Patient-specific in-vivo QA in MRGRT: 3D EPID dosimetry for the Unity MR-linac

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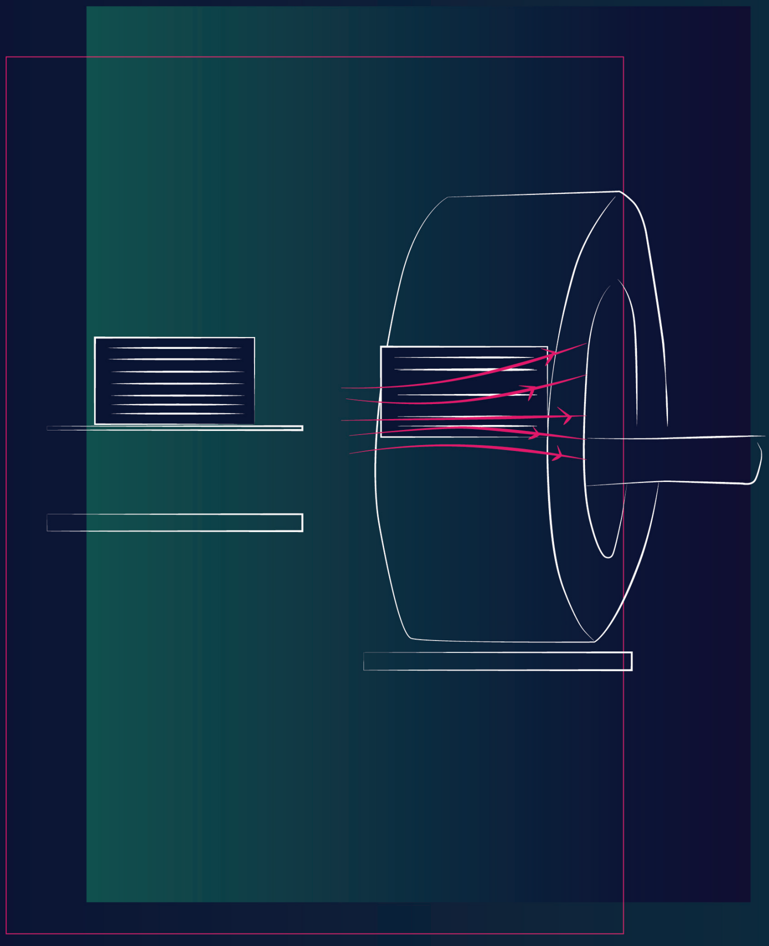

1.

INTRODUCTION

1.1. Radiotherapy

Radiotherapy is one of the main treatment options for cancer, besides surgery and medical oncology. It is estimated that 60% of cancer patients [1] receive it alone or in combination with other treatment modalities. The aim of this non-invasive and local treatment is to stop proliferation and eradicate malignant cells by exposing them to a high dose of ionizing radiation while minimizing the dose to the surrounding healthy tissue [2]. When irreparable damage has been done, the body will eliminate these cells. For body sites/tumor types where radiotherapy is generally applied, healthy cells typically have better and faster mechanisms to repair radiation damage than malignant cells, resulting in a higher sensitivity of tumor tissue to radiation damage. Furthermore, the higher the radiation dose to the target volume, the higher the probability that the malignant cells are killed. However, this is constrained by the accuracy of delivering high doses only to the tumorous cells while sparing the healthy tissue.

In the conventional radiotherapy workflow, a pre-treatment Computed Tomography (CT) scan of the patient is made in treatment position. This scan is used to delineate relevant anatomical structures such as the organs at risk (OAR), the gross tumor volume (GTV), clinical target volume (CTV) and the planning target volume (PTV), which results from applying a margin to the CTV to account for uncertainties (e.g. due to organ motion). Next, the optimal dose distribution is computed in the treatment planning system (TPS) balancing the prescribed target dose aims and OAR dose constraints.

1.2. Advances in radiotherapy treatment delivery

Radiotherapy techniques have changed significantly over the past few decades, thanks to improvements in engineering and computing.

