

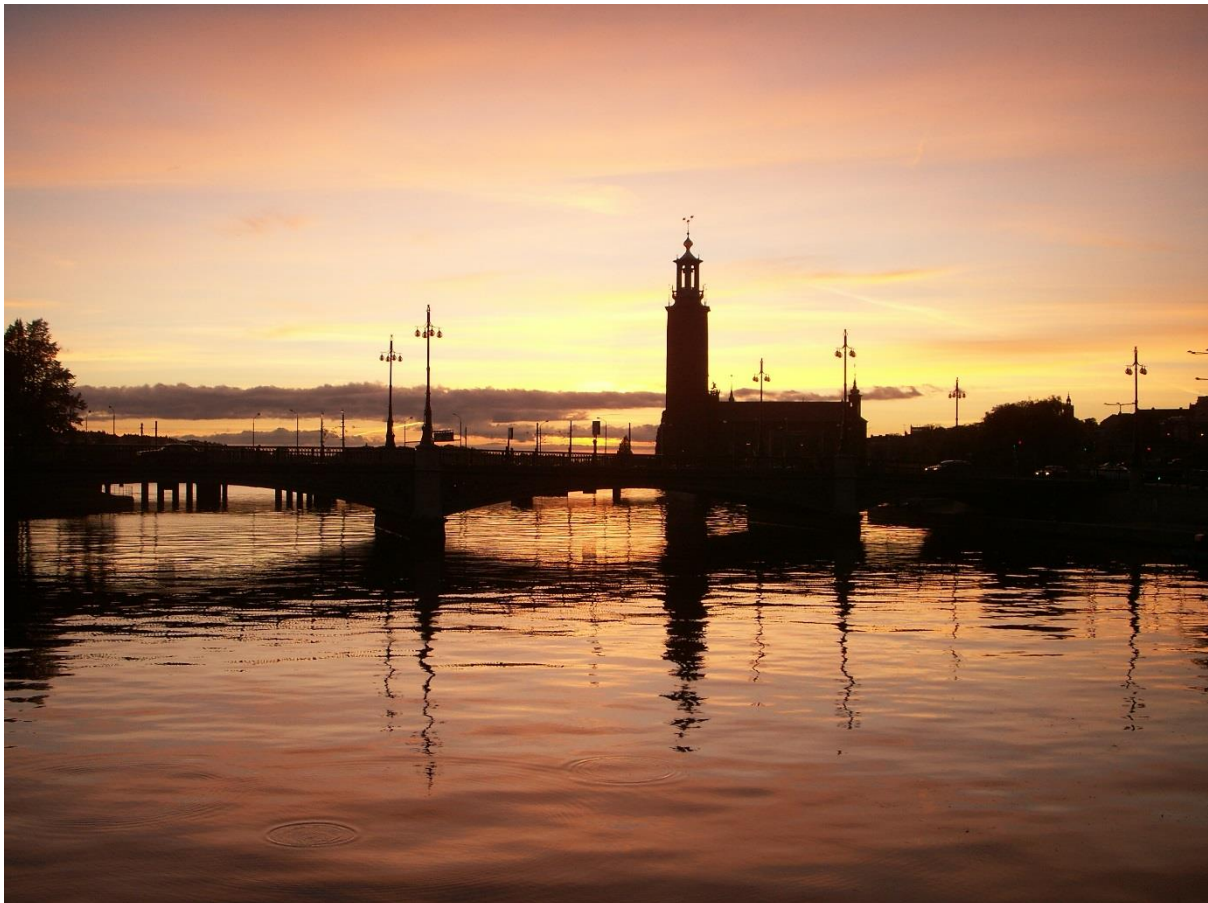


**SWEDISH NATIONAL COMMITTEE FOR
RADIATION PROTECTION RESEARCH**
THE ROYAL SWEDISH ACADEMY OF SCIENCES

Workshop on **Risk of Secondary Cancer Following Radiotherapy**

September 8-9, 2016

The Royal Swedish Academy of Sciences, Stockholm, Sweden



Sponsored by:

**RADIUMHEMMETS
FORSKNINGSFONDER**



Workshop - Risk of secondary cancer following radiotherapy

8-9 September 2016, Stockholm, Sweden

Ionising radiation is a two-edged sword with respect to cancer. On the one hand it is successfully used for treating malignant tumours; on the other hand it is a well-known carcinogen. During the last decades the life expectancy for many cancer patients has increased due to improvements in both early detection and therapy methods and therefore late effects become a matter of concern for the long term survivors of cancer therapy. Radiation-induced cancers are increasingly mentioned among these concerns, albeit they are still regarded as the inevitable price for success of modern radiation treatment. However, a broad array of treatment techniques and equipment, including heavy ions and protons, are nowadays available which are capable of delivering variable, but therapeutically isoeffective dose distribution patterns to tumours and healthy tissues. Hence, including the aspect of cancer risk in the treatment optimisation process is possible and becomes increasingly important. Nevertheless, major concerns are uncertainties about the level of risk from modern techniques, the lack of appropriate control groups in epidemiological studies, insufficient knowledge about mechanisms of cancers induced by radiotherapy, including the influence of reverse causation, and the lack of data about the relationship between cancer-inducing genetic effects and cell killing in tissues receiving fractionated radiation doses and dosimetric uncertainties.

This workshop aims to revisit the *Janus-faced* nature of radiotherapy with respect to cancer from a multidisciplinary perspective. It will address the four pillars on which the study of the risk of secondary cancer stand: **Epidemiology, Radiobiology, Dosimetry and Mathematical Modelling**. Each of these will have a dedicated session complemented by discussion sessions merging the different perspectives. We hope that the workshop will generate new ideas and approaches to estimate the risk of secondary cancers leading to a safer use of radiotherapy.

On behalf of the organizers:

Andrzej Wojcik *Centre for Radiation Protection Research, Stockholm University*

Iuliana Toma-Dasu *Medical Radiation Physics, Stockholm University and Karolinska Institutet*

Emely Lindblom *Medical Radiation Physics, Stockholm University*

Welcome to Stockholm!



