Considerations on Potential Regulatory Actions for Radiation Protection in Radiotherapy: Monitoring Unwanted Radiation Exposure

Abel Julio González[1]*

[1]*Autoridad Regulatoria Nuclear, Av. del Libertador 8250, Ciudad de Buenos Aires [1429], Argentina*
*Corresponding author's e-mail: abel_j_gonzalez@yahoo.com

Abstract: The objective of this paper is to present a discussion document on potential regulatory actions for monitoring adventitious unwanted radiation exposure in radiotherapy. That document was jointly prepared by the Argentine Nuclear Regulatory Authority (Autoridad Regulatoria Nuclear, ARN) and the International Atomic Energy Agency [IAEA]. The document introduces, describes and discusses the concepts of *unwanted radiation exposures in radiotherapy* (URERs), *unwanted doses in radiotherapy* (UDRs), *proxies* of UDRs, and *prospective increase of primary malignancies attributable to radiotherapy* (PIPMAR). It is concluded that it seems to be desirable that regulators with competence in the radiation protection of patients investigate further the issue of PIPMARs. For the purpose of controlling properly radiation protection of patients undergoing radiotherapy, particularly the requirements of justification of individual radiotherapy and optimization of the radiation protection of the individual patient, it is highly convenient for regulatory authorities that URERs be assessed and their UDRs be monitored and registered. Therefore, regulatory authorities should consider exploring regulatory actions for requiring monitoring and registering of URERs and their UDRs. Several techniques and proxies are available for this purpose.

KEYWORDS: Radiation Protection of Patients; Radiotherapy; Adventitious Radiation Exposure.

1. INTRODUCTION

The objective of this paper is presenting a discussion *document* (hereinafter referred to as the *document*) suggesting potential regulatory actions for monitoring adventitious unwanted radiation exposure in radiotherapy.

On 18 September 2015, the Argentine Nuclear Regulatory Authority (Autoridad Regulatoria Nuclear, ARN) and the Secretariat of the International Atomic Energy Agency (IAEA) agreed on '*Practical Arrangements*' setting forth the framework for non-exclusive cooperation between the Parties in the area of radiation safety and monitoring. A relevant activity agreed to be pursued under the 'Practical Arrangements' was the 'development of regulatory guidance on radiological protection in radiotherapy, addressing in particular the potential increase in the risk of second cancers'.

On August 05, 2017, ARN and the OIEA finalized and published a jointly prepared document under the title ***'Considerations on potential regulatory actions for radiation protection in radiotherapy: monitoring unwanted radiation exposure in radiotherapy'*** [1], clearly indicating that it was just a discussion document.

2. BASIC CONCEPTS

Four main concepts are used in the document, as follows:

2.1. Unwanted radiation exposures in radiotherapy

Unwanted radiation exposures in radiotherapy (URERs) are radiation exposures of a patient undergoing radiotherapy that are adventitious exposures; namely, URERs are neither wished nor desired but are unavoidably and unintentionally incurred during radiotherapy procedures.

2.2. Unwanted doses in radiotherapy

Unwanted doses in radiotherapy (UDRs) are the adventitious doses due to URERs incurred by patients undergoing radiotherapy. UDRs are additional to the prescribed radiotherapy doses to the prescribed volume, which can be incurred in any part of the body. UDRs can be monitored and recorded, either by measurement or estimation, through dosimetric quantities or suitable *proxies.*

2.3. Proxies of UDRs

The quantification of UDRs often means the measurement of *proxies*, i.e. substitutes. Proxies of UDRs are measurable quantities substituting a UDR that cannot be measured directly. Proxies can be physical quantities and also biological quantities.

2.4. Prospective increase of primary malignancies attributable to radiotherapy

The definition of *prospective increase of primary malignancies attributable to radiotherapy* (PIPMARs) is subtly more precise than what usually is indistinctly termed 'second cancers', 'secondary cancers' or 'second primary cancers, and it is identified with the acronym SPC [2]. The various SPC's definitions being used are ambiguous and could be construed as comprising only cancers being developed in the primary treatment field. PIPMARs are defined as comprising all unwanted adventitious malignant sequelaes of radiotherapy, which are remaining latent and manifest after the treatments. PIPMARs do not only include solid cancers but also leukaemia, i.e. include all malignancies. PIPMARs are not metastases of the original malignancy, but primary malignancies. PIPMARs are not limited to second primary malignancies but to the entire sequence of metastases that could originate from them.

