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CONSIDERATIONS ON POTENTIAL REGULATORY ACTIONS FOR RADIATION PROTECTION IN RADIOTHERAPY:

MONITORING UNWANTED RADIATION EXPOSURE IN RADIOTHERAPY

A proposal for further discussion drafted by Autoridad Regulatoria Nuclear of Argentina and the Secretariat of the International Atomic Energy Agency

(Product from the Practical Arrangements between the International Atomic Energy Agency and the Autoridad Regulatoria Nuclear of Argentina on cooperation in the area of radiation safety and monitoring)

I. INTRODUCTION

BACKGROUND

(1) On September 18, 2015, the Autoridad Regulatoria Nuclear (ARN) [1] of Argentina and the Secretariat of the International Atomic Energy Agency (IAEA)[2], hereinafter termed 'the Parties', agreed on 'Practical Arrangements' setting forth the framework for non-exclusive cooperation between the Parties in the area of radiation safety and monitoring. The agreement was reconfirmed and partially enhanced during ceremony presided by the Chairman of ARN, Néstor Masriera, and the Deputy Director General of the IAEA, Juan Carlos Lentijo, with the presence of the Argentine Ambassador, Rafael Mariano Grossi, in the framework of the 60th Annual Regular Session of the IAEA General Conference, in Vienna, on September 30, 2016.

(2) The Practical Arrangements identify activities in which cooperation between the Parties may be pursued subject to their respective mandates, governing regulations, rules, policies and procedures. A relevant activity agreed to be pursued is the '*development of regulatory guidance on radiological protection in radiotherapy, addressing in particular the potential increase in the risk of second cancers*'. The proposal described herein is a result of such activity.

[1] The ARN is the Argentinean national body competent in the regulation of nuclear and radiological safety, safeguards and physical security, therefore regulating various sources of radiation exposure. As a national regulator it succeeds the National Nuclear Regulatory Entity (1994-1997) and the regulatory branch of the National Atomic Energy Commission (1950-1994). It was created in 1997 by National Law No. 24,804, as an autarchic entity in the jurisdiction of the Presidency of Argentina. It is charged of regulating those activities in order to, *inter alia*, protect people, the environment and future generations of the harmful effects of ionizing radiation. It also has the function of advising the Argentine government in matters within its competence and being proactive in meeting the needs of the stakeholders.

[2] The IAEA was created in 1957 in response to the deep fears and expectations generated by the discoveries and diverse uses of nuclear technology. A relevant statutory function of the IAEA is to establish standards of safety and to provide for their application. The IAEA has established international radiation protection standards, including standards for the protection of patients, in co-sponsorship with other relevant international organizations of the UN family.

(3) Two major international endeavours have confirmed that there is scope for reducing radiological risks associated to both diagnostic and therapeutic uses of radiation without reducing the medical benefits: the International Conference on the Radiological Protection of Patients in Diagnostic and Interventional Radiology, Nuclear Medicine and Radiotherapy, held in Málaga in 2001 (the Málaga Conference)[3], and the follow up International Conference on Radiation Protection in Medicine: Setting the Scene for the Next Decade', which took place in Bonn, Germany in 2012 (the Bonn Conference) [4].

(4) Overall the recommendations from the Málaga and Bonn Conferences concluded that the relevant international organizations should convene expert groups, including experts from professional societies and regulatory bodies, to formulate action plans for future work relating to the radiological protection of patients. There was recognition that everyone in the health care community has a role to play in improving radiation protection of patients undergoing radio-diagnosis or radiotherapy.

(5) Following the Málaga and Bonn Conferences great advances were achieved in the radiation protection of patients undergoing radio-diagnostic procedures. These include the establishment of international standards under the aegis of the IAEA (see hereinafter, 'international standards'). However, regulatory advancements for radiation protection in radiotherapy have been more limited.

(6) There have also been vast advances in radiotherapy treatment modalities. These have allowed for a significant reduction of the normal tissue volumes receiving relatively high doses. However, in many cases these modalities may lead to the irradiation of larger volumes of the body to low doses.

(7) It is important to note that advances in radiotherapy techniques, together with improvements in the early detection of cancer and also in supportive care, have contributed to steady gains in the expectation of survival of patients suffering cancers. As a result, the prospective risk of long-term surviving patients to incur '*second primary cancers*' attributable to radiotherapy is becoming an important issue particularly for paediatric patients.

(8) The prospective risk of such '*second primary cancers*' is associated to the radiation exposure incurred in the curse of radiotherapy procedures. Most of this exposure is therapeutic but some adventitious exposures are unavoidable. Regulatory requirements for monitoring these exposures are very limited.

(9) This document explores relevant radiation protection issues in radiotherapy and presents some considerations on potential regulatory actions for monitoring and recording exposures incurred in radiotherapy procedures. The document particularly addresses ***unwanted radiation exposure in radiotherapy***, namely not wished or desired

[3] INTERNATIONAL ATOMIC ENERGY AGENCY. Radiological Protection of Patients in Diagnostic and Interventional Radiology, Nuclear Medicine and Radiotherapy. Proceedings of an international Conference held in Málaga, 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. IAEA, 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, Vienna, 2015. Proceedings series, ISSN 0074–1884. STI/PUB/1663. ISBN 978–92–0–103914–9

exposures that however are incurred unavoidably and unintentionally during radiotherapy procedures; these will be identified hereinafter with the acronym ***URER*** [5]. URERs can be monitored and recorded, either by measurement or estimation, through the use of dosimetric quantities or suitable *proxies*.

(10) URERs may be associated with prospective increases in the incidence of those '*second primary cancers*'. These malignancies will be more precisely termed '***prospective increase of primary malignancies attributable to radiotherapy***' and will be hereinafter identified with the acronym ***PIPMAR*** (see hereinafter for a discussion on PIPMAR *vis-à-vis* 'second primary cancers').

(11) It is to be noted that, already in 2013, the United Nations Scientific Committee on the Effects of Atomic Radiation had warned the United Nations General Assembly UNGA on the importance to evaluate potential radiation effects on children after cancer radiotherapy[6]. After that early warning, UNSCEAR addressed the issue of 'second cancers after radiotherapy' in its reporting of its sixty-third session to the (UNGA), which took place in Vienna on 27 June-1 July 2016[7]. UNSCEAR then decided to elaborate working material for an in-depth discussion on a proposal for estimating 'second cancers after radiotherapy'. The UNSCEAR representations of France and Argentina worked in this initiative. More recently, at its sixty-fourth session on 29 May–2 June 2017 UNSCEAR, adopted a report informing UNGA that it discussed plans for a new project on 'second primary cancers after radiotherapy' and was fostering th development of an *ad hoc* project plan and its implementation. Moreover, UNSCEAR UNSCEAR is therefore fully engaged in estimating 'second cancers after radiotherapy'.

(12) The UNSCEAR decision to address this issue is extremely significant. The challenge of PIPMAR is real since a very large cohort of latent sufferers is probably being amassed and might potentially manifest in the future. The time seems to be ripe for considering potential regulatory actions for radiation protection in radiotherapy related to this situation.

(13) It is underlined that the reporting in this document should be considered as *interim*, namely the output is transistory until more permanent suggestions are agreed by consensus among all parties concerned, including relevant regulatory bodies of IAEA Member States.

AIM

(14) The ultimate aim of the document is to suggest exploring the possibility of potential regulatory requirements for monitoring and recording URERs.

[5] The adjective *unwanted*, i.e.., not wished or desired, is used as a simplification of the more proper adjective *adventitious*. The latter derives from the Latin *adventus*, the past participle of the verb *advenire*, and it carries the proper meaning of *happening unintentionally*. It is however not a common word and therefore, for reasons of simplification, the term *unwanted* will be used in this document for qualifying doses that were not intended but were delivered as residual of the intended exposures.

[6] UNSCEAR 2013

[7] United Nations General Assembly. Official Records, Seventy-first session, Supplement No. 46, document A/71/46, §27.

(15) Additional aims are to facilitate both, understanding and potential quantification of PIPMARs, and also implementing radiation protection recommendations for patients undergoing radiotherapy. Appropriate estimates of URERs seems to be essential for implementing internationally adopted fundamental safety principles, such as justifying radiological procedures and optimizing radiation protection[8].

(16) Finally, a long term aspiration of the document is to improve the currently available information on the characteristics and potential size of PIPMARs in order to facilitate the developing of preventive health policies for patients who might be subjected to potential increases in their likelihood of suffering these malignancies.

> **It should be underlined, however, that the considerations and suggestions in this document should not be construed as recommending any public health action in relation to PIPMAR**.

It is presumed that these actions are the responsibility of public health authorities rather than of regulatory bodies controlling radiation exposure.

SCOPE

(17) In addition to this ***introduction***, describing the background, aim, scope, and intended audience, the document comprehends,

(i) a comprehensive review of the ***basic concepts*** and their interpretations and explanations, as they are used in radiotherapy, including the dosimetric and volumetric quantities and the different radiotherapy techniques, and additional terminology required by the suggestions herein, such as definitions related to URERs and PIPMARs;

(ii) a general ***discussion*** on the relevant issues, including a description of the international fostering of information exchange, an analysis of the population that might be affected, the potential estimation of PIPMARs, the expected detriment, and the issue of individual sensitivity;

(iii) an exploration of the potential techniques available for ***estimating URERs*** and ***PIPMARs***, including exploring proxies of established quantities and estimates based on modelling assessments, physical measurements and biological dosimetry;

(iv) a review of the relevant ***regulatory policies***, including the international and national radiation protection paradigm and the derived international standards; and, last but not least,

(v) an ***epilogue summarizing the suggestions and proposals***.

(18) Under the current radiation protection paradigm, increases in the incidence of malignancies attributable to radiation may arise from any situation involving radiation exposure, however small radiation doses could be, including exposure during radiological medical procedures[9]. This document, however, concentrate in URERs,

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

[9] These include radiation imaging or therapeutic procedures, such as in diagnostic radiology, nuclear medicine or radiation therapy, or any image guided interventional procedure or other interventional

namely on radiation doses essentially attributable to radiotherapy. Notwithstanding this focus, and taking into account the growing participation of imaging techniques in radiotherapy, the contribution of radiological imaging for radiotherapy purposes also plays an important role in the discussion.

AUDIENCE

(19) The document is intended to address mainly relevant bodies with responsibilities in the regulation of the protection of patients undergoing radiotherapy, in particular those associated with radiation monitoring. However the audience may be broad and includes oncologists, clinicians, epidemiologists, medical physicists, health physicists, dosimetrists, paediatricians, cardiologists, health-care professionals, government personnel involved with radiotherapy and, last but not least the patients themselves.

procedure, involving radiation delivered by a generator, by a device containing a sealed source or by unsealed sources, or by means of administered radiopharmaceuticals.

II. BASIC CONCEPTS

(20) When dealing with radiation protection in radiotherapy, a recurrent problem is the deficiency for a common, universally recognized understanding of basic concepts and related glossaries. Hereinafter, a discussion on some concepts being used in this document is provided.

QUANTITIES

Dosimetric quantities

(21) The International Commission on Radiological Units and Measurements (ICRU) and the International Commission on Radiological Protection (ICRP) have provided substantive recommendations on dosimetric quantities. The relevant international standards have established an official glossary for some of these quantities[10]. The definitions of these established quantities are available elsewhere but are included hereinafter for completeness.