Delivery of highly conformal dose distributions enveloping the shape of complex target volumes while avoiding neighboring healthy tissue has become feasible. Simultaneously, treatment complexity has increased from rectangular fields via 3D-conformal treatments to intensity-modulated radiotherapy (IMRT), volumetric arc therapy (VMAT) and tumor motion tracking using planning 4D CT images. Meanwhile patient setup verification has evolved from the use of portal films and 2D megavoltage (MV) imaging to 3D volumetric kV imaging using cone-beam CT (CBCT).

1.3. Imaging techniques

Currently, several imaging modalities are available in the pre-treatment phase. Examples are CT [3], positron emission tomography (PET) [4], single photon emission tomography (SPECT) [5], ultrasound (US) [6] and magnetic resonance imaging (MRI) [7]. In addition to being used for tumor localization, most of these modalities are employed to visualize tumor tissue characteristics, like cell density, hypoxia or perfusion. Based on this information the dose can be prescribed heterogeneously to the tumor, giving a higher dose to high risk regions. By applying this 'dose painting' based on tumor characteristics the treatment of different kinds of malignancies may be improved [8–13].

1.4. Patient specific QA in conventional linacs

1.4.1. Why QA?

With the increase of complexity in radiotherapy treatments over the years, serious incidents have been reported [14–20] and protocols have been established to learn from past errors [21,22]. Even though these incidents are recognized to be uncommon events, their impact on patients, staff and radiation oncology in general are harmful. Hence, a demand for more robust and better quality assurance (QA) techniques has developed. While quality assurance aims at making sure that quality goals will be met in general, quality control (QC) is the regulatory process through which the quality goals are measured for specific standard cases. Quality assurance does not only reduce the likelihood of incidents to occur, it also increases the probability that they will be recognized and rectified sooner in case they occur.

1.4.2. Why patient specific QA

Patient specific QA entails the dosimetric verification of individual patient treatments (i.e. compares planned and measured dose distributions, either in a phantom geometry or using *in-vivo* data acquired during treatment), and aims to detect and reduce clinically relevant dosimetric deviations [23–25]. *In-vivo* dosimetry involves acquiring dose measurements during treatment delivery, reconstructing patient dose if needed, and comparing it to the intended dose.

Several tools for dosimetric patient specific QA exist; ionization chambers, diode array detectors, radiochromic film, polymer gel, and electronic portal imaging devices (EPIDs) are most commonly applied. In the following sections, the use of these tools for both pre-treatment and *in-vivo* QA is discussed.

1.4.3. Pre-treatment QA

'Pre-treatment QA' in radiotherapy is the general term for dose measurements performed in a phantom geometry. The patient plan is delivered to a phantom geometry containing a type of detector. The treatment plan is recalculated on the phantom geometry, and the measured and planned dose distributions are compared.

Radiochromic film is typically placed between the slabs of a polystyrene phantom. Given its high spatial resolution, it can be used for verification of highly conformal dose distributions such as generated by IMRT [26–31]. Thanks to its near tissue equivalence, radiochromic film can be used for 3D dosimetry by embedding multiple films between stacks of phantom slabs. Disadvantages of the use of radiochromic film are the need for elaborate calibration procedures and an impractical and tedious measurement procedure.

The use of point detectors such as ionization chambers (IC) or diodes [32,33] for dosimetry in radiotherapy has been extensively studied [34–39], and is considered the ground truth for absolute dosimetry. In pre-treatment QA, single detectors or 2D detector arrays are positioned inside a phantom to measure the absorbed dose in a point or plane. The spatial resolution of 2D arrays, however, tends to be poor in comparison to film, as the number of detectors that can be embedded is constricted by spatial limitations.

Polymer gel dosimetry has been used for pre-treatment 3D volumetric dosimetry in phantoms [40–43]. The gel dosimeter has potential for volumetric measurements with sub-mm spatial resolution. A major impediment to the introduction of gel dosimetry as a clinical tool, however, has been its complexity in terms of experimental handling.

