Radiotherapy for lung cancer
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Discussion

1. Radiotherapy for NSCLC

RT is currently the cornerstone in the treatment of inoperable NSCLC patients. Moreover, it might be possible that in the future early stage operable patients will be irradiated (as an alternative for thoracotomy). It is already known that higher doses of irradiation yield a greater proportion of complete response, higher tumour control and better survival in irradiated lung cancer patients [1,2]. Nevertheless, the possibility to apply higher doses and to add chemotherapy to radiotherapy is limited by the increased probability of treatment related toxicity. Improved patient selection, as well as newly developed high accuracy irradiation techniques and optimizing predictive toxicity models were subject of studies included in this thesis (Chapter 2-7) and will be discussed below.

2. Use of PET scan in the Treatment of Lung Cancer Patients

Tumour stage and performance status are currently the most important prognostic factors for lung cancer patients. Appropriate staging is of major concern and modifications of the Tumour (T) Nodal (N) Metastasis (M) staging system of the IASLC Lung Cancer Staging Project are published in 2007 [3]. This project evaluated data from 46 sources in more than 19 countries (i.e. 67,725 cases of non-small cell lung cancer (NSCLC) treated by all modalities of care between 1990 and 2000) whereby a training subset and a validation subset was used. From these data some changes were proposed (e.g. T2b N0 M0 cases are moved from stage IB to stage IIA, T2a N1 M0 cases from stage IIB to stage IIA, and T4 N0-1 M0 cases from stage IIIB to stage IIIA). These proposed changes might improve the alignment of TNM stage with prognosis and possibly in treatment but are based on data post-dated the period of PET scanning. The introduction of the Positron Emission Tomography (PET) scans in the diagnostic work up has significantly improved the sensitivity of mediastinal nodal staging compared to the sensitivity of the CT scan alone [4,5]. Unforeseen distant metastasis can also be detected by PET scan to differentiate candidates for curative or palliative treatment regimens. Additionally to staging, PET scans can be used to determine the border between tumour tissue and distally located collapsed lung tissue (atelectasis) [6]. As a result, the introduction of the PET scan has influenced the delineation of the target volume [7-11]. Following studies showed that the dose to non-tumour tissue was reduced for many patients if the PET scan information was used additional to the CT scan for tumour delineation [10,12-16]. In addition, better tumour dose coverage might be achieved if tumour definition is based on both CT and PET scans [13,17-19]. Therefore, a pre-RT PET scan is currently a standard procedure in the irradiation treatment of lung cancer patients.
2.1 Prognostic Value of FDG PET Scan and Clinical Implication

The hotspots on PET scans are regions with a high glucose uptake (with high accumulation of the glucose analogue [18F]-fluoro-2-deoxy-D-glucose (FDG)) representing tissues with a high metabolism (e.g. heart musculature, brain tissue and tumours). Aggressive tumours have a higher metabolism (glycolysis) which was already observed by Warburg in the early 19th century [20]. It has been shown that prognostic factors like tumour doubling time, glucose transporter proteins Glut 1 and Glut 3 and proliferation markers Ki-67 [21-23] are correlated with the amount of FDG in the tumour [24-26]. Calculation of the Standardized Uptake Value (SUV) (see paragraph 2.3) is a semi-quantitive method to objectify the amount of FDG in the tumour. The hypothesis that the SUV can be used as a surrogate marker of poor prognostic tumour characteristics was evaluated in lung patients who underwent surgery. Significantly higher pre-operatively measured SUVs were observed in patients with poor outcome compared to patients with favourable outcome [27-33]. The additional value of the SUV for operable patients is however limited because the tumour itself is available for pathology review after surgical resection. For inoperable patients on the other hand, the prognostic value of the SUV (besides performance status and TNM stage) would be of additional value since not all tumour characteristics can be retrieved from biopsies. Moreover, biopsies are not always available (e.g. failed biopsy or because of a contra indication for invasive procedures). As a consequence the prognostic pre-irradiation SUV is of major interest.

