radiobiological mechanisms that determine the resistance or sensitivity of tumors to fractionated radiotherapy include the number and intrinsic radiation sensitivity of cancer stem cells, tumor hypoxia and reoxygenation during treatment, repopulation between radiotherapy fractions and redistribution of surviving, cycling cells after a radiation-induced cell cycle blockade (Baumann et al. 2016).

More geometric and anatomical precision approaches have been employed in an effort to address the biological heterogeneity characteristic of cancer and to improve radiotherapy outcomes (Caudell et al. 2017). Pathological approaches also have potential; for example, immunochemical expression of p16 (INK4A) which is associated with the human papillomavirus (HPV) infection, has an impact on treatment response and survival in patients with head and neck cancer treated with radiotherapy (Lassen et al. 2009). According to a single-arm, phase 2 study in 2017 (Chen et al. 2017), chemo-radiotherapy for HPV-associated squamous-cell carcinoma of the oropharynx with radiation doses reduced by 15-20% was associated with high progression-free survival and an improved toxicity profile compared with historical regimens using standard doses. In addition, genomic approaches are developing gene signatures of tumor radiosensitivity; for example, the gene expression-based radiation sensitivity index and the linear quadratic model used to derive the genomic-adjusted radiation dose (GARD) has shown the potential to predict clinical outcomes in breast cancer, lung cancer, glioblastoma and pancreatic cancer (Scott et al. 2017). In 2016, high-throughput gene expression techniques and clinical and genomic databases were used to develop and validate a 24-gene expression signature (the Post-Operative Radiation Therapy Outcomes Score or PORTOS) that predicts response to post-prostatectomy radiotherapy in matched training and validation cohorts of patients with prostate cancer (Zhao et al. 2016). The study showed that patients with high PORTOS had a lower incidence of distant metastasis than patients with low scores (Zhao et al. 2016).

However, the pathways and biological processes of normal tissue, which underpin radiation response at the individual level, remain to be fully defined. Most previous radiation studies, such as those on rare genetic disorders (Baple et al. 2014; Toss et al. 2015; Yokote et al. 2017), risk

genomic aberrations such as SNPs, copy number variations (CNVs) and insertions and deletions (INDELs) associated with adverse effects of radiation therapy (Zhang et al. 2010; Yin et al. 2011, 2012; Edvardsen et al. 2013; Tang et al. 2016) and radiation-induced biological response studies (Hei et al. 2008; Prise and O'Sullivan 2009; Blyth and Sykes 2011), have used a candidate gene approach to investigate potential genetic biomarkers that correlate with radiation hypersensitivity. Furthermore, several recent oncological studies have shown the clinical importance of interaction between the tumor and the host immune system, and therapeutic attempts to activate the host immune system to kill tumor cells have shown some clinical efficacy (Mouw et al. 2017). In fact, several groups have reported improved local control and distant disease control when checkpoint blockade immunotherapy is added to radiation in different tumor types (Sharabi et al. 2015). Systematic responses to radiation detected at the blood proteome and metabolome levels are also related to the intensity of radiation-induced toxicity, including inflammatory responses (Jelonek et al. 2017). These results indicate that some immune responses contribute radiation-induced carcinogenesis and individual radiosensitivity.

