Radiation therapy of upper gastrointestinal cancers with scanned proton beams
A treatment planning study
Gracinda Mondlane

Abstract
Proton beam therapy (PBT), using scanned beams, is an emerging modality used for the treatment of cancer. The clinical advantages of PBT, compared to commonly used photon beam therapy, have been demonstrated in different studies. However, the techniques used for planning and delivering treatments with photon beams have gradually been improved over the years. With the introduction of PBT in the clinic, guidelines to select patients to photon- or proton-beam therapy are indispensable.

A simple approach used for selecting patients for PBT is based on the patient age. The paediatric patient group is considered to be the most radiosensitive and, therefore, in larger need of RT techniques that provide improved sparing of the organs at risk (OARs). With the increasing number of cancer clinics with access to PBT, combined with the constant clinical need of reducing the frequency of acute and late toxicities, there has been an increased use of PBT also for adult patients. At present, there is only limited clinical follow-up data available regarding the outcome of PBT for different tumour sites, in particular for extra-cranial tumours. The use of proton beams for such cancer treatments is, on the other hand, well-established. Therefore, the expected benefit of using proton beams in cancer therapy can be translated from the results obtained in the clinical experience attained from photon-beam treatments. The evaluation of the different uncertainties influencing the radiotherapy (RT) of different tumour sites carried out with photon- or proton-beams, will also create an improved understanding of the feasibility of treating cancer with scanned proton beams instead of with photon beams.

The comparison of two distinct RT modalities is normally performed by studying the calculated dose distributions superimposed on the patient CT images and by evaluating the dosimetric values obtained from the dose volume histograms (DVHs). The dosimetric evaluation can be complemented with treatment outcome predictions in terms of local disease control and normal tissue toxicity. In this regard, radiobiological models can be an indispensable tool for the prediction of the outcome of cancer treatments performed with different types of ionising radiation. These estimates can in turn be used in the decision process for selecting patients for treatments with a specific RT modality.

This thesis consists of five articles. In these studies, treatment plans for RT with scanned proton-beams have been prepared and compared with clinical plans used for photon-beam based RT. For this purpose, dosimetric and biological-model based evaluations of these plans were performed. These studies were carried out for two distinct upper gastrointestinal (GI) cancers, namely, gastric cancer (GC) and liver metastases. RT treatments with both conventional fractionation schemes (implemented in the planning for the GC treatments) and hypofractionated regimens (implemented in the planning for the liver metastases cases) were considered. For the GC cases, the impact of changes in tissue density, resulting from a variable gas content (which can be observed inter-fractionally), was investigated. Proton therapy was found to provide the possibility to reduce the doses given to normal tissues surrounding the target volumes, compared to photon RT. This dose reduction with PBT resulted in reduced risks for both treatment-induced normal tissue toxicities and secondary malignancies. The impact of the introduced density changes on the dose distributions were found to be more pronounced for the PBT plans, if plan robustness approaches were disregarded. The findings presented in this thesis can be of clinical importance in the selection process between different RT modalities.

Keywords: Treatment planning, gastric cancer, liver metastases, photon beam therapy, proton beam therapy, dosimetric comparison, normal tissue complication probability, risk of radiation-induced secondary cancer, patient selection.

Stockholm 2018
http://urn.kb.se/resolve?urn=urn:nbn:se:diva-158411


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RADIATION THERAPY OF UPPER GASTROINTESTINAL CANCERS WITH SCANNED PROTON BEAMS

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A treatment planning study

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To my family, from Mozambique and Sweden
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List of scientific publications

This thesis is based on the following papers, which are referred to by their Roman numerals.

Paper I: Mondlane G, Gubanski M, Lind P A, Henry T, Ureba A, Siegbahn A. **Dosimetric comparison of plans for photon- or proton-beam based radiosurgery of liver metastases.** *International Journal of Particle Therapy.* 3(2); 2016; p277-284. DOI: http://dx.doi.org/10.14338/IJPT-16-00010.1


Paper V: Mondlane G, Ureba A, Gubanski M, Lind P A, Siegbahn A. **Evaluation of the risk for radiation-induced liver disease following photon- or proton-beam radiosurgery of liver metastases.** *Submitted manuscript.*

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Related publication not included in this thesis:
Lideståhl A, Mondlane G, Gubanski M, Lind P A, Siegbahn A. **Normal tissue toxicity following radiotherapy with photon- or scanned proton-beams in patients with thymic tumours.** *Submitted manuscript.*
Author’s contribution to the publications

My contributions to the papers, included in the present thesis, are as follows:

- **Paper I**: I was involved in the design of the study and in the selection of the method used. I participated in the analysis of the results obtained and also wrote the manuscript.

- **Paper II**: I took part in the design of the study, the analysis of the results and wrote the manuscript.

- **Paper III**: I participated in the conception of the study, in particular regarding the choice of the models to be used in the assessment of the risk of radiation-induced secondary cancer. I performed the calculations of the risk for radiation-induced secondary cancer and analysed the obtained results. I also wrote the manuscript.

- **Paper IV**: I designed the study and prepared the proton beam therapy treatment plans. I performed the analysis necessary to choose a suitable NTCP-model and the model parameters for the different organs at risk studied. I performed the calculations of the normal tissue complication probability. In this article, I also made the analysis of the results and wrote the manuscript.

- **Paper V**: I performed the planning and design of the study. I prepared the treatment plans for scanned proton-beam therapy. I took part in the evaluation and choice of the normal tissue complication probability model and the parameters for the organs at risk studied. I performed the NTCP calculations and analysis of the results. I also wrote the manuscript.
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List of abbreviations

\(^{18}\text{FDG-PET}\) 18-fluorodeoxyglucose positron-emission tomography
3D Three dimensional
3D-CRT Three-dimensional conformal radiotherapy
4D-CT Four-dimensional computed tomography
AAA Analytical Anisotropic Algorithm
AP/PA Anterioposterior/Posterioranterior
CRITICS Chemoradiotherapy after induction chemotherapy in cancer of the stomach
CT Computed tomography
CTV Clinical target volume
DO Density override
DVH Dose-volume histogram
EAR Excess absolute risk
EUD Equivalent uniform dose
GC Gastric cancer
GI Gastrointestinal
GLOBOCAN Global Cancer Incidence, Mortality and Prevalence
GTV Gross target volume
HCC Hepatocellular carcinoma
HU Hounsfield unit
ICRP International Commission on Radiation Protection
ICRU International Commission on Radiation Units and measurements
IGRT Image-guided radiation therapy
IMAT Intensity-modulated arc therapy
IMPT Intensity-modulated proton therapy
IMRT Intensity-modulated radiation therapy
ITV Internal target volume
LET Linear energy transfer
\(\text{LET}_d\) Dose-averaged linear energy transfer
LKB Lyman-Kutcher-Burman
LNT Linear-no-threshold
LQ Linear quadratic
MC Monte Carlo
MLC Multi-leaf collimator
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NTCP</td>
<td>Normal tissue complication probability</td>
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<td>OAR</td>
<td>Organ at risk</td>
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<td>OED</td>
<td>Organ equivalent dose</td>
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<td>PBS</td>
<td>Proton beam scanning</td>
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<td>PBT</td>
<td>Proton beam therapy</td>
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<td>PCS</td>
<td>Proton convolution superposition</td>
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<td>PET</td>
<td>Positron-emission tomography</td>
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<tr>
<td>PTV</td>
<td>Planning target volume</td>
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<tr>
<td>QUANTEC</td>
<td>Quantitative Analyses of Normal Tissue Effects in the Clinic</td>
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<tr>
<td>RBE</td>
<td>Relative biological effectiveness</td>
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<td>RILD</td>
<td>Radiation-induced liver disease</td>
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<tr>
<td>RT</td>
<td>Radiotherapy</td>
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<td>SBRT</td>
<td>Stereotactic-body radiation therapy</td>
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<tr>
<td>SFUD</td>
<td>Single-field uniform dose</td>
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<td>SOBP</td>
<td>Spread-out Bragg peak</td>
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<td>SWOG</td>
<td>Southwest Oncology Group</td>
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<tr>
<td>TCP</td>
<td>Tumour control probability</td>
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<tr>
<td>TERMA</td>
<td>Total energy released per unit mass</td>
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<tr>
<td>UNSCEAR</td>
<td>United Nations Scientific Committee on the Effects of Atomic Radiation</td>
</tr>
<tr>
<td>VMAT</td>
<td>Volumetric-modulated arc therapy</td>
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<tr>
<td>WLRT</td>
<td>Whole-liver radiation therapy</td>
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Declaration

Parts of this thesis have been taken from my Licentiate thesis, with varying levels of modifications. Sections 1.1 – 1.4 were taken from my Licentiate thesis with major modifications. Minor modifications were introduced in Chapter 2 and section 3.3, which were also taken from my Licentiate thesis.
1 Introduction

1.1 Background

Immediately after the discovery of x rays by W.K. Röntgen in the year 1895 (Röntgen, 1895), the medical use of this kind of radiation was suggested (Tracy, 1897). Only a few months later, x rays were used for the production of images in medicine (Tracy, 1897; Sternbach and Varon, 1993; Robison, 1995). One year later, x rays were used for treatment of some dermatological malignancies (Robison, 1995). Initially, the x-ray energies used for therapy were low (<200 kV). With such low energies, successful treatments of superficial organs could be provided. These low-energy beams were attenuated to a large degree before reaching larger depths in tissue. This fact made the low energy x rays unsuitable for treatment of lesions deeply located in the body. Developments in accelerator technology and in radionuclide production later in the 20th century led to the introduction of high energy (MV) photons in radiotherapy (RT), which remedied some of these problems. External photon-beam therapy is today a standardized form of cancer care and is most commonly carried out with beam energies ranging from the energy of $^{60}$Co gamma rays to linear accelerator produced x-ray energies as high as 20 MV. The intensity-modulated irradiation techniques have also been introduced as standard methods in the clinic. These methods have enabled more conformal treatments of disease located close to sensitive structures.

High-energy heavy charged particles were available for research for the first time after the invention of the cyclotron in 1929 by Ernest Lawrence. The use of proton beams for RT was suggested by Robert Wilson in 1946 (Wilson, 1946), based on the depth-dose characteristics of proton beams. The first patient treatment was performed in 1954, using 340-MeV proton beams (the range in tissue was approximately 63 cm) produced by the synchrocyclotron at the Lawrence Berkeley Laboratory (Lawrence, 1957; Marks et al., 2010). The first patient had metastatic breast cancer disease and received irradiation of the pituitary gland (Lawrence, 1957; Lawrence et al., 1958). A cross-firing technique, in which the dose given to the target volume was situated in the plateau region of the depth-dose curve, was used. In Europe, the first patient treatment using proton beams was done in 1957 with the 185-MeV synchrocyclotron at the Gustaf Werner Institute (Uppsala, Sweden), where the use of the spread-out Bragg peak (SOBP) was implemented for the first time in proton-beam treatment (Larsson et al., 1959). The Gustaf Werner Institute was
the first to use a ridge filter to create a spread-out Bragg peak (SOBP) with proton beams used for treatment.

Today, there is an increased use of proton beam therapy (PBT) (Jermann, 2015). The advantages of PBT, compared to x ray therapy, are mainly related to reduced integral doses to the surrounding healthy tissue, while providing an improved target dose conformity. This can be expected to result in reduced frequencies of early and late side effects, sometimes observed after treatments of different tumour sites (Paganetti, 2012; Yock and Caruso, 2012). The proton beams have a finite range in tissue and a sharp dose gradient (fall-off) is produced behind the targeted disease. While these characteristics enable selectivity in the treatment with proton beams, they cause on the other hand, an increased sensitivity to anatomical changes and patient setup uncertainties.

One of the main sources of treatment delivery uncertainties in PBT is organ motion (described in section 2.2.1), in particular for the PBT delivered with the spot-scanning technique. For this reason, PBT of tumours located in sites influenced by organ motion, e.g., thorax and abdomen, is still challenging to perform. Another source of uncertainty in the PBT delivery is the inter-fraction variation of the internal-organ composition, e.g. gas filling (described in section 2.2.2). It introduces tissue-density changes which cause fluctuations in the proton range. The impact of the uncertainties introduced by anatomical changes remains an issue of concern, despite the advances made in the strategies used for their mitigation. Different strategies are being used for organ motion mitigation in current clinical practice (see section 2.2.1). Apart from keeping the uncertainties present during the RT process under control, it is also important to perform treatment-planning studies to evaluate the advantages of new RT modalities, compared to the standard method used in the clinic. Different clinical scenarios should be investigated for which the strength of either treatment choice is made clear.