For 51 inoperable patients irradiated with a curative intend (stage I-IIIB) the SUV was calculated on the pre-RT PET scan. The SUV proved to be an independent prognostic factor besides performance status and stage for the disease specific survival and overall survival (Chapter 2). The significant different disease specific survival of patients with high SUV tumours and low SUV tumours might be a reflection of the aggressiveness of the tumour. More complex is the observation that lower SUVs were predictive for better tumour response observed at a CT scan after RT (Chapter 2). Higher proliferation rates (of more aggressive tumours) are correlated with higher sensitivity for irradiation [34] (i.e. higher SUVs would have had higher response rates). Nevertheless, higher SUVs were observed for worse response rates (Chapter 2). It might be that these tumours had a (fast) re-growth after irradiation observed at the post-RT CT scan. A correlative study comparing pre and post PET scans as function of the tumour response and survival is interesting to reveal this issue. Mac Manus et al. showed that patients with a complete metabolic response (i.e. PET response) had significantly better outcome [35] but unfortunately no information was given of the pre-treatment SUV. Aerts et al. [36] reported worse survival for patients with residual metabolic active areas. These patients had a significantly higher pre-RT SUV value compared to patients with a complete metabolic response. As
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expected, an overlap was observed between the pre-RT high SUV region and the residual metabolic active areas.

In Chapter 2, the important question is raised whether tumours with high SUV values should be treated more aggressively to raise the probability of cure. To solve this issue a study is initiated to boost high SUV areas (i.e. dose escalation to the tumour region with the highest SUV value or the whole tumour, see paragraph 5.5). Hopefully, patients with high SUV will benefit from this new treatment technique/dose escalation resulting in improved outcome comparable to patients with lower SUV values.

2.2 Other PET Tracers

The degree of hypoxia is an important determinant of treatment response, relapse-free survival, and overall prognosis, which is independent of the treatment modality used in cancer patients [37,38]. Although higher glycolysis is observed in hypoxic cells (i.e. Pasteur effect [39,40]) it is known for NSCLC tumours that the FDG uptake is not correlated with hypoxia of the tumour [41,42]. Consequently, FDG PET scans are not appropriate to discriminate oxidized tumour cells from radio resistant hypoxic tumour cells and other tracers visualizing hypoxia are of great interest as potential tumour boost areas [43]. Fluoromisonidazole (FMISO) is a derivative of the nitroimidazole group, which have been investigated as hypoxic cell sensitizer. Other derivates of nitroimidazole has shown radiosensitizing effects, e.g.[44]. Comparable to the FDG SUV of Chapter 2, also the FMISO SUV is predictive for treatment outcome [45]. Moreover, using FMISO-guided IMRT it was feasible to escalate the dose to radio-resistant hypoxic zones without exceeding the normal tissue tolerance in head and neck cancer patients [46]. Fluoroazomycin arabinoside (FAZA) is another derivative of nitroimidazole and has shown promising results in in-vitro studies [47]. As a result, not only tumour regions with a high FDG uptake are interesting regions for higher doses but also tumour regions with a high uptake of hypoxic tracer should be investigated for this (see paragraph 5.5).