As Fig. 3 shows, according to some systemic reviews on candidate gene biomarkers (Andreassen and Alsner 2009; Rattay and Talbot 2014), we re-summarized a number of key radiation-induced cellular responses and candidate gene biomarkers for consideration, from cell to whole-body levels: Oxidative stress response genes (*e.g., GSTA1, GSTP1, TXNRD2*, and *SOD2,* encoding glutathione S-transferase A1 (GSTA1), glutathione S-transferase P1 (GSTP1), thioredoxin reductase 2 (TXNRD2), and superoxide dismutase 2 (SOD2), respectively), DNA damage response genes (*e.g., TP53, ATM, ATR, BRCA1/2, RAD51, WRN, LIG4, PTEN, XRCC1, PCNA, MGMT*, and *MSH3*, encoding P53, ataxia-telangiectasia mutated, ataxia-telangiectasia and Rad3-related protein (ATR), breast cancer type 1/2 susceptibility protein (BRCA1/2), RAD51, WRN, DNA ligase 4 (LIG4), phosphatase and tensin homolog (PTEN), X-ray repair cross-complementing protein 1 (XRCC1), proliferating cell nuclear antigen (PCNA), O-6-methylguanine-DNA methyltransferase (MGMT), and MutS homolog 3 (MSH3)), cellular response/bystander signaling genes (*e.g., TNF, TGFβ1, VEGF*, and *SMADs*, encoding tumor necrosis factor, transforming growth factor beta 1 (TGFβ1), vascular endothelial growth factor (VEGF), and SMADs) and immune response genes (*e.g.*, *IL6, IL8, IFNβ, STING*, and *IRF3,* encoding interleukin 6, 8, interferon beta, transmembrane protein 173 (TMEM173), and interferon regulatory factor 3).

Radiogenomic approach for determining specific personalized risk index

While candidate gene approaches have made a certain amount of progress, they have largely been unsuccessful at identifying robust biomarkers of radiosensitivity at the individual level, because of the lack of an integrated understanding of individual radiosensitivity (Andreassen and Alsner 2009). Normal tissue toxicity following radiotherapy varies among cancer patients, based on clinical observations of patients with severe adverse effects. The characterization of this radiosensitivity in patients requires caution, as the risk of developing a particular normal tissue reaction depends to a considerable degree on the target organ (Herskind et al. 2016). In addition, radiation research has shown that some DNA repair-related genes show organ- and tissue-specific expression (Chao and Lipkin 2006; Dion 2014). Taken together, these realities indicate that we should be aware that challenges with regard to the specificity of radiosensitivity are a significant limitation of the candidate gene approach.

Recognizing the shortcomings of previous approaches and coincident with advances in genotyping technology, recent research has shifted toward broader, genome-wide approaches such as GWAS to exhaustively identify specific genetic risk factors in a specific cancer patient treated with radiotherapy. In fact, a 2016 meta-analysis from four major cohort reports (RAPPER (Burnet et al. 2006), RADIOGEN (Rosenstein et al. 2014), Gene-PARE (Ho et al. 2006) and CCI cohorts (Kerns et al. 2013)) showed specific risk SNPs of late toxicity following radiotherapy for prostate cancer, four SNPs associated with the increase of rectal bleeding (rs141044160 on 23q23, rs6999859 on 8q21.13, rs360071 on 1q42.12, and rs7432328 on 3p26.1), eight SNPs with urinary frequency (rs17599026 on 5q31.2, rs11574532 on 12q13.13, rs7366282 on 1q41, rs4534636 on 12p13.31, rs8098701 on 18q21.1, rs10101158 on 8q24.3, rs10209697 on 2q36.1, and rs7356945 on 6p24.1) and eight SNPs with decreased stream (rs7720298 on 5p15.2, rs17362923 on 8p23.2, rs76273496 on 1q31.3, rs2203205 on 23q21.1, rs141342719 on 5q23.3, rs673783 on 18p11.32, rs62091368 on 18p11.32, and rs144596911 on 3q28) (Kerns et al. 2016). Furthermore, three SNPs reached genome-wide significance: rs17599026 on 5q31.2 with urinary frequency (OR 3.12, 95% CI 2.08-4.69, P value = 4.16×10^{-8}), rs7720298 on 5p15.2 with decreased urine stream (OR 2.71, 95% CI 1.90-3.86, P value = 3.21×10^{-8}) and rs11230328 on 11q12.2 with Standardized Total Average Toxicity score (Barnett et al. 2012) (Beta 0.31, 95% CI 0.21-0.41, P value = 6.27×10^{-10}) (Kerns et al. 2016). In combination with physiological and lifestyle factors, a prostate cancer radiotherapy-specific personalized risk index can be estimated by these genomic factors, which will enable us to more precisely predict adverse effects for prostate cancer patients treated with radiotherapy (Fig. 3). This radiogenomic approach to specific cancer patients can provide strong evidence to improve our understanding of adverse effects following radiotherapy.