(22) The basic dosimetric quantities established for purposes of radiation protection are:

- the physical quantity *absorbed dose*,
- the radiation protection quantities *equivalent dose* in organs and *effective dose* in the whole body,
- the measurable quantity *equivalent dose*.

The quantities *absorbed dose*, *equivalent dose*, *effective* dose and *dose equivalent* (including its derived quantities *ambient, directional and personal dose equivalent*) are described in Annex I.

(23) In relation to measurable dosimetric quantities, a relevant quantity could be defined for the sole purposes of this document. This is the adventitious dose caused by URERs and incurred by patients undergoing radiotherapy. This quantity could be termed '***unwanted dose in radiotherapy***', and identified with the acronym ***UDR***. UDRs are additional to the prescribed radiotherapy doses to a prescribed volume, and are incurred in any part of the body.

(24) In principle, all doses incurred outside the *planning target volume (PTV)* (see hereinafter) are by definition UDRs. Notwithstanding, a fraction of the doses delivered in the PTV may also be conceptually considered unwanted. These are the doses that generate malignant mutated surviving cells rather than those killing malignant cells or not triggering any effect. However, the fraction of UDRs among the doses delivered to the planning target volume does not unavoidably need to be included in the UDRs. This is basically for two reasons: (i) with current knowledge and technology it is unfeasible to identify separately proper radiotherapy doses and UDRs; and (ii) the high doses expected to be delivered in that volume might presuppose the prominence of cell killing over surviving cells carrying malignant mutations

[10] IAEA safety glossary: terminology used in nuclear safety and radiation protection : 2007 edition. Vienna : International Atomic Energy Agency, 2007. STI/PUB/1290. ISBN 92–0–100707–8

(25) As it will be argued in the 'discussion' hereinafter, the use of the recommended dosimetric quantities for monitoring URERs and estimating and recording UDRs can be questioned due to a number of issues. Monitoring of URERs require the use of ***proxies***.

Proxies

(26) The 'measurement' of dose often means the measurement of a *proxy* (i.e. substitute), e.g. a measurable quantity for a dosimetric quantity that cannot be measured directly. For the purpose of this document *proxy* means indirect measuremnts that approximates or represents URERs and UDRs in the absence of a direct dosimetric measure. Proxies can be physical quantities, e.g. measurable dosimetric quantities, and also biological quantities, e.g. measurable biological indicators.

Volumetric Quantities

(27) Since radiotherapy is a localised treatment, the definition of tumour and target volumes is vital to successful execution, requiring the best possible characterisation of location and extent of tumour, sub-clinical spread and geometric variations. Diagnostic imaging, including help and advice from diagnostic specialists, is therefore essential for radiotherapy planning. Three main volumes are defined for radiotherapy planning[11], namely: ***gross tumour volume (GTV)***[12], ***clinical target volume (CTV)***[13] and ***planning target volume (PTV)***[14].

(28) Radiotherapy planning must always consider critical normal tissue structures, known as organs at risk (OARs). In some specific circumstances, it is necessary to add a margin analogous to the PTV margin around an OAR to ensure that the organ cannot receive a higher- dose; this gives a planning organ at risk volume (PRV). This applies to an organ such as the spinal cord, where damage to a small amount of normal tissue would produce a severe clinical manifestation. The concepts of GTV, CTV and PTV have been enormously helpful in developing modern radiotherapy. Radiotherapy planning is also dependent on high quality imaging.

(29) The ICRU also provides some additional guidance on volumetric nomenclature. According to ICRU "tissues not included in the CTV or not delineated as dose limiting OARs should still be specifically delineated and named the *remaining volume at risk*

[11] Neil G Burnet, Simon J Thomas, Kate E Burton, and Sarah J Jefferies. Defining the tumour and target volumes for radiotherapy, Cancer Imaging. 2004; 4(2): 153–161. Published online 2004 Oct 21. doi: 10.1102/1470-7330.2004.0054. PMCID: PMC1434601

[12] Gross tumor volume (GTV) describes the position and extent of gross tumor, i.e. what can be seen, palpated or imaged, which definition has been improved by developments in imaging

[13] Clinical target volume (CTV) contains the GTV, plus a margin for sub-clinical disease spread which therefore cannot be fully imaged. (The CTV is the most difficult to precise because it cannot be accurately defined for an individual patient, but future developments in imaging, especially towards the molecular level (possible microscopicy extension), should allow more specific delineation of the CTV). The CTV is important because this volume must be adequately treated to achieve cure.

[14] Planning target volume (PTV) is defined in international standards as the 'geometrical concept used in radiation therapy for planning medical treatment with consideration of the net effect of movements of the patient and of the tissues to be irradiated, variations in size and shape of the tissues, and variations in beam geometry such as beam size and beam direction. It is, in sum, a geometric concept designed to ensure that the radiotherapy dose is actually delivered to the CTV, which allows for uncertainties in planning or treatment delivery.

(RVR)." In addition, ICRU indicates that "the absorbed dose to the RVR can be useful in estimating the risk of late effects, such as carcinogenesis"[15].

RADIOTHERAPY TECHNIQUES

(30) Radiotherapy techniques using radiation emission, and particularly the relevant radiotherapy equipment, have been evolving significantly over the last decade. They include: two-dimensional radiotherapy (2D-RT), three-dimensional conformal radiotherapy (3D-CRT), volumetric modulated arc therapy (VMAT), tomotherapy (*IGRT approach), image - guided radiation therapy (IGRT), stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT), particle therapy (hadron therapy), auger therapy (AT), and brachytherapy. Annex II reviews the denotations of these techniques and some dosimetric considerations in relation to UDRs.

(31) It should be noted however that URERs and PIPMARs are not only an unwanted outcome of the above radiotherapy techniques but also of radiotherapy techniques that incorporate radioactive substances into the body. Over the last years, concerns on this problem have been growing, e.g. on techniques using radioiodine for therapeutic purposes[16]. While these techniques will not be discussed specifically, many of the considerations in this document also apply to them *mutatis mutandi*.

III. DISCUSSION

PIPMAR *vis-à-vis* 'SECOND PRIMARY CANCERS'

(32) As indicated before, in this proposal the prospective detriment attributable to URERs is identified as *prospective increase of primary malignancies attributable to radiotherapy or PIPMAR*. PIPMAR should be considered an unwanted adventitious malignant sequel of radiotherapy, which may remain latent and manifest several years after the treatments.

(33) Malignancies associated to PIPMARs are not metastases of the original malignancy being treated by radiotherapy, but are primary malignancies, which risk for development is increased by the unwanted radiation exposure that the patient incurs because of the radiotherapy.

(34) Therefore, in the frame of the radiation protection system of ICRP, PIPMAR is correlated to a radiation detriment attributable to radiotherapy, namely an expectation of radiation harm that includes the dimension of probability and which is conceptually and retrospectively assignable to radiotherapy.

(35) However, the prospective potential radiation detriment attributable to radiotherapy has been characterized in the literature somehow differently. It has been termed '*second cancers*', '*secondary cancers*' and '*second primary cancers*', and usually nominated with the English acronym SPC. This document suggests that there

[15] ICRU Publication 83

[16] Nilton Lavatori Correa, Lidia Vasconcellos de Sa and Rossana Corbo Ramalho de Mello. Estimation of Second Primary Cancer Risk after Treatment with Radioactive Iodine for Differentiated Thyroid Carcinoma. THYROID, Volume 27, Number 2, 2017. DOI: 10.1089/thy.2016.0266

are a number of reasons for changing the nomination from SPC to PIPMAR (or similar), as follows:

- The potential radiation detriment after radiotherapy does not only include solid cancers but also leukaemia and therefore it is more proper to refer to malignancy, i.e. the state or presence of a malignant progressive disease be it cancerous tumours or leukaemia. Such malignancies can be more properly qualified as
  - 'prospective', i.e., potentially occurring in the future, and
  - (proper) 'primary', i.e., earliest in time or order, and not caused by or based on the malignancy that has been treated (and expectedly cured) with radiotherapy.
- PIPMAR's malignancies are not limited to second primary malignancies but to the entire sequence of metastases that could originate from the second primary malignancy.
- The various expressions for SPCs have been used ambiguously and sometimes could be construed as comprising only cancers being developed in the primary treatment field.
- The definition of SPC was originally based on traditional criteria for describing a radiation-induced carcinoma[17], which can be summarized as follows:
  (i) a radiation-induced cancer must have arisen in an irradiated field;
  (ii) a sufficient latency period, preferably more than four years, must have elapsed between the initial irradiation and the presumed induced cancer;
  (iii) the biopsy of the treated tumour and of the supposed induced tumour must present different histology; and,
  (iv) the tissue in which the alleged induced tumour arose must have been metabolically and genetically normal prior to radiation exposure.
- Confusedly, another set of criteria for the attribution of a malignant tumour to the effects of radiation were later defined[18]. Use of the expression "SPCs" has generally been based on these criteria, which can be summarized as follows.
  (i) there must be antecedents of irradiation prior to tumour manifestation;
  (ii) the cancer must be produced within the prior irradiation field;
  (iii) there must be pathological evidence of damage to surrounding tissues attributable to radiation; and,
  (iv) the latency between the previous irradiation and the development of the cancer must be a long interval.
- In particular, the criterion demanding that the SPC should originate within the irradiation field has been considered critical. Some reports on side effects of radiotherapy have focused on SPCs produced in the field of the radiotherapy irradiation and sometimes even restricted to effects in the planning target volume.

[17] Cahan et al. (1948)
[18] Goolden (1951)

(36) It seems therefore that that there are subtle but importance differences between PIPMARs and SPCs that justify changing the description of this detriment. Significantly, many references to SPCs are limited to a fraction of malignancies associated with PIPMARs. Namely, they refer to cancers developing in the primary treatment field, and might not necessarily consider malignancies that may develop outside the treatment field.

(37) PIPMAR occurrences have been proven in a limited number of epidemiological studies of patients who have undergone radiotherapy. Its existence is also predictable by many radio-epidemiological studies of populations exposed to radiation, including patients who underwent radio-diagnostic procedures, and by relevant studies of radiobiology and molecular biology.

(38) The following Table summarizes few estimates related to primary cancers and potential PIPMARs, which are available in the literature:

Primary cancer	PIPMAR	Contributing/modifying factors
Hodgkin's Lymphoma	Breast Lung Esophageal Stomach Pancreatic Colorectal Skin Thyroid Sarcoma Head and neck Mesothelioma Leukemia	Chemotherapy (leukaemia and lung cancer) Young age at radiation treatment (breast cancer) Smoking (lung cancer) Sun exposure (skin cancer) Reduced immune function
Testicular	Lung Thyroid Esophageal Stomach Pancreatic Colorectal Renal Bladder Sarcoma Mesothelioma Leukemia	Underlying predisposition (contralateral testicular cancer) Chemotherapy (leukemia) Young age at radiation treatment (solid tumor)
Breast	CBC Lung Sarcoma Esophageal Leukemia	Underlying predisposition (CBC) Chemotherapy (leukemia) Hormonal therapy (endometrial cáncer) Young age at radiation treatment (CBC)
Prostate	Bladder Colorectal Sarcoma Lung	
Cervical	Bladder Renal Rectal Uterine Ovarian	Smoking HPV infection

Table: Primary cancers and PIPMARs[19]

[19] Adapted from NCRP Report N° 170, 2012

RADIATION PROTECTION IN RADIOTHERAPY

(39) The fostering of information exchange on the radiation protection of patients undergoing radio-diagnosis had been significant at the international level, but it has been limited about protection on radiotherapy. The issue was subjected to a deep debate at the international level for the first time, at the Málaga, Conference, in Spain, in 2001 where, for the first time internationally, there was a warning on PIPMARs indicating that '*radiation to normal tissue has a number of possible negative sequelæ including the possible induction of secondary cancers*'. [20]

(40) One of the latest international information exchanges on the subject has been the Bonn Conference, in Bonn, Germany in 2012. While the Bonn Conference was very successful in focusing efforts for the next decade in order to maximize the positive impact of future international work in radiation protection in medicine, the reference to PIPMAR was extremely limited. Only a paper[21] warned that in the past radiation oncologists focused mainly on curing cancers with little consideration for secondary cancer, but recently the situation has been changing: while high precision photon radiotherapy methods are superior to conventional radiotherapy in the dose distribution delivered to the tumour, a large volume of surrounding normal tissues may be exposed to low levels of dose.