2.3 Methodological Problems of the SUV

A major problem calculating the SUV is the non-standardized calculation method. This problem is not only known for SUV calculated from FDG PET scans but also for the hypoxic tracers as FMISO[45]. Differences in injected tracer, scanning time (i.e. time after injection), reconstruction algorithms, filters, scanner characteristics, sinogram noise and quantification methods might lead to (structural) inter-institutional SUV differences [48]. Even the calculation of a SUV differs between SUV studies; e.g. a SUVmean can be calculated as a mean value within a region of the tumour or a SUVmax can be determined within the whole tumour. Because the calculation of the SUV is subject to many uncertainties, comparisons of results
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achieved in different institutes should be interpreted with caution. In 2008 the first meta-analysis of studies evaluating the SUV as prognostic parameters was published [49] including our study of Chapter 2. Of the 13 studies in the meta-analysis, 11 studies showed a significant worse outcome for patients with a high SUV. All authors of these studies were asked to provide the individual patient data for a meta-analysis based on individual patient data. Since the PET scans can not be interpreted uniformly, the outcome of this work in progress based on individual patient outcome data might be complicated. More uniform scanning protocols and better (inter- and intra) institutional collaboration between the departments of RT and nuclear medicine is warranted for optimal use of the prognostic value of the PET scan. This should be performed since the PET scan is an important tool in the work-up of lung cancer patients and the SUV information is provided for free and can and should be used to improve the treatment strategy for the individual lung patient.

3. Radiotherapy Induced Lung Toxicity

The introduction of new irradiation techniques (e.g. 3D conformal radiotherapy and Intensity-Modulated Radiotherapy Treatment) facilitates reduction of high dose regions to tumour surrounding tissue. Nevertheless, lung tissue will always be included in the irradiation field and might even receive lower dosis to larger volumes. Cellular molecules (e.g. peptides, lipids, and DNA) are damaged directly and indirectly via the interaction with ionizing radiation and will result in an up-regulation of cascades of cytokines mediating pathologic changes (e.g. transforming growth factor beta-1 [50] and IL-6 [51]). For lung, these physiological and pathological responses to irradiation can be divided in an early (i.e. inflammatory) and late (i.e. fibrosis) phase resulting in subsequently related clinical symptoms.

3.1 Radiation Pneumonitis

The early phase, called radiation pneumonitis (RP), can occur weeks to months after thoracic radiotherapy and is a serious complication. Accurately scoring of RP is a tedious work complicated by the possibility of exacerbation of pulmonary comorbidities and/or tumour progression. The diagnosis and treatment of RP should therefore be performed with much caution.

RP is commonly scored according to the National Cancer Institute – Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 2 or the Southwest Oncology Group (SWOG) toxicity scales. In general, Grade 1 is scored for radiographic changes without symptoms. Grade 2 RP is scored after steroids had been prescribed. Grade 3 RP is scored after oxygen is required and grade 4 for assisted ventilation. Grade 5 is scored after death due to RP. The diagnosis of RP by the clinicians should be performed uniformly, robustly and reproducible. For example, before grading and scoring RP as an event, the symptoms should relieve after treatment is initiated.
and the diagnosis should have been confirmed by radiological changes. Moreover, the adverse events should be scored and graded by physicians experienced in the diagnosis of RP. To date, the NCI-CTCAE version 3 criteria is introduced for RP whereby grade 2 is defined as symptomatic but not interfering with activities daily living (ADL) and grade 3 as symptomatic but interfering with ADL. This grading system may be more influenced by the subjective sensation of both the patient and the physician concerning the ADL.

Scoring radiation induced lung toxicity using the dyspnoea grading system of the NCI-CTCAE version 3 [52] is complicated since dyspnoea can be caused by other reasons than RT induced toxicity. Moreover, to be able to predict radiation induced pulmonary (function) changes as function of patients and/or treatment characteristics, the dyspnoea scores after RT (or other endpoints) should be evaluated relative to the baseline score pre-RT and not as an absolute score [53].

