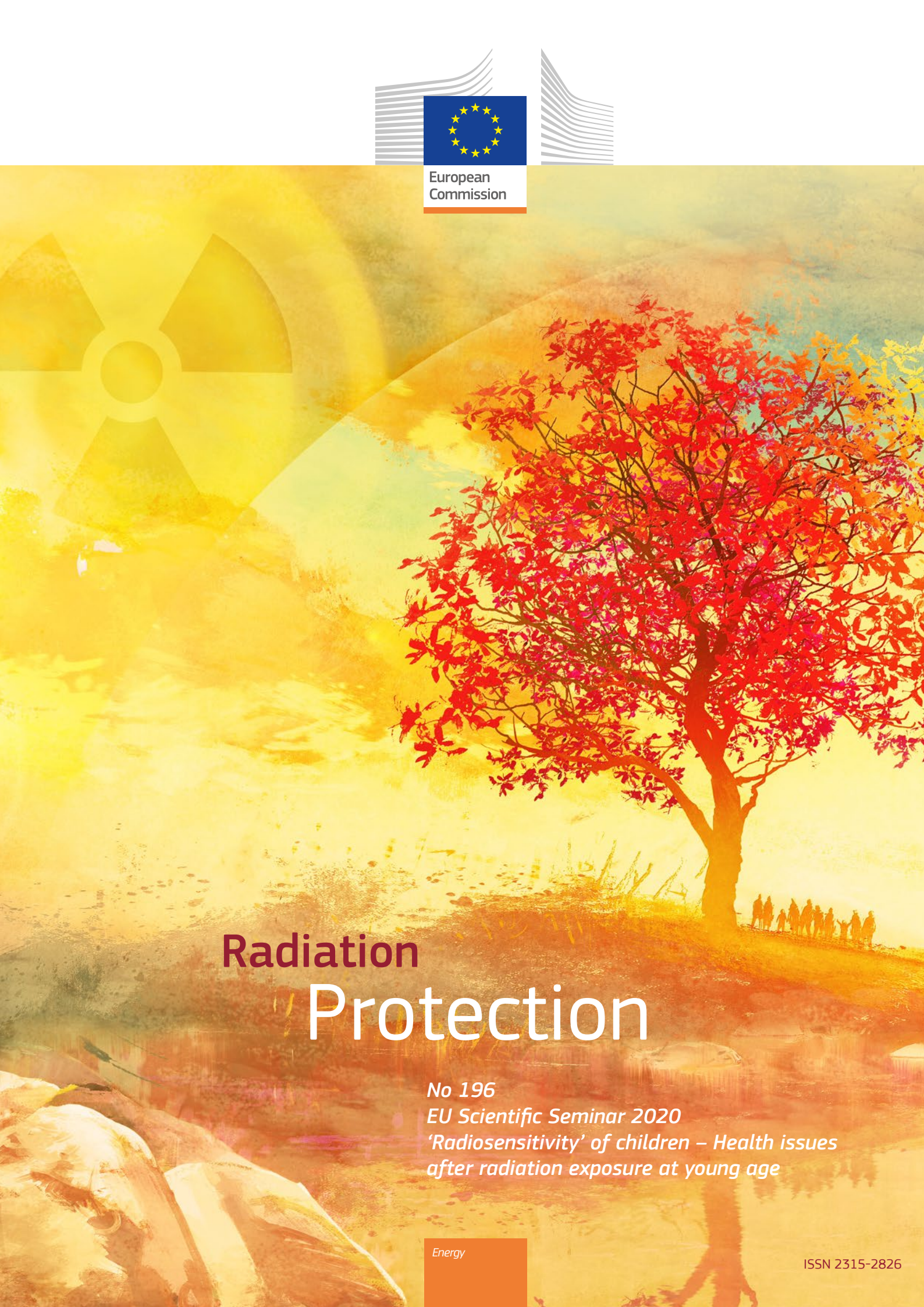

Radiation Protection

No 196

EU Scientific Seminar 2020

'Radiosensitivity' of children – Health issues after radiation exposure at young age

Energy

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EU Scientific Seminar 2020

"Radiosensitivity" of children – Health issues after radiation exposure at young age

Proceedings of a scientific seminar held via WebEx on
1 December 2020

Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts

Directorate-General for Energy

Directorate D — Nuclear Energy, Safety and ITER

Unit D3 — Radiation Protection and Nuclear Safety

2021

Foreword

Luxembourg, November 2021

The European Commission organises every year, in cooperation with the Group of Experts referred to in Article 31 of the Euratom Treaty, a Scientific Seminar on emerging issues in Radiation Protection – generally addressing new research findings with potential policy and/or regulatory implications. Leading scientists are invited to present the status of scientific knowledge in the selected topic. Based on the outcome of the Scientific Seminar, the Group of Experts referred to in Article 31 of the Euratom Treaty may recommend research, regulatory or legislative initiatives. The European Commission takes into account the conclusions of the Experts when setting up its radiation protection programme. The Experts' conclusions are valuable input to the process of reviewing and potentially revising European radiation protection legislation and may assist in the implementation of Council Directive 2013/59/Euratom (Basic Safety Standards Directive).

In December 2020, the EU Scientific Seminar covered the issue *"Radiosensitivity" of children – Health issues after radiation exposure at young age*. Internationally renowned scientists presented the following topics:

- Individual Response to Ionising Radiation – Radiosensitivity of Children
- Cancer risks after radiation exposure of children – overview of epidemiological studies (short-term and long-term exposures)
- Neurocognitive effects after radiation exposure of children
- Dosimetry and dosimetric challenges in paediatric radiology and radiotherapy.

The presentations were followed by a round table discussion, in which the speakers and additional invited experts discussed potential *policy implications and research needs under the key areas of:*

- Cumulative doses in medicine – risks for children
- Dosimetry challenges of radiation dose estimation – unwanted doses
- Combined effects of ionising radiation and other environmental/chemical factors as a function of age.

The Group of Experts discussed this information and drew conclusions that are relevant for consideration by the European Commission and other international bodies.

Contents

Individual Response to Ionising Radiation – Radiosensitivity of Children

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Abstract

It is often assumed that children are more vulnerable to radiation exposure than adults. This statement is only partly true and strongly depends not only on the analysed effects but also on the exact age and organ at risk. Generally, children tolerate higher lethal total body doses than people at advanced ages. However, this does not transcribe into fewer long-term effects than in adult survivors. Following paediatric radiotherapy, some 60-90 % of childhood cancer survivors will develop one or more chronic health conditions, and 20-80 % will experience severe or life-threatening complications. Tissue tolerances to therapeutic radiation doses are variably different from that in adults, with some organs more and some less sensitive. With respect to radiation-induced cancers, for a given radiation dose, children are generally at a higher risk of tumour induction than adults but the radiosensitivity varies between organs and caution needs to be taken not to overgeneralise. High radiosensitivity in children is observed for leukaemia, thyroid, skin and brain cancer, while a low sensitivity is observed for lung cancer. Breast and uterine cancer sensitivity is linked to puberty. For other cancer types, there is no clear impact of age on the level of risk.

1. Introduction

The United Nations Convention on the Rights of the Child[2] states in the preamble that "the child, by reason of his physical and mental immaturity, needs special safeguards and care, including appropriate legal protection, before as well as after birth". Implicit in this statement is the assumption that the child, defined as a human being below the age of 18, is particularly vulnerable. With respect to radiological protection, the term "vulnerable" translates into "radiosensitive". But can we simply assume that children are generally more radiosensitive than adults?

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[2] https://www.unicef.org/child-rights-convention

Before attempting at answering this question it must be recalled that radiation effects are divided into two types: tissue (deterministic) and stochastic effects. The fundamental difference between the two types of effects is that the former are caused by inflammatory response and cell killing while the latter by accumulation of mutations in surviving cells. Mutations can lead to transformation of normal into malignant cells. Deterministic effects include organ and tissue damage as well as the acute radiation syndrome, while stochastic effects include cancer, non-cancer disease, and hereditary effects (ICRP 103, 2007; Wojcik and Martin, 2015).

Cell killing results in tissue damage that triggers tissue healing processes. It is known that wound healing and tissue regenerative capacity declines with age (Gosain and DiPietro, 2004). Hence, it could be assumed that children are more radioresistant than adults with respect to deterministic effects. On the other hand, adults are characterised by a lower level of organisational and maturational processes, and have a shorter life expectancy, so healing processes may be associated with lower probability of complications. It appears that some factors inherent to childhood are responsible for a high radiosensitivity and others for a low radiosensitivity, as compared to adults. A summary of the factors is given in figure 1.

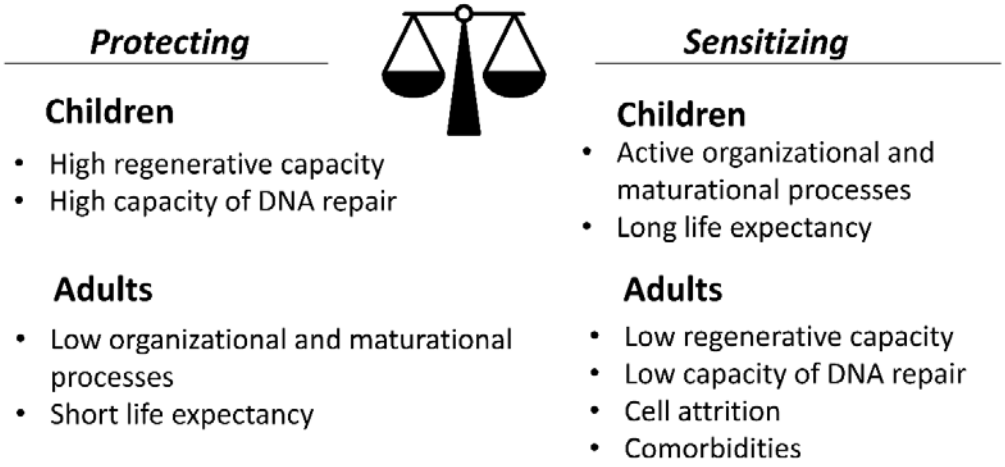

Figure 1. *Factors responsible for protecting against and sensitising towards deterministic effects of radiation of children and adults.*

With respect to stochastic effects, Scholz (1994) gave three reasons why children are more radiosensitive than adults: firstly, because of long life expectancy and the high potential for development of the primary injury (DNA mutations) into a malignancy; secondly because a high frequency of cell division (such as those in a growing organism) is associated with a high risk of accumulating mutations that can lead to a malignancy; and thirdly because of rapid accumulation of bone-seeking radionuclides in growing bones, with the possible consequence of an alteration of the immune system, resulting not only in impaired defence against infection, but also in impaired ability to recognise and kill cancer cells. These factors appear convincing and they align with our general understanding of the hallmarks of cancer (Hanahan and Weinberg, 2011). The interesting question is whether children are radiosensitive with respect to all cancer types or

whether there are some cancer forms for which they are equally or even more radioresistant than adults.

The aim of the publication is to give a concise overview of the modulating effect of age-at-exposure on deterministic and stochastic effects of radiation.

2. Deterministic (tissue) effects

Deterministic effects are subdivided into early and late effects. In connection with the acute radiation syndrome, early effects are described as the prodromal phase and late effects as the acute phase (Bertho et al., 2004). Late effects occur after a latency period which is proportional to the dose but also to the type of effect. In radiotherapy, early effects are defined as those occurring during 90 days following therapy onset. All effects occurring thereafter are defined as late (Dorr, 2015).

2.1 Acute effects – lethality after whole body exposure

The acute radiation syndrome can have lethal consequences and the dose that leads to 50 % lethality is termed LD_{50}. The LD_{50} can be used as a measure of radiation tolerance, with a low value indicating high sensitivity and high value high resistance. The impact of age on LD_{50} in humans cannot be measured in a controlled, experimental setup, so estimates must be inferred from animal experiments. In the aftermath of atomic bomb explosions in Hiroshima and Nagasaki and the following onset of the atomic age, many animal experiments were carried out to determine factors influencing the individual response to radiation (Wojcik and Harms-Ringdahl, 2019; Zander et al., 2019).

With respect to age at exposure as a risk modifier, the results have been recently summarised (Stricklin et al., 2020). It appears that the radiosensitivity during childhood is higher than during adulthood, but lower than in the elderly. The pattern is shown in figure 2, based on results of experiments on mice (Crosfill et al., 1959; Spalding et al., 1965). A simple mechanistic explanation of this pattern does not exist but it can be assumed to result from changing balance of factors shown in figure 1.

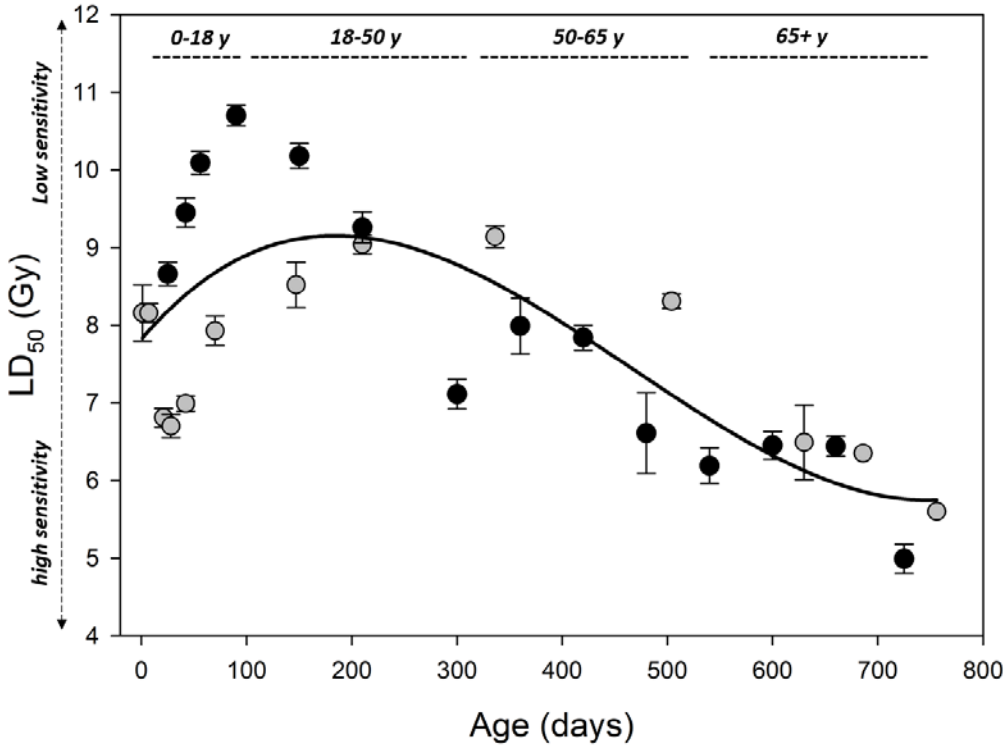

Figure 2. *LD_{50} in mice exposed to an acute dose of gamma radiation at different ages. A high LD_{50} is indicative of high resistance. Pooled results from Crosfill et al. (1959) and Spalding et al (1965). Results of Spalding were multiplied by 1.5 to align with results of Crosfill. Error bars represent standard errors. Numbers below the top margin indicate the respective human age in years (based on Stricklin et al. 2020). Solid line shows the fit according to the equation $LD = y+ad+bd^2+cd^3$, where y, a, b and c are fit coefficients and d is the age in days.*

2.2 Acute and delayed effects after medical radiation exposure

A wealth of data exists on the risk of developing deterministic effects in organs and tissues of adult patients receiving high local radiation doses during the course of radiotherapy (UNSCEAR, 2013). These data allow defining total doses and doses per fraction that particular organs can tolerate without developing severe late effects. Respective results are scarce for children, this being due to low number of patients and also the long time for late effects to manifest, making data acquisition and interpretation challenging, especially since no standardised protocols exist. Younger children have a higher risk for late effects than older children so observations must be stratified into age groups, further reducing the already poor statistical power of the data. Also, late effects that are assessed today result from radiotherapies carried out in times when three-dimensional treatment planning systems were not available. Consequently, significant uncertainties exist regarding doses absorbed by normal tissues where late effects occurred. Determination of tolerance doses is therefore difficult.

It is estimated that 75 %-100 % of children undergoing radiotherapy will develop some measurable late effects (Krasin et al., 2010; Constine et al., 2019). The age at treatment has a particularly strong modifying effect on the risk of developing neurocognitive effects

and muscle and bone growth disturbances. The corresponding risk for adults is below 50 %, irrespective of age at exposure (Krasin et al., 2010). There is thus an urgent need to determine dose constraints for organs of paediatric cancer patients that will help in reducing the incidence and severity of late effects. To this end, a volunteer research collaboration of physicians, medical physicists, epidemiologists and mathematical modelers was recently set-up to analyze normal tissue radiation dose/volume response relationships for paediatric cancer patients (Constine et al., 2019). No data have been published yet.

An interesting question is whether all organs in paediatric patients are at a higher risk of developing late effects as compared to adults. UNSCEAR (2013) undertook the effort to summarise available information on the relative sensitivity of organs and tissues of paediatric cancer patients. The results for selected organs are shown in table 1.

Table 1: *Sensitivities relative to adults of selected organs and tissues in paediatric cancer patients of developing late effects. Grey tone marks strong level of evidence. Source: UNSCEAR (2013).*

	Sensitivity vs adult			
Organ	**Less**	**Same**	**More**	**Effect**
Bladder			**X**	Reduction in capacity
Bone marrow	**X**			Less available marrow when older
Brain			**X**	Neurocognitive reduction
Breast hypoplasia			**X**	Most severe during puberty
Cataracts			**X**	
Cerebrovascular			**X**	Stroke
Heart			**X**	Growth prevention, valvular abnormalities
Immune			**?**	
Kidney		**X**		
Lung	**X**			Capacity decrease if chest wall growth is inhibited
Musculoskeletal			**X**	Hypoplasia, deformity, osteochondroma
Neuroendocrine		**X**		Reduction in hormone secretion
Ovaries	**X**			
Testes			**X**	Sperm and hormone reduction
Thyroid autoimmune			**?**	
Thyroid hypofunction		**X**		
Thyroid nodules			**X**	
Uterus			**X**	Uterine vasculature impaired

Strong evidence exists showing a high radiosensitivity of paediatric bladder, brain, heart, musculoskeletal tissue, testes and the thyroid with respect of nodule development. This effect can be explained by active maturational and organisational processes in the organs. Interestingly, no difference in radiosensitivity is evident for effects in the kidney, neuroendocrine tissue and for thyroid function. Bone marrow, ovaries and lung show an inversed age-at-exposure effect, with children being more resistant than adults. There is solid evidence for a high radioresitance of bone marrow and this could be explained by a

high regenerative capacity of immune competent cells which do not form a solid tissue where organisational processes could be impaired. The evidence for high radioresistance of ovaries is weak. Metzger et al. (2013) reported that a higher dose is required for pre-pubertal as compared to pubertal gonadal irradiation to induce treatment-associated female reproductive and sexual dysfunction. However, no mechanistic explanation was given. UNSCEAR report authors explain the high radioresistance of the lung by the fact that children have less pre-existing diseases, fewer co-morbid conditions and better repair capability than adults. The same argument is given by Krasin et al. (2010) who at the same time points out that a simple comparison of doses that induce pulmonary effects may be misleading, because the effects and treatment-indicating disease conditions in children and adults may not be compatible. The effects among children include radiation fibrosis and alterations in pulmonary function while those in adults include radiation pneumonitis. The presence of cancer in the lung itself is uncommon among children and common among adults. Finally, diagnostic certainty of lung injury's relation to radiotherapy is high among children and moderate, and at times very unclear, among adults due to comorbid conditions. More generally, treatment of paediatric cancer is often different than that of adults because of the frequently aggressive nature of childhood malignancies (Constine et al., 2019). Thus, conclusions about the relative radiosensitivity of organs and tissues in children and adults based on reactions to radiotherapy are associated with large uncertainties.

3. Stochastic effects

The major stochastic effect of radiation is cancer and the most informative source of information on radiation-induced cancer are the survivors of atomic bombs dropped on Hiroshima and Nagasaki – the Life Span Study (LSS). The reason for this is the relatively large cohort size, complete dosimetric information and good follow up. Initial data collection focused on cancer mortality, while later analyses were based on cancer incidence (Ozasa et al., 2019). While cancer incidence is about twice as high as mortality, the derived risk factors per unit dose are the same (Ozasa et al., 2019). Hence, no further notice will be taken whether the results on age as risk modifier came from mortality or incidence registries.

3.1 Age as risk modifier for pooled cancer sites

The number of solid cancer cases attributed to radiation was ca 850 during the observation period 1958-1998 (Preston et al., 2007). The majority of these cases were induced by radiation doses below 1 Gy, where the statistical power is poor, especially below 0.2 Gy (Ozasa et al., 2012). Stratifying the data according to age at exposure and cancer site further reduces the statistical power. Consequently, results on the age-related risk of solid cancer are strong for all cancers pooled and for the most common cancers, while they are weak or non-existent for others. Apart from LSS, data also exist from medical exposure of children for non-malignant diseases such as *tinea capitis* (Modan et al., 1974) and haemangioma (Karlsson et al., 1998). Also, large studies have been published on cancers induced by paediatric computed tomography but their validity has been questioned due the problem of reversed causation (Boice, 2015). The results described below come mainly from the LSS, with some input from studies on the treatment of non-malignant diseases.

Cancer risk can be expressed as relative risk (RR) defined as the ratio of risk in the exposed group to that in the unexposed group and excess absolute risk (EAR) defined as cancer rate in the irradiated group minus the rate in the corresponding unexposed group. Irrespective of the age at exposure, excess relative risk (ERR), which is the relative risk minus 1, decreases with attained age as the incidence of tumours due to other causes increases. Conversely, EAR increases with attained age as radiation-induced cancers occur after a latency period. ERR is the preferred index of the strength of a potential causal association (UNSCEAR, 2013) so the data shown below will mainly focus on ERR.

Sex-averaged excess relative risk and excess absolute risk estimates for all solid cancers at attained age 70 after exposure to 1 Gy at ages 10, 30 and 50 years for the period 1958-1998 were calculated by Preston et al. (2007) and are shown in figure 3. Both ERR and EAR gradually decline with age at exposure with the risk level at the age 50 being half of that at age 10.

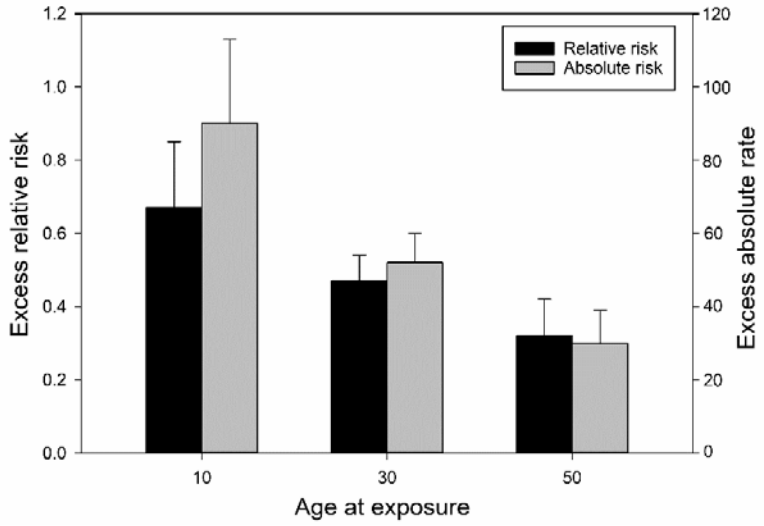

Figure 3. *Sex-averaged excess relative risk and excess absolute rate estimates for all solid cancers at attained age 70 after exposure to 1 Gy at ages 10, 30 and 50 years. Excess absolute rate is expressed per 10 000 person years. Error bars indicate 90 % confidence intervals. Source: Preston et al. (2007).*

3.2 Age as risk modifier for site specific cancers

Site-specific, sex-averaged excess relative risk estimates for solid cancers at attained age 70 after exposure to 1 Gy at age ranges 0-9, 10-19, 20-39 and 40+ years are shown in table 2. A single ERR value is given for cancer sites where an age-at-exposure effect was not detected, either due to its lack or due to insufficient statistical power to detect it. An exception is uterus, where an elevated risk is seen only for ages between 11-15 at exposure (Utada et al., 2018). An analysis of the 90 % confidence interval reveals that the ERR values are associated with large uncertainties. Lower confidence limits below 0 indicate lack of significantly enhanced level of risk. Cancer sites that are not enhanced by radiation exposure are rectum, pancreas, cervix, kidney and liver (marked in italics in table 2). It should be noted that the ERR for brain cancer at age 0-9 was derived from

studies of children treated by radiation for *tinea capitis* (Modan et al., 1974; UNSCEAR, 2013).

Table 2: *Site-specific, sex-averaged excess relative risk estimates for solid cancers at attained age 70 after exposure to 1 Gy at different age categories. Error bars given in brackets indicate 90 % confidence intervals. Within each age-at-exposure group the ERR varies as a power of attained age. NA: not available. Cancer sites marked in italics are not significantly elevated. Source: Preston et al. (2007), UNSCEAR (2013) and Utada et al. (2018).*

	ERR per 1 Gy (90 % CI)			
	Age at exposure group			
Site	**0-9**	**10 - 19**	**20-39**	**40+**
Brain	2.9 (0.8-5.5)	0.88 (0.28-1.78)	0.64 (<0-1.82)	<0 (<0-0.51)
Thyroid	1.5 (0.47-3.9)	1.2 (0.5-2.5)	0.46 (0.11-1.1)	0.31 (<0-0.92)
Other solid	1.65 (0.69-3.5)	NA	0.91 (0.50-1.4)	0.51 (0.14-1.1)
Stomach	0.63 (0.22-1.4)	0.38 (0.19-0.68)	0.38 (0.22-0.56)	0.23 (0.06-0.42)
Skin	2.28 (0.04-7.8)	NA	1.7 (0.003-0.55)	0.01 (0.00-0.08)
Breast	0.78 (0.38-1.5)	1.2 (0.69-1.9)	0.83 (0.48-1.3)	0.54 (<0-1.4)
Oral cavity	0.39 (0.11-0.76)			
Esophagus	0.52 (0.15-1.0)			
Rectum	*0.19 (<0-0.47)*			
Pancreas	*0.26 (<0-0.68)*			
Uterus	0.73 (0.03-1.87)			
Cervix	*0.0 (<0-0.31)*			
Ovary	0.61 (0.00-1.5)			
Prostate	0.11 (0.1-0.54)			
Kidney	*0.13 (<0-0.75)*			
Colon	0.45 (0.13-1.3)	0.54 (0.25-1.0)	0.54 (0.23-0.92)	0.51 (<0-1.3)
Liver	*0.28 (<0-0.63)*	*0.61 (0.18-1.3)*	*0.18 (<0-0.44)*	*0.44 (<0-1.1)*
Bladder	-0.09 (<0-5.1)	1.3 (0.16-3.9)	1.1 (0.33-2.2)	1.4 (0.47-2.8)
Lung	0.66 (<0-2.0)	0.57 (0.23-1.1)	0.79 (0.48-1.2)	1.2 (0.71-1.7)

In order to facilitate the interpretation of data shown in table 2 with respect to cancer sites for which children are differently radiosensitive than adults, significant results are graphically shown in figure 4. Data are expressed as ratios of the risk for exposure at age 40+ to that for exposure at age 0-9. An ERR ratio lower than 1 indicates cancers for which children are more sensitive than adults and an ERR higher than 1 ratio indicates the opposite. Children appear to be less sensitive than adults for cancer of the lung and colon. Results for cancer of the bladder are uncertain due to the lack of significant effect at age 0-9 and similarly for colon due to the lack of significant effect at age 40+. Age at exposure does not seem to modify the risk of prostate (although a trend for decreasing ERR with increasing age at exposure was recently reported (Mabuchi et al., 2020)), ovary, oesophagus and ovary cancers, while for all other cancers, children are more sensitive than adults.

