Out-of-field doses from proton therapy and doses from CBCT imaging
Risk of radiation-induced second cancer from modern radiotherapy
Oscar Ardenfors

Academic dissertation for the Degree of Doctor of Philosophy in Medical Radiation Physics at Stockholm University to be publicly defended on Friday 30 November 2018 at 09.00 in Rehabsalen, Norrbacka, S2 plan 01, Karolinska Universitetssjukhuset, Solna.

Abstract
The use of ionizing radiation for treatment of cancer diseases is continuously increasing as patient survival is improving and new treatment techniques are emerging. While this development is beneficial for curing primary tumors, concerns have been raised regarding the unwanted dose contribution to healthy tissues of patients and the associated risk of radiation-induced second cancer (RISC). This is especially important for younger patients receiving radiotherapy more often than before and for whom the risk of developing RISC is elevated in comparison to the typical adult radiotherapy patient. In order to estimate the risk of RISC associated with modern radiotherapy and imaging, the associated radiation doses must be determined.

Patients undergoing radiotherapy receive in-field doses from the primary beam but also out-of-field doses originating from secondary radiation produced in the beamline and within the patient. Over the last years, the use of proton pencil beam scanning (PBS) therapy has rapidly increased due to its potential to reduce the in-field doses to healthy tissues in comparison to photon therapy. One of the drawbacks with proton therapy is the production of neutrons capable of travelling large distances and depositing out-of-field doses to organs located far from the primary treatment field. The dose reduction associated with proton PBS therapy could consequently be affected by the out-of-field doses originating from secondary radiation.

The sharp dose gradients associated with modern treatment techniques, such as photon intensity-modulated radiotherapy (IMRT) and proton PBS therapy require more frequent and accurate patient imaging in comparison to conventional treatment techniques such as three-dimensional conformal radiotherapy (CRT). Setup verification images could be acquired with cone-beam computed tomography (CBCT) producing three-dimensional patient images at the cost of an increased patient dose in comparison to planar x-ray imaging. Concerns have been raised regarding the cumulative patient doses from repeated CBCT imaging versus the dose-saving benefits associated with modern radiotherapy techniques like IMRT and proton PBS.

In this thesis, a study on the in-field and out-of-field doses to healthy tissues from photon IMRT and CRT treatments of head and neck tumors showed that the risk of RISC was unaffected by the employed treatment technique and indicated that the lifetime risk of cancer induction was of the order of 1-2%.

Results from measurements and Monte Carlo simulations showed that the out-of-field absorbed doses and equivalent doses associated with proton PBS treatments of brain tumors were up to 60 µGy/Gy and 150 µSv/Gy, respectively. The risk of RISC associated with these out-of-field doses was in the range of approximately one induced cancer in ten thousand treated patients. A simulation study on the doses from a proton gantry-mounted CBCT system showed that repeated CBCT imaging could result in cumulative organ doses of almost 2 Gy. The conclusion from these studies is that the dose-sparing effects of proton PBS therapy are not overshadowed by the out-of-field doses originating from secondary radiation for brain tumor treatments, but that the cumulative doses from repeated CBCT imaging could have a relevant impact on the overall dose reduction.

Stockholm 2018
http://urn.kb.se/resolve?urn=urn:nbn:se:su:diva-161044


Department of Physics
Stockholm University, 106 91 Stockholm
OUT-OF-FIELD DOSES FROM PROTON THERAPY AND DOSES FROM CBCT IMAGING

Oscar Ardenfors
Out-of-field doses from proton therapy and doses from CBCT imaging

Risk of radiation-induced second cancer from modern radiotherapy

Oscar Ardenfors
“I am adding and subtracting
I'm controlling and composing
I'm the operator with my pocket calculator”

/Kraftwerk (Pocket Calculator, 1981)
The use of ionizing radiation for treatment of cancer diseases is continuously increasing as patient survival is improving and new treatment techniques are emerging. While this development is beneficial for curing primary tumors, concerns have been raised regarding the unwanted dose contribution to healthy tissues of patients and the associated risk of radiation-induced second cancer (RISC). This is especially important for younger patients receiving radiotherapy more often than before and for whom the risk of developing RISC is elevated in comparison to the typical adult radiotherapy patient. In order to estimate the risk of RISC associated with modern radiotherapy and imaging, the associated radiation doses must be determined.

Patients undergoing radiotherapy receive in-field doses from the primary beam but also out-of-field doses originating from secondary radiation produced in the beamline and within the patient. Over the last years, the use of proton pencil beam scanning (PBS) therapy has rapidly increased due to its potential to reduce the in-field doses to healthy tissues in comparison to photon therapy. One of the drawbacks with proton therapy is the production of neutrons capable of travelling large distances and depositing out-of-field doses to organs located far from the primary treatment field. The dose reduction associated with proton PBS therapy could consequently be affected by the out-of-field doses originating from secondary radiation.

The sharp dose gradients associated with modern treatment techniques, such as photon intensity-modulated radiotherapy (IMRT) and proton PBS therapy require more frequent and accurate patient imaging in comparison to conventional treatment techniques such as three-dimensional conformal radiotherapy (CRT). Setup verification images could be acquired with cone-beam computed tomography (CBCT) producing three-dimensional patient images at the cost of an increased patient dose in comparison to planar x-ray imaging. Concerns have been raised regarding the cumulative patient doses from repeated CBCT imaging versus the dose-saving benefits associated with modern radiotherapy techniques like IMRT and proton PBS.

In this thesis, a study on the in-field and out-of-field doses to healthy tissues from photon IMRT and CRT treatments of head and neck tumors showed that the risk of RISC was unaffected by the employed treatment technique and indicated that the lifetime risk of cancer induction was of the order of 1-2%. 

Abstract
Results from measurements and Monte Carlo simulations showed that the out-of-field absorbed doses and equivalent doses associated with proton PBS treatments of brain tumors were up to 60 µGy/Gy and 150 µSv/Gy, respectively. The risk of RISC associated with these out-of-field doses was in the range of approximately one induced cancer in ten thousand treated patients. A simulation study on the doses from a proton gantry-mounted CBCT system showed that repeated CBCT imaging could result in cumulative organ doses of almost 2 Gy. The conclusion from these studies is that the dose-sparing effects of proton PBS therapy are not overshadowed by the out-of-field doses originating from secondary radiation for brain tumor treatments, but that the cumulative doses from repeated CBCT imaging could have a relevant impact on the overall dose reduction.

Stråldosbidraget för patienter som behandlas med strålbehandling kan delas in i inom-fält doser från primärstrålningen och utom-fält doser från sekundärstrålning som bildats i material i strålbehandlingsmodaliteten eller i patienten. Under de senaste åren har användandet av protonbehandlingar med ”pencil beam scanning” (PBS) ökat på grund av förmågan att leverera dosfördelningar med lägre inom-fält doser till frisk vävnad i jämförelse med strålbehandling med fotoner. En av nackdelarna med protonbehandlingar är den ökade produktionen av neutroner vilka kan färdas långa sträckor och deponera utom-fält doser till vävnader långt från det primära bestrålningssområdet. Minskningen av inom-fält doser för protonbehandlingar med PBS kan följaktligen motverkas av en ökning av utom-fält doserna.

De skarpa dosgradienter som används inom moderna strålbehandlingstekniker såsom ”intensity-modulated radiotherapy” med fotoner (IMRT) eller protonbehandlingar med PBS kräver mer frekvent och noggrann bildtagning av patienten i jämförelse med konventionella behandlingstekniker såsom tredimensionell ”conformal radiotherapy” (CRT). Dessa röntgenbildtagningar genomförs ofta med s.k. ”cone-beam computed tomography” (CBCT) vilket ger tredimensionella patientbilder till priset av en ökad stråldos jämfört med planara röntgenbilder. Då dessa bildtagningar genomförs vid upprepade tillfällen under strålbehandlingen kan den totala stråldosen från bildtagning med CBCT uppgå till nivåer som kan ha en negativ effekt på den totala dosbesparingen som kan uppnås med moderna behandlingstekniker.

I en av studierna i denna avhandling undersökes hur risken för strålningsinducerad cancer för behandlingar av huvud-hals-tumörer skiljde sig
beroende på om patienten behandlades med IMRT eller CRT. Resultatet visade att risken var i princip oberoende av behandlingsteknik och att den totala risken för sekundärcancer från både inom-fält- och utom-fält doser var ungefär 1-2%.

Resultat från mätningar och Monte Carlo simuleringar visade att de högsta absorberade utom-fält doserna och ekvivalenta utom-fält doserna från protonbehandlingar av hjärntumörer med PBS var ungefär 60 µGy/Gy och 150 µSv/Gy. Risken för strålningsinducerad cancer från dessa utom-fält doser motsvarade ungefär en inducerad cancer per tiotusen behandlade patienter. En simuleringssstudie av stråldoser från ett CBCT-system monterat på ett protonantry visade att de totala stråldoserna från upprepade bildtagningar kunde uppgå till nästan 2 Gy. Slutsatsen från dessa studier är att minskningen av inom-fält doser för protonbehandlingar med PBS ej överskuggas av utom-fält doserna vid behandlingar av hjärntumörer, men att upprepad bildtagning med CBCT kan ha en relevant påverkan på den totala dosreduktionen.
List of papers

The following publications are included in this thesis:

Paper I: Modelling of a proton spot scanning system using MCNP6

Paper II: Out-of-field doses from secondary radiation produced in proton therapy and the associated risk of radiation-induced cancer from a brain tumor treatment

Paper III: Impact of irradiation setup in proton spot scanning brain therapy on organ doses from secondary radiation
O. Ardenfors, I. Gudowska, A. M. Flejmer and A. Dasu, Radiation Protection Dosimetry, 180(1-4), 261-266, 2018

Paper IV: Organ doses from a proton gantry-mounted cone-beam computed tomography system characterized with MCNP6 and GATE

Paper V: Are IMRT treatments in the head and neck region increasing the risk of secondary cancers?

Related publications not included in this thesis:

Paper VI: Radiation burden from secondary doses to patients undergoing radiation therapy with photons and light ions and radiation doses from imaging modalities
Paper VII: **Radiation protection measurements with the variance-covariance method in the stray radiation fields from photon and proton therapy facilities.**

Paper VIII: **Monte Carlo simulations of spatial LET distributions in clinical proton beams.**
L. Grzanka, O. Ardenfors and N. Bassler, *Radiation Protection Dosimetry*, 180(1-4), 296-299, 2018

Paper IX: **Reduced acquisition times in whole body bone scintigraphy using a noise-reducing Pixon®-algorithm—a qualitative evaluation study**
Author’s contribution

Paper I: I designed the study together with the co-authors. I performed the simulations and evaluated the results. I wrote the major part of the manuscript.

Paper II: I designed the study together with the co-authors and participated in the measurements. I carried out the simulations and developed the CT-import tool. I performed the risk calculations together with my co-authors and wrote the major part of the manuscript.

Paper III: I designed the study together with the co-authors, performed the simulations, and wrote the major part of the manuscript.

Paper IV: I designed the study and performed the measurements together with my co-authors. I carried out the MCNP6 simulations and wrote the major part of the manuscript.

Paper V: I took part in designing the study and created the dose plans for the CRT patients. I performed the measurements with my co-authors. I calculated the risks and evaluated the results together with my co-authors. I wrote the major part of the manuscript.