SWEDISH NATIONAL COMMITTEE FOR
RADIATION PROTECTION RESEARCH
THE ROYAL SWEDISH ACADEMY OF SCIENCES

Workshop - Risk of secondary cancer following radiotherapy

8-9 September 2016, Stockholm, Sweden

Invited speakers:

James M. Allan – Newcastle University

John Damilakis – University of Crete

Alexandru Dasu – The Skandion Clinic

Mats Hansson – Uppsala University

Michael Hauptmann – Netherlands Cancer Institute

Roger Harrison – University of Newcastle upon Tyne

Stephen F. Kry – University of Texas MD Anderson Cancer Center

Loredana Marcu – University of Oradea, Romania and University of Adelaide, Australia

Lindsay Morton – US National Cancer Institute

Ludvig P. Muren – Århus University

Leslie L. Robison – St. Jude Children's Research Hospital

Wayne D. Newhauser – Louisiana State University and Mary Bird Perkins Cancer Center

Uwe Schneider – University of Zurich

Teemu Siiskonen – Radiation and Nuclear Safety Authority, Helsinki

Klaus Trott – University of Pavia

Florent de Vathaire – Institute Gustave Roussy

Workshop - Risk of secondary cancer following radiotherapy

8-9 September 2016, Stockholm, Sweden

September 8, 2016		
Introductory lecture		
08:30-09:00	Radiation therapy – a two edge sword	Iuliana Toma-Dasu
Session 1 – Epidemiological evidence for radiotherapy induced secondary cancer Chairperson: Emely Lindblom		
09:00-09:40	Radiation epidemiology for cancer radiotherapy in the US	Lindsay Morton
09:40-10:20	Radiation epidemiology for cancer radiotherapy in Europe	Florent de Vathaire
<i>Coffee break</i>		
10:40-11:20	Statistical methods in radiation epidemiology	Michael Hauptmann
11:20-12:00	The childhood cancer survivor study	Leslie L. Robison
<i>Lunch break - Klubbvillan</i>		
Session 2 - Radiobiology Chairperson: Siamak Haghdooost		
13:10-13:50	Mechanisms of therapy-related carcinogenesis	James M. Allan
13:50-14:30	Photons – radiobiological issues related to the risk of second malignancies	Loredana Marcu
<i>Coffee break</i>		
14:50-15:50	Special features of the stochastic effects of radiation in particle therapy	Klaus Trott
<i>Coffee break</i>		
16:15-17:00	General discussion	Moderator: Mats Harms-Ringdahl

19:30 *Conference dinner at Stadshuskällaren*

Workshop - Risk of secondary cancer following radiotherapy

8-9 September 2016, Stockholm, Sweden

September 9, 2016		
Session 3 - Dosimetry		
Chairperson: Irena Gudowska		
09:00-09:40	Secondary doses from particle therapy	Wayne D. Newhauser
09:40-10:20	Radiation doses from imaging	Teemu Siiskonen
<i>Coffee break</i>		
10:40-11:20	Measuring secondary doses in RT	Stephen F. Kry
11:20-12:00	Input to epidemiological studies and dose-risk models	Roger Harrison
<i>Lunch break</i>		
Session 4 – Risk of secondary cancer models		
Chairperson: Iuliana Toma-Dasu		
13:00-13:40	Review of the risk models for radiotherapy	Alexandru Dasu
13:40-14:20	Bridging epidemiology and modelling	Uwe Schneider
<i>Coffee break</i>		
14:40-15:10	Model-based predictions of secondary cancer risk following particle therapy	Ludvig Muren
15:10-15:40	Risk of secondary cancers after radiotherapy for benign diseases	John Damilakis
<i>Coffee break</i>		
16:00-16:30	Acknowledging the complexity of risk information	Mats Hansson
16:30-17:00	General discussion and concluding remarks	Moderator: Andrzej Wojcik

General information and directions

Venue

The workshop venue is The Royal Swedish Academy of Sciences, located at Lilla Frescativägen 4A, 114 18 Stockholm. The venue is most easily reached by metro or by the local tram called *Roslagsbanan*. The stop to get off at is called *Universitetet* for both options. Please use this website to plan your trip:

<http://sl.se/en/>

Tickets for all metro lines, trams, trains and buses have to be bought in advance. Please visit an SL Center (located in larger metro stops such as *T-centralen*) or one of the convenience stores to be found at basically all metro and train stations (*Pressbyrån* or *Seven-Eleven*).



Conference dinner

On Thursday, September 8 at **19:30**, the conference dinner will be held at *Stadshuskällaren*, located in Stockholm City Hall on Hantverkargatan 1, 105 35 Stockholm. The bus stop *Stadshuset* is located just by the City Hall, and buses number 3 and 50 stop there. Please refer to the above mentioned website to plan your trip.

Please also note that it is **not possible** to purchase tickets at the bus stop or on the bus, so make sure to have a valid ticket for the return trip.





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Speaker abstracts

A focus issue of *Physica Medica: European Journal of Medical Physics* will be based on the lectures presented at the workshop.

With a submission deadline of December 31 2016, the focus issue will be published in April 2017.



Speaker abstract

Mechanisms of therapy-related carcinogenesis

James M. Allan

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Therapy-related cancers arise as a consequence of prior chemotherapy and/or radiotherapy, usually given for a first cancer. A detailed knowledge of the causative exposure has made it easier to identify key somatic genetic events responsible for disease initiation and progression, and to model these in cells and animals. For example, the study of chemotherapy-related cancers has elucidated discrete mechanisms of carcinogenesis, including those associated with loss of DNA repair in cancers developing subsequent to alkylating chemotherapy, and gene translocation in cancers after treatment with anthracycline-based chemotherapy. In contrast, relatively little is known about the molecular mechanisms that drive the development of radiogenic cancer, despite ionising radiation being identified as a potent human carcinogen several decades ago. Epidemiological studies have shown that some women, particularly adolescents and young adults, are at increased risk of developing breast cancer following exposure to ionising radiation and that risk is dose-dependent. To identify genetic alterations responsible for driving radiogenic breast transformation, we have established a breast epithelial cell model system and identified somatic gene mutations (copy number alterations and base substitutions) arising as a consequence of exposure to fractionated doses of X-rays. Using this model we identified numerous alterations of the *c-MYC* gene, encoding a promiscuous transcription factor that is frequently dysregulated in human cancer. Critically, *c-MYC* alterations were observed in primary human mammary epithelial cells within days after radiation exposure, identifying mutation at this locus as a putative initiating event in radiogenic breast cancer. Using these data it is possible to develop a testable model describing the acquisition of somatic mutations in radiogenic breast cancer, which may also apply to other cancers.

