Considerations on the use of the terms radiosensitivity and radiosusceptibility

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Received 18 April 2018, revised 22 May 2018
Accepted for publication 7 June 2018
Published 21 June 2018

Abstract
The separate use of the terms ‘radiosensitivity’ and ‘radiosusceptibility’ has been suggested to describe variability in the risk of, respectively, adverse tissue reactions (deterministic effect) following radiotherapy and radiation-induced cancer (stochastic effect). The aim of this note is to present arguments against such distinction. We feel that it is premature to make a concrete final judgement on these definitions because of the limited understanding of the mechanisms underlying individual sensitivity to both radiation-related cancers and radiation-related tissue injury. Moreover, the exclusive application of ‘radiosensitivity’ in relation to deterministic effects and the term ‘radiosusceptibility’ in relation to cancer carries the risk of being wrongly interpreted as evidence for a high, genetically driven sensitivity to radiation in all patients who develop adverse tissue reactions and a high genetic susceptibility to cancer in those who develop radiation-induced malignancies. There is a need for further research to better define these phenomena and their interrelationships.

Keywords: radiosensitivity, cancer, radiosusceptibility
Introduction

The authors of two recent publications encourage the separate use of the terms ‘radiosensitivity’ and ‘radiosusceptibility’ to describe variability in the risk of, respectively, adverse tissue reactions following radiotherapy (understood and defined by ICRP as tissue injuries or deterministic effects [1]) and radiation-induced cancer (understood and defined as stochastic effects [1]) [2, 3]. Moreover, the term ‘radiodegeneration’ was suggested in connection with non-cancer effects such as cataracts and circulatory disease [2, 3], where their classification as deterministic or stochastic is not straightforward [4]. The authors claim that the use of the single term ‘radiosensitive’ not only causes confusion but may have legal consequences, because radiation effects have different mechanistic backgrounds and levels of risk per unit dose, so ‘in the case of judgement, the court will be obliged to consider such difference’ [3].

We wish to share our point of view favouring the continued use of the term radiosensitivity in relation to both deterministic and stochastic effects. Furthermore, we argue that it is premature to make a concrete final judgement on these definitions.

Radiosensitivity or sensitivity to radiation-induced health effects

The term radiosensitivity is a compound word consisting of two stems: ‘radiation’ and ‘sensitivity’. Since the stem ‘radiation’ is unequivocal, the case raised by Britel et al [3] is related to the stem ‘sensitivity’. A search in the online English Oxford dictionary (https://en.oxforddictionaries.com/definition/sensitivity) reveals that the word is polysemous. The noun ‘sensitivity’ is defined as ‘the quality or condition of being sensitive’, while the adjective ‘sensitive’ is defined as ‘quick to detect or respond to slight changes, signals, or influences’, ‘having or displaying a quick and delicate appreciation of others’ feelings’ and ‘kept secret or with restrictions on disclosure to avoid endangering security’. The original Latin word for the term ‘sensitive’ is ‘sentire’. It is also polysemous, because it means ‘to feel’, ‘to hear’ and ‘to smell’ (https://en.wiktionary.org/wiki/sentire). The multiple meanings of the word ‘sensitive’ are apparently not a source of legal problems. Hence, it is unlikely that this will be the case when the word ‘radiosensitivity’ is used both in the context of individual variability in radiation-induced deterministic and stochastic effects. Moreover, using ‘radiosensitivity’ to describe both deterministic and stochastic effects is intuitive given that mechanisms for both sets of effects are still not fully understood, and it is thus difficult to categorically define what effects should fall under purely ‘deterministic’ versus ‘stochastic’.