(41) The International Commission on Radiological Protection, ICRP, created a working group to study the issue of cancers attributable to radiotherapy but its work remained unfinished [see hereinafter]. The issue was discussed at recent ICRP symposia[22].

(42) The National Radiation Protection Council of the United States, NCRP, published a detailed report on 'second primary cancers and cardiovascular diseases after radiotherapy'[23] [see hereinafter], which provides a comprehensive review of the major epidemiological studies that have evaluated the risk of developing SPC (in addition to cardiovascular disease) in patients whose treatments included radiotherapy, focusing on retrospective epidemiological studies of cancer survivors who received radiation therapies, mainly photons, and also considers what potential implications these retrospective data from historical radiotherapy may have on contemporary radiotherapy.

(43) Other relevant information exchangewere performed in USA. The National Cancer Institute (NCI) published a comprehensive summary of studies of new malignancies in participants in epidemiological studies[24]. The BEIR VII report[25] also published radiation-related dose-response models that have been used to predict the risk of treatment with contemporary radiotherapy techniques.

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[20] Ib. pp 152. Goodenough D.J. Lessons Learned in Radiology.
[21] Ib.pp 75-80. Yonekura, Y. Impact of New Treatment Technology on Patient Protection in Radiotherapy.
[22] SigUDRson A. ICRP Committee 1. Genetic predisposition to radiation-related cancer and potential implications for risk assessment. ICRP Symposium on the International System of Radiological Protection. Bethesda MD, 2011
[23] NCRP Report No. 170 NCRP Publications, Bethesda, MD, 2011. ISBN: 978- 0-9823843-9-8.
[24] Curtis and National Cancer Institute (US)], "New malignancies among cancer survivors SEER cancer registries , 1973-2000, "in NIH Publication No. 05-5302 (National Cancer Institute, Washington, DC, 2006), pp. 1v
[25] BEIR VII

POPULATION AFFECTED

(44) The size of the population of concern to be affected by PIPMAR could be estimated taking into account the following:

- the general incidence of neoplastic malignancies in the population,
- the fraction of patients suffering cancer that are treated with radiotherapy, and
- the expected fraction of survivors

However, it should be noted that there are not available single, simple and comprehensive references over the precise number of malignancies, radiotherapy courses, and survivors of radiotherapy and, in particular, on their evolution with time.

Incidence of malignancies

(45) The incidence of neoplastic malignancies is substantial and therefore the number of people affected is very large. Some summary quantitative information available[26] indicates that "overall, there were 14.1 million new cases and 8.2 million deaths in 2012". National data for a population of around 40,000,000 people show that approximately 1,200 children and adolescents up to 15 years of age are diagnosed with cancer each year in this population.

(46) The available information on the incidence of neoplastic malignancies is vast. Cancer Incidence in Five Continents (CI5) project is the result of a long collaboration between the International Agency for Research on Cancer and the International Association of Cancer Registries. The series of monographs, published every five years, has become the reference source of data on the international incidence of cancer. The CI5 databases provide access to detailed information on the incidence of cancer recorded by cancer registries (regional or national) worldwide in three formats: CI5 I-X: Cancer incidence in five continents volumes I TO X, CI5PLUS: Cancer incidence in five continents time trends, and CI5 X: Cancer incidence in five continents, Volume X.[27]

(47) The overall objective of the Cancer Incidence in Five Continents (CI5) series is to make available comparable data on cancer incidence from as wide a range of geographical locations worldwide as possible. Traditionally, this has been through publication of volumes containing tabulations of cancer incidence rates at approximately five year intervals. The volumes contain three basic elements:

- tabulations from individual registries presenting incidence rates according to sex, age group, and cancer site;
- summary tables permitting comparisons between registries;
- tables presenting indices of the validity and completeness of the different contributions.

Each volume has seen substantial innovation with a view to providing more information while preserving the basic core data and layout. The cancer registries that have provided the data are members of the International Association of Cancer Registries.

(48) The CI5plus database contains updated annual incidence rates for 118 selected populations from 102 cancer registries published in CI5, for the longest period available

[26] Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012,
[27] See http://ci5.iarc.fr/Default.aspx

(up to 2007), for all cancers and 27 major types. In addition, groups of cancer registries in the same country have been added. CI5plus can be used for time trends analyses, but differences over time in registration practices and coding make it necessary to interpret trends with caution.

(49) The Cancer Incidence in Five Continents (CI5) Volume X website is published approximately every five years and provides comparable high quality statistics on the incidence of cancer from cancer registries around the world. Volume X contains information from 290 cancer registries in 68 countries about cancers diagnosed from 2003 to 2007. This website contains several utilities enabling the comparison of cancer rates across diverse populations and allows understanding of the bUDRen of cancer in different regions of the world.

Patients being treated with radiotherapy

(50) It should be noted that not all cancers are treated with radiotherapy. However, radiotherapy treatments are increasing as the practice becomes available in developing countries. UNSCEAR estimated that "in the period 1997–2007 … about 4.7 million patients were treated with external beam radiation therapy, while 0.4 million were treated with brachytherapy" annually [28]. The current global number of treatment is likely much larger,

(51) Paediatric radiotherapy is extremely important for PIPMAR. Children with lymphoma, leukemia, brain tumors, sarcomas, Wilm's tumor, neuroblastoma and liver cancer are typically treated with radiation therapy. From early diagnosis, appropriate treatment, and comprehensive patient care, the possibility of survival has increased to 70-80 percent, even up to 90 percent in cases of some tumours.

Expected survivors

(52) Due to advances in cancer therapy, early detection and improved patient care, the number of cancer survivors has increased over the years, and is estimated internationally to have tripled in the last half century. In the developed world, it is now estimated that the number of cancer survivors represents approximately 3.5% of the population. It is estimated that approximately half of these survivors had received radiotherapy as part of their cancer treatment. Therefore, the cohort of concern to be affected by PIPMAR is larger than 1% of the population.

(53) The expectation of PIPMAR is strongly dependent of the age of the patients undergoing radiotherapy. While patients suffering neoplastic malignancies are mainly old people, the younger patients are those expected to be significantly affected because of the relatively long latency of radiation-induced malignancies –which is about five years for leukaemia and a decade for solid cancers. The cured patients whose life expectancy is much longer than a decade constitute a population at risk for PIPMARs. Paediatric patients are an important group in this category.

[28] UNSCEAR. Sources and Effects of Ionizing Radiation. Volume I: Sources: Report to the General Assembly, Scientific Annexes A and B. UNSCEAR 2008 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.10.XI.3. United Nations, New York, 2010. {U017}

ASSESSMENTS

(54) Many assessments are being performed on the number of patients with multiple primary cancers following radiotherapy. The National Council on Radiation Protection and Measurements (NCRP) of the United States of America (US) has reported that the number is growing[29]

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(55) The US National Cancer Institute's Surveillance, Epidemiology, and Outcomes Program (SEER) reports that multiple primary cancers account for approximately 16% (one-sixth) of all incident cancers. While only a small proportion of all these cancers appear to be due to radiotherapy[30], there seems to be a very significant relative excess risk in paediatric patients. Irradiation of normally healthy tissues as a consequence of radiotherapy treatments appears to be one of the potential causes of such an increased risk of developing primary cancers.

(56) In a specific study, the relative risk of those primary cancers in 11 cohorts of cancer patients was estimated to be 1.31 when comparing patients with radiotherapy to the general population (95% CI: 1.15-1.49). However, this high relative risk does not appear to be due solely to radiation since the relative risk for non-irradiated cancer patients was reported to be 1.12, compared to the general population. It has been argued that the actual excess radiation risk due to radiotherapy should be evaluated comparing cancer patients who received radiotherapy versus those who did not receive it, which would provide a better indication of the carcinogenic role of radiotherapy. [31]

(57) UNSCEAR, has made estimates of the radiation exposure of patients undergoing radiodiagnosis and radiotherapy. Detailed information on the issue has been regularly provided to the UN General Assembly. It should be noted, however, that until now UNSCEAR has neither provided estimates of PIPMAR nor of SPCs. Moreover UNSCEAR estimates are generally retrospective and do not regularly include prospective assessments.

(58) Epidemiological data on PIPMARs are generally limited to SPCs in populations of radiotherapy patients who have been treated with 2D-RT. Innovations in radiotherapy treatments, such as dynamic IMRT, VMAT, and SBRT/SRS, result in larger proportions of low-dose regions where normal tissues are exposed to low dose levels that have been linked to second cancers and cardiac toxicities. However, epidemiological data associated with new radiotherapy treatments are rare if any and they are unlikely to appear for some years due to the long latency time of radiation-induced malignancies.

(59) The new radiotherapy techniques may lead to higher stochastic radiation risks. Advances in imaging, treatment planning, and dose administration are giving radiation oncologists the ability to more and more closely target the tumour while minimizing the dose to other organs at risk. The transition from 2D-RT to 3D-CRT and further to the new procedures, generically referred to in paragraph 33, and radiotherapy techniques referred to in Annex I, has resulted in clear changes in the dose distribution at which prior clinical experience and SPC studies were based.

[29] NCRP 170
[30] Curtis et al., 2006; Morton et al., 2010
[31] Suit study (2007),

(60) In general, the new radiotherapy techniques appear to increase doses at the target volume, which includes the tumour and a limited amount of normal tissue. It also appears to be an overall reduction in the volume of normal tissues receiving high doses. However, particularly in the case of IMRT, there is a larger volume of normal tissue irradiated at low doses of radiation. In addition, in comparison to 2D-RT and 3D-CRT, IMRT requires a significantly higher number of monitor units of the machine to administer a comparable prescribed dose, resulting in a dose increase to the whole body as a result of the increased leakage and scatter radiation. Also, the increased use of imaging procedures associated to these new radiotherapy techniques adds an additional dose to the patient.

DETRIMENT

(61) For the purpose of patient protection any relevant quantity to be considered should characterize the detriment derived from PIPMAR and be defined in a manner consistent with the paradigm used by international radiation protection standards.

(62) The term detriment is used as a mathematical expectation of harm. It means the total harm that might eventually be incurred by individuals or by a group of individuals that is subject to exposure and by its descendants as a result of exposure to radiation from a source. In the case of PIPMARs it may be considered as an expression of the damage to health which could be experienced by individuals who have incurred radiotherapy.