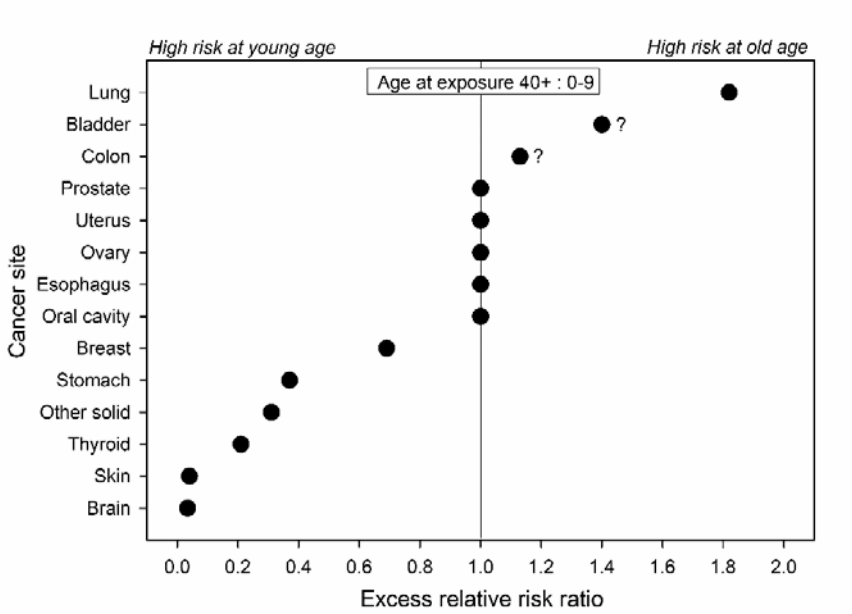

Figure 4. *Summary of site-specific excess relative risk effect modification for age at exposure, defined as the ratio of the risk for exposure at age 40+ to that for exposure at age 0-9. The vertical line at ratio 1.0 corresponds to no variation in the ERR. ERR ratios were calculated from results shown in table 2. ?: uncertain results due to lack of significance of the risk values forming the dividend or the divisor.*

3.3 Age related risk for outlying cancer sites

Apart from solid cancer, radiation induces malignancies of the bone marrow, specifically acute and chronic myelocytic leukaemia and acute lymphocytic leukaemia (Hsu et al., 2013). Data on leukaemia is usually shown separately from solid cancers because of the particular incidence vs time-after-exposure response: short latency period and subsequent decline to background level. As for solid cancers with a low ERR ratio, the leukaemia risk also largely depends on the age at exposure, with children being at a much higher risk than adults (Figure 5). For age at exposure 30 and higher the ERR is 4.0 (2.1-6.9) (Hsu et al., 2013) which is nearly 20 times lower than at age 10. Leukaemia is a rare disease so the EAR is relatively small but the ERR for exposure during childhood is very high.

Even though the EAR Leukaemia is small, leukaemia is the most common type of childhood malignancy, accounting for about 30 % of all diagnoses in children less than 15 years of age in economically developed regions of the world (Laurier et al., 2014). Why is the ERR for leukaemia so high during childhood? Although the development of leukaemia is, similarly as for other malignancies, a multistep process (Hanahan and Weinberg, 2011), it appears that the first step occurs *in utero* converting a haematopoietic precursor or stem-cell to a preleukaemic clone (Laurier et al., 2014), with radiation exposure during childhood acting as the promoting agent. This coincides with a high rate of cell growth and poor immunosurveillance (Rubin et al., 2010) that are associated with an elevated risk of cancer (Hanahan and Weinberg, 2011). The fact that the ERR increase shows a temporal pattern suggests an effective elimination of preleukaemic clones during adulthood.

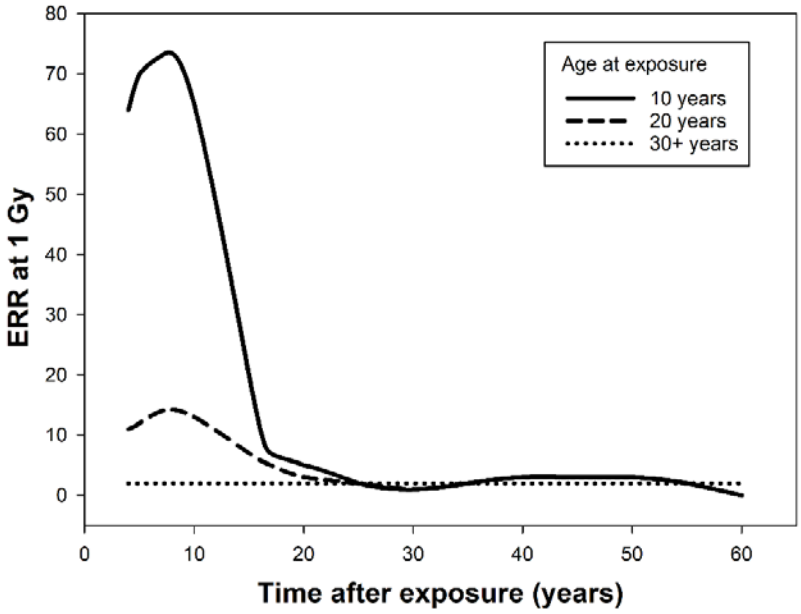

Figure 5. *Gender-averaged excess relative risk for leukaemia as a function of time after exposure. Source: UNSCEAR (2013).*

A high ERR during childhood is also observed for brain, thyroid and non-melanoma skin cancers. Not only is the ERR for these cancer sites higher in children as compared to adults but the ERR strongly declines during the first years of life (Shore et al., 2002; Smoll et al., 2016; Iglesias et al., 2017). This observation corresponds to the expected, particularly high relative risk of radiation-induced malignancies during a developmental period characterised by rapid tissue development (Rubin et al., 2010). What is surprising is the lack of such distinct age-at-exposure effect for other cancer sites. Why is this so? A mechanistic answer to this question is currently lacking.

Three cancer types show truly outstanding relationships between risk and age at exposure: breast, uterine and lung cancer and they will be discussed in greater detail. The ERR of breast cancer is somewhat higher at age 0-9 than 40+ (table 2), but it peaks during the period of puberty. This may be explained by the high rise in oestrogen and the resulting development of the breast tissue into a highly branched epithelial network which is mediated by rapid stem cell proliferation. What is interesting is that age at menarche is a very strong modifier of the ERR: for a given dose the ERR decreased with increasing age at menarche and this effect is visible irrespective of the attained age (Brenner et al., 2018). It is likely that an early menarche, which is associated with a high oestrogen level, interacts with some early developmental processes of the breast tissue, potentiating the effect of radiation. Radiation does not seem to increase the ERR of uterine cancer outside the age of puberty (Utada et al., 2018). Mid-puberty (11–15 years) appears to be the period of highest susceptibility to radiation, corresponding to a process of thickening of the endometrium and increase in uterine volume. This development precedes menarche, consequently, the window of sensitivity for uterine cancer is on average 2–3 years earlier than the respective window for the breast cancer (Utada et al., 2018).

Radiation-induced lung cancer shows an increasing ERR with age at exposure. This means that for this cancer site children are more radioresistant than adults. Indeed, for both females and males, the absolute risk of lung cancer induced at the age of 50+ is 3 times higher than at the age of 0-19 (Cahoon et al., 2017). How can this be? A possible explanation is the accumulation of mutations in the lung tissue due to intake of polluted air so that the probability that radiation exposure induces the final molecular event initiating cancer development increases with age. The unanswered question is why this effect is not seen for other cancer sites.

4. Conclusions

The general perception that children are more sensitive to radiation than adults are is only partly true. For early deterministic effects children are more sensitive than people of advanced age, but less sensitive than middle-aged adults. The reason for this is complex and involves an interplay of various sensitising and protecting factors, the balance of which changes with age at exposure. For late deterministic effects children are more sensitive than adults, but not for all organs and tissues. The reason for this is not understood and significant uncertainties exist regarding dosimetry and quantification of effects.

For cancer effects UNSCEAR (2013) states that regardless of the applied cancer model, children are significantly more radiosensitive than adults for only about 25 % of tumour types. For other cancer sites, age at exposure is either not a risk modifying factor or there is an inversed relationship between age and risk. The complex relationship between age at exposure and the risk of different tumour types is graphically summarised in figure 6.

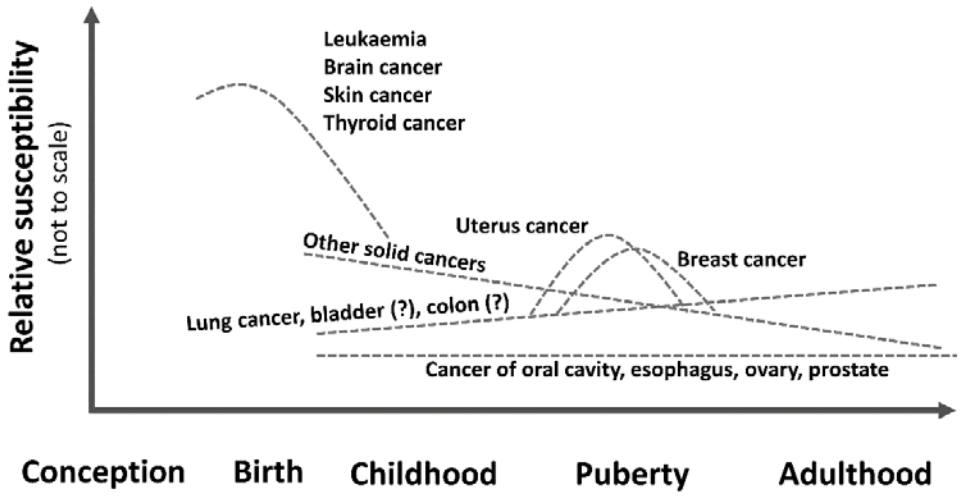

Figure 6. *Schematic overview of the relationship between the relative susceptibility and age at exposure. Concept based on a presentation by Kotaro Ozasa given at the 5th International Symposium on the System of Radiological Protection, Adelaide, 18-21 November 2019.*

Thus, as stated by UNSCEAR (2013) "in a discussion of effects of childhood radiation exposure, generalisations are best avoided and attention should be directed to the specifics of the exposure, age at exposure, absorbed dose to certain tissues, attained age at the time of assessment, and the particular effects of interest".

Acknowledgments

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Cancer risks after radiation exposure of children – overview of epidemiological studies

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Abstract

A raised risk of most forms of cancer following the receipt of moderate and high acute doses of ionising radiation is established; there remains debate over the level of risk posed by low doses or doses received at a low dose-rate. For a particular type of cancer, the dose-dependent excess risk will be modified by a number of factors, including the age at which the exposure occurs. A young age-at-exposure is especially important at increasing the excess risk per unit dose for leukaemia and thyroid cancer, although other cancers, such as female breast cancer, also show notable variations in risk with the age at which the exposure occurs. Studies of leukaemia and thyroid cancer have demonstrated how age-at-exposure and time-since-exposure combine to produce an overall temporal pattern of excess risk: for leukaemia, the excess risk appears as a "wave" with time-since-exposure, with the crest highest for young age-at-exposure, while for thyroid cancer, the proportional increase in risk is greatest at the youngest ages at exposure, but this persists into later life when many of the excess cases will be incident. Even so, this enhanced ERR/Gy for young age-at-exposure does not occur for all cancers, lung cancer being an example.

1. Introduction

Ionising radiation is an established cause of cancer (International Agency for Research on Cancer 2012). The additional risk of cancer consequent to exposure to radiation depends on the absorbed dose received, the type of radiation involved in the exposure (e.g., gamma-rays or alpha-particles), the organs/tissues exposed (e.g., pancreas or red bone marrow) and potentially the temporal nature of the exposure (e.g., whether the dose was received briefly or over a protracted period) (Kamiya et al. 2015; McLean et al. 2017). This excess risk of cancer produced by a particular level of exposure may be expressed through a dose-response relationship, in which the additional risk over a specific period is defined for specific doses received, such as a linear no-threshold or quadratic dose-response. However, the nature of the dose-response will be modified by certain factors, the most important of which are sex, age-at-exposure and time-since-exposure (or equivalently, attained age), although under certain circumstances other factors may be important, such as the level of tobacco smoking in relation to the risk of lung cancer (Wakeford 2012b).

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Much of the evidence on the risk of cancer following exposure to radiation comes from the experience of the Japanese survivors of the atomic-bombings of Hiroshima and Nagasaki in August 1945, although this evidence is complemented by many other studies, such as of lung cancer after exposure to radon and its radioactive decay products in underground mines and in residences (UNSCEAR 2008b). Of particular importance in the study of the Japanese atomic-bomb survivors is the LifeSpan Study (LSS), a cohort study of ~86,500 survivors who have organ/tissue dose estimates and were alive at the start of follow-up in October 1950; mortality and cancer incidence have been determined in these survivors from this time, but although leukaemia, lymphoma and multiple myeloma incidence has been recorded from 1950, the incidence of other cancers (solid cancers) has only been recorded since 1958 (Ozasa et al. 2019). Cancer risk models, primarily from the LSS data, have been developed by a number of expert groups including the International Commission on Radiological Protection (ICRP 2007), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2008b), and the Seventh Committee on the Biological Effects of Ionising Radiations (BEIR VII) of the US National Research Council (NRC 2006). These risk models describe how, for various types of cancer, the excess cancer risk depends on the dose of radiation received (the dose-response), and also how the excess risk is affected by the main risk modifying factors (Wakeford 2012b, 2012a).

The Japanese atomic-bomb survivors experienced a brief exposure to principally gamma radiation (with a relatively small component of neutrons). Consequently, these risk models apply directly only to these exposure conditions, and certain assumptions have to be made if the models are applied to other types of radiation (e.g., alpha-particles) or the dose is delivered over a protracted period (e.g., chronic low dose-rate exposure). Further, the models are derived from a Japanese population exposed in the mid-twentieth century, so some thought has to be given to the application of these models to other populations, possibly with different background cancer risk levels, such as a European population (Wakeford 2012b).

Risk models may be expressed in terms of either the Excess Relative Risk, ERR, or the Excess Absolute Risk, EAR – the ERR is the proportional increase in risk produced by the specific radiation exposure in relation to the background absolute risk in the absence of the exposure, while the EAR is the additional risk above the background absolute risk. With sufficiently sophisticated modelling, whether the excess risk is expressed in terms of the ERR or EAR does not usually matter as far as the population upon which the models are based is concerned, but if these models are applied to another population with different background rates then the transfer of risk between populations (i.e., ERR, EAR or some combination of the two) will be important (Wakeford 2012b).

2. All Solid Cancers Combined

To illustrate how the excess radiation-related risk of all solid cancers combined is modified by sex, age-at-exposure and time-since-exposure, the BEIR VII risk model for the incidence of all solid cancers combined (excluding thyroid cancer and non-melanoma skin cancer, NMSC, which are treated separately from the other solid cancers) is adopted (NRC 2006), as slightly modified by the US National Cancer Institute (NCI) (Berrington de Gonzalez et al. 2012).

Figure 1 shows the result of using the BEIR VII/NCI solid cancer incidence ERR model with a uniform whole-body absorbed dose of 100 mGy of low-LET radiation, in terms of modification by age-at-exposure and time-since-exposure (and attained age) for males (upper plot) and females (lower plot). A Dose and Dose-Rate Effectiveness Factor, DDREF, of 1 is assumed so there is no reduction in risk at low doses or low dose-rates. It will be seen that the proportional increase in risk is greatest for young ages at exposure, the ERR rising to a peak around 10 years after exposure and then falling away steadily with time-since-exposure, although some ERR remains present long after exposure. The proportional increase in risk is greater in females than in males. For a whole-body dose of 100 mGy of low-LET radiation, the peak in ERR for male infants represents a doubling of the background risk, and approaching a 180 % proportional increase in risk for female infants. This peak in ERR notably decreases with increasing age-at-exposure.

Figure 2 shows the equivalent application of the BEIR VII/NCI solid cancer incidence EAR model to a uniform whole-body dose of low-LET radiation. Here it will be seen that the largest numbers of excess cases occur later in life, but that even in old age the largest numbers of excess cases occur among those exposed at the youngest ages. Hence, the excess radiation-related risk persists for many years after exposure and the largest EAR values occur for exposure at the youngest ages.

The reason why the different temporal patterns of ERR and EAR shown in Figures 1 and 2 are compatible can be appreciated from Figure 3, which shows the rate of cancer incidence by sex and attained age for all cancers diagnosed in the UK during 2015-2017. So, although Figure 1 demonstrates that the ERR is greatest for those exposed at a young age, 10 or so years after exposure, the background rate of cancer at these attained ages is low resulting in few additional cases. However, the ERR persists, to some extent, throughout the remainder of life and a proportional increase in risk at old ages operates on a much higher background risk producing many more excess cases in old age than earlier in life (Figure 3).

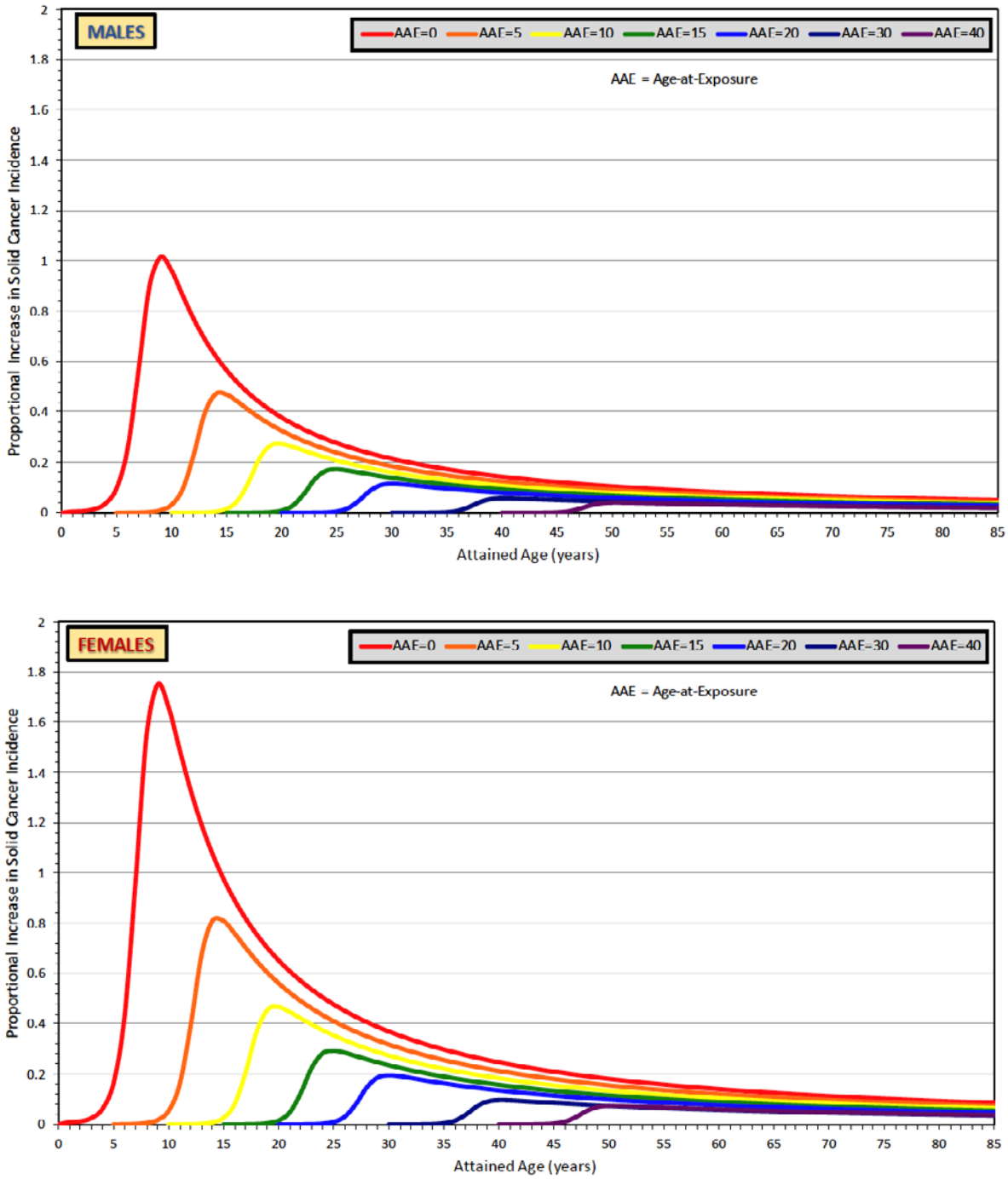

Figure 1. *Variation of the Excess Relative Risk (ERR) of All Solid Cancers (excluding thyroid cancer and non-melanoma skin cancer) Incidence for Males (upper plot) and Females (lower plot), with Age-At-Exposure, AAE, and Time-Since-Exposure (and Attained Age), following the receipt of a uniform whole-body absorbed dose of* ***100 mGy*** *of low-LET radiation, according to the BEIR VII/NCI all solid cancers ERR model, with a Dose and Dose-Rate Effectiveness Factor (DDREF) of 1.*

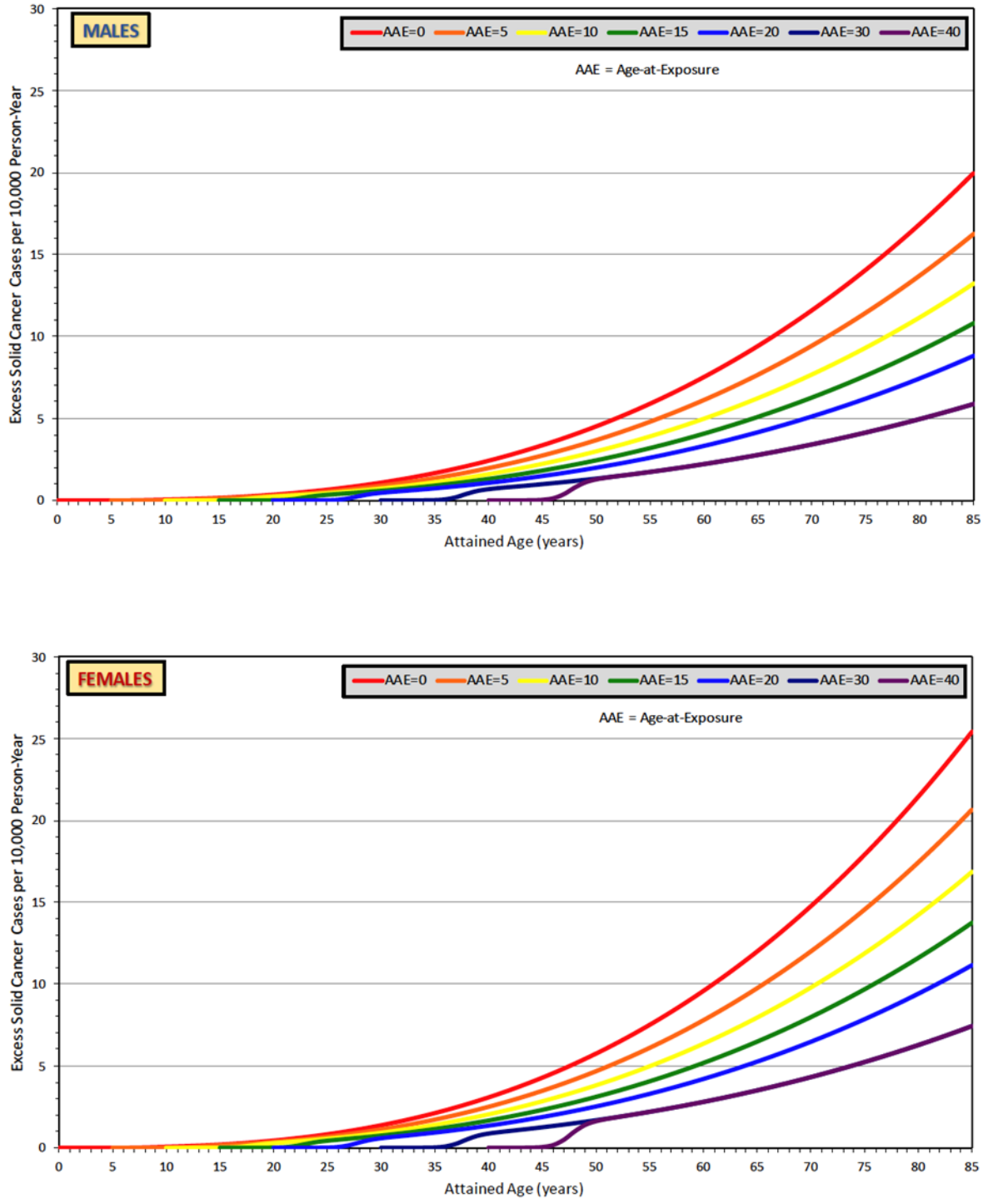

Figure 2. *Variation of the Excess Absolute Risk (EAR) of All Solid Cancers (excluding thyroid cancer and non-melanoma skin cancer) Incidence for Males (upper plot) and Females (lower plot), with Age-At-Exposure, AAE, and Time-Since-Exposure (and Attained Age), following the receipt of a uniform whole-body absorbed dose of* ***100 mGy*** *of low-LET radiation, according to the BEIR VII/NCI all solid cancers EAR model.*

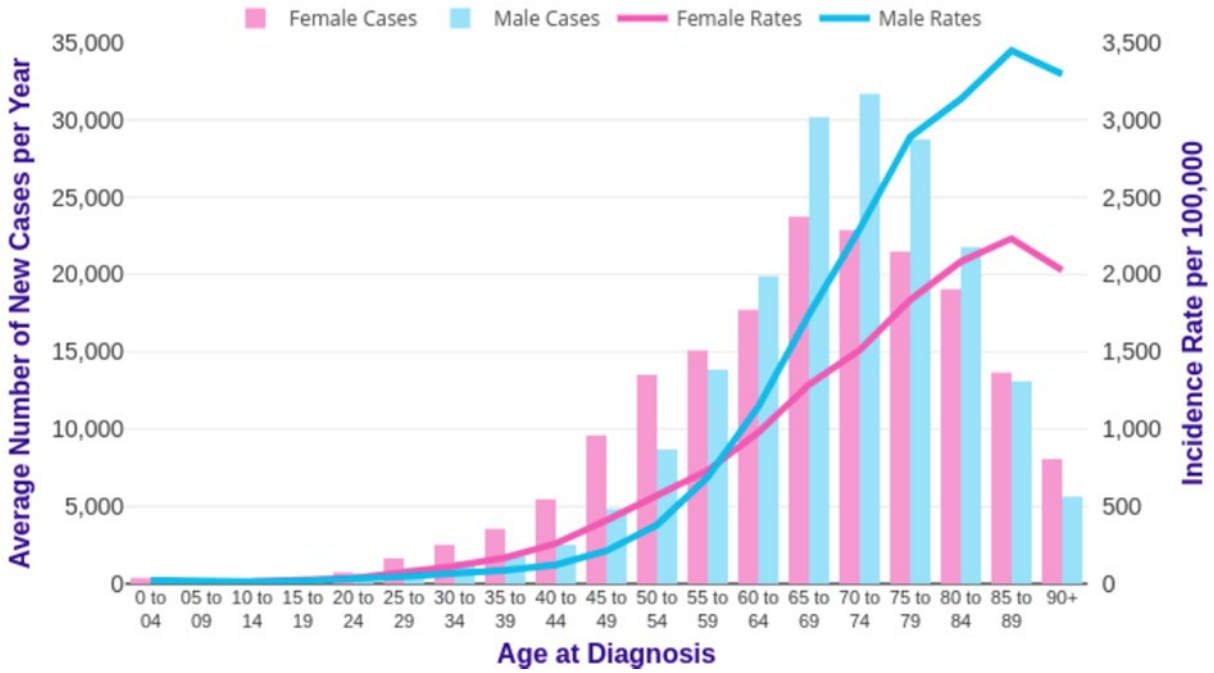

Figure 3. *Variation of the average numbers of new incident cases per year by attained age group, and the average age-specific incidence rates per year, in the UK during 2015-2017 by sex for all cancers (excluding non-melanoma skin cancer). (Source: Cancer Research UK)*

A warning needs to be sounded here because the all solid cancers incidence risk models of BEIR VII/NCI (but also of ICRP and UNSCEAR) are based upon data generated from the LifeSpan Study of the Japanese atomic-bomb survivors as analysed by Preston et al. (2007); incident cases were those diagnosed during 1958-1998. At the end of follow-up 52 % of the survivors were still alive, and only 9 % of those less than 10 years of age at the time of the bombings had died. Consequently, substantial information on cancer incidence in the atomic-bomb survivors, particularly among those exposed at a young age, is still to be gathered as the LSS continues, and risk models are likely to change, as the recent study of solid cancer incidence during 1958-2009 illustrates (Grant et al. 2017).

