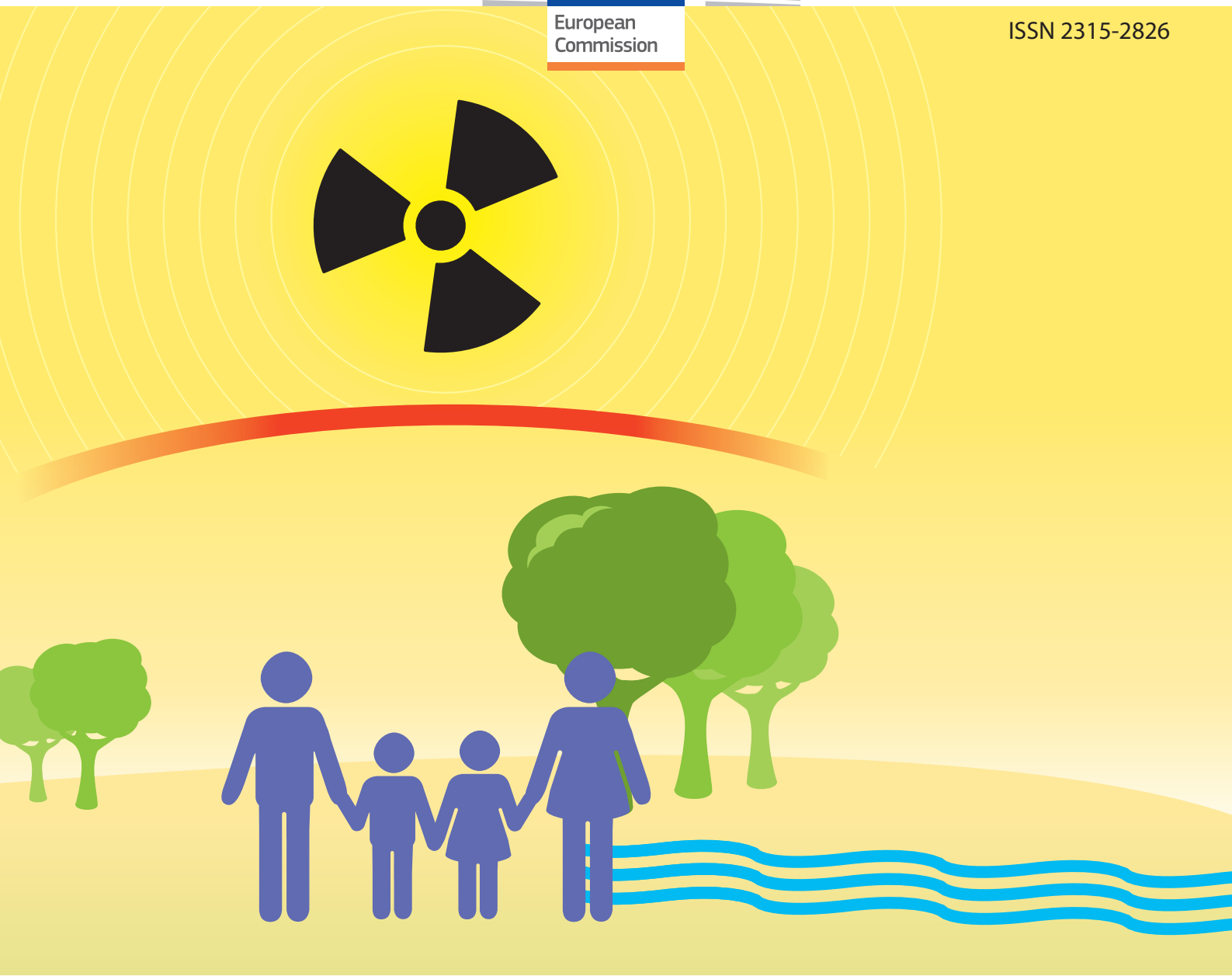
European Commission

ISSN 2315-2826



Radiation Protection

N° 182

EU Scientific Seminar 2013

"Radiation induced long-term health effects after medical exposure"

Energy

EUROPEAN COMMISSION

RADIATION PROTECTION N° 182

EU Scientific Seminar 2013

"Radiation induced long-term health effects after medical exposure"

Proceedings of a scientific seminar held in Luxembourg on 19 November 2013

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

Directorate-General for Energy
Directorate D — Nuclear Safety and Fuel Cycle
Unit D3 — Radiation Protection
2015

Europe Direct is a service to help you find answers to your questions about the European Union.

Freephone number (*)**:**

00 800 6 7 8 9 10 11

(*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

More information on the European Union is available on the Internet (http://europa.eu).

Luxembourg: Publications Office of the European Union, 2015

EU Scientific Seminar 2013: "Radiation induced long-term health effects after medical exposure"
2015 — pp. 62 — 21 × 29.7 cm

Print version:

Num cat.: MJ-XA-15-001-EN-C
ISBN: 978-92-79-45372-4
doi:10.2833/917394

online version:

Num cat.: MJ-XA-15-001-EN-N
ISBN: 978-92-79-45371-7
doi:10.2833/225347

Printed in Luxembourg

PRINTED ON ELEMENTAL CHLORINE-FREE BLEACHED PAPER (ECF)

FOREWORD

Luxembourg, November 2014

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.

In 2013, the EU Scientific Seminar covered the issue *Radiation induced long-term health effects after medical exposure*. Internationally renowned scientists working in this field presented current knowledge on

- Dosimetry in radio-diagnostic procedures – risk issues and research needs;
- Second primary cancers in adults after radiotherapy – an epidemiological review;
- Cardiovascular diseases after radiotherapy;
- Late effects in children after radiotherapy;
- CT scan studies – present results and the future; and on
- Risk communication.

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

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

I. Alehno
Head of Radiation Protection Unit

CONTENTS

FOREWORD 3
CONTENTS 5
1 Dosimetry in radio-diagnostic procedures – risk issues and research needs 7
1.1 Introduction 7
1.2 Radiological examination frequencies and doses in Europe 7
1.3 Questions rising from frequency and dose surveys 9
1.4 Status and development needs in patient dosimetry 9
1.5 Exposure risk assessment and communication 10
1.6 Needs to support exposure optimisation 10
1.7 Risk levels in specific group of patients and applications 11
1.8 Conclusions 11
1.9 Bibliography 12
2 Second primary cancers in adults after radiotherapy – an epidemiological review 13
2.1 Abstract 13
2.2 Introduction 13
2.3 Methods 14
2.4 Results 14
2.5 Discussion 14
2.6 Acknowledgements 15
2.7 References 20
3 Cardiovascular diseases after radiotherapy 23
3.1 Introduction 23
3.2 Clinical endpoints 23
3.3 Radiotherapy trials and cardiovascular disease: the breast cancer case 24
3.4 Dose-volume responses of cardiac disease following radiation therapy 24
3.5 RIHD radiotherapy data: availability and limitation 25
3.6 Cardiovascular disease and modern radiotherapy approaches for breast cancer radiation therapy 26
3.7 References 27
4 Late effects in children after radiotherapy 31
4.1 Summary 31
4.2 Introduction 31
4.3 Material and methods 32
4.4 Results 33
4.5 Discussion 34
4.6 Conclusions 34
4.7 Acknowledgement 34
4.8 Tables and figures 35
4.9 Literature 38
5 CT scan studies – present results and the future 41

5.1 Introduction 41
5.2 Early concerns and risk projections 42
5.3 The first empirical data 43
5.4 Current research 44
5.5 The future 45
5.6 Conclusions 45
5.7 References 46
6 Risk communication 47
6.1 Introduction 47
6.2 Inspect, diagnose, treat 47
6.3 The unpredictable factor: perception of risk 48
6.4 End Notes 52
7 SUMMARY 53
7.1 Introduction 53
7.2 The Article 31 Group of Experts and the rationale of the RIHSS seminars 53
7.3 Key Highlights of Presentations at Scientific Seminar on Radiation Induced Long-term Health Effects after Medical Exposure 54
7.4 Summary of the Roundtable discussion 58
8 Conclusions 61

1 DOSIMETRY IN RADIO-DIAGNOSTIC PROCEDURES – RISK ISSUES AND RESEARCH NEEDS

Renato Padovani

Medical Physics Dpt, Udine University Hospital, Udine, Italy

1.1 Introduction

The present status of dosimetry and radiation risk assessment in diagnostic and interventional radiology and the possible research and regulatory actions are discussed.

The data on examination frequency and patient and population dose assessment in Europe, derived from the recent EU supported project DosaDataMed2 are commented. The large differences between countries in examination frequencies and cumulative population doses are addressing questions on the effectiveness that research outcomes, guidelines and regulations of the last 20 years have had on the radiological practice in Europe.

On patient dosimetry, equipment and patient specific dose quantities implemented in the practice are discussed and needs for research and industrial developments identified. In particular, patient specific dose quantities, e.g. organ doses, are not easily available for the lack of dosimetry models and software tools implemented in radiological equipment. These developments are pre-requisite for a proper risk assessment, facilitating at the same time the communication of the risk levels both, to staff and patients. This is of particular importance for the risk assessment in specific pathologies, in adult and paediatric patients, that require repeated and frequent radiological examinations.

Finally, optimisation methods and tools are instruments supporting the daily QA practice. More advanced techniques and software tools can better support staff in designing and optimising radiological procedures.

Advancements in all these area, together with more stringent regulations, will certainly support a higher level of justification and exposure optimisation maintaining, at the same time, the European leadership in the radiation protection of medical exposure.

1.2 Radiological examination frequencies and doses in Europe

The DoseDataMed2 European Commission supported project, adopting the EU guidance for the estimation of population doses from medical x-ray procedures (1), has performed in 2011 a survey on 36 European countries to estimate the frequency and the patient and population doses derived from radiology, interventional radiology and nuclear medicine practice (2). Only six of the European countries provided comprehensive data on the radiological procedures while most of the countries could provide limited data, only for the so-called Top20 group of examinations as defined in the EC guidelines. For this reason, for most countries the overall data, estimated from the reduced set of data, are affected by inherent large uncertainties. Also with this limitation these data represent the first attempt to compare radiological practice and to assess exposures at European level. The Figure 1a reports the frequencies of diagnostic and interventional radiology procedures per 1000 inhabitants for

the European countries. Comparing countries with similar GDP it is recognized a wide range of frequencies with a factor of about 4, from less than 0.5 procedures per year and per caput up to over 2. The Figure 1b, reporting data without plain radiography contribution, better visualizes the large variability in the frequency of high dose procedures: also for this sub-set of data it is recognized a range of about 4, from 0.05 up to 0.25 proc/year per caput.

These results are addressing important questions on the adoption and effective use of referral criteria and on the methods implemented for a better justification of the radiological examinations and, in general, on the existing need to harmonise the radiological practice in Europe. The questions should be addressed both to Ministries of health and to medical communities of the countries with higher examination frequencies to identify causes and to adopt remedial actions. It is trivial the fact that a higher frequency implies a higher cost of the diagnostic service, both for the required personnel and radiological equipment.

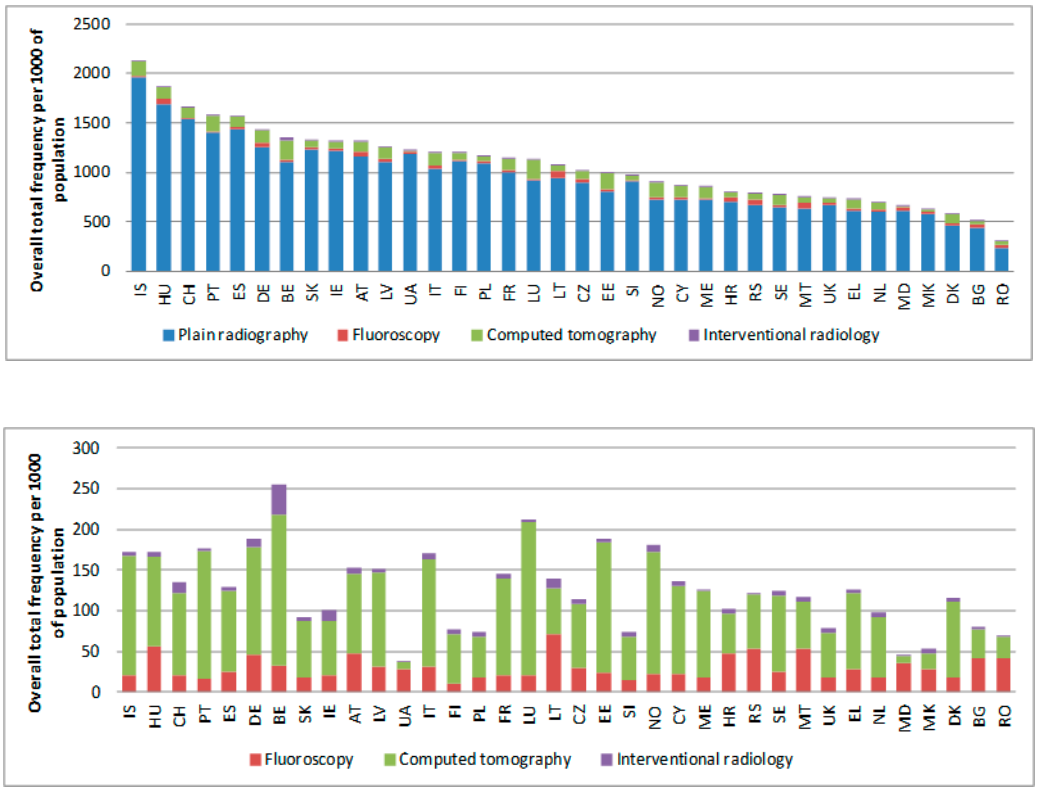


Figure 1: Total frequencies of diagnostic and interventional radiology procedures per 1000 of population for different countries, including plain radiography (including dental), fluoroscopy, CT and interventional radiology (upper). Without plain radiography (lower) (2).

The combined information of frequencies and individual mean doses have provided the estimation of population dose (Figure 2). The per caput effective dose has a great variability, ranging from about 0.3 up to almost 2 mSv per year, a factor of about 6. It is seen that the main contribution is from CT examinations with very large variability from country to country, from about 0.1 up to 1.5 (factor 15). In average, CT practice is contributing to 60% of the total collective dose from x-ray practice.

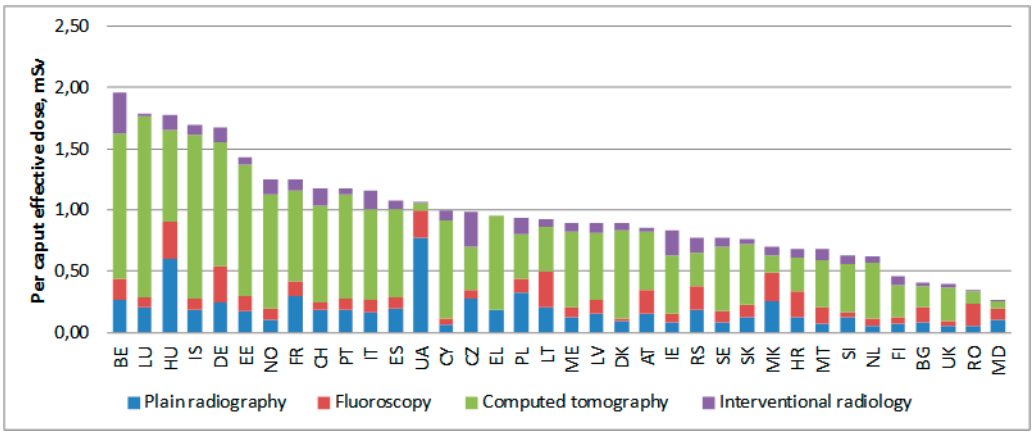


Figure 2: Per caput effective doses for different countries (from DDM2 Report (2)).

1.3 Questions rising from frequency and dose surveys

In the last 20 years several European and national research programmes have been developed to assess the optimisation level of the radiological practice and to develop methods and instruments for a better justification and optimisation of the practice. In particular, the concept of the diagnostic reference levels (DRLs) has been developed and introduced in the regulations of several countries. Again, regulation and guidelines on education and training in radiation protection and on the clinical audit have been developed and almost all the countries are conducting extensive and periodical training initiative. These actions have been spread the safety culture in the medical exposure sector bringing to important results in some countries, e.g. the low frequency and doses in countries like UK, Finland and the Netherland, to mention countries with a high GPD. In these countries, the implementation of quality assurance programmes, the regular monitoring of patient doses and the periodic update of DRLs together with the development of the medical physics and audit practice in the diagnostic area are certainly factors that have contributed to these positive results.

But, the large differences in frequency and doses in most of the remaining countries are posing questions on the effective implementation of justification and optimisation instruments and on the not sufficient efforts to put in practice regulations and recommendations.

1.4 Status and development needs in patient dosimetry

The ICRU Report 74 and the IAEA TRS 457 have developed a harmonised system for patient dosimetry in diagnostic and interventional radiology (3) (4). Mathematical phantoms have been widely used in Monte Carlo simulations for organ dose computations since their development in the 70th, while tomographic or voxel phantoms, derived from patients' CT images, have been introduced in late 80th and their use are quite common in research studies in the last 10 years. Now, the ICRP with the report 110 is recommending the use of the voxel patient models to improve dose assessment accuracy and, subsequently, the accuracy of risk assessment (5). To take advantage of these advancement in dosimetry and also of the DICOM standards and to provide useful instruments for the daily practice, Monte Carlo organ dose calculation tools should be developed to automatically extract patient and technical data from the stored images and from the DICOM radiation dose structured reports

(RDSR). Simulations should be extended also the most recent imaging techniques, like tomosynthesis, MSCT and conebeamCT.

The increasing contribution to population dose of CT and interventional radiology practices together with the developments of the imaging technology are now requiring further dosimetry developments. In CT: (i) the computed tomography dose index (CTDI), a dose quantity equipment-specific, is not an accurate metric when applied to wide MSCT beams, CTs with 64 or more detector rows, and a new metric should be adopted; (ii) the routine clinical use of angular current modulation is determining a non-uniform irradiation of the patient's body and the dosimetry tools cannot make accurate estimations if the CT is not providing modulation data.

In high dose interventional radiology practice with fluoroscopy guide, the peak skin dose is a limiting factor in conducting a safe procedure. The development of patient models and the patient-to-equipment geometry registration are prerequisite for the development of dosimetric models providing skin dose maps in real time during the procedure: industry standards and software tools should be developed and implemented in interventional equipment.

ConebeamCT is a novel imaging technique with increased use in radiotherapy, dental and angiography procedures. Kerma-area product is the dose metric today used but, when the beam is not fully intercepted by the patients' body, this quantity represents an overestimation of the dose and a more appropriate dose metrics should be developed.

1.5 Exposure risk assessment and communication

Effective dose is a fortunate synthetic metric to quantify radiation risk of workers and general public, it allows comparison with the dose limits and easy communication of risk levels. This metric is also frequently and improperly used to quantify and compare radiation risk of patients of age, gender and pathologies with very different radiation risk factors from those applied in the effective dose calculation. Seen the relevance of medical exposure levels compared to other human made exposures, it is probably necessary to develop a synthetic metric to quantify with the required accuracy the stochastic risk of medical exposures. An appropriate quantity can also support an improved communication of risk levels to practitioners, referral clinicians and, in general, to patients and public.

1.6 Needs to support exposure optimisation

The evidences of non-optimised and harmonised radiological practices are probably requesting the development of more advanced or different optimisation tools to support practitioners in designing and conducting optimised procedures. Here some examples.

Today exposure optimisation methods are not supported by intelligent tools supporting the design of a new imaging protocol. As an example, the design of a procedure aiming to maximise the contrast of linear structures on a moving cardiac background can be facilitated by a physical model to apply to the object and an observer model to calculate the resulting raw image.

