Letter to the Editor

Comment on ‘Considerations on the use of the terms radiosensitivity and radiosusceptibility’ by Wojcik et al

Dear Sirs,

In order to avoid any confusion about the terms describing the different clinical features of radiation response, we recently proposed the use of the terms ‘radiosensitivity’ and ‘radiosusceptibility’ to discriminate the radiation-induced (RI) tissue reactions from the RI cancers, respectively (Foray et al 2016, Britel et al 2018). In this journal, Wojcik et al recommended using the term ‘radiosensitivity’ indifferently (Wojcik et al 2018). Through this letter, we would like to explain again why it is so important to define univocally the clinical features of radiation response.

Jargon that should be defined from clinical observations

Radiation research is a multidisciplinary and complex field whose technical jargon may make it inaccessible to the public and contribute to radiophobia. The pioneers of radiation introduced in 1907 the term ‘radiosensitivity’ to describe RI cutaneous reactions while they were aware that radiation might also cause cancers. In fact, they did not use the term ‘radiosensitivity’ to describe RI cancers, likely because there was already evidence that cutaneous burns and cancers were different from the clinical point of view (Britel et al 2018). From the 1950s, an enormous and laudable effort was provided to develop the notion of efficient dose to quantify and compare the RI risks linked to specific irradiated organs. However, probably far from the clinical field, experts in radiological protection did not introduce specific expressions to describe the very large spectrum of clinical consequences of radiation response and, unlike pioneers, they indifferently used the single term ‘radiosensitivity’. Consequently, to date, the meaning of ‘radiosensitivity’ depends on its context, which is understood only by experts: ‘radiosensitivity of the skin’ means ‘erythema’; ‘radiosensitivity of the breast’ means ‘RI breast cancer’ and ‘radiosensitivity of the eyes’ means ‘cataracts’. This confusion is inasmuch unacceptable as RI tissue reactions, cancers and cataracts are clearly different from a clinical and biological point of view. Furthermore, RI tissue reactions, cancers and cataracts do not have the same consequences vis-à-vis the legal and regulatory point of view. Finally,
these lines of evidence are also shared by the public even if the intrinsic mechanisms from which they come are not completely known (Britel et al 2018).

To avoid such confusion and on the basis of a semantic analysis of four different corpora representing millions of books and articles from 1895 to 2017, we proposed the following definitions: ‘radiosensitivity’ as any clinical and cellular consequences of IR attributable to cell death (e.g. tissue reactions); ‘radiosusceptibility’ as RI cancers or any RI feature that is attributable to cell transformation; ‘radiodegeneration’ to describe any aspects of IR response attributable to aging (Foray et al 2016). Despite this confusion as described previously, Wojcik et al proposed to maintain the polysemous use of the term ‘radiosensitivity’ (Wojcik et al 2018).

-How to illustrate the confusion due to the use of the single term ‘radiosensitivity’:

Let us take some current examples: (1) Patients who suffer from Li–Fraumeni syndromes caused by p53+/− mutations are at high risk of cancer (notably breast cancer) but at low risk of post-radiotherapy tissue reactions (Foray et al 2016, Britel et al 2018). If we follow the recommendations of Wojcik et al these patients are ‘radiosensitive’ and ‘not radiosensitive’. In practice, for clinicians, radiotherapy is allowed for Li–Fraumeni patients, but their age and the area to be treated will be crucial factors in the treatment plan. If patients were at risk of tissue reactions, the principle of a radiotherapy itself would have been called into question. By following our recommendations, Li–Fraumeni patients are considered as ‘radiosusceptible’ but ‘not radiosensitive’.

(2) Sarcoma is known to be a tumor type rather resistant to radiotherapy but it is also known to be induced by radiation. Again, by following the proposal of Wojcik et al sarcoma would be considered as ‘not radiosensitive’ tumors and ‘radiosensitive’ tissue while we proposed to say that sarcoma are not radiosensitive but may be radiosusceptible.