An EPID (Electronic Portal Imaging Device) is a 2D detector that captures high-energy radiation, originally developed as an imaging device for patient position verification [44,45]. EPIDs are mounted opposite to the radiation source and hence detect the radiation after it has left the phantom or patient. It was soon noted that EPIDs are also suitable for dosimetry [46], as the detected signal is proportional to the dose incident on the panel. For that purpose, it is necessary that pixel intensity is converted to dose, either at the panel level or by back-projecting it into the phantom geometry. EPIDs have the benefit that they can be used either for pre-treatment or *in-vivo* dosimetry.

Fluence detectors [47,48] are mounted on the linac head and can serve as an alternative to dose measurement devices in a phantom. When used in combination with a dose calculation engine, the dose distribution delivered to the patient geometry can be estimated. Besides pre-treatment verification, measurements can also be performed during treatment, allowing for dosimetric verification based on data obtained during patient treatment. A similar method for dose reconstruction uses the linac log files [49,50] as input. In this case, the linac log files (obtained pre-treatment or during treatment) are used, in combination with a dose calculation engine, to reconstruct dose in a certain geometry. However, the main drawback of log-file approaches is that they rely on the output of the linac.

Despite the effort and support from industry to develop accurate detectors, the use of pre-treatment dosimetry systems leaves some intrinsic issues unsolved:

- the measurements are performed in a phantom geometry. Therefore, the location of any observed dose deviations cannot be related to the patient geometry, complicating assessment of clinical impact.
- dosimetric deviations occurring during patient treatment remain undetected[51,52].
- the measurements require linac time and workload due to experimental setup and data analysis

The first issue is currently being addressed by radiotherapy QA vendors by transfer of measured dose onto the patient anatomy (using the planning CT scan). The latter two issues are fundamentally unsolvable by means of pre-treatment verification.

1.4.4. In-vivo QA

In *in-vivo* dosimetry the dose delivered to the patient is estimated from a measurement performed during treatment. Such measurements can be achieved with detectors positioned in the body of the patient, or with measuring devices located in front of or behind the patient, in combination with a scan of the actual geometry of the patient. Next, the determined dose is compared to the intended dose as calculated by the TPS. Different methods are currently being employed for *in-vivo* dosimetry, based on point-based measurements [53,54], or EPIDs [55–57] [58–61].

The use of point detectors for *in-vivo* dosimetry [62–64] normally involves invasive routines, and often only provides a single point measurement, which makes it not ideal for IMRT.

EPIDs are nowadays the most important 2D transit detectors. The first *in-vivo* dosimetric application was exit-dosimetry [65–68], where the dose in the EPID located behind the patient, was verified. Two approaches can be distinguished when using EPID for *in-vivo* dosimetry: in forward approaches [56,69] the acquired portal dose is compared to the predicted dose at the EPID level, whereas in a back-projection approach [70] the acquired portal dose is used to reconstruct dose in the patient geometry [71] and compared to the planned dose either in 2D or 3D. In the forward approach, the clinical interpretation of potential discrepancies is difficult as the connection with the patient geometry is missing. The back-projection approach, on the other hand, does not suffer from this drawback. When used for back-projection *in-vivo* dosimetry, the (planning) CT scan of the patient is used in combination with EPID images acquired during treatment. Using the transmission calculated from the CT scan, the dose information in the EPID image is back-projected into the patient geometry, with the EPID reconstructed 2D or 3D dose in the patient geometry as a result.

Interest for EPID based *in vivo* dosimetry has increased in the last years. As patient specific QA has become mandatory in several countries, vendors of radiotherapy QA systems , such as DosiSoft [72], SunNuclear

[73], IBA[74] and Elekta[75] have released tools for *in vivo* dosimetry.

The use of fluence detectors or log file based dose reconstruction, in combination with the daily anatomy of the patient (for example CBCT) [49,50,76–81], are potentially powerful methods for patient dose reconstruction. However, the limited capability of these systems to detect patient related errors and the lack of clinically available products makes that these solutions are not widely adopted.

