Summary
External beam radiotherapy is a heavily used treatment modality for therapeutic and palliative patients burdened by cancer. The clinical outcome of some cancers treated with radiotherapy is to date unsatisfactory, resulting in poor survival times, debilitating toxicities, or late secondary tumors. Preclinical radiotherapy represents one approach to try and identify promising new radiotherapy treatment regimes. In this thesis, a thorough examination of the dosimetric aspects of an image-guided small animal irradiator has been examined and a preclinical research study has been undertaken.

A general introduction into cancer and the need and use for preclinical research is outlined in Chapter 1. A literature review is followed in Chapter 2, in which early conformal animal radiation work is identified. In this review, the ideal operating parameters for small animal irradiation that would best replicated clinical radiotherapy are outlined including beam size, image quality, and targeting accuracy. Currently, the best small animal image guided irradiators do not meet the ideal resolution of 30 µm, beam diameter 0.5 mm, or a required targeting accuracy 0.1 mm, though they do closely approach these capabilities. This review also outlines the need to reduce the treatment energy from 6 MV to orthovoltage energies. The review also identifies all the existing centers that posses one of these image-guided small animal irradiators; four years ago these numbered 11, and now exceed 40 institutions and growing. Critically, this review article also acknowledges the lack of a treatment planning system for small animals, which became a major development within our research group.

In Chapter 3, together with two other institutions we explore the considerations when commissioning small animal irradiators. What we found was that for the same device, model x-ray tube, dose rates can vary (± 10 %) and that independent machine-specific commissioning is required. We also found that backscatter is a significant contribution to the dose at the target and strongly dependent on the beam size, and not on object size as long as the object is as big as the field. The out-of-field dose was found to be less than 1%. Differences in the manufacturing of the collimator dimensions were identified between institutions as well as system flex that requires routine calibration.

In Chapter 4, full Monte Carlo modeling of the x-ray tube, specimen and the flat-panel, of an image-guided small animal micro-IR is performed and compared to measurements. The results were very promising but did reveal the complexity to modeling the smallest collimated fields below 3mm, which are focal spot occluded. Significant drops in output (~30% drop) were also observed for the smallest 1-and 2-mm beam. We were also to successfully model the sensitivity response of the imaging panel with good agreement to experimental measurements. We managed to quantify the contribution of scatter-glare of the within the panel. There was also very good agreement between imaging situation and the experimentally measured projection images, which we now recognizing a potential method to validate tissue assignment for small animals the compositions of which are not well known. We also found the penumbra of larger fields can be sensitivity to positions in alignment of the collimator and the source. Finally, this work provided the basis as proof of principle work for performing electron-
ic portal imaging dosimetry, or dose guided radiation therapy, though image lag remains still a technical challenge.

**Chapter 5** is a study that was initiated based on the observed finding in the previous chapter that source modeling is an important aspect of modeling these small animal irradiators. We wanted to be able to quantify the tolerance of the collimators to small shifts in alignment, which necessitated modeling the source distribution and finding a method to create faster calculations as tracking electrons hitting the anode of an x-ray tube is a rather computationally intensive step. In the end, we were able to create an analytical source model that was 1200 times faster than using Monte Carlo methods to perform dose calculations. The analytical model was used to investigate the fluence of the focal spot, which showed the effect of different focal spot sizes and shapes on output.

**Chapter 6** outlines the development of SmART-Plan, our small animal treatment planning software – the first commercially developed software available for preclinical small animal image-guided irradiators. SmART-Plan was developed in Matlab and interacts with the EGSnrc code Dosxynrc to perform dose calculations. SmART-Plan uses pre-calculated phase-space files, which rely on the analytical model described in the previous chapter to rapidly produce large phase-space files. In this article, we outline the requirements of a small animal treatment planning system and emphasize the workflow differences between preclinical and clinical treatment planning systems. We demonstrate the accuracy in uniform and heterogeneous phantoms, which have not been shown previously by any competing calculation method. We also demonstrate the feasibility of a multi-target treatment planning system based on MC calculations.

In **Chapter 7**, a large small animal research study is performed based on the all of the work from the previous chapters. The large-scale research study was used to investigate normal tissue toxicity in the lungs of mice and to assess the progression of radiation induce lung fibrosis through the use of micro-CT. In this study we used and validated deformable registration methods of mice lungs. We demonstrated the progression of intensity increases for conformal lung irradiation in a common breed of mice and show that when compared to literature the onset and the severity of lung changes is less severe for larger irradiation of the same dose.

In **Chapter 8**, a general discussion again summarizes the findings within this thesis, reports the progress image-guided small animal irradiators as well as outlines current challenges in delivery and tissue assignment in mice. A small portion of this chapter is dedicated to the ongoing research efforts of small animal irradiation as well as future developments of small animal irradiation including the use of bioluminescent imaging – a promising new area of preclinical radiation research.