3. PIPMARs AND RADIATION PROTECTION

In the frame of the international radiation protection system, PIPMARs are correlated to a radiation detriment attributable to radiotherapy. PIPMARs therefore become a conjectural expectation of radiation harm that is conceptually and retrospectively assignable to radiotherapy.

While the US National Council on Radiation Protection & Measurements warned that there was a wealth of knowledge on the risk of SPC following radiation therapy indicating clear increases following high-dose and scatter-dose radiation, one of the first international call of attention on the issue of PIPMARs occurred at the International Conference on Radiological Protection of Patients in Diagnostic and Interventional Radiology, Nuclear Medicine and Radiotherapy [3], which took place in Malaga, Spain, in 2001, where it was declared that 'radiation to normal tissue has a number of possible negative sequelæ including the possible induction of secondary cancers'. This Conference triggered an international response aimed at the protection of patients.

The Malaga Conference was followed by the International Conference on Radiation Protection in Medicine: Setting the Scene for the Next Decade[4], which took place in Bonn, Germany in 2012, where it was declared that 'even with high precision photon radiotherapy, a large volume of surrounding normal tissues may be exposed to low levels of dose'.

The growing interest for the issue of PIPMARs has recently arrived to the highest international level: the United Nations General Assembly (UNGA). On 13 December 2019, UNGA adopted a Resolution [5] in which it '…supports the intentions and plans of [the United Nations Scientific Committee on the Effects of Atomic Radiation] UNSCEAR for conducting its programme of work

of scientific review and assessment on behalf of the General Assembly, in particular…..*its assessments of second primary cancer after radiotherapy*…'

The interest on the radiation protection of patients undergoing radiotherapy is enhanced by the size of the population of concern to be affected by PIPMAR. The general incidence of malignancies is known to be high: in the order of quarter of the population may suffer a malignancy. The fraction of patients suffering malignancies that are treated with radiotherapy have increase enormously. In the developed world it may reach around half of sufferers. Finally, the expected fraction of survivors has also been steadily increasing. With the fraction of cures increasing year after year, the cohort subjected to PIPMARs may comprehend millions of people!
Obviously many confounding factors may affect this prospective cohort, including lifestyle factors, such as smoking habits and diet, genetic susceptibility; and, proneness to radiation-induced malignancies or radio-susceptibility. But in any case, the size of a cohort is such that its radiation protection can not be ignored.

4. REGULATION

Given the existence of PIPMARs and the size of the prospective cohort of sufferers, regulatory authorities with responsibilities of radiation protection face a number of ethical dilemmas. Should regulatory authorities be concerned about PIPMARs?. Should regulatory authorities be passive vis-à-vis PIPMARs? Should they engage in promoting regulatory policies that could benefit the affected patients? What actions might they take?

An ethical outcome could be straightforward: recognizing the existence of URERs and their potentiality for PIPMARs, undertake regulatory actions requiring that UDRs attributable to URERs be properly monitored and recorded either directly or trough UDRs' proxies. This is the epilogue suggestion of this document!

4.1 Evolution of the International Regulation

Recommending an international radiation protection paradigm is the remit of the International Commission on Radiological Protection (ICRP), which in its recommendations indicate that 'the work of ICRP helps to prevent cancer and other diseases and effects associated with exposure to ionising radiation'. A specific ICRP body, ICRP Committee 3, is concerned with protection of persons and unborn children when ionising radiation is used for medical diagnosis, therapy, or for biomedical research. Notwithstanding, the response of ICRP to the issue of PIPMAR has been somehow limited. While the issue is implicitly mentioned in ICRP recommendations, for instance in recommendations on radiological protection in ion beam radiotherapy, no specific ICRP recommendations have been developed on how to deal with PIPMARs, even in the ICRP latest recommendations [6].

The IAEA is the only international intergovernmental organization with specific statutory functions in radiation protection. In response to this mandate, it issued radiation protection and safety measures in March 1960 [7], and subsequently approved basic safety standards (BSS) for radiation protection in June 1962 [8]. These were the first international radiation protection standards. A revised version of the BSS was published in 1967 [9]. It is to be noted that all these earlier international standards ignored the protection of patients.[10] .

