Chapter 9

General discussion and future directions

The survival of patients with locally-advanced lung cancer is still poor, and strategies including escalation of the radiation dose, use of concurrent chemoradiotherapy and tailoring systemic therapy in accordance to the molecular characteristics of tumors are all being explored as means to improve outcomes. This thesis will focus on the first two areas. As both these approaches can be associated with significant toxicity, improvements in the therapeutic ratio (i.e. the ratio of the maximally tolerated dose to the minimally curative dose) are needed. Image-guided radiotherapy (IGRT) is a rapidly evolving tool that can facilitate high-dose, high-precision radiotherapy with acceptable side-effects. Historically, radiotherapy has always been 'image-guided' as imaging is incorporated in every step of the process ranging from target definition, treatment planning and delivery to treatment verification. In the last two decades, IGRT has evolved from conventional radiographic film imaging to 3D CT-based radiotherapy. Currently, 4DCT based modalities, which allow for temporal and spatial changes to be visualized are also available (1). This thesis describes a number of approaches that can further advance IGRT in the areas of target definition, treatment delivery and treatment verification for locally advanced lung tumors.

Target definition

The therapeutic ratio can be increased by the use of smaller target volumes, for example by omitting elective nodal irradiation (2,3). However, target definition is a crucial step as contouring is extremely susceptible to variation due to the lack of contrast, low image resolution, imaging artifacts and uncertainties in the clinician's interpretation. Since target definition represents the first step in the radiotherapy process, uncertainties related to this aspect of radiotherapy may lead to significant systematic errors, which in turn may have great impact on outcomes such as local recurrence rates or excessive toxicity. Furthermore, intra- and inter-observer variations may become even more critical in an era of increasing use of more conformal treatment strategies. Results of an international contouring study using a CD-ROM based contouring program (chapter 3) indeed showed that significant contouring variations exist even among experienced radiation oncologists and that the use of standardized target definitions is important for reducing these variations. In addition, they also stress the importance of peer

review in multi-center clinical trials, and have resulted in the implementation of a web-based infrastructure for analyzing real-time data in trials such as Lung ART.

The work described in this thesis is based on 4DCT scans, but the integration of functional imaging such as 18-Fluoro-2-Deoxy-Glucose positron emission tomography (^{18}FDG-PET) may play a greater role in target definition in the future. ^{18}FDG-PET has already proven its value in staging lung cancer, as its sensitivity and specificity in defining mediastinal nodal metastases (67–91% and 82-96% respectively) are superior to those of only a CT scan (50–71% and 66–89%, respectively) (4). However, the extent to which ^{18}FDG-PET contributes to the accuracy of target definition remains an area of active research. Several studies have reported that ^{18}FDG-PET can significantly reduce both intra- and inter-observer contouring variations (5-9). Based on its relatively high sensitivity and specificity in mediastinal staging it seems logical to define PET-based mediastinal fields. However, nearly 10% of patients who have a CT and PET negative mediastinum were found to have occult nodal metastases when evaluated using endo-bronchial and endo-esophageal ultrasound-guided biopsies (10). For the primary tumor, recent data from patients with lung cancer indicate that PET does not always accurately predict tumor localization based on pathology (11,12). Similar findings have been reported in animal studies where discrepancies were found between PET images and the underlying microscopic tumors, suggesting that the finite resolution of PET should be taken into account when strategies such as FDG-PET-based 'dose-painting' are considered (13). In addition, issues regarding the approach for PET-based target volume contouring (i.e. absolute standardized uptake value [SUV] threshold or source to background ratio techniques) (14) and the existence of motion-induced artifacts (15) need to be resolved. The limitations of using PET for defining tumor edge or for deriving motion encompassing strategies was also highlighted by results of our recent study on 4DCTs of a motion phantom and patients with peripheral lung tumors, which showed that PET-based target volumes did not fully correspond to those volumes treated with stereotactic radiotherapy (16).

In the future, magnetic resonance imaging (MRI) may also play a role in target definition and treatment verification. The benefit of MRI over a PET or CT scan lies in its superior visualization of soft tissues and justifies its routine use into

target definition for several tumor sites (i.e. prostate cancer or brain tumors). The role of MRI in defining the extent of lung cancer has not been established yet, but its additional value may lie in demarcating the tumor from the heart, large blood vessels or in contouring tumors of the superior sulcus. In addition, MRI-guided IGRT is expected to become clinically available in the near future; a prototype linear accelerator with an incorporated MR scanner has been developed in Utrecht (17). Both the avoidance of ionizing radiation and superiority in visualizing soft tissues compared to MV and kV-imaging, will allow for improved real-time imaging and tumor tracking.