Optimisation tools for high dose interventional procedures are also necessary to help practitioners to conduct procedures with minimal risk of skin burns. Real time skin dose maps and patient dose archives, with dose map information from previous procedures, can

efficiently prevent skin burns and allow identifying patients to submit to clinical follow-up, taking into account information from multiple interventional procedures.

Inter-hospital dose benchmarking can represent a necessary support for the optimisation and audit practice. For this purpose regional/national patient dose database should be recommended and developed. Existing and under development standards like DICOM RDSR, IHE REM profile and hospital IT systems (radiological information systems - RIS and picture archiving and communication systems - PACS) are today allowing to build these large archives. Data mining tools can provide periodic information to staff, including comparisons between hospitals, compliance with DRLs and cumulative individual doses. Such archives are also facilitating a frequent update of national and local DRLs.

Very few EU countries have initiated audits in medical exposure practices, the recommended methodology to identify non optimised practices. Regulation and guidelines exists and EU should encourage countries to conduct audits to support harmonisation and optimisation of radiological practices.

Staff exposure in interventional practice is probably not known in several hospitals as reported by the ISEMIR project (6). Not harmonised monitoring methods between countries and hospitals, low compliance with hospital rules by the staff and dated dosimetry technology are factors explaining this lack of information. And, the new dose limit for the lens of the eyes is posing new challenges on methods and accuracy of eye dosimetry when individual protective tools are used. The development of specifically designed active personal dosimeters with the capability to transfer information to a hospital (and national) archive can represent a necessary step to improve monitoring practice. The archived information can also be conveniently linked to the archived information on patient exposure contained in the structured report (RDSR), supporting also the exposure optimisation process of patient and staff.

1.7 Risk levels in specific group of patients and applications

It is well known that pathologies like ESKD (end stage kidney disease), IBD (inflammatory bowel disease), CAD (coronary artery disease) and HT (heart transplant) on adults and lymphoma, Crown disease, CHD (congenital heart disease) and haemophilia and bleeding disorders on children are requiring frequent radiological examinations. The existence of large cumulative individual doses is confirmed by this simple analysis of 6 months of radiological records in my hospital: (i) 2.4% of CT adult patients have received a DLP of more than 6700 mGycm (corresponding to approximately 100 mSv of effective dose for a adult standard man), (ii) a 28 years old man with 8 CTs has received 210 mSv. Recently, a study has associated patients with several head and neck CT examinations with an increased risk of cataracts (7).

The evidences of such high cumulative exposure levels are supporting the yet expressed need for patient dose archiving and periodic analysis and audits.

1.8 Conclusions

Since the 80s outcomes from European researches have been the bases for the implementation of actions, regulations and safety culture in medical exposure. These developments are representing a model for the harmonisation and optimisation of the

medical exposure at worldwide level. But, due to the still existence of large variability of justification and optimisation levels, there is the need to continue this effort:

- continuing to develop dose metrics and dosimetry tools
- developing advanced optimisation methods and implementing them in existing and new coming technologies and practices
- improving knowledge on low dose radiation risks
- developing communication strategies of radiation risk in medical exposure

With the aim to deliver a harmonised radiological practice to all European citizens, these advancements will contribute to maintain European leadership in this field.

1.9 Bibliography

1. European Commission, 2008. European guidance on estimating population doses from medical x-ray procedures, Radiation protection n° 154. s.l.: Radiation Protection 154.
2. EC, Radiation Protection No. 180, Medical Radiation Exposure of the European Population, part 1. Directorate-General for Energy, Radiation Protection, 2014
3. International Commission on Radiation Unites and Measurements Report 74, 2006. Patient Dosimetry for X Rays used in Medical Imaging. s.l.: ICRU, Bethesda, USA.
4. IAEA TRS 457, 2007. Dosimetry in Diagnostic Radiology: An International Code of Practice. s.l.: IAEA.
5. ICRP Publication 110, 2009. Adult Reference Computational Phantoms. s.l.: Annals of ICRP (39) 2, 1-166.
6. ISEMIR Report, 2013. Report on the Pilot Survey on Obtaining Occupational Exposure Data in Interventional Cardiology. s.l.: IAEA http://www-ns.iaea.org/tech-areas/communication-networks/orpnet/documents/wgic-second-survey-full-report.pdf.
7. Mei-Kang Yuan et al., 2013. Repeated exposure to head and neck CT is significantly associated with increased risk of cataracts. s.l.: AJR (201) 626-630.

2 SECOND PRIMARY CANCERS IN ADULTS AFTER RADIOTHERAPY – AN EPIDEMIOLOGICAL REVIEW

Mark P. Little

Radiation Epidemiology Branch, Division of Cancer Epidemiology & Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

2.1 Abstract

A substantial part of non-environmental population radiation exposure occurs as a result of radiotherapy for cancer. The patterns of cancer risk after fractionated high-dose radiation are much less well understood than those after lower-dose exposures. In particular, there is uncertainty about the shape of the dose-response curve at high doses, and the magnitude of the second cancer risk per unit dose.

We reviewed the available evidence from epidemiologic studies of cancers in populations that received exposure from radiotherapy in adulthood. We included 18 eligible studies, with a total of 3374 cancer cases or deaths. While risks were generally less in the radiotherapeutically exposed populations than in comparable (age, sex matched) subpopulations of the Japanese atomic bomb survivors, with the discrepancy particularly pronounced for second leukaemia risk, there was little evidence that the dose-response curve was non-linear in the direction of a down-turn in risk, even at organ doses of ≥ 60Gy.

2.2 Introduction

In medical practice the occurrence of a primary cancer within a previously irradiated field leads to the clinically persuasive, but epidemiologically unsubstantiated view that this pathology is radiation-related. The field may have been heavily irradiated during a course of radiotherapy (RT) or subjected to lower doses of radiation as a result of scatter. The multifactorial nature of carcinogenesis, the often appreciable but variable period of latency, and the changing nature of the therapeutic intervention complicate any interpretation. Developing the first disease as well as surviving it implies that the population at risk for developing a cancer after treatment is subject to multiple processes of selection and will consequently be somewhat different from the general population, although in general, cancer rates in medically treated groups are not markedly different from those of the general population [1-2].

The Japanese atomic bomb survivor Life Span Study (LSS) cohort is the principal source of data used to estimate risks of radiation-related cancer [3-5]. The atomic bomb survivors are unusual among exposed populations in that both sexes and a wide range of ages were exposed, comparable with those of a general population [6]. Most medically treated groups are more restricted in the age/sex mix. For example, the International Radiation Study of Cervical Cancer patients (IRSCC), which consists of a cohort of women followed up after treatment for cancer of the cervix, were all treated as adults, most above the age of 40 [7-8]. Organ doses among those treated with radiotherapy tend to be higher than those received by

the Japanese atomic bomb survivors, although there are some exceptions, e.g., breast doses in the IRSCC patients [8].

This paper seeks to compare quantitatively the cancer risk estimates derived from the latest LSS cancer data [6, 9-11] with cancer incidence and mortality risks observed in groups of patients who received substantial doses of ionizing radiation in the course of treatment for a variety of malignant and non-malignant conditions. The analysis will compare the relative risks obtained from these two data sources and determine their statistical compatibility. This paper is largely based on various surveys of cancer risks in persons treated with radiotherapy for first primary cancer or for other benign conditions [12-15].

2.3 Methods

The data used come from two recently published reviews [13-15]. We have minimally updated the studies relating to solid cancer (Table 1) and leukaemia (Table 2) from these. In particular Table 2 details excess relative risk per Gy (ERR/ Gy) in studies of patients treated with radiotherapy for benign conditions as well as for cancer, together with those in comparable (age, sex, follow-up matched) LSS subpopulations, and is based on the corresponding Table (8) in the review of Little [13], whereas Table 1 is restricted to studies following persons treated for and surviving first primary cancer, and subject to various other restrictions (on mean dose, and numbers of tabulated points available to estimate dose response) in the meta-analysis of Berrington de Gonzalez et al [15]. Table 1 makes use of BEIR VII models [5] to estimate the risk that would have been predicted from the LSS.

2.4 Results

We included 18 eligible studies, with a total of 3374 cancer cases or deaths, with average absorbed organ doses ranging from near 0 up to 200 or more Gy (Tables 1, 2). Many of the studies, and the majority of the studies of solid cancer, were case-control studies, many of which were nested case-control studies within a cohort.

As can be seen from Tables 1-2 and Figure 1, risks are generally much less in most RT exposed populations than in comparable subsets of the LSS, and the ratio of LSS risk: RT risks tends to be higher for leukaemia than for solid cancer. For example, for solid cancers the ratio of LSS risks: RT risks ranges from 0.52 to 31.89 (Table 1), whereas for leukaemia the ratio of risks ranges from 1.72 to 524 (Table 2).

Figure 2 demonstrates that the ratio of RT: LSS risks tend to decrease with increasing organ dose for solid cancers, but this pattern is not observed for leukaemia.

2.5 Discussion

In this paper, the relative risk of cancer induced by radiotherapy in groups treated for a variety of medical conditions is compared with the cancer relative risks in the LSS. For most cancer sites the ERR in the LSS are significantly greater than those in the second cancer studies, as shown by the final columns of Tables 1 and 2 and Figure 1. Even when the differences between the ERRs in the LSS and the medical series do not approach

conventional levels of statistical significance, ERR tend to be higher in the Japanese data than in the radiotherapy studies.

One plausible explanation of this is that this reflects the effects of cell sterilizing effects of the high dose RT, which would tend to remove malignantly transformed cells, a conclusion tentatively supported by a previous review paper [13]. However, a previous systematic review of second solid cancers after treatment for cancer suggested that, in general, there was little support for a plateau or a downturn in solid cancer risk at high doses with the exception of second thyroid cancer [15]. Nevertheless, the ERR/Gy is lower than from acute lower-dose exposures in the LSS or other lower-dose studies, often as much as 5-10 times lower [15]; the exact magnitude of the reduction in risk varied according to second cancer, and even by cancer sub-type (e.g., meningioma, glioma). Berrington de Gonzalez et al suggested that uniform adjustment factors for cell killing and fractionation effects for all solid cancer sites may result in misleading risk projections and comparisons for second cancer risks from high-dose fractionated radiotherapy [15].

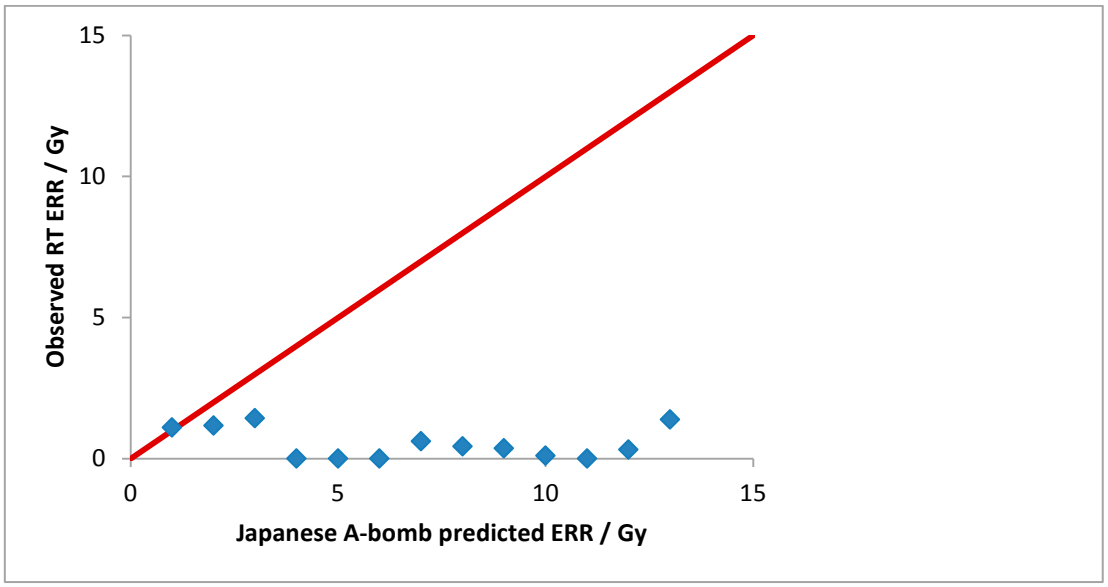
However, the results from these human data do not support the traditional cell killing/inactivation model or the animal data, which predicts a down-turn in the dose-response relationship at doses as low as 5 Gy [16]. Although the confidence intervals were often wide in the many of the studies reviewed elsewhere [15], especially for the highest dose categories, in many studies there was no clear evidence of a downturn or plateau in the risk even at doses of 40 Gy or more. Although for thyroid cancer there was such a downturn [15], this was not evident until at least 20 Gy, vastly in excess of the level suggested by in vitro measures of cell killing, which imply that about half of the irradiated cells would be inactivated by a dose of 1 Gy [17]. Lack of a downturn in the dose-response is consistent with theoretical models that incorporate repopulation as well as cell killing after high dose radiotherapy [18-20]. Formal statistical comparison of the theoretical models with the entirety of the human data presented here would be an important next step. These comparisons should take account of the various additional uncertainties in the human data that may influence the shape of the dose-response curve that were described above. For leukemia there was a clear downturn in the dose-response relationship after moderate and high dose radiation exposure in most studies at levels above 3-5 Gy [21], and the review by Little [13] suggested that second leukaemia excess risk was generally much lower than would be expected from the LSS. Theoretical mechanisms have been suggested that account for these observations, taking account of the known transfer of hematopoietic stem cells between bone marrow compartments [19, 20].

2.6 Acknowledgements

This work was supported by the Intramural Research Program of the National Institutes of Health, the National Cancer Institute, Division of Cancer Epidemiology and Genetics.

Figure 1: Relative risk for subsequent cancer in radiotherapeutically (RT) exposed compared with risk in comparable Japanese atomic bomb subpopulations. The solid red line in each figure is the diagonal (X=Y)

Solid cancers



Leukemia

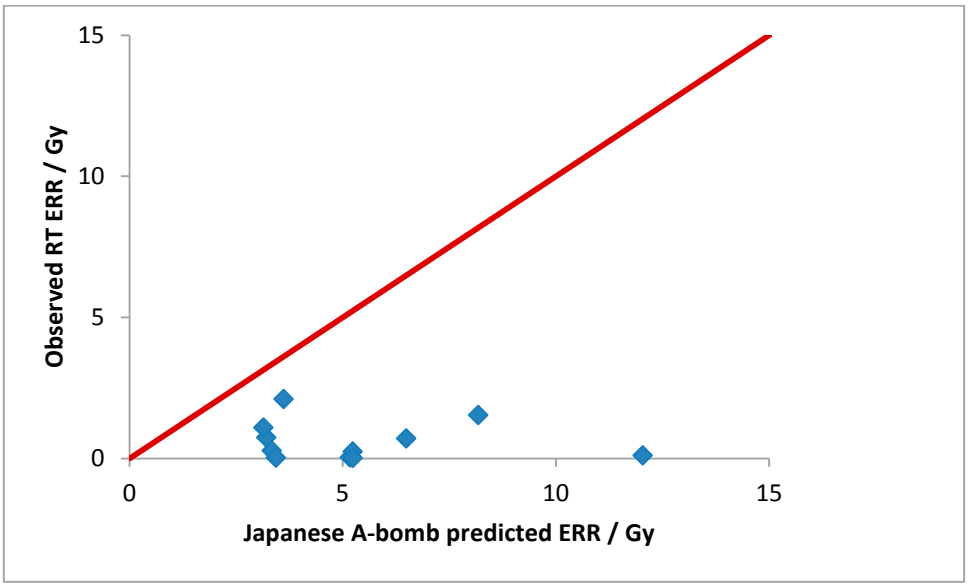
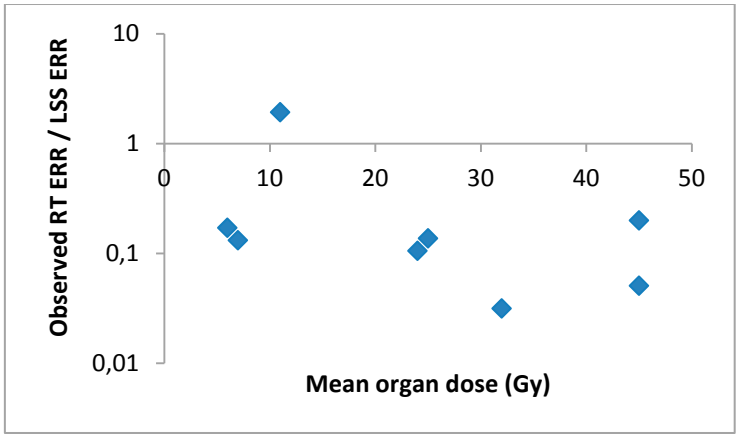


Figure 2: Ratio of [excess relative risk for subsequent cancer in radiotherapy (RT) population]: [excess relative risk in comparable subsets of Japanese atomic bomb survivors LSS], according to the estimated mean absorbed radiation organ dose (Gy)

Solid cancers



Leukemia

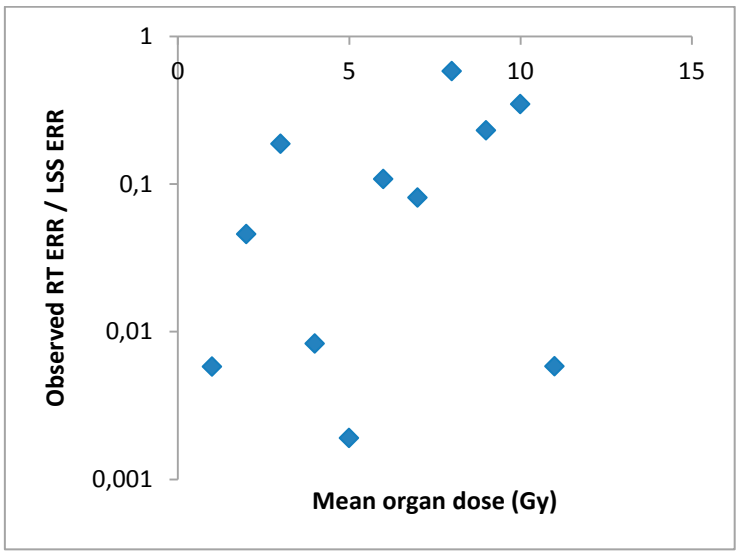


Table 1: Excess relative risks /Gy for second solid cancers among survivors of first cancer predominantly treated in adulthood (taken from [15]), and comparison with risk in a similar (age, sex, follow-up matched) Japanese atomic bomb survivor subpopulation, estimated via use of BEIR VII models [5]

Reference	2nd cancer	1st cancer	Cases	Controls	Age at 1st cancer range (mean)	Age at 2nd cancer, mean	Dose to controls, average	Dose to controls, maximum	Study ERR Gy^{-1} (95% CI)	BEIR VII ERR Gy^{-1}	Ratio
Travis et al [22]	Breast	Hodgkin disease	105	266	13-30 (22)	41	25	61	0.15 (0.04-0.73)	1.1	7.34
Inskip et al [23]	Lung	Breast	61	120	35-72 (50)	68	6	23	0.20 (-0.62-1.03)	1.17	5.87
Gilbert et al [24]	Lung	Hodgkin disease	227	455	9-81 (49)	59	24	60+	0.15 (0.057-0.39)	1.43	9.56
Boice et al [8]	Bone sarcoma	Cervix	15	155	<45-65+ (45-54)	67	22	10+	0.02 (-0.03-0.21)	NA	-
Boice et al [8]	Soft tissue sarcoma	Cervix	46	598	<45-65+ (45-54)	67	7	10+	-0.05 (-0.11-0.13)	NA	-
Rubino et al [25]	Sarcoma	Breast	14	98	35-77 (55)	62	19	80	0.05 (<0-1.18)	NA	-
Morton et al [26]	Esophagus	Breast	252	488	28-88 (59)	74	7	45	0.08 (0.04-0.16)	0.61	7.64
van den Belt-Dusebout et al [27]	Stomach	Testes & Hodgkin disease	42	126	20-50+ (34)	51	11	40	0.84 (0.12-15.6)	0.43	0.52
Boice et al [8]	Colon	Cervix	409	759	<45-65+ (45-54)	68	24	40+	0.00 (-0.01-0.02)	0.36	-
Boice et al [8]	Rectum	Cervix	488	901	<45-65+ (45-54)	68	45	60+	0.02 (0-0.04)	0.1	5.04
Boice et al [8]	Uterine corpus	Cervix	313	469	<45-65+ (45-54)	68	165	200+	NA (NA)	NA	-
Boice et al [8]	Ovary	Cervix	309	560	<45-65+ (45-54)	68	32	60+	0.01 (-0.02-0.14)	0.32	31.89
Boice et al [8]	Bladder	Cervix	273	520	<45-65+ (45-54)	68	45	60+	0.07 (0.02-0.17)	1.38	19.78