(63) The detriment is understood as a multi-attribute concept whose main components would be the probability of fatal malignancies and the weighted probability of a nonfatal malignancies, and the shortening of life expectancy if malignancies occurred (weighted effect of severe heritable effects might also be considered following URERs). Whatever be the proxies decided to quantify URERs and PIPMARs they should reflect the detriment attributable to PIPMARs.

ESTIMATING URERs and PIPMARs

(64) The estimations of URERs and PIPMAR could be pragmatically approached by developing a database of typical UDRs for different radiotherapy techniques, patient groups and treatment areas and diagnosis, through the detailed systematic literature survey. Much of the necessary data is likely available in many scientific studies focusing on measuring the doses to normal tissue from radiotherapy or imaging procedures, and the required data can be measured systematically in research institutions. The database should contain the specific radiotherapy techniques, the specific patient groups, different treatment areas/diagnoses and related UDRs.

(65) Notwithstanding the above, a more formal calculation of detriment due to PIPMARs caused by URERs in patients exposed to radiotherapy is a complex task given the incidence of the various attributes associated to the concept of detriment.

(66) In radiation protection practice, it has been recommended that the quantity '*effective dose*' is an appropriate indicator of detriment due to stochastic effects. The international radiation protection standards establish that the *effective dose* is a measure of dose designed to reflect the amount of radiation detriment likely to result from the

dose and assume that the 'detriment-adjusted nominal risk coefficient of dose', which includes the risks of all cancers and hereditary effects, is 5% per sievert (Sv) of effective dose[32].Thus the effective dose is designed to quantify the radiation risk of stochastic effects, whereby the term 'radiation risks' is used with the same denotation that in international standards, namely it refers to the likelihood of occurrence of detrimental health effects of radiation exposure.

(67) However, the recommended system of dosimetric quantities in general (and the *effective dose* in particular) may present a number of challenges for the purposes of monitoring URERs, including the following:

- While the basics quantity of the established dosimetric system, the *absorbed dose*, is a physical quantity (namely a physical property of the phenomenon ionizing radiation, which can be quantified by measurement and can be traceable over time), the *equivalent dose* and the *effective dose* are neither measurable nor traceable quantities. They are defined as a weighted absorbed dose, with changing weighting factors over time[33]. Since they are neither measurable nor traceable a separate quantity for monitoring had to be defined, the *dose equivalent*. The *dose equivalent* was originally created with the main purpose of measuring radiation fields and it does not appear to be tailored to the purposes of monitoring URERs.
- Moreover, the *equivalent dose* and the *effective dose* are defined on the assumption that doses will not be very high (namely, they would be expected to be below or around regulatory limits that are not applicable to patients). Therefore, these quantities are in principle inapplicable to doses that could be expected from URERs (which could be relatively high).
- The weighting of the *equivalent dose* to obtaining the *effective dose* is done over many organs and tissues. The resulting quantity could not be appropriate for dealing with usually inhomogeneous exposure such as URERs, even if the doses were in the range for which the quantity is applicable.

(68) Thus, the *equivalent dose* and the *effective dose* cannot be used for monitoring purposes of URERs. In fact, the ICRP has recognized that the use of *effective dose* in medical applications may be inappropriate and that it would be more useful to calculate the risks for specific age and gender groups, using *equivalent dose* or *absorbed dose* in organs and tissues and age-related risk factors[34]. But the *equivalent dose* has problems of its own as described before, including the fact that is not measurable and therefore not prone for monitoring. The physical quantity *absorbed dose* does not have these problems, but it should not be forgotten that the *absorbed dose* is not a proper indicator of detriment – in fact, the radiation protection quantities *equivalent dose* and *effective dose* were introduced precisely because of this limitation of the *absorbed dose*. The resolution of the resulting conundrum is at the rout of monitoring medical exposures in general and URERs in particular.

[32] BSS §1.4

[33] E.g., significant changes in the ICRP recommended tissue weighting factors in ICRP Publication 60 were adopted in ICRP Publication 103

[34] ICRP Publication 103, paragraph 71

(69) The main challenge for quantifying URERs and PIPMARs seems therefore to explore the possibility of using appropriate *proxies*, which – as indicated heretofore – could be provided by physical or biological dosimetry.

PHYSICAL DOSIMETRY

(70) Physical dosimetry associated to radiotherapy is widely covered in the literature and this document will not deal with it. But it is interesting to explore proxies of dosimetric quantities for estimating URERs.

(71) In occupational and public radiation protection the *proxy* of *effective dose* for external radiation is the *personal dose equivalent*. While it is at least questionable that the same *proxy* could be used for medical exposures in general and for URERs in particular, it is interesting to explore a number of alternatives for estimating *personal dose equivalent* incurred due to URERs attributable to specific radiotherapy treatment. Alternatives for such estimation include theoretical calculations of *personal dose equivalent* making use of phantoms and modelling; physical measurements of *personal dose equivalent* in various points of the patient followed by modelling and adequate combinations of these alternatives. Annex III describe some ongoing dosimetric estimations of URERs and PIPMARs.

BIOLOGICAL DOSIMETRY

(72) Biological indicators in the patient exposed to radiotherapy, such as those resulting from the technique termed '*biological dosimetry*', provide other potential *proxies* for estimating URERs and PIPMARs. Biological dosimetry is a simpler technique widely available, which could allow for reasonable estimates.

(73) The biological dosimetry *proxies* for both URERs and PIPMARs would be chromosomal aberrations. It should be noted that the estimates provided by biological dosimetry will include the designed exposure for treatment purposes plus URER incurred by radiotherapy patients. Nevertheless, the proxy could be used as a higher indicator of URERs or, differentially, for deducting URER. This *proxy* can also be used to assess differences in URERs among patients undergoing similar treatments. It is underlined that such differential assessments always present issues of accuracy and precision that should be carefully evaluated. Annex IV describes relevant biological dosimetry techniques which could be applicable for estimating URERs and PIPMARs.

CONFOUNDING FACTORS - SUSCEPTIBILITY

(74) Apart from lifestyle factors, such as smoking habits and diet, genetic susceptibility is a major confounding factor in determining PIPMARs. Genetic susceptibility is an age related component, as it seems much more likely to find cases of cancers involving a germ line mutation in children than in adults.

(75) Another important confounding factor is radio-sensitivity. It is noteworthy that the historical meaning of radio-sensitivity has changed and now has two different denotations: (a) the capacity of a given irradiated individual or organ to show a specific reaction of toxicity to radiation (cellular death, tissue inflammation, etc.), corresponding to the loss of proliferative capacity observed *in vitro* (the historical definition of radio-

sensitivity); and (b) the risk of radiation-induced genomic instability and cancer, which should be illustrated by the more appropriate term “susceptibility to radiation induced cancer”(radio-susceptibility)[35].

(76) Radio-susceptibility defined as the proneness to radiation-induced cancer[36] is a particular human response to ionizing radiation, which varies among individuals. It has thus been suggested that individuals who are genetically susceptible to cancer manifest this by exhibiting increased DNA radio-susceptibility[37].

(77) Another aspect that should be considered in estimating PIPMAR is the assessment of individual radio-susceptibility. Considering that the increased risk of a second cancer, particularly in children, has been unequivocally demonstrated after radiotherapy to treat Hodgkin's disease (HD), the direct extrapolation of these significant data deserves a word of caution (e.g. in a paediatric series the risk of breast cancer was 75 times the risk that is found in the general population[38]).

(78) Recent data have found that, at equal doses given to the breast for other types of childhood cancers, the risk of secondary breast cancer was significantly higher in Hodgkin's disease patients treated with radiotherapy compared to other paediatric patients, suggesting a specific radio-susceptibility for patients with Hodgkin's disease [39], reinforcing the idea of individual radio-susceptibility as an important confounding factor to be considered.

(79) Consequently, it can be hypothesized that individuals exhibiting increased DNA radio-susceptibility are prone to incur malignancies. These individuals are likely to be those who may experience higher PIPMAR. It could be suggested that time might be ripe for screening patients with increased DNA radio-susceptibility who could be the main candidates to suffer PIPMARs.

[35]Nicolas Foray, Catherine Colin, Michel Bourguignon. 100 Years of Individual Radiosensitivity. Radiology 2012; 264:627–631
[36] ICRP, 1999
[37] Shahidi, 2007 ; Rothfuss, 2000
[38] Bhatia, 1996
[39] Guibout-2005, Travis 2006

IV. REGULATORY POLICIES

(80) Regulatory policies for protecting people against the detrimental effects of radiation are based on scientific knowledge, ethical values, accepted protection paradigms and international standards. The scientific basis of radiation protection regulations is provided by the estimates of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) described heretofore, and they are not to be described further in this document.

(81) The following sections address:

- ethical issues confronting regulatory authorities with respect to PIPMARs,
- radiation protection international and national radiation protection paradigms associated to PIPMARs,
- international standards related to the radiation protection of patients, including specific requirements for:
  - justification of radiotherapy procedures,
  - optimization of the radiation protection of patients undergoing radiotherapy and,
  - related requirements of monitoring.

ETHICAL ISSUES

(82) The potential large impact of PIPMAR in the future seems to be undeniable. However, estimating PIPMAR in long-term survivors is not easy. The long-term risks of new radiotherapy treatments, such as particle therapy, have not yet been determined and are unlikely to be apparent for many years. There are no epidemiological data on the new radiotherapy techniques and they are unlikely to appear for many years due to the long latency time of radiation-induced malignancies.

(83) Confronting the reality of PIPMAR, regulatory authorities having the mandate of protecting people from the deleterious effects of radiation exposure confront a difficult ethical dilemma: whether to be passive before the challenge posed by PIPMAR or to engage in examining regulatory approaches that could benefit the affected patients. This is an ethical dilemma that radiation regulatory authorities will confront explicitly or implicitly. The outcome may be different in different societies. If the decision is to undertake some regulatory action, an early objective appears to be improving knowledge about PIPMAR for progressing in the application of the regulatory principles of justification and optimization (see hereinafter). An apparent regulatory action for this objective could be requiring that URERs be properly monitored and recorded, which is the epilogue suggestion of this document (see Epilogue, hereinafter).

(84) Another ethical issue refers to further actions that health authorities might undertake after being acquainted with information on URERs and PIPMAR. They might decide to keep the information anonymously and used for different public health purposes. They might otherwise decide to inform the patient on his/her prospective risk and take some actions to protect the patient against such risk. Between these two extremes there is a range of possibilities. A justification for the first option could be construed from a hypothesis: should the patient know that he/she is at risk, he would strongly pursue paths of early diagnosis of potential harm. This would be giving rise to what it appears to be a serious problem in modern medicine, the so-called *individual*

health assessment (IHA) of asymptomatic persons, namely investigations for asymptomatic individuals made available to those who may consider they are at risk of a disease. The dilemma in this case is whether individual knowledge of PIPMAR and further diagnostic actions should be considered IHA of asymptomatic persons, or an essential component of a risk-informed survivorship care for cancer patients who no longer require active treatment. The answer to this dilemma has ethical connotations and may differ among countries.

