PhD thesis: “Exploiting tumor and lung heterogeneity with radiotherapy”

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The thesis was successfully defended on December 3, 2010 at the Maastricht University, The Netherlands.

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Keywords: dose-painting, megavoltage cone-beam CT, 18F-fluorodeoxyglucose (FDG), non-small cell lung cancer (NSCLC), positron emission tomography (PET)

Introduction
At present, the five year survival of locally advanced stage non-small cell lung cancer (NSCLC) patients is around 13%. The poor prognosis is due to a high rate of local tumor failure and distant metastasis. One experimental approach to increase local tumor control, is to selectively boost the most aggressive regions of the tumor. This is referred to as dose-painting.

Also the lungs are composed of subvolumes with differences in "tolerance" for radiation dose and functional importance. Specifically sparing the lung regions that are more susceptible for radiation damage, may decrease the risk of complications. In other words, with the same risk of side-effects, more dose can be delivered to the tumor if the most complication prone regions of the lungs are spared. The first goal of this thesis was to investigate how differences in radiosensitivity in the tumor and lungs can be assessed and exploited to improve local tumor control in NSCLC patients.

The clinical introduction of dose-painting techniques is not without risks. Because of the high dose levels (>80 Gy), the steep dose gradients and the small target volumes, a small misalignment of the patient and/or tumor can have large consequences. A high dosimetric accuracy is required for a safe treatment delivery. To verify is the planned dose was accurately delivered to the patient, 3D dose verification is needed. For this purpose a 3D scan is required of the patient at the time of treatment. The scan must be calibrated to electron density. A technique capable of imaging the patient on the treatment couch is cone-beam CT. But cone-beam CT scans experience artifacts and are therefore not suitable for accurate dose calculations. The second goal of this thesis was to develop a method to correct the cone-beam scans such that they can be used for 3D dose verification for dose-painting treatments.

Overview of the chapters
Chapter 2 of the thesis presents a comprehensive review of the rationale behind exploiting tumor and lung heterogeneity with radiotherapy (*Lambin, Petit et al, Radiother Oncol. 2010 96:145-52*). It deals with how differences in radiosensitivity can be assessed and how the amount of dose needed to the radioresistant regions can be determined. Also important

considerations are brought forward with respect to the quality control and evaluation of these treatments.

Chapter 3 describes a modeling study that investigates the potential of dose-painting based on tumor hypoxia, an important cause of radioresistance (*Petit et al., Phys Med Biol. 2009 54:2179-96*). It was estimated that a dose distribution matched to the hypoxia levels could be as effective as a uniform dose distribution with 30% more total dose. These results are very promising and have stimulated further research into dose-painting. However, hypoxia is very difficult to measure with non-invasive imaging techniques and the temporal stability is at the best questionable.

Another potential target for dose-painting is the amount of glucose consumption in different parts of the tumor assessed with FDG-PET scans. Regions with a high FDG uptake are more radioresistant than regions with a low uptake (*Aerts, van Baardijk, Petit et al, Radiother Oncol. 2009 Jun;91(3):386-92*), but it is not clear how much more dose the radioresistant regions require. Chapter 4 describes a methodology to determine the amount of dose needed to cure different parts of the tumor based on FDG uptake (*Petit et al. Radiother Oncol. 2009,;91(3):393-8*). The method was tested on data of 39 patients that were treated with a homogeneous dose to the tumor. It turned out that, to extract dose-response relationships for different FDG uptake levels, data is needed of patients treated with different dose levels to the same tumor. These data are currently being collected in a clinical phase II trial.

Chapter 5 demonstrates that FDG-PET can also be used to identify patients with an increased risk of lung toxicity (*Petit et al. Int J Radiat Oncol Biol Phys. 2010 doi:10.1016/j.ijrobp.2010.06.016*). Patients with high FDG uptake in the lungs (excluding the tumor), *before* the start of radiotherapy, had a four times higher risk on radiation induced lung toxicity than patients without abnormal FDG uptake in the lungs. A dose of only a few gray to the high FDG uptake regions was needed to further increase the risk. Not only suggest these results that FDG can be used to identify patients with an increased risk of complications, but also that FDG can be used to identify regions of the lung that should be spared specifically from radiation dose.

In the second part of the thesis a method has been developed to correct cupping and truncation artifacts of MV cone-beam CT scans, acquired of the patients during treatment, such that the scans can be calibrated to electron density. Chapter 6 describes how cupping artifacts can be corrected and how the corrected scans can be calibrated to electron density and be used for accurate dose calculations (Petit *et al. Med Phys. 2008, 35:849-65*). Chapter 7 extends the applicability of the method to body parts that are larger than the limited field-of-view of the cone-beam scanner, such as the thorax and abdomen (*Petit et al. Radiother Oncol. 2010, 94:359-66*). In Chapter 8 the feasibility of the method is demonstrated for lung cancer patients that have had multiple cone-beam CT scans during therapy (van Elmpt, Petit *et al. Radiother Oncol. 2010, 94:188-94*). It is shown that the corrected cone-beam scans can be used for accurate 3D dose calculations, allowing treatment verification, treatment adaptation and improved evaluation of dose-painting treatments.

Conclusions

De modeling study predicts that radiation therapy can be much more efficient using hypoxia based dose-painting. However, at present it is not possible to quantitatively image hypoxia, non-invasively and on a routine basis. An alternative is to boost the tumor regions with a high FDG uptake. These regions are difficult to control with the conventional amount of radiation dose. Therefore a phase II trail has opened recently in the Netherlands to investigate FDG based dose-painting for NSCLC patients (http://clinicaltrials.gov/ct2/show/NCT01024829). Using cone-beam CT scans and applying the proposed correction strategy, 3D dose verification is feasible for dose-painting treatments. In addition we have shown that a high FDG uptake in the lungs (excluding the tumor) before the start of treatment is an independent prognostic factor for radiation induced lung toxicity.