1.2 Physical characteristics of photon- and proton-beams

The possible interaction mechanisms of a specific type of ionizing radiation determine the pattern of the energy deposition in matter. In a macroscopic description, the photon interactions with matter are characterised by beam attenuation and scatter. There is also a decrease of the beam fluence with the distance from the source (according to the inverse square law). The most important interaction mechanisms of photon beams, regarding the energy deposition in matter, are photoelectric effect, Compton scattering and pair production. In these three interaction mechanisms, energy of the primary photons is transferred to orbital electrons, secondary photons and to electron-positron pairs. The produced secondary photons continue to transfer their energy to
matter. The produced electrons and positrons are responsible for the majority of ionizations and excitations in matter. The x ray interaction processes result in a depth-dose distribution characterized by an entrance dose followed by a build-up region that extends to the depth where the maximum energy is deposited, e.g., for a field size of $5 \times 5 \text{ cm}^2$ the depth of maximum energy deposition in water is 2.5 cm for 10 MV photons (Podgorsak, 2006). Beyond the depth of dose maximum, the dose decreases exponentially with increasing depth in matter (Figure 1A).

In contrast to photons, protons are heavy charged particles with a rest mass of $1.6727\times10^{-24} \text{ g}$ (938.3 MeV/c$^2$) and a charge of $1.602\times10^{-19} \text{ C}$. When traversing matter, protons undergo inelastic Coulomb interactions with orbital electrons, Coulomb interactions with atomic nucleus and nuclear reactions. Proton Coulomb interactions with the atomic nucleus are mainly elastic interactions and result in the proton changing its direction of travel. Many such interactions along the proton trajectory result in the so-called multiple Coulomb scattering. Inelastic interactions of protons with the atomic nucleus can result in nuclear reactions and disintegration and, with only a small probability, bremsstrahlung production. In the nuclear reactions, the incident proton enters the nucleus, which subsequently may emit a proton, deuteron, triton, heavier ions or neutrons and gamma rays. The contribution from inelastic proton interactions with the atomic nucleus to the energy deposition in matter is very small.

Figure 1. Depth-dose profiles in water for photon beams (A) and proton beams (B). In A, the depth-dose profile of one 6 MV photon beam (green curve) and the profile of two parallel opposed 6 MV beams (red curve), normalised for the dose at 23 cm, are presented. In B, depth-dose profiles of 14 monoenergetic proton beams (energies between 176 and 200 MeV) weighed to produce a 5.2 cm wide spread-out Bragg peak (black curve) at 21 cm in a water phantom, are displayed.

Inelastic Coulomb interactions of protons with atomic electrons are the main mechanism of proton-energy deposition in matter. The Coulomb collisions with orbital electrons are accompanied by small energy transfers to the
electrons along the nearly rectilinear proton path in tissue. The maximum energy transfer occurs at the end of the proton range in the so-called Bragg peak. The Bragg peak is the hallmark of the dose distributions produced by heavy charged particles, including protons. The proton beams produce a depth-dose profile which is characterized by a substantial entrance dose which then increases slowly until it reaches a maximum dose at the depth where the Bragg peak is located, close to its maximum range. Beyond this maximum range, the dose drops to zero (Figure 1B). The range of charged particles depends on the particle type, initial kinetic energy and on the density of the material through which it passes. For example, proton beams of initial energy 230 MeV have a range of around 33 cm in water (ICRU, 1993; Gottschalk, 2012), while for heavier ions, such as carbon ions, much higher kinetic energies per nucleon are required to reach this depth in water (Owen, Lomax and Jolly, 2016).

For clinical applications, Bragg peaks produced by protons of different monoenergetic (pristine) energies are used to irradiate a target with a certain extension in depth. Weighting factors are then determined for the different energies used with the aim of producing a high and uniform target dose, which is conformal to the tumour (the SOBP). The creation of a SOBP will cause increased dose levels, proximal to the target, compared to the depth-dose curves for monoenergetic proton beams, as illustrated in Figure 1B.

1.3 Radiobiological considerations for photon- and proton-beams

The specific interaction properties of different types of ionizing radiation can make the produced radiobiological effect different from that observed following irradiations with standard photon beams. To take this difference into account, the concept of relative biological effectiveness (RBE) was introduced. The RBE is defined as the ratio between the dose of a reference radiation (generally $^{60}$Co gamma rays or 250 kVp x rays) and the dose of a selected type of radiation, which produces the same biological endpoint. For proton beams, a generic RBE value of 1.1 has been proposed by ICRU (ICRU, 2007). This RBE value has been accepted in current proton therapy standard practice. In studies performed in vitro and in vivo, it has been demonstrated that the RBE of proton-beams is not constant (Paganetti et al., 2002). Despite this fact, the proton dose is normally prescribed in $^{60}$Co equivalent Gy, assuming a constant RBE value of 1.1. In an extensive review of experimental and clinical data, Paganetti et al. (Paganetti et al., 2002) described the dependence of the RBE of proton beams on the linear energy transfer (LET), tissue, endpoint, and dose per fraction. For a given tissue type characterised by a given sensitivity to fractionation (described by the $\alpha/\beta$ parameter of the linear quadratic (LQ) model), the RBE increases with decreasing dose and with increasing
LET for proton LET values relevant in current clinical practice (Gerweck and Kozin, 1999; Tilly et al., 2005; Hall and Giaccia, 2012). For clinical proton beams a monotonous RBE-LET relationship has been observed. Thus, the determination of the LET will also give a description of the RBE of proton beams. Since the energy deposition of proton beams at the microscopic level is homogeneous, the LET of proton beams can be calculated in terms of dose-averaged LET (LET$_d$) (Grassberger et al., 2011). The LET$_d$ is then determined by considering, at the voxel level, all the contributions from the different particles contributing to the energy deposition.

The LET$_d$ increases with depth towards the end of the proton range (Grassberger et al., 2011). This leads to an increase in the proton RBE with depth along the SOBP, which also causes the biological effective range of the proton beams to increase with a few millimetres beyond the distal edge of the SOBP (Paganetti and Goitein, 2000). The fast increase in the LET$_d$, and hence in the RBE, beyond the distal edge of the SOBP is caused by the LET$_d$ contribution from the created secondary protons in this region (Grassberger and Paganetti, 2011; Grassberger et al., 2011). This fact raises concerns when the distal edge of the proton beams is positioned adjacent to critical organs at risk (OARs).

Different models, with which a variable RBE can be predicted, have been proposed by e.g., (Dale and Jones, 1999; Wilkens and Oelfke, 2004; Tilly et al., 2005; Wedenberg, Lind and Härdemark, 2013; McNamara, Schuemann and Paganetti, 2015). These models were derived with the LQ model as starting point. Most of these RBE models are based on cell survival data obtained from studies *in-vitro*. Due to the lack of clinical data, RBE models for predicting the normal tissue complication probability (NTCP) of the critical normal tissues in RT have not been published. Therefore, the proposed RBE models are also used to estimate the NTCP. The increased use of proton therapy will provide new clinical data, which will add to the current knowledge of the radiobiological effects of proton beams. In the studies performed in the accompanying articles of this thesis, a constant RBE value of 1.1 was used, since it is widely used in current proton therapy clinical practice.

In radiation protection, the different biological effects produced by different types of ionizing radiation are in general taken into consideration by using radiation weighting factors. This procedure was also suggested by the International Commission on Radiation Protection (ICRP). In this context, a radiation-weighting factor of 2 has been recommended for proton beams (ICRP, 2007).
1.4 Modes of photon and proton-beam treatment delivery

High energy x rays (4 – 20 MV) used in external beam therapy are produced in linear accelerators, in which electrons are accelerated to high kinetic energies, before they collide with a high atomic-number target material (e.g., Tungsten). Photon-beam treatments (for deep-seated tumours) can be delivered with three-dimensional conformal radiotherapy (3D-CRT) or with intensity-modulated radiation therapy (IMRT). The goal of either 3D-CRT or IMRT is to maximize the local tumour control while minimizing the doses given to the OARs. In 3D-CRT, treatments are generally delivered with x ray beams of uniform fluence. When required, wedge filters or compensators can be used to modify the beam fluence profile, to counterbalance any contour irregularities and/or to produce more uniform composite dose distributions (IMRT Collaborative Working Group, 2001). The later introduced technique, IMRT, makes use of photon beams of variable fluences, which are computer-calculated using the inverse planning approach. Computer-controlled multi-leaf collimators (MLCs) can be used to deliver IMRT in three different ways: (1) use of multi-segmented static fields (also known as the step-and-shoot technique) (IMRT Collaborative Working Group, 2001), (2) use of static fields and dynamic MLC, which moves in function of time during the beam delivery (Boyer and Yu, 1999) and (3) using dynamic MLCs to shape the fields with a simultaneous gantry rotation, the intensity-modulated arc therapy (IMAT) (Yu, 1995), later known as volumetric-modulated arc therapy (VMAT). In another form of IMRT, the patient is treated using fan beams delivered slice by slice with longitudinal translation of the patient, in an approach similar to computed tomography (CT) image acquisition (tomotherapy) (Mackie et al., 1993).

Proton beams which are currently used for cancer treatment are generated in cyclotrons or in synchrotrons (Schippers, 2016). The primary proton beams produced by these accelerators is narrow and do not cover the extent of the typical target volumes in RT. Two distinct beam delivery approaches are therefore employed in PBT: the passive-scattering and the active-scanning methods. In passive-scattering systems, a scattering foil (or two, in case of larger fields) is used to produce a wider cross section of the beam area with a uniform fluence of protons. The proton beam is then laterally shaped by using two-dimensional collimators, in close analogy to photon treatments (Pedroni, 1994). The beam modulation in depth, necessary to create the SOBP, is performed by positioning a variable-range shifter in the beam (Pedroni, 2000). The addition of Bragg peaks, shifted in depth and appropriately weighted, yields a uniform high-dose region (Slopsema, 2012). With the active scanning systems, on the other hand, a narrow pencil-beam is moved laterally (in the plane transversal to the beam direction) by means of magnetic deflection. A
variable range modulation (Pedroni, 2000) is performed along the longitudinal direction of the beam (in depth). When using cyclotrons, this can be done by placing a degrader immediately after the beam has been extracted from the accelerator or by using beam modifying devices (fast range shifter or modulator) in front of the patient in the treatment nozzle (Schippers, 2016). The proton range is then adjusted, as a function of the beam position in both transverse directions, to cover the target. The treatment delivery with scanning-beams can be done using the single-field uniform dose (SFUD) technique, or with the intensity modulated proton therapy (IMPT) method, which has been described by Lomax (Lomax, 1999). In SFUD, the dose is optimised so that each field will deliver a uniform dose to the target volume. With the IMPT method, on the other hand, each single field will produce inhomogeneous dose distributions in the target volume, but the resulting overall target dose, produced by all fields, will be homogeneous.

The passive scattering technique was the first proton therapy delivery technique implemented in the clinic. It requires the use of beam- and patient-specific hardware (e.g., scattering foils, collimators and compensators), which in turn, are sources of scattered radiation and also produce additional patient dose proximal to the target (Paganetti, 2016). There is also neutron production in these beam modifiers which should be taken into consideration (Schneider et al., 2002; Schneider and Hälg, 2015). This hardware is not required for dose delivery with the spot-scanning technique, which therefore allows increased protection of the OARs from unnecessary doses. The sparing of the OARs is also enhanced with the active-scanning method due to its capability for variable range modulation. However, in contrary to passive scattering, the active-scanning method is highly sensitive to organ motion (Bert and Durante, 2011).

1.5 Treatment planning aspects for photon- and proton-beam therapy

The treatment planning is one of the steps performed prior to the actual treatment in RT. Modern RT makes use of computer-based treatment planning systems (TPS), which perform the dose computation for an optimised beam geometry and a given beam energy. It requires information about the patient composition data, the beam produced by the accelerator used for treatment and the prescribed dose. Most of the TPSs use CT images as the patient material composition data. However, sometimes the CT images do not provide sufficiently accurate material information, e.g. the CT numbers saturate for higher atomic number materials (for example, surgical clips). Furthermore, the soft tissue contrast in CT images is relatively poor and organ functional information is limited. Thus, images obtained from other imaging modalities,
e.g., magnetic resonance imaging (MRI), ultrasonography and positron emission tomography (PET), are sometimes also used in treatment planning as a complement to the CT images.