1.4.5. Comparison metrics

Traditionally, the comparison between planned and measured dose distributions, both in 2D and 3D, is performed by means of γ-analysis 82, a method to determine the shortest distance in normalized dose-distance space between measured and reference dose curves. Both distance and dose difference are normalized using reference values, typically 3 mm (distance) and 3% (dose).

Dose Volume Histograms (DVHs) are histograms relating radiation dose to tissue volume. They are most commonly used as a dose evaluation tool, to compare dose distributions (e.g. from different plans or from measurement and planning) and to summarize 3D dose distributions in a graphical 2D format. Thus, they can provide an informative description of the deviations observed between delivered and planned dose distributions. Correlation studies showed clinical equivalence for γ- and DVH-based methods [83,84].

1.5. 3D in-vivo EPID dosimetry at the Antoni Van Leeuwenhoek - Netherlands Cancer Institute

At the Netherlands Cancer Institute – Antoni Van Leeuwenhoek (NKI-AVL), 3D *in-vivo* EPID dosimetry, based on a back-projection method is the QA tool used for routinely verifying all radiotherapy treatments.

An algorithm was developed to use the EPID not only as a positioning tool, but also as a 2D transit dosimeter [70] for 3D CRT and IMRT treatments. Soon after, an extension of this work to for 3D verification was built [58,85]. This was necessary to develop a tool capable of acquiring continuous EPID movies of VMAT treatments to verify arc therapy [59]. Later, the method was improved for the presence of inhomogeneities in or near the irradiated volume[86]. Since August 2011, the EPID-based dose reconstruction and γ-evaluation software runs automatically[87] for almost all treatments, yielding a dosimetry report for inspection within minutes after treatment delivery without any manual intervention. Further developments to the method have been made, such as the use of the 'virtual' reconstruction technique [88], which uses in-air EPID images to reconstruct the dose to any CT scan (phantom-less pre-treatment), and online EPID dosimetry [89] to stop the linac *during* treatment in case a large deviation is detected.

These improvements in automation allow for *in vivo* verification of almost all treatments with acceptable workload. When compared to phantom based dose verification, measurement time is greatly reduced, at the cost of an increase in inspection work. The clinical experience with the large scale in vivo dosimetry program has been shown [51,90].

1.6. The Unity MR-linac

Compared to other commonly used imaging modalities in radiotherapy, MRI provides superior soft-tissue contrast and thus a clear view of both tumorous tissue and OARs. MR imaging uses no ionizing radiation and can therefore be repeated without increasing the patient radiation burden. These properties make MRI an excellent candidate for image guidance. Therefore, the integration of an MRI in a radiotherapy system has been an area of interest and recently, treatment machines combining a radiation source with an MRI system have been developed and are clinically used. In our department, the Unity MR-linac (Elekta AB, Stockholm, Sweden) [91,92] has been installed and clinical treatments started in September 2018. At the time of completion of this thesis, a total of 270 plans have been irradiated at the Unity MR-linac in our department (170 prostate, 42 rectum and 56 oligo metastases).

The Elekta Unity combines a linear accelerator with a 1.5 T MRI scanner (Philips Medical Systems, Best, the Netherlands), and is equipped with an EPID (XRD 1642 AP, Perkin Elmer Optoelectronics, Wiesbaden, Germany) mounted on a rotating ring gantry, opposite to the 7 MV flattening filter free (FFF) accelerator head, allowing for simultaneous beam irradiation, EPID acquisition and MR imaging [93]. The source-to-isocenter distance is 143.5 cm, and the source-to-detector distance (SDD) is 265.3 cm, resulting in a magnification factor of 1.84 (**Figure 1**). The central region of the cryostat is designed free of gradient coils and shimming hardware, allowing for minimal and homogenous attenuation of the beam by the cryostat. The dimension of this free-of-coils region determines the size of homogenously attenuated beams received by the EPID, allowing for a maximum field size at the isocenter of X=±11 cm and Y=±4.8 cm. Note that the EPID was included in the system for the purpose of machine QA and not for patient imaging or portal dosimetry. It lies in a non-centered position with respect to the beam axis. As a result, beams can only be completely captured if their field size at isocenter is smaller than X=±11 cm, Y=[-11, +8] cm, completely encompassing the aforementioned region of homogeneous attenuation.