Table 2: Excess relative risks (ERR) of leukemia among those exposed predominantly in adulthood to radiation therapy, and in comparable (age, sex, follow-up matched) subpopulations of the Japanese atomic bomb survivor Life Span Study (LSS) data, with 95% CI (taken from [13])

Reference	1st cancer endpoint or other treatment	2nd cancer endpoint	Age at exposure range (mean) (years)	Follow-up (mean) (years)	Average dose (Sv)[a]	Dose range (Sv)[a]	Cases or deaths	LSS cases or deaths[b]	ERR estimate (Sv^{-1})[a]	LSS ERR estimate (Sv^{-1})[b]	Ratio
Boice *et al.* [7]	Cervical cancer	Incidence	<30->75	1->40 (NA)	7.1	0.5-25.2	134[c]	35	0.03 (-0.06,0.12)[c]	5.17 (1.99,11.93)[d ##]	172.3
Kaldor *et al.* [28]	Hodgkin disease	Incidence	42, 37[e]	1->10 (NA)	Unknown	0->20	163	192	0.24 (0.04,0.43)	5.24 (3.58,7.55)[f ###]	21.8
Curtis *et al.* [29]	Breast cancer	Incidence	<50-> 70 (most over 50)	1.5->12.5 (5)	7.5	0->11	34	15	1.53 (-18.18,21.25)[g]	8.18 (1.86,33.51)[h]	5.35
Curtis *et al.* [30]	Uterine corpus cancer	Incidence	Most >55 (62)	1–>28 (4.9)	5.4	0->14.9	151	10	0.10 (<0,0.23)	12.04 (2.23,67.35)[i #]	120.4
Boivin *et al.* [31]	Hodgkin disease	Incidence	<15->55 (29)	1-44 (mean 8.1)	Unknown	0->30[j]	122	192	0.01 (0.00,0.02)[j]	5.24 (3.58,7.55)[f ###]	524
Damber *et al.* [32]	Benign locomotor lesions	Incidence	<20->70 (53)	0->19.6 (19.6)	0.39	<0.06->1.04	61[c]	91	0.70 (-0.43,3.48)[c]	6.49 (3.76,10.99)[k ##]	9.27
Travis *et al.* [33]	Testicular cancer	Incidence	<30->50 (39)	0->17.3 (6.8)	13.6, 12.3[l]	7.9-23.8	26	64	0.27 (0.02,1.2)[m]	3.34 (1.57,6.36)[n ##]	12.4
Inskip *et al.* [34]	Benign uterine disease	Mortality	13-89 (46.5)	0-59.9 (24.9)	1.19	0-11	43[c]	97	2.1 (0.19,9.49)[c]	3.62 (1.91,6.29)[o]	1.72
Darby *et al.* [35]	Benign uterine disease	Mortality	23-65 (45.5)	2-49 (27.7)	1.3	<1.02->1.68	12	73	0.74 (-0.11,1.59)	3.21 (1.40,6.23)[p #]	4.34
Little *et al.* [36]	Peptic ulcer	Mortality	<35->55 (49)	1-51 (21.5)	0.60	0-4.4	14[q]	136	1.09 (-0.02,4.93)[q]	3.14 (1.81,5.07)[r]	2.88
Weiss *et al.* [37]	Ankylosing spondylitis	Mortality	1->35 (18.1)	<25->55 (NA)	4.38	0->14	60	167	0.02 (-0.07,0.29)	3.44 (2.14,5.24)[s ###]	172

[a] unless otherwise stated, all doses and risks are in terms of bone-marrow dose;
[b] in all analyses of risks in the LSS incidence data the three main radiogenic leukaemia subtypes (acute myeloid leukaemia, acute lymphocytic leukaemia, chronic myeloid leukaemia) are analysed together, using bone-marrow dose;
[c] acute leukaemia and chronic myeloid leukaemia;
[d] calculation based on females, age at exposure >40 years;
[e] average values for men and women, respectively;
[f] calculation based on full cohort;
[g] 95% CI are Wald-based (likelihood bounds did not converge);
[h] calculation based on females, age at exposure >40 years, time since exposure <20 years;
[i] calculation based on females, age at exposure >50 years;
[j] calculation based on dose to lymph nodes;
[k] calculation based on age at exposure >20 years, time since exposure <30 years;
[l] average values for cases and controls not exposed to alkylating agents, respectively;
[m] calculation based on those patients not exposed to alkylating agents;
[n] calculation based on males, age at exposure 20-59 years;
[o] calculation based on females, age at exposure >15 years;
[p] calculation based on females, age at exposure 25-64 years;
[q] leukaemia excluding chronic lymphocytic leukaemia;
[r] calculation based on age at exposure >30 years;
[s] calculation based on age at exposure >20 years;
[#] LSS and radiation therapy ERR statistically inconsistent with $p<0.05$;
[##] LSS and radiation therapy ERR statistically inconsistent with $p<0.01$;
[###] LSS and radiation therapy ERR statistically inconsistent with $p<0.001$

2.7 References

1. Smith PG, Doll R, Radford EP. Cancer mortality among patients with ankylosing spondylitis not given X-ray therapy. BrJRadiol 1977;50(598):728-34.
2. Curtis RE, Boice JD, Jr., Kleinerman RA, et al. Summary: multiple primary cancers in Connecticut, 1935-82. NatlCancer InstMonogr 1985;68:219-42.
3. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). UNSCEAR 2006 Report. Annex A. Epidemiological Studies of Radiation and Cancer. New York: United Nations, 2008:13-322.
4. International Commission on Radiological Protection (ICRP). The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. AnnICRP 2007;37(2-4):1-332 doi: S0146-6453(07)00031-0 [pii];10.1016/j.icrp.2007.10.003 [doi][published Online First: Epub Date]|.
5. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation NRC. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII - Phase 2. Washington, DC, USA: National Academy Press, 2006:1-406.
6. Ozasa K, Shimizu Y, Suyama A, et al. Studies of the mortality of atomic bomb survivors, report 14, 1950-2003: an overview of cancer and noncancer diseases. RadiatRes 2012;177(3):229-43 doi: 10.1667/RR2629.1 [pii][published Online First: Epub Date]|.
7. Boice JD, Jr., Blettner M, Kleinerman RA, et al. Radiation dose and leukemia risk in patients treated for cancer of the cervix. JNatlCancer Inst 1987;79(6):1295-311.
8. Boice JD, Jr., Engholm G, Kleinerman RA, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. RadiatRes 1988;116(1):3-55.
9. Preston DL, Kusumi S, Tomonaga M, et al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. RadiatRes 1994;137(2 Suppl):S68-S97.
10. Pierce DA, Shimizu Y, Preston DL, et al. Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950-1990. RadiatRes 1996;146(1):1-27.
11. Preston DL, Ron E, Tokuoka S, et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. RadiatRes 2007;168(1):1-64 doi: RR0763 [pii];10.1667/RR0763.1 [doi][published Online First: Epub Date]|.
12. Little MP, Muirhead CR, Haylock RG, et al. Relative risks of radiation-associated cancer: comparison of second cancer in therapeutically irradiated populations with the Japanese atomic bomb survivors. RadiatEnvironBiophys 1999;38(4):267-83.
13. Little MP. Comparison of the risks of cancer incidence and mortality following radiation therapy for benign and malignant disease with the cancer risks observed in the Japanese A-bomb survivors. IntJRadiatBiol 2001;77(4):431-64 doi: 10.1080/09553000010022634 [doi][published Online First: Epub Date]|.
14. Little MP. Cancer after exposure to radiation in the course of treatment for benign and malignant disease. Lancet Oncol 2001;2(4):212-20 doi: S1470-2045(00)00291-6 [pii];10.1016/S1470-2045(00)00291-6 [doi][published Online First: Epub Date]|.
15. Berrington de GA, Gilbert E, Curtis R, et al. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. IntJRadiatOncolBiolPhys 2013;86(2):224-33 doi: S0360-3016(12)03512-2 [pii];10.1016/j.ijrobp.2012.09.001 [doi][published Online First: Epub Date]|.
16. Lea DE. Actions of radiations on living cells. Cambridge: Cambridge University Press, 1946.

17. Deschavanne PJ, Fertil B. A review of human cell radiosensitivity in vitro. IntJRadiatOncolBiolPhys 1996;34(1):251-66.

18. Sachs RK, Brenner DJ. Solid tumor risks after high doses of ionizing radiation. ProcNatlAcadSciUSA 2005;102(37):13040-45 doi: 0506648102 [pii];10.1073/pnas.0506648102 [doi][published Online First: Epub Date]|.

19. Shuryak I, Sachs RK, Hlatky L, et al. Radiation-induced leukemia at doses relevant to radiation therapy: modeling mechanisms and estimating risks. JNatlCancer Inst 2006;98(24):1794-806 doi: 98/24/1794 [pii];10.1093/jnci/djj497 [doi][published Online First: Epub Date]|.

20. Little MP. A multi-compartment cell repopulation model allowing for inter-compartmental migration following radiation exposure, applied to leukaemia. JTheorBiol 2007;245(1):83-97 doi: S0022-5193(06)00450-4 [pii];10.1016/j.jtbi.2006.09.026 [doi][published Online First: Epub Date]|.

21. Little MP, Weiss HA, Boice JD, et al. Risks of leukemia in Japanese atomic bomb survivors, in women treated for cervical cancer, and in patients treated for ankylosing spondylitis. Radiation Research 1999;152(3):280-92.

22. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290(4):465-75 doi: 10.1001/jama.290.4.465 [doi];290/4/465 [pii][published Online First: Epub Date]|.

23. Inskip PD, Stovall M, Flannery JT. Lung cancer risk and radiation dose among women treated for breast cancer. JNatlCancer Inst 1994;86(13):983-88.

24. Gilbert ES, Stovall M, Gospodarowicz M, et al. Lung cancer after treatment for Hodgkin's disease: focus on radiation effects. RadiatRes 2003;159(2):161-73.

25. Rubino C, Shamsaldin A, Le MG, et al. Radiation dose and risk of soft tissue and bone sarcoma after breast cancer treatment. Breast Cancer ResTreat 2005;89(3):277-88 doi: 10.1007/s10549-004-2472-8 [doi][published Online First: Epub Date]|.

26. Morton LM, Gilbert ES, Hall P, et al. Risk of treatment-related esophageal cancer among breast cancer survivors. AnnOncol 2012;23(12):3081-91 doi: mds144 [pii];10.1093/annonc/mds144 [doi][published Online First: Epub Date]|.

27. van den Belt-Dusebout AW, Aleman BM, Besseling G, et al. Roles of radiation dose and chemotherapy in the etiology of stomach cancer as a second malignancy. IntJRadiatOncolBiolPhys 2009;75(5):1420-29 doi: S0360-3016(09)00105-9 [pii];10.1016/j.ijrobp.2009.01.073 [doi][published Online First: Epub Date]|.

28. Kaldor JM, Day NE, Clarke EA, et al. Leukemia following Hodgkin's disease. NEnglJMed 1990;322(1):7-13.

29. Curtis RE, Boice JD, Jr., Stovall M, et al. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. NEnglJMed 1992;326(26):1745-51.

30. Curtis RE, Boice JD, Jr., Stovall M, et al. Relationship of leukemia risk to radiation dose following cancer of the uterine corpus. JNatlCancer Inst 1994;86(17):1315-24.

31. Boivin JF, Hutchison GB, Zauber AG, et al. Incidence of second cancers in patients treated for Hodgkin's disease. JNatlCancer Inst 1995;87(10):732-41.

32. Damber L, Larsson LG, Johansson L, et al. A cohort study with regard to the risk of haematological malignancies in patients treated with x-rays for benign lesions in the locomotor system. I. Epidemiological analyses. Acta Oncol 1995;34(6):713-19.

33. Travis LB, Andersson M, Gospodarowicz M, et al. Treatment-associated leukemia following testicular cancer. JNatlCancer Inst 2000;92(14):1165-71.

34. Inskip PD, Kleinerman RA, Stovall M, et al. Leukemia, lymphoma, and multiple myeloma after pelvic radiotherapy for benign disease. RadiatRes 1993;135(1):108-24.

35. Darby SC, Reeves G, Key T, et al. Mortality in a cohort of women given X-ray therapy for metropathia haemorrhagica. IntJCancer 1994;56(6):793-801.

36. Little MP, Stovall M, Smith SA, et al. A reanalysis of curvature in the dose response for cancer and modifications by age at exposure following radiation therapy for benign disease. IntJRadiatOncolBiolPhys 2013;85(2):451-59 doi: S0360-3016(12)00582-2 [pii];10.1016/j.ijrobp.2012.04.029 [doi][published Online First: Epub Date]|.

37. Weiss HA, Darby SC, Fearn T, et al. Leukemia mortality after X-ray treatment for ankylosing spondylitis. RadiatRes 1995;142(1):1-11.

3 CARDIOVASCULAR DISEASES AFTER RADIOTHERAPY

Giovanna Gagliardi

Section of Radiotherapy Physics and Engineering, Dept. of Medical Physics
Karolinska University Hospital, Stockholm, Sweden

3.1 Introduction

The general term to indicate cardiovascular disease following radiation therapy is RIHD (Radiation induced heart disease). It refers to the clinical and pathological conditions of the heart and large vessels resulting from therapeutic irradiation (Stewart *et al*. 1995).

RIHD has been observed in a tiny percentage of patients treated with radiation for breast cancer, lymphoma, seminoma, lung cancer and in the past for peptic ulcers. Cardiovascular disease has also been found in atomic bomb survivors. RIHD following radiotherapy (RT) of breast cancer and Hodgkin's lymphoma has been extensively investigated (see review: Gagliardi *et al* 2010, Nilsson 2012a).

Based on the hypothesis that radiation damage occurred predominantly in highly proliferative tissue, the heart was considered to be radiation resistant until the 1960s. In fact the heart's embryotic morphogenesis is complete by the 8th week of gestation; at an age of 6 months the proliferation of myocites is complete and the adult number of myocites exists. Endothelial and connective tissue cells, essential for heart function, have low proliferative activity (Nilsson 2012a).

Experimental studies from the 1960s onwards showed instead that the heart and the vasculature were radiosensitive structures. It was demonstrated that pericarditis, myocardium fibrosis and coronary artery disease could be caused by radiation therapy (Stewart *et al* 1978). In particular a high incidence of coronary artery disease was found in children irradiated for Hodgkin's lymphoma (Joenssu 1989).

3.2 Clinical endpoints

Pericardial disease, congestive heart failure, ischemic heart disease and valvular disease are the main components of the RIHD spectrum. These complications can show up after months (e.g. pericarditis) or years (e.g. congestive heart failures, ischemic heart disease such as myocardial infarction and cardiac death). Some of these events have a long latency; furthermore they are relatively common also in non-irradiated populations. Hence large studies based on large patient populations, in form of randomized trials or population-based studies, are the ones which have provided most information on RIHD.

Pericardial disease (pericarditis and chronic pericardial effusion) develops from months to years after RT and is usually uncommon in acute form, i.e. during radiation therapy. About 20% of the cases become chronic (Carmel *et al* 1976, Gagliardi *et al* 2010).

Ischemic heart disease was found to correlate with irradiation after meta-analysis of randomized clinical trials (e.g. EBCTCG 2005). The patho-physiological mechanism is macroangiopathy and atherosclerosis of arteries post radiation cannot easily be

discriminated from atherosclerosis induced by other causes. An increased risk of Ischemic Heart Disease and ischemic stroke has been found, especially in patients irradiated for Hodgkins Lymphoma (Aleman *et al* 2007) and breast cancer (Correa *et al* 2007, Nilsson 2012a).

Stenosis and insufficiencies of the valves have also been observed after irradiation (Brosius *et al* 1981); however for breast cancer patients the risk was not clearly associated with radiation therapy (Hooning *et al* 2007, Harris *et al* 2006). For Hodgkins patients, valvular insufficiency has shown to be more common than stenosis - up to a 34-fold increased risk of valvular regurgitation (Glanzmann *et al* 1994, Lund *et al* 1996, Heidenreich *et al* 2003).

In general it is important to note that different parts of the heart can be involved in RIHD, each playing a role in the onset of a specific endpoint.

3.3 Radiotherapy trials and cardiovascular disease: the breast cancer case

Breast cancer is the most common female malignancy and the first cause of death in women globally (Nilsson 2012a, Benson *et al* 2012). The prognosis has continuously improved as time has gone on; as an example, in Sweden survival has increased from about 50% to approx. 80% in the period between 1960 and 2009 (Nilsson 2012a). In early breast cancer it has been shown that radiation therapy can reduce the risk of death from breast cancer itself (Henson *et a*l 2013, EBCTCG 2011). Several studies have however indicated an increase in heart disease related to radiotherapy (e.g. Gagliardi et al 2010). In particular randomized clinical trials and meta-analysis have shown benefit from radiation therapy in the reduction of local recurrences and breast cancer deaths (Nilsson 2012a, Overgaard et al 1999, EBCTCG 2005), but long follow-up studies have indicated an excess mortality from heart disease (EBCTCG 2005). An increase of cardiac deaths has been shown in earlier radiotherapy trials (Cuzick et al 1994), while the results are not yet clear when considering more modern recent situations and treatment techniques probably due to a short follow-up (Henson et al 2013).

3.4 Dose-volume responses of cardiac disease following radiation therapy

A dose response relationship between dose-volume and pericarditis has been indicated by several analyses. Data on dose-response curves quantifying pericarditis have been provided mainly by studies on patients who received radiation therapy for Hodgkin's disease and for oesophagus cancer. In one study, in patients in whom the RT field was estimated to include > 50% of the external heart contour, an overall pericarditis rate of about 6% was found (Stewart et al 1978). Three-dimensional dose information has provided further information on pericarditis risk following irradiation; two such studies involved a modern and complete data-set related to pericarditis following irradiation for oesophagus cancer (Martel et al 1998, Wei et al 2008). In the study by Martel the dose per fraction was the strongest predictor - no cases were found in patients receiving a dose lower than 3.5 Gy per fraction, for the given total dose. Wei's study showed that the risk of pericardial effusion increased with increasing dose to the perdicardium; a mean dose of 26 Gy was found to be a discriminator - the risk of pericarditis fell from 73% to 13% after a follow up of 18 months. Note that in both cases the volume at risk, i.e. the pericardium, was delineated and the dose distribution was quantified within the pericardium.

The quantification of the dose-response relationship for ischemic heart disease, and especially for cardiac mortality, has been a major issue of investigation over several decades (Gagliardi et al 2001, Gagliardi et al 2010, Nilsson 2012a, Darby et al 2013). The risk of ischemic heart disease in women after radiotherapy for breast cancer has recently been studied in a large cohort of patients. This is a population—based cohort study of major coronary events (myocardial infarction, coronary revascularization, death from ischemic heart disease) (Darby et al 2013). One result of this investigation, which is retrospective and refers to data on patients treated between 1958 and 2001 in Sweden and Denmark, is that the rate of major coronary events increases linearly with the mean dose to the heart. The increase becomes manifest from 5 years after radiotherapy and continues for at least 20 years after radiotherapy, and the absolute increase in risk is larger in women with cardiac risk factors at the time of radiotherapy. The best predictor of risk in this study was mean heart dose even when this was compared to the mean dose to the left descendent artery, which is a specific, potentially more radiosensitive heart subvolume (Nilsson 2012b).