Presentation given on Thursday, September 8 at 13:10-13:50.

Speaker abstract

Risk of secondary cancers after radiotherapy for benign diseases

John Damilakis

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Radiation therapy has been used to treat cancer patients. However, there is also a number of patients in radiation oncology departments being treated for benign conditions and benign tumours. In these cases, radiotherapy involves the use of moderate doses, usually 10-40 Gy in many fractions. The risk of secondary cancers after radiotherapy for benign diseases should be known to weigh benefits and risks of radiotherapy against alternative therapies such as anti-inflammatory drugs. Moreover, this information is important for radiation oncologists and referring physicians to evaluate benefits and risks of radiotherapy for a patient and inform the patient accordingly. The risk of secondary cancers after radiotherapy for benign diseases varies considerably depending mainly on the type of tissues and organs within or close to the radiation field, the age of the patient and radiation dose. This risk can be assessed from patient cohorts exposed to radiotherapy for non-malignant diseases. However, this approach requires a very long-term patient follow-up due to the long latency for cancer development after treatment. Moreover, the collection of epidemiological data is rather difficult and most of these studies are based on a relatively small number of subjects undergoing radiotherapy for benign diseases. Alternatively, the risk can be assessed using phantom studies and mathematical models. In these studies, the estimated probabilities for radiotherapy-induced malignancies are limited by the uncertainties of the applied models employed for risk assessment. During this presentation, the risk of secondary cancers after radiotherapy for several benign diseases will be presented and methods of risk assessment and their advantages and limitations will be explained and discussed.

Presentation given on Friday, September 9 at 15:10-15:40.

Speaker abstract

Models for the risk of secondary cancers from radiotherapy

Alexandru Dasu

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The interest in the induction of secondary tumours following radiotherapy has greatly increased as developments in detecting and treating the primary tumours have improved the life expectancy of cancer patients. It is currently accepted that radiotherapy leads to a small but significant risk of inducing cancers which is often referred to as ‘the price to pay’ for the effectiveness of this treatment modality. However, most of the knowledge on the current levels of risk come from patients treated many decades ago with radiotherapy techniques that are no longer used. Indeed, developments of irradiation techniques take place at a much faster pace than the progression of the carcinogenesis process and therefore results could not be easily extrapolated to newer treatment forms. Thus, the patterns of irradiation from historically-used orthovoltage radiotherapy and contemporary techniques like conformal radiotherapy with megavoltage radiation, intensity modulated radiation therapy with photons or with particles are quite different, as is the production of secondary particles in each of these techniques. Furthermore, the increased interest in individualised treatment options raises the question of evaluating and ranking the different treatment plan options from the point of view of the risk for cancer induction, in parallel with the quantification of other long-term effects. It is therefore inevitable that models for risk assessment will have to be used to complement the knowledge from epidemiological studies and to make predictions for newer forms of treatment for which clinical evidence is not yet available. This presentation will review the mathematical models that could be used to predict the risk of secondary cancers from radiotherapy-relevant dose levels, as well as the approaches and factors that have to be taken into account when including these models in the clinical evaluation process. These include the effects of heterogeneous irradiation, secondary particles production, imaging techniques, interpatient variability and other confounding factors that introduce uncertainties in risk estimations.

Presentation given on Friday, September 9 at 13:00-13:40.

Speaker abstract

Acknowledging the complexity of risk information

Mats G. Hansson

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There is no risk free society, hence a need to find an appropriate balance between benefit and risk. This is the basic challenge in all medical interventions, drug development and also in radiotherapy. The task of science is to define and assess the elements in the benefit-risk calculation but where to strike a balance is a task that requires information to and collaboration with the patient. Risk communication is a delicate matter and there is evidence that patient estimates of relative risk are at odds with what clinicians believe that the patient has understood. Numeric probabilities are interpreted differently in different contexts such as family history, etiology, environmental factors, stress and worry. Risk and probability are two separate concepts that should not be conflated. In my presentation I will give a short overview of the challenges involved in communication of risk to patients and also suggest how we may get a better grip on patient perceptions and evaluations of risk.

Presentation given on Friday, September 9 at 16:00-16:30.

Speaker abstract

Dosimetry input to epidemiological studies and dose-risk models

Roger Harrison

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Tyne, UK

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This presentation describes some aspects of out-of-field dosimetry in radiotherapy, as the basis for the estimation of second cancer induction and other late effects following treatment. It draws on experience gained by the work of EURADOS Working Group 9 (Radiation Dosimetry in Radiotherapy). The potential advantages of studying radiotherapy patients from a radiation protection point of view include the very large world-wide radiotherapy patient population, dose variation within the body from tens of Gy (target) to tens of mGy (extremities) and well documented, accurate and controlled dose delivery and follow-up. Determination of the complete dose description throughout the body may involve a complex synthesis of therapy and imaging exposures from several modalities and techniques.

The choice of phantoms for out-of-field dose measurement is reviewed, from water tanks to anthropomorphic phantoms. An important aspect of out-of-field dosimetry is the development of Monte Carlo and analytical models (for use in conjunction with treatment planning systems) which need to be validated by experimental data. Examples of out-of-field data and their value are given from the recent work of EURADOS Working Group 9 in photon and proton treatment simulations. In summary, the basic technology for out-of-field dosimetry is available, with commercially available phantoms and established dosimetry using TL, RPL, OSL, PADC and bubble detectors. However, only a limited number of measurements per organ is usually possible, leading to insufficient spatial resolution if doses to organ sub-structures are required. Other future challenges include mixed field dosimetry in proton and ion radiotherapy, the development of small neutron detectors for in-phantom measurements, measurements in dose gradients close to the target volume, the dosimetry of critical sub-structures in organs at risk and the development of widely applicable mathematical out-of-field models, verified by experiment.

Presentation given on Friday, September 9 at 11:20-12:00.