1.5.1 Delineation of structures

The delineation of the structures in the RT treatment planning, which include the OARs and the target volumes, is done on the patient images. The recommendations issued by the ICRU (ICRU, 1999, 2010) are normally followed. The delineation of the OARs is performed based on these guidelines, in a similar manner for the treatment planning with either photon- or proton-beams. For the delineation of the target volumes, a gross tumour volume (GTV), encompassing the clinically demonstrable disease, is delineated. From the GTV, a clinical target volume (CTV) is determined by adding a margin around the GTV, which accounts for the possible microscopic spread of the disease. The delineation of the CTV is based on the clinical knowledge about how cancer cells migrate from the volume where they originate. The delineation of the GTV and CTV follow the same guidelines for both photon- and proton-beam treatments, as these structures are independent on the beam type used for treatment. The planning target volume (PTV), however, is a geometrical concept used during the treatment planning to ensure that the prescribed dose is actually delivered to the CTV. In this context, the design of the PTV will depend on the random and systematic uncertainties present before and during the course of the treatment delivery, and consequently will also depend on the treatment modality.

In photon-beam therapy planning, the PTV is designed to account for the daily uncertainties in patient positioning and beam alignment during planning and treatment delivery by adding a setup margin to the CTV. The variations in tumour size, shape and location within the patient are also taken into consideration during the PTV delineation by the addition of an internal margin to the CTV. One commonly used method for determining the required CTV-to-PTV margin in photon RT was proposed by van Herk et al. (van Herk et al., 2000), and can be used to ensure that a CTV dose-coverage of at least 95 % of the prescribed dose will be obtained for 90 % of the patients.

In the RT planning carried out for the treatment with proton beam scanning (PBS), on the other hand, beam-specific PTVs which account for setup and range uncertainty are required (ICRU, 2007). The implementation of these beam-specific PTVs is done through the delineation of the PTVs for each field or through implementation of dose margins to the CTV in the beam-design algorithms (ICRU, 2007). However, the ICRU recommends that the standard photon PTV is also still delineated in the treatment planning with proton beams, for reporting purposes. Studies reporting different approaches to design beam-specific PTVs have been published. For example, Park et al. (Park
et al., 2012), presented an approach to design beam-specific PTVs, which can be used in the SFUD planning performed for treatments with scanned-proton beams. This approach accounts for setup errors, range uncertainties and tissue heterogeneities along the beam path. Plans prepared using this approach were shown to be more robust compared to plans based on the conventional photon PTV (Park et al., 2012).

In some of the studies presented in the accompanying papers (paper I, II and III), the PTV used in the photon-beam planning was used as the target volume in the planning for PBT as well. This approach was selected to facilitate comparisons of the plans in terms of PTV and CTV dose-coverage. To further account for the proton-specific uncertainties and hence perform a more realistic comparison of the photon- and proton-beam plans, approaches to account for the proton-beam range uncertainty were adopted in the more recent studies which form a part of this thesis (papers IV and V).

1.5.2 Treatment-field setup

In RT, the choice of treatment modality depends on the treatment site, tumour type and the intent of the treatment. Many variables, each with varying degree of clinical importance, needs to be considered in the selection of the best field configuration for a specific tumour site (Bedford et al., 1999). In photon RT implemented with 3D-CRT, a collimator aperture, which is adapted for to the shape of the PTV, is selected for each beam. This is done to guarantee a conformal dose to the PTV, taking into account the beam penumbra. This selection is made using the beam’s-eye-view. Beam arrangements from two parallel opposed beams, tangential beams and multiple coplanar or non-coplanar beams can be selected. For example, tangential beams are usually used in RT of breast cancer, while for liver tumours multiple coplanar beams are preferred. The use of three or more beams, enhances the sparing of the OARs, compared to when parallel opposed beams are used, as the entrance and exit doses do not coincide (Childs and Lord, 2007).

The ultimate upper limit of the number of fields which can be used in photon RT is represented by the continuous beam-on arc technique. This method was primarily implemented with the conformal technique. However, both the target-dose conformity and the sparing of the OARs were compromised. With the development of IMRT, the arc delivery technique was perfected. IMRT requires the use of intensity-modulation systems, which includes among others the dynamic MLCs (Källman et al., 1988; Yu, 1995). With the possibility to produce modulated beams, the treatment delivery can be performed using the multiple static-field setup or with continuous beam delivery (e.g., VMAT). This allows for improved dose-conformation around the target volumes with low dose levels given to the OARs surrounding the target.
The fields used in PBT, on the other hand, are delivered from fixed angles, regardless of whether the passive-scattering or active-scanning methods are employed to deliver the treatment. The possibility of delivering arc-based proton therapy has been suggested (Sandison et al., 1997). However, this delivery technique has still not been developed for clinical applications. With PBT, the treatments can be delivered with single beams, as it is possible to produce conformal, homogeneous dose in the target volume with only a single beam. Due to the need for improved sparing of the OARs that are located proximal to the target volume, e.g., the skin, at least two proton fields are preferred. The clinical implementation of proton therapy using PBS is complicated by the susceptibility of these beams to different sources of uncertainties (as discussed in section 2.2). The implementation of approaches to minimize the effects of these uncertainties is, therefore, necessary during treatment planning and delivery. Furthermore, the design of the field arrangement requires that appropriate beam angles, which are robust in the presence of tissue density heterogeneities, along and adjacent to the beams, are selected. Moreover, due to the increase of the biological range of proton beams at the distal edge (as discussed in section 1.3), fields stopping at locations with critical structures should be avoided.

1.5.3 Dose calculation and plan optimization

The main requirement on a clinical TPS is that it must provide a fast and highly accurate three-dimensional (3D) dose calculation (Oelfke and Scholz, 2006). Several algorithms, based on different formalisms, have been developed for clinical dose calculation. The obtained dose distributions with these algorithms are the sole means to access the treatment parameters and their connection with the expected treatment outcome (see section 3).

The algorithms used for dose calculation in RT can be subdivided into three classes, namely, the correction-, model-, and Monte Carlo (MC)-based algorithms (Oelfke and Scholz, 2006; Khan, 2010). The correction-based algorithms are semi-empirical models, which are based on measurements in homogeneous media, e.g., water phantoms. To characterize the patient heterogeneities, several correction methods are incorporated. These methods include (1) attenuation corrections for contour irregularities, beam intensity modifiers and for tissue heterogeneities (based on the radiologic path length), (2) scatter corrections, and (3) geometric corrections based on the inverse-square law (Khan, 2010).

Model-based algorithms rely on physical models which describe the radiation transport in media (Oelfke and Scholz, 2006). With the model-based algorithms, the absorbed dose is predicted from the fluence of the primary photon-beam (expressed in terms of the total energy released per unit mass –
TERMA (Ahnesjö, Andreo and Brahme, 1987)) and a dose kernel of the produced secondary particles. The model-based algorithms make use of two distinct classes of dose kernels, namely the point-spread kernel and the pencil-beam kernel (Mohan, Chui and Lidofsky, 1986; Ahnesjö, 1989). While the point-spread kernel considers that the dose contribution in a given point in water is created by the interaction of the primary photon energy of a given energy, the pencil-beam kernel is obtained by integrating all point-spread kernels along an infinite line in the medium (Oelfke and Scholz, 2006). The dose kernels used in these algorithms are pre-calculated using MC methods or assessed by measurements in homogeneous medium, generally water phantoms (Oelfke and Scholz, 2006). To account for the density heterogeneities in the patient data when using the point-spread kernel, the density scaling is employed, which consists in scaling the average electron density along the line connecting the point of primary interaction to the point of interest. With the pencil-beam kernel, on the other hand, the radiological pathlength along the central axis of the pencil beam is used to account for the tissue heterogeneities. By implementing these two dose kernels, different approaches with different degrees of approximations have been introduced for dose calculation. These include the pencil-beam convolution (Mohan, Chui and Lidofsky, 1986), superposition/convolution (Mackie, Scrimger and Battista, 1985; Ahnesjö, Andreo and Brahme, 1987), collapsed-cone (Ahnesjö, 1989), among others.

The model-based algorithms described above have been incorporated in TPSs used for photon-beam treatment planning. For proton-beam dose calculation, the convolution superposition algorithm is widely used (Clasie, Paganetti and Kooy, 2012). The application of this algorithm for scanned-proton beams requires that a correction for large scattering angles (i.e., the beam halo effect) is incorporated (Clasie, Paganetti and Kooy, 2012). The Analytical Anisotropic Algorithm (AAA) (Varian Medical Systems) used for photon dose calculation and the Proton Convolution Superposition (PCS) algorithm (Varian Medical Systems) used for proton dose calculation in Eclipse TPS (Varian Medical Systems), are two examples of model-based algorithms.

By enabling a complete description of all components of the radiation source and the interactions in the heterogeneous patient composition, the MC-based algorithms represent the most accurate method used for dose calculation in RT. Compared to the MC-based algorithms, the model-based algorithms present limitations when calculating the dose in the interfaces with density heterogeneities. Furthermore, with the MC-based algorithms the dose is calculated in terms of dose-to-tissue (Paganetti, 2009). This is an advantage compared to the correction- and model-based algorithms, since the dose calculation in these two classes of algorithms is provided in terms of dose-to-water. However, the dose-to-tissue, as calculated by MC-based algorithms, is generally converted to dose-to-water, since the dose-to-water is the standard of RT (Paganetti, 2009).
In a study performed by Grassberger and collaborators (Grassberger et al., 2014), the dose distributions produced by passive-scattered proton beams in 18 lung cancer patients calculated using a TPS (pencil beam algorithm, XiO, Computerized Medical System) were compared to those obtained using an MC-based algorithm. Due to the presence of density heterogeneities, the TPS predicted more extended proton ranges compared to the MC-based algorithm. Moreover, the dose calculated at the periphery of the lung tumours was found to be lower when using the MC-based algorithm, due to the degradation of the lateral penumbra, which is underestimated by the analytical algorithm used by the TPS.

For the case of dose distributions produced by photon beams, Tsuruta et al. (Tsuruta et al., 2014) compared the performance of two analytical dose-calculation algorithms (Acuros XB and AAA) against a MC-based algorithm (XVMC), for dose calculation in photon-based stereotactic body radiation therapy (SBRT) of lung tumours. The Acuros XB algorithm was found to provide similar results as the XVMC algorithm, while slightly different results were obtained when the AAA algorithm was used (Tsuruta et al., 2014).

In regard to treatment plan optimisation, its aim is to find a suitable balance between TCP and sparing of the OARs. In 3D-CRT, the plan optimization is performed manually, using the forward planning concept (Xiao et al., 2000). Different beam-setup parameters are chosen by the planner and the resulting dose distribution is calculated. In IMRT, in contrast to 3D-CRT, inverse planning is used (IMRT Collaborative Working Group, 2001). In inverse planning, the desired dose distribution in the target volume and the dose restrictions for the surrounding tissues are specified in terms of objective functions and normal tissue constraints, before the dose calculation begins. A computer optimization is then performed in such a way that the beam fluence required to reach the specified objectives, are calculated. The plan objectives set for the target volumes can be chosen to make the resulting dose distribution homogeneous. Inhomogeneous dose distributions, as used in SBRT, can also be produced in the target volumes.

In proton therapy using PBS, two optimisation approaches can be used, namely, the SFUD and the IMPT methods. The difference between these two methods has been presented in section 1.4. Regardless if SFUD or IMPT is selected, the optimisation process follows the inverse planning approach, in analogy with the IMRT techniques. Nevertheless, the SFUD/IMPT optimisation is computationally more demanding than that performed for IMRT, as the planning for SFUD/IMPT requires that additional aspects of proton-related uncertainties are considered. For the SFUD approach, Park et al. (Park et al., 2012) has demonstrated that the use of field-specific PTVs can take these uncertainties into account. This approach is not suitable for IMPT, due to the characteristics of the dose delivered by single fields. A robust optimisation for IMPT plan optimisation, in which a simulation of the effects of setup and
range uncertainties are performed, is often considered necessary (Chen et al., 2012; Liu et al., 2012). In this manner, an evaluation of the robustness of the calculated proton dose distribution, in the presence of uncertainties, can be performed.

The final step in treatment planning is to perform a plan evaluation (discussed in section 3), to verify whether the treatment plan meets the clinical requirements before it is used for the actual treatment.