A specific dose-response relationship for cardiac mortality following radiotherapy has been previously studied in two major groups, Hodgkin's lymphoma patients and breast cancer patients (Gagliardi et al 2001, Gagliardi et al 2010). Patients treated for Hodgkin's Lymphoma have shown an increase in cardiac mortality for heart doses greater than 30 Gy (Hancock et al, 1993). It has to be underlined that these data refer to older studies with larger treatment irradiation volumes, which nowadays are much smaller. A dose-volume response relation for long-term cardiac mortality following breast cancer irradiation was derived from data from two randomized trials of surgery with and without RT; an increase in cardiac mortality had been found in the group treated with radiotherapy (Høst et al 1986, Rutqvist et al 1992). The analysis suggested that dose, and to a lesser degree the irradiation volume, determines the dose-response curve for long-term cardiac mortality (Gagliardi et al 1996). In this analysis the dose to the whole heart was analysed, i.e. homogeneous radiation sensitivity was assumed, without considering the dose distribution in substructures of potentially greater relevance like the left descendent artery.

The relationship between heart irradiation and cardiac perfusion defects has been studied in a prospective analysis. For <5% of the left ventricle (LV) included in the tangential fields an incidence lower than 20% was found, while for >5% the incidence was higher than 50% (Das et al 2005, Marks et al 2005).

3.5 RIHD radiotherapy data: availability and limitation

The quantification of dose-response curve(s) for RIHD is a complex process. The methodology does not differ from that employed for other endpoints. However, compared to other situations, the scarcity of clinical data, the latency of the endpoint, and the fact that the clinical endpoints are also common in the non-irradiated population make the whole issue challenging.

Dose-volume data from irradiation, i.e. data from the dose distribution in specific (sub)volumes of the heart, together with clinical outcome data are necessary to determine the dose-response curve for the given endpoint. In RIHD both clinical and dose-volume data quantification is not as straightforward as, for instance, in the case of radiation-induced complications following prostate irradiation (Fiorino et al 2009) or radiation-induced pneumonitis (Marks et al 2010), where dose-volume response studies can be performed prospectively. In these latter cases several independent prospective studies have provided similar results, both in terms of dose-response curves and of identification of risk factors. This is definitely the case for the dose-response curves for radiation-induced rectal bleeding

and the identification of risk factors such as abdominal surgery before irradiation (Fiorino et al 2009, Peeters et al 2006).

In RIHD the situation is intrinsically different. Clinical endpoint assessment requires randomized trials of irradiated vs non-irradiated populations, or alternatively large population studies; furthermore these studies also require a long follow-up in case of ischemic heart disease. The studies are retrospective, which complicate the understanding of the role and of the influence of other cardiac risk factors. The retrospective nature of the studies inevitably mean that irradiation data are in general many years old and therefore refer to periods when treatment planning systems were not based on Computed Tomographs of patient anatomy and thus volumetric calculations were not possible (often referred to as 3D planning). This means that most radiotherapy data have to be simulated and calculated on 'model' patients; the dose distribution in the heart volume cannot be reconstructed on an individual basis (Gagliardi et al 1996, Gagliardi et al 2010, Taylor et al 2009, Darby et al 2013). For the cases of pericarditis and cardiac perfusion defects, studies with individual and complete dose-volume information are instead now available (Wei et al 2008, Marks et al 2005).

The study of the dose-response curve for specific clinical complications requires ideally the ability to test the hypothesis of the role of different substructures, whose irradiation determines the development of the given clinical complication (e.g. Left Descendent Artery). Again, treatment planning simulation and the need to simulate the individual irradiations using a/some model situations place limits on the investigation. However, assumptions and comparisons between different scenarios, as for instance the determination of the dose-response curve based on the dose distribution in one single volume and/or several subvolumes, can provide a reference frame which at least enables us to assess the impact of different assumptions (Gagliardi et al 1996, Taylor et al 2007).

The potential interactions between heart and lung irradiation have also to be further studied (Van Luijk et al 2007, Ghobaldi et al 2012, Tucker et al 2013), in order to create a 'global' understanding of the physiological effects of radiation therapy to the thorax.

3.6 Cardiovascular disease and modern radiotherapy approaches for breast cancer radiation therapy

In breast cancer radiation therapy, dose prescriptions (i.e. the dose to the tumor volume and the number of fractions) have remained substantially unchanged over the years. In contrast the definition of the target volumes in breast cancer has gone through some modifications, for instance following the criteria for the inclusion/non-inclusion of the lymph nodes of the internal mammary chain in the radiation therapy target volume. The change of the target volumes has also implied a change of treatment techniques. Dose distributions in the heart and in the relevant substructures are now different to before (Taylor et al 2007, Taylor et al 2009, Taylor et al 2011).

Clear and definite data on the dose-response relationships in RIHD with modern techniques are however not yet available. Some parts of the heart can still receive high doses; this is especially the case of the Left Anterior Descending Coronary Artery located close to the left breast (e.g. Lorenzen et al 2013). The large number of patients treated for breast cancer, the steadily improving prognosis and consequently the potential relevance of the long-term side effects of heart irradiation still suggest a cautious approach.

Nowadays there is a large variability among radiotherapy centres in target definition, in the dose prescription, in the dose-volume constraints to the heart, and in the criteria for accepting violations of the constraints. As a consequence there will be also considerable variability between centres in the risks of cardiac complications.

Several techniques are now available to keep the heart out of the irradiation field, either through technical solutions, e.g. synchronizing the irradiation to the breathing cycle, or choosing to irradiate only the high-risk volumes, as in the case of Accelerated Partial Breast Irradiation. With this approach high doses of radiation are delivered in fewer fractions to the tumor bed after surgery; the high risk area is the target, while the surrounding normal tissue is spared. This technique requires an accurate delineation of the target volume (the lumpectomy cavity), which is a challenge in itself due to the significant variation in the way target is delineated, depending on the clinician (e.g. Yang et al 2013). Another approach consists in treating patients prone instead of supine; a recent study provides some evidence for replacing the standard supine treatment by a prone one, and with a hypo-fractionated treatment (Mulliez et al 2013). Other special technical solutions, combining the prone position and special equipment for dose delivery has also been suggested (Ödén et al 2013).

To weigh the probability of tumor control against the probability of normal-tissue complication is a routine part of radiation therapy, just as the balance between treatment and side effects is part of medical science in general. Compared to most other medical treatments, radiation therapy is definitely one of those where the exposure, specifically the dose distribution in the target/tumor and in the normal tissues, is very accurately quantified, monitored and nowadays retrievable thanks to Oncology Information Systems which are the backbone of radiation therapy departments. The daily dose distribution as well as the dose distribution over a whole course of radiation therapy, together with imaging sets of the irradiated volumes before, during, after radiation therapy, are provided by technology which is becoming standard in many parts of the world.

There are still open issues in the study of the risk of cardiovascular disease after radiation therapy, such as the identification of radiosensitive sub-volumes in the heart and of their specific dose-response curves together with the identification of patients which are at major risk of complication due to other treatments and/or co-morbidities. In the breast cancer cases the indications are however that the risk for women who receive radiation treatment with modern techniques should be lower than in the past (Henson et al 2013). In this frame, the communication of the risk and benefits of the treatments to both professionals and to the public appears to be a subject of major relevance; some considerations about this will be provided in the lecture.

3.7 References

Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood, 2007, 109:1878-1886.

Benson JR, Jatoi I, The global breast cancer burden. Future Oncol 2012, 8(6), 697-702.

Brosius F,C., et al, Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3500 rads to heart. Am J . Med 1981, 70(3):519-30.

Carmel RJ, Kaplan HS. Mantle irradiation in Hodgkin's disease. An analysis of technique, tumour eradication, and complications. Cancer 1976;37:2813-2825.

Correa CR, Litt HI, Hwang WT, et al. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. J Clin Oncol 2007;25:3031–3037.

Cuzick J, Stewart H, Rutqvist L, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol. 1994: 12(3):447-53.

Darby S, Ewertz M, Mc Gale P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013:368,11:987-998.

Das SK, Baydusch AH, Zhou S, et al. Predicting radiotherapy-induced cardiac perfusion defects. Med Phys 2005: 32 (1):19-27.

Early Breast Cancer Trialists' Collaborative Group EBCTCG: Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomized trials. Lancet 2005;366:2087–2106.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG: Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707-16.

Fiorino C, Valdagni R, Rancati T et al. Dose-volume effects for normal tissues in external radiotherapy: pelvis. Radiother Oncol. 2009; 93(2):153-67.

Gagliardi G, Lax I, Ottolenghi A, et al. Long-term cardiac mortality after radiotherapy of breast cancer – application of the relative seriality model. Br J Radiol 1996;69:839–846.

Gagliardi G, Lax I, Rutqvist LE. Partial irradiation of the heart. Semin Radiat Oncol 2001;7:224–233.

Gagliardi G, Constine LS, Moissenko V et al. Radiation dose-volume effects in the heart. 2010; 76 (3). S77-S85.

Glanzmann C, Huguenin P, Lutolf UM, et al. Cardiac lesions after mediastinal irradiation for Hodgkin's disease. Radiother Oncol. 1994;30:43-54.

Ghobaldi G, Van der Veer S, Bartelds B et al: Physiological interaction of heart and lung in thoracic irradiation Int J Radiat Oncol Biol Phys 2012;84(5):639-46.

Hancock SL, Tucker MA, Hoppe RT et al. Factors affecting late mortality from heart disease after treatment of Hodkgin's disease. J Am Med Assoc 1993; 270:1949-1955.

Harris EE, Correa C, Hwang WT, et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. J Clin Oncol 2006;24:4100–4106.

Heidenreich P, Hancock S, Lee B et al. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol. 2003, 42:743-749.

Henson KE, McGale P, Taylor C, Darby SC. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. Br J Cancer. 2013; 108(1):179-82.

Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst 2007;99:365–375.

Høst H, Brennhovd I, Loeb M. Postoperative radiotherapy in breast cancer - long term results from the Oslo study. Int J Radiat Oncol Biol Phys 1986;12:727–732.

Joensuu H. Acute myocardial infarction after heart irradiation in young patients with Hodgkin's disease. Chest. 1989;95(2):388-90.

Lorenzen EL, Taylor CW, Maraldo M, et al Inter-observer variation in delineation of the heart and left anterior descending coronary artery in radiotherapy for breast cancer: a multi-centre study from Denmark and the UK. Radiother Oncol. 2013;108(2):254-8.

Lund MB, Ihlen H, Voss BM, et al. Increased risk of heart valve regurgitation after mediastinal radiation for Hodgkin's disease: an echocardiographic study. Heart. 1996;75:591-595.

Marks LB, Yu X, Prosnitz RG et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. Int J Radiat Oncol Biol Phys, 2005;63(1):214-223.

Marks LB, Bentzen SM, Deasy JO et al. Radiation dose-volume effects in the lung. 2010; 76 (3). S70-S76.

Martel MK, Sahijdak WM, Ten Haken RK, et al., Fraction size and dose parameters related to the incidence of pericardial effusions. Int J Radiat Oncol Biol Phys, 1998;40(1):155-161.

Mulliez T, Veldeman L, van Greveling A et al Hypofractionated whole breast irradiation for patients with large breasts: A randomized trial comparing prone and supine positions. Radiother Oncol. 2013;108(2):203-8.

Nieder C, Schill S, Kneschaurek, et al. Influence of different treatment techniques on radiation dose to the LAD coronary arteries. Radiation Oncology 2007, 2: 20.

Nilsson G, Cardiovascular side effects in breast cancer, PhD dissertation, Uppsala University, 2012, ISBN 978-91-554-8446-0. (2012 a).

Nilsson G, Holmerg L, Garmo H et al: Distribution of coronary artery stenosis after radiation for breast cancer. J Clin Oncol 2012, 30(4): 383 -386. (2012 b).

Overgaard M et al. Post-operative radiotherapy in high risk pose menopausal breast cancer patients with given adjuvant tamoxifen: Danish breast cancer cooperative group 82c randomized trials, Lancet 1999, 353 (9165), 1641-48.

Peeters ST, Hoogeman MS, Heemsbergen WD et al. Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: normal tissue complication probability modeling. Int J Radiat Oncol Biol Phys. 2006;66(1):11-9.

Rutqvist LE, Lax I, Fornander T et al. Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer. Int. J. Radiat. Oncol. Biol. Phys. 1992; 22:887-896.

Stewart JR, Fajardo LF, Gillette SM et al. Radiation injury to the heart. Int J Radiat Oncol Biol Phys 1995; 31(5), 1205-11.

Stewart JR, Fajardo LF. Cancer and coronary artery disease, Int J Radiat Oncol Biol Phys 1978;4 (9-10), 915-6.

Taylor CW, Nisbet A, McGale P, et al. Cardiac exposures in breast cancer radiotherapy: 1950s-1990s. Int J Radiat Oncol Biol Phys 2007;69:1484–1495.

Taylor CW, Nisbet A, McGale P et al, Cardiac doses from Swedish breast cancer radiotherapy since the 1950s. Radiother Oncol. 2009:90(1):127-35.

Taylor CW, Brønnum D, Darby SC, et al. Cardiac dose estimates from Danish and Swedish breast cancer radiotherapy during 1977-2001. Radiother Oncol. 2011, 100(2):176-83.

Tucker SL, Liao Z, Dinh J et al: Is there an impact of heart exposure on the incidence of radiation pneumonitis? Analysis of data from a large clinical cohort. Acta Oncol. 2014; 53(5):590-6.

Van Luijk P, Faber H, Meertens H, et al: The impact of heart irradiation on dose-volume effects in the rat lung. Int J Radiat Oncol Biol Phys 2007;69(2): 552-559

Yang TJ, Tao R, Elkhuizen PH, et al: Tumor bed delineation for external beam accelerated partial breast irradiation: A systematic review. Radiother Oncol. 2013, 108(2):181-9

Wei X, Liu HH, Tucker SL, et al. Risk factors for pericardial effusion in inoperable esophageal cancer patients treated with definitive chemoradiation therapy. Int. J. Radiat. Oncol. Biol. Phys. 2008;70:707-714.

Ödén J, Toma-Dasu J, Yu CX et al. Dosimetric comparison between intra-cavitary breast brachytherapy techniques for accelerated partial breast irradiation and a novel stereotactic radiotherapy device for breast cancer: GammaPod™. Phys. Med. Biol. 2013, 58, 4409–4421.

4 LATE EFFECTS IN CHILDREN AFTER RADIOTHERAPY

Normann Willich

Münster, Germany, for the RiSK consortium

4.1 Summary

The German Registry for the Detection of Late Sequelae after Radiotherapy in Childhood and Adolescence (RiSK) records detailed data of therapeutic irradiations and early and late toxicities following radiotherapy in children and adolescents who were treated in the therapy optimizing studies of German Society of Paediatric Oncology and Haematology (GPOH). Data collection is made prospectively, therapy study independent and Germany wide.

Organ tolerances are established by assigning radiation doses to organs or organ volumes.

Also combined treatment modalities with surgery and/or drug therapy are considered.

The aim is to optimize the treatment guidelines with respect to irradiation and its interaction with other treatment modalities particularly for future GPOH therapy optimization studies.

Till November 2013, 1578 Patients were documented. 262 of these had proton treatments. First/second/third line therapy was given to ~ 90%/~10%/~0.4% of the patients. Radiotherapy basis documentation forms and acute toxicity documentation forms are available for 1623 resp.1299 treatments. 3296 late effect documentation forms are available.

Evaluations of early toxicities of lung, liver, skin, salivary glands, lower gastrointestinal tract and of late toxicity in kidney, lung, thyroid and salivary glands showed that severe toxicities grade 3 and 4 are generally rare. In some organs (such as lungs) the lower toxicities (grade 1 and 2) occur below the so-called tolerance doses TD 5/5 depending on the irradiated partial volumes of organ.

The results of the project may have an impact on the optimization of radiation therapy in future therapy optimizing studies and on after-care programs. Improved information for children and parents may result in addition too.

The registry may also serve as a model for or as a module in a comprehensive general registry for all oncologic patients in Germany

4.2 Introduction

The use of radiotherapy is an important treatment option in the curative treatment of malignant diseases in childhood the use of radiotherapy. Radiotherapy is generally well documented with respect to its effect on the respective tumours and is reliably evidenced from the analysis of study results since the early 1980s. The significant increases in cure rates in children and adolescents in the past 30 years, going back even to the improvement of radiotherapy [1], have increasingly focused the interest in the issue of side effects of tumour treatments [2, 3].

As with any therapeutic method, a trade-off between benefits to be expected and side effects and complications to be taken into account is also made in the use of radiotherapy. The

radiogenic side effects can be divided into acute, i.e. during or immediately after radiation treatment occurring side effects, and in late effects, which become manifest after months or years after radiotherapy. As acute side effects in the course of radiation therapy may require supportive care and usually subside after completion of radiation therapy quickly, late effects generally are not reversible. Hence, they actually are limiting in the practice of radiotherapy. The occurrence of such late effects depends on the different irradiated organs as well as the applied single and total doses, and also on a combination of radiation therapy with medication and / or operations. In addition, there is often a significant age dependency, with younger patients being more affected by late effects. Also individual differences in radiation sensitivity are known.

On the incidence and in particular concerning the expression of radiogenic side effects systematic studies are largely lacking so far. Whilst numerous retrospective treatment reports describe the occurrence of different radiotherapy-associated sequelae, they deal in almost all publications with relatively small number of cases, and their general significance is controversial. Since late effects after radiotherapy may occur only after many years, many of these studies are based on radiotherapy techniques which are no longer used today. Many of these analyses have disregarded important questions for accurate irradiation performance and dosing as well as for the importance of sequentially or simultaneously administered chemotherapy and surgical interventions.

4.3 Material and methods

With the support of the German Childhood Cancer Foundation eV, it has become possible in Germany since February 2004, to establish a comprehensive, study-wide prospective detection of radiation therapy in the context of therapy optimization studies of the Society for Paediatric Oncology and Haematology (GPOH) with special reference to radiation doses to organs at risk. A study centre and the Registry for the Detection of Late Sequelae after Radiotherapy in Childhood and Adolescence (RiSK) "were established at the Clinic for Radiotherapy - Radiation Oncology -, University Hospital of Münster. In this registry, the detailed exposure data of the performed radiation treatments and, on the other hand, the acute and late effects observed during follow up are documented prospectively. The aim is to establish dose-response relationships for various organs and part of organs as a function of age and treatment modality (combination of radiation treatment with surgery and / or drug therapy) and thus to optimize the treatment guidelines for radiotherapy and its interactions with other treatment modalities, especially in the future GPOH studies [4]. In addition, information on particularly risky situations can be expressed in the individual case from the registry.

The registry is integrated into the structures of oncology in children and adolescents [5]. It cooperates closely with the Working Group of Paediatric Radiation Oncology (APRO), which mainly includes the radiation oncologists responsible in the therapy optimization studies of GPOH. The Working Group is a unit of the German Society for Radiation Oncology (DEGRO) and the German Society of Paediatric Oncology and Haematology (GPOH) [6]. The activity of the registry is anchored in the treatment protocols of therapy optimization studies of GPOH, so that the data exchange between the study centres of the GPOH and the participating hospitals with the registry is guaranteed with the consent of the parents or the patients. There is close cooperation with the LESS- (Late Effects Surveillance System) group of GPOH, which focuses on the analysis of side effects of drug therapies within the GPOH studies. There are also common data analyses with this group with appropriate data exchange [7]. There are also collaborations with other research groups in the GPOH that deal with the analysis of late effects of treatments [8]. Together with the German Childhood

Cancer Registry and the Working Group for Quality of Life of GPOH the RiSK project is part of the consortium Late Effects of GPOH.