Speaker abstract

Statistical methods in radiation epidemiology

Michael Hauptmann

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Radiation epidemiology is perhaps the most quantitative field of epidemiology, characterized by the availability of large cohorts of exposed subjects. Detailed estimates of absorbed organ dose are often calculated for nested case-control samples. Moreover, extensive knowledge on radiation carcinogenesis informs model building, leading to risk models rarely used in other areas of epidemiology, e.g., linear no-threshold models. The commonly used linear excess relative risk model has less favourable asymptotic properties than standard exponential models. This can lead to bias in small studies. Two other areas of risk model uncertainty are the shape of the dose-response relationship, which is addressed by evaluating curvature, e.g., using splines, and whether the joint effects of radiation and other risk factors are multiplicative or additive. Recently, methods have been applied which more comprehensively use the often available dose distribution within an organ or subject. All described methods will be illustrated using recent cohort and case-control data of secondary cancer among survivors of cancers at various sites.

Presentation given on Thursday, September 8 at 10:40-11:20.



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Speaker abstract

Determining the dose outside the treatment field

Stephen F. Kry

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Department of Radiation Physics

The University of Texas MD Anderson Cancer Center

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This talk will be comprised of two sections. The first is practical information on how to actually assess the dose outside the treatment field. The second section is educational on how doses are assessed in the context of radiation epidemiology studies.

First, techniques and limitations will be highlighted on the three main methods of assessing dose outside the treatment field: treatment planning system calculations, measurement (x-rays and neutrons), and Monte Carlo. Recommendations will be made that are consistent with the new AAPM task group report (TG-158) on the measurement and calculation of dose to non-target structures. This talk will highlight the inaccuracy of commercial treatment planning systems beyond ~3 cm from the field edge. It will also highlight the magnitude of error introduced in x-ray measurements because of the differences in the radiation field outside versus inside the treatment in terms of differences in the spectra, dose, and dose rate. Very serious and common pitfalls in neutron measurements will be discussed, particularly addressing the challenges of in vivo neutron dosimetry. Finally, Monte Carlo methods will be explored, including the extent of modeling required for calculations outside the treatment field. Second, methods for dose determination in radiation epidemiology studies will be explored. This will include the personalized method, where each patient's record is abstracted and the dose to arbitrary points in the patient is calculated. It will also include the representative case method, where each treatment approach is considered and the dose from each approach is calculated. The basic workflow of each method will be outlined along with the limitations and major sources of uncertainty for each of the two methods. These sources of uncertainty will be contrasted with the uncertainties identified in the first part of this presentation.

Presentation given on Friday, September 9 at 10:40-11:20.

Speaker abstract

Photons – radiobiological issues related to the risk of second malignancies

Loredana G. Marcu

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Photons are widely used in radiotherapy and while they are low LET radiation, can still pose a risk in developing second primary cancer (SPC). Due to the physics of photons that distribute energy inside but also outside the target volume, out-of-field irradiation is an important component of SPC risk assessment. While there is large epidemiological evidence supporting this risk, future studies should augment epidemiology with radiobiological explanations for a better understanding of the underlying processes. Furthermore, high-energy photons are linked to the production of neutrons in the linac head, which have higher RBEs thus represent an added potential towards SPC.

There are several factors that impact second cancer risk which can be analysed from a radiobiological perspective and these are: age at irradiation, type of irradiated tissue, irradiated volume, treatment technique, previous irradiation (radiological investigations). Age-dependence has radiobiological foundation given by the higher radiosensitivity of young as compared to adult cells. This difference in radiosensitivity was shown to be correlated to the type of the irradiated tissue. Furthermore, age-dependent radiation sensitivity has a bimodal distribution, since aging cells present an increase in the oxidative stress, which can promote premalignant cells. Telomere dysfunction is also linked to radiosensitivity as radiation exacerbates the effect of telomere attrition by further compromising genomic instability.

Non-targeted effects such as radiation-induced genomic instability, bystander or abscopal effects could also impact on the risk of SPC. Recent studies show that beside the known cellular changes, bystander effects can also be manifested through increased cell proliferation, which could be a culprit for SPC development. Furthermore, new evidence on the existence of tumour-specific cancer stem cells that are long-lived and more quiescent and radioresistant than non-stem cancer cells can raise questions about their association with SPC risk.

Presentation given on Thursday, September 8 at 13:50-14:30.

Speaker abstract

Risk of subsequent malignancies after radiotherapy among adults

Lindsay M. Morton, PhD

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With substantial improvements in prognosis after a cancer diagnosis as well as aging of the population, the number of cancer survivors has increased dramatically in recent decades. Today, approximately one in five cancers occurs in an individual with a prior history of cancer. Because the occurrence of subsequent malignancies is a major cause of morbidity and mortality in this population, understanding determinants of subsequent malignancies and identifying patients with the highest risks has important clinical and public health implications. Radiotherapy has been a fundamental component of treatment for many malignancies, and yet also has been associated with risk for subsequent malignancies. Recent studies have helped to clarify the magnitude and shape of the radiation dose-response relation following radiotherapy for a number of tissues, such as upper gastrointestinal malignancies. Importantly, nearly all tissues studied to date demonstrate a linear increase in risk with increasing dose, with the exception of thyroid cancer, for which there is a downturn in risk at approximately 20 Gy. As radiotherapy techniques change, subsequent malignancy risks will need re-evaluation. A particularly key consideration is the volume of normal tissue irradiated at various dose levels, since some evidence suggests that risks may be higher for a given dose when a larger volume of tissue is irradiated, and because conformal radiotherapy techniques alter the dose distributions – decreasing the amount of tissue receiving the highest doses but increasing the amount of tissue receiving low to moderate doses (e.g., 1-10 Gy). Increasingly, factors that modify radiation-related subsequent malignancy risks are being identified, including certain systemic therapies, germline genetic susceptibility, and lifestyle factors. These factors provide clues to the mechanisms of radiation-induced carcinogenesis and identify patients at the highest risk who might benefit the most from intensive screening during long-term follow-up.

Presentation given on Thursday, September 8 at 09:00-09:40.

Speaker abstract

Model-based predictions of secondary cancer risk following particle therapy

Ludvig P. Muren

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Innovations in radiotherapy have contributed considerably to increasing the survival rates for several cancer diseases. Along with this development, increasing attention is given to the risks for causing treatment-induced side effects, also including serious long-term consequences. Radiation-induced secondary cancers are among the most severe late side effects of radiotherapy, often occurring decades after treatment.