1.6 Aim of this thesis

The aim of this thesis was to study how photon- or proton-beam therapy of gastrointestinal malignancies in the upper abdomen can be performed, to determine for which typical cases that either technique would be the most suitable. A radiobiological model-based approach for selecting individual patients to photon- or scanned proton-beam therapy was also evaluated.
2 Radiotherapy of gastrointestinal cancers in the upper abdomen

2.1 Gastrointestinal cancers in the upper abdomen

Gastrointestinal (GI) cancers encompass cancers in the GI tract, i.e., cancers originating in the oesophagus, stomach, liver, gallbladder, pancreas, biliary system, small and large intestines (or colon and rectum) and anus. RT of cancers arising in the GI tract are highly influenced by inter- or intra-fraction anatomical changes. In this thesis, the current state of the art clinical use of photon beams and the potential use of scanned proton beams in RT of gastric cancer and liver malignancies were evaluated and compared.

2.1.1 Liver malignancies

Liver malignancies can be primary liver cancer or metastatic disease in the liver. Primary liver cancer is the second leading cause of cancer-related death worldwide, being the fifth most prevalent cancer type for men and the ninth for women (Ferlay et al., 2015). Primary malignancies in the liver include hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, cystadenocarcinoma and primary sarcoma (Edge et al., 2010). Of these, the HCC is the most common, accounting for 85 - 90% of the primary liver malignancies (Lafaro, Demirjian and Pawlik, 2015). The main mode of metastatic dissemination of primary liver cancer is via the hepatic veins. The lungs and bones are the most common sites of metastatic spread (Edge et al., 2010). Furthermore, the liver is the most common site of metastatic spread for several malignancies, mainly from primary GI tumours (Brodt, 2011). In this context, around 50% of colorectal cancer patients will be diagnosed with metastatic spread to the liver (Wiering et al., 2008; Tan et al., 2014). Metastatic disease in the liver accounts for more than 90% of the malignant lesions diagnosed in the liver (Khandani, 2008).

Diagnosis of liver malignancies is generally made with one or a combination of the following methods: histopathology, analysis of serum biomarkers and anatomical imaging techniques (Llovet, Burroughs and Bruix, 2003). Biopsy is only performed in case the radiologic studies do not result in conclusive results due to the risk of needle-track seeding. Radiological modalities
used for diagnosis include ultrasonography, CT, MRI and angiography. Helical CT and contrast-enhanced MRI are considered to be the best diagnostic techniques (Llovet, Burroughs and Bruix, 2003). Furthermore, contrast-enhanced MRI has been shown to be more accurate than x ray CT studies for diagnosis of liver diseases (Jankowski and Hawk, 2013). Besides the anatomical imaging techniques, the use of functional imaging, such as PET, in combination with CT and/or MRI increases the sensitivity and specificity in the detection of liver lesions (Jankowski and Hawk, 2013).

Surgical resection is considered a golden standard therapeutic modality in treating colorectal liver oligo-metastases and primary liver cancer (Wiering et al., 2008). However, most patients with liver metastases (approximately 70-90 %) are not eligible for liver resection (Scorsetti, Clerici and Comito, 2014) due to extent of the disease or morbidity. Other localised treatment techniques, including transarterial chemoembolization, radiofrequency ablation and SBRT, present promising control rates for the cases when curative surgery is unfeasible (Hung, 2005; Di Carlo, 2014). For these cases, focal ablative RT using SBRT has been reported to achieve the high control rates with limited liver complications. The development of radiation-induced liver disease (RILD) can limit the use of RT of liver lesions. However, the liver tolerates high therapeutic doses, provided that the dose is delivered to a limited volume of the liver (Dawson et al., 2002). Based on this fact, it has been possible to deliver ablative doses to treat limited volumes of the liver using SBRT. Høyer et al. (Høyer et al., 2012) reported 1- and 2-year local-control rates between 70-100 % and 60-90 %, respectively, in their study of SBRT of liver metastases. These control rates are comparable to the best results obtained with radiofrequency ablation. The use of proton beams to further spare the remaining healthy part of the liver, may potentially produce better therapeutic outcomes after these treatments. In paper I, the potential for an improved dosimetric sparing of the OARs with IMPT-based radiosurgery, compared to photon-beam based SBRT, was demonstrated (Mondlane et al., 2016). 

In current clinical practice, external photon-beam RT of liver metastases can be performed with low-dose whole-liver radiotherapy (WLRT) or with a radiosurgery approach for tumour ablation in a hypofractionated setting (Høyer et al., 2012). The former treatment is performed for cases of diffuse liver metastases with the goal of symptom relief to improve the quality of life of the patient. The aim of the latter treatment is to improve the survival rates when treating oligo-metastases in the liver. Furthermore, selected patients, generally with large tumours, can be treated with RT delivered with a conventional fractionated regimen (Dawood, Mahadevan and Goodman, 2009; Høyer et al., 2012). Ablation of liver metastases using external beam RT is often performed using the SBRT technique. The safe delivery of very large doses per fraction in SBRT requires effective patient immobilization and precise target localization (Martin and Gaya, 2010). This is often achieved by
the use of an external, well-defined three-dimensional coordinate system, the stereotactic body frame, combined with CT imaging in the treatment room immediately before the treatment. The stereotactic body frame was developed by Lax et al. (Lax et al., 1994). The method used to position this frame is similar to that used to position the frame employed for intracranial radiosurgery with the Gamma Knife (Elekta AB). However, today only few treatment centers still use the stereotactic body frame in SBRT. The common patient immobilisation in SBRT involves the use of abdominal compression combined with internal markers (implanted in the proximity of the lesion) and with the use of cone-beam CT. With SBRT, high doses can be delivered to extracranial targets located in different parts of the body, e.g., the liver, in a few fractions.

Recently, additional methods used for patient positioning and motion reduction have been introduced in the clinic. These include, controlled breath hold, gating and tracking. In addition, the target delineation can be done in different breathing phases using four-dimensional CT (4D-CT) image studies. The internal target volume (ITV) concept is then used to account for the target motion. With the recent advances in the image-guided radiation therapy (IGRT) methodologies (Jaffray, 2012; Shimizu et al., 2014; Mori et al., 2016), the daily changes of the target position and shape can be monitored using different imaging techniques (Vautravers-Dewas et al., 2011; Høyer et al., 2012; Aitken and Hawkins, 2015). Generally, the doses administrated in SBRT are between 30 and 60 Gy, given in 1 to 6 fractions (Høyer et al., 2012).

2.1.2 Gastric cancer

Gastric cancer is the fifth most common cancer type and the third leading cause of cancer death worldwide for both sexes according to the 2012 GLOBOCAN cancer statistics (Ferlay et al., 2015). It accounts for 8 % of the total cancer cases and 10 % of the cancer deaths worldwide (Nasrabadi et al., 2014). Ninety percent of the stomach cancers are adenocarcinomas which can be further divided into intestinal and diffuse types. The remainder are mainly lymphomas (up to 8 %) and leiomyosarcomas (1 – 3 %) (Cassidy et al., 2002; Van Cutsem et al., 2016). Diffuse carcinomas are poorly differentiated and occur throughout the stomach. The intestinal type of gastric cancer is ulcerative and well differentiated. It is often originating in the distal part of the stomach (Nyren and Adami, 2002).

Endoscopy and biopsy are still the gold standards in the diagnosis of gastric cancers (Jankowski and Hawk, 2013). Abdominal CT studies with barium as contrast agent have been used for radiological diagnosis and staging of gastric cancer. Another radiological modality that can be important to assess early outcome of neoadjuvant chemotherapy is 18-fluorodeoxyglucose PET
(18FDG-PET) (Jankowski and Hawk, 2013). 18FDG-PET also plays an important role in the detection of distant metastases (Podoloff et al., 2009) arising from primary GC. Because most of the GC cases (in the western countries) are diagnosed at later stages, this disease has a poor prognosis and hence, a high mortality rate. Only a limited number of therapeutic options are available.

The modalities available for the treatment of resectable GC include surgery and a number of adjuvant therapies, such as peri- and post-operative chemotherapy, postoperative RT, perioperative chemoradiotherapy, perioperative targeted RT (Jankowski and Hawk, 2013; Gubanski, 2015). Surgery is the main curative treatment-modality of choice. However, for cases of non-resectable GC, chemotherapy plays an important role (Glimelius et al., 1997; Janunger et al., 2001; Gubanski et al., 2010). The role of chemoradiotherapy has been evidenced in the SWOG-directed Intergroup 0116 trial, in which an overall survival of 9 months was reported (Macdonald et al., 2001). Based on the results of this trial, the combination of chemoradiotherapy after surgery is being studied in the ongoing CRITICS trial (Dikken et al., 2011) in Europe in which GC patients undergo perioperative chemoradiotherapy. The GC patients, included in the studies presented in this thesis (papers II and IV), took part in the CRITICS trial and they received RT delivered with photon beams.

Typically, a total prescription dose of 45 Gy, given in 25 fractions of 1.8 Gy each, is used in RT of GC (Smalley et al., 2002; Wieland et al., 2004; Leong et al., 2005; Morganti et al., 2013; Dionisi et al., 2014; Gubanski, 2015; Namysł-Kaletka et al., 2015). However, in the report by Namysł-Kaletka et al. (Namysł-Kaletka et al., 2015) a total dose of 50.4 Gy was used for R1 resection cases with a microscopic infiltrating margin. The RT delivery has initially been performed using two opposing fields, also known as the anteroposterior/posterioranterior (AP/PA) setup, following the results of the Intergroup 0116 trial. Multi-field setup with 3D-CRT has been reported to improve both the target dose-coverage and the sparing of the OARs (Leong et al 2005). This setup has also been suggested by Smalley and co-authors (Smalley et al., 2002) for cases when the preoperative CT was available for guidance in the definition of the target volume. IMRT has been shown to create a better target dose conformity while further reducing the dose given to critical structures (Dionisi et al., 2014).

The target delineation for GI cancers is generally based on the results obtained in clinical trials, mainly the Intergroup 0116 study. In the study by Macdonald et al. (Macdonald et al., 2001), the PTV consisted of the tumour bed defined using CT studies performed with barium as contrast agent, regional lymphatic nodes and volumes located 2 cm beyond the proximal and distal margins of the resections. Another method which is used to derive the target volume in RT of GC was suggested in the study by Smalley et al.
(Smalley et al., 2002). The location of the regional failure after surgical resection defines the areas to be posteriorly irradiated; these areas include the tumour bed, the anastomosis or stumps and the regional lymphatics. In the most recent CRITICS trial, the CTV included the tumour bed, anastomosis and regional lymph nodes (Dikken et al., 2011). The PTV was then delineated by expanding the CTV with 10 mm in all directions. As for the case of liver metastases, the use of IGRT and adaptive approaches is crucial for the success of RT of GC. These methods may help to decrease the effects of intra- and inter-fractional geometric variations (organ motion and setup errors) during the delivery of the radiation dose.

RT of GC involves the irradiation of a large target volume. The feasibility of using proton beams in adjuvant treatment of GC has been evaluated in a static setting in a previous study (Dionisi et al., 2014). However, GC RT is affected by intra-fraction respiratory motion, daily changes in the disposition of the organs in the abdomen and also, changes in the density of the contents of the stomach itself. These perturbing factors will influence, to a certain degree, the outcome of RT of GC when using scanned proton beams.

2.2 Challenges in radiotherapy of GI cancers

RT of GI cancers is challenging to perform, even when using photon beams. This is due to the physiological changes (organ motion, changes in the organ fillings or in the shape and size of the target volume) occurring within the patient during the dose delivery of one fraction and/or changes occurring between fractions. PBT is even more sensitive to different sources of uncertainties that may be present at different stages of the RT process.

2.2.1 Impact of organ motion

The dose distributions produced by proton beams are affected by intra-fractional changes caused by organ motion. This makes proton therapy of tumours located in moving organs, e.g., liver, challenging. Organ motion is the source of interplay effects (Phillips, 1992), dose blurring, and dose deformation caused by the density variations (Engelsman, Schwarz and Dong, 2012; De Ruysscher et al., 2015). These three effects are also present during photon RT of moving targets (Bortfeld, Jiang and Rietzel, 2004). In photon RT delivery, the dose blurring is the dominant issue (Bortfeld, Jiang and Rietzel, 2004) while in PBS (IMPT specifically), it is the interplay effect (Engelsman, Schwarz and Dong, 2012). While dose deformation and dose blurring are independent of the proton beam delivery technique, i.e., they are present when using either the passive-scattering or the PBS method (Bert and Durante,
the interplay effect is a specific issue for PBS of moving targets. Eliminating simultaneously these three unwanted consequences of organ motion is still not possible in the clinic (Engelsman, Schwarz and Dong, 2012). Motion mitigation strategies include the use of margins, gating (Furukawa et al., 2007; Lu et al., 2007), dose repainting or rescanning (Zenklusen, Pedroni and Meer, 2010; Knopf, Hong and Lomax, 2011), tracking (Murphy, 2004), motion minimization (e.g., breath hold, abdominal pressure) and robust planning (Engelsman, Schwarz and Dong, 2012). Albeit tumour tracking or motion minimization alone are the best methods for removing simultaneously the three negative effects of organ motion (Engelsman, Schwarz and Dong, 2012), a combination of the different strategies may be used to more efficiently mitigate these effects. For example, in the study by Zhang et al. (Zhang et al., 2015), a combination of gating and rescanning was shown to better preserve the dose homogeneity for targets in the liver, compared to when either gating or scanning alone were used.