Parts of this thesis have been reproduced from the licentiate thesis “Secondary doses to healthy tissues from radiotherapy and modern imaging techniques” by Oscar Ardenfors, 2017.

Some formulations in the abstract and introduction have been reproduced and the general context is similar. Chapter 2 is influenced by chapter 3 in the licentiate thesis and some formulations have been reproduced. Some formulations in the beginning of chapter 3 and sections 3.2 and 3.3.1 have been reproduced and figures 5 and 6 have been reproduced. Chapter 4 is based on chapter 5 in the licentiate thesis and figure 8 is based on figure 8 in the licentiate thesis.
## Contents

Abstract iii  
Sammanfattning v  
List of papers vii  
Author’s contribution ix  
Contents xi  
Abbreviations xiii  

1. Introduction 1  
2. Doses to healthy tissues from radiotherapy and CBCT imaging 5  
   2.1. Dose categorization 5  
   2.2. Proton therapy 7  
      2.2.1. Proton interactions 10  
      2.2.2. Secondary neutrons and photons 12  
      2.2.3. RBE of neutrons 13  
   2.3. Photon therapy 14  
      2.3.1. Photon interactions 16  
   2.4. CBCT imaging 17  
      2.4.1. Kilovoltage x-ray interactions 19  
3. Monte Carlo simulations 21  
   3.1. Modelling intra-nuclear cascades 22  
   3.2. Modelling human anatomy 23  
   3.3. Validation of Monte Carlo beam models 25  
      3.3.1. Proton PBS model 26  
      3.3.2. CBCT beam model 27  
   3.4. Uncertainties in organ dose simulations 28  
4. Risk of radiation-induced second cancer 31  
   4.1. Mechanisms behind RISC 32  
   4.2. Current knowledge of the risk of RISC 33  
   4.3. Modelling the risk 34  
5. Conclusions 39  
6. Summary of papers 41  
Acknowledgements 45  
References 47
Abbreviations

BEIR  Biological effects of ionizing radiation
CBCT  Cone-beam computed tomography
CRT   Conformal radiotherapy
CT    Computed tomography
DVH   Dose-volume histogram
DICOM Digital Imaging and Communications in Medicine
DSB   Double strand break
EURADOS European Radiation Dosimetry Group
GATE  Geant4 Application for Tomographic Emission
HU    Hounsfield unit
ICRP  International Commission on Radiological Protection
IGRT  Image-guided radiotherapy
IMRT  Intensity-modulated radiotherapy
INC   Intra-nuclear cascade
IDD   Integral depth dose
LAR   Lifetime attributable risk
LET   Linear energy transfer
LNT   Linear-no-threshold
MLC   Multileaf collimator
MU    Monitor unit
LSS   Life span study
MCNP  Monte Carlo N-particle
OAR   Organ at risk
OBI   On-board imaging
PBS   Pencil beam scanning
PDF   Probability distribution function
RBE   Relative biological effectiveness
RISC  Radiation-induced second cancer
SOBP  Spread out Bragg peak
TPS   Treatment planning system
VMAT  Volumetric modulated arc therapy
1. Introduction

The role of ionizing radiation in modern medicine has advanced over the last decades with new techniques emerging, improving both diagnostic accuracy and treatment outcome. While the benefits of this development outweigh the drawbacks, there are still concerns regarding the adverse effects associated with ionizing radiation that cannot be neglected. One of the major health-related drawback of irradiating large cohorts of patients with ionizing radiation for diagnostic and therapeutic purposes is the associated risk of radiation-induced second cancer (RISC) (BEIR 2006, Hall and Giaccia 2006). As young patients receive radiotherapy more often and long-term survival is improving, the number of patients developing RISC is expected to increase highlighting the importance of minimizing the unwanted dose contribution to healthy tissues (Dasu and Toma-Dasu 2014, Yock et al 2014, Kry et al 2017).

Over the last decade, the use of proton therapy for treating cancers such as brain tumors has increased. Proton therapy is a suitable treatment option for tumors with complex shapes for which the physical properties of protons allow for a greater sparing of the surrounding healthy tissues in comparison to photon external beam radiotherapy (denoted photon therapy henceforth). One of the disadvantages of using protons for delivering radiotherapy is the production of secondary radiation in both the beamline and within the patient. The largest concern associated with this radiation is the production of secondary neutrons capable of depositing patient doses over large distances and causing higher biological damage than e.g. photon radiation (Durante and Paganetti 2016, Kry et al 2017).

Although protons are associated with an increase in production of secondary neutrons, studies have indicated that the out-of-field doses attributed to neutrons are similar for proton pencil beam scanning (PBS) therapy and photon therapy (Hälg et al 2014, Stolarczyk et al 2018). Considering the increase in dose contribution from secondary photons produced in photon therapy, the total out-of-field doses from proton PBS therapy could be lower than the corresponding total out-of-field doses from high-energy photon therapy (Hälg et al 2014, Lillhök et al 2017, Stolarczyk et al 2018). The sparing of in-field doses to healthy tissues in proton PBS therapy is therefore not expected to be overshadowed by an increase in out-of-field doses originating from secondary radiation. These out-of-field doses could however be of importance with regard to the risk of RISC and should consequently be considered when evaluating the dose to the patient.
Modern radiotherapy techniques, such as photon therapy delivered with intensity-modulated radiotherapy (IMRT) or proton therapy delivered with the PBS technique, produce dose distributions with steep dose gradients increasing the need for accurate patient positioning in comparison to older treatment techniques such as three-dimensional conformal radiotherapy (CRT). Patients undergoing radiotherapy with modern techniques are consequently being imaged more frequently for setup verification in conjunction with the treatment delivery. The major drawback of these repeated image acquisitions, often acquired using cone-beam computed tomography (CBCT), is the associated dose burden potentially adding up to doses corresponding to one treatment fraction if the imaging is performed on a daily basis throughout an entire radiotherapy treatment course (Alaei and Spezi 2015). While repeated CBCT imaging has the potential to improve tumor localization at the time of treatment delivery and reduce the dose to adjacent healthy tissues, the associated dose burden remains an important issue.

Epidemiological data on the risk of RISC associated with modern treatment techniques are scarce as the latency of RISC spans over several decades impeding such risk evaluations for patients undergoing treatments nowadays. The risk of RISC must instead be estimated using theoretical risk models based on available epidemiological data of e.g. survivors of the atomic bombings and medically irradiated patients. Accurate patient doses are essential for modelling the dose-dependent risk and the total dose burden to the patient from both the radiotherapy treatment and the concomitant diagnostic imaging should consequently be considered for such risk estimations (Harrison 2017).

Out-of-field doses originating from secondary radiation are usually not calculated in clinical treatment planning systems (TPS) as these doses are several orders of magnitude lower than the in-field doses. The analytical dose kernels employed for calculating dose distributions in TPS are time efficient but cannot calculate the many interactions associated with e.g. the transportation of secondary neutrons in human tissue. It has been shown that TPS employed for photon therapy treatments often underestimate the out-of-field doses when compared to measurements (Miljanić et al 2014, Majer et al 2017). Calculations of out-of-field doses from proton PBS therapy are preferably carried out using Monte Carlo simulations suitable also for determining doses from CBCT imaging (Titt et al 2012, Farah et al 2014, Newhauser and Zhang 2015, Ding et al 2018). In order to perform reliable dose calculations based on Monte Carlo simulations, the model used for the simulations should be validated against measurements of the specific application (Ding et al 2008, Farah et al 2014).

The aim of this thesis was to assess the out-of-field doses to patients undergoing proton PBS therapy of brain tumors and to evaluate the doses with regard to the risk of RISC. A clinical proton PBS system was characterized
with the Monte Carlo code Monte Carlo N-particle 6 (MCNP6) (Goorley et al 2016) in paper I and out-of-field organ doses originating from secondary radiation produced in conjunction with proton therapy treatments were calculated in papers II and III. Measurements of out-of-field doses from proton PBS therapy were performed at the Skandion Clinic in Uppsala, Sweden, and used to evaluate the Monte Carlo model in paper II. Additionally, the risk of RISC originating from the out-of-field doses associated with a proton PBS treatment of a brain tumor was estimated in paper II.

In paper IV, a clinically employed proton gantry-mounted CBCT system was modelled with two different Monte Carlo codes and organ doses from various imaging procedures were determined. Doses and beam characteristics of the proton gantry-mounted CBCT system were determined from measurements carried out at the Skandion Clinic and were used to characterize the Monte Carlo models employed in paper IV.

In paper V, the risk of RISC originating from the in-field and out-of-field doses associated with photon IMRT and CRT treatments of head and neck tumors was studied.
2. Doses to healthy tissues from radiotherapy and CBCT imaging

Patients undergoing radiotherapy or diagnostic imaging with ionizing radiation always receive unwanted doses to healthy tissues. This dose contribution can give rise to non-stochastic effects and long-term stochastic effects such as RISC (Hall and Giaccia 2006, Kry et al. 2017). The non-stochastic effects dominate in organs receiving doses higher than an effect-specific dose threshold and if this threshold is exceeded, both the probability and severity of the effect increases with dose. Non-stochastic effects are usually considered in radiotherapy due to the relatively high doses (typically several grays) required to induce such effects. The severity of the long-term stochastic effects is invariant with dose but the probability of occurring is dose-dependent. Thus, stochastic effects are of importance for all dose levels (further discussed in chapter 4).

The focus of this thesis was to evaluate the patient doses associated with modern radiotherapy treatments and CBCT imaging procedures with regard to the risk of RISC\(^1\). The classification of the different dose contributions used throughout this thesis is described in 2.1 and a schematic representation of the types of radiation giving rise to these doses is shown in Figure 1.

2.1. Dose categorization

When patients undergo radiotherapy treatments, the primary radiation gives rise to in-field doses to organs at risk (OAR) located inside or close to the primary radiation field (Xu et al. 2008, Kry et al. 2017). The lateral distribution of these doses can be controlled with e.g. beam collimation or steering magnets depending on the type of radiation, whereas the entrance and exit doses to healthy tissues are determined by the interaction processes inside the patient and the energy of the radiation. The in-field doses decrease rapidly with distance from the irradiated target, especially when employing techniques with sharp dose gradients such as photon IMRT and proton PBS. As the in-field doses can be rather high (up to tens of grays), the adjacent OAR are affected by both non-stochastic and stochastic effects.

\(^1\) The induction of non-stochastic effects was not within the scope of this thesis.
Interactions between the primary radiation and human tissue or beamline material result in scattered primary particles and secondary particles, both which constitute what is commonly denoted as secondary radiation. This secondary radiation give rise to in-field doses and out-of-field doses to organs located outside the primary treatment field (Xu et al 2008, Durante and Paganetti 2016, Kry et al 2017). The scattered radiation constitutes the largest contribution in out-of-field doses close to the irradiated target, and for larger distances the contribution from secondary particles is dominant (Kry et al 2017). In the case of uncharged secondary radiation, such as neutrons and photons, the out-of-field doses can be deposited far from the primary target volume. The magnitude of these out-of-field doses thus decrease more slowly with increasing distance from the primary radiation field in comparison to the in-field doses. This effect has been demonstrated for high energy photon treatments where the out-of-field doses have been shown to be relatively constant with distance from the primary treatment field (Hälg et al 2014). Out-of-field absorbed and equivalent doses per absorbed dose to the target are typically in the order of mGy/Gy and mSv/Gy or lower (Xu et al 2008, Hälg et al 2014, Kry et al 2017). These doses are below the threshold at which non-stochastic effects occur, and are therefore usually evaluated with regard to secondary late effects such as cancer induction.