3.2 Predictors for Radiation Pneumonitis

For patients irradiated with conventional fractionated radiotherapy schemes it is known that the lung dose and volume is predictive for RP [54-56]. The dose predicting RP can be expressed as a mean lung dose (MLD) or as a percentage of lung volume receiving more than a threshold dose x (Vx). There is no consensus or consistency between institutes which dose parameter should be used for the prediction of RP. Rodriguez performed a systematic review and concluded that the MLD showed the most consistent results to predict RP [57]. Also after this study including 14 studies, publications proved that Dose Volume Histograms (DVH) derived parameters were predictive for the incidence of RP [58,59]. However, the dose calculation algorithms that were used were inferior to currently used algorithms whereby large differences can be found [60]. Moreover, significant differences can be found between NTCP models calculated as function of dose parameters calculated with different algorithms. Also other factors are contributively for disappointing true positive and false negative predictive values (or in clinical terminology; some patients receiving low lung dose are still developing serious treatment induced complaints after radiotherapy). Retrospectively evaluated characteristics as prior thoracic irradiation, age, smoking history, performance status, lung function, chronic obstructive pulmonary disease (COPD) and sex [61-65] were predictive for RP. However, no study is currently available whereby these factors, which were predictive for RP, were prospectively validated. In the collaborative study of the Duke University with the Netherlands Cancer Institute (NKI) pre-RT criteria were defined which were possibly predictive for the development of RP (Chapter 3). Dosimetric and pulmonary functional parameters (from perfusion SPECT scan and pulmonary function tests) were derived from one cohort of patients (from the Duke University) and validated in the patients treated at the NKI. The prospectively developed model was unable
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to accurately segregate patients into high vs. low risk groups. Nevertheless, for both cohorts a correlation was observed between dose parameters and the incidence of RP. Additional work is needed to identify prospectively and validated predictors for RT-induced lung injury. These predictors will be able to select patients who are candidate to receive a more aggressive treatment or patients who are likely to develop serious treatment related toxicity (and should not be treated with an intensified treatment).

3.3 Radiation Pneumonitis after Hypofractionated RT

In contrast to the dose-response evaluations described in conventional fractionated RT, the relation between dose and RP after hypofractionated RT is unknown. Nevertheless, fatal RP toxicities were observed [66] and a possible dose-effect relation is of great interest. Other publications reported a wide range of the incidence of RP (0-29%) [66-71]. The first problem of dose response analysis is the large heterogeneity of treatment techniques, dose parameters and the scoring system of RP. To perform a dose-response analysis, a sufficient number of patients and events are necessary. Until recently only a limited number of institutes performed hypofractionated RT hampering dose-response analysis. Secondly, because only small lung tumours were treated by hypofractionated RT the amount of lung tissue receiving (high) doses is low. This results in a narrow dose range complicating a dose-response analysis. Thirdly, the analysis is complicated because of the uncertainty how to recalculate the physical dose into a biological equivalent lung dose (paragraph 4.1 and 4.2).

Since encouraging tumour control rates are demonstrated, the number of institutes using hypofractionated RT for lung tumours has been increasing in a short period of time (also in the Netherlands). Consequently, the knowledge of a (possibly) dose-response relationship is essential in optimizing hypofractionated RT. To date, it is uncertain whether multiple targets and/or larger tumour volumes can be (re)treated safely. The Hokkaido University in Japan was one of the few departments who applied hypofractionated RT for malignant pulmonary lesions soon after the introduction by Blomgren et al. [72] in 1995. In the following years, this group extended the use of hypofractionated RT since severe toxicities were not observed. Follow up was carefully performed and treatment regimens were adapted on empirical basis; i.e. if no toxicity was observed the dose was increased or larger/multiple lesions were irradiated and if no local recurrence was observed smaller safety margins were used).

As a result, a unique data set within a wide dose range was available. For a group of 128 patients a dose-response relation was observed for RP which was comparable with conventional treated patients (Chapter 4). For the higher dose range a steeper increase for the NTCP fit of the hypofractionated treated group of patients was observed. However, for both group of patients, less data was available in the high dose range and the difference in the high dose range was not significant.

The great importance of this study is that also for hypofractionated schedules the
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lung dose can be used to estimate the probability to develop RP for larger tumour volumes and/or re-irradiations. In addition, also the time interval between treatment and the incidence of RP was comparable for the two groups. As a result, there is no clinical reason to assume that the physiological process developing RP after hypofractionated RT is different from conventional fractionated RT. That this dose effect relation can be extended to larger fraction doses can be hypothesized but should be confirmed. In our institute only few (7%) incidences of RP were observed after 54 Gy in 3 fractions. As previously mentioned, the MLD range is limited because only small tumours were irradiated and the incidence is too low for a robust dose-response analysis.