The interplay effect refers to the degradation of the dose distribution caused by the motion of a target relative to the dynamic dose-delivery of the pencil beam. This effect was first observed by Phillips (Phillips, 1992) in his study of the effects of organ motion on the target-dose homogeneity when using the PBS technique. The interplay effect can be handled by means of multiple rescanning, motion minimization and tumour tracking. The interplay effect is not mitigated by adding lateral margins (Engelsman, Schwarz and Dong, 2012). The use of lateral margins helps to improve the dose coverage of the CTV, but not the quality of the dose distribution (i.e., good target-dose homogeneity). Other treatment-specific strategies for mitigation of the interplay effect in PBS include the use of conventional fractionation, larger spot sizes and smaller spot spacing (Phillips, 1992; Dowdell et al., 2013; Grassberger et al., 2013). Conventional fractionation acts similar to multiple rescanning (Dowdell et al., 2013). When the dose is delivered in a single fraction or in hypofractionated regimens, the target motion can deteriorate the dose homogeneity within the target. On the other hand, when the dose is delivered in several fractions, the hot and cold spots which are present in individual fractions add up, producing an acceptable overall dose homogeneity in the target. The use of larger spot sizes reduces the interplay effect as the dose from adjacent spots can overlap laterally, removing the dose heterogeneities. The drawback of this strategy is that the use of larger pencil-beam spot sizes results in reduced dose gradients at the edge of the target.

The dose blurring refers to the loss of sharpness of the dose gradients due to target motion (Bortfeld, Jiang and Rietzel, 2004). This results in enlargements of the penumbra at the edges of the beam. This effect can also be observed inter-fractionally if treatment setup errors or changes in the organ disposition occur between the treatment fractions. Dose blurring is the smallest
of the three motion-related effects (Bert and Durante, 2011) and can be reduced by means of motion minimization and target tracking (Engelsman, Schwarz and Dong, 2012). The use of margins and robust planning may also address this issue. However, multiple rescanning is not effective for the mitigation of the dose blurring (Knopf and Lomax, 2014).

Dose deformation, on the other hand, is related to fluctuations of the proton range due to changes in the tissue density along the beam path. It can be, caused by bony structures, e.g., ribs, moving in and out the beam path. More will be discussed about dose deformation in section 2.2.2. Due to the finite range of proton beams, the effect of organ motion may be pronounced if there are variations in tissue heterogeneities along the beam path (Lomax, 2008). The further development of IGRT and of adaptive therapy will help to reduce systematic errors and to improve the mitigation of the overall effects of organ motion.

2.2.2 Impact of varying density heterogeneities

Variations in tissue heterogeneities can occur intra-fractionally due to, for example, organ motion or inter-fractionally due to different factors such as setup errors and/or changes in the organ disposition and filling. A fluctuating tissue-density in the proton beam path enhances the range uncertainties (Lomax, 2008), which results in a degradation of the dose distribution, in particular at the distal edge of the SOBP (Sawakuchi et al., 2008). In a planning study of GC RT, performed with photon- and proton-beams (paper II) (Mondlane et al., 2017b), it was shown that the introduction of a water-like material within the abdomen, replacing the gas cavities, caused an under-dosage of the PTV in the proton-beam based plans. An extension of the proton beam range into the normal tissue, located posterior to the target, was also reported when the abdominal air cavities in the original CT sets were enlarged. This resulted in additional doses given to the OARs. On the other hand, the modifications of the planning CT sets only affected the corresponding photon plans to a minor extent (Figure 2 and Figure 3).

In addition to the uncertainty related to tissue-density variations as discussed previously, proton-beam specific uncertainties, such as range straggling and multiple Coulomb scattering will also lead to variations in the range of the proton beams. The effect of the density variations can be expected to be more enhanced by these factors. Goitein and Sisterson (Goitein and Sisterson, 1978) studied the influence of thick slivers of bone in tissue on the proton-beam propagation. They found that multiple scattering is the main source of degradation of the Bragg peak. On the other hand, Urie et al. (Urie et al., 1986) found that the density heterogeneities could only cause a shift of the position of the Bragg peak in the absence of multiple Coulomb scattering.
These early studies of the dosimetric consequences of density variations introduced in the proton beam path were performed using passively-scattered proton beams. The spot-scanning IMPT technique makes use of incident fields, within which the proton fluence is variable. This will augment the sensitivity to density heterogeneities (Lomax, 2008). These uncertainties, if not accounted for, can cause errors in the treatment delivery.
Figure 2. Planned dose distributions for a stomach cancer patient. The dosimetric impact of replacing the gas cavities in the abdomen by water-equivalent material, or expanding isotropically the air cavities by 5 mm, is shown. The dose distributions calculated with the photon plan are displayed above the corresponding proton plan for each scenario: (a) original CT sets (b) CT sets with extra water filling and (c) CT sets with extra air filling. (Mondlane et al., 2017b)
Figure 3. DVHs calculated with VMAT and SFUD for a stomach cancer patient: (a) comparison of the VMAT and the SFUD plans performed on original CT image sets, (b) VMAT plans and (c) SFUD plans prepared on the original CT image sets (full lines), CT sets with extra water filling (dashed lines) and on CT sets with extra air filling (dotted lines). (Modified from Mondlane et al., 2017b)
3 Treatment plan evaluation

Treatment plan evaluation refers to the qualitative and quantitative analysis of the dose distributions obtained during treatment planning. It is carried out with a varying degree of ambition prior to the treatment delivery, and it can also be used for comparing plans based on different radiation treatment modalities. In addition to the dosimetric evaluation, the treatment planning evaluation can also involve an analysis of the estimated TCP and NTCP and the assessed risk of radiation-induced secondary cancers following the treatment.

3.1 Dosimetric evaluation of treatment plans

The qualitative evaluation of the dose distributions calculated by a TPS is in general performed by evaluating the relevant isodose levels and the overall obtained 3D dose distributions (Figure 4).

*Figure 4. Dose distributions in the axial plane for two liver metastases patients (representing a large (upper panels) and a small (lower panels) PTV) planned for SBRT implemented with volumetric-modulated arc therapy (VMAT, A-1), three-dimensional conformal radiotherapy (3D-CRT, B-1), and planned with IMPT (A-2 and B-2). (Modified from (Mondlane et al., 2016)).*
Quantitatively, the plan evaluation is performed by evaluating the dose and dose-volume metrics for the target volumes and the OARs. These dosimetric values are obtained from the TPS, and are expressed in terms of the dose to a certain volume of a structure and in terms of the calculated DVHs (Figure 5). However, the use of DVHs in treatment planning evaluation is connected to uncertainties, since the 3D spatial information of energy deposition in tissue is lost when the dose distribution is reduced to the DVH representation.

![Figure 5](image.png)

**Figure 5.** DVHs obtained for two liver metastases patients (shown in Figure 4) planned with SBRT performed with VMAT (left) and 3D-CRT (right) (full lines). The corresponding DVHs for the IMPT plans for these two patients are shown with dot-dashed lines. The left panel shows the DVHs for the dose distributions presented in Figure 4 (A-1) and (A-2), and the right panel shows the DVHs for the dose distributions presented in Figure 4 (B-1) and (B-2). (Modified from Mondlane et al., 2016)

If the PBT plan is optimised using a robust optimisation, an evaluation of the DVHs for the nominal scenario and for the different uncertainty scenarios is performed (Figure 6). In general, a robustness criterion is set for the CTV (and/or for the critical OARs). The robustness evaluation is thereafter used to evaluate if the robustness criteria set during the optimisation were met. However, even if a robustness evaluation of the treatment plan is performed, the nominal dose distribution is still the one used to make clinical decisions. This is based on the fact that the nominal plan is associated with the largest probability of occurrence, compared to the simulated scenarios (Li et al., 2011; Fredriksson and Bokrantz, 2016).
Figure 6. DVHs, assuming different uncertainty scenarios, obtained for the CTV (black lines) and for the healthy part of the liver (red lines), for a liver metastases patient planned for IMPT. A setup uncertainty of 1 cm in the axial direction and 0.5 cm in the axial plane was assumed together with a 3.5 % uncertainty in the CT Hounsfield numbers calibration.

There are a few dose-indexes which are commonly used to describe the properties of the dose distributions, regarding the dose-coverage of the target volume, such as the conformity and the homogeneity indexes. For the OARs, certain dose-volume metrics have been shown to be correlated to a probability of occurrence of toxicity following RT. Values of these variables and the associated risk have been published by Emami (Emami et al., 1991), and later refined and summarised in the Quantitative Analyses of the Normal Tissues Effects in the Clinic (QUANTEC) studies (Marks et al., 2010) at the time when more clinical patient follow-up data was available. For example, the dose-volume threshold value for observing the classic RILD (at a rate of less than 5 %), after RT of liver metastases with a hypofractionated dose regimen, is $D_{\text{mean}} < 20$ Gy according to QUANTEC. However, the tabulated data depends on the type of treatment and fractionation schedule used and does not take the radiosensitivity variation among the patients into consideration.

3.2 Radiobiological evaluation of treatment plans
The aim of RT is to eradicate the cancer cells while minimizing the irradiation of the sensitive tissues surrounding the target. A large therapeutic ratio, which describes the probability of uncomplicated cure, is desired. By focusing the radiation beams on larger accumulations of tumour cells, a maximal tumour control probability can be achieved while providing a minimal complication probability in the normal tissues. Since in most of the cases in RT, the irradiation of critical OARs cannot be avoided, it is always desired to improve the
therapeutic ratio. This can be achieved either by maintaining the prescribed dose at the same level to achieve the same local tumour control while decreasing the dose given to the normal tissues to reduce the frequency of the normal tissue complications, or by increasing the prescribed dose to achieve a better local tumour control without necessarily increasing the risk for normal tissue complications. A quantitative description of the dose-response relationships for the tumour and for the normal tissues is given by the TCP and the NTCP relationships, illustrated in Figure 7.

Figure 7. Illustration of the tumour control probability (blue line) and the normal tissue complication probability (red line).

Both the TCP and the NTCP can be described by sigmoid dose-response curves. The probabilities of both tumour control and normal tissue complication increase with increasing dose.

3.2.1 TCP modelling

Different models for estimating the TCP have been developed, which can provide estimates of the biological response of the tumours to irradiation. The TCP is commonly estimated with a model based on Poisson statistics, which was first proposed by Munro and Gilbert (Munro and Gilbert, 1961). This model is based on the LQ-model formalism. Assuming that the number of surviving tumour cells after irradiation can be predicted by Poisson statistics, the TCP can be calculated with Equation (1),

$$TCP = \exp[-\rho_0 V \exp(-\alpha D - \beta dD)]$$

(1)

where, the Poisson-model parameter is given by the cell survival described with the LQ model. In equation (1), $\rho_0$ is the initial density of the clonogenic
cells, here assumed as being uniformly distributed over the whole tumour volume $V$, $\alpha$ and $\beta$ are the linear and the quadratic parameters of the LQ model and, $D$ and $d$ represent, respectively, the total dose and the delivered fraction dose. For heterogeneous irradiations, Equation (1) can be modified into Equation (2). The overall TCP is then given by the product of the TCPs for all the volume elements in the tumour volume,

$$TCP = \prod V_i \exp \left[-\rho_0 V_i \exp \left\{-\alpha D_i \left(1 + \frac{\beta}{\alpha} d_i \right)\right\}\right]$$

where $V_i$ is the volume receiving a total dose $D_i$ given a dose $d_i$ per fraction. The inter-patient variation in radiosensitivity can be included in Equation (2) by considering that the linear parameter of the LQ model, $\alpha$, is Gaussian distributed over a population of patients with a mean value $\bar{\alpha}$ and a standard deviation $\sigma_\alpha$ (Nahum and Tait, 1992), i.e.,

$$TCP = \frac{1}{\sigma_\alpha \sqrt{2\pi}} \int_0^\infty \left\{\left(\prod V_i \exp \left[-\rho_0 V_i \exp \left(-\alpha D_i \left(1 + \frac{\beta}{\alpha} d_i \right)\right)\right]\right) \times \exp \left[-\frac{(\alpha - \bar{\alpha})^2}{2 \sigma^2_\alpha}\right]\right\} d\alpha$$

(3)

### 3.2.2 NTCP modelling

The computation of the NTCP can be performed using different empirical models, e.g., the model proposed by Lyman (Lyman, 1985), semi-mechanistic models, e.g., the seriality model proposed by Källman et al. (Källman, Agren and Brahme, 1992) and phenomenological models, e.g., the equivalent uniform dose (EUD) suggested by Niemierko (Niemierko, 1997). In the studies performed in this thesis, the Lyman-Kutcher-Burman (LKB) model (Lyman, 1985; Kutcher and Burman, 1989; Kutcher et al., 1991), which is extensively used to assess NTCP from DVH data, was used. This model is a 4-parameter error function predicting a sigmoid dose-response, i.e.,

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t \exp \left(-\frac{x^2}{2}\right) dx$$

(4)

where $t$ in Equation (4) is given by,

$$t = \frac{D_{max} - TD_{50}(1) \cdot v^{-n}}{m \cdot TD_{50}(1) \cdot v^{-n}}$$

(5)

$TD_{50}(1)$ is the tolerance dose which leads to 50% complication probability for uniform irradiation of the whole volume of the organ. $v$ is the fractional volume irradiated with uniform dose, $n$ and $m$ are model parameters which
describe the volume dependence of the NTCP and the slope of the dose-response curve, respectively. The LKB-model parameters $n$, $m$ and $TD_{50}(1)$ for different OARs have been tabulated by Emami et al. (Emami et al., 1991).