In papers II and III, the secondary radiation produced in conjunction with proton PBS treatments was studied using Monte Carlo simulations. The out-of-field doses originating from secondary radiation produced in various brain tumor treatments were calculated and the corresponding risk of RISC was estimated. In paper V, the in-field and out-of-field doses associated with photon therapy treatments of head and neck tumors delivered with the CRT and IMRT technique were studied. The organ doses were subsequently used to evaluate the risk of RISC associated with these two treatment techniques. The in-field and out-of-field doses to healthy tissues from proton therapy treatments and photon therapy treatments are discussed in 2.2 and 2.3, respectively.

The doses from imaging are considerably lower than the in-field doses from radiotherapy and are therefore usually evaluated in the same context as the out-of-field doses, ergo with regard to RISC (Alaei and Spezi 2015, Ding et al 2018). Unlike radiotherapy, where the treatment field is shaped to cover the target volume, the field sizes in diagnostic imaging usually cover a large portion of the patient (Alaei and Spezi 2015). The field size of typical CBCT systems could be up to 40×40 cm² and the associated doses are consequently not limited to organs located adjacently to the target volume. In paper IV, organ doses from CBCT imaging with a proton gantry-mounted CBCT system were determined using Monte Carlo simulations. The patient doses originating from CBCT imaging are discussed in 2.4.
2. Doses to healthy tissues from radiotherapy and CBCT imaging

Figure 1. Schematic representation of the types of radiation giving rise to in-field and out-of-field doses in radiotherapy and doses from CBCT imaging.

2.2. Proton therapy

The main rationale of using protons for radiotherapy purposes is the possibility to produce dose distributions that cannot be achieved in photon radiotherapy (Wilson 1946, Paganetti 2012, Newhauser and Zhang 2015). Due to their mass and charge, protons interact with matter in a fundamentally different manner in comparison to photons. Proton therapy has traditionally been delivered with the passive scattering technique in which a beam of constant energy is modulated using a range modulator, an in-beam scatterer, and a range compensator in order to create a conformal dose distribution to the target. Modern proton therapy facilities often employ the PBS technique in which the proton range is modulated by varying the energy of the beam and the lateral conformity is achieved by steering the beam with magnets located in the treatment head.

Besides the implications regarding the production of secondary radiation associated with the passive scattering technique (further described below), one of the drawbacks associated with this technique is that the apertures used to modify the shape of the beam are patient-specific and must be manufactured before the initiation of a treatment session. This is not an issue in PBS, as the beam is usually not modified using physical apertures except for special patient cases where a range shifter might be used to modulate the proton range. For such cases the production of secondary neutrons, due to interactions taking place in the range shifter, is greatly increased (Trinkl et al 2017).
The in-field doses to healthy tissues in proton therapy mainly originate from primary and secondary protons, typically corresponding to 90-99.7% and up to 8-10% of the absorbed dose depending on the depth (Grassberger and Paganetti 2011, Newhauser and Zhang 2015). The characteristic shape of a depth dose curve for protons in the clinical energy range of ~50-250 MeV is manifested by a low-dose plateau region up until the depth of the Bragg peak at which the protons deposit the remaining kinetic energy over a short distance (further described in 2.2.1). The doses to regions located before the Bragg peak are thus much lower than the doses to the target volume and the proton dose deposited behind the Bragg peak is practically negligible. However, clinical practice requires the use of several proton energies to cover the entire target volume with Bragg peaks leading to a spread out Bragg peak (SOBP). The largest contribution to the in-field doses to healthy tissues in proton PBS therapy thus originate from the plateau region where the entrance dose can correspond to more than half the maximum dose to the target (Newhauser & Zhang 2015).

Unlike ions with atomic number \((Z) > 1\), protons do not produce a large fragmentation tail of heavier elements with high relative biological effectiveness\(^2\) (RBE) at the distal part of the Bragg peak (Durante and Paganetti 2016). The small contribution in dose to this region mainly originates from secondary protons produced from nuclear interactions of neutrons (Paganetti 2002). The RBE of the protons is however clinically relevant and cannot be neglected. The proton RBE is usually implemented by multiplying the absorbed doses calculated by the TPS with a factor of 1.1 (ICRU 2007). Although a constant RBE of 1.1 is the most common implementation of RBE in proton therapy, several methods of implementing a RBE that varies with linear energy transfer (LET), dose and biological endpoint have been proposed (Paganetti 2014b).

The out-of-field doses in proton therapy are dominated by scattered primary protons and secondary neutrons and photons produced through non-elastic nuclear interactions (Xu et al 2008, Farah et al 2015, Durante and Paganetti 2016, Kry et al 2017). These non-elastic nuclear interactions take place as protons are transported through the beamline and within the patient, giving rise to both externally and internally produced secondary radiation. Approximately 20% of all protons will undergo non-elastic nuclear interactions in water for a typical treatment plan (Durante and Paganetti 2016). The secondary radiation produced in the beamline is primarily an issue when employing the passive scattering technique as the beam passes through a number of components before exiting the treatment head producing much higher levels of secondary radiation in comparison to the PBS technique.

\(^2\) RBE is defined as the ratio between the absorbed dose from a reference radiation (e.g. Co-60 gamma radiation) and the absorbed dose from the radiation of interest required to induce the same biological effect (Hall and Giaccia 2006).
2. Doses to healthy tissues from radiotherapy and CBCT imaging

where the number of apertures in the treatment head are much fewer (Durante and Paganetti 2016, Kry et al 2017).

However, in the case of out-of-field dose assessments, the secondary radiation produced from interactions in the nozzle should be considered also for the PBS technique (Grassberger et al 2015). This was emphasized in paper II where simulations of out-of-field absorbed doses produced in the nozzle of a proton PBS system corresponded to up to 70% of the total out-of-field absorbed dose to certain detector positions. These doses were however low in absolute numbers, ranging from 0.4 to 1.8 mGy for a full treatment course, and were assessed outside an irradiated phantom. The vast majority of the out-of-field doses in proton PBS therapy nonetheless originate from secondary radiation produced within the patient (Hultqvist and Gudowska 2010, Kry et al 2017).

Typical clinical TPS are not aimed at accurately calculating out-of-field doses originating from secondary radiation (Newhauser and Zhang 2015, Kry et al 2017). The complexity of the secondary radiation field is more accurately modelled with Monte Carlo simulations capable of individual particle tracking unlike the analytical dose kernels employed in most clinical TPS (Titt et al 2012, Farah et al 2014, Newhauser and Zhang 2015). Analytical models for calculating out-of-field doses in proton therapy have been proposed (Zhang et al 2010) although none have been clinically implemented on a larger scale.

An extensive effort in characterizing the secondary radiation associated with proton PBS therapy has been made through measurements and Monte Carlo simulations by the European Radiation Dosimetry Group (EURADOS) (Farah et al 2015, Mares et al 2016, Farah et al 2017, Knežević et al 2017, Mojžeszek et al 2017, Stolarczyk et al 2018). These studies have highlighted the complexity associated with the secondary radiation field produced in proton PBS irradiations and, among several other findings, demonstrated that the neutron energy distribution varies greatly depending on primary proton energy and detector position relative to the incident beam.

Studies on secondary radiation produced in proton PBS treatments have shown that the associated out-of-field doses are several orders of magnitude lower than the in-field doses (Hälg et al 2014, Stolarczyk et al 2018). This was confirmed in papers II and III as the highest out-of-field absorbed dose per treatment dose and equivalent dose per treatment dose to organs from proton PBS treatments of brain tumors were approximately 43 µGy/Gy and 150 µSv/Gy, respectively. The maximum cumulative equivalent dose from an entire treatment was in the range of approximately 10 mSv. This dose is orders of magnitude lower than both the in-field doses to healthy tissues in radiotherapy and the cumulative doses from repeated CBCT imaging.

A plausible development within the field of treatment planning is that Monte Carlo techniques will replace the analytical dose kernels employed in current clinical TPS (Paganetti 2014a). While this evolution would allow for patient-specific calculations of out-of-field doses, the problem associated with
limitations in patient geometry for treatment planning would remain. The computed tomography (CT) used for treatment planning is usually limited to the anatomical region surrounding the target volume, preventing dose calculations in more remote regions. The need to assess the out-of-field doses associated with new treatment techniques could consequently remain an important issue even after a largescale transition to Monte Carlo based TPS.

Given the low magnitude of the out-of-field doses produced in proton PBS therapy, future patient-specific Monte Carlo calculations of these doses might be considered unnecessary. However, in order to omit such calculations, the low magnitude of the out-of-field doses associated with a specific treatment technique must be confirmed. This emphasizes the need to determine the out-of-field doses associated with new proton therapy techniques.

2.2.1. Proton interactions

When a proton traverses matter, the negatively charged atomic electrons are attracted by the electromagnetic force and a fraction of the proton kinetic energy is transferred to the electrons through inelastic Coulomb interactions. Due to the large difference in mass (proton-to-electron mass ratio = 1836), the proton trajectory is very little affected by the atomic electrons as illustrated in Figure 2a. For a clinical proton energy of 200 MeV, the maximum energy transfer to an electron is roughly 0.5 MeV, corresponding to a range in water of less than 2 mm (Newhauser and Zhang 2015). As the vast majority of all proton-to-electron energy transfers are much lower, the energy deposition is localized along the proton track.

The inelastic Coulomb interactions can be described by the electronic stopping power that increases as the kinetic energy of the protons decrease to a maximum around ~0.05-0.1 MeV in water. The protons will deposit the majority of the remaining kinetic energy at the depth where the energy has decreased to the level corresponding to the maximum electronic stopping power giving rise to the Bragg peak. The continuous energy-loss through inelastic Coulomb interactions of the protons leading to termination at the Bragg peak is what defines the range of the protons and varies with initial kinetic energy and electron density of the material. The energy deposition of individual protons traversing through a medium varies and this effect is denoted as energy straggling. The cumulative effects of proton energy straggling give rise to a non-sharp distal fall-off of the dose distribution at the depth of the Bragg peak.
2. Doses to healthy tissues from radiotherapy and CBCT imaging

The traversing protons can also undergo elastic and non-elastic interactions with the atomic nuclei of the medium. Elastic scattering occurs when the traversing protons are repelled by the positively charged nuclei deflecting the proton trajectory (Figure 2b). A small fraction of the proton kinetic energy can be transferred to the recoiling nucleus that remains unexcited. The cumulative effect of several elastic scatterings can result in a substantial change in the proton trajectory. These repeated elastic interactions are denoted *multiple Coulomb scattering* and give rise to the lateral spread of a proton beam.

The proton can also undergo non-elastic nuclear interactions as illustrated in Figure 2c. The target nucleus can then de-excite in a complex intra-nuclear cascade (INC) in which secondary protons, neutrons, gamma rays and heavier particles can be produced. Due to the heavy mass of the secondary ions, the kinetic energy is primarily deposited locally whereas neutrons and gamma rays have the potential to travel large distances and deposit energy far from the location of the nuclear interaction. The secondary protons produced in nuclear interactions can amount to roughly 10% of the deposited absorbed dose from a therapeutic proton beam, whereas secondary heavier ions amount to less than 1% (Grassberger and Paganetti 2011, Newhauser and Zhang 2015).