The precise doses of radiation at the critical organs of the body are registered in standardized questionnaires which have been developed in cooperation with the APRO. For this the generally available modern tools of computerized three-dimensional treatment planning with the corresponding analytical possibilities of organ loads are used. This also allows the accurate recording of dose burden of organ portions in the form of dose-volume histograms, for example for lungs, kidneys, liver and heart. For dose detection at gonads or thyroid gland also direct dose measurements at patients are used. The observed levels of toxicity are graded according the score of RTOG / EORTC. After appropriate data control, the data is transferred to the register [9].

4.4 Results

Until November 2013, 1578 Patients were documented from 62 centres. There were 1623 radiotherapy basis documentation forms (first therapy ~ 90%, recurrence 1 ~10%, recurrence 2 ~0.4%). 1299 documentations of acute toxicity and 3296 documentations of late toxicity were recorded.

So far, analyses of the dose(-volume-)effect relationships after radiotherapy in childhood were done with respect to acute toxicity for lungs, liver, skin, salivary glands, lower gastrointestinal tract [10], and with respect to late toxicity for kidneys [11], lungs, salivary glands and thyroid gland [12]. Further analyses are in progress.

The existing analyses showed that severe toxicities grade 3 and 4 are generally rare (fig. 1 and 2). Out of 74 patients whose kidneys had been lying partially or entirely in the irradiated region, 65 had no late toxicity, seven a maximum late toxicity grade 1, two a maximum late toxicity grade 2, while late toxicity grade 3 or 4 did not occur [11].

A similar picture emerged in the evaluation of pulmonary toxicity. Of 120 patients with documentation of acute toxicity 100 patients had a toxicity grade 0, sixteen patients had grade 1, two patients had grade 2, while the toxicities grade 3 and 4 did not occur [10].

With regard to late toxicity no toxicity was documented for 74 patients, fourteen patients had grade 1, four patients had grade 2, three patients had grade 3, and one patient had grade 4. Three of the four patients with grade 3 and 4 toxicities had significant special features (1 x phrenic nerve paralysis, 1 x reirradiation in recurrent lung tumour, 1 x severe postoperative scarring), which made them to risk patients with respect to radiation

The fact that the serious toxicities rarely occurred reflects the generally careful behaviour of the radiation therapists who respected obviously the well-known approximate tolerance limits (TD 5/5) of the various organs. This is also obvious from fig. 3, which shows the dose volume histograms of 167 patients with thoracic irradiation. Normally the approximate tolerance limit of the lung is said to be at about 20 Gy. Accordingly, fig. 3 demonstrates that whole lung irradiation was carried out with doses of 15 Gy to <20 Gy (the curves between the indicated dose values are linearly interpolated), but that doses of more than 20 Gy were administered only to smaller and smaller lung parts.

Multivariate analysis of the acute toxicities of lung revealed that even at lower doses low toxicities were recorded when the irradiated lung volume had reached a certain level (Fig. 4). This relationship was significant over the dose range of 5 to 15 Gy for grade 1 toxicities [10] and was also significant for maximum chronic toxicity grade 2 at a dose of 15 Gy (Fig.5).

4.5 Discussion

Analyses of this kind, basing on a higher number of cases and going more into details, can obviously provide information about the tolerance of organs and parts of organs and may therefore be of help in the design of future therapeutic trials.

With a larger number of cases also the investigation of possible age dependence and the time course of the occurrence and the development of toxicities should be possible. The special value of such studies lies in the fact that the data base is derived from current and modern clinical patient treatments, so that the analysed treatment techniques are not already obsolete, as is the case with many retrospective analyses.

The registry can also provide information on requirements in the aftercare. An analysis of 264 patients in which at least parts of the thyroid and / or the pituitary gland had been located in the irradiation field, resulted in a significant dose dependency in the development of latent hypothyroidism after a median follow up time of 40 months. In the different dose groups (prophylactic cranial irradiation 12 Gy, direct irradiation of the thyroid gland 15-25 Gy, direct irradiation of the thyroid gland >25 Gy, cranio-spinal axis irradiation with thyroid gland doses of about 30-36 Gy) dose-dependent pathological T3-, T4- and TSH levels developed in about 60% after five years in the highest dose group (Fig. 6a). The comparison with Figure 6b, which shows the beginning of the substitution of thyroid hormone makes it clear that obviously the substitution took place only after a longer observation period and then not in all cases [12]. Here the registry data demonstrate that attention is to be paid to the development of a least latent hypothyroidism in the follow-up.

The idea of a prospective registry study to collect radiotherapy-related toxicities in the context of multimodal therapy of tumour diseases in childhood and adolescence was only possible after the mid-1990s, when the computerized three-dimensional treatment planning was everywhere present in Germany. Because of the long latency time of chronic side effects of radiotherapy the study is in its character a long-term project, which needs still an increase of patient numbers in order to perform more detailed analyses regarding age, fractionation, combination therapies with drugs and / or surgery as well as the time of occurrence and course of side effects. It is helpful, therefore, that in Sweden a similar register has developed, which operates substantially identical to the German registry, so that a data pooling will be possible.

4.6 Conclusions

The German Registry for the Detection of Late Sequelae after Radiotherapy in Childhood and Adolescence (RiSK) collects detailed radiation treatment data and side effects of treatment in a prospective way. The results of the project may have an impact on the optimization of radiation therapy in future therapy optimizing studies and on after-care programs. Improved information for children and parents may result in addition too. The registry may also serve as a model for or as a module in a comprehensive general registry for all oncologic patients in Germany.

4.7 Acknowledgement

This work is supported is supported by Deutsche Kinderkrebsstiftung e. V..

4.8 Tables and figures

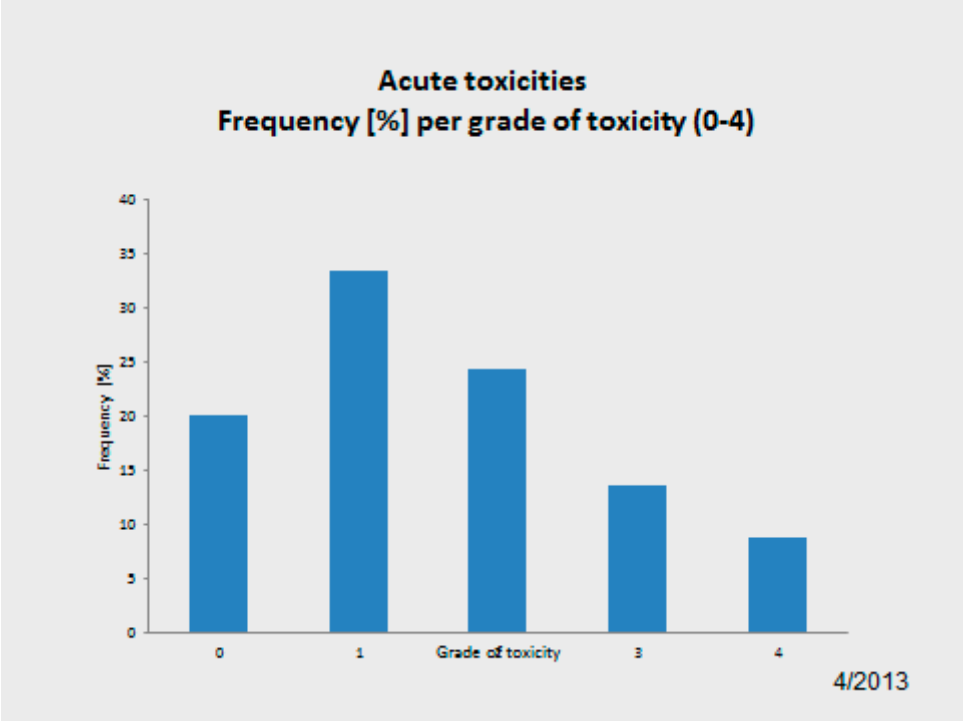


Figure 1: Acute toxicities. Frequency [%] per grade of toxicity [0 – 4]

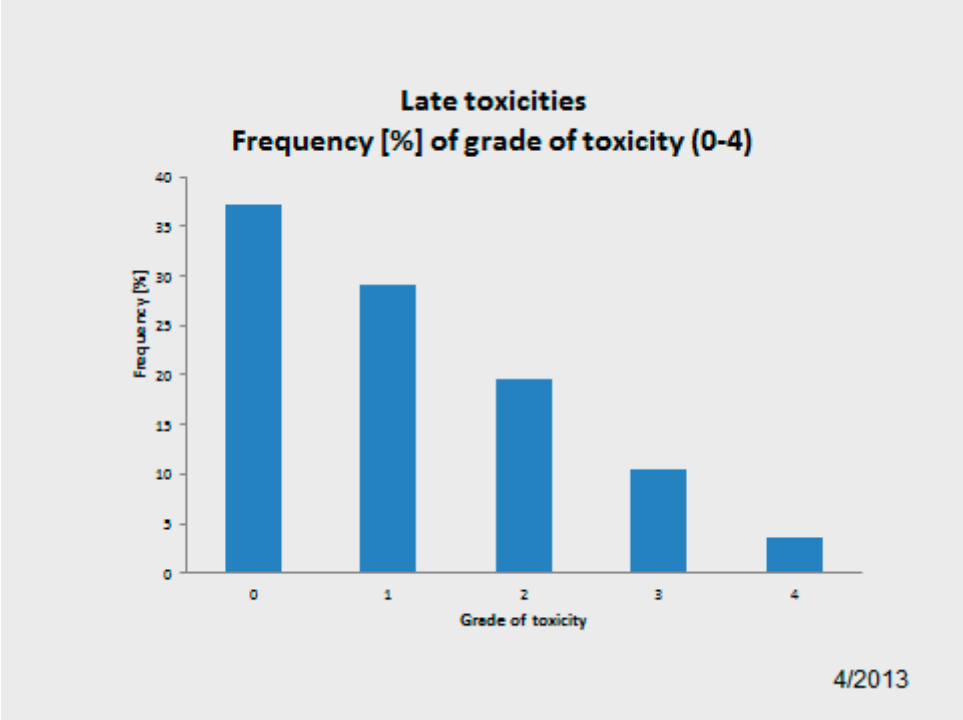


Figure 2: Late toxicities: Frequency [%] per grade of toxicity [0 – 4]

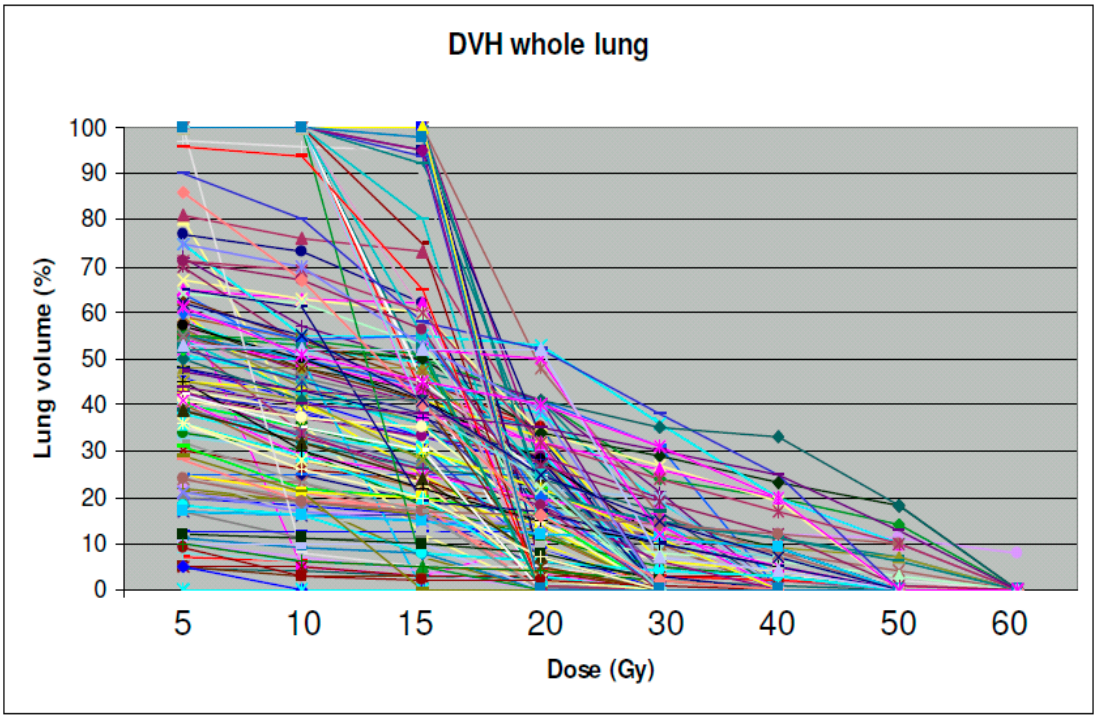


Figure 3: Dose-volume-histograms whole lungs. N = 167

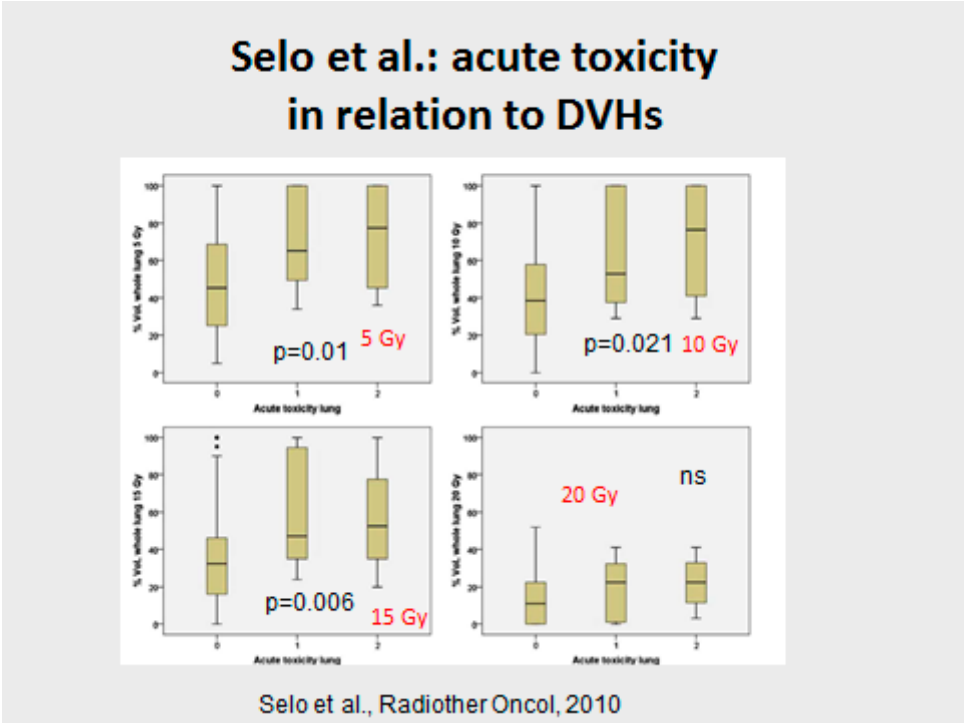


Figure 4: Dose distributions in the whole lung in patients with and without acute side effects for V5, V10, V15, V20, representing the lung volume exposed to 5, 10, 15 and 20 Gy. Significant findings in comparison of patients without and with grade 1 side effects for V5, V10 and V15 (10)

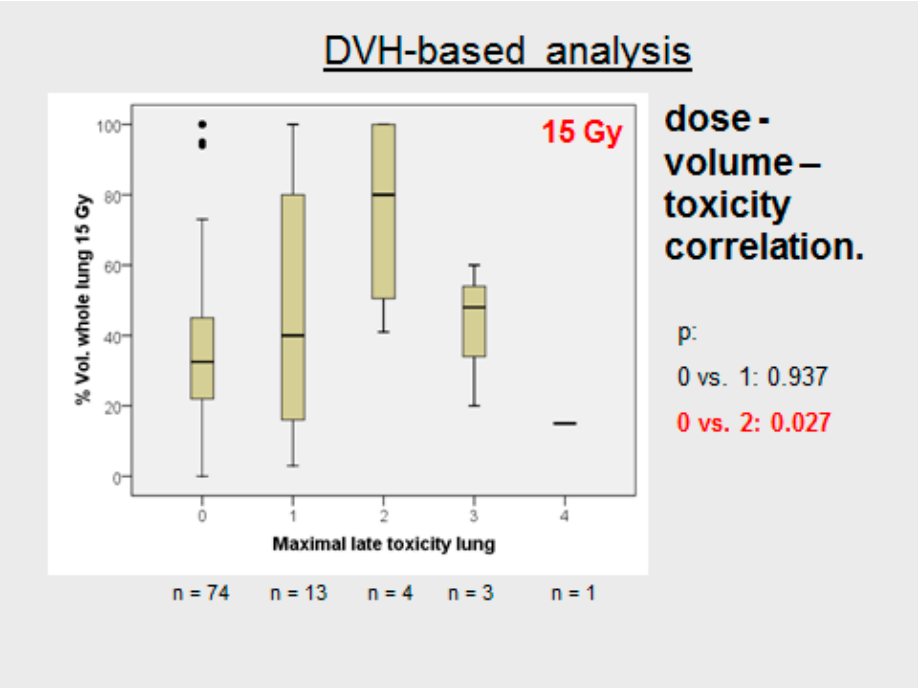


Figure 5: **Dose distributions in the whole lung in patients with and without late side effects for V15, representing the lung volume exposed to 15 Gy. Significant finding in comparison of patients without and with grade 2 side effects for V15**

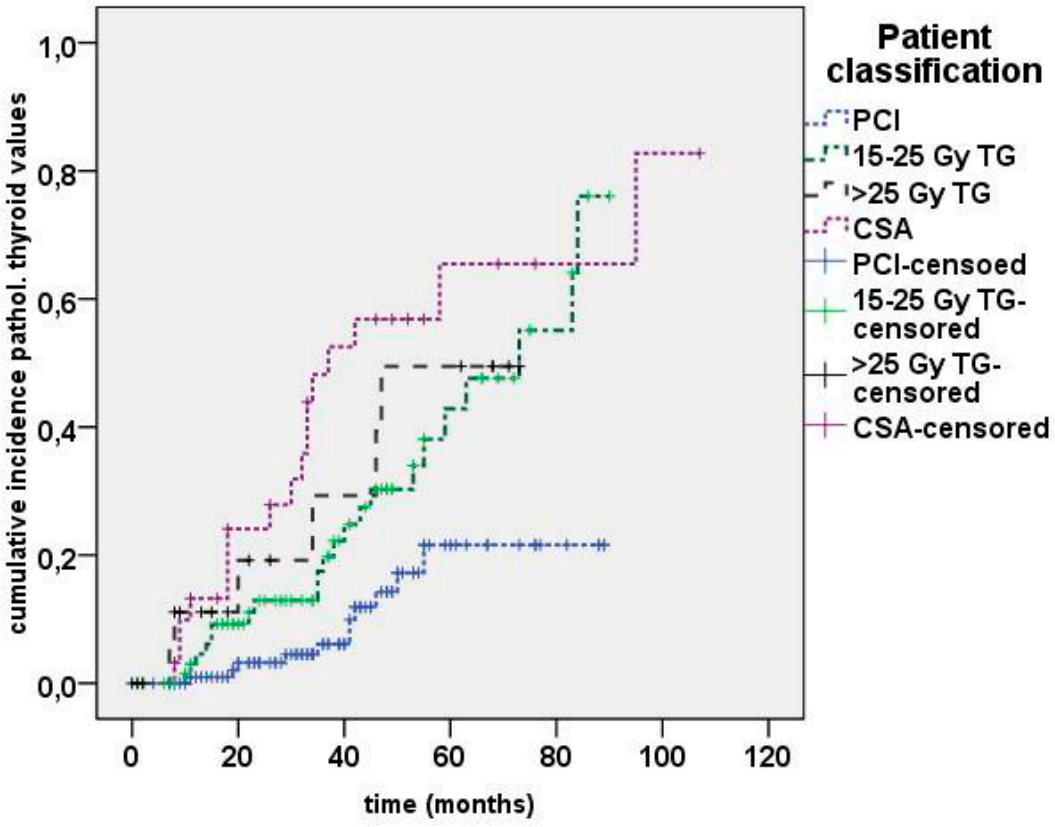


Figure 6a: Cumulative incidence of pathologic T3-, T4-, and TSH levels. Differences between subgroups are statistically significant (p=<0.000). PCI = prophylactic cranial irradiation; TG = thyroid gland irradiation; CSA = craniospinal axis irradiation (12)