Because the fraction dose is altered from conventional schemes other radiation induced toxicities than RP should be taken into account (paragraph 4.2). For example, recent studies showed an increased risk for brachial plexus toxicity for brachial plexus doses > 26 Gy in 3-4 fractions [73], chest wall pain for chest wall volumes > 30 cm³ receiving 30 Gy in 3-5 fractions [74] and skin toxicity if only 3 beams were used or if only a limited distance between tumour and skin was present [75]. For other reported toxicities the evidence that the clinical complications were caused by the high fraction dose was less strong (e.g. patients treated on centrally located tumours died from centrally located bleeding but for these patients tumour progression was found at this location or patients died due to pneumonitis but the pneumonitis had a bacterial origin) [76].

In conclusion, for fraction doses up to 12 Gy larger volumes and re-irradiation can safely be given concerning RP and other toxicities. For fraction dose of 18 Gy and higher, the incidence of RP is very low due to small volumes but caution should be taken for other (late term) toxicities.

3.4 Long term Pulmonary Toxicity

After the acute phase, long term radiation induced lung tissue damage is characterized by pulmonary fibrosis. This is an irreversible and progressive process of scar tissue in the lungs initiated by collagen deposition by fibroblasts. This results in narrowing of alveolar spaces, thickening of the interstitial layer and a diminished lung volume. Although the pathological processes and the radiological findings are well defined, the clinical implications are uncertain. The long term effect of radiotherapy for lung cancer patients is even more complicated to evaluate than the above described relation between dose and RP. Again, the pulmonary co-morbidity and poor prognosis hampers robust clinical analysis. For lymphoma and breast cancer patients (a patient group with a better prognosis and less pulmonary co-morbidity) a partial recovery from early radiation toxicity was observed between 3 and 18 months after radiotherapy. However, after 18 months, local lung function did not further improve [77]. To evaluate the long term effect of irradiation for lung cancer patients repetitive
pulmonary function tests were performed for 34 patients selected by a long term disease free survival and available pulmonary function tests (Chapter 5). An acute deterioration of pulmonary function after RT without improvement at long term was observed. For the pulmonary compromised patients suffering from COPD a larger decline of the pulmonary function at long term was observed. Likely, the COPD and radiotherapy consolidate the pulmonary impairment induced by the one or the other. Importantly, there was a trend of pulmonary function decline as a function of the lung dose. Consequently, these results are very important since it illustrates that long term surviving patients might have to deal with serious pulmonary side effects which might result in an impaired quality of life.

3.5 Radioprotective Agents

In contrast to radiosensitizing agents, the contribution of agents preventing or reducing radiation induced toxicity is less investigated in clinical trials. The protective value of corticosteroids for RP observed in an animal study [78] could not be confirmed in a clinical study [79]. The use of the immunomodulating and anti-inflammatory agent Pentoxifylline (with effects on hypoxia, inhibition of DNA repair and apoptosis [80]) was protective in a small group (n=40) of breast and lung cancer patients concerning radiation induced lung toxicity [81] although a larger phase III trial could not confirm these results [82]. Another small randomized trial showed a survival benefit in the group patients receiving Pentoxifylline but no toxicity data was given [83]. Angiotensin converting enzyme inhibitor showed anti-fibrotic activity in the lung of irradiated rats [84] but a clinical study could not confirm these results [85]. More promising is a cytoprotective agent Amifostine which is a prodrug that is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically-active free thiol metabolite. The metabolite can act as a scavenger of free radicals generated in tissues exposed to radiation. Amifostine concomitantly given decreased radiation-induced pulmonary injury without diminishing the therapeutic effect of radiation in randomized controlled trials for patients with locally advanced lung cancer [86-88]. Nevertheless, radioprotective agents are not generally used in the clinic. The use of radioprotective agents in future (dose-escalation) trials should be encouraged to evaluate the potential beneficial effect of these agents.
4. Biological Equivalent Dose Calculation after Hypofractionated RT