Apertures located in the beamline of a radiotherapy system are often made from brass alloys consisting of copper isotopes. Cross-sections of the total non-elastic nuclear interactions of protons in water and Cu-63 generated using MCNP6 are presented in Figure 3.

![Figure 2. Schematic representation of three proton interaction processes: (a) inelastic Coulomb interactions with the atomic electrons, (b) elastic nuclear scattering, (c) non-elastic nuclear interaction.](image-url)
2.2.2. Secondary neutrons and photons

In proton PBS therapy, where the protons pass through very few materials before exiting the nozzle, the largest neutron contribution originates from within the patient (Hultqvist and Gudowska 2010, Kry et al 2017). However, as seen in Figure 3, protons are more prone to undergo non-elastic nuclear interactions in high Z materials. Depending on the associated partial cross-sections for neutron production, a thin slab of high Z material in the nozzle could consequently correspond to a relevant increase in the production of secondary neutrons for proton PBS.

Unlike charged particles and photons, the interactions between neutrons and atomic electrons are negligible and instead the neutron interactions are dominated by nuclear interactions. Consequently, neutrons are capable of travelling large distances in the human body. The energy distribution of the secondary neutrons produced in proton PBS therapy typically show a peak at thermal energies below ~0.5 eV, a peak at energies in the MeV range originating from nuclear de-excitation processes, and a high energy peak with fast neutrons with energies ranging from ~20 MeV up to energies of the primary protons (Kry et al 2017). The height and shapes of the peaks vary greatly with spatial positioning and primary proton energy (Farah et al 2015, Mares et al 2016). The largest part of the neutron dose to the patient is

![Figure 3. Cross-sections of total non-elastic nuclear interactions of protons (solid) and non-elastic photonuclear reactions of photons (dashed) in Cu-63 and water. Data generated with default MCNP6 cross-section tables (Chadwick et al 1999, 2011, Pelowitz 2013).](image-url)
deposited from the fast forward-directed neutrons generated from direct proton-neutron interactions (Durante and Paganetti 2016, Kry et al 2017).

The neutron energy deposition in human tissue is dominated by the following nuclear interactions (Attix 1986):

- **Elastic scattering** in which the energy and trajectory of the neutron is altered and the target nucleus remains unexcited. Elastic scattering is the dominating source of dose deposition in human soft tissues for neutrons with kinetic energies above approximately 10 keV.

- **Neutron capture** in which thermal neutrons are absorbed by the nuclei of e.g. hydrogen or nitrogen, resulting in the emission of gamma radiation or secondary protons.

- **Non-elastic scattering** in which neutrons with energies above several MeV excites the nucleus and the neutron lose a large amount of energy and secondary radiation is emitted from the nucleus as it de-excites.

The contribution to out-of-field dose from secondary photon radiation in both PBS and passive scattering proton therapy is lower than the contribution from neutrons, amounting to up to ~16% of the total out-of-field dose in proton PBS (Demarco et al 2013). The photon radiation is mainly produced through nuclear de-excitations following non-elastic nuclear interactions and the energy of the secondary photons is typically a few MeV (Demarco et al 2013). The production of proton bremsstrahlung is practically negligible.

### 2.2.3. RBE of neutrons

*In-vitro* experiments have shown that neutrons cause higher biological damage per unit absorbed dose than radiation with low LET and that the amount of damage varies with neutron energy (Tanaka et al 1999, ICRP 2007, Durante and Paganetti 2016). Most of these experiments were carried out for neutron energies of up to ~20 MeV and experimental data of human response for high-energy neutrons produced in clinical proton therapy beams is scarce (Xu and Paganetti 2010).

The neutron RBE has been shown to vary with LET, dose, number of dose fractions, dose-rate and biological endpoint (Hall and Giaccia 2006). The variation in RBE with regard to endpoint implies that for a given type of irradiation, the RBE varies differently with LET, dose etc. when considering e.g. cell death or induction of mutations as biological endpoint.

The biological damage of neutrons is mainly induced due to the secondary charged particles produced from nuclear interactions. As stated in 2.2.2, elastic nuclear scattering is the dominating neutron interaction with regard to dose deposition in human tissue. Furthermore, the most common type of
neutron elastic scattering in human tissue occurs between neutrons and hydrogen and consequently, this is the largest source of neutron dose contribution in clinical radiotherapy (Paganetti 2002). The RBE of neutrons thus depends on the RBE of the secondary charged particles, which in turn varies with LET, dose, biological endpoint and particle type.

One of the main reasons for assessing the out-of-field doses associated with proton PBS therapy in this thesis was to evaluate the associated risk of RISC. The risk of RISC depends on the biological effects induced by the radiation and should consequently be estimated using absorbed doses weighted with the factors related to these effects. Thus, out-of-field equivalent doses originating from proton PBS treatments of brain tumors were calculated in papers II and III. The equivalent doses were calculated through multiplying the energy-differentiated organ absorbed dose with the energy-dependent neutron radiation weighting factor, \( w_R \), introduced by the International Commission on Radiological Protection (ICRP) (ICRP 2007).

It should be emphasized that the \( w_R \) was introduced by the ICRP for radiation protection purposes and that it represents a weighting factor related to biological damage as a function of neutron energy. It should not be regarded as an accurate description of the biological effectiveness of neutrons. The uncertainties associated with the \( w_R \) are further discussed in 3.4.

## 2.3. Photon therapy

The main principle of treating patients with photon therapy is to irradiate a patient with several radiation fields from different angles achieving a prescribed dose to the target volume while minimizing the dose to healthy tissues. Photon therapy treatments are usually delivered with the CRT or IMRT technique. In CRT, a uniform target dose is typically achieved by irradiating the patient with multiple coplanar fields that are modulated with regard to shape using multileaf collimators (MLC). In IMRT, the patient is generally irradiated with more fields than in CRT and the intensity of each field is modulated through both varying the beam output and modulating the MLC. The treatment plans used to deliver IMRT are calculated using inverse treatment planning in which a set of objectives are predefined and an optimized treatment plan is calculated by the TPS. The IMRT treatment plans can consequently be highly sophisticated involving many fields with complex MLC shapes continuously moving during irradiation producing advanced dose distributions with sharper dose gradients than in CRT (Kry et al 2017).

Modern linear accelerators often have the capacity to deliver IMRT treatments while simultaneously rotating the gantry around the patient. The irradiation fields are then distributed over a large number of angles around the patient. This treatment technique is called volumetric modulated arc therapy.
2. Doses to healthy tissues from radiotherapy and CBCT imaging

(VMAT) and has the advantage of shorter irradiation times than both CRT and IMRT (Wolff et al 2009).

While both IMRT and VMAT can create dose distributions with superior target conformity and sparing of OAR in comparison to CRT, both techniques produce a spread of the entrance dose over a larger volume (Xu et al 2008, Kry et al 2017). This implies that patients undergoing IMRT or VMAT treatments receive a larger portion of low doses to healthy tissues in comparison to patients undergoing CRT treatments. Interestingly, this was not found in paper V in which dose distributions from CRT and IMRT treatments of head and neck cancers were compared and used to evaluate the risk of RISC in ten patients. The findings in paper V indicated that head and neck patients treated with CRT received in-field doses to healthy tissues mainly in the region below ~5 Gy or in the region above ~50 Gy. Furthermore, patients treated with IMRT mainly received in-field doses in the intermediate dose region of approximately 5-50 Gy. It should be emphasized that this study was performed on head and neck patients for 6 MV treatments and that the spread of entrance dose associated with IMRT would be expected to be more evident for irradiations of larger anatomical regions such as the abdomen or the thorax.

Another implication associated with IMRT treatments is that the use of more fields and beam modulation requires an increase in the number of monitor units\(^3\) (MU) employed for delivering the same target dose as for CRT treatments (Xu et al 2008, Kry et al 2017). The large amount of beam modulation in IMRT treatments results in photons being scattered in the collimators and depositing out-of-field doses in the irradiated patient. The out-of-field doses are also a result of photons escaping the housing of the treatment head and photons undergoing photonuclear interactions with the aperture of the treatment head (further described in 2.3.1).

Collimator scatter, head leakage and photonuclear interactions in the treatment head are all proportional to the number of MU per unit dose employed for a treatment irradiation and an increase in MU thus corresponds to an increase in the out-of-field doses. It should be noted that an increase in MU mainly causes an increase in the out-of-field doses in regions further away from the primary target (Kry et al 2017). The out-of-field doses in tissues located close to the primary field are dominated by patient scatter, which varies depending on the employed irradiation technique and field size. This was demonstrated in paper V as the average out-of-field dose to the lungs per MU was roughly three times higher for CRT treatments in comparison to IMRT treatments of head and neck tumors with 6 MV photons. The increase in MU associated with IMRT was consequently cancelled out by a decrease in dose per MU when compared to CRT. This implies that assuming a single

---

\(^3\) Monitor units are proportional to the dose deposited by the photons passing through the monitoring ionization chamber in the treatment head.
linear relationship between MU and dose could lead to erroneous results when comparing out-of-field doses from different treatment techniques.

The influence of irradiating patients with IMRT instead of CRT with regard to the risk of RISC was studied in paper V. As stated above, a redistribution of the patient dose distributions from the low and high dose region to the intermediate region was found when irradiating with IMRT instead of CRT. This dose redistribution was shown to have little effect on the risk of RISC which was rather unaffected by the employed treatment technique. More details on the risk calculations are described in chapter 4.

The secondary photon radiation produced in photon therapy can give rise to out-of-field doses of up to three orders of magnitude more than for proton PBS therapy (Stolarczyk et al 2018). Considering that the out-of-field doses from secondary neutrons have been shown to be rather similar for high-energy photon therapy and proton PBS therapy, the total out-of-field doses from high-energy photon therapy irradiations could be higher than the corresponding total out-of-field doses from proton PBS irradiations (Hälg et al 2014, Lillhök et al 2017, Stolarczyk et al 2018).

2.3.1. Photon interactions

The interaction processes of photons traversing through matter differ from those of charged particles. A charged particle with a given kinetic energy cannot penetrate matter beyond a specific depth while a photon could potentially travel through a thick block of matter without undergoing any interactions. The reason for this is that the uncharged photons are unaffected by the Coulomb forces of the surrounding atomic electrons and nuclei. Instead of undergoing continuous interactions, photons usually undergo few interactions in which a majority of the kinetic energy is lost (Attix 1986). The stochastic nature of the photon interactions makes it impossible to predict the fate of an individual photon but the attenuation of a photon beam can be characterized as a negative exponential function.

The photon interactions relevant with regard to dose depositions in human tissues in the clinical energy range of approximately 1-20 MV are dominated by Compton scattering (Attix 1986). Thus, the vast majority of the in-field doses in photon therapy originate from the primary beam as the photons undergo Compton scattering with the atomic electrons.

As seen in Figure 3, photons with energies greater than \(~10\) MeV can undergo non-elastic photonuclear interactions with the atomic nucleus in high \(Z\) materials, which can give rise to secondary neutrons through \((\gamma,n)\) reactions. The photons can undergo non-elastic photonuclear interactions in the primary collimator in the treatment head and in other apertures such as the anode target, flattening filter or the MLC. The cross-section for non-elastic
Photonuclear interactions in human tissues, such as water in Figure 3, is however negligible (Kry et al. 2017).