The carcinogenic effect of radiation is established, however, with considerable uncertainties related to the effects of dose heterogeneity, age, gender, fractionation, radiation species and other patient-specific patterns. Follow-up data of radiotherapy patients with respect to secondary cancer stems from a pool of quite different treatment regimens and techniques. Due to the lack of consistent biological and epidemiologic data for the various scenarios of radiotherapy, the radiation dose-response relationship of cancer-induction is currently not known in sufficient detail. The rapid advances in radiotherapy seldom make room for adequate assessment of such late occurring effects within the life-time of a specific radiotherapy technique. To support the development of new techniques, methods for predicting long term effects from the treatment therefore becomes vital in order to confidently introduce new approaches.

Particle therapy has a considerable potential for reducing the irradiated volumes of healthy tissues. This is in general expected to have a positive effect on the risks of radiation-induced cancer. However, the carcinogenic effects of protons and heavier ions involve additional uncertainties related to radio-sensitivity and relative biological effects (RBE). These additional components must be studied in greater detail for protons, and become even more pronounced for the heavier ions. In this work we therefore investigated risks of secondary cancers for two different patient groups with respect to multiple RT techniques including use of photons, electrons, protons and carbon ions. A range of secondary cancer risk models were used for comparison of the different radiotherapy techniques for paediatric cranio-spinal irradiation (CSI) as well as a wider modelling study for radiotherapy of prostate cancer.

In the studies of the paediatric patients there was a clear tendency in favour of CSI with protons with respect to secondary cancer risk. In the prostate studies the differences in secondary cancer risk profiles (for the bladder and rectum) were less pronounced for the investigated radiotherapy techniques. Our studies have shown that future studies investigating risks of radiation-induced cancer should include multiple models as well as considering uncertainties emerging from variations in patient anatomy and organ motion. Reliable predictive models for late effects, including models for secondary cancer are vital components for exploring the use of particle therapy and for identifying the most suitable patient candidates for particle therapy.

Presentation given on Friday, September 9 at 14:40-15:10.



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Speaker abstract

External Beam Radiotherapies: The Physics of Radiation Exposures

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The high incidence of second cancers in long term cancer survivors calls for new strategies to improve outcomes. Specifically, while many second cancers develop near radiation treatment fields, the current practice for clinical treatment planning neglects most or all of the radiation dose outside the treatment field. Consequently, current practice does not attempt to predict or minimize second cancer risks for individual patients. This talk will present recent research that aims to overcome these limitations by creating dose algorithms that are suitable for routine use for patients receiving proton and photon beam radiotherapies. These include measurements, Monte Carlo simulations, and physics-based analytical models to predict radiation doses. The intervals of greatest interest include 6-20 MV photon beam energy and 70-250 MeV proton beam energy. We will review current capabilities and limitations of various approaches and implications for practical use in whole body dose reconstructions of relevance to radiogenic second cancers. Directions for future research will be discussed.

Presentation given on Friday, September 9 at 09:00-09:40.



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Speaker abstract

Investigation of the risk of subsequent neoplasms within the Childhood Cancer Survivor Study cohort

Leslie L. Robison

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In the US over 83% of children diagnosed with a malignancy will achieve five-year survival. Currently, it is estimated that there are more than 420,000 survivors of childhood cancer in the U.S. The Childhood Cancer Survivor Study (CCSS) is a multi-institutional, multi-disciplinary collaborative research resource, funded by the US National Cancer Institute (U24 CA55727), comprised of a cohort of over 24,000 five-year survivors of childhood cancer diagnosed between 1970-1999, and a comparison sibling cohort. Through the establishment of this well-characterized cohort, the CCSS resource permits investigators to conduct high quality and high impact research to understand how the diagnosis of cancer and associated therapeutic exposures impact long-term morbidity, including the occurrence of subsequent neoplasms. A strength of this cohort is the high level of treatment exposure data including cumulative doses of chemotherapeutic agents and region- and organ-specific radiation dosimetry. Research conducted within CCSS has addressed second neoplasms relative to incidence, populations at highest (and lowest) risk, host and therapeutic risk factors, and temporal changes in patterns of occurrence. Examples of recent research include: (1) impact of the volume of tissue irradiated on risk of secondary breast cancer and the substantial risk for women who received moderate doses of radiation to large chest volumes for Wilms Tumor or other neoplasms; (2) lack of risk among women who received craniospinal radiation for prophylaxis for CNS leukemia or treatment of certain CNS tumors; (3) documentation that the cumulative incidence of breast cancer among females exposed to radiation therapy involving the breast exceeds that of women with BRCA mutations; and, (4) definition of risk of breast cancer among women who did not receive radiation therapy. We have had significant impact in other areas including enumeration of the continued risk of therapy-related subsequent neoplasms among survivors who are now in their 5th and 6th decades of life. We also observed that those who survive their first subsequent neoplasm remain at significant risk for multiple neoplasms. Lastly, research is underway to investigate genetic risks for subsequent neoplasm using genotyping and whole exome sequencing of germline DNA from samples in the CCSS biorepository.

Presentation given on Thursday, September 8 at 11:20-12:00.

Speaker abstract

Risk of secondary cancers: Bridging epidemiology and modeling

Uwe Schneider

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In developed countries, more than half of all cancer patients receive radiotherapy at some stage in the management of their disease. However, a radiation-induced secondary malignancy can be the price of success if the primary cancer is cured or at least controlled. Therefore, there is increasing concern regarding radiation-related second cancer risks in long-term radiotherapy survivors and a corresponding need to be able to predict cancer risks at high radiation doses. Of particular interest are second cancer risk estimates for new radiation treatment modalities such as intensity modulated radiotherapy, intensity modulated arc-therapy, proton and heavy ion radiotherapy. The long term risks from such modern radiotherapy treatment techniques have not yet been determined and are unlikely to become apparent for many years, due to the long latency time for solid tumor induction. Most information on the dose-response of radiation-induced cancer is derived from data on the A-bomb survivors who were exposed to gamma-rays and neutrons. Since, for radiation protection purposes, the dose span of main interest is between zero and one Gy, the analysis of the A-bomb survivors is usually focused on this range.

With increasing cure rates, estimates of cancer risk for doses larger than one Gy are becoming more important for radiotherapy patients. One major difference between the A-bomb survivor data and RT-patients is that the A-bomb survivors were irradiated with more or less constant dose whereas radiotherapy patients are irradiated with highly non-uniform dose distributions, in particular in organs and tissues adjacent to the treated volume. The correlation between dose and risk is therefore non-trivial.

