Chapter 13
The Carcinogenic Risk in Radiation Medicine

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Introduction: Evidence for Carcinogenic Radiation Risks

Fewer than ten years after the discovery of Roentgen rays, in 1903, the first radiation-induced cancer was diagnosed in a Roentgen technologist. In many of the radiology pioneers, repeated local exposure to Roentgen rays caused skin atrophy and chronic inflammation, called roentgenoderm. Later, many of them developed skin cancer, always situated within the chronic roentgenoderm. This anatomical correlation between roentgenoderm and skin cancer was proof of causation in the radiation-exposed individual. Until 1950, radiation protection was concerned mainly with radiation-induced cancer in the individual radiologist and patient, caused by this radiobiological mechanism.

The concepts of radiation carcinogenesis and aims of radiation protection changed fundamentally through the Life Span Study in the A-bomb survivors of Hiroshima and Nagasaki, arguably the greatest epidemiological study of all times. A total of 120,000 study participants were identified in 1948 to be followed up until death; 27,000 inhabitants who were not in their city in August 1945 served as controls. In each of nearly 80,000 exposed inhabitants who survived the early effects of the bombs, the radiation doses in different organs were individually determined. In nearly half of them, the mean dose was similar to those received by modern radiology imaging procedures, the highest doses were around 5% of the doses applied to the tumour in cancer patients. The Japanese Koseki register permitted the determination of the causes of death in nearly 100% of the study participants. There has been a steady stream of publications of the results of this huge research programme. They form the most important basis of radiation risk management and of all rules and regulations in radiation protection today.

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Of about 80,000 exposed A-bomb survivors with known doses, at the time of the last analysis (Ozasa et al. 2012) 50,000 had died, and causes of death were verified. In 11,000, the cause of death was cancer. By relating cancer rates to individual doses it was estimated that overall, about 500 of the fatal cancers were caused by the A-bomb radiation, and thus the cancer rate in the A-bomb survivors attributable to radiation exposure was about 1%. With increasing latency, the absolute carcinogenic risk was increasing, approximately in line with the "spontaneous" cancer risk.

Rules and Regulations to Protect Workers from Carcinogenic Radiation Risks

The results of this epidemiological study were used to develop exposure limits for radiation workers and the general population. This was only possible by neglecting factors which affected the individual radiation risk. In 1977, the International Commission on Radiation Protection (ICRP) designed this method of risk estimation which was applicable to the average person, independent of age, sex and anatomical dose distribution (ICRP 1977). It is based on the quantification of radiation exposure as a virtual dose, called "effective dose", with the unit Sievert (Sv). This is the mean absorbed doses (in Gy) in a list of critical organs which are multiplied with fixed organ weighting factors. These range from 0.01 to 0.12, and all organ weighting factors sum to 1.0. These organ-weighted mean organ doses are then added up. The type of radiation is also weighted by factors ranging from 1 to 20. This procedure is certainly not compatible with individual risk estimation as required in radiation medicine. Organs at risk vary through life: the thyroid is most radiosensitive at the age of 3, decreases by a factor of about 10 until adolescence, moreover, sensitivity is higher in females than males; the radio-sensitivity of the mammary gland is very low in males, in females it is highest around menarche, decreases gradually in adulthood to be close to zero after menopause. By using constant organ weighting factors in risk estimation of individuals, cancer risks may be underestimated or overestimated by orders of magnitude. Another factor which dramatically varies between organs is risk dependence on dose inhomogeneity within the critical organ. All these are reasons which prompted the ICRP to warn strongly against using this method of risk estimation in individuals. The "effective dose" has no place in radiation medicine; the "dose" unit Sv may be useful in protective risk management in radiation workers or the population at large, but not in medical applications of radiation to individual patients. Unfortunately, due to lack of generally accepted alternatives, it is still used in medical radiology, both in diagnostic radiology and in radiotherapy.