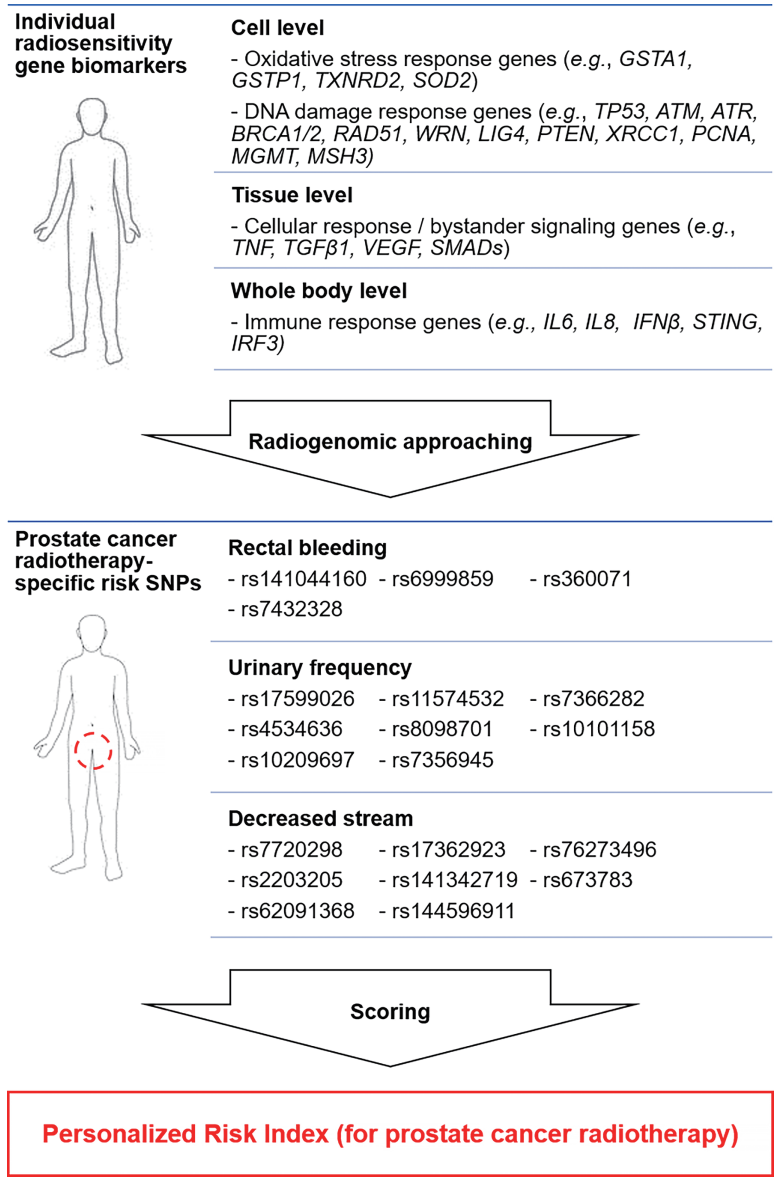

Fig. 3. Development of prostate cancer-specific personalized risk index.