The third revision of the BSS was published by the IAEA as the 1982 Edition of Safety Series No. 9 [11] and was jointly sponsored by *inter alia* the WHO. These standards required that medical exposure should be subject to the radiation protection requirements of justification [of medical

procedures] and optimization [of protection during the procedures] [12], thus becoming the **first international standards involving requirements for the protection of patients**.

A substantial revision of the BSS was approved in 1996. The 'International Basic Safety Standards for Protection Against Ionizing Radiation and for the Safety of Radiation Sources' were issued as IAEA Safety Standards 115 [13], with a wide co-sponsorship of international organizations including WHO. They included for the first time a set of comprehensive international radiation protection requirements for 'medical exposures'. The requirements included *interalia* responsibilities, justification of medical exposures, optimization of protection for medical exposures and explicit requirements for therapeutic exposure.

The latest revision of the international standards is the 'Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards' [14],. They are supported by Fundamental Safety Principles [15], which are cosponsored by all relevant intergovernmental organizations: the European Atomic Energy Community (Euratom), the Food and Agriculture Organization of the United Nations (FAO), the International Labour Organization (ILO), the International Maritime Organization (IMO), the OECD Nuclear Energy Agency (OECD/NEA), the Pan American Health Organization (PAHO), the United Nations Environment Programme (UNEP) and the World Health Organization (WHO). They emphasize and expand the international requirements for the protection of patients, including requirement for the protection of patients undergoing radiotherapy.

4.2 Relevant International and Intergovernmental Radiation Protection Requirements

In short, the international and intergovernmental radiation protection requirements requires that medical exposures be justified and that radiation protection options be optimized and any of these requirements involves monitoring of the situation.

4.2.1. *Justification of medical exposures in radiotherapy*

In relation to the purpose of the suggestions in the document, the requirement of justification can be defined as follows: Any decision to undertake radiotherapy in a patient, which would alter the radiation exposure of the patient, should do more good than harm. The ICRP has suggested that medical exposures would call for a different and more detailed approach to the process of justification. The principal aim of medical exposures, including radiotherapy, is to do more good than harm to the patient.

The requirement of justification applies at three levels in radiotherapy. At the first level, the use of radiation in medicine has to be accepted as doing more good than harm. At the second level, a specified radiotherapy procedure with a specified objective shall be defined and justified with the aim of judging whether the radiotherapy procedure will bring more good than harm. At the third level, the application of the procedure to an individual patient should be justified, i.e., the particular application should be judged to do more good than harm to the individual patient. This third level is the relevant level for the purposes of the suggestions in the document.

It follows that it is essential for the regulator to be able to estimate URERs and their UDRs in order to enforce compliance with the justification requirement.

4.2.2. *Optimization of radiation protection in radiotherapy*

The optimization of radiation protection applied to radiotherapy requires that the protection of the patients should be the best under the prevailing circumstances, namely that URERs and their UDRs

should be kept as low as reasonably achievable, all factors being taken into account. Therefore, optimization involves not only delivering the prescribed dose to the tumour, but also planning the protection of healthy tissues outside the target volume and thus protection against PIPMAR.

The international standards establish specific design and operational requirements for optimization, as follows:

- In relation to design considerations the standards require that registrants and licensees, in cooperation with suppliers, shall ensure that radiotherapy equipment, and software that could influence the delivery of medical exposure is used only if it conforms to the applicable standards of the International Electrotechnical Commission and the International Organization for Standardization or to national standards adopted by the regulatory body.
- In relation to operational considerations, the standards establish that for therapeutic radiological procedures, the radiological medical practitioner, in cooperation with the medical physicist and the medical radiation technologist, shall ensure that for each patient the exposure of volumes other than the planning target volume is kept as low as reasonably achievable consistent with delivery of the prescribed dose to the planning target volume within the required tolerances.

It follows that it is essential for the regulator to be able to estimate URERs and their UDRs. in order to enforce compliance with the optimization principle.

4.2.3. *Monitoring*

The regulatory need to be acquainted with URERs and their UDRs implicitely bring to the regulatory need of requiring monitoring of URERs, namely the measurement of UDRs or their proxies related to the assessment of exposure to radiation and the interpretation of the results.

The superseded international radiation protection standards, issued in 1996 notably required that ‘when competent authorities review existing [medical] examinations or treatments involving exposures to radiation, they should take into account the somatic and genetic detriment of such exposures’ [16]. *Mutatis mutandi*, this statement could be considered the first international requirement for monitoring exposure in radiotherapy. Remarkably, those superseded standards also required that registrants and licensees shall ensure that ‘the patient be informed of possible risks’ [17].

