Chapter 1

Introduction and outline of the thesis
Introduction

This thesis is focused on (1) the assessment and implementation of advanced radiotherapy technologies and treatment techniques, and (2) high-precision hypofractionated radiotherapy.

It was estimated that in 2008, an additional 3.2 million Europeans were affected by cancer and 1.7 million lost their lives to this disease [1]. The most frequently diagnosed non-skin tumors were colorectal cancer (approximately 14% of new cases), breast cancer (13%) and lung cancer (12%), and the most common causes of death were those from lung (20%), colorectal (12%) and breast cancer (8%) - all solid tumors. The most frequently used treatment modalities for such tumors, either alone or in combination, are surgery, radiotherapy and systemic therapy. Treatment intent may be curative or palliative, depending on the extent of the disease, efficacy of the available therapies and patient-specific factors including physical condition, comorbidity and personal preference. Radiotherapy may have a role to play in the treatment of up to 50% of cancer patients and contributes to cure in about 40% of cases where this is achieved [2].

Radiotherapy has a history of little more than 100 years. Rontgen discovered x-rays in 1895 and the first reports of their therapeutic use appeared in 1896 [3,4]. Within a few years of this, reports began to appear about the successful treatment of benign and malignant tumors located on the surface of the body and deep within the patient. Single large dose treatments and those made up of many smaller fractions were tried and initial descriptions of normal tissue responses were described [4,5]. It soon became clear that (1) radiotherapy could be a very effective local treatment for solid tumors provided that a high enough dose was given, and (2) that large single fraction treatments were associated with a greater risk of normal tissue toxicity [5,6]. In the early years treatment planning and delivery methods were basic and there was only limited ability to identify the target and spare internal organs. Furthermore, the absence of a quantitative physical measurement for applied dose meant that practitioners relied upon clinical signs such as the acute skin reaction as a therapeutic guide. Although such limitations have largely been addressed, the paradigm of treatments consisting of many small fractions continues to dominate. This is known as conventionally fractionated radiotherapy, with typical fraction sizes of 1.8-2 Gray.
The reasons for this include radiobiological considerations concerning reductions in normal tissue toxicity and historical precedent. In some cases local reimbursement arrangements may also be influential. The use of hypo-fractionated treatments (>2Gy per fraction) tends to be reserved for certain clinical scenarios, including relatively small tumors in favorable locations, tumors that are more sensitive to higher fraction sizes and for short-courses of palliative radiotherapy (Table 1). Their popularity is driven, in part, by the fact that fraction for fraction, larger fractions are relatively more potent, and a treatment can be completed in fewer sessions. The latter may be advantageous to patients and healthcare systems. It also makes it more practical to treat patients with advanced disease using higher dose radiotherapy, which can facilitate new treatment paradigms [7-10].

The synergy between technology and biology is what makes radiotherapy an effective treatment. Technology is an enabler. Advances in treatment planning, delivery and imaging systems facilitate the safe application of potent radiobiological dose-fractionation schedules. And although technical advances have so far been unable to circumvent completely the biological barriers posed by the limited ability of normal tissues to tolerate high fraction doses, the envelope is gradually being pushed out [11]. One major challenge is that contemporary photon radiotherapy is delivered as external beam treatment from a medical linear accelerator (Figure 1). In this scenario, the solid tumor is usually located inside the patient where it is surrounded by normal tissues of varying sensitivity to the adverse effects of radiation deposited along the beam path (Figure 2). This frequently limits the dose that can be delivered to the tumor without causing excessive toxicity, which can reduce the likelihood of durable tumor control or cure.

Table 2 highlights several recent developments in radiotherapy technology. These technologies are now routinely available with the purchase of current radiotherapy treatment systems, or they may be retrofitted to previous generation platforms. They have enhanced the accuracy, precision and safety of treatment delivery, and have increased the confidence of medical teams to deliver high-dose radiation to the tumor, while limiting the dose to critical normal tissues. Coupled with advances in patient stratification using prognostic molecular markers, this has begun to create an interesting juncture in radiation oncology, one where the ability to identify patients
with better odds of survival is challenging previous paradigms of disease management and permitting a more individualized approach to patients [12].

The combination of advanced technology and increased availability moves certain techniques beyond the exclusive realm of a few pioneering departments, placing them, at least in theory, within the grasp of many. However this creates numerous challenges. There is still an incomplete understanding of how best to use certain technologies, coupled with limited data on the gains that can be expected in return for increased investment. In some situations there is a lack of comparative clinical data to demonstrate that the efficacy of these treatment strategies is equivalent to, or better than, more conventional approaches. There is also considerable variation in the availability of personnel with appropriate clinical experience and knowledge which means that institutions and healthcare systems need to be actively engaged in managing ‘knowledge acquisition’ in order to realize the full potential of specific treatments, and to obtain maximum patient benefit for their investment. This challenging environment is made more difficult by the escalating costs of cancer care, barriers to the successful implementation of technology, increased consumer awareness and persuasive marketing [13-15]. This requires a critical approach to the use of new technologies including real-world evaluations, a willingness to transfer knowledge, and practical strategies to increase the efficiency and success of technology implementation. The papers contained within this thesis address these issues.