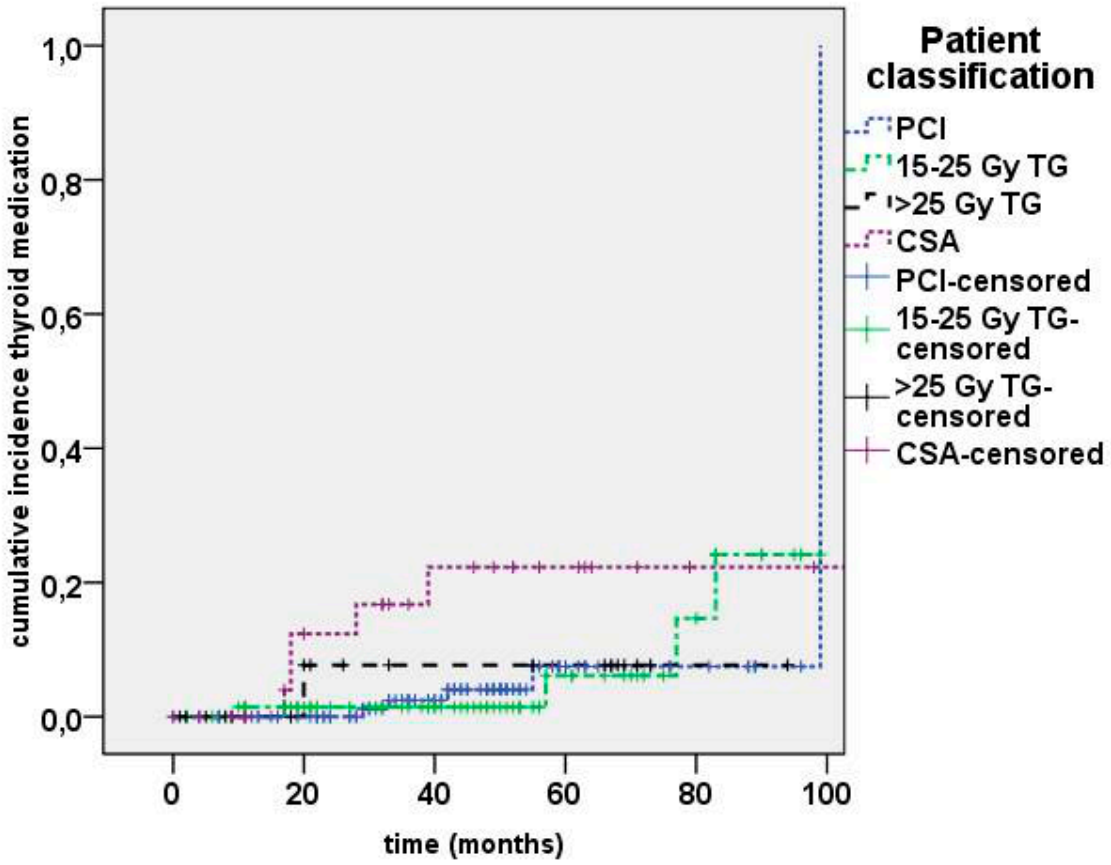


Figure 6b: Cumulative incidence of thyroid hormone substitution (12)

4.9 Literature

[1] Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer. A report from the childhood cancer survivor study. JAMA 2003;290:1583–92.

[2] Leisenring WM, Mertens AC, Armstrong GT, et al. Pediatric cancer survivorship research: Experience of the Childhood Cancer Survivor Study. J Clin Oncol 2009;27:2319-2327.

[3] Robison LL, Armstrong GT, Boice JD, et al. The Childhood Cancer Survivor Study: A national cancer institute–supported resource for outcome and intervention research. J Clin Oncol 2009;27:2308-2318.

[4] Willich N, Ernst I, Pape H, Rübe C, Timmermann B, Asadpour B, Kortmann RD, Bölling T. Evaluation of side effects after radiotherapy in childhood and adolescence: From

retrospective case reports to a prospective, multicentric and trans-national approach. Strahlenther Onkol. 2009 Aug;185 Suppl 2:3-4.

[5] Calaminus G, Kaatsch P. Position paper of the Society of Pediatric Oncology and Hematology (GPOH) on (long-term) surveillance, (long-term) follow-up and late effect evaluation in pediatric oncology patients. Klin Padiatr. 2007;219:173-178.

[6] Kortmann RD, Bongartz R, Dieckmann K, Dunst J, Flentje M, Gademann G, Christiansen H, Kamprad FH, Karstens JH, Pape H, Rühl U, Schmidt BF, Willich N, Schulz-Ertner D, Schwarz R, Timmermann B, Pohl F, Klingebiel T, Jürgens H, Rübe C: 46. t [Requirements and performance profile of the Paediatric Radiation Oncology Working Group (APRO): evaluation of the present situation and description of future developments] Klin Padiatr. 2007 May-Jun;219(3):166-72.

[7] Paulides M, Dörr HG, Stöhr W, Bielack S, Koscielniak E, Klingebiel T, Jürgens H, Bölling T, Willich N, Sauer R, Langer T, Beck JD. Thyroid function in paediatric and young adult patients after sarcoma therapy: a report from the Late Effects Surveillance System. Clinical endocrinology 2007; 66: 727–731.

[8] Schellong G, Riepenhausen M, Bruch C, Kotthoff S, Vogt J, Bölling T, Dieckmann K, Pötter R, Heinecke A, Brämswig J, Dörffel W.: 8 .Late valvular and other cardiac diseases after different doses of mediastinal radiotherapy for Hodgkin disease in children and adolescents: report from the longitudinal GPOH follow-up project of the German-Austrian DAL-HD studies. Pediatr Blood Cancer. 2010 Dec 1;55(6):1145-52.

[9] Bölling T, Schuck A, Pape H, Rübe C, Pöllinger B, Timmermann B, Kortmann RD, Dieckmann K, Willich N. Study protocol of the German “Registry for the Detection of Late Sequelae after Radiotherapy in Childhood and Adolescence” (RiSK). Radiat Oncol. 2008 Apr 21;3:10.

[10] Selo N, Bölling T, Ernst I, Pape H, Martini C, Rübe C, Timmermann B, Fischedick K, Kortmann RD, Gerß J, Koch R, Willich N. Acute toxicity profile of radiotherapy in 690 children and adolescents: RiSK Data. Radiother Oncol. 2010 Oct;97(1):119-26. Epub 2010 May 31.

[11] Bölling T, Ernst I, Pape H, Martini C, Rübe C, Timmermann B, Fischedick K, Kortmann RD, Willich N. Dose-volume analysis of radiation nephropathy in children: Preliminary report of the RiSK Consortium. Int J Radiat Oncol Biol Phys. 2011 Jul 1;80(3):840-4. Epub 2010 Jul 16.

[12] Bölling T, Geisenheiser A, Pape H, Martini C, Rübe C, Timmermann B, Fischedick K, Kortmann RD, Gerss J, Koch R, Willich N. 8. Hypothyroidism after head-and-neck radiotherapy in children and adolescents: preliminary results of the "Registry for the Evaluation of Side Effects After Radiotherapy in Childhood and Adolescence" (RiSK). Int J Radiat Oncol Biol Phys. 2011 Dec 1;81(5):e787-91. Epub 2010 Dec 16.

5 CT SCAN STUDIES – PRESENT RESULTS AND THE FUTURE

Mark S. Pearce

Institute of Health & Society, Newcastle University, UK

5.1 Introduction

Computed tomography (CT) imaging is a valuable, sometimes life-saving diagnostic tool, and new clinical applications continue to be identified. It is a relatively recent introduction to medical practice with the first developments in the 1960s mainly attributed to Allan Cormack and Godfrey Hounsfield. The first CT of a patient, a head scan, took place in 1971 and just eight years later Cormack and Hounsfield were jointly awarded the Nobel Prize for Physiology or Medicine for their developmental work with CT and the way that it had already improved clinical radiology practice.

CT works by sending several X-ray beams through a patient simultaneously from different angles, as opposed to a single beam in standard X-ray radiography. This creates a cross-section, or slice. The X-rays are detected after they have passed through the body and their strength is measured. Beams that have passed through less dense tissue such as the lungs will be stronger, while beams passing through denser tissue, such as bone, will be weaker. These strengths are then computed to estimate the relative density of the different tissues within the scan field, and a two-dimensional image is displayed on a digital monitor for viewing.

CT scans are available worldwide at over 30,000 centres and usage is continuing to increase. CT was originally developed for brain imaging, but has since advanced to mean that almost any part of the body can be imaged for a wide range of clinical reasons. CT remains especially useful for assessing the brain, particularly checking or bleeding, aneurisms or brain injuries (as it is much quicker than MRI, although MRI can depict brain anatomy in more detail than can CT). It can also be used to locate solid tumours and abscesses throughout the body and to assess suspected internal injuries such as damage to the kidneys, liver, spleen or bone. In some healthcare settings, CT is used for suspected appendicitis, but historically this has not been the case in countries such the United Kingdom where a physical examination, and possibly scanning using ultrasound takes place. While mainly used for diagnostic purposes it is also used in treatment planning and monitoring, for example prior to and after radiotherapy, and also for the guidance of biopsies.

Although similar trends in increasing use of CT have been seen in many countries (Brenner, 2012), the use of CT varies widely between populations, with the highest usage rates in Japan and the United States (US). In 2011, current usage of CT was 80 million per year in the US and 3 million per year in the United Kingdom (UK) (Brenner, 2012). As the US is about 5 times the size of the UK, this difference in CT usage reflects much more than just differences in population size. Effectively, it can translate as the US having 5 times the CT use of the UK when population size is taken into account, although it may be lessened if multiple scans per patient are higher in the US than in the UK. It is also likely that the cultural aspects of the differences in healthcare systems play a role, for example, payment for healthcare, profits from using CT and greater legal consequences of errors could all be

involved. However, clinical training and philosophical views on CT use, for example, related to the suspected appendicitis example given earlier, will also impact on CT usage.

In the UK, just 11% of all medical imaging examinations are CT scans, but despite this being a low proportion of medical examinations it makes up nearly 70% of the total collective dose to the UK population from medical X-ray examinations. The dose from one CT scan is thought to range widely, from 5 to 100mSv (Hall & Brenner, 2008), with dose being dependent on a number of factors, including the part of the body scanned, the age, size and sex of the patient, the type of scanner, the machine settings (and how they are used, which introduces an operator component as well as differences in protocols). Globally, CT scans have the highest contribution (approximately 4 million person-Sv/year) of any diagnostic imaging modality to the collective effective dose (UNSCEAR, 2010).

5.2 Early concerns and risk projections

The main early fears surrounding the use of CT, particularly CT in young people arose in 2001, with three papers in one issue of the American Journal of Roentgenology (Brenner et al, 2001; Donnelly et al, 2001; Paterson et al, 2001). The study by Brenner et al estimated that of the 1.5 million children in the US who had CT scans of the head and abdomen every year, around 1,500 of those would eventually die from a cancer induced by the radiation of those scans (Brenner et al, 2001).

The other papers focussed on the doses that children were receiving and strategies for dose reduction. Donnelly et al showed that too many of the CT scans done in the United States were giving children adult size doses - much higher doses than were necessary (Donnelly et al, 2001). This prompted more risk projection studies, most of which used expected doses and extrapolated expected cancer risks, i.e. they had no or little empirical data. Projections were often limited to certain types of scans, often with only mortality outcomes, which is not the best approach for cancers with good survival rates. They also used risk projection models based on modern protocol adjustments, which may not have been relevant to exposures in the past. Risk projection modelling is still on-going, with a focus on children, who are more radiosensitive than adults and have a longer expected remaining lifespan in which to demonstrate radiation effects. A paper from Miglioretti et al published in 2013 took a similar approach to that by Brenner et al over ten years earlier. They estimated that the use of CT in children had risen to 4 million CT scans per year in the United States, reflecting the use of faster CT scanners and less need for sedation. They modelled the risks associated with childhood CT in seven US healthcare systems and estimated both effective and organ doses. With these doses, they projected that the 4 million CT scans in children would lead to nearly 5,000 excess cancers. They concluded that reducing the doses to the 25% highest exposed patients would prevent 43% of these cancers. One of the questions this prompts is whether we should be looking to reduce doses to all patients or just the highest 25% exposed, and whether reducing dose can be done by reducing scan usage in a way that would then reduce the risk of cancer.

Risk projection models are very useful, particularly as they have publicised the need for further radiation protection and the use of the ALARA (As Low As Reasonably Achievable) principle, and the Image Gently campaign in the US. They have also been very useful for prompting and justifying the need for empirical research through which direct observations of the relative health effects in populations that we are trying to protect can be made.

5.3 The first empirical data

The first empirical study to be published, in the Lancet in 2012, focussed on leukaemia and brain tumours in the UK (Pearce et al, 2012). Patients in the cohort had to have had one or more CT scans between 1985 and 2002, be first scanned before reaching the age of 22 years and free from cancer at the time of their first CT. Information on patients was obtained from radiology departments with available electronic radiology information system data of sufficient quality, as well as some film and paper records from a small number of hospital trusts. This gave basic information for dosimetric purposes (date and type of scan and the age and sex of the patient). Typical CT machine settings for young people taken from UK wide surveys in 1989 and 2001 were then added. Finally, these data were combined with those from hybrid computational phantoms and Monte Carlo radiation transport techniques to give estimated absorbed organ doses (Kim et al, 2012).

The patient data were linked with the National Health Service Central Registry to obtain cancer incidence, mortality and loss to follow-up, for example, from notified emigrations. Given the concerns that patients with existing cancer or symptoms may have a number of scans, scans in the 5 years previous to a brain tumour diagnosis were excluded, with a 2 year exclusion for leukaemia (although there is little to suggest that patients with leukaemia would have a CT for related symptoms). Sensitivity analyses were also done, including a 10 year exclusion period for brain tumours to address the issues of potential reverse causation.

The main findings of the UK study were that there were significant associations between the estimated radiation doses and subsequent incidence of leukaemia in brain tumours. The excess relative risk (ERR) for leukaemia in relation to red bone marrow dose was 0.036 per mGy (95% CI 0.005, 0.120, p=0.0097). For brain tumours, the ERR in relation to brain dose was 0.23 per mGy (95% CI 0.10, 0.049, p<0.0001). These results suggest that a tripling of risk of leukaemia would be at around 50mGy and for brain tumours at around 60mGy. Assuming typical current doses to children in the UK, this would need 5-10 head CTs to give a 50mGy to the red bone marrow, but only 2-3 head CTs to give 60mGy to the brain. Excluding all CT scans in the ten years prior to brain tumour diagnosis gave a higher dose response than in the original analysis with a 5 year exclusion. This is the opposite to what would be expected if bias from a CT-related diagnosis was driving the findings and this goes against the suggestions that the findings are only due to reverse causation.

There are a number of strengths and weaknesses in the UK study. The use of empirical data and the cohort approach avoided recall bias, so by taking exposure data from medical records there was no contact with participants and no potential for bias. The UK has nationwide cancer registration with 97% ascertainment. A careful approach to avoid those with existing cancers was taken, as is evident by the sensitivity analyses that showed that brain tumour risks remained increased with a ten year exclusion. Reverse causation should not be an issue for the leukaemia data. There is still a chance that some patients would have had CT scans for more than ten years before eventually being diagnosed with a brain tumour when the initial scan was effectively for the same symptoms, but the number of such patients is likely to be very small. The dosimetry was an improvement on previous estimates and provided organ doses. However, there are still likely to be uncertainties.

The second empirical study came from Australia and was published in the British Medical Journal in 2013 (Matthews et al, 2013). They also used a cohort study and studied 10.9 million people identified through the Australian Medicare system. Patients were aged under 20 years at the time of the first CT and scans were between 1985-2005. The exposed cohort included 680,211 patients, so was much larger than the UK study. The dosimetry was less detailed than in the UK study and primarily based on effective doses. When considering all cancers combined between the exposed and unexposed groups, they showed that the incident rate ratios (IRR) fell with increasing lag times. With a lag time of just one year the IRR was 1.24 (95% CI 1.20, 1.29), at five years it was 1.21 (95% CI 1.16, 1.26) and at ten

years the IRR fell to 1.18 (95% CI 1.11, 1.24). This clearly demonstrates some aspects of reverse causation within their findings. With an exclusion time of one year for all cancers this would include many solid tumours where it can easily take a year for a diagnosis to be made. However, similar to the interpretation of the UK study, the incident ratio was still significantly raised at ten years, suggesting again that reverse causation would not explain the findings. They also produced IRRs for specific cancers and found raised IRRs for nearly all cancer types. However, this prompts some further concerns, because raised rates were found for Hodgkin's Lymphoma and melanoma which are not normally associated with radiation risks. In addition, despite finding raised rates for nearly all cancer types, they did not find significantly raised rates of breast cancer or lymphoid leukaemia, which are thought to have a radiation component in their aetiology.

The Australian CT study shares a number of strengths and weaknesses with the UK study, but there are some additional points to consider. The first is their definition of exposed individuals. The study is missing exposures from tertiary hospitals, excluding a large exposed patient group and meaning that some of the unexposed would really have been exposed. It also means that there are likely to be missing exposures where patients classed as exposed were also treated at the tertiary hospitals. However, missing such data is likely to mean that the results are underestimating an association between CT scan use and cancer risk, rather than being the reason for the association existing.

5.4 Current research

Before the UK and Australia studies were published, similar studies were underway in Canada, Israel, Sweden and France. In 2011, a new EU-funded collaborative study called EPI-CT began, following a successful feasibility study (CHILD-MED-RAD, also funded through the Euratom programme). EPI-CT has a number of objectives. The first is to establish a large multi-national European cohort of paediatric and young adult patients who have received CT scans. This will allow a description of the patterns of use of CT over time and between countries. A major aim of EPI-CT is to make further improvements to CT dosimetry for this patient group by using parameter data downloaded from Picture Archiving Communication System (PACS) (Thierry-Chef et al, 2013). This is possible using the PerMoS software developed in Luxembourg (Jahnen et al, 2011). While this is unlikely to be possible for the entire multi-national European cohort, particularly as many of the scans to be included precede the introduction of PACS, this will improve the dosimetry for the cohort studies. Subsequently, the primary aim is to evaluate the radiation related risk of cancer in the combined cohort. There are also two further parts to EPI-CT that are outside the epidemiology aspects. The first concerns dose and image optimisation, with an aim of providing recommendations for a harmonised approach to CT optimisation for paediatric patients all across Europe. There is also a sub-study to pilot the testing of biological markers of CT irradiation effects (El-Saghire et al, 2013).

Another new study is underway in Brazil, initially looking at trends in CT usage, with plans to establish an epidemiology study using the EPI-CT protocol. One of the main advantages of this international collaboration is that most studies are using a similar study design and are collaborating over dosimetry methods. This will allow pooling of data in the future with much greater statistical power than just one study alone.