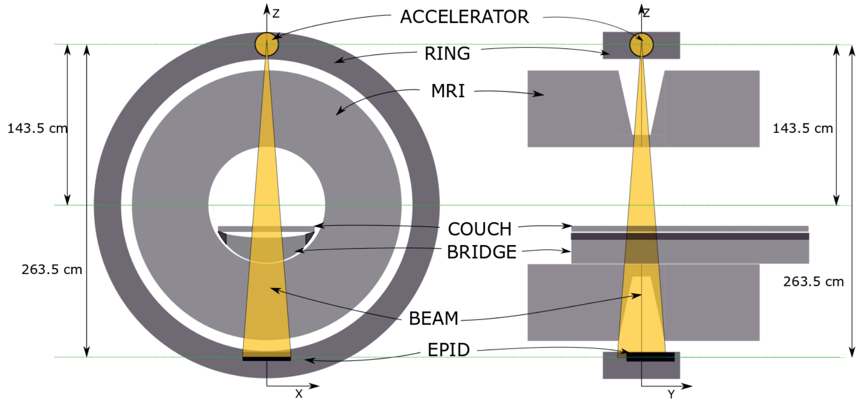

Figure 1.1: Schematic drawing of the Unity MR-linac cross sections. The EPID (black rectangle) is positioned behind the MRI housing, rotating on a ring gantry. Moreover, In the Y direction, the beam center is not aligned with the center of the panel, so parts of large fields cannot be captured.

Moreover, the EPID frame is divided into a 'central' region receiving un-attenuated signal and an 'outer' region receiving signal with extra attenuation and scatter due to exceeding the free-coils region. Since the detector is displaced 5.7 cm in the cranial direction with respect to the beam axis, fields exceeding 8.1 cm in the caudal direction at isocenter plane cannot be entirely acquired by the EPID and parts of the beam fall outside the panel (**Figure 2**).

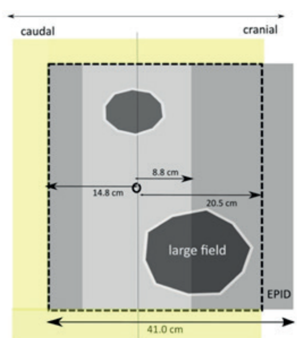

Figure 1.2: Schematic drawing of the EPID and a maximum irradiated square field arriving to the panel (yellow). Beams at the level of the EPID are received in a central unattenuated region (light grey) and in an outer attenuated region (dark grey). In the

context of this thesis, a field is considered 'large' if the corresponding acquired EPID image contains signal in the outer region. The dashed black rectangle represents the cropped EPID image used for dose reconstruction.

Unlike in conventional linacs, the Unity couch and bridge use high density materials. The complexity of their shape (darker gray in bridge structure) has to be taken into account in the TPS.

Adaptive radiotherapy (ART) strategies in MRI-guided radiotherapy (MRIgRT) aim to optimize the delivered dose distribution to the daily anatomy. In the Unity MR-linac, daily adaptation to patient position variations is not done by couch translations but by online re-planning. A reference plan is created using the planning CT and for each fraction an MRI scan is made prior to treatment to adjust the delivery to the daily anatomy/position. For that purpose, two strategies are available: the virtual couch shift (or 'adapt to position') workflow is a shift of the treatment plan to compensate for set-up deviations only. Alternatively, 'adapt to shape' is a re-contouring strategy not only to correct for positional shifts, but also changes in the shape of the anatomy [94–96]. More complex techniques that at this moment are not clinically adopted, require full re-optimization of the plan to account for all anatomical and setup changes. This translates into daily adaptations, which bring high flexibility and adaptability to improve treatments, but it puts high demands the on-line imaging modalities and the timescale on which a full plan must be adapted or even created and approved.