4.1 Linear Quadratic Model

For conventional fractionated RT the physical dose can be converted into a biological equivalent dose using the linear quadratic (LQ) model [89-91]. The LQ model is a simple mathematical model fitting log cell survival data as function of the dose and additionally enables clinical iso-effect calculations of fractionation schemes with different doses per fraction. Whether the calculation of the biological equivalent lung dose should be performed similarly for conventional fractionated as for hypofractionated schemes is an important question. The clinical applicability of the LQ model at higher fraction doses is uncertain and is questioned/discussed by many investigators [92-96]. Hall and Brenner [96] estimated from the iso-effect data of van der Kogel [97] (i.e. late-responding damage to the rat spinal cord) and Douglas and Fowler [98] (i.e. acute damage to the mouse skin) that the LQ model would be valid for single doses up to 20 Gy. Consequently, no differences would have been expected between different fractionation schemes if the equivalent doses (calculated with the LQ model) are similar. However, no clinical study validated this hypothesis. The fact that RP is the most evaluated toxicity endpoint after lung irradiation (whereby the LQ model with an \(\alpha/\beta\) ratio of 3 Gy is generally accepted [56,99,100]) emphasize not only the clinical relevance but also the scientific importance of these results. Therefore, RP is an appropriate endpoint to evaluate the LQ model and modifications of the LQ model. Using the Normal Tissue Complication Probability (NTCP) model of Lyman [101] the curves of the probability of developing RP as a function of the mean lung dose were similar for hypofractionated RT and conventional fractionated RT if an \(\alpha/\beta\) ratio of 3 Gy was used (Chapter 4). However, it should be questioned whether lung doses corrected according to modified LQ models might improve the predictive value (Chapter 6).

4.2 Modifications of the Linear Quadratic Model

4.2.1 Theoretical background

It is already known for a long time (1954) that for the high dose region the log cell survival is linear and not bending as represented by the definition of the LQ model [102]. To evaluate this issue, modifications of the LQ model were proposed based on cell line and animal iso-effect data [103,104]. These modifications fitted the experimental data better but clinical data was not evaluated. One of the above mentioned modifications of the LQ model was based on the Lethal-Potentially Lethal (LPL) model [105] and was developed by Guerrero et al. [104] (based on cell survival and animal toxicity data). The LPL was superior to the LQ model at higher dose regions fitting the experimental data. Nevertheless, the dose range where the LQ model started to deviate from the LPL model was rather large (cell lines: 0.6 Gy to 37.7 Gy, animal toxicity data: 2.6 Gy to 100 Gy). Carlone et al. [106] showed that
this modification proposed by Guerrero et al. [104] resulted in a LQ model with a linear extension and proposed the nomenclature of the linear-quadratic-linear model (LQL model) of the log cell survival as function of the dose for the high dose range [106]. More recently, Park et al. [103] used a linear extension of the log cell survival as function of the dose for doses higher than a threshold dose (i.e. transition dose $d_T$).

### 4.2.2 Clinical applicability

Because the modified LQ model by Guerrero et al. [104] and Park et al. [103] fitted the experimental data better after high single dose RT, this LQL model was evaluated with the clinical data set of Chapter 4. A linear extension of the log cell survival as function of the dose for doses higher than a threshold dose (i.e. transition dose $d_T$) was used for different values of $d_T$. The LQL model did not improve the Normal Tissue Complication Probability (NTCP) fits predicting RP for any of the evaluated $d_T$ (Chapter 6).