(3) It is said in numerous International Commission on Radiological Protection (ICRP) reports that ‘children are more radiosensitive than adults’ (e.g. ICRP 2001). This sentence is a recurrent source of questions for patients, public, journalists and even lawyers (Britel et al 2018). First, it can be deduced from this sentence that any child will become radioresistant when he reaches adulthood. Second, it should be understood that children exposed to radiation in their childhood may be at higher risk of cancer than non-exposed children, whether they suffer from a genetic disease or not. However, children are not necessarily at high risk of post-radiotherapy tissue reactions. Hence, to the notable exception of well-characterised genetic diseases associated with tissue hyper-radiosensitivity like ataxia telangiectasia, clinicians endeavor to eventually reduce the radiation dose in radiotherapy for children in order to limit the risk of RI cancers rather than to avoid potential adverse tissue reactions (Foray et al 2016).

(4) It is said that ‘women are more radiosensitive than men’ (e.g. ICRP 2007). Similarly to the previous example, this sentence is related to RI cancers rather than to severe post-radiotherapy reactions. Indeed, the breast is one of the most RI cancer-prone organs: the risk of RI cancer becomes independent of gender when breast cancers are omitted. Conversely, notwithstanding the differences between tumor types, there is no evidence that women show more, and more severe post-radiotherapy reactions than men (German Commission on Radiological Protection 2009). Again, by following the proposal of Wojcik et al women will be more radiosensitive than men with regard to RI cancers and not more radiosensitive than men with regard to post-radiotherapy tissue reactions.

-Semantic differences between sensitivity and susceptibility: Wojcik et al used the Latin root to demonstrate that the term ‘sensitivity’ is polysemous. We agree. But the problem is the polysemy of the term ‘radiosensitivity’. Interestingly, a similar semantic approach applied to the term ‘susceptibility’ would lead to the conclusion that, unlike ‘sensitivity’,
‘susceptibility’ introduces the notion of probability. As an example, to be ‘susceptible’ to a pathology does not mean, like ‘sensitivity’, that one necessarily suffers from this pathology but that the risk of pathology occurrence is higher than normal. Hence, ‘susceptibility’ may also reflect the stochastic nature of cancer proneness while ‘sensitivity’ introduces the deterministic nature of tissue toxicity. By keeping the only term ‘radiosensitivity’, one therefore loses these two important notions, while the distinction between deterministic and stochastic effects is one of the most important bases of ICRP recommendations (ICRP 2001, 2007).

-Radiosensitivity and radiosusceptibility are not necessarily genetic: The definitions that we proposed are done independently of any hypothesis about the origin of the pathology. It is noteworthy that ‘genetic susceptibility’ is univocal while ‘radiosusceptibility’ reflects a high risk of cancers induced by radiation without additional hypothesis. This statement is also relevant for ‘radiosensitivity’ and ‘radiodegeneration’. Furthermore, Wojcik et al based their arguments on the failure of some assays to reliably predict radiosensitivity/radiosusceptibility/radiodegeneration. The lack of specificity of predictive assays does not question the clinical evidence that these three notions are different: again, it is not necessary to know each detail of each molecular mechanism to admit that RI tissue reactions, cancers and cataracts are different.

-Some arguments against a better definition of the different clinical consequences of radiation response are difficult to understand: In the section about ‘radiosusceptibility’ of Wojcik et al, citations were provided from some ICRP reports to challenge our approach. It was recognised thereafter that a similar term was used in the AGIR report (Health Protection Agency 2013) but finally considered that, from their own intuition, ‘radiosusceptibility’ is not appropriate. Let us remind again that the paper by Britel et al (2018) is the result of an objective analysis of four corpora representing thousands of books and papers and notably concerns all the citations of the terms related to sensitivity and susceptibility in ICRP reports (Britel et al 2018). In addition, unlike the non-objective statement of the authors about ‘radiodegeneration’ that they said ‘we abandoned’, Britel et al simply focused on the radiosensitivity and radiosusceptibility terms and not on ‘radiodegeneration’.

Conclusions

Hence, the major error that radiobiologists can commit is to forget/deny the clinical reality and the good understanding of the public of certain aspects of our research field: more and more patients, and more and more individuals, have access to knowledge and terms about radiation. One of the most deleterious consequences of a status quo in the use of the term ‘radiosensitivity’ may get the opposite of what radiobiologists wish: radiophobia, doubt and misunderstanding. Hence, the definitions of biological and clinical consequences of radiation response should not be a sensitive case, depending on a context that would be only understood by experts. To the contrary, these definitions should faithfully reflect the scientific advance of our field because any confusion is susceptible to move us further away from the public and the other scientific and medical communities.

Yours faithfully,

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