Moreover, it has to be appreciated that the all solid cancers risk models combine diverse cancer types that are likely to behave differently in their response to radiation exposure – the all solid cancers risk models should be seen as a "broad brush" approach to assessing radiation-related solid cancer risk, incorporating specific types of cancer with potentially different dose-responses and different influences of risk modifying factors. In particular, this is relevant to the variation of risk with age-at-exposure, and Volume II of the UNSCEAR 2013 Report (UNSCEAR 2013) examines in some detail the effects of radiation exposure of children.

The UNSCEAR (2013) review found that there is a clearly increased risk for exposure in childhood when compared with exposure in adulthood for breast, skin and brain cancers, and also for leukaemia and thyroid cancer (considered separately below). Overall, this represents ~25 % of cancer types having a greater excess risk per unit dose for young ages at exposure. For ~15 % of cancer types (e.g., bladder cancer) the excess risk per

unit dose appears to be about the same in children as in adults, while for ~10 % of cancer types (e.g., lung cancer) the risk would appear to be lower in childhood (possibly those types of cancer strongly influenced by environmental risk factors, such as tobacco smoking for lung cancer). For ~20 % of cancers (e.g., oesophagus) the evidence is too weak to draw reliable conclusions and for the remaining ~30 % of cancers (e.g., Hodgkin lymphoma) the evidence for a radiation-related excess risk at any age is equivocal.

So, although the risk models for all solid cancers combined, as considered above, give an indication of how the excess risk of solid cancers following exposure to radiation not only varies with dose but also is modified by sex, age-at-exposure and time-since-exposure (and attained age), it must be borne in mind that the component solid cancer types vary in both the level of their response to radiation exposure and in the modification of risk by factors such as age-at-exposure. However, Figures 1 and 2 do illustrate how age-at-exposure is an important factor to be taken into account when assessing radiation risks, and how it broadly modifies the ERR and EAR of solid cancers and how it is related to risk modification by time-since-exposure (and attained age).

Recently, studies of solid cancer incidence in the LSS have demonstrated important risk modifying factors for certain cancer types. A study of female breast cancer found that age at menarche is a particularly strong modifier of risk: the risk of breast cancer decreased significantly with increasing age at menarche and the highest ERR/Gy values were found for those exposed around menarche (Brenner et al. 2018). A study of uterine cancer found that the radiation-related excess risk of cancer of the uterine body was confined to those irradiated as girls aged 11-15 years, suggesting a particular sensitivity of the uterus in puberty (Utada et al. 2018). These studies illustrate the value of careful investigation of specific types of cancer as follow up of the LSS continues and a greater proportion of those exposed at a young age are included in the studies.

3. Leukaemia

Leukaemia (cancer of the white blood cells) was the first cancer to be definitively linked to radiation exposure, and was found to be in excess in the Japanese atomic-bomb survivors in the late-1940s, just a few years after the bombings. Expert groups such as BEIR VII (NRC 2006) and UNSCEAR (2008b) have used the LSS leukaemia mortality data for 1950-2000 (Preston et al. 2004) to derive ERR and EAR models for leukaemia.

Figure 4 shows the BEIR VII/NCI leukaemia ERR model for males and females, and presents the variation of ERR with age-at-exposure and time-since-exposure (and attained age) following the receipt of a dose of 10 mGy of low-LET radiation by the red (active) bone marrow (RBM), the tissue of origin for leukaemia. There is little difference between the sexes (see upper and lower plots of Figure 4), but a marked variation with age-at-exposure and time-since-exposure is clearly apparent. The ERR appears as a temporal "wave" with time-since-exposure and the peak of the wave is notably greatest for youngest ages at exposure – the proportional increase in leukaemia risk over background is ~60 % for an infant receiving a RBM dose of 10 mGy from low-LET radiation.

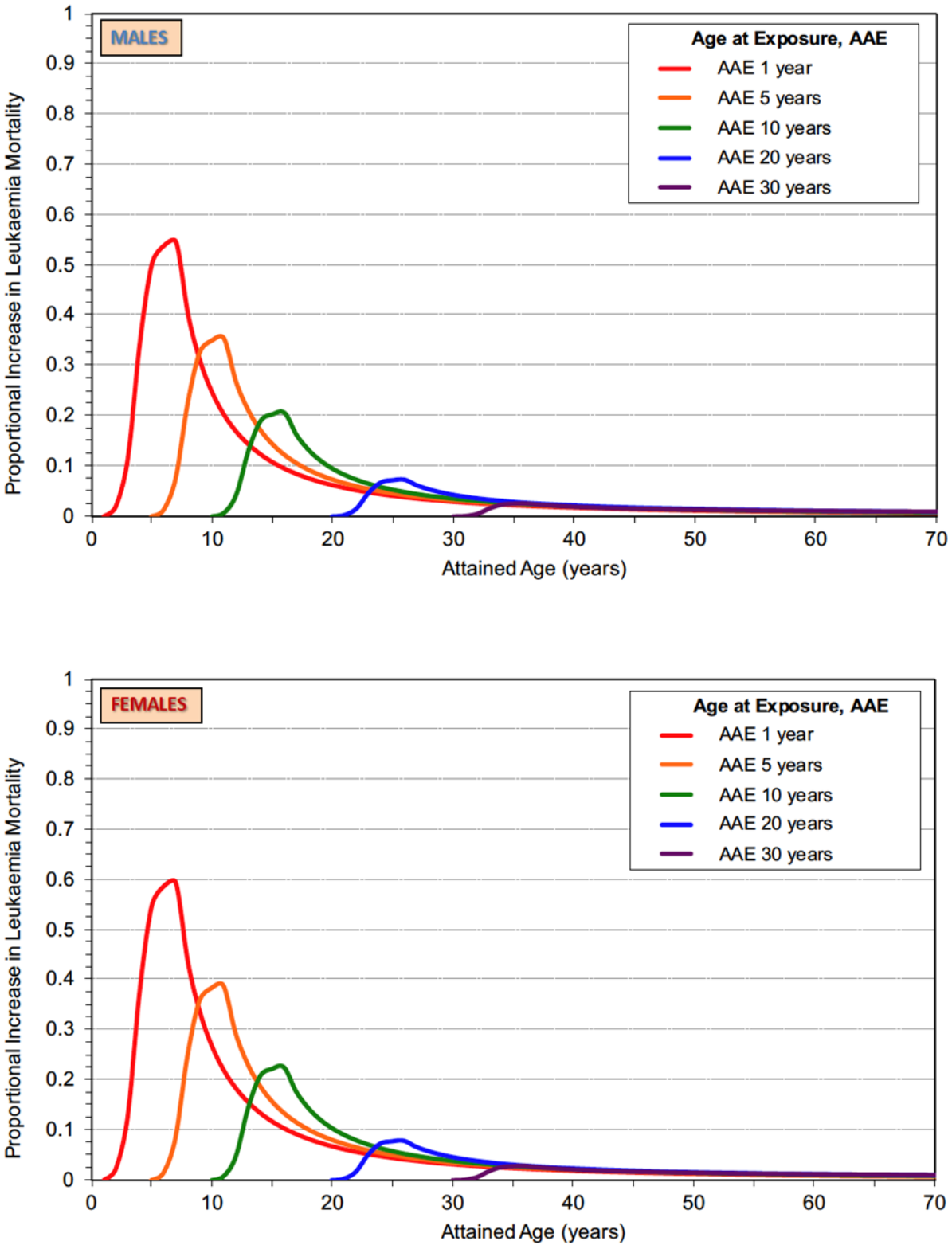

Figure 4. *Variation of the Excess Relative Risk (ERR) of Leukaemia Mortality for Males (upper plot) and Females (lower plot), with Age-At-Exposure, AAE, and Time-Since-Exposure (and Attained Age), following the receipt of a red bone marrow absorbed dose of* ***10 mGy*** *of low-LET radiation, according to the BEIR VII/NCI leukaemia ERR model.*

The leukaemia EAR following a RBM dose of 10 mGy low-LET radiation as predicted by the BEIR VII/NCI EAR model is shown in Figure 5. In contrast to the pattern of EAR for all solid cancers combined, as shown in Figure 2, the EAR is greatest at the youngest ages at exposure (and for males the peak EAR is approaching twice that for females) then falls away with increasing time-since-exposure to a level below that for exposure during adult life. The temporal "wave" of EAR at the youngest ages may be appreciated by considering the background absolute risk of leukaemia with attained age, as shown in Figure 6. Unlike solid cancer background rates (Figure 3), the leukaemia background absolute rate, while showing an increase at older ages, also has a notable level of incidence during the childhood years – in fact, leukaemia is the commonest cancer in childhood. Thus, unlike for all solid cancers combined, for leukaemia the temporal wave of ERR at young ages at exposure is reflected in a temporal wave of EAR.

However, as noted by Walsh and Kaiser (2011), caution is required in assessing the leukaemia model predictions for young ages at exposure, particularly for low RBM doses. For Japanese atomic-bomb survivors dying of leukaemia in the attained age range of 5-9 years, that is, an age-at-exposure range of 0-4 years (recalling that leukaemia deaths were only recorded systematically from 1950), there were just four deaths, all among those receiving neutron-RBE-weighted absorbed doses to the RBM in excess of 1 Gy. In the attained age range of 10-14 years (an age-at-exposure range of 5-9 years) there were six leukaemia deaths, with a neutron-RBE-weighted RBM dose range of 0-3.4 Gy. Thus, the leukaemia risk models, when addressing young ages at exposure and particularly at low-to-moderate RBM doses, are based upon limited data, and this needs to be borne in mind when considering what uncertainties are associated with model predictions.

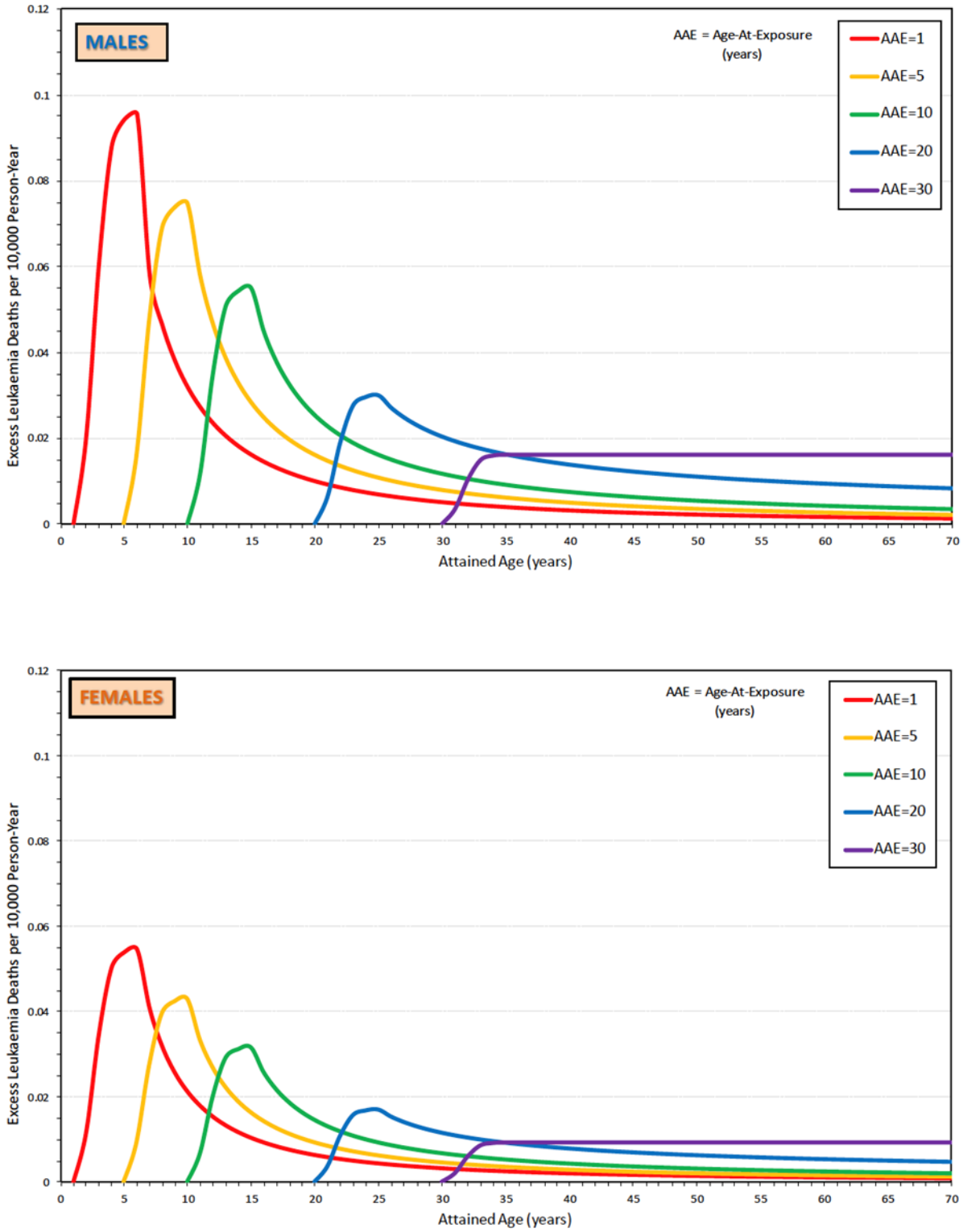

Figure 5. *Variation of the Excess Absolute Risk (EAR) of Leukaemia Mortality for Males (upper plot) and Females (lower plot), with Age-At-Exposure, AAE, and Time-Since-Exposure (and Attained Age), following the receipt of a red bone marrow absorbed dose of* ***10 mGy*** *of low-LET radiation, according to the BEIR VII/NCI leukaemia EAR model.*

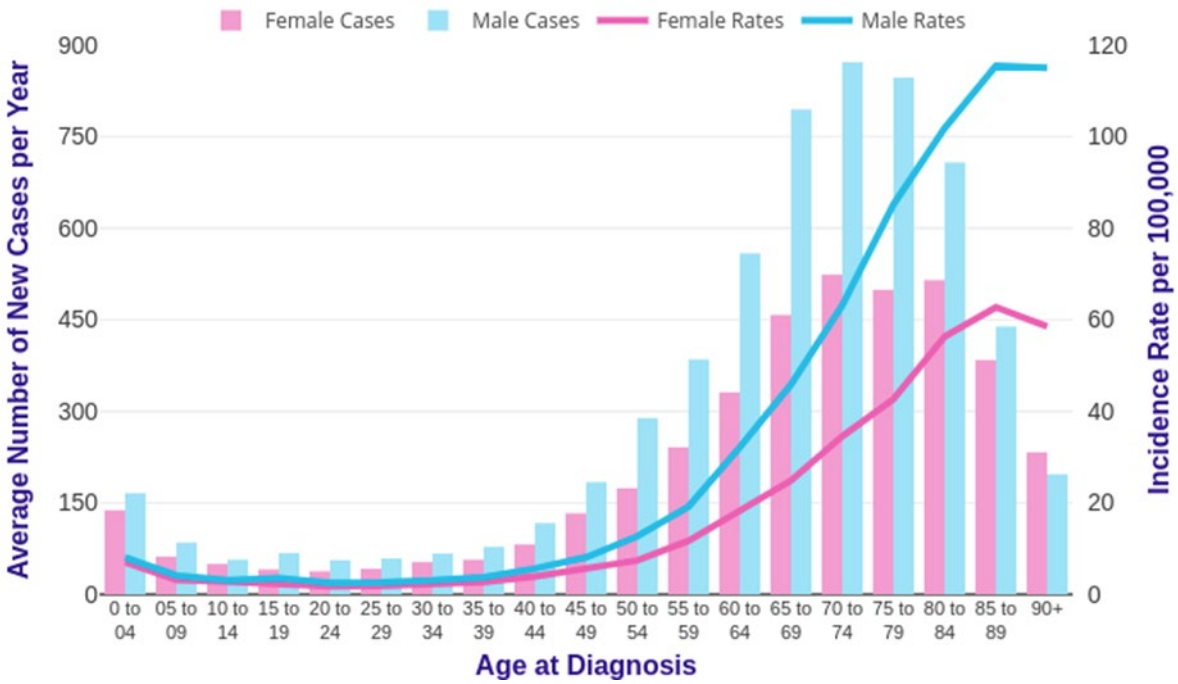

Figure 6. *Variation of the average numbers of new incident cases per year by attained age group, and the average age-specific incidence rates per year, in the UK during 2015-2017 by sex for leukaemia. (Source: Cancer Research UK)*

Nonetheless, it is of interest to consider the potential implications of the conventional leukaemia risk models (NRC 2006; UNSCEAR 2008b; ICRP 2007). The predicted temporal "wave" of radiation-related excess leukaemia risk following exposure at young ages (see Figures 4 and 5) suggests that the average annual RBM dose from natural sources of background radiation in Great Britain (England, Wales and Scotland) of ~1.4 mSv may account for roughly 15-20 % of British childhood leukaemia cases (Wakeford, Kendall, and Little 2009; Little, Wakeford, and Kendall 2009; Kendall, Little, and Wakeford 2011). However, statistical power calculations (Little et al. 2010) show that a large case-control study of at least 8000 cases covering the whole of Great Britain would be required to achieve an 80 % power of detecting this excess risk; those investigations of the risk of childhood leukaemia from natural background radiation that had been conducted previously are unlikely to have had sufficient power to have been able to detect the predicted level of risk. Even so, the extensive data held by the British National Registry of Childhood Tumours allow a study this large to be carried out.

A serious impediment is that a case-control study this large cannot perform measurements of radiation levels in the homes (and ideally also in previous homes) of all study participants, so cumulative exposures have to be estimated from models based upon existing radiation survey data. Owing to the interest in domestic exposure to radon and the consequent risk of lung cancer, extensive data on radon levels in the home are available in the UK, but information on indoor gamma radiation levels is not so extensive, and it is gamma radiation rather than radon exposure that provides most of the dose to the RBM. In an initial case-control study of childhood cancer incidence in Great Britain in relation to natural background radiation doses, Kendall et al. (2013) found a statistically significant association between the cumulative dose of radiation received by a child

(based on the dose-rate estimate for the maternal residence at the birth of the child) and leukaemia for gamma radiation, but not radon, and no association for other childhood cancers, which is what the standard models would predict. However, this finding was not repeated in a large study carried out in France (Demoury et al. 2017) and further research is required to progress understanding of the potential link between natural background radiation and childhood leukaemia (and other childhood cancers), and estimates of RBM doses is a particularly important aspect of this further work (Mazzei-Abba et al. 2020).

Recently, Little et al. (2018) conducted an analysis of pooled data from nine cohorts of persons exposed to external sources of radiation in childhood (but not as a treatment for cancer, which poses difficulties such as the concomitant treatment by chemotherapy). The analysis included ~262,500 individuals each receiving a mean RBM dose <100 mGy, including the Japanese atomic-bomb survivors and patients from eight cohorts exposed for medical reasons. Statistically significant dose-responses in the RBM dose range 0-100 mGy were found for the acute leukaemias (acute lymphoblastic leukaemia ERR/100 mGy = 4.7 (95 % CI: 0.4, 18.7) and acute myeloid leukaemia ERR/100 mGy = 1.6 (95 % CI: 0.1, 4.1)) but not for chronic myeloid leukaemia (ERR/100 mGy = -0.6 (95 % CI: <-0.6, 1.4)). These findings indicate a discernibly increased risk of acute leukaemia following exposure in childhood to RBM doses <100 mGy. For all acute leukaemias combined, the statistically significant excess risk did not depend on the inclusion of data from the LSS cohort, the data from the other eight cohorts giving an ERR/100 mGy = 1.8 (95 % CI: 0.22, 4.7).

There has been a dramatic increase in population exposure to radiation for medical reasons in the economically developed world, largely due to the increase in computed tomography (CT) scanning. This provides an opportunity to investigate the impact on cancer risk of CT scans, particularly for those exposed in childhood. Such studies need to be large to have reasonable statistical power to detect the predicted excess risk, and sufficiently good records are required to link children who have undergone CT scans to cancer registries. The first large study was conducted in the UK (Pearce et al. 2012) and was a cohort study of ~176,500 patients first examined with CT in Great Britain during 1985-2002 when <22 years of age. Cancers diagnosed during 1985-2008 were identified through linkage to cases in the national cancer registries. The initial analysis was of leukaemia (with a dose-lag of two years) and brain tumours (with a dose-lag of five years), using estimates of RBM and brain doses per CT scan from details contained in medical records – leukaemia was selected because of its established relationship with radiation exposure and brain tumours because of the substantial proportion of CT scans in childhood that are of the head. The mean length of follow-up was ~10 years.

Pearce et al. (2012) reported an ERR/Gy = 36 (95 % CI: 5, 120) for all leukaemia incidence, including cases of myelodysplastic syndrome (MDS, a pre-leukaemic condition), although if MDS was excluded the ERR/Gy fell to 19 (95 % CI: -12, 79). From the LSS leukaemia incidence data (which do not include cases of MDS), for those exposed at <20 years of age and 5-14 years since exposure, ERR/Sv = 45 (95 % CI: 16, 188), so the findings are compatible. For brain tumours, the British CT scan study found an ERR/Gy = 23 (95 % CI: 10, 49). This compares with the estimate using the LSS brain cancer incidence data of ERR/Sv = 6.1 (95 % CI: 0.1, 63), for those <20 years of age at the time of the bombings and incident 13-19 years since exposure (bearing in mind that registration of solid tumours only commenced in 1958). It would seem that the findings of this study of CT scans were broadly in line with those of the LSS, although caution is

required in the role of MDS in the leukaemia association, and the brain tumour ERR/Gy may be somewhat higher than would be expected.

Further CT scan studies have now been conducted and, for example, a cohort study in the Netherlands of ~168,000 children who received CT scans during 1979-2012 while <18 years of age (Meulepas et al. 2019) found a discernibly raised ERR/Gy for brain tumours, ERR/Gy = 8.6 (95 % CI: 2, 22), but not for leukaemia, ERR/Gy = 2.1 (95 % CI: -1.2, 24). However, the rather wide confidence intervals for the ERR/Gy estimates obtained from the CT scan studies will be noted, so the individual study findings are compatible with a range of radiation-related risks.

A major difficulty with studies of medical exposure is that this occurs because a patient is ill or suspected of being ill. For diagnostic exposures, this can give rise to confounding by indication and reverse causation; reverse causation occurs when a CT scan is carried out because of the undiagnosed presence of a slow-growing tumour, and confounding by indication occurs when a cancer pre-disposing condition produces (in its own right) a higher frequency of CT scanning. Confounding by indication and/or reverse causation would appear to be present in at least some CT scan studies (Walsh et al. 2014; Boice 2015), and its influence upon the results of CT scan studies has been the subject of investigation (Journy et al. 2016; Meulepas et al. 2016; Berrington de Gonzalez et al. 2016). Dealing with the reasons for CT scans being carried out is an important issue that is not easily addressed, conveniently accessible medical records giving this information not being readily available, and the outcome of a European-wide study of CT scans in childhood, EPI-CT (Bernier et al. 2019), is awaited to see if it can shed light on this subject.