As the analysis of epidemiological studies and risk modeling is currently performed separately, the dose-response relationship for a particular organ, which is obtained from epidemiology, is usually taken as the input for risk modeling. This approach has several disadvantages. The size of a diagnosed tumor is already of the order of cm and thus, if detected in a highly inhomogeneously irradiated organ, it is nearly impossible to obtain the correct dose which correlates to tumor induction. Not to mention other dose uncertainties, such as patient movement, the impact of fractionation on the dose distribution, anatomical changes and others. Organ specific dose-response relationships are therefore subject to large errors not only in the obtained risk, but also in the estimated dose.

An alternative method is proposed to derive risk models for second cancer induction, which combines risk modeling and epidemiological data analysis. Risk models can be optimized in an iterative procedure by assuming certain organ specific risk models. The risk models can then be applied to the dose-volume histograms of the whole organ at risk which yields ERR or EAR for the specific patient cohort. The determined modeled risk can then be compared to the observed risk. If the calculated risk deviates from observed risk the model is adjusted accordingly. The advantage of this method is that the cancer risk values used for modeling are not dose stratified and thus subject to a smaller error. In addition the exact dose to the tumor must not be known as the optimization of the dose-response model is performed by predicting a whole organ risk based on dose volume histograms. The disadvantage is, that modeling and epidemiologic studies are mixed up.



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In the periphery, far away from the treated volume, the deposited dose is usually small (< 1 Gy) and much more homogeneously distributed than close to the target. Thus, the application of the risk models obtained from the A-bomb survivors is justified. However, in the periphery the largest remaining uncertainty is the precise knowledge of the dose distribution. Dose calculation and/or measurement are as precise as approximately 5% in the treated volume of the patient. However, in the periphery dose errors can reach 100% and more. The use of erroneous dose data can lead to wrong risk estimates. Therefore a lot of effort is undertaken to produce precise dose computations in the whole patient volume.

Presentation given on Friday, September 9 at 13:40-14:20.

Speaker abstract

Radiation doses from imaging

Teemu Siiskonen

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Imaging with ionizing radiation has become an integral part of a modern radiotherapy treatment process. Many different imaging modalities are used, some of which are better optimized dose-wise than others. Traditionally, the doses from imaging in radiotherapy have been largely neglected, based on the reasoning that the therapeutic doses are of different order of magnitude and small additional doses do not cause any significant additional harm. However, with new modalities and more frequent imaging the situation may have changed, especially when the organs and tissues outside the planning treatment volume (PTV) are considered. Moreover, imaging practices vary a lot between radiotherapy centres and it should not be taken as granted that the doses from imaging are insignificant.

Various approaches have been suggested to estimate the patient organ doses, as conversion coefficients from measured quantity to organ doses are not routinely available like in diagnostic imaging. In practice, Monte Carlo simulations based on real patient anatomy are needed. Imaging is not confined to the anatomical region the primary therapeutic beam traverses – the imaged region may extend 5 to 20 cm beyond the PTV. At 10 cm distance from the PTV the dose from imaging can contribute some 20-50% to the total absorbed dose. It is necessary to know the actual imaging parameters in simulations since even the order of magnitude of exposure may change with the level of optimization and imaging technique used. Important factors that affect the dose are the imaging technique (e.g. kV radiographs or kV cone beam CT in patient setup), use of bow-tie filter in CBCT, selection of the imaged region and the use of dose-sparing techniques such as MRI.

Presentation given on Friday, September 9 at 09:40-10:20.

Speaker abstract

Special features of second cancer risk after particle radiotherapy (neutrons)

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The main argument for considering the use of charged particle radiations in radiotherapy is their favourable dose distribution. This is particularly beneficial, when critical normal organs or tissues are anatomically close to the PTV. Only for reasons of anatomical geometry is the main indication for using protons or other charged particles the radiotherapy of childhood cancer. Impressive as dose distributions in physical treatment plans appear, there are also radiobiological aspects which need to be considered and which are related to the biological effectiveness of doses from particle exposures which have not been completely resolved yet. The general assumption of a constant RBE of 1.1 can no longer be upheld. Experimental data and theoretical considerations suggest that within the particle tracks, the RBE is variable and, in particular just behind the Bragg peak may assume values which have to be taken into account in situations when critical organs and tissues are close to the PTV margin. Even more controversial are the biological effects of the neutrons which are inevitably produced when high energy particles interact with matter. Neutron doses (in Gy) are very small compared to low LET scatter doses but outside the PTV may become critical in second cancer risk estimations if RBE values as recommended by ICRP for neutrons of different energies are used, or even more so if measured doses are multiplied with maximal RBE values extracted from epidemiological or experimental studies (with RBE values up to 100). On the other hand, a large follow-up study of patients treated with scattered neutrons suggested a lower second cancer risk than after contemporary photon irradiations. The experimental RBE studies and their use in second cancer risk estimation will be critically evaluated and results of the recently completed EC-funded project ANDANTE will be presented. From these studies I conclude that the methods recommended by ICRP for estimation of cancer risks after exposure of populations should not be used in medical exposures since they are based on numerous averaging assumptions and are thus unsafe in individual risk estimations. Moreover, the unit Sievert (Sv) has no place in medical applications of radiations, however, I do not see any convincing alternative, today. New ideas for research are urgently needed.

Presentation given on Thursday, September 8 at 14:50-15:50.



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Submitted abstract

Estimated risk of radiation induced contra lateral breast cancer following chest wall irradiation by conformal wedge field and forward intensity modulated radiotherapy technique for post mastectomy breast cancer patients

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Background: Epidemiological studies have reported the increasing incidence of radiation induced Secondary Cancer (SC) in breast cancer patients after Radiotherapy (RT). The most common SC reported is Contra Lateral Breast (CLB). Therefore the present study is an attempt to estimate the SC risk of CLB following 3D Conformal Radiotherapy Techniques (3DCRT) including Wedge field and forward Intensity Modulated Radiotherapy (fIMRT) based on Organ Equivalent Dose (OED). This is the most affordable treatment for breast cancer patients in India.