However, these requirements were not repeated in the new international standards, perhaps because they were considered obvious. Notwithstanding, the new standards require programmes of quality assurance in radiotherapy including those for monitoring equipment [18].

The new standards require that calibrations of radiotherapy units be subject to independent verification prior to clinical use [19]. They also include specific requirements for the release of patients, such as that registrants and licensees shall ensure that there are arrangements in place to ensure appropriate radiation protection for members of the public and for family members before a patient is released following radionuclide therapy [20].

They moreover include requirements for recording, including the following: ‘for radiation therapy, a description of the planning target volume, the dose to the centre of the planning target volume, and the maximum and minimum doses delivered to the planning target volume, or equivalent alternative information on doses to the planning target volume, the doses to relevant organs as selected by the radiological medical practitioner, the dose fractionation, and the overall treatment time’ [21].

Notwithstanding these current international radiation protection requirements for radiotherapy, it should be underlined that there is an absence of specific and unambiguous requirements on the monitoring or even gross assessment of URERs and their UDRs and their proxies.

In summary, it appears to be essential that regulators be acquainted with URERs and know the attributable UDRs, either directly or throw proxies, in order to enforce compliance with the international and intergovernmental requirements of justification of radiotherapy for individual patients and optimization of protection of the patient in order to ensure that such protection be the best under the prevailing circumstances.

5. CONCLUSIONS

From the document summarized here, it can be concluded that: it seems to be desirable that regulators with competence in the radiation protection of patients investigate further the issue of PIPMARs.

The current international standards require that radiotherapy procedures be generically justified. While such generic justification are expected to be carried out in conjunction with appropriate professional bodies and to be reviewed from time to time with account taken of advances in knowledge and technological developments, the relevant regulatory authority is entrusted with the regulatory control of justification. It seems that in order to be able to control properly such generic justifications of specific radiotherapy procedures, there would be convenient for the authorities to benefit from a wide knowledge of URERs and their UDRs. Systematic monitoring and registering of URERs and their UDRs would be a helpful tool for controlling the justification of prospective procedures.

The current international standards also require that the radiation protection of patients undergoing radiotherapy be optimized. While approaches to optimization in radiotherapy are expected to be evaluated in conjunction with appropriate professional bodies, the relevant regulatory authority is entrusted with the regulatory control of optimization. Optimization could be interpreted as reducing URERs and their UDRs to a level that is as low as reasonably achievable under the prevailing circumstances, taking account that radiotherapy procedures are expected to deliver prescribed therapeutic doses. Again, systematic monitoring and registering of URERs and their UDRs would be a helpful tool for controlling the optimization of protection in justified radiotherapy procedures.

It appears therefore that, for the purpose of controlling properly radiation protection of patients undergoing radiotherapy, it is highly convenient for regulatory authorities that URERs and their UDRs be monitored and registered and that regulatory actions be explored for requiring monitoring and registering of URERs and their UDRs. Several techniques and proxies are available for this purpose, from physical measurements followed by sophisticated computerized assessment programmes to the relatively inexpensive and widely available biological dosimetry.

It is consequently suggested that the IAEA in consultation with regulatory authorities of its Member States explore the possibility to establish international guidance for assisting national authorities in establishing requirements for monitoring and recording URERs and their UDRs.

6. CAVEAT

The sole intention of this document is to suggest exploring the feasibility of regulatory requirements for monitoring and registering of URERs and their UDRs, for *inter alia* facilitating the implementation of the already established regulatory requirements of justification and optimization.

In particular, the suggestions herein should not be construed as recommendations for, or implications on, any potential actions that health authorities might consider in relation to PIPMARs or as taking a position on the issue of individual health assessment of asymptomatic persons.

7. ACKNOWLEDGMENTS

Acknowledgments are given to:

- Miroslav Pinak , Head of the IAEA Radiation Safety & Monitoring Section, who was the initiator of the 'Practical Arrangements' initiative.
- Marina Di Giorgio, Director of ARN, and Ola Holmberg, Head of the IAEA Radiation Protection of Patients Unit, who were the main co-authors, from ARN and IAEA respectively, of the document presented in this paper.