Outline of the thesis

Introduction Chapter 1 presents the thesis context and outline. Chapter 2 reviews modern external beam radiotherapy, highlighting the clinical application of recent technological advances and contemporary challenges.

Imaging and treatment planning Advances in imaging have helped to improve tumor visualization. However the relationship between the size of the tumor seen on imaging and its true dimensions is incompletely described, as are the spatial correlation between findings on imaging, and functional and structural tumor heterogeneity. These factors are relevant to delineating the tumor target and selectively targeting tumor sub-regions. Studies correlating radiology and pathology
are one way of investigating these characteristics, but available methodologies need further refinement. The study described in Chapter 3 focuses on the development of a methodology for performing such studies in lung tumors. Chapter 4 discusses the use of current imaging strategies for high-precision spine radiotherapy. Accurate delineation of target and critical structures forms the basis of high-precision radiotherapy, but inaccurate or inconsistent contouring is one of the weakest links in the overall treatment chain. It may adversely affect plan quality and it risks reducing the potential gains from other strategies such as proton beam therapy. Chapter 5 highlights that contouring differences are present even amongst experienced practitioners and describes the development of new tools designed to identify and reduce contouring variation. These tools may also have a role in knowledge transfer and quality assurance.

**Treatment delivery and immobilization** With the increasing indications for high precision radiotherapy, recent advances in treatment delivery such as volumetric intensity-modulated radiotherapy appear well suited to complex treatment planning and efficient treatment delivery. Whether this kind of technology is indeed ‘better’ than the existing options needs to be evaluated. Chapter 6 compares it to conventional fixed-beam intensity-modulated radiotherapy for high-precision spine treatments. The robust delivery of complex dose distributions requires correct and stable patient positioning during treatment delivery. Chapter 7 describes the treatment delivery strategy in use at our center to meet these goals, focusing on the effectiveness of comfortable, simple and reproducible patient positioning.

**Imaging after treatment** The impressive results of stereotactic lung radiotherapy and the increasing availability of advanced technologies that facilitate such techniques are leading to their widespread uptake. However it is becoming clear that imaging characteristics of symptomatic or asymptomatic normal tissue responses to this treatment have been incompletely characterized, and that these may confound the use of conventional approaches, such as RECIST criteria, for evaluating tumor response. Chapter 8 describes the incidence and morphology of computed tomography changes that can be expected in the lung after stereotactic radiotherapy. Analogous with drug therapies, the application and diffusion of new technology needs to be accompanied by ‘post-marketing’ awareness for new patterns of toxicity and normal tissue change.
As stereotactic lung radiotherapy becomes widely adopted, more patients, including some who may be potentially operable, are being treated. The early detection of a minority of patients at risk for treatment failure, who may be eligible for salvage options has now emerged as an important challenge, however it may be confounded by the kinds of treatment related changes described above. Chapter 9 describes the initial outcomes from a pilot study of metabolic imaging as a tool for early response evaluation.

**Implementation of new technologies** The previous chapters have illustrated that there is a wide variety of advanced technologies available today in radiation oncology. Integral to realizing the potential of such technologies and treatment techniques is their safe, timely and effective implementation. This relies on the development of departmental and system-wide strategies to acquire, deploy and use equipment in a manner that recognizes clinical priorities and makes best use of available financial and human resources. The critical application of technology and the acquisition and dissemination of knowledge are central to the delivery of value-added healthcare. Such issues are explored further in Chapters 10-12, which include practical implementation strategies. Advances in technology for treatment planning and delivery, including image-guided delivery, have facilitated the resurgence in biologically potent, high-dose per fraction radiotherapy schedules. In addition to treating patients with localized disease, this is also making it practical to investigate new treatment paradigms such as the ablation of multiple metastases. Chapter 13 is a mini-review exploring the rationale for this paradigm in more detail.
Table 1 Some of the features of conventional and hypo-fractionated radiotherapy, palliative and curative intent treatment and emerging treatment paradigms