According to several previous candidate gene studies, a number of key radiation-induced cellular responses and candidate gene biomarkers have been reported:(Andreassen and Alsner 2009; Rattay and Talbot 2014) oxidative stress response genes (*e.g.*, *GSTA1, GSTP1, TXNRD2, SOD2*), DNA damage response genes (*e.g.*, *TP53, ATM, ATR, BRCA1/2, RAD51, WRN, LIG4, PTEN, XRCC1, PCNA, MGMT, MSH3*), cellular response/bystander signaling genes (*e.g.*, *TNF, TGFβ1, VEGF, SMADs*) and immune response genes (*e.g.*, *IL6, IL8, IFNβ, STING, IRF3*). The radiogenomic approach can select specific risk genomic aberrations associated with adverse effects of radiation therapy from a vast amount of candidate gene biomarker data. According to a meta-analysis of GWAS in 2016 (Kerns et al. 2016), specific risk SNPs of late toxicity following radiotherapy for prostate cancer are as follows: four SNPs associated with an increase in rectal bleeding (rs141044160 on 23q23, rs6999859 on 8q21.13, rs360071 on 1q42.12, and rs7432328 on 3p26.1), eight SNPs with urinary frequency (rs17599026 on 5q31.2, rs11574532 on 12q13.13, rs7366282 on 1q41, rs4534636 on 12p13.31, rs8098701 on 18q21.1, rs10101158 on 8q24.3, rs10209697 on 2q36.1, and rs7356945 on 6p24.1) and eight SNPs with decreased stream (rs7720298 on 5p15.2, rs17362923 on 8p23.2, rs76273496 on 1q31.3, rs2203205 on 23q21.1, rs141342719 on 5q23.3, rs673783 on 18p11.32, rs62091368 on 18p11.32, and rs144596911 on 3q28). By taking physiological and lifestyle factors into account, a multivariable predictive model—the prostate cancer radiotherapy-specific personalized risk index—can construct these genomic data.

GSTA1, glutathione S-transferase alpha 1; *GSTP1*, glutathione S-transferase Pi 1; *TXNRD2*, thioredoxin reductase 2; *SOD2*, superoxide dismutase 2; *TP53* tumor protein p53; *ATM*, ataxia telangiectasia mutated; *ATR*, ataxia telangiectasia and Rad3-related protein; *BRCA1/2*, breast cancer susceptibility gene 1/2: *LIG4*, DNA ligase IV; *PTEN*, phosphatase and tensin homolog; *XRCC1*, X-ray repair cross complementing 1; *PCNA*, proliferating cell nuclear antigen; *MGMT*, O6-methly-guanly-methyl-transferase; *MSH3*, MutS homolog 3; *TNF*, tumour necrosis factor; *TGFβ1*, transforming growth factor-*β*1; *VEGF*, vascular endothelial growth factor; *IL6*, interleukin 6; *IL8*, interleukin 8; *IFNβ*, interferon *β*; *STING*, stimulator of interferon genes ; *IRF3*, interferon regulatory factor 3.

Application of personalized risk index for precision radiotherapy

With radiotherapy, only a subset of any patient population will develop radiosensitivity-related normal tissue damage; however, little information is available to identify those individuals in advance. Furthermore, earlier searches for clinical biomarkers associated with radiotherapy toxicity were hindered by the use of multiple and different endpoints (such as acute radiation syndrome (Dörr and Meineke 2011), radiation pneumonitis (Huang et al. 2015), radiation dermatitis (Borghini et al. 2014), and radiation-related secondary carcinogenesis (Brenner et al. 2003)), which created confusion. Consequently, today's standard protocols are designed using doses that minimize the incidence of severe adverse effects, based on all patients (Kerns et al. 2014).

A screening panel that could identify high-radiation risk patients based on patient-specific factors would clearly enable more personalized treatment. One possible candidate for such a screening panel is a specific personalized risk index for each target organ, constructed out of clinical and radiogenomic databases. For example, as Fig. 4 shows, prostate cancer patients could be divided into sub-groups on the basis of their prostate cancer radiotherapy-specific personalized risk indices. High-risk patients could be selected for other non-radiation therapies or treated with a lower dose of radiation, while those with low radiation risks could receive higher doses than they would under standard protocols to increase the cure rate.

This type of screening for physiological, lifestyle and genomic variants that predispose patients to increased or decreased radiosensitivity would have unquestionable clinical utility. There are some difficulties of these concepts for clinical application. In an epidemiological cohort study of radiation, the researchers collected the data of the total radiation dose each participant was exposed to; however, it is technically difficult to have a clear grasp of their accurate irradiation situations, because of the lack of detailed exposure information (Fukunaga and Prise 2018). This is one of the possible technical limitations of the current epidemiological approach to radiation. Furthermore, there is no quantitative evidence regarding the extent of modification of radiation risk in human population by various physiological, lifestyle and genetic factors. Therefore, due to such