1.7. QA on the Unity MR-linac

Due to the complexity of the Unity MR-linac workflows and the little experience all centers have with it, independent dosimetric verification is highly desirable. The daily adaptation of the treatment plan to the actual anatomy force us to revisit existing concepts of patient specific QA.

- pre-treatment QA: corresponds to the verification of the reference plan. The value of such a verification is limited, as this plan will not actually be irradiated. Its main use is to test for transfer errors, the validity of TPS dose calculation and the deliverability of the treatment plan.

- online sanity check of the adapted plan: pre-treatment evaluation of the adapted plan. This can be performed using an independent dose recalculation in a separate TPS or with a sanity checks of the treatment plan data. The goal is to prevent gross errors in dose calculation or data transfer.

- QA of the adapted plan: is a dosimetric verification of the daily adapted plan. This can only be performed post-treatment, as there is no opportunity for delivery to a phantom geometry between plan creation and patient delivery. Its main use is to test for transfer errors and the validity of TPS dose calculation.

- in-vivo QA of the adapted plan: in-vivo dosimetric verification of the delivered adapted plan using measurements acquired during treatment. It verifies the actual delivery on the geometry of the patient. Besides transfer errors and TPS dose calculation, it can potentially detect all possible deviations between planning and delivery, as it is an independent end-to-end check. It would be most straightforward to analyze the result after treatment delivery. However, certain in-vivo tools like EPID dosimetry have the potential for real-time in-vivo QA, with the possibility of dosimetric QA for trailing and gating techniques and to interrupt the treatment machine upon gross error detection.

Currently, at the Netherlands Cancer Institute – Antoni van Leeuwenhoek, pre-treatment QA of the reference plans and QA of the adapted plans is performed using the OCTAVIUS 4D MRI system (PTW, Freiburg, Germany). Other centers use similar devices such as Delta4 Phantom+ MR (Scandidos, Uppsala, Sweden). The use of such devices for dosimetric verification of Unity MR-linac treatments is time-consuming [97–100]. As a result, in most clinics dosimetric verification of the daily adapted plans is limited to a few fractions only. Furthermore, in our institute a fast sanity check has been developed, which is applied for each adapted plan [101]. To our knowledge, all users of the Unity MR-linac apply pre-treatment sanity checks or independent dose calculations to all adapted treatment fractions.

A new element in the Unity MR-linac treatment chain compared to conventional workflows, is the use of MRI for treatment planning by transformation of the daily MRI into a synthetic CT[102–104]. This presents a new element in the radiotherapy chain, of which no large-scale clinical experience is present yet, and which is not verifiable using log file-based approaches. This is one of the motivations for the use of EPID dosimetry as a complementary method to perform an independent end-to-end check of the whole chain. Errors related to data transfer, MLC calibration and dose calculation [105] can be caught in pre-treatment QA or QA of the adapted plan. Additionally, errors in patient set-up and synthetic CT creation can be detected using *in-vivo* portal dosimetry.

1.8. 3D in-vivo EPID for the Unity MR-linac: the back-projection algorithm

The EPID in the Unity MR-linac is positioned on the outside of the cryostat, which means that beams arrive to the panel after traversing the patient, but also after traversing the cryostat twice. The panel therefore receives the beam signal with an extra component of scatter and attenuation that does not correspond to what the patient received, as opposed to a conventional linac (**Figure 3**).