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| Conventional fractionation | • Typically 1.8-2 Gray (Gy) per fraction up to 60-70Gy or more.  
  • Usually treating once per day, weekdays only, can take 6-7 weeks to finish. |
| Hypo-fractionation | • Fraction sizes above 2Gy  
  • 2.75 and 3Gy frequently used (e.g. 55 or 60Gy in 20 fractions over 4 weeks for the radical treatment of non-small cell lung cancer [NSCLC]).  
  • More extreme hypo-fractionation schedules include 3 fractions of 18Gy delivered twice a week for peripherally located early-stage NSCLC in medically inoperable patients, and single fractions of 15-21Gy for patients with a limited number of relatively small brain metastases.  
  • Variation in fractionation for the same indication between centers and geographical locations partly explained by treatment philosophy, empirical clinical experience (e.g. likelihood of local control with acceptable toxicity), and access to treatment (e.g. patient distance from treatment center and institutional resources such as the number of treatment machines and staff).  
  • Normal tissues relatively less forgiving of large fraction sizes and large total doses delivered in shorter overall times.  
  • For all treatments, but especially those delivering high doses next to critical normal tissues (1) careful target and organ at risk (OAR) delineation is necessary (2) dose should be concentrated on the target with relative sparing of OAR (3) the use of additional margins around the target for treatment-related uncertainties should be kept as small as possible and (4) the position of the target and OAR should be verified during treatment to ensure that the intended dose distribution is indeed delivered to the patient. |
| Palliative treatment | • Typically intended to relieve symptoms in patients with advanced (e.g. metastatic) cancer. Often uses the minimum dose required for this. However life prolongation and durable local control in the face of improving survival for certain patients with advanced cancers are also valid goals.  
  • These are increasingly being facilitated by hypo-fractionated treatments that can be delivered over relatively short time frames.  
  • Low dose palliative treatments (e.g. a single fraction of 8Gy for bone pain from metastases) often use relatively generous margins around the target to avoid missing, especially when they are delivered without any image-guidance, they also tend to use simple treatment techniques to make them easy and quick to plan and deliver.  
  • Especially, but not exclusively, if the total dose rises then smaller margins and more sophisticated planning and delivery techniques are often preferred, especially if trying to minimize morbidity or the risk of adverse reactions with systemic therapies |
| Radical-intent treatment | • Depending on tumor type and size of treatment volume, this often involves high total doses.  
  • It requires good target and OAR designation, careful consideration of how best to arrange the dose distribution to treat the target and spare OAR, appropriately tight uncertainty margins and robust treatment delivery aided by image-guidance to correctly position the target and verify that critical structures are appropriately located |
| Emerging treatment paradigms | • High total doses are being used to try and control or ablate tumors in patients with limited volume metastasized disease (‘oligometastases’).  
  • This extends the full potential of advanced radiotherapy technologies to new groups of patients.  
  • Additional groups who may also benefit include those requiring re-irradiation or complex palliation |
**Table 2** Factors that have contributed to the recent resurgence of high-precision radiotherapy

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| Limited visualization of tumor and critical structures, including target motion | • Improvements in multi-modal imaging, image fusion technology for radiation treatment planning and the advent of 4-dimensional computed tomography (CT) to capture target motion.  
  • At the time of treatment, in-room kilo- and mega-voltage image-guidance technologies, including linear accelerator mounted cone-beam CT, implanted fiducial markers and external surface/surrogate tracking strategies have been developed to monitor and track the position of the target and stability of the patient.  
  • A range of patient immobilization solutions has also been created, involving various degrees of complexity and patient restraint.                                                                                                                   |
| Limited ability to conform high-dose region to the target and avoid critical normal structures | • Development of inverse-planned intensity modulated radiotherapy, multiple fixed-beam and intensity modulated and dynamic arc delivery methods that allow for greater freedom in designing high-dose distributions that conform to the shape of the target, and fall off rapidly beyond this.                                                      |
| Uncertainty over the delivered dose                                        | • Improvements in dose calculation algorithms have reduced differences between calculated and delivered dose and improved the ability to account for differences in tissue density along the path of the photon beam.                                                                                                         |
| Practical solutions for precise patient positioning and its verification  | • Non-invasive frameless immobilization makes patient positioning easier, in-room imaging technologies allow for frequent verification of the target itself, or of appropriate surrogate.                                                                                                                                    |
| Lack of clinical data                                                      | • There has been an increase in the volume of non-randomized data supporting safety and effectiveness of dose-escalated radiotherapy, using conventional and hypo-fractionated treatments. This includes early-stage non-small cell lung cancer and lung, liver and spine metastases.  
  • The majority of this data is single institutional. However, more recently population-based data has been presented in support of stereotactic body radiotherapy for early-stage lung cancer.  
  • There is also a substantial accumulation of clinical data, albeit much of it from a relatively selected group of centers, describing the effectiveness and toxicity of certain dose-fractionation schedules and delivery techniques.  
  • Although they remain incomplete, especially for hypo-fractionated treatments above 8 Gray/fraction, such data is essential for the development of models that can predict the radiobiological effects of a given radiotherapy scheme. |
**Figure 1** A modern linear accelerator (A) for external beam radiotherapy, the photon beam comes out of the treatment head (B), which is mounted on a gantry (C) that can rotate around the patient lying on the movable treatment couch (D). The combination of a couch that can be moved in multiple directions and an imaging system mounted on the accelerator (E) allows the patient and the tumor to be positioned correctly for treatment.

**Figure 2** This illustrates the challenge of using external beams to treat a paraspinal tumor (A) in close proximity to a critical normal structure, in this case the spinal cord (B) and other organs at risk including the kidneys (C). A sufficient dose must be delivered to the complex-shaped tumor volume whilst adequately sparing normal tissues.
References