The LKB model is only applicable for the ideal case of uniform irradiation of the OARs. In real clinical situations, the healthy organs and tissues are heterogeneously irradiated with a wide range of doses. The use of the LKB model in the assessment of NTCP requires a mathematical transformation of the inhomogeneous dose distribution to a biologically equivalent single-step DVH (Friedland and Kundrát, 2014), representing the irradiation of a limited fraction of the organ with a uniform dose. The resulting DVH is assumed to produce the same NTCP as the original DVH.

The effective volume method (Kutcher and Burman, 1989; Kutcher et al., 1991), shown in Equation (6), has been proposed to transform an inhomogeneous three-dimensional dose distributions into an equivalent homogeneous irradiation of a limited fraction of the organ, $V_{eff}$, with a dose equal to the maximum dose $D_{max}$ in the original DVH,

$$V_{eff} = \sum_i v_i (D_i/D_{max})^{1/n} \quad (6)$$

Alternatively, the transformation in Equation (6) can be presented in terms of a reduction of the DVH to the equivalent irradiation of the whole organ with an effective dose $D_{eff}$, given by

$$D_{eff} = (\sum_i v_i D_i)^{1/n} \quad (7)$$

The $D_{eff}$ given by Equation (7) is equivalent to the generalized EUD introduced by Niemierko (Niemierko, 1999), which is widely used in plan comparisons and optimizations in the clinic.

### 3.3 Risk of radiation-induced secondary cancer

Deterministic effects arising from clinical exposure to ionizing radiation may appear shortly after irradiation (early responding tissues) or much later (late responding tissues). These deterministic effects do not occur if a threshold dose is not exceeded (ICRP, 2007). On the other hand, for stochastic effects, such as radiation-induced secondary cancers, there is no lower threshold dose below which these effects will not appear (ICRP, 2007). Current knowledge, regarding the incidence of radiation-induced secondary cancers, is based on epidemiological studies. These consist of long-term follow-up studies of populations accidentally exposed to ionizing radiation, e.g. the A-bomb survivors (Preston et al., 2007; Heidenreich and Cullings, 2010). These population studies included individuals who received whole-body irradiation with low doses
of a mixture of different types of ionizing radiation. According to these studies, the observed relative frequency of secondary cancers was found to be higher for individuals that were irradiated at younger ages, and decreases with increasing age at the time of irradiation. However, the irradiation pattern, i.e. whole-body irradiation, to which the population in the epidemiological studies were exposed, differs from that used in RT.

Currently, there is not sufficient long-term follow-up data available, regarding cancer-induction in different organs, for patients treated with modern RT techniques. Therefore, the use of radiobiological models may play an important role to predict the risk of cancer-induction following RT. Different mechanistic and phenomenological models, predicting the risk of radiation-induced secondary malignancies, have been proposed. For low doses (D << 1 Gy), the linear no-threshold (LNT) model for estimating the dependence of cancer-risk on the dose is normally assumed. This model was obtained by fitting a linear function to data obtained in epidemiological studies (Figure 8). However, it can only be expected to be valid for irradiations with low-doses and low dose-rates. Its validity in the RT dose range has been questioned. The LNT model does not consider the cell sterilization observed at high doses and, therefore, it predicts higher cancer-risks than expected (Daşu et al., 2005; Schneider et al., 2005).

Figure 8. Illustration of the three distinct dose-risk relationship models for radiation-induced secondary neoplasms after radiotherapy: linear model (red line), plateau model (black curve) and bell-shaped model (blue curve).
Several models which are valid also in the high dose region (relevant for RT) have been proposed by e.g., (UNSCEAR, 1993; Davis, 2004; Daşu et al., 2005; Sachs and Brenner, 2005; Schneider et al., 2005; Schneider, 2009). These models predict a linear dose-risk dependence at low doses (Figure 8). At high doses, some of these models predict a saturation of the risk with increasing dose (the plateau model), while other models predict an exponential decrease of the risk with increasing dose (the linear-exponential or bell-shaped model), Figure 8. There is no consensus regarding the superiority of one model over another.

The risk of radiation-induced cancer in patients receiving RT at younger ages is expected to be higher, as the life expectancy for these patients can be long compared to the time required for carcinogenesis to take place (Miralbell et al., 2002). It has been suggested that a reduction of the frequency of radiation-induced secondary cancers can be achieved with PBT, based on the reduction of the integral doses that is made possible. Because there still is insufficient patient data from treatments using proton beams, treatment planning comparisons can be meaningful to assess these suggested advantages of PBT compared to standard photon RT. As reported in the study presented in paper III (Mondlane et al., 2017a), the reduction of the integral doses with PBT was found to lead to a potential reduction of the cancer risks for patients who had earlier been treated for liver metastases with photon-beam based SBRT and later re-planned for IMPT-based radiosurgery. PBT has also been shown to provide lower cancer-risks, compared to photon-beam RT, even when including the contributions from doses deposited by out-of-field radiation (neutrons in PBT and scattered photons in photon RT) in the risk estimations (Schneider et al., 2006; Taddei et al., 2010). The low doses deposited by these out-of-field radiations are in the range of validity of the linear dose-risk relationship.

As mentioned earlier, different models predicting the risk of secondary cancers following RT have been proposed. These models are based on different assumptions regarding the biological mechanisms which lead to radiation-induction of cancer. In this thesis, the cancer-risk models proposed by Schneider et al. (Schneider et al., 2005; Schneider, 2009; Schneider, Sumila and Robotka, 2011) and by Daşu and co-authors (Daşu et al., 2005) were applied.

3.3.1 The Schneider et al. model

The model proposed by Schneider and co-authors was derived from a definition of the organ excess absolute risk (EAR\textsubscript{org}). The EAR\textsubscript{org} can be obtained from the product of the organ equivalent dose (OED) (Schneider et al., 2005) and a modifying factor which is dependent of both the age at exposure and the attained age. This modifying factor is of importance for cases in which the evaluation of cancer-risk for one single RT technique is performed. However, when comparing the cancer-risks produced by two distinct RT modalities, the
ratio of the EAR\textsubscript{org} can be determined. This simplifies the calculations since the modifying factor can be divided out, when the risk is determined separately for each patient. As a result, the ratio of the risks determined for two RT modalities will be given by the ratio of the OEDs for a given organ.

The OED can be determined using a dose-response relationship, if the organ DVH is known, \textit{i.e.},

\begin{equation}
OED = \frac{1}{\sum_i v_i} \sum_i v_i \times RED(D_i)
\end{equation}  

where, \(v_i\) is the volume of the \(i\text{th}\) bin of the DVH receiving dose \(D_i\) and \(RED(D_i)\) is the dose-response relationship used in the risk model.

With the Schneider \textit{et al.} model, the risks of inducing carcinomas and sarcomas can be estimated with two distinct mechanistic models (Schneider, 2009). These models take into account the cell-kill at high doses as well as the repopulation/repair of cells between two dose-fractions. The mechanistic model describing carcinoma induction is presented in Equation (9),

\begin{equation}
RED(D) = \frac{e^{-\alpha' D}}{\alpha'R} \left( 1 - 2R + R^2 e^{\alpha' D} - (1 - R)^2 e^{-\alpha' R} \right)
\end{equation}

where, \(R\) describes the repopulation/repair of the tissue between two dose fractions. The value of \(R\) is 0 if no repair occurs and 1 if full repair has taken place. The parameter \(\alpha'\) is defined using the LQ model and is proportional to the number of cells reduced by cell killing,

\begin{equation}
\alpha' = \alpha + \beta d_i = \alpha + \beta \frac{D_i}{d_T} d_T
\end{equation}

where \(D_T\) and \(d_T\) are the prescribed dose and the corresponding dose per fraction, respectively. \(D_i\) and \(d_i\) are defined as for Equation (2). The parameters \(\alpha\) and \(\beta\) are the linear and quadratic LQ-model parameters, respectively.

From Equation (9), three-distinct dose-response models can be derived. The linear dose response is derived from Equation (9), in the limit of low doses, \textit{i.e.} \(D \to 0\). The dose-response is then predicted by the organ mean dose. The linear-exponential dose-response is derived from Equation (9) by completely neglecting the repopulation/repair effect, \textit{i.e.} in the limit of \(R \to 0\). The plateau dose-response relationship is derived from Equation (9), by considering that complete repopulation/repair takes place, \textit{i.e.} in the limit of \(R \to 1\).

The mechanistic model, describing the induction of sarcomas, is given by Equation (11),
\[
RED(D) = \frac{e^{-\alpha_D}}{\alpha_R} \left(1 - 2R + R^2 e^{\alpha_D} - (1 - R)^2 e^{-\alpha_R R} - \alpha' RD\right)
\]  

(11)

To account for repopulation/repair in the mechanistic model describing the sarcoma induction, Schneider (Schneider, 2009) used different values of the parameter \( R \) (0.1, 0.5 and 1).

3.3.2 The Dasu et al. model

The Dasu et al. (Daşu et al., 2005) model of risk assessment is derived based on the LQ model for cell-survival. It is based on the general equation proposed by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1993), with which, the competition between cell survival and mutation induction can be considered over the whole dose range. In the low dose region, this model predicts a linear increase of the risk with increasing dose, as the induction of mutations is more predominant. In the high dose region, on the other hand, the cell-kill is more dominant and the model predicts an exponential decrease in the risk with increasing dose. This results in a bell-shaped dose-response relationship (illustrated in Figure 8).

The Dasu et al. model, shown in Equation (12), takes both the treatment fractionation and the heterogeneous dose-distribution in the irradiated normal tissues into account:

\[
Total risk_{organ} = \frac{1}{\Sigma i} \sum_i v_i \times \left\{ \left(\alpha_1 D_i + \frac{\beta_1 D_i^2}{n}\right) \times \exp \left[ -\left(\alpha_2 D_i + \frac{\beta_2 D_i^2}{n}\right) \right] \right\}
\]

(12)

where \( v_i \) and \( D_i \) are defined as for Equation (2), \( n \) is the number of fractions, the parameters \( \alpha_1 \) and \( \beta_1 \) describe the induction of carcinogenic mutations and \( \alpha_2 \) and \( \beta_2 \) describe the cell survival in the irradiated organs. The parameter \( \alpha_1 \) is the organ-specific age- and sex-averaged risk-coefficient for cancer-induction given by ICRP 103 (ICRP, 2007). For other radiation qualities (e.g., proton beams), this parameter is derived from Equation (12) in the limit of low doses, where the linear dose and cancer risk relationship is valid. The \( \alpha_1/\beta_1 \) parameter for the induction of mutations is uncertain. In the study by Dasu et al. (Daşu et al., 2005), the parameter \( \beta_1 \) was calculated under the assumption that the same value of the \( \alpha/\beta \) ratio is valid for the induction of mutations as for cell survival.
3.4 Patient selection for photon- or proton-beam therapy

3.4.1 Overview of patient selection in radiotherapy

The advances made in RT have introduced numerous RT modalities for cancer treatment. Due to this development, there is a need to find a method to select the best treatment modality for each individual patient case. Different factors, e.g., tumour site, patient age, intent of treatment and cost-effectiveness, can be incorporated in the clinical decision support used for patient selection. Regardless of the criterion used for selecting the most appropriate RT technique for a particular patient, the main goal is still to select the available treatment modality which provides the widest therapeutic window.