2.4. CBCT imaging

Diagnostic imaging with ionizing radiation results in rather low doses for a vast majority of all patients being imaged and typical organ doses from a single diagnostic procedure are in the mGy or cGy range (Stock et al. 2012). However, due to the high number of patients undergoing diagnostic procedures, the dose from imaging constitutes a large fraction of the total population dose (BEIR 2006). Under the assumption of a linear relationship between dose and risk of RISC for low doses (see chapter 4), the image-associated dose contribution is highly relevant with regard to the risk of RISC. Furthermore, the use of image-guided radiotherapy (IGRT), in which the patient is repeatedly imaged over the course of radiotherapy, has increased rapidly over the last decade (Alaei and Spezi 2015). Patients undergoing IGRT can receive doses from imaging of the order of Gy (Ding et al. 2018) and the image-associated dose burden for these patients can consequently no longer be disregarded as low doses.

Patient doses associated with diagnostic imaging vary greatly with different types of imaging modalities, imaging parameters and patient anatomy (Gudowska et al. 2014, ICRP 2015, Ding et al. 2018). Repeated patient imaging is usually performed with on-board imaging (OBI) devices capable of acquiring planar x-ray images or CBCT images, where the latter technique has been increasingly employed after being introduced in the late 1990’s (Alaei and Spezi 2015). The success of CBCT imaging using OBI devices for IGRT purposes can be explained by the volumetric information in CBCT images, which addresses the increasing demands for accurate patient positioning due to the sharp dose gradients associated with modern treatment techniques such as IMRT.

One of the main concerns with CBCT imaging is the high dose burden that can be up to 10-100 times higher in comparison to planar x-ray imaging (Ding et al. 2018). Another implication with CBCT is the potential increase in integral dose due to the relatively large field size, up to around $40 \times 40 \text{ cm}^2$ (Alaei and Spezi 2015). As the CBCT rotates around the patient, a larger region of healthy tissues is being irradiated in comparison to planar imaging and doses are deposited in organs located relatively far from the primary radiotherapy target. It should be emphasized that the information from CBCT images can be used to reduce the margins surrounding the target volume and consequently reduce the dose to adjacently located OAR (Maund et al. 2014, Ariyaratne et al. 2016). The proper use of CBCT imaging can thus also lead to a reduction in doses to healthy tissues.
While IGRT with CBCT has been used for photon therapy applications for many years, CBCT systems mounted on proton gantries have become commercially available only in recent years and are now being more frequently employed in the clinic. The ability to reduce the doses to healthy tissues is one of the key raisons d'être for proton therapy (Paganetti 2012, Newhauser and Zhang 2015). Reducing the target margins could therefore be even more important for several proton therapy treatments than for corresponding photon therapy treatments. This could result in a more frequent use of CBCT imaging for proton therapy patients, which would be justified in the case of improved target coverage and reduced doses to OAR. However, concerns exist on whether a default use of repeated CBCT imaging for a majority of patients undergoing proton therapy could compromise the dose-saving benefits associated with protons.

In paper IV, patient doses from imaging with a proton gantry-mounted CBCT system were determined from Monte Carlo simulations. The cumulative organ doses from repeated daily CBCT imaging ranged between 0.2-1.6 Gy with the maximum dose deposited in the femoral heads when imaging with a pelvis protocol. The dose of 1.6 Gy corresponds to roughly 3% of a prescribed target dose of 50 Gy and is below the suggested level of 5% at which the image dose should be considered for treatment planning calculations (Ding et al 2018). Neglecting an additional organ dose of almost 2 Gy could however seem unjustified as this contribution could result in a total organ dose exceeding the dose threshold used for treatment planning.

Unfortunately, as the in-field doses to healthy tissues from radiotherapy greatly exceed the doses from imaging, it is not uncommon that both justification and optimization are disregarded in imaging of radiotherapy patients (Alaei and Spezi 2015). This is an increasing concern with regard to the risk of RISC as the image-associated doses are expected to increase and younger patients, more prone to develop radiation-induced cancers, are receiving radiotherapy more often (Dasu and Toma-Dasu 2014, Yock et al 2014, Kry et al 2017).

Previous studies on CBCT systems mounted on photon therapy gantries have shown that organ doses are somewhat constant for a given imaging protocol (except for high-density tissues receiving higher doses) (Stock et al 2012, Nelson and Ding 2014). This was also seen in paper IV, as the average absorbed doses to soft tissues located inside the CBCT imaging field were similar for a given imaging protocol. A clinical implementation of the doses from repeated CBCT imaging could consequently be done by simply adding the average organ doses associated with a specific imaging protocol to the dose-volume histograms (DVH) calculated from the dose distribution of the radiotherapy treatment. This would result in DVH more accurately representing the actual organ doses in comparison to neglecting the dose from CBCT imaging which is current clinical practice.
2.4.1. Kilovoltage x-ray interactions

The photoelectric effect is the dominating interaction process in tissue for kilovoltage x-rays from CBCT imaging. The cross-section for the photoelectric effect increases with increasing $Z$ as illustrated by the mass attenuation coefficients and the x-ray energy spectrum in Figure 4. Consequently, the absorbed doses to bone tissues from CBCT imaging determined in paper IV were roughly two times higher than the corresponding doses to soft tissues.

This demonstrates the importance of determining the absorbed dose to a medium when performing organ dose assessments for CBCT imaging. If organ doses from diagnostic procedures are derived from measurements performed with detectors calibrated for dose to water, the doses to bone tissues could be highly underestimated. It has been shown that the doses to high-density tissues from CBCT imaging can be up to four times higher than the corresponding doses to soft tissues (Ding and Coffey 2009, Walters et al 2009).

Figure 4. Mass attenuation coefficients for photoelectric effect (PE) and Compton effect in compact bone (ICRU) and water adopted from XCOM (Berger et al 2010) together with a normalized 120 kV x-ray spectrum generated with the Spekcalc software (Poludniowski et al 2009).
2. Doses to healthy tissues from radiotherapy and CBCT imaging
3. Monte Carlo simulations

Monte Carlo simulations have been employed in the field of radiation since the 1940s and for medical physics applications for over 50 years (Metropolis 1987, Rogers 2006). The principle behind the Monte Carlo method is to calculate the result of a task using stochastic algorithms with random numbers as input. If a high enough number of independent random numbers is scored, the distribution of the result will regress towards a normal distribution in accordance with the central limit theorem. For radiation transport applications, the principle behind the Monte Carlo technique is based on sampling of random numbers over various probability distributions defined from interaction cross-sections. The transport of particles is calculated sequentially and the interaction probabilities are sampled from experimentally evaluated cross-section libraries or calculated using different physics models.

In this thesis, the general purpose code MCNP6 (Los Alamos National Laboratory, Los Alamos, USA) (Goorley et al 2016) was used to simulate radiation transport in papers I-IV. The simulation of multiple scattering of charged particles in MCNP6 is computed using the condensed history method (Berger 1963) in which the energy loss and energy straggling of the particle is averaged over one major step length and the angular scattering and production of secondary particles is sampled in several substeps (Pelowitz 2013). The Landau and Vavilov theories are used to sample the energy straggling of electrons and protons, respectively. The angular deflection is sampled from a probability distribution based on the Goudsmit-Saunderson theory for electrons and from a modified Gaussian approximation of the Rossi theory for protons. The Bertini model was used to simulate nuclear interactions as further described in 3.1.

The accuracy of any Monte Carlo simulation is highly correlated to the performance of the computational processes and physics libraries, but also with the accuracy of the problem description. I.e. the setup of the simulation problem should accurately represent the true nature of the problem. For simulations of radiation transport in human tissue, the geometrical representation of the human anatomy could have a large impact on the results. An approach for representing human anatomy in Monte Carlo simulations with MCNP6 developed in this thesis is described in 3.2.

To ensure an accurate representation of the true nature of a simulation problem, the Monte Carlo simulations should be validated against
measurements. The methodology behind the validation procedures carried out in this thesis is presented in 3.3.

3. Monte Carlo simulations

22

3.1. Modelling intra-nuclear cascades

As described in chapter 2, hadrons such as protons and neutrons can undergo elastic and non-elastic interactions with the atomic nuclei of the medium. These interactions may include nucleons being hit by primary particles or by secondary nucleon projectiles produced from previous nuclear interactions. The complex chain of interactions involved in non-elastic nuclear interactions cannot be accurately modelled using conventional Monte Carlo particle tracking and are instead often modelled with an INC model.

In the Bertini INC model (Bertini 1963) used in the MCNP6 simulations in this thesis, the protons or neutrons are treated as free particles within the nucleus and the interaction cross-sections are based on free hadron-nucleon cross-sections (Ferrari and Sala 1996). The nucleus is considered as a cold Fermi gas and the only quantum interplay between the nucleons follows that of the Pauli exclusion principle stating that two nucleons are restricted from having identical sets of quantum numbers, i.e. occupying the same quantum state. The nucleus potential acting on an incoming projectile varies with distance from the center of the nucleus as the nucleus is divided in discrete spheres of different nucleon densities. All intra-nuclear interactions are modelled independently and secondary particles produced within the nucleus are handled identical to primary particles.

The INC modelling is initiated by a description of the target nucleus followed by the determination of a spatial point of interaction from sampling over a geometrical probability distribution (Ferrari and Sala 1996). After the point of interaction has been determined, the interaction probability is sampled from the free hadron-nucleon cross-sections. If the kinetic energy of the secondary particles is above an energy cutoff value, the particle transport is further simulated until the next interaction or until the particle escapes the nucleus.

When the energy of the remaining nucleons has decreased below an energy threshold, the INC stage is followed by a pre-equilibrium stage in which the configuration and excitation energy of the nucleus is determined. When the configuration of the residual nucleus is completed, the evaporation stage of the nucleus is modelled and nucleons and light fragments are emitted. The evaporation stage continues until the excitation energy of the nucleus is below the energy required for particles to be emitted from the nucleus. At this stage, the probability of the residual nucleus to breakup is modelled. In the final de-excitation stage, the excitation energy of the remaining nucleus is emitted as gamma radiation after which the INC modelling is terminated.
3. Monte Carlo simulations

One of the drawbacks associated with the INC modelling is that many of the model assumptions become more approximate with decreasing projectile energy resulting in a reduction in accuracy for incoming projectiles with kinetic energies below ~100-200 MeV (Ferrari and Sala 1996). It should therefore be emphasized that although Monte Carlo simulations of non-elastic nuclear interactions using INC models provide a highly sophisticated simulation tool, INC modelling is based on numerous assumptions and simplifications associated with large uncertainties. This highlights the importance of validating Monte Carlo models against measurements as further discussed in 3.3.

However, the stepwise calculations of INC models make them highly suitable for implementation in Monte Carlo transport codes. Furthermore, INC models are more time efficient and more accurate in reproducing experimental data than analytical approaches (Ferrari and Sala 1996).

3.2. Modelling human anatomy

The geometry in MCNP6 is based on cell structures defined by surfaces (Pelowitz 2013). All space in which the radiation transport is calculated must consist of cells with specified material definitions and mass densities. Such cells are made up by surfaces or so-called *macrobodies* representing standard geometrical shapes (spheres, cylinders etc.). This standard approach for building geometries in MCNP6 has its limitations when simulating complex geometries such as the human anatomy. Indeed, the major parts of the human body can be represented by blocks of geometrical shapes consisting of e.g. water or air, but an accurate representation of the many tissue heterogeneities of a human requires higher precision.