Material and Methods: RT plans treating the chest wall with conformal wedge field and fIMRT plans were created for 30 breast cancer patients. The risks of radiation induced cancer were estimated for the CLB using dose-response models accounting various degrees of cell sterilisation: a linear model, a linear-plateau model and a bell-shaped model also full dose response accounting for fractionated RT on the basis of OED.

Results: The plans were found to be ranked quite differently according to the choice of model; based on linear dose response model the fIMRT offers statistically significant lower risk compared to Enhanced Dynamic Wedge (EDW) technique (p-0.0089) and insignificant difference between fIMRT and Physical Wedge (PW) technique (p-0.054). The widely used plateau dose response model based estimation shows significantly lower SC risk associated with fIMRT technique compared to both wedge field techniques (fIMRT vs EDW p-0.013, fIMRT vs PW p-0.04). Full dose response model shows insignificant difference between all three techniques in the view of second CLB cancer. Finally the bell shaped model predicts interestingly that PW offers significantly higher risk compared to both fIMRT and EDW techniques (fIMRT vs PW p-0.0003, EDW vs PW p-0.0032).

Conclusion: In conclusion, the SC risk estimations of the CLB revealed that there is a clear relation between risk associated with wedge field and fIMRT technique depending on the choice of model selected for risk comparison.

Submitted abstract

Optimized Magnetic Resonance Spectroscopy for Timely Detection of Radiation-Induced Ovarian Cancer

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Exposure to ionizing radiation has been implicated as a risk factor for ovarian cancer [1-3]. This radiation exposure is often related to treatment of cervical cancer and/or to X-ray-based diagnostic imaging of the pelvic region. Ovarian cancer is generally detected late after spread outside the true pelvis (Stage III or IV) with very poor survival. Stage Ia ovarian cancer has five-year survival rates above 90% [4]. Due to the lack of accurate methods for early detection, screening for ovarian cancer is not generally performed. In vivo magnetic resonance spectroscopy (MRS) would be an excellent candidate for early ovarian cancer detection, because it is non-invasive, it surpasses anatomic imaging to identify metabolic features of cancer, and is free of ionizing radiation. We recently performed a meta-analysis of 13 studies and found that with standard signal processing through the fast Fourier transform (FFT), in vivo MRS insufficiently distinguished 134 cancerous from 114 benign ovarian lesions [5]. The fast Padé transform (FPT), an advanced signal processor with high-resolution and quantification-equipped capabilities is well-suited to handling MRS time signals from the ovary, as demonstrated in proof-of-concept studies [6]. Most recently, we applied the FPT to MRS time signals encoded in vivo on a 3 T scanner, echo time of 30 ms, from a borderline serous cystic ovarian tumor [5]. The FPT-processed total shape spectrum was better resolved than with the FFT. Numerous metabolites, including potential cancer biomarkers, were identified and quantified by the FPT. Among these were isoleucine, valine, lipids, lactate, alanine, lysine, choline, phosphocholine and myoinositol. Many of these metabolites are difficult if not impossible to detect with FFT-based processing of in vivo encoded MRS time signals from the ovary. Overall, Padé-optimized MRS holds promise for surveillance of women who are at increased risk of ovarian cancer due to ionizing radiation exposure.

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Submitted abstract

Preliminary attempt to estimate NTCP and secondary cancer risk for heart and lung after proton or photon radiation therapy in pediatric medulloblastoma

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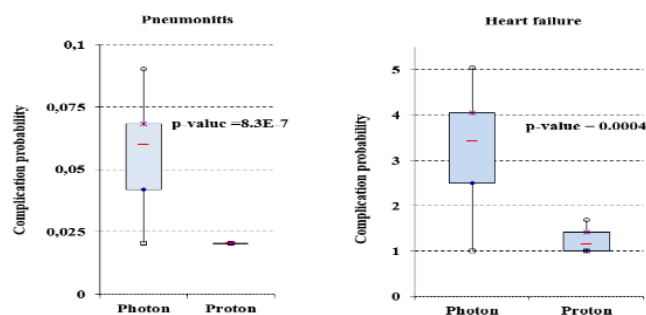
Introduction: The aim of this study is to develop a practical method to estimate and compare the normal tissue complication probability (NTCP) and the risk of radiation-induced late side effects in pediatric patients treated for a medulloblastoma.

Material and methods: Two treatment plans were generated for pediatric patients for conformal photon radiotherapy and proton therapy. The same dose prescriptions for posterior fossa and craniospinal irradiation were used for both plans. The logistic function and linear-quadratic function were used to estimate the lung pneumonitis and heart failure [1,2]. The organ equivalent dose (OED) model was used to estimate the risk of secondary cancer [3]. The estimation of the toxicity and the second cancer risk is based on average dose derived from dose volume histogram (DVH). Wilcoxon paired test was used to calculate p-value.

Results: In the frame of ProtonShare development, 17 cases were studied. Overall, heart and lungs showed a very considerable decreasing dose with proton plans compared to photon. Proton achieved lower mean dose for lung and heart leading to lower organ-equivalent dose. Consequently, the NTCP for lung and heart were significantly lower using proton plans, $p < 0.05$.

Conclusions: In the medulloblastoma, the choice of protons therapy can be supported by quantitative arguments coming from modelization of late effects. A solid base is provided by the DVH, providing an accurate dose calculation. However, beyond the technical feasibility, demonstrated here, the confidence level of such prediction still needs considerable effort to constrain models by the clinical reality.

Figure 1: Boxplot for estimated long term risks inducing pneumonitis and heart failure, and secondary lung cancer between photon and proton treatment modalities.





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Submitted abstract

The effect of mean dose or voxel-wise calculation in prediction of radiation-induced secondary cancers

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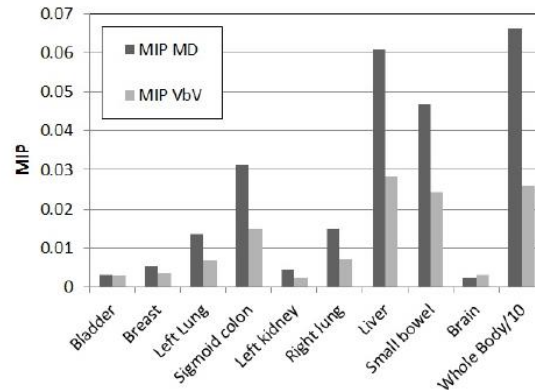
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Purpose/Objective: More than half of cancer patients receive radiotherapy for radical or palliative purposes. Increasing survival rates in cancer patients make it important to study late side-effects, including secondary radiation-induced cancers. Although a number of predictive models exist, the absolute accuracy of these models in the radiotherapy dose range is limited partly due to scarcity of data and partly by extrapolation beyond historical data bounds. One of the challenges faced with applying models to the highly spatially varying dose distributions produced in modern radiotherapy is dose heterogeneity within organs at risk. The aim of this work is to investigate the difference between using mean dose (MD) and high-resolution voxel-by-voxel dose (VbV) maps for calculating malignant induction probability (MIP).

