Radiotherapy for lung cancer
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Appendices

Summary

Lung cancer is the most common cause of cancer related deaths. Radiotherapy (RT) is an important treatment modality for lung cancer patients since many patients are inoperable. The inoperability is caused by the often advanced stage of lung cancer at presentation but also because the physical performance of many patients is insufficient to undergo surgery (often due to pulmonary comorbidity).

The prognosis of irradiated lung cancer patients is poor due to a high probability of early progression of the tumour and/or metastasis. To improve the prognosis, higher doses should be given to the tumour and the selection of patients benefitting from this higher doses should be improved. Currently, the choice of treatment, which are categorized fractionation schemes, are mainly determined by the tumour stage and the patients’ physical performance. Individualized regimens whereby the dose to the tumour is escalated as function of tumour/patient characteristics and normal tissue tolerance is a promising treatment approach. This new principle of treatment requires advanced irradiation techniques, adequate models predicting the normal tissue complication probability and a good patient selection. These topics are evaluated and discussed in the studies included in this thesis.

\[^{18}F\]fluorodeoxyglucose (FDG) positron emission tomography (PET) scans is a standard investigation performed during the work up of lung cancer patients for staging and RT delineation purposes. The FDG uptake in the tumour can be determined by the Standardized Uptake Value (SUV). The maximum SUV was of significant prognostic value for the disease specific and overall survival of the patient (Chapter 2). The prognostic value was independent from tumour stage and patients’ performance (Chapter 2). As a result, the maximum SUV value can play an important role in the selection of patients and tumour regions benefitting from dose escalation which is investigated in ongoing studies.

Normal tissue complication probability (NTCP) models are important to estimate the risk of adverse events. A dangerous side effect for lung cancer patients is radiation pneumonitis (RP). Previous studies found a relation between dose and RP after conventional fractionated RT. No functional lung parameters were found to have a contributively value to predict RP prospectively and the lung dose remains the most important parameter estimating the probability of RP (Chapter 3). The difficulty to improve predictive models reflects the complexity of this topic and the need for more studies.

Calculating tumour control and normal tissue complication probabilities from dose parameters requires a dose conversion. For conventional fractionated RT the linear
Summary

The quadratic (LQ) model is extensively validated and generally used for dose conversion to estimate the probabilities of clinical endpoints (i.e. tumour control and normal tissue toxicity). Although the use of hypofractionated RT for lung tumours is increasing, the relation between dose and RP is unknown. Also the applicability of the LQ model is uncertain.

A similar relation between the probability of RP as function of the dose was observed between hypofractionated RT and conventional fractionated RT (Chapter 4). Moreover, the time onset of RP was similar between hypofractionated RT and conventional fractionated RT (Chapter 4).

The LQ model can also be used for the dose conversion after hypofractionated RT to estimate the probability of RP (Chapter 6). Modifications of the LQ model according to cell data, did not improve the predictive value of the lung dose predicting RP (Chapter 6). The dose response relation for RP and the validation of the LQ model after hypofractionated RT is of great interest for current clinical practise (e.g. irradiating larger tumours and re-irradiations) and future trials (e.g. defining dose constraints).

Since lung cancer has a poor prognosis, little is known about the long term consequences of RT on the pulmonary function. The pulmonary function of a group of lung cancer patients fortunate with a long term disease free survival was irreversible deteriorated at longer follow up (Chapter 5). The pulmonary function of patients suffering from pulmonary co-morbidity declined more compared to other patients (Chapter 5). The decline seems to be correlated with the lung dose (Chapter 5). This study is indicative of what can be expected if the prognosis of lung cancer patients is improving. As a result, all possibilities to limit the lung dose should be investigated, explored and applied.

More sophisticated irradiation techniques whereby higher doses to the tumour and lower doses to normal structures can be planned and delivered are dependent on the verification of what is thought to be irradiated and what is truly irradiated. Consequently, appropriate imaging techniques, visualising the regions of interest (tumour and normal structures), before and after irradiation are of great importance. The introduction of linear accelerators equipped with a Cone Beam CT (CBCT) scanner is a major improvement for visualising the tumour and normal structures. Nevertheless, older verification techniques are still in wide spread use. Comparing the CBCT with the older verification technique showed significant difference (Chapter 7). The patients setup variability is underestimated if the older technique is used (Chapter 7). Knowledge about this difference is important for the irradiation of patients and new treatment protocols should only be implemented with much caution and sufficient quality control.