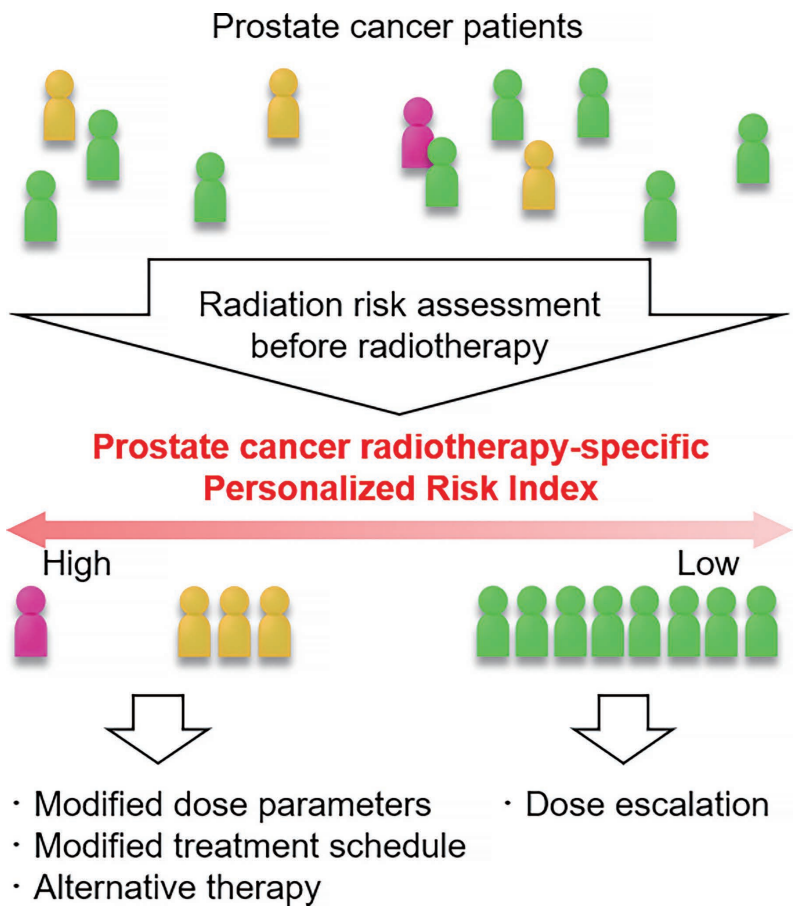

Fig. 4. Clinical application of prostate cancer radiotherapy-specific personalized risk index.
As a multivariable predictive model, the prostate cancer radiotherapy-specific personalized risk index could be used to classify prostate cancer patients according to the risk of developing adverse effects following radiotherapy. With clinical information such as the patient's will and tumor aggressiveness, sorting results could be used to modify treatment with maximal precision for each prostate cancer patient.

limitations, it should be very careful to bring our proposals into practice. However, for the realization of precision radiotherapy, a personalized radiation risk assessment before determining a course of radiotherapy is essential. We expect that the application of the personalized risk index we propose would make radiotherapy more efficient, improve the quality of care and provide better individual outcomes in the longer term.

Biobank Research for Radiogenomics

One major focus in the development of precision medicine is the assembly of a large cohort of individuals willing to share their electronic medical records, genomic data and biological specimens (Ashley 2015). Since biobanks are complex systems of systematically programmed storage of human material and associated data, research using biobanks has recently become an integral part of precision medicine (Kinkorová 2015). From the viewpoint of radiation research, the principle of connecting genomic data and radiation risk across cohorts is of significant interest. Most biological specimens from biobanks, such as patient-derived blood, biopsy specimens and induced pluripotent stem cells (iPSCs) (Shi et al. 2017), are potentially useful for the development of radiogenomics. The advancement of genetic technology (*e.g.*, a single-cell genome sequence (Haque et al. 2017)) will enable us to reduce the number of such samples needed for valid assessment.