The recently increased interest in the use of proton beams for cancer treatment was based on the possibility to reduce the integral doses given to the patients, which has been shown to reduce the normal tissue toxicity and the treatment-induced secondary cancers. This fact led to the indication of proton therapy mainly for paediatric patients in Sweden (Björk-Eriksson and Glimelius, 2005; Greco and Wolden, 2007; Hardy and Bridge, 2008), as the organs and tissues of these patients are still in development and hence more prone to the stochastic biological effects caused by RT. The potential of PBT to reduce the treatment-induced secondary cancers compared to photon RT has been demonstrated (Chung et al., 2013; Mondlane et al., 2017a). With the recent growth in number of PBT centers, the use of the tissue sparing potential of PBT has begun to be explored also for adult patients. However, the methods for delivering RT with photon beams have reached an advanced stage. Techniques such as VMAT can nowadays also be used to produce highly conformal doses to the target volumes with low toxicity levels. This is the main reason why the photon RT techniques still are the treatment of choice for most patients and tumour sites. However, there are cases for which the photon-beam techniques do not provide the best RT treatment. For example, this includes cases where high doses are needed for tumour eradication and when the delivery of such high doses is limited by the radiosensitivity of neighbouring critical organs. This has introduced the need to evaluate the individual patients, for whom PBT could provide a significant advantage, compared to the best available photon RT techniques.

3.4.2 Model-based approach for patient selection to radiotherapy with photon- or proton-beams

The use of RT in the clinic is based on the balance between TCP and NTCP. A high local tumour control is desired combined with a low probability of normal tissue toxicity. However, in some cases, this ideal scenario is difficult
to reach. Two different approaches can therefore be used to widen the therapeutic window: (1) the TCP level can be maintained constant and the NTCP lowered; otherwise (2) the NTCP can be kept constant and the TCP increased. In this perspective, PBT can be explored to achieve either of these scenarios, compared to what is obtained with the standard photon RT.

The local tumour control and the normal tissue toxicity following RT are normally evaluated in patient follow-up studies, which are conducted following the completion of RT. With the introduction of new RT modalities, it is necessary to estimate the probabilities of local treatment failure and radiation-induced toxicities, prior to treatment. This allows for an evaluation of whether the use of new modalities will be made with any clinical gain for the patient. However, there is a lack of patient follow-up data from new RT modalities, which makes the use of in silico treatment plan comparison more meaningful.

In this context, several approaches for selecting patients to PBT have been proposed. In one of these models, the benefit of PBT is evaluated in terms of the reductions of treatment-induced side-effects, through the use of NTCP models and dosimetric plan comparisons (Langendijk et al., 2013; Widder et al., 2016). This approach is being implemented in the selection process for PBT in the Netherlands and has been proposed for patients in Denmark. The vast experience of the use of photon beams in the clinic is used to validate the NTCP models that subsequently will be employed in NTCP predictions for PBT. With this approach, the actual observed toxicities following the completion of PBT will be used to update the NTCP models used for PBT. As the treatments given with new RT modalities can be more expensive than those given with standard photon-beam techniques, there is a need to include the cost-effectiveness aspect in the patient selection framework. With this aim, Cheng et al. extended the approach proposed by Langendijk and co-authors to also include a comparison of the cost-effectiveness of the two treatment modalities in the selection process, as illustrated in Figure 9 (Cheng et al., 2016).

![Figure 9. Description of the system for patient selection consisting of 3 major pipelines (Cheng et al., 2016)](image-url)
Although the high installation cost of new proton treatment centers is a drawback of PBT (Hardy and Bridge, 2008; Doyen et al., 2016), the expected improvements in local tumour control rates with PBT could potentially lead to a reduced need of other complementary treatments, such as re-irradiations, salvage surgery and palliative chemotherapy (Doyen et al., 2016). Studies evaluating the cost-effectiveness of PBT have been performed, aiming to justify its use in certain treatments. For instance, proton therapy was found to be more cost-effective for medulloblastoma paediatric patients, compared with photon RT (Lundkvist, Ekman, Ericsson, Jönsson, et al., 2005). For breast cancer patients, PBT can be expected to be cost-effective, provided that the patients with high risk of developing cardiac failure, radiation pneumonitis and morbidity are selected for PBT (Lundkvist, Ekman, Ericsson, Isacsson, et al., 2005).

An important task in the NTCP-model based approach is to determine the threshold level of the NTCP reduction that could be translated into a significant clinical gain (Widder et al., 2016) for the different OARs and treatment sites involved. The NTCP thresholds can be defined based on the clinical experience and on the knowledge of the impact of the model uncertainties on the estimated NTCP values. For instance, to perform plan comparisons, high quality (and realistic) plans for PBT need to be retrospectively prepared. This in turn, demands that uncertainties related to the treatment planning and delivery are taken into account in the plans used for patient selection (Arts et al., 2017). Most dosimetric studies, comparing photon and proton treatments, are made using the PTV as defined for photon RT, without accounting for the proton specific uncertainties. This might thoughtlessly favour the proton plans. In the study of the impact of density changes in GC RT, presented in paper II (Mondlane et al., 2017b), the proton plans were shown to be dosimetrically superior compared to the photon plans. However, it was also shown that the introduction of density changes affected the proton plans drastically, while the photon plans maintained their high quality. The importance of including robustness objectives when planning for PBT was shown in a later study involving the same patients (paper IV), as can be observed in the DVH comparison shown in Figure 10 (Mondlane et al., 2018a). In this study, the robustly optimised proton-SFUD plans were found to be insensitive to the introduced density changes.

Several factors affect the uncertainties involved in the NTCP estimations. For example, it has been shown that the use of different dose calculation algorithms influences the resulting dose distributions (Flejmer et al., 2015), and hence, the estimated NTCPs (Hedin and Bäck, 2013). This was also shown in the study by Bijman et al. (Bijman et al., 2017), which indicated the need to reduce the uncertainties in the NTCP-model predictions prior to their use in the clinic. The impact of disregarding the variable proton RBE in the NTCP
estimations has also been shown (Tilly et al., 2005). In addition, the parameters used for NTCP-model predictions are also connected to uncertainties, mostly related to the inter-patient variation of radiosensitivity (Yorke, 2001; Tsougos et al., 2007).

**Figure 10.** Median DVHs calculated for the CTV and the OARs for eight GC patients, planned for VMAT (full lines) and proton-SFUD plans prepared on CT image sets with density override of air cavities (replaced with water HUs) (dot-dashed lines) and thereafter recalculated on the original CT image sets (dotted lines). (Mondlane et al., 2018a).
Despite the fact that most of the proposed model-based approaches for patient selection are inclined to evaluate the benefits of PBT in terms of reductions of normal tissue toxicity, efforts have also been made to consider the benefits in terms of local tumour control. This applies to the cases for which dose escalation is desired, e.g., in SBRT treatments, without compromising the sparing of the critical structures located in the proximity of the target volume. For example, in the study presented in paper V (Mondlane et al., 2018b), the possibility to deliver ablative doses to liver tumours with reduced integral dose and NTCP for the healthy part of the liver, compared to photon SBRT plans, was demonstrated. Dose escalation can also be of interest for re-irradiations cases, where PBT can also be expected to improve the therapeutic ratio without any unwanted damage of the OARs (Eekers et al., 2016; Chao et al., 2017).
4 Summary of attached papers

4.1 Studies on liver metastases

4.1.1 Papers I and III: Dosimetric comparison and the risk of radiation-induced secondary cancer following radiosurgery of liver metastases with photon- or scanned proton-beams

The aim of the studies presented in these two papers was to investigate the potential of scanned proton beams to improve the sparing of the OARs (Paper I) and to reduce the risk of radiation-induced secondary cancers (Paper III) following radiosurgery of liver metastases, compared to the clinical plans prepared for SBRT. Ten patients who previously received photon-beam based SBRT at Karolinska University Hospital were included in this study. For each patient, a proton plan using the IMPT method was retrospectively prepared aiming to achieve a similar PTV-dose coverage as for the photon SBRT plan. A pairwise comparison of the dose volume values obtained from the treatment plans and the estimated risks of treatment-induced secondary cancers was performed for the two treatment modalities studied. A similar target dose coverage as with the photon-beam based SBRT could be obtained with IMPT. The IMPT plans resulted in an improved sparing of the OARs, including the healthy part of the liver, which is the most critical OAR in RT of liver malignancies. The dose reductions with IMPT were later (paper III) shown to lead to reduced risks of radiation-induced secondary cancers, estimated with both the Schneider- and the Dasu-model.

4.1.2 Paper V: Evaluation of the risk for radiation-induced liver disease following photon- or proton-beam radiosurgery of liver metastases

The possibility of reducing the frequency of secondary cancers following RT with proton beams has been used as a rationale for introducing this treatment modality in the clinic. This advantage is in general explored for the paediatric patients, whose organs are still in development and hence, are more radiosensitive. The clinical use of scanned-proton beams can also offer advantages in
terms of reductions of deterministic unwanted effects following treatment, which can be advantageous also for adult patients. In this context, an approach based on a radiobiological assessment of the reduction of toxicities with PBT has to be built for selecting potential patients to receive PBT, instead of photon RT. In the study presented in this paper, a model-based approach for selecting patients with liver malignancies to IMPT, based on the potential reduction of RILD, was performed. In contrast to the IMPT plans prepared for the studies presented in papers I and III, a selective robust optimisation of the IMPT plans was performed in paper V. This involved a CTV-based robust optimisation (which included setup and proton range uncertainties) performed simultaneously with a conventional optimisation of the PTV. This allowed for dosimetric plan evaluations of the proton plans in which the proton range uncertainties were included during the planning. Furthermore, the NTCP for RILD was estimated using the LKB-model and the latest model-parameters relevant for partial liver irradiation. A pairwise comparison of the NTCP values for RILD obtained with the photon SBRT and IMPT plans, showed that lower risks for RILD were obtained with IMPT for the majority of the patients. The study presented in this paper can also be applicable to patients with primary liver cancer, for whom the reduction of RILD is of larger importance.

4.2 Studies on gastric cancer

4.2.1 Paper II: Comparison of gastric-cancer radiotherapy performed with VMAT or SFUD proton therapy

The study presented in Paper II aimed to perform a dosimetric comparison of gastric cancer RT performed with photon VMAT and with scanned-proton SFUD. This dosimetric comparison also involved an evaluation of the effects of density changes on the dose distributions obtained in the plans prepared for VMAT and SFUD. To perform this study, clinical treatment plans were extracted for eight GC patients previously treated with VMAT at Karolinska University Hospital. For each patient, a proton plan was prepared using the SFUD method, with the same PTV as used for the VMAT plans. A pairwise dosimetric comparison for the OARs showed that SFUD improved the sparing of the OARs, compared to VMAT. The original CT image sets for these patients were then artificially modified to simulate two distinct worst-case scenarios of density changes: (1) the original volumes of the air cavities present on the original CT images were isotropically expanded by 0.5 cm and (2) the original volumes of air cavities were filled with water-equivalent material. When recalculating the dose distributions obtained in the original VMAT and SFUD plans in these modified CT-sets, it was found that the photon plans were more robust in the presence of the density changes, while the proton
plans were more deteriorated. This study highlighted the need of robust approaches to mitigate the effects of density changes in PBT of GC.

4.2.2 Paper IV: Estimation of NTCP following gastric cancer RT with photons or scanned proton beams

The dosimetric study performed in paper IV was based on the results obtained in paper II, and consisted of the search for a robust strategy to mitigate the effects of density changes in the treatment planning for PBT performed with scanned-proton beam SFUD. In the SFUD planning performed for this study, a density override (DO) of the air cavities present in the original CT image sets was performed. The HUs of the air cavities was substituted with water-equivalent HUs. SFUD plans were thereafter prepared by using field-specific PTVs and CTV-based robust optimisation, accounting for setup and range uncertainties. The resulting SFUD plans (SFUD_{opt}) was then recalculated on the original CT image sets to create the SFUD_{ver} plans.