The first reason for this might be that the evaluated $d_T$ (0, 5, 7 and 9 Gy) were not the appropriate values for lung tissue. However, no higher values could be evaluated because if the $d_T$ approaches the highest fraction dose the dose calculated by the LQL model will approach the dose calculated by the LQ model. As a result, the NTCP fits of the LQL model with $d_T$'s of 7 and 9 Gy were approaching the NTCP fit of the LQ model because fraction doses from 6 to 12 Gy were examined (only a limited part of the distribution of doses per fraction was larger than these $d_T$ values).

The possibility to evaluate higher transition doses for schemes with higher fraction doses were also investigated (Chapter 6). Also for fraction doses of 18 Gy per fraction the introduction of a higher $d_T$ values (> 10 Gy) would lead to imperceptible differences between the dose calculated with the LQ and the LQL model. Consequently, it might be questioned whether a higher $d_T$ can be clinically evaluated in the future due to limited amount of lung tissue receiving these high doses. Animal studies might elucidate the hypothesis that the lung dose should be calculated according to the LQL model with higher $d_T$ values for lung tissue irradiated with higher (>> 18 Gy) fraction doses. On the other hand higher $d_T$ values will apparently not be of additional value in clinical practise.

Another reason that the LQL model did not improve the NTCP fit is that the used dose parameter is not appropriate for this analysis. The mean lung dose is a parameter whereby the high dose and low dose regions are averaged over the whole lung. The percentage lung volume receiving doses higher than a certain threshold dose is another frequently used parameter (see paragraph 3.2). In our analysis it was observed that the MLD and the higher threshold dose parameters were preferable above low threshold dose parameters. In addition, radiographic changes in symptomatic patients are mainly located in high dose lung regions [107,108]. Consequently, parameters
reflecting lung volume receiving high dose might be better suitable for this analysis. Again, to exclude clinical confounding factors, animal studies should be performed to evaluate different dose parameters. Nevertheless, our results indicate that new irradiation techniques with conformal orientated continuous irradiation (with high percentages lung volume receiving low doses, e.g. rapid arc and tomotherapy) will not be correlated with an increased incidence of RP. [56,94,100].

The complexity of scoring RP (paragraph 3.1) may confound the dose-effect relation. Local dose effect relation derived from follow up SPECT perfusion changes or follow up CT density changes are other (possibly more objective) endpoints and has proven to be of additional value predicting radiation induced lung toxicity after conventional fractionated RT[109,110]. Clinical studies are ongoing to evaluate sequential SPECT scans after hypofractionated RT. Since the differences between the LQL model and LQ model originate from the high dose region, especially dose effect relations in the high dose region are of interest which can be derived from SPECT and CT scans. Another reason to study this is that higher doses per fraction is mainly influencing late term toxicity; late responding tissue is observed to have more bending (i.e. lower $\alpha/\beta$ ratio,) than early responding tissue. Because late term toxicity is clinically difficult to evaluate (paragraph 3.4), again, SPECT and CT changes are interesting end-points to evaluate the LQL model.

5. Accurate Targeting of the Irradiation

5.1 Setup errors

The introduction of 3D conformal RT and intensity-modulated RT (IMRT) enables conformal delivery of the irradiation to the tumour with the advantage of sparing normal tissue. However, the delivery of dose to the tumour with a conformal treatment plan is more difficult than if large irradiation fields are given since the position of the target is subject to geometric uncertainties due to variability in patient positioning and internal organ motion [111,112]. These geometric uncertainties can be divided in random errors ($\sigma$) (i.e. deviations that occurs between different fractions) and systematic errors ($\Sigma$) (i.e. deviation between the patient/tumour position of the treatment plan and the average patient/tumour position during treatment).

5.2 Electronic Portal Imaging Device

Setup errors can be verified by electronic portal image device (EPID) measurements performed during the treatment using the megavolt photons of the linear accelerator as source. According to these measurements, corrections can be performed in the remaining number of fractions (i.e. off-line correction protocol). An off-line correction protocol is reducing the systematic errors (random errors can only be corrected by an online correction protocol). Studies evaluating these setup errors
found similar results in the order of about 2 mm in all directions [113-115]. However, the accuracy of the EPID measurements itself could not be evaluated because a reference procedure (i.e. golden standard) was lacking.