Radiosensitivity as used to describe adverse tissue reactions

Britel et al write that ‘the English term ‘radiosensitivity’ and its French and German equivalents were historically used by the pioneers of radiation to describe the radiation-induced skin burns’ [3]. In fact, the term radiosensitivity was not used to describe radiotherapy-related adverse tissue effects, but to explain their sigmoid dose response relationship. In his seminal paper from 1936, Hermann Holthusen plotted the likelihood of both tumour cure probability and normal tissue complication probability as a function of dose and claimed that the slope of both sigmoid curves was due to individually variable sensitivity of patients to radiation [5]. The quoted statement of Britel et al appears to reflect a wide-spread belief that all radiotherapy patients who develop adverse tissue effects are ‘radiosensitive’, while those who do not are ‘normosensitive’. Inherent to this belief is the assumption that the so understood ‘radiosensitivity’ is intrinsic, meaning genetically determined [6–8]. However, if
genetic susceptibility was the major risk-modifying factor for adverse tissue effects, then studies trying to correlate the ex vivo sensitivity of cells isolated from radiotherapy patients with the occurrence of early or late effects would have been successful. This, however, is not the case, despite more than 20 years of intense research \cite{9, 10}. As pointed out by the authors of the AGIR report, the risk of developing adverse tissue reactions depends on a multitude of factors \cite{9}. Some of them are likely to have a genetic origin, but there is substantial evidence for the impact of lifestyle factors such as smoking, alcohol consumption, diet, lack or excessive physical activity, physical injuries or hygiene. Moreover, as elegantly pointed out by Munro and Gilbert already in 1961, the sigmoidal dose response curve for tumour cure can be explained by the stochastic nature of radiation-induced cell kill \cite{11}. The fact that late adverse tissue effects are partly a consequence of cell death \cite{12} indicates that chance also plays a role with respect to the probability of developing side effects to radiotherapy, having nothing to do with variability in intrinsic individual radiosensitivity. In this context, it is interesting to note that stochastic molecular processes are believed to influence many phenotypic variations limiting the possibility of predicting susceptibility to complex diseases \cite{13}.

**Radiosusceptibility as used to describe proneness to radiation-induced cancer**

Foray et al \cite{2} refer to ICRP 79 \cite{14} when they define radiosusceptibility as ‘proneness to radiation-induced cancer’. However, ICRP 79 does not use the term ‘radiosusceptibility’. Rather, the ICRP report mentions ‘tumorigenic radiosensitivity in cancer-prone genetic conditions’. Interestingly, the authors of the AGIR report \cite{9} use the term ‘susceptibility to radiation carcinogenesis’, which can be shortened to ‘radiosusceptibility’. However, ‘radiosusceptibility’ is considered to be a form of ‘radiosensitivity’, parallel to ‘tissue radiosensitivity for cancer’.

The aetiology of cancer is highly complex and background risk is determined not only by genetics but other risk factors \cite{15, 16}. The authors of the AGIR report make it quite clear that uncertainty exists as to how far genetic susceptibility to cancer is related to radiosensitivity for cancer, largely due to a lack of knowledge on the relevant underlying mechanisms. This is reflected in the uncertainty regarding the choice of the risk model when transferring cancer risks between populations having different background rates of a particular cancer. While the multiplicative excess relative risk model assumes that the background risk influences the radiation-induced risk, the additive absolute risk model assumes no such influence. In view of the uncertainty, ICRP 103 \cite{1} recommends a 50:50 mix of both models for cancers at most sites when transferring risks between populations. There is a threat that the explicit use of the term ‘radiosusceptibility’ may be misunderstood to imply that genetic susceptibility is always at the basis of tumorigenic radiosensitivity.

**Radiodegeneration as used to describe radiation-induced non-cancer effects**

The term radiodegeneration was introduced by Foray et al \cite{2} and is defined as ‘non-cancer effects that are often considered attributable to mechanisms other than cell death, and include cataracts and circulatory disease’. This definition does not raise any controversy in view of the largely unresolved mechanisms of the effects \cite{4, 9} and the authors discuss this problem extensively. However, they do not give any suggestion as to how the term should be used to grade individual sensitivities to non-cancer effects—a difficult task given that there is no...
standard basis by which to describe individuals as highly or weakly radiodegenerative. This may be the reason that the term was abandoned in the later publication by Britel et al [3].

Conclusions

At present, there is no compelling reason why the term ‘radiosensitivity’ should not be used in connection with adverse tissue reactions following radiotherapy and radiation-induced cancer and non-cancer effects, provided that the effect which it refers to is clearly defined. The exclusive application of ‘radiosensitivity’ in relation to deterministic effects and the term ‘radiosusceptibility’ in relation to cancer carries the risk of being wrongly interpreted as evidence of a high, genetically driven sensitivity to radiation in all patients who develop adverse tissue reactions and a high genetic susceptibility to cancer in those who develop radiation-induced malignancies. Given that we have only a limited understanding of the mechanisms underlying individual sensitivity to both radiation-related cancers and radiation-related tissue injury, it is premature to draw hard distinctions between the phenomena that have been described to date or their definitions. There is a need for further research to better define these phenomena and their interrelationships. Furthermore, there are important considerations on where any measured cut-off point that distinguishes those who are sensitive from those who are not may lie; such issues will be critical in the practical implementation of any tests for radiosensitivity.

Conflicts of interest

The authors declare no conflicts of interest. The views expressed in this manuscript do not necessarily represent the official position of the Office of Global Affairs, or the US Department of Health and Human Services.

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