Treatment delivery and verification

The use of smaller radiation fields can be achieved using approaches such as respiratory-gated radiotherapy (RGRT). However, the accuracy of tumor targeting with this approach has been challenged as it is commonly not triggered by the tumor position, but by the use of an external surrogate. Repeated verification of the correlation between an external surrogate with the internal anatomy is ideal, but this may lead to an unacceptable increase in clinical workload. Therefore, an extra margin is often added in order to account for the uncertainties related to RGRT. Although our results have shown this margin to be sufficient (chapter 5), one should be aware that changes in breathing patterns may result in a shift in tumor position, particularly for mobile tumors (chapter 4). Our results stress the importance of using adequate margins, which can only be further reduced when advanced (4D) verification approaches ensure reproducible patient positioning and actual tumor localization.

Use of the cone-beam CT (CBCT) is a recent development in IGRT with the potential to facilitate the reduction of safety margins. A CBCT allows for volumetric imaging and is superior in visualizing bony anatomy and soft tissue compared to planar MV and kV imaging techniques (18,19). Recent studies have shown that the CBCT contributes to higher geometric accuracy by improving setup using the bony anatomy (20,21). Use of the tumor for positional verification in locally-advanced disease is challenging at present as a CBCT is not of diagnostic quality and its relatively poor contrast resolution results in difficulties discriminating nodes from other mediastinal structures (22). Implantation of fiducials as surrogate for tumor

position has been used for treatment verification (23), but drawbacks include the risk of a pneumothorax and the migration of fiducials (24,25). Consequently, intra-fraction motion in locally advanced tumors cannot be adequately visualized using CBCT scans. In addition, its relatively long acquisition time results in a blurred vision of the tumor comparable to a slow CT or an average intensity projection of a 4DCT scan. Respiration-correlated CBCT scans have been developed (26), but are not routinely available for clinical use.

Improved tools for 4D verification are needed and an example of such a tool is a software program permitting both the assessment of tumor motion from fluoroscopic images and respiratory waveforms from the RPM-system (Intra-fraction Motion Review [IMR]) (Varian medical systems, Palo Alto, CA). The tool is currently being validated and the first results show a good correlation between tumor position and the respiratory waveforms (27). These results suggest that IMR may be used in the future to calibrate the relationship between external surrogates and internal anatomy.

Research using surrogates for 4D verification is ongoing. Our study evaluating the value of internal surrogates in predicting 3D tumor position has shown the carina to be a better predictive surrogate compared to the diaphragm (chapter 6). However, even when the carina is used in a model to predict 3D tumor position, significant residual prediction errors remain. Consequently, a predictive model based on the input of internal surrogates is not reliable enough for clinical use yet, and needs further optimization. We are currently collaborating with other groups in order to refine models for inferring both nodal and tumor volumes from multiple anatomical surrogates such as the carina, xyphoid, nipples and midsternal position (28).

Image-guided treatment delivery is impaired by the lack of sufficient tissue contrast when using time-integrated electronic portal imaging (TI-EPI) for evaluating the reproducibility of the internal anatomy during RGRT. Consequently, it was necessary to use surrogates such as bronchial structures in some cases and therefore we have been unable to study peripheral tumors (chapter 5). Another area for improvement is the process of image registration. Rigid body algorithms were the only tools available to us for co-registering images during the work described in this thesis (chapter 4-7). Deformable registration allows for the estimation of the

spatial relationship between volume elements of corresponding structures across image data (29). Differences in patient position, weight loss and other changes in geometry during repeated imaging can be resolved using this tool. A recent study of our group confirmed rapid review of target volumes on repeat CBCT scans and detection of changes in target volumes during treatment using a deformable registration tool (30). Deformable registration may play a significant role in future IGRT and adaptive radiotherapy.