In recent years, the number of biobanks has dramatically increased in support of industry and academic genomic research in disease prevention, prediction, diagnosis and treatment (Watson et al. 2010; Gaskell and Gottweis 2011; De Souza and Greenspan 2013; Olson et al. 2014; Chalmers et al. 2016). As Fig. 5 shows, large-scale biobanks have been established around the world, including the Kaiser Permanente (US), the BioVU (US), the Precision Medicine Initiative (US), the deCODE (Iceland), the UK Biobank (UK), the LifeGene (Sweden), the Estonian Biobank (Estonia), the China Kandoorie Biobank (China), the Korea Biobank Network (Korea) and the BioBank Japan (Japan). Thus, despite the fact that many biobanks deal with human samples and raise a number of ethical, legal and social issues (ELSI) (Budimir et al. 2011; Caulfield and Murdoch 2017), researchers today can access large numbers of samples for their own projects.

In a generally accepted classification, there are two types of biobanks: population-based (PB) and disease-oriented (DB) biobanks (Kinkorová 2015). The Delaware-based biotechnology company deCODE Genetics successfully partnered with the Icelandic Parliament (Althing) in 1998 to create and operate a centralized database of non-identifiable health data: the world's first PB biobank (Swede et al. 2007). The PB specimens would be useful for radiogenomics to assess the frequency of gene biomarkers and to estimate the radiogenomic diversity in a large population, if suitable genomic biomarkers could be further defined. Most of the large-scale biobanks around the world are PB types, while DB biobanks are limited (Nagai et al. 2017). The oldest large-scale DB biobank in the world, BioBank

Fig. 5. Large-scale biobanks around the world.
There are many biobanks around the world, from single-hospital to international facilities operating in both industry and academia. The number of large-scale biobanks has been dramatically increasing since the 1990s.

Japan, was launched in 2003; 200,000 patients were enrolled in the project (Nagai et al. 2017). DB biobanks allow for the novel identification of susceptibility genes for individual radiosensitivity because large numbers of radiation toxicity cases are registered. The DB specimens would thus be useful for examining radiation sensitivity and toxicity and for investigating the relationship between radiation risk and gene biomarkers.

A PB biobank in Japan, the Tohoku Medical Megabank (ToMMo), is collecting biospecimens such as blood and urine from approximately 150,000 Japanese participants who have given informed consent (Kuriyama et al. 2016). ToMMo has provided genomic data over the Internet, such as the Integrative Japanese Genome Variation Database (iJGVD, available at https://ijgvd.megabank.tohoku.ac.jp/) (Nagasaki et al. 2015; Yamaguchi-Kabata et al. 2015). Using the iJGVD, we recently studied genomic variations in individual radiosensitivity among a large population. Although the present sample size remains too small and needs to be expanded, the iJGVD clearly has potential for future innovations from the perspective of precision medicine (Fukunaga et al. 2017). Our previous study found that a large number of individuals have SNPs associated with the risk of developing radiation pneumonitis, indicating that radiosensitivity has a greater than expected genetic diversity (Fukunaga et al. 2016). Consideration of these patients and heterozygous carriers with other radiosensitivity disorders such as A-T have the potential to reveal a much wider than expected individual variation in radiosensitivity. This would have a significant impact on the radiation research field and would cause changes in current radiological protection concepts. There are several areas of research into precision radiotherapy that have been proposed as being key to advance the field, such as full image guidance, rapid automated generation of summed dose maps and specific biomarker profiles of tumors (Baumann et al. 2016); however, further results of both radiogenomic and biobank studies will place increasing clinical importance on radiation risk assessment at the individual level, such as the use of the personalized dose and personalized risk index.

Conclusion

In the era of precision medicine, we need a novel conceptual framework of radiotherapy and radiation risk assessment for individuals, such as the proposed "personalized dose" and "personalized risk index," that consider physiological, lifestyle and genomic factors. It is true that the underlying mechanisms of individual radiosensitivity remain unclear and quantification of the personalized risk index awaits complete definition. However, further advancements in radiogenomics and biobank research offer genuine promise for creating such novel conceptual models. We hope that our opinion pieces will stimulate scientific debate in this area and accelerate research towards precision approaches in radiotherapy and risk assessments.

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Conflict of Interest

The authors declare no conflict of interest.

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