A study of cardiac catheterisations in the UK investigated ~11,250 patients who underwent cardiac catheterisations while <23 years of age (Harbron et al. 2018); these patients also received CT scans. Standardised Incidence Ratios (SIRs) for cancers were: leukaemia, 1.73 (95 % CI: 0.47, 4.43); lymphoma, 9.15 (95 % CI: 5.75, 13.97), with non-Hodgkin lymphoma (NHL), 19.49 (95 % CI: 11.60, 30.92); and brain cancer, 1.57 (95 % CI: 0.32, 4.57), indicating a dramatically increased risk of lymphoma incidence, in particular, NHL incidence. The ERR/Gy for leukaemia combined with lymphoma was a staggering 541 (95 % CI: 104, 1807). These were remarkable results that demanded an explanation. It was found that all 22 cases of lymphoma occurred after organ transplantation, and it is likely that the markedly raised SIR for lymphoma was due to the use of immunosuppressant drugs. If the organ transplant patients were removed from the analyses, the SIR for lymphoma reduced to zero and the ERR/Gy for leukaemia combined with lymphoma reduced to 18 (95 % CI: -2, 96). This study illustrates the need for the care that must be taken in conducting studies of medical irradiation and of the interpretation of their findings.

In this respect, of interest are the studies of childhood cancer and a previous abdominal X-ray examination of the pregnant mother. Case-control studies have consistently found raised relative risks associated with an antenatal X-ray examination, for childhood leukaemia and other cancers in children (Doll and Wakeford 1997). A persistent concern has been whether confounding by indication could be an explanation for this association, but investigations have not identified a confounding factor. One concern is the results of the Japanese atomic-bomb survivors exposed *in utero* – no case of childhood leukaemia has been found, although 2 cases of childhood cancers other than leukaemia were incident, a marginally statistically significant excess. Even though only 0.2 case of

leukaemia would have been expected, so that the upper 95 % confidence limit for the observed to expected case ratio is 15, the absence of a case of leukaemia is disconcerting (Wakeford and Little 2003; Wakeford 2008). However, a study of stable chromosome aberrations in blood sampled at the age of 40 years from survivors exposed *in utero* could provide insight into this matter. Remarkably, although an excess of translocations was found in survivors receiving doses <100 mGy, at higher doses the expected increase in translocations was absent. Blood was also sampled from some of the mothers of the *in utero* exposed survivors and the expected increase in translocations was found (Ohtaki et al. 2004). It may be that those cells from which leukaemia arises are especially sensitive to radiation-induced damage *in utero* and are killed by moderate doses, to be replaced by stem cells that have escaped significant damage. Whether this is a viable explanation, and whether any effect extends beyond birth will be the subject of further research.

There has been some concern following reports of excess cases of childhood leukaemia near certain nuclear installations that the risk of childhood leukaemia consequent to intakes of discharged radionuclides may have been grossly underestimated, possibly because, for example, alpha-particle-emitting radionuclides deposit closer to sensitive cells in the RBM than is assumed (Wakeford 2014a, 2013; Wakeford, Darby, and Murphy 2010; COMARE 2016). One approach to addressing this suggestion is to examine whether the radioactive fallout from atmospheric nuclear weapons testing has had a detectable impact on childhood leukaemia incidence rates around the world – this fallout consists of radionuclides that are also to be found in discharges from nuclear installations (UNSCEAR 2000). The release of activity from nuclear weapons testing is surprisingly large, and fallout radionuclides are readily detected in the environment (Warneke et al. 2002). Table 1 shows the activity releases of a number of radionuclides in comparison with the quantities released during the Chornobyl accident in 1986 (UNSCEAR 2000). The peak of weapons testing took place in the late-1950s and early-1960s, leading to a temporal "wave" of radiation doses from inhalation and ingestion of fallout radionuclides, which were larger in the Northern Hemisphere where most of the weapons testing took place (Figure 7).

Table 1. *Activities of particular radionuclides released by atmospheric nuclear weapons testing and a comparison with the activities released by the Chornobyl nuclear accident in 1986.*

Radionuclide	Nuclear Weapons Testing (PBq)	Chornobyl Accident (PBq)
I-131	675,000	1800
Cs-137	948	85
Sr-90	622	10
α-particle-emitting isotopes of plutonium	11	0.1

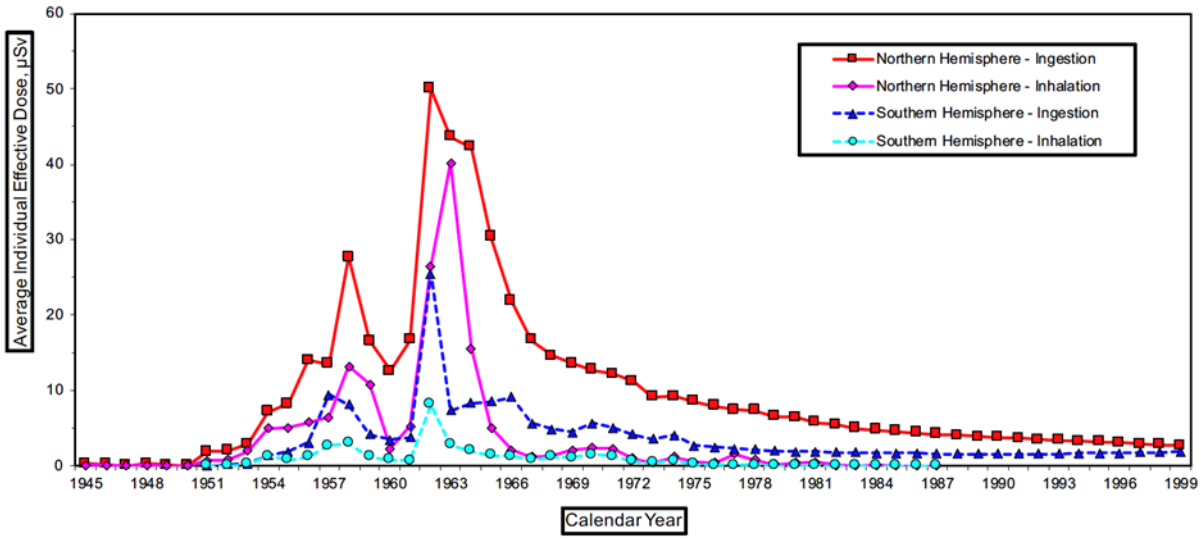

Figure 7. *Average annual effective doses in the Northern and Southern Hemispheres from inhalation and ingestion of radionuclides produced in atmospheric nuclear weapons testing (UNSCEAR 2000).*

However, large and reliable childhood cancer registries were not common in the 1960s, and childhood leukaemia mortality data are not an acceptable alternative because treatment success was steadily increasing at this time. However, as shown in Figure 8, childhood leukaemia incidence rates from those registries with dependable data have not shown a temporal "wave" of excess leukaemia cases following the peak of fallout (Wakeford, Darby, and Murphy 2010; Wakeford 2014b). This does not mean that fallout did not increase the risk of childhood leukaemia, only that the risk from fallout has not been seriously underestimated, which was the issue under investigation.

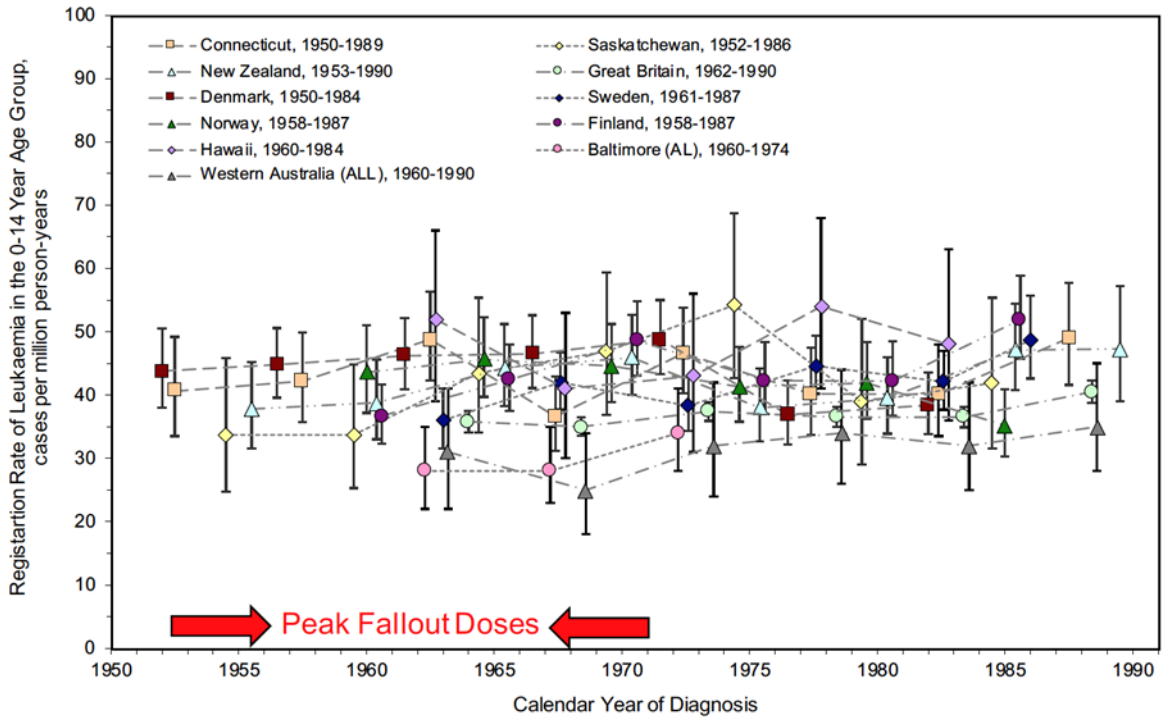

Figure 8. *Incidence rate of all leukaemias (except where indicated otherwise) among children aged 0-14 years, 1950-1990. Incidence data from eleven cancer registries. Error bars show 95 % confidence intervals for rates. (Wakeford, Darby, and Murphy 2010; Wakeford 2014b). AL, acute leukaemia; ALL, acute lymphoblastic leukaemia.*

4. Thyroid Cancer

It has been recognised for some time that children have a particularly high proportional increase in the risk of thyroid cancer per unit dose received by the thyroid gland, but that this notable increase in ERR/Gy does not persist into adult life. Ron et al. (1995) analysed data pooled from seven studies (including the LSS) of thyroid cancer and exposure to low-LET radiation from external sources and found that the ERR/Gy for those exposed in childhood was 7.7 (95 % CI: 2.1, 29), but that there was little apparent risk beyond an age-at-exposure of 20 years. The BEIR VII Committee (NRC 2006) developed a thyroid cancer ERR model based upon the findings of Ron et al. (1995), and this model, slightly modified by the US NCI (Berrington de Gonzalez et al. 2012), is illustrated in Figure 9, where the ERR following the receipt of a thyroid dose of 100 mGy at various ages at exposure is shown in relation to increasing time-since-exposure. Although the BEIR VII/NCI ERR model does have a dependence on sex, Figure 9 shows the sex-averaged ERR because it is the dependency on age-at-exposure and time-since-exposure that is of interest here; the BEIR VII Committee did not present a thyroid cancer EAR model, just the ERR model.

The BEIR VII/NCI ERR model for thyroid cancer shows the markedly increased ERR/Gy for younger ages at exposure (a thyroid dose of 100 mGy received in infancy effectively doubling the risk of thyroid cancer within ten years of exposure), which then decreases with increasing age-at-exposure, but a striking feature of the model is that after 7-8 years since exposure the ERR remains constant throughout the remainder of life. The

implication is that following exposure in childhood, most of the excess cases will occur later in life when the background absolute risk is greatest, as Figure 10 illustrates – the proportional increase in risk remains constant with time-since-exposure, but multiplies a greater background absolute risk later in life, especially for females.

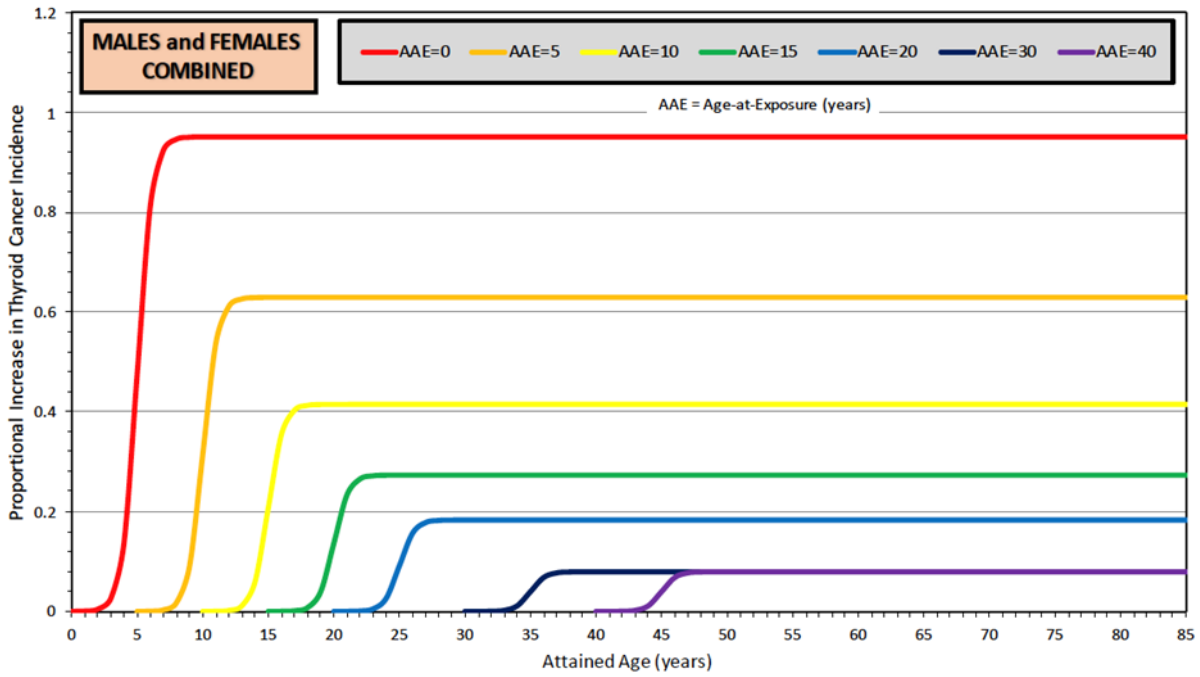

Figure 9. *Variation of the sex-averaged Excess Relative Risk (ERR) of Thyroid Cancer Incidence with Age-At-Exposure, AAE, and Time-Since-Exposure (and Attained Age), following the receipt of a thyroid absorbed dose of* ***100 mGy*** *of low-LET radiation, according to the BEIR VII/NCI thyroid cancer ERR model.*

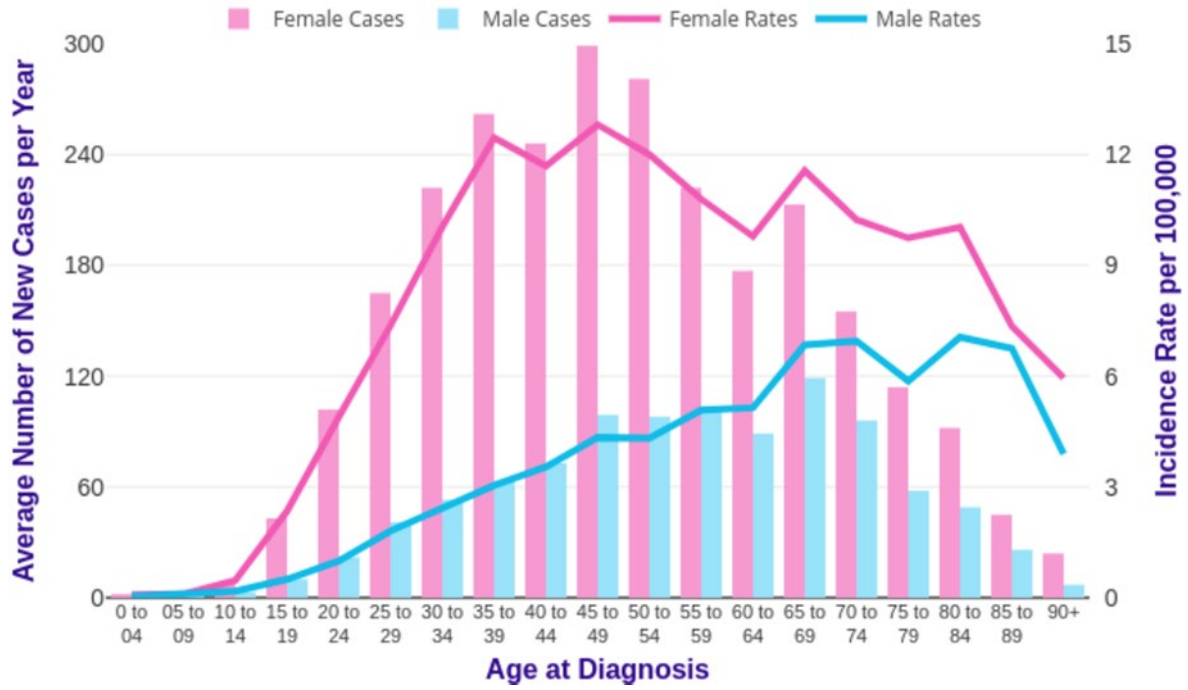

Figure 10. *Variation of the average numbers of new incident cases per year by attained age group, and the average age-specific incidence rates per year, in the UK during 2015-2017 by sex for thyroid cancer. (Source: Cancer Research UK)*

The ERR models for thyroid cancer derived by expert committees from data for those exposed to external sources of radiation immediately invite an investigation of thyroid cancer incidence among those children who received high thyroid doses as a consequence of drinking milk heavily contaminated with radioisotopes of iodine (principally iodine-131) released during the Chornobyl nuclear reactor accident in northern Ukraine in April 1986. It is estimated that ~1.8 EBq of iodine-131 was released during the accident (UNSCEAR 2008a), and once taken into the body, radioiodine is concentrated in the thyroid gland. Greater than 10,000 children from Ukraine, Belarus and the Russian Federation are estimated to have received thyroid doses >1 Gy, largely from the consumption of milk. Given this level of exposure and the predicted ERR/Gy from the study of Ron et al. (1995), it is unsurprising that excess cases of thyroid cancer could be readily detected by geographical studies of thyroid cancer incidence in the surrounding areas (Yamashita 2014; UNSCEAR 2008a). Recently, UNSCEAR estimated that in Ukraine, Belarus and the four most contaminated regions of the Russian Federation during the period 1991-2015, ~5000 cases of thyroid cancer among those <18 years of age in 1986 were attributable to exposure following the Chornobyl accident, with an uncertainty range of 1400 to 10,000 cases.

A number of cohort and case-control studies of thyroid cancer incidence around Chornobyl have been conducted. The most reliable of these, the Belarusian and Ukrainian cohorts, involve those who were at a young age at the time of the accident and whose thyroid doses were measured by thyroid monitoring before iodine-131 (half-life, 8 days) had decayed; the cohort members receive regular screenings of their thyroid glands to detect disease, and an important aspect is that these screenings are uniform with respect to estimated thyroid dose to avoid screening bias. Table 2 compares the ERR/Gy

estimates for thyroid cancer incidence obtained from these studies and compares the risk estimates with those obtained from analyses of pooled data from cohort studies of those exposed to external sources of radiation. Risk estimates are broadly comparable.

Table 2. *Case-control and cohort studies of thyroid cancer in the vicinity of Chornobyl, showing ERR/Gy estimates and 95 % confidence intervals, and a comparison with ERR/Gy estimates from studies of pooled data from exposures to external sources of radiation. ERR/Gy estimates relate to those exposed while <15 years of age, except where indicated otherwise.*

Exposure	Study	ERR/Gy (95 % CI)
External	Pooled Analysis (Ron et al. 1995)	7.7 (2.1, 29)
External	Pooled Analysis (Veiga et al. 2016)	5.5 (4.1, 7.5)
Chornobyl	Case-control (Belarus & Russia) (Cardis et al. 2005)	4.5 (1.2, 7.8)
Chornobyl	Case-control* (Bryansk, Russia) (Kopecky et al. 2006) * <20 years of age at exposure	48.7 (4.8, 1151)
Chornobyl	Cohort* (Ukraine) (Tronko et al. 2006) * <18 years of age at exposure	5.2 (1.7, 27)
Chornobyl	Cohort* (Belarus) (Zablotska et al. 2011) * <18 years of age at exposure	2.2 (0.8, 5.5)
Chornobyl	Cohort* (Ukraine) (Brenner et al. 2011) * <18 years of age at exposure	1.9 (0.4, 6.3)

The study of Ron et al. (1995) has been updated by Veiga et al. (2016), who analysed pooled data from 12 studies of thyroid cancer following exposure to external sources of radiation, consisting of the LSS and 11 studies of radiotherapy patients first exposed while <20 years of age. The ERR at a thyroid dose of 1 Gy was estimated to be 5.5 (95 % CI: 4.1, 7.5), which compares with the earlier estimate from the study of Ron et al. (1995) of 7.7 (95 % CI: 2.1, 29). The risk of thyroid cancer was elevated within 10 years of exposure, continued to increase for 20-30 years after exposure before declining, but the increased risk persisted for greater than 50 years after exposure (Veiga et al. 2016). In this respect, a dose-related excess of thyroid cancer is still present in the LSS some 60 years after exposure, although the excess risk has decreased with increasing time-since-exposure (Furukawa et al. 2013).

Lubin et al. (2017) analysed data from the nine studies considered by Veiga et al. (2016) that included those receiving thyroid doses <200 mGy. A linear dose-response fitted the data below 200 mGy, with a slope (ERR/Gy) of 11.1 (95 % CI: 6.6, 19.7). Limiting the analysis to doses <100 mGy produced a linear dose-response with ERR/Gy = 9.6 (95 % CI: 3.7, 17.0). The upper 95 % confidence limit for a dose threshold was 40 mGy. The increased risk persisted for >45 years after exposure, was greater at younger ages at exposure and decreased with increasing time-since-exposure. The degree to which the

ERR/Gy decreases with time-since-exposure is uncertain due to sparse data, but the decline of ERR/Gy with increasing time-since-exposure is indicative of a need to modify the BEIR VII/NCI thyroid cancer ERR model with its constant ERR with time-since-exposure (Figure 9). Nonetheless, the study of Lubin et al. (2017) shows that an increased risk of thyroid cancer can be detected some 50 years after exposure, which has clear implications for the population of children in the vicinity of Chornobyl who received high thyroid doses in 1986 following the consumption of milk heavily contaminated with radioiodine.

The Fukushima Dai-ichi nuclear accident in March 2011 also released radioiodine into the environment. Much of the release to atmosphere was carried east over the Pacific Ocean, but an area to the north-west of the nuclear site was contaminated a few days after the start of the releases. The iodine-131 release was ~10 % of the Chornobyl release, leading to thyroid doses received by the most exposed infant of <100 mGy, which are much less than the doses received after the Chornobyl accident (UNSCEAR 2014). Somewhat disturbing, then, were suggestions that thyroid cancers among those <18 years of age at the time of the accident detected in a large thyroid screening programme covering the whole of Fukushima Prefecture were attributable to exposures from the accident (Tsuda et al. 2016), but the flaws in this suggestion were pointed out by a number of commentators, e.g., by Wakeford et al. 2016). A similar experience with thyroid screening in South Korea in the early-2000s (Ahn, Kim, and Welch 2014) strongly suggests that the small thyroid tumours found in thyroid screening programmes are the result of enhanced detection by sensitive ultrasound equipment rather than radiation exposure, and there are other aspects of the observed cases that support this interpretation. Indeed, an IARC Expert Group has now recommended against screening after nuclear accidents because of the problems of "overdiagnosis" (Togawa et al. 2018). Hence, it is unlikely that the thyroid cancers being detected by the Fukushima screening programme are related to radiation exposure from the accident, but it will be important to continue monitoring the incidence of thyroid cancer (and other cancers) to be sure that risks have not been underestimated.

5. Conclusions

Age-at-exposure is an important modifier of the risk of cancer following the receipt of a particular dose of radiation, and the degree of modification varies between cancer types. Exposure at a young age is particularly important for the raised risks of leukaemia and thyroid cancer following irradiation. These two cancers illustrate two different aspects of age-at-exposure as a risk modifying factor: for leukaemia, the excess risk is expressed as a temporal "wave" with the peak excess risk notably greatest at the youngest ages at exposure, but the increase in risk only persists to a limited extent into later life; for thyroid cancer, the proportional increase in risk is also greatest at young ages at exposure, but persists for decades after exposure so that the largest number of excess cases occurs years after exposure when the background risk is highest. The models upon which these predictions are based are supported to a reasonable extent by studies, in particular recent studies of pooled data from those exposed to low doses. Continuing studies of the Japanese atomic-bomb survivors are revealing interesting features of certain cancers at young ages at exposure, such as female breast cancer and uterine cancer. Continued follow-up of the LSS will provide growing evidence from those exposed at the youngest ages, because these survivors are reaching an age at which serious

disease and death are increasingly likely. It will be necessary to update radiation risk models as evidence accrues.

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Neurocognitive effects after radiation exposure of children

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Abstract

The brain undergoes ionising radiation (IR) exposure in many clinical situations, particularly during radiotherapy for malignant brain tumours. Cranial radiation therapy is related with the hazard of long-term neurocognitive decline. Cognition is a set of functions ensuring the ability to think, learn, reason, image and remember. These functions start to develop in utero, continue until young adulthood, and start to decline at older ages. In fact, radiotherapy-related neurocognitive defects are prevalent in children where they represent a major detrimental side effect of life-saving procedures. In addition, these detrimental effects closely correlate with age at treatment, and younger age associates with more severe neurocognitive deficiencies. Beside therapeutic use, diagnostic radiation is an indispensable tool of modern medicine. X-ray imaging, including computed tomography (CT) scans, is an essential diagnostic instrument for numerous illnesses and has a crucial role in monitoring disease and anticipating prognosis. However, the growing use of CT procedures on children raises concern over the long-term health risk associated with medical radiologic diagnostics. Accumulating evidence suggests that various degrees of cognitive deficit can develop after much lower doses of ionising radiation, as well. Nevertheless, results of available epidemiological studies are sparse and not always consistent, the risk estimates are prone to bias and confounding factors, and the biological mechanisms of relevance for health risks are not known especially at low/moderate doses. Accumulating evidence in animal models suggests that radiation-induced cognitive decline involves damage in multiple neural cell types, causing structural and functional alterations in the brain blood vessels and in glial cell populations, reducing neurogenesis in the hippocampus, altering neuronal function, and increasing neuroinflammation. Overall, brain radiation injury leads to a persistent alteration in the brain's milieu, with inflammation playing a crucial role.