The Carcinogenic Risks of Patients Undergoing Radiological Procedures

The problem is particularly urgent in *diagnostic radiology*. A patient who asks for information about the potential cancer risk from a planned diagnostic procedure is usually given a number (xx mSv) taken from tables which are designed for completely different purposes, such as for reporting the increase in radiological procedures in different countries and the associated overall radiation exposure e.g. in the reports of the United Nations Scientific Committee on Atomic Radiations (UNSCEAR). Few patient understand these numbers, and doctors feel obliged to make comparisons to everyday experiences of patients such as "this is the same as the exposure from cosmic radiation by flying from Germany to New York or the same as 2-week holidays in the Swiss Alps". Patients will quickly recognize that these comparisons are nothing but implausible excuses playing down justified concerns. This way, much trust is being lost. In fact, these comparisons are scientifically incorrect, if not rotten. There are only few studies which directly investigated the carcinogenic risk of diagnostic radiology procedures. There is only one study which provided reliable data on the risk of children to develop leukaemia caused by pelvimetric radiological investigations in pregnancy. A large epidemiological study on cancer risk from CT examinations in childhood (called EPI-CT) is currently funded by the European Commission; however, problems such as retrospective dosimetry are severe and may lead to uncertainty in the interpretation of the findings. There is urgent need to develop new approaches for the quantification and communication of carcinogenic risks in diagnostic radiology (Brenner 2008). Currently, the ICRP is discussing this problem and new recommendations are eagerly awaited.

The carcinogenic risk problem in *radiotherapy* is different. Treatment planning begins with the definition of the "target volume", i.e. the tissue volume which contains cancer stem cells. Because a hallmark of tumour cells is their ability to infiltrate into neighbouring tissue structure, this volume is always bigger than the tumour which is visible e.g. in radiological imaging. Only if all tumour stem cells are sterilized by a high radiation dose can a cure be achieved. On the other hand, in organs close to the target volume, high radiation doses may also damage normal tissues and lead to early or late morbidities. The art of the radiation oncologist is to find the right balance between chance of elimination of all tumour stem cells and keeping the severity of late normal tissue effects in the neighbouring normal organs and tissues at an acceptable level. Intensive research in clinical and translational radiation oncology has led to successful radiotherapy treatment planning and delivery.

Today, for most cancer diseases, overall local tumour control rates are over 50%, i.e. the treated cancer will not return in the treated volume during the remaining life time of the patient. Only if the cancer was much advanced and has spread to organs and tissues outside the treated body region before the start of radiotherapy, local tumour control does not mean cure. In the vast majority of irradiated patients, early

and late normal tissue side effects, if they occur at all, are mild and do not impact on the quality of life of the cured patient. Overall, with the use of advanced, modern radiotherapy techniques, the rate of severe late normal tissue side effects, i.e. those which cause chronic pain or decrease of organ function, is low, in most types of cancer diseases less than 1% of treated patients. However, as a result of this success, which was unimaginable just a generation ago, the carcinogenic risk of radiation therapy has become a top issue in translational research: Treatment-induced second cancers may be more frequent today than severe late normal tissue damage. However, this risk of second cancers induced by treatment of a first cancer with anti-cancer drugs and/or radiotherapy is currently not included in the treatment plan optimisation. Most of these second cancers will occur only several decades after the radiation treatment which cured the first cancer (de Gonzalez et al. 2011). No wonder that the radiation oncologist or medical oncologist who treated the first cancer is rarely confronted with the second cancer which may have been induced by his successful treatment of the patient.

A plethora of detailed or large clinical follow-up studies on the factors which determine the size of this risk have been published since the groundbreaking study on second cancer risk after radiotherapy of prostate cancer by Brenner et al. in the year 2000 (Brenner et al. 2000). Most of the studies with long-term follow-up relate to patients who were treated at a time when modern, high-precision radiotherapy did not exist yet. On the other hand, many studies which examine the risk of radiation-induced second cancers in patients treated with state-of-the-art radiotherapy techniques lack the necessary follow-up since treatment-induced second cancers generally occur long after the usual patient follow-up of 5 years. Moreover, different studies use different effect criteria which make comparisons, conclusions and recommendations for clinical use difficult. Their frequency can only be determined by careful epidemiological studies, preferentially nested case control studies in large patient groups which are documented in state-of-the art cancer registries such as those in Denmark. These case control studies have to be based on detailed information about the local radiation dose at the site of the second cancer in the individual patient and in the control patients at risk. Such studies are, however, very rare (Grantzau et al. 2014). Yet, there can be no doubt that both chemotherapy and radiotherapy may cause second cancers. In radiotherapy, the risk appears to depend on the radiation dose and its anatomical distribution in critical organs. In chemotherapy, much less is known about the relationship between drug concentrations and doses in critical organs. Moreover, drugs and their combinations change very frequently and dose/exposure reconstruction long after treatment is much more difficult than after radiotherapy.