Materials and Methods: A 3D conformal radiotherapy (3DCRT) and actively scanned proton plans were used for an adult patient and a teenage patient with medulloblastoma. MIP is calculated for each patient using the linear-quadratic (LQ), linear (LIN) and linear-no-threshold (LNT) models with in-house developed code. MIPs calculated using the mean dose to the organs as well as voxel-by-voxel dose are compared for individual organs and the whole body.

Results: Whole body MIPMD for the adult patient ranged between 0.337 and 0.929, while MIPVbV ranged between 0.078 and 0.929 with choice of model. MIPMD for the teenage patient ranged between 0.222 and 0.834, while MIPVbV ranged between 0.057 and 0.834 (Table 1). For the LNT model, where MIP is linear with dose, the MD and VbV results are identical, as expected. For the nonlinear LQ and LIN models, significant differences in MIP can be seen. Organ-specific MIPs vary over a wide range (Figure 1), although MIPMD is higher than MIPVbV by an average factor of 1.7 (adult) and 1.6 (teenage) for both the LQ and LIN models for 3DCRT plans and an average factor of 3.1 (adult) and 2.3 (teenage) for proton plans. Use of MD gives consistently higher MIP estimates than VbV calculation in areas of dose heterogeneity (note reversal of this trend in the brain, which has a uniform high dose).

Adult Patient				
Model	MIP _{Photon-MD}	MIP _{Proton-MD}	MIP _{Photon-VbV}	MIP _{Proton-VbV}
LQ	0.663	0.346	0.261	0.099
LIN	0.637	0.337	0.238	0.078
LNT	0.929	0.643	0.929	0.643
Teenage Patient				
Model	MIP _{Photon-MD}	MIP _{Proton-MD}	MIP _{Photon-VbV}	MIP _{Proton-VbV}
LQ	0.454	0.229	0.180	0.068
LIN	0.428	0.222	0.164	0.057
LNT	0.834	0.554	0.834	0.554



Conclusions: Results demonstrate large systematic differences between the risk estimates produced using either mean dose or voxel-by-voxel calculation. Although the relative relation between MIP_{Photon} and MIP_{Proton} remains broadly constant, using mean dose in heterogeneous dose distributions potentially overestimates MIP and, by association, secondary cancer risk.

Submitted abstract

A comparative study of the calculated risks of radiation-induced cancer for photon- and proton-beam based radiosurgery of liver metastases

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Introduction: The potential of proton therapy to spare the healthy tissues, compared to photon radiotherapy, has been demonstrated in several studies. However, even a small dose to the organs at risk (OAR) may be capable of inducing long term detriments after radiotherapy. This study aims to investigate the potential of intensity modulated proton therapy (IMPT) to reduce the risk of radiation-induced secondary cancers, compared to stereotactic body radiation therapy (SBRT), when used for radiosurgery of liver metastases.

Methods and materials: Ten patients previously treated for liver metastases with photon-beam based SBRT have been retrospectively planned for radiosurgery with IMPT. The SBRT plans were used as reference plans for comparison. For all patients, two-field IMPT plans were prepared with the objective of obtaining a similar target-dose coverage as for the corresponding reference plans. Treatment plan comparisons were performed in terms of risk of radiation-induced secondary cancers. The risks of radiation-induced secondary malignancies were estimated using two distinct models. With one of these models, proposed by Dasu *et al.* (2005), the risk of fatal cancer and the total risk of cancer were estimated. The second model has been proposed by Schneider *et al.* (2009, 2011). With this model the risk of carcinoma induction was calculated using three different dose-response relationships, *i.e.*, the linear, the linear-exponential and the plateau model. With the Schneider model the risk for sarcoma induction was also estimated. The plans were compared pairwise with a two-sided Wilcoxon signed-rank test with a significance level of 0.05.

Results: The risks of total and fatal cancer induction were lower in IMPT compared to SBRT plans ($p = 0.002$). IMPT provided lower risks of carcinoma induction for the skin, lungs, normal liver and the remaining part of the body. The risk of observing sarcomas in bone was also lower in IMPT compared to SBRT plans ($p = 0.002$).

Conclusion: The results of this study indicate that IMPT-based radiosurgery of liver metastases may provide a reduction of risks of radiation-induced secondary cancers compared to photon-beam based SBRT.

Submitted abstract

Second cancer modelling: a necessary complement to the treatment planning systems

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Secondary cancer associated to RT is an issue of growing concern and it should to be taken into account during the planning of treatments, with curative purposes, of primary cancers. Second malignancies are due to dose deposited outside the target volume as a consequence of stray photons and neutrons contamination (if $E > 10$ MV). However, neither out-of-field dosimetry nor the predictive models of the carcinogenic processes are a solved issue. It is accepted that the accuracy of out-of-field (also termed peripheral) dose calculations by Treatment Planning Systems (TPS) is poor. And yet, these peripheral doses are responsible for 50% of the second radiation-induced cancers. Our group faced this challenge back in 2007. As a result, analytical models for the estimation of photon and neutron peripheral equivalent doses were proposed [1-3] and validated [4]. Those models are applicable to isocentric treatments delivered with linacs from any vendor using conformal or modulated techniques (3D-CRT, IMRT, VMAT or SBRT) with any available energy (FF and FFF). They are based on simple data input (basic patient anthropometrical and other geometric treatment data) which allows automated calculation of peripheral dose, either prospective or retrospectively. The implementation of the corresponding scripts on the Pinnacle TPS is under development [5]. These models are allowing the estimation of secondary cancer risks, so that it can be considered as an additional parameter in RT planning optimization.

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