8. REFERENCES

[1] AUTORIDAD REGULATORIA NUCLEAR & INTERNATIONAL ATOMIC ENERGY AGENCY. Considerations on potential regulatory actions for radiation protection in radiotherapy: monitoring unwanted radiation exposure in radiotherapy (A discussion document prepared jointly by the Autoridad Regulatoria Nuclear [ARN] of Argentina and the International Atomic Energy Agency). Buenos Aires, Vienna, 2017.
https://www.iaea.org/resources/article/considerations-on-potential-regulatory-actions-for-radiation-protection-in-radiotherapy

[2] NATIONAL COUNCIL ON RADIATION PROTECTION & MEASUREMENTS. NCRP Report No. 170, Second Primary Cancers and Cardiovascular Disease After Radiation Therapy..

[3] INTERNATIONAL ATOMIC ENERGY AGENCY. International Conference on Radiological Protection of Patients in Diagnostic and Interventional Radiology, Nuclear Medicine and Radiotherapy [2001, Malaga, Spain]. Radiological protection of patients in diagnostic and interventional radiology, nuclear medicine and radiotherapy : proceedings of an international conference held in Malaga, Spain, 26–30 March 2001, organized by the International Atomic Energy Agency...[et al.]. Proceedings series, ISSN 0074–1884. STI/PUB/1113. ISBN 92–0–101401–5. International Atomic Energy Agency, Vienna, 2001.

[4] INTERNATIONAL ATOMIC ENERGY AGENCY. Radiation Protection in Medicine: Setting the Scene for the Next Decade. Proceedings of an International Conference, Bonn, 3-7 December 2012. IAEA Proceedings series, ISSN 0074-1884. STIIPUB/1663. ISBN 978-92-0-103914-9. International Atomic Energy Agency, Vienna, 2015.

[5] UNITED NATIONS GENERAL ASSEMBLY. Resolution 74/81 on Effects of atomic radiation, adopted by the General Assembly on 13 December 2019. Document A/74/407. https://www.unscear.org/docs/GAreports/2019/A_RES_74_81_E.pdf

[6] INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, The 2007 Recommendations of the International Commission on Radiological Protection, Publication 103, Elsevier, 2007.

[7] INTERNATIONAL ATOMIC ENERGY AGENCY, The Agency's Health and Safety Measures, INFCIRC/18, IAEA, Vienna, 1960, and The Agency's Safety Standards and Measures, INFCIRC/18/Rev. 1, IAEA, Vienna, 1976.

[8] INTERNATIONAL ATOMIC ENERGY AGENCY, Basic Safety Standards for Radiation Protection, Safety series No. 9, IAEA, Vienna, 1962.

[9] INTERNATIONAL ATOMIC ENERGY AGENCY, Basic Safety Standards for Radiation Protection [1967 Edition], Safety Series No. 9, IAEA, Vienna, 1967.

[10] Ib. BSS 1967. §2.3 [a].

[11] INTERNATIONAL ATOMIC ENERGY AGENCY, Basic Safety Standards for Radiation Protection [1982 Edition], Safety Series No. 115, IAEA, Vienna, 1982.

[12] Ib. BSS 1982 §601.

[13] INTERNATIONAL ATOMIC ENERGY AGENCY, International Basic Safety Standards for Protection Against Ionizing Radiation and for the Safety of Radiation Sources [BSS]. IAEA, Vienna, 1996. Safety series, ISSN 0074-1892 ; 115. Safety standards. STI/PUB/996. ISBN 92-0-104295-7

[14] INTERNATIONAL ATOMIC ENERGY AGENCY. Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards: General Safety Requirements. IAEA safety standards series, ISSN 1020-525X ; no. GRS Part 3. STI/PUB/1531. ISBN 978–92–0–120910–8. International Atomic Energy Agency, Vienna, 2011

[15] INTERNATIONAL ATOMIC ENERGY AGENCY Fundamental safety principles: safety fundamentals. IAEA safety standards series, ISSN 1020-525X ; No. SF-1. STI/PUB/1273. ISBN 92–0–110706–4. International Atomic Energy Agency, Vienna, 2006.

[16] Ib. BSS 1982 §604.

[17] Ib. BSS 2011 §II.18 [e].

[18] Ib. BSS 2011 §3.170

[19] Ib. BSS 2011 §3.166 [c].

[20] Ib. BSS 2011 §3.177 et seq.

[21] Ib. BSS 2011 §3.184 [d]