INTERNATIONAL RADIATION PROTECTION PARADIGM

(85) Recommending an international radiation protection paradigm has been the remit of the ICRP. In its own words 'the work of ICRP helps to prevent cancer and other diseases and effects associated with exposure to ionising radiation'[40]. Since 1928, ICRP has developed, maintained, and elaborated the international system of radiological protection that is used world-wide as a universal benchmark for radiological protection standards, legislation, guidelines, programmes, and practice. In fact the international radiation protection standards (see hereinafter) take into account the ICRP recommendations.

(86) 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[41]. In sum, while the issue of secondary cancers is implicitly mentioned in ICRP recommendations, for instance in its relatively recent recommendations on radiological protection in ion beam radiotherapy [42], no specific ICRP recommendations have been developed on how to deal with PIPMARs.

NATIONAL RADIATION PROTECTION PARADIGMS

[40] Official web page of ICRP. http://www.icrp.org/index.asp

[41] In its 2005 meeting in Geneva, ICRP Commmittee 3 discussed "Radiation protection issues of modern radiotherapy techniques". A draft report on "Evaluation and management of secondary cancers in radiation therapy" (as a joint project with ICRU) was discussed by the Committee as its 2007 meeting in Berlin. A task group had the expectation 'to finish this document during 2008 [which] should be ready for publication early in 2009'. At the meeting in Mallorca in 2008, the Committee followed up of the document indicating that it should be finished early in 2009 and requesting rapid publication 'as many papers are likely to be published in the next year'. In 2009, during its meeting in Porto, the 'ongoing documents' treated by the Committee included 'Secondary cancer risk after modern radiotherapy; practical recommendations' (new title) with the expectation that the draft will now be ready by mid 2010 for consideration and approval by the Committee through circulation. In its meeting in Hong Kong in 2010 the status of the draft was again discussed. In the 2011 meeting in Washington DC, a new task group is proposed on 'secondary cancer after modern radiotherapy'. In its 2012 meeting in Vienna the Committee was presented with the progress on a report on 'Practical Radiological Protection Recommendations on Mitigating Secondary Cancer Risks in Modern Radiation Oncology' (new title), with the expectation that the next draft would be 'ready in mid-2013 and shall be considered in next meeting of C3 in 2013'. However, in its 2013 meeting in Abu Dhabi, the Committee decided not to pursue further work on 'Practical Radiological Protection Recommendations on Mitigating Secondary Cancer Risks in Modern Radiation Oncology' and "encourage authors to publish part of the produced material as a scientific article in journal and training material for ICRP website".

[42] ICRP. Radiological Protection in Ion Beam Radiotherapy. ICRP Publication 127. Ann. ICRP 43(4).

(87) While ICRP was considering the issue of secondary cancers after radiotherapy, the NCRP[43] issued a publication on the subject[44]. There do not seem to be many similar publications from other national organizations recommending paradigms for radiation protection in radiotherapy. The NCRP report can be considered one of the earliest and perhaps unique national efforts on this subject. It focuses on, but it is not limited to, SPCs. It also address cardiovascular disease (termed CVD) attributable to radiotherapy.

(88) The NCRP report informs that advances in cancer therapy, early detection of cancer, and supportive care have contributed to steady gains in the five year relative survival rate for all cancers considered together, reaching 66.1 % between 1999 and 2006. These successes are associated with a tripling of the number of cancer survivors in the United States since 1971, and the numbers are growing by 2 % each year. As of 2007, there were ~12 million men and women in the United States with a history of cancer, representing 3.5 % of the population. Radiation remains a cornerstone of successful cancer treatment, with 50 % of all patients estimated to have received radiation therapy for the management of their cancer. For many patients, the gains in survival have come at the price of serious treatment-associated late effects. The report identifies SPCs and CVD as two of the most frequent and important life-threatening events associated with radiation therapy. Multiple primary cancers, now account for approximately one in six of all incident cancers reported each year to the National Cancer Institute Surveillance, Epidemiology and End Results Program; as indicated before, this SEER statistic refers to MPCs, not SPCs, and it is important to make this distinction.

(89) The NCRP report provides a comprehensive and current assessment of the risk of SPC and CVD following radiation therapy among the growing number of cancer survivors worldwide. The report focuses on the complex epidemiologic and dosimetry issues surrounding past, conventional, and the new radiation therapy modalities and techniques, including intensity-modulated radiation therapy and proton-beam therapy. Major epidemiologic studies are reviewed that have provided estimates of the risk of SPC and CVD following exposure to therapeutic doses of radiation in children, adolescents, and adults. Special attention is given to those cancer sites for which dose-response relationships between radiation dose and SPC or CVD have been provided.

(90) The report emphasizes that there is a wealth of knowledge on the risk of SPC following radiation therapy indicating clear increases following high-dose and scatter-dose radiation. For example, radiation-specific increases in such are reported for breast, lung, thyroid, brain, bone, soft tissue, and leukaemia. Past and current approaches to

[43] The NCRP is an institution was chartered by the U.S. Congress in 1964. The Charter of the NCRP (Public Law 88-376) states its objectives as follows: "To: collect, analyze, develop and disseminate in the public interest information and recommendations about (a) protection against radiation (referred to herein as radiation protection) and (b) radiation measurements, quantities and units, particularly those concerned with radiation protection; provide a means by which organizations concerned with the scientific and related aspects of radiation protection and of radiation quantities, units and measurements may cooperate for effective utilization of their combined resources, and to stimulate the work of such organizations; develop basic concepts about radiation quantities, units and measurements, about the application of these concepts, and about radiation protection; cooperate with the International Commission on Radiological Protection, the Federal Radiation Council, the International Commission on Radiation Units and Measurements, and other national and international organizations, governmental and private, concerned with radiation quantities, units and measurements and with radiation protection.

[44] NCRP Report No. 170, Second Primary Cancers and Cardiovascular Disease After Radiation Therapy.

estimate individual specific doses to organs outside the primary treatment fields from various radiation modalities are also summarized in the NCRP report.

INTERNATIONAL STANDARDS

(91) The international standards for the protection of patients undergoing radiological diagnosis or treatment are a relatively new development. International initiatives related to the radiological risks potentially attributable to URERs incurred during radiotherapy procedures are at an even earlier stage of development.

(92) 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[45], and subsequently approved basic safety standards (BSS) for radiation protection in June 1962[46]. These were the first international radiation protection standards. A revised version of the BSS was published in 1967[47]. These earlier standards did not include the protection of patients.[48] .

(93) The third revision of the BSS was published by the IAEA as the 1982 Edition of Safety Series No. 9[49] 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)[50], thus becoming the first international standards involving requirements for the protection of patients.

(94) A substantial revision of the BSS were 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[51], 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 *inter alia* responsibilities, justification of medical exposures, optimization of protection for medical exposures and explicit requirements for therapeutic exposure.

(95) The latest revision of the international standards is the '*Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards*'[52], which again are

[45] INTERNATIONAL ATOMIC ENERGY AGENCY, The Agency's Health and Safety Measures, INFCIRC/18, IAEA, Vienna (1960); The Agency's Safety Standards and Measures, INFCIRC/18/Rev. 1, IAEA, Vienna (1976).
[46] INTERNATIONAL ATOMIC ENERGY AGENCY, Basic Safety Standards for Radiation Protection, Safety series No. 9, IAEA, Vienna (1962).
[47] INTERNATIONAL ATOMIC ENERGY AGENCY, Basic Safety Standards for Radiation Protection (1967 Edition), Safety Series No. 9, IAEA, Vienna (1967).
[48] Ib. 1967. §2.3 (a).
[49] INTERNATIONAL ATOMIC ENERGY AGENCY, Basic Safety Standards for Radiation Protection (1982 Edition), Safety Series No. 9, IAEA, Vienna (1982).
[50] Ib. 1982 §601.
[51] 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
[52] INTERNATIONAL ATOMIC ENERGY AGENCY. Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards: General Safety Requirements. IAEA, Vienna, 2011. IAEA safety standards series, ISSN 1020-525X ; no. GRS Part 3. STI/PUB/1531. ISBN 978–92–0–120910–8

cosponsored by basically all relevant international organizations including the WHO. Hereinafter the current relevant radiation protection requirements established in these standards are described.

RELEVANT RADIATION PROTECTION REQUIREMENTS

(96) It is clear from the analyses heretofore that there might be a growing regulatory concern regarding the risks of PIPMAR, particularly in radiotherapy patients who are long-term survivors. Response to these concerns may affect public protection policies for these patients, including monitoring the unwanted exposure they have incurred.

(97) In order to implement these policies, there is an unavoidable need: to be able to predict the individual risk of PIPMAR in the individuals of the affected population, that is, the probability that these malignancies manifest in the individuals of that group during the rest of their life.

(98) It is reasonable to question that the matter has not matured enough for concrete suggestions of radiation protection policies. In this respect the radiation protection regulatory authorities face a couple of dilemmas, as follows: (i) Should they be concerned about a health risk that shows a limited epidemiological manifestation itself but which, according to current scientific knowledge is latent?; and (ii) What actions should they take? The radiation protection paradigm requires that justified medical exposures be justified, radiation protection options be optimized and risks should be restricted, and any of these principles involves monitoring of the situation.

Justification of medical exposures in radiotherapy

(99) In relation to the purpose of this document, the principle 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.

(100) According the ICRP recommendations, the principle of justification would apply 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 is 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).

(101) International standards have followed ICRP recommendations requiring that exposures shall be justified by weighing the expected therapeutic benefits that they yield against the radiation detriment that they might cause, with account taken of the benefits and the risks of available alternative techniques that do not involve medical exposure. The justification of medical exposure for an individual patient shall take into account (particularly for patients who are pregnant or breast-feeding or paediatric) of: the appropriateness of the request; the urgency of the procedure; the characteristics of

the radiotherapy exposure; the characteristics of the individual patient; and relevant information from the patient's previous radiological procedures.

(102) It follows from this analysis that it is essential for the regulator to be able to estimate URERs in order to enforce compliance with the justification principle.

Optimization of radiation protection in radiotherapy

(103) The principle of optimization of radiation protection applied to radiotherapy would indicate that protection of the patients should be the best under the prevailing circumstances, namely that URERs should be kept as low as reasonably achievable, all factors being taken into account.

(104) In radiotherapy, 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.

(105) International standards have followed the ICRP recommendations on optimization and have established design and operational requirements, 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.

(106) It follows from this analysis that it is essential for the regulator to be able to estimate URERs in order to enforce compliance with the optimization principle.

Monitoring

(107) The regulatory need to be acquainted with URERs implicitely bring to the regulatory need of requiring *monitoring*[53] of URERs.

(108) The superseded international radiation protection standards, issued in 1996 notably required that '*when competent authorities review existing examinations or treatments involving exposures to radiation, they should take into account the somatic and genetic detriment of such exposures*'[54]. *Mutatis mutandi*, this statement could be considered the first international requirement for monitoring exposure in radiotherapy.

[53] The IAEA safety glossary defines *monitoring* as *inter alia* the measurement of dose or dose rate related to the assessment of exposure to radiation and the interpretation of the results.
[54] Ib.1982 §604.

Remarkably, those superseded standards also required that registrants and licensees shall ensure that '*the patient be informed of possible risks*'[55].

(109) However, these requirements were not repeated in the revised international standards, perhaps because they were considered obvious. Notwithstanding, the new standards require programmes of quality assurance in radiotherapy including those for monitoring equipment[56].