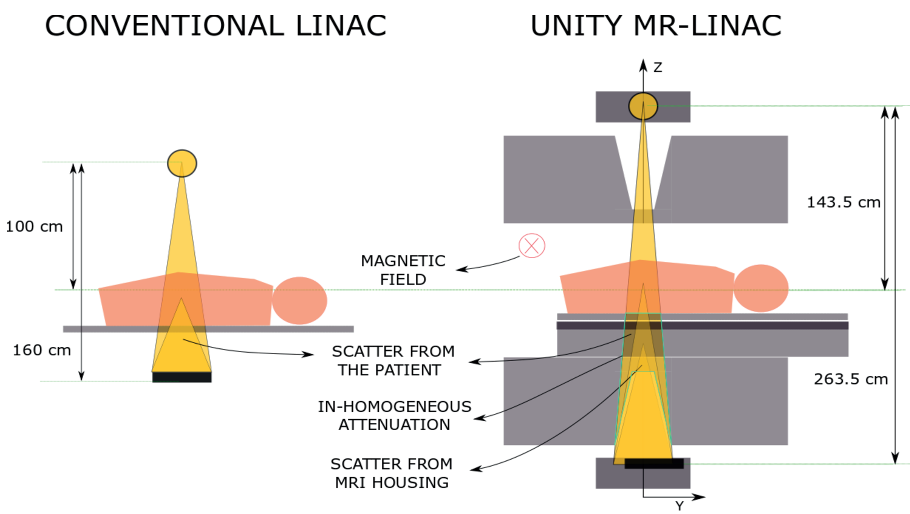

Figure 1.3: Schematic drawing of the conventional linac (left) and the Unity MR-linac (right) treatment delivery cross-sections. In conventional linacs, the EPID (black rectangle) is positioned behind the patient and the determination of the primary portal dose requires the modeling of the scatter from the patient towards the EPID. In the Unity MR-linac, the EPID lies behind the MRI housing, on the ring gantry. An aperture around the cryostat allows for minimum attenuation of the beam entering the bore, but due to divergence, this aperture is insufficient on the exit side, where the beam is larger and travels through this extra source of scatter and in-homogeneous attenuation. This complicates the determination of the primary portal dose as input for the back-projection algorithm.

The main task when adapting portal dosimetry for the Unity MR-linac is to develop models to describe the effects of the extra scatter and attenuation on the portal dose, i.e., to obtain the primary portal dose that would be arriving to the panel if the MRI were not present. New steps were added to the algorithm to account for these effects, the changes in the sensitivity of the panel due its position with respect to the beam, and a gantry angle dependent dose response. Furthermore, adjustments were made to account for the new system characteristics (source to isocenter distance, source to detector distance, EPID position with respect to beam axes, etc.).

In the Unity MR-linac, the Lorentz force produced by the constant 1.5 T magnetic field deflects the paths of moving electrons, thus redistributing the absorbed dose. A remarkable phenomenon of the B-field is the electron return effect (ERE), caused by secondary electrons that exit the patient being directed back into it, increasing the surface dose. The presence of the B-field potentially complicates a MR-linac portal dosimetry method in two ways. First, there is the influence of the B-field on the panel and second, the dose redistribution due to the B-field might have to be taken into account in the back-projection of dose.

1.9. Thesis Objectives

The aim of this thesis was to extend the existing portal dosimetry method, routinely applied in the clinic for *in vivo* verification of all radiotherapy treatments, to the Unity MRI-linac system, and to provide experimental evidence that both pre-treatment and *in-vivo* 3D portal dosimetry are feasible for the Elekta Unity MR-linac.

1.10. Thesis Outline

The work presented in this thesis is organized as follows. **Chapter 2** describes the physics and practical issues to account for the extra scatter and attenuation received by the panel, as well as changes in photon energy spectrum when the beam traversed a mock-up of the MRI scanner. A characterization of the EPID panel in the Unity MR-linac was performed in **Chapter 3**. The purpose of this study was to validate the feasibility of using the panel as a dosimeter. A collection of EPID and ionization chamber (IC) dose measurements were performed and compared to similar measurements for conventional linacs. **Chapter 4** describes a proof of concept of the adapted back-projection algorithm for 2D dose reconstruction for three cardinal gantry angles. The results were compared to measurements using a 2D IC array. **Chapter 5** presents the first clinical pre-treatment and *in-vivo* verification results of patient treatments at the MR-linac, comparing 3D EPID back-projected and planned dose distributions. In **Chapter 6**, the use of a deep learning method to correct EPID image distortions due to beam attenuation and scatter, allowing for the use of the entire EPID image for dose reconstruction. **Chapter 7** provides a general discussion, a future perspective and conclusions on the research performed regarding EPID dosimetry for the Unity MR-linac.