In this presentation, an overview of the available data on the risk of radiation exposure in the development of cognitive impairment in children and the underlying mechanisms has been discussed. Research gaps in current understanding of the pathophysiological mechanism for radiation-related neurocognitive effects at low/moderate radiation doses from the experimental perspective have been examined. Assessing whether

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low/moderate doses of radiation affect cognition is important both for Public Health and radiation protection.

1. Introduction

Environmental stressors, including ionising radiations, have the capacity to negatively influence the development of all of the body's organ systems. The severity of the impairment depends on the extent of exposure, and most importantly, on the timing during the developmental process. Early insults can lead to a broad range of lifelong problems both physical and mental.

Brain development begins well before birth and continues through the early adult years. The biology of this process is influenced by (i) the genes that are passed on from the parents to the child, (ii) by the environment of the mother's womb, and (iii) by the world the child experiences during infancy and childhood. When it is immature, the brain is peculiarly susceptible to adverse impacts on the development of its basic circuits. This may result in permanent impairment, thereby leading to a wide range of lifelong adverse impacts on learning, behavior, and health that impose devastating human and financial costs.

Cognition - the set of functions ensuring the ability to think, learn, reason, image and remember (Forns et al., 2011) - starts to develop in utero, continues until young adulthood and begins to decline at older ages. Behind genetic factors, environmental agents, including ionising radiation, may influence and determine the trajectory of cognitive development and decline.

During the developmental phase, the brain experiences a phase of marked growth in size. The curve of brain weight gain, expressed as the percentage of adult brain weight as a function of age, in fact, is not linear with time, but shows a period of more rapid growth defined as brain growth spurt. It peaks around birth in humans, and postnatal day 10 (P10) in mice. This phase represents the most vulnerable period for the brain, where a slightest disturbance may have deep effects on growth and development. The brain growth spurts corresponds to highest sensitivity to toxicant exposure, with neurotoxic manifestation in the adult mice (Eriksson et al., 2000).

2. Cognitive decline in the clinical setting

The first evidence of detrimental effects of ionising radiation on cognition appeared in 1982, when a report on Israeli children affected by *tinea capitis* and treated by X-rays (mean brain dose of 130 rads) to eradicate the disease has been published (Ron et al., 1982). About 11,000 of the exposed children were evaluated for evidence of radiation effects on central nervous system (CNS) almost 20 years later. While not all comparisons were statistically significant, there was a consistent trend for the irradiated subjects to exhibit more often signs of central nervous system impairment compared to the unexposed group. The irradiated children had (i) lower examination scores on scholastic aptitude, (ii) intelligence quotient (IQ) and (iii) psychologic tests, (iv) completed fewer school grades, and (v) had an increased risk for mental hospital admissions for certain disease categories. A slightly higher frequency of mental retardation was also suggested.

These effects lead the authors to conclude that radiation to the immature brain may cause damage to the central nervous system.

Many other evidences of increased risk for cognitive deficits came from studies relative to brain tumour survivors after radiation therapy, where young age survivors have been reported with poor neurocognitive outcome (Castellino et al., 2014). Patients may develop motor, intellectual, visual, and psychoemotional dysfunctions, with moderate to severe disabilities. Younger age at diagnosis, higher cranial irradiation dose, larger irradiated brain volume, and longer time since treatment are risk factors for worse neurocognitive outcomes (Roman and Sperduto, 1995). Neurocognitive problems are also commonly experienced by survivors of acute lymphoblastic leukemia (ALL) treated with CNS prophylaxis. Cranial radiation carries particular risk to memory function, especially the process of forming new memories of events or facts that is sub served by the hippocampus in the medial temporal lobe (Krull et al., 2018).

The time-line of radiation therapy-induced brain injury is traditionally classified into acute, early delayed and late delayed, based on time between radiotherapy and the onset of side-effects. While acute and early delayed effects are generally transient, cognitive decline may become manifest many months to years after irradiation and get progressively worse (Chu et al., 2020).

The frequency of radiation-induced cognitive impairment varies among studies and it is influenced by a number of factors such as: i) patient age at exposure; ii) age at cognitive assessment; iii) definition of neurocognitive impairment; iv) tumour type; v) disease progression; vi) radiotherapy modality (whole brain, partial brain, stereotactic) vii) radiation dose; viii) use of multimodal treatments, including concurrent chemotherapy and surgical procedures. Therefore, although the occurrence of cognitive dysfunction that significantly affects the quality of life is well recognised in paediatric patients undergoing radiation therapy, determining and comparing the frequency of such a cognitive decline in the clinical setting remain challenging.

In addition, studying human brain tissues is hampered by several potential technical obstacles. Standardisation of essential methodological requirements would also be needed, e.g., the maximum pre-mortem agonal period, maximum time elapsed from death to tissue fixation and fixation times. Moreover, the ability to access human samples should be facilitated by establishing brain-tissue bank/s from large patient cohorts open to researchers. Open data repositories of human neurogenomics should be organised.

Overall, radiation-dependent cognitive decline is challenging to address in epidemiological studies and moving from association towards mechanistic studies to elucidate pathogenesis of radiation-induced cognitive impairment may benefit greatly from experimental studies.

3. Mechanistic studies to elucidate pathogenesis of radiation-induced cognitive impairment in animal models

Understanding of the factors modulating brain radiation response may be of help to minimise the risk of adverse effects and towards the identification of early prevention measures against radiation-dependent adverse effects. Experimental studies may shed

light on the factors influencing brain radiation response such as, age at exposure, genetic background-dependence of radiation-induced effects and combined effects of ionising radiations and other environmental/chemical factors. The use of animal models is therefore critical for improving the mechanistic understanding of radiation-induced cognitive effects.

3.1 Behavioral tests

Radiation-induced impairment of cognitive function and memory may also be detected in rodents. Behavioral tests are considered the best available strategy to uncover brain functions in animal experiments. The use of one test is not ideal and a number of behavioral tests have been developed to detect and quantify the presence of motor and memory impairments in rodent models. These deficits might be detected even several months after irradiation. An example of these tests is represented by the spontaneous behavior in a novel environment (home cage and bedding material), that measures the animal's habituation capability over the one-hour observational period. When the mouse enters the new cage it starts with a high exploratory activity during the first 20 min and low activity counts at the end of the 60 min. This behavioral profile represents a normal pattern for mouse adaptation to a novel home environment. Two months after irradiation with 500 mGy at perinatal mouse age (P3 or P10), the irradiated mice were shown to be significantly hypoactive during the first 20 minutes and very hyperactive during the last 20 min period. Disruption of the spontaneous behavioral profile is indicative of lack of habituation and cognitive dysfunction. This was not observed when the mice were irradiated at older age (P19), indicating that perinatal age represents a critical age window for induction of developmental radiation-induced neurotoxicity in mice (Eriksson et al., 2016).

3.2 Potential mechanisms of radiation-induced neurocognitive effects

The mechanism of radiation-induced brain injury is multifactorial and complex, involving dynamic interactions between multiple cell types. Potential mechanisms triggering radiation-induced cognitive impairment are:

- Vascular damage (blood-brain barrier disruption)
- Decline in oligodendrocytes and other glial cells
- Neuroinflammation caused by activated microglia
- Impaired hippocampal neurogenesis
- Altered function of adult neurons

All these alterations, thought to occur concomitantly, are likely to contribute to pathogenesis of radiation-induced cognitive impairment.

Vascular Damage

The blood–brain barrier (BBB) is a highly selective semipermeable border of endothelial cells that restrict the passage of most soluble molecules, from the systemic circulation, into the CNS. The BBB is composed of endothelial cells, pericytes, and astrocyte end-feet that form tight junctions. Irradiation can impair the integrity of the BBB altering neurovascular permeability and allowing inflammatory cells to enter the brain and propel neuroinflammation (Trnovec et al., 1990).

Oligodendrocytes

The mechanisms of neurotoxicity from radiation therapy include demyelination (Wong et al., 2015). Oligodendrocytes are responsible for the myelin production in the CNS. Irradiation of CNS induces depletion of oligodendrocytes (Irvine and Blakemore, 2007) and suppresses, at least transiently, the production of oligodendrocyte progenitors.

Neuroinflammation caused by activated microglia

Microglia are resident mononuclear phagocytes that maintain brain microenvironment homeostasis and provide immune defense. After insults to the brain, they become activated by rounding of the cell body, retraction of cell processes and proliferation. Microglia activation plays an important role in phagocytosis of dead cells (Sierra et al., 2013). However, persistent microglia activation contributes to chronic inflammation and negatively affects neuronal structures, results in decreased synaptic plasticity and has been implicated in the pathophysiology of brain injury (Ramlackhansingh et al., 2011). Activated microglial cells initiate an inflammatory response by releasing pro-inflammatory cytokines and ROS. Studies in hippocampal and cortical regions isolated from irradiated rat brains showed significantly upregulated expression of inflammation markers interleukin 6 (IL-6), interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α) (Lee et al., 2010). This pro-inflammatory state can be cytotoxic to surrounding cells and can propagate tissue damage and cause secondary injury. Microglia activation might be detected even months after irradiation indicating the persistence of the neuroinflammatory process (Mizumatsu et al., 2003). Selective inhibition of microglia-mediated neuroinflammation has been shown to mitigate radiation-induced cognitive impairment (Jenrow et al., 2013). After whole-brain irradiation with 10 Gy, selective inhibition of proinflammatory microglial cytokines through administration of MW-151 for 28 days, was reported to alleviate radiation-induced neuroinflammation up to 9 months post-irradiation and potently mitigate radiation-induced behavioral deficits.

Impaired hippocampal neurogenesis

Impaired hippocampal neurogenesis is now recognised as one of the major mechanism of radiation-induced brain injury (Tomé et al., 2016; Kempf et al., 2014; Casciati et al., 2016). It was in the middle 1960s, when it was first shown that similar to other vertebrates, adult neurogenesis also occurs in mammals and that new nervous system cells continue to grow in the brain, even as animals get older, overturning the traditional dogma that no new neurons are made in the adult mammalian brain (Altman and Das, 1967). This discovery remained almost unnoticed until 1996, when the capacity for neurogenesis in the hippocampus in adult life was demonstrated in mice (Kuhn et al., 1996; Kempermann et al., 1997), and soon after it was proven in the adult human brain throughout the life cycle (Eriksson et al., 1998). Nowadays, the hippocampus is considered one of the two major sites of adult neurogenesis in the brain. Learning memory is known to be dependent on proper hippocampus functionality. In fact, abnormalities in the hippocampal neurogenesis are related with neurological disorders such as epilepsy, Alzheimer's disease and depression (Cho et al., 2015; Mu and Gage, 2011).

In the dentate gyrus (DG) of the hippocampus, continuous neurogenesis is observed throughout life and the majority of neurons are generated postnatally, with thousands of new neurons produced in the DG of rodents each day. Neurogenesis is a highly dynamic

process, whose extent is regulated by intrinsic and external factors (Aimone et al., 2014). It is promoted by voluntary physical exercises (Olah et al., 2009) and negatively regulated by aging and stress (Gould et al., 1999; Maxwell et al., 1986). Hippocampus adult neurogenesis is a multistep process. Different cellular populations reside in the DG, distinguishable for their morphology and expression of cellular markers (Casciati et al., 2016; Toda and Gage, 2018). From the largely quiescent neural stem cell pool (NSC), also called radial glial-like cells (RGLs), to mature, integrated and functional neurons, NSCs and their progeny transit through several intermediate developmental stages (Figure 1). First, the quiescent population of NSCs (GFAP+) is activated to generate proliferating transit-amplifying cells that enlarge the pool of neurogenic cells (Sox2+, PCNA+). Some of these progenitors start to express the neuronal migration protein doublecortin (DCX) that labels new-born neurons and finally the differentiation marker NeuN that labels the mature neurons. Of note, radiation-induced modifications in the rate of neurogenesis can be investigated through evaluation of stage-specific cell population in the DG.

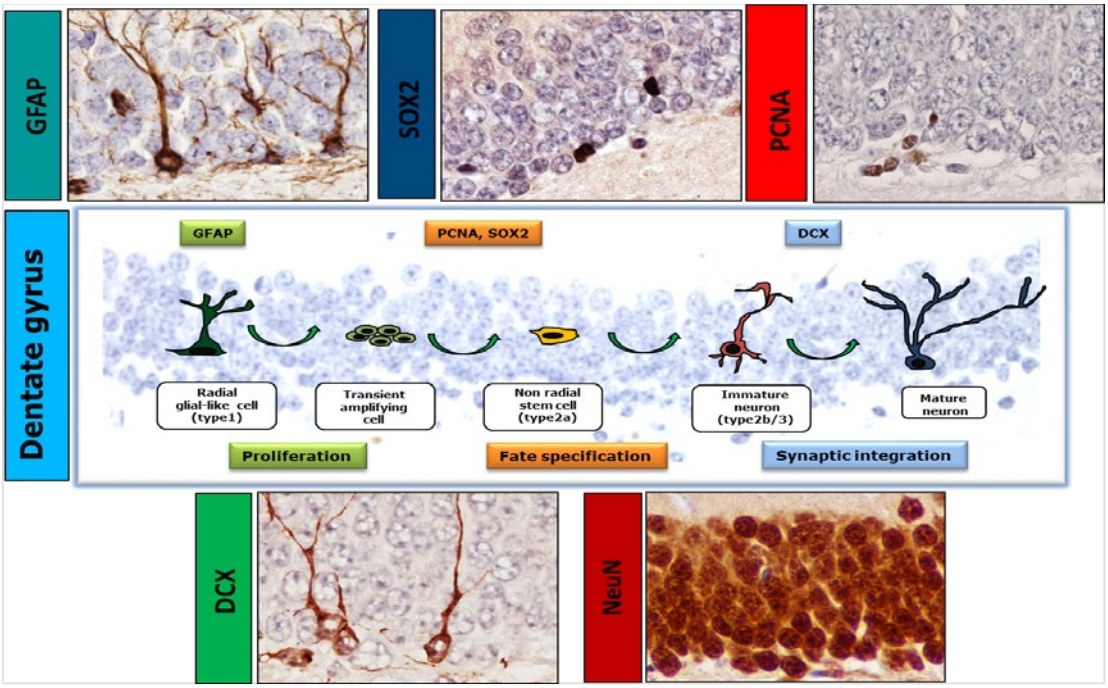

Figure 1. Cell types in neuronal development of the DG and immunohistological markers for staging hippocampal neurogenesis. Local stem cells pass through several distinct morphologically and genetically identifiable stages, most notably a slowly dividing radial glial cell (RGC) stage (GFAP+) and a more rapidly proliferating neural progenitor stage (SOX2+, PCNA+) before becoming new-born neuron (DCX+), and integrating into the adult dentate gyrus network (NeuN+).

Impairment of neurogenesis in the hippocampus following whole-brain irradiation is now referred to as one of the principal mechanisms of radiation-induced cognitive dysfunction. One of the first experimental evidences come from a study in which irradiation with 5 Gy of X-rays has been shown to significantly reduce the production of new neurons at 1 and 3 months post-irradiation in mice (Rola et al., 2004). Reduced neurogenesis was

associated with a chronic inflammatory response and with spatial memory retention deficits. These data demonstrated that irradiation of young animals induces a long-term impairment of subgranular zone (SGZ) neurogenesis that is associated with hippocampal-dependent memory deficits.

The importance of hippocampal neural stem cells (NSCs) in radiation-induced cognitive decline is revealed by experiments showing that in rodents, radiation-dependent impairment of cognitive function can be partially rescued by NSC transplantation (Acharya et al., 2011). Intra-hippocampal transplantation with human NSC in irradiated athymic nude rats at 2 days post-irradiation protect the irradiated engrafted animals from decline of cognitive performance. These rats, in fact, exhibited significantly less cognitive decline than irradiated sham-engrafted animals and acted indistinguishably from unirradiated controls.

The critical role of hippocampus in the pathogenesis of radiation-induced neurocognitive effects is also underlined by the observation that hippocampal avoidance (HA) seems to reduce the short-term memory decline in adults receiving whole-brain radiation therapy (Gondi et al., 2014). In a study examining the association between hippocampal dose and memory in survivors of childhood or adolescent low-grade glioma, it was shown that survivors of paediatric low-grade gliomas suffer memory decline and greater hippocampal dose is associated with greater decline in memory (Acharya et al., 2019). Although the merit of HA in paediatric brain tumour patients is still unexplored, reducing hippocampal dose may represent a memory preserving treatment strategy that may be greater in children than adults, because of the higher vulnerability to radiation injury.

Altered function of adult neurons

Dendrites, the branched projections of a neuron, are essential for synaptic contacts. Thus, dendritic morphology is important for many aspects of neural function, including signal propagation and information processing. Spines undergo experience-dependent morphological changes in live animals and even small changes in dendritic spines may have marked effects on synaptic function, plasticity and patterns of connectivity in neuronal circuits (Kitanishi et al., 2009). Notably, dendritic spine pathology is involved in a number of neuropsychiatric disorders (Nishiyama, 2019). In normal subjects, spine numbers increase around birth, therefore spines are selectively eliminated during childhood and adolescence to the adult levels. In autism spectrum disorders, exaggerated spine formation or incomplete pruning in childhood may lead to increased spine numbers. In schizophrenia, exaggerated spine pruning in late childhood or adolescence may lead to the emergence of symptoms. In Alzheimer's disease, spines are rapidly lost in late adulthood, suggesting perturbed spine maintenance mechanisms that may underlie cognitive decline (Penzes et al., 2011).

Brain has been classically regarded as a radioresistant organ, and neurons as essentially inert to radiation. However, recent work suggests that radiation-induced adverse effects on cognition may also be promoted by alterations in mature neuronal networks. Two recent studies documented dose-dependent (0.1-1 Gy) and persistent (10 and 30 days post-irradiation) reduction in dendritic complexity in mouse hippocampal neurons, detected as a reduction in dendrite branching length compared to unexposed control. Immature filopodia, showed the greatest radiation sensitivity compared to mature spine morphologies (Parihar and Limoli, 2013; Parihar et al., 2015). Alteration in synaptic proteins is also observed in the hippocampus after irradiation. Long-term increased

expression of postsynaptic density protein (PSD-95) and microtubule-associated protein 2 (MAP-2) have been reported in the hippocampus after irradiation of neonatal mice (P10). These proteins have a role in spine formation, maturation and stability of dendrites (Kempf et al., 2014). Dendritic spine pathology and altered expression of synaptic proteins may therefore be one of the pathophysiological mechanisms in radiation-induced brain damage.

Overall, irradiation has been shown to induce a wide spectrum of cellular damage that elicits a global stress response. The complexity of the progressive cognitive disability due to brain radiation exposure cannot be fully explained by alteration of a single cell type, and the pathogenesis of radiation-induced cognitive injury is likely dependent on dynamic connections between multiple cell types (i.e., neurons, microglia and astrocytes). Therefore, radiation-induced cognitive decline might be a consequence of alterations in the vasculature, in glial and neuronal cell functions, in neurogenesis rate or due to neuroinflammation.

4. Brain radiation effects at low radiation doses

Much focus has been directed towards the study of adverse radiation effects following radiotherapeutic doses, but less is known on how exposure to low/moderate doses affects normal brain development during early postnatal life. Molecular mechanisms at high doses might be different from those acting at low dose.

Computed tomography (CT) has been established as one of the most informative diagnostic radiology examinations. The use of CT scans has increased over the past decades and particularly in the field of paediatric diagnostic and adult screening. CT scans are accountable for 40-70 % of the medical dose in the population (Bernier et al., 2012) and head CT scans contributed to almost 15 % of the total collective effective dose in the general population (Mettler et al., 2000; Mettler et al., 2008). The growing use of CT procedures on children raises concern over the long-term health risk, because of the radiosensitivity of children. Estimations of brain doses during CT scans show an increasing trend with decreasing patient age. Children under 5 years of age for head CT are exposed to an absorbed dose to the brain in the range of 50/100 mGy/scan (Brenner and Hall, 2007; Trattner et al., 2014).

A large amount of uncertainty remains concerning the impact of low dose ionising radiation on the brain and especially for neurocognitive effects after radiation exposure of children. Publications trends in the PubMed database illustrates that moving from the terms “ionizing radiations and brain” to “low-dose ionizing radiation and brain” markedly reduced the number of citations (4800 vs 372) (Figure 2). In addition, searching for “low dose ionizing radiations and child brain” further decreased the publications retrieved (45). Even fewer hits were yielded for “low dose ionizing radiations and neurocognitive effects” (10) showing the paucity of data on this topic.

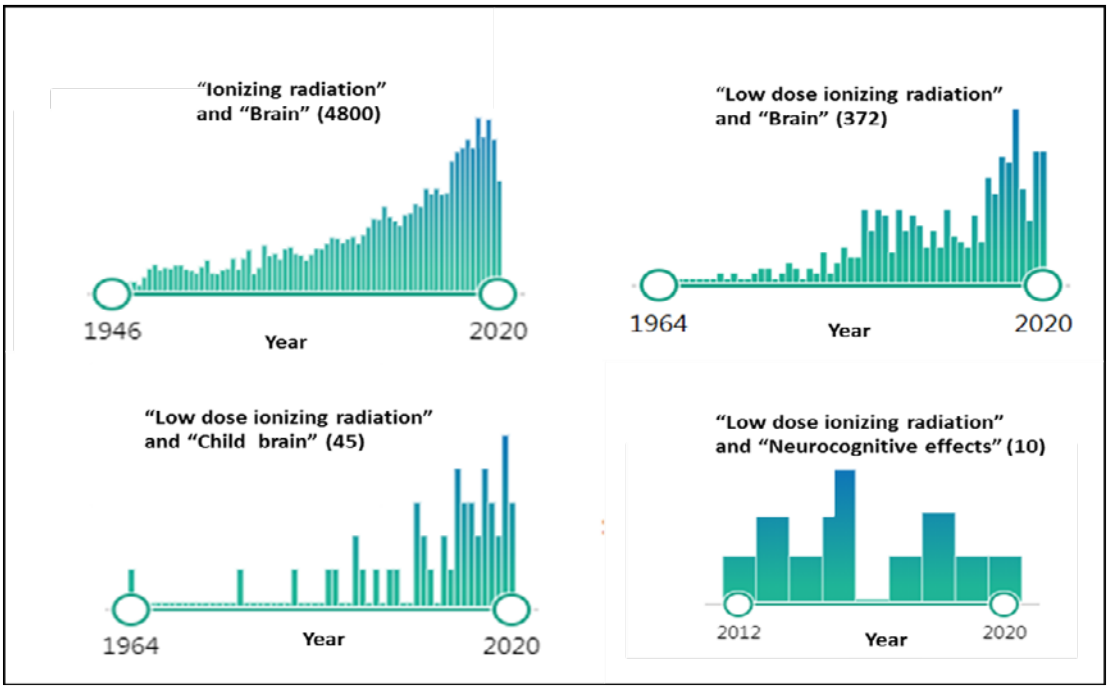

Figure 2. *Publications trends in the PubMed database. Moving from the terms "ionizing radiation" and "brain" to "low-dose ionizing radiation" and "brain" markedly reduced the hits (4800 vs 372). In addition, the search for "low dose ionizing radiation" and "child brain" further decreased the publications retrieved (45). Even fewer results were yielded for "low dose ionizing radiation" and "neurocognitive effects" (10) showing the extreme lack of research on this topic.*

The publication of results of the Swedish Haemangioma study (Hall et al., 2004), associating low radiation doses (120-150 mGy) during infancy with cognitive decline during adult life, stimulated interest in the potential non-cancer effects of low/moderate doses of ionising radiation. Very recently, on this topic, a systematic review examining the neurodevelopmental effects of low/moderate doses received during fetal life, childhood and adolescence in 26 selected manuscripts has been published (Pasqual et al., 2020a). The most informative studies were: i) A-bomb survivors, ii) Tinea capitis, iii) Haemangioma cohorts. However, the selected studies were heterogeneous in terms of outcome and exposure assessment. The strength of evidence for an effect on general cognition and language was retained limited, and the evidence for an effect on other neurodevelopment domains was considered inadequate. To implement epidemiological studies on cognitive radiation-induced effects, limitations such as the small size of the cohorts, limited dose estimation, confounding factors, and low outcome specificity for cognitive measure need to be overcome.

Some of the recently funded EURATOM projects focused on neurocognitive radiation effects. One of the aims of "CEREBRAD" [Cognitive and Cerebrovascular Effects Induced by Low Dose Ionising Radiation; (http://www.cerebrad-fp7.eu/)], was assessing the long-term cellular and molecular alterations induced by low-dose irradiation in the hippocampus. In one experimental set, mice were whole-body irradiated at perinatal age (P10), subjected to behavioral tests between 2 and 6 months of age, and evaluated for changes in adult hippocampal neurogenesis. Persistent impairment of memory and cognition was detected at doses ≥ 500 mGy, as well as alterations in synaptic proteins

and defects in neurogenesis, involving depletion of RGL ($GFAP^+$), proliferative precursors ($PCNA^+$ and $Ki67^+$), and mature neurons (NeuN+) at 6 months post-irradiation. We also detected microglia activation (CD11b) and increased number of $GFAP^+$ astrocytes in the hilus after irradiation indicative of a persistent neuroinflammation after exposure to low/moderate radiation doses (0.1-1Gy). Altogether, both neurological and behavioral effects were detected at dose > 0.5 Gy suggesting a threshold around this dose for hippocampal-dependent memory deficits (Kempf et al., 2014).

In the EURATOM funded project "SEPARATE" (Systemic Effect of Partial-body Exposure to Low Radiation Doses), a multi-omics approach was applied to investigate out-of-target radiation responses in the hippocampus. Mice irradiated with low/moderate radiation doses (0.1 Gy or 2 Gy) in the lower third of the body with the upper two third shielded, displayed changes in non-coding RNAs and proteins, as well as defects in neurogenesis very similar to those showed by whole-body irradiated mice, providing a proof of principle of the existence of out-of-target radiation response in the hippocampus (Pazzaglia et al., 2021). This might have important implications on radiation therapy, therefore, further investigations to disentangle direct and out-of-field effects deriving from radiation exposure are recommended.

The importance of assessing the consequences of exposure to low/moderate doses of ionising radiation on non-cancer effects, including neurocognitive decline, is also highlighted in the strategic research agenda (SRA) of MELODI (www.melodi-online.eu), a European Platform dedicated to low dose radiation risk research, where this topic has been set out as a key priority for epidemiological and experimental studies. Under the framework of MELODI, during a workshop devoted to "Non-cancer effects of low doses of ionizing radiation", held in April 2019 at Sitges (Spain), an interdisciplinary group of experts in neurocognitive radiation effects (biologists, epidemiologists, dosimetrists and clinicians) summarised the state of knowledge on this topic and elaborated recommendations for future studies in this area. Overall evidences were presented of cognitive effects for low/moderate doses radiation both from experimental studies and epidemiology. However, it was stressed that efforts for a better characterisation of the effects are needed, including specific cognitive functions or disease affected by radiation exposure, and for a better understanding of the mechanisms (Pasqual et al., 2020b).