(110) The new standards require that calibrations of radiotherapy units be subject to independent verification prior to clinical use[57] . They also include specific requirements for the release of patients after radionuclide therapy, 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[58].

(111) 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*'[59].

(112) 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.

[55] Ib. BSS §II.18 (e).
[56] BSS §3.170
[57] Ib. §3.166 (c).
[58] Ib. §3.177 et seq.
[59] Ib. §3.184 (d)

VI. EPILOGUE

(113) From the analyses and discussions in the document, 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.

(114) 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. Systematic monitoring and registering of URERs would be a helpful tool for controlling the justification of prospective procedures.

(115) 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 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 would be a helpful tool for controlling the optimization of protection in justified radiotherapy procedures.

(116) 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 be monitored and registered and that regulatory actions be explored for requiring monitoring and registering of URERs. 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.

(117) 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.

(118) Finally, it is once more noted and further underlined, that it is not the intention of this document to suggest any other action than exploring the feasibility of regulatory requirements for monitoring and registering of URERs, with the only purpose of ensuring that the already established radiation protection regulatory requirements of justification and optimization be properly implemented. In particular, the suggestions in this document 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.

ANNEX I

QUANTITIES

(I. 1) The *absorbed dose* is the fundamental physical quantity for quantifying dose. It is defined as the quotient between the mean energy imparted by ionizing radiation to matter in a volume element and the mass of matter in such volume element. The energy can be averaged over any defined volume, the average dose being equal to the total energy imparted in the volume divided by the mass in the volume. Absorbed dose is defined at a point; for the average dose in a tissue or organ, its unit is the gray (Gy), equal to 1 J/kg (formerly, the rad was used).

(I. 2) The *equivalent dose* is an organ/tissue related radiation protection quantity defined as the sum of the absorbed doses delivered by radiations of given types averaged over a tissue or organ, weighted by specified *radiation weighting factors* for each radiation type. Equivalent dose is a measure of the dose to a tissue or organ designed, for radiation protection purposes, to reflect the amount of harm caused: thus values of equivalent dose to a specified tissue from any type(s) of radiation can be compared directly. The unit of equivalent dose is the sievert (Sv), equal to 1 J/kg. The rem, equal to 0.01 Sv, is sometimes used as a unit of equivalent dose and effective dose.

(I. 3) The *effective dose* is the whole-body related radiation protection quantity. It is defined as a summation of the tissue equivalent doses, each multiplied by appropriate tissue weighting factors. The effective dose is a measure of dose designed to reflect the amount of radiation detriment likely to result from the dose. Values of effective dose from any type(s) of radiation and mode(s) of exposure can be compared directly. The unit of effective dose is the sievert (Sv), equal to 1 J/kg. The rem, equal to 0.01 Sv, is sometimes used as a unit of equivalent dose and effective dose.

(I. 4) Both, the *equivalent dose* and the *effective dose*, are not measurable quantities and therefore they are not amenable for monitoring. For this purpose the dose equivalent is used as a *proxy* or substitute quantity.

(I. 5) The *dose equivalent* is the quantity amenable for monitoring purposes. It is defined as product of the absorbed dose at a point in the tissue or organ and the appropriate quality factor for the type of radiation giving rise to the dose. It is classified as:

- *ambient dose equivalent*, which is dose equivalent that would be produced by the corresponding aligned and expanded field in the ICRU sphere at a defined depth (for strongly penetrating radiation such depth is recommended to be 10 mm) on the radius opposing the direction of the aligned field, which is used as a directly measurable proxy.
- *directional dose equivalent*, which is the dose equivalent that would be produced by the corresponding expanded field in the ICRU sphere at a specific depth (the recommended value of depth for weakly penetrating radiation is 0.07 mm) on a radius in a specified direction, which is used as a directly measurable proxy (i.e. substitute) for equivalent dose in the skin for use in monitoring of external exposure.

- *personal dose equivalent*, which is the dose equivalent in soft tissue below a specified point on the body at an appropriate depth; this is used in international standards as a directly measurable proxy (i.e. substitute) for equivalent dose in tissues or organs or (with deep of 10 mm) for effective dose, in individual monitoring of external exposure, which is recommended by the International Commission on Radiation Units and Measurements[60] as a simplification of the two separate concepts of individual dose equivalent, penetrating, and individual dose equivalent, superficial, as defined[61].

[60] INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS, Quantities and Units in Radiation Protection Dosimetry, Rep. 51, ICRU, Bethesda, MD (1993); and INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS, Fundamental Quantities and Units for Ionizing Radiation, Rep. 60, ICRU, Bethesda, MD (1998).
[61] INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS, Determination of Dose Equivalents Resulting from External Radiation Sources, Rep. 39, ICRU, Bethesda, MD (1985)

ANEEX II

RADIOTHERAPY TECHNIQUES

Two-dimensional radiotherapy (2D-RT)

(II. 1) Two-dimensional radiotherapy is a conventional external beam radiation therapy where the dose distribution is calculated in 2D planes and delivered using therapy cobalt units or medical linear accelerators generating high energy photons. It mainly consists of single beams of radiation delivered from one to four directions.

Three-dimensional conformal radiotherapy (3D-CRT)

(II. 2) Three-dimensional conformal radiotherapy enables design and delivery of radiotherapy treatment plans based on 3-D image data (acquired using CT, MRI imaging) with treatment fields individually shaped using multileaf collimator (MLC) and a variable number of beams to treat only the target tissue.

2D-RT *vis-à-vis* 3D-CRT

(II. 3) Study comparison between 2D-RT and 3D-CRT techniques for the treatment of different tumor types (e.g. head and neck, breast, prostate, spinal cancer) showed no significant difference in dose coverage and distribution in the target volume. However, 3D-CRT provided better sparing of OARs (e.g. heart, lungs, spinal cord) than the 2D-RT technique, with lower average mean dose for each OAR. In addition, conventional technique has also much lower conformity index (CI) regardless of treatment site[62] [63] .

(II. 4) The transition from 2D-RT to 3D-CRT and/or IMRT has resulted in an increase in dose to the patient's target volume that includes tumor and a limited amount of normal tissue, and an overall reduction in the volume of normal tissues receiving a high dose. However, particularly in the case of IMRT/IGRT, there is a larger volume of normal tissue that is irradiated to low radiation doses[64].

Intensity modulated radiation therapy (IMRT)

(II. 5) Intensity modulated radiation therapy is using highly tailored computing applications to perform optimization and treatment with modulated radiation fluence. It allows the implementation of highly conformal, even concave, dose distributions to a 3-D target volume, while at the same time minimizing the dose to an acceptable level to the surrounding normal structures. IMRT can be delivered using either 2-D physical

[62] Ragazzi, et al. Use of dose-volume histograms and biophysical models to compare 2D and 3D irradiation techniques for non-small cell lung cancer. The British Journal of Radiology. 1999, 72 (855): 279-88.
[63] Åsa Palm & Karl-Axel Johansson (2007). A review of the impact of photon and proton external beam radiotherapy treatment modalities on the dose distribution in field and out-of-field; implications for the long-term morbidity of cancer survivors, Acta Oncologica, 46:4, 462-473.
[64] James A. PUDRy (2008). Dose to normal tissues outside the radiation therapy patient's treated volume: A review of different radiation therapy techniques. Health Phys 95(5): 666-676.

compensators or MLC systems employing: binary delivery; “sliding window” delivery (i.e. dynamic MLC or DMLC); or “step and shoot” delivery (static MLC or SMLC).

(II. 6) IMRT is capable of producing dose distributions that conform to the PTV, however this technique requires significantly larger number of monitor units (MUs) than 2D-RT and 3D-CRT to deliver a comparable prescribed dose. This results in an increase in the dose outside the boundary of the primary collimator due to the increased amount of leakage and scatter radiation. In addition, a large volume of normal tissue is being irradiated to low radiation doses due to the larger number of beams and beam directions used[65].

(II. 7) A comparison of IMRT and 3D-CRT techniques for brain or base of skull pediatric cases showed similar tumor coverage for both techniques. The peripheral doses (measured at the position of the thyroid, breast, ovary and testes) were lower for IMRT in the region close to the target (thyroid), apparently due to the reduced internal scatter from a smaller effective field size for sliding window dynamic MLC. However, the IMRT delivery resulted in higher doses than 3D-CRT to the more distant regions, presumably due to the higher monitor units and resulting increased head leakage.

(II. 8) The estimated average dose from five cases to the thyroid point for one fraction for 3D-CRT was 1.23 cGy compared to 0.84 cGy for the IMRT. For the breast point, the average dose from 3D-CRT plan was 0.20 cGy compared to 0.52 cGy for the IMRT. For the ovary interest point, the average dose from the 3D-CRT plan was 0.011 cGy compared to 0.076 cGy for the IMRT. For the testes interest point, the average dose from the 3D-CRT plan was 0.013 cGy, compared to 0.047 cGy for the IMRT. The estimated total dose (delivered over an entire treatment course of 30 fractions) to the thyroid, breast, ovary, and testes points were 25 cGy, 15.6 cGy, 2.3 cGy, and 1.4 cGy, respectively for the IMRT technique and 37 cGy, 6 cGy, 1.2 cGy, and 0.4 cGy, respectively for the 3D-CRT technique. A total body dose of 45 cGy was delivered with the IMRT technique, and of 44 cGy was delivered with the 3D-CRT technique[66].

(II. 9) Average absorbed dose values (per treatment Gy) in the different anatomic regions were also measured during the treatment of prostate cancer for IMRT (10 MV and 18 MV) and Tomotherapy technique, using anthropomorphic phantom loaded with TLD detectors. For 18 MV IMRT dose values varied from 2.28 mGy/Gy for head and neck region, 3.25 mGy/Gy for thorax region, to 88.40 mGy/Gy in pelvis region. For 10 MV IMRT dose values varied from 0.49 mGy/Gy for head and neck region, 1.45 mGy/Gy for thorax region, to 53.19 mGy/Gy in pelvis region. For 6 MV Tomotherapy treatment (TT) dose values varied from 0.47 mGy/Gy for head and neck region, 1.09 mGy/Gy for thorax region, to 64.05 mGy/Gy in pelvis region. It was observed that the highest absorbed doses are related to the 18 MV IMRT modality, particularly at distances located further away from the treatment site (head and neck). On the other

[65] James A. PUDRy (2008). Dose to normal tissues outside the radiation therapy patient’s treated volume: A review of different radiation therapy techniques. Health Phys 95(5): 666-676.

[66] David B. Mansur, Eric E. Klein, Beth P. Maserang. Measured peripheral dose in pediatric radiation therapy: A comparison of intensity-modulated and conformal techniques, Radiotherapy and Oncology, Volume 82, Issue 2, February 2007, Pages 179-184, ISSN 0167-8140.

hand, 10 MV IMRT and 6 MV TT showed very similar behaviour in terms of peripheral doses[67].

Volumetric modulated arc therapy (VMAT)

(II. 10) Volumetric modulated arc therapy delivers radiation by rotating gantry (usually 360° rotating fields with one or more arcs), changing speed and shape of the beam with a multileaf collimator (MLC) - "sliding window" system of moving - and fluence output rate (dose rate) of the medical linear accelerator.

(II. 11) The potential advantages of VMAT include a large reduction in treatment time and concomitant reduction in the number of MUs required to deliver a given fraction size. However, VMAT, just as IMRT and Tomotherapy, also delivers low dose to a larger volume of normal tissue than 3D-CRT[68].

