Chapter 14

General Discussion and Future Directions

Advanced radiotherapy technologies are now widely available in countries such as the Netherlands and United States. This coincides with an increased interest in the effectiveness of treatments using high doses per fraction, attempts to expand the clinical indications for intensive radiotherapy treatments and a progressive blurring of the distinction between treatments delivered with radical or palliative intent. The pace of development has highlighted certain deficiencies in our current knowledge (Table 1), and demonstrated that adoption curves for new treatments and technologies are frequently long. Refining clinical techniques and accumulating evidence of clinical benefit is therefore only part of the process. It is essential also to focus on disseminating practical clinical knowledge and developing strategies for the effective implementation of advanced technologies and treatment techniques. These inter-related themes formed the background to this thesis (Figure 1).

The work presented describes the stepwise approach used at the VU University Medical Center to extend the application of high dose stereotactic treatments to routine patient care. Specific areas highlighted in this thesis are the use of stereotactic body radiotherapy (SBRT) for patients with oligometastatic cancer, refining SBRT for patients with spine tumors, and the radiological findings after lung SBRT. Further novel applications of high precision image-guided and intensity modulated radiotherapy that are currently being pursued at our center include SBRT for the re-irradiation of lung tumors and the combination of conventionally fractionated mediastinal irradiation and SBRT for the primary lung tumor(s). Our group is also involved in clinical studies to evaluate the safe use of SBRT for patients with (oligo)metastatic cancer [1].

We will increasingly focus on improvements in the efficiency of relatively complex treatments like SBRT. One example of this is the clinical use of very high dose rate, flattening filter free (FFF) radiotherapy treatment beams. These can deliver more radiation in a given time than standard beams, potentially increasing the speed of treatment delivery. However, although fast treatment delivery is attractive, there are potential drawbacks, one of which is that if patients move during irradiation then there may be larger differences between the planned and delivered dose. Although it would be desirable to be able to monitor patient and target position during treatment delivery, many current linear accelerators lack such capabilities. This highlights

another focus for our group, namely exploiting the potential of in-room imaging technology. As an example, we are collaborating with industry to evaluate the use of digital tomosynthesis (DTS) for positional verification of the spine and soft-tissues, including the treatment target (e.g. lung tumor), in the hope that this may represent one solution to some of these problems. Faster delivery has also highlighted that much of the time taken to perform high-precision radiotherapy is spent accurately positioning the patient and intermittently verifying this (Chapter 7). Efficient imaging technology and clinical routines are therefore required to maximize treatment quality and patient convenience.

In order to ensure the appropriate clinical integration of new developments in high-precision SBRT, our work will continue to also focus on the key issue of knowledge transfer and implementation through several practical initiatives. These include the development and use of customized packages to assist other centers with the implementation of advanced radiotherapy technology and techniques. In addition, data-mining is being performed using our extensive database of more than 1000 SBRT cases in order for example to correlate specific aspects of treatment planning to clinical outcomes, including treatment toxicity and efficacy. This is necessary to better understand the relationship between dose and normal tissue toxicity and the kinds of doses that critical organs can safely be exposed to during SBRT. At the moment such dose limits are largely empirical and the understanding of what determines the development of toxicity and the inherent sensitivity of certain organs is limited. While pooling data about dose and toxicity may yield more information, what is important in developing dose-toxicity models is to know the dose that was actually received during treatment, rather than the dose that was planned, since the two may not be the same (for example if the patient moves). This requires the technology to be able to accurately measure and sum doses over multiple fractions and deformable image registration is being investigated for this purpose.

A specific area of research that merits more attention is the development of knowledge acquisition and implementation strategies. The latter comes from a conviction that in many healthcare systems implementation is the rate-limiting step in the diffusion and uptake of technologies and effective treatments [2,3]. An effective strategy is an essential component of implementation and as the complexity and