The dosimetric comparison performed in this study, showed that comparable dose-volume values was obtained for all the structures with the two SFUD plans, while the VMAT plans resulted in similar or higher dose-volume values for the OARs. This result indicated that SFUD plans which are robust against density changes can be obtained for GC RT. In addition to the dosimetric plan comparison performed, a comparison of the calculated values of NTCP for the different endpoints was also carried out. The NTCP assessment was done using the LKB-model. Significant reductions of the NTCP values for the left kidney were obtained with SFUD. This can be of clinical relevance for cases in which the preservation of the renal function after RT is one of the main treatment objectives.
5 Summary and outlook

The use of RT in cancer treatment is connected to induction of toxicity, which can be observed at different time points following the treatment. For this reason, the clinical use of ionising radiation has to be made in such a way that it brings more benefits than harm to the patient. Proton beams have the potential to further spare the healthy tissue surrounding the tumour volumes, compared to photon beams. This advantage has been increased with the introduction of scanned beams, which provides the potential to reduce the short and long term side-effects which may appear following treatment. The increase of the local control rates and in the life expectancy of RT patients, which has been witnessed in the recent years, has also made the reduction of the frequency of treatment-induced side-effects more important. For this reason, the use of proton beams is not only of interest for treating paediatric patients, but also could be beneficial for treatments of adult patients, when the goal is to improve the sparing of the critical OARs. In this context, there is a current need to determine the patient groups that can be indicated for proton therapy, based on the improved sparing of the OARs. This clinical benefit of PBT has to be justified and weighed against the costs of proton therapy. The treatment feasibility must also be studied, based on the uncertainties that can be anticipated.

The lack of clinical data on patient follow-up after PBT limits the knowledge of the clinical evidence supporting the use of proton beams. The vast knowledge obtained from studies of the outcome of photon-beam based RT techniques could therefore be used to retrospectively identify the individual patients that could benefit from receiving PBT. In the studies presented in the accompanying papers, plans prepared for PBT implemented with SFUD and IMPT methods were shown to significantly reduce the irradiations of the critical organs, for both the GC and liver metastases patients. The dosimetric advantages observed also indicated that the normal tissue toxicity (GC and liver metastases) and the risk for treatment-induced secondary cancers (liver metastases) could be reduced. Based on these findings, the selection of individual GI cancer patients for PBT can be performed, aiming to reduce the treatment-induced side-effects. There is, however, a need to make a clinical validation of the toxicity prediction models prior to their clinical use, as large uncertainties are involved in the risk estimations. These include, among others, the use of toxicity model-parameters which were derived from photon-
beam treatment outcome data. More extensive follow-up data for proton-beam treatments will only be available with the increased use of PBT in the clinic.

The use of scanned proton beams in the management of GI cancers is still limited, as this kind of beam delivery is highly influenced by patient-related uncertainties, such as inter-fraction variations in tissue density. This limitation of PBT was shown in the studies on GC presented in this thesis, where the SFUD plans were found to be less robust against the introduced density changes, compared to the plans prepared for photon RT. The use of robust approaches in PBT treatment plans resulted in plans which not only maintained a good plan quality in the presence of density changes, but also provided an improved sparing of the OARs, compared to the corresponding photon VMAT plans. The recent development of image guidance and adaptive approaches in RT could lead to important improvements also for PBT of GI cancers. The studies presented in this thesis can be used for guidance when evaluating new clinical applications of scanned proton beams for the treatment of GI cancers located in the upper abdomen.
Sammanfattning

Protonterapi med skannade strålar är en metod som nyligen har blivit tillgänglig för strålbehandling av cancer. De kliniska fördelarna med protonstråle-baserad radioterapi, jämfört med den vanligtvis använda fotonstråle-baserade radioterapin, har tidigare blivit visade i olika vetenskapliga rapporter. Metoderna som används för att planera och för att ge behandlingar med fotoner har dock gradvis förbättrats över en längre tid. När möjligheten att ge behandlingar med protoner introduceras kliniskt är det av stor betydelse att det finns riktlinjer för hur selektionen av patienter ska gå till.

En metod som används för att hantera urvalet av patienter till protonterapi är baserad på patientens ålder. Den pediatriska patientgruppen anses vara den mest strålkänsliga och därför i större behov av mer skonsamma strålbehandlingstekniker. Det ökande antalet cancerkliniker som har tillgång till protonterapi, kombinerat med det ständigt närvarande behovet av att reducera frekvensen av akuta och sena biverkningar, har lett till en ökad användning av protonterapi även för vuxna patienter. För närvarande finns det begränsad kliniska uppföljningsdata avseende utfallet av protonbehandling av olika tumörgrupper, särskilt för extrakraniella tumörer. Användningen av fotonstrålar för den typen av behandling är å andra sidan väletablerad. Den förväntade kliniska nyttan av extrakraniell protonstrålbehandling kan därför uppskattas enbart baserat på den kliniska erfarenhet som erhållits med fotonbehandlingar. Därför är utvärderingen av olika osäkerheter som kan påverka radioterapin av olika tumörtyper av betydelse för att skapa en förbättrad förståelse för lämpligheten av att behandla dessa med skannade protonstrål, i stället för med fotoner.

Jämförelsen av två olika radioterapimetoder utförs normalt genom att studera formen av de beräknade dosfördelning adderade på patientens CT bildstudier med inritade riskorgan och målvolymer och genom att utvärdera de dosimetriska värdena som erhållits från dos-volymphistogram. Den dosimetrisk utvärderingen kan kompletteras med uppskattningar av behandlingsutfallet i termer av lokal tumörkontroll och toxicitet. I detta hänseende kan radiobiologiska modeller vara ett värdefullt verktyg. Resultaten av dessa beräkningar kan i sin tur användas för att välja den mest lämpliga radioterapimodaliteten för individuella patienter.

Denna avhandling består av fem artiklar. I dessa studier har behandlingsplaner med skannade protonstrål förberetts och jämförts med fotonbaserade
Radioterapia com protões (RTP), usando feixe de protões rastreados (FPR) é uma modalidade emergente no tratamento de câncer. As vantagens clínicas da RTP, comparadas com a radioterapia usando feixe de fotões (RTF) foram previamente demonstradas em diferentes estudos. No entanto, as técnicas usadas para a planificação e tratamento usando feixes de fotões vem sendo desenvolvidas ao longo dos anos. Com a introdução de feixes de protões na clínica, directrizes de selecção de pacientes a serem tratados com radioterapia usando feixe de fotões ou de protões são indispensáveis.

Uma simples aproximação usada na selecção de pacientes a serem tratados com RTP é baseada na idade dos pacientes. O grupo de pacientes pediátricos é considerado como tendo maior sensibilidade à radiação ionizante, comparado com os pacientes adultos. Consequentemente, os pacientes infantes estão em maior demanda de métodos para proteger os tecidos normais. Porém, o crescimento do número de centros de tratamento de câncer usando feixes de protões em combinação com a necessidade de reduzir a frequência dos efeitos colaterais agudos e tardios, tem levado ao aumento do uso da RTP também para pacientes adultos. Actualmente existe informação limitada acerca de resultados clínicos de pacientes tratados com RTP em diferentes tumores, em particular para os casos de tumores extracranianos. Por outro lado, o uso de feixe de fotões na radioterapia destes tumores está bem estabelecido. Por esta razão, os benefícios esperados do uso de feixe de protões no tratamento de câncer podem ser transferidos dos resultados obtidos da experiência clínica adquirida com o uso de feixe de fotões. A avaliação das diferentes fontes de incertezas que influenciam a radioterapia de diferentes locais de câncer usando feixes de fotões ou de protões, irá melhorar a compreensão da viabilidade do tratamento do câncer com FPR, ao invés de feixe de fotões.

A comparação de duas modalidades radioterapêuticas distintas é normalmente efetuada por meio da avaliação das distribuições de dose superpostas nas imagens de tomografia computadorizada do paciente e da avaliação dos valores dosimétricos obtidos a partir dos histogramas de dose e volume. A avaliação dosimétrica pode também ser complementada com as previsões dos resultados dos tratamentos em termos do controlo local tumoral e dos efeitos colaterais nos tecidos normais. Neste contexto, modelos radiobiológicos podem constituir uma ferramenta indispensável na previsão dos resultados da radioterapia implementada com diferentes tipos de radiação ionizante. O uso
de modelos radiobiológicos poderá afinal providenciar meios de seleção individual de pacientes a serem tratados com radioterapia usando feixes de fotões ou protões.

Esta dissertação consiste em cinco artigos publicados, sendo que nesses estudos foram criados planos de tratamento com FPR. Estes planos foram posteriormente comparados com os planos clínicos utilizados para o tratamento usando feixe de fotões. A comparação dos planos de tratamento consistiu na avaliação dosimétrica e biológica da radioterapia usando feixe de fotões e feixes de protões rastreados. Estes estudos foram realizados para dois locais distintos de câncer gastrointestinal, nomeadamente, o câncer gástrico (CG) e metástases no figado. Para o caso de CG, o impacto das variações de densidade dos tecidos resultantes das variações de gases no abdômen (que pode se observar entre frações de tratamento) foram também estudados. Nesta tese foram considerados dois regimes de fracionamento do tratamento, i.e., o fracionamento convencional (implementado na planificação do tratamento de CG) e o hipofracionamento (implementado na planificação do tratamento de metástases no figado). A RTP providenciou a possibilidade de redução da dose depositada nos tecidos normais localizados ao redor dos volumes alvos, comparado com a RTF. A redução da dose integral nos órgãos em risco com RTP resultou na redução dos riscos de efeitos colaterais nos tecidos normais e de cânceres secundários. O impacto das variações de densidade nas distribuições de dose foi vista como pronunciada nos planos de RTP, desde que estratégias de planificação robusta tenham sido ignoradas. Os resultados apresentados nesta dissertação são de importância clínica no processo de seleção de modalidades distintas de radioterapia.
Acknowledgements

My studies were financially supported by the Swedish International Development Cooperation Agency (Sida) through the International Science Programme (ISP, Uppsala University).

I would like to express my deepest gratitude to:

Albert Siegbahn, my major supervisor, for all the moments throughout the process of my education. For your patience and guidance, for the interesting discussions and for motivating me to carry out this work. For being constantly present and available, not only for the work-related issues, but also for matters beyond work. Thank you.

Michael Gubanski and Iuliana Toma-Dasu, my co-supervisors, for all the attention and for being available for me whenever I had questions. In special to Michael Gubanski, thank you for providing me with the clinical data I used in all the work I performed. I wouldn’t have made it without your support regarding the clinical aspects of my work.

Ana Ureba, Albert Siegbahn, Michael Gubanski and Pehr A. Lind, my collaborators and co-authors, for all the hard work, for the fruitful discussions and effective team work. In special to Ana, thank you very much for all profound discussions, for transferring to me your expertise and also for your fine sense of details. I want also to thank you Ana for your friendship, motivation and unconditional willingness to help.

Per-Erik Tegnér, my mentor, for all the guidance and support.

Maja Malmberg, my friend, who played the role of an informal mentor along the way until today. Thank you for all you advice, guidance, all the fikas and conversations we had and, above all, for the motivation and expertise you transferred to me through your own experience.

Bruno Sorcini and Bo Nilsson, for the interesting discussions which greatly improved the thesis and the work presented in the accompanying papers. In special to Bo Nilsson, thank you for taking your time to read both my Licentiate and the present thesis.

Carlos Lucas, former Director of Cooperation at Eduardo Mondlane University (UEM), and Alexandre M. Maphossa, Medical Radiation Physics
Programme Coordinator at UEM, thank you for giving me the opportunity to pursue my higher-education studies in Sweden.

**Mona Holgerstrand** for all the abundant laughter and fruitful conversations.

**Sasikala Govindharajan** for a warm friendship and endless laughter even through the Swedish Winter.

My family in Mozambique (specially my brave mother **Anastância Maguengue** and in loving memory of my grandmother **Rosa Mugabe**). You are my source of motivation and unfortunately I had to leave you to pursue my academic journey. I have missed you all in every second I have been away, but I know that whenever you are alright so will I be as well. On this part of the frame, I want also to express my warmest gratitude to my family in Sweden (and around the world), who life gave me the opportunity to meet and share my life with, for all the support and continuous presence throughout my journey. For the unconditional love, respect and understanding, I dedicate this work to you, my family.

Finally, I would like to take this opportunity to specially show my warmest gratitude to my fiancé **Richard Johansson** for his love, constant presence, patience and for believing in me when no one else did. I want also to thank you Love for motivating me to carry on even when moving through very heavy waters.

*Khanimambo (thank you)!*
References


ICRU (1993) ICRU 49: Stopping powers and ranges for protons and alpha particles. Bethesda, Maryland, USA.