5.5 The future

While this entire report comprises my own personal views, this is especially true of the following, in which I outline where I think we need to make improvements to both policy and research within this field. Firstly, we need more empirical evidence as to what the risks associated with CT are. This will come from the on-going and planned studies. We need further risk-based analyses of all the cohorts, including pooling of cohorts for greater statistical power to give us the ability to look at rarer cancer types and sub-types. We need to be able to do more in terms of incorporating uncertainties into our analyses, primarily the uncertainties in dosimetry. This work is on-going within the UK CT Study and within EPI-CT. We need more long-term follow-up of all these cohorts, which will require funding, and we need more cohorts to be added, including those from different types of countries with different healthcare settings or at different stages of development (for example, as we are already trying to do in Brazil). It would also be useful to have similar studies in adults, but this is much more difficult as the level of confounding from lifestyle factors will be much greater than would apply to studies of children and young adults.

One of the current limitations for some countries is the lack of national cancer registries. This is demonstrable within EPI-CT where the cohorts for France and Germany will be relatively smaller than they could have been due to the lack of nationwide adult cancer registration. This means that they can only include younger patients, while those countries with nationwide adult registries can include young adults as well as the entire paediatric age range. Within Europe, it would be very useful for research purposes to have high quality cancer registration in every country, covering all ages.

Most of the work within radiation epidemiology considers cancer. While this is the most established causal effect in terms of radiation, there is a growing interest in non-cancer conditions such as cardiovascular disease, cataracts and cognition. We need to be able to establish more registries of non-cancer conditions, for example, for cataracts, so that we can have a better way of really establishing whether low dose radiation may have an effect on non-cancer outcomes. Related to this, is the need for better and easier data linkage throughout Europe, to link with other data such as disease or congenital anomalies registries. While the protection of personal information is very important, the improvements in information safety are often inadvertently restricting our abilities to work as epidemiologists.

We need continued improvements in dosimetry, but also better availability of indication data (that is a true reflection of the indication rather than reporting system). We need more harmonised ethical approval systems. As has been seen in EPI-CT, the regulations vary in the different European countries as to what researchers are allowed to do and how the approval systems work. Again, the key is to make research easier to do when involved in such important patient protection studies.

5.6 Conclusions

There is still much to do to fully understand the risks associated with the radiation exposures from CT scans in young people. Small excess risks associated with CT have been shown in two studies using empirical data so far. In the UK study, we talked about a tripling of risk. However, if you multiply something small by 3 you still have something small, so if CT is used appropriately then the immediate benefits will always out-weigh the small risks. The key word here is ‘appropriately’. Simply put, of utmost importance is that, where CT is used it should only be used where fully justified from a clinical perspective.

5.7 References

Brenner DJ. Minimising medically unwarranted computed tomography scans. Ann ICRP 2012; 41: 161-169.

Brenner DJ, Elliston CD, Hall EJ, Berdon W. Estimated risks of radiation-induced fatal cancer from paediatric CT. AJR Am J Roentgenol 2001; 176; 289-96.

Donnelly LF, Emery KH, Brody AS, et al. Minimizing radiation dose for paediatric body applications of single-detector helical CT: strategies at a large children's hospital. AJR Am J Roentgenol 2001; 176; 303-306.

El-Saghire H, Michaux A, Thierens H, Baatout S. Low doses of ionizing radiation induce immune-stimulatory responses in isolated human primary monocytes. Int J Mol Med. 2013; 32: 1407-14.

Jahnen, A.; Kohler, S.; Hermen, J.; Tack, D.; Back, C. Automatic computed tomography patient dose calculation using DICOM header metadata. Radiat. Prot. Dosimetry 2011, 147, 317–320.

Kim KP, Berrington de Gonzalez A, Pearce MS et al. Development of a database of organ doses for paediatric and young adult CT scans in the United Kingdom. Radiat Prot Dosim 2012; 150, 415-426.

Miglioretti DL, Johnson E, Williams A, et al. The use of computed tomography in paediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr 2013; 167: 700-707.

Matthews JD, Forsythe AV, Brady Z, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. Br Med J 2013; 346: f2360.

Paterson A, Frush DP, Donnelly LF. Helical CT of the body: are settings adjusted for paediatric patients? AJR Am J Roentgenol 2001; 176; 297-301.

Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet 2012; 380: 499-905.

Thierry-Chef I, Dabin J, Friberg EG, et al. Assessing Organ Doses from Paediatric CT Scans—A Novel Approach for an Epidemiology Study (the EPI-CT Study). Int. J. Environ. Res. Public Health 2013; 10, 717-728.

UNSCEAR, 2010. Sources and effects of ionising radiation. Volume 1. United Nations, New York.

6 RISK COMMUNICATION

Gaya M Gamhewage

World Health Organization, Geneva

6.1 Introduction

Communicating risk is core work in both public health and clinical medicine. Much has been learnt since the late 1980's when it emerged as an area of communications in its own right. While many health and medical professionals now better understand how risk should be communicated, few use a systematic approach to determine the best strategy for risk communications.

6.2 Inspect, diagnose, treat

Many doctors, experts and communicators make a single fatal mistake when they approach communications which sets them off the right path to effective risk communications. They tend to start on the "message" – what we are going to say to the patient or other "target group". A great deal of time and effort is invested in crafting messages and communications products like leaflets and posters. But health communications is like any other field in medicine or health. The diagnosis of the problem (analysis the problem that is either manifest or hidden, and an understanding of the patient or the audience) is the most important element in treating the condition (communications strategies, channels and products).

The first critical and strategic step in communicating risk is to clarify the change you want to see in your target audiences – patients and their families – as a result of your communications. This shifts the focus from what we as communicators and experts want to say, to focussing on a change or outcome in the patient's thinking, motivation or behaviour. An example of an outcome we desire is "the patients or his or her family is convinced to trust the expert's advice, and not demand unnecessary procedures." In the communications world, this is called finding your SOCO- the single overarching communication outcome. The SOCO is not the message. It is the change that we want to see.

Step two looks in depth at the different audiences (patients and all those who influence them) and at their views on the issue being communicated versus the energy they will invest in either agreeing or disagreeing with the change you want to see. All these audiences – those who agree and those who disagree with you, those in your patient's personal circle or in the wider world - will influence your patient's reaction to what you say. See figure 1.

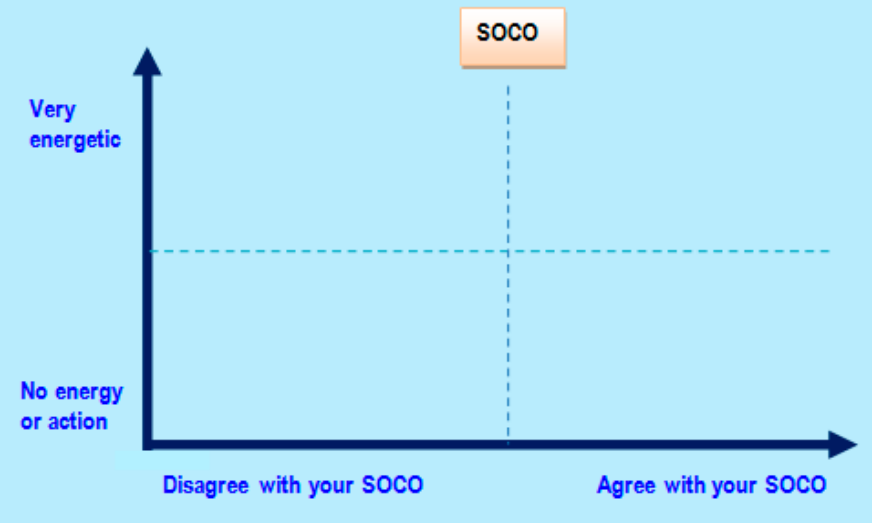


Figure 1: Audience Analysis framework

The third step deals with choosing a risk communications strategy for the patient. One practical model builds on Peter Sandman's framework for communicating risk. The model, which has been tested extensively and adapted by the World Health Organization for communicating a wide range of risks to the public, places emphasis on the perception, beliefs and emotional reaction of the target audience as well as the facts and evidence that underpin our communications.

6.3 The unpredictable factor: perception of risk

How the public and experts view risk can sometimes be diametrically opposed. Experts tend to evaluate a hazard, like clinical exposure to radiation, as being high only when there is evidence that the outcome can lead to high levels of mortality, morbidity, disability and financial loss. Therefore for experts, big hazard (along with exposure and vulnerability) means big risk. But decades of psychological, anthropological, sociological and communications research indicates that people affected by a threat respond in more complex ways that though logic.

In is now accepted that people use heuristics[1], the simple, efficient rules- to form judgments and make decisions. Heuristics are mental shortcuts that usually involve focusing on one aspect of a complex problem while ignoring others. These rules make life and decision making simple and work well under most circumstances. But they can lead to systematic deviations from logic, probability or rational choice theory. Perception of risk is influenced by many factors including controllability of the hazard, the level of voluntariness in exposure, its novelty and magnitude, the risk of fatal outcomes, however remote, the effect on future generations [2] and a myriad of cultural beliefs. It is often not based on the facts and figures you will use to make your case for or against a health intervention. Perception may not be detectable in what the patient says, but is often evident in how he or she behaves.

Another framework for understanding why people can be complacent about a real risk or outraged when there is no real danger, can be explained by the Social Amplification of Risk

[1] In the early 1970s, psychologists Amos Tversky and Daniel Kahneman demonstrated three heuristics that underlie a wide range of intuitive judgments.
[2] Slovic et al.

Framework (SARF), which outlines how communications of risk events pass from the sender through intermediate stations to a receiver and in the process serve to amplify or attenuate perceptions of risk. All links in the communication chain, individuals, groups, media, etc., contain filters through which information is sorted and understood. The main thesis of SARF states that risk events interact with individual psychological, social and other cultural factors in ways that either increase or decrease public perceptions of risk. Behaviours of individuals and groups then generate secondary social or economic impacts while also increasing or decreasing the physical risk itself.

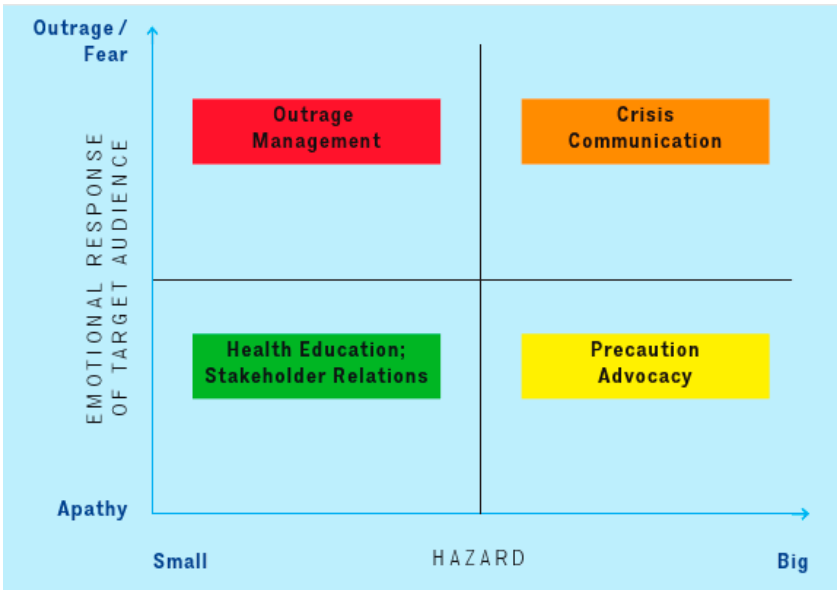


Figure 2: Risk communications strategies[3]

Therefore the perception of risk and the emotional response of the audience for a particular hazard (ranging from apathy to fear and outrage) is the next step of analysis or diagnosis for risk communication (figure 2). This emotional response of the target audience is then analyzed against the extent of the hazard as determined by technical experts. Based on this analysis, one of four risk communications strategies can be used to communicate risk: education and surveillance; precautionary advocacy; crisis communication; or outrage management. As changes occur in the perception or the magnitude of the risk over time, and changing circumstances, the analysis is repeated and the best current strategy applied. The most important thing to note is that there is no single risk communication strategy. For each of the four strategies there are key approaches and activities.

1. **Precaution advocacy**: This is when there is a real danger of harm (high risk), but low levels of emotional engagement by the audience (apathy or disengagement). An example is when patients demand a treatment or diagnostic procedure out of fear or concern for getting the best medical service (i.e. a demand for CT scan in paediatric patients when there is no clinical indication, or demand for antibiotics when there is no evidence or low likelihood of a bacterial infection). They are complacent or apathetic about the risk (of unnecessary high dose of radiation, and antibiotic resistance in these examples). In this strategy, we need to increase the patient's level of emotional engagement by warning them, using emotive language and images, of why there is a real danger and how this can be minimized. This does not mean scare the patient, but to increase their concern to match those of the experts. The key message is "watch out!"

[3] Modified from Peter Sandman.

2. **Outrage management**: This is at the opposite end of the spectrum from the first strategy. Here people are outraged without a reason to be so. A good example is when in a clinical setting there is a death associated with a vaccine, even when an investigation has ruled out the vaccine as a reason. The main strategy here is to calm people down, without being patronizing or disrespectful. First acknowledge their concerns as legitimate even if they are unfounded. Demonstrate listening by talking about these fears and concerns ***before*** explaining the facts and why there is no danger. The key message here is "calm down."
3. **Crisis communications**: Use this strategy when there is a real or potential danger and people are emotionally engaged (concerned, frightened, outraged). The most important thing to do here is to be fast, open and transparent. Be the first to make the statement on the problem even when the information is incomplete. State what you know ("we are investigating reports of …., we have heard that…., we are concerned that…"), state what you don't know at this time; and state what you are doing to find out more and resolve the situation. Show empathy and caring. Do not over-reassure. Communicate first, communicate often, and communicate frequently and predictably using the channels that the public and patients use. Address and dispel rumours and misinformation as soon as they arise. The key message here is "we are in this together".
4. **Communications surveillance**: This is the strategy to use when the hazard is relatively low, and the levels of emotional engagement by the public are also low. This is a great strategy to listen to people's concerns and identify outrage early on. In clinical settings, this can be done by analysing what patients say during consultations, running focus group discussions, doing surveys, regular meetings with colleagues and by listening to what patients groups and others are saying on the channels of their choice (web-sites, blogs, twitter, face book, meetings, etc.).

The best practice in risk communications is emerging:

- don't focus just on the facts, but get the facts right;
- make a connection with the patient, listen to their concerns, give them the right conditions to ask the questions that really matter to them;
- be truthful, admit what you know, what don't know; and what you are doing about the problem;
- and use graphics and images to make complex ideas and figures earlier to understand;
- use multiple channels and focus on the channels ***of their choice***;
- always show you care and under no circumstances do anything that will diminish the trust they have in you.

But just as more and more experts and scientists are beginning to learn about audience perception, the world has changed yet again. More and more people get health advice on the internet and on social media. 35% of the world´s population uses internet[4], and this figure is much higher in the European region. Smartphones have changed the way we live, communicate and form opinions. One in every five minutes spent on the internet is estimated to be spent on social networks which focus on the exchange of views amongst trusted friends and colleagues, instead of exchanging evidence-based information that experts rely on. Our patients, and their families and friends, exchange opinion, views, beliefs, preferences and prejudices at least as much as facts.

Increasing levels of health literacy and democratic thinking mean that the public is much more engaged in protecting and improving their health. This also means that of doctors, experts and governments are no longer viewed as the undisputed, sole source of trusted

[4] International telecommunication Union, 2013.

information or as the ultimate authority on health issues. Trust, the core currency that experts need to transact with patients, is declining.

This evolving form of health information seeking, and several decades of experience in communicating risk, introduces a new set of complexities that we must deal with in order to remain effective in our communications with patients.

The policy implications of this fast-changing and complex situation are clear.

1. **Conduct more systemic research as well as review of existing research on how risk is communicated**.
   The current research needs to be reviewed; and research gaps, especially for operational research need to be identified. Considering the diversity of the European region, with a range of socio, economic, cultural and political systems, as well as with large numbers of migrants from non-European cultures, research needs to be commissioned on key issues including, but not limited to the following:
   - How is risk perceived among different groups (including migrants to Europe)?
   - What factors that influence trust in experts and authorities in a range of European countries?
   - What role are social media and new media playing in risk communications in Europe?
   - What are the best practices in communicating risk in clinical settings in EU countries?

2. **Rewire the way we approach risk communications through capacity building.**
   Risk communications is a clinical and public health intervention, not just an afterthought. Therefore:
   - Train of teams of health practitioners, not just doctors, on general principles of and clinical application of the most current science and practice of risk communications is essential.
   - Switch our model of communicating what we know, into one of listening to our patients' fears and concerns and communicating in a way understandable and comfortable for them.
   - Infuse current and future generations of medical and health professionals with this approach and training, from including risk communications in the curricula of medical and nursing schools all the way to include seasoned clinicians through continuing education.

3. **Engage civil society and patients groups in risk communications ensured through policy, not left to chance**.
   Find systemic opportunities and create procedures for proactively identifying and responding to public and patient fears, rumours and misinformation:
   - Regular clinical discussions on patient and public concerns
   - Monitor blogs, websites and social media
   - Commission routine knowledge, attitude and practice surveys (KAP)
   - Meet with patients groups at regular intervals

4. **Track our progress with surveys of patients and how they rate our communications, as well as how closely they follow our advice.**
   Always monitor and evaluate our progress in risk communications:
   - Feedback forms in the waiting room and after consultations
   - On-line surveys
   - Focus group discussions on specific issues or following critical events

6.4 End Notes

1. The author is the head of Communications Capacity Building at the World health organization headquarters in Geneva, Switzerland with responsibility to help Governments around the world build sustainable capacity for risk and emergency communications. She is a former journalist, medical doctor and public health expert with qualifications in medicine, capacity building, health communications and international policy making and negotiation.
2. Apart from those mentioned in the footnotes, material in this paper are drawn from WHO's operational and inter-governmental work on risk communications from 2008-2013 as well as the following:

    - Participant's Handbook; WHO Communications Training Programme, 2011;
    - Peter Sandman. www.psandman.com

7 SUMMARY

Prepared by Dr René Huiskamp
Nuclear Research and consultancy Group NRG, The Netherlands, on behalf of the Working Party "Research Implications on Health and Safety Standards" of the Article 31 Group of Experts[5]

7.1 Introduction

This document provides the background, summarizes the presentations and the results of the round-table discussion, and tries to emphasize the potential implications of the Scientific Seminar on "Radiation Induced Long-term Health Effects after Medical Exposure", held in Luxembourg on 19 November 2013. It takes into account the discussions that took place during the seminar and during the subsequent meeting of the Article 31 Group of Experts, although it is not intended to report in an exhaustive manner all the opinions that were expressed. The document has been submitted for comments to the lecturers, as far as their contributions were concerned.

7.2 The Article 31 Group of Experts and the rationale of the RIHSS 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 EU Basic Safety Standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation. According to the Euratom Treaty and to their Code of Ethics, this group of experts has to give priority to the protection of health, to the safety and to the development of the best available operational radiation protection. For doing so, they have to follow carefully the scientific and technological developments and the new data coming from the world of research, particularly when these could affect the health of the exposed persons.

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. On the basis of input from the Directorate General Research of the European Commission and of information provided by individual members of the Article 31 Group of Experts, the Working Party RIHSS proposes relevant themes to the Article 31 Group that could be discussed during a subsequent seminar. After selection of the theme and approval of a draft programme by the Article 31 Group, the Working Party 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 from their own country, take part in the seminars and act as peer reviewers. The Commission convenes the seminars on the day before a meeting of

5 Besides R. Huiskamp (who was acting as rapporteur for the seminar), 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: L. Lebaron-Jacobs, A. Friedl, S. Risica, P. Smeesters (Chairperson of the WP), and R. Wakeford. They were assisted by S. Mundigl from the European Commission.

the Article 31 Group, in order that members of the Group can discuss the potential implications of the combined scientific results. 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 also valuable input to the process of reviewing and potentially revising European radiation protection legislation.