(II. 12) The results of the measurement of regional peripheral doses (PD) for head and neck cancer comparing VMAT and Tomotherapy technique showed no systematic difference of PDs grouped per region. Doses were evaluated with an anthropomorphic phantom loaded with TLD detectors. The mean values were obtained by averaging over the different TLD chips, in each organ and /or region. Average absorbed dose (per treatment Gy) for VMAT technique ranges from 0.62 mGy/Gy (pelvis region), 1.97 mGy/Gy (thorax region), to 342.60 mGy/Gy (head and neck region). In case of Tomotherapy technique, average absorbed doses varies from 0.45 mGy/Gy (pelvis region), 1.59 mGy/Gy (thorax region), to 372.12 mGy/Gy (head and neck region)[69].

Tomotherapy (*IGRT approach)

(II. 13) Tomotherapy delivers radiation using a rotating intensity modulated fan beam and temporally modulated binary collimator that rapidly moves leaves in and out of the slit-beam to create the non-uniform x-ray beam fluence. Serial, or axial, tomotherapy dose distributions are delivered slice by slice, with patients being sequentially translated through the linac gantry rotational plane between slices. Helical tomotherapy distributions are delivered without interruption. Patients are translated smoothly through the bore of the machine as its gantry continuously rotates[70].

(II. 14) Helical tomotherapy treatment delivery requires significantly longer beam-on times than those used by conventional linac. However, because the helical tomotherapy delivery system was designed to minimize radiation leakage, the PD is equal to or less

[67] E. D'Agostino, R. Bogaerts, G. Defraene, L. de Freitas Nascimento, F. Van den Heuvel, D. Verellen, M. Duchateau, W. Schoonjans, F. Vanhavere. Peripheral Doses in Radiotherapy: a Comparison between IMRT and Tomotherapy. Radiation Measurements, 57 (2013), pp. 62–67.
[68] D. Palma, E. Vollans, K. James, et al. Volumetric modulated arc therapy for delivery of prostate radiotherapy: Comparison with intensity-modulated radiotherapy and three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys, 72 (2008), pp. 996–1001.
[69] E. D'Agostino, R. Bogaerts, G. Defraene, L. de Freitas Nascimento, F. Van den Heuvel, D. Verellen, M. Duchateau, W. Schoonjans, F. Vanhavere. Peripheral Doses in Radiotherapy: a Comparison between IMRT and Tomotherapy. Radiation Measurements, 57 (2013), pp. 62–67.
[70] Fenwick, J. D., Tome, W. A., Soisson, E. T., Mehta, M. P., & Rock Mackie, T. (2006). Tomotherapy and other innovative IMRT delivery systems. Semin Radiat Oncol. 16, 199–208.

than the published PD for conventional MLC IMRT delivery[71]. See above the comparison of PD for Tomotherapy, IMRT, and VMAT techniques.

Image - guided radiation therapy (IGRT)

(II. 15) Image - guided radiation therapy refers broadly to treatment delivery using modern imaging methods, in target and non-target structures and RT definition, design and delivery. This technique may be combining real-time imaging of one or more small medical implantable devices inside or close to the tumor with real-time adjustment of the therapeutic beams. There are multiple types of technology that can be used for IGRT:

- Electronic portal imaging devices (kV, MV)
- kV CT-on-rails
- CBCT (kV, MV)
- MVCT
- Ultrasound (US)
- Magnetic resonance imaging (MRI)
- Positron Emission Tomography (PET)

(II. 16) While diagnostic CT effective doses are in the range of 2 to 10 mSv, imaging doses (CT-on-rails) can be reduced further by a factor of 2-4 when used for daily targeting. This is because the image quality from low-dose CT imaging is sufficient for image alignment. kV-CBCT imaging dose varies widely depending on the acquisition technique used. Doses, reported in the literature, were ranging from 0.1 to 2cGy per acquisition. The imaging doses used for MV-CBCT were ranging from 0.7 to 10.8 cGy per scan. Over a 35 fraction course of treatment, the extra dose delivered from CBCT to the lens, brainstem, and spinal cord could reach 2, 1.7 and 1.4 Gy respectively, pushing organs above set tolerances. The fan-beam MVCT imaging doses range from 0.7 to 4 cGy and depend on the selected CT pitch and the image anatomy thickness[72]. Dose can, therefore, cumulate from 3 to 370 cGy over a course of treatment, above the threshold doses reported in the literature for secondary malignancy occurrence[73].

Stereotactic Radiosurgery (SRS) & Stereotactic Body Radiotherapy (SBRT)

(II. 17) **Stereotactic Radiosurgery** is a non-invasive radiotherapy method which refers to the precise and focused delivery of a single, high dose of radiation in a single session and has been used to treat various intracranial and skull base lesions. Highly conformal isodose distribution and a very steep dose gradient of dose fall-off beyond the prescribed isodose line enable the delivery of an ablative dose of radiation to intracranial and skull base lesions. :

(II. 18) **Stereotactic Body Radiotherapy** is based on the same principle as SRS with the difference that it uses multiple treatment sessions, usually 3-5, and delivers treatment to areas outside the brain (e.g. pelvis, lung, bone, and spine).

[71] Ramsey, Chester R., et al. Out-of-field dosimetry measurements for a helical tomotherapy system. Journal of Applied Clinical Medical Physics, 2006, 7.3: 1-11.
[72] Australia/New Zealand Position Paper: Position Paper on Image Guided Radiation Therapy (IGRT) 2015.
[73] Bissonnette et al.: QA for image-guided radiation therapy utilizing CT-based technologies: A report of the AAPM TG-179. (2012).

(II. 19) Stereotactic radiotherapy and radiosurgery treatment plans can be created and delivered using different devices, such as LINAC with stereotactic cones and MLC, CyberKnife system, Tomotherapy system, Gamma Knife unit, and Proton therapy (passive scattering technique or beam scanning including IMPT).

(II. 20) Peripheral doses absorbed during simulated stereotactic treatment of a brain lesion (5 Gy prescribed to the target for each technique) ranged from of 4.1 mGy (Gamma Knife) to 62.8 mGy (LINAC with cones) in the thyroid, from 2.3 (TomoTherapy) to 30 mGy (preshielding CyberKnife) in the sternum, from 1.7 (TomoTherapy) to 20 mGy (preshielding CyberKnife) in the upper part of the lungs, from 0.98 (Gamma Knife) to 15 mGy (preshielding CyberKnife) in the lower part of the lungs, and between 0.3 (Gamma Knife) and 10 mGy (preshielding CyberKnife) in the gonads[74].

(II. 21) For ocular melanoma stereotactic treatments simulated on the anthropomorphic phantom (the normalizing tumor dose for all experiments was 56 Gy), a proton beam employing no double scattering system delivers the lowest peripheral doses proximally to the contralateral eye (9-12 mSv) and thyroid (less than 10 mSv) when compared to radiosurgery with the Model C Gamma Knife (402-2380 mSv for contralateral eye, 190 for thyroid) or CyberKnife (46-255 mSv for contralateral eye, 196 mSv for thyroid). At distal locations in the pelvis, peripheral doses delivered with proton (4-7 mSv) and Gamma Knife (13 mSv) are of an order of magnitude smaller than those delivered with CyberKnife (117 – 132 mSv)[75].

Particle therapy (Hadron therapy)

(II. 22) Particle therapy (or Hadron therapy) is a radiotherapy technique utilizing hadrons, i.e. protons, neutrons, pions, ions (alphas, C, Ne). Hadron beams allow highly conformal treatment (where the beam conforms to the shape of the tumour) of deep-seated tumours with great accuracy, while delivering minimal doses to surrounding tissues.

(II. 23) ***Boron Neutron Capture Therapy*** might be considered as a type of secondary particle therapy, as the selective killing of tumor cells is mostly from energetic ions (alpha-particle and a Lithium-7 nucleus) produced by the secondary nuclear reaction after the boron isotope B-10, specifically accumulated in tumor cells, adsorbs a neutron.

(II. 24) Intensity modulated proton beam therapy (IMPT) significantly reduces the integral non-target dose (prostate cancer RT study). It has potential to preserve target dose homogeneity while simultaneously minimizing the dose delivered to OARs. Proton beam therapy (PBT) as well as IMRT improved coverage for target volumes, but PBT results in less dose to the normal tissues.

(II. 25) The estimation of the body mean non-target (excluding PTV) integral dose for Proton radiotherapy, 3D-CRT, and IMRT in Stage I Non-small-cell lung cancer showed

[74] Di Betta, Erika, et al. Evaluation of the peripheral dose in stereotactic radiotherapy and radiosurgery treatments. Medical physics, 2010, 37: s. 3587.
[75] Zytkovicz, A., et al. Peripheral dose in ocular treatments with CyberKnife and Gamma Knife radiosurgery compared to proton radiotherapy. Physics in medicine and biology, 2007, s. 5957-5971.

a significant reduction of normal tissue dose by Proton radiotherapy. The integral dose was reduced from 5.3 Gy at 66Gy (2 Gy/fraction) and 7.0 Gy at 87.5 Gy (escalated dose, 2.5 Gy/fraction) with photon therapy to 2.1 Gy at 66 CGE (Cobalt Gray equivalents, in 2-CGE fractions) and 2.7 Gy at 87.5 CGE (in 2.5-CGE fractions) with proton therapy (60-61 % absolute improvement). The spinal cord maximal doses were 14.1 Gy and 18 Gy with photon therapy and 4.7 Gy and 5.6 Gy with proton therapy at doses 66 Gy (CGE) and 87.5 Gy (CGE), respectively. This indicates that proton treatment significantly reduced dose to normal tissues, in this case to the lungs, esophagus, spinal cord, and heart even with the dose escalation, compared with standard dose photon therapy, either 3D or IMRT[76].

Auger therapy (AT)

(II. 26) Auger therapy is a form of radiation therapy which relies on a large number of low-energy electrons emitted by the Auger effect to damage cancer cells. It differs from other types of radiotherapy in that electrons emitted via the Auger effect (Auger electrons) are released in large numbers with low kinetic energy and therefore they affect cells over a very short range, on the order of nanometers, i.e., less than the size of a single cell. This very short-range delivery of energy permits highly targeted therapies. Auger therapeutics involve small molecules, capable of entering cells of interest and binding to specific sub-cellular components, which contain heavy atoms capable of emitting Auger electrons.

Brachytherapy

(II. 27) Brachytherapy (also called internal radiation therapy) is delivered by placing radioactive sources inside or next to the area requiring treatment on a temporary or permanent basis. It allows using a higher total dose of radiation to treat more-specific areas of the body in less time than conventional external beam radiation therapy, while reducing the probability of unnecessary damage to surrounding healthy tissues.