5. Conclusions, experimental gaps and recommendations for future studies

The studies reviewed here provided an overview of the available data on the effects of radiation exposure for development of cognitive impairment in children and of the underlying mechanisms. Our understanding of the pathophysiological mechanisms of radiation brain injury is rapidly expanding but still very far from being complete. Understanding the factors modulating brain radiation response may help to minimise the harmful effects and to identify early prevention measures against adverse radiation effects that are a serious concern in children. There are a number of research gaps in our knowledge, and underexplored areas that should be clarified. Research topics and recommendations for future epidemiological and experimental studies are listed below:

- Cognitive decline at low/moderate radiation doses is challenging to address in epidemiological studies. Considering the effect modification of age at exposure

and age at cognitive assessment is an important issue for the interpretation of results of epidemiological studies. Understanding of the effect of co-exposure in particular medical settings is also important.

- Notwithstanding the importance of rodent models in elucidating the pathogenesis of radiation-induced neurocognitive effects, the validity for humans should also be investigated. To this aim, establishing brain-tissue banks from large patient cohorts open to researchers would be needed.
- Development of further research on the mechanisms acting at low/moderate radiation dose, that may not be identical to those at high dose, has to be fostered.
- Multidisciplinary approaches including collection of suitable biological samples, comprehensive cognitive function assessment, precise dosimetry to different brain structures and multi-omics approaches to elucidate genetic and epigenetic mechanisms of radiation-induced neurocognitive effects at low/moderate radiation doses should be implemented.
- Identification of genetic susceptibility factors in radiation-induced cognitive dysfunction at low doses in children.
- Mechanistic investigations on the contribution of ”out-of-target“ neurocognitive effects.
- Investigations on long-term benefits on neurocognitive outcome of proton therapy for paediatric patients with brain tumour and related mechanistic experimental studies in mice (Baliga and Yock, 2019; Dutz et al., 2020; Kahalley et al., 2019).
- Investigation on long-term benefits on neurocognitive effects of ultra-high dose-rate (>100 Gys-1) FLASH radiotherapy in paediatric patients to spare healthy tissues (Simmons et al., 2019; Montay-Gruel et al., 2017).

Overall, more research in large epidemiological cohorts and animal models is needed to improve the understanding of radiation-induced cognitive effects especially at low doses. Results may then be translated into recommendations for improving radiation protection of young patients undergoing diagnostic and therapeutic medical procedures. Recognition of children’s vulnerability to radiation effects should stimulate new investments in children’s health research. To protect human health, and especially the health of infants and children, represents the paradigm for radiation protection.

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Dosimetry and dosimetric challenges in paediatric radiology and radiotherapy

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Abstract

Patient specific dosimetry is of paramount importance in paediatric applications due to their significantly increased radiation sensitivity in comparison to adults. Paediatric patients have a higher risk to develop cancer compared to adults that obtain an equivalent amount of radiation dose. Exposure of children to ionising radiation has a longer expectancy in which it may provoke the development of radiation-induced issues such as cancer or as future parents, may increase hazard for passing on radiation-induced genetic disorders in the following generations. Considering the individual characteristics of children, it is important to reconsider diagnostic applications and therapy schemes in terms of personalisation and calculation of exact amount of absorbed dose per organ and patient.

The TRS 457 (IAEA, 2007) recommendation, suggests that dose measurements should be made whenever possible, both on patients and phantoms. The use of phantoms enables repeatability and standardisation of measurements as well as a rapid evaluation of results, but not accurate and personalised dose estimation for a specific patient. Clinical measurements could complement the above outcome and are usually made using Thermoluminescent dosimeters (TLDs) or Optically Stimulated Luminescence dosimeters (OSLs). The main problem with TLDs is that there is typically a 0.1 mGy minimum absorbed dose to produce a reasonably accurate result. Modern techniques to assess organ and effective dose induced by medical imaging procedures are based on physical or computational phantoms.

Computer-based phantoms have the ability to represent a limitless amount of body types and have the potential to assess patient-specific organ and effective dose. Recently, researchers have focused their studies on the production of an ideal 'hybrid' model as an evolution to computerised models. This hybrid model combines the realism of a voxelized phantom and the flexibility of a mathematical phantom. The anatomical virtual

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anthropomorphic models have been evolved a lot to successfully meet the standards of clinical practice.

Monte Carlo (MC) simulations on the other hand are broadly acknowledged as a fundamental technique to investigate the physics of nuclear medicine, radiology, radiation therapy, and dosimetry. When the MC methods are combined with precise paediatric computational phantoms, they may serve as the gold standard for the accurate assessment of absorbed dose in terms of personalised dosimetry. Organ absorbed dose is essential for paediatric patients, where major organ variations appear in comparison to adults' anatomies.

The establishment and the optimisation of dosimetry protocols in paediatric acquisitions is therefore of high social and scientific interest. At the same time, there are critical concerns and multiple parameters to consider. The first challenge is the computational time and the need of extensive computing resources for the implementation of precise realistic MC simulations, with low statistical uncertainties, that consider patient specific characteristics. The second challenge is the establishment of several clinical protocols used in paediatric diagnosis and therapy based on individualised patient information. Finally, in clinical practice absolute radiation dose measurements to the various organs and to the patient in total is not an easy task to perform. The rapid evolution of computer science in terms of Artificial Intelligence can play a key role in the optimisation of the established paediatric clinical protocols in terms of personalisation.

1. Introduction

Radiation sensitivity of children is a fact that needs to be considered when ionising radiation is used for imaging or therapeutic purposes. Children have a high potential to develop radiation induced cancer due to their longer life expectancy. They also have a higher risk of invoking genetic aberrations to their reproductive cells, which may be transferred to next generations (NRC, 2006). Because of the sensitive characteristics of paediatric patients, special measures must be performed for their radiation protection, when diagnostic (Radiography/CT/SPECT/PET) or therapeutic (Radiation Therapy / Brachytherapy / Targeted Radionuclide Therapy) procedures are being used.

Since late 1940s, the scientific community has been studying dose assessments from internal radiation sources (Marinelli, Quimby *et al.*, 1948). Due to the progress done, the administered dosage to paediatric patients has been optimised but is still adjusted to the different size by the suggested adult dose without considering the special characteristics of the patient (Fahey, Treves *et al.*, 2011, Treves, Davis *et al.*, 2008). MIRD Pamphlet No. 17 (Bolch, Bouchet *et al.*, 1999) in 1999 was a step forward for personalised dosimetry as it proposed the use of a dose conversion factor; the S-value. The S-value factor was considering every type of radiation, energy, and source and target combination for dosimetry studies that used non-uniform activity distribution. They could therefore assess the radiation absorbed dose in tissues or even organs of human and rodent anatomies at the voxel level.

Building on the MIRD guidelines, advanced techniques to measure organ radiation dose use anthropomorphic computational phantoms, which describe the human anatomy in great accuracy and also can be modified for personalisation purposes (Chapple, Willis *et al.*, 2002, Xu and Eckerman, 2009). Furthermore, recent studies have introduced a new

type of computational phantoms, the "hybrid" phantoms that use voxelized segmentations in parallel with polygon or triangular mesh to produce phantoms with mathematical flexibility in terms of shape, size and resolution (Bolch, Lee *et al.*, 2010, Kim, Yeom *et al.*, 2020, Lee, Lodwick *et al.*, 2007).

Monte Carlo (MC) techniques have been extensively used to describe the interaction of ionising radiation with matter in medical procedures. The combination of MC simulations with highly detailed anthropomorphic computational phantoms can serve to assess the absorbed dose in any region of the human anatomy (Sarrut, Bardies *et al.*, 2014). With the aid of such techniques, it can be calculated that there are major organ variations at paediatric patients in comparison with adults. Such techniques could lead to personalised dosimetry and optimisation of medical procedures using ionising radiation (Papadimitroulas, Kostou *et al.*, 2019).

The development of Artificial Intelligence (AI) algorithms is considered an immensely growing field that can be used in various applications considering the radiosensitive group of children. AI algorithms can be applied either for diagnostic or for therapy procedures. They can also be used for accurate dosimetry assessments, by predicting the absorbed dose in a target region and advance image processing concerning image denoising, organ or tumour delineations or even tumour classification. Recently developed algorithms have shown amazing results on even predicting the biodistribution of pharmaceutical radionuclides.

This article aims to provide a holistic description of recent developments in the above-mentioned fields. Modern medicine can benefit from the advanced MC simulations and AI techniques that can be exploited to optimise radiation dosimetry protocols in paediatric acquisitions, as they are of high social, scientific, and economic interest.

2. Radiology procedures

Because of their sensitivity, children could be exposed to ionising radiation for imaging purposes only when there is no non-ionising alternative such as ultrasonography (US) or magnetic resonance imaging (MRI), and when there is a definite diagnostic/medical benefit. The imaging protocols must be adjusted to the children anatomical characteristics and not to the age of the paediatric patient. Such cases have been reported in the Image Gently Campaign by the Image Gently Alliance (Don, Macdougall *et al.*, 2013). It should also be stated that newer imaging devices used in radiology procedures have a big impact in reducing radiation burden to the patient while providing images of adequate diagnostic quality. Therefore, for paediatric patients such devices, that use direct digital detectors, must be used (digital radiography, *etc.*) (Hermann, Fauber *et al.*, 2012).

EuroSafe (ESR, 2014), a dose awareness campaign was introduced on 2014 to implement a reasonable dose management strategy. Furthermore, additional guidelines, like the Dose Check Standard from the National Electrical Manufacturers Association (NEMA), were also published (NEMA, 2010).

Furthermore, Dose management software applications started being used for reasonable dose management. Dose monitoring systems (DMS) are the next generation software tools aiming to optimise dose assessment in radiology departments. They obtain

information on dose outliers and monitor the effect of protocol adjustment to evaluate imaging protocols and radiation dose. DMS will be integrated in all systems soon, as they are used to monitor patient dose; and when upgraded they will be able to make personalised dosimetry calculations (Samei, Tian *et al.*, 2014).

There are several guidelines that have been proposed for paediatric examinations, such as the use of automatic exposure control (AEC) coupled with calipers, the use of maximum available kilovoltage peak (KVp) coupled with the minimum amount of milliampere seconds (mAs) as well as special charts to modify each examination based on the size of paediatric patients (Don, Macdougall *et al.*, 2013, Hermann, Fauber *et al.*, 2012, Kleinman, Strauss *et al.*, 2010, Knight, 2014). Several organisations have also proposed that anti-scatter grids should not be used, when paediatric examinations take place (ACR, 2008).

Computed tomography (CT) is one of the diagnostic procedures with the highest radiation dose burden to the patient, but still 10 % of 100 million/year CT procedures are performed to non-adult patients. As already stated, because of the larger life expectancy and the rapid cell replication, the assessed life-time rise in cancer risk to develop malignancies for 1-year children has been calculated to 0.18 % and 0.07 % for abdomen and head scans, respectively (Toma, Cannata *et al.*, 2017). More specifically, a CT examination could cause leukemia with a life-time risk of 1-in-7,500, or brain cancer 1-in-1,000 (Brenner and Hall, 2012). Meulepas *et al.* studied the increase of brain tumour risk for paediatric patients, by CT-related radiation (Meulepas, Ronckers *et al.*, 2019). Studies have also been conducted on the prevention of future CT-induced cancers. Their results showed that by lowering the examination dose to the patient by 40 %, the probability of future cancers could be reduced up to 40 % (Journy, Lee *et al.*, 2017, Kendall, Little *et al.*, 2013, Miglioretti, Johnson *et al.*, 2013, Spycher, Lupatsch *et al.*, 2015). Epidemiologic studies showed that paediatric CTs appear to be consistent with the linear non-threshold assumption (LNT). The LNT model implies that there is no safe dose of ionizing radiation; however, adverse effects from low dose and low-dose rate (LDR) exposures are not detectable (Leuraud, Richardson *et al.*, 2015, Richardson, Cardis *et al.*, 2015).

In Europe, several new techniques have been introduced to lower radiation doses to paediatric patients from CT examinations. Application of such techniques has led to 90 % decrease in radiation exposure. These techniques include diagnostic reference levels (DRLs) for children using AEC and the implementation of special weight-based color-coded CT body protocols (Image-Gently, 2014, Singh, Kalra *et al.*, 2009, Toma, Cannata *et al.*, 2017). More analytically, paediatric CT procedures are adjusted in terms of patient weight or age, body area scanned, study indication (e.g., images with higher noise should be accepted only if they are of appropriate diagnostic quality), no overlapped scan areas, use of DRLs (Brody, Frush *et al.*, 2007, Ogbole, 2010).

In clinical routine, the precise calculation of the organ dose to any patient needs be performed. To this direction, CT devices provide clinicians with the parameters of either the volumetric CT dose index ($CTDI_{vol}$) or with the dose length product (DLP), which is the product of $CTDI_{vol}$ multiplied by the scan length (AAPM, 2008). The DLP considers the total energy deposited (and consequently the potential biological effect) attributable to the whole scan length.

The potential biological effects by any irradiation depend both on the radiation dose and on the biological sensitivity of the tissue or organ irradiated.

To quantify the whole-body radiation burden, the effective dose has been defined; it is measured in Sieverts (Sv). To this purpose, the k-factors have been defined as the Effective Dose per DLP (mSv mGy^{-1} cm^{-1}), which are connected to the radiosensitivity of each tissue. They were later expanded taking specific values for children of several ages. MC simulations are used for the k-factors calculation, starting with stylised phantoms and progressing to anthropomorphic, highly-detailed computational phantoms. There have also been studies on the optimisation of various scanning protocols (Deak, Smal *et al.*, 2010, Huda, Ogden *et al.*, 2008, Romanyukha, Folio *et al.*, 2016).

However, already published k-factors have been determined using MC simulations and reference phantoms and when used in clinical practice, the calculated effective dose tends to be over- or under-estimated. Size-specific dose estimates (SSDE) is another way to help towards the calculation of effective dose and minimise the deviations that are produced, when k-factors are used. Nevertheless, this technique carries uncertainties associated with the heterogeneity and the variation of the human body anatomy, that could lead to the overestimation of dose up to 38% (Moore, Brady *et al.*, 2014, Schmidt, Saltybaeva *et al.*, 2013).

Effective dose has been determined using experimental measurements on physical anthropomorphic phantoms, as well as calculated utilizing MC simulations (Caon, 2004, Chapple, Willis *et al.*, 2002, DeMarco, 2005, Fujii, Aoyama *et al.*, 2007, Zhang, Li *et al.*, 2013). MC simulations usually employ a precise model of the CT scanner, as well as a detailed computational personalised phantom of the patient (Turner, Zhang *et al.*, 2011, Turner, Zhang *et al.*, 2009). Currently, several software applications exist that estimate the effective dose of a CT procedure based on simplistic stylised adult models resulting in inaccurate dosimetry or absorbed dose calculation (Lee, Kim *et al.*, 2012). Such examples are: a) CTDosimetry (Impactscan), b) CTDOSE (Heron, 1993), c) eXposure (Radimetrics, 2012), and d) WinDose (Kalender, Schmidt *et al.*, 1999).

CT-Expo (Stamm and Nagel, 2002) includes primary paediatric models generated with the use of tomographic data. Newer dosimetric calculators (Ban, Takahashi *et al.*, 2011, CT_Imaging, Lee, Kim *et al.*, 2015) are based both on adult and paediatric voxelized models (Lee, Lodwick *et al.*, 2010, Xu, 2014) to eliminate dosimetry errors. VirtualDose (Ding, Gao *et al.*, 2015) includes realistic computational phantoms representing patients of various ages, body sizes, body masses, as well as pregnant females at three gestational stages; various scanners, protocols and tube current modulation (TCM) are also included. Several groups have focused their research on paediatric patients (Gao, Quinn *et al.*, 2017, Gu, Bednarz *et al.*, 2009, Kost, Fraser *et al.*, 2015, Lee, Lee *et al.*, 2007, Li, Samei *et al.*, 2011, Muryn, Morgan *et al.*, 2017, Papadakis, Perisinakis *et al.*, 2016, Schlattl, Zankl *et al.*, 2012, StratonJ, Lee *et al.*, 2006, Tian, Li *et al.*, 2014). DoseWatch (Inc.) is able to calculate Anteroposterior (AP) and Lateral (LAT) lengths for each examination using projections from the scout view. By implementing real-time monitoring of patient dose using DMS increases CT technologists' dose awareness and leads to the examinations' overdose minimisation due to human error (Boos, Meineke *et al.*, 2016, Heilmaier, Zuber *et al.*, 2016).

The number of studies concerning the paediatric dosimetry using MC simulations has increased over the last years.

The MC toolkit MCNP5 was used by Straton *et al*. to simulate the irradiation of newborns by a 16-slice helical scanner (Straton, Lee *et al.*, 2006). Li *et al*. introduced a new method to relate dose with the risk taking into account the patient size and not only age (Li, Samei *et al.*, 2011) and they also expanded their research to forty-two different patient models (Tian, Li *et al.*, 2014) utilising an updated version of the MC toolkit PENELOPE. Several studies have also been performed to evaluate the already used CT protocols on pregnant women and their fetus in terms of dosimetry (Gu, Bednarz *et al.*, 2009, Kobayashi, Haba *et al.*, 2020).

Schlattl *et al*. estimated the impact of tube current modulation on the dose for the case of paediatric patients using the EGS, MC toolkit (Schlattl, Zankl *et al.*, 2012). Another study was performed for dose calculations on 40 paediatric patients using Geant4, MC toolkit (Kost, Fraser *et al.*, 2015, Xie and Zaidi, 2019). Stepusin *et al.* concluded that when computational hybrid phantoms are used to match a patient's anatomy, they are superior, in terms of dosimetric calculations' accuracy, to reference phantoms (Stepusin, Long *et al.*, 2017).

MC studies have also been conducted to assess dosimetry for fluoroscopic guide cardiac procedures on paediatric patients. High-detailed, patient-specific and hybrid phantoms were used (Marshall, Borrego *et al.*, 2018).

The importance of dosimetry in radiology could be summarised in the next few lines. It is important to justify the requirement of each radiological practice, and examine the possibility of using alternative methods that don't involve radiation exposure to the patient (IAEA, 2014, EU, 2014). But when it is inevitable to use radiological imaging techniques, detailed protocols must be used, to produce adequate image quality with the minimum dose, while utilizing protective shielding to the extend possible. Adequate patient placement, correct collimation of the field size, and accurate definition of radiation exposure parameters should be emphasised for the optimisation of every radiology procedure. Establishment of more accurate calculation techniques for dosimetry could further optimise the radiology protocols.

Furthermore, it should be stated that recent technological evolutions have made low tube voltage scans and iterative reconstruction algorithms widely used approaches for low-dose paediatric procedures. The careful implementation of the correct methodology is critical for the optimisation of the procedure in terms of dose and image quality (Geyer, Schoepf *et al.*, 2015, Yu, Bruesewitz *et al.*, 2011). Studies showed that iterative reconstruction techniques could reduce the dose by more than 57 % and even up to 80 % (Katsura, Matsuda *et al.*, 2012, Miéville, Berteloot *et al.*, 2013, Neroladaki, Botsikas *et al.*, 2013, Yoon, Kim *et al.*, 2015).

3. Nuclear Medicine procedures

Nuclear Medicine (NM) uses radiopharmaceuticals to image the functionality of tissues and organs with the aim to early diagnose diseases and improve patient's response to therapeutic procedures (Treves, Baker *et al.*, 2011). NM is considered a low dose procedure compared to radiotherapy. However, several parameters need be standardised to optimise image quality and minimise radiation dose (Chawla, Federman *et al.*, 2010, Fahey, Treves *et al.*, 2011). It should be stated that there are limited data, with large

uncertainties, on the long-term effects of radiation exposure and on the risk estimation of radiation procedures of less than 100 mSv (AAPM, 2017, HPS, UNSCEAR, 2012).

Each radiopharmaceutical provides its own biodistribution. Radiopharmaceuticals follow a specific pathway by the time they are injected, the time they accumulate to the target organs, and the time that these radiopharmaceuticals are discarded from the body or their radiation is reduced to almost negligible quantities. To describe this procedure, the time-activity kinetic function of a radiopharmaceutical is used in simulations or mathematical dosimetry calculations.

Several methods have been proposed for radiation dose decrease in NM procedures. They can be summarised to the following: i. proper application of the procedure; ii. improvement of the dose guidelines; iii. adjustment of the imaging settings; iv. upgraded image processing algorithms and v. the evolution of precocious imaging systems (Treves, Falone *et al.*, 2014).

Each procedure protocol includes specific guidelines to ensure the optimal performance of the examination. Physicians are responsible to choose the correct tactic and implement the corresponding guidelines. Inappropriate choices can lead to increasing absorbed doses and decreasing the comfort of the patient.

Several studies, performed to investigate doses administered to paediatric patients by NM procedures, led to concerns that initiated the establishment of paediatric data, according to the ALARA concept (As Low As Reasonably Achievable) (Gelfand, Parisi *et al.*, 2011, Treves, Davis *et al.*, 2008). Consequently, since 2010, guidelines are being published alongside with toolkits, accredited by several organisations such as the SNMMI, and EANM (Gordon, Piepsz *et al.*, 2011, Treves and Lassmann, 2014). The various available guidelines today estimate administered activities to the patient on scalings related to the body weight of the patient. These scalings differ and don't necessarily lead to the same values of administered activities. There were also studies which reported that only few clinicians follow the guidelines (Fahey, Bom *et al.*, 2015, Fahey, Ziniel *et al.*, 2016, Grant, Gelfand *et al.*, 2015).

As already stated, by precisely adjusting the parameters of imaging protocols the administered dose can be minimised. The choice of the optimal detector, or the most efficient type of procedure as well as the correct framing, reduce drastically the radiation dose (Taylor, Folks *et al.*, 2017). Developments on the image processing techniques have resulted to the reduction of radiation dose, as well as of the total time of the procedure (Gelfand, 2010, Mawlawi, Yahil *et al.*, 2007). Furthermore, iterative image reconstruction produces high-quality images in lower radiation exposure times (Hricak, Brenner *et al.*, 2011, Small, Chow *et al.*, 2012).

The aforementioned approaches towards limiting radiation dose to paediatric patients are enhanced by the use of advanced imaging systems, which employ more efficient detectors and updated algorithms for filtration and image reconstruction as well as improved positioning of the patient (Van Audenhaege *et al.*, 2015, Zaidi, 2006).

3.1. MIRD – Dosimetry Formalism

The Medical Internal Radiation Dose (MIRD) Committee of the American Society for Nuclear Medicine (SNM) has proposed a specific methodology to estimate the absorbed dose for each procedure (Bolch, Eckerman Keith *et al.*, 2009, Hindorf, Linden *et al.*,

2003, ICRU, 2011). The MIRD protocol suggests that several variables must be considered for dosimetry purposes (depending on whether we want 'voxel' or tissue/organ dosimetry), such as: the administered radiopharmaceutical activity, the proportion of radionuclide decay (physical half-life), the ratio of energy/type per decay (spectrum data), the ratio of administered activity located in each source organ (time activity function and uptake), the duration of time the source organ is emitting, the amount of decays in the source organ (cumulative activity), the ratio of energy absorbed in the target organ from the source organ (absorbed fractions) and the organ's mass. According to MIRD Pamphlet No. 17 (Bolch, Bouchet *et al.*, 1999), the main methods for fast dose calculation purposes (except a direct MC simulation) are the Dose Point Kernel (DPK) and the Voxel S-Value (VSV) approach.

A DPK, either for electrons or for photons, is the radial distribution of the absorbed dose around an isotropic point (or voxel) source of radiation in a spherical homogeneous medium. The calculation of the absorbed dose at a target region, basically, is a superposition of the total contribution from all the surrounding point sources. One can speed up this process by using a Fast-Fourier-Transformation (FFT) or a Fast-Hartley Transformation (FHT) as shown in Equation 1 below.

$$D_{(x,y,z)} = (A \otimes DPK)_{(x,y,z)} = \left(\sum_{x'}\sum_{y'}\sum_{z'} A_{(x',y',z')}\right) DPK_{(x-x',y-y',z-z')} \quad Eq.\,(1)$$

where A is the 3D activity matrix (either SPECT or PET scans).

On the other hand, in the VSV approach the absorbed dose to a target region is calculated as the product of time-integrated activity $\tilde{A}$ and the S value as shown below in Equation 2.

$$\widetilde{D}_{(voxel_k)} = \sum_{h=0}^{N} \tilde{A}_{voxel_h} \times S_{(voxel_k \leftarrow voxel_h)} \quad Eq.\,(2)$$

where S value is the absorbed dose rate per unit activity and k and h are the target and source voxel respectively. According to MIRD schema, the calculation of any S value that corresponds to a specific voxel geometry is estimated with MC simulations according to Equation 3.

$$S_{(voxel_k \leftarrow voxel_h)} = \sum_i \Delta_i \times \frac{\Phi_{i(voxel_k \leftarrow voxel_h)}}{m_{voxel_k}} \quad Eq.\,(3)$$

where Δ_i is the particles' i mean energy emitted per decay, $\Phi_{i(\mathrm{voxel_k} \leftarrow \mathrm{voxel_h})}$ is the fraction of the energy deposited in voxel k per the energy emitted by the voxel h and $m_{\mathrm{voxel_k}}$ is the mass of the target voxel k. Lists of S values databases are reported in the literature with various variants e.g. various voxel geometries, target and source tissues, monoenergetic electrons or photons (Grimes and Celler, 2014, Kostou, Papadimitroulas *et al.*, 2016, Lanconelli, Pacilio *et al.*, 2012).

The main drawback of both approaches lies on their inability to consider different tissues within a region of the body (especially for bone and lung tissue). To address this issue, several studies have been conducted. A density correction method was proposed by Dieudonne *et al.* (Dieudonne, Hobbs *et al.*, 2013), while Mikell *et al.* (Mikell, Cheenu Kappadath *et al.*, 2016) and Sanchez-Garcia M *et al.* (Sanchez-Garcia, Gardin *et al.*,

2015) proposed the implementation of a grid Boltzmann solver and a collapse cone superposition method respectively. Finally, as children are considered more radiosensitive than adults due to the different level of replicating cells (Robbins, 2008) several methods have been proposed for paediatric dosimetry. Such methods apply variations of the SVS approach to cope with the heterogeneities and anatomical variations by developing patient-specific computational phantoms (Xie, Bolch *et al.*, 2013) (Papadimitroulas, Erwin *et al.*, 2018)).