A high-accuracy representation of the human anatomy can be found in a CT image of the human body. The information stored in CT images corresponds to the attenuation of x-rays in individual voxels and is expressed in Hounsfield units (HU). The information in a CT image thus reveals both the precise position of a specific voxel and its attenuation properties. In order to implement this information in Monte Carlo simulations, the HU must be converted into mass densities and elemental compositions.

The conversion from HU to mass densities can be performed using a stoichiometric calibration curve (Schneider *et al* 1996). A stoichiometric calibration curve can be derived from a parametrization of the HU values associated with a specific CT scanner. By measuring the HU of materials with known compositions, the constants of the parametrization can be determined and a relation between mass density and HU valid for tissues can be obtained by using representative elemental compositions of human tissues. The corresponding conversion of HU to elemental compositions in this thesis was
Monte Carlo simulations derived from a study by Schneider et al. (Schneider et al. 2000) reporting the elemental composition of 24 different HU intervals.

Thus, each voxel in a CT image can be represented with a mass density and elemental composition as required to perform Monte Carlo simulations. The standard geometrical shapes used to build geometries in MCNP6 do not allow for a representation of CT data. Instead, lattice structures filled with repeated small structures (e.g. CT voxels) can be used for geometrical representations of CT images of the human body. As the MCNP6 package does not include a tool for importing CT data, an in-house Matlab script (Mathworks, Natick, USA) was developed to convert CT data into MCNP6-compatible lattice structures used for simulations of human anatomy in papers II-IV.

The HU of the CT voxels were divided into 24 bins with specific mass densities and elemental compositions. The elemental composition of each bin was obtained from the HU-to-elemental composition conversion and the mass density of each bin was calculated from a stoichiometric calibration curve. Thus, the original CT data was converted into 24 materials with specific mass densities and elemental compositions assigned to lattice structures representing the human anatomy. The anatomic lattice representation was subsequently scaled from the original 512×512 matrix size to a 128×128 matrix size enabling faster Monte Carlo simulations.

An example of a whole-body phantom CT dataset converted from original Digital Imaging and Communications in Medicine (DICOM) format through Matlab rebinning to MCNP6 lattice geometry is presented in Figure 5.

![Figure 5](image.png)

**Figure 5.** CT geometry of a whole-body phantom displayed as: (a) original 512×512 DICOM image, (b) 128×128 rebinned data in Matlab and (c) 128 × 128 rebinned lattice structure in MCNP6.
3.3. Validation of Monte Carlo beam models

The accuracy of the physical interactions and processes computed by a Monte Carlo code is related to the quality of the implemented cross-sections and physics models employed for the simulations. Assuming that all physical processes are satisfactory modelled and that the geometry is well represented, the Monte Carlo model should still be validated for its specific application (Ding et al 2008, Farah et al 2014). Inaccurate modelling of a Monte Carlo problem could yield misleading results with high precision but poor accuracy (further described in 3.4). Errors originating from inaccurate descriptions of the true nature of a problem may be hard to discover for complex simulations involving several different steps. It is therefore important that the Monte Carlo model used for simulating the problem is validated against dedicated measurements of the modelled problem. The validation can also include comparisons with beam models constructed using different Monte Carlo codes or with the same code but using different settings for the physics interactions.

In paper I, a proton PBS system was characterized in MCNP6 and validated against measurements performed at a clinical proton therapy facility. This beam model was subsequently further developed and used to simulate secondary radiation produced in conjunction with proton irradiations in paper II and the results were validated against measurements. In paper IV, a proton gantry-mounted CBCT system was characterized with both MCNP6 and the Geant4 Application for Tomographic Emission (GATE) (Jan et al 2004). The two codes were validated against each other and against measurements. The general methodology employed for validating the Monte Carlo models in papers I, II and IV may be summarized in the following three steps:

Characterization: The Monte Carlo model is characterized and built using input data such as vendor specifications and measurement data.

Reproducibility: The Monte Carlo model is iteratively developed until it can accurately reproduce results from measurements.

Validation: The Monte Carlo model is used to simulate an independent experiment and the output is validated against measurements.

The characterization of a Monte Carlo beam model could in principle be carried out without using measured data as input and without confirming the reproducibility against measurements. If a complete description of all parameters associated with e.g. a proton therapy facility is known, the complete beamline could be modelled and only the final validation would be necessary to ensure an accurate beam model. However, a complete model of a proton therapy facility is neither time efficient nor justified if the purpose is to simulate the protons impinging on the patient. Instead, the Monte Carlo beam model is usually characterized using measured data of e.g. integral depth.
dose (IDD) curves and spatial profiles. Such measurements provide information about the characteristics of the proton beam but do not reveal the underlying physical properties, such as energy distribution and beam divergence. These properties must instead be modelled based on qualified assumptions using vendor specifications and knowledge of the specific system. The properties can subsequently be evaluated through a comparison between simulations and measurements (reproducibility). Examples of the construction of a proton PBS model and a CBCT system are described in 3.3.1 and 3.3.2, respectively.

3.3.1. Proton PBS model

The MCNP6 model of a clinical proton PBS system in paper I was constructed from measured data of IDD curves in water and lateral beam profiles in air. As the entire beamline was not modelled, the energy distribution and beam divergence were modelled using data from measurements and knowledge regarding the specific beamline. Thus, the spatial profiles of proton spots of different energies were characterized using Gaussian spatial distributions based on measured beam profiles at different positions in air. The energy distribution was defined as a probability distribution function (PDF) using a symmetrical Gaussian-like distribution and a low-energy tail corresponding to the protons scattered in the treatment head. The beam model was then used to reproduce the measurements of the IDD curves and spatial profiles, and the model was iteratively developed until a satisfactory reproducibility was achieved. The beam model was then validated against absorbed dose IDD curves determined from absolute dosimetry reference measurements.

An example of the beam construction is shown in Figure 6 illustrating how the agreement of the IDD curve for 160 MeV protons in water was improved as the PDF of the energy distribution was developed.
3. Monte Carlo simulations

Figure 6. Three different energy probability distribution functions (PDF) for 160 MeV protons (left panels) with corresponding integral depth dose (IDD) curves in water (right panel). The black IDD curves correspond to measurements, red IDD curves correspond to MCNP6 simulations, and green dashed curves illustrate point-by-point percentage differences between simulations and measurements.

3.3.2. CBCT beam model

The construction of the CBCT system in paper IV was similar as for the proton PBS system in paper I. The CBCT system was first characterized from specifications provided by the vendor and measurements of central-axis depth dose curves in water and spatial distributions in air. As for the proton beam, this measured data did not disclose the physical properties such as energy distribution or beam divergence. These properties were instead modelled based on qualified assumptions and knowledge of x-ray energy distributions, beam filtering and collimation. The MCNP6 and GATE beam models were iteratively developed until the measured data could be accurately reproduced.

The beam models were then validated against absorbed doses determined from measurements with a calibrated ionization chamber for several different positions and imaging protocols. Spatial profiles of the CBCT imaging field in air determined from measurements using a Lynx scintillation detector (IBA dosimetry, Schwarzenbruck, Germany) and simulations with the MCNP6
Monte Carlo simulations beam model together with central-axis line profiles are presented in Figure 7. The spatial profiles of the CBCT field were determined in air at 64 cm before isocenter.

**Figure 7.** Normalized spatial profiles of a proton gantry-mounted CBCT imaging field determined in air from measurements with the Lynx scintillation detector (a) and simulations using the MCNP6 beam model (b). Normalized line profiles along x-axis (c) and y-axis (d). Black dots correspond to the measured profile and red curve corresponds to MCNP6 simulations.

3.4. Uncertainties in organ dose simulations

The uncertainties associated with scoring different quantities in Monte Carlo simulations consist of a statistical component and a systematic component. The statistical uncertainty of a tally output in MCNP6 is calculated as the relative uncertainty defined as the ratio between the standard deviation of the tallied quantity and the mean value of the tally output (Pelowitz 2013). While the statistical component is a measure of the precision of the simulation, the systematic uncertainty determines the accuracy of the simulations with regard to representing the true nature of the problem. The systematic uncertainty is affected by several factors such as the accuracy in calculations of the physical interactions by the Monte Carlo code and also by the setup of the simulation problem. It is therefore possible to perform a simulation with a high precision
(low statistical uncertainty) but a low accuracy (high systematic uncertainty) if the nature of the problem is not correctly modelled.

In papers II, III and IV, the human geometry was modelled using lattice structures converted from CT data of real patients and a whole-body phantom as described in 3.2. While this approach provides a higher accuracy in representing the human anatomy than e.g. phantoms built from simple geometrical shapes, the introduction of systematic uncertainties from this conversion cannot be ruled out. However, the conversion of CT data for the simulations of organ doses from CBCT imaging in paper IV were done using two different approaches for MCNP6 and GATE and the good agreement between the two codes indicates that potential systematic errors originating from the CT conversion were small.

The calculation of out-of-field absorbed doses and equivalent doses from proton PBS treatments in papers II and III are associated with systematic uncertainties originating from the potential errors in experimental geometry and uncertainties in the cross-section data and the employed physics models. The systematic uncertainties of the out-of-field equivalent doses in paper II were estimated as 20% of the calculated equivalent doses. This value was twice the estimated uncertainty of the absorbed out-of-field doses. The main reason for the large uncertainties in the calculated equivalent doses originates from the ICRP radiation weighting factor, $w_R$, used for the calculations. The $w_R$ was originally introduced by the ICRP for radiation protection purposes and is defined for external irradiations. Thus, implementing it for proton therapy applications where radiation is produced and transported within patients is not ideal (Xu and Paganetti 2010, Kry et al 2017).

The reason for including the equivalent dose and not only the absorbed dose, which is a more fundamental quantity in the sense that it has not been modified with a theoretical weighting factor, was that the absorbed dose does not correspond to the biological effect of the radiation. One of the main rationales behind determining the out-of-field doses associated with proton PBS therapy was to estimate the risk of RISC. This requires that the biological effect of the radiation be taken into account. The large uncertainties associated with the out-of-field equivalent doses were thus necessary in order to carry out estimations of the risk of RISC. While the precise magnitude of the uncertainties associated with calculations of out-of-field equivalent doses is debatable, several studies have suggested that the uncertainties of similar dose quantities originating from secondary radiation produced in proton therapy could be up to 40% of the determined dose quantity (Polf and Newhauser 2005, Farah et al 2014).

As further described in chapter 4, estimations of the risk of RISC are associated with large uncertainties, which should be recognized when drawing conclusions from such studies. This is valid also for equivalent doses originating from secondary radiation.
3. Monte Carlo simulations
4. Risk of radiation-induced second cancer

The unwanted dose contribution to healthy tissues from radiotherapy and CBCT imaging described in chapter 2 can give rise to stochastic effects such as RISC. Radiation-induced tumors are hard to identify due to the long latency associated with these tumors (up to several decades) and that the histological characteristics cannot reveal whether a particular tumor has been induced by radiation (ICRP 2007). Reliable dose-risk relationships are preferably established from retrospective epidemiological studies comparing tumor incidence in large cohorts of irradiated and un-irradiated patients over a long follow-up period. Such studies have demonstrated an elevated risk of RISC for patients undergoing medical irradiations with ionizing radiation (Brenner et al 2000, Pearce et al 2012, Grantzau et al 2013, Mathews et al 2013, Schaapveld et al 2015). The risk of RISC may vary for different irradiation patterns, i.e. fractionation schedules and dose distributions. The large differences in irradiation patterns between modern and older treatment techniques thus complicate the implementation of risk models derived from epidemiological studies based on old patient data to modern treatment techniques (Dasu and Toma-Dasu 2014). The dose records for healthy OAR, especially for out-of-field tissues, are often inadequate and incomplete further complicating retrospective risk estimations. Also, the risk of RISC is affected by numerous personal factors such as genetic susceptibility and smoking (ICRP 2007).