7.3 Key Highlights of Presentations at Scientific Seminar on Radiation Induced Long-term Health Effects after Medical Exposure

Renato Padovani - *Dosimetry in Radiodiagnostic Procedures, Risk Issues and Research Needs.*

The preliminary results of a large survey (DoseDataMed 2) on patient doses from the radiodiagnostic procedures (X-ray and nuclear medicine) in the European Union show a two-fold difference in the frequency and a three-fold difference in collected effective dose of X-ray procedures between countries. These differences can be attributed to different referral criteria and level of optimisation between countries. Nevertheless the mean effective dose level in Europe (1.1 mSv/y) is low compared to that observed in the US (> 3 mSv/y) and Japan (2 mSv/y).

The development of referral criteria, guidelines, optimisation tools, dose reference level assessments and digital imaging & electro technical standardisation have contributed to some extent to this low level of exposure in Europe.

With respect to patient dosimetry, ICRU and IAEA have provided guidelines and definitions to determine equipment specific dose quantities. ICRP has adopted voxel-based phantoms with a detailed representation of the human anatomy to determine organ dose coefficients for both internal and external radiation sources.

However, with computed tomography (CT), a technology that contributes most to medical exposure, equipment specific dose information such as computed tomography dose index (CTDI) is underestimating dose with wide beams and is not patient specific. For cone beam CT no solid dosimetry method is available and kerma air product is being used instead of CTDI. Regarding fluoroscopy, no real time skin dose dosimetry exists.

Dr Padovani states that patient specific dosimetry should use computational models that are procedure specific and take into account age, gender and size of the patient. Radiological equipment specific dosimetry should be harmonised and include anatomical information of the patient.

Optimisation of radiological procedures involves the use of the concept diagnostic reference level (DRL) developed in the 90's. Dr Padovani clearly indicates that the DRL has been successfully adopted, but DRL's have never been updated and are not related any more to current practice. Furthermore, compliance with a DRL is often regarded as an optimised practice. The DRL should be redefined for its role, assessment and use. Possibly, an "achievable reference level" should be introduced. From a regulatory side, more stringent requirements, external auditing and patient dose registries are needed.

Optimisation of radiological procedures also needs real time dose distribution, which takes into account computation of cumulative exposures. In addition patient dose archives using standardised reporting like a radiation dose structured report will help to compare technical

and clinical protocols, to determine inter-hospital variability in practices and to assess if patient follow-up after high doses is needed.

Mark Little – *Second Primary Cancers in Adults after Radiotherapy – an Epidemiological Review*

When datasets involving secondary primary cancer after radiotherapy are compared with age- and sex-matched subsets of the A-bomb survivor data, the excess relative risk (ERR)/Sv after radiotherapy for numerous cancer types tends to be considerably lower that after the A-bomb exposure. This is also true when the BEIR VII A-bomb derived risks with high dose (> 5 Gy) are used for comparison.

In addition, the ratio of the observed ERR after radiotherapy and the BEIR VII ERR tends to decrease with increasing mean organ dose, suggesting that cell sterilisation might be involved.

If specific second cancer sites are compared, this is particularly true for lung and leukaemia but less prominent for thyroid and breast.

In the case of breast cancer in women treated for Hodgkin's disease, relative risk clearly increases linearly with dose indicating that cell sterilization is not involved. The observed relative risk is however lower than observed in the A-bomb data set. Similar patterns have also been observed for bladder and rectal cancer in women treated for cervical cancer. In contrast, for colon and sarcoma cancer no increase of relative risk was observed in this data set.

An explanation for these findings could be involvement of stem cell repopulation in exposed tissue. Sachs and Brenner developed a repopulation model that includes cell killing and transformation and repopulation by stem cells. Transformed cells are allowed to repopulate different rate than normal cells. This model predicts the observed data for breast and thyroid cancer well when repopulation complete and mutant cells repopulate at the same rate as normal cells without a cell-killing component. However this is not the case for leukaemia and lung where risks are much less after radiotherapy.

For leukaemia, the repopulation model of Sachs and Brenner does not take in account that a rapid repopulation of bone marrow occurs after radiotherapy. The haemopoietic stem cells (HSC) originate from bone marrow or circulating blood. In addition, the role of cytokines, speed of recruitment of HSC and global or local control is not addressed. Modelling studies showed that only when joint global repopulation and rapid recruitment from HSC's to or from the blood is allowed for, risks per unit dose approach those observed in A-bomb data.

Second, dosimetric heterogeneity is not considered whereas this is an important factor for bone marrow after radiotherapy. In many radiotherapy data sets, 100 fold differences in dose to red bone marrow compartments have been observed. This is illustrated by a 3-cohort leukaemia analysis performed by Dr Little including Japanese A-bomb survivors leukaemia incidence data, UK ankylosing spondylitis patients leukaemia mortality study and the International radiation study of cervical cancer leukaemia incidence where a significant trend in relative risk for radiogenic leukaemia and a highly significant heterogeneity of red bone marrow dose between the datasets could be observed.

Dr Little indicates that a number of other considerations could play a role. Most analyses use relative risk when analysing a population of patients possibly prone to have secondary cancers. These populations have higher background cancer rates that are offset by lower radiation-associated relative risks. Dr Little suggests the use of excess absolute risk for comparisons. In addition, confounding factors like adjuvant chemotherapy should be taken into account since many chemotherapy regimes are highly leukaemogenic.

Giovanna Gagliardi – *Cardiovascular Disease after Radiotherapy*

The ideal radiation source to be used in radiation therapy, the so-called “Infinitron” delivers 100% of its energy to a tumour and zero to the surrounding tissue. Although this machine does not exist, brachytherapy, short-range radiation sources within a tumour, approaches this ideal. However, the common used radiotherapy devices deliver their dose from outside body to the target volume within the body with unavoidable energy deposition in surrounding healthy tissue. Radiation treatment will always be optimised to get best tumour control while minimizing healthy tissue related complications.

When for instance, the thorax is irradiated, besides the heart, lung, oesophagus, ribs and liver will receive considerable doses. With radiotherapy regimens for breast cancer, lung and heart are the normal structures at risk. Using treatment planning systems and dose-volume histograms, expressing the percentage of a volume of a structure receiving a certain dose, radiotherapy is optimised. A parameter being used to predict complications in the optimisation process is the V20, the volume of a structure receiving 20 Gy.

Dr Gagliardi points out that radiation-induced heart disease is a spectrum of clinical symptoms: pericarditis, myocardial disease, valvular defects and coronary artery disease.

Clinical data mainly comes from patients treated with radiotherapy for breast cancer, lymphoma, seminoma or lung cancer. Early studies in the 60’s already indicated that the heart is radiosensitive with the vascular component of the heart being most sensitive. Dr Gagliardi indicates that older studies lack adequate dose distribution information and need dose reconstruction.

However, a recent study involving radiotherapy of 101 patients with oesophagus cancer and excellent dose distribution data, showed that V30 < 46% and a mean dose to the pericardium < 26 Gy are good predictive parameters to prevent pericarditis, an acute radiation-induced heart disease.

If one considers modelling of cardiac mortality, long term effect after radiotherapy, the clinical data is limited due to low number of events and long-term complications and lack of 3-D dosimetrical data. After 3 D reconstruction of the treatment techniques a steep dose-effect relationship for cardiac mortality could be derived characterized by a D50 equal to 52.3 Gy and only a weak volume effect. A recently published population based case control study on ischemic heart disease in women treated for breast cancer shows that the rate of major coronary events increases linearly with mean dose to the heart by 7.4% / Gy with a latency period between 5-30 years after irradiation. Women with pre-existing cardiac risk factors have a higher absolute risk from radiotherapy than other women.

Dr Gagliardi also indicates that due to the fact that the target description and treatment techniques have changed, risks for woman irradiated today are considerably lower. For women receiving RT after 1982, almost no evidence of any radiation related increase in heart disease mortality compared to earlier treatments is observed. The currently used predictive parameter for long term cardiac mortality is V25 < 10%.

Open issues to be addressed are quantification of dose volume response for relevant substructures like the left descendent artery, more specific dose volume predictor parameters and identification of women at risk.

Communication about radiotherapy related risk of cardiovascular disease needs to be done carefully or otherwise patients will refrain from therapy.

In the discussion following the presentation, it was said that besides the heart the left descendent artery is possibly also a relevant target. On the question whether proton therapy could lower the dose to the heart, it was stated that for specific situations proton therapy could be better. Conventional therapy is better for routine use and does well.

Normann Willich – *Acute and Late Effects in Children after Radiotherapy: The RISK Project*

Dr Willich described the first results from the German Registry for the detection of late sequelae after radiotherapy in childhood and adolescence (RiSK) project. This registry contains data concerning early and late toxicities following radiotherapy in children and adolescents who were treated in the therapy optimizing studies of German Society of Pediatric Oncology and Hematology (GPOH).

Patient recruitment involved 1578 cases and 62 treatment centres. 262 of these had proton treatments.

Analysis was performed on acute toxicity of liver and salivary glands, acute and late of the lung and bowel and late effects in the kidney and thyroid gland.

In 80% of the cases acute effects were observed and in 73% late effects. Grade 3 & 4 toxicity was rare.

Dr Willich presented in more detail the preliminary results of 167 cases where the lung was involved and a dose volume histogram was available. In general, total lung volume received up to 15 Gy. 120 patients had documentation of acute toxicity and 95 patients showed late effects. Using a dose volume histogram analysis, a significant correlation between grade 2 late toxicity and dose volume receiving 15 Gy was observed indicating late effects lower than the tolerance dose for lung (20-22 Gy).

In the discussion following the presentation, questions were asked about late effects in the proton therapy treated patients. However data was limited. In as much dose rate is involved Dr Willich indicated that based on the shielding used during radiotherapy dose rate probably plays a role. The Risk project involves about 25% of the treatment centres in Germany.

Mark Pearce – *CT Scan Studies – Present Results and the Future*

CT is very useful, sometimes lifesaving, tool that is available worldwide at over 3000 centres. In the UK 11% of all medical imaging examinations involves CT and CT attributes 68% of the total collective dose to the UK population from medical exposure.

The frequency of CT scans in the UK and Europe is about 5 times lower than in the US due to different health care systems and differences in philosophy and training of clinicians.

Initial risk projection studies by Brenner and Donnelly showed 1 in 1000 children receiving CT will develop cancer and that children receive adult-size doses. This led to awareness and the “Image gently” campaign.

Dr Pearce pointed out that empirical data are needed to complement the projection studies and presented the UK CT scan study. In this retrospective cohort study, significant linear associations were shown between the estimated radiation doses provided by CT scans to red bone marrow and brain and subsequent incidence of leukaemia and brain tumours.

Use of CT scans in children to deliver cumulative doses of about 50 mGy might almost triple the risk of leukaemia and doses of about 60 mGy might triple the risk of brain cancer. Because these cancers are relatively rare, the cumulative absolute risks are small. Sensitivity analysis showed that when all scans were excluded 10 years prior to a brain tumour a steeper dose-response curve was observed.

Dr Pearce also reviewed the Australian CT study. This study reported increased incidence rate ratios (IRR) for nearly all cancers including Hodgkin’s lymphoma and melanoma known to be not ionising radiation related. IRR’s were not elevated with breast cancer or lymphoid leukaemia, known to be associated with ionising radiation.

The IRR’s decreased with increasing lag times indicating reversed causation.

Dr Pearce then presented international collaborative studies, like the EU funded study EPI-CT. This study aims for a paediatric and young adult patient cohort with individual estimates of organ-specific doses. In addition dose and image optimisation methods are to be developed.

Regarding future needs for CT scan epidemiology, a.o. Non-cancer effects like cataracts should be included, continuous improvement in dosimetry and harmonised ethical approval systems are needed.

Dr Pearce concluded that the clinical benefits outweigh the small absolute risks in most settings when CT is used appropriately. Where CT is used, it should only be used when fully justified from a medical perspective.

During the discussion, the question was raised whether a correlation could be observed between time after CT and the effect. This was not done since larger samples sizes are needed. The dose data from the CT studies can be used to limit dose and effect and could be used for an optimisation tool like the DRL.

Gaya Gamhewage – *Risk Communicating*

Risk communication has considerably changed. In the old days, an expert told unidirectional patients what action to take. Nowadays it is bilateral or multidirectional communication between experts and patients so that they are able to take informed decisions to protect themselves.

The outcome wanted is to engage the patient in understanding risks and benefits of radiological intervention. You need to know your audience and be aware that the public risk perception is different. Public risk perception is not only hazard driven but also directional proportional to level of emotional response evoked. Cultural, personal and subjective factors play a role.

Dr Gamhewage points out that focussing on facts is the biggest mistake a health professional can make. Experts are no longer trusted. The public acquires health advice through Internet. Media like to harvest fear.

If one is involved in risk communication, remember that perception is reality, engagement is the key, use the platforms and channels your audience is using, be consistent in your message and demonstrate listening, and show that you care.

Dr Gamhewage concluded with policy implications. Research should be done on public perception. Training of teams not individuals, systematically in all professions. Civil society should be involved. The impact should be evaluated using satisfaction surveys and is advice followed.

During the discussion, the question was raised what to do when data are not clear. The advice is to communicate that the data is incomplete. When risk versus benefit is equal one should invest in more communication moments, be truthful and make clear that there are risks but recommend your viewpoint. A number of examples involving media were mentioned where public risk perception was clearly influenced.

7.4 Summary of the Roundtable discussion

Ausra Kesminiene, Eugenio Picano, Renato Padovani, Mark Little, Giovanna Gagliardi, Normann Willich, Mark Pearce, Gaya Gamhewage, Richard Wakeford (Moderator)

The round table discussion started with a moderator's introduction by Dr Wakeford in which he gave a short overview about the fact that medically exposed groups complement the evidence derived from the A bomb survivors. However, care in interpretation of data is required due to fact that exposure to radiation occurs because of known or suspected disease, radiotherapy requires high and localised doses and accurate dose estimates often are lacking. This is illustrated in the Australian CT study presented by Dr Pearce where an 24% increase of cancer after CT scan exposure is reported but the possibility of reversed causality (i.e. that the early symptoms of undetected cancer, or of factors that predispose to cancer, were the indications for the CT scans rather than CT scans causing the cancers) plays a role.

Hereafter, Dr Kesminiene presented a short summary of evidence and limitations on linking diagnostic X-rays with cancer increase in patients. The requirements of good epidemiological studies need large cohorts, sufficiently long follow-up, good dosimetry and diagnostically quality, information on confounding factors and multidisciplinary teams to address the mechanism.

Dr Picano presented the concept of 5 A's for use medical radiation in cardiovascular imaging: Appropriateness, Awareness, Audit, Accountability and Advancing knowledge.

In response to the presentations, it was stated that part of our policy should be practical: use the ALARA concept and the dose saving techniques of the CT machine. Manufacturers should provide well-trained application specialists that help to implement the dosimetry features of CT machines. Radioprotection is teamwork; it involves the medical profession, scientific community, and technology manufacturers.

Diagnostic reference levels (DRL) optimised for image quality and dose should be used to reduce doses. Parameter harmonisation between CT- machines is needed.

With respect to dosimetry it was mentioned that current treatment planning systems are not well performing in the low dose regions and need refinement to get accurate dose calculations in normal tissues. Uncertainty in doses will always remain at organ level but need an assessment of uncertainty.

Epidemiology of patients exposed to medical imaging or radiotherapy is often hampered by lack of funding for lifetime follow-up.

8 CONCLUSIONS

Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts[6]

Radiation induced long-term health effects after medical exposure have gained an increasing interest.

The advances in therapy for primary cancer have increased the overall survival of patients thus increasing the risk for adverse outcomes. Radiation therapy is in most cases an essential part of the therapy strategy for cancer and has been associated with risk of long term adverse effects like organ dysfunction and development of secondary cancers.

Secondly, the more frequent use of CT in diagnostic X-ray procedures worldwide has contributed considerably to an increase in collective effective dose. CT delivers much higher radiation doses than done with conventional diagnostic X-ray procedures. Depending on the CT procedure, this dose increase is in the order of 5 up to 400 fold the dose received with conventional diagnostic X-ray procedures. This results in effective doses up to about 100 mSv and raises the concern about future cancer risks. The risk to individuals is likely to be small but due to the large number of persons exposed involved, the risk projection models show that number of future cancers could be substantial.

Epidemiology studies show that there is a radiotherapy related risk for a number of second primary cancer types but that these risks are lower than those observed in the A-bomb survivor cohort. The cancer risk estimation after radiotherapy is influenced by the (usually non-uniform) dose to the radiosensitive target distant from the radiotherapy target volume and accurate dose estimates are often lacking. Conventional radiotherapy treatment planning systems do not calculate doses to all radiosensitive organs, but usually those close to the target volume itself and are not accurate in calculating low doses. In this context new dosimetric tools are needed.

The determination of excess relative risk per Sv might be influenced by cell sterilization in and repopulation of the radiosensitive target. In addition, most analysed cohorts involve persons that are exposed to radiation because of known or suspected disease and are also subjected to other treatment modalities like chemotherapy.

With respect to organ dysfunction after radiotherapy, a causal relationship exists between the dose to the relevant radiosensitive organ and the observed side effect but risk estimates for late effects are hampered by accurate dose estimates in the exposed radiosensitive organ during radiotherapy. More effort is needed to get an accurate dose volume response for the relevant substructures, like the left descendant artery and delineation of parts of the heart in the case of cardiovascular disease. Dose volume predictors can be used during treatment planning to optimise the radiotherapy and to minimise possible side effects in relevant organs but need further specification. In the case of radiation related mortality from heart disease after radiotherapy for breast cancer, modern treatment techniques and change of target reduced the frequency of side effects.

Concerning the use of CT, epidemiology studies clearly show that there is a significant association between the estimated radiation doses and subsequent incidence of cancer.

[6] 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 these conclusions: A. Friedl, L. Lebaron-Jacobs, R. Huiskamp, S. Risica, P. Smeesters (Chairperson of the WP), and R. Wakeford. They were assisted by S. Mundigl from the European Commission.

Care in interpretation is required since exposure occurs because of known or suspected disease. In some studies, the possibility of reversed causation cannot be excluded.

It is important to stress that the immediate benefits of CT outweigh the observed risks when CT is used appropriately. In this context, justification of the use of CT is important.

The observed intra-variation in dose per CT study type indicates a requirement for further optimisation and harmonisation of procedures and a different approach in using dose reference levels. An achievable dose level in relation to image quality and dose might be preferable. Harmonisation of specifications for manufacturers could help reducing CT doses.

With respect to epidemiology, there is still a need for large-scale studies with sufficient follow-up. Adequate follow-up can only be organised if sufficient means are provided. These studies should be multidisciplinary and also cover objectives like optimisation of radiation protection and treatment.

Communication of risk of radiation induced long-term health effects after medical exposure requires more than communicating facts. It involves two-way communication. Factors like trust, transparency, empathy and patients perception play an important role. Consultation of the Internet is competing with the medical community as source of information. The medical community should be trained in risk communication.

HOW TO OBTAIN EU PUBLICATIONS

Free publications:

- one copy:
  via EU Bookshop (http://bookshop.europa.eu);
- more than one copy or posters/maps:
  from the European Union's representations (http://ec.europa.eu/represent_en.htm);
  from the delegations in non-EU countries (http://eeas.europa.eu/delegations/index_en.htm);
  by contacting the Europe Direct service (http://europa.eu/europedirect/index_en.htm) or calling 00 800 6 7 8 9 10 11 (freephone number from anywhere in the EU) (*).

  (*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Priced publications:

- via EU Bookshop (http://bookshop.europa.eu).

MJ-XA-15-001-EN-N

Publications Office