4. Radiation Therapy procedures

Most of the paediatric malignancies are usually approached with a multimodal therapeutic strategy. Cytotoxic chemotherapy, radical surgery as well as radiation therapy are all therapeutic approaches often used in children, that can, however, be accompanied by a high risk of local failure as well as significant adverse reactions.

As far as radiotherapy is concerned, recent advances include the development of modalities, such as the External Beam Radiation Therapy (EBRT) or intensity modulated radiation therapy (IMRT), that have been shown to improve local control on paediatric patients suffering from various malignancies without affecting significantly the surrounding critical tissues (Bhatnagar and Deutsch, 2006, Marcus, Grier *et al.*, 1997). Examples of these therapeutic strategies are documented in the study of Huang *et al.* that demonstrated lower rates of hearing impairment in children with medulloblastoma who received a combination of cisplatin and IMRT versus children that received a combination of cisplatin and 3-D conformal radiation (Huang, Teh *et al.*, 2002). Further reports demonstrated similar promising results, such as the study by Penagaricano *et al.*, that showed a homogeneity of dose distribution in miscellaneous paediatric tumours with minimal toxicity in the surrounding healthy tissues (Penagaricano, Papanikolaou *et al.*, 2004). However, limitations of this method include the irradiation of numerous fields with low doses, which could result in phenomena of late onset toxicity, such as secondary tumours in previously healthy tissues (Bhatnagar and Deutsch, 2006).

When it comes to brachytherapy, important advantages include significantly lower risks of late-onset toxicity, as this procedure is designed to address small tumour volumes with high radiation doses and a sharp dose fall-off with optimised sparing of the surrounding organs. This results in optimised local control with an acceptable safety profile, as seen in the study of Viani *et al.*, that assesses the use of high dose rate brachytherapy alone (HBRT) or in combination with external beam radiotherapy (EBRT) in paediatric soft tissue sarcomas (Viani, Novaes *et al.*, 2008). Similar results are presented in further studies where brachytherapy is successfully used in various paediatric tumours, such as bladder carcinoma or rhabdomyosarcoma, with encouraging results in terms of efficacy and safety (Maurer, Beltangady *et al.*, 1988, Rodeberg, Anderson *et al.*, 2011, Saltzman and Cost, 2018). However, a recent study by Romano *et al.*, demonstrated that there are significant dose-volume effect relationships for the occurrence of anorectal morbidity in paediatric patients undergoing brachytherapy treatment for various pelvic malignancies, thus indicating that even in such elaborated therapeutic strategies there is still room for optimisation (Romano, Simon *et al.*, 2021).

Unresectable paediatric malignancies, such as various types of liver tumours, novel approaches include the use of transarterial radioembolisation (TARE) utilising

radioisotopes, e.g. ^{90}Y (Aguado, Dunn *et al.*, 2020, Aguado, Ristagno *et al.*, 2019). Aguado *et al.* reported the case of children with chemorefractory hepatoblastoma and managed to show a decrease in tumour size followed by a surgical resection after a TARE-^{90}Y treatment (Aguado, Dunn *et al.*, 2020). Another retrospective study of the same group on 10 paediatric patients who underwent TARE-^{90}Y treatment for liver malignancy, documented that 3 out of the 10 patients that received a retreatment achieved the longest survival periods (range, 17–20 months), while one patient managed to be transplanted 6 weeks after the TARE-^{90}Y treatment (Aguado, Ristagno *et al.*, 2019).

Cancer of the brain and the central nervous system (CNS) is the second most common of all pediatric cancers. A recommended technique for radiation therapy in paediatric patients is proton beam therapy (PBT). PBT has been utilised for over 20 years to treat malignancies that have arisen in childhood. Some initial clinical results were published by MacDonald *et al.* (MacDonald, Safai *et al.*, 2008), who made a dosimetric comparison between intensity-modulated radiation therapy (IMRT), intensity-modulated proton therapy (IMPT) and 3D conformal proton beam. Their final conclusion was that PBT procedures showed excellent early outcomes for the treatment of patients with localised ependymoma. No significant late toxicity was reported in patients followed up for more than 5 years. Dose distributions for proton therapy compared favorably to IMRT plans. The IMPT could further reduce dose to critical structures.

In 2011, a study published by Beltran *et al.* (Beltran, Roca *et al.*, 2012) compared 5-field IMRT, 3-field double-scatter proton therapy (DSPT), and 4-field IMPT, all of which were modelled in Eclipse 8.1 treatment-planning system (Varian Medical Systems, Palo Alto, CA). They studied paediatric Craniopharyngioma and they concluded that there are dosimetric and conformity advantages to use protons over photons. Using PBT in general and IMPT in particular, can greatly reduce the dose to normal tissues, thereby potentially reducing side effects. They also raised a concern regarding the potential hazard of neutron dose from PBT. Other studies have shown that the neutron dose for IMPT is quite low (Schneider, Agosteo *et al.*, 2002) compared to the reduction of the risk for secondary malignancies by the integral dose (Miralbell, Lomax *et al.*, 2002).

One more study was presented by Boehling *et al.* (Boehling, Grosshans *et al.*, 2012) for the treatment of paediatric Craniopharyngioma, comparing 3D Conforman PBT, IMPT and IMRT. They concluded that PBT can reduce dose to healthy tissues at both low- and high-dose levels. They observed that the significant sparing of healthy tissues from low-dose radiation could be of special importance in the treatment of paediatric patients. They also raised a consideration on the side impact of secondary neutron dose.

Radiation therapy procedures of the brain and the CNS could lead to radiation induced cerebral necrosis (RICN). In a study published by Freund *et al.* (Freund, Zhang *et al.*, 2015), they investigated the predictive risk of RICN, when volumetric modulated arc therapy (VMAT) or PBT are utilised. Two PBTs were studied, the passively scattered proton therapy (PSPT) and IMPT. Their findings indicated that any PBT, when compared to VMAT, can reduce the predicted risk of RICN. The ratio of risk seemed sensitive to proton range uncertainty, but always better than VMAT.

A very focused study was presented by Takizawa et al. (Takizawa, Oshiro *et al.*, 2015), which described in detail the way that a large rhabdomyosarcoma of the body trunk of a 1-year-old girl was treated. Chemotherapy together with PBT were utilised, as the tumour was inoperable. IMRT plan was also investigated as alternative. In the IMRT plan,

the 60 % of the liver volume received radiation dose of more than 20 Gy, while on the PBT plan only the 34 % of the liver volume received more than 20 Gy, thus reducing side effects. Furthermore, PBT reduced the extent of low dose areas around the irradiated volume.

Mizumoto *et al.* (Mizumoto, Oshiro *et al.*, 2015) published a study on PBT for paediatric ependymoma. They compared PBT to conformal photon radiation therapy (CPRT), and they resulted in a more than 50 % dose reduction to the healthy tissue with the PBT approach. Using predictive models to measure the Intelligence Quotient (IQ) deterioration of the child, PBT results in less deterioration (median, 5.4 points), when compared to CPRT (median, 10.7 points).

Stoker *et al.* (Stoker, Vora *et al.*, 2018) compared IMPT to VMAT for whole brain radiation therapy. They demonstrated the capability of IMPT to maintain target coverage, while substantially improving dose homogeneity within the whole brain target, as well as reducing dose to critical structures including cochlea and lenses. They focused their study on reducing the dose to the hippocampi, due to the neurocognitive importance of it. Only, IMPT was able to achieve the low dose threshold of 7.3 Gy to no more than 40 % of the Hippocampi volume that results to statistically significant cognitive benefit.

In a more recent study, eleven paediatric patients with intracranial germ cell tumors (IGCT) were investigated by Correia *et al.* (Correia, Terribilini *et al.*, 2019), for the comparison of three methods for radiation therapy, namely pencil beam scanned protons (PBS-PT), IMRT and VMAT. They concluded that based on the ALARA concept, PBS-PT could be an improved alternative to photons for IGCT, as it seemed to reduce dose exposure to the surrounding healthy tissue, while kept good target coverage and better conformity.

A simulation study was made by Zhang *et al.* (Zhang, Knopf *et al.*, 2014), to investigate the effect of image guided tumour tracking with PBS-PT. Their results showed that due to the presence of organ deformation, online pencil beam adaption is only able to compensate dose variations at each Bragg peak position, and as such, residual motion effects induced by the motions in the entrance path of the pencil beam cannot be further mitigated. More research is needed towards this path.

To summarise, radiation therapy in paediatric oncology is a complex procedure and requires different approaches and treatment plans based on the characteristics of the individual patient. The challenge is always to minimise the dose absorbed by healty tissues, while malignancies absorb sufficient amount of dose for their disintegration. There are advanced techniques such as IMRT and VMAT that have been commonly used. Considering the advances in technology, PBT, including Pencil Beam Scanning, seems to be an upgraded radiation therapy procedure based on the special characteristics of protons (Bragg peak). PBT aims to minimise the dose to the healthy tissues. There are several obstacles that need be overcome such as the accessibility to treatment centers that have protons generators. The investigation of the biological effect of the scatter radiation produced by protons (e.g. neutrons) seems be an important topic to by studied, as already stated in the cited literature.

5. Advanced computational techniques

5.1. Computational Phantoms

To be able to model clinical practices, various computational phantoms have been developed over the last few years. The first generation of phantoms were simple geometrical stylised anthropomorphic ones proposed by the MIRD community. Those phantoms used simple geometrical volumes representing the anatomy of organs. Based on those models, as well as on clinical segmentations, new models were introduced, which were named voxelized phantoms. The newest models are called hybrid and they combine the detailed description of human anatomy produced by segmentation procedures, as well as the dynamic behaviour of stylised phantoms.

More analytically, the ICRP Committee II developed constraints for the maximum permissible activities using radionuclides that could be delivered to a person (ICRP, 1959). The human body was simulated as a set of spheres of different size, whose size and composition were modelled according to the anatomical features of the "standard man". Fisher and Snyder developed the first phantom of the current generation (Snyder, Ford *et al.*, 1969). This phantom used plenty of geometric structures to generate a more anatomically precise representation of the human body. MC techniques used this stylised phantom to simulate the interaction of radiation with these structures. This phantom's atomic composition and density was in accordance with the guidelines provided by the Reference Man contained in the ICRP report (ICRP, 1975). As previously reported, the MIRD method (Loevinger, Budinger *et al.*, 1988) employs S-values together with agent-specific biokinetic data and has been extensively used for internal dosimetry to assess organ doses for a variety of radionuclides. Nevertheless, dose assessment is only valid for persons who have similar characteristics as the Reference Man. There are significant dose variations in reality due to the difference in human organ geometries and tissue heterogeneities compared to the corresponding stylised structures. This has been the cutting-edge technology for two decades and is still used in internal dose estimation. Cristy and Eckerman (Cristy and Eckerman, 1987) produced more modern computational phantoms that made the calculation of doses for different persons, in terms of size and age, possible. Six phantoms were designed, which were supposed to describe female and male children and adults. The S-value libraries were provided by the MIRDOSE computer software (Stabin, 1996). Six more computational phantoms of children were created by Lee *et al.* (Lee, Williams *et al.*, 2005). They are tomographic computational models and offer clear advantages over stylised models such as the MIRD. University of Florida (UF) hybrid reference phantoms (Geyer, O'Reilly *et al.*, 2014) allow manual modification to adapt anthropometry.

The entire background and evolution of anatomical computational models has been reviewed in the handbook of Anatomical Models for Radiation Dosimetry (Xu and Eckerman, 2009). Xu et al. (Xu, Chao *et al.*, 2000) proposed a newer method than MIRD, the VIP-Man, an image-based whole-body adult male model, which was constructed using colour photographs.

Another approach was followed by the ITIS foundation, which developed the "Virtual Family". These surface-based anatomical models included two paediatric models (Christ, Kainz *et al.*, 2010). Two years later, they expanded their library with the "Virtual Classroom", incorporating four more paediatric models according to healthy clinical Magnetic Resonance Imaging (MRI) data (Gosselin, 2014).

Johnson et al. demonstrated how hybrid phantoms can be modified to produce patient specific hybrid phantoms. They produced 25 adult male, and 15 paediatric female models, based on the UF hybrid adult male (UFHADM) and the UF hybrid 10-year-old female (UFH10F) (Johnson, Whalen *et al.*, 2009).

There is a widely used family of realistic 4D anthropomorphic models (XCAT model(Norris, Zhang *et al.*, 2014)) that were produced by DUKE University with the use of non-uniform rational b-spline (NURBS) and subdivision (SD) surfaces at ages of reference namely newborn, 1, 5, 10, and 15 years.

The male and female anatomies of the adult phantom (XCAT adult) (Segars, Sturgeon *et al.*, 2010) were originally designed to imitate the structure of organs as seen on imaging data, but they were later changed to fit the real dimensions of human organs, for both male and female phantoms. They contain a variety of anatomical structures, being closer to reality. Later in 2013 (Segars, Bond *et al.*, 2013), 58 new 4D adult BMI (body-mass-indices) based phantoms were developed that extended the standard XCAT model by using real patient CT data. For the paediatric extension, new segmentations and manual corrections have been used to address the anatomical variations that exist in organs and bones. XCAT phantoms are high-detailed models that contain more than 3,000 organ structures. This kind of detail is important when imaging procedures need to be simulated. They also contain time dependent anatomical variations such as respiratory and cardiac motions. In 2015, Segars et al. (Segars, Norris *et al.*, 2015) extended those phantoms with a series of 64 paediatric phantoms that vary in terms of age, height and body mass percentiles.

In 2017, Xie *et al.* generated the biggest database available still today, incorporating 1,100 paediatric phantoms of both genders according to the Virtual Population (Xie, Kuster *et al.*, 2017). The database includes newborn, 1, 2, 5, 10 and 15-year-old children, which were later remodeled to create phantoms with 10th, 25th, 50th, 75th and 90th percentiles of body parameters, namely body mass, length, standing height and height/stature ratio (SSR). The organ masses of heart, kidney, liver and lung follow the same trend as the ICRP reference phantoms (ICRP, 2009), when compared in terms of age.

In 2020, ICRP published the report 145 (Kim, Yeom *et al.*, 2020), which contains the updated reference phantoms called mesh-type reference computational phantoms (MRCPs), which are hybrid dynamic phantoms and can be used to produce non-reference phantoms of various sizes to estimate organ doses in personalised detailed way (Yeom, Choi *et al.*, 2019).

5.2. Monte Carlo simulations

In Medical Physics, MC simulations are used to calculate various dosimetry parameters, as they offer the ability to use mathematical calculations in combination with random generators. MC simulations are considered the gold standard for internal radiation dosimetry. Because of the large number of calculations, MC simulations tend to be time-consuming in computational resources. Nevertheless, due to technological advances they have been adapted to run on computing clusters/grids of Central Processing Units (CPUs), Hyper Performance Computers (HPCs), as well as on Graphics Processing Units (GPUs) for acceleration purposes.

Various MC codes have been made available for such purposes, such as EGS (Nelson, Hirayama*et al.*, 1985), ITS (Halbleib and Kensek, 1992), MCNP (Brown, 2003), ETRAN (Seltzer, 1991), PENELOPE (Sempau, Acosta *et al.*, 1997, Sempau, Fernandez-Vare *et al.*, 2003) and Geant4 (Agostinelli and Allison, 2003). Based on these codes, several toolkits have been developed to make MC simulations more easily accessible, such as GATE (Jan and Benoit, 2011, Jan, Santin *et al.*, 2004), GGEMS (Bert, Benoit *et al.*, 2016), GAMOS (Arce and Rato, 2008), TOPAS (Perl, Shin *et al.*, 2012), GATE-RTion (Grevillot, Boersma *et al.*, 2020) and PTSIM (Akagi and Aso, 2011).

GATE (Sarrut, Bardies *et al.*, 2014) is a state-of-the-art open-source toolkit developed by the international OpenGATE collaboration (OpenGATE collaboration) and can be used for medical radiation therapy and imaging applications (RT, CT, SPECT, PET, Dosimetry).

Monte Carlo methods have been proved to be the most accurate and modern procedures for internal dosimetry calculations (Furhang, Chui *et al.*, 1997, Grimes and Celler, 2014, Marcatili, Villoing *et al.*, 2015). These methods are now extensively getting into the clinical routine due to the creation of easy-to-use and practical programs, like RADAR, Celldose, Minerva, 3D-RD, DOSIMG, DPM and OEDIPE (Champion, Zanott-Fregonara *et al.*, 2008, Chiavassa, Bardiès *et al.*, 2005, Descalle, Hartmann *et al.*, 2003, DoseInfo, Liu, Ljungberg *et al.*, 2001, Prideaux, Song *et al.*, 2007, Wilderman and Dewaraja, 2007). In the research field, different groups have developed various software applications for NM dosimetry, such as the MCNP (Botta, Mairani *et al.*, 2013, Bolch *et al.*, 2013, Wayson, Lee *et al.*, 2012, Yoriyaz, Stabin *et al.*, 2001), FLUKA (Botta, Mairani *et al.*, 2013), and Geant4 (Kost, Dewaraja *et al.*, 2015, Marcatili, Pettinato *et al.*, 2013). Furthermore, the GATE MC toolkit (Sarrut, Bardiès *et al.*, 2014) has been extensively used for internal dosimetry (Belley, Wan *et al.*, 2014, Ferrer, Chouin *et al.*, 2007, Momennezhad, Nasseri *et al.*, 2016, Papadimitroulas, 2017, Papadimitroulas, Erwin *et al.*, 2018, Parach, Rajabi *et al.*, 2011, Saeedzadeh, Sarkar *et al.*, 2012, Visvikis, Bardies *et al.*, 2006).

Concerning the radiotherapy field, a comparison of MC methods with a clinical Treatment Planning System for Proton therapy dose distribution to children has been published in the literature (Jia, Beltran *et al.*, 2012). Additionally, in terms of radiotherapy research, Chatzipapas *et al*. modelled and validated several commercial brachytherapy seeds, which could be directly applied in MC simulations for radiation therapy on paediatric applications (Chatzipapas, Papadimitroulas *et al.*, 2016).

Realistic MC simulations are probably the most accurate tools for executing dosimetric calculations, but they have not yet been integrated into the clinical routine, mainly because they usually have a high computational time, as well as the time for the model development is extensive. This time is consumed both in the modelling procedure as well as in the simulation *per se*. To overcome computational limitations, several approaches have been proposed such as the use of Grids and clusters which can result in statistics close to the clinical protocols, in a reasonable time. Additional solutions are the GPU implementations and the use of speed-up methods like Variance Reduction Techniques (VRTs), cuts in physics modelling or accelerated tracking algorithms for the particle transportation, although their application and effect on results accuracy should be further evaluated for each application (Sarrut, Bardies *et al.*, 2014).

Another limitation in MC simulations, is the simulation of ground truth data that are not available due to several reasons. Some of them are the source shielding, the interseed

attenuation, tissue heterogeneity, bio-kinetics or activity biodistributions and exact patients' anatomy. Furthermore, preprocessing of the clinical data is needed, prior to their incorporation in the MC simulators. This procedure introduces inaccuracies, as well as effects deriving from the imaging scanners (such as the Partial Volume effect in PET/SPECT images) that must be considered to properly adapt the modelling (Papadimitroulas, 2017, Papadimitroulas, Loudos *et al.*, 2013).

5.3. Use state-of-the-art Artificial Intelligence (AI) algorithms

Our science follows a path that tends to develop intelligent machines able to offer solutions based on extensive calculations. To this direction, an important addition is the explosive evolution of GPUs, that accelerate such calculations. In addition, the limited availability and significant cost of GPUs has been met via the development of special platforms offering access to cloud computing capabilities to everyone (Google). Equally important for the optimal function of AI algorithms is the access to large databases (GRNET), which has been facilitated via the evolution of Big Data.

AI refers to a special form of computational knowledge, that enables machines to recognise pre-determined patterns in large data pools and use them to perform specific assignments, with a high probability of success (Daldrup-Link, 2019). In particular, the identification of the aforementioned data patterns is conducted with the use of Machine Learning (ML) and Deep Learning (DL) algorithms (Gatos, Tsantis *et al.*, 2017, Gatos, Tsantis *et al.*, 2016, Gatos, Tsantis *et al.*, 2017, Gatos, Tsantis *et al.*, 2019, Gatos, Tsantis *et al.*, 2015, Kagadis, Drazinos *et al.*, 2020, Mandelias, Tsantis *et al.*, 2013, Tsantis, Spiliopoulos *et al.*, 2014). These algorithms, which basically constitute a subset of AI, can process large input data volumes and develop models so as to reach accurate predictions or accomplish complex tasks rapidly (Daldrup-Link, 2019, Li, Samei *et al.*, 2011). The integration of AI and information technology in medicine is an immensely growing field, since it offers various advances in terms of optimisation of multiple health-care-related parameters (Daldrup-Link, 2019, Li, Samei *et al.*, 2011). Examples of these parameters include technology-assisted diagnosis, image processing, machine-guided improvement of therapeutic strategies, as well as the development of universal electronic medical records or even machine-assisted drug development (Daldrup-Link, 2019).

The valuable assistance of AI for medical purposes is particularly seen in the field of oncology, especially when it comes to paediatric patients (Daldrup-Link, 2019, Li, Samei *et al.*, 2011)]. As far as the parameter of image processing is concerned, multiple studies have been conducted to either improve image quality, by reducing the unwanted noise and optimise the point scatter function (Kang, Min *et al.*, 2017, Wang, Fang *et al.*, 2019), or to reduce radiation exposure, when performing diagnostic scans. Shen *et al.* (Shen, Zhao *et al.*, 2019) used 2D projection radiographs to create 3D tomographic X-ray images by training a deep-learning model. They applied their model to three patients and showed that this algorithm could be used to help clinicians in image-guided interventional procedures.

Tumour staging is another area where DL-algorithms have shown potential, through the successful detection of non-tumorous pathologies as well as their differentiation from actual malignancies, both in adults as well as in children (Daldrup-Link, 2019). Examples of such advances include the study by Helm *et al.* (Helm, Silva *et al.*, 2009), where the presented algorithm managed to detect and characterise suspicious nodules on paediatric CT-chest scans (Helm, Silva *et al.*, 2009). Further studies, performed mostly on adult

patients, with a potential of future application also in the paediatric population, include the use of Convolution Neural Networks (CNN) to detect and classify malignant processes in various organs, such as breast (Becker, Mueller *et al.*, 2018), brain (Soltaninejad, Yang *et al.*, 2017), liver (Linguraru, Richbourg *et al.*, 2012), bone tissue (Perk, Bradshaw *et al.*, 2018), *etc.*

In terms of predictive dosimetry in Nuclear Medicine, DL algorithms rely on input training data in the form of PET and CT scans to accurately predict the total radioactivity distribution during radiation treatments, as seen in the study by Lee *et al.* (Lee, Hwang *et al.*, 2019) in which a deep CNN was used to predict the absorbed dose in the voxel level. Patches of PET and CT data were used to train the CNN, which was then able to predict the dose rate maps. Their results were compared to the ground truth of MC simulations. Other studies assess the use of attention-gated generative adversarial networks (GANs) which rely on information concerning patient anatomy and basic imaging to develop dose prediction models, also in comparison to other algorithms, as presented in the study by Kearney *et al.* (Kearney, Chan *et al.*, 2020).

The limitations of the integration of AI modalities in the field of paediatric oncology are based mostly on the lack of large-scale imaging and clinical data that could serve as input data sets for ML and DL algorithms, due to the low incidence of most malignancies in the paediatric population (Daldrup-Link, 2019, Li, Samei *et al.*, 2011). To overcome this potential obstacle, however, transfer-learning approaches using initially adult-oriented data sets have been developed (Daldrup-Link, 2019, Li, Samei *et al.*, 2011), such as in the study of Chang *et al.* (Chang, Lafata *et al.*, 2020), where a dual-discriminator conditional-GAN could assess anatomical variations and tissue heterogeneities based on multi-contrast computational phantoms (Chang, Lafata *et al.*, 2020). Furthermore, the application of DL-algorithms could actually be used to upgrade the aforementioned deficient databases, as seen with the example of GAN (Goodfellow, Pouget-Abadie *et al.*, 2014) and cross-modal image processing, which results in the generation of pseudo-images with high resemblance to the original.

Taking into consideration all the above facts, it can be said that AI-based technology is a useful tool that can assist the clinicians into optimising dosimetry studies in their everyday clinical practice, not only in terms of diagnosis, but also in terms of personalised treatment planning and prediction of therapeutic outcomes. More AI medical models are likely to develop rapidly and emerge in the next few years for the diagnosis and management of different paediatric diseases. The latest promising advances of this field indicate that clinicians –even of expert level– manage to obtain better results with the help of AI-based technologies (Brown, Browning *et al.*, 2019, Hosny, Parmar *et al.*, 2018).

6. Conclusion / Future prospects

Available literature on paediatric dosimetry evaluation and optimisation with the aid of computer science and Artificial Intelligence is fastly evolving. Technology needs to be adapted, to develop more extensive phantom databases that provide clinicians and researchers a variety of computational phantoms for personalised studies. MC simulations need to be faster, so it becomes possible to produce results in real clinical time, while keeping uncertainties to the minimum possible value. To this aim, it will eventually become possible to foretell the outcome of a radiation therapy procedure,

using data produced on diagnostic acquisitions. This way, procedures could be optimised, to minimise the radiation burden to healthy tissues, while preserving diagnostic quality or therapeutic result using the personalised characteristics of each patient.

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Summary

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on behalf of the

Working Party "Research Implications on Health and Safety Standards" (WP RIHSS) of the Group of Experts referred to in Article 31 of the Euratom Treaty[6]

1. Introduction

This chapter provides the rationale of EU Scientific Seminars, summarises the individual presentations, and the roundtable discussion on policy implications and research needs of this year's Scientific Seminar on *"Radiosensitivity" of children – Health issues after radiation exposure at young age*. It takes into account the discussions that took place during the seminar, although it is not intended to report in an exhaustive manner all the opinions that were expressed. These proceedings have been submitted for comments to the lecturers and round-table participants, as far as their contributions were concerned.

2. The Article 31 Group of Experts and the rationale of the scientific seminars

The Article 31 Group of Experts is a group of independent scientific experts referred to in Article 31 of the Euratom Treaty, which assists the European Commission in the preparation of the Euratom Basic Safety Standards for the protection of the health of workers and members of the public against the dangers arising from ionising radiation. This Group of Experts has to give priority to protection of health, to safety and to development of the best available operational radiation protection. To this end, the Group of Experts is committed to proactively scanning new or emerging issues in science and technology, and ongoing developments in the area of radiation protection and informing the European Commission on potential policy implications.