Increased life expectancies for patients undergoing radiotherapy or imaging with ionizing radiation are always associated with an elevated risk of RISC as the probability for a tumor to develop increases if the patient survives for a longer period of time. The increased patient survival associated with the continuous improvement in diagnostic accuracy and treatment outcome together with the positive effects associated with cancer screening could consequently result in an increased risk of RISC (Kry et al 2017). This is especially relevant for young patients expected to live for many years after irradiation (Dasu and Toma-Dasu 2014, Yock et al 2014).

While the relatively low risk of RISC is a small price to pay for an individual patient possibly being cured from cancer, the risk of RISC is highly relevant when considering large populations. Consequently, the risk of RISC...
should always be kept at a minimum without compromising the diagnostic accuracy or treatment outcome.

### 4.1. Mechanisms behind RISC

Experiments on animals and cell cultures have shown that the DNA in the cell nuclei is the most critical target of ionizing radiation with regard to biological effects (ICRP 2007). The most important type of DNA damage induced by ionizing radiation is the double strand break (DSB) in which both strands on the DNA chain are damaged. Although the DSB are less likely to occur than single strand breaks, the DSB are more difficult to repair and consequently associated with an increased probability of causing cell death or cell mutations (Hall and Giaccia 2006).

If a DNA damage is misrepaired and the cell manages to undergo cell division, the DNA damage will be transferred to the daughter cells. The properties of these mutated cells vary depending on the DNA sequence (gene) affected by the DNA damage. One of the most important cell functions with regard to carcinogenesis is the ability to control the cell reproduction. If the mutated cell fails to regulate this function (e.g. through inactivation of the p53 gene), the cell could undergo uncontrolled cell division possibly resulting in a population of malignant cells. This cell population could ultimately develop into a self-supporting cancer tumor capable of invasion of surrounding healthy tissues (Hall and Giaccia 2006).

The DNA damage can be caused through direct and indirect action, where the former type dominates for radiation with high LET. For photons, the free electrons produced through Compton and photoelectric interactions can induce DNA damage through direct actions in which the electrons interact with the atomic electrons of the atoms in the DNA directly or through indirect actions in which the electrons interact with the surrounding molecules giving rise to free radicals subsequently damaging the DNA (Hall and Giaccia 2006).

The increased LET of heavier particles is associated with an increased probability of DNA damage through direct actions producing a higher number of DSB leading to an increased RBE in comparison to low LET radiation such as photon radiation. It has been shown that the dense ionization tracks associated with high LET radiation can induce complex clusters of many types of DNA damages that may amount to as much as 90% of the total DNA damage (ICRP 2007).

Neutrons do not undergo interactions with the atomic electrons but with the atomic nuclei and the DNA damage induced by neutrons is consequently mainly a result of the energy depositions from the secondary charged particles produced from nuclear interactions. Most neutron-induced DNA damages originate from direct actions of protons produced from elastic nuclear scatter between neutrons and hydrogen (Hall and Giaccia 2006).
4.2. Current knowledge of the risk of RISC

The current knowledge of the risk of RISC is based primarily on the life span study (LSS) of the survivors of the atomic bombings in Hiroshima and Nagasaki, and to some extent life span studies of occupational workers or medically irradiated patients (Hall and Giaccia 2006, ICRP 2007). The available epidemiological data from the whole-body irradiations associated with the atomic bombings indicate that the risk of RISC is linear in the range of approximately 100 mSv to ~2 Sv and the linear-no-threshold (LNT) model is widely accepted as an approximation of the risk-response for lower doses (BEIR 2006, Hall and Giaccia 2006, ICRP 2007). More recent epidemiological data suggest that the LNT model could be valid down to doses of only a few mSv (Preston et al 2012).

The risk of RISC is higher for younger patients and while the magnitude of this increase in risk is uncertain, it has been suggested that the lifetime risk of solid cancer induction after a whole-body exposure of 100 mSv could be doubled for an age at exposure of 10 years in comparison to 30 years (Preston et al 2012). One of the difficulties associated with deriving risk estimates as function of age at exposure is that the trends in risk are concealed by the increased risk of non-radiation-induced cancer associated with higher attained ages.

The validity of the LNT model in the low dose region has been subject for debate for decades. Indeed, a simple linear response of cancer induction could be considered as an oversimplification with regard to the underlying biological mechanisms. However, the large uncertainties of the risk-response in this dose region warrant a conservative approach and the LNT model is therefore considered the most reasonable model within the field of radiation protection (BEIR 2006, ICRP 2007).

The risk-response of tissues receiving higher doses, typically from radiotherapy treatments, is also a topic with diverse opinions. Some epidemiological data exist for this dose region, e.g. the induction of leukemia has been best represented by a linear-quadratic bell-shaped dose-risk response with a declining risk of RISC for doses above approximately 3 Gy (Hall and Giaccia 2006). The associated uncertainties of such studies are however large due to inter-organ variability, inadequate dose recordings and the lack of large patient cohorts (in comparison to the low dose region where a considerably larger population of diagnostic patients is included). If a reliable dose-risk response would be established in the high dose region, the risk of RISC could be implemented in the clinical decision process when deciding between e.g. surgery or radiotherapy (Dasu and Toma-Dasu 2014).

Previous studies have reported an increase in RISC in organs located close to the irradiated primary tumor receiving doses up to approximately 6 Gy
4. Risk of radiation-induced second cancer

(Dörr and Herrmann 2002, Diallo et al 2009). These studies indicate that the highest incidence of radiation-induced tumors for patients undergoing radiotherapy is evident in organs receiving rather high in-field doses. Long-span epidemiological studies on photon radiotherapy have shown that the associated risk of RISC is in the range of 0.5-1.4% (Brenner et al 2000, Grantzau et al 2013). Epidemiological studies on the risk of RISC following proton therapy are scarce although preliminary results indicate a possible decrease in risk in comparison with photon treatments (Chung et al 2013, Eaton et al 2015). It could be anticipated that the improved sparing of adjacent tissues in proton PBS therapy is associated with a decrease in risk of RISC (Hall 2006, Schneider et al 2006, Braunstein and Nakamura 2013, Newhauser and Zhang 2015).

4.3. Modelling the risk

While all estimations of the risk of RISC are associated with large uncertainties, the LNT model is generally accepted for risk assessment in the low dose region where epidemiological data is scarce (BEIR 2006, Hall and Giaccia 2006, ICRP 2007). The results of the LSS and other epidemiological studies have shown inter-organ variabilities in the risk of RISC and these variations have been implemented in different risk models to compute organ-specific risk estimates.

One example of a linear risk model for low doses is the biological effects of ionizing radiation (BEIR) VII model that can be used to estimate the lifetime attributable risk (LAR) of RISC (BEIR 2006). The BEIR VII model was used in paper II to estimate a LAR of approximately 0.01% from the out-of-field doses originating from a proton PBS therapy of a brain tumor. The LAR is calculated for different organs based on organ-specific risk coefficients and baseline risks and subsequently summarized over all organs.

The slope of the linear risk-response varies with the risk coefficient employed for the calculations. As most risk coefficients used for estimating the risk of RISC are based on the same input data, the differences in risk predictions between different risk models mainly originate from assumptions associated with extrapolating the risk coefficients derived from the LSS study.

For the high dose region, several different models have been proposed for estimating the risk of RISC. The majority of these models (excluding the LNT model for higher doses) employ either a bell-shaped response in which the risk increases until a point at which cell killing becomes high enough to reduce the risk, or a plateau-shaped response where the risk increases with dose up to a limit after which it flattens out (Dasu and Toma-Dasu 2014). As the predictions made by these theoretical models can be at least partially validated against epidemiological data, the predictions of a risk model should be compared against the available data (Hall and Giaccia 2006). Consequently,
the models used for estimating the risk of RISC in the high dose region should predict a linear dose-risk response in the low dose region reflecting the available epidemiological data.

The dose-risk responses for a linear, bell-shaped and plateau-shaped risk model are shown in Figure 8 where the low dose region in which all models predict a linear relationship is indicated. The limitation of the linear model in the high dose region is illustrated as the risk exceeds 100% after a certain dose level, indicating that a linear model with a constant slope should be employed only in the low dose region.

![Figure 8](image.png)

**Figure 8.** Three risk models used for calculating the risk of radiation-induced second cancer (RISC). The gray box indicates the low dose region where all models predict a linear response.

It could be argued that the model parameters in the risk estimation models should mainly be considered as fitting parameters. Indeed, the parameters of some risk models could be partially explained by the biological mechanisms behind cancer induction. However, the complex biological processes of radiation-induced cancer are difficult to represent using only a few parameters. This does not imply that the risk models are inaccurate, only that the mechanisms behind cancer induction should not be oversimplified.

Theoretical estimations of the risk of RISC are associated with large uncertainties originating from several different sources of errors, complicating the possibility to estimate the uncertainty associated with a final estimated risk value. The stochastic nature of cancer induction prevents accurate predictions.
4. Risk of radiation-induced second cancer

of risk values for individuals exposed to radiation. The risk estimate will always be expressed as a probability and considering the very large uncertainties associated with such estimates, calculations of absolute risks for individual patients are not recommended. Individual risk estimates can however be used during the clinical decision process to compare the risk of RISC associated with different patient irradiations.

The high dose gradients associated with modern treatment techniques such as photon IMRT and proton PBS therapy produce large dose heterogeneities in OAR located close to the irradiated tumor volume. These heterogeneities could have large impact on the predicted risks and should consequently be considered when assessing the risk in these organs. Instead of calculating the risk using the average organ dose, the risk could be calculated in sub-volumes or dose intervals and summarized to estimate the total risk to an organ (this was done in paper V). Other factors to be considered when calculating the risk of RISC include organ volume or mass, dose rates, fractionation schedules and radiation quality (Dasu and Toma-Dasu 2014).

In paper V, the risk of RISC from photon IMRT and CRT treatments was estimated and compared for patients treated for head and neck cancer. The risks were calculated using two bell-shaped models and one plateau-shaped model and the results suggested that the risk was in the order of 1-2% and unaffected by the employed treatment technique. While more studies with longer follow-up periods are needed, this finding has been supported by studies indicating that IMRT treatments are not associated with an elevated risk of RISC in comparison to CRT treatments (McDonald et al 2008, Journy et al 2016).

In order to evaluate the predictions made by a theoretical risk model against epidemiological data, it is essential that the patient dose has been accurately determined. As seen in Figure 8, the risk models predict different risks depending on the dose. Thus, the estimated risk of RISC differs depending on whether e.g. only the in-field dose contribution from a radiotherapy treatment is used for the risk calculation or if the additional dose contribution from out-of-field doses and doses from repeated CBCT imaging are included. While this effect could be limited for the low out-of-field doses produced in proton PBS therapy, the additional dose contribution from repeated CBCT imaging could have a relevant impact on the calculated risk values.