The risk of second cancer induction is particularly high in paediatric radiotherapy. Large childhood cancer survivor registries in the USA (Robison LL for the Childhood Cancer Survivor Study 2009) and in Europe (Winter et al. 2015) demonstrate that with the treatment concepts and modalities applied some 30 years ago, the risk of second cancers related to the primary treatment is much higher than the risk of failure to cure the primary malignancy. These registries have been much improved recently and now also contain detailed information on more than 30,000

young cancer patients who have been treated with and cured by a variety of multimodal treatment concepts, most of them including radiotherapy alongside surgery and chemotherapy. This aggressive treatment saved their lives but at a high cost. Many developed psychological, neurocognitive and hormonal long-term deficits as well as diseases in organs which were close to the treatment volume, such as disorders of heart function. Yet, most concern focuses on the risk of treatment-induced second cancers. One of the most informative studies on the risk of radiotherapy-related second cancer after primary cancer in childhood is that of the German Working Group on the Long-Term Sequelae of Hodgkin's Disease, in which five consecutive clinical studies on altogether over 2500 patients who had been treated for Hodgkin's disease with different radiation doses and concepts were evaluated after follow-up of between 18 and 34 years. In the main follow-up (Dörffel et al. 2015), altogether 147 s malignant neoplasms were observed; the risk after 30 years of follow-up was 18.7%. Most of the second malignancies (85%) occurred in the irradiated tissue volume. Of particular importance is the study which focussed on the incidence of breast cancer in girls treated with different prescribed radiation doses for Hodgkin's disease (Schellong et al. 2014). Twenty-six cases of breast cancer were diagnosed in 590 young women after a follow-up of more than 14 years. The mean latency of the breast cancer cases was 20 years, at a mean age of 36 years. With increasing age of the patients, the breast cancer risk rose sharply, and at the attained age of 45, the absolute risk of developing a radiotherapy-related breast cancer was about one in five patients, which is 24 times the risk in a healthy women, but similar to the breast cancer risk of a woman who carries a BRCa mutation.

The current state of knowledge does not permit the development of algorithms which can be used in routine radiotherapy to optimize radiotherapy treatment plans which combine and balance a high rate of tumour cure (local and systemic) with an acceptable severity of late normal tissue effects (such as pain which can be treated effectively, functional deficits which can be compensated, fatigue and depression). Medical care for those late morbidities may be a long-term medical duty. The looming possibility that the primary treatment may have failed and the cancer may recur, and even worse, that the treatment which destroyed the cancer may have caused a second cancer, is, besides the health risk, a very severe psychological stress for many patients. Much more research effort should focus on the wide spectrum of long-term somatic and psychological health problems of the cured patient.

Worldwide, intensive research is in progress to develop methods to reduce the risk of therapy-induced second cancers without decreasing the chance of cure of the individual patient. Quite a few have been published, but all are based, inevitably, on assumptions and simplifications, which make them interesting for research purposes but not reliable for clinical oncology practice. One of the most important deficits is the fact that most are based on the effective dose concept, which by definition should not be used to estimate risk for the individual patient.

Conclusion

1. The communication of carcinogenic radiation risks to patients in diagnostic and therapeutic radiology is unacceptably poor and needs to be improved.
2. Although in radiotherapy of adult cancer patients the risk of therapy-induced second cancers is low, there is evidence that this risk can be further reduced by including this risk in the treatment planning process, yet currently no optimisation criteria are available. This problem is particularly important in radiotherapy of children.
3. Clinical and translational research in radiation oncology needs to focus on the long neglected field of treatment-induced second cancers. Currently, there is more interest in speculative modelling than in in-depth research into the potential criteria of optimizing radiation dose distribution in particular critical organs and clinical scenarios. We need new concepts and methods to reduce the carcinogenic risk in therapeutic radiation medicine.

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