In this context, a Scientific Seminar is devoted every year to emerging issues in Radiation Protection – generally addressing new research findings with potential policy and/or regulatory implications. Following suggestions from the Working Party Research Implications on Health and Safety Standards (WP RIHSS), the Article 31 Group of Experts

[6] The Scientific Seminar was chaired by P. Smeesters. L. Lebaron-Jacobs was acting as rapporteur. In addition, the following members of the Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts contributed to the preparation of this overview P. Olko, F. Bochicchio, I. Prilic, A. Dumitrescu. They were assisted by F. Tzika and S. Mundigl from the European Commission.

selects the topic of the seminar. After selection of the topic and approval of the programme by the Article 31 Group of Experts, the WP RIHSS deals with the preparation and the follow up of the seminar. Leading scientists are invited to present the status of scientific knowledge in the selected topic. Additional experts, identified by members of the Article 31 Group of Experts from their own country, take part in the seminars and act as peer reviewers. The Commission usually convenes these seminars in conjunction with a meeting of the Article 31 Group of Experts to allow the Group to discuss potential implications of the presented scientific results. Due to the developments with the covid19 pandemic and resulting restrictions as regards physical meetings, this year's Scientific Seminar took place online. This allowed inviting also experts representing several professional associations with interest in the topic of the seminar. Based on the outcome of the Scientific Seminar, the Article 31 Group of Experts may recommend research, regulatory or legislative initiatives. The Experts' conclusions are valuable input to the setting up of the European Commission's radiation protection programme, and to the process of reviewing and potentially revising European radiation protection legislation.

3. Key highlights of the presentations at the Scientific Seminar on "Radiosensitivity" of children – Health issues after radiation exposure at young age

Patrick Smeesters – Objectives of the seminar and introduction to the topic

The Scientific Seminars May 2017, on *emerging issues with regard to organ doses*, and November 2017, on e*pigenetic effects – potential impact on radiation protection,* concluded that there is a need to pay renewed attention to "radiosensitivity" of children. They also highlighted some challenging issues among which the radiation-induced effects observed at low (less than 100 mSv) and intermediate (100-500 mSv) doses to organs suchs as the brain (particularly in children and after in utero irradiation) and the cardiovascular system. During the Scientific Seminar 2019 on *developments in nuclear medicine – new radioisotopes in use and associated challenges*, the experts identified among the concluded research challenges the long-term risks from low-dose internal exposure of children undergoing nuclear medicine procedures. New driving mechanisms are currently under study, such as epigenetic ones, which do not imply mutations of nuclear DNA as initial events, but rather present a cumulative character and lead to effects of combined exposures. An additional issue is that early life stresses, and irradiation in particular, during the early prenatal period may perturb the developmental epigenetic programming, which in turn is crucial for normal brain maturation. Non-cancer effects at low and moderate cumulative doses (neurocognitive, circulatory ...), epigenetic effects (to embryo, foetus ...) and individual radiosensitivity are qualified as potential "game-changers" in the Joint Roadmap for radiation protection research, established under the H2020 CONCERT European Joint Programme, with the age at exposure (children) holding a special role throughout these issues. New evidence regarding radiation-induced effects needs to be evaluated in terms of potential impact for the system of radiation protection.

This year's Scientific Seminar on *"Radiosensitivity" of children – Health issues after radiation exposure at young age* aimed to review and discuss new data in the relevant fields of research, which may have potential impact on management of exposure of "children" (incl. infants, embryos and foetuses) in various situations. In line with the

standing objective of all Scientific Seminars, it also aimed to identify potential research needs and priorities in the field of "radiosensitivity" of children and discuss potential policy implications.

Andrzej Wojcik - Individual Response to Ionising Radiation – Radiosensitivity of Children

This review points out the modulating effect of age-at-exposure on deterministic and stochastic effects of radiation. For many years, children have been considered as more radiosensitive than adults are. However, this assumption is only partly true and strongly depends not only on the analysed effects but also on the exact age and organ at risk. Regarding early deterministic effects, children are more radiosensitive than people of advanced age but less sensitive than middle-aged adults. For late deterministic effects children are more sensitive than adults, but not for all organs and tissues. In terms of stochastic effects, children are more radiosensitive than adults. Nevertheless, the analysis is not so simple because in general, children are overall more radiosensitive considering all cancer types but they are equally or even more radioresistant than adults regarding some cancer types. There are protecting or sensitising factors responsible for differences in radiosensitivity between children and adults and increasing uncertainties, such as the level of organisational and maturational processes or life expectancy, or treatment specificities of paediatric cancer due to the frequently aggressive nature of childhood malignancies. Mechanisms are not fully explained and there are possible ways of investigation: mutations, elimination of damaged cells, co-exposures. Some studies show that long-term survivors of paediatric cancer are more likely to have diminished health status and to die prematurely (second cancer, myocardial infarction…) than are adults who never had childhood cancer. For example, the PENTEC (Pediatric Normal Tissue Effects in the Clinic) study was carried out in 2019 to explore and define normal tissue tolerance in developing children as a function of radiation dose/volume, type and scheduling of chemotherapy and surgery to ameliorate or prevent normal tissue damage in paediatric cancer patients. This study showed the need to understand normal tissue tolerances to radiation and systemic therapy across the age spectrum, and raised major issues such as the lack of recorded doses to normal tissues for patients treated many years ago, relatively small sample size reports of paediatric late effects and non-uniform evaluation methods and scales of toxicity. It is estimated that 75-100 % of children undergoing radiotherapy will develop some measurable late effects, with the age at treatment having a strong modifying effect on the risk of developing neurocognitive effects and muscle and bone growth disturbances. The corresponding risk for adults is below 50 %, irrespective of age at exposure. There is thus an urgent need to determine dose constraints for organs of paediatric cancer patients that will help in reducing the incidence and severity of late effects. To this end, data that PENTEC collaboration may publish are of particular interest.

Some aspects of exposure have to be considered too: after whole body exposure radiosensitivity regarding acute effects, i.e. acute radiation syndrome with potential lethal consequences, during childhood is higher than during adulthood, but lower than in the elderly. However, results in regards of acute and delayed effects after medical radiation exposure of children are difficult to interpret, owing to small patient cohorts, the long time to onset of late pathologies and the absence of standardized protocols. What about the doses to normal tissues? For the late effects assessed today, there are not enough good data on conditions of exposure, because they result from radiotherapies where the focus was on cure and not on modalities of treatment. Nevertheless, even if

significant uncertainties in terms of dosimetry and quantification of effects exist, it is considered that younger children have a higher risk for late effects than older children do.

Considering stochastic effects, particularly high relative risk of radiation-induced malignancies has been highlighted during the developmental period characterised by rapid tissue development. However, distinct age-at-exposure effect should be considered as risk modifier for site-specific cancers. The UNSCEAR report on the effects of ionising radiation on children (2013) concludes that for only about 25 % of tumour types, children are significantly more radiosensitive than adults, and for other cancer sites, age at exposure is either not a risk modifying factor or there is an inversed relationship between age and risk. Thus, the Committee recommends avoiding generalisations and focusing on the specifics of the exposure, age at exposure, absorbed dose to certain tissues, attained age at the time of assessment, and the particular effects of interest.

Richard Wakeford - Cancer risks after radiation exposure of children – overview of epidemiological studies

The cancer risk per unit radiation dose is modified by factors such as sex, age-at-exposure and time-since-exposure. Age-at-exposure is an important factor influencing the lifetime excess risk of radiation-related cancer incidence. The higher life expectancy of children produces a higher lifetime risk because an increased risk persists over an extended period for most types of cancer. However, some studies show that after exposure there is an intrinsically higher proportional increase in risk per unit dose (ERR/Gy) over a particular period in children when compared with adults for a number of types of cancer. The UNSCEAR report on the effects of ionising radiation on children (2013) shows a clear increased risk for exposure in childhood (versus adulthood) for about 25 % of cancers (leukaemia and thyroid, breast, skin and brain cancers). About 15 % of cancers (e.g., bladder) appear to have about the same level of risk, while others (about 10 %, e.g., lung) have a lower risk. However, for about 20 % of cancers (e.g., oesophagus) the evidence is too weak to draw conclusions, and for about 30 % the evidence for a risk at any age at exposure is equivocal.

For Japanese atomic bomb survivors dying of leukaemia, there were four deaths in all children who attained the age range of 5-9 years (age at exposure 0-4 years); all the deaths occurred in children who were exposed at doses higher than 1 Gy to their red bone marrow. Six deaths from leukaemia occurred in all children in the attained age range of 10-14 years (age at exposure 5-9 years), and these deaths were in children exposed at a dose range of 0-3.4 Gy. Thus, risk modelling has weaknesses, as illustrated by the LSS (Hiroshima and Nagasaki survivors), showing that leukaemia mortality data for childhood exposure are limited.

Some large nationwide studies of childhood leukaemia incidence in relation to natural background gamma radiation doses have been conducted, with mixed results. A British study found an association between childhood leukaemia incidence and gamma radiation dose at the level predicted by standard models, but a French study did not. Thus, further research is required, including on estimates of RBM doses, to be able to draw reliable conclusions.

After the Chernobyl accident, the eventual number of excess cases of thyroid cancer among those exposed at a young age will largely depend on the persistence and variation

with time since exposure of the excess risk. A dose-related excess of thyroid cancer is still present among the Japanese atomic bomb survivors 60 years after exposure, although some evidence exists for a decrease in excess relative risk.

Population exposure to radiation for medical reasons has increased significantly. So, medically exposed groups could offer a valuable complement to evidence derived from the Japanese atomic bomb survivors, but caution in interpretation of medical studies is required because exposure to ionising radiation for a known or suspected disease may bias the risk estimates, and accurate dose estimates are often lacking. In the British CT Scan Cohort Study, 176,500 patients were first examined with CT in Great Britain during 1985-2002 when <22 years of age. Cancers were diagnosed during 1985-2008 and identified through the UK national cancer registry. The follow-up was about 10 years on average. Leukaemia was selected because of its established relationship with radiation exposure and brain tumours because of the substantial proportion of head CT scans in childhood. The results of this study of CT scans were broadly in line with those of the LSS, but they have to be interpreted cautiously due to the consideration of myelodysplastic syndrome included with leukaemia in the study, and imply that the brain tumour excess relative risk may be higher than would be expected. Dealing with the reasons for CT scans being carried out is an important issue that is not easily addressed, conveniently accessible medical records giving this information not being readily available, and the outcome of a European-wide study of CT scans in childhood, EPI-CT, is awaited to see if it can shed light on this subject.

The results of studies of childhood leukaemia incidence rates after atmospheric nuclear weapons testing fallout have not shown an excess of leukaemia cases following the peak of fallout, suggesting that the risk from intakes of radionuclides has not been seriously underestimated, which was the issue under investigation.

Simonetta Pazzaglia - Neurocognitive effects after radiation exposure of children

Behind genetic factors, environmental agents including ionising radiation influence and determine the way of cognitive development and decline. The developing brain is exposed to ionizing radiation in a number of clinical situations related to medical diagnostics and therapy.

A study involved 20,000 Israeli children who were treated for tinea capitis by X-rays to eradicate the disease between 1950 and 1960. The mean brain dose received by these children was 130 rads. Almost 20 years later, radiation effects on the central nervous system were evaluated in about 11,000 of the irradiated children and in two non-irradiated, tinea-free comparison groups (ethnic, sex- and age-matched individuals from the general population, and siblings). The authors concluded that radiation to the immature brain might cause damage to the central nervous system.

After radiotherapy of CNS cancers, young age survivors have poor neurocognitive outcomes. They may develop motor, intellectual, visual, and psycho emotional dysfunctions, with moderate to severe disabilities. Younger age at diagnosis, higher cranial irradiation dose, larger brain volume irradiated, and longer time since treatment are risk factors for worse neurocognitive outcomes. Cranial radiation carries particular risk to memory function, especially to the process of forming new memories of events or facts that is subserved by the hippocampus in the medial temporal lobe. Neurocognitive

problems are also commonly experienced by survivors of acute lymphoblastic leukemia (ALL) treated with CNS prophylaxis.

Traditionally, radiation-induced brain-injury is classified into acute, early and late delayed based on time between radiotherapy and the onset of side effects. While acute and early delayed effects are generally transient, cognitive decline may become manifest many months to years after irradiation and get progressively worse. Although cognitive dysfunction significantly affects the quality of life in paediatric patients that underwent radiation therapy, determining and comparing the frequency of cognitive decline in the clinical setting remains challenging.

Several potential technical obstacles hamper studying human brain tissues. Consequently, moving from association studies towards mechanistic studies to elucidate pathogenesis of radiation-induced cognitive impairment require animal models that may shed light on the factors influencing brain radiation response. Brain radiation injury is multifactorial and complex, involving dynamic interactions between multiple cell types. Microglia activation may be detected even months after irradiation indicating the persistence of neuro-inflammatory process that can be cytotoxic to surrounding cells and can propagate tissue damage and cause secondary injury. Moreover, impairment of neurogenesis in the hippocampus following whole-brain irradiation is referred to as one of the most important mechanisms of radiation-induced cognitive dysfunction. Survivors of paediatric low-grade gliomas experience decline in memory and show higher vulnerability to radiation injury than adults. The influence of hippocampic avoidance in brain tumours of children should be further investigated. Fortunately, some studies show that stem cells replacement could offer a promising strategy for functionally restoring cognition in irradiated animals.

Although brain has been classically regarded as a radioresistant organ, and neurons as essentially inert to radiation, some studies show that radiation-induced adverse effects on cognition may also be promoted by alterations in mature neuronal networks. Irradiation induces a wide spectrum of cellular damage that elicits a global stress response. The complexity of neurocognitive effects after irradiation cannot be fully explained by alteration of a single cell type, and the pathogenesis of radiation-induced cognitive injury is likely dependent on dynamic connections between multiple cell types (i.e., neurons, microglia and astrocytes).

Until not long time ago, adverse radiation effects following radiotherapeutic doses have been investigated, but much attention should be focused on how exposure to low/moderate doses may affect normal brain development during early postnatal life due to different molecular mechanisms than those encountered at high doses. For example, the growing use of CT procedures on children raises concern over the long-term health risk.

Multidisciplinary approaches including collection of suitable biological samples, comprehensive cognitive function assessment, precise dosimetry to different brain structures and multi-omic approaches to elucidate genetic and epigenetic mechanisms of radiation-induced neurocognitive effects at low/moderate radiation doses should be implemented. Overall, more research in large epidemiological cohorts and animal models are needed to improve the understanding of radiation-induced cognitive effects. Results may then be translated into recommendations for improving radiation protection of patients undergoing diagnostic and therapeutic medical procedures.

George C. Kagadis - Dosimetry and dosimetric challenges in paediatric radiology and radiotherapy

Children are often exposed to ionising radiation for diagnostic examination purposes. It permits to establish earlier diagnosis of disease and treatment, to improve patient outcomes. Patient specific dosimetry is important in paediatric applications due to their significantly increased radiation sensitivity in comparison to adults. Paediatric patients have a higher risk to develop cancer compared to adults exposed to an equivalent radiation dose. Moreover, the longer life expectancy of children, and thus longer period for radiation-induced side effects, and the potential to pass on as future parents radiation-induced genetic effects should lead to reconsider diagnostic procedures and therapy schemes that should reflect individual characteristics of children. Maintaining high diagnostic image quality, delivering accurate therapeutic radiation dose sparing normal tissue, and minimizing doses are challenging.

CT technology that shortens scanning times and improves resolution has increased accuracy and usefulness. Modelling and validating the radiotherapy unit that is going to be used is needed and *ad hoc* Monte Carlo (MC) simulations have to be carried out for the individual patient before therapy to personalise and assess the exact absorbed dose per organ and patient. Computer-based phantoms offer the potential to represent a limitless amount of body types and anatomies. The most recent development of hybrid models that combine the realism of a voxelized phantom and the flexibility of a mathematical phantom in terms of shape/size/resolution, enable meeting the standards of clinical practice. Employing such patient specific models in MC simulations offers new potential in personalised dosimetry for paediatric patients for whom heterogeneities and anatomical variations need to be accounted for when optimising medical procedures.

Generic and dedicated codes for many applications exist. For example, Geant4 Application for Emission Tomography (GATE) is an open-source Monte Carlo toolkit validated and dedicated to SPECT, PET, CT, and RT simulations assessing dose distribution with a flexibility to model unlimited set of anatomies according to age, sex, size, a potential to estimate patient-specific organ and effective dose. This should help the clinician optimise procedures based on individual patient characteristics in real time, and before the procedure of exposure. A project named ERROR (European Union's Horizon 2020 research and innovation program), recently conducted by a consortium of five partners from Europe, applied such optimisation procedures. Furthermore, over the years algorithms have been developed to utilise patient anatomy and raw imaging information to predict radiation dose and consequently improve radiotherapy plan quality, to develop the 3D reconstruction image of a patient from 2D projections, and deep convolutional neural networks have been used to estimate dose rate maps. The rapid evolution of these codes can play a key role in the personalisation of the paediatric protocols of medical exposure. The latest advances in the AI-based information technology provide a useful tool to assist optimising dosimetry in clinical practise e.g. for diagnosis, personalised treatment planning and prediction of dose distributions in nuclear medicine. In the next few years, AI medical models are expected to emerge for the diagnosis and management of paediatric medical procedures.

4. Summary of the roundtable discussion: policy implications and research needs

Maria Del Rosario Perez (WHO), Roger Harrison, Per Eriksson, Patrick Smeesters (Moderator)

Maria del Rosario Perez - Cumulative radiation doses in medicine: risks for children

UNSCEAR 2013 Report on the effects of ionising radiation on children stated that they are more sensitive to environmental hazards and have a longer life span than adults to develop long-term health effects like cancer. Recurrent imaging procedures in children may result in significant cumulative doses and associated radiation risks. Consequently, a balanced approach is required to inform policies, considering benefits and harms between performing and not performing imaging exams. Medical profession's general underlying beliefs may lead to unnecessary recurrent imaging, so repositioning advocacy, education and training are needed for both professionals and the wider community. However, high cumulative doses from recurrent imaging are not necessarily the result of lack of compliance with the fundamental principles of justification and optimisation. Cumulative medical exposure should not be confounded with overuse of radiation. Recurrent imaging procedures may be indicated for particular clinical conditions: the process of justification applies to each procedure, in the context of the entire health care pathway, to ensure that they will cause more good than harm. In addition to assessing the incremental dose and associated risk for each individual procedure, an integrated approach may be warranted to consider cumulative dose and lifetime attributable risk (LAR) taking into account gender, age at exposure and attained age.

Some policy actions are needed to enhance protection of children. Regarding justification, overly optimistic expectations about recurrent imaging should be countered. Concerning optimisation, radiation dose management for every single exam should be ensured when recurrent imaging is indicated for diagnosis, image-guided interventions and follow-up. Safety culture should be instilled in prospectively identified care pathways that may need recurrent imaging in children.

Even if the radiation dose for an individual procedure may be relatively low, the public health issue concerns the increasingly large paediatric population exposed and the cumulative exposure increasing the risk of cancer in individual patients. In paediatric procedures, typical radiation doses may be used for comparative purposes. However, when referring to radiation risks associated with medical exposures, the organ dose (rather than the effective dose) is the appropriate quantity to consider.

In this context, the research agenda should consider long-term epidemiological studies on medical exposure in childhood, organ dose databases, dose distribution data, and interaction with other exposures or therapies. In addition, studies on biological mechanisms relevant for assessing low-dose radiation risks of exposure during childhood (e.g. DNA damage and repair, epigenetic effects, genomic instability, individual radiosensitivity, persistence of change, clinical relevance and actual health effects across lifetime, influence of the age, sex, dose and dose rate, radiation quality, acute versus fractionated or protracted exposure) should be continued.

Roger Harrison - Dosimetry challenges of radiation dose estimation – unwanted doses

For children exposed to ionising radiation for medical purposes, there is a need to develop robust and widely applicable techniques for organ dose estimation in diagnostic radiology and radiotherapy. The exposure conditions in therapy and diagnosis are markedly different. Diagnostic imaging is generally characterised by low effective doses (between 0.1 and 10 mSv), there are no detailed absorbed dose distributions for individual patients and surrogate dose quantities (e.g. kerma-area product, CTDI) and conversion factors are required. Organ dosimetry is usually based on phantom measurements and Monte Carlo simulations. On the other hand, radiotherapy is characterised by a wide range of doses between 10 mGy and tens of Gy, well-established target dosimetry, but less well developed methods for out-of-field dosimetry.

A study on craniospinal irradiation for medulloblastoma using passively scattered proton beams showed that, in general, the absorbed dose in the treatment volume could be calculated with confidence, but that techniques for dose calculation and measurement in the out-of-field volume were more problematical. The goal is first to determine the complete absorbed dose distribution throughout the body and then, using risk factors together with data such as age at exposure, attained age, gender and genetic profile, to estimate the corresponding distributions of second cancer incidence. As part of this process, the efficacy of Monte Carlo and analytical dose models should be verified experimentally.

Many combinations of imaging and treatment modalities are possible in radiotherapy (x-ray linear accelerators, proton and ion beam systems, brachytherapy, targeted molecular radiotherapy) and associated imaging (on-board imaging systems, CT, PET, SPECT). A Working Group (WG9) from the European Radiation Dosimetry Group (EURADOS) has highlighted future dosimetry research needs for proton and ion beam radiotherapy, high dose rate scanning beams and ultra-high dose rate FLASH therapy, spot-scanning arc therapy, and mixed field dosimetry (neutrons, protons, photons). WG9 together with EURADOS WG12 (Dosimetry in Medical Imaging), have also highlighted the need for developing methodologies for estimating the total dose to the patient from both radiotherapy and concomitant imaging. The establishment of links between nano- micro- and macro-dosimetry and radiobiology is also important. A more extensive evaluation of future radiation dosimetry research is given in the EURADOS Strategic Research Agenda (SRA).

As an example of out of field dosimetry work by WG9, organ doses have been assessed in clinical conditions in anthropomorphic paediatric phantoms which received a simulated treatment of a brain tumour with intensity modulated radiotherapy (IMRT) and 3D conformal radiotherapy (3D CRT). Comparison of measured doses and doses calculated by the treatment planning system (TPS) showed, amongst other findings, that the TPS underestimated out-of-field doses for both IMRT and 3D CRT.

WG12 have also highlighted the need to assess skin and organ doses in interventional radiology and cardiology and patient-specific dose estimates in CT imaging.

The ongoing European-funded project HARMONIC (Health effects of cArdiac fluoRoscopy and MOderN radIotherapy in paediatriCs) aims at exploring the long-term health effects

of radiation treatment in children, specifically cancer patients treated with modern radiotherapy techniques and cardiac patients treated with X-ray guided imaging procedures. The effects of childhood exposure to a wide range of doses of ionising radiation from these medical procedures are under investigation. HARMONIC is expected to provide much needed information on the effects of low to moderate doses of radiation on humans, help optimise treatment plans in young patients to reduce the risk of late toxicities and contribute to improving patient care and quality of life.

Per Eriksson - Combined effects of ionizing radiation and environmental/chemical factors as a function of age

Neonatal animal models are used to explore and predict developmental neurotoxic effects from ionising radiation, environmental and pharmaceutical agents. There is an ongoing research on the combined effects of ionising radiation and anaesthetic or analgesic or sedative agents, and on ionising radiation and anaesthetics and neuroprotective agents. Some studies carried out in adult mice showed that there was a disruption of the adult brain function with an increased susceptibility. Moreover, alteration in neurochemical composition (neuroprotein tau) and structural changes in hippocampal neurons could be observed. Other results show that ionising radiation can interact with anaesthetics to exacerbate developmental neurotoxicity and that these neurotoxic manifestations are persistent. An important point is that the developmental neurotoxic effects are seen at doses where neither gamma radiation nor the environmental/pharmaceutical agents cause any effects.

In conclusion, ionising radiation can interact with environmental toxicants (MeHg, nicotine, paraquat) and commonly used anaesthetic (ketamine) to shift the dose-response curve towards lower radiation doses. Moreover, ionising radiation alone or in combination with these chemicals can induce both acute and persistent effects on neuroproteins and structural changes in hippocampal neurons.

Conclusions[7]

Based on the presentations and the discussions during the Scientific Seminar, the experts of the Working Party RIHSS identified the following important issues:

- Epidemiology would contribute a lot with a long-term follow-up of cohorts exposed during childhood but also radiobiology with an easier access to biological samples from these cohorts to establish collection whose analysis could be complementary to epidemiology studies. What is missing are the funds to carry out research for a good assessment of children radiosensitivity.

- There are gaps in scientific knowledge on ionising radiation effects on children. For example, neuro-cognitive effects dealing with epigenetic effects after *in utero* exposure is challenging. Combined effects of ionising radiation and pollutants is a very important issue, but practically ignored in the radiation protection field.

- On the other hand, there are many studies on radiosensitivity of children, the results of which could be analysed with a view to provide clarifications for a less adult-driven conservative use of medical exposure on children and improve individual child patient care.

- A 75-100 % of children undergoing radiotherapy will develop some measurable late effects, with the age at treatment having a strong modifying effect on the risk of developing neurocognitive effects and muscle and bone growth disturbances. Thus, there is an urgent need to determine dose constraints for organs of paediatric cancer patients to assist in reducing the incidence and severity of late effects.

- Recognition of children's vulnerability to radiation effects should stimulate new investments in children's health research. To protect human health, and especially the health of infants and children, represents the paradigm for radiation protection.

- Some of the identified dosimetry challenges, especially in early-age radiotherapy and radiodiagnosis, include: individualised dosimetry in medicine (therapy and diagnosis), dosimetry of the primary and scattered radiation involving proton and ion beams, combined doses as an input to epidemiology studies, need for experimental verification of computational dosimetry, and need to enhance inter-institutional and international collaboration with a view to support research and innovation as well as harmonisation.

- While recurrent imaging procedures in children may result in significant cumulative doses and associated radiation risks, a balanced approach is required to inform policies, considering benefits and harms of such procedures. The requirements of justification and optimisation apply to each procedure/exam, in the context of the entire health care pathway (diagnosis, image-guided

[7] These conclusions were prepared by: L. Lebaron-Jacobs, P. Olko, A. Dumitrescu, F. Bochicchio, I. Prlic and P. Smeesters. They were assisted by F. Tzika and S. Mundigl from the European Commission.

interventions and follow-up). Safety culture should be instilled in prospectively identified care pathways that may need recurrent imaging in children.

- Effective dose can be used as a rough indicator of risk provided that the appropriate risk modifying factors (age, sex, population group) are properly taken into account, but unfortunately, this is not often done when effective dose is used outside its "design basis".

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