The total dose contribution should be implemented before employing a risk model to estimate the risk of RISC as the risk originating from different dose contributors is additive only in the low dose region where the dose-risk response is assumed linear. In the higher dose region, the non-linearity of the risk models prohibits separate risk calculations to be summed.

The ultimate purpose of studying the relation between dose and the risk of RISC is to derive a relationship with a reasonably low associated uncertainty. The answer to this task could be found in the field of radiobiology (e.g. by discovering a specific biomarker for the risk of RISC) or within the field of
epidemiology by deriving a reliable dose-risk-response from a large dataset of irradiated patients. As described in the brief overview of carcinogenesis in 4.1, the development of tumors is usually regarded as a multistep process (BEIR 2006). The possibility to find a single biomarker associated with the entire process of tumor development could therefore be difficult or even impossible. While there are many problems associated with retrospective epidemiological studies of irradiated patients, it could be that the key for unveiling a more accurate dose-risk response than today could be found through these studies. In order to conduct reliable epidemiological studies on the risk of RISC, it is essential that the total dose to the patient is determined and that all dose contributions are considered.
4. Risk of radiation-induced second cancer
5. Conclusions

The fundamental role of ionizing radiation in modern medicine is likely to be further consolidated as overall life expectancies increase and more efficient treatment techniques are emerging. One major concern with this development is that after a patient has undergone diagnostic imaging and radiotherapy, the total dose burden to the healthy tissues will not be known, nor stored. Instead of considering the sum of all different dose contributions, normal practice considers the various dose contributions as individual. This issue is becoming more concerning as the number of diagnostic procedures increases and young patients undergo radiotherapy more often. While the success of modern treatments and imaging techniques is beneficial for the patient, the associated risk of RISC could be better understood in the future if the additional dose contribution from repeated CBCT imaging and out-of-field doses would be stored together with the in-field doses from radiotherapy treatments.

The disadvantages of modern treatment techniques such as photon IMRT and proton PBS should be regarded in the light of the large clinical benefits associated with these treatments. While the implementation of new treatment techniques should be carried out with caution, alarming statements of potential drawbacks could result in under-usage of superior treatments. In contrast to several studies published at the time when IMRT was clinically introduced, the results in paper V indicated that photon IMRT treatments of head and neck tumors are not associated with an elevated risk of RISC when compared to photon CRT and no such tendency has yet been reported in epidemiological studies.

The findings of this thesis have shown that the out-of-field doses in proton PBS therapy of brain tumors and the associated risk of RISC are low and that the doses from IGRT procedures performed with a proton gantry-mounted CBCT system can add up to almost 2 Gy. The potential dose-sparing associated with proton PBS therapy was not overshadowed by the out-of-field doses from treatments of brain tumors but could be compromised if CBCT imaging is repeatedly employed without clinical justification. As the use of CBCT for proton therapy applications is emerging, a potential increase in the incidence of RISC could be anticipated. It is therefore highly desirable that the doses from CBCT imaging are stored together with the in-field doses from the radiotherapy procedures to allow for accurate evaluations between future risk predictions and epidemiological data of cancer induction for patients undergoing treatment today.
5. Conclusions

Studies on patient doses from modern treatment techniques and imaging procedures are continuously being conducted together with epidemiological and theoretical studies on the risk of RISC. The desire to accurately determine the risk of RISC associated with a specific radiotherapy treatment or diagnostic imaging session is however far from being realized. Future studies on patient doses from radiotherapy treatments and imaging are thus needed to increase the knowledge of the associated biological effects such as RISC in order to justify the radiation doses to healthy tissues from modern radiotherapy and imaging.
6. Summary of papers

Paper I

In this paper, a clinical proton PBS system was characterized with MCNP6. The beam model was constructed using input parameters obtained from beam commissioning including IDD curves in water and spatial profiles in air. The MCNP6 beam model was evaluated with regard to IDD curves and spatial profiles for proton energies between 60-226 MeV. The beam model was subsequently validated against absolute dosimetry measurements and the average agreement in the integral of the absorbed dose IDD curves was 0.8%. The signal losses due to lateral proton scattering when employing an ionization chamber with a limited detector diameter (4.08 cm) for IDD measurements were also investigated. The signal loss increased with increasing proton energy with a maximum signal loss of 7% for 226 MeV protons.

Paper II

The beam model developed in paper I was used to simulate out-of-field doses for irradiations of a cubic water phantom and a whole-body phantom with various proton irradiation setups. The simulations were validated against measurements performed with tissue-equivalent proportional counters. The out-of-field absorbed doses ranged between 0-135 μGy/Gy and the average agreement between measurements and simulations was 17%. The MCNP6 beam model was used to simulate the contribution of out-of-field doses originating from radiation produced in the nozzle and the results showed that this contribution, although low in absolute terms, could amount to as much as 70% of the dose. Additionally, the beam model was used to simulate a brain tumor treatment and scoring the out-of-field doses from secondary radiation. The organ doses were used to estimate the risk of RISC using the BEIR VII model for LAR calculations and the estimated risk of cancer induction from a brain tumor treatment was approximately 1 in 10000.
Paper III
In this paper, the variations in out-of-field doses from proton PBS treatments due to different irradiation setups and patient sizes were studied. The MCNP6 beam model was used to simulate a brain tumor treatment of one adult patient and one pediatric patient. Both patient treatments were simulated using a lateral field setup and a vertex field setup. The highest equivalent doses were 141 µSv/Gy for the pediatric patient and 134 µSv/Gy for the adult patient. The organ doses were higher for the vertex irradiation in both patients, however all differences were low in absolute terms indicating that the impact of different irradiation setups in proton PBS treatments of centrally located brain tumors is low.

Paper IV
In paper IV, a proton gantry-mounted CBCT system was modelled with MCNP6 and GATE. The two beam models were characterized using measurement data of central-axis depth dose curves in water and spatial profiles in air. The beam models were validated against absorbed doses determined from measurements performed on the CBCT system. The characterized beam models were subsequently used to simulate organ doses from various CBCT acquisitions and the influence of performing 200° anterior and posterior scans was studied. The results showed that organ doses from single CBCT acquisitions ranged between 6-54 mGy corresponding to a maximum cumulative dose of 1.6 Gy for daily CBCT imaging over an entire treatment course. The results also showed that anterior scans were associated with higher organ doses per mAs in comparison to posterior scans or full rotational scans.

Paper V
The aim of this study was to investigate if IMRT treatments of head and neck tumors were associated with an increased risk of RISC in comparison to CRT treatments. Ten patients were included in the study and one IMRT and one CRT treatment plan was created for each patient. The dose distributions from the two treatment techniques were used to calculate the risk of RISC to all patients using two bell-shaped risk models and one plateau-shaped model. The results showed that the risk in individual organs varied between the two treatment techniques but the total risk was relatively constant and in the order of 1-2%, indicating that IMRT was not associated with an increased risk of RISC in comparison to CRT for head and neck treatments. The results also showed that patients treated with CRT received integral doses mainly in the low dose and high dose region, whereas IMRT patients received integral doses in the intermediate dose region (~5-50 Gy). This contradicted some previous
6. Summary of papers

claims that IMRT is always associated with an increase in volumes receiving low doses.
Acknowledgements

First of all, I would like to thank my supervisor Irena Gudowska for your invaluable support throughout my entire time as a PhD student. Your knowledge and company have made these years both inspiring and fun. Your ability to always question results and keeping a critical point of view when reviewing research is truly inspiring.

I would like to thank Alexandru Dasu for your support ever since our collaboration when I was a MSc student. You have always taken your time to answer my questions and stayed up late to perform measurements either in Linköping or in Uppsala. Your devotion to the field of medical physics and curiosity in new research is very inspirational.

I would like to thank Cathrine Jonsson for all your support during my first time as a PhD student when I was working in parallel at the nuclear medicine department. Although I was away from the clinic half of the time, you always gave me your full support in pursuing my research and for that I am truly grateful.

Furthermore, I would like to thank Mariusz Kopeć for your help in learning me the basics of MCNP and for your company during my first summer as a PhD student. I want to thank Jan Lillhök and Linda Persson for your help and collaboration in performing measurements in Uppsala and also for your company throughout our collaborations. Thank you to my mentor Sören Holst for pleasant lunch discussions throughout the years. Thank you to all my colleagues at the nuclear medicine department. Thank you to the physicists involved in the beam commissioning at the Skandion Clinic for providing measurement data for paper I.

I would like to thank the people at MSF, especially Iuliana Toma-Dasu for many inspiring discussions and for making MSF a fun and inspiring group to work with. I would also like to thank Niels Bassler for appreciated input to this thesis and a nice collaboration in paper VIII. Thank you to Mona for your administrative support. Thank you to all my junior colleagues with whom I have shared many fun moments, especially during our late karaoke nights in Japan. An extra thanks to Jakob, Emely, Thomas and Helena for your valuable input to this thesis and company over the years.

Finally, I would like to thank my wife EvaMaria, my parents Anette and Peter and my sister Matilda for not being physicists and thereby keeping me somewhat sane during my time as a PhD student.
References


Attix F H 1986 *Introduction to Radiological Physics and Radiation Dosimetry* (Strauss GmbH, Morlenbach: John Wiley & Sons, Inc.)


Demarco J, Kupelian P, Santhanam A and Low D 2013 Shielding implications for secondary neutrons and photons produced within the patient during IMPT Med. Phys. 40 071701


Dörr W and Herrmann T 2002 Cancer induction by radiotherapy: Dose dependence and spatial relationship to irradiated volume *J. Radiol. Prot.* **22** A117–21


Ferrari A and Sala P R 1996 The Physics of High Energy Reactions (Workshop on Nuclear Reaction Data and Nuclear Reactors Physics, Design and Safety)


ICRP 2015 Radiological Protection in Cone Beam Computed Tomography (CBCT). ICRP Publication 129 Ann. ICRP 44


ICRU 2007 Prescribing, Recording, and Reporting Proton-Beam Therapy (ICRU report 78)


Journy N M Y, Morton L M, Kleinerman R A, Bekelman J E and Berrington de Gonzalez A 2016 Second Primary Cancers After Intensity-Modulated vs 3-Dimensional Conformal Radiation Therapy for Prostate Cancer JAMA Oncol. 2 1368–70


51


Metropolis N 1987 The beginning of the Monte Carlo method Los Alamos Sci. 125–30


Nelson A P and Ding G X 2014 An alternative approach to account for patient organ doses from imaging guidance procedures Radiother. Oncol. 112 112–8


Paganetti H 2014a Monte Carlo simulations will change the way we treat patients with proton beams today Br. J. Radiol. 87 20140293


Paganetti H 2012 Proton therapy physics (Boca Raton, FL: CRC Press/Taylor & Francis)


Pelowitz D B 2013 *MCNP6 User’s Manual, Version 1.0* (Los Alamos National Laboratory)


Rogers D W O 2006 Fifty years of Monte Carlo simulations for medical physics *Phys Med Biol* **51** R287-301


Stock M, Palm A, Altendorfer A, Steiner E and Georg D 2012 IGRT induced dose burden for a variety of imaging protocols at two different anatomical sites *Radiother. Oncol.* **102** 355–63


Xu X G and Paganetti H 2010 Better radiation weighting factors for
neutrons generated from proton treatment are needed *Radiat. Prot. Dosimetry* **138** 291–4