(II. 28) Several studies have compared brachytherapy techniques with external radiotherapy in the terms of doses absorbed by various organs during the certain treatment. The largest doses to internal organs (spleen, heart) during the simulations of breast cancer treatment were measured for the wedge compensation technique, 2300 mSv and 2.7 Gy respectively (the doses were expressed in Gy when discussing the risk of cardiomyopathy and in mSv when discussing the risk of secondary cancers). Smaller scatter doses are induced using breast IMRT, respectively 810 mSv and 1.1 Gy, or 3D-CRT partial breast irradiation, respectively 130 mSv and 0.7 Gy. Dose to the lung is also smaller for IMRT and 3D-CRT compared to the wedge technique. For multicatheter HDR brachytherapy a large dose is delivered to the heart, 3.6 Gy, the spleen receives 1171 mSv and the lung receives 2471 mSv. In contrast, breast seeds implant (^{103}Pd) is associated with lower dose to most integral organs than HDR

[76] Joe Y. Chang, Xiaodong Zhang, Xiaochun Wang, Yixiu Kang, Beverly Riley, Stephen Bilton, Radhe Mohan, Ritsuko Komaki, James D. Cox, Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in Stage I or Stage III non–small-cell lung cancer, International Journal of Radiation Oncology*Biology*Physics, Volume 65, Issue 4, 15 July 2006, Pages 1087-1096, ISSN 0360-3016, http://doi.org/10.1016/j.ijrobp.2006.01.052.

brachytherapy, with 44 mSv delivered to the spleen, 0.7 Gy to the heart, and 790 mSv to the lung[77].

(II. 29) Organ doses to nearby regions while comparing HDR brachytherapy and external radiotherapy (four-field box technique) for patients with cervical cancer were higher for brachytherapy than for external beam therapy. On the contrary, organ doses to distant treatment regions were higher for external beam therapy due to out-of-field radiation resulting from scattering and leakage in the gantry head. The lowest doses were received by the brain (external radiotherapy: 15.82 mGy; brachytherapy: 2.49 mGy), the thyroid and the lung received (external radiotherapy: 75.58 mGy, 81.53 mGy respectively; brachytherapy: 5.70 mGy, 26.94 mGy respectively), and the highest doses were measured in the right kidney (external radiotherapy: 655.17 mGy; brachytherapy: 215.2 mGy)[78].

[77]J.P. Pignol, B.M. Keller, A. Ravi. Doses to internal organs for various breast radiation techniques – implications on the risk of secondary cancers and cardiomyopathy. Radiat Oncol, 6 (2011), p. 5.

[78] Lee, B., Ahn SH, Kim H, Son J, et al. Secondary cancer-incidence risk estimates for external radiotherapy and high-dose-rate brachytherapy in cervical cancer: phantom study. J Appl Clin Med Phys. 2016 Sep 8;17(5):6087.

Annex III

ONGOING ESTIMATES

(III.1) Many efforts are under way to estimate the order of magnitude of doses due to URERs. The American Association of Physicists in Medicine (AAPM)[79] has created an 'ad hoc' committee to deal with this issue[80] to review the dosimetry of non-target and out-of-field exposures using experimental and computational approaches. Studies on historical patients can provide comprehensive information about secondary effects from out-of-field doses when combined with long-term patient follow-up, thus providing significant insight into projecting future outcomes of patients undergoing modern-day treatments. Also, Monte Carlo modelling has been developed as a means of determining doses located outside the primary beam. It has been reported that 'out-of-field doses can be as high as 900 to 1800 mGy assuming historical prescription doses of 30 to 60 Gy and should be considered when correlating late effects with normal tissue dose'[81].

(III.2) The risks of developing a solid tumour after radiation exposure are reasonably well described by linear dose–response functions in the dose range from 0.2 to 2 Sv. However, epidemiology does not provide the necessary information for SPCs in radiotherapy patients, in which a small volume is exposed to high doses, and the rest of the body to low doses. The SPC risk is then calculated using models: usually, the linear-no-threshold (LNT) assumption is adopted at low doses, whereas models taking into account competition between cell killing and transformation are used in the high dose region. Physical doses are converted into dose equivalents using weighting factors at low doses or RBE values at high doses, and then the risk of cancer incidence or mortality is estimated by the product of the equivalent dose and organ-, age- and gender-specific risk coefficients, which have been mostly derived from A-bomb survivors. The models are affected by substantial uncertainties, which can only be reduced with a better understanding of the mechanism of radiogenic carcinogenesis.

(III.3) Taken together, data suggest that particle therapy is typically not causing an increase in the dose to distal organs compared with high-energy IMRT. However, great care should be taken in comparing these values, which generally refer to the effective dose, a controversial radiological unit. Indeed, effective doses use tissue weighting factors that are estimated by several stochastic end points, and do not include any age- or gender dependence in cancer risk. Especially for paediatric patients, the assumption that weighting factors are independent of age at exposure is tenuous. Cancer is a tissue-specific disease, and there is no evidence that the shape of the dose–response curve is the same for different organs.

(III.4) Current risk models and risk estimation models are used to provide the clinicians with tools for justification and optimization evaluations when deciding a treatment or

[79] The AAPM is an USA scientific and professional organization, composed of more than 8000 scientists whose clinical practice is dedicated to ensuring accuracy, safety and quality in the use of radiation in medical procedures such as medical imaging and radiation therapy.

[80] The AAPM TG Committee No.158 entitled, 'Measurements and Calculations of Doses outside the Treatment Volume from External-Beam Radiation Therapy'

[81] Petroccia H, Olguin E, Culberson W, Bednarz B, Mendenhall N, Bolch W. A Monte Carlo Study of Out-Of-Field Doses From Cobalt-60 Teletherapy Units Intended for Historical Correlations of Dose to Normal Tissue. Med Phys. 2016 Jun; 43(6):3317. doi: 10.1118/1.4955548 SU-C-BRC-01

designing new therapeutic protocols. The various available models appear to be helpful to compare the risks associated with the different techniques. However, it is probably unreasonable to try to calculate with these models a precise second cancer risk for a given treatment of a given patient, but rather at this time the calculations should be used as a guide rather than an absolute.

(III.5) It should be noted that while approaches of dose modelling and calculations through theoretical estimations and physical measurements are feasible, they can became cumbersome and particularly untailored to simple radiotherapy practices; they may become simpler with the most modern computerized equipment

ANNEX IV

BIOLOGICAL DOSIMETRY

(IV. 1) The objective of biological dosimetry is to estimate the dose in persons presumed or proven to be exposed to ionizing radiation from biological samples. Biological dosimetry laboratories are widely available and are usually accredited as a test laboratory under ISO standards.

(IV. 2) Observed frequency of aberrations in lymphocytes is interpreted in terms of dose following a dose-response calibration curve. Calibration curves are performed by *in vitro* exposure of blood samples to different doses of appropriate radiation quality. As the biological endpoint considered is chromosomal aberration, the frequency of aberrations reflects the dose in the lymphocytes cell nucleus. For the radiation types usually used in radiotherapy, such dose is a very good dose approximation of the soft tissue dose. This is because the diameter of the lymphocyte nucleus is small, approx. 6 μm, compared to the ranges of secondary particles produced by that radiation, so the Bragg-Gray cavity theory can be applied. However, there are exceptions for radiotherapy with heavy particles.

(IV. 3) The dose value obtained by referring the frequency of aberrations represents an average dose in the lymphocytes. This could approach an average of the whole body because the lymphocytes are widely distributed in the body.

(IV. 4) The classic paradigm in radiobiology states that the primary target of ionizing radiation is the DNA macromolecule that constitutes the genetic material of all living organisms contained in the cell nucleus and which is organized into chromosomes that can be visualized and studied only during cell division (mitosis or meiosis). The passage of an ionizing trace, through the nucleus, induces chromosomal ruptures whose anomalous joining, through the enzymes of cellular repair, gives rise to the so-called chromosomal aberrations and their cytoplasmic derivatives, the micronuclei. According to their stability through successive cycles of cell division, the chromosomal aberrations can be classified in:

- Unstable, their number declines over time after overexposure to ionizing radiation (dicentric and micronuclei)
- Stable, persist in time after overexposure (translocations and inversions).

The current paradigm in biological dosimetry includes both effects: the classic (directed to the DNA) and the non-directed.

Conventional cytogenetic technique

(IV. 5) At present, the quantification of unstable chromosomal aberrations (dicentrics-DC-) is the most widely used method in biological dosimetry. The induction of dicentrics is radiation specific, only a few chemical agents such as bleomycin and endoxan are radiomimetic. Thus, the presence of dicentrics allows to determine exposure to ionizing radiation (accidental, occupational and medical).The method has a high sensitivity (0.1 Gy for low LET radiation) and a well-known dose dependence up to about 5 Gy. This methodology allows estimation of the acute equivalent dose to the

whole body, but can be modified to estimate the dose in prolonged or inhomogeneous exposures.

(IV. 6) The DC assay remains the international biodosimetry “gold standard” for recent radiation exposures and is the technique with which newer biodosimetric approaches are compared. The DC assay can detect exposure to 0.1 Gy if up to 1000 cells are analysed and, based on the distortion of the Poisson distribution of the number of aberrations/cell, differentiates between partial and whole body exposures or to high or low LET radiation.

(IV. 7) The DC assay has a low background, a high comparability between the *in vivo* and *in vitro* dose response and a low inter-individual variability. The scoring of DC based on chromosomal morphology requires a high level of expertise, and time to analyse large numbers of cells. Automated DC scoring systems have been developed and international networks have attempted to harmonize manual and automated scoring approaches. However, automated DC scoring detects only half of the Giemsa stained dicentrics and rejects many metaphases. Technical advances permitting high through-put analysis should allow investigations into the low dose exposures.

Micronucleus (MN) technique

(IV. 8) MN are spherical cytoplasmic bodies, detected at the interface, smaller and morphologically identical to the cellular nucleus. They originate from acentric fragments or whole chromosomes that are delayed in the cellular division and fail in their incorporation to the descendent nuclei.

(IV. 9) The well-established and standardized CBMN assay in PBLs remains a significant biodosimetry tool for IR exposure and a potential alternative to the DC assay, as it requires less time for evaluation of the results and cytogenetic expertise. One of the disadvantages of the test is its reduced sensitivity for the detection of radio-induced damage by low doses of low LET radiation due to its high spontaneous frequency, which also shows a wide inter-individual variability. It is suggested that several factors called "confounding" contribute to the observed variability. It can be improved using centromeric probes and used for retrospective dosimetry. Nevertheless, it does not achieve the sensitivity and specificity of the DC assay.

Fluorescence In Situ Hybridization (FISH) technique

(IV. 10) Since dicentrics are characterized because their frequency decreases over time after exposure, stable chromosomal aberrations (translocations) are considered to represent an adequate indicator for the dosimetric evaluation of past exposures (retrospective dosimetry), because the translocations are not negatively selected during the mitotic division in the hemopoietic stem cell compartment, and are considered stable over time. These translocations, which are considered cytogenetic biomarkers of persistent effects, can be identified by the FISH technique.

(IV. 11) Unlike dicentrics, the frequency of translocations does not decline to values close to zero but reaches an asymptotic value, other than zero, which appears to be dose dependent, allowing translocations to retain their capacity to be used for dosimetric purposes for years after exposure. These characteristics determine that this methodology is a candidate for its application in epidemiological studies.

(IV. 12) Translocation frequency was found to be linearly related to individual red bone marrow dose from incorporated Sr-89/90 above 300 mGy >50 years after irradiation in the Techa River residents. The FISH translocation assay is also informative for combined external gamma and internal doses from Sr-90, albeit with fairly large uncertainties. A significant linear relationship between translocations and red bone marrow dose >300 mGy from past prolonged external gamma-radiation exposure was also found in studies of Mayak workers.

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