Even with the use of IGRT, aggressive treatment schedules using combinations of concurrent chemoradiotherapy and/or planned surgery can still result in significant toxicity (chapter 8) (31). Patients with locally-advanced NSCLC are a heterogenous group with significant co-morbidity, and so approaches using risk-stratification are important to select those patients with stage III disease most likely to benefit. Recently, clinical guidelines for the evaluation of fitness for radical treatment have been developed (32), and it has been suggested that up to 59% of stage III NSCLC patients are ineligible for concurrent treatment if criteria based on co-morbidity and age used in phase III clinical trials were applied (33). However, improved IGRT techniques may allow for reduced toxicity and for more patients to undergo chemoradiotherapy. Implementation of concurrent chemoradiotherapy at the VUmc is based on radiation planning parameters predicting pulmonary toxicity (figure 1), in addition to the patients' fitness to undergo systemic doses of chemotherapy. According to this 'treatment paradigm', patients are eligible for radical treatment if the V_{20}<42%, while respecting dose constraints to other organs at risk. Patients at high risk for a radiation pneumonitis (i.e. V_{20}≥35%) undergo RGRT with the specific aim to reduce V_{20} (34,35). As recent data indicated that reducing the volume of lung tissue irradiated to low doses was important (36-38), effort was also made to lower the V_5. Analysis of clinical outcomes of this treatment paradigm in our own patients shows acceptable toxicity when advances in IGRT are used to deliver tailored radiotherapy (39).

Besides the technical improvements in IGRT, future advances in the treatment of locally-advanced lung cancer are also likely to be driven by better understanding of the molecular pathways of disease, use of novel markers for functional imaging (i.e. tracers to allow for imaging hypoxia, cell proliferation or apoptosis) and by the exploitation of the molecular mechanisms underlying radiosensitivity (40).

Such developments will improve our knowledge of tumor metabolism, location and response and may therefore lead to enhanced target definition, more effective radiotherapy, but also facilitate the role of adaptive radiotherapy (41). However, we anticipate that optimal IGRT will remain the cornerstone of such treatment schemes.

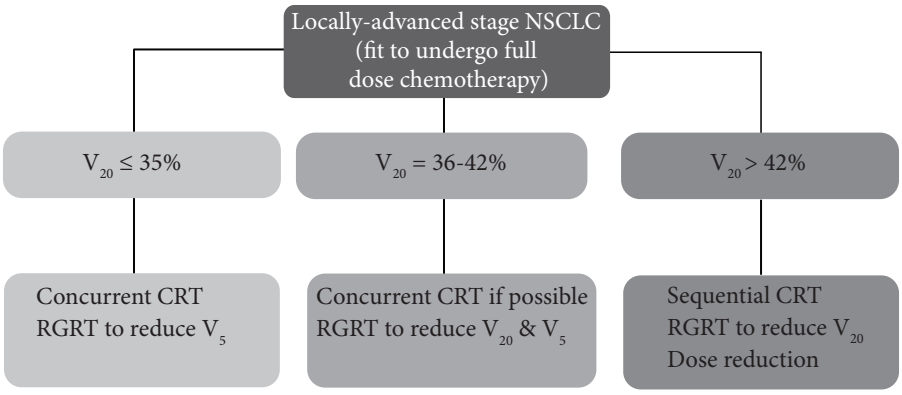

Figure 1. VUMC treatment paradigm for locally-advanced stage lung cancer NSCLC: non-small-cell lung cancer; V_{20}: volume of normal lung tissue (total lung volume minus planned target volume) receiving ≥20 Gy; V5: volume of normal lung tissue (total lung volume minus planned target volume) receiving ≥5 Gy; CRT: concurrent chemoradiotherapy; RGRT: respiratory-gated radiotherapy.

CONCLUSION

The aim of the studies described in this thesis was to improve the quality of radiotherapy for locally-advanced lung cancer. The cornerstone of optimal radiotherapy is a correct definition of the target volume, and we showed that decreases in inter-observer contouring variability could be achieved using clear contouring protocols. Our findings contributed to the decision to implement real-time quality assurance in an international phase III trial. We utilized imaging tools in order to study changes in intra- and inter-fractional anatomy during a course

of radiotherapy. Using time-integrated electronic portal imaging, we showed that accurate delivery of respiration-gated radiotherapy was possible. However, caution should be exercised as changes in breathing pattern can lead to changes in tumor position, and the relationship between tumor position and external surrogates may also vary. We found that changes in tumor geometry after 3 weeks of treatment had little impact on treatment plans, which suggested that there was no need for a routine repeat of treatment planning in the majority of patients. Use of CBCT may identify volumetric changes that merit re-planning. The optimization of all these different steps in the radiotherapy planning and delivery process will allow for tailored treatment delivery, with the goal of reducing toxicity and facilitating full-dose concurrent chemo-radiotherapy for locally-advanced lung cancer.

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