5.3 Conebeam CT Scanner
A CBCT scanner consists of a kV source and imager with the central axis perpendicular to the treatment beam verifying the position of anatomical structures and tumour [116]. Consequently, the data from the kV CBCT allows accurate measurements of the systematic and random setup errors. With the introduction of the kV CBCT differences measured by EPID and CBCT according to the patient setup could be evaluated accurately (Chapter 7). The setup errors measured with CBCT were generally larger than those measured with EPID whereby the largest difference was observed in the cranial-caudal and anterior-posterior direction. Because it can be assumed that the CBCT system is the golden standard (confirmed by the highly accurate and precise measurements [117]) it should be questioned what causes the difference between the CBCT and EPID. First, the time interval between the CBCT and EPID measurements might introduce differences. However, Van Herk et al. [118] investigated the time interval between the CBCT registration and the EPID measurements. They observed that differences between the digital reconstructed radiographs (DRR) from the CBCT scans and the corresponding EPID images were smaller than < 1 mm [119]. Rotations (which can be measured by CBCT and not by EPID [120]) were not expected to influence the results significantly since only a weak correlation between the rotations and the differences between CBCT and EPID was observed (Chapter 7). It might be hypothesized that the region of interest (ROI) on the EPID (the vertebra, clavicles and ribs) is more subject to (respiratory) motion than the ROI of the CBCT. This should have resulted in larger setup errors for the EPID compared to the CBCT (region of interest was the vertebra). However, this is the opposite of what was observed (Chapter 7).

Registration of the images of the EPID is more difficult due to the poorer quality compared to CBCT images. As a result, fewer corrections might be applied because they were not considered as necessary. Consequently, an underestimation of the setup error, which was statistically significant, was found (Chapter 7).

5.4 Correction protocols
For conventional fractionated RT treatment schedules mainly off-line correction protocols are used to correct for systematic setup errors. However for hypofractionated regimens only a few fractions with a very high dose are given and high irradiation accuracy is a necessity whereby also random setup errors should be minimized. Also inter-fraction changes of tumour volume, tumour position and pulmonary anatomy and a differential motion between multiple targets can have a major influence on the
delivered dose. Knowledge of the target position(s) and motion is therefore essential before irradiation. Using an online correction protocol whereby not only the patient position is verified but also the target position and motion is determined is possible by the introduction of a 4D-CBCT scan. This scan provides information whether the current treatment plan is covering the target or that the position should be corrected before the irradiation is delivered. In current practice, before all hypofractionated irradiation fractions a 4D-CBCT is performed. For conventional RT treatments a 4D-CBCT is acquired weekly (after a daily acquisition in the first week).

5.5 Dose Escalation and Adaptive Radiotherapy
For higher tumour control probabilities (TCP) dose escalation is needed. For total doses up to 66 Gy, only 17 % one year tumour control is observed (without chemotherapy) [121]. TCP modelling studies estimated that for a TCP of 50% the dose should be escalated to more than 84 Gy in fraction doses of 1.8-2 Gy [122]. Since dose escalation is limited due to toxicity reduction of the normal tissue dose is needed. 4D CT treatment planning [123], the use of specific respiratory position scans (i.e. mid-ventilation scan) [124] and modified IMRT techniques [125,126] can reduce the normal tissue dose as retrospectively observed in dose modelling studies. Limiting the dose escalation to specific tumour regions of interest and not the whole tumour (paragraph 2.1 and 2.2) may also limit the dose to the normal structures. The success rate of these techniques is dependent on the accuracy of the knowledge of the tumour position (and specific tumour regions). Consequently, the introduction of accurate imaging modalities (e.g. CBCT) on the treatment machines whereby adaptive RT can be applied will have a major impact on the prognosis of lung cancer patients in the near future.
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General discussion


