In **chapter 2**, the pivotal role of radiotherapy in the treatment of cancer is underscored by a review of new developments and techniques. These advances will facilitate further improvements in treatment outcomes with the use of ‘image-guided radiotherapy’ (IGRT), a process which uses tumor imaging both prior to, and during, a course of radiotherapy.

Results of an international contouring study are presented in **Chapter 3**. The Lung Adjuvant Radiotherapy Trial (LungART) is a new phase III trial in which patients who have undergone a resection for a non-small cell lung cancer with mediastinal nodal metastases are randomized to either post-operative radiotherapy (PORT) or to observation. As variations in radiotherapy planning volumes used for PORT can significantly influence both toxicity and risks of local recurrence, we studied contouring variations among international experts. A validated CD-ROM based contouring program was used to assess contours on planning CT scans of two patients. Significant inter-clinician variation was observed even among experts, but variation was greatly reduced when the same experts repeated their contours after the Lung ART protocol was provided to them. This finding emphasizes the need for standardized contouring protocols and a quality assurance program for trials utilizing modern IGRT approaches.

Concurrent chemoradiotherapy is the standard of care in locally-advanced non-small cell lung cancer, but is associated with significant toxicity. Strategies for using smaller treatment fields have been developed in order to reduce toxicity. Respiratory-gated radiotherapy (RGRT) is an approach which mitigates the impact of motion by irradiating the tumor in only pre-selected phases (‘gates’) of respiration during which the tumor is relatively immobile. Since lung tumors are difficult to visualize, this gated treatment delivery is often triggered by using an external surrogate of tumor position, such as the motion of the abdominal wall. A reproducible breathing pattern during a treatment course is preferable in order to ensure accuracy but this is not always achieved in routine clinical practice. In **chapter 4**, the changes in lung volume and position of internal target volumes (ITV) at both end-inspiration and end-expiration were analyzed in 22 patients who had undergone a 4DCT scan during both free breathing and audio-coaching. Total lung volumes were increased by an average of 10% when audio-coaching was performed. The observed mean displacement in lung tumor position was predominantly in cranio-caudal direction, and displacements exceeding 5 mm were only seen in tumors for which baseline motion exceeded 10 mm. This finding indicates that attempts to modify tumor motion by altering respiratory patterns, e.g. audio-coaching, should be
consistently performed during planning and delivery in order to avoid introducing systematic errors.

As the reproducibility of the relationship between external surrogates and tumor position has been questioned, we studied the reproducibility of internal anatomy during audio-coached end-inspiratory gated radiotherapy (chapter 5). Time-integrated electronic portal images of 11 patients were used to verify mean intra-fractional positions of moving structures during audio-coached gated radiotherapy at end-inspiration. This analysis revealed systematic ($\sum$) and random ($\sigma$) errors in position of the lung tumor (or an adjacent bronchial structure) of 1.8 mm and 1.3 mm, respectively, in medio-lateral direction and 1.7 mm and 1.7 mm, respectively, in cranio-caudal direction. These initial results indicate that reproducible internal anatomy can be achieved in patients who were treated using concurrent chemoradiotherapy.

When external surrogates are used to trigger gated radiotherapy, phase shifts between the positions of external and internal anatomy may result in an inconsistent relationship. We postulated that the correlation between the 3D lung tumor position and internal surrogates may prove to be more reliable. As both carina and diaphragm are easily visualized on megavoltage and kilovoltage images, the relationship between these two surrogates and 3D lung tumor position was studied using repeat 4DCT scans (chapter 6). The carina position appeared to correlate better with 3D tumor position than that of the diaphragm. A model to predict 3D tumor position based upon information on position of both surrogates was developed. The model revealed large residual prediction errors, which were greater for the diaphragm than for the carina. Therefore, we concluded that this prediction model is not acceptable for clinical use.

The use of gated radiotherapy allows for smaller margins but may also increase the risk of a geometric error. Both the planning target volume and dosimetric profile are based on a single pre-treatment scan, and 4DCT analyses of potential geometric errors during treatment are lacking. Since any change may result in either under-dosage of the target, or over-dosage of critical structures, a prospective trial was performed in which a 4DCT scan was repeated in 24 patients undergoing concurrent chemoradiotherapy after 15 treatment fractions (chapter 7). A mean decrease in planning target volume of 8% was seen in 15 patients, while an increase was seen in 6 patients. A clinical decision to modify the treatment plan was only required in one patient. Thus, the role of adaptive radiotherapy appeared to be limited in this group of
patients. However, the use of more conformal planning might have led to a higher incidence of inadequate target coverage, and further research is warranted to identify patients at high risk of geometric inaccuracies.

Recent guidelines recommend concurrent chemoradiotherapy as the treatment of choice in locally-advanced lung cancer, but surgery may be beneficial in patients in whom downstaging of mediastinal disease is achieved using induction chemoradiotherapy. Commonly used preoperative induction chemoradiotherapy schemes limit radiation doses ranging from 46 Gy to 50 Gy in order to limit the risks of increasing operative mortality. The latter is in contrast to curative schemes, where radiation doses typically range from 60 Gy to 66 Gy. Consequently, any ‘gaps’ introduced for mediastinal re-staging may have a detrimental impact on the survival of the majority of patients who may ultimately be unsuitable for surgery. In chapter 8, we evaluated a treatment strategy that was designed to limit the duration of detrimental treatment gaps. The approach involved 3 cycles of chemo-radiotherapy using image-guided, involved-field radiotherapy to around 50 Gy, followed by invasive mediastinal re-staging. The observed treatment toxicity was acceptable, and this strategy limited gaps in treatment delivery in the patients who did not achieve downstaging of mediastinal disease.