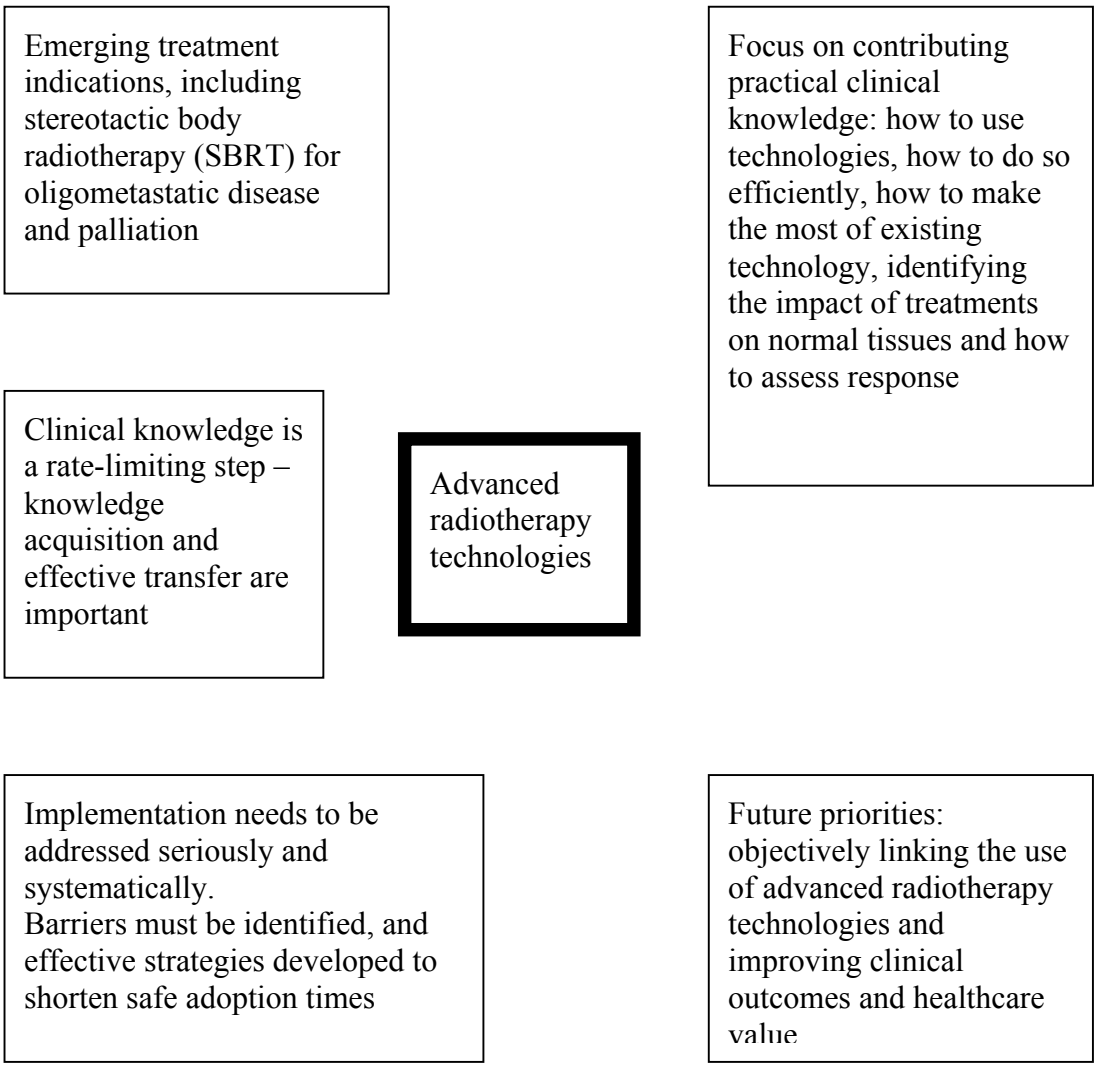
intensity of treatments increases, the finer details of how we use technology become even more important. This is illustrated for example by the treatment planning for large-tumor lung SBRT, specifically the amount of low dose in the contra-lateral lung [4], and more recently sub-optimal planning and inadequate sparing of organs at risk has been implicated as a possible factor in the disappointing results of dose escalation in patients with locally advanced non-small cell lung cancer [5]. This highlights a natural synergy between the focus on technical radiotherapy and implementation, which is a central theme in this thesis. More efficient mechanisms for knowledge transfer and technology adoption may also help to reduce the cost of providing advanced radiotherapy [6]. In combination with appropriately designed studies that can more effectively establish the clinical evidence in support of technologies or new treatments, this is an important part of making sure that such treatments are viable [7,8]. Although limited research has been conducted on the most effective ways to implement advanced radiotherapy technologies or new techniques [2], there is a substantial amount of analysis and research that we can draw on from other sources [9] (Chapter 12)

The overall goal of this systematic approach is to improve treatment techniques and to facilitate the adoption of technologies and treatments in order to improve patient care, extend treatment options and deliver better value for both patients and healthcare providers.

Table 1: Limitations in clinical practice of radiation oncology highlighted by the work presented in this thesis

Limitation	Issues to be addressed
The relationship between imaging and actual tumor extent (Chapter 3)	• How can imaging improve target delineation? • How can inter-observer variation be consistently reduced (Chapter 5)? • Even small deviations between planned and received dose have been estimated to result in significant reductions in the probability of tumor control, which may adversely affect the therapeutic ratio
Dissemination of key considerations in imaging for high precision radiotherapy (Chapter 4)	• Need for accessible and proven solutions to common scenarios • Need for practical manuscripts that highlight important considerations in designing imaging protocols for high-precision radiotherapy • Need to avoid reinventing the wheel
Insufficiently rigorous comparisons of new technologies (Chapter 6)	• There are weaknesses in technology assessment and comparison studies • Bias when comparing technologies needs to be minimized • A lack of practical experience among the investigators with one or more of the technologies under evaluation may result in erroneous conclusions
Incomplete understanding of optimal positioning for high-precision treatments (Chapter 7)	• The optimum patient-specific solution to comfortable, reproducible and stable positioning is not always apparent • Patient anxiety, comfort and analgesia may be important and motion can occur despite near-rigid external devices
Difficulty in evaluating treatment response and distinguishing tumor from normal tissue reaction (Chapter 9)	• Normal tissue reactions to high-dose radiation may obscure treatment response evaluation and render conventional scoring systems inadequate • When new treatment techniques or dose-fractionation schemes are introduced, sufficient attention needs to be paid to their impact on target response and the pattern of normal tissue reactions
Insufficient attention paid to implementation and knowledge transfer (Chapters 10-12)	• Many implementation and change projects fail or deliver below expectation • Rather than acknowledging uncomfortable realities, a lack of resources is commonly invoked as a reason for this • A systematic approach to implementation is all too often lacking • Equipment acquisition is often accompanied by inadequate attention to implementation and maximizing return on investment
Limitations are being identified in existing treatment paradigms (Chapter 13)	• Advances in technology, patient selection and systemic therapy are challenging and changing treatment paradigms • Robust clinical data is needed to bring about wider change, however in the meantime there is room for personalized approaches to patient care and institutional policies

Figure 1. The inter